



## Clinical trial results:

**Non-randomized phase-IV-study to investigate the efficacy of FOLFIRI in combination with cetuximab in the first-line treatment of metastatic colorectal cancer including a regular dermal prophylaxis to prevent acneforme follicular exanthema**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2010-019885-10 |
| Trial protocol           | DE             |
| Global end of trial date | 09 July 2017   |

### Results information

|                                   |                                                           |
|-----------------------------------|-----------------------------------------------------------|
| Result version number             | v1 (current)                                              |
| This version publication date     | 22 July 2018                                              |
| First version publication date    | 22 July 2018                                              |
| Summary attachment (see zip file) | DERMATUX<br>(DERMATUX_CSR_E3_Synopsis_v2.0_29May2018.pdf) |

### Trial information

#### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | Dermatux |
|-----------------------|----------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01315990 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                |
|------------------------------|--------------------------------------------------------------------------------|
| Sponsor organisation name    | University Medical Centre Mainz (represented by the board of directors)        |
| Sponsor organisation address | Langenbeckstr. 1, Mainz, Germany,                                              |
| Public contact               | Clinical Research Organisation, iOMEDICO AG, 0049 761152420, info@iomedico.com |
| Scientific contact           | Clinical Research Organisation, iOMEDICO AG, 0049 761152420, info@iomedico.com |

Notes:

### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |              |
|------------------------------------------------------|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 09 July 2017 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 09 July 2017 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 09 July 2017 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

To assess the progression free survival (one year) of patients with treatment of FOLFIRI and cetuximab, combined with an regular dermal prophylaxis.

Protection of trial subjects:

Informed consent of patient has been obtained in accordance with § 40 I 3 No. 3 Lit. b), II 1 AMG and § 40 I 3 No. 3 Lit. c). IIa 1&2 AMG by each investigator prior to inclusion of each patient in the study. The nature, objective and importance of the study, the possible benefits and disadvantages or risks, and the study procedures were explained to each patient orally and in writing. The patients were informed that their participation was voluntary, that they were free to withdraw from the study at any time, and that choosing not to participate would not impact on the patient's care or future treatment. The patients were also informed that, by signing the Informed Consent Form, they explicitly permitted authorized representatives of the sponsor and the regulatory authorities access to study-related personal data to the extent permitted by the applicable law(s) and/or regulations without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) and/or regulations. The patients were also informed that their consent to access their data might not be revoked. Each patient was given sufficient time to read and discuss the ICF with the investigator prior to giving his/her written consent. Before entry to the study and prior to the conduct of any study-related procedure consent was recorded by means of the patient's dated signature. The patient was then given a copy of the information sheet and his/her signed consent form. The consent form was retained by the investigator as part of the study records. The investigator did not undertake any investigation specifically required only for the clinical study until valid consent had been obtained. The terms of the consent and when it was obtained were also documented in the case report form (CRF).

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 03 January 2011 |
| Long term follow-up planned                               | Yes             |
| Long term follow-up rationale                             | Efficacy        |
| Long term follow-up duration                              | 3 Years         |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 55 |
| Worldwide total number of subjects   | 55          |
| EEA total number of subjects         | 55          |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 28 |
| From 65 to 84 years                       | 26 |
| 85 years and over                         | 1  |

## Subject disposition

### Recruitment

Recruitment details:

The investigators enrolled patients based on the pre-defined inclusion and exclusion criteria.

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 55 |
| Number of subjects completed | 54 |

### Pre-assignment subject non-completion reasons

|                            |                       |
|----------------------------|-----------------------|
| Reason: Number of subjects | Protocol deviation: 1 |
|----------------------------|-----------------------|

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

Blinding implementation details:

Not applicable.

### Arms

|           |                        |
|-----------|------------------------|
| Arm title | Study treatment (mITT) |
|-----------|------------------------|

Arm description:

Study treatment consisted of cetuximab (IMP), irinotecan, folic acid, 5-fluorocil (FOLFIRI) and patients received a pre-defined dermal prophylaxis including vitamin K1 ointment and additional oral doxycycline.

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Cetuximab             |
| Investigational medicinal product code | ATC code: L01XC06     |
| Other name                             | Erbitux®              |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Cetuximab (according to SmPC): Wk 1: 120 min i.v. infusion (400 mg cetuximab per m<sup>2</sup> body surface area), followed by 60 min i.v. infusions (250 mg cetuximab per m<sup>2</sup>) on day 1 and 8 for up to 1 year or until PD, severe toxicity, CR, secondary operability, treatment refusal, investigator decision, death, or until patient was lost to FU (prior to the first infusion, patients received premedication with an antihistamine and a corticosteroid. This premedication was recommended prior to all subsequent infusions).

FOLFIRI scheme, every 2 weeks: Irinotecan 180 mg/m<sup>2</sup> (d1), folic acid (FA) 400 mg/m<sup>2</sup>, 120 min (d1), 5-fluorouracil (5-FU) 400 mg/m<sup>2</sup> bolus (d1), 5-FU 2,400 mg/m<sup>2</sup> i.v. for a duration of 46 hours (d1-2).

Prophylactic skin treatment: Reconval K1® ointment (0.1%) on the face, chest, and fingers once daily in the evening plus doxycycline 100 mg p.o. once daily in the morning and in the evening (in case of grade 3+ exanthema, rescue therapy with topical Dermatop® (0.25%) was initiated).

| <b>Number of subjects in period 1<sup>[1]</sup></b> | <b>Study treatment (mITT)</b> |
|-----------------------------------------------------|-------------------------------|
| Started                                             | 54                            |
| Completed                                           | 35                            |
| Not completed                                       | 19                            |
| Physician decision                                  | 5                             |
| Patient's wish                                      | 6                             |
| Other reason                                        | 1                             |
| Inacceptable toxicity                               | 3                             |
| Protocol deviation                                  | 4                             |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 55 patients were screened and gave written informed consent. One patient was excluded before start of treatment phase (screening failure). Therefore, patient baseline characteristics have been analysed for mITT population (n=54) and PP population (n=46).

## Baseline characteristics

### Reporting groups

| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Overall trial (overall period) |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                |
| For the treatment of all patients with mCRC, the commercial available monoclonal IgG1 antibody cetuximab was given in combination with chemotherapy (FOLFIRI, every 2 weeks) according to the respective SmPCs. Prophylactic skin treatment consisted of Reconval K1® ointment (0.1%) on the face, chest, and fingers once daily in the evening plus doxycycline 100 mg p.o. once daily in the morning and in the evening. In case of grade 3+ exanthema, rescue therapy with topical corticoid prednicarbate cream (Dermatop® 0.25%) was initiated. Patients were treated for up to 12 months, survival follow-up was conducted for 3 years after the last patient was treated for 12 months. |                                |

| Reporting group values               | Overall trial (overall period) | Total |  |
|--------------------------------------|--------------------------------|-------|--|
| Number of subjects                   | 54                             | 54    |  |
| Age categorical                      |                                |       |  |
| Units: Subjects                      |                                |       |  |
| Adults (18-64 years)                 | 28                             | 28    |  |
| From 65-84 years                     | 25                             | 25    |  |
| 85 years and over                    | 1                              | 1     |  |
| Age continuous                       |                                |       |  |
| Units: years                         |                                |       |  |
| median                               | 63.9                           |       |  |
| full range (min-max)                 | 44.7 to 86.2                   | -     |  |
| Gender categorical                   |                                |       |  |
| Units: Subjects                      |                                |       |  |
| Female                               | 23                             | 23    |  |
| Male                                 | 31                             | 31    |  |
| Previous (neo)adjuvant tumor therapy |                                |       |  |
| Units: Subjects                      |                                |       |  |
| Yes                                  | 10                             | 10    |  |
| No                                   | 44                             | 44    |  |
| Previous radio therapy               |                                |       |  |
| Units: Subjects                      |                                |       |  |
| yes                                  | 3                              | 3     |  |
| no                                   | 51                             | 51    |  |
| Previous tumor surgery               |                                |       |  |
| Units: Subjects                      |                                |       |  |
| yes                                  | 37                             | 37    |  |
| no                                   | 17                             | 17    |  |
| Tumor stage at primary diagnosis     |                                |       |  |
| Units: Subjects                      |                                |       |  |
| stage II                             | 1                              | 1     |  |
| stage III                            | 11                             | 11    |  |
| stage IV                             | 39                             | 39    |  |
| missing                              | 3                              | 3     |  |
| Localization of tumor                |                                |       |  |
| Units: Subjects                      |                                |       |  |
| Colon                                | 40                             | 40    |  |
| Rectum                               | 14                             | 14    |  |

|                                                                  |              |    |  |
|------------------------------------------------------------------|--------------|----|--|
| Confirmed K-RAS wild type                                        |              |    |  |
| K-RAS exon 12-13                                                 |              |    |  |
| Units: Subjects                                                  |              |    |  |
| yes                                                              | 54           | 54 |  |
| no                                                               | 0            | 0  |  |
| ECOG Performance Status                                          |              |    |  |
| Units: Subjects                                                  |              |    |  |
| ECOG 0                                                           | 31           | 31 |  |
| ECOG 1                                                           | 23           | 23 |  |
| Age at primary diagnosis (years)                                 |              |    |  |
| Units: years                                                     |              |    |  |
| median                                                           | 63.3         |    |  |
| full range (min-max)                                             | 44.6 to 82.0 | -  |  |
| Time from primary diagnosis to development of metastases (weeks) |              |    |  |
| Units: weeks                                                     |              |    |  |
| median                                                           | 0.4          |    |  |
| full range (min-max)                                             | 0.0 to 814.3 | -  |  |
| Age at development of metastases (years)                         |              |    |  |
| Units: years                                                     |              |    |  |
| median                                                           | 63.7         |    |  |
| full range (min-max)                                             | 44.6 to 85.5 | -  |  |
| Time from primary diagnosis to development of metastases (weeks) |              |    |  |
| Units: weeks                                                     |              |    |  |
| median                                                           | 0.4          |    |  |
| full range (min-max)                                             | 0.0 to 814.3 | -  |  |

### Subject analysis sets

|                            |                              |
|----------------------------|------------------------------|
| Subject analysis set title | Per-Protocol Population (PP) |
| Subject analysis set type  | Per protocol                 |

#### Subject analysis set description:

The Per-protocol set consisted of all patients who had received at least at least 3 cycles of the planned combination therapy including pre-defined skin care (Reconval K1® ointment and Doxycycline, as well as Dermatotop® ointment, if applicable) according to the protocol. Patients were also eligible if treatment had to be stopped prematurely (within the first 3 cycles) due to early progression (including early death).

| Reporting group values | Per-Protocol Population (PP) |  |  |
|------------------------|------------------------------|--|--|
| Number of subjects     | 46                           |  |  |
| Age categorical        |                              |  |  |
| Units: Subjects        |                              |  |  |
| Adults (18-64 years)   | 25                           |  |  |
| From 65-84 years       | 20                           |  |  |
| 85 years and over      | 1                            |  |  |
| Age continuous         |                              |  |  |
| Units: years           |                              |  |  |
| median                 | 63.9                         |  |  |
| full range (min-max)   | 44.7 to 86.2                 |  |  |

|                                                                                     |              |  |  |
|-------------------------------------------------------------------------------------|--------------|--|--|
| Gender categorical<br>Units: Subjects                                               |              |  |  |
| Female                                                                              | 19           |  |  |
| Male                                                                                | 27           |  |  |
| Previous (neo)adjuvant tumor therapy<br>Units: Subjects                             |              |  |  |
| Yes                                                                                 | 6            |  |  |
| No                                                                                  | 40           |  |  |
| Previous radio therapy<br>Units: Subjects                                           |              |  |  |
| yes                                                                                 | 3            |  |  |
| no                                                                                  | 43           |  |  |
| Previous tumor surgery<br>Units: Subjects                                           |              |  |  |
| yes                                                                                 | 31           |  |  |
| no                                                                                  | 15           |  |  |
| Tumor stage at primary diagnosis<br>Units: Subjects                                 |              |  |  |
| stage II                                                                            | 1            |  |  |
| stage III                                                                           | 7            |  |  |
| stage IV                                                                            | 35           |  |  |
| missing                                                                             | 3            |  |  |
| Localization of tumor<br>Units: Subjects                                            |              |  |  |
| Colon                                                                               | 33           |  |  |
| Rectum                                                                              | 13           |  |  |
| Confirmed K-RAS wild type                                                           |              |  |  |
| K-RAS exon 12-13                                                                    |              |  |  |
| Units: Subjects                                                                     |              |  |  |
| yes                                                                                 | 46           |  |  |
| no                                                                                  | 0            |  |  |
| ECOG Performance Status<br>Units: Subjects                                          |              |  |  |
| ECOG 0                                                                              | 25           |  |  |
| ECOG 1                                                                              | 21           |  |  |
| Age at primary diagnosis (years)<br>Units: years                                    |              |  |  |
| median                                                                              | 63.3         |  |  |
| full range (min-max)                                                                | 44.6 to 82.0 |  |  |
| Time from primary diagnosis to<br>development of metastases (weeks)<br>Units: weeks |              |  |  |
| median                                                                              | 0.1          |  |  |
| full range (min-max)                                                                | 0.0 to 814.3 |  |  |
| Age at development of metastases<br>(years)<br>Units: years                         |              |  |  |
| median                                                                              | 63.7         |  |  |
| full range (min-max)                                                                | 44.6 to 85.5 |  |  |
| Time from primary diagnosis to<br>development of metastases (weeks)<br>Units: weeks |              |  |  |

|                      |              |  |  |
|----------------------|--------------|--|--|
| median               | 0.1          |  |  |
| full range (min-max) | 0.0 to 814.3 |  |  |

|  |  |  |  |
|--|--|--|--|
|  |  |  |  |
|  |  |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Study treatment (mITT)       |
| Reporting group description:<br>Study treatment consisted of cetuximab (IMP), irinotecan, folic acid, 5-fluorocil (FOLFIRI) and patients received a pre-defined dermal prophylaxis including vitamin K1 ointment and additional oral doxycycline.                                                                                                                                                                                                                          |                              |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Per-Protocol Population (PP) |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Per protocol                 |
| Subject analysis set description:<br>The Per-protocol set consisted of all patients who had received at least at least 3 cycles of the planned combination therapy including pre-defined skin care (Reconval K1® ointment and Doxycycline, as well as Dermatotop® ointment, if applicable) according to the protocol. Patients were also eligible if treatment had to be stopped prematurely (within the first 3 cycles) due to early progression (including early death). |                              |

### Primary: 1-year PFS rate (Progression-free survival after one year)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1-year PFS rate (Progression-free survival after one year) <sup>[1]</sup> |
| End point description:<br>1-year PFS rate (rate of patients free of progression after one year): For progression-free survival (PFS), the timespan between registration until progression of disease (PD) or death from any cause was calculated (Kaplan-Meier method). Twelve (mITT population) and seven patients (PP population) were censored within the first year after registration.                                                                           |                                                                           |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Primary                                                                   |
| End point timeframe:<br>Progression-free survival (PFS) rate one year after patient registration.                                                                                                                                                                                                                                                                                                                                                                     |                                                                           |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: No formal statistical test was performed for the primary objective, since recruitment was stopped after 55 enrolled patients (33% of the 165 planned) leading to a marked reduction of power to establish an anticipated increase of 1-year PFS rate from 25% to 35%. |                                                                           |

| End point values                 | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|----------------------------------|------------------------|------------------------------|--|--|
| Subject group type               | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed      | 54                     | 46                           |  |  |
| Units: Percentage of patients    |                        |                              |  |  |
| number (confidence interval 95%) | 25.9 (15.3 to 43.9)    | 27.3 (16.2 to 46.1)          |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Response rate (ORR)

|                                                                                                                                                                                                                               |                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| End point title                                                                                                                                                                                                               | Objective Response rate (ORR) |
| End point description:<br>The objective response rate (ORR) is the frequency of patients in whom CR or PR could be achieved. In addition post-hoc outcome analyses were conducted subgrouped according to acneiform exanthema |                               |

grade (mITT population; grade 3-4 vs. 0-2). Out of 54 patients 8 patients experienced an acneiform follicular exanthema grade 3-4 [ORR: 50.0% (n=4)] and 46 patients had an exanthema grade 0-2 [ORR: 65.2% (n=30)].

|                                                                                                        |           |
|--------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                         | Secondary |
| End point timeframe:                                                                                   |           |
| Relevant response evaluations during study treatment phase until EOT for any reason (up to 12 months). |           |

| End point values              | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|-------------------------------|------------------------|------------------------------|--|--|
| Subject group type            | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed   | 54                     | 46                           |  |  |
| Units: Percentage of patients |                        |                              |  |  |
| number (not applicable)       |                        |                              |  |  |
| CR                            | 5.6                    | 6.5                          |  |  |
| PR                            | 57.4                   | 60.9                         |  |  |
| OR (CR+PR)                    | 63.0                   | 67.4                         |  |  |
| SD                            | 14.8                   | 13.0                         |  |  |
| PD                            | 11.1                   | 13.0                         |  |  |
| Not assessable                | 11.1                   | 6.5                          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Rate of secondary resections of liver metastases with curative intent

|                                                                                                                                                                    |                                                                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| End point title                                                                                                                                                    | Rate of secondary resections of liver metastases with curative intent |
| End point description:                                                                                                                                             |                                                                       |
| The rate of secondary resections of liver metastases is defined as percentage of patients with liver metastases who had liver surgery after start of chemotherapy. |                                                                       |
| End point type                                                                                                                                                     | Secondary                                                             |
| End point timeframe:                                                                                                                                               |                                                                       |
| After start of chemotherapy until end of study (EOS).                                                                                                              |                                                                       |

| End point values                                | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|-------------------------------------------------|------------------------|------------------------------|--|--|
| Subject group type                              | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed                     | 45 <sup>[2]</sup>      | 41 <sup>[3]</sup>            |  |  |
| Units: Percentage of patients                   |                        |                              |  |  |
| number (not applicable)                         |                        |                              |  |  |
| Resection of liver metastases (curative intent) | 8.9                    | 4.9                          |  |  |

Notes:

[2] - In the mITT population 45 patients had liver metastases at inclusion.

[3] - In the PP population 41 patients had liver metastases at inclusion.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival (PFS)

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Progression-free survival (PFS) |
|-----------------|---------------------------------|

End point description:

Progression-free survival (PFS) was defined as the time span from registration until progression or death from any cause, whatever happened first. Fourteen (mITT population) and nine patients (PP population) were censored.

Additional post-hoc analysis of Progression free survival related to severity grade of the acneiform follicular exanthema grade 0-2 vs grade 3-4 was performed (mITT population). The median PFS was 8.2 months (95%-CI 4.7 to 27.5 months) in patients with a grade 3-4 exanthema (n=8) and it was 8.6 months (95% CI 6.6 to 11.2 months) in patients with a grade 0-2 exanthema (n= 46). The grade of the exanthema had minor impact on PFS.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Timeframe from registration until progression or death from any cause, whatever happened first.

| End point values                 | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|----------------------------------|------------------------|------------------------------|--|--|
| Subject group type               | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed      | 54                     | 46                           |  |  |
| Units: months                    |                        |                              |  |  |
| median (confidence interval 95%) | 8.48 (7.72 to 11.24)   | 8.48 (6.34 to 11.27)         |  |  |

|                            |                       |
|----------------------------|-----------------------|
| Attachments (see zip file) | DERMATUX_PFS_mITT.pdf |
|----------------------------|-----------------------|

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival (OS)

|                 |                       |
|-----------------|-----------------------|
| End point title | Overall survival (OS) |
|-----------------|-----------------------|

End point description:

Overall survival was defined as the time span from registration until death. Twelve (mITT population) and 8 patients (PP-population) were censored.

In addition, post-hoc analysis of OS related to the severity grade of the acneiform follicular exanthema was performed (mITT population).

Median OS (months; [95% CI]) for subgrouped patients was:

No exanthema (n=6): 7.6 [1.0 - NA];  
 CTCAE grade 1 (n=25): 24.3 [16.0 - 42.7];  
 CTCAE grade 2 (n=15): 38.0 [7.9 - 48.7];  
 CTCAE grade 3 (n=8): 29.7 [6.0 - 41.8];

A post-hoc exploratory cox regression analysis was performed for OS focusing on several known prognostic markers: For ECOG performance status (ECOG 1 vs. ECOG 0 at baseline: HR=2.68, p=0.007), response to first-line therapy (no response vs response: HR=3.36, p=0.002) and liver limited disease (not liver-limited vs. liver-limited disease, HR=2.26, p=0.029) a relation to OS could be seen, while higher grade acneiform rash as well as CEA level did not show a trend towards better OS.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Timeframe from registration until death, for any reason. All deaths were included, whether they occurred on study treatment or during follow-up (following treatment discontinuation).

| End point values                 | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|----------------------------------|------------------------|------------------------------|--|--|
| Subject group type               | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed      | 54                     | 46                           |  |  |
| Units: months                    |                        |                              |  |  |
| median (confidence interval 95%) | 26.22 (18.56 to 41.82) | 25.95 (18.46 to 37.68)       |  |  |

|                            |                      |
|----------------------------|----------------------|
| Attachments (see zip file) | DERMATUX_OS_mITT.pdf |
|----------------------------|----------------------|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of acneiform follicular exanthema (highest CTCAE grade)

|                 |                                                                   |
|-----------------|-------------------------------------------------------------------|
| End point title | Incidence of acneiform follicular exanthema (highest CTCAE grade) |
|-----------------|-------------------------------------------------------------------|

End point description:

Rate of patients experiencing acneiform follicular exanthema (highest CTCAE grade) during treatment phase (up to 12 months).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessment and grading of acneiform follicular exanthema was performed once a week from first cetuximab dose until EOT (up to 12 months).

| End point values                  | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|-----------------------------------|------------------------|------------------------------|--|--|
| Subject group type                | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed       | 54                     | 46                           |  |  |
| Units: Percentage of patients     |                        |                              |  |  |
| number (not applicable)           |                        |                              |  |  |
| No acneiform follicular exanthema | 11.1                   | 8.7                          |  |  |

|               |      |      |  |  |
|---------------|------|------|--|--|
| CTCAE grade 1 | 46.3 | 50.0 |  |  |
| CTCAE grade 2 | 27.8 | 23.9 |  |  |
| CTCAE grade 3 | 14.8 | 17.4 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of paronychia (highest CTCAE grade)

|                                                                                                                                                 |                                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| End point title                                                                                                                                 | Incidence of paronychia (highest CTCAE grade) |
| End point description:<br>Rate of patients experiencing a paronychia (highest CTCAE grade) during treatment phase (up to 12 months).            |                                               |
| End point type                                                                                                                                  | Secondary                                     |
| End point timeframe:<br>Assessment and grading of a paronychia was performed once a week from first cetuximab dose until EOT (up to 12 months). |                                               |

| End point values              | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|-------------------------------|------------------------|------------------------------|--|--|
| Subject group type            | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed   | 54                     | 46                           |  |  |
| Units: Percentage of patients |                        |                              |  |  |
| number (not applicable)       |                        |                              |  |  |
| No paronychia                 | 51.9                   | 45.7                         |  |  |
| CTCAE grade 1                 | 25.9                   | 30.4                         |  |  |
| CTCAE grade 2                 | 20.4                   | 21.7                         |  |  |
| CTCAE grade 3                 | 1.9                    | 2.2                          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of skin fissures [hand and foot] (highest CTCAE grade)

|                                                                                                                                                  |                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| End point title                                                                                                                                  | Incidence of skin fissures [hand and foot] (highest CTCAE grade) |
| End point description:<br>Rate of patients experiencing skin fissures (highest CTCAE grade) during treatment phase (up to 12 months).            |                                                                  |
| End point type                                                                                                                                   | Secondary                                                        |
| End point timeframe:<br>Assessment and grading of skin fissures was performed once a week from first cetuximab dose until EOT (up to 12 months). |                                                                  |

| End point values              | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|-------------------------------|------------------------|------------------------------|--|--|
| Subject group type            | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed   | 54                     | 46                           |  |  |
| Units: Percentage of patients |                        |                              |  |  |
| number (not applicable)       |                        |                              |  |  |
| No skin fissure               | 24.1                   | 17.4                         |  |  |
| CTCAE grade 1                 | 44.4                   | 47.8                         |  |  |
| CTCAE grade 2                 | 29.6                   | 32.6                         |  |  |
| CTCAE grade 3                 | 1.9                    | 2.2                          |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of acneiform follicular exanthema (CTCAE grade $\geq 2$ )

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Incidence of acneiform follicular exanthema (CTCAE grade $\geq 2$ ) |
|-----------------|---------------------------------------------------------------------|

End point description:

Rate of Patients experiencing acneiform follicular exanthema (CTCAE grade  $\geq 2$ ) during treatment phase (up to 12 months).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessment and grading of acneiform follicular exanthema was performed once a week from first cetuximab dose until EOT (up to 12 months).

| End point values              | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|-------------------------------|------------------------|------------------------------|--|--|
| Subject group type            | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed   | 54                     | 46                           |  |  |
| Units: Percentage of patients |                        |                              |  |  |
| number (not applicable)       |                        |                              |  |  |
| CTCAE grade $\geq 2$          | 42.6                   | 41.3                         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of paronychia (CTCAE grade $\geq 2$ )

|                 |                                                 |
|-----------------|-------------------------------------------------|
| End point title | Incidence of paronychia (CTCAE grade $\geq 2$ ) |
|-----------------|-------------------------------------------------|

End point description:

Rate of patients experiencing a paronychia (CTCAE grade  $\geq 2$ ) during treatment phase (up to 12 months).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessment and grading of paronychia was performed once a week from first cetuximab dose until EOT (up to 12 months).

| End point values              | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|-------------------------------|------------------------|------------------------------|--|--|
| Subject group type            | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed   | 54                     | 46                           |  |  |
| Units: Percentage of patients |                        |                              |  |  |
| number (not applicable)       |                        |                              |  |  |
| CTCAE grade $\geq 2$          | 22.3                   | 23.9                         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of skin fissures [hand and foot] (CTCAE grade $\geq 2$ )

|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | Incidence of skin fissures [hand and foot] (CTCAE grade $\geq 2$ ) |
|-----------------|--------------------------------------------------------------------|

End point description:

Rate of patients experiencing skin fissures (CTCAE grade  $\geq 2$ ) during treatment phase (up to 12 months).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessment and grading of skin fissures was performed once a week from first cetuximab dose until EOT (up to 12 months).

| End point values              | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|-------------------------------|------------------------|------------------------------|--|--|
| Subject group type            | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed   | 54                     | 46                           |  |  |
| Units: Percentage of patients |                        |                              |  |  |
| number (not applicable)       |                        |                              |  |  |
| CTCAE grade $\geq 2$          | 31.5                   | 34.8                         |  |  |

### Statistical analyses

No statistical analyses for this end point

**Secondary: Time to onset of acneiform follicular exanthema (CTCAE grade ≥2)**

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | Time to onset of acneiform follicular exanthema (CTCAE grade ≥2) |
|-----------------|------------------------------------------------------------------|

End point description:

Assessment and grading of acneiform follicular exanthema was performed once a week from first cetuximab dose until EOT (up to 12 months). Time to onset was calculated for patients experiencing acneiform follicular exanthema (CTCAE grade ≥2) during treatment phase (up to 12 months).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Time to onset of an acneiform follicular exanthema ≥grade 2 was calculated from first cetuximab dose until date of first documentation of ≥grade 2 symptoms.

| End point values              | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|-------------------------------|------------------------|------------------------------|--|--|
| Subject group type            | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed   | 23 <sup>[4]</sup>      | 19 <sup>[5]</sup>            |  |  |
| Units: weeks                  |                        |                              |  |  |
| median (full range (min-max)) | 4.0 (1.0 to 27.9)      | 4.0 (1.0 to 27.9)            |  |  |

Notes:

[4] - An acneiform follicular exanthema ≥grade 2 was observed in 23 patients out of 54 patients.

[5] - An acneiform follicular exanthema ≥grade 2 was observed in 19 patients out of 46 patients.

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Time to onset of paronychia (CTCAE grade ≥2)**

|                 |                                              |
|-----------------|----------------------------------------------|
| End point title | Time to onset of paronychia (CTCAE grade ≥2) |
|-----------------|----------------------------------------------|

End point description:

Assessment and grading of paronychia was performed once a week from first cetuximab dose until EOT (up to 12 months). Time to onset was calculated for patients experiencing paronychia (CTCAE grade ≥2) during treatment phase (up to 12 months).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Time to onset of a paronychia ≥grade 2 was calculated from first cetuximab dose until date of first documentation of ≥grade 2 symptoms.

| End point values              | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|-------------------------------|------------------------|------------------------------|--|--|
| Subject group type            | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed   | 12 <sup>[6]</sup>      | 11 <sup>[7]</sup>            |  |  |
| Units: weeks                  |                        |                              |  |  |
| median (full range (min-max)) | 15.4 (2.0 to 37.0)     | 16.0 (9.0 to 37.0)           |  |  |

Notes:

[6] - A paronychia  $\geq$  grade 2 was observed in 12 patients out of 54 patients.

[7] - A paronychia  $\geq$  grade 2 was observed in 11 patients out of 46 patients.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to onset of skin fissures [hand and foot] (CTCAE grade $\geq 2$ )

|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| End point title | Time to onset of skin fissures [hand and foot] (CTCAE grade $\geq 2$ ) |
|-----------------|------------------------------------------------------------------------|

End point description:

Assessment and grading of skin fissures was performed once a week from first cetuximab dose until EOT (up to 12 months). Time to onset was calculated for patients experiencing skin fissures (CTCAE grade  $\geq 2$ ) during treatment phase (up to 12 months).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Time to onset of skin fissures  $\geq$  grade 2 was calculated from first cetuximab dose until date of first documentation of  $\geq$  grade 2 symptoms.

| End point values              | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|-------------------------------|------------------------|------------------------------|--|--|
| Subject group type            | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed   | 17 <sup>[8]</sup>      | 16 <sup>[9]</sup>            |  |  |
| Units: weeks                  |                        |                              |  |  |
| median (full range (min-max)) | 19.9 (3.1 to 38.0)     | 19.9 (3.1 to 38.0)           |  |  |

Notes:

[8] - Skin fissures  $\geq$  grade 2 were observed in 17 patients out of 54 patients.

[9] - Skin fissures  $\geq$  grade 2 were observed in 16 patients out of 46 patients.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of acneiform follicular exanthema (at last patient examination)

|                 |                                                                           |
|-----------------|---------------------------------------------------------------------------|
| End point title | Incidence of acneiform follicular exanthema (at last patient examination) |
|-----------------|---------------------------------------------------------------------------|

End point description:

Rate of patients experiencing acneiform follicular exanthema (CTCAE grade) at the time of last patient examination during treatment phase (up to 12 months).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessment and grading of acneiform follicular exanthema was performed at the time of last patient examination during treatment phase (EOT).

| End point values                  | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|-----------------------------------|------------------------|------------------------------|--|--|
| Subject group type                | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed       | 54                     | 46                           |  |  |
| Units: Percentage of patients     |                        |                              |  |  |
| number (not applicable)           |                        |                              |  |  |
| No acneiform follicular exanthema | 48.1                   | 50.0                         |  |  |
| CTCAE grade 1                     | 38.9                   | 39.1                         |  |  |
| CTCAE grade 2                     | 13.0                   | 10.9                         |  |  |
| CTCAE grade 3                     | 0.0                    | 0.0                          |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of paronychia (at last patient examination)

|                 |                                                       |
|-----------------|-------------------------------------------------------|
| End point title | Incidence of paronychia (at last patient examination) |
|-----------------|-------------------------------------------------------|

End point description:

Rate of patients experiencing paronychia (CTCAE grade) at the time of last patient examination during treatment phase (up to 12 months).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessment and grading of paronychia was performed at the time of last patient examination during treatment phase (EOT).

| End point values              | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|-------------------------------|------------------------|------------------------------|--|--|
| Subject group type            | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed   | 54                     | 46                           |  |  |
| Units: Percentage of patients |                        |                              |  |  |
| number (not applicable)       |                        |                              |  |  |
| No paronychia                 | 83.4                   | 80.4                         |  |  |
| CTCAE grade 1                 | 14.8                   | 17.4                         |  |  |
| CTCAE grade 2                 | 1.9                    | 2.2                          |  |  |
| CTCAE grade 3                 | 0.0                    | 0.0                          |  |  |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Incidence of skin fissures [hand an foot] (at last patient examination)**

---

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Incidence of skin fissures [hand an foot] (at last patient examination) |
|-----------------|-------------------------------------------------------------------------|

End point description:

Rate of patients experiencing acneiform follicular exanthema (CTCAE grade) at the time of last patient examination during treatment phase (up to 12 months).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessment and grading of acneiform follicular exanthema was performed at the time of last patient examination during treatment phase (EOT).

---

| End point values              | Study treatment (mITT) | Per-Protocol Population (PP) |  |  |
|-------------------------------|------------------------|------------------------------|--|--|
| Subject group type            | Reporting group        | Subject analysis set         |  |  |
| Number of subjects analysed   | 54                     | 46                           |  |  |
| Units: Percentage of patients |                        |                              |  |  |
| number (not applicable)       |                        |                              |  |  |
| No skin fissures              | 69.5                   | 65.2                         |  |  |
| CTCAE grade 1                 | 27.8                   | 30.4                         |  |  |
| CTCAE grade 2                 | 3.7                    | 4.3                          |  |  |
| CTCAE grade 3                 | 0.0                    | 0.0                          |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

TEAE were recorded from onset of study treatment (first application) to 30 days after the last dose of study treatment.

Adverse event reporting additional description:

Systematic evaluation of toxicity was performed at start of each cycle (skin toxicities), and continuously for AEs. The severity grade of AEs, the start and stop dates, the resolution and date of resolution, and the relationship to study drug was documented.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |                                            |
|-----------------------|--------------------------------------------|
| Reporting group title | Study treatment (Safety analysis set/mITT) |
|-----------------------|--------------------------------------------|

Reporting group description:

Adverse Events (AEs) were graded according to the NCI Common Terminology Criteria v.3.0. Adverse events were recorded during study treatment and until 30 days after treatment end (TEAEs).

Extend of exposure: Patients received systemic therapy (cetuximab plus FOLFIRI) for a median duration of 20.5 weeks ranging from 2.0 to 64.1 weeks, or a median of 10 cycles, ranging from 1 to 30 cycles.

Patients received cetuximab therapy for a median duration of 20.1 weeks ranging from 1.0 to 64.1 weeks, or a median of 9.5 cycles, ranging from 1 to 30 cycles. Chemotherapeutic agents were also mostly administered for 20.1 weeks or 9.5 cycles.

Skin prophylaxis was administered for a median of 139 days (19.86 weeks), ranging from 14 to 434 days (2 to 62 weeks). Doxycycline was given for a median of 126 days (18.0 weeks), ranging from 7 to 434 days (1 to 62 weeks), and Reconval K1® ointment was given for a median of 139 days (19.86 weeks), ranging from 14 to 433 days (2 to 61.86 weeks).

| Serious adverse events                                              | Study treatment<br>(Safety analysis<br>set/mITT) |  |  |
|---------------------------------------------------------------------|--------------------------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                                                  |  |  |
| subjects affected / exposed                                         | 28 / 54 (51.85%)                                 |  |  |
| number of deaths (all causes)                                       | 42                                               |  |  |
| number of deaths resulting from adverse events                      | 5                                                |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                                  |  |  |
| Malignant neoplasm progression                                      |                                                  |  |  |
| subjects affected / exposed                                         | 1 / 54 (1.85%)                                   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                                            |  |  |
| deaths causally related to treatment / all                          | 0 / 1                                            |  |  |
| Vascular disorders                                                  |                                                  |  |  |
| Deep vein thrombosis                                                |                                                  |  |  |
| subjects affected / exposed                                         | 2 / 54 (3.70%)                                   |  |  |
| occurrences causally related to treatment / all                     | 0 / 2                                            |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                            |  |  |

|                                                      |                |  |  |
|------------------------------------------------------|----------------|--|--|
| Hypotension                                          |                |  |  |
| subjects affected / exposed                          | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Thrombosis                                           |                |  |  |
| subjects affected / exposed                          | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Pain                                                 |                |  |  |
| subjects affected / exposed                          | 2 / 54 (3.70%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General physical health deterioration                |                |  |  |
| subjects affected / exposed                          | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Mucosal inflammation                                 |                |  |  |
| subjects affected / exposed                          | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Oedema peripheral                                    |                |  |  |
| subjects affected / exposed                          | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Pyrexia                                              |                |  |  |
| subjects affected / exposed                          | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Immune system disorders                              |                |  |  |
| Hypersensitivity                                     |                |  |  |
| subjects affected / exposed                          | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Pulmonary embolism                              |                |  |  |
| subjects affected / exposed                     | 2 / 54 (3.70%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pleural effusion                                |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Injury, poisoning and procedural complications  |                |  |  |
| Spinal fracture                                 |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Cardiac failure                                 |                |  |  |
| subjects affected / exposed                     | 2 / 54 (3.70%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Acute myocardial infarction                     |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Cardiogenic shock                               |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Nervous system disorders                        |                |  |  |
| Syncope                                         |                |  |  |
| subjects affected / exposed                     | 2 / 54 (3.70%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood and lymphatic system disorders            |                |  |  |
| Febrile neutropenia                             |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Neutropenia                                     |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Diarrhoea                                       |                |  |  |
| subjects affected / exposed                     | 3 / 54 (5.56%) |  |  |
| occurrences causally related to treatment / all | 3 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Abdominal pain                                  |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Anal fissure                                    |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Anal haemorrhage                                |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ascites                                         |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Constipation                                    |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastritis erosive                               |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrooesophageal reflux disease                |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Subileus                                        |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Renal failure acute                             |                |  |  |
| subjects affected / exposed                     | 2 / 54 (3.70%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Calculus ureteric                               |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Haematuria                                      |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hydronephrosis                                  |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ureteric stenosis                               |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| Pneumonia                                       |                |  |  |
| subjects affected / exposed                     | 2 / 54 (3.70%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Bronchopneumonia                                |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastroenteritis caliciviral                     |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Gastrointestinal infection                      |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infection                                       |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Viral infection                                 |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Dehydration                                     |                |  |  |
| subjects affected / exposed                     | 2 / 54 (3.70%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypocalcaemia                                   |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypokalaemia                                    |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypomagnesaemia                                 |                |  |  |
| subjects affected / exposed                     | 1 / 54 (1.85%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Study treatment<br>(Safety analysis<br>set/mITT) |  |  |
|-------------------------------------------------------|--------------------------------------------------|--|--|
| Total subjects affected by non-serious adverse events |                                                  |  |  |
| subjects affected / exposed                           | 52 / 54 (96.30%)                                 |  |  |
| Investigations                                        |                                                  |  |  |
| Weight decreased                                      |                                                  |  |  |
| subjects affected / exposed                           | 5 / 54 (9.26%)                                   |  |  |
| occurrences (all)                                     | 7                                                |  |  |
| Haemoglobin decreased                                 |                                                  |  |  |
| subjects affected / exposed                           | 3 / 54 (5.56%)                                   |  |  |
| occurrences (all)                                     | 5                                                |  |  |
| Blood magnesium decreased                             |                                                  |  |  |
| subjects affected / exposed                           | 3 / 54 (5.56%)                                   |  |  |
| occurrences (all)                                     | 3                                                |  |  |
| Nervous system disorders                              |                                                  |  |  |
| Paraesthesia                                          |                                                  |  |  |
| subjects affected / exposed                           | 3 / 54 (5.56%)                                   |  |  |
| occurrences (all)                                     | 3                                                |  |  |
| General disorders and administration site conditions  |                                                  |  |  |
| Fatigue                                               |                                                  |  |  |
| subjects affected / exposed                           | 25 / 54 (46.30%)                                 |  |  |
| occurrences (all)                                     | 29                                               |  |  |
| Mucosal inflammation                                  |                                                  |  |  |
| subjects affected / exposed                           | 16 / 54 (29.63%)                                 |  |  |
| occurrences (all)                                     | 21                                               |  |  |
| Oedema peripheral                                     |                                                  |  |  |

|                                      |                  |  |  |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed          | 9 / 54 (16.67%)  |  |  |
| occurrences (all)                    | 11               |  |  |
| Pain                                 |                  |  |  |
| subjects affected / exposed          | 4 / 54 (7.41%)   |  |  |
| occurrences (all)                    | 6                |  |  |
| Blood and lymphatic system disorders |                  |  |  |
| Neutropenia                          |                  |  |  |
| subjects affected / exposed          | 15 / 54 (27.78%) |  |  |
| occurrences (all)                    | 27               |  |  |
| Anaemia                              |                  |  |  |
| subjects affected / exposed          | 5 / 54 (9.26%)   |  |  |
| occurrences (all)                    | 5                |  |  |
| Leukopenia                           |                  |  |  |
| subjects affected / exposed          | 3 / 54 (5.56%)   |  |  |
| occurrences (all)                    | 5                |  |  |
| Immune system disorders              |                  |  |  |
| Hypersensitivity                     |                  |  |  |
| subjects affected / exposed          | 4 / 54 (7.41%)   |  |  |
| occurrences (all)                    | 4                |  |  |
| Gastrointestinal disorders           |                  |  |  |
| Diarrhoea                            |                  |  |  |
| subjects affected / exposed          | 24 / 54 (44.44%) |  |  |
| occurrences (all)                    | 34               |  |  |
| Nausea                               |                  |  |  |
| subjects affected / exposed          | 19 / 54 (35.19%) |  |  |
| occurrences (all)                    | 27               |  |  |
| Vomiting                             |                  |  |  |
| subjects affected / exposed          | 10 / 54 (18.52%) |  |  |
| occurrences (all)                    | 12               |  |  |
| Stomatitis                           |                  |  |  |
| subjects affected / exposed          | 5 / 54 (9.26%)   |  |  |
| occurrences (all)                    | 9                |  |  |
| Constipation                         |                  |  |  |
| subjects affected / exposed          | 6 / 54 (11.11%)  |  |  |
| occurrences (all)                    | 7                |  |  |
| Ascites                              |                  |  |  |

|                                                  |                                                                                                                                                                                           |  |  |
|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 3 / 54 (5.56%)<br>3                                                                                                                                                                       |  |  |
| Respiratory, thoracic and mediastinal disorders  |                                                                                                                                                                                           |  |  |
| Cough                                            |                                                                                                                                                                                           |  |  |
| subjects affected / exposed<br>occurrences (all) | 5 / 54 (9.26%)<br>5                                                                                                                                                                       |  |  |
| Dyspnoea                                         |                                                                                                                                                                                           |  |  |
| subjects affected / exposed<br>occurrences (all) | 4 / 54 (7.41%)<br>4                                                                                                                                                                       |  |  |
| Dyspnoea exertional                              |                                                                                                                                                                                           |  |  |
| subjects affected / exposed<br>occurrences (all) | 4 / 54 (7.41%)<br>4                                                                                                                                                                       |  |  |
| Epistaxis                                        |                                                                                                                                                                                           |  |  |
| subjects affected / exposed<br>occurrences (all) | 3 / 54 (5.56%)<br>3                                                                                                                                                                       |  |  |
| Skin and subcutaneous tissue disorders           |                                                                                                                                                                                           |  |  |
| Skin fissures                                    | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed<br>occurrences (all) | 40 / 54 (74.07%)<br>58                                                                                                                                                                    |  |  |
| Rash                                             | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed<br>occurrences (all) | 34 / 54 (62.96%)<br>47                                                                                                                                                                    |  |  |
| Nail bed inflammation                            | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed<br>occurrences (all) | 25 / 54 (46.30%)<br>30                                                                                                                                                                    |  |  |
| Alopecia                                         | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed<br>occurrences (all) | 16 / 54 (29.63%)<br>16                                                                                                                                                                    |  |  |
| Dermatitis acneiform                             | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed<br>occurrences (all) | 8 / 54 (14.81%)<br>13                                                                                                                                                                     |  |  |
| Pruritus                                         | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |

|                                             |                                                                                                                                                                                           |  |  |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
|                                             | value for general nsAE reporting.)                                                                                                                                                        |  |  |
| subjects affected / exposed                 | 6 / 54 (11.11%)                                                                                                                                                                           |  |  |
| occurrences (all)                           | 9                                                                                                                                                                                         |  |  |
| Dry skin                                    | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed                 | 7 / 54 (12.96%)                                                                                                                                                                           |  |  |
| occurrences (all)                           | 8                                                                                                                                                                                         |  |  |
| Dermatitis                                  | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed                 | 5 / 54 (9.26%)                                                                                                                                                                            |  |  |
| occurrences (all)                           | 8                                                                                                                                                                                         |  |  |
| Palmar-plantar erythrodysaesthesia syndrome | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed                 | 4 / 54 (7.41%)                                                                                                                                                                            |  |  |
| occurrences (all)                           | 5                                                                                                                                                                                         |  |  |
| Rash maculo-papular                         | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed                 | 3 / 54 (5.56%)                                                                                                                                                                            |  |  |
| occurrences (all)                           | 3                                                                                                                                                                                         |  |  |
| Skin reaction                               | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed                 | 2 / 54 (3.70%)                                                                                                                                                                            |  |  |
| occurrences (all)                           | 3                                                                                                                                                                                         |  |  |
| Acne                                        | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed                 | 1 / 54 (1.85%)                                                                                                                                                                            |  |  |
| occurrences (all)                           | 1                                                                                                                                                                                         |  |  |
| Eczema                                      | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed                 | 1 / 54 (1.85%)                                                                                                                                                                            |  |  |
| occurrences (all)                           | 1                                                                                                                                                                                         |  |  |
| Hyperhidrosis                               | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed                 | 1 / 54 (1.85%)                                                                                                                                                                            |  |  |
| occurrences (all)                           | 1                                                                                                                                                                                         |  |  |
| Intertrigo                                  | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed                 | 1 / 54 (1.85%)                                                                                                                                                                            |  |  |
| occurrences (all)                           | 1                                                                                                                                                                                         |  |  |

|                                    |                                                                                                                                                                                           |  |  |
|------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| Palmar erythema                    | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed        | 1 / 54 (1.85%)                                                                                                                                                                            |  |  |
| occurrences (all)                  | 1                                                                                                                                                                                         |  |  |
| Skin disorder                      | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed        | 1 / 54 (1.85%)                                                                                                                                                                            |  |  |
| occurrences (all)                  | 1                                                                                                                                                                                         |  |  |
| Skin exfoliation                   | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed        | 1 / 54 (1.85%)                                                                                                                                                                            |  |  |
| occurrences (all)                  | 1                                                                                                                                                                                         |  |  |
| Skin lesion                        | Additional description: (All non-serious AE related to MedDRA SOC "Skin and subcutaneous tissue disorders" are reported despite pre-defined 5% cut-off value for general nsAE reporting.) |  |  |
| subjects affected / exposed        | 1 / 54 (1.85%)                                                                                                                                                                            |  |  |
| occurrences (all)                  | 1                                                                                                                                                                                         |  |  |
| Infections and infestations        |                                                                                                                                                                                           |  |  |
| Conjunctivitis                     |                                                                                                                                                                                           |  |  |
| subjects affected / exposed        | 3 / 54 (5.56%)                                                                                                                                                                            |  |  |
| occurrences (all)                  | 3                                                                                                                                                                                         |  |  |
| Metabolism and nutrition disorders |                                                                                                                                                                                           |  |  |
| Hypokalaemia                       |                                                                                                                                                                                           |  |  |
| subjects affected / exposed        | 7 / 54 (12.96%)                                                                                                                                                                           |  |  |
| occurrences (all)                  | 11                                                                                                                                                                                        |  |  |
| Hypomagnesaemia                    |                                                                                                                                                                                           |  |  |
| subjects affected / exposed        | 4 / 54 (7.41%)                                                                                                                                                                            |  |  |
| occurrences (all)                  | 4                                                                                                                                                                                         |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                         |
|------------------|-------------------------------------------------------------------------------------------------------------------|
| 16 April 2012    | Substantial AM #1 (protocol v3.0, 22-Mar-2012; prolongation of recruitment phase)                                 |
| 25 March 2013    | Substantial AM #2 (protocol v4.0, 01-Feb-2013; exclusion of expl. transl. research)                               |
| 21 February 2014 | Substantial AM #3 (protocol v5.0, 16-Jan-2014; Premature end of recruitment after enrollement of the 55. patient) |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No formal statistical test was performed for the primary objective, since recruitment was stopped after 55 enrolled patients (33% of the 165 planned) leading to a marked reduction of power to establish an increase of 1-year PFS rate from 25% to 35%

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28197787>