RATIONALE-307 Long-term Outcomes: First-line Tislelizumab (TIS) Plus Chemotherapy (chemo) vs Chemo Alone for Advanced Squamous (sq) NSCLC

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FPN: 1323P

13-17 SEP 2024
ESMO CONGRESS Barcelona Spain

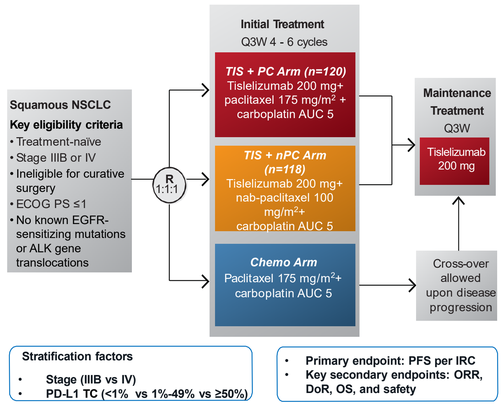
BACKGROUND

- Tislelizumab is a humanized monoclonal antibody with high affinity and binding specificity for 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-307 study (NCT03594747), tislelizumab + chemotherapy (chemo) significantly extended progression-free survival (PFS) vs chemo as first-line treatment in patients with advanced squamous NSCLC.[3]
- This study led to the approval of tislelizumab + chemo as a standard of care for squamous NSCLC in the first-line setting in China and Europe.
- Here we report the updated outcomes of RATIONALE-307 with approximately 4 years of follow-up.

METHODS

- Eligible patients with previously untreated advanced squamous NSCLC were randomized 1:1:1 to receive tislelizumab + chemo (two arms: tislelizumab + PC [paclitaxel and carboplatin], tislelizumab + nPC [nab-paclitaxel and carboplatin]) or chemo (PC) alone **(Fig. 1).**
- Patients allocated to the chemo arm were allowed to cross over to tislelizumab monotherapy upon disease progression.
- Patients with long-term exposure (LTE) to tislelizumab were defined as those who received ≥35 cycles of tislelizumab treatment.
- Biomarker testing was performed on baseline tumor samples, including PD-L1 protein expression (VENTANA PD-L1 [SP263] assay), tumor mutational burden (TMB), genomic alterations (OncoScreen Plus), and gene expression profiling (EdgeSeq Precision IO Panel).

Figure 1. Study design



Abbreviations

AUC, Area Under the Curve; Chemo, chemotherapy; CI, confidence interval; D, day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group; HR, hazard ratio; im-AE, immune-mediated adverse event; IRC, independent review committee; ITT, intention-to-treat; LTE, long-term exposure; mo, months; nPC, nab-paclitaxel and carboplatin; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PC, paclitaxel and carboplatin; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; sq, squamous; TC, tumor cell; TIS, tislelizumab; TMB, tumor mutation burden.

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Acknowledgments: We would like to thank the investigators, the site support staff, and especially the patients for participating in this study. This study was sponsored by BeiGene.

Declaration of interests: Dr Zhijie Wang declares no potential conflict of interest.

CONCLUSIONS

- **Tislelizumab + chemo maintained long-term clinical meaningful survival benefits compared with chemo alone, with no new safety signals, despite a high in-study cross-over rate of 58.7%**
  - **4-yr OS rates: 32.2% with tislelizumab + PC vs 26.0% with tislelizumab + nPC vs 19.2% with chemo alone**
- **Patients with long-term exposure (≥35 cycles) to tislelizumab achieved high ORR and long-term survival, with higher expression of PD-L1 and T cell inflammation signature, as well as a FAT1 enriched mutational profile**

RESULTS

Patients

- 360 patients were randomly assigned (tislelizumab + PC, n=120; tislelizumab + nPC, n=119; chemo, n=121).
- As of April 28, 2023, median time from randomization to data cutoff was 50.3 mo (range, 46.5-57.0).

Updated efficacy and safety

- Clinically meaningful OS improvement with tislelizumab + chemo was well maintained vs. chemo alone with extended follow-up
  - Tislelizumab + PC vs. chemo: median 26.1 mo vs 19.4 mo; HR 0.67 (95% CI, 0.49 - 0.92) (**Fig. 2A**)
  - Tislelizumab + nPC vs. chemo: median 23.3 mo vs 19.4 mo; HR 0.82 (95% CI, 0.60 - 1.11) (**Fig. 2B**)
- OS benefit with tislelizumab + chemo was sustained, with 4-year OS rates of 32.2% (95% CI, 23.8 - 40.9) and 26.0% (95% CI, 18.3 - 34.4), versus 19.2% (95% CI, 12.0 - 27.7), respectively (**Fig. 2**).
- In the chemo arm, 77 (63.6%) patients received subsequent anti-PD-(L)1 therapy, including 71 (58.7%) who crossed over to tislelizumab in-study; analyses adjusted for in-study cross-over effect with the two-stage method further confirmed the OS benefits with tislelizumab + chemo (cross-over adjusted median OS of chemo: 16.0 mo; HRs 0.53 and 0.65, respectively; **Fig. 3A & B**).
- PFS benefits with tislelizumab + chemo vs. chemo were also maintained at this updated analysis (**Fig. 4**).
- Tislelizumab plus chemotherapy was tolerable, with no new safety signals identified with extended follow-up.

Figure 2. Kaplan-Meier curves of OS

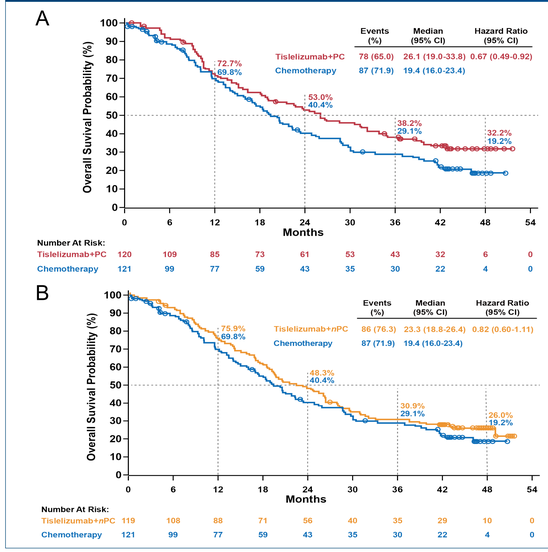


Figure 3. Kaplan-Meier curves of two-stage-adjusted OS

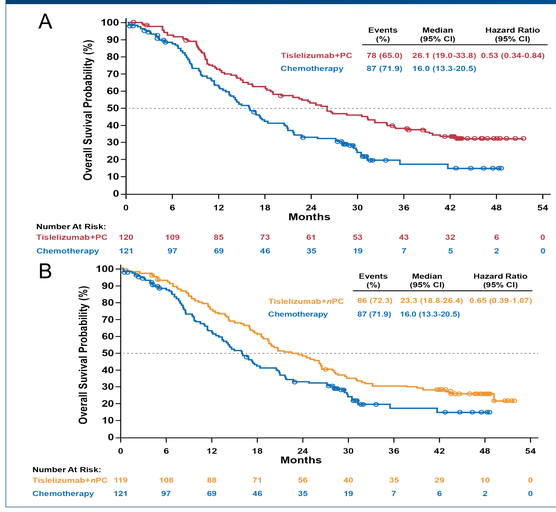
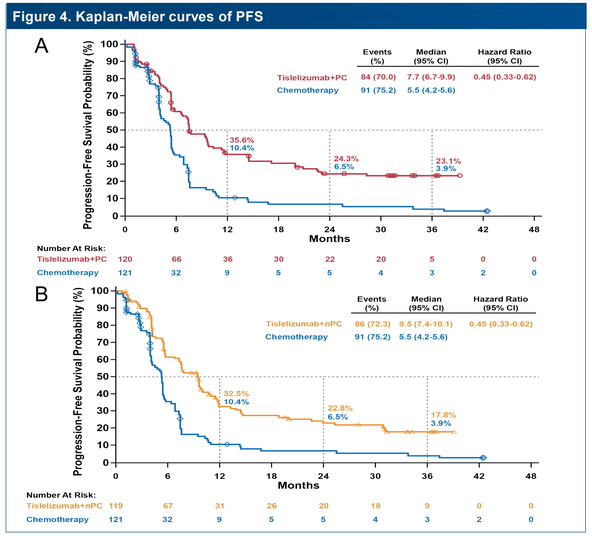


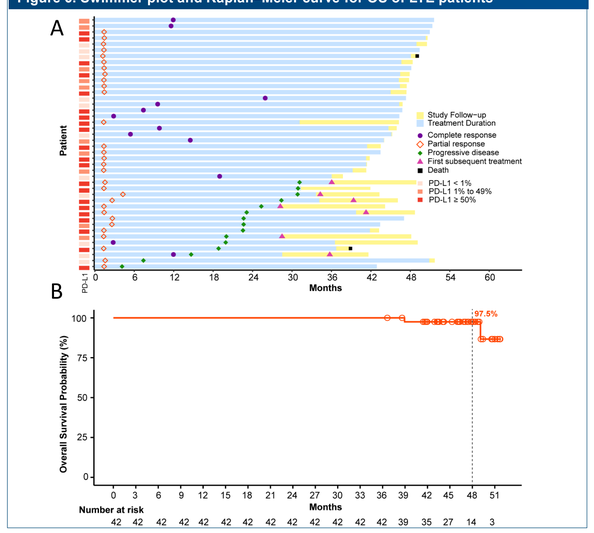
Figure 4. Kaplan-Meier curves of PFS



Outcomes in patients who received ≥35 cycles of tislelizumab

- A total of 42 (17.6%) patients received ≥35 cycles of tislelizumab (LTE) in tislelizumab + chemo arms, with a median of 58 (range 37-71) treatment cycles .
- 73.8% of patients had PD-L1 TC ≥1% (TC ≥50%, 50.0%), and 26.2% patients had PD-L1 TC <1%. Other baseline characteristics were generally similar to the total ITT population of tislelizumab plus chemo arms.
- ORR was 100% (CR, n=11; PR, n=31; **Fig. 6A**), and median DOR was not reached.
- Median OS was not reached. 4-year OS rate was 97.5% (95% CI, 83.5%-99.6%) (**Fig. 6B**).
- The profile of imAEs in LTE patients was similar to the overall population of tislelizumab + chemo arms.

Figure 6. Swimmer plot and Kaplan–Meier curve for OS of LTE patients



Molecular features of LTE patients in tislelizumab + chemo arms

- The baseline tumor tissues from LTE patients had higher PD-L1 expression and T cell inflammation signature levels, while the TMB status was similar between LTE vs non-LTE **(Fig.7A)**
- FAT1 alterations were enriched in LTE vs non-LTE (34.6% vs 15.4%, *P*=0.028); A numerically lower frequency was observed in NFE2L2, KEAP1, STK11, JAK1/2, and B2M in LTE vs non-LTE **(Fig.7B)**

Figure 7. Molecular features in LTE patients in tislelizumab + chemo arms