



Clinical trial results:

An Open-Label, Multicenter, Randomized, Phase 1b/2 Study of E7050 in Combination with Cetuximab versus Cetuximab Alone in the Treatment of Platinum-Resistant Squamous Cell Carcinoma of the Head and Neck Summary

EudraCT number	2011-000773-31
Trial protocol	GB
Global end of trial date	04 September 2017

Results information

Result version number	v2 (current)
This version publication date	10 March 2022
First version publication date	30 October 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	E7050-702
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01332266
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	300 Tice Boulevard, Woodcliff Lake, New Jersey, United States, 07677
Public contact	Eisai Medical Information, Eisai Inc., +1 888-274-2378, esi_oncmedinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., +1 888-274-2378, esi_oncmedinfo@eisai.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	04 September 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine whether subjects with platinum-resistant squamous cell carcinoma of the head and neck (SCCHN) who receive either Golvatinib (E7050) administered with Cetuximab or Cetuximab alone experience greater benefit.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008). - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312. - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states. - Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Korea, Republic of: 36
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Ukraine: 36
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	95
EEA total number of subjects	0

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)	69
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 28 investigative sites in the Republic of Korea, Ukraine, United Kingdom, and the United States from 19 September 2011 to 04 September 2017.

Pre-assignment

Screening details:

This study consists of two phases Phase 1b and Phase 2. Phase 1b: 12 subjects were enrolled and received the study treatment; Phase 2: 83 subjects were enrolled and received the study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b: Cohort 1: Golvatinib 200 mg + Cetuximab 400 mg/m ²

Arm description:

Subjects with platinum-resistant SCCHN received golvatinib 200 milligram (mg) tablets, orally, once daily (run-in period) and cetuximab 400 milligram per square meter (mg/m²) intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles for determining MTD or RP2D, until the occurrence of progressive disease (PD), unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Cetuximab 400 mg/m ²
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles.

Investigational medicinal product name	Golvatinib 200 mg
Investigational medicinal product code	
Other name	E7050
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received golvatinib 200 mg tablets, orally, once daily (run-in period) of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles.

Arm title	Phase 1b: Cohort 2: Golvatinib 300 mg + Cetuximab 400 mg/m ²
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Arm description:

Subjects with platinum-resistant SCCHN received golvatinib 300 mg tablets, orally, once daily (run-in period) and cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles for determining MTD or RP2D, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Arm type	Experimental
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Investigational medicinal product name	Golvatinib 300 mg
Investigational medicinal product code	
Other name	E7050
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received golvatinib 300 mg tablets, orally, once daily (run-in period) of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles.

Investigational medicinal product name	Cetuximab 400 mg/m ²
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles.

Arm title	Phase 1b: Cohort 3: Golvatinib 400 mg + Cetuximab 400 mg/m ²
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Arm description:

Subjects with platinum-resistant SCCN received golvatinib 400 mg tablets, orally, once daily (run-in period) and cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles for determining MTD or RP2D, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Cetuximab 400 mg/m ²
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles.

Investigational medicinal product name	Golvatinib 400 mg
Investigational medicinal product code	
Other name	E7050
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received golvatinib 400 mg tablets, orally, once daily (run-in period) of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles.

Arm title	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²
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Arm description:

Subjects with platinum-resistant SCCN received golvatinib 400 mg (RP2D) tablets, orally, once daily and cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles. After 6 cycles, at the discretion of the investigator, subjects who experienced clinical benefit could continue for as long as clinical benefit was sustained and the treatment was well tolerated, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Arm type	Experimental
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Investigational medicinal product name	Golvatinib 400 mg
Investigational medicinal product code	
Other name	E7050
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received golvatinib 400 mg (RP2D) tablets, orally, once daily (run-in period) of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles.

Investigational medicinal product name	Cetuximab 400 mg/m ²
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles.

Arm title	Phase 2: Arm 2: Cetuximab 400 mg/m ²
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Arm description:

Subjects with platinum-resistant SCCHN received cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles. After 6 cycles, at the discretion of the Investigator, subjects who experienced clinical benefit could continue for as long as clinical benefit was sustained and the treatment was well tolerated, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Cetuximab 400 mg/m ²
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles.

Number of subjects in period 1	Phase 1b: Cohort 1: Golvatinib 200 mg + Cetuximab 400 mg/m ²	Phase 1b: Cohort 2: Golvatinib 300 mg + Cetuximab 400 mg/m ²	Phase 1b: Cohort 3: Golvatinib 400 mg + Cetuximab 400 mg/m ²
Started	4	5	3
Completed	0	0	0
Not completed	4	5	3
Consent withdrawn by subject	1	1	1
Physician decision	-	-	-
Symptomatic deterioration	-	-	-
Death	3	3	2
Progression Disease	-	-	-
Lost to follow-up	-	1	-

Number of subjects in period 1	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²	Phase 2: Arm 2: Cetuximab 400 mg/m ²
Started	42	41
Completed	0	0
Not completed	42	41
Consent withdrawn by subject	2	2
Physician decision	3	1
Symptomatic deterioration	-	1
Death	33	36
Progression Disease	2	1
Lost to follow-up	2	-

Baseline characteristics

Reporting groups

Reporting group title	Phase 1b: Cohort 1: Golvatinib 200 mg + Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCHN received golvatinib 200 milligram (mg) tablets, orally, once daily (run-in period) and cetuximab 400 milligram per square meter (mg/m²) intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles for determining MTD or RP2D, until the occurrence of progressive disease (PD), unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Reporting group title	Phase 1b: Cohort 2: Golvatinib 300 mg + Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCHN received golvatinib 300 mg tablets, orally, once daily (run-in period) and cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles for determining MTD or RP2D, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Reporting group title	Phase 1b: Cohort 3: Golvatinib 400 mg + Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCHN received golvatinib 400 mg tablets, orally, once daily (run-in period) and cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles for determining MTD or RP2D, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Reporting group title	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCHN received golvatinib 400 mg (RP2D) tablets, orally, once daily and cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles. After 6 cycles, at the discretion of the investigator, subjects who experienced clinical benefit could continue for as long as clinical benefit was sustained and the treatment was well tolerated, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Reporting group title	Phase 2: Arm 2: Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCHN received cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles. After 6 cycles, at the discretion of the Investigator, subjects who experienced clinical benefit could continue for as long as clinical benefit was sustained and the treatment was well tolerated, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Reporting group values	Phase 1b: Cohort 1: Golvatinib 200 mg + Cetuximab 400 mg/m ²	Phase 1b: Cohort 2: Golvatinib 300 mg + Cetuximab 400 mg/m ²	Phase 1b: Cohort 3: Golvatinib 400 mg + Cetuximab 400 mg/m ²
Number of subjects	4	5	3
Age categorical			
Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	70.0 ± 8.29	58.8 ± 12.58	59.3 ± 5.51
Gender categorical Units: Subjects			
Female	2	0	0
Male	2	5	3
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	3	5	3
Unknown or Not Reported	0	0	0
Race Units: Subjects			
Asian	2	3	3
Black or African American	0	1	0
White	2	1	0
Unknown or Not Reported	0	0	0
Eastern Cooperative Oncology Group Performance Status (ECOG PS)			
ECOG PS is used by doctors and researchers to assess how a subject's disease is progressing, assess how the disease affects the daily living activities of the subject and determine appropriate treatment and prognosis. 0=Fully Active (Most Favorable Activity); 1=Restricted activity but ambulatory; 2=Ambulatory but unable to carry out work activities; 3=Limited Self-Care; 4=Completely Disabled, No self-care (Least Favorable Activity); 5=Dead.			
Units: Subjects			
ECOG: 0 (Fully Active)	1	0	0
ECOG: 1(Restricted in Physical Activity; Ambulatory)	3	4	3
ECOG: 2 (Ambulatory and Capable of All Self-care)	0	1	0
ECOG: 3 (Capable of Only Limited Self-care)	0	0	0
ECOG: 4 (Completely Disabled)	0	0	0
ECOG: 5 (Dead)	0	0	0
Not Specified	0	0	0

Reporting group values	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²	Phase 2: Arm 2: Cetuximab 400 mg/m ²	Total
Number of subjects	42	41	95
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	58.4 ± 11.04	53.9 ± 9.84	-
Gender categorical Units: Subjects			
Female	4	7	13
Male	38	34	82

Ethnicity			
Units: Subjects			
Hispanic or Latino	1	0	2
Not Hispanic or Latino	41	41	93
Unknown or Not Reported	0	0	0
Race			
Units: Subjects			
Asian	16	12	36
Black or African American	1	0	2
White	24	29	56
Unknown or Not Reported	1	0	1
Eastern Cooperative Oncology Group Performance Status (ECOG PS)			
ECOG PS is used by doctors and researchers to assess how a subject's disease is progressing, assess how the disease affects the daily living activities of the subject and determine appropriate treatment and prognosis. 0=Fully Active (Most Favorable Activity); 1=Restricted activity but ambulatory; 2=Ambulatory but unable to carry out work activities; 3=Limited Self-Care; 4=Completely Disabled, No self-care (Least Favorable Activity); 5=Dead.			
Units: Subjects			
ECOG: 0 (Fully Active)	10	10	21
ECOG: 1(Restricted in Physical Activity; Ambulatory)	28	24	62
ECOG: 2 (Ambulatory and Capable of All Self-care)	1	3	5
ECOG: 3 (Capable of Only Limited Self-care)	0	0	0
ECOG: 4 (Completely Disabled)	0	0	0
ECOG: 5 (Dead)	0	0	0
Not Specified	3	4	7

End points

End points reporting groups

Reporting group title	Phase 1b: Cohort 1: Golvatinib 200 mg + Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCN received golvatinib 200 milligram (mg) tablets, orally, once daily (run-in period) and cetuximab 400 milligram per square meter (mg/m²) intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles for determining MTD or RP2D, until the occurrence of progressive disease (PD), unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Reporting group title	Phase 1b: Cohort 2: Golvatinib 300 mg + Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCN received golvatinib 300 mg tablets, orally, once daily (run-in period) and cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles for determining MTD or RP2D, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Reporting group title	Phase 1b: Cohort 3: Golvatinib 400 mg + Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCN received golvatinib 400 mg tablets, orally, once daily (run-in period) and cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles for determining MTD or RP2D, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Reporting group title	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCN received golvatinib 400 mg (RP2D) tablets, orally, once daily and cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles. After 6 cycles, at the discretion of the investigator, subjects who experienced clinical benefit could continue for as long as clinical benefit was sustained and the treatment was well tolerated, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Reporting group title	Phase 2: Arm 2: Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCN received cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles. After 6 cycles, at the discretion of the Investigator, subjects who experienced clinical benefit could continue for as long as clinical benefit was sustained and the treatment was well tolerated, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Primary: Phase 1b: Number of Subjects With Dose-limiting Toxicities (DLTs) as Per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v4.0)

End point title	Phase 1b: Number of Subjects With Dose-limiting Toxicities (DLTs) as Per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v4.0) ^{[1][2]}
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End point description:

DLT: adverse events graded as NCI CTCAEv4.0 occurring ≤28 days after treatment. Events as: Non-hematological: 1) Grade ≥3 peripheral neuropathy; 2) Grade 3 fatigue or 2 point decline in ECOG PS that

persisted for >7 days;3)Grade >=3 nausea,vomiting despite optimal antiemetic treatment;4)Any nonhematologic toxicity of Grade >=3,with exceptions as alopecia,single laboratory values out of normal range,hypersensitivity reaction; Hematological 1)Grade 4 neutropenia lasting >7 days; 2)Febrile neutropenia as fever >=38.5 degree celsius with absolute neutrophil count <1.0*10⁹ per liter(/L);3)Grade 3 thrombocytopenia with nontraumatic bleeding requiring platelet transfusion;4)Grade 4 thrombocytopenia with/without nontraumatic bleeding.Safety population:subjects enrolled and randomized to treatment in study,except for those who drop out of the study prior to receiving any study treatment, or were without any safety assessments following the first dose of study treatment.

End point type	Primary
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End point timeframe:

Cycle 1 (Cycle length is equal to [=] 28 days)

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 analysed for this endpoint.

[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: Only data from Phase 1b are included in this endpoint.

End point values	Phase 1b: Cohort 1: Golvatinib 200 mg + Cetuximab 400 mg/m ²	Phase 1b: Cohort 2: Golvatinib 300 mg + Cetuximab 400 mg/m ²	Phase 1b: Cohort 3: Golvatinib 400 mg + Cetuximab 400 mg/m ²	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	5	3	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Plasma Concentration of Golvatinib When Given in Combination With Cetuximab

End point title	Phase 1b: Plasma Concentration of Golvatinib When Given in Combination With Cetuximab ^{[3][4]}
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End point description:

Data was not collected and analyzed for this outcome measure because no pharmacokinetic analysis was conducted in this study due to incomplete pharmacokinetic sample bioanalysis due to unresolved queries leading to inadequate calculations and limited data interpretability.

End point type	Primary
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End point timeframe:

Cycle 1: 0-48 hours post-dose (Each cycle=28 days)

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 analysed for this endpoint.

[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: Only data from Phase 1b are included in this endpoint.

End point values	Phase 1b: Cohort 1: Golvatinib 200 mg + Cetuximab 400 mg/m ²	Phase 1b: Cohort 2: Golvatinib 300 mg + Cetuximab 400 mg/m ²	Phase 1b: Cohort 3: Golvatinib 400 mg + Cetuximab 400 mg/m ²	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[5]	0 ^[6]	0 ^[7]	
Units: Unitless				

Notes:

[5] - Data was not collected and analyzed because no pharmacokinetic analysis was done.

[6] - Data was not collected and analyzed because no pharmacokinetic analysis was done.

[7] - Data was not collected and analyzed because no pharmacokinetic analysis was done.

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Number of Subjects With Grade 3 or Higher Treatment-emergent Adverse Events (TEAEs)

End point title	Phase 2: Number of Subjects With Grade 3 or Higher Treatment-emergent Adverse Events (TEAEs) ^{[8][9]}
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End point description:

TEAEs are defined as an adverse event that has an onset date, or a worsening in severity from baseline (pre-golvatinib), on or after the first dose of golvatinib. The severity was graded according to CTCAE v4.0. Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. Grade 4 Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to adverse event. Safety population: all subjects enrolled and randomized to treatment in study, except for those who drop out of the study prior to receiving any study treatment, or were without any safety assessments following the first dose of study treatment.

End point type	Primary
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End point timeframe:

Up to 5 years 11 months

Notes:

[8] - 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 analysed for this endpoint.

[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: Only data from Phase 2 are included in this endpoint.

End point values	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²	Phase 2: Arm 2: Cetuximab 400 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: subjects	21	21		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Number of Subjects With Markedly Abnormal Vital Sign Values

End point title	Phase 2: Number of Subjects With Markedly Abnormal Vital Sign Values ^{[10][11]}
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End point description:

Safety population was defined as all subjects enrolled and randomized to treatment in study, except for those who drop out of the study prior to receiving any study treatment, or were without any safety assessments following the first dose of study treatment.

End point type	Primary
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End point timeframe:

Up to 4 years 4 months

Notes:

[10] - 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 analysed for this endpoint.

[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: Only data from Phase 2 are included in this endpoint.

End point values	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²	Phase 2: Arm 2: Cetuximab 400 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Number of Subjects With Markedly Abnormal Physical Examinations Findings

End point title	Phase 2: Number of Subjects With Markedly Abnormal Physical Examinations Findings ^{[12][13]}
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End point description:

Physical examination was performed and included evaluation of 1) General appearance, 2) Head; Eyes; Ears; Nose; Throat (HEENT), 3) Neck, 4) Heart, 5) Chest (Including Lungs), 6) Abdomen, 7) Extremities, 8) Skin, 9) Lymph Nodes, and 10) neurological status. Here, number of subjects with markedly abnormal physical examinations were reported. Safety population was defined as all subjects enrolled and randomized to treatment in study, except for those who drop out of the study prior to receiving any study treatment, or were without any safety assessments following the first dose of study treatment.

End point type	Primary
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End point timeframe:

Up to 4 years 4 months

Notes:

[12] - 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 analysed for this endpoint.

[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: Only data from Phase 2 are included in this endpoint.

End point values	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²	Phase 2: Arm 2: Cetuximab 400 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: subjects				
General Appearance	5	6		
HEENT	20	17		
Neck	24	22		
Heart	1	0		
Chest (Including Lungs)	4	5		
Abdomen	6	3		
Extremities	2	0		
Skin	4	5		
Lymph Nodes	13	15		
Neurologic	3	5		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Number of Subjects With Markedly Abnormal Electrocardiogram (ECG) Values

End point title	Phase 2: Number of Subjects With Markedly Abnormal Electrocardiogram (ECG) Values ^{[14][15]}
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End point description:

Safety population was defined as all subjects enrolled and randomized to treatment in study, except for those who drop out of the study prior to receiving any study treatment, or were without any safety assessments following the first dose of study treatment.

End point type	Primary
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End point timeframe:

Up to 4 years 4 months

Notes:

[14] - 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 analysed for this endpoint.

[15] - 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: Only data from Phase 2 are included in this endpoint.

End point values	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²	Phase 2: Arm 2: Cetuximab 400 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Progression-free Survival (PFS)

End point title	Phase 2: Progression-free Survival (PFS) ^[16]
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End point description:

PFS is defined as the time from the date of randomization until the earlier of the following two events: the date of PD or the date of death based on response evaluation criteria in solid tumor (RECIST) version 1.1. PD is defined as at least a 20 percent (%) increase or 5 millimeter (mm) increase in the sum of diameters of target lesions (taking as reference the smallest sum on study) recorded since the treatment started or the appearance of 1 or more new lesions. PFS was estimated and analyzed using Kaplan Meier method. Modified Intent-to-Treat (MITT) analysis set included all subjects randomized in the applicable study arm who received any comparator or study drug. As planned, data for this endpoint was analyzed and collected till primary completion date.

End point type	Secondary
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End point timeframe:

From the date of randomization until the earlier of the following two events: the date of PD or the date of death (Up to approximately 4 years 4 months)

Notes:

[16] - 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: Only data from Phase 2 are included in this endpoint.

End point values	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²	Phase 2: Arm 2: Cetuximab 400 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: weeks				
median (confidence interval 95%)	15.71 (12.14 to 23.86)	15.71 (9.29 to 18.71)		

Statistical analyses

Statistical analysis title	Phase 2: Arm 1; Arm 2
Comparison groups	Phase 2: Arm 2: Cetuximab 400 mg/m ² v Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²

Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.46

Secondary: Phase 2: Percentage of Subjects With PFS at Week 12

End point title	Phase 2: Percentage of Subjects With PFS at Week 12 ^[17]
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End point description:

PFS rate at week 12 was defined as the percentage of subjects who were still alive without disease progression at 12 weeks from the date of randomization. PFS is defined as the time from the date of randomization until the earlier of the following two events: the date of PD or the date of death based on RECIST v1.1. PD is defined as at least a 20% increase or 5 mm increase in the sum of diameters of target lesions (taking as reference the smallest sum on study) recorded since the treatment started or the appearance of 1 or more new lesions. PFS rate was estimated and analyzed using Kaplan Meier method. MITT analysis set included all subjects randomized in the applicable study arm who received any comparator or study drug.

End point type	Secondary
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End point timeframe:

At Week 12

Notes:

[17] - 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: Only data from Phase 2 are included in this endpoint.

End point values	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²	Phase 2: Arm 2: Cetuximab 400 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: percentage of subjects				
number (confidence interval 95%)	68.9 (50.79 to 81.44)	59.4 (41.90 to 73.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Time to Progression (TTP)

End point title	Phase 2: Time to Progression (TTP) ^[18]
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End point description:

TTP is defined as the time from the date of randomization until the date of PD based on RECIST v1.1. PD is defined as at least a 20% increase or 5 mm increase in the sum of diameters of target lesions (taking

as reference the smallest sum on study) recorded since the treatment started or the appearance of 1 or more new lesions. TTP was estimated and analyzed using Kaplan Meier method. MITT analysis set included all subjects randomized in the applicable study arm who received any comparator or study drug. As planned, data for this endpoint was analyzed and collected till primary completion date.

End point type	Secondary
End point timeframe:	
From the date of randomization until the date of PD (Up to approximately 4 years 4 months)	

Notes:

[18] - 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: Only data from Phase 2 are included in this endpoint.

End point values	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²	Phase 2: Arm 2: Cetuximab 400 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: weeks				
median (confidence interval 95%)	15.43 (12.14 to 23.14)	16.00 (9.29 to 19.14)		

Statistical analyses

Statistical analysis title	Phase 2: Arm 1; Arm 2
Comparison groups	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ² v Phase 2: Arm 2: Cetuximab 400 mg/m ²
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.73

Secondary: Phase 2: Overall Survival (OS)

End point title	Phase 2: Overall Survival (OS) ^[19]
End point description:	
OS is defined as the time from the date of randomization until the date of death. OS was analyzed using Kaplan Meier method. MITT analysis set included all subjects randomized in the applicable study arm who received any comparator or study drug. Here "Overall number of subjects analyzed" signifies subjects with events (death). As planned, data for this endpoint was analyzed and collected till primary completion date.	
End point type	Secondary
End point timeframe:	
From the date of randomization until the date of death (Up to approximately 4 years 4 months)	

Notes:

[19] - 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: Only data from Phase 2 are included in this endpoint.

End point values	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²	Phase 2: Arm 2: Cetuximab 400 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	36		
Units: weeks				
median (confidence interval 95%)	39.71 (28.43 to 49.71)	36.71 (28.00 to 44.43)		

Statistical analyses

Statistical analysis title	Phase 2: Arm 1; Arm 2
Comparison groups	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ² v Phase 2: Arm 2: Cetuximab 400 mg/m ²
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.37

Secondary: Phase 2: Percentage of Subjects With Overall Response

End point title	Phase 2: Percentage of Subjects With Overall Response ^[20]
End point description:	
Overall response rate is defined as percentage of subjects with complete response (CR) or partial response (PR) based on RECIST v1.1. CR is defined as the disappearance of all target and non-target lesions (non-lymph nodes). All pathological lymph nodes (whether target or non-target) must have a reduction in their short axis to <10 mm. PR is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. MITT analysis set included all subjects randomized in the applicable study arm who received any comparator or study drug. As planned, data for this endpoint was analyzed and collected till primary completion date.	
End point type	Secondary

End point timeframe:

From the date of randomization until CR or PR (Up to approximately 4 years 4 months)

Notes:

[20] - 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: Only data from Phase 2 are included in this endpoint.

End point values	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²	Phase 2: Arm 2: Cetuximab 400 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: percentage of subjects				
number (confidence interval 95%)	9.5 (0.7 to 18.4)	4.9 (0 to 11.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 5 years 11 months

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Phase 1b: Cohort 1: Golvatinib 200 mg + Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCHN received golvatinib 200 mg tablets, orally, once daily (run-in period) and cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles for determining MTD or RP2D, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Reporting group title	Phase 1b: Cohort 2: Golvatinib 300 mg + Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCHN received golvatinib 300 mg tablets, orally, once daily (run-in period) and cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles for determining MTD or RP2D, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Reporting group title	Phase 1b: Cohort 3: Golvatinib 400 mg + Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCHN received golvatinib 400 mg tablets, orally, once daily (run-in period) and cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles for determining MTD or RP2D, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Reporting group title	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCHN received golvatinib 400 mg (RP2D) tablets, orally, once daily and cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by cetuximab 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles. After 6 cycles, at the discretion of the investigator, subjects who experienced clinical benefit could continue for as long as clinical benefit was sustained and the treatment was well tolerated, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Reporting group title	Phase 2: Arm 2: Cetuximab 400 mg/m ²
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Reporting group description:

Subjects with platinum-resistant SCCHN received cetuximab 400 mg/m² intravenous infusion, once on Day 1 of Cycle 1, followed by 250 mg/m² intravenous infusion, once on Days 8, 15 and 22 of Cycle 1 in a 28-days treatment cycle for up to 6 subsequent cycles. After 6 cycles, at the discretion of the Investigator, subjects who experienced clinical benefit could continue for as long as clinical benefit was sustained and the treatment was well tolerated, until the occurrence of PD, unacceptable toxicity, withdrawal of consent, withdrawal by the investigator, lost to follow-up, or death, whichever occurred first.

Serious adverse events	Phase 1b: Cohort 1: Golvatinib 200 mg + Cetuximab 400 mg/m ²	Phase 1b: Cohort 2: Golvatinib 300 mg + Cetuximab 400 mg/m ²	Phase 1b: Cohort 3: Golvatinib 400 mg + Cetuximab 400 mg/m ²
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	4 / 5 (80.00%)	2 / 3 (66.67%)
number of deaths (all causes)	3	3	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse Drug Reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asphyxia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Aspiration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Aspiration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stridor			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Airway Obstruction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol Poisoning			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Post Procedural Haemorrhage subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericardial Effusion subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Tachycardia subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Depressed Level Of Consciousness subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical Ileus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral Cavity Fistula			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Haemorrhage Subcutaneous			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Back Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain In Jaw			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis Acute			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal Infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²	Phase 2: Arm 2: Cetuximab 400 mg/m ²	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 42 (35.71%)	15 / 41 (36.59%)	
number of deaths (all causes)	33	36	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypotension			

subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
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			
Adverse Drug Reaction			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asphyxia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 42 (2.38%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal Pain			
subjects affected / exposed	1 / 42 (2.38%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	2 / 42 (4.76%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Stridor			
subjects affected / exposed	1 / 42 (2.38%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Airway Obstruction			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol Poisoning			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial Effusion			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus Tachycardia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Depressed Level Of Consciousness			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			

subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 42 (0.00%)	3 / 41 (7.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 42 (4.76%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical Ileus			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral Cavity Fistula			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal Haemorrhage			

subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Vomiting			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Haemorrhage Subcutaneous			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neck Pain			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain In Jaw			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (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			
Cellulitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	3 / 42 (7.14%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis Acute			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Infection			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 42 (2.38%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	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	Phase 1b: Cohort 1: Golvatinib 200 mg + Cetuximab 400 mg/m ²	Phase 1b: Cohort 2: Golvatinib 300 mg + Cetuximab 400 mg/m ²	Phase 1b: Cohort 3: Golvatinib 400 mg + Cetuximab 400 mg/m ²
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	5 / 5 (100.00%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

TUMOUR PAIN subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
Vascular disorders Flushing subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0
Hypertension subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 3	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
General disorders and administration site conditions OEDEMA PERIPHERAL subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	2 / 5 (40.00%) 2	1 / 3 (33.33%) 1
MUCOSAL INFLAMMATION subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
CHEST PAIN subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
Asthenia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 5 (20.00%) 1	1 / 3 (33.33%) 1
FACE OEDEMA subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
LOCALISED OEDEMA subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal Pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	2 / 3 (66.67%)
occurrences (all)	1	0	3
PRODUCTIVE COUGH			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	3 / 4 (75.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
HAEMOPTYSIS			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nasal Ulcer			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
INSOMNIA			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Investigations			
Neutrophil Count Decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	3
PROTEIN TOTAL DECREASED			

subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
WEIGHT DECREASED			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS Worsened			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	9
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	0 / 4 (0.00%)	3 / 5 (60.00%)	0 / 3 (0.00%)
occurrences (all)	0	4	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 3 (66.67%)
occurrences (all)	0	3	2
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
LETHARGY			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Dysgeusia			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 4	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0
Ear and labyrinth disorders Otorrhoea subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
Eye disorders Blepharitis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
Eyelid oedema subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0
Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0
Pinguecula subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
Gastrointestinal disorders ORAL PAIN subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
STOMATITIS subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
Abdominal Pain Upper subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1
Abdominal Pain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	2
Constipation			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	2 / 3 (66.67%)
occurrences (all)	2	1	2
Diarrhoea			
subjects affected / exposed	2 / 4 (50.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	2	1	1
Dyspepsia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Dysphagia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
HAEMORRHOIDS			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Anal pruritus			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Oesophageal ulcer			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
PRURITUS			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	2 / 3 (66.67%)
occurrences (all)	0	1	3

Skin Fissures			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Skin Ulcer			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
DRY SKIN			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
ONYCHOMADESIS			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dermatitis Acneiform			
subjects affected / exposed	3 / 4 (75.00%)	0 / 5 (0.00%)	2 / 3 (66.67%)
occurrences (all)	6	0	3
Erythema			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
POLLAKIURIA			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
PROTEINURIA			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
DYSURIA			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Haematuria			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
BACK PAIN			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Muscle Spasms			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
NECK PAIN			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Periarthritis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Paronychia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
LOWER RESPIRATORY TRACT INFECTION			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
Candida infection subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0
Metabolism and nutrition disorders			
Decreased Appetite subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	2 / 5 (40.00%) 2	1 / 3 (33.33%) 1
HYPERCALCAEMIA subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1
HYPOALBUMINAEMIA subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1
Hypocalcaemia subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	2 / 5 (40.00%) 2	1 / 3 (33.33%) 2
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	2 / 5 (40.00%) 2	0 / 3 (0.00%) 0
Hypomagnesaemia subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 3	1 / 5 (20.00%) 1	1 / 3 (33.33%) 1
HYPONATRAEMIA subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 3 (33.33%) 1
Hypophosphataemia subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 5 (0.00%) 0	2 / 3 (66.67%) 6

Non-serious adverse events	Phase 2: Arm 1: Golvatinib 400 mg + Cetuximab 400 mg/m ²	Phase 2: Arm 2: Cetuximab 400 mg/m ²	
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Total subjects affected by non-serious adverse events subjects affected / exposed	42 / 42 (100.00%)	38 / 41 (92.68%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) TUMOUR PAIN subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 4	2 / 41 (4.88%) 2	
Vascular disorders Flushing subjects affected / exposed occurrences (all) Hypertension subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0 0 / 42 (0.00%) 0	0 / 41 (0.00%) 0 0 / 41 (0.00%) 0	
General disorders and administration site conditions OEDEMA PERIPHERAL subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) MUCOSAL INFLAMMATION subjects affected / exposed occurrences (all) CHEST PAIN subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all) FACE OEDEMA subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) LOCALISED OEDEMA	0 / 42 (0.00%) 0 3 / 42 (7.14%) 3 4 / 42 (9.52%) 6 3 / 42 (7.14%) 3 5 / 42 (11.90%) 5 0 / 42 (0.00%) 0 5 / 42 (11.90%) 5	0 / 41 (0.00%) 0 1 / 41 (2.44%) 2 1 / 41 (2.44%) 1 1 / 41 (2.44%) 1 1 / 41 (2.44%) 1 0 / 41 (0.00%) 0 5 / 41 (12.20%) 5	

subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 41 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
PRODUCTIVE COUGH			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Epistaxis			
subjects affected / exposed	3 / 42 (7.14%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
Dyspnoea			
subjects affected / exposed	1 / 42 (2.38%)	3 / 41 (7.32%)	
occurrences (all)	1	3	
Cough			
subjects affected / exposed	3 / 42 (7.14%)	2 / 41 (4.88%)	
occurrences (all)	3	2	
HAEMOPTYSIS			
subjects affected / exposed	2 / 42 (4.76%)	3 / 41 (7.32%)	
occurrences (all)	2	3	
Nasal Ulcer			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	3 / 42 (7.14%)	1 / 41 (2.44%)	
occurrences (all)	3	1	
INSOMNIA			
subjects affected / exposed	1 / 42 (2.38%)	3 / 41 (7.32%)	
occurrences (all)	1	3	
Substance-induced psychotic disorder			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Investigations			

Neutrophil Count Decreased subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 41 (0.00%) 0	
PROTEIN TOTAL DECREASED subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 41 (0.00%) 0	
WEIGHT DECREASED subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 6	3 / 41 (7.32%) 3	
EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS Worsened subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	3 / 41 (7.32%) 3	
Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	10 / 42 (23.81%) 12	3 / 41 (7.32%) 3	
Blood Alkaline Phosphatase Increased subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 4	0 / 41 (0.00%) 0	
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	0 / 41 (0.00%) 0	
Aspartate Aminotransferase Increased subjects affected / exposed occurrences (all)	10 / 42 (23.81%) 10	2 / 41 (4.88%) 3	
Injury, poisoning and procedural complications Hip fracture subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 41 (0.00%) 0	
Nervous system disorders LETHARGY subjects affected / exposed occurrences (all) Dizziness	3 / 42 (7.14%) 4	1 / 41 (2.44%) 2	

subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 41 (0.00%) 0	
Dysgeusia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	0 / 41 (0.00%) 0	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 41 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 5	5 / 41 (12.20%) 6	
Ear and labyrinth disorders Otorrhoea subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 41 (0.00%) 0	
Eye disorders Blepharitis subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 41 (0.00%) 0	
Eyelid oedema subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 41 (0.00%) 0	
Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 41 (0.00%) 0	
Pinguecula subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 41 (0.00%) 0	
Gastrointestinal disorders ORAL PAIN subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 4	0 / 41 (0.00%) 0	
STOMATITIS subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	2 / 41 (4.88%) 3	
Abdominal Pain Upper			

subjects affected / exposed	3 / 42 (7.14%)	1 / 41 (2.44%)	
occurrences (all)	3	1	
Abdominal Pain			
subjects affected / exposed	4 / 42 (9.52%)	1 / 41 (2.44%)	
occurrences (all)	8	1	
Nausea			
subjects affected / exposed	19 / 42 (45.24%)	3 / 41 (7.32%)	
occurrences (all)	35	3	
Constipation			
subjects affected / exposed	10 / 42 (23.81%)	3 / 41 (7.32%)	
occurrences (all)	13	3	
Diarrhoea			
subjects affected / exposed	10 / 42 (23.81%)	4 / 41 (9.76%)	
occurrences (all)	22	4	
Dyspepsia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Dysphagia			
subjects affected / exposed	5 / 42 (11.90%)	2 / 41 (4.88%)	
occurrences (all)	6	2	
HAEMORRHOIDS			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	14 / 42 (33.33%)	2 / 41 (4.88%)	
occurrences (all)	19	2	
Anal pruritus			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Oesophageal ulcer			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
PRURITUS			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	

Rash			
subjects affected / exposed	19 / 42 (45.24%)	8 / 41 (19.51%)	
occurrences (all)	22	9	
Skin Fissures			
subjects affected / exposed	4 / 42 (9.52%)	0 / 41 (0.00%)	
occurrences (all)	5	0	
Skin Ulcer			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
DRY SKIN			
subjects affected / exposed	5 / 42 (11.90%)	1 / 41 (2.44%)	
occurrences (all)	7	1	
RASH MACULO-PAPULAR			
subjects affected / exposed	4 / 42 (9.52%)	5 / 41 (12.20%)	
occurrences (all)	5	12	
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	3 / 42 (7.14%)	2 / 41 (4.88%)	
occurrences (all)	4	2	
ONYCHOMADESIS			
subjects affected / exposed	1 / 42 (2.38%)	3 / 41 (7.32%)	
occurrences (all)	1	3	
Dermatitis Acneiform			
subjects affected / exposed	10 / 42 (23.81%)	7 / 41 (17.07%)	
occurrences (all)	17	9	
Erythema			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
POLLAKIURIA			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
PROTEINURIA			
subjects affected / exposed	6 / 42 (14.29%)	2 / 41 (4.88%)	
occurrences (all)	7	2	
DYSURIA			

subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Haematuria			
subjects affected / exposed	3 / 42 (7.14%)	1 / 41 (2.44%)	
occurrences (all)	4	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
BACK PAIN			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Muscle Spasms			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
NECK PAIN			
subjects affected / exposed	3 / 42 (7.14%)	2 / 41 (4.88%)	
occurrences (all)	3	2	
PAIN IN EXTREMITY			
subjects affected / exposed	3 / 42 (7.14%)	1 / 41 (2.44%)	
occurrences (all)	4	1	
Periarthritis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Paronychia			
subjects affected / exposed	4 / 42 (9.52%)	0 / 41 (0.00%)	
occurrences (all)	10	0	
Upper Respiratory Tract Infection			

subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 42 (7.14%)	1 / 41 (2.44%)	
occurrences (all)	3	1	
Candida infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	10 / 42 (23.81%)	3 / 41 (7.32%)	
occurrences (all)	12	3	
HYPERCALCAEMIA			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Hyperglycaemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
HYPOALBUMINAEMIA			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Hypocalcaemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Hypokalaemia			
subjects affected / exposed	3 / 42 (7.14%)	2 / 41 (4.88%)	
occurrences (all)	4	2	
Hypomagnesaemia			
subjects affected / exposed	2 / 42 (4.76%)	3 / 41 (7.32%)	
occurrences (all)	3	5	
HYPONATRAEMIA			
subjects affected / exposed	0 / 42 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Hypophosphataemia			

subjects affected / exposed	3 / 42 (7.14%)	1 / 41 (2.44%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2011	Amendment 01: The maximum dose to be tested was changed from 360 mg to 400 mg (with additional information in the Introduction to justify the change). Additional PK sampling times were added. For subjects experiencing clinical benefit after six cycles, continuing treatment was changed from cetuximab with or without golvatinib to golvatinib with or without cetuximab or cetuximab alone, depending on original treatment arm. Revised procedure for crushing tablets. Changed time for radiological scans from every two cycles to every eight weeks for the first six cycles and then at least every 12 weeks thereafter. Added efficacy endpoints to be used for evaluation of the secondary objective. Added postdose PK samples for Day 8 and 15 of Cycle 1 and Day 1 of all subsequent cycles in Phase 1b. Added nonoptional predose PK trough samples to Day 1, Day 15, and Day 22 of Cycle 1 and Day 1 of all subsequent cycles of Phase 2. Added nonoptional predose blood sample to Day 1 of all cycles for cetuximab immunogenicity determination. Specified that subjects should arrive at clinic in a fasted state on days that PK samples were to be drawn. Added visit schedule modification for subjects continuing beyond Cycle 6. Added 4-week washout period from any previous anticancer therapy (Exclusion Criterion 4). Added active hemoptysis as an exclusion criterion. Allowed for intrasubject dose escalation of golvatinib in Phase 1b in consultation with the Medical Monitor and provided the next highest dose had been deemed tolerable. Changed frequency of pregnancy test in female subjects of childbearing potential. Clarified that if one agent was held for toxicity, the other agent may have been continued as long as toxicity for the second agent was not suspected. The role of the DSMC was clarified.
14 October 2011	Amendment 02: The Introduction was updated with new PK data. Changed the golvatinib sampling period from Day -7 through Day -4 of Cycle 1 in Phase 1b to Day -2 and -1 of Cycle 1. Removed serial PK sampling on Days 1 and 2 of Cycle 1 for both Phase 1b and the optional Phase 2 sampling. A "Rationale for the Current Study" subsection was added to the Introduction. Clarified that after discontinuation of study treatment, follow-up would be until death. Clarified treatment options for subjects continuing past Cycle 6. Clarified prior cetuximab treatment allowed in Phase 1b, only allowed in Phase 2 if administered in combination with radiotherapy. Changed to allow prior antiangiogenic therapy in Phase 1b. Clarified that subjects could take golvatinib with or without food and clarified for subjects on golvatinib who experienced nausea to take golvatinib with food and antiemetic therapy per local guidelines and Investigator practice. Updated the definition of SAEs to conform with new FDA guidelines.
17 September 2012	Amendment 03: Added disease progression to Section 4.4.3 "Patient Withdrawal". Clarified that for subjects participating in the optional PK sampling, the predose samples on Days 15 and 22 of Cycle 1 would serve as the nonoptional predose trough samples. Provided language clarifying the use of anti-emetics medication to Section 5.1.4 "Precautions". Provided guidance for treatment of subjects with elevated alkaline phosphatase to Section 5.1.4 "Precautions". Modified the cetuximab supply information. Moved the caution for subjects who were taking drugs that were strong or moderate inhibitors and/or inducers of cytochrome P450 3A4 from excluded medications to allowed medications. Clarified that progression of disease would not be considered an AE or SAE. Clarified that if iodinated CT contrast was contraindicated, CT of the chest may have been performed without IV contrast.
05 November 2014	Amendment 04: Removed the long-term overall survival follow-up. Revised language requiring central reading of radiological scans. Revised language regarding scans after the first 6 treatment cycles. After the first 6 treatment cycles, radiological scans will be in accordance with local institutional guidelines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

No pharmacokinetic analysis was conducted in this study due to incomplete pharmacokinetic sample bioanalysis due to unresolved queries leading to inadequate calculations and limited data interpretability.
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Notes: