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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ABSTRACT

Background: First-line TIS + chemo improved PFS vs chemo in patients (pts) with metastatic NSQ NSCLC without sensitizing EGFR/ALK alterations in the RATIONALE-304 study (NCT03663205). Here, we reported updated results with around 4-year follow-up and outcomes of pts with long-term exposure (LTE) to TIS.

Methods: Pts were randomized 2:1 to receive 4–6 cycles of TIS + carboplatin/cisplatin and pemetrexed or chemo alone every 3 weeks, followed by maintenance TIS + pemetrexed or pemetrexed only, until PD/unacceptable toxicity. The primary endpoint was PFS assessed by IRC; secondary points included OS and safety. Crossover from the chemo 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 334 randomized pts (TIS + chemo, n = 223; chemo, n = 111) in the ITT population, median time from randomization to data cutoff (Apr 26, 2023) was 49.4 mo (range, 44.9–57.1). 37.8% (42/111) of pts crossed over to receive TIS monotherapy. Median PFS was 9.8 vs 7.6 mo with TIS + chemo vs chemo (HR, 0.61, 95% CI 0.46–0.82). Median OS was 21.4 vs 20.1 mo (stratified HR, 0.87, 95% CI 0.65–1.17), with 4-Y OS rates of 32.8% vs 29.7%, respectively. After adjusting for the in-study crossover effect, the stratified OS HR was 0.67 (95% CI 0.48–0.95). 38 pts (17.0%) with LTE were observed in TIS + chemo arm, with median treatment cycles of 52.5 (range, 36–77), ORR of 100% (CR, n=10; PR, n=28), and 4-Y OS rate of 89.3%. The profile of imAEs in LTE pts was generally similar to the overall population of TIS + chemo arm. Higher PD-L1 expression, TMB, tumor inflammation signature levels (TISL), and a notable enrichment of LRP1B mutations in LTE-note (61.9%, 13/21) vs 14.0% (13/93)) were observed in LTE pts.

Conclusions: The OS benefit trend was well maintained, with a clinically promising 4-Y OS rate of 32.8% in TIS + chemo arm. Among pts in the TIS + chemo arm, LTE pts showed higher ORR and long-

term survival, with higher baseline PD-L1 expression, TMB, and TISL; the presence of LRP1B mutation may be an indicator for potential LTE of TIS treatment.