RATIONALE-304 Long-term Outcomes: First-line Tislelizumab (TIS) + Chemotherapy (chemo) vs Chemo for Locally Advanced or Metastatic Nonsquamous (NSQ) NSCLC

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CONCLUSIONS

- **Tislelizumab + chemo demonstrated clinically meaningful OS benefit as first-line treatment for locally advanced or metastatic nonsquamous NSCLC, with a promising 4-year OS rate of 32.8%; no new safety signals were observed with the extended follow-up.**
- **Patients with long-term exposure (≥35 cycles) to tislelizumab achieved high ORR and long-term survival, with higher expression of PD-L1, T cell inflammation signature, and TMB.**

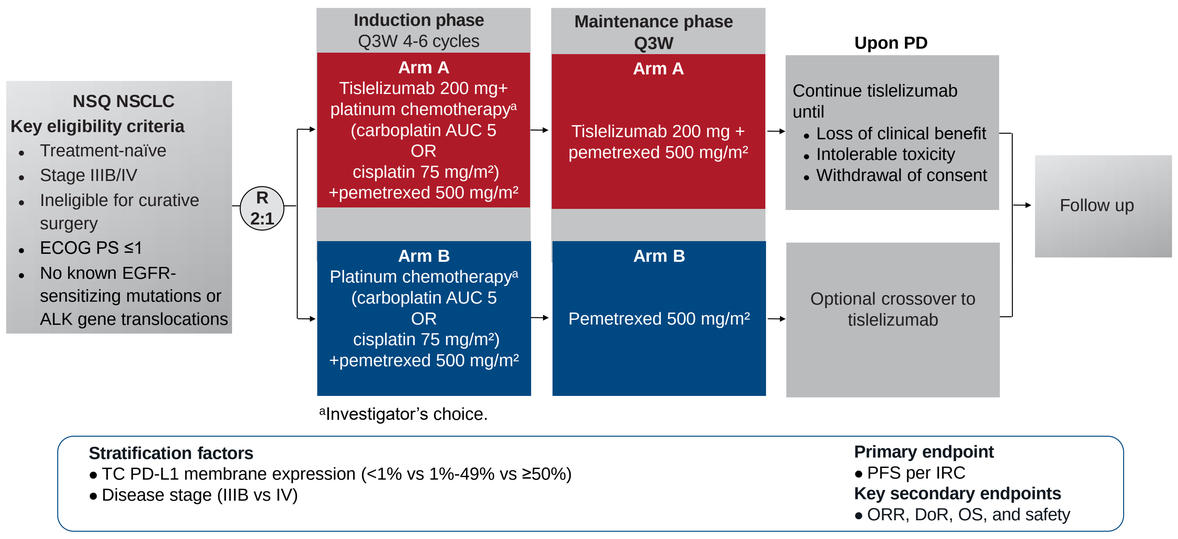
BACKGROUND

- Tislelizumab is a humanized monoclonal antibody with high affinity and binding specificity for programmed death-1 (PD-1), and was specifically engineered to minimize Fcγ receptor binding on macrophages.[1,2] It has demonstrated survival benefits across a variety of advanced solid tumors, including non-small cell lung cancer (NSCLC).[3-7]
- In the phase 3 RATIONALE-304 study (NCT03663205), tislelizumab + chemotherapy (chemo) significantly prolonged progression-free survival (PFS) vs chemo alone as first-line treatment in patients with advanced non-squamous NSCLC.[3,8,9] This study led to the approval of tislelizumab + chemo as a standard of care for nonsquamous NSCLC in the first-line setting in China.[10]
- Here, we report the updated outcomes with approximately 4-year follow-up and outcomes of patients with long-term exposure (LTE) to tislelizumab.

METHODS

- Eligible patients with systemic treatment-naïve advanced nonsquamous NSCLC were randomized 2:1 to receive 4 to 6 cycles of tislelizumab + chemo or chemo alone, followed by maintenance tislelizumab + pemetrexed or pemetrexed alone **(Fig. 1)**.
- Patients allocated to the chemo arm were allowed to cross over to tislelizumab monotherapy upon disease progression.
- LTE patients were defined as those who received ≥35 cycles of tislelizumab treatment in the tislelizumab + chemo arm.
- Biomarker testing was performed on baseline tumor samples, including programmed death ligand-1 (PD-L1) protein expression (VENTANA PD-L1 [SP263] assay), tumor mutational burden (TMB) and genomic alterations (OncoScreen Plus), and gene expression profiling (EdgeSeq Precision IO Panel).

Figure 1. Study design



[a]Investigator's choice.

Stratification factors
- TC PD-L1 membrane expression (<1% vs 1%-49% vs ≥50%)
- Disease stage (IIIB vs IV)

Primary endpoint
- PFS per IRC

Key secondary endpoints
- ORR, DoR, OS, and safety

RESULTS

Patients

- Between July 2018 and July 2019, 334 patients were randomly assigned (tislelizumab + chemo, n=223; chemo, n=111).
- As of April 26, 2023, median time from randomization to data cutoff was 49.4 mo (range, 44.9-57.1).

Updated efficacy and safety

- With approximately 4-year follow-up, tislelizumab + chemo demonstrated clinically meaningful OS benefit with 4-year OS rate of 32.8% (95% CI, 26.5%-39.2%) **(Fig. 2)**.
- Analyses adjusted for in-study cross-over effect with the two-stage method indicated an OS improvement with tislelizumab + chemo vs chemo only, showing a HR of 0.67 (95% CI, 0.48-0.95; median OS:21.4 mo vs 15.1 mo) **(Fig. 2)**
  - 58 patients (52.3%) received subsequent immunotherapy in chemo arm, including 42 patients (37.8%) crossed over to tislelizumab in-study.
- PFS benefits with tislelizumab + chemo vs chemo were also maintained at this updated analysis **(Fig. 3)**.
- The ORR (57.8% vs 36.9%), and CR rate (6.3% vs 1.8%) were higher in tislelizumab + chemo arm than in chemo arm, which was consistent with previous reports.[4,11]
- Tislelizumab plus chemotherapy was tolerable, with no new safety signals identified with extended follow-up.

Figure 2. Kaplan-Meier curves of OS

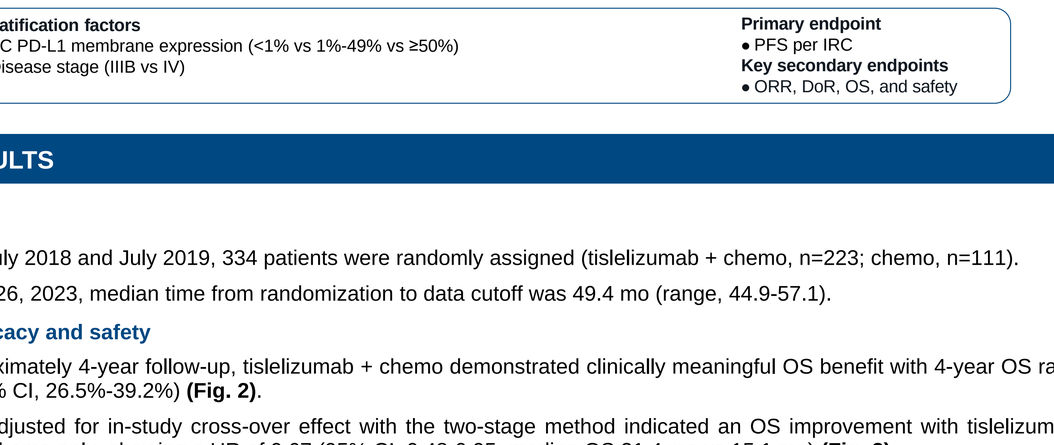
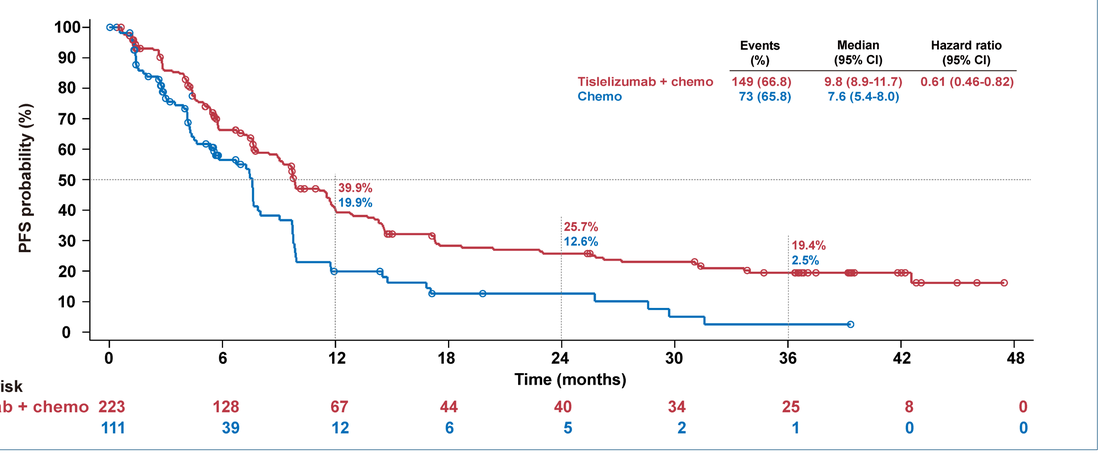


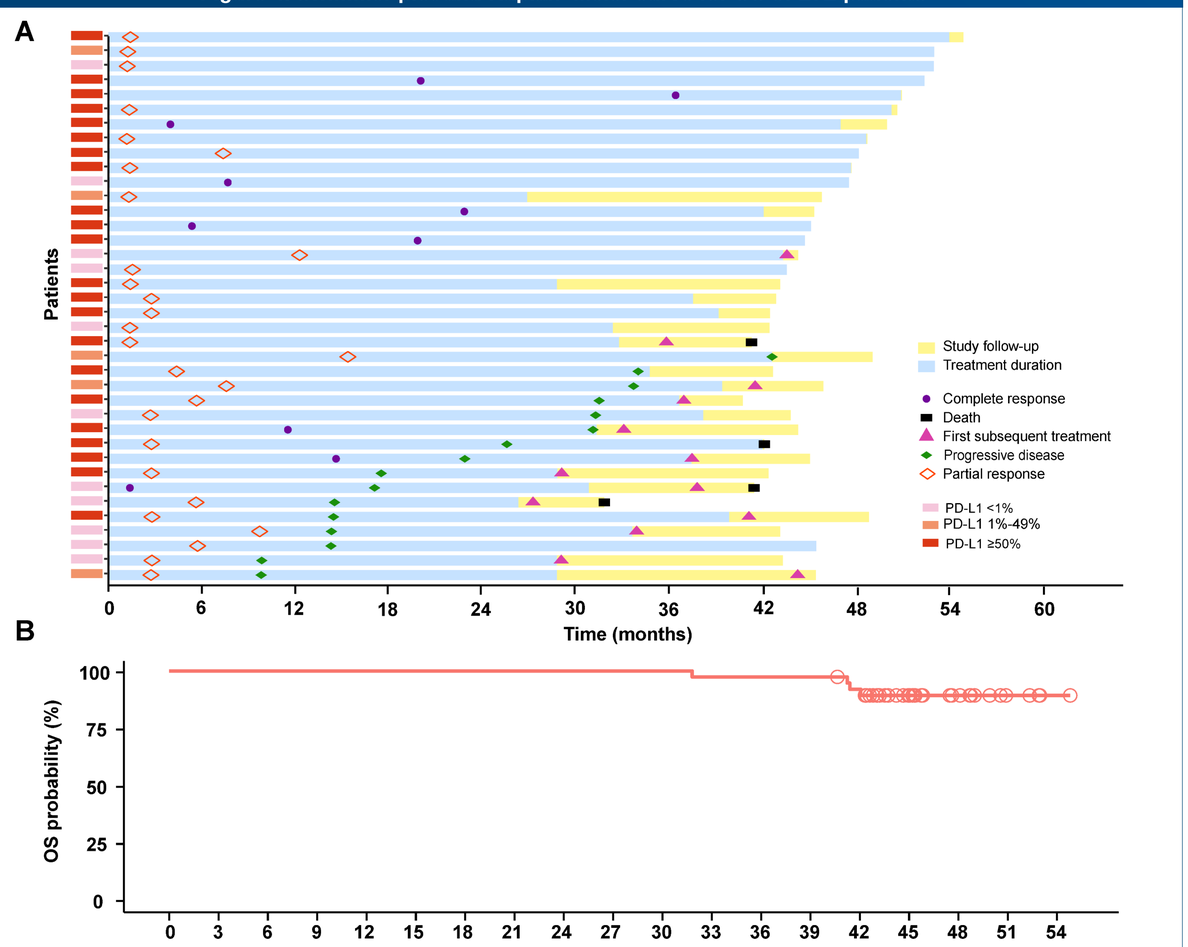
Figure 3. Kaplan-Meier curves of PFS



Outcomes in patients who received ≥35 cycles of tislelizumab

- A total of 38 (17.0%) patients received ≥35 cycles of tislelizumab (LTE), with a median of 52.5 (range, 36-77) treatment cycles.
- The proportions of PD-L1 TC ≥50%, 1-49% and <1% were 57.9%, 13.2% and 28.9% in LTE patients, respectively. Other baseline characteristics were generally similar to the IIT population of tislelizumab + chemo arm.
- The ORR was 100% (CR, n=10; PR, n=28; **Fig. 4A**), and median DoR was not reached.
- Median OS was not reached. The 4-year OS rate was 89.3% (95% CI, 73.8%-95.8%; **Fig. 4B**).
- The profile of immune-mediated adverse events in LTE patients was similar to the overall population of tislelizumab + chemo arm.

Figure 4. Swimmer plot and Kaplan–Meier curve for OS of LTE patients



Molecular features of LTE patients in tislelizumab + chemo arm

- Higher baseline PD-L1 expression, T cell inflammation signature levels, and TMB was observed in LTE vs non-LTE patients **(Fig. 5)**.
- Genomic alterations of LRP1B and PTPRD were enriched in LTE vs non-LTE patients (LRP1B: 61.9% vs 14.0%, adjusted p-value <0.05; PTPRD: 38.1% vs 5.4%, adjusted p-value <0.05)。

Figure 5. Molecular features of LTE patients in tislelizumab + chemo arm

References

1. Zhang T, et al. *Cancer Immunol Immunother*. 2018; 67: 1079-1090.
2. Hong Y, et al. *FEBS Open Bio*. 2021; 11: 782-792.
3. Wang J, et al. *JAMA Oncol*. 2021; 7(5): 709-717
4. Lu S, et al. *J Thorac Oncol*. 2021; 16(9): 1512-1522.
5. Xu J, et al. *Lancet Oncol*. 2023; 24: 483-95.
6. Qiu M, et al. *BMJ*. 2024; 385: e078876.
7. Cheng Y, et al. *J Thorac Oncol*. 2024; 19(7): 1073-1085.
8. Lu S, et al. *ESMO Open*. 2024; 103728.
9. Lu S, et al. *J Thorac Oncol*. 2021; 16(9): 1512-1522.
10. NMPA. https://www.nmpa.gov.cn/zwfw/sdxx/sdxxyp/yppjfb/20210622215839168.html. Accessed February 24, 2022
11. Lu S, et al. 2022 ESMO IO, 138P.

Abbreviations: AUC, area under curve; chemo, chemotherapy; CI, confidence interval; CR, complete response; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IRC, independent review committee; LTE, long-term exposure; m, month; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; R, randomized; TC, tumor cell; TIS, tislelizumab; TMB, tumor mutation burden; TPS, tumor proportion score.

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