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/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.

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/m^2 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/m^2 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/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.

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/m^2 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/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.

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/m^2 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 lst Reported Disease/Relapse			
Units: months			
arithmetic mean	38.8	29.9	50.9
standard deviation	± 49.46	± 37.18	± 62.60
Time from First Documented Metastatic Disease/Relapse to Randomization			
Units: months			
arithmetic mean	2.1	4.2	1.6
standard deviation	± 5.08	± 18.39	± 1.70
Time from Primary Diagnosis to Randomization			
Units: months			
arithmetic mean	43.7	35.5	52.5
standard deviation	± 54.60	± 40.51	± 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 lst 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/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 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/m^2 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/m^2 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 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	6 / 60 (10.00%)	3 / 64 (4.69%)	2 / 64 (3.13%)
occurrences (all)	7	3	2
Oedema peripheral			
subjects affected / exposed	17 / 60 (28.33%)	12 / 64 (18.75%)	10 / 64 (15.63%)
occurrences (all)	33	18	11
Pain			
subjects affected / exposed	3 / 60 (5.00%)	3 / 64 (4.69%)	6 / 64 (9.38%)
occurrences (all)	3	3	8
Pyrexia			
subjects affected / exposed	12 / 60 (20.00%)	5 / 64 (7.81%)	8 / 64 (12.50%)
occurrences (all)	24	6	13
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	3 / 60 (5.00%)	9 / 64 (14.06%)	2 / 64 (3.13%)
occurrences (all)	3	13	3
Hypersensitivity			
subjects affected / exposed	0 / 60 (0.00%)	5 / 64 (7.81%)	0 / 64 (0.00%)
occurrences (all)	0	7	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 60 (0.00%)	2 / 64 (3.13%)	5 / 64 (7.81%)
occurrences (all)	0	2	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 60 (20.00%)	17 / 64 (26.56%)	7 / 64 (10.94%)
occurrences (all)	22	19	8
Dyspnoea			
subjects affected / exposed	7 / 60 (11.67%)	15 / 64 (23.44%)	11 / 64 (17.19%)
occurrences (all)	14	19	20
Dyspnoea exertional			
subjects affected / exposed	2 / 60 (3.33%)	4 / 64 (6.25%)	1 / 64 (1.56%)
occurrences (all)	3	5	1
Epistaxis			
subjects affected / exposed	3 / 60 (5.00%)	5 / 64 (7.81%)	2 / 64 (3.13%)
occurrences (all)	3	6	2
Nasal congestion			

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

subjects affected / exposed	4 / 60 (6.67%)	5 / 64 (7.81%)	1 / 64 (1.56%)
occurrences (all)	6	5	1
Overdose			
subjects affected / exposed	1 / 60 (1.67%)	6 / 64 (9.38%)	2 / 64 (3.13%)
occurrences (all)	1	8	2
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 60 (5.00%)	1 / 64 (1.56%)	3 / 64 (4.69%)
occurrences (all)	3	1	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 60 (5.00%)	11 / 64 (17.19%)	9 / 64 (14.06%)
occurrences (all)	3	15	10
Dysgeusia			
subjects affected / exposed	9 / 60 (15.00%)	9 / 64 (14.06%)	4 / 64 (6.25%)
occurrences (all)	12	17	5
Headache			
subjects affected / exposed	17 / 60 (28.33%)	14 / 64 (21.88%)	12 / 64 (18.75%)
occurrences (all)	21	18	13
Hypoaesthesia			
subjects affected / exposed	2 / 60 (3.33%)	4 / 64 (6.25%)	2 / 64 (3.13%)
occurrences (all)	2	17	2
Neuropathy peripheral			
subjects affected / exposed	4 / 60 (6.67%)	11 / 64 (17.19%)	3 / 64 (4.69%)
occurrences (all)	7	21	3
Neurotoxicity			
subjects affected / exposed	4 / 60 (6.67%)	3 / 64 (4.69%)	0 / 64 (0.00%)
occurrences (all)	17	10	0
Paraesthesia			
subjects affected / exposed	4 / 60 (6.67%)	7 / 64 (10.94%)	2 / 64 (3.13%)
occurrences (all)	4	16	2
Peripheral sensory neuropathy			
subjects affected / exposed	14 / 60 (23.33%)	14 / 64 (21.88%)	5 / 64 (7.81%)
occurrences (all)	27	26	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	3 / 60 (5.00%)	1 / 64 (1.56%)	1 / 64 (1.56%)
occurrences (all)	3	2	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 60 (21.67%)	9 / 64 (14.06%)	7 / 64 (10.94%)
occurrences (all)	17	15	11
Back pain			
subjects affected / exposed	3 / 60 (5.00%)	14 / 64 (21.88%)	6 / 64 (9.38%)
occurrences (all)	4	18	7
Bone pain			
subjects affected / exposed	7 / 60 (11.67%)	5 / 64 (7.81%)	8 / 64 (12.50%)
occurrences (all)	7	7	12
Muscular weakness			
subjects affected / exposed	1 / 60 (1.67%)	2 / 64 (3.13%)	4 / 64 (6.25%)
occurrences (all)	1	3	4
Musculoskeletal chest pain			
subjects affected / exposed	3 / 60 (5.00%)	3 / 64 (4.69%)	3 / 64 (4.69%)
occurrences (all)	6	3	4
Musculoskeletal pain			
subjects affected / exposed	1 / 60 (1.67%)	2 / 64 (3.13%)	4 / 64 (6.25%)
occurrences (all)	1	3	6
Myalgia			
subjects affected / exposed	14 / 60 (23.33%)	14 / 64 (21.88%)	4 / 64 (6.25%)
occurrences (all)	22	36	7
Neck pain			
subjects affected / exposed	3 / 60 (5.00%)	3 / 64 (4.69%)	4 / 64 (6.25%)
occurrences (all)	3	3	8
Pain in extremity			
subjects affected / exposed	8 / 60 (13.33%)	7 / 64 (10.94%)	4 / 64 (6.25%)
occurrences (all)	11	7	4
Spinal pain			
subjects affected / exposed	3 / 60 (5.00%)	1 / 64 (1.56%)	0 / 64 (0.00%)
occurrences (all)	3	2	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 occurrences (all)	1 / 60 (1.67%) 1	12 / 64 (18.75%) 13	5 / 64 (7.81%) 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: