# 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:<br>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:<br>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<br>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<br>Units: years | | | |
| median | 16 | 16 | |
| full range (min-max) | 9 to 21 | 9 to 21 | - |
| Gender categorical<br>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<br>occurrences (all) | 6 / 50 (12.00%)<br>7 | 0 / 25 (0.00%)<br>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