

RATIONALE-305: Post-treatment immuno-oncology (IO) adjustment analysis to assess tislelizumab (TIS) treatment (tx) effect vs placebo (PBO)

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Background

In the phase 3 RATIONALE-305 trial (NCT03777657), patients (pts) with HER2– unresectable locally advanced gastric or gastroesophageal junction cancer (aG/GEJC) were randomized 1:1 to 1L TIS or PBO + chemotherapy (CT; capecitabine [CAP] + oxaliplatin [OX] or cisplatin + 5-fluorouracil; ≤6 cycles, optional CAP continuation for CAPOX recipients). TIS + CT improved OS vs PBO + CT despite a higher rate of subsequent IO (S-IO) tx usage in the control arm (TIS + CT, 65 [13.0%] vs PBO + CT, 98 [19.8%]). S-IO tx can diminish the observed OS difference between the tx and control arms (ATTRACTION-4 study; Kang *Lancet Oncol* 2022) and obscure the tx effect. Here we present a post hoc analysis evaluating the effect of S-IO tx usage on survival in RATIONALE-305.

Methods

Data cutoff date: 28 Feb 2024. Baseline (BL) and efficacy data from pts who were alive at the termination of per-protocol tx (post-progressive disease [PD] OS >0) were analyzed. Pts were stratified by S-IO usage (Yes [2L and 3L only] vs No). Two-stage method was applied to estimate the counterfactual OS by assuming no S-IO received in two arms; hazard ratio (HR) in ITT population was also reported.

Results

A total of 894 pts were analyzed (TIS + CT, n = 437; PBO + CT, n = 457). Differences between pts who did vs did not receive S-IO were observed (**Table**). In the PBO + CT group: median OS (95% CI) was prolonged in the S-IO arm (16.9 [15.0-24.0] mo) vs the No S-IO arm (12.7 [11.9-14.0] mo); post-PD median OS (95% CI) favored pts who received S-IO (11.7 [8.7-14.0] mo) vs No S-IO (6.0 [5.5-7.6] mo). The same pattern was observed for the TIS +CT arm. Two-stage adjusted OS showed that HR (95% CI) further favored TIS tx: adjusted, 0.77 (0.67-0.88) vs unadjusted, 0.79 (0.69-0.90).

Conclusions

In RATIONALE-305, S-IO usage was more prevalent in Asia and pts with a lower disease burden. S-IO usage resulted in a narrowing of the magnitude of benefit between TIS and PBO arms. This analysis suggests a greater tx effect of TIS in pts with aG/GEJC.

Table

Parameter	Tis		PBO	
	No S-IO n=389	S-IO n=48	No S-IO n=375	S-IO n=82
Age, median, y	60.0	55.0	61.0	61.0
<65 y	267 (68.6)	35 (72.9)	238 (63.5)	56 (68.3)
Male	269 (69.2)	28 (58.3)	267 (71.2)	55 (67.1)
Region: East Asia	290 (74.6)	46 (95.8)	274 (73.1)	75 (91.5)
≥3 metastatic sites	127 (32.6)	18 (37.5)	125 (33.4)	21 (25.6)
Liver met	155 (39.8)	12 (25.0)	142 (37.9)	31 (37.8)
Peritoneal met	164 (42.2)	28 (58.3)	164 (43.7)	33 (40.2)
Primary tumor site: GEJ	73 (18.8)	7 (14.6)	70 (18.7)	19 (23.2)
PD-L1 TAP score ≥5%	217 (55.8)	22 (45.8)	201 (53.6)	48 (58.5)
Prior (neo)adjuvant tx or surgery	120 (30.8)	24 (50.0)	125 (33.3)	31 (76.8)
ORR, % [95% CI]	48.1 (43.2-53.0)	52.1 (38.3-65.5)	40.3 (35.4-45.3)	47.6 (37.1-58.2)
n (%) unless stated				