FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

February 10, 2022

BLA 761222
Sintilimab
Innovent Biologics (Suzhou) Co., Ltd.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the sintilimab BLA 761222 to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	Accelerated approval
AE	Adverse event
ALK	Anaplastic lymphoma kinase
Anti-PD-(L)1	Anti-PD-1/anti-PD-L1
AUC	Area under the concentration-time curve
BICR	Blinded independent central review
BLA	Biologics license application
CFR	Code of Federal Regulations
C_{max}	Maximum observed concentration
DCO	Data cutoff
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
FDA	Food and Drug Administration
GCP	Good clinical practice
HR	Hazard ratio
IC	Immune cells
ICH	International Council of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH E5	ICH Guidance E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data
ICH E17	ICH Guidance E17 – General Principles for Planning and Design of Multiregional Clinical Trials
IEC	Independent ethics committee
IND	Investigational new drug
ITT	Intention-to-treat
IV	Intravenously
MRCT	Multiregional clinical trial
NCA	Noncompartmental analysis
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NR	Not reached
NSCLC	Non-small cell lung cancer
NSQ	Non-squamous
ODAC	Oncologic Drugs Advisory Committee
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamics
PD-1	Programmed cell death protein-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
PopPK	Population pharmacokinetics

Q3W	Every 3 weeks
RA	Regular approval
RECIST	Response Evaluation Criteria in Solid Tumors
SOC	Standard of care
SQ	Squamous
TC	Tumor cells
TMB	Tumor mutation burden
TPS	Tumor proportion score

1. EXECUTIVE SUMMARY

1.1 Proposed Indication and Current Landscape

On March 16, 2021, Innovent Biologics (Suzhou) Co., Ltd. submitted a biologics license application (BLA) for sintilimab (TRADENAME), based on a trial conducted exclusively in China.

The Applicant is seeking the following indication:

- TRADENAME in combination with pemetrexed and platinum-based chemotherapy is indicated for the first-line treatment of adult patients with Stage IIIB, IIIC, or Stage IV non-squamous non-small cell lung cancer (NSCLC) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

Sintilimab is a monoclonal IgG4 antibody targeting the programmed cell death protein-1 (PD-1) cell surface membrane receptor. Sintilimab was studied in combination with pemetrexed and platinum-based chemotherapy in Study CIBI308C302 (ORIENT-11), an ongoing, randomized, double-blind trial conducted exclusively in China. The study met its primary endpoint, progression-free survival (PFS) by Blinded Independent Central Review (BICR).

The FDA is convening the Oncologic Drugs Advisory Committee (ODAC) to discuss the use of single country foreign data to support a U.S. marketing application.

1.2 Regulatory Considerations

The trial design, patient population, and statistical analysis plan of ORIENT-11 closely resemble landmark lung cancer trials which established immune checkpoint inhibitors as part of initial treatment regimens. This application reflects an increasing number of oncology development programs based solely or predominantly on clinical data from China, with over 25 applications in drug development phases, planned to be submitted, or currently under review.

The Code of Federal Regulations (CFR) is a codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the U.S. Federal Government. Title 21 of the CFR is reserved for rules of the FDA.

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

- The foreign data are applicable to the U.S. population and U.S. medical practice.

- The studies have been performed by clinical investigators of recognized competence.
- FDA is able to validate the data through an onsite inspection or other appropriate means.

Failure of an application to meet any of these criteria will result in the application not being approvable based on the foreign data alone. FDA will apply this policy in a flexible manner according to the nature of the drug and the data being considered.[1]

FDA's evaluation of foreign data is also framed by International Council of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) consensus guidelines. Both ICH Guidance E5 (ICH E5) and more recently ICH Guidance E17 (ICH E17) directly address the acceptance of foreign data from single countries, and should be used in tandem.[2,3,4] The Applicant cites the CFR and ICH E5 as rationale for their approach, however, omits ICH E17, a critical international consensus document which promotes the use of multiregional clinical trials (MRCTs) as the preferred approach to drug development.[4]

The current trend of marketing applications to the FDA, based on foreign data from single country trials, is a departure from decades of MRCTs as the consistent approach to drug development. Multiregional clinical trials tend to be large, randomized trials, which allow an evaluation of consistency of treatment effects among regions. The 2017 ICH E17 guidance reinforces the MRCT as the optimal method for concurrent global registration based on an emerging consensus that trials requiring international collaboration were preferred over single country trials.

ORIENT-11 is not consistent with the principles outlined in ICH E17, thus does not allow for an evaluation of consistency of treatment effects across geographic regions and subpopulations. The data from ORIENT-11 are not applicable to the U.S. population and U.S. medical practice, based on the selected endpoint and control arm. The characteristics of patients enrolled in ORIENT-11 differ from U.S. patients with advanced non-squamous NSCLC. The pharmacokinetics (PK) data are insufficient to make definitive conclusions regarding applicability to a diverse U.S. patient population. While clinical site inspections have been initiated, they cannot fully capture the heterogeneity of data quality and study conduct across numerous clinical sites. Prior participation of study investigators in MRCTs may increase confidence in study conduct, however, investigators in ORIENT-11 have had limited interactions with the FDA.

The NSCLC treatment landscape includes many front-line immunotherapy options conferring advantages in overall survival (OS) whereas ORIENT-11 was powered for PFS. While PFS is an acceptable clinical endpoint, it is less clinically meaningful, and OS remains the preferred endpoint when it can be reasonably assessed. Overall survival was not formally tested in

ORIENT-11, and approval based on a different endpoint than OS risks loss of gains in survival for U.S. patients. Given there are multiple approved agents with OS advantage formally demonstrated with statistical significance, flexibility regarding applicability of results from ORIENT-11 is not indicated or favorable for U.S. patients.

The Applicant cites their data in parallel with other agents with a statistically tested OS advantage, however each study must independently demonstrate efficacy and safety for the specific drug, rather than relying on a class effect. Approval of a first line immune checkpoint inhibitor regimen based on a PFS endpoint would be a departure from our regulatory approval standards to date for first line immunotherapy approvals in metastatic NSCLC.

It is important to note that the FDA may not consider drug pricing or competition in its regulatory decision making. Cost and drug pricing should not be included as a topic for discussion in this ODAC meeting.

Topics for discussion at the ODAC meeting include:

- Multiregional clinical trials represent the preferred approach to global drug development as described in ICH E17. Importantly, MRCTs allow for a structed exploration of consistency of treatment effect across regions and subpopulations.
- The results from ORIENT-11 are not applicable to U.S. patients or U.S. medical practice based on 21 CFR 314.106. The trial was conducted without FDA consultation or oversight, with a comparator arm and endpoint (PFS) that do not meet U.S. regulatory standards or align with U.S. medical practice. Comparison of sintilimab to an approved drug would ensure that there is no loss in OS advantage.
- ORIENT-11 is not reflective of a diverse U.S. population, and does not account for both known and unknown differences amongst populations.
- The FDA may apply policies on applicability of foreign data in a flexible manner according to the nature of drug and data being considered. ORIENT-11 closely resembles existing MRCTs, yet was powered for a less clinically meaningful endpoint. The trial results do not fulfill an unmet need, thus do not warrant regulatory flexibility when considering applicability to a U.S. population.
- Should additional data be required to demonstrate applicability to the U.S. population given ORIENT-11 was conducted in a single foreign country?

2. BACKGROUND

2.1 NSCLC Therapeutic Landscape

For front line metastatic NSCLC, all immunotherapy approvals to date have been predicated on a statistically significant improvement in OS.

Standard of care treatment regimens for front line metastatic NSCLC in the U.S. have included immune checkpoint inhibitors with chemotherapy since 2017, based on the results from KEYNOTE-189.[5] FDA initially granted accelerated approval to pembrolizumab in combination with pemetrexed and platinum chemotherapy for the first-line treatment of non-squamous NSCLC; this was converted to a regular approval in 2018 based on results from KEYNOTE-189 with demonstration of OS benefit. Given its landmark improvement in OS, the KEYNOTE-189 regimen established a new treatment paradigm of adding immunotherapy to chemotherapy for treatment of patients with newly diagnosed metastatic NSCLC. Subsequent approvals using atezolizumab, and nivolumab with ipilimumab plus chemotherapy provided additional front-line options, replacing chemotherapy as the first line treatment choice for U.S. patients.[6,7] Updated analysis with four years of follow up from KEYNOTE-189 continue to demonstrate durable OS advantage.[8]

For FDA approved therapies of anti-PD-(L)1 antibodies in combination with platinum-doublet chemotherapy for non-squamous NSCLC, the median OS is approximately 16 - 22 months.

2.2 FDA Approved Therapies for Advanced NSCLC (Biomarker Negative)

Table 1: Summary of FDA Approved First Line Therapies for Metastatic Non-squamous NSCLC*

Drug(s)	Approval Year	Approval Endpoint and Efficacy
Pembrolizumab (w/ pemetrexed and platinum)	2017 (AA) 2018 (RA)	Median PFS: 8.8 vs. 4.9 mos; HR 0.52 (95% CI 0.43, 0.64) Median OS: NR vs. 11.3 mos; HR 0.49 (95% CI 0.38, 0.64)
Atezolizumab (w/ carboplatin, paclitaxel, bevacizumab)	2018	Median OS: 19.2 vs. 14.7 mos; HR 0.78 (95% CI 0.64, 0.96)
Atezolizumab (w/ carboplatin and nab-paclitaxel)	2019	Median OS: 18.6 vs. 13.9 mos; HR 0.80 (95% CI 0.64, 0.99)
Nivolumab and Ipilimumab (w/ platinum-doublet)	2020	Median OS: 14.1 vs. 10.7 mos; HR 0.69 (96.71% CI 0.55, 0.87)

* Only FDA approvals for unselected PD-L1 populations are included.
Abbreviations: AA – accelerated approval; RA – regular approval; HR – hazard ratio

3. REGULATORY INTERACTIONS BETWEEN FDA AND THE APPLICANT

ORIENT-11 was not conducted under an IND, thus was performed without FDA consultation or oversight. The trial was initiated in August of 2018, however the FDA was not made aware of the study until April 2020, after top-line data demonstrated a statistically significant improvement in PFS. Table 2 summarizes key interactions between the FDA and the Applicant.

Table 2: Key Interactions between FDA and Applicant regarding Sintilimab for NSCLC

Date	Description
April 2020	Applicant submitted meeting package with topline results from ORIENT-11, informing FDA of their plans to submit a US marketing application. FDA expressed concerns regarding applicability and generalizability of ORIENT-11 to a U.S. population. (See 21 CFR 314.50(d)(5)(v) and the guidance for industry on the *Collection of Race and Ethnicity Data in Clinical Trials*.)[9,10]
August 2020	Meeting between the Applicant and FDA to discuss the acceptability of data from ORIENT-11 as the basis of a BLA submission for sintilimab, and the proposed non-clinical and clinical pharmacology data package. FDA indicated that the impact of intrinsic and extrinsic ethnic factors on the exposure, efficacy, and safety of sintilimab must be addressed in a BLA submission.
March 2021	Applicant submitted BLA 761222 for the following indication: sintilimab in combination with pemetrexed and platinum chemotherapy for the first-line treatment of non-squamous NSCLC.

4. STUDY CIBI308C302 (ORIENT-11)

4.1 Study Design

ORIENT-11 is an ongoing, randomized, double-blind trial conducted exclusively in China to evaluate the efficacy and safety of sintilimab or placebo in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of locally advanced (i.e., Stage IIIB or IIIC disease not amenable to surgical resection or chemoradiation with curative intent) or metastatic non-squamous NSCLC without sensitizing EGFR mutations or ALK rearrangements. A total of 397 patients were randomized 2:1 to receive four cycles of sintilimab (n=266) or placebo (n=131) in combination with pemetrexed and investigator's choice of platinum-based chemotherapy followed by sintilimab or placebo in combination with maintenance pemetrexed until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Patients on the placebo arm with confirmed disease progression are permitted to crossover to receive sintilimab monotherapy for up to 24 months at the discretion of the investigator.

Patients were stratified at randomization by sex (male vs female), platinum chemotherapy (cisplatin vs carboplatin), and PD-L1 expression (TPS <1% vs ≥1%). The primary endpoint is PFS by BICR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Descriptive

secondary endpoints, without a formal plan for statistical testing, include OS, overall response rate (ORR) by BICR per RECIST v1.1, and duration of response (DOR).

4.2 Patient Selection

Key inclusion criteria:

- Eastern Cooperative Oncology Group (ECOG) performance status ≤1
- Histologically or cytologically confirmed Stage IIIB/IIIC, Stage IV, or recurrent non-squamous NSCLC (per the 8th edition of International Association for the Study of Lung Cancer and the American Joint Committee on Cancer). Patients with Stage IIIB/IIIC disease should not be eligible for surgery or chemoradiation with curative intent.
- No prior systemic anticancer therapy for advanced or recurrent non-squamous NSCLC
- Ineligible for EGFR- or ALK-targeted therapy, with documented evidence of absence of sensitizing EGFR mutations and ALK gene rearrangements
- Measurable disease by CT or MRI per RECIST v1.1 criteria

4.3 Statistical Analysis Plan

The sample size calculation of ORIENT-11 assumes 90% power to detect a 3.2-month improvement in median PFS (corresponding to a HR of 0.65) with a type I error rate of 0.05 (2-sided). Given these parameters, the required sample size was 378 patients and 263 PFS events were required for the final analysis. One interim analysis was planned when 70% of planned PFS events (184 PFS events) occurred with boundary calculation based on an O'Brien-Fleming alpha spending function.

A formal testing plan for OS or other secondary endpoints was not pre-specified.

4.4 Efficacy Results

4.4.1 Patient Disposition

Table 3: Patient Disposition for ORIENT-11 (November 15, 2019 Data Cutoff [DCO] Date)

Disposition	Sintilimab + Chemotherapy N=266	Placebo + Chemotherapy N=131
Treatment ongoing	151 (57%)	46 (35%)
Crossover to sintilimab	N/A	35 (27%)
Alive and in follow-up	65 (24%)	21 (16%)[a]
Study discontinued[b]	50 (19%)	29 (22%)[c]

Disposition	Sintilimab + Chemotherapy N=266	Placebo + Chemotherapy N=131
Reason for treatment discontinuation		
Disease progression	77 (29%)	61 (47%)
Patient withdrawal/ request	18 (7%)	11 (8%)
Adverse events	8 (3.0%)	8 (6%)
Death	8 (3.0%)	3 (2.3%)
Other reasons	4 (1.5%)	2 (1.5%)

[a] Excludes 24 patients who crossed over to sintilimab arm and are still in follow-up

[b] Includes patients who died during treatment or who are in follow-up after treatment discontinuation

[c] Excludes 11 patients who crossed over to sintilimab arm and then discontinued the study

4.4.2 Demographics and Baseline Characteristics of ORIENT-11

Table 4: Demographics and Baseline Characteristics for Patients Enrolled to ORIENT-11

Characteristic	Sintilimab + Chemotherapy N=266	Placebo + Chemotherapy N=131
Age, median (range)	61 (30 – 75)	61 (35 – 75)
Sex, male	204 (77%)	99 (76%)
ECOG PS		
0	76 (29%)	34 (26%)
1	190 (71%)	97 (74%)
Disease Stage		
IIIB/IIIC	21 (8%)	15 (11%)
IV	245 (92%)	116 (89%)
PD-L1 Expression		
TPS < 1%	85 (32%)	44 (34%)
TPS ≥ 1%	181 (68%)	87 (66%)
Smoking Status		
Current/Former Smoker	171 (64%)	87 (66%)
Never Smoker	95 (36%)	44 (34%)
Platinum Choice		
Cisplatin	71 (27%)	33 (25%)
Carboplatin	195 (73%)	98 (75%)
Brain Metastases		
No	230 (86%)	109 (83%)
Yes	36 (14%)	22 (17%)

4.4.3 Primary Analysis of PFS by BICR for ORIENT-11

Table 5: Results of Progression-Free Survival by BICR Analysis[a]

	Sintilimab + Chemotherapy N=266	Placebo + Chemotherapy N=131
No. Events (%)	112 (42)	86 (66)
Disease progression	94 (35)	81 (62)
Death	18 (7)	5 (3.8)
Median in months (95% CI)[b]	8.9 (7.1, 11.3)	5.0 (4.8, 6.2)
Hazard Ratio (95% CI)[c]	0.48 (0.36, 0.64)	
p-value[d]	0.0000004	

Source: Reviewer generated table – adtte dataset (submitted by Applicant)

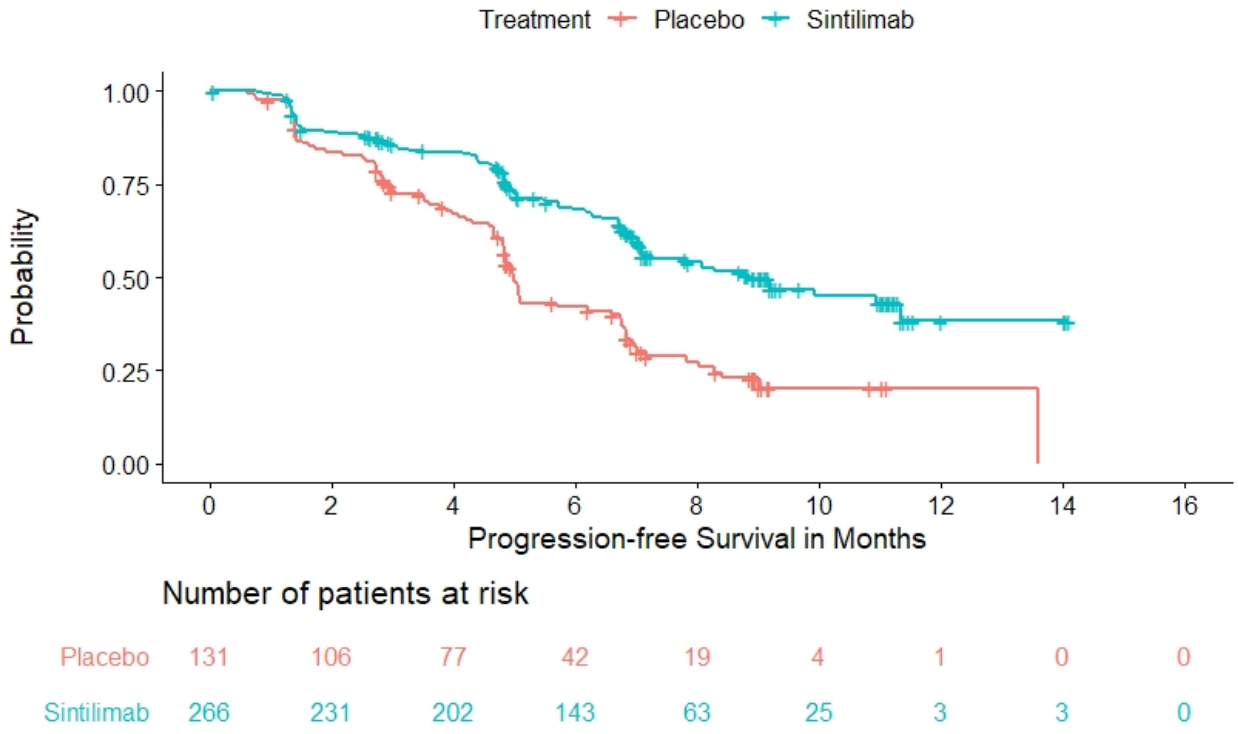
[a] Data cut-off date: November 15, 2019

[b] Kaplan-Meier estimate

[c] Stratified Cox proportional hazard model using Efron's method

[d] Two-sided p-value; alpha-boundary 0.01958 (interim analysis)

Figure 1: Kaplan-Meier Curve for Progression-Free Survival by BICR



Source: Reviewer generated plot – adtte dataset (submitted by Applicant; DCO November 15, 2019)

4.4.4 Descriptive Secondary Analyses for ORIENT-11

Results of secondary endpoints OS, ORR, and DOR are descriptive as they were not formally tested as a part of the pre-specified statistical analysis plan. Based on an updated analysis of OS with 207 total events observed and a DCO date of January 15, 2021, the median OS was not reached (NR) (95% CI 19.6, not evaluable [NE]) in the sintilimab arm compared to 16.8 months (95% CI 11.0, 18.5) in the placebo arm (HR 0.6; 95% CI 0.45, 0.79) (FDA generated results based on adtte2 dataset submitted by the Applicant). Based on a DCO date of November 15, 2019, the ORR was 52% (95% CI 46, 58) for the sintilimab arm compared to 30% (95% CI 22, 38) for the placebo arm (FDA generated results based on addrs dataset submitted by the Applicant). The median DOR is NR (95% CI 8.0, NE) for the sintilimab arm compared to 5.5 months (95% CI 4.1, NE) for the placebo arm (FDA generated results based on adtte dataset submitted by the Applicant).

The Applicant provides several calculations of OS based on various data-cutoffs and assuming different means for controlling the Type I error of the multiple analyses, all of which were retrospective and exploratory as there was no pre-specified plan for the statistical testing of OS. Specifically, the Applicant did not specify a formal testing plan for OS with a method to control for Type I error for testing multiple endpoints. In addition, the Applicant did not pre-specify an event time for the final analysis of OS; therefore, we cannot determine what percentage of observed events have occurred to calculate alpha boundaries from spending functions such the O'Brien-Fleming boundaries presented in the Applicant briefing document. Without a detailed, pre-specified analysis plan for statistical testing, these post-hoc observed results can only be considered hypothesis-generating as there is no scientific rigor to rely upon when considering whether the results are true findings or due to chance.

4.5 Safety Results

The safety analysis of sintilimab in combination with pemetrexed and platinum chemotherapy is based on 397 patients in ORIENT-11 who received four cycles of sintilimab 200 mg (n=266) or placebo (n=131) every 3 weeks in combination with pemetrexed 500 mg/m^2 and either cisplatin 75 mg/m^2 or carboplatin AUC 5, followed by sintilimab 200 mg or placebo in combination with pemetrexed 500 mg/m^2 for up to 24 months.

The Applicant presents safety data in the Applicant briefing document and FDA has nothing to add. Table 6 summarizes the overall safety profile of sintilimab in combination with pemetrexed and platinum chemotherapy.

Table 6: Overall Summary of Safety for ORIENT-11

	Sintilimab + Chemotherapy N=266 n (%)	**Placebo + Chemotherapy N=131 n (%)**
All-causality Adverse Events (AEs)		
Any Grade	265 (100)	131 (100)
Grade 3-4	158 (59)	69 (53)
Grade 5	6 (2.3)	11 (8)
Serious Adverse Events (SAEs)	75 (28)	44 (34)
AEs Leading to Interruption	125 (47)	63 (48)
AEs Leading to Discontinuation	14 (5)	12 (9)

5. ADDITIONAL PK DATA REQUIRED TO SUPPORT DOSAGE, EFFICACY, AND SAFETY FOR U.S. PATIENTS

The Applicant recommends a dosage of sintilimab 200 mg intravenously (IV) once every 3 weeks (Q3W). From data provided by the Applicant, sintilimab PD-1 receptor occupancy on peripheral CD3+ T cells in Chinese patients with solid tumors reached near saturation levels (≥95%) over the full dosing interval following multiple dosing across the dose range from 1 mg/kg to 10 mg/kg (0.4 to 4-fold the proposed dosage of 200 mg in an 80 kg patient). The Applicant used noncompartmental analyses (NCA) and population PK (popPK) analyses to compare PK characteristics of Asian and U.S. patients. PopPK analyses were conducted using data from 514 total patients, including only 39 U.S. patients with solid tumors from Study CIBI308A102 (n=30 White patients, n=5 Black patients, n=3 Asian patients, and n=1 Native American patient). A multivariate popPK model examined various intrinsic factors including body weight and race. FDA analyses based on the data provided suggest no clinically significant difference in PK between Whites and Asians, or a significant effect of body weight on PK. However, the limited U.S. patients enrolled in this program do not represent the ethnic and racial diversity of patients with non-squamous NSCLC in the U.S. It is standard for FDA to require sparse PK collection in trials with registrational intent, inclusive of the ITT population (i.e., U.S. patient cohort), in order to support efficacy and safety and the dosage selected for registration.

Given the significant uncertainties on the limited clinical data representing the proposed U.S. patient population, additional PK data are needed to support efficacy and safety from patients that are representative of the U.S. patient population.

6. EVALUATION OF FOREIGN DATA: FEDERAL REGULATIONS AND ICH GUIDANCES

The CFR is the codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the Federal Government. Evaluation for foreign data as the sole basis in support of a U.S. marketing application, as well as studies not conducted under IND, are discussed in 21 CFR 312 and 314.

The ICH has also issued guidelines pertaining to the acceptance of foreign clinical data and MRCTs. The ICH was established in 1990 with global regulatory authorities and the pharmaceutical industry to harmonize scientific and technical requirements of clinical trials and medicinal products around the world.[11] The ICH currently includes 19 regulatory and industry members, including the China National Medical Products Administration (NMPA) which officially joined in June 2017.[12]

The ICH E17 is the most recent and relevant guidelines for global, harmonized drug development through the strategic use of MRCTs. Multiregional clinical trials foster more efficient drug development avoiding duplication of clinical trials, enabling earlier access to innovative therapies, and harmonizing standards of care.

Prior to ICH E17, principles described in ICH E5 served as the basis for evaluation of foreign data. Today, ICH E5 and ICH E17 should be used in tandem when designing and conducting MRCTs.

Herein, we highlight relevant portions of the CFR and ICH Guidances.

6.1 Evaluation of Foreign Clinical Data per 21 CFR Sections 312.120 and 314.106

The framework for evaluation of foreign data not conducted under an IND is governed by the 21 CFR 312.120 which incorporates recommendations and guidelines from ICH Guidances.[13]

Per 21 CFR 314.106, an application based solely on foreign clinical data **may** be approved if:

- The foreign data are applicable to the U.S. population and U.S. medical practice,
- The studies are performed by investigators of recognized competence, and
- There is FDA validation of trial data through on-site inspections or other appropriate means.[1]

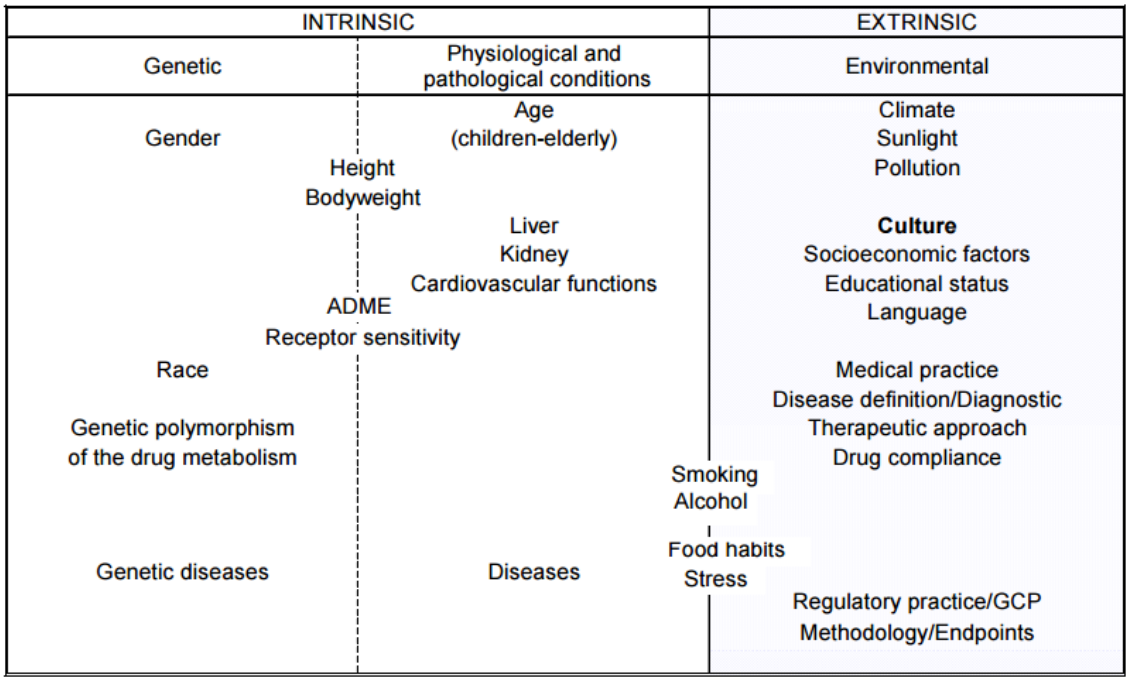
Failure to meet any of these criteria will result in an application not being approvable based on the foreign data alone. FDA will apply this policy in a flexible manner according to the nature of the drug and the data being considered.[1]

6.2 ICH Guidance E5 - Ethnic Factors in the Acceptability of Foreign Clinical Data (1998)

The ICH Guidance E5 on Ethnic Factors in the Acceptability of Foreign Clinical Data was developed in part to facilitate access to drugs in countries whose populations had limited representation in clinical trials, including Asian countries. Regulatory authorities from countries with limited representation in clinical trials often required additional data to "bridge" the clinical data to their populations and medical practices. ICH E5 recommends a framework for evaluating the impact of ethnic factors on the efficacy and safety of a drug at a particular dosage and dose regimen. Ethnic factors are defined as those factors relating to the genetic and physiologic (intrinsic) and the cultural and environmental (extrinsic) characteristics of a population.

Figure 2 provides examples of intrinsic and extrinsic factors which a drug may be sensitive to.

Figure 2: Intrinsic and Extrinsic Ethnic Factors May Impact the Efficacy and Safety of Drugs



Source: ICH Guidance E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data

The primary objective of ICH E5 is to minimize duplicative clinical trials by outlining three steps (i.e., assessment of the data package, sensitivity to ethnic factors, and bridging data package) to determine the acceptability of foreign data as the basis of a marketing application:

- **Assessment of the data package**: Before extrapolation of the foreign data can be considered, the complete clinical data package should contain:

- Adequate characterization of PK, pharmacodynamics (PD), dose response, efficacy, and safety in the population of the foreign region(s).
- The trials should be:
  - Designed and conducted according to regulatory standards in the new region, e.g., choice of controls, and should be conducted according to good clinical practice (GCP).
  - Be adequate and well controlled.
  - Utilize endpoints that are considered appropriate for assessment of treatment.
- Characterization in a population relevant to the new region of the PK, and where possible, PD and dose response for PD endpoints. This characterization could be performed in the foreign region in a population representative of the new region or in the new region.

- **Assessment of sensitivity to ethnic factors**: A determination must be made on the product's sensitivity to ethnic factors. See Figure 2 above.

- **Assessment of the bridging data package**: Based on the product's sensitivity to ethnic factors and the likelihood that such factors could affect a product's safety or efficacy, a regulatory agency can make a judgment about the requirement for a bridging study. A bridging study is a study performed in the new region that will allow extrapolation of the foreign data to the population in the new region. For the new region, bridging studies may provide:
  - PD data
  - Clinical data on efficacy, safety, dosage, and dose regimen

6.3 Current use of single-country trials for me-too drug development programs not envisioned in ICH E5

The ICH E5 framework was envisioned to fulfill an unmet medical need for patients in parts of the world that did not participate in MRCTs. Bridging studies were designed to extrapolate data from one patient population to another in order to bring novel and innovative therapies to more patients.

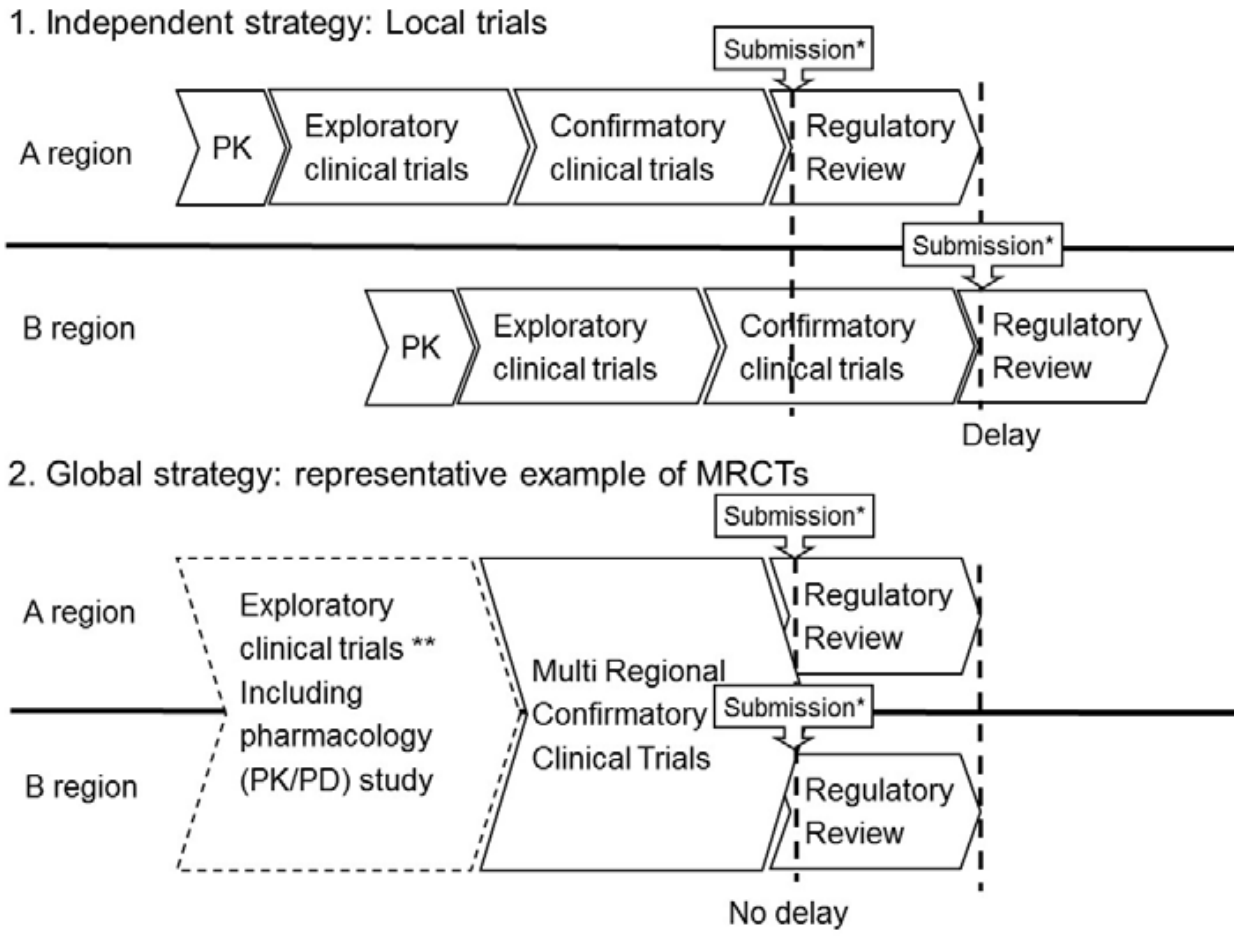
Bridging studies, however, are inherently limited and may not fully address concerns regarding generalizability since they are smaller, tend to be non-randomized, and rely on response rate or PD comparisons rather than time to event endpoints such as OS. Bridging studies may be even more inadequate when attempting to "bridge" data from a single country or region to a diverse demographic population.

Importantly, to establish substantial evidence of effectiveness per 21 CFR 314.126, the typical regulatory standard is two adequate and well controlled trials.[14] Based upon the characteristics of the first trial, an additional trial *convincing on its own* (i.e., an adequate and well-controlled trial that is not merely a bridging study), may be needed to demonstrate effectiveness.

6.4 Paradigm Shift: ICH Guidance E17 - General Principles on the Planning and Design of MRCTs

In 2017, ICH provided an additional guidance document discussing concurrent global registration strategies using MRCTs. This guidance reflected an emerging consensus that trials requiring international collaboration were preferred over single country trials. In ICH E17, importance is placed on the strategic use of MRCTs throughout all phases of drug development, rather than conducting trials from single countries or limited regions. Figure 3 illustrates the potential for earlier access to new drugs worldwide with the use of MRCTs:

Figure 3: Local versus Global Clinical Trial Strategies for Drug Development



Source: ICH Guidance E17 - General Principles on the Planning and Design of Multiregional Clinical Trials

ICH E17 outlines basic principles of good MRCTs:

- Strategic use of properly designed and executed MRCTs in drug development programs to increase efficiency of drug development.
- Early identification and examination of intrinsic and extrinsic factors important to the drug development program.
- Strategic allocation of the sample size to different regions to allow evaluation of regional consistency of the treatment effect.
- Prespecified pooling of regions or subpopulations, based on established knowledge about similarities, to provide flexibility in sample-size allocation to regions, facilitate the assessment of regional consistency, and support regulatory decision-making.
- Structured exploration to examine the consistency of treatment effects across regions and subpopulations.
- Ensuring high quality of study design and conduct in accordance with ICH E6 (i.e., according to good clinical practices [GCP]) in all regions to ensure the study results are interpretable.
- Efficient communication among sponsors and regulatory authorities during the planning stage of MRCTs, with the goal of obtaining acceptance of a global approach to study design across the different regulatory regions.

7. EFFICACY AND SAFETY OF ANTI-PD-(L)1 ANTIBODIES IN ASIAN AND NON-ASIAN PATIENTS

Per 21 CFR 314.106, for acceptance of an application based solely on foreign data, the data must be applicable to a U.S. population, and the drug must be demonstrated to be insensitive to ethnic factors per ICH E5. Existing data are limited in evaluating the impact of race on the efficacy and safety of anti-PD-(L)1 antibodies. However, some exploratory analyses suggest potential differences between Asian and non-Asian patients.

The Applicant cites a 2019 FDA exploratory pooled analysis of outcomes in Asian patients with metastatic NSCLC receiving immune checkpoint inhibitors in randomized trials submitted to the FDA.[15] Most Asian patients were located geographically in Asia (90%). While the comparative treatment benefit from immune checkpoint inhibitors relative to chemotherapy did not appear to differ between Asian and non-Asian patients, Asian patients had a better prognosis with better unadjusted and adjusted median OS for each treatment in each line of therapy. This finding highlights that there may be both known and unknown differences in Asian and non-Asian patients with NSCLC which affect prognosis. This pooled analysis included both non-squamous and squamous histologies, and it's possible that findings may differ if the analysis was limited to non-squamous NSCLC.

Additional exploratory analyses have compared the efficacy and safety of immune checkpoint inhibitors in Asian and non-Asian patients with NSCLC and other solid tumors. Results consistently suggest superior survival benefit in Asian patients.[16-18] Simultaneously, other analyses suggest important potential differences in safety, including increased rates of immune-mediated pneumonitis in Asian patients.[18]

While these observations are intriguing, they are based on exploratory, retrospective analyses or cross-trial comparisons of different anti-PD-(L)1 antibodies in heterogeneous treatment settings. The impact of known and unknown differences in ethnic factors on the efficacy and safety of sintilimab and other anti-PD-(L)1 antibodies would be ideally assessed with a structured evaluation across geographic regions within prospective MRCTs. (See ICH E17).

8. KEY REVIEW ISSUES

ORIENT-11 raises significant questions regarding data from a single foreign country to support a U.S. approval and its generalizability to a diverse American population. ORIENT-11 does not align with principles described in ICH E17 and does not fulfill the regulatory statutes outlined in 21 CFR 314.106. Study results from ORIENT-11 are not applicable to U.S. patients and medical practice. Clinical investigators who participated in ORIENT-11 have had minimal interactions with the FDA and their prior participation in MRCTs that led to FDA approvals is unknown. While site inspections are important to assess data conduct and integrity, the scope of inspections are limited and only provide a sampling of data. As this application does not fulfill an unmet need for U.S. patients with non-squamous NSCLC, regulatory flexibility is not warranted.

8.1 ORIENT-11 does not align with principles described in ICH E17, and was not a multiregional clinical trial

Well-conducted MRCTs allow investigation of safety and efficacy in the overall population, as well as investigation of the potential impact of intrinsic and extrinsic ethnic factors on the treatment effect across geographic regions and populations. Conducted in a single country, ORIENT-11 does not permit investigation of consistency of trial results across regions and patient populations, including for patients with non-squamous NSCLC in the U.S. ORIENT-11 does not align with any of the seven principles of a good MRCT per ICH E17, as described in Section 6.4 above.

8.2 ORIENT-11 is not applicable to the U.S. population and U.S. medical practice

8.2.1 Different practice standards between U.S. and China: ORIENT-11 comparator arm not applicable to U.S. standard of care

The Applicant failed to seek regulatory advice in established FDA milestone meetings regarding the potential for U.S. registration. ORIENT-11 was initiated in China using a comparator arm of

chemotherapy alone. This treatment paradigm is not reflective of U.S. standard of care and would not have been able to enroll patients in the U.S. where immune checkpoint inhibitors have been approved since 2017 for front-line metastatic NSCLC and widely accepted by U.S. practitioners. ORIENT-11 enrolled its first patient after pembrolizumab with chemotherapy was converted from accelerated to regular approval based on the OS advantage demonstrated in KEYNOTE-189. ORIENT-11 would not have garnered support or accrual from U.S. investigators during the time of its enrollment in China. While immune checkpoint inhibitors were not approved in China at the time of study initiation, pembrolizumab with chemotherapy gained approval in China approximately seven months after the first patient was enrolled in ORIENT-11.

Thus, per ICH E5, ORIENT-11 is not applicable to U.S. standard of care.

Many applicants seeking U.S. registration based solely on data from China are deploying similar strategies, using dated comparator arms in me-too trials which would have difficult accruing in the U.S. and many other countries in which the innovator drug in the same drug class is already approved.

8.2.2 ORIENT-11 study endpoint not applicable to U.S. medical practice based on precedent for OS endpoint for all prior NSCLC immune checkpoint inhibitor approvals

ORIENT-11 was powered for PFS, without statistical testing for OS. Overall survival is generally the preferred endpoint in oncology clinical trials when it can be reasonably assessed. To date, all FDA approvals of first-line immunotherapy-based regimens for metastatic NSCLC have been based on a statistically significant improvement in OS.[5-7,19] FDA approvals of first-line immunotherapy-based regimens for metastatic NSCLC are shown in Table 7.

Table 7: FDA Approvals of First-Line Immunotherapy-Based Regimens for Metastatic NSCLC

Drug(s)	Indication*	Approval Endpoint (Year)
Pembrolizumab	NSCLC (PD-L1 TPS ≥50%)	OS (2016)
Pembrolizumab	NSQ-NSCLC (w/ pemetrexed and platinum chemotherapy)	PFS (2017)[AA] OS (2018)
Pembrolizumab	SQ-NSCLC (w/ carboplatin and paclitaxel or nab-paclitaxel)	OS (2018)

Drug(s)	Indication*	Approval Endpoint (Year)
Atezolizumab	NSQ-NSCLC (w/ carboplatin, paclitaxel, & bevacizumab)	OS and PFS (2018)
Pembrolizumab	NSCLC (PD-L1 TPS ≥1%)	OS (2019)
Atezolizumab	NSQ-NSCLC (w/ carboplatin & nab-paclitaxel)	OS and PFS (2019)
Nivolumab/Ipilimumab	NSCLC (PD-L1 TPS ≥1%)	OS (2020)
Nivolumab/Ipilimumab	NSCLC (w/ platinum-doublet chemotherapy)	OS (2020)
Atezolizumab	NSCLC (PD-L1 TC ≥50% or IC ≥10%)	OS (2020)
Cemiplimab-rwlc	NSCLC (PD-L1 TPS ≥50%)	OS (2021)

* Indicated for all NSCLC histologies unless otherwise noted
Abbreviations: AA – accelerated approval; NSQ – non-squamous; SQ – squamous; TPS – tumor proportion score; TC – tumor cells; IC – immune cells

The Applicant stated that PFS was selected as the primary endpoint for ORIENT-11 given concerns that the treatment effect on OS may be confounded by crossover from the placebo arm to sintilimab after disease progression. As of January 15, 2021, 46% of patients on the placebo arm have crossed over to receive sintilimab. While concerns of confounding of the observed treatment effect on OS due to crossover are valid, crossover was permitted in other studies of immunotherapy-based regimens for the first-line treatment of NSCLC which ultimately demonstrated OS benefit. For example, a total of 85 out of 206 patients (41%) on the placebo arm of KEYNOTE-189 received either pembrolizumab or another anti-PD-(L)1 antibody at the time of disease progression.[5]

With several FDA approved treatment options for U.S. patients predicated on OS, and as there is no evidence that sintilimab provides a safety or efficacy advantage over available therapy, there is no impetus for regulatory flexibility to accept foreign data based on an endpoint with less clinical significance (i.e., PFS). Multiple immune checkpoint inhibitors have demonstrated a statistically significant, formally tested, advantage in OS. Acceptance of PFS for a me-too trial design and drug, in a trial population that does not reflect a U.S. demographic, represents a departure from the FDA regulatory precedent in this space. The risk of loss of demonstrated, formally tested survival advantage for patients could be mitigated by a direct comparison of sintilimab to an approved agent.

The CFR notes that FDA will apply the evaluation of foreign data policy in a flexible manner, according to the nature of the drug and the data being considered. Given the multitude of checkpoint inhibitors available, and use of PFS instead of OS, ORIENT-11 does not warrant a flexible approach to interpretation of single country data.

8.2.3 Known and unknown differences in intrinsic and extrinsic factors between patients in ORIENT-11 and the U.S. suggest possible differences between U.S. and Chinese patients

The characteristics of patients enrolled in ORIENT-11 are not consistent with characteristics of patients in the U.S. with Stage IV NSCLC.

ICH E17 outlines a plan to address intrinsic and extrinsic factors prior to initiation of an MRCT. Having patients from diverse national, ethnic, and racial backgrounds may allow for an evaluation of consistency of treatment effects across subgroups. While an MRCT would allow for a structured exploration of regional consistency of efficacy and safety of sintilimab, this application relies on clinical trial data from a single foreign country. Of concern, prior analyses of anti-PD-(L)1 antibodies in Asian and non-Asian patients suggest there may be important differences in efficacy and safety between patients in ORIENT-11 compared to the U.S. population. (See Section 7).

Compared to patients in the U.S., the population of patients in ORIENT-11 is younger, more male, fewer are current or former smokers, and all are Asian.[20,21] Table 10 summarizes known differences in the demographics and baseline characteristics of patients in ORIENT-11 compared to patients in the U.S. which affect the applicability of the study results.

Table 8: Known Differences between Patients in ORIENT-11 and U.S. Patients

Patients in ORIENT-11	U.S. Patients with Non-Squamous NSCLC
• Median age 61 • 76% male • 65% current/former smokers • 100% Asian (from China)	• Median age 70 at diagnosis • ~ 50% male • ~85% current/former smokers • ~79% White • ~15% Black • ~6% Asian

There may be additional differences with an unknown impact on the efficacy and safety of sintilimab, including use of concomitant and herbal medications. Within ORIENT-11, at least 63% of patients were reported as having received concomitant traditional Chinese medications. Regional differences in the practice of medicine, including the diagnosis and therapeutic approach for patients with non-squamous NSCLC, may additionally present an unknown impact

on study results. (See 21 CFR 312.120 and ICH E5). For example, patients in the U.S. with Stage IIIB or IIIC NSCLC are typically treated with chemoradiation with curative intent followed by durvalumab per standard of care practices[22], however, 9% of patients in ORIENT-11 had Stage IIIB or IIIC NSCLC and did not receive definitive chemoradiation.

8.2.4 ORIENT-11 is not reflective of the diverse ethnic subgroups within the U.S. population

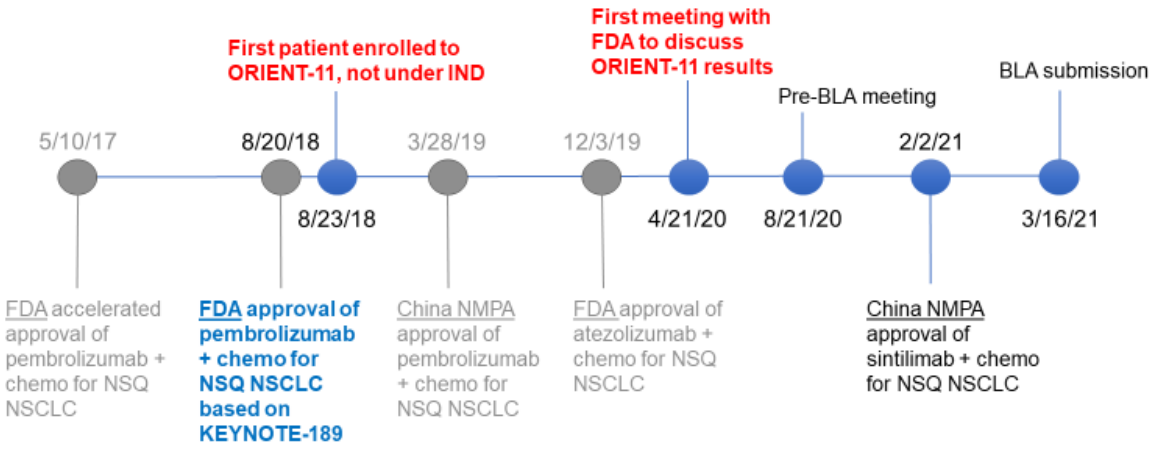
ORIENT-11 was conducted exclusively in China and enrolled a patient population which lacks the racial and ethnic diversity of the U.S. population, notably with regards to currently underserved groups. With the exception of one trial (Study CIBI308A102) of 39 patients with advanced endometrial cancer and other solid tumors in the U.S., all supportive trials were also conducted solely in China.

A basic tenet for FDA approval is that study populations should represent the populations for which the therapeutic product is intended, to ensure external validity of trial results.[23] (See 21 CFR 312.120 and ICH E5). Although China is considered a multi-ethnic country of 56 ethnic groups[24], it does not represent the ethnic diversity of the U.S. Furthermore, ORIENT-11 does not align with broad initiatives and renewed commitment across the pharmaceutical industry for equitable representation in clinical trials.[23,25-27]

8.3 Per 21 CFR 312.120, studies not conducted under IND must conform to GCP: ORIENT-11 lacked FDA consultation and oversight

ORIENT-11 was not conducted under an IND and FDA was not involved during the planning or implementation of the study. Importantly, if the Applicant had requested FDA feedback during the planning stage of ORIENT-11, FDA may have advised that sintilimab be compared to an existing FDA approved anti-PD-L-1 based regimen.[28] The first patient was enrolled to ORIENT-11 on August 23, 2018, while the first interaction between the Applicant and FDA was not until April 21, 2020, as shown in Figure 4.

Figure 4: Timing of ORIENT-11 relative to US Standards of Care



Per 21 CFR 312.120, studies not conducted under IND must conform to GCP, including review and approval by an independent ethics committee (IEC) before initiating a study and ongoing oversight by the IEC during the study. The name and address of the IEC that reviewed the study and a statement that the IEC meets the definition in 21 CFR 312.3 should be provided.[29] The Applicant must maintain records supporting such statement, including records of the names and qualifications of IEC members, and make these records available for FDA review upon request. A summary of the IEC's decision to approve or modify and approve the study, or to provide a favorable opinion should also be provided to the FDA.

While the Applicant included information about their IEC in materials provided to the FDA, it is unclear what role they had in addressing issues of informed consent, given the approval of pembrolizumab during enrollment of ORIENT-11.

8.4 Informed consent not updated to reflect changing standards of care per GCP

Per the ICH Guidance E6 on Good Clinical Practice (GCP), trials should be conducted with ethical principles rooted in the Declaration of Helsinki. (See 21 CFR Sections 50 and 312.120 and ICH E6).[13,30,31] An overarching principle is that the rights, safety, and well-being of patients are the most important considerations and should prevail over the interests of science and society. Patients should be adequately and well consented for clinical trials. (See 21 CFR 50.20 and ICH E6).[31,32] The informed consent form should be revised, and other written information should be provided to patients as new important information becomes available. The patient should be informed and reconsented in a timely manner if new information emerges that may be relevant to their willingness to continue participation in the trial.

The informed consent form for ORIENT-11 did not explicitly outline alternatives to trial enrollment, including treatment with any available approved therapies or participation on

alternative clinical trials. Rather, the informed consent form broadly indicated that study investigators should discuss alternative treatment options with patients.

The ORIENT-11 informed consent was not revised nor was reconsent required to update patients on the Chinese approval of pembrolizumab in combination with pemetrexed and platinum-chemotherapy despite showing a survival benefit over chemotherapy alone. Instead, all three versions of the informed consent relied on the study doctor to discuss treatment options.

8.5 Clinical inspections limited in scope, ORIENT-11 investigators with limited prior participation in MRCTs

Clinical inspections have been initiated for ORIENT-11 per 21 CFR 312.68.[33] Although an essential component of FDA review, site inspections are limited in breadth to assess data integrity. Only a sampling of clinical trial sites is inspected which cannot fully capture the heterogeneity of data quality and study conduct across sites. Historical reports of fraudulent or substandard data quality highlight the value of conducting MRCTS, in which sites would vary by size, region, and prior experience in trials leading to U.S. FDA registration. While prior experience with applicants and study investigators may bolster confidence in trial conduct and data integrity, FDA has had only limited interactions with the Applicant and investigators for ORIENT-11.

8.6 ORIENT-11 does not address an unmet need and does not warrant regulatory flexibility

ORIENT-11 relies on clinical data from China which closely resembles previously conducted MRCTs which led to U.S. approval, and does not fulfill an unmet need. The trial utilizes a lesser endpoint in PFS than endpoints used for approval of currently available therapies in this space, and offers no advantage in safety or mode of administration to the U.S. patient population. The majority of oncology drug development in China is for immune checkpoint inhibitors, most of which is duplicative of existing multiregional development programs. The degree of regulatory flexibility in determining the acceptability of data from a single country and its generalizability to a new population should be balanced against the drug's innovation. Diseases which are more common in Asia than in the U.S., such as hepatocellular carcinoma or nasopharyngeal carcinoma, and for which there may be difficulty enrolling to an MRCT due to small patient populations depending on the region, may warrant regulatory flexibility. However, NSCLC is a common tumor in the U.S. and worldwide, thus studies in this disease should ideally be MRCTs as described in the ICH E17 guidance.

9. SUMMARY

Multiregional clinical trials are the preferred international standard for drug development per ICH E17. These trials tend to be large, randomized, and allow for an evaluation of consistency of treatment effects across geographic regions. Multiregional clinical trials are meant to satisfy the requirements of multiple regulatory authorities. Multiregional clinical trials foster more efficient drug development avoiding duplication and earlier global access to novel therapeutics. The Applicant seeks U.S. approval of sintilimab, an immune checkpoint inhibitor for front-line metastatic NSCLC based on a trial conducted exclusively in China, not under IND. ORIENT-11 met its primary endpoint of PFS, however the trial and results do not meet criteria outlined in 21 CFR 312.120 and 314.106 for acceptance of foreign data.

The application is reflective of an increasing number of oncology development programs based solely or predominantly on clinical data from China. The Applicant did not consult with the FDA regarding trial design or conduct, including selection of endpoint and control arm. This single country trial closely resembles MRCTs in NSCLC which led to FDA approval prior to study initiation. The patient population in ORIENT-11, as a single country trial, does not reflect the diversity of the American population, with both known and unknown differences in intrinsic and extrinsic factors. Acceptance of single country foreign data which does not reflect the diversity of a U.S. population challenges the widespread industry commitment to patient equity and inclusion of underrepresented populations. While clinical site inspections may be performed, they cannot fully capture the heterogeneity of data quality and study conduct across numerous clinical sites. Investigators in ORIENT-11 have had limited prior interactions with the FDA and an unknown level of prior participation in MRCTs that led to FDA approvals. Importantly, the extent of past participation in MRCTs may provide added confidence in trial conduct and data integrity. The NSCLC treatment landscape includes many front-line immunotherapy options conferring advantages in OS whereas ORIENT-11 was powered for PFS.

The Applicant proposes an additional study which would be conducted in China, the U.S., and the European Union comparing two doses of sintilimab in 150 patients. The primary endpoint is ORR in 100 patients planned to receive the sintilimab 200 mg Q3W dose. This proposal would not address the concerns regarding endpoint selection. Rather, sintilimab should be compared directly to an approved immune checkpoint inhibitor in a MRCT to ensure that a survival advantage is maintained.

Sintilimab does not fulfill an unmet need for U.S. patients with NSCLC, limiting the degree of regulatory flexibility that is warranted regarding the acceptability of this data to support FDA approval.

Rather than pursue a large number of duplicative development programs exclusively in China, patients in China should be participants in MRCTs. Multiregional clinical trials should be strategically conducted with global participation to ensure broad access for all patients in all regions of the world.

We ask the committee to discuss whether additional data should be required to demonstrate applicability to the U.S. population given this trial was conducted in a single foreign country.

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