ONCOLOGIC DRUGS ADVISORY COMMITTEE
BRIEFING DOCUMENT

SINTILIMAB INJECTION

INDICATION: FIRST-LINE TREATMENT OF STAGE IIIB, IIIC, OR STAGE IV NONSQUAMOUS NSCLC WITH NO EGFR OR ALK GENOMIC TUMOR ABERRATIONS

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LIST OF ABBREVIATIONS

Abbreviation or Special Term	Definition
1L	First-line
1L-C	First-line combination with chemotherapy
2L	Second-line
AA	Accelerated approval
ADA	Antidrug antibody
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
Atezo	Atezolizumab
AUC	Area under the concentration-time curve
Bev	Bevacizumab
BIRRC	Blinded Independent Radiographic Review Committee
BLA	Biologics License Application
Carbo	Carboplatin
CD	Cluster of differentiation
CDx	Companion diagnostic
CFR	Code of Federal Regulations
Chemo	Chemotherapy
cHL	classic Hodgkin's lymphoma
$C_{H/L}$	Constant domain heavy/light
CI	Confidence interval
Cis	Cisplatin
CL	Clearance
C_{max}	Maximum observed concentration
$C_{max,4}$	Individual maximum concentrations in Cycle 4
$C_{max,ss}$	Steady-state maximum concentration
C_{min}	Minimum observed concentration
$C_{min,1}$	Trough concentration in Cycle 1
CNS	Central nervous system
CRF	Case report form
CSCO	Chinese Society of Clinical Oncology
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-antigen 4

Abbreviation or Special Term	Definition
CV%	Percent coefficient of variation
D	Day
DCO	Data cutoff
DCR	Disease control rate
Doc	Docetaxel
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ESCC	Esophageal squamous cell carcinoma
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FPFV	First patient first visit
F/U	Follow-up
GCP	Good Clinical Practice
GE	Gastroesophageal
Gem	Gemcitabine
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HCC	Hepatocellular carcinoma
HL	Hodgkin's lymphoma
HR	Hazard ratio
IC	PD-L1 stained tumor-infiltrating immune cells
ICH	International Council on Harmonisation
ICI	Immune checkpoint inhibitor
ID	Identification
iDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IND	Investigational New Drug
Ipi	Ipilimumab
irAE	Immune-related adverse event
IRR	Infusion-related reaction
ITT	Intent-to-treat
IV	Intravenous
K_D	Dissociation constant
LPLV	Last patient last visit
mAb	Monoclonal antibody

Abbreviation or Special Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of patients
Nab	Nanoparticle albumin-bound
NCA	Noncompartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NET	Neuroendocrine tumor
Nivo	Nivolumab
NK	Natural killer
NMPA	National Medical Products Administration
NOAEL	No-observed-adverse-effect level
NR	Not reached
NSCLC	Non-small cell lung cancer
nsqNSCLC	Nonsquamous non-small cell lung cancer
OBF	O'Brien-Fleming boundary
ODWG	Organ Dysfunction Working Group
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
Pacl	Paclitaxel
PD	Pharmacodynamics; Progressive disease
PD-1	Programmed death-1
PD-1/L1	Programmed death-1/programmed death-ligand 1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
Pem	Pemetrexed
Pembro	Pembrolizumab
PFS	Progression-free survival
Ph	Phase
PK	Pharmacokinetic(s)
$PM_{2.5}$	Fine particulate matter ≤2.5 microns in diameter)
PMC	Post-marketing commitment
PopPK	Population pharmacokinetics
PPS	Per-Protocol Set
PS	Performance status
PSUR	Periodic Safety Update Report

Abbreviation or Special Term	Definition
PT	Preferred term
Q	Quartile
Q2W	Every 2 weeks
Q3W	Every 3 weeks
R	Randomization
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
RPSFTM	Rank-preserving structural failure time model
r/r	Relapsed/refractory
SA	Sensitivity analysis
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
sqNSCLC	Squamous non-small cell lung cancer
SS	Steady state; Safety Set
$t_{1/2}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TKI	Tyrosine kinase inhibitor
TNM	Tumor, node, metastasis
TPS	Tumor proportional score
TRAE	Treatment-related adverse event
TTR	Time to response
US	United States
VEGFR2	Vascular endothelial growth factor receptor 2
$V_{H/L}$	Variable loop heavy/light

1.0 EXECUTIVE SUMMARY

Innovent Biologics, is a publicly traded, global pharmaceutical company headquartered in Suzhou, China, with a mission to bring high-quality, affordable medicines to global patients. Innovent is seeking United States (US) marketing approval of sintilimab in combination with pemetrexed and platinum-based chemotherapy for the treatment of first-line nonsquamous non-small cell lung cancer (NSCLC) without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. In 2015, Innovent and Eli Lilly entered into a collaboration agreement for the co-development of multiple products in China, including sintilimab. In 2020, Innovent and Lilly broadened their strategic alliance to pursue sintilimab approval globally.

Sintilimab is a potent selective, anti-programmed death-1 (PD-1) immune checkpoint inhibitor and is approved for multiple indications in China. Based on the results from a pivotal Phase 3 study "A Randomized, Double-blind, Phase 3 Study Evaluating the Efficacy and Safety of Sintilimab or Placebo in Combination With Pemetrexed and Platinum-Based Chemotherapy in the First-line Treatment of Advanced or Recurrent Nonsquamous Non-Small Cell Lung Cancer" (ORIENT-11), which was conducted in mainland China, sintilimab in combination with pemetrexed and platinum chemotherapy as first-line treatment of patients with NSCLC with no EGFR or ALK genomic tumor aberrations was approved by the National Medical Products Administration (NMPA) on 03 February 2021. The data summarized in this briefing document support a positive benefit-risk for sintilimab for use in patients with Stage IIIB, IIIC, or IV nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations. In addition, data are presented to demonstrate that the results of ORIENT-11 are applicable to US patients and hence the criteria for use of foreign data as the sole basis for US marketing approval (Code of Federal Regulations (CFR) Section 21 CFR 314.106(b)) have been met.

1.1 Proposed Indication and Dose

Proposed indication	TRADENAME in combination with pemetrexed and platinum-based chemotherapy is indicated for the first-line treatment of patients with Stage IIIB, IIIC, or Stage IV nonsquamous non-small cell lung cancer (NSCLC) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.
Proposed dose	The recommended dosage of TRADENAME is 200 mg administered as an intravenous infusion over 30 minutes to 60 minutes every 3 weeks. Continue TRADENAME until disease progression,unacceptable toxicity, or a maximum of 24 months.

1.2 Regulatory Considerations

Innovent met with the US Food and Drug Administration (US FDA) on 3 occasions in 2020 prior to submitting the Biologics License Application (BLA) in March of 2021. At those meetings, agreement was reached on the various elements necessary for the submission including details regarding the safety analysis plans, proposal for immune-related adverse event (irAE) evaluation, electronic data sets, and submission of updated progression-free survival (PFS) and overall survival (OS) data as part of the 4-month Safety Update. Given that ORIENT-11 was conducted solely in China, FDA requested that the submission "include a discussion of how the study population adequately represents the U.S. patient population in terms of disease characteristics,

sex, race/ethnicity, age, and standards of care." Additionally, FDA indicated that they "may make a request for post-marketing data in a population representative of the US population as a post-marketing commitment (PMC)". Since that time, Innovent has proactively proposed a study for FDA consideration (Type C meeting, October 2021) that was intended to generate data in a diverse NSCLC population representative of the US population.

Section 21 CFR 314.106(b) outlines 3 requirements for use of foreign data as the sole basis for marketing approval:

- The foreign data are applicable to the US population and US medical practice.
- The studies have been performed by clinical investigators of recognized competence.
- The data may be considered valid without the need for an onsite inspection by the US FDA, or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an onsite inspection or other appropriate means.

With respect to the first requirement, evidence supporting the applicability of the data from ORIENT-11 to the US population and medical practice is summarized in Section 1.7 and Section 8.0. Part of this evaluation includes characterization of sintilimab's sensitivity to ethnic factors as described in International Conference on Harmonisation (ICH) Guidance E5 (Ethnic Factors in the Acceptability of Foreign Clinical Data).[1]

Regarding the latter 2 requirements, ORIENT-11 was a well-designed trial conducted in accordance with Good Clinical Practice (GCP) and Western standards at 48 academic sites across China in a wide range of large, medium, and small cities. The clinical investigators were GCP-certified medical oncologists with prior Phase 3 clinical trial experience. Various procedures were employed to ensure data integrity, including site audits performed by an Independent Quality Unit, site level oversight by an Ethics Committee, and robust data collection and handling by a Clinical Research Organization. Progression-free survival was assessed by a Blinded Independent Radiographic Review Committee (BIRRC) through a globally recognized and validated vendor (PAREXEL), and an independent Data Monitoring Committee (iDMC) reviewed the interim analysis results. Finally, FDA has completed both a Sponsor GCP assessment and multiple GCP site inspections to evaluate the integrity of the data and compliance to GCPs, while Good Manufacturing Procedure (GMP) manufacturing site inspections were yet to be scheduled by FDA at the time of the writing of this briefing document.

1.3 Treatment Landscape for Advanced Nonsquamous NSCLC in the US and China

1.3.1 Epidemiology of NSCLC in US and China

Lung cancer was the leading cause of cancer-related death in the US in 2021.[2] An estimated 235,000 new cases and an estimated 132,000 deaths occur annually. The non-small cell histology accounts for the majority (85%) of lung cancers.[3] In the US, the predominant histology has shifted from squamous to adenocarcinoma associated with decreasing incidence of smoking,[4] and the same is true in China, where adenocarcinoma now dominates.[5]

The main difference between Chinese and US lung adenocarcinoma cases is the frequency of EGFR-activating mutations (~50% in China[6,7] versus 15% in US whites and 12% in US blacks[8]); however, ORIENT-11 and multiple Phase 3 studies of checkpoint inhibitor use in first-line NSCLC excluded patients with EGFR-mutated NSCLC because their standard treatment is

EGFR-targeted therapy. Importantly, in patients without dominant activating mutations, such as EGFR, tumor genetic sequencing showed extensive similarity between cases from China and the US.[9,10] When patients with EGFR mutations and other oncogenic alterations are excluded, the characteristics of patients with Stage IV NSCLC in the US and China entered into registrational randomized trials are very similar with regard to clinical characteristics such as age, nonsquamous histology, programmed death-ligand 1 (PD-L1) status, and Eastern Cooperative Oncology Group (ECOG) performance status.

1.3.2 Management of NSCLC in US and China

Diagnostic criteria and treatment standards for nonsquamous NSCLC lacking oncogenic alterations are similar in the US and China.[11-13] Most patients present with advanced disease, resulting in limited treatment options and a poor prognosis. Currently, in the US, patients without oncogenic alterations are typically treated, depending on PD-L1 status, with either single-agent immunotherapy, the combination of a PD-1/L1 monoclonal antibody (mAb) plus chemotherapy, or a combination of PD-1 plus cytotoxic T-lymphocyte-antigen 4 (CTLA-4) mAbs, as first-line therapy.[11] Before the approval of checkpoint inhibitors in both US and China, pemetrexed and platinum-based chemotherapy was the most widely used therapy for nonsquamous NSCLC. Although several PD-1/L1) agents have since been approved in the US for first-line treatment of NSCLC, only pembrolizumab is approved in combination with pemetrexed and platinum-based chemotherapy. The combination of a checkpoint inhibitor (pembrolizumab in the US and sintilimab in China) with pemetrexed and platinum-based chemotherapy is currently the most widely used chemoimmunotherapy regimen. Chemoimmunotherapy has dramatically improved clinical outcomes versus chemotherapy alone. Refer to Section 2.0 for details. The efficacy of chemoimmunotherapy has not shown ethnic sensitivity.[14,15] Section 8.2 describes in more detail the lack of ethnic sensitivity of these therapies; specifically, Asian patients with metastatic NSCLC treated with immune checkpoint inhibitors demonstrated relatively consistent OS and PFS benefits compared to non-Asian patients.[16]

1.4 Overview of Sintilimab

Sintilimab is a novel recombinant, fully human, immunoglobulin (Ig) G4 mAb that binds to the PD-1 receptor with high affinity (dissociation constant [K_D] of 0.07 nM) and potently blocks its interaction with its ligands PD-L1 and PD-L2, thereby reactivating tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and enhancing antitumor immunity. Refer to Section 3.0 for details.

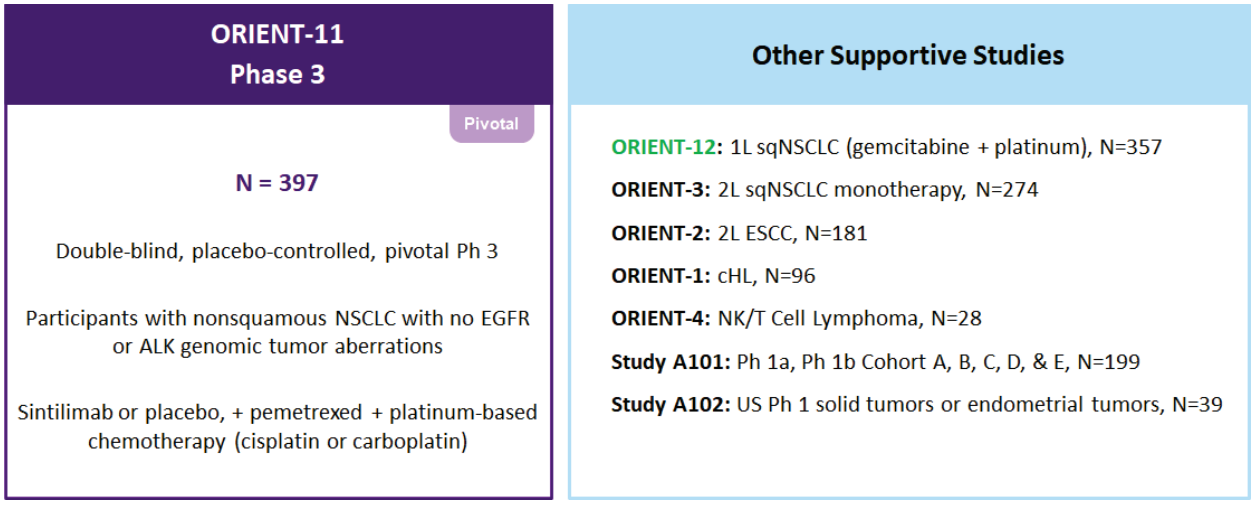
1.5 Sintilimab Clinical Development Program

As of November 2021, sintilimab has been evaluated in more than 4,000 clinical trial patients across multiple tumor types, including more than 600 patients with nonsquamous NSCLC. In addition, cumulatively, more than 170,000 patients have been treated with sintilimab in the postmarketing setting across various tumor types in China.

The efficacy and safety of sintilimab in combination with pemetrexed and cisplatin or carboplatin in patients with Stage IIIB/C or Stage IV nonsquamous NSCLC was demonstrated in the pivotal Phase 3 ORIENT-11 study and supported by data from Cohort D of the Phase 1b Study A101 (A101) (**Figure A**). Both studies were conducted in mainland China. In addition, the

Phase 1 Study A102 (A102) provides supportive safety and pharmacokinetics (PK) data for sintilimab in US patients. These 3 studies plus 5 other supportive studies across various other tumor types, totaling 1,045 sintilimab patients, form the foundation of the safety database for sintilimab.

Figure A Sintilimab Clinical Studies Supporting the Nonsquamous NSCLC Indication



Abbreviations: 1L = first-line; 2L = second-line; ALK = anaplastic lymphoma kinase; cHL = classic Hodgkin's lymphoma; EGFR =epidermal growth factor receptor; ESCC = esophageal squamous cell carcinoma; N = number of patients; NK = natural killer; NSCLC = non-small cell lung cancer; Ph = Phase; sqNSCLC = squamous non-small cell lung cancer; US = United States.

1.5.1 Summary of Clinical Pharmacology

Across the sintilimab dose range of 1 to 10 mg/kg in patients with advanced solid tumors, following a single infusion, the occupancy of PD-1 receptor by sintilimab on circulating T cells was >95% (Figure 7). Even at the lowest dose of 1 mg/kg, receptor occupancy was consistently high over the 28-day period, indicating that there is a wide therapeutic dose range for efficacy. This implies that the 200 mg every 3 weeks (Q3W) dose, which is approximately equivalent to 2.6 mg/kg (based on US patient population median weight of 77 kg[17]), has at least a 2-fold margin to deliver a full pharmacologic effect in both Chinese and US populations.

A Phase 1b study (A102) was conducted to characterize the PK of sintilimab in 39 US patients and allowed comparison to a cohort of 463 Chinese patients (Figure 11). Sintilimab demonstrated a comparable PK profile between Chinese and US patients across the body weight range of 37 to 124 kg.

Sintilimab has demonstrated linear PK over the dose range of 1 to 10 mg/kg, with a half-life ($t_{1/2}$) of approximately 20 days. Intrinsic factors such as race, tumor type (Figure 10), age, creatinine clearance, mild hepatic impairment per National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria, ECOG performance status, and antidrug antibodies (ADAs) had no effect on sintilimab PK. The combined effect of body weight, sex, and baseline albumin concentration accounted for <20% of the total variability in exposure. The median weight difference between the US and China cohorts was approximately 15 kg. This would result in approximately 10% lower exposure in the US population. Given the linear PK over the dose range of 1 to 10 mg/kg and the 2-fold margin of PD-1 receptor occupancy, these factors,

including the effect of body weight on PK, are not clinically relevant. These findings for sintilimab PK are consistent with what would be anticipated for a fully human IgG4 mAb.[18]

Refer to Section 5.0 for details of clinical pharmacology.

1.5.2 Summary of Clinical Efficacy

The efficacy of sintilimab in combination with pemetrexed and platinum-based chemotherapy as first-line treatment for nonsquamous NSCLC was demonstrated in the pivotal Phase 3 ORIENT-11 study. Sintilimab plus chemotherapy demonstrated clinically meaningful treatment effects across all endpoints including PFS, OS, objective response rate (ORR), and duration of response (DOR) compared with chemotherapy alone. Key efficacy results are summarized below. Refer to Section 6.0 for a detailed efficacy presentation. The dosing regimen evaluated in ORIENT-11 was selected based on the Phase 1 dose-escalation trial A101.

1.5.2.1 Phase 1 Study A101 (Cohort D, nsqNSCLC)

Study A101 was an open-label, single-arm, multicenter, Phase 1, dose-escalation and expansion study of sintilimab administered alone or in combination with chemotherapy in patients with advanced cancers. Based on the safety, PK profile, and receptor occupancy data, 200 mg Q3W was determined as the recommended Phase 2 dose, and this dosing regimen was used for the expansion cohorts. Twenty-one treatment-naive patients with inoperable Stage IIIB or Stage IV (based on American Joint Committee on Cancer [AJCC] Cancer Staging Manual, 7th edition) nonsquamous NSCLC without genomic aberrations were enrolled into expansion Cohort D and treated with sintilimab 200 mg Q3W in combination with pemetrexed and cisplatin.

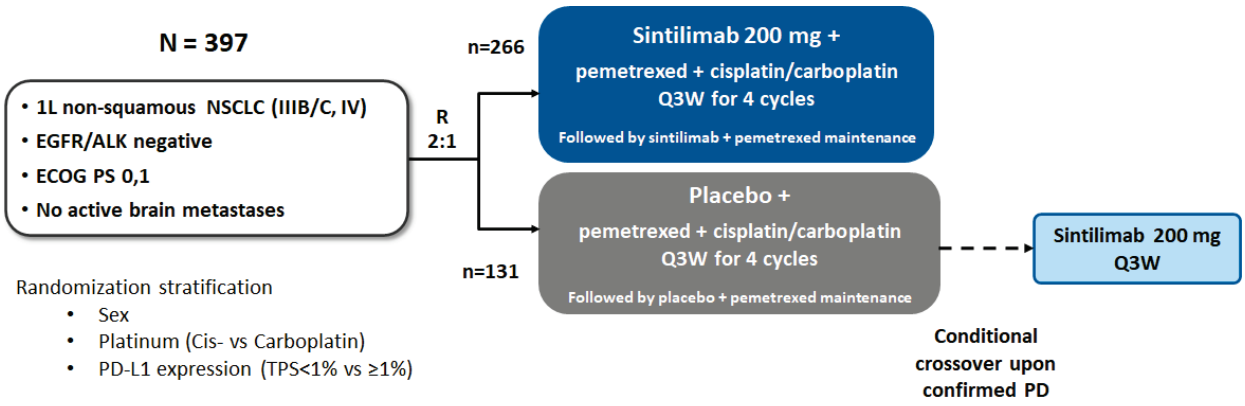
The confirmed ORR was 52.4% (95% confidence interval [CI]: 29.8, 74.3), and median DOR has not been reached. The median PFS was 12.4 months and the median OS was 18.6 months. Study A101 provided early proof-of-concept data and led to the initiation of ORIENT-11.

1.5.2.2 Pivotal Phase 3 ORIENT-11 Study

Study Design

ORIENT-11 was a randomized, double-blind, placebo-controlled, Phase 3 study conducted in mainland China. The study was designed to assess the addition of sintilimab to pemetrexed and physician's choice of platinum-based chemotherapy (cisplatin or carboplatin) as first-line treatment of patients with Stage IIIB/C (who were ineligible for radical surgery or chemoradiation with curative intent) or Stage IV (based on AJCC Cancer Staging Manual, 8th edition) nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations (**Figure B**). Eligible patients were stratified by sex, PD-L1 expression level (tumor proportion score [TPS] <1% vs ≥1%), and type of platinum-based chemotherapy (cisplatin vs carboplatin) and randomized 2:1 to sintilimab (200 mg Q3W) plus pemetrexed and platinum-based chemotherapy (n=266) or placebo plus pemetrexed and platinum-based chemotherapy (n=131). Patients initially randomized to the placebo combination arm were allowed to conditionally crossover to receive sintilimab monotherapy if confirmed disease progression was observed.

Figure B ORIENT-11 Study Schema



Abbreviations: 1L = first-line; ALK = anaplastic lymphoma kinase; BIRRC = Blinded Independent Radiographic Review Committee; DCR = disease control rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; N = number of patients; n = number of patients in specified category; NSCLC = non-small cell lung cancer; ORR =objective response rate; OS = overall survival; PD = progressive disease; PD-L1 = programmed death-ligand 1; PFS =progression-free survival; PS = performance status; Q3W = every 3 weeks; R = randomization; TPS =tumor proportional score; TTR = time to response.
Enrollment period: August 2018-July 2019.

The primary endpoint was PFS as assessed by BIRRC using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. PFS was selected as primary endpoint because it is a clinically relevant endpoint in NSCLC and not confounded by crossover, considering the study allowed crossover to sintilimab monotherapy by design. Secondary endpoints were OS, ORR, disease control rate (DCR), time to response (TTR), DOR, and safety. Assuming a substantial PFS improvement (hazard ratio [HR]=0.65), a target number of 263 PFS events were required to provide approximately 90% power under a 2-sided $\alpha = 0.05$. The primary PFS interim analysis was planned after 184 events (70%) were observed. The interim analysis 2-sided alpha boundary of 0.015 was based on an O'Brien-Fleming spending function. Alpha control for secondary endpoints, including OS, was not prespecified in the statistical analysis plan. The time of final OS analysis was defined in the protocol amendment post interim analysis as approximately 2 years after last patient randomized or when 65% patients died, whichever occurred first. ORIENT-11 used an iDMC composed of 3 independent external experts (2 oncologists and a biostatistician) from major academic institutions or cancer centers in China. All iDMC members had served as DMC members on other Phase 3 studies, including multiregional studies.

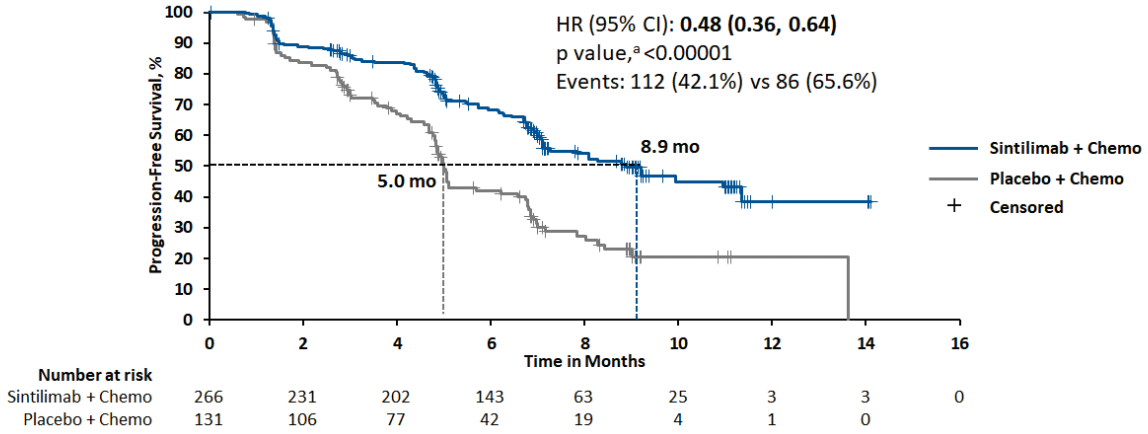
Results

A total of 397 patients were randomized between August 2018 and July 2019 and treated with sintilimab plus chemotherapy (n=266) or placebo plus chemotherapy (n=131). Most patients (~90%) had Stage IV disease. At the interim PFS analysis (data cutoff [DCO], 15 November 2019), the median duration of follow-up was 8.9 months (range, 0.6 to 14.8 months). Overall, 43.2% of patients in the sintilimab arm and 64.9% of patients in the placebo arm had discontinued study treatment. The most common reason for discontinuation was progressive disease. At the interim analysis, 27% of patients in the placebo arm had crossed over per protocol to receive sintilimab monotherapy. Demographic and baseline disease characteristics were generally similar between the treatment arms.

Primary Efficacy Endpoint

At the interim PFS analysis, treatment with sintilimab plus chemotherapy demonstrated a statistically significant and clinically meaningful improvement in PFS, compared with placebo plus chemotherapy (HR=0.48; 95% CI: 0.36, 0.64; p<0.00001) (**Figure C**). The Kaplan-Meier estimates for PFS showed an early separation between the treatment arms beginning at approximately 1.5 months that was sustained throughout the observation period. Consistent PFS benefit was observed across all prespecified subgroups and the ancillary subgroups of Stage IIIB/C (HR=0.17; 95% CI: 0.06, 0.48) and Stage IV (HR=0.53; 95% CI: 0.39, 0.72) disease.

Figure C Progression-Free Survival by BIRRC (ITT Population) – ORIENT-11



Abbreviations: BIRRC = Blinded Independent Radiographic Review Committee; Chemo = chemotherapy; CI = confidence interval; CSR = clinical study report; HR = hazard ratio; ITT = intent-to-treat.
[a] Interim analysis α boundary based on 198 PFS events is 0.01958
Data cutoff date: 15 November 2019.

Secondary Efficacy Endpoints

Consistent treatment benefits were observed across all relevant secondary endpoints, including OS, ORR, DCR, and DOR, demonstrating the robust benefit to patients treated with sintilimab plus chemotherapy compared with those treated with placebo plus chemotherapy.

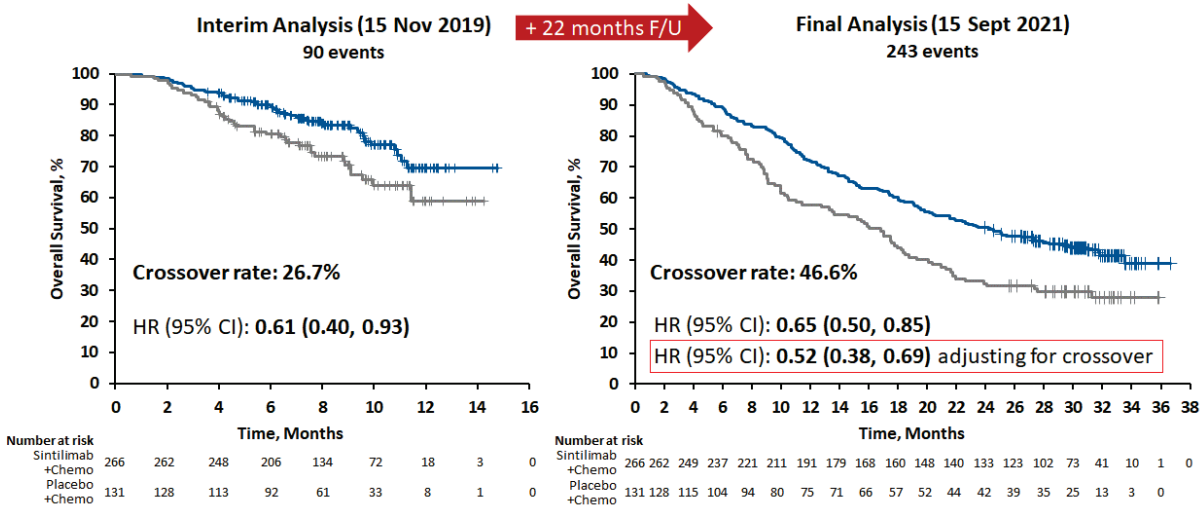
Overall Survival

Four survival analyses were conducted. The first was conducted at the time of the interim PFS analysis (primary PFS endpoint), the second 6 months later with FDA agreement, the third at the time of the 120-day Safety Update, and the fourth at the final analysis. The OS HR was consistent across these analyses, ranging from 0.6 to 0.65, despite the increase in crossover rate over time.

At the interim OS analysis (DCO, 15 November 2019), OS data were not mature. Fifty-one events (19.2%) occurred in the sintilimab arm and 39 events (29.8%) in the placebo arm. The Kaplan-Meier estimates for OS showed an early separation with an HR of 0.61 (95% CI: 0.40, 0.93) (**Figure D**). At the final OS analysis (DCO, 15 September 2021), with median follow-up of 31 months, there were 151 events (56.8%) in the sintilimab arm and 92 events (70.2%) in the placebo arm. Median OS was 24.2 months in the sintilimab arm and 16.8 months in the placebo arm. Despite the high crossover rate (47%), the OS treatment effect continued to favor the

sintilimab arm (HR=0.65; 95% CI: 0.50, 0.85). After adjustment for the cross over based on rank-preserving structural failure time model, the OS HR was 0.52 (95% CI: 0.38, 0.69).

Figure D Overall Survival (ITT Population) – ORIENT-11



Abbreviations: CI = confidence interval; F/U = follow-up; HR = hazard ratio; ITT = intent-to-treat.

Gatekeeping for secondary endpoints was not prespecified. To better interpret the OS results, we retrospectively calculated the O'Brien-Fleming and Bonferroni boundaries to adjust for multiplicity. At the time of final analysis, the observed p value based on the log-rank test was 0.00135, which is smaller than both the O'Brien-Fleming boundary (0.04058) and Bonferroni boundary (0.01250). This indicates that had OS been tested hierarchically after meeting the primary endpoint, it would have met conventional statistical significance.

Objective Response (RECIST 1.1)

At the interim analysis in the intent-to-treat (ITT) population, the BIRRC-assessed confirmed ORR was higher in the sintilimab arm than in the placebo arm (51.9% vs 29.8%). The BIRRC-assessed DCR was also improved in the sintilimab arm compared with the placebo arm (86.8% vs 75.6%). The BIRRC-assessed median DOR was not reached in the sintilimab arm and was 5.5 months (95% CI: 4.1, 10.9) in the placebo arm (HR=0.54; 95% CI: 0.29, 1.0). Sintilimab plus chemotherapy showed a higher and more durable response, which contributed to prolonged PFS and OS.

1.5.2.3 Efficacy Conclusions

In the Phase 3 ORIENT-11 study, sintilimab in combination with chemotherapy demonstrated clinically meaningful treatment effects across all endpoints tested, including PFS, OS, and ORR, compared with chemotherapy alone. The study met the primary endpoint of PFS at the interim efficacy analysis (HR=0.48; 95% CI: 0.36, 0.64; p<0.00001), demonstrating statistically significant and clinically meaningful benefit of substantial magnitude to support full marketing approval. The treatment effect of sintilimab was consistent across all prespecified subgroups. The OS analysis demonstrated a robust and clinically meaningful treatment effect, despite the high crossover rate of 47% at the final analysis (HR=0.65; 95% CI: 0.50, 0.85).

1.5.3 Summary of Clinical Safety

The combination of sintilimab and chemotherapy was generally well tolerated and manageable with dose interruption and supportive care in ORIENT-11. The overall safety profile is considered acceptable and consistent with that of approved PD-1/L1 inhibitors, with no new safety signal identified. The incidence of immune-mediated adverse events (AEs) was similar to that expected during the treatment of lung cancer participants with immunotherapy agents in combination with chemotherapy. Key safety results are summarized below. Refer to Section 7.0 for a detailed safety presentation.

1.5.3.1 Exposure

In ORIENT-11, all 397 randomized patients received at least 1 dose of study therapy. The majority of patients in both treatment arms completed 4 cycles of sintilimab plus chemotherapy (88.3%) or placebo plus chemotherapy (83.2%). The median duration of exposure was longer for sintilimab than placebo (31.0 vs 24.0 weeks, respectively). Similarly, the median duration of pemetrexed exposure was longer in the sintilimab arm than in the placebo arm (31.3 vs 23.6 weeks, respectively). Exposure to cisplatin or carboplatin was comparable between the treatment arms, with >80% of patients completing the protocol-defined maximum of 4 cycles. The median relative dose intensity of sintilimab was high (97.1%) and consistent with the targeted dose, demonstrating that sintilimab was well tolerated in patients with nonsquamous NSCLC.

1.5.3.2 Treatment-Emergent Adverse Events

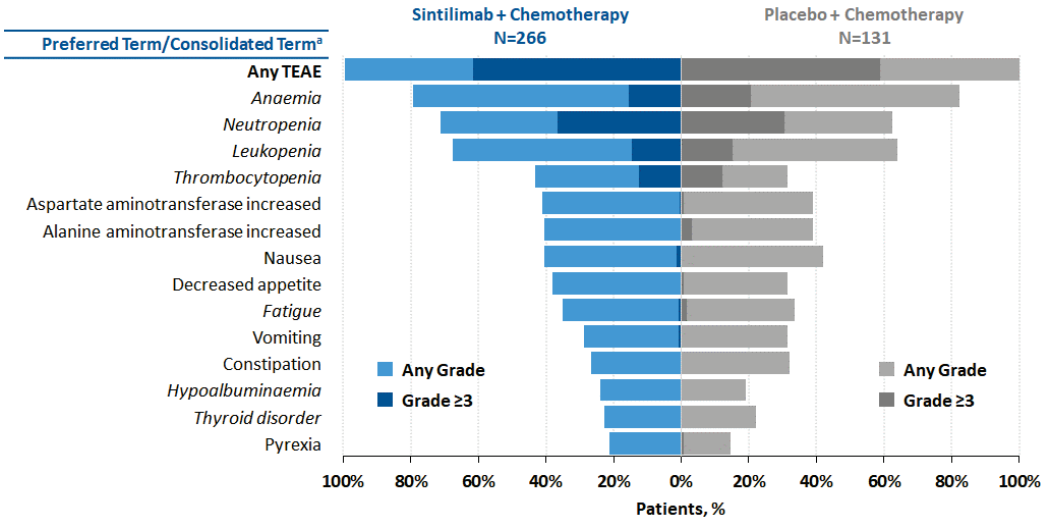
Overview of Treatment-Emergent Adverse Events

At the interim analysis (DCO, 15 November 2019), the majority of patients in both the sintilimab and placebo arms experienced at least 1 treatment-emergent adverse event (TEAE) during the double-blind period of the study (99.6% vs 100%). The incidence of Grade ≥3 events (61.7% vs 58.8%), serious adverse events (SAEs; 28.2% vs 29.8%), and TEAEs leading to discontinuation of any study treatment component (6.0% v 8.4%) or all study treatment (3.0% vs 6.1%) was similar between the sintilimab and placebo arms. Fewer TEAEs leading to death occurred in the sintilimab arm than in the placebo arm (2.3% vs 6.9%). The updated safety analysis (DCO, 15 January 2021) further corroborates the safety conclusion from the interim analysis, with no new safety signal identified.

Common Treatment-Emergent Adverse Events

TEAEs occurring in ≥20% of patients during the double-blind treatment phase of ORIENT-11 are summarized in **Figure E**. The most common TEAEs were as expected for the proposed regimen. In general, the addition of sintilimab did not increase the incidence of the most common AEs associated with chemotherapy.

Figure E Common TEAEs (≥20% in Sintilimab Arm) During Double-Blind Period – ORIENT-11

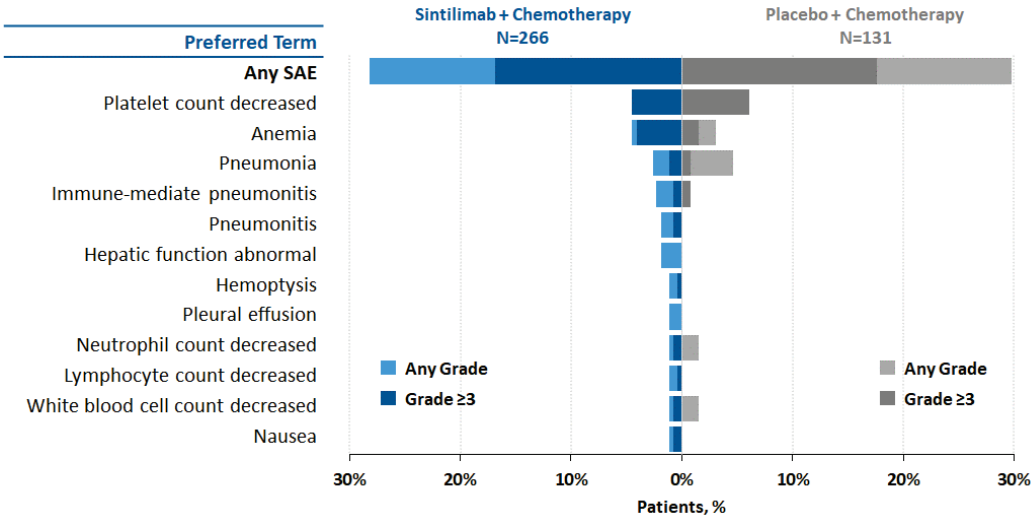


Abbreviations: N = number of patients; TEAE = treatment-emergent adverse event.
Note: This figure does not include data from crossover.
[a] Terms in italics are consolidated terms.
Data cutoff date: 15 November 2019.

Treatment-Emergent Serious Adverse Events

Treatment-emergent SAEs occurred at a similar rate between the sintilimab and placebo arms (28% vs 30%). The most common SAE preferred terms, including platelet count decreased and anemia, are known adverse reactions of chemotherapy with the highest incidence of Grade ≥3 severity (**Figure F**).

Figure F Serious Adverse Events (>1% in Sintilimab Arm) During Double-Blind Period – ORIENT-11



Abbreviations: N = number of patients; SAE = serious adverse event.
Note: This figure does not include data from crossover.
Data cutoff date: 15 November 2019.

At the primary analysis DCO in November 2019, the incidence of all-cause death was 19.2% in the sintilimab arm and 29.8% in the placebo arm; the primary reason for death in both groups was disease progression (16.9% vs 20.6%). Death due to AE was reported in 2.3% and 8.4% of patients, respectively.

Immune-Related Adverse Events

Sponsor adjudication of irAEs was conducted for the sintilimab arm using a predefined structured process. The overall incidence of irAEs and of individual types of irAEs in ORIENT-11 and all sintilimab-treated patients (**Table A**) is consistent with that of other PD-1/L1 inhibitors. Most irAEs were low grade and manageable.

Table A Sponsor-Adjudicated Immune-Related AEs (Incidence >1%) – ORIENT-11 and All Sintilimab-Treated Patients

Immune-related category Immune-related subcategory (if applicable)	Patients, %			
	ORIENT-11 (N=266)		All sintilimab treated (N=1045)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any irAE	**33.1**	**5.6**	**39.6**	**9.2**
Endocrinopathy	20.3	0	25.3	0.7
Hypothyroidism	12.0	0	16.7	0.2
Hyperthyroidism	10.2	0	9.7	0
Thyroid disorder	3.0	0	4.9	0
Pancreatitis and elevation of amylase/lipase	7.1	1.9	7.7	3.2
Elevation of amylase	6.8	1.9	5.1	1.6
Elevation of lipase	0.4	0	3.5	1.8
Pneumonitis	7.1	1.5	6.3	2.7
Skin adverse reaction	4.9	1.1	7.3	1.4
Hepatitis and hepatotoxicity	0.4	0.4	1.0	1.0

Abbreviations: AE = adverse event; irAE = immune-related adverse event; N = number of patients.
Data cutoff date: 15 November 2019.

1.5.3.3 Safety Conclusions

The safety profile of sintilimab in combination with pemetrexed and platinum-based chemotherapy in ORIENT-11 is acceptable, with toxicities that were tolerable and generally manageable with dose interruptions and supportive care. Additionally, the safety profile is consistent with the known and well described safety profiles of approved PD-1/L1 inhibitors, with no new safety concerns identified. Immune-related AEs were generally low grade and manageable. Infusion-related reactions were uncommon and manageable.

1.6 Benefit-Risk Conclusions

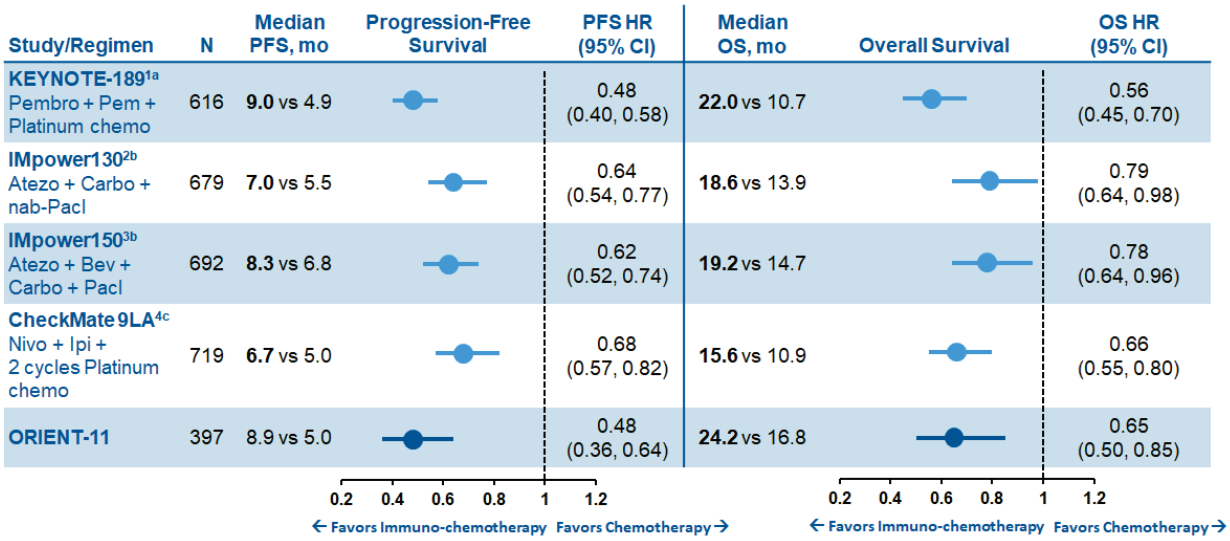
Based on the totality of the data, sintilimab in combination with pemetrexed and platinum-based chemotherapy has demonstrated a positive benefit-risk profile for use as first-line therapy in patients with Stage IIIB, IIIC, or IV nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations.

1.7 Applicability of Results to the US Population

As stated earlier, the US CFR includes 3 specific requirements for acceptance of foreign data in an application for the basis of marketing approval. Two of those criteria were previously discussed in Section 1.2 and are considered addressed. The third requirement is that *the foreign data are applicable to the US population and US medical practice*.[19] This regulation in conjunction with guidance from the ICH E5 provides a framework for evaluating the impact of ethnic factors on a drug's effect.[1] Thus, the applicability of the sintilimab data for the treatment of first-line nonsquamous NSCLC in combination with chemotherapy can be considered based on 3 principles:

1. *Similar clinical practice standards between China and the US.* Clinical practice standards are constantly evolving. At the time ORIENT-11 was initiated in August 2018, pembrolizumab plus pemetrexed and platinum-based chemotherapy had been adopted as the new standard of care in the US based on results of KEYNOTE-189. At that time, the chemotherapy backbone of platinum plus pemetrexed followed by maintenance pemetrexed was and had been the standard of care for many years in China, and second-line PD-1/L1 mAbs were available; however, first-line chemoimmunotherapy had not yet been adopted for nonsquamous NSCLC. Today, chemoimmunotherapy is an approved first-line option in China, and clinical practice guidelines for the treatment of nonsquamous NSCLC have converged in the US and China.
2. *Similar PK and pharmacodynamics of sintilimab between Chinese and US patients.* As summarized in Section 1.5.1, the intrinsic factors evaluated including race, age, sex, body weight, tumor type, and renal and hepatic function showed no clinically important effects on the PK profile of sintilimab. It is well known that the PK of IgG mAbs is not sensitive to pharmacogenetic differences.[18] In addition, exposure-receptor occupancy, exposure-efficacy, and exposure-safety analyses demonstrate that the dose of 200 mg Q3W lies on the plateau portion of the exposure-response curve. This, combined with the fact that sintilimab has a linear PK profile and wide therapeutic dose range for efficacy, indicates that sintilimab is not sensitive to ethnic factors.
3. *Similar efficacy and safety of sintilimab between Chinese and US patients.* A published FDA meta-analysis comparing clinical outcomes in non-Asian and Asian patients with metastatic NSCLC who were treated with immune checkpoint inhibitors in the first-line setting showed relatively consistent OS and PFS outcomes in non-Asian and Asian patients.[16] When data from ORIENT-11 were compared to these data, the HRs for both OS and PFS were consistent with the FDA meta-analysis (Figure 19). In addition, similar efficacy was demonstrated when ORIENT-11 was compared with other anti-PD-1/L1 trials conducted in largely Western patients and according to Western standards (**Figure G**).[20-23] A pooled analysis of the safety profile of sintilimab monotherapy across the clinical program showed that, although a limited number of US patients were included in the analysis, the data suggest a generally comparable safety profile in Chinese and US patients.

Figure G Efficacy Outcomes Across ORIENT-11 and PD-1/L1 Registration Studies in First-Line Treatment of Nonsquamous NSCLC Without EGFR or ALK Genomic Tumor Aberrations



Abbreviations: Atezo = atezolizumab; Bev = bevacizumab; Carbo = carboplatin; chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; Ipi = ipilimumab; N = number of patients; nab = nanoparticle albumin-bound; Nivo = nivolumab; OS = overall survival; Pacl = paclitaxel; PD-1/L1 = programmed death-1/programmed death-ligand 1; Pem = pemetrexed; Pembro = pembrolizumab; PFS = progression-free survival.

[a] Primary endpoints were OS and PFS by blinded independent central radiology review.

[b] Co-primary endpoints were investigator-assessed PFS and OS.

[c] Primary endpoint was OS.

Data cutoff for ORIENT-11 was 15 September 2021 for OS and 15 November 2019 for PFS.

1. Gadgeel S, et al. *J Clin Oncol.* 2020;38(14):1505-17.
2. West H, et al. *Lancet Oncol*. 2019;20(7):924-37.
3. Socinski MA, et al. *N Engl J Med.* 2018;378(24):2288-301.
4. Paz-Ares L, et al. *Lancet Oncol*. 2021;22:198-211.

Together, these findings support the conclusion that the data from ORIENT-11 are applicable to the US population for the intended indication.

2.0 DISEASE STATE AND TREATMENT OPTIONS

2.1 Epidemiology, Treatment Landscape, and Patient Characteristics of NSCLC

Lung cancer was the leading cause of cancer-related death in the United States (US) in 2021.[2] An estimated 235,000 new cases and an estimated 132,000 deaths occur annually. The non-small cell histology accounts for the majority (85%) of lung cancers.[3] In the US, the predominant histology has shifted from squamous to adenocarcinoma associated with decreasing incidence of smoking,[4] and the same is true in China, where adenocarcinoma now dominates.[5]

The main difference between Chinese and US lung adenocarcinoma cases is the frequency of epidermal growth factor receptor (EGFR)-activating mutations; however, ORIENT-11 and multiple Phase 3 studies of checkpoint inhibitor use in first-line non-small cell lung cancer (NSCLC) excluded patients with EGFR-mutated NSCLC because their standard treatment is EGFR-targeted therapy. The prevalence of EGFR-activating mutations in lung adenocarcinoma is ~50% in China,[6,7] which is consistent with that in Asian patients regardless of nationality[7] and that in Native American patients,[15] versus 15% in US whites and 12% in US blacks.[8] The Asian American population is 7.2% of the total US population.[24] Importantly, in patients without dominant activating mutations, such as EGFR, tumor genetic sequencing showed extensive similarity between cases from China and the US.[9,10]

The characteristics of patients with Stage IV NSCLC in the US and China entered into registrational randomized trials are very similar with regard to clinical characteristics. When patients with EGFR mutations and other oncogenic alterations are excluded,, the median age of eligible patients in China for ORIENT-11 was 61 years, which is similar to that in Western patients recruited into registrational NSCLC patients across the last decades (58-66 years).[25-31] Their nonsquamous histology, programmed death-ligand 1 (PD-L1) status, and Eastern Cooperative Oncology Group (ECOG) performance status in ORIENT-11 are all similar proportionally to what is seen in the US population and other Western patients. For example, in the randomized Phase 2 trial of pemetrexed plus platinum versus the same chemotherapy plus pembrolizumab in 123 patients with nonsquamous NSCLC recruited in the US,[32] where 87% were white, 8% Asian and 3% black, the PD-L1 expression levels were similar to the follow-up trial KEYNOTE-189,[26] which recruited a similar proportion of white patients: 25% of patients in the US and 2% in East Asia (Japan).

2.2 Diagnostic and Treatment Standards Between US and China

The diagnostic and treatment standards between the US and China are generally similar (Table 1). The treatment guidelines in the US are dominated by the National Comprehensive Cancer Network (NCCN) guidelines and the Chinese guidelines are largely derived from the NCCN guidelines. The same staging and pathologic classification system are used. The American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th edition was developed with substantial contribution of Asian patients (44% of 94,708 patients).[33] Molecular testing and PD-L1 biomarker testing are routinely used.[11]

Currently, in the US, patients without oncogenic alterations are typically treated, depending on PD-L1 status, with either single-agent immunotherapy, the combination of a programmed death-1/programmed death-ligand 1 (PD-1/L1) monoclonal antibody (mAb) plus chemotherapy, or the combination of PD-1 plus cytotoxic T-lymphocyte-antigen 4 (CTLA-4) mAbs, as first-line therapy.[11] The chemotherapy backbone used in the US and China tends to be very similar.

Cisplatin, or more commonly carboplatin, plus pemetrexed is the most common doublet used in both countries. Additionally, the predominant treatment selection for second-line therapy in the US and China is taxanes. The efficacy of immunotherapy or chemotherapy has not shown ethnic sensitivity.[14,15] Section 8.2 describes in more detail the lack of ethnic sensitivity of these therapies; specifically, Asian patients with metastatic NSCLC treated with immunotherapy demonstrated relatively consistent overall survival (OS) and progression-free survival (PFS) benefits compared to non-Asian patients.[16]

Table 1 Diagnostic and Treatment Standards for NSCLC in the US and China as of 2021

Factor	United States	China
Treatment guidelines	NCCN 2021 Version 4	CSCO 2021
Staging system	AJCC Cancer Staging Manual, 8th edition	
Pathology	2015 World Health Organization classification	
Standard genetic testing[a]	EGFR, ALK	
PD-L1 biomarker testing	PD-L1 CDx per product label	
1L treatment options[a]	Pembro + chemo Pembro or Atezo for PD-L1 ≥50%	
	Atezo + bevacizumab + chemo Nivo + ipi + chemo Nivo + ipi for PD-L1 TPS ≥1% Cemiplimab for PD-L1 ≥50%	Sintilimab or camrelizumab or tislelizumab + chemo
Standard of care chemotherapy backbone	Platinum-based chemo: cisplatin or carboplatin with Pemetrexed/Bevacizumab/Gemcitabine/Docetaxel/Paclitaxel/Vinorelbine	

Abbreviations: 1L = first-line; AJCC = American Joint Committee on Cancer; ALK = anaplastic lymphoma kinase; Atezo = atezolizumab; CDx = companion diagnostic; chemo = chemotherapy; CSCO = Chinese Society of Clinical Oncology; EGFR = epidermal growth factor receptor; ipi = ipilimumab; NCCN = National Comprehensive Cancer Network; Nivo = nivolumab; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; Pembro = pembrolizumab; TPS = tumor proportional score; US = United States.
[a] Based on Category 1 recommendations.

2.3 Nonsquamous NSCLC Treatment Patterns in the US and China

2.3.1 Preferred Treatment Options for Nonsquamous NSCLC

Various factors influence first-line treatment decisions and practices for NSCLC. These factors include comorbidity, performance status, histology, molecular features of the cancer, and anticipated patient tolerance to treatment.

In the US, the current standard first-line treatment option for patients with advanced or metastatic nonsquamous NSCLC in the absence of driver mutations (i.e., EGFR- and anaplastic lymphoma kinase [ALK]-negative disease) include several approved PD-1/L1 agents.[11] Typically, patients receive one of these agents either as monotherapy or, more often, in combination with platinum-based chemotherapy. The options for second-line therapy in this population are typically other cytotoxic agents, either as single agents or the combination of ramucirumab and docetaxel.

The treatment algorithm for NSCLC patients in China is similar to that in the US. As mentioned, the one significant difference is the higher proportion of patients with oncogenic alterations in China. Those patients are typically treated with targeted therapy and are not included in the proposed indication for sintilimab. For the approximately one third of patients without oncogenic

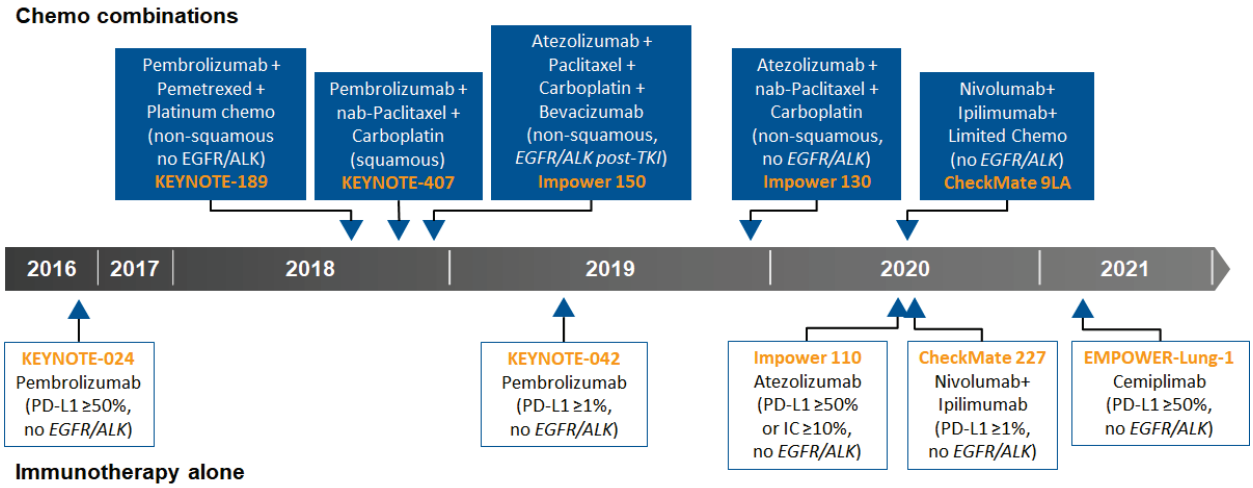
alterations in the first-line setting, there are a number of approved PD-1/L1 inhibitors in China used either as monotherapy in high PD-L1 expressers or, more commonly, in combination with platinum-based chemotherapy.

2.3.2 Role of Immune Checkpoint Inhibitors in NSCLC

PD-1/L1 inhibitors have transformed the treatment landscape for NSCLC, and they are now the first-line standard of care for the majority of patients with Stage IV disease. These agents were first approved in the US in 2016 as monotherapy in the second-line setting (Figure 1).[34] In August 2018, with the full approval of pembrolizumab based on KEYNOTE-189, PD-1/L1 inhibitors moved to first-line therapy, largely in combination with standard chemotherapy regimens, regardless of PD-L1 status, or as single agents for PD-L1–high tumors. Since then, multiple other PD-1/L1 inhibitors, in combination with various chemotherapy regimens, have been approved as first-line therapy for both squamous and nonsquamous NSCLC. However, the only PD-1 inhibitor approved in combination with pemetrexed plus platinum-based chemotherapy is pembrolizumab.

Many of these regimens are also approved in China, but their approval came a bit later. For example, the KEYNOTE-189 regimen was approved in China in March 2019.

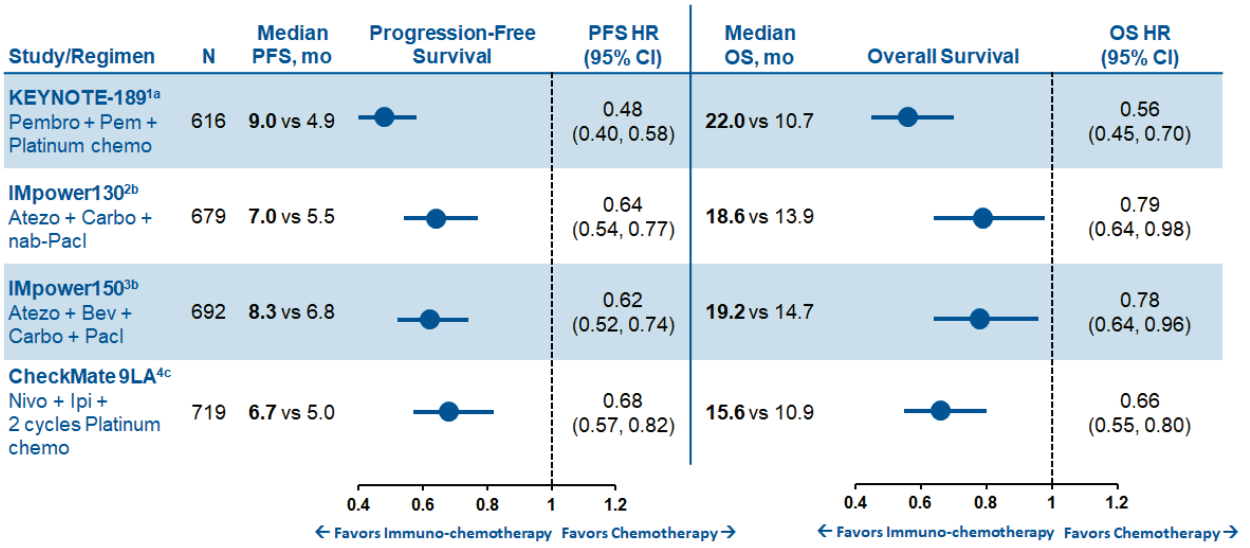
Figure 1 First-Line Approval for Immunotherapy in NSCLC in the US



Abbreviations: ALK = anaplastic lymphoma kinase; Chemo = chemotherapy; EGFR = epidermal growth factor receptor; IC = PD-L1 stained tumor-infiltrating immune cells; Nab = nanoparticle albumin-bound; NSCLC = non-small cell lung cancer; PD-L1 = programmed cell death-ligand 1; TKI = tyrosine kinase inhibitor; US = United States.
Data from Zhou F, et al. *Cell Mol Immunol*. 2021;18(2):279-93.

Figure 2[20-23] compares the reported PFS and overall survival (OS) benefit achieved with various PD-1/L1 inhibitors in the first-line setting. It shows that this class of agents all have broadly similar efficacy in NSCLC, regardless of the chemotherapy backbone used. They also have broadly similar safety profiles.

Figure 2 Efficacy Across the PD-1/L1 Class



Abbreviations: Atezo = atezolizumab; Bev = bevacizumab; Carbo = carboplatin; chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; Ipi = ipilimumab; N = number of patients; nab = nanoparticle albumin-bound; Nivo = nivolumab; OS = overall survival; Pacl = paclitaxel; PD-1/L1 = programmed death-1/programmed death-ligand 1; Pem = pemetrexed; Pembro = pembrolizumab; PFS = progression-free survival.

[a] Primary endpoints were OS and PFS by blinded independent central radiology review.

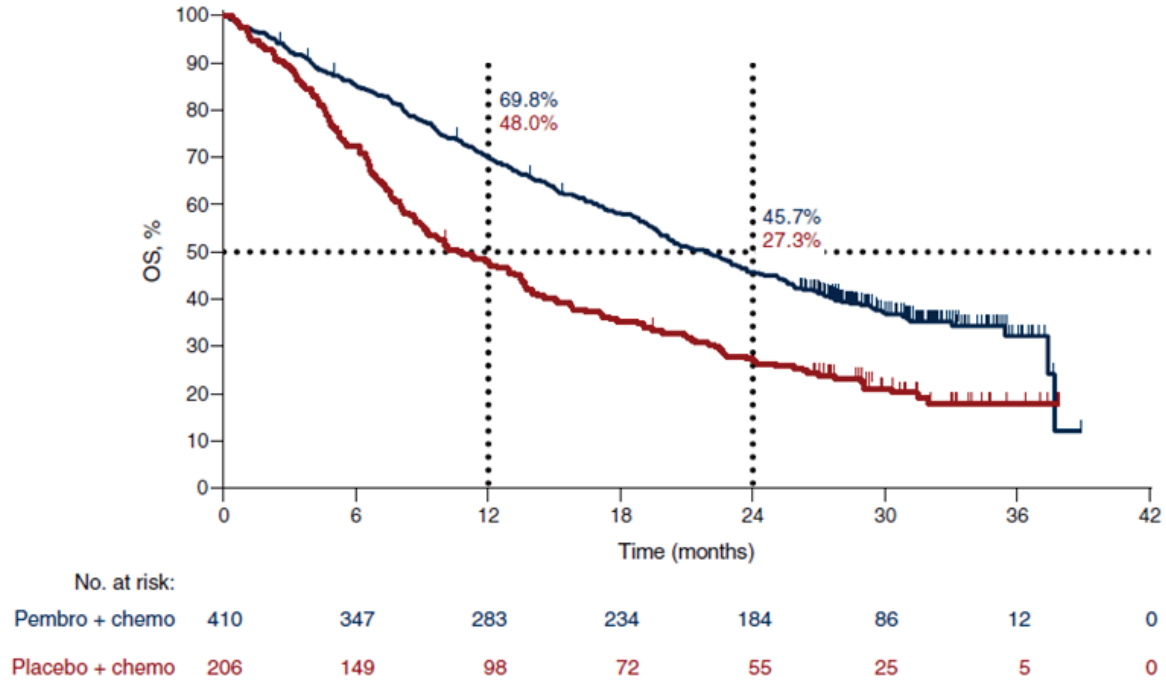
[b] Co-primary endpoints were investigator-assessed PFS and OS.

[c] Primary endpoint was OS.

1. Gadgeel S, et al. *J Clin Oncol.* 2020;38(14):1505-17.
2. West H, et al. *Lancet Oncol*. 2019;20(7):924-37.
3. Socinski MA, et al. *N Engl J Med.* 2018;378(24):2288-301.
4. Paz-Ares L, et al. *Lancet Oncol*. 2021;22(2):198-211.

The results from KEYNOTE-189 established the combination of pembrolizumab plus pemetrexed and platinum-based chemotherapy as the standard of care for NSCLC in the US. PFS in the pembrolizumab arm was nearly doubled at 9.0 months compared with 4.9 months in the placebo arm (Figure 2[20-23]). The final OS analysis, shown in Figure 3,[35] demonstrated a median survival of 22 months in the pembrolizumab arm versus 10.6 months in the control arm (hazard ratio [HR]=0.56; 95% confidence interval [CI]: 0.46, 0.69).

Figure 3 KEYNOTE-189 Final Overall Survival Analysis



Abbreviations: chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.
Adapted from Rodriguez-Abreu D, et al. *Ann Oncol*. 2021;32(7):881-895.
Data cutoff: 20 May 2019; median follow-up = 31.0 months (range, 26.5-38.8 months).

2.4 Conclusions

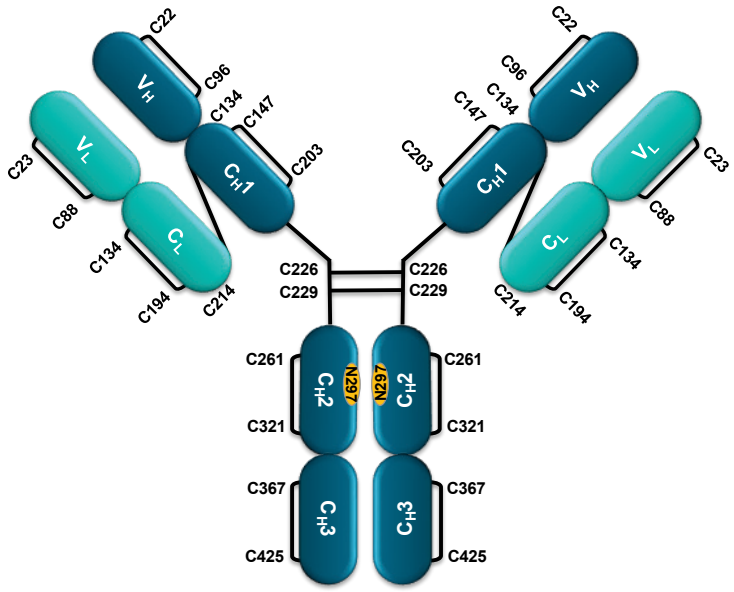
The disease characteristics of both US and Chinese patients are similar, with the exception of the percentage of oncogenic alterations. Both the diagnostic and treatment standards and treatment patterns are similar between the 2 countries. In both the US and China, immunotherapy has dramatically improved outcomes in lung cancer patients, and pemetrexed and platinum is the most widely used chemotherapy regimen for nonsquamous NSCLC. Despite the large number of PD-1/L1 agents approved for NSCLC, only one, pembrolizumab, is a single-agent checkpoint inhibitor approved in combination with pemetrexed plus platinum-based chemotherapy.

3.0 SINTILIMAB OVERVIEW

3.1 Physicochemical Properties of Sintilimab

Sintilimab is a novel recombinant human immunoglobulin (Ig)G4 mAb that has been optimized using Adimab (a US-based company) yeast display technology for enhanced in vitro binding affinity, and it is produced by Chinese hamster ovary cells. Sintilimab is composed of 2 identical Ig kappa light chains and 2 identical Ig gamma heavy chains. Each heavy chain contains a single N-linked glycosylation site at N297. The predominant form of oligosaccharides at the N297 site on either arm is G0F. To eliminate Fab arm exchange, the -CPSC-sequence in the hinge region of wild-type IgG4 is mutated to -CPPC-sequence (i.e., serine at position 228 is mutated to proline). The schematic diagram of sintilimab is depicted in Figure 4.

Figure 4 Structure of Sintilimab



Abbreviations: C_H = constant domain heavy; C_L = constant domain light; V_H = variable loop heavy; V_L = variable loop light.

3.2 Mechanism of Action of Sintilimab

Sintilimab binds to an epitope on the PD-1 receptor with high affinity (dissociation constant [K_D] of 0.07 nM) and exhibits potent blockage of its interaction with its ligands PD-L1 and PD-L2, thereby reactivating tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and enhancing antitumor immunity.[36,37]

4.0 OVERVIEW OF SINTILIMAB DEVELOPMENT PROGRAM

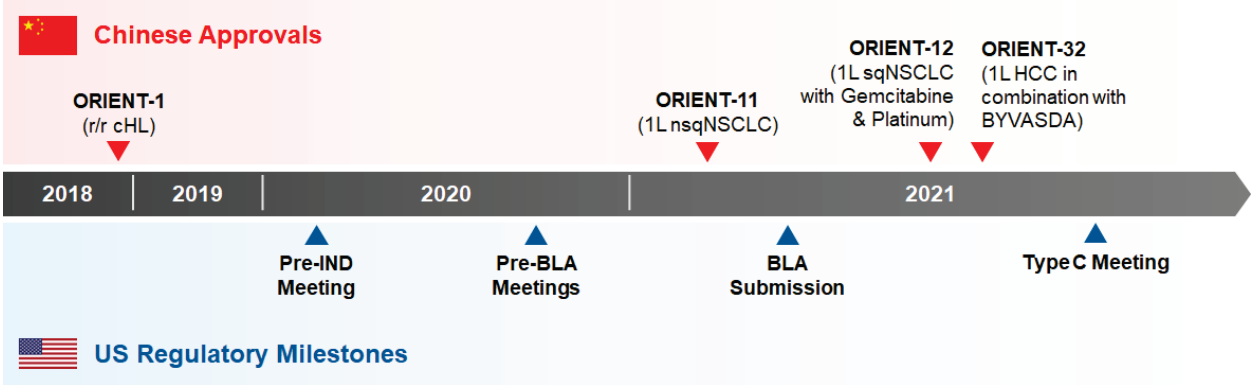
4.1 Regulatory History

In December 2018, sintilimab monotherapy was conditionally approved by the National Medical Products Administration (NMPA; formerly the China Food and Drug Administration) for the treatment of relapsed or refractory classical Hodgkin's lymphoma after failure of at least 2 lines of systemic chemotherapy (Figure 5). On 02 February 2021, sintilimab was approved by the NMPA for the first-line treatment of Stage IIIB/C and Stage IV nonsquamous NSCLC when used in combination with pemetrexed and platinum-based chemotherapy. On 03 June 2021, sintilimab in combination with gemcitabine and platinum-based chemotherapy was approved by the NMPA for the first-line treatment of squamous NSCLC. In June 2021, sintilimab in combination with bevacizumab biosimilar (BYVASDA®; vascular endothelial growth factor inhibitor) was approved by the NMPA for the first-line treatment of advanced or unresectable hepatocellular carcinoma.

In the US (Figure 5), Innovent met with FDA on 3 occasions in 2020, prior to submitting the Biologics License Application (BLA) in March of 2021. At those meetings, agreement was reached on the various elements necessary for the submission, including details regarding the safety analysis plans, proposal for immune-related adverse event (irAE) evaluation, electronic data sets, and submission of updated PFS and OS data as part of the 4-month Safety Update. Given that ORIENT-11 was conducted solely in China, FDA requested that the submission "include a discussion of how the study population adequately represents the U.S. patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care." Of note, FDA indicated that they "may make a request for post-marketing data in a population representative of the US population as a post-marketing commitment (PMC)." Since that time, Innovent has proactively proposed a study for FDA consideration (Type C meeting, October 2021) that was intended to generate data in a diverse NSCLC population representative of the US population.

Ultimately, the sintilimab BLA was submitted to FDA in March 2021 and accepted for review in May 2021. During the mid-cycle meeting with FDA (30 August 2021), there was an agreement for Innovent to provide updated OS based on the September 2021 data cutoff (DCO); these data were subsequently submitted in December 2021.

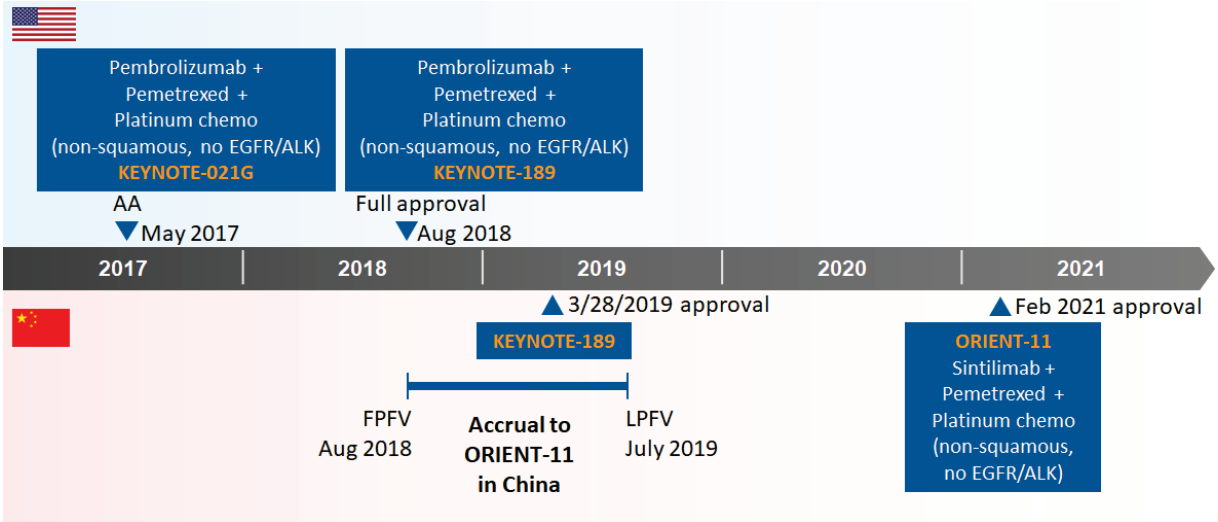
Figure 5 Sintilimab Regulatory History



Abbreviations: 1L = first-line; BLA = Biologics License Application; cHL = classic Hodgkin's lymphoma; HCC = hepatocellular carcinoma; IND = Investigational New Drug; nsqNSCLC = nonsquamous non-small cell lung cancer; r/r = relapsed/refractory; sqNSCLC = squamous non-small cell lung cancer; US = United States.

In China, the approval of sintilimab in combination with pemetrexed and platinum-based chemotherapy for first-line treatment of nonsquamous NSCLC was based on data from the pivotal Phase 3 ORIENT-11 study, which was fully enrolled in China from August 2018 to July 2019 (Figure 6). The current standard of care combination regimen of pembrolizumab, pemetrexed, and platinum-based chemotherapy, based on results from KEYNOTE-189, was approved in the US in August 2018, yet it was not approved in China until March 2019, just prior to the completion of ORIENT-11 enrollment.

Figure 6 Timing of ORIENT-11 Relative to Approval of KEYNOTE-189 Regimen in the United States and China



Abbreviations: AA = accelerated approval; ALK = anaplastic lymphoma kinase; chemo = chemotherapy; EGFR = epidermal growth factor receptor; FPFV = first patient first visit; LPLV = last patient last visit.

4.2 Nonclinical Overview

A comprehensive panel of nonclinical studies was designed and conducted to evaluate the mechanism of action, in vitro and in vivo efficacy, pharmacokinetics (PK)/pharmacodynamics

(PD), and safety profile of sintilimab to support the BLA submission of sintilimab for the treatment of cancer patients.

In vitro and in vivo studies were conducted to characterize the nonclinical pharmacology profile of sintilimab, including its specific binding to PD-1, ligand-blocking activity, and functional inhibition of PD-1 pathways. Overall, sintilimab demonstrated high affinity to human PD-1 (K_D of 0.07 nM)[36] and can block the PD-1 pathways and activate T cells, thereby exerting a significant antitumor effect (74% to 96%) in a human NSCLC xenograft model.

In a single-dose intravenous (IV) PK study in cynomolgus monkeys over a dose range of 1 to 30 mg/kg, PK of sintilimab was generally dose-proportional, with a half-life ($t_{1/2}$) of approximately 5 days and a clearance rate of 0.3 mL/h/kg. Dose-dependent PD-1 receptor occupancy by sintilimab on cluster of differentiation (CD)3^+ T cells was demonstrated after a single IV infusion.

The nonclinical safety/toxicology studies were designed according to International Conference on Harmonisation (ICH) S6 and ICH S9 guidelines and conducted under Good Laboratory Practice standards of either the US FDA (Code of Federal Regulations [CFR] 21, Part 58) or NMPA and Organisation for Economic Co-operation and Development. Overall, no adverse findings were observed in cynomolgus monkeys following IV infusion of sintilimab at doses up to 200 mg/kg once weekly for 4 weeks or once every 2 weeks for 26 weeks. The no-observed-adverse-effect level (NOAEL) in both studies was the highest dose administered (200 mg/kg). No effects on safety pharmacology endpoints including blood pressure, electrocardiogram interval measurements or waveform analysis, neurological, or respiratory evaluations were observed. Embryofetal toxicity in the form of increased resorptions and a decreased pregnancy rate was noted at the high dose of 200 mg/kg in a reproductive study in New Zealand rabbits. The fetal NOAEL was 40 mg/kg. Notwithstanding the reduced potency of sintilimab for rabbit PD-1, this study was able to identify predicted embryofetal hazards, which are supported by a comprehensive literature-based assessment of the effects of PD-1/L1 axis blockade on reproductive function. Moreover, there were no important changes in in vitro cytokine release assay with human blood or peripheral blood mononuclear cell supernatant. In a tissue cross-reactivity study, sintilimab demonstrated similar and expected binding patterns across normal human and cynomolgus monkey tissues.

Together, the described package of nonclinical pharmacology, PK/PD, and toxicology studies supports the BLA registration of sintilimab for locally advanced or metastatic NSCLC.

4.3 Clinical Development Overview

Sintilimab has been evaluated in more than 4,000 clinical trial patients across multiple tumor types, including more than 600 patients with nonsquamous NSCLC. Other malignancies evaluated included hepatocellular carcinoma, esophageal cancer, classical Hodgkin lymphoma, neuroendocrine tumors, natural killer/T-cell lymphoma, melanoma, gastric cancer, colorectal cancer, and other solid tumors. Positive results from these studies have been reported.[38-42]

Eight of these clinical studies can be considered as supportive (Table 2) and were included as part of the BLA. The most relevant clinical efficacy, safety, and PK results for sintilimab in combination with pemetrexed and platinum-based chemotherapy in patients with Stage IIIB/C or Stage IV nonsquamous NSCLC are provided by the pivotal Phase 3 Study CIBI308C302 (ORIENT-11) and Cohort D of the supportive Phase 1b Study CIBI308A101 (A101). Both

studies were conducted in mainland China. In addition, a Phase 1b Study CIBI308A102 (A102) supports the safety and PK of sintilimab in US patients (N=39), who were predominately female with endometrial cancer. These 3 studies, together with the remaining 5 clinical studies, were included in the pooled safety analyses, as described in Section 7.1.

Table 2 Overview of Sintilimab Clinical Studies Supporting the Nonsquamous NSCLC Indication

Study ID	Phase	Indication	Treatment arms	Number of patients	DCO date
Pivotal Efficacy and Safety Study					
CIBI308C302 (ORIENT-11)	3	1L nsqNSCLC	Sintilimab + Pem + Cis/Carbo vs Placebo + Pem +Cis/Carbo	397 (266 vs 131)	Interim: 15Nov2019 Updated: 15Sep2021
Supportive Efficacy and Safety Study					
Cohort D of CIBI308A101	1b	1L nsqNSCLC	Sintilimab + Pem + Cis	21	17Apr2019
Supportive Safety and PK Study in US Patients					
CIBI308A102	1b	Solid or endometrial tumors	Sintilimab	39	15Apr2020
Additional Supportive Studies Included in Pooled Safety Analyses					
CIBI308C303 (ORIENT-12)	3	1L sqNSCLC	Sintilimab + Gem + Cis/Carbo vs Placebo + Gem +Cis/Carbo	357 (179 vs 178)	25Mar2020
Cohort C of CIBI308A101	1b	≥2L NSCLC	Sintilimab	37	17Apr2019
Cohort E of CIBI308A101	1b	1L sqNSCLC	Sintilimab + Gem + Cis	20	17Apr2019
CIBI308C301 (ORIENT-3)	3	2L sqNSCLC	Sintilimab vs Doc	274 (144 vs 130)	30Sep2019
Phase 1a of CIBI308A101	1a	Solid tumors	Sintilimab	12	10Oct2018[a]
Cohort A of CIBI308A101	1b	Advanced melanoma	Sintilimab	22	17Apr2019
Cohort B of CIBI308A101	1b	Advanced tumors of digestive system and neuroendocrine malignancy	Sintilimab	87	17Apr2019
CIBI308B201 (ORIENT-1)	2	r/r cHL	Sintilimab	96	30Sep2019
CIBI308A201 (ORIENT-2)	2	2L ESCC	Sintilimab vs Pacl or Irinotecan	181 (94 vs 87)	02Oct2019
CIBI308D201 (ORIENT-4)	2	r/r NK/T-cell lymphoma, nasal type	Sintilimab	28	28Feb2020

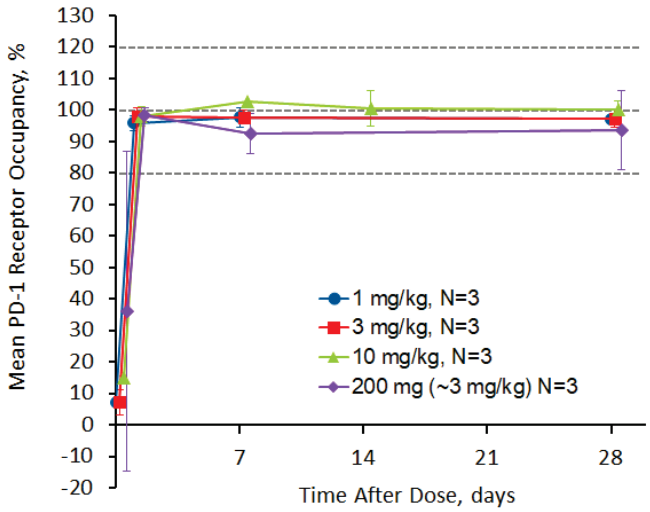
Abbreviations: 1L = first-line; 2L = second-line; Carbo = carboplatin; cHL = classical Hodgkin's lymphoma; Cis = cisplatin; D = day; DCO = data cutoff; Doc = docetaxel; ESCC = esophageal squamous cell carcinoma; Gem = gemcitabine; ID = identification; NK = natural killer; NSCLC = non-small cell lung cancer; nsqNSCLC = nonsquamous non-small cell lung cancer; Pacl = paclitaxel; Pem = pemetrexed; Q2W = every 2 weeks; Q3W = every 3 weeks; r/r = relapsed/refractory; sqNSCLC = squamous non-small cell lung cancer; US = United States.
Note: The sintilimab dose regimen across these studies was 200 mg D1 Q3W, except for the Phase 1a dose-escalation portion of CIBI308A101, in which 4 dose levels were evaluated: 1 (N=3), 3 (N=3), or 10 mg/kg Q2W (N=3), or 200 mg D1 Q3W (N=3).
[a] Safety snapshot data received on 10 October 2018; last data entry on 18 September 2018.

5.0 CLINICAL PHARMACOLOGY

5.1 Pharmacodynamics

Sintilimab PD-1 receptor occupancy on peripheral blood $CD3^+$ T cells was assessed using a flow cytometry assay (Figure 7).[36] Twelve patients with advanced solid tumors were given IV infusions of sintilimab (1 mg/kg, 3 mg/kg, 200 mg, or 10 mg/kg) either every 2 weeks (Q2W) or every 3 weeks (Q3W). Results showed that sintilimab at a single dose of 1 mg/kg (n=3) was able to quickly (within 24 hours) bind the majority of PD-1 receptors (mean ≥95%) on peripheral $CD3^+$ T cells. This level of receptor occupancy on peripheral blood $CD3^+$ T cells was maintained during the dosing interval (28 days) and during long-term treatment. The results of PD-1 receptor occupancy assay using 3 mg/kg (N=3), 200 mg (N=3), and 10 mg/kg (N=3) of sintilimab were similar to the results following treatment with 1 mg/kg. These results indicate that there exists a large range of exposures that correspond to a high level of PD-1 receptor occupancy.

Figure 7 PD-1 Receptor Saturation of Sintilimab



Abbreviations: N = number of patients; PD-1 = programmed death-1.
Measured on circulating CD3 T cells.
Adapted from Wang J, et al. *MAbs*. 2019;11(8):1443-51.

5.2 Pharmacokinetics

The PK of sintilimab has been characterized in patients with various types of cancer from 4 studies: A101, A102, CIBI308B201 (B201), and ORIENT-11. Population PK (PopPK) analyses assessed the potential effect of a range of intrinsic factors on the PK of sintilimab based on the pooled data in Chinese patients and US patients from these 4 studies.

Sintilimab exhibited linear PK characteristics within the dose range of 1 to 10 mg/kg, with a $t_{1/2}$ of approximately 20 days (Figure 8). As shown in Table 3, after administration of 200 mg sintilimab given as a monotherapy as an IV infusion over 30 to 60 minutes, PK parameters of sintilimab were comparable between Chinese and US patients. The PK parameters of sintilimab were similar in Chinese patients when sintilimab was administered alone or in combination with platinum and pemetrexed.

Table 3 Comparison of Noncompartmental Pharmacokinetic Parameters of Sintilimab Between US Monotherapy and Chinese Monotherapy and Combination Therapy (Sintilimab in Combination With Pemetrexed and Cisplatin) After a Single 200 mg Dose

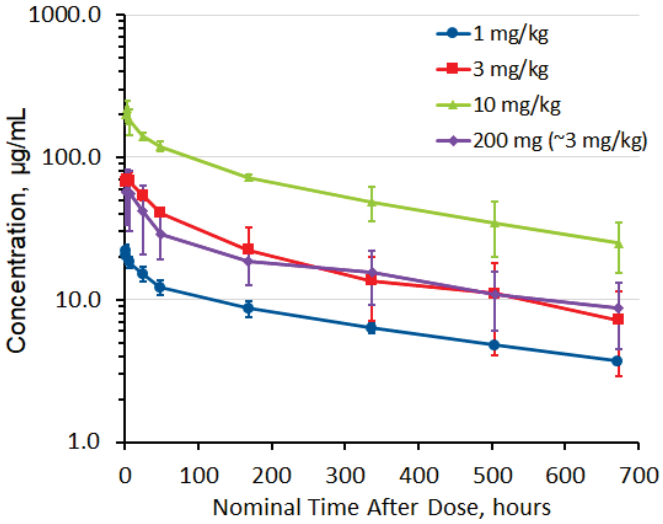
	Sintilimab (200 mg Q3W) administered as:				
	Monotherapy in Chinese patients			Monotherapy in US patients	Combination with pemetrexed and platinum-based chemotherapy in Chinese patients
Parameter	Cohort A CIBI308A101 (N=22)	Cohort B CIBI308A101 (N=57)	Cohort C CIBI308A101 (N=37)	CIBI308A102[a] (N=13)	ORIENT-11 (N=263)
CL (mL/h) (CV%)	9.8 (51.6)	9.0 (59.5)	12.3 (38.1)	12.5 (53.0)	11.3 (39.0)
$t_{1/2}$ (day) (CV%)	13.4 (47.9)	14.7 (63.7)	11.5 (52.3)	14.3 (32.1)	12.7 (37.0)
C_{max} (µg/mL) (CV%)	68.8 (25.1)	71.5 (24.5)	64.1 (26.1)	55.8 (18.5)	66.0 (16.0)
$AUC_{0\text{-}inf}$ (h*µg/mL) (CV%)	20,400 (51.6)	22,300 (59.5)	16,300 (38.1)	16,000 (53.0)	17,699 (39.0)[b]
C_{min} (µg/mL) (CV%)	12.8 (69.5)	14.4 (47.8)	9.4 (117.3)	10.5 (55.9)	10.5 (68.1)

Abbreviations: AUC = area under the concentration-time curve; CL = clearance; C_{max} = maximum observed concentration; C_{min} = minimum observed concentration; CV = coefficient of variation; PK = pharmacokinetics; N = number of patients; Q3W = every 3 weeks; $t_{1/2}$ = terminal half-life; US = United States.

[a] PK parameters reported for 13 of the 39 patients in the study.

[b] Calculated using the formula: AUC = dose/clearance.

Figure 8 Serum Sintilimab Concentration-Time Curve After Cycle 1 Intravenous Infusion – Study CIBI308A101

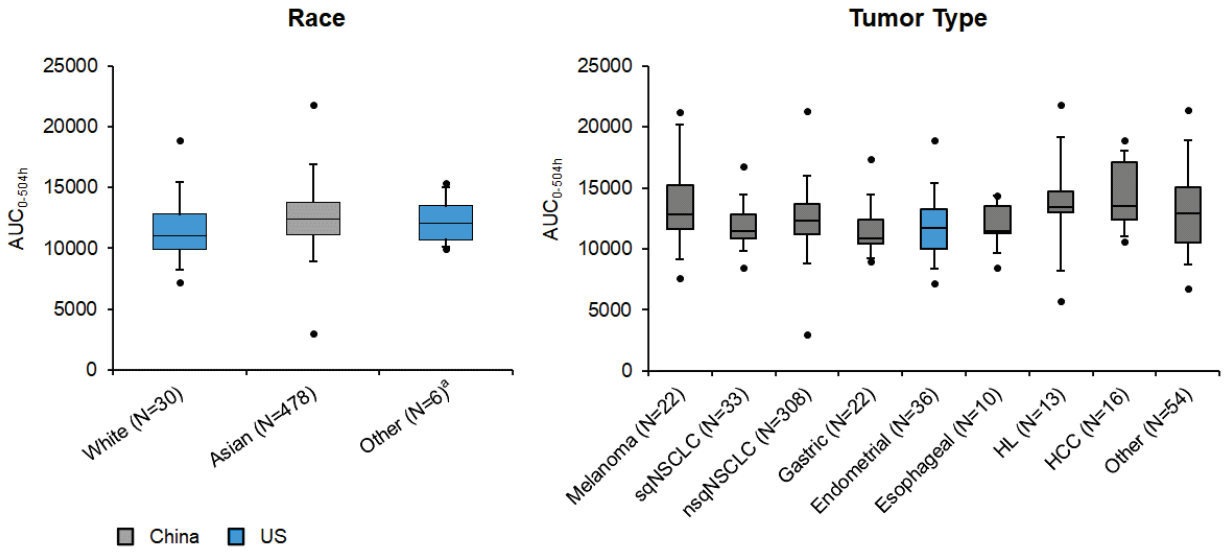


PopPK analyses were conducted using 4,230 serum sintilimab concentration records from 514 patients with advanced malignant tumors (n=199; A101), relapsed or refractory classical Hodgkin lymphoma (n=13; B201), advanced or relapsed nonsquamous NSCLC (n=263; ORIENT-11), or advanced/metastatic solid malignancies (n=39; 102).

A wide range of covariates were assessed, including race, tumor type, age, creatinine clearance (37.1 to 272.2 mL/min), mild hepatic impairment (National Cancer Institute Organ Dysfunction

Working Group [NCI-ODWG] criteria), ECOG performance status, and antidrug antibody (ADA) and were found to have no effect on sintilimab PK (Figure 9).

Figure 9 Impact of Intrinsic Factors (Race and Tumor Type) on PK Profile of Sintilimab in Chinese and US Patients

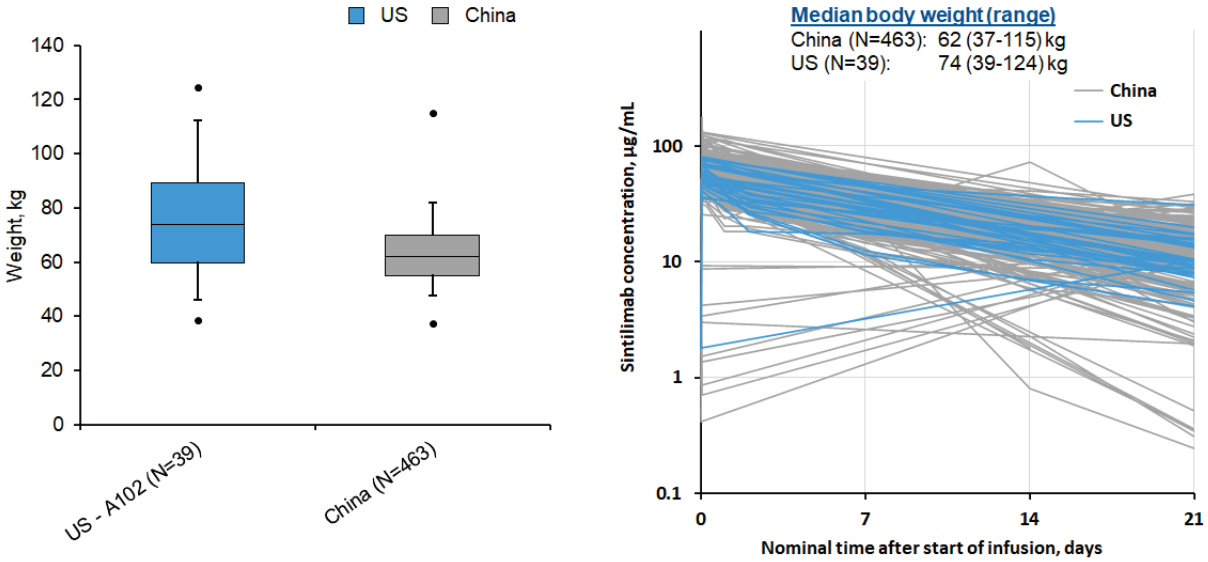


Abbreviations: AUC = area under the concentration-time curve; HCC =hepatocellular carcinoma; HL, Hodgkin's lymphoma; N = number of patients; nsqNSCLC = nonsquamous non-small cell lung cancer; PK = pharmacokinetics; sqNSCLC = squamous non-small cell lung cancer; US = United States.
[a] Other race included 5 Black or African American and 1 American Indian or Alaskan Native.

As illustrated in Figure 10, although body weight distribution differed between US and Chinese cohorts, the range of body weight between the 2 populations overlapped and the observed individual PK profile of sintilimab in US patients (in blue) enrolled in the Phase 1b study (A102) was comparable to that observed in Chinese patients (in gray). The median weight difference between the US[43-45] and Chinese patients with NSCLC is approximately 15 kg. The PopPK analysis has indicated that the 15-kg weight difference would result in approximately a 10% lower exposure in the US population. The combined effect of body weight, sex, and baseline albumin concentration on PK only accounted for <20% of the total variability in sintilimab exposure. Therefore, these effects, including the body weight effect on PK, are not clinically important.

As an IgG mAb, sintilimab is largely eliminated by catabolism; therefore, drug-drug interactions and other extrinsic factors are not expected to have an effect on sintilimab PK.[46]

Figure 10 Impact of Intrinsic Factors (Weight) on PK Profile of Sintilimab in Chinese and US Patients



Abbreviations: N = number of patients; PK = pharmacokinetics; US = United States.

5.3 Exposure-Response Relationships

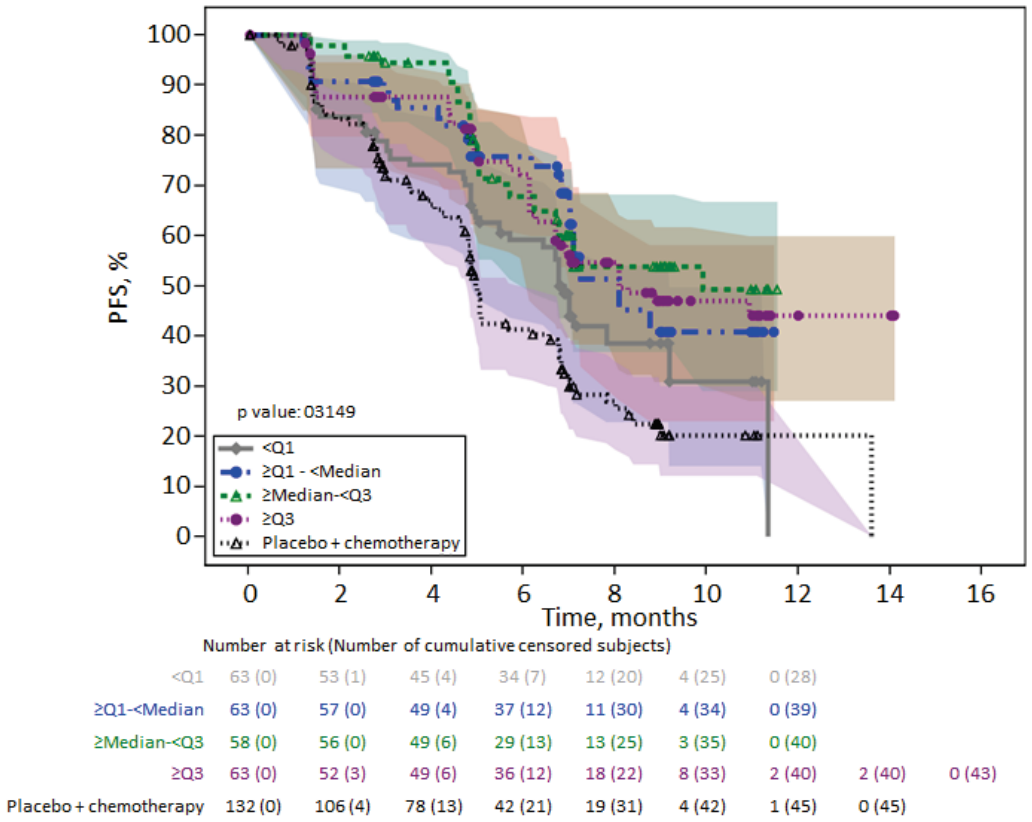
For exposure-efficacy analysis, concentrations from individual patients in ORIENT-11 were divided into quartiles, and PFS was stratified by quartiles of exposure. Results from the analysis suggested that all quartiles have shown clinical benefit when compared with the placebo arm (Figure 11). There does not appear to be a consistent and clinically meaningful exposure-efficacy relationship across the exposure range following 200 mg Q3W. Due to the narrow exposure range following a single dose level studied and the imbalance of baseline characteristics, especially the ECOG status in the first quartile (Table 4), caution should be exercised when interpreting the exposure-response analysis because the results may be influenced by confounding factors such as disease severity rather than a direct PK-related impact of exposure on efficacy.[17,47] Given the linear PK and near saturated levels of PD-1 receptor occupancy observed across a range of dose levels (1 to 10 mg/kg), the 200 mg Q3W dose regimen is likely positioned in the plateauing region of the exposure-response curves.

Table 4 Baseline Characteristics by $C_{min,1}$ Quartile

Baseline characteristics	Quartile 1 <Q1 (N=64)	Quartile 2 ≥Q1 - <Median (N=63)	Quartile 3 ≥Median - <Q3 (N=62)	Quartile 4 ≥Q3 (N=67)
Sex, n (%)				
Male	54 (84)	51 (81)	54 (87)	38 (57)
Female	10 (16)	12 (19)	8 (13)	29 (43)
ECOG performance status, n (%)				
0	11 (17)	21 (33)	23 (37)	21 (31)
1	53 (83)	42 (67)	39 (63)	46 (69)

Abbreviations: $C_{min,1}$ = trough concentration in Cycle 1; ECOG = Eastern Cooperative Oncology Group; N = number of patients; Q = quartile.

Figure 11 Exposure-Response Relationship for Sintilimab in Phase 3 ORIENT-11



Abbreviations: $C_{min,1}$ = trough concentration in Cycle 1; ECOG =Eastern Cooperative Oncology Group; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PS = performance status; Q = quartile.
Note: Red curve for <Q1 $C_{min,1}$ group, Blue curve for >Q1 and<median $C_{min,1}$ group, Green curve for ≥median and <Q3 $C_{min,1}$ group, Purple curve for ≥Q3 $C_{min,1}$ group).
Note: Ten sintilimab combination-treated participants without observed Cycle 1 C_{min} are excluded.
Note: This curve and the number at risk are based on adjusted Kaplan-Meier estimate. The weights are calculated using propensity score weighting method to balance baseline factors (sex, age, PD-L1, Platinum types, ECOG PS, weight, brain metastasis and stage of disease). The number at risk is weighted and rounded to the nearest integer.
Note: p value is obtained by log-rank test to test the homogeneity only in sintilimab combination-treated participants by 4 quartile groups based on sintilimab $C_{min,1}$.

For exposure-safety analyses, no exposure-dependent AEs were observed between different quartiles of individual peak concentrations (C_{max}) in Cycle 4 and at steady state (Table 5).

Table 5 Incidence of Sintilimab-Related ≥Grade 3 Adverse Event Stratified by $C_{max,4}$ and $C_{max,ss}$ Quartiles

Quartile stratifications	<Q1 (N=65)	≥Q1 - <Median (N=66)	≥Median - <Q3 (N=66)	≥Q3 (N=66)
$C_{max,4}$ (%)	24.6	24.2	25.8	19.7
$C_{max,ss}$ (%)	24.6	28.8	22.7	18.2

Abbreviations: $C_{max,4}$ = individual maximum concentrations in Cycle 4; $C_{max,ss}$ = steady-state maximum concentrations; N = number of patients; Q = quartile.

5.4 Immunogenicity

A total of 1,132 immunogenicity samples were collected from 266 patients in the sintilimab combination group in ORIENT-11. Overall, the results indicated a low incidence of immunogenicity, with 5.4% treatment-emergent ADA and 4.2% neutralizing antibody detection in patients with nonsquamous NSCLC treated with sintilimab plus chemotherapy. Immunogenicity had no clinically meaningful impact on PK, efficacy, or safety of sintilimab.

5.5 Clinical Pharmacology Conclusions

Sintilimab has the PK characteristics of an IgG4 mAb that is insensitive to ethnicity. A range of intrinsic factors, including race, tumor type, age, sex, creatinine clearance, mild hepatic impairment (by NCI definition), and ECOG performance status, and ADAs had no clinically meaningful impact on the PK/exposure profile of sintilimab. As an IgG mAb, sintilimab is largely eliminated by catabolism; therefore, drug-drug interactions and other extrinsic factors are not expected to have an effect on sintilimab PK.

The PK profile of sintilimab is comparable between the US and Chinese patient populations, and weight has no clinically meaningful impact on PK. The linear PK and near saturated levels of PD-1 receptor occupancy across the 1- to 10-mg/kg dose range, suggest that the 200-mg Q3W dosing regimen (equivalent to approximately 2.6 mg/kg for the US patient population) is likely positioned in the plateau region of the exposure-response curve. The 200-mg Q3W dosing regimen demonstrated statistically significant and clinically meaningful improvement in PFS and a tolerable safety profile in ORIENT-11. Therefore, the totality of data supports the use of 200 mg as an IV infusion over 30 to 60 minutes Q3W in US patients with nonsquamous NSCLC.

6.0 CLINICAL EFFICACY

Evidence for the efficacy of sintilimab in combination with pemetrexed and platinum-based chemotherapy in the first-line treatment of nonsquamous NSCLC is derived primarily from the pivotal Phase 3 ORIENT-11 study (N=397) and Cohort D of the Phase 1b single-arm Study A101 (N=21). The dosing regimen evaluated in ORIENT-11 was selected based on Study A101.

6.1 Phase 1b Study A101 (Cohort D)

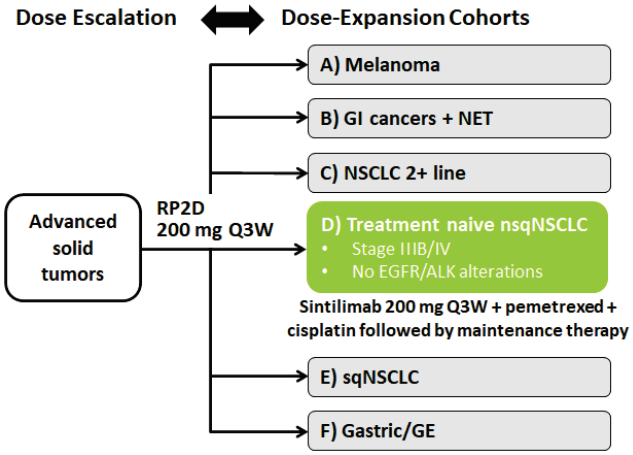
6.1.1 Study Design and Methods

Study A101 was an open-label, multicenter, Phase 1a/1b dose-escalation and -expansion study of sintilimab administered alone or in combination with chemotherapy in patients with advanced cancers. In Cohort D, treatment-naive Chinese patients with inoperable Stage IIIB or Stage IV (per AJCC 7th edition) nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations were enrolled and the safety and preliminary efficacy of sintilimab in combination with pemetrexed and cisplatin was evaluated. The DCO for this cohort was 17 April 2019.

Eligible patients received sintilimab (200 mg) in combination with chemotherapy (pemetrexed and cisplatin) for 4 cycles, followed by maintenance treatment with sintilimab in combination with pemetrexed until disease progression, intolerable toxicity, withdrawal of informed consent, 24 months of treatment with sintilimab, death, or other reasons for discontinuation of study treatment (whichever occurred first).

The Cohort D study design is illustrated in Figure 12.

Figure 12 A101 (Cohort D) Study Design



Abbreviations: ALK = anaplastic lymphoma kinase; CI = confidence interval; EGFR = epidermal growth factor receptor; GE = gastroesophageal; GI = gastrointestinal; NET = neuroendocrine tumor; NR = not reached; NSCLC = non-small cell lung cancer; nsqNSCLC = nonsquamous non-small cell lung cancer; ORR = overall response rate; PFS = progression-free survival; RP2D = recommended Phase 2 dose; sqNSCLC = squamous non-small cell lung cancer; Q3W = every 3 weeks; TRAE = treatment-related adverse event
Note: Cohort G (treatment-naive locally advanced or metastatic high-grade neuroendocrine tumors) and Cohort H (advanced neuroendocrine tumors that progress after first-line therapy) are not shown.

Efficacy endpoints were investigator-assessed objective response rate (ORR), PFS, disease control rate (DCR), duration of response (DOR), and time to response (TTR; according to

Response Evaluation Criteria in Solid Tumors [RECIST] v1.1), and OS. The efficacy data presented are based on all patients who received at least 1 dose of study drug.

6.1.2 Patient Disposition

As of the DCO date (17 April 2019), 13 of the 21 patients (61.9%) who were enrolled in Cohort D of Phase 1b Study A101 had discontinued study treatment. The most common reason for sintilimab discontinuation in Study A101 was progressive disease (53.8%).

6.1.3 Demographic and Baseline Characteristics

The baseline characteristics and efficacy results of Cohort D patients were comparable with that of ORIENT-11. Among the 21 patients enrolled, the median age was 62 (range, 46 to 69) years. The majority of patients were male (76.2%) and had Stage IV disease (76.2%). Most patients (90.5%) had an ECOG performance status score of 1.

6.1.4 Efficacy Results

Results of Study A101 Cohort D showed evidence of antitumor activity based on investigator-assessed efficacy evaluation in 21 patients (Table 6). Median PFS was 12.4 months and the median OS was 18.6 months. The ORR was 52.4% (95% CI: 29.8, 74.3), and median DOR has not been reached.

Table 6 Summary of Efficacy (Investigator-assessed) – A101 (Cohort D)

Statistic	Sintilimab + chemotherapy (N=21)
Progression-free survival	
Number of events, n (%)	11 (52.4)
Number censored, n (%)	10 (47.6)
Median PFS,[a] months (95% CI)	12.4 (3.0, NR)
Overall survival	
Number of events, n (%)	9 (42.9)
Number censored, n (%)	12 (57.1)
Median OS,[a] months (95% CI)	18.6 (5.2, NR)
Objective response rate	
% (95% CI)[b]	52.4 (29.8, 74.3)
Complete response, n (%)	0
Partial response, n (%)	11 (52.4)
Stable disease, n (%)	5 (23.8)
Progressive disease, n (%)	3 (14.3)
Not evaluable, n (%)	2 (9.5)
Disease control rate	
% (95% CI)[b]	76.2 (52.8, 91.8)
Duration of response (months)	
Number of events, n (%)	3 (27.3)
Number censored, n (%)	8 (72.7)
Median DOR,[a] months (95% CI)	NR (5.75, NR)

Abbreviations: CI = confidence interval; DOR = duration of response; N = number of patients; n = number of patients in specified category; NR = not reached; OS = overall survival; PFS = progression-free survival.

[a] Median was estimated based on unstratified Kaplan-Meier method.

[b] 95% CI is estimated based on Clopper-Pearson method.

Based on these encouraging results, the ORIENT-11 study was initiated.

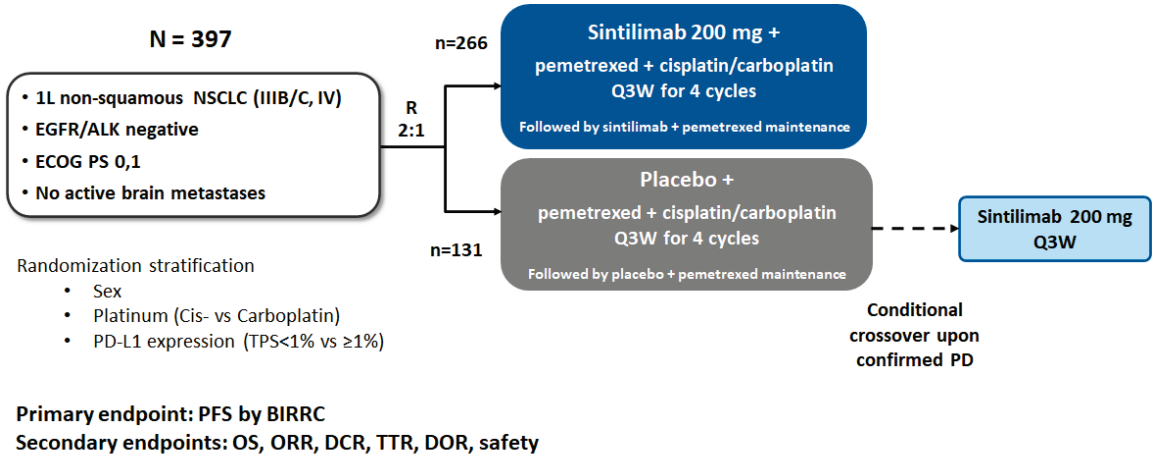
6.2 Primary Phase 3 Study CIBI308C302 (ORIENT-11)

6.2.1 Study Design and Methods

ORIENT-11 is an ongoing randomized (2:1), double-blind, placebo-controlled, Phase 3 study conducted in mainland China. The study enrolled patients with Stage IIIB/C (per AJCC 8th edition, who were ineligible for radical surgery or chemoradiation with a curative intent) or metastatic or recurrent Stage IV nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations.

Patients were to receive 4 cycles of sintilimab (200 mg Q3W) or placebo administered in combination with pemetrexed and cisplatin or carboplatin, followed by maintenance therapy with sintilimab or placebo in combination with pemetrexed. The maximum treatment duration was 24 months. Randomization was stratified by sex, PD-L1 expression[1] level (tumor proportion score [TPS] <1% vs ≥1%) using the Agilent 22C3 assay at a central laboratory (Covance, Shanghai), and type of platinum chemotherapy (cisplatin vs carboplatin). Patients initially randomized to the placebo combination arm with confirmed disease progression were allowed to conditionally crossover to receive sintilimab monotherapy at the discretion of the investigator if all protocol-specific criteria were met. The ORIENT-11 study design is illustrated in Figure 13.

Figure 13 ORIENT-11 Study Design



Abbreviations: 1L = first-line; ALK = anaplastic lymphoma kinase; BIRRC = Blinded Independent Radiographic Review Committee; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; N = number of patients; n = number of patients in specified category; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-L1 = programmed cell death-ligand 1; PFS = progression-free survival; PS = performance status; Q3W = every 3 weeks; R = randomization; TPS = tumor proportional score; TTR = time to response.
Enrollment period: August 2018-July 2019.

The primary endpoint of this study was PFS by Blinded Independent Radiographic Review Committee (BIRRC) using RECIST 1.1, and central imaging was by a validated vendor (PAREXEL). Secondary endpoints were OS, ORR, DCR, TTR, DOR, and safety.

[1] PD-L1 expression was assessed in archival or freshly prepared formalin-fixed paraffin-embedded tumor tissue collected during patient screening by immunohistochemistry.

6.2.1.1 Choice of Primary Endpoint

During the initial study design discussion with NMPA, PFS was chosen as the primary endpoint. PFS is a valid primary endpoint in first-line NSCLC that is not confounded by post-discontinuation therapy, considering the study allowed crossover by design. Moreover, PFS correlates with OS, if a large magnitude of treatment effect is observed.

6.2.1.2 Choice of Combination and Comparator Agent

The encouraging clinical activity for sintilimab in combination with pemetrexed and cisplatin in previously untreated patients with nonsquamous NSCLC from Study A101 led to the design and execution of the pivotal trial ORIENT-11 in mainland China. At the time of study initiation, the combination of pemetrexed in combination with a platinum agent was a recognized and accepted regulatory standard of care in China for the treatment of nonsquamous NSCLC and therefore an appropriate control arm. The design of ORIENT 11 was also agreed with NMPA and approved by all ethics review boards who reviewed this study.

6.2.1.3 Key Eligibility Criteria

ORIENT-11 enrolled patients ≥18 to ≤75 years of age with a histologically or cytologically confirmed diagnosis of locally advanced (Stage IIIB/C), metastatic, or recurrent (Stage IV) nonsquamous NSCLC. Patients with Stage IIIB/C nonsquamous NSCLC were eligible if they were not suitable for radical surgery or chemoradiation with curative intent. Other key inclusion criteria were documented absence of sensitizing EGFR mutations and ALK gene rearrangements, ECOG performance status of 0 or 1, no prior systemic antineoplastic therapy for advanced nonsquamous NSCLC, and adequate organ function.

Patients were excluded if they met any of the following key exclusion criteria: predominantly squamous NSCLC histology; received prior anti-PD-1, anti-PD-L1, or anti-PD-L2 agents; received Chinese medications with anti-lung cancer indications or immunomodulatory drugs within 2 weeks prior to first dose; received radiotherapy in lung at a dose of >30 Gy within 6 months prior to first dose; active autoimmune disease requiring systemic therapy; and had not adequately recovered from toxicity and/or complications caused by interventions prior to starting study treatment (i.e., ≤ Grade 1 or to baseline, excluding asthenia or alopecia).

6.2.1.4 Data Monitoring Committee

ORIENT-11 utilized an independent Data Monitoring Committee (iDMC) composed of 3 external, independent experts (2 oncologists and a biostatistician) from major academic institutions or cancer centers in China. All iDMC members had served as DMC members on other Phase 3 studies, including multiregional studies.

Per the charter, following the conclusion of an iDMC safety/efficacy data review meeting, the iDMC could make recommendations of continuing or suspending the enrollment of new patients or discontinuing the clinical trial. Furthermore, the iDMC could also propose protocol changes to the implementation of the study, including protocol revisions.

6.2.1.5 Statistical Analysis Methods

The sample size of the study was based on the primary efficacy endpoint, which was PFS as assessed by BIRRC. It was assumed that the median PFS time of patients receiving sintilimab

treatment would be improved from 6 months to 9.2 months (with HR=0.65). With an enrollment time projection of 15 months, a projected follow-up time of 8 months, and an estimated dropout rate of 0.5% per month, to provide approximately 90% power under a 2-sided alpha = 0.05, a total of 378 patients (2:1 randomization ratio) were needed to be randomized to obtain the required 263 PFS events. The interim PFS analysis was planned after 184 (70%) events were observed. The interim analysis boundary was based on an O'Brien-Fleming spending function, where the alpha spent at the interim analysis was 0.015 (2-sided). The boundary was met at the interim analysis, and the iDMC recommended to continue the study as planned. The secondary endpoint was not alpha controlled. The time of final OS analysis was defined in the protocol amendment post interim analysis as approximately 2 years after last patient randomized or when 65% patients died, whichever occurred earlier.

6.2.1.6 Data Sets Analyzed

The data presented herein for ORIENT-11 include the interim analyses for efficacy and safety (DCO, 15 November 2019).

Overall survival data and post-discontinuation therapy from the final analysis, with a DCO of 15 September 2021 and a total of 243 OS events, are also presented.

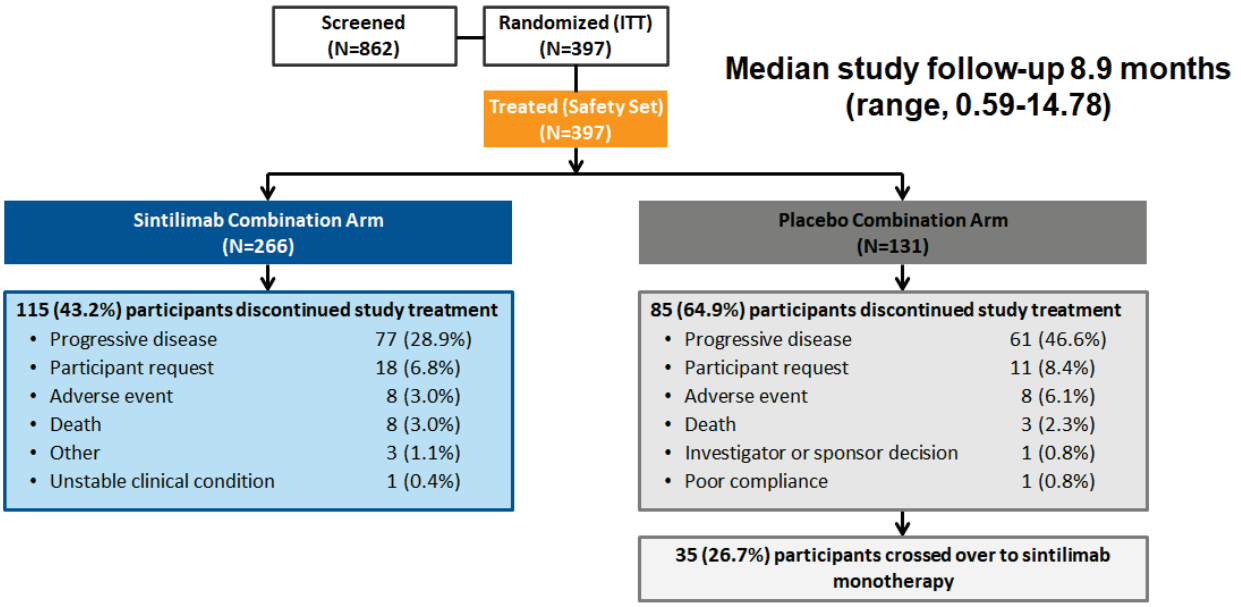
Efficacy analyses for ORIENT-11 are based on the intent-to-treat (ITT) population, defined as all randomized patients, with allocation to treatment arms as randomized.

6.2.2 Patient Disposition

ORIENT-11 was a well-controlled study conducted at 48 academic sites in China. Overall, 862 patients were screened, of whom 465 were screen failures (Figure 14). The main reasons for screen failure were sensitizing EGFR mutations or ALK gene rearrangements (44.5%), any disease, treatment, or laboratory abnormality that may interfere with study results or participation (7.1%), symptomatic central nervous system metastases (6.2%), breast feeding (4.9%), and Stage IIIB/C disease amenable to treatment with curative intent (3.0%). A total of 397 patients with nonsquamous NSCLC were randomized (2:1) to the sintilimab combination arm (N=266) or placebo combination arm (N=131). These patients constitute the ITT population.

As of the interim analysis DCO date (15 November 2019), the median follow-up time was 8.9 months (range, 0.6 to 14.8 months) as measured from randomization to death or last known alive date. A total of 197 patients (151 in the sintilimab combination arm and 46 in the placebo combination arm) continued to receive study treatment. The most common reason for discontinuation was progressive disease (28.9% in the sintilimab combination arm; 46.6% in the placebo combination arm). Thirty-five patients (26.7%) randomized to the placebo combination arm subsequently received crossover treatment with sintilimab monotherapy.

Figure 14 Patient Disposition – ORIENT-11



Abbreviations: ITT = intent-to-treat; N = number of patients.
Data cutoff date: 15 November 2019.

6.2.3 Demographic and Baseline Characteristics

Overall, there were no observed imbalances in patient demographics or baseline characteristics (Table 7) between the treatment arms that would impact the interpretation of the efficacy results. The median age of patients was 61 years (range, 30 to 75 years). The majority of patients in both treatment arms were male, had an ECOG performance status score of 1, and did not have brain metastases. Most patients had Stage IV disease.

Table 7 Demographics and Baseline Characteristics – ORIENT-11 (ITT Population)

Characteristics	Sintilimab + chemotherapy (N=266)	Placebo + chemotherapy (N=131)
Sex, n (%)		
Male	204 (76.7)	99 (75.6)
Female	62 (23.3)	32 (24.4)
Age, years		
Median (SD)	59.9 (8.35)	59.5 (8.73)
Median (range)	61 (30-75)	61 (35-75)
≤60 years, n (%)	126 (47.4)	60 (45.8)
>60 years, n (%)	140 (52.6)	71 (54.2)
Race, n (%)		
Chinese	266 (100.0)	131 (100.0)
ECOG performance status, n (%)		
0	76 (28.6)	34 (26.0)
1	190 (71.4)	97 (74.0)

Characteristics	Sintilimab + chemotherapy (N=266)	Placebo + chemotherapy (N=131)
Platinum (entry on CRF), n (%)		
Cisplatin	71 (26.7)	33 (25.2)
Carboplatin	195 (73.3)	98 (74.8)
Smoking status, n (%)		
Never	95 (35.7)	44 (33.6)
Current	49 (18.4)	23 (17.6)
Former	122 (45.9)	64 (48.9)
Duration since diagnosis, months		
Mean (SD)	1.47 (2.26)	1.66 (2.65)
Median (range)	0.92 (0.03-20.24)	1.02 (0.33-17.54)
PD-L1 expression level (entry on CRF), n (%)		
<1%	85 (32.0)	44 (33.6)
≥1%	181 (68.0)	87 (66.4)
Disease staging, n (%)		
IIIB	14 (5.3)	6 (4.6)
IIIC	7 (2.6)	9 (6.9)
IV	245 (92.1)	116 (88.5)
Brain metastasis, n (%)		
Yes	36 (13.5)	22 (16.8)
No	230 (86.5)	109 (83.2)
Prior adjuvant chemotherapy, n (%)	6 (2.3)	10 (7.6)
Prior surgery for lung cancer, n (%)	30 (11.3)	19 (14.5)
Prior radiotherapy for lung cancer, n (%)	11 (4.1)	9 (6.9)

Abbreviations: CRF = case report form; ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; N = number of patients; n = number of patients in specified category; PD-L1 = programmed death-ligand 1; SD = standard deviation.

6.2.4 Efficacy Results

6.2.4.1 Primary Efficacy Endpoint: Progression-free Survival

In the primary analysis (using the ITT population based on BIRRC assessment), treatment with sintilimab in combination with pemetrexed and platinum-based chemotherapy demonstrated a statistically significant and clinically meaningful PFS improvement compared with the placebo combination arm (HR=0.48, 95% CI: 0.36, 0.64; p<0.00001 [interim analysis 2-sided alpha threshold = 0.01958]) (Table 8). The median PFS was 8.9 and 5.0 months in the sintilimab and placebo combination arms, respectively.

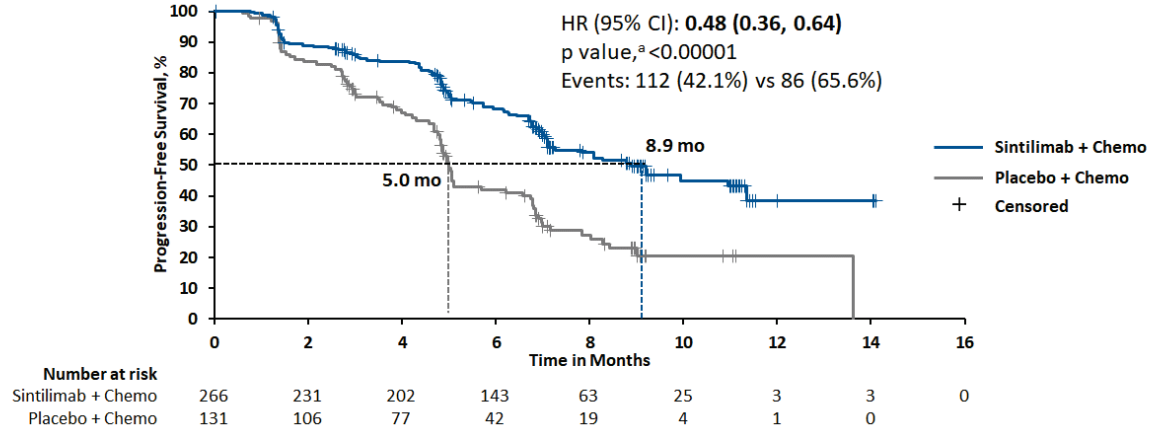
Table 8 BIRRC-Assessed Progression-Free Survival – ORIENT-11 (Interim Analysis [DCO, 15 November 2019]; ITT Population)

Statistic	Sintilimab + chemotherapy (N=266)	Placebo + chemotherapy (N=131)
PFS at interim analysis[a]		
Number of events, n (%)	112 (42.1)	86 (65.6)
Number censored, n (%)	154 (57.9)	45 (34.4)
Median PFS,[b] months (95% CI)	8.9 (7.1, 11.3)	5.0 (4.8, 6.2)
Stratified HR[c] (95% CI)	0.48 (0.36, 0.64)	
Stratified log-rank p value[d]	<0.00001	

Abbreviations: BIRRC = Blinded Independent Radiographic Review Committee; CI = confidence interval; DCO = data cutoff; HR = hazard ratio; ITT = intent-to-treat; N = number of patients; n = number of patients in specified category; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.
Note: Responses were assessed according to RECIST version 1.1.
[a] Data cutoff date of 15 November 2019.
[b] Median was estimated based on unstratified Kaplan-Meier method.
[c] Hazard ratio was obtained from a Cox proportional hazard regression model with treatment group as independent variable and adjusted for stratification factors at randomization.
[d] P value was calculated using a stratified log-rank test with the same stratification factors as randomization strata.

The Kaplan-Meier PFS curves show an early separation between the treatment arms beginning at approximately 1.5 months and that was sustained throughout the entire observation time period (Figure 15).

Figure 15 BIRRC-Assessed Progression-Free Survival (Interim Analysis; DCO 15 November 2019) – ORIENT-11 (ITT Population)



Abbreviations: BIRRC = Blinded Independent Radiographic Review Committee; Chemo = chemotherapy; CI = confidence interval; CSR = clinical study report; HR = hazard ratio; ITT = intent-to-treat.
[a] Interim analysis α boundary based on 198 PFS events is 0.01958
Data cutoff date: 15 November 2019.

The statistical significance, magnitude of the PFS treatment effect, and robustness of the primary PFS analysis results were supported by sensitivity analyses, with observed HRs ranging between 0.48 and 0.62, each with p≤0.0005 (Table 9).

Table 9 Sensitivity Analyses of Progression-Free Survival – ORIENT-11

Analysis	Hazard ratio (95% CI)	p value
Primary PFS analysis by BIRRC assessment		
PFS analysis in the ITT population	0.48 (0.36, 0.64)	<0.00001
PFS sensitivity analyses by BIRRC assessment		
PFS analysis in the FAS population (N=390)	0.48 (0.36, 0.64)	<0.00001
PFS analysis in the PPS population (N=386)	0.48 (0.36, 0.64)	<0.00001
SA1[a] of PFS in the ITT population	0.48 (0.36, 0.64)	<0.00001
SA2[b] of PFS in the ITT population	0.51 (0.39, 0.67)	<0.00001
PFS sensitivity analysis by investigator assessment		
PFS analysis in the ITT population	0.62 (0.47, 0.81)	0.00050

Abbreviations: BIRRC = Blinded Independent Radiographic Review Committee; CI = confidence interval; FAS = Full Analysis Set; ITT = intent-to-treat; PD = progressive disease; PFS = progression-free survival; PPS = Per-Protocol Set; SA = sensitivity analysis.

[a] SA1: Censor PFS to the last adequate tumor scan prior to missing ≥2 consecutive tumor assessments.

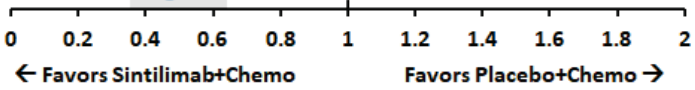
[b] SA2: Set treatment discontinuation or starting new anticancer treatment without PD or death as events.

Data cutoff date: 15 November 2019.

A PFS treatment benefit for the sintilimab combination was consistently observed across all prespecified subgroups (Figure 16).

Figure 16 BIRRC-Assessed Progression-Free Survival Across Prespecified Subgroups – ORIENT-11 (ITT Population)

Subgroup	Sintilimab + Chemotherapy	Placebo + Chemotherapy	HR (95% CI)
Total	112/266	86/131	0.48 (0.36, 0.64)
Sex			
Male	84/204	68/99	0.44 (0.32, 0.61)
Female	28/62	18/32	0.60 (0.33, 1.10)
Age group			
≤60 years	48/126	40/60	0.43 (0.28, 0.67)
>60 years	64/140	46/71	0.53 (0.36, 0.77)
ECOG performance status at baseline			
0	29/76	21/34	0.48 (0.27, 0.86)
1	83/190	65/97	0.49 (0.35, 0.68)
Platinum			
Cisplatin	34/71	23/33	0.53 (0.31, 0.90)
Carboplatin	78/195	63/98	0.46 (0.33, 0.64)
PD-L1 expression level[a]			
<1%	39/77	25/40	0.62 (0.37, 1.03)
≥1%	69/181	60/87	0.39 (0.27, 0.55)
Smoking status			
Former/Current	70/171	60/87	0.45 (0.32, 0.63)
Never	42/95	26/44	0.56 (0.34, 0.92)
Brain metastasis			
Yes	19/36	14/22	0.58 (0.28, 1.18)
No	93/230	72/109	0.47 (0.34, 0.64)



Abbreviations: BIRRC = Blinded Independent Radiographic Review Committee; Chemo = chemotherapy; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ITT = intent-to-treat; PD-L1 = programmed death-ligand 1.
[a] Only includes evaluable patients.
Data cutoff date: 15 November 2019.

Table 10 summarizes the PFS analysis of BIRRC-assessed by Stage IIIB/C and Stage IV disease. A PFS treatment benefit for the sintilimab combination arm was observed across Stage IIIB/C and Stage IV disease.

Table 10 BIRRC-Assessed Progression-Free Survival by Stage IIIB-C and Stage IV Disease – ORIENT-11 (ITT Population)

Stage	Sintilimab + chemo vs Placebo + chemo (N)	Events	Median (months)	HR (95% CI) by stratified Cox regression
IIIB/C	21 vs 15	5 vs 13	NR vs 4.9	0.17 (0.06, 0.48)
IV	245 vs 116	107 vs 73	8.1 vs 5.0	0.53 (0.39, 0.72)

Abbreviations: BIRRC = Blinded Independent Radiographic Review Committee; Chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; N = number of patients; NR = not reached.
Data cutoff date: 15 November 2019.

6.2.4.2 Secondary Efficacy Endpoints

ORIENT-11 was initially designed in consultation with NMPA. Based on NMPA consultation, the study was powered for PFS, assuming a PFS HR of 0.65. Thus, gatekeeping for the secondary endpoints was not prespecified.

Overall, consistent treatment benefits were observed across multiple, clinically relevant secondary endpoints, including OS, ORR, DCR, and DOR, reinforcing the positive effect of the sintilimab combination.

6.2.4.2.1 Overall Survival

Survival status was collected using phone calls every 90 days after treatment discontinuation and safety follow-up. The methods of analyzing the OS were predefined in the protocol and statistical analysis plan (SAP). Vital status of most patients was within the planned survival follow-up window.

At the time of interim analysis (DCO, 15 November 2019), OS was not mature with 51 events (19.2%) had occurred in the sintilimab combination arm and 39 events (29.8%) had occurred in the placebo combination arm. The median OS had not been reached in either treatment arm (Table 11). The OS Kaplan-Meier curves showed an early separation with an HR of 0.61 (95% CI: 0.40, 0.93) (Figure 17).

Updated OS data were provided to the FDA 3 times: (1) per agreement at the pre-IND meeting with a DCO of 15 May 2020 (representing an additional 6 months of follow-up from the interim OS DCO), (2) per agreement at the pre-BLA meeting with a DCO of 15 January 2021 (representing an additional 14 months of follow-up from the interim OS DCO), and (3) per agreement at the mid-cycle meeting with a DCO of 15 September 2021 (representing an additional 22 months of follow-up from the interim OS DCO, here denoted as final analysis). Data from the final OS analysis are presented herein. Consistent with the OS data at the interim analysis for PFS and with the OS data from subsequent DCOs in May 2020 and January 2021, a marked benefit in OS was observed for patients on the sintilimab treatment arm.

At the DCO of the final OS analysis (15 September 2021), there were 151 events (56.8%) in the sintilimab combination arm and 92 events (70.2%) in the placebo combination arm (Table 11). Sixty-one patients (46.6%) in the placebo combination arm had crossed over to sintilimab

monotherapy as permitted by the protocol. The Kaplan-Meier curve showed an early and sustainable separation with a HR of 0.65 (95% CI: 0.50, 0.85; p=0.00135). Median OS was 24.2 months in sintilimab combination arm and 16.8 months in the placebo combination arm (Table 11 and Figure 17). The OS rates for the sintilimab combination arm versus placebo combination arm were 89.1% versus 80.1% at 6 months, 71.8% versus 57.8% at 12 months, and 60.2% versus 43.9% at 18 months.

Table 11 Summary of Overall Survival (Interim and Final Analyses) – ORIENT-11 (ITT Population)

Statistics	Interim OS analysis (DCO date, 15 Nov 2019)		Final OS analysis (DCO date, 15 Sep 2021)	
	Sintilimab + chemotherapy (N=266)	Placebo + chemotherapy (N=131)	Sintilimab + chemotherapy (N=266)	Placebo + chemotherapy (N=131)
Number of events, n (%)	51 (19.2)	39 (29.8)	151 (56.8)	92 (70.2)
Number censored, n (%)	215 (80.8)	92 (70.2)	115 (43.2)	39 (29.8)
Overall survival				
Median[a] (95% CI), months	NR (NR, NR)	NR (11.4, NR)	24.2 (19.6, 31.0)	16.8 (11.0, 18.5)
Stratified HR[b] (95% CI)	0.61 (0.40, 0.93)		0.65 (0.50, 0.85)	
Log-rank p value (2-sided)[c]	0.01921		0.00135	
OS rate[a] at				
6 months (95% CI)	89.6 (85.2, 92.8)	80.4 (72.4, 86.3)	89.1 (84.7, 92.3)	80.1 (72.2, 86.0)
12 months (95% CI)	69.6 (59.6, 77.6)	58.9 (44.7, 70.7)	71.8 (66.0, 76.8)	57.8 (48.8, 65.7)
18 months (95% CI)	NR	NR	60.2 (54.0, 65.7)	43.9 (35.3, 52.2)

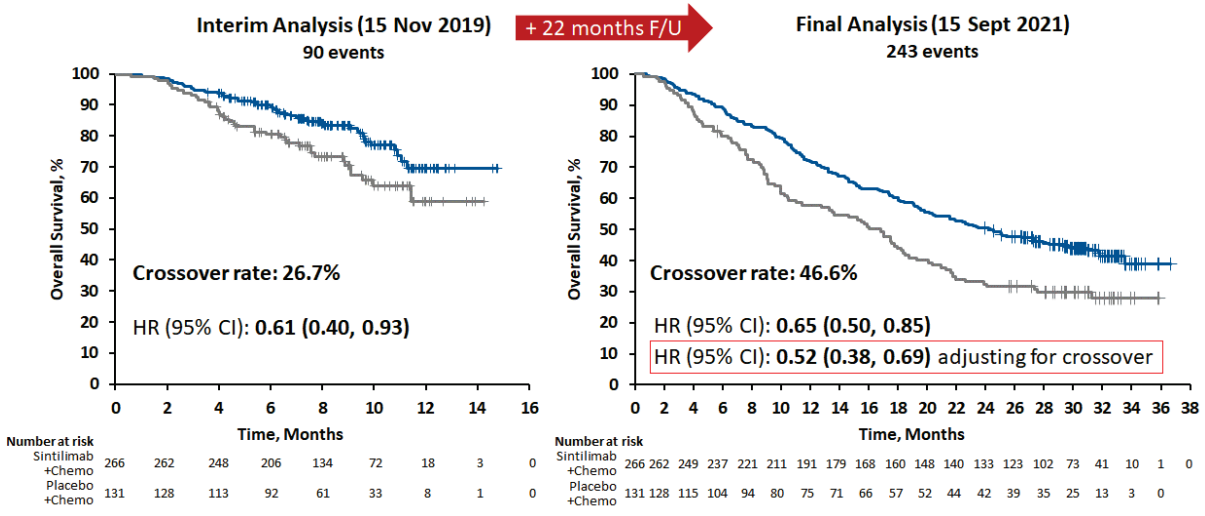
Abbreviations: CI = confidence interval; DCO = data cutoff; HR = hazard ratio; ITT = intent-to-treat; N = number of patients; n = number of patients in specified category; NR = not reached; OS = overall survival.

[a] Median survival rates were estimated based on unstratified Kaplan-Meier method.

[b] Hazard ratio was obtained from a Cox proportional hazard regression model adjusted for stratification factors at randomization.

[c] P value was calculated using a stratified log-rank test with the same stratification factors as randomization strata.

Figure 17 Kaplan-Meier Estimate of Overall Survival With Crossover to Sintilimab (Interim and Final Analyses) – ORIENT-11 (ITT Population)



Abbreviations: Chemo = chemotherapy; CI = confidence interval; F/U = follow-up; HR = hazard ratio; ITT = intent-to-treat.

To help interpret the observed OS p value at final analysis, the O'Brien-Fleming and Bonferroni p-value boundaries were retrospectively calculated to adjust for multiple OS analyses (4 analysis DCOs) (Table 12). The final OS analysis p value based on a log-rank test was 0.00135, which is smaller than the O'Brien-Fleming and Bonferroni boundaries.

Table 12 Retrospectively Calculated Overall Survival P-Value Boundary

Analysis	PFS interim (15 Nov 2019)	FDA agreement (15 May 2020)	120-day Safety Update (15 Jan 2021)	Final analysis (15 Sep 2021)
OS events	90	149	207	243
OS HR (95% CI)	0.61 (0.40, 0.93)	0.61 (0.44, 0.84)	0.60 (0.45, 0.79)	0.65 (0.50, 0.85)
OBF boundary[a]	0.00046	0.00826	0.02770	0.04058
Bonferroni boundary[a]	0.01250	0.01250	0.01250	0.01250
Observed p value	**0.01921**	**0.00250**	**0.00027**	**0.00135**

Abbreviations: FDA = US Food and Drug Administration; HR = hazard ratio; OBF = O'Brien-Fleming boundary; PFS = progression-free survival.
[a] Post-hoc adjustment for multiplicity.

Prespecified OS analyses were conducted to assess the impact of sintilimab monotherapy crossover treatment, where the crossover rates were 26.7% at the interim analysis (DCO, 15 November 2019) and 46.6% at the final analysis (DCO, 15 September 2021) (Table 13).

Although not formally alpha controlled, based on predefined analysis methods, the OS HR is robust with prolonged survival follow-up. After adjustment of crossover effect by rank-preserving structural failure time model, the OS HR is 0.52 (95% CI: 0.38, 0.69). In addition, the OS results are comparable with other checkpoint inhibitors in first-line NSCLC. Therefore, the observed OS results are unlikely due to chance.

Table 13 Sensitivity Analyses of Overall Survival for Crossover Effect – ORIENT-11

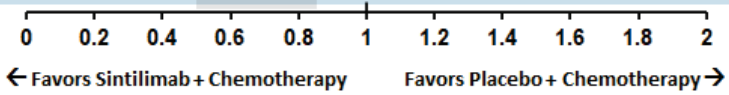
Prespecified OS sensitivity analyses	Hazard ratio (95% CI)[c]	P value[c]
Interim OS analysis (DCO, 15 Nov 2019)	**0.61 (0.40, 0.93)**	**0.01921**
OS analysis based on RPSFTM[a]	0.56 (0.33, 0.95)	0.02147
OS analysis based on 2-stage estimation method[b]	0.51 (0.33, 0.77)	0.00128
Final OS analysis (DCO, 15 Sep 2021)	**0.65 (0.50, 0.85)**	**0.00135**
OS analysis based on RPSFTM[a]	0.52 (0.38, 0.69)	0.00001
OS analysis based on 2-stage estimation method[b]	0.49 (0.315, 0.72)	0.00003

Abbreviations: CI = confidence interval; CRF = case report form; DCO = data cutoff; OS = overall survival; RPSFTM = rank-preserving structural failure time model.
[a] Counterfactual survival time for placebo combination group is adjusted using RPSFTM with re-censoring for crossover effect, and 95% CI is estimated using bootstrapping method with seed 1.
[b] Counterfactual survival time for placebo combination group is adjusted using 2-stage estimated method without re-censoring for crossover effect.
[c] p value is from stratified log-rank test, and hazard ratio is obtained from a stratified Cox proportional hazards regression model with treatment group as factor, and CRF stratification factors at randomization as stratification variables.

As of the DCO date for the final analysis (15 September 2021), the prespecified subgroup analyses of OS were performed to further evaluate the treatment effect (Figure 18). In the ITT population, the point estimate OS HR favored the sintilimab combination arm across prespecified subgroups. The degree of variability observed in effect size across subgroups is within the range expected for a study of this size with this number of subgroup analyses.

Figure 18 Overall Survival Across Prespecified Subgroups (Final Analysis [DCO, 15 September 2021]) – ORIENT-11 (ITT Population)

Subgroup	Sintilimab + Chemotherapy Events/N	Placebo + Chemotherapy Events/N	Hazard Ratio (95% CI)
Total	151/266	92/131	0.654 (0.503, 0.849)
Sex			
Male	116/204	75/99	0.572 (0.427, 0.766)
Female	35/62	17/32	0.991 (0.555, 1.771)
Age group			
≤60 years	62/126	38/60	0.589 (0.394, 0.881)
>60 years	89/140	51/71	0.709 (0.500, 1.007)
ECOG performance status at baseline			
0	35/76	22/34	0.598 (0.346, 1.033)
1	116/190	70/97	0.674 (0.498, 0.911)
Platinum			
Cisplatin	40/71	26/33	0.530 (0.323, 0.871)
Carboplatin	111/195	66/98	0.696 (0.512, 0.946)
PD-L1 expression level (CRF)[a]			
<1%	51/77	29/40	0.754 (0.477, 1.194)
≥1%	94/181	62/87	0.557 (0.403, 0.768)
Smoking status			
Former/Current	96/171	66/87	0.560 (0.408, 0.768)
Never	55/95	26/44	0.905 (0.565, 1.450)



Abbreviations: CI = confidence interval; CRF = case report form; DCO = data cutoff; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ITT = intent-to-treat; N = number of patients; PD-L1 = programmed death-ligand 1.
HR and 95% CI are estimated using a stratified Cox proportional hazard regression model with treatment group, subgroup variable and their interaction as factor, and CRF stratification factors at randomization variable as stratification variables. Subgroup variable should be excluded from stratificationvariables if it coincides with the stratification variable.
[a] Only includes evaluable patients.
Data cutoff date: 15 September 2021.

Table 14 summarizes the subsequent anticancer therapies patients received after study treatment in ORIENT-11 at the time of final OS analysis (DCO, 15 September 2021). Overall, approximately half of patients in the placebo arm received immune checkpoint inhibitors as subsequent anticancer therapy.

Table 14 Subsequent Anticancer Therapy (Final Analysis [DCO, 15 September 2021]) – ORIENT-11 (ITT Population)

Therapy	Number (%) of patients	
	Sintilimab + chemo (N=266)	Placebo + chemo (N=131)
Any subsequent therapy after study treatment (including crossover)[a]	**135 (50.8)**	**89 (67.9)**
Immunotherapy	39 (14.7)	72 (55.0)
Sintilimab	23 (8.6)	66 (50.4)
Crossover to sintilimab per protocol (post-progression)	0	61 (46.6)
Received sintilimab off study	23 (8.6)	8 (6.1)
Other PD-1/L1 inhibitors	17 (6.4)	11 (8.4)
Chemotherapy	93 (35.0)	34 (26.0)
Taxanes	67 (25.2)	25 (19.1)
Platinum compounds	42 (15.8)	15 (11.5)
Pyrimidine analogs	15 (5.6)	5 (3.8)
Other antineoplastic agents	13 (4.9)	2 (1.5)
VEGFR2 tyrosine kinase inhibitors	55 (20.7)	16 (12.2)
EGFR tyrosine kinase inhibitors	8 (3.0)	7 (5.3)
Monoclonal antibodies[b]	43 (16.2)	18 (13.7)

Abbreviations: Chemo = chemotherapy; DCO = data cutoff; EGFR = epidermal growth factor receptor; ITT = intent-to-treat; N = number of patients; PD-1/L1 = programmed death-1/programmed death-ligand-1; VEGFR2 = vascular endothelial growth factor receptor 2.
Note: Subsequent surgery and radiotherapy for lung cancer after last double-blind treatment are not reported.
[a] Including per-protocol crossover to sintilimab monotherapy.
[b] Excluding PD-1/L1 inhibitor.

6.2.4.2.2 Objective Response Rate, Disease Control Rate, and Duration of Response

In the ITT population, the BIRRC-assessed ORR was higher in the sintilimab combination arm than in the placebo combination arm (51.9% vs 29.8%, respectively) (Table 15). The BIRRC-assessed DCRwas also improved in the sintilimab combination arm versus the placebo combination arm (86.8% vs 75.6%, respectively). The BIRRC-assessed median DOR was not reached in the sintilimab combination arm but was 5.5 months (95% CI: 4.1, 10.9) in the placebo combination arm (HR=0.54; 95% CI: 0.29, 1.0). The sintilimab combination demonstrated a higher and more durable response, which contributed to prolonged PFS and OS.

Table 15 Summary of Objective Response Rate, Disease Control Rate, and Duration of Response (Interim Analysis) – ORIENT-11 (ITT Population)

Statistics	Interim OS Analysis (DCO date, 15 Nov 2019)	
	Sintilimab + chemo (N=266)	Placebo + chemo (N=131)
Objective response rate[a]		
% (95% CI)	51.9 (45.70, 58.02)	29.8 (22.10, 38.38)
p value[b]	0.00003	

Statistics	Interim OS Analysis (DCO date, 15 Nov 2019)	
	Sintilimab + chemo (N=266)	Placebo + chemo (N=131)
Disease control rate[a]		
% (95% CI)	86.8 (82.18, 90.66)	75.6 (67.30, 82.65)
p value[b]	0.0055	
Duration of response		
Number of events,[c] n (%)	38 (27.5)	17 (43.6)
Number censored, n (%)	100 (72.5)	22 (56.4)
Median DOR,[d] months (95% CI)	NR (7.98, NR)	5.52 (4.14, 10.94)
Stratified HR[e] (95% CI)	0.540 (0.293, 0.995)	

Abbreviations: Chemo = chemotherapy; CI = confidence interval; DCO = data cutoff; DOR = duration of response; HR = hazard ratio; ITT = intent-to-treat; N = number of patients; NR = not reached; OS = overall survival.

[a] 95% CI is estimated based on Clopper-Pearson method.

[b] Descriptive p value was calculated using Miettinen-Nurminen method.

[c] Based on patients who responded to treatment (sintilimab combination arm: 138; placebo combination arm: 39).

[d] Median was estimated based on unstratified Kaplan-Meier method.

[e] HR was obtained from a Cox proportional hazard regression model with treatment group as independent variable and adjusted for stratification factors at randomization.

6.2.4.3 Exploratory Endpoints

6.2.4.3.1 Quality of Life Assessment

Patient-reported quality of life was assessed using the Lung Cancer Symptom Scale and European Organization for Research and Treatment of Cancer Core Questionnaire (V3.0 Chinese version), which were administered to patients before the first dose, at each imaging evaluation, and at the first end-of-treatment visit.

There was no significant differences or deterioration of scores on these scales with the addition of sintilimab to pemetrexed and platinum.

6.3 Overall Efficacy Conclusions

In the Phase 3 ORIENT-11 study, sintilimab in combination with pemetrexed and platinum-based chemotherapy demonstrated clinically meaningful treatment effects across all endpoints, including PFS, OS, and ORR, compared with chemotherapy alone. This study met its primary endpoint of PFS at the interim efficacy analysis (HR=0.48; 95% CI: 0.36, 0.64; p<0.00001), demonstrating statistically significant and clinically meaningful benefit of substantial magnitude to support full approval. For patients treated with sintilimab in combination with pemetrexed and platinum-based chemotherapy there was a reduction in the risk of death compared to patients treated with placebo in combination with pemetrexed and platinum-based chemotherapy. This was true at the time of the interim efficacy analysis for PFS when the primary endpoint was met and continued at subsequent OS analyses, including the final OS analysis in September 2021 (HR=0.65; 95% CI: 0.50, 0.85; p=0.00135).

7.0 CLINICAL SAFETY

Overall, the safety profile of sintilimab in combination with pemetrexed and platinum-based chemotherapy in patients with treatment-naive nonsquamous NSCLC and no EGFR or ALK genomic tumor aberrations (indicated population) is acceptable, with toxicities that were tolerable and generally manageable with dose interruptions and supportive care.

In general, the addition of sintilimab did not appear to increase the frequency of adverse events (AEs) that are commonly associated with chemotherapy regimens involving pemetrexed and a platinum-based drug. Immune-related adverse events (irAEs) were generally low grade and clinically manageable with appropriate surveillance and intervention. The safety profile is consistent with the known safety profile of approved PD-1/L1 inhibitors, with no new safety signals relative to the class identified.

7.1 Safety Datasets

The safety and tolerability of sintilimab in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of patients with Stage IIIB/C or Stage IV nonsquamous NSCLC is based primarily on the safety assessment from the pivotal Phase 3 ORIENT-11 study, specifically the double-blind treatment prior to any crossover.

The safety assessment was supplemented by data from pooled analyses that included

- Patients with NSCLC (either squamous or nonsquamous) treated with sintilimab as monotherapy (N=181) or in combination with chemotherapy (N=486) (**Pool 2**). The pool includes ORIENT-11, Cohort D and E of Study A101, and Study C303.
- Patients with various tumor types treated with sintilimab as monotherapy or in combination with chemotherapy (N=1,045) (**Pool 3**). This pool includes the NSCLC studies included in Pool 2) plus studies in other tumor types (Cohort A and B of A101, A102, B201, A201, and D201). This dataset was primarily used to assess irAEs.

An analysis of the sintilimab safety profile in US patients, predominantly female patients with advanced endometrial cancer, compared with Chinese patients with various tumor types is provided in Section 7.4.3. In addition, the 120-day Safety Update (DCO, 15 January 2021) for ORIENT-11 further corroborates the safety conclusion from the interim analysis (i.e., at which time the study met the primary endpoint), with no new safety signal identified.

7.2 Extent of Exposure

In ORIENT-11, sintilimab was administered IV Q3W. Treatment continued until disease progression, occurrence of intolerable toxicity, 24 months of sintilimab treatment, or another criterion for discontinuation was met.

All 397 randomized patients received at least 1 dose of any study therapy, and the Safety Set population consisted of 266 patients in the sintilimab combination arm and 131 patients in the placebo combination arm.

The median relative dose intensity was high and consistent with the targeted dose in both treatment arms (sintilimab: 97.1%; placebo: 97.4%), demonstrating that sintilimab was well tolerated in patients with nonsquamous NSCLC.

The median duration of sintilimab/placebo exposure was higher in the sintilimab combination arm than in the placebo combination arm (31.0 weeks [median of 10 cycles received] vs 24.0 weeks [median of 7 cycles received], respectively) (Table 16). Similarly, the median duration of pemetrexed was higher in the sintilimab combination arm than in the placebo combination arm (31.3 weeks [median of 10 cycles received] vs 23.6 weeks [median of 7 cycles received], respectively). Exposure to cisplatin or carboplatin was consistent between the treatment arms, with >80% of patients completing the maximum 4 cycles of platinum doublet chemotherapy.

Table 16 Extent of Exposure – ORIENT-11 (SS Population)

Parameter	Sintilimab + chemotherapy (N=266)	Placebo + chemotherapy (N=131)
Patients completed ≥4 cycles of treatment, n (%)	235 (88.3)	109 (83.2)
Median (range) duration of drug exposure, weeks		
Sintilimab/placebo	30.95 (3.0-65.1)	24.00 (3.0-62.6)
Pemetrexed	31.25 (3.0-65.1)	23.60 (3.0-62.6)
Cisplatin or carboplatin	12.10 (3.0-17.1)	12.10 (3.0-16.1)
Median (range) number of cycles administered		
Sintilimab/placebo	10.0 (1-21)	7.0 (1-21)
Pemetrexed	10.0 (1-21)	7.0 (1-21)
Cisplatin or carboplatin	4.0 (1-4)	4.0 (1-4)
Median (range) relative dose intensity, %		
Sintilimab/placebo	97.1 (59.7-103.7)	97.4 (74.7-103.5)
Pemetrexed	96.1 (43.2-104.2)	96.7 (68.1-104.9)
Cisplatin	97.1 (78.4-102.9)	95.6 (76.1-101.6)
Carboplatin	94.8 (48.1-125.6)	95.4 (54.5-116.6)

Abbreviations: N = number of patients; SS = Safety Set.
Data cutoff date: 15 November 2019.

7.3 Adverse Events

All AEs were graded using CTCAE v4.03.

7.3.1 Overview of Adverse Events

Most patients experienced at least 1 treatment-emergent adverse event (TEAE) of any grade (Table 17). The incidence of Grade ≥3 TEAEs, treatment-emergent serious adverse events (TESAEs), and TEAEs leading to any drug interruption, permanent discontinuation of any drug, or study discontinuation were similar between treatment arms. Treatment-emergent AEs leading to death on study treatment and infusion-related reactions (IRRs) were low.

Table 17 Overview of Adverse Events During Double-blind Treatment Period – ORIENT-11 (SS Population)

Patients with	Number (%) of patients	
	Sintilimab + chemotherapy (N=266)	Placebo + chemotherapy (N=131)
Any TEAE	265 (99.6)	131 (100.0)
Treatment-related TEAE[a]	264 (99.2)	130 (99.2)
Grade ≥3 TEAE	164 (61.7)	77 (58.8)
Treatment-related Grade ≥3 TEAE[a]	151 (56.8)	68 (51.9)
Treatment-emergent SAE	75 (28.2)	39 (29.8)
Investigator-determined irAE[b]	115 (43.2)	48 (36.6)
Grade ≥3 irAE	16 (6.0)	8 (6.1)
Sponsor-adjudicated irAE[c]	88 (33.1)	NA
Grade ≥3 irAE	15 (5.6)	NA
Investigator-reported IRR[d]	6 (2.3)	1 (0.8)
TEAE leading to death	6 (2.3)	9 (6.9)
Treatment-related TEAE leading to death[a]	2 (0.8)	4 (3.1)
TEAE leading to permanent discontinuation of any study treatment	16 (6.0)	11 (8.4)
TEAE leading to permanent discontinuation of sintilimab or placebo	14 (5.3)	9 (6.9)
TEAE leading to permanent discontinuation of all study treatment	8 (3.0)	8 (6.1)
TEAE leading to interruption of any study treatment[e]	129 (48.5)	63 (48.1)
TEAE leading to interruption of sintilimab or placebo[e]	125 (47.0)	62 (47.3)
TEAE leading to study discontinuation	5 (1.9)	8 (6.1)
Treatment-related TEAE leading to study discontinuation[a]	1 (0.4)	4 (3.1)

Abbreviations: AE = adverse event; CRF, case report form; irAE = immune-related adverse event; IRR = infusion-related reaction; N = number of patients; NA = not applicable; SAE =serious adverse event; SS = Safety Set; TEAE = treatment-emergent adverse event.
Note: TEAEs during the double-blind treatment period were AEs that first occurred or worsened in severity from baseline within the time a patient received the first dose of study treatment to 90 days after the last dose of study treatment or start of crossover treatment, whichever occurred first.
Note: This table does not include data from crossover.
[a] As assessed by the investigator.
[b] Investigator-determined irAEs were collected in the CRF. Typically, the determination was completed in a blinded fashion unless the investigator was already unblinded.
[c] Only potential irAEs in the sintilimab combination arm were adjudicated.
[d] IRRs were determined and reported by investigators as instructed by the protocol.
[e] Dose interruption was collected at the investigator's determination of the reason for temporary discontinuation of the treatment.
Data cutoff date: 15 November 2019.

7.3.2 Common Treatment-Emergent Adverse Events

Table 18 presents the most frequently reported TEAEs (at least 10% incidence in either treatment arm, regardless of grade or causality) in descending order of frequency. If an event was analyzed as a consolidated term, the incidence of the event in this table is the consolidated term, otherwise, the incidence of the event uses the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) incidence.

In general, the addition of sintilimab to pemetrexed and platinum-based chemotherapy did not result in clinically significant increased rates of chemotherapy-related toxicities. The AE profile observed in the placebo combination arm was consistent with the known safety profile of

pemetrexed and platinum-based chemotherapy. Overall, the TEAE profile reflected the known safety profile of anti-PD-1 drugs, or events expected to occur within the disease setting of Stage IIIB/C or Stage IV nonsquamous NSCLC.

The events of any grade (consolidated terms are *italicized*) that occurred in at least 10% of patients and at a 5-percentage point higher incidence in the sintilimab combination arm were *neutropenia*, *thrombocytopenia*, decreased appetite, *hypoalbuminemia*, pyrexia, *hyperglycemia*, and *lymphopenia* (Table 18). The majority of between-group differences in the incidence of TEAEs were observed in low-grade (Grades 1 or 2) events, with most Grade ≥3 events being similar between treatment arms except for *neutropenia*.

The majority of Grade ≥3 TEAEs that occurred in both treatment arms were Grade 3 events, with low and similar incidence rates of Grades 4 and 5 TEAEs between treatment arms. The clinically relevant event (Grade ≥3) that occurred in at least 10% of patients and at a higher (at least 2-percentage points) incidence in the sintilimab combination arm was *neutropenia* (Grade ≥3: 36.5% vs 30.5% [Grade 4: 5.6% vs 7.6%; no Grade 5 events]) (Table 18).

Table 18 Common Treatment-Emergent Adverse Events Occurring in ≥10% of Patients in Either Treatment Arm by Preferred Term/Consolidated Term During Double-blind Treatment Period – ORIENT-11 (SS Population)

Preferred term *Consolidated term*	Number (%) of patients			
	Sintilimab + chemotherapy (N=266)		Placebo + chemotherapy (N=131)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with any TEAE	265 (99.6)	164 (61.7)	131 (100.0)	77 (58.8)
Anemia[a]	211 (79.3)	41 (15.4)	108 (82.4)	27 (20.6)
Neutropenia[b]	189 (71.1)	97 (36.5)	82 (62.6)	40 (30.5)
Leukopenia[c]	180 (67.7)	39 (14.7)	84 (64.1)	20 (15.3)
Thrombocytopenia[d]	115 (43.2)	33 (12.4)	41 (31.3)	16 (12.2)
Aspartate aminotransferase increased	109 (41.0)	1 (0.4)	51 (38.9)	1 (0.8)
Alanine aminotransferase increased	108 (40.6)	0	51 (38.9)	4 (3.1)
Nausea	108 (40.6)	4 (1.5)	55 (42.0)	0
Decreased appetite	101 (38.0)	0	41 (31.3)	1 (0.8)
Fatigue[e]	93 (35.0)	2 (0.8)	44 (33.6)	2 (1.5)
Vomiting	77 (28.9)	2 (0.8)	41 (31.3)	0
Constipation	71 (26.7)	0	42 (32.1)	0
Hypoalbuminemia[f]	64 (24.1)	0	25 (19.1)	0
Thyroid disorder[g]	61 (22.9)	0	29 (22.1)	0
Pyrexia	56 (21.1)	0	19 (14.5)	1 (0.8)
Rash[h]	49 (18.4)	4 (1.5)	23 (17.6)	3 (2.3)
Hyperglycemia[i]	41 (15.4)	3 (1.1)	13 (9.9)	0
Edema[j]	38 (14.3)	1 (0.4)	13 (9.9)	1 (0.8)
Diarrhea	35 (13.2)	1 (0.4)	15 (11.5)	1 (0.8)
Lymphopenia[k]	34 (12.8)	6 (2.3)	10 (7.6)	1 (0.8)
Cough	33 (12.4)	0	16 (12.2)	0
Gamma-glutamyltransferase increased	33 (12.4)	4 (1.5)	14 (10.7)	3 (2.3)
Hypokalemia[l]	31 (11.7)	4 (1.5)	12 (9.2)	4 (3.1)
Hyponatremia[m]	30 (11.3)	12 (4.5)	16 (12.2)	5 (3.8)
Insomnia	30 (11.3)	0	9 (6.9)	0

Preferred term *Consolidated term*	Number (%) of patients			
	Sintilimab + chemotherapy (N=266)		Placebo + chemotherapy (N=131)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Dizziness	28 (10.5)	0	8 (6.1)	0
Proteinuria	28 (10.5)	0	13 (9.9)	1 (0.8)
Upper respiratory tract infection	27 (10.2)	0	12 (9.2)	2 (1.5)
Pneumonia	22 (8.3)	7 (2.6)	15 (11.5)	5 (3.8)
Weight decreased	22 (8.3)	2 (0.8)	23 (17.6)	2 (1.5)
Productive cough	19 (7.1)	0	17 (13.0)	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; SS = Safety Set; TEAE = treatment-emergent adverse event.
Note: TEAEs during the double-blind treatment period were AEs that first occurred or worsened in severity from baseline within the time a patient received the first dose of study treatment to 90 days after the last dose of study treatment or start of crossover treatment, whichever occurred first.
Note: A patient is counted once at each level of patient summarization if the patient reported one or more events.
Note: MedDRA Version 22.1 was used for coding.
[a] Includes anemia, hemoglobin decreased, red blood cell decreased, hematocrit decreased, iron deficiency anemia.
[b] Includes neutrophil count decreased.
[c] Includes white blood cell decreased.
[d] Includes platelet count decreased, thrombocytopenia.
[e] Includes asthenia, fatigue.
[f] Includes hypoalbuminemia, blood albumin decreased.
[g] Includes hypothyroidism, blood thyroid-stimulating hormone increased, hyperthyroidism, blood thyroid-stimulating hormone decreased, thyroxine free increased, tri-iodothyronine free increased, thyroxine increased, tri-iodothyronine increased.
[h] Includes rash, dermatitis, rash erythematous, dermatitis allergic rash maculo-papular, drug eruption, dermatitis acneiform.
[i] Includes blood glucose increased, hyperglycemia.
[j] Includes edema peripheral, face edema, peripheral swelling, generalized edema, localized edema.
[k] Includes lymphocyte count decreased.
[l] Includes hypokalemia, blood potassium decreased.
[m] Hyponatremia, blood sodium decreased.
Data cutoff date: 15 November 2019.

7.3.3 Deaths

At the interim analysis for PFS, the incidence of death was higher in the placebo combination arm than in the sintilimab combination arm (29.8% vs 19.2%, respectively). In both arms, the majority of deaths were due to disease progression (20.6% vs 6.9%, respectively). Across the overall treatment period (including both the double-blind and crossover treatment phases), 6 (2.3%) patients in the sintilimab combination arm and 11 (8.4%) patients from the placebo combination arm died due to a TEAE.

During the double-blind treatment period, TEAEs leading to death (TEAE with fatal outcome) occurred in 6 (2.3%) patients in the sintilimab combination arm and 9 (6.9%) patients in the placebo combination arm (Table 19). Two (0.8%) deaths in the sintilimab combination arm (cardiac failure, febrile neutropenia) and 3 (2.3%) deaths in the placebo combination arm (cardiac failure, interstitial lung disease, cerebral artery embolism) were considered by the investigator as related to sintilimab or placebo. There was no clear pattern or tendency of fatal TEAEs.

Table 19 Treatment-Emergent Adverse Events Leading to Deaths During Double-blind Treatment Period by MedDRA System Organ Class and Preferred Term – ORIENT-11 (SS Population)

MedDRA system organ class Preferred term	Number (%) of patients	
	Sintilimab + chemotherapy (N=266)	Placebo + chemotherapy (N=131)
TEAE leading to death	6 (2.3)	9 (6.9)
Cardiac disorders	**2 (0.8)**	**2 (1.5)**
Cardiac failure	1 (0.4)[a]	1 (0.8)[a]
Cardiovascular disorder	1 (0.4)	0
Pericarditis constrictive	0	1 (0.8)
Respiratory, thoracic and mediastinal disorders	**2 (0.8)**	**2 (1.5)**
Asphyxia	1 (0.4)	0
Respiratory failure	1 (0.4)	0
Dyspnea	0	1 (0.8)
Interstitial lung disease	0	1 (0.8)[a]
Blood and lymphatic system disorders	**1 (0.4)**	**0**
Febrile neutropenia	1 (0.4)[a]	0
Nervous system disorders	**1 (0.4)**	**3 (2.3)**
Cerebral hemorrhage	1 (0.4)	0
Cerebral artery embolism	0	1 (0.8)[a]
Cerebral infarction	0	1 (0.8)
Cerebrovascular accident	0	1 (0.8)
Infections and infestations	**0**	**1 (0.8)**
Pneumonia	0	1 (0.8)[b]
Investigations	**0**	**1 (0.8)**
Platelet count decreased	0	1 (0.8)[a]

Abbreviations: AE, adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; SS = Safety Set; TEAE = treatment-emergent adverse event.
Note: TEAEs during the double-blind treatment period were AEs that first occurred or worsened in severity from baseline within the time a patient received the first dose of study treatment to 90 days after the last dose of study treatment or start of crossover treatment, whichever occurred first.
Note: AEs are sorted by descending frequency in system organ class, then descending frequency of preferred term within system organ class, in the sintilimab combination arm.
Note: MedDRA (version 22.1) was used for coding. A patient was counted once at each level of patient summarization if the patient reported one or more events.
[a] Event considered related to sintilimab or placebo by the investigator.
[b] Primary cause of death by investigator was disease progression. This patient had disease progression confounded by recurring pneumonia. The disease progression status was confirmed by independent radiology group.
Data cutoff date: 15 November 2019.

7.3.4 Treatment-Emergent Serious Adverse Events

Similar percentages of patients in the sintilimab combination arm and the placebo combination arm had any-grade TESAEs (28.2% vs 29.8%, respectively) and Grade ≥3 TESAEs (16.9% vs 17.6%, respectively) (Table 20). In both treatment arms, all TESAE terms were reported at a low incidence.

The individual TESAEs that occurred in ≥2 patients with a ≥1% higher incidence in the sintilimab combination arm versus the placebo combination arm were anemia (4.5% vs 3.1%), immune-related pneumonitis (2.3% vs 0.8%), pneumonitis (1.9% vs 0), hemoptysis (1.1% vs 0),

hepatic function abnormal (1.9% vs 0), nausea (1.1% vs 0), pleural effusion (1.1% vs 0), and lymphocyte count decreased (1.1% vs 0).

Table 20 Treatment-Emergent Serious Adverse Events Occurring in ≥2 Patients in the Sintilimab Combination Arm by MedDRA System Organ Class, Preferred Term, and Maximum Severity During Double-blind Treatment Period – ORIENT-11 (SS Population)

MedDRA system organ class Preferred term	Number (%) of patients			
	Sintilimab + chemotherapy (N=266)		Placebo + chemotherapy (N=131)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with at least one TESAE	75 (28.2)	45 (16.9)	39 (29.8)	23 (17.6)
Respiratory, thoracic and mediastinal disorders	**25 (9.4)**	**10 (3.8)**	**3 (2.3)**	**3 (2.3)**
Immune-related pneumonitis	6 (2.3)	2 (0.8)	1 (0.8)	1 (0.8)
Pneumonitis	5 (1.9)	2 (0.8)	0	0
Hemoptysis	3 (1.1)	1 (0.4)	0	0
Pleural effusion	3 (1.1)	0	0	0
Interstitial lung disease	2 (0.8)	0	1 (0.8)	1 (0.8)
Respiratory failure	2 (0.8)	2 (0.8)	0	0
Investigations	**18 (6.8)**	**13 (4.9)**	**10 (7.6)**	**9 (6.9)**
Platelet count decreased	12 (4.5)	12 (4.5)	8 (6.1)	8 (6.1)
Neutrophil count decreased	3 (1.1)	2 (0.8)	2 (1.5)	0
Lymphocyte count decreased	3 (1.1)	1 (0.4)	0	0
White blood cell count decreased	3 (1.1)	2 (0.8)	2 (1.5)	0
Blood and lymphatic system disorders	**16 (6.0)**	**14 (5.3)**	**4 (3.1)**	**2 (1.5)**
Anemia	12 (4.5)	11 (4.1)	4 (3.1)	2 (1.5)
Thrombocytopenia	2 (0.8)	2 (0.8)	0	0
Infections and infestations	**13 (4.9)**	**6 (2.3)**	**13 (9.9)**	**5 (3.8)**
Pneumonia	7 (2.6)	3 (1.1)	6 (4.6)	1 (0.8)
Gastrointestinal disorders	**9 (3.4)**	**4 (1.5)**	**1 (0.8)**	**0**
Nausea	3 (1.1)	2 (0.8)	0	0
Abdominal pain	2 (0.8)	0	0	0
Upper gastrointestinal hemorrhage	2 (0.8)	1 (0.4)	0	0
Vomiting	2 (0.8)	1 (0.4)	0	0
Cardiac disorders	**8 (3.0)**	**4 (1.5)**	**3 (2.3)**	**2 (1.5)**
Atrial fibrillation	2 (0.8)	0	0	0
Cardiac failure	2 (0.8)	1 (0.4)	1 (0.8)	1 (0.8)
Hepatobiliary disorders	**5 (1.9)**	**0**	**0**	**0**
Hepatic function abnormal	5 (1.9)	0	0	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PT = preferred term; SOC = system organ class; SS = Safety Set; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.
Note: TEAEs during the double-blind treatment period were AEs that first occurred or worsened in severity from baseline within the time a patient received the first dose of study treatment to 90 days after the last dose of study treatment or start of crossover treatment, whichever occurred first.
Note: AEs are sorted by descending frequency in SOC, then descending frequency of PT within SOC, in the sintilimab combination arm. A patient is counted once at each level of patient summarization if the patient reported one or more events.
Note: AEs were graded using NCI CTCAE version 4.03. MedDRA (version 22.1) was used for coding.
Data cutoff date: 15 November 2019.

The most common treatment-related TESAEs occurring in the sintilimab or placebo combination arms were immune-related pneumonitis (2.3% vs 0.8%), platelet count decreased (1.5% vs 2.3%), anemia (1.5% vs 2.3%) and hepatic function abnormal (1.5% vs 0), respectively. Any-grade treatment-related TESAEs occurring in ≥2 patients with a ≥1% higher incidence in the sintilimab combination arm versus placebo combination arm were immune-related pneumonitis (2.3% vs 0.8%), pneumonitis (1.1% vs 0), and hepatic function abnormal (1.5% vs 0).

7.3.5 Treatment-Emergent Adverse Events Leading to Study Treatment Interruptions

The percentage of patients who had at least 1 TEAE leading to interruption of sintilimab or placebo (sintilimab: 47.0% vs placebo: 47.3%) or any study treatment (sintilimab combination arm: 48.5% vs placebo combination arm: 48.1%) was comparable across treatment arms (Table 21). Anemia was the most common any-grade TEAE leading to interruption of sintilimab/placebo (sintilimab: 13.9% vs placebo: 17.6%) and any component of the combination (sintilimab combination arm: 14.3% vs placebo combination arm: 17.6%).

Table 21 Treatment-Emergent Adverse Events Leading to Treatment Interruption Occurring in ≥2% of Patients in the Sintilimab Combination Arm During Double-blind Treatment Period – ORIENT-11 (SS Population)

MedDRA system organ class Preferred term	Number (%) of patients			
	Sintilimab + chemotherapy (N=266)		Placebo + chemotherapy (N=131)	
	Sintilimab	Any component	Placebo	Any component
Any TEAE leading to treatment interruption	125 (47.0)	129 (48.5)	62 (47.3)	63 (48.1)
Investigations	**55 (20.7)**	**57 (21.4)**	**26 (19.8)**	**26 (19.8)**
Neutrophil count decreased	23 (8.6)	24 (9.0)	10 (7.6)	10 (7.6)
Platelet count decreased	18 (6.8)	18 (6.8)	9 (6.9)	9 (6.9)
White blood cell count decreased	17 (6.4)	17 (6.4)	7 (5.3)	7 (5.3)
Alanine aminotransferase increased	9 (3.4)	9 (3.4)	5 (3.8)	5 (3.8)
Aspartate aminotransferase increased	6 (2.3)	6 (2.3)	3 (2.3)	3 (2.3)
Blood and lymphatic system disorders	**40 (15.0)**	**41 (15.4)**	**23 (17.6)**	**23 (17.6)**
Anemia	37 (13.9)	38 (14.3)	23 (17.6)	23 (17.6)
Infections and infestations	**23 (8.6)**	**23 (8.6)**	**12 (9.2)**	**12 (9.2)**
Pneumonia	11 (4.1)	11 (4.1)	5 (3.8)	5 (3.8)
Respiratory, thoracic and mediastinal disorders	**15 (5.6)**	**16 (6.0)**	**8 (6.1)**	**9 (6.9)**
Pneumonitis	7 (2.6)	7 (2.6)	3 (2.3)	3 (2.3)
General disorders and administration site conditions	**11 (4.1)**	**13 (4.9)**	**7 (5.3)**	**7 (5.3)**
Asthenia	6 (2.3)	6 (2.3)	5 (3.8)	5 (3.8)
Hepatobiliary disorders	**6 (2.3)**	**6 (2.3)**	**1 (0.8)**	**1 (0.8)**
Hepatic function abnormal	6 (2.3)	6 (2.3)	0	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; PT = preferred term; SOC = system organ class; SS = Safety Set; TEAE = treatment-emergent adverse event.
Note: TEAEs during the double-blind treatment period were AEs that first occurred or worsened in severity from baseline within the time a patient received the first dose of study treatment to 90 days after the last dose of study treatment or start of crossover treatment, whichever occurred first.
Note: AEs are sorted by descending frequency in SOC, then descending frequency of PT within SOC, in the sintilimab combination arm. A patient is counted once at each level of patient summarization if the patient reported one or more events.

Note: MedDRA (version 22.1) was used for coding.
Data cutoff date: 15 November 2019.

7.3.6 Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Treatment

The percentage of patients who had at least 1 TEAE leading to discontinuation of sintilimab or placebo (sintilimab: 5.3% vs placebo: 6.9%) or any study treatment (sintilimab combination arm: 6.0% vs placebo combination arm: 8.4%) was low and comparable across treatment arms, indicating that the combination treatment was generally tolerable (Table 22). The most common TEAEs leading to discontinuation of sintilimab or placebo were immune-related pneumonitis (sintilimab: 1.5% vs placebo: 0.8%) and platelet count decreased(sintilimab: 0.4% vs placebo: 1.5%).

Table 22 Treatment-Emergent Adverse Events Leading to Permanent Treatment Discontinuation Occurring in ≥1 Patient in the Sintilimab Combination Arm During Double-blind Treatment Period – ORIENT-11 (SS Population)

MedDRA system organ class Preferred term	Number (%) of patients			
	Sintilimab + chemotherapy (N=266)		Placebo + chemotherapy (N=131)	
	Sintilimab	Any component	Placebo	Any component
Any patient with TEAE leading to permanent treatment discontinuation	14 (5.3)	16 (6.0)	9 (6.9)	11 (8.4)
Respiratory, thoracic and mediastinal disorders	**7 (2.6)**	**8 (3.0)**	**3 (2.3)**	**3 (2.3)**
Immune-related pneumonitis	4 (1.5)	4 (1.5)	1 (0.8)	1 (0.8)
Respiratory failure	2 (0.8)	2 (0.8)	0	0
Epistaxis	0	1 (0.4)	0	0
Pneumonitis	1 (0.4)	1 (0.4)	0	0
Blood and lymphatic system disorders	**2 (0.8)**	**3 (1.1)**	**0**	**0**
Anemia	1 (0.4)	1 (0.4)	0	0
Febrile neutropenia	1 (0.4)	1 (0.4)	0	0
Thrombocytopenia	0	1 (0.4)	0	0
Investigations	**2 (0.8)**	**3 (1.1)**	**2 (1.5)**	**3 (2.3)**
Platelet count decreased	1 (0.4)	2 (0.8)	2 (1.5)	2 (1.5)
Hemoglobin decreased	1 (0.4)	1 (0.4)	0	0
Red blood cell count decreased	1 (0.4)	1 (0.4)	0	0
Cardiac disorders	**2 (0.8)**	**2 (0.8)**	**1 (0.8)**	**1 (0.8)**
Cardiac failure	1 (0.4)	1 (0.4)	0	0
Immune-related myocarditis	1 (0.4)	1 (0.4)	0	0
Hepatobiliary disorders	**1 (0.4)**	**1 (0.4)**	**0**	**0**
Hepatic function abnormal	1 (0.4)	1 (0.4)	0	0
Immune system disorders	**1 (0.4)**	**1 (0.4)**	**0**	**0**
Hypersensitivity	1 (0.4)	1 (0.4)	0	0
Skin and subcutaneous tissue disorders	**1 (0.4)**	**1 (0.4)**	**0**	**0**
Vitiligo	1 (0.4)	1 (0.4)	0	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; PT = preferred term; SOC = system organ class; SS = Safety Set; TEAE = treatment-emergent adverse event.

Note: TEAEs during the double-blind treatment period were AEs that first occurred or worsened in severity from baseline within the time a patient received the first dose of study treatment to 90 days after the last dose of study treatment or start of crossover treatment, whichever occurred first.
Note: AEs are sorted by descending frequency in SOC, then descending frequency of PT within SOC, in the sintilimab combination arm. A patient is counted once at each level of patient summarization if the patient reported one or more events.
Note: MedDRA (version 22.1) was used for coding.
Data cutoff date: 15 November 2019.

7.3.7 Adverse Events of Special Interest

The ORIENT-11 study protocol did not define AEs of special interest. Immune-related AEs and IRRs are described in this section.

7.3.7.1 Immune-Related Adverse Events

The mechanism of sintilimab involves inhibition of immune checkpoints, resulting in T-cell activation and proliferation, which is associated with a spectrum of adverse reactions resembling autoimmune reactions and is different from other systemic therapies such as cytotoxic chemotherapy. Signs and symptoms of irAEs were diligently monitored and managed as directed in the ORIENT-11 study protocol.

As previously agreed with the FDA, medical adjudication was performed to identify all possibly immune-mediated events occurring following sintilimab use. All AEs whose PT belonged to a prespecified irAE PT list were identified as a potential irAE and evaluated following specific rules, as well as necessary medical judgment to minimize subjective bias.

During the double-blind treatment phase of ORIENT-11, 88 patients (33.1%) experienced Sponsor-adjudicated irAEs, of whom 15 patients (5.6%) experienced irAEs that were Grade ≥3 (Table 23). The most frequent irAEs by PT with an incidence of ≥5% by immune-related category were immune-related endocrinopathy (20.3%), immune-related pancreatitis, elevation of amylase/lipase (7.1%), and immune-related pneumonitis (7.1%).

The most frequent irAEs by PT with an incidence of ≥5% were hypothyroidism (12.0%), hyperthyroidism (10.2%), and amylase increased (6.8%).

Table 23 Immune-Related Adverse Events by Immune-Related Category During Double-blind Treatment Period – ORIENT-11 (SS Population)

Immune-related category Immune-related subcategory (if applicable)	Number (%) of patients Sintilimab + chemotherapy (N=266)	
	Any grade	Grade ≥3
Patients with at least one irAE	88 (33.1)	15 (5.6)
Immune-related endocrinopathy	54 (20.3)	0
Hypothyroidism	32 (12.0)	0
Hyperthyroidism	27 (10.2)	0
Thyroid disorders	8 (3.0)	0
Immune-related pancreatitis and elevation of amylase/lipase	19 (7.1)	5 (1.9)
Elevation of lipase	1 (0.4)	0
Elevation of amylase	18 (6.8)	5 (1.9)
Immune-related pneumonitis	19 (7.1)	4 (1.5)
Immune-related skin adverse reactions	13 (4.9)	3 (1.1)
Hematologic toxicity	1 (0.4)	1 (0.4)

Immune-related category Immune-related subcategory (if applicable)	Number (%) of patients	
	Sintilimab + chemotherapy (N=266)	
	Any grade	Grade ≥3
Immune-related nervous system toxicity	1 (0.4)	1 (0.4)
Immune-related cardiovascular toxicity	1 (0.4)	1 (0.4)
Immune-related hepatitis and hepatoxicity	1 (0.4)	1 (0.4)
Musculoskeletal toxicity	1 (0.4)	1 (0.4)
Other	1 (0.4)	1 (0.4)

Abbreviations: AE = adverse event; irAE = immune-related adverse event; N = number of patients; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SS = Safety Set; TEAE = treatment-emergent adverse event.
Note: TEAEs during the double-blind treatment period were AEs that first occurred or worsened in severity from baseline within the time a patient received the first dose of study treatment to 90 days after the last dose of study treatment or start of crossover treatment, whichever occurred first.
Note: AEs are sorted by descending frequency in the irAE category. A patient is counted once at each level of patient summarization if the patient reported one or more events.
Note: AEs were graded using NCI CTCAE version 4.03.
Data cutoff date: 15 November 2019.

7.3.7.2 Infusion-Related Reactions

Sintilimab may cause severe or life-threatening IRRs, including severe hypersensitivity or anaphylactic reactions, with signs and symptoms usually appearing during or shortly after the drug infusion and usually resolving completely within 24 hours after completing the infusion. Investigators were required to report signs and symptoms they suspected to be IRRs in the Case Report Form (CRF).

Table 24 summarizes treatment-emergent IRRs reported by the investigators. The incidence of any-grade IRRs was low in both treatment arms (sintilimab combination arm: 2.3%; placebo combination arm: 0.8%). Grade ≥3 IRRs were rare (sintilimab combination arm: 0.8%; placebo combination arm: 0). Infusion-related reactions were manageable. Of the 6 patients in the sintilimab combination arm with IRRs, 2 patients had events of Grade 3 severity and 1 patient discontinued study treatment due to a Grade 3 event of hypersensitivity.

Table 24 Infusion-Related Reactions Occurring During Double-blind Treatment Period by MedDRA System Organ Class, Preferred Term, and Maximum Severity – ORIENT-11 (SS Population)

MedDRA system organ class Preferred term	Number (%) of patients			
	Sintilimab + chemotherapy (N=266)		Placebo + chemotherapy (N=131)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
IRRs reported by investigator	6 (2.3)	2 (0.8)	1 (0.8)	0
General disorders and administration site conditions	**3 (1.1)**	**0**	**0**	**0**
Infusion site pain	1 (0.4)	0	0	0
Infusion site swelling	1 (0.4)	0	0	0
Pyrexia	1 (0.4)	0	0	0
Immune system disorders	**1 (0.4)**	**1 (0.4)**	**1 (0.8)**	**0**
Hypersensitivity	1 (0.4)	1 (0.4)	1 (0.8)	0

MedDRA system organ class Preferred term	Number (%) of patients			
	Sintilimab + chemotherapy (N=266)		Placebo + chemotherapy (N=131)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Injury, poisoning and procedural complications	**1 (0.4)**	**0**	**0**	**0**
Infusion-related reaction	1 (0.4)	0	0	0
Investigations	**1 (0.4)**	**1 (0.4)**	**0**	**0**
Blood pressure increased	1 (0.4)	1 (0.4)	0	0
Skin and subcutaneous tissue disorders	**1 (0.4)**	**0**	**0**	**0**
Rash	1 (0.4)	0	0	0

Abbreviations: AE = adverse event; IRR = infusion-related reaction; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PT = preferred term; SOC = system organ class; SS = Safety Set; TEAE = treatment-emergent adverse event.
Note: IRRs reported by the investigator are summarized under each PT coded based on original AE terms collected.
Note: TEAEs during the double-blind treatment period were AEs that first occurred or worsened in severity from baseline within the time a patient received the first dose of study treatment to 90 days after the last dose of study treatment or start of crossover treatment, whichever occurred first.
Note: AEs are sorted by descending frequency in SOC, then descending frequency of PT within SOC, in total column under sintilimab combination. A patient is counted once at each level of patient summarization if the patient reported one or more events.
Note: AEs were graded using NCI CTCAE version 4.03. MedDRA (version 22.1) was used for coding.
Data cutoff date: 15 November 2019.

7.4 Sintilimab Safety Profile in Pooled Safety Datasets

7.4.1 Overall Summary of Adverse Events – Combo and Monotherapy NSCLC (Pool 2)

Within the Combo NSCLC (Pool 2) dataset, the safety profile of sintilimab in combination with various chemotherapies in squamous and nonsquamous NSCLC was generally similar to the safety profile seen in the indicated nonsquamous NSCLC population. The incidence of any-grade and Grade ≥3 TEAEs, TESAEs, and TEAEs leading to discontinuation of sintilimab or placebo was similar in both treatment groups. The majority of differences in the incidence of TEAEs between treatment groups were observed in low-grade (Grades 1-2) events. The incidence of Grade ≥3 TEAEs in the Combo NSCLC (Pool 2) was higher than that in first-line nonsquamous NSCLC (Pool 1) (70.8% vs 59.9%, respectively), which was driven by higher incidences of platelet count decreased, neutrophil decreased, white blood cell decreased, and anemia.

7.4.2 Immune-Related Adverse Events – Sintilimab Combo and Monotherapy All (Pool 3)

Across tumor types, irAEs were also analyzed for different pools. Sponsor-adjudicated irAEs are the primary source for the irAE analyses as presented in Section 7.3.7.1.

Based on the results from Pool 3, the incidence of irAEs was independent of tumor type. Sponsor-adjudicated irAEs occurred in 39.6% of all patients who received sintilimab treatment across various tumor types (N=1,045) (Table 25). Any-grade irAE categories with an incidence of ≥5% included immune-related endocrinopathy (25.3%), immune-related pancreatitis (7.7%), elevation of amylase/lipase (7.7%), immune-related skin adverse reactions (7.3%), and immune-related pneumonitis (6.3%). Most irAEs were low grade; 9.2% of patients had Grade ≥3 irAEs.

The overall patterns and incidence of Grade ≥3 irAEs were comparable to that expected for the class of immune-modulating therapies.

Table 25 Immune-Related Adverse Events – ORIENT-11 and All Sintilimab (>1% of Patients)

	Patients (%)			
	ORIENT-11 (N=266)		All sintilimab treated (N=1045)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
At least one immune-related adverse event	33.1	5.6	39.6	9.2
Endocrinopathy	20.3	0	25.3	0.7
Hypothyroidism	12.0	0	16.7	0.2
Hyperthyroidism	10.2	0	9.7	0
Thyroid disorders	3.0	0	4.9	0
Pancreatitis and elevation of amylase/lipase	7.1	1.9	7.7	3.2
Elevation of amylase	6.8	1.9	5.1	1.6
Elevation of lipase	0.4	0	3.5	1.8
Pneumonitis	7.1	1.5	6.3	2.7
Skin adverse reaction	4.9	1.1	7.3	1.4
Hepatitis and hepatotoxicity	0.4	0.4	1.0	0.7

7.4.3 Safety Profile of Sintilimab in US Versus Chinese Patients

Due to the small number of US patients, in which all but 3 patients had endometrial cancer, who received sintilimab monotherapy (N=39) in comparison to Chinese patients who received sintilimab monotherapy in various tumor types (N=520), the comparison of the safety profile between the 2 populations is limited. No notable safety findings or new safety concerns were revealed in the comparison of the sintilimab safety profile in these 2 populations (Table 26).

Table 26 Safety Profiles of Sintilimab Monotherapy Between Chinese and US Populations Across Tumor Types

Adverse event categories	Monotherapy all (Pool 3), n (%)	
	Chinese population Sintilimab monotherapy (N=520)	US population[a] Sintilimab monotherapy (N=39)
TEAE	500 (96.2)	37 (94.9)
Grade ≥3 TEAE	225 (43.3)	20 (51.3)
Treatment-related TEAE	408 (78.5)	22 (56.4)
Treatment-related Grade ≥3 TEAE	100 (19.2)	7 (17.9)
TESAE	154 (29.6)	15 (38.5)
Grade ≥3 TESAE	114 (21.9)	15 (38.5)
Treatment-related TESAE	72 (13.8)	5 (12.8)
Treatment-related Grade ≥3 TESAE	50 (9.6)	4 (10.3)
TEAE leading to sintilimab discontinuation	72 (13.8)	4 (10.3)
Grade ≥3 TEAE leading to sintilimab discontinuation	60 (11.5)	4 (10.3)
Treatment-related TEAE leading to sintilimab discontinuation	42 (8.1)	3 (7.7)
Treatment-related Grade ≥3 TEAE leading to sintilimab discontinuation	33 (6.3)	3 (7.7)
TEAE leading to dose interruption	148 (28.5)	8 (20.5)
Grade ≥3 TEAE leading to dose interruption	84 (16.2)	4 (10.3)

Adverse event categories	Monotherapy all (Pool 3), n (%)	
	Chinese population Sintilimab monotherapy (N=520)	US population[a] Sintilimab monotherapy (N=39)
Treatment-related TEAE leading to dose interruption	91 (17.5)	7 (17.9)
Treatment-related Grade ≥3 TEAE leading to dose interruption	45 (8.7)	4 (10.3)
TEAE leading to death	26 (5.0)	1 (2.6)
Treatment-related TEAE leading to death	10 (1.9)	0

Abbreviations: N = number of patients; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; US = United States.
[a] Predominantly female population with endometrial cancer.

7.5 Postmarketing Safety Experience

The cumulative exposure to sintilimab is approximately 170,000 patients.

From December 2019 to December 2020 (reporting period of the Periodic Safety Update Report [PSUR]), 143,333 patients were exposed to sintilimab. There were 552 spontaneous reports involving 1,071 AEs for an estimated incidence of 0.39% (552/143,333 patients). The most commonly reported (≥20 cases) AEs were rash (55 [0.04%]), pyrexia (52 [0.04%]), bone marrow failure (48 [0.03%]), pruritus (47 [0.03%]), chills (39 [0.03%]), asthenia (34 [0.02%]), anorexia (26 [0.02%]), backache (23 [0.02%]), diarrhea (23 [0.02%]), and dyspnea (20 [0.01%]).

During the PSUR reporting period, there were 293 reports involving 458 serious adverse events (SAEs) for an estimated incidence of 0.2% (293/143,333 patients). The most commonly reported SAEs (≥10 cases) were bone marrow failure (48 [0.03%]), hypothyroidism (17 [0.01%]), immune-mediated myocarditis (16 [0.01%]), abnormal hepatic function, immune-mediated hepatitis, immune-mediated pneumonia, rash (13 [0.01%] each), pruritus (12 [0.01%]), pulmonary inflammation and platelet count decreased (10 [0.01%] each).

Together, there were no new safety signals, and the benefit-risk ratio for the approved indications remains positive.

7.6 Overall Safety Conclusions

At the interim PFS analysis of ORIENT-11, the safety profile of sintilimab in combination with pemetrexed and platinum-based chemotherapy in patients with Stage IIIB/C and Stage IV previously untreated nonsquamous NSCLC, when compared to placebo plus pemetrexed and platinum-based chemotherapy, was acceptable. No new safety concerns relative to the class were identified. Sintilimab in combination with pemetrexed and platinum-based chemotherapy demonstrated a manageable and tolerable safety profile similar to the established safety profiles of other anti-PD-1 therapies currently approved for the first-line treatment of NSCLC. Chemotherapy-related toxicities were generally similar between the sintilimab combination and placebo combination arms. The addition of sintilimab to pemetrexed and platinum-based chemotherapy did not appear to increase the incidence of interruption or permanent discontinuation of chemotherapy. The types, incidence, and severity of irAEs did not differ from those expected in lung cancer patients treated with anti-PD-1 checkpoint inhibitors in combination with chemotherapy. In general, the irAEs were manageable with interruption of sintilimab therapy, appropriate use of corticosteroids, and supportive care. Infusion-related

reactions were also uncommon and manageable. Immune-related AEs and IRRs will be managed according to proposed product labeling.

Analysis of pooled safety data did not identify any new safety signals from that observed in the pivotal ORIENT-11 study. The incidence of irAEs was not driven by tumor type. Although only a limited number of US patients were included in the sintilimab safety analysis, results did not raise any additional safety signal.

Continuous pharmacovigilance of sintilimab in the postmarketing setting in China also did not identify additional safety concerns, corroborating an acceptable safety profile.

8.0 APPLICABILITY OF RESULTS TO US POPULATION

The preceding efficacy and safety sections showed that, based on data from the pivotal ORIENT-11 study conducted in China, sintilimab has a favorable benefit-risk ratio when added to standard first-line pemetrexed and platinum-based chemotherapy in nonsquamous NSCLC. This section presents evidence that the data from ORIENT-11 are generalizable to the US population in this indication without the need for duplicative studies.

8.1 Foreign Data as the Sole Basis for Marketing Approval

Use of data from ORIENT-11 to support US FDA approval of sintilimab plus pemetrexed and cisplatin or carboplatin in the proposed indication is dependent on meeting the regulations outlined in 21CFR314.106(b) for use of foreign data as the sole basis for marketing approval. These US regulations are addressed in various sections of this briefing document:

US Regulation	Regulation Text	Addressed in Briefing Document
21CFR314.106(b)(2)	The studies have been performed by clinical investigators of recognized competence	Section 1.2
21CFR314.106(b)(3)	The data may be considered valid without the need for an onsite inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an onsite inspection or other appropriate means	Section 1.2
21CFR314.106(b)(1)	The foreign data are applicable to the US population and US medical practice	Section 8.2

Abbreviations: CFR = Code of Federal Regulations; FDA = US Food and Drug Administration; US =United States.

The discussion below represents an assessment of the evidence supporting the applicability of data from ORIENT-11 in a Chinese population to a US population and medical practice.

8.2 Framework for Applicability of Sintilimab Data to US Population

The US CFR states that an "application based solely on foreign clinical data meeting US criteria for marketing approval may be approved if…the foreign data are applicable to the US population and US medical practice" (21CFR314.106).[19] The applicability of a foreign clinical data package is further explored in ICH E5 (Ethnic Factors in the Acceptability of Foreign Clinical Data). This guidance is particularly important as it provides considerations with respect to "regulatory and development strategies that will permit adequate evaluation of the influence of ethnic factors while minimising duplication of clinical studies and supplying medicines expeditiously to patients for their benefit."[48-50]

ICH E5, in conjunction with the aforementioned US regulation, provides a framework for evaluating the impact of ethnic factors on a drug's effect. Taken together, the applicability of the sintilimab data to US patients can be considered based on 3 principles:

- First, there must be similar clinical practice standards between China and the US.
- Second, it must be demonstrated that the drug is insensitive to ethnic factors and that there are no clinically meaningful differences in the PK or PD of the drug between Chinese and US patients based on an analysis of factors that may differ between these populations.

- Third, it must be reasonable to anticipate, based on evidence that the drug is insensitive to ethnic factors, that the efficacy and safety of sintilimab in the US population will be similar to that demonstrated in the Chinese population studied in ORIENT-11. Furthermore, there must be sufficient clinical experience with the drug class to provide reassurance that the class behaves similarly in patients in the 2 regions with respect to efficacy and safety.

ICH E5 makes note of the importance of contributions that a class of drugs may have on the evaluation of the acceptability of foreign data, which is particularly true for the PD-1/L1 class. Specifically, ICH E5 states the following which underpins the subsequent assessments:

> *The clinical experience with other members of the drug class in the new region will also contribute to the assessment of the medicine's sensitivity to ethnic factors. It may be easier to conclude that the pharmacodynamic and clinical behavior of a medicine will be similar in the foreign and new regions if other members of the pharmacologic class have been studied and approved in the new region with dosing regimens similar to those used in the original region.*

8.2.1 Similarities in Clinical Practice Standards Between China and US

As described in Section 2.2, clinical practice standards are constantly evolving. At the time ORIENT-11 was initiated in 2018, the chemotherapy backbone of pemetrexed plus platinum followed by maintenance pemetrexed had been the standard of care in China for many years. During the conduct of ORIENT-11, first-line PD-1/L1 mAbs in combination with chemotherapy had not yet been adopted. Today, PD-1/L1 mAbs combined with chemotherapy is an approved first-line option, and clinical practice guidelines in this area have converged in the US and China.

Regarding the staging systems for NSCLC, both the US and China use AJCC 8th edition, disease classification is by World Health Organization 2015, genetic testing is comparable as assessed in the US and China by the College of American Pathologists, and PD-L1 biomarker testing uses the same companion diagnostic per the product label (Table 1).

The diagnostic and treatment standards between the US and China are generally similar (Table 1). The treatment guidelines in the US are dominated by the NCCN guidelines, and the Chinese guidelines are largely derived from the NCCN guidelines. The same staging and pathologic classification system are used. The AJCC Cancer Staging Manual, 8th edition, was developed with substantial contribution of Asian patients (44% of 94,708 patients).[33] Molecular testing and PD-L1 biomarker testing are routinely used.[11]

First-line immunotherapy options are mostly overlapping and include either monotherapy or combinations with chemotherapy. Finally, the chemotherapy backbone used in the US and China tends to be very similar. Cisplatin, or more commonly carboplatin, plus pemetrexed is the most common doublet used in both countries. Additionally, the predominant treatment selection for second-line therapy in the US and China is taxane-based chemotherapy.

In summary, the management of patients is closely aligned in the US and China. Additionally, the patients enrolled in ORIENT-11 were diagnosed and treated with sintilimab as would be done in the US based on the proposed label.

8.2.2 Similarities in Sintilimab PK and PD Profile Between a Chinese and US Population

Sintilimab exhibited linear PK over the 1 to 10 mg/kg dose range, with a $t_{1/2}$ of approximately 20 days. As an IgG mAb, sintilimab is largely eliminated by catabolism; therefore, drug-drug interactions and other extrinsic factors are not expected to have an effect on sintilimab PK..[46]

PopPK analyses were conducted using data from 514 patients, 39 of whom were from the US, and included data after the first dose and the trough concentrations throughout treatment. A multivariate PopPK model examined a wide range of intrinsic factors, including body weight, race, tumor type, age, sex, albumin concentration, and renal and hepatic function, and showed no clinically important effects on the PK of sintilimab (Figure 9). Although, body weight distribution differed between the US and Chinese cohorts, the range of body weight between the 2 populations overlapped (Figure 10). The Phase 1 study characterizing the PK of sintilimab in 39 US patients versus 463 Chinese patients demonstrated comparable individual PK profiles in both groups. The median body weight of NSCLC patients is approximately 15 kg heavier in the US than in China, which would only result in an approximately 10% lower exposure in US patients based on the PopPK analysis. Greater than 95% receptor occupancy of PD-1 by sintilimab on circulating $CD3^+$ cells was observed across the dose range of 1 to 10 mg/kg in patients with advanced solid tumors following a single infusion (Figure 7). In fact, even at the lowest dose of 1 mg/kg, we observed consistently high receptor occupancy over 28 days after a single dose, indicating a wide therapeutic dose range for efficacy. This implies that the 200 mg Q3W dose, which is approximately equivalent to 2.6 mg/kg (based on US population median weight of 77 kg[17]), has at least a 2-fold margin to deliver a full pharmacologic effect in both Chinese and US populations and would not be affected by differences in body weight.

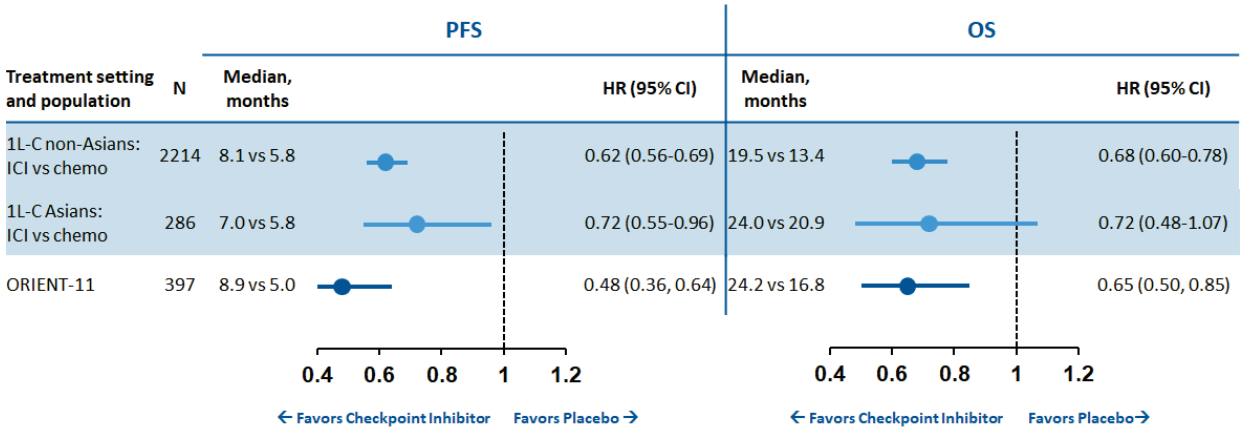
The PK and PD characteristics of sintilimab are consistent with what would be anticipated for a fully human IgG4 mAb. Given the linear PK of sintilimab, the fact that receptor occupancy, efficacy, and safety are on the plateau of the exposure-response curve, and the large therapeutic window for efficacy, ethnic differences are not expected to affect the efficacy or safety of sintilimab.

8.2.3 Similarities in Sintilimab Efficacy and Safety Between Chinese and US Population

8.2.3.1 Similarities in Efficacy

A published FDA meta-analysis, based on data from 11 randomized controlled trials, compared clinical outcomes (OS and PFS) between Asian and non-Asian patients with metastatic NSCLC who were treated with immune checkpoint inhibitors in the first- or second-line setting.[16] The analysis was based on trials submitted to FDA between 2014 and 2018. For those studies conducted in the first-line setting, the Asian group, although smaller, demonstrated relatively consistent OS and PFS outcomes compared to the non-Asian group (Figure 19[16]). Based on extrapolation using the meta-analysis outcome, ORIENT-11 predicts compelling HRs for both OS and PFS in the non-Asian population.

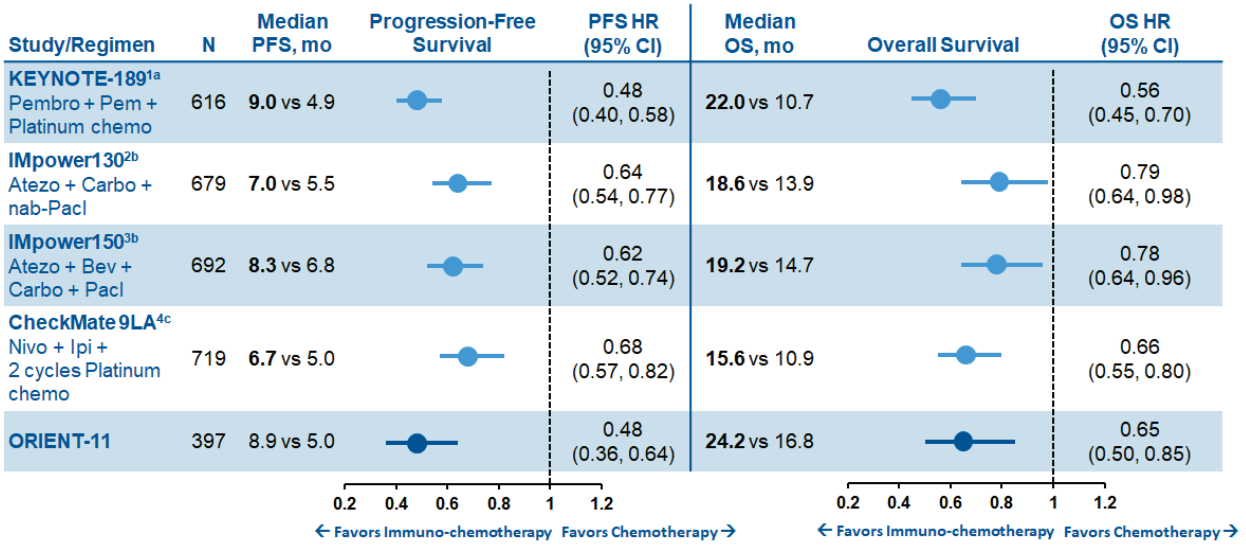
Figure 19 FDA Meta-Analysis of NSCLC Trials in Asian and Non-Asian Populations



Abbreviations: 1L-C = first-line combination with chemotherapy; chemo = chemotherapy; CI = confidence interval; FDA = US Food and Drug Administration; HR = hazard ratio; ICI = immune checkpoint inhibitor; N = number of patients; NR = not reached; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival.
Note: ORIENT-11 was not included in the FDA analysis but was added by the Sponsor for comparison.
Data cutoff for ORIENT-11 was 15 January 2021 for OS and 15 November 2019 for PFS.
Data, in part, from Chang E, et al, *J Clin Oncol*. 2019;37(suppl 15):e20690.

In a cross-study comparison of PFS and OS outcomes in ORIENT-11 in a Chinese population and global registration studies of pembrolizumab, atezolizumab, and nivolumab conducted in a largely Western population, comparable efficacy outcomes were observed (Figure 20).[20-23] Thus, although these global registration studies enrolled only a small number of Asian patients (~2%),[26] the observed PFS and OS benefits are very similar, and in all of these trials, the ORR increased with the addition of the anti-PD-1/L1 antibody.

Figure 20 Efficacy Outcomes Across ORIENT-11 and PD-1/L1 Registration Studies in First-Line Treatment of Nonsquamous NSCLC Without EGFR or ALK Genomic Tumor Aberrations



Abbreviations: Atezo = atezolizumab; Bev = bevacizumab; Carbo = carboplatin; chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; Ipi = ipilimumab; N = number of patients; nab = nanoparticle albumin-bound; Nivo = nivolumab; OS

= overall survival; Pacl = paclitaxel; PD-1/L1 = programmed death-1/programmed death-ligand 1; Pem = pemetrexed; Pembro = pembrolizumab; PFS = progression-free survival.
[a] Primary endpoints were OS and PFS by blinded independent central radiology review.
[b] Co-primary endpoints were investigator-assessed PFS and OS.
[c] Primary endpoint was OS.
Data cutoff for ORIENT-11 was 15 September 2021 for OS and 15 November 2019 for PFS.
1. Gadgeel S, et al. *J Clin Oncol.* 2020;38(14):1505-17.
2. West H, et al. *Lancet Oncol*. 2019;20(7):924-37.
3. Socinski MA, et al. *N Engl J Med.* 2018;378(24):2288-301.
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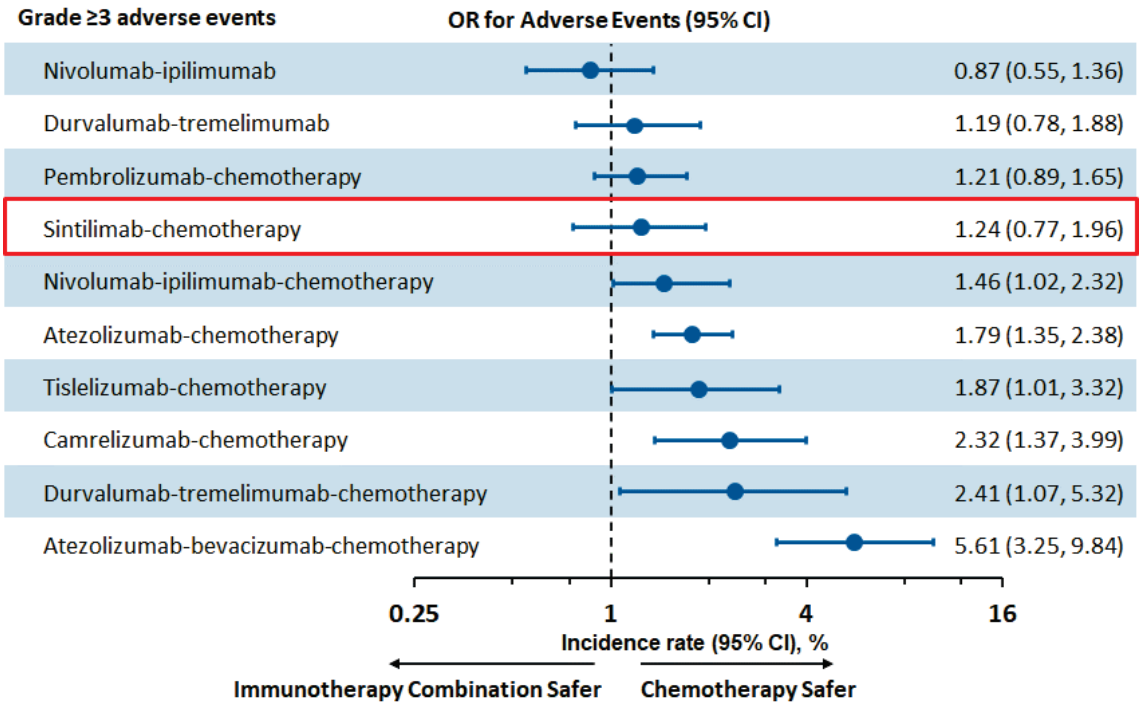
8.2.3.2 Similarities in Safety

The safety profile of sintilimab was compared across Chinese and US populations. Although only a limited number of US patients were included in the sintilimab safety analysis, results did not raise any additional safety signal. Recently, a large meta-analysis compared the safety profile of first-line immunotherapy combinations in patients with NSCLC.[51] This meta-analysis includes data from 8,278 patients enrolled in 16 randomized controlled trials involving 10 different chemoimmunotherapy combinations. The methodology used for this meta-analysis aligned with the Preferred Reporting Items for Systematic Reviews and Meta Analyses, and the protocol is registered in the relevant database to ensure transparency and reliability. Figure 21[51] shows the odds ratio for ≥Grade 3 AEs. The safety profile of sintilimab in combination with pemetrexed and platinum chemotherapy, shown in the red box, is comparable to other agents in the class.

Figure 21 Meta-Analysis Comparing Safety Profile of First-Line Immunotherapy Combinations in NSCLC Patients



Abbreviations: CI = confidence interval; NSCLC = non-small cell lung cancer; OR = odds ratio.
Adapted from *J Thorac Oncol*. 2021;16(7):1099-117. Liu L, et al. Efficacy and safety of first-line immunotherapy combinations for advanced NSCLC: a systematic review and network meta-analysis. Copyright 2021 with permission from Elsevier.

9.0 BENEFIT-RISK OF SINTILIMAB AND APPLICABILITY TO US PATIENTS

Based on the totality of the data, sintilimab in combination with pemetrexed and platinum-based chemotherapy has demonstrated a positive benefit-risk profile for first-line use in patients with Stage IIIB, IIIC, or IV nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations.

With respect to the framework for demonstrating applicability, it is evident that clinical practice standards are similar between China and the US. Second, regarding potential ethnic sensitivity, there were no clinically important effects of intrinsic factors on the PK profile of sintilimab. It is well known that the PK of IgG mAbs is not sensitive to pharmacogenetic differences. In addition, sintilimab has a linear PK profile and a wide therapeutic dose range for efficacy. Therefore, we conclude that its PK/PD profile is insensitive to ethnicity. Third, there is ample evidence, based on extensive clinical experience with PD-1/L1 antibodies across different populations, to provide reassurance that the efficacy and safety of sintilimab in the US population will be similar to that observed in ORIENT-11. Taken together, these findings suggest that the data from ORIENT-11 are applicable to the US population and clinical practice, and they support the approval of sintilimab for the proposed indication.

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