



Clinical trial results:

Multimodal therapy with and without cetuximab in patients with locally advanced esophageal carcinoma. An open-label phase III trial

Summary

EudraCT number	2009-016584-10
Trial protocol	DE HU AT
Global end of trial date	09 December 2018

Results information

Result version number	v1 (current)
This version publication date	01 April 2023
First version publication date	01 April 2023

Trial information

Trial identification

Sponsor protocol code	SAKK 75/08
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01107639
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS-ID: DRKS00003758

Notes:

Sponsors

Sponsor organisation name	Swiss Group for Clinical Cancer Research (SAKK)
Sponsor organisation address	Effingerstrasse 33, Bern, Switzerland, 3008
Public contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer, +41 31389 91 91, sakccc@sakk.ch
Scientific contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer, +41 31389 91 91, sakccc@sakk.ch

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	25 September 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the efficacy of neoadjuvant radiochemotherapy (RCT) combined with immunotherapy followed by adjuvant immunotherapy compared with the same schedule without immunotherapy (neoadjuvant and adjuvant).

Protection of trial subjects:

Protection of trial subjects was ensured by Safety Monitoring, i.e. assessment of adverse events, serious adverse events, adverse drug reactions, and the continuous assessment of laboratory values and vital signs.

Background therapy:

(1) Induction phase comprising two cycles of chemotherapy with docetaxel 75 mg/m², cisplatin 75 mg/m², followed by (2) radiochemotherapy (RCT) with 45 Gy, docetaxel 20 mg/m² and cisplatin 25 mg/m², weekly for 5 weeks and subsequent (3) surgery.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	01 May 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 37
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 99
Country: Number of subjects enrolled	Switzerland: 151
Worldwide total number of subjects	300
EEA total number of subjects	149

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)	198
From 65 to 84 years	102
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 300 patients were enrolled at 53 centers in four European countries between May 2010 and December 2013.

Pre-assignment

Screening details:

Eligibility criteria of a patient were checked by the investigator. Once a patient fulfils all inclusion criteria and not any of the exclusion criteria, he/she was enrolled.

Period 1

Period 1 title	Randomization
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cetuximab

Arm description:

Cetuximab arm at baseline.

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux®
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Inductionphase with concomitant neoadjuvant cetuximab 250 mg/m² weekly, followed by chemoradiation and surgery, with subsequent adjuvant cetuximab 500 mg/m² biweekly for 3 months.

Arm title	Control
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Arm description:

Control arm at baseline.

Arm type	Control
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Cetuximab	Control
Started	149	151
Completed	149	151

Period 2

Period 2 title	Induction Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Cetuximab
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Arm description:

Cetuximab arm in inductionphase.

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux®
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Inductionphase with concomitant neoadjuvant cetuximab 250 mg/m² weekly, followed by chemoradiation and surgery, with subsequent adjuvant cetuximab 500 mg/m² biweekly for 3 months.

Arm title	Control
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Arm description:

Control arm in inductionphase.

Arm type	Control
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No investigational medicinal product assigned in this arm

Number of subjects in period 2	Cetuximab	Control
Started	149	151
Completed	140	145
Not completed	9	6
Consent withdrawn by subject	3	1
Death	2	1
Ineligibility (primary metastatic)	1	-
Unacceptable Toxicity	3	3
Progressive disease	-	1

Period 3

Period 3 title	Radiationchemotherapy
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cetuximab
Arm description: Cetuximab arm in radiochemotherapy phase.	
Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux®
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Inductionphase with concomitant neoadjuvant cetuximab 250 mg/m2 weekly, followed by chemoradiation and surgery, with subsequent adjuvant cetuximab 500 mg/m2 biweekly for 3 months.

Arm title	Control
Arm description: Control arm in radiochemotherapy phase.	
Arm type	Control
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Cetuximab	Control
Started	140	145
Completed	132	130
Not completed	8	15
Consent withdrawn by subject	3	2
Death	-	1
PO / extend of disease	3	5
Ineligibility (primary metastatic)	-	1
Comorbidities / poor performance status	2	6

Period 4

Period 4 title	Surgery
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Cetuximab
Arm description: Cetuximab arm at surgery.	
Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux®
Pharmaceutical forms	Infusion
Routes of administration	Infusion
Dosage and administration details: Inductionphase with concomitant neoadjuvant cetuximab 250 mg/m ² weekly, followed by chemoradiation and surgery, with subsequent adjuvant cetuximab 500 mg/m ² biweekly for 3 months.	
Arm title	Control
Arm description: Control arm at baseline.	
Arm type	Control
No investigational medicinal product assigned in this arm	

Number of subjects in period 4	Cetuximab	Control
Started	132	130
Completed	100	0
Not completed	32	130
No adjuvant therapy (Control arm)	-	127
Withdrawal of IC, toxicity during neoadj. therapy	10	-
Complications post surgery, poor general condition	10	-
Death	8	-
PO / extend of disease	-	2
Ineligibility (primary metastatic)	-	1
PO	2	-
Mistake by site	2	-

Period 5	
Period 5 title	Therapy after surgery
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Cetuximab
Arm description: Cetuximab arm at baseline.	
Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux®
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Inductionphase with concomitant neoadjuvant cetuximab 250 mg/m² weekly, followed by chemoradiation and surgery, with subsequent adjuvant cetuximab 500 mg/m² biweekly for 3 months.

Number of subjects in period 5	Cetuximab
Started	100
Completed	100

Baseline characteristics

Reporting groups

Reporting group title	Cetuximab
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Reporting group description:

Cetuximab arm at baseline.

Reporting group title	Control
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Reporting group description:

Control arm at baseline.

Reporting group values	Cetuximab	Control	Total
Number of subjects	149	151	300
Age categorical			
Units: Subjects			
Adults (18-64 years)	99	99	198
From 65-84 years	50	52	102
Gender categorical			
Units: Subjects			
Female	19	18	37
Male	130	133	263

End points

End points reporting groups

Reporting group title	Cetuximab
Reporting group description: Cetuximab arm at baseline.	
Reporting group title	Control
Reporting group description: Control arm at baseline.	
Reporting group title	Cetuximab
Reporting group description: Cetuximab arm in inductionphase.	
Reporting group title	Control
Reporting group description: Control arm in inductionphase.	
Reporting group title	Cetuximab
Reporting group description: Cetuximab arm in radiochemotherapy phase.	
Reporting group title	Control
Reporting group description: Control arm in radiochemotherapy phase.	
Reporting group title	Cetuximab
Reporting group description: Cetuximab arm at surgery.	
Reporting group title	Control
Reporting group description: Control arm at baseline.	
Reporting group title	Cetuximab
Reporting group description: Cetuximab arm at baseline.	
Subject analysis set title	Cetuximab (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Cetuximab arm of the full analysis set.	
Subject analysis set title	Control (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Control arm of the full analysis set.	

Primary: PE | Progression free survival (PFS)

End point title	PE Progression free survival (PFS)
End point description: Progression-free survival (PFS) was calculated from the date of randomization until one of the following events, whichever came first: (1) Tumor progression at any time (progression of primary tumor or local lymph nodes, appearance of new lesions), (2) Recurrence at local, regional or distant site after surgery, (3) Death from any cause. The primary endpoint PFS was calculated for all patients in the ITT population. 174 (Cetuximab arm: 78 Control arm: 96) patients (58.6%) experienced an event.	
*Note: Upper confidence interval of median PFS (for cetuximab arm) not reached. Dummy data ("9999") entered due to database restrictions.	
End point type	Primary

End point timeframe:

From randomization until occurrence of tumor progression (incl. local/regional occurrence after surgery) or death.

End point values	Cetuximab (ITT)	Control (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	148	149		
Units: PFS (years)				
median (confidence interval 95%)	3.8 (2.0 to 99999)	2.0 (1.5 to 2.8)		

Statistical analyses

Statistical analysis title	PE Log Rank and Hazard Ratio
Statistical analysis description: Log Rank test and Hazard Ratio for PFS	
Comparison groups	Cetuximab (ITT) v Control (ITT)
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.072
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.03

Secondary: SE | Overall survival (OS)

End point title	SE Overall survival (OS)
End point description: OS was calculated from the date of randomization until the date of death from any cause. Patients not experiencing an event were censored at the last date they were known to be alive. OS was calculated for all patients in the ITT population. 156 (Cetuximab arm: 72 Control arm: 84) patients (52.5%) died. Upper confidence interval of median OS (for cetuximab arm) not reached. Dummy data ("9999") entered due to database restrictions.	
End point type	Secondary
End point timeframe: From randomization until death.	

End point values	Cetuximab (ITT)	Control (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	148	149		
Units: OS (years)				
median (confidence interval 95%)	5.7 (3.8 to 9999)	3.0 (2.2 to 5.9)		

Statistical analyses

Statistical analysis title	OS Log Rank and Hazard Ratio
Statistical analysis description: Log Rank test and Hazard Ratio for OS	
Comparison groups	Cetuximab (ITT) v Control (ITT)
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.135
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.08

Secondary: SE | OS rate

End point title	SE OS rate
End point description:	
End point type	Secondary
End point timeframe: At year 1, 2, 3, 4 and 5.	

End point values	Cetuximab (ITT)	Control (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	148	149		
Units: OS rate (%)				
number (confidence interval 95%)				
1 year	85.3 (78.4 to 90.2)	78.9 (71.4 to 84.7)		
2 years	71.3 (63.2 to 78.0)	63.2 (54.8 to 70.4)		
3 years	62.2 (53.8 to 69.9)	51.5 (43.1 to 59.3)		
4 years	57.3 (48.7 to 64.9)	45.3 (37.1 to 53.1)		
5 years	53.6 (45.0 to 61.4)	44.6 (36.4 to 52.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: SE | PFS after surgery (PFS-OP)

End point title	SE PFS after surgery (PFS-OP)
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End point description:

PFS-OP was only calculated for operated patients from date of surgery to an event. 147 (Cetuximab arm: 69 | Control arm: 77) patients (57.0%) experienced an event.

Upper confidence interval of median PFS-OP (for cetuximab arm) not reached. Dummy data ("9999") entered due to database restrictions.

End point type	Secondary
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End point timeframe:

From date of surgery to an event.

End point values	Cetuximab (ITT)	Control (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131 ^[1]	127 ^[2]		
Units: PFS-OP (years)				
median (confidence interval 95%)	3.7 (1.8 to 9999)	2.1 (1.6 to 5.1)		

Notes:

[1] - Only for operated patients.

[2] - Only for operated patients.

Statistical analyses

Statistical analysis title	PFS-OP Log Rank and Hazard Ratio
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Statistical analysis description:

Log Rank test and Hazard Ratio for PFS of operated patients from date of surgery.

Comparison groups	Cetuximab (ITT) v Control (ITT)
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Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.351
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.19

Secondary: SE | Time to Progression (TTP)

End point title	SE Time to Progression (TTP)
End point description:	
Time to progression was defined as time from randomization to one of the following events, whichever came first: (1) Tumor progression at any time (progression of primary tumor or local lymph nodes, appearance of new lesions), (2) Recurrence at local, regional or distant site after surgery, (3) Death due to tumor	
TTP was calculated for all patients in the ITT population. 130 (Cetuximab arm: 58 Control arm: 72) patients (44.1%) experienced an event.	
*Note: Median TTP (cetuximab arm) and upper confidence intervals of median TTP (both arms) were not reached. Dummy data ("9999") entered due to database restrictions.	
End point type	Secondary
End point timeframe:	
From randomization until event.	

End point values	Cetuximab (ITT)	Control (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	148	149		
Units: TTP (years)				
median (confidence interval 95%)	9999 (3.1 to 9999)	3.3 (2.0 to 9999)		

Statistical analyses

Statistical analysis title	TTP Log Rank and Hazard Ratio
Comparison groups	Cetuximab (ITT) v Control (ITT)

Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.106
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.06

Secondary: SE | Time to loco-regional failure after R0-resection

End point title	SE Time to loco-regional failure after R0-resection
End point description:	
This endpoint was only derived for patients with R0-resection. It was calculated from date of surgery to date of first documented loco-regional failure. Loco-regional failure was defined as tumor recurrence within the radiotherapy field. Death caused by tumor was counted as an event.	
Time to loco-regional failure after R0-resection was calculated for all patients with R0-resection from date of surgery to an event. 60 (Cetuximab arm: 22 Control arm: 38) patients (24.2%) experienced an event.	
*Note: Median Time to loco-regional failure and upper and lower confidence intervals not reached (both arms). Dummy data ("9999") entered due to database restrictions.	
End point type	Secondary
End point timeframe:	
From date of surgery to date of first documented loco-regional failure.	

End point values	Cetuximab (ITT)	Control (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125 ^[3]	123 ^[4]		
Units: Time to loco-regional failure (years)				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[3] - Only patients with R0-resection.

[4] - Only patients with R0-resection.

Statistical analyses

Statistical analysis title	Time to loco-reg. fail Log Rank and Hazard Ratio
Comparison groups	Cetuximab (ITT) v Control (ITT)

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.018
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	0.91

Secondary: SE | Loco-regional failure after R0-resection rate

End point title	SE Loco-regional failure after R0-resection rate
End point description:	
End point type	Secondary
End point timeframe:	
At year 1, 2, 3, 4 and 5.	

End point values	Cetuximab (ITT)	Control (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125 ^[5]	123 ^[6]		
Units: Loco-regional failure rate (%)				
number (confidence interval 95%)				
1 year	88.2 (80.5 to 93.0)	85.6 (77.5 to 90.9)		
2 years	85.0 (76.6 to 90.5)	71.2 (61.4 to 79.0)		
3 years	79.3 (69.9 to 86.0)	64.1 (53.7 to 72.8)		
4 years	78.0 (68.3 to 85.0)	62.9 (52.4 to 71.7)		
5 years	78.0 (68.3 to 85.0)	62.9 (52.4 to 71.7)		

Notes:

[5] - Only for patients with R0-resection.

[6] - Only for patients with R0-resection.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Time to distant failure after R0-resection

End point title	SE Time to distant failure after R0-resection
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End point description:

This endpoint was only derived for patients with R0-resection. It was calculated from date of surgery to date of first documented distant failure (either distant failure or both loco-regional and distant failure). Death caused by tumor was counted as an event.

Time to distant failure after R0-resection was calculated for all patients with R0-resection from date of surgery to an event. 80 (Cetuximab arm: 40 | Control arm: 40) patients (32.3%) experienced an event.

*Note: Median Time to loco-regional failure and upper confidence intervals not reached (both arms). Dummy data ("9999") entered due to database restrictions.

End point type	Secondary
End point timeframe:	
From date of surgery to date of first documented distant failure.	

End point values	Cetuximab (ITT)	Control (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125 ^[7]	123 ^[8]		
Units: Time to distant failure (years)				
median (confidence interval 95%)	9999 (6.0 to 9999)	9999 (5.6 to 9999)		

Notes:

[7] - Only for patients with R0-resection.

[8] - Only for patients with R0-resection.

Statistical analyses

Statistical analysis title	Time to dist. failure Log Rank and Hazard Ratio
Comparison groups	Cetuximab (ITT) v Control (ITT)
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.838
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.48

Secondary: SE | Distant failure after R0-resection rate

End point title	SE Distant failure after R0-resection rate
End point description:	
End point type	Secondary
End point timeframe:	
At year 1, 2, 3, 4 and 5.	

End point values	Cetuximab (ITT)	Control (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125 ^[9]	123 ^[10]		
Units: Distant failure rate (%)				
number (confidence interval 95%)				
1 year	82.9 (74.7 to 88.6)	83.2 (74.9 to 88.9)		
2 years	73.4 (64.2 to 80.6)	69.3 (59.5 to 77.1)		
3 years	67.6 (57.9 to 75.5)	67.0 (57.1 to 75.2)		
4 years	64.4 (54.5 to 72.6)	65.7 (55.6 to 74.1)		
5 years	64.4 (54.5 to 72.6)	63.9 (53.5 to 72.7)		

Notes:

[9] - Only for patients with R0-resection.

[10] - Only for patients with R0-resection.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Pathological remission

End point title	SE Pathological remission
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End point description:

Pathological remission was assessed according to the tumor regression model of Mandard. TRG 1 (pCR) was defined as complete regression, absence of histologically identifiable residual cancer and fibrosis extending through the different layers of the esophageal wall, with or without granuloma. | TRG 2 was defined as presence of rare residual cancer cells scattered through the fibrosis. | TRG 3 was defined as increase in the number of residual cancer cells, but fibrosis still predominant. | TRG 4 was defined as residual cancer outgrowing fibrosis. | TRG 5 was defined as absence of regressive changes

Pathological remission (=TRG 1+2). It was calculated only for patients who had undergone a surgical resection.

End point type	Secondary
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End point timeframe:

After surgery.

End point values	Cetuximab (ITT)	Control (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131 ^[11]	127 ^[12]		
Units: Patients with TRG1 + 2 (%)				
number (not applicable)				
No	32.1	35.4		
Yes	67.2	64.6		
Missing	0.8	0.0		

Notes:

[11] - Only for patients who had undergone a surgical resection.

[12] - Only for patients who had undergone a surgical resection.

Statistical analyses

Statistical analysis title	Pathological remission Chi-Square Test
Comparison groups	Cetuximab (ITT) v Control (ITT)
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.93

Secondary: SE | R0-resection

End point title	SE R0-resection
End point description:	
R0-resection was defined as no residual tumor (meaning thus neither microscopic nor macroscopic). It was a macroscopically complete removal by a non-contaminated operation with wide or radical margin.	
The R0-resection rate was reported only for patients who had undergone a surgical resection.	
End point type	Secondary
End point timeframe:	
After surgery.	

End point values	Cetuximab (ITT)	Control (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131 ^[13]	127 ^[14]		
Units: Patients (%)				
number (not applicable)				
Resection R0	95.4	96.6		
Resection R1	3.8	3.1		
Missing	0.8	0.0		

Notes:

[13] - Only for patients who had undergone a surgical resection.

[14] - Only for patients who had undergone a surgical resection.

Statistical analyses

Statistical analysis title	R0-resection Fisher's exact test
Comparison groups	Cetuximab (ITT) v Control (ITT)
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	3.1

Secondary: SE | Completion of therapy

End point title	SE Completion of therapy
End point description: Completion of therapy was defined as: (1) Two cycles of neoadjuvant chemo(immuno)therapy (dose reductions are allowed); (2) At least 39.6 Gy of RT together with at least 75% of the doses of each drug of the concomitant chemo(immuno)therapy; (3) Performed surgery (independent of resection status); (4) Being alive 60 days postoperatively; (5) At least five of the six doses of adjuvant cetuximab therapy (arm A).	
End point type	Secondary
End point timeframe: At particular study milestones.	

End point values	Cetuximab	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	151		
Units: Patients (%)				
number (not applicable)				
Two cycles of neoadjuvant therapy	96.0	96.7		
At least 39.6 Gy of RT	92.6	92.1		
At least 75% of the doses of each drug of RCT	85.2	88.7		
Was surgery performed?	88.6	86.1		
Alive 60 days postoperatively	85.9	82.1		
At least five doses of adjuvant cetuximab therapy	53.7	0		
Completion of therapy	48.3	72.8		

Statistical analyses

No statistical analyses for this end point

Secondary: SE | In-hospital mortality

End point title	SE In-hospital mortality
End point description: In-hospital mortality was defined as any form of death (therapy, cancer or other related) occurring after surgery but while the patient remained in hospital.	
End point type	Secondary
End point timeframe: After surgery.	

End point values	Cetuximab (ITT)	Control (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132 ^[15]	130 ^[16]		
Units: Patients (%)				
number (not applicable)	6.1	3.1		

Notes:

[15] - Only for postoperative patients.

[16] - Only for postoperative patients.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Compliance with radiotherapy standards

End point title	SE Compliance with radiotherapy standards
End point description: The compliance with radiotherapy standards was assessed within the quality assurance program for selected patients. Deviations of radiotherapy were assessed within the quality assurance program. They were divided into major and minor deviations: [A] Major deviations: (i) The 95% isodose does not encompass the complete GTV; (ii) Less than 85% of the PTV are encompassed by the 95% isodose, if normal tissue restrictions are not fully exploited; (iii) Exceeding one or more normal tissue dose restriction by > 15%; (iv) Largely inadequate volumes of interest (GTV, CTV, PTV, normal tissue) or irradiated volumes [B] Minor deviations: (i) Any deviations not fulfilling the criteria of major deviations	
End point type	Secondary
End point timeframe: From randomization.	

End point values	Cetuximab (ITT)	Control (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37 ^[17]	41 ^[18]		
Units: Patients (%)				
number (not applicable)				
Largely inadequate volumes or irradiated volumens	2.7	0		

The 95% isodose does not encompass complete GTV	0	2.4		
Minor deviations	43.2	65.9		

Notes:

[17] - Only selected patients of the assurance program.

[18] - Only selected patients of the assurance program.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: PE | PFS rate

End point title	PE PFS rate
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End point description:

End point type	Other pre-specified
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End point timeframe:

At 1, 2, 3, 4 and 5 years.

End point values	Cetuximab (ITT)	Control (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	148	149		
Units: PFS rate (%)				
number (confidence interval 95%)				
1 year	74.3 (66.3 to 80.7)	72.7 (64.7 to 79.1)		
2 years	58.3 (49.8 to 65.8)	50.0 (41.7 to 57.8)		
3 years	51.2 (42.8 to 59.0)	41.0 (33.0 to 49.8)		
4 years	49.0 (40.6 to 56.9)	38.8 (30.9 to 46.7)		
5 years	47.6 (39.2 to 55.5)	38.1 (30.2 to 45.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization until end of study, i.e. during induction phase, RC(I)T and within 30 days after its end. Late AEs were followed up in the follow-up phase.

Adverse event reporting additional description:

Patients were instructed by the investigator to report the occurrence of any AE. The investigator assessed and recorded all AEs observed during the study. Late AEs (in the Follow-up phase) were observed until disease progression.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	Cetuximab
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Reporting group description:

Cetuximab arm at baseline.

Reporting group title	Control
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Reporting group description:

Control arm at baseline.

Serious adverse events	Cetuximab	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	111 / 149 (74.50%)	109 / 151 (72.19%)	
number of deaths (all causes)	72	85	
number of deaths resulting from adverse events	15	17	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal cancer			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 149 (0.67%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypopharyngeal cancer	Additional description: One patient in Cetuximab arm: Laryngeal-hypopharyngeal cancer Grade 3.		
subjects affected / exposed	2 / 149 (1.34%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oropharyngeal cancer			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 149 (0.67%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Prostate cancer			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine neuroendocrine tumour			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 149 (0.67%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm	Additional description: Extrathyroidal manifestation of pre-existing papillary thyroid carcinoma requiring surgery Grade 3.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			

subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Femoral artery embolism			
Additional description: Peripheral ischemia due to (recurrent) acute arterial femorocrural embolism.			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
Additional description: One patient: Syncope Grade 3 associated with hypotension due to bleeding of tumor and decompensated antihypertensive therapy; one patient: Tachycardia Grade 1 (NOS), hypotension Grade 3, cold sweating.			
subjects affected / exposed	2 / 149 (1.34%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphorrhoea			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
Additional description: Dizziness Grade 3 due to orthostatic hypotension Grade 3 and paroxysmal benign vertigo.			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
Additional description: Arterial occlusion Grade 3 (A. iliaca) with existing overcross bypass due to chronic peripheral artery occlusion disease requiring thrombectomy.			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
Additional description: One patient in Control arm: Venous thrombosis Grade2, diarrhea Grade2, renal insufficiency Grade 2.			

subjects affected / exposed	3 / 149 (2.01%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Jejunostomy closure			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
Additional description: One patient in Cetuximab arm: Pain Grade 3 (retrosternal) with nausea Grade 2, vomiting Grade 2			
subjects affected / exposed	2 / 149 (1.34%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
Additional description: One patient in Cetuximab arm: Fever Grade 1, chills Grade2; one patient in Control arm: Fever Grade 1, chills Grade1.			
subjects affected / exposed	2 / 149 (1.34%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
Additional description: One event: Abdominal and peritoneal infection Grade 4 (abscess formation) in context of jejunal feeding tube dysfunction requiring open small intestine resection; other event: Abdominal pain G2 in the context of removal of defective feeding tube			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehiscence			
Additional description: Patient in Cetuximab arm: Cervical anastomosis dehiscence with abscess formation (wound infection Grade 3).			
subjects affected / exposed	1 / 149 (0.67%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
Additional description: One patient: Fatigue Grade 3 leading to vertigo Grade 3; one patient: Hypotension Grade 2 in context of fatigue Grade 3.			
subjects affected / exposed	3 / 149 (2.01%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration subjects affected / exposed	1 / 149 (0.67%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation	Additional description: Fever Grade 1 in context of mucositis Grade 3.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 149 (0.67%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death	Additional description: Sudden death Grade 5 arrhythmia suspected.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	3 / 149 (2.01%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome	Additional description: One patient in Cetuximab arm: Respiratory insufficiency due to ARDS in the context of pulmonary CMV infection (lung infection).		

subjects affected / exposed	2 / 149 (1.34%)	4 / 151 (2.65%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	1 / 1	1 / 1	
Aspiration			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chylothorax			
subjects affected / exposed	3 / 149 (2.01%)	3 / 151 (1.99%)	
occurrences causally related to treatment / all	2 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis	Additional description: Epistaxis Grade 3 (phenprocoumon treatment), bronchial infection Grade 2 (normal Absolute Neutrophil Count).		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups	Additional description: Hiccups Grade 3 in context of dysphagia Grade 2 and vomiting Grade 2.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagobronchial fistula			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax	Additional description: One patient in Cetuximab arm: Pneumothorax Grade 2 after lung biopsy, one patient in Control arm: Pain (periumbilical and epigastral) Grade 3 in context of seropneumothorax.		

subjects affected / exposed	1 / 149 (0.67%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism	Additional description: One patient in Control arm: Postoperative death due to pulmonary embolism (suspected) Grade 5.		
subjects affected / exposed	3 / 149 (2.01%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary mass	Additional description: Multiple bilateral pulmonary nodules requiring video-assisted thoroscopic resection (histologically inflammation, no malignancy) Grade 3.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure	Additional description: One patient: Respiratory failure Grade 5 due to chronic bronchitis with recurrent respiratory infections, extreme post-surgical muscular weakness.		
subjects affected / exposed	0 / 149 (0.00%)	3 / 151 (1.99%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Tracheal fistula	Additional description: One patient: Weight loss Grade 2 due to anorexia and adipsia in context of tracheal fistula.		
subjects affected / exposed	2 / 149 (1.34%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety	Additional description: Confusion Grade 1 in context of anxiety attack Grade 1.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Drug abuse			

subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Product issues			
Device dislocation	Additional description: One patient: Extravasation with inflammation due to port-a-cath needle dislocation Grade 2; one patient: Vomiting Grade 2 due to dislocated stent requiring stent removal.		
subjects affected / exposed	2 / 149 (1.34%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased	Additional description: One patient: Fever Grade 1, elevated CRP; one patient: Fever Grade 1, elevated CRP, suspicion of esophageal fistula.		
subjects affected / exposed	2 / 149 (1.34%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased	Additional description: Two patients in Cetuximab arm: Fever Grade 1, white blood cell decreased Grade 3.		

subjects affected / exposed	2 / 149 (1.34%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic leak	Additional description: Revision surgery due to persistent thoracic anastomotic leak with persistent broncho-esophageal fistula Grade 4.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic stenosis	Additional description: One patient in Control arm: Dysphagia Grade 1 due to cervical anastomotic stenosis Grade 2; Two patients in Cetuximab arm: Dysphagia Grade 2 due to esophageal anastomotic stenosis (1); Esophag. obstruction Grade 3 (thoracic anastomosis stricture) (2)		
subjects affected / exposed	2 / 149 (1.34%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic ulcer	Additional description: Esophageal pain Grade 2 due to Candida esophagitis and thoracic anastomotic ulcers.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture	Additional description: Bone fracture (femur) due to fall Grade 3.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak	Additional description: Gastrointestinal anastomotic leak in conjunction with various other conditions for 3 patients in Cetuximab arm and 3 patients in Control arm (e.g. fistula, pulmonary disorder/infection, requiring re-surgery).		
subjects affected / exposed	9 / 149 (6.04%)	15 / 151 (9.93%)	
occurrences causally related to treatment / all	9 / 9	15 / 15	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal stoma complication	Additional description: Local skin irritation due to leaking jejunostomy tube (pain Grade 3 skin).		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia	Additional description: Abdominal incisional hernia Grade 3 requiring omentoplasty.		

subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	8 / 149 (5.37%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	8 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture	Additional description: Bone fracture (leg) due to trauma Grade 3.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation oesophagitis	Additional description: Patient in Cetuximab arm: Weight loss Grade (G)2 due to radiotherapy (RT)-induced esophagitis G3; two patients in Control arm: Dysphagia G3 due to RT induced esophagitis G2 [1] Nausea G3, vomiting G3, gastritis due to post-RT esophagitis [2]).		
subjects affected / exposed	1 / 149 (0.67%)	3 / 151 (1.99%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture	Additional description: Back pain Grade 3 due to vertebra fracture (Th12 and L3) in context of osteoporosis.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence	Additional description: Wound dehiscence Grade 3 (hiatushernia).		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 149 (1.34%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Atrial flutter	Additional description: Syncope Grade 3 in context of atrial flutter.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial tachycardia			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete	Additional description: Asystole Grade 4 due to AV-Block 3rd degree.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest	Additional description: One patient in control arm: Cardiac arrest Grade 4 before extubation after gastric pull-up.		
subjects affected / exposed	1 / 149 (0.67%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure	Additional description: One patient in Cetuximab arm: Cardiac failure Grade 5 with respiratory insufficiency; one patient in Control arm: Heart failure Grade 3 with consecutive dyspnea Grade 2		
subjects affected / exposed	1 / 149 (0.67%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Left ventricular dysfunction	Additional description: Left ventricular systolic dysfunction Grade 4, dyspnea Grade 4.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pericarditis constrictive			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Right ventricular dysfunction	Additional description: Pericardial effusion Grade 3 with right ventricular dysfunction Grade 3.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular dysfunction	Additional description: Acute dyspnea Grade 3 due to left ventricular dysfunction.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness	Additional description: Depressed level of consciousness Grade 3 due to opioide use.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness	Additional description: Dizziness Grade 3, nausea Grade 2, fatigue Grade 2.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Laryngeal nerve palsy			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia	Additional description: Fatigue Grade 2 in context of post-zoster neuralgia.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 149 (0.67%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paresis	Additional description: Aphonia Grade 3 due to vocal cord paresis.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: One patient in Control arm: Fatigue grade 2 in context of anemia grade 3.		
subjects affected / exposed	0 / 149 (0.00%)	3 / 151 (1.99%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia	Additional description: Febrile neutropenia in conjunction with other conditions for 2 patients in Cetuximab arm (i.e. diarrhea/stomatitis [1] diarrhea/platelet count decreased [2]) and 3 patients in Control arm (i.e. diarrhea [1] dysphagia [2] diarrhea/vomiting [3]).		
subjects affected / exposed	10 / 149 (6.71%)	10 / 151 (6.62%)	
occurrences causally related to treatment / all	10 / 10	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia	Additional description: Neutropenia in conjunction with other conditions for 2 patients in Control arm (i.e. colitis [1] leukocytopenia [2]).		
subjects affected / exposed	1 / 149 (0.67%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness neurosensory	Additional description: Hearing impaired Grade 3 (labyrinthine hearing loss)		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tinnitus			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Dacryostenosis acquired	Additional description: Docetaxel induced lacrimal duct stenosis (watering eyes Grade 3) requiring surgery.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis	Additional description: One patient in Cetuximab arm: Diarrhea Grade 3 due to colitis Grade 3; one patient in Control arm: Diarrhea Grade 3 due to pancolitis, urinary tract infection Grade 3		
subjects affected / exposed	3 / 149 (2.01%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation	Additional description: Abdominal pain Grade 2 due to constipation Grade 2.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic hernia	Additional description: One patient: Small intestinal obstruction Grade 3 due to diaphragmatic herniation; one patient: Subileus Grade 3 due to diaphragmatic hernia requiring surgical intestinal reposition.		

subjects affected / exposed	4 / 149 (2.68%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: Diarrhoea in conjunction with other conditions for 3 patients in Cetuximab arm (i.e. dehydration [1] two events (dehydration +/- hypokalemia) [2] worsening of general condition [3]) and 2 patients in Control arm (i.e. fatigue[1] dehydration [2])		
subjects affected / exposed	5 / 149 (3.36%)	7 / 151 (4.64%)	
occurrences causally related to treatment / all	5 / 6	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction	Additional description: Duodenal obstruction Grade 3 due to postoperative adhesions followed lung infection Grade 5.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Duodenal perforation			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage	Additional description: One patient: Dyspnea Grade 3 and anorexia Grade 3 due to anemia Grade 4 associated with a bleeding ulcer of the duodenal bulb.		
subjects affected / exposed	2 / 149 (1.34%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation	Additional description: Abdominal pain Grade 3 due to peritonitis secondary to perforated duodenal ulcer Grade 3 related to premedication (dexamethasone) and concomitant medication (acetyl salicylic acid).		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia	Additional description: Dysphagia in conjunction with various other conditions for 4 patients in Cetuximab arm and 8 patients in Control arm (including aspiration, fever, nausea, vomiting and others).		

subjects affected / exposed	15 / 149 (10.07%)	24 / 151 (15.89%)	
occurrences causally related to treatment / all	15 / 19	20 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis	Additional description: Syncope due to enteritis Grade 2 with dehydration Grade 2.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric fistula	Additional description: Cervical abscess, gastric fistula Grade 3		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage	Additional description: One patient: Gastric hemorrhage Grade 3 due to ulcers		
subjects affected / exposed	2 / 149 (1.34%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric stenosis			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis	Additional description: Acute epigastric pain Grade 3 in context of esophagitis Grade 3 and antrum gastritis Grade 3.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive	Additional description: Dehydration Grade 1 and nausea Grade 1 associated with erosive antrum gastritis.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 149 (1.34%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal motility disorder	Additional description: Patient in Cetuximab arm: Postoperative intestinal motility disturbance Grade 2 with dehydration Grade 2 and weight loss Grade 2; patient in Control arm: Functional passage disturbance of the gastric sleeve		

	Grade 3 with consecutive vomiting Grade 3		
subjects affected / exposed	1 / 149 (0.67%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis	Additional description: Gastric conduit necrosis requiring re-surgery Grade 4.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain	Additional description: Gastrointestinal pain Grade 3 due to nephro- and cholelithiasis.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroesophageal reflux disease	Additional description: Dysphagia Grade 3 in context of reflux esophagitis.		
subjects affected / exposed	0 / 149 (0.00%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus	Additional description: Ileus Grade 4 requiring laparotomy and adhesiolysis.		
subjects affected / exposed	3 / 149 (2.01%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation	Additional description: Colonic perforation Grade 4 after colonoscopy with polypectomy.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus	Additional description: Death due to adhesion ileus with ischemic intestinal wall necrosis (Grade 5).		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Mouth haemorrhage	Additional description: Oral hemorrhage Grade 2 in context of anticoagulation.		

subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea	Additional description: Nausea in conjunction with other conditions for 3 patients in Cetuximab arm (i.e. anorexia/dehydration [1] abdominal pain [2] esophageal stent insertion [3]) and 2 patients in Control arm (i.e. anorexia/insomnia [1] dehydration [2]).		
subjects affected / exposed	7 / 149 (4.70%)	3 / 151 (1.99%)	
occurrences causally related to treatment / all	8 / 9	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal fistula	Additional description: One patient in Control arm: Esophageal fistula Grade 4 progressing to mediastinitis.		
subjects affected / exposed	2 / 149 (1.34%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal motility disorder	Additional description: One event: Dysphagia Grade 3 in context of functional esophageal hiatus motility disturbance; other event: Vomiting Grade 3 in context of functional esophageal hiatus motility disturbance.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction	Additional description: Patient in Cetuximab arm: Dysphagia Grade 3 due to subtotal tumor related esophageal obstruction; patient in Control arm: Dysphagia Grade 3 due to esophageal obstruction with food remainder.		
subjects affected / exposed	1 / 149 (0.67%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal perforation			
subjects affected / exposed	0 / 149 (0.00%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis	Additional description: One patient in Control arm: Dehydration Grade 3 due to esophageal stenosis, gastric tube insertion.		
subjects affected / exposed	2 / 149 (1.34%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer	Additional description: Esophageal ulcer Grade 3 with esophageal hemorrhage Grade 2.		

subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis	Additional description: Oesophagitis in conjunction with other conditions for 2 patients in Cetuximab arm (anorexia/dehydration/dysphagia [1] partial ileus [2]) and 3 patients in Control arm (epigastric pain [1] pain/dysphagia [2], odynophagia/dysphagia/nausea [3]).		
subjects affected / exposed	6 / 149 (4.03%)	10 / 151 (6.62%)	
occurrences causally related to treatment / all	5 / 6	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis haemorrhagic	Additional description: Fever Grade 3 in context of infection Grade 3 and hemorrhagic esophagitis Grade 3 with persistent nausea.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis ulcerative			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum	Additional description: Pneumoperitoneum (Grade 3) consecutive to feeding tube insertion.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis	Additional description: Patient in Cetuximab arm: Stomatitis/Pharyngitis Grade 3.		
subjects affected / exposed	1 / 149 (0.67%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus	Additional description: Subileus G2 consecutive to laparotomical adhesiolysis before trial treatment start		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth disorder	Additional description: Fever Grade 1 in context of odontopathy.		

subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: Vomiting in conjunction with various other conditions for 4 patients in Cetuximab arm and 5 patients in Control arm (including chest pain, nausea, pain, anorexia, dehydration, syncope and others).		
subjects affected / exposed	4 / 149 (2.68%)	8 / 151 (5.30%)	
occurrences causally related to treatment / all	4 / 4	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal adhesions	Additional description: Abdominal pain due to intestinal adhesions and internal herniation.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis	Additional description: Infectious choledochus stenosis Grade 3 due to dislocated choledochus stent.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cirrhosis alcoholic	Additional description: Liver cirrhosis (alcohol induced Grade 3) with ascites Grade 2 requiring drain insertion.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perforation bile duct	Additional description: Abdominal pain Grade 4 due to biliary peritonitis in context of Ductus choledochus leak requiring revision laparotomy.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury in conjunction with other conditions for 3 patients in Cetuximab arm (i.e. nausea/diarrhea [1] edema limbs [2] requiring hemodialysis [3]) and 1 patient in Control arm (i.e. vomiting).		
subjects affected / exposed	9 / 149 (6.04%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	8 / 9	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nephrolithiasis	Additional description: Renal colic Grade 3 due to nephrolithiasis, temporary uretral splint insertion.		

subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone erosion	Additional description: Back pain Grade 3 due to progressive Th6 erosion in context of upper mediastinal infection (Staph. aureus).		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis	Additional description: Pseudo-gout and gout-arthritis Grade 3 (knee).		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis	Additional description: Osteitis (ventral rib 5) with chronic super-infection (Pseudomonas aeruginosa) in context of wound healing disorder Grade 3 after protocol surgery.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection	Additional description: Abdominal infection due to dislocated PEG.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess	Additional description: Abdominal pain G3 due to abscess formation (abdominal wall) requiring revision and percutaneous drainage.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			

subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site abscess			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection	Additional description: One patient in Control arm: Port-a-cath infection Grade 3 requiring surgical revision.		
subjects affected / exposed	2 / 149 (1.34%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			

subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 149 (0.67%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis	Additional description: Endophthalmitis Grade 3 with preceding keratitis Grade 3 and consecutive retinal detachment Grade 3.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection	Additional description: Fever Grade 1 due to suspected Gastrointestinal infection, diarrhea Grade 1, vomiting Grade 1.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection	Additional description: One patient in Cetuximab arm: Fever Grade 1 in context of infection of unknown origin.		
subjects affected / exposed	2 / 149 (1.34%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion	Additional description: Cervical esophageal anastomotic leak Grade 3, pleural effusion Grade 3, pleural empyema Grade 3.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis	Additional description: Back pain Grade 3 (lumbal spine) due to intervertebral discitis (metastasis unlikely).		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Localised infection	Additional description: Patient in Cetuximab arm: Clavus infection Grade 3 (big toe) requiring clavus ablation.		
subjects affected / exposed	1 / 149 (0.67%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	3 / 149 (2.01%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile infection			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Pneumonia in conjunction with various other conditions for 5 patients in Cetuximab arm and 3 patients in Control arm (including fever, thromboembolic event, esophageal anastomotic leak, respiratory failure/insufficiency and others).		
subjects affected / exposed	8 / 149 (5.37%)	8 / 151 (5.30%)	
occurrences causally related to treatment / all	7 / 8	8 / 8	
deaths causally related to treatment / all	2 / 2	1 / 1	
Pneumonia aspiration	Additional description: One patient in Control arm: Respiratory failure Grade 5 in context of aspiration pneumonia.		
subjects affected / exposed	1 / 149 (0.67%)	2 / 151 (1.32%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pseudomonas infection	Additional description: Pseudomonas aeruginosa infection Grade 3 with fever Grade 2.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: Sepsis in conjunction with various other conditions for 6 patients in Cetuximab arm and 5 patients in Control arm (including pleural empyema, lung infection/respiratory insufficiency, febrile neutropenia, and others).		

subjects affected / exposed	7 / 149 (4.70%)	7 / 151 (4.64%)	
occurrences causally related to treatment / all	5 / 7	7 / 7	
deaths causally related to treatment / all	1 / 1	3 / 3	
Septic shock	Additional description: Patient in Cetuximab arm: Pulmonary fibrosis leading to pulmonary infection and subsequent septic shock Grade 5.		
subjects affected / exposed	1 / 149 (0.67%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Systemic bacterial infection	Additional description: Systemic Enterobacter infection Grade 3.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection	Additional description: Upper respiratory infection with fever Grade 2.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite	Additional description: Decreased appetite in conjunction with other conditions for 4 patients in Cetuximab arm (i.e. dehydration [1] diarrhea [2] dysgeusia/diarrhea [3]; dehydration [4]) and 1 patient in Control arm (i.e. fatigue/dehydration/depression).		
subjects affected / exposed	5 / 149 (3.36%)	6 / 151 (3.97%)	
occurrences causally related to treatment / all	5 / 5	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration	Additional description: One patient in Control arm: Dehydration Grade 3 with presyncope Grade 2, nausea Grade 3, dysphagia Grade 2, diarrhea Grade 1.		
subjects affected / exposed	2 / 149 (1.34%)	3 / 151 (1.99%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diabetes mellitus	Additional description: Hyperglycemia Grade 3 in context of diabetes.		
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia	Additional description: Hypercalcemia Grade 4 (following calcium substitution for hypocalcemia), creatinine increase Grade 3.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia	Additional description: Hypocalcemia Grade 4, acute kidney injury Grade 1, seizure Grade 3, worsening of general condition Grade 3.		
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia	Additional description: One patient in Cetuximab arm: Hypokalemia Grade 3, nausea Grade 2, vomiting Grade 2, fatigue Grade 2; one patient in Control arm: Hypokalemia Grade 4 due to dysphagia Grade 3.		
subjects affected / exposed	2 / 149 (1.34%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia	Additional description: One patient: Hypomagnesemia Grade 4, esophagitis Grade 3, fatigue Grade 3.		
subjects affected / exposed	2 / 149 (1.34%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cetuximab	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	149 / 149 (100.00%)	151 / 151 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 149 (11.41%)	19 / 151 (12.58%)	
occurrences (all)	27	30	
Hypotension			
subjects affected / exposed	18 / 149 (12.08%)	15 / 151 (9.93%)	
occurrences (all)	20	16	
Embolism			
subjects affected / exposed	11 / 149 (7.38%)	7 / 151 (4.64%)	
occurrences (all)	15	9	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	11 / 149 (7.38%)	9 / 151 (5.96%)	
occurrences (all)	14	12	
Fatigue			
subjects affected / exposed	108 / 149 (72.48%)	103 / 151 (68.21%)	
occurrences (all)	217	179	
Pyrexia			
subjects affected / exposed	25 / 149 (16.78%)	17 / 151 (11.26%)	
occurrences (all)	27	19	
Non-cardiac chest pain			
subjects affected / exposed	8 / 149 (5.37%)	14 / 151 (9.27%)	
occurrences (all)	8	16	
Pain			
subjects affected / exposed	12 / 149 (8.05%)	11 / 151 (7.28%)	
occurrences (all)	13	12	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	13 / 149 (8.72%)	6 / 151 (3.97%)	
occurrences (all)	13	7	
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	30 / 149 (20.13%) 37	28 / 151 (18.54%) 30	
Dyspnoea subjects affected / exposed occurrences (all)	34 / 149 (22.82%) 44	14 / 151 (9.27%) 18	
Epistaxis subjects affected / exposed occurrences (all)	17 / 149 (11.41%) 20	12 / 151 (7.95%) 14	
Dysphonia subjects affected / exposed occurrences (all)	4 / 149 (2.68%) 4	8 / 151 (5.30%) 11	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	10 / 149 (6.71%) 11	7 / 151 (4.64%) 8	
Insomnia subjects affected / exposed occurrences (all)	10 / 149 (6.71%) 11	11 / 151 (7.28%) 11	
Investigations Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	12 / 149 (8.05%) 16	5 / 151 (3.31%) 6	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	10 / 149 (6.71%) 11	3 / 151 (1.99%) 3	
Blood creatinine increased subjects affected / exposed occurrences (all)	25 / 149 (16.78%) 33	36 / 151 (23.84%) 48	
Neutrophil count decreased subjects affected / exposed occurrences (all)	33 / 149 (22.15%) 37	36 / 151 (23.84%) 37	
Pancreatic enzymes decreased subjects affected / exposed occurrences (all)	12 / 149 (8.05%) 13	17 / 151 (11.26%) 17	
Platelet count decreased			

subjects affected / exposed occurrences (all)	95 / 149 (63.76%) 102	94 / 151 (62.25%) 97	
Weight decreased subjects affected / exposed occurrences (all)	66 / 149 (44.30%) 110	57 / 151 (37.75%) 89	
White blood cell count decreased subjects affected / exposed occurrences (all)	22 / 149 (14.77%) 27	17 / 151 (11.26%) 18	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	18 / 149 (12.08%) 23	14 / 151 (9.27%) 18	
Dysaesthesia subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 9	5 / 151 (3.31%) 5	
Dysgeusia subjects affected / exposed occurrences (all)	52 / 149 (34.90%) 84	46 / 151 (30.46%) 73	
Paraesthesia subjects affected / exposed occurrences (all)	17 / 149 (11.41%) 22	17 / 151 (11.26%) 22	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	21 / 149 (14.09%) 33	25 / 151 (16.56%) 35	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	102 / 149 (68.46%) 168	112 / 151 (74.17%) 190	
Ear and labyrinth disorders			
Hypoacusis subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 15	3 / 151 (1.99%) 3	
Tinnitus subjects affected / exposed occurrences (all)	10 / 149 (6.71%) 14	18 / 151 (11.92%) 24	
Vertigo			

subjects affected / exposed occurrences (all)	13 / 149 (8.72%) 17	8 / 151 (5.30%) 9	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	35 / 149 (23.49%)	25 / 151 (16.56%)	
occurrences (all)	45	28	
Constipation			
subjects affected / exposed	47 / 149 (31.54%)	49 / 151 (32.45%)	
occurrences (all)	55	57	
Diarrhoea			
subjects affected / exposed	96 / 149 (64.43%)	93 / 151 (61.59%)	
occurrences (all)	144	121	
Dumping syndrome			
subjects affected / exposed	8 / 149 (5.37%)	10 / 151 (6.62%)	
occurrences (all)	8	10	
Dyspepsia			
subjects affected / exposed	15 / 149 (10.07%)	25 / 151 (16.56%)	
occurrences (all)	15	27	
Dysphagia			
subjects affected / exposed	81 / 149 (54.36%)	82 / 151 (54.30%)	
occurrences (all)	117	111	
Oesophageal pain			
subjects affected / exposed	9 / 149 (6.04%)	14 / 151 (9.27%)	
occurrences (all)	9	14	
Oesophageal stenosis			
subjects affected / exposed	12 / 149 (8.05%)	16 / 151 (10.60%)	
occurrences (all)	12	16	
Oesophagitis			
subjects affected / exposed	16 / 149 (10.74%)	21 / 151 (13.91%)	
occurrences (all)	16	23	
Gastrointestinal pain			
subjects affected / exposed	5 / 149 (3.36%)	9 / 151 (5.96%)	
occurrences (all)	7	11	
Stomatitis			
subjects affected / exposed	62 / 149 (41.61%)	33 / 151 (21.85%)	
occurrences (all)	82	39	

Nausea			
subjects affected / exposed	97 / 149 (65.10%)	104 / 151 (68.87%)	
occurrences (all)	153	162	
Abdominal pain upper			
subjects affected / exposed	8 / 149 (5.37%)	8 / 151 (5.30%)	
occurrences (all)	8	8	
Vomiting			
subjects affected / exposed	64 / 149 (42.95%)	56 / 151 (37.09%)	
occurrences (all)	85	72	
Gastrooesophageal reflux disease			
subjects affected / exposed	28 / 149 (18.79%)	22 / 151 (14.57%)	
occurrences (all)	31	26	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	63 / 149 (42.28%)	66 / 151 (43.71%)	
occurrences (all)	116	107	
Dry skin			
subjects affected / exposed	34 / 149 (22.82%)	6 / 151 (3.97%)	
occurrences (all)	49	6	
Erythema multiforme			
subjects affected / exposed	9 / 149 (6.04%)	1 / 151 (0.66%)	
occurrences (all)	11	1	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	15 / 149 (10.07%)	4 / 151 (2.65%)	
occurrences (all)	28	5	
Pruritus			
subjects affected / exposed	13 / 149 (8.72%)	2 / 151 (1.32%)	
occurrences (all)	15	2	
Dermatitis acneiform			
subjects affected / exposed	98 / 149 (65.77%)	4 / 151 (2.65%)	
occurrences (all)	181	5	
Rash maculo-papular			
subjects affected / exposed	23 / 149 (15.44%)	0 / 151 (0.00%)	
occurrences (all)	43	0	
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	17 / 149 (11.41%) 19	11 / 151 (7.28%) 15	
Pain in extremity subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 13	10 / 151 (6.62%) 10	
Infections and infestations			
Mucosal infection subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 8	5 / 151 (3.31%) 5	
Rash pustular subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 16	1 / 151 (0.66%) 1	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	81 / 149 (54.36%) 138	66 / 151 (43.71%) 100	
Hyperkalaemia subjects affected / exposed occurrences (all)	13 / 149 (8.72%) 21	18 / 151 (11.92%) 22	
Hypocalcaemia subjects affected / exposed occurrences (all)	64 / 149 (42.95%) 100	46 / 151 (30.46%) 62	
Hypokalaemia subjects affected / exposed occurrences (all)	65 / 149 (43.62%) 101	44 / 151 (29.14%) 57	
Hypomagnesaemia subjects affected / exposed occurrences (all)	87 / 149 (58.39%) 159	59 / 151 (39.07%) 90	
Hyponatraemia subjects affected / exposed occurrences (all)	53 / 149 (35.57%) 80	47 / 151 (31.13%) 60	
Vitamin D deficiency subjects affected / exposed occurrences (all)	5 / 149 (3.36%) 5	8 / 151 (5.30%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2010	The protocol was updated to reflect the safety recommendations from Merck and Paul-Ehrlich-Institut.
01 May 2011	The protocol was updated to specify some safety issues and to make general clarifications and corrections.
01 June 2012	The protocol was updated to specify some scientific issues and to implement general clarifications and corrections.

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.

Limitations are that (1) the planned event rate for the primary analysis was not reached, (2) the inclusion of both SCC and adenocarcinoma patients, (3) lack of prospectively test for potential biomarkers of EGFR-inhibition.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32111181>

<http://www.ncbi.nlm.nih.gov/pubmed/33055589>