Clinical trial results:
International Randomized Study to Evaluate the Addition of Docetaxel to the Combination of Cisplatin-5-fluorouracil (TCF) vs. Cisplatin-5-fluorouracil (CF) in the Induction Treatment of Nasopharyngeal Carcinoma (NPC) in Children and Adolescents

Summary

EudraCT number	2007-001211-33
Trial protocol	ES GR FR IT DE Outside EU/EEA
Global end of trial date	24 April 2012

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	23 July 2015

Trial information

Trial identification

Sponsor protocol code	EFC10339

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00565448
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Aventis Recherche & Developpement
Sponsor organisation address	1 Avenue PIerre Brossolette, Chilly Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi Aventis Recherche & Developpement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Aventis Recherche & Developpement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000029-PIP01-07
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 May 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 April 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the complete response rate of docetaxel to the combination of cisplatin-5-fluorouracil (TCF) compared to cisplatin-5-fluorouracil (CF) in the Induction treatment of nasopharyngeal carcinoma (NPC).

Protection of trial subjects:

Pediatric Subjects: The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.
Adult Subjects: Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	22 November 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Algeria: 1
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	China: 4
Country: Number of subjects enrolled	India: 5
Country: Number of subjects enrolled	Indonesia: 2
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Morocco: 16

Country: Number of subjects enrolled	Philippines: 4
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	Tunisia: 10
Country: Number of subjects enrolled	Turkey: 15
Worldwide total number of subjects	75
EEA total number of subjects	6

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)	5
Adolescents (12-17 years)	56
Adults (18-64 years)	14
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from November 2007 until October 2008. The study was conducted at 26 centers in 14 countries.

Pre-assignment

Screening details:

Screening occurred the week prior to induction.

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	Docetaxel /Cisplatin/5-FU

Arm description:

Docetaxel 75 mg/m² in combination with Cisplatin 75 mg/m² on Day 1 and 5-Fluorouracil 750 mg/m²/day on Days 1 to 4 every 3 weeks as induction therapy.
Consolidation treatment: radiation therapy for 7-8 weeks and 3 cycles of cisplatin 100 mg/m² every 3 weeks.

Arm type	Experimental
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	XRP6976
Other name	Taxotere
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel intravenous (IV) infusion over 1 hour.

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

Dosage and administration details:

Cisplatin IV infusion over 6 hours.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-Fluorouracil IV continuous infusion.

Arm title	Cisplatin/5-FU

Arm description:

Cisplatin 80 mg/m² on Day 1 and 5-Fluorouracil 1000 mg/m²/day on Days 1 to 4 every 3 weeks as induction therapy.
Consolidation treatment: radiation therapy for 7-8 weeks and 3 cycles of cisplatin 100 mg/m² every 3

weeks.

Arm type	Active comparator
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Cisplatin IV infusion over 6 hours.	
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 5-Fluorouracil IV continuous infusion.	

Number of subjects in period 1	Docetaxel /Cisplatin/5-FU	Cisplatin/5-FU
Started	50	25
Completed	47	23
Not completed	3	2
Disease progression	1	-
Adverse event	1	2
Withdrawal by Subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	Docetaxel /Cisplatin/5-FU

Reporting group description:

Docetaxel 75 mg/m² in combination with Cisplatin 75 mg/m² on Day 1 and 5-Fluorouracil 750 mg/m²/day on Days 1 to 4 every 3 weeks as induction therapy.
Consolidation treatment: radiation therapy for 7-8 weeks and 3 cycles of cisplatin 100 mg/m² every 3 weeks.

Reporting group title	Cisplatin/5-FU

Reporting group description:

Cisplatin 80 mg/m² on Day 1 and 5-Fluorouracil 1000 mg/m²/day on Days 1 to 4 every 3 weeks as induction therapy.
Consolidation treatment: radiation therapy for 7-8 weeks and 3 cycles of cisplatin 100 mg/m² every 3 weeks.

Reporting group values	Docetaxel /Cisplatin/5-FU	Cisplatin/5-FU	Total
Number of subjects	50	25	75
Age categorical Units: Subjects			
Infants from 28 days to 23 months	0	0	0
Children from 2 years to <12 years	4	1	5
Adolescents from 12 years to <16 years	20	10	30
Adolescents >=16	26	14	40
Age continuous Units: years			
median	16	16	
full range (min-max)	9 to 21	9 to 21	-
Gender categorical Units: Subjects			
Female	15	6	21
Male	35	19	54

End points

End points reporting groups

Reporting group title	Docetaxel /Cisplatin/5-FU

Reporting group description:

Docetaxel 75 mg/m² in combination with Cisplatin 75 mg/m² on Day 1 and 5-Fluorouracil 750 mg/m²/day on Days 1 to 4 every 3 weeks as induction therapy.
Consolidation treatment: radiation therapy for 7-8 weeks and 3 cycles of cisplatin 100 mg/m² every 3 weeks.

Reporting group title	Cisplatin/5-FU

Reporting group description:

Cisplatin 80 mg/m² on Day 1 and 5-Fluorouracil 1000 mg/m²/day on Days 1 to 4 every 3 weeks as induction therapy.
Consolidation treatment: radiation therapy for 7-8 weeks and 3 cycles of cisplatin 100 mg/m² every 3 weeks.

Primary: Number of Subjects With Complete Response (CR)

End point title	Number of Subjects With Complete Response (CR)

End point description:

CR assessed by independent reviewers, according to the Modified Response Evaluation Criteria in Solid Tumors (RECIST) from the National Cancer Institute (NCI). Disease response evaluated after the completion of the induction treatment and prior to the radiation treatment. CR defined as the complete disappearance of the target and non-target lesion(s) identified at baseline after radiological evaluation by Magnetic Resonance Imaging (MRI) only. ITT population: all randomized subjects.

End point type	Primary

End point timeframe:

after the completion of the induction treatment (up to 9 weeks)

End point values	Docetaxel /Cisplatin/5-FU	Cisplatin/5-FU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	25		
Units: subjects	1	0		

Statistical analyses

Statistical analysis title	Docetaxel /Cisplatin/5-FU vs Cisplatin/5-FU

Statistical analysis description:

The Fisher’s exact test was used to compare the CR proportions.

Comparison groups	Docetaxel /Cisplatin/5-FU v Cisplatin/5-FU

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [1]
Method	Fisher exact

Notes:

[1] - There was no formal power calculation. A selection design was used to determine how many subjects would be accrued to correctly select the treatment group with the best CR rate with 80% probability.

Secondary: Docetaxel Area Under the Plasma Concentration-time Curve (AUC) in the Docetaxel/Cisplatin/5-FU Group

End point title	Docetaxel Area Under the Plasma Concentration-time Curve (AUC) in the Docetaxel/Cisplatin/5-FU Group[2]

End point description:

AUC estimated by Bayesian method using concentration–time data for each subject and the previously defined adult population model as prior information (with validity of the estimation verified). Subjects who were randomized to docetaxel/cisplatin/5-FU and had evaluable docetaxel pharmacokinetic (PK) sample.

End point type	Secondary

End point timeframe:

Three plasma samples: one just before then 45 minutes and 5 hour after the end of cycle 1 infusion

Notes:

[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: Since the analysis was related to docetaxel AUC, only arm receiving docetaxel was selected.

End point values	Docetaxel /Cisplatin/5-FU			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: µg*h/mL				
arithmetic mean (standard deviation)	3.43 (± 2.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response (OR)

End point title	Overall Response (OR)

End point description:

OR was classified as CR, partial response (PR), stable disease (SD), progressive disease (PD) or Unknown on completion of both induction and radiation treatment and assessed according to the Modified RECIST from the NCI. CR was defined as the disappearance of all target lesions (TLs) and non-TLs. PR was defined as ≥30% decrease in the sum of the longest diameters (LD) of TLs, taking as reference the disease measurement done at study entry. PD was defined as ≥20% increase in the sum of the LD of TLs, taking as a reference the smallest disease measurement recorded at study entry or the appearance of ≥1 new lesions or unequivocal progression of non-TLs. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. ITT population: all randomized subjects.

End point type	Secondary

End point timeframe:

after the completion of the consolidation treatment (up to 18 weeks)

End point values	Docetaxel /Cisplatin/5-FU	Cisplatin/5-FU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	25		
Units: subjects				
CR	1	1		
PR	43	20		
SD	2	1		
PD	2	0		
Unknown	0	0		
Missing	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Rate

End point title	Overall Survival (OS) Rate

End point description:

OS rate was the percentage of subjects who survived 3 years after completion of consolidation treatment period. The Kaplan-Meier method was used to estimate OS rate. ITT population: all randomized subjects.

End point type	Secondary

End point timeframe:

3 years after the end of the consolidation treatment period (up to 40 months from randomization)

End point values	Docetaxel /Cisplatin/5-FU	Cisplatin/5-FU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	25		
Units: percentage of subjects				
number (confidence interval 95%)	85.7 (75.9 to 95.5)	78 (60.8 to 95.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are treatment-emergent that is AEs that developed/worsened and death that occurred during the 'on treatment period' (from first dose up 30 days after administration of the last cycle [maximum cycle 3]). Safety population: all subjects who received at least one cycle of any component of the study drug combination.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Docetaxel /Cisplatin/5-FU

Reporting group description:

Docetaxel 75 mg/m² in combination with Cisplatin 75 mg/m² on Day 1 and 5-Fluorouracil 750 mg/m²/day on Days 1 to 4 every 3 weeks as induction therapy.
Consolidation treatment: radiation therapy for 7-8 weeks and 3 cycles of cisplatin 100 mg/m² every 3 weeks.

Reporting group title	Cisplatin/5-FU

Reporting group description:

Cisplatin 80 mg/m² on Day 1 and 5-Fluorouracil 1000 mg/m²/day on Days 1 to 4 every 3 weeks as induction therapy.
Consolidation treatment: radiation therapy for 7-8 weeks and 3 cycles of cisplatin 100 mg/m² every 3 weeks.

Serious adverse events	Docetaxel /Cisplatin/5-FU	Cisplatin/5-FU	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 50 (40.00%)	11 / 25 (44.00%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood Creatinine Increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin Decreased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Haemorrhage			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (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			
Ataxia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 50 (2.00%)	2 / 25 (8.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	0 / 50 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Bone Marrow Failure			
subjects affected / exposed	0 / 50 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Bone Marrow Aplasia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Febrile Neutropenia			
subjects affected / exposed	5 / 50 (10.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	7 / 7	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia/Neutrophil Count			
subjects affected / exposed	4 / 50 (8.00%)	2 / 25 (8.00%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (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	2 / 50 (4.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 50 (6.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss Syndrome			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	2 / 50 (4.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
subjects affected / exposed	2 / 50 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Prerenal Failure			
subjects affected / exposed	0 / 50 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Central Line Infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis Bacterial			
subjects affected / exposed	0 / 50 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative Wound Infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	0 / 50 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	3 / 50 (6.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 50 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 50 (2.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Docetaxel /Cisplatin/5-FU	Cisplatin/5-FU	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 50 (98.00%)	23 / 25 (92.00%)	
Vascular disorders			
Phlebitis			
subjects affected / exposed	3 / 50 (6.00%)	0 / 25 (0.00%)	
occurrences (all)	12	0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	5 / 50 (10.00%)	0 / 25 (0.00%)	
occurrences (all)	9	0	
Fatigue			
subjects affected / exposed	8 / 50 (16.00%)	1 / 25 (4.00%)	
occurrences (all)	17	1	
Mucosal Inflammation			
subjects affected / exposed	5 / 50 (10.00%)	3 / 25 (12.00%)	
occurrences (all)	8	7	
Pyrexia			
subjects affected / exposed	11 / 50 (22.00%)	5 / 25 (20.00%)	
occurrences (all)	15	8	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	4 / 50 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	5	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 50 (10.00%)	0 / 25 (0.00%)	
occurrences (all)	10	0	
Epistaxis			
subjects affected / exposed	8 / 50 (16.00%)	0 / 25 (0.00%)	
occurrences (all)	12	0	
Oropharyngeal Pain			
subjects affected / exposed	4 / 50 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	11	0	
Pharyngeal Inflammation			
subjects affected / exposed	3 / 50 (6.00%)	4 / 25 (16.00%)	
occurrences (all)	8	5	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 50 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	10	0	
Depression			
subjects affected / exposed	3 / 50 (6.00%)	0 / 25 (0.00%)	
occurrences (all)	7	0	
Investigations			

Alanine Aminotransferase Increased			
subjects affected / exposed	3 / 50 (6.00%)	1 / 25 (4.00%)	
occurrences (all)	12	1	
Aspartate Aminotransferase Increased			
subjects affected / exposed	4 / 50 (8.00%)	1 / 25 (4.00%)	
occurrences (all)	9	1	
Platelet Count Decreased			
subjects affected / exposed	3 / 50 (6.00%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Weight Decreased			
subjects affected / exposed	20 / 50 (40.00%)	8 / 25 (32.00%)	
occurrences (all)	57	27	
Weight Increased			
subjects affected / exposed	4 / 50 (8.00%)	1 / 25 (4.00%)	
occurrences (all)	18	2	
White Blood Cell Count Decreased			
subjects affected / exposed	7 / 50 (14.00%)	2 / 25 (8.00%)	
occurrences (all)	25	3	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	2 / 50 (4.00%)	2 / 25 (8.00%)	
occurrences (all)	3	4	
Radiation Skin Injury			
subjects affected / exposed	11 / 50 (22.00%)	1 / 25 (4.00%)	
occurrences (all)	22	3	
Thermal Burn			
subjects affected / exposed	5 / 50 (10.00%)	2 / 25 (8.00%)	
occurrences (all)	12	3	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	4 / 50 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	13	0	
Headache			
subjects affected / exposed	8 / 50 (16.00%)	1 / 25 (4.00%)	
occurrences (all)	9	1	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	14 / 50 (28.00%)	3 / 25 (12.00%)	
occurrences (all)	58	4	
Bone Marrow Failure			
subjects affected / exposed	3 / 50 (6.00%)	1 / 25 (4.00%)	
occurrences (all)	10	2	
Leukopenia			
subjects affected / exposed	6 / 50 (12.00%)	1 / 25 (4.00%)	
occurrences (all)	18	3	
Lymphopenia			
subjects affected / exposed	6 / 50 (12.00%)	0 / 25 (0.00%)	
occurrences (all)	26	0	
Neutropenia/Neutrophil Count			
subjects affected / exposed	20 / 50 (40.00%)	7 / 25 (28.00%)	
occurrences (all)	49	16	
Thrombocytopenia			
subjects affected / exposed	3 / 50 (6.00%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Ear and labyrinth disorders			
Ototoxicity			
subjects affected / exposed	7 / 50 (14.00%)	6 / 25 (24.00%)	
occurrences (all)	27	20	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	10 / 50 (20.00%)	3 / 25 (12.00%)	
occurrences (all)	13	5	
Abdominal Pain Upper			
subjects affected / exposed	11 / 50 (22.00%)	2 / 25 (8.00%)	
occurrences (all)	14	2	
Constipation			
subjects affected / exposed	7 / 50 (14.00%)	0 / 25 (0.00%)	
occurrences (all)	13	0	
Diarrhoea			
subjects affected / exposed	15 / 50 (30.00%)	3 / 25 (12.00%)	
occurrences (all)	21	4	
Dry Mouth			

subjects affected / exposed	9 / 50 (18.00%)	5 / 25 (20.00%)	
occurrences (all)	26	13	
Dyspepsia			
subjects affected / exposed	3 / 50 (6.00%)	0 / 25 (0.00%)	
occurrences (all)	5	0	
Dysphagia			
subjects affected / exposed	12 / 50 (24.00%)	7 / 25 (28.00%)	
occurrences (all)	31	19	
Nausea			
subjects affected / exposed	33 / 50 (66.00%)	10 / 25 (40.00%)	
occurrences (all)	126	28	
Odynophagia			
subjects affected / exposed	3 / 50 (6.00%)	1 / 25 (4.00%)	
occurrences (all)	4	1	
Salivary Hypersecretion			
subjects affected / exposed	3 / 50 (6.00%)	0 / 25 (0.00%)	
occurrences (all)	7	0	
Stomatitis			
subjects affected / exposed	30 / 50 (60.00%)	5 / 25 (20.00%)	
occurrences (all)	65	12	
Vomiting			
subjects affected / exposed	47 / 50 (94.00%)	21 / 25 (84.00%)	
occurrences (all)	189	78	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	29 / 50 (58.00%)	1 / 25 (4.00%)	
occurrences (all)	169	4	
Dermatitis			
subjects affected / exposed	7 / 50 (14.00%)	4 / 25 (16.00%)	
occurrences (all)	12	11	
Rash			
subjects affected / exposed	4 / 50 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	5	0	
Skin Hyperpigmentation			
subjects affected / exposed	5 / 50 (10.00%)	3 / 25 (12.00%)	
occurrences (all)	10	6	

Renal and urinary disorders			
Nephropathy Toxic			
subjects affected / exposed	4 / 50 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	7	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 50 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Infections and infestations			
Folliculitis			
subjects affected / exposed	5 / 50 (10.00%)	0 / 25 (0.00%)	
occurrences (all)	17	0	
Oral Candidiasis			
subjects affected / exposed	8 / 50 (16.00%)	0 / 25 (0.00%)	
occurrences (all)	15	0	
Sinusitis			
subjects affected / exposed	2 / 50 (4.00%)	3 / 25 (12.00%)	
occurrences (all)	2	3	
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 50 (6.00%)	2 / 25 (8.00%)	
occurrences (all)	8	9	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	21 / 50 (42.00%)	5 / 25 (20.00%)	
occurrences (all)	49	13	
Hypocalcaemia			
subjects affected / exposed	4 / 50 (8.00%)	1 / 25 (4.00%)	
occurrences (all)	5	1	
Hypokalaemia			
subjects affected / exposed	6 / 50 (12.00%)	1 / 25 (4.00%)	
occurrences (all)	8	1	
Hypomagnesaemia			
subjects affected / exposed	6 / 50 (12.00%)	0 / 25 (0.00%)	
occurrences (all)	11	0	
Hyponatraemia			

subjects affected / exposed occurrences (all)	6 / 50 (12.00%) 7	0 / 25 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2007	- Changed the total number of subjects to be randomized from 51 to 72. - Modified inclusion criteria to include subjects ≤21 years of age. - Revised Sections 7, 9, and 12 to clarify study procedures.
14 November 2007	- Added regular cardiac surveillance during each visit for administration of chemotherapies that included vital signs as: heart rate, blood pressure and electrocardiogram (ECG) as medically indicated to now mandatory clinical examinations at induction phase and reflected in Study Flowchart. - Added the following exclusion criterion: "Hypersensitivity to one of the drugs or their excipients". - Made administrative changes to reflect changes in study personnel.
03 December 2007	- Revised the radiation rules for consolidation therapy. - Clarified inclusion criterion on age required for study entry to >1 month to ≤21 years of age at the time of diagnosis. - Added a description of how to calculate glomerular filtration rate (GFR). - Revised hydration regimen by allowing magnesium sulfate (MgSO4). - Clarified that the RECIST criteria used for CR evaluation were modified by employing volumetric assessment of the primary NPC tumor and associated adenopathy. - Clarified that the MRI scan required at screening was to the head and neck area. - Added computed tomography (CT)/MRI scan of chest, abdomen and/or pelvis as well as a bone scan if the presence of distant metastases was suspected. - Added hematology and biochemistry analyses at the screening visit to serve as baseline and removed the requirement for these tests prior to Cycle 1. - Added recommendations regarding audiology, oral, and dental examinations. - Clarified times of disease assessment. - Increased the number of PK samples from 20 to 25. - Introduced the potential analysis of response based on disease staging. - Revised study flow chart.
28 October 2010	The reason for this amendment was to clarify study procedures as it relates to safety reporting and study treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported