BLA 761222 ODAC

Sintilimab BLA in non-squamous NSCLC

U.S. Food & Drug Administration
Oncologic Drugs Advisory Committee
February 10, 2022
Introduction

Lana Shiu, MD
Senior Vice President, Global Regulatory Affairs
Innovent Biologics USA, Inc.
Introduction to Innovent Biologics

- Global biopharmaceutical company headquartered in Suzhou, China
- 6000+ employees on 4 continents
- 6 products commercialized in China
- >25 products in development
- Mission to develop high-quality and affordable medicines
- Collaboration with Eli Lilly since 2015
Sintilimab Is a Novel PD-1 Inhibitor

- Recombinant fully human IgG4 monoclonal antibody

- Binds PD-1 with high affinity (Kd of 0.07 nM) and exhibits potent PD-1 signaling blockade

- Well-tolerated in multiple GLP toxicity studies including repeat-dose in monkeys (200 mg/kg) up to 26 weeks

### Sintilimab Demonstrated Positive Efficacy Results in 9 Pivotal Studies

<table>
<thead>
<tr>
<th>Target Indication (Study Name)</th>
<th>N</th>
<th>Met Primary Endpoint</th>
<th>Regulatory Status in China</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L Non-squamous NSCLC (ORIENT-11)&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>397</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>1L Squamous NSCLC (ORIENT-12)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>357</td>
<td>✓</td>
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<tr>
<td>2L Squamous NSCLC (ORIENT-3)</td>
<td>290</td>
<td>✓</td>
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<tr>
<td>EGFR TKI failed NSCLC (ORIENT-31)</td>
<td>600</td>
<td>✓</td>
<td>Submitted</td>
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<tr>
<td>r/r classic Hodgkin’s Lymphoma (ORIENT-1)&lt;sup&gt;4,5&lt;/sup&gt;</td>
<td>96</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>1L Esophageal Squamous Cell Carcinoma (ORIENT-15)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>676</td>
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<tr>
<td>2L Esophageal Squamous Cell Carcinoma (ORIENT-2)&lt;sup&gt;7&lt;/sup&gt;</td>
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<tr>
<td>1L Gastric Cancer (ORIENT-16)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>650</td>
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<td>1L Hepatocellular Carcinoma (ORIENT-32)&lt;sup&gt;9&lt;/sup&gt;</td>
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</table>

- Approved for 4 indications in China
- Post-marketing safety data on more than 170,000 patients

Proposed Indication and Dosing

Indication

Sintilimab in combination with pemetrexed and platinum-based chemotherapy is indicated for the first-line treatment of 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.

Dosing Regimen

200 mg via IV every 3 weeks
## Regulatory History of Sintilimab in China and US

### Chinese Approvals

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Approval Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>ORIENT-1</td>
<td>(r/r cHL)</td>
</tr>
<tr>
<td>2020</td>
<td>ORIENT-11</td>
<td>(1L nsqNSCLC)</td>
</tr>
<tr>
<td>2021</td>
<td>ORIENT-12</td>
<td>(1L sqNSCLC with Gemcitabine &amp; Platinum)</td>
</tr>
<tr>
<td></td>
<td>ORIENT-32</td>
<td>(1L HCC in combination with BYVASDA)</td>
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### US Regulatory Milestones

<table>
<thead>
<tr>
<th>Year</th>
<th>Milestone</th>
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</thead>
<tbody>
<tr>
<td>2018</td>
<td>Pre-IND Meeting</td>
</tr>
<tr>
<td>2019</td>
<td>Pre-BLA Meetings</td>
</tr>
<tr>
<td>2020</td>
<td>BLA Submission</td>
</tr>
<tr>
<td>2021</td>
<td>Type C Meeting</td>
</tr>
</tbody>
</table>
Why We Are Here Today

• Discuss the applicability of ORIENT-11 to support a US approval
• Address key review issues noted in the FDA Briefing Document

• US Regulations and ICH Guidelines provide the Framework for the Use of Foreign Data to support FDA Approval
  – 21CFR314.106(b) (Foreign Data as the Sole Basis for Marketing Approval)
  – ICH E5 (Ethnic Factors in the Acceptability of Foreign Clinical Data)
## What You Will Hear Today

| Treatment Landscape | • Non-squamous NSCLC diagnosis, staging, and treatment are similar in US and China  
|                     | • Pemetrexed + platinum chemotherapy is the most commonly used chemotherapy regimen in nsqNSCLC in US and China |
| Efficacy            | • ORIENT-11 met the primary endpoint of PFS at interim analysis  
|                     | • Analysis of OS showed a robust and clinically meaningful treatment effect |
| Safety              | • Sintilimab + chemotherapy has an acceptable safety profile consistent with that of approved PD-1/L1 inhibitors |
| Applicability to the US Population | • Clinical practice standards are similar in the US and China  
|                     | • PK/PD profile is insensitive to ethnicity, based on analysis of intrinsic factors  
|                     | • Efficacy and safety of sintilimab in US population will be similar to those in ORIENT-11 |
## Agenda

<table>
<thead>
<tr>
<th>Section</th>
<th>Speaker</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
<td>Lana Shiu, MD</td>
<td>Sr. Vice President, Global Regulatory Affairs, Innovent Biologics USA, Inc.</td>
</tr>
<tr>
<td><strong>Treatment Landscape in NSCLC</strong></td>
<td>Mark A. Socinski, MD</td>
<td>Advent Health Cancer Institute</td>
</tr>
<tr>
<td><strong>ORIENT-11 Efficacy and Conduct</strong></td>
<td>Eduard Gasal, MD</td>
<td>President, Innovent Biologics USA, Inc.</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Maria Fernanda Fernandes, MD</td>
<td>Sr. Medical Advisor, Global Patient Safety Oncology, Eli Lilly</td>
</tr>
<tr>
<td><strong>Applicability to US Population</strong></td>
<td>David R. Ferry, MD, PhD</td>
<td>Vice President, Oncology Medical Strategy, Eli Lilly</td>
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</table>
### Additional Experts

<table>
<thead>
<tr>
<th><strong>Misako Nagasaka, MD, PhD</strong></th>
<th><strong>Eli Lilly</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Associate Clinical Professor</td>
<td>Ben Anderson, PhD (Moderator)</td>
</tr>
<tr>
<td>University of California, Irvine</td>
<td>Global Product Leader</td>
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<td></td>
<td>Eric Dozier, MBA</td>
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<td>Vice President, Oncology</td>
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<td>Yong Lin, PhD</td>
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<td>Principal Research Scientist, Biostatistics</td>
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<td>Lan Ni, PhD</td>
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<td></td>
<td>Head of Global PK/PD &amp; Pharmacometrics</td>
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<td></td>
<td>Matthew Rotelli, PhD</td>
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<tr>
<td></td>
<td>Sr. Advisor, Bioethics</td>
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</table>
Treatment Landscape in NSCLC

Mark A. Socinski, MD
Executive Medical Director
Advent Health Cancer Institute
Member, Thoracic Oncology Program
Epidemiology and Treatment Landscape of Stage IV NSCLC in the United States

- Lung cancer was the leading cause of cancer deaths in the US in 2018\(^1\)
  - Estimated 235,000 cases in 2021
  - Estimated 132,000 deaths in 2021
- \(~80\%\) of lung cancer is NSCLC\(^1\)
- Current clinical practice for Stage IV NSCLC
  - Comprehensive genomic testing for oncogenic driver mutations/alterations
    \((EGFR, ALK, ROS1, RET, \text{ etc.})\)
  - Patients without genomic alterations are treated with chemo-immunotherapy or
    single-agent immunotherapy depending on PD-L1 status

Key Characteristics of Stage IV Nonsquamous NSCLC

- **PD-L1 Status**: 60% TPS 2-4, 40% TPS 4-10
- **ECOG PS**: 60% PS 1, 73% PS 0

**Proportion of nsqNSCLC with driver mutations/alterations**:
- ~30% in Multiregional clinical trials
- ~65% in ORIENT-11

**Patients, %**

## Current Treatment Algorithm for nsqNSCLC in the United States

### Non-squamous Advanced NSCLC Patients (Stage IV)

#### 1L
- **POSITIVE** for Oncogene Driver Alterations (EGFR+, ALK+, ROS1+, BRAF+, NTRK+, RET+, or METexon14+)
  - EGFR, ALK, ROS1, BRAF, NTRK, RET, or MET inhibitor

#### 2L
- **Other EGFR, ALK, ROS1, BRAF, NTRK, RET, or MET inhibitor**

#### 3L
- **Chemotherapy**

#### PD-1/L1 agent ± Platinum-based chemotherapy
- Nivolumab, pembrolizumab, or atezolizumab
- Ramucirumab + docetaxel
- Nab-paclitaxel

#### Alternate chemotherapy
- Best supportive care

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*For patients not previously treated with immunotherapy; Pembrolizumab is approved for NSCLC patients with PD-L1≥1%.*

**ALK=Anaplastic Lymphoma Kinase; BRAF=v-raf Murine Sarcoma Viral Oncogene Homolog B; EGFR=Epidermal Growth Factor Receptor; KRAS=Kirsten Rat Sarcoma Viral Oncogene Homolog; MET=Circulating Hepatocyte Growth Factor; NTRK=Neurotrophic Tyrosine Receptor Kinase; RET=Ret Proto-oncogene; ROS1=ROS Proto-oncogene.*


### Current Treatment Algorithm for NSCLC in China

#### Non-squamous Advanced NSCLC Patients (Stage IV)

- **~65%**
- **~35%

#### POSITIVE for Oncogene Driver Alterations (EGFR+, ALK+, ROS1+)

- **1L**
  - EGFR, ALK, ROS1 inhibitor

- **2L**
  - Other EGFR, ALK, ROS1 inhibitor

- **3L**
  - Chemotherapy

#### NEGATIVE for Oncogene Driver Alterations

- **1L**
  - PD-1/L1 agent ± platinum-based chemotherapy
  - Platinum-based chemotherapy ± bevacizumab

- **2L**
  - Nivolumab
  - Docetaxel; pemetrexed
  - Best supportive care (PS 3-4)

- **3L**
  - Nivolumab
  - Docetaxel; pemetrexed
  - Anlotinib

**PD-1/L1 agents approved in China**

- Pembrolizumab
- Atezolizumab
- Camrelizumab
- Sintilimab
- Tislelizumab
## Diagnostic and Treatment Standards in US and China Are Similar

<table>
<thead>
<tr>
<th>Factor</th>
<th>United States</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment guidelines</td>
<td>NCCN 2021 version 4&lt;sup&gt;1&lt;/sup&gt;</td>
<td>CSCO 2021&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>Staging system</td>
<td>AJCC Cancer Staging Manual, 8th edition&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Pathology</td>
<td>2015 WHO classification</td>
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<tr>
<td>Standard genetic testing&lt;sup&gt;a&lt;/sup&gt;</td>
<td>EGFR, ALK</td>
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<tr>
<td>PD-L1 biomarker testing</td>
<td>PD-L1 CDx per product label</td>
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<tr>
<td>1L immunotherapy options for patients without driver alterations&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pembrolizumab + chemo</td>
<td>Pembrolizumab for PD-L1 ≥1% or atezolizumab for PD-L1 ≥50%</td>
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<tr>
<td></td>
<td>Atezolizumab + bevacizumab + chemo</td>
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<td></td>
<td>Nivolumab + ipilimumab + chemo</td>
<td></td>
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<tr>
<td></td>
<td>Nivolumab + ipilimumab for PD-L1 TPS ≥1%</td>
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<td></td>
<td>Cemiplimab for PD-L1 ≥50%</td>
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<td></td>
<td>Pembrolizumab for PD-L1 TPS 1% - 49% is Category 2</td>
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<tr>
<td></td>
<td>Nivolumab + ipilimumab for PD-L1 TPS ≥1%</td>
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<td></td>
<td>Pembrolizumab for PD-L1 TPS ≥1% or atezolizumab for PD-L1 ≥50%</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on Category 1 recommendations.  <sup>b</sup> Based on Category 1 recommendations (pembrolizumab for PD-L1 TPS 1% - 49% is Category 2).

First-Line Approvals for Immunotherapy in NSCLC in the US

Chemotherapy combinations

- **Pembrolizumab + pemetrexed + platinum chemo (non-squamous, no EGFR/ALK)**
  - **KEYNOTE-024**

- **Pembrolizumab + nab-paclitaxel + carboplatin (squamous)**
  - **KEYNOTE-407**

- **Atezolizumab + paclitaxel + carboplatin + bevacizumab (non-squamous, no EGFR/ALK)**
  - **IMpower150**

- **Atezolizumab + nab-paclitaxel + carboplatin (non-squamous, no EGFR/ALK)**
  - **IMpower130**

- **Nivolumab + ipilimumab + limited chemo (no EGFR/ALK)**
  - **CheckMate 9LA**

**Immunotherapy**

- **KEYNOTE-042**
  - Pembrolizumab (PD-L1 ≥1%, no EGFR/ALK)

- **IMpower110**
  - Atezolizumab (PD-L1 ≥50% or IC ≥10%, no EGFR/ALK)

- **CheckMate 227**
  - Nivolumab + ipilimumab (PD-L1 ≥1%, no EGFR/ALK)

- **EMPOWER-Lung-1**
  - Cemiplimab (PD-L1 ≥50%, no EGFR/ALK)

FDA Approved Drugs for PD-L1 ≥50% (All Priority Review)
All Used Chemotherapy Doublet Control Arms

**KEYNOTE-024**
Pembrolizumab (PD-L1 ≥50%, no EGFR/ALK)
US approval

**EMPOWER-Lung-1**
Cemiplimab (PD-L1 ≥50%, no EGFR/ALK)
US approval

Accrual to **KEYNOTE-024**
Sep 2014 - Oct 2015

Accrual to **EMPOWER-Lung-1**
Exclusively Outside US
Jun 2017 - Feb 2020

Accrual to **IMpower110**
Jul 2015 - Feb 2018

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*Top enrolling countries: Turkey, Russia, Ukraine, Georgia.*

## Comparable Efficacy Across the PD-1/L1 Class in nsqNSCLC

<table>
<thead>
<tr>
<th>Study/Regimen</th>
<th>N</th>
<th>Median PFS, mo</th>
<th>Progression-Free Survival</th>
<th>PFS HR (95% CI)</th>
<th>Median OS, mo</th>
<th>Overall Survival</th>
<th>OS HR (95% CI)</th>
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<tbody>
<tr>
<td><strong>KEYNOTE-189</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>616</td>
<td>9.0 vs 4.9</td>
<td></td>
<td>0.48 (0.40, 0.58)</td>
<td>22.0 vs 10.7</td>
<td></td>
<td>0.56 (0.45, 0.70)</td>
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<tr>
<td>Pembro + pem + platinum chemo</td>
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<tr>
<td><strong>IMpower130</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>679</td>
<td>7.0 vs 5.5</td>
<td></td>
<td>0.64 (0.54, 0.77)</td>
<td>18.6 vs 13.9</td>
<td></td>
<td>0.79 (0.64, 0.98)</td>
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<tr>
<td>Atezo + carbo + nab-pacl</td>
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<tr>
<td><strong>IMpower150</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>692</td>
<td>8.3 vs 6.8</td>
<td></td>
<td>0.62 (0.52, 0.74)</td>
<td>19.2 vs 14.7</td>
<td></td>
<td>0.78 (0.64, 0.96)</td>
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<tr>
<td>Atezo + bev + carbo + pacl</td>
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<tr>
<td><strong>CheckMate 9LA</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>719</td>
<td>6.7 vs 5.0</td>
<td></td>
<td>0.68 (0.57, 0.82)</td>
<td>15.6 vs 10.9</td>
<td></td>
<td>0.66 (0.55, 0.80)</td>
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<tr>
<td>Nivo + ipi + 2 cycles platinum chemo</td>
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</tbody>
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<sup>a</sup> Primary endpoints were OS and PFS by blinded independent central radiology review; <sup>b</sup> Co-primary endpoints were investigator-assessed PFS and OS; <sup>c</sup> Primary endpoint was OS.

KEYNOTE-189 Established a Standard of Care in 1L nsqNSCLC in the United States

<table>
<thead>
<tr>
<th></th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>PFS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9.0 vs 4.9</td>
<td>0.48 (0.40, 0.58)</td>
</tr>
<tr>
<td>Final OS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22.0 vs 10.6</td>
<td>0.56 (0.46, 0.69)</td>
</tr>
<tr>
<td>ORR&lt;sup&gt;b&lt;/sup&gt;, %</td>
<td>48.0 vs 19.4</td>
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</tbody>
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Data cutoff: May 20, 2019; Median follow-up=31.0 months (range, 26.5-38.8 mo).

Figure adapted from Annals of Oncology, 32(7), Rodriguez-Abreu D, et al, Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189, 881-895, Copyright 2021, with permission from Elsevier.
Conclusions

- Disease characteristics of both Chinese and US patients are similar with the exception of oncogenic alterations
- Diagnostics and treatment standards/patterns are similar in the US and China
- Immunotherapy has dramatically improved outcomes in lung cancer patients
- Pemetrexed and platinum is the most widely used chemotherapy in nsqNSCLC in both the US and China
- Only pembrolizumab is approved in the US in combination with pemetrexed and platinum for nsqNSCLC
ORIENT-11 Efficacy and Conduct

Eduard Gasal, MD
President
Innovent Biologics USA, Inc.
ORIENT-11 Phase 3 Pivotal Study Schema

Enrollment: Aug 2018 – Jul 2019

N=397

- 1L non-squamous NSCLC (IIIB/C, IV)
- EGFR/ALK negative
- ECOG PS 0,1
- No active brain metastases

Randomization stratification
- Sex
- Platinum (cisplatin vs carboplatin)
- PD-L1 expression (TPS <1% vs ≥1%)

Primary endpoint: PFS by BIRRC
Secondary endpoints: OS, ORR, DCR, TTR, DOR, safety

Sintilimab 200 mg + pemetrexed + cisplatin/carboplatin Q3W for 4 cycles
Followed by sintilimab + pemetrexed maintenance

Placebo + pemetrexed + cisplatin/carboplatin Q3W for 4 cycles
Followed by placebo + pemetrexed maintenance

Conditional crossover upon confirmed PD

Selection of Control Arm, Endpoints, and Study Analysis
ORIENT-11

- Pemetrexed and platinum chemotherapy was an appropriate control arm in China
  - KN189 regimen approved in China March 2019 (ORIENT-11 80% accrued)
- PFS was primary endpoint
  - PFS is clinically relevant endpoint in first-line NSCLC
  - PFS not confounded by post-progression therapy
- For an HR=0.65, 263 PFS events required to ensure 90% power at a 2-sided alpha=0.05
- Interim PFS analysis was planned when 184 (70%) events observed
- OS was a secondary endpoint
  - No alpha assigned; method of analysis was pre-specified in SAP
Experienced and Qualified Sites and Investigators
ORIENT-11

• 48 academic sites across China
  – Previous experience with multiregional clinical trials
  – 10 sites have had 17 prior FDA inspections (2 are part of current application)
  – 23 sites participated in trials that led to FDA approval

• All investigators are board-certified oncologists trained in ICH GCPs
  – 46 of 48 primary investigators previously participated in multiregional clinical trials
  – 9 participated in at least one clinical trial that ultimately led to the drug being approved by FDA
Study Conduct
ORIENT-11

- PFS assessed by blinded independent radiology review committee (BIRRC) managed through a globally recognized and validated vendor (PAREXEL)
  - Review committee was comprised of North American and European radiologists
- PD-L1 TPS (Dako 22C3), PK, and ADA assessed by central vendor (Covance)
- Independent data monitoring committee (iDMC) reviewed interim analysis
  - Efficacy boundary met; iDMC recommended to continue the study
# Patient Disposition
## ORIENT-11 Interim Analysis

**Data cutoff date:** 15 Nov 2019

### Randomized (ITT) (N=397)

- **Treated (Safety Set) (N=397)**
  - 85 (64.9%) participants discontinued study treatment
    - Progressive disease: 61 (46.6%)
    - Participant request: 11 (8.4%)
    - Adverse event: 8 (6.1%)
    - Death: 3 (2.3%)
    - Investigator or sponsor decision: 1 (0.8%)
    - Poor compliance: 1 (0.8%)
    - Unstable clinical condition: 1 (0.4%)
  - 35 (26.7%) participants crossed over to sintilimab monotherapy

### Sintilimab + Chemo (N=266)

- 115 (43.2%) participants discontinued study treatment
  - Progressive disease: 77 (28.9%)
  - Participant request: 18 (6.8%)
  - Adverse event: 8 (3.0%)
  - Death: 8 (3.0%)
  - Other: 3 (1.1%)
  - Unstable clinical condition: 1 (0.4%)

### Placebo + Chemo (N=131)

- 85 (64.9%) participants discontinued study treatment
  - Progressive disease: 61 (46.6%)
  - Participant request: 11 (8.4%)
  - Adverse event: 8 (6.1%)
  - Death: 3 (2.3%)
  - Investigator or sponsor decision: 1 (0.8%)
  - Poor compliance: 1 (0.8%)

**Median study follow-up:** 8.9 months (range, 0.59-14.78)
## Baseline Characteristics Balanced Between Treatment Groups

**ORIENT-11**

<table>
<thead>
<tr>
<th></th>
<th>Sintilimab + Chemo (N=266)</th>
<th>Placebo + Chemo (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>204 (76.7)</td>
<td>99 (75.6)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>61.0 (30-75)</td>
<td>61.0 (35-75)</td>
</tr>
<tr>
<td>ECOG PS score=1, n (%)</td>
<td>190 (71.4)</td>
<td>97 (74.0)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>253 (95.1)</td>
<td>123 (93.9)</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB/C, n (%)</td>
<td>21 (7.9)</td>
<td>15 (11.5)</td>
</tr>
<tr>
<td>IV, n (%)</td>
<td>245 (92.1)</td>
<td>116 (88.5)</td>
</tr>
<tr>
<td>Brain metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, n (%)</td>
<td>36 (13.5)</td>
<td>22 (16.8)</td>
</tr>
<tr>
<td>PD-L1 TPS (per CRF), n (%)a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>77 (28.9)</td>
<td>40 (30.5)</td>
</tr>
<tr>
<td>≥1%</td>
<td>181 (68.0)</td>
<td>87 (66.4)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker (current/former)</td>
<td>171 (64.3)</td>
<td>87 (66.4)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>95 (35.7)</td>
<td>44 (33.6)</td>
</tr>
</tbody>
</table>

* Only includes evaluable patients.
Study Met Primary Endpoint of PFS at Interim Analysis
ORIENT-11 ITT

HR (95% CI): $0.48 \ (0.36, \ 0.64)$
p value, $^a$ < 0.00001
Events: 112 (42.1%) vs 86 (65.6%)

$a$ Interim analysis (cut-off date - Nov 2019) $\alpha$ boundary based on 198 PFS events is 0.01958.
Reprinted from Journal of Thoracic Oncology, 15 / 10, Yang Y, et al, Efficacy and safety of sintilimab plus pemetrexed and platinum as first-line treatment for locally advanced or metastatic nonsquamous NSCLC: a randomized, double-blind, phase 3 study (oncology program by Innovent anti-PD-1-11), 1636-1646, Copyright 2020, with permission from Elsevier.
Progression-Free Survival
Stage III(B/C) vs ITT

Data cutoff date - Nov 2019

Stage IIIB/C
N=36

ITT
N=397

HR (95% CI): 0.17 (0.06, 0.48)

HR (95% CI): 0.48 (0.36, 0.64)

Number at risk
Sintilimab + Chemo 21 21 19 16 8 3 0
Placebo + Chemo 15 14 10 5 1 1 0

266 231 202 143 63 25 3 3 0
131 106 77 42 19 4 1 0
Consistent Overall Survival Benefit With Longer Follow-up

ORIENT-11 ITT

Interim Analysis (15 Nov 2019)a
90 events

- 22 months F/U

Final Analysis (15 Sept 2021)b
243 events

Crossover rate: 26.7%

HR (95% CI): 0.61 (0.40, 0.93)

Crossover rate: 46.6%

HR (95% CI): 0.65 (0.50, 0.85)


b After the interim PFS, a protocol amendment defined the final analysis to occur when approximately 65% of deaths observed or 2 years after last patient randomized.
Results of Sequential OS Analyses Indicate the Statistical Boundary Adjusted for Multiplicity Would Have Been Crossed

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OS events</td>
<td>90</td>
<td>149</td>
<td>207</td>
<td>243</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.61 (0.40, 0.93)</td>
<td>0.61 (0.44, 0.84)</td>
<td>0.60 (0.45, 0.79)</td>
<td>0.65 (0.50, 0.85)</td>
</tr>
<tr>
<td>OBF boundary</td>
<td>0.00046</td>
<td>0.00826</td>
<td>0.02770</td>
<td>0.04058</td>
</tr>
<tr>
<td>Bonferroni boundary</td>
<td>0.01250</td>
<td>0.01250</td>
<td>0.01250</td>
<td>0.01250</td>
</tr>
<tr>
<td>Observed p value</td>
<td><strong>0.01921</strong></td>
<td><strong>0.00250</strong></td>
<td><strong>0.00027</strong></td>
<td><strong>0.00135</strong></td>
</tr>
</tbody>
</table>

Had OS been tested hierarchically after meeting the primary endpoint, it would have met conventional statistical significance.
Summary
ORIENT-11

- High quality study conducted by competent investigators and experienced sites
- Sintilimab in combination with pemetrexed and platinum-based chemotherapy demonstrated clinically meaningful treatment effect across all endpoints
  - PFS HR (95% CI): 0.48 (0.36, 0.64); p<0.00001
- Overall survival consistently favored sintilimab despite high crossover rate
  - Interim OS analysis: HR (95% CI): 0.61 (0.40, 0.93)
  - Final OS analysis: HR (95% CI): 0.65 (0.50, 0.85)
Safety

Maria Fernandes, MD
Senior Medical Advisor, Global Patient Safety
Eli Lilly and Company
## Overview of Safety Profile During Double-Blind Period\(^a\)

**ORIENT-11**

<table>
<thead>
<tr>
<th></th>
<th>Sintilimab + Chemo (N=266)</th>
<th>Placebo + Chemo (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE</td>
<td>99.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>61.7</td>
<td>58.8</td>
</tr>
<tr>
<td>TEAE related to sintilimab or placebo</td>
<td>82.7</td>
<td>80.9</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>23.7</td>
<td>20.6</td>
</tr>
<tr>
<td>SAE</td>
<td>28.2</td>
<td>29.8</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>16.9</td>
<td>17.6</td>
</tr>
<tr>
<td>TEAE leading to discontinuation to all study treatment</td>
<td>3.0</td>
<td>6.1</td>
</tr>
<tr>
<td>TEAE leading to discontinuation of sintilimab or placebo</td>
<td>5.3</td>
<td>6.9</td>
</tr>
<tr>
<td>TEAE leading to death</td>
<td>2.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Related to sintilimab or placebo</td>
<td>0.8</td>
<td>2.3</td>
</tr>
</tbody>
</table>

\(^a\) Does not include data from crossover.
# Comparable Incidence of TEAEs Across Treatment Groups

**ORIENT-11 (≥20% in Sintilimab Arm)**

<table>
<thead>
<tr>
<th>Preferred Term/Consolidated Term</th>
<th>Sintilimab + Chemo (N=266)</th>
<th>Placebo + Chemo (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any TEAE</strong></td>
<td>Any Grade</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Anemia</td>
<td>Grade ≥3</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asp. aminotransferase increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al. aminotransferase increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Any Grade</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>Grade ≥3</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Any Grade</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Thyroid disorder</td>
<td>Grade ≥3</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- *Terms in italics are consolidated terms.*
- Data cutoff: 15 Nov 2019.
## Immune-Related Adverse Events\textsuperscript{a}
### ORIENT-11 & All Sintilimab (>1% Patients)

<table>
<thead>
<tr>
<th></th>
<th>ORIENT-11 N=266</th>
<th>All Sintilimab Treated N=1045</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>At least one irAE</td>
<td>33.1</td>
<td>5.6</td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>20.3</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>12.0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>10.2</td>
<td>0</td>
</tr>
<tr>
<td>Thyroid disorders</td>
<td>3.0</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatitis and elevation of amylase/lipase</td>
<td>7.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Elevation of amylase</td>
<td>6.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Elevation of lipase</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>7.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Skin adverse reaction</td>
<td>4.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Hepatitis and hepatotoxicity</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Sponsor adjudicated.

Overall Safety Conclusions

- Safety profile of sintilimab in combination with pemetrexed + platinum chemotherapy in ORIENT-11 is acceptable and consistent with the known safety profile of PD-1/L1 inhibitors in combination with chemotherapy for the same indication.
- Post-marketing safety data available on ~170,000 patients treated with sintilimab with no new safety signal.
- Risks will be appropriately managed through product labeling.
Applicability to US Population

David Ferry, MD, PhD
Vice President, Oncology Medical Strategy
Eli Lilly and Company
Foreign Data as the Sole Basis for Marketing Approval

The studies have been performed by clinical investigators of recognized competence
21 CFR 314.106(b)(2)

The data may be considered valid without the need for an on-site inspection by FDA
or, if FDA considers such an inspection to be necessary, FDA is able to validate the data
through an on-site inspection or other appropriate means 21 CFR 314.106(b)(3)

The foreign data are applicable to the U.S. population and U.S. medical practice
21 CFR 314.106(b)(1)
Framework for Applicability of Sintilimab Data to the US Population

- Clinical Practice Standards in China vs US
- Factors Affecting PK/PD
- Efficacy and Safety
## Diagnostic and Treatment Standards in US and China Are Similar

<table>
<thead>
<tr>
<th>Factor</th>
<th>United States</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment guidelines</td>
<td>NCCN 2021 version 4&lt;sup&gt;1&lt;/sup&gt;</td>
<td>CSCO 2021&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Staging system</td>
<td>AJCC Cancer Staging Manual, 8th edition&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Pathology</td>
<td>2015 WHO classification</td>
<td></td>
</tr>
<tr>
<td>Standard genomic testing&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;i&gt;EGFR, ALK&lt;/i&gt;</td>
<td></td>
</tr>
<tr>
<td>PD-L1 biomarker testing</td>
<td>PD-L1 CDx per product label</td>
<td></td>
</tr>
<tr>
<td>1L immunotherapy options for patients without driver mutations&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pembrolizumab + chemo</td>
<td>Sintilimab, atezolizumab, camrelizumab, or tislelizumab + chemo</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab for PD-L1 ≥1% or atezolizumab for PD-L1 ≥50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atezolizumab + bevacizumab + chemo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nivolumab + ipilimumab + chemo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nivolum + ipilimumab for PD-L1 TPS ≥1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cemiplimab for PD-L1 ≥50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pembretexed/Bevacizumab/Gemcitabine/Docetaxel/Paclitaxel/Vinorelbine</td>
<td>Platinum-based chemo: cisplatin or carboplatin</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on Category 1 recommendations.  
<sup>b</sup> Based on Category 1 recommendations (pembrolizumab for PD-L1 TPS 1% - 49% is Category 2).

Sintilimab Demonstrated Linear PK and Receptor Saturation Across 1-10 mg/kg Dose Range in Patients (Study A101)

![Graph showing concentration vs time for 1 mg/kg, 3 mg/kg, 10 mg/kg, and 200 mg (~3 mg/kg) doses of sintilimab.](image)

![Graph showing mean PD-1 receptor occupancy over time for 1 mg/kg, 3 mg/kg, 10 mg/kg, and 200 mg (~3 mg/kg) doses of sintilimab.](image)

a Measured on circulating CD3 T cells.

Right image adapted from Durable blockade of PD-1 signaling links preclinical efficacy of sintilimab to its clinical benefit, Wang J, et al, mAbs, 2019, by permission of the publisher Informa UK Limited trading as Taylor & Francis Ltd, [http://www.tandfonline.com](http://www.tandfonline.com).
Intrinsic Factors: Weight and Race Had No Clinically Important Effect on PK of Sintilimab

Median body weight (range)
China (N=463): 62 (37-115) kg
US (N=39): 74 (39-124) kg

Race

AUC<sub>0-504h</sub>

White (N=30) Asian (N=478) Other (N=6)  

China US

* Other race included 5 Black or African American and 1 American Indian or Alaska Native.
ICH E5 (R1) Ethnic Factors in the Acceptability of Foreign Clinical Data

“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.”

<table>
<thead>
<tr>
<th>Type</th>
<th>Study/Regimen</th>
<th>United States</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Combinations</strong></td>
<td>KEYNOTE-189 Pembrolizumab + pemetrexed + platinum chemotherapy (non-squamous, no EGFR/ALK)</td>
<td>200 mg every 3 weeks or 400 mg every 6 weeks</td>
<td>200 mg every 3 weeks or 400 mg every 6 weeks</td>
</tr>
<tr>
<td></td>
<td>KEYNOTE-407 Pembrolizumab + nab-paclitaxel + carboplatin (squamous)</td>
<td>200 mg every 3 weeks or 400 mg every 6 weeks</td>
<td>200 mg every 3 weeks or 400 mg every 6 weeks</td>
</tr>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-042</td>
<td>Pembrolizumab (PD-L1 ≥1%, no EGFR/ALK)</td>
<td>200 mg every 3 weeks or 400 mg every 6 weeks</td>
<td>200 mg every 3 weeks or 400 mg every 6 weeks</td>
</tr>
<tr>
<td>IMpower110</td>
<td>Atezolizumab (PD-L1 ≥50% or IC ≥10%, no EGFR/ALK)</td>
<td>840 mg every 2 weeks or 1200 mg every 3 weeks or 1680 mg every 4 weeks</td>
<td>1200 mg every 3 weeks</td>
</tr>
</tbody>
</table>
**FDA Meta-Analysis of NSCLC Trials Demonstrates Similar OS and PFS Benefits in Asian and Western Populations**

<table>
<thead>
<tr>
<th>Treatment setting and population</th>
<th>N</th>
<th>Median, months</th>
<th>HR (95% CI)</th>
<th>Median, months</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L-C non-Asians: ICI vs chemo</td>
<td>2214</td>
<td>8.1 vs 5.8</td>
<td>0.62 (0.56, 0.69)</td>
<td>19.5 vs 13.4</td>
<td>0.68 (0.60, 0.78)</td>
</tr>
<tr>
<td>1L-C Asians: ICI vs chemo</td>
<td>286</td>
<td>7.0 vs 5.8</td>
<td>0.72 (0.55, 0.96)</td>
<td>24.0 vs 20.9</td>
<td>0.72 (0.48, 1.07)</td>
</tr>
<tr>
<td>ORIENT-11</td>
<td>397</td>
<td>8.9 vs 5.0</td>
<td>0.48 (0.36, 0.64)</td>
<td>24.2 vs 16.8</td>
<td>0.65 (0.50, 0.85)</td>
</tr>
</tbody>
</table>

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

1L-C=First-line combination with chemotherapy; ICI=immune checkpoint inhibitor.

Sintilimab Demonstrates a Comparable Safety Profile to Other Checkpoint Inhibitors in NSCLC

Grade ≥3 Adverse Events

<table>
<thead>
<tr>
<th>Immunotherapy Combination</th>
<th>Incidence rate (95% CI), %</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>0.87 (0.55, 1.36)</td>
<td></td>
</tr>
<tr>
<td>Durvalumab + tremelimumab</td>
<td>1.19 (0.78, 1.88)</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab + chemotherapy</td>
<td>1.21 (0.89, 1.65)</td>
<td></td>
</tr>
<tr>
<td>Sintilimab + chemotherapy</td>
<td>1.24 (0.77, 1.96)</td>
<td></td>
</tr>
<tr>
<td>Nivolumab + ipilimumab + chemotherapy</td>
<td>1.46 (1.02, 2.32)</td>
<td></td>
</tr>
<tr>
<td>Atezolizumab + chemotherapy</td>
<td>1.79 (1.35, 2.38)</td>
<td></td>
</tr>
<tr>
<td>Tislelizumab + chemotherapy</td>
<td>1.87 (1.01, 3.32)</td>
<td></td>
</tr>
<tr>
<td>Camrelizumab + chemotherapy</td>
<td>2.32 (1.37, 3.99)</td>
<td></td>
</tr>
<tr>
<td>Durvalumab + tremelimumab + chemotherapy</td>
<td>2.41 (1.07, 5.32)</td>
<td></td>
</tr>
<tr>
<td>Atezolizumab + bevacizumab + chemotherapy</td>
<td>5.61 (3.25, 9.84)</td>
<td></td>
</tr>
</tbody>
</table>

- 16 studies – 8278 patients
- Quality of included studies studied by Cochrane risk of bias
- Preferred reporting items for systematic reviews for meta-analysis

**ORIENT-11 Data Are Applicable to the US Population**

<table>
<thead>
<tr>
<th>Clinical Practice</th>
<th>PK/PD</th>
<th>Efficacy &amp; Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Similar clinical practice standards in United States and China</td>
<td>No clinically important difference; PK/PD profile is insensitive to ethnicity</td>
<td>Efficacy and safety of sintilimab are anticipated to be similar in the US population as they were in ORIENT-11</td>
</tr>
</tbody>
</table>
FDA’s Key Review Issues
ICH E17 Guidance on Planning and Design of Multiregional Clinical Trials Is Not Applicable

- Intent of study was only for registration in China
- Consideration of foreign data governed by US regulation 21CFR314.106(b)

**Foreign Data as the Sole Basis for Marketing Approval**

- The studies have been performed by clinical investigators of recognized competence 21CFR314.106(b)(2)
- The data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means 21CFR314.106(b)(3)
- The foreign data are applicable to the U.S. population and U.S. medical practice 21CFR314.106(b)(1)
Applicability of Comparator Arm to US Standard of Care

- Control arm was standard of care in China
- Agreement with China Health Authority and approved by IRBs
- Same comparator used to establish the US standard of care

Sintilimab 200 mg +

\[
\text{pemetrexed + cisplatin/carboplatin Q3W for 4 cycles}
\]

Followed by sintilimab + pemetrexed maintenance

Placebo +

\[
\text{pemetrexed + cisplatin/carboplatin Q3W for 4 cycles}
\]

Followed by placebo + pemetrexed maintenance
Precedent for OS Endpoint to Support Approval

- PFS may be appropriate with large magnitude of treatment effect
- Although no alpha assigned for OS, result is compelling and reassuring
- PFS and OS results consistent with class
Known and Unknown Differences in Intrinsic and Extrinsic Factors

- Efficacy and safety data from ORIENT-11 are compelling and consistent with similar studies of PD-1/L1 inhibitors
- No clinically important PK differences between White and Asian or based on body weight
- Available data for sintilimab and other PD-1/L1 inhibitors demonstrate lack of sensitivity to ethnic differences across regions, consistent with ICH E5
- We are committed to collecting additional PK data in diverse patients in the post-market setting

ICH E5 Appendix D

The following properties of a compound make it less likely to be sensitive to ethnic factors:

- Linear pharmacokinetics (pK)
- A flat pharmacodynamic (PD) (effect-concentration) curve for both efficacy and safety in the range of the recommended dosage and dose regimen (this may mean that the medicine is well-tolerated)
- A wide therapeutic dose range\(^a\) (again, possibly an indicator of good tolerability)
- Minimal metabolism or metabolism distributed among multiple pathways
- High bioavailability, thus less susceptibility to dietary absorption effects
- Low potential for protein binding
- Little potential for drug-drug, drug-diet and drug-disease interactions
- Non-systemic mode of action
- Little potential for inappropriate use

Data in Patients Representative of US NSCLC Population

- The data from ORIENT-11 are applicable to the diverse US population
- We support increasing diversity in clinical trials
- We are committed to ongoing discussions with FDA regarding a post-marketing study in a diverse population
Data in Patients Representative of US NSCLC Population
Noninferiority Study Is Not Recommended

Study population

Key Eligibility Criteria
- Untreated nsqNSCLC
- Stage IV or IIIB/C ineligible for surgery or local therapy
- No EGFR or ALK genetic alteration
- Measurable disease
- ECOG PS 0 or 1

Primary Endpoint: Compare OS between sintilimab + chemo vs pembrolizumab + chemo
Secondary Endpoints: PFS, ORR, Safety
Statistical Assumptions: Non-inferiority margin of HR=1.15, 1632 events will yield 80% power to detect the noninferiority of sintilimab combination therapy at a 2-sided alpha level of 0.05
Data in Patients Representative of US NSCLC Population
Post-marketing Concept Based on Preliminary Feedback From FDA

Objective: Compare PK/efficacy/safety of sintilimab + chemotherapy in Western patients vs Chinese patients

Study population

Key Eligibility Criteria
- Untreated nsqNSCLC
- Stage IV or IIIB/C ineligible for surgery or local therapy
- No EGFR or ALK genetic alteration
- Measurable disease
- ECOG PS 0 or 1

Sintilimab (Q3W) + chemo (Q3W)

100 Western patients

50 Chinese patients

ORIENT-11 Sintilimab-treated Chinese patients

N=150

Primary endpoint: ORR\textsuperscript{a}
Secondary endpoints: Dose evaluation, PFS, OS, PK, PRO

Sintilimab (Q6W) + chemo (Q3W)

33 Western + 17 Chinese patients

N=50

Intended to compare Q3W vs Q6W sintilimab dosing schedules

\textsuperscript{a} sensitivity analysis that leverages additional Chinese patients from ORIENT-11 will be conducted. Patients would be randomized between sintilimab Q3W and Q6W dosing arms.
**FDA Consultation and Oversight**

- Study was intended for registration in China
- Study conducted under GCP and applicable US regulations
- Met with FDA on 3 occasions in 2020

<table>
<thead>
<tr>
<th>2018</th>
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<th>2020</th>
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<tr>
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<td>Type C Meeting</td>
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Updating Informed Consent Form

- At the time of study initiation, the informed consent form was reasonable and appropriate.

Excerpts from the trial level ICF

Your study doctor will discuss with you if there are any other approaches that can be used to treat your disease. If you decide not to participate in this study, please consult your study doctor about other treatment options.

If there is a release of new information that may affect your decision to continue participating in this study, your study doctor will inform you as soon as possible.

- The Sponsor should have updated the trial level ICF, giving the sites the opportunity to update the local ICF according to their policies and procedures.
Clinical Inspections and Experience of Investigators With Multiregional Clinical Trials

- Full access given to FDA for inspections
  - 2 inspections conducted as part of this application
- 10 of 48 sites previously inspected by FDA (17 inspections)
  - 12 resulted in no action indicated
  - 4 resulted in voluntary action indicated
  - 1 action pending
- 48% of sites have participated in a study that led to FDA approval

- Investigators were board-certified oncologists trained on ICH GCP
- 95% of investigators had previously participated in multiregional clinical trials
Regulatory Flexibility

- Substantial evidence of efficacy and safety provided by ORIENT-11
- Additional treatment options warranted
Innovent | Lilly Conclusion: 
Data From Sintilimab BLA Support Approvability

- Positive benefit/risk profile established

- Data are applicable and support US regulatory approval of sintilimab for the proposed indication
  - Sintilimab can provide another important option for nsqNSCLC

- Committed to working collaboratively with FDA to provide additional post-marketing data in US patients
Supportive Slides
PFS in PD-L1 Subgroups Tested
ORIENT-11

**TPS <1% (PD-L1 negative)**
(77 vs 40)

HR = 0.62
(95% CI 0.37, 1.03)

**TPS 1-49%**
(74 vs 26)

HR = 0.51
(95% CI 0.28, 0.93)

**TPS ≥50% (High)**
(107 vs 61)

HR = 0.31
(95% CI 0.19, 0.48)

Data cutoff date: 15 Nov 2019
Pre-BLA Meeting Minutes - August 21, 2020

Does the Agency agree with the proposed safety database and the cutoff date of each study?

**FDA Response:** Overall, the proposed safety database and the cutoff date of each study are acceptable. However, FDA does not agree with your proposal to present safety data from patients in the US separately from safety data from patients in China. These data should be included in Pool 3 with other patients who received sintilimab as a single agent with a flag in the dataset identifying the 39 patients enrolled in Study CIBI308A102.

In addition, please note that FDA may make a request for post-marketing data in a population representative of the US population as a post-marketing commitment (PMC).

**Innovent's 8/20/2020 E-mail Response:** Innovent acknowledges the Agency's
Accrual by Study Site

Notes: 3 sites only enrolled 1 patient each are not included (site 24, site 30, site 10)
P Value Boundary Assuming Continue Look by the Time of Final Analysis

Observed P-value is lower than the most conservative boundaries at final analysis.
### Approval and المراجعات المطلوبة

<table>
<thead>
<tr>
<th>Approval</th>
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<th>NCT Code</th>
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<td><a href="https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenvatinib-unresectable-hepatocellular-carcinoma">https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenvatinib-unresectable-hepatocellular-carcinoma</a></td>
<td>A Multicenter, Randomized, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma</td>
<td>NCT01761266</td>
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<td>10, 49</td>
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History of Improvement on Data Integrity in China

- **2015.7** China Healthy Authorities released announcement to require all applicants completing clinical trial data self-check before submission to ensure data integrity.

- **2016.1** The State Council of Peoples Republic of China announced that self-checks were completed for all clinical trials to be submitted. Furthermore, on-site inspections were also carried out to evaluate data integrity as prerequisite before NDA approval.

- **2017.6** China joined the ICH;

- **2017.8** The Supreme People's Court of The People's Republic of China released regulations/legislations to ensure data integrity of clinical trials. Data fraud is considered as a crime by criminal law.

- **2015.11** China Healthy Authorities released regulations/legislations to ensure data integrity of clinical trials

- **2018.6** “Due to strict regulatory supervision and high cost of breaking the law, deliberate data fraud is almost impossible”

Accrual in ORIENT-11
- FPFV Aug 2018
- LPFV July 2019