Zolbetuximab: A New First-Line Option for CLDN18.2-Positive Gastric Cancer?

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Gastric and gastroesophageal junction (GEJ) adenocarcinoma remains a significant challenge in oncology, particularly in its advanced, unresectable, or metastatic forms. Current first-line treatment options are limited, highlighting an urgent need for novel therapies. Recent Phase 3 clinical trials have investigated zolbetuximab, a monoclonal antibody targeting claudin-18 isoform 2 (CLDN18.2), in combination with standard chemotherapy regimens for patients with CLDN18.2-positive, HER2-negative advanced gastric or GEJ adenocarcinoma.

KEY TAKEAWAYS

- The Pivot: Zolbetuximab, a CLDN18.2-targeting antibody, significantly improved survival outcomes when added to first-line chemotherapy for specific gastric/GEJ adenocarcinomas.
- The Data: In SPOTLIGHT, median progression-free survival was 10.61 months with zolbetuximab + mFOLFOX6 vs. 8.67 months with placebo (HR 0.75; p=0.0066). In GLOW, median progression-free survival was 8.21 months with zolbetuximab + CAPOX vs. 6.80 months with placebo (HR 0.687; p=0.0007).
- The Action: Clinicians should consider CLDN18.2 testing for patients with HER2-negative, locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma to identify those who may benefit from zolbetuximab-based regimens.

Targeting CLDN18.2 in Gastric Cancer

Claudin-18 isoform 2 (CLDN18.2) is a tight junction protein expressed in normal gastric cells, and its expression is maintained in a significant proportion of malignant gastric and gastroesophageal junction (GEJ) adenocarcinoma cells. This makes CLDN18.2 an attractive therapeutic target for these cancers. Zolbetuximab is a first-in-class monoclonal antibody designed to specifically target CLDN18.2, leading to tumor cell death. Given the unmet need for improved first-line treatment options for patients with advanced gastric or GEJ adenocarcinoma, two global, randomized, double-blind, placebo-controlled Phase 3 trials, SPOTLIGHT and GLOW, were conducted to evaluate the efficacy and safety of zolbetuximab in combination with different standard chemotherapy regimens.

SPOTLIGHT Trial: Zolbetuximab with mFOLFOX6

The SPOTLIGHT trial (NCT03504397) enrolled 565 patients with CLDN18.2-positive (defined as ≥75% of tumor cells showing moderate-to-strong membranous CLDN18 staining), HER2-negative, previously untreated, locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. Patients were randomized 1:1 to receive either zolbetuximab (800 mg/m² loading dose followed by 600 mg/m² every 3 weeks) plus mFOLFOX6 (modified folinic acid, fluorouracil, and oxaliplatin regimen, every 2 weeks) or placebo plus mFOLFOX61.

The primary endpoint was progression-free survival (PFS) as assessed by an independent review committee. Secondary endpoints included overall survival (OS) and safety. The median follow-up for PFS was 12.94 months in the zolbetuximab group and 12.65 months in the placebo group1.

GLOW Trial: Zolbetuximab with CAPOX

The GLOW trial (NCT03653507) similarly investigated zolbetuximab as a first-line treatment. This study enrolled 507 patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. Patients were randomized 1:1 to receive zolbetuximab plus CAPOX (capecitabine and oxaliplatin) or placebo plus CAPOX2.

The primary endpoint for GLOW was also PFS, with OS as a key secondary endpoint. Both trials aimed to determine if adding zolbetuximab to standard chemotherapy could improve outcomes for this specific patient population.

Key Findings from SPOTLIGHT and GLOW

Both SPOTLIGHT and GLOW trials met their primary and key secondary endpoints, demonstrating significant clinical benefits with the addition of zolbetuximab to chemotherapy.

SPOTLIGHT Results:

• Progression-Free Survival: Zolbetuximab plus mFOLFOX6 significantly reduced the risk of disease progression or death compared with placebo plus mFOLFOX6 (hazard ratio [HR] 0.75, 95% CI 0.60-0.94; p=0.0066). The median PFS was 10.61 months (95% CI 8.90-12.48) in the zolbetuximab group versus 8.67 months (95% CI 8.21-10.28) in the placebo group1.

• Overall Survival: Zolbetuximab treatment also showed a significant reduction in the risk of death compared with placebo (HR 0.75, 95% CI 0.60-0.94; p=0.0053)1.

• Safety: Treatment-emergent grade 3 or worse adverse events occurred in 87% of patients in the zolbetuximab group versus 78% in the placebo group. The most common grade 3 or worse adverse events were nausea, vomiting, and decreased appetite. Treatment-related deaths occurred in five (2%) patients in the zolbetuximab group versus four (1%) patients in the placebo group. No new safety signals were identified1.

GLOW Results:

• Progression-Free Survival: Zolbetuximab plus CAPOX significantly improved PFS (median, 8.21 months versus 6.80 months with placebo; HR=0.687; 95% CI, 0.544-0.866; P=0.0007)2.

• Overall Survival: A significant improvement in OS was also observed (median, 14.39 months versus 12.16 months with placebo; HR=0.771; 95% CI, 0.615-0.965; P=0.0118)2.

• Safety: Grade ≥3 treatment-emergent adverse events were similar between the zolbetuximab (72.8%) and placebo (69.9%) groups2.

Clinical Implications

The consistent findings from both the SPOTLIGHT and GLOW trials suggest that zolbetuximab, when combined with mFOLFOX6 or CAPOX, may represent a new first-line treatment option for patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. The observed

improvements in both progression-free survival and overall survival are clinically meaningful for a patient population with limited therapeutic choices.

Why this matters for clinical practice today:

These results underscore the growing importance of molecular profiling in gastric and GEJ adenocarcinoma. Identifying CLDN18.2 positivity (defined as ₴5% of tumor cells showing moderate-to-strong membranous CLDN18 staining) will become a critical step in the diagnostic workup for patients with advanced HER2-negative disease. The availability of a targeted therapy like zolbetuximab could shift treatment paradigms, offering a personalized approach that extends survival for a specific subgroup of patients. Clinicians should integrate CLDN18.2 testing into their routine practice to ensure eligible patients can access this potentially beneficial treatment.

Limitations and Next Steps

While both trials demonstrated positive outcomes, it is important to note the increased incidence of grade 3 or worse adverse events, particularly gastrointestinal events like nausea, vomiting, and decreased appetite, in the zolbetuximab arms. These side effects will require careful management in clinical practice. Further research may focus on optimizing patient selection, exploring potential biomarkers for even greater response rates, and investigating zolbetuximab in earlier disease stages or in combination with other novel agents. Long-term follow-up data will also be valuable to fully understand the sustained benefits and safety profile of this new therapeutic approach.

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