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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CONCLUSIONS

- The RATIONALE-213 study final analysis results demonstrate that PET-guided neoadjuvant treatment with TIS plus CT or CRT exhibits promising efficacy for R-ESCC, with pathological complete response (pCR) rates of 30.0% and 34.4% in PET-CT–assessed responders and nonresponders
- The safety/tolerability profile of TIS plus CT or CRT was tolerable, with no new signals reported
- Our findings support that a PET-CT–guided approach may help optimize neoadjuvant treatment of R-ESCC

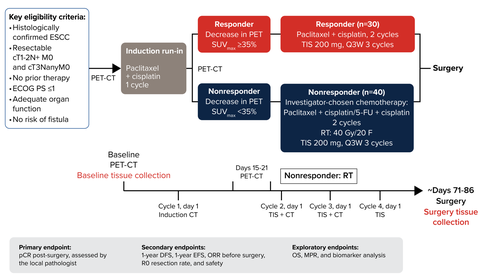
INTRODUCTION

- Preoperative CRT followed by surgical resection is the recommended standard of care for locally advanced R-ESCC.[1] However, preoperative CRT may have additional safety concerns, leading to some patients receiving neoadjuvant CT rather than neoadjuvant CRT[2]
- PET-CT–assessed response, particularly changes in maximum standardized uptake value (SUV_{max}) after induction CT, has shown predictive value for pCR, potentially optimizing neoadjuvant treatment selection[3]
- TIS has been shown to improve survival outcomes in patients with advanced or metastatic ESCC[4,5]
- Here, we report the final analysis of the RATIONALE-213 study

METHODS

- RATIONALE-213 (NCT04974047) was a phase 2, multicenter study conducted in China that evaluated the efficacy and safety of PET-CT–guided neoadjuvant TIS + CT/CRT in patients with R-ESCC (**Figure 1**)

Figure 1. Study Design



Abbreviations: 5-FU, 5-fluorouracil; cT, clinical primary tumor; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; F, fraction; M0, no distant metastasis; MPR, major pathological response; N, regional lymph nodes; ORR, objective response rate; OS, overall survival; Q3W, every 3 weeks; RT, radiotherapy.

RESULTS

Patient Disposition and Baseline Characteristics

- At data cutoff (October 25, 2024), median study follow-up time was 25.5 months (range: 3.6-37.3), and of the 70 patients enrolled, treatment was completed in 64 (91.4%) (29 responders [96.7%] and 35 nonresponders [87.5%])
- At initial diagnosis, the majority of enrolled patients (68.6%) had stage III disease (**Table 1**), and no patients had metastatic disease at study entry
- In general, patient demographic and baseline characteristics were representative of the target patient population
- Among the 30 responders, 29 (96.7%) completed three cycles of TIS and 27 (90.0%) completed CT. Among the 40 nonresponders, 34 (85.0%) completed three cycles of TIS and CT and 34 (85.0%) completed 40 Gy of radiotherapy
- Among responders, 20 (66.7%) underwent surgery, and among nonresponders, 32 (80.0%) underwent surgery
  - The primary reason that patients did not undergo surgery was patient refusal (responders n=6/10 and nonresponders n=5/8)

Table 1. Patient Demographic and Baseline Characteristics (Safety Analysis Set)

	Responders (n=30)	Nonresponders (n=40)	Total (N=70)
Median age, years (range)	67.5 (47-75)	63.5 (51-79)	64.0 (47-79)
Age ≥65, n (%)	18 (60.0)	16 (40.0)	34 (48.6)
Male, n (%)	24 (80.0)	38 (95.0)	62 (88.6)
ECOG performance status, n (%)			
0	15 (50.0)	17 (42.5)	32 (45.7)
1	15 (50.0)	23 (57.5)	38 (54.3)
Disease status at initial diagnosis, n (%)			
II	7 (23.3)	8 (20.0)	15 (21.4)
III	18 (60.0)	30 (75.0)	48 (68.6)
IVA	5 (16.7)	2 (5.0)	7 (10.0)
Primary location of esophageal cancer, n (%)			
Upper thoracic	3 (10.0)	8 (20.0)	11 (15.7)
Middle thoracic	16 (53.3)	16 (40.0)	32 (45.7)
Lower thoracic	10 (33.3)	15 (37.5)	25 (35.7)
Esophagogastric junction	1 (3.3)	1 (2.5)	2 (2.9)
PD-L1 expression, n (%)			
TAP score ≥10%	15 (50.0)	7 (17.5)	22 (31.4)
TAP score <10%	12 (40.0)	24 (60.0)	36 (51.4)
Unknown	3 (10.0)	9 (22.5)	12 (17.1)

Abbreviations: PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity.

Efficacy

- Clinical efficacy was observed in both responders and nonresponders, as evidenced by the pCR and MPR rates shown in **Table 2**
- High R0 resection rates were observed in both cohorts, indicating that the PET-CT–guided neoadjuvant treatment with TIS + CT in responders and TIS + CRT in nonresponders did not negatively affect surgical resection
- The ORR and percentages of residual viable tumor in responders and nonresponders are shown in **Table 2**
- Exploratory analysis showed a higher pCR rate in patients with a baseline tumor PD-L1 TAP score of ≥10% in both cohorts in the efficacy-evaluable analysis set
  - In responders, the pCR rates were 62.5% (95% confidence interval [CI]: 24.5, 91.5), 0.0% (95% CI: 0.0, 33.6), and 33.3% (95% CI: 0.8, 90.6) in patients with tumor PD-L1 scores of ≥10%, <10%, and unknown status, respectively
  - In nonresponders, the pCR rates were 50.0% (95% CI: 11.8, 88.2), 26.3% (95% CI: 9.1, 51.2), and 42.9% (95% CI: 9.9, 81.6) in patients with tumor PD-L1 scores of ≥10%, <10%, and unknown status, respectively
- Median OS in both responders and nonresponders was not reached. The 12-month OS rates are shown in **Table 2**

Table 2. Efficacy Outcomes

	Efficacy-Evaluable Analysis Set[a]	
	Responders (n=20)	Nonresponders (n=32)
pCR, n (%) [95% CI][b]	6 (30.0) [11.9, 54.3]	11 (34.4) [18.6, 53.2]
MPR, n (%)[c,d] [95% CI][b]	9 (45.0) [23.1, 68.5]	18 (56.3) [37.7, 73.6]
Percentage of residual viable tumor, n (%)		
0	6 (30.0)	11 (34.4)
0 to ≤10	3 (15.0)	7 (21.9)
10 to ≤25	1 (5.0)	1 (3.1)
25 to ≤50	3 (15.0)	4 (12.5)
>50	7 (35.0)	8 (25.0)
R0 resection, n (%)	19 (95.0)	29 (90.6)
	Safety Analysis Set With Measurable Disease at Baseline	
	Responders (n=21)	**Nonresponders (n=33)**
ORR, n (%)[e] [95% CI][b]	15 (71.4) [47.8, 88.7]	14 (42.4) [25.5, 60.8]
	Safety Analysis Set	
	Responders (n=30)	**Nonresponders (n=40)**
Median OS, months (95% CI)	NR (NE, NE)	NR (21.2, NE)
12-month OS rate, % (95% CI)	83.3 (64.5, 92.7)	76.9 (60.3, 87.3)

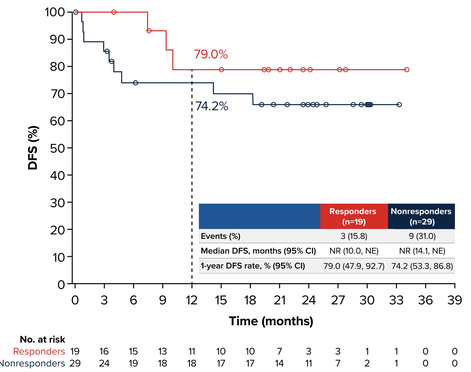
[a]The efficacy-evaluable analysis set included all patients who received neoadjuvant treatment followed by surgery. [b]95% CI was estimated using the Clopper–Pearson method. [c]MPR rate is defined as the proportion of patients with ≤10% residual viable tumor in the resected primary tumor and all resected lymph nodes after completion of neoadjuvant therapy. [d]One patient did not have disease stage and percentage of residual viable tumor information. [e]ORR is defined as the proportion of patients with PR or CR before surgery, as assessed by the investigator per RECIST v1.1.

Abbreviations: CR, complete response; NE, not estimable; NR, not reached; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

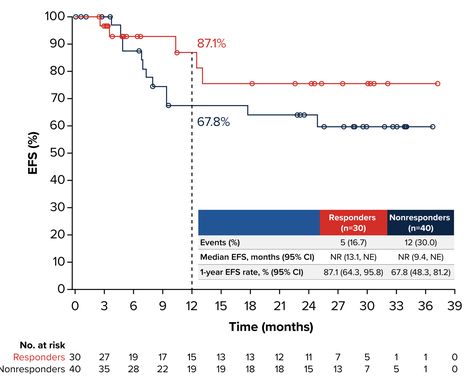
- The median investigator-assessed DFS in the efficacy-evaluable analysis set with R0 resection was not reached in both responders and nonresponders. The 1-year DFS rates in responders and nonresponders are shown in **Figure 2A**
- The median EFS in the safety analysis set was not reached in both responders and nonresponders. The 1-year EFS rates in responders and nonresponders are shown in **Figure 2B**

Figure 2. Kaplan–Meier Plots of Investigator-Assessed (A) DFS (Efficacy-Evaluable Analysis Set With R0 Resection) and (B) EFS (Safety Analysis Set)

A



B



DFS was defined as the time from the first date of no disease to local or distant recurrence or death due to any cause, whichever occurred first. EFS was defined as the time from first dose date to any of the following events, whichever occurred first: progression of disease that precluded definitive surgery, local or distant recurrence, or death due to any cause.

Safety/Tolerability Profile

- Treatment-emergent adverse events (TEAEs) were observed in most patients across both cohorts, with similar any-grade rates. Higher grade ≥3 and serious TEAEs were observed in nonresponders (**Table 3**)
- Treatment-related adverse events (TRAEs) were also common in both groups, with grade ≥3 and serious TRAEs occurring more frequently in nonresponders
  - Grade ≥3 TRAEs occurring in ≥10% of patients aligned with the known toxicity profiles of CT or CRT; the most commonly reported was neutrophil count decreased in both responders (36.7%) and nonresponders (70.0%)
  - Grade ≥3 TRAEs were primarily due to CT (50% of responders and 82.5% of nonresponders), whilst grade ≥3 TRAEs related to TIS were reported in 10% of responders and 22.5% of nonresponders
- No TRAEs leading to death were reported
- TEAEs led to any treatment discontinuation in a small proportion of patients in both groups
- TEAEs leading to surgery delay and TEAEs leading to surgery cancellation are reported in **Table 3**
- All immune-mediated adverse events (imAEs) were mild or moderate (grade 1 or 2) in severity; the most commonly reported imAE was rash in both responders (10.0%) and nonresponders (5.0%)

Table 3. Safety Summary (Safety Analysis Set)

	Responders (n=30)	Nonresponders (n=40)
Patients with any TEAEs, n (%)	30 (100.0)	39 (97.5)
Grade ≥3	24 (80.0)	34 (85.0)
Serious	8 (26.7)	12 (30.0)
Leading to death	0 (0.0)	2 (5.0)
Patients with any TRAEs, n (%)	28 (93.3)	39 (97.5)
Grade ≥3	15 (50.0)	33 (82.5)
Serious	5 (16.7)	7 (17.5)
TEAEs leading to any treatment discontinuation, n (%)	1 (3.3)	3 (7.5)
TEAEs leading to surgery cancellation, n (%)	1 (3.3)	0 (0.0)
TEAEs leading to surgery delay, n (%)	0 (0.0)	4 (10.0)

Adverse events were graded for severity using Common Terminology Criteria for Adverse Events v5.0. TRAEs included events considered by the investigator to be related to study treatments or with missing assessment of the causal relationship. Deaths here excluded those caused by disease under study.

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DISCLOSURES

ZZ, **LL**: Employment with BeOne Medicines and stock or other ownership; **AK**: Employment with BeOne Medicines (at the time of study) and stock or other ownership; **LC**, **YL**, **XY**, **MK**, **XM**, **LT**, **JL**, **HJ**: No disclosures.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeOne Medicines, Ltd. (formerly known as BeiGene, Ltd.). Medical writing support was provided by Nitya Venkataraman, PhD, of Parexel, and supported by BeOne Medicines.

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Presented at ASCO, May 30-June 3, 2025, Chicago, IL, USA