ORIENT-11: sintilimab + pemetrexed + platinum as first-line therapy for locally advanced or metastatic non-squamous NSCLC

Li Zhang¹, Yunpeng Yang¹, Zhehai Wang², Jian Fang³, Qitao Yu⁴, Baohui Han⁵, Shundong Cang⁶, Gongyan Chen⁷, Xiaodong Mei⁸, Zhixiong Yang⁹, Rui Ma¹⁰, Minghong Bi¹¹, Xiubao Ren¹², Jianying Zhou¹³, Baolan Li¹⁴

¹ State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, China; ² Shandong Cancer Hospital, China; ³ Peking University Cancer Hospital, China; ⁴ Tumor hospital of Guangxi Zhuang Autonomous Region, China; ⁵ Shanghai Chest Hospital, China; ⁶ Henan provincial people’s hospital, China; ⁷ Harbin Medical University Cancer Hospital, China; ⁸ Anhui Provincial Hospital, China; ⁹ Affiliated Hospital of Guangdong Medical University, China; ¹⁰ Liaoning Cancer Hospital, China; ¹¹ The First Affiliated Hospital of Bengbu Medical College, China; ¹² Tianjin Cancer Institute & Hospital, China; ¹³ The First Affiliated Hospital Zhejiang University, China; ¹⁴ Beijing Chest Hospital, Capital Medical University, China
• Prof. Li Zhang has the following to disclose
  - Research grants from Eli Lilly & Co, and Pfizer, Inc
• This study is sponsored by Innovent Biologics, Inc. and Eli Lilly & Co
Sintilimab is a fully human IgG4 monoclonal antibody that blocks the binding of PD-1 to PD-L1 or PD-L2, with high affinity to human PD-1 and high PD-1 receptor occupancy.

In a phase 1b study, sintilimab plus pemetrexed/platinum demonstrated tolerable safety profile and promising efficacy in previously untreated non-squamous (nsq) NSCLC patients.

This randomized, double-blind, phase 3 study is to evaluate the efficacy and safety of sintilimab in combination with pemetrexed and platinum as first-line therapy in nsq-NSCLC patients.
"Key Eligibility Criteria"
- Untreated nsq-NSCLC (Stage IIIB/C ineligible for surgery or local therapy and IV)
- No EGFR or ALK genetic alteration
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment

"Stratification Factors:"
- Gender (male vs. female)
- Platinum (cisplatin vs. carboplatin), and
- PD-L1 expression (TPS<1% vs ≥1%)

"Endpoints"
- Primary: Progression-free survival by independent radiologic review committee (IRRC)
- Secondary: Overall survival, Response rate, Duration of response, Time to response and Safety

"Analysis Population"
- Efficacy: Intention-to-treat (ITT)
- Safety: All patients who received ≥1 dose of study medication
• **Sample size**
  - Planned to enroll 378 patients (in 2:1 ratio) to achieve 263 PFS events;
  - Actual enrollment: 397 patients.

• **Overall alpha for study**
  - Study had 90% power to detect a HR for PFS of 0.65 at one-sided $\alpha=0.025$;
  - Protocol specified 1 interim analysis before the final analysis.

• **Interim analysis**
  - Planned to perform when 70% of PFS events achieved, with an one-sided $\alpha=0.0075$;
  - Data cut-off date: Nov. 15, 2019;
  - Median follow-up: 8.9 months (range: 0.6 to 14.8);
  - Observed number of events: 198 events.
Disposition of Study Treatment

397 patients randomly allocated

Sintilimab combination
266 allocated and treated

- 151 (56.8%) ongoing
- 115 (43.2%) discontinued
  - 77 (28.9%) Disease progression
  - 18 (6.8%) Patient requirement
  - 8 (3.0%) Adverse events
  - 8 (3.0%) Death
  - 1 (0.4%) Clinically unstable
  - 3 (1.1%) Others

Placebo combination
131 allocated and treated

- 46 (35.1%) ongoing
- 85 (64.9%) discontinued
  - 61 (46.6%) Disease progression
  - 11 (8.4%) Patient requirement
  - 8 (6.1%) Adverse events
  - 3 (2.3%) Death
  - 1 (0.7%) Physician decision
  - 1 (0.7%) Poor compliance

Crossover
35 in-study sintilimab (31.3% of ITT)
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sintilimab + Chemo (N=266)</th>
<th>Placebo + Chemo (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age</strong> (range) - yrs</td>
<td>61 (30 - 75)</td>
<td>61 (35 - 75)</td>
</tr>
<tr>
<td><strong>Gender, male - n (%)</strong></td>
<td>204 (76.7%)</td>
<td>99 (75.6%)</td>
</tr>
<tr>
<td><strong>ECOG PS score, 1 - n (%)</strong></td>
<td>190 (71.4%)</td>
<td>97 (74.0%)</td>
</tr>
<tr>
<td><strong>Disease stage - n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB/IIIC</td>
<td>21 (7.9%)</td>
<td>15 (11.5%)</td>
</tr>
<tr>
<td>IV</td>
<td>245 (92.1%)</td>
<td>116 (88.5%)</td>
</tr>
<tr>
<td><strong>Brain metastases - n (%)</strong></td>
<td>36 (13.5%)</td>
<td>22 (16.8%)</td>
</tr>
<tr>
<td><strong>Platinum Choice - n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>71 (26.7%)</td>
<td>33 (25.2%)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>195 (73.3%)</td>
<td>98 (74.8%)</td>
</tr>
<tr>
<td><strong>Smoking status - n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>95 (35.7%)</td>
<td>44 (33.6%)</td>
</tr>
<tr>
<td>Current or former</td>
<td>171 (64.3%)</td>
<td>87 (66.4%)</td>
</tr>
<tr>
<td><strong>PD-L1 TPS - n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>85 (32.0%)</td>
<td>44 (33.6%)</td>
</tr>
<tr>
<td>≥1%</td>
<td>181 (68.0%)</td>
<td>87 (66.4%)</td>
</tr>
</tbody>
</table>
Progression-free survival by IRRC

**Number at Risk (Cumulative Censored Number)**
- **Sint+Chemo**
  - 266(0)
  - 231(6)
  - 202(22)
  - 143(46)
  - 63(101)
  - 25(131)
  - 3(151)
  - 3(151)
  - 0(154)
- **PL+Chemo**
  - 131(0)
  - 106(4)
  - 77(13)
  - 42(21)
  - 19(31)
  - 4(42)
  - 1(45)
  - 0(45)
  - 0(45)

**mPFS**
- **5.0 mo (4.8, 6.2)**
- **8.9 mo (7.1, 11.3)**

**Events**
- **Sint+chemo**: 42.1%
- **PL+chemo**: 65.6%

**HR (95% CI)**
- Sint+chemo: 0.482 (0.362, 0.643)
- PL+chemo: <0.00001
HR (95%) and P-Value are from Cox regression model stratified by randomization stratification variables.
**PFS in PD-L1 TPS subgroup by IRRC**

**TPS <1%**
- **mPFS**: 5.1 mo (95% CI: 4.6, 7.8)
- **HR**: 0.664 (95% CI: 0.406, 1.086)

**TPS 1%-49%**
- **mPFS**: 4.8 mo (95% CI: 2.5, 8.0)
- **HR**: 0.503 (95% CI: 0.276, 0.918)

**TPS ≥ 50%**
- **mPFS**: 5.0 mo (95% CI: 4.3, 6.8)
- **HR**: 0.310 (95% CI: 0.197, 0.489)

**Number at Risk (Cumulative Censored Number)**
- **Sint+Chemo**: 85 (0) 69 (3) 60 (6) 48 (7) 23 (22) 11 (32) 2 (40) 0 (42)
- **PL+Chemo**: 44 (0) 37 (2) 26 (7) 16 (7) 8 (11) 1 (17) 0 (18) 0 (18)
- **Sint+Chemo**: 74 (0) 62 (2) 52 (8) 31 (20) 13 (30) 4 (36) 0 (39)
- **PL+Chemo**: 26 (0) 18 (2) 12 (4) 6 (5) 4 (7) 1 (9) 0 (10)
- **Sint+Chemo**: 107 (0) 100 (1) 90 (8) 64 (19) 27 (49) 10 (63) 1 (72) 1 (72) 0 (73)
- **PL+Chemo**: 61 (0) 51 (0) 39 (2) 20 (9) 7 (13) 2 (16) 1 (17) 0 (17) 0 (17)
Overall survival

**Number at Risk (Cumulative Censored Number)**

<table>
<thead>
<tr>
<th></th>
<th>Sint+Chemo</th>
<th>PL+Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>266(0)</td>
<td>131(0)</td>
</tr>
<tr>
<td>2 months</td>
<td>262(0)</td>
<td>128(0)</td>
</tr>
<tr>
<td>4 months</td>
<td>248(1)</td>
<td>113(2)</td>
</tr>
<tr>
<td>6 months</td>
<td>206(33)</td>
<td>92(14)</td>
</tr>
<tr>
<td>8 months</td>
<td>134(93)</td>
<td>61(38)</td>
</tr>
<tr>
<td>10 months</td>
<td>72(147)</td>
<td>33(60)</td>
</tr>
<tr>
<td>12 months</td>
<td>20(197)</td>
<td>8(84)</td>
</tr>
<tr>
<td>14 months</td>
<td>18(197)</td>
<td>1(91)</td>
</tr>
<tr>
<td>16 months</td>
<td>3(212)</td>
<td>0(215)</td>
</tr>
</tbody>
</table>

**Events**

- 6 months: 6

**6-mo OS rate**

- Sint+Chemo: 19.2%
- PL+Chemo: 29.8%

**HR (95% CI)**

- Sint+Chemo: 0.609 (0.400, 0.926)
- PL+Chemo: 0.01921

**P**

- Sint+Chemo: 0.01921
- PL+Chemo: 0.01921
Response rate and duration by IRRC

<table>
<thead>
<tr>
<th></th>
<th>Sinti+chemo (N=266)</th>
<th>Placebo+chemo (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response Rate, n(%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>3 (1.1%)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>135 (50.8%)</td>
<td>39 (29.8%)</td>
</tr>
<tr>
<td>SD</td>
<td>93 (35.0%)</td>
<td>60 (45.8%)</td>
</tr>
<tr>
<td>PD</td>
<td>27 (10.2%)</td>
<td>25 (19.1%)</td>
</tr>
<tr>
<td><strong>ORR, % (95%CI)</strong></td>
<td>51.9% (45.7%, 58.0%)</td>
<td>29.8% (22.1%, 38.4%)</td>
</tr>
<tr>
<td><strong>DCR, % (95%CI)</strong></td>
<td>86.8% (82.2%, 90.7%)</td>
<td>75.6% (67.3%, 82.7%)</td>
</tr>
<tr>
<td><strong>Duration of response, mo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median ( 95%CI )</td>
<td>NR ( 8.0, NR )</td>
<td>5.5 ( 4.1, 10.9 )</td>
</tr>
<tr>
<td><strong>Time to response, mo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median ( 95%CI )</td>
<td>1.5 ( 1.2, 7.0 )</td>
<td>2.6 ( 1.2, 5.1 )</td>
</tr>
</tbody>
</table>

*Stratified Miettinen-Nurminen method*
### Exposure to Study Treatment

<table>
<thead>
<tr>
<th></th>
<th>Sinti+chemo (N=266)</th>
<th>Placebo+chemo (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment duration, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sintilimab/Placebo</td>
<td>7.0 mo (3.3)</td>
<td>5.9 mo (3.1)</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>7.0 mo (3.3)</td>
<td>5.8 mo (3.1)</td>
</tr>
<tr>
<td>Cisplatin/Carboplatin</td>
<td>2.7 mo (0.5)</td>
<td>2.7 mo (0.6)</td>
</tr>
<tr>
<td>Complete 4 cycles of platinum treatment, n (%)</td>
<td>235 (88.3%)</td>
<td>109 (83.2%)</td>
</tr>
</tbody>
</table>

### Safety Summary

<table>
<thead>
<tr>
<th></th>
<th>Sinti+chemo (N=266)</th>
<th>Placebo+chemo (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>265 (99.6%)</td>
<td>131 (100.0%)</td>
</tr>
<tr>
<td>Grade 3-5 AE</td>
<td>164 (61.7)</td>
<td>77 (58.8)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>75 (28.2)</td>
<td>39 (29.8)</td>
</tr>
<tr>
<td>AE led to death</td>
<td>6 (2.3)</td>
<td>9 (6.9)</td>
</tr>
<tr>
<td>AE led to any treatment discontinuation</td>
<td>16 (6.0)</td>
<td>11 (8.4)</td>
</tr>
<tr>
<td>Immune related AE</td>
<td>115 (43.2)</td>
<td>48 (36.6)</td>
</tr>
<tr>
<td>Grade 3-5 irAE</td>
<td>15 (5.6)</td>
<td>8 (6.1)</td>
</tr>
</tbody>
</table>
Anemia
Decreased neutrophil count
Decreased WBC
Decreased platelet count
Increased AST
Increased ALT
Nausea
Decreased appetite
Asthenia
Vomiting
Constipation
Pyrexia

Adverse events in ≥ 20% of patients in any group
Immune-related adverse events in ≥ 2% of patients in any group

- Hypothyroidism
- Rash
- Increased AST
- Increased ALT
- Increased blood TSH
- Hyperthyroidism
- Diarrhoea
- Immune-mediated pneumonitis
- Decreased blood TSH
- Increased amylase
- Pruritus
- Increased free thyroxine

Grade
1-2
3-5

Sinti+chemo
PL+chemo
The addition of sintilimab to pemetrexed/platinum significantly improved PFS compared to placebo combination:
- PFS 8.9 vs. 5.0 months, HR=0.482
- The benefit was seen across key clinical subgroups

ORR was also improved (51.9% vs 29.8%) with durable response.

Sintilimab combination demonstrated nominally significant improvement of OS (HR=0.609).

Manageable safety profile and no new safety signals were observed.
We thank all of the patients, their families, investigators and healthcare professionals who take part in this trial.