Ipilimumab or FOLFOX in Combination With Nivolumab and Trastuzumab in HER2 Positive EsophagoGastric Adenocarcinoma (INTEGA)

ClinicalTrials.gov Identifier: NCT03409848

Recruitment Status: Recruiting
First Posted: January 24, 2018
Last Update Posted: March 23, 2018

See Contacts and Locations

Sponsor:
AIO-Studien-gGmbH

Collaborator:
Bristol-Myers Squibb

Information provided by (Responsible Party):
AIO-Studien-gGmbH

Study Details | Tabular View | No Results Posted | Disclaimer

How to Read a Study Record

Study Description Go to

Brief Summary:

The INTEGA study assesses therapy Options for advanced or metastatic esophagogastric Adenocarcinoma in patients overexpressing human epidermal receptor type 2 (HER2 positive patients). Current treatment options in this situation include chemotherapy based palliative treatment in combination withTrastuzumab.

Recent studies have shown that immunotherapy with Nivolumab or Ipilimumab after previous chemotherapy can also improve survival in esophagogastric cancer.

This study assesses the efficacy of two experimental first line treatment strategies: A) Chemo-free immunotherapy with Trastuzumab, Nivolumab and Ipilimumab and B) addition of Nivolumab to the standard regimen (FOLFOX chemotherapy and Trastuzumab).

Condition or disease	Intervention/treatment	Phase
Gastric Cancer Esophageal Cancer Adenocarcinoma Gastric HER2 Positive Gastric Cancer Metastatic Gastric Cancer GastroEsophageal Cancer	Drug: Nivolumab Drug: Ipilimumab	Phase 2

Detailed Description:

Gastric cancer is the fifth most common cancer in the world, and the third leading cause of cancer death in both sexes worldwide.

Surgical resection is currently the only curative treatment option for gastric cancer; however, ~50% of patients have metastatic disease at the time of diagnosis and chemotherapy is the mainstay of palliation in this setting.

Trastuzumab, in combination with chemotherapy, significantly improved survival in patients with overexpression of HER2.

In regard of the very limited therapeutic landscape of HER2 positive EGA, compared to breast cancer, further treatment options to relevantly improve the outcome is warranted. The integration of check-point inhibitors (e.g. Nivolumab, Ipilimumab) into the first line setting either within a chemotherapy-free combination arm or within an intensified standard arm of FOLFOX and trastuzumab with nivolumab may be able to improve the current limited survival of median 14 months.

Study Design

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Study Type:	Interventional (Clinical Trial)
Estimated Enrollment:	97 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Ipilimumab or FOLFOX in Combination With Nivolumab and Trastuzumab in Previously Untreated HER2 Positive Locally Advanced or Metastatic EsophagoGastric Adenocarcinoma
Actual Study Start Date:	March 1, 2018
Estimated Primary Completion Date:	October 2021
Estimated Study Completion Date:	January 2022

Resource links provided by the National Library of Medicine

Drug Information available for: Trastuzumab Ipilimumab Nivolumab

Genetic and Rare Diseases Information Center resources: Stomach Cancer Esophageal Cancer

U.S. FDA Resources

Arms and Interventions

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Arm	Intervention/treatment
Experimental: A: Chemo-free immunotherapy Week 1-12 Trastuzumab 6mg/kg d1 every 3 weeks (loading dose 8mg/kg) Nivolumab 1mg/kg i.v. d1 every 3 weeks Ipilimumab 3mg/kg i.v. d1 every 3 weeks Week 13 till EOT (max treatment period 12 months) Trastuzumab 4mg/kg d1 every 2 weeks Nivolumab 240mg i.v. d1 every 2 weeks	Drug: Nivolumab Chemo-free immunotherapy with Nivolumab, Ipilimumab, Trastuzumab Drug: Ipilimumab Chemo-free immunotherapy with Nivolumab, Ipilimumab, Trastuzumab
Experimental: B: Chemo- / immunotherapy	Drug: Nivolumab

Trastuzumab 4mg/kg d1 every 2 weeks (loading dose 6mg/kg) Nivolumab 240mg i.v. d1 every 2 weeks mFOLFOX6 every 2 weeks Oxaliplatin at a dose of 85 mg/m2 IV over two hours (day 1) 5-FU 400 mg/m2 IV bolus (day 1) LV at a dose of 400 mg/m2 iv over two hours (day 1) 5-FU at a dose of 2400 mg/m2 IV over 46 hours (day 1-3) Max Treatment period 12 months	Addition of Nivolumab to Standard therapy (chemotherapy and Trastuzumab)

Outcome Measures

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Primary Outcome Measures :

1. Overall Survival [Time Frame: Milestone at 12 months, max observation period 48 months]

   Overall survival including milestone rate at 12 months

Secondary Outcome Measures :

1. Incidence of Treatment-Emergent Adverse Events [Safety and Tolerability] [Time Frame: 48 months]

   according to Common Terminology Criteria for Adverse Events and to the obtained data on vital signs, clinical parameters and feasibility of the regimen

2. Progression Free Survival [Time Frame: 48 months]

   Response Evaluation Criteria in Solid Tumors (RECIST 1.1.)

3. Response Rate [Time Frame: 15 months]

   Response Rate (RR) according to RECIST v1.1

4. Health related Quality of Life [Time Frame: 48 months]

   EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer - Quality of Life Core Questionnaire (30 items) Version 3.0. The QLQ-C30 is composed of multi-item scales and single-item measures, including five functional scales, three symptom scales, a global health status / QoL scale, and six single items.

All of the scales and single-item measures have a score range from 0 to 100. A high score shows a high response level. A high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems

5. Health related Quality of Life [Time Frame: 48 months]

   EORTC STO-22 (European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire Gastric Module (STO = stomach) (22 items), comprising five multi-item and four single-item subscales. The multi-item subscales include questions about dysphagia (4 items), dietary restriction (5 items), pain (3 items), upper gastro-esophageal symptoms such as reflux (3 items), and emotional problems such as anxiety (3 items). The single-item subscales include questions related to four gastric cancer-specific symptoms: dry mouth, body image, hair loss, and problems with taste. Items are assessed on a 4-level numerical scale with 1= "not at all", 2= "a little", 3= "quite a bit", and 4= "very much". Scores are linearly converted and summated into a scaled score from 0 to 100, with a higher score representing a worse QOL.

6. Translational research tumor block [Time Frame: 48 months]

   Tumor-infiltrating lymphocytes (TiL) repertoire determination from tumor

7. Translational research blood - immunoprofiling [Time Frame: Up to 7 weeks]

   Liquid biopsy next-generation sequencing (NGS) immunoprofiling (TCRβ & IgH) before treatment initiation and before second cycle to determine response predictive immune signature

8. Translational research blood - circulating Tumor cells (CTC) [Time Frame: 48 months]

   CTC will be evaluated for changes in HER2 and PD-L1 status

9. Translational research blood - circulating Tumor DNA (ctDNA) [Time Frame: 48 months]

   ctDNA will be evaluated for HER signaling alterations

10. Central Imaging Review - ORR [Time Frame: 48 months]

    Retrospective central radiological review of ORR according to modified RECIST

11. Central Imaging Review - PFS [Time Frame: 48 months]

Retrospective central radiological review of PFS according to modified RECIST

Eligibility Criteria

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Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	18 Years and older (Adult, Senior)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

1. All subjects must have inoperable, advanced or metastatic GC or GEJ carcinoma and have histologically confirmed predominant adenocarcinoma. The documentation of GEJ involvement can include biopsy, endoscopy, or imaging.
2. Subjects must have HER2-positive disease defined as either IHC 3+ or IHC 2+, the latter in combination with ISH+, as assessed locally on a primary or metastatic tumour (Note: Availability of formalin-fixed paraffin-embedded (FFPE) representative tumor tissue for central confirmation of HER2 is mandatory (Preferably fresh biopsy))
3. Subject must be previously untreated with systemic treatment (including HER 2 inhibitors) given as primary therapy for advanced or metastatic disease.
4. Prior adjuvant or neoadjuvant chemotherapy, radiotherapy and/or chemoradiotherapy are permitted as long as the last administration of the last regimen (whichever was given last) occurred at least 6 months prior to randomization.
5. Subjects must have measurable or evaluable non-measurable disease as assessed by the investigator, according to RECIST v1.1 (Appendix D).
6. ECOG performance status score of 0 or 1 (Appendix B).
7. Screening laboratory values must meet the following criteria (using NCI CTCAE v.4.03):

- WBC ≥ 2000/μL
- Neutrophils ≥ 1500/uL
- Platelets ≥ 100x10^3/μL
- Hemoglobin ≥ 9.0 g/dL
- eGFR ≥ 30ml/min (e.g. MDRD formula, appendix G)
- AST ≤ 3.0 x ULN (or ≤ 5.0X ULN if liver metastases are present)
- ALT ≤ 3.0 x ULN (or ≤ 5.0X ULN if liver metastases are present)
- Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN)

8. Males and Females, ≥ 18 years of age
9. Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.
10. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.
11. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug. Women must not be breastfeeding.
12. WOCBP must use a highly effective method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo 5 half-lives. The terminal half-lives of nivolumab and ipilimumab are approximately 25 days and 15 days, respectively. WOCBP should use an adequate method to avoid pregnancy for approximately 5 months (30 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of investigational drug.
13. Males who are sexually active with WOCBP must agree to follow instructions for method (s) of contraception for a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo 5 half-lives. The terminal half-lives of nivolumab and ipilimumab are approximately 25 days and 15 days, respectively. Males who are sexually active with WOCBP must continue contraception for approximately 7 months (90 days plus the time required for nivolumab to undergo 5 half-lives) after the last dose of investigational drug. In addition, male subjects must be willing to refrain from sperm donation during this time.

Exclusion Criteria:

1. Malignancies other than disease under study within 5 years prior to inclusion, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma

in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)

2. Subjects with untreated known CNS metastases. Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization.
3. History of exposure to the following cumulative doses of anthracyclines (epirubicin > 720 mg/m2, doxorubicin or liposomal doxorubicin > 360 mg/m2, mitoxantrone > 120 mg/m2 and idarubicin > 90 mg/m2, other (e.g., liposomal doxorubicin or other anthracycline greater than the equivalent of 360 mg/m2 of doxorubicin). If more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m2 of doxorubicin
4. Baseline LVEF value < 55%, assessed by echocardiogram [ECHO], multigated acquisition (MUGA) scan, or cardiac magnetic resonance imaging (MRI) scan
5. Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll. For any cases of uncertainty, it is recommended that the medical monitor be consulted prior to signing informed consent.
6. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
7. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
8. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.
9. Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive study drug.
10. Significant acute or chronic infections including, among others:

- Any positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- Any positive test result for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.

11. History of allergy or hypersensitivity to study drug or any constituent of the products
12. Participation in another clinical study with an investigational product during the last 30 days before inclusion
13. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.
14. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].

Contacts and Locations

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Information from the National Library of Medicine NIH NLM

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT03409848***

Contacts

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Locations

Germany

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Sponsors and Collaborators

AIO-Studien-gGmbH

Bristol-Myers Squibb

Investigators

Principal Investigator: Alexander Stein, Dr. Universitätsklinikum Hamburg-Eppendorf Hubert

More Information

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Additional Information:

AIO - Working Group for Medical Oncology from the German Cancer Society EXIT

AIO-Studien-gGmbH EXIT

Responsible Party:	AIO-Studien-gGmbH
ClinicalTrials.gov Identifier:	NCT03409848 History of Changes
Other Study ID Numbers:	AIO-STO-0217
	2017-000624-10 (EudraCT Number)
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Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD: No

Studies a U.S. FDA-regulated Drug Product: No

Studies a U.S. FDA-regulated Device Product: No

Additional relevant MeSH terms:

Adenocarcinoma	Gastrointestinal Diseases
Stomach Neoplasms	Stomach Diseases
Esophageal Neoplasms	Head and Neck Neoplasms
Carcinoma	Esophageal Diseases
Neoplasms, Glandular and Epithelial	Nivolumab
Neoplasms by Histologic Type	Trastuzumab
Neoplasms	Antibodies, Monoclonal
Gastrointestinal Neoplasms	Antineoplastic Agents

Digestive System Neoplasms
Neoplasms by Site
Digestive System Diseases

Immunologic Factors
Physiological Effects of Drugs