Randomized, phase 3 study of tislelizumab versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma (HCC): RATIONALE-301 age ≥65 years subgroup

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Abstract:

Background: HCC is one of the most commonly diagnosed cancers globally, with an increasing number of patients affected in the ≥65 years age group. In the phase 3, open-label RATIONALE-301 trial (NCT03412773), tislelizumab, a PD-1 inhibitor, showed non-inferior overall survival (OS) vs sorafenib (hazard ratio 0.85, 95% confidence interval [CI]: 0.71, 1.02) and a favorable safety profile in first-line treatment of patients with unresectable HCC. Here, we present results from the subgroup of patients aged ≥65 years in RATIONALE-301.

Method: Systemic therapy-naïve adults with histologically confirmed HCC (Barcelona Clinic Liver Cancer [BCLC] Stage C or Stage B that was not amenable to/progressed after loco-regional therapy, Child-Pugh A), with ≥1 measurable lesion (RECIST v1.1) and an ECOG PS ≤1 were randomized (1:1) to tislelizumab (200 mg intravenously every 3 weeks) or sorafenib (400 mg orally twice daily) until disease progression, intolerable toxicity, or withdrawal. The primary endpoint was OS; secondary endpoints included objective response rate (ORR) and progression-free survival (PFS) by blinded independent review committee, and safety.

Results: In total, 255 of the 674 randomized patients were in the ≥65 years subgroup (tislelizumab: n=134, sorafenib: n=121), with median (m) age of 71.0 years (range 65-86). At data cutoff (July 11, 2022), median survival follow-up was 38.9 months in the tislelizumab arm vs 39.9 months in the sorafenib arm. The majority of patients in the ≥65 years subgroup were enrolled in Europe/USA and Japan (66.3% vs 36.9%), had less advanced disease (BCLC Stage B: 33.3% vs

22.3%; Stage C: 66.7% vs 77.7%; extrahepatic spread: 51.4% vs 61.9%; distant metastases: 49.0% vs 58.5%), more satisfactory performance status (ECOG PS 0: 61.2% vs 54.0%), and fewer viral infections (uninfected: 41.6 % vs 24.0%) vs the overall population, respectively. Patients in the ≥65 years subgroup had a numerically longer mOS (18.2 months [95% CI: 11.6, 24.2] vs 14.2 months [95% CI: 10.5, 19.2]) in the tislelizumab vs sorafenib arm, respectively; mOS in the ≥65 years subgroup was longer than in the overall population (15.9 months [95% CI: 13.2, 19.7] vs 14.1 months [95% CI: 12.6, 17.4]) in the tislelizumab arm only. Patients in the ≥65 years subgroup had a higher confirmed ORR (18.7% vs 4.1%; odds ratio 5.4 [95% CI: 2.0, 14.7]) and shorter mPFS (3.1 months [95% CI: 2.1, 4.2] vs 3.9 months [95% CI: 2.3, 5.4]) in the tislelizumab vs sorafenib arm, respectively. Similar to the overall population, tislelizumab-treated patients in the ≥65 years subgroup experienced lower incidences of ≥grade 3 treatment-emergent adverse events (46.6% vs 62.5%) and ≥grade 3 treatment-related adverse events (20.3% vs 52.5%) vs sorafenib-treated patients.

Conclusions: In the subgroup of patients aged ≥65 years in the RATIONALE-301 trial, tislelizumab demonstrated numerically longer mOS and a higher ORR vs sorafenib; the longer mOS observed with tislelizumab in this subgroup vs the overall population could be attributed to regional imbalances and more favorable baseline characteristics observed in the subgroup. Tislelizumab showed a favorable safety profile vs sorafenib in the ≥65 years subgroup, consistent with the overall population.