GLOW: Phase 3 Study of First-line Zolbetuximab + CAPOX Versus Placebo + CAPOX in Claudin18.2$^+$/HER2$^-$ Advanced/Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

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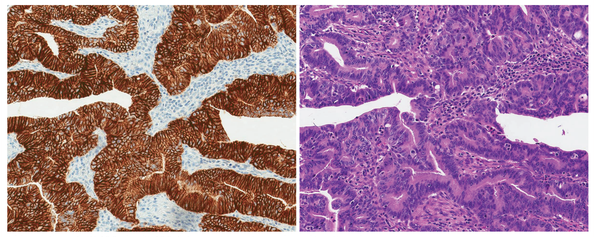
European Society for Medical Oncology-Asia
20-22 November 2020 | Virtual Congress

BACKGROUND

- Despite advances in treatment, gastric/gastroesophageal junction adenocarcinoma (G/GEJ) remains a leading cause of cancer-related death worldwide[1]
- The standard first-line chemotherapeutic regimen for advanced G/GEJ consists of fluoropyrimidine with platinum-based combinations, such as capecitabine + oxaliplatin (CAPOX)[2]
- Despite therapeutic efforts, median progression-free survival (PFS) of 4 to 7 months and median overall survival (OS) of 9 to 13 months is currently what can be expected[2]
- 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 G/GEJ; however, the frequency of their expression in G/GEJ is limited[3,4]
  - 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 adenocarcinoma
- 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)[5]; however, upon malignant transformation, structural loss in G/GEJ cells may allow antibodies more access to previously unavailable CLDN18.2[6]
- Data suggests that CLDN18.2 is a highly prevalent therapeutic target in G/GEJ (**Figure 1**), with low (~12%) overlap of expression with HER2[3]; CLDN18.2 expression is maintained in G/GEJ metastases[5]

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

A. CLDN18.2 **B. Hematoxylin/Eosin**



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

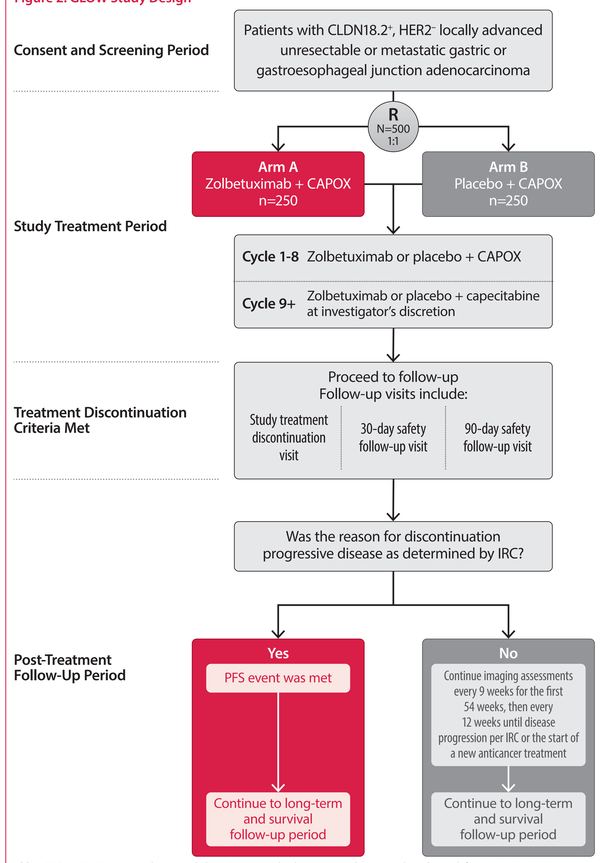
- Zolbetuximab is a chimeric IgG1 monoclonal antibody that specifically binds to CLDN18.2 and mediates tumor cell death through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity[7,8]
- In preclinical models of G/GEJ, treatment with certain chemotherapeutics sensitized tumor 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[6,9]
- Zolbetuximab, as a single agent[8,10] 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 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%[8]

METHODS

Study Design and Objectives

- Patients with CLDN18.2$^+$/HER2-negative (HER2$^-$) locally advanced unresectable or metastatic G/GEJ adenocarcinoma not previously treated with chemotherapy will be randomized 1:1 to receive either zolbetuximab or placebo in combination with CAPOX chemotherapy (**Figure 2**)
- This double-blind, placebo-controlled phase 3 study (NCT03653507) is being conducted in ~500 adult patients from ~130 centers globally

Figure 2. GLOW Study Design



Abbreviations: CAPOX, capecitabine + oxaliplatin; CLDN18.2, claudin 18.2; HER2, human epidermal growth factor receptor 2; IRC, independent review committee; OS, overall survival; PFS, progression-free survival; R, randomized.

A new, double-blind, placebo-controlled, randomized phase 3 study is evaluating the efficacy and safety of zolbetuximab plus capecitabine and oxaliplatin, compared with placebo plus capecitabine and oxaliplatin, as first-line treatment in patients with claudin 18.2-positive/human epidermal growth factor receptor 2-negative advanced or metastatic gastric or gastroesophageal junction adenocarcinoma.

- The primary objective of this study is to evaluate the efficacy of zolbetuximab plus CAPOX compared with placebo plus CAPOX (as first-line treatment) as measured by 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)
- The key secondary efficacy objective is to evaluate efficacy as measured by OS of zolbetuximab plus CAPOX compared with placebo plus CAPOX
  - Other secondary efficacy objectives are to compare objective response rate (ORR) and duration of response(DoR), assessed by IRC per RECIST v1.1, between treatment arms
- The safety and tolerability of zolbetuximab's profile, as 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, is a secondary objective
- Other secondary objectives include 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 plus STO22 Belching subscale, Global Pain (GP), and the EuroQOL Five Dimensions Questionnaire 5L (EQ5D-5L) questionnaires

Patient Population

- The patient population includes approximately 500 adult (≥18 years) patients with a histologically and radiologically confirmed (RECIST v1.1) diagnosis of locally advanced unresectable or metastatic G/GEJ whose tumors are CLDN18.2$^+$/HER2$^-$ and who have not been previously treated for metastatic disease with chemotherapy
  - Tumor tissue will be collected at screening to determine CLDN18.2 and HER2 status (if unknown) by central testing; patients will be considered CLDN18.2$^+$ if ≥75% of tumor cells demonstrate moderate-to-strong membranous immunohistochemistry staining
- 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 first dose of study treatment, are ineligible

Study Treatment

- Patients will be randomized 1:1 to receive zolbetuximab or placebo in combination with CAPOX
  - Zolbetuximab will be administered by IV infusion as an 800 mg/m^2 loading dose (Cycle 1, Day 1) followed by 600 mg/m^2 on Day 1 of each 21-day cycle thereafter; placebo will be administered by IV infusion on Day 1 of every 21-day cycle
  - Oxaliplatin (130 mg/m^2) will be administered by IV on Day 1 of each 21-day cycle for up to eight cycles; capecitabine (1000 mg/m^2) will be administered orally twice daily on Days 1-14 of each 21-day cycle
    - From Cycle 9 onward, capecitabine may be administered at the investigator's discretion
- Randomization of patients will be stratified by region (Asia vs non-Asia), number of organs with metastatic sites (0 to 2 vs ≥ 3), and prior gastrectomy (yes or no)
- All patients will receive zolbetuximab or placebo until IRC-confirmed disease progression, toxicity requiring study treatment cessation, start of another anticancer treatment, or other treatment discontinuation criteria are met
- Dose increase or dose reduction for zolbetuximab/placebo will not be allowed

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 subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) based on IRC per RECIST v1.1
  - The DoR is defined as the time from the date of the first response of CR or PR (whichever is first recorded), 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 will be summarized; these include nausea, vomiting, abdominal pain, anemia, neutropenia, and hypersensitivity/infusion-related reaction
- 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 of Cycles 1-3 (every 3 weeks), as well as Day 1 of Cycles 5, 9, 13, and 17, and 30 and 90 days post zolbetuximab/placebo treatment
- While the study is ongoing, a formal OS interim analysis is planned when the final PFS analysis occurs with the prespecified number of PFS events
  - The Independent Data Monitoring Committee may recommend terminating the study for favorable results at interim OS analysis

Trial Status

- As of September 11, 2020, 153 study sites were activated

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Conflict of Interest

RX: No conflicts of interest to disclose. **JA:** Astellas – fees for advisory and research grant. **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, Merck Sharp & Dohme, Merck Serano, Bayer, Bristol-Myers Squibb, Lilly, Taiho, Daiichi Sankyo, Astellas, BeiGene, GreenCross, Samyang Biopharm, Hanmi, Genexine, GSK, Pfizer, Boehringer Ingelheim, MacroGenics, Boston Biomedical, FivePrime, Curis, Takeda, Ono, CKD Pharma – paid consulting/advisory and/or grants. **DC:** Astellas, Merck, Bristol-Myers Squibb, Lilly, Gritstone, Taiho, Genentech/Roche, Daichii 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, Bristol-Myers Squibb, Biontech, Lilly, Elsevier, Infomedica, Merck, Merck Sharp & Dohme, Roche, Servier, Amgen – personal fees and/or grants. **KS:** Astellas, Lilly, Ono Pharmaceutical, Daiinppon Sumitomo Pharma, Daiichi Sankyo, Taiho Pharmaceutical, Chuai Pharma, Merck Sharp & Dohme, Medi Science, Bristol-Myers Squibb, Takeda, Pfizer, Novartis, AbbVie, Yakult – personal fees and/or grants. **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. **AA, JP:** Astellas – employment. **MS:** No conflicts of interest to disclose.

Acknowledgments

This study was supported Astellas Pharma, Inc. Financial support for the development of this presentation, including medical writing and editorial assistance under the authors' guidance, provided by Patrick Tucker, PhD, Cathy R. Weiss, PhD, and Elizabeth Hermans, PhD, of OPEN Health Medical Communications, was funded by Astellas Pharma, Inc. (Northbrook, IL, USA).