Association of tumor response with survival in patients with unresectable hepatocellular carcinoma treated with first-line tislelizumab versus sorafenib: Results from the RATIONALE-301 study

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Background and aims: Tislelizumab (TIS) is a monoclonal antibody with high affinity and binding specificity to programmed cell death protein 1. In RATIONALE-301 (NCT03412773) TIS was non-inferior to sorafenib (SOR) for overall survival (OS) as first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (HCC); OS superiority vs SOR was not met. We evaluated the association of response with survival in pts from the RATIONALE-301 study.

Methods: In this phase 3, open-label study, systemic therapy-naïve adult pts with histologically confirmed Barcelona Clinic Liver Cancer Stage B/C HCC were randomized (1:1) to receive TIS (200 mg intravenous every 3 weeks) or SOR (400 mg orally twice daily) until disease progression, intolerable toxicity, or withdrawal. The primary endpoint was OS; secondary efficacy endpoints included progression-free survival (PFS) and best overall response (BOR; per RECIST v1.1) by blinded independent review committee. We assessed OS and PFS according to BOR (complete response [CR] vs partial response [PR] vs stable disease [SD] vs progressive disease [PD]). Limitation of this analysis is related to its retrospective nature.

Results: Overall, 674 pts were randomized (TIS: n = 342; SOR: n = 332). At data cutoff (Jul 11, 2022), minimum study follow up was 33 months. Pt characteristics were generally balanced at baseline in both arms. Survival outcomes across response categories are presented in the table. Response was associated with longer median OS and PFS for

both arms. The OS rate at 24 months was higher in responders treated with TIS vs SOR (TIS; OS: 91.7%, 95% CI: 79.4, 96.8; SOR; OS: 72.2%, 95% CI: 45.6, 87.4).

Conclusions: Though there are limitations in the analysis, response achieved on treatment with TIS was associated with better survival vs SOR, in pts with unresectable HCC.

Table:

	Tislelizumab (n = 342)			**Sorafenib (n = 332)**			**Hazard Ratio***	
	n (%)	**mOS, mo (95% CI)**	**mPFS, mo (95% CI)**	**n (%)**	**mOS, mo (95% CI)**	**mPFS, mo (95% CI)**	**OS (95% CI)**	**PFS (95% CI)**
Responders	49 (14.3)	NE (NE, NE)	38.2 (21.7, NE)	18 (5.4)	38.8 (21.9, NE)	15.9 (10.4, 32.4)	0.34 (0.14, 0.80)	0.38 (0.18, 0.79)
Non-responders	274 (80.1)	13.3 (11.0, 15.9)	2.1 (2.1, 2.1)	280 (84.3)	14.1 (13.1, 17.4)	2.5 (2.1, 4.1)	1.00 (0.83, 1.21)	1.43 (1.18, 1.73)
CR	10 (2.9)	NE	NE (28.2, NE)	1 (0.3)	NE	NE	NE	NE
PR	39 (11.4)	NE	29.5 (13.1, 45.0)	17 (5.1)	38.8 (19.0, NE)	13.3 (10.4, 19.0)	0.41 (0.17, 0.96)	0.50 (0.24, 1.04)
SD	94 (27.5)	24.0 (19.4, 29.3)	4.9 (4.2, 6.2)	139 (41.9)	19.1 (15.2, 21.7)	6.5 (6.2, 8.2)	0.73 (0.54, 1.00)	1.23 (0.88, 1.71)
PD	169 (49.4)	9.9 (8.6, 10.9)	2.0 (2.0, 2.1)	121 (36.4)	10.4 (7.6, 13.4)	2.1 (2.0, 2.1)	1.05 (0.81, 1.35)	1.13 (0.89, 1.42)

**Unstratified hazard ratio of tislelizumab vs sorafenib*
CI, confidence interval; CR, complete response; NE, not estimable; mo, months; mOS, median overall survival; PD, progressive disease; mPFS, median progression-free survival; PR, partial response; SD, stable disease