A Multicenter Open-label Phase II Trial to Evaluate Nivolumab and Ipilimumab for 2nd Line Therapy in Elderly Patients With Advanced Esophageal Squamous Cell Cancer (RAMONA)

ClinicalTrials.gov Identifier: NCT03416244

Recruitment Status: Recruiting
First Posted: January 31, 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 Description

Brief Summary:

Cancer - including esophageal squamous cell cancer (ESCC) - is a disease of the elderly but little is known about the biology and progression of cancers in these patients.

While most patients receive chemotherapy and/or chemo-radiation as first treatment, no treatment standard for following treatments has been established so far and there is a clear unmet medical need, especially for elderly patients.

Hence, this study assesses the efficacy and safety of two experimental immunotherapy regimens (Nivolumab monotherapy or Nivolumab/Ipilimumab combination) in elderly patients with advanced esophageal squamous cell cancer.

Condition or disease	Intervention/treatment	Phase
Esophageal Cancer Oesophageal Cancer Oesophageal Cancer Metastatic Esophageal Cancer Metastatic Esophageal Cancers NOS Oesophageal Cancer Nos GastroEsophageal Cancer Gastrooesophageal Cancer	Drug: Nivolumab Drug: Ipilimumab	Phase 2

Detailed Description:

Cancer - including esophageal squamous cell cancer (ESCC) - is a disease of the elderly, more than 60% of all tumors arise in patients with the age of 65 years or older. In contrast, little is known about the biology and progression of cancers in these patients, since most clinical trials enroll patients with age limits of 70 or 75 years.

While most patients undergo chemotherapy and/or chemo-radiation in first-line, the role of second-line therapy is less well understood. No treatment standard has been established so far and there is a clear unmet medical need. This is particularly true for geriatric patients for whom palliative systemic therapies are especially challenging.

Hence, the primary objective of this trial is to demonstrate a significant survival benefit of two experimental immunotherapy regimens (Nivolumab monotherapy or Nivolumab/Ipilimumab combination) in elderly patients with advanced esophageal squamous cell cancer compared to historical data of standard chemotherapy regimens.

Study Design

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Study Type:	Interventional (Clinical Trial)
Estimated Enrollment:	75 participants
Allocation:	Non-Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	A Multicenter Open-label Phase II Trial to Evaluate Nivolumab and Ipilimumab for 2nd Line Therapy in Elderly Patients With Advanced Esophageal Squamous Cell Cancer
Actual Study Start Date:	February 21, 2018
Estimated Primary Completion Date:	September 2019
Estimated Study Completion Date:	January 2021

Resource links provided by the National Library of Medicine

Drug Information available for: Ipilimumab Nivolumab

Genetic and Rare Diseases Information Center resources: Esophageal Cancer

U.S. FDA Resources

Arms and Interventions

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Arm	Intervention/treatment
Experimental: A: Nivolumab / Ipilimumab combination treatment Nivolumab 240 mg fixed dose IV every 2 weeks; Additionally, after 7 week safety assessment Ipilimumab 1mg/kg IV every 6 weeks	Drug: Nivolumab Nivolumab 240 mg IV fixed dose every two weeks Drug: Ipilimumab Ipilimumab 1mg/kg IV every six weeks (starting in week 7 after safety assessment)
Experimental: B. Nivolumab monotherapy	Drug: Nivolumab

Nivolumab 240 mg fixed dose IV every 2 weeks	Nivolumab 240 mg IV fixed dose every two weeks

Outcome Measures

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Primary Outcome Measures :

1. Overall survival [Time Frame: 36 months]

   OS measured from first dose of 2nd line therapy to the date of death

Secondary Outcome Measures :

1. Time to QoL deterioration [Time Frame: 36 months]

   Time to QoL deterioration defined as a loss of ≥ 10 points in the EORTC QLQ-C30 compared to base-line

2. Progression free survival [Time Frame: 36 months]

   Time from first dosing date to the date of the first documented tumor progression

3. Objective Response rate [Time Frame: 36 months]

   Proportion of treated subjects with response from baseline

4. Duration of response [Time Frame: 36 months]

   Time from first confirmed response to the date of the documented progressive disease or death

5. Duration of treatment [Time Frame: 36 months]

   Time from date of first dose of Nivolumab monotherapy until permanent discontinuation of either NIVO mono therapy or NIVO/IPI combination treatment.

6. Cumulative dose intensity [Time Frame: 36 months]

   Cumulative dose for each IMP

7. Quality of Life [Time Frame: 36 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

8. Quality of Life [Time Frame: 36 months]

   EORTC QLQ-ELD14 (European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire Module for elderly Cancer patients (14 items), comprising five multi-item and two single-item subscales. The multi-item subscales include questions about mobility (3 items), worries about others (2 items), worries (3 items), maintaining purpose (2 items), and burden of illness (2 items). The single-item subscales include questions related to joint stiffness and Family support. 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 or better QOL for purpose and family support.

9. Incidence of Treatment-Emergent Adverse Events [Time Frame: 36 months]

   AE/SAE evaluation

Eligibility Criteria

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Ages Eligible for Study:	65 Years and older (Adult, Senior)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

1. Written informed consent including participation in translational research and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening Evaluations
2. Age ≥ 65 years at time of study entry
3. Histologically confirmed advanced stage esophageal squamous cell carcinoma in 2nd line:
   - stage 4 OR
   - stage 3 non-responder to radio-chemotherapy OR
   - stage 3 with early relapse < 6 month after chemo-radiation
4. Patients treated with Carboplatin/Paclitaxel (+/- radiotherapy) or other chemotherapy in 1st line
5. Geriatric status: SlowGo or GoGo according to G8 and DAFI assessment (G8 > 14 points or CGA/DAFI 0.2 < 0.35)
6. At least 1 measurable lesion according to RECIST 1.1
7. Karnofsky performance status ≥ 50
8. Sufficient cardiac functional reserve defined as ejection fraction > 50%
9. Adequate blood count, liver-enzymes, and renal function:
   - neutrophil count > 1.5 x 10^6/mL
   - WBC ≥ 3000/µL
   - Platelet count ≥ 100 x 10^9/L (>100,000 per mm^3)
   - hemoglobin ≥ 9 g/dL
   - INR ≤ 1.5 and PPT ≤ 1.5 x lower limit during the last 7 days before therapy
   - AST (SGOT)/ALT (SGPT) < 3 x institutional upper limit of normal (5 x lower limit in case of liver metastases)
   - bilirubin < 1.5 x ULN
   - Serum creatinine ≤ 1.5 x institutional ULN or creatinine clearance (CrCl) ≥ 30 mL/min (if using the Cockcroft-Gault formula below):

Female CrCl = (140 - age in years) x weight in kg x 0.85 / 72 x serum creatinine in mg/dL Male CrCl = (140 - age in years) x weight in kg x 1.00 / 72 x serum creatinine in mg/dL

10. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving Nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational products (Nivolumab, Ipilimumab). Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception)
11. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up

Exclusion Criteria:

1. Patients < 65 years of age
2. Frail patients (DAFI score ≥ 0.35)
3. Esophageal adenocarcinomas, neuroendocrine tumors
4. Prior therapy with an anti-programmed cell death protein 1 (anti-PD-1), anti-PD−L1, anti-programmed cell death-ligand 2 (anti-PD-L2), anti-CD137 (4-1BB ligand, a member of the Tumor Necrosis Factor Receptor [TNFR] family), or anti-cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibody (including Ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)
5. Participation in another clinical study with an investigational product during the last 30 days before inclusion or 7 half-lifes of previously used trial medication, whichever is longer
6. Previous treatment in the present study (does not include screening failure).
7. Any condition or comorbidity that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results, including but not limited to:
    1. Major surgery ≤ 28 days prior first dose of study treatment
    2. Anticancer treatment during the last 30 days prior to start of Nivolumab monotherapy treatment, including systemic therapy or major surgery [palliative radiotherapy has to be completed at least 2 weeks prior to start of study treatment]
    3. History of interstitial lung disease
    4. Known acute or chronic pancreatitis
    5. Known active HBV, HCV or HIV infection
    6. Active tuberculosis

7. Any other active infection (viral, fungal or bacterial) requiring systemic therapy
8. History of allogeneic tissue/solid organ transplant
9. Diagnosis of immunodeficiency or patient is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of Nivolumab monotherapy treatment.
10. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Exceptions: Subjects with vitiligo, hypothyroidism, diabetes mellitus type I or resolved childhood asthma/atopy are an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with Hashimoto thyroiditis, hypothyroidism stable on hormone replacement or psoriasis not requiring treatment are not excluded from the study.
11. Live vaccine within 30 days prior to the first dose of Nivolumab monotherapy treatment or during study treatment.
12. Other clinically significant active malignancy requiring treatment OR less then 5 years disease free interval of another primary malignancy
13. Clinically significant or symptomatic cardiovascular/cerebrovascular disease (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) within 6 months before enrollment
14. History or clinical evidence of CNS metastases Exceptions are: Subjects who have completed local therapy and who meet both of the following criteria: i. are asymptomatic AND ii. have no requirement for steroids 6 weeks prior to start of Nivolumab monotherapy treatment. Screening with CNS imaging (CT or MRI) is required only if clinically indicated or if the subject has a history of CNS metastases

8. Medication that is known to interfere with any of the agents applied in the trial
9. Has known hypersensitivity to Nivolumab or Ipilimumab or any of the constituents of the products
10. Any other efficacious cancer treatment except protocol specified treatment at study start
11. Patient has received any other investigational product within 28 days of study entry
12. Patient has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier. [Subjects with ≤ Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the study.]

13. Female subjects who are pregnant, breast-feeding or male/female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year). [Acceptable methods of contraception are: implants, injectable contraceptives, combined oral contraceptives, intrauterine pessaries (only hormonal devices), sexual abstinence or vasectomy of the partner]. Women of childbearing potential must have a negative pregnancy test (serum β-HCG) at screening.
14. Patient with any significant history of non-compliance to medical regimens or with inability to grant reliable informed consent.
15. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.
16. 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): ***NCT03416244***

Contacts

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AIO-Studien-gGmbH

Bristol-Myers Squibb

Investigators

Principal Investigator: Matthias Ebert, Prof. Dr. Universitätsmedizin Mannheim, Heidelberg U

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:	NCT03416244 History of Changes
Other Study ID Numbers:	AIO-STO-0117
	2017-002056-86 (EudraCT Number)
	CA209-9DD (Other Grant/Funding Number: Bristol-Myers Squibb)
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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:

Esophageal Neoplasms
Neoplasms
Neoplasms, Squamous Cell
Carcinoma, Squamous Cell
Gastrointestinal Neoplasms
Digestive System Neoplasms
Neoplasms by Site
Head and Neck Neoplasms
Gastrointestinal Diseases
Neoplasms, Glandular and Epithelial
Neoplasms by Histologic Type
Carcinoma
Nivolumab
Antibodies, Monoclonal
Antineoplastic Agents

Digestive System Diseases
Esophageal Diseases
Immunologic Factors
Physiological Effects of Drugs