SKIP - A double-blind placebo-controlled randomized multicenter phase II trial of skin toxicity treatment in subjects with metastatic colorectal carcinoma receiving panitumumab

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Final Study Report

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Sponsor:

GMIHO

Gesellschaft für Medizinische Innovation Hämatologie und Onkologie mbH

Coordinating Investigator:

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Author of Final Study Report:

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Study Start Date – End Date:
(15 Aug 2011 – 27 May 2013)

Synopsis

Sponsor: Gesellschaft für Medizinische Innovation Hämatologie Onkologie mbH
Test Product: Doxycycline
Active Component: Doxycycline
TITLE: **SKIP - A double-blind placebo-controlled randomized multicenter phase II trial of skin toxicity treatment in subjects with metastatic colorectal carcinoma receiving panitumumab**
Protocol version 1.0 of 23-Aug-2010 Amendment according to requests of the ethics committee: Protocol version 2.0 of 18-Apr-2011 (version that obtained approval by the ethics committee and as amended version by the competent authority). **Amendments:** o Non-substantial amendment 1: Protocol version of 2.1 of 14-Jul-2011 o Amendment 2: Protocol version 3.0 of 21-Dec-2011 o Change of sponsor address: Protocol version 4.0 of 25-Jun-2012
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Active Component: Doxycycline

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Test Product: Doxycycline
Active Component: Doxycycline
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First patient in: 19 / August / 2011

Last patient out: 14 / March /2013

Temporary halt of recruitment due to concerns about insufficient recruitment rate from 30-Apr-2012 to 1-Jul-2012

Early termination of the trial on 14-May-2013 due to insufficient recruitment rate despite unchanged clinical and scientific relevance of the investigated question and due to a recent scientific information and consecutive change of the panitumumab indication, that only patients with wild-type RAS (i.e. wild-type KRAS and NRAS in exons 2, 3, and 4) metastatic colorectal cancer should be treated instead of all patients with wild-type KRAS as previously done.

Rational:

Skin toxicities affect patients' quality of life and thus threaten patients' compliance to therapy. There is an urgent need for evidence-based treatment recommendations for the prevention and management of panitumumab –associated skin toxicities. The study aimed to compare the efficacy and safety of a manageable preemptive treatment with oral doxycycline in combination with a supportive topical regimen containing erythromycin cream (2 %) over duration of 12 weeks on the occurrence and grade of panitumumab induced skin toxicities in a double-blind, controlled randomized setting. Basic skin treatment with or without doxycycline was discontinued at the end of study treatment after 12 weeks or until a value of 6-10 was observed on the visual analogue scale (VAS), whichever was sooner.

Primary objective:

To compare the patient rated efficacy of preemptive basic skin treatment with or without doxycycline on the occurrence and grade of panitumumab induced skin toxicities and resulting in the end of study treatment.

Number of patients (planned and analyzed):

It was planned to include 94 patients, 47 per group, as according to the sample size calculation 42 eligible patients per group were needed to achieve a power of 80% and a rate of 10% of non-eligible patients was assumed.

After study duration of 1 year and 7 months only eleven patients had been enrolled despite all efforts including extension of the number of participating trial centers. Only 9 out of these 11 patients had received at least one dose of study medication. Thus no confirmatory analysis was possible and only selected parameters were assessed in descriptive manner.

Indication:

Management of skin toxicity due to treatment with panitumumab in patients with wild-type *KRAS* metastatic mCRC.

Inclusion criteria:

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1. *Up to Protocol Version 2.1*
   Patients with advanced or metastatic mCRC and non-mutated (wild-type) *KRAS* who were planned to receive treatment with panitumumab monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens and without prior treatment with epidermal growth factor receptor (EGFR) antibody
   Protocol Version 3.0 and 4.0
   Patients with wild-type *KRAS* metastatic colorectal cancer (mCRC) who were planned to receive treatment with panitumumab
   • In first-line in combination with FOLFOX
   or
   • In second-line in combination with FOLFIRI if they had received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan)
   or
   • As monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens
   and who had not received any prior treatment with EGFR antibody
2. Man or woman 18 years of age or older
3. Signed and dated informed consent before the start of specific protocol procedures
4. ECOG (Eastern Cooperative Oncology Group) performance status of 0, 1, or 2
5. Bilirubin ≤ 1.5 x ULN, SGOT/SGPT ≤ 2.5 x ULN, AP ≤ 3 x ULN if no evidence of liver metastases
   or
   Bilirubin ≤ 3 x ULN, SGOT/SGPT ≤ 5 x ULN, AP ≤ 5 x ULN if evidence of liver metastases

   Women of child-bearing potential had to use adequate highly effective methods of contraception. Since doxycyline might reduce efficacy of hormonal contraceptives, women of child-bearing potential had to use double-barrier methods within 4 weeks before first intake of study medication, during study participation and at least 6 weeks after last intake of study medication even if using hormonal contraceptives. Women were considered to be of child-bearing potential unless they were ≥ 50 years old and for more than 2 years amenorrhoic or unless they were surgically sterile.

Exclusion criteria:

1. Absence of any of the above-listed inclusion criteria
2. *Protocol Version 3.0 and 4.0*
   Unknown *KRAS* or mutated *KRAS* of mCRC
3. Any serious medical condition or psychiatric illness that would have interfered with the patient's ability to sign the informed consent form
4. Allergic reaction to one of the medications to be used
5. Subject allergic to panitumumab or any components of the panitumumab formulation or treatment regimen
6. Prior treatment with EGFR antibody
7. CYP3A4 enzyme inducers, inhibitors, and substrates (eg, phenytoin, phenobarbital, carbamazepine, ketoconazole, rifampicin, rifabutin, and St. John's Wort) ≤ 2 weeks before randomization (itraconazole had to be used with caution)
8. Subjects with hypersensitivity to doxycycline, other tetracyclines, or ingredients of

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doxycycline capsules

9. Systemic treatment with antibiotics which had been completed less than 7 days prior to randomization
10. Pregnant and/or breast-feeding women
11. Active participation in other clinical studies in the previous 4 weeks
12. Serious liver function disorders
13. History of, or evidence of, interstitial pneumonitis or pulmonary fibrosis
14. Person who had been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.

Test product, dose and mode of administration, batch number:

Patients with wild-type *KRAS* mCRC, who received treatment with panitumumab according to the European label and summary of product characteristics (SmPC) were given a basic preemptive skin management for panitumumab induced skin toxicities with or without doxycycline in a double-blind placebo-controlled manner (100 mg twice daily as hard capsule oral use). Preemptive skin treatment started one day before panitumumab treatment and lasted as long as the patients assessed their skin toxicities as adequately and sufficiently treated up to a maximal duration of 12 weeks.

For all patients additional measures of the skin management comprised:

- Skin moisturizers were to be applied to face, hands, neck, back and chest daily in the morning upon rising.
- Before going outdoors sunscreen (PABA free, sun protection factor ≥ 15, UVA/UVB protection) was to be applied to exposed areas.
- Topical antibacterial erythromycin cream (2%) was to be applied to face, hands, feet, neck, back and chest at bedtime.

Investigational medicinal products:

- **<u>Doxycycline 100 mg</u>** twice daily as hard capsules for oral use
  In those patients who experienced no occurrence of any skin toxicity or only skin toxicities with NCI CTCAE grade < 2 during the first 4 weeks of skin treatment, the dose was reduced to doxycycline 100 mg once daily for the remaining treatment duration.

  Manufacturer:

  Corden Pharma GmbH
  Otto-Hahn-Strasse
  68723 Plankstadt, Germany

Doxycycline 100 mg capsules manufactured by ALIUD® PHARMA GmbH, Gottlieb-Daimler-Str. 19, 89150 Laichingen, Germany were used to process the study medication doxycycline (with identical labeling and packaging for verum and placebo).

The **batch numbers** of doxycycline were 641DE120052 and 641DE110015.

- **<u>Panitumumab</u>**

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Test Product: Doxycycline

Active Component: Doxycycline

Panitumumab treatment was given according to the European label and SmPC. Panitumumab was prescribed by the investigator as commercially available panitumumab (Vectibix®). Thus no batch numbers are available. The recommended dose of panitumumab according to the SmPC was 6 mg/kg every two weeks. Dose modifications of panitumumab were up to investigator's discretion but had to be in accordance with the SmPC of Vectibix®.

Duration of treatment:

Only four of the nine treated patients received preemptive skin treatment with doxycycline or placebo over the intended time interval of about 85 days. Two patients discontinued preemptive skin treatment after 21 days and 24 days of first treatment with panitumumab, due to skin toxicity ≥ 6 on a VAS scale according to patient's self assessment. Three patients discontinued skin treatment prematurely due to progression of the underlying metastatic colorectal cancer requiring end of treatment with panitumumab.

Reference therapy, dose and mode of administration, batch number:

There was no reference therapy with a comparator. The test product was compared to placebo and the placebo had to be taken identically to doxycycline: 100 mg twice daily as hard capsule for oral use.

In those patients who experienced no occurrence of any skin toxicity or only skin toxicities with NCI CTCAE grade < 2 during the first 4 weeks of skin treatment, the dose was reduced to 100 mg once daily for the remaining treatment duration.

Manufacturer of placebo:

Corden Pharma GmbH
Otto-Hahn-Strasse
68723 Plankstadt, Germany

The **batch numbers** of the placebo were identical to those of verum: 641DE120052 and 641DE110015.

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Criteria for evaluation:

Efficacy:

Due to the low number of only nine patients in the intent-to-treat population no confirmatory analysis with regard to the primary and secondary efficacy endpoints was performed.

According to the study protocol the following parameters of efficacy should have been analyzed.

The primary endpoint was defined as time until unblinding of skin therapy allocation (basic skin treatment with or without doxycycline) due to insufficient efficacy (i.e. unbearable skin toxicity, measured by patient's allocating point 6 through 10 on a visual analogue scale).

Secondary endpoints and parameters of efficacy are listed below:

- Incidence of ≥ grade 2 skin toxicities of any type over 12 weeks or until a value of 6-10 is observed on the VAS, whichever is sooner
- Incidence of specific ≥ grade 2 skin toxicities over 12 weeks or until a value of 6-10 is observed on the VAS, whichever is sooner - overall and for the different treatment schemata (FOLFOX + Pan, FOLFIRI +Pan, Pan mono)
- Time to first occurrence of specific ≥ grade 2 skin toxicities - overall and for the different treatment schemata (FOLFOX + Pan, FOLFIRI +Pan, Pan mono)
- Most severe specific ≥ grade 3 skin toxicities of interest over 12 weeks or until a value of 6-10 is observed on the VAS, whichever is sooner - overall and for the different treatment schemata (FOLFOX + Pan, FOLFIRI +Pan, Pan mono)
- Time to the first most severe specific ≥ grade 3 skin toxicities of interest - overall and for the different treatment schemata (FOLFOX + Pan, FOLFIRI +Pan, Pan mono)
- Panitumumab dose reduction due to specific skin toxicities of interest over 12 weeks or until a value of 6-10 is observed on the VAS, whichever is sooner
- Scores in DLQI under preemptive basic skin treatment with or without doxycycline Type, incidence and severity of doxycycline related adverse events
- Type, incidence and severity of panitumumab related adverse events
- Response rate to panitumumab/ combination of panitumumab with FOLFOX/combination of panitumumab with FOLFIRI over 12 weeks or until a value of 6-10 is observed on the VAS, whichever is sooner (only if patient received at least 8 weeks of study treatment)

The specific skin toxicities of interest in the context of this protocol are: pruritus, rash acneiform, erythroderma, papulopustular rash, rash pustular, dry skin, paronychia, nail changes (nail loss and nail ridging), skin infection, skin ulceration.

The relevant National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI) v 4.0 for skin and subcutaneous tissue disorders and infections and infestations grading will be used to capture the intensity of these specific skin toxicities. A copy of the CTCAE version 4.0 can be downloaded from the CTEP homepage: (http://ctep.info.nih.gov).

Safety:

AEs were recorded from the first dose of study medication until 30 days after the last application of study medication. The severity of an AE was graded according to NCI-CTCAE version 4.0. The Medical Dictionary of Regulatory Activities (MedDRA) version 16.1 was used for the coding of adverse events. All adverse events assessed as 'certainly', 'probably', 'possibly' related to study medication were considered as cases of adverse drug reactions.

All AEs were analyzed in descriptive manners.

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Statistical methods:

Until the early termination of the trial only 11 patients had been randomized. Only 9 out of these 11 patients had received at least one dose of study medication, because one patient withdrew his consent to study participation before the first application of study medication and another patient was found to be not eligible before the first application of study medication.

Thus only 9 patients were evaluated as intent-to treat population and safety population. Due to the low number of patients no confirmatory analysis with regard to the primary and secondary efficacy endpoints could be performed and only selected efficacy and safety parameters were assessed in descriptive manner.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Three patients had received panitumumab monotherapy, 5 patients FOLFOX chemotherapy in combination with panitumumab and one patient FOLFIRI chemotherapy in combination with panitumumab according to the SmPC of Vectibix®.

SAFETY RESULTS:

All patients of the safety population experienced several adverse events.

6 of 9 patients (67%) experienced a serious adverse event (SAE), one of these 6 patients experienced 2 SAEs. None of these SAEs were assessed to be at least possibly related to either doxycycline/placebo or panitumumab. No skin and subcutaneous tissue disorders were reported as SAEs.

Date of the report: 18.12.2013