



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 (DERMATUX_CSR_E3_Synopsis_v2.0_29May2018.pdf)

Trial information

Trial identification

Sponsor protocol code	Dermatux
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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:

Subjects enrolled per age group	
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
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Number of subjects completed	54
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Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 1
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Period 1

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

Not applicable.

Arms

Arm title	Study treatment (mITT)
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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
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Investigational medicinal product name	Cetuximab
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Investigational medicinal product code	ATC code: L01XC06
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Other name	Erbitux®
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Pharmaceutical forms	Solution for infusion
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Routes of administration	Intravenous use
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Dosage and administration details:

Cetuximab (according to SmPC): Wk 1: 120 min i.v. infusion (400 mg cetuximab per m² body surface area), followed by 60 min i.v. infusions (250 mg cetuximab per m²) 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/m² (d1), folic acid (FA) 400 mg/m², 120 min (d1), 5-fluorouracil (5-FU) 400 mg/m² bolus (d1), 5-FU 2,400 mg/m² 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).

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

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)
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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 Units: Subjects			
Female	19		
Male	27		
Previous (neo)adjuvant tumor therapy Units: Subjects			
Yes	6		
No	40		
Previous radio therapy Units: Subjects			
yes	3		
no	43		
Previous tumor surgery Units: Subjects			
yes	31		
no	15		
Tumor stage at primary diagnosis Units: Subjects			
stage II	1		
stage III	7		
stage IV	35		
missing	3		
Localization of tumor 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 Units: Subjects			
ECOG 0	25		
ECOG 1	21		
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	0.1		
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	0.1		
full range (min-max)	0.0 to 814.3		

End points

End points reporting groups

Reporting group title	Study treatment (mITT)
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Reporting group 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.

Subject analysis set title	Per-Protocol Population (PP)
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Subject analysis set type	Per protocol
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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 Dermatop® 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) ^[1]
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End point description:

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
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End point timeframe:

Progression-free survival (PFS) rate one year after patient registration.

Notes:

[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.

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)
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End point description:

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
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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 ^[2]	41 ^[3]		
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)
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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
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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
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Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
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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
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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
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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)
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End point description:

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

End point type	Secondary
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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:	Rate of patients experiencing a paronychia (highest CTCAE grade) during treatment phase (up to 12 months).
End point type	Secondary
End point timeframe:	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:	Rate of patients experiencing skin fissures (highest CTCAE grade) 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)				
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 ≥ 2)

End point title	Incidence of acneiform follicular exanthema (CTCAE grade ≥ 2)
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End point description:

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

End point type	Secondary
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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 ≥ 2	42.6	41.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of paronychia (CTCAE grade ≥ 2)

End point title	Incidence of paronychia (CTCAE grade ≥ 2)
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End point description:

Rate of patients experiencing a paronychia(CTCAE grade ≥ 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 ≥ 2	22.3	23.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of skin fissures [hand and foot] (CTCAE grade ≥ 2)

End point title Incidence of skin fissures [hand and foot] (CTCAE grade ≥ 2)

End point description:

Rate of patients experiencing skin fissures (CTCAE grade ≥ 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 ≥ 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)
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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
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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 ^[4]	19 ^[5]		
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)
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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
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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 ^[6]	11 ^[7]		
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)
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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
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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 ^[8]	16 ^[9]		
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)
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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
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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

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)
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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
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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		

Statistical analyses

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Study treatment (Safety analysis set/mITT)
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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 (Safety analysis 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		
Gastroesophageal 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 %

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

subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed occurrences (all)	5 / 54 (9.26%) 5		
Dyspnoea			
subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 4		
Dyspnoea exertional			
subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 4		
Epistaxis			
subjects affected / exposed occurrences (all)	3 / 54 (5.56%) 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 occurrences (all)	40 / 54 (74.07%) 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 occurrences (all)	34 / 54 (62.96%) 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 occurrences (all)	25 / 54 (46.30%) 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 occurrences (all)	16 / 54 (29.63%) 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 occurrences (all)	8 / 54 (14.81%) 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 erythrodysesthesia 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:

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 a increase of 1-year PFS rate from 25% to 35%

Notes:

Online references

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