A PHASE 3, RANDOMIZED, OPEN-LABEL STUDY TO COMPARE THE EFFICACY OF TISLELIZUMAB (BGB-A317) VERSUS CHEMOTHERAPY AS SECOND-LINE THERAPY FOR ADVANCED UNRESECTABLE/METASTATIC ESOPHAGEAL SQUAMOUS CELL CARCINOMA (ESCC)

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Immune Checkpoint Inhibitors as Treatment for Esophageal Cancer

- Approximately 40% of patients with esophageal cancer are diagnosed with advanced unresectable or metastatic disease, which progresses rapidly, having a 5-year survival rate of less than 5%[1,2]

- The availability of highly effective and generally tolerable treatment options is limited for those with advanced or metastatic disease who have failed first-line treatment[3–5]

- Inhibition of programmed cell death protein-1 (PD-1) has demonstrated antitumor activity and was generally well tolerated in patients with advanced unresectable or metastatic ESCC[6,7]

[1]Lin M, Li YP, Wu SG, et al. *Onco Targets Ther*. 2016;9:6435–6444; [2]Drahos J, Wu M, Anderson WF, et al. *PLoS One*. 2013;8(7):e67913; [3]Song Z, Zhang Y. *Onco Targets Ther*. 2014;7:1875–1881; [4]Thallinger CM, Raderer M, Hejna M. *J Clin Oncol*. 2011;29(35):4709–4714; [5]Albertsson M, Johansson B, Friesland S, et al. *Med Oncol*. 2007;24(4): 407–412; [6]Doi T, Piha-Paul SA, Jalal SI, et al. *J Clin Oncol*. 2018;36(1):61–67. [7]Kudo T, Hamamoto Y, Kato K, et al. *Lancet Oncol*. 2017;18(5):631–639.

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

- Tislelizumab is a humanized IgG4 monoclonal antibody with high affinity/specificity for PD-1

- Tislelizumab was specifically engineered to minimize binding to FcγR on macrophages, thereby abrogating antibody-dependent T-cell clearance, a potential mechanism of resistance to anti-PD-1 therapy

PD-1 mAb with FcγR binding
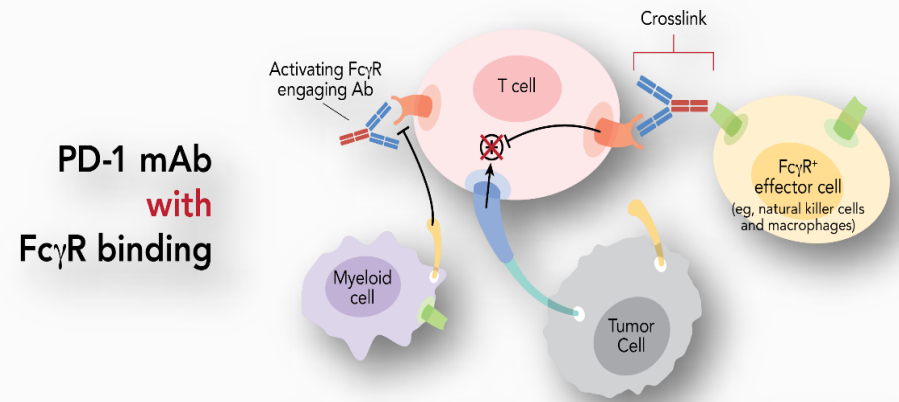
Crosslinking may bridge suppressive cells and CD4+/CD8+ T cells to constrain their antitumor ability

Tislelizumab without FcγR binding
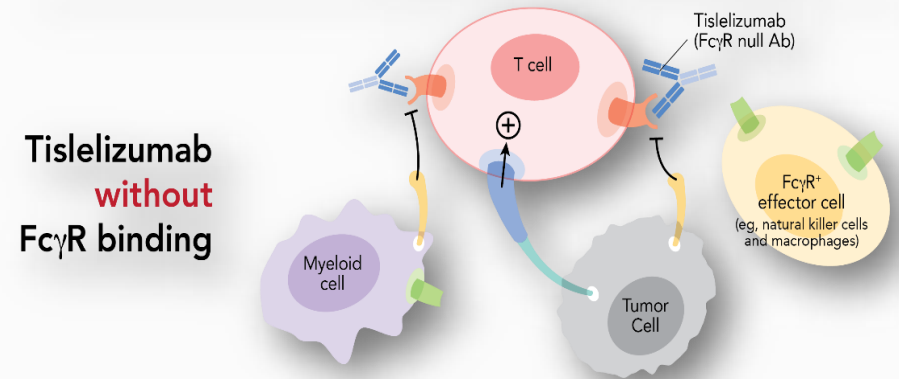
No bridging FcγR+ cells and no activating PD-1 pathway

Figure modified from Dahan R, et al. *Cancer Cell*. 2015;28:285–295.
Abbreviations: Ab, antibody; PD-1, programmed cell death-1.

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Antitumor Activity of Tislelizumab as Single-agent Treatment for Esophageal Cancer (EC)

- A first-in-human study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and had preliminary antitumor effects in patients with advanced solid tumors, including EC[1,2]

  – The recommended dose of   tislelizumab is 200 mg, given intravenously (IV) every 3 weeks (Q3W)

- Phase 2 and 3 clinical studies evaluating tislelizumab in patients with advanced solid tumors are ongoing

[1]Desai J, Markman B, Sandhu SK, et al. *J Immunother Cancer.* 2016;4(suppl 1):154; [2]Desai J, Millward M, Chao Y, et al. *Ann Oncol.* 2017;28(suppl 5):v122–v141.

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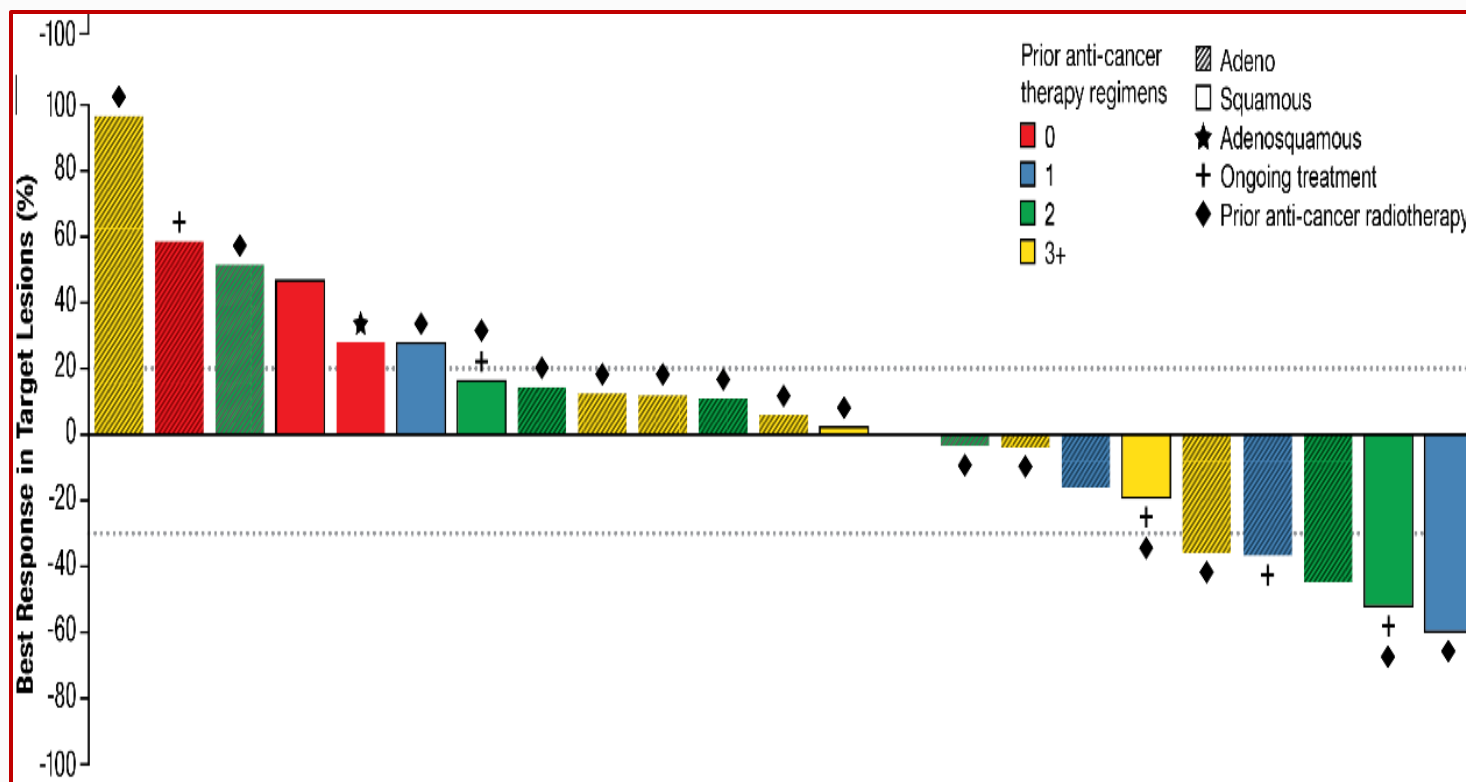# Maximum Tumor Reduction in Patients with EC

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Study Design

- This phase 3, randomized, controlled, open-label study (NCT03430843) was designed to evaluate the efficacy and safety of tislelizumab compared with investigator-chosen chemotherapy for second-line treatment of advanced unresectable/metastatic ESCC
    - Approximately 450 patients will be enrolled globally
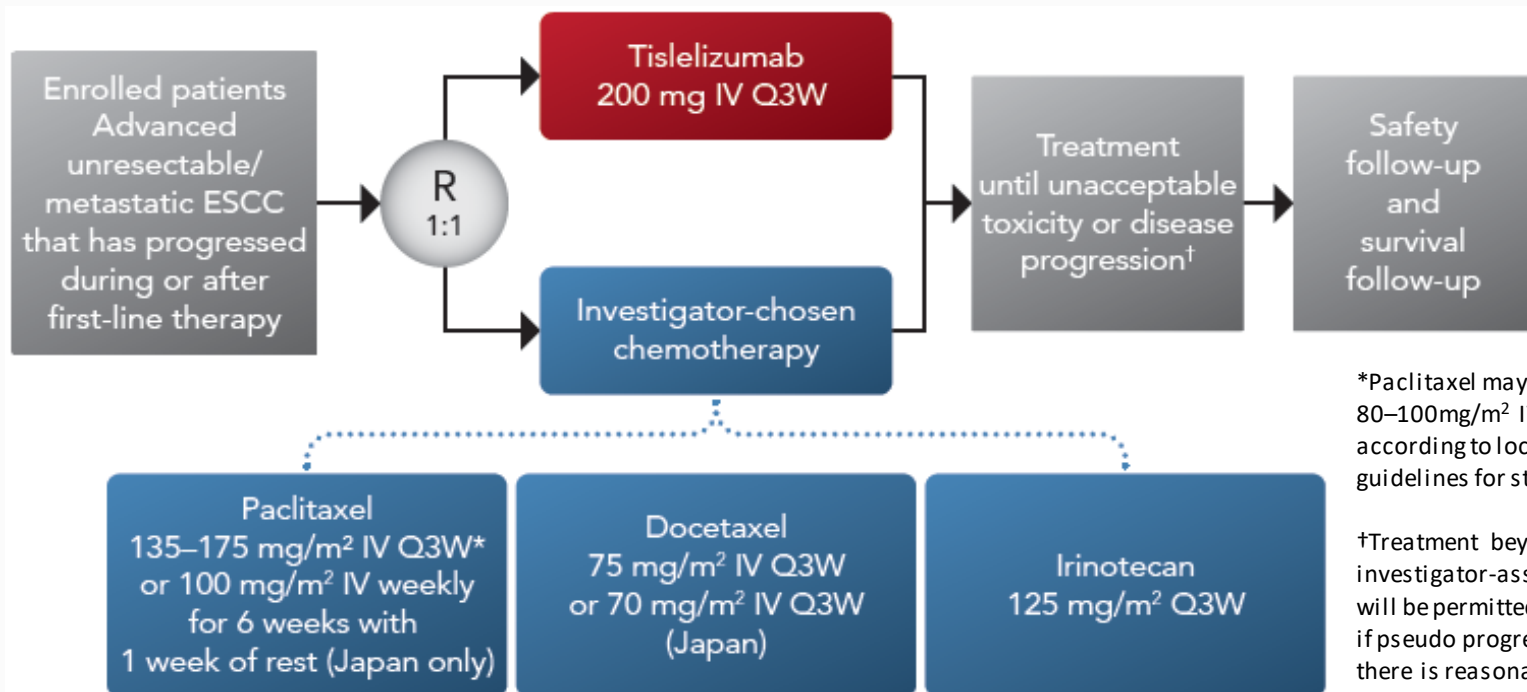
*Paclitaxel may also be given in doses of 80–100mg/m^2 IV on a weekly schedule, according to local and/or country specific guidelines for standard of care.

†Treatment beyond the initial investigator-assessed disease progression will be permitted in the tislelizumab arm if pseudo progression is suspected or there is reasonable belief that the patient could derive benefit from the treatment.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; IV, intravenously; Q3W, once every 3 weeks; R, randomization.

Study Endpoints

	Content
Primary	• To compare overall survival (OS) for tislelizumab with that for chemotherapy
Secondary	• To compare tislelizumab versus chemotherapy for objective response rate (ORR), progression-free survival (PFS), and duration of response (DoR), along with health-related quality of life, and safety and tolerability

Study Population: Key Inclusion Criteria

- Adult patients, aged ≥18 years, will be enrolled if they have the following:

- Histologically confirmed ESCC that has progressed during or after first-line therapy for unresectable/metastatic disease

- At least one measurable/evaluable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

- An Eastern Cooperative Oncology performance status score of ≤1

Study Population: Key Exclusion Criteria

- Ineligible for any of the treatments of protocol-specified chemotherapy (paclitaxel/docetaxel/irinotecan)

- Received two or more prior systemic treatments for advanced/metastatic unresectable ESCC

- Had palliative radiation treatment for ESCC within 14 days of study treatment initiation

- A history of gastrointestinal perforation and/or fistula or aortoesophageal fistula within 6 months of randomization

- Apparent tumor invasion into organs located adjacent to the esophageal disease site that are at an increased risk of fistula

- Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage

- Active hepatitis C, untreated chronic hepatitis B, or if they are carriers of chronic hepatitis B virus (HBV) whose HBV DNA is higher than 500 IU/mL

Study Treatment

- Patients will be randomized 1:1 to receive either tislelizumab 200 mg IV Q3W (Day 1 of each 21-day cycle) or investigator chosen chemotherapy:

Paclitaxel 135–175 mg/m2 IV Q3W (Day 1 of each 21-day cycle) or 100 mg/m2 IV weekly for 6 weeks with 1 week of rest (Japan only)	Docetaxel 75 mg/m2 or 70 mg/m2 (Japan only) IV Q3W (Day 1 of each 21-day cycle)	Irinotecan 125 mg/m2 IV Q3W (Day 1, Day 8 of each 21-day cycle)

- Randomization will be stratified by region, ECOG performance status, and chemotherapy option

Study Treatment

- Treatment will be administered until disease progression, intolerable toxicity, or treatment discontinuation for other reasons
  - Patients on the tislelizumab arm will be permitted to continue tislelizumab treatment beyond radiological progression if clinical benefit is observed per investigator's discretion
- There will be no dose reduction of tislelizumab in this study; dose delays or interruptions of less than 12 weeks will be permitted; a maximum of two dose reductions will be permitted for each chemotherapeutic agent
  - Chemotherapy-related toxicities (with the exception of alopecia or grade 2 fatigue) must have resolved to baseline or grade 0–1 prior to administration of the next chemotherapy dose

Study Assessments and Statistical Analysis

- The primary endpoint will be OS for tislelizumab versus investigator-chosen chemotherapy, with the analysis performed using a two-sided, stratified log-rank test (α=0.05); data will be presented as Kaplan–Meier survival probability plots
  - An interim analysis of OS is planned
- The secondary endpoints of ORR (the proportion of patients with complete response or partial response), PFS, and DoR will be assessed by the investigator using RECIST v1.1 criteria
  - Tumor assessments will occur at baseline, every 6 weeks for 6 months, then every 9 weeks until disease progression
  - ORR will be analyzed using a Cochran-Mantel-Haenszel test, adjusting for selected stratification factors, and PFS will be assessed using the Kaplan–Meier method

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Study Assessments and Statistical Analysis

- Health-related quality of life will be assessed using the EORTC QLQ-C30 index, the EORTC QLQ esophageal cancer module OES18, and the generic health state instrument EuroQol 5D

- Safety/tolerability will be assessed by monitoring adverse events (AEs; occurring up to 30 days after the last dose of the study drug), monitoring immune-related AEs (occurring up to 90 days after the last dose of the study drug), and through physical examinations, vital signs, and electrocardiograms

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The authors wish to acknowledge the investigative center study staff as well as recognize those from BeiGene, Ltd. who have substantially contributed to this study.

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