Vyloy® (zolbetuximab-clzb) – New orphan drug approval

- On October 18, 2024, Astellas announced the FDA approval of Vyloy (zolbetuximab-clzb), in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are claudin (CLDN) 18.2 positive as determined by an FDA-approved test.

- In 2024, it is estimated that 26,890 people will be diagnosed with gastric or GEJ cancer and 10,880 will die from the disease in the U.S.

    - In the SPOTLIGHT and GLOW clinical trials, approximately 38% of patients screened had tumors that were CLDN18.2 positive.

- Vyloy is a novel CLDN18.2-directed cytolytic antibody and the first FDA approved targeted therapy for CLDN18.2.

- The efficacy of Vyloy was evaluated in SPOTLIGHT, a double-blind, randomized study in 565 patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors were CLDN18.2 positive. Patients were randomized to receive Vyloy in combination with mFOLFOX6 (combination chemotherapy regimen) or placebo in combination with mFOLFOX6. The major efficacy measure was progression free survival (PFS). Additional efficacy measures were overall survival (OS), objective response rate (ORR) and duration of response (DOR).

    - Median PFS was 10.6 months in the Vyloy arm vs. 8.7 months in the placebo arm (hazard ratio [HR] 0.751, 95% CI: 0.598, 0.942; p = 0.0066).
    - Median OS was 18.2 months in the Vyloy arm vs. 15.5 months in the placebo arm (HR 0.750, 95% CI: 0.601, 0.936; p = 0.0053).
    - The ORR was 40.3% (95% CI: 34.5, 46.3) in the Vyloy arm vs. 39.7% (95% CI: 34.0, 45.7) in the placebo arm.
    - The median DOR was 10.3 months (95% CI: 8.3, 10.9) in the Vyloy arm vs. 10.5 months (95% CI: 7.7, 13.3) in the placebo arm.

- The efficacy of Vyloy was also evaluated in GLOW, a double-blind, randomized study in 507 patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors were CLDN18.2 positive. Patients were randomized to receive Vyloy in combination with CAPOX (chemotherapy combination regimen) or placebo in combination with CAPOX. The major efficacy measure was PFS. Additional efficacy outcome measures were OS, ORR, and DOR.

    - Median PFS was 8.2 months in the Vyloy arm vs. 6.8 months in the placebo arm (HR 0.687, 95% CI: 0.544, 0.866; p = 0.0007).
    - Median OS was 14.4 months in the Vyloy arm vs. 12.2 months in the placebo arm (HR 0.771, 95% CI: 0.615, 0.965; p = 0.0118).
    - The ORR was 32.3% (95% CI: 26.6, 38.4) in the Vyloy arm vs. 31.2% (95% CI: 25.6, 37.3) in the placebo arm.
    - The median DOR was 8.3 months (95% CI: 6.3, 11.4) in the Vyloy arm vs. 6.2 months (95% CI: 6.0, 7.6) in the placebo arm.

- Warnings and precautions for Vyloy include hypersensitivity reactions, including anaphylaxis reactions, and infusion related reactions; and severe nausea and vomiting.

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- The most common adverse reactions (≥ 15%) with Vyloy use were nausea, vomiting, fatigue, decreased appetite, diarrhea, peripheral sensory neuropathy, abdominal pain, constipation, decreased weight, hypersensitivity reactions, and pyrexia.

- The most common laboratory abnormalities (≥ 15%) with Vyloy use were decreased neutrophil count, decreased leucocyte count, decreased albumin, increased creatinine, decreased hemoglobin, increased glucose, decreased lymphocyte count, increased aspartate aminotransferase, decreased platelets, increased alkaline phosphatase, increased alanine aminotransferase, decreased glucose, decreased sodium, increased phosphate, decreased potassium, and decreased magnesium.

- The recommended dose of Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is as follows:

    - First dose: 800 mg/m^2 intravenously
    - Subsequent doses:
        - 600 mg/m^2 intravenously every 3 weeks, or
        - 400 mg/m^2 intravenously every 2 weeks
    - Treatment should be continued until disease progression or unacceptable toxicity.

- Patients should be selected for treatment using an FDA-approved test. Information on FDA-approved tests for the detection of CLDN18.2 is available at http://www.fda.gov/CompanionDiagnostics.

- Astellas' launch plans for Vyloy are pending. Vyloy will be available as a 100 mg lyophilized powder in a single-dose vial.