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Spotlight

SPOTlight on GLOW

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The GLOW randomized double-blind phase 3 trial[1] shows that Claudin-18.2 targeting antibody zolbetuximab combined with capecitabine and oxaliplatin improves outcome compared to placebo and chemotherapy as first-line treatment in Claudin-18.2-positive, HER2-negative gastric or gastroesophageal junction adenocarcinomas.

Unresectable or metastatic adenocarcinomas of the stomach or gastroesophageal junction (GEJ) is a very deadly and difficult-to-treat cancer. First-line palliative treatment usually consists of a platinum-fluoropyrimide doublet, which prolongs survival to approximately 1 year[2] and improves quality of life compared to best supportive care.[3] Dependent on the biomarker profile, PD-1 inhibition or HER2-targeting agents can be added to the chemotherapy, which improves the median overall survival (OS) from 11 to ~14 months. Around 60% of tumors have PD-L1 CPS scores ≥5, and ~10% of gastric cancers are human epidermal growth factor receptor 2 (HER2) positive. Thus, personalized therapeutic strategies are not yet available for all patients.

The newest biomarker and molecular target in this disease is Claudin-18.2 (CLDN18.2), a tight junction protein that maintains the barrier function of gastric mucosa and is usually not expressed on the cell surface. Upon malignant transformation, CLDN18.2 becomes visible on the cell surface and therefore accessible to monoclonal antibodies, such as zolbetuximab.[4] After binding to CLDN18.2, zolbetuximab stimulates cellular and soluble immune effectors that activate antibody-dependent cytotoxicity (ADCC) and complement-dependent cytotoxicity and thereby initiates an anti-tumor immune response. CLDN18.2 is highly expressed (defined as >75% of cancer cells with moderate to high expression) in ~40% of HER2-negative gastric cancers. The expression rate of CLDN18.2 may vary, however, depending on the patient's region of origin. In studies utilizing the same monoclonal antibody (clone 43–14A), the rate was 53.0% in Germany,[5] contrasting with a higher rate of 87.0% in Japan.[6]

With the publication of the GLOW study in *Nature Medicine*,[1] Shah et al. showed that zolbetuximab improves survival when combined with chemotherapy as first-line treatment in CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma. In the GLOW study, a total of 507 patients from 166 different sites in 18 distinct countries were randomized 1:1 to zolbetuximab with capecitabine and oxaliplatin (CAPOX) or placebo with CAPOX. GLOW met its primary endpoint with a median progression-free survival (PFS) of 8.21 vs. 6.80 months (hazard ratio [HR] 0.687 [95% CI 0.544–0.866]; p = 0.0007) and a median OS of 14.39 vs. 12.16 months (HR 0.771 [0.615–0.965]; p = 0.0018). The incidence of serious adverse events was similar between both treatment arms (47.2% vs. 49.8%), but >grade-3 nausea and vomiting occurred more often in the zolbetuximab arm (68.5% and 66.1%, respectively) compared to the placebo arm (50.2% and 30.9%, respectively).

Thereby results of the GLOW study nicely align with the publication of the concurrently conducted randomized phase 3 SPOTLIGHT trial.[7] This study demonstrated that the addition of zolbetuximab to an alternative first-line chemotherapy, 5-fluorouracil and oxaliplatin (FOLFOX), improves median PFS from 8.67 months to 10.61 months (HR 0 · 751 [95% CI 0 · 589–0·942 p = 0 · 0066]) and median OS from 15.54 months to 18.23 (HR 0 · 750 [0 · 601–0·936]; p = 0 · 0053). While the control arm in the SPOTLIGHT trial had a remarkable good prognosis of 15.5 months, which suggests that CLDN18.2-expressing tumors have a generally better prognosis, this was not observed in the GLOW trial (12.2 months). As the authors discuss, this difference in survival of the control arms can likely be attributed to differences in patient selection. The GLOW trial encompassed a larger number of patients from mainland China, whereas SPOTLIGHT featured patients from Japan and Korea, regions known for generally better patient prognosis. Also, within the GLOW trial it was observed that patients from Japan derived the most benefit from the addition of zolbetuximab. All together, these data confirm that CLDN18.2 by itself has no prognostic value. At this moment, zolbetuximab is awaiting approval from the FDA and EMA, but if approved, zolbetuximab would be the first CLDN18.2-targeted therapy available for patients with gastric cancer.

Interestingly, zolbetuximab showed efficacy in almost all subgroups except for cancers with a GEJ tumor location. Although GEJ adenocarcinomas formed a small subgroup (16%), these results might indicate that GEJ tumors have a distinct molecular or immunological background compared to gastric adenocarcinomas. This finding contrasts with a recent clinical and molecular characterization of CLDN18.2-expressing adenocarcinomas[8] that did not identify clear association between CLDN18.2 expression and molecular features except for

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KRAS amplification status. Also, a recent analysis of real-world data did not show a difference in efficacy of cytotoxic therapy among patients with esophageal adenocarcinoma, GEJ, or gastric cancer.[9] However, one could speculate that the function of CLDN18.2 may vary across different anatomical locations in the human body, potentially leading to differences in the effect of zolbetuximab. Moreover, variances in the immune microenvironment between distinct tumor locations may lead to varying levels of activation of ADCC and complement-dependent cytotoxicity upon the binding of zolbetuximab to CLDN18.2.

While we are awaiting the immunogenicity analyses within the GLOW trial, immune characterization of CLDN18.2-positive cancers in previous studies reported enhanced T cell infiltration in CLDN18.2-positive tumors compared to CLDN18.2-negative cancers, which might suggest that these tumors are more sensitive to immune stimulating strategies.[10] In the GLOW trial, 21.9% of CLDN18.2-positive tumors were also PD-L1 positive (CPS $\geq$5). Together, this raises the question whether these patients should combine chemotherapy with PD-1 inhibitors, with anti-CLN18.2, or with a combination of both. The ongoing ILLUSTRO trial (NCT03505320) that tests the efficacy of zolbetuximab in combination with PD-1 inhibitors will likely provide the answer. Until then zolbetuximab may be the best choice in scenarios where targeted strategies are not presently available, specifically in the niche of gastric cancers that are PD-L1 negative and HER2 negative.

DECLARATION OF INTERESTS

HWMvL reports (all payments are made to their institution) a consultant or advisory role for AstraZeneca, Beigene, BMS, and MSD (all related to checkpoint inhibitors) and for Amphera, Daiichi-Sankyo, Dragonfly, Eli Lilly, Nordic Pharma, and Servier; research funding, medication supply, or both from Incyte, Merck, Roche, and Servier (all related to checkpoint inhibitors) and from Bayer, BMS, Celgene, Janssen, Eli Lilly, Nordic Pharma, and Philips; and speaker roles for Astellas (related to checkpoint inhibitors), Benecke, Daiichi-Sankyo, JAAP, Medtalks, Novartis, and Travel Congress Management. S.D. reports a consultant or advisory role for BMS (related to checkpoint inhibitors); research funding, medication supply, or both from Incyte (related to checkpoint inhibitors); and speaker roles for Servier, BMS, and Benecke.

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