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

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Background

First-line TIS + chemo has improved PFS vs chemo alone for advanced sq-NSCLC in RATIONALE-307 (NCT03594747). Here, we reported the long-term outcomes in the ITT population and in patients (pts) with long-term exposure (LTE) to TIS.

Methods

Pts were randomized 1:1:1 to receive TIS + paclitaxel + carboplatin (T+PC arm), TIS + *nab*-paclitaxel + carboplatin (T+nPC arm), or paclitaxel + carboplatin (PC arm). The primary endpoint was PFS; OS was a secondary endpoint. Crossover from PC arm to TIS monotherapy was permitted after PD, OS was adjusted by two-stage method. LTE was defined as ≥35 cycles of TIS treatment. PD-L1 expression, TMB, gene expression profiling, and genetic alterations were assessed on baseline tumor samples.

Results

Among the 360 randomized pts (T+PC arm, n=120; T+nPC arm, n=119; PC arm, n=121), median time from randomization to data cutoff (Apr 28, 2023) was 50.3 mo (range, 46.5-57.0). 58.7% (71/121) of pts crossed over to receive TIS monotherapy. The improvement in PFS with TIS + chemo vs chemo (mPFS, 5.5 mo) was maintained, with mPFS of 7.7 mo (HR, 0.45; 95% CI 0.33-0.62) for T+PC and 9.5 mo (HR, 0.45; 95% CI 0.33-0.62) for T+nPC. Median OS was 26.1 vs 19.4 mo with T+PC vs PC (HR, 0.67; 95% CI 0.49-0.92), and 23.3 vs 19.4 mo with T+nPC vs PC (HR, 0.82; 95% CI, 0.60-1.11). 4-y OS rates were 32.2% for T+PC, 26.0% for T+nPC, and 19.2% for PC. After adjusting for the in-study crossover effect, the stratified HRs were 0.53 (95% CI 0.34-0.84) and 0.65 (95% CI 0.39-1.07), respectively. 42 (17.6%) pts with LTE were observed in TIS+chemo arms, with median treatment cycles of 58 (range 37-71), 4-y OS rate of 97.5%, and ORR of 100% (CR, n=11; PR, n=31). The profile of imAEs in LTE pts was similar to the overall population of TIS + chemo arms. Higher PD-L1 expression, tumor inflammation signature levels (TISL), and enriched *FAT1* mutations (LTE vs non-LTE, 34.6% [9/26] vs 15.4% [23/149]) were observed in LTE pts.

Conclusions

The OS benefit favoring TIS + chemo was well maintained, with clinically promising 4-y OS rates of 32.2% with T+PC and 26.0% withT+nPC. LTE pts achieved higher ORR and long-term survival, with higher baseline PD-L1 expression and TISL; the *FAT1* mutation may play an indicative role for LTE, which needs to be further explored.