Clinical trial results:
A PHASE II, OPEN-LABEL, RANDOMIZED STUDY OF MEHD7945A VERSUS CETUXIMAB IN PATIENTS WITH RECURRENT/METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK WHO HAVE PROGRESSED DURING OR FOLLOWING PLATINUM BASED CHEMOTHERAPY

Summary

EudraCT number	2011-005539-22
Trial protocol	BE DE GB ES HU IT BG
Global end of trial date	22 June 2015

Results information

Result version number	v1 (current)
This version publication date	23 July 2016
First version publication date	23 July 2016

Trial information

Trial identification

Sponsor protocol code	GO28076

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01577173
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 June 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the efficacy, as measured by progression free survival (PFS), of MEHD7945A (administered every 2 weeks) versus cetuximab (administered weekly) in subjects with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN)

- To evaluate the efficacy, as measured by PFS, of MEHD7945A (administered every 2 weeks) versus cetuximab (administered weekly) in subjects with R/M SCCHN whose tumors express high levels of heregulin (HRG)

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 July 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Romania: 21
Country: Number of subjects enrolled	United States: 33
Worldwide total number of subjects	120
EEA total number of subjects	77

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)	72
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 121 subjects were randomized to treatment in the study. However, 1 subject received no study treatment; therefore 120 subjects were enrolled and received at least 1 dose of study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	MEHD7945A

Arm description:

Subjects with R/M SCCHN who had progressed during or following platinum-based chemotherapy received MEHD7945A 1100 milligrams (mg) as an intravenous (IV) infusion every 2 weeks until disease progression or intolerable toxicity.

Arm type	Experimental
Investigational medicinal product name	MEHD7945A
Investigational medicinal product code	
Other name	Duligotuzumab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received MEHD7945A 1100 mg as an IV infusion every 2 weeks.

Arm title	Cetuximab

Arm description:

Subjects with R/M SCCHN who had progressed during or following platinum-based chemotherapy received cetuximab 400 milligrams per metre squared (mg/m^2) as an IV infusion for a loaded dose followed by cetuximab 250 mg/m^2 as an IV infusion once weekly until disease progression or intolerable toxicity.

Arm type	Active comparator
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cetuximab 400 mg/m^2 as a loaded dose followed by cetuximab 250 mg/m^2 weekly.

Arm title	Cetuximab then MEHD7945A

Arm description:

Subjects with disease progression on the cetuximab arm could receive MEHD7945A upon confirmation of progressive disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Arm type	Experimental

Investigational medicinal product name	MEHD7945A
Investigational medicinal product code	
Other name	Duligotuzumab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received MEHD7945A 1100 mg as an IV infusion every 2 weeks after having confirmed progressive disease on cetuximab therapy.

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cetuximab 400 mg/m^2 as a loaded dose followed by cetuximab 250 mg/m^2 weekly.

Number of subjects in period 1	MEHD7945A	Cetuximab	Cetuximab then MEHD7945A
Started	59	37	24
Completed	0	0	0
Not completed	59	37	24
Death	44	30	17
Study terminated by sponsor	7	7	5
Lost to follow-up	5	-	1
Withdrawal by subject	3	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	120	120	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	61.8		
standard deviation	± 10.1	-	
Gender categorical Units: Subjects			
Female	19	19	
Male	101	101	

End points

End points reporting groups

Reporting group title	MEHD7945A

Reporting group description:

Subjects with R/M SCCHN who had progressed during or following platinum-based chemotherapy received MEHD7945A 1100 milligrams (mg) as an intravenous (IV) infusion every 2 weeks until disease progression or intolerable toxicity.

Reporting group title	Cetuximab

Reporting group description:

Subjects with R/M SCCHN who had progressed during or following platinum-based chemotherapy received cetuximab 400 milligrams per metre squared (mg/m^2) as an IV infusion for a loaded dose followed by cetuximab 250 mg/m^2 as an IV infusion once weekly until disease progression or intolerable toxicity.

Reporting group title	Cetuximab then MEHD7945A

Reporting group description:

Subjects with disease progression on the cetuximab arm could receive MEHD7945A upon confirmation of progressive disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Subject analysis set title	Cetuximab, plus Cetuximab then MEHD7945A (Pre)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects randomized to cetuximab who did not cross-over, plus pre-crossover data for subjects randomized to cetuximab who crossed over to MEHD7945A.

Subject analysis set title	MEHD7945A, plus Cetuximab then MEHD7945A (Post)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects randomized to MEHD7945A, plus post-crossover data for subjects randomized to cetuximab who crossed over to MEHD7945A.

Subject analysis set title	Cetuximab, then MEHD7945A (Post)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Post-crossover data for subjects randomised to cetuximab who crossed over to MEHD7945A.

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)[1][2]

End point description:

PFS was defined as the time from randomisation to documented disease progression assessed by the investigator using RECIST v1.1 or death from any cause, whichever occurred first. Progressive disease was defined as a 20% increase in the sum of the longest diametre of target lesions, the appearance of new lesions and increase of at least 5 millimetre (mm) in the sum of diametres of target lesions. All randomised subjects.

End point type	Primary

End point timeframe:

From the time of randomisation until disease progression or death (approximately 3 years)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data in the endpoint was planned to be reported for the reporting groups MEHD7945A and Cetuximab, plus Cetuximab then MEHD7945A (Pre) only.

End point values	MEHD7945A	Cetuximab, plus Cetuximab then MEHD7945A (Pre)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	59	62		
Units: months				
median (confidence interval 90%)	4.21 (2.79 to 4.67)	4.01 (2.96 to 4.99)		

Statistical analyses

No statistical analyses for this end point

Primary: PFS in Subjects whose Tumors Express High Levels of Heregulin

End point title	PFS in Subjects whose Tumors Express High Levels of Heregulin[3][4]

End point description:

PFS was defined as the time from randomisation to documented disease progression assessed by the investigator using RECIST v1.1 or death from any cause, whichever occurred first. Progressive disease was defined as a 20% increase in the sum of the longest diametre of target lesions, the appearance of new lesions and increase of at least 5 mm in the sum of diametres of target lesions. All randomised subjects and whose tumors expressed high levels of heregulin.

End point type	Primary

End point timeframe:

From the time of randomisation until disease progression or death (approximately 3 years)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data in the endpoint was planned to be reported for the reporting groups MEHD7945A and Cetuximab, plus Cetuximab then MEHD7945A (Pre) only.

End point values	MEHD7945A	Cetuximab, plus Cetuximab then MEHD7945A (Pre)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	26	28		
Units: months				
median (confidence interval 90%)	2.79 (2.2 to 4.21)	5.54 (4.01 to 7.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with an Objective Response

End point title	Percentage of Subjects with an Objective Response[5]

End point description:

Objective response was defined as a complete response (CR) or a partial response (PR) according to RECIST v1.1. CR was defined as complete disappearance of all target lesions and non-target disease. PR was defined as a >=30% decrease under baseline of the sum of diametres of all target lesions. All randomised subjects.

End point type	Secondary

End point timeframe:

Approximately 3 years

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The data in the endpoint was planned to be reported for the reporting groups MEHD7945A and Cetuximab, plus Cetuximab then MEHD7945A (Pre) only.

End point values	MEHD7945A	Cetuximab, plus Cetuximab then MEHD7945A (Pre)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	59	62		
Units: Percentage of Subjects				
number (confidence interval 90%)	11.9 (6.35 to 20.74)	14.5 (8.3 to 23.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Disease Control

End point title	Percentage of Subjects with Disease Control[6]

End point description:

Disease control was defined as a CR, PR, or stable disease (SD) according to RECIST v1.1. CR was defined as complete disappearance of all target lesions and non-target disease. PR was defined as at >=30% decrease under baseline of the sum of diametres of all target lesions. SD was defined as steady state of disease with neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease. All randomised subjects.

End point type	Secondary

End point timeframe:

Approximately 3 years

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The data in the endpoint was planned to be reported for the reporting groups MEHD7945A and Cetuximab, plus Cetuximab then MEHD7945A (Pre) only.

End point values	MEHD7945A	Cetuximab, plus Cetuximab then MEHD7945A (Pre)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	59	62		
Units: Percentage of Subjects				

number (confidence interval 90%)	76.3 (65.81 to 84.71)	61.3 (50.7 to 71.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response

End point title	Duration of Objective Response[7]

End point description:

Duration of objective response was defined as the time from the first occurrence of a documented objective response to documented disease progression or death from any cause, whichever occurred first. Objective response was defined as a CR or a PR according to RECIST v1.1. CR was defined as complete disappearance of all target lesions and non-target disease. PR was defined as a >=30% decrease under baseline of the sum of diametres of all target lesions. All randomised subjects.

End point type	Secondary

End point timeframe:

From the first occurrence of objective response to disease progression or death from any cause (approximately 3 years)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The data in the endpoint was planned to be reported for the reporting groups MEHD7945A and Cetuximab, plus Cetuximab then MEHD7945A (Pre) only.

End point values	MEHD7945A	Cetuximab, plus Cetuximab then MEHD7945A (Pre)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	59	62		
Units: months				
median (confidence interval 90%)	5.42 (3.98 to 5.55)	4.3 (4.14 to 13.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression

End point title	Time to Disease Progression[8]

End point description:

Time to disease progression is defined as the time from randomisation to documented disease progression. Progressive disease was defined as a 20% increase in the sum of the longest diametre of target lesions, the appearance of new lesions and increase of at least 5 mm in the sum of diametres of target lesions. All randomised subjects.

End point type	Secondary

End point timeframe:

From the time of randomisation until disease progression (approximately 3 years)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data in the endpoint was planned to be reported for the reporting groups MEHD7945A and Cetuximab, plus Cetuximab then MEHD7945A (Pre) only.

End point values	MEHD7945A	Cetuximab, plus Cetuximab then MEHD7945A (Pre)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	59	62		
Units: months				
median (confidence interval 90%)	4.63 (4.07 to 5.49)	4.07 (3.38 to 5.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival[9]

End point description:

Overall survival was defined as the time from randomisation to death from any cause. All randomised subjects.

End point type	Secondary

End point timeframe:

From the time of randomisation until death from any cause (approximately 3 years)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data in the endpoint was planned to be reported for the reporting groups MEHD7945A and Cetuximab, plus Cetuximab then MEHD7945A (Pre) only.

End point values	MEHD7945A	Cetuximab, plus Cetuximab then MEHD7945A (Pre)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	59	62		
Units: months				
median (confidence interval 90%)	7.16 (5.29 to 9.23)	8.67 (6.44 to 10.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with an Adverse Event (AE)

End point title	Number of Subjects with an Adverse Event (AE)[10]

End point description:

An AE was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. The safety population included all subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Approximately 3 years

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data in the endpoint was planned to be reported for the reporting groups MEHD7945A, Cetuximab, plus Cetuximab then MEHD7945A (Pre), MEHD7945A, plus Cetuximab then MEHD7945A (Post), Cetuximab, then MEHD7945A (Post) only.

End point values	MEHD7945A	Cetuximab, plus Cetuximab then MEHD7945A (Pre)	MEHD7945A, plus Cetuximab then MEHD7945A (Post)	Cetuximab, then MEHD7945A (Post)
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	59	61	81	22
Units: subjects	58	59	79	21

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Plasma Concentration of MEHD7945A

End point title	Minimum Plasma Concentration of MEHD7945A[11]

End point description:

Subjects who had at least 1 pharmacokinetic assessment. Here 'n' signifies the number of subjects evaluable at specified time points. Here, 99999 indicates geometric mean and geometric co-efficient of variation because more than one-third values are less than reportable.

End point type	Secondary

End point timeframe:

Pre-dose on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 8 Day 1

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data in the endpoint was planned to be reported for the reporting groups MEHD7945A and Cetuximab then MEHD7945A only.

End point values	MEHD7945A	Cetuximab then MEHD7945A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	22		
Units: microgram per milliliter (mcg/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 Pre-dose (n=59,21)	99999 (± 99999)	99999 (± 99999)		
Cycle 2 Day 1 Pre-dose (n=55,21)	31.6 (± 49.3)	49.2 (± 51.5)		

Cycle 3 Day 1 Pre-dose (n=54,17)	53.8 (± 48.9)	52.9 (± 55)		
Cycle 4 Day 1 Pre-dose (n=41,12)	59.5 (± 49)	84.9 (± 46.1)		
Cycle 8 Day 1 Pre-dose (n=13,5)	51 (± 94.8)	115 (± 35.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration of MEHD7945A

End point title	Maximum Plasma Concentration of MEHD7945A[12]

End point description:

Subjects who had at least 1 pharmacokinetic assessment. Here 'n' signifies the number of subjects evaluable at specified time points.

End point type	Secondary

End point timeframe:

30 minutes post-dose on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 8 Day 1

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data in the endpoint was planned to be reported for the reporting groups MEHD7945A and Cetuximab then MEHD7945A only.

End point values	MEHD7945A	Cetuximab then MEHD7945A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	22		
Units: microgram per milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 30 minutes Post-dose (n=58,21)	279 (± 23.2)	195 (± 35.3)		
Cycle 2 Day 1 30 minutes Post-dose (n=54,21)	311 (± 27.4)	362 (± 25)		
Cycle 3 Day 1 30 minutes Post-dose (n=53,17)	356 (± 23.1)	402 (± 25.1)		
Cycle 4 Day 1 30 minutes Post-dose (n=40,12)	344 (± 28.9)	447 (± 30.9)		
Cycle 8 Day 1 30 minutes Post-dose (n=13,4)	319 (± 38.6)	455 (± 12.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a Positive Anti-MEHD7945A Sample

End point title	Percentage of Subjects With a Positive Anti-MEHD7945A Sample[13]

End point description:

Subjects' samples were evaluated at baseline and at post-baseline for anti-therapeutic antibodies. The

analysis population included any subject with an anti-therapeutic antibody sample at baseline and at least one post-baseline sample.

End point type	Secondary

End point timeframe:

Baseline and any time post baseline (approximately 3 years)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data in the endpoint was planned to be reported for the reporting groups MEHD7945A and Cetuximab then MEHD7945A only.

End point values	MEHD7945A	Cetuximab then MEHD7945A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	22		
Units: Percentage of Subjects				
number (not applicable)				
Baseline (n=58,17)	8.6	0		
Post-baseline (n=48,22)	2.1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the randomisation of the first subject to the clinical cutoff date (22JUN2015) (Approximately 3 years)

Adverse event reporting additional description:

An AE was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. The safety population included all subjects who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	All subjects

Reporting group description:

Subjects with R/M SCCHN who had progressed during or following platinum-based chemotherapy received MEHD7945A and cetuximab as documented in the study.

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 120 (38.33%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral artery stenosis			

subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest discomfort				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	2 / 120 (1.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Face oedema				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	2 / 120 (1.67%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Performance status decreased				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ulcer				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory failure			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		

Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Atrioventricular block			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			

subjects affected / exposed	2 / 120 (1.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Epilepsy				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 120 (0.83%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	3 / 120 (2.50%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				

subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mouth haemorrhage			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Oral dysaesthesia			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fistula			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess neck			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Device related infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Lung infection			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Pneumonia necrotising			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory tract infection			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 120 (95.83%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	7 / 120 (5.83%)		
occurrences (all)	18		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	20		
Hypotension			
subjects affected / exposed	7 / 120 (5.83%)		
occurrences (all)	21		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	17 / 120 (14.17%)		
occurrences (all)	58		
Chest pain			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	14		
Chills			
subjects affected / exposed	11 / 120 (9.17%)		
occurrences (all)	38		

Fatigue			
subjects affected / exposed	39 / 120 (32.50%)		
occurrences (all)	132		
Mucosal inflammation			
subjects affected / exposed	18 / 120 (15.00%)		
occurrences (all)	71		
Oedema peripheral			
subjects affected / exposed	9 / 120 (7.50%)		
occurrences (all)	27		
Pain			
subjects affected / exposed	7 / 120 (5.83%)		
occurrences (all)	28		
Pyrexia			
subjects affected / exposed	23 / 120 (19.17%)		
occurrences (all)	74		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	22		
Dyspnoea			
subjects affected / exposed	17 / 120 (14.17%)		
occurrences (all)	51		
Epistaxis			
subjects affected / exposed	7 / 120 (5.83%)		
occurrences (all)	27		
Haemoptysis			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	21		
Productive cough			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	15		
Rhinorrhoea			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	12		
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	4 / 120 (3.33%) 11 5 / 120 (4.17%) 15		
Investigations Weight decreased subjects affected / exposed occurrences (all)	18 / 120 (15.00%) 73		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	4 / 120 (3.33%) 13		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Presyncope subjects affected / exposed occurrences (all)	6 / 120 (5.00%) 22 22 / 120 (18.33%) 90 2 / 120 (1.67%) 8		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	14 / 120 (11.67%) 77		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	3 / 120 (2.50%) 11		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Constipation	5 / 120 (4.17%) 15		

subjects affected / exposed	17 / 120 (14.17%)		
occurrences (all)	83		
Diarrhoea			
subjects affected / exposed	46 / 120 (38.33%)		
occurrences (all)	184		
Dry mouth			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	15		
Dyspepsia			
subjects affected / exposed	7 / 120 (5.83%)		
occurrences (all)	26		
Dysphagia			
subjects affected / exposed	9 / 120 (7.50%)		
occurrences (all)	30		
Mouth ulceration			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	18		
Nausea			
subjects affected / exposed	31 / 120 (25.83%)		
occurrences (all)	163		
Oral pain			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	20		
Stomatitis			
subjects affected / exposed	13 / 120 (10.83%)		
occurrences (all)	44		
Vomiting			
subjects affected / exposed	25 / 120 (20.83%)		
occurrences (all)	144		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	8 / 120 (6.67%)		
occurrences (all)	44		
Dermatitis acneiform			
subjects affected / exposed	26 / 120 (21.67%)		
occurrences (all)	104		

Dry skin			
subjects affected / exposed	19 / 120 (15.83%)		
occurrences (all)	62		
Erythema			
subjects affected / exposed	10 / 120 (8.33%)		
occurrences (all)	56		
Nail discolouration			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	8		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	7 / 120 (5.83%)		
occurrences (all)	26		
Pruritus			
subjects affected / exposed	11 / 120 (9.17%)		
occurrences (all)	43		
Rash			
subjects affected / exposed	37 / 120 (30.83%)		
occurrences (all)	223		
Rash maculo-papular			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	42		
Skin fissures			
subjects affected / exposed	19 / 120 (15.83%)		
occurrences (all)	74		
Skin ulcer			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	13		
Swelling face			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	20		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	11		
Back pain			

subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	20		
Muscle spasms			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	15		
Muscular weakness			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	20		
Myalgia			
subjects affected / exposed	8 / 120 (6.67%)		
occurrences (all)	25		
Neck pain			
subjects affected / exposed	10 / 120 (8.33%)		
occurrences (all)	31		
Pain in jaw			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	23		
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 120 (4.17%)		
occurrences (all)	13		
Candida infection			
subjects affected / exposed	3 / 120 (2.50%)		
occurrences (all)	11		
Conjunctivitis			
subjects affected / exposed	13 / 120 (10.83%)		
occurrences (all)	66		
Oral candidiasis			
subjects affected / exposed	4 / 120 (3.33%)		
occurrences (all)	13		
Paronychia			
subjects affected / exposed	22 / 120 (18.33%)		
occurrences (all)	105		
Pharyngitis			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences (all)	8		

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 120 (17.50%)		
occurrences (all)	68		
Dehydration			
subjects affected / exposed	8 / 120 (6.67%)		
occurrences (all)	25		
Hypokalaemia			
subjects affected / exposed	16 / 120 (13.33%)		
occurrences (all)	65		
Hypomagnesaemia			
subjects affected / exposed	29 / 120 (24.17%)		
occurrences (all)	117		
Hypophosphataemia			
subjects affected / exposed	8 / 120 (6.67%)		
occurrences (all)	29		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2012	Study GO28076 had been amended primarily to address comments and recommendations received from study investigators regarding enrollment of patients who have failed platinum-based therapy and are not eligible for local focal therapy as well as reducing the wash-out period required for non-biologic therapies prior to initiating study treatment. Additional changes had been made to ensure enrollment of at least 80 HPV-negative patients and to align the duration of pregnancy prevention with the duration of safety follow-up.
12 February 2013	Study GO28076 had been amended primarily to update clinical data from the Phase I study, DAF4873g, as of 25 November 2012, including results from QT analyses (see Section 1.2.2) and to add triplicate electrocardiogram (ECG) monitoring for patients treated with MEHD7945A in Arms A and Ax.

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.

Study terminated early by Sponsor in Sep. 2014 due to primary analysis indicating primary endpoint of PFS improvement with MEHD47945A over Cetuximab was not met. One subject remained on MEHD7945A at the investigator’s request until June 2015.

Notes: