RATIONALE-315: Outcomes by 3 Versus 4 Neoadjuvant Cycles of Perioperative Tislelizumab Plus Chemotherapy in Resectable NSCLC

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CONCLUSIONS

- In these exploratory analyses from RATIONALE-315, patients with resectable NSCLC had improved efficacy with perioperative tislelizumab versus control after completing 3 or 4 neoadjuvant treatment cycles
  - Improved MPR and pCR rates were observed with perioperative tislelizumab versus control after completing 3 or 4 neoadjuvant cycles
  - After completion of 3 versus 4 neoadjuvant tislelizumab plus chemotherapy cycles, an improvement trend in EFS favored patients with 4 cycles who had MPR, and EFS benefit was similar for those with 3 or 4 cycles who achieved pCR after surgery
  - Additional cycles did not appear to confer higher pathological response rates, while efficacy compared with control was maintained regardless of cycle number
- A manageable and acceptable safety profile was observed with 3 or 4 neoadjuvant cycles of tislelizumab versus control in the overall and neoadjuvant phases
- These results provide valuable information for clinical decision making, highlighting the safety and efficacy of perioperative tislelizumab as a treatment in patients with resectable NSCLC

INTRODUCTION

- In RATIONALE-315 (NCT04379635), perioperative tislelizumab plus neoadjuvant chemotherapy showed significant improvement versus placebo plus neoadjuvant chemotherapy in event-free survival (EFS), overall survival (OS), major pathological response (MPR) rate, and pathologic complete response (pCR) rate with manageable safety in resectable stage II-IIIA non-small cell lung cancer (NSCLC)[1,2]
- Determining the optimal number of neoadjuvant cycles for patients with resectable NSCLC is important to balance treatment benefits with associated adverse events (AEs)[3,4]
- This exploratory analysis investigated clinical outcomes by number of completed neoadjuvant treatment cycles of tislelizumab plus chemotherapy versus placebo plus chemotherapy in the neoadjuvant phase

METHODS

Trial Design

- In RATIONALE-315, patients with untreated stage II-IIIA NSCLC were randomized (1:1) to neoadjuvant tislelizumab plus chemotherapy followed by surgery and adjuvant tislelizumab (tislelizumab arm) or neoadjuvant placebo plus chemotherapy followed by surgery and adjuvant placebo (control arm) for up to 8 cycles (**Supplemental Figure 1. Study Design**; scan QR code to the right to access)
- Primary and key secondary endpoints were reported previously[1,2]

Assessments

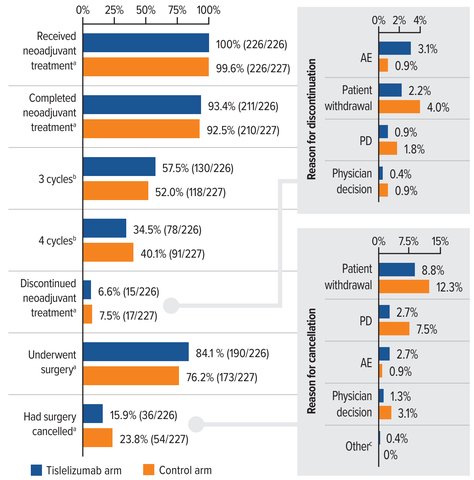
- In this exploratory analysis, MPR, pCR, and EFS were analyzed in patients who received 3 cycles versus 4 cycles (physician's choice) of neoadjuvant tislelizumab plus chemotherapy or placebo plus chemotherapy
  - Differences in MPR and pCR in the tislelizumab and control arms were calculated using the Cochran–Mantel–Haenszel method
  - MPR and pCR were further analyzed by subgroups of patients who received 3 or 4 cycles of neoadjuvant tislelizumab plus chemotherapy
  - No comparison was made within control arms due to insufficient number of responders

RESULTS

Patients

- As of March 7, 2025, 208/226 patients completed 3 (n=130) or 4 (n=78) cycles of neoadjuvant tislelizumab, and 209/226 patients completed 3 (n=118) or 4 (n=91) cycles of neoadjuvant placebo (**Figure 1**)
  - Overall, neoadjuvant treatment was discontinued in 15 (6.6%) patients from the tislelizumab arm and 17 (7.5%) patients from the control arm
  - Overall, surgery was cancelled for 36 (15.9%) patients from the tislelizumab arm and 54 (23.8%) patients from the control arm

Figure 1. Patient Disposition (ITT Analysis Set)



The ITT analysis set included all randomized patients. [a]Denominator based on randomized patients (tislelizumab, n=226; control, n=227). [b]Some patients also completed treatment with 1-2 neoadjuvant cycles at the investigator's discretion. [c]One patient withdrew to receive study treatment and surgery in another hospital.
Abbreviations: AE, adverse event; ITT, intent-to-treat; PD, progressive disease.

- Baseline characteristics were balanced across treatment arms and cycle number, except disease stage where more stage II patients received 3 neoadjuvant cycles and more stage IIIA patients received 4 neoadjuvant cycles (**Table 1**)
- Median (range) follow-up was 38.5 (0.1-57.0) months

Table 1. Baseline Demographics and Disease Characteristics

	3 cycles		4 cycles	
	Tislelizumab n=130	Control n=118	Tislelizumab n=78	Control n=91
Median age, years (range)	62.0 (30-80)	64.0 (36-75)	62.0 (43-75)	62.0 (42-78)
Sex, n (%)				
Female	9 (6.9)	14 (11.9)	9 (11.5)	6 (6.6)
Male	121 (93.1)	104 (88.1)	69 (88.5)	85 (93.4)
ECOG PS, n (%)				
0	79 (60.8)	79 (66.9)	51 (65.4)	63 (69.2)
1	50 (38.5)	39 (33.1)	27 (34.6)	28 (30.8)
Missing	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Smoking status, n (%)				
Current	25 (19.2)	29 (24.6)	18 (23.1)	21 (23.1)
Former	87 (66.9)	67 (56.8)	48 (61.5)	58 (63.7)
Never	18 (13.8)	22 (18.6)	12 (15.4)	12 (13.2)
Histology,[a] n (%)				
Squamous	103 (79.2)	88 (74.6)	62 (79.5)	71 (78.0)
Non-squamous	27 (20.8)	29 (24.6)	15 (19.2)	19 (20.9)
Other[b]	0 (0.0)	1 (0.8)	1 (1.3)	1 (1.1)
Disease stage,[a,c] n (%)				
II	55 (42.3)	49 (41.5)	25 (32.1)	36 (39.6)
IIIA	74 (56.9)	68 (57.6)	52 (66.7)	53 (58.2)
PD-L1 expression,[d] n (%)				
<1%[e]	59 (45.4)	51 (43.2)	33 (42.3)	35 (38.5)
≥1%	71 (54.6)	67 (56.8)	45 (57.7)	56 (61.5)

[a]From case report form. [b]Patients with mixed histology were categorized as Other. [c]One patient with stage IB disease (received 3 tislelizumab cycles) and 4 patients with stage IIIB disease (1 received 3 placebo cycles, 1 received 4 tislelizumab cycles, and 2 received 4 placebo cycles) were mistakenly enrolled and are protocol deviations. [d]Measured by central laboratory. [e]Includes not evaluable/indeterminate.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death ligand-1.

MPR and pCR

- MPR and pCR rates were improved in the tislelizumab arm versus control arm after completing 3 or 4 neoadjuvant cycles (**Table 2**)
  - The difference in MPR and pCR rates between treatment arms were similar regardless of number of neoadjuvant cycles

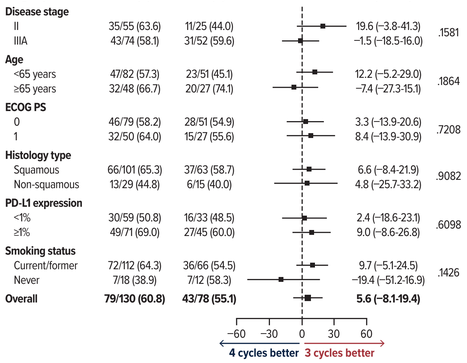
Table 2. MPR and pCR by Number of Neoadjuvant Cycles

	Tislelizumab		Control		MPR difference, % (95% CI)
	n	MPR, n (%)	n	MPR, n (%)	
ITT	226	127 (56.2)	227	34 (15.0)	41.1 (33.2-49.1)
3 cycles	130	79 (60.8)	118	19 (16.1)	44.6 (33.9-55.2)
4 cycles	78	43 (55.1)	91	15 (16.5)	38.7 (25.4-52.0)
	n	pCR, n (%)	n	pCR, n (%)	pCR difference, % (95% CI)
ITT	226	92 (40.7)	227	13 (5.7)	35.0 (27.9-42.1)
3 cycles	130	56 (43.1)	118	7 (5.9)	37.1 (27.6-46.7)
4 cycles	78	33 (42.3)	91	6 (6.6)	35.7 (23.6-47.8)

Abbreviations: CI, confidence interval; ITT, intent-to-treat; MPR, major pathological response; pCR, pathological complete response.

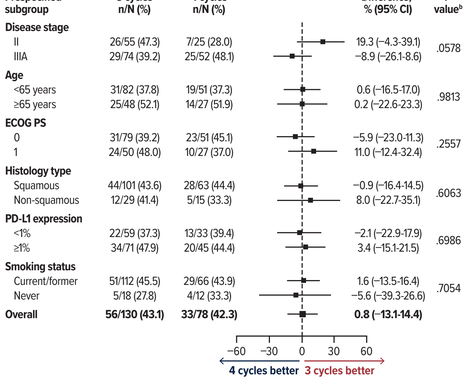
- The differences in MPR rates were similar across all prespecified subgroups within the tislelizumab arm (**Figure 2**)
- Among prespecified subgroups in the tislelizumab arm, the differences in pCR rates were mostly similar except for disease stage, which strongly correlated with number of neoadjuvant cycles completed (P=.0578; **Figure 3**)

Figure 2. Forest Plot of MPR Difference in the Tislelizumab Arm by Number of Completed Neoadjuvant Cycles in Prespecified Subgroups



[a]Difference = 3 cycles – 4 cycles (4 cycles as reference); 95% CI determined using Miettinen–Nurminen method. [b]Breslow–Day P value tested for homogeneity of odds ratios across subgroup levels (interaction test).
Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; MPR, major pathological response; PD-L1, programmed cell death ligand-1.

Figure 3. Forest Plot of pCR Difference in the Tislelizumab Arm by Number of Completed Neoadjuvant Cycles in Prespecified Subgroups

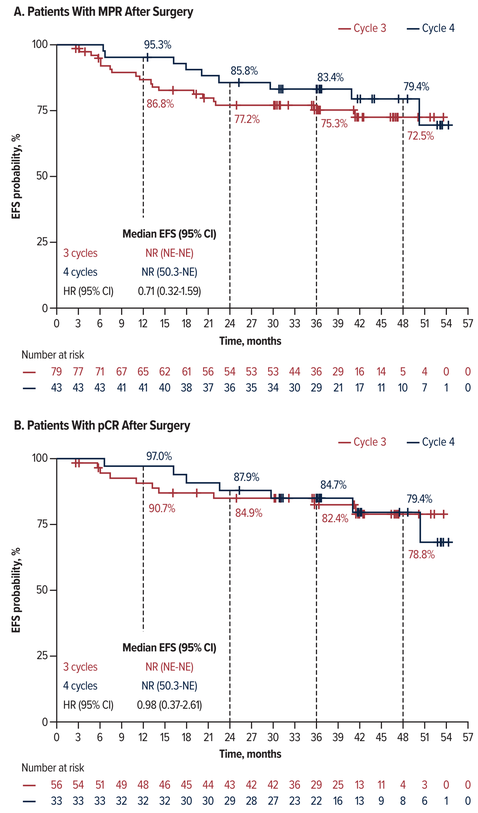


[a]Difference = 3 cycles – 4 cycles (4 cycles as reference); 95% CI determined using Miettinen–Nurminen method. [b]Breslow–Day P value tested for homogeneity of odds ratios across subgroup levels (interaction test).
Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; pCR, pathologic complete response; PD-L1, programmed cell death ligand-1.

EFS

- Within the tislelizumab arm, an improvement trend was observed favoring patients treated with 4 neoadjuvant cycles who had MPR (**Figure 4A**), while similar EFS benefit was observed in those treated with 3 versus 4 cycles who achieved pCR after surgery (**Figure 4B**)
- 1-, 2-, 3-, and 4-year EFS rates were similar in patients from the tislelizumab arm who had MPR or pCR regardless of number of completed cycles (**Figure 4**)

Figure 4. EFS in the Tislelizumab Arm by Number of Completed Neoadjuvant Cycles



Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; MPR, major pathological response; NE, not estimable; NR, not reached; pCR, pathological complete response.

Safety

- As reported at interim analysis, tislelizumab plus platinum-based doublet chemotherapy as neoadjuvant treatment followed by adjuvant tislelizumab treatment showed a manageable and acceptable safety profile[2]
- Safety from the overall phase of perioperative treatment is summarized in **Table 3**
  - A slightly higher proportion of patients in the tislelizumab arm experienced grade ≥3 treatment-related treatment-emergent adverse events (TRAEs) and serious TRAEs versus control, with a similar trend in those patients who received 3 versus 4 cycles of neoadjuvant treatment versus control
  - Grade ≥3 TRAEs and those leading to death or discontinuation were low in both arms with a trend towards being slightly higher in those who received 3 or 4 neoadjuvant cycles of tislelizumab versus control
  - More immune-mediated adverse events (imAEs) and grade ≥3 imAEs were experienced by patients in the tislelizumab arm versus the control arm
- In contrast with the overall phase, TRAEs in the neoadjuvant phase were generally consistent and manageable across treatment arms and cycle number (**Table 4**)
  - More imAEs and grade ≥3 imAEs were experienced in the tislelizumab arm versus the control arm

Table 3. Summary of TRAEs and imAEs From the Overall Phase

	All patients		3 cycles		4 cycles	
n (%)	Tislelizumab n=226	Control n=226[a]	Tislelizumab n=130	Control n=118	Tislelizumab n=78	Control n=91
Any TRAE	224 (99.1)	225 (99.6)	129 (99.2)	118 (100)	78 (100)	90 (98.9)
Grade ≥3	165 (73.0)	152 (67.3)	92 (70.8)	73 (61.9)	60 (76.9)	67 (73.6)
Serious	35 (15.5)	20 (8.8)	21 (16.2)	8 (6.8)	11 (14.1)	5 (5.5)
Leading to death	4 (1.8)	2 (0.9)	4 (3.1)	2 (1.7)	0 (0.0)	0 (0.0)
Leading to treatment discontinuation	21 (9.3)	7 (3.1)	8 (6.2)	4 (3.4)	8 (10.3)	1 (1.1)
Any imAE	91 (40.3)	41 (18.1)	49 (37.7)	23 (19.5)	33 (42.3)	14 (15.4)
Grade ≥3	21 (9.3)	7 (3.1)	12 (9.2)	4 (3.4)	6 (7.7)	1 (1.1)
Grade ≥3 imAEs in ≥2 patients by PT						
Pneumonitis	7 (3.1)	0 (0.0)	5 (3.8)	0 (0.0)	1 (1.3)	0 (0.0)
Skin adverse reaction	5 (2.2)	0 (0.0)	1 (0.8)	0 (0.0)	2 (2.6)	0 (0.0)
Hepatitis	4 (1.8)	5 (2.2)	3 (2.3)	3 (2.5)	1 (1.3)	0 (0.0)
Hypothyroidism	2 (0.9)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes mellitus	1 (0.4)	2 (0.9)	1 (0.8)	1 (0.8)	0 (0.0)	1 (1.1)

AEs were graded for severity using CTCAE v5.0. [a]One patient in the ITT population received no treatment and was excluded from the safety analysis.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; imAE, immune-mediated adverse event; ITT, intent-to-treat; PT, preferred term; TRAE, treatment-related treatment-emergent adverse event.

Table 4. Summary of TRAEs and imAEs From the Neoadjuvant Phase

	All patients		3 cycles		4 cycles	
n (%)	Tislelizumab n=226	Control n=226[a]	Tislelizumab n=130	Control n=118	Tislelizumab n=78	Control n=91
Any TRAE	223 (98.7)	225 (99.6)	128 (98.5)	118 (100)	78 (100)	90 (98.9)
Grade ≥3	156 (69.0)	150 (66.4)	85 (65.4)	72 (61.0)	58 (74.4)	66 (72.5)
Serious	18 (8.0)	16 (7.1)	11 (8.5)	5 (4.2)	4 (5.1)	4 (4.4)
Leading to death	2 (0.9)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to treatment discontinuation	20 (8.8)	19 (8.4)	5 (3.8)	9 (7.6)	7 (9.0)	7 (7.7)
Any imAE	63 (27.9)	32 (14.2)	36 (27.7)	16 (13.6)	19 (24.4)	12 (13.2)
Grade ≥3	12 (5.3)	6 (2.7)	8 (6.2)	3 (2.5)	2 (2.6)	1 (1.1)
Grade ≥3 imAEs in ≥2 patients by PT						
Skin adverse reaction	4 (1.8)	0 (0.0)	1 (0.8)	0 (0.0)	1 (1.3)	0 (0.0)
Pneumonitis	3 (1.3)	0 (0.0)	3 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis	2 (0.9)	4 (1.8)	2 (1.5)	2 (1.7)	0 (0.0)	0 (0.0)
Hypophysitis	1 (0.4)	2 (0.9)	1 (0.8)	1 (0.8)	0 (0.0)	1 (1.1)

AEs were graded for severity using CTCAE v5.0. [a]One patient in the ITT population received no treatment and was excluded from the safety analysis.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; imAE, immune-mediated adverse event; ITT, intent-to-treat; PT, preferred term; TRAE, treatment-related treatment-emergent adverse event.

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DISCLOSURES

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