A phase 3 study of chemotherapy + pembrolizumab vs chemotherapy + placebo as neoadjuvant/adjuvant treatment for patients with gastric or gastroesophageal junction (G/GEJ) cancer: KEYNOTE-585 - Trial in progress

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Introduction: Pembrolizumab monotherapy demonstrated promising efficacy and manageable safety in patients with advanced metastatic G/GEJ adenocarcinoma who have received ≥2 prior lines of therapy, resulting in FDA approval for patients with PD-L1-positive tumors (combined positive score [CPS] ≥1) whose disease progressed on or after ≥2 prior lines of therapy. When combined with cisplatin and 5-fluorouracil (5-FU), pembrolizumab demonstrated promising efficacy and manageable safety in patients with previously untreated metastatic G/GEJ cancer in the phase 2 KEYNOTE-059 study. Combining chemotherapy with pembrolizumab in the neoadjuvant/adjuvant setting may be beneficial for patients with locally advanced, resectable G/GEJ cancer. KEYNOTE-585 (ClinicalTrials.gov, NCT03321426) is a phase 3, randomized, double-blind study to evaluate the efficacy and safety of chemotherapy + pembrolizumab versus chemotherapy + placebo as neoadjuvant/adjuvant treatment for locally advanced resectable G/GEJ cancer.

Methods: Key eligibility criteria are age ≥18 years; previously untreated localized G/GEJ adenocarcinoma (Siewert type 2 or 3 tumor; eligibility of Siewert type 1 tumors is limited to those for whom planned treatment is perioperative chemotherapy and resection), defined by T3 or greater primary lesion or the presence of any positive clinical nodes without evidence of metastatic disease; planned surgery after preoperative chemotherapy; Eastern Cooperative Oncology Group performance status 0/1; adequate organ function; no active autoimmune disease. Eligible patients will be randomly assigned in a 1:1 ratio to receive chemotherapy + pembrolizumab (arm 1) or chemotherapy + placebo (arm 2). Patients will receive neoadjuvant (preoperative) chemotherapy + pembrolizumab every 3 weeks (Q3W) for 3 cycles (arm 1) or chemotherapy + placebo Q3W for 3 cycles (arm 2) followed by surgery, then adjuvant chemotherapy + pembrolizumab Q3W for 3 cycles (arm 1) or chemotherapy + placebo Q3W for 3 cycles (arm 2). The monotherapy with pembrolizumab (arm 1) or placebo (arm 2) Q3W for 11 cycles; treatment will occur for up to 17 cycles. Chemotherapy is cisplatin 80 mg/m² 2 IV + either capecitabine 1000 mg/m² orally twice daily or 5-FU 800 mg/m² 2 IV (investigator’s choice). Pembrolizumab 200 mg was administered IV. In a separate safety cohort, 5-FU 2600 mg/m² 2 IV + docetaxel 50 mg/m² 2 IV + oxaliplatin 85 mg/m² 2 IV + leucovorin 200 mg/m² 2 IV every 2 weeks (FLOT) is being evaluated as a potential chemotherapy option. If adequate safety is demonstrated, FLOT may be incorporated as a chemotherapy backbone option in the main study. Primary end points are overall survival, event-free survival per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), by central review, and pathologic complete response (no invasive disease and histologically negative nodes) rate by central review. Secondary end points include safety and tolerability and disease-free survival per RECIST v1.1 by central review. Adverse events will be graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and will be monitored for 30 or 90 days after treatment. Patients will be followed for survival status until death, withdrawal of consent, or study end, whichever occurs first. Planned enrollment is 800 patients in the main study and 60 patients in the safety cohort.