**POLESTAR – Phase IIA trial of short-term chemotherapy and pembrolizumab, followed by Pembrolizumab and OLaparib as firstline therapy in Her-2 negative gastric/gastroESophageal-juncTion (GEJ) AdenocaRcinoma**

| **AIO-assoziierte Studie** | |
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| Studiennummer/-Code: | **AIO-STO-0121/ass - POLESTAR** |
| Status: | in Vorbereitung |
| Rekrutierungszeitraum | Geplant: 2022 - 2023 |
| Weitere Zentren: | Nicht benötigt |
| Zentren: | geplant: 11 |
| Patienten: | geplant: 31 |
| Letzte Aktualisierung | März 2022 |

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| Study type | Interventional, single-arm, open-label, multicenter phase II trial |
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| Sponsor<br><br><br><br>Project Management Sponsor | Institut für Klinische Krebsforschung IKF GmbH<br>at Krankenhaus Nordwest<br>Steinbacher Hohl 2-26<br>60488 Frankfurt am Main<br><br>Tanita Brulin, Dr. Claudia Pauligk<br>Tel: +49 69 / 76 01-3906<br>Email: brulin.tanita@ikf-khnw.de; pauligk.claudia@ikf-khnw.de |
| Objectives / Endpoints (efficacy, safety) | The primary objective of this phase II study is to assess the overall survival at 1 year. Secondary objectives are the assessment of the objective response rate, the best overall response, time to tumor progression, overall survival, treatment feasibility rate along with safety and toxicity of the treatment.<br><br>Primary endpoint<br>• Overall survival (OS) rate at 1 year<br><br>Secondary Endpoints<br>• Progression-free survival, defined as time from enrollment to disease progression according to RECIST 1.1 and iRECIST or death due to any cause.<br>• Objective response rate (ORR), defined as the percentage of patients with complete response (CR) or partial response (PR) according to RECIST 1.1 and iRECIST.<br>• Best overall response, defined as the best response recorded from enrollment to treatment discontinuation for any reason.<br>• Time to tumor progression (TTP), defined as time from enrollment to disease progression according to RECIST 1.1 and iRECIST.<br>• Overall survival (OS), defined as time from enrollment to the date of death of any cause.<br>• Feasibility rate, defined as 1 - severe toxicity/withdrawal rate before the fourth cycle of pembrolizumab/olaparib has been completed.<br>• Safety and toxicity: Adverse events will be recorded and graded according to version 5.0 of National Cancer Institute Common Toxicity Criteria (NCI-CTC). |

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| Background / Rationale | Pembrolizumab as monotherapy has shown non-inferiority in comparison to a platinum-based chemotherapy in Her-2 negative patients with a PD-L1 CPS ≥ 1. However, response rate and progression-free survival are inferior in comparison to a platinum-based chemotherapy. In addition, early mortality during the first year is higher with pembrolizumab than with chemotherapy. Early results from Checkmate 649 and Keynote 590 suggest a superior outcome of chemotherapy combined with a PD-1 inhibitor in a PD-L1 all-comers population. Given these results, the optimal duration of chemotherapy is unknown, taking into consideration that the best response is usually seen during the first three months of treatment and that a prolonged oxaliplatin-based therapy is associated with an increased risk of higher-grade sensory polyneuropathy. In addition, several phase II trials have shown that a platinum-compound can be omitted after several months of treatment without negatively affecting overall survival (Park. Euro J Cancer 2017; Haag 2020) and avelumab has shown a comparable outcome as maintenance therapy irrespective of PD-L1 expression in a phase III trial. HRD alterations are found in approximately 15-20% of patients with esophagogastric adenocarcinoma; given the limited efficacy of PARP inhibitors in patients with platinum-refractory disease, an early use in patients with platinum-sensitive disease should be preferred.<br>In addition, preclinical data suggest a synergistic effect of a combined PD-1 inhibitor and a PARP inhibitor including patients without a specific HRD mutation as highlighted by the following data<br>• Impaired DNA repair induced by PARP inhibitors could generate DNA damage that leads to increase of the neoantigen load [Brown et al. 2018].<br>• DNA damages and DDR deficiencies induce the activation of cGAS–STING and NF-κB pathways, leading to inflammation and infiltration of tumors by immune cells across multiple types of cancers, a prerequisite of tumor-killing effect of ICI [Strickland et al. 2016]. PARP inhibitors lead to an upregulation of PD-L1 expression, which might improve activity of PD-1 inhibition [Jiao et al. 2017].<br>• The antitumor activity of PARPi has been observed in patients with platinum-sensitive tumors regardless of BRCA1/2 mutation or HRD status, suggesting an alternative mechanism unrelated to conventional lethal synthetic-mediated cytotoxic effects [Mirza et al. 2016].<br>As a consequence, there is a strong rationale for the combination of olaparib and pembrolizumab as consolidation therapy after a three-months chemo-immunotherapy in patients with platinum-sensitive, Her-2 negative esophagogastric adenocarcinoma independent of PD-L1 CPS status and independent of the HRD mutational status.. Given the high response rate and high-disease control rate achieved in PD-L1 all-comers with the combination of PD-1 inhibitors and platinum-based chemotherapy, this initial cytotoxic therapy will be helpful to ensureAn initial short-term chemotherapy could be helpful to ensure an early disease control in patients with a high tumor load before efficacy of immunotherapy combined with the PARP inhibitor can be observed, thus avoiding a symptomatic deterioration during the first weeks of treatment. |
| Population | Patients with metastatic or locally unresectable, histologically confirmed Her-2 negative adenocarcinoma of the gastroesophageal junction (AEG I-III according to Sievert´s classification) or the stomach. |
| Inclusion/exclusion criteria | Patients must meet all of the following **<u>Inclusion Criteria</u>** for trial participation:<br>1. Metastatic or locally unresectable, histologically confirmed Her-2 negative (as assessed locally by a certified test) adenocarcinoma of the gastroesophageal junction (AEG I-III according to Sievert´s classification) or the stomach.<br>2. Adjuvant/neoadjuvant or perioperative chemotherapy or chemoradiotherapy must have been finished at least 6 months before start of the study intervention.<br>3. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. |

4. Ability for oral intake of the study drug.
5. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of esophagogastric adenocarcinoma will be enrolled in this study.
6. Male participants: A male participant must agree to use a contraception as detailed in the 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.
7. Female participants: A female participant is eligible to participate if she is not pregnant , not breastfeeding, and at least one of the following conditions applies:
   a. Not a woman of childbearing potential (WOCBP) as defined in protocol OR
   b. A WOCBP who agrees to follow the contraceptive guidance as given in protocol during the treatment period and for at least 6 months after the last dose of study intervention.
8. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.
9. Have measurable or evaluable disease based on RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
10. Have provided archival tumor tissue sample. FFPE tissue blocks are preferred to slides.
11. Have adequate organ function as defined in the following table. Specimens must be collected within 14 days prior to the start of study intervention.

| System | Laboratory Value |
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| Hematological | |
| Absolute neutrophil count (ANC) | ≥ 1500/μL |
| Platelets | ≥ 100 000/μL |
| Hemoglobin | ≥ 9.0 g/dL or ≥ 5.6 mmol/L[a] |
| Renal | |
| Measured or calculated[b] creatinine clearance | ≥ 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 (≤ 5 × ULN for participants with liver metastases) |
| Coagulation | |
| International normalized ratio (INR) OR prothrombin time (PT) 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] Creatinine clearance (CrCl) should be calculated per institutional standard.

**Patients who meet at least one of the following Exclusion Criteria are not eligible for trial participation:**

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| | 1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to start of study intervention. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.<br>2. Has 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). Has received any previous treatment with a PARP inhibitor, including Olaparib.<br>3. Has received prior systemic anti-cancer therapy for metastatic or locally advanced (irresectable) disease. A prior neoadjuvant or adjuvant chemotherapy is allowed (see inclusion criterion 2)<br>4. Persistent clinically relevant toxicities, CTCAE Grade > 2 caused by previous cancer treatment.<br>5. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.<br>6. Participant received colony-stimulating factors (eg, 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.<br>7. Participant is unable to swallow orally administered medication or has a gastrointestinal disorder affecting absorption.<br>8. Major surgery within 2 weeks of starting study intervention and patients must have recovered from any effects of any major surgery.<br>9. Participant is currently receiving either strong (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) inhibitors of cytochrome P450 (CYP)3A4 that cannot be discontinued for the duration of the study. The required washout period prior to starting olaparib is 2 weeks. *Note: a current list of strong/moderate inhibitors of CYP3A4 can be found at the following website:* https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers<br>10. Participant is currently receiving either strong (phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate (eg. bosentan, efavirenz, modafinil) inducers of CYP3A4 that cannot be discontinued for the duration of the study. The required washout period prior to starting olaparib is 5 weeks for phenobarbital and 3 weeks for other agents. *Note: a current list of strong/moderate inducers of CYP3A4 can be found at the following website:* https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers<br>11. Concomitant use of drugs inhibiting DPD activity (including sorivudine, brivudine), the required wash out phase is 4 weeks before start of the study intervention.<br>12. 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.<br>13. 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.<br>14. 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.<br>15. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) |

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| | or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.<br>16. 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.<br>17. Participant has myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or with features suggestive of MDS/AML.<br>18. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously completely resected brain metastases may participate if there is no sign of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention.<br>19. Has severe hypersensitivity (≥ Grade 3) to FOLFOX or CAPOX-based chemotherapy, olaparib, pembrolizumab and/or any of its excipients.<br>20. 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/capecitabine after discussion with the coordinating investigator and sponsor [https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/]<br>21. 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.<br>22. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.<br>23. Has an active infection requiring systemic therapy.<br>24. Has a known history of Human Immunodeficiency Virus (HIV) infection (known HIV1/HIV2 antibodies positive).<br>25. Has a known history of/active Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA is detected) infection.<br>26. 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.<br>27. 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.<br>28. Has had an allogenic tissue/solid organ transplant. |
| Investigational and control drugs | Study drugs: Pembrolizumab, Olaparib<br>Study treatment: modified FOLFOX-6 or CAPOX plus Pembrolizumab, followed by Pembrolizumab and Olaparib |
| Investigational and Control Arm, Dose, regimen, treatment cycle | <u>Chemotherapy plus Pembrolizumab 2 cycles à 6 weeks:</u><br><br><u>Pembrolizumab+mod FOLFOX-6:</u><br>• Pembrolizumab 400 mg 30 min. day 1 **<br>• Oxaliplatin 85 mg/m² 2h day 1, 15, 29 |

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| | • Leucovorin* 400 mg/m² 2h day 1, 15, 29<br>• 5-FU 400 mg/m² bolus, followed by 2.400 mg/m² 46h day 1, 15, 29<br><br>The cycle is repeated on day 43.<br><br>(*) Note: Leucovorin can be replaced by sodium folinate that is given according to local guideline.<br>(**) Pembrolizumab has to be applied before chemotherapy<br>**or**<br><u>Pembrolizumab+CapOx:</u><br>• Pembrolizumab 400 mg 30 min. day 1 **<br>• Oxaliplatin 130 mg/m² 2h day 1,22<br>• Capecitabine 1.000 mg/m² bid. day 1-14, 22-35<br><br>The cycle is repeated on day 43.<br><br>(**) Pembrolizumab has to be applied before chemotherapy<br>.<br><u>Consolidation phase Pembrolizumab and Olaparib max 16 cycles à 6 weeks:</u><br>• Pembrolizumab 400 mg 30 min. day 1<br>• Olaparib 300 mg bid. cont. day 1 to 42<br><br>The cycle is repeated on day 43. |
| Statistical considerations | Platinum-based chemotherapy alone leads to a one-year survival rate of about 45%, the same survival rate has been observed with pembrolizumab monotherapy in patients with PD-L1 CPS ≥ 1 [18]. Assuming a higher efficacy of the combination of pembrolizumab and olaparib among patients with HR mutations, the one-year survival rate in the cohort with HR alterations is expected to be 75%, whereas the expected one-year survival rate for patients without HR mutations is 65%. Considering a prevalence rate of 20% for patients with one of the predefined HR alterations an overall one-year survival rate of 67% is expected in the total trial population.<br>A single stage design for pilot studies according to Fleming [51] will be applied to test the null-hypothesis that the true 1-year OS rate in study subjects is ≤ 45% (P0) against a one-sided alternative that the 1-year OS rate ≥ 67 % (Pa):<br>H0: P ≤ P0 HA: P ≥ PA<br>With an alpha of 5% and a power of 80%, 31 patients are required based on the assumptions that the experimental therapy would be rated as unacceptable, if the actual one-year survival rate was only 45% or lower, or that on the other hand, the therapy regimen would be considered to be a promising candidate for further development, if the true one-year survival rate amounted to 67% or more.<br><br>If the number of surviving patients is 19 or more, the null hypothesis that P ≤ 0.45 is rejected with an |

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| | actual type I error rate of 0.05. If the number of surviving patients is 18 or less, the alternative hypothesis that P ≥ 0.67 is rejected with a target error rate of 0.2 and an actual error rate of 0.19. There is no full interim analysis planned for this study, due to the small sample size and the relatively short recruitment period. |
| Key dates | FPFV (planned): Q2 2022<br>max. 55 months from FPI to LPO<br>consisting of:<br>12 months recruiting (FPI to LPI)<br>+ max. 25 months of treatment (LPFT to LPLT)<br>+ max 18 months FU for OS after LPLT |
| Number of patients, and location | Total number of patients: 31<br>Location of sites: Germany |
| Number of enrolled pts. | 0, trial in preparation |
| Participating centers | 11 in total |