Tislelizumab (TIS; BGB-A317) plus chemotherapy (CT)/chemoradiotherapy (CRT) as positron emission tomography (PET)-guided neoadjuvant (n) treatment (tx) for resectable esophageal squamous cell carcinoma (R-ESCC): RATIONALE-213 final analysis

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Background: Studies have shown overall survival improvements with nCRT + surgery vs surgery alone in locally advanced ESCC. However, preoperative CRT may have additional safety concerns, leading to some patients (pts) receiving nCT rather than nCRT. PET-computed tomography maximum standardized uptake value (SUV_{max}) change after induction CT (IC) has been shown to have reliable predictive value of pathological complete response (pCR) for R-ESCC in pts with nCRT and may optimize neoadjuvant tx selection. TIS (anti-PD-1) has improved survival in pts with ESCC. We report the final analysis of RATIONALE-213, a phase 2, open-label, multicenter study in China evaluating PET-guided nTIS + CT/CRT in R-ESCC (NCT04974047).

Methods: Eligible adult pts had histologically confirmed R-ESCC (cT1-2N + M0 or cT3N any M0), ECOG performance status 0/1, adequate organ function, no fistula risk, and had received no prior tx. Pts had a baseline (BL) PET scan, 1 cycle of IC (cisplatin-paclitaxel [Cis-Pac]), and a PET scan 15-21 days later. Pts were grouped into 2 cohorts by response to IC based on the percentage decrease in 2nd PET SUV_{max} in the primary tumor: responders (R, ≥35%) or nonresponders (NR, <35%). Both cohorts received 3 cycles of TIS 200 mg IV Q3W, the first 2 with CT (2 cycles Cis-Pac) for R, or with CRT (2 cycles investigator [Inv]-chosen CT [Cis-Pac, or 5-FU + Cis] + RT [40 Gy/20 fractions]) for NR, then surgery.

Primary endpoint was pCR per local pathologist. Secondary endpoints were 1-year disease-free survival (DFS), 1-year event-free survival (EFS), objective response rate (ORR) before surgery, R0 resection rate by Inv, and safety.

Results: Of 70 pts enrolled, 15 (21.4%), 48 (68.6%), and 7 (10.0%) had stage II, III, and IVA disease at BL, respectively. As of 25 Oct 2024 (median follow-up 25.5 mo), 30 pts were R and 40 NR. Of R, 20 (66.7%) had surgery. Of NR, 32 (80.0%) had surgery. Efficacy endpoints are shown in the table. Median DFS and EFS were not reached for R and NR. Grade ≥3 treatment-related adverse events (TRAEs) in R (15 [50.0%]) and NR (33 [82.5%]) were consistent with known CT or CRT toxicity; serious TRAEs occurred in 5 R (16.7%) and 7 NR (17.5%). No TRAEs led to surgery cancellation or death.

	R	NR
pCR,[a] n (%)	6 (30.0)	11 (34.4)
(95% CI)	(11.9, 54.3)	(18.6, 53.2)
1-year DFS,[b] %	79.0	74.2
(95% CI)	(47.9, 92.7)	(53.3, 86.8)
1-year EFS,[c] %	87.1	67.8
(95% CI)	(64.3, 95.8)	(48.3, 81.2)
R0 resection,[a] n (%)	19 (95.0)	29 (90.6)
ORR,[d] n (%)	15 (71.4)	14 (42.4)

[a]Efficacy analysis set (EAS) R=20; NR=32
[b]EAS with R0 resection R=19; NR=29
[c]Safety analysis set (SAS) R=30; NR=40
[d]SAS with measurable disease at BL R=21; NR=33

Conclusions: A PET-guided approach may help optimize neoadjuvant tx of R-ESCC. nTIS + CT/CRT showed promising efficacy and a tolerable safety profile in both responders and nonresponders.