Tislelizumab in Combination With Chemotherapy as Treatment for Chinese Patients With Esophageal Squamous Cell Carcinoma (ESCC)

Jianming Xu[1], Nong Xu[2], Xianglin Yuan[3], Buhai Wang[4], Yuxian Bai[5], Enxiao Li[6], Xiang Li[7], Xin Wang[7]

[1]307 Hospital of the Chinese People's Liberation Army, Beijing, China; [2]The First Affiliated Hospital of Zhejiang University, Hangzhou, China; [3]Tongji Hospital, Wuhan, China; [4]Northern Jiangsu People's Hospital, Yangzhou, China; [5]Harbin Medical University Cancer Hospital, Harbin, China; [6]First Affiliated Hospital of Xi'an Jiao Tong University, Xi'an, China; [7]BeiGene(Beijing) Co., Ltd., Beijing, China

2019 年 CSCO 年会 厦门

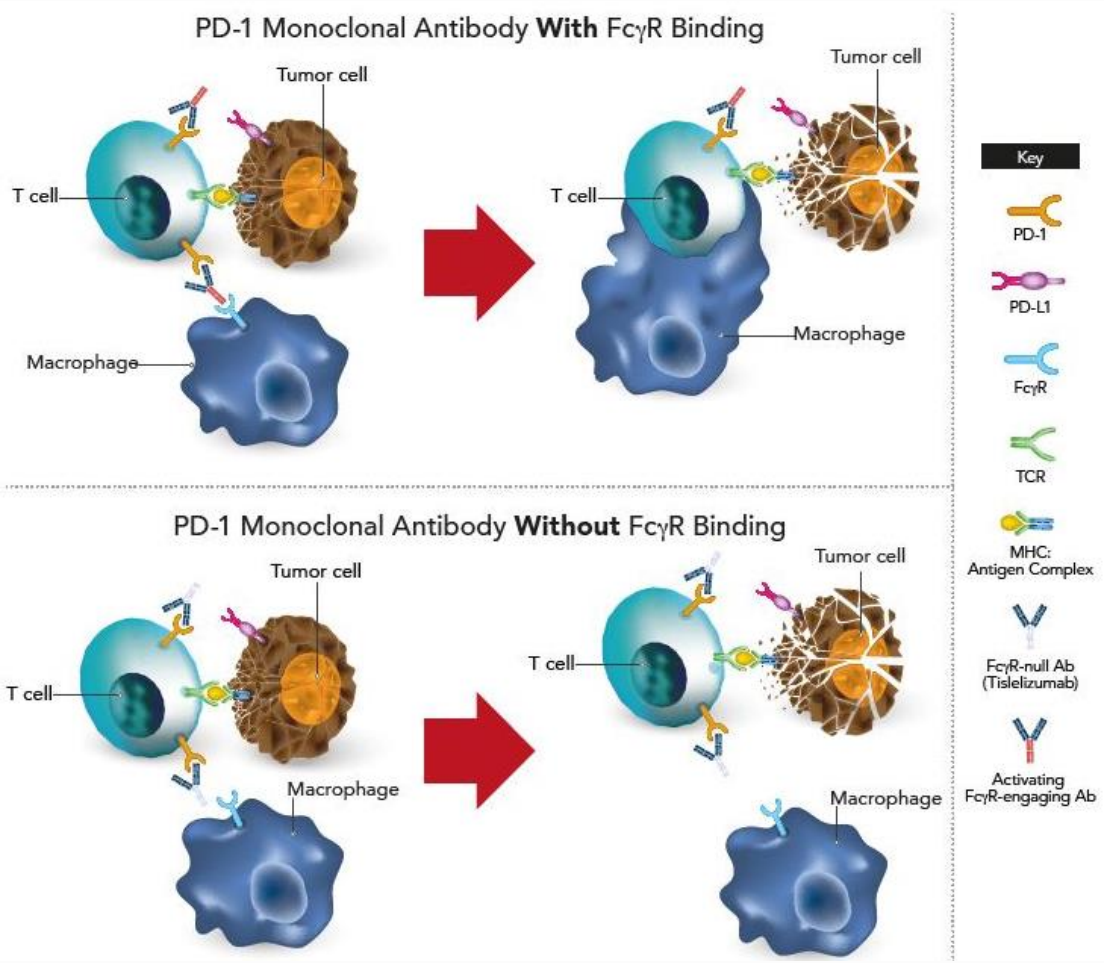
Esophageal Squamous Cell Carcinoma

- Esophageal cancer is the seventh most common cancer worldwide and the sixth most common cause of cancer-related deaths[1]
  - Esophageal squamous cell carcinoma (ESCC) remains the predominant histological subtype and has a higher prevalence in Asian countries[2,3]
  - Chemotherapy is the standard first-line treatment for patients with ESCC, but is associated with poor prognosis[4,5]
- Anti-PD-1 antibodies have demonstrated promising antitumor activity and manageable safety in patients with advanced unresectable or metastatic ESCC[6,7]
- There are no reported results evaluating anti-PD-1 antibodies in combination with chemotherapy for the first-line treatment of advanced ESCC

1. Bray F, et al. *CA Cancer J Clin.* 2018;68(6):394-424; 2. Arnold M, et al. *Gut*. 2015;64(3):381-387; 3. Abbas G, Krasna M. *Ann Cardiothorac Surg.* 2017;6(2):131-136; 4. Ajani JA. *J Natl Compr Canc Netw*. 2019;17(7):855-883; 5. Kojima T and Doi T. *Curr Oncol Rep.* 2017;19(5):33; 6. Kojima T, et al. *J Clin Oncol*. 2019;37(suppl 4):2; 7. Doi T, et al. *J Clin Oncol.* 2018;36:61-67.

Tislelizumab: A Uniquely Engineered Anti-PD-1 Monoclonal Antibody

- Tislelizumab is an investigational humanized IgG4 monoclonal antibody with high affinity/specificity for PD-1[1]
- Tislelizumab was engineered to minimize binding to FcγR on macrophages, in order to abrogate antibody-dependent phagocytosis, a potential resistance to anti-PD-(L)1 therapy[1,2]

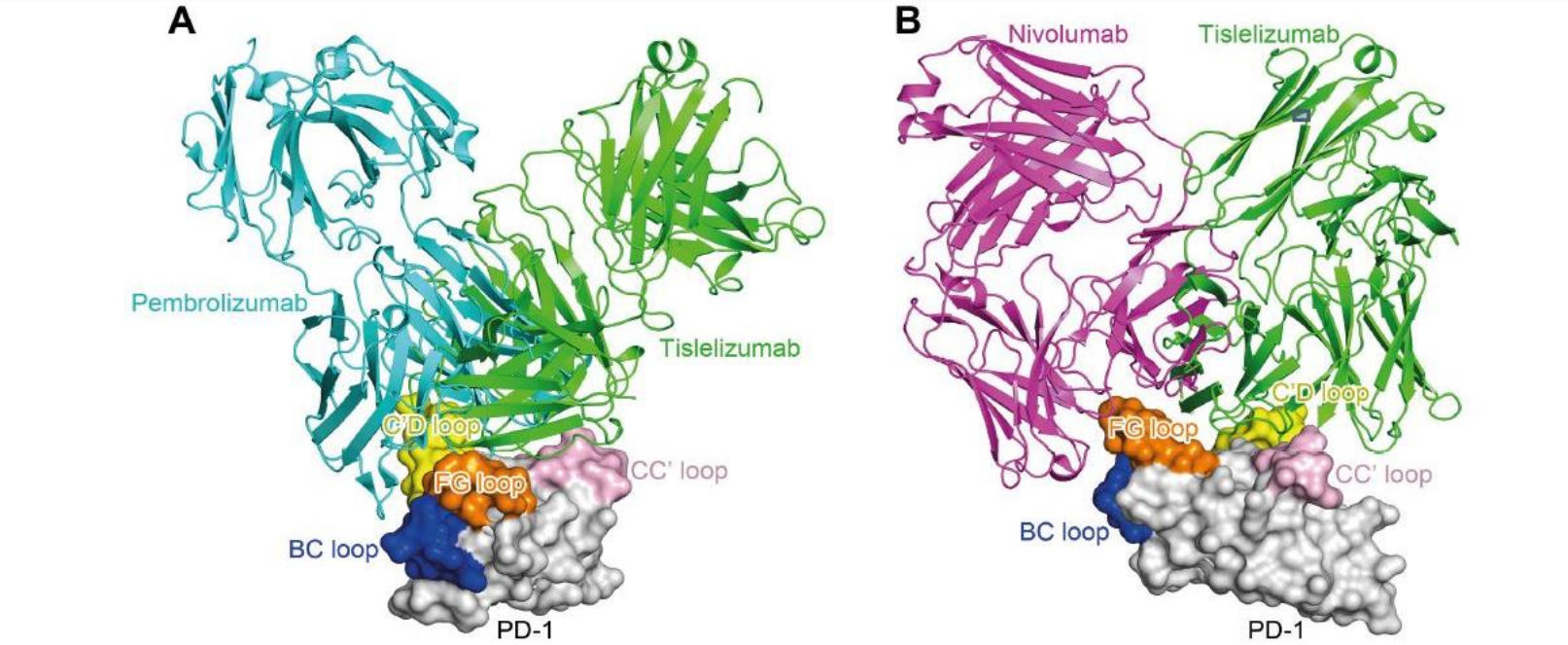


Abbreviations: Ab, antibody; MHC, major histocompatibility complex; PD-1, programmed death-1 receptor; PD-L1, programmed death ligand-1; TCR, T-cell receptor.

1. Zhang T, et al. *Cancer Immunol Immunother.* 2018;67:1079-1090. 2. Dahan R, et al. Cancer Cell. 2015;28:543.

Tislelizumab Binding Orientation to PD-1 Is Different From Pembrolizumab (A) and Nivolumab (B)

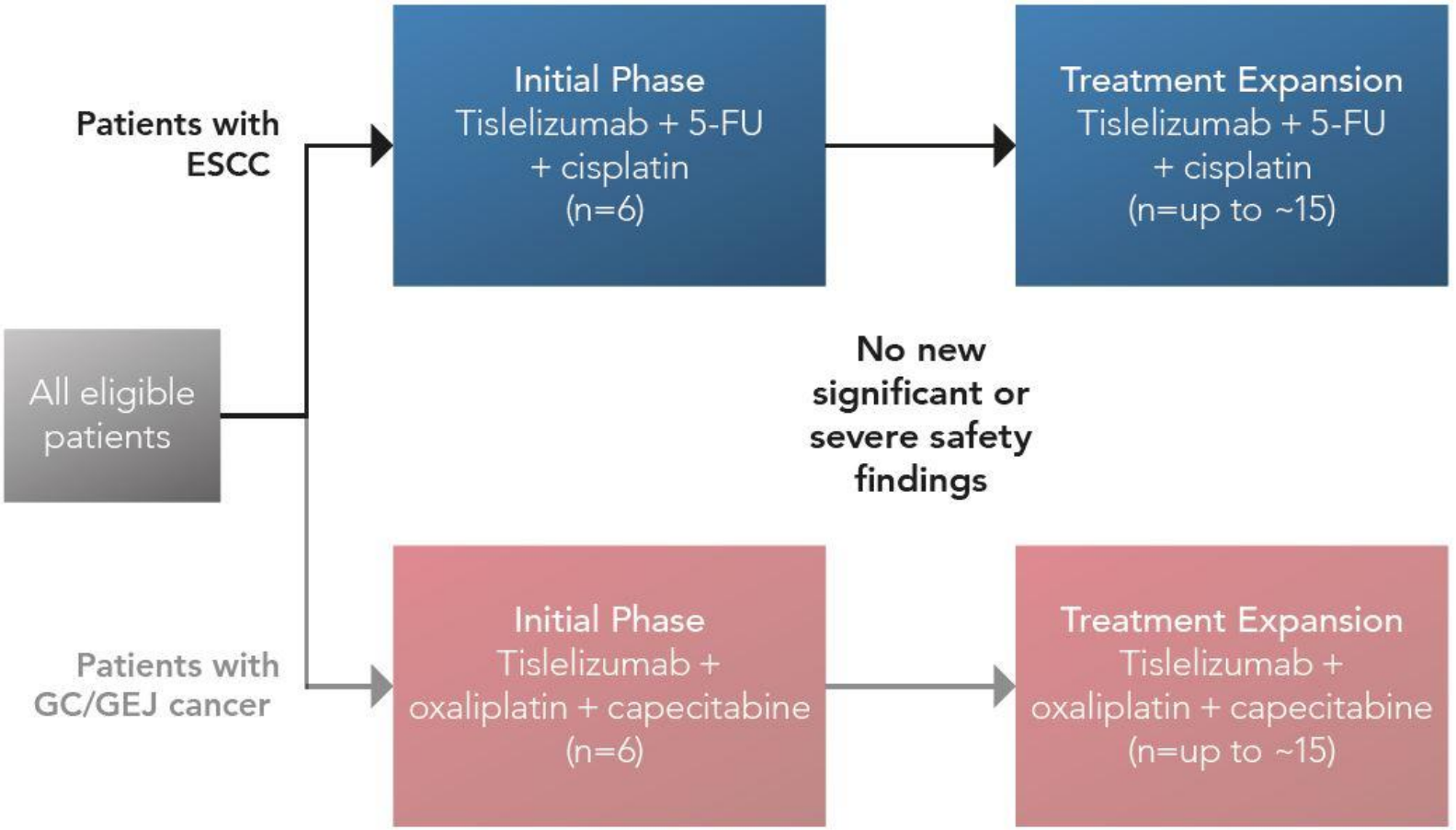
- The binding surface on PD-1 for tislelizumab partially overlaps with that for pembrolizumab, but differs significantly from that for nivolumab[1]
- Tislelizumab shows higher affinity to PD-1 than pembrolizumab and nivolumab with ~100- and 50-fold slower off-rates, respectively[1]



PD-1, tislelizumab, and nivolumab are colored in gray, green, cyan and magenta, respectively. The BC, CC', C'D and FG loops are colored in blue, pink, yellow and orange, respectively. **Abbreviation:** PD-1 programmed death-1 receptor.

1. Feng Y, et al. American Association of Cancer Research Annual Meeting; 2019. Abstract 4048.

BGB-A317-205: A Two-Cohort Phase 2 Study



Abbreviations: ESCC, esophageal squamous cell carcinoma; 5-FU, 5-fluorouracil; GC, gastric cancer; GEJ, gastroesophageal junction.

Demographics and Baseline Disease Characteristics

- As of 31 March 2019, 15 patients with ESCC had received study treatment
  - A total of 4 patients (27%) remained on treatment

	ESCC (N=15)
Median age, years (range)	61 (47-68)
Male, n (%)	14 (93.3)
ECOG PS, n (%)	
0	4 (26.7)
1	11 (73.3)
Median time from initial diagnosis to study entry, months (range)	2.4 (0.4-42.8)
Tumor stage, n (%)	
Stage III	3 (20.0)
Stage IV	10 (66.7)
Not applicable	1 (6.7)
Unknown/other	1 (6.7)
Patients with prior anticancer therapy, n (%)	3 (20.0)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESCC, esophageal squamous cell carcinoma.

Data cut-off: 31 Mar 2019

Overview of Treatment-Emergent Adverse Events

- The most common treatment-emergent adverse events (TEAEs) after treatment with tislelizumab in combination with chemotherapy were anemia (n=12) and decreased appetite (n=11)
- Five patients discontinued tislelizumab due to TEAEs (pneumonitis, tracheal fistula, increased AST, lung infection, and autoimmune dermatitis; n=1 each)

	ESCC (N=15)
Any TEAE	15 (100.0)
Grade ≥3 AE	13 (86.7)
Serious AE	8 (53.3)
AE leading to tislelizumab discontinuation	5 (33.3)
AE leading to death	1 (6.7)
Immune-related AE	12 (80.0)
AEs reported as related to chemotherapy*	15 (100.0)
Chemotherapy-related ≥ grade 3 AE	11 (73.3)
AEs reported as related to tislelizumab*	14 (93.3)
Tislelizumab-related ≥ grade 3 AE	10 (66.7)
Tislelizumab-related serious AE	6 (40.0)

Data presented as n (%). *Treatment-related AEs included AEs noted by the investigator as possibly unrelated as well as those missing a causal relationship. **Abbreviations:** TEAE, treatment-emergent adverse event; ESCC, esophageal squamous cell carcinoma.

Data cut-off: 31 Mar 2019

Adverse Events Considered Related to Treatment* Occurring in >20% of Patients With ESCC

- Adverse events reported in this cohort were consistent with the known tolerability profile of PD-1 inhibitors in combination with chemotherapy and were mostly mild to moderate in severity
- The most common treatment-related AEs were deceased appetite (chemotherapy, n=11; tislelizumab, n=10) and anemia (chemotherapy, n=11; tislelizumab, n=9)

	Chemotherapy-related (n=15)				Tislelizumab-related (n=15)	
	Cisplatin		5-FU			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Patients with ≥1 related AE	**15 (100.0)**	**11 (73.3)**	**15 (100.0)**	**10 (66.7)**	**14 (93.3)**	**10 (66.7)**
Decreased appetite	11 (73.3)	1 (6.7)	11 (73.3)	1 (6.7)	10 (66.7)	1 (6.7)
Anemia	11 (73.3)	2 (13.3)	11 (73.3)	2 (13.3)	9 (60.0)	2 (13.3)
Nausea	9 (60.0)	0	9 (60.0)	0	6 (40.0)	0
Leukopenia	8 (53.3)	2 (13.3)	8 (53.3)	2 (13.3)	6 (40.0)	2 (13.3)
Vomiting	6 (40.0)	4 (26.7)	6 (40.0)	4 (26.7)	5 (33.3)	3 (20.0)
Decreased weight	6 (40.0)	1 (6.7)	6 (40.0)	1 (6.7)	5 (33.3)	0
Decreased neutrophil count	6 (40.0)	0	6 (40.0)	0	6 (40.0)	0
Decreased white blood cell count	6 (40.0)	0	6 (40.0)	0	5 (33.3)	0
Asthenia	5 (33.3)	1 (6.7)	5 (33.3)	1 (6.7)	5 (33.3)	0
Hypoalbuminemia	5 (33.3)	0	5 (33.3)	0	5 (33.3)	0
Hyponatremia	4 (26.7)	2 (13.3)	4 (26.7)	2 (13.3)	5 (33.3)	3 (20.0)
Decreased platelet count	4 (26.7)	1 (6.7)	4 (26.7)	1 (6.7)	3 (20.0)	1 (6.7)
Neutropenia	4 (26.7)	1 (6.7)	4 (26.7)	1 (6.7)	3 (20.0)	1 (6.7)
Dizziness	4 (26.7)	0	4 (26.7)	0	3 (20.0)	0

Data presented as n (%). *Treatment-related AEs included AEs noted by the investigator as possibly unrelated as well as those missing a causal relationship. **Abbreviations:** AE, adverse event; 5-FU, 5-fluorouracil.

Data cut-off: 31 Mar 2019

Potential Immune-Related Adverse Events

- A total of 12 patients (80.0%) experienced 23 immune-related AEs (irAEs)
  - Rash and pruritus (n=3 each), autoimmune dermatitis, increased ALT, and lung infection (n=2 each) were the only irAEs occurring in ≥2 patients
- The majority of irAEs (n=18/23) were mild to moderate in severity
  - Five grade ≥3 irAEs were reported in 4 patients; lung infection was the only irAE of grade ≥3 occurring in more than 1 patient

Immune-Related Adverse Events Occurring in ≥2 Patients

	Any Grade	Grade ≥3
Patients with ≥1 immune-related AE	**12 (80.0)**	**4 (26.7)**
Rash	3 (20.0)	0
Pruritus	3 (20.0)	0
Transaminases increased		
Increased AST	2 (13.3)	1 (6.7)
Increased ALT	2 (13.3)	0
Lung infection	2 (13.3)	2 (13.3)
Autoimmune dermatitis	2 (13.3)	1 (6.7)

Data presented as n (%). **Abbreviations:** AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Data cut-off: 31 Mar 2019

Serious Treatment-Emergent Adverse Events

- The only serious treatment-emergent adverse events (regardless of attribution) occurring in more than 1 patient were dysphagia (n=3) and fatigue (n=2)
  - Of these, only 1 case each of dysphagia and fatigue was considered possibly related to tislelizumab*
- One patient experienced a fatal AE (hepatic dysfunction), which was considered mainly related to progressive disease, and was considered also possibly related to study treatment or underlying type B hepatitis

*Tislelizumab-related AEs included AEs noted by the investigator as possibly unrelated as well as those missing a causal relationship.

Data cut-off: 31 Mar 2019

Responses to Tislelizumab Plus Chemotherapy in Patients With ESCC

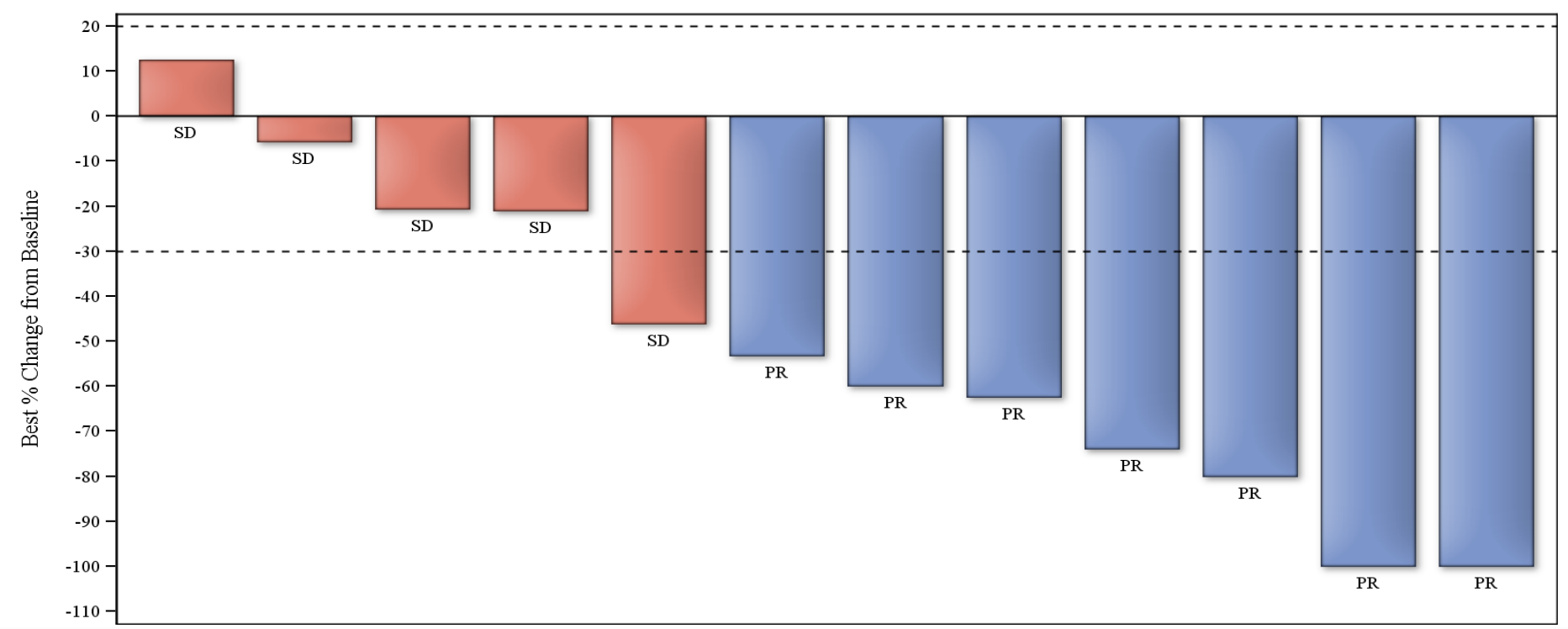
- The objective response rate (ORR) for patients with ESCC was 46.7%; 7 of 15 patients had confirmed partial response
  - No patients had progressive disease; 3 were missing a post-baseline radiographic assessment

	ESCC (N=15)
BOR per RECIST v1.1, confirmed	
Complete response (CR), n (%)	0
Partial response (PR), n (%)	7 (46.7)
Stable disease (SD), n (%)	5 (33.3)
Progressive disease (PD), n (%)	0
Missing/Not evaluable, n (%)	3 (20.0)
Median time to response, weeks (IQR)	**10.0 (9.1-10.1)**
ORR (CR+PR), % (95% CI)	**46.7 (21.3-73.4)**
DCR (CR+PR+SD), % (95% CI)	**80.0 (51.9-95.7)**

Disease assessment by radiographic imaging was performed every 9 weeks during first 12 months and every 12 weeks thereafter.
Abbreviations: BOR, best overall response; CI, confidence interval; DCR, disease control rate; IQR, interquartile range; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Data cut-off: 31 Mar 2019

Responses to Tislelizumab Plus Chemotherapy, Continued

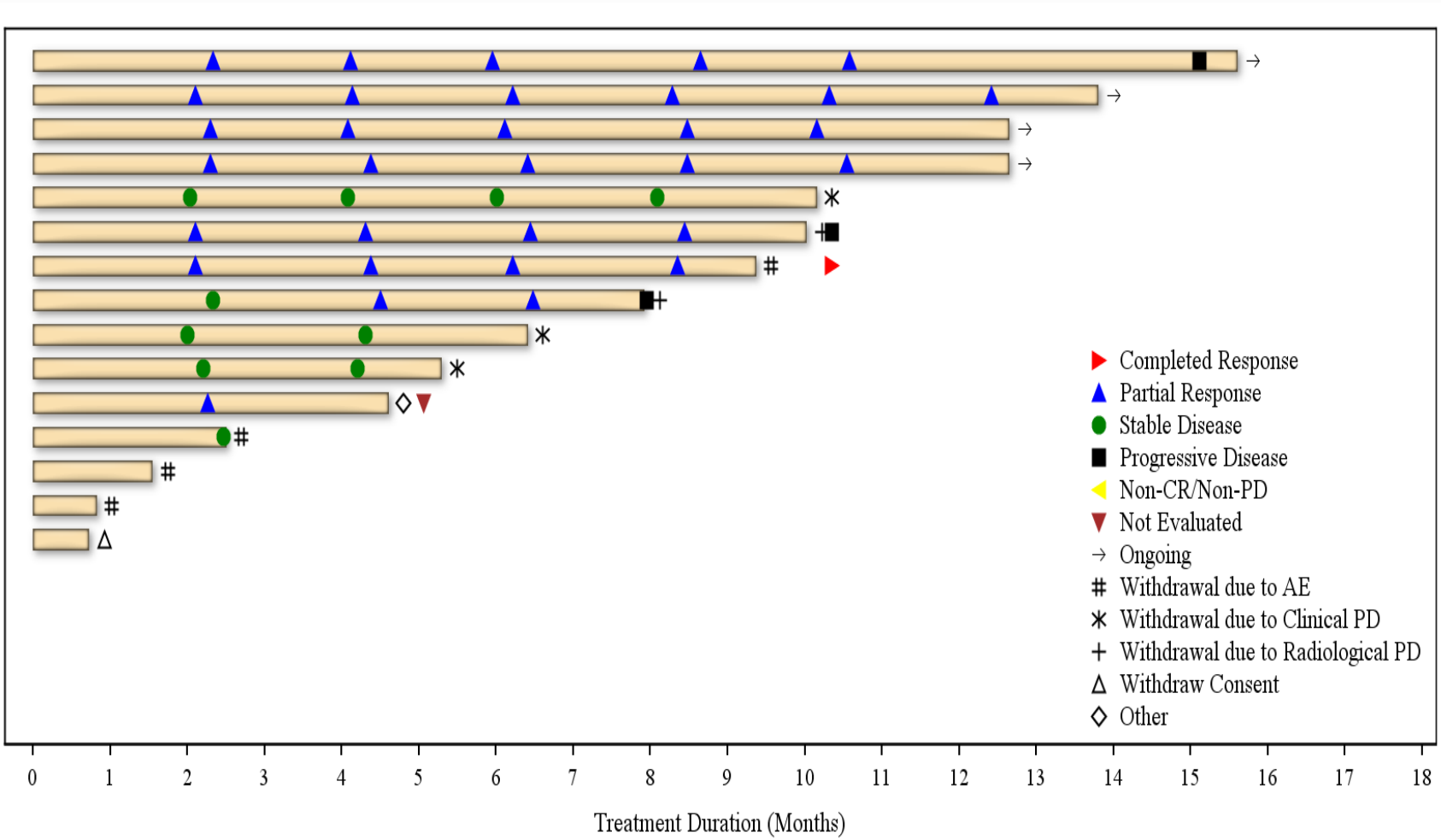


Abbreviations: PR, partial response; SD, stable disease.

Data cut-off: 31 Mar 2019

Tumor Response in Patients With ESCC

- Median duration of response was 12.8 months (95% CI: 3.5-12.8)

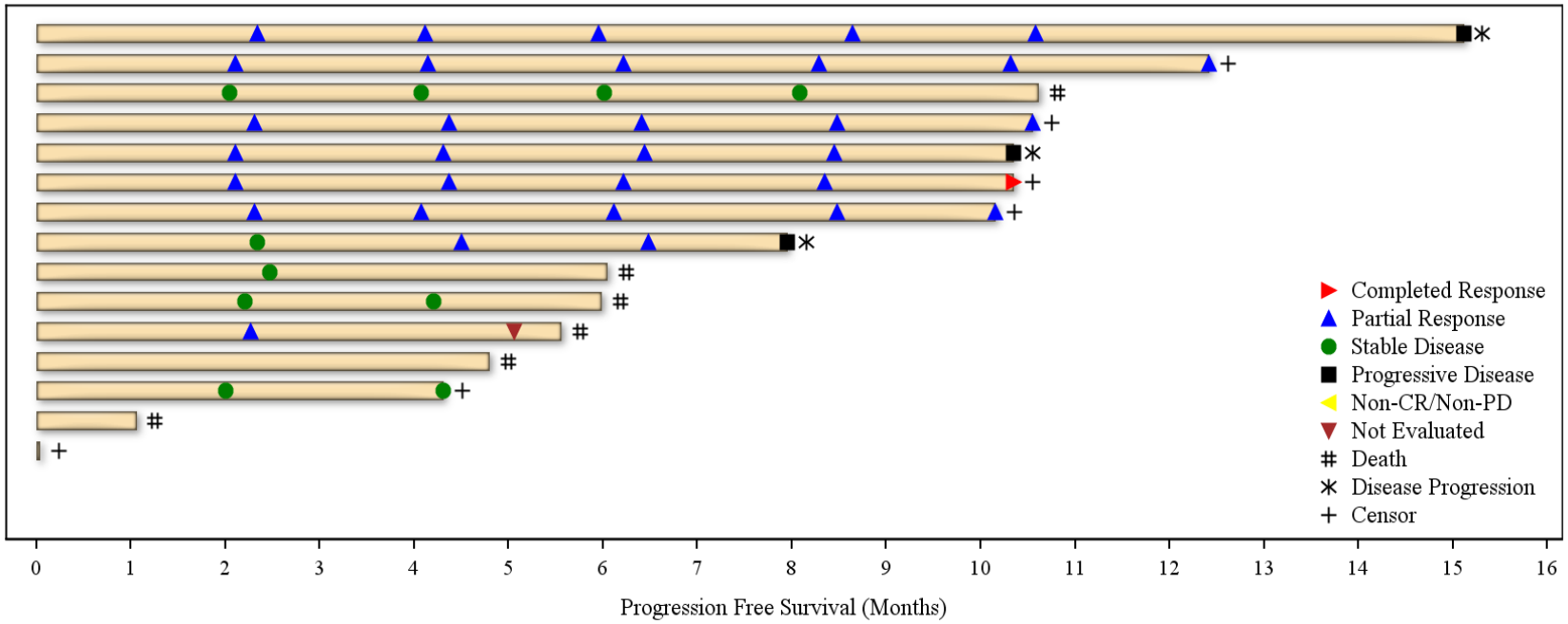


Abbreviations: AE, adverse event; CR, complete response; PD, progressive disease.

Data cut-off: 31 Mar 2019

Progression-Free Survival in Patients With ESCC

- Median progression-free survival (PFS) was 10.4 months (95% CI: 5.6-15.1)



Abbreviations: CR, complete response; PD, progressive disease.

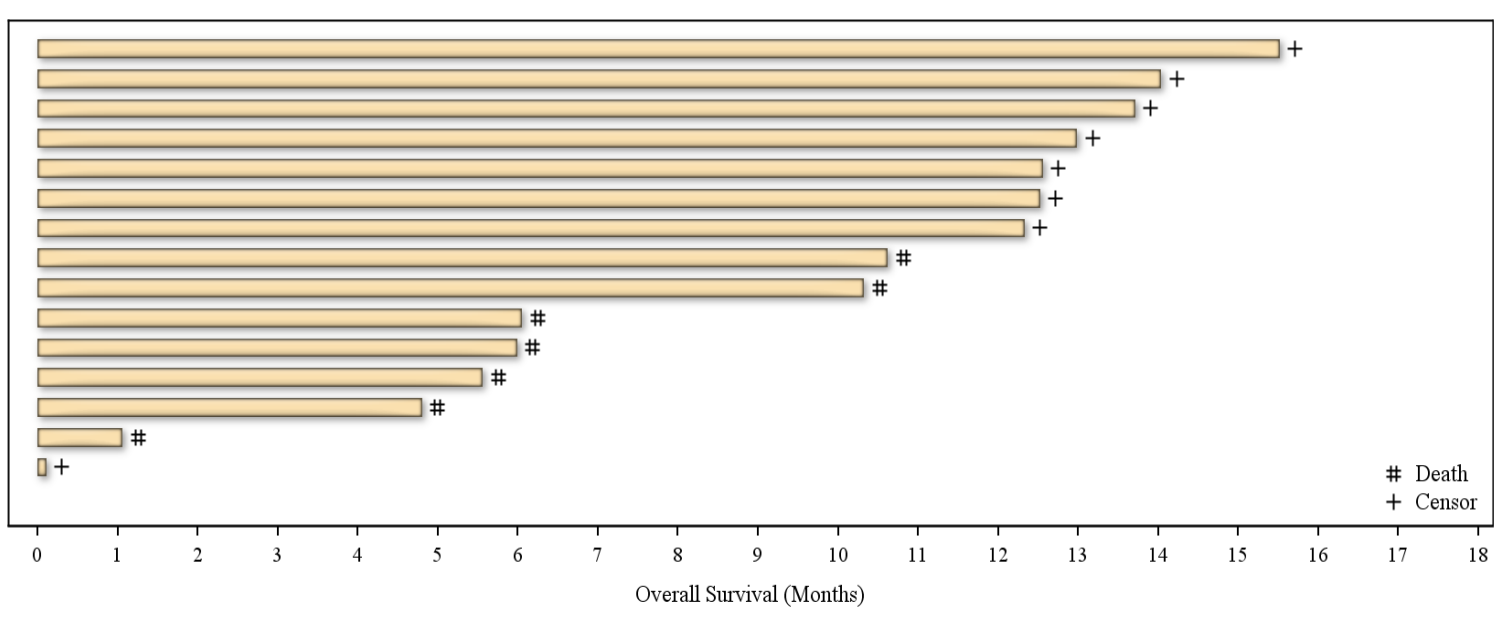
	ESCC (N=15)
Median PFS, months (95% CI)	10.4 (5.6-15.1)
Event-free rate at 6 months, % (95% CI)	70 (37.8-87.4)
Event-free rate at 1 year, % (95% CI)	30 (6.2-59.6)

Abbreviations: CI, confidence interval; ESCC, esophageal squamous cell carcinoma; PFS, progression-free survival.

Data cut-off: 31 Mar 2019

Overall Survival in Patients With ESCC

- Despite a median follow-up of 13.0 months (95% CI: 12.3-14.0), median overall survival (OS) had not been reached



	ESCC
Median OS, months (95% CI)	NR
OS rate at 6 months, % (95% CI)	71 (40.6-88.2)
OS rate at 1 year, % (95% CI)	50 (22.9-72.2)

Abbreviations: CI, confidence interval; ESCC, esophageal squamous cell carcinoma; NR, not reached; OS, overall survival.

Data cut-off: 31 Mar 2019

Conclusions

- Adverse events reported in the ESCC cohort of this study were consistent with the safety profile of tislelizumab observed in previous studies with other tumor types and were generally of low severity
- Tislelizumab plus chemotherapy demonstrated preliminary antitumor activity in patients with ESCC
  - The ORR was driven by partial responses and was 46.7% with median duration of response 12.8 months.
  - Despite a median follow-up of 13.0 months, median OS had not been reached; median PFS was 10.4 months
- The preliminary safety profile and antitumor activity support continued development of tislelizumab plus chemotherapy in patients with ESCC
  - A phase 3 study (NCT03783442) has been initiated to examine tislelizumab in combination with chemotherapy as first-line treatment in patients with advanced ESCC

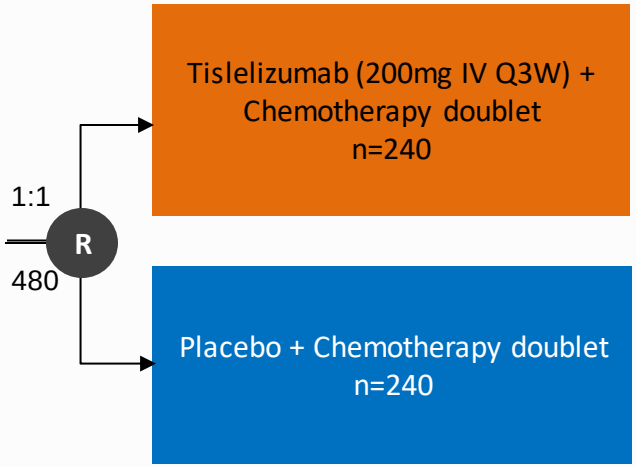
Data cut-off: 31 Mar 2019

BGB-A317-306: A Randomized, Placebo-controlled, Double-blind Phase 3 Study (NCT03783442)

RATIONALE 306

Key Eligibility Criteria

- Stage IV (metastatic), unresectable ESCC at first diagnosis OR unresectable, locally advanced recurrent or metastatic ESCC without prior systemic therapy for this disease stage
- ECOG PS 0-1
- Excluding those still eligible for dCRT/RT
- Excluding those with prior therapies targeting PD-1, PD-L1, or PD-L2
- Excluding those with severe malnutrition



Treatment until disease progression, intolerable toxicity, or withdrawal for other reasons

Study Endpoints

Primary: PFS (assessed by BIRC) & OS
Secondary: ORR, DOR, HRQoL , safety
Exploratory: DCR, PFS2, biomarkers, PK, ADA

Stratification factors

- Geographic region (Asia [excluding Japan] vs Japan vs Rest of World)
- Prior definitive therapy (yes vs no)
- ICC (platinum/fluoropyrimidine vs platinum/paclitaxel)

Chemotherapy doublet

- DDP/OXA + fluoropyrimidine (5-FU or CAP) **or**
- DDP/OXA + PTX

Global study including 16 countries/regions: China, Taiwan, Korea, Japan, United States, European Union, Australia and Russia

Abbreviations: ADA, anti-drug antibody; BIRC=blinded independent review committee; CAP, capecitabine; dCRT, definitive chemo-radiotherapy; DDP, cisplatin; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; HRQoL, health-related quality of life; ICC, investigator's choice of chemotherapy; ORR, objective response rate; OS, overall survival; OXA, oxaliplatin; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PD-L2, programmed death-ligand 2; PFS, progression-free survival; PK, pharmacokinetics; PTX, paclitaxel; Q3W, every 3 weeks; RT, radiotherapy.

Study Status

Study BGB-A317-306 is actively enrolling patients globally

RATIONALE 306

- 16 countries participating
  - ~165 sites