Sintilimab for Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer (NSCLC)

FDA Opening Remarks
Oncologic Drugs Advisory Committee (ODAC) Meeting
February 10, 2022

Harpreet Singh, MD
Director, Division of Oncology 2
Office of Oncologic Diseases
Outline

• ORIENT-11 Study Design and Results

• Regulatory Framework for Evaluation of Foreign Data
  - Code of Federal Regulations (CFR)
  - International Council of Harmonisation (ICH) Guidances E5 and E17

• Key Review Issues: Generalizability to U.S. Population

• Discussion and Voting Question for ODAC
**Key Eligibility Criteria**
- Untreated NSQ-NSCLC Stage IIIB/C or IV
- No EGFR or ALK alteration
- ECOG PS 0 or 1

**Stratification Factors**
- Male vs female
- Cisplatin vs carboplatin
- PD-L1 (TPS <1% vs ≥1%)

**Primary endpoints**: Progression-free survival (PFS) by independent radiologic review committee (IRRC)

**Descriptive secondary endpoints**: OS (no α-allocation), overall response rate (ORR), duration of response (DOR)

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**ORIENT-11 Primary Efficacy Results: PFS by IRRC**

|                              | Sintilimab + Chemo  
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</tr>
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<td>Hazard ratio (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
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</tr>
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<td>p-value&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
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</table>

Data cut-off (DCO): November 15, 2019

<sup>a</sup> Kaplan-Meier estimate

<sup>b</sup> Stratified Cox proportional hazard model using Efron’s method

<sup>c</sup> Two-sided p-value; α bound 0.01958 (interim analysis)

Overall Survival, Overall Response Rate, and Duration of Response were descriptive endpoints not formally tested.
Increasing Number of Single Country Trials

- ORIENT-11 trial design, enrollment criteria, and statistical assumptions closely resemble landmark NSCLC trials which changed treatment paradigm to include immune checkpoint inhibitors.

- Reflects at least 25 oncology development programs conducted exclusively in China, many of which closely resemble prior multiregional clinical trials (MRCTs).

- Per ICH E17 guidance, MRCTs preferred approach to globally harmonized drug development.

ICH – International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
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  – Studies performed by investigators of recognized competence
  – FDA validation of data through on-site inspection or other appropriate means

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 nature of drug and data being considered

Source: 21 CFR 314.106
ICH Guidance: E5 Bridging → E17 MRCT

E5 (1998): sequential bridging from trial in one region to trial in new region

Bridging studies fulfilled unmet need.
Inherently limited ability to demonstrate applicability.
Sequential strategy delayed access to important drugs.
Consider intrinsic and extrinsic factors

E17 (2017): MRCT then evaluate regional consistency
Consider regional variability during planning of MRCT

A 20-year journey from local mindset to global mindset for efficient drug development and to ensure safe and effective drugs worldwide
Asian Countries Participation in MRCTs

Oncology Submissions to the FDA: Patient Enrollment by Geographic Region
ICH E17: Multiregional Clinical Trials (MRCTs)

- Most U.S. drug applications based on international MRCTs
- Allows evaluation of regional consistency (i.e., safety and efficacy evaluated across geographic regions and subpopulations)
- Enables earlier access worldwide to therapies
- Avoids duplication of trials and need for bridging studies
- Promotes international harmonization of standard of care practices \(\rightarrow\) facilitates enrollment for future global trials

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KEYNOTE-189: Landmark Approval of Pembrolizumab + Chemotherapy Based on OS

Regular approval based on statistically significant improvement in OS

Source: KEYTRUDA (Pembrolizumab) USPI
Control Arm Inapplicable to U.S. Medical Practice

• Enrollment to ORIENT-11 began after FDA approval of pembrolizumab/chemotherapy (KEYNOTE-189) which demonstrated statistically significant OS benefit for patients with nonsquamous NSCLC

• ORIENT-11 could not have been conducted in the United States
  – Lack of investigator support given substandard chemotherapy comparator arm
  – Available FDA approved therapies conferred survival advantage

If consulted, FDA would have likely advised direct comparison of sintilimab to an approved anti-PD-(L)1/chemotherapy regimen with OS endpoint
<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Indication*</th>
<th>Approval Endpoint (Year)</th>
</tr>
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<tbody>
<tr>
<td>Pembrolizumab</td>
<td>NSCLC (TPS ≥50%)</td>
<td>OS (2016)</td>
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<tr>
<td>Pembrolizumab</td>
<td>NSQ-NSCLC (w/ pemetrexed and platinum chemo)</td>
<td>PFS (2017)AA; OS (2018)</td>
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<td>SQ-NSCLC (w/ carboplatin and paclitaxel or nab-paclitaxel)</td>
<td>OS (2018)</td>
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<tr>
<td>Nivolumab/Ipilimumab</td>
<td>NSCLC (TPS ≥1%)</td>
<td>OS (2020)</td>
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<tr>
<td>Nivolumab/Ipilimumab</td>
<td>NSCLC (w/ platinum-doublet chemo)</td>
<td>OS (2020)</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>NSCLC (TC ≥50% or IC ≥10%)</td>
<td>OS (2020)</td>
</tr>
<tr>
<td>Cemiplimab-rwlc</td>
<td>NSCLC (TPS ≥50%)</td>
<td>OS (2021)</td>
</tr>
</tbody>
</table>

* Indicated for all NSCLC histologies unless otherwise noted
AA – Accelerated Approval
NSQ – nonsquamous; SQ – squamous

www.fda.gov
ORIENT-11 not reflective of U.S. population

• Compared to U.S. patients with NSCLC, patients in ORIENT-11 were younger, predominantly male, lower rates of smoking

• Unknown impact of concomitant (herbal) medications

• Unknown impact of differences in body weight/composition

• Fails to address persistent underrepresentation of racial and ethnic minorities in drug development
FDA Validation of Data Limited in Scope

- Few selected clinical sites unable to fully capture heterogeneity in trial conduct and data quality
- Prior participation in MRCTs, as well as previously reported challenges to data integrity are key factors
- ORIENT-11 investigators with limited MRCT experience leading to FDA registration

Applicability to U.S. Population: Applicant Position

1. Similar clinical practice standards between China and U.S. Standard of care in China at time of trial initiation (2018) not applicable to U.S. patients, who had shifted to first-line immunotherapy

2. Similar pharmacokinetics (PK) and pharmacodynamics (PD) of sintilimab between Chinese and U.S. patients
   Insufficient PK data provided to conclude similarity to diverse U.S. population, best evaluated in a MRCT

3. Similar efficacy and safety of sintilimab between Chinese and U.S. patients
   Retrospective, exploratory analyses with mixed results, best evaluated in a MRCT
ORIENT-11 Not Applicable to U.S. Population

- **Comparator arm and endpoint (PFS)** not consistent with U.S. medical practices and regulatory standards
  - ORIENT-11 lacked FDA consultation and oversight

- **Study population** not reflective of diverse U.S. population

- **Informed consent** not updated to reflect changing standard of care (SOC) as required per good clinical practice (GCP)

- **Inspections limited in scope** to assess trial conduct and data integrity

**Therapeutic landscape does not warrant regulatory flexibility.**
Applicant’s Proposal for Non-Comparative Study Examining Two Doses of Sintilimab

- Untreated NSQ-NSCLC, Stage IIIB/C or IV
- Patients from U.S., Europe, and China N=150

Sintilimab 200 mg Q3W + chemotherapy n=100

Sintilimab 400 mg Q6W + chemotherapy n=50

Primary Endpoint: ORR

Does not address applicability issues → possible trial would compare sintilimab to approved anti-PD-(L) antibody with OS endpoint
ORIENT-11 Not Envisioned in ICH E5, Not Aligned with ICH E17

- ICH E5 guidance on bridging not intended for “me too” drugs
  - Does not fulfill an unmet regional need

- If designed as a well-conducted MRCT, ORIENT-11 would have:
  - Involved early communication with international regulatory authorities
    → selection of appropriate comparator, OS endpoint
  - Permitted structured exploration of regional consistency of results
  - Addressed concerns about applicability to U.S. population
Building Equity through MRCTs

- MRCTs strengthened by additional regional participants
- Increased diversity may address underrepresentation of ethnic minorities in drug development
- Increased global participation in MRCTs provides a framework to establish regulatory experience
- Patient centered approach expedites therapeutic advances
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Voting Question

Should additional clinical trial(s) demonstrating applicability to U.S. patients and U.S. medical care be required prior to a final regulatory decision?
Sintilimab for Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer (NSCLC)

FDA Presentation
Oncologic Drugs Advisory Committee (ODAC) Meeting
February 10, 2022

Paz J. Vellanki, MD, PhD
Clinical Reviewer, Thoracic and Head and Neck Cancer
Division of Oncology 2, Office of Oncologic Diseases
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Harpreeet Singh, M.D., Director, DO2
Martha Donoghue, M.D., Deputy Director, DO2
Erin Larkins, M.D., Supervisory Associate Director, DO2
Nicole Drezner, M.D., Cross-Discipline Team Leader and Clinical Team Leader, DO2
Paz Vellanki, M.D., Ph.D., Clinical Reviewer, DO2
Shenghui Tang, Ph.D., Director, DBV
Yuan-Li Shen, Ph.D., Deputy Director, DBV
Pallavi Mishra-Kalyani, Ph.D., Statistical Team Leader, DBV
Somak Chatterjee, Ph.D., Statistical Reviewer, DBV
Atiqur Rahman, Ph.D., Director, OCP
Jeanne Fourie Zirkelbach, Ph.D., Clinical Pharmacology Team Leader, OCP
Catharine Bulik, Ph.D., Clinical Pharmacology Reviewer, OCP
Jiang Liu, Ph.D., Pharmacometrics Team Leader, DPM
Ye Xing, Ph.D., Pharmacometrics Reviewer, DPM
John Leighton, Ph.D., Director, DHOT
Emily Wearne, Ph.D., Pharmacology Toxicology Team Leader, DHOT
Amy Skinner, Ph.D., Pharmacology Toxicology Reviewer, DHOT
Haocheng Yan, Ph.D., Product Quality Team Leader, OBP
Gunther Boekhoudt, Ph.D., Product Quality Reviewer, OBP
Lee Pai-Scherf, M.D., Site Inspections Reviewer, OSI
Karen Bleich, M.D., Site Inspections Team Leader, OSI
Jana Highsmith, Regulatory Health Project Manager, DRO-ORO
Richard Pazdur, M.D., Director, OCE
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FDA Mission

The U.S. Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

FDA does not consider cost or drug pricing in regulatory decision making.
**Key Eligibility Criteria**
- Untreated NSQ-NSCLC Stage IIIB/C or IV
- No EGFR or ALK alteration
- ECOG PS 0 or 1

**Stratification Factors**
- Male vs female
- Cisplatin vs carboplatin
- PD-L1 (TPS <1% vs ≥1%)

**Primary endpoints**: Progression-free survival (PFS) by independent radiologic review committee (IRRC)

**Descriptive secondary endpoints**: overall survival (OS; no α-allocation), overall response rate (ORR), duration of response (DOR)

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**ORIENT-11: Sintilimab + Chemotherapy for NSCLC Conducted Exclusively in China**

- Placebo + Pemetrexed + Cisplatin OR Carboplatin for 4 cycles
- Sintilimab + Pemetrexed + Cisplatin OR Carboplatin for 4 cycles
- Placebo up to 24 months + Pemetrexed
- Sintilimab up to 24 months + Pemetrexed

R 2:1 crossover

47% crossed over at final analysis
## Demographics and Baseline Characteristics

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<td><strong>Age, median (range)</strong></td>
<td>61 (30 – 75)</td>
<td>61 (35 – 75)</td>
</tr>
<tr>
<td><strong>Sex, Male</strong>*</td>
<td>204 (77%)</td>
<td>99 (76%)</td>
</tr>
<tr>
<td><strong>Race, Chinese (mainland China)</strong></td>
<td>266 (100%)</td>
<td>131 (100%)</td>
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<tr>
<td><strong>ECOG, PS 1</strong></td>
<td>190 (71%)</td>
<td>97 (74%)</td>
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<td><strong>Disease Stage</strong></td>
<td></td>
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<td>Stage IIIB/IIIC</td>
<td>21 (8%)</td>
<td>15 (11%)</td>
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<td>Stage IV</td>
<td>245 (92%)</td>
<td>116 (89%)</td>
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<td><strong>PD-L1</strong>*</td>
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<td>&lt;1%</td>
<td>85 (32%)</td>
<td>44 (34%)</td>
</tr>
<tr>
<td>≥1%</td>
<td>181 (68%)</td>
<td>87 (66%)</td>
</tr>
<tr>
<td><strong>Current/Former Smoker</strong></td>
<td>171 (64%)</td>
<td>87 (66%)</td>
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<tr>
<td><strong>Platinum Choice</strong>*</td>
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<tr>
<td>Cisplatin</td>
<td>71 (27%)</td>
<td>33 (25%)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>195 (73%)</td>
<td>98 (75%)</td>
</tr>
<tr>
<td><strong>Brain Metastases</strong></td>
<td>36 (14%)</td>
<td>22 (17%)</td>
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* Stratification Factor
Primary Efficacy Results: PFS by IRRC

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- Kaplan-Meier estimate
- Stratified Cox proportional hazard model
- Two-sided p-value; interim \( \alpha \) bound 0.01958

Overall Survival, Overall Response Rate, and Duration of Response were descriptive endpoints not formally tested.
## Summary of Safety

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<td></td>
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<td><strong>All-cause AEs</strong></td>
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<tr>
<td>Any Grade</td>
<td></td>
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<tr>
<td>Grade 3-4</td>
<td>265 (100%)</td>
<td>131 (100%)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>158 (59%)</td>
<td>69 (53%)</td>
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<tr>
<td></td>
<td>6 (2.3%)</td>
<td>11 (8%)</td>
</tr>
<tr>
<td><strong>SAEs</strong></td>
<td>75 (28%)</td>
<td>44 (34%)</td>
</tr>
<tr>
<td><strong>AEs Leading to Interruption</strong></td>
<td>125 (47%)</td>
<td>63 (48%)</td>
</tr>
<tr>
<td><strong>AEs Leading to Discontinuation</strong></td>
<td>14 (5%)</td>
<td>12 (9%)</td>
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Legal Framework and FDA Guidances

Law

Regulations
Issued by Federal government to carry out legislation

Guidances
Represent FDA’s current thinking

Food, Drug, and Cosmetic Act

Code of Federal Regulations (CFR)
Title 21 pertains to food & drugs

Guidance to Industry and Investigators
Includes ICH Guidances

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• FDA will apply this policy in a flexible manner according to nature of drug and data being considered

Source: 21 CFR 314.106
Considerations for Regulatory Flexibility

FDA will apply 21 CFR 314.106 in a flexible manner according to nature of drug and data being considered.

• Unmet medical need

• Rare disease: MRCTs difficult to conduct

• Novel drug class
Oncology Drug Development
Harmonized by ICH Guidelines

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) established in 1990

ICH brings together global regulatory authorities and the pharmaceutical industry; China officially joined as a member in 2017

Goal of ICH to harmonize scientific and technical requirements of medicinal products to ensure safe, effective, and high-quality medicines worldwide

ICH guidances used and applied by FDA, and often incorporated into Code of Federal Regulations (CFR)

Source: ich.org
1998 ICH E5 Guidance for Acceptability of Foreign Data

Assessment of data package

• Are clinical trials applicable to regulatory standards in new region, including primary endpoint and control arm?
• Trials adequate and well-controlled?

Sensitivity to ethnic factors

• Extrinsic factors: associated with environment and culture
• Intrinsic factors: define/identify a subpopulation

Need for bridging study

• Based on likelihood that ethnic and extrinsic factors could affect a product’s safety or efficacy

ICH – International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Ethnic Factors May Impact Drug Efficacy and Safety (ICH E5 and E17)

<table>
<thead>
<tr>
<th>INTRINSIC</th>
<th>EXTRINSIC</th>
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<tbody>
<tr>
<td>Genetic</td>
<td>Environmental</td>
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<tr>
<td>Gender</td>
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<td>Height</td>
<td>Sunlight</td>
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<td>Bodyweight</td>
<td>Pollution</td>
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<td>Liver</td>
<td>Culture</td>
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<td>ADME &amp; Receptor sensitivity</td>
<td>Socioeconomic factors</td>
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<tr>
<td>Genetic polymorphism of the drug metabolism</td>
<td>Educational status</td>
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<td>Genetic diseases</td>
<td>Language</td>
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<td>Medical practice</td>
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<td>Disease definition/Diagnostic</td>
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<td>Therapeutic approach</td>
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<td>Drug compliance</td>
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<td>Alcohol</td>
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<td></td>
<td>Food habits</td>
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<td>Stress</td>
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<td></td>
<td>Regulatory practice/GCP</td>
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<td></td>
<td>Methodology/Endpoints</td>
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</tbody>
</table>

Source: ICH E5 Guidance – Ethnic Factors in the Acceptability of Foreign Clinical Data
Bridging Studies Inherently Limited

1) Bridging studies may not address concerns regarding generalizability
   – Often smaller, non-randomized
   – Less clinically meaningful endpoints compared to original trial
   – May provide additional pharmacodynamic and clinical data but not sufficient to support a marketing application

2) Reliance on bridging trials resulted in delayed access

Limitations with bridging studies → increased participation in MRCTs
ICH Guidance: E5 Bridging → E17 MRCT

A 20-year journey from local mindset to global mindset for efficient drug development and to ensure safe and effective drugs worldwide

E5 (1998): sequential bridging from trial in one region to trial in new region

- Consider intrinsic and extrinsic factors

Bridging studies fulfilled unmet need.

- Inherently limited ability to demonstrate applicability.
- Sequential strategy delayed access to important drugs.

E17 (2017): MRCT then evaluate regional consistency

- Consider regional variability during planning of MRCT
Increased Asian Participation in MRCTs

Oncology Submissions to the FDA: Patient Enrollment by Geographic Region

- China
- Rest of Asia
- USA
- Rest of World
MRCT Represents Efficient Drug Development

- Earlier access to therapies across different regions
- Avoid duplication of trials and need for bridging studies
- Promote international harmonization

MRCT – multiregional clinical trial
ICH E17 Guiding Principles for MRCTs

1. Strategic use of MRCT’s in drug development
2. Intrinsic/extrinsic factors identified early
3. Strategic allocation of sample size to regions
4. Pre-specified pooling of regions or subpopulations
5. **Structured exploration of consistency across regions and subpopulations**
6. Ensure high quality study design and conduct across regions (ICH E6)
7. Communication with regulatory authorities during planning of MRCTs
Inclusion of Diverse Populations in Cancer Drug Development

• Study populations should represent intended populations¹

• Racial and ethnic minorities underrepresented in trials

• Project Equity: FDA Oncology Center of Excellence initiative to promote diversity in clinical trials and generate data in more representative patient groups

• Commitments and initiatives for inclusion and diversity across pharmaceutical industry², professional societies³, and patient advocacy groups⁴

¹ Fashoyin-Aje L, Beaver JA, Pazdur R. Jama Oncol. 2021
² Quilici E, www.pharmexec.com, Driving diversity and inclusion, February 2021
³ Clarifyhealth.com, Diversity and inclusion in oncology clinical trials, October 2021
⁴ Kim ES et al., J Clin Oncol, October 2017
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• Regulatory Framework for Evaluation of Foreign Data
  - Code of Federal Regulations (CFR)
  - International Council of Harmonisation (ICH) Guidances E5 and E17

• Key Review Issues: Generalizability to U.S. Population

• Discussion and Voting Question for ODAC
KEYNOTE-189: Landmark Approval of Pembrolizumab + Chemotherapy Based on OS

Regular approval based on statistically significant improvement in OS

Source: KEYTRUDA (Pembrolizumab) USPI
**ORIENT-11 Initiated after Change in U.S. Standard of Care**

- **5/10/17**: FDA accelerated approval of pembrolizumab + chemo for NSQ NSCLC based on KEYNOTE-189
- **8/20/18**: First patient enrolled to ORIENT-11, not under IND
- **8/23/18**: First meeting with FDA to discuss ORIENT-11 results
- **3/28/19**: China NMPA approval of pembrolizumab + chemo for NSQ NSCLC
- **4/21/20**: BLA submission
- **2/2/21**: China NMPA approval of sintilimab + chemo for NSQ NSCLC
- **3/16/21**: ORIENT-11 Initiated after Change in U.S. Standard of Care

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Control Arm Inapplicable to U.S. Medical Practice

• Enrollment to ORIENT-11 began after FDA approval of pembrolizumab/chemotherapy (KEYNOTE-189) which demonstrated statistically significant OS benefit for patients with nonsquamous NSCLC

• ORIENT-11 could not have been conducted in the United States
  – Lack of investigator support given substandard chemotherapy comparator arm
  – Available FDA approved therapies conferred survival advantage

If consulted, FDA would have likely advised direct comparison of sintilimab to an approved anti-PD-(L)1/chemotherapy regimen with OS endpoint
### Precedent of Overall Survival as Approval Endpoint for Immunotherapy Approvals for Metastatic NSCLC

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Indication*</th>
<th>Approval Endpoint (Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>NSCLC (TPS ≥50%)</td>
<td>OS (2016)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>NSQ-NSCLC (w/ pemetrexed and platinum chemo)</td>
<td>PFS (2017)^AA; OS (2018)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>SQ-NSCLC (w/ carboplatin and paclitaxel or nab-paclitaxel)</td>
<td>OS (2018)</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>NSQ-NSCLC (w/ carboplatin, paclitaxel, &amp; bevacizumab)</td>
<td>OS and PFS (2018)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>NSCLC (TPS ≥1%)</td>
<td>OS (2019)</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>NSQ-NSCLC (w/ carboplatin &amp; nab-paclitaxel)</td>
<td>OS and PFS (2019)</td>
</tr>
<tr>
<td>Nivolumab/Ipilimumab</td>
<td>NSCLC (TPS ≥1%)</td>
<td>OS (2020)</td>
</tr>
<tr>
<td>Nivolumab/Ipilimumab</td>
<td>NSCLC (w/ platinum-doublet chemo)</td>
<td>OS (2020)</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>NSCLC (TC ≥50% or IC ≥10%)</td>
<td>OS (2020)</td>
</tr>
<tr>
<td>Cemiplimab-rwlc</td>
<td>NSCLC (TPS ≥50%)</td>
<td>OS (2021)</td>
</tr>
</tbody>
</table>

* Indicated for all NSCLC histologies unless otherwise noted

AA – Accelerated Approval
NSQ – nonsquamous; SQ – squamous
ORIENT-11 Endpoint Not Applicable to U.S. Regulatory Standards

• Statistically significant benefit in PFS

• However, OS not statistically tested in ORIENT-11 despite precedent for OS endpoint for approvals in metastatic NSCLC

• For other combination therapies with anti-PD-(L)1 antibodies, OS benefit demonstrated despite crossover in trials → weakens Applicant’s position that OS could not have been reasonably tested

• Acceptance of PFS risks loss of gains in OS seen with prior approvals
Applicability to U.S. Population: Applicant Position

1. Similar clinical practice standards between China and U.S.
   Standard of care in China at time of trial initiation (2018) not applicable to U.S. patients, who had shifted to first-line immunotherapy

2. Similar pharmacokinetics (PK) and pharmacodynamics (PD) of sintilimab between Chinese and U.S. patients
   Insufficient PK data provided to conclude similarity to diverse U.S. Population; best evaluated in a MRCT

3. Similar efficacy and safety of sintilimab between Chinese and U.S. patients
   Retrospective, exploratory analyses suggest potential differences; best evaluated in a MRCT
Known Differences Between Patients in U.S. and ORIENT-11

U.S. population with non-squamous NSCLC$^{1,2}$

- Median age 70 at diagnosis
- ~ 50% male
- ~ 85% current/former smokers
- ~ 79% White
- ~ 15% Black
- ~ 6% Asian

ORIENT-11

- Median age 61
- 76% male
- 65% current/former smokers
- 100% Chinese

$^1$ Howlader N et al., SEER Cancer Statistics Review, 1975 - 2017
$^2$ United States Census Bureau: April 1, 2010 to July 1, 2019
# Comparison of Baseline Characteristics

<table>
<thead>
<tr>
<th>U.S. Patients with Nonsquamous NSCLC&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>KEYNOTE-189&lt;sup&gt;3&lt;/sup&gt; Pembrolizumab N=616</th>
<th>ORIENT-11&lt;sup&gt;4&lt;/sup&gt; Sintilimab N=397</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Countries of Enrollment, n</strong></td>
<td>N/A</td>
<td>16</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>~79% White, ~15% Black, ~6% Asian</td>
<td>94% White, 2.3% Black, 2.9% Asian</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100% Asian (all Chinese)</td>
</tr>
<tr>
<td><strong>Sex, male</strong></td>
<td>~50%</td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>76%</td>
</tr>
<tr>
<td><strong>Current/former smokers</strong></td>
<td>~85%</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65%</td>
</tr>
<tr>
<td><strong>Age, median at diagnosis (range)</strong></td>
<td>~70</td>
<td>64 (34 – 84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>61 (30 – 75)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Howlader N et al., SEER Cancer Statistics Review, 1975 – 2017
<sup>2</sup> United States Census Bureau: April 1, 2010 to July 1, 2019
<sup>3</sup> KEYTRUDA (Pembrolizumab) USPI
<sup>4</sup> ORIENT-11 Clinical Study Report and Datasets
Unknown Impact of Differences Between Study Population in ORIENT-11 and U.S. Patients

• Diagnosis and management of NSCLC (e.g., decision for chemoradiation)

• Concomitant medications, including herbal medications
  – 69% of patients in ORIENT-11 received at least one herbal medication primarily for adverse events (50%) or prophylactic measures (22%)*

• Body weight and composition

• Unknown regional differences

* Applicant Analysis (data cutoff date: January 15, 2021)
Additional PK Data Needed to Support Dosage, Efficacy, and Safety for U.S. Patients

- Population pharmacokinetic (PopPK) analyses compared pharmacokinetic (PK) characteristics of Chinese (n=475) and U.S. patients (n=39)

- U.S. patients (none with NSCLC): n=30 White, n=5 Black, n=3 Asian, n=1 Native American

- Modeling and simulation data suggest no clinically significant difference in PK between White and Chinese patients, or significant effect of body weight on PK

- However, limited U.S. patients do not represent ethnic and racial diversity of U.S.

- FDA standard to request sparse PK collection inclusive of intent-to-treat (ITT) population (i.e., U.S. patient cohort) → additional PK data needed to support efficacy and safety for U.S. patients
Exploratory Analyses Suggest Differences Between Asian and Non-Asian Patients: Need MRCTs

• Epidemiologic studies suggest Asian ethnicity favorable prognostic factor for OS for NSCLC, in general\(^1\)-\(^3\)

• Exploratory studies suggest longer OS with anti-PD-(L)1 antibodies for Asians compared to non-Asians\(^4\)-\(^7\)

• Differences in clinicopathological characteristics (smoking history, driver mutations, PD-L1 expression, tumor mutation burden) may contribute to differential survival\(^6\)

• Potential differences in safety, including increased pneumonitis in Asian patients\(^7\)

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\(^1\) Ahn MJ, *J Thorac Oncol*, 2010  
\(^2\) Kawaguchi T, *J Thorac Oncol*, 2010  
\(^3\) Ou SH, *J Thorac Oncol*, 2009  
\(^4\) Peng L, *Oncoimmunology*, 2020  
\(^5\) Chang E et al., ASCO Abstract, 2019  
\(^6\) Qian J, *Int J Cancer*, 2020  
\(^7\) Peng L, *J Thorac Dis*, 2018
Informed Consent Not Updated to Reflect New Approvals with OS Benefit (GCP)

<table>
<thead>
<tr>
<th>Version</th>
<th>Effective Date</th>
<th>Discussion of Other Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>May 11, 2018</td>
<td>Reliance on study doctor to discussion options</td>
</tr>
<tr>
<td>2.0</td>
<td>January 29, 2019</td>
<td>Reliance on study doctor to discussion options</td>
</tr>
<tr>
<td>3.0</td>
<td>August 13, 2019</td>
<td>Reliance on study doctor to discussion options</td>
</tr>
<tr>
<td>March 28, 2019*: Pembrolizumab plus pemetrexed and platinum chemotherapy approved for first-line treatment of nonsquamous NSCLC in China</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Informed consent form **not** updated to discuss pembrolizumab approval in China, which demonstrated overall survival benefit.
FDA Site Inspections
(21 CFR 312.68, 312.120, 812.145)

• Requirement for new molecular entities
• Performed to verify accuracy and reliability of clinical trial data
• Not all clinical trial sites inspected → only a sampling of data
• 2016 report by China’s State Food and Drug Administration that 80% of clinical trial data from China were “fraudulent or substandard”¹

¹ Woodhead M, BMJ, 2016
Uncertain Level of Past Participation of ORIENT-11 Sites in MRCTs

• Prior participation in MRCTs may help provide confidence in trial conduct and data integrity; however, uncertain level of prior participation for ORIENT-11 investigators

• Estimate of prior participation in MRCTs based on participation in trials conducted in both U.S. and China
  – 10 of 48 sites with prior FDA inspections (14 total inspections in Oncology or Hematology)
  – Queried Applicant but unable to indicate 1) number of patients enrolled in MRCTs per site or 2) MRCTs which led to U.S. approval

• Minimal FDA interactions and no prior FDA site inspections for Applicant
Multiple FDA Approved Anti-PD-(L)1 Antibodies with OS Benefit

Pembrolizumab Atezolizumab Nivolumab

Source: KEYTRUDA (Pembrolizumab) USPI
Source: TECENTRIQ (Atezolizumab) USPI
Source: KEYTRUDA (Pembrolizumab) USPI

- ORIENT-11 does not fulfill unmet need
- Does not merit regulatory flexibility when considering applicability
- Approval based on PFS would diverge from current regulatory standards
- The Applicant compares sintilimab to other first-line therapies, however each must be evaluated on its own merit

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Applicant’s Proposal for Non-Comparative Study Examining Two Doses of Sintilimab

- Untreated NSQ-NSCLC, Stage IIIB/C or IV
- Patients from U.S., Europe, and China
  \( N=150 \)

Sintilimab 200 mg every 3 weeks + chemotherapy
\( n=100 \)

Sintilimab 400 mg every 6 weeks + chemotherapy
\( n=50 \)

Primary Endpoint: ORR

Does not address applicability issues → possible trial would compare sintilimab to approved anti-PD-(L) antibody with OS endpoint
Proposed Study Does Not Address FDA Concerns

• Dose-finding study rather than study to address concerns of generalizability to U.S. population

• Small study (n=150)

• Less clinically meaningful endpoint (ORR)

• Proposed study does not address applicability issues → alternatively, a possible trial to address FDA concerns would compare sintilimab to an approved anti-PD-(L)1 antibody with an OS endpoint
ORIENT-11 Not Envisioned in ICH E5, Not Aligned with ICH E17

• ICH E5 guidance on bridging not intended for “me too” drugs
  – Does not fulfill an unmet regional need

• If designed as a well-conducted MRCT, ORIENT-11 would have:
  – Involved early communication with international regulatory authorities
    → selection of appropriate comparator, OS endpoint
  – Permitted structured exploration of regional consistency of results
  – Addressed concerns about applicability to U.S. population
ORIENT-11 Not Applicable to U.S. Population

- **Comparator arm** and **endpoint (PFS)** not consistent with U.S. medical practices and regulatory standards
  - ORIENT-11 lacked FDA consultation and oversight

- **Study population** not reflective of diverse U.S. population

- **Informed consent** not updated to reflect changing standard of care (SOC) as required per good clinical practice (GCP)

- **Inspections limited in scope** to assess trial conduct and data integrity

*Therapeutic landscape does not warrant regulatory flexibility.*
Building equity through multiregional clinical trials
Outline

• ORIENT-11 Study Design and Results

• Regulatory Framework for Evaluation of Foreign Data
  - Code of Federal Regulations (CFR)
  - International Council of Harmonisation (ICH) Guidances E5 and E17

• Key Review Issues: Generalizability to U.S. Population

• Discussion and Voting Question for ODAC
Discussion

• Discuss the generalizability of ORIENT-11 to a U.S. population and U.S. medical practice.

• Discuss potential clinical trials (if any) which may address issues of applicability of ORIENT-11 to a U.S. population.
Voting Question

Should additional clinical trial(s) demonstrating applicability to U.S. patients and U.S. medical care be required prior to a final regulatory decision?
BACK-UP SLIDES
FDA Position on Post-hoc OS Analyses

• A formal statistical analysis plan for testing OS was not included for ORIENT-11
  - There was no pre-specified event time for the final analysis of OS

• The applicant has conducted post-hoc analyses assuming various methods for Type I error control for multiple testing of OS at various time points
  - However, this is impossible to do, as to calculate an information fraction (observed events/total number events at final analysis) for these analyses, one must have a pre-specified event-time for the final analysis

Without a detailed, pre-specified analysis plan for statistical testing, these post-hoc 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.