NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. FDA collaborated with Australia's Therapeutic Goods Administration (TGA), and Switzerland's Swissmedic (SMC)). While the conclusions and recommendations expressed herein reflect FDA's completed review of the application, the applications may still be under review at the other regulatory agencies.

In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA or the other Regulatory Authorities.

Application Type	BLA
Application Number(s)	761234
Priority or Standard	Priority
Submit Date(s)	July 19, 2021
Received Date(s)	July 19, 2021
PDUFA Goal Date	March 19, 2022
Division/Office	Division of Oncology 3/Office of Oncologic Diseases
Review Completion Date	March 18, 2022
Established Name	nivolumab and relatlimab in a fixed dose combination (FDC)
(Proposed) Trade Name	Opdualag
Pharmacologic Class	Anti-PD1 inhibitor and LAG-3 inhibitor
Code name	BMS-986213
Applicant	Bristol-Myers Squibb Company
Formulation(s)	Injection, for intravenous use
Dosing Regimen	Nivolumab 480 mg and relatlimab 160 mg administered intravenously every 4 weeks
Applicant Proposed Indication(s)/Population(s)	OPDUALAG is a combination of relatlimab, a lymphocyte activation gene-3 (LAG-3) blocking antibody, and nivolumab, a programmed death receptor-1 (PD-1) blocking antibody, indicated for the treatment of adults and pediatric patients (12 years and older (b) (4) with unresectable or metastatic melanoma
Recommendation on Regulatory Action	Traditional Approval
Recommended Indication(s)/Population(s) (if applicable)	OPDUALAG is a combination of nivolumab, a programmed death receptor-1 (PD-1) blocking antibody, and relatlimab, a lymphocyte activation gene-3 (LAG-3) blocking antibody,

	indicated for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma

Table of Contents

Reviewers of Multi-Disciplinary Review and Evaluation 16

Additional Reviewers of Application 16

Glossary 19

1 Executive Summary 22

1.1. Product Introduction 22

1.2. Conclusions on the Substantial Evidence of Effectiveness 22

1.3. Benefit-Risk Assessment (BRA) 24

1.4. Patient Experience Data 28

2 Therapeutic Context 30

2.1. Analysis of Condition 30

2.2. Analysis of Current Treatment Options 31

3 Regulatory Background 34

3.1. U.S. Regulatory Actions and Marketing History 34

3.2. Summary of Presubmission/Submission Regulatory Activity 34

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety 36

4.1. Office of Scientific Investigations (OSI) 36

4.2. Product Quality 37

4.3. Clinical Microbiology 37

4.4. Devices and Companion Diagnostic Issues 37

5 Nonclinical Pharmacology/Toxicology 38

5.1. Executive Summary 38

5.2. Referenced NDAs, BLAs, DMFs 40

5.3. Pharmacology 40

5.3.1. Primary pharmacology 40

5.3.1.5. Evaluation of Anti-LAG-3 and Anti-PD-1 Antibodies Alone and in Combination in the Sa1N Fibrosarcoma Tumor Model 45

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5.3.1.6. Evaluation of Anti-LAG-3 and Anti-PD-1 Antibodies Alone and in Combination in the MC38 Colon Adenocarcinoma Tumor Model 46
5.3.2. Secondary Pharmacology 50
5.3.3. Safety Pharmacology 51
5.4. ADME/PK 51
5.5. Toxicology 56
5.5.1. General Toxicology 56
5.5.2. Genetic Toxicology 69
5.5.3. Carcinogenicity 69
5.5.4. Reproductive and Developmental Toxicology 70
5.5.5. Other Toxicology Studies 76

6 Clinical Pharmacology 79
6.1. Executive Summary 79
6.2. Summary of Clinical Pharmacology Assessment 81
6.2.1. Pharmacology and Clinical Pharmacokinetics 81
6.2.2. General Dosing and Therapeutic Individualization 82
6.2.2.1. General Dosing 82
6.2.2.2. Therapeutic Individualization 87
6.2.2.3. Outstanding Issues 89
6.3. Comprehensive Clinical Pharmacology Review 90
6.3.1. General Pharmacology and Pharmacokinetic Characteristics 90
6.3.2. Clinical Pharmacology Questions 99
6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness? 99
6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought? 104
6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors? 109
6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy? 113

7 Sources of Clinical Data 115

7.1. Table of Clinical Studies 115

8 Statistical and Clinical Evaluation 118

8.1. Review of Relevant Individual Trials Used to Support Efficacy 118

8.1.1. Pivotal Phase 3 Study CA224047 (RELATIVITY -047) 118

8.1.1.1. Trial Design 118

8.1.1.2. Study Endpoints 122

8.1.1.3. Statistical Analysis Plan and Amendments 124

8.1.1.4. Protocol Amendments 128

8.1.2. Study Results - Pivotal Study CA224047 129

8.1.2.1. Compliance with Good Clinical Practices 129

8.1.2.2. Financial Disclosure 129

8.1.2.3. Patient Disposition 130

8.1.2.4. Protocol Violations/Deviations 131

8.1.2.5. Table of Demographic Characteristics 132

8.1.2.6. Other Baseline Characteristics 134

8.1.2.7. Treatment Compliance, Concomitant Medications, and Rescue Medication Use 136

8.1.2.8. Efficacy Results – Primary Endpoint 137

8.1.2.9. Data Quality and Integrity 148

8.1.2.10. Efficacy Results – Secondary and other relevant endpoints 149

8.1.2.11. Dose/Dose Response 153

8.1.2.12. Durability of Response 154

8.1.2.13. Persistence of Effect 154

8.1.2.14. Efficacy Results – Exploratory PRO endpoints 154

8.1.2.15. Additional Analyses Conducted on the Individual Trial 155

8.1.3. Supportive Phase 1/2 Study CA224020 (RELATIVITY -020) 156

8.1.4. Study Results - Supportive Study CA224020 157

8.1.5. Integrated Review of Effectiveness 159

8.1.6. Assessment of Efficacy Across Trials 159

8.1.7. Integrated Assessment of Effectiveness 160

8.2. Review of Safety 161

8.2.1. Safety Review Approach 162
8.2.2. Review of the Safety Database 165
8.2.2.1. Overall Exposure 165
8.2.2.2. Relevant characteristics of the safety population: 167
8.2.2.3. Adequacy of the Safety Database 170
8.2.3. Adequacy of Applicant's Clinical Safety Assessments 170
8.2.3.1. Issues Regarding Data Integrity and Submission Quality 170
8.2.3.2. Categorization of Adverse Event 171
8.2.3.3. Routine Clinical Tests 173
8.2.4. Safety Results from Pivotal Study CA224047 174
8.2.4.1. Deaths 175
8.2.4.2. Serious Adverse Events 183
8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects 184
8.2.4.4. Dose Interruption/Reduction Due to Adverse Effects 188
8.2.4.5. Significant Adverse Events 191
8.2.4.6. Treatment Emergent Adverse Events and Adverse Reactions 197
8.2.4.7. Laboratory Findings 201
8.2.4.8. Vital Signs 203
8.2.4.9. Electrocardiograms (ECGs) 203
8.2.4.10. QT 204
8.2.4.11. Immunogenicity 204
8.2.5. Safety from Supportive Phase 1/2 Study CA224020 (RELATIVITY -020) 204
8.2.6. Analysis of Submission-Specific Safety Issues 206
8.2.6.1. Myocarditis and Troponin Elevation 206
8.2.6.2. Central Nervous System AEs 209
8.2.6.3. Hypersensitivity (including anaphylactic reaction) 212
8.2.6.4. Adolescents 213
8.2.7. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability 214
8.2.8. Safety Analyses by Demographic Subgroups 215
8.2.9. Specific Safety Studies/Clinical Trials 223
8.2.10. Additional Safety Explorations 223

8.2.10.1. Human Carcinogenicity or Tumor Development 223
8.2.10.2. Human Reproduction and Pregnancy 223
8.2.10.3. Pediatrics and Assessment of Effects on Growth 224
8.2.10.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound 224
8.2.11. Safety in the Postmarket Setting 224
8.2.11.1. Safety Concerns Identified Through Postmarket Experience 224
8.2.11.2. Expectations on Safety in the Postmarket Setting 225
8.2.12. Integrated Assessment of Safety 226

SUMMARY AND CONCLUSIONS 228
8.3. Statistical Issues 228
8.4. Conclusions and Recommendations 229

9 Advisory Committee Meeting and Other External Consultations 231

10 Pediatrics 231

11 Labeling Recommendations 232

12 Risk Evaluation and Mitigation Strategies (REMS) 238

13 Postmarketing Requirements and Commitment 238

14 Division Director (DHOT) (NME ONLY) 239

15 Division Director (OCP) 239

16 Division Director (OB) 239

17 Division Director (Clinical) 240

18 Office Director (or designated signatory authority) 240

19 Appendices 240
19.1. References 240
19.2. Financial Disclosure 241
19.3. Nonclinical Pharmacology/Toxicology 242
19.4. OCP Appendices (Technical documents supporting OCP recommendations) 242
19.4.1. Bioanalytical Methods 242

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

19.4.2. Population PK Analysis 253
19.4.2.1. Executive Summary 253
19.4.2.2. PPK Assessment Summary 255
19.4.3. Exposure-Response Analysis 283
19.4.3.1. ER (efficacy) Executive Summary 283
19.4.3.2. ER (efficacy) Assessment Summary 283
19.4.3.3. ER (safety) Executive Summary 301
19.4.3.4. ER (safety) Assessment Summary 301
19.4.3.5. Overall benefit-risk evaluation based on E-R analyses 313
19.5. Additional Safety Analyses Conducted by FDA 314
19.6. List of References 314

Table of Tables

Table 1: Applicant - FDA-approved IO and Targeted Therapies for Systemic Treatment of Advanced, Unresectable Melanoma in Routine Clinical Use (NCCN Guidelines)....33
Table 2: Applicant - Relevant Relatlimab Regulatory History....34
Table 3: Applicant - Primary Pharmacology: Relatlimab (BMS-986016) In Vitro Target Binding Profile....41
Table 4: Applicant - Primary Pharmacology: Relatlimab (BMS-986016) In Vitro Receptor-Ligand Blocking Profile....42
Table 5: Applicant - Primary Pharmacology: Relatlimab (BMS-986016) In Vitro Functional Profile....43
Table 6: Applicant - Primary Pharmacology: Number of Sa1N Tumor-free Mice and Percent Tumor Growth Inhibition Following IP Administration of Anti-LAG-3 mAb Alone....45
Table 7: Applicant - Primary Pharmacology: Number of Sa1N Tumor-free Mice and Percent Tumor Growth Inhibition Following IP Administration of Anti-LAG-3 mAb and Anti-PD-1 Antibodies Individually or in Combination....45
Table 8: Applicant - Primary Pharmacology: Number of MC38 Tumor-free Mice and Percent Tumor Growth Inhibition Following IP Administration of Anti-LAG-3 and Anti-PD-1 Antibodies Individually or in Combination....46
Table 9: Applicant - ADME/PK: Summary of ADME Characteristics and Pharmacokinetic Parameters....51
Table 10: Applicant - Toxicokinetics: Overview of Toxicokinetics Data....54
Table 11: Applicant - General Toxicology: Four-week Intravenous Combination Toxicity Study in Monkeys with a 6-Week Recovery....57
Table 12: Applicant - General Toxicology: Study DN12123 Four-week Intravenous Combination Toxicity Study in Monkeys with a 6-Week Recovery/DCN 930070016....58
Table 13: Applicant - General Toxicology: Three-Month Intermittent Intravenous Infusion (QW) Toxicity Study in Monkeys with a 10-Week Post Dose Recovery....65
Table 14: Applicant - General Toxicology: Study DN16053 Three-Month Intermittent Intravenous Infusion (QW) Toxicity Study in Monkeys with a 10-Week Post Dose Recovery....66
Table 15: Applicant - Reproductive and Developmental Toxicology: Anti-LAG-3 C9B7W mAb: Intra-Peritoneal Study of Embryo-Fetal Development in Mice....71
Table 16: Applicant - Reproductive and Developmental Toxicology: Study DN17040 anti-LAG-3 C9B7W mAb: Intra-Peritoneal Study of Embryo-Fetal Development in Mice....72
Table 17: Applicant - Other Toxicology Studies: In Vitro Cytokine Release and Lymphocyte Activation Assessment using Human Peripheral Blood Mononuclear Cells....76
Table 18: Applicant - Other Toxicology Studies: Tissue Cross-Reactivity Study of Fluoresceinated BMS-986016 in a Full Human Tissue Panel and a Limited Cynomolgus Monkey Tissue Panel....77
Table 19: Applicant - Predicted Relatlimab Exposures for All Subjects at Nivo+rela 240/80 mg Q2W or 480/160 mg Q4W....82
Table 20: Applicant - Predicted Peripheral Relatlimab Receptor Occupancy for Melanoma Subjects at Nivo+rela 240/80 mg Q2W or 480/160 mg Q4W....83

Table 21: ORR and PFS between 160/480 vs 480/480 mg Q4W in treatment naïve melanoma patients in Study CA224020 Part E 85
Table 22: Incidence of IRRs and infusion related hypersensitivity in Study CA224047 86
Table 23: Incidence of IRRs and infusion related hypersensitivity in Study CA224020 86
Table 24: Applicant - General Pharmacology and Pharmacokinetic Characteristics 90
Table 25: Applicant - Summary of sLAG-3 and IFNγ in Studies CA224020 and CA224047 91
Table 26: Applicant - Geometric Mean (CV%) of Relatlimab Exposures at Proposed Nivo+rela 480/160 mg Q4W Dose 92
Table 27: Applicant - Summary of Predicted Dose-Normalized Relatlimab Exposures and Accumulation Ratio by Dose 92
Table 28: Drug-related AEs and AEs leading to discontinuation/delays in Study CA224020 and CA224047 107
Table 29: Applicant - Listing of Clinical Trials Relevant to this BLA 115
Table 30: Applicant - CA224047 Study Design Details 119
Table 31: Applicant - Key Study CA224047 Procedures and Schedule 121
Table 32: Applicant - CA224047 Key Endpoints 124
Table 33: Applicant - CA224047 Statistical Analysis Plan 126
Table 34: Concordance for PD-L1 status (b) (4) and AJCC M stage (IRT vs. RAVE CRF) 127
Table 35: Applicant - CA224047 Protocol Amendments - Key Changes 128
Table 36: Applicant - Subject Disposition, All Enrolled, Randomized, and Treated Subjects in CA224047 130
Table 37: Applicant - Summary of Relevant Protocol Deviations - All Randomized Subjects in CA224047 131
Table 38: Applicant - Demographic Characteristics Summary, All Randomized Subjects in CA224047 132
Table 39: Applicant - Baseline Disease Characteristics, All Randomized Subjects in CA224047 134
Table 40: Applicant - Primary Efficacy Endpoint of PFS per BICR, All Randomized Subjects in CA224047 137
Table 41: Secondary Efficacy Endpoint of Overall Survival, All Randomized Subjects 149
Table 42: Secondary Efficacy Endpoints of Objective Response Rate and Duration of Response, All Randomized Subjects 153
Table 43: Applicant - Safety Population 165
Table 44: Applicant - Duration of Study Therapy Summary, All Treated Subjects in CA224047 165
Table 45: Applicant - Duration of Study Therapy Summary, All Nivo+Rela 480/160 mg Q4W Subjects in CA224020 165
Table 46: Applicant - Cumulative Dose and Relative Dose Intensity, CA224047 and CA224020166
Table 47: Summary of Treatment Exposure for Pivotal Trial CA224047 167
Table 48: Demographic Characteristics of Safety Population 168
Table 49: Applicant - Summary of Safety, All Treated Subjects in CA224047 174
Table 50: Summary of Deaths 176

Table 51: AEs Resulting in Death 177
Table 52: Narratives for Deaths other than Disease Progression: Nivolumab-Relatlimab Arm 178
Table 53: Adverse Events Leading to Any Study Treatment Withdrawal 185
Table 54: Applicant - Dose Delay, Dose Infusion Interruption, and Infusion Rate Reduction, All Treated Subjects in CA224047 188
Table 55: Applicant - Summary of IMAEs and OESIs, All Treated Subjects in CA224047 191
Table 56: Applicant - Onset, Management, and Resolution of Immune-Mediated Myocarditis and Troponin Elevation Treated with Immune-Modulating Medication within 100 days of Last Dose - Nivo+rela FDC and Nivolumab Monotherapy Q4W Treated Subjects 191
Table 57: Patients with Grade 3-4 AEs ≥ 1% on Pivotal Study CA224047 196
Table 58: Applicant - Adverse Reactions in ≥ 15% of Patients Receiving Nivo+Rela FDC in CA224047 197
Table 59: Patient with AEs ≥ 10% on Pivotal Study CA224047 199
Table 60: Applicant - Laboratory Values Worsening from Baseline[a] Occurring in ≥ 15% of Patients on Nivo+Rela FDC and Nivolumab in CA224047 201
Table 61: Laboratory Abnormalities Occurring in ≥ 10% of Patients on Pivotal Study CA224047 202
Table 62: ADA Assessments Summary - All Treated Subjects with Baseline and At Least One Post-Baseline Assessment in Study CA224047 197
Table 63: Summary of Safety - All Nivolumab 480 mg + Relatlimab 160 mg Q4W Treated Subjects in CA224020 205
Table 64: Incidence of Central Nervous System Toxicity Composite term 211
Table 65: Applicant - Any Grade Drug-Related Adverse Events ≥ 10% by Age, Sex, and Region, All Treated Subjects in CA224047 215
Table 66: Applicant - Proposed Risk Management Strategy 227
Table 67: Determination of relatlimab (BMS-986016) method MTD021 (applied for analysis for relatlimab samples from Study CA224020 and CA224047) 242
Table 68: Determination of nivolumab (BMS-936558) method ICD 416 (applied for analysis for nivolumab samples from Study CA224020) 247
Table 69: Determination of nivolumab (BMS-936558) method MTD035 (applied for analysis for nivolumab samples from Study CA224047) 250
Table 70: Applicant - Summary of Covariates by Patient Population in the Relatlimab Population Pharmacokinetic Analysis Dataset 263
Table 71: Applicant - Summary of Covariates by Patient Population in the Nivolumab Population Pharmacokinetic Analysis Dataset 264
Table 72: Applicant - Summary of Covariates in the Nivolumab Population Pharmacokinetic Analysis Dataset by Adolescents (≥ 12 to 17 years) and Pediatrics (< 12 years) 266
Table 73: Applicant - Parameter Estimates of the Final Relatlimab Population Pharmacokinetic Model 267
Table 74: Applicant - Parameter Estimates of the Full Nivolumab Population Pharmacokinetic Model 268

Table 75: Applicant - Summary of Exposures and Baseline Covariates in the Exposure-Response of PFS Analysis Dataset, by Patient Population 288
Table 76: Applicant - Summary of Exposures and Baseline Covariates in the Exposure-Response of OR Analysis Dataset, by Patient Population 289
Table 77: Applicant - Parameter Estimates of Relatlimab Peripheral Receptor Occupancy Model 290
Table 78: Applicant - Parameter Estimates of Exposure-Response of PFS Full Model..... 291
Table 79: Applicant - Parameter Estimates of Exposure-Response of OR Full Model 291
Table 80: ORR summary in Study CA224020 by prior treatment and dosing group 300
Table 81: Applicant - Summary of Exposures and Baseline Covariates in the Exposure-Response of Gr2+ IMAE and Gr3+ DRAE Analysis Dataset..... 305
Table 82: Applicant - Parameter Estimates of Exposure-Response of Gr2+ IMAE Full Model ... 306
Table 83: Applicant - Parameter Estimates of Exposure-Response of Gr3+ DRAE Full Model ... 307

Table of Figures

Figure 1: Relatlimab binding to LAG-3-mFc fusion protein....48
Figure 2: Relatlimab (BMS-986016) blocks human LAG-3 binding to MHC class II Daudi cells (left) and FGL1 (right) 48
Figure 3: Enhanced activation of superantigen-stimulated human PBMCs by relatlimab alone and in combination with nivolumab 49
Figure 4: Tumor growth curves of anti-LAG-3 (C9B7W) and anti-PD-1 (4H2) treated tumor bearing mice 50
Figure 5: Applicant - Model Predicted Hazard Ratio of PFS for Relatlimab Cavgd28 in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Nivolumab 480 mg Q4W Regimen 99
Figure 6: Applicant - Model Predicated Odds Ratio of OR for Relatlimab Cavgd28 in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Nivolumab 480 mg + Relatlimab 160 mg Q4W Regimen 99
Figure 7: Applicant - Predicted Relatlimab Exposures for Adolescent Subjects at Subjects (b) (4) 100
Figure 8: Applicant - Predicted Nivolumab Exposures for Adolescent Subjects at (b) (4) 101
Figure 9: Applicant - Model Predicted Hazard Ratio of Gr2+ IMAEs in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Nivolumab 480 mg Q4W Regimen 104
Figure 10: Applicant - Model Predicted Hazard Ratio of Gr3+ DRAEs in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Nivolumab 480 mg Q4W Regimen 104
Figure 11: Applicant - Predicted Relatlimab Exposures at 160 mg Q4W by Body Weight Quartiles in Adults 109
Figure 12: Applicant - Distribution of Model Predicted Relatlimab Exposures (Cavg1 and Cavgss) at 160 mg Q4W by Hepatic Function 110
Figure 13: Applicant - Distribution of Model Predicted Relatlimab Exposures (Cavg1 and Cavgss) at 160 mg Q4W by Renal Function 110
Figure 14: Applicant - Covariate Effects on Full Relatlimab PPK Model 111
Figure 15: Applicant - CA224047 Study Design Schematic 118
Figure 16: Applicant - CA224047 Kaplan-Meier Plot of Progression-free Survival per BICR, All Randomized Subjects 138
Figure 17: Applicant - CA224047 Forest Plot of Treatment Effect on PFS in Pre-Defined Subsets, All Randomized Subjects 139
Figure 18: Kaplan-Meier Plot of PFS per Investigator, All Randomized Subjects 142
Figure 19: Kaplan-Meier Plot of Overall Survival, All Randomized Subjects 150
Figure 20: Forest Plot of Overall Survival in Pre-defined Subgroup, All Randomized Subjects 151
Figure 21: Applicant - Covariate Effects on Full Nivolumab Pharmacokinetic Model Parameters 270

Figure 22: Applicant - Population Predicted and Individual Predicted versus Observed Concentration (Full Relatlimab Population Pharmacokinetic Model) by Patient Population 271
Figure 23: Applicant - Conditional Weighted Residuals versus Time after First Dose by Patient Population (Full Relatlimab Population Pharmacokinetic Model) 272
Figure 24: Applicant - Conditional Weighted Residuals versus Time after Previous Dose (Full Relatlimab Population Pharmacokinetic Model) 273
Figure 25: Applicant - Conditional Weighted Residuals versus Population Predicted Concentration by Patient Population (Full Relatlimab Population Pharmacokinetic Model) 274
Figure 26: Applicant - Observed versus Predicted Population Average and Individual Concentration in Adult 1L MEL, Adult Prior-IO MEL, Adult Others, and Pediatric Subjects (< 18 Years) [Full Nivolumab Population Pharmacokinetic Model] 275
Figure 27: Applicant - CWRES versus Time after First Dose in Adult 1L MEL, Adult Prior IO MEL, Adult Others, and Pediatric Subjects (< 18 Years) [Full Nivolumab Population Pharmacokinetic Model] 275
Figure 28: Applicant - CWRES versus Time after Previous Dose in Adult 1L MEL, Adult Prior-IO MEL, Adult Others, and Pediatric Subjects (< 18 Years) [Full Nivolumab Population Pharmacokinetic Model] 276
Figure 29: Applicant - CWRES versus Population Predicted Serum Concentration in Adult 1L MEL, Adult Prior-IO MEL, Adult Others, and Pediatric Subjects (< 18 Years) [Full Nivolumab Population Pharmacokinetic Model] 276
Figure 30: Applicant - Prediction-Corrected Visual Predictive Check of Relatlimab Concentrations versus Actual Time after Previous Dose in 1L MEL and Prior-IO MEL Subjects Who Received 80 mg Q2W and 160 mg Q4W Dosing Regimen (Full Population Pharmacokinetic Model 277
Figure 31: Applicant - Prediction-Corrected Visual Predictive Check of Nivolumab Concentrations versus Actual Time after Previous Dose in Adult 1L MEL and Adult Prior-IO MEL at 240 mg Q2W or 480 mg Q4W (Nivolumab + relatlimab) [Full Nivolumab Population Pharmacokinetic Model 278
Figure 32: Applicant - Predicted Relatlimab Exposures (Cavg1 and Cavgss) at 160 mg Q4W (Nivolumab + relatlimab) by Body Weight Quartiles in Adults 279
Figure 33: Applicant - Predicted Nivolumab Exposures (Cavg1 and Cavgss) at 480 mg Q4W (Nivolumab + relatlimab) by Body Weight Quartiles in Adult 1L MEL 280
Figure 34: Extrapolation simulation of relatlimab in adolescent patients. 282
Figure 35: Applicant - Visual Predictive Check of Peripheral Receptor Occupancy versus Individual Predicted Relatlimab Concentration 293
Figure 36: Applicant - Model Evaluation of Exposure-Response of PFS Analysis, by Population Type 294
Figure 37: Applicant - Visual Predictive Check of Observed OR Versus Relatlimab Exposure, by Population Type 295
Figure 38: Applicant - Estimated Covariate Effects of the E-R of PFS (Full Model) 296
Figure 39: Applicant - Estimated Covariate Effects of E-R of OR (Full Model) 297

Figure 40: Applicant - Distribution of Model Predicted Relatlimab Peripheral RO (ROavg1 and ROavgss) for Nivo 480 mg + Rela 160 mg Q4W by Drug Product (FDC, SAV Co-administration, SAV Sequential) 298
Figure 41: Applicant - Model Predicted Hazard Ratio of PFS in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Nivolumab 480 mg Q4W Regimen 299
Figure 42: Applicant - Model Predicted Odds Ratio of OR in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Relatlimab 160 mg + Nivolumab 480 mg Q4W Regimen 299
Figure 43: The relationship of PFS with relatlimab and nivolumab exposure in study CA224047 300
Figure 44: Simulation of peripheral RO with the RO model and population PK model for relatlimab in adolescent subjects 301
Figure 45: Applicant - Model Evaluation of Exposure-Response of Gr2+ IMAEs, by Treatment in MEL Subjects 308
Figure 46: Applicant - Model Evaluation of Exposure-Response of Gr3+ DRAEs, by Treatment in MEL Subjects 309
Figure 47: Applicant - Estimated Covariate Effects of E-R of Gr2+ IMAEs (Full Model) 310
Figure 48: Applicant - Estimated Covariate Effects of E-R of Gr3+ DRAEs (Full Model) 311
Figure 49: Applicant - Model Predicted Hazard Ratio of Gr2+ IMAEs in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Nivolumab 480 mg Q4W Regimen 312
Figure 50: Applicant - Model Predicted Hazard Ratio of Gr3+ DRAEs in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Nivolumab 480 mg Q4W Regimen 312

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Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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Endotoxin Evaluator	
Container Safety Evaluator	
Viral Safety Evaluator	

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Quality Assessor Peer	
Non-Clinical Assessor	

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

	Non-Clinical Assessor Peer	(b) (6)
	Risk Management Assessor	
	Risk Management Assessor Peer	
	Regulatory Project Manager	

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AJCC	American Joint Committee on Cancer
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BICR	Blinded Independent Central Review
BLA	biologics license application
BMS	Bristol Myers Squibb
BRAF	B-Raf proto-oncogene
BUN	Blood urea nitrogen
Cavg	average concentration
Cavg1	average concentration after the first dose
Cavgd28	average concentration over the first 28 days
Cavgss	average concentration at steady-state
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
Cmax	maximum concentration
Cmax1	maximum concentration after the first dose
Cmax	maximum concentration at steady-state
Cminss	minimum concentration
Cmin1	minimum concentration after the first dose
Cmind28	minimum concentration over the first 28 days
Cminss	minimum concentration at steady-state
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CSR	clinical study report
CTLA-4	cytotoxic T lymphocyte associated protein 4
CV	coefficient of variation
DBL	database lock
DCR	disease control rate
DDI	drug-drug interaction
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	durability of response

DRAE	drug-related adverse event
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ED50	dose to achieve half maximal effect
Emax	maximum response
EQ-5D-3L	3-level version of the EQ-5D health status measure
E-R	exposure-response
FA	final analysis
FACT-M	Functional Assessment of Cancer Therapy - Melanoma
FDA	Food and Drug Administration
FDC	fixed dose combination
FSH	follicle-stimulating hormone
GLP	good laboratory practice
GM	geometric mean
Gr2+	Grade 2 or greater
Gr3+	Grade 3 or greater
HR	hazard ratio
IA	interim analysis
ICH	International Conference on Harmonization
ICI	immune checkpoint inhibitor
IgG4	Immunoglobulin G4
IMAE	immune-mediated adverse event
IMM	immune-modulating medication
IND	Investigational New Drug
IO	immuno-oncology
IRT	Interactive Response Technology
IV	intravenous
K-M	Kaplan-Meier
LAG-3	lymphocyte-activation gene 3
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MEL	melanoma
MHC	major histocompatibility complex
MTD	maximum tolerated dose
NAb	neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
nivo	nivolumab
NME	new molecular entity
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
OESI	other event of special interest
OR	objective response

ORR	objective response rate
OS	overall survival
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PFS	progression-free survival
PFS2	progression-free survival after the next line of subsequent therapy
PI	prescribing information
PK	pharmacokinetics
PPK	population pharmacokinetic
PR	partial response
PREA	Pediatric Research Equity Act
prior-IO	subjects who progressed while on prior IO therapy
PRO	patient reported outcome
PSP	pediatric study plan
PSUR	Periodic Safety Update report
PT	preferred term
QW	once weekly
Q2W	every 2 weeks
Q4W	every 4 weeks
rela	relatlimab
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
REMS	risk evaluation and mitigation strategy
RO	receptor occupancy
SAE	serious adverse event
SAP	statistical analysis plan
SAV	single agent vial
sLAG-3	soluble LAG-3
SOC	standard of care
t1/2	effective half-life
TEAE	treatment emergent adverse event
TSH	thyroid stimulating hormone
TTR	time to response
ULN	upper limit of normal
UK	United Kingdom
US	United States

1 Executive Summary

1.1. Product Introduction

Nivolumab and relatlimab-rmbw is a fixed drug product (FDC) product (referred to as nivolumab-relatlimab FDC) consisting of nivolumab, a humanized programed death receptor-1 (PD-1) antibody and the new molecular entity (NME) relatlimab, a fully humanized lymphocyte activation gene 3 (LAG-3) antibody.

At the time of submission of the current Biologics Licensing Application (BLA) 761234 on July 19, 2021, nivolumab-relatlimab FDC was not yet approved for any indication in the United States. The Applicant's proposed indication at the time of the BLA submission was as follows:

> OPDUALAG is (b) (4) indicated for the treatment of adults and pediatric patients (12 years and older (b) (4) with unresectable or metastatic melanoma.

The Applicant's proposed dosing regimen was 480 mg nivolumab and 160 mg relatlimab every 4 weeks for adults and (b) (4) every 4 weeks in pediatric patients ≥12 years and ≥40 kg, via intravenous (IV) infusion over 30 minutes.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from Study CA224047 to support its claims of safety and effectiveness. Study CA224047, is a randomized (1:1), adaptive-design, double-blind study which evaluated nivolumab-relatlimab FDC versus single agent nivolumab in 714 patients with previously untreated, unresectable, or metastatic melanoma (American Joint Committee on Cancer [AJCC]) staging system Stage III or Stage IV. Patients were randomized to study treatment until disease progression or unacceptable toxicity occurred. The primary endpoint was progression free survival (PFS) as determined by Blinded Independent Central Review (BICR) using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines. The key secondary endpoints were overall survival (OS) and objective response rate (ORR) as determined by BICR using RECIST v1.1.

The review team concluded that the application contained the results of an adequate and well controlled trial which provided substantial evidence that nivolumab-relatlimab FDC administered at a dose of 480 mg/160 mg every 4 weeks to adult patients and pediatric patients 12 years of age or older (who weigh at least 40 kg) with previously untreated Stage III

and Stage IV melanoma is safe and effective. Study CA224047 demonstrated a statistically significant and clinically meaningful improvement in PFS in patients randomized to the nivolumab-relatlimab FDC arm compared to those who were randomized to the nivolumab arm (hazard ratio [HR] of 0.75 [95% CI: 0.62, 0.92], p=0.0055). While the OS analysis was not statistically significant at the time of the final PFS analysis or at the time of the final analysis, (HR of 0.80 [95% CI: 0.64, 1.01]), median OS was not reached (95% CI: 34.2, NR) in the nivolumab-relatlimab FDC arm and was 34.1 months (95% CI: 25.2, NR) in the nivolumab arm. Although adolescent patients ages 12-17 were eligible for Study CA224047, none were enrolled; therefore, simulations for adolescent patients were performed for dose selection based on adult data to support the recommended dosage of nivolumab-relatlimab FDC in pediatric patients 12 years or older who weigh at least 40 kg.

The safety profile of relatlimab-nivolumab has been adequately characterized based on data from Study CA224047 and by additional supportive data submitted from other studies in the nivolumab-relatlimab FDC development program. The review team finds that the magnitude of improvement in the observed PFS in the CA224047 trial represents a clinical benefit that outweighs the risks associated with increased adverse events in the indicated patient population. Although a statistically significant effect on OS was not observed, evaluation of deaths as part of the safety assessment did not indicate a detrimental effect on survival.

Therefore the review team recommends granting traditional approval to nivolumab-relatlimab FDC for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

There are approximately 106,110 cases of melanoma estimated to be diagnosed in the US in 2021; this represents almost 5.6% of all new cancer diagnoses with an overall survival (OS) of 93% (SEER data 2011-2017). According to SEER data (2004-2017) patients with regional disease have a 5-years survival of 66% while those with metastatic disease have a 5-year survival of 24%. There are several FDA-approved therapies for the treatment of patients with advanced or metastatic melanoma. Dacarbazine and interferon were both approved prior to the development of immune checkpoint inhibitors (ICIs) and have not demonstrated a survival benefit. In addition, their toxicity profile has made them less desirable treatment options for patients. Improvements in outcomes have been demonstrated with the advent of immunotherapeutic drugs as both single agents and in combination for patients with advanced or metastatic melanoma. Ipilimumab was the first therapy to demonstrate an improvement in OS among patients with advanced melanoma in randomized, controlled trials. Nivolumab and pembrolizumab have shown an improved OS, progression-free survival (PFS), and objective response rate (ORR), than ipilimumab alone. In KEYNOTE-006, pembrolizumab demonstrated a statistically significant improvement in OS and PFS compared to ipilimumab (HR: 0.69 [0.52, 0.90] and 0.58 [0.47, 0.72], respectively). In CheckMate 067, nivolumab demonstrated an improvement in median PFS and OS compared to ipilimumab (HR: 0.57 [0.47, 0.69] and 0.63 [0.50, 0.78], respectively). Combination therapy with nivolumab plus ipilimumab in CheckMate 067 also showed significantly longer PFS and OS with nivolumab plus ipilimumab compared with ipilimumab alone (HR: 0.42 [0.34, 0.51] and 0.55 [0.44, 0.69], respectively); this regimen is also approved. However, due to the increased toxicity with the nivolumab plus ipilimumab combination (e.g., leading to early discontinuation for this combination regimen), there remains an unmet need for effective therapies with better safety profiles.

The Applicant submitted data from Study CA224047 to support approval of nivolumab-relatlimab FDC for the treatment of adult patients and pediatric patients 12 years of age or older (b) (4) with unresectable or metastatic melanoma. A favorable benefit-risk assessment has been established for nivolumab-relatlimab FDC based on demonstration of a statistically significant and clinically important improvement in PFS in patients who were randomized to the nivolumab-relatlimab FDC arm compared to those who were randomized to the nivolumab arm (HR of 0.75 [95% CI: 0.62, 0.92], p =0.0055). At the time of the original data cutoff for PFS, OS was not statistically significant (~76% of events had occurred). At FDA's request, final OS was submitted. The final analysis of OS was not statistically significant (HR of 0.80 [95% CI: 0.64, 1.01]); median OS was not reached (95% CI: 34.2, NR) in the nivolumab-relatlimab FDC arm and was 34.1 months (95% CI: 25.2, NR) in the nivolumab arm.

The data submitted to support the safety review of nivolumab-relatlimab FDC is adequate to characterize toxicity in patients with unresectable or metastatic melanoma. The safety event profile in patients who received nivolumab-relatlimab FDC is comparable with the toxicity observed with nivolumab monotherapy. The slightly higher incidence of SAEs, discontinuations due to AEs and Grade 3-4 AEs observed in patients treated with nivolumab-relatlimab FDC, was expected given that a similar trend what has been observed with other combination immunotherapy development programs. There was not an increased risk of death due to AEs observed in patients treated with nivolumab-relatlimab FDC. A review of the safety dataset did not reveal any unexpected safety events associated with nivolumab-relatlimab FDC. Overall nivolumab-relaltimab FDC demonstrates a positive benefit-risk profile as a treatment option for adult patients and pediatric patients 12 years of age or older (b) (4) with unresectable or metastatic melanoma.

Risk minimization strategies have been instituted via management guidelines included in the product labeling and Medication Guide. Adverse events thought to be clinically significant were identified in patients treated with nivolumab-relatlimab FDC. These clinically significant AEs include IMAEs previously listed in the Warnings and Precautions section of the nivolumab label, myocarditis, and infusion-related reactions and will all be included in the Warnings and Precautions section of the nivolumab-relatlimab FDC label.

The review team recommends traditional of nivolumab-relatlimab FDC for the treatment of adult patients and pediatric patients 12 years and older (b) (4) with unresectable or metastatic melanoma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Melanoma accounts for 5.6% of all cancers. • It was estimated that there will be 106,110 new cases of cutaneous melanoma in the US and 7,180 patients will die of this disease in 2021 (SEER 2021). • Stage III disease has a 5-year survival of 66% and those with Stage IV	Melanoma is a serious and life-threatening condition. Historically, the prognosis for advanced melanoma had been poor. With the introduction of novel immune-modulating agents for melanoma, outcomes have improved significantly; however, there exists a

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	disease, the 5-year survival is 24%. • The majority of new cases of melanoma affect White individuals more than any other racial group in the US, with the average rate of new invasive melanoma cases observed to be 28.0 in Whites, 1.0 in Blacks, 5.6 in American Indians/Alaskan Natives, 1.3 in Asians and 4.6 in Hispanics per 100,000 (CDC 2012 – 2016).	need for additional therapy for patients with advanced melanoma.
Current Treatment Options	• FDA-approved therapies for the treatment of unresectable or metastatic melanoma include interferon, dacarbazine, pembrolizumab, ipilimumab, and nivolumab. In addition, there are several targeted treatment options for patients with BRAF mutations, which include dabrafenib and trametinib, vemurafenib and cobimetinib, and encorafenib and binimetinib. • Interferon and dacarbazine are limited by toxicity and have not demonstrated a survival benefit. • In CheckMate 066 and CheckMate 067, nivolumab showed an improvement in PFS and OS compared to dacarbazine and ipilimumab, respectively. • In Keynote-006, pembrolizumab demonstrated an improvement in PFS and OS when compared to ipilimumab. • In CheckMate 067, ipilimumab and nivolumab showed an improvement in PFS and OS compared to ipilimumab; however, use of the combination results in increased toxicity. Serious adverse reactions (74%), adverse reactions leading to permanent discontinuation (47%) or to dosing delays (58%), and Grade 3 or 4 adverse reactions (72%) occurred in patients treated with ipilimumab and nivolumab.	Current treatment options that include immune checkpoint inhibitors (ICIs) for patients with Stage III or Stage IV cutaneous melanoma regardless of BRAF mutation status have shown improved outcomes as compared to historical outcomes with interferon and dacarbazine. Combination ICI therapy for patients with previously untreated melanoma has shown superior outcomes to treatment with single-agent ICIs; however, these ICI combinations have been associated with increased toxicity. There exists a need for novel combination therapies that can further improve long-term outcomes with an improved safety profile that can overcome treatment-related resistance mechanisms.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Approximately 50% of patients receiving single agent anti-PD-1 inhibitors will experience primary disease progression (intrinsic resistance) or develop an initial response with subsequent disease progression (acquired resistance).	
Benefit	• In Study CA224047, nivolumab-relatlimab FDC demonstrated a statistically significant and clinically meaningful improvement in PFS compared to nivolumab (HR]=0.75 [95% CI: 0.62, 0.92], p =0.0055). • At the time of the submission, OS data was still immature. FDA requested and reviewed the final OS analysis during the review of the BLA. Statistical significance for OS was not observed; however, there was no detriment in OS for nivolumab-relatlimab FDC compared to nivolumab.	The study met its primary objective with nivolumab-relatlimab FDC demonstrating superiority in PFS over nivolumab with no detriment in OS. A robust effect on PFS that is clinically meaningful can and has been used to support approval of drugs intended for the treatment of advanced melanoma.
Risk and Risk Management	• The safety population included 355 patients from CA224047 and 1379 patients from Study CA224020 (a single-arm phase 1/2 study) in the intended population who were administered nivolumab-relatlimab FDC at the proposed dose. • The primary risks of nivolumab-relatlimab FDC are immune-mediated adverse reactions (IMAEs) including myocarditis, and hypersensitivity/infusion-related reactions (IRRs). • The most common adverse reactions (≥ 20%) in order of decreasing frequency were musculoskeletal pain, fatigue, rash, pruritus, arthralgia, and diarrhea. The most common laboratory abnormalities (≥ 20%) worsening from baseline were decreased hemoglobin, increased ALT, increased AST, and decreased sodium. • Serious adverse reactions including fatal events occurred in 34% of patients on nivolumab-relatlimab FDC.	The observed safety profile of nivolumab-relatlimab FDC is acceptable when assessed in the context of the treatment of a life-threatening disease. No new significant safety concerns were identified during review. The majority of adverse reactions to nivolumab-relatlimab FDC were manageable with dosage modifications. The risks of severe and serious adverse reactions of myocarditis, CNS effects, hypersensitivity/IRRs, and IMAEs are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of product labeling. There were no significant safety concerns identified during the review of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Grade 3 or 4 adverse reactions occurred in 39% of patients treated with nivolumab-relatlimab FDC.	the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS).

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as			Section 8.1.1.2 Study endpoints
			x	Patient reported outcome (PRO)	Section 8.2.7 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability
			☐	Observer reported outcome (ObsRO)	
			☐	Clinician reported outcome (ClinRO)	
			☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	☐	Patient-focused drug development or other stakeholder meeting summary reports			[e.g., Section 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data			
	☐	Natural history studies			
	☐	Patient preference studies (e.g., submitted studies or scientific publications)			
	☐	Other: (Please specify)			
☐	Patient experience data that was not submitted in the application, but was considered in this review.				

X X

Cross-Disciplinary Team Leader
Jamie Brewer, MD

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Melanoma accounts for 75% of skin cancer deaths in the US (death rate 2.3 per 100,000 persons between 2014-2018),[1] and while rare in the pediatric population, is the second leading cause of cancer in adolescents over the age of 15, with an incidence of over 10 per million in 15 to 19 year-olds.

Melanoma is a heterogeneous and complex disease with various clinical factors and genetic defects playing a key role in outcomes. Approximately 50% of cutaneous melanomas bear oncogenic driver mutations in the BRAF gene, which is associated with a worse prognosis. Clinical factors associated with poor survival include elevated LDH, visceral metastases (notably liver and brain), multiple metastatic sites, and poor performance status.

The prognosis of late-stage metastatic disease was extremely poor (5-year survival rate of 25% between 2009-2015) until the advent of targeted and immuno-therapies (see Section 2.2). Combination BRAF/MEK agents yield high initial responses in the subgroup of melanoma patients with BRAF tumor mutations. However, a considerable proportion of these melanoma patients progress while on treatment and these therapies are unsuitable for those with BRAF wild type disease. Immunotherapies are effective in both BRAF wild-type and mutated melanoma. Unfortunately however, a majority of patients receiving anti-PD-1 monotherapy will have progression within 8 months of treatment initiation.[2,3] Available combination therapies using an anti-PD-1 backbone, including combinations with immune or molecularly targeted therapies, increase progression-free and overall survival, but do so at the cost of considerably increased toxicity.

The combination of nivolumab and relatlimab in a convenient FDC vial offers the potential for a clinically meaningful PFS and a manageable safety profile for patients with unresectable or metastatic melanoma.

The FDA's Assessment:

In general, FDA agrees with the Applicant's characterization and assessment of the disease. According to SEER data (2004-2017) patients with regional disease have a 5-year survival of 66% and those with metastatic disease have a 5-year survival of 24%. Melanoma is more common among individuals of fair complexion and those who have been exposed to natural or artificial sunlight over long periods of time. The incidence of cutaneous melanoma is most common in men versus women with the rate of new cases being 34.7 versus 22.1 per 100,00 persons, respectively. There are more new cases of invasive melanoma among Whites than any other

racial or ethnic group, with the rate per 100,000 in the US as follows: White 28.0, Black 1.0, American Indian/Alaskan Native 5.6, Asian 1.3, Hispanic 4.6 (CDC 2012 – 2016). The highest incidence of melanoma occurs in the age group of 65-74 years (25%) with a median age at diagnosis of 65. (SEER 2014-2018)

Data has shown that more than 50% of patients with melanoma treated with nivolumab or pembrolizumab will experience disease progression (Johnson, et al 2020). Outcomes have significantly improved with the approvals of immune checkpoint inhibitors both as single agents and in combination.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Immunotherapy has markedly changed the treatment landscape for patients with advanced and metastatic melanoma since the initial approval of ipilimumab (Yervoy®) in 2011, increasing the median OS from 6 - 9 months[4,5,6] to 19.9 months.[7] Since then, 2 checkpoint inhibitors (nivolumab, pembrolizumab) targeting the PD-1 pathway have built on the foundation of ipilimumab, extending median OS to 31 to 36.9 months and incurring a lower frequency and severity of side effects.[7,8,9] Further benefit was realized with the addition of ipilimumab to nivolumab, which has unprecedented 5-year OS rate of 52% for patients with advanced melanoma.[4,5,7] However, this was at the expense of increased toxicity, with high grade (Grade 3/4) TRAEs observed in 59% in the nivolumab + ipilimumab group compared with 23% in those receiving nivolumab monotherapy, and TRAEs leading to discontinuation in 42% vs 13%, respectively.[7] Data with extended follow-up showed durable outcomes with a 6.5 year OS rate of 49% for nivolumab + ipilimumab.[10]

In addition to immunotherapy, treatment options for patients with BRAF mutated melanoma include targeted BRAF/MEK combination therapy. While these agents are effective in roughly half of patients with BRAF mutated disease, most patients acquire resistance over time. Recently, approaches to combine targeted therapy with immunotherapy have demonstrated improved PFS and duration of response; however, the impact on OS is not yet known and increased toxicity is observed.

While immunotherapy has become a cornerstone of the melanoma treatment armamentarium, there is still a considerable proportion of patients who fail to respond to these therapies or respond but then later relapse. There are no approved or standard approaches to treating these patients once they progress after receiving anti-PD-1 therapy. The efficacy of ICI beyond initial progression has not been evaluated by prospective randomized trials in well-defined unselected populations who are refractory to anti-PD-1. Additionally, the durability of responses to ICI

treatment beyond progression is poorly documented in these retrospective analyses.[11,12] A recent retrospective study reported a median OS of 6.8 months after disease progression on these agents.[13] Another study in which patients were retreated with immunotherapy following failure on initial anti-PD-1 therapy demonstrated 1 year OS rates of 57% for patients treated with ipilimumab plus anti-PD-1 therapy compared to 38% for ipilimumab therapy alone.[14] However, a recent retrospective analysis of real-world Flatiron Health data (2014 - 2019)[15] revealed that over 40% of BRAF mutant and 60% of BRAF wild-type patients did not initiate a new treatment after disease progression on anti-PD-1, highlighting an unmet need to identify effective and tolerable therapies in this setting.[15]

Currently, 9 immunotherapy and/or BRAF/MEK targeted regimens are FDA approved and used in routine clinical practice for the treatment of unresectable or metastatic melanoma (Table 1).

Table 1: Applicant - FDA-approved IO and Targeted Therapies for Systemic Treatment of Advanced, Unresectable Melanoma in Routine Clinical Use (NCCN Guidelines)

		Nivolumab (CM066)	Nivolumab + Ipilimumab (CM067)	Nivolumab (CM67)	Pembrolizumab (KN006)	Dabrafenib + Trametinib (COMBI-d)	Dabrafenib + Trametinib (COMBI-v)	Vemurafenib + Cobimetinib (coBRIM)	Encorafenib + Binimetinib (COLUMBUS)	Atezolizumab + Cobimetinib + Vemurafenib (IMspire150)
Study design	Primary Endpoint	OS	PFS, OS	PFS, OS	PFS, OS	PFS	OS	PFS	PFS	PFS
	BRAF status	WILD TYPE	AC	AC	AC	MUTANT	MUTANT	MUTANT	MUTANT	MUTANT
	Study Arms	**O** (n=210) vs **Dacarbazine** (n=208)	**O+Y** (n=314) vs **Y** (n=315)	**O** (n=316) vs **Y** (n=315)	**P** (n=279 Q2W, n=277 Q3W) vs **I** (n=278)	**D+T** (n=211) vs **Dabrafenib** (n=212)	**D+T** (n=352) vs **Vemurafenib** (n=352)	**V+C** (n=247) vs **Vemurafenib** (n=248)	**E+B** (n=192) vs **Vemurafenib** (n=191)	**T+C+V** (n=230) vs **Placebo+C+V** (n=258)
Efficacy	mPFS (mos) (HR)	**mFU 6.8m: Investigator** 5.1 vs 2.2 (HR 0.43)	**mFU 12.2m: Investigator** 11.5 vs 2.9 (HR 0.42)	**mFU 12.2m: Investigator** 6.9 vs 2.9 (HR 0.57)	**mFU 7.9m: BICR** 5.5m/4.1m vs 2.8m (HR 0.58)	**mFU 9m: Investigator** 9.3 vs 8.8 (HR 0.75)	**mFU 11m: Investigator** 11.4 vs 7.3 (HR 0.56)	**mFU 7.3m: Investigator** 9.9 vs 6.2 (HR 0.51)	**mFU 16.6m: BICR** 14.9 vs 7.3 (HR 0.54)	**mFU 18.9m: Investigator** 15·1 vs 10·6 (HR 0.78)
	mOS (mos) (HR)	**Min FU 60m:** 37.3 vs 11.2 (HR 0.5)	**Min FU 60m:** NR vs 19.9 (HR 0.52)	**Min FU 60m:** 36.9 vs 19.9 (HR 0.63)	**mFU 66.7m:** 32.7 vs 15.9 (HR 0.74)	**mFU 22m** (pooled): 25.9m	**mFU 22m** (pooled): 25.9m	**mFU 21.2m:** 22.5 vs 17.4	**mFU 60.6m:** 33.6 vs 16.9 (HR 0.62)	**mFU 18.9m:** 28.8 vs 25.1 (HR 0.85)
Safety	D/C due to any grade AE/Rs	**mFU 6.8m:** 6.8% vs 11.7% (AEs)	**mFU 12.2m:** 36.4% vs 14.8% (ARs)	**mFU 12.2m:** 7.7% vs 14.8% (ARs)	**mFU 7.9m:** 4%/6.9% vs 9.4% (ARs)	**mFU 20m:** 11% vs 7% (AEs)	**mFU 11m:** 13% vs 12% (AEs)	**mFU 14.2m:** 11% vs 7% (ARs)	**mFU 16.6m:** 6% vs 14% (ARs)	**mFU 18.9m:** 13% vs 16% (AEs)

Abbreviations: mFU = median follow-up

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of the available therapies for patients with previously untreated unresectable or metastatic melanoma with or without a BRAF mutation.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Opdualag™ (nivolumab and relatlimab-rmbw) is a FDC product with the NME relatlimab in combination with the marketed drug nivolumab (BLA 125554). Opdualag is currently not marketed in the US or any other country. The clinical development program is being conducted under (b) (4) 136382 (parent IND for the FDC vial, BMS-986213, nivolumab with relatlimab) with the Division of Oncology 3.

The FDA's Assessment:
FDA agrees with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 2: Applicant - Relevant Relatlimab Regulatory History

Date/IND#	Content
14-Aug-2013 **Initial** (b) (4)	Submission of IND and protocol **CA224020** - *A Phase 1 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Relatlimab Administered Alone and in Combination with Nivolumab, in Advanced Solid Tumors.*
27-May-2015 (b) (4)	**Type C Mtg:** To obtain advice and agreement on BMS's proposal for an alternate method for coadministration of the nivolumab and relatlimab combination (CA224020 Protocol Part D).
21-Jul-2017 (b) (4)	**Type B Mtg:** End of Phase 1 Meeting Discussed development plan for nivolumab and relatlimab in patients with melanoma whose disease has progressed during anti-PD(L)1 therapy; advice on the proposed patient population; target ORR and DOR to support accelerated approval
18-Aug-2017 (b) (4)	Granted: Orphan Drug Designation #17-5950 Stage 2b-4 Melanoma
22-Dec-2017 **Initial 136,382**	Submission of Initial IND and protocol **CA224047** - *A Randomized, Double-Blind Phase 2/3 Study of Relatlimab+Nivolumab (FDC) vs Nivolumab in Subjects with Previously Untreated Metastatic or Unresectable Melanoma.*
8-Jan-2018 (b) (4)	**Type C Meeting** re: Amending protocol CA224020 to include an arm that includes a FDC vial of nivolumab+relatlimab.

28-Oct-2019 **136,382**	**Advice/IR** regarding DMC suggestion to amend SAP to add interim PFS
20-Nov-2019 **136,382**	**Fast Track Designation Granted** for nivo+rela FDC for the treatment of patients with metastatic or unresectable melanoma.
24-Mar-2020 **136,382**	**Type F iPSP Meeting**. FDA was in general agreement with the proposed pediatric plans.
15-Sep-2020 **136,382**	**Agreed iPSP**
25-Nov-2020 **136,382**	**CA224047** Protocol Amendment and CSR SAP amendment. Purpose: elevate OS to the first secondary analysis, incorporating 2 potential interim analyses for OS. The primary analysis remained unchanged.
19-Jan-2021 **136,382**	**Type C Administrative Pre-BLA WRO comments**. To gain feedback and align with FDA on the content and technical format of a planned BLA and to reach agreement on the modules to be submitted for early review.
2-Apr-2021 **136,382**	**Type B - PreBLA CMC Mtg, WRO**
30-Apr-2021 **136,382**	Accepted into RTOR pilot program
7-May-2021 **136,382**	**Type B - PreBLA Mtg**

The FDA's Assessment:

As a high-level overview of regulatory actions, FDA agrees with the Applicant. Additional details for some of the interactions include:

- On September 13, 2019, a telephone conference was held between the Applicant and FDA. The Applicant informed FDA about follow-up communications, initiated by the Chair of the Data monitoring Committee (DMC), in which the DMC Chair informed BMS that the trial met the pre-specified criteria to proceed to the "Phase 3" portion of the trial and that, based on the effect size observed, BMS plans to add a second interim analysis for efficacy.
- The October 28, 2019 Advice/Information Request sent to the Applicant based on FDA review of version 3 of protocol CA224047 stated that FDA did not agree with a second interim analysis of PFS and that FDA did not agree to halting the trial based on an interim analysis of <80% of the planned events.
- The Agreed iPSP was for a partial waiver for patients <12 years of age and included a plan to assess the pediatric age group ≥12 years of age to < 18 years of age.
- The Type B preBLA meeting minutes were issued to the Applicant on May 7, 2021. FDA requested the Applicant provide a timeline for the interim analysis 2 results for OS and to submit these to the BLA when available.
- The original BLA submission submitted on July 19, 2021 included the final PFS data. The results of OS at IA1 were not statistically significant. On December 17, 2021, the

Applicant submitted updated OS data based on the results of the unblinded IA2 OS analysis (data cutoff date of October 28, 2021).

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology 3 consulted OSI to discuss an audit of overall trial conduct. Three clinical investigators were selected for audit, Drs. Long (Site 0042), Alavez (Site 0092), and Ramirez (Site 0094). Inspections of Drs. Alvarez (Site 0092), and Ramirez (Site 0094) were conducted on site. Due to site and travel restrictions related to the COVID-19 pandemic, the inspection of Dr. Long was conducted as a remote regulatory assessment.

During the inspection of Site 0042 no discrepancies were identified between the source documents and the data line listings for patient enrollment. All patients enrolled at the site met eligibility criteria. A subset of records were reviewed for protocol deviations and SAEs and no unreported protocol deviations or AEs were noted. The imaging assessment dates at the site were compared to the dates of the imaging studies in the data listings, and there were no imaging studies that had not been sent to the central imaging facility.

During the inspection of Site 0092 it was noted that two patients were enrolled on study who did not meet eligibility criteria due to insufficient follow up after radiotherapy for CNS metastases. This deviation does not appear to have affected the interpretation of study data or biased the study results in favor of efficacy. Of the two patients with this eligibility protocol deviation, one patient was enrolled to each study arm and both patients progressed quickly after starting study treatment due to disease progression. The site inspector did not find evidence that safety had been compromised for these patients. Additional regulatory violations were identified which included the late reporting of SAEs, minor unreported AEs, and several additional protocol violations that included not documenting consent from the study monitor to treat patients after progression or when exclusion criteria were met. In all instances, the inspection findings are adequately reported in the CSR and data listings. The protocol deviations were largely reports and corrected when possible. There was no evidence of compromised patient safety or data integrity. The Investigator's reporting of SAEs and dates of disease progression were accurate. This site was closed to further enrollment by the Applicant after their site audit in August 2019 due to these violations.

During the inspection of Site 0094 no discrepancies between the source documents and the

data line listings for subject enrollment and disposition were noted. All local imaging was performed and sent to the central imaging facility as per the protocol. The date of tumor assessment by the BICR was compared to the source data and there were no discrepancies. There were four patients who experienced minor AEs that were not entered into the electronic system used to convey study data to the Applicant. However two of these patients had low grade laboratory abnormalities that were reported in the lab data to the BLA. There was no evidence of patient harm and the AEs that were not reported do not impact the safety profile of the combination regimen.

Based on the results of these inspections, the study appears to have been conducted adequately and the data generated by the inspected entities appear to be acceptable in support of this BLA.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761234 for Opdualag (nivolumab-relatlimab FDC) manufactured by Bristol-Myers Squibb Company. The data submitted in this application are adequate to support the conclusion that the manufacture of Opdualag is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

During the review cycle, the Applicant agreed to two post-marketing commitments to re-evaluate the acceptance criteria for potency of relatlimab after 30 lots of drug product have been manufactured and to develop an endotoxin release method that is able to reliably detect endotoxin in the drug product and to develop an endotoxin release method for the drug product which mitigates the low endotoxin recovery (LER) effect. See Section 13 for additional information regarding postmarketing commitments. Refer to the OPQ full review for additional details of the product quality submission.

4.3. Clinical Microbiology

Refer to the OPQ Executive Summary and full review.

4.4. Devices and Companion Diagnostic Issues

This submission did not require a device or companion diagnostic.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Nivolumab is an IgG4 monoclonal antibody directed against human programmed cell death 1 (PD-1), a receptor expressed on activated CD4+ and CD8+ T cells, natural killer (NK) cells, B cells, and monocytes. PD-1 interaction with its ligands, PD-L1 and PD-L2, leads to downregulation of T cell responses, including T cell proliferation and cytokine production, and limits immune-destruction of tissues, including tumor tissues. Relatlimab (BMS-986016) is a monoclonal IgG4 antibody directed against lymphocyte activation gene-3 (LAG-3), a receptor expressed on activated CD4+ and CD8+ T cells, and a subset of NK cells. LAG-3 binds to the major histocompatibility complex (MHC) class II and promotes regulatory T cell activity. Bristol-Meyers Squibb (BMS) has submitted the current BLA to support the use of a fixed-dose combination of nivolumab and relatlimab at a 3:1 protein mass ratio in patients with unresectable or metastatic melanoma. The established pharmacologic class is a combination of PD-1 blocking antibody and LAG-3 blocking antibody.

Nivolumab is approved for use in patients with melanoma and no new nonclinical pharmacology or toxicology data was submitted for nivolumab. Therefore the focus of the data contained in the current BLA submission is the pharmacology and toxicology of relatlimab.

In an in vitro assay, relatlimab bound the loop insertion sequence of the D1 domain of human LAG-3 with a K_D of 0.12 nM and recombinant human LAG-3-mFc fusion protein with an EC_{50} value of 0.49 nM. In activated human T cells, relatlimab bound LAG-3 with a K_D of 0.51 nM. In biochemical assays, relatlimab inhibited the interactions of LAG-3 with its ligands MHC class II and fibrinogen-like protein 1 (FGL1) with EC_{50} values of 0.67 nM and 0.02 nM, respectively. Functionally, relatlimab stimulated T cell activation as measured by IL-2 secretion in mouse 3A9 cells co-cultured with peptide pulsed, MHC-matched, antigen-presenting cells and human LAG-3 T cell hybridoma cells (EC_{50} for peptide responsiveness by the T cells in the presence of relatlimab was 1.05 nM). Relatlimab did not exhibit induction of antibody-dependent cellular toxicity (ADCC) or complement-dependent cytotoxicity (CDC) on LAG-3+ activated human T cells.

In cell based assays, relatlimab bound to Chinese hamster ovary (CHO) cells that were engineered to overexpress human LAG-3 and ex vivo activated human T cells with average EC_{50} values of 2.33 nM and 0.11 nM, respectively. Relatlimab bound to CHO cells that overexpressed cynomolgus LAG-3 and activated primary cynomolgus T cells with average EC_{50} values of 28.73 nM and 29.11 nM, respectively. Relatlimab did not bind LAG-3 expressing mouse 3A9 cells.

Thus, cynomolgus monkey is a toxicologically relevant species in which to study relatlimab, but in vitro binding affinity is reduced 12 to 265-fold as compared to human.

In vivo, the anti-tumor activity of relatlimab was evaluated in mice implanted with various human tumor cell lines. Because relatlimab does not bind mouse LAG-3, a murine surrogate anti-LAG-3 antibody was utilized. In these studies, administration of murine anti-LAG-3 resulted in mild to moderate tumor growth inhibition as compared to vehicle controls.

The Applicant also submitted pharmacology data to support the clinical combination of relatlimab and nivolumab. In human peripheral blood mononuclear cells (PBMCs), single agent relatlimab enhanced the stimulation of human PBMC cultures by *Staphylococcus aureus* enterotoxin B superantigen (SEB). Combining relatlimab with nivolumab increased T cell activation above basal SEB stimulation compared to either agent alone. In vivo, the anti-tumor activity of murine surrogates for relatlimab and nivolumab was assessed in xenograft mouse models of human tumors. In these studies, combination anti-LAG-3 and anti-PD-1 showed anti-tumor activity that was superior to either single agent treatment.

Secondary pharmacology, stand-alone safety pharmacology, and ADME studies were not conducted with relatlimab.

To assess its safety, the Applicant conducted GLP-compliant toxicology studies for relatlimab of up to 13-weeks in cynomolgus monkeys. In monkeys, treatment with relatlimab at ≥30 mg/kg (approximately 9 times the clinical exposure of 19353.6 ng·h/mL [estimated AUC_{0-t} at steady state] at the recommended dose of 160 mg every 4 weeks) resulted in minimal decreases in cytotoxic T cell counts and increases in regulatory and total T cells counts in female animals. T cell findings were reversible within a 10-week recovery period.

A published study in rhesus macaques indicated that PD-1 blockade may increase the severity of tuberculosis infections. *Mycobacterium tuberculosis* infected rhesus macaques treated with a primatized anti-PD-1 blocking monoclonal antibody developed increased bacterial loads and worse disease as compared to isotype treated controls.[16]

Genotoxicity and carcinogenicity studies were not warranted. There is no significant risk of cytokine release syndrome due to the administration of relatlimab alone or in combination with nivolumab based on in vitro assays.

To assess relatlimab effects on embryo-fetal development, the Applicant conducted studies in mice using murine surrogate anti-LAG-3 antibodies. In the definitive embryo-fetal development study, female CBA/CaJ mice were bred using both syngeneic and allogeneic breeding models and treated with the anti-LAG-3 C9B7W monoclonal antibody, a murine surrogate of relatlimab,

on Gestation Days 6, 8, 10, 12, and 14 at doses of 25 or 51.5 mg/kg. At doses up to 51.5 mg/kg, there were no observed effects on maternal health or embryo-fetal viability in either syngeneic or allogeneic litters.

Based on the mechanism of action of relatlimab and nivolumab, and based on data from embryo-fetal development studies conducted with nivolumab, the prescribing information includes a warning for embryo-fetal risk. The label also advises females of reproductive potential to use contraception for at least 5 months after the last dose of OPDUALAG, consistent with nivolumab labeling. No studies were conducted to investigate the effect of relatlimab on fertility or on the presence of relatlimab in breast milk. Because many drugs are secreted in milk, the label includes a warning not to breastfeed during treatment with OPDUALAG for 5 months after the final dose, consistent with nivolumab labeling.

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of OPDUALAG.

5.2.Referenced NDAs, BLAs, DMFs

The Applicant's Position:
The nonclinical data contained in the planned BLA are from studies that used relatlimab or surrogate anti-LAG-3 antibodies, either alone or in combination with nivolumab or surrogate anti-PD-1 antibodies. The nonclinical nivolumab data has been well characterized and can be referred to in the nivolumab BLA 125554.

5.3.Pharmacology

Section 5.3 summarizes the in vitro characterization of relatlimab and the in vivo evaluation of surrogate antibodies specific for mouse LAG-3 and PD-1.

5.3.1. Primary pharmacology

5.3.1.1. Relatlimab In Vitro Target Binding Profile

Relatlimab (BMS-986016) binds with high affinity (KD=0.12 nM) to the loop insertion sequence of the D1 domain of human LAG-3 and binds to primary activated human T cells with an estimated EC50 of 0.11 nM.

Table 3: Applicant - Primary Pharmacology: Relatlimab (BMS-986016) In Vitro Target Binding Profile

Type of Study	Test System	Assay Type	Binding Potency	Study No.	Location in Dossier
BMS-986016 binding to recombinant human LAG-3 protein	Recombinant human LAG-3-Fc protein binding	SPR (KD)	0.12 nM	BDX-1408-241	4.2.1.1
BMS-986016 binding to LAG-3-mFc fusion protein	Recombinant human LAG-3-mFc binding	ELISA (EC50)	0.49 nM	BDX-1408-242	4.2.1.1
BMS-986016 binding to LAG-3 insertion-loop peptide	Synthetic LAG-3 Domain 1 insertion-loop peptide binding	ELISA (EC50)	0.44 nM	BDX-1408-242	4.2.1.1
BMS-986016 binding to CHO-huLAG-3	Binding to CHO cells overexpressing full length human LAG-3	Flow cytometry (EC50)	2.33 nM	BDX-1408-243	4.2.1.1
BMS-986016 binding to activated human T cells	Binding to anti-CD3 + anti-CD28 activated primary human CD4+ T cells at 72h post stimulation	Flow cytometry (EC50)	0.11 nM	BDX-1408-243	4.2.1.1
BMS-986016 binding affinity to LAG-3 by Scatchard assay	Binding to activated primary human CD4+ T cells; ^{125}I-labeled vs. unlabeled BMS-986016	Scatchard assay (KD)	0.51 nM	BDX-1408-243	4.2.1.1
BMS-986016 binding to CHO-cynoLAG-3	Binding to CHO cells over-expressing full length cynomolgus LAG-3	Flow cytometry (EC50)	28.73 nM	BDX-1408-243	4.2.1.1
BMS-986016 binding to activated cyno CD4+ T cells	Binding to anti-CD3 + anti-CD28 activated primary cynomolgus CD4+ T cells at 72h post stimulation	Flow cytometry (EC50)	29.11 nM	BDX-1408-243	4.2.1.1
BMS-986016 binding to mouse LAG-3	Binding to 3A9 mouse T cell hybridoma cell line overexpressing full length mouse LAG-3	Flow cytometry (EC50)	No measurable binding	BDX-1408-249	4.2.1.1

Abbreviations: CHO, Chinese hamster ovary (cells); cyno, cynomolgus (monkey); EC50, half maximal stimulatory effect concentration; ELISA, enzyme-linked immunosorbent assay; huLAG-3, human LAG-3; KD, equilibrium dissociation constant; mFC, mouse fragment crystallizable region (Fc region).; muLAG-3, mouse LAG-3.

5.3.1.2. Relatlimab In Vitro Receptor-Ligand Blocking Profile

Relatlimab (BMS-986016) blocks the interaction of LAG-3 receptor with ligands MHC II (EC50=0.67 nM) and FGL1 (EC50=0.02 nM) in biochemical assays.

Table 4: Applicant - Primary Pharmacology: Relatlimab (BMS-986016) In Vitro Receptor-Ligand Blocking Profile

Type of Study	Test System	Assay Type	Binding Potency	Study No.	Location in Dossier
BMS-986016 blockade of soluble LAG-3-mFc binding to MHC Class II+ cells	Binding of recombinant huLAG-3-mFc fusion protein to MHC II-positive Daudi human B cell lymphoma cell line	Flow cytometry (IC50)	0.67 nM	BDX-1408-244	4.2.1.1
Binding of Human LAG-3-mFc to Human FGL1-mFc	Binding of recombinant huLAG-3-mFc fusion protein to recombinant huFGL1-mFc fusion protein	ELISA (EC50)	0.085 nM	IO00330	4.2.1.1
BMS-986016 blockade of LAG-3 binding to FGL1	Blockade by BMS-986016 of recombinant huLAG-3-mFc fusion protein binding to recombinant huFGL1-mFc fusion protein	ELISA (IC50)	0.02 nM	IO00330	4.2.1.1
BMS-986016 blockade of LAG-3 binding to FGL1	Blockade by BMS-986016 of recombinant huLAG-3-mFc fusion protein binding to recombinant huFGL1-mFc fusion protein	Biolayer interferometry	Measurable receptor-ligand binding signal attenuation in the presence titrated mAb	IO00330	4.2.1.1

Abbreviations: EC50, half maximal stimulatory effect concentration; ELISA, enzyme-linked immunosorbent assay; FGL1, Fibrinogen-like protein 1; huLAG-3-mFc, human LAG-3-mFc; IC50, half-maximal inhibitory effect concentration; mFc, mouse fragment crystallizable region (Fc region); MHC II, major histocompatibility complex II.

5.3.1.3. Relatlimab In Vitro Functional Profile

In in vitro cell-based co-culture assays, relatlimab (BMS-986016) functionally blocks the inhibitory effect of LAG-3 engagement by MHC II alone (IC50 1.05-1.39 nM) and by combined FGL1 + MHC II (IC50=0.95 nM). Relatlimab alone modestly stimulated ex vivo peripheral T cell cytokine responses following superantigen stimulation, but when combined with nivolumab, elicited responses that were greater than blocking either receptor individually. Relatlimab exhibited no evidence of Fc-mediated effector function.

Table 5: Applicant - Primary Pharmacology: Relatlimab (BMS-986016) In Vitro Functional Profile

Type of Study	Test System	Assay Type	Blocking Potency	Study No	Location in Dossier
Functional blockade by BMS-986016 of LAG-3 interaction with MHC II	Peptide Antigen-specific mouse 3A9-human LAG-3 T cell hybridoma in coculture with MHC II matched APC in the presence of titrated BMS-986016	Cell co-culture with cytokine ELISA readout of mouse IL-2 expression (IC50)	1.05-1.39 nM	BDX-1408-245 IO00330	4.2.1.1
Functional blockade by BMS-986016 of LAG-3 interaction with MHC II and FGL1	3A9-human LAG-3 T cell line in co-culture with MHC II matched APC co-expressing membrane-bound human FGL1 in the presence of titrated BMS-986016	Co-culture with measurement of secreted mouse IL-2 after 16h	0.95 nM	IO00330	4.2.1.1
Superantigen SEB activation of human PBMCs with BMS-986016 alone or in combination with nivolumab	Primary human PBMCs stimulated 72h by SEB in the presence of titrated BMS-986016	Cell co-culture with cytokine; ELISA readout of human IL-2 expression (IC50)	SEB-stimulated peripheral blood T cells secreted up to 58% more IL-2 in the presence of BMS-986016 compared to isotype control antibody and 112% more IL-2 in the presence of combined nivolumab + relatlimab compared to control antibody + nivolumab, across 2 assay formats.	BDX-1408-246	4.2.1.1

Type of Study	Test System	Assay Type	Blocking Potency	Study No	Location in Dossier
Lack of effector functions associated with BMS-986016	ADCC, in vitro co-culture human PBMC with labelled allogeneic CD4+ T cells in the presence of titrated BMS-986016 or control; measurement of released label after 1h CDC, evaluation of complement-mediated killing of CD4+ T cells after 4h	ADCC cell lysis/ killing assay; CDC cell viability assay	No evidence of effector function by BMS-986016 in over > 3 logs of antibody concentration (up to 50 µg/mL for CDC and up to 10 µg/mL for ADCC assays), while anti-human MHC Class I and anti-CD30 antibodies (positive control) induced CDC or ADCC cell lysis.	BDX-1408-247	4.2.1.1

Abbreviations: ADCC, antibody dependent cell cytotoxicity; APC, antigen-presenting cells; CDC, complement-dependent cytotoxicity; ELISA, enzyme-linked immunosorbent assay; FGL1, Fibrinogen-like protein 1; huLAG-3, human LAG-3; IC50, half-maximal inhibitory effect concentration; IL-12, interleukin 12; MHC Class II, major histocompatibility complex II; mFc, mouse fragment crystallizable region (Fc region); PBMC, peripheral blood mononuclear cells; SEB, staphylococcus enterotoxin B superantigen.

5.3.1.4. Activity of Anti-LAG3 Antibody Alone and in Combination with Anti-PD-1 Antibody in Syngeneic Mouse Tumor Models

In vivo the efficacy of an anti-mouse LAG-3 antibody was evaluated either alone or in combination with anti-mouse PD-1 antibody. Anti-tumor efficacy was evaluated in the Sa1N fibrosarcoma and MC38 colon adenocarcinoma mouse syngeneic tumor models. To target LAG-3 and PD-1 receptors in the mouse, surrogate rat antibodies specific for mouse LAG-3 (clone C9B7W and clone 19C7) and mouse PD-1 (clone 4H2) were used.

5.3.1.5. Evaluation of Anti-LAG-3 and Anti-PD-1 Antibodies Alone and in Combination in the Sa1N Fibrosarcoma Tumor Model

A/J mice were implanted subcutaneously in the flank with the immunogenic Sa1N tumor and staged to initiate antibody dosing approximately 7d post implant following randomization.

Table 6: Applicant - Primary Pharmacology: Number of Sa1N Tumor-free Mice and Percent Tumor Growth Inhibition Following IP Administration of Anti-LAG-3 mAb Alone

Treatment Days	Treatment Group	Tumor-free Mice[a]	TGI (%)[b] Day 41
7, 10, 14	Anti-LAG-3 19C7 30 mg/kg	6/10	100
7, 10, 14	Anti-LAG-3 19C7 10 mg/kg	4/10	95.1
7, 10, 14	Anti-LAG-3 19C7 3.3 mg/kg	6/10	97.5
7, 10, 14	Anti-LAG-3 19C7 1 mg/kg	3/10	53.6
7, 10, 14	IgG1 30 mg/kg	0/10	N/A

Abbreviations: IgG1, immunoglobulin G1.

Source: Study BDX-1408-251 / Dossier Location 4.2.1.1.

[a] Number of tumor-free mice at the end of the study (Day 60) / total number of mice in group (N=10).

[b] Tumor growth inhibition (TGI) calculated as: % TGI = {1-[(Tt-To)/(Ct-Co)]}x100 where:
Ct = the median tumor volume (mm^3) of isotype control-treated mice (C) at time, t
Tt = median tumor volume (mm^3) of test article-treated mice (T) at time, t
To = median tumor size of test article-treated group at treatment initiation
Co = median tumor size of isotype control-treated group at treatment initiation.

Table 7: Applicant - Primary Pharmacology: Number of Sa1N Tumor-free Mice and Percent Tumor Growth Inhibition Following IP Administration of Anti-LAG-3 mAb and Anti-PD-1 Antibodies Individually or in Combination

Study Number	Treatment Days	Treatment Group	Tumor-free Mice[a]	TGI (%)[b] Day 28 or 32
MDX-1106-059-R	7, 10, 14	Control (IgG1) 30 mg/kg	1/10	N/A

Study Number	Treatment Days	Treatment Group	Tumor-free Mice[a]	TGI (%)[b] Day 28 or 32
	7, 10, 14	Anti-PD-1 (4H2) 10 mg/kg + IgG1 10 mg/kg	0/10	64
	7, 10, 14	Anti-LAG-3 (C9B7W) 10 mg/kg + IgG1 10 mg/kg	4/10	99
	7, 10, 14	Anti-LAG-3 (C9B7W) 10 mg/kg + Anti-PD-1 (4H2) 10 mg/kg	8/10	99
BDX-1408-224	9, 14, 17	Control (IgG1) 20 mg/kg	1/10	N/A
	9, 14, 17	Anti-PD-1 (4H2) 10 mg/kg	0/10	62
	9, 14, 17	Anti-LAG-3 (C9B7W) 10 mg/kg	2/10	41
	9, 14, 17	Anti-LAG-3 (C9B7W) 10 mg/kg + Anti-PD-1 (4H2) 10 mg/kg	9/10	100

Abbreviations: IgG1, immunoglobulin G1.

Source: Study MDX-1106-059-R / Dossier Location 4.2.1.1.
Study BDX-1408-224 / Dossier Location 4.2.1.1.

[a] Number of tumor-free mice at the end of the study (Day 56) / total number of mice in group (N=10).

[b] Tumor growth inhibition (TGI) at Day 32 for Study MDX-1106-059-R and at Day 28 for Study BDX-1408-224.
TGI was calculated as: % TGI = {1-[(Tt-To)/(Ct-Co)]}x100 where:
Ct = the median tumor volume (mm^3) of isotype control-treated mice (C) at time, t
Tt = median tumor volume (mm^3) of test article-treated mice (T) at time, t
To = median tumor size of test article-treated group at treatment initiation
Co = median tumor size of isotype control-treated group at treatment initiation.

5.3.1.6. Evaluation of Anti-LAG-3 and Anti-PD-1 Antibodies Alone and in Combination in the MC38 Colon Adenocarcinoma Tumor Model

C57BL/6 mice were implanted subcutaneously with the MC38 colon adenocarcinoma tumor and staged to initiate antibody dosing approximately 7d post implant following randomization.

Table 8: Applicant - Primary Pharmacology: Number of MC38 Tumor-free Mice and Percent Tumor Growth Inhibition Following IP Administration of Anti-LAG-3 and Anti-PD-1 Antibodies Individually or in Combination

Study Number	Treatment Days	Treatment Group	Tumor-free Mice[a]	TGI (%)[b] Day 24
MDX-1408-206-R	7, 10, 14	Control (IgG1) 10 mg/kg	0/10	N/A
	7, 10, 14	Anti-PD-1 (4H2) 10 mg/kg	4/10	94

Study Number	Treatment Days	Treatment Group	Tumor-free Mice[a]	TGI (%)[b] Day 24
	7, 10, 14	Anti-LAG-3 (C9B7W) 10 mg/kg	0/10	3
	7, 10, 14	Anti-LAG-3 (C9B7W) 10 mg/kg + Anti-PD-1 (4H2) 10 mg/kg	7/10	100
BDX-1408-207	8, 11, 14	Control (IgG1) 20 mg/kg	0/10	N/A
	8, 11, 14	Anti-PD-1 (4H2) 10 mg/kg + IgG1 10 mg/kg	4/10	94
	8, 11, 14	Anti-LAG-3 (C9B7W) 10 mg/kg + IgG1 10 mg/kg	0/10	3
	8, 11, 14	Anti-LAG-3 (C9B7W) 10 mg/kg + Anti-PD-1 (4H2) 10 mg/kg	8/10	100

Abbreviations: IgG1, immunoglobulin G1.

Source: Study MDX-1408-206-R / Dossier Location 4.2.1.1.
Study BDX-1408-207 / Dossier Location 4.2.1.1.

[a] Number of tumor-free mice at the end of the study/total number of mice in group (N=10).

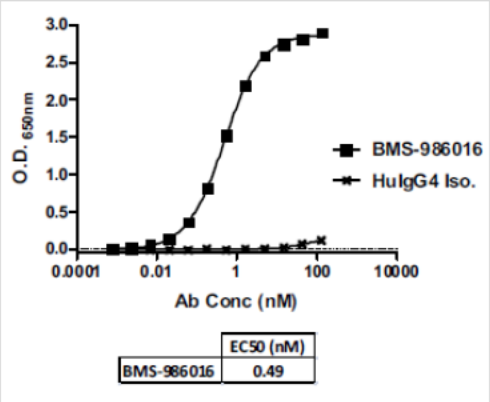
[b] Tumor growth inhibition (TGI) calculated as: % TGI = {1-[(Tt-To)/(Ct-Co)]}x100 where:
Ct = the median tumor volume (mm^3) of isotype control-treated mice (C) at time, t
Tt = median tumor volume (mm^3) of test article-treated mice (T) at time, t
To = median tumor size of test article-treated group at treatment initiation
Co = median tumor size of isotype control-treated group at treatment initiation.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the pharmacology of relatlimab and relatlimab in combination with nivolumab. The following data has been included to support the Applicant's position:

- The binding potency of relatlimab was assessed in biochemical assays. Relatlimab bound a recombinant human LAG-3-mFc fusion protein with an EC_{50} value of 0.49 nM (Figure 1).

Figure 1: Relatlimab binding to LAG-3-mFc fusion protein

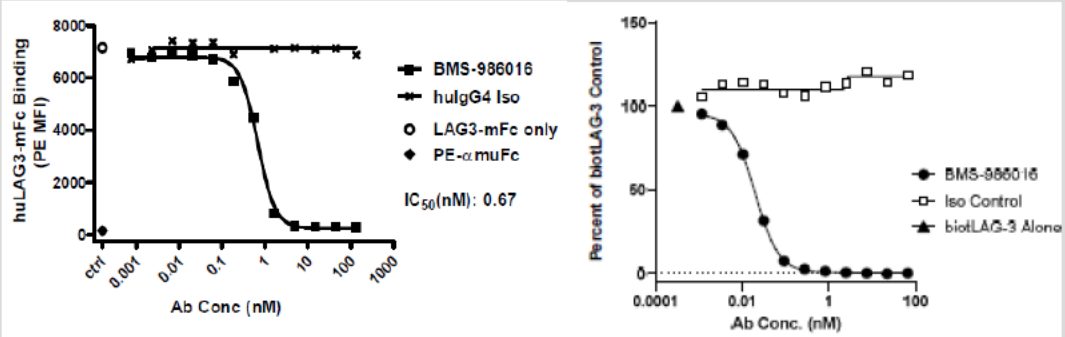


	EC50 (nM)
BMS-986016	0.49

(Source: Applicant figure reproduced from Study BDX-1408-242. Relatlimab (BMS-986016) binding to recombinant human LAG-3-mFc fusion protein was measured via ELISA.)

- To determine the biological relevance of animal species for toxicology studies, flow cytometry studies were conducted to compare the binding of relatlimab to CHO cells over-expressing human or cynomolgus LAG-3 and to activated human or cynomolgus T cells (Study BDX-1408-234). Relatlimab bound to CHO-huLAG-3 cells and ex vivo activated human T cells with average EC_{50} values of 2.33 nM and 0.11 nM, respectively. Relatlimab bound to CHO-cynoLAG- 3 and activated primary cynomolgus T cells with average EC_{50} values of 28.73 nM and 29.11 nM, respectively. Thus, cynomolgus monkey is a toxicologically relevant species in which to study relatlimab, but binding affinity for human cells is 12 to 265-fold higher than for monkey. The binding of relatlimab to 3A9 cells that were transfected to over-express mouse LAG-3 was also assessed; no binding was detected (Study BDX-1408-249).
- The ability of relatlimab to block the interactions between the LAG-3 receptor and its ligands MHC class II and FGL1 (Figure 2) was assessed.

Figure 2: Relatlimab (BMS-986016) blocks human LAG-3 binding to MHC class II Daudi cells (left) and FGL1 (right)

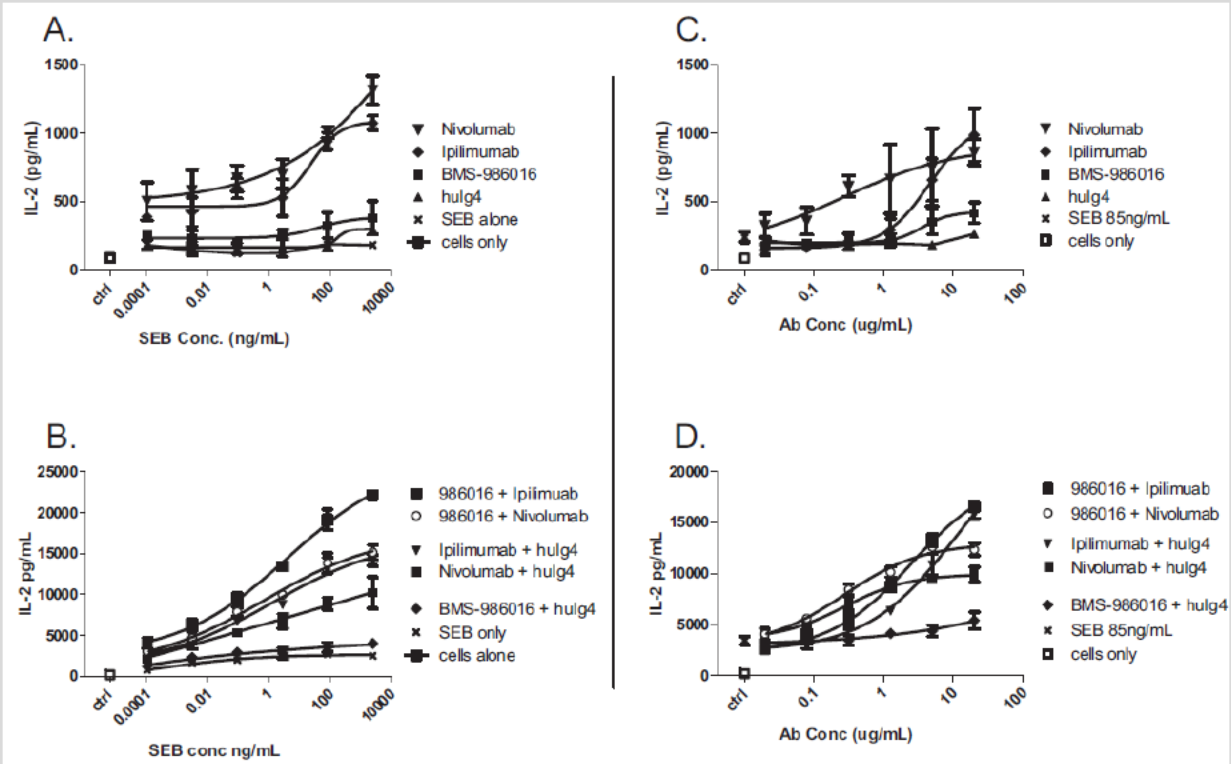


(Source: Applicant figure reproduced from Studies BDX-1408-244 and IO00330. Relatlimab (BMS-

986016) binding to MHC class II+ human Daudi B lymphoma cells was measured via flow cytometry. Relatlimab blockade of recombinant human LAG-3 to recombinant human FGL1 was measured by ELISA)

- The Applicant examined the functional activity of relatlimab and relatlimab in combination with nivolumab (Study BDX-1408-246). Briefly, human PBMCs were cultured in the presence of the superantigen SEB with or without relatlimab, nivolumab, ipilimumab, and isotype antibody controls. Activation of PBMCs was measured by IL-2 secretion. In 15/18 donors tested, single agent relatlimab enhanced the basal stimulation of human PBMC cultures by superantigen SEB (a 15 to 58% increase vs. control antibody over two assay formats.) Combining relatlimab with either nivolumab or ipilimumab resulted in increased T cell activation above basal SEB stimulation (a 70% to 356% increase vs. control combination over two assay formats) compared to any single agent (Figure 3).

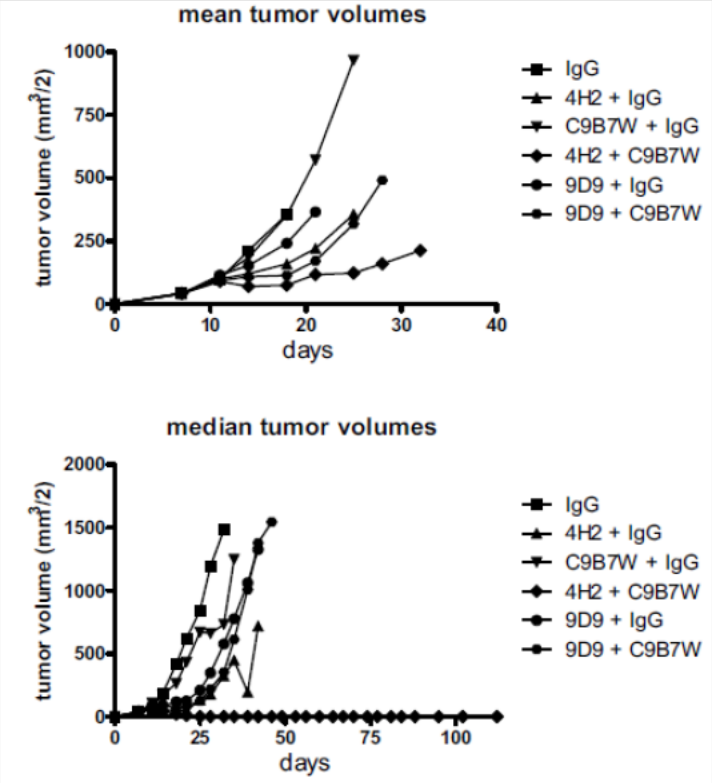
Figure 3: Enhanced activation of superantigen-stimulated human PBMCs by relatlimab alone and in combination with nivolumab



(Source: Applicant figure reproduced from Study BDX-1408-246. Representative data from two donors shows relatlimab (BMS-986016) increased PBMC simulation as compared to controls (A and C). Combination nivolumab/relatlimab increased PBMC stimulation as compared to either single agent (B and D).)

- In vivo anti-tumor studies of a murine anti-LAG-3 antibody alone or in combination with a murine anti-PD-1 (see Applicant Table 8 for study summary) were conducted. Treatment with anti-LAG-3 antibody showed little inhibition of the growth of MC38 tumors in mice when administered alone. Treatment with the anti-PD-1 antibody inhibited tumor growth (4/10 mice tumor free after treatment). Combination anti-LAG-3 and anti-PD-1 showed enhanced anti-tumor activity compared to either single agent (8/10 mice tumor-free after treatment, Figure 4).

Figure 4: Tumor growth curves of anti-LAG-3 (C9B7W) and anti-PD-1 (4H2) treated tumor bearing mice



(Source: Applicant figure reproduced from Study BDX-1408-207)

5.3.2. Secondary Pharmacology

The Applicant's Position:

Since relatlimab is a monoclonal antibody with a selective target and mechanism of action, and does not belong to a drug or chemical class expected to have off-target effects, studies of secondary pharmacodynamics were not conducted.

The FDA's Assessment:

FDA agrees.

5.3.3. Safety Pharmacology

The Applicant's Position:
In accordance with ICH S7A, evaluations of the potential effects of administration of relatlimab were evaluated in pivotal toxicity studies. The results of those studies are presented in Section 5.5.1.

The FDA's Assessment:
Stand-alone safety pharmacology studies were not warranted.

5.4.ADME/PK

The Applicant's Position:
Single-dose and repeat-dose studies were conducted to characterize the nonclinical PK and toxicokinetics of relatlimab (BMS-986016) following IV administration in cynomolgus monkeys (NCPK57/4.2.2.2 and DN12123/4.2.3.2). In monkeys, exposure of relatlimab was dose-proportional following single IV doses from 3 to 30 mg/kg and repeat doses from 30 to 100 mg/kg. Relatlimab has a long half-life (133 to 249 h and 414 to 740 h after single and repeat dosing, respectively), with limited extravascular distribution (as indicated by the observed Vss in monkeys equivalent to vascular volume, which ranged from 62 to 79 mL/kg), and a serum clearance of 0.12 to 0.22 mL/h/kg. In accordance with the ICHS6[R1] guidance, no protein binding, tissue distribution, metabolism, or excretion studies were conducted in nonclinical species with relatlimab as it is a protein mAb therapeutic. The expected in vivo degradation of mAbs is via biochemical pathways that are independent of CYP enzymes.[17] Therefore, mAbs such as relatlimab are not expected to be a victim or perpetrator of CYP-mediated DDI when co-administered with substrates or inhibitors of these enzymes. In the 4-week GLP-compliant monkey toxicity study, there were no apparent PK DDIs between relatlimab and nivolumab (BMS-936558) when administered in combination following sequential IV dosing. At the 100 mg/kg dose level, there was no change in relatlimab drug exposure when dosed in combination with nivolumab compared to relatlimab dosed alone (AUC[0-168h] 514,000 µg·h/mL versus 474,000, respectively).

Table 9: Applicant - ADME/PK: Summary of ADME Characteristics and Pharmacokinetic Parameters

Absorption:	
Type of Study	Single-dose PK of Relatlimab
Test System/Sex/ Number of Animals	Monkey/Male/ 1 or 2 per dose group
Method of Administration	IV Bolus
Vehicle/ Formulation	Dulbecco's Phosphate Buffered Saline without calcium and magnesium, pH7.4/solution

Study Number	NCPK57		
Dossier Location	4.2.2.2		
Dose (mg/kg)	**3**	**16.5**	**30**
AUC(INF) (µg•h/mL)	19036	100064	139012, 203973
CLTs (mL/h/kg)	0.16	0.16	0.22, 0.15
Vss (L/kg)	0.070	0.079	0.062, 0.068
T-HALF (h)	272	276	133, 249

Note: Values are from individual animals.

Type of Study	Repeat-dose PK of Relatlimab and Nivolumab				
Test System/Sex/ Number of Animals	Monkey/ Male and female combined/5 of each sex per dose level				
Method of Administration	IV infusion once weekly for 5 doses				
Vehicle/ Formulation	Relatlimab: 10 mM sodium citrate, 10 mM phosphate buffer, 150 mM NaCl, and 0.05% Tween 80, pH 5.5/ solution Nivolumab: 20 mM sodium citrate, 50 mM NaCl, 3.0% mannitol, µM diethylenetriamine pentetic acid, diethylenetriamine pentetic acid, 0.02% polysorbate 80, pH 6.0 /solution				
Study Number	DN12123				
Dossier Location	4.2.3.2				
Analyte	**BMS-986016**	**BMS-986016**	**BMS-986016**	**BMS-936558**	**BMS-936558**
Dose of relatlimab/ nivolumab (mg/kg/week):	**30/0**	**100/0**	**100/50**	**0/50**	**100/50**
Cmax (µg/mL) [a]	851	2210	2330	1260	1210
Cmax (µg/mL) [b]	1450	4310	4460	1730	1800/1880[e]
Tmax (h) [a]	0.50	5.2	0.50	0.50	0.50
Tmax (h) [b]	5.2	5.8	5.7	0.50	0.50/0.50[e]
AUC(0-168 h) (µg·h/mL) [a]	74,400	218,000	213,000	110,000	106,000
AUC(0-168 h) (µg·h/mL) [b]	169,000	474,000	514,000	193,000	182,000/ 200,000[e]
Observed T-HALF (h) [c]	490	460	740	540/580[e]	430
Study No./Dossier Location: NCPK57/4.2.2.2					
Population PK Analysis[d]					
T-HALF (h)	414			NA	NA
CLTs (mL/h/kg)	0.12			NA	NA
Vss (mL/kg)	72			NA	NA

[a] Day 1.

[b] Day 22 (after the fourth dose).

[c] Estimated by non-linear regression of the concentration vs time data on day 29 (after the fifth dose).

[d] Estimated by population PK analysis of the pooled data (N = 30) following weekly intravenous dosing (a total of 5 doses) of 30 and 100 mg/kg of BMS-986016 alone and 100 mg/kg of BMS-986016 combined with 50 mg/kg BMS-936558 (Nivolumab). Population PK values were calculated for BMS-986016 only.

[e] Parameters calculated with/without monkeys positive for anti-BMS-936558 antibodies. Average values were reported.

Abbreviations: NA - not applicable.

Distribution In accordance with regulatory guidelines for biotechnology-derived pharmaceuticals (ICH S6[R1]), no tissue distribution or protein binding studies with relatlimab have been conducted in animals.
In the single-dose PK (NCPK57) and repeat-dose (DN12123) studies in monkeys, the volume of distribution of relatlimab at steady-state (Vss) ranged from 62 to 79 mL/kg, suggesting limited extravascular distribution.

Metabolism No in vitro or in vivo metabolism studies have been conducted using relatlimab. The expected in vivo degradation of a mAb is to small peptides and amino acids via biochemical pathways that are independent of cytochrome P450 cytochrome (CYP) enzymes.[17]

Excretion No studies were specifically conducted to evaluate the excretion of relatlimab in animals. In accordance with regulatory guidelines for biotechnology-derived pharmaceuticals (ICH S6[R1]), no mass balance studies with relatlimab have been conducted in animals or humans.

Pharmacokinetic Drug Interactions
The expected in vivo degradation of mAbs is via biochemical pathways that are independent of CYP enzymes.[17] Therefore, mAbs such as relatlimab are not expected to be a victim or perpetrator of CYP-mediated DDI when co-administered with substrates or inhibitors of these enzymes.

In the 4-week GLP-compliant monkey toxicity study, there were no apparent PK DDIs between relatlimab (BMS-986016, 100 mg/kg) and nivolumab (BMS-936558, 50 mg/kg) when administered in combination following sequential IV dosing as relatlimab drug exposure did not change when dosed in combination with nivolumab compared to relatlimab dosed alone (AUC[0-168h] 514,000 µg·h/mL versus 474,000, respectively).

Integrative summary table of Cmax and AUC parameters across toxicology studies (general, reproductive, and carcinogenicity, if conducted).
Refer to Table 10

Tabulation of any exposure margins used in proposed labeling. Not applicable as exposure margins from general toxicology studies are not presented in the proposed label.

Table 10: Applicant - Toxicokinetics: Overview of Toxicokinetics Data

Species/Strain	Monkey/cynomolgus (except where indicated otherwise)											
Sex	**Male**						**Female**					
	LAG3.1-G4P[a]/Relatlimab			**Nivolumab**			**LAG3.1-G4P[a]/ Relatlimab/C9B7W[b]**			**Nivolumab**		
Parameter	**Cmax (μg/mL)**	**AUC (0-168h)[c] (μg•h/mL)**	**T-HALF (h)**	**Cmax (μg/mL)**	**AUC (0-168h)[c] (μg•h/mL)**	**T-HALF (h)**	**Cmax (μg/mL)**	**AUC (0-168h)[c] (μg•h/mL)**	**T-HALF (h)**	**Cmax (μg/mL)**	**AUC (0-168h)[c] (μg•h/mL)**	**T-HALF (h)**
Study DS10061 Four-week Intermittent-dose (QW) Intravenous Exploratory Combination Pharmacodynamic and Toxicity Study in Monkeys												
50 mg/kg/wk LAG3.1-G4P	1,740	219,000	NC	NA	NA	NC	2,170	243,000	NC	NA	NA	NA
10/50 mg/kg/wk LAG3.1-G4P/ nivolumab	554	60,300	NC	1,860	181,000	NC	313	20,400	NC	1,590	161,000	NC
50/50 mg/kg/wk LAG3.1-G4P/ nivolumab	2,130	211,000	NC	1,500	128,000	NC	2,150	209,000	NC	1,720	191,000	NC
Study DN12123 Four-week Intravenous Combination Toxicity Study in Monkeys with a 6-Week Recovery												
30 mg/kg/wk relatlimab	1,530	173,000	460	NA	NA	NA	1,360	164,000	540	NA	NA	NA
100 mg/kg/wk relatlimab	4,240	493,000	400	NA	NA	NA	4,390	449,000	630	NA	NA	NA
50 mg/kg/wk nivolumab	NA	NA	NA	1,620	182,000	480/500[e]	NA	NA	NA	1,850	204,000	600
100/50 mg/kg/wk relatlimab/ nivolumab	4,250	501,000	1,000	1,650/ 1,780[d]	155,000/ 185,000[d]	360	4,720	530,000	590	1,980	216,000	540

Species/Strain	Monkey/cynomolgus (except where indicated otherwise)											
Sex	**Male**						**Female**					
	LAG3.1-G4P[a]/Relatlimab			**Nivolumab**			**LAG3.1-G4P[a]/ Relatlimab/C9B7W[b]**			**Nivolumab**		
Parameter	**Cmax (μg/mL)**	**AUC (0-168h)[c] (μg•h/mL)**	**T-HALF (h)**	**Cmax (μg/mL)**	**AUC (0-168h)[c] (μg•h/mL)**	**T-HALF (h)**	**Cmax (μg/mL)**	**AUC (0-168h)[c] (μg•h/mL)**	**T-HALF (h)**	**Cmax (μg/mL)**	**AUC (0-168h)[c] (μg•h/mL)**	**T-HALF (h)**
Study DN16053 Three-month Intermittent Intravenous Infusion (QW) Toxicity Study in Monkeys with a 10-week Post Dose Recovery												
30 mg/kg/week relatlimab[e]	3,100/ 4,270	418,000/ 523,000	890/ 1,100	NA	NA	NA	2,570/ 2,940	354,000/ 407,000	610/ 540	NA	NA	NA
100 mg/kg/week relatlimab[e]	10,100/ 12,900	1,380,000/ 1,790,000	820/NA	NA	NA	NA	8,200/ 8,410	968,000/ 1,050,000	390/ 440	NA	NA	NA
Study DN17040 Anti-LAG-3 C9B7W mAb: Intra-peritoneal Study of Embryo-fetal Development in Mice												
25 mg/kg anti-LAG-3 C9B7W	NA	NA	NA	NA	NA	NA	476	39,000	NC	NA	NA	NA
51.5 mg/kg anti-LAG-3	NA	NA	NA	NA	NA	NA	857	57,500	NC	NA	NA	NA
Study DN18169 Single-dose Subcutaneous Toxicokinetic and Local Tolerance Study in Monkeys												
100 mg/kg relatlimab	1,600	206,000	NC	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: CDR = Complementarity determinant region; NA = Not applicable; NC = Not calculated; wk = Week.

[a] Study DS10061 utilized LAG3.1-G4P, the parent compound of relatlimab, which differs by 2 amino acids in the heavy chain CDR2 sequence.

[b] Study DN17040 utilized C9B7W, a surrogate antibody that binds to murine LAG-3.

[c] Day 22 steady state AUC(0-168h) for DS16001 and DN12123; Day 85 steady state AUC(0-168h) for DN16053; Day 1 AUC(0-168h) for DN18169; and, Day 10 AUC(0-144h) for DN17040.

[d] Parameters calculated with/without monkeys positive for anti-drug/nivolumab antibodies.

[e] Parameters calculated with/without monkeys positive for anti-drug/relatlimab antibodies; N=1 monkey/group/sex without detectable anti-drug/relatlimab antibodies.

The FDA's Assessment:
FDA agrees that no protein binding, tissue distribution, metabolism, or excretion studies were warranted. The safety margins for the doses administered in the animal toxicology study have been calculated and are shown below. The parameters were calculated using exposure levels ($AUC_{0\text{-}168h}$) of animals without anti-drug antibodies. Parameters were not adjusted for dosing schedule.

	Relatlimab	Nivolumab
Human AUC0-t, ss (µg·h/mL) at steady state	19353.6	63369.6
Study DN12123 Four-week toxicity study		
Dose mg/kg (relatlimab/nivolumab)	Fold change from human exposure (by AUC)	
30/0	9	.
100/0	24	.
0/50	.	3
100/50	27	3
Study DN16053 13-week toxicity study		
Dose mg/kg	Fold change from human	
30	24	.
100	73	.

5.5.Toxicology

5.5.1. General Toxicology

The Applicant's Position:
The cynomolgus monkey was selected as the toxicology species because relatlimab binds to macaque LAG-3, albeit less strongly than to human LAG-3, and is pharmacologically active in monkeys (i.e.,, increases T cell subsets and responses to immunogenic challenge).[18,19,20] In GLP-compliant studies up to 3 months in duration, relatlimab was generally well tolerated by cynomolgus monkeys when administered IV QW up to 100 mg/kg. In the 3-month study, 1 male monkey at 30 mg/kg exhibited clinical observations (including tremors, decreased activity, hunched posture, retching, and/or emesis) and complement activation that were considered to be secondary to relatlimab-related treatment-emergent ADAs and, therefore, were not factored in determining the NOAEL. The NOAEL was considered to be 100 mg/kg/week. In the 1-month study, relatlimab was administered at up to 100mg/kg alone and at 100 mg/kg in combination with 50 mg/kg of nivolumab and was well tolerated in all monkeys when administered alone and in 8 of 9 monkeys in the combination group, while moribundity in 1 male monkey was attributed

to central nervous system vasculitis. Histopathological findings in this monkey included the following: slight lymphoplasmacytic inflammation of the choroid plexus; minimal to moderate lymphohistiocytic inflammation of the vasculature of the brain parenchyma, meninges, and spinal cord; and minimal to moderate mixed-cell inflammation of the epididymis, seminal vesicles, and testes. Additional findings in the combination group were limited to minimal to slight lymphoplasmacytic inflammation of the choroid plexus in the brain in both sexes and minimal lymphohistiocytic inflammation of the vasculature of the brain parenchyma in 1 male monkey. See Section 8.2.1 for details of neurologic monitoring within the clinical trial safety assessments.

Table 11: Applicant - General Toxicology: Four-week Intravenous Combination Toxicity Study in Monkeys with a 6-Week Recovery

Study Title	Four-week Intravenous Combination Toxicity Study in Monkeys with a 6-Week Recovery
Study Number	DN12123
Study Type	Repeat-dose
eCTD Location	4.2.3.2
GLP Compliance	Yes
Key Drug-related Adverse Findings: • Slight lymphoplasmacytic inflammation of the choroid plexus • Minimal to moderate lymphohistiocytic inflammation of the vasculature of the brain parenchyma, meninges, and spinal cord • Minimal to moderate mixed-cell inflammation of the epididymis, seminal vesicles, and testes	
Methods	
Frequency of Dosing	Weekly
Relatlimab/nivolumab Dose	0/0, 30/0, 100/0, 0/50, 100/50 mg/kg/dose
Route of Administration	Intravenous
Formulation/Vehicle	
BMS-986016 (relatlimab)	(b) (4)
BMS-936558 (nivolumab)	(b) (4)
Species/Strain	Monkey/cynomolgus
Number/Sex/Group	5 males/5 females
Age	3-6 years old
Satellite groups	Not applicable

Table 12: Applicant - General Toxicology: Study DN12123 Four-week Intravenous Combination Toxicity Study in Monkeys with a 6-Week Recovery/DCN 930070016

Relatlimab Dose (mg/kg/week)	**0 (Control)**		**30**		**100**		**0**		**100**	
Nivolumab Dose (mg/kg/week)	**0 (Control)**		**0**		**0**		**50**		**50**	
Number of Animals	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Toxicokinetics										
Cmax (μg/mL)										
Day 1	--	--	714	988	1,940	2,480	1,270	1,240	2,210/ 1,130	2,460/ 1,300
Day 22	--	--	1,530	1,360	4,240	4,390	1,620	1,850	4,250/ 1,650 1,780[a]	4,720/ 1,980
AUC(0-168h) (μg•h/mL)										
Day 1	--	--	64,800	83,900	191,000	246,000	111,000	108,000	222,000/ 104,000	205,000/ 109,000
Day 22	--	--	173,000	164,000	493,000	449,000	182,000	204,000	501,000/ 155,000 185,000[a]	530,000/ 216,000
Anti-drug Antibody, Number of Immunopositive Animals Considered Treatment-Emergent										
BMS-986016										
Pretest	0/5	0/5	0/5	0/5	0/5	0/5	1/5	1/5	0/5	3/5
Day 8	0/5	0/5	1/5	3/5	4/5	1/5	1/5	2/5	1/5	3/5
Day 15	0/5	0/5	1/5	2/5	3/5	3/5	1/5	2/5	3/5	4/5
Day 22	0/5	0/5	0/5	2/5	1/5	0/4	1/5	1/5	2/5	3/4
Day 29	0/5	0/5	0/5	3/5	1/5	0/4	1/5	1/5	3/5	3/4
Day 36 (Recovery)	0/2	0/2	0/2	1/2	1/2	1/1	0/2	1/2	1/2	1/1
Day 43 M/44 F (Recovery)	0/2	0/2	0/2	2/2	1/2	1/1	0/2	1/2	1/2	1/1
Day 50 (Recovery)	0/2	0/2	0/2	2/2	1/2	1/1	0/2	1/2	1/2	1/1
Day 57 (Recovery)	0/2	0/2	0/2	2/2	1/2	1/1	0/2	1/2	1/2	1/1
Day 64 (Recovery)	0/2	0/2	0/2	2/2	1/2	0/1	0/2	1/2	1/2	0/1
Day 71 (Recovery)	0/2	0/2	0/2	1/2	1/2	0/1	0/2	1/2	1/2	1/1

Relatlimab Dose (mg/kg/week)	**0 (Control)**		**30**		**100**		**0**		**100**	
Nivolumab Dose (mg/kg/week)	**0 (Control)**		**0**		**0**		**50**		**50**	
Number of Animals	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
BMS-936558										
Pretest	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
Day 8	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
Day 15	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
Day 22	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	1/5	0/5
Day 29	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	1/5	0/5
Day 36 (Recovery)	0/2	0/2	0/2	0/2	0/2	0/1	0/2	0/2	0/1	0/1
Day 43 M/44 F (Recovery)	0/2	0/2	0/2	0/2	0/2	0/1	1/2	0/2	0/1	0/1
Day 50 (Recovery)	0/2	0/2	0/2	0/2	0/2	0/1	1/2	0/2	0/1	0/1
Day 57 (Recovery)	0/2	0/2	0/2	0/2	0/2	0/1	1/2	0/2	0/1	0/1
Day 64 (Recovery)	0/2	0/2	0/2	0/2	0/2	0/1	1/2	0/2	0/1	0/1
Day 71 (Recovery)	0/2	0/2	0/2	0/2	0/2	0/1	1/2	0/2	0/1	0/1
Noteworthy Findings										
Died or Sacrificed Moribund	0	00	0	0	0	1[b]	0	0	1[c]	1[d]
Body Weight (%[e]) - Day 29	4.86 kg	3.52 kg	+1	-3	+1	-3	-2	-2	-7	-5
Feeding behavior (qualitative)										
Decreased	--	--	--	--	--	--	--	--	1	--
Water Consumption	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Clinical Observations										
Decreased activity	--	--	--	--	--	1[c]	--	--	1	--
Feces, absent/scant	--	--	--	--	--	--	--	--	1	--
Feces, unformed/liquid	--	--	1[f]	--	--	1[f]	--	--	1	3[f]
Nasal discharge, red/clear	--	--	--	--	--	--	--	--	1	--
Shivering	--	--	--	--	--	--	--	--	1	--
Physical Examinations[g]										
Activity, decreased	--	--	--	--	--	--	--	--	1	--
Dehydration	--	--	--	--	--	--	--	--	1	--
Discharge, red	--	--	--	--	--	--	--	--	1	--
Feces, absent	--	--	--	--	--	--	--	--	1	--
Hunched posture	--	--	--	--	--	--	--	--	1	--
Sneezing	--	--	--	--	--	--	--	--	1	--

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Relatlimab Dose (mg/kg/week)	**0 (Control)**		**30**		**100**		**0**		**100**	
Nivolumab Dose (mg/kg/week)	**0 (Control)**		**0**		**0**		**50**		**50**	
Number of Animals	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Ophthalmoscopy	--	--	--	--	--	--	--	--	--	--
Electrocardiography	--	--	--	--	--	--	--	--	--	--
Hematology										
Basophils (E3/µL)										
Day -11	0.02	--	0.03*	--	0.02	--	0.02	--	0.02	--
(% diff from control)			(+50)		(0)		(0)		(0)	
Day -6M/-5F	0.03	--	0.02	--	0.03	--	0.02	--	0.02	--
(% diff from control)			(-33)		(0)		(-33)		(-33)	
Day 8	0.06	--	0.05	--	0.07	--	0.04	--	0.06	--
(% diff from control)			(-17)		(+17)		(-33)		(0)	
Day 30	0.03	--	0.02	--	0.04	--	0.03	--	0.40**	--
(% diff from control)			(-33)		(+33)		(0)		(+1233)	
Red blood cells (E6/µL)[h]										
Day -11	--	--	--	--	--	--	--	--	6.98	--
Day -6	--	--	--	--	--	--	--	--	6.84	--
Day 8	--	--	--	--	--	--	--	--	6.38	--
Day 30	--	--	--	--	--	--	--	--	5.03	--
Hemoglobin (g/dL)[h]										
Day -11	--	--	--	--	--	--	--	--	15.1	--
Day -6	--	--	--	--	--	--	--	--	14.9	--
Day 8	--	--	--	--	--	--	--	--	14.0	--
Day 30	--	--	--	--	--	--	--	--	10.6	--
Hematocrit (%)[h]										
Day -11	--	--	--	--	--	--	--	--	51.5	--
Day -6	--	--	--	--	--	--	--	--	51.6	--
Day 8	--	--	--	--	--	--	--	--	46.8	--
Day 30	--	--	--	--	--	--	--	--	35.0	--

Relatlimab Dose (mg/kg/week)	**0 (Control)**		**30**		**100**		**0**		**100**	
Nivolumab Dose (mg/kg/week)	**0 (Control)**		**0**		**0**		**50**		**50**	
Number of Animals	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Coagulation										
Fibrinogen (mg/dL)[h]										
Day -11	--	--	--	--	--	--	--	--	249	--
Day -6	--	--	--	--	--	--	--	--	256	--
Day 8	--	--	--	--	--	--	--	--	255	--
Day 30	--	--	--	--	--	--	--	--	611	--
Serum Chemistry	--	--	--	--	--	--	--	--	--	--
Urinalysis	--	--	--	--	--	--	--	--	--	--
Immunotoxicology										
Peripheral Blood CD4 Regulatory T cells (mean % of CD3+CD4+CD8- lymphocytes)										
Pretest	4.92	--	5.66	--	5.83	--	5.58	--	5.24	--
Day 15	5.54	--	6.39	--	6.18	--	7.38	--	6.97	--
Day 30	5.26	--	6.55	--	6.19	--	7.26	--	7.21	--
Splenic CD4 regulatory T cells (mean % of CD3+CD4+CD8- splenic lymphocytes)										
Day 30	5.61	6.81	8.47	7.09	6.11	7.17	10.92	8.04	8.25	9.00
Splenic naive CD4 T cells (mean % of CD3+CD4+CD8- splenic lymphocytes)										
Day 30	54.54	50.33	47.83	56.43	57.6	50.22	46.54	47.43	46.54	42.23
Splenic central memory CD4 T cells (mean % of CD3+CD4+CD8- splenic lymphocytes)										
Day 30	36.09	39.78	40.04	33.70	34.18	38.08	39.42	40.81	42.25	44.26
Splenic naive CD8 T cells (mean % of CD3+CD8+CD4- splenic lymphocytes)										
Day 30	44.43	46.02	43.12	62.89	52.00	57.51	40.46	43.81	55.54	44.50
Splenic central memory CD8 T cells (mean % of CD3+CD8+CD4- splenic lymphocytes)										
Day 30	24.85	21.34	23.76	18.94	22.11	20.04	26.01	26.44	26.20	23.89
Splenic CD25+Foxp3+ CD8 T cells (mean % of CD3+CD8+CD4- splenic lymphocytes)										
Day 30	0.77	0.54	1.38	0.93	0.74	1.01	1.23	1.28	0.94	1.16
KLH Ex-Vivo Recall Response, mean % IFNγ+, CD4+CD8- T-cells										
Pretest	0.05	0.08	0.05	0.07	0.09	0.08	0.05	0.07	0.05	0.09
Day 22	0.14	0.13	0.16	0.23	0.22	0.33	0.29	0.37	0.42	0.67
KLH Ex-Vivo Recall Response, mean % TNFα+ CD4+CD8- T-cells										
Pretest	0.04	0.07	0.04	0.07	0.10	0.08	0.07	0.07	0.07	0.07
Day 22	0.22	0.22	0.29	0.47	0.54	0.67	0.29	0.61	0.54	0.88

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Relatlimab Dose (mg/kg/week)	**0 (Control)**		**30**		**100**		**0**		**100**	
Nivolumab Dose (mg/kg/week)	**0 (Control)**		**0**		**0**		**50**		**50**	
Number of Animals	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Immunotoxicology (continued)										
KLH Ex-Vivo Recall Response, mean % CD69+ CD4+CD8- T-cells										
Pretest	0.07	0.06	0.07	0.05	0.12	0.05	0.09	0.06	0.14	0.07
Day 22	0.51	0.56	0.61	1.02	0.91	1.79	0.53	1.32	0.93	1.63
KLH Ex-Vivo Recall Response, mean % CD69+IFNγ+ CD4+CD8- T-cells										
Pretest	0.01	0.01	0.02	0.00	0.05	0.00	0.01	0.00	0.03	0.00
Day 22	0.06	0.05	0.07	0.12	0.13	0.20	0.17	0.23	0.29	0.49
KLH Ex-Vivo Recall Response, mean % CD69+TNFα+ CD4+CD8- T-cells										
Pretest	0.02	0.01	0.02	0.01	0.06	0.02	0.03	0.02	0.04	0.02
Day 22	0.18	0.17	0.23	0.42	0.47	0.59	0.24	0.54	0.45	0.81
KLH Ex-Vivo Recall Response, mean % CD69+TNFα+IFNγ+ CD4+CD8- T-cells										
Pretest	0.00	0.00	0.00	0.00	0.04	0.00	0.00	0.00	0.01	0.00
Day 22	0.04	0.04	0.05	0.10	0.12	0.16	0.13	0.18	0.23	0.40
End-of-Dose: Number Evaluated:	3	3	3	3	3	4[i]	3	3	4[i]	4[i]
Organ Weights	--	--	--	--	--	--	--	--	--	--
Gross Pathology	--	--	--	--	--	--	--	--	--	--
Histopathology										
Brain - Inflammation, lymphoplasmacytic, choroid plexus										
Minimal	0	0	0	0	0	0	1	2	3	1
Slight	0	0	0	0	0	0	0	0	1[h]	1
Brain - Inflammation, lymphohistiocytic, vascular, parenchyma										
Minimal	0	0	0	0	0	0	0	0	1	0
Moderate	0	0	0	0	0	0	0	0	1[h]	0
Brain - Inflammation, lymphohistiocytic, meninges										
Mild	0	0	0	0	0	0	0	0	1[h]	0

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Relatlimab Dose (mg/kg/week)	**0 (Control)**		**30**		**100**		**0**		**100**	
Nivolumab Dose (mg/kg/week)	**0 (Control)**		**0**		**0**		**50**		**50**	
Number of Animals	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Epididymides - Inflammation, mixed cell										
Moderate	0	NA	0	NA	0	NA	0	NA	1[h]	NA
Spinal Cord (cervical and lumbar) - Inflammation, lymphohistiocytic, central canal and vascular										
Minimal	0	0	0	0	0	0	0	0	1[h]	0
Seminal vesicles - Inflammation, mixed cell										
Slight	0	NA	0	NA	0	NA	0	NA	1[h]	NA
Testes (Rete testis) - Inflammation, mixed cell										
Slight	0	NA	0	NA	0	NA	0	NA	1[h]	NA
Post-Dose Evaluation[j] - Numbers evaluated	2	2	2	2	2	1	2	2	1	1
Immunotoxicology										
Peripheral Blood CD4 Regulatory T cells (mean % of CD3+CD4+CD8- lymphocytes)										
Day 72	5.80	--	6.46	--	5.78	--	5.17	--	11.58	--
Splenic naive CD4 T cells (mean % of CD3+CD4+CD8- splenic lymphocytes)										
Day 72	55.25	44.01	38.78	58.38	55.60	56.20	62.31	29.09	30.19	35.44
Splenic central memory CD4 T cells (mean % of CD3+CD4+CD8- splenic lymphocytes)										
Day 72	34.89	44.72	49.36	32.96	34.54	33.70	27.44	55.34	55.02	48.41
Splenic naive CD8 T cells (mean % of CD3+CD8+CD4- splenic lymphocytes)										
Day 72	55.75	51.20	49.68	51.68	51.30	60.61	59.53	25.57	35.64	21.44
Splenic central memory CD8 T cells (mean % of CD3+CD8+CD4- splenic lymphocytes)										
Day 72	19.41	23.43	24.04	19.92	23.34	22.17	21.41	41.06	49.45	31.03
Splenic CD25+Foxp3+ CD8 T cells (mean % of CD3+CD8+CD4- splenic lymphocytes)										
Day 72	0.61	0.82	0.98	0.90	1.04	1.46	0.88	1.39	1.02	1.15

Relatlimab Dose (mg/kg/week)	0 (Control)		30		100		0		100	
Nivolumab Dose (mg/kg/week)	0 (Control)		0		0		50		50	
Number of Animals	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5	M: 5	F: 5
Histopathology										
Brain - Inflammation, lymphoplasmacytic, choroid plexus										
Slight	0	0	0	0	0	0	1	1	1	1

Abbreviations: -- = No noteworthy findings; ◆ = Not conducted; DTPA = Diethylenetriaminepentetic acid; KLH = Keyhole limpet hemocyanin; NA = Not applicable; NaCl = Sodium chloride.

* $P \leq 0.05$, ** $P \leq 0.01$ Dunnett's Test

[a] Represents values excluding and including animals showing assay positives for anti-nivolumab antibodies.

[b] From Days 8 to 15, 1 female monkey (Animal No. 3202) treated with 100 mg/kg relatlimab presented with decreased activity (Days 8 to 10), lethargy (Day 8), hunched and abnormal posture (Day 8), heart sound murmur (Days 8 to 9), pallor of the gums (Days 8 to 11, 15), discoloration at the bleeding site (Days 8 to 15), red discoloration on left hindlimb (Days 8 to 11, 14 to 15), swollen left hindlimb (Days 8 to 15), and left hindlimb lameness (Days 8 to 15). Hematological evaluations on Day 8 showed noteworthy decreases in red blood cell count, hemoglobin concentration and hematocrit consistent with blood loss, which were exacerbated by Day 15. This monkey was euthanized on Day 15 for decreases in red blood cell mass parameters. At necropsy, red gelatinous content compatible with a blood clot was noted within the deep musculature of the left thigh, which was histopathologically confirmed to be a hematoma. The cause of death of Animal No. 3202 was attributed to trauma related to bleeding procedures, and unrelated to relatlimab administration.

[c] On Days 26 to 29, 1 male monkey (Animal No. 5103) treated with 100 mg/kg/week relatlimab and 50 mg/kg/week nivolumab presented with increased body temperature (40.4°C on Day 26), shivers (Days 26 to 29), red or clear nasal discharge (Days 27 to 28), fecal changes (unformed, scant, or absent feces: Days 27 to 29), decreased feeding behavior and mild dehydration (Days 28 to 29), sneezing (Day 29), decreased activity (Days 28 to 29), and hunched posture (Day 29). This monkey was euthanized on Day 29 prior to the last administered dose of relatlimab/nivolumab for poor clinical condition. There were no gross necropsy findings. Histopathological findings in this monkey included: lymphoplasmacytic inflammation of the choroid plexus (slight); lymphohistocytic inflammation of the vasculature of the brain parenchyma (moderate), meninges (mild), spinal cord (cervical and lumbar regions; minimal); mixed cell inflammation of the epididymes (moderate), seminal vesicles (slight), and rete testes (slight). Mortality of Animal No. 5103 was considered related to nivolumab and relatlimab treatment.

[d] One female monkey (Animal No. 5204) treated with 100 mg/kg/week relatlimab and 50 mg/kg/week nivolumab presented with abdominal distension, painful abdomen, decreased activity, moderate dehydration, pallor of the gums, hunched posture, weak pulse in the right hindlimb, and body cool to touch. Upon sedation for emergency procedures, there was a notable decrease in body temperature (33.4°C), and clinical findings were found to be related to significant abdominal bloat. The monkey was subsequently euthanized for poor clinical condition. Upon necropsy, complete torsion of the distal colon was diagnosed. Histopathology confirmed mucosal necrosis and hemorrhage of the colon. The cause of death of Animal No. 5204 was attributed to colonic torsion and unrelated to administration of nivolumab and relatlimab.

[e] At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

[f] With the exception of Animal No. 5103 fecal findings were considered incidental and not related to test-article treatment due to low incidence and sporadic nature.

[g] Relatlimab- and nivolumab-related physical examination findings observed in 1 male (Animal No. 5103) at 100 mg/kg/week relatlimab and 50 mg/kg/week nivolumab included decreased activity, mild dehydration, red nasal discharge, absent feces, hunched posture, sneezing, slight shivering of both forelimbs, and elevated body temperature (40.4ºC).

[h] Values reflect Animal No. 5103 treated with 100 mg/kg/week relatlimab and 50 mg/kg/week nivolumab from Group 5, which was euthanized on Day 29 due to fever, nasal discharge and inappetence, had decreases in red blood cell count, hematocrit, hemoglobin concentration and hematocrit (0.74×, 0.71×, and 0.68× second pretest values, respectively). This male also had a notable increase in fibrinogen (2.39× second pretest value) which correlated with the inflammation observed in the central nervous system and male reproductive tract although there were no notable changes in leukocytes in blood.

[i] Number evaluated includes early death of Animal Nos. 3202, 5103, and 5204.

[j] All relatlimab- and nivolumab-related effects on all parameters recovered except where indicated.

Table 13: Applicant - General Toxicology: Three-Month Intermittent Intravenous Infusion (QW) Toxicity Study in Monkeys with a 10-Week Post Dose Recovery

Study Title	Three-Month Intermittent Intravenous Infusion (QW) Toxicity Study in Monkeys with a 10-Week Post Dose Recovery
Study Number	DN16053
Study Type	Repeat-dose
eCTD Location	4.2.3.2
GLP Compliance	Yes
Key Drug-related Adverse Findings: None	
Methods	
Frequency of Dosing	Weekly
Relatlimab Dose	0, 30, 100 mg/kg/dose
Route of Administration	Intravenous
Formulation/Vehicle	(b) (4)
Species/Strain	Monkey/cynomolgus
Number/Sex/Group	6 males/6 females
Age	4-7 years old
Satellite groups	Not applicable

Table 14: Applicant - General Toxicology: Study DN16053 Three-Month Intermittent Intravenous Infusion (QW) Toxicity Study in Monkeys with a 10-Week Post Dose Recovery

Weekly Dose (mg/kg/dose):	(0) Control		30		100	
No. of Animals:	M:6	F:6	M:6	F:6	M: 6	F: 6
Toxicokinetics: BMS-986016						
Cmax (µg/mL)						
Day 1	--	--	953	887	3,480	3,000
Day 85[a]	--	--	3,100/4,270	2,570/2,940	10,100/12,900	8,200/8,410
Mean Sex-combined Values Day 1	--		920		3,240	
Mean Sex-combined Values Day 85[a]	--		2,810/3,605		9,150/10,700	
AUC(0-168h) (µg•h/mL)						
Day 1	--	--	93,400	78,900	322,000	264,000
Day 85[a]	--	--	418,000/523,000	354,000/407,000	1,380,000/ 1,790,000	968,000/ 1,050,000
Mean Sex-combined Values Day 1	--		86,200		293,000	
Mean Sex-combined Values Day 85[a]	--		383,000/465,000		1,180,000/1,420,000	
Anti-drug Antibody, Number of Immunopositive Animals Considered Treatment Emergent						
Day 1 (Pretest)	♦	♦	1/6	2/6	2/6	1/6
Day 8	♦	♦	4/6	4/6	3/6	4/6
Day 15	♦	♦	5/6	5/6	5/6	5/6
Day 22	♦	♦	5/6	5/6	5/6	5/6
Day 29	♦	♦	5/6	5/6	2/6	4/6
Day 43	♦	♦	5/6	4/6	2/6	3/6
Day 57	♦	♦	4/6	4/6	4/6	2/6
Day 71	♦	♦	4/6	4/6	2/6	3/6
Day 85	♦	♦	3/6	2/6	1/6	4/6
Day 99 (Recovery)	♦	♦	1/2	1/2	0/2	1/2
Day 113 (Recovery)	♦	♦	1/2	0/2	0/2	1/2
Day 127 (Recovery)	♦	♦	1/2	0/2	2/2	1/2
Day 141 (Recovery)	♦	♦	0/2	0/2	1/2	1/2
Day 155 (Recovery)	♦	♦	0/2	0/2	1/2	1/2

Weekly Dose (mg/kg/dose):	**(0) Control**		**30**		**100**	
No. of Animals:	**M:6**	**F:6**	**M:6**	**F:6**	**M: 6**	**F: 6**
Noteworthy Findings						
Died or Sacrificed Moribund	0	0	0	0	0	0
Body Weight (%)[b] - Day 91	8.38 kg	3.52 kg	-4	-5	+2	+3
Food Evaluation	--	--	--	--	--	--
Water Consumption	♦	♦	♦	♦	♦	♦
Clinical Observations	--	--	See footnote[c]	--	See footnote[d]	--
Veterinary Examinations	--	--	--	--	--	--
Ophthalmoscopy	--	--	--	--	--	--
Electrocardiography	--	--	--	--	--	--
Hematology	--	--	--	--	--	--
Coagulation	--	--	--	--	--	--
Serum Chemistry	--	--	--	--	--	--
Urinalysis	--	--	--	--	--	--
Urine Chemistry	--	--	--	--	--	--
T-Cell Dependent Antibody Response	--	--	--	--	--	--
Immunophenotyping (Relative Percentage)						
Peripheral Blood Immunophenotyping						
Regulatory CD4+ Lymphocytes (CD45+/CD4+/CD25+/FoxP3+)						
Prestudy 1	4.263	2.853	2.483	3.098	2.578	3.207
Prestudy 2	3.960	3.267	2.825	3.232	2.622	2.235
Day 61M/Day 57F	3.775	1.843	3.018	2.232	3.350	2.395
Week 13	4.087	3.710	3.562	4.658	3.112	4.402
Spleen Immunophenotyping						
Cytotoxic T Lymphocytes (CD45+/CD3+/CD8+)						
Week 13	28.643	19.665	21.913	16.173	24.868	22.093
Regulatory CD4+ Lymphocytes (CD45+/CD4+/CD25+/FoxP3+)						
Week 13	3.458	3.778	2.818	5.598	2.950	6.448

Weekly Dose (mg/kg/dose):	**(0) Control**		**30**		**100**	
No. of Animals:	**M:6**	**F:6**	**M:6**	**F:6**	**M: 6**	**F: 6**
Regulatory CD8+ Lymphocytes (CD45+/CD8+/CD25+/FoxP3+)[e] Week 13	0.498	0.748	0.388	1.230	0.540	1.533
Ex vivo Recall Response Assessment	--	--	--	--	--	--
End-of-Dose - Number Evaluated:	4	4	4	4	4	4
Organ Weights	--	--	--	--	--	--
Gross Pathology	--	--	--	--	--	--
Histopathology	--	--	--	--	--	--
Post-dose Evaluation[f] - Number Evaluated	2	2	2	2	2	2
Died or Sacrificed Moribund	0	0	0	0	0	0

Abbreviations: -- = No noteworthy findings; ♦ = Not conducted; ADA = Anti-drug antibody; DTPA = Diethylenetriaminepentaacetic acid; QW = Once weekly.

[a] Values were calculated with data from all available monkeys/only monkeys without detectable anti-drug/relatlimab antibodies. N = 1 monkey/group/sex without detectable anti-drug/relatlimab antibodies.

[b] At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

[c] Starting on Day 36 and throughout the dosing period, a single male at 30 mg/kg exhibited transient clinical observations such as tremors, decreased activity, hunched posture, retching and/or emesis, observations which based on onset after repeated dosing and immediacy to dose administration are consistent with a secondary response to treatment-emergent ADAs (elicited by administration of relatlimab). Corresponding decreases in relatlimab exposure, decreases in serum complement activity and increases in plasma complement split factor 3a were also noted in this monkey, indicative of complement fixation of drug/ADA-complexes. Therefore, the clinical observations noted in this monkey were considered a secondary response to ADAs rather than a direct effect of relatlimab and were not factored in the determination of the no-observed-adverse-effect-level.

[d] Incidents of decreased activity, weakness, abnormal breathing sounds, labored breathing and/or non-sustained convulsions immediately post dose were noted sporadically and inconsistently throughout the dosing period for one 100 mg/kg male. These observations were considered unrelated to relatlimab given the irregular incidence noted above, absence of similar observations in other monkeys in this study and in a prior 1 month toxicity study, and inconsistency with the expected pharmacological activity related to inhibition of LAG-3.

[e] Week 24: Recovery of the increase of CD8 regulatory lymphocytes in spleens is difficult to determine, as the values in the 30 mg/kg dosed females were still higher than control animals.

[f] All relatlimab-related effects on all parameters recovered.

The FDA's Assessment:

- FDA agrees with the Applicant's assessment of the 4-week study.
  - Findings of slight to moderate inflammation of the spinal cord and brain (perivascular parenchyma, choroid plexus, and meninges) were observed when monkeys were dosed with combination nivolumab + relatlimab.
  - Inflammation of the choroid plexus was also observed in animals treated with nivolumab alone. Additionally, mononuclear cell infiltrate of the choroid plexus, meninges, perivascular parenchyma, and spinal cord was reported in the 4-week GLP toxicology study conducted in support of BLA 125554 for nivolumab at doses as low as 1 mg/kg administered once weekly. Thus, inflammation/infiltration affecting the brain and spinal cord in monkeys appear to be associated with nivolumab and are consistent with its immune-stimulating mechanism of action. These findings appear to be exacerbated by the addition of relatlimab treatment, which acts to further stimulate the immune system.
- FDA generally agrees with the Applicant's assessment of the 13-week repeat dose toxicology study of relatlimab. The main findings were of minimal severity and were comprised mainly of decreases in cytotoxic T cells and increases in regulatory and total T cells counts in females ≥30 mg/kg. Findings were reversible.

5.5.2. Genetic Toxicology

The Applicant's Position:

As described in ICH S6 guidance, the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology derived pharmaceuticals because it is not expected that these substances would interact directly with DNA or other chromosomal material. Thus, genotoxicity studies for relatlimab have not been conducted.

The FDA's Assessment:

Based on the biologic properties of nivolumab and relatlimab, genetic toxicology studies were not warranted.

5.5.3. Carcinogenicity

The Applicant's Position:

Relatlimab is a mAb and is not expected to cause carcinogenicity via a genotoxic mechanism. Genotoxicity and carcinogenicity studies for relatlimab have not been conducted.

The FDA's Assessment:

Carcinogenicity studies were not warranted for the proposed indication.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Relatlimab is not cross-reactive in rodents or rabbits. Accordingly, the reproductive tract (organ weights and histopathological evaluation) was assessed in the 3-month toxicity study conducted in sexually mature monkeys and confirmed no effects. Developmental toxicity studies were performed in mice using surrogate anti-LAG-3 antibodies that bind to murine LAG-3.

Developmental and reproductive toxicology studies were conducted in mice using both syngeneic and allogeneic breedings, the latter of which is designed to elicit feto-maternal tolerance through mating of genetically distinct mouse strains in which paternally contributed alloantigens induce an immune response in the pregnant dam. Due to the lack of cross-reactivity of relatlimab in rodent species, surrogate anti-mouse LAG-3 antibodies (clone MLAG3.4 MG1-D265A [19C7] or C9B7W) were used. Both antibodies were well tolerated by dams at the highest dose tested, and there were no maternal or developmental toxicities detected in either syngeneic or allogeneic breedings, with resulting maternal and developmental NOAELs of 50 mg/kg (MLAG3.4 MG1D265A [19C7]) and 51.5 mg/kg (C9B7W). Exposures observed in the GLP study, DN17040, were up to approximately 11 times higher than those observed for relatlimab at the clinical dose of 160 mg (based on AUC, and with a 2X correction for differences in dosing frequency and duration), with no maternal or developmental effects in either syngeneic or allogeneic breedings. Despite these results, the risk for adverse human pregnancy outcomes associated with relatlimab administration is considered to be of concern for 2 reasons: 1) checkpoint targets, including LAG-3, are likely to have a role in maintaining maternal tolerance to the developing fetus and 2) the present indication requires that relatlimab be administered in combination with nivolumab, which has been shown to increase third trimester pregnancy loss in cynomolgus monkeys. See Section 8.2.1 for details of pregnancy testing within the CA224047 safety assessments.

Table 15: Applicant - Reproductive and Developmental Toxicology: Anti-LAG-3 C9B7W mAb: Intra-Peritoneal Study of Embryo-Fetal Development in Mice

Study Title:	anti-LAG-3 C9B7W mAb: Intra-Peritoneal Study of Embryo-Fetal Development in Mice
Study Number	DN17040
Study Type	Embryo-fetal Development
eCTD Location	4.2.3.5.2
GLP Compliance	Yes
Key Drug-related Adverse Findings: None	
Methods	
Frequency of Dosing	Gestation Day (GD) 6 to 14 (dosed GD 6, 8, 10, 12, and 14)
Allogeneic (DBA/2J:CBA/CaJ) dose	0, 25, 51.5, 0 mg/kg
Syngeneic (CBA/CaJ:CBA/CaJ) dose	0, 51.5 mg/kg
Route of Administration	Intraperitoneal
Formulation/Vehicle	Sterile phosphate buffered saline
Species/Strain	Mouse/ CBA/CaJ (treated F, untreated M) and DBA/2J (untreated M)
Number/Sex/Group	22-24 females
Age	10-15 weeks at receipt
Satellite groups	Not applicable

Table 16: Applicant - Reproductive and Developmental Toxicology: Study DN17040 anti-LAG-3 C9B7W mAb: Intra-Peritoneal Study of Embryo-Fetal Development in Mice

	Allogeneic (DBA/2J:CBA/CaJ)			Syngeneic (CBA/CaJ:CBA/CaJ)[a]		
Dose (mg/kg):	**0 (Control) Group 4**	**25 Group 5**	**51.5 Group 6**	**0 (Control) Group 9**	**0 (Control) Group 7**	**51.5 Group 8**
Dams:						
Toxicokinetics: anti-LAG-3 C9B7W mAb - GD 10						
Cmax (µg/mL)	--	476	857	♦	♦	♦
AUC(0-144h) (µg•h/mL)	--	39,000	57,500	♦	♦	♦
Anti-drug Antibodies, Number of Immunopositive Animals						
GD 10 48 h	♦	0/5	0/5	♦	♦	♦
GD 10 144 h	♦	0/5	0/5	♦	♦	♦
GD 18	♦	5/19	3/22	♦	♦	6/22
No. Pregnant/No. Assigned to Study	23/23	23/24	22/22	22/22	22/22	22/22
No. Died or Sacrificed Moribund	1	4	0	0	0	0
No. Aborted or with Total Resorption of Litter	0	0	0	0	0	0
Clinical Observations	--	--	--	--	--	--
Necropsy Observations	--	--	--	--	--	--
Gestation Body Weight (%[b])						
GD 0	21.1 g	-1	0	20.4 g	20.5 g	0
GD 6	23.0 g	-2	0	22.4 g	22.0 g	0
GD 18	35.2 g	-2	0	35.7 g	34.8 g	-1
Gestation Body-Weight Change (%[b])						
GD 6-14	5.6 g	+7	+7	6.1 g	5.9 g	-5
Gestation Food Consumption(%[b])						
GD 6-14	4.6 g	+4	+15	4.0 g	4.4 g	4.5
Mean No. Corpora Lutea	9.9	9.6	9.9	9.3	9.5	9.6
Mean No. Implantations	9.6	9.2	9.6	9.0	9.3	8.9
Mean % Preimplantation Loss[c]	3.0	4.4	2.5	2.8	2.5	7.4

Dose (mg/kg):	Allogeneic (DBA/2J:CBA/CaJ)			Syngeneic (CBA/CaJ:CBA/CaJ)[a]		
	0 (Control) Group 4	25 Group 5	51.5 Group 6	0 (Control) Group 9	0 (Control) Group 7	51.5 Group 8
Litters (caesarian-delivered GD 18):						
No. Evaluated	22	19	22	22	22	22
Mean No. Live Fetuses	7.8	8.3	8.1	7.5	7.8	7.3
Mean % Viable Fetuses	81.3	90.1	84.4	82.8	82.8	80.3
Mean No. Resorptions	1.7	0.9	1.4	1.6	1.5	1.6
No. of Litters with Dead Fetuses	1	0	0	0	0	0
Mean % Postimplantation Loss[d]	18.7	9.9	15.6	17.2	17.2	19.7
Mean Fetal Body Weight/Litter (g)	0.85	0.84	0.87	0.94	0.83	0.85
Fetal Sex Ratios (Mean % Male Fetuses/Litter)	49.6	46.9	47.9	48.2	49.8	51.0
Summary of Gross External, Visceral, and Skeletal Anomalies [N (% per Litter)]:[e]						
No. Fetuses Examined/No. Litters Examined	172/22	157/19	179/22	164/22	171/22	160/22
External Malformations	0 (0.0)	2 (1.3)	0 (0.0)	3 (1.8)	1 (0.8)	2 (1.4)
External Variations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Soft Tissue Malformations	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.5)	0 (0.0)
Soft Tissue Variations	7 (3.1)	2 (1.2)	10 (5.0)	4 (2.2)	1 (0.4)	4 (2.7)
Skeletal Malformations	4 (2.1)	4 (2.4)	5 (2.7)	3 (1.8)	3 (1.7)	3 (1.7)
Skeletal Variations	296 (88.7)	257 (89.1)	294 (89.6)	312 (93.5)	272 (91.9)	254 (93.6)
Fetal Gross External Anomalies [N (% per Litter)]:[e]						
No. Fetuses Examined/ No. Litters Examined	172/22	157/19	179/22	164/22	171/22	160/22
Cyclopia (M)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Craniorhachischisis (M)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Amelia (M)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Exencephaly with or without Open Eyelid (M)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Omphalocele (M)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Cleft Palate (M)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.8)
Apodia (M)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Ectrodactyly (M)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.6)
Hemimelia (M)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.6)

	Allogeneic (DBA/2J:CBA/CaJ)			Syngeneic (CBA/CaJ:CBA/CaJ)[a]		
Dose (mg/kg):	**0 (Control) Group 4**	**25 Group 5**	**51.5 Group 6**	**0 (Control) Group 9**	**0 (Control) Group 7**	**51.5 Group 8**
Fetal Visceral Anomalies [N (% per Litter)]:						
No. Fetuses Examined/No. Litters Examined	172/22	157/19	179/22	164/22	171/22	160/22
Retroesophageal Aortic Arch (M)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.5)	0 (0.0)
Lungs- Lobular Agenesis (M)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Spleen - Pale (V)	5 (2.6)	2 (1.2)	9 (4.5)	4 (2.2)	0 (0.0)	4 (2.7)
Spleen - Small (V)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Accessory Spleen(s) (V)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Major Blood Vessel Variation (V)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Fetal Skeletal Anomalies [N (% per Litter)]:[e]						
No. Fetuses Examined/No. Litters Examined	172/22	157/19	179/22	164/22	171/22	160/22
Vertebral Anomaly with or without Associated Rib Anomaly (M)	2 (1.1)	1 (0.5)	0 (0.0)	3 (1.8)	1 (0.5)	2 (1.2)
Sternebra(e) Malaligned (Severe) (M)	1 (0.5)	2 (1.2)	4 (2.2)	1 (0.5)	0 (0.0)	0 (0.0)
Costal Cartilage Anomaly (M)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rib Anomaly (M)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	2 (1.3)	0 (0.0)
Fetal Skeletal Anomalies [N (% per Litter)]:[e]						
Sternebrae Fused (M)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
6 Cervical Vertebrae (M)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Vertebral Centra Anomaly (M)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bent Limb Bone(s) (M)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
25 Presacral Vertebrae (V)	133 (77.3)	121 (77.7)	142 (80.6)	139 (84.1)	151 (88.2)	140 (88.0)
Accessory Skull Bone(s) (V)	73 (42.2)	62 (39.5)	75 (41.3)	75 (45.8)	58 (33.3)	60 (36.5)
7th Cervical Rib(s) (V)	74 (43.4)	59 (37.9)	63 (36.2)	82 (50.5)	36 (21.7)	32 (19.4)
14th Rudimentary Rib(s) (V)	1 (0.6)	1 (0.7)	1 (0.4)	1 (0.8)	1 (0.5)	2 (1.2)
Sternebra(e) Malaligned (slight or moderate) (V)	11 (7.0)	9 (5.7)	9 (5.6)	10 (6.2)	8 (4.6)	4 (2.2)
Sternebra(e) #5 and/or #6 Unossified (V)	3 (1.6)	3 (1.8)	1 (0.6)	1 (0.6)	5 (2.8)	1 (0.5)
Reduced Ossification of the 13th Rib(s) (V)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	3 (1.9)
7th Sternebra (V)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.8)	0 (0.0)	0 (0.0)
Metacarpal(s) and/or Metatarsal(s) Unossified (V)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	5 (2.5)	5 (3.2)

	Allogeneic (DBA/2J:CBA/CaJ)			Syngeneic (CBA/CaJ:CBA/CaJ)[a]		
Dose (mg/kg):	**0 (Control) Group 4**	**25 Group 5**	**51.5 Group 6**	**0 (Control) Group 9**	**0 (Control) Group 7**	**51.5 Group 8**
Fetal Skeletal Anomalies [N (% per Litter)]:[e]						
Reduced Ossification of the Skull (V)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	6 (2.9)	7 (4.8)
Sternebra(e) #1, #2, #3 and/or #4 Unossified (V)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
14th Full Rib(s) (V)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Pelvic Girdle Malpositioned (V)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Vertebral Centra Unossified (V)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)

Abbreviations: -- = No noteworthy findings; ♦ = Not conducted; GD = Gestation day; M = Malformation; NA = Not applicable; V = Variations.
For statistical analyses, control Group 4 was compared to Groups 5 and 6; control Group 7 was compared to Group 8.

[a] Due to an error, the wrong strain of females was used to generate syngeneic pregnancies for Groups 1-3 (CBA/J males mated to CBA/CaJ females), resulting in allogeneic pregnancies. No test-article related effects were noted and this data is not reported in this table.

[b] For controls, group means are shown. For treated groups, percent differences from respective controls are shown.

[c] Preimplantation loss calculated as: [(corpora lutea - implantation) ÷ corpora lutea] x 100.

[d] Postimplantation loss calculated as: [(dead + resorbed conceptuses) ÷ implantations] x 100.

[e] All percentages were calculated on the basis of the number of live fetuses in each group.

The FDA's Assessment:

- FDA agrees that treatment with anti-LAG-3 did not show adverse effects on pregnant mice or fetuses at doses up to 51.5 mg/kg in both syngeneic and allogeneic breeding schemes.
- Calculating safety margins relative to human exposures with surrogate molecules is generally not appropriate.
- In Study DN12123 (4-week toxicology study), minimal to moderate mixed-cell inflammation of the epididymis, seminal vesicles, and testes was observed in male monkeys treated with combination nivolumab and relatlimab. Mineralization of the seminal vesicles was also observed.

5.5.5. Other Toxicology Studies

The Applicant's Position:

In exploratory in vitro assays, neither relatlimab alone nor relatlimab in combination with nivolumab induced cytokine release or resulted in T, B, or NK cellular activation in human PBMCs.

Table 17: Applicant - Other Toxicology Studies: In Vitro Cytokine Release and Lymphocyte Activation Assessment using Human Peripheral Blood Mononuclear Cells

Study Title	In Vitro Cytokine Release and Lymphocyte Activation Assessment using Human Peripheral Blood Mononuclear Cells
Study Number/	DN13043
Study Type	Cytokine Release
eCTD Location	4.2.3.7.7
GLP Compliance	No

Key Drug-related Adverse Findings:

- None; relatlimab did not induce cytokine release when presented to human PBMCs and there was no evidence of T- or NK-cell activation, as measured by surface expression of CD25 and CD69.

Study No.	Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	No. per Group and Sex
DN13043	Human PBMCs[a]	In vitro	NA	0.03, 0.1, 0.3, 1, 3, or 10 μg/well	10 normal healthy donors

Abbreviations: IFN = Interferon; IL = Interleukin; NA = Not applicable; NK = Natural killer; PBMC = Peripheral blood mononuclear cell.

[a] A mouse anti-human super-agonistic anti-CD28 mAb TGN 5.11A1 was used as positive control and comparator in these assays. A chimeric murine monoclonal antibody (anti-L6 IgG4) with a modified human IgG4 Fc tail, with 100% identical Fc sequence homology to relatlimab, was used as negative control. Immobilization of test agents (relatlimab, TGN 5.11A1, L6-IgG4, and/or nivolumab) was achieved by dry coating each agent directly in cell culture plates at multiple concentrations ranging from 0.03 to 10 μg/well. Purified PBMCs from 10 normal healthy donors (0.15×10^6 cells/well) were evaluated. Following 18 and 66 hours of incubation, aliquots of cell supernatant were collected for multiplex cytokine analysis. The cytokines evaluated included: IL-1β, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12p70, IFN-γ, and TNF-α. Concurrently, T and NK cells were also evaluated for cell surface expression of activation markers, CD25 and CD69, using flow cytometry.

Table 18: Applicant - Other Toxicology Studies: Tissue Cross-Reactivity Study of Fluoresceinated BMS-986016 in a Full Human Tissue Panel and a Limited Cynomolgus Monkey Tissue Panel

Study Title:	Tissue Cross-Reactivity Study of Fluoresceinated BMS-986016 in a Full Human Tissue Panel and a Limited Cynomolgus Monkey Tissue Panel
Study Number	DN13006
Study Type:	Tissue Cross-reactivity
eCTD Location:	4.2.3.7.7
GLP Compliance:	Yes
Key Drug-related Adverse Findings: • None	

Study No.	Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	No. per Group and Sex
DN13006	Human and Cynomolgus Monkey[a]	In vitro	NA	5 or 25 µg/mL relatlimab-FITC	3 donors/tissue (human) or 3 animals/tissue (cynomolgus monkey)

Abbreviations: NA = Not applicable; CHO = Chinese hamster ovary; KLH = Keyhole limpet hemocyanin; relatlimab-FITC = Fluorescein isothiocyanate conjugated-relatlimab.

[a] Comprehensive panel of 36 normal human tissues from 3 donors per tissue and limited panel of normal cynomolgus monkey tissues (which included cerebellum, cerebral cortex, choroid plexus, epididymis and spleen) from 1 donor per tissue was evaluated. Anti-KLH-g4P-FITC, a human monoclonal antibody with a different antigenic specificity from relatlimab-FITC, was used a control article. Slides with cryosections of CHO cells transfected with human LAG-3 (CHO/huLag3 cells) or cynomolgus monkey LAG-3 (CHO/cynoLag3 cells) were used as positive protein controls, and slides with cryosections of untransfected CHO cells were used as negative protein controls. Using an indirect immunoperoxidase procedure, the staining of relatlimab-FITC was compared to that of anti-KLH-g4P-FITC.

The FDA's Assessment:

- FDA agrees that results from the in vitro studies indicate that relatlimab alone and in combination with nivolumab presents a low risk for cytokine release.
- Tissue cross-reactivity: plasma membrane/plasma membrane granule staining was observed with relatlimab-FITC in mononuclear leukocytes in the bladder, colon, esophagus, small intestine, kidney, lung, lymph node, thymus, tonsil, cervix, and endometrium. Additional plasma membrane/plasma membrane granules staining was observed in hematopoietic cells in the bone marrow. Cytoplasm/cytoplasmic granule staining was observed in endocrine cell epithelium in the pituitary. Given the literature reports of LAG-3-expressing cells in germinal centers and interfollicular T-cell areas of normal human lymphoid tissues (lymph node, tonsil, spleen, thymus, bone marrow and MALT), the staining of mononuclear leukocytes and hematopoietic cells observed in this study appears consistent with the mechanism of action of relatlimab.

X	X
X	X
Elizabeth Spehalski Primary Reviewer	Matthew Thompson Supervisor

6 Clinical Pharmacology

6.1.Executive Summary

The FDA's Assessment:
This BLA is for a fixed dose combination (FDC) product with the marketed drug nivolumab in combination with a new molecular entity (NME) relatlimab for treatment of adult patients and pediatric patients 12 years of age and older (b) (4) with unresectable or metastatic melanoma.

Efficacy, safety, pharmacokinetic (PK), pharmacodynamic, and immunogenicity data in support of this marketing application are based on pivotal study CA224047 with the FDC and study CA224020 with relatlimab administered over the dose range of 20 – 800 mg every two weeks (Q2W) and in combination with nivolumab over the dose range of 20 – 240 mg Q2W and 160 – 1440 mg Q4W. The recommended dosage is 480 mg nivolumab and 160 mg relatlimab Q4W in adult patients and pediatric patients ≥ 12 years and ≥ 40 kg.

The Office of Clinical Pharmacology has reviewed the information contained in BLA 761234. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized in the table below.

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
Pivotal or supportive evidence of effectiveness	The evidence of the effectiveness of nivolumab-relatlimab FDC comes from Study CA224047. The primary endpoint of progression-free survival (PFS) was statistically significant for nivolumab-relatlimab FDC vs nivolumab monotherapy with median PFS of 10.1 months in the nivolumab-relatlimab FDC arm (95% CI: 6.4, 15.7) and 4.6 months in the nivolumab arm (95% CI: 3.4, 5.6). The estimated stratified PFS hazard ratio was 0.75 (95% CI: 0.62, 0.92). The combination of nivolumab and relatlimab in the FDC arm in Study CA224047 demonstrates improvement in efficacy over single agent nivolumab.
General dosing instructions	The recommended dosage regimen of nivolumab-relatlimab FDC is: Adult patients and pediatric patients 12 years of age or

	older who weigh at least 40 kg: 480 mg nivolumab and 160 mg relatlimab Q4W administration as an intravenous infusion over 30 minutes
Dosing in patient subgroups (intrinsic and extrinsic factors)	Pediatric patients ≥ 12 years and ≥ 40 kg: The Applicant proposed (b) (4) However, FDA recommends the same adult flat dosing regimen of nivolumab-relatlimab FDC in adolescents with BW ≥ 40 kg given that (1) no adolescent PK or efficacy/safety data for relatlimab are available, (2) (b) (4) (3) a flat exposure-safety relationship was identified for relatlimab up to 1440 mg Q4W in combination with nivolumab and (4) flat exposure-safety relationship for nivolumab in the dose range of 0.1 – 10 mg/kg Q2W. Race and Ethnicity: The effects of race on the PK of nivolumab and relatlimab have not been adequately characterized as approximately 92% and 95% of the patients were White in the population PK analysis datasets for nivolumab and relatlimab, respectively. Renal and Hepatic Impairment: Population PK analyses suggest that the exposures of nivolumab and relatlimab were similar among patients with mild or moderate hepatic or renal impairment compared with patients with normal organ function who were treated with nivolumab and relatlimab.
Immunogenicity	In Study CA224047, the incidences of treatment-emergent (TE)-ADA and neutralizing antibodies (NAb) against nivolumab and relatlimab were low. Following treatment with nivolumab-relatlimab FDC, the incidence of TE-ADA of nivolumab was 3.8% (11/288) compared to 5.9% (16/272) following the treatment of nivolumab monotherapy; and the incidence of TE-ADA against

	relatlimab was 5.6% (16/286). Following the treatment with nivolumab-relatlimab FDC, only one patient developed TE-NAb against nivolumab or TE-NAb against relatlimab. Also, only one patient developed TE-NAb against nivolumab following administration of nivolumab monotherapy. The effects of TE-ADAs and TE-NAbs on the exposures of nivolumab and relatlimab, safety or efficacy are inconclusive due to their low incidences.
Labeling	The Applicant and FDA have reached an agreement on the FDA and Applicant proposed revisions to the labeling.

6.2.Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

Mechanism of Action

Nivolumab and relatlimab are ICIs. LAG-3 is a T cell receptor that binds to its ligands, such as MHC Class II, and regulates an inhibitory immune pathway that inhibits T cell proliferation, effector function and cytokine production, and the development of memory T cells. Relatlimab is a human IgG4 monoclonal antibody that binds to the LAG-3 receptor and releases the LAG-3 mediated inhibition of immune response by blocking interaction with its ligands. Relatlimab as a single agent exhibits modest in vitro functional activity in restoring effector function of exhausted T cells, promoting cytokine signaling and, ultimately, an anti-tumor response.

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

PD-1 and LAG-3, two distinct inhibitory immune checkpoint pathways, act synergistically on effector T cells, leading to the development of T-cell exhaustion and impaired cytotoxic function. In preclinical studies, combined nivolumab (anti-PD-1) and relatlimab (anti-LAG3) mediated inhibition enabled T-cell activation, increased IFNγ production, and restored effector function of exhausted T cells, more than the effects of either antibody alone. LAG-3 blockade potentiated the anti-tumor activity of PD-1 blockade in murine syngeneic tumor models, inhibiting tumor

growth and promoting tumor regression. Clinical data are consistent with these results, suggesting that an enhanced T-cell activation of combined relatlimab and nivolumab mediates an improved anti-tumor immune response compared to nivolumab monotherapy.

Pharmacokinetics

Relatlimab exhibits nonlinear and time-varying PK. Nonlinearity in relatlimab PK represents ~31% of total relatlimab CL at the recommended dose of relatlimab 160 mg Q4W when given in combination with nivolumab 480 mg Q4W. Relatlimab Cavg1 increased dose proportionally at doses ≥ 160 mg Q4W. Following rela 160 mg + nivo 480 mg Q4W administration, steady-state concentrations of relatlimab are reached by ~16 weeks with ~2-fold systemic accumulation. Approximately 97% of Cmaxss achieved with the proposed dosing regimen is predicted to be eliminated in 68.6 days. Relatlimab baseline CL in subjects receiving relatlimab monotherapy and nivo + rela SAV (when given sequential or coadministered) was similar to subjects receiving nivo+rela FDC (≤ 5% and ≤ 18%, respectively).

Nivolumab PK has been previously well-characterized to support the approval of nivolumab in multiple indications and tumor types, including advanced metastatic melanoma. In this application, nivolumab PK was characterized when given in combination with relatlimab and described by a linear 2-compartment model with time-varying CL. Nivolumab baseline CL in subjects receiving nivolumab monotherapy or nivo + rela SAV was similar (≤ 5% difference) compared with subjects receiving nivo+rela FDC. The magnitude of the reductions in nivolumab CL over time were also similar between nivo+rela and nivolumab monotherapy with a maximal reduction of 21.1% in adult 1L melanoma subjects. Thus, no PK interaction between nivolumab and relatlimab was observed when these agents were given in combination.

Baseline body weight was found to have a potentially clinically relevant (> 20%) effect on relatlimab CL (Figure 14). The magnitude of the differences in exposure by body weight quartiles are not expected to be clinically relevant, given the observed flat relatlimab E-R relationship for efficacy and safety (Sections 6.3.2.1 and 6.3.2.2).

The FDA's Assessment:

FDA agrees with the Applicant's position on the pharmacokinetics of nivolumab and relatlimab.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

Table 19: Applicant - Predicted Relatlimab Exposures for All Subjects at Nivo+rela 240/80 mg Q2W or 480/160 mg Q4W

Exposure (µg/mL)	Nivo+rela 480/160 Q4W Geo. Mean (%CV) N = 1703	Nivo+rela 240/80 Q2W Geo. Mean (%CV) N = 1703	% Diff GM[a]
Cmin1	4.69 (56)	4.09 (42.2)	-12.8

Exposure (µg/mL)	Nivo+rela 480/160 Q4W Geo. Mean (%CV) N = 1703	Nivo+rela 240/80 Q2W Geo. Mean (%CV) N = 1703	% Diff GM[a]
Cmax1	41.2 (24.5)	20.6 (24.5)	-50
Cavg1	13.7 (28.3)	8.81 (24.5)	-35.7
Cmind28	4.69 (56)	7.08 (44.4)	51
Cavgd28	13.7 (28.3)	10.7 (27.4)	-21.9
Cminss	11.4 (71.6)	16.2 (59.6)	42.1
Cmaxss	55.5 (31.7)	38.4 (36.7)	-30.8
Cavgss	24.4 (48)	23.9 (47.6)	-2.05

[a] Percent difference calculated relative to the reference exposure for FDC 480/160 Q4W.
Cavg1 = average concentration after the first dose (Day 14 for Q2W; Day 28 for Q4W); Cmax1 = maximum concentration after the first dose; Cmin1 = minimum concentration after the first dose (Day 14 for Q2W; Day 28 for Q4W)

Table 20: Applicant - Predicted Peripheral Relatlimab Receptor Occupancy for Melanoma Subjects at Nivo+rela 240/80 mg Q2W or 480/160 mg Q4W

Receptor Occupancy or Exposure (µg/mL)	Nivo+rela 240/80 Q2W Geo. Mean (%CV) N = 907	Nivo+rela 480/160 Q4W Geo. Mean (%CV) N = 907	% Diff GM[a]
ROtrough1(%)	61.7 (18.6)	61.9 (24.2)	-0.323
ROavg1 (%)	74 (8.78)	78.3 (9.32)	-5.49
ROtroughss (%)	81.2 (12.6)	74.1 (20.1)	9.58
ROavgss (%)	85.2 (7.84)	84.3 (8.76)	1.07

[a] Percent difference calculated for 240/80 Q2W relative to the reference RO and exposure for 480/160 Q4W.
ROtrough1 = minimum peripheral RO after the first dose (Day 1 to 14 for Q2W; Day 1 to 28 for Q4W)
ROavg1 = average peripheral RO after the first dose (Day 14 for Q2W; Day 28 for Q4W)

The Applicant's Position:

The proposed dose of nivo+rela FDC in adult patients ≥ 18 years is 480/160 mg Q4W administered by IV infusion over ~30 minutes.

The proposed dose of nivo+rela FDC in pediatric patients ≥ 12 years and weighing at least 40 kg [redacted] (b) (4) Q4W administered by IV infusion over ~30 minutes.

Selection of the Doses and Regimen

In Phase 1/2b study CA224020, multiple doses, regimens, and administration types were studied. Initially in Parts B and C, nivo+rela was administered by sequential infusion (nivolumab first, followed by relatlimab SAV infusion within 15 to 30 minutes). As the study progressed, in Parts D and E, nivolumab and relatlimab SAV were mixed in the same infusion bag and administered over

approximately 60 minutes (coadministration). In addition, the FDC of nivo+rela was administered in Part D1 and chosen for pivotal study CA224047.

A flat dose regimen of nivolumab 240 mg Q2W or 480 mg Q4W is the approved therapeutic dose for advanced melanoma. Given the flat dosing of nivolumab, and in the interest of patient convenience, a flat dose of nivo+rela was assessed in Phase 1/2 study CA224020.

Based on preliminary data from CA224020 Part B (nivo+rela dose escalation), the initial dose selected for expansion cohorts (including melanoma subjects) in Part C was nivo 240 mg + rela 80 mg Q2W, which induced responses in heavily previously treated subjects with advanced solid tumors. As the less frequent relatlimab 160 mg Q4W dose provides similar Cavgss (Table 19) and peripheral RO (Table 20) to that of relatlimab 80 mg Q2W, the Q4W dosing regimen was chosen for evaluation in the pivotal study CA224047. In order to ensure dose optimization, extensive clinical safety and efficacy data with nivo+rela 240/80 mg Q2W, 480/160 mg Q4W, and 480/480 mg Q4W regimens in metastatic melanoma were generated.

The FDC drug product was developed to facilitate convenient preparation, efficient administration, and decrease potential dosing errors.

Confirmation of the Dose and Schedule

Clinical efficacy and safety data from the pivotal study CA224047 confirmed the benefit-risk of the proposed dose in adult melanoma subjects (Table 41). The benefit-risk of nivo+rela 480/160 mg Q4W regimen is supported by E-R efficacy and E-R safety analyses performed using data from 1L and prior-IO melanoma patients (Sections 6.3.2.1 and 6.3.2.2). The proposed (b) (4) The shorter than studied relatlimab infusion of time of 30 min is proposed as it will offer convenience to patients, caregivers, and healthcare providers and is supported by lack of associations between dose and infusion or hypersensitivity reactions, higher studied infusion rates (up to 1440 mg over 60 minutes), and PPK analyses (Section 6.3.2.2).

The FDA's Assessment:

The effectiveness of nivolumab-relatlimab FDC product in previously untreated adult patients with unresectable, metastatic melanoma has been demonstrated in Study CA224047.

The proposed dosing regimen of nivolumab-relatlimab FDC in adult patients is supported by the following:

- A wide dosage range of relatlimab has been evaluated from dose-finding cohorts in

Study CA224020 to characterize the dose- and exposure-response relationships for activity and safety
  - Relatlimab monotherapy: 20 – 800 mg Q2W
  - In combination regimen: nivolumab 20 – 240 Q2W and relatlimab 160 – 1440 Q4W
- Model predicted peripheral LAG-3 receptor occupancy on CD8+ effector memory T cells at steady state were 74.1% at trough concentration (C_{trough}) and 84.3% at average concentration (C_{avg}) following the administration of nivolumab 480 mg and relatlimab 160 mg Q4W.
- Flat dose-response for ORR and PFS between nivolumab 480/relatlimab 160 mg vs nivolumab 480/ relatlimab 480 mg Q4W. In Study CA224020 Part E, nivolumab 480/ relatlimab 480 mg Q4W did not provide significantly greater clinical benefit, reflected as an increased ORR or PFS, compared with nivolumab 480/relatlimab 160 mg Q4W in patients who have not received prior systemic anticancer therapy for unresectable or metastatic melanoma (Table 21).

Table 21: ORR and PFS between 160/480 vs 480/480 mg Q4W in treatment naïve melanoma patients in Study CA224020 Part E

	Nivolumab 480/relatlimab 160 mg Q4W N = 34	Nivolumab 480/relatlimab 480 mg Q4W N = 36
ORR per BICR		
N responders (%)	11 (32.4)	12 (33.3)
95% CI	(17.4, 50.5)	(18.6, 51.0)
BICR-assessed PFS, months		
Events, n (%)	9 (26.5)	12 (33.3)
Median (95% CI)	Not reached	11.1 (3.55, -)

Source: Study CA224020 CSR
BICR: Blinded Independent Central Review

- Flat exposure-response relationship for safety events (Grade ≥ 2 immune-mediated adverse reactions (IMARs) and Grade ≥ 2 ARs) across relatlimab exposure range using pooled data from Study CA224020 and CA224047.
- Nivolumab is indicated for the treatment of unresectable or metastatic melanoma as a single agent or in combination with ipilimumab. The recommended dosing regimen is 240 mg Q2W or 480 mg Q4W by IV infusion over 30 minutes.

- In Study CA224020 and CA224047, relatlimab was administered as monotherapy or in combination with nivolumab over 60 minutes infusion duration. Model simulations suggest that there is no significant exposure difference of relatlimab between 30 and 60 mins infusion duration.
- Incidence of IRRs/infusion related hypersensitivity were generally low and similar across dose levels in Study CA224047 and CA224020 (Table 22 and Table 23).

Table 22: Incidence of IRRs and infusion related hypersensitivity in Study CA224047

Patient number (%)	FDC (N = 355)		Nivo Mono (N = 359)	
	All Grade	Grade 3	All Grade	Grade 3
Infusion Related Reactions	21 (6)	0	13 (4)	1 (0.3)
Hypersensitivity (infusion related reaction)	4 (1.1)	0	4 (1.1)	0

Source: FDA analysis

Note: No drug withdrawal in the nivolumab-relatlimab FDC arm and 2 drug withdrawals in nivolumab monotherapy arm due to IRRs; no dose reductions due to IRRs.

Table 23: Incidence of IRRs and infusion related hypersensitivity in Study CA224020

	Nivolumab/relatlimab dose level (mg)							
Patient number (%)	**480/1440 (N = 19)**		**480/480 (N = 133)**		**480/320 (N = 8)**		**480/240 (N = 8)**	
	All Grade	Grade 3	All Grade	Grade 3	All Grade	Grade 3	All Grade	Grade 3
Infusion Related Reactions	1 (5)	0	5 (4)	0	1 (13)	0	1 (13)	0
Hypersensitivity (infusion related reaction)	0	0	0	0	0	0	0	0
	240/240 (N = 8)		**480/160 (N = 412)**		**240/80 (N = 743)**		**240/20 (N= 9)**	
	All Grade	Grade 3	All Grade	Grade 3	All Grade	Grade 3	All Grade	Grade 3

Infusion Related Reactions	2 (25)	0	8 (2)	0	44 (6)	0	1 (11)	0
Hypersensitivity (infusion related reaction)	0	0	3 (0.7)	1 (0.2)	7 (0.9)	0	0	0

Source: FDA analysis

Note: No IRRs/infusion related hypersensitivity reactions reported in cohorts: 960/480 mg (n = 17), 160/240 mg (n = 8) and 20 /80 mg (n = 7);

Only two drug withdrawals due to IRRs in Cohort 80/240 mg; no dose reductions due to IRRs.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

There were no clinically relevant effects (defined as a < 20% effect) on nivolumab or relatlimab PK of the intrinsic or extrinsic factors evaluated; these included age, sex, race, albumin (relatlimab only), LDH, ECOG status, renal function (measured eGFR) and hepatic function (Section 6.3.2.3); therefore, therapeutic individualization of nivo+rela FDC based on these factors is not required.

Baseline body weight was found to have a potentially clinically relevant (> 20%) effect on nivolumab and relatlimab PK and albumin had a > 20% effect on nivolumab PK. These effects are not expected to be clinically relevant given the flat E-R relationships for efficacy and safety seen for nivolumab and relatlimab. Therefore, no dose adjustment is recommended in adults.

In adolescents subjects ≥ 12 years and ≥ 40 kg, (b) (4) Refer to Section 6.3.2.2 for the dose justification in adults and adolescents.

The FDA's Assessment:

- Population PK analyses for nivolumab suggest that
  - The effects of eGFR, age (1 to 92 years), ECOG performance status, and sex on nivolumab baseline CL were statistically significant; however, they were not considered clinically relevant (<20%). The impact effect of race on the pharmacokinetics of nivolumab alone and nivolumab in combination with relatlimab is unknown as >90% of study participants were White.
  - Nivolumab baseline CL values were similar in patients with previously untreated melanoma and in patients with melanoma previously treated with an IO therapy receiving nivolumab monotherapy, nivolumab and relatlimab SAV or nivolumab-relatlimab FDC.
  - Baseline body weight and albumin levels were found to have >20% effect on

nivolumab CL. Adolescent patients had 36% lower baseline CL than those of adult patients when the effect of body weight was taken into account.
  - The predicted exposures of nivolumab were similar among patients with different hepatic and renal impairment status (normal, mild or moderate).
- Population PK analyses for relatlimab suggest that
  - Age (17 – 92 years), sex, Eastern Cooperative Oncology Group (ECOG) performance status, estimated glomerular filtration rate (eGFR), baseline lactate dehydrogenase (LDH), patient population (1L melanoma, melanoma previously treated with an IO therapy, and other tumor types), and drug product (FDC, single agent vial (SAV) coadministration, SAV sequential administration, relatlimab monotherapy) were statistically significant covariates; however, the magnitude of the differences was not considered to be clinically relevant (≤ 20%).
  - Clearance (CL), volume of distribution of the peripheral compartment (V_P), and volume of distribution of the central compartment (V_C) of relatlimab were higher in patients with higher baseline body weight.
  - Manufacture processes ((b) (4) Process (b) (4)), LAG-3 expressions, hepatic impairment (mild and moderate), renal impairment (mild and moderate) were not statistically significant covariates on the PK of relatlimab.
- The exposure-response relationship for PFS was flat across the relatlimab exposure ranges of the tested combination dosing regimens (nivolumab 480 mg and relatlimab 160 mg Q4W, nivolumab 240 mg and relatlimab 80 mg Q2W, and nivolumab 480 mg and relatlimab 480 mg Q4W).
- Objective response rate (ORR) was positively associated with relatlimab exposure (C_{avgd28}). Predicted probability of ORR was higher with nivolumab 480 mg + relatlimab 480 mg Q4W compared with nivolumab 240 mg + relatlimab 80 mg Q2W and nivolumab 480 mg + relatlimab 160 mg Q4W8. Despite the trend towards higher ORR with higher exposure, it should be noted that ORR lacks the associated DOR considered to be of clinical benefit.
- The risk of Grade ≥2 IMARs was predicted to be higher in the nivolumab + relatlimab combination treatment regimens compared to nivolumab monotherapy; however, the risk of Grade ≥2 IMARs was not increased by higher relatlimab dosage (480 mg vs. 160 mg Q4W) in the combination regimens.
- The risk of Grade ≥3 ARs was positively associated with relatlimab exposure, resulting in a higher risk in nivolumab + relatlimab combination compared with nivolumab monotherapy. Nivolumab exposure was not evidently associated with the risk of Gr3+ ARs. The risk was similar across the range of relatlimab exposures (Cavgd28) produced by the studied combination dosing regimen in Studies CA224020 and CA224047, suggesting a flat exposure-response relationship for Grade ≥ 3 ARs over this exposure range.

- FDA had concern for potential subtherapeutic dosing in adolescents with body weight (BW) ≥ 40 kg at the proposed dosage of [redacted] (b) (4) due to no pediatric data in relatlimab, uncertainties in extrapolating the adolescent effects on the PK of relatlimab based on nivolumab data and large safety margin of relatlimab in clinical studies. FDA recommends the same adult flat dosing regimen of nivolumab-relatlimab FDC in adolescents with BW ≥ 40 kg . Refer to section 6.3.2.2 for more details.

6.2.2.3. Outstanding Issues

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

6.3.Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Table 24: Applicant - General Pharmacology and Pharmacokinetic Characteristics

Physicochemical Properties	
Chemical structure and molecular weight	BMS-986213 is a FDC product of nivolumab and relatlimab. Nivolumab is a human IgG4 PD-1-specific mAb with a molecular weight of 146 kDa. Relatlimab is a human IgG4 LAG-3-specific mAb with a molecular weight of 148 kDa.
Administration, formulation type, strengths	Nivo+rela FDC is available in a 20 mL vial containing 240 mg nivolumab and 80 mg relatlimab to be administered through IV infusion over 30 min.
Pharmacology	
Mechanism of Action	See Section 6.2.1.
PD	**Receptor Occupancy:** The relationship between peripheral RO and relatlimab serum concentration follows a hyperbolic (Emax) relationship with an EC50 of 1.95 µg/mL (RSE: 11%) and Emax of 94.1% (RSE: 1.64%). The Cmin and time-averaged RO with 160 mg Q4W relatlimab after first dose is predicted to be 61.9% and 78.3%, respectively and at steady-state the corresponding values are predicted to be 74.1% and 84.3%, respectively. Nivolumab has been shown to saturate peripheral RO at doses well below 480 mg Q4W.[21] **Soluble LAG-3:** A rela dose-dependent decrease in unbound LAG-3 in the blood (sLAG-3) was observed with nivo + rela SAV combination therapy with Q2W and Q4W regimens (Table 25). In CA224047, decreases in sLAG-3 were observed in subjects treated with nivo+rela FDC, indicating a rela specific PD effect. **IFNγ/IFNγ-inducible chemokines:** In CA224020, no consistent treatment-induced changes were observed for serum IFNγ or IFNγ-inducible chemokines in subjects treated with rela monotherapy, with the exception of modest median increases in CXCL9 seen at C1D29 compared to baseline for rela doses of 80 mg (17.49%), 240 mg (2.99%), and 800 mg (21.13%). In subjects treated with nivo + rela SAV, however, consistent increases in IFNγ (median increases of 87.50 - 204.88% in CA224020 Part B Q4W dose escalation cohort) and IFNγ-inducible chemokines (CXCL9, CXCL10 and IL-2Rα) were observed;

however, these did not appear to be dose-dependent. The level of IFNγ increased across three Part D1 cohorts: nivo+rela 240/80 mg Q2W (65.53%), 480/160 mg Q4W coadministration (52.38%), and 480/160 mg Q4W FDC (32.26%). Overall, no significant difference in other PD changes (sLAG3 and IFNγ-inducible chemokines) was observed between these cohorts (Table 25).

In CA224047, IFNγ in the blood increased with administration of nivo+rela FDC and nivolumab monotherapy; the increases were approximately 2-fold higher in the nivo+rela FDC arm vs the nivolumab monotherapy arm (Table 25). These data are supportive of nivo+rela FDC induced increases in T cell activation and IFNγ production and increased clinical benefit relative to nivolumab monotherapy.

No significant differences in PD changes (sLAG3 and IFNγ or IFNγ-inducible chemokines) were observed in subjects treated with nivo + rela SAV 240/80 mg Q2W or 480/160 mg Q4W coadmin or nivo+rela FDC in Part D1 of CA224020 (Table 25).

Table 25: Applicant - Summary of sLAG-3 and IFNγ in Studies CA224020 and CA224047

	CA224020			CA224047			
	Nivo+rela 240/80 mg Q2W (Coadmin)	**Nivo+rela 480/160 mg Q4W (Coadmin)**	**Nivo+rela 480/160 mg Q4W FDC**	**Nivo+rela 480/160 mg Q4W FDC**		**Nivo 480 mg Q4W**	
	C1D29	C1D29	C1D29	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose
sLAG-3							
Median change	-55.65%	-56.00%	-62.14%	-20.2%	-42.8%	14.9%	10.3%
IFNγ							
Median change	65.53%	52.38%	32.26%	105.6%	108.0%	56.3%	50.7%

CD4+ and CD8+ T cell subsets: No apparent treatment-induced changes in T cell subsets were detected in subjects treated with rela monotherapy at doses up to 800 mg. Consistent trends of increases in proliferating and activated CD4+ and CD8+ central and effector memory T cell subsets on Day 8 were observed after the first dose of combination treatment over the rela SAV 20 mg + nivo 80 mg to rela SAV 160 mg + nivo 480 mg dose ranges.

QT/QTc Prolongation	Nivo+rela had no clinically relevant effect on the QTc interval duration and there was no apparent relationship between serum relatlimab concentration and change in QTcF interval duration in patients with solid tumors.
General Information	
Bioanalysis	The assay to determine serum nivo concentrations was precise and accurate, with a quantitation range of 0.2 to 6.5 µg/mL. The presence of rela at 200 µg/mL (or a ratio of 333:1 [200:0.6 µg/mL] of rela:nivo) in serum did not interfere with

	nivo quantitation. In the samples tested for nivo concentrations, the highest observed concentration of relatlimab was < 200 µg/mL. The assay to determine serum rela concentration was precise and accurate with a quantitation range of 50 to 3200 ng/mL. The presence of nivo at 300 µg/mL (or a ratio of 2000:1 [300:0.15 µg/mL] of nivo:rela) in serum did not interfere with rela quantitation. In the samples tested for rela concentrations, the highest observed concentration of nivo was < 300 µg/mL.
Dose or exposure range tested in clinical trials	Relatlimab monotherapy (Q2W): 20 to 800 mg Nivo + rela SAV (Q2W): 80+20 to 240+240 mg; Nivo + rela SAV (Q4W): 480+160 to 480+1440 mg (See Table 29) Nivo+rela FDC (Q4W): 480+160 mg
Max Tolerated Dose	MTD was not reached with relatlimab as monotherapy or in combination with nivolumab.
Exposures at Proposed Dose Regimen	Steady-state concentrations of relatlimab are reached by 16 weeks. **Table 26: Applicant - Geometric Mean (CV%) of Relatlimab Exposures at Proposed Nivo+rela 480/160 mg Q4W Dose**

	Cmax1 (µg/mL)	Cmin1 (µg/mL)	Cavg1 (µg/mL)	Cmaxss (µg/mL)	Cminss (µg/mL)	Cavgss (µg/mL)
Previously untreated MEL (reference population), N = 333	44.4 (23.3)	5.7 (49.5)	14.8 (25.3)	62.2 (30.1)	15.3 (64.3)	28.8 (44.8)

Abbreviations: Cavg = average concentration; Cmax = maximum concentration; Cmin = minimum concentration (1 = after the first dose and ss = at steady state).

Dose Proportionality	The PPK based dose proportionality assessment indicate a dose proportional increase in relatlimab Cavg1 after the first dose at doses ≥ 160 mg Q4W. **Table 27: Applicant - Summary of Predicted Dose-Normalized Relatlimab Exposures and Accumulation Ratio by Dose**

Dose	N	Dose-normalized Cavg1 (µg/mL/mg dose)[a]	Dose-normalized Cavg,ss (µg/mL/mg dose)[a]	RAC[b]
20 mg Q2W	21	0.099 (31.4)	0.17 (60.4)	1.72 (30.8)
80 mg Q2W	736	0.103 (24.7)	0.265 (46.9)	2.58 (29.1)
160 mg Q2W	8	0.129 (25.1)	0.376 (39)	2.93 (34.7)
240 mg Q2W	12	0.11 (24.2)	0.323 (38.2)	2.94 (23.8)
800 mg Q2W	8	0.123 (25.9)	0.384 (31.9)	3.11 (11.2)
160 mg Q4W	734	0.0921 (26.3)	0.172 (46.9)	1.87 (26.5)
240 mg Q4W	8	0.0784 (45.3)	0.133 (66.9)	1.69 (25.4)

	320 mg Q4W	8	0.0915 (21.7)	0.158 (39.1)	1.73 (25.6)
	480 mg Q4W	132	0.0978 (27.2)	0.189 (41.4)	1.93 (21.6)
	960 mg Q4W	17	0.104 (19.1)	0.187 (27.7)	1.8 (14.4)
	1440 mg Q4W	19	0.113 (24.4)	0.24 (42.6)	2.13 (26.7)
	[a] Dose normalized concentration calculated as µg/mL per mg of dose. [b] RAC = Cavg,ss/Cavg1 In CA224047, nivolumab geometric mean Cmin,ss in the nivo+rela FDC arm was similar to the nivolumab arm with a geometric mean ratio of 0.931 (95% CI: 0.855–1.013). In CA224020, nivolumab exposures (Ceoi and Ctrough) and relatlimab exposures (Cmax and AUC(TAU)) were similar in nivo + rela SAV coadministration and nivo+rela FDC with geometric mean ratios (nivo + rela SAV to FDC) were of approximately 1.0.				
Accumulation	As predicted following nivo 480 mg + rela 160 mg Q4W at steady-state (by PPK analyses), the relatlimab accumulation index is ~2-fold.				
Distribution	The geometric mean (CV%) of the Vss of nivolumab is 6.65 L (19.2%) and relatlimab is 6.65 L (19.8%).				
Metabolism	Nivolumab and relatlimab are mAbs that are expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.				
Elimination: Terminal half-life and CL	Nivolumab CL decreases over time, with a mean maximal reduction from baseline (CV%) of 21.1% (16.3%) [geometric mean CL (CV%), 7.57 mL/h (40.1%) at steady state and 9.59 mL/h (40.3%) after the first dose] and the terminal t1/2 (CV%) is 26.5 days (36.4%). Relatlimab CL decreases over time, with a mean maximal reduction from baseline (CV%) of 9.7% (26.2%) [geometric mean CL (CV%), 5.48 mL/h (41.3%) at steady state and 6.06 mL/h (38.9%) after the first dose]. Approximately 97% of the maximum steady-state concentration is predicted to be eliminated by 68.6 days.				
Immunogenicity	Assays for nivo ADA and NAb are drug tolerant up to 800 µg/mL and 400 µg/mL of nivo concentrations in samples, respectively. In clinical study samples, nivolumab concentrations were less than 200 µg/mL at time-points where ADAs were measured, thus the assay demonstrated appropriate drug tolerance. The presence of relatlimab at 200 µg/mL in serum did not interfere with the detection of the nivolumab ADA and NAb. In clinical study samples tested for nivo ADA and NAb, concentrations of rela were generally less than 200 µg/mL. Assays for rela ADA and NAb are drug tolerant up to 100 µg/mL of rela concentrations in samples. The rela concentrations in clinical samples assayed for rela ADA were less than 100 µg/mL, except for dosing regimens of 800 mg Q2W, 960 mg Q4W, and 1440 mg Q4W in Study CA224020, in which rela concentrations were generally less than 200 µg/mL at trough time-points where ADA and NAb were measured. The presence of nivo at 300 µg/mL and 200 µg/mL in serum did not				

	interfere with the detection of rela ADA and NAb respectively. In clinical study samples tested for rela ADA and NAb, concentrations of nivo were less than 200 µg/mL. Following nivo+rela FDC administration, the incidence of treatment emergent anti-nivo ADA and NAb and anti-rela ADA and NAb are low and has no apparent impact on safety and efficacy (Section 8.2.4.11). Based on PPK analyses, immunogenicity has no clinically meaningful effect on the PK of nivo and rela.

The Applicant's Position:

The pharmacology and clinical PK of relatlimab as monotherapy or in combination with nivolumab is well characterized and supports the pharmacology and clinical PK understanding of nivo+rela FDC.

The FDA's Assessment:

The FDA's assessment of nivolumab-relatlimab FDC for general pharmacology and pharmacokinetic characteristics is summarized in the table below.

Physicochemical Properties	
Chemical structure and molecular weight	FDA agrees with the Applicant's position.
Administration, formulation type, strengths	FDA agrees with the Applicant's position.
Pharmacology	
Mechanism of Action	FDA agrees with the Applicant's position.
PD	**LAG-3 peripheral receptor occupancy:** In Study CA224020, relatlimab demonstrated a dose-dependent increase in LAG-3 receptor occupancy on CD8+ T cells. The percentages of receptor occupancy at C_{trough} on C1D29 were comparable following administration of nivolumab + relatlimab 240/80 mg Q2W, 480/160 mg Q4W coadministration, and 480/160 mg Q4W FDC.

	Median Levels of LAG-3 Receptor Occupancy in Part B, Part D, and Part E in Study CA224020 **Rela+Nivo Dose** / **N** / **RO (%)** **Q4W (Cycle 1, Day 29)** 160/480 mg — 65 — 66.880 480/480 mg — 12 — 81.025 960/480 mg — 12 — 94.165 1440/480 mg — 8 — 103.050 *Source: Study CA224020 CSR* Model predicted peripheral LAG-3 receptor occupancy on CD8+ effector memory T cells at steady state were 74.1% at C_{trough} and 84.3% at C_{avg} following the administration of nivolumab 480 mg and relatlimab 160 mg Q4W. **Soluble LAG-3:** FDA agrees with the Applicant's position.
QT/QTc Prolongation	As monoclonal antibodies, nivolumab and relatlimab are not expected to cause QT/QTc prolongation. Therefore, QT evaluation for nivolumab-relatlimab FDC is not required.
General Information	
Bioanalysis	Enzyme-linked immunosorbent assay (ELISA), chemiluminescence was used to quantify nivolumab and relatlimab serum concentrations. The presence of nivolumab at 300 µg/mL (or a ratio of 2000:1 [300:0.15 µg/mL] of nivolumab: relatlimab) in serum did not interfere with relatlimab quantitation. The presence of relatlimab at 200 µg/mL (or a ratio of 333:1 [200:0.6 µg/mL] of relatlimab :nivolumab) in serum did not interfere with nivolumab quantitation. In Study CA224020 and CA224047, nivolumab concentrations were > 300 µg/mL and relatlimab concentrations were > 200 µg/mL in some patient samples; however, the concentration ratios of nivolumab and relatlimab were within the limits that the presence of nivolumab or relatlimab did not interfere with quantitation of nivolumab or relatlimab.
Dose or exposure range tested in clinical trials	FDA agrees with the Applicant's position.
Max Tolerated	FDA agrees with the Applicant's position.

<table>
<tr><td>Dose</td><td></td></tr>
<tr><td>Exposures at Proposed Dose Regimen</td><td>FDA agrees with the Applicant's position.</td></tr>
<tr><td>Dose Proportionality</td><td>The PPK based dose proportionality assessment indicated a dose proportional increase in relatlimab C_{avg1} after the first dose at doses ≥ 160 mg Q4W.
Applicant's Summary of Predicted Dose-Normalized Relatlimab Exposures and Accumulation Ratio by Dose
<table>
<tr><th>Dose</th><th>N</th><th>Dose-normalized Cavg1 (µg/mL/mg dose)[a]</th><th>Dose-normalized Cavgss (µg/mL/mg dose)[a]</th><th>RAC[b]</th></tr>
<tr><td>20 mg Q2W</td><td>21</td><td>0.099 (31.4)</td><td>0.17 (60.4)</td><td>1.72 (30.8)</td></tr>
<tr><td>80 mg Q2W</td><td>736</td><td>0.103 (24.7)</td><td>0.265 (46.9)</td><td>2.58 (29.1)</td></tr>
<tr><td>160 mg Q2W</td><td>8</td><td>0.129 (25.1)</td><td>0.376 (39)</td><td>2.93 (34.7)</td></tr>
<tr><td>240 mg Q2W</td><td>12</td><td>0.11 (24.2)</td><td>0.323 (38.2)</td><td>2.94 (23.8)</td></tr>
<tr><td>800 mg Q2W</td><td>8</td><td>0.123 (25.9)</td><td>0.384 (31.9)</td><td>3.11 (11.2)</td></tr>
<tr><td>160 mg Q4W</td><td>734</td><td>0.0921 (26.3)</td><td>0.172 (46.9)</td><td>1.87 (26.5)</td></tr>
<tr><td>240 mg Q4W</td><td>8</td><td>0.0784 (45.3)</td><td>0.133 (66.9)</td><td>1.69 (25.4)</td></tr>
<tr><td>320 mg Q4W</td><td>8</td><td>0.0915 (21.7)</td><td>0.158 (39.1)</td><td>1.73 (25.6)</td></tr>
<tr><td>480 mg Q4W</td><td>132</td><td>0.0978 (27.2)</td><td>0.189 (41.4)</td><td>1.93 (21.6)</td></tr>
<tr><td>960 mg Q4W</td><td>17</td><td>0.104 (19.1)</td><td>0.187 (27.7)</td><td>1.8 (14.4)</td></tr>
<tr><td>1440 mg Q4W</td><td>19</td><td>0.113 (24.4)</td><td>0.24 (42.6)</td><td>2.13 (26.7)</td></tr>
</table>
[a] Dose normalized concentration calculated as µg/mL per mg of dose.
[b] RAC = $C_{avg,ss}/C_{avg1}$
In CA224047, nivolumab geometric mean $C_{min,ss}$ values in the nivolumab-relatlimab FDC arm were similar to the nivolumab arm with a geometric mean ratio of 0.931 (95% CI: 0.855–1.013). In CA224020, relatlimab exposures (C_{max} and $AUC_{(TAU)}$) and nivolumab exposures (C_{eoi} and C_{trough}) were similar in nivolumab and relatlimab SAV coadministration and nivolumab-relatlimab FDC with geometric mean ratios (nivolumab and relatlimab SAV to FDC) were of approximately 1.0.</td></tr>
<tr><td>Accumulation</td><td>As predicted following nivolumab 480 mg and relatlimab 160 mg Q4W at steady-state (by PPK analyses), the relatlimab accumulation index is ~2-fold.</td></tr>
<tr><td>Distribution</td><td>The geometric mean (CV%) of the Vss is 6.6 L (19.2%) for nivolumab and 6.6 L (19.8%) for relatlimab, respectively.</td></tr>
<tr><td>Metabolism</td><td>FDA agrees with the Applicant's position.</td></tr>
</table>

Elimination: Terminal half-life and CL	Nivolumab CL decreases over time, with a mean maximal reduction from baseline (CV%) of 21.1% (16.3%) [geometric mean CL (CV%), 7.6 mL/h (40.1%) at steady state and 9.6 mL/h (40.3%) after the first dose] and the terminal t1/2 (CV%) is 26.5 days (36.4%). Relatlimab CL decreases over time, with a mean maximal reduction from baseline (CV%) of 9.7% (26.2%) [geometric mean CL (CV%), 5.5 mL/h (41.3%) at steady state and 6.1 mL/h (38.9%) after the first dose]. Approximately 97% of the maximum steady-state concentration is predicted to be eliminated by 68.6 days.
Immunogenicity	Bridging ligand-binding electrochemiluminescence immunoassay was used to quantify ADAs against nivolumab and relatlimab. Assays for nivolumab ADA and NAb are drug tolerant up to 800 µg/mL and 400 µg/mL of nivolumab concentrations in samples, respectively. The presence of relatlimab at 200 µg/mL in serum did not interfere with the detection of the nivolumab ADA and NAb. In Study CA224047 and CA224020, nivolumab trough concentrations > 800 µg/mL were not observed in one sample analyzed. In Study CA224047, no relatlimab trough concentrations > 200 µg/mL were observed in 1068 analyzed pre-dose samples. In Study CA224020, relatlimab trough concentration > 200 µg/mL in 18 samples among 5899 analyzed pre-dose samples. Assays for relatlimab ADA and NAb are drug tolerant up to 100 µg/mL of relatlimab concentrations in samples. The presence of nivolumab at 300 µg/mL and 200 µg/mL in serum did not interfere with the detection of relatlimab ADA and NAb respectively. In Study CA224047, arelatlimab trough concentration > 100 µg/mL was observed in one sample (135 µg/mL). In Study CA224020, a relatlimab trough concentration > 100 µg/mL was observed in 56 samples. Nivolumab trough concentration was > 300 µg/mL in one sample in Study CA224047 (418 µg/mL) and Study CA224020 (304 µg/mL), respectively. In Study CA224047, following FDC and nivolumab monotherapy administration, the incidence of treatment emergent ADAs against nivolumab and relatlimab are low and are lower than ADA+ rates reported in nivolumab USPI.

Patient # (%)	Nivolumab-relatlimab FDC	Nivolumab Mono

	Relatlimab (n = 286)	Nivolumab (n = 288)	n = 272
ADA+	16 (5.6)	11 (3.8)	16 (5.9)
NAb	1 (0.3)	1 (0.3)	1 (0.4)

The effect of ADAs on the PK, safety or efficacy of nivolumab-relatlimab FDC cannot be adequately assessed based on the low incidence rate.

Patient # (%)	**Nivolumab-relatlimab FDC**				**Nivolumab Monotherapy**	
	Relatlimab		Nivolumab			
	ADA+ (n = 16)	ADA- (n = 270)	ADA+ (n = 11)	ADA- (n = 277)	ADA+ (n = 16)	ADA- (n = 256)
IRR	0	21 (7.8)	1 (9.7)	20 (7.2)	0	13 (5.1)
Infusion related hypersensitivity	0	0	0	0	2	0

The effects of NAb against nivolumab and relatlimab on the PK, safety and efficacy of nivolumab-relatlimab FDC cannot be adequately assessed based on the low incidence rate.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Figure 5: Applicant - Model Predicted Hazard Ratio of PFS for Relatlimab Cavgd28 in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Nivolumab 480 mg Q4W Regimen

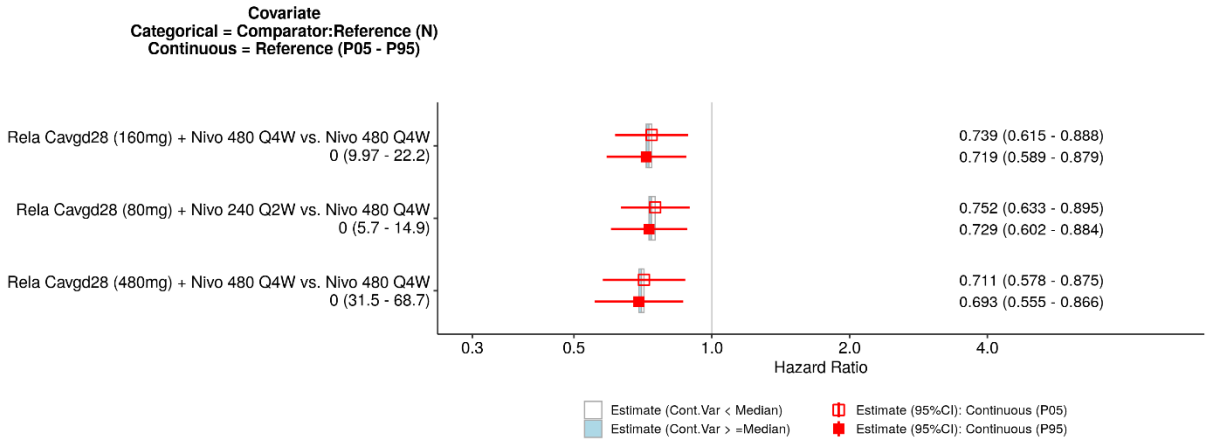


Figure 6: Applicant - Model Predicated Odds Ratio of OR for Relatlimab Cavgd28 in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Nivolumab 480 mg + Relatlimab 160 mg Q4W Regimen

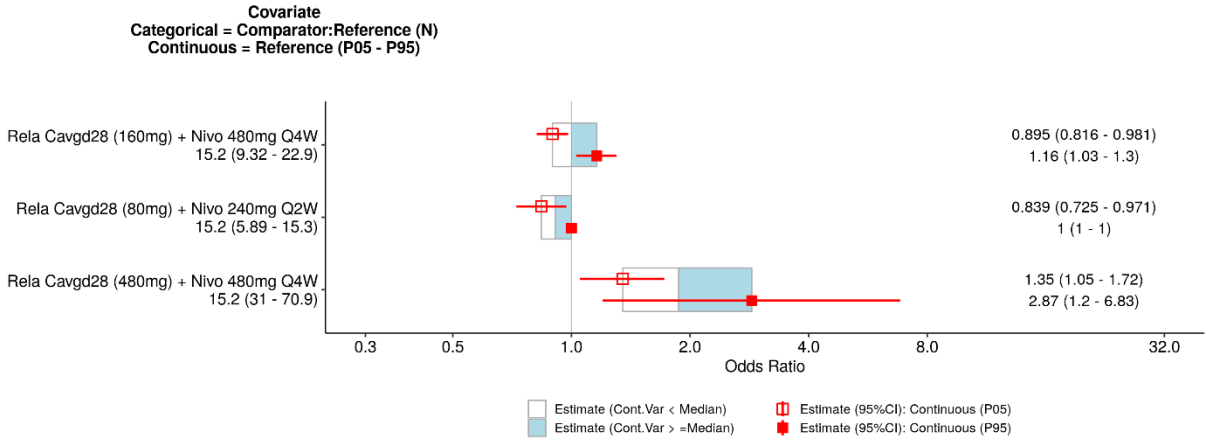


Figure 7: Applicant - Predicted Relatlimab Exposures for Adolescent Subjects at Subjects at (b) (4) (b) (4)

Figure 8: Applicant - Predicted Nivolumab Exposures for Adolescent Subjects at (b) (4) (b) (4)

The Applicant's Position:

The clinical pharmacology program, including E-R analyses for efficacy and PK based extrapolation of clinical efficacy to pediatrics patients, provides the supportive evidence of a clinically meaningful benefit of nivo+rela FDC in adults and pediatrics patients (≥ 12 years and weighing at least 40 kg) with unresectable or metastatic melanoma.

Evidence of effectiveness was obtained from pivotal study CA224047 in 714 subjects with previously untreated unresectable or metastatic melanoma (Section 8.1.2.8). Phase 1/2 study

CA224020 provides further supportive evidence of efficacy based on ORR (BICR), DOR, and PFS in subjects with previously untreated (1L) advanced melanoma at 240/80 mg Q2W and melanoma previously treated with IO therapy (prior-IO) receiving 240/80 mg Q2W and 480/160 mg Q4W (Section 8.1.4).

To support the clinical efficacy at the proposed dose of nivo+rela 480/160 mg Q4W, an E-R analysis of efficacy using PFS as a key primary analysis endpoint was conducted using pooled data from 1L and prior-IO melanoma patients enrolled in CA224047 and CA224020. Nivo+rela resulted in a significant reduction in the risk of disease progression or death due to any cause compared to nivolumab monotherapy, providing evidence for the contribution of relatlimab to efficacy (Figure 5). The improvement in efficacy was similar across the range of relatlimab exposures produced by the studied nivo+rela dosing regimens (240/80 mg Q2W, 480/160 mg Q4W, and 480/480 mg Q4W) suggesting a flat E-R relationship for PFS and supporting the proposed dose of relatlimab 160 mg Q4W.

In addition, an E-R analysis of efficacy using objective response as the endpoint was conducted using data from study CA224020 in 1L melanoma and prior-IO melanoma patients. The probability of OR was significantly associated with relatlimab exposure (Cavgd28), although the E-R relationship is relatively flat (Figure 6). Despite that observation, it is likely that the probability of having a response would be similar across the range of relatlimab exposures based on the following reasons: 1) wide 95% CI for predicted odds ratio at the 5th and 95th percentile of 480/480mg Q4W relatlimab exposures relative to median relatlimab Cavgd28 exposure with nivo + rela 480/160 mg Q4W (Figure 6) and 2) OR may not be a good indicator of clinical benefit as it lacks the DOR component. The PFS end point captures the DOR component and the flat E-R from PFS analysis indicates that there is no additional clinical benefit with the higher dose of 480/480 mg Q4W.

The proposed (b) (4)

Similar systemic exposures of nivolumab and relatlimab were achieved from both SAV and FDC drug product. This supports the bridging of clinical efficacy and safety data of Phase 1/2b study CA224020 to that of the pivotal Phase 3 study.

The FDA's Assessment:
FDA agrees with the Applicant's position on the supportive evidence of effectiveness provided by the exposure-response analyses for efficacy in adult patients.

FDA does not agree with the Applicant's extrapolation simulation results for relatlimab in pediatric patients. See Section 6.3.2.2 and 19.4.2 for additional details.

Nivolumab and relatlimab development in pediatrics

The clinical safety and efficacy of relatlimab were evaluated in Study CA224020 and CA224047. No pediatric patients were enrolled in these 2 studies.

An Agreed Initial Pediatric Study Plan (Agreed iPSP) for nivolumab in combination with relatlimab, in an FDC vial for the treatment of previously untreated metastatic or unresectable melanoma was issued on September 15, 2020. Summary of the Agreed iPSP:

- Proposal to evaluate nivolumab in combination with relatlimab in melanoma
  - PK-based extrapolation of efficacy in adolescent patients (≥ 12 to < 18 years) with melanoma. A model-based simulation will be performed to predict exposures in adolescent patients with melanoma and provide comparison with corresponding exposures from the target efficacious dose in the adult melanoma population.
  - A waiver in patients with melanoma aged < 12 years, as extrapolation of efficacy to these patients would not be appropriate given the biologic and molecular genetic differences between the disease in adults and in children less than 12 years of age.
- Proposal to evaluate nivolumab in combination with relatlimab in pediatric patients with Classical Hodgkin lymphoma (cHL) and Non-Hodgkin lymphoma (NHL)
  - The Applicant conducted a non-clinical, pediatric tumor biomarker study in both solid tumor and hematologic malignancies. LAG-3 expression was detected (≥1% expression) in only 1 of 55 samples of solid or brain tumors with the positive detection in an atypical teratoid rhabdoid tumor. In contrast, LAG-3 expression was detected in 27 of 36 samples from patients with lymphoma.
  - (b) (4)

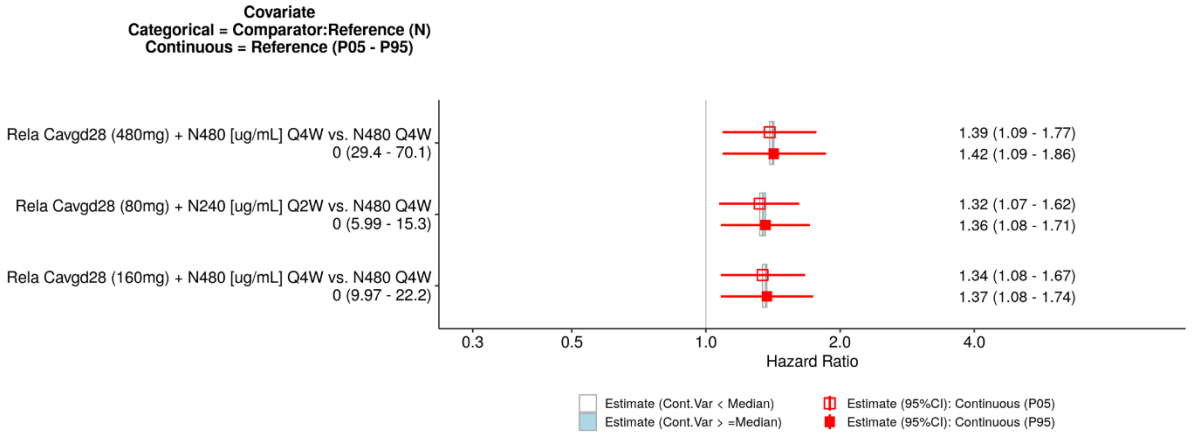
Based on the previous interactions with the FDA regarding the development of nivolumab and relatlimab in pediatrics, a PK-based extrapolation approach was proposed to match the exposure of nivolumab and relatlimab in adult patients to support the use of nivolumab-relatlimab FDC in adolescents. The rationale for this approach was based on the similarity of the disease in adult and adolescent patients with advanced melanoma, and the expected similarity in the response to treatment.

See also Section 6.3.2.2 for FDA's evaluation on the proposed dosing regimen in pediatric patients.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

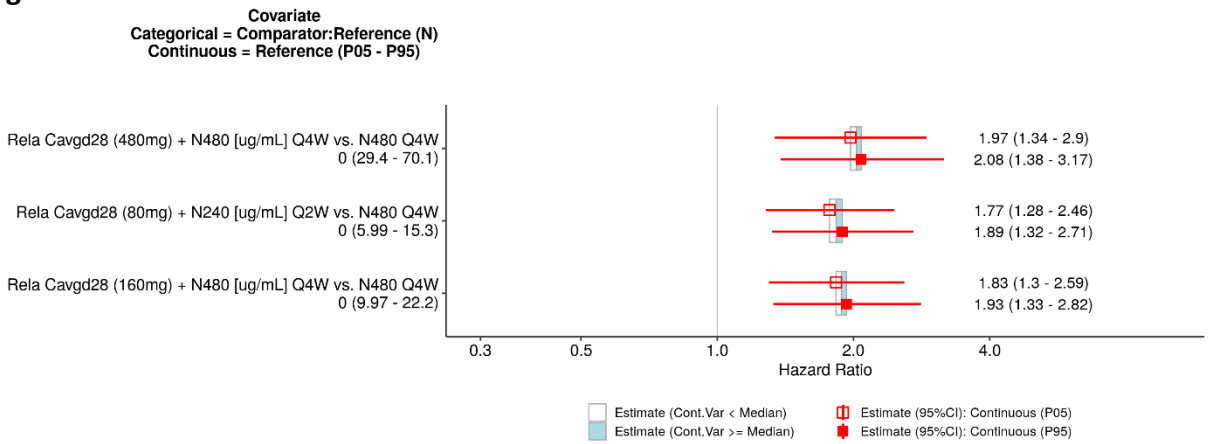
Data:

Figure 9: Applicant - Model Predicted Hazard Ratio of Gr2+ IMAEs in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Nivolumab 480 mg Q4W Regimen



Note: N480: Nivolumab 480 mg

Figure 10: Applicant - Model Predicted Hazard Ratio of Gr3+ DRAEs in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Nivolumab 480 mg Q4W Regimen



Note: N480: Nivolumab 480 mg

The Applicant's Position:

The proposed dose of nivo+rela FDC of 480/160 mg Q4W in adults ≥ 18 years (b) (4)

(b) (4) by IV infusion over ~30 minutes is appropriate for the indicated population. The recommended dose regimen was supported by the clinical data and clinical pharmacology – pharmacometrics analyses.

The nivolumab + relatlimab FDC dose selection in 1L melanoma and prior-IO melanoma was supported with dose ranging clinical efficacy and safety data from the Phase 1/2b study CA224020 (Sections 8.1.4 and 8.2.5). This dose regimen is further confirmed by the clinical efficacy and safety data in previously untreated melanoma in the pivotal Phase 3 study CA224047 (Sections 8.1.2 and 8.2.4). The FDC drug product was selected to provide convenient infusion preparation and rapid administration as well as to decrease dosing and administration errors.

Justification for Flat dose in Adults

The integration of nivolumab and relatlimab E-R findings for both efficacy and safety support the recommended flat dose of nivo+rela FDC at 480 mg nivolumab + 160 mg relatlimab Q4W for the treatment of adults with metastatic or unresectable melanoma. Although body weight had a > 20% on PK of relatlimab, the magnitude of the difference in exposure by body weight quartile are not expected to be clinically relevant, given the flat relatlimab E-R relationships for efficacy (Section 6.3.2.1) and safety. E-R safety analyses that included data from CA224047 and CA224020 in solid tumor patients showed that nivo+rela resulted in higher risk of Gr3+ DRAEs and Gr2+ IMAEs compared with nivolumab monotherapy. The increase in risk was similar across the range of relatlimab exposures produced by the studied nivo+rela dosing regimens, suggesting a flat E-R relationship for safety (Figure 9 and Figure 10).

(b) (4)

Justification for Shorter 30 minute Infusion Duration

While administration of nivo+rela FDC using a 30-minute infusion time has not been evaluated, no clinically meaningful differences in the frequency of hypersensitivity/infusion-related reactions are expected when nivo+rela FDC is administered over a 30 min infusion compared with the 60 min infusion used in the pivotal study CA224047, based on the following:

- There were no apparent associations between dose and infusion or hypersensitivity reactions
  - No cases were reported with nivo + rela SAV 480/960 mg Q4W (0/17)
  - 1 Grade 2 event (1/15) with nivo + rela SAV 480/1440 mg Q4W that resolved with acetaminophen and did not lead to treatment discontinuation.
  - All infusion related reactions reported with coadministration of nivo + rela SAV 480/480 mg infused over 60 minutes were Grade 1-2 and where treatment for hypersensitivity reaction was indicated, resolved with use of acetaminophen.
  - There were no treatment discontinuations due to infusion reactions.
- Nivo+rela FDC has been safely administered as a 60 minute infusion over long treatment periods (up to 31.5 months; Table 48). Infusion reactions, including high-grade hypersensitivity reactions, were uncommon (5.9%) with no high-grade events reported with nivo+rela FDC treatment (Section 8.2.6.3).
- The relatlimab infusion rate of ~5 mg/min from 30 min infusion for the proposed dose of nivo+rela FDC is well below the infusion rate of 24 mg/min used in the administration of the highest relatlimab dose of 1440 mg infused over 60 min in Study CA224020 Part B, which was well-tolerated.
- The total protein infusion rate of 21 mg/min from a 30 min infusion of the proposed nivo+rela FDC dose is the same as the total protein infusion rate of achieved from the highest nivo+rela dose of 480/1440 mg Q4W given sequentially over 90 min.
- Based on PPK, the infusion durations of 30 min or 60 min are not predicted to impact the PK profile of either relatlimab or nivolumab, as the systemic exposures (ie, Cmax, Cmin and Cavg) following nivo+rela FDC using 30-min or 60-min infusion times are predicted to be similar (<1% different) with single or multiple dose administration.

<u>The FDA's Assessment:</u>
FDA agrees with the Applicant's position on the proposed dosing regimen for adult patients. However, FDA has concerns with potential subtherapeutic dosing in adolescents (b) (4)

(b) (4)

- (b) (4)

Due to the uncertainties as mentioned above, FDA proposes the same adult flat dosing regimen of nivolumab-relatlimab FDC in adolescents with BW ≥ 40 kg based on the following considerations:

- Potential lower exposure using weight-based dosing for relatlimab and nivolumab may result in lower efficacy
- Flat exposure-response relationship for safety for the combination of nivolumab and relatlimab
- Relatlimab has been studied in combination with nivolumab at a dose of 1440 mg Q4W in more than 100 patients and was associated with a tolerable safety profile.
- Nivolumab has been studied at 20 mg/kg Q2W and demonstrated an apparent flat exposure-response relationship for safety.
- In Study CA224020 and CA224047, drug-related AEs and AEs leading to discontinuation/delays were not higher in adult patients with lower body weight (Table 28)

Table 28: Drug-related AEs and AEs leading to discontinuation/delays in Study CA224020 and CA224047

Study CA224047	**< 50 kg (N = 6)**		**≥ 50 – < 80 kg (N = 170)**		**≥ 80 kg (N = 179)**	
Patient # (%)	Any Grade	Grade ≥ 3+	Any Grade	Grade ≥ 3+	Any Grade	Grade ≥ 3+
Drug-related AEs	6 (100)	2 (33)	170 (100)	40 (24)	179 (100)	32 (18)
Drug-related SAEs	1 (17)		14 (8)		21 (12)	

Drug-related AEs leading to DC	1 (17)	1 (17)	10 (6)	8 (5)	26 (15)	13 (7)
Drug-related AEs leading to delays/interruptions	1 (17)	0	22 (13)	7 (4)	44 (25)	8 (4)
Study CA224020 (relat 160 + nivo 480 mg)	**< 50 kg (N = 17)**		**≥ 50 – < 80 kg (N = 215)**		**≥ 80 kg (N = 178)**	
Patient # (%)	Any Grade	Grade ≥ 3+	Any Grade	Grade ≥ 3+	Any Grade	Grade ≥ 3+
Drug-related AEs	17 (100)	3 (18)	215 (100)	38 (18)	178 (100)	23 (13)
Drug-related SAEs	2 (12)		28 (13)		14 (8)	
Drug-related AEs leading to DC	1 (6)	1 (6)	17 (8)	13 (6)	9 (5)	6 (3)
Drug-related AEs leading to delays/interruptions	1 (6)	0	1 (0.5)	0	6 (3)	0

Source: FDA analysis

Adolescents (≥ 12 years) with body weigh < 40 kg

Based on the following considerations, FDA agrees with not including adolescents with body weight < 40 kg in the indicated population. This recommendation is supported by the following:

- Body weight is identified as a significant covariate on the PK of nivolumab and relatlimab in adults.
- In pediatric studies, nivolumab was only evaluated in 1 adolescent (14 years) with baseline body weight of 39.7 kg. The model-predicted exposures of nivolumab in adolescents with body weight < 40 kg is uncertain as the pediatric effect in the population PK models is based on adolescents who had body weight ≥40 kg
- Unable to predict relatlimab exposure for adolescents with body weight < 40 kg using

the population PK models due to lack of relatlimab PK data in pediatrics

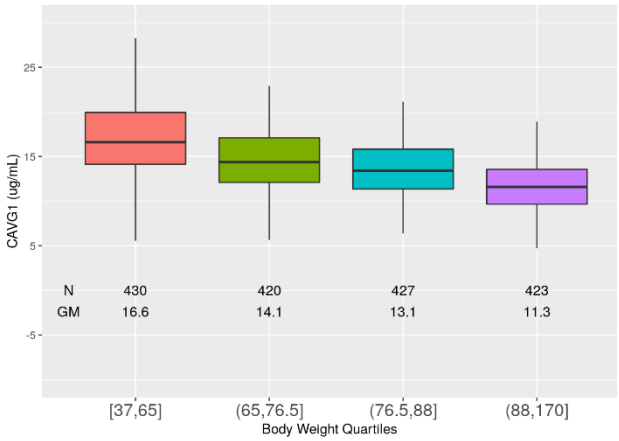
- Fixed dose combination of nivolumab and relatlimab (3: 1), which makes the dosages of nivolumab and relatimab have to be administered to patients as 3:1 and preclude any other dosing ratios.
- There is not an unmet clinical need in this population. Ipilimumab, a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody is indicated for treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older with no body weight restrictions.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

Figure 11: Applicant - Predicted Relatlimab Exposures at 160 mg Q4W by Body Weight Quartiles in Adults

A) Cavg1



B) Cavgss

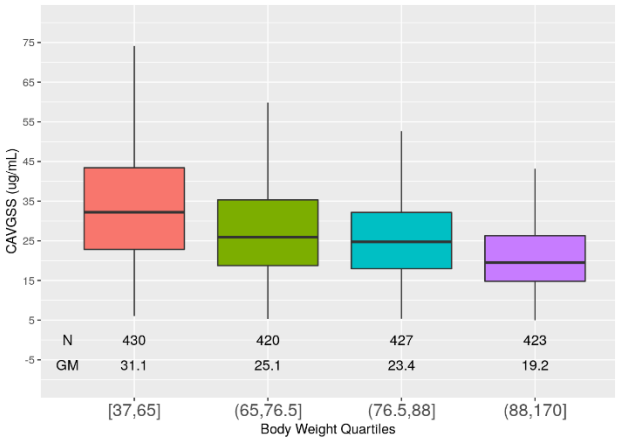


Figure 12: Applicant - Distribution of Model Predicted Relatlimab Exposures (Cavg1 and Cavgss) at 160 mg Q4W by Hepatic Function

A) Cavg1 **B) Cavgss**

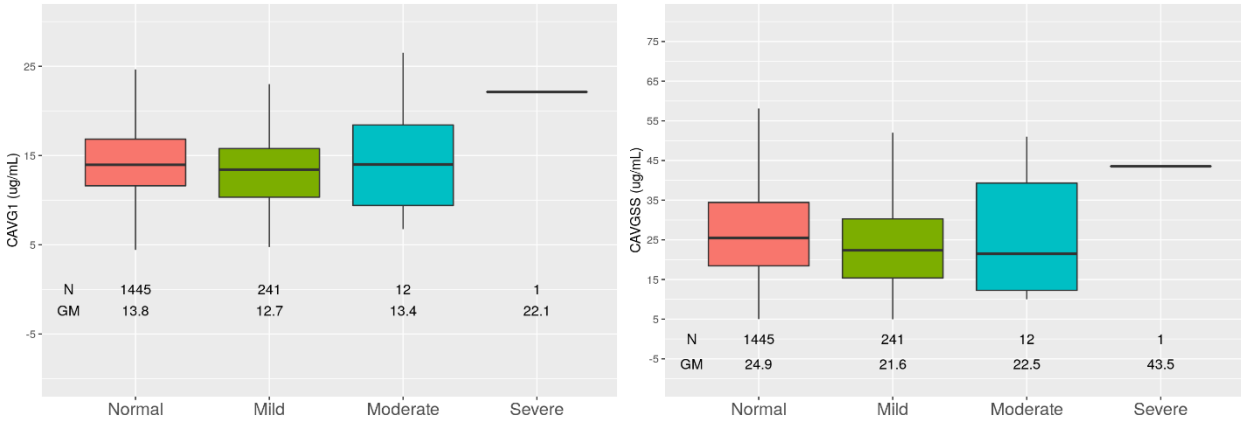
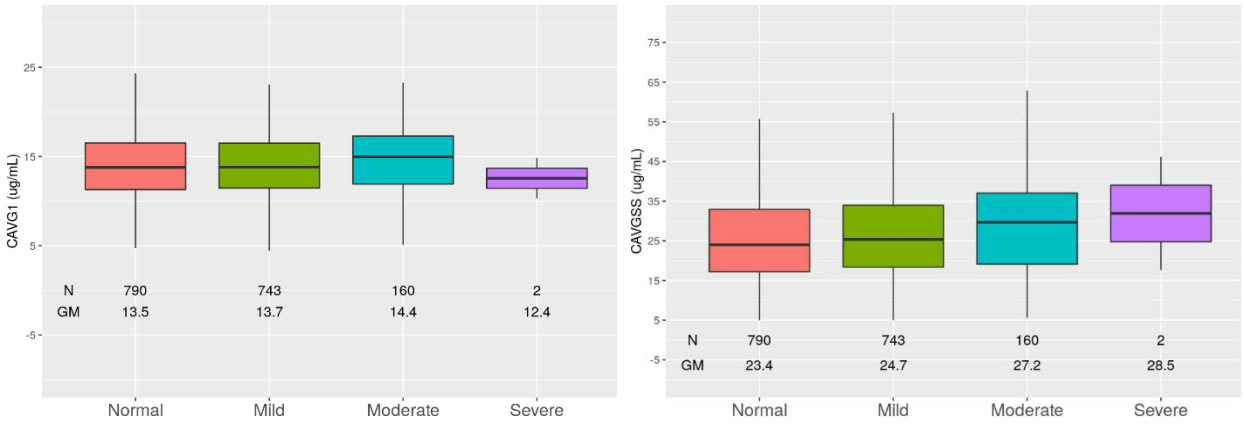


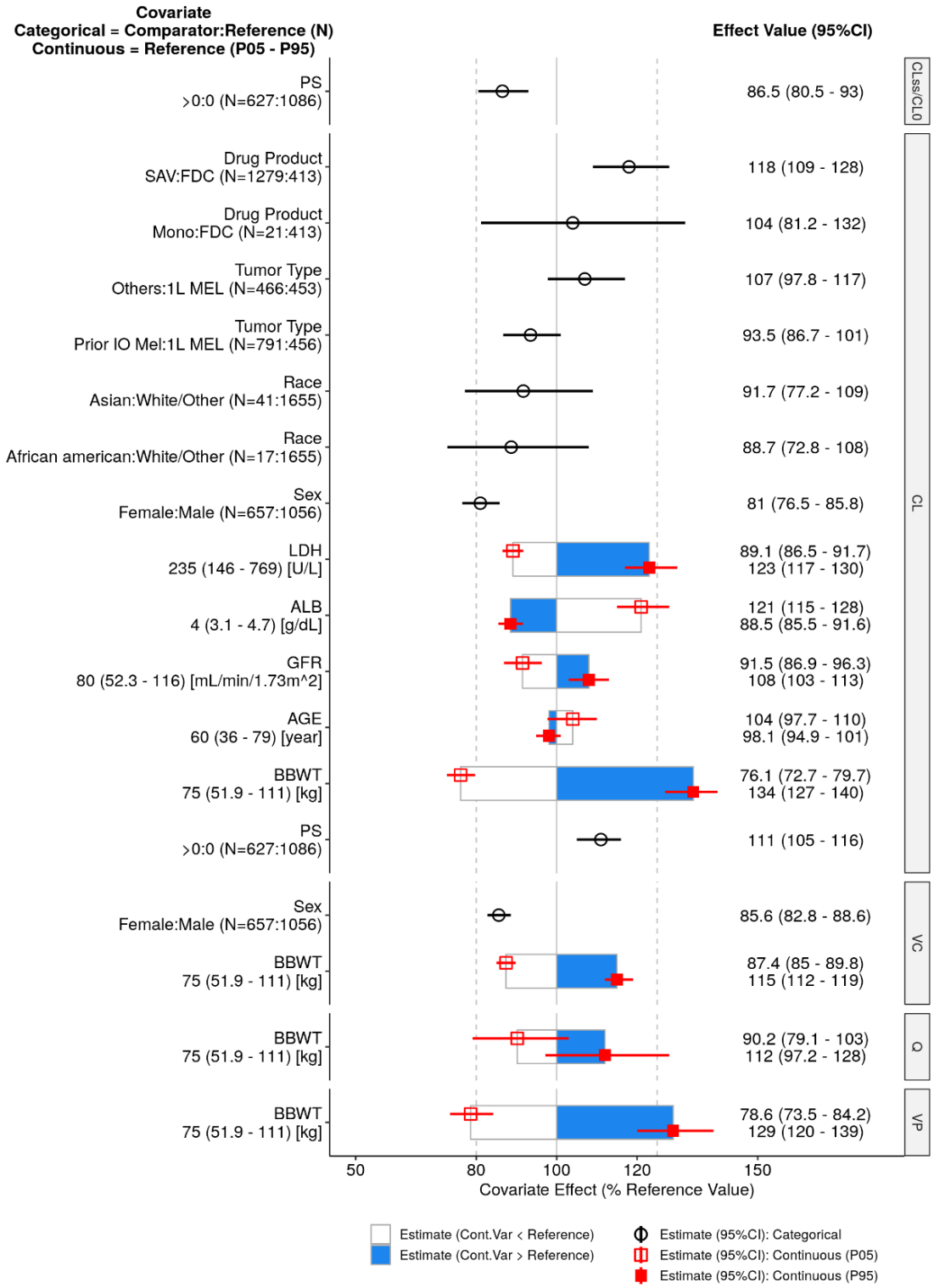
Figure 13: Applicant - Distribution of Model Predicted Relatlimab Exposures (Cavg1 and Cavgss) at 160 mg Q4W by Renal Function

A) Cavg1 **B) Cavgss**



Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Figure 14: Applicant - Covariate Effects on Full Relatlimab PPK Model



Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).

Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Note 3: Reference subject is a 60-year old white male, weighing 75 kg, with 1L MEL, baseline eGFR of 90 mL/min/1.73 m^2, baseline ALB of 4 g/dL, baseline LDH (normalized to upper limit of normal) of 0.8, a normal PS status (PS = 0), and receiving relatlimab/nivolumab FDC. $EMAX_{REF}$ is a typical value of change in magnitude of CL in a reference subject. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 75 kg. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 125% of this value.

Note 4: PS appeared twice in the figure. Baseline CL of relatlimab in subjects with PS > 0 was higher than subjects with PS = 0 by 11%, whereas the reduction of relatlimab CL over time was more significant in subjects with PS > 0 than subjects with PS = 0 by 14%.

Note 5: $CLss/CL0 = e^{EMAX}$

Of all tested covariates, only baseline body weight had an effect on relatlimab CL that could be potentially clinically relevant (> 20% effect). The analysis showed that relatlimab CL and VP increase with increasing body weight (Figure 14).

Relatlimab exposures at steady state after flat dosing were 31% lower in patients with higher body weight (at 95th percentile) and 26% higher in patients with lower body weight (at 5th percentile) relative to the median body weight (75 kg). Given the flat relatlimab E-R relationships for efficacy and safety, the differences in relatlimab exposures by body weight are not expected to have a clinically meaningful effect.

Similarly, of the tested covariates, only baseline body weight and albumin had a > 20% effect on nivolumab CL, which are not expected to be clinically relevant given the flat E-R relationships for efficacy and safety.

For nivo+rela 480/160 mg Q4W, the geometric means of relatlimab Cavg1 and Cavgss among subjects with normal hepatic function vs mild/moderate hepatic impairment and subjects with normal renal function vs mild/moderate renal impairment were similar (< 10%) (Figure 12 and Figure 13); similar findings were observed for nivolumab Cavg1 and Cavgss. There were a limited number of subjects with severe hepatic impairment or severe renal impairment; therefore, the impact on the PK is unknown.

The Applicant's Position:

No, there is no need for alternative dosing regimen for subpopulations based on the intrinsic factors evaluated. No dose adjustment in the proposed dose regimen is required (b) (4)

The FDA's Assessment:

FDA agrees with Applicant's position that there is no need for an alternative dosing regimen for subpopulations based on the intrinsic factors evaluated.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:
No formal DDI study was conducted with nivo+rela FDC. Nivolumab and relatlimab are IgG4 monoclonal antibodies and mAbs are not direct inhibitors/inducers of drug metabolizing enzymes and are eliminated by metabolic pathways that are divergent from small molecules, direct DDIs between mAbs and small molecules are unlikely. However, literature reports suggest therapeutic proteins that are modulators of cytokines may indirectly affect expression of cytochrome P450 enzyme.[22]

Levels of cytokines quantified in CA224020 and CA224047 including IL6, IL10 IL1β, IL12p70, and TNFα are mostly near or below the assay lower limit of quantification in nivo+rela treated patients. Nivo+rela treatment resulted in increases in IFNγ and IFNγ-induced chemokines IFNat, but clinically meaningful effect of IFNγ and IFNγ-induced chemokines on the expression or stability of CYP enzymes has not been reported.[22]

The Applicant's Position:
Food-drug interactions are not applicable as nivo+rela FDC is administered as an IV infusion. Nivo+rela FDC is considered to have low potential to affect PK of other drugs based on the lack of any clinically relevant effect on cytokines in peripheral circulation of nivo+rela.

Nivolumab and relatlimab are IgG4 monoclonal antibodies, which is likely to eliminated via several pathways similar to that of other antibodies, ie, degradation by catabolism/proteolysis (mainly by enzymes in the cells of reticuloendothelial system), Fc gamma receptor-mediated clearance, target-mediated clearance, nonspecific endocytosis, and formation of immune-complexes followed by complement- or Fc receptor-mediated clearance mechanism. These enzymes or pathways are not known to be inhibited or induced by drugs; therefore, it is unlikely that other drugs will have impact on the PK of nivolumab and relatlimab.

There was no clinically relevant PK interaction between nivolumab and relatlimab when administered in combination.

The FDA's Assessment:
FDA agrees with Applicant's position.

X X

X	X
Hongfei Zhang Primary Reviewer	Hong Zhao Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 29: Applicant - Listing of Clinical Trials Relevant to this BLA

Study	Design *Primary Objective*	No. Subjects Planned	Population	Dose/Schedule	Randomized or Treated (N)	Support
CA224047 to Support Efficacy and Safety						
RELATIVITY-047 IND: 136,382 NCT03470922 Countries: 25 Sites: 114	Phase 2/3 randomized, double blind study of BMS-986213 vs nivolumab *PFS per BICR*	700	**Adults and adolescents (≥ 12 years) with histologically confirmed Stage III or IV MEL with no prior systemic therapy**	Nivo+rela 480/160 mg Q4W **FDC** vs nivo 480 mg Q4W	714	Safety, efficacy, PK, IMG
CA224020 to Support Clinical Pharmacology, Safety and Efficacy						
RELATIVITY-020 (b) (4) NCT01968109 Countries: 14 Sites: 53	Phase 1/2a open-label study of relatlimab alone and in combination with nivolumab	A: 12-36	Solid tumors, IO naive	Rela SAV 20 to 800 mg Q2W[a]	17	PK, safety
		A1: 12-24	NSCLC/RCC, prior anti-PD-(L)1 allowed	Rela SAV 800 mg Q2W	8	PK, safety, efficacy
		B: 24-72	Solid tumors	Nivo + rela SAV 80/20 mg Q2W to 480/1440 mg Q4W[b]	107	PK, safety
		C: 560	**MEL, prior anti-PD-1**	Nivo 240 mg + rela SAV 80 mg Q2W **sequential administration**	151	Safety, efficacy
			MEL, first-line		66	

	Safety, tolerability, preliminary efficacy		Solid tumors		329	
			Bladder, IO naïve	Nivo 480 mg + rela SAV 160 mg Q4W **sequential administration**	37	
		D1: 300	**MEL, prior anti-PD-1;** focused eligibility	Nivo 240 mg + rela SAV 80 mg Q2W **coadmin**	189[c]	PK, safety, efficacy
				Nivo 480 mg + rela SAV 160 mg Q4W **coadmin**	83	
				Nivo+rela 480/160 mg Q4W **FDC**	82	
		D2: 250	**MEL, prior anti-PD-1;** expanded eligibility	Nivo 480 mg + rela SAV 160 mg Q4W **coadmin**[d]	164	Safety, efficacy
		E: 225[e]	**MEL, prior anti-PD-1**	Nivo 480 mg + rela SAV 480 mg Q4W **coadmin**	95	Safety, E-R
			MEL, first-line MEL	Nivo 480 mg + rela SAV 160 mg Q4W **coadmin**	38	
				Nivo 480 mg + rela SAV 480 mg Q4W **coadmin**	38	
		Total	Rela Monotherapy		25	
			Nivo+rela Combination		1379	

Note: Study CA224020 studied single agent vial relatlimab (BMS-986016) in combination with Opdivo except in Part D1, Arm 3 where the FDC formulation was used.

[a] Rela monotherapy dose escalation: 20 mg, 80 mg, 240 mg, and 800 mg Q2W

[b] Nivo+rela dose escalation: 80/20, 240/20, 240/80, 240/160, and 240/240 mg Q2W; 480/160, 480/240, 480/320, 480/480, 480/960, and 480/1440 mg Q4W. Note, per protocol doses could go up to 480/1600 mg Q4W; however, the highest dose studied was 480/1440 mg Q4W.

[c] 1 adolescent subject was treated

[d] Per protocol, there was a 480/240 mg Q4W cohort; however, no subjects were enrolled at this dose.

[e] 1L MEL cohorts in Part E are currently enrolling.

The FDA's Assessment:

FDA agrees with the Applicant's description of CA224047 and CA224020. For this application, the clinical data for the FDA's analysis of efficacy and safety were based on data from Study CA224047 (RELATIVITY-047). There were no patients in study CA224020 with

previously untreated melanoma who received the nivolumab-relatlimab FDC product.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Pivotal Phase 3 Study CA224047 (RELATIVITY -047)

8.1.1.1. Trial Design

The Applicant's Description:

CA224047 is a global, double-blind, randomized, adaptive Phase 2/3 study comparing nivo+rela FDC to nivolumab in patients with previously untreated, unresectable or metastatic melanoma (Figure 15). Participants were randomized 1:1 to treatment with BMS-986213 (nivolumab + relatlimab 480/160 mg IV Q4W FDC) or nivolumab 480 mg IV Q4W, and study treatment was continued until unacceptable toxicity, disease progression, withdrawal of consent, or end of study. There were 4 stratification factors as outlined in Table 30.

On-study tumor assessments began 12 weeks from randomization and continued every 8 weeks up to Week 52, and every 12 weeks thereafter until BICR-confirmed disease progression or treatment discontinuation, whichever occurred later. Treatment beyond initial investigator-assessed RECIST v1.1-defined progression was permitted if the participant had investigator-assessed clinical benefit and was tolerating study treatment.

As an adaptive trial, 425 participants were initially randomized within the Phase 2 study and enrollment was then paused for the pre-planned PFS IA. On 26-Aug-2019, the study transitioned to a full Phase 3 study based on the DMC recommendation that the pre-specified PFS HR threshold of ≤ 0.8 was met, enrolling an additional 289 patients for a total of 714 randomized subjects. The study remained double-blinded. Subjects enrolled in Phase 2 continued on treatment and are therefore integrated into the Phase 3 analyses presented in this submission.

Figure 15: Applicant - CA224047 Study Design Schematic

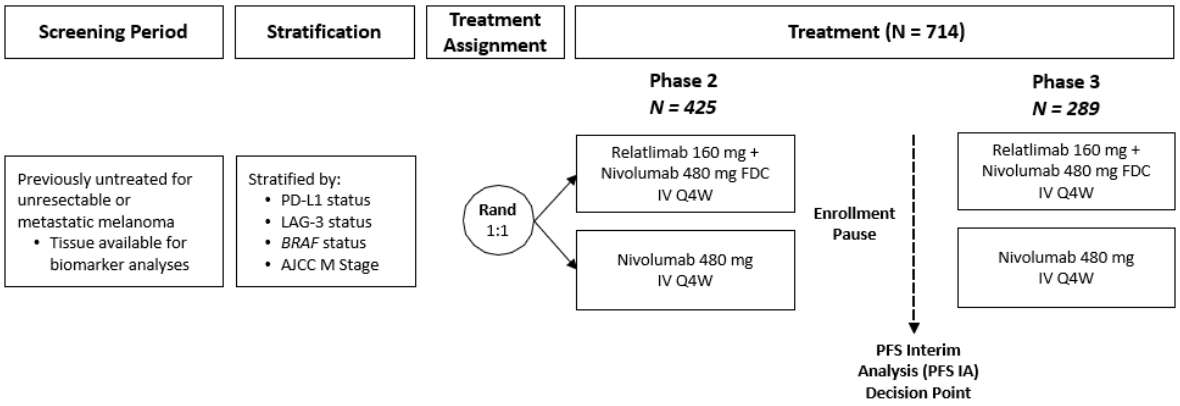


Table 30: Applicant - CA224047 Study Design Details

Design Aspect	Description
Adaptive phase 2/3 design	CA224047 was an adaptive study permitting rapid determination of whether there was sufficient signal of efficacy for nivo+rela FDC in an all-comer population (PFS HR ≤ 0.8) to proceed seamlessly to a full Phase 3 trial, while integrating the ability to pause and complete as a Phase 2 study to analyze biomarker subpopulations if required. This design maximized the speed of development and minimized the number of randomized subjects required to demonstrate proof of efficacy, while still maintaining the rigor of a well-powered, double-blind, randomized, controlled trial.
Study enrollment dynamics	Due to the adaptive design, there was a planned enrollment pause between Phase 2 and 3. The delay permitted all randomized subjects in Phase 2 to have a minimum follow-up of 12 weeks (target 150 PFS events) for the pre-planned PFS IA as outlined in the SAP. Additionally, the global COVID-19 pandemic started in the last quarter of 2019. At this time, the Phase 2 portion of the study was fully randomized and being followed, and the study had proceeded to Phase 3 on the DMC recommendation at PFS IA. The pandemic slowed the pace of study enrollment for a period of approximately 6 months (March 2020-August 2020), during the height of the first wave of the international pandemic impact. The enrollment pause and the pandemic enrollment slow-down resulted in a prolonged period of enrollment and randomization for CA224047 with the last patient randomized in December 2020, and thereby, a wide range of follow up, and a short minimum follow-up at the time of the primary endpoint (PFS) final analysis. See Section 8.1.1.2 for implications to the study endpoints.
Blinding	CA224047 was a double-blind study in order to minimize bias, limit thresholds for classification of progression between the arms (which could subsequently affect treatment duration between the arms and have an impact on the primary endpoint of PFS), and curtail bias in reporting, classification, and management of AEs. As outlined in the SAP, BMS, subjects, investigators, and site staff were blinded (study remained double-blinded) to the study therapy administered through PFS FA. The key secondary objective of OS was analyzed by the DMC per OS IA1 but was not statistically significant; therefore, the study will continue to OS IA2, and the participants, investigators, and site staff remained blinded to study treatment. Additionally, evaluation of PFS was conducted by a blinded third party, allowing for independent review of the data and even further reduction in the risk of bias for the primary endpoint analysis.
Choice of control group	Nivolumab is one of the established standards of care in the treatment of unresectable or metastatic melanoma, and as a comparator, supports evaluation of the contribution of components of the fixed dose combination of nivo+rela.
Dose selection	Refer to Section 6.2.2.1.

Patient population	Key Inclusion Criteria • Adult and pediatric (≥ 12 years) patients with histologically confirmed, unresectable stage III or stage IV melanoma per the AJCC staging criteria (8th edition). Baseline measurable disease (RECIST v1.1) and an ECOG performance status of 0-1, with no history of prior systemic treatment for unresectable or metastatic melanoma. • Patients were required to have known BRAF status and pre-treatment tumor samples submitted to determine PD-L1 and LAG-3 status prior to randomization. Participants with indeterminate or unevaluable PD-L1 or LAG-3 status results were not permitted to randomize, to support full evaluation of the prognostic and predictive value of these biomarkers with respect to the disease and the investigational regimen under study. Key Exclusion Criteria • Patients with uveal melanoma, active, untreated brain metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, a history of prior malignancy active within 3 years (except locally cured cancers), a history of myocarditis, and those with a baseline elevated troponin >2xULN were excluded from the trial. • Patients who received prior anti-cancer therapy for advanced melanoma. Specified prior adjuvant or neoadjuvant melanoma therapies were permitted if all related AEs either returned to baseline or stabilized (anti-PD-1, anti-CTLA-4, or BRAF-MEK containing regimen if ≥ 6 months between last dose and date of recurrence; interferon with last dose ≥ 6 weeks before randomization). These inclusion/exclusion criteria are in line with other clinical trials in advanced and metastatic melanoma, apart from permitting adolescents to enroll. The inclusion and exclusion criteria are also reflective of a general advanced and metastatic melanoma population, except for the exclusion of patients with active, untreated brain metastases and patients with an ECOG performance status of higher than 1. The exclusion criterion of brain metastases was implemented due to a lack of evidence and expert consensus on the optimal clinical management for these patients, and the ECOG score requirements were in place to protect patient safety.
Assignment to Treatment	Randomized centrally using IRT in a 1:1 ratio and stratified by: PD-L1 status (≥ 1% vs < 1% expression), LAG-3 status (≥ 1% vs < 1% expression), BRAF status (V600 mutation positive vs wild type), and AJCC (8th edition) M stage (M0/M1any[0] vs M1any[1]). These stratification factors were selected to ensure balance between the treatment arms for the known advanced melanoma prognostic factors of AJCC M stage (including LDH), BRAF status, and PD-L1 status, and for the novel biomarker LAG-3.
Dose modification/ discontinuation	No dose modifications for either treatment were permitted.

Treatment compliance	Treatment compliance for all study treatments was monitored by drug accountability, medical record, and electronic CRF.
Subject completion, discontinuation, or withdrawal	Treatment was to continue until progression, unacceptable toxicity, or study ends; there was no option to complete treatment. Patients who withdrew consent were not replaced. All patients who discontinued study treatment were to comply with protocol specified follow-up procedures (Table 31).
Concurrent medications	Any medications that could impact the interpretability of the primary or key secondary endpoints were prohibited, including the following: LAG-3 targeting agents, immunosuppressive agents and immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents), and concurrent anti-neoplastic therapy.
Study Committees	The following committees ensured the integrity of the study: • An external, independent DMC was established to provide oversight for, and analysis of, safety and efficacy considerations at regular intervals of approximately 6 months. • A BICR committee reviewed tumor assessments to determine tumor response per RECIST v1.1 criteria for the analysis of PFS and ORR.

Key procedures and schedule (Table 31): Screening was 28 days and study follow-up was 100 days. Survival follow-up continued until withdrawal of consent or death.

During screening, PD-L1 and LAG-3 testing were centrally conducted by trained pathologists. PD-L1 status was defined using the Dako 28-8 assay and a 1% cutoff (tumor cell expression). LAG-3 expression was determined with a commercially available reagent (mouse monoclonal antibody 17B4) using a validated assay and a 1% cutoff. Positive staining was defined as cytoplasmic and/or partial or complete plasma membrane staining of any intensity of cells morphologically resembling lymphocytes relative to all cells within the overall tumor region (including tumor cells, macrophages/histiocytes, lymphocytes, plasma cells, myeloid cells, dendritic cells, giant cells, and stromal cells).

Table 31: Applicant - Key Study CA224047 Procedures and Schedule

	Tumor Assessments	**Vital Signs, ECG, Lab tests**[a]	**AEs**	**SAEs**	**Troponin**
Screening	Required	Required within 14 days of randomization	Not Required	Required	Required
On-study	Week 12 then every 8 wks (± 7 days) to Week 52 then every 12 wks (± 7 days) until the later of BICR-	Every 4 weeks (Within 3 days prior to dosing for each cycle)	Continuous	Continuous	C1D1: predose[b] C1D14: ± 5 days C2D1: predose[b] C2D14: ± 5 days C3D1: predose[b]

	confirmed disease progression or treatment discontinuation				
Follow-up	As above	30 days and 100 days from last dose[b]	30 days and 100 days from last dose[b]	30 days and a minimum of 100 days from last dose[c]	N/A
Survival follow-up	As above	Not Required	Not Required	If considered related to study drug or protocol-specified procedure	Not Required

[a] Labs included hematology (hemoglobin, hematocrit, total leukocyte count, including differential, and platelet count), serum chemistry (AST, ALT, total bilirubin, alkaline phosphatase, gamma-glutamyl transferase, creatinine, BUN or serum urea level, glucose, LDH, uric acid, albumin, sodium, potassium, chloride, calcium, phosphorus, magnesium, TSH, Creatinine clearance, FSH), troponin, and urinalysis (protein, glucose, blood, leukocyte esterase or leukocyte, specific gravity, and pH) within 14 days of randomization. Serology (hepatitis C antibody or hepatitis C RNA, hepatitis B surface antigen, HIV-1 and HIV-2 antibodies) within 28 days of randomization. For HIV: testing at sites where locally mandated. All clinical safety laboratory assessments were performed locally.

[b] Within 3 days prior to D1

[c] If date of discontinuation is > 100 days after the last dose then only one follow-up visit needs to be completed.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the pivotal trial Study CA224047. The comparator arm of nivolumab monotherapy is considered appropriate and consistent with the current standard of care for the systemic treatment of unresectable or metastatic melanoma. In general, the key eligibility criteria for patients with unresectable or metastatic melanoma by stage, baseline measurable disease, and exclusion of patients with uveal melanoma were similar to other studies that evaluated immune checkpoint inhibitors in the first line setting. Only patients enrolled in Checkmate-066 were required to be BRAF-wild type. The only study to allow enrollment of adolescent patients 12-17 years was study CA224047; however, no patients in this age group were enrolled. Specific criteria to allow for treatment beyond initial disease progression were outlined in the protocol.

8.1.1.2. Study Endpoints

The Applicant's Description:

The endpoints used to assess the efficacy profile of nivo+rela FDC in CA224047 (Table 32) are consistent with other registrational studies exploring the use of anti-cancer agents in subjects

with unresectable or metastatic melanoma. The primary endpoint measure, PFS per BICR, is not confounded by post-study treatment therapies and has been demonstrated to correlate with OS in a meta-analysis of randomized controlled trials of anti-PD-(L)1 agents in metastatic melanoma.[23] PFS has been recognized as an acceptable regulatory endpoint with the approval of several agents in melanoma, and as a clinically relevant endpoint as illustrated by the recent incorporation of atezolizumab/vemurafenib/cobimetinib into the 2020/2021 NCCN Clinical Practice Guidelines for Melanoma. In CA224047, evaluation of PFS was conducted by BICR using RECIST version 1.1 criteria allowing for independent review of the data, and even further reduction in the risk of bias for the primary endpoint analysis. The BICR process employed a 'dual reader with adjudication' paradigm: two independent reviewers (both blinded to study treatment arm and data) read each image on a rolling basis, and adjudication by an independent third review took place if required after all expected images were received, or at the time of investigator request for PD confirmation.

During the course of the study, the order of the Phase 3 secondary endpoint hierarchical testing was revised to OS, followed by ORR, and two OS IAs were added. This modification was made based on the relative importance of OS and ORR in the melanoma landscape. In clinical practice, the importance of OS was illustrated by the practice-changing report of 5-year survival outcomes for patients with advanced and unresectable melanoma in Study CA209067. From a statistical perspective, a meta-analysis of clinical trials evaluating checkpoint inhibitor effectiveness was published, concluding that differences in ORR were only moderately correlated with significant differences in PFS or OS, suggesting ORR to have limitations as a surrogate in this context.

The interim analyses for OS were added to support the change in the secondary endpoint testing hierarchy (Table 30). At the time of the primary endpoint FA, OS data were not statistically significant, with ~76% information fraction (ie, 227 of the required 300 deaths for the final OS analysis). The hierarchical ORR final analysis requires 7 months of follow-up for all randomized subjects to allow the data to mature. The timing of OS IA2 (at 90% information fraction) was based on an estimate that it will be conducted halfway between OS IA1 and the OS FA.

The key exploratory endpoints were chosen to support contextualization of the primary and secondary results. For example, the biomarker analyses will support understanding of the predictive and prognostic values of PD-L1 and LAG-3 in this disease setting and study regimen, and the duration of response will support understanding of the durability of the treatment effect. PFS2 is an intermediate endpoint of interest to assess potential impact of study treatment on subsequent therapy, which may be in the form of a detriment (for example, due to long-term toxicity or reduction in efficacy of follow-on regimen), or benefit, due to persistence of initial treatment effects.

Table 32: Applicant - CA224047 Key Endpoints

Endpoint	Description
Primary	PFS was defined as the time between the date of randomization and the first date of documented progression, or death due to any cause, whichever occurs first.
Secondary	Hierarchical testing of OS followed by ORR by BICR.
Exploratory	DOR, TTR, efficacy by LAG-3 expression and PD-L1 status, safety, PK, immunogenicity, PROs, PFS2, and treatment-free interval.

The FDA's Assessment:
FDA agrees with the Applicant's description of the study endpoints. PFS has been used as a regulatory endpoint in the metastatic melanoma setting. PFS was used in previous clinical trials in the proposed indication as the primary endpoint to demonstrate effectiveness and support traditional approval. In CHECKMATE-067 and KEYNOTE-006, the co-primary endpoints were PFS and OS. In CHECKMATE-066, the primary endpoint was OS with PFS was a key secondary endpoint. Notably, when the effect on PFS is statistically robust and clinically important, this endpoint can support traditional approval when assessed in the context of an overall acceptable risk profile.

Note that there was an update to the SAP during review that eliminated the need for OS IA2. See Section 8.1.1.3 for more details.

8.1.1.3. Statistical Analysis Plan and Amendments

The Applicant's Description:
Efficacy analyses were performed on the population of all randomized subjects (all subjects from the global study population who were randomized using the IRT).

For the primary endpoint, the primary definition of PFS censors subjects at subsequent therapy. A secondary definition of PFS (ITT definition), irrespective of subsequent therapy, was employed as a sensitivity analysis. The influence of baseline and demographic characteristics on PFS treatment effect among all randomized subjects was evaluated via pre-specified subgroup analyses, including biomarker status (LAG-3, PD-L1, BRAF, and interaction of PD-L1 and LAG-3), advanced melanoma prognostic factors (including baseline AJCC M- and disease stages, LDH, ECOG status, histology subtype, and tumor burden), and patient demographics.

Stratification Factors
Four stratification factors were used for CA224047 at randomization: PD-L1 status, LAG-3 status, BRAF status, and AJCC v8 M-stage.

In Sep-2018, prospectively-assessed, centrally reviewed tumor samples originating for PD-L1 testing from the (b) (4) facility were identified as having a lower proportion of PD-L1 positive cases at the ≥ 1% threshold compared with study design

assumptions. All previous BMS PD-L1 data from other BMS studies were generated at (b) (4) and the Study CA224047 data were generated at (b) (4). Root cause analysis revealed that samples were under-scored by pathologists at the (b) (4) facility. A decision was taken to switch to using the (b) (4) facility for PD-L1 scoring for Study CA224047. All Phase 2 study samples scored for PD-L1 at (b) (4) were used prospectively for randomization stratification. The (b) (4) facility was used to evaluate samples for all enrolled subjects for randomization stratification during the Phase 3 portion of the study. Phase 2 study samples were also re-scored (N = 423) at (b) (4) During the rescoring, pathologists were blinded to the previous PD-L1 score. Monitoring of PD-L1 re-scoring was not performed by BMS. The SAP V1.0 was approved (approval date: 18-Dec-2018) prior to the PFS IA, indicating evaluations from (b) (4) (Phase 3 and re-scored Phase 2 samples) would be used as the data variable for the primary efficacy analyses, and a sensitivity analysis of the PFS primary endpoint would be performed using the originally scored PD-L1 to assess the impact of the discrepancies.

CA224047 employed a new staging AJCC v8 (2018) criteria that were introduced for classifying melanoma patients, which integrates LDH level within the M sub-stages. In Sep-2018, during the routine clinical and statistical monitoring of blinded M-stage stratification, it was observed that sites were not reliably including LDH lab values into the staging classification needed for randomization, likely due to confusion with the updated AJCC staging criteria. For future IRT entries, specification was included when selecting from M0/M1any0 or M1any1 to minimize selection errors (ie, “any0” was labelled as normal LDH and “any1” was labelled as elevated LDH). In addition, actions were taken to ensure the RAVE data entries were accurate, including data comparison between IRT and RAVE, updating the eCRF pages in a migration to more accurately reflect the AJCC v8 nomenclature. Finally, a memo was sent to sites to clarify M stage strata. In order to ensure accuracy of the M stage stratification factor per AJCC v8 criteria for statistical analysis, a decision was made that the AJCC v8 M stage would be programmed by extracting the actual lab LDH values and the metastasis stage data directly from RAVE. This was pre-specified in SAP V2.0 (approval date: 23-Nov-2020).

These changes are not expected to impact the data analysis, and a sensitivity analysis was planned in the SAP using the IRT original scores for all subjects to assess the impact of the discrepancies. No issues were identified with other two study stratification factors (LAG-3 and BRAF mutation status), and therefore the primary endpoint analysis was based on the IRT values for these factors.

COVID-19 pandemic

The COVID-19 pandemic contributed to enrollment (Table 30) and administrative challenges. Due to the potential for delays in study drug administration, imaging, and safety assessments, mitigation steps were taken to collect data and monitor the impact of the pandemic. Sites were encouraged to use lab and imaging locations that were convenient for the participant to support continuation of the safety and efficacy assessments. The SAP was amended to incorporate a pre-specified COVID-19 sensitivity analysis for the primary endpoint if at least 10% of PFS events were

attributed to COVID-19.

Table 33: Applicant - CA224047 Statistical Analysis Plan

Endpoint	Description
Primary (PFS)	The analysis of PFS by BICR to compare nivo+rela FDC vs nivolumab monotherapy was based on a 2-sided log-rank test stratified by LAG-3 expression (≥ 1% vs < 1%), , BRAF status (mutation positive/wild-type), and AJCC (8th edition) M-stage (M0/M1any[0]/M1any[1]). PD-L1 was removed from stratification because it led to subgroups with fewer than 10 subjects. This decision was pre-specified in SAP V2.1. Hazard ratios and corresponding 2-sided 95% CI were estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. At the time of the 09-Mar-2021 DBL, the actual number of events was 391.
Secondary (OS IA1)	At the time of the 09-Mar-2021 DBL, the first interim analysis for OS (OS IA1) was performed by the DMC with 227 deaths and the boundary for statistical significance for OS was p-value < 0.01944 (2-sided). A two-sided log rank test stratified by LAG-3 expression (≥ 1% vs < 1%), BRAF mutation status (positive/wild-type), and AJCC (8th edition) M Stage (M0/M1any[0]/M1any[1]) was used by the DMC to compare nivo+rela vs nivolumab monotherapy. The HR and corresponding two-sided 95% CI were estimated using a Cox proportional hazards model with treatment arm as a single covariate, stratified by the above factors. Per OS IA1, OS was analyzed by the DMC but was not statistically significant; therefore, BMS and investigators remain blinded to OS summary results.
Safety	Safety is presented by descriptive statistics using MedDRA version 23.1 and NCI-CTCAE version 5.0. All on-study AEs, drug-related AEs, SAEs, drug-related SAEs, IMAEs, or OESI were tabulated using worst grade per NCI-CTCAE version 5.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function were summarized using worst grade per NCI-CTCAE version 5.0 criteria. Frequency, management, and resolution of IMAEs were analyzed.
Other	Descriptive statistics are presented for immunogenicity and patient quality of life analyses.

The FDA's Assessment:

FDA agrees with the Applicant's description of the statistical analysis plan and adds the following:

1. Per the Applicant, the overall type-1 error rate for the study is 2-sided 0.05. Although not formally tested, an administrative alpha penalty of 0.001 was used for the PFS IA. The analysis of the final PFS and two key secondary endpoints, OS and ORR, will be controlled using all remaining unspent alpha (2-sided 0.049) with a hierarchical testing procedure. Specifically, OS will be formally tested only after statistical significance is shown for PFS using the Lan-DeMets alpha spending function approximating the O'Brien-Fleming type of boundary, and ORR will be formally tested only after statistical significance is shown for OS.
2. Per the Applicant, ORR is defined as the number of randomized patients who achieve a

best overall response of complete response (CR) or partial response (PR) based on BICR assessments per RECIST v1.1 divided by the number of randomized patients. A two-sided Cochran-Mantel-Haenszel (CMH) test stratified by LAG-3 expression (≥ 1% vs < 1%), BRAF mutation status (positive/wild-type), and AJCC (8th edition) M Stage (M0/M1any[0]/M1any[1]) will be employed to compare nivolumab-relatlimab FDC vs nivolumab monotherapy. Additionally, ORRs and corresponding 95% exact CIs will be calculated using the Clopper Pearson method.

3. On October 20, 2021, the Applicant submitted an amendment (SAP version 4.0 dated October 12, 2021) to FDA. The SAP was updated to state that, if at least 290 events are observed before the second interim analysis of OS (i.e., deaths accumulate more quickly than anticipated), OS IA2 will no longer be performed; instead the final OS analysis will be conducted and if this occurs, the Applicant and not the DMC, will analyze the OS data and be unblinded to OS results. After reviewing the SAP amendment, FDA sent an Information Request requesting that the Applicant include the rationale/justification for this change in the SAP. On November 12, 2021, the Applicant submitted SAP version 5.0 dated October 25, 2021 to FDA, specifying that the decision to remove OS IA2 and go straight to the final OS analysis was made with full knowledge of how many deaths were currently in the database, but with no knowledge of the OS analysis by treatment arm.

In addition, as noted in the Applicant's position above and stated in the SAP, the values used for the stratified randomization were different from the values used for the primary and secondary analyses for the two randomization stratification factors: PD-L1 (≥ 1% vs < 1%) and AJCC (8th edition) M Stage (M0/M1any[0]/M1any[1]). FDA notes that concordance was 82.6% comparing PD-L1 values scored from (b) (4) for the 425 patients randomized during Phase 2 part of the study, and was 82.9% comparing AJCC v8 M stage defined per IRT and per RAVE CRF for the 714 patients randomized during Phase 2 and Phase 3 part of the study (Table 34).

Table 34: Concordance for PD-L1 status (b) (4) and AJCC M stage (IRT vs. RAVE CRF)

PD-L1				
	(b) (4)			
(b) (4)	Nivolumab-relatlimab FDC (N=215)		Nivolumab (N=210)	
	< 1%/Non-quantifiable N (%)	≥ 1% N (%)	< 1% /Non-quantifiable N (%)	≥ 1% N (%)
< 1%/Non-quantifiable	118 (55)	13 (6)	113 (54)	16 (8)
≥ 1%	21 (10)	63 (29)	24 (11)	57 (27)

PD-L1				
	(b) (4)			
(b) (4)	Nivolumab-relatlimab FDC (N=215)		Nivolumab (N=210)	
	< 1%/Non-quantifiable N (%)	≥ 1% N (%)	< 1% /Non-quantifiable N (%)	≥ 1% N (%)
AJCC M Stage				
	IRT			
RAVE CRF	Nivolumab-relatlimab FDC (N=355)		Nivolumab (N=359)	
	M0/M1any[0]	M1any[1]	M0/M1any[0]	M1any[1]
M0/M1any[0]	183 (52)	49 (14)	187 (52)	50 (14)
M1any[1]	12 (3.4)	111 (31)	11 (3.1)	111 (31)

Source: FDA generated analysis based on sponsor submitted data [ADSL.xpt] (DCO: March 9, 2021).

FDA generally prefers that stratified analyses be performed using the stratification factor values at randomization (per IRT). However, in this case, FDA acknowledges the Applicant's rationale and does not object to the Applicant's pre-specified plan to conduct the primary and secondary analyses using stratification factor values not collected at randomization for PD-L1 expression and AJCC M stage. In particular, FDA notes the following:

1. FDA examined the between arm balance in baseline characteristics within the PD-L1 subgroups as defined by (b) (4) and the AJCC M Stage subgroups as defined by RAVE CRF and did not observe any notable imbalances.
2. For the primary and secondary efficacy analyses, PD-L1 was removed from the model as a stratification factor due to fewer than 10 subjects in at least one of the 16 strata (as pre-specified in the SAP). Thus, the only remaining stratification factor included in the model that was not based on IRT was AJCC M stage. Sensitivity analyses of PFS per BICR and OS were conducted using the AJCC M stage values per IRT and showed consistent results. See Sections 8.1.2.8 and 8.1.2.10 for more details.

8.1.1.4. Protocol Amendments

The Applicant's Description:
The CA224047 protocol underwent 3 global amendments after the original protocol was issued on 18-Dec-2017 (Table 35).

Table 35: Applicant - CA224047 Protocol Amendments - Key Changes

Revision No. Date	Description

Rev 01 15-Aug-2018	Changed the primary endpoint for Phase 2 and the interim analysis endpoint to decide continuation to a Phase 3 study from ORR to PFS, as PFS is the better indicator of a clinically meaningful outcomes. Phase 3 endpoint of PFS was not changed. Updated the reference NCI-CTCAE grading criteria from version 4.0 to 5.0. Of note, Grade 1 myocarditis was removed as an event term in CTCAE v5. Administrative Letter 4 (dated 05-Sep-2018) instructed site to report drug-related asymptomatic troponin elevation events, regardless of an ability to identify an imaging correlate of myocardial inflammation, as a related troponin elevation.
Rev 02 22-Feb-2019	Added a Phase 3 exploratory objective of PFS2 Revised the order of the Phase 3 secondary endpoints hierarchical testing strategy (1. ORR, 2. OS).
Rev 03 23-Nov-2020	Revised the order of hierarchical testing for the Phase 3 secondary endpoints. OS was made the first secondary endpoint evaluated in the hierarchy, followed by ORR, as OS is considered a more relevant endpoint for evaluation of clinical benefit in the melanoma landscape (ie, 5-year CHECKMATE 067 results). Added two IA of OS.

The FDA's Assessment:
FDA agrees with the Applicant's description of key protocol changes. FDA notes one additional key change for protocol revision 01 which provided for an update to the PFS interim analysis to include all randomized participants from Phase 2.

8.1.2. Study Results - Pivotal Study CA224047

8.1.2.1. Compliance with Good Clinical Practices

The Applicant's Description:
The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with Good Clinical Practice, as defined by the International Council for Harmonisation and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21 CFR 50).

The FDA's Assessment:
FDA agrees with the Applicant's position. There is no evidence that compliance with good clinical practices was violated during conduct of Study CA224047.

8.1.2.2. Financial Disclosure

The Applicant's Position:
Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Sub-investigators). There were no notable findings based on a review of the financial disclosure information for CA224047.

The FDA's Assessment:

Information on investigators' financial disclosures was reviewed; overall, FDA did not identify any concerning potential sources of bias stemming from this information.. A total of 884 principal investigators or sub-investigators participated in Study CA224047; one investigator did not complete a financial disclosure form. There were 7 principal investigators or sub-investigators who reported disclosable financial interests. This included 5 principal investigators or sub-investigators who received significant payments of other sorts, one investigator with a significant equity interest, and one investigator who received significant payments of other sorts and had financial arrangements with the Applicant due to their (b) (4) during the conduct of this trial.. In all, 2.1% of the study population in Study CA224047 was enrolled by investigators reporting financial disclosures. The use of a double-blind study design and an Independent Radiology Review Committee (IRRC) to assess the primary efficacy endpoint further decrease the likelihood of bias. FDA considers that it is unlikely that the reported financial disclosures led to significant bias in the conduct of the study. Additional information is provided in Section 19.2

8.1.2.3. Patient Disposition

Data:

Table 36: Applicant - Subject Disposition, All Enrolled, Randomized, and Treated Subjects in CA224047

	Total
ENROLLED	1281 (100.0)
RANDOMIZED	714 (55.7)
NOT RANDOMIZED	567 (44.3)
REASON FOR NOT RANDOMIZED	
ADVERSE EVENT	6 (0.5)
SUBJECT WITHDREW CONSENT	41 (3.2)
DEATH	12 (0.9)
POOR/NON-COMPLIANCE	2 (0.2)
SUBJECT NO LONGER MEETS STUDY CRITERIA	465 (36.3)
ADMINISTRATIVE REASONS BY SPONSOR	6 (0.5)
OTHER	35 (2.7)
REASON FOR NOT RANDOMIZED DUE TO COVID-19	1 (0.1)
SUBJECT WITHDREW CONSENT	1 (0.1)

	Nivo+rela FDC N = 355	Nivolumab N = 359	Total N = 714
TREATED	355 (100.0)	359 (100.0)	714 (100.0)
ONGOING TREATMENT	117 (33.0)	126 (35.1)	243 (34.0)
COMPLETED TREATMENT	1 (0.3)	0	1 (0.1)
DISCONTINUED TREATMENT	237 (66.8)	233 (64.9)	470 (65.8)
REASON FOR DISCONTINUATION OF TREATMENT			
DISEASE PROGRESSION	129 (36.3)	165 (46.0)	294 (41.2)
STUDY DRUG TOXICITY	63 (17.7)	32 (8.9)	95 (13.3)
SUBJECT REQUEST TO DISCONTINUE*	19 (5.4)	12 (3.3)	31 (4.3)
STUDY TREATMENT			
ADVERSE EVENT UNRELATED TO STUDY DRUG	12 (3.4)	14 (3.9)	26 (3.6)

OTHER	7 (2.0)	4 (1.1)	11 (1.5)
DEATH	2 (0.6)	3 (0.8)	5 (0.7)
MAXIMUM CLINICAL BENEFIT	2 (0.6)	1 (0.3)	3 (0.4)
SUBJECT WITHDREW CONSENT	1 (0.3)	2 (0.6)	3 (0.4)
LACK OF EFFICACY	1 (0.3)	0	1 (0.1)
POOR/NON COMPLIANCE	1 (0.3)	0	1 (0.1)
REASON FOR DISCONTINUATION OF TREATMENT DUE TO COVID-19	2 (0.6)	4 (1.1)	6 (0.8)
OTHER	0	1 (0.3)	1 (0.1)
DISEASE PROGRESSION	1 (0.3)	0	1 (0.1)
ADVERSE EVENT UNRELATED TO STUDY DRUG	1 (0.3)	3 (0.8)	4 (0.6)
ONGOING STUDY	237 (66.8)	227 (63.2)	464 (65.0)
DISCONTINUED STUDY	118 (33.2)	132 (36.8)	250 (35.0)
REASON FOR DISCONTINUATION OF STUDY			
DEATH	107 (30.1)	118 (32.9)	225 (31.5)
LOST TO FOLLOW-UP	5 (1.4)	5 (1.4)	10 (1.4)
SUBJECT WITHDREW CONSENT	4 (1.1)	9 (2.5)	13 (1.8)
OTHER	1 (0.3)	0	1 (0.1)
NOT REPORTED	1 (0.3)	0	1 (0.1)
REASON FOR DISCONTINUATION OF STUDY DUE TO COVID-19	2 (0.6)	4 (1.1)	6 (0.8)
DEATH	2 (0.6)	4 (1.1)	6 (0.8)

Percentages based on subjects entering phase.

* The primary reason for subject request to discontinue treatment was 'patient decision' in both arms.

The Applicant's Description:

The first subject was enrolled on 11-Apr-2018. Subject randomization was completed as of 16-Dec-2020, and the study is ongoing. Data are reported based on a 09-Mar-2021 clinical DBL. 1281 subjects were enrolled and 714 subjects were randomized: 355 to the nivo+rela FDC arm, 359 to the nivolumab arm (Table 36). All randomized subjects were treated. The most common reason for treatment discontinuation was progressive disease in both arms. While the overall percentage of subjects who discontinued treatment was similar, a higher percentage within the nivolumab arm discontinued due to disease progression compared with the nivo+rela FDC arm, while discontinuation due to study drug toxicity was more frequent in the nivo+rela FDC arm.

The FDA's Assessment:

FDA agrees with the Applicant's description of patient disposition. More patients on the nivolumab-relatlimab FDC arm discontinued study treatment due to toxicity which is consistent with the higher toxicity profile of other ICI combination regimens as compared to single agent ICIs. More patients on the nivolumab arm discontinued due to disease progression.

8.1.2.4. Protocol Violations/Deviations

Data:

Table 37: Applicant - Summary of Relevant Protocol Deviations - All Randomized Subjects in CA224047

	Number of Subjects (%)		
	Nivo+rela FDC N = 355	Nivolumab N = 359	Total N = 714
SUBJECTS WITH AT LEAST ONE DEVIATION	8 (2.3)	6 (1.7)	14 (2.0)
AT ENTRANCE	8 (2.3)	6 (1.7)	14 (2.0)

HISTOLOGICALLY UNCONFIRMED DIAGNOSIS	0	1 (0.3)	1 (0.1)
PRIOR SYSTEMIC ANTICANCER/PROHIBITED THERAPY	5 (1.4)	3 (0.8)	8 (1.1)
BASELINE IMAGE PERFORMED OUTSIDE REQUIRED WINDOW	3 (0.8)	2 (0.6)	5 (0.7)

Using the original IRT values for PD-L1, and not the rescore.

The Applicant's Position:

Relevant protocol deviations were defined as those that could affect the interpretability of key efficacy study results, are programmable deviations from the clinical database, and are protocol specific. Subjects with relevant protocol deviations were included in the primary endpoint analysis on an intention-to-treat basis. A pre-specified sensitivity analysis was planned to exclude subjects with a relevant protocol deviation if more than 10% of subjects reported these deviations. This criterion was not met so the analysis was not performed.

Relevant protocol deviations were balanced across treatment arms (Table 37). There were no on-treatment relevant protocol deviations.

There was one relevant protocol deviation within the 'wrong histological diagnosis ' category. This patient had an initial diagnosis of melanoma at study entry based on consistent histology; however, this diagnosis was amended to clear cell sarcoma shortly after randomization and receipt of study drug, on the basis of evaluation of new histology samples acquired while the subject was on study.

As the number of relevant deviations was low, affecting less than 3% of the randomized patient population and was balanced between study arms, these deviations are not considered to have affected the interpretability of the study results.

8.1.2.5. Table of Demographic Characteristics

Data:

Table 38: Applicant - Demographic Characteristics Summary, All Randomized Subjects in CA224047

	Nivo+rela FDC N = 355	Nivolumab N = 359	Total N = 714
AGE (YEARS)			
N	355	359	714
MEAN	61.2	61.2	61.2
MEDIAN	63.0	62.0	63.0
MIN , MAX	20 , 94	21 , 90	20 , 94
SD	14.1	14.0	14.0
AGE CATEGORIZATION (%)			
>= 18 AND < 65	187 (52.7)	196 (54.6)	383 (53.6)
>= 65 AND < 75	102 (28.7)	103 (28.7)	205 (28.7)
>= 75 AND < 85	60 (16.9)	53 (14.8)	113 (15.8)
>= 65	168 (47.3)	163 (45.4)	331 (46.4)
>= 75	66 (18.6)	60 (16.7)	126 (17.6)
>= 85	6 (1.7)	7 (1.9)	13 (1.8)
SEX (%)			
MALE	210 (59.2)	206 (57.4)	416 (58.3)
FEMALE	145 (40.8)	153 (42.6)	298 (41.7)

RACE (%)			
WHITE	342 (96.3)	348 (96.9)	690 (96.6)
BLACK OR AFRICAN AMERICAN	0	5 (1.4)	5 (0.7)
AMERICAN INDIAN OR ALASKA NATIVE	0	1 (0.3)	1 (0.1)
OTHER	7 (2.0)	4 (1.1)	11 (1.5)
NOT REPORTED	6 (1.7)	1 (0.3)	7 (1.0)
ETHNICITY (%)			
HISPANIC OR LATINO	27 (7.6)	20 (5.6)	47 (6.6)
NOT HISPANIC OR LATINO	144 (40.6)	147 (40.9)	291 (40.8)
NOT REPORTED	184 (51.8)	192 (53.5)	376 (52.7)
COUNTRY BY GEOGRAPHIC REGION (%)			
USA/CANADA	45 (12.7)	34 (9.5)	79 (11.1)
EUROPE	174 (49.0)	190 (52.9)	364 (51.0)
LATIN AMERICA (CENTRAL/SOUTH AMERICA)	104 (29.3)	106 (29.5)	210 (29.4)
AUSTRALIA/NZ	32 (9.0)	29 (8.1)	61 (8.5)

The Applicant's Position:

The study was conducted in 114 sites in 25 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Columbia, Denmark, Finland, France, Germany, Greece, Israel, Italy, Mexico, New Zealand, Norway, Poland, Romania, Russian Federation, Spain, Sweden, UK, USA).

Baseline demographic characteristics in all randomized subjects were largely balanced between the nivo+rela FDC and nivolumab arms, and were representative of an unresectable or metastatic melanoma population with respect to these characteristics including age, race, and gender (Table 38).[24] The study population included ~18% of subjects ≥ 75 years of age, including almost 2% who were above the age of 85 years. Although the study permitted patients aged 12 and above to enter, no adolescents were enrolled.

The FDA's Assessment:

FDA agrees with the Applicant's summary of "relevant" protocol deviations and demographic characteristics. The sponsor defined relevant protocol deviations as those that would affect interpretability of key study results. Overall the number of reported "relevant" protocol deviations was low in both treatment arms; however, there was a numerically higher number of protocol deviations on the nivolumab-relatlimab FDC arm compared to the nivolumab monotherapy arm (8 versus 6). This higher number was related to more patients on the nivolumab-relatlimab FDC arm who had received prior anticancer or prohibited therapies (5 versus 3) and who had a baseline image performed outside the required window (3 versus 2). The relevant protocol deviations described are unlikely to have had a meaningful effect on interpretation of the study results. FDA also assessed the complete list of protocol deviations of which relevant protocol deviations were a subset. Additional protocols deviations are included in Table 39. FDA has concluded that it is unlikely any of the additional protocol deviations affect the accuracy or reliability of the study data.

Table 39: Additional Protocol Deviations, All Randomized Patients CA224047

	Nivolumab-relatlimab FDC N=355 n (%)	Nivolumab N=359 n (%)	Total N=714 N (%)
No measurable disease at baseline	3 (0.8)	1 (0.3	4 (0.6)
Radiotherapy completed <2 weeks prior to study treatment administration	1 (0.3)	1 (0.3)	2 (0.3)
Active brain metastases or leptomenigeal disease	0	1 (0.3)	1 (0.1)
Brain disease treated with whole brain radiation	1 (0.3)	0	1 (0.1)
Tumor assessment not performed on time	1 (0.3)	6 (1.7)	7 (1.0)

Source: Appendix 2.3 of the CSR

Key demographic characteristics were generally balanced between treatment arms. The median age of patients in the trial was 63 years, slightly lower than the median age at diagnosis (65 years) reported in the SEER registry. Melanoma occurs predominantly in the White patient population (approximately 94% of all cases diagnosed in the US [CDC 2012-2016]). While the proportion of patients enrolled in study CA224047 by race appears generally representative of the racial composition of melanoma cases in the US, and is comparable to enrollment by race in other trials (Whites 97-99.5%), the trial included very few patients of American Indian/Alaskan Native or Black/African American race and no patients of Asian race which may limit the generalizability of the study results to historically underrepresented populations.

FDA notes that only 8.8% of randomized patients were enrolled in the United States which appears limited as compared to other studies evaluating ICIs in patients with melanoma.

8.1.2.6. Other Baseline Characteristics

Data:

Table 40: Applicant - Baseline Disease Characteristics, All Randomized Subjects in CA224047

	Number of Subjects (%)		
	Nivo+rela FDC N = 355	Nivolumab N = 359	Total N = 714
AJCC STAGE v8 AT STUDY ENTRY			
UNRESECTABLE STAGE III	35 (9.9)	23 (6.4)	58 (8.1)
METASTATIC STAGE IV	320 (90.1)	335 (93.3)	655 (91.7)
UNKNOWN OR NOT REPORTED	0	1 (0.3)	1 (0.1)
BASELINE METASTASIS STAGE			
M0	35 (9.9)	23 (6.4)	58 (8.1)

M1	1 (0.3)	3 (0.8)	4 (0.6)
M1A	77 (21.7)	107 (29.8)	184 (25.8)
M1B	85 (23.9)	88 (24.5)	173 (24.2)
M1C	151 (42.5)	127 (35.4)	278 (38.9)
M1D	6 (1.7)	11 (3.1)	17 (2.4)
BRAF STATUS (%)			
MUTATION POSITIVE	136 (38.3)	139 (38.7)	275 (38.5)
MUTATION WILD-TYPE	219 (61.7)	220 (61.3)	439 (61.5)
MELANOMA SUBTYPE CLASSIFICATION			
CUTANEOUS ACRAL	41 (11.5)	41 (11.4)	82 (11.5)
CUTANEOUS NON ACRAL	249 (70.1)	254 (70.8)	503 (70.4)
MUCOSAL	23 (6.5)	28 (7.8)	51 (7.1)
OTHER	42 (11.8)	36 (10.0)	78 (10.9)
HISTORY OF BRAIN METASTASIS			
YES	6 (1.7)	13 (3.6)	19 (2.7)
NO	349 (98.3)	346 (96.4)	695 (97.3)
PERFORMANCE STATUS (ECOG) (FOR>= 18 YEARS OLD) (%)			
0	236 (66.5)	242 (67.4)	478 (66.9)
1	119 (33.5)	117 (32.6)	236 (33.1)
BASELINE BIOMARKER			
PD-L1 < 1%/NON-QUANTIFIABLE	209 (58.9)	212 (59.1)	421 (59.0)
PD-L1 >= 1%	146 (41.1)	147 (40.9)	293 (41.0)
LAG-3 < 1% EXPRESSION	87 (24.5)	90 (25.1)	177 (24.8)
LAG-3 >= 1% EXPRESSION	268 (75.5)	269 (74.9)	537 (75.2)
BASELINE LDH LEVEL (%)			
<= ULN	224 (63.1)	231 (64.3)	455 (63.7)
> ULN	130 (36.6)	128 (35.7)	258 (36.1)
NOT REPORTED	1 (0.3)	0	1 (0.1)
<= 2 X ULN	322 (90.7)	328 (91.4)	650 (91.0)
>2 X ULN	32 (9.0)	31 (8.6)	63 (8.8)
NOT REPORTED	1 (0.3)	0	1 (0.1)

Note: PD-L1 values were evaluated at (b) (4)

The Applicant's Position:

Baseline characteristics in all randomized subjects were balanced between the nivo+rela FDC and nivolumab arms, other than a higher percentage of subjects in the nivo+rela FDC arm with an AJCC v8 metastasis stage of M1c, a poor prognostic factor relative to lower stage disease. The baseline characteristics were largely representative of a population previously untreated for unresectable or metastatic melanoma (Table 30). A minority of subjects had tumors positive for LAG-3 at a 5% cutoff (35.7%), and PD-L1 at a 5% and 10% cut-off (24.4% and 19.6%, respectively).

The FDA's Assessment:

FDA agrees with the Applicant's summary of the baseline disease characteristics. Baseline disease characteristics were generally balanced between treatment arms. FDA noted that there were 78 (11%) patients having "other" listed as the Melanoma Subtype Classification in Table 40. FDA requested additional information from the Applicant for these patients to permit a more detailed review across subgroups. The Applicant submitted a table for other subtypes listed by Investigators on the CRF. In total. there were 20 additional subtypes. Only "subcutaneous" and "superficial spreading" other melanoma subtypes had >1 patient represented with 2 patients each; the other "other" subtypes (included acral lentiginous, cutaneous [superficial spreading subtype], and epithelioid) each had one patient represented. i.

The small numbers of patients represented for these additional subtypes of melanoma precluded further analyses.. There was a larger proportion of patients in Latin America that had cutaneous acral melanoma than other geographic regions, 26% versus 1.6%-7%, respectively. Patients in Canada had the smallest proportion of patients with cutaneous non-acral as compared to other regions, 38% versus 61%-80%, respectively.

8.1.2.7. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance: Per protocol, skipped doses were not permitted, but could be delayed. Treatment schedules were largely adhered to. The most common reason for dose delay was AEs for both arms, and most delays lasted ≤ 42 days. AEs accounted for the delay in a higher percentage of subjects receiving nivo+rela FDC, and the delays were longer (between 15-42 days) for a higher percentage of subjects in this arm (Table 58).

The percentage of patients experiencing dose delays was evenly distributed between treatment arms, and therefore unlikely to affect interpretation of the study results. Treatment compliance was monitored by routine monitoring of clinical source documentation and drug accountability as well as by the subject's medical record and CRF. Extent of exposure data are presented in Section 8.2.2.1.

Concomitant Medications: A similar proportion of subjects used concomitant medications overall (97.2% vs 94.4% in the nivo+rela FDC and nivolumab arms, respectively). However, there were differences in concomitant medication use in the two treatment arms across multiple therapeutic classes, largely with respect to higher use of corticosteroids in the nivo+rela FDC arm.

Immune-modulating Medications: A higher percentage of patients in the FDC arm were treated with corticosteroids and immunosuppressants for AEs (50.4% vs 35.4% in the nivolumab arm). Overall, for patients prescribed IMMs for IMAEs, there did not appear to be consistent differences in the median duration of treatment between the two treatment groups. The most frequently reported AEs of any grade that required IMMs were:

- Nivo+rela FDC: rash (6.2%), arthralgia (5.1%), pruritus (4.8%), and diarrhea (4.2%).
- Nivolumab: rash (3.6%), pruritus (3.3%), diarrhea (2.2%), and arthralgia (2.2%).

There is unlikely to be a detrimental effect on the interpretation of the outcomes of this study, as the use of IMMs was higher in the FDC arm, which would bias the results against the study treatment rather than the comparator arm.

Subsequent Anti-Cancer Therapy: A similar proportion of patients received subsequent anti-cancer therapies across the two treatment arms, including radiotherapy, surgery, and systemic agents (35.5% in the nivo+rela FDC arm and 37.3% in the nivolumab arm). Of those, 27.9% and 29.8% received subsequent systemic therapy in the nivo+rela FDC and nivolumab arms respectively, of whom 9.0% and 12.8% received immunotherapy (anti-PD-[L]1, anti-CTLA-4,

other), and 11.5% and 13.9% received BRAF/MEK inhibitors, respectively.

The FDA's Assessment:
FDA agrees with the Applicant's summary of treatment compliance, concomitant medication use, and subsequent anti-cancer therapies. There was a numerically higher incidence of dose delays for patients on the nivolumab-relatlimab FDC arm compared to the nivolumab monotherapy arm (39% versus 36%). Although adverse events were the most common reason for dose delay in both treatment arms, they were a more frequent cause on the nivolumab-relatlimab FDC arm (70% versus 60%). This pattern of dose delay due to adverse events appears to be consistent with toxicity profiles associated with combination immune checkpoint inhibitor regimens. There were no notable differences observed in the use of concomitant medications across geographic regions. FDA considers it unlikely that the incidence of dose delays or use of concomitant medications resulted in any significant bias that may affect the interpretation of study results.

8.1.2.8. Efficacy Results – Primary Endpoint

Data:

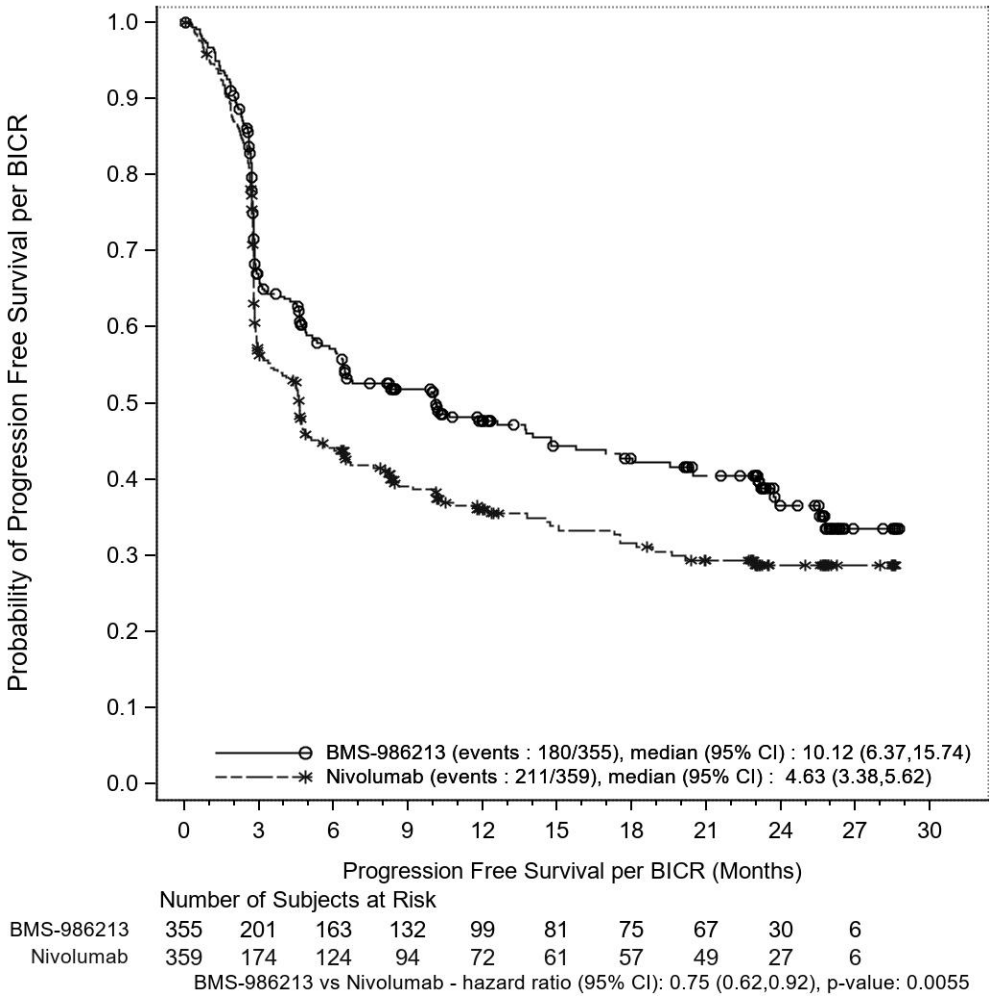
Table 41: Applicant - Primary Efficacy Endpoint of PFS per BICR, All Randomized Subjects in CA224047

	Nivo+rela FDC N = 355	Nivolumab N = 359
Events, n (%)	180 (50.7%)	211 (58.8%)
Median PFS (95% CI), mo.[a]	10.12 (6.37, 15.74)	4.63 (3.38, 5.62)
HR (95% CI)[b]	0.75 (0.62, 0.92)	
Stratified log-rank p-value	0.0055	
6-month PFS Rates (95% CI), %[a]	57.2 (51.5, 62.5)	44.1 (38.5, 49.5)
12-month PFS Rates (95% CI), %[a]	47.7 (41.8, 53.2)	36.0 (30.5, 41.6)

[a] Based on Kaplan-Meier estimates.

[b] Stratified Cox proportional hazards model. HR is nivo+rela 480/160 mg Q4W over nivolumab 480 mg Q4W.

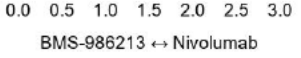
Figure 16: Applicant - CA224047 Kaplan-Meier Plot of Progression-free Survival per BICR, All Randomized Subjects



Note: statistical model for HR and p-value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3 (≥ 1% vs < 1%), BRAF (mutation positive vs mutation wild-type), AJCC M-stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from stratification because it led to subgroups with fewer than 10 subjects. Symbols represent censored observations.

Figure 17: Applicant - CA224047 Forest Plot of Treatment Effect on PFS in Pre-Defined Subsets, All Randomized Subjects

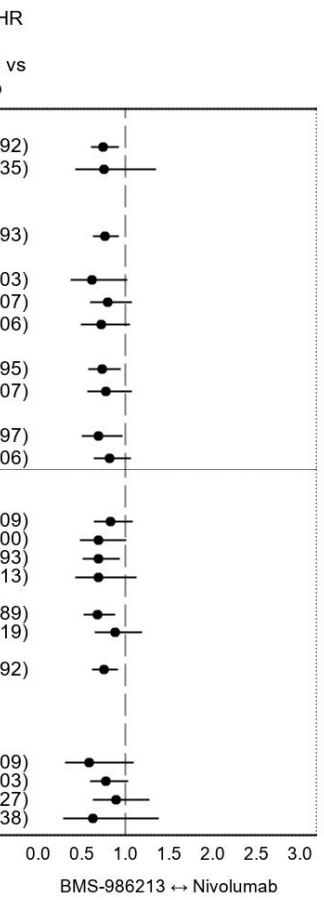
		BMS-986213		Nivolumab		
	N	N of events (N of subjects)	mPFS (95% CI)	N of events (N of subjects)	mPFS (95% CI)	Unstratified HR (95% CI) BMS-986213 vs Nivolumab
OVERALL	714	180 (355)	10.12 (6.37,15.74)	211 (359)	4.63 (3.38,5.62)	0.76 (0.62, 0.92)
LAG-3 STATUS AT BASELINE USING 1% CUTOFF						
LAG-3 >= 1%	537	131 (268)	12.58 (6.67,23.10)	151 (269)	4.76 (4.47,8.61)	0.75 (0.59, 0.95)
LAG-3 < 1%	177	49 (87)	4.83 (2.86,10.05)	60 (90)	2.79 (2.79,4.63)	0.78 (0.54, 1.15)
LAG-3 STATUS AT BASELINE USING 5% CUTOFF						
LAG-3 >= 5%	255	53 (121)	19.55 (10.09, N.A.)	66 (134)	10.15 (5.36,19.61)	0.81 (0.57, 1.17)
LAG-3 < 5%	459	127 (234)	6.37 (4.60,13.70)	145 (225)	2.89 (2.79,4.53)	0.70 (0.55, 0.89)
PD-L1 STATUS AT BASELINE USING 1% CUTOFF						
PD-L1 >= 1%	293	68 (146)	15.74 (10.09,25.79)	67 (147)	14.72 (5.09, N.A.)	0.95 (0.68, 1.33)
PD-L1 < 1%/NON-QUANTIFIABLE	421	112 (209)	6.37 (4.60,11.83)	144 (212)	2.92 (2.79,4.50)	0.66 (0.51, 0.84)
PD-L1 STATUS AT BASELINE USING 5% CUTOFF						
PD-L1 >= 5%	174	33 (88)	N.A. (13.70, N.A.)	36 (86)	19.61 (6.67, N.A.)	0.86 (0.54, 1.38)
PD-L1 < 5%/NON-QUANTIFIABLE	540	147 (267)	6.51 (4.86,10.68)	175 (273)	3.48 (2.83,4.63)	0.73 (0.58, 0.90)
PD-L1 STATUS AT BASELINE USING 10% CUTOFF						
PD-L1 >= 10%	140	29 (71)	N.A. (5.85, N.A.)	26 (69)	N.A. (10.48, N.A.)	1.13 (0.66, 1.92)
PD-L1 < 10%/NON-QUANTIFIABLE	574	151 (284)	8.31 (5.32,13.70)	185 (290)	3.48 (2.83,4.63)	0.69 (0.56, 0.86)
BRAF MUTATION STATUS						
BRAF MUTANT	275	67 (136)	10.09 (4.60,23.10)	83 (139)	4.60 (2.96,6.47)	0.74 (0.54, 1.03)
BRAF WILD-TYPE	439	113 (219)	10.12 (5.85,16.95)	128 (220)	4.63 (2.86,6.57)	0.76 (0.59, 0.98)
AJCC STAGE						
M0/M1any[0]	469	104 (232)	16.95 (10.68,23.79)	130 (237)	5.36 (4.63,10.15)	0.71 (0.55, 0.92)
M1any[1]	245	76 (123)	3.02 (2.79,4.90)	81 (122)	2.79 (2.76,4.50)	0.79 (0.58, 1.09)
BASELINE METASTASIS STAGE						
M0	58	17 (35)	6.77 (2.83, N.A.)	13 (23)	4.86 (2.86, N.A.)	0.94 (0.45, 1.94)
M1	4	0 (1)	N.R.	0 (3)	N.R.	
M1a	184	29 (77)	17.51 (9.92, N.A.)	55 (107)	9.20 (3.15,18.83)	0.62 (0.39, 0.97)
M1b	173	37 (85)	23.79 (6.51, N.A.)	54 (88)	4.76 (3.48,8.48)	0.57 (0.38, 0.87)
M1c	278	94 (151)	4.63 (2.83,10.09)	83 (127)	2.86 (2.79,4.63)	0.86 (0.64, 1.16)
M1d	17	3 (6)	N.R.	6 (11)	4.60 (0.99, N.A.)	
DISEASE STAGE AT STUDY ENTRY						
STAGE III	58	17 (35)	6.77 (2.83, N.A.)	13 (23)	4.86 (2.86, N.A.)	0.94 (0.45, 1.94)
STAGE IV	655	163 (320)	10.18 (6.37,16.95)	198 (335)	4.60 (3.15,5.62)	0.75 (0.61, 0.92)
HISTOLOGY (DISEASE SUBTYPE)						
CUTANEOUS ACRAL	82	31 (41)	3.32 (2.76,5.22)	29 (41)	2.79 (2.79,4.83)	0.84 (0.50, 1.39)
CUTANEOUS NON ACRAL	503	111 (249)	19.55 (10.09,25.79)	139 (254)	5.09 (4.53,9.20)	0.73 (0.57, 0.93)
MUCOSAL	51	14 (23)	8.31 (2.76,10.22)	19 (28)	2.92 (2.73,8.21)	0.72 (0.36, 1.45)
OTHER	78	24 (42)	6.37 (2.83,23.72)	24 (36)	3.07 (2.76,10.48)	0.77 (0.44, 1.36)
BASELINE LDH						
<= ULN	455	100 (224)	17.51 (11.83,23.79)	127 (231)	5.36 (4.60,8.61)	0.70 (0.54, 0.91)
> ULN	258	79 (130)	4.01 (2.79,5.52)	84 (128)	2.79 (2.76,4.50)	0.80 (0.59, 1.09)



Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Figure 17: Applicant - CA224047 Forest Plot of Treatment Effect on PFS in Pre-Defined Subsets, All Randomized Subjects

		BMS-986213		Nivolumab		
	N	N of events (N of subjects)	mPFS (95% CI)	N of events (N of subjects)	mPFS (95% CI)	Unstratified HR (95% CI) BMS-986213 vs Nivolumab
BASELINE LDH						
<= 2 x ULN	650	158 (322)	13.70 (8.31,20.47)	186 (328)	4.70 (4.47,7.62)	0.75 (0.60, 0.92)
> 2 x ULN	63	21 (32)	2.63 (2.00,2.79)	25 (31)	1.71 (1.48,2.56)	0.75 (0.42, 1.35)
HISTORY OF BRAIN METASTASES						
YES	19	3 (6)	N.R.	7 (13)	4.60 (1.48, N.A.)	
NO	695	177 (349)	10.12 (6.37,15.74)	204 (346)	4.63 (3.15,5.62)	0.76 (0.62, 0.93)
TUMOR BURDEN AT BASELINE PER BICR						
< Q1	156	26 (74)	25.79 (13.77, N.A.)	37 (82)	10.15 (4.63, N.A.)	0.62 (0.37, 1.03)
Q1 to <Q3	314	84 (161)	10.05 (5.32,17.51)	96 (153)	4.83 (3.15,7.62)	0.80 (0.60, 1.07)
>=Q3	159	53 (84)	2.86 (2.73,6.34)	53 (75)	2.76 (1.97,3.38)	0.72 (0.49, 1.06)
BASELINE ECOG PS						
0	478	108 (236)	18.04 (10.09,25.56)	136 (242)	4.83 (3.48,8.48)	0.74 (0.57, 0.95)
1	236	72 (119)	4.83 (3.32,6.51)	75 (117)	4.11 (2.76,4.63)	0.78 (0.56, 1.07)
SMOKING STATUS						
CURRENT/FORMER	265	59 (127)	10.15 (6.34, N.A.)	80 (138)	4.63 (2.92,8.08)	0.69 (0.49, 0.97)
NEVER SMOKED	425	115 (213)	10.05 (4.63,14.03)	125 (212)	4.63 (2.86,6.47)	0.82 (0.64, 1.06)
AGE CATEGORIZATION						
>=12 and <18	0					
>=18 and <65	383	99 (187)	6.47 (3.06,14.75)	117 (196)	4.57 (3.02,5.36)	0.83 (0.64, 1.09)
>=65 and <75	205	50 (102)	13.70 (6.34, N.A.)	60 (103)	4.60 (2.83,10.15)	0.69 (0.47, 1.00)
>=65	331	81 (168)	13.70 (6.51,23.72)	94 (163)	4.70 (2.86,8.48)	0.69 (0.51, 0.93)
>=75	126	31 (66)	11.83 (6.11, N.A.)	34 (60)	5.65 (2.83,17.28)	0.69 (0.42, 1.13)
SEX						
MALE	416	98 (210)	13.77 (6.51,25.56)	123 (206)	4.63 (3.02,6.51)	0.68 (0.52, 0.89)
FEMALE	298	82 (145)	6.08 (3.06,10.68)	88 (153)	4.63 (2.83,8.21)	0.88 (0.65, 1.19)
RACE						
WHITE	690	172 (342)	10.18 (6.37,16.95)	204 (348)	4.63 (3.48,5.65)	0.75 (0.61, 0.92)
BLACK OR AFRICAN AMERICAN	5			4 (5)	N.R.	
ASIAN	0					
OTHER	12	5 (7)	N.R.	2 (5)	N.R.	
REGION						
USA/CANADA	79	18 (45)	23.16 (6.47, N.A.)	21 (34)	3.75 (2.79,17.54)	0.58 (0.31, 1.09)
EUROPE	364	90 (174)	9.92 (5.16,18.04)	111 (190)	4.63 (2.89,6.67)	0.78 (0.59, 1.03)
LATIN AMERICA	210	60 (104)	4.83 (3.12,8.31)	66 (106)	3.38 (2.79,6.51)	0.90 (0.63, 1.27)
AUSTRALIA/NZ	61	12 (32)	N.A. (10.22, N.A.)	13 (29)	20.14 (4.57, N.A.)	0.63 (0.29, 1.38)



Note: HR and median (displayed as N.R.) are not computed for subset category with less than 10 subjects per treatment group.
N.A.: not applicable, median or limit of CI not estimable.

The Applicant's Position:

With a median follow up of 13.21 months (range: 0.0 - 33.1 months; defined as time between randomization date and last known alive date (for subjects who are alive) or death at the time of DBL on 09-Mar-2021, the primary endpoint of PFS by BICR and censoring for subsequent therapy (primary definition), was statistically significant and clinically meaningful for nivo+rela FDC vs nivolumab (Table 41). Median PFS in the nivo+rela FDC arm (10.12 months [95% CI: 6.37, 15.74]) was approximately 5.5 months longer compared to the nivolumab arm (4.63 months [95% CI: 3.38, 5.62]), and nivo+rela FDC demonstrated a higher PFS rate at 6 months and 12 months compared to nivolumab. For the primary endpoint of PFS per BICR, separation of the KM curves favoring nivo+rela FDC over nivolumab monotherapy occurred at ~3 months, at the time of the first on-study assessment, and this treatment effect was sustained through the period of follow up.

Efficacy favored nivo+rela FDC across major subgroups as defined by stratification factors, including AJCC v.8 M-status, LAG-3 and PD-L1 expression levels, and BRAF status (Figure 17), providing strong support for the clinical benefit of the combination of nivo+rela FDC relative to nivolumab for treatment of subjects with unresectable or metastatic melanoma.

Meaningful clinical benefit was seen regardless of LAG-3 expression, and nivo+rela FDC was favored across LAG-3 subgroups. While numerically lower HR point estimates were observed among subjects with lower PD-L1 expression compared to high PD-L1 expression (defined by 1%, 5%, or 10% thresholds), corresponding CIs were overlapping. Therefore, no conclusions can be made regarding differential benefit of nivo+rela FDC vs nivolumab according to PD-L1 status. CA224047 was designed to assess the benefit of nivo+rela FDC in an all-comer population, and was not powered to compare outcomes by biomarker subgroups.

The FDA's Assessment:

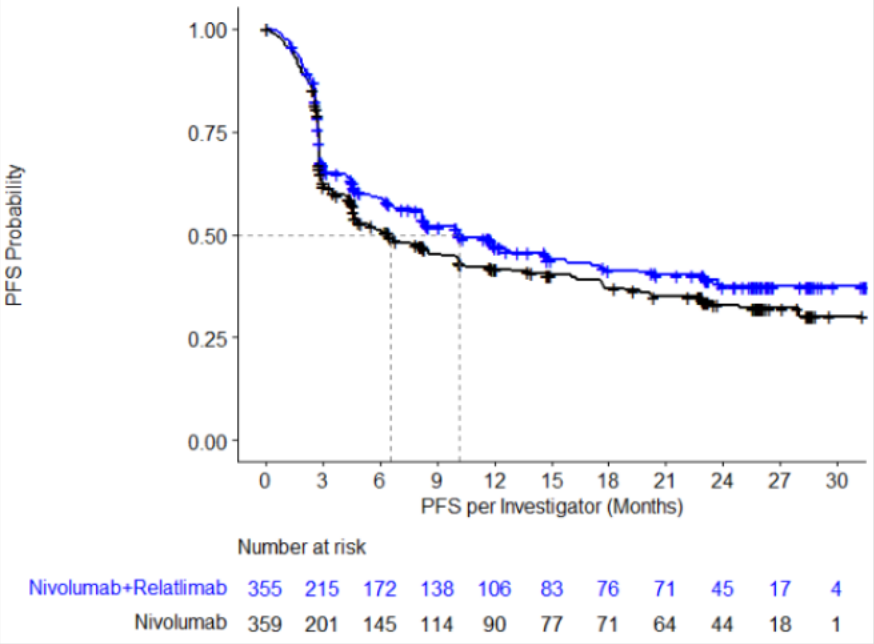
FDA agrees that CA224047 demonstrated a statistically significant improvement in PFS; the results of the final PFS analysis based on 391 BICR-assessed PFS events favored the nivolumab-relatlimab FDC arm with an estimated stratified PFS HR of 0.75 (95% CI: 0.62, 0.92 and a two-sided p-value less than the pre-specified alpha level of 0.049. The estimated median PFS was 10.1 months (95% CI: 6.4, 15.7) for the nivolumab-relatlimab FDC arm compared to 4.6 months (95% CI: 3.4, 5.6) for with the nivolumab arm, representing a 5.5 month improvement in median PFS.

To evaluate the potential effect of missing data, FDA confirmed the Applicant's sensitivity analysis that censored patients at the last assessment date prior to the PFS event for patients with two or more consecutively missing assessments prior to the PFS event. Using the stratified Cox regression model, the estimated PFS HR was 0.76 (95% CI: 0.62, 0.93), which was consistent with the primary analysis. In addition, FDA performed another sensitivity analysis where, instead of values collected per RAVE, the actual values collected per IRT were used for the AJCC M stage when performing the stratified PFS analysis; the estimated HR was 0.75 (95% CI: 0.62, 0.92) which was consistent with the primary analysis.

The SAP specified that the final PFS analysis would be conducted when 365 BICR-assessed PFS events had occurred, instead of the 391 PFS events that were actually observed. FDA conducted a sensitivity analysis based on 365 BICR-assessed PFS events. The estimated median PFS was 10.7 months (95% CI: 6.4, 18.0) for patients treated with nivolumab-relatlimab FDC vs. 4.6 months (95% CI: 3.4, 6.0) for patients treated with nivolumab, and the estimated stratified PFS HR was 0.73 (95% CI: 0.59, 0.89) in favor of the nivolumab-relatlimab FDC arm, which was consistent with the primary PFS analysis at 391 events.

Concordance between BICR and investigator-assessed PFS was 83.7% on the nivolumab-relatlimab FDC arm and 85.5% on the nivolumab arm in all randomized patients. The number of PFS events assessed by investigator (184 on the nivolumab-relatlimab FDC arm and 203 on the nivolumab arm) was similar to the number of events assessed by BICR (180 on the nivolumab-relatlimab FDC arm and 211 on the nivolumab arm). The observed improvement in PFS in patients treated with nivolumab-relatlimab FDC was smaller using investigator-assessed PFS as compared to the primary analysis using the BICR-assessed PFS; the stratified HR for investigator-assessed PFS in all randomized patients was 0.85 (95% CI: 0.69, 1.03), favoring the nivolumab-relatlimab FDC arm, with a median PFS of 10.2 months (95% CI: 8.2, 14.8) on the nivolumab-relatlimab FDC arm and 6.5 months (95% CI: 4.6, 10.1) on the nivolumab arm. Figure 18 shows the Kaplan-Meier curves for investigator-assessed PFS in all randomized patients.

Figure 18: Kaplan-Meier Plot of PFS per Investigator, All Randomized Subjects



Source: FDA generated analysis based on sponsor submitted data [ADEFTTES.xpt] (DCO: March 9, 2021).

The Applicant also presented the 6-month and 12-month PFS rates by treatment arms, however

the FDA considers these as exploratory analyses only. The point estimate of event rates at a fixed time point for a time-to-event endpoint can be misleading because it does not represent the entire effect size of treatment and the chosen landmark time is arbitrary.

On December 17, 2021, the Applicant submitted an updated subject-level analysis dataset, ADSL.xpt, at the October 28, 2021 database lock as part of the submission of the final OS data. On January 11, 2022, FDA sent an Information Request letter to the Applicant after noticing that, for subject (b) (6), the analysis value for baseline AJCC M Stage (variable 'STRAT4') was different from the value in the originally submitted ADSL.xpt data at the March 9, 2021 database lock. On January 14, 2022, the Applicant provided justification for the discrepancy and stated that the subject was erroneously categorized at the March 9, 2021 database lock due to a rounding issue in SAS that impacted the derivation. To assess the impact of this value change, FDA performed a sensitivity analysis using the updated ADSL.xpt dataset for the stratified PFS analysis. The estimated HR was 0.75 (95% CI: 0.62, 0.92) and the nominal p-value was 0.0055 based on stratified log-rank test, which were the same as the primary analysis using the original ADSL.xpt dataset.

FDA also agrees with the subgroup analyses presented by the Applicant (Figure 17). Overall, the subgroup analyses performed showed that there were no outlier subgroups and the treatment effect was generally consistent with that of the all randomized patients. Among the subgroup of patients enrolled in the United States (n=63), the HR was 0.40 (95% CI: 0.19, 0.84).

FDA conducted additional examination of PD-L1 subgroups due to concern that there may be detrimental effects as PD-L1 expression levels increased for patients treated with nivolumab-relaltlimab FDC compared to patients treated with nivolumab. In addition, FDA was concerned that the differences observed in PFS for the patients with higher levels of PD-L1 expression may also be observed in OS in patients with higher levels of PD-L1 expression (see section 8.1.2.10 for FDA analysis). FDA also examined baseline disease characteristics that have potential prognostic implications to evaluate if any of the characteristics or any toxicity-related events (see Section 8.2.8 for FDA analysis) may be contributing to the differences seen in PFS outcomes in the subgroups of patients with higher PD-L1 expression.

Results of subgroup analyses in patients with high PD-L1 status (i.e., PD-L1+ tumor expression level with cutoffs of ≥1%, ≥5% and ≥10%) showed higher observed HRs compared to the observed HRs in the corresponding subgroups of patients with PD-L1 negative tumors. Among patients with tumors with PD-L1 expression levels of ≥1%, ≥5% and ≥10%, the observed HRs were 0.95, 0.86, and 1.13, respectively, whereas among patients with PD-L1 negative tumors at expression levels of <1%, <5% and <10%, the observed HRs were 0.66, 0.73, and 0.69, respectively. FDA notes that the PD-L1 negative subgroups also include a total of 34 patients with non-quantifiable PD-L1 expression.

To further assess the clinical meaningfulness of the observed differences in HR observed between subgroups defined based on the PD-L1 cutoff levels, FDA examined certain baseline disease characteristics (e.g., LAG-3, LDH, baseline AJCC M stage, and baseline metastatic stage) of randomized patients across the PD-L1 subgroups (Table 42, Table 43, and Table 44).

Table 42: Baseline Disease Characteristics by PD-L1 Expression Level (1% cutoff)

	PD-L1 negative/non-identifiable			PD-L1 positive (≥1% cutoff)		
	Nivolumab-relatlimab FDC	Nivolumab	Overall	Nivolumab-relatlimab FDC	Nivolumab	Overall
	(N=209)	(N=212)	(N=421)	(N=146)	(N=147)	(N=293)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Baseline biomarker						
LAG-3 < 1%	75 (36)	83 (39)	158 (38)	12 (8)	7 (4.8)	19 (7)
LAG-3 ≥ 1%	134 (64)	129 (61)	263 (63)	134 (92)	140 (95)	274 (94)
LAG-3 < 5%	168 (80)	170 (80)	338 (80)	66 (45)	55 (37)	121 (41)
LAG-3 ≥ 5%	41 (20)	42 (20)	83 (20)	80 (55)	92 (63)	172 (56)
AJCC stage V8 at study entry						
Unresectable Stage III	22 (11)	11 (5)	33 (8)	13 (9)	12 (8)	25 (9)
Metastatic Stage IV	187 (90)	200 (94)	387 (92)	133 (91)	135 (92)	268 (92)
Unknown/not reported	0 (0)	1 (0.5)	1 (0.2)	0	0	0
Baseline LDH						
≤ ULN	131 (63)	128 (60)	259 (62)	93 (64)	103 (70)	196 (67)
> ULN	77 (37)	84 (40)	161 (38)	53 (36)	44 (30)	97 (33)
Not reported	1 (0.5)	0	1 (0.2)	0	0	0
≤ 2×ULN	187 (90)	190 (90)	377 (90)	135 (93)	138 (94)	196 (67)
> 2×ULN	21 (10)	22 (10)	43 (10)	11 (7.5)	9 (6)	97 (33)
Not reported	1 (0.5)	0	1 (0.2)	0	0	0
Baseline AJCC M stage						
M0/M1any[0]	134 (64)	133 (63)	267 (63)	98 (67)	104 (71)	202 (69)
M1any[1]	75 (36)	79 (37)	154 (37)	48 (33)	43 (29)	91 (31)
Baseline BRAF status						
Mutant	81 (39)	79 (37)	160 (38)	55 (38)	60 (41)	115 (39)
Wild-type	128 (61)	133 (63)	261 (62)	91 (62)	87 (59)	178 (61)
Baseline metastasis stage (CRF)						
M0	22 (11)	11 (5)	33 (8)	13 (9)	12 (8)	25 (9)

	PD-L1 negative/non-identifiable			PD-L1 positive (≥1% cutoff)		
	Nivolumab-relatlimab FDC	Nivolumab	Overall	Nivolumab-relatlimab FDC	Nivolumab	Overall
	(N=209)	(N=212)	(N=421)	(N=146)	(N=147)	(N=293)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
M1	1 (0.5)	3 (1.4)	4 (1.0)	0	0	0
M1A	50 (24)	57 (27)	107 (25)	27 (19)	50 (34)	77 (26)
M1B	44 (21)	51 (24)	95 (23)	41 (28)	37 (25)	78 (27)
M1C	91 (44)	84 (40)	175 (42)	60 (41)	43 (29)	103 (35)
M1D	1 (0.5)	6 (2.8)	7 (1.7)	5 (3.4)	5 (3.4)	10 (3.4)
Gender						
Female	91 (44)	90 (43)	181 (43)	54 (37)	63 (43)	117 (40)
Male	118 (57)	122 (59)	240 (57)	92 (63)	84 (57)	176 (60)
Region						
USA/Canada	21 (10)	20 (9)	41 (10)	24 (16)	14 (10)	38 (13)
Europe	107 (51)	110 (52)	217 (52)	67 (46)	80 (54)	147 (50)
Latin America	65 (31)	66 (31)	131 (31)	39 (27)	40 (27)	79 (27)
Australia/New Zealand	16 (8)	16 (8)	32 (8)	16 (11)	13 (9)	29 (10)

Source: FDA generated analysis based on sponsor submitted data [ADSL.xpt] (DCO: March 9, 2021).

Table 43: Baseline Disease Characteristics by PD-L1 Expression Level (5% cutoff)

	PD-L1 negative/non-identifiable			PD-L1 positive (≥5% cutoff)		
	Nivolumab-relatlimab FDC	Nivolumab	Overall	Nivolumab-relatlimab FDC	Nivolumab	Overall
	(N=267)	(N=273)	(N=540)	(N=88)	(N=86)	(N=174)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Baseline biomarker						
LAG-3 < 1%	82 (31)	90 (33)	172 (32)	5 (6)	0	5 (2.9)
LAG-3 ≥ 1%	185 (69)	183 (67)	368 (68)	83 (94)	86 (100)	169 (97)
LAG-3 < 5%	199 (75)	205 (75)	404 (75)	35 (40)	20 (23)	55 (32)
LAG-3 ≥ 5%	68 (26)	68 (25)	136 (25)	53 (60)	66 (77)	119 (68)
AJCC stage V8 at study entry						
Unresectable Stage III	27 (10)	15 (6)	42 (8)	8 (9)	8 (9)	16 (9)
Metastatic Stage IV	240 (90)	257 (94)	497 (92)	80 (91)	78 (91)	158 (91)
Unknown/not reported	0	1 (0.4)	1 (0.2)	0	0	0

	PD-L1 negative/non-identifiable			PD-L1 positive (≥5% cutoff)		
	Nivolumab-relatlimab FDC	Nivolumab	Overall	Nivolumab-relatlimab FDC	Nivolumab	Overall
	(N=267)	(N=273)	(N=540)	(N=88)	(N=86)	(N=174)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Baseline LDH						
≤ ULN	165 (62)	165 (60)	330 (61)	59 (67)	66 (77)	125 (72)
> ULN	101 (38)	108 (40)	209 (39)	29 (33)	20 (23)	49 (28)
Not reported	1 (0.4)	0	1 (0.2)	0	0	0
≤ 2×ULN	239 (90)	245 (90)	484 (90)	83 (94)	83 (97)	166 (95)
> 2×ULN	27 (10)	28 (10)	55 (10)	5 (6)	3 (3.5)	8 (4.6)
Not reported	1 (0.4)	0	1 (0.2)	0	0	0
Baseline AJCC M stage						
M0/M1any[0]	170 (64)	171 (63)	341 (63)	62 (71)	66 (77)	128 (74)
M1any[1]	97 (36)	102 (37)	199 (37)	26 (30)	20 (23)	46 (26)
Baseline BRAF status						
Mutant	106 (40)	106 (39)	212 (39)	30 (34)	33 (38)	63 (36)
Wild-type	161 (60)	167 (61)	328 (61)	58 (66)	53 (62)	111 (64)
Baseline metastasis stage (CRF)						
M0	27 (10)	15 (6)	42 (8)	8 (9)	8 (9)	16 (9)
M1	1 (0.4)	3 (1.1)	4 (0.7)	0	0	0
M1A	58 (22)	78 (29)	136 (25)	19 (22)	29 (34)	48 (28)
M1B	59 (22)	63 (23)	122 (23)	26 (30)	25 (29)	51 (29)
M1C	118 (44)	106 (39)	224 (42)	33 (38)	21 (24)	54 (31)
M1D	4 (1.5)	8 (2.9)	12 (2.2)	2 (2.3)	3 (3.5)	5 (2.9)
Gender						
Female	113 (42)	112 (41)	225 (42)	32 (36)	41 (48)	73 (42)
Male	154 (56)	161 (59)	315 (58)	56 (64)	45 (52)	101 (58)
Region						
USA/Canada	31 (12)	23 (8)	54 (10)	14 (16)	11 (13)	25 (14)
Europe	137 (53)	146 (54)	283 (52)	37 (42)	44 (51)	81 (47)
Latin America	79 (30)	83 (30)	162 (30)	25 (28)	23 (27)	48 (28)
Australia/New Zealand	20 (8)	21 (8)	41 (8)	12 (14)	8 (9)	20 (12)

Source: FDA generated analysis based on sponsor submitted data [ADSL.xpt] (DCO: March 9, 2021).

Table 44: Baseline Disease Characteristics by PD-L1 Expression Level (10% cutoff)

	PD-L1 negative/non-identifiable			PD-L1 positive (≥10% cutoff)		
	Nivolumab-relatlimab FDC	Nivolumab	Overall	Nivolumab-relatlimab FDC	Nivolumab	Overall
	(N=284) N (%)	(N=290) N (%)	(N=574) N (%)	(N=71) N (%)	(N=69) N (%)	(N=140)
Baseline biomarker						
LAG-3 < 1%	84 (30)	90 (31)	174 (30)	3 (4.2)	0	3 (2.1)
LAG-3 ≥ 1%	200 (70)	200 (69)	400 (70)	68 (96)	69 (100)	137 (98)
LAG-3 < 5%	210 (74)	210 (72)	420 (73)	24 (34)	15 (22)	39 (28)
LAG-3 ≥ 5%	74 (26)	80 (28)	154 (27)	47 (66)	54 (78)	101 (72)
AJCC stage V8 at study entry,						
Unresectable Stage III	29 (10)	17 (6)	46 (8.0)	6 (9)	6 (9)	12 (9)
Metastatic Stage IV	255 (90)	272 (94)	527 (92)	65 (92)	63 (91)	128 (91)
Unknown/not reported	0	1 (0.3)	1 (0.2)	0	0	0
Baseline LDH						
≤ ULN	177 (62)	177 (61)	354 (62)	47 (66)	54 (78)	101 (72)
> ULN	106 (37)	113 (39)	219 (38)	24 (34)	15 (22)	39 (28)
Not reported	1 (0.4)	0	1 (0.2)	0	0	0
≤ 2×ULN	255 (90)	261 (90)	516 (90)	67 (94)	67 (97)	134 (96)
> 2×ULN	28 (10)	29 (10)	57 (10)	4 (6)	2 (2.9)	6 (4.3)
Not reported	1 (0.4)	0	1 (0.2)	0	0	0
Baseline AJCC M stage						
M0/M1any[0]	183 (64)	183 (63)	366 (64)	49 (69)	54 (78)	103 (74)
M1any[1]	101 (36)	107 (37)	208 (36)	22 (31)	15 (22)	37 (26)
Baseline BRAF status						
Mutant	110 (39)	112 (39)	222 (39)	26 (37)	27 (39)	53 (38)
Wild-type	174 (61)	178 (61)	352 (61)	45 (63)	42 (61)	87 (62)
Baseline metastasis stage (CRF)						
M0	29 (10)	17 (6)	46 (8.0)	6 (9)	6 (9)	12 (9)
M1	1 (0.4)	3 (1.0)	4 (0.7)	0	0	0
M1A	60 (21)	84 (29)	144 (25)	17 (24)	23 (33)	40 (29)
M1B	67 (24)	68 (23)	135 (24)	18 (25)	20 (29.0)	38 (27)
M1C	123 (43)	109 (38)	232 (40)	28 (39)	18 (26)	46 (33)
M1D	4 (1.4)	9 (3.1)	13 (2.3)	2 (2.8)	2 (2.9)	4 (2.9)

	PD-L1 negative/non-identifiable			PD-L1 positive (≥10% cutoff)		
	Nivolumab-relatlimab FDC	Nivolumab	Overall	Nivolumab-relatlimab FDC	Nivolumab	Overall
	(N=284) N (%)	(N=290) N (%)	(N=574) N (%)	(N=71) N (%)	(N=69) N (%)	(N=140)
Gender						
Female	113 (40)	119 (41)	232 (40)	32 (45)	34 (49)	66 (47)
Male	171 (60)	171 (59)	342 (60)	39 (55)	35 (51)	74 (53)
Region						
USA/Canada	34 (12)	25 (9)	59 (10)	11 (16)	9 (13)	20 (14)
Europe	147 (52)	155 (53)	302 (53)	27 (38)	35 (51)	62 (44)
Latin America	81 (29)	87 (30)	168 (29)	23 (32)	19 (28)	42 (30)
Australia/New Zealand	22 (8)	23 (8)	45 (8)	10 (14)	6 (9)	16 (11)

Source: FDA generated analysis based on sponsor submitted data [ADSL.xpt] (DCO: March 9, 2021).

As shown in Table 42, Table 43, and Table 44, there are imbalances in some prognostic baseline disease characteristics (e.g., LAG-3, LDH, baseline AJCC M stage and baseline metastatic stage) between treatment arms for patients with PD-L1 positive expression of ≥1, 5, and 10%. These imbalances, coupled with the small numbers of patients and small number of events in each subgroup, suggests that PD-L1 expression level alone may not be the only characteristic to conclusively demonstrate the benefits of (or lack thereof) treatment in these subgroups. An analysis of adverse events (Section 8.2.8) did not identify a toxicity-related explanation for the differences in treatment effect between the treatment arms in each subgroup.

FDA considers the results of post-hoc subgroup analyses to be exploratory and should be interpreted with caution. Further, in subgroups not specifically defined by randomization stratification factors, the comparison between groups may be confounded by observed or non-observed factors, particularly for subgroups with a small number of events.. Therefore, no conclusion can be drawn regarding the efficacy of nivolumab-relatlimab FDC compared to nivolumab monotherapy in patients with different levels of PD-L1+ tumor expression.

8.1.2.9. Data Quality and Integrity

The Applicant's Position:

There were no issues identified for data quality or integrity from CA224047. Compliance audits of 4 sites were performed as part of implementing quality assurance, and audit certificates are provided as applicable in the individual study reports. The quality of data collected and analyzed was monitored according to BMS standard operating procedures. Additionally, the DMC routinely

monitored the study and did not request any modifications.

The FDA's Assessment:
FDA did not identify any issues regarding data integrity and submission quality during review of this application. See Section 4.1 for additional information.

8.1.2.10. Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:
The key secondary objective of OS was analyzed by the DMC per the first planned OS interim analysis but was not statistically significant; therefore, BMS remains blinded to OS and response results at this time. Per the SAP, ORR will only be tested hierarchically upon achieving statistical significance for OS at either OS IA2 (currently projected in October 2021 when 270/300 deaths occur) or the final analysis.

The FDA's Assessment:
FDA agrees with the Applicant's position regarding the results of the first planned interim analysis (IA1) for OS.

To perform a comprehensive risk:benefit assessment, FDA requested the results of the results of the analyses of IA1 and IA2 OS; IA1 OS analysis were directly released to FDA through the DMC to preserve study blindness. The original BLA submission submitted on July 19, 2021 included the final PFS data given the results of OS were based on IA1 and were not statistically significant. During the review of the application, BMS submitted updated OS data based on the results of the unblinded IA2 OS analysis (data cutoff date of October 28, 2021). .

The final OS analysis results are presented in Table 45 and Figure 19. At the time of the final OS analysis, a total of 297 (41.6% maturity) patients had OS events among all 714 randomized patients: 137 (38.6%) patients in the nivolumab-relatlimab FDC arm and 160 (44.6%) patients in the nivolumab arm. The median OS was not reached for patients treated with nivolumab-relatlimab FDC vs. 34.1 months (95% CI: 25.2, NR) for patients treated with nivolumab. Based on the stratification factors' values for the October 28, 2021 ADSL.xpt dataset, the HR was 0.80 (95% CI: 0.64, 1.01) in favor of nivolumab-relatlimab FDC arm. The 2-sided p-value for log-rank test did not reach the level of statistical significance with alpha boundary of 0.043 for the OS final analysis.

Table 45: Secondary Efficacy Endpoint of Final Overall Survival, All Randomized Subjects

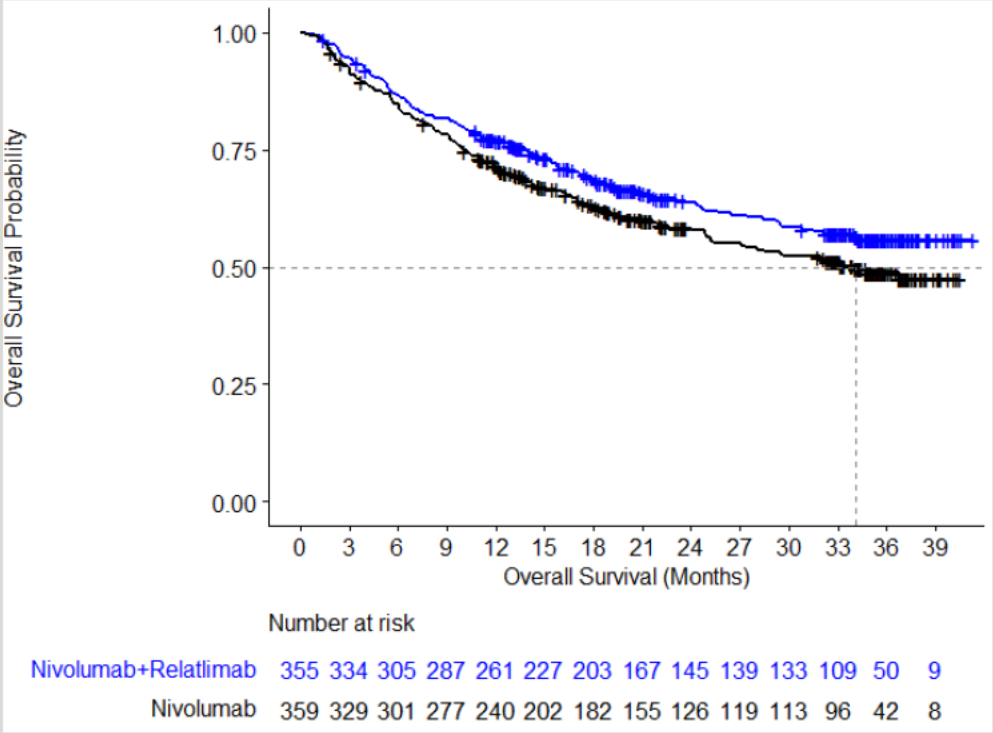
	Nivolumab-relatlimab FDC N=355	Nivolumab N=359
Events, n (%)	137 (39)	160 (45)

	Nivolumab-relatlimab FDC N=355	Nivolumab N=359
Median OS (95% CI), mo.[a]	NR (34.2, NR)	34.1 (25.2, NR)
HR (95% CI)[b]	0.80 (0.64, 1.01)	
Stratified log-rank p-value	0.0593	

[a] Based on Kaplan-Meier estimates.

[b] Stratified Cox proportional hazards model. HR is nivo+rela 480/160 mg Q4W over nivolumab 480 mg Q4W.
NR: not reached, median or limit of CI not estimable.
Source: FDA generated analysis based on sponsor submitted data [ADEFTTES.xpt] (DCO: October 28, 2021).

Figure 19: Kaplan-Meier Plot of Final Overall Survival, All Randomized Subjects



Source: FDA generated analysis based on sponsor submitted data [ADEFTTES.xpt] (DCO: October 28, 2021).

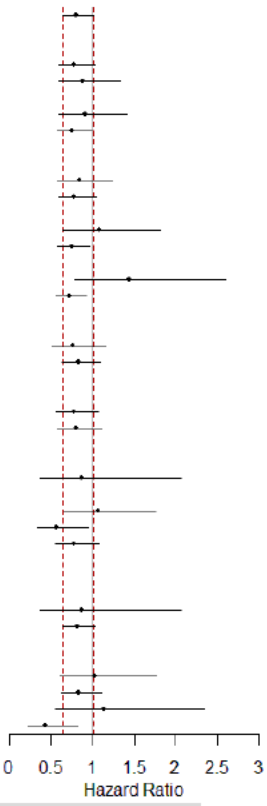
To investigate the impact of value change for the stratification factor of AJCC M Stage (variable 'STRAT4') as explained in Section 8.1.2.8, FDA performed a sensitivity analysis using the original March 9, 2021 ADSL.xpt dataset for the stratified OS analysis. The estimated HR was 0.80 (95% CI: 0.64, 1.01) and the nominal p-value was 0.0570 based on stratified log-rank test, which were very similar to the primary analysis. In addition, FDA performed another sensitivity analysis in which the actual values collected per IRT were used for the AJCC M stage when performing the stratified OS analysis instead of values collected per RAVE. The estimated HR was 0.80 (95% CI: 0.64, 1.01) was the same as the primary analysis.

FDA also conducted exploratory subgroup analyses of OS to assess the consistency of treatment

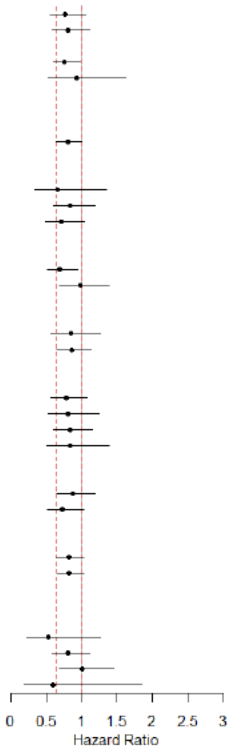
effect across potential or expected prognostic factors. The OS subgroup results were generally consistent with that of the all randomized population and did not show detriment in OS for the majority of the subgroups (Figure 20).

Figure 20: Forest Plot of Final Overall Survival in Pre-defined Subgroup, All Randomized Subjects

	Nivo+Rela FDC			Nivolumab			
	N	No.(%) events	mOS (95% CI)	N	No.(%) events	mOS (95% CI)	Unstratified HR (95% CI)
Overall	355	137 (38.6)	NA (34.2,NA)	359	160 (44.6)	34.1 (25.2,NA)	0.81 (0.64,1.01)
LAG-3 at baseline							
≥ 1%	268	94 (35.1)	NA (NA,NA)	269	111 (41.3)	NA (28.5,NA)	0.78 (0.59,1.03)
< 1%	87	43 (49.4)	24.5 (15.4,NA)	90	49 (54.4)	22.6 (15.1,33.2)	0.88 (0.59,1.33)
≥ 5%	121	38 (31.4)	NA (NA,NA)	134	44 (32.8)	NA (36.8,NA)	0.91 (0.59,1.41)
< 5%	234	99 (42.3)	NA (29.2,NA)	225	116 (51.6)	25.2 (18.3,33.2)	0.75 (0.57,0.98)
PD-L1 at baseline							
≥ 1%	146	48 (32.9)	NA (NA,NA)	147	56 (38.1)	NA (32,NA)	0.84 (0.57,1.24)
< 1%/Non-quantifiable	209	89 (42.6)	NA (27.4,NA)	212	104 (49.1)	27 (17.1,NA)	0.78 (0.59,1.04)
≥ 5%	88	30 (34.1)	NA (29.2,NA)	86	28 (32.6)	NA (34.7,NA)	1.08 (0.65,1.81)
< 5%/Non-quantifiable	267	107 (40.1)	NA (32.2,NA)	273	132 (48.4)	27.3 (19.5,NA)	0.75 (0.58,0.96)
≥ 10%	71	25 (35.2)	NA (28.5,NA)	69	19 (27.5)	NA (36.8,NA)	1.43 (0.79,2.6)
< 10%/Non-quantifiable	284	112 (39.4)	NA (34,NA)	290	141 (48.6)	27 (19.5,NA)	0.72 (0.56,0.92)
BRAF at baseline							
Mutant	136	41 (30.1)	NA (NA,NA)	139	51 (36.7)	NA (29.5,NA)	0.76 (0.51,1.15)
Wild-type	219	96 (43.8)	34.2 (24.7,NA)	220	109 (49.5)	27.3 (19.1,36.8)	0.83 (0.63,1.09)
AJCC M stage							
M0/M1any[0]	232	67 (28.9)	NA (NA,NA)	237	83 (35)	NA (36.8,NA)	0.77 (0.56,1.07)
M1any[1]	123	70 (56.9)	17.1 (10.8,31.5)	122	77 (63.1)	14.3 (9.1,20.1)	0.81 (0.58,1.11)
Baseline metastasis stage							
M0	35	12 (34.3)	NA (17.2,NA)	23	9 (39.1)	NA (13.2,NA)	0.87 (0.36,2.05)
M1	1	0 (0)		3	2 (66.7)		
M1a	77	28 (36.4)	NA (25.7,NA)	107	36 (33.6)	NA (33.2,NA)	1.07 (0.65,1.76)
M1b	85	24 (28.2)	NA (NA,NA)	88	38 (43.2)	36.8 (19.5,NA)	0.57 (0.34,0.95)
M1c	151	70 (46.4)	34.2 (17.9,NA)	127	70 (55.1)	22.1 (13.8,33.2)	0.78 (0.56,1.08)
M1d	6	3 (50)		11	5 (45.5)	NA (1.6,NA)	
Disease stage at study entry							
Stage III	35	12 (34.3)	NA (17.2,NA)	23	9 (39.1)	NA (13.2,NA)	0.87 (0.36,2.05)
Stage IV	320	125 (39.1)	NA (34,NA)	335	150 (44.8)	33.2 (25.2,NA)	0.81 (0.64,1.03)
Histology (disease subtype)							
Cutaneous acral	41	26 (63.4)	12.6 (6.5,27.4)	41	27 (65.9)	13.7 (10.9,21.6)	1.03 (0.6,1.77)
Cutaneous non acral	249	81 (32.5)	NA (NA,NA)	254	95 (37.4)	NA (33.2,NA)	0.82 (0.61,1.11)
Mucosal	23	14 (60.9)	21.4 (9.1,34)	28	16 (57.1)	14.1 (7.5,NA)	1.13 (0.55,2.34)
Other	42	16 (38.1)	NA (19.4,NA)	36	22 (61.1)	18.7 (9.1,36.8)	0.43 (0.22,0.82)



	Nivo+Rela FDC			Nivolumab			
	N	No.(%) events	mOS (95% CI)	N	No.(%) events	mOS (95% CI)	Unstratified HR (95% CI)
Baseline LDH							
≤ ULN	224	64 (28.6)	NA (NA,NA)	231	80 (34.6)	NA (NA,NA)	0.76 (0.55,1.06)
> ULN	130	72 (55.4)	17.1 (10.8,34)	128	80 (62.5)	14.5 (9.7,21)	0.8 (0.58,1.1)
≤ 2 x ULN	322	109 (33.9)	NA (NA,NA)	328	136 (41.5)	NA (29.6,NA)	0.76 (0.59,0.97)
> 2 x ULN	32	27 (84.4)	4.1 (2.4,6.5)	31	24 (77.4)	4.2 (2.3,9.7)	0.93 (0.53,1.63)
History of brain metastases							
Yes	6	3 (50)		13	5 (38.5)		
No	349	134 (38.4)	NA (34.2,NA)	346	155 (44.8)	34.1 (25.2,NA)	0.8 (0.64,1.01)
Tumor burden at baseline per BICR							
< Q1	74	13 (17.6)	NA (NA,NA)	82	19 (23.2)	NA (NA,NA)	0.67 (0.33,1.35)
Q1 to < Q3	161	61 (37.9)	NA (29.6,NA)	153	67 (43.8)	36.8 (24.9,NA)	0.84 (0.59,1.19)
≥ Q3	84	50 (59.5)	17 (10.8,34)	75	53 (70.7)	9.1 (5.7,18.7)	0.71 (0.48,1.05)
ECOG PS							
0	236	73 (30.9)	NA (NA,NA)	242	99 (40.9)	NA (32,NA)	0.69 (0.51,0.94)
1	119	64 (53.8)	18.2 (14.5,29.6)	117	61 (52.1)	19.5 (12.1,NA)	0.98 (0.69,1.38)
Smoking							
Current/Former	127	43 (33.9)	NA (34.2,NA)	138	53 (38.4)	NA (29.6,NA)	0.85 (0.57,1.27)
Never smoked	213	91 (42.7)	NA (29.2,NA)	212	100 (47.2)	29.5 (22.1,NA)	0.85 (0.64,1.13)
Age							
≥ 18 and < 65	187	66 (35.3)	NA (NA,NA)	196	85 (43.4)	36.8 (24.9,NA)	0.78 (0.57,1.08)
≥ 65 and < 75	102	40 (39.2)	NA (24.8,NA)	103	46 (44.7)	33.2 (21.6,NA)	0.81 (0.53,1.24)
≥ 65	168	71 (42.3)	NA (24.7,NA)	163	75 (46)	33.2 (22.1,NA)	0.83 (0.6,1.15)
≥ 75	66	31 (47)	25.7 (18.2,NA)	60	29 (48.3)	29.5 (8.9,NA)	0.84 (0.5,1.39)
Sex							
Male	210	79 (37.6)	NA (32.2,NA)	206	83 (40.3)	NA (29.5,NA)	0.88 (0.65,1.2)
Female	145	58 (40)	NA (29.6,NA)	153	77 (50.3)	27 (18.3,34.7)	0.73 (0.52,1.03)
Race							
White	342	131 (38.3)	NA (34.2,NA)	348	153 (44)	34.7 (27,NA)	0.81 (0.64,1.03)
Black or African American	355	137 (38.6)	NA (34.2,NA)	354	156 (44.1)	34.7 (25.4,NA)	0.82 (0.65,1.04)
Other/Unknown	7	4 (57.1)		5	2 (40)		
Region							
USA/Canada	45	9 (20)	NA (NA,NA)	34	12 (35.3)	NA (19.5,NA)	0.53 (0.22,1.26)
Europe	174	69 (39.7)	NA (30.8,NA)	190	84 (44.2)	34.7 (24.9,NA)	0.8 (0.58,1.1)
Latin America	104	54 (51.9)	23.1 (12.6,29.6)	106	57 (53.8)	19.5 (14.1,28.5)	1 (0.69,1.45)
Australia/NZ	32	5 (15.6)	NA (NA,NA)	29	7 (24.1)	NA (NA,NA)	0.59 (0.19,1.85)



Hazard ratio (HR) < 1 favored nivolumab-relatlimab FDC to be associated with a longer OS than nivolumab.
HRs and medians are not computed for subgroup categories with < 10 subjects per treatment group. HRs are calculated using Cox proportional hazards model with randomized treatment as the only covariate.
NA.: not applicable, median or limit of CI not estimable.
Area within the red dashed lines represents the 95% CI for the overall (all patients) stratified HR.
Source: FDA reviewer generated analysis based on sponsor submitted data [ADSL.xpt and ADEFTTES.xpt] (DCO: October 28, 2021).

Similar to the PFS subgroup analyses results shown in Figure 17, the OS subgroup analyses in patients with tumors with high PD-L1 status (i.e., Similar to the PFS subgroup analyses results shown in Figure 17, the OS subgroup analyses in patients with tumors with high PD-L1 status (i.e., PD-L1+ tumor expression level with cutoffs of ≥1%, ≥5% and ≥10%) also resulted in higher observed HRs as compared to the observed HRs in the corresponding subgroups of patients with PD-L1 negative tumors. Among patients with PD-L1 expression levels of ≥1%, ≥5% and ≥10%, the observed HRs were 0.84, 1.08, and 1.43, respectively, whereas among patients with PD-L1 negative tumors at expression levels of <1%, <5% and <10%, the observed HRs were 0.78, 0.75, and 0.72, respectively. However, as noted in Section 8.1.2.8, the imbalances observed in some prognostic baseline disease characteristics (see Table 42, Table 43, and Table 44), coupled with the small numbers of patients and small number of events in each of the subgroups, suggests that PD-L1 expression level alone may not conclusively indicate differential effects on OS in these subgroups. Therefore, no conclusion can be drawn regarding the efficacy of

nivolumab-relatlimab FDC compared to nivolumab monotherapy in patients with different levels of PD-L1+ tumor expression.

In addition, the HRs for subgroups of baseline metastasis stage ('M1a') and histology ('Cutaneous acral' and 'Mucosal') were also slightly greater than 1. However, since the numbers of patients and number of events in these subgroups were small, the HR may not provide a reliable estimate of the treatment effect on OS in the given subgroups. Therefore, results in these exploratory subgroup analyses need to be interpreted with caution.

Objective Response Rate and Duration of Response:
The results of the analyses of ORR and DoR per BICR analyses results are shown in Table 46Table 45.

Table 46: Objective Response Rate and Duration of Response by BICR

	Nivolumab-relatlimab FDC N=355	Nivolumab N=359
Confirmed Best Objective Response (BOR) per BICR, n (%)		
Complete Response (CR)	58 (16)	51 (14)
Partial Response (PR)	95 (27)	66 (18)
Stable Disease (SD)	61 (17)	59 (16)
Progressive Disease (PD)	105 (30)	149 (42)
NonCR/NonPD	9 (2.5)	6 (1.7)
Not Evaluable (NE)	27 (8)	28 (8)
ORR		
% (95% CI)[a]	43 (38, 48)	33 (28, 38)
DoR per BICR		
Median (95% CI), mo[b]	NR (30, NR)	NR (30, NR)

[a] Two-sided 95% exact confidence interval computed using the Clopper-Pearson method.
[b] Based on Kaplan-Meier estimates.
NR: not reached, median or limit of CI not estimable.
Source: FDA generated analysis based on sponsor submitted data [ADEFRESP.xpt] (DCO: October 28, 2021).

A sensitivity analysis of ORR per investigator assessment showed consistent results, with an ORR of 46.5% (95% CI: 41.2, 51.8) in the nivolumab-relatlimab FDC arm versus 37.0% (95% CI: 32.0, 42.3) in the nivolumab arm. Of the patients who had a response, median DoR per BICR was not reached for both arms at the data cutoff date. Among the responders, 83.7% had DoR follow-up for at least 6 months for nivolumab-relatlimab FDC arm, and 80.3% for nivolumab arm.

8.1.2.11. Dose/Dose Response

The Applicant's Position:

See Section 8.1.4 for efficacy results at a different dosing regimen (nivo 240 mg + rela SAV 80 mg Q2W). E-R analyses over different dose regimens are presented in Sections 6.3.2.1 and 6.3.2.2.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.1.2.12. Durability of Response

The Applicant's Position:
There was a separation of the PFS KM curves starting at the time of the first tumor assessment (12 weeks), which was sustained though the period of follow up to date.

The FDA's Assessment:
FDA acknowledges the Applicant's position based on KM curves presented in Figure 16. In addition, FDA notes that there are no data on durability of response beyond what is presented in Table 46.

8.1.2.13. Persistence of Effect

Data:
PFS2 was defined as the time from randomization to documented progression after the next line of therapy, per investigator assessment, or to death from any cause, whichever occurred first. Subjects who were alive and without progression after the next line of therapy were censored at their last known alive date. Median PFS2 per investigator were N.A. (95% CI: 21.75, N.A.) and 20.04 (95% CI: 15.44, 25.13) months for nivo+rela FDC vs nivolumab monotherapy, respectively. HR favored the nivo+rela FDC arm over the nivolumab monotherapy arm: 0.77 (95% CI: 0.61, 0.97).

The Applicant's Position:
PFS2 is an endpoint that supports measurement of longer-term clinical benefit and has been shown to correlate with OS in meta-analyses. The PFS2 result demonstrates that the PFS benefit for nivo+rela FDC persists after the initial treatment.

The FDA's Assessment:
Although FDA confirms the accuracy of the Applicant's results, PFS2 is considered an exploratory endpoint not suitable to support regulatory decision-making. Furthermore, the Applicant's analysis was not adjusted for multiplicity.

8.1.2.14. Efficacy Results – Exploratory PRO endpoints

The Applicant's Position:
No detriment was identified in the exploratory PRO analyses for the addition of relatlimab to

nivolumab compared with nivolumab in monotherapy as measured by valid and reliable scales: the FACT-M, EQ-5D-3L utility score and VAS. In addition, across both arms, there was no clinically significant worsening over time, based on the minimal clinically important differences in these measurements.

The FDA's Assessment:
FDA reviewed the data presented in the CSR assessing patient-reported outcome using the FACT-M, EQ-5D-3L utility score and VAS but did not conduct independent analyses to replicate all the results. Because there was no pre-specified statistical testing procedure or alpha allocation for any PRO endpoints, all PRO analyses are considered exploratory and no conclusions can be drawn from these results.

FDA has the following additional comments regarding the PRO analyses for this trial:

1. Per the Applicant, EQ-5D-3L, FACT-M and Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaires assessments are scheduled after randomization but prior to first dose, at on-study clinic visits while on treatment [Day 1 of each treatment cycle], and at Follow-Up Visit #1 [30 (±7) days from the last dose or coincide with the date of discontinuation (±7 days) if date of discontinuation is greater than 42 days after last dose] and Follow-Up Visit #2 [100 (±7) days from last dose of study treatment]. After follow-up visits have been completed, EQ-5D-3L and FACT-M melanoma subscale (MS) will be assessed at subsequent Survival Follow-Up Visits [every 3 months (±14 days)]. Whereas all participants will complete the EQ-5D-3L, only those ≥ 18 years of age at baseline will be asked to complete the FACT-M and WPAI:GH.
2. Per the CSR, compliance rates were estimated using the number of subjects eligible for a PRO assessment at a given scheduled visit. The CSR reported that compliance rates were generally high (≥ 85%) across baseline and all on-treatment visits and comparable between treatment arms for all measures, and compliance rates during the follow-up and survival follow-up visits were low (10 - 40%) and comparable between treatment arms. However, it should be noted that the Applicant stated in the CSR that 'there was a data collection issue (specifically, unemployed subjects skipped the item about disease interfering with their daily activities) for the WPAI:GH score.
3. The EQ-5D-3L is a composite that incorporates self-reported ability to function, pain, and general health status as filled out by the patient. This instrument is a generic preference based measure intended to provide a health utility index value for use in economic analyses and lacks content validity for use in estimating clinical benefit for the purposes of labeling claims, though we acknowledge that this instrument is often used by other regulatory authorities and/or payers.

8.1.2.15. Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Sensitivity analyses that were pre-specified in the SAP to assess robustness of the primary analysis to the following assumptions included:

- Censoring for subsequent therapy
- Constant hazards assumption
- Crossover of treatment effect across strata
- Adjustment for potentially important covariates.

The primary objective of the study was to compare the PFS (as determined by BICR) between treatment groups in all randomized subjects. The primary definition of PFS censoring for subsequent anticancer therapy was used in this analysis, with a resulting HR of 0.75.

1) A sensitivity analysis of PFS per BICR regardless of subsequent therapy showed similar results to the primary analysis with a HR of 0.76, leading to the conclusion that the results were robust to the adjustment for prior therapy.
2) The constant hazards assumption was checked by the addition of a time-dependent covariate, defined by treatment by time interaction, into the stratified Cox regression model. A two-sided Wald Chi-square p-value of less than 0.1 may indicate a potential non-constant treatment effect. The p-value was 0.1497, indicating no evidence of a non-constant hazard.
3) The potential for crossover of treatment effect was tested using a Gail and Simon test between treatment and strata for PFS per BICR, primary definition. The p-value for qualitative interaction between treatment and strata was 0.9466, indicating no crossover of treatment effect between strata.
4) A multivariate analysis was performed to assess the primary endpoint adjusting for baseline LDH level (≤ ULN, > ULN), age (< 65, ≥ 65), sex (male, female), ECOG (0, 1), brain metastases (yes, no). The treatment effect HR was 0.74, which was consistent with the primary analysis, indicating robustness to inclusion of these covariates.

The FDA's Assessment:
FDA notes that these sensitivity analyses presented by the Applicant are considered exploratory. However, FDA acknowledges that the results of the sensitivity analyses appear to be supportive of the robustness of the study results.

8.1.3. Supportive Phase 1/2 Study CA224020 (RELATIVITY -020)

8.1.3.1. Trial Design

The Applicant's Description:
CA224020 is a Phase 1/2 dose-escalation and cohort expansion study of the safety, tolerability, and efficacy of relatlimab administered alone and in combination with nivolumab in advanced solid tumors. CA224020 consisted of dose escalation (Parts A and B) and cohort expansion (Parts A1, C, D1, D2, and E). Data are based on a DBL of 25-Feb-2021.

Parts A, A1, and B, Advanced Solid Tumors: Part A evaluated the safety and tolerability of multiple

ascending doses of relatlimab monotherapy (n = 17). Part A1 Dose Expansion evaluated relatlimab 800 mg IV Q2W in subjects with NSCLC (n = 4) and RCC (n = 4). Part B evaluated escalating doses of nivolumab in combination with relatlimab administered sequentially, either Q2W or Q4W (Part B, n = 107)

Part C Expansion, Select Disease Cohorts: Part C evaluated the safety, tolerability and preliminary efficacy of sequential infusions of nivo 240 mg + rela SAV 80 mg Q2W in disease-restricted cohorts (n = 546), including two advanced melanoma cohorts: 66 subjects with previously untreated, unresectable or metastatic melanoma and 151 subjects with malignant melanoma who progressed on prior-IO therapy. Part C also included a cohort of bladder cancer subjects treated with nivolumab 480 mg and relatlimab 160 mg Q4W (n = 37).

Part D, Melanoma Previously Treated with Prior IO: Part D evaluated the safety, tolerability and efficacy in a homogenously defined cohort of melanoma subjects. Key eligibility criteria included refractory or relapsed disease within 3 months of last dose of anti-PD-1 therapy, documented progression while on prior anti-PD-1 containing regimen, and, for those with BRAF mutations, progression on a single line of a BRAF inhibitor.

Subjects in Part D1 were randomized across 3 arms:

- Arm 1: nivo 240 mg + rela SAV 80 mg Q2W coadministration (n = 189)
- Arm 2: nivo 480 mg + rela SAV 160 mg Q4W coadministration (n = 83)
- Arm 3: nivo+rela 480/160 mg Q4W FDC (BMS-986213) (n = 82)

Initially, the protocol allowed for enrollment to Arm 1. After revised protocol 09, the subjects were randomized 1:1:1 across the 3 arms. Once enrollment to Arm 1 was complete, subjects were randomized 1:1 to Arms 2 and 3.

Additional subjects with advanced melanoma were treated with nivo 480 mg + rela 160 mg Q4W (coadministered) in Part D2 (n = 164), which had a broader eligibility criteria with respect to the allowed prior therapies and performance status.

Part E, Melanoma: Part E was designed to measure exposure-response. Two cohorts of melanoma subjects are enrolled in Part E: 95 subjects who progressed on prior-IO treated with rela SAV 480 mg + nivo 480 mg Q4W and subjects with previously untreated, unresectable or metastatic melanoma randomized 1:1 to nivo 480 mg + rela SAV 160 mg Q4W (n = 38) and nivo 480 mg + rela SAV 480 mg Q4W (n = 38). Continued enrollment, assessment and follow-up of Part E is ongoing.

8.1.4. Study Results - Supportive Study CA224020

The Applicant's Description:

Part D1, Arm 1 (rela SAV 80 + nivo 240 mg Q2W): Melanoma Previously Treated with IO Therapy

Results from Part D, Arm 1 cohort expansion provide supportive evidence of the antitumor activity of nivolumab + relatlimab, long-term clinical benefit as demonstrated by ORR, DOR, and

tolerability in unresectable or metastatic melanoma (the proposed indication).

189 subjects with advanced melanoma who progressed while on anti-PD-1 therapies (refractory or relapsed disease within 3 months of last dose of anti-PD-1 therapy) were enrolled. The median age was 63.0 (range: 17 to 92). At study entry, 96.3% of subjects had Stage IV disease, 65.6% had M1c disease; 10.1% had brain metastases, and 33.3% had liver metastases. Baseline LDH levels were > ULN in 45.5% of subjects, with LDH levels ≥ 2x ULN in 14.8% of subjects; 17.5% of subjects were BRAF mutation positive, and 58.6% of subjects had LAG-3 expression ≥ 1%. All 189 subjects were treated with 1 (44.4%), 2 (40.2%), or 3 (11.6%) prior lines of systemic therapy. All subjects were treated with prior-IO therapy; 41.3% were treated with anti-CTLA4 therapy (alone or in combination with anti-PD-1) and 100% with anti-PD-1 therapy; 43.9% had progressive disease as their best response to prior anti-PD-1; 17.5% of subjects were treated with BRAF inhibitors.

Nivo+rela showed promising clinical benefit as noted by a BICR-confirmed ORR of 11.8% (95% CI: 7.6, 17.4), with 8 CRs, 14 PRs, and a DCR of 37.1%. The median TTR was 15.2 weeks. Responses were durable, median DOR was not reached at a minimum follow-up of 28.0 months. The majority of responders, 12/22 (54.5%) had ongoing responses.

The coprimary objective of Part D1 was to demonstrate preliminary efficacy in subjects with LAG-3 expression ≥ 1% based on the assumption that responses were associated with LAG-3 expression. The sample size was chosen to ensure the lower limit of the 95% CI for ORR exceeded 10% with an assumed observed ORR of 18% (as discussed with the agency at the end-of-phase 1 meeting in July 2017). Tumor response in the subgroup of LAG-3 expressing (≥ 1%) subjects (n = 109) was consistent with that of the entire cohort; ORR was 11.9% (95% CI: 6.5, 19.5), with 6 CRs and 7 PRs; the DCR was 39.4% and mDOR was not reached. Consistent with results in Study CA224047, where benefit was seen regardless of LAG-3 expression, Part D1 results showed that responses were observed in both subjects with LAG-3 expression ≥ 1% and ≤ 1%.

These deep and durable responses observed with the nivo+rela combination in a heavily pretreated patient population with numerous poor prognostic factors are likely to represent clinical benefit to patients with advanced relapsed or refractory melanoma previously treated with immunotherapies. The clinical management of patients following anti-PD-1 therapy failure is challenging, and a standard of care is lacking with limited evidence of activity of re-treatment with single agent anti-PD-1. Results from Part D1 demonstrated antitumor activity and durable clinical benefit with nivolumab and relatlimab combination in a patient population with a significant, unmet medical need.

Part D1, Arm 3 (nivo+rela 480/160 FDC Q4W): Melanoma Previously Treated with IO Therapy
Antitumor response was also observed in a cohort of 82 subjects with advanced melanoma (same patient population as Arm 1) who were treated with the to-be-marketed FDC formulation. BICR-confirmed ORR was 18.3% (95% CI: 10.6, 28.4), with 4 CRs, 11 PRs, and a DCR of 48.8%. The median TTR was 15.7 weeks. The median DOR was 18.4 months at a minimum follow-up of 19.4 months. The majority of responders, 9/15 (60.%), had ongoing responses.

Part C (nivo 240 mg + rela SAV 80 mg Q2W): Previously Untreated, Unresectable or Metastatic Melanoma

Part C evaluated safety and preliminary efficacy of nivo 240 mg + rela SAV 80 mg Q2W (sequential infusions) in 66 subjects with previously untreated, unresectable or metastatic melanoma. The median age was 64.5 (range: 24 to 87 years). At study entry, 61 (92.4%) subjects had Stage IV disease. Baseline LDH levels were > ULN in 24 (36.4%) subjects and 18 (27.3%) subjects were BRAF mutation positive.

Treatment with nivo 240 mg + rela SAV 80 mg Q2W resulted in a clinically meaningful rate of objective, durable responses in subjects with unresectable or metastatic melanoma. With a minimum follow-up time of 31.9 months, BICR confirmed ORR was 47.0% (95% CI: 34.6, 59.7). A CR was achieved in 11 (16.7%) subjects and a PR in 20 (30.3%) subjects. The confirmed disease control rate (CR+PR+SD ≥ 12w) was 59.1%. The median TTR was 8.1 weeks (95% CI: 7.71, 14.71), and responses were durable: median DOR was not reached (range 1.9 to 43.7 months). The majority of the responders (18/31 [58.1%]) had ongoing responses at the time of data cutoff. Median PFS per BICR was 12.7 months (95% CI: 3.71, 18.17) and median OS was 34.6 months (95% CI: 18.6, NA).

While OS and PFS benefits associated with nivo+rela treatment relative to currently available therapies cannot be concluded from a single-arm trial, the available data (specifically the deep and durable responses, and promising PFS results from this cohort, with over 2 years of minimum follow up) are supportive of the clinical benefit observed with nivo+rela treatment in unresectable or metastatic melanoma.

The FDA's Assessment: Given that Study CA224020 was a non-randomized trial with response rate as the primary efficacy endpoint and a study population that differed from the proposed indication in this application (i.e., previously untreated advanced melanoma), FDA considered Study CA224020 to be a supportive trial and did not independently verify its results.

8.1.5. Integrated Review of Effectiveness

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.1.6. Assessment of Efficacy Across Trials

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.1.7. Integrated Assessment of Effectiveness

The Applicant's Position:

CA224047 demonstrates that nivo+rela FDC delivers a statistically significant PFS benefit in patients with unresectable or metastatic melanoma, compared to nivolumab monotherapy, a current standard of care. The estimated 25% risk reduction in PFS events and median PFS benefit of 5.49 months is clinically meaningful for patients.[25,26] PFS favored nivo+rela FDC across major subgroups as defined by the stratification factors, including AJCC v.8 M-status, LAG-3, and PD-L1 expression levels, and BRAF status.

CA224047 is a large, adequately-powered clinical trial that provides substantial evidence of effectiveness for the proposed indication. The adaptive seamless study design permitted efficiency in terms of duration of development and number of subjects required to test the hypothesis, without compromising the robustness of the trial conduct. The study was randomized and double-blinded, using an established surrogate primary endpoint of PFS that was independently-assessed through a BICR. The key prognostic factors for advanced melanoma were balanced between the treatment arms through stratification and randomization. Issues arising through study conduct including PD-L1 re-scoring, documentation of M staging, the enrollment pause, and impact of COVID-19 as outlined in Section 8.1.1.3, were handled according to criteria pre-specified in the SAP which was completed in advance of the DBL. The strength of the study conclusions were further supported through sensitivity analyses (Section 8.1.2.15). The subjects included in the study were largely representative of the advanced melanoma patient population in the US in terms of demographics and disease characteristics, and were in line with other clinical trials in this disease area.

Data from Phase 1/2 study CA224020 provide further supportive evidence of the efficacy, and the potential for meaningful long-term clinical benefit, with nivo+rela combination in unresectable or metastatic melanoma, including subjects with advanced (relapsed or refractory) melanoma previously treated with immunotherapies, a population with a high unmet need and no available therapies.

CA224047 was a global, well-controlled clinical trial, and the efficacy data support the proposed indication. Opdualag at the recommended dose delivers clinically meaningful and statistically significant benefit for patients with unresectable or metastatic melanoma.

The FDA's Assessment:

CA224047 was a well-designed, well-conducted, randomized (1:1), double-blinded, active-controlled clinical trial comparing nivolumab-relatlimab FDC (480 mg/160 mg) administered intravenously (IV) Q4W, with nivolumab 480 mg IV Q4W in patients with previously untreated unresectable or metastatic melanoma. The trial demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of PFS by BICR (HR=0.75 [95% CI: 0.62, 0.92]; p=0.0055), corresponding to a 5.5-month improvement in median PFS). PFS is considered an acceptable primary endpoint to support traditional approval in advanced

melanoma when the trial is adequate and well controlled and the effect is robust and deemed clinically important in the context of an overall acceptable safety profile. . Although adolescent patients who were 12-17 years of age were eligible to participate in CA224047, no patients in this age group were enrolled. The efficacy of nivolumab-relatlimab FDC in adolescent patients ≥12 years of age who weigh at least 40 kg was extrapolated from adult patient data based on similarity in disease and similarity of expected E-R to ICI therapy (See Section 6 and 10 for additional details).

FDA noted that only 8.8% of randomized patients were enrolled in the United States. FDA notes that the percentages of patients enrolled in other studies evaluating melanoma in the US appears higher with ranges from 7% to 91%. Overall, FDA considers the study population of CA224047 to be generally representative of the US population that would be considered for treatment with nivolumab-relatlimab FDC. Enrollment of patients by race was comparable to enrollment by race in other trials and generally representative of the incidence by race of melanoma in the US. Multiple sensitivity analyses conducted by the Applicant and FDA confirmed the robustness of the PFS results, and the degree of concordance between BICR and investigator assessment of PFS was acceptable. The key secondary endpoint of OS at the final analysis suggested no detrimental effect on overall survival and did not demonstrate a statistically significant improvement in patients randomized to nivolumab-relatlimab FDC (HR 0.80 [95% CI: 0.64, 1.01]; p=0.0570).

FDA notes that although subgroup analyses for the primary endpoint of PFS and the secondary endpoint of OS were generally consistent with overall findings in the ITT population, the type I error of tests for subgroup analyses was not controlled. Therefore, FDA considers all subgroup analyses to be descriptive and hypothesis-generating only and caution should be applied when interpreting the results of these analyses. For example, FDA noted that the observed HR was higher for patients with high PD-L1 tumor expression level for both PFS and OS endpoints compared to the observed HRs in the corresponding subgroups of patients with PD-L1 low tumors. However, given the aforementioned limitations of subgroup analyses, observed imbalances in baseline disease characteristics between treatment arms, the small numbers of patients and small number of events in each of the subgroups, and the inconsistency in the effect across PD-L1 cutoffs and endpoints, the evaluation of PD-L1 expression level as a predictive biomarker for efficacy in this clinical setting remains exploratory. Overall, the effectiveness of nivolumab-relatlimab FDC was also supported by consistent demonstration of a trend for higher efficacy, albeit not statistically significant, in the nivolumab-relatlimab FDC arm compared to nivolumab for the key secondary endpoint of ORR where ORR was 43.1% (95%CI: 37.9, 48.4) in nivolumab-relatlimab FDC arm vs. 32.6% (95% CI: 27.8, 37.7) in nivolumab arm.

8.2. Review of Safety

The FDA's Assessment:

The primary safety data supporting this application are based on Study CA224047, a double-blind, randomized, adaptive Phase 2/3 study comparing nivolumab-relatlimab FDC to nivolumab in 714 patients (355 patients on the nivolumab-relatlimab FDC arm vs 359 patients on the nivolumab arm) with previously untreated, unresectable or metastatic melanoma. The safety analysis population consisted of patients who received at least one dose of the fixed-dose combination consisting of 480 mg nivolumab and 160 mg relatlimab IV Q4W or 480 mg nivolumab IV Q4W. Therapy continued until unacceptable toxicity, disease progression, withdrawal of consent, or end of study. While the safety analysis is primarily based on data reflecting a database lock date of March 9, 2021, the FDA also reviewed the 120-day safety update which provided an additional 4 months of safety data beyond the primary safety analysis with results up to the cut-off date of June 30, 2021, as well as safety data submitted at the time of the final OS analysis to assess for the presence of excess deaths in the nivolumab-relatlimab FDC arm.

The safety profile, including adverse events of special interest (AEOSI) and immune-mediated AEs, in patients who received nivolumab-relatlimab FDC is generally consistent with the established and well characterized safety profile of nivolumab. Overall, a review of the safety profile of the CA224047 safety dataset did not reveal new or unexpected safety events with the addition of relatlimab to nivolumab in patients with unresectable or metastatic melanoma. Treatment with nivolumab-relatlimab FDC did not result in excess deaths compared to the control arm.

8.2.1. Safety Review Approach

The Applicant's Description:

The primary safety analysis group relevant to the proposed indication of metastatic or unresectable melanoma consists of 355 subjects treated with nivo+rela FDC 480/160 mg Q4W in the pivotal study CA224047 (Table 29). The overall exposure to nivo+rela FDC within CA224047 is considered adequate to support characterization of the safety profile of this novel regimen, and permits comparison to the profile of nivolumab monotherapy, a current standard of care.

Additional supportive safety data is provided for all subjects with various tumor types (n = 412), including those with previously untreated melanoma (n = 38) who received at least one dose of nivo+rela 480/160 Q4W (the proposed dosing regimen) in CA224020 (Table 66). Data were not pooled between Studies CA224047 and CA224020 due to the differences in study populations, dose levels and formulations utilized as well as differences in CTCAE grading versions (Section 8.2.2); this was agreed to at the administrative pre-BLA meeting. The safety results from the pivotal study CA224047 are presented in Section 8.2.4. A summary of the safety in supportive study CA224020 is presented separately in Section 8.2.5.

The effect of relatlimab alone or in combination with nivolumab on QTc was performed for subjects in Parts A and B in CA224020. The preMarket drug-included liver injury assessment was

completed using the pooled data from CA224020, CA224060 ,and CA224047 studies.

The issues that warranted increased attention during the conduct of these studies include:

- Based on the MOA, the key expected drug toxicities were related to immune activation; therefore, particular attention was paid to detecting and reporting IMAEs and OESIs (Section 8.2.4.5).
- Myocarditis was identified as an important potential risk due to the observation of early, lethal myocarditis in LAG-3/PD-1 double knockout mouse models, coupled with emerging literature describing a low risk of severe checkpoint inhibitor-associated myocarditis in the post approval setting. Troponin monitoring was included in Study CA224047 as a pilot to determine if increased surveillance could support identification of asymptomatic myocarditis, and to permit characterization of the frequency and severity of myocarditis with nivo+rela FDC compared with an established anti-PD-1 monotherapy (Sections 8.2.3.2, 8.2.3.3, and 8.2.10.2). The timeframe of 2 months was selected was based on the median time-to-onset of observed myocarditis cases within Study CA224020 and the broader nivolumab program at the time of implementation. Both myocarditis and troponin elevation terms are OESIs (see Section 8.2.4.5), permitting a thorough characterization of the potential risk of myocarditis identified in the pre-clinical testing.
- As described in Section 5.5.1, CNS vasculitis and mild inflammation of the choroid plexus and brain vasculature were observed during pre-clinical general toxicity testing in cynomolgus monkeys. Due to the rare, but known, risk of immune-mediated events of the CNS with established immuno-oncology agents, CNS adverse event terms were added to the OESI category to support detection and reporting, including demyelination, meningitis and encephalitis. There are no routine laboratory or imaging evaluations that would enhance safety monitoring for CNS events within these clinical studies beyond clinical observation.
- Because both nivolumab and relatlimab contain only human immunoglobulin protein sequences, they have a low risk of inducing immunogenicity or associated infusion or hypersensitivity reactions. Given a theoretical risk of infusion reactions with the FDC formulation, a safety lead-in was employed for the first 18 subjects randomized in Study CA224047 to monitor for Grade 3 or 4 infusion reactions. No risks were identified.

There were no clinical holds for safety during the development program for relatlimab.

The FDA's Assessment:

The FDA safety review focused on analyses of the incidences of key adverse event (AE) categories including fatal and nonfatal SAEs, AEs resulting in permanent discontinuation of one or more of the study drugs, AEs requiring dose-modifications, common AEs, Grade > 3 AEs, and AESIs in patients receiving nivolumab with or without relatlimab. FDA agrees with the Applicant's position regarding the general safety review approach, and has the following additions:

1. FDA noted the central nervous system (CNS) adverse event (AE) terms added to the other events of special interest (OESI) category (including demyelination, meningitis and encephalitis), and performed a thorough investigation of data regarding neurotoxicity, including a comprehensive composite term of related preferred terms (PTs). An information request (IR) was sent to the Applicant regarding the conservative inclusion of CNS PTs and discussed in Section 8.2.6.2.
2. FDA agrees with the Applicant's position to assess infusion related reactions (IRR) as a type of hypersensitivity reaction (See Section 8.2.6.3) as multiple preferred terms were used to describe these events. This allows a more accurate assessment of IRR using pooled terms (i.e. "IRR vs hypersensitivity/infusion reaction").
3. FDA considers the methods used to assess myocarditis, including troponin monitoring twice weekly for the first 2 months (based on the median time-to-onset of observed myocarditis in Study CA224020) reasonable. During Study CA224047, the reference NCI-CTCAE grading criteria were updated from version 4.0 to 5.0. As a result of this change, Grade 1 myocarditis (previously defined as asymptomatic with laboratory or cardiac imaging abnormalities in CTCAE v4.0) was not included as an adverse event in CTCAE v5. Administrative letter 4 (dated 05-Sep-2018) instructed sites to code drug-related asymptomatic troponin elevation events, regardless of an ability to identify an imaging correlate of myocardial inflammation, as a drug-related troponin elevation, such that both myocarditis and troponin elevation terms were included as OESIs. See Sections 8.2.6.1 and 8.2.4.5.

The Applicant identified select AEs for closer evaluation based on the following 4 guiding principles:

1. AEs that may differ from, or be more severe than, AEs caused by non-immunotherapies
2. AEs that may require immunosuppression (e.g., corticosteroids) as part of their management
3. AEs whose early recognition and management may mitigate severe toxicity
4. AEs for which multiple adverse event or preferred terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization.

FDA agrees with each select AE category including AEs regardless of causality, and events occurring within 30 days of the last dose of study drug. Immune-mediated adverse events (IMAEs) included endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash. Multiple preferred terms describing each of these IMAEs were grouped into endocrine, GI, hepatic, pulmonary, renal, skin, and hypersensitivity/infusion reaction AE categories and included AEs occurring within 100 days of the last dose. FDA agrees with the definition of OESIs categorized as events that do not fulfill all criteria to qualify as select AEs or IMAEs but are still considered clinically significant. OESIs included the following categories: myositis/rhabdomyolysis, myocarditis, demyelination, Guillain-Barré syndrome, pancreatitis,

uveitis, encephalitis, myasthenic syndrome, graft versus host disease, troponin elevation, and meningitis.

8.2.2. Review of the Safety Database

The safety population is defined as all subjects who received at least one dose of study medication.

8.2.2.1. Overall Exposure

Data:

Table 47: Applicant - Safety Population

Safety Database for the Study Drug Individuals exposed to nivo+rela 480/160 mg Q4W (as SAV or FDC) in this development program		
	Nivo+rela FDC	**Nivo**
Pivotal study CA224047	355	359
	Nivo+rela 480/160 mg Q4W	
Supportive study CA224020	Total = 412	
Part B	8 (sequential admin)	
Part C	37 (sequential admin)	
Part D1 Arm 2	83 (coadmin)	
Part D1 Arm 3	82 (FDC)	
Part D2	164 (coadmin)	
Part E	38 (coadmin)	

Table 48: Applicant - Duration of Study Therapy Summary, All Treated Subjects in CA224047

	Nivo+rela FDC N = 355	Nivolumab N = 359
DURATION OF THERAPY (MONTHS)		
MEAN (MIN, MAX)	9.0 (0.0, 31.5)	9.2 (0.0, 32.2)
MEDIAN	5.55	4.86
>= 3 MONTHS (%)	239 (67.3)	241 (67.1)
>= 6 MONTHS (%)	175 (49.3)	159 (44.3)
>= 9 MONTHS (%)	143 (40.3)	131 (36.5)
>= 12 MONTHS (%)	104 (29.3)	101 (28.1)
>= 15 MONTHS (%)	71 (20.0)	76 (21.2)

Table 49: Applicant - Duration of Study Therapy Summary, All Nivo+Rela 480/160 mg Q4W Subjects in CA224020

	1L MEL 480/160 mg Q4W N = 38	**All 480/160 mg Q4W Treated Subjects N = 412**
Duration of Nivo and Rela Therapy, weeks		

Mean (SD)	28.1 (22.42)	30.7 (33.40*)
Median (Min- Max)	20.0 (4 - 77)	16.0 (2 - 158)

Note: Duration of therapy(weeks) for Q4W = (last dose date - first dose date + 28)/7.
* Numbers in the table are reported for rela: nivo duration of therapy SD = 33.45.

Table 50: Applicant - Cumulative Dose and Relative Dose Intensity, CA224047 and CA224020

	CA224047		CA224020	
	Nivo+rela FDC N = 355	**Nivolumab N = 359**	**1L MEL 480/160 mg Q4W N = 38**	**All 480/160 mg Q4W Treated Subjects N = 412**
Number of Doses				
Mean (SD)	10.2 (8.67)	10.5 (9.73)	6.8 (5.47)	6.0 (7.79*)
Median (Min - Max)	7.0 (1 - 35)	6.0 (1 - 35)	5.0 (1 - 19)	3.0 (0 - 37)
Cumulative Rela Dose per Subject, mg				
Mean (SD)	6555.055** (5549.6498)	-	1094.7 (875.98)	1186.0 (1286.76)
Median (Min - Max)	4480.000 (640.00 - 22400.00)	-	800.0 (160 - 3040)	640.0 (160 - 5920)
Cumulative Nivo Dose per Subject, mg				
Mean (SD)	-	5043.354 (4674.8113)	3284.2 (2627.95)	3555.8 (3858.68)
Median (Min - Max)	-	2880.000 (480.00 - 16800.00)	2400.0 (480 - 9120)	1920.0 (480 - 17760)
Relative Dose Intensity, n (%)				
< 50%	0	0	0	2 (0.5)*
50% to < 70%	5 (1.4)	9 (2.5)	0	5 (1.2)
70% to < 90%	41 (11.5)	45 (12.5)	4 (10.5)	25 (6.1)*
90% to < 110%	309 (87.0)	304 (84.7)	34 (89.5)	299 (72.6)*
≥ 110%	0	1 (0.3)	0	0
Not reported	0	0	0	81 (19.7)*

Note: Cumulative dose is the sum of all actual doses that a subject received. Relative dose intensity is defined as actual dose a subject received divided by planned dose.
* Numbers in the table are reported for rela: nivo no. of doses SD = 7.78; intensity < 50% = 3 (0.7%), 70 - < 90% = 27 (6.6%); 90% to < 110% = 295 (71.6%), and not reported = 82 (19.9%).
** Numbers are cumulative for rela FDC

The Applicant's Position:

The overall exposure to the nivo+rela FDC in Study CA224047 is considered adequate to support characterization of the safety profile of this novel regimen in the intended patient population, and meets the minimum specified in ICH E1A guideline.

Both nivo+rela FDC and nivolumab were well-tolerated, with a high percentage of patients receiving ≥ 90% of the planned dose intensity (87.0% vs 84.7%; Table 50). The median number of nivo+rela FDC doses and median duration of therapy received were similar to that of nivolumab monotherapy (Table 48, Table 50), with comparable numbers of subjects across treatment arms

continuing on treatment for 12 months or longer (29.3% in the nivo+rela FDC arm vs 28.1% in the nivolumab arm; Table 48).

In Study CA224020, the overall exposure to nivo+rela in all subjects who received at least one dose of nivo+rela 480/160 Q4W (n = 412), including in subjects with previously untreated melanoma (Part E; n = 38) provides additional safety information relating to the same dose and schedule of nivo+rela, including in patients in the intended indication. In subjects with previously untreated melanoma the median number of doses received was 5, corresponding to a median treatment duration of 20.0 weeks. In all subjects who received at least one dose of nivo 480 mg + rela SAV 160 mg Q4W the median duration of treatment for nivo+rela was 16 weeks, and for subjects who received nivo+rela FDC it was 19.8 weeks.

The FDA's Assessment:
FDA agrees with the Applicant's presentation of exposure and presents the data in a different tabular form in Table 51 below:

Table 51: Summary of Treatment Exposure for Pivotal Trial CA224047

	Nivolumab-relatlimab FDC N=355 N (%)	Nivolumab N=359 N (%)	Total N=714 N (%)
Treatment Duration in months			
Mean (SD)	9 (8)	9 (9)	9 (9)
Median (Min - Max)	6 (0 - 31)	5 (0 - 32)	6 (0 - 32)
Cumulative Dose (mg)			
Mean (SD)	6555 (5546)	5043 (4672)	5795 (5179)
Median (Min - Max)	4480 (640 - 22400)	2880 (480 - 16800)	3840 (480 - 22400)
Number of Doses Received			
Mean (SD)	10 (9)	11 (10)	10 (9)
Median (Min - Max)	7 (1 - 35)	6 (1 - 35)	6 (1 - 35)
Relative Dose Intensity (%)			
Mean (SD)	96 (7)	96 (8)	96 (7)
Median (Min - Max)	100 (61 - 103)	100 (63 - 120)	100 (61 - 120)

Source: ADSL (Subject-Level Analysis Dataset) - 2021-05-12, Customized ADEXS (Drv Exposure Summary Analysis Dataset) - 2021-05-12. Variables used: USUBJID, TRT01A, SAFFL, PARAM, AVAL

Note that while the Applicant and FDA reached the same incidence for treatment exposure, Table 51 displays the relative dose intensity mean at 96 (7-8% per arm) with a total RDI of 7%, and a median range of 61-120. The overall exposure was similar between arms in pivotal Study CA224047 and is considered adequate to support characterization of the safety profile.

8.2.2.2. Relevant characteristics of the safety population:

The Applicant's Description:

In CA224047, demographic and baseline disease characteristics in the safety population were well balanced between the nivo+rela FDC and the nivolumab arms. The characteristics represented a diverse population with respect to age, sex, and geographical region. Overall, 46.4% were above the age of 65, 17.6% above the age of 75, and 1.8% above the age of 85 years. These baseline characteristics are representative of the US advanced melanoma population (Section 8.1.2.5), supporting applicability of the study findings to routine clinical practice.

Of note, subjects with severe hepatic or renal impairment, and those on concomitant immunosuppressant medications including > 10 mg/day prednisone equivalents (unless for adrenal replacement) were excluded.

In CA224020, the safety population of all subjects who received at least one dose of nivo+rela 480/160 Q4W (n = 412) includes subjects with various advanced malignancies. However, the majority of the subjects had unresectable or metastatic melanoma (165 subjects from Part D1, 164 subjects from Part D2, 38 subjects from Part E, and 1 subject from Part B). In this pooled group of subjects, the median age was 63 years (range: 21 to 91), with a similar percentage of males (56.6%) and females (43.4%) and majority (94.4%) of subjects were of white race.

The baseline demographics and disease characteristics of subjects with previously untreated melanoma treated with the proposed dosing regimen, 480/160 Q4W (Part E; n = 38) in CA224020 were: median age was 63 years (range: 32 to 90), with a similar percentage of males (63.2%) and females (36.8%), and all subjects were of White race.

The FDA's Assessment:

FDA agrees with the Applicant's description of the demographic and baseline disease characteristics of the safety population as represented by Table 52 below. FDA notes that although melanoma occurs much less frequently in Black/African American, Asian and American Indian/Alaskan Native patients, the few numbers of patients in the CA224047 who are members of these demographic groups limits the assessment of safety in these groups.

Table 52: Demographic Characteristics of Safety Population

	Nivolumab-relatlimab FDC N=355 N (%)	Nivolumab N=359 N (%)	Total N=714 N (%)
Gender			
M	210 (59)	206 (57)	416 (58)
F	145 (41)	153 (43)	298 (42)
Age			
Mean (SD)	61 (14)	61 (14)	61 (14)
Median (Min - Max)	63 (20 - 94)	62 (21 - 90)	63 (20 - 94)
Age Group			

	Nivolumab-relatlimab FDC N=355 N (%)	Nivolumab N=359 N (%)	Total N=714 N (%)
<65	187 (53)	196 (55)	383 (54)
>=65	168 (47)	163 (45)	331 (46)
ECOG			
0	236 (66)	242 (67)	478 (67)
1	119 (34)	117 (33)	236 (33)
Race			
WHITE	342 (96)	348 (97)	690 (97)
OTHER	7 (2.0)	4 (1.1)	11 (1.5)
*	6 (1.7)	1 (0.3)	7 (1.0)
BLACK OR AFRICAN AMERICAN	0 (0)	5 (1.4)	5 (0.7)
AMERICAN INDIAN OR ALASKA NATIVE	0 (0)	1 (0.3)	1 (0.1)
Ethnicity			
*	184 (52)	192 (53)	376 (53)
NOT HISPANIC OR LATINO	144 (41)	147 (41)	291 (41)
HISPANIC OR LATINO	27 (8)	20 (6)	47 (7)
Country			
MEX	49 (14)	48 (13)	97 (14)
USA	37 (10)	26 (7)	63 (9)
BRA	30 (8)	25 (7)	55 (8)
DEU	29 (8)	35 (10)	64 (9)
ITA	28 (8)	26 (7)	54 (8)
AUS	27 (8)	27 (8)	54 (8)
FRA	25 (7)	19 (5)	44 (6)
ESP	20 (6)	14 (3.9)	34 (4.8)
POL	17 (4.8)	21 (6)	38 (5)
FIN	15 (4.2)	14 (3.9)	29 (4.1)
CHL	14 (3.9)	18 (5)	32 (4.5)
GRC	8 (2.3)	10 (2.8)	18 (2.5)
ROU	8 (2.3)	18 (5)	26 (3.6)
CAN	8 (2.3)	8 (2.2)	16 (2.2)
COL	7 (2.0)	4 (1.1)	11 (1.5)
AUT	6 (1.7)	5 (1.4)	11 (1.5)
NZL	5 (1.4)	2 (0.6)	7 (1.0)

	Nivolumab-relatlimab FDC N=355 N (%)	Nivolumab N=359 N (%)	Total N=714 N (%)
ARG	4 (1.1)	11 (3.1)	15 (2.1)
SWE	4 (1.1)	7 (1.9)	11 (1.5)
ISR	4 (1.1)	6 (1.7)	10 (1.4)
RUS	4 (1.1)	3 (0.8)	7 (1.0)
GBR	2 (0.6)	5 (1.4)	7 (1.0)
BEL	2 (0.6)	3 (0.8)	5 (0.7)
NOR	1 (0.3)	2 (0.6)	3 (0.4)
DNK	1 (0.3)	2 (0.6)	3 (0.4)

*Source: * represents missing data values from the sponsor, including NULL, empty text, and white space.*
Source: ADSL (Subject-Level Analysis Dataset) - 2021-05-12. Variables used: USUBJID, TRT01A, SAFFL, SEX, AAGE, AGEGR1, ECOGPS, RACE, ETHNIC, COUNTRY

The safety and the ITT population are identical. See Table of Demographic Characteristics for details regarding the ITT population in 8.1.2.5.

8.2.2.3. Adequacy of the Safety Database

The Applicant's Description:
The size of the CA224047 safety database and duration of follow-up are considered adequate to provide a reasonable estimate of adverse reactions that may occur with nivo+rela FDC treatment. Additionally, there are safety data from supportive Phase 1/2 study CA224020 across doses, regimens and malignancies. Safety data from CA224047 and CA224020 were generally consistent, with no unexpected safety signals observed (Table 53 and Table 66).

Together, data from CA224047 and CA224020 allow for a thorough assessment of the safety profile of the nivo+rela combination in the intended patient population, including characterization of common AEs and SAEs, and informing labeling and risk management strategies.

The FDA's Assessment:
The FDA agrees that the safety database supporting the application is adequate in size with sufficient duration of treatment with the investigational regimen at the proposed dose for a thorough assessment of adverse events. Overall, the disease characteristics of the study population are relevant to the target US population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

8.2.3.1. Issues Regarding Data Integrity and Submission Quality

The Applicant's Description:

Compliance audits were performed as part of implementing quality assurance, and audit certificates are provided as applicable in the individual study reports. The quality of data collected and analyzed was monitored according to BMS standard operating procedures. No issues with data quality and integrity of the submitted datasets were identified, which are of sufficient quality and completeness to permit a detailed analysis of safety. Both studies were monitored by a DMC throughout the course of trial conduct, and no safety concerns were identified.

Multiple measures were taken to minimize the impact of COVID-19 on the conduct of the clinical studies and analysis of data. Policies and internal guidance(s) were developed by the Sponsor for study conduct and monitoring activities, adapted as needed to accommodate changes to site and country policies. Additional information regarding COVID-19 was collected for protocol deviations, treatment and study discontinuations, dose delays, AEs, and overall survival. Remote visit information was collected for unscheduled, follow-up, and survival visits. A risk assessment due to the COVID-19 pandemic was performed for clinical study data quality, completeness, scientific integrity, and statistical interpretability prior to the DBL. Based on these assessments, the COVID-19 pandemic did not substantially impact data collection or the frequency or nature of important protocol deviations.

The FDA's Assessment:
FDA acknowledges the Applicant's position; the review did not uncover any data integrity issues related to safety. FDA agrees that the BLA submission was complete.

8.2.3.2. Categorization of Adverse Event

The Applicant's Description:
Safety was assessed by the monitoring and recording of AEs, concomitant medications, targeted physical examination findings and laboratory testing. Assessment of AEs included the type, frequency, grade, and causality of events, and particular attention was paid to the recording of SAEs, AEs leading to drug discontinuation, and deaths. AEs and SAEs were followed up until the resolution, stabilization, or until the participant was lost to follow up. AEs in CA224047 were categorized using MedDRA version 23.1 by SOC and PT and NCI-CTCAE version 5.0, and CA224020 used NCI-CTCAE version 4.0.

- Definitions of AEs and SAEs were included in the protocol, and all treatment-emergent AEs (including events considered drug-related and non-related, but excluding pre-existing conditions that did not worsen) were collected from initiation of study treatment using a safety window of 30 and 100 days after last dose.
- Further events of additional interest (IMAEs and OESIs) were monitored to comprehensively characterize the safety profile of the nivo+rela FDC, and were specified based on the potential risks identified during pre-clinical testing and the product mechanism of action, as well as the observed findings in the early clinical studies for nivo+rela FDC (Section 8.2.1).
- IMAE Case Definitions: IMAEs are defined as those select AEs (based on a predefined list of MedDRA v23.1 PTs) occurring within an extended follow-up period (100 days of the last dose

of study drug) that were considered potentially immune-mediated by the investigator and, with the exception of endocrine events, treated with IMMs and have no clear alternate etiology. IMAE are based on the PTs from the well-established nivolumab study program.

- Resolution of IMAEs: Defined by either complete resolution (having resolution date in CRF) or improvement to baseline grade among all "clustered" AEs in this category. Improvement to the grade at baseline implies that all different events in the clustered AE should at least improve to the corresponding (i.e., same PT) baseline grade.
- Frequency of Occurrence: The frequency of the AE was defined as the proportion of subjects with the worse CTCAE grade over all treated subjects.
- Recurrence of IMAEs: Patients who experience IMAEs may be rechallenged with study drug. Re-challenge is considered to occur when the study drug is administered after the onset of the IMAE. Recurrence is defined when, after improvement of the IMAE, a new or worsening IMAE of the same category occurs on or post re-challenge.
- Unresolved IMAE: Events that worsen into Grade 5 events (death) or have a resolution date equal to the date of death are considered unresolved. IMAEs with resolution dates that are missing, continuing or unknown are also considered unresolved.
- "Clustered" AEs: For each patient and specified IMAE category, the corresponding AE records are collapsed when: 1) multiple AE records have the same onset date; 2) The onset date of an event record is either the same day or 1 day later than the resolution data of a preceding event record (contiguous events); 3) The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events). Overlapping or contiguous on-treatment AEs within a specific IMAE category or subcategory are collapsed into what is termed "clustered" AE.

- OESIs are events of interest that do not fulfill all criteria to qualify as IMAEs and may differ from those caused by non-immunotherapies, but may require immunosuppression. Analyses of OESIs had extended follow-up (100-day window). The OESIs comprise a list of preferred terms grouped by specific category (myositis/rhabdomyolysis, myocarditis, demyelination, Guillain-Barre syndrome, pancreatitis, uveitis, encephalitis, myasthenic syndrome, GVHD, troponin elevation, and meningitis).

The FDA's Assessment:

FDA agrees with the Applicant's description of methods for coding, categorizing, and grading AEs and the procedures for interrogating the safety data for pre-specified IMAE, and OESI. FDA described the assessment and agreement with the categorization of PTs for composite AEs, IMAE, and OESI in Section 8.2.1.

FDA notes IMAEs are defined as AEs that meet all of the following criteria, per protocol:

- Events occurring within 100 days of the last dose.
- Events, regardless of causality, treated with immune-modulating medication "IMM"
  - Of note, endocrine AEs such as adrenal insufficiency, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis were

considered IMAEs regardless of IMM use since endocrine drug reactions are often managed without IMM.

- Events with no clear alternate etiology based on investigator assessment, or with an immune-mediated component.

Any discussion in the label of nivolumab-relatlimab FDC regarding IMARs (immune mediated adverse reactions) reflects the above description which was defined in the pivotal trial CA224047 (RELATIVITY-47), and should not be misinterpreted as a reference to all adverse reactions that occur in the setting of immune checkpoint inhibitor therapy. (See Section 11).

8.2.3.3. Routine Clinical Tests

The Applicant's Description:

The pre-dose laboratory testing performed within the CA224047 and CA224020 protocol-specified schedules of activities was considered adequate and in line with routine clinical practice. Monitoring for laboratory toxicities using local labs (non-fasted) was required prior to each dose and during the follow-up phase until all study treatment-related toxicities resolved, returned to baseline, or were deemed irreversible. In addition to routine safety lab testing, CA224047 and CA224020 required supplemental troponin and pregnancy testing. Regular pregnancy testing was required as the effect of nivo+rela FDC in pregnancy is not yet known, and as described in Table 31, troponin monitoring was incorporated during the first two months of study therapy as a means of enhanced cardiac surveillance. Of note, troponin is not typically monitored during immunotherapy treatment in routine clinical practice due to uncertain benefit.

Laboratory values considered clinically significant by the investigator or meeting the study definition of SAE were required to be reported as AEs. Additionally, any laboratory values leading to study drug discontinuation, interruption of study drug, or results requiring the subject to receive specific corrective therapy were to be reported as AEs if not otherwise previously reported. AEs were to be managed per the adverse event criteria for delay, resume, and discontinue of treatment details provided in the protocol. To ensure that relevant on-study laboratory values were captured independent of this classification, analyses of all hematology and serum chemistry laboratory abnormalities were performed for all treated subjects including while receiving treatment and for a safety window of 30 and 100 days after the last dose of study drug. In the laboratory summary tables, unless otherwise specified, subjects are counted only once for each lab parameter according to their worst on treatment CTC grade.

The FDA's Assessment:

FDA agrees with the Applicant's description of the routine clinical and laboratory assessments obtained during Study CA224047. Routine laboratory assessments were required within 14 days of randomization, every 4 weeks during study treatment (within 3 days prior to dosing in each cycle), and at 30 and 100 days after the last dose of study treatment. FDA noted the assessment of troponin monitoring as twice weekly for the first 2 months for assessment of myocarditis, as

described in Section 8.2.1

8.2.4. Safety Results from Pivotal Study CA224047

Table 53: Applicant - Summary of Safety, All Treated Subjects in CA224047

	No. of Subjects (%)			
Safety Parameters	**Nivo+rela FDC (N = 355)**		**Nivolumab (N = 359)**	
Deaths	108 (30.4)		119 (33.1)	
Primary Reason for Death				
Disease	90 (25.4)		99 (27.6)	
Study Drug Toxicity	3 (0.8)		2 (0.6)	
Unknown	1 (0.3)		2 (0.6)	
Other[a]	14 (3.9)		16 (4.5)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	121 (34.1)	91 (25.6)	105 (29.2)	74 (20.6)
≥ 1% of Subjects in Any Treatment Group				
Malignant neoplasm progression	13 (3.7)	11 (3.1)	19 (5.3)	12 (3.3)
Colitis	4 (1.1)	3 (0.8)	1 (0.3)	0
Diarrhoea	4 (1.1)	2 (0.6)	2 (0.6)	2 (0.6)
Back pain	4 (1.1)	3 (0.8)	2 (0.6)	0
Myocarditis	4 (1.1)	2 (0.6)	1 (0.3)	0
Adrenal insufficiency	4 (1.1)	4 (1.1)	0	0
Drug-related SAEs	50 (14.1)	33 (9.3)	28 (7.8)	17 (4.7)
≥ 1% of Subjects in Any Treatment Group				
Colitis	4 (1.1)	3 (0.8)	1 (0.3)	0
Diarrhoea	4 (1.1)	2 (0.6)	1 (0.3)	1 (0.3)
Myocarditis	4 (1.1)	2 (0.6)	1 (0.3)	0
All-causality AEs leading to DC	69 (19.4)	41 (11.5)	41 (11.4)	23 (6.4)
≥ 1% of Subjects in Any Treatment Group				
Pneumonitis	5 (1.4)	2 (0.6)	1 (0.3)	1 (0.3)
Malignant neoplasm progression	5 (1.4)	4 (1.1)	9 (2.5)	7 (1.9)
Myocarditis	5 (1.4)	2 (0.6)	0	0
Drug-Related AEs leading to DC	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)
≥ 1% of Subjects in Any Treatment Group				
Pneumonitis	5 (1.4)	2 (0.6)	1 (0.3)	1 (0.3)
Myocarditis	5 (1.4)	2 (0.6)	0	0
All-causality AEs	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
≥ 10% of Subjects in Any Treatment Group				
Fatigue	102 (28.7)	5 (1.4)	72 (20.1)	2 (0.6)
Asthenia	44 (12.4)	2 (0.6)	32 (8.9)	0
Pyrexia	39 (11.0)	0	32 (8.9)	1 (0.3)
Diarrhoea	81 (22.8)	4 (1.1)	60 (16.7)	5 (1.4)
Nausea	60 (16.9)	2 (0.6)	52 (14.5)	0

Constipation	38 (10.7)	2 (0.6)	22 (6.1)	0
Pruritus	88 (24.8)	0	62 (17.3)	2 (0.6)
Rash	59 (16.6)	3 (0.8)	48 (13.4)	2 (0.6)
Vitiligo	39 (11.0)	0	36 (10.0)	0
Arthralgia	84 (23.7)	6 (1.7)	53 (14.8)	2 (0.6)
Back pain	47 (13.2)	5 (1.4)	29 (8.1)	1 (0.3)
Urinary tract infection	37 (10.4)	2 (0.6)	29 (8.1)	2 (0.6)
Headache	62 (17.5)	1 (0.3)	42 (11.7)	1 (0.3)
Decreased appetite	52 (14.6)	2 (0.6)	26 (7.2)	1 (0.3)
Cough	48 (13.5)	1 (0.3)	37 (10.3)	0
Hypothyroidism	54 (15.2)	0	43 (12.0)	0
Anaemia	48 (13.5)	7 (2.0)	34 (9.5)	11 (3.1)
Drug-related AEs	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
≥ 5% of Subjects in Any Treatment Group				
Pruritus	83 (23.4)	0	57 (15.9)	2 (0.6)
Fatigue	82 (23.1)	4 (1.1)	46 (12.8)	1 (0.3)
Rash	55 (15.5)	3 (0.8)	43 (12.0)	2 (0.6)
Arthralgia	51 (14.4)	3 (0.8)	26 (7.2)	1 (0.3)
Hypothyroidism	51 (14.4)	0	43 (12.0)	0
Diarrhoea	48 (13.5)	3 (0.8)	33 (9.2)	2 (0.6)
Vitiligo	37 (10.4)	0	35 (9.7)	0
Nausea	29 (8.2)	0	15 (4.2)	0
ALT increased	28 (7.9)	5 (1.4)	11 (3.1)	2 (0.6)
Asthenia	28 (7.9)	0	14 (3.9)	0
AST increased	26 (7.3)	5 (1.4)	8 (2.2)	1 (0.3)
Decreased appetite	26 (7.3)	0	9 (2.5)	0
Myalgia	25 (7.0)	1 (0.3)	14 (3.9)	0
Hyperthyroidism	21 (5.9)	0	22 (6.1)	0
Headache	21 (5.9)	0	6 (1.7)	0
Infusion related reaction	21 (5.9)	0	13 (3.6)	0
Dry mouth	19 (5.4)	0	11 (3.1)	0

MedDRA version 23.1; CTC version 5.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

[a] The verbatim terms reported for the 'other' reasons for death were as follows: in the nivo+rela FDC arm: death not specified, aspiration pneumonia, myocardial infarction, septic shock (3 subjects), aspiration pneumonia (septicemia), medical history and respiratory failure not related to study treatment, respiratory failure aggravated by disease progression, neoplasm progression and SARS COV2 infection, pneumonia, suspected COVID-19, COVID-19 infection, and acute myocardial infarction; in the nivo arm: inadvertent pain medication overdose, acute respiratory insufficiency, arteria basiliaris thrombosis, progressive pulmonary insufficiency, coronavirus, COVID-19 (2 subjects), COVID-19 complications, sudden death, complications of cerebrovascular event, acute myocardial infarction (2 subjects), coronary ischemia, cardiac shock, septic shock and atypical pneumonia, and respiratory insufficiency.

8.2.4.1. Deaths

The Applicant's Description:

The majority of deaths in both treatment arms were due to disease progression. The frequency of deaths attributed to study drug toxicity was low and similar between the nivo+rela (n = 3) and nivolumab (n = 2) arms (Table 53). Causes of study drug toxicity-related deaths were hemophagocytic lymphohistiocytosis, acute edema of lung, and pneumonitis in the nivo+rela arm and sepsis and myocarditis, and worsening of pneumonia in the nivolumab arm. These deaths were largely attributed to an immune-mediated etiology. Similarly, the frequency and nature of deaths due to AEs of any cause were similar between the nivo+rela FDC (n = 14) and nivolumab (n = 16) arms, including deaths recorded as related to COVID-19. Of the 7 subjects who died due to COVID-19 (3 in the nivo+rela FDC arm and 4 in the nivolumab monotherapy arm), 5 subjects had already experienced disease progression per BICR prior to death.

The FDA's Assessment:

FDA agrees with the incidence of deaths from the Applicant's Table 53. AEs resulting in death, within 30 days after the last dose of drug, and beyond 30 days after the last dose of drug, are described below in Table 54. Deaths due to AEs assessed by FDA were consistent with the Applicant's assessment above in Table 53: Applicant - Summary of Safety, All Treated Subjects in CA224047 and were balanced between treatment arms.

Table 54: Summary of Deaths

	Nivolumab-relatlimab FDC N=355 N (%)	Nivolumab N=359 N (%)	Total N=714 N (%)
Total Deaths	**108 (30)**	**119 (33)**	**227 (32)**
Disease	90 (25)	99 (28)	189 (26)
Other	14 (3.9)	16 (4.5)	30 (4.2)
Study Drug Toxicity	3 (0.8)	2 (0.6)	5 (0.7)
Unknown	1 (0.3)	2 (0.6)	3 (0.4)
Within 30 days after last dose	**10 (2.8)**	**18 (5)**	**28 (3.9)**
Other	7 (2.0)	7 (1.9)	14 (2.0)
Disease	1 (0.3)	8 (2.2)	9 (1.3)
Study Drug Toxicity	1 (0.3)	1 (0.3)	2 (0.3)
Unknown	1 (0.3)	2 (0.6)	3 (0.4)
Beyond 30 days after last dose	**51 (14)**	**60 (17)**	**111 (16)**
Disease	35 (10)	42 (12)	77 (11)
Other	12 (3.4)	15 (4.2)	27 (3.8)
Study Drug Toxicity	3 (0.8)	1 (0.3)	4 (0.6)
Unknown	1 (0.3)	2 (0.6)	3 (0.4)

Source: ADSL (Subject-Level Analysis Dataset) - 2021-05-12. Variables used: USUBJID, TRT01A, SAFFL, DTHCAUS, DTH30TFL, DTH100FL, DTHDT, DTHFL, TRTEDT]

According to the ADAE dataset, fatal/Grade 5 AEs had an attribution to study drug in 7 (2%) patients on nivolumab-relatlimab FDC and 11 (3.1%) patients on nivolumab. AEs resulting in death included terms such as "malignant neoplasm progression" and "other" which may confound the assessment of AEs resulting in death (see Table 54). FDA reviewed each patient narrative for death not related to disease progression in patients treated with nivolumab-relatlimab FDC and summarized in Table 56

Table 55: AEs Resulting in Death

	Nivolumab-relatlimab FDC N=355 N (%)	Nivolumab N=359 N (%)	Total N = 714 N (%)
Death due to AEs	**19 (5)**	**20 (6)**	**39 (5)**
Malignant Neoplasm Progression	8 (2.3)	9 (2.5)	17 (2.4)
Acute Myocardial Infarction	1 (0.3)	1 (0.3)	2 (0.3)
Asthenia	1 (0.3)	0 (0)	1 (0.1)
Covid-19	1 (0.3)	1 (0.3)	2 (0.3)
Covid-19 Pneumonia	1 (0.3)	0 (0)	1 (0.1)
Death	1 (0.3)	1 (0.3)	2 (0.3)
Metastases To Central Nervous System	1 (0.3)	0 (0)	1 (0.1)
Pneumonia	1 (0.3)	1 (0.3)	2 (0.3)
Pneumonitis	1 (0.3)	0 (0)	1 (0.1)
Pulmonary Edema	1 (0.3)	0 (0)	1 (0.1)
Respiratory Failure	1 (0.3)	2 (0.6)	3 (0.4)
Sepsis	1 (0.3)	0 (0)	1 (0.1)
Septic Shock	1 (0.3)	0 (0)	1 (0.1)
Sudden Death	0 (0)	2 (0.6)	2 (0.3)
Atypical Pneumonia	0 (0)	1 (0.3)	1 (0.1)
Basilar Artery Thrombosis	0 (0)	1 (0.3)	1 (0.1)
Cerebrovascular Accident	0 (0)	1 (0.3)	1 (0.1)

Source: ADSL (Subject-Level Analysis Dataset) - 2021-05-12, ADAE (Analysis Adverse Events) - 2021-05-12. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEBODSYS, AEDECOD, AEOUT, AESDTH, AETOXGRN

Deaths due to AEs considered unrelated to study drug by investigators were balanced between treatment arms, including deaths attributed to COVID-19 (3 patients in the nivolumab-relatlimab FDC arm and 4 patients in the nivolumab monotherapy arm).

Table 56: Narratives for Deaths other than Disease Progression: Nivolumab-Relatlimab FDC Arm

Patient ID	Age/Sex	Investigator Reported Primary Cause of Death	Reviewer Comment
CA224047- (b) (6)	76/F	Death NOS	28 days after the 2nd infusion day, the patient developed Grade 1 diarrhea (related), steroids started and the diarrhea resolved. 13 days after the 3rd infusion day, the patient developed Grade 1 events of immune mediated hepatitis and diarrhea (related) that were treated with steroids and antibiotics. 6 days later the patient was scanned and had PD. 86 days after the 3rd (last) dose, the patient was hospitalized with Grade 3 sepsis and died 11 days later and died due to "unknown reason." An autopsy was not performed.
CA224047- (b) (6)	86/M	Aspiration PNA	28 days after the 8th infusion, the patient was diagnosed with Grade 2 events of Sjogren's syndrome (related) and started on steroids. 79 days after the 8th infusion, the patient was hospitalized due to Grade 4 aspiration PNA (not related) and died 9 days later. An autopsy was not performed.
CA224047- (b) (6)	79/M	Hemophagocytic lymphohistiocytosis: **Related**	Patient had PD on Day 254 and therapy was discontinued on Day 260 (last dose on Day 253). 29 days after the 10th (last) infusion day, the patient was hospitalized due to Grade 3 hypophysitis (not related). Steroids were administered and 48 days after the 10th (last) infusion day, the patient was hospitalized due to Grade 3 adrenocorticotropic hormone deficiency (not related). The patient was treated and discharged and on Day 322, 69 days after the 10th (last) infusion day, the patient hospitalized due to Grade 4 hemophagocytic lymphohistiocytosis (related), with cytopenia, increased ferritin, hypofibrinogenemia, EBV in the bone marrow and splenomegaly. Chest x-ray showed streaky, patchy consolidation in the cardio phrenic angle and treatment with IVIg, rituximab, and anakinra was administered. On Day 335 the patient died and an

Patient ID	Age/Sex	Investigator Reported Primary Cause of Death	Reviewer Comment
			autopsy was not performed.
CA224047- (b) (6)	75/M	Septic shock	On Day 69, 2 days after the 3rd infusion day, the patient was hospitalized due to Grade 2 influenza. On Day 261 the patient had progressive disease and therapy was discontinued on Day 295 (last dose was Day 267). On Day 303 the patient was hospitalized due to Grade 3 septic shock (not related) became progressively sick and died on Day 310. An autopsy was not performed.
CA224047- (b) (6)	70/M	Aspiration PNA and septic shock	On Day 104, 17 days after the 4th infusion, the patient developed Grade 3 confusional state (not related), with no treatment administered and no further details. On Day 116, 29 days after the 4th infusion, during hospitalization the patient was diagnosed with Grade 3 sepsis (not related) which presented with aspiration PNA. The patient died the next day (Day 117) and no autopsy was performed.
CA224047- (b) (6)	73/M	Death	On Day 20, 19 days after the 1st infusion day, the patient experienced a Grade 5 event dying of unknown reasons (not related) at their residence. The patient had previously been asymptomatic. No autopsy was performed. The patient had a history of hypertension, and was taking bisoprolol, furosemide, and losartan.
CA224047- (b) (6)	78/F	Septic shock	On Day 182, 15 days after the 7th infusion day, the patient was hospitalized due to Grade 3 gastric volvulus (not related) associated with lack of appetite. Digestive endoscopy showed gastric torsion. The patient was treated with medical management and the gastric volvulus resolved. On Day 183 the patient underwent trans hiatal hernioplasty. On Day 185 (18 days after the 7th infusion day) the patient was transferred to intensive care unit due to Grade 3 septic shock (not related) associated with respiratory failure and hypotension, and died on Day 186, An autopsy was not performed.
CA224047- (b) (6)	75/M	Pulmonary edema: **Related**	On Day 41 the patient experienced dyspnea and signs of lobar pneumopathy; 20 days after the 2nd infusion day, the patient died of pulmonary edema (related).

Patient ID	Age/Sex	Investigator Reported Primary Cause of Death	Reviewer Comment
			An autopsy was not performed. The study therapy was discontinued with the last dose received on Day 29.
CA224047- (b) (6)	48/M	Suspected covid	On Day 92 the patient had PD by RECIST but was treated beyond progression, and on Day 147 therapy was discontinued with the last dose received on Day 121. On Day 209 88 days after the 5th infusion day, the patient suspected COVID-19 infection due to rapidly progressive dyspnea, and COVID-19 related death of a close contact. Testing for SARS-CoV-2 was negative. The patient did not receive treatment and refused hospital admission. On the same day (Day 209), the patient died and no autopsy was performed.
CA224047- (b) (6)	75/F	Respiratory failure	This patient had a history of Type 2 diabetes. On Day 98 (4th infusion) the patient was diagnosed with Grade 2 hyperthyroidism (related) associated with hypercalcemia, and received steroids. On Day 152 the patient was hospitalized and discontinued from the study due to hip fracture with the last dose of study treatment on Day 98. During the hospitalization the patient's blood glucose level was elevated. On Day 158 (60 days after the 4th infusion) the patient died of respiratory failure (not related). The patient did not receive any treatment for respiratory failure. The physician suspected that cause of death may have been caused by pulmonary embolism or an infection with sepsis. No autopsy was performed.
CA224047- (b) (6)	47/M	Respiratory failure exacerbated by PD	On Day 74 (17 days after the 3rd infusion) the patient was diagnosed with Grade 3 COVID-19 infection (underlying symptoms of cough, phlegm, dyspnea, and fever), and PD (CNS and retina). On Day 77, the patient died of respiratory failure (last dose drug Day 57).
CA224047- (b) (6)	71/M	Pneumonitis: **Related**	On Day 184 (44 days after the 6th infusion) the patient experienced Grade 2 rash (related) and was treated with a prolonged course of steroids. On Day 440 (18 days after the 12th infusion day) the patient was hospitalized due to Grade 3 pneumonitis (related) associated with dyspnea and Klebsiella and

Patient ID	Age/Sex	Investigator Reported Primary Cause of Death	Reviewer Comment
			Staphylococcus positive lung washings. On Day 479 the patient died (57 days after the 12th infusion) and the last day of drug was Day 422.
CA224047- (b) (6)	67/F	PNA	On Day 78 RECIST 1.1 showed PD. On Day 419, 26 days after the 14th infusion day, the patient died due to pneumonia (not related). Earlier, on the same day (Day 419) the study therapy was discontinued due to the event of pneumonia, with the last dose received on Day 393. No autopsy was performed. The patient was reported to be on a prolonged course of steroids due to "pulmonary toxicity," "AE," "other," and "arthralgia" which had been administered until the patient died.
CA224047- (b) (6)	71/M	Covid	On Day 415 (6 days after the 15th infusion) the patient presented with Grade 1-2 fever (body temperature not available) and dry cough for 10 days and was diagnosed with COVID-19 pneumonia (not related) with the last dose of drug on Day 409. The patient had progressive symptoms and died on Day 419. There was no autopsy.
CA224047- (b) (6)	68/M	Acute MI	On Day 1, an ECG showed 1st degree conduction block and supraventricular tachycardia. On Day 26 (25 days after the 1st infusion day) the patient died of acute MI (not related). No autopsy was performed.

Source: Reviewer generated table from patient narratives submitted in the CSR, Module 5.3.5.3, SCS 2.7.4
M=male, F-female, PNA=pneumonia, PD=progressive disease, MI=myocardial infarction

On the nivolumab arm reported causes of death included inadvertent pain medication overdose, acute respiratory insufficiency, arteria basiliaris thrombosis, progressive pulmonary insufficiency, coronavirus, COVID-19 (2 patients), COVID-19 complications, sudden death, complications of cerebrovascular event, acute myocardial infarction (2 patients), coronary ischemia, cardiac shock, septic shock and atypical pneumonia, and respiratory insufficiency.

Hemophagocytic lymphohistiocytosis (HLH) has been reported in the post-marketing experience of patients who have received nivolumab and in the literature. The occurrence of fatal HLH in patient CA224047- (b) (6) is consistent with postmarketing experience with nivolumab (Hantel, 2018; U.S. package insert, Opdivo, accessed on 8 Dec 2021) and was not considered unexpected. Immune-mediated pneumonitis is a known, potential severe and fatal immune-mediated adverse reaction reported in the label for nivolumab (U.S. package insert,

Opdivo, accessed on 8 Dec 2021) that has been observed with nivolumab single agent use and combination use with ipilimumab. The occurrence of fatal immune-mediated pneumonitis is consistent with the observed toxicity profile for nivolumab and was not considered unexpected.

Patient CA224047-(b) (6) was reported as having multiple comorbid medical conditions such as diabetes with unknown HGBA1C status, and hip fracture which increases the risk of associated pulmonary embolism and may have contributed to this patient's respiratory failure and death. This patient's death was not attributed to nivolumab-relatlimab FDC and based on the ongoing health issues at the time of death, FDA considers this a reasonable assessment. Other causes of death such as aspiration pneumonia and septic shock in patients with cancer can be due to a compromised health status, and therefore, FDA agrees that nivolumab-relatlimab FDC would not necessarily be a causative factor in these patients' death.

Patient CA224047-(b) (6) had a MI that the investigator did not attribute to nivolumab-relatlimab FDC. While an acute MI differs from myocarditis, the rapid onset of toxicity after the first dose (On Day 1, ECG had shown 1st degree conduction block and supraventricular tachycardia. On Day 26 the patient died of acute MI) resembles the rapid onset observed in patients with myocarditis on Study CA224-073 (Additional information provided in Section 8.2.6.1). FDA sent an Information Request (IR) to the Applicant for additional information regarding Patient CA224047-(b) (6), who was a 68-year-old male with stage IV melanoma (metastatic to lymph nodes, chest wall and kidneys), and an ECOG PS of 1. A screening LDH was elevated at baseline >2x upper level of normal (values ranging between 6.8-7.6x institutional ULN) and the screening ECG was abnormal, demonstrating first-degree atrioventricular block (PR interval 293 msec), a prolonged QRS duration (168 msec), non-specific intraventricular conduction block, and a prolonged QTcB interval (Bazett's) of 459 msec. Concomitant medications prior to study enrollment were prednisone (10 mg daily), ondansetron, pregabalin, omeprazole, sodium bicarbonate, and tramadol. On Day 26, the patient died. The patient did not report any adverse events or changes to concomitant medications. The death certificate states the following causes of death: 1) acute myocardial infarction 2) malignant melanoma of 6 months of evolution.

FDA sent an IR for additional information regarding patient CA224047-(b) (6), whose cause of death was reported as "death", and to inquire how autopsy reports were sought. Patient CA224047-(b) (6) was a 73-year-old male with stage IV melanoma (metastatic to lymph nodes, lung, liver, chest wall, bone and adrenal glands) diagnosed approximately 8 months prior to study enrollment, with an ECOG PS of 1 at study entry. He had a history of hypertension that was treated with bisoprolol, furosemide, and losartan, and was an ex-smoker of 20 pack-years. His baseline ECG showed "unspecified diffuse changes in ventricular repolarization" and a prolonged QT interval (reported values: QT interval 452 msec; QTcF interval [Fridericia's] 415 msec). During screening, the patient's troponin level was elevated at 1.9x the institutional ULN. A cardiac MRI was performed as part of the protocol-mandated cardiac evaluation and

demonstrated no signs of myocarditis. Notably, the patient's troponin level was elevated to 3x the institutional ULN on study Day 1, which should have resulted in a treatment delay per protocol. The protocol-specified Day 14 troponin measurement was not performed. The family contacted the treatment center and reported that the patient died at home on Day 20. The patient had not reported any recent adverse events or changes to concomitant medications. The cause of death was undetermined, no autopsy was performed, and the family did not forward the death certificate to the research team. The investigator assessed the event as not related to the study medication. The patient had multiple poor prognostic indicators at the time of study entry and several risk factors for cardiovascular disease.

The Applicant's assessment in regards to the additional 2 patients with underlying cardiac conditions who ultimately died of sudden death and acute MI concluded that even after further queries to the investigators, there is no clinical data, medical evaluation, or report of symptoms to suggest a drug-related cause of death for patients CA224047-(b) (6) and CA224047-(b) (6) FDA agrees with their assessment and these patients will not be included in the nivolumab-relatlimab FDC label as fatal deaths due to drug toxicity (See Section 11, Section 8.2.6.1, and Section 8.2.4.5).

Patient CA224047-(b) (6) was on a prolonged course of steroids, which can be associated with immunosuppression and increased risk of infections. This patient died of pneumonia which may be indirectly related to steroid use initiated to treat adverse reactions related to the study drug regimen, but not necessary due to direct toxicity of the drug.

FDA agrees with BMS's assessment of 3 (0.8%) fatal adverse reactions in patients who were treated with nivolumab-relatlimab FDC which included HLH, acute edema of the lung, and pneumonitis.

8.2.4.2. Serious Adverse Events

The Applicant's Description:

The overall frequencies of SAEs (all-causality and drug-related) were higher in the nivo+rela than in nivolumab arm (Table 53). The nature of SAEs was similar between treatment groups, and drug-related SAEs largely comprised IMAEs in both study arms.

The most frequent drug-related SAEs (occurring in ≥ 1% of subjects), were colitis, diarrhea, and myocarditis. Drug-related myocarditis was infrequent at 1.1% and 0.3% in the nivo+rela FDC and nivolumab treatment arms, respectively, of which 0.6% were Grade 3-4 in the nivo+rela FDC arm).

Of SAEs attributed to study drug by the investigator, there were 4 reported events total that are considered rare for immuno-oncology agents in the nivo+rela FDC arm affecting individual subjects (hemolytic anemia, Guillain-Barré syndrome, Vogt-Koyanagi-Harada disease and

hemophagocytic lymphohistiocytosis), and 1 event in the nivolumab monotherapy arm (acquired hemophilia).

The FDA's Assessment:
FDA agrees with the Applicant's assessment of serious adverse events (SAE) including the incidences noted in Table 53 based on an analysis of SAEs (including disease progression related SAEs) that occurred within 30 days from last dose of study treatment. A total of 121 patients (34%) on the nivolumab-relatlimab FDC arm experienced SAEs vs 105 patients (29%) on the nivolumab arm. The incidences are similar and take into account SAEs coded as "malignant neoplasm progression" and other disease progression terms which should be excluded. It should be noted that data presented in the label for SAEs are from safety analyses that include adverse events, excluding disease progression related adverse events, observed between the first dose and 100 days after the last dose of study drug resulting in a SAE incidence of 36% for patients treated with nivolumab-relatlimab FDC. This approach is thought to provide a more comprehensive and clinically relevant description of drug safety.

FDA notes that serious immune related adverse events (IMAES) occurred on both arms. There was no difference in incidence $\geq$ 2% of any SAE between treatment arms. Given the known risk for IMAEs associated with anti-PD-1/L1 antibodies and the potential risk of myocarditis in relation to relatlimab administration that was demonstrated in nonclinical and prior clinical studies, the increased frequency of IMAEs (colitis, diarrhea) and myocarditis in patients receiving nivolumab-relatlimab FDC is not unexpected. This risk will be addressed in the nivolumab-relatlimab FDC label (Section 11). Myocarditis is discussed further in Section 8.2.4.5, and Section 8.2.6.1.

The SAEs of Grade 3 hemolytic anemia, Grade 2 Guillain-Barré syndrome, Grade 3 Vogt-Koyanagi-Harada disease, and Grade 4 HLH (the latter of which was reviewed under Section 8.2.4.1) that occurred on the nivolumab-relatlimab FDC arm are described in nivolumab labelling, and are considered expected adverse reactions for nivolumab-relatlimab FDC. Due to the rare occurrence (1 each) of these ARs specific information about each AR was not included separately in the Warnings and Precautions section of the nivolumab-relatlimab FDC label. These ARs are listed under the "Other Immune-Mediated Adverse Reactions" subsection in the drug labelling (See Section 11).

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Description:
In CA224047, the overall frequencies of AEs leading to discontinuation were higher in the nivo+rela FDC than in nivolumab arm (Table 53). The most common Aes leading to discontinuation (> 1%) were pneumonitis, malignant neoplasm progression, and myocarditis; however, frequencies were low. There were protocol-mandated requirements for discontinuing drug due to Aes, which were appropriate and in line with criteria in the well-established

nivolumab program.

The FDA's Assessment:

The incidence of all-causality AEs (including disease progression adverse events) leading to discontinuation were higher in patients on the nivolumab-relatlimab FDC arm (n=69; 19%) than on the nivolumab arm (n=41; 11%). While FDA generally agrees with the assessment of drug discontinuation that the Applicant presented above and in Table 53, FDA has identified 6 patients (1.7%) (5 patients with a PT of myocarditis and 1 patient with a PT of immune-mediated myocarditis) with drug discontinuation due to myocarditis. It should be noted that throughout the rest of the review document the Applicant reports an incidence of 1.7% (n=6) with 100% patient discontinuations due myocarditis. Although an incidence of discontinuation due to myocarditis of 1.7% may be quantitatively "low", it is greater than the nivolumab arm in which no patients discontinued due to myocarditis. Myocarditis is listed under Warnings and Precautions in the nivolumab label under "Other Immune-Mediated Adverse Reactions" (U.S. package insert, Opdivo, accessed on 16 Dec 2021), and will be included in the nivolumab-relatlimab FDC labeling as a subheading ("Immune-Mediated Myocarditis") under Warnings and Precautions (see Section 11). The data presented in the nivolumab-relatlimab FDC label for permanent treatment discontinuations due to adverse events are from safety analyses that excluded disease progression related adverse events and resulted in an incidence of 18% for patients treated with nivolumab-relatlimab FDC.

There were no AEs leading to withdrawal of any study treatment that were reported in a higher proportion of patients (≥2% difference) on the nivolumab-relatlimab FDC arm compared with the nivolumab arm. AEs leading to drug discontinuations are presented in Table 57, and includes all terms in the dataset, even if the term is not generally considered to be an AE possibly related to study treatment, note "Malignant Neoplasm Progression".

Table 57: Adverse Events Leading to Any Study Treatment Withdrawal

	Nivolumab-relatlimab FDC N=355 n (%)	Nivolumab N=359 n (%)	Total N=714 N (%)
All	**69 (19)**	**41 (11)**	**110 (15)**
Diarrhea[1]	7 (2.0)	1 (0.3)	8 (1.1)
Pneumonitis[2]	6 (1.7)	1 (0.3)	7 (1.0)
Malignant Neoplasm Progression	5 (1.4)	9 (2.5)	14 (2.0)
Myocarditis[3]	6 (1.7)	0 (0)	5 (0.7)
Acute Kidney Injury[4]	3 (0.8)	1 (0.3)	4 (0.6)
Fatigue[5]	3 (0.8)	0 (0)	3 (0.4)
Adrenal Insufficiency	2 (0.6)	0 (0)	2 (0.3)
ALT increase	2 (0.6)	0 (0)	2 (0.3)

	Nivolumab-relatlimab FDC N=355 n (%)	Nivolumab N=359 n (%)	Total N=714 N (%)
Encephalitis	2 (0.6)	0 (0)	2 (0.3)
Musculoskeletal Pain[6]	2 (0.6)	1 (0.3)	3 (0.4)
Myositis	2 (0.6)	0 (0)	2 (0.3)
Neuropathy Peripheral[7]	2 (0.6)	1 (0.3)	3 (0.4)
Abdominal Pain[8]	1 (0.3)	1 (0.3)	2 (0.3)
Adrenal Gland Cancer	1 (0.3)	0 (0)	1 (0.1)
Adrenocortical Insufficiency	1 (0.3)	0 (0)	1 (0.1)
Anemia	1 (0.3)	0 (0)	1 (0.1)
Alkaline Phos Increased	1 (0.3)	1 (0.3)	2 (0.3)
Breast Cancer	1 (0.3)	0 (0)	1 (0.1)
Bursitis	1 (0.3)	0 (0)	1 (0.1)
Cough[9]	1 (0.3)	0 (0)	1 (0.1)
Covid-19 Pneumonia	1 (0.3)	0 (0)	1 (0.1)
Decreased Appetite	1 (0.3)	0 (0)	1 (0.1)
Disease Progression	1 (0.3)	0 (0)	1 (0.1)
Dry Eye	1 (0.3)	0 (0)	1 (0.1)
Dry Mouth	1 (0.3)	0 (0)	1 (0.1)
Dyspnea[10]	1 (0.3)	0 (0)	1 (0.1)
GGT Increased	1 (0.3)	0 (0)	1 (0.1)
Gastritis	1 (0.3)	0 (0)	1 (0.1)
Glaucoma	1 (0.3)	0 (0)	1 (0.1)
Guillain-Barre Syndrome	1 (0.3)	0 (0)	1 (0.1)
Hemolytic Anemia	1 (0.3)	0 (0)	1 (0.1)
Hepatitis	1 (0.3)	0 (0)	1 (0.1)
Hyponatremia	1 (0.3)	0 (0)	1 (0.1)
Hypothyroidism[11]	1 (0.3)	0 (0)	1 (0.1)
Cholangitis	1 (0.3)	0 (0)	1 (0.1)
Jaundice	1 (0.3)	0 (0)	1 (0.1)
Lymphadenopathy	1 (0.3)	0 (0)	1 (0.1)
Metabolic Acidosis	1 (0.3)	0 (0)	1 (0.1)
Edema[12]	1 (0.3)	1 (0.3)	2 (0.3)
Optic Neuritis	1 (0.3)	0 (0)	1 (0.1)
Pain	1 (0.3)	0 (0)	1 (0.1)
Pneumonia[13]	1 (0.3)	1 (0.3)	2 (0.3)
Polymyalgia Rheumatica	1 (0.3)	0 (0)	1 (0.1)

	Nivolumab-relatlimab FDC N=355 n (%)	Nivolumab N=359 n (%)	Total N=714 N (%)
Pulmonary Edema	1 (0.3)	0 (0)	1 (0.1)
Sepsis	1 (0.3)	0 (0)	1 (0.1)
Septic Shock	1 (0.3)	0 (0)	1 (0.1)
Sjogren's Syndrome	1 (0.3)	0 (0)	1 (0.1)
Spinal Cord Compression	1 (0.3)	0 (0)	1 (0.1)
Spinal Fracture	1 (0.3)	0 (0)	1 (0.1)
Troponin Increased	1 (0.3)	1 (0.3)	2 (0.3)
Tubulointerstitial Nephritis	1 (0.3)	1 (0.3)	2 (0.3)
Vitiligo	1 (0.3)	0 (0)	1 (0.1)
Vogt-Koyanagi-Harada	1 (0.3)	0 (0)	1 (0.1)
Vomiting[14]	1 (0.3)	0 (0)	1 (0.1)
Rash[15]	0 (0)	3 (0.8)	3 (0.4)
Ascites	0 (0)	2 (0.6)	2 (0.3)
Infusion Related Reaction	0 (0)	2 (0.6)	2 (0.3)
Acquired Hemophilia	0 (0)	1 (0.3)	1 (0.1)
Autoimmune Hepatitis	0 (0)	1 (0.3)	1 (0.1)
Autoimmune Uveitis	0 (0)	1 (0.3)	1 (0.1)
Basilar Artery Thrombosis	0 (0)	1 (0.3)	1 (0.1)
Cerebrovascular Accident	0 (0)	1 (0.3)	1 (0.1)
Covid-19	0 (0)	1 (0.3)	1 (0.1)
Dermatitis Psoriasiform	0 (0)	1 (0.3)	1 (0.1)
Hepatitis Toxic	0 (0)	1 (0.3)	1 (0.1)
Hepatocellular Injury	0 (0)	1 (0.3)	1 (0.1)
Hepatotoxicity	0 (0)	1 (0.3)	1 (0.1)
Immune-mediated Hepatitis	0 (0)	1 (0.3)	1 (0.1)
Lipase Increased	0 (0)	1 (0.3)	1 (0.1)
Myocardial Infarction	0 (0)	1 (0.3)	1 (0.1)
Pancreatitis	0 (0)	1 (0.3)	1 (0.1)
Platelet Count Increased	0 (0)	1 (0.3)	1 (0.1)
Pleural Effusion	0 (0)	1 (0.3)	1 (0.1)
Pruritus	0 (0)	1 (0.3)	1 (0.1)
Respiratory Failure	0 (0)	1 (0.3)	1 (0.1)
Transaminases Increased	0 (0)	1 (0.3)	1 (0.1)
Troponin T Increased	0 (0)	1 (0.3)	1 (0.1)
Uveitis	0 (0)	1 (0.3)	1 (0.1)

Source: reviewer generated table from ADSL (Subject-Level Analysis Dataset) - 2021-05-12, ADAE (Analysis Adverse Events) - 2021-05-12. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER
ALT=Alanine Aminotransferase, GGT=gamma glutamyl transferase Alkaline pho=Alkaline phosphatase

1 Diarrhea includes PT terms DIARRHOEA, COLITIS, ENTERITIS, AUTOIMMUNE COLITIS, FREQUENT BOWEL MOVEMENTS
2 Pneumonitis includes PT terms PNEUMONITIS, ORGANISING PNEUMONIA, INTERSTITIAL LUNG DISEASE
3 Myocarditis includes PT terms ALLERGIC MYOCARDITIS, AUTOIMMNE MYOCARDITIS, EOSINOPHILIC MYOCARDITIS, GIANT CELL MYOCARDITIS, HYPESENSITIVITY MYOCARDITIS, IMMUNE-MEDIATED MYOCARDITIS, MYOCARDITIS
4 Acute Kidney Injury includes PT terms RENAL FAILURE, ACUTE KIDNEY INJURY, AZOTAEMIA, RENAL IMPAIRMENT, NEPHROPATHY TOXIC
5 Fatigue includes PT terms FATIGUE, ASTHENIA
6 Musculoskeletal Pain includes PT terms ARTHRALGIA, BACK PAIN, MYALGIA, PAIN IN EXTREMITY, NECK PAIN, ARTHRITIS, SPINAL PAIN, MUSCULOSKELETAL PAIN, NON-CARDIAC CHEST PAIN, MUSCULOSKELETAL CHEST PAIN, BONE PAIN, MUSCULOSKELETAL STIFFNESS, MUSCULOSKELETAL DISCOMFORT
7 Neuropathy Peripheral includes PT terms PARAESTHESIA, NEUROPATHY PERIPHERAL, HYPOAESTHESIA, NEURALGIA, DYSAESTHESIA, PERIPHERAL SENSORY NEUROPATHY, POLYNEUROPATHY, HYPERAESTHESIA, PERIPHERAL MOTOR NEUROPATHY
8 Abdominal Pain includes PT terms ABDOMINAL PAIN, ABDOMINAL PAIN UPPER, GASTROINTESTINAL PAIN, ABDOMINAL DISCOMFORT, ABDOMINAL PAIN LOWER, ABDOMINAL TENDERNESS, HEPATIC PAIN
9 Cough includes PT terms COUGH, PRODUCTIVE COUGH, UPPER-AIRWAY COUGH SYNDROME
10 Dyspnea includes PT terms DYSPNOEA, DYSPNOEA EXERTIONAL, DYSPNOEA AT REST
11 Hypothyroidism includes PT terms HYPOTHYROIDISM, AUTOIMMUNE HYPOTHYROIDISM
12 Edema includes PT terms OEDEMA PERIPHERAL, EYE OEDEMA, EYELID OEDEMA, OEDEMA, GENERALISED OEDEMA,
LIP OEDEMA, TESTICULAR OEDEMA, SCROTAL OEDEMA, LOCALISED OEDEMA
13 Pneumonia includes PT terms PNEUMONIA, LOWER RESPIRATORY TRACT INFECTION, ATYPICAL PNEUMONIA, PNEUMONIA BACTERIA
14 Vomiting includes PT terms VOMITING, RETCHING
15 Rash includes PT terms RASH, RASH MACULO-PAPULAR, DERMATITIS, RASH ERYTHEMATOUS, RASH MACULAR, RASH PAPULAR, ECZEMA, RASH PRURITIC, SKIN EXFOLIATION, RASH PUSTULAR, DERMATITIS ACNEIFORM, PEMPHIGOID, DERMATITIS BULLOUS, PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME, DRUG ERUPTION, LICHEN PLANUS, RASH MORBILLIFORM, DYSHIDROTIC ECZEMA, RASH VESICULAR, PENILE RASH

8.2.4.4. Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 58: Applicant - Dose Delay, Dose Infusion Interruption, and Infusion Rate Reduction, All Treated Subjects in CA224047

	Nivo+rela FDC N = 355	Nivolumab N = 359
Dose Delays		
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	140 (39.4)	130 (36.2)
NUMBER OF DOSE DELAYED PER SUBJECT		
0	215 (60.6)	229 (63.8)
1	80 (22.5)	81 (22.6)
2	33 (9.3)	25 (7.0)
3	21 (5.9)	10 (2.8)

>= 4	6 (1.7)	14 (3.9)
TOTAL NO. OF DOSE DELAYED/TOTAL NO. OF DOSES RECEIVED[A]	235/3282 (7.2)	227/3416 (6.6)
REASON FOR DOSE DELAY[B]		
ADVERSE EVENT	164 (69.8)	136 (59.9)
OTHER	67 (28.5)	86 (37.9)
NOT REPORTED	4 (1.7)	5 (2.2)
LENGTH OF DOSE DELAY[B]		
4 - 7 DAYS	68 (28.9)	94 (41.4)
8 - 14 DAYS	46 (19.6)	41 (18.1)
15 - 42 DAYS	108 (46.0)	82 (36.1)
> 42 DAYS	13 (5.5)	10 (4.4)
REASON FOR DOSE DELAY DUE TO COVID-19[B]		
ADVERSE EVENT	7 (3.0)	13 (5.7)
OTHER	20 (8.5)	21 (9.3)
Infusion Interruptions		
SUBJECTS WITH AT LEAST ONE INFUSION INTERRUPTED (%)	22 (6.2)	20 (5.6)
NUMBER OF INFUSIONS INTERRUPTED PER SUBJECT		
0	333 (93.8)	339 (94.4)
1	14 (3.9)	16 (4.5)
2	8 (2.3)	4 (1.1)
3	0	0
>= 4	0	0
TOTAL NO. OF INFUSIONS INTERRUPTED/NO. OF DOSES RECEIVED	30/3637 (0.8)	24/3775 (0.6)
REASON FOR INFUSION INTERRUPTION[C]		
HYPERSENSITIVITY REACTION	22 (73.3)	15 (62.5)
INFUSION ADMIN ISSUES	2 (6.7)	5 (20.8)
OTHER	6 (20.0)	4 (16.7)
Infusion Rate Reductions		
SUBJECTS WITH AT LEAST ONE INFUSION WITH IV RATE REDUCED (%)	15 (4.2)	8 (2.2)
NUMBER OF INFUSIONS WITH IV RATE REDUCTIONS PER SUBJECT (%)		
0	340 (95.8)	351 (97.8)
1	8 (2.3)	4 (1.1)
2	0	3 (0.8)
3	1 (0.3)	0
>= 4	6 (1.7)	1 (0.3)
TOTAL NO. OF IV RATES REDUCED/NO. OF DOSES RECEIVED	72/3637 (2.0)	40/3775 (1.1)
REASON FOR IV RATE REDUCTION[D]		
HYPERSENSITIVITY REACTION	28 (38.9)	6 (15.0)
INFUSION ADMIN ISSUES	2 (2.8)	1 (2.5)
OTHER	42 (58.3)	33 (82.5)
NOT REPORTED	0	0

A dose was considered as actually delayed if the delay is exceeding 3 days for nivo+rela FDC or Nivolumab.

[A] TOTAL NUMBER OF DOSES RECEIVED is excluding first dose.

[B] Percentages are computed out of the total number of doses delayed.

[C] Percentages are computed out of the total number of doses interrupted by treatment group.

[D] Percentages are computed out of the total number of infusions with IV rate reduction by treatment group.

The Applicant's Description:

Per protocol, dose reductions were not permitted within CA224047. 39.4% of subjects in the nivo+rela FDC arm and 36.2% of subjects in the nivolumab monotherapy arm had at least 1 dose delayed, mainly due to AEs (69.8% and 59.9%, respectively) (Table 58). Dose delays accounted for only ~6-7% of all doses received by subjects, and dose delays lasted ≤ 42 days in the majority of subjects. AEs accounted for the delay in a higher percentage of subjects receiving nivo+rela FDC, and the delays were longer (between 15-42d) for a higher percentage of subjects in this arm. Very few dose delays were due to COVID-19 (27 in the nivo+rela FDC arm and 34 in the

nivolumab arm). The majority of "other" reasons for IV rate reduction in both arms were previous infusion reactions.

The most frequently reported all causality AEs leading to dose delay in the nivo+rela FDC arm were: troponin increased (3.9%), diarrhea (3.9%), AST increased (2.8%), troponin T increased (2.8%), ALT increased (2.3%), arthralgia (2.3%), and hypothyroidism (2.3%).

The primary reason for nivolumab dose delay was due to AEs (59.9%) (Table 58). The most frequently reported all causality AEs leading to dose delay were: troponin increased (3.3%), troponin T increased (2.5%), and diarrhea (2.2%).

Dose interruption occurred in a low percentage of subjects and was similar between the two treatment arms (6.2% and 5.6% in the nivo+rela FDC and nivolumab arms, respectively; Table 58).

Interrupted infusions due to Grade 2 infusion-related reactions were required to be restarted at 50% of the original rate after resolution of symptoms; if no further complications ensued after 30 minutes, the rate could have been increased to 100% of the original infusion rate; however, sites could choose to continue using a reduced rate for subsequent cycles as prophylaxis to infusion reactions. 4.2% of subjects in the nivo+rela FDC arm and 2.2% of subjects in the nivolumab monotherapy arm had at least 1 rate reduction. Of these rate reductions, 38.9% of the nivo+rela FDC arm were due to reported hypersensitivity reactions and 15.0% in the nivolumab monotherapy arm. When reviewed at a patient level, more than half of the reported rate reductions due to hypersensitivity in the nivo+rela FDC arm were prophylactic in nature occurring after a prior infusion interruption with rate reduction and not associated with an acute infusion interruption while more than 80% of the reported rate reductions due to hypersensitivity in the nivolumab monotherapy were due to hypersensitivity reactions with an acute interruption.

The FDA's Assessment:

FDA agrees with the Applicant that the incidences of AEs requiring any dose-modification and AEs resulting in dose interruption were higher in the nivolumab-relatlimab FDC arm as compared to the nivolumab arm. However, FDA assessed the incidence of interruption of drug due to an AE using the AEACN variable in the ADAE dataset resulting in an incidence of dose interruption due to adverse events of 45% on nivolumab-relatlimab FDC compared with 38% on nivolumab alone, which differs from the 1st part of Table 58.

In a response from the Applicant it was stated that the analysis presented in Table 58 is based on a calculation of time between study drug doses using exposure data and considering a dose delayed if the time between doses exceeded 3 days beyond the expected 28 days between doses. The Applicant proposed to present data for adverse event-related dose interruptions in the nivolumab-relatlimab FDC label from a safety analyses that used investigator-reported dose interruptions and resulted in an incidence of 43% for patients treated with nivolumab-relatlimab FDC. FDA has independently verified this result and agrees with the Applicant's proposal to include investigator-reported adverse event-related dose interruptions.

Dose reductions were not allowed per protocol, but there was 1 dose reduction (0.3%) on the nivolumab-relatlimab FDC arm due to breast pain. See section 11 for a summary of label negotiations.

8.2.4.5. Significant Adverse Events

Data:

Table 59: Applicant - Summary of IMAEs and OESIs, All Treated Subjects in CA224047

	No. of Subjects (%)			
Safety Parameters	**Nivo+rela FDC (N = 355)**		**Nivolumab (N = 359)**	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality IMAEs within 100 days of last dose Treated with Immune Modulating Medication				
Diarrhea/Colitis	24 (6.8)	4 (1.1)	11 (3.1)	5 (1.4)
Hepatitis	20 (5.6)	14 (3.9)	9 (2.5)	4 (1.1)
Pneumonitis	13 (3.7)	2 (0.6)	6 (1.7)	2 (0.6)
Nephritis/Renal Dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)
Rash	33 (9.3)	2 (0.6)	24 (6.7)	5 (1.4)
Hypersensitivity/Infusion Reactions	4 (1.1)	0	4 (1.1)	0
All-causality Endocrine IMAEs within 100 days of last dose With or Without Immune Modulating Medication				
Adrenal Insufficiency	15 (4.2)	5 (1.4)	3 (0.8)	0
Hypophysitis	9 (2.5)	1 (0.3)	3 (0.8)	1 (0.3)
Hypothyroidism	59 (16.6)	0	47 (13.1)	0
Thyroiditis	10 (2.8)	0	5 (1.4)	0
Hyperthyroidism	22 (6.2)	0	24 (6.7)	0
Diabetes Mellitus	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)
All-causality OESIs within 100 days of last dose* With or Without Immune Modulating Medication				
Troponin Event	41 (11.5)	1 (0.3)	36 (10.0)	2 (0.6)
Uveitis	6 (1.7)	1 (0.3)	5 (1.4)	2 (0.6)
Myocarditis	6 (1.7)	2 (0.6)	2 (0.6)	0
Pancreatitis	4 (1.1)	0	4 (1.1)	1 (0.3)
Encephalitis	2 (0.6)	2 (0.6)	2 (0.6)	2 (0.6)
Myositis/Rhabdomyolysis	2 (0.6)	1 (0.3)	0	0
Guillain-Barre Syndrome	1 (0.3)	0	0	0

MedDRA version 23.1 CTCAE version 5.0.

*No events of myasthenic syndrome, demyelination, graft versus host disease, or meningitis were reported.

Table 60: Applicant - Onset, Management, and Resolution of Immune-Mediated Myocarditis and Troponin Elevation Treated with Immune-Modulating Medication within 100 days of Last Dose - Nivo+rela FDC and Nivolumab Monotherapy Q4W Treated Subjects

OESI Category/ Total # of Subj. with an event	% Subj. with Any Grade/ Grade 3 OESIs	% Subj. with OESI leading to DC/Dose Delay	% Subj. with OESIs Receiving IMM/High-dose Corticosteroids[a]	Median Duration IMM (range), wks	% Subj. with Resolution of OESI[b,c,d]	Median[e] Time to Resolution (range), wks[f]
Nivo+rela FDC						
Myocarditis N = 6	1.7/0.6	1.7/0	100.0/100.0	8.86 (2.7 - 15.7)	100	3.00 (0.4 - 14.0)
Troponin Elevation N = 3*	0.8/0	0.3/0.3	100.0/100.0	10.00 (4.0 - 16.3)	100	8.00 (6.1 - 20.3)
Nivolumab						
Myocarditis N = 2	0.6/0	0.3/0.6	100.0/100.0	23.00 (12.3 - 33.7)	50.0	N.A. (6.6 - 13.7+)
Troponin Elevation N = 1	0.3/0.3	0/0.3	100.0/100.0	4.29 (4.3 - 4.3)	100	7.29 (7.3 - 7.3)

* One subject who experienced troponin elevation also experienced myocarditis in the nivo+rela FDC arm and appears in both OESI categories.

[a] Denominator is based on the number of subjects who experienced the event.

[b] Subjects who experienced IMAE without worsening from baseline grade were excluded from time to resolution analysis.

[c] Events without a stop date or with a stop date equal to the death as well as grade 5 events are considered unresolved.

[d] For each subject, the longest duration of IMAEs where immune modulation is considered.

[e] From Kaplan-Meier estimation.

[f] Symbol + indicates a censored value.

The Applicant's Description:

Immune-mediated Adverse Events

Across IMAE categories, frequency of events was generally higher in the nivo+rela FDC arm than the nivolumab arm. Across IMAE categories, the majority of events were Grade 1-2 and manageable using the established management algorithms, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered. Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy.

Other Events of Special Interest

OESIs (regardless of causality or IMM treatment, with extended follow up) were infrequent in both treatment arms (Table 59).

Myocarditis was reported infrequently, at 1.7% and 0.6% in the nivo+rela FDC and nivolumab monotherapy arms, respectively, and a minority were high grade (Grade 3-4) events (0.6% vs 0%, respectively). In the nivo+rela FDC treatment arm, all observed myocarditis events were manageable within established IMAE management practices and resolved (Table 60). There were no overall differences in the median time to resolution or median duration of immunosuppression between the study arms. There was 1 fatal event in the nivolumab arm. The cause of death was attributed to a combination of myocarditis and bacterial sepsis due to

immune suppression for management of myocarditis.

Troponin elevation events were reported in 41 subjects (11.5%) in the nivo+rela FDC arm and 36 subjects (10.0%) in the nivolumab monotherapy arm, in the context of routine troponin monitoring during the first two months of study therapy and a protocol requirement for cardiac assessment. In addition to a subject in the nivo+rela FDC arm who was recorded as treated with steroids for both myocarditis and elevated troponin and therefore appears in both categories (Table 60). 3 subjects with troponin elevation events were treated with immune-modulating medication: 2 (0.6%) subjects vs 1 (0.3%) subject in the nivo+rela FDC and nivolumab monotherapy arms, respectively. One of these 3 subjects, treated with corticosteroids in the nivo+rela FDC arm, had myocardial inflammation on MRI but was asymptomatic; the other 2 subjects did not have radiographic confirmation of myocarditis.

However, these 3 events represented a minority of the troponin elevation events observed within the study, most of which required no immunosuppression. Overall, there was no substantial difference in the rate or grade of troponin elevation events between study arms.

The FDA's Assessment:

FDA generally agrees with the inclusion of IMAEs and OESI as significant AEs. The incidences of IMAEs was generally higher in the nivolumab-relatlimab FDC arm than the nivolumab arm. FDA agrees with the inclusion of IMAEs within the Warnings and Precautions of product labelling (See Section 11) including known IMAEs observed in patients treated with nivolumab.

Immune-mediated pneumonitis occurred in 3.7% (13/355) of patients receiving nivolumab-relatlimab FDC, including Grade 3 (0.6%), and Grade 2 (2.3%) adverse reactions. Pneumonitis led to permanent discontinuation of nivolumab-relatlimab FDC in 0.8% and withholding of nivolumab-relatlimab FDC in 1.4% of patients. Systemic corticosteroids were required in 100% (13/13) of patients with pneumonitis. Pneumonitis resolved in 85% of the 13 patients. Of the 5 patients in whom nivolumab-relatlimab FDC was withheld for pneumonitis, 5 reinitiated nivolumab-relatlimab FDC after symptom improvement; of these, none had recurrence of pneumonitis.

Immune-mediated colitis or diarrhea occurred in 7% (24/355) of patients receiving nivolumab-relatlimab FDC, including Grade 3 (1.1%) and Grade 2 (4.5%) adverse reactions. Colitis led to permanent discontinuation of nivolumab-relatlimab FDC in 2% and withholding of nivolumab-relatlimab FDC in 2.8% of patients. Systemic corticosteroids were required in 100% (24/24) of patients with diarrhea or colitis. Colitis resolved in 83% of the 24 patients. Of the 10 patients in whom nivolumab-relatlimab FDC was withheld for colitis, 9 reinitiated nivolumab-relatlimab FDC after symptom improvement; of these, 67% had recurrence of colitis.

Immune-mediated hepatitis occurred in 5.6% (20/355) of patients receiving nivolumab-relatlimab FDC, including Grade 4 (0.6%), Grade 3 (3.4%), and Grade 2 (1.4%) adverse reactions. Hepatitis led to permanent discontinuation of nivolumab-relatlimab FDC in 1.7% and

withholding of nivolumab-relatlimab FDC in 2.3% of patients. Systemic corticosteroids were required in 100% (20/20) of patients with hepatitis. Hepatitis resolved in 70% of the 20 patients. Of the 8 patients in whom nivolumab-relatlimab FDC was withheld for hepatitis, 6 reinitiated nivolumab and relatlimab FDC after symptom improvement; of these, 50% had recurrence of hepatitis.

Immune-Mediated Endocrinopathies
Adrenal insufficiency occurred in 4.2% (15/355) of patients receiving nivolumab-relatlimab FDC, including Grade 3 (1.4%) and Grade 2 (2.5%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of nivolumab-relatlimab FDC in 1.1% and withholding of nivolumab-relatlimab FDC in 0.8% of patients. Approximately 87% (13/15) of patients with adrenal insufficiency received hormone replacement therapy. Systemic corticosteroids were required in 87% (13/15) of patients with adrenal insufficiency. Adrenal insufficiency resolved in 33% of the 15 patients. Of the 3 patients in whom nivolumab-relatlimab FDC was withheld for adrenal insufficiency, all 3 reinitiated nivolumab-relatlimab FDC after symptom improvement.

Hypophysitis occurred in 2.5% (9/355) of patients receiving nivolumab-relatlimab FDC, including Grade 3 (0.3%) and Grade 2 (1.4%) adverse reactions. Hypophysitis led to permanent discontinuation of nivolumab-relatlimab FDC in 0.3% and withholding in 0.6% of patients. All (9/9) of patients with hypophysitis received hormone replacement therapy. Systemic corticosteroids were required in 100% (9/9) of patients with hypophysitis. Hypophysitis resolved in 22% of the 9 patients. Of the 2 patients in whom nivolumab-relatlimab FDC was withheld for hypophysitis, none reinitiated drug after symptom improvement.

Thyroiditis occurred in 2.8% (10/355) of patients receiving nivolumab-relatlimab FDC, including Grade 2 (1.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of nivolumab-relatlimab FDC. Thyroiditis led withholding of nivolumab-relatlimab FDC in 0.3% of patients. Systemic corticosteroids were required in 20% (2/10) of patients with thyroiditis. Thyroiditis resolved in 90% of the 10 patients. For the 1 patient in whom nivolumab-relatlimab FDC was withheld for thyroiditis, drug was reinitiated after symptom improvement without recurrence of thyroiditis.

Hyperthyroidism occurred in 6% (22/355) of patients receiving nivolumab-relatlimab FDC, including Grade 2 (1.4%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of nivolumab-relatlimab FDC. Hyperthyroidism led to withholding of nivolumab-relatlimab FDC in 0.3% of patients. Systemic corticosteroids were required in 23% (5/22) of patients. Hyperthyroidism resolved in 82% of the 22 patients. For the 1 patient in whom nivolumab-relatlimab FDC was withheld for hyperthyroidism, drug was reinitiated after symptom improvement without recurrence of hyperthyroidism.

Hypothyroidism occurred in 17% (59/355) of patients receiving nivolumab-relatlimab FDC,

including Grade 2 (11%) adverse reactions. Hypothyroidism led to the permanent discontinuation of nivolumab-relatlimab FDC in 0.3% and withholding in 2.5% of patients. None of the patients with hypothyroidism required systemic corticosteroids. Hypothyroidism resolved in 12% of the 59 patients. Of the 9 patients in whom nivolumab-relatlimab FDC was withheld for hypothyroidism, 6 reinitiated drug after symptom improvement; of these, 33% had recurrence of hypothyroidism.

Type 1 Diabetes Mellitus occurred in 0.3% (1/355) of patients receiving nivolumab-relatlimab FDC, a Grade 3 (0.3%) adverse reaction, and no cases of diabetic ketoacidosis. Diabetes did not lead to the permanent discontinuation or withholding in any patient.

Immune-mediated nephritis and renal dysfunction occurred in 2% (7/355) of patients receiving nivolumab-relatlimab FDC, including Grade 3 (1.1%) and Grade 2 (0.8%) adverse reactions. Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of nivolumab-relatlimab FDC in 0.8% and withholding in 0.6% of patients. Systemic corticosteroids were required in 100% (7/7) of patients with nephritis and renal dysfunction. Nephritis and renal dysfunction resolved in 71% of the 7 patients. Of the 2 patients in whom nivolumab-relatlimab FDC was withheld for nephritis or renal dysfunction, 1 reinitiated drug after symptom improvement without recurrence of nephritis or renal dysfunction.

Immune-mediated rash occurred in 9% (33/355) of patients, including Grade 3 (0.6%) and Grade 2 (3.4%) adverse reactions. Immune-mediated rash did not lead to permanent discontinuation of nivolumab-relatlimab FDC. Immune-mediated rash led to withholding of nivolumab and relatlimab FDC in 1.4% of patients. Systemic corticosteroids were required in 88% (29/33) of patients with immune-mediated rash. Rash resolved in 70% of the 33 patients. Of the 5 patients in whom nivolumab-relatlimab FDC was withheld for immune-mediated rash, 4 reinitiated drug after symptom improvement; of these, 25% had recurrence of immune-mediated rash.

Myocarditis was identified as an important potential risk based on observations in preclinical models, in addition to literature describing a risk of severe checkpoint inhibitor-associated myocarditis in the post approval setting (Palaskas, 2020; Johnson 2016). FDA agrees with the categorization of myocarditis as a significant AE, and the incidences of 1.7% and 0.6% in the nivolumab-relatlimab FDC and nivolumab monotherapy arms, respectively; Grade 3-4 events 0.6% vs 0%, respectively. FDA describes this analysis in detail in Section 8.2.6.1. Due to the higher incidence and severity compared to nivolumab monotherapy, myocarditis was raised to a standalone AR in the label under Warnings and Precautions, see Section 11; previously for the nivolumab label, it had been listed under “Other immune-mediated adverse reactions” (U.S. package insert, Opdivo, accessed on 16 Dec 2021).

FDA included an analysis of Grades 3-4 AEs in the assessment of significant AEs (see Table 61). With the exception of anemia and rash, the incidence of significant AEs were higher on the nivolumab-relatlimab FDC arm compared to the nivolumab arm. FDA agrees with the Applicant that IMAEs and OESI were manageable, and that there was an overall low incidence of Grades 3-4 AEs.

Table 61: Patients with Grade 3-4 AEs ≥ 1% on Pivotal Study CA224047

	Nivolumab-relatlimab FDC N=355 N (%)	Nivolumab N=359 N (%)	Total N=714 N (%)
All patients	**140 (39)**	**114 (32)**	**254 (36)**
Musculoskeletal And Connective Tissue Disorders			
Musculoskeletal Pain (GT)	15 (4.2)	6 (1.7)	21 (2.9)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)			
Malignant Neoplasm Progression	11 (3.1)	14 (3.9)	25 (3.5)
General Disorders And Administration Site Conditions			
Fatigue (GT)	7 (2)	2 (0.6)	9 (1.3)
Gastrointestinal Disorders			
Diarrhea (GT)	7 (2)	5 (1.4)	12 (1.7)
Blood And Lymphatic System Disorders			
Anemia	7 (2)	11 (3.1)	18 (2.5)
Investigations			
Lipase Increased	6 (1.7)	3 (0.8)	9 (1.3)
Aspartate Aminotransferase Increased	5 (1.4)	2 (0.6)	7 (1)
Alanine Aminotransferase Increased	5 (1.4)	4 (1.1)	9 (1.3)
Weight Decreased	4 (1.1)	0	4 (0.6)
Gamma-glutamyl transferase Increased	4 (1.1)	4 (1.1)	8 (1.1)
Skin And Subcutaneous Tissue Disorders			
Rash (GT)	5 (1.4)	7 (1.9)	12 (1.7)
Metabolism And Nutrition Disorders			
Hyponatremia	5 (1.4)	1 (0.3)	6 (0.8)
Hyperglycemia	5 (1.4)	5 (1.4)	10 (1.4)
Vascular Disorders			
Hypertension (GT)	5 (1.4)	5 (1.4)	10 (1.4)

	Nivolumab-relatlimab FDC N=355 N (%)	Nivolumab N=359 N (%)	Total N=714 N (%)
Respiratory, Thoracic And Mediastinal Disorders			
Dyspnea (GT)	5 (1.4)	1 (0.3)	6 (0.8)
Endocrine Disorders			
Adrenal Insufficiency	4 (1.1)	0	4 (0.6)
Renal And Urinary Disorders			
Acute Kidney Injury (GT)	4 (1.1)	1 (0.3)	5 (0.7)
Infections And Infestations			
Pneumonia (GT)	3 (0.8)	6 (1.7)	9 (1.3)

Source: ADSL (Subject-Level Analysis Dataset) - 2021-05-12, ADAE (Analysis Adverse Events) - 2021-05-12. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER
Group Diarrhea (GT) includes PT terms DIARRHEA, COLITIS, AUTOIMMUNE COLITIS,
Group Musculoskeletal Pain (GT) includes PT terms ARTHRALGIA, BACK PAIN, PAIN IN EXTREMITY, NON-CARDIAC CHEST PAIN, MYALGIA, NECK PAIN, SPINAL PAIN, ARTHRITIS,
Group Hypertension (GT) includes PT terms HYPERTENSION, HYPERTENSIVE CRISIS,
Group Fatigue (GT) includes PT terms FATIGUE, ASTHENIA,
Group Dyspnea (GT) includes PT terms DYSPNOEA,
Group Rash (GT) includes PT terms RASH, RASH MACULO-PAPULAR, LICHEN PLANUS, RASH ERYTHEMATOUS, RASH PUSTULAR, RASH MACULAR, DERMATITIS, ECZEMA,
Group Pneumonia (GT) includes PT terms PNEUMONIA, ATYPICAL PNEUMONIA, LOWER RESPIRATORY TRACT INFECTION,
Group Acute Kidney Injury (GT) includes PT terms ACUTE KIDNEY INJURY, RENAL FAILURE

8.2.4.6. Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 62: Applicant - Adverse Reactions in ≥ 15% of Patients Receiving Nivo+Rela FDC in CA224047

Adverse Reaction	Nivo+rela FDC (n = 355)		Nivolumab (n = 359)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	39	2.0	29	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	30	2.3	20	0.8
Arthralgia	24	1.7	15	0.6
Skin and Subcutaneous Tissue				
Rash[c]	27	1.4	19	1.4
Pruritus	25	0	17	0.6

Adverse Reaction	Nivo+rela FDC (n = 355)		Nivolumab (n = 359)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea	23	1.1	17	1.4
Nausea	17	0.6	14	0
Nervous System				
Headache	17	0.3	12	0.3
Endocrine				
Hypothyroidism[d]	15	0	12	0

[a] Includes fatigue and asthenia.
[b] Includes musculoskeletal pain, back pain, bone pain, musculoskeletal discomfort, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, and spinal pain.
[c] Includes rash, erythematous rash, macular rash, maculopapular rash, morbilliform rash, papular rash, pruritic rash, vesicular rash, pustular rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis psoriasiform, and drug eruption.
[d] Includes hypothyroidism and autoimmune hypothyroidism.

The Applicant's Description:

For labeling purposes, adverse reactions (grouped by system organ class and presented by CTC grade) for the proposed regimen that were reported in ≥ 10% of subjects treated with nivo+rela FDC in CA224047 were included in Section 6.1 of the USPI; see Table 62. The most common adverse reactions reported in ≥ 15% of the patients treated with nivo+rela FDC nivo+rela FDC were fatigue, musculoskeletal pain, rash, pruritus, headache, cough, and hypothyroidism.

Overall, the safety profile of nivo+rela combination therapy was consistent with the known mechanisms of action of nivolumab and relatlimab. Most AEs were low grade (Grades 1-2). No new types of clinically important events were identified and the majority are manageable in the clinical setting with concomitant medications.

The FDA's Assessment:

FDA analysis of TEAEs and TEARs included group terms standard to the Oncology Center of Excellence (OCE) labelling practices as described below in Table 63, which may result in slight variation in the incidence of adverse events compared to the Applicant's Table 62. The most common (≥20%) adverse reactions, including laboratory abnormalities, that occurred in the patients treated with nivolumab-relatlimab FDC were fatigue (39%), decreased hemoglobin (37%), increased AST (30%), musculoskeletal pain (30%), rash (27%), increased ALT (26%), pruritus (25%), arthralgia (24%), decreased sodium (24%), and diarrhea. The most common (≥20% with a difference between arms of >5%) adverse reactions, including laboratory abnormalities, were musculoskeletal pain (45% vs 32%), fatigue (39% vs 29%), decreased hemoglobin (37% vs 31%), increased AST (30% vs 22%), rash (28% vs 21%), pruritis (25% vs 17%), and diarrhea (24% vs 17%). See Table 63 and final labelling Section 11.

Table 63: Patient with AEs ≥ 10% on Pivotal Study CA224047

	Nivolumab-relatlimab FDC N=355			Nivolumab N=359			Total N=714		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
All	345 (97)	133 (37)	0	339 (94)	98 (27)	16 (4.5)	684 (96)	231 (32)	23 (3.2)
General Disorders And Administration Site Conditions									
Fatigue (GT)	139 (39)	7 (2)	0	104 (29)	2 (0.6)	0	243 (34)	9 (1.3)	0
Pyrexia (GT)	39 (11)	0	0	32 (9)	1 (0.3)	0	71 (10)	1 (0.1)	0
Gastrointestinal Disorders									
Diarrhea (GT)	84 (24)	7 (2)	0	62 (17)	5 (1.4)	0	146 (20)	12 (1.7)	0
Nausea	60 (17)	2 (0.6)	0	52 (14)	0	0	112 (16)	2 (0.3)	0
Abdominal Pain (GT)	45 (13)	1 (0.3)	0	46 (13)	3 (0.8)	0	91 (13)	4 (0.6)	0
Constipation	38 (11)	2 (0.6)	0	22 (6)	0 (0.0)	0	60 (8)	2 (0.3)	0
Skin And Subcutaneous Tissue Disorders									
Rash (GT)	101 (28)	5 (1.4)	0	75 (21)	7 (1.9)	0 (0.0)	176 (25)	12 (1.7)	0
Pruritus	88 (25)	0	0	62 (17)	2 (0.6)	0	150 (21)	2 (0.3)	0
Vitiligo	39 (11)	0	0	36 (10)	0	0	75 (11)	0	0
Musculoskeletal And Connective Tissue Disorders									
Musculoskeletal Pain (GT)	158 (45)	15 (4.2)	0	114 (32)	5 (1.4)	1 (0.3)	272 (38)	20 (2.8)	1 (0.1)
Infections And Infestations									
Urinary Tract Infection (GT)	37 (10)	2 (0.6)	0	30 (8)	2 (0.6)	0	67 (9)	4 (0.6)	0
Nervous System Disorders									
Headache (GT)	64 (18)	1 (0.3)	0	43 (12)	1 (0.3)	0	107 (15)	2 (0.3)	0
Neuropathy Peripheral (GT)	37 (10)	2 (0.6)	0	19 (5)	2 (0.6)	0	56 (8)	4 (0.6)	0
Metabolism And Nutrition Disorders									

	Nivolumab-relatlimab FDC N=355			Nivolumab N=359			Total N=714		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Decreased Appetite	52 (15)	2 (0.6)	0	26 (7)	1 (0.3)	0	78 (11)	3 (0.4)	0
Respiratory, Thoracic And Mediastinal Disorders									
Cough (GT)	52 (15)	1 (0.3)	0	40 (11)	0	0	92 (13)	1 (0.1)	0
Endocrine Disorders									
Hypothyroidism (GT)	60 (17)	0	0	50 (14)	0	0	110 (15)	0 (0.0)	0
Blood And Lymphatic System Disorders									
Anemia	48 (14)	7 (2)	0	34 (9)	11 (3.1)	0	82 (11)	18 (2.5)	0

Source: ADSL (Subject-Level Analysis Dataset) - 2021-05-12, ADAE (Analysis Adverse Events) - 2021-05-12. Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER
Group Musculoskeletal Pain (GT) includes PT terms PAIN IN EXTREMITY, BACK PAIN, ARTHRALGIA, SPINAL PAIN, MYALGIA, NECK PAIN, ARTHRITIS, MUSCULOSKELETAL CHEST PAIN, BONE PAIN, MUSCULOSKELETAL PAIN, MUSCULOSKELETAL STIFFNESS, MUSCULOSKELETAL DISCOMFORT,
Group Rash (GT) includes PT terms RASH, RASH MACULAR, RASH ERYTHEMATOUS, DERMATITIS, ECZEMA, RASH MACULO-PAPULAR, LICHEN PLANUS, PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME, RASH PAPULAR, DERMATITIS ACNEIFORM, RASH PRURITIC, SKIN EXFOLIATION, PEMPHIGOID, DYSHIDROTIC ECZEMA, DERMATITIS BULLOUS, RASH MORBILLIFORM, DRUG ERUPTION, RASH VESICULAR,
Group Abdominal Pain (GT) includes PT terms ABDOMINAL PAIN, ABDOMINAL PAIN UPPER, ABDOMINAL PAIN LOWER, ABDOMINAL DISCOMFORT, GASTROINTESTINAL PAIN, ABDOMINAL TENDERNESS,
Group Diarrhea (GT) includes PT terms DIARRHOEA, COLITIS, AUTOIMMUNE COLITIS, ENTERITIS, FREQUENT BOWEL MOVEMENTS,
Group Urinary Tract Infection (GT) includes PT terms URINARY TRACT INFECTION, CYSTITIS,
Group Headache (GT) includes PT terms HEADACHE, MIGRAINE,
Group Fatigue (GT) includes PT terms FATIGUE, ASTHENIA,
Group Neuropathy Peripheral (GT) includes PT terms HYPOAESTHESIA, PARAESTHESIA, NEUROPATHY PERIPHERAL, POLYNEUROPATHY, DYSAESTHESIA, NEURALGIA, HYPERAESTHESIA, PERIPHERAL MOTOR NEUROPATHY, PERIPHERAL SENSORY NEUROPATHY,
Group Pyrexia (GT) includes PT terms PYREXIA,
Group Cough (GT) includes PT terms COUGH, PRODUCTIVE COUGH, UPPER-AIRWAY COUGH SYNDROME,
Group Hypothyroidism (GT) includes PT terms HYPOTHYROIDISM, AUTOIMMUNE HYPOTHYROIDISM,

See discussion of submission specific primary safety concerns re: myocarditis, CNS AEs, and hypersensitivity reactions in Sections 8.2.6.1, 8.2.6.2, and 8.2.6.3.]

8.2.4.7. Laboratory Findings

Data:

Table 64: Applicant - Laboratory Values Worsening from Baseline[a] Occurring in ≥ 15% of Patients on Nivo+Rela FDC and Nivolumab in CA224047

Laboratory Abnormality	Nivo+rela FDC		Nivolumab	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased AST	30	2.3	22	1.4
Increased ALT	26	3.2	25	2.0
Hyponatremia	24	1.2	20	0.6
Increased alkaline phosphatase	19	0.6	17	0.9
Increased creatinine	19	0	16	0
Hematology				
Anemia	37	2.7	31	3.5
Lymphopenia	26	3.8	29	1.2

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: NIVOLUMAB-RELATLIMAB group (range: 80 to 342 patients) and nivolumab group (range: 85 to 345 patients).

In the laboratory summary tables, unless otherwise specified, subjects were counted only once for each lab parameter according to their worst on treatment CTC grade (worst being the highest CTC grade).

The Applicant's Position:

The majority of laboratory abnormalities were of low grade (Grade 1-2). The percentage of subjects with laboratory tests that worsened to Grade 3 or 4 relative to baseline was low, with a < 3% difference in the nivo+rela FDC arm for AST and ALT elevation, hyponatremia, and lymphopenia (Table 64). The USPI provides a table summarizing laboratory abnormalities that worsened relative to baseline (US conventional units) in ≥ 15% of nivo+rela-treated subjects in CA224047.

The FDA's Assessment:

FDA agrees with The Applicant's Table 64 and has included an additional laboratory summary table for laboratory values worsening from baseline at an incidence of ≥ 10% per arm (Table 65).

Table 65: Laboratory Abnormalities Occurring in ≥ 10% of Patients on Pivotal Study CA224047

	Nivolumab-relatlimab FDC N=355		Nivolumab N=359		Total N=714	
	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
HEMOGLOBIN (G/DL) - Decreased	126/337 (37)	9/337 (2.7)	107/344 (31)	12/344 (3.5)	233/681 (34)	21/681 (3.1)
ASPARTATE AMINOTRANSFERASE (AST), LOCAL LAB (U/L) - Increased	103/342 (30)	8/342 (2.3)	76/345 (22)	5/345 (1.4)	179/687 (26)	13/687 (1.9)
LYMPHOCYTES (ABSOLUTE), LOCAL LAB (10^9/L) - Decreased	89/280 (32)	7/280 (2.5)	67/277 (24)	8/277 (2.9)	156/557 (28)	15/557 (2.7)
ALANINE AMINOTRANSFERASE (ALT), LOCAL LAB (U/L) - Increased	88/342 (26)	11/342 (3.2)	85/345 (25)	7/345 (2.0)	173/687 (25)	18/687 (2.6)
HYPONATREMIA (MMOL/L) - Decreased	82/340 (24)	4/340 (1.2)	71/345 (21)	2/345 (0.6)	153/685 (22)	6/685 (0.9)
SODIUM, LOCAL LAB (MEQ/L) - Decreased	82/340 (24)	4/340 (1.2)	71/345 (21)	2/345 (0.6)	153/685 (22)	6/685 (0.9)
CREATININE, LOCAL LAB (MG/DL) - Increased	66/340 (19)	0/340	56/345 (16)	0/345	122/685 (18)	0/685
ALKALINE PHOSPHATASE (ALP), LOCAL LAB (U/L) - Increased	65/338 (19)	2/338 (0.6)	60/345 (17)	3/345 (0.9)	125/683 (18)	5/683 (0.7)
HYPERKALEMIA (MMOL/L) - Increased	50/340 (15)	6/340 (1.8)	56/345 (16)	3/345 (0.9)	106/685 (15)	9/685 (1.3)
POTASSIUM, LOCAL LAB (MEQ/L) - Increased	50/340 (15)	6/340 (1.8)	56/345 (16)	3/345 (0.9)	106/685 (15)	9/685 (1.3)
TROPONIN (T AND I) (UG/L) - Increased	49/347 (14)	8/347 (2.3)	37/344 (11)	4/344 (1.2)	86/691 (12)	12/691 (1.7)
CALCIUM, TOTAL, LOCAL LAB (MG/DL) - Decreased	47/334 (14)	2/334 (0.6)	48/336 (14)	2/336 (0.6)	95/670 (14)	4/670 (0.6)
HYPOCALCEMIA (MMOL/L) - Decreased	47/334 (14)	2/334 (0.6)	48/336 (14)	2/336 (0.6)	95/670 (14)	4/670 (0.6)
ABSOLUTE NEUTROPHIL COUNT DRV. (10^9/L) - Decreased	41/335 (12)	0/335	30/344 (9)	0/344	71/679 (10)	0/679
LEUKOCYTES, LOCAL LAB (10^9/L) - Decreased	41/337 (12)	0/337	43/344 (13)	0/344	84/681 (12)	0/681
HYPOMAGNESEMIA (MMOL/L) - Decreased	40/333 (12)	2/333 (0.6)	35/344 (10)	0/344	75/677 (11)	2/677 (0.3)

	Nivolumab-relatlimab FDC N=355		Nivolumab N=359		Total N=714	
	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
MAGNESIUM, LOCAL LAB (MEQ/L) - Decreased	40/333 (12)	2/333 (0.6)	35/344 (10)	0/344	75/677 (11)	2/677 (0.3)
NEUTROPHILS, LOCAL LAB (10^9/L) - Decreased	34/334 (10)	0/334	25/344 (7)	0/344	59/678 (9)	0/678
BILIRUBIN, TOTAL, LOCAL LAB (MG/DL) - Increased	26/342 (8)	1/342 (0.3)	38/345 (11)	3/345 (0.9)	64/687 (9)	4/687 (0.6)
LYMPHOCYTES (ABSOLUTE) (10^9/L) - Decreased	21/57 (37)	3/57 (5)	25/70 (36)	1/70 (1.4)	46/127 (36)	4/127 (3.1)
GLUCOSE, LOCAL LAB (MG/DL) - Decreased	16/158 (10)	0/158	12/153 (8)	0/153	28/311 (9)	0/311

Source: ADSL (Subject-Level Analysis Dataset) - 2021-05-12, ADZL (Lab Analysis Dataset US Units) - 2021-05-12. Variables used: USUBJID, TRT01A, SAFFL, PARAM, ABLFL, AVAL, ANRLO, ANRHI, TRTEDT, ADT, TRTSDT, ADY, ATOXGRN

FDA agrees that the majority of laboratory abnormalities were of low grade (Grade 1-2), with a low (< 3%) difference in laboratory abnormalities between the nivolumab-relatlimab FDC arm and nivolumab monotherapy. An incidence of ≥ 15% for laboratory abnormalities will be reflected in drug labelling, see Section 11.

8.2.4.8. Vital Signs

The Applicant's Description:
In CA224047, vital signs were monitored and recorded at the site per institutional standard of care during screening and treatment visits. These assessments were intended to be used as safety monitoring by the treating physician.

The FDA's Assessment:
The FDA agrees with the Applicant's analysis of vital signs.

8.2.4.9. Electrocardiograms (ECGs)

The Applicant's Position:
No significant changes in the longitudinal ECG assessments (including median change from baseline in the PR interval and QT_C parameters) were seen for subjects within the two treatment arms of CA224047, and there were no remarkable differences seen between treatment arms.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment of ECG changes.

8.2.4.10. QT

The Applicant's Description:
Not applicable for Study CA224047, QT prolongation was assessed in Parts A and B of Phase 1/2 Study CA224020 (see Table 24).

The FDA's Assessment:
The FDA agrees that specific QT studies were not conducted.

8.2.4.11. Immunogenicity

The Applicant's Description:
In Study CA224047, the incidence of treatment-emergent anti-relatlimab antibodies and NAb against relatlimab were 5.6% and 0.3%, respectively, in the nivo+rela FDC arm. The incidence of treatment emergent anti-nivolumab antibodies and NAb against nivolumab in the nivo+rela FDC arm (3.8% and 0.3%, respectively) was similar to that observed in the nivolumab arm (5.9% and 0.4%, respectively).

Based on an assessment of the rate of AEs of hypersensitivity or infusion reactions by ADA status, the occurrence of nivolumab or relatlimab ADA did not appear to have an effect on safety. Of all nivo+rela FDC treated subjects who were evaluable for ADA, hypersensitivity/infusion reaction AEs were experienced by 22 (7.9%) in nivolumab ADA-negative subjects and 23 (8.5%) in relatlimab ADA-negative subjects, compared to 2 (12.5%) in nivolumab ADA-positive subjects and 0 in relatlimab ADA-positive subjects.

Based on the assessment of the presence of ADA and NAb in relation to PFS, there was no apparent trend showing an effect of ADA or NAb on the efficacy of nivo+rela FDC. The 2 subjects with neutralizing ADA to relatlimab or nivolumab in the nivo+rela FDC arm showed PFS time in the range of 95% CI of median PFS for the nivo+rela FDC arm (95% CI: 6.37, 15.74), and 1 subject with neutralizing ADA in nivolumab monotherapy arm showed PFS time longer than the median PFS (4.63 months) observed in nivolumab monotherapy arm.

The FDA's Assessment:
See Section 6. FDA agrees that the incidence of treatment-emergent (TE) ADA and NAb were low in Study CA224047. Due to their low incidences, no conclusions can be made on the impact of TE-ADAs and TE-NAbs on the safety of nivolumab and relatlimab FDC.

8.2.5. Safety from Supportive Phase 1/2 Study CA224020 (RELATIVITY -020)

The Applicant's Position:
The supportive safety data from CA224020 provided comprehensive safety understanding of multiple dosing regimens of relatlimab monotherapy and nivo+rela in subjects with selected advanced or recurrent malignancies, including melanoma. The overall safety profile of nivo+rela

was acceptable. Treatment with nivo+rela was overall safe and tolerable in treated subjects, with no MTD identified in the dose range studied (80/20 mg Q2W to 480/1440 mg Q4W).

Safety data from subjects with previously untreated melanoma treated with the proposed dosing regimen, 480/160 Q4W (Part E; n = 38) and from all subjects who received at least one dose of nivo+rela 480/160 Q4W (n = 412) from CA224020 are presented side-by-side in Table 66. The safety data presented for CA224020 are based on a DBL of 25-Feb-2021.

Table 66: Summary of Safety - All Nivolumab 480 mg + Relatlimab 160 mg Q4W Treated Subjects in CA224020

	No. of Nivo+rela 480/160 mg Treated Subjects (%)			
	1L MEL		Total	
Safety Parameters	**N = 38**		**N = 412**	
Deaths	5 (13.2)		249 (60.4)	
Primary Reason for Death				
Disease	4 (10.5)		235 (57.0)	
Status indicated death	0		1 (0.2)	
Other[a]	1 (2.6)		11 (2.7)	
Unknown	0		2 (0.5)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	19 (50.0)	13 (34.2)	164 (39.8)	126 (30.6)
Drug-related SAEs	8 (21.1)	6 (15.8)	38 (9.2)	32 (7.8)
≥ 2 of Subjects				
Colitis	0	0	4 (1.0)	3 (0.7)
Diarrhoea	0	0	3 (0.7)	2 (0.5)
Immune-mediated enterocolitis	0	0	2 (0.5)	2 (0.5)
Autoimmune hepatitis	1 (2.6)	1 (2.6)	2 (0.5)	2 (0.5)
Myocarditis	0	0	2 (0.5)	1 (0.2)
Hypophysitis	0	0	2 (0.5)	2 (0.5)
All-causality AEs leading to DC	4 (10.5)	4 (10.5)	50(12.1)	38 (9.2)
Drug-Related AEs leading to DC	4 (10.5)	4 (10.5)	26 (6.3)	20(4.9)
≥ 2 of Subjects				
Colitis	0	0	2 (0.5)	2 (0.5)
All-causality AEs	35 (92.1)	18 (47.4)	392 (95.1)	174 (42.2)
Drug-related AEs	28 (73.7)	10 (26.3)	282 (68.4)	59 (14.3)
≥ 15% of subjects in any treatment group				
Asthenia	6 (15.8)	0	35 (8.5)	0
Fatigue	6 (15.8)	0	61 (14.8)	0
Pruritus	8 (21.1)	0	54 (13.1)	0
Rash	6 (15.8)	0	40 (9.7)	1 (0.2)
Hypothyroidism	7 (18.4)	0	29 (7.0)	0

The verbatim terms reported for the 'other' reasons for death were:

- pneumonia (n = 2), multiple cerebral infarction, intraparenchymal intracranial hemorrhage, respiratory failure, COVID-19 infection, uncontrolled A-FIB (no sign of myocarditis), pulmonary infection, false passage on

epistaxis, cardiac arrest, and progression of disease (CA224020-45-1184. Note that this death was after LPLV on 07JAN2021).

MedDRA version 23.1, CTC version 4.0

The safety data from subjects with previously untreated melanoma and from all subjects who received at least one dose of nivo+rela at the proposed dosing regimen was generally consistent with the safety findings from CA224047, and did not reveal any new safety signal.

The FDA's Assessment:

FDA acknowledges the supportive data submitted from 412 patients with selected advanced or recurrent malignancies, including 38 patients with previously untreated melanoma, treated at the proposed dosing regimen for nivolumab-relatlimab FDC enrolled in the supportive study CA224020. While data from this study helps to further characterize the safety of nivolumab-relatlimab FDC at the proposed dosing regimen, the safety assessment of nivolumab-relatlimab FDC was primarily based on Study CA224047.

8.2.6. Analysis of Submission-Specific Safety Issues

8.2.6.1. Myocarditis and Troponin Elevation

Data:

Refer to Sections 8.2.3.2 and 8.2.11.2 for background of rationale and conduct of troponin monitoring in Study CA224047. Study CA224047 is the first randomized, double-blind IO trial to incorporate prospective troponin monitoring into the protocol. This was implemented in parallel with other measures to reduce the risk of myocarditis, and/or risk of poor outcomes from myocarditis, including exclusion of patients with a history of myocarditis and those with elevated troponin > 2x ULN at baseline, and, similar to other IMAEs, incorporation of a myocarditis management algorithm within the protocol.

In Study CA224047, myocarditis was infrequent in both study arms, despite the troponin surveillance during the first two months of therapy (1.7% vs 0.6% in the nivo+rela FDC arm and nivolumab monotherapy arm, respectively; see Section 8.2.4.5). The majority of myocarditis events occurred in the first 2 months, were manageable within established IMAE management practices, and resolved.

In addition to a subject in the nivo+rela FDC arm who was recorded as treated with steroids for both myocarditis and elevated troponin and therefore appears in both OESI categories, 3 subjects with troponin elevation events were treated with immune modulating medications: 2 (0.6%) subjects vs 1 (0.3%) subject in the nivo+rela FDC and nivolumab arms, respectively. One of these 3 subjects, treated with corticosteroids in the nivo+rela FDC, had myocardial inflammation on MRI but was asymptomatic; the other 2 subjects did not have radiographic confirmation of myocarditis and a clinical decision was made to treat with corticosteroids. However, these 3 events represented a minority of the troponin elevation events observed within the study, most of which required no immunosuppression. Overall, the rate, duration, or grade of troponin

elevation events were similar between the study arms.

Based on the results, troponin monitoring is not considered to have utility for routine clinical use. Of the reported troponin elevation AEs, there was a large proportion of 'false positive' events across both treatment arms (i.e., troponin elevations requiring no treatment with IMM). Furthermore, despite regular protocol-mandated troponin measurement and a requirement for cardiac assessment in subjects with raised troponin values, a low frequency of myocarditis events was identified, with only a small (< 2%) difference in myocarditis frequency observed between the nivo+rela FDC and nivolumab arms. The majority of subjects who developed myocarditis in the nivo+rela FDC arm had other symptoms or indicators, in addition to the abnormal troponin values.

Troponin is a sensitive, but non-specific, marker of cardiac pathology. Asymptomatic troponin elevation has been reported in up to 10% in the general cancer patient population, and may be a predictor of all-cause mortality.[27,28] While myocarditis is a recognized risk with IO therapy, routine troponin monitoring has not been recommended by clinical guidelines due to a lack of demonstrated value in preventing morbidity or mortality.[29,30,31] Due to low specificity of this test, troponin monitoring may be associated with risk, including dose delay or premature checkpoint inhibitor cessation[29] (with a potential for suboptimal tumor response), potential for over-treatment with immunosuppressants (with a risk of corticosteroid-related morbidity and susceptibility to infection), as well as the cost and inconvenience of cardiac work-up to patients and the healthcare systems. The myocarditis-related fatality event in Study CA224047 was attributed to a combination of myocarditis and sepsis from immunosuppression, and occurred despite early identification of myocarditis by troponin monitoring.

There is now high awareness among clinical practitioners of the risk of immune-mediated myocarditis with IO agents, and guidelines for IO toxicity management including myocarditis are available globally.[30,31] For routine clinical practice, careful patient follow-up, a high index of suspicion, and management according to well-established IO treatment algorithms is appropriate[29,30,31] to detect myocarditis and prevent poor outcomes.

The Applicant's Position:

Please refer to Section 8.2.1 for discussion on troponin monitoring in Studies CA224047 and CA224020.

The FDA's Assessment:

Myocarditis was identified as an important potential adverse event in preclinical mouse models (see Section 5) and has been reported in the literature in association with checkpoint inhibitor-administration in the post approval setting (Palaskas, 2020). Myocarditis has also been identified as an IMAE associated with nivolumab (Johnson, 2016). During the development of nivolumab-relatlimab FDC, an event of Grade 4 myocarditis was reported in May 2016 in Study CA224020 at the nivolumab-relatlimab FDC dose of 240/240 mg IV Q2W. To mitigate this risk, the Applicant instituted troponin monitoring and increased cardiac surveillance in Study CA224047 to determine whether increased surveillance could support early identification of

myocarditis and to further characterize the frequency and severity of myocarditis in patients treated with nivolumab-relatlimab FDC compared with an established anti-PD-1 monotherapy. Troponin (local standard), cardiac troponin T (cTnt), or cardiac troponin I (cTnI) was assessed predose on days 1 and 14 of each cycle. Amendment 3 (Nov 23, 2020), clarified that troponin elevations will require cardiac evaluation to evaluate for imaging correlate of myocardial inflammation.

The proposed dose of nivolumab-relatlimab FDC administered to patients enrolled in Study CA224047 was 480 mg of nivolumab and 160 mg of relatlimab administered every 4 weeks, lower than the dose received by the patients on trial CA224073 who experienced myocarditis.

In the FDA analysis of myocarditis, the composite PT included: allergic myocarditis, autoimmune myocarditis, eosinophilic myocarditis, giant cell myocarditis, hypersensitivity myocarditis, immune-mediated myocarditis, and myocarditis. For details of categorization of PTs and AEs, see "Other Events of Special Interest" in Sec 8.2.4.5.

Myocarditis occurred at the incidence of 1.7% on the nivolumab-relatlimab FDC arm and 0.6% on the nivolumab arm; Grade 3-4 events were 0.6% vs 0%, respectively. This include 5 patients with a PT of myocarditis and one patient with a PT of immune-mediated myocarditis. The majority of myocarditis events occurred in the first 2 months and all 6 patients were administered immune modulating medication (IMM), specifically systemic steroids. The median duration of time on IMM was 8.9 weeks (range: 2.7 - 15.7) and all patients had resolution of myocarditis with a median of 3 weeks (range 0.4-14). Myocarditis led to permanent discontinuation of nivolumab-relatlimab FDC in 1.7% of patients compared to 0% on the nivolumab arm.

Adverse events of troponin elevation (composite term included PTs: troponin I increased, troponin T increased, troponin increased) were observed more commonly than myocarditis events, and were reported in 41 (12%) patients on the nivolumab-relatlimab FDC arm and 36 (10%) patients on the nivolumab arm. In addition to a patient on the nivolumab-relatlimab FDC arm who was recorded as treated with steroids for both myocarditis and elevated troponin, 3 patients with troponin elevation events were treated with IMM: 2 (0.6%) patients vs 1 (0.3%) patient in the nivolumab-relatlimab FDC and nivolumab arms, respectively. One of these 3 patients, treated with corticosteroids in the nivolumab-relatlimab FDC arm, had myocardial inflammation on MRI but was asymptomatic; the other 2 patients did not have radiographic confirmation of myocarditis and a clinical decision was made to treat with corticosteroids. Overall, the rate, duration, or grade of troponin elevation events were similar between the study arms.

FDA generally agreed with the Applicant's assessment of myocarditis and troponin after reviewing patient narratives. However, FDA sent clarifying IRs to get additional details and

narratives for patients who were identified by FDA as potentially having experienced fatal adverse events that were suspected to be due to myocarditis.

1. Patient CA224047-(b) (6) is a 73 year old male with underlying cardiac disease treated with nivolumab-relatlimab FDC who experienced sudden death on study Day 20 (See discussion in Section 8.2.4.1). At screening this patient was noted to have an elevated troponin 1.9x institutional ULN and an abnormal ECG with "unspecified diffuse changes in ventricular repolarization" and a prolonged QT interval. There was no evidence of myocarditis on a protocol mandated cardiac MRI and it was reported that this patient did not report any signs or symptoms of myocarditis. Although this patient's troponin was elevated 3x institutional ULN, follow up assessment was not conducted on Day 14 as indicated in protocol.

2. Patient CA224047-(b) (6) is a 68 year old male who experienced an MI that the investigator did not attribute to nivolumab-relatlimab FDC. This patient was noted to have a baseline ECG with 1st degree conduction block, supraventricular tachycardia and prolonged QTcB interval (Bazett's). This patient died on study Day 26 and cause of death was reported as acute myocardial infarction.

Despite the temporal relation of cardiac events to the time of death in both of the above patients, there is insufficient information to make a determination that these are myocarditis-related deaths, and therefore they will not be described in product labelling (See Section 11).

The incidence of myocarditis or increased troponin on CA224047 demonstrates a disparity between arms of worsening cardiac disease with nivolumab-relatlimab FDC compared with nivolumab monotherapy, albeit small (1.7% vs 0.3%, respectively, for myocarditis; 12% vs 10%, respectively, for increased troponin). While the frequency of myocarditis and increased troponin was higher with nivolumab-relatlimab FDC compared with nivolumab monotherapy in Study CA224047 (1.7% vs 0.3%, respectively, for myocarditis; 12% vs 10%, respectively, for increased troponin), myocarditis is a known risk of checkpoint inhibition and the proposed pharmacovigilance activities will support patient safety in the post-marketing setting. Myocarditis was included as a standalone warning within the Warnings and Precautions of the product label, and specific guidance on monitoring and management of these events is provided (see Section 11.)

8.2.6.2. Central Nervous System AEs

Data:

Refer to Section 8.2.1 for background of rationale for monitoring of CNS OESIs within Study CA224047. OESIs of the CNS, including encephalitis (0.6% in both arms), meningitis (0 events), and demyelination (0 events) were uncommon, well balanced between treatment arms, and without increase in the nivo+rela FDC arm (Table 59).

The Applicant's Position:
Overall, the CNS OESIs were infrequent, and there is no evidence that CNS AEs are increased in terms of frequency or severity with nivo+rela FDC. Due to the rare, but known, risk of immune-mediated AEs of the CNS with established IO agents, close monitoring of patients and management according to well established IO treatment algorithms is appropriate.

The FDA's Assessment:
Review of preclinical data for nivolumab-relatlimab FDC showed a signal for central nervous system vasculitis and inflammation of the choroid plexus in cynomolgus monkeys (See Section 5.5.1). There is a known risk of CNS toxicity in immunotherapy, as noted in the label for nivolumab (U.S. package insert, Opdivo, accessed on 8 Dec 2021). Due to the known risk of immune-mediated CNS events with immuno-oncology agents, the Applicant added CNS adverse event terms to the OESI category to support detection and reporting. There are no routine laboratory or imaging evaluations that were added to safety monitoring for CNS events.

OESI categories were discussed in Section 8.2.1 and Section 8.2.3.2. Specific to CNS AEs, the composite adverse event of encephalitis included PTs: acute disseminated encephalomyelitis, acute encephalitis with refractory, repetitive partial seizures, autoimmune encephalopathy, bickerstaff's encephalitis, encephalitis, encephalitis allergic, encephalitis autoimmune, encephalitis brain stem, encephalitis hemorrhagic, encephalitis lethargica, encephalitis toxic, immune effector cell-associated neurotoxicity syndrome, immune-mediated encephalitis, limbic encephalitis, lupus encephalitis, noninfective encephalitis, panencephalitis, rasmussen encephalitis, subacute sclerosing panencephalitis. A composite term for demyelination events included the following PTs: anti-myelin-associated glycoprotein associated polyneuropathy, autoimmune demyelinating disease, demyelinating polyneuropathy, demyelination. The composite term for "Other" meningitis events included the following PTs: choriomeningitis lymphocytic, meningitis, meningitis aseptic, meningitis noninfective, meningitis viral. OESIs of the central nervous system, including encephalitis, meningitis, and demyelination events were uncommon and balanced between treatment arms.

Three patients in the nivolumab-relatlimab FDC arm experienced encephalitis (2 Grade 3, and 1 Grade 2), while 2 patients in the nivolumab arm experienced encephalitis (Grade 4 and Grade 3). No patients in either arm reported meningitis and demyelination events. Of the encephalitis events reported in the nivolumab-relatlimab FDC arm, all events were manageable with established IMAE management practices including steroid use, and resolved (range of duration 6-60 days).

To determine whether a safety signal for CNS events was present in patients treated with nivolumab-relatlimab FDC, FDA compiled a broad composite term for CNS toxicity inclusive of: *meningitis, encephalitis, autoimmune encephalitis, myelitis, demyelination, myasthenic syndrome/myasthenia gravis, myasthenia gravis exacerbation, Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy, dizziness, peripheral and sensory neuropathy (including*

peripheral neuropathy and peripheral sensorimotor neuropathy), neuritis, peroneal nerve palsy, headache, postural dizziness, positional vertigo, vertigo, migraine, hyper(a)esthesia, hypo(a)esthesia, par(a)esthesia, dys(a)esthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy. With this expanded term, there were more CNS events overall on the relatlimab-nivolumab FDC arm compared to nivolumab monotherapy (31% vs 23%, respectively), with a comparable incidence of Grade 3-4 toxicity per arm (1.7% for nivolumab-relatlimab FDC and 1.1% for nivolumab), see Table 67.

Table 67: Incidence of Central Nervous System Toxicity Composite term

	Nivolumab-relatlimab FDC N=355			Nivolumab N=359		
Preferred Term (%)	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3-4 n (%)**	**Grade 5 n (%)**
TOTAL SUBJECTS WITH AN EVENT	111 (31)	6 (1.7)	0	83 (23)	4 (1.1)	0
Headache	64 (18)	1 (0.3)	0	48 (13)	1 (0.3)	0
Dizziness	21 (6)	0	0	24 (7)	0	0
Paraesthesia	18 (5)	2 (0.6)	0	5 (1.4)	0	0
Vertigo	17 (4.8)	0	0	7 (1.9)	0	0
Neuropathy peripheral	8 (2.3)	0	0	4 (1.1)	1 (0.3)	0
Hypoaesthesia	7 (2.0)	0	0	5 (1.4)	1 (0.3)	0
Migraine	3 (0.8)	0	0	1 (0.3)	0	0
Encephalitis	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Peripheral sensory neuropathy	2 (0.6)	0	0	0	0	0
Dysaesthesia	1 (0.3)	0	0	1 (0.3)	0	0
Guillain-Barre syndrome	1 (0.3)	0	0	0	0	0
Hyperaesthesia	1 (0.3)	0	0	0	0	0
Optic neuritis	1 (0.3)	1 (0.3)	0	1 (0.3)	0	0
Peripheral motor neuropathy	1 (0.3)	0	0	0	0	0
Peripheral sensorimotor neuropathy	1 (0.3)	0	0	0	0	0
Polyneuropathy	1 (0.3)	0	0	1 (0.3)	0	0
Vertigo positional	0	0	0	1 (0.3)	0	0

MedDRA Version 23.1 CTC Version 5.0
Includes events reported between first dose and 100 days after last dose of study therapy.
Program Source: BMS_GBS\CA224\DZA72884\Biostatistics\Production\Tables\EBR_008\rt-ae-neurcompcat.sas

Source: copied by reviewer from Applicant response to FDA Information Request, Table 1, submitted 1 Dec 2021.

The most common CNS AEs (≥ 2%) were headache (18%), dizziness (6%), paresthesia (5%), vertigo (4.8%), peripheral neuropathy (2.3%), and hypoesthesia (2%) in the nivolumab-relatlimab FDC arm, and headache (13%) and dizziness (7%) in the nivolumab arm.

Overall, there were 6 patients with Grades 3-4 CNS events using the composite term in the nivolumab-relatlimab FDC arm (1.7%) and 4 patients in the nivolumab monotherapy arm (1.1%).

In the nivolumab-relatlimab FDC arm, the reported high grade neurologic composite events were headache (1 patient), optic neuritis (1 patient), encephalitis (2 patients), and paresthesia (2 patients). The AE onset timing ranged from Day 16 for a patient with encephalitis, to Day 647 for the patient with headache. The AE duration ranged from 2 days for a patient with optic neuritis to 60 days for a patient with encephalitis. The study drug was not changed for 3 patients (1 patient with headache and 2 with paresthesia). The study drug was withdrawn for 1 patient with optic neuritis and 2 patients with encephalitis. The CNS composite events resolved in 5 patients, but a paresthesia event was ongoing in 1 patient at the time of data cut-off.

Overall, the incidence of CNS adverse events was higher on the nivolumab-relatlimab FDC arm (31%) compared to nivolumab (23%), but not necessarily higher grade. CNS adverse events were manageable and not unexpected in patients treated with immunotherapy. CNS toxicity does not meet evidentiary standards for inclusion in the label under Warnings and Precautions.

8.2.6.3. Hypersensitivity (including anaphylactic reaction)

Data:
Table 59.

The Applicant's Position:
Among the all-causality AEs, infusion-related reactions were of low frequency, with less than 2.5% difference in all grade events (5.9% vs 3.6% in the FDC arm vs nivolumab monotherapy arms respectively). The events were manageable with no high grade events in the FDC arm vs 0.3% in the nivolumab arm; there were no serious events in the FDC arm compared with 0.6% in the nivolumab arm. The proportion of infusion related events treated with immune-modulating medications was low and balanced between arms (1.1% vs 1.1%). The two infusion reaction events that led to discontinuation were in the nivolumab arm, with no infusion reaction events leading to discontinuation of treatment with nivo+rela FDC.

The FDA's Assessment:
Study CA224047:
The incidence of all grade hypersensitivity/IRR was 7% (23/355) vs 4.2% (15/359) in the nivolumab-relatlimab FDC arm vs nivolumab arms, respectively. The proportion of hypersensitivity/IRR treated with immune-modulating medication was higher in the nivolumab arm (53% vs 35%), of which 17% in the nivolumab-relatlimab FDC arm vs 7% in the nivolumab arm were treated with high dose steroids; all events resolved. There were no Grade 3-4 toxicity or serious hypersensitivity/IRR in patients on the nivolumab-relatlimab FDC, compared with 0.3% Grade 3-4 toxicity and 0.6% serious events in patients on the nivolumab arm. The two IRR

that led to discontinuation were on the nivolumab arm with no IRR leading to discontinuation of treatment with nivolumab-relatlimab FDC.

Study CA224020:
An increase in rates of hypersensitivity/IRR was not observed in the dose escalation (Part B) of Study CA224020 in patients treated with nivolumab in combination with relatlimab at doses up to 480 mg for nivolumab and 1440 mg for relatlimab. The incidence of hypersensitivity/IRR was 8% (n=107) and all events were Grade 1-2.

The incidence of hypersensitivity/IRR with nivolumab monotherapy has been reported in the product label as 6.4% and was similar to the incidence observed with nivolumab-relatlimab FDC in both the pivotal and supportive trials (6.5% in Study CA224047, and 8% in Study CA224020). The incidence of hypersensitivity/IRR in Study CA224047 for the nivolumab arm was noted to be lower (4.2%) compared to what has been reported in the label for nivolumab (6.4%). FDA cautions that no conclusions should be made regarding this difference due to the limitations of cross-trial comparisons and the smaller sample size of the nivolumab population in Study CA224047. Hypersensitivity/IRR will be included in the Warnings and Precautions section of the nivolumab-relatlimab FDC product label. (See Section 11).

8.2.6.4. Adolescents

Data:
Although the CA224047 study permitted enrollment of patients aged 12 and above, no adolescents were ultimately randomized into the trial.

One adolescent subject with advanced or metastatic melanoma who progressed while on IO therapy was treated with nivo 240 mg + rela SAV 80 mg Q2W (coadministration) in Part D1 of study CA224020. This subject was a 17 year old from Spain, with melanoma previously treated with nivolumab. The subject was randomized to D1 240/80 Q2W cohort on (b) (6) with the last dose received on (b) (6) The subject discontinued study medication for disease progression, and death was reported with date (b) (6). Adverse events experienced by this patient and considered to be drug-related by the investigator included vitiligo (Grade 1; onset date (b) (6) and troponin increase (grade 1; onset date (b) (6)

The Applicant's Position:
The safety in adolescent subjects is anticipated to be similar to the safety profile observed in adults.

The FDA's Assessment:
See Section 6, Section 10, and OCP Appendix 19.4 for additional information related to pharmacokinetic studies used to support the extrapolation of the effectiveness of nivolumab-relatlimab FDC in adults to patients ≥ 12 to < 18 years of age with unresectable or metastatic melanoma.

8.2.7. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

PRO data were collected via FACT-M and EQ-5D-3L questionnaires. Regardless of increased AEs with nivo+rela FDC, the proportions of patients who responded "Quite a Bit" or "Very Much" on GP5 of the FACT-M ("I am bothered by side effects of treatment") were comparable and low (less than 7% at visits where more than 10 subjects in each treatment arm) in both treatment arms over time.

The Applicant's Position:
The overall review of the PRO results did not identify a substantial decrement in symptoms, quality of life, or function suggesting that there was no suggestion of tolerability difference between nivo+rela FDC compared with nivolumab monotherapy.

The FDA's Assessment:
The analyses of PRO data were considered exploratory in nature and were not formally evaluated in Study CA224047 because there was no pre-specified statistical testing procedure or alpha allocation for any PRO endpoints.

8.2.8. Safety Analyses by Demographic Subgroups

Data:

Table 68: Applicant - Any Grade Drug-Related Adverse Events ≥ 10% by Age, Sex, and Region, All Treated Subjects in CA224047

	Nivo+rela 480/160 mg Q4W N = 355				Nivolumab 480 mg Q4W N = 359			
Age Category	**≥ 18 - < 65 N = 187**	**≥ 65 - < 75 N = 102**	**≥ 75 N = 66**		**≥ 18 - < 65 N = 196**	**≥ 65 - < 75 N = 103**	**≥ 75 N = 60**	
Total	**150 (80.2)**	**80 (78.4)**	**58 (87.9)**		**136 (69.4)**	**76 (73.8)**	**39 (65.0)**	
Pruritus	40 (21.4)	29 (28.4)	14 (21.2)		27 (13.8)	22 (21.4)	8 (13.3)	
Rash	30 (16.0)	15 (14.7)	10 (15.2)		20 (10.2)	16 (15.5)	7 (11.7)	
Vitiligo	18 (9.6)	13 (12.7)	6 (9.1)		22 (11.2)	11 (10.7)	2 (3.3)	
Fatigue	41 (21.9)	23 (22.5)	18 (27.3)		27 (13.8)	12 (11.7)	7 (11.7)	
Diarrhea	28 (15.0)	11 (10.8)	9 (13.6)		23 (11.7)	7 (6.8)	3 (5.0)	
Hypothyroidism	26 (13.9)	18 (17.6)	7 (10.6)		32 (16.3)	7 (6.8)	4 (6.7)	
Arthralgia	24 (12.8)	15 (14.7)	12 (18.2)		14 (7.1)	8 (7.8)	4 (6.7)	
Decreased appetite	7 (3.7)	9 (8.8)	10 (15.2)		5 (2.6)	2 (1.9)	2 (3.3)	
Sex	**Male N = 210**		**Female N = 145**		**Male N = 206**		**Female N = 153**	
Total	**165 (78.6)**		**123 (84.8)**		**145 (70.4)**		**106 (69.3)**	
Pruritus	47 (22.4)		36 (24.8)		34 (16.5)		23 (15.0)	
Rash	31 (14.8)		24 (16.6)		23 (11.2)		20 (13.1)	
Vitiligo	23 (11.0)		14 (9.7)		26 (12.6)		9 (5.9)	
Fatigue	46 (21.9)		36 (24.8)		24 (11.7)		22 (14.4)	
Diarrhea	26 (12.4)		22 (15.2)		18 (8.7)		15 (9.8)	
Nausea	13 (6.2)		16 (11.0)		8 (3.9)		7 (4.6)	
Hypothyroidism	33 (15.7)		18 (12.4)		21 (10.2)		22 (14.4)	
Arthralgia	37 (17.6)		14 (9.7)		18 (8.7)		8 (5.2)	
Region	**US/Canada N = 45**	**Europe N = 174**	**Latin America N = 104**	**Australia/NZ N = 32**	**US/Canada N = 34**	**Europe N = 190**	**Latin America N = 106**	**Australia/NZ N = 29**
Total	43 (95.6)	139 (79.9)	75 (72.1)	31 (96.9)	29 (85.3)	128 (67.4)	70 (66.0)	24 (82.8)
Pruritus	14 (31.1)	34 (19.5)	16 (15.4)	19 (59.4)	8 (23.5)	33 (17.4)	14 (13.2)	2 (6.9)
Rash	10 (22.2)	22 (12.6)	12 (11.5)	11 (34.4)	7 (20.6)	20 (10.5)	8 (7.5)	8 (27.6)

	Nivo+rela 480/160 mg Q4W N = 355				Nivolumab 480 mg Q4W N = 359			
Rash maculo-papular	5 (11.1)	1 (0.6)	1 (1.0)	2 (6.3)	5 (14.7)	2 (1.1)	0	1 (3.4)
Vitiligo	2 (4.4)	18 (10.3)	10 (9.6)	7 (21.9)	3 (8.8)	11 (5.8)	14 (13.2)	7 (24.1)
Fatigue	19 (42.2)	31 (17.8)	12 (11.5)	20 (62.5)	13 (38.2)	16 (8.4)	6 (5.7)	11 (37.9)
Asthenia	0	23 (13.2)	5 (4.8)	0	0	12 (6.3)	2 (1.9)	0
Pyrexia	2 (4.4)	6 (3.4)	4 (3.8)	0	4 (11.8)	2 (1.1)	1 (0.9)	0
Diarrhea	6 (13.3)	28 (16.1)	9 (8.7)	5 (15.6)	5 (14.7)	16 (8.4)	8 (7.5)	4 (13.8)
Nausea	10 (22.2)	13 (7.5)	4 (3.8)	2 (6.3)	1 (2.9)	6 (3.2)	5 (4.7)	3 (10.3)
Hypothyroidism	6 (13.3)	18 (10.3)	20 (19.2)	7 (21.9)	3 (8.8)	13 (6.8)	21 (19.8)	6 (20.7)
Arthralgia	11 (24.4)	28 (16.1)	5 (4.8)	7 (21.9)	1 (2.9)	15 (7.9)	3 (2.8)	7 (24.1)
Myalgia	6 (13.3)	10 (5.7)	9 (8.7)	0	2 (5.9)	7 (3.7)	3 (2.8)	2 (6.9)
ALT increased	9 (20.0)	13 (7.5)	6 (5.8)	0	4 (11.8)	6 (3.2)	1 (0.9)	0
AST increased	5 (11.1)	15 (8.6)	6 (5.8)	0	2 (5.9)	4 (2.1)	2 (1.9)	0
Decreased appetite	7 (15.6)	13 (7.5)	6 (5.8)	0	2 (5.9)	4 (2.1)	1 (0.9)	2 (6.9)
Infusion-related reaction	6 (13.3)	5 (2.9)	7 (6.7)	3 (9.4)	0	7 (3.7)	5 (4.7)	1 (3.4)
Dry mouth	2 (4.4)	6 (3.4)	0	11 (34.4)	0	6 (3.2)	2 (1.9)	3 (10.3)
Abdominal pain	2 (4.4)	1 (0.6)	2 (1.9)	2 (6.3)	2 (5.9)	0	1 (0.9)	3 (10.3)
Hyperthyroidism	1 (2.2)	12 (6.9)	6 (5.8)	2 (6.3)	0	13 (6.8)	6 (5.7)	3 (10.3)
Pneumonitis	2 (4.4)	5 (2.9)	2 (1.9)	4 (12.5)	1 (2.9)	4 (2.1)	4 (3.8)	0
Sinusitis	0	0	0	1 (3.1)	0	0	1 (0.9)	3 (10.3)

MedDRA Version 23.1. CTC Version 5.0.
Includes events reported between first dose and 30 days after last dose of study therapy.

The Applicant's Description:
In Study CA224047, the frequencies of all-causality, drug-related AEs, and high grade AEs in the nivo+rela arm for subgroups by gender and age group were similar to the AE frequencies reported for the overall study populations by treatment. For subgroups based on race, most subjects were clustered in a single category (White), although this is consistent with the patient groups seen in routine clinical practice for advanced/metastatic melanoma. Very low sample sizes in other categories of race limit the interpretability of potential differences. No clinically significant effect of race on PK of nivolumab or relatlimab was observed. For subgroups based on geographic region, the rates of overall AEs was generally higher in the US and Australia.

There were no consistent differences observed in the frequencies of all-causality or drug-related AEs, SAEs, or AEs leading to discontinuation between PD-L1 expression subgroups (1% and 10% cutoffs) or LAG-3 expression subgroups (1% and 5% cutoffs).

The FDA's Assessment:
FDA generally agrees with the Applicant's assessment. There was a slight numerical increase in TEAEs occurring in females compared to males (85% versus 79%). The evaluation of safety by demographic subgroup is limited by the small number of patients enrolled from some racial and ethnic subgroups. Therefore a definitive conclusion regarding the consistency of the safety profile of nivolumab-relatlimab FDC cannot be made for all subgroups; however the safety of nivolumab-relatlimab FDC has been adequately demonstrated in Study CA224047 and further characterized by data collected in Study CA224020.

Table 69: Summary of Safety for Study CA224047 by PD-L1 Status

	PD-L1 negative/indeterminate		PD-L1 positive (≥1% cutoff)	
	nivolumab-relatlimab FDC (n=209) n (%)	nivolumab (n=212) n (%)	nivolumab-relatlimab FDC (n=146) n (%)	nivolumab (n=147) n (%)
All Deaths	71 (34)	75 (35)	36 (25)	41 (28)
disease progression	59 (28)	66 (31)	30 (21)	30 (20)
Adverse event	12 (6)	9 (4.2)	5 (3.4)	9 (6)
unknown	0	0	1 (0.7)	2 (1.4)
SAEs	95 (45)	88 (42)	60 (41)	52 (35)
permanent discontinuation	45 (22)	25 (12)	36 (25)	31 (21)
dosage interruptions	83 (40)	78 (37)	73 (50)	46 (31)
dose reduced	0	0	1 (0.7)	0
Grade 3+4 AEs	83 (40)	74 (35)	56 (38)	43 (29)

	PD-L1 negative/indeterminate		PD-L1 positive (≥5% cutoff)	
	nivolumab-relatlimab FDC (n=267) n (%)	nivolumab (n=273) n (%)	nivolumab-relatlimab FDC (n=88) n (%)	nivolumab (n=86) n (%)
All Deaths	84 (31)	94 (34)	23 (26)	22 (26)
disease progression	70 (26)	82 (30)	19 (22)	14 (16)
Adverse event	14 (5)	10 (3.7)	3 (3.4)	8 (9)
unknown	0	2 (0.7)	1 (1.1)	0
SAEs	117 (44)	112 (41)	38 (43)	28 (33)
permanent discontinuation	59 (22)	35 (13)	22 (25)	21 (24)
dosage interruptions	114 (43)	95 (35)	42 (48)	29 (34)
dose reduced	1 (0.4)	0	0	0
Grade 3+4 AEs	103 (39)	90 (33)	36 (41)	27 (31)
	PD-L1 negative/indeterminate		PD-L1 positive (≥10% cutoff)	
	nivolumab-relatlimab FDC (n=284) n (%)	nivolumab (n=290) n (%)	nivolumab-relatlimab FDC (n=71) n (%)	nivolumab (n=69) n (%)
All Deaths	88 (31)	102 (35)	19 (27)	14 (20)
disease progression	74 (26)	87 (30)	15 (21)	9 (13)
Adverse event	14 (4.9)	13 (4.5)	3 (4.2)	5 (7)
unknown	0	2 (0.7)	1 (1.4)	0
SAEs	121 (43)	105 (36)	31 (44)	23 (33)
permanent discontinuation	62 (22)	37 (13)	19 (27)	19 (28)
dosage interruptions	124 (44)	100 (34)	32 (45)	24 (35)
dose reduced	1 (0.8)	0	0	0
Grade 3+4 AEs	111 (39)	94 (32)	28 (39)	23 (33)

Source: reviewer generated table using ADSL and ADAE datasets

Table 42: Baseline Disease Characteristics by PD-L1 Expression Level (1% cutoff)

	1% cutoff					
	PD-L1 negative/non-identifiable			PD-L1 positive		
	Nivolumab-relatlimab FDC N=209 N (%)	Nivolumab N=212 N (%)	Overall N=421 N (%)	Nivolumab-relatlimab FDC N=146 N (%)	Nivolumab N=147 N (%)	Overall N=293 N (%)
Baseline biomarker						

	1% cutoff					
	PD-L1 negative/non-identifiable			PD-L1 positive		
	Nivolumab-relatlimab FDC	Nivolumab	Overall	Nivolumab-relatlimab FDC	Nivolumab	Overall
	N=209 N (%)	N=212 N (%)	N=421 N (%)	N=146 N (%)	N=147 N (%)	N=293 N (%)
LAG-3 < 1%	75 (36)	83 (39)	158 (38)	12 (8)	7 (4.8)	19 (7)
LAG-3 ≥ 1%	134 (64)	129 (61)	263 (63)	134 (92)	140 (95)	274 (94)
LAG-3 < 5%	168 (80)	170 (80)	338 (80)	66 (45)	55 (37)	121 (41)
LAG-3 ≥ 5%	41 (20)	42 (20)	83 (20)	80 (57)	92 (63)	172 (59)
AJCC stage V8 at study entry						
Unresectable Stage III	22 (11)	11 (5)	33 (8)	13 (9)	12 (8)	25 (9)
Metastatic Stage IV	187 (90)	200 (94)	387 (92)	133 (91)	135 (92)	268 (92)
Unknown/not reported	0 (0)	1 (0.5)	1 (0.2)	0	0	0
Baseline LDH						
≤ ULN	131 (63)	128 (60)	259 (62)	93 (64)	103 (70.0)	196 (67)
> ULN	77 (37)	84 (40)	161 (38)	53 (36)	44 (30)	97 (33)
Not reported	1 (0.5)	0	1 (0.2)	0	0	0
≤ 2×ULN	187 (90)	190 (90)	377 (90)	135 (93)	138 (94)	196 (67)
> 2×ULN	21 (10)	22 (10)	43 (10)	11 (8)	9 (6)	97 (33)
Not reported	1 (0.5)	0	1 (0.2)	0	0	0
Baseline AJCC M stage						
M0/M1any[0]	134 (64)	133 (63)	267 (63)	98 (67)	104 (71)	202 (69)
M1any[1]	75 (36)	79 (37)	154 (37)	48 (33)	43 (29)	91 (31)
Baseline BRAF status						
Mutant	81 (39)	79 (37)	160 (38)	55 (38)	60 (41)	115 (39)
Wild-type	128 (61)	133 (63)	261 (62)	91 (62)	87 (59)	178 (61)
Baseline metastasis stage (CRF)						
M0	22 (11)	11 (5)	33 (8)	13 (9)	12 (8)	25 (9)
M1	1 (0.5)	3 (1.4)	4 (1.0)	0	0	0
M1A	50 (24)	57 (27)	107 (25)	27 (19)	50 (34.0)	77 (26)
M1B	44 (21)	51 (24)	95 (23)	41 (28)	37 (25)	78 (27)
M1C	91 (44)	84 (40)	175 (42)	60 (41)	43 (29)	103 (35)
M1D	1 (0.5)	6 (2.8)	7 (1.7)	5 (3.4)	5 (3.4)	10 (3.4)
Gender						
Female	91 (44)	90 (43)	181 (43)	54 (37)	63 (43)	117 (40)
Male	118 (57)	122 (58)	240 (57)	92 (63.0)	84 (57)	176 (60.)
Region						

	1% cutoff					
	PD-L1 negative/non-identifiable			PD-L1 positive		
	Nivolumab-relatlimab FDC N=209 N (%)	Nivolumab N=212 N (%)	Overall N=421 N (%)	Nivolumab-relatlimab FDC N=146 N (%)	Nivolumab N=147 N (%)	Overall N=293 N (%)
USA/Canada	21 (10.)	20 (9)	41 (10)	24 (16)	14 (10)	38 (13)
Europe	107 (51)	110 (52)	217 (52)	67 (46)	80 (54)	147 (50)
Latin America	65 (31)	66 (31)	131 (31)	39 (27)	40 (27)	79 (27)
Australia/New Zealand	16 (8)	16 (8)	32 (8)	16 (11)	13 (9)	29 (10)

Source: Statistical reviewer generated table

Table 43: Baseline Disease Characteristics by PD-L1 Expression Level (5% cutoff)

	5% cutoff					
	PD-L1 negative/non-identifiable			PD-L1 positive		
	Nivolumab-relatlimab FDC N=267 N (%)	Nivolumab N=273 N (%)	Overall N=540 N (%)	Nivolumab-relatlimab FDC N=88 N (%)	Nivolumab N=86 N (%)	Overall N=174 N (%)
Baseline biomarker						
LAG-3 < 1%	82 (31)	90 (33)	172 (32)	5 (6)	0	5 (2.9)
LAG-3 ≥ 1%	185 (69)	183 (67)	368 (68)	83 (94)	86 (100)	169 (97)
LAG-3 < 5%	199 (75)	205 (75)	404 (75)	35 (40)	20 (23)	55 (32)
LAG-3 ≥ 5%	68 (26)	68 (25)	136 (25)	53 (60)	66 (77)	119 (68)
AJCC stage V8 at study entry						
Unresectable Stage III	27 (10)	15 (6)	42 (8)	8 (9)	8 (9)	16 (9)
Metastatic Stage IV	240 (90)	257 (94)	497 (92)	80 (91)	78 (91)	158 (91)
Unknown/not reported	0	1 (0.4)	1 (0.2)	0	0	0
Baseline LDH						
≤ ULN	165 (62)	165 (60)	330 (61)	59 (67)	66 (78)	125 (72)
> ULN	101 (38)	108 (40)	209 (39)	29 (33)	20 (23)	49 (28)
Not reported	1 (0.4)	0	1 (0.2)	0	0	0
≤ 2×ULN	239 (90)	245 (90)	484 (90)	83 (94)	83 (97)	166 (95)
> 2×ULN	27 (10)	28 (10)	55 (10)	5 (6)	3 (3.5)	8 (4.6)
Not reported	1 (0.4)	0	1 (0.2)	0	0	0
Baseline AJCC M stage						
M0/M1any[0]	170 (64)	171 (63)	341 (63)	62 (71)	66 (77)	128 (74)

	5% cutoff					
	PD-L1 negative/non-identifiable			PD-L1 positive		
	Nivolumab-relatlimab FDC N=267 N (%)	Nivolumab N=273 N (%)	Overall N=540 N (%)	Nivolumab-relatlimab FDC N=88 N (%)	Nivolumab N=86 N (%)	Overall N=174 N (%)
M1any[1]	97 (36.3)	102 (37)	199 (37)	26 (30)	20 (23)	46 (26)
Baseline BRAF status						
Mutant	106 (40)	106 (39)	212 (39)	30 (34)	33 (38)	63 (36)
Wild-type	161 (60)	167 (61)	328 (61)	58 (66)	53 (62)	111 (64)
Baseline metastasis stage (CRF)						
M0	27 (10)	15 (6)	42 (8)	8 (9)	8 (9)	16 (9)
M1	1 (0.4)	3 (1.1)	4 (0.7)	0	0	0
M1A	58 (22)	78 (29)	136 (25)	19 (27)	29 (34)	48 (28)
M1B	59 (22)	63 (23)	122 (23)	26 (30)	25 (29)	51 (29)
M1C	118 (44)	106 (39)	224 (42)	33 (38)	21 (24)	54 (31)
M1D	4 (1.5)	8 (2.9)	12 (2.2)	2 (2.3)	3 (3.5)	5 (2.9)
Gender						
Female	113 (42)	112 (41)	225 (42)	32 (36)	41 (48)	73 (42)
Male	154 (58)	161 (59)	315 (58)	56 (64)	45 (52)	101 (58)
Region						
USA/Canada	31 (12)	23 (8)	54 (10)	14 (16)	11 (13)	25 (14)
Europe	137 (51)	146 (54)	283 (52)	37 (42)	44 (51)	81 (47)
Latin America	79 (30)	83 (3)	162 (30)	25 (28)	23 (27)	48 (28)
Australia/New Zealand	20 (8)	21 (8)	41 (8)	12 (14)	8 (9)	20 (12)

Source: Statistical reviewer generated table

Table 44: Baseline Disease Characteristics by PD-L1 Expression Level (10% cutoff)

	10% cutoff					
	PD-L1 negative/non-identifiable			PD-L1 positive		
	Nivolumab-relatlimab FDC N=284 n (%)	Nivolumab N=290 n (%)	Overall N=574 n (%)	Nivolumab-relatlimab FDC N=71 n (%)	Nivolumab N=69 n (%)	Overall N=140 n (%)
Baseline biomarker						
LAG-3 < 1%	84 (30)	90 (31)	174 (30)	3 (4.2)	0	3 (2.1)
LAG-3 ≥ 1%	200 (70)	200 (69)	400 (70)	68 (96)	69 (100)	137 (98)

	10% cutoff					
	PD-L1 negative/non-identifiable			PD-L1 positive		
	Nivolumab-relatlimab FDC N=284 n (%)	Nivolumab N=290 n (%)	Overall N=574 n (%)	Nivolumab-relatlimab FDC N=71 n (%)	Nivolumab N=69 n (%)	Overall N=140 n (%)
LAG-3 < 5%	210 (74)	210 (72)	420 (73)	24 (34)	15 (22)	39 (28)
LAG-3 ≥ 5%	74 (26)	80 (28)	154 (27)	47 (66)	54 (78)	101 (72)
AJCC stage V8 at study entry						
Unresectable Stage III	29 (10)	17 (6)	46 (8)	6 (9)	6 (9)	12 (9)
Metastatic Stage IV	255 (90)	272 (94)	527 (92)	65 (92)	63 (91)	128 (91)
Unknown/not reported	0	1 (0.3)	1 (0.2)	0	0	0
Baseline LDH						
≤ ULN	177 (62)	177 (61)	354 (62)	47 (66)	54 (78)	101 (72)
> ULN	106 (37)	113 (39)	219 (38)	24 (34)	15 (22)	39 (28)
Not reported	1 (0.4)	0	1 (0.2)	0	0	0
≤ 2×ULN	255 (90)	261 (90)	516 (89)	67 (94)	67 (97)	134 (96)
> 2×ULN	28 (10)	29 (10)	57 (10)	4 (6)	2 (2.9)	6 (4.3)
Not reported	1 (0.4)	0	1 (0.2)	0	0	0
Baseline AJCC M stage						
M0/M1any[0]	183 (64)	183 (63)	366 (64)	49 (69)	54 (78)	103 (74)
M1any[1]	101 (36)	107 (37)	208 (36)	22 (31)	15 (22)	37 (26)
Baseline BRAF status						
Mutant	110 (39)	112 (39)	222 (39)	26 (37)	27 (39)	53 (38)
Wild-type	174 (61)	178 (61)	352 (61)	45 (63)	42 (61)	87 (62)
Baseline metastasis stage (CRF)						
M0	29 (10)	17 (6)	46 (8)	6 (9)	6 (9)	12 (9)
M1	1 (0.4)	3 (1.0)	4 (0.7)	0	0	0
M1A	60 (21)	84 (29)	144 (25)	17 (24)	23 (33)	40 (29)
M1B	67 (24)	68 (23)	135 (24)	18 (25)	20 (29)	38 (27)
M1C	123 (43)	109 (38)	232 (40)	28 (39)	18 (26)	46 (33)
M1D	4 (1.4)	9 (3.1)	13 (2.3)	2 (2.8)	2 (2.9)	4 (2.9)
Gender						
Female	113 (40)	119 (41)	232 (40)	32 (45)	34 (49)	66 (47)
Male	171 (60)	171 (59)	342 (60)	39 (55)	35 (51)	74 (53)
Region						
USA/Canada	34 (12)	25 (9)	59 (10)	11 (16)	9 (13)	20 (14)
Europe	147 (52)	155 (53)	302 (53)	27 (38)	35 (51)	62 (44)

	10% cutoff					
	PD-L1 negative/non-identifiable			PD-L1 positive		
	Nivolumab-relatlimab FDC N=284 n (%)	Nivolumab N=290 n (%)	Overall N=574 n (%)	Nivolumab-relatlimab FDC N=71 n (%)	Nivolumab N=69 n (%)	Overall N=140 n (%)
Latin America	81 (29)	87 (30)	168 (29)	23 (32)	19 (28)	42 (30)
Australia/New Zealand	22 (8)	23 (8)	45 (8)	10 (14)	6 (9)	16 (11)

Source: Statistical reviewer generated table

Based on this exploratory analysis, there does not appear to be an explanation for the higher PFS HR observed in the PD-L1 subgroups based on the 1%, 5% and 10% cut off. The imbalances in baseline characteristics noted in Table 42, Table 43, and Table 44 may offer an additional factor for consideration and suggests that PD-L1 expression level alone may not be an optimal biomarker to guide treatment decisions (See Sections 8.1.2.8 and 8.1.7).

8.2.9. Specific Safety Studies/Clinical Trials

The Applicant's Description:
Not applicable.

The FDA's Assessment:
FDA agrees with the Applicant's position that this section is not applicable.

8.2.10. Additional Safety Explorations

8.2.10.1. Human Carcinogenicity or Tumor Development

The Applicant's Description:
Not applicable.

The FDA's Assessment:
FDA agrees with the Applicant's position that this section is not applicable.

8.2.10.2. Human Reproduction and Pregnancy

The Applicant's Description:
Not applicable.

The FDA's Assessment:
FDA agrees with the Applicant's position that this section is not applicable.

8.2.10.3. Pediatrics and Assessment of Effects on Growth

The Applicant's Description:
Not applicable.

The FDA's Assessment:
FDA agrees with the Applicant's position that this section is not applicable.

8.2.10.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Description:
Higher doses of relatlimab up to 1440 mg in combination with nivolumab have been studied and were well-tolerated by patients without higher toxicity. Therefore, the observed physiological effect is minimal. However, in case of over dosage, the patient should be closely monitored for immune-adverse reactions and treated appropriately. There is no known antidote for nivolumab and/or relatlimab overdose.

No cases of withdrawal symptoms related to nivolumab and/or relatlimab were reported during human clinical trials. Nivolumab and/or relatlimab may have a minor influence on the ability to drive and use machines due to fatigue, which is a very common side effect of nivo+rela FDC. Patients should be advised not to drive or use machines if they feel tired.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.11. Safety in the Postmarket Setting

8.2.11.1. Safety Concerns Identified Through Postmarket Experience

The Applicant's Description:
The fixed dose combination of nivolumab and relatlimab is not marketed in any territory.

Nivolumab
Based on pharmacovigilance activities conducted by BMS Worldwide Patient Safety, review of post-marketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab. The safety profile of nivolumab in the post-marketing setting remains manageable. Post-marketing data for nivolumab are subject to continued active pharmacovigilance monitoring and are reported as per applicable post-marketing safety reporting requirements. Continuous safety monitoring ensures that updated safety information is available in a timely manner and that any future changes to the benefit-risk profile of nivolumab are appropriately managed and reported.

The FDA's Assessment:
Nivolumab-relatlimab FDC has not been approved for marketing in any country to date and there is no postmarket data available for safety analyses at this time.

8.2.11.2. Expectations on Safety in the Postmarket Setting

The Applicant's Description:

The safety profile of nivo+rela FDC has been well characterized and compared to an established standard of care, nivolumab, through the pivotal double-blind randomized study CA224047, and further safety data provided in the supportive study CA224020. As expected based on the mechanism of action, the key toxicities of nivo+rela FDC are related to immune-activation in keeping with other well-established immuno-oncology agents, and further potential safety issues are not expected beyond the risks conveyed in the proposed labelling.

The following patient populations were either excluded or had limited experience during the development of nivo+rela FDC: patients < age 12 years of age, patients with active autoimmune disease, patients with a history of severe hepatic or renal impairment, or in patients on concomitant immunosuppressant medications, patients with a history of myocarditis, patients with an ECOG PS ≥ 2, pregnant or breastfeeding females, patients with active or untreated brain or leptomeningeal metastases and patients with uveal melanoma.

- Patients < 12 years of age were excluded as the initial clinical development of nivo+rela FDC limited to adult patients.
- Patients on systemic immunosuppressants were excluded from clinical trials due to their potential interference with the pharmacodynamic activity of nivo+rela FDC.
- Patients with active autoimmune disease were excluded from clinical trials as further immune activation may increase risk of immune-related adverse events.
- Patients with a history of myocarditis were excluded as the cardiac risk for nivo+rela FDC was unknown.
- Patients with an ECOG performance score ≥ 2 were excluded as potential for higher risk to patient safety with development of AEs in this group compared with lower performance status.
- Patients with severe renal or hepatic impairment have not been studied during the nivo+rela FDC development. Both drugs are mAbs that are not metabolized by the liver nor cleared by the kidney.
  - No clinically important differences in nivolumab or relatlimab exposures were found between patients with mild/moderate hepatic impairment and patients with normal hepatic function (Figure 12) or mild/moderate renal impairment and patients with normal renal function (Figure 13).
- Patients with active or untreated brain or leptomeningeal metastases were excluded as this subpopulation has a significantly worse prognosis
- Patients with uveal melanoma were excluded as this subpopulation has a significantly worse prognosis

The safety profile in these special populations is anticipated to be similar to those studied in the sense that the primary concern is IMAEs; however, the nivo+rela FDC should be administered

with caution in these special populations.

The nivo+rela FDC long term safety, including growth development disorders, has not been studied in adolescent patients ≥ 12 years and older with unresectable or metastatic melanoma. (b) (4)

Regular pregnancy testing was required per protocol as the effect of nivo+rela FDC in pregnancy and breastfeeding are not yet known. In routine clinical practice, however, cancer patients are thoroughly counselled against pregnancy by their HCPs before commencing IO agents.

Based on the known risk of myocarditis with IO agents and the clinical importance of myocarditis (Section 8.2.1), vigilance is required in routine clinical practice. Myocarditis will be a standalone warning within the proposed product label, and myocarditis management guidance will be incorporated. In addition, the Patient Pocket Guide together with the Patient Wallet Card will outline symptoms that should prompt immediate contact with the healthcare provider.

Routine pharmacovigilance will be conducted to monitor for unexpected adverse events.

The FDA's Assessment:
FDA agrees with the Applicant's position. Potential safety concerns beyond the risks observed in clinical trials of relatlimab and described in product labeling are not expected. Routine pharmacovigilance will also be conducted by FDA to monitor for unexpected adverse events. The review teams determined that a REMS is not required to ensure safe and effective use of nivolumab-relatlimab FDC. Nivolumab-relatlimab FDC will be prescribed by oncologists who are trained on how to monitor, diagnose, and manage serious adverse reactions caused by immune checkpoint inhibitor drugs in accordance with FDA-approved labeling. Additionally, standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

8.2.12. Integrated Assessment of Safety

The Applicant's Description:
The totality of the safety data from 355 subjects from CA224047 and 1379 subjects from Study CA224020 demonstrate that the safety profile of nivo+rela is manageable and reflective of the MOA of nivolumab and relatlimab in subjects with unresectable or metastatic melanoma. The overall exposure to the nivo+rela FDC within CA224047 and CA224020 is considered adequate to support characterization of the safety profile of this novel regimen including > 1700 patients, including 437 patients treated with at least one dose of study drug at the intended presentation, dose, and dosing schedule. The included subjects are largely representative of the proposed patient population and in line with other clinical trials in this disease setting.

In CA224047, which permitted a randomized, double-blind comparison against an established standard of care, nivolumab monotherapy, the nature of AEs was similar between treatment groups, however, the overall frequencies of all-causality and drug-related SAEs, high grade AEs,

and AEs leading to discontinuation were numerically higher in the nivo+rela FDC arm compared with the nivolumab arm. No new types of clinically important events were identified with the combination when compared to nivolumab monotherapy. The most frequent drug-related AEs (occurring in ≥ 5% of subjects) were: pruritus, fatigue, rash, arthralgia, hypothyroidism, diarrhea, vitiligo, nausea, ALT increased, asthenia, AST increased, decreased appetite, myalgia, hyperthyroidism, headache, infusion related reaction, and dry mouth; these AEs were predominantly of low grade. IMAEs, including those that were severe (Grade 3-4), were higher in the nivo+rela FDC arm; however, they were manageable using the established treatment algorithms for nivolumab. Most all causality IMAEs (except for endocrine events) had resolved at the time of DBL; the median time to resolution ranged from 0.1 to 130.1+ weeks. OESIs occurred at a low rate in both the nivo+rela FDC and nivolumab arms. Myocarditis was infrequent at 1.7% and 0.6% in the two treatment arms respectively, and most cases were of low grade and resolved. Events of elevated troponin were balanced between the nivo+rela FDC and nivolumab arms.

In conclusion, the safety profile of nivo+rela FDC is manageable, in the context of the observed clinical activity, and manageable using well established guidelines.

A Risk Management Plan for nivo+rela FDC is included in this application dossier and is summarized in Table 70.

Table 70: Applicant - Proposed Risk Management Strategy

Important Identified Risks	**Pharmacovigilance activities**	**Risk Minimization Measures**
Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related endocrinopathies Immune-related nephritis and renal dysfunction Immune-related skin ARs Immune-related myocarditis Other immune-related ARs	**Routine** Monitoring and evaluation of individual case safety reports, expedited reporting, PSUR reporting and signal detection activities.	**Routine** Product label – For all immune-related ARs • Recommendations to interrupt of discontinue product and initiation of corticosteroids to treat immune-related ARs • Inclusion of specific clinical measures to address these risks (b) (4)
Important Potential Risk		
Embryofetal toxicity	**Routine**	**Routine**
Missing Information		
(b) (4)		

The FDA's Assessment:
The evaluation of the safety of nivolumab-relatlimab FDC at the proposed dosage in adult and

adolescent (≥12 years of age who weigh at least 40 kg) patients with unresectable or metastatic melanoma was based primarily on 714 patients randomized in Study CA224047 who received at least one dose of study drug (nivolumab-relatlimab FDC: 355 patients; nivolumanb: 359 patients). The Applicant included in their safety review an integrated safety analysis that incorporated data from the supportive trial CA224020, specifically the 437 patients (38 of which had previously untreated melanoma) treated with the proposed dosage of nivolumab-relatlimab FDC.

Overall, the safety profile for nivolumab-relatlimab FDC in Study CA224047 is consistent with the types of AEs expected for nivolumab. No new safety signals associated with nivolumab-relatlimab FDC were observed; however, some expected AEs, such as myocarditis, CNS effects, and hypersensitivity reactions/IRR, were observed in increased frequency or severity with administration of nivolumab-relatlimab FDC compared to nivolumab monotherapy. There was also a higher incidence of Grade 3-4 AEs, SAEs, AEs leading to discontinuations and dose interruption, and AESIs with administration of nivolumab-relatlimab FDC.

While the incidence of adverse events occurring in the 412 patients in Study CA224020 who received the proposed dose of nivolumab-relatlimab FDC varied (higher incidence of SAEs and Grade 3-4 AEs) from what was observed in Study CA224047, the types of adverse events observed were generally consistent between the two studies.

Further exploratory safety analyses of PD-L1 subgroups were conducted due to an observed increase in HR for PFS and OS as the PD-L1 expression cut off level increased (≥1%, ≥5%, and ≥10%). There was no identifiable safety signal observed in patients with positive PD-L1 tumor expression that appeared to contribute to the difference observed in HR. Specifically, there was no evidence that this difference may be due to more treatment-related toxicity or treatment-related adverse events resulting in death on the nivolumab-relatlimab FDC arm in each PD-L1+ subgroup.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

No major statistical issues were identified that impacted the results or interpretation of the primary efficacy result of PFS per BICR and key secondary efficacy results of OS and ORR per BICR for the CA224047 trial. CA224047 showed a statistically significant improvement in favor of the nivolumab-relatlimab FDC arm with respect to PFS by BICR. The final OS analysis was not statistically significant but showed no detrimental effect. The analysis of ORR per BICR suggested an improvement in the nivolumab-relatlimab FDC arm compared to nivolumab, but this potential difference was not tested statistically due to the pre-defined order for hierarchical testing. Beyond the primary and key secondary endpoints, FDA considers all other

analyses, including PRO analyses, descriptive and exploratory.

8.4. Conclusions and Recommendations

The FDA's Assessment:

FDA concludes that the results of Study CA224047 demonstrate that nivolumab-relatlimab FDC provides a statistically significant and clinically meaningful improvement in PFS in patients with previously untreated unresectable or metastatic melanoma who were randomized to receive nivolumab-relatlimab FDC compared to patients randomized to receive nivolumab. PFS is considered an acceptable endpoint to demonstrate the effectiveness of a new therapeutic in this patient population. The safety profile of nivolumab-relatlimab FDC at the proposed recommended dosage of 480 mg and 160 mg every 4 weeks is acceptable in the context of patients with a serious and life-threatening condition and is manageable with guidelines provided in product labeling. Overall, the review team concludes that the data in the application support a favorable benefit:risk assessment for nivolumab-relaltimab FDC in the indicated population and recommends traditional approval for the following indication:

Opdualag is indicated for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.

X X

Jiaxin Fan
Primary Statistical Reviewer

Joyce Cheng
Statistical Team Leader

X X

Leslie Doros
Primary Clinical Reviewer for Efficacy

Leigh Marcus
Primary Clinical Reviewer for Safety

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

X _____

Jamie R. Brewer
Clinical Team Leader (Acting)

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
The Division did not refer the application to the Oncologic Drug Advisory Committee (ODAC) or seek input from Special Government Employees (SGEs) for this BLA as no significant review issues were identified during the review of this application.

10 Pediatrics

The Applicant's Position:
An initial agreed PSP was obtained on 15-Sept-2020, which consisted of a partial waiver from the requirements of PREA for patients < 12 years of age. The agreed upon iPSP was for the following indication: nivolumab+relatlimab as a FDC in a single vial for the treatment of metastatic or unresectable melanoma. Based on the preliminary assessments of the data available to date and the current body of evidence regarding clinical relevance of LAG-3 expression across pediatric tumors, the Sponsor proposes to only evaluate nivolumab+relatlimab in cHL and NHL. This study protocol was submitted on 25-Feb-2021 (b) (4)

BMS plans to seek approval in adolescents based on extrapolation of the effectiveness in adults to patients ≥ 12 to < 18 years of age with unresectable or metastatic melanoma. No deferral is planned.

To extrapolate efficacy in adolescent melanoma subjects, a modeling and simulation analysis was used to predict exposures in adolescent subjects with melanoma for comparison with corresponding exposure from the target efficacious dose in the adult melanoma population (refer to Section 6.2). The nivo+rela FDC demonstrated a favorable benefit-risk profile for adult subjects with metastatic or unresectable melanoma and is extrapolated to provide a similar benefit-risk profile in pediatric subjects (≥ 12 years and weighing at least 40 kg) with metastatic or unresectable melanoma because of similarity in disease and similarity of expected E-R to IO therapy.

To support the extrapolation of safety to adolescent subjects, clinical safety data from Studies CA224047 and CA224020 in subjects with unresectable or metastatic melanoma or solid tumors were analyzed by body weight (< 50 vs ≥ 50 kg) and age (young adults aged 18 - 30 years). The low body weight (< 50 kg) cut-off was chosen as this body weight would result in higher exposures given the flat dosing regimen for nivo+rela FDC. As the median age in CA224047 was 63.0 years, a cohort of young adults was chosen to confirm no evidence of an altered safety profile by age. The safety profile of the combination of nivolumab and relatlimab in subjects with advanced melanoma with low body weight (< 50 kg) was generally similar to the safety profile in subjects with a body weight ≥ 50 kg, and no consistent trend was seen for higher frequency or severity of AEs with decreasing body weight. The safety profile of nivolumab in combination with relatlimab

appears also to be well-tolerated and manageable in subjects 18 to ≤ 30 years of age.

The FDA's Assessment:
FDA generally agrees with the Applicant's position. In the iPSP, the Applicant requested a partial wavier for children less than 12 years of age due to the impossible or highly impractical nature of conducting studies in this patient population. Although patients 12-17 years of age were allowed to enroll in study CA224047, no patients enrolled. To support the indication in patients 12-17 years of age, the Applicant used a modeling and simulation analysis to look for potential exposure differences. FDA recommends the same adult flat dosing regimen of nivolumab-relatlimab FDC in adolescents with BW ≥ 40 kg given that (1) no adolescent PK or efficacy/safety data for relatlimab are available, (2) potential lower exposure for nivolumab and relatlimab with the BW-based dosing may result in lower efficacy, (3) a flat exposure-safety relationship was identified for relatlimab up to 1440 mg Q4W in combination with nivolumab and (4) flat exposure-safety relationship for nivolumab in the dose range of 0.1 – 10 mg/kg Q2W.

See Section 6 and OCP Appendix 19.4 for additional information related to pharmacokinetic studies used to support the extrapolation of the effectiveness of nivolumab-relatlimab FDC in adults to patients ≥ 12 to <18 years of age with unresectable or metastatic melanoma.

11 Labeling Recommendations

The Applicant's Position:
The clinical data provided in this BLA demonstrate the clinical benefit and safety of the use of nivolumab + relatlimab FDC for the treatment of adult patients with unresectable or metastatic melanoma.

The FDA's Assessment:
[The table below summarizes changes to the proposed prescribing information (PI) made by FDA. See the final approved prescribing information for Opdualag (nivolumab-relatlimab-rmbw) accompanying the approval letter for more information.

Section	Proposed Labeling	Approved Labeling
1. Indications and Usage	OPDUALAG™ is indicated for the treatment of adults and pediatric patients (12 years and older (b) (4) with unresectable or metastatic melanoma.	FDA removed (b) (4) and revised to the following: OPDUALAG™ is indicated for the treatment of adult and pediatric patients 12 years of

		age or older with unresectable or metastatic melanoma.
2. Dosage and Administration	2.1 Recommended Dosage ...	FDA removed the (b) (4) and revised to use the 480 mg nivolumab and 160 mg relatlimab dosage for adult patients and pediatric patients 12 years and older who weigh at least 40 kg. FDA added: "The recommended dosage for pediatric patients 12 years of age or older who weigh less than 40 kg has not been established."
2. Dosage and Administration	2.3 Preparation and Administration ...	FDA revised to consolidated redundant preparation instructions for different patient populations to provide one set of instructions in a table with maximum infusion volume and concentration ranges to better organize and improve readability. FDA revised to clarify the proposed storage instructions for the prepared infusion when diluted and when prepared undiluted.
5. Warnings and Precautions	5.1 Severe and Fatal Immune-Mediated Adverse Reactions ...	FDA revised to remove (b) (4) FDA revised immune-mediated pneumonitis to remove (b) (4)

		(b) (4) FDA revised the hypophysitis, thyroid disorder, Type 1 diabetes mellitus, nephritis with renal dysfunction, and dermatologic adverse reactions information to add management instructions as follows: "Withhold or permanently discontinue OPDUALAG depending on severity".
5. Warnings and Precautions	5.2 Infusion-Related Reactions ...	FDA revised from (b) (4) to include all IRRs (7%).
6. Adverse Reactions	6.1 Clinical Trials Experience ...	FDA revised to add the most common adverse reactions leading to dosage interruption and permanent discontinuation. FDA revised to add a statement identifying the most common laboratory abnormalities. FDA revised adverse reaction rates for musculoskeletal pain (All Grades- (b) (4) to 45%; Grade 3-4 (b) (4) to 4.2%) and rash using similar grouped terms. FDA added common adverse reactions for decreased appetite and cough to the adverse reactions table. FDA added: "Clinically relevant adverse reactions in <15% of

		patients who received OPDUALAG included vitiligo, adrenal insufficiency, myocarditis, and hepatitis."
8. Specific Populations	8.1 Pregnancy …	FDA revised to add "(Based on) findings in animals"… and to remove (b) (4) FDA revised the "Data" section for relatlimab to remove an (b) (4)
8. Specific Populations	8.2 Lactation …	FDA removed a proposed statement (b) (4)
8. Specific Populations	8.3 Females and Males of Reproductive Potential …	FDA added: "OPDUALAG can cause fetal harm when administered to a pregnant woman."
8. Specific Populations	8.4 Pediatric Use …	FDA revised to add: "The safety and effectiveness of OPDUALAG have not been established in pediatric patients 12 years of age or older who weigh less than 40 kg, and pediatric patients younger than 12 years of age."
11. Description	…	FDA revised to add the required pharmacological class, dosage form, route of

		administration, and pH of the product.
12. Clinical Pharmacology	12.1 Mechanism of Action ...	FDA revised to remove (b) (4) to focus information related to the mechanism of action for relatlimab on the reduction of the LAG-3 receptor pathway immune response inhibition. FDA revised general information for T cell response and cytokine activity to focus information on the mechanism of action for nivolumab to the PD-1 and PD-L1 and L2 receptor pathways.
12. Clinical Pharmacology	12.2 Pharmacodynamics ...	FDA revised to remove (b) (4) FDA added: "The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of OPDUALAG have not been fully characterized." FDA removed (b) (4)
12. Clinical Pharmacology	12.3 Pharmacokinetics ...	FDA revised to add comparisons to the recommended dosage for the

		doses used to characterize pharmacokinetics and the half life of relatlimab (Elimination). FDA revised the specific population information from (b) (4) to "are unknown" for severe renal impairment or severe hepatic impairment. FDA revised pediatric patient information to: "The exposures of nivolumab and relatlimab in pediatric patients 12 years of age or older who weigh at least 40 kg are expected to be in the range of exposures in adult patients at the recommended dosage."
12. Clinical Pharmacology	12.6 Immunogenicity …	FDA revised to implement and align with recommended statements in the new immunogenicity guidance and added the treatment duration for immunogenicity sampling and results provided.
14. Clinical Studies	…	FDA revised to clarify that patients with Stage III (unresectable) or IV melanoma were enrolled to the study. FDA revised to add information on trial population characteristics for Black, American Indian/Alaskan Native races and Hispanic ethnicity.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
The safe use of nivolumab-relatlimab FDC can be adequately implemented in the postmarketing setting without issuing a REMS for this drug product. The product label for nivolumab-relatlimab FDC includes information on common and clinically significant adverse reactions that have been observed with nivolumab-relatlimab FDC and across the checkpoint inhibitor drug class. Product labeling also includes dose modification and management guidelines for these events. Risk management based on labeling and routine pharmacovigilance is expected to ensure the safe use of nivolumab-relatlimab FDC.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
The review team recommends issuing the following postmarketing requirements and postmarketing commitments:

Pediatric PMR:

4222-1: Conduct study CA224069 (A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of Relatlimab Plus Nivolumab in Pediatric and Young Adult Participants with Recurrent or Refractory Classical Hodgkin Lymphoma and Non-Hodgkin Lymphoma) to further characterize the safety, pharmacokinetics, pharmacodynamics and efficacy of relatlimab in combination with nivolumab in participants 0 to <30 years of age with relapsed or refractory Hodgkin lymphoma and an exploratory assessment in Non-Hodgkin lymphoma. Include at least 6 patients 0-11 years old and 6 patients 12-17 years old.

4222-2: Conduct a study, Study 2 (Modeling and Simulation/Extrapolation Study), to further characterize the pharmacokinetics and evaluate the dose regimen of nivolumab and relatlimab combination therapy in pediatric lymphoma.

CMC PMC:

4222-3: Re-evaluate the lot release and stability acceptance criteria for the potency (cell-based) - relatlimab test for relatlimab drug substance and Opdualag drug product after the manufacture of 30 drug product lots with the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.

4222-4: Develop an endotoxin release method for the drug product which mitigates the low endotoxin recovery (LER) effect and to submit the results of the LER study performed at (b) (4) with 3 lots of drug product, the endotoxin method qualification with 3 lots of drug product and the updated endotoxin method. The updated endotoxin method will replace the rabbit pyrogen testing upon approval of the supplement.

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

I concur with the analyses and conclusions of the FDA review team as presented above, and recommend approval of nivolumab-relatlimab-rmbw for the treatment of adult patients and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.

X

Lola A. Fashoyin-Aje, MD, MPH
Deputy Director, Division of Oncology 3

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.1. References

The Applicant's References:
Refences are located at the end of this document in Section 19.6.

The FDA's References:
Refences are located at the end of this document in Section 19.6 after the references from BMS.

19.2. Financial Disclosure

The Applicant's Position:
A list of all investigators in CA224047 will be provided and will include a financial disclosure package which provides the details of the process followed for collecting financial disclosures, table of investigators with disclosable interests reported by investigators, and if applicable, a table with due diligence efforts for the collection of missing financial disclosures. If/when an investigator reported disclosable financial interest, an assessment of the potential bias will be included.

The FDA's Assessment:
Below are the covered clinical studies from study CA224047. FDA agrees with the Applicant's assessment.

Covered Clinical Study (Name and/or Number):* CA224047

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 884		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 1 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

Data:
All data presented in Section 5.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA agrees.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Bioanalytical Methods

The Office of Clinical Pharmacology review team has assessed the acceptability of the following bioanalytical methods used in clinical studies CA224047 and CA224020. Summaries of method performance are provided in Table 71, Table 72, and Table 73 based on the information submitted in the BLA.

- Method MTD021: A chemiluminescent assay to measure BMS-986016 in human serum - Table 71
- Method ICD 416: An electrochemiluminescent (ECL) assay for determination of BMS-936558 in human serum - Table 72
- Method MTD035: An ECL Immunoassay for the measurement of Nivolumab in human serum – Table 73

Both the method validation and sample analysis for relatlimab were performed at (b) (4) Method ICD 416 validation and sample analysis for nivolumab in Study CA224020 were performed at (b) (4) Method MTD035 validation and sample analysis for nivolumab in Study CA224020 were performed at (b) (4)

Table 71: Determination of relatlimab (BMS-986016) method MTD021 (applied for analysis for relatlimab samples from Study CA224020 and CA224047)

Bioanalytical method review summary	Validation of method MTD 021 was adequate for determination of bms-986016 in human serum.		
Bioanalytical method validation report name, and amendments	Validation of a chemiluminescent assay to measure BMS-986016 in human serum Report No.: 930119405 4.0, Addendum 01 (additional stability assessment), Addendum 02 (additional assessment of selectivity in disease samples), Addendum 03 (evaluation the effect of co-medications nivolumab (BMS-936558) and ipilimumab (BMS-734016) on the quantitation of BMS-986016 and to evaluate storage at -80°C for at least 1166 days)		
Method description	This ELISA technology utilizes a chemiluminescent substrate that reacts with horseradish peroxidase conjugate to generate a luminescent signal that is proportional to the concentration of BMS-986016 in the serum. Briefly, this method uses a monoclonal antibody specific for BMS-986016 as the capture antibody, and uses BMS-986016 as the reference standard. The standards, quality controls, and validation samples in neat human serum are diluted to the minimum required dilution (MRD) of 50 (i.e., 2% human serum) and then added to the ELISA plate. The captured BMS-986016 is detected using a biotinylated monoclonal antibody specific for BMS-986016, followed by NeutrAvidin conjugated with horseradish peroxidase (NeutrAvidin-HRP). A luminol-based substrate specific for peroxidase is added and the resulting chemiluminescence is measured on a microplate reader.		
Materials used for calibration curve & concentration	BMS-986016 drug product: lot No. 3C83978 Calibrator concentrations: 50,000 (anchor), 6,400 (anchor), 3,200, 2,500, 1,600, 800, 400, 200, 100, and 50 ng/mL		
Validated assay range	50 (LLOQ) – 3200 (ULOQ) ng/mL		
Material used for QCs & concentration	BMS-986016 drug product: lot No. 3C83978 and AAC0467 QC concentrations: 50 (LLOQ), 150 (LQC), 500 (MQC), 2400 (HQC), 3200 (ULOQ), 500,000 (dilution QC) ng/mL		
Minimum required dilutions (MRDs)	1:50		
Regression model & weighting	Four-parameter (4PL) Marquardt with $1/Y^2$ weighting		
Validation Parameters	**Method Validation Summary**		**Acceptability**
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to upper limit of quantitation (ULOQ)	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-4.0 to 3.8%	Yes

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Per bioanalytical method validation (BMV), At least 75% and a minimum of 6 non-zero calibrators without anchor points and LBA: ±20% bias (±25% at lower limit of quantitation [LLOQ]), ≤ 20%CV			
	Cumulative precision (%CV) from LLOQ to ULOQ	0.5 to 2.5%	Yes
QCs performance during accuracy & precision Per BMV, LBA QCs: ±20% bias (±25% at LLOQ), ≤ 20%CV and ≤ 30% total error (≤ 40% at LLOQ)	Cumulative accuracy (%bias) across all QCs	3.75 to 8.00%	Yes
	Inter-batch %CV across all QCs	1.43 to 4.93%	Yes
	Percent total error (TE) across all QCs	5.18 to 12.13%	Yes
Selectivity	Selectivity in Melanoma: No Spike (blank): 10/10 samples were < LLOQ LLOQ Spike: 10/10 samples within ± 25% Bias HQC Spike: 10/10 samples within ± 20% Bias **Ten individual normal human serum (NHS) and ten individual bladder cancer human serum (CS) samples were analyzed unspiked, spiked at the LLOQ, and at the HQC levels of BMS-986016.** • All 10 unspiked NHS results were BLOQ, 10 NHS spiked at LLOQ (50 ng/mL) measured between 45.1 to 48.2 ng/mL (% Bias ranged from -9.8% to -3.6%), and 10 NHS spiked at HQC (2,400 ng/mL) measured between 2,170 and 2,420 ng/mL (%Bias ranged from -9.6% to 0.8%). • Ten CS spiked at LLOQ (50 ng/mL) measured between 43.5 to 61.3 ng/mL (% Bias ranged from -13.0% to 22.6%), and 10 CS spiked at HQC (2,400 ng/mL) measured between 2,150		Yes

	and 2,430 ng/mL (% Bias ranged from -10.4% to 1.3%). • For the ten unspiked individual CS, CS01, CS02 and CS03 showed high analyte concentrations (90.5, 267 and 1,870 ng/mL, respectively) in Run 3. The unspiked CS were retested in Runs #8, where all ten unspiked CS results were BLOQ. a third run needs to be conducted. • The set of 10 unspiked CS were retested in Runs #20, where 9 of 10 results were BLOQ. CS1 gave a result of 1,040 ng/mL with a %CV of 129.8%. • In Addendum 02, 73 disease state human serum samples were tested unspiked, and spiked at the LLOQ and HQC levels with BMS-986016. Of 73 unspiked samples, 72 were below the lower limit of quantitation (98.6%). For LLOQ-spiked samples, five samples failed due to unacceptable %bias (chronic lymphocytic leukemia, esophageal cancer, hepatocellular carcinoma HBV, multiple myeloma and other), for a sample passing rate of 93.2%. For HQC-spiked samples, three samples failed due to unacceptable %bias (esophageal cancer, hepatocellular carcinoma HBV, and multiple myeloma), for a sample passing rate of 95.9%.	
Interference & specificity	The effect of the soluble target of BMS-986016, human LAG-3, on the quantification of BMS-986016 was evaluated at the maximum expected level of LAG- 3. • Pooled normal human serum (PNHS) was spiked with 100 ng/mL of Lag 3 and analyzed. The sample result was BLOQ. Lag 3 was also spiked into samples with final BMS-986016 concentrations equivalent to the LQC and HQC levels. • LQCs spiked with 100 ng/mL of human Lag 3 gave %Bias values from -0.7% to 1.3%. • HQCs spiked with 100 ng/mL of human Lag 3 gave %Bias values from 3.3% to 7.1%.	

	The effect of BMS-936558, a concomitant medication, on the quantification of BMS-986016 was evaluated at the maximum expected level of BMS-936558. • PNHS was spiked with 150 µg/mL of BMS-936558 and analyzed. The sample result was BLOQ. • LQCs spiked with 150 µg/mL of BMS-936558 gave %Bias values from 8.0% to 10.0%. • HQCs spiked with 150 µg/mL of BMS-936558 gave %Bias values from 7.5% to 10.0%. • In Addendum 03, blank sample containing nivolumab at 300 µg/mL quantitated BLOQ; 100% of LQC-spiked samples containing Nivolumab at 300 µg/mL recovered within ± 20% of the nominal concentration; 100% of HQC-spiked samples containing Nivolumab at 300 µg/mL recovered within ± 20% of the nominal concentration.	
Hemolysis effect	No interfering effects for hemolysis at approximately 1100 mg/dL and minimal interference at the concentration of HQC 2400 ng/mL.	Yes
Lipemic effect	No interfering effects of lipids at > 300 mg/dL	Yes
Dilution linearity & hook effect	Dilutional linearity was observed up to 1:4096 No hook effect was observed for samples with nominal concentrations of 500,000, 125,000, 31,250, and 7,813 ng/mL.	Yes
Bench-top/process stability	18 hours and 6 minutes at room temperature	Yes
Freeze-Thaw stability	12 cycles stored at -80 °C.	Yes
Long-term storage	Up to 338 days at -20 °C Up to 1431 days at -80 °C Up to 82 days at -20 °C, then 708 days at -80 °C	Yes
Method Performance in Study CA224020 (Interim CSR Appendix 8.1.1)		
Assay passing rate	531/574 = 92.5%	Yes
Standard curve performance	Cumulative bias range: -2.7 to 2.7% Cumulative precision: ≤ 5.6% CV	Yes

QC performance	Cumulative bias range: -3.2 to -2.3% Cumulative precision: ≤ 7.8% CV Cumulative total error: ≤ 10.9%	Yes
Method reproducibility	Incurred Sample Reproducibility (ISR) Samples Tested for ISR = 1146 (10.1% of total number of samples) Samples Passing ISR = 1044 ISR Passing Rate = 91.1%	Yes
Study sample analysis/ stability	All Standards/QCs and study samples were stored and analyzed within the established documented stability conditions. Study samples were analyzed within 1388 days from date of collection stored at <-70 °C.	
Lipemic and hemolyzed samples	Provided through IR. There were 617 (5.6%) hemolyzed samples and 1 (0.01%) lipemic sample.	
Method Performance in Study CA224047 (CSR Appendix 8.3)		
Assay passing rate	82/97 = 84.5%	
Standard curve performance	Cumulative bias range: -3.7 to 3.2% Cumulative precision: ≤ 5.4% CV	
QC performance	Cumulative bias range: -4.2 to 0.7% Cumulative precision: ≤ 7.6% CV Cumulative total error: ≤ 10.6%	
Method reproducibility	Incurred Sample Reproducibility (ISR) Samples Tested for ISR = 180 (10.3% of total number of samples) Samples Passing ISR = 176 ISR Passing Rate = 97.8%	
Study sample analysis/ stability	Study samples were analyzed within 847 days from date of collection stored at <-70 °C.	
Lipemic and hemolyzed samples	Provided through IR. There were 80 (4.6%) hemolyzed samples and no lipemic sample.	

Table 72: Determination of nivolumab (BMS-936558) method ICD 416 (applied for analysis for nivolumab samples from Study CA224020)

Bioanalytical method review summary	Validation of method ICD 416 was adequate for determination of nivolumab in human serum.
Bioanalytical method validation report name, and amendments	Validation of a quantitative determination of BMS-936558 in human serum by electrochemiluminescent (ECL) Assay Report No.: 930057755 Addendum 02 (selectivity), Addendum 08 (interference and hemolysis), Addendum 22 (lipemic)
Method description	Samples are diluted to the assay MRD (1:100) in Assay Buffer and

	then mixed with a reaction buffer consisting of Biotin-MDX-1106 anti-idiotype clone 1106.2438.12B4E11D11 and Tag-MDX-1106 anti-idiotype clone 1106.2437.16B10H7B8. During incubation BMS-936558 binds to both the biotinylated anti-idiotype clone 1106.2438.12B4E11D11 as well as the Tag-MDX-1106 anti-idiotype clone 1106.2437.16B10H7B8, forming a complex. Following this, the complexed samples are added to an MSD streptavidin plate. The biotinylated anti-idiotype clone binds to the streptavidin coating and the ruthenium metal chelate (Tag) acts as the ECL label. Plates are read on the MSD Sector Imager 6000 after the addition of a tripropylamine-containing read buffer. During reading, the ruthenium produces a chemiluminescent signal that is directly proportional to the concentration of the BMS-936558 on the plate.		
Materials used for calibration curve & concentration	BMS-936558 drug product supplied by Bristol-Myers Squibb Reference Standard lot I-M48A-05, 1.0 mg/mL Drug Product lot 0D56606, 10.0 mg/mL Calibrator concentrations: 0.1 (anchor), 0.2, 0.3, 1.0, 2.5, 4.0, 5.5, 6.5 µg/mL		
Validated assay range	0.2 to 6.5 µg/mL		
Material used for QCs & concentration	BMS-936558 drug product supplied by Bristol-Myers Squibb Reference Standard lot I-M48A-05, 1.0 mg/mL Drug Product lot 0D56606, 10.0 mg/mL QC concentrations: 0.2 (LLOQ), 0.3 (back-up LLOQ), 0.6 (LQC), 1.5 (MQC), 4.8 (HQC), 6.5 (ULOQ), 100 (dilution QC) µg/mL		
Minimum required dilutions (MRDs)	1:100		
Regression model & weighting	Four-parameter logistic regression, no weighting		
Validation Parameters	**Method Validation Summary**		**Acceptability**
Calibration curve performance during accuracy & precision Per BMV, At least 75% and minimum of 6 non-zero calibrators without anchor points and	No of standard calibrators from LLOQ to upper limit of quantitation (ULOQ)	7	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-8.10 to 4.32%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 7.70%	Yes

LBA: ±20% bias (±25% at lower limit of quantitation [LLOQ]), ≤ 20%CV			
QCs performance during accuracy & precision Per BMV, LBA QCs: ±20% bias (±25% at LLOQ), ≤ 20%CV and ≤ 30% total error (≤ 40% at LLOQ)	Cumulative accuracy (%bias) across all QCs	-10.5 to 5.02%	Yes
	Inter-batch %CV across all QCs	≤ 10.1%	Yes
	Percent total error (TE) across all QCs	5.63 to 20.6%	Yes
Selectivity	Selectivity in Melanoma: No Spike (blank): 10/10 samples were < LLOQ LLOQ Spike: 9/10 samples within ± 20% Bias HQC Spike: 9/10 samples within ± 20% Bias		Yes
Interference & specificity	No interference with relatlimab up to 200 µg/mL at LQC (0.6 µg/mL) and HQC (4.8 µg/mL) spiked concentrations. No interference with anti-BMS-936558 (nivolumab) antibodies up to 0.1 µg/mL at LQC concentration, and 1.0 µg/mL at HQC concentration. There is interference in the quantitation of the LQC level when anti-BMS-936558 antibody is present at concentration of ≥ 1.00 µg/mL and of the HQC level when anti-BMS-936558 antibody is present at concentration of ≥ 10 µg/mL.		Yes
Hemolysis effect	No interference with Hemolysis at level ≤ 1100 mg/dL at the Blank, LQC and HQC spiked concentrations.		Yes
Lipemic effect	No interference with Lipids at levels > 300 mg/dL at the Blank, LQC and HQC spiked concentrations.		Yes
Dilution linearity & hook effect	Dilutional linearity was observed up to 1:400 No hook effect was observed up to 100 µg/mL at MRD.		Yes
Bench-top/process stability	Up to 96 hours at room temperature		Yes
Freeze-Thaw stability	9 cycles stored at -80 °C.		Yes
Long-term storage	Up to 515 days at -20 °C		Yes

	Up to 2373 days at -80 °C	
Method Performance in Study CA224020 (Interim CSR Appendix 8.1.4)		
Assay passing rate	465/469 = 99.1%	Yes
Standard curve performance	Cumulative bias range: -0.634 to 4.58% Cumulative precision: ≤ 4.09% CV	Yes
QC performance	Cumulative bias range: -1.12 to 5.97% Cumulative precision: ≤ 11.0% CV Cumulative total error: ≤ 17.0%	Yes
Method reproducibility	Incurred Sample Reproducibility (ISR) Samples Tested for ISR = 1076 (total samples: 9900, >10% of total number of samples) Samples Passing ISR = 1063 ISR Passing Rate = 98.8%	Yes
Study sample analysis/ stability	Study samples were analyzed within 1307 days from date of collection stored at <-70 °C.	
Lipemic and hemolyzed samples	10 hemolyzed samples with the hemolysis levels ≥ 550 mg Hb/dL were identified.	

Table 73: Determination of nivolumab (BMS-936558) method MTD035 (applied for analysis for nivolumab samples from Study CA224047)

Bioanalytical method review summary	Validation of method MTD 035 was adequate for determination of nivolumab in human serum.
Bioanalytical method validation report name, and amendments	Validation of an Electrochemiluminescent Immunoassay for the Measurement of Nivolumab (BMS-936558) in Human Serum Report No.: 930092958 7.0
Method description	This ECL assay is designed to detect nivolumab in human serum. Calibrators, controls and samples are diluted to the assay MRD (1:100) in Assay Buffer and then mixed with a reaction buffer consisting of a 1.00 µg/mL solution of biotin-anti-nivolumab-idiotype clone (12B4E11D11) and ruthenium-anti-nivolumab-idiotype clone (16B10H7B8). This mixture is allowed to incubate for approximately 90 minutes with gentle shaking at room temperature prior to transfer to a blocked MSD-SA plate. During this incubation, nivolumab binds to both the biotin anti-idiotype clone as well as the ruthenium-anti-idiotype clone, forming a complex. Following this, the complexed samples are added to an MSD streptavidin plate. The Biotin anti-idiotype clone binds to the streptavidin coating and the ruthenium metal chelate acts as the ECL label. Plates are read on the MSD Sector Imager after the addition of a tripropylamine-containing read buffer. During reading, the

	ruthenium produces a chemiluminescent signal that is directly proportional to the concentration of the nivolumab on the plate. Analyte concentrations are determined by interpolation from the standard curve.		
Materials used for calibration curve & concentration	BMS-936558, supplied by Bristol-Myers Squibb: Reference Standard lot 241388ARS, 9.9mg/mL (used in validation) Working Reference Standard lot 427067WRS, 9.8 mg/mL (used in validation addendums and CA224047 sample analysis) Working Reference Standard lot 3106487-1, 10.0 mg/mL (used in validation addendums and CA224047 sample analysis) Calibrator concentrations: 0.1 (anchor), 0.2, 0.3, 1.0, 2.5, 4.0, 5.5, 6.5 µg/mL		
Validated assay range	0.2 to 6.5 µg/mL		
Material used for QCs & concentration	BMS-936558, Supplied by Bristol-Myers Squibb: Reference Standard lot 241388ARS, 9.9mg/mL (used in validation) Working Reference Standard lot 427067WRS, 9.8 mg/mL (used in validation addendums and CA224047 sample analysis) Working Reference Standard lot 3106487-1, 10.0 mg/mL (used in validation addendums and CA224047 sample analysis) QC concentrations: 0.2 (LLOQ), 0.6 (LQC), 1.5 (MQC), 4.8 (HQC), 6.5 (ULOQ), 100 (dilution QC) µg/mL		
Minimum required dilutions (MRDs)	1:100		
Regression model & weighting	Four-parameter logistic regression, no weighting		
Validation Parameters	**Method Validation Summary**		**Acceptability**
Calibration curve performance during accuracy & precision Per BMV, At least 75% and minimum of 6 non-zero calibrators without anchor points and	No of standard calibrators from LLOQ to upper limit of quantitation (ULOQ)	7	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-0.8 to 4.7%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 6.9%	Yes

LBA: ±20% bias (±25% at lower limit of quantitation [LLOQ]), ≤ 20%CV			
QCs performance during accuracy & precision Per BMV, LBA QCs: ±20% bias (±25% at LLOQ), ≤ 20%CV and ≤ 30% total error (≤ 40% at LLOQ)	Cumulative accuracy (%bias) across all QCs	-6.0 to -0.6%	Yes
	Inter-batch %CV across all QCs	≤ 3.8%	Yes
	Percent total error (TE) across all QCs	3.0 to 8.3%	Yes
Selectivity	Selectivity in Melanoma: No Spike (blank): 10/10 samples were < LLOQ LLOQ Spike: 9/10 samples within ± 20% Bias HQC Spike: 8/10 samples within ± 20% Bias		Yes
Interference & specificity	No interference with anti-BMS-936558 (nivolumab) antibodies up to 0.1 µg/mL at LQC concentration, and 1.0 µg/mL at HQC concentration. There is interference in the quantitation of the LQC level when anti-BMS-936558 antibody is present at concentration of ≥ 1.0 µg/mL and of the HQC level when anti-BMS-936558 antibody is present at concentration of ≥ 10 µg/mL.		Yes
Hemolysis effect	No interference with Hemolysis at level ≤ 1100 mg/dL at the Blank, LQC and HQC spiked concentrations.		Yes
Lipemic effect	No lipemic sample in Study CA224047.		
Dilution linearity & hook effect	Dilutional linearity was observed up to 1:200 No hook effect was observed up to 100 µg/mL at MRD.		Yes
Bench-top/process stability	Up to 19 hours at room temperature		Yes
Freeze-Thaw stability	6 cycles stored at -80 °C		Yes
Long-term storage	Ongoing, up to 29 days at -80 °C		Yes
Cross Validation of Method ICD416 and Method MTD035			
Method MTD035 was cross validated to Method ICD416 using 4 levels of QCs and 30 individual incurred sample pools			

Difference Between Methods (% Difference) in 4 QCs	LQC (0.6 µg/mL): -7.2% MQC (1.5 µg/mL): 5.0% HQC (4.8 µg/mL): 5.1% DCQ (100 µg/mL): -3.6%	
Difference Between Methods 30 Individual Sample Pools	-14.2% (Range -26.2% to 7.5%)	
Method Performance in Study CA224047 (CSR Appendix 8.4)		
Assay passing rate	144/156 = 92.3%	Yes
Standard curve performance	Cumulative bias range: -3.0 to 5.2% Cumulative precision: ≤ 4.4% CV	Yes
QC performance	Cumulative bias range: 0.0 to 3.0% Cumulative precision: ≤ 10.3% CV Cumulative total error: ≤ 13.3%	Yes
Method reproducibility	Incurred Sample Reproducibility (ISR) Samples Tested for ISR = 343 (total samples: 3443, 10.0% of total number of samples) Samples Passing ISR = 334 ISR Passing Rate = 97.4%	Yes
Study sample analysis/ stability	Study samples were analyzed within 974 days from date of collection stored at <-70 °C.	
Lipemic and hemolyzed samples	Provided through IR. There were 123 (3.6%) hemolyzed samples and no lipemic sample.	

19.4.2. Population PK Analysis

19.4.2.1. Executive Summary

The FDA's Assessment:

Population PK analyses of nivolumab and relatlimab were submitted to support the BLA for a FDC product with nivolumab and relatlimab for the treatment of adult and pediatric patients (12 years or older and weighing at least 40 kg) with unresectable or metastatic melanoma. PK of nivolumab and relatlimab were characterized in the report and the exposures of nivolumab and relatlimab were compared in different dosing regimens and populations. As there were no adolescent patients involved in the study with relatlimab, extrapolation simulations for adolescent patients were performed for dose selection in adolescents. In general, the population PK analysis was acceptable, while there is some concern about the extrapolation simulation of relatlimab in adolescent patients. (b) (4)

(b) (4)

A new extrapolation simulation with relatlimab population PK model was performed and a flat dose of relatlimab 160 mg Q4W in adolescent patients showed similar exposure as adult subjects.

19.4.2.2. PPK Assessment Summary

The Applicant's Position:

General Information	
Objectives of PPK Analysis	• To characterize the PK of relatlimab, including effects of key intrinsic and extrinsic covariates on relatlimab PK parameters, in subjects with advanced solid tumors (including 1L and prior IO MEL) who received relatlimab alone or in combination with nivolumab. • To characterize the PK of nivolumab in adult and pediatric subjects with solid tumors, who received nivolumab alone and in combination with relatlimab, and assess the impact of relatlimab on nivolumab PK. • To compare key measures of nivolumab and relatlimab exposures between nivolumab 240 mg + relatlimab 80 mg Q2W and nivolumab 480 mg + relatlimab 160 mg Q4W. • To compare key measures of nivolumab and relatlimab exposure after sequential or coadministration of the OPDIVO® with relatlimab SAV product, or administration of the FDC product at nivolumab 480 mg + relatlimab 160 mg Q4W. • To compare nivolumab and relatlimab exposures in adolescent subjects (≥ 12 to 17 years) for select FDC (1:3) doses with adult population receiving FDC dose at nivolumab 480 mg + relatlimab 160 mg Q4W and identify the dose regimen that would produce comparable target exposures as in adults.
Studies Included	Nivolumab + relatlimab Studies: CA224020 and CA224047 Nivolumab Studies: MDX1106-01 [CA209001], MDX1106-03 [CA209003], ONO-4538-01 [CA209005], CA209017, ONO-4538-02 [CA209051], CA209057, CA209063, CA209070
Dose(s) Included	Relatlimab Monotherapy: 20, 80, 240, or 800 mg Q2W Nivo+rela: 80/20, 240/20, 240/80, 240/160, and 240/240 mg Q2W and 480/160, 480/240, 480/320, 480/480, 480/960, or 480/1440 mg Q4W Nivolumab Monotherapy: 0.1, 0.3, 1, 3, or 10 mg/kg Q2W; 1, 3, 10, and 20 mg/kg Q3W for 1st dose, followed by Q2W; 3 mg/kg Q2W; 2 mg/kg Q3W; 480 mg Q4W

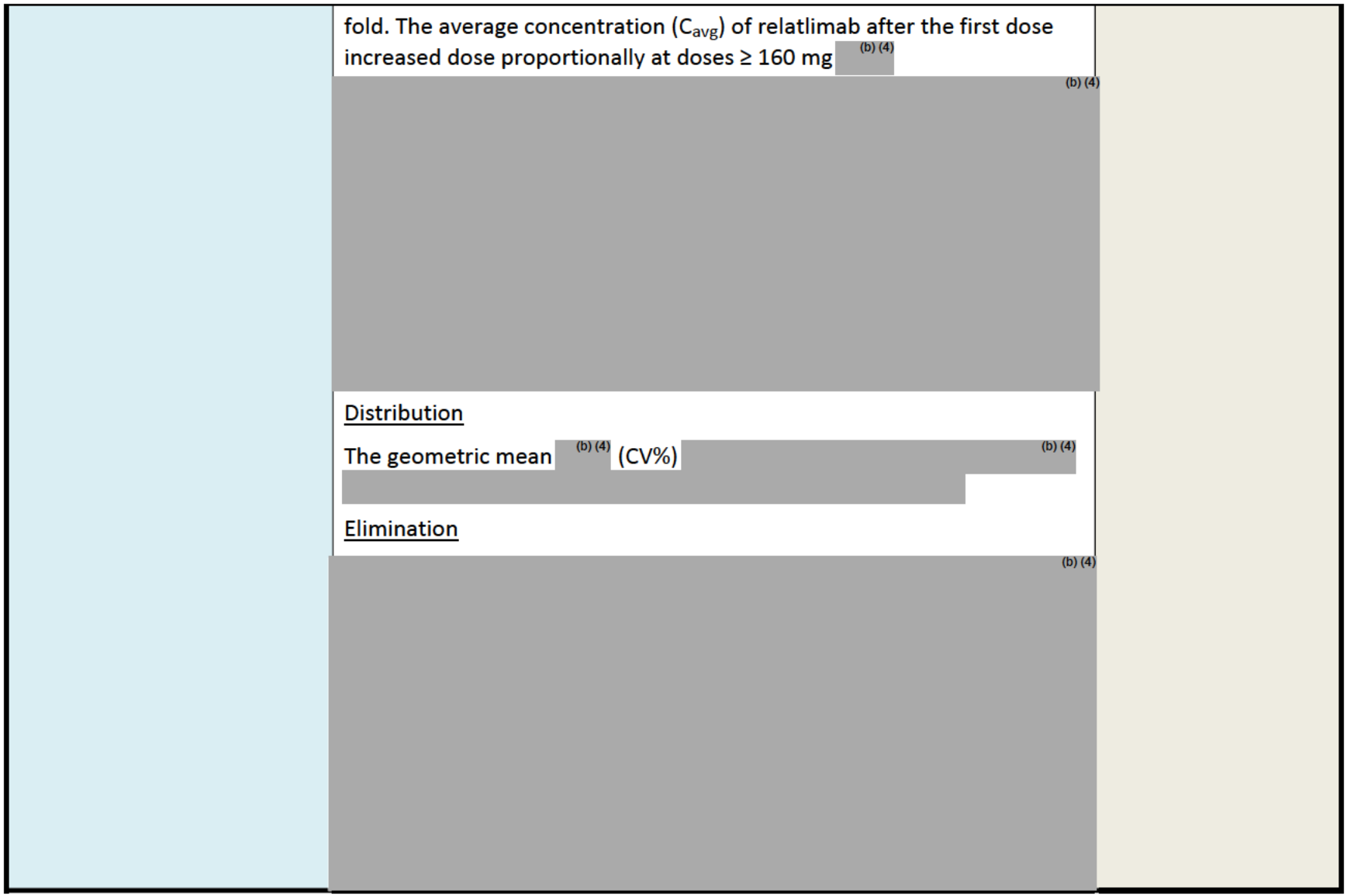
Population Included		Adult subjects with solid tumors including unresectable or metastatic melanoma, NSCLC, MEL, RCC, HCC, SCCHN, CRC, gastric cancer, and bladder cancer Pediatric subjects with recurrent or refractory tumors treated with nivolumab monotherapy
Population Characteristics (Table 74, Table 75, and Table 76)	General	Relatlimab PPK dataset • Median (range) age: 62 (17, 92) years • Median (range) baseline body weight: 76.5 (37, 170) kg • Sex, n (%): 1056 (61.6) males, 657 (38.4) females • Race, n (%): White: 1624 (94.8), Black/African American: 17 (1.0), Asian: 41 (2.4), Other: 26 (1.5), Missing: 5 (0.3) Nivolumab PPK dataset (overall patient population) • Median (range) age: 62 (1, 92) years • Median (range) baseline body weight: 75.3 (9.3, 170) kg • Sex, n (%): 1826 (61.4) males, 1148 (38.6) females • Race, n (%): White: 2728 (91.7), Black/African American: 71 (2.4), Asian: 116 (3.9), Other: 51 (1.7), Missing: 8 (0.3)
	Organ Impairment	Renal function was defined based on eGFR. Relatlimab PPK dataset: • Hepatic (NCI), n (%): normal: 1451 (84.7), mild: 245 (14.3), moderate: 12 (0.7), severe: 1 (0.1), and missing: 4 (0.2) • Median (range) eGFR: 88.5 (25.7, 159) mL/min/1.73 m^2 Nivolumab PPK dataset • Hepatic (NCI), n (%): normal: 2583 (86.9), mild: 366 (12.3), moderate: 13 (0.4), severe: 1 (0.0), and missing: 11 (0.4) • Median (range) eGFR: 88 (25.7, 202) mL/min/1.73 m^2
	Pediatrics (if any)	Median (range) age: 10 (1, 17) years Median (range) baseline body weight: 39.6 (9.3, 99.4) kg Sex, n (%): 28 (56.0) males, 22 (44.0) females

		Race, n (%): White: 39 (78.0), Black/African American: 4 (8.0), Asian: 5 (10.0), Other: 2 (4.0)
No. of Patients, PK Samples, and BLQ		Relatlimab Dataset: 1713 subjects, 10015 samples (465 excluded as below LLOQ) Nivolumab Dataset: 2974 subjects, 17680 samples (220 excluded as below LLOQ)
Sampling Schedule	Rich Sampling	• Relatlimab monotherapy and in combination with nivolumab: Study CA224020 Cycle 1, 3: Day 1 predose, 1 h (EOI), 4 h, 24 h, 96 h, and 168 h; predose on Day 15, Cycle 1: predose on Days 29 and 43, Cycle 2: Day 1 predose and 1 h (EOI); predose on Day 15, Cycles 5, 7, 9, until end of treatment: Day 1 predose, Follow-up: 30, 60, and 135-day visits • Nivolumab in combination with relatlimab: Study CA224020 Cycle 1, 3: Day 1 predose, 1 h (EOI), 4 h, 24 h, 96 h, and 168 h; predose on Day 15, Cycle 1: predose on Days 29 and 43, Cycle 2: Day 1 predose and 1 h (EOI); predose on Day 15, Cycles 5, 7, 9, until end of treatment: Day 1 predose, Follow-up: 30, 60, and 135-day visits • Nivolumab monotherapy: – Study CA209001 Predose, 30 minutes into dosing, immediately post-infusion, and 30 minutes, 1 h, 2 h, 4 h, 6 h, 8 h, 24 h, 48 h, and 72 h post-infusion end time; on Days 8, 15, 22, 29, 43, 57, 71, and 85 – Study CA209003 Cycle 1: Day 1 (after 60-minute infusion, 4 h, and 8 h); Days 2, 3, 5, 8, and 15, Cycle 2: Day 1 (pre-infusion), Cycle 3: Day 1 (pre-infusion, after 60-minute infusion); Days 2, 3, 5, 8, and 15
	In ITT Population	Study CA224047 Cycle 1: predose, 1 h (EOI); Cycle 2: predose; Cycle 6: predose, 1 h (EOI); Every 4th dose after Cycle 6: predose; Follow-up: 30 and 100-day visits
Covariates Evaluated	Static	Relatlimab PPK Analysis: Age, sex, race, baseline body weight, baseline eGFR, baseline albumin, baseline LDH, ECOG performance status, patient population, combination therapy, drug product Nivolumab PPK Analysis: Age, sex, baseline body weight, baseline eGFR, baseline albumin, ECOG performance status, patient population, combination therapy, drug product
	Time-varying	No time varying covariates were evaluated in the PPK analysis

Final Model	Summary	Acceptability [FDA's comments]
Software and Version	The PPK analysis was performed using the nonlinear mixed effects modeling (NONMEM 7.4) computer program, compiled using GNU Fortran 7.5.0, and all exploratory data analyses and presentations of data used R (version 4.0.2 or higher). The VPC, non parametric bootstrap, and PPK model for relatlimab were executed through PsN 4.9.0.	Acceptable
Model Structure	Relatlimab PPK Analysis: 2-compartment, zero-order IV infusion PK model with parallel nonlinear and time-varying linear CL that decreased with time (maximal reduction of 20%) Nivolumab PPK Analysis: 2 compartment, zero-order IV infusion PK model with time-varying CL.	Acceptable
Model Parameter Estimates	Table 77 (relatlimab) and Table 78 (nivolumab)	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Relatlimab PPK Analysis: Relatlimab parameters were estimated with adequate precision (Table 77). Relative high RSE for parameter estimates CL_{AGE}, $CL_{RACE\text{-}AA}$, $CL_{RACE\text{-}ASIAN}$, CL_{MONO} were observed, mainly due to the relative small magnitude of effects or small sample size. The shrinkage values were around 20-30% except for ETA_EMAX (52.4%) and ETA_VP (45.5%). VP was well estimated with RSE% of 2.38%, and RSE% for Emax was 40.9% with a point estimate of -0.053 (95% CI: -0.0955% - -0.0105%), indicating a small degree of decrease in clearance with time. Bootstrap was not conducted during the PPK analysis mainly due to the long run time. The 95% CI were from asymptotic standard error reported by NONMEM. Nivolumab PPK Analysis: Nivolumab parameters were precisely estimated (Table 78) except for effects on CL_{RAAA}, CL_{OTH}, and $EMAX_{COMBO}$, which was due to the small magnitude of effects and consequently the uncertainties in the estimated effects are small despite the high RSE.	Acceptable

	Based on 1000 Bootstrap calculations, the effect of African American on CL, Adult Others on CL, and relatlimab combination on Emax was 104% (95% CI, 96-113%), 99.5 (95%CI, 95.4-104%), and 99.2% (95% CI, 94.4-104%), respectively, indicating a small effect size. The shrinkage values: Eta shrinkage (%): ETA_CL: 11.2; ETA_VC: 22.7; ETA_EMAX: 43.6; EPS shrinkage (%): 15.2 (see footnote of Table 78). The relatively higher ETA-shrinkage for Emax is unlikely to impact individual exposures, since ETA shrinkage for CL and VC are relatively low, which are the primary parameters important for the EBE-derived exposures. In the current PPK analysis, The Emax parameter is well estimated with a meaningful magnitude of decrease of -0.198 (RSE 11.8%, 95% CI -0.251 to -0.151). The ETA on Emax is also well estimated with a point estimate of 0.0797 (RSE 14.2%, 95% CI 0.0597 to 0.109) (Table 78).	
BLQ for Parameter Accuracy	Relatlimab PPK Analysis: PK samples with BLQ were excluded from the PPK analysis. Exclusion of BLQ is not expected to impact PPK parameter estimates as only approximately 5% of total PK concentrations had BLQ. Nivolumab PPK Analysis: PK samples with BLQ were excluded from the PPK analysis. Exclusion of BLQ is not expected to impact PPK parameter estimates as only approximately 1% of total PK concentrations had BLQ.	Acceptable
GOF, VPC	Figure 22, Figure 23, Figure 24, Figure 25, Figure 26, Figure 27, Figure 28, Figure 29, Figure 30, and Figure 31	Acceptable
Significant Covariates and Clinical Relevance	Figure 14 and Figure 21. Relatlimab PPK Analysis: See Section 6.2.1 and 6.3.2.3. Nivolumab PPK Analysis: Effects of covariates on nivolumab CL: The effects of eGFR, age, race (Asian), PS, and sex on nivolumab baseline CL were statistically significant, however they were not considered clinically relevant (< 20%). There were covariate effects of baseline body weight (23% higher CL in subjects with 95th percentile of body weight relative to	Acceptable. Based on the updated population PK model of nivolumab that included more pediatric patients; adolescent patients

	median body weight) and albumin (28% higher CL in subjects with 5th percentile of albumin relative to median albumin) on baseline CL, which are not expected to be clinically relevant. Adolescent subjects had 36% lower baseline CL than those of adult 1L MEL subject. Effects of covariates on nivolumab VC: There were covariate effects of baseline body weight (25% higher VC in subjects with 95th percentile of body weight relative to median body weight) and sex (13% lower VC in females than males) on VC. Adolescent subjects had 16% lower VC than those of adult subjects.	(b) (4) .
Analysis Based on Simulation (optional)	Refer to Figure 7 and Figure 8 for pediatric dose simulations. The only covariate that was significant and had a >20% impact was body weight; refer to Figure 32 (relatlimab) and Figure 33 (nivolumab).	Pediatric simulation of nivolumab was acceptable. However, there is concern about the simulation of relatlimab in adolescent patients, which is detailed in the FDA's assessment.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	The PK of relatlimab following the administration of Nivolumab-relatlimab (b) (4) characterized in patients with various cancers who received relatlimab (b) (4) 20 to 800 mg (b) (4) 160 to 1440 mg (b) (4) as a monotherapy or in combination with nivolumab (b) (4) of 80 or 240 mg (b) (4) or 480 mg (b) (4) Steady-state concentrations of relatlimab were reached by 16 weeks with an every 4-week regimen and the systemic accumulation was 1.9-	In general, the description in section 12.3 of the labeling is acceptable. Edits will be added in the final labeling language.



Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

	Specific Populations The following factors had no clinically important effect on the (b) (4) of nivolumab and relatlimab: age (range: 17 to 92 years), sex, race, mild or moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin [TB] less than or equal to upper limit of normal [ULN] and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). The (b) (4) of severe renal (b) (4) hepatic impairment on the pharmacokinetics of nivolumab and relatlimab (b) (4) unknown. Pediatric patients: (b) (4)	

Table 74: Applicant - Summary of Covariates by Patient Population in the Relatlimab Population Pharmacokinetic Analysis Dataset

Covariate	Adult 1L MEL N = 456	Adult Prior-IO MEL N = 791	Adult Others N = 466	Total N = 1713
Age (years)				
Mean (SD)	61.2 (14)	60.9 (13.4)	59.7 (11.5)	60.7 (13.1)
Median (min, max)	63 (20, 90)	62 (17, 92)	61 (18, 88)	62 (17, 92)
Baseline Body Weight (kg)				
Mean (SD)	80.9 (18.6)	79.1 (18.4)	73.3 (16.8)	78 (18.3)
Median (min, max)	80 (39, 163)	77 (41.1, 170)	71.5 (37, 145)	76.5 (37, 170)
Missing, n (%)	0	3 (0.379)	0	3 (0.175)
Sex N (%)				
Male	266 (58.3)	473 (59.8)	317 (68.0)	1056 (61.6)
Female	190 (41.7)	318 (40.2)	149 (32.0)	657 (38.4)
Race N (%)				
White	443 (97.1)	750 (94.8)	431 (92.5)	1624 (94.8)
Black/African American	0	7 (0.9)	10 (2.1)	17 (1.0)
Asian	1 (0.2)	29 (3.7)	11 (2.4)	41 (2.4)
Other	7 (1.5)	5 (0.6)	14 (3.0)	26 (1.5)
Missing	5 (1.1)	0	0	5 (0.3)
Baseline Serum Albumin (g/dL)				
Mean (SD)	4.14 (0.457)	3.96 (0.473)	3.75 (0.478)	3.95 (0.492)
Median (min, max)	4.2 (2.1, 5.2)	4 (2, 6)	3.8 (2.2, 4.8)	4 (2, 6)
Missing, n (%)	23 (5.04)	69 (8.72)	37 (7.94)	129 (7.53)
Baseline Lactate Dehydrogenase (U/L)				
Mean (SD)	355 (417)	377 (482)	272 (227)	342 (411)
Median (min, max)	238 (60, 4641)	237 (85, 7464)	206 (90, 2367)	230 (60, 7464)
Missing, n (%)	2 (0.439)	11 (1.39)	1 (0.215)	14 (0.817)
Baseline eGFR, (mL/min/1.73 m^2)				
Mean (SD)	86.7 (18.6)	86.8 (18.5)	86.6 (20.9)	86.7 (19.2)
Median (min, max)	89.6 (25.7, 132)	88 (34.2, 144)	89.5 (27.3, 159)	88.5 (25.7, 159)
Missing, n (%)	6 (1.32)	2 (0.253)	0	8 (0.467)
Liver Dysfunction Group N (%)				
Group A: Normal	396 (86.8)	701 (88.6)	354 (76.0)	1451 (84.7)
Group B: Mild	53 (11.6)	84 (10.6)	108 (23.2)	245 (14.3)
Group C: Moderate	5 (1.1)	3 (0.4)	4 (0.9)	12 (0.7)
Group D: Severe	1 (0.2)	0	0	1 (0.1)
Missing	1 (0.2)	3 (0.4)	0	4 (0.2)
Baseline LAG-3 Expression N (Covance) [1% cutoff]				
Negative	100 (21.9)	246 (31.1)	0	346 (20.2)
Positive	281 (61.6)	379 (47.9)	0	660 (38.5)

Covariate	Adult 1L MEL N = 456	Adult Prior-IO MEL N = 791	Adult Others N = 466	Total N = 1713
Unknown	75 (16.4)	166 (21.0)	466 (100.0)	707 (41.3)
Baseline ECOG Performance Status N (%)				
0	322 (70.6)	540 (68.3)	224 (48.1)	1086 (63.4)
1	134 (29.4)	240 (30.3)	227 (48.7)	601 (35.1)
2	0	11 (1.4)	3 (0.6)	14 (0.8)
Missing	0	0	12 (2.6)	12 (0.7)
ADA N (%)				
Negative[a]	422 (92.5)	726 (91.8)	374 (80.3)	1522 (88.8)
Positive[b]	34 (7.5)	65 (8.2)	92 (19.7)	191 (11.2)
Manufacturing Process N (%)[c]				
Process (b) (4)	0	5 (0.6)	30 (6.4)	35 (2.0)
Process	63 (13.8)	411 (52.0)	230 (49.4)	704 (41.1)
Process	10 (2.2)	14 (1.8)	15 (3.2)	39 (2.3)
Process	0	0	1 (0.2)	1 (0.1)
(b) (4)	333 (73.0)	80 (10.1)	0	413 (24.1)
Missing	50 (11.0)	281 (35.5)	190 (40.8)	521 (30.4)
Therapy N (%)				
Combination Therapy	456 (100.0)	791 (100.0)	445 (95.5)	1692 (98.8)
Monotherapy	0	0	21 (4.5)	21 (1.2)

[a] Subjects without presence of ADAs at all sampling times.
[b] Subjects with presence of ADAs at ≥ 1 sampling time during the study.
[c] First occurrence of manufacturing process was considered.

Table 75: Applicant - Summary of Covariates by Patient Population in the Nivolumab Population Pharmacokinetic Analysis Dataset

Covariate	Adult 1L MEL N = 936	Adult Prior IO MEL N = 777	Adult Others N = 1211	Pediatric Subjects N = 50	Total N = 2974
Age (years)					
Mean (SD)	61 (13.9)	61 (13.3)	61.1 (11)	10.5 (4.71)	60.2 (14.1)
Median (Min, Max)	63 (20, 90)	62 (23, 92)	62 (18, 88)	10 (1, 17)	62 (1, 92)
Baseline Body Weight (kg)					
Mean (SD)	79.6 (18.8)	79 (18.5)	74.9 (17.5)	41.6 (24.2)	76.9 (19)
Median (Min, Max)	78.2 (34.1, 163)	77 (41.1, 170)	72.7 (32.8, 158)	39.6 (9.3, 99.4)	75.3 (9.3, 170)
Missing N (%)	0	3 (0.386)	1 (0.0826)	0	4 (0.134)
Sex N (%)					
Male	542 (57.9)	464 (59.7)	792 (65.4)	28 (56.0)	1826 (61.4)
Female	394 (42.1)	313 (40.3)	419 (34.6)	22 (44.0)	1148 (38.6)
Race N (%)					
White	870 (92.9)	736 (94.7)	1083 (89.4)	39 (78.0)	2728 (91.7)
Black/African American	7 (0.7)	7 (0.9)	53 (4.4)	4 (8.0)	71 (2.4)

Covariate	Adult 1L MEL N = 936	Adult Prior IO MEL N = 777	Adult Others N = 1211	Pediatric Subjects N = 50	Total N = 2974
Asian	40 (4.3)	29 (3.7)	42 (3.5)	5 (10.0)	116 (3.9)
Other	13 (1.4)	5 (0.6)	31 (2.6)	2 (4.0)	51 (1.7)
Missing	6 (0.6)	0	2 (0.2)	0	8 (0.3)
Baseline Serum Albumin (g/dL)					
Mean (SD)	4.15 (0.467)	3.96 (0.472)	3.84 (0.492)	3.76 (0.927)	3.97 (0.498)
Median (Min, Max)	4.2 (2.1, 5.2)	4 (2, 6)	3.9 (1.9, 5.2)	4 (2.3, 4.7)	4 (1.9, 6)
Missing N (%)	30 (3.21)	69 (8.88)	59 (4.87)	43 (86)	201 (6.76)
Baseline Lactate Dehydrogenase (U/L)					
Mean (SD)	355 (452)	376 (485)	305 (253)	639 (NA)	340 (394)
Median (Min, Max)	234 (60, 5004)	236 (85, 7464)	220 (90, 3085)	639 (639, 639)	230 (60, 7464)
Missing N (%)	7 (0.748)	11 (1.42)	18 (1.49)	49 (98)	85 (2.86)
Baseline eGFR (mL/min/1.73 m^2)					
Mean (SD)	86.9 (18.9)	86.7 (18.3)	84 (21)	119 (28.6)	86.2 (20.3)
Median (Min, Max)	89.8 (25.7, 140)	88 (34.2, 144)	86.3 (27.3, 159)	120 (43.5, 202)	88 (25.7, 202)
Missing N (%)	10 (1.07)	2 (0.257)	2 (0.165)	0	14 (0.471)
Liver Dysfunction Group N (%)					
GROUP A: Normal	822 (87.8)	691 (88.9)	1026 (84.7)	44 (88.0)	2583 (86.9)
GROUP B: Mild	103 (11.0)	80 (10.3)	177 (14.6)	6 (12.0)	366 (12.3)
GROUP C: Moderate	5 (0.5)	3 (0.4)	5 (0.4)	0	13 (0.4)
GROUP D: Severe	1 (0.1)	0	0	0	1 (0.0)
Missing	5 (0.5)	3 (0.4)	3 (0.2)	0	11 (0.4)
Tumor Type N (%)					
1L MEL	936 (100.0)	0	0	0	936 (31.5)
Prior-IO MEL	0	777 (100.0)	0	1 (2.0)	776 (26.1)
NSCLC	0	0	727 (60.0)	0	727 (24.4)
Other Tumor Type	0	0	484 (40.0)	49 (98.0)	533 (17.9)
Missing	0	0	0	0	0
Baseline ECOG Performance Status N (%)					
0	638 (68.2)	529 (68.1)	423 (34.9)	14 (28.0)	1604 (53.9)
1	295 (31.5)	237 (30.5)	767 (63.3)	28 (56.0)	1327 (44.6)
2	3 (0.3)	11 (1.4)	9 (0.7)	8 (16.0)	31 (1.0)
Missing[a]	0	0	12 (1.0)	0	12 (0.4)
ADA N (%)					
Negative[b]	829 (88.6)	712 (91.6)	989 (81.7)	47 (94.0)	2577 (86.7)
Positive[c]	107 (11.4)	65 (8.4)	222 (18.3)	3 (6.0)	397 (13.3)
Missing	0	0	0	0	0
Drug Products N (%)					
Nivo Monotherapy	480 (51.3)	0	771 (63.7)	49 (98.0)	1300 (43.7)
SAV coadministration	62 (6.6)	516 (66.4)	0	1 (2.0)	579 (19.5)
SAV sequential	60 (6.4)	182 (23.4)	440 (36.3)	0	682 (22.9)
FDC	334 (35.7)	79 (10.2)	0	0	413 (13.9)

[a] Subjects with performance status values of 6 were included in missing category.

[b] Subjects without presence of ADAs at all sampling times.

[c] Subjects with presence of ADAs at ≥ 1 sampling time during the study.

Table 76: Applicant - Summary of Covariates in the Nivolumab Population Pharmacokinetic Analysis Dataset by Adolescents (≥ 12 to 17 years) and Pediatrics (< 12 years)

Covariate	Pediatrics (< 12 years) N = 26	Adolescents (12-17 years) N = 24	Total N = 50
Age (years)			
Mean (SD)	6.62 (2.7)	14.8 (1.87)	10.5 (4.71)
Median (Min, Max)	7 (1, 10)	15 (12, 17)	10 (1, 17)
Baseline Body Weight (kg)			
Mean (SD)	22.5 (9.18)	62.3 (17.1)	41.6 (24.2)
Median (Min, Max)	20.1 (9.3, 49.1)	59.8 (39.7, 99.4)	39.6 (9.3, 99.4)
Sex N (%)			
Male	14 (53.8)	14 (58.3)	28 (56.0)
Female	12 (46.2)	10 (41.7)	22 (44.0)
Race N (%)			
White	20 (76.9)	19 (79.2)	39 (78.0)
Black/African American	2 (7.7)	2 (8.3)	4 (8.0)
Asian	3 (11.5)	2 (8.3)	5 (10.0)
Other	1 (3.8)	1 (4.2)	2 (4.0)
Baseline Serum Albumin (g/dL)			
Mean (SD)	4.06 (0.802)	3 (0.99)	3.76 (0.927)
Median (Min, Max)	4.4 (2.7, 4.7)	3 (2.3, 3.7)	4 (2.3, 4.7)
Missing N (%)	21 (80.8)	22 (91.7)	43 (86)
Baseline Lactate Dehydrogenase (U/L)			
Mean (SD)	NA	639 (NA)	639 (NA)
Median (Min, Max)	NA	639 (639, 639)	639 (639, 639)
Missing N (%)	26 (100)	23 (95.8)	49 (98)
Baseline eGFR (mL/min/1.73 m^2)			
Mean (SD)	120 (28.9)	117 (28.7)	119 (28.6)
Median (Min, Max)	120 (43.5, 202)	120 (66.9, 179)	120 (43.5, 202)
Missing N (%)	0	0	0
Liver Dysfunction Group N (%)			
GROUP A: Normal	21 (80.8)	23 (95.8)	44 (88.0)
GROUP B: Mild	5 (19.2)	1 (4.2)	6 (12.0)
Missing	0	0	0
Tumor Type N (%)			
Prior-IO MEL	0	1 (4.2)	1 (2.0)
Other Tumor Type	26 (100.0)	23 (95.8)	49 (98.0)
Baseline ECOG Performance Status N (%)			
0	8 (30.8)	6 (25.0)	14 (28.0)
1	14 (53.8)	14 (58.3)	28 (56.0)
2	4 (15.4)	4 (16.7)	8 (16.0)
ADA N (%)			
Negative[a]	25 (96.2)	22 (91.7)	47 (94.0)
Positive[b]	1 (3.8)	2 (8.3)	3 (6.0)
Drug Products N (%)			
Nivo Monotherapy	26 (100.0)	23 (95.8)	49 (98.0)
SAV coadministration	0	1 (4.2)	1 (2.0)

[a] Subjects without presence of ADAs at all sampling times.

[b] Subjects with presence of ADAs at ≥ 1 sampling time during the study.

Table 77: Applicant - Parameter Estimates of the Final Relatlimab Population Pharmacokinetic Model

Parameter [Units][a,b]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% CI[e]
Fixed Effects				
$CL0_{REF}$ [mL/h]	θ_1	6.97	0.251 (3.61)	6.48 - 7.46
VC_{REF} [L]	θ_2	4.13	0.0431 (1.04)	4.04 - 4.21
Q_{REF} [mL/h]	θ_3	25.5	1.12 (4.37)	23.3 - 27.7
VP_{REF} [L]	θ_4	2.97	0.0667 (2.25)	2.83 - 3.10
VMAX [mg/h]	θ_5	0.0776	0.00325 (4.18)	0.0713 - 0.084
KM [mg/L]	θ_6	1.47	0.158 (10.7)	1.16 - 1.78
CL_{WTB}	θ_9	0.722	0.0632 (8.75)	0.598 - 0.846
$V1_{WTB}$	θ_{10}	0.370	0.0399 (10.8)	0.292 - 0.449
$V2_{WTB}$	θ_{12}	0.633	0.0824 (13.0)	0.472 - 0.795
T50 [h]	θ_{13}	3.19E+03	80.9 (2.54)	3.03E+03 - 3.35E+03
EMAX	θ_{14}	-0.0492	0.0213 (43.4)	-0.0910 - -0.00733
Hill	θ_{15}	4.03	0.353 (8.77)	3.34 - 4.72
CL_{BGFR}	θ_{17}	0.234	0.0498 (21.3)	0.137 - 0.332
CL_{ALB}	θ_{18}	-0.868	0.103 (11.9)	-1.07 - -0.665
CL_{BLDH}	θ_{19}	0.991	0.144 (14.5)	0.708 - 1.27
CL_{SEX}	θ_{20}	-0.199	0.0285 (14.3)	-0.254 - -0.143
CL_{PS}	θ_{23}	0.120	0.0258 (21.5)	0.0697 - 0.171
CL_{SAV}	θ_{27}	0.156	0.0307 (19.7)	0.0960 - 0.216
VC_{SEX}	θ_{28}	-0.154	0.0179 (11.6)	-0.189 - -0.119
$EMAX_{PS}$	θ_{29}	-0.148	0.0359 (24.2)	-0.219 - -0.0780
Random Effects				
ZCL	$\omega_{1,1}$	0.144 (0.379)	0.00913 (6.34)	0.126 - 0.162
ZV1	$\omega_{2,2}$	0.0633 (0.252)	0.00283 (4.47)	0.0578 - 0.0689
ZV2	$\omega_{3,3}$	0.170 (0.412)	0.0102 (6.00)	0.150 - 0.190
ZVmax	$\omega_{4,4}$	0.203 (0.451)	0.0141 (6.93)	0.176 - 0.231
ZEMAX	$\omega_{5,5}$	0.101 (0.318)	0.00909 (9.00)	0.0831 - 0.119
ZCL:ZV1	$\omega_{1,2}$	0.0462 (0.484)	0.00436 (9.43)	0.0376 - 0.0547
Residual Error				
Additive Error [µg/mL]	θ_8	0.357	0.00895 (2.51)	0.340 - 0.375
Proportional Error [-]	θ_7	0.204	0.00107 (0.523)	0.202 - 0.207

Note 1: $CL0_{REF}$ is the typical value of clearance in a reference subject, 60-year old white male, weighing 75 kg, with 1L MEL, baseline eGFR of 90 mL/min/1.73 m^2, baseline ALB of 4 g/dL, baseline LDH (normalized to upper limit of normal) of 0.8, a normal PS status (PS = 0), and receiving nivo+rela FDC. $EMAX_{REF}$ is a typical value of change in magnitude of CL in a reference subject. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 75 kg. These reference values were aligned with the nivolumab PPK model reference values.

Note 2: Eta shrinkage (%): ETA_CL: 26.9; ETA_VC: 20.9; ETA_V2: 45.8; ETA_Vmax: 30.8; ETA_Emax: 52.1, EPS shrinkage (%): 17.7

Note 3: Condition no: 58

Abbreviations: ALB = baseline albumin; BGFR = baseline estimated glomerular filtration rate; BLDH = baseline lactate dehydrogenase; CI = confidence interval; HILL = coefficient for time-varying CL; IIV = interindividual variability; Km = concentration at which the rate of elimination is half of the maximum value; MONO = monotherapy; OTHER

TUMOR = other tumor types, not 1L MEL or prior-IO MEL; PS = performance score; Q = intercompartmental CL; RSE = relative standard error; T50 = time at which CL achieves half of the maximum value; VC = central volume; Vmax = maximum rate of elimination via the nonlinear pathway; VP = peripheral volume; WTB = baseline body weight.

[a] Parameters with fixed values (not estimated) are denoted with a superscript 'f' after the names, with the fixed value given in the Estimate column.

[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters.

[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$).

[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate).

[e] Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance.*

Table 78: Applicant - Parameter Estimates of the Full Nivolumab Population Pharmacokinetic Model

Parameter [Units][a,b]	Symbol	Estimate[c]	Standard Error, (RSE%)[d]	95% CI[e]
Fixed Effects				
CLO_{REF} [mL/h]	θ_1	9.72	0.230 (2.36)	9.28 - 10.1
VC_{REF} [L]	θ_2	4.02	0.0290 (0.722)	3.96 - 4.08
Q_{REF} [mL/h]	θ_3	31.4	1.86 (5.93)	28.4 - 34.8
VP_{REF} [L]	θ_4	2.68	0.0713 (2.66)	2.56 - 2.82
CL_{WTB}	θ_7	0.543	0.0357 (6.59)	0.473 - 0.613
CL_{AGE}	θ_8	-0.101	0.0338 (33.6)	-0.170 - -0.0286
CL_{GFR}	θ_9	0.122	0.0293 (24.0)	0.0583 - 0.189
CL_{ALBB}	θ_{11}	-0.965	0.0647 (6.70)	-1.09 - -0.839
CL_{FEMALE}	θ_{12}	-0.164	0.0170 (10.4)	-0.198 - -0.129
CL_{PS}	θ_{13}	0.135	0.0173 (12.8)	0.0998 - 0.170
CL_{RAAA}	θ_{14}	0.0360	0.0379 (105)	-0.0405 - 0.120
CL_{RAAS}	θ_{15}	-0.114	0.0316 (27.9)	-0.181 - -0.0536
VC_{WTB}	θ_{16}	0.586	0.0237 (4.05)	0.537 - 0.632
VC_{SEX}	θ_{17}	-0.134	0.0121 (9.03)	-0.159 - -0.110
$EMAX_{REF}$	θ_{18}	-0.198	0.0234 (11.8)	-0.251 - -0.151
T50 [h]	θ_{19}	2.05E+03	127 (6.22)	1.81E+03 - 2.34E+03
HILL	θ_{20}	2.94	0.392 (13.4)	2.23 - 3.86
CL_{IOMEL}	θ_{21}	-0.172	0.0267 (15.5)	-0.225 - -0.111
CL_{OTH}	θ_{22}	-0.00499	0.0216 (433)	-0.0473 - 0.0413
CL_{ADO}	θ_{23}	-0.449	0.0959 (21.4)	-0.644 - -0.250
CL_{SAV}	θ_{24}	0.0328	0.0240 (73.3)	-0.0141 - 0.0815
CL_{MONO}	θ_{25}	0.0499	0.0246 (49.3)	0.00249 - 0.100
$EMAX_{PS}$	θ_{26}	-0.0971	0.0254 (26.2)	-0.146 - -0.0422
$EMAX_{COMBO}$	θ_{27}	-0.00830	0.0245 (296)	-0.0572 - 0.0434
$EMAX_{IOMEL}$	θ_{28}	0.179	0.0322 (18.0)	0.114 - 0.249
$EMAX_{OTH}$	θ_{29}	-0.0332	0.0270 (81.3)	-0.0891 - 0.0185
CL_{PED}	θ_{30}	-0.966	0.127 (13.2)	-1.25 - -0.732
VC_{PED}	θ_{31}	-0.382	0.0501 (13.1)	-0.491 - -0.283
VC_{ADO}	θ_{32}	-0.171	0.0429 (25.0)	-0.253 - -0.0867
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.122 (0.349)	0.00554 (4.54)	0.111 - 0.134

Parameter [Units][a,b]	Symbol	Estimate[c]	Standard Error, (RSE%)[d]	95% CI[e]
ZVC [-]	$\omega_{2,2}$	0.0683 (0.261)	0.00407 (5.95)	0.0602 - 0.0761
ZEMAX [h]	$\omega_{4,4}$	0.0797 (0.282)	0.0113 (14.2)	0.0597 - 0.109
ZCL:*ZVC*	$\omega_{1,2}$	0.0465 (0.510)	0.00321 (6.90)	0.0402 - 0.0529
Residual Error				
PERR [-]	θ_6	0.200	0.00303 (1.51)	0.194 - 0.206
RESERR[f]	$\sigma_{1,1}$	1.00 (1.00)	NA	NA

Note 1: $CL0_{REF}$ is the typical value of clearance in a reference subject with 1L MEL, receiving nivo+rela FDC, 60-year old white male, baseline eGFR of 90 mL/min/1.73 m^2, baseline ALB of 4 g/dL, weighing 75 kg, and with a normal PS status (PS = 0). $EMAX_{REF}$ is a typical value of change in magnitude of CL in a reference adult 1L MEL subject receiving nivolumab monotherapy with PS = 0. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 75 kg. These reference values represent the approximate median values in the PPK analysis dataset.

Note 2: Eta shrinkage (%): ETA_CL: 11.2; ETA_VC: 22.7; ETA_EMAX: 43.6; EPS shrinkage (%): 15.2

Note 3: The condition number for the full model is 104.

Abbreviations: CI = confidence interval; HILL = coefficient for time-varying CL; Q = intercompartmental CL; RSE = relative standard error; T50 = time at which CL achieves half of the maximum value; VC = central volume; VP = peripheral volume.

[a] Parameters with fixed values (not estimated) are denoted with a superscript 'f' after the names, with the fixed value given in the Estimate column.

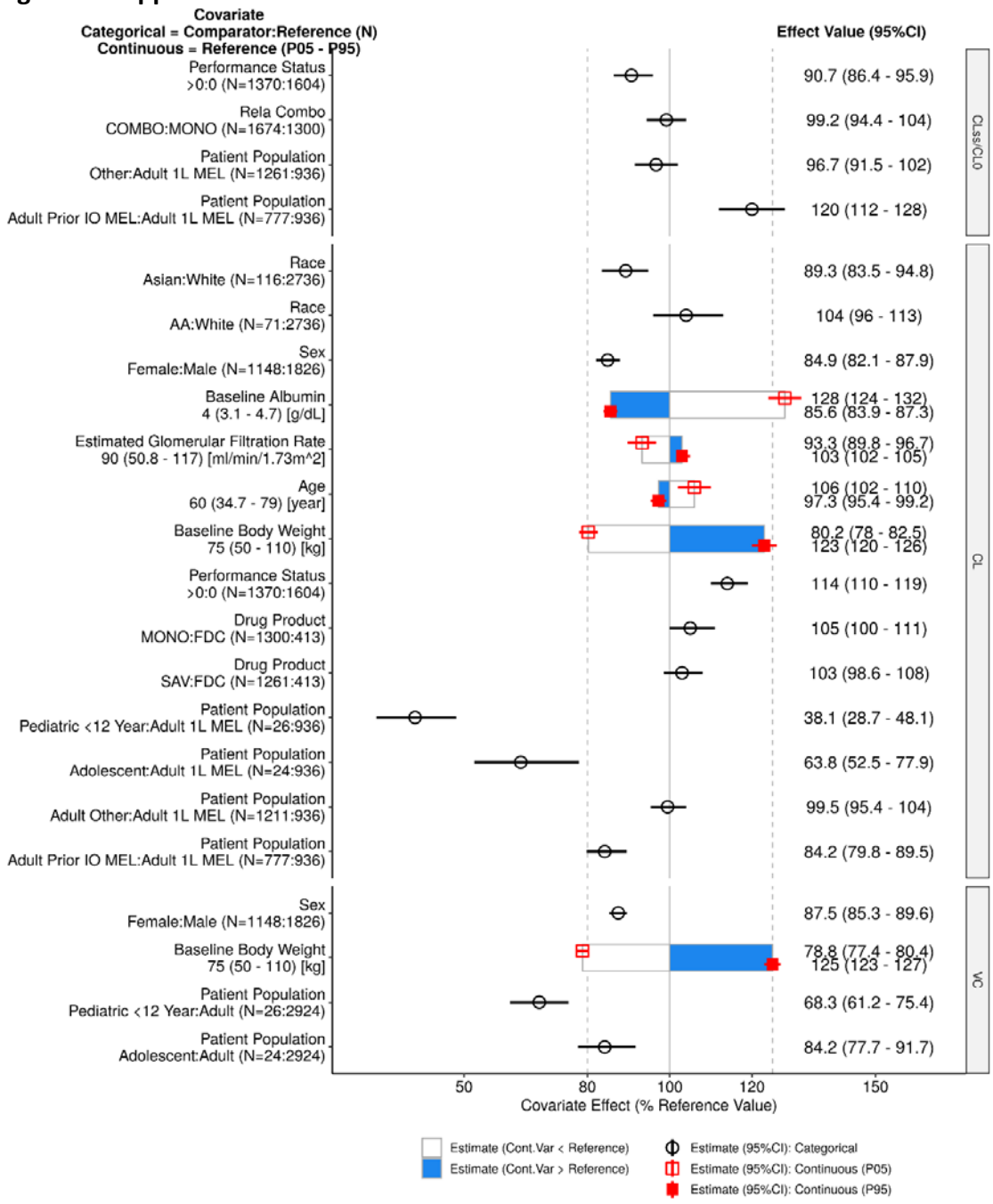
[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters.

[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$).

[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate).

[e] Confidence intervals of Random Effects and Residual Error parameters are for Variance or Covariance.

Figure 21: Applicant - Covariate Effects on Full Nivolumab Pharmacokinetic Model Parameters



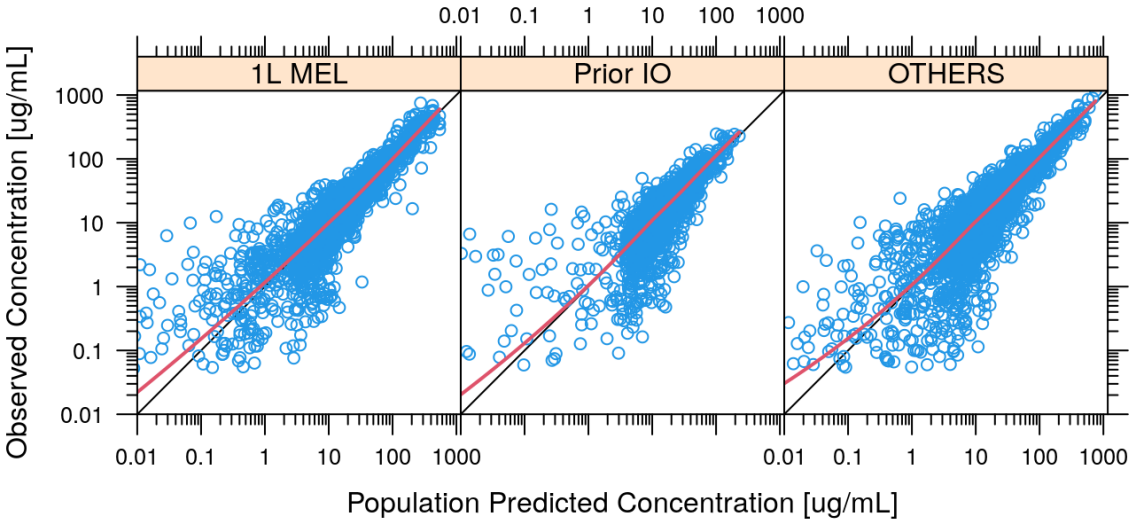
Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).

Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Note 3: Reference subject is a 60-year old male, white/other race, WTB = 75 kg, PS = 0, BALB = 4 g/dL, baseline eGFR = 90 mL/min/1.73 m^2, received nivo+rela FDC, and with 1L MEL. Parameter estimate in a reference subject is considered as 100% (vertical solid line), and dashed vertical lines are at 80% and 125% of this value.

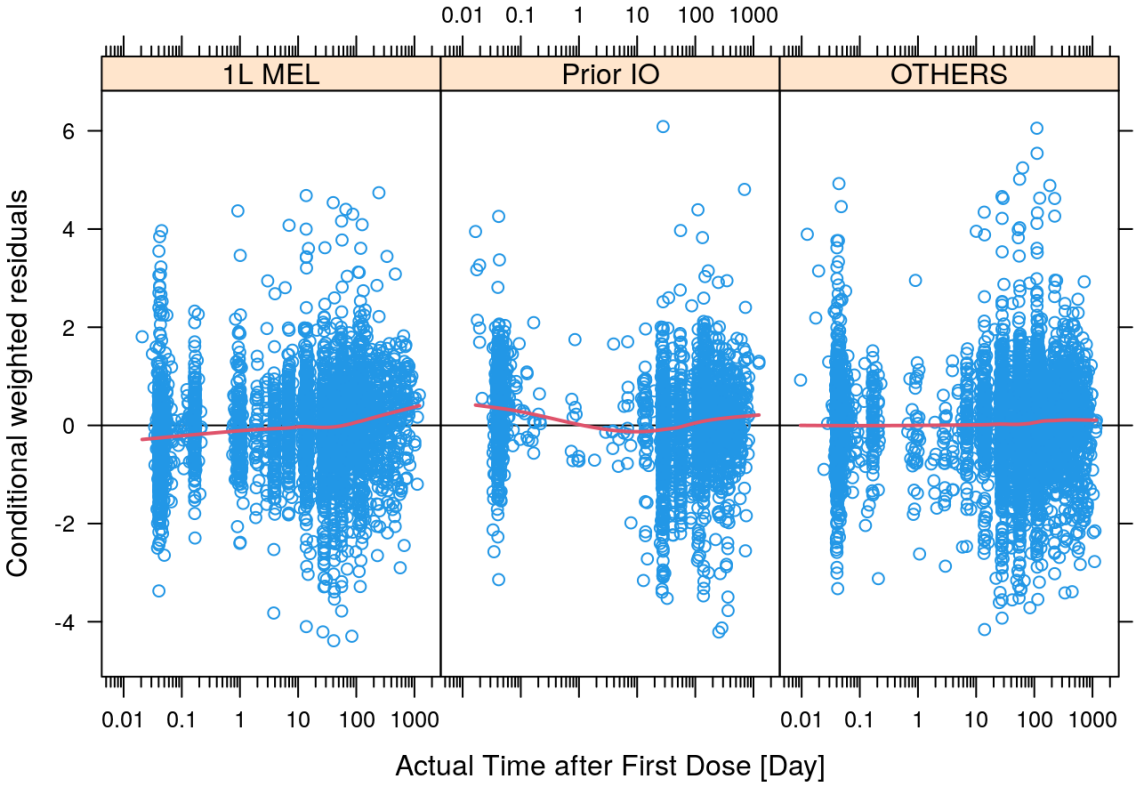
Note 4: Confidence Interval values are taken from bootstrap calculations (753 successful out of a total of 1,000).
Note 5: The effect of WTB was also added on Q and VP, and their estimates were fixed to be similar to that CL and VC, respectively.
Note 6: PS appeared twice in the figure. Baseline CL of nivolumab in subjects with PS > 0 was higher than subjects with PS = 0 by 14%, whereas the reduction of nivolumab CL over time was more significant in subjects with PS > 0 than subjects with PS = 0 by 9%.
Note 7: Patient population appeared 3 times in the figure, including the effect on baseline CL, CL_{ss}/CL_0, and VC. For the effect on the CL_{ss}/CL_0, pediatric subjects were combined with 'Adult Other.'
Note 8: CLss/CL0 = e^{EMAX}

Figure 22: Applicant - Population Predicted and Individual Predicted versus Observed Concentration (Full Relatlimab Population Pharmacokinetic Model) by Patient Population



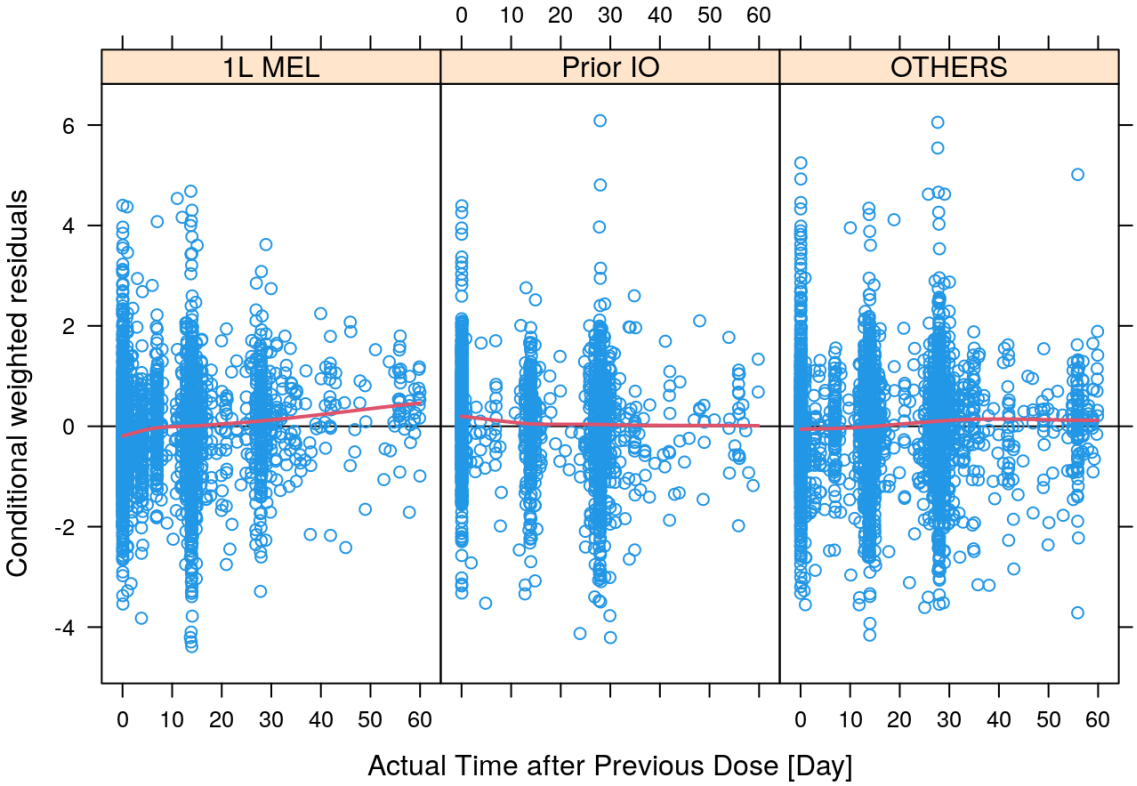
Note: Solid red line represents linear regression line; solid black line represents line of identity.

Figure 23: Applicant - Conditional Weighted Residuals versus Time after First Dose by Patient Population (Full Relatlimab Population Pharmacokinetic Model)



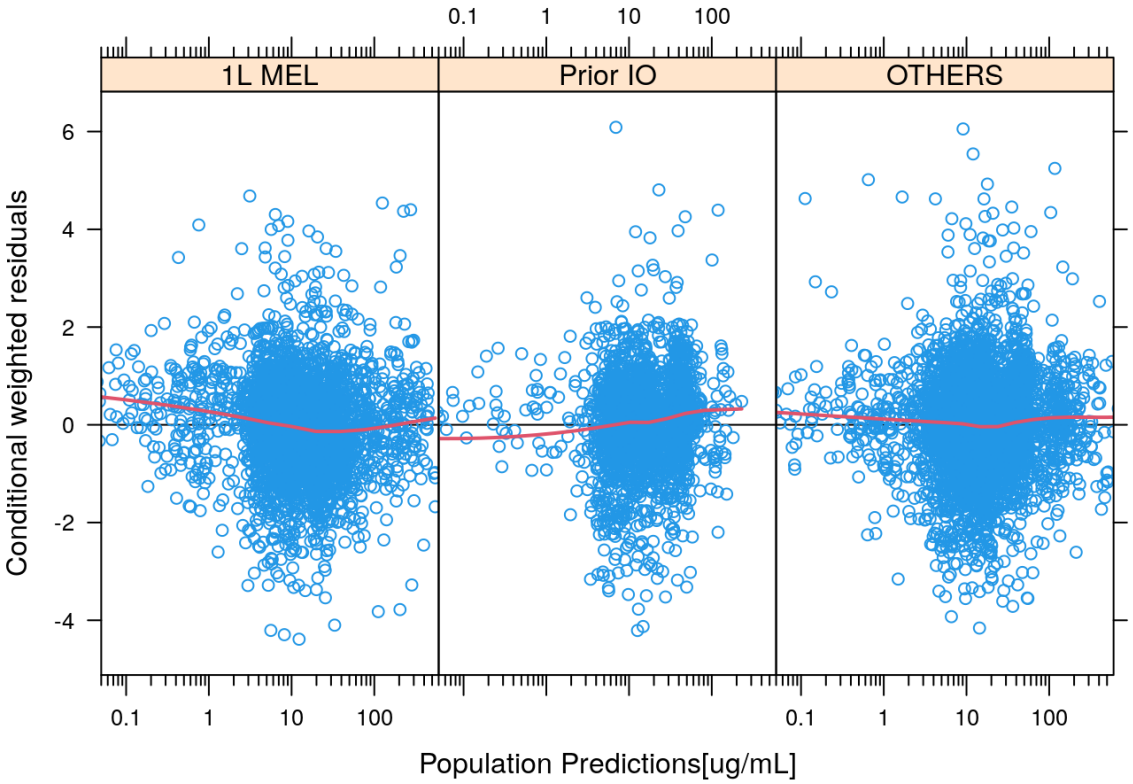
Note: Solid red line represents linear regression line; solid black line represents line of identity.

Figure 24: Applicant - Conditional Weighted Residuals versus Time after Previous Dose (Full Relatlimab Population Pharmacokinetic Model)



Note: Solid red line represents linear regression line; solid black line represents line of identity.

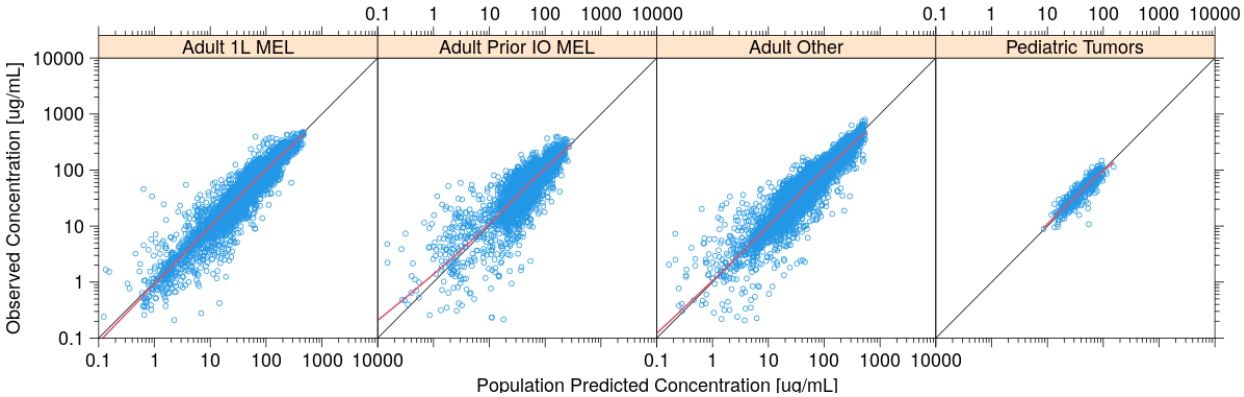
Figure 25: Applicant - Conditional Weighted Residuals versus Population Predicted Concentration by Patient Population (Full Relatlimab Population Pharmacokinetic Model)



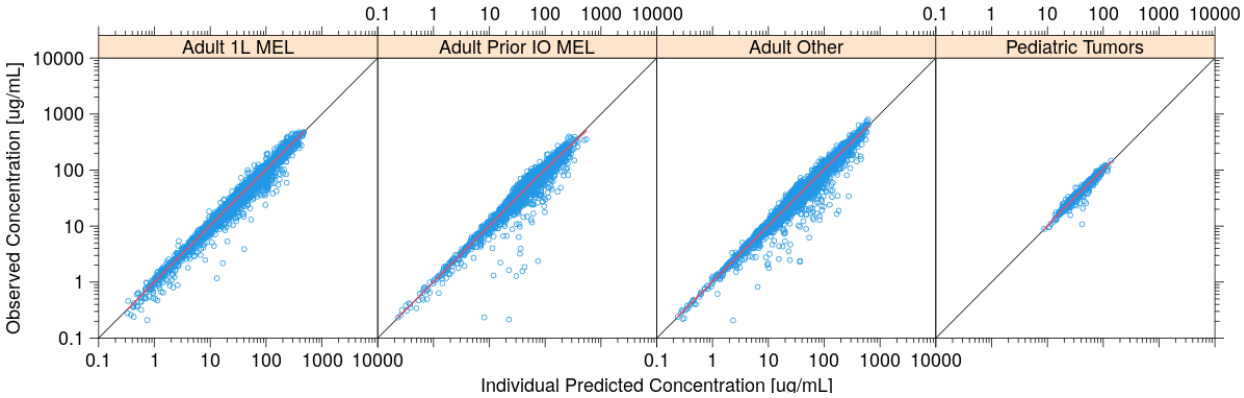
Note: Solid red line represents linear regression line; solid black line represents line of identity.

Figure 26: Applicant - Observed versus Predicted Population Average and Individual Concentration in Adult 1L MEL, Adult Prior-IO MEL, Adult Others, and Pediatric Subjects (< 18 Years) [Full Nivolumab Population Pharmacokinetic Model]

A) Population Prediction



B) Individual Prediction



Note 1: Solid red line represents linear regression line. Solid black line represents line of identity.
Note 2: Include all subjects treated with nivo+rela or nivo mono.

Figure 27: Applicant - CWRES versus Time after First Dose in Adult 1L MEL, Adult Prior IO MEL, Adult Others, and Pediatric Subjects (< 18 Years) [Full Nivolumab Population Pharmacokinetic Model]

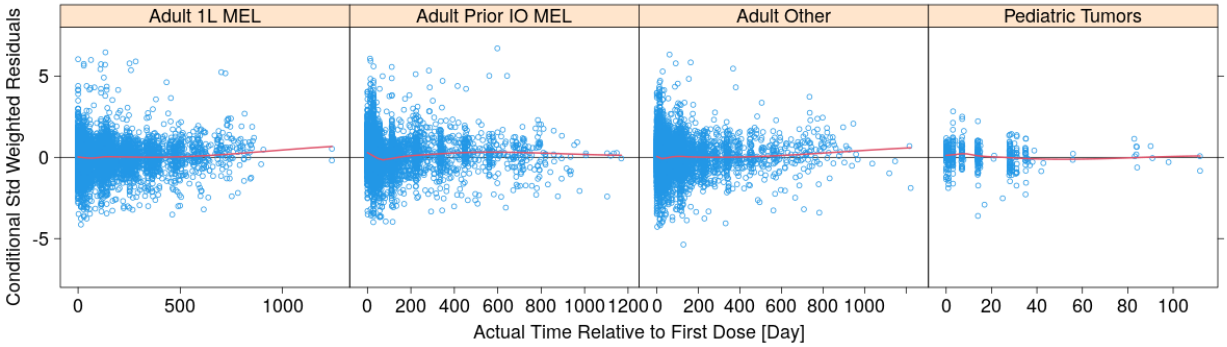


Figure 28: Applicant - CWRES versus Time after Previous Dose in Adult 1L MEL, Adult Prior-IO MEL, Adult Others, and Pediatric Subjects (< 18 Years) [Full Nivolumab Population Pharmacokinetic Model]

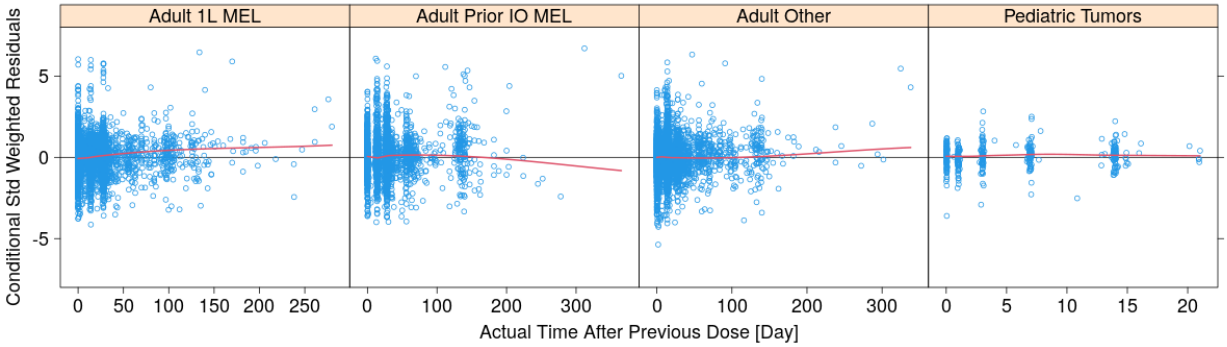


Figure 29: Applicant - CWRES versus Population Predicted Serum Concentration in Adult 1L MEL, Adult Prior-IO MEL, Adult Others, and Pediatric Subjects (< 18 Years) [Full Nivolumab Population Pharmacokinetic Model]

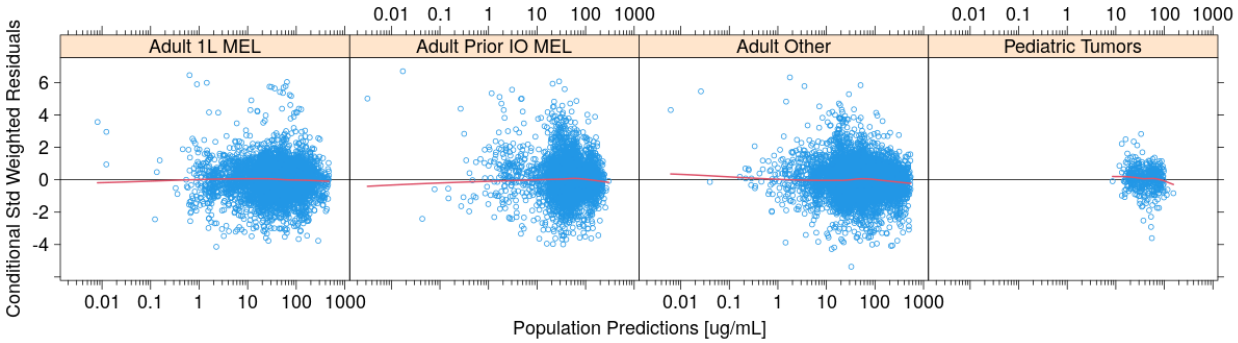


Figure 30: Applicant - Prediction-Corrected Visual Predictive Check of Relatlimab Concentrations versus Actual Time after Previous Dose in 1L MEL and Prior-IO MEL Subjects Who Received 80 mg Q2W and 160 mg Q4W Dosing Regimen (Full Population Pharmacokinetic Model

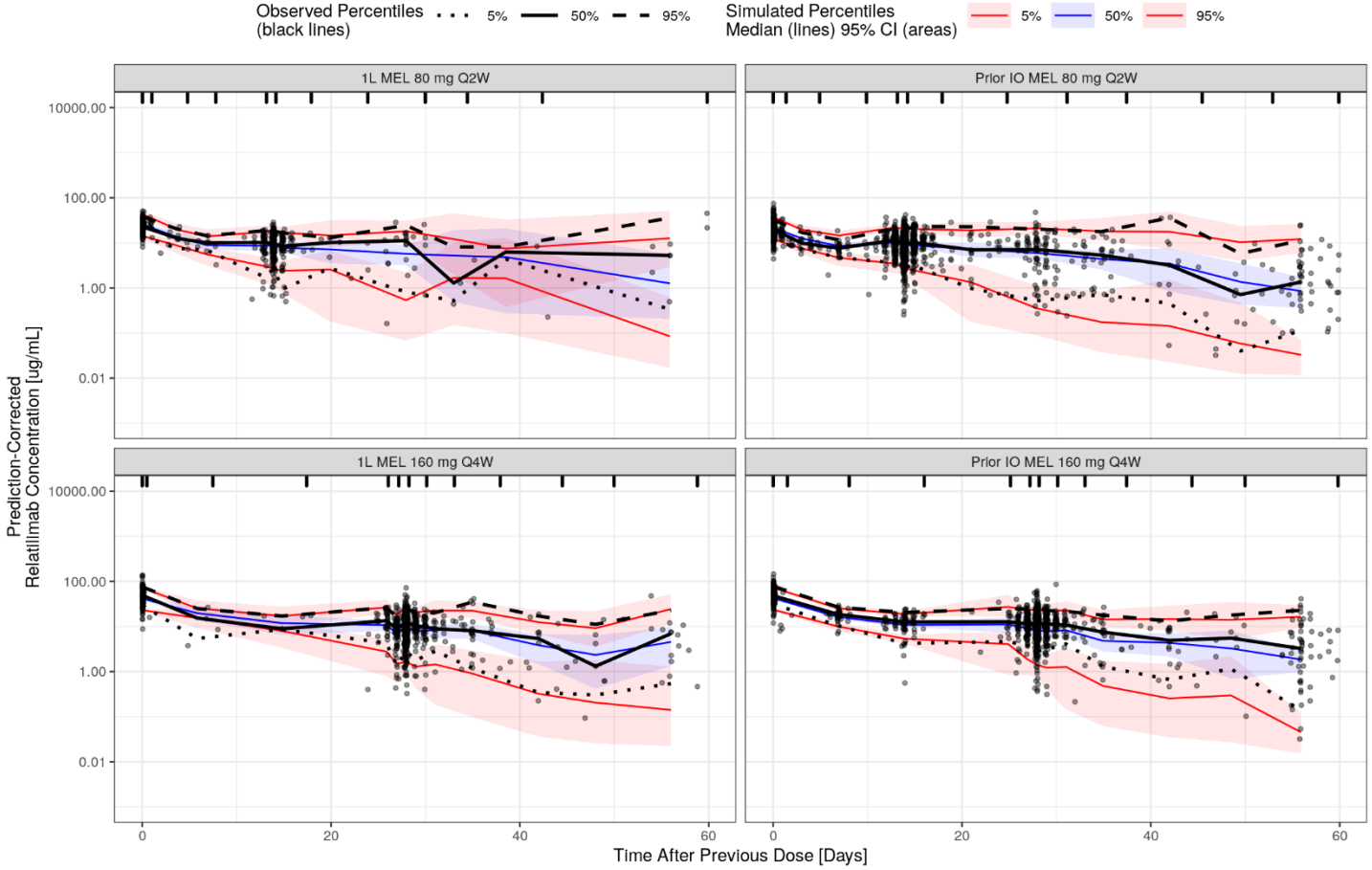


Figure 31: Applicant - Prediction-Corrected Visual Predictive Check of Nivolumab Concentrations versus Actual Time after Previous Dose in Adult 1L MEL and Adult Prior-IO MEL at 240 mg Q2W or 480 mg Q4W (Nivolumab + relatlimab) [Full Nivolumab Population Pharmacokinetic Model

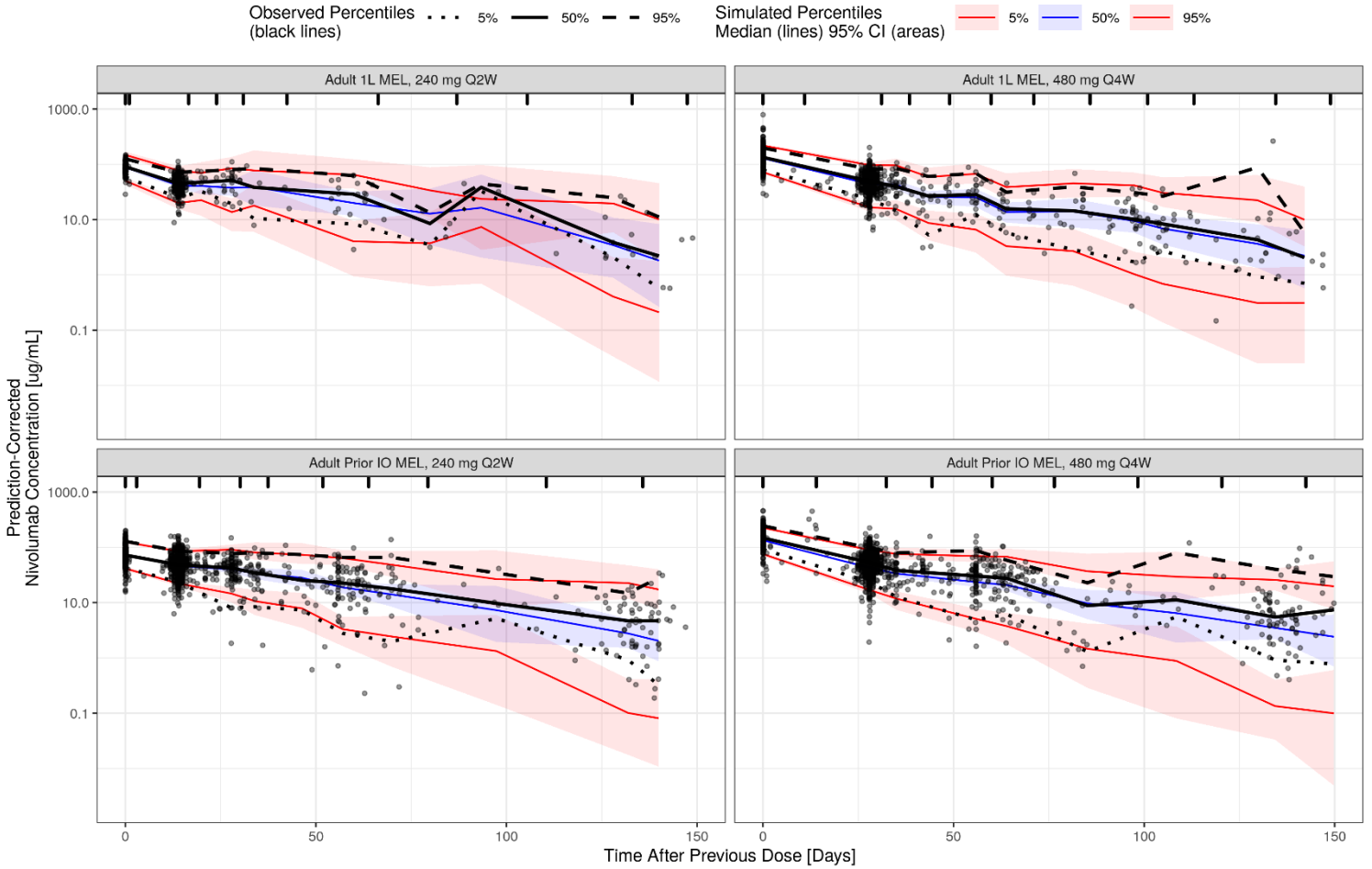
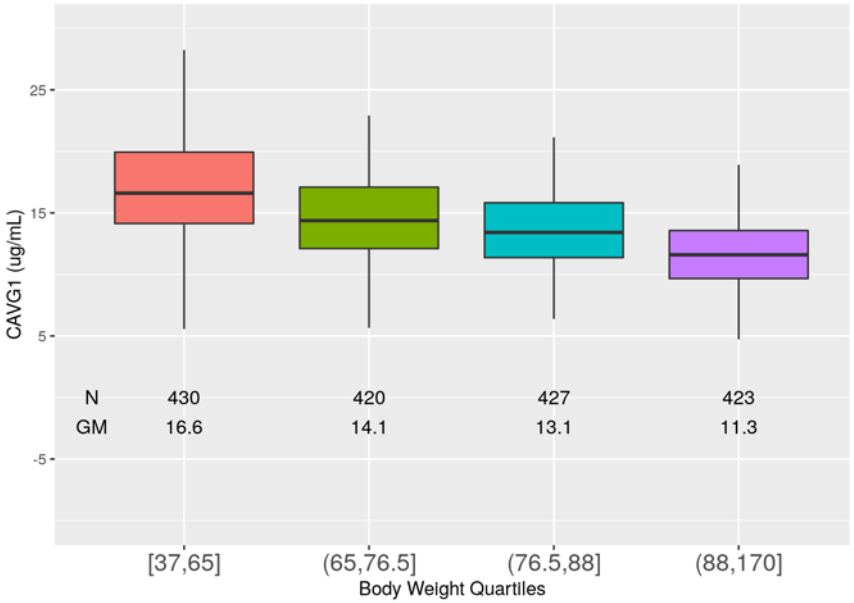


Figure 32: Applicant - Predicted Relatlimab Exposures (Cavg1 and Cavgss) at 160 mg Q4W (Nivolumab + relatlimab) by Body Weight Quartiles in Adults

A) Cavg1



B) Cavgss

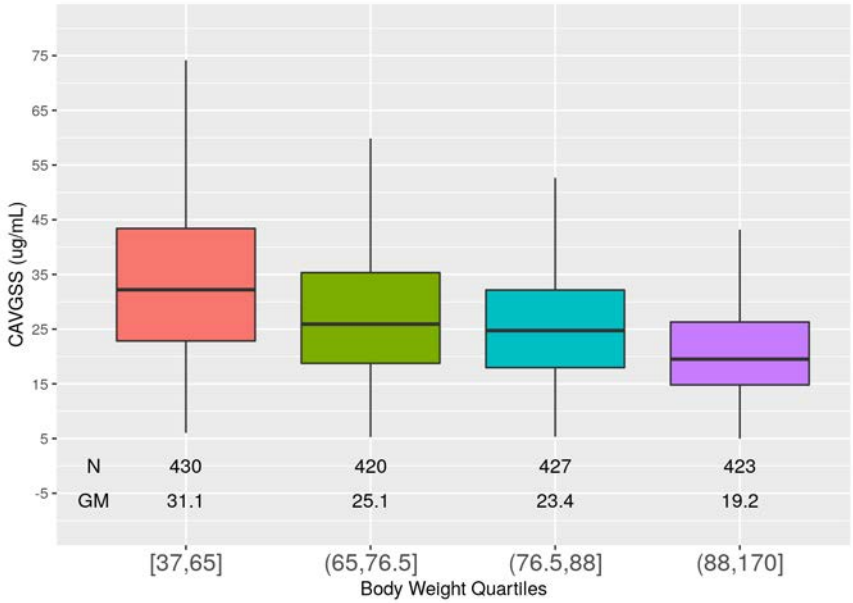
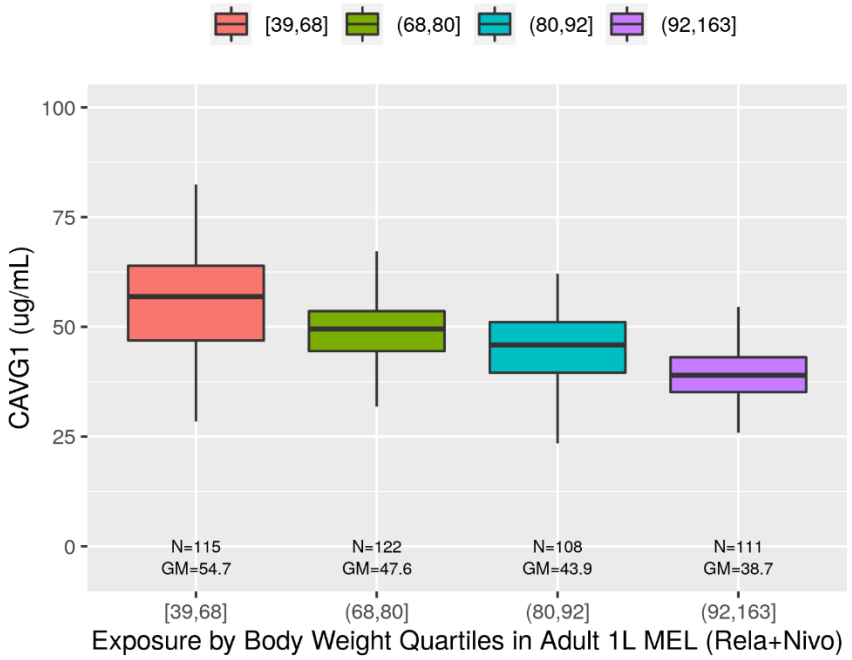
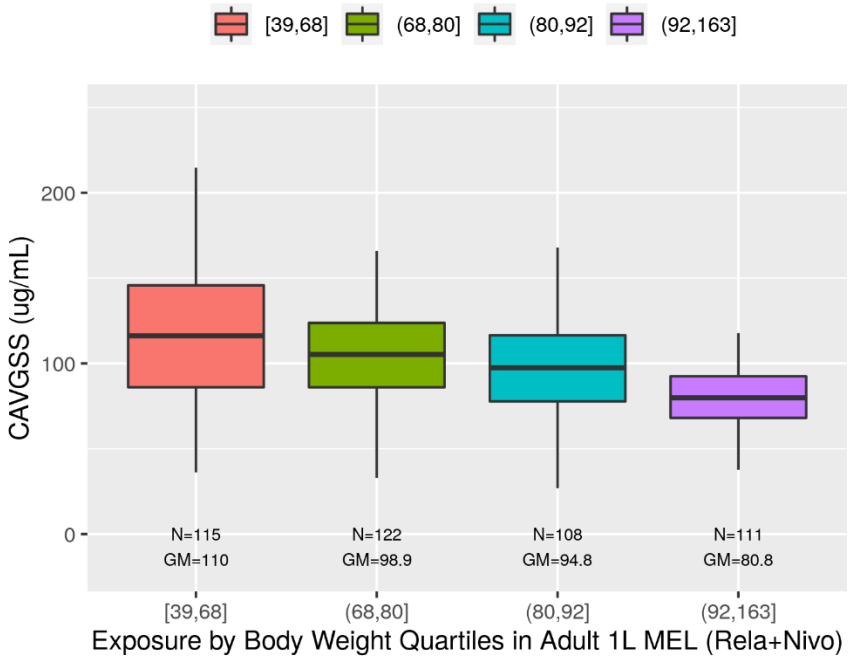


Figure 33: Applicant - Predicted Nivolumab Exposures (Cavg1 and Cavgss) at 480 mg Q4W (Nivolumab + relatlimab) by Body Weight Quartiles in Adult 1L MEL

A) Cavg1



B) Cavgss



The FDA's Assessment:

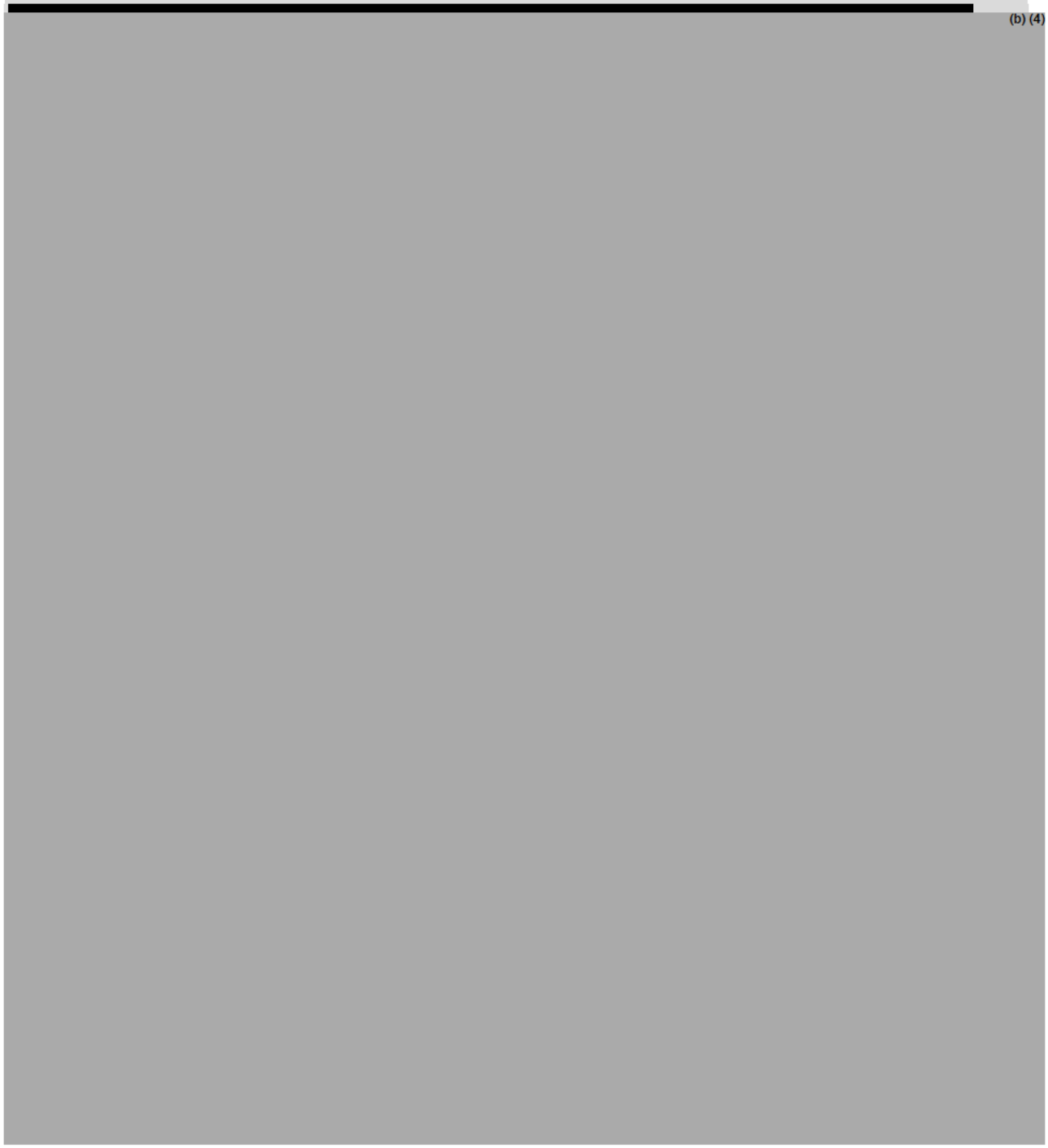
The population PK models developed by the Applicant were verified by the reviewer. The models appear to be generally acceptable based on the agreement between observations and predictions. Although baseline bodyweight was identified as significant covariate for both nivolumab and relatlimab, the proposed flat dose for adult patients is acceptable given the relatively flat ER efficacy and safety relationships. For nivolumab, adolescent patients with solid tumor had about 36% lower baseline CL than that of adult patients with untreated unresectable or metastatic melanoma in the original model. An updated nivolumab population PK model was submitted by the Applicant in an information request (b) (4)

As there were no adolescent patients involved in the study for relatlimab, an extrapolation simulation study was applied by the Applicant to simulate the PK of relatlimab in adolescents. In the simulation, the adolescent effect on CL in nivolumab population PK model was added to the linear clearance of relatlimab because of the similarity in the PK of these IgG4 monoclonal antibodies. FDA does not agree with the extrapolation simulation for relatlimab (b) (4)

For adolescent patients with bodyweight ≥40 kg, a flat dose of relatlimab at 160 mg Q4W showed similar exposure as adult patients. (b) (4)

Figure 34: Extrapolation simulation of relatlimab in adolescent patients.

(b) (4)



19.4.3. Exposure-Response Analysis

19.4.3.1. ER (efficacy) Executive Summary

The FDA's Assessment:

ER efficacy analysis of nivolumab and relatlimab were submitted to support the BLA. Sigmoid Emax model was built to characterize the relationship between relatlimab peripheral RO and relatlimab concentration. The predicted peripheral RO at the proposed dose following the first dose (ROavg1) and at steady state (ROavgss) were similar across different drug products for FDC, SAV coadministration, and SAV sequential administration in the melanoma population. A flat PFS relationship was achieved across the range of exposures produced by nivolumab 240 mg and relatlimab 80 mg Q2W, nivolumab 480 mg and relatlimab 160 mg Q4W, and nivolumab 480 mg and relatlimab 480 mg Q4W. No clear difference in ORR was observed among patients receiving nivolumab 480 mg and relatlimab 480 mg Q4W, nivolumab 240mg and relatlimab 80 mg Q2W or nivolumab 480mg and relatlimab 160 mg Q4W in patients with unresectable and metastatic melanoma that has not previously been treated.

19.4.3.2. ER (efficacy) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		**Exposure-Response Analysis of Biomarkers: Peripheral RO** • To characterize the relationship between relatlimab concentration and peripheral RO. • To compare key measures of relatlimab peripheral RO between relatlimab 80 mg + nivolumab 240 mg Q2W, relatlimab 160 mg + nivolumab 480 mg Q4W, and relatlimab 480 mg + nivolumab 480 mg Q4W. • To compare key measures of relatlimab peripheral RO after sequential or coadministration of OPDIVO® [BMS-936558; nivolumab] + the relatlimab SAV product [BMS-986016] or administration of the nivo+rela FDC at relatlimab 160 mg + nivolumab 480 mg Q4W. **Exposure-Response Analysis of Efficacy: PFS and OR** • To characterize the relationship between nivolumab and relatlimab exposure and PFS in 1L melanoma and prior-IO melanoma subjects. • To characterize the relationship between nivolumab and relatlimab exposure and the probability of achieving an OR (defined as CR or PR) in 1L melanoma and prior-IO melanoma subjects. • To compare predicted efficacy (PFS and OR) of nivolumab 240 mg + relatlimab 80 mg Q2W, nivolumab 480 mg + relatlimab 160 mg Q4W, and nivolumab 480 mg + relatlimab 480 mg Q4W in 1L melanoma and prior-IO melanoma subjects.
Studies Included		RO and OR: Study CA224020. PFS: Studies CA224020 and CA224047 These two studies investigated the efficacy and safety of relatlimab and nivolumab combination in the target population in unresectable or metastatic melanoma patients.
Endpoints		RO, PFS, and OR
No. of Patients (total, and with individual PK)		RO: 134, PFS: 1529, OR: 858
Population Characteristics (Table 79 [PFS], Table 80 [ORR])	General	RO: N/A PFS: • Median (range) age: 62 (17, 92) years • Median (range) baseline body weight: 78 (39, 170) kg

		• Sex, n (%): 898 (58.7) males, 631 (41.3) females OR: • Median (range) age: 62 (17, 92) years • Median (range) baseline body weight: 77.5 (39, 170) kg • Sex, n (%): 508 (59.2) males, 350 (40.8) females	
	Pediatrics (if any)	Not specifically evaluated.	
Dose(s) Included		Nivo+rela 240/80 mg Q2W, 480/160 mg Q4W, and 480/480 mg Q4W	
Exposure Metrics Explored (range)		RO: relatlimab serum concentration values predicted using the actual doses administered PFS and OR: Relatlimab and nivolumab Cmind28 and Cavgd28	
Covariates Evaluated		RO: N/A PFS and OR: Age, baseline body weight, baseline albumin, baseline LDH [*ULN], baseline tumor size, sex, patient population, baseline LAG-3 expression, baseline PD-L1 expression, BRAF status, M-Stage Status, ECOG status, baseline nivolumab CL	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		RO: E-R of RO was characterized by a sequential PK-PD model building approach. The relationship between relatlimab exposure and peripheral RO was characterized by a sigmoid Emax model. PFS: E-R of PFS was characterized by time-to-event modeling using Cox proportional hazard methodology. The model with log-linear relatlimab Cavgd28 and log-linear nivolumab Cavgd28 was selected as this full model provided the best fit to the data, in the presence of other covariates. OR: E-R of OR was characterized using logistic regression methodology. The model with linear relatlimab Cavgd28 and log-linear nivolumab Cavgd28 was selected as this full model provided the best fit to the data, in the presence of other covariates.	Acceptable

Model Parameter Estimates	Table 81 (RO), Table 82 (PFS) and Table 83 (OR)	Acceptable
Model Evaluation	Figure 35 (RO), Figure 36 (PFS), and Figure 37 (OR)	Acceptable
Covariates and Clinical Relevance	RO: N/A, Figure 38 (PFS), Figure 39 (OR)	Acceptable
Simulation for Specific Population	N/A	N/A
Visualization of E-R relationships	Figure 40 (RO), Figure 41 (PFS), and Figure 42 (OR)	Acceptable
Overall Clinical Relevance for E-R	RO: The predicted peripheral RO was similar between rela 80 mg + nivo 240 mg Q2W and nivo 480 mg + rela 160 mg Q4W dose regimens. The model predicted average relatlimab peripheral RO at nivo 480 mg + rela 160 mg Q4W following the first dose (ROavg1) and at steady state (ROavgss) were similar across different drug products for FDC, SAV coadministration, and SAV sequential administration in the melanoma population. PFS: Predicted HRs of PFS were similar across the range of exposures produced by nivo 240 mg + rela 80 mg Q2W, nivo 480 mg + rela 160 mg Q4W, and nivo 480 mg + rela 480 mg Q4W suggesting a flat E-R relationship. OR: Predicted probability of OR was higher with nivo 480 mg + rela 480 mg Q4W compared with nivo 240 mg + rela 80 mg Q2W and nivo 480 mg + rela 160 mg Q4W. The E-R relationships of relatlimab and nivolumab were not dependent upon covariate values for both PFS and OR (interactions with covariates were not significant). Despite the trend towards higher OR with higher exposure, it should be noted that OR lacks the DOR component of clinical benefit, whereas the PFS end point captures the DOR component and the	Acceptable

	flat E-R from PFS analysis indicates that there is no additional clinical benefit with the higher dose of 480/480 mg Q4W.	
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	No E-R efficacy results are provided in Section 12.2 of the USPI.	N/A

Table 79: Applicant - Summary of Exposures and Baseline Covariates in the Exposure-Response of PFS Analysis Dataset, by Patient Population

Covariate	1L MEL N=775	Prior-IO MEL N=754	Total N=1529
Sex N (%)			
Male	449 (57.9)	449 (59.5)	898 (58.7)
Female	326 (42.1)	305 (40.5)	631 (41.3)
Baseline LAG-3 Expression N (%)			
Negative	182 (23.5)	240 (31.8)	422 (27.6)
≥ 1- <5%	275 (35.5)	210 (27.9)	485 (31.7)
≥ 5%	248 (32.0)	165 (21.9)	413 (27.0)
Unknown	70 (9.0)	139 (18.4)	209 (13.7)
Baseline PD-L1 Expression (5% cutoff) N (%)			
Positive	186 (24.0)	189 (25.1)	375 (24.5)
Negative	554 (71.5)	419 (55.6)	973 (63.6)
Unknown	35 (4.5)	146 (19.4)	181 (11.8)
BRAF Status N (%)			
Mutation	289 (37.3)	199 (26.4)	488 (31.9)
Wild-type	479 (61.8)	528 (70.0)	1007 (65.9)
Missing	7 (0.9)	27 (3.6)	34 (2.2)
M-Stage Status N (%)			
M0	53 (6.8)	0 (0)	53 (3.5)
M1	3 (0.4)	0 (0)	3 (0.2)
M1A	191 (24.6)	98 (13.0)	289 (18.9)
M1B	186 (24.0)	105 (13.9)	291 (19.0)
M1C	317 (40.9)	498 (66.0)	815 (53.3)
M1D	12 (1.5)	0 (0)	12 (0.8)
Missing	13 (1.7)	53 (7.0)	66 (4.3)
ECOG Status N (%)			
0	536 (69.2)	511 (67.8)	1047 (68.5)
1	239 (30.8)	232 (30.8)	471 (30.8)
2	0 (0)	11 (1.5)	11 (0.7)
Age [yr]			
Mean (SD)	61.2 (14.1)	61.1 (13.4)	61.1 (13.7)
Median (Min, Max)	63 (20, 90)	62 (17, 92)	62 (17, 92)
Baseline Body Weight [kg]			
Mean (SD)	80.3 (18.2)	79 (18.3)	79.6 (18.2)
Median (Min, Max)	79.1 (39, 163)	77 (41.1, 170)	78 (39, 170)
Missing, N (%)		3 (0.398)	3 (0.196)
Baseline Albumin [g/dL]			
Mean (SD)	4.14 (0.466)	3.95 (0.471)	4.05 (0.478)
Median (Min, Max)	4.2 (2.1, 5.2)	4 (2, 6)	4.1 (2, 6)
Missing, N (%)	26 (3.35)	69 (9.15)	95 (6.21)
Baseline LDH [*ULN]			
Mean (SD)	1.21 (1.24)	1.4 (1.61)	1.3 (1.43)
Median (Min, Max)	0.885 (0.13, 12.5)	0.944 (0.346, 21.7)	0.911 (0.13, 21.7)
Missing, N (%)	2 (0.258)	10 (1.33)	12 (0.785)

Covariate	1L MEL N=775	Prior-IO MEL N=754	Total N=1529
Baseline Tumor Size [cm]			
Mean (SD)	7.11 (5.81)	9.06 (6.42)	8.1 (6.2)
Median (Min, Max)	5.5 (1, 54.8)	7.54 (1.1, 42.9)	6.46 (1, 54.8)
Missing, N (%)	82 (10.6)	41 (5.44)	123 (8.04)
Baseline Nivolumab Clearance [mL/h]			
Mean (SD)	10.1 (4.16)	9.13 (4.47)	9.63 (4.34)
Median (Min, Max)	9.11 (2.87, 37.8)	8.13 (1.64, 42.5)	8.74 (1.64, 42.5)
Relatlimab Cavg at Day 28 [ug/mL]			
Mean (SD)	9.64 (10.9)	17.6 (13.9)	13.5 (13.1)
Median (Min, Max)	10.4 (0, 69.4)	13.1 (3.77, 97.5)	12.1 (0, 97.5)
Nivolumab Cavg at Day 28 [ug/mL]			
Mean (SD)	46.9 (11.2)	47.7 (15.5)	47.3 (13.5)
Median (Min, Max)	46.1 (17.5, 99.8)	45.3 (14.5, 145)	45.7 (14.5, 145)

Table 80: Applicant - Summary of Exposures and Baseline Covariates in the Exposure-Response of OR Analysis Dataset, by Patient Population

Covariate	1L MEL N=106	Prior-IO MEL N=752	Total N=858
Sex N (%)			
Male	61 (57.5)	447 (59.4)	508 (59.2)
Female	45 (42.5)	305 (40.6)	350 (40.8)
Baseline LAG-3 Expression N (%)			
Negative	13 (12.3)	239 (31.8)	252 (29.4)
≥ 1- <5%	12 (11.3)	210 (27.9)	222 (25.9)
≥ 5%	15 (14.2)	165 (21.9)	180 (21.0)
Unknown	66 (62.3)	138 (18.4)	204 (23.8)
Baseline PD-L1 Expression (5% cutoff) N (%)			
Positive	24 (22.6)	189 (25.1)	213 (24.8)
Negative	58 (54.7)	419 (55.7)	477 (55.6)
Unknown	24 (22.6)	144 (19.1)	168 (19.6)
BRAF Status N (%)			
Mutation	29 (27.4)	199 (26.5)	228 (26.6)
Wild-type	70 (66.0)	526 (69.9)	596 (69.5)
Missing	7 (6.6)	27 (3.6)	34 (4.0)
M-Stage Status N (%)			
M1A	17 (16.0)	98 (13.0)	115 (13.4)
M1B	21 (19.8)	104 (13.8)	125 (14.6)
M1C	57 (53.8)	497 (66.1)	554 (64.6)
Missing	11 (10.4)	53 (7.0)	64 (7.5)
ECOG Status N (%)			
0	86 (81.1)	510 (67.8)	596 (69.5)
1	20 (18.9)	231 (30.7)	251 (29.3)
2	0 (0)	11 (1.5)	11 (1.3)
Age [yr]			
Mean (SD)	61.8 (14)	61.1 (13.4)	61.2 (13.4)
Median (Min, Max)	63.5 (24, 90)	62 (17, 92)	62 (17, 92)

Baseline Body Weight [kg]			
Mean (SD)	80.8 (18.1)	78.9 (18.3)	79.2 (18.2)
Median (Min, Max)	79.6 (39, 144)	77 (41.1, 170)	77.5 (39, 170)
Missing, N (%)		3 (0.399)	3 (0.35)
Baseline Albumin [g/dL]			
Mean (SD)	4.11 (0.446)	3.95 (0.471)	3.97 (0.471)
Median (Min, Max)	4.2 (2.7, 4.9)	4 (2, 6)	4 (2, 6)
Missing N (%)	18 (17)	69 (9.18)	87 (10.1)
Baseline LDH [*ULN]			
Mean (SD)	1.15 (0.992)	1.4 (1.61)	1.37 (1.55)
Median (Min, Max)	0.904 (0.387, 8.52)	0.944 (0.346, 21.7)	0.94 (0.346, 21.7)
Missing, N (%)	1 (0.943)	10 (1.33)	11 (1.28)
Baseline Tumor Size [cm]			
Mean (SD)	6.37 (4.69)	9.06 (6.41)	8.73 (6.29)
Median (Min, Max)	4.96 (1.12, 22.2)	7.54 (1.1, 42.9)	7.24 (1.1, 42.9)
Missing, N (%)	7 (6.6)	41 (5.45)	48 (5.59)
Baseline Nivolumab Clearance [mL/h]			
Mean (SD)	9.78 (4.51)	9.12 (4.47)	9.21 (4.48)
Median (Min, Max)	8.58 (4.38, 36.1)	8.12 (1.64, 42.5)	8.18 (1.64, 42.5)
Relatlimab Cavg at Day 28 [ug/mL]			
Mean (SD)	18.9 (15.4)	17.6 (13.9)	17.7 (14.1)
Median (Min, Max)	12.6 (4.48, 69.4)	13.1 (3.77, 97.5)	13.1 (3.77, 97.5)
Nivolumab Cavg at Day 28 [ug/mL]			
Mean (SD)	43.5 (11.2)	47.7 (15.5)	47.2 (15.1)
Median (Min, Max)	42.3 (17.5, 76.2)	45.3 (14.5, 145)	45 (14.5, 145)

Table 81: Applicant - Parameter Estimates of Relatlimab Peripheral Receptor Occupancy Model

Parameter[a] (units)	Symbol	Estimate[b]	Standard Error (RSE%)[c]	95% Confidence Interval[d]
Fixed Effects				
Emax (%RO)[e]	θ_1	94.1	1.54 (1.64)	91.1-97.2
EC50 (ug/mL)	θ_2	1.95	0.205 (10.5)	1.59 - 2.40
Random Effects				
Var(EMAX)	$\omega_{1,1}$	0.00217 (0.0466)	0.00192 (88.2)	-0.00158 - 0.00593
Residual Error				
Additive (ug/mL)	θ_4	-0.0126	0.00088 (6.98)	-0.0143 - -0.0109

[a] Random Effects and Residual Error parameter names
[b] Random Effects and Residual Error parameter estimates are shown as Variance (Standard Deviation) for diagonal elements (ωi,i or σi,i)
[c] RSE% is the relative standard error (Standard Error as a percentage of Estimate)
[d] Confidence intervals of Random Effects and Residual Error parameters are for Variance

Table 82: Applicant - Parameter Estimates of Exposure-Response of PFS Full Model

Predictor Variable[a]	Estimate	SE[b]	RSE%[c]	HR Coefficient[d] (95% CI)
Log (rela Cavgd28) [ug/mL]	-0.0329	0.01021	31.04	0.9676 (0.9485, 0.9872)
Log (nivo Cavgd28) [ug/mL]	0.3711	0.2435	65.62	1.449 (0.8992, 2.336)
Nivo CL [mL/hr]	0.07264	0.01479	20.36	1.075 (1.045, 1.107)
Age [yr]	-0.003396	0.002437	71.74	0.9966 (0.9919, 1.001)
Sex [Female:Male]	0.01487	0.07231	486.2	1.015 (0.8809, 1.17)
Body Weight [kg]	-0.008139	0.0022	27.04	0.9919 (0.9876, 0.9962)
Albumin [g/L]	-0.09541	0.07971	83.54	0.909 (0.7775, 1.063)
Log (LDH) [≥ULN]	0.3595	0.06684	18.59	1.433 (1.257, 1.633)
Tumor Size [cm]	0.004622	0.006013	130.1	1.005 (0.9929, 1.017)
LAG-3 Status (1%-5%:<1%)	-0.166	0.08069	48.61	0.847 (0.7231, 0.9922)
LAG-3 Status (≥ 5%:<1%)	-0.3156	0.0955	30.26	0.7294 (0.6049, 0.8795)
LAG-3 Status (Missing:<1%)	-0.2446	0.1359	55.56	0.783 (0.5999, 1.022)
PD-L1 Status [≥ 5%:< 5%]	-0.3517	0.08663	24.63	0.7035 (0.5936, 0.8336)
PD-L1 Status [Missing:< 5%]	-0.0576	0.1384	240.3	0.944 (0.7197, 1.238)
BRAF status [Mutation:Wildtype]	-0.01066	0.07013	658.1	0.9894 (0.8623, 1.135)
Performance Score [≥1:0]	0.04798	0.07152	149.1	1.049 (0.9119, 1.207)
Population type [Prior IO Melanoma:1L Melanoma]	0.8458	0.08738	10.33	2.33 (1.963, 2.765)
M-Stage status [M1C/M1D: M0/M1A/M1B]	0.2608	0.072	27.6	1.298 (1.127, 1.495)
M-Stage status [Missing: M0/M1A/M1B]	-0.1411	0.1698	120.3	0.8684 (0.6226, 1.211)

[a] Relatlimab and Nivolumab Cavgd28 (in units of µg/mL) increases by one unit for approximately 2.7-fold increase in Cavgd28

[b] SE: Standard Error

[c] RSE: Relative Standard Error (100* SE/Estimate)

[d] Increase in hazard for every unit increase of the predictor variable

Table 83: Applicant - Parameter Estimates of Exposure-Response of OR Full Model

Predictor Variable[a]	Estimate	SE[b]	RSE%[c]	Odds ratio Coefficient[d] (95% CI)
Intercept	-1.08	0.421	38.9	0.339 (0.148, 0.773)
Rela Cavgd28) [ug/mL]	0.0189	0.00799	42.3	1.02 (1, 1.04)
Log (nivo Cavgd28) [ug/mL]	-2.57	0.899	34.9	0.0762 (0.0131, 0.444)
Nivo CL [mL/hr]	-0.278	0.0757	27.2	0.757 (0.653, 0.879)
Age [yr]	0.0091	0.00839	92.2	1.01 (0.993, 1.03)
Sex [Female:Male]	-0.128	0.242	190	0.88 (0.547, 1.42)
Body Weight [kg]	0.00843	0.00697	82.7	1.01 (0.995, 1.02)
Albumin [g/L]	-0.207	0.287	139	0.813 (0.463, 1.43)
Log (LDH) [≥ULN]	-0.241	0.283	117	0.786 (0.451, 1.37)

Predictor Variable[a]	Estimate	SE[b]	RSE%[c]	Odds ratio Coefficient[d] (95% CI)
Tumor Size [cm]	-0.0363	0.0269	74.1	0.964 (0.915, 1.02)
LAG-3 Status (1%-5%:<1%)	0.685	0.348	50.9	1.98 (1, 3.93)
LAG-3 Status (≥ 5%:<1%)	1.26	0.356	28.3	3.53 (1.76, 7.09)
LAG-3 Status (Missing:<1%)	1.34	0.38	28.4	3.81 (1.81, 8.02)
PD-L1 Status [≥5%:< 5%]	0.186	0.261	141	1.2 (0.722, 2.01)
PD-L1 Status [Missing:< 5%]	-0.523	0.336	64.4	0.593 (0.307, 1.15)
BRAF status [Mutation:Wildtype]	0.221	0.229	104	1.25 (0.796, 1.96)
Performance Score [≥1:0]	-0.339	0.269	79.2	0.712 (0.421, 1.21)
Population type [Prior IO Melanoma:1L Melanoma]	-1.26	0.286	22.7	0.284 (0.162, 0.498)
M-Stage status [M1C/M1D: M0/M1A/M1B]	-0.51	0.229	44.9	0.601 (0.383, 0.941)
M-Stage status [Missing: M0/M1A/M1B]	0.0152	0.392	2580	1.02 (0.471, 2.19)

[a] Nivolumab Cavgd28 (in units of µg/mL) increases by one unit for approximately 2.7-fold increase in Cavgd28

[b] SE: Standard Error

[c] RSE: Relative Standard Error (100*SE/Estimate)

[d] Odds ratio increase for a unit increase in the predictor variable

Figure 35: Applicant - Visual Predictive Check of Peripheral Receptor Occupancy versus Individual Predicted Relatlimab Concentration

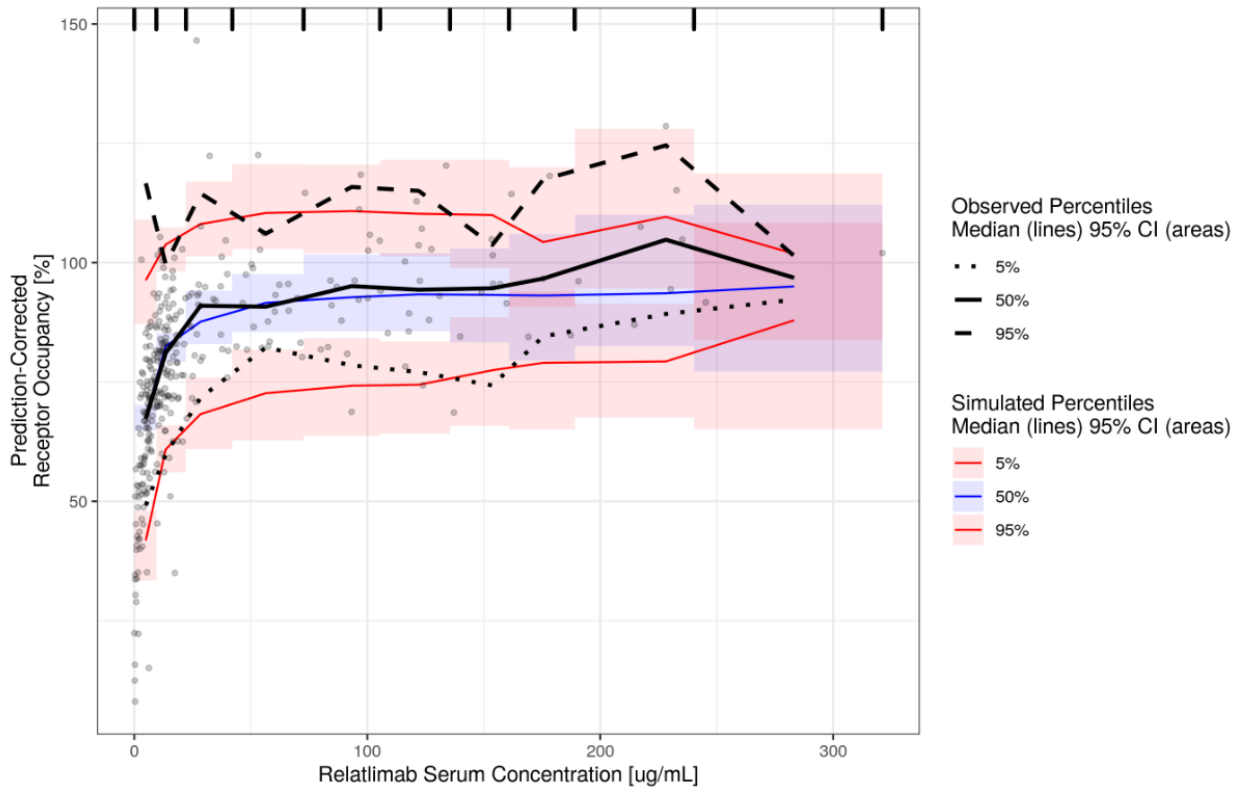


Figure 36: Applicant - Model Evaluation of Exposure-Response of PFS Analysis, by Population Type

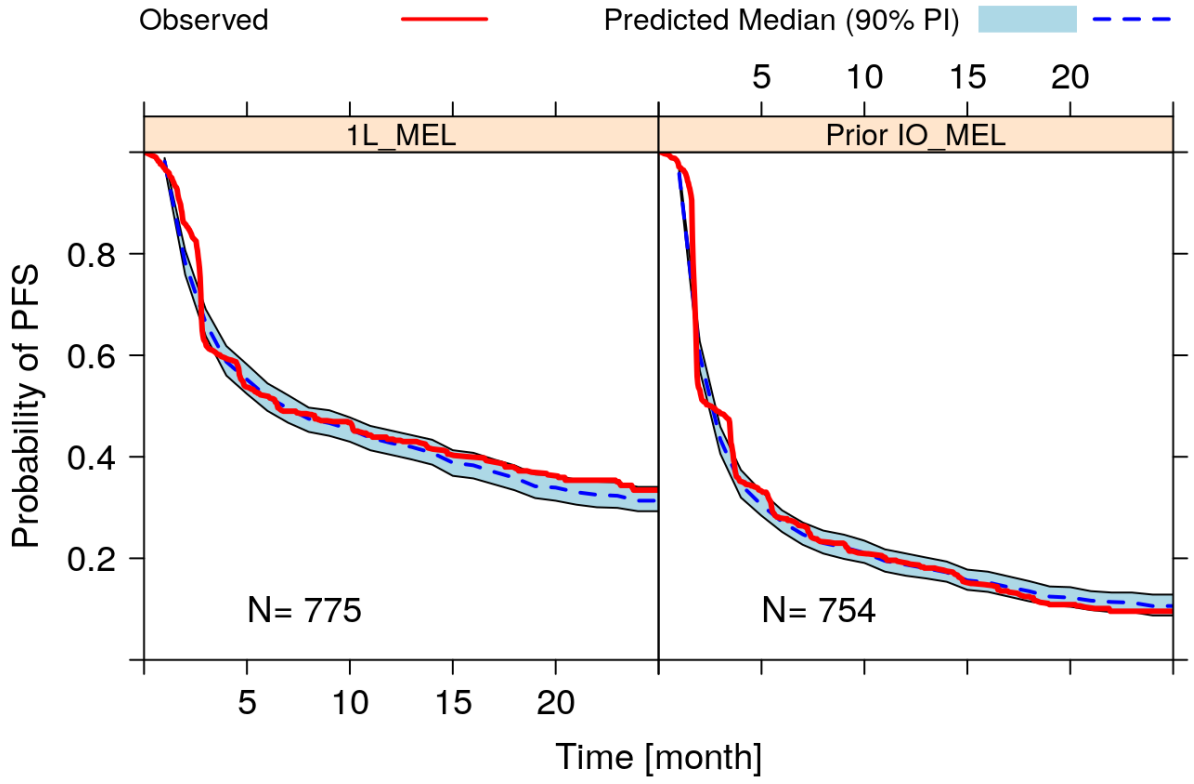


Figure 37: Applicant - Visual Predictive Check of Observed OR Versus Relatlimab Exposure, by Population Type

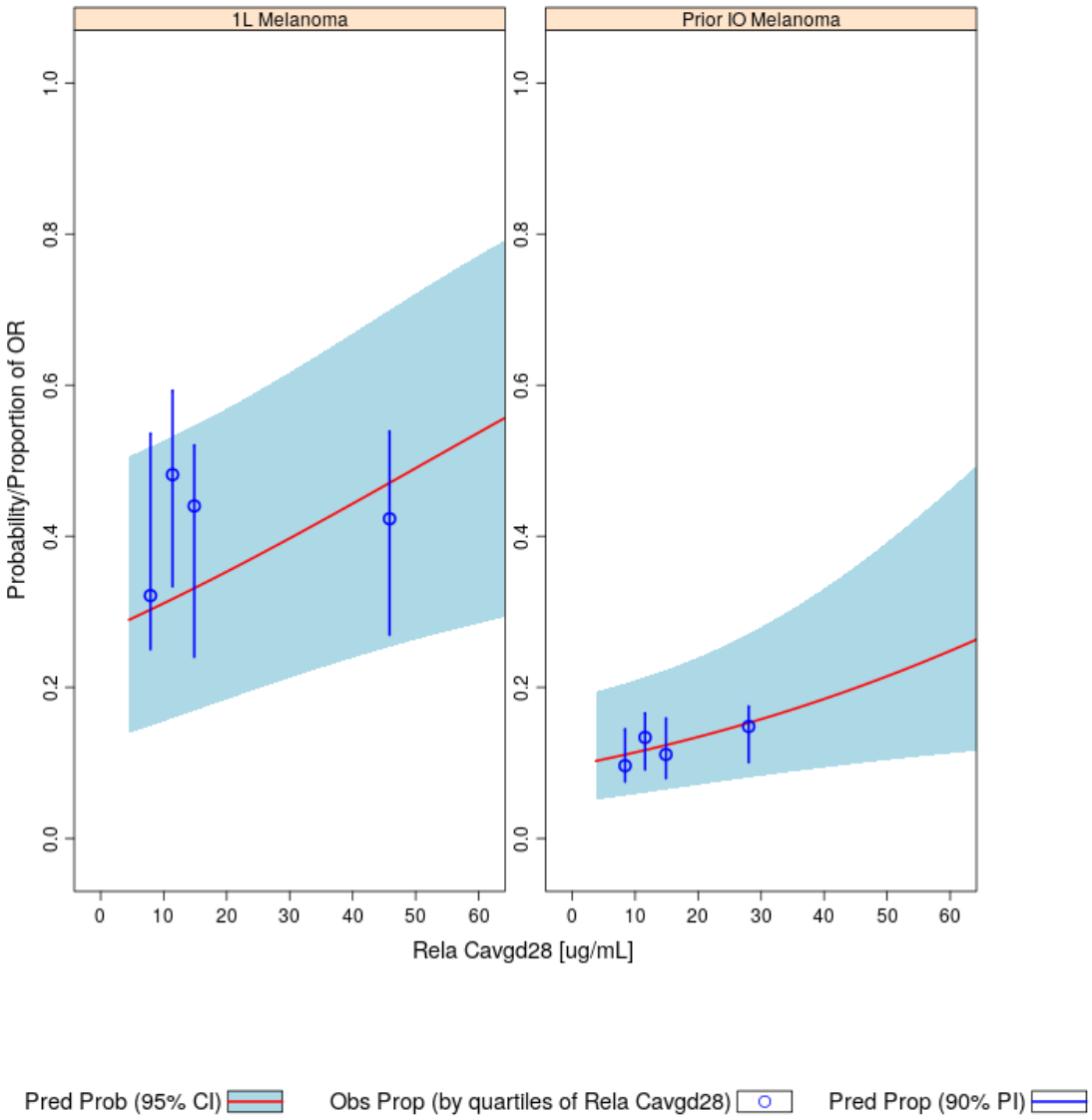
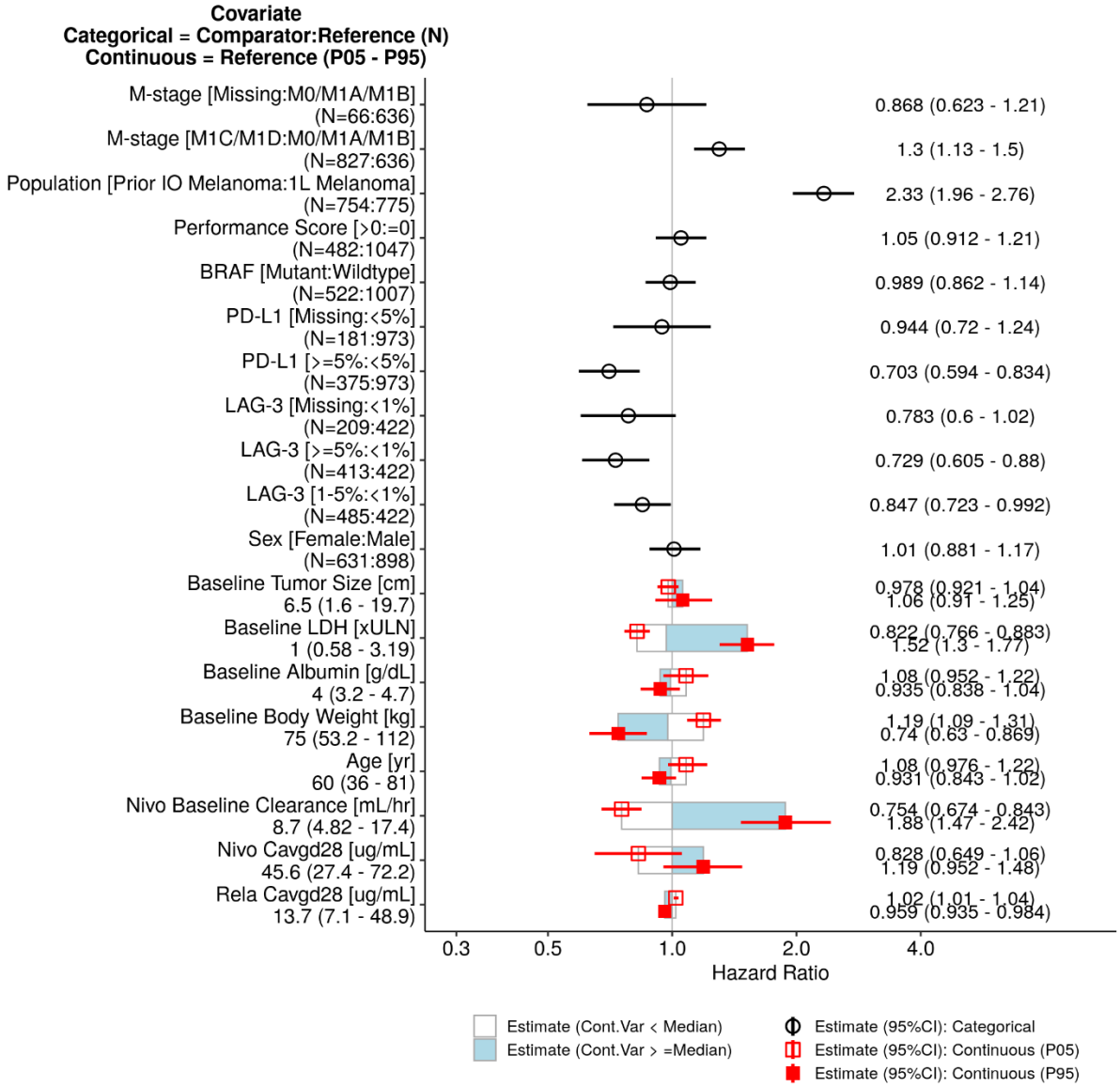
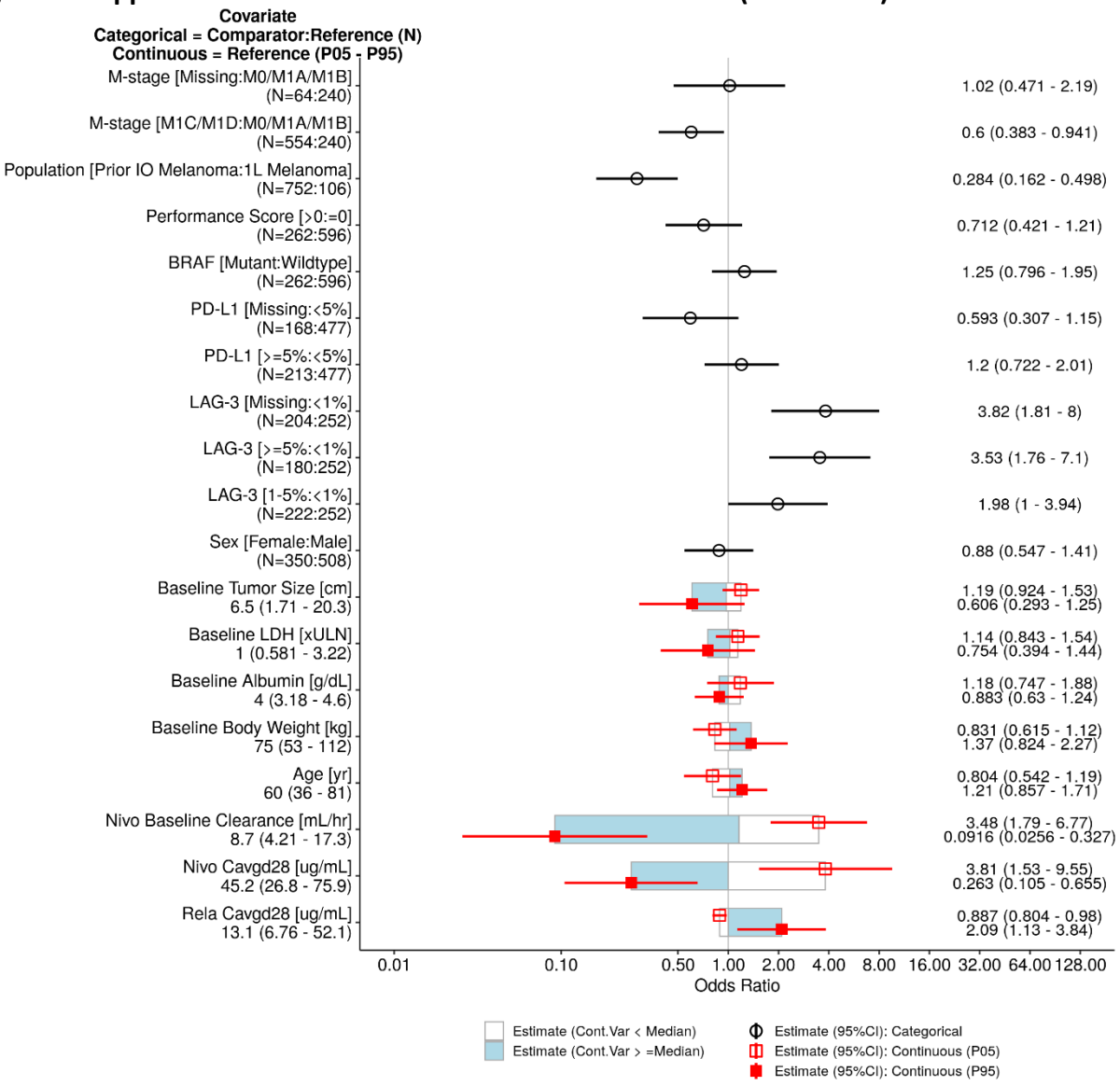


Figure 38: Applicant - Estimated Covariate Effects of the E-R of PFS (Full Model)



Note: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by horizontal width of boxes (horizontal lines). Open/shaded width of boxes represents the range of covariate effects from the reference to the 5th/95th percentile of the covariate.
Reference subject is a 60-year old male, weighing 75 kg, with 1L MEL, baseline ALB of 4 g/dL, baseline LDH normalized to the upper limit of normal (ULN) LDH of 1, a normal performance score status (performance score = 0), baseline tumor size of 6.5 cm, LAG-3 expression of <1%, PD-L1 expression of <5%, a wildtype BRAF status, and a M-Stage status of M0/M1A/M1B.

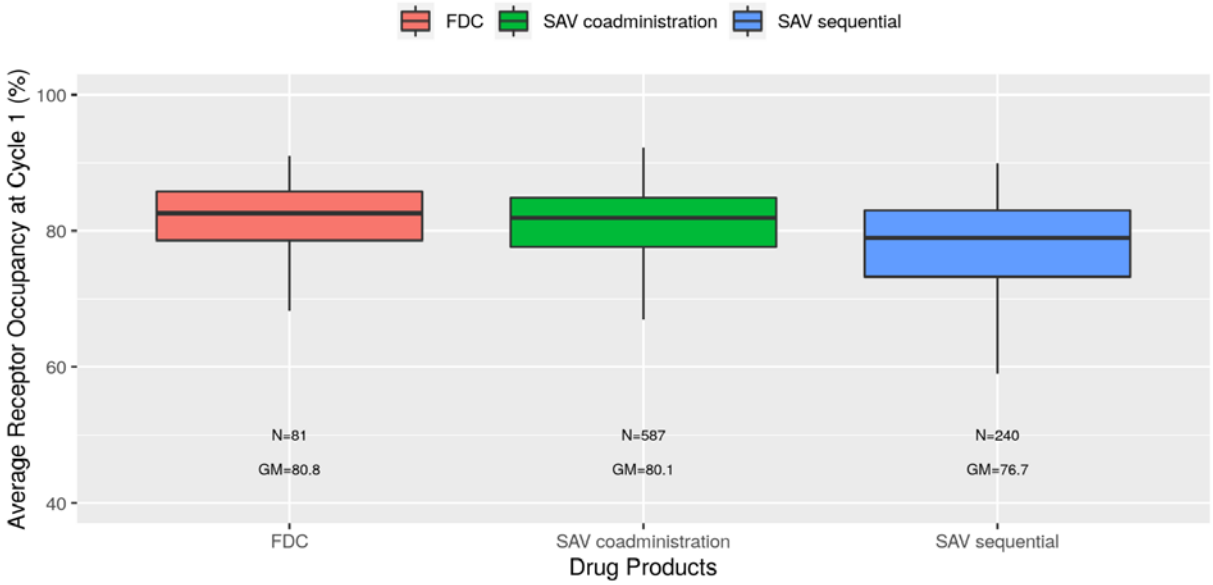
Figure 39: Applicant - Estimated Covariate Effects of E-R of OR (Full Model)



Note: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by horizontal width of boxes (horizontal lines). Open/shaded width of boxes represents the range of covariate effects from the reference to the 5th/95th percentile of the covariate.
Reference subject is a 60-year old male, weighing 75 kg, with 1L MEL, baseline ALB of 4 g/dL, baseline LDH normalized to the upper limit of normal (ULN) LDH of 1, a normal performance score status (performance score = 0), baseline tumor size of 6.5 cm, LAG-3 expression of <1%, PD-L1 expression of <5%, a wildtype BRAF status, and a M-Stage status of M0/M1A/M1B.

Figure 40: Applicant - Distribution of Model Predicted Relatlimab Peripheral RO (ROavg1 and ROavgss) for Nivo 480 mg + Rela 160 mg Q4W by Drug Product (FDC, SAV Co-administration, SAV Sequential)

A) ROavg1



B) ROavgss

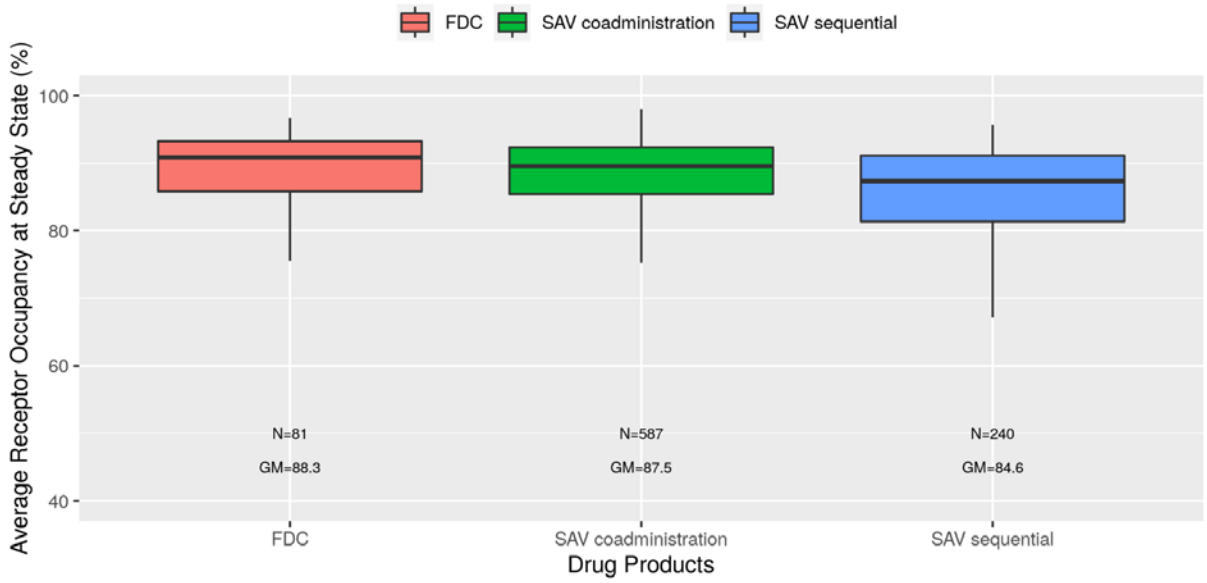


Figure 41: Applicant - Model Predicted Hazard Ratio of PFS in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Nivolumab 480 mg Q4W Regimen

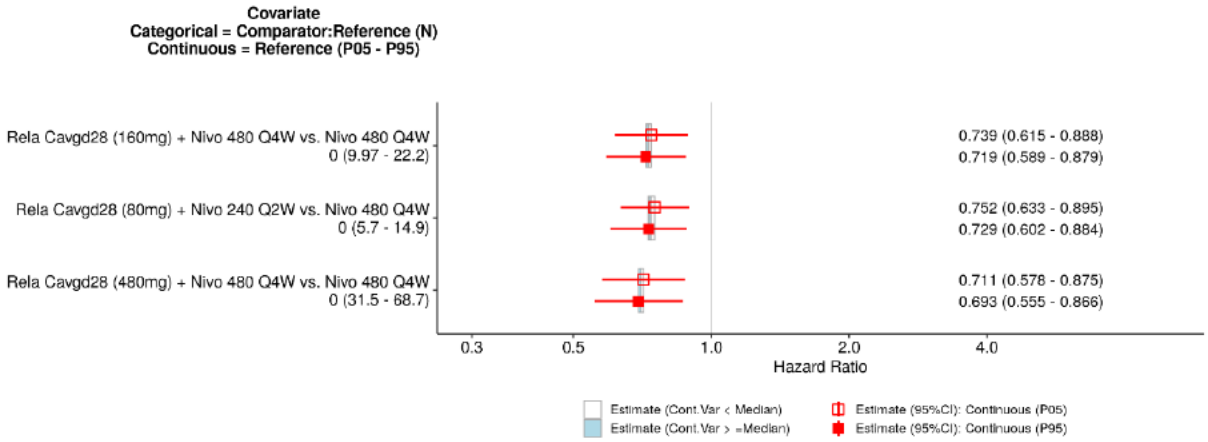
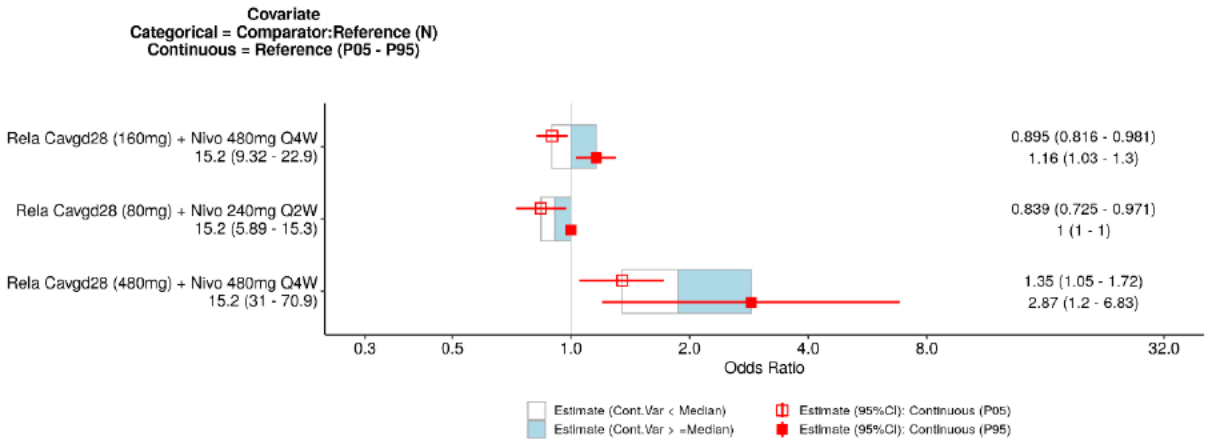


Figure 42: Applicant - Model Predicted Odds Ratio of OR in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Relatlimab 160 mg + Nivolumab 480 mg Q4W Regimen

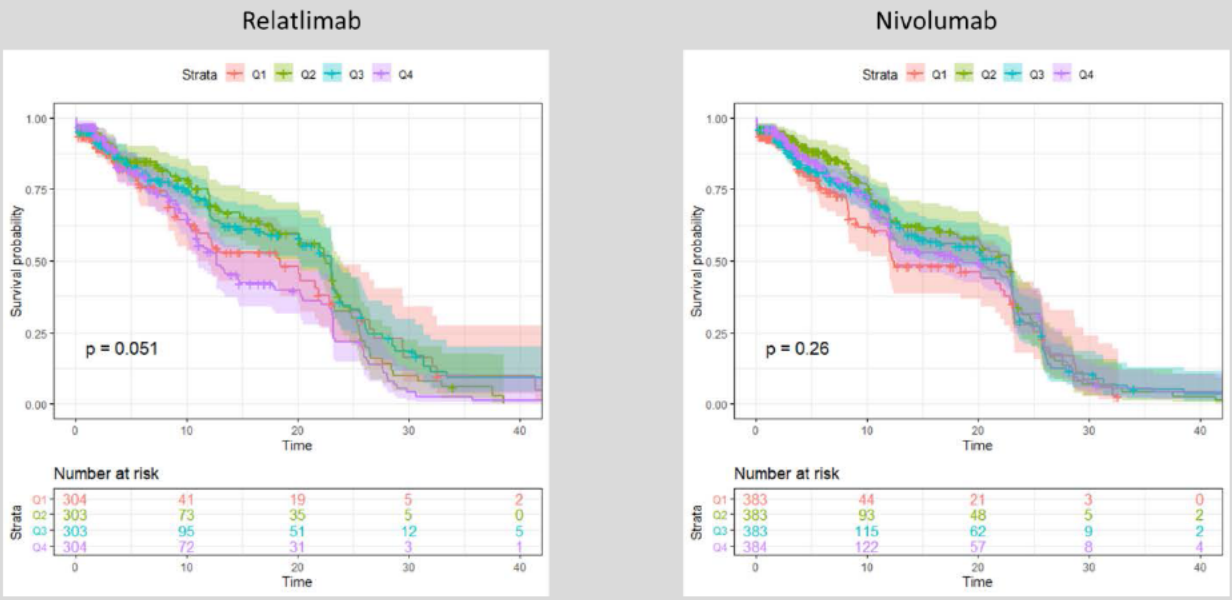


<u>The FDA's Assessment:</u>

The Applicant's analysis was checked by the reviewer. Relatively flat E-R efficacy relationships were observed for PFS in Study CA224047 (Figure 40). In study CA224020, no clear difference in ORR was observed between patients receiving nivo./rela. 480 mg/480 mg Q4W and nivo./rela 240 mg/80 mg Q2W or 480 mg/160 mg Q4W. For patients without prior immunotherapy, ORR was similar at all three doses (Table 84). A higher response rate was not observed with a higher dose of relatlimab (480 mg Q4W). The sigmoid Emax model for RO was acceptable. (b) (4)

Figure 44).

Figure 43: The relationship of PFS with relatlimab and nivolumab exposure in study CA224047



Source: FDA's analysis

Table 84: ORR summary in Study CA224020 by prior treatment and dosing group

Prior Treatment	Dosing Group	Formation	N	ORR
1L MEL	R80/N240 Q2W	SAV-sequential	57	25 (44%)
	R160/N480 Q4W	SAV-coadministration	27	10 (37%)
	R480/N480 Q4W	SAV-coadministration	22	9 (41%)
Prior IO MEL	R80/N240 Q2W	SAV-coadministration	189	22 (12%)
	R80/N240 Q2W	SAV-sequential	160	22 (14%)
	R160/N480 Q4W	SAV-coadministration	247	20 (8%)
	R160/N480 Q4W	FDC	81	15 (19%)
	R480/N480 Q4W	SAV-coadministration	100	13 (13%)

Source: FDA's analysis

Figure 44: Simulation of peripheral RO with the RO model and population PK model for relatlimab in adolescent subjects

19.4.3.3. ER (safety) Executive Summary

The FDA's Assessment:

ER safety analyses of relatlimab and nivolumab were submitted to support the BLA. The ER safety relationship between safety endpoints (Gr2+ IMAEs and Gr3+ DRAEs) and the exposure of nivolumab and relatlimab were characterized in patients with advanced solid tumors (including 1L melanoma and melanoma previously treated with IO therapy) who received nivolumab in combination with relatlimab. Flat ER relationships for the risk of Gr2+ IMAEs and Gr3+ DRAEs with relatlimab exposure were observed across the range of relatlimab exposures in Studies CA224020 and CA224047. Although a positive relationship of Gr2+ IMAEs with nivolumab exposure was observed, the results were inconclusive due to the limited dose range of nivolumab (240 mg Q2W and 480 mg Q4W) in the study.

19.4.3.4. ER (safety) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		To characterize the relationship between relatlimab concentration and safety in subjects with advanced solid tumors (including 1L melanoma and prior IO melanoma) who received relatlimab in combination with nivolumab.
Study Included		Studies CA224020 and CA224047. These two studies investigated the efficacy and safety of nivolumab and relatlimab combination in the target population in unresectable or metastatic melanoma patients.
Population Included		Subjects with solid tumors, including unresectable or metastatic melanoma
Endpoint		Gr2+ IMAEs and Gr3+ DRAEs
No. of Patients (total, and with individual PK)		ER Gr2+ IMAEs and Gr3+ DRAEs: 1994
Population Characteristics (Table 85)	General	• Median (range) age: 62 (17, 92) years • Median (range) baseline body weight: 76.7 (37, 170) kg • Sex, n (%): 1213 (60.8) males, 781 (39.2) females
	Organ impairment	Not specifically evaluated.
	Pediatrics (if any)	Not specifically evaluated.
	Geriatrics (if any)	Not specifically evaluated.
Dose(s) Included		Nivo+rela 240/80 mg Q2W, 480/160 mg Q4W, and 480/480 mg Q4W
Exposure Metrics Explored (range)		Nivolumab and relatlimab Cmax1 and Cavgd28
Covariates Evaluated		Age, baseline body weight, baseline albumin, baseline LDH [*ULN], baseline tumor size, sex, patient population, baseline LAG-3 expression, baseline PD-L1 expression, BRAF status, ECOG status

Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	E-R of Gr2+ IMAEs and Gr3+ DRAEs were characterized by time-to-event modeling using Cox proportional hazard methodology. For both Gr2+ IMAEs and Gr3+ DRAEs, the model with log-transformed relatlimab Cavgd28 and linear nivolumab Cavgd28 provided the best fit to the data. .	Acceptable
Model Parameter Estimates	Table 86 (Gr2+ IMAEs) and Table 87 (Gr3+ DRAEs)	Acceptable
Model Evaluation	Figure 45 (Gr2+ IMAEs) and Figure 46 (Gr3+ DRAEs)	Acceptable
Covariates and Clinical Relevance	Figure 47 (Gr2+ IMAEs) and Figure 48 (Gr3+ DRAEs)	Acceptable
Simulation for Specific Population	N/A	N/A
Visualization of E-R relationships	Figure 49 (Gr2+ IMAEs) and Figure 50 (Gr3+ DRAEs)	Acceptable
Overall Clinical Relevance for ER	Gr2+ IMAEs: The risk of Gr2+ IMAEs was significantly associated with nivolumab and relatlimab exposure, resulting in a higher risk in nivolumab + relatlimab combination compared with nivolumab monotherapy. Gr3+ DRAEs: The risk of Gr3+ DRAEs was significantly associated with relatlimab exposure, resulting in a higher risk in nivolumab + relatlimab combination compared with nivolumab monotherapy. Nivolumab exposure was not significantly associated with the risk of Gr3+ DRAEs. For both Gr2+ IMAEs and Gr3+ DRAEs, the risk was similar across the range of relatlimab exposures (Cavgd28) produced by the studied combination dosing regimen in Studies CA224020 and CA224047, supporting a flat E-R relationship over this exposure	The result observed with nivolumab might be inconclusive due to the relative narrow dose range (240 mg Q2W and 480 mg Q4W).

	range. The E-R relationships of nivolumab and relatlimab were not dependent upon covariate values (interactions with covariates was not significant).	
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	No E-R safety results are provided in Section 12.2 of the USPI.	N/A

Table 85: Applicant - Summary of Exposures and Baseline Covariates in the Exposure-Response of Gr2+ IMAE and Gr3+ DRAE Analysis Dataset

Covariate	1L MEL N = 778	Prior-IO MEL N = 777	Other N = 439	Total N = 1994
Sex N (%)				
Male	451 (58.0)	464 (59.7)	298 (67.9)	1213 (60.8)
Female	327 (42.0)	313 (40.3)	141 (32.1)	781 (39.2)
Baseline LAG-3 Expression N (%)				
Negative	182 (23.4)	240 (30.9)	0 (0)	422 (21.2)
≥ 1 - <5%	275 (35.3)	210 (27.0)	0 (0)	485 (24.3)
≥ 5%	248 (31.9)	165 (21.2)	0 (0)	413 (20.7)
Unknown	73 (9.4)	162 (20.8)	439 (100.0)	674 (33.8)
Baseline PD-L1 Expression (5% cutoff) N (%)				
Positive	187 (24.0)	191 (24.6)	94 (21.4)	472 (23.7)
Negative	556 (71.5)	437 (56.2)	263 (59.9)	1256 (63.0)
Unknown	35 (4.5)	149 (19.2)	82 (18.7)	266 (13.3)
BRAF Status N (%)				
Mutation	290 (37.3)	208 (26.8)	6 (1.4)	504 (25.3)
Wild-type	480 (61.7)	540 (69.5)	18 (4.1)	1038 (52.1)
Unknown	0 (0)	1 (0.1)	0 (0)	1 (0.1)
Missing	8 (1.0)	28 (3.6)	415 (94.5)	451 (22.6)
ECOG Status N (%)				
Missing	0 (0)	0 (0)	12 (2.7)	12 (0.6)
0	539 (69.3)	529 (68.1)	213 (48.5)	1281 (64.2)
1	239 (30.7)	237 (30.5)	211 (48.1)	687 (34.5)
2	0 (0)	11 (1.4)	3 (0.7)	14 (0.7)
Age [yr]				
Mean (SD)	61.2 (14)	61 (13.4)	60 (11.4)	60.8 (13.2)
Median (Min, Max)	63 (20, 90)	62 (17, 92)	62 (18, 88)	62 (17, 92)
Baseline Body Weight [kg]				
Mean (SD)	80.3 (18.2)	79.1 (18.4)	73.5 (16.8)	78.3 (18.2)
Median (Min, Max)	79.3 (39, 163)	77 (41.1, 170)	71.5 (37, 145)	76.7 (37, 170)
Missing, N (%)		3 (0.386)		3 (0.15)
Baseline Albumin [g/dL]				
Mean (SD)	4.14 (0.466)	3.96 (0.472)	3.74 (0.482)	3.99 (0.496)
Median (Min, Max)	4.2 (2.1, 5.2)	4 (2, 6)	3.8 (2.2, 4.8)	4 (2, 6)
Missing N (%)	26 (3.34)	69 (8.88)	36 (8.2)	131 (6.57)
Baseline LDH [*ULN]				
Mean (SD)	1.21 (1.24)	1.38 (1.59)	1.1 (0.934)	1.25 (1.33)
Median (Min, Max)	0.886 (0.13, 12.5)	0.943 (0.344, 21.7)	0.859 (0.432, 9.54)	0.898 (0.13, 21.7)
Missing, N (%)	2 (0.257)	11 (1.42)	1 (0.228)	14 (0.702)
Baseline Tumor Size [cm]				
Mean (SD)	7.11 (5.81)	9.06 (6.42)	8.14 (5.37)	8.11 (6.05)
Median (Min, Max)	5.5 (1, 54.8)	7.54 (1.1, 42.9)	6.69 (1.07, 28.1)	6.53 (1, 54.8)
Missing, N (%)	85 (10.9)	64 (8.24)	100 (22.8)	249 (12.5)
Relatlimab Cavg at Day 28 [ug/mL]				
Mean (SD)	9.68 (10.9)	19.9 (22.7)	17.7 (28.3)	15.4 (21.1)
Median (Min, Max)	10.5 (0, 69.4)	13.3 (1.25, 274)	10.7 (1.32, 216)	11.7 (0, 274)

Covariate	1L MEL N = 778	Prior-IO MEL N = 777	Other N = 439	Total N = 1994
Relatlimab Cmax1 [ug/mL]				
Mean (SD)	27.5 (30.6)	50 (55.4)	41.3 (76.2)	39.3 (54.2)
Median (Min, Max)	30 (0, 184)	36.5 (4.04, 567)	20.5 (4.45, 523)	25.3 (0, 567)
Nivolumab Cavg at Day 28 [ug/mL]				
Mean (SD)	46.8 (11.2)	47.8 (15.9)	38.8 (10.7)	45.5 (13.6)
Median (Min, Max)	46.1 (17.5, 99.8)	45.4 (12.2, 147)	37.5 (11.2, 87.7)	44 (11.2, 147)
Nivolumab Cmax1 [ug/mL]				
Mean (SD)	123 (38.3)	105 (49.3)	74.9 (31.8)	106 (45.5)
Median (Min, Max)	119 (40.4, 514)	101 (18.6, 359)	65.9 (16.5, 238)	103 (16.5, 514)

Table 86: Applicant - Parameter Estimates of Exposure-Response of Gr2+ IMAE Full Model

Predictor Variable[a]	Estimate	SE[b]	RSE%[c]	HR Coefficient[d] (95% CI)
Log rela Cavgd28 [µg/mL]	0.03167	0.01234	38.96	1.032 (1.008, 1.057)
Nivo Cavgd28 [µg/mL]	0.008835	0.003723	42.13	1.009 (1.002, 1.016)
Age [yr]	-0.003751	0.003077	82.05	0.9963 (0.9903, 1.002)
Sex [Female:Male]	-0.05369	0.08912	166	0.9477 (0.7958, 1.129)
Body Weight [kg]	0.004806	0.002481	51.61	1.005 (0.9999, 1.01)
Albumin [g/L]	-0.3262	0.09357	28.68	0.7216 (0.6007, 0.8669)
Log(LDH) [≥ ULN]	0.258	0.09173	35.55	1.294 (1.081, 1.549)
Tumor Size [cm]	-0.01549	0.008858	57.2	0.9846 (0.9677, 1.002)
LAG-3 Status (≥1% - <5%:<1%)	0.06035	0.1205	199.7	1.062 (0.8388, 1.345)
LAG-3 Status (≥ 5%:<1%)	0.01314	0.1311	997.7	1.013 (0.7836, 1.31)
LAG-3 Status (Missing:<1%)	0.2374	0.1504	63.34	1.268 (0.9443, 1.703)
PD-L1 Status [≥ 5%:< 5%]	0.1182	0.09541	80.73	1.125 (0.9335, 1.357)
PD-L1 Status [missing:< 5%]	-0.1353	0.1365	100.9	0.8735 (0.6684, 1.141)
BRAF Status [mutation:wild type]	0.01561	0.09625	616.5	1.016 (0.8411, 1.227)
BRAF Status [missing:wild type]	0.1404	0.1384	98.6	1.151 (0.8773, 1.509)
Performance Score [≥ 1:0]	0.05494	0.08511	154.9	1.056 (0.8942, 1.248)
Patient Population [Prior IO:1L]	-0.4291	0.08682	20.23	0.6511 (0.5492, 0.7718)

[a] Continuous predictors have indicated by [unit], and categorical predictors by [comparator:reference].

[b] SE: Standard Error

[c] RSE: Relative Standard Error (100*SE/Estimate)

[d] Increase in hazard for every unit increase in continuous predictor variables; for categorical variables, it represents the hazard ratio of the comparator group to reference group. Relatlimab Cavgd28 (in units of µg/mL) increases by one unit for approximately 2.7-fold increase in Cavgd28

Table 87: Applicant - Parameter Estimates of Exposure-Response of Gr3+ DRAE Full Model

Predictor Variable[a]	Estimate	SE[b]	RSE%[c]	HR Coefficient[d] (95% CI)
Log rela Cavgd28 [µg/mL]	0.0658	0.01906	28.96	1.068 (1.029, 1.109)
Nivo Cavgd28 [µg/mL]	0.003408	0.005391	158.2	1.003 (0.9929, 1.014)
Age [yr]	-9.46E-05	0.004465	4720	0.9999 (0.9912, 1.009)
Sex [Female:Male]	-0.09353	0.1294	138.4	0.9107 (0.7067, 1.174)
Body Weight [kg]	-0.00744	0.003856	51.84	0.9926 (0.9851, 1)
Albumin [g/L]	-0.2056	0.1367	66.48	0.8142 (0.6229, 1.064)
Log(LDH) [≥ ULN]	0.1311	0.1357	103.5	1.14 (0.8739, 1.487)
Tumor Size [cm]	0.003251	0.01251	384.9	1.003 (0.979, 1.028)
LAG-3 Status (1%-5%:<1%)	0.1474	0.1782	120.9	1.159 (0.8172, 1.643)
LAG-3 Status (≥ 5%:<1%)	0.1235	0.1888	152.9	1.131 (0.7814, 1.638)
LAG-3 Status (Missing:<1%)	0.01656	0.2184	1319	1.017 (0.6627, 1.56)
PD-L1 Status [≥ 5%:< 5%]	0.3278	0.1332	40.64	1.388 (1.069, 1.802)
PD-L1 Status [missing:< 5%]	0.2477	0.1956	78.96	1.281 (0.8732, 1.88)
BRAF Status [mutation:wild type]	-0.06737	0.1387	205.9	0.9348 (0.7123, 1.227)
BRAF Status [missing:wild type]	-0.008798	0.199	2261	0.9912 (0.6712, 1.464)
Performance Score [≥ 1:0]	-0.04911	0.1256	255.8	0.9521 (0.7443, 1.218)
Patient Population [Prior IO:1L]	-0.3141	0.1239	39.45	0.7304 (0.5729, 0.9312)

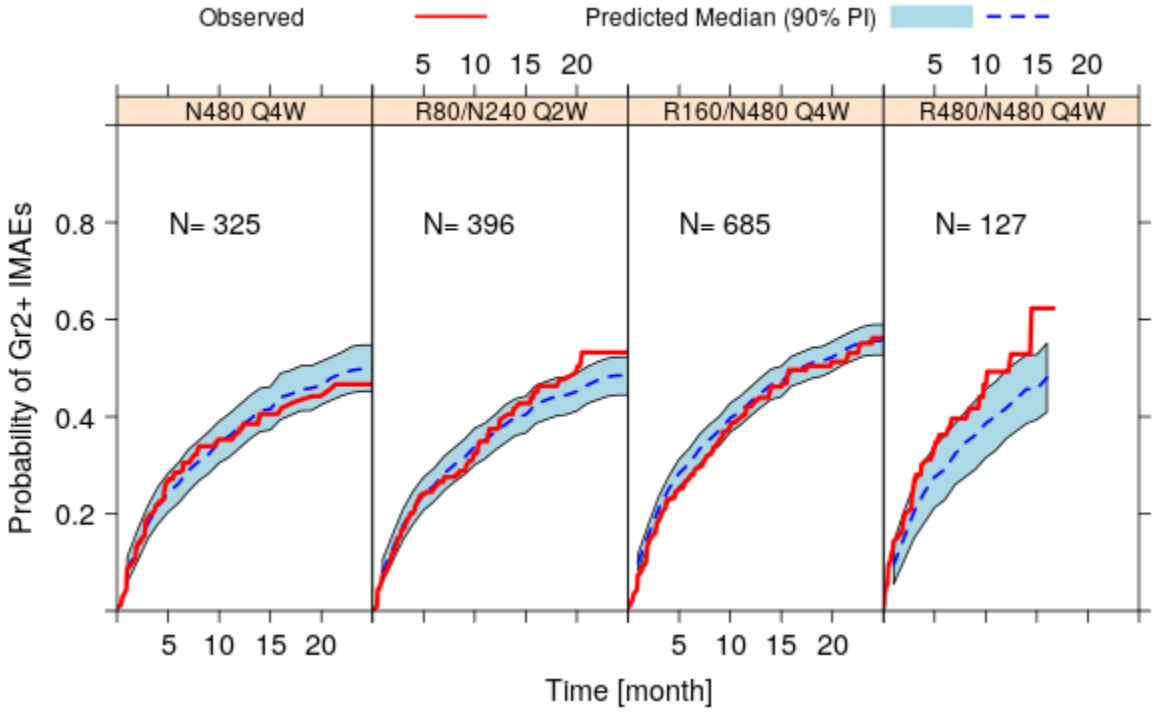
[a] Continuous predictors have indicated by [unit], and categorical predictors by [comparator:reference].

[b] SE: Standard Error

[c] RSE: Relative Standard Error (100*SE/Estimate)

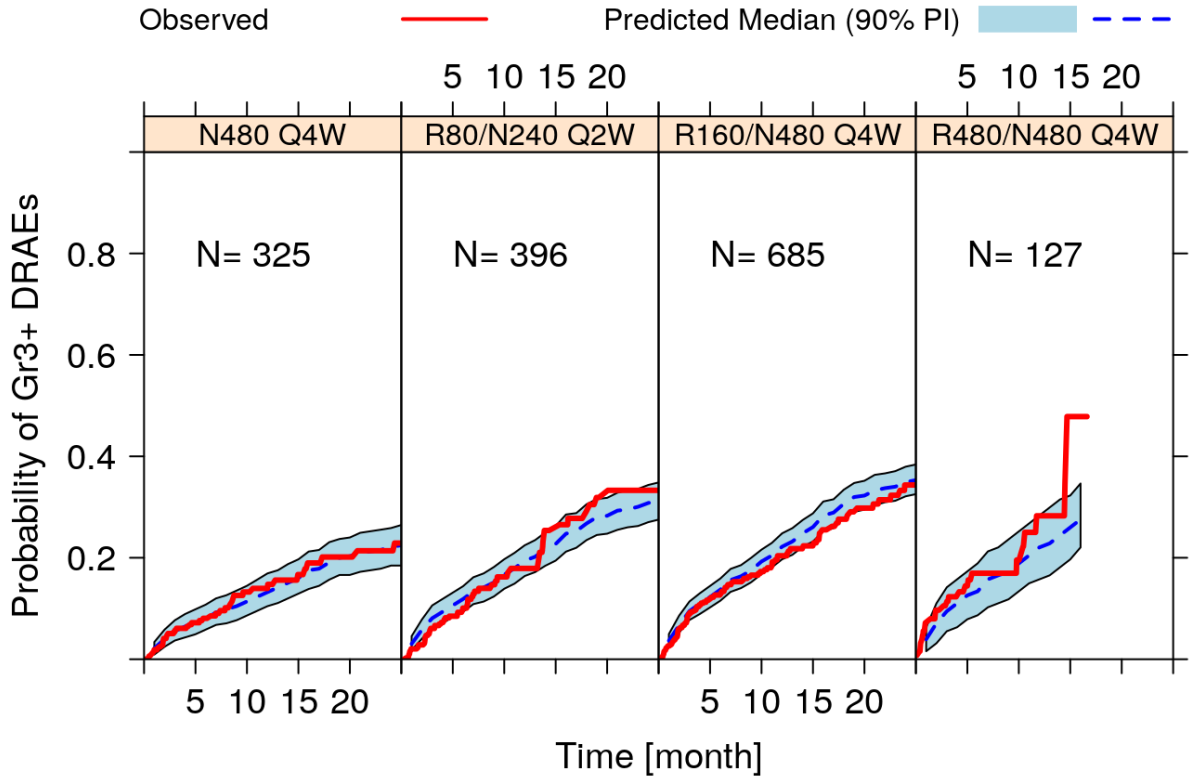
[d] Increase in hazard for every unit increase in continuous predictor variables; for categorical variables, it represents the hazard ratio of the comparator group to reference group. Relatlimab Cavgd28 (in units of g/mL) increases by one unit for approximately 2.7-fold increase in Cavgd28

Figure 45: Applicant - Model Evaluation of Exposure-Response of Gr2+ IMAEs, by Treatment in MEL Subjects



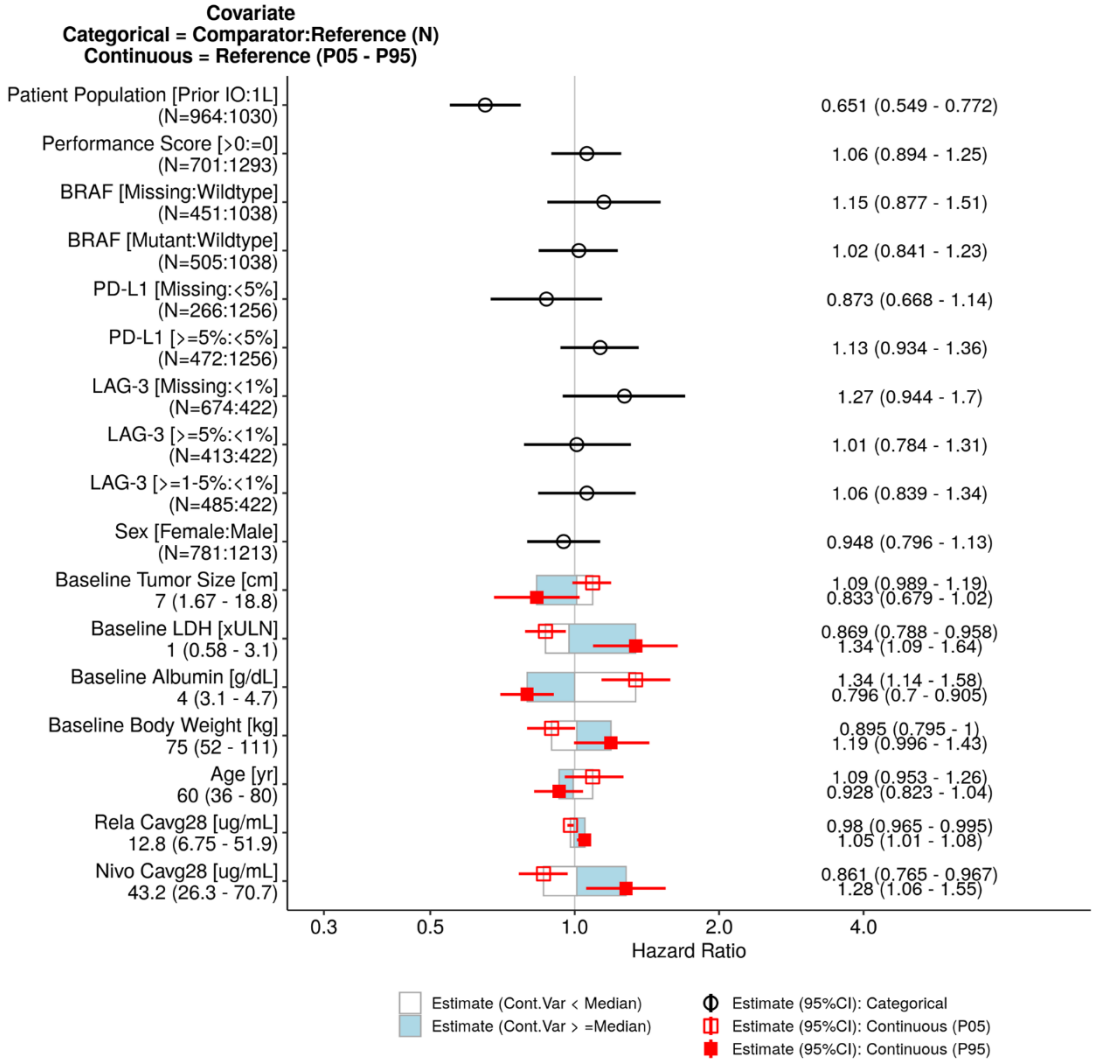
Note: R160: Relatlimab 160 mg Q4W; N480: nivolumab 480 mg Q4W, R80: Relatlimab 80 mg Q2W; N240: nivolumab 240 mg Q2W
Only treatment arms with more than 100 MEL subjects are presented

Figure 46: Applicant - Model Evaluation of Exposure-Response of Gr3+ DRAEs, by Treatment in MEL Subjects



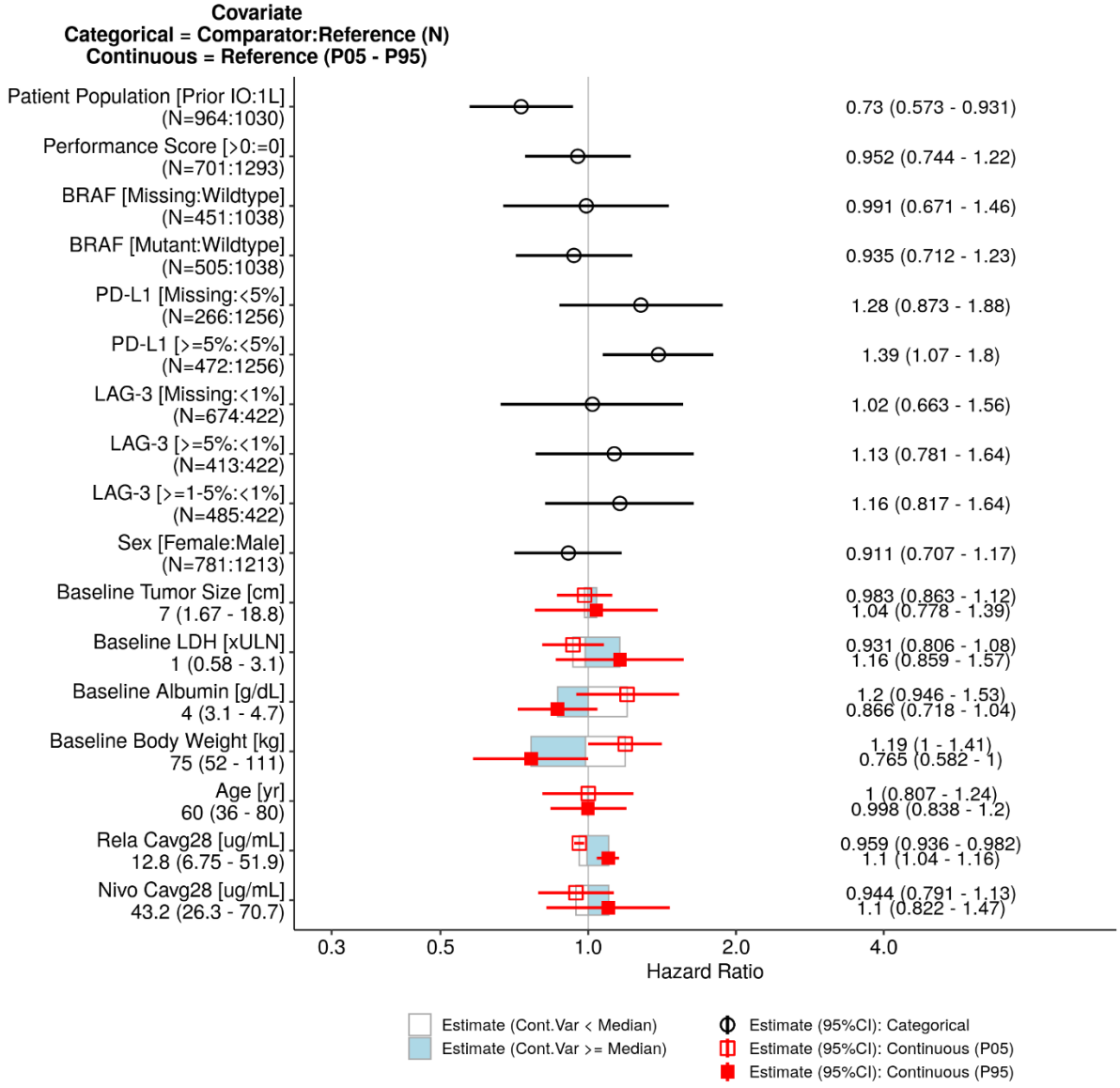
Note: R160: Relatlimab 160 mg Q4W; N480: nivolumab 480 mg Q4W, R80: Relatlimab 80 mg Q2W; N240: nivolumab 240 mg Q2W

Figure 47: Applicant - Estimated Covariate Effects of E-R of Gr2+ IMAEs (Full Model)



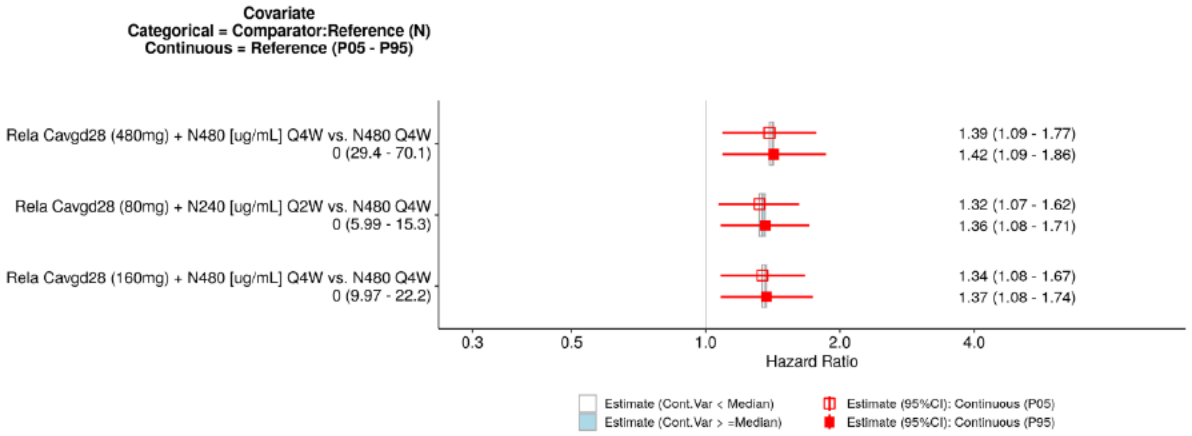
Note: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by horizontal width of boxes (horizontal lines). Open/shaded width of boxes represents the range of covariate effects from the reference to the 5th/95th percentile of the covariate.
Reference subject is a 60-year old male, weighing 75 kg, with 1L MEL, baseline ALB of 4 g/dL, baseline LDH normalized to the upper limit of normal (ULN) LDH of 1, a normal performance score status (performance score = 0), baseline tumor size of 6.5 cm, LAG-3 expression of < 1%, PD-L1 expression of < 5%,and a wildtype BRAF status.

Figure 48: Applicant - Estimated Covariate Effects of E-R of Gr3+ DRAEs (Full Model)



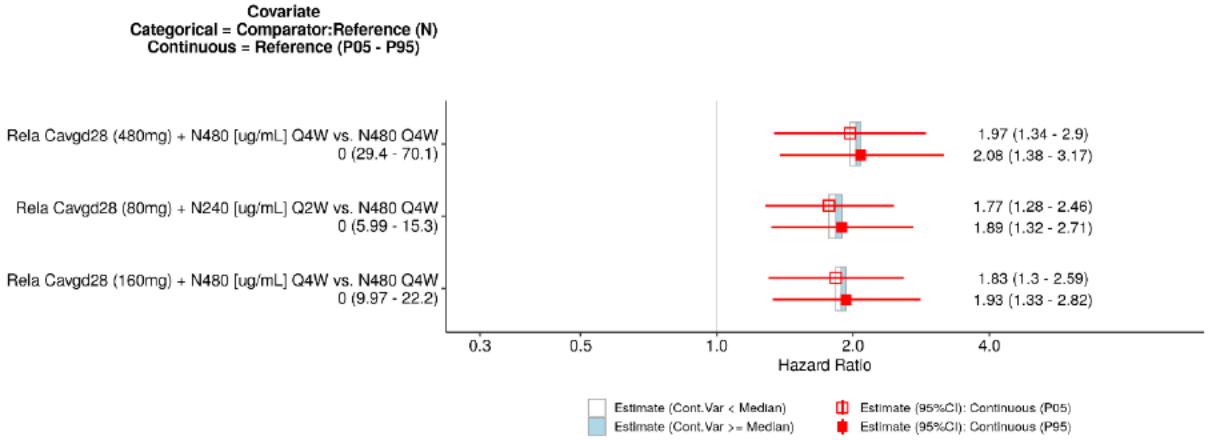
Note: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by horizontal width of boxes (horizontal lines). Open/shaded width of boxes represents the range of covariate effects from the reference to the 5th/95th percentile of the covariate.
Reference subject is a 60-year old male, weighing 75 kg, with 1L MEL, baseline ALB of 4 g/dL, baseline LDH normalized to the upper limit of normal (ULN) LDH of 1, a normal performance score status (performance score = 0), baseline tumor size of 6.5 cm, LAG-3 expression of < 1%, PD-L1 expression of < 5%,and a wildtype BRAF status.

Figure 49: Applicant - Model Predicted Hazard Ratio of Gr2+ IMAEs in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Nivolumab 480 mg Q4W Regimen



Note: N480: nivolumab 480 mg Q4W

Figure 50: Applicant - Model Predicted Hazard Ratio of Gr3+ DRAEs in Nivolumab + Relatlimab Combination Dose Regimens Relative to Median Cavgd28 of Nivolumab 480 mg Q4W Regimen



The FDA's Assessment:

The Applicant's analysis was verified by the reviewer. In the Applicant's ER safety analysis, positive relationships were observed for Gr2+ IMAEs with relatlimab and nivolumab exposure and Gr3+ DRAEs with relatlimab exposure. For both Gr2+ IMAEs and Gr3+ DRAEs, the risk was similar across the range of relatlimab exposures (Cavg) produced by the studied combination dosing regimen in Studies CA224020 and CA224047, supporting a flat E-R relationship over this exposure range. Patients with prior immunotherapy had slightly lower risk of Gr2+ IMAEs and Gr3+ DRAEs. For patients that received relatlimab 80 mg Q2W, 160 mg Q4W or 480 mg Q4W, no clear differences were observed among the different dose groups. For nivolumab, the result of ER safety analysis might be limited as patients only received the nivolumab 240 mg Q2W or

480 mg Q4W dose regimens. The exposure range of nivolumab is relatively narrow and the result may be inconclusive. Based on the previous reviews, risk of Gr3+ DRAEs and AEs leading to discontinuation or death did not increase with Cavg,ss by doses ranging from 0.1 to 10 mg/kg nivolumab.

19.4.3.5. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

An E-R analysis of efficacy using PFS as a key primary analysis endpoint was conducted using pooled data from 1L and prior-IO melanoma patients enrolled in CA224047 and CA224020. The PFS was significantly associated with relatlimab exposure, resulting in a longer PFS compared to nivolumab monotherapy, providing evidence for the contribution of relatlimab to efficacy. However, the improvement in efficacy was similar across the range of relatlimab exposures produced by the studied nivo+rela dosing regimens (240/80 mg Q2W, 480/160 mg Q4W, and 480/480 mg Q4W) suggesting a flat E-R relationship for PFS and supporting the proposed dose of relatlimab 160 mg Q4W.

In addition, an E-R analysis of efficacy using OR as the endpoint was conducted using data from Study CA224020 in 1L melanoma and prior-IO melanoma patients. The probability of OR was significantly associated with relatlimab exposure (Cavgd28), resulting in a higher probability of OR with increase in relatlimab exposure. Predicted probability of OR was higher with nivo+rela 480/480 mg Q4W compared with nivo+rela 240/80 mg Q2W and nivo+rela 480/160 mg Q4W; however, the 95% CI for odds ratio was wide with nivo 480 mg + rela 480 mg Q4W. Despite the trend towards higher OR with higher relatlimab exposure based on the data from CA224020 study, it should be noted that OR lacks the DOR component of clinical benefit, whereas the PFS end point captures the DOR component and the flat E-R from PFS analysis indicates that there is no additional clinical benefit with the higher dose of rela + nivo 480/480mg Q4W.

E-R safety analyses that included data from Studies CA224020 and CA224047 in solid tumor subjects showed that the risk of Gr3+ DRAEs and Gr2+ IMAEs was significantly associated with relatlimab exposure resulting in higher risk of these events in nivo+rela compared with nivolumab monotherapy. However, the increase in risk was similar across the range of relatlimab exposures produced by the studied nivo+rela dosing regimens including the higher dose of 480/480 mg Q4W, suggesting a flat E-R relationship for safety.

The integration of nivolumab and relatlimab E-R findings for both efficacy and safety support the recommended dose of nivo+rela 480/160 mg FDC Q4W for the treatment of metastatic or unresectable melanoma.

The FDA's Assessment:

FDA agrees with the Applicant's position on the overall benefit-risk evaluation based on E-R analyses.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
See each specific subsection within the body of the Assessment Aid.

19.6. List of References

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Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD	Office of Clinical Pharmacology	Sections: 6; 19.4	**Select one:** ☒Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2022.03.17 15:10:37 -04'00'			
Clinical Reviewer	Leigh Marcus, M.D.	Division of Oncology 3	Sections: parts of: 1.2, 1.3, 7, 8.2, 8.4, 9, 10, 11, 12,	**Select one:** ☒Authored ☐Approved
	Signature: Leigh J. Marcus -S Digitally signed by Leigh J. Marcus -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013338033, cn=Leigh J. Marcus -S Date: 2022.03.15 16:16:12 -04'00'			
Clinical Reviewer	Leslie Doros, M.D.	Division of Oncology 3	Sections: 1, 2, 3, 7, 8.1, 8.4, 10, 19.1, 19.2	**Select one:** ☒Authored ☐Approved
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	Signature: Jiaxin Fan -S (Affiliate) Digitally signed by Jiaxin Fan -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2003223210, cn=Jiaxin Fan -S (Affiliate) Date: 2022.03.17 14:41:02 -04'00'			
Statistical Team Leader	Joyce Cheng, Ph.D.	Division of Biometrics 5	Sections: 1, 8	**Select one:** ☒Authored ☒Approved
	Signature: Joyce Cheng -S Digitally signed by Joyce Cheng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joyce Cheng -S, 0.9.2342.19200300.100.1.1=2001702039 Date: 2022.03.16 14:49:09 -04'00'			
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	Signature: William F. Pierce -S Digitally signed by William F. Pierce -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S Date: 2022.03.14 15:01:58 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Jamie Brewer, M.D.		Sections: All	**Select one:** ☒Approved
	Signature: Refer to final assessment aid.			
Deputy Division Director (Clinical)	'Lola Fashoyin-Aje, M.D., M.P.H		Sections: All	**Select one:** ☒Approved
	Signature: Refer to final assessment aid.			

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My signature indicates that I have considered the FDA assessments and recommendations included in this Review in determining the regulatory action.