

**AIO-STO-0317: A randomized, open-label Phase II efficacy and safety study of Atezolizumab in combination with FLOT versus FLOT alone in patients with gastric cancer and adenocarcinoma of the oesophago-gastric junction (MO30039) – The DANTE Trial**

**AIO-Studie**

Studiennummer/-Code:	AIO-STO-0317 - DANTE-Trial	
Status:	Rekrutierung beendet	
Rekrutierungszeitraum	2018-2020	
Weitere Zentren:	sind leider nicht möglich	
Zentren:	geplant:	initiiert:
Patienten:	geplant: 295	aktuell eingeschlossen: 295
Letzte Aktualisierung	15.10.2020	

Study type	Multicenter, randomized, open label phase II study
Protocol Code	MO30039 / DANTE
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Sponsor	IKF Klinische Krebsforschung GmbH at Krankenhaus Nordwest Steinbacher Hohl 2-26 60488 Frankfurt am Main
Project Management Sponsor	Lisa Waberer Tel: +49 69 / 76 01-4211 Email: waberer.lisa@ikf-khnw.de
Investigational and control drugs	Atezolizumab FLOT (backbone therapy)
Objectives	<p><u>Primary Efficacy Objective</u></p> <ul style="list-style-type: none"> <li>to compare progression/disease-free survival (PFS/DFS) in patients with locally advanced, operable esophagogastric adenocarcinoma receiving perioperative FLOT with atezolizumab versus FLOT alone in the intent to treat population (ITT) and where PFS/DFS is defined as the time from randomization to disease progression or relapse after surgery or death from any cause</li> </ul> <p><u>Secondary Efficacy Objectives</u></p> <ul style="list-style-type: none"> <li>Pathological complete regression (pCR, TRG 1a by Becker) rate where pCR is defined as the absence of residual tumor based on evaluation of the resected esophagogastric specimen in the primary by a central reference pathologist</li> <li>Pathological complete and subtotal regression (TRG1a/b by Becker). TRG1a/b is defined as &lt; 10% residual tumor per tumor bed based on evaluation of the resected esophagogastric specimen in the primary by a central reference pathologist.</li> <li>TRG1a and TRG1a/b in the sampled regional lymph nodes.</li> <li>R0 resection rate where R0 resection is defined as a microscopically margin negative resection with no gross or microscopic tumor remains in</li> </ul>

	<p>the areas of the primary tumor and/or sampled regional lymph nodes based on evaluation by the local pathologist.</p> <ul style="list-style-type: none"> <li>• Overall survival (OS) where OS is defined as the time from randomization to death from any cause</li> <li>• The immune cell infiltration rate determined by comparing the density of CD8-positive cells in tumor biopsies obtained from the same tumor location at baseline and after two and four cycles of study treatment..</li> </ul> <p><u>Safety Objectives</u></p> <ul style="list-style-type: none"> <li>• Incidence, frequency, severity, and timing of adverse events (AEs)</li> <li>• Changes in vital signs, physical findings, and clinical laboratory results</li> <li>• Perioperative morbidity and mortality</li> </ul>
<p>Study design</p>	<p>This is a multicenter, randomized, controlled, open-label study comparing perioperative atezolizumab with FLOT chemotherapy versus FLOT alone in patients with locally advanced, operable adenocarcinoma of the stomach or GEJ.</p> <p>The study will evaluate the safety and efficacy of the study treatment regimens. The study includes an evaluation of rate of immune cell infiltration into the esophagogastric tumor tissue following two and four cycles of neoadjuvant therapy.</p> <p>Potential study participants will be assessed for eligibility during a 28-day screening period that includes central verification of clinical stage and eligibility. Eligible patients will be enrolled and randomized to perioperative treatment with either atezolizumab with FLOT (Arm A) or FLOT alone (Arm B). Randomization will occur in a 1:1 ratio with stratification by clinical nodal stage (N+ vs. N-), location of the primary (GEJ type I vs. GEJ type II/II vs. stomach), and MSI-status (MSI-high vs. MSI-low/MSI-stable). Quantitative PDL-1 mRNA expression [high vs. intermediate vs. low] will be performed but not used as stratification factor.</p> <p>Following randomization, study patients will enter the study treatment period which will last approximately 22 to 52 weeks depending on treatment arm and timing of surgery.</p> <p><b>Arm A: Atezolizumab with FLOT:</b>  Patients randomized to treatment Arm A will receive atezolizumab + FLOT in four 2-week treatment cycles as described below prior to undergoing surgery. Following surgery, patients will receive four further 2-week cycles of atezolizumab + FLOT followed by 8 additional 3-week treatment cycles with atezolizumab alone (maintenance setting: 1,200 mg q3w). FLOT can be deescalated to FLO, FLT or FL in case of chemo-related toxicity at any time and at the discretion of investigator.</p> <p><b>Arm B: FLOT alone:</b> Patients randomized to Arm B will receive FLOT alone for four 2-week treatment cycles prior to surgery. Following surgery, patients will receive four further 2-week cycles of chemotherapy alone. FLOT can be deescalated to FLO, FLT or FL in case of chemo-related toxicity at any time and at the discretion of investigator.</p> <p>In both study arms, surgery is recommended to occur 4 weeks after the last administration of pre-operative study therapy. Post-operative treatment is recommended to start 6 to 8 weeks (to a maximum of 12 weeks) after surgery. Study specifications for surgical resection are consistent with national guidelines. Surgical approaches will be tailored to the individual patient according to local standards with the goal of achieving R0-resection of the primary tumor. All resection samples will be submitted for central evaluation of histopathological regression.</p> <p>During the treatment period, safety assessments conducted with results reviewed prior to each study treatment include hematology, serum chemistry, physical exam, and recording of concomitant medications and AEs. AEs will be graded according to the National Cancer Institute's Common Terminology</p>

	<p>Criteria for Adverse Events (NCI CTCAE) v4.03. Disease assessments will be conducted at screening, prior to surgery and every 3 months thereafter, until disease progression, relapse or death or end of the study. Assessments will include CT or MRI of the chest and abdomen. Disease assessment at screening will also include laparoscopy as clinically indicated (i.e. T3 or T4 tumors of diffuse type histology in the stomach or upon request of the central review) to confirm eligibility. There will be central review of the patient records including the reports of endoscopy, endoscopic ultrasound (if applicable), histology, CT and/MRI, and laparoscopy (if applicable) prior to randomization. The review is conducted by an oncologist and a surgeon. Additional assessments may be conducted as clinically indicated in accordance with local standards of care.</p> <p>Following a study visit, approximately 28 days after completion of study treatment, patients will enter the follow-up period. During this period, they will be followed every 3 months for disease status until first relapse or progression, and survival.</p> <p>Note: there will be a Safety Run-in Phase comprising the first 10 patients enrolled into the experimental study arm A and completed neoadjuvant treatment, but before surgery. Data of the first 10 patients in Arm A will be reviewed by the lead investigators and by the independent data monitoring committee (IDMC).</p> <p>Once approximately 40 patients (20/treatment arm) have completed neoadjuvant treatment cycles and surgery, the IDMC will review all available safety data (including perioperative morbidity and mortality) before providing a recommendation whether to continue, modify or terminate the study. Enrollment will be halted for this review. The IDMC will be responsible for continued safety review over the remainder of the study period.</p>
<p>Therapy schedule</p>	<p><b><u>Arm A: Atezolizumab with FLOT</u></b></p> <p><u>Atezolizumab</u> Day 1 q2w: 840 mg/m<sup>2</sup> IV over 1 hour combined with: <u>FLOT</u></p> <p>docetaxel Day 1 q2w: 50 mg/m<sup>2</sup> IV over 2 hours oxaliplatin Day 1 q2w: 85 mg/m<sup>2</sup> IV over 2 hours leucovorin Day 1 q2wk: 200 mg/m<sup>2</sup> IV over 1 hour 5-FU Day 1 q2wk: 2600 mg/m<sup>2</sup> IV over 24 hours</p> <p>pre-operative: four cycles; post-operative four cycles</p> <p><u>Atezolizumab alone</u> (8 cycles following completion of post-operative atezolizumab/chemotherapy) Atezolizumab Day 1 q3w: 1,200 mg/m<sup>2</sup> IV over 1 hour</p> <p><b><u>Arm B: FLOT alone</u></b></p> <p>FLOT as described in Arm A. pre-operative: four cycles; post-operative four cycles</p>
<p>Inclusion criteria</p>	<p>Patients must meet the following criteria to be eligible for the study:</p> <ul style="list-style-type: none"> <li>• Have provided written informed consent</li> <li>• In the investigator’s judgement, is willing and able to comply with the study protocol including the planned surgical treatment</li> <li>• Female and male patients* ≥ 18 years of age</li> </ul>

- Diagnosed with histologically confirmed adenocarcinoma of the GEJ (Type I-III) or the stomach (cT2, cT3, cT4, any N category, M0), or (any T, N+, M0) that:
  1. is not infiltrating any adjacent organs or structures by CT or MRI evaluation
  2. does not involve peritoneal carcinomatosis
  3. 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.
- No prior cytotoxic or targeted therapy
- No prior partial or complete esophagogastric tumor resection
- ECOG  $\leq$  1
- Availability of a representative tumor specimen that is suitable for determination of PD-L1 and MSI status via central testing; PD-L1 and MSI assessment will be performed prior to randomization. The analysis requires paraffin embedded biopsy samples. Patients are included in the trial upon available results only.
- Females of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 5 months after the last study treatment. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (has not had  $\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Males must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below:
  1. With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of 1% per year during the treatment period and for at least 3 months after the last dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period. Men

	<p>with a pregnant partner must agree to remain abstinent or to use a condom for the duration of the pregnancy.</p> <ul style="list-style-type: none"> <li>• Adequate hematological, hepatic and renal function as indicated by the following parameters: <ol style="list-style-type: none"> <li>1. Leukocytes <math>\geq 3.000/\text{mm}^3</math>, platelets <math>\geq 100.000/\text{mm}^3</math> without transfusion, absolute neutrophil count (ANC) <math>\geq 1500/\text{mm}^3</math> without granulocyte colony-stimulating factor support, Hemoglobin <math>\geq 90</math> g/L (9 g/dL) - Patients may be transfused to meet this criterion.</li> <li>2. Bilirubin <math>\leq 1.5</math> x upper limit of normal, aspartate transaminase and alanine transaminase <math>\leq 2.5</math> x upper limit of normal, alkaline phosphatase <math>\leq 2.5</math> x upper limit of normal</li> <li>3. Serum creatinine <math>\leq 1.5</math> x upper limit of normal, or glomerular filtration rate <math>&gt; 45</math> ml/min</li> <li>4. Serum albumin <math>\geq 25</math> g/L (2.5 g/dL)</li> <li>5. For patients not receiving therapeutic anticoagulation: INR or aPTT <math>\leq 1.5</math> x ULN; for patients receiving therapeutic anticoagulation: stable anticoagulant regimen</li> </ol> </li> </ul> <p>* There are no data that indicate special gender distribution. Therefore patients will be enrolled in the study gender-independently.</p>
<p>Exclusion criteria</p>	<ol style="list-style-type: none"> <li>1. 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 atezolizumab formulation</li> <li>2. Any known contraindication (including hypersensitivity) to docetaxel, 5-FU, leucovorin, or oxaliplatin.</li> <li>3. History of autoimmune disease including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.  <u>Note:</u> History of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone, or controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible based on consultation with the sponsor's medical monitor. Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met: <ul style="list-style-type: none"> <li>• Rash must cover <math>&lt; 10\%</math> of body surface area</li> <li>• Disease is well controlled at baseline and requires only low-potency topical corticosteroids</li> <li>• No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months</li> </ul> </li> <li>4. Prior allogeneic bone marrow transplantation or prior solid organ transplantation</li> <li>5. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, idiopathic pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan.  <u>Note:</u> History of radiation pneumonitis within the radiation field (fibrosis) is permitted.</li> </ol>

6. Positive test for human immunodeficiency virus (HIV)
7. Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test prior to randomization) or hepatitis C  
Note: Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen antibody test) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction testing is negative for HCV ribonucleic acid (RNA).
8. Active tuberculosis
9. Uncontrolled tumor-related pain; Patients requiring pain medication must be on a stable regimen at study entry
10. Administration of a live, attenuated vaccine within four weeks prior to start of enrollment, or anticipation that such a live attenuated vaccine will be required during the study or within 5 months after the last dose of atezolizumab
11. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibodies
12. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within four weeks or five half-lives of the drug, whichever is longer, prior to study enrollment
13. Treatment with systemic corticosteroids or other systemic immunosuppressive medications within 2 weeks prior to study enrollment. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.
14. Requirement for use of denosumab during the study. Patients who are receiving denosumab for any reason (including hypercalcemia) must be willing and eligible to receive a bisphosphonate instead while in the study.
15. Significant cardiovascular disease, such as cardiac disease (New York Heart Association Class II or greater), myocardial infarction or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmias, or unstable angina.
16. Clinically significant valvular defect
17. History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer
18. Known central nervous system metastases
19. Peripheral polyneuropathy  $\geq$  NCI CTCAE grade 2
20. Serum albumin  $<$  2.5 g/dL.
21. Uncontrolled or symptomatic hypercalcemia (ionized calcium  $>$  1.5 mmol/L, calcium  $>$  12 mg/dL or corrected serum calcium  $>$  ULN)
22. Serious infection requiring oral or IV antibiotics within 14 days prior to study enrollment
23. Chronic inflammatory bowel disease
24. Clinically significant active gastrointestinal bleeding
25. Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment
26. Evidence of any other disease, neurologic or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of any of the study medications, puts the patient at higher risk for treatment-related complications or may affect the interpretation of study results
27. Participation in another interventional clinical study  $\leq$  30 days prior to study enrollment or planned participation in such a study at the same time as this study
28. Receipt of an investigational drug within 28 days prior to initiation of study drug
29. Pregnancy or breast feeding, or planning to become pregnant within 5 months after the end of treatment.  
 Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.

Sample size	295 patients will be randomized into the study at a 1:1 ratio.
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