Tislelizumab Plus Chemotherapy/Chemoradiotherapy as Neoadjuvant Treatment for Resectable Esophageal Squamous Cell Carcinoma

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Conclusions

In patients with resectable esophageal squamous cell carcinoma (R-ESCC), tislelizumab plus chemotherapy/chemoradiotherapy demonstrated promising pathological complete response (pCR) rates in positron emission tomography/computed tomography (PET/CT)-assessed responders (chemotherapy cohort, 28.6%) and nonresponders (chemoradiotherapy cohort, 33.3%).

In the BGB-A317-213 study, tislelizumab plus chemotherapy/chemoradiotherapy showed a tolerable safety profile, with no new safety signals. The PET/CT-guided approach may help optimize neoadjuvant treatment for R-ESCC.

Background

For patients with locally advanced R-ESCC, preoperative chemoradiotherapy followed by esophagectomy is the current standard of care.[1] However, implementation of preoperative chemoradiotherapy is not satisfactory for various reasons, including greater safety concerns than with neoadjuvant chemotherapy alone.[2]

PET/CT-assessed response has been shown to be predictive of outcomes after induction chemotherapy,[3] and may help optimize neoadjuvant treatment selection in R-ESCC. Tislelizumab is an anti-programmed cell death protein 1 monoclonal antibody with high affinity to PD-1 that was designed to minimize Fc gamma receptor binding on macrophages.[4,5]

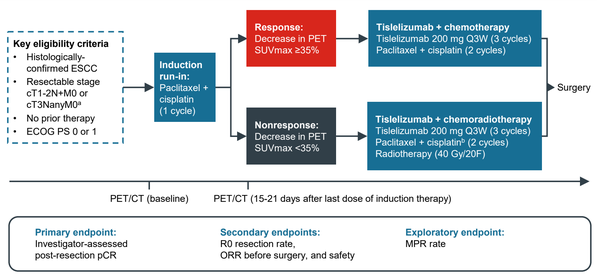
Tislelizumab has been shown to improve survival outcomes in patients with advanced or metastatic ESCC,[6,7] and has demonstrated encouraging antitumor activity when combined with chemotherapy as neoadjuvant therapy in patients with R-ESCC.[8]

BGB-A317-213 (NCT04974047) is an ongoing, phase 2, multicenter study conducted in China to investigate the efficacy and safety of PET/CT-guided neoadjuvant treatment with tislelizumab plus chemotherapy/chemoradiotherapy in patients with R-ESCC. We report primary analysis results.

Methods

- Patients with R-ESCC and no prior therapy were enrolled and, after a baseline PET/CT scan, received one cycle of induction paclitaxel plus cisplatin chemotherapy, followed by a second PET/CT scan (**Figure 1**)
- Patients were categorized into PET-assessed responder or nonresponder cohorts, and allocated to tislelizumab plus chemotherapy or tislelizumab plus chemoradiotherapy, respectively, followed by surgery (**Figure 1**)
- The primary endpoint was investigator-assessed post-resection pCR and secondary endpoints included R0 resection rate, objective response rate before surgery, and safety
- Major pathological response rate was assessed as an exploratory endpoint

Figure 1. Study Design



[a]By American Joint Committee on Cancer Staging Manual 8th Edition. [b]Investigators were also permitted to choose 5-fluorouracil plus cisplatin, but this option was not used. **Abbreviations:** ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; F, fraction; MPR, major pathological response; ORR, objective response rate; pCR, pathological complete response; PET/CT, positron emission tomography/computed tomography; Q3W, every 3 weeks; SUV, standardized uptake value.

Results

Baseline Characteristics and Treatment Exposure

- Of the 70 patients enrolled, most (68.6%) had stage III disease at initial diagnosis (**Table 1**)
- All patients received induction chemotherapy; 30 patients were PET/CT-assessed responders and 40 patients were nonresponders (**Table 1**)
- Among the 30 responders, 27 (90.0%) completed three cycles of tislelizumab and chemotherapy (paclitaxel and cisplatin)
- Among the 40 nonresponders, 32 (80.0%) completed three cycles of tislelizumab and chemotherapy (paclitaxel and cisplatin), and 34 (85.0%) completed 40 Gy of radiotherapy
- At data cutoff (April 17, 2023), median study follow-up time was 9.7 months (range: 3.6 to 19.9)

Table 1. Patient Baseline Characteristics (Safety Analysis Set)

	Responders (n=30)	Nonresponders (n=40)	Total (N=70)
Age			
Median, years (range)	67.5 (47-75)	63.5 (51-79)	64.0 (47-79)
Age ≥65 years, n (%)	18 (60.0)	16 (40.0)	34 (48.6)
Male, n (%)	24 (80.0)	38 (95.0)	62 (88.6)
ECOG PS, n (%)			
0	15 (50.0)	17 (42.5)	32 (45.7)
1	15 (50.0)	23 (57.5)	38 (54.3)
Disease stage 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)

Data cutoff: April 17, 2023. **Abbreviation:** ECOG PS, Eastern Cooperative Oncology Group performance status.

Efficacy

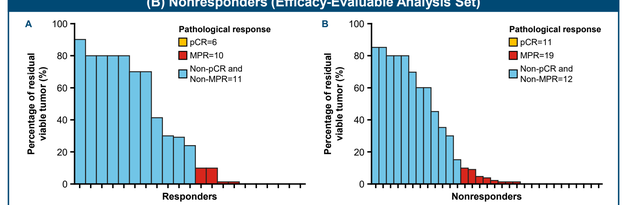
- Among the 30 responders, 21 underwent surgery, with a pCR rate of 28.6% (n=6/21; 95% CI: 11.3, 52.2) and a R0 resection rate of 95.2% (n=20/21) (**Table 2**)
- Among the 40 nonresponders, 33 underwent surgery, with a pCR rate of 33.3% (n=11/33; 95% CI: 18.0, 51.8) and a R0 resection rate of 90.9% (n=30/33) (**Table 2**)
- Percentage of residual viable tumor in responders and nonresponders is presented in **Figure 2**

Table 2. Efficacy Summary

	Responders (n=21)	Nonresponders (n=33)
Efficacy-Evaluable Analysis Set[a]		
pCR, n (%); [95% CI][b]	6 (28.6); [11.3, 52.2]	11 (33.3); [18.0, 51.8]
MPR,[c] n (%); [95% CI][b]	10 (47.6); [25.7, 70.2]	19 (57.6); [39.2, 74.5]
Percentage of residual viable tumor, n (%)		
0	6 (28.6)	11 (33.3)
0 to ≤10	4 (19.0)	8 (24.2)
10 to ≤25	1 (4.8)	1 (3.0)
25 to ≤50	3 (14.3)	3 (9.1)
>50	7 (33.3)	8 (24.2)
R0 resection, n (%)	20 (95.2)	30 (90.9)
Patients With Measurable Disease at Baseline in Safety Analysis Set[d]		
ORR,[e] n (%); [95% CI][b]	15 (71.4); [47.8, 88.7]	14 (42.4); [25.5, 60.8]
Best overall response, n (%)		
Complete response	1 (4.8)	3 (9.1)
Partial response	14 (66.7)	11 (33.3)
Stable disease	5 (23.8)	15 (45.5)
Progressive disease	1 (4.8)	1 (3.0)
Could not be determined[f]	0 (0.0)	3 (9.1)

Data cutoff: April 17, 2023. [a]Efficacy-evaluable analysis set includes all patients who receive neoadjuvant treatment followed by surgery; [b]95% CI was estimated using the Clopper-Pearson method. [c]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]Safety analysis set includes all enrolled patients who receive one or more dose of any component of study drugs; [e]ORR before surgery; [f]Included patients with no post-baseline response assessment or assessed as not evaluable per Response Evaluation Criteria in Solid Tumors version 1.1. **Abbreviations:** CI, confidence interval; MPR, major pathological response; ORR, objective response rate; pCR, pathological complete response.

Figure 2. Percentage of Residual Viable Tumor in (A) Responders and (B) Nonresponders (Efficacy-Evaluable Analysis Set)



Data cutoff: April 17, 2023. Data for two nonresponders were not reported; one patient had surgery performed at another hospital and the results were not available, another patient's pathological results were reported after data cutoff (non-pCR and non-MPR). **Abbreviations:** MPR, major pathological response; pCR, pathological complete response.

Safety

- Treatment-related treatment-emergent adverse events (TRAEs) of grade ≥3 were reported in 46.7% of responders and 82.5% of nonresponders (Table 3)
  - The profile of grade ≥3 TRAEs reported in ≥10% patients is in line with the known toxicity profile of chemotherapy or chemoradiotherapy, which included neutrophil count decreased (36.7%) among responders, and neutrophil count decreased (65.0%), white blood cell count decreased (47.5%), lymphocyte count decreased (17.5%), and anemia (12.5%) among nonresponders
  - The majority of grade ≥3 TRAEs were related to chemotherapy (46.7% in responders and 80.0% in nonresponders)
  - Treatment-emergent adverse events (TEAEs) related to tislelizumab of grade ≥3 were reported in 10.0% and 22.5% of patients in the responder and nonresponder cohorts, respectively
- No TRAEs leading to death were reported, few patients experienced TEAEs leading to treatment discontinuation or surgery delay, and no patients had surgery cancelled due to a TEAE
- All immune-mediated adverse events were grade 1 or 2

Table 3. Safety Summary (Safety Analysis Set)

Patients, n (%)	Responders (n=30)	Nonresponders (n=40)
TEAE of any grade	30 (100.0)	40 (100.0)
Treatment-related[a]	28 (93.3)	40 (100.0)
TEAE of grade ≥3	24 (80.0)	34 (85.0)
Treatment-related[a]	14 (46.7)	33 (82.5)
Serious TEAE	8 (26.7)	12 (30.0)
Treatment-related[a]	5 (16.7)	8 (20.0)
TEAE leading to death	1 (3.3)	1 (2.5)
Treatment-related[a]	0 (0.0)	0 (0.0)
TEAE leading to any treatment discontinuation	1 (3.3)	4 (10.0)
TEAE leading to surgery cancellation	0 (0.0)	0 (0.0)
TEAE leading to surgery delay	1 (3.3)	5 (12.5)
Immune-mediated adverse events	5 (16.7)	5 (12.5)

Data cutoff: April 17, 2023. Incidences of adverse events in responders and nonresponders are not suitable for direct comparison due to the limited sample sizes. [a]Any study treatment component related TEAEs, including tislelizumab, chemotherapy, or radiotherapy, excluding surgery. **Abbreviation:** TEAE, treatment-emergent adverse event.

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Disclosures

Longqi Chen is a principal investigator of BeiGene (institutional relationship with non-financial interests).