



Clinical trial results:

A Phase 2/3, Multi-Center, Open-Label, Randomized Study of Weekly nab®-Paclitaxel in Combination with Gemcitabine or Carboplatin, Compared to Gemcitabine/Carboplatin, as First Line Treatment in Subjects with Estrogen Receptor (ER), Progesterone Receptor (PgR), and HER2 Negative (Triple Negative) Metastatic Breast Cancer

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2013-000113-20 |
| Trial protocol | AT ES DE GB IT PT GR FR |
| Global end of trial date | 28 October 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 12 November 2017 |
| First version publication date | 12 November 2017 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | ABI-007-MBC-001 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01881230 |
| 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 M.D., Celgene, 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 | 16 December 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-----------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 28 October 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

Evaluate the benefit and risk profiles of the two nab-paclitaxel experimental arms and identify which nab-paclitaxel combination that will be used in the Phase 3 portion of the study.

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection and Biomarker Consent

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 01 October 2013 |
| 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 | Australia: 1 |
| Country: Number of subjects enrolled | Canada: 8 |
| Country: Number of subjects enrolled | United States: 83 |
| Country: Number of subjects enrolled | Brazil: 19 |
| Country: Number of subjects enrolled | Austria: 6 |
| Country: Number of subjects enrolled | Germany: 5 |
| Country: Number of subjects enrolled | Greece: 7 |
| Country: Number of subjects enrolled | Italy: 27 |
| Country: Number of subjects enrolled | Portugal: 6 |
| Country: Number of subjects enrolled | Spain: 16 |
| Country: Number of subjects enrolled | United Kingdom: 13 |
| Worldwide total number of subjects | 191 |
| EEA total number of subjects | 80 |

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) | 140 |
| From 65 to 84 years | 51 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This multicenter study was conducted by investigators in 11 countries in North America, Europe, Australia and South America, and enrolled participants at a total of 86 sites.

Pre-assignment

Screening details:

Participants were randomized 1:1:1 stratified by disease free interval (≤ 1 year; > 1 year), to facilitate the selection of the nab-paclitaxel experimental arm for evaluation in the Phase 3 portion of the study.

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 | Arm A: nab-Paclitaxel plus Gemcitabine |

Arm description:

Participants received nab-Paclitaxel 125 mg/m² on Days 1 and 8 by intravenous (IV) administration followed by gemcitabine 1000 mg/m² on Days 1 and 8 by IV administration in each 21-day treatment cycle. Participants continued treatment until progressive disease (PD), unacceptable toxicity, required palliative radiotherapy or surgical intervention of lesion(s), withdrawal from study treatment, withdrawal of study consent, participant refusal or the investigator felt it was no longer in the best interest of the participant to continue on treatment.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | nab-Paclitaxel |
| Investigational medicinal product code | ABI-007 |
| Other name | Abraxane |
| Pharmaceutical forms | Concentrate and solvent for solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

nab-Paclitaxel 125 mg/m² on Days 1 and 8 by intravenous (IV) administration Days 1 and 8 of each 21-day treatment cycle.

| | |
|--|-----------------|
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | |
| Other name | Gemzar |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Gemcitabine 1000 mg/m² on Days 1 and 8 by IV administration of each 21-day treatment cycle.

| | |
|------------------|-------------------------------------|
| Arm title | Arm B: nab-Paclitaxel + Carboplatin |
|------------------|-------------------------------------|

Arm description:

Participants received nab-Paclitaxel 125 mg/m² on Days 1 and 8 by IV administration followed by Carboplatin area under the curve 2 (AUC 2) on Days 1 and 8 in each 21-day treatment cycle. Participants continued treatment until progressive disease (PD), unacceptable toxicity, required palliative radiotherapy or surgical intervention of lesion(s), withdrawal from study treatment, withdrawal of study consent, participant refusal or the investigator felt it was no longer in the best interest of the participant to continue on treatment.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | Paraplatin |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Carboplatin AUC 2 on days 1 and 8 of each 21-day treatment cycle.

| | |
|--|---|
| Investigational medicinal product name | nab-Paclitaxel |
| Investigational medicinal product code | ABI-007 |
| Other name | Abraxane |
| Pharmaceutical forms | Concentrate and solvent for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

nab-Paclitaxel 125 mg/m² on Days 1 and 8 by IV administration on days 1 and 8 of each 21-day treatment cycle.

| | |
|------------------|----------------------------------|
| Arm title | Arm C: Gemcitabine + Carboplatin |
|------------------|----------------------------------|

Arm description:

Participants received Gemcitabine 1000 mg/m² on Days 1 and 8 by IV administration, followed by carboplatin AUC 2 on Days 1 and 8 by IV administration in each 21-day treatment cycle. Participants continued treatment until progressive disease (PD), unacceptable toxicity, required palliative radiotherapy or surgical intervention of lesion(s), withdrawal from study treatment, withdrawal of study consent, participant refusal or the investigator felt it was no longer in the best interest of the participant to continue on treatment.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | |
| Other name | Gemzar |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Gemcitabine 1000 mg/m² on Days 1 and 8 by IV administration of each 21-day treatment cycle.

| | |
|--|--|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | Paraplatin |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Carboplatin AUC 2 on days 1 and 8 of each 21-day treatment cycle.

| Number of subjects in period 1 | Arm A: nab-Paclitaxel plus Gemcitabine | Arm B: nab-Paclitaxel + Carboplatin | Arm C: Gemcitabine + Carboplatin |
|---------------------------------------|--|-------------------------------------|----------------------------------|
| Started | 61 | 64 | 66 |
| Safety Population | 60 | 64 | 64 |
| Treated as Randomized | 60 | 64 | 64 |
| Treatment Discontinuation | 60 | 64 | 64 |
| Completed | 0 | 0 | 0 |
| Not completed | 61 | 64 | 66 |
| Adverse event, serious fatal | 2 | - | 1 |

| | | | |
|--|----|----|----|
| Physician decision | 4 | 3 | 6 |
| Untreated: Withdrawal before study start | 1 | - | - |
| Untreated: Miscellaneous | - | - | 1 |
| Miscellaneous | 3 | 3 | - |
| Given commercial drug | - | - | 2 |
| Consent withdrawn by subject | 6 | 4 | 6 |
| Adverse event, non-fatal | 9 | 13 | 12 |
| Symptomatic deterioration | 3 | 3 | 1 |
| Untreated: Death | - | - | 1 |
| Progressive Disease | 31 | 35 | 36 |
| Non-compliance with study drug | 1 | 2 | - |
| Protocol deviation | 1 | 1 | - |

Baseline characteristics

Reporting groups

| | |
|---|--|
| Reporting group title | Arm A: nab-Paclitaxel plus Gemcitabine |
| Reporting group description: | |
| Participants received nab-Paclitaxel 125 mg/m ² on Days 1 and 8 by intravenous (IV) administration followed by gemcitabine 1000 mg/m ² on Days 1 and 8 by IV administration in each 21-day treatment cycle. Participants continued treatment until progressive disease (PD), unacceptable toxicity, required palliative radiotherapy or surgical intervention of lesion(s), withdrawal from study treatment, withdrawal of study consent, participant refusal or the investigator felt it was no longer in the best interest of the participant to continue on treatment. | |
| Reporting group title | Arm B: nab-Paclitaxel + Carboplatin |
| Reporting group description: | |
| Participants received nab-Paclitaxel 125 mg/m ² on Days 1 and 8 by IV administration followed by Carboplatin area under the curve 2 (AUC 2) on Days 1 and 8 in each 21-day treatment cycle. Participants continued treatment until progressive disease (PD), unacceptable toxicity, required palliative radiotherapy or surgical intervention of lesion(s), withdrawal from study treatment, withdrawal of study consent, participant refusal or the investigator felt it was no longer in the best interest of the participant to continue on treatment. | |
| Reporting group title | Arm C: Gemcitabine + Carboplatin |
| Reporting group description: | |
| Participants received Gemcitabine 1000 mg/m ² on Days 1 and 8 by IV administration, followed by carboplatin AUC 2 on Days 1 and 8 by IV administration in each 21-day treatment cycle. Participants continued treatment until progressive disease (PD), unacceptable toxicity, required palliative radiotherapy or surgical intervention of lesion(s), withdrawal from study treatment, withdrawal of study consent, participant refusal or the investigator felt it was no longer in the best interest of the participant to continue on treatment. | |

| Reporting group values | Arm A: nab-Paclitaxel plus Gemcitabine | Arm B: nab-Paclitaxel + Carboplatin | Arm C: Gemcitabine + Carboplatin |
|--|--|-------------------------------------|----------------------------------|
| Number of subjects | 61 | 64 | 66 |
| 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) | 43 | 48 | 49 |
| From 65-84 years | 18 | 16 | 17 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 53.7 | 54.3 | 56.7 |
| standard deviation | ± 12.16 | ± 11.96 | ± 10.87 |
| Gender, Male/Female Units: Subjects | | | |
| Female | 61 | 64 | 66 |
| Male | 0 | 0 | 0 |

| | | | |
|---|----|----|----|
| Race | | | |
| Units: Subjects | | | |
| Black or African American | 9 | 6 | 8 |
| White | 50 | 55 | 54 |
| Unknown or Not Reported | 2 | 3 | 4 |
| 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 | 34 | 38 | 42 |
| 1 = Restrictive but ambulatory | 25 | 26 | 22 |
| 2 = Ambulatory but unable to work | 1 | 0 | 0 |
| Missing | 1 | 0 | 2 |
| Disease Free Interval by Clinical Interpretation | | | |
| Disease Free Interval is defined as period of being absent of disease less than or equal to one year or free of disease greater than one year. | | | |
| Units: Subjects | | | |
| ≤ 1 year | 17 | 16 | 20 |
| > 1 year | 43 | 48 | 45 |
| Missing | 1 | 0 | 1 |
| Stage of Primary Diagnosis | | | |
| Stage of Diagnosis as indicated in the American Joint Committee on Cancer Staging Manual (AJCC) | | | |
| Units: Subjects | | | |
| Stage 0 | 0 | 1 | 0 |
| Stage IA | 7 | 6 | 11 |
| Stage IB | 0 | 0 | 0 |
| Stage IIA | 14 | 9 | 15 |
| Stage IIB | 8 | 7 | 9 |
| Stage IIIA | 9 | 10 | 3 |
| Stage IIIB | 3 | 3 | 5 |
| Stage IIIC | 3 | 3 | 2 |
| Stage IV | 11 | 17 | 10 |
| Missing | 6 | 8 | 11 |
| Triple-Negative at Primary Diagnosis | | | |
| Triple-Negative Breast Cancer defined as estrogen receptor (ER) negative, progesterone receptor (PgR) negative, and human epidermal growth factor receptor 2 (HER2) negative. | | | |
| Units: Subjects | | | |
| Triple Negative Breast Cancer | 51 | 53 | 48 |
| Non-Display of Triple Negative Breast Cancer | 10 | 11 | 18 |
| Triple-Negative at Latest Diagnosis | | | |
| Triple-Negative Breast Cancer defined as estrogen receptor (ER) negative, progesterone receptor (PgR) negative, and human epidermal growth factor receptor 2 (HER2) negative | | | |
| Units: Subjects | | | |
| Triple-Negative at Latest Diagnosis | 60 | 62 | 65 |
| Non-Display of Triple Negative Breast Cancer | 1 | 2 | 1 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Time from Diagnosis to 1st Reported Disease/Relapse Units: months arithmetic mean standard deviation | 38.8 ± 49.46 | 29.9 ± 37.18 | 50.9 ± 62.60 |
| Time from First Documented Metastatic Disease/Relapse to Randomization Units: months arithmetic mean standard deviation | 2.1 ± 5.08 | 4.2 ± 18.39 | 1.6 ± 1.70 |
| Time from Primary Diagnosis to Randomization Units: months arithmetic mean standard deviation | 43.7 ± 54.60 | 35.5 ± 40.51 | 52.5 ± 62.37 |

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 191 | | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 140 | | |
| From 65-84 years | 51 | | |
| 85 years and over | 0 | | |
| Age Continuous Units: years arithmetic mean standard deviation | - | | |
| Gender, Male/Female Units: Subjects | | | |
| Female | 191 | | |
| Male | 0 | | |
| Race Units: Subjects | | | |
| Black or African American | 23 | | |
| White | 159 | | |
| Unknown or Not Reported | 9 | | |
| 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 | 114 | | |
| 1 = Restrictive but ambulatory | 73 | | |
| 2 = Ambulatory but unable to work | 1 | | |

| | | | |
|---|-----|--|--|
| Missing | 3 | | |
| Disease Free Interval by Clinical Interpretation | | | |
| Disease Free Interval is defined as period of being absent of disease less than or equal to one year or free of disease greater than one year. | | | |
| Units: Subjects | | | |
| ≤ 1 year | 53 | | |
| > 1 year | 136 | | |
| Missing | 2 | | |
| Stage of Primary Diagnosis | | | |
| Stage of Diagnosis as indicated in the American Joint Committee on Cancer Staging Manual (AJCC) | | | |
| Units: Subjects | | | |
| Stage 0 | 1 | | |
| Stage IA | 24 | | |
| Stage IB | 0 | | |
| Stage IIA | 38 | | |
| Stage IIB | 24 | | |
| Stage IIIA | 22 | | |
| Stage IIIB | 11 | | |
| Stage IIIC | 8 | | |
| Stage IV | 38 | | |
| Missing | 25 | | |
| Triple-Negative at Primary Diagnosis | | | |
| Triple-Negative Breast Cancer defined as estrogen receptor (ER) negative, progesterone receptor (PgR) negative, and human epidermal growth factor receptor 2 (HER2) negative. | | | |
| Units: Subjects | | | |
| Triple Negative Breast Cancer | 152 | | |
| Non-Display of Triple Negative Breast Cancer | 39 | | |
| Triple-Negative at Latest Diagnosis | | | |
| Triple-Negative Breast Cancer defined as estrogen receptor (ER) negative, progesterone receptor (PgR) negative, and human epidermal growth factor receptor 2 (HER2) negative | | | |
| Units: Subjects | | | |
| Triple-Negative at Latest Diagnosis | 187 | | |
| Non-Display of Triple Negative Breast Cancer | 4 | | |
| Time from Diagnosis to 1st Reported Disease/Relapse | | | |
| Units: months | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Time from First Documented Metastatic Disease/Relapse to Randomization | | | |
| Units: months | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Time from Primary Diagnosis to Randomization | | | |
| Units: months | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Arm A: nab-Paclitaxel plus Gemcitabine |
| Reporting group description: Participants received nab-Paclitaxel 125 mg/m ² on Days 1 and 8 by intravenous (IV) administration followed by gemcitabine 1000 mg/m ² on Days 1 and 8 by IV administration in each 21-day treatment cycle. Participants continued treatment until progressive disease (PD), unacceptable toxicity, required palliative radiotherapy or surgical intervention of lesion(s), withdrawal from study treatment, withdrawal of study consent, participant refusal or the investigator felt it was no longer in the best interest of the participant to continue on treatment. | |
| Reporting group title | Arm B: nab-Paclitaxel + Carboplatin |
| Reporting group description: Participants received nab-Paclitaxel 125 mg/m ² on Days 1 and 8 by IV administration followed by Carboplatin area under the curve 2 (AUC 2) on Days 1 and 8 in each 21-day treatment cycle. Participants continued treatment until progressive disease (PD), unacceptable toxicity, required palliative radiotherapy or surgical intervention of lesion(s), withdrawal from study treatment, withdrawal of study consent, participant refusal or the investigator felt it was no longer in the best interest of the participant to continue on treatment. | |
| Reporting group title | Arm C: Gemcitabine + Carboplatin |
| Reporting group description: Participants received Gemcitabine 1000 mg/m ² on Days 1 and 8 by IV administration, followed by carboplatin AUC 2 on Days 1 and 8 by IV administration in each 21-day treatment cycle. Participants continued treatment until progressive disease (PD), unacceptable toxicity, required palliative radiotherapy or surgical intervention of lesion(s), withdrawal from study treatment, withdrawal of study consent, participant refusal or the investigator felt it was no longer in the best interest of the participant to continue on treatment. | |

Primary: Kaplan-Meier Estimates of Progression-Free Survival (PFS) Based on Investigator Assessment.

| | |
|--|---|
| End point title | Kaplan-Meier Estimates of Progression-Free Survival (PFS) Based on Investigator Assessment. |
| End point description: PFS was defined as the time from the date of randomization to the date of disease progression or death from any cause on or prior to the data cutoff date for the statistical analysis, whichever occurred earlier. Tumor responses were assessed using triple-negative metastatic breast cancer, Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and defined as: Complete response (CR) is the disappearance of all target lesions; Partial response (PR) occurs when at least a 30% decrease in the sum of diameters of target lesions from baseline; Stable disease is neither sufficient shrinkage to qualify for a PR nor sufficient increase of lesions to qualify for Progressive disease (PD); Progressive Disease- is at least a 20% increase in the sum of diameters of target lesions from nadir. Intent to Treat (ITT) population includes all randomized participants regardless of whether they received any (Investigational Product) IP or had any efficacy assessments collected. | |
| End point type | Primary |
| End point timeframe: From date of randomization to data cut-off date of 16 December 2016; total length of time on study was 31 months for Arm A, 34 months for Arm B and 35 months for Arm C | |

| End point values | Arm A: nab-Paclitaxel plus Gemcitabine | Arm B: nab-Paclitaxel + Carboplatin | Arm C: Gemcitabine + Carboplatin | |
|----------------------------------|--|-------------------------------------|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 61 | 64 | 66 | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.5 (4.1 to 7.0) | 8.3 (5.7 to 10.6) | 6.0 (4.7 to 7.2) | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|--|
| Statistical analysis description: | |
| For stratified analysis, the stratified log-rank test and stratified Cox proportional hazards model were used, where the stratification factor is the disease free interval (≤ 1 year; > 1 year). | |
| Comparison groups | Arm B: nab-Paclitaxel + Carboplatin v Arm A: nab-Paclitaxel plus Gemcitabine |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0183 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.692 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.089 |
| upper limit | 2.629 |

| Statistical analysis title | Statistical Analysis 2 |
|---|--|
| Statistical analysis description: | |
| For stratified analysis, the stratified log-rank test and stratified Cox proportional hazards model were used, where the stratification factor is the disease free interval (≤ 1 year; > 1 year). | |
| Comparison groups | Arm B: nab-Paclitaxel + Carboplatin v Arm C: Gemcitabine + Carboplatin |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0152 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.581 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.373 |
| upper limit | 0.904 |

| | |
|--|---|
| Statistical analysis title | Statistical Analysis 3 |
| Statistical analysis description: For stratified analysis, the stratified log-rank test and stratified Cox proportional hazards model were used, where the stratification factor is the disease free interval (≤ 1 year; > 1 year). | |
| Comparison groups | Arm C: Gemcitabine + Carboplatin v Arm A: nab-Paclitaxel plus Gemcitabine |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8599 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.039 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.676 |
| upper limit | 1.597 |

Secondary: Percentage of Participants with an Objective Confirmed Complete or Partial Overall Response by Investigator Assessment.

| | |
|-----------------|---|
| End point title | Percentage of Participants with an Objective Confirmed Complete or Partial Overall Response by Investigator Assessment. |
|-----------------|---|

End point description:

Percentage of participants with an objective confirmed complete or partial overall response according to RECIST 1.1 and defined as: A complete response (CR) was the disappearance of all target lesions; a partial response is at least a 30% decrease in the sum of diameters of target lesions from baseline; stable disease is neither sufficient shrinkage to qualify for PR nor sufficient increase of lesions to qualify for Progressive disease (PD); progressive disease- is at least a 20% increase in the sum of diameters of target lesions from nadir. Intent to treat (ITT) includes all randomized participants regardless of whether they received any IP or had any efficacy assessments collected.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Disease response was assessed every 6 weeks; from date of randomization to data cut-off date of 16 December 2016; total length of time on study was 31 months for Arm A, 34 months for Arm B and 35 months for Arm C.

| End point values | Arm A: nab-Paclitaxel plus Gemcitabine | Arm B: nab-Paclitaxel + Carboplatin | Arm C: Gemcitabine + Carboplatin | |
|----------------------------------|--|-------------------------------------|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 61 | 64 | 66 | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 39.3 (27.1 to 52.7) | 73.4 (60.9 to 83.7) | 43.9 (31.7 to 56.7) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Initiated Cycle 6 Receiving Doublet Combination Therapy

| | |
|-----------------|--|
| End point title | Percentage of Participants who Initiated Cycle 6 Receiving Doublet Combination Therapy |
|-----------------|--|

End point description:

The percentage of participants who initiated Cycle 6 receiving doublet combination therapy was one of the criteria. ITT includes all randomized participants regardless of whether they received any IP or had any efficacy assessments collected. ITT population for those who initiated Cycle 6 doublet combination therapy.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 6.

| End point values | Arm A: nab-Paclitaxel plus Gemcitabine | Arm B: nab-Paclitaxel + Carboplatin | Arm C: Gemcitabine + Carboplatin | |
|-----------------------------------|--|-------------------------------------|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 61 | 64 | 66 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 55.7 (42.5 to 68.5) | 64.1 (51.1 to 75.7) | 50.0 (37.4 to 62.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates of Overall Survival

| | |
|-----------------|--|
| End point title | Kaplan-Meier Estimates of Overall Survival |
|-----------------|--|

End point description:

Overall survival was defined as the time from the date of randomization to the date of death (from any cause). The ITT population includes all randomized participants regardless of whether the participant received any IP or had any efficacy assessments collected.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of randomization to data cut-off date of 16 December 2016; total length of time on study was 31 months for Arm A, 34 months for Arm B and 35 months for Arm C.

| End point values | Arm A: nab-Paclitaxel plus Gemcitabine | Arm B: nab-Paclitaxel + Carboplatin | Arm C: Gemcitabine + Carboplatin | |
|----------------------------------|--|-------------------------------------|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 61 | 64 | 66 | |
| Units: months | | | | |
| median (confidence interval 95%) | 12.1 (9.4 to 15.9) | 16.8 (11.3 to 20.6) | 12.6 (10.1 to 16.6) | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|--|
| Statistical analysis description: | |
| Hazard ratios and associated two-sided 95% confidence intervals were estimated using stratified Cox proportional hazard model. The stratification factor is the disease free interval (≤ 1 year; > 1 year). | |
| Comparison groups | Arm B: nab-Paclitaxel + Carboplatin v Arm A: nab-Paclitaxel plus Gemcitabine |
| Number of subjects included in analysis | 125 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1579 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.375 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.882 |
| upper limit | 2.143 |

| Statistical analysis title | Statistical Analysis 2 |
|---|--|
| Statistical analysis description: | |
| Hazard ratios and associated two-sided 95% confidence intervals were estimated using stratified Cox proportional hazard model. The stratification factor is the disease free interval (≤ 1 year; > 1 year). | |
| Comparison groups | Arm B: nab-Paclitaxel + Carboplatin v Arm C: Gemcitabine + Carboplatin |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2945 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.796 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 1.221 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Hazard ratios and associated two-sided 95% confidence intervals were estimated using stratified Cox proportional hazard model. The stratification factor is the disease free interval (≤ 1 year; > 1 year).

| | |
|---|---|
| Comparison groups | Arm C: Gemcitabine + Carboplatin v Arm A: nab-Paclitaxel plus Gemcitabine |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6691 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.101 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.708 |

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 AEs that began or worsened with an onset date on or after the date of the first dose of IP through 28 days after the last dose. A serious AE (SAE) is any AE which results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; constitutes an important medical event. The severity of AEs was graded based on the participant's symptoms according to the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0); Grade 1 = Mild – transient or mild discomfort; no medical intervention required; Grade 2 = Moderate – mild to moderate limitation in activity; Grade 3 = Severe; Grade 4 = Life threatening; Grade 5 = Death. The safety population includes all randomized subjects who received at least 1 dose of IP.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization through to 28 days after the last dose of IP; up to data cut off date of 16 Dec 2016; maximum treatment duration of study drug exposure was 108.3 weeks for Arm A, 83 weeks for Arm B, 110.1 weeks for Arm C

| End point values | Arm A: nab-Paclitaxel plus Gemcitabine | Arm B: nab-Paclitaxel + Carboplatin | Arm C: Gemcitabine + Carboplatin | |
|--|--|-------------------------------------|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 60 | 64 | 64 | |
| Units: participants | | | | |
| Any TEAE | 60 | 63 | 64 | |
| Any Grade 3 or Higher TEAE | 46 | 51 | 54 | |
| Treatment-related TEAE | 59 | 62 | 60 | |
| Treatment-related, Grade 3 or Higher TEAE | 35 | 43 | 46 | |
| Serious TEAE | 22 | 20 | 25 | |
| Treatment-related Serious TEAE | 10 | 9 | 13 | |
| TEAE Leading to Discontinuation (D/C) of IP | 16 | 29 | 15 | |
| Treatment Related (TR) TEAE Leading to D/C of IP | 12 | 27 | 12 | |
| TEAE Leading to Dose Reduction (DR) of IP | 23 | 20 | 25 | |
| Treatment related TEAE Leading to DR of IP | 31 | 20 | 23 | |
| TEAE Leading to Dose Interruption (DI) of IP | 27 | 50 | 50 | |
| TR TEAE Leading to DI of IP | 16 | 44 | 44 | |
| TEAE leading to D/C of nab-Paclitaxel | 11 | 17 | 0 | |
| TR TEAE leading to D/C of nab-Paclitaxel | 22 | 13 | 0 | |
| TEAE leading to DR of nab-Paclitaxel | 21 | 19 | 0 | |
| TR TEAE leading to DR of nab-Paclitaxel | 31 | 19 | 0 | |
| TEAE leading to DI of nab-Paclitaxel | 27 | 50 | 0 | |
| TR TEAE leading to DI of nab-Paclitaxel | 13 | 44 | 0 | |
| TEAE leading to D/C of Gemcitabine | 7 | 0 | 13 | |
| TR TEAE leading to D/C of Gemcitabine | 18 | 0 | 9 | |
| TEAE leading to DR of Gemcitabine | 18 | 0 | 25 | |
| TR TEAE leading to DR of Gemcitabine | 31 | 0 | 23 | |
| TEAE leading to DI of Gemcitabine | 24 | 0 | 49 | |
| TR TEAE leading to DI of Gemcitabine | 0 | 0 | 43 | |
| TEAE leading to D/C of Carboplatin | 0 | 28 | 15 | |
| TR TEAE leading to D/C of Carboplatin | 0 | 25 | 12 | |
| TEAE leading to DR of Carboplatin | 0 | 17 | 21 | |
| TR TEAE leading to DR of Carboplatin | 0 | 17 | 20 | |
| TEAE leading to DI of Carboplatin | 0 | 50 | 50 | |
| TR TEAE leading to DI of Carboplatin | 0 | 44 | 43 | |
| TEAE Leading to Death | 2 | 1 | 2 | |
| Treatment Related TEAE leading to death | 1 | 0 | 1 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Dose Modifications (Reductions and Interruptions)

| | |
|--|---|
| End point title | Percentage of Participants Experiencing Dose Modifications (Reductions and Interruptions) |
| End point description: The number of participants with dose modifications occurring during the treatment period. Dose reductions and interruptions are typically caused by clinically significant laboratory abnormalities and /or TEAEs/toxicities. The safety population includes all randomized participants who received at least 1 dose of IP. | |
| End point type | Secondary |
| End point timeframe: From date of first dose to data cut off of date of 16 December 2016; maximum treatment duration of study drug exposure was 108.3 weeks for nab-paclitaxel + gemcitabine, 83 weeks for nab-paclitaxel + carboplatin, 110.1 weeks for gemcitabine + Carboplatin | |

| End point values | Arm A: nab-Paclitaxel plus Gemcitabine | Arm B: nab-Paclitaxel + Carboplatin | Arm C: Gemcitabine + Carboplatin | |
|-----------------------------------|--|-------------------------------------|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 60 | 64 | 64 | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| ≥ 1 DR for both IPs | 33.3 | 46.9 | 51.6 | |
| ≥ one DI for both IPs | 38.3 | 70.3 | 73.4 | |
| ≥ one dose missed for both IPs | 48.3 | 45.3 | 56.3 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Discontinued From all Study Treatment Due to TEAEs

| | |
|--|---|
| End point title | Percentage of Participants who Discontinued From all Study Treatment Due to TEAEs |
| End point description: Treatment-emergent adverse events (TEAEs) were defined as any AEs that begin or worsen with an onset date on or after the date of the first dose of IP through 28 days after the last dose. The Safety/Treated population includes all randomized participants who received at least 1 dose of IP. | |
| End point type | Secondary |
| End point timeframe: From date of first dose to data cut off of date of 16 December 2016; maximum treatment duration of study drug exposure was 108.3 weeks for nab-paclitaxel + gemcitabine, 83 weeks for nab-paclitaxel + carboplatin, 110.1 weeks for gemcitabine + carboplatin. | |

| End point values | Arm A: nab-Paclitaxel plus Gemcitabine | Arm B: nab-Paclitaxel + Carboplatin | Arm C: Gemcitabine + Carboplatin | |
|-----------------------------------|--|-------------------------------------|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 60 | 64 | 64 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 21.7 (12.1 to 34.2) | 26.6 (16.3 to 39.1) | 21.9 (12.5 to 34.0) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization through to 28 days after the last dose of IP; up to the data cut-off date of 16 December 2016; AEs collected and monitored for 39 months.

Adverse event reporting additional description:

Maximum treatment duration of study drug exposure was 108.3 weeks for Arm A, 83 weeks for Arm B and 110.1 weeks for Arm C.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Arm A: nab-Paclitaxel + Gemcitabine |
|-----------------------|-------------------------------------|

Reporting group description:

Subjects received nab-Paclitaxel 125 mg/m² on Days 1 and 8 by intravenous (IV) administration followed by gemcitabine 1000 mg/m² on Days 1 and 8 by IV administration of each 21-day treatment cycle. Subjects continued treatment until progressive disease (PD), unacceptable toxicity, required palliative radiotherapy or surgical intervention of lesion(s), withdrawal from study treatment, withdrawal of study consent, participant refusal or the investigator felt it was no longer in the best interest of the participant to continue on treatment.

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Arm B: nab-Paclitaxel + Carboplatin |
|-----------------------|-------------------------------------|

Reporting group description:

Subjects received nab-Paclitaxel 125 mg/m² on Days 1 and 8 by IV administration followed by Carboplatin AUC 2 on Days 1 and 8 of each 21-day treatment cycle. Subjects continued treatment until progressive disease (PD), unacceptable toxicity, required palliative radiotherapy or surgical intervention of lesion(s), withdrawal from study treatment, withdrawal of study consent, participant refusal or the investigator felt it was no longer in the best interest of the participant to continue on treatment.

| | |
|-----------------------|----------------------------------|
| Reporting group title | Arm C: Gemcitabine + Carboplatin |
|-----------------------|----------------------------------|

Reporting group description:

Subjects received Gemcitabine 1000 mg/m² on Days 1 and 8 by IV administration, followed by carboplatin AUC 2 on Days 1 and 8 by IV administration of each 21-day treatment cycle. Subjects continued treatment until progressive disease (PD), unacceptable toxicity, required palliative radiotherapy or surgical intervention of lesion(s), withdrawal from study treatment, withdrawal of study consent, participant refusal or the investigator felt it was no longer in the best interest of the participant to continue on treatment.

| Serious adverse events | Arm A: nab-Paclitaxel + Gemcitabine | Arm B: nab-Paclitaxel + Carboplatin | Arm C: Gemcitabine + Carboplatin |
|---|-------------------------------------|-------------------------------------|----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 22 / 60 (36.67%) | 20 / 64 (31.25%) | 25 / 64 (39.06%) |
| number of deaths (all causes) | 0 | 1 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Metastases to bone | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to meninges | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| | | | |
|---|----------------|----------------|----------------|
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 2 / 64 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspiration | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | | |
|---|----------------|----------------|----------------|--|
| Dyspnoea | | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 1 / 64 (1.56%) | 2 / 64 (3.13%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Hypoxia | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 2 / 64 (3.13%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 2 / 64 (3.13%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Respiratory tract congestion | | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Palpitations | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sensory disturbance | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Anaemia | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 2 / 64 (3.13%) | 4 / 64 (6.25%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | 5 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 3 / 64 (4.69%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 2 / 64 (3.13%) | 2 / 64 (3.13%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 2 / 64 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticular perforation | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 64 (1.56%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Nodular regenerative hyperplasia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Rash | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 2 / 64 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Breast cellulitis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Device related infection | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related sepsis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 1 / 64 (1.56%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 2 / 64 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 2 / 64 (3.13%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Arm A: nab-Paclitaxel + Gemcitabine | Arm B: nab-Paclitaxel + Carboplatin | Arm C: Gemcitabine + Carboplatin |
|---|--|--|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 59 / 60 (98.33%) | 63 / 64 (98.44%) | 62 / 64 (96.88%) |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 64 (0.00%) | 4 / 64 (6.25%) |
| occurrences (all) | 1 | 0 | 4 |
| Hot flush | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 5 / 64 (7.81%) | 2 / 64 (3.13%) |
| occurrences (all) | 4 | 5 | 2 |
| Hypertension | | | |
| subjects affected / exposed | 8 / 60 (13.33%) | 4 / 64 (6.25%) | 1 / 64 (1.56%) |
| occurrences (all) | 8 | 5 | 1 |
| Lymphoedema | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 6 / 64 (9.38%) | 3 / 64 (4.69%) |
| occurrences (all) | 2 | 6 | 3 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 13 / 60 (21.67%) | 10 / 64 (15.63%) | 15 / 64 (23.44%) |
| occurrences (all) | 58 | 31 | 36 |
| Chills | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 3 / 64 (4.69%) | 2 / 64 (3.13%) |
| occurrences (all) | 6 | 4 | 2 |
| Fatigue | | | |
| subjects affected / exposed | 33 / 60 (55.00%) | 32 / 64 (50.00%) | 24 / 64 (37.50%) |
| occurrences (all) | 82 | 60 | 34 |
| Generalised oedema | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 4 / 64 (6.25%) | 2 / 64 (3.13%) |
| occurrences (all) | 3 | 5 | 2 |
| Non-cardiac chest pain | | | |

| | | | |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 6 / 60 (10.00%) 7 | 3 / 64 (4.69%) 3 | 2 / 64 (3.13%) 2 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 17 / 60 (28.33%) 33 | 12 / 64 (18.75%) 18 | 10 / 64 (15.63%) 11 |
| Pain subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 3 / 64 (4.69%) 3 | 6 / 64 (9.38%) 8 |
| Pyrexia subjects affected / exposed occurrences (all) | 12 / 60 (20.00%) 24 | 5 / 64 (7.81%) 6 | 8 / 64 (12.50%) 13 |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 9 / 64 (14.06%) 13 | 2 / 64 (3.13%) 3 |
| Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 5 / 64 (7.81%) 7 | 0 / 64 (0.00%) 0 |
| Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 2 / 64 (3.13%) 2 | 5 / 64 (7.81%) 5 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 12 / 60 (20.00%) 22 | 17 / 64 (26.56%) 19 | 7 / 64 (10.94%) 8 |
| Dyspnoea subjects affected / exposed occurrences (all) | 7 / 60 (11.67%) 14 | 15 / 64 (23.44%) 19 | 11 / 64 (17.19%) 20 |
| Dyspnoea exertional subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 3 | 4 / 64 (6.25%) 5 | 1 / 64 (1.56%) 1 |
| Epistaxis subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 5 / 64 (7.81%) 6 | 2 / 64 (3.13%) 2 |
| Nasal congestion | | | |

| | | | |
|---|-----------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 6 / 64 (9.38%) 6 | 1 / 64 (1.56%) 1 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 4 | 5 / 64 (7.81%) 6 | 0 / 64 (0.00%) 0 |
| Pleural effusion subjects affected / exposed occurrences (all) | 5 / 60 (8.33%) 7 | 2 / 64 (3.13%) 2 | 1 / 64 (1.56%) 1 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 2 / 64 (3.13%) 2 | 1 / 64 (1.56%) 1 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 2 / 64 (3.13%) 2 | 3 / 64 (4.69%) 3 |
| Depression subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 4 | 2 / 64 (3.13%) 2 | 7 / 64 (10.94%) 7 |
| Insomnia subjects affected / exposed occurrences (all) | 8 / 60 (13.33%) 12 | 12 / 64 (18.75%) 13 | 11 / 64 (17.19%) 11 |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 6 / 60 (10.00%) 16 | 0 / 64 (0.00%) 0 | 5 / 64 (7.81%) 11 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 6 / 60 (10.00%) 11 | 0 / 64 (0.00%) 0 | 4 / 64 (6.25%) 9 |
| Weight decreased subjects affected / exposed occurrences (all) | 8 / 60 (13.33%) 12 | 4 / 64 (6.25%) 4 | 3 / 64 (4.69%) 3 |
| Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 5 / 64 (7.81%) 6 | 1 / 64 (1.56%) 1 |
| Fall | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 6 | 5 / 64 (7.81%) 5 | 1 / 64 (1.56%) 1 |
| Overdose subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 6 / 64 (9.38%) 8 | 2 / 64 (3.13%) 2 |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 1 / 64 (1.56%) 1 | 3 / 64 (4.69%) 3 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 11 / 64 (17.19%) 15 | 9 / 64 (14.06%) 10 |
| Dysgeusia subjects affected / exposed occurrences (all) | 9 / 60 (15.00%) 12 | 9 / 64 (14.06%) 17 | 4 / 64 (6.25%) 5 |
| Headache subjects affected / exposed occurrences (all) | 17 / 60 (28.33%) 21 | 14 / 64 (21.88%) 18 | 12 / 64 (18.75%) 13 |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | 4 / 64 (6.25%) 17 | 2 / 64 (3.13%) 2 |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 7 | 11 / 64 (17.19%) 21 | 3 / 64 (4.69%) 3 |
| Neurotoxicity subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 17 | 3 / 64 (4.69%) 10 | 0 / 64 (0.00%) 0 |
| Paraesthesia subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 4 | 7 / 64 (10.94%) 16 | 2 / 64 (3.13%) 2 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 14 / 60 (23.33%) 27 | 14 / 64 (21.88%) 26 | 5 / 64 (7.81%) 6 |
| Blood and lymphatic system disorders | | | |

| | | | |
|-----------------------------|------------------|------------------|------------------|
| Anaemia | | | |
| subjects affected / exposed | 25 / 60 (41.67%) | 33 / 64 (51.56%) | 30 / 64 (46.88%) |
| occurrences (all) | 58 | 77 | 104 |
| Leukopenia | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 12 / 64 (18.75%) | 14 / 64 (21.88%) |
| occurrences (all) | 9 | 18 | 53 |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 6 / 64 (9.38%) | 5 / 64 (7.81%) |
| occurrences (all) | 3 | 8 | 13 |
| Neutropenia | | | |
| subjects affected / exposed | 24 / 60 (40.00%) | 43 / 64 (67.19%) | 44 / 64 (68.75%) |
| occurrences (all) | 76 | 155 | 258 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 8 / 60 (13.33%) | 18 / 64 (28.13%) | 34 / 64 (53.13%) |
| occurrences (all) | 35 | 53 | 112 |
| Eye disorders | | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 4 / 64 (6.25%) | 1 / 64 (1.56%) |
| occurrences (all) | 2 | 4 | 1 |
| Vision blurred | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 3 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 9 / 64 (14.06%) | 5 / 64 (7.81%) |
| occurrences (all) | 5 | 17 | 6 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 7 / 64 (10.94%) | 5 / 64 (7.81%) |
| occurrences (all) | 5 | 8 | 6 |
| Constipation | | | |
| subjects affected / exposed | 13 / 60 (21.67%) | 27 / 64 (42.19%) | 25 / 64 (39.06%) |
| occurrences (all) | 18 | 35 | 36 |
| Diarrhoea | | | |
| subjects affected / exposed | 25 / 60 (41.67%) | 26 / 64 (40.63%) | 13 / 64 (20.31%) |
| occurrences (all) | 42 | 41 | 16 |
| Dry mouth | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 60 (5.00%) | 2 / 64 (3.13%) | 1 / 64 (1.56%) |
| occurrences (all) | 3 | 2 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 2 / 64 (3.13%) | 4 / 64 (6.25%) |
| occurrences (all) | 3 | 2 | 4 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 1 / 64 (1.56%) | 1 / 64 (1.56%) |
| occurrences (all) | 3 | 1 | 1 |
| Nausea | | | |
| subjects affected / exposed | 26 / 60 (43.33%) | 34 / 64 (53.13%) | 27 / 64 (42.19%) |
| occurrences (all) | 54 | 65 | 55 |
| Stomatitis | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 14 / 64 (21.88%) | 8 / 64 (12.50%) |
| occurrences (all) | 12 | 24 | 8 |
| Vomiting | | | |
| subjects affected / exposed | 18 / 60 (30.00%) | 13 / 64 (20.31%) | 11 / 64 (17.19%) |
| occurrences (all) | 29 | 18 | 22 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 33 / 60 (55.00%) | 25 / 64 (39.06%) | 7 / 64 (10.94%) |
| occurrences (all) | 41 | 35 | 8 |
| Dry skin | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Erythema | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 5 / 64 (7.81%) | 3 / 64 (4.69%) |
| occurrences (all) | 9 | 9 | 3 |
| Pruritus | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 9 / 64 (14.06%) | 4 / 64 (6.25%) |
| occurrences (all) | 6 | 12 | 5 |
| Rash | | | |
| subjects affected / exposed | 8 / 60 (13.33%) | 3 / 64 (4.69%) | 2 / 64 (3.13%) |
| occurrences (all) | 8 | 4 | 3 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |

| | | | |
|--|------------------------|------------------------|-----------------------|
| Rash pruritic subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 1 / 64 (1.56%) 2 | 1 / 64 (1.56%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 13 / 60 (21.67%) 17 | 9 / 64 (14.06%) 15 | 7 / 64 (10.94%) 11 |
| Back pain subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 4 | 14 / 64 (21.88%) 18 | 6 / 64 (9.38%) 7 |
| Bone pain subjects affected / exposed occurrences (all) | 7 / 60 (11.67%) 7 | 5 / 64 (7.81%) 7 | 8 / 64 (12.50%) 12 |
| Muscular weakness subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 2 / 64 (3.13%) 3 | 4 / 64 (6.25%) 4 |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 6 | 3 / 64 (4.69%) 3 | 3 / 64 (4.69%) 4 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 2 / 64 (3.13%) 3 | 4 / 64 (6.25%) 6 |
| Myalgia subjects affected / exposed occurrences (all) | 14 / 60 (23.33%) 22 | 14 / 64 (21.88%) 36 | 4 / 64 (6.25%) 7 |
| Neck pain subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 3 / 64 (4.69%) 3 | 4 / 64 (6.25%) 8 |
| Pain in extremity subjects affected / exposed occurrences (all) | 8 / 60 (13.33%) 11 | 7 / 64 (10.94%) 7 | 4 / 64 (6.25%) 4 |
| Spinal pain subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 1 / 64 (1.56%) 2 | 0 / 64 (0.00%) 0 |
| Infections and infestations | | | |

| | | | |
|------------------------------------|------------------|------------------|------------------|
| Bronchitis | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 5 / 64 (7.81%) | 1 / 64 (1.56%) |
| occurrences (all) | 2 | 5 | 1 |
| Cellulitis | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 2 / 64 (3.13%) | 0 / 64 (0.00%) |
| occurrences (all) | 11 | 2 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 4 / 64 (6.25%) | 2 / 64 (3.13%) |
| occurrences (all) | 1 | 4 | 3 |
| Sinusitis | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 2 / 64 (3.13%) | 0 / 64 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 6 / 60 (10.00%) | 7 / 64 (10.94%) | 2 / 64 (3.13%) |
| occurrences (all) | 8 | 9 | 4 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 11 / 64 (17.19%) | 6 / 64 (9.38%) |
| occurrences (all) | 6 | 12 | 7 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 15 / 60 (25.00%) | 14 / 64 (21.88%) | 10 / 64 (15.63%) |
| occurrences (all) | 18 | 22 | 12 |
| Dehydration | | | |
| subjects affected / exposed | 6 / 60 (10.00%) | 1 / 64 (1.56%) | 3 / 64 (4.69%) |
| occurrences (all) | 7 | 1 | 3 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 5 / 64 (7.81%) | 2 / 64 (3.13%) |
| occurrences (all) | 6 | 7 | 2 |
| Hypokalaemia | | | |
| subjects affected / exposed | 8 / 60 (13.33%) | 12 / 64 (18.75%) | 7 / 64 (10.94%) |
| occurrences (all) | 10 | 21 | 11 |
| Hypomagnesaemia | | | |

| | | | |
|-----------------------------|----------------|------------------|----------------|
| subjects affected / exposed | 1 / 60 (1.67%) | 12 / 64 (18.75%) | 5 / 64 (7.81%) |
| occurrences (all) | 1 | 13 | 6 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 07 February 2014 | The main changes in Amendment 1 were based on recommendations from the Scientific Steering Committee, Institutional Review Boards and Ethics Committees, and Principal Investigators. They included modification to the requirement for mandatory participation in biomarker studies, changes to inclusion/exclusion criteria, and management of toxicities by allowing subjects to continue in the study on monotherapy. - Biomarker collection was updated to optional participation. - Changes to inclusion/exclusion criteria were: o Disease free interval for patients that received neoadjuvant or adjuvant therapy prior to study entry was defined depending on the regimen previously received. o The time permitted for the administration of bone targeted therapies was expanded to any time during the screening and treatment periods, since an impact on outcomes had not been proven in this patient population. o Changes permitted the administration of warfarin, as well as other anticoagulation therapies, during the trial. The 7-day wash-out period for anticoagulants prior to randomization was also eliminated. These changes were supported by the absence of clinical evidence contraindicating the use of anticoagulants during nab-paclitaxel treatment. - Toxicity management was updated to allow monotherapy in the case when hypersensitivity or other toxicity specifically related to one of the drugs demanded discontinuation, and there was potential benefit to maintaining treatment with the second component of the particular doublet. |
| 01 July 2015 | Included DMC conclusions and recommendations. - Changed event-driven analyses to time-driven. A final Phase 2 analysis was to be conducted approximately 12 months after the last subject had been randomized. - Length of study was updated to reflect approximately 80 months, with a Phase 2 enrollment of 24 months and a Phase 2 follow-up of 12 months. - Sample size was reduced from 240 subjects (80 per treatment arm) to approximately 180 subjects (60 per treatment arm) to reflect the number of subjects randomized at the time of the decision to stop enrollment per DMC recommendations. - Clarified exploratory endpoints and objectives. Time to death was determined by the secondary objective and the secondary endpoint of overall survival. Exploratory objectives and endpoints of time to second line therapy or death were clarified to time to second line therapy. - With the identification of nab-paclitaxel plus carboplatin as the experimental treatment arm for further investigation, all references to a Phase 3 treatment of nab-paclitaxel plus gemcitabine were removed. |

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.

Due to changes in the treatment landscape since the trial initiation, including the initiation of trials with immunotherapy drugs, successful enrollment of the Phase 3 part was considered unlikely and was not conducted; no safety signals were raised.

Notes: