FAST: An international, multicenter, randomized, phase II trial of epirubicin, oxaliplatin, and capecitabine (EOX) with or without IMAB362, a first-in-class anti-CLDN18.2 antibody, as first-line therapy in patients with advanced CLDN18.2+ gastric and gastroesophageal junction (GEJ) adenocarcinoma.

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- Abstract
- Journal of clinical oncology

Стр. LBA4001

Background: Claudin18.2 (CLDN18.2) is a tight junction protein expressed by several cancers including gastric and GEJ adenocarcinoma. IMAB362 is a chimeric monoclonal antibody that mediates specific killing of CLDN18.2-positive cancer cells by activation of immune effector mechanisms. IMAB362 has demonstrated single-agent activity and was safe and tolerable in patients (pts) with pretreated gastric cancer. **Methods:** Pts with advanced/recurrent gastric and GEJ cancer were centrally evaluated for CLDN18.2 expression by IHC (validated CLAUDETECT18.2 Kit). Eligible pts had a CLDN18.2 expression of ≥ 2+ in ≥ 40% tumor cells, an ECOG PS of 0–1 and were not eligible for trastuzumab. Pts were randomized 1:1 to first-line EOX (epirubicin 50 mg/m^2 and oxaliplatin 130 mg/m^2 d1, and capecitabine 625 mg/m^2 bid, d1–21; qd22) with or without IMAB362 (loading dose 800 mg/m^2, then 600 mg/m^2 d1, qd21). The study was extended by an exploratory Arm3 (N = 85) to investigate a high dose IMAB362 (1000 mg/m^2) plus EOX, (not subject here). The primary study endpoint was PFS (Arm 1 v 2, 70% power, HR 0.72, 1-sided p = 0.1). **Results:** 730 pts were consented, of whom 352 pts (48%) were tested CLDN18.2+ per protocol criteria. Of those, 161 pts (median age, 58 yrs; male 64%; gastric, 80%; GEJ, 16%; esophageal, 4%) were randomized into Arms1 and 2. The study met its endpoints. IMAB362 plus EOX improved PFS (median 5.7 v 7.9 mon; HR 0.5; 95% CI 0.35–0.78, 1-sided p = 0.001) and OS (median 8.7 v 12.5 mon; HR 0.5, 95% CI 0.28–0.73) compared to EOX alone. In the subpopulation with very high CLDN18.2 expression (≥ 2+ intensity in ≥ 70% tumor cells), efficacy was more pronounced (PFS, 6.1 vs 9.1 mon; HR 0.46; OS, 9.3 v 16.6 mon; HR 0.44). Most common IMAB362-related adverse events included vomiting, neutropenia, and anemia, which were mostly of NCI-CTC grade 1/2. Grade 3/4 events were not significantly increased by IMAB362. **Conclusions:** IMAB362 combined with first-line chemotherapy exhibited a clinically relevant benefit in PFS and OS and a favorable risk/benefit profile. Clinical trial information: NCT01630083.

http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.18_suppl.LBA4001