UKE Paper of the Month October 2025

Perioperative pembrolizumab, trastuzumab and FLOT in HER2-positive localized esophagogastric adenocarcinoma: a phase 2 trial

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ABSTRACT:

Perioperative treatment strategies for HER2-positive esophagogastric adenocarcinoma remain suboptimal. Here in the open-label, phase 2 IKF/AIO PHERFLOT trial, we evaluated the safety and efficacy of adding pembrolizumab and trastuzumab to FLOT chemotherapy in patients with localized HER2-positive esophagogastric adenocarcinoma. The primary endpoints are the pathological complete response rate and the 2-year disease-free survival rate. Secondary endpoints include the R0 resection rate, feasibility and safety. Exploratory endpoints include clinical efficacy in molecularly defined subgroups. In this prespecified interim analysis, given the limited median follow-up period of 14.8 months, only one of the primary endpoints, the pathological complete response rate, and selected secondary endpoints, including the R0 resection rate, feasibility and safety, are reported here. Among 31 enrolled patients, 30 proceeded to R0 resection, and one patient declined surgery without disease progression. The combination regimen resulted in grade ≥3 treatment-related serious adverse events in 48.4% of patients (15 out of 31) aligning with established toxicity profiles of the respective agents and no treatment-related deaths. After four cycles of therapy, the pathological complete response rate was 48.4% (95% confidence interval 30.2–66.9; 15 out of 31) in the intention-to-treat population, and the subtotal regression rate (TRG1b according to Becker classification) was 19.4% (95% confidence interval 7.5–37.5; 6 out of 31), resulting in a major pathological response rate of 67.7% (95% confidence interval 48.6–83.3; 21 out of 31). Responses tended to be enriched in tumors with strong HER2 expression (immunohistochemistry 3+), high PD-L1 combined positive scores and lower T stage, but were also observed in substantial fractions of HER2 immunohistochemistry 2+/ISH+, T3 or T4 and combined positive scores <10 tumors. These findings support the feasibility and antitumor activity of perioperative chemoimmunotherapy targeting HER2 and PD-1 and warrant further validation in randomized trials. ClinicalTrials.gov registration: NCT05504720.

STATEMENT:

This study is the first to combine immune checkpoint inhibition, HER2-targeted therapy, and FLOT chemotherapy in the perioperative treatment of HER2-positive esophagogastric adenocarcinoma. We demonstrate that this approach is feasible and appears more effective than the current standard of care in terms of complete pathological response. Although disease-free survival data are not yet mature, the present findings indicate that this regimen warrants evaluation in a randomized trial against the current standard therapy for HER2-positive EGA. Moreover, with approximately half of the patients achieving a pathological complete response at the time of surgery, these results support the exploration of future surgery-free treatment strategies based on this combination.

BACKGROUND:

This trial was initiated by Eray Goekkurt and Alexander Stein from the Hämatoonkologische Praxis Eppendorf, affiliated with the UCCH, together with Joseph Tintelnot from the II. Department of Medicine. Translational samples were processed and analyzed in the laboratories of Mascha Binder (formerly at the University Medical Center Halle, now at the Universitätsspital Basel) and Joseph Tintelnot (II. Department of Medicine and Institute for Inflammation and Carcinogenesis, HCTI). The trial was sponsored by the IKF, supported by a research grant from MSD Sharp & Dohme GmbH, and eleven centers across Germany participated in patient recruitment.