PLEASE NOTE: *This trial has been registered retrospectively.*

Trial Description

Title

A Phase 1, Open-Label, Non-Randomized, Dose-Finding, Safety and Tolerability Study of Orally Administered Teysuno (S-1) in Combination with Epirubicin and Oxaliplatin in Patients with Advanced Solid Tumors: Part 2 – Esophagogastric Cancer

Trial Acronym

TPU-S1119

URL of the trial

[---]*

Brief Summary in Lay Language

The objective of this clinical trial is to investigate the safety and determine the maximum tolerated dose of S-1 (Teysuno) in combination with Epirubicin and Oxaliplatin as well as to document any antitumor activity in this combination in patients with solid tumor cancers for which no treatment exists. The recommended dose of S-1 identified from this trial will be the dose level used in future clinical trials of S-1 in combination with Epirubicin and Oxaliplatin.
This trial contains 2 phases and the treatment cycle in both phases of the trial will last 21 days:
•The first phase (dose finding): approximately 3 weeks.
•The second phase (extension):
allows patients to continue treatment after they have completed the first phase. Patients will be in the second phase of the trial for as long as their study doctor feels they are receiving benefit from S-1 or until they choose to discontinue.

A small group of 3 patients, will be treated with a dose of 25 mg/m² S-1 in combination with fixed doses of Epirubicin and Oxaliplatin to find the most appropriate dose of S-1.

If less than 2 patients show intolerable effects, 3 additional patients will be enrolled at the same dose level and the maximum tolerated dosing regimen will be established by treating further 6 patients. If the treatment is tolerated by less than 2 out of 3 patients, the dose of 20 mg/m², as established in Part 1 of this study (for patients with solid tumors) will be determined as the maximum tolerated dosing regimen for these patients as well.
Once the maximum tolerated dosing regimen has been determined and up to 12 patients have been treated at this dose, enrollment into the study will end.

Brief Summary in Scientific Language

The goal of the current study is to investigate the safety and determine the maximum tolerated dose (MTD) of S-1 in combination with oxaliplatin and

epirubicin in patients with advanced or metastatic solid tumors. The standard 3-weekly dosing of oxaliplatin and epirubicin will be administered with escalating S-1 doses (14 days of S-1 with 7 days recovery) until the MTD is achieved.

Organizational Data

- DRKS-ID: **DRKS00005941**
- Date of Registration in DRKS: **2014/02/26**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **no**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **837.420.11 (7962) , Ethik-Kommission bei der Landesärztekammer Rheinland-Pfalz**

Secondary IDs

- Universal Trial Number (UTN): **U1111-1145-1509**
- EudraCT-No.
(for studies acc. to Drug Law): **2011-003471-11**
- BfArM-No.: **4037704**
- Other Secondary-ID: **DRKS00004844 (DRKS-ID Studienteil/ study part 1)**

Health condition or Problem studied

- ICD10: **C00-C75 - Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic and related tissue**

Interventions/Observational Groups

- Arm 1: **Each treatment cycle is 3 weeks (14 days of S-1 treatment and 7 days recovery). Patients will be treated with the following dosing regimen:**
S-1 20 mg/m2/dose BID
Oxaliplatin 130 mg/m2 and epirubicin 50 mg/m2 1x/cycle

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Single arm study**
- Blinding: **[---]***
- Who is blinded: **[---]***

Study Type: **Interventional**

Study Type Non-Interventional: **[---]***

Allocation: **Single arm study**

Blinding: **[---]***

Who is blinded: **[---]***

- Control: **Uncontrolled/Single arm**
- Purpose: **Treatment**
- Assignment: **Single (group)**
- Phase: **I**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **N/A**

Primary Outcome

To investigate the safety and determine the maximum tolerated dose (MTD) of S-1 25 mg/m2, when combined with epirubicin 50 mg/m2 and oxaliplatin 130 mg/m2 in patients with advanced or metastatic esophagogastric cancer as first line therapy.
Standard safety monitoring and grading using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 will be used.

Secondary Outcome

To document any antitumor activity observed with S-1 administered in this combination
treatment regimen.
Tumor assessments will be performed throughout the study period and analyzed using Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Version 1.1, 2009). Computed tomography (CT) scans will be performed at the end of every 3 cycles.

Countries of recruitment

- DE **Germany**
- CZ **Czech Republic**
- UK **United Kingdom**

Locations of Recruitment

- University Medical Center **I. Med. Klinik und Poliklinik Gastrointestinale Onkologie, Mainz**

- Medical Center **Klinikum Mutterhaus d. Borromäerinnen, Abt. Innere Medizin, Trier**
- University Medical Center **Comprehensive Cancer Center der LMU- Medizinische Klinik und Poliklinik III, München**
- Medical Center **The Christie NHS Foundation Trust- Oak Treatment Center , Manchester**
- Medical Center **Masarykův onkologický ústav Klinika komplexní onkologické péče, Brno**
- Medical Center **Fakultní nemocnice Hradec Králové Klinika onkologie a radioterapie, Hradec Králové**
- Medical Center **Fakultní nemocnice Olomouc Onkologická klinika, Olomouc**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2013/10/14**
- Target Sample Size: **12**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **International**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

1. Has given written informed consent.
2. Is ≥18 years of age.
3. Has advanced or metastatic esophagogastric adenocarcinoma.
4. No previous treatment for advanced or metastatic disease.
5. Is able to take medications orally.
6. Has ECOG performance status 0 or 1 on Cycle 1, Day 1.
7. Has a life expectancy of at least 3 months.
8. Left ventricular ejection fraction (LVEF) ≥ the lower limit of normal (LLN) for the institution.
9. Serum troponin T and creatine phosphokinase (CPK)-MB values ≤ upper limit of Normal (ULN) for the institution.
10. Has adequate organ function as defined by the following criteria:
a. Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤2.5 x ULN; if liver function abnormalities are due to underlying liver metastasis, AST (SGOT) and ALT (SGPT) ≤5 x ULN.
b. Total serum bilirubin of ≤1.5 x ULN.
c. Absolute neutrophil count of ≥1,500/mm3 (ie, ≥1.5 x 109/L by International Units [IU])
(excluding measurements obtained within 7 days after administration of G-CSF).
d. Platelet count ≥100,000/mm3 (IU: ≥100 x 109/L) (excluding measurements obtained within 7 days after transfusion).

e. Hemoglobin value of ≥9.0 g/dL (excluding measurements obtained within 7 days after transfusion).
f. Creatinine clearance ≥60 mL/min based on calculated creatinine clearance (Cockcroft-Gault32 formula) or 24-hour urine collection.
11. Is willing and able to comply with scheduled visits, treatment plan, lab tests and other study procedures.

Exclusion criteria

1. Has had treatment with any of the following within the specified time frame prior to study drug administration:
a. Major surgery within prior 4 weeks (the surgical incision should be fully healed prior to study drug administration).
b. Radiotherapy within prior 4 weeks.
c. Previous chemotherapy.
i. Any investigational agent received either concurrently or within the last 30 days.
j. Current enrollment in another interventional clinical study.
2. Has a serious illness or medical condition(s) including, but not limited to, the following:
a. Known brain metastasis or leptomeningeal metastasis.
b. Known acute systemic infection.
c. Myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, cerebrovascular accident or transient ischemic attack, pulmonary embolism, or deep vein thrombosis within the last 12 months.
d. Symptomatic congestive heart failure (New York Heart Association [NYHA] class III or IV e. Ongoing cardiac dysrhythmias (≥Grade 2), atrial fibrillation (any grade), or prolongation of QTc interval (>450 msec for males; >470 msec for females).
f. Hypertensive crisis or severe hypertension that is not controlled.
g. Chronic nausea, vomiting, or diarrhea considered to be clinically significant in the opinion of the Investigator.
h. ≥Grade 1 peripheral neuropathy.
i. Recent hemoptysis, coagulopathy and other bleeding disorders considered by the Investigator to be clinically significant.
j. Known nephrotic syndrome (proteinuria >2 g/24 hours).
k. Known clinically significant interstitial lung disease or pulmonary fibrosis.
l. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.
m. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the Investigator would make the patient inappropriate for entry into this study.
3. Is receiving concomitant treatment with the following drugs that may interact with S-1:
a. Sorivudine, brivudine, uracil, eniluracil, cimetidine, folinate/folinic acid, and dipyridamole (may enhance S-1 activity).
b. Nitroimidazoles, including metronidazole and misonidazole (may enhance S-1 activity)
c. Methotrexate (may enhance S-1 activity)
d. Clozapine (may increase risk and severity of hematologic toxicity with S-1)
e. Allopurinol (may diminish S-1 activity).
f. Phenytoin (S-1 may enhance phenytoin activity).
g. Flucytosine, a fluorinated pyrimidine antifungal agent (may enhance S-1 activity).

4. Is receiving concomitant treatment with the following drugs that may interaction with epirubicin:
a. Cimetidine (may increase the area under the plasma concentrationtime curve [AUC] of epirubicin).
b. Dexverapamil (may alter the pharmacokinetics of epirubicin).
c. Quinine (may accelerate the initial distribute on of epirubicin from blood into the tissues and may have an influence on the red blood cells partitioning of epirubicin).
d. Interferon alfa-2b (may cause a reduction in both the terminal elimination half-life and the total clearance of epirubicin).
5. Is a pregnant or lactating female.
6. Has known hypersensitivity to 5-FU, epirubicin, oxaliplatin or other platinum compounds.
7. Patients with reproductive potential who refuse to use an adequate means of contraception (including male patients). Contraceptive measures must be taken by both male and female patients during and up to 6 months after stopping treatment with S-1.

Addresses

■ **Primary Sponsor**

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3741 LM Baarn
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E-mail: **[---]***
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■ **Contact for Scientific Queries**

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Sources of Monetary or Material Support

- **Commercial (pharmaceutical industry, medical engineering industry, etc.)**

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Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

Status

- Recruitment Status: **Recruiting complete, follow-up complete**
- Study Closing (LPLV): **2015/06/04**

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*
**** This entry means that data is not displayed due to insufficient data privacy clearing.*