

Final Analysis of RATIONALE-301: Randomized, Phase 3 study of tislelizumab versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma

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**Introduction:** Tislelizumab (TIS), an anti-PD-1 monoclonal antibody, has demonstrated durable responses and was well tolerated as monotherapy in 2L+ treatment in patients (pts) previously treated systemically for unresectable HCC (Ducreux et al, 2021). TIS has been further evaluated against sorafenib (SOR) in a global randomized Phase 3 study (RATIONALE-301; NCT03412773) as 1L treatment in adult pts with unresectable HCC.

**Methods:** Systemic therapy-naïve adults with histologically confirmed HCC BCLC Stage B/C who were not amenable to or progressed after loco-regional therapy, Child-Pugh A, with  $\geq 1$  measurable lesion per RECIST v1.1, and an ECOG PS  $\leq 1$  were eligible. Pts were randomized 1:1 to receive TIS (200 mg IV Q3W) or SOR (400 mg PO BID) until disease progression, intolerable toxicity, withdrawal, or no longer benefiting from therapy. The primary endpoint was OS; secondary endpoints included ORR, PFS, and DOR by blinded independent review committee, and safety. Non-inferiority of OS between TIS and SOR was tested against the non-inferiority margin of 1.08.

**Results:** A total of 674 pts were randomized (n=342, TIS; n=332, SOR); at data cutoff (11 Jul 2022) minimum study follow up was 33 months (mo). In this final analysis, RATIONALE-301 met its primary endpoint of OS non-inferiority (mOS: 15.9 mo [TIS] vs 14.1 mo [SOR]; stratified HR: 0.85 [95.003% CI: 0.712, 1.019]). TIS was associated with higher ORR (14.3% vs 5.4%) and more durable responses (mDoR: 36.1 mo vs 11.0 mo) compared with SOR. Median PFS with TIS was 2.2 mo and 3.6 mo with SOR (HR: 1.1 [95% CI: 0.92, 1.33]). Median treatment duration was longer with TIS vs SOR (4.1 mo vs 2.7 mo). The safety profiles for both treatments were consistent with prior reports. Incidence rates of grade  $\geq 3$  AEs (48.2% vs 65.4%) and AEs leading to discontinuation (10.9% vs 18.5%) were lower with TIS compared with SOR; AEs leading to death were low across both treatments (4.4%, TIS; 5.2%, SOR). Immune-mediated AEs occurring in  $\geq 5\%$  TIS-treated pts were hepatitis (5.3%) and hypothyroidism (5.3%).

**Conclusions:** Single-agent TIS demonstrated clinically meaningful OS benefit that was non-inferior to SOR with a favorable safety profile as a 1L treatment option for pts with unresectable HCC.