Purpose

More than 50% of patients with esophageal cancer have locally advanced or metastatic disease at presentation. The use of chemotherapy for this patient group is increasing with the intention of local and distant tumor control, improving quality of life and prolongation of survival.

Previous data suggested not only that EGFR antibody targeted therapy may be safely combined with cisplatin and 5-FU but also may increase the efficacy of standard cisplatin / 5-FU regime.

In the present study, patients with nonresectable, advanced or metastatic esophageal squamous cell cancer (ESCC) will receive chemotherapy or chemotherapy plus panitumumab every 3 weeks until disease progression occurs.

The primary objective is to demonstrate superiority of 5-FU, Cisplatin and Panitumumab over 5-FU and Cisplatin alone in terms of overall survival in esophageal cancer.
Panitumumab for Patients With Nonresectable, Advanced or Metastatic Esophageal Cancer

Cisplatin plus continuous 5-fluorouracil as the standard of care regimens. Taxanes and anthracyclins are effective at prolongation of survival. The most frequently used agents are 5-fluorouracil, cisplatin, with or without various chemotherapy for this patient group is increasing with the intention of local and distant tumor control, improving quality of life and prolongation of survival. More than 50% of patients with esophageal cancer have locally advanced or metastatic disease at presentation. The use of chemotherapy for this patient group is increasing with the intention of local and distant tumor control, improving quality of life and prolongation of survival. The most frequently used agents are 5-fluorouracil, cisplatin, with or without various anthracyclines. Cisplatin plus continuous 5-fluorouracil are the standard of care regimens. Taxanes and anthracyclines are eligible agents for possible future studies, however with higher incidences of toxicities and life threatening complications. Response rates for single agents range from 15%-30% . Combination regimens usually tend to produce higher response rates and occasionally patients achieve complete responses (0%-11%). However, with the combination regimens, the median survival time remains clearly less than 10 months, mostly between 4-8 months [Homs MY et al]. In comparison of different chemotherapy protocols, there was no consistent benefit of any specific chemotherapy regimen. So far, cisplatin combined with 5-fluorouracil is one of the approved standard regimens in esophageal cancer worldwide [Medical Research Council Esophageal Cancer Group]. This so called three-weekly MRC regimen has a better toxicity profile than the four weekly CF regimen given in Central Europe with the higher Cisplatin dose [Lorenzen S et al], but less overall chemotherapy given per 4 months.

Advances in molecular biology and new molecular technologies can possibly contribute to improvement of response to neoadjuvant or palliative therapy in ESCC patients as well. EGFR1 blockade with platinum-based chemotherapy already significantly improved response rates as well as the progression-free and overall survival compared to chemotherapy alone in patients with head and neck tumors, which are also squamous cancers [Vermorken JB et al].

Even more, the Arbeitsgemeinschaft Internistische Onkologie (AIO) has performed a randomized phase II study of the EGFR antibody cetuximab plus cisplatin/5-fluorouracil versus cisplatin/5-fluorouracil alone in first-line metastatic ESCC [Lorenzen S et al]. For a maximum of six 28-day cycles, patients received cisplatin 100 mg/m2(2), day 1, plus 5-FU 1000 mg/m2(2) days 1-5 (CF), either alone or in combination with cetuximab (CET-CF). The primary endpoint was tumor response. From 62 eligible patients included, 32 receiving CET-CF and 30 CF. Cetuximab weekly did not exacerbate grade 3/4 toxicity, except for rash (6% vs 0%) and diarrhea (16% vs 0%). The overall response rate according to RECIST criteria were 19% and 13% and the disease control rates, were 75% and 57% for the CET-CF and CF arms, respectively. With a median follow-up of 21.5 months, the median progression-free survival was 5.9 and 3.6 months and median overall survival 9.5 and 5.5 months for CET-CF and CF, respectively. No KRAS codon 12/13 tumor mutations were identified in the 37 evaluated samples.

Thus, with respect to the AIO data and in concordance with the head and neck data by Vermorken, EGFR1 antibody targeted therapy may not only be safely combined with CF, but may also very likely increase the efficacy of standard CF, particularly with regard to a chosen primary endpoint of overall survival. Therefore, the aim of this study is to investigate if the overall survival of patients with squamous cell carcinoma of the esophagus can be prolonged if panitumumab is added to the standard CF chemotherapy.

### Eligibility

Ages Eligible for Study: 18 Years and older

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Criteria

Inclusion Criteria:

1. Signed written informed consent
2. Male or female ≥18 years of age
3. Histologically proven squamous cell carcinoma of the esophagus, which is not curatively resectable* or locally recurrent disease and both not eligible** for definitive radiochemotherapy, or clearly metastatic disease (Tx, Nx, M1, locally unresectable T4, Nx, M0 or TX, N3, M0)* or residual (post-resection) disease not eligible** for definitive radiochemotherapy
   - resectability has to be defined prior to randomization according to local standards:
     - T-stage, N-stage, performance status/nutritional status, co-morbidity (pulmonary function, other), tumor location upper third of the esophagus, relation to other organs/structures, patient refusal, other reasons.
   - eligibility to definitive radiochemotherapy will be determined according to local standards based on the extent of disease, performance status/nutritional status, co-morbidity (pulmonary function, other), volume of neighboring organs within the radiation field, patient refusal, other reasons.
4. Measurable or non-measurable disease according to RECIST 1.1
5. ECOG 0-1
6. Women of child-bearing potential must have a negative pregnancy test
7. Laboratory requirements
   - Hematologic Function:
     - Absolute neutrophil count ≥1.5x10^9/L
     - Platelet count ≥100x10^9/L
     - Leukocyte count ≥ 3.0x10^9/L
     - Hemoglobin ≥ 9 g/dL or 5.59 mmol/l
   - Hepatic Function:
     - Total bilirubin ≤ 1.5 time the upper normal limit (UNL)
     - AST ≤ 2.5xUNL in absence of liver metastases, or ≤5xUNL in presence of liver metastases
     - ALT ≤ 2.5xUNL in absence of liver metastases, or ≤5xUNL in presence of liver metastases
   - Renal Function:
     - Creatinine clearance ≥50 mL/min according to Cockcroft-Gault formula
   - Metabolic Function:
     - Magnesium ≥ lower limit of normal
     - Calcium ≥ lower limit of normal.

Exclusion Criteria:

1. Previous chemotherapy of esophageal cancer except for neoadjuvant treatment without recurrence within 6 months after the end of treatment.
2. Concurrent radiotherapy involving target lesions used for this study. Concurrent palliative radiation for non-target lesions is allowed if other lesions are available outside the involved field. Previous pre-operative or post-operative radiotherapy is allowed.
3. Previous exposure to EGFR-targeted therapy
4. Other previous malignancy with exception of a history of a previous curatively treated basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix or other curatively treated malignant disease without recurrence after at least 5 years of follow-up
5. Known brain metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids
6. Serious concomitant disease or medical condition that in the judgment of the investigator renders the subject at high risk of treatment complication or reduces the probability of assessing clinical effect.
7. Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤1 year before enrolment
8. Inadequate pulmonary function according to the investigator’s judgment, history of interstitial lung disease e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan.
9. Hearing loss ≥ NCI-CTC V 4.03 Grade 3
10. Subject pregnant or breast feeding, or planning to become pregnant within 6 months after the end of treatment.
11. Subject (male or female) is not willing to use highly effective methods of contraception (per institutional standard) during treatment and for 6 months (male or female) after the end of treatment.
12. Contraindications to receive any platin, 5-FU or panitumumab
13. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days prior to treatment start
14. Known drug abuse/alcohol abuse
15. Peripheral polyneuropathy ≥ NCI-CTC V 4.03 Grade 2
16. Chronic inflammatory bowels diseases
17. Social situations limiting the compliance with the study requirements.

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT01627379

Contacts

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Cisplatin and 5-FU +/- Panitumumab for Patients With Nonresectable, Advanced or Metastatic Nonresectable Advanced or Metastatic Esophageal Squamous Cell Cancer

Locations
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Sponsors and Collaborators
AIO-Studien-gGmbH

Investigators
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More Information

Additional Information:

Related Info [83]

Publications:


Keywords provided by AIO-Studien-gGmbH:
nonresectable advanced metastatic esophageal squamous cell cancer Panitumumab

Additional relevant MeSH terms:
Carcinoma, Squamous Cell Neoplasms, Squamous Cell Esophageal Diseases Neoplasms, Glandular and Epithelial Neoplasms by Histologic Type Neoplasms Gastrointestinal Diseases Cisplatin Fluorouracil Antibodies, Monoclonal Antineoplastic Agents Therapeutic Uses Pharmacologic Actions Radiation-Sensitizing Agents Physiological Effects of Drugs Antimetabolites Molecular Mechanisms of Pharmacological Action Antimetabolites, Antineoplastic Immunosuppressive Agents Immunologic Factors

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