Clinical trial results:
A Phase 2, Multicenter, International, Single Arm Study to Assess the Safety and Efficacy of Single Agent CC-486 (Oral Azacitidine) in Previously Treated Subjects With Locally Advanced or Metastatic Nasopharyngeal Carcinoma

Summary

EudraCT number	2014-001745-25
Trial protocol	ES GR IT
Global end of trial date	20 April 2017

Results information

Result version number	v2 (current)
This version publication date	14 June 2018
First version publication date	02 May 2018
Version creation reason	• Correction of full data set One of the Baseline Characteristics unit type was corrected.

Trial information

Trial identification

Sponsor protocol code	CC-486-NPC-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02269943
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, United States, 07901
Public contact	Clinical Trial Disclosure, Celgene Corporation, 01 888-260-1599, ClinicalTrialDisclosure@Celgene.com
Scientific contact	Ileana Elias, MD, Celgene Corporation, 01 647-968-4300, Ilelias@Celgene.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	08 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 April 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of CC-486 in subjects with nasopharyngeal carcinoma (NPC)

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection and Pharmacokinetic Consent; this study was conducted in accordance with the guidelines of current Good Clinical Practice including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 February 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	28 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Tunisia: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Spain: 7
Worldwide total number of subjects	36
EEA total number of subjects	22

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)	29
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multicenter study with 17 sites from the United States, Canada, France. Greece, Italy, Spain, Taiwan, Singapore and Tunisia.

Pre-assignment

Screening details:

Participants were enrolled according to a Simon 2-stage design. The first 6 participants of Asian-Pacific Island ethnicity received 200 mg/day CC-486 on days 1-14 of each 21-day cycle to monitor safety and tolerability; if there were no safety concerns, subsequent participants of Asian-Pacific Island ethnicity would receive the 300 mg daily dose

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CC-486 200 mg

Arm description:

Asian-Pacific island participants received CC-486 200 mg tablets by mouth (PO) on days 1-14 of each 21-day cycle until radiologic disease progression, unacceptable toxicity, adverse event, a new anticancer therapy is begun, withdrawal of consent, subject refusal, physician decision, or death. If well tolerated, and there were no safety concerns, subsequent participants of Asian-Pacific Island ethnicity were administered CC-486 300-mg PO daily for 14 days of a 21-day cycle. Subjects completed the study in accordance with protocol guidelines.

Arm type	Experimental
Investigational medicinal product name	CC-486
Investigational medicinal product code	
Other name	Oral Azacitidine
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

CC-486 200 mg tablets on Days 1-14 of each 21-day treatment cycle

Arm title	CC-486 300 mg

Arm description:

Participants received CC-486 300 mg tablets by mouth on days 1-14 of each 21-day cycle until radiologic disease progression, unacceptable toxicity, adverse event (AE), a new anticancer therapy is begun, withdrawal of consent, subject refusal, physician decision, or death. Subjects completed the study in accordance with protocol guidelines.

Arm type	Experimental
Investigational medicinal product name	CC-486
Investigational medicinal product code	
Other name	Oral Azacitidine
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

CC-486 300 mg tablets on Days 1 to 14 of each 21-day treatment cycle

Number of subjects in period 1	CC-486 200 mg	CC-486 300 mg
Started	6	30
Study Drug Discontinued	6	30
Completed	0	0
Not completed	6	30
Adverse event, serious fatal	-	1
Adverse event, non-fatal	1	10
Progressive Disease	5	17
Symptomatic Deterioration	-	2

Baseline characteristics

Reporting groups	
Reporting group title	CC-486 200 mg
Reporting group description:	
Asian-Pacific island participants received CC-486 200 mg tablets by mouth (PO) on days 1-14 of each 21-day cycle until radiologic disease progression, unacceptable toxicity, adverse event, a new anticancer therapy is begun, withdrawal of consent, subject refusal, physician decision, or death. If well tolerated, and there were no safety concerns, subsequent participants of Asian-Pacific Island ethnicity were administered CC-486 300-mg PO daily for 14 days of a 21-day cycle. Subjects completed the study in accordance with protocol guidelines.	
Reporting group title	CC-486 300 mg
Reporting group description:	
Participants received CC-486 300 mg tablets by mouth on days 1-14 of each 21-day cycle until radiologic disease progression, unacceptable toxicity, adverse event (AE), a new anticancer therapy is begun, withdrawal of consent, subject refusal, physician decision, or death. Subjects completed the study in accordance with protocol guidelines.	

Reporting group values	CC-486 200 mg	CC-486 300 mg	Total
Number of subjects	6	30	36
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	25	29
From 65-84 years	2	5	7
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	53.2	52.2	
standard deviation	± 11.70	± 11.60	-
Sex: Female, Male Units: Subjects			
Female	2	5	7
Male	4	25	29
Race/Ethnicity, Customized Units: Subjects			
Asian|	6	7	13
White|	0	23	23
Race/Ethnicity, Customized Units: Subjects			
Hispanic|	0	0	0
Non-Hispanic or Latino|	6	30	36
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG performance status 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)			
Units: Subjects			
0 = Fully Active|	4	11	15
1 = Restrictive but ambulatory|	2	18	20
2 = Ambulatory but unable to work|	0	1	1
3 = Limited Self-Care|	0	0	0
Nasopharyngeal Cancer (NPC) Diagnosis Types			
The 3 types of NPC, based on how the cancer cells look under the microscope include: 1. Undifferentiated Nasopharyngeal Carcinoma 2. Poorly Differentiated Nasopharyngeal Carcinoma 3. Other			
Units: Subjects			
Undifferentiated Nasopharyngeal Carcinoma|	2	21	23
Poorly Differentiated Nasopharyngeal Carcinoma|	2	9	11
Other|	2	0	2
Participants with Prior Anti-Cancer Therapies			
Units: Subjects			
Prior Systemic Anticancer Therapy	6	29	35
No Prior Anticancer Therapy	0	1	1
Time From Initial Diagnosis to First Dose			
Units: years			
arithmetic mean	3.60	3.86	
standard deviation	± 3.204	± 3.358	-

End points

End points reporting groups

Reporting group title	CC-486 200 mg

Reporting group description:

Asian-Pacific island participants received CC-486 200 mg tablets by mouth (PO) on days 1-14 of each 21-day cycle until radiologic disease progression, unacceptable toxicity, adverse event, a new anticancer therapy is begun, withdrawal of consent, subject refusal, physician decision, or death. If well tolerated, and there were no safety concerns, subsequent participants of Asian-Pacific Island ethnicity were administered CC-486 300-mg PO daily for 14 days of a 21-day cycle. Subjects completed the study in accordance with protocol guidelines.

Reporting group title	CC-486 300 mg

Reporting group description:

Participants received CC-486 300 mg tablets by mouth on days 1-14 of each 21-day cycle until radiologic disease progression, unacceptable toxicity, adverse event (AE), a new anticancer therapy is begun, withdrawal of consent, subject refusal, physician decision, or death. Subjects completed the study in accordance with protocol guidelines.

Primary: Percentage of Participants who Achieved a Complete or Partial Response According to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Based on an Independent Radiology Assessment (IRA)

End point title	Percentage of Participants who Achieved a Complete or Partial Response According to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Based on an Independent Radiology Assessment (IRA)[1]

End point description:

Overall response rate was defined as the percentage of participants with a Complete Response (CR) or Partial Response (PR), confirmed no less than 4 weeks after the criteria for response were first met, based on independent radiology assessment according to RECIST 1.1 criteria. Complete response was defined as the disappearance of all target lesions and non-target lesions; Partial response is at least a 30% decrease from baseline in the sum of diameters of target lesions with no progression of non-target lesions and no new lesions or disappearance of target lesions with persistence of one or more non-target lesions from baseline. The Efficacy Evaluable Population (EEP) included all enrolled participants who met eligibility criteria and either received 2 cycles of CC-486 at any dose and discontinued treatment for progressive disease (PD) or received 4 cycles of CC-486 and had a baseline and at least 2 post-screening tumor assessments.

End point type	Primary

End point timeframe:

Tumor response was assessed every (Q) 6 weeks for the first 3 evaluations then Q 9 weeks until disease progression. As of the cut-off date of 08 August 2017; the median duration of treatment was 257 days for the 200 mg dose and 114.5 days for 300 mg dose

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: Since this is an open-label, single arm study with limited sample size, treatment comparisons are not applicable. Therefore no formal statistical analyses were conducted.

End point values	CC-486 200 mg	CC-486 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[2]	20		
Units: percentage of participants				
number (confidence interval 90%)	0 (-99999 to 99999)	15.0 (4.2 to 34.4)		

Notes:

[2] - 99999 = Confidence Interval (CI) could not be calculated due to zero subjects with a response.

Statistical analyses

No statistical analyses for this end point

Primary: Kaplan Meier Estimate of Progression-Free Survival (PFS) Based on an Independent Radiology Assessment According to RECIST 1.1 Criteria

End point title	Kaplan Meier Estimate of Progression-Free Survival (PFS) Based on an Independent Radiology Assessment According to RECIST 1.1 Criteria[3]

End point description:

PFS was defined as the time from the first day of the study treatment to the date of disease progression or death (any cause) on or prior to the data cut-off date for the statistical analysis, whichever occurred earlier, based on an independent radiology assessment of response using RECIST v1.1 criteria. Progressive disease was defined as at least a 20% increase in the sum of diameters of target or non-target lesions from nadir or appearance of a new lesion. The Efficacy Evaluable Population included all enrolled participants who met eligibility criteria and either received 2 cycles of CC-486 at any dose and discontinued treatment for progressive disease or received 4 cycles of CC-486 and had a baseline and at least 2 post-screening tumor assessments.

End point type	Primary

End point timeframe:

From Day 1 of study drug up to the data cut off date of 08 August 2017; median follow-up time for censored participants was 12.3 months

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: Since this is an open-label, single arm study with limited sample size, treatment comparisons are not applicable. Therefore no formal statistical analyses were conducted.

End point values	CC-486 200 mg	CC-486 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[4]	20		
Units: months				
median (confidence interval 90%)	6.2 (1.4 to 99999)	4.4 (1.6 to 7.3)		

Notes:

[4] - 99999 = Upper limit of the confidence interval (CI) was not reached due to limited number of events

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimate of Overall Survival

End point title	Kaplan Meier Estimate of Overall Survival

End point description:

Overall survival was the time from the first dose of study drug to patient death from any cause. Participants who did not die were censored at the last known time the patient was alive date or the clinical data cutoff date, whichever was earlier. The Efficacy Evaluable Population included all enrolled participants who met eligibility criteria and either received 2 cycles of CC-486 at any dose and discontinued treatment for progressive disease or received 4 cycles of CC-486 and had a baseline and at

least 2 post-screening tumor assessments.

End point type	Secondary

End point timeframe:

From Day 1 of study treatment to the first date of progressive disease or death; up to data cut-off date of 08 August 2017; overall median follow-up time for censored participants was 20.4 months

End point values	CC-486 200 mg	CC-486 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[5]	20[6]		
Units: months				
median (confidence interval 90%)	18.0 (15.9 to 99999)	99999 (12.5 to 999999)		

Notes:

[5] - 99999 = The upper limit of the CI for PFS could not be calculated due to limited number of events

[6] - 99999= The median and upper limits of the CI could not be calculated due to limited number of events

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Stable Disease for ≥ 16 Weeks from the Date of the First Treatment, or CR or PR According to RECIST 1.1 Criteria and Based on an Independent Radiology Assessment

End point title	Percentage of Participants with Stable Disease for ≥ 16 Weeks from the Date of the First Treatment, or CR or PR According to RECIST 1.1 Criteria and Based on an Independent Radiology Assessment

End point description:

Disease Control Rate (DCR) was defined as the percentage of participants with a CR, PR, confirmed ≥ 4 weeks after the criteria for response were first met or stable disease for ≥ 16 weeks from the first treatment, based on IRA using RECIST 1.1 criteria. A complete response was defined as the disappearance of all target lesions and non-target lesions; a partial response was defined as at least a 30% decrease from baseline in the sum of diameters of target lesions with no progression of non-target lesions and no new lesions or disappearance of target lesions with persistence of one or more non-target lesions from baseline; stable disease was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase of lesions to qualify for PD. The EEP = all enrolled participants who met eligibility and either received 2 cycles of CC-486 at any dose and discontinued CC-486 for PD or received 4 cycles of CC-486 and had a baseline and at least 2 post-screening tumor assessments.

End point type	Secondary

End point timeframe:

Tumor response was assessed every 6 weeks for the first 3 evaluations then every 9 weeks until disease progression. As of the cut-off date of 08 August 2017 the median duration of treatment was 257 days for the 200 mg dose and 114.5 days for 300 mg dose

End point values	CC-486 200 mg	CC-486 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	20		
Units: percentage of participants				
median (confidence interval 90%)	60.0 (18.9 to 92.4)	50.0 (30.2 to 69.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment Emergent Adverse Events

End point title	Number of Participants with Treatment Emergent Adverse Events

End point description:

Treatment-emergent adverse events (TEAEs) were defined as any adverse event (AE) or serious adverse event (SAE) that occurred or worsened on or after the day of the first dose of the investigational product (IP) through 28 days after the last dose of IP. In addition, any SAE with an onset date more than 28 day after the last dose of IP that was assessed by the investigator as related to IP was considered a TEAE. The severity of AEs was graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 and based on the following scale: Grade 1 = Mild Grade 2 = Moderate Grade 3 = Severe Grade 4 = Life threatening Grade 5 = Death.

End point type	Secondary

End point timeframe:

From date of first dose of study treatment to 28 days after last dose of study treatment; up to final data cut-off date of 08 August 2017; median treatment duration was 257 days for CC-486 200 mg and 114.5 days for CC-486 300 mg

End point values	CC-486 200 mg	CC-486 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	30		
Units: Participants				
Any TEAE|	6	30		
Any TEAE Related to IP|	6	28		
Any Serious TEAE|	4	12		
Any Serious TEAE Related to IP|	3	7		
Any CTCAE Grade 3 or 4 TEAE|	6	20		
Any CTCAE Grade 3 or 4 TEAE Related to IP|	6	16		
Any TEAE Leading to Death|	1	1		
Any TEAE Leading to Dose Reduction|	5	9		
Any TEAE Leading to Drug Interruption|	4	9		
Any TEAE Leading to IP Discontinuation|	1	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve from Time 0 to the Time of the Last Quantifiable Concentration Of CC-486 (AUC-t)

End point title	Area Under the Plasma Concentration-time Curve from Time 0 to the Time of the Last Quantifiable Concentration Of CC-486 (AUC-t)

End point description:

Area under the plasma concentration-time curve from Time 0 to the time of the last quantifiable concentration, calculated by linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing. The PK population includes participants with evaluable CC-486 plasma PK profiles.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 1 Day 14

End point values	CC-486 200 mg	CC-486 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	30		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1|	390.0 (± 58.8)	351.7 (± 87.5)		
Cycle 1 Day 14|	130.3 (± 995.5)	461.3 (± 104.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration -Time Curve from 0 Extrapolated to Infinity (AUC-inf, AUC0-∞) Of CC-486

End point title	Area Under the Plasma Concentration -Time Curve from 0 Extrapolated to Infinity (AUC-inf, AUC0-∞) Of CC-486

End point description:

Area under the plasma concentration-time curve from Time 0 extrapolated to infinity, calculated as [AUCt + Ct/ λz]. Ct is the last quantifiable concentration. No AUC extrapolation was performed with unreliable λz. If AUC %Extrap was ≥25%, AUC inf was not reported. The PK population includes participants with evaluable CC-486 plasma PK profiles.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 1 Day 14

End point values	CC-486 200 mg	CC-486 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	30		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1|	392.5 (± 58.3)	354.9 (± 87.1)		
Cycle 1 Day 14|	138.0 (± 802.1)	466.0 (± 104.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) Of CC-486

End point title	Maximum Observed Concentration (Cmax) Of CC-486

End point description:

Maximum observed plasma concentration, obtained directly from the observed concentration versus time data. The PK population includes participants with evaluable CC-486 plasma PK profiles.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 1 Day 14

End point values	CC-486 200 mg	CC-486 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	30		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1|	266.3 (± 53.8)	170.7 (± 95.0)		
Cycle 1 Day 14|	102.7 (± 412.0)	287.0 (± 50.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Concentration (Tmax) Of CC-486

End point title	Time to Reach Maximum Concentration (Tmax) Of CC-486

End point description:

Time to Cmax, obtained directly from the observed concentration versus time data. The PK population includes participants with evaluable CC-486 plasma PK profiles.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 1 Day 14

End point values	CC-486 200 mg	CC-486 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	30		
Units: Hours				
median (full range (min-max))				
Cycle 1 Day 1|	1.0 (0.50 to 1.5)	1.3 (0.50 to 1.5)		
Cycle 1 Day 14|	1.0 (0.0 to 2.0)	1.0 (0.50 to 3.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-Life (t1/2) of CC-486

End point title	Terminal Half-Life (t1/2) of CC-486

End point description:

Terminal phase half-life in plasma, calculated as [(ln 2)/λz]. t1/2 was only calculated when a reliable estimate for λz could be obtained. The PK population includes participants with evaluable CC-486 plasma PK profiles.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 1 Day 14

End point values	CC-486 200 mg	CC-486 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	30		
Units: Hours				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1|	0.562 (± 23.1)	0.635 (± 24.2)		
Cycle 1 Day 14|	0.584 (± 17.2)	0.640 (± 32.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Total Clearance (CL/F) Of CC-486

End point title	Apparent Total Clearance (CL/F) Of CC-486

End point description:

Apparent volume of distribution, calculated as [(CL/F)/λz]. The PK population includes participants with evaluable CC-486 plasma PK profiles.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 1 Day 14

End point values	CC-486 200 mg	CC-486 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	30		
Units: Liters/hour				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1| Cycle 1 Day 14|	509.5 (± 58.3) 1450 (± 802.1)	845.3 (± 87.1) 643.7 (± 104.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (Vz/F) Of CC-486

End point title	Apparent Volume of Distribution (Vz/F) Of CC-486

End point description:

Apparent volume of distribution, calculated as [(CL/F)/λz]. The PK population includes participants with evaluable CC-486 plasma PK profiles.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 1 Day 14

End point values	CC-486 200 mg	CC-486 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	30		
Units: Liters				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1| Cycle 1 Day 14|	412.9 (± 42.9) 1221 (± 581.3)	774.6 (± 78.6) 594.8 (± 69.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 of CC-486 until 28 days after the last dose and those SAEs made known to the Investigator at any time thereafter that are suspected of being related to CC-486; up to final cut-off date of 08 August 2017

Adverse event reporting additional description:

Median duration of study treatment was 257 days for CC-486 200 mg and 114.5 days for CC-486 300 mg

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	CC-486 300 mg

Reporting group description:

Participants received CC-486 300 mg tablets by mouth on days 1-14 of each 21-day cycle until radiologic disease progression, unacceptable toxicity, adverse event (AE), a new anticancer therapy is begun, withdrawal of consent, subject refusal, physician decision, or death.

Reporting group title	CC-486 200 mg

Reporting group description:

Asian-Pacific island participants received CC-486 200 mg tablets by mouth (PO) on days 1-14 of each 21-day cycle until radiologic disease progression, unacceptable toxicity, adverse event, a new anticancer therapy is begun, withdrawal of consent, subject refusal, physician decision, or death. If well tolerated, and there were no safety concerns, subsequent participants of Asian-Pacific Island ethnicity were administered CC-486 300-mg PO daily for 14 days of a 21-day cycle

Serious adverse events	CC-486 300 mg	CC-486 200 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 30 (40.00%)	4 / 6 (66.67%)	
number of deaths (all causes)	18	4	
number of deaths resulting from adverse events	0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 30 (0.00%)	2 / 6 (33.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Brain oedema			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 30 (6.67%)	2 / 6 (33.33%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Cataract			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (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			
Septic shock			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia			

subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 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	CC-486 300 mg	CC-486 200 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 30 (96.67%)	6 / 6 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Asthenia			
subjects affected / exposed	8 / 30 (26.67%)	0 / 6 (0.00%)	
occurrences (all)	20	0	
Facial pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	5 / 30 (16.67%)	3 / 6 (50.00%)	
occurrences (all)	10	3	
Hypothermia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	3	
Non-cardiac chest pain			

subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Oedema peripheral			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	8 / 30 (26.67%)	1 / 6 (16.67%)	
occurrences (all)	11	2	
Reproductive system and breast disorders			
Menstrual disorder			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Cough			
subjects affected / exposed	6 / 30 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	7	1	
Nasal congestion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Rhinorrhoea			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Anxiety			

subjects affected / exposed	3 / 30 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 30 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	7	1	
Alanine aminotransferase increased			
subjects affected / exposed	5 / 30 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	15	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 30 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Blood creatinine increased			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	1	2	
C-reactive protein increased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Neutrophil count decreased			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	1	2	
Weight decreased			
subjects affected / exposed	5 / 30 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	10	0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	

Dizziness			
subjects affected / exposed	3 / 30 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	4	1	
Facial paralysis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hypoaesthesia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	2 / 30 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Neuropathy peripheral			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 30 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	10	3	
Leukopenia			
subjects affected / exposed	4 / 30 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	9	0	
Neutropenia			
subjects affected / exposed	9 / 30 (30.00%)	3 / 6 (50.00%)	
occurrences (all)	24	12	
Thrombocytopenia			
subjects affected / exposed	3 / 30 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	9	2	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Ear pain			

subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
Eye oedema			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Abdominal distension			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	10 / 30 (33.33%)	1 / 6 (16.67%)	
occurrences (all)	18	1	
Abdominal pain upper			
subjects affected / exposed	3 / 30 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Dental caries			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	10 / 30 (33.33%)	3 / 6 (50.00%)	
occurrences (all)	17	6	
Dyspepsia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Dysphagia			
subjects affected / exposed	4 / 30 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Inguinal hernia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nausea			

subjects affected / exposed	18 / 30 (60.00%)	6 / 6 (100.00%)	
occurrences (all)	36	9	
Stomatitis			
subjects affected / exposed	4 / 30 (13.33%)	2 / 6 (33.33%)	
occurrences (all)	4	3	
Oesophagitis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Toothache			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	23 / 30 (76.67%)	3 / 6 (50.00%)	
occurrences (all)	47	7	
Skin and subcutaneous tissue disorders			
Pain of skin			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Decubitus ulcer			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	3 / 30 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Pruritus generalised			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Rash maculo-papular			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	4 / 30 (13.33%)	1 / 6 (16.67%)	
occurrences (all)	5	1	
Arthralgia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 6 (33.33%)	
occurrences (all)	2	2	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 30 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Neck pain			
subjects affected / exposed	3 / 30 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	3	3	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Diverticulitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Nosocomial infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Oral candidiasis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Pneumonia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Sinusitis			

subjects affected / exposed	2 / 30 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Respiratory tract infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Skin infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 30 (26.67%)	2 / 6 (33.33%)	
occurrences (all)	12	2	
Hyperammonaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	3	2	
Hyperkalaemia			
subjects affected / exposed	3 / 30 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	4	1	
Hypocalcaemia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 6 (16.67%)	
occurrences (all)	1	2	
Hypoglycaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Hypokalaemia			
subjects affected / exposed	3 / 30 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	3	5	

Hypomagnesaemia			
subjects affected / exposed	5 / 30 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	6	1	
Hyponatraemia			
subjects affected / exposed	3 / 30 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	7	0	
Metabolic acidosis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2014	1. Provided more conservative Dose Adjustment Guidelines for nonhematologic toxicities Section 8.2.2 as requested and agreed to, with the FDA; for consistency and ease of investigators, applied similar guidelines to hematologic toxicities. 2. Provided guidance in Section 8.2 Treatment Administration and Schedule, in the event of an emetic event shortly after ingestion of daily dose of CC-486, as agreed with the Agency. 3. Provided consistency between Section 5 ToE and text in Section 6 on bone scan assessments schedules; updated the footnotes in the Table of Events (ToE) with specific hematology, chemistry, and coagulation laboratory parameters being assessed, as agreed with the Agency. 4. An administrative change clarified the definition of PFS in Section 3.1 Primary Endpoints. 5. An administrative change deleted duplicate assessments being conducted on EBV-DNA biomarkers (in plasma and serum) in Sections 3.3 Exploratory Endpoints, Section 6.5 Biomarkers, and those in Section 5 ToE and Section 6 Procedures.
03 April 2015	1. Established an iDMC as requested by the Competent Authority (CA) in France. The update was reflected in the Protocol Summary, Section 10.1 Statistical Analysis Overview, and Section 10.10.1 iDMC and provided additional monitoring of the safety and efficacy data of this study. 2. Added the secondary endpoint of DCR as requested by the EC in Singapore. 3. In Section 7.3, subjects with undifferentiated or poorly differentiated NPC that was locally advanced or metastatic was clarified to include those subjects who received definitive chemoradiation treatment and had disease progression within 6 months could have been eligible at the investigator's discretion. 4. Provided further guidance in Section 7.3 regarding Exclusion Criterion #10 on hepatitis, with the addition of new Section 8.2.5 Guidelines for Screening and Management of Hepatitis B and C. 5. Provided further guidance in Section 7.3 Exclusion Criteria, as requested by the CA in Italy with the addition of the new Exclusion Criterion #11 of a subject with active bleeding or a pathological condition that carried a high risk of bleeding, or was at risk of pseudoaneurysm of the internal carotid artery, and carotid blowout syndrome. 6. Created Section 8.2.5 Guidelines for Screening and Management of Hepatitis B and C to provide further guidance in the screening and management of subjects for hepatitis. 7. Updated Section 1.3.2 CC-486 in NPC as of January 2015 data, and updated Section 1.4 Rationale for further clarity. 8. Made minor changes throughout to align Section 5 ToE, Section 6 Procedures, Section 6.1 Treatment Period, and Section 18 References, with the guidance described in Section 8.2.5 Guidelines for Screening and Management of Hepatitis B and C. 9. Promoted greater consistency within Table 4: Dose Adjustments and Dose Delays for Toxicity. 10. Clarified Section 9.1 Permitted Concomitant Medication and Procedures and aligned with new guidance on the screening and management of subjects for hepatitis.
23 September 2016	1. Added language to allow subjects who were still receiving CC-486 to continue receiving treatment in a CC-486 roll-over protocol.

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.

The review of the efficacy data from the trial participants did not support proceeding to Stage 2 as the protocol-defined criteria of > 4 responders (a best response of CR or PR) in Stage 1 was not reached and the study was terminated.

Notes: