1 STUDY SYNOPSIS

Name of Sponsor GMIHO mbH
Treatment Combination treatment consisting of gemcitabine, cisplatin, and panitumumab (experimental arm only)
Title of study PURO—An open-label, randomised, multicentre, phase II study to evaluate the efficacy of chemotherapy with gemcitabine and cisplatin in combination with the EGF receptor antibody panitumumab (GemCisP) versus GemCis in the first-line therapy of locally advanced/metastatic urothelial carcinoma in patients with wild-type HRAS
Investigators and study centres Principal (coordinating investigator): Prof. Dr. med. Kurt Miller, Charité, Berlin cf. section 3 for a complete list of participating institutions
Publication NA
Studied period 2010 - 2012
Phase of development Phase II
Primary objective The primary objective of the study is to assess the efficacy of the combination consisting of gemcitabine/cisplatin and panitumumab in patients with wild-type HRAS (non-mutated status). The progression-free survival rate at 12 months will be compared to expectations derived from historical data, which are verified by a

randomised control group without the antibody.

Secondary objectives

- Determination of tumour response
- Duration of response
- Overall survival
- Documentation of adverse effects
- Quality of life survey

Number of patients

Planned: 124

Analysed: 2

Criteria for inclusion

- Histologically or cytologically confirmed, unresectable urothelial carcinoma of the bladder or the upper urinary tract
- Wild-type HRAS
- Male and female subjects > 18 years of age
- General condition ECOG 0-1
- Life expectancy at least 12 weeks
- Women of child-bearing potential: negative pregnancy test and use of effective contraception (oral contraceptive, coil); men: use of adequate male contraception (condom) for up to 3 months after discontinuation of panitumumab therapy
- Locally advanced or metastatic disease (T3b,T4 and/or N+ and/or M+)
- At least one unidimensionally measurable lesion detectable in CT or MRI corresponding to the RECIST criteria
- Adequate haematological, hepatic, renal and metabolic function parameters:
  - Leukocytes > 3000/mm³, ANC ≥ 1500/mm³, platelets ≥ 100,000/mm³, hemoglobin > 9 g/dl
  - Creatinine clearance ≥ 50 ml/min and serum creatinine ≤ 1.5 x upper limit of normal
  - Bilirubin ≤ 1.5 x upper limit of normal, GOT-GPT ≤ 2.5 x upper limit of normal in absence of liver metastases, or ≤ 5 x upper limit of normal in presence of liver metastases, AP ≤ 5 x upper limit of normal

- Magnesium ≥ lower limit of normal; calcium ≥ lower limit of normal
- INR and PTT < 1.5 x the upper limit of the normal reference range

Criteria for exclusion

- HRAS mutation
- Absence of any of the above-listed inclusion criteria
- Dialysis-dependence following nephrectomy
- Patients with cerebral tumours and/or cerebral metastases
- Clinically significant cardiovascular disease in (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤ 1 year before enrolment.
- Patients with uncontrolled hypertension; systolic blood pressure > 150 mmHg or diastolic blood pressure > 90 mmHg despite optimal medical treatment
- History of interstitial lung disease, e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan.
- Patients with thrombotic or embolic events, such as stroke or pulmonary embolism
- Patients with recent or known history of haemorrhagic diathesis
- Known significant neurological or psychiatric disorders, including dementia and epileptic seizures
- Serious inflammatory eye conditions, hearing impairment
- Pulmonary (pO2 < 60 mmHg), haemopoietic (e.g. serious bone marrow aplasia), hepatic or renal disorders
- Patients with poorly controlled diabetes mellitus
- Serious bacterial or fungal infections (>grade 2 NCI CTC Version 3)
- Chronic hepatitis B or C; HIV infection
- Autoimmune disease
- Allergic reaction to one of the medications to be used
- Status post organ transplantation
- Status post autologous bone marrow transplantation or stem cell transplantation in the 4 months prior to study commencement
- Manifest secondary malignancy or other form of cancer in the previous 5 years (excluding basalioma, in situ cervical cancer, incidental prostatic cancer)
- Subject pregnant or breast feeding, or planning to become pregnant within 6

months after the end of treatment

- Subject (male or female) is not willing to use highly effective methods of contraception (per institutional standard) during treatment and for 3 months (male or female) after the end of treatment (adequate: oral contraceptives, intrauterine device or barrier method in conjunction with spermicidal jelly).
- Active participation in other clinical studies in the previous 4 weeks
- Prior systemic therapy with cytostatics or immunotherapeutic agents
- Concurrent use of other anticancer treatments after study commencement
- Intravesical chemotherapy in the previous 4 weeks
- Radiotherapy in the previous 4 weeks
- Previous radiotherapy in which all lesions to be used for the evaluation of tumour response were irradiated
- Patients in a closed institution according to an authority or court decision

Test product, dose and mode of administration

Treatment schema (experimental arm):

Gemcitabine: 1250 mg/m², day 1 and 8, i.v., q3

Cisplatin: 70 mg/m², day 2, i.v., q3

Panitumumab 9 mg/kg/body weight, i.v., day 1, q3

Duration of treatment

If possible, the chemotherapy/antibody combination were to be administered for up to 6 cycles or until diagnosis of disease progression (if occurring earlier). If not prevented by fulminating early progression or severe toxicity, a minimum of two cycles should be applied.

Reference product, dose and mode of administration

Treatment schema (reference arm):

Gemcitabine: 1250 mg/m², day 1 and 8, i.v., q3

Cisplatin: 70 mg/m², day 2, i.v., q3

Criteria for evaluation: Efficacy, safety

Efficacy criteria are tumor response, duration of response, progression-free survival (rate), overall survival. The primary endpoint assessment is performed according to RECIST criteria and standards.

Statistical methods

Due to the early termination of the trial with only two patients randomised, only case descriptions are provided. The originally planned methods of statistical evaluation are described in section 7 of the protocol.

Summary – Conclusions: Efficacy results, safety results, conclusion

The study had to be closed early due to insufficient recruitment. Only two patients were included. Thus, it is not possible to draw any conclusions on the efficacy or safety of this treatment regimen.