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Oral presentation 32　Chemotherapy for advanced gastric cancer

First-line tislelizumab + chemotherapy for gastric/gastroesophageal junction (G/GEJ) adenocarcinoma

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COI Disclosure

Ken Kato, MD, PhD

In connection with the presentation, I disclose COI with the following companies/organizations:

1. A position of a board member or advisor: Beigene, ONO, BMS, MSD.
2. Stock holdings: No
3. Patent royalties: No
4. Honoraria for lectures: ONO, BMS
5. Honoraria for manuscripts: No
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7. Receiving travel expenses or gifts: No

Introduction – G/GEJ adenocarcinoma

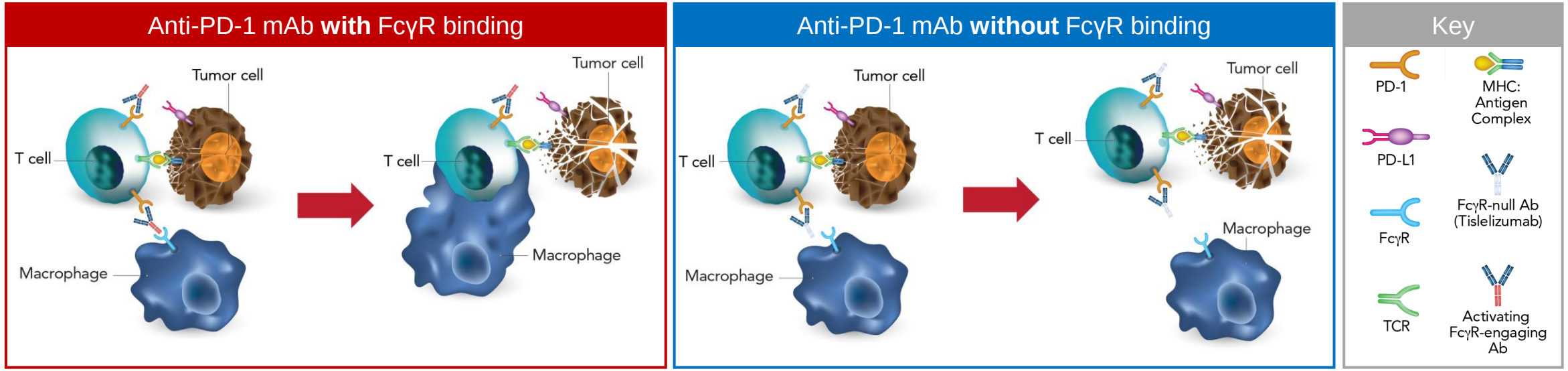
- Gastric cancer is the fourth most common cause of cancer-related death worldwide[1]
- For patients with locally advanced or metastatic G/GEJ adenocarcinoma, the main treatment options include irinotecan, taxane, fluoropyrimidine, and platinum-based combination chemotherapy regimens[2]
- Immune checkpoint inhibitors, such as anti-PD-1 monoclonal antibodies, have demonstrated promising antitumor activity, as single agents and in combination with chemotherapeutic agents, across multiple malignancies, including G/GEJ adenocarcinoma[3–8]

G/GEJ, gastric or gastroesophageal junction; PD-1, programmed cell death protein-1

1. IARC. Press release No 292 – Latest Global Cancer Data, 15 December 2020 (available at https://www.iarc.who.int/wp-content/uploads/2020/12/pr292_E.pdf; accessed 19 January 2021); 2. Jou, et al. *World J Gastroenterol* 2016; 3. Roviello, et al. *Tumour Biol* 2016; 4. Moehler, et al. *Ann Oncol* 2020; 5. Kato, et al. *Ann Oncol* 2020; 6. Boku, et al. *Ann Oncol* 2020; 7. Kang et al. *Lancet* 2017; 8. Bang, et al. *Gastric Cancer* 2019

Introduction – Tislelizumab

- Tislelizumab is a humanized anti-PD-1 mAb engineered to minimize binding of FcγR on macrophages to abrogate antibody-dependent phagocytosis[1–3]



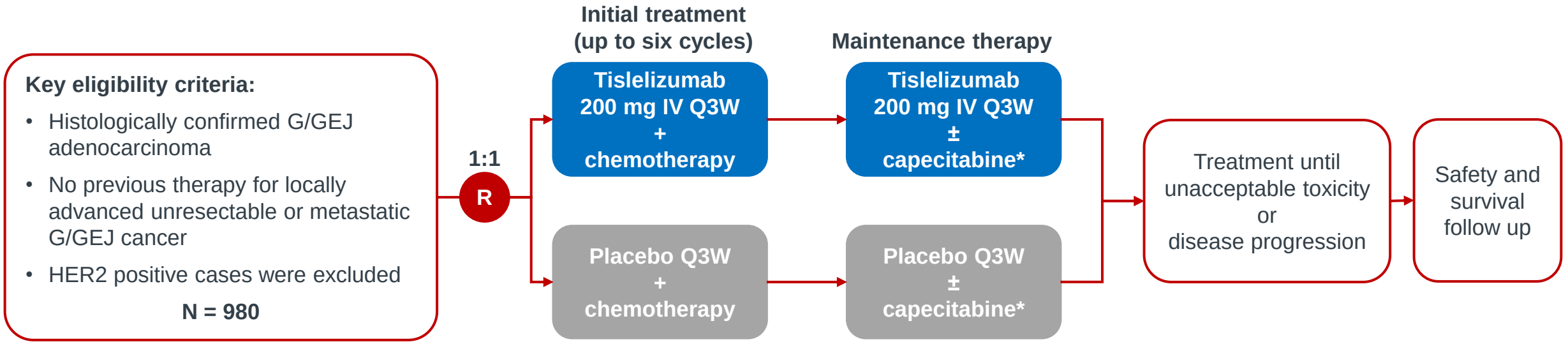
- Early phase studies have reported that tislelizumab ± chemotherapy is well tolerated and has encouraging antitumor activity in patients with G/GEJ adenocarcinoma[4–7]
- In a Phase 2 study of tislelizumab + oxaliplatin/capecitabine as first-line treatment in patients with locally advanced/metastatic G/GEJ adenocarcinoma (n = 15), confirmed ORR and DCR were 46.7% and 80.0%, respectively, with a median time to response of 9.3 weeks[7]

DCR, disease control rate; G/GEJ, gastric or gastroesophageal junction; mAb, monoclonal antibody; ORR, overall response rate; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1

1. Zhang, et al. *Cancer Immunol Immunother* 2018; 2. Dahan, et al. *Cancer Cell* 2015; 3. Qin, et al. *Future Oncol* 2019; 4. Desai, et al. *J Immunother Cancer* 2016; 5. Desai, et al. *Ann Oncol* 2017; 6. Bai, et al. *J Clin Oncol* 2019; 7. Xu, et al. *Clin Cancer Res* 2020

RATIONALE-305 (NCT03777657) – Study design

A global, randomized, double-blind, placebo-controlled, Phase 3 clinical study comparing the efficacy and safety of tislelizumab plus platinum and fluoropyrimidine vs placebo plus platinum and fluoropyrimidine as first-line treatment in patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma



Stratification by:	**Chemotherapy options (investigator-chosen):**
• Regions of enrollment • Peritoneal metastasis • PD-L1 expression • Investigator-chosen chemotherapy	• Oxaliplatin 130 mg/m^2 IV (day 1) + capecitabine 1000 mg/m^2 PO BID (day 1–14), Q3W **or** • Cisplatin 80 mg/m^2 IV (day 1) + 5-FU 800 mg/m^2/day continuous IV (day 1–5), Q3W

Site numbers to date: China including Taiwan, N=56; Japan, N=30; Korea, N=10; US, N=15; EU, N=55

*Capecitabine as maintenance therapy is optional only for oxaliplatin and capecitabine regimen and may be administered until disease progression, intolerable toxicity, or another treatment discontinuation criterion is met.

5-FU, 5-fluorouracil; BID, twice daily; G/GEJ, gastric or gastroesophageal junction; IV, intravenous; PO, orally; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; R, randomized

RATIONALE-305 (NCT03777657) – Endpoints

Primary endpoint:

- OS in the ITT and PD-L1+ analysis sets

Secondary endpoints:

- PFS, ORR and DOR
- HRQoL
- Safety

Exploratory endpoints:

- DCR, CBR, TTR and PFS2
- Predictive biomarkers (e.g. PD-L1)
- PK
- ADAs

PD-L1 expression:

- Assessed using the visually-estimated combined positive score (vCPS) from the VENTANA PD-L1 (SP263) assay

ADAs, anti-drug antibodies; CBR, clinical benefit rate; DCR, disease control rate; DOR, duration of response; HRQoL, health-related quality of life; ITT, intent-to-treat; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PFS2, PFS after next line of treatment; PK, pharmacokinetics; TTR, time to response

RATIONALE-305 (NCT03777657) – Key points summary

Design:	Randomized, double-blind, placebo-controlled, Phase 3 study
Setting:	First-line treatment in patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma
Comparators:	Tislelizumab plus platinum and fluoropyrimidine vs placebo plus platinum and fluoropyrimidine
Primary endpoint:	OS in the ITT and PD-L1+ analysis sets

G/GEJ, gastric or gastroesophageal junction; ITT, intent-to-treat; OS, overall survival; PD-L1, programmed death-ligand 1