DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

(b) (4)

WRITTEN REQUEST – AMENDMENT 2

Bristol-Myers Squibb
Attention: Noemi C. Guma, Ph.D.
Director, Global Regulatory Safety and
Biometrics, US Oncology
3401 Princeton Pike, B.3043C
Lawrence NJ, 08648

Dear Dr. Guma:

Please refer to your correspondence dated March 1, 2018, requesting changes to FDA's September 11, 2014, Written Request for pediatric studies for nivolumab.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on September 11, 2014, and as amended on April 11, 2016, remain the same. (**Text added is underlined. Text deleted is strikethrough.)**

Background:

The safety, pharmacokinetics (PK), and clinical activity of nivolumab have been assessed in ~~a completed dose-finding study,~~ multiple clinical studies and further investigations are ongoing in additional studies sponsored by Bristol-Myers Squibb (BMS) in adult patients, alone or in combination with ipilimumab and other investigational and approved products. Nivolumab is approved for the treatment of patients with advanced ~~with~~ non-small cell lung cancer, melanoma, renal cell carcinoma, Hodgkin's lymphoma, head and neck squamous cell carcinoma, urothelial carcinoma, and hepatocellular carcinoma. Nivolumab in combination with ipilimumab is approved for the treatment of melanoma and renal cell carcinoma. Nivolumab is approved for patients 12 years or older with microsatellite instability (MSI-H) metastatic colorectal cancer. ~~other tumor types, and in a dose-finding, safety and tolerability study, of nivolumab administered in combination with ipilimumab~~.

Ipilimumab is a human monoclonal antibody that targets the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4)~~, another checkpoint inhibitor~~. Ipilimumab, as a single-agent, is approved for the treatment of adult patients with ~~metastatic or unresectable~~ melanoma and in combination with nivolumab for the treatment of renal cell carcinoma. Ipilimumab has been studied as a single-agent in a dose-escalation study conducted in pediatric patients. From this pediatric study, it appears that the types and per-patient incidence of immune-related adverse drug reactions are similar between ~~certain~~ pediatric patients ~~(~~≥12 years of

age or older) and adult patients. The clinical experience in pediatric patients < less than 12 years of age is limited and is still under investigation. The similarity of the safety profile between pediatric and adult patients suggests that adverse treatment effects of CTLA-4 blockade do not depend on patients' stage of development above age 12 years.

There is a strong scientific rationale supporting the use of multiple checkpoints inhibitors, concomitantly and sequentially. Several ongoing clinical studies are exploring this treatment strategy. The adverse reaction profile of nivolumab when administered in combination with ipilimumab observed in Study CA209004 (metastatic melanoma patients) showed that the frequency and severity of treatment-related adverse drug reactions in patients receiving nivolumab in combination with ipilimumab were greater than that reported in patients treated with nivolumab alone. These adverse drug reactions are managed by following algorithms for early intervention and dose delays/modifications.

The eEfficacy of nivolumab, alone or in combination with ipilimumab, in pediatric patients aged ≥ 4 months to < 18 years cannot be extrapolated from adult data and will be determined by the studies outlined in the this Written Request (WR).

Clinical Studies:

Study 1: Multicenter, open-label Phase 1/2 study of nivolumab monotherapy and in combination with ipilimumab. The study is planned to enroll 70 subjects and consists of 3 4 portions:

- Part A: Administration of nivolumab as a single agent to characterize PK and evaluate safety/adverse reaction profile.
- Part B: Administration of nivolumab as a single agent to characterize anti-tumor activity in one of more pediatric tumor types.
- Part C: Administration of nivolumab in combination with ipilimumab to characterize the adverse reaction profile and determine tolerable dosage schedules for the combination.
- Part D: Administration of nivolumab in combination with ipilimumab in one or more tumor types using the recommended Phase 2 doses (RP2D) for the combination.

- *Indication(s) to be studied:*
  - Part A: Patients with refractory or relapsed solid malignant tumors.

    Part B: Patients with Ewing sarcoma, osteosarcoma, rhabdomyosarcoma, or neuroblastoma, Hodgkin lymphoma, Non-Hodgkin lymphoma, and melanoma enrolled in four separate cohorts, respectively. Additional tumor types may be added in additional cohorts based on results from the ongoing biomarker study, relevant adult experience, or unmet medical needs.
  - Part C: Patients with refractory or relapsed solid malignant tumors.

- Part D: Patients with selected disease-specific cohorts (neuroblastoma, rhabdomyosarcoma, Non-Hodgkin lymphoma, osteosarcoma or Ewing sarcoma).

- *Age Group in which the study will be performed:*
  - Part A: Children and adolescents from 1 to <18 years of age.
  - Part B, neuroblastoma, rhabdomyosarcoma, refractory Ewing sarcoma or peripheral primitive neuroectodermal tumors, Hodgkin lymphoma, Non-Hodgkin lymphoma cohorts: Children, adolescents and young adults from 1 to ≤30 years of age.
  - Part B, melanoma cohort: Children and adolescents from 1 to <18 years of age.
  - Part C: Children and adolescents ~~from1~~ from 1 to <18 years of age.
  - Part D1-D6: Children, adolescents and young adults from 1 to ≤ 30 years of age.

  Patients <1 year of age will not be enrolled due to rarity of the specific cancer types to be studied in infants < 1 year of age and since only relapsed and refractory patients will be studied.

  At least three patients will be enrolled in the first dose level. Twelve patients are planned for the second dose level in Parts A and C, with at least 6 patients from 1 to <12 years of age and 6 patients from 12 to <18 years of age. However, the final protocol including the number of patients in each part of the study will be agreed upon with FDA prior to enrollment of the first subject in the study.

- *Objectives of Study:*
  - Primary objectives:
    - Part A: to determine the adverse reaction profile of nivolumab in patients aged 1 to ~~<18~~ < 18 years of age.
    - Part B: to assess and describe any preliminary evidence of anti-tumor activity in specific pediatric tumor types in patients aged 1 to <18 years of age.
    - Part C: to determine the adverse reaction profile of the nivolumab, when administered in combination with ipilimumab in patients aged 1 to <18 years of age.
    - Part D: to assess and describe any preliminary evidence of anti-tumor activity of nivolumab in combination with ipilimumab in specific pediatric tumor types in patients aged 1 to < 30 years of age.
  - Secondary objectives: to assess the ~~pharmacokinetics~~ PK and immunogenicity of nivolumab.

- Descriptive statistical analysis will be used to describe the study results for each of the ~~three~~ four Parts; cohorts in Part B will be analyzed individually and not pooled for analysis of Part B.

- *Regimen:*

  The final protocol for Study 1, including the dosing regimen, will be agreed upon by FDA prior to enrollment of the first subject in the study.

  - Nivolumab monotherapy safety and tumor specific expansion portions: nivolumab monotherapy administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression. ~~Dose de-escalation guided by observation of DLTs will be allowed within the protocol to ensure patient safety. When this portion of the trial confirms safety and appropriate exposures at the 3 mg/kg or another dose level, the study will proceed to enroll patients into a number of tumor specific dose expansion cohorts as well as the combination safety portion.~~
  - Nivolumab and ipilimumab combination portion: ~~This portion will include a dose-escalating safety evaluation of nivolumab and ipilimumab at dose levels of 1+ 1mg/kg and 3 + 1mg/kg, respectively. Once the combination dose is determined, the cohort regimen will be: nivolumab 1mg/kg or 3 mg/kg combined with ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by nivolumab 3mg/kg every 2 weeks until progression.~~ The RP2D has been established as nivolumab 3 mg/kg IV and ipilimumab 1 mg/kg IV every 3 weeks for a maximum of 4 doses followed by nivolumab as a single agent at 3 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity.

- ~~*Timeframe for submitting report of the study: Q2 2018.*~~

Study 2*:* Randomized, active-controlled trial to evaluate the safety and efficacy of nivolumab and of nivolumab administered in combination with ipilimumab for the treatment of patients from 0 to <18 years of age diagnosed with specific solid tumors, based on results of Study 1. Elements of study design such as endpoints, choice of comparator, dosage and treatment regimen, sample size and eligibility criteria will depend on the pediatric tumors chosen for further study. Final protocol and statistical analysis plan for Study 2, and any amendments to the WR, will be agreed upon with FDA prior to enrollment of the first subject in the study.

- *Statistical information, including power of study(ies) and statistical assessments:*

  Descriptive statistical analysis will be used to describe the study results for all parts; cohorts in Part B will be analyzed individually and not pooled for analysis of Part B. A Simon's optimal two stage design will be used for Parts B1-6 and B8 (B7 is an additional non-statistical cohort for patients with unresectable, metastatic, relapsed or refractory melanoma will remain open for enrollment). In the event that a cohort in a given disease group in Part B is completed after Stage 1 because no responses are observed, a cohort in the same disease group will open to up to 10 evaluable patients

in Part D. Nivolumab will not be considered of sufficient interest for further evaluation in a disease category if the true response rate is 5% and will be considered to demonstrate sufficient activity if the true response rate is 25%. If nivolumab has a true response rate of 5%, the rule described above will identify it of sufficient activity for further study with probability 0.07 (type I error), and the trial will have an expected sample size of 14 with 60% probability of early termination. If nivolumab has a true response rate of 25%, the rule described above will identify it of sufficient activity for further study with probability 0.88 (power against the alternative hypothesis P =0.25).

- ~~*Timeframe for submitting report of the study:* Study completion: 4Q, 2025~~

~~*You may request amendments to the WR based on review of results from Study 1.*~~

Pharmacokinetic Analyses:

• ~~*Additional*~~ *Pharmacokinetic Analyses:*

Upon completion of Part A of Study 1, a population pharmacokinetic (PPK) model will be developed to characterize the PK of ~~monotherapy~~ nivolumab as a single-agent in pediatric patients ~~subjects~~. During development, the PPK model will use data from Study 1 and selected trials ~~studies~~ in adults with cancer.

The PPK model-based simulation will be employed to assure that the nivolumab dosing regimen as a single-agent and in combination with ipilimumab achieves exposures similar to that produced in adults with the recommended single- agent dosing regimen for treatment of melanoma; these data will be considered in the design of Study 2. This model will be updated with data from Study 1, ~~Study NCI7458 (~~the trial evaluating the safety and activity of ipilimumab in pediatric patients~~)~~, and selected trials ~~studies~~ of ipilimumab in adults with cancer. Data from all completed trials in adults and pediatric patients may be combined to explore exposure-response relationships for measures of safety and activity in pediatric patients.

Extraordinary results:

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this WR ~~Written Request~~. If you believe this is the case, you must contact the FDA to seek an amendment. It is solely within the FDA's discretion to decide whether it is appropriate to issue an amendment.

Biological product information:

- *dosage form:*

  nivolumab is supplied ~~as a lyophilized powder, for injection; the current strength is 100mg/Vial (10mg/mL). A 40 mg/vial (10 mg/mL) strength is being developed with the same formulation.~~ in a 100 mg/10 mL vial and ipilimumab is supplied as a 200 mg/40 mL vial. The excipients used in the formulation are suitable for pediatric use.

- *route of administration:*

  intravenous administration

- *regimen*

  - Study 1, Parts A and B: nivolumab 3 mg/kg administered ~~intravenously (~~IV~~)~~ over 60 minutes every 2 weeks until progression. ~~Dose de-escalation, guided by observation of dose limiting toxicities (DLTs), will be allowed within the protocol to ensure patient safety. When this portion of Study 1 confirms safety the study will proceed to enroll patients into a number of tumor specific dose expansion cohorts as well as the combination safety portion.~~
  - Study 1, Part C: ~~This portion of Study 1 will include a dose escalating safety evaluation of nivolumab and ipilimumab at dose levels of 1mg/kg nivolumab in combination with 1 mg/kg ipilimumab (dose level 1) and with 3mg/kg nivolumab and ipilimumab at 1mg/kg (dose level 2). Once the optimal doses of ipilimumab in combination with nivolumab is determined, the cohort regimen will be: nivolumab 1mg/kg or 3mg/kg combined with either ipilimumab 1 mg/kg or 3mg/kg every 3 weeks for 4 doses followed by nivolumab 3mg/kg every 2 weeks until progression.~~ The RP2D has been established as nivolumab 3 mg/kg IV and ipilimumab 1 mg/kg IV every 3 weeks for a maximum of 4 doses followed by nivolumab as a single agent at 3 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity.
  - Study 1, Part D: This portion of Study 1 will evaluate the RP2D of 3 mg/kg of nivolumab IV in combination with 1 mg/kg ipilimumab IV every 3 weeks for a maximum of 4 doses followed by 3mg/kg nivolumab as a single agent given every 2 weeks until disease progression or unacceptable toxicity.

Timeframe for submitting reports of the study(ies):

Reports of the above studies must be submitted to the Agency on or before December 31, 2022 ~~Q2,2018~~ for Study 1 and on or before December 31, 2025 ~~in 2021~~ for Study 2. Please keep in mind that pediatric exclusivity can attach only to existing exclusivity, if any, that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, if there is unexpired exclusivity that is eligible for

pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such exclusivity is otherwise due to expire.

If FDA has not determined whether nivolumab is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this formal pediatric ~~Written Request~~WR, nor any request for exclusivity made by you confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated September 11, 2014, as amended by this letter and by previous amendment(s) dated April 11, 2016, must be submitted to the Agency on or before December 31, 2025, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

If FDA has not determined whether nivolumab is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this Written Request amendment, nor any request for exclusivity made by you, confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.

Submit reports of the studies as biologics license application (BLA) / supplement to an approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission to the Office of New Drugs, Immediate Office, Therapeutic Biologics and Biosimilars Team, 10903 New Hampshire Ave, Building 22, Mail Stop 6411, Silver Spring, MD 20993. If you wish to fax it, the fax number is 301-796-9855.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Meredith Libeg, Senior Regulatory Health Project Manager, at (301) 796-1721.

Sincerely,
{See appended electronic signature page}
Gregory Reaman, M.D.
Associate Director for Oncology Sciences
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Complete Copy of Written Request – Amendment 2

ATTACHEMENT 1
WRITTEN REQUEST (WR) – AMENDMENT 2

These studies investigate the potential use of nivolumab in the treatment of pediatric patients with solid tumors, specifically diseases that were metastatic at presentation or recurred after standard treatment. Despite the dramatic improvement in survival observed in the last 3-4 decades as a result of the multidisciplinary approach applied overall to pediatric solid malignancies, the outcome of patients with recurrent or metastatic tumors remains poor. Improvements in the outcomes of children with refractory solid malignancies through biologic therapies aimed at enhancing the patient's immune response against the tumor represent an area of interest.

Immuno-oncology agents are designed to target the same pathways tumor cells use to evade recognition and destruction by the immune system, increasing the immune system's capability to attack tumor cells ("checkpoint inhibitors"). Nivolumab is a fully human monoclonal immunoglobulin (IgG4 subtype) that targets the programmed death–1 (PD-1) cell surface membrane receptor. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens and self-antigens.

Nivolumab is administered intravenously (IV). The excipients used in the formulation are suitable for pediatric use.

The safety, pharmacokinetics (PK), and clinical activity of nivolumab have been assessed in multiple clinical studies and further investigations are ongoing in additional studies sponsored by Bristol-Myers Squibb (BMS) in adult patients, alone or in combination with ipilimumab and other investigational and approved products. Nivolumab is approved for the treatment of patients with advanced non-small cell lung cancer, melanoma, renal cell carcinoma, Hodgkin's lymphoma, head and neck squamous cell carcinoma, urothelial carcinoma, and hepatocellular carcinoma. Nivolumab in combination with ipilimumab is approved for the treatment of melanoma and renal cell carcinoma. Nivolumab is approved for patients 12 years or older with microsatellite instability (MSI-H) metastatic colorectal cancer.

Ipilimumab is a human monoclonal antibody that targets the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). Ipilimumab, as a single-agent, is approved for the treatment of adult patients with melanoma and in combination with nivolumab for the treatment of renal cell carcinoma Ipilimumab has been studied as a single-agent in a dose-escalation study conducted in pediatric patients. From this pediatric study, it appears that the types and per-patient incidence of immune-related adverse drug reactions are similar between pediatric patients 12 years of age or older and adult patients. The clinical experience in pediatric patients less than 12 years of age is limited and is still under investigation. The similarity of the safety profile between pediatric and adult patients suggests that adverse treatment effects of CTLA-4 blockade do not depend on patients' stage of development above age 12 years.

The efficacy of nivolumab, alone or in combination with ipilimumab, in pediatric patients aged ≥ 4 months to < 18 years will be determined by the studies outlined in this Written Request (WR).

FDA is not requesting studies in neonates because solid tumors are infrequently diagnosed in the neonatal period. Those rare tumors which are rarely diagnosed generally do not require chemotherapy intervention.

To obtain needed pediatric information on nivolumab, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Food and Drug Administration Amendments Act of 2007, and pursuant to section 351(m) of the Public Health Service Act (the PHS Act), as amended by the Biologics Price Competition and Innovation Act of 2009, that you submit information from the studies described below.

- *Nonclinical study(ies):*

  Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Biomarker studies:*

  Results of biomarkers studies, as well as initial clinical activity data may be used to prioritize pediatric tumor types for future clinical evaluation. Expression of PD-L1 on tumor cells may predict clinical responses to nivolumab. This hypothesis is being evaluated using a validated PD-L1 immunohistochemistry (IHC) assay and scoring method as part of the ongoing clinical studies in adult patients with solid tumors. In these studies, patients are not selected based on PD-L1 status, but PD-L1 IHC data will be retrospectively determined and analyzed for correlation with efficacy outcomes. The mechanisms of PD-L1-PD1 interaction between tumor cells and T cells in pediatric tumors are expected to be similar to that seen in adults.

  The results of on-going non-clinical studies of PD-L1 expression by individual cells and proportion of cells expressing PD-L1 within specific pediatric tumors by IHC on archived or newly-obtained tumor samples must be submitted to support the selection of specific pediatric tumors for focused clinical investigation to be included in the clinical studies described below, since PD-L1 expression by pediatric tumors has not been well characterized to date. A spectrum of pediatric solid tumors including Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, Non-Hodgkin's lymphoma) will be evaluated using archival material.

  If sufficient tissue is available following PD-L1 assessment, analysis of the presence and functional status of tumor-infiltrating lymphocytes (TIL) will be performed, to further elucidate tumor types that may have a higher likelihood of eliciting an immune response and which may predict response to nivolumab.

- *Clinical studies:*

  Study 1: Multicenter, open-label Phase 1/2 study of nivolumab monotherapy and in combination with ipilimumab. The study is planned to enroll 70 subjects and consists of 4 portions:

  - Part A: Administration of nivolumab as a single agent to characterize PK and evaluate safety/adverse reaction profile.
  - Part B: Administration of nivolumab as a single agent to characterize anti-tumor activity in one of more pediatric tumor types.
  - Part C: Administration of nivolumab in combination with ipilimumab to characterize the adverse reaction profile and determine tolerable dosage schedules for the combination.
  - Part D: Administration of nivolumab in combination with ipilimumab in one or more tumor types using the recommended Phase 2 doses (RP2D) for the combination.

  - *Indication(s) to be studied:*
    - Part A: Patients with refractory or relapsed solid malignant tumors.

      Part B: Patients with Ewing sarcoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma, Hodgkin lymphoma, Non-Hodgkin lymphoma, and melanoma enrolled in separate cohorts. Additional tumor types may be added in additional cohorts based on results from the ongoing biomarker study, relevant adult experience, or unmet medical needs.
    - Part C: Patients with refractory or relapsed solid malignant tumors.
    - Part D: Patients with selected disease-specific cohorts (neuroblastoma, rhabdomyosarcoma, Non-Hodgkin lymphoma, osteosarcoma or Ewing sarcoma).

  - *Age Group in which the study will be performed:*
    - Part A: Children and adolescents from 1 to <18 years of age.
    - Part B, neuroblastoma, rhabdomyosarcoma, refractory Ewing sarcoma or peripheral primitive neuroectodermal tumors, Hodgkin lymphoma, Non-Hodgkin lymphoma cohorts: Children, adolescents and young adults from 1 to ≤30 years of age.
    - Part B, melanoma cohort: Children and adolescents from 1 to <18 years of age.
    - Part C: Children and adolescents from 1 to <18 years of age.
    - Part D1-D6: Children, adolescents and young adults from 1 to ≤ 30 years of age.

    Patients <1 year of age will not be enrolled due to rarity of the specific cancer types to be studied in infants < 1 year of age and since only relapsed and refractory patients will be studied.

At least three patients will be enrolled in the first dose level. Twelve patients are planned for the second dose level in Parts A and C, with at least 6 patients from 1 to <12 years of age and 6 patients from 12 to <18 years of age. However, the final protocol including the number of patients in each part of the study will be agreed upon with FDA prior to enrollment of the first subject in the study.

- *Objectives of Study:*
  - Primary objectives:
    - Part A: to determine the adverse reaction profile of nivolumab in patients aged 1 to < 18 years of age.
    - Part B: to assess and describe any preliminary evidence of anti-tumor activity in specific pediatric tumor types in patients aged 1 to <18 years of age.
    - Part C: to determine the adverse reaction profile of the nivolumab, when administered in combination with ipilimumab in patients aged 1 to <18 years of age.
    - Part D: to assess and describe any preliminary evidence of anti-tumor activity of nivolumab in combination with ipilimumab in specific pediatric tumor types in patients aged 1 to < 30 years of age.
  - Secondary objectives: to assess the PK and immunogenicity of nivolumab.
  - Descriptive statistical analysis will be used to describe the study results for each of the four Parts; cohorts in Part B will be analyzed individually and not pooled for analysis of Part B.

- *Regimen:*

  The final protocol for Study 1, including the dosing regimen, will be agreed upon by FDA prior to enrollment of the first subject in the study.
  - Nivolumab monotherapy safety and tumor specific expansion portions: nivolumab monotherapy administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression.
  - Nivolumab and ipilimumab combination portion: The RP2D has been established as nivolumab 3 mg/kg IV and ipilimumab 1 mg/kg IV every 3 weeks for a maximum of 4 doses followed by nivolumab as a single agent at 3 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity.

- *Drug specific safety concerns:*

  Based on the immune-mediated mechanism of action, BMS anticipates that the nature and frequency of the expected nivolumab-related adverse events would be similar in children and adults, but the activity and safety of nivolumab as well as appropriate doses for use in younger pediatric patients needs to be identified.

Procedures to mitigate risks instituted across the clinical program for nivolumab in adults include guidance to investigators over potential risks regarding management of treatment-induced autoimmune disease affecting the lungs, gastrointestinal tract, liver, endocrine system, skin, and kidneys. These guidelines include nivolumab dosing recommendations and treatment interventions (e.g., corticosteroid use). Similar guidelines are anticipated to be applicable in children to mitigate risks, with possible additional monitoring for potential toxicities specific to the pediatric population, including potential effects on the endocrine system, immune status and growth and development.

Study 2*:* Randomized, active-controlled trial to evaluate the safety and efficacy of nivolumab and of nivolumab administered in combination with ipilimumab for the treatment of patients from 0 to <18 years of age diagnosed with specific solid tumors, based on results of Study 1. Elements of study design such as endpoints, choice of comparator, dosage and treatment regimen, sample size and eligibility criteria will depend on the pediatric tumors chosen for further study. Final protocol and statistical analysis plan for Study 2, and any amendments to the WR, will be agreed upon with FDA prior to enrollment of the first subject in the study.

- *Indication(s) to be studied:*

  Pediatric patients diagnosed with specific solid tumors determined based on results of Study 1.

- *Age Group in which the study will be performed:*

  Patients from 0 to <18 years of age.

- *Objectives of Study:*

  - Primary objective: To evaluate the clinical benefit of nivolumab as a single agent or administered in combination with ipilimumab relative to standard of care therapy in one or more specific pediatric tumors.
  - Secondary objectives: To evaluate objective response rates of nivolumab as a single agent or administered in combination with ipilimumab relative to standard of care therapy; to evaluate safety and tolerability; to assess pharmacokinetics; and to assess immunogenicity.

- *Statistical information, including power of study(ies) and statistical assessments:*

  Descriptive statistical analysis will be used to describe the study results for all parts; cohorts in Part B will be analyzed individually and not pooled for analysis of Part B. A Simon's optimal two stage design will be used for Parts B1-6 and B8 (B7 is an additional non-statistical cohort for patients with unresectable, metastatic, relapsed or refractory melanoma will remain open for enrollment). In the event that a cohort in a given disease group in Part B is completed after Stage 1 because no responses are observed, a cohort in the same disease group will open to up to 10 evaluable patients in Part D. Nivolumab will not be considered of sufficient interest for further

evaluation in a disease category if the true response rate is 5% and will be considered to demonstrate sufficient activity if the true response rate is 25%. If nivolumab has a true response rate of 5%, the rule described above will identify it of sufficient activity for further study with probability 0.07 (type I error), and the trial will have an expected sample size of 14 with 60% probability of early termination. If nivolumab has a true response rate of 25%, the rule described above will identify it of sufficient activity for further study with probability 0.88 (power against the alternative hypothesis P =0.25).

- *Regimen:*

  Dose and regimen to be selected based on the results of Study 1. The PK analysis using data from Study 1 must be completed before the efficacy trial to inform dosing. Results of Study 1 must be reported to the FDA prior to the initiation of additional clinical studies.

- *Drug specific safety concerns:*

  Refer to previous section under Study 1.

- *Pharmacokinetic Analyses:*

  Upon completion of Part A of Study 1, a population pharmacokinetic (PPK) model will be developed to characterize the PK of nivolumab as a single-agent in pediatric patients. During development, the PPK model will use data from Study 1 and selected trials in adults with cancer.

  The PPK model-based simulation will be employed to assure that the nivolumab dosing regimen as a single-agent and in combination with ipilimumab achieves exposures similar to that produced in adults with the recommended single-agent dosing regimen for treatment of melanoma; these data will be considered in the design of Study 2. This model will be updated with data from Study 1, the trial evaluating the safety and activity of ipilimumab in pediatric patients, and selected trials of ipilimumab in adults with cancer. Data from all completed trials in adults and pediatric patients may be combined to explore exposure-response relationships for measures of safety and activity in pediatric patients.

- *Representation of Ethnic and Racial Minorities:*

  The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities.

- *Extraordinary results:*

  In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this WR. If you believe this is the case, you must contact the FDA to seek an amendment. It is solely within the FDA's discretion to decide whether it is appropriate to issue an amendment.

- *Biological product information:*

  - *dosage form:*

    nivolumab is supplied in a 100 mg/10 mL vial and ipilimumab is supplied as a 200 mg/40 mL vial. The excipients used in the formulation are suitable for pediatric use.

  - *route of administration:*

    intravenous administration.

  - *regimen*

    - Study 1, Parts A and B: nivolumab 3 mg/kg administered IV over 60 minutes every 2 weeks until progression.
    - Study 1, Part C: The RP2D has been established as nivolumab 3 mg/kg IV and ipilimumab 1 mg/kg IV every 3 weeks for a maximum of 4 doses followed by nivolumab as a single agent at 3 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity.
    - Study 1, Part D: This portion of Study 1 will evaluate the RP2D of 3 mg/kg of nivolumab IV in combination with 1 mg/kg ipilimumab IV every 3 weeks for a maximum of 4 doses followed by 3mg/kg nivolumab as a single agent given every 2 weeks until disease progression or unacceptable toxicity.

- *Labeling that may result from the study(ies):*

  You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the FD&C Act, regardless of whether the study(ies) demonstrate that nivolumab is safe, pure, and potent, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the FD&C Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted:*

  You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the FD&C Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 600.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf.

- *Timeframe for submitting reports of the study(ies):*

  Reports of the above studies must be submitted to the Agency on or before December 31, 2022 for Study 1 and on or before December 31, 2025 for Study 2. Please keep in mind that pediatric exclusivity can attach only to existing exclusivity, if any, that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, if there is unexpired exclusivity that is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such exclusivity is otherwise due to expire.

If FDA has not determined whether nivolumab is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this formal pediatric WR, nor any request for exclusivity made by you confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.

- *Response to Written Request:*

  Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC WRITTEN REQUEST STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a biologics license application (BLA) or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Office of New Drugs, Immediate Office, Therapeutic Biologics and Biosimilars Team, 10903 New Hampshire Ave, Building 22, Mail Stop 6411, Silver Spring, MD 20993. If you wish to fax it, the fax number is 301-796-9855.

In accordance with section 505A(k)(1) of the FD&C Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this WR within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the WR (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this WR, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this WR are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GREGORY H REAMAN
07/03/2018