SPOTLIGHT: Phase 3 Study of Zolbetuximab + mFOLFOX6 Versus Placebo + mFOLFOX6 in First-line Claudin18.2^{+}/HER2^{-} Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

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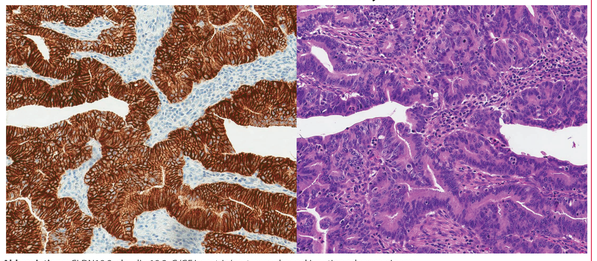
BACKGROUND

- Despite advances in treatment, gastric/gastroesophageal junction adenocarcinoma (G/GEJ) remains a leading cause of cancer-related death worldwide,[1] with disproportionate incidence and mortality rates reported for people from Eastern Asia[2,3]
- Fluorouracil (5-FU), folinic acid, and oxaliplatin (mFOLFOX6) is an accepted chemotherapy for first-line treatment of locally advanced/metastatic G/GEJ[4]
- Human epidermal growth factor receptor 2 (HER2) and immune checkpoint inhibitors (ie, programmed death ligand-1 [PD-L1]) are promising targets/biomarkers for targeted treatment in GC/GEJ; however, the frequency of their expression in G/GEJ is limited[5]
  - Due to these limitations, there is a need for therapeutic targets/biomarkers beyond HER2 and PD-L1
- Claudin 18.2 (CLDN18.2) is a targetable biomarker in G/GEJ
- In healthy tissue, CLDN18.2, a tight junction protein, is confined to gastric mucosa (ie, cells in the pit and base regions of gastric glands)[6]; however, upon malignant transformation, structural loss in G/GEJ cells may allow antibodies more access to previously unavailable CLDN18.2[7]
- Data suggests that CLDN18.2 is a highly prevalent therapeutic target in G/GEJ (**Figure 1**), with low (~12%) overlap of expression with HER2[5]; CLDN18.2 expression is maintained in GC metastases[6]

Figure 1. CLDN18.2 Staining in G/GEJ Tissue Sample



Abbreviations: CLDN18.2, claudin 18.2; G/GEJ, gastric/gastroesophageal junction adenocarcinoma.

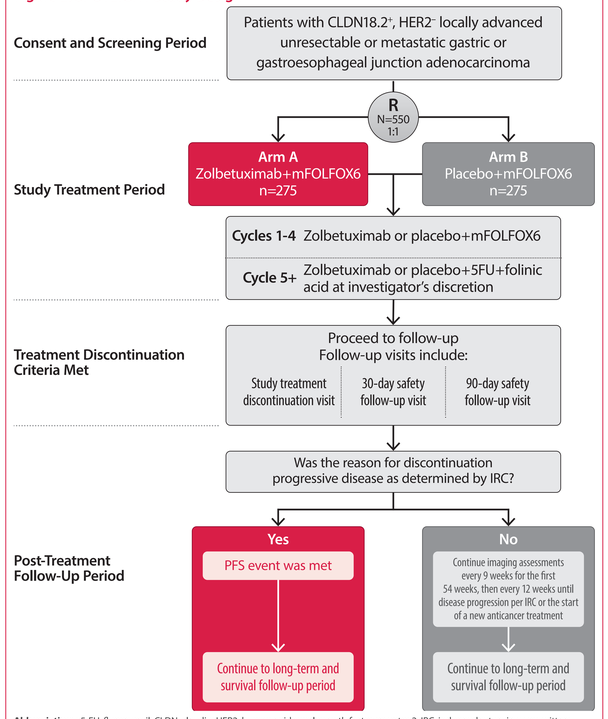
- Zolbetuximab is a chimeric IgG1 monoclonal antibody that specifically binds to CLDN18.2 and mediates cell death through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity[8,9]
- In preclinical models of G/GEJ, treatment with chemotherapy sensitized tumor cell lines to zolbetuximab-mediated mechanisms by increasing CLDN18.2 expression; improved antitumor activity was observed in xenografted mice treated with zolbetuximab plus chemotherapy compared with mice treated with chemotherapy alone[7]
- Zolbetuximab, as a single agent[9,10] and in combination with chemotherapy,[11] was generally well tolerated and has demonstrated antitumor activity in patients with CLDN18.2-postive (CLDN18.2^{+}) G/GEJ
  - As first-line therapy, zolbetuximab, in combination with epirubicin, oxaliplatin, and capecitabine (EOX), showed statistically significantly prolonged survival compared with EOX alone in patients with CLDN18.2^{+} advanced G/GEJ[11]
  - In patients with recurrent/refractory locally advanced or metastatic CLDN18.2^{+} G/GEJ who had received ≥1 prior line of chemotherapy, single-agent zolbetuximab demonstrated a clinical benefit rate of 23%[9]

METHODS

SPOTLIGHT Study Design and Objectives

- This phase 3, double-blind, placebo-controlled study (NCT03504397) will enroll ~550 adult patients from global sites, including China, Japan, Korea, and Taiwan
- Patients with CLDN18.2^{+}/ HER2-negative (HER2^{-}) locally advanced unresectable or metastatic G/GEJ who have not been previously treated with chemotherapy will be eligible
- Patients will be randomized 1:1 to receive either zolbetuximab plus mFOLFOX6 or placebo plus mFOLFOX6 (**Figure 2**)

Figure 2. SPOTLIGHT Study Design



Abbreviations: 5-FU, fluorouracil; CLDN, claudin; HER2, human epidermal growth factor receptor 2; IRC, independent review committee; mFOLFOX6, 5-FU, folinic acid, and oxaliplatin; OS, overall survival; PFS, progression-free survival; R, randomized.

- The primary objective of this study is to evaluate the efficacy of zolbetuximab plus mFOLFOX6 compared with placebo plus mFOLFOX6 (as first-line treatment) as measured by progression-free survival (PFS) in patients with CLDN18.2^{+}/HER2^{-} locally advanced unresectable or metastatic G/GEJ
  - Progression-free survival will be assessed by independent review committee (IRC) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
- Comparison of overall survival (OS) is the key secondary efficacy objective; other secondary objectives included the evaluation of objective response rate (ORR) and duration of response (DoR)
  - All ORR and DoR will be assessed by IRC per RECIST v1.1
- Evaluation of zolbetuximab's safety/tolerability profile is a secondary objective and will be assessed by monitoring the incidence and severity of adverse events (AEs), as well as changes in clinical laboratory results, vital signs, electrocardiograms, and Eastern Cooperative Oncology Group performance status
- Evaluation of the pharmacokinetic profile and immunogenicity of zolbetuximab, as well as treatment effects on health-related quality-of-life (HRQoL), as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and QLQ-OG25, and the EuroQOL Five Dimensions 5L (EQ5D-5L) questionnaires, are secondary objectives

Study Population

- Adult patients (according to local regulations) with a histologically and radiologically confirmed diagnosis of locally advanced unresectable or metastatic GC/GEJ with measurable disease according to RECIST v1.1 whose tumors are CLDN18.2^{+}/HER2^{-} and who have not been previously treated for metastatic disease with chemotherapy
  - Patients who have received systemic immunosuppressive therapy, including systemic corticosteroids within 14 days prior to first dose of study treatment, or have received other investigational agents or devices within 28 days prior to the first dose of study treatment, are ineligible
- During screening, central testing of tumor tissue will determine CLDN18.2 and HER2 status (if unknown); patients will be considered CLDN18.2^{+} if ≥75% of tumor cells demonstrate moderate-to-strong immunohistochemistry membranous staining

Study Treatment

- Patients will be randomized 1:1 to receive zolbetuximab or placebo in combination with mFOLFOX6
  - Randomization will be stratified by region (Asia vs non-Asia), number of organs with metastatic sites (0-2 vs ≥3), and prior gastrectomy (yes or no)
- Zolbetuximab will be administered by intravenous (IV) infusion as an 800-mg/m^2 loading dose (Cycle 1, Day 1) followed by 600 mg/m^2 on Day 22 of Cycle 1, thereafter 600 mg/m^2 on Days 1 and 22 of each 42-day cycle; placebo will be administered by IV infusion on Days 1 and 22 of every 42-day cycle
  - All antiemetic premedication will be given a minimum of 30 minutes prior to zolbetuximab/placebo treatment
- Oxaliplatin (85 mg/m^2) will be administered by IV on Days 1, 15, and 29 of each 42-day cycle for up to four cycles (12 treatments)
- Folinic acid (400 mg/m^2) will be administered by IV on Days 1, 15, and 29 of each 42-day cycle for up to four cycles; folinic acid can be continued beyond four cycles based on investigator's judgement
  - Levo-folinic acid may be given as deemed appropriate by the investigator in accordance with institutional standard of care
  - In Japan only, folinic acid can be substituted for levofolinate (200 mg/m^2); levofolinate will be administered by IV on Days 1, 15, and 29 of each 42-day cycle for up to four cycles and can be continued beyond four cycles based on investigator's judgement
- A 5-FU (400 mg/m^2) IV bolus, followed by a 5-FU (2400 mg/m^2) IV infusion administered over 46-48 hours, will be administered by IV on Days 1, 15, and 29 of each 42-day cycle for up to four cycles and continued beyond four cycles based on investigator's judgement
- All patients will receive zolbetuximab or placebo until IRC-confirmed disease progression, toxicity requiring study treatment cessation, start of another anticancer treatment, or until other treatment discontinuation criteria are met
- Dose increase or dose reduction for zolbetuximab/placebo will not be allowed

Study Assessments

- Radiologic imaging will be evaluated at screening, every 9 weeks for the first 54 weeks, and then every 12 weeks thereafter
  - Progression-free survival is defined as the time from the date of randomization until the date of radiological disease progression, as assessed by IRC, or until death due to any cause, whichever is earlier
  - Overall survival is defined as the time from the date of randomization until the documented date of death from any cause
  - Objective response rate is defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) based on IRC per RECIST v1.1
  - Duration of response is defined as the time from the date of the first response of CR or PR (whichever is recorded first), as assessed by IRC, to the date of radiological progression or death, whichever is earlier
  - The distribution of PFS, OS, and DoR will be estimated for each treatment arm using Kaplan-Meier methodology and compared between treatment arms using stratified log-rank tests
    - For PFS, OS, and DoR, a stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% confidence interval
  - A comparison of ORR between treatment arms will be performed using a stratified Cochran-Mantel-Haenszel test
  - Safety and tolerability will be assessed over the course of the study by monitoring the incidence and severity of AEs using NCI-CTCAE guidelines
    - Adverse events of special interest (ie, nausea/vomiting/abdominal pain, hypersensitivity reactions, infusion-related reactions, anemia, neutropenia) will be summarized
- Patients will complete HRQoL assessments at screening, every 3 weeks during study treatment, at study treatment discontinuation, and 30 and 90 days post zolbetuximab/placebo treatment
- Sampling for pharmacokinetics and immunogenicity will occur on Day 1 and Day 22 of Cycle 1 as well as Day 1 of Cycle 2 (PK only), Day 1 of Cycles 3, 5, 7, and 9, and 30 and 90 days post zolbetuximab/placebo treatment
- While the study is ongoing, a formal OS interim analysis is planned

Trial Status

- As of September 11, 2020, 198 sites have been activated

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Conflict of Interest

KS: Astellas, Lilly, Ono Pharmaceutical, Dainippon Sumitomo Pharma, Daiichi Sankyo, Taiho Pharmaceutical, Chuai Pharma, MSD, Medi Science, Bristol-Myers Squibb, Takeda, Pfizer, Novartis, AbbVie, Yakult – personal fees and/or grants. **SA:** Bristol-Myers Squibb, Celgene, Lilly, Merck, Roche, Servier, Nordic Bioscience, Hospira, Medac, Novartis, Roche Pharma AG, Vifor Pharma – paid for speakers' bureau and/or research funding and/or consulting/advisory. **YB:** AstraZeneca, Novartis, Genentech/Roche, MSD, Merck Serano, Bayer, BMS, Lilly, Taiho, Daiichi Sankyo, Astellas, BeiGene, GC Pharma, Samyang Biopharm, Hanmi, Genexine, GSK, Pfizer, Boreinger-Ingleheim, MacroGenics, Boston Biomedical, Five Prime, Curis, Takeda, Ono, CKD Pharma – paid consulting/advisory and/or grants. **DC:** Astellas, Merck, BMS, Lilly, Gritstone, Taiho, Genentech/Roche, Daiichi Sankyo – honoraria as a consultant. **PE:** Merck, Astellas, Celgene, Lilly, Loxo, Taiho – consultant. **DI:** Astellas – honoraria as a consultant. **SK:** Astellas – personal fees. **FL:** Astellas, AstraZeneca, BMS, Biontech, Lilly, Elsevier, Infomedica, Merck, MSD, Roche, Servier, Amgen – personal fees and/or grants. **MS:** No conflicts of interest to disclose. **EC:** Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Incyte, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier, Amgen, Boehringer Ingelheim, Ipsen, Roche – personal fees and/or research grant/funding. **RX:** No conflicts of interest to disclose. **AA, JP:** Astellas – employment. **JA:** Astellas – fees for advisory and research grant.

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