Surgical Outcomes from RATIONALE-315: Randomised, Double-Blind, Phase 3 Study of Perioperative Tislelizumab with Neoadjuvant Chemotherapy in Resectable NSCLC

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Declaration of Interests

• Dongsheng Yue reports no conflicts of interest
Background

- Surgery offers the highest likelihood of cure for patients with resectable, early-stage NSCLC; however, the 5-year tumour recurrence rate can be as high as 67% (depending on disease stage)\textsuperscript{1-5}

- At the interim analysis of RATIONALE-315 (NCT04379635), perioperative TIS (anti-PD-1 mAb) plus neoadjuvant PtDb CT showed statistically significant and clinically meaningful improvements in MPR, pCR rates, and EFS vs PBO + PtDb CT as neoadjuvant treatment in patients in China with resectable stage II-IIIA NSCLC, as well as a tolerable and manageable safety profile\textsuperscript{6-7}

Here we present and report on key surgery outcomes from this study

Abbreviations: EFS, event-free survival; mAb, monoclonal antibody; MPR, major pathological response; NSCLC, non-small cell lung cancer; PBO, placebo; pCR, pathological complete response; PD-1, programmed-death 1; PtDb CT, platinum-based doublet chemotherapy; TIS, tislelizumab.

RATIONALE-315 Study Design

**Key eligibility criteria**
- Resectable stage II-IIIA NSCLC per AJCC 8th Cancer Staging Manual (eligible for R0 resection)
- ECOG PS 0 or 1
- EGFR/ALK WT

**Stratification**
- Histology (squamous vs non-squamous)
- Disease stage (II vs IIIA)
- PD-L1 expression (≥21% vs <1%/not evaluable/indeterminate)

**ClinicalTrials.gov Identifier:** NCT04379635. Median study follow-up: 22.0 months (range: 0.1-38.4); data cut-off: August 21, 2023.

**Primary endpoints:**
- MPR rate by BIPR and EFS by BICR

**Secondary endpoints:**
- pCR rate by BIPR
- OS, EFS by investigator, safety (and others not reported here)

**Exploratory endpoint:**
- Surgery outcomes

**Neoadjuvant phase** (3-4 cycles)
- TIS (200 mg IV Q3W) + PtDb CT

**Adjuvant phase** (up to 8 cycles)
- TIS (400 mg IV Q6W)

**Surgery**
- PBO (IV Q3W) + PtDb CT
- PBO (IV Q6W)

**PtDb CT**
- Squamous: cisplatin/carboplatin + paclitaxel
- Non-squamous: cisplatin/carboplatin + pemetrexed

**Abbreviations:** AJCC, American Joint Committee on Cancer; ALK, anaplastic large-cell lymphoma kinase; BICR, blinded independent central review; BIPR, blinded independent pathology review; EGFR, epidermal growth factor receptor; IV, intravenously; MPR, major pathological response; NSCLC, non-small cell lung cancer; OS, overall survival; PBO, placebo; pCR, pathological complete response; PD-L1, programmed death-ligand 1; PtDb CT, platinum-based doublet chemotherapy; Q3W, once every 3 weeks; Q6W, once every 6 weeks; R, randomised; R0, pathological complete resection of the primary tumour; TIS, tislelizumab; WT, wild-type.
## Demographics and Baseline Characteristics

### ITT Analysis Set

<table>
<thead>
<tr>
<th></th>
<th>TIS arm (N=226)</th>
<th>PBO arm (N=227)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR), years</td>
<td>62.0 (57.0-67.0)</td>
<td>63.0 (56.0-68.0)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>205 (90.7)</td>
<td>205 (90.3)</td>
</tr>
<tr>
<td>Asian race, n (%)</td>
<td>226 (100.0)</td>
<td>227 (100.0)</td>
</tr>
<tr>
<td>ECOG PS 1, n (%)</td>
<td>83 (36.7)</td>
<td>73 (32.2)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/former</td>
<td>193 (85.4)</td>
<td>190 (83.7)</td>
</tr>
<tr>
<td>Never</td>
<td>33 (14.6)</td>
<td>37 (16.3)</td>
</tr>
<tr>
<td><strong>Histology</strong>, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>179 (79.2)</td>
<td>175 (77.1)</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>45 (19.9)</td>
<td>50 (22.0)</td>
</tr>
<tr>
<td>Disease stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>92 (40.7)</td>
<td>91 (40.1)</td>
</tr>
<tr>
<td>IIIA</td>
<td>132 (58.4)</td>
<td>133 (58.6)</td>
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<thead>
<tr>
<th></th>
<th>TIS arm (N=226)</th>
<th>PBO arm (N=227)</th>
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<tbody>
<tr>
<td><strong>cT status</strong>, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>19 (8.4)</td>
<td>18 (8.2)</td>
</tr>
<tr>
<td>T2</td>
<td>126 (55.8)</td>
<td>120 (52.9)</td>
</tr>
<tr>
<td>T3</td>
<td>57 (25.2)</td>
<td>64 (28.2)</td>
</tr>
<tr>
<td>T4</td>
<td>24 (10.6)</td>
<td>25 (11.0)</td>
</tr>
<tr>
<td><strong>cN status</strong>, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>60 (26.5)</td>
<td>54 (23.8)</td>
</tr>
<tr>
<td>N1</td>
<td>84 (37.2)</td>
<td>93 (41.0)</td>
</tr>
<tr>
<td>N2</td>
<td>82 (36.3)</td>
<td>79 (34.8)</td>
</tr>
<tr>
<td><strong>PD-L1 expression</strong>, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>89 (39.4)</td>
<td>84 (37.0)</td>
</tr>
<tr>
<td>≥1%</td>
<td>130 (57.5)</td>
<td>132 (58.1)</td>
</tr>
<tr>
<td>Not evaluable/indeterminate</td>
<td>7 (3.1)</td>
<td>11 (4.8)</td>
</tr>
</tbody>
</table>

* One patient in the TIS arm had a missing ECOG PS. * Histology by CRF; mixed histology was categorized as “Other” (n=2 [0.9%] in each arm). * One patient (TIS arm) with disease stage IB and four patients with disease stage IIIB were incorrectly enrolled.

Abbreviations: cN, clinical node; CRF, case report form; cT, clinical T stage at baseline; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; ITT, intention-to-treat; PBO, placebo; PD-L1, programmed death-ligand 1; TIS, tislelizumab.
Patient Disposition

ITT Analysis Set

N=453 patients randomised

TIS arm N=226

226 (100.0%) received neoadjuvant tx\textsuperscript{a}
- 211 (93.4%) completed neoadjuvant tx\textsuperscript{a,b}

190 (84.1%) received definitive surgery\textsuperscript{a,c}
- 168 (74.3%) received adjuvant TIS\textsuperscript{a}
  - 106 (46.9%) completed adjuvant tx\textsuperscript{a}
    - 11 (4.9%) adjuvant TIS ongoing

PBO arm N=227

226 (99.6%) received neoadjuvant tx\textsuperscript{a}
- 210 (92.5%) completed neoadjuvant tx\textsuperscript{a,b}

173 (76.2%) received definitive surgery\textsuperscript{a,c}
- 147 (64.8%) received adjuvant PBO\textsuperscript{a}
  - 101 (44.5%) completed adjuvant PBO\textsuperscript{a}
    - 8 (3.5%) adjuvant PBO ongoing

\textsuperscript{a} Denominator based on randomised patients. \textsuperscript{b} Completion of neoadjuvant treatment is based on whether patients received 3 to 4 cycles of neoadjuvant treatments. \textsuperscript{c} Patients received postoperative radiotherapy (3 in TIS arm, 5 in PBO arm).

Abbreviations: ITT, intention-to-treat; PBO, placebo; TIS, tislelizumab; tx, treatment.

Median study follow-up: 22.0 months (range: 0.1-38.4). The ITT analysis set included all randomised patients.

- 36 (15.9%) surgery cancellation\textsuperscript{a}
  - Patient withdrawal 20 (8.6%)
  - Progressive disease 6 (2.7%)
  - Adverse event 6 (2.7%)
  - Physician decision 3 (1.3%)
  - Other 1 (0.4%)
- 22 (9.7%) did not receive adjuvant tx\textsuperscript{a}
  - Patient withdrawal 10 (4.4%)
  - Adverse event 7 (3.1%)
  - Physician decision 4 (1.8%)
  - Progressive disease 1 (0.4%)

- 26 (11.5%) did not receive adjuvant tx\textsuperscript{a}
  - Patient withdrawal 13 (5.7%)
  - Adverse event 4 (1.8%)
  - Physician decision 7 (3.1%)
  - Progressive disease 2 (0.9%)

- 20 (8.8%) patient withdrawal
- 6 (2.7%) progressive disease
- 6 (2.7%) adverse event
- 3 (1.3%) physician decision
- 1 (0.4%) other

- 13 (5.7%) patient withdrawal
- 4 (1.8%) adverse event
- 7 (3.1%) physician decision
- 2 (0.9%) progressive disease

- 28 (12.3%) surgery cancellation\textsuperscript{a}
- 17 (7.5%) progressive disease
- 2 (0.9%) adverse event
- 7 (3.1%) physician decision
Objective Response Rate Before Surgery by BICR

ITT Analysis Set

<table>
<thead>
<tr>
<th>Response Category</th>
<th>TIS arm (N=226)</th>
<th>PBO arm (N=227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1 (0.4)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Partial response</td>
<td>160 (70.8)</td>
<td>122 (53.7)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>54 (23.9)</td>
<td>94 (41.4)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4 (1.8)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Could not be determined</td>
<td>7 (3.1)</td>
<td>6 (2.6)</td>
</tr>
</tbody>
</table>

- ORR, including patients who had a best overall response of CR or PR before surgery, was higher in the TIS arm than in the PBO arm (risk difference of 15.9% [95% CI: 7.3%-24.5%])

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Abbreviations: BICR, blinded independent central review; CI, confidence interval; CR, complete response; ITT, intention-to-treat; ORR, objective response rate; PBO, placebo; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; TIS, tislelizumab.
Surgical Delay by Disease Stage
Safety Analysis Set (Surgery)

<table>
<thead>
<tr>
<th></th>
<th>All Stages</th>
<th>Stage II</th>
<th>Stage IIIA</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>TIS arm</td>
<td>PBO arm</td>
<td>TIS arm</td>
</tr>
<tr>
<td></td>
<td>(N=190)</td>
<td>(N=173)</td>
<td>(N=74)</td>
</tr>
<tr>
<td>Patients with delayed surgery, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>31 (16.3)</td>
<td>22 (12.7)</td>
<td>19 (25.7)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (6.3)</td>
<td>6 (3.5)</td>
<td>9 (12.2)</td>
</tr>
<tr>
<td>Related to COVID-19</td>
<td>19 (10.0)</td>
<td>16 (9.2)</td>
<td>10 (13.5)</td>
</tr>
<tr>
<td></td>
<td>8 (4.2)</td>
<td>7 (4.0)</td>
<td>6 (8.1)</td>
</tr>
<tr>
<td>Length of surgery delay, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 weeks</td>
<td>22 (11.6)</td>
<td>18 (10.4)</td>
<td>14 (18.9)</td>
</tr>
<tr>
<td>&gt;2 and ≤4 weeks</td>
<td>5 (2.6)</td>
<td>3 (1.7)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>&gt;4 and ≤6 weeks</td>
<td>1 (0.5)</td>
<td>1 (0.6)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>&gt;6 weeks</td>
<td>2 (1.1)</td>
<td>0 (0.0)</td>
<td>2 (2.7)</td>
</tr>
</tbody>
</table>

- Median (IQR) time from randomisation to definitive surgery was 13.4 (11.6-15.0) weeks with TIS and 12.7 (11.4-14.9) weeks with PBO for all patients with definitive surgery.
- Median (IQR) time from last neoadjuvant dose to definitive surgery was 5.5 (5.0-6.0) weeks with TIS and 5.3 (5.0-5.9) weeks with PBO for all patients with definitive surgery.

Abbreviations: IQR, interquartile range; PBO, placebo; TIS, tislelizumab.

* Defined as when date of surgery is beyond 6 weeks after last neoadjuvant treatment dose. ** Length of surgery delay is defined as (surgery start date - last neoadjuvant treatment date - 6 weeks)*7/7 for patients having surgery delayed.

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**Surgical Approach**

**Safety Analysis Set (Surgery)**

![Graphs showing surgical approach results for open, minimally invasive, and minimally invasive to thoracotomy approaches.](image)

- **Open**
  - TIS: 34, 31, 36, 47
  - PBO: 41, 32, 47, 60

- **Minimally Invasive**
  - TIS: 60, 65, 57, 50
  - PBO: 50, 61, 43, 61

- **Minimally Invasive to Thoracotomy**
  - TIS: 6, 9, 7, 8
  - PBO: 4, 7, 7, 11

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**Notes:**

- Patients with all stages of disease and definitive surgery.
- Denominator based on patients with definitive surgery.

**Abbreviations:**

- PBO: placebo
- TIS: tislelizumab

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The most common type of surgical procedure was lobectomy regardless of disease stage in both treatment arms.

Fewer pneumonectomies were reported in the TIS arm vs the PBO arm (16 [8.4%] vs 21 [12.1%]).

Abbreviations: PBO, placebo; TIS, tislelizumab.
Completeness of Resection

Safety Analysis Set (Surgery)

• R0, R1, and R2 resection rates were similar regardless of disease stage in both treatment arms
• Median (IQR) number of lymph nodes dissected was similar between treatment arms: 18.0 (11.0-24.0) for the TIS arm and 16.0 (10.0-23.0) for the PBO arm

[Graph showing completeness of resection for all disease stages, Stage II, and Stage IIIA]

Abbreviations: IQR, interquartile range; PBO, placebo; R0, pathological complete resection of the primary tumour; TIS, tislelizumab; un, uncertain.

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## Hospital Stay by Surgery Type and Disease Stage

### Safety Analysis Set (Surgery)

<table>
<thead>
<tr>
<th></th>
<th>TIS arm (N=190)</th>
<th>PBO arm (N=173)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of hospital stay, median (IQR), days</strong></td>
<td>7.0 (5.0-9.0)</td>
<td>7.0 (6.0-9.0)</td>
</tr>
<tr>
<td><strong>Length of hospital stay by surgery type, median (IQR), days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobectomy</td>
<td>6.0 (5.0-8.0)</td>
<td>7.0 (5.0-9.0)</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>8.0 (7.0-11.0)</td>
<td>7.0 (5.0-8.0)</td>
</tr>
<tr>
<td>Sleeve lobectomy</td>
<td>8.0 (6.0-13.5)</td>
<td>7.0 (6.0-7.5)</td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>6.0 (5.0-9.0)</td>
<td>8.0 (6.0-10.0)</td>
</tr>
<tr>
<td><strong>Length of hospital stay by disease stage, median (IQR), days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>7.0 (6.0-9.0)</td>
<td>7.0 (5.0-9.0)</td>
</tr>
<tr>
<td>IIIA</td>
<td>7.0 (6.0-9.0)</td>
<td>7.0 (6.0-9.0)</td>
</tr>
</tbody>
</table>

- Hospital stay rates were similar regardless of surgery type and disease stage in both treatment arms
- Median duration of surgery (2.7 vs 2.8 hours) was similar between arms

**Abbreviations:** IQR, interquartile range; PBO, placebo; TIS, tislelizumab.
90-Day Postoperative Complications Summary

Safety Analysis Set (Surgery)

- The 30-day and 90-day postsurgery mortality rates were 2 (0.9%) and 3 (1.3%) patients in the TIS arm, and 2 (0.9%) and 4 (1.8%) patients in the PBO arm, respectively.

Abbreviations: PBO, placebo; TIS, tislelizumab.

*Adverse events assessed as postoperative complications from the date of surgery up to 90 days after surgery were included. Denominator based on safety analysis set (overall).
Conclusions

- In the RATIONALE-315 study, perioperative TIS plus neoadjuvant PtDb CT did not impact the feasibility and completeness of surgery
  - R0 resections were achieved in a similar percentage of patients in both arms (TIS: 95%, PBO: 93%)
  - 6.3% (TIS arm) and 3.5% (PBO arm) of surgical delays were due to adverse events, with the majority of the delays not exceeding 2 weeks
  - The median duration of surgery, length of hospital stays, and number of lymph nodes dissected were similar between the TIS and PBO arms
  - In the TIS arm, a higher proportion of patients received minimally invasive surgery compared with the PBO arm (TIS: 60%, PBO: 50%)
- The safety profile of perioperative TIS plus neoadjuvant PtDb CT was manageable, and treatment with TIS was not associated with increased rates of postoperative complications
- Taken together with previously reported statistically significant improvement in MPR, pCR, and EFS, these data support the use of perioperative TIS plus neoadjuvant PtDb CT for patients with resectable stage II-IIIA NSCLC

Abbreviations: EFS, event-free survival; MPR, major pathological response; NSCLC, non-small cell lung cancer; PBO, placebo; pCR, pathological complete response; PtDb CT, platinum-based doublet chemotherapy; R0, pathological complete resection of the primary tumour; TIS, tislelizumab.

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