PHERFLOT – Pembrolizumab and trastuzumab in combination with FLOT in the perioperative treatment of HER2-positive, localized esophagogastric adenocarcinoma - A phase II trial of the AIO study group

AIO-Studie	
Studiennummer/-Code:	**AIO-STO-0321 - PHERFLOT**
Status:	in Vorbereitung
Rekrutierungszeitraum	Geplant: 2022 - 2023
Weitere Zentren:	Möglich
Zentren:	geplant: 10
Patienten:	geplant: 30
Letzte Aktualisierung	März 2022

Study type	Interventional, single-arm, open-label, multicenter phase II trial
Lead Coordinating Investigator	Dr. med. Eray Gökkurt Hämatologisch-Onkologische Praxis Eppendorf University Cancer Center Hamburg Eppendorfer Landstrasse 42 20249 Hamburg
Sponsor Project Management Sponsor	Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main Dr. Claudia Pauligk Tel: 069 / 76 01-3906 Email: pauligk.claudia@ikf-khnw.de
Objectives / Endpoints (efficacy, safety)	The primary objective of this phase II study is to demonstrate the efficacy of the FLOT/trastuzumab/pembrolizumab regimen in terms of an improvement in disease free survival (DFS) according to RECIST v1.1 and an increase in the pathological complete response (pCR) rate compared to historical controls (interim read out after surgery of last patient in study with 18 months recruitment after 24 months). Secondary objectives are further efficacy and tolerability parameters, including overall response rate according to RECIST v1.1, R0 resection rate, overall survival, safety, and tolerability (including perioperative morbidity). CO-Primary Endpoints: DFSR@2 is defined as the proportion of patients being tumor/disease free and alive 2 years after enrolment. The pCR rate is defined as the absence of residual tumor based on evaluation of the resected esophagogastric specimen in the primary tumor by local pathology. Secondary Endpoints • ORR – percentage of patients with CR or partial response (PR) according to RECIST 1.1. • R0 resection - microscopically margin negative resection with no gross or microscopic tumor remains in the areas of the primary tumor and/or sampled regional lymph nodes • OS – time from enrolment to the date of death of any cause • Feasibility rate - severe toxicity/withdrawal rate before the last postoperative administration of pembrolizumab/trastuzumab/FLOT has been completed.

	• (Serious) adverse events - recorded and graded according to NCI-CTCAE V5.0. Occurrence of (serious) adverse events at any time during the study. Description by nature (System Organ Class and Preferred Term), severity and causal relationship to drug administration. Explorative Endpoint: Assessment whether clinical efficacy correlates with molecularly-defined subgroups (PD-L1 expression, MSI subtypes, and others).
Background / Rationale	The overall outcome of esophagogastric cancer, although relevantly improving during the last decades, remains poor with more than 50% of patients recurring and consecutively dying despite aggressive treatments including perioperative chemotherapy and resection. Thus, further improvements are urgently required. Different combination regimens of chemotherapy (fluoropyrimidins, oxaliplatin +/- docetaxel) with pembrolizumab and/or trastuzumab has shown clinically relevant activity with a manageable safety pattern in recent phase II and III trials. Based on these data, particularly the KEYNOTE 585 trial with FLOT and pembrolizumab [Bang 2019] and HER-FLOT and PETRARCA with FLOT and trastuzumab +/- pertuzumab in the perioperative setting with high efficacy in perioperative treatment and good tolerability of the respective regimen, the PHERFLOT regimen seems safe and tolerable and yields a high potential to improve the limited prognosis of HER2 positive esophagogastric cancer patients. In addition, the close meshed monitoring of the IDMC (particular the run-in safety analysis) will detect any potential unexpected adverse events.
Population	Patients with HER2 positive, localized esophagogastric adenocarcinoma
Inclusion/exclusion criteria	Participants are eligible to be included in the study only if all of the following criteria apply: 1. The participant provides written informed consent for the trial. 2. Male/female* participants who are at least 18 years of age on the day of signing informed consent. *There are no data that indicate special gender distribution. Therefore, patients will be enrolled in the study gender-independently. 3. In the investigator's judgement, participant is willing and able to comply with the study protocol including the planned surgical treatment 4. Histologically confirmed adenocarcinoma of the GEJ (Type I-III according to Sievert´s classification) or the stomach (cT2, cT3, cT4, any N category, M0), or (any T, N+, M0) that: • is not infiltrating any adjacent organs or structures by CT or MRI evaluation • does not involve peritoneal carcinomatosis • is considered medically and technically resectable Note: the absence of distant metastases must be confirmed by CT or MRI of the thorax and abdomen, and, if there is clinical suspicion of osseous lesions, a bone scan. If peritoneal carcinomatosis is suspected clinically, its absence must be confirmed by laparoscopy. Diagnostic laparoscopy is mandatory in patients with T3 or T4 tumors of the diffuse type histology in the stomach. 5. Participants must have HER2-positive disease defined as either IHC 3+ or IHC 2+, the latter in combination with ISH+, as assessed locally on primary tumor (see Appendix 4)

6. Participants must be candidates for potential curative resection as determined by the treating surgeon
7. No prior systemic-anti cancer therapy (e.g. cytotoxic or targeted agents or radiotherapy)
8. No prior partial or complete esophagogastric tumor resection
9. ECOG (Eastern Cooperative Oncology Group) performance status score of 0 or 1
10. Male participants: A male participant must agree to use a contraception as detailed in Appendix 2 of this protocol during the treatment period and for at least 6 months after the last dose of study intervention and refrain from donating sperm during this period.

Female participants: A female participant is eligible to participate if she is not pregnant (see 2), not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in Appendix 2

OR

- A WOCBP who agrees to follow the contraceptive guidance as given in Appendix 2 during the treatment period and for at least 7 months after the last dose of study intervention.

11. Participants have adequate organ function as defined in the following table (Table below). Specimens must be collected within 14 days prior to enrolment (also to be repeated if older than 14 days at day of first treatment).

Adequate organ function laboratory values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1500/µL
leucocytes	≥ 3000/µL
Thrombocytes	≥ 100000/µL
Hemoglobin	≥ 9.0 g/dL or ≥ 5.6 mmol/L[a]
Renal: Measured or calculated[b] creatinine clearance (CrCl)	≥ 50 mL/min
Hepatic	
Total bilirubin	≤ 1.5 ×ULN OR direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 × ULN
Coagulation	

International normalized ratio (INR) OR prothrombin time (PT) and activated partial thromboplastin time (aPTT)	≤ 1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within the last 2 weeks.

[b] CrCl should be calculated per institutional standard.

Participants are excluded from the study if any of the following criteria apply:

1. Participants with involved retroperitoneal (e.g. para-aortal, paracaval or interaortocaval lymph nodes) or mesenterial lymph nodes (distant metastasis!)
2. A WOCBP who has a positive urine pregnancy test within 72 hours prior to start of study intervention (see Appendix 2). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
3. Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137).
4. Participant received colony-stimulating factors (e.g. granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF] or recombinant erythropoietin) within 28 days prior to the first dose of study intervention.
5. Major surgery within 2 weeks of starting study intervention and patients must have recovered from any effects of any major surgery.
6. Concomitant use of drugs inhibiting (dihydropyrimidine dehydrogenase) DPD activity (including sorivudine, brivudine), the required wash out phase is 4 weeks before start of the study intervention.
7. Inadequate cardiac function (LVEF value < 55 %) as determined by echocardiography
8. Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (e.g., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation > 500 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome.
9. Participant has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.
10. Participant is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.
11. Participant has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

	12. Participant has a known additional malignancy that is progressing or has required active treatment within the past 2 years. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded. 13. Participant has myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or with features suggestive of MDS/AML. 14. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion protein; known hypersensitivity to Chinese hamster ovary cell products or to any component of the pembrolizumab or trastuzumab formulation 15. Any known contraindication (including hypersensitivity) to docetaxel, 5-FU, folinic acid/leucovorin, or oxaliplatin. 16. Known DPD deficiency. Patients with a reduced DPD activity (CPIC activity score of 1.0-1.5) might participate in the study and receive a reduced dosage of 5-FU after discussion with the coordinating investigator and sponsor [https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/] 17. Participant has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed. 18. Participant has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease. 19. Participant has an active infection requiring systemic therapy. 20. Participant has a known history of Human Immunodeficiency Virus (HIV) infection 21. Participant has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA is detected) infection. 22. Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan, previous allogenic bone marrow/blood transplantation or any psychiatric disorder or substance abuse that prohibits obtaining informed consent. 23. Participant is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 6 months after the last dose of study intervention. 24. Participant has had an allogenic tissue/solid organ transplant.
Investigational and control drugs	Study drugs: Pembrolizumab, Trastuzumab FLOT according to clinical standard

Investigational and Control Arm, Dose, regimen, treatment cycle	<u>Preoperative Study-Treatment*:</u> ○ Pembrolizumab: 200 mg flat dose IV over 30 min, d1, d22, d43 ○ Trastuzumab: loading dose 8 mg/kg IV over 90 min, d1 6 mg/kg IV over 30 min**, d22, d43 ○ FLOT: Docetaxel 50 mg/m² IV over 1 hour Oxaliplatin 85 mg/m² IV over 2 hours Folinic Acid*** 200 mg/m² IV over 1 hour 5-FU**** 2600 mg/m² IV over 24 hours Every 2 weeks (d1, d15, d29, d43*) *Therapy can also be administered over two days, administering pembrolizumab/trastuzumab on first day and FLOT on following day at timepoints where combination is planned. **if initial dose was well tolerated ***Folinic acid can be applied according to local standards (product & dosing). ****See protocol for dose adjustments in patients with a reduced DPD activity <u>Surgical Resection</u> is recommended to be scheduled 4-6 weeks after last preoperative treatment. <u>Postoperative Study-Treatment:</u> Within 4-10 weeks after Surgery ○ Combination of Pembrolizumab/Trastuzumab/FLOT as described above, d1-d43 followed by combination of ○ Pembrolizumab(200 mg flat dose) and ○ Trastuzumab: (6 mg/kg) for up to 11 further cycles (Q3W). In total patients will receive up to 17 pembrolizumab/trastuzumab administrations (including pre- and postoperative applications).
Statistical considerations	The trial is designed as single arm, multicenter, open-label, phase II study, which aims to show therapeutic efficacy of the experimental regimen pembrolizumab and trastuzumab in combination with FLOT. The co-primary endpoints are the pathological complete response rate (pCR) and the disease-free survival rate after 2 years (DFSR@2). The efficacy assumptions can be obtained from the PETRARCA and the HER-FLOT study.28,29 In the PETRARCA study pCR rate in the standard FLOT arm was 12%. This could be increased to 22% with trastuzumab plus FLOT in the HER-FLOT trial and to 35% with trastuzumab, pertuzumab and FLOT in the PETRARCA trial. We envisage that the pCR rate for pembrolizumab, trastuzumab and FLOT could increase to 30% or more. Hence, for the experimental regimen to be considered as a desirable candidate for further development, the pCR of 30% should be achieved, but if it is 12% or less the experimental arm would be insufficient for further development. Formally, the hypothesis testing for the first co-primary endpoint can be defined as: H0: P≤ 0.12 versus H1: P≥0.30 The current sample size calculation is based on pCR improvement from 12% to 30% with a one-sided alpha of 5% and a beta of 20% in a Fleming single stage phase II procedure. Thus, 27 patients are required.

	Concurrently, for DFS the respective sample size calculation would be an improvement of DFS rate at 2 years from 50% (results of the FLOT 4 trial)10 to 70% the hypothesis testing for the second co-primary endpoint can be defined as: H0: P≤ 0.5 versus H1: P≥0.7 with a one-sided alpha of 0.1 and 80% power in a Fleming single stage phase II procedure, 27 patients are needed. Thus, a sample size of 27 patients is sufficient for both co-primary endpoints considering that the co-primary endpoints are homogeneous, no inflation of type II error is expected. We therefore keep the statistical power at 80% for both co-primary endpoints. Considering a drop-out rate of 10%, a total number of 30 patients will be enrolled.
Estimated duration of trial	max. 32 months from FPI to LPLT, followed by max. 24 months of survival follow up consisting of: 18 months recruiting (FPI to LPI) + max. 14 months of treatment (LPFT to LPLT) + max 24 months FU for OS after LPLT
Number of patients, and location	Total number of patients: 30 Location of sites: Germany
Number of enrolled pts.	0, trial in preparation
Participating centers	10 in total