Combining Zanidatamab, FOLFOX, and Pembrolizumab as First-Line Therapy for HER2/PD-L1–Positive Gastroesophageal Adenocarcinoma – the phase II IKF/AIO ZANGEA trial with translational analysis

Joseph Tintelnot[1], Eray Gökkurt[2], Salah-Eddin Al-Batran[3], Dirk Arnold[4], Thomas Dechow[5], Thomas Ettrich[6], Thorsten Götze[3], Kathrin Heinrich[7], Annika Kurreck[8], Sylvie Lorenzen[9], Markus Moehler[10], Viktor Rempel[11], Anke Schlenska-Lange[12] and Alexander Stein[2]

1 II. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 2 Hematology-Oncology Practice Eppendorf (HOPE), Hamburg, Germany; 3 Institute of Clinical Cancer Research, Krankenhaus Nordwest, Frankfurt, Germany; 4 Asklepios Klinik Altona, Hamburg, Germany; 5 Onkologie Ravensburg, Ravensburg, Germany; 6 I. Department of Medicine, University Hospital Ulm, Ulm, Germany; 7 Klinikum München Großhadern, München, Germany; 8 Charité – Universitaetsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Hematology, Oncology, and Cancer Immunology, Berlin, Germany; 9 Rechts der Isar Hospital, Technical University of Munich Germany; 10 Universitaetsmedizin Mainz, Mainz, Germany; 11 St. Anna Hospital Herne, Herne, Germany; 12 Barmherzige Brueder Regensburg Hospital, Regensburg, Germany

Introduction and objectives

Gastroesophageal adenocarcinoma (GEA) presents a substantial global health challenge as the number of cases continues to rise. The current standard approach for treating metastatic HER2/PD-L1 positive GEA involves a combination of doublet chemotherapy, which consists of a platinum compound and a fluoropyrimidine, in combination with trastuzumab and pembrolizumab[1]. Recently, the phase 3 HERIZON-GEA-01 trial has shown improved survival for zanidatamab in combination with CAPOX or 5-fluorouracil and cisplatin with the PD-1 inhibitor tislelizumab compared to chemotherapy and trastuzumab[2]. Zanidatamab is a HER2-directed biparatopic antibody that binds to the HER2 extracellular domains 2 and 4 in a trans configuration, facilitating the formation of distinct HER2 clusters on the cell surface increasing HER2 internalization and reducing total cellular HER2[3]. Treatment with zanidatamab reduces phosphorylation of EGFR, HER2, HER3 and downstream signaling through the MAP- and PI3-kinase pathways. In addition to direct effects on tumor cells, zanidatamab exerts several immune-mediated effects that include CDC, ADCC, and ADCP in HER2-expressing cancer cells. The key objective of this trial is to gain experience with the combinations of zanidatamab, modified FOLFOX, and pembrolizumab, as limited experience is currently available. Furthermore, biomarkers that predict response and toxicity are lacking. We and others have recently described plasma biomarkers, particularly T cell receptor richness and the neutrophil-to-lymphocyte ratio (NLR), as predictors of benefit from chemotherapy, immunotherapy, and anti-HER2 antibodies in metastatic HER2-positive GEA[4,5]. In addition to plasma markers, we will assess patients' diet, microbiota, and microbiota-derived metabolites, as these are important mediators of therapy response in patients with advanced cancer[6]. We therefore include a broad translational research program to identify predictors of response, as well as potential predictors of diarrhea, a frequently occurring side effect of HER2-targeting agents[2].

Trial Design

The ZANGEA trial is an open-label, single-arm, multicenter, translational phase II trial designed to assess the efficacy, safety, tolerability and translational aspects of zanidatamab in combination with FOLFOX and pembrolizumab in patients with 1st line HER2/PD-L1-positive GEA. In total, 80 patients ($\alpha = 0.05$, power 80%; PFS@12: 41.3% vs 55.3%) will be recruited. The primary endpoint is the progression-free survival rate after 12 months. Secondary objectives include safety and tolerability, efficacy in terms of objective response rate, progression-free and overall survival and translational markers, such as blood-based signatures (e.g. inflammatory cytokines), microbiota signatures, dietary patterns or microbiota derived metabolites that may correlate with therapy response or side-effects (Figure 1).
Recruitment started in December 2025.

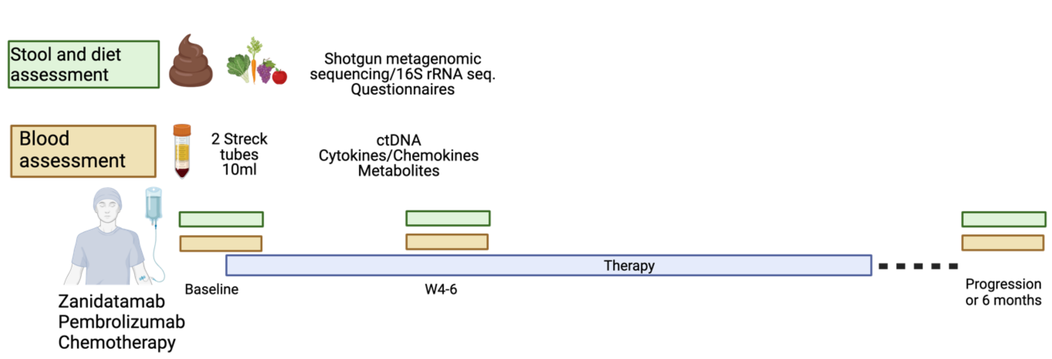

Figure 1: Overview of treatment and translational research.

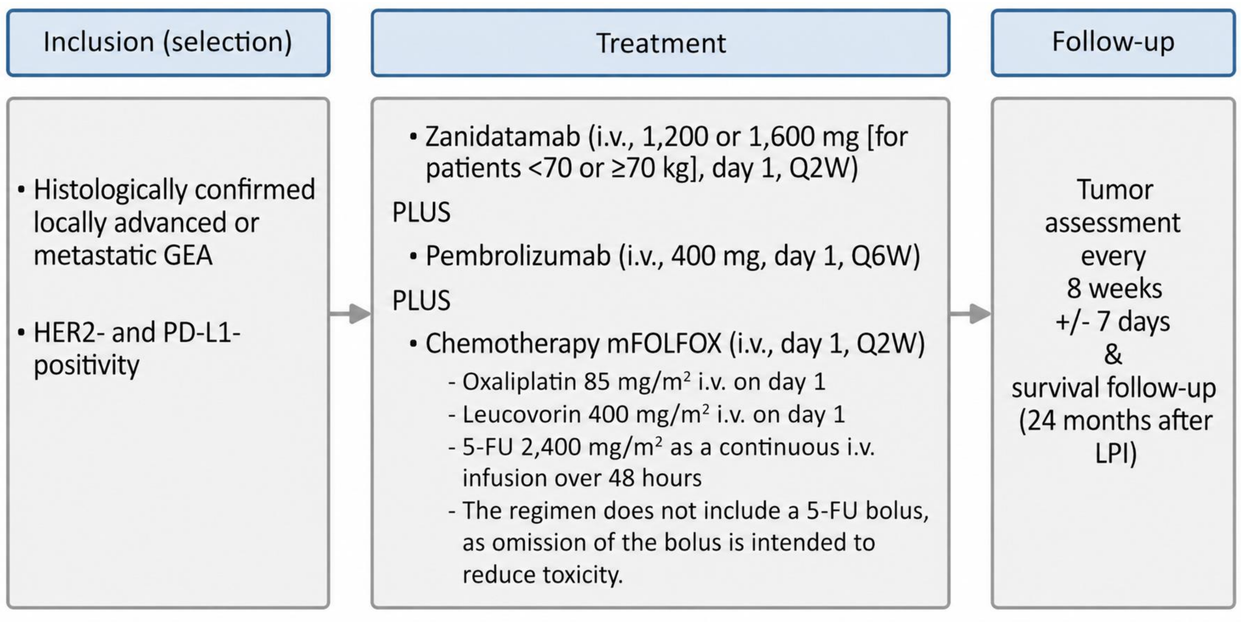

Figure 2. Overview of the trial design.

Table 1: Overview of key inclusion and exclusion criteria.

Key Inclusion criteria	Key Exclusion criteria
➢ Histologically confirmed diagnosis of GEA ➢ Locally advanced or metastatic disease ➢ Histologically confirmed HER2-positive (defined as IHC 3+ or IHC 2+ with ISH+) and PD-L1-positive (combined positive score CPS ≥ 1) disease (by local testing) ➢ ECOG performance status of ≤ 1 ➢ Measurable disease per RECIST 1.1 criteria ➢ Patient is ≥ 18 years of age at time of signing the written informed consent ➢ No prior anti-HER2 treatment ➢ perioperative immunotherapy allowed, if stopped >6 months before enrolement	➢ Patient has any known contraindication including allergy or hypersensitivity to the trial drugs ➢ Abnormal baseline left ventricular ejection fraction (LVEF < 50%) ➢ Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of trial drug administration ➢ Subjects with active, known, or suspected autoimmune disease.

First author contact information:
Dr. med. Joseph Tintelnot
j.tintelnot@uke.de

Last author contact information:
Prof. Dr. med. Alexander Stein
stein@hope-hamburg.de

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First author conflicts of interest:

Dr. med. Joseph Tintelnot is employed at University Medical Center Hamburg-Eppendorf

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Lecturing/Proctoring: BeOne, Servier
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