Clinical trial results:
A randomized phase III 2-arm trial of paclitaxel plus bevacizumab vs. capecitabine plus bevacizumab for the first-line treatment of HER2-negative locally recurrent or metastatic breast cancer

Summary

EudraCT number	2007-005828-32
Trial protocol	AT CZ HU LV SK BG
Global end of trial date	15 December 2014

Results information

Result version number	v1 (current)
This version publication date	08 November 2019
First version publication date	08 November 2019

Trial information

Trial identification

Sponsor protocol code	CECOG/BC 1.3.005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00600340
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CECOG (Central European Cooperative Oncology Group)
Sponsor organisation address	Schlagergasse 6/6, Vienna, Austria, A-1090
Public contact	Waehringer Guertel 18-20 A-1090 Vienna Austria, Prof. Christoph Zielinski, M.D., christoph.zielinski@meduniwien.ac.at
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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	30 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2014
Global end of trial reached?	Yes
Global end of trial date	15 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To show non-inferiority of Arm B versus Arm A in terms of overall survival (OS). Overall survival is assessed as time from date of randomization until date of death.
Study Treatment, given until progression of disease, unacceptable toxicity of withdrawal of consent:
Arm A: Bevacizumab plus Paclitaxel
Arm B: Bevacizumab plus Capecitabine

Protection of trial subjects:

For patients who stopped chemotherapy or the companion drug for any reason before disease progression (e.g. toxicity), the chemotherapy or companion drug was given as monotherapy until disease progression. If toxicity required a dosing delay or interruption of paclitaxel or capecitabine of more than three weeks, the patient was withdrawn from study treatment for toxicity reasons, but continued with the companion drug.
In cases of a first occurrence of a serious bevacizumab-related toxicity (grade 3 or 4), bevacizumab treatment was temporarily (for a max of 6 weeks) suspended. Bevacizumab was permanently suspended for a second occurrence of a serious bevacizumab-related toxicity.
Additionally, any patient who experienced the following events permanently discontinued bevacizumab:
• Reversible Posterior Leucoencephalopathy Syndrome (RPLS)
• Grade 3/4 hemorrhagic/bleeding events
• Any grade of arterial thromboembolism
• Grade 4 hypertension (hypertensive crisis)
• Grade 4 proteinuria (nephrotic syndrome)
• Grade 3/4 left ventricular dysfunction (CHF)
• Any grade of Gastrointestinal perforation
• Any grade of Tracheo-esophageal fistula
• Any grade 4 non-gastrointestinal fistula
• Any grade of hypersensitivity/allergic reactions related to bevacizumab.

Background therapy: -

Evidence for comparator:

Results from a phase III trial (E2100) indicate that the addition of bevacizumab to first-line paclitaxel significantly improves PFS (hazard ratio 0.48 [95% CI: 0.39–0.59], p=0.0001, median 6.7 vs 13.3 months).
A phase III trial demonstrated that the addition of bevacizumab to capecitabine in heavily pretreated patients significantly improves response rate. In this trial, 462 heavily pre-treated patients were randomised to treatment with standard-dose single-agent capecitabine (1,250 mg/m2 twice daily, days 1–14 every 21 days) or the same capecitabine regimen plus bevacizumab 15 mg/kg on day 1 every 21 days. The response rate was 20% with the combination versus 9% with single-agent capecitabine (p=0.001). However, the significantly superior response rate did not translate into improved PFS (hazard ratio 0.98 [95% CI: 0.77–1.25], p=0.857; median 4.9 vs. 4.2 months, respectively) or overall survival (median 15.1 vs 14.5 months, respectively).
The preliminary results of a single-arm phase II study of bevacizumab plus capecitabine in the first-line setting suggest that the combination is more active earlier in the disease course. In this study, patients received capecitabine 1,000 mg/m2 administered twice-daily for 14 days followed by a 7-day rest period in combination with bevacizumab 15 mg/kg every 21 days. Grade 4 adverse events were rare and the only grade 3 toxicities occurring in >5% of patients were hand-foot syndrome (13%), pain (10%), fatigue (7%) and diarrhoea (6%). Interim results for the first part of this crossover study indicated that with a median follow-up of 12.9 months (range 0.5-20.7), the median Time to progression (TTP) for the Intent-to-treat population (n=106) was 5.7 months (range 4.9-8.4) and 8.9 months (range7.5-13.6) in the estrogen receptor (ER) positive patient population. Corresponding results for overall survival for the

ITT vs ER positive populations were 16.0+ months vs 16.6+ months, respectively.

Actual start date of recruitment	10 September 2008
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	Poland: 36
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Austria: 75
Country: Number of subjects enrolled	Bulgaria: 13
Country: Number of subjects enrolled	Czech Republic: 37
Country: Number of subjects enrolled	Hungary: 162
Country: Number of subjects enrolled	Latvia: 27
Country: Number of subjects enrolled	Bosnia and Herzegovina: 26
Country: Number of subjects enrolled	Croatia: 12
Country: Number of subjects enrolled	Israel: 105
Country: Number of subjects enrolled	Romania: 42
Country: Number of subjects enrolled	Serbia: 14
Worldwide total number of subjects	564
EEA total number of subjects	419

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)	419
From 65 to 84 years	143
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 604 patients were screened and 564 randomized between September 10, 2008 and August 30, 2010, in 51 sites in 12 countries (Austria: 9, Bosnia: 1, Bulgaria: 3, Croatia: 5, Czech Republic: 4, Hungary: 4, Israel: 5, Latvia: 2, Poland: 6, Romania: 5, Serbia: 3, Slovakia: 4).
564 pats in ITT population, 561 in safety, 533 in per-protocol.

Pre-assignment

Screening details:

604 patients were screened for eligibility, 40 of these were not randomized: 38 did not meet the inclusion criteria, 2 declined to participate.

Period 1

Period 1 title	Overall trial (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

Arm description:

Patients in this arm received a combination of bevacizumab plus paclitaxel in cycles of 28 days as first-line treatment. Treatment continued until first progression of disease (PD), unacceptable toxicity or withdrawal of patient's consent. For patients who stopped chemotherapy for any reason before PD, bevacizumab was to be given as monotherapy until PD.
Bevacizumab 10mg/kg i.v., days 1 and 15, every 4 weeks
Paclitaxel 90mg/m², days 1, 8 and 15, every 4 weeks

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab dose of 10 mg/kg on days 1 and 15, every 4 weeks. Patient's weight at screening was used to determine the dose to be used for the duration of the study. In case of weight change by more than 10% during the study, the dose had to be recalculated. Bevacizumab was administered as an i.v. infusion initially over 90 minutes (following the administration of paclitaxel). If the first infusion was well tolerated, the second infusion could be delivered over a 60-minute period. If the 60-minute infusion was well tolerated, all subsequent infusions could be delivered over a 30-minute period.
Bevacizumab was to be stored at 2 to 8°C and was to be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute with sodium chloride (0.9%) solution for injection, up to a total volume of 100 mL. For heavier patients receiving doses of 10 or 15 mg/kg, the dose might be made up to 200 or 250 mL with sodium Chloride (0.9%) solution.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel in dose of 90 mg/m² on days 1, 8 and 15, every 4 weeks. Obtained commercially in vials of 30 mg (5.0 mL) and 100 mg (16.7 mL) and supplied with solvent. This was further diluted in 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, 5% Dextrose and 0.9% Sodium Chloride Injection, USP or 5% Dextrose in Ringer´s Injection to a final concentration of 0.3 to 1.2 mg/mL, prior to administration.

Recommended pretreatment with oral corticosteroids (such as dexametaxone), difenhidramina and H2 antagonists (such as ranitidine) to reduce the severity of hypersensitivity reactions.
Paclitaxel was be administered as a 1-hour i.v. infusion before bevacizumab and with the appropriate co-medications.

Arm title	Arm B

Arm description:

Patients in Arm B received combination treatment with bevacizumab plus capecitabine as first-line treatment in cycles of 21 days, until first progression of disease (PD), unacceptable toxicity or withdrawal of patient consent. For patients who stopped chemotherapy for any reason before PD, bevacizumab was to be given as montherapy until PD.
Bevacizumab 15 mg/kg i.v. on day 1 every 3 weeks
Capecitabine 1000 mg/m² twice-daily on days 1-14, every 3 weeks

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab dose of 15 mg/kg on day 1, every 3 weeks. Patient's weight at screening was used to determine the dose to be used for the duration of the study. In case of weight change by more than 10% during the study, the dose had to be recalculated. Bevacizumab was administered as an i.v. infusion initially over 90 minutes (following the administration of paclitaxel). If the first infusion was well tolerated, the second infusion could be delivered over a 60-minute period. If the 60-minute infusion was well tolerated, all subsequent infusions could be delivered over a 30-minute period.
Bevacizumab was to be stored at 2 to 8°C and was to be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute with sodium chloride (0.9%) solution for injection, up to a total volume of 100 mL. For heavier patients receiving doses of 10 or 15 mg/kg, the dose might be made up to 200 or 250 mL with sodium Chloride (0.9%) solution.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dose of twice-daily 1000 mg/m² on days 1-14, every 3 weeks. To be taken orally twice daily in equally divided doses morning and evening for a total daily dose of 2000 mg/m² on days 1-14, with the first dose occurring in the morning of day 1 and the last dose occurring on the evening of day 14 for a total of 28 doses. The morning and evening dose should be given approximately 12 hours apart, and taken within 30 minutes after the ingestion of food with approximately 200 mL of water, ideally after the breakfast and evening meal.
Patients who were 65 years of age or older had an initial 25% capecitabine dose reduction.
The daily dose was derived by determining the body surface area (BSA) from the nomogram in Appendix 5 of the study protocol. If body weight varied during the study, it was assumed that the body surface area would remain approximately constant (i.e. no dose adjustments for changes in body weight were done).

Number of subjects in period 1	Arm A	Arm B
Started	285	279
Completed	285	279

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Patients in this arm received a combination of bevacizumab plus paclitaxel in cycles of 28 days as first-line treatment. Treatment continued until first progression of disease (PD), unacceptable toxicity or withdrawal of patient's consent. For patients who stopped chemotherapy for any reason before PD, bevacizumab was to be given as monotherapy until PD. Bevacizumab 10mg/kg i.v., days 1 and 15, every 4 weeks Paclitaxel 90mg/m², days 1, 8 and 15, every 4 weeks	
Reporting group title	Arm B
Reporting group description:	
Patients in Arm B received combination treatment with bevacizumab plus capecitabine as first-line treatment in cycles of 21 days, until first progression of disease (PD), unacceptable toxicity or withdrawal of patient consent. For patients who stopped chemotherapy for any reason before PD, bevacizumab was to be given as montherapy until PD. Bevacizumab 15 mg/kg i.v. on day 1 every 3 weeks Capecitabine 1000 mg/m² twice-daily on days 1-14, every 3 weeks	

Reporting group values	Arm A	Arm B	Total
Number of subjects	285	279	564
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)	218	201	419
From 65-84 years	66	77	143
85 years and over	1	1	2
Age continuous Units: years			
median	59	59	
inter-quartile range (Q1-Q3)	49 to 64	48 to 65	-
Gender categorical Units: Subjects			
Female	284	275	559
Male	1	4	5
Race Units: Subjects			
Caucasian/White	283	278	561
Black	1	0	1
Other	1	1	2
Menopausal status Units: Subjects			
Pre-menopausal	52	52	104
Post-menopausal	232	223	455

Male patients	1	4	5
ECOG PS Units: Subjects			
ECOG 0	193	179	372
ECOG 1	75	91	166
ECOG 2	16	7	23
Missing	1	2	3
Estrogen receptor (ER) Units: Subjects			
Positive	215	201	416
Negative	68	77	145
Unknown	2	1	3
Progesterone Receptor (PgR) Units: Subjects			
Positive	167	168	335
Negative	118	109	227
Unknown	0	2	2
Estrogen and progesterone receptor Units: Subjects			
ER and PgR negative	63	67	130
ER or PgR positive	221	212	433
ER and PR unknown or negative	1	0	1
ECG result Units: Subjects			
Normal	243	246	489
Abnormal	39	30	69
Not performed	3	3	6
Method for brain imaging			
No brain CT or MRI was required if the patient did not show signs/symptoms of CNS involvement or other unexplained neurological symptoms.			
Units: Subjects			
CT	18	19	37
MRI	3	2	5
No brain CT/MRI	264	258	522
Result of brain CT/MRI			
No brain CT or MRI was required if the patient did not show signs/symptoms suggestive of CNS involvement or other unexplained neurological symptoms.			
Units: Subjects			
No metastasis	21	21	42
No brain CT/MRI	264	258	522
Stage at primary diagnosis: Primary tumor (T) Units: Subjects			
Tis	1	2	3
T1	66	72	138
T2	130	118	248
T3	26	32	58
T4	45	38	83
TX	16	16	32
Missing	1	1	2
Stage at primary diagnosis: Regional lymph nodes (N)			

Units: Subjects			
N0	78	62	140
N1	97	116	213
N2	55	51	106
N3	26	22	48
NX	28	27	55
Missing	1	1	2
Stage at primary diagnosis: Distant metastasis (M) Units: Subjects			
M0	222	219	441
M1	62	59	121
Missing	1	1	2
Current stage of locally recurrent/metastatic tumor Units: Subjects			
Locally recurrent breast cancer	2	0	2
Metastatic breast cancer	282	279	561
Missing	1	0	1
Disease free interval after therapy of primary breast cancer Units: Subjects			
Yes	214	215	429
No	71	64	135
Disease free interval			
Disease free interval set to 0 months (No DFI), if the patient did not receive previous therapy fo primary breast cancer or if the patient was not disease free after previous therapy of Primary breast cancer			
Units: Subjects			
No DFI	71	64	135
DFI <=12 months	14	10	24
DFI >12 and <=24 months	52	34	86
DFI >24 months	148	171	319
Metastatic lesions			
Patients can have multiple sites with metastatic lesions.			
Units: Subjects			
At least one metastatic lesion	282	279	561
No metastatic lesions	3	0	3
Imaging methods Units: Subjects			
CT	270	261	531
MRI	8	12	20
X-ray	7	6	13
Target and non-target lestions Units: Subjects			
Target lesions only	34	22	56
Non-target lesions only	65	49	114
Both	185	208	393
None	1	0	1
Number of target lesions Units: Subjects			
0 lesions	66	49	115
1 lesion	48	49	97

2 lesions	41	49	90
3 lesions	47	39	86
4-5 lesions	44	57	101
>=6 lesions	39	36	75
Number of organs with metastases Units: Subjects			
>=3	105	124	229
<3	180	155	335
Previous hormonal therapy			
LR/MBC = for locally recurrent / metastatic breast cancer			
Units: Subjects			
Neoadjuvant/adjuvant only	113	112	225
LR/MBC only	25	33	58
Both	37	25	62
Other	0	1	1
None	110	108	218
Previous neoadjuvant chemotherapy Units: Subjects			
Anthracycline and taxane	16	11	27
Anthracycline, no taxane	41	33	74
Taxane, no anthracycline	5	5	10
No anthracycline, no taxane, other	2	3	5
none	221	227	448
Previous adjuvant chemotherapy Units: Subjects			
Anthracycline and taxane	21	25	46
Anthracycline, no taxane	83	89	172
Taxane, no anthracycline	16	12	28
No anthracycline, no taxane, other	30	25	55
None	135	128	263
Previous neoadjuvant/adjuvant chemotherapy Units: Subjects			
Yes	180	176	356
No	105	103	208
Previous radiotherapy Units: Subjects			
Yes	191	194	385
No	94	85	179
Previous surgery Units: Subjects			
Yes	241	239	480
No	44	40	84
Sum of longest diameter of target lesions Units: Subjects			
No lesions	66	49	115
1 - 5 cm	86	83	169
>5 - 10 cm	64	77	141
>10 cm	69	70	139
Previous neoadjuvant/ adjuvant hormonal therapy only with anti-			

estrogens Units: Subjects			
Yes	87	89	176
No	198	190	388
Bone metastatic lesions Units: Subjects			
Yes	158	151	309
No	127	128	255
Lung metastatic lesions Units: Subjects			
Yes	112	122	234
No	173	157	330
Liver metastatic lesions Units: Subjects			
Yes	113	126	239
No	172	153	325
Skin metastatic lesions Units: Subjects			
Yes	13	9	22
No	272	270	542
Soft tissue metastatic lesions Units: Subjects			
Yes	69	63	132
No	216	216	432
Lymph node metastatic lesions Units: Subjects			
Yes	146	171	317
No	139	108	247
Lung and/ or liver metastatic lesions Units: Subjects			
Yes	185	203	388
No	100	76	176
Soft tissue and/ or bone metastatic lesions only Units: Subjects			
Yes	41	23	64
No	244	256	500
Other metastatic lesions			
Metastatic lesions in locations other than bone, lung, liver, skin, soft tissue and lymph nodes			
Units: Subjects			
Yes	19	25	44
No	266	254	520
Previous neoadjuvant/adjuvant chemotherapy with anthracycline Units: Subjects			
Yes	145	144	289
No	140	135	275
Previous neoadjuvant/adjuvant chemotherapy with taxane Units: Subjects			
Yes	57	50	107
No	228	229	457

Previous neoadjuvant/adjuvant chemotherapy with other medications			
Excluding anthracycline and taxane			
Units: Subjects			
Yes	26	26	52
No	259	253	512
Previous total mastectomy Units: Subjects			
Yes	131	135	266
No	154	144	298
Previous breast conserving surgery Units: Subjects			
Yes	111	99	210
No	174	180	354
Previous biopsy/ aspiration Units: Subjects			
Yes	54	48	102
No	231	231	462
Other previous surgery			
Surgery other than total mastectomy, breast conserving surgery, biopsy, aspiration			
Units: Subjects			
Yes	35	29	64
No	250	250	500
Previous neoadjuvant radiotherapy Units: Subjects			
Yes	8	9	17
No	277	270	547
Previous adjuvant radiotherapy Units: Subjects			
Yes	167	171	338
No	118	108	226
Previous radiotherapy for relief of metastatic bone pain Units: Subjects			
Yes	32	44	76
No	253	235	488
Previous hormonal therapy for LR/MBC only with anti-estrogens			
LR/MBC = locally recurrent/metastatic breast cancer			
Units: Subjects			
Yes	18	29	47
No	267	250	517
Previous hormonal therapy for LR/MBC only with aromatase inhibitors			
LR/MBC = locally recurrent/metastatic breast cancer			
Units: Subjects			
Yes	17	23	40
No	268	256	524
Previous hormonal therapy for LR/MBC only with LH-RH analogues			
LR/MBC = locally recurrent/metastatic breast cancer			
Units: Subjects			
Yes	1	4	5

No	284	275	559
Previous neoadjuvant/ adjuvant hormonal therapy only with aromatase inhibitors Units: Subjects			
Yes	56	56	112
No	229	223	452
Previous neoadjuvant/ adjuvant hormonal therapy only with LR-RH analogues Units: Subjects			
Yes	12	15	27
No	273	264	537
Previous neoadjuvant/ adjuvant hormonal therapy only with progesterone Units: Subjects			
Yes	0	1	1
No	285	278	563
Previous neoadjuvant/ adjuvant hormonal therapy only with other therapies			
Other neoadjuvant/ adjuvant hormonal therapies excluding anti-estrogens, aromatase Inhibitors, LR-RH analogues, and progesterone			
Units: Subjects			
Yes	0	1	1
No	285	278	563
Height Units: cm			
arithmetic mean	162.0	162.3	
standard deviation	± 6.60	± 6.48	-
Weight Units: kg			
arithmetic mean	71.97	72.90	
standard deviation	± 15.679	± 14.350	-
BSA Units: m^2			
arithmetic mean	1.760	1.773	
standard deviation	± 0.1834	± 0.1688	-
Systolic blood pressure Units: mmHg			
arithmetic mean	127.9	128.7	
standard deviation	± 12.91	± 13.85	-
Diastolic blood pressure Units: mmHg			
arithmetic mean	78.1	77.9	
standard deviation	± 8.23	± 9.34	-
Heart rate Units: beats per minute			
arithmetic mean	79.7	79.1	
standard deviation	± 11.27	± 11.41	-
Body temperature Units: °C			
arithmetic mean	36.55	36.47	

standard deviation	± 0.265	± 0.305	-
LVEF			
Units: percent			
arithmetic mean	63.4	62.6	
standard deviation	± 5.32	± 6.26	-
Time since diagnosis of adenocarcinoma			
Adenocarcinoma histologically of cytologically confirmed.			
Units: months			
arithmetic mean	55.2	58.9	
standard deviation	± 56.46	± 55.09	-
Time since diagnosis of LR or MT			
LR or MT = locally recurrent of metastatic tumor			
Units: months			
arithmetic mean	5.7	7.6	
standard deviation	± 14.77	± 19.11	-
Disease free interval			
Disease free interval was set to 0 months (No DFI) if the patient did not receive previous therapy for primary breast cancer or the patient was not disease free after previous therapy for primary breast cancer.			
Units: months			
arithmetic mean	43.6	48.0	
standard deviation	± 48.84	± 48.53	-
Number of target lesions			
Units: number			
arithmetic mean	2.7	2.8	
standard deviation	± 2.52	± 2.42	-
Sum of longest diameters of target lesions			
Units: cm			
arithmetic mean	6.758	6.872	
standard deviation	± 7.4372	± 6.6679	-

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Patients in this arm received a combination of bevacizumab plus paclitaxel in cycles of 28 days as first-line treatment. Treatment continued until first progression of disease (PD), unacceptable toxicity or withdrawal of patient's consent. For patients who stopped chemotherapy for any reason before PD, bevacizumab was to be given as monotherapy until PD.
Bevacizumab 10mg/kg i.v., days 1 and 15, every 4 weeks
Paclitaxel 90mg/m², days 1, 8 and 15, every 4 weeks

Reporting group title	Arm B

Reporting group description:

Patients in Arm B received combination treatment with bevacizumab plus capecitabine as first-line treatment in cycles of 21 days, until first progression of disease (PD), unacceptable toxicity or withdrawal of patient consent. For patients who stopped chemotherapy for any reason before PD, bevacizumab was to be given as montherapy until PD.
Bevacizumab 15 mg/kg i.v. on day 1 every 3 weeks
Capecitabine 1000 mg/m² twice-daily on days 1-14, every 3 weeks

Primary: Overall Survival (PP population)

End point title	Overall Survival (PP population)

End point description:

OS defined as time from randomization to date of death from any cause. Patients without recorded death were censored at the date the patient was last known to be alive. For the adjusted HR, the stratification factors at randomization were used.
OS was analyzed at two looks, one interim look and the final analysis. Due to group sequential testing, the overall significance level alpha = 0.025 was spent on both looks according to Lan-DeMets spending method with O'Brien-Fleming-type boundaries. Alpha spent at interim after 47% of information was 0.0010. Alpha spent at final analysis after 99% of information was 0.0250.

End point type	Primary

End point timeframe:

Median Overall Survival (OS), associated stratified Hazard Ratio(HR) (pre-specified primary endpoint) and unstratified HR (sensitivity analysis) assessed after a median observation time of 54.3 months in arm A and 55.7 months in arm B.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266[1]	265[2]		
Units: months				
median (confidence interval 95%)	30.2 (25.6 to 32.6)	26.1 (22.3 to 29.0)		

Notes:

[1] - Per protocol population

[2] - Per-protocol population

Attachments (see zip file)	Kaplan-Meier Plot for OS by Arm (PP Population)/gkmeos_tg_p.

Statistical analyses

Statistical analysis title	HR of Arm B vs. Arm A for OS (interim, stratified)

Statistical analysis description:

Based on Cox proportional hazards model adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of age)
HR is the hazard rate of Arm B divided by hazard rate of Arm A.

Comparison groups	Arm B v Arm A
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1983 [3]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.042
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	1.689

Notes:

[3] - Based on approach using repeated confidence intervals, with one-sided 97.5% repeated confidence intervals

Statistical analysis title	HR of Arm B vs. Arm A for OS (final, stratified)

Statistical analysis description:

Based on Cox proportional hazards model adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of Age)
HR is the hazard rate of Arm B divided by hazard rate of Arm A.

Comparison groups	Arm B v Arm A
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.007 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.018
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	1.261

Notes:

[4] - Based on approach using repeated confidence intervals, with one-sided 97.5% repeated confidence intervals. Non-inferiority margin was a HR of 1.33.

Statistical analysis title	HR of Arm B vs. Arm A for OS (interim, unstrat.)

Statistical analysis description:

Based on unadjusted Cox proportional hazards model.
HR is the hazard rate of Arm B divided by hazard rate of Arm A.

Comparison groups	Arm B v Arm A

Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2024 [5]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.058
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	1.674

Notes:

[5] - Based on approach using repeated confidence intervals, with one-sided 97.5% repeated confidence intervals. Non-inferiority margin was a HR of 1.33.

Statistical analysis title	HR of Arm B vs. Arm A for OS (final, unstratified)

Statistical analysis description:

Based on unadjusted Cox proportional hazards model.
HR is the hazard rate of Arm B divided by hazard rate of Arm A.

Comparison groups	Arm B v Arm A
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0612 [6]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.134
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	1.386

Notes:

[6] - Based on approach using repeated confidence intervals, with one-sided 97.5% repeated confidence intervals. Non-inferiority margin was a HR of 1.33.

Primary: Overall Survival (ITT population)

End point title	Overall Survival (ITT population)

End point description:

OS defined as time from randomization to date of death from any cause. Patients without recorded death were censored at the date the patient was last known to be alive. For the adjusted HR, the stratification factors at randomization were used.
OS was analyzed at two looks, one interim look and the final analysis. Due to group sequential testing, the overall significance level alpha = 0.025 was spent on both looks according to Lan-DeMets spending method with O'Brien-Fleming-type boundaries. Alpha spent at interim after 50% of information was 0.0014. Alpha spent at final analysis after 99% of information was 0.0250.

End point type	Primary

End point timeframe:

Median Overall Survival (OS), associated stratified Hazard Ratio(HR) (pre-specified primary endpoint) and unstratified HR (sensitivity analysis) assessed after a median observation time of 54.3 months in arm A and 55.7 months in arm B.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285[7]	279[8]		
Units: months				
median (confidence interval 95%)	29.5 (25.3 to 32.4)	26.0 (22.3 to 29.0)		

Notes:

[7] - ITT population

[8] - ITT population

Attachments (see zip file)	Kaplan-Meier Plot for OS by Arm (ITT Population)/gkmeos_tg_i.

Statistical analyses

Statistical analysis title	HR of Arm B vs. Arm A for OS (interim, stratified)

Statistical analysis description:

Based on Cox proportional hazards model adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of Age)
HR is the hazard rate of Arm B divided by hazard rate of Arm A.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1534 [9]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.027
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	1.606

Notes:

[9] - Based on approach using repeated confidence intervals, with one-sided 97.5% repeated confidence intervals

Statistical analysis title	HR of Arm B vs. Arm A for OS (final, stratified)

Statistical analysis description:

Based on Cox proportional hazards model adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of Age)
HR is the hazard rate of Arm B divided by hazard rate of Arm A.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0085 [10]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.035

Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	1.273

Notes:

[10] - Based on approach using repeated confidence intervals, with one-sided 97.5% repeated confidence intervals

Statistical analysis title	HR of Arm B vs. Arm A for OS (interim, unstrat.)

Statistical analysis description:

Based on unadjusted Cox proportional hazards model.
HR is the hazard rate of Arm B divided by hazard rate of Arm A.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1778 [11]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.058
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	1.623

Notes:

[11] - Based on approach using repeated confidence intervals, with one-sided 97.5% repeated confidence intervals

Statistical analysis title	HR of Arm B vs. Arm A for OS (final, unstratified)

Statistical analysis description:

Based on unadjusted Cox proportional hazards model.
HR is the hazard rate of Arm B divided by hazard rate of Arm A.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.049 [12]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.126
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	1.37

Notes:

[12] - Based on approach using repeated confidence intervals, with one-sided 97.5% repeated confidence intervals

Secondary: Observation time (ITT population)

End point title	Observation time (ITT population)

End point description:

Median observation time estimated with reverse Kaplan-Meier methods

End point type	Secondary

End point timeframe:

Observation time (in months) is defined as time from randomization to the day the patient was last confirmed to be alive. In case of patient death the time was censored at the day of death.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285[13]	279[14]		
Units: months				
median (confidence interval 95%)	54.3 (53.1 to 57.5)	55.7 (53.7 to 58.1)		

Notes:

[13] - ITT population

[14] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response (ITT population)

End point title	Best overall response (ITT population)

End point description:

End point type	Secondary

End point timeframe:

The best overall response according to the RECIST criteria is the best response recorded from the start of the treatment until disease progression/recurrence or within 28 days of last intake of study medication in the Study Treatment Phase

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285[15]	279[16]		
Units: Patients				
Complete response	10	2		
Partial response	115	74		
Stable disease	127	138		
Progressive disease	18	47		
Not evaluable	15	18		

Notes:

[15] - ITT population

[16] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response (PP population)

End point title	Best overall response (PP population)

End point description:

End point type	Secondary

End point timeframe:

The best overall response according to the RECIST criteria is the best response recorded from the start of the treatment until disease progression/recurrence or within 28 days of last intake of study medication in the Study Treatment Phase

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266[17]	265[18]		
Units: Patients				
Complete response	10	2		
Partial response	111	72		
Stable disease	117	130		
Progressive disease	17	45		
Not evaluable	11	16		

Notes:

[17] - PP population

[18] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Unconfirmed best overall response (ITT population)

End point title	Unconfirmed best overall response (ITT population)

End point description:

Complete and partial response in this summary did not require a confirmation by a second tumor assessment

End point type	Secondary

End point timeframe:

The best overall response according to the RECIST criteria is the best response recorded from the start of the treatment until disease progression/recurrence or within 28 days of last intake of study medication in the Study Treatment Phase

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285[19]	279[20]		
Units: patients				
Complete response	16	4		
Partial response	147	101		
Stable disease	89	109		
Progressive disease	18	47		
Not evaluable	15	18		

Notes:

[19] - ITT population

[20] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Unconfirmed best overall response (PP population)

End point title	Unconfirmed best overall response (PP population)

End point description:

Complete and partial response in this summary did not require a confirmation by a second tumor assessment

End point type	Secondary

End point timeframe:

The best overall response according to the RECIST criteria is the best response recorded from the start of the treatment until disease progression/recurrence or within 28 days of last intake of study medication in the Study Treatment Phase

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266[21]	265[22]		
Units: patients				
Complete response	16	4		
Partial response	141	96		
Stable disease	81	104		
Progressive disease	17	45		
Not evaluable	11	16		

Notes:

[21] - PP population

[22] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate and disease control rate (ITT population)

End point title	Objective response rate and disease control rate (ITT population)

End point description:

Objective response rate (ORR) is defined as the proportion of patients with complete response or partial response. Disease control rate (DCR) is defined as the proportion of patients with complete response, partial response and stable disease

End point type	Secondary

End point timeframe:

The best overall response according to the RECIST criteria is the best response recorded from the start of the treatment until disease progression/recurrence or within 28 days of last intake of study

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285[23]	279[24]		
Units: patients				
Objective response	125	76		
Disease control	252	214		

Notes:

[23] - ITT population

[24] - ITT population

Statistical analyses

Statistical analysis title	OR of objective response and CMH test (stratified)

Statistical analysis description:

OR is the odds for objective response of Arm B divided by the odds for objective response of Arm A
Based on Cochran-Mantel-Haenszel test adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of age)

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.67

Statistical analysis title	OR of disease control and CMH test (stratified)

Statistical analysis description:

OR is the odds for disease control of Arm B divided by the odds for disease control of Arm A
Based on Cochran-Mantel-Haenszel test adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of age)

Comparison groups	Arm A v Arm B

Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.7

Statistical analysis title	Difference in ORR in Arm B vs. Arm A
Statistical analysis description: Difference calculated as ORR in Arm B minus ORR in Arm A	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	-17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24
upper limit	-9

Statistical analysis title	Difference in DCR in Arm B vs. Arm A
Statistical analysis description: Difference calculated as DCR in Arm B minus DCR in Arm A	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	-12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18
upper limit	-6

Secondary: Objective response rate and disease control rate (PP population)

End point title	Objective response rate and disease control rate (PP population)

End point description:

Objective response rate (ORR) is defined as the proportion of patients with complete response or partial response. Disease control rate (DCR) is defined as the proportion of patients with complete response, partial response and stable disease

End point type	Secondary

End point timeframe:

The best overall response according to the RECIST criteria is the best response recorded from the start of the treatment until disease progression/recurrence or within 28 days of last intake of study medication in the Study Treatment Phase

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266[25]	265[26]		
Units: patients				
Objective response	121	74		
Disease control	238	204		

Notes:

[25] - PP population

[26] - PP population

Statistical analyses

Statistical analysis title	OR of objective response and CMH test (stratified)

Statistical analysis description:

OR is the odds for objective response of Arm B divided by the odds for objective response of Arm A
Based on Cochran-Mantel-Haenszel test adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of age)

OR is the odds of Arm B divided by the odds of Arm A

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.65

Statistical analysis title	OR of disease control and CMH test (stratified)

Statistical analysis description:

OR is the odds for disease control of Arm B divided by the odds for disease control of Arm A
Based on Cochran-Mantel-Haenszel test adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of age)

OR is the odds of Arm B divided by the odds of Arm A.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	0.65

Statistical analysis title	Difference in ORR in Arm B vs. Arm A

Statistical analysis description:

Difference calculated as ORR in Arm B minus ORR in Arm A

Comparison groups	Arm B v Arm A
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	-18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26
upper limit	-10

Statistical analysis title	Difference in DCR in Arm B vs. Arm A

Statistical analysis description:

Difference calculated as DCR in Arm B minus DCR in Arm A

Comparison groups	Arm A v Arm B

Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	-12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19
upper limit	-6

Secondary: Unconfirmed objective response rate and disease control rate (ITT population)

End point title	Unconfirmed objective response rate and disease control rate (ITT population)

End point description:

Objective response rate (ORR) is defined as the proportion of patients with complete response or partial response. Disease control rate (DCR) is defined as the proportion of patients with complete response, partial response and stable disease. Complete and partial response in this summary did not require a confirmation by a second tumor assessment

End point type	Secondary

End point timeframe:

The best overall response according to the RECIST criteria is the best response recorded from the start of the treatment until disease progression/recurrence or within 28 days of last intake of study medication in the Study Treatment Phase

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285[27]	279[28]		
Units: patients				
Objective response	163	105		
Disease control	252	214		

Notes:

[27] - ITT population

[28] - ITT population

Statistical analyses

Statistical analysis title	OR of objective response and CMH test (stratified)

Statistical analysis description:

OR is the odds for objective response of Arm B divided by the odds for objective response of Arm A
Based on Cochran-Mantel-Haenszel test adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of age)

OR is the odds of Arm B divided by the odds of Arm A

Comparison groups	Arm A v Arm B

Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.63

Statistical analysis title	OR of disease control and CMH test (stratified)

Statistical analysis description:

OR is the odds for disease control of Arm B divided by the odds for disease control of Arm A
Based on Cochran-Mantel-Haenszel test adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of age)
OR is the odds of Arm B divided by the odds of Arm A

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.7

Statistical analysis title	Difference in ORR in Arm B vs. Arm A

Statistical analysis description:

Difference calculated as ORR in Arm B minus ORR in Arm A

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	-20

Confidence interval	
level	95 %
sides	2-sided
lower limit	-28
upper limit	-11

Statistical analysis title	Difference in DCR in Arm B vs. Arm A
Statistical analysis description:	
Difference calculated as DCR in Arm B minus DCR in Arm A	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	-12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18
upper limit	-6

Secondary: Unconfirmed objective response rate and disease control rate (PP population)

End point title	Unconfirmed objective response rate and disease control rate (PP population)

End point description:

Objective response rate (ORR) is defined as the proportion of patients with complete response or partial response. Disease control rate (DCR) is defined as the proportion of patients with complete response, partial response and stable disease. Complete and partial response in this summary did not require a confirmation by a second tumor assessment

End point type	Secondary

End point timeframe:

The best overall response according to the RECIST criteria is the best response recorded from the start of the treatment until disease progression/recurrence or within 28 days of last intake of study medication in the Study Treatment Phase

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266[29]	265[30]		
Units: patients				
Objective response	157	100		
Disease control	238	204		

Notes:

[29] - PP population

Statistical analyses

Statistical analysis title	OR of objective response and CMH test (stratified)

Statistical analysis description:

OR is the odds for objective response of Arm B divided by the odds for objective response of Arm A
Based on Cochran-Mantel-Haenszel test adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of age)

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.6

Statistical analysis title	OR of disease control and CMH test (stratified)

Statistical analysis description:

OR is the odds for disease control of Arm B divided by the odds for disease control of Arm A
Based on Cochran-Mantel-Haenszel test adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of age)

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.39

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	0.65

Statistical analysis title	Difference in ORR in Arm B vs. Arm A
Statistical analysis description:	
Difference calculated as ORR in Arm B minus ORR in Arm A	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	-21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30
upper limit	-13

Statistical analysis title	Difference in DCR in Arm B vs. Arm A
Statistical analysis description:	
Difference calculated as DCR in Arm B minus DCR in Arm A	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	-12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19
upper limit	-6

Secondary: Progression Free Survival (ITT population)

End point title	Progression Free Survival (ITT population)

End point description:

Progression Free Survival (PFS) is defined as time from randomization to date of documented progression or date of death due to any cause, whichever occurred first. Patients without recorded progression or death were censored at the last date they were known to have not progressed. Patients who were randomized and had no post-baseline tumor assessment were censored on the day of randomization.

End point type	Secondary

End point timeframe:

Median PFS, associated stratified Hazard Ratio (HR).

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285[31]	279[32]		
Units: months				
median (confidence interval 95%)	10.9 (10.3 to 12.9)	8.1 (6.8 to 8.9)		

Notes:

[31] - ITT population

[32] - ITT population

Attachments (see zip file)	KM plots for PFS (ITT population)/gkmepfs_tg_i.jpg

Statistical analyses

Statistical analysis title	HR of Arm B vs. Arm A for PFS (stratified)

Statistical analysis description:

HR is the hazard rate of Arm B divided by hazard rate of Arm A.
Based on Cox proportional hazards model adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of Age)

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0066 [33]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	1.61

Notes:

[33] - Two-sided log-rank test adjusted by stratification factors at randomization

Secondary: Progression Free Survival (PP population)

End point title	Progression Free Survival (PP population)

End point description:

Progression Free Survival (PFS) is defined as time from randomization to date of documented progression or date of death due to any cause, whichever occurred first. Patients without recorded progression or death were censored at the last date they were known to have not progressed. Patients who were randomized and had no post-baseline tumor assessment were censored on the day of randomization.

End point type	Secondary

End point timeframe:

Median PFS, associated stratified Hazard Ratio (HR).

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266[34]	265[35]		
Units: months				
median (confidence interval 95%)	10.9 (10.3 to 12.9)	8.2 (7.1 to 9.2)		

Notes:

[34] - PP population

[35] - PP population

Attachments (see zip file)	KM-Plot_PFS (PP population)/gkmepfs_tg_p.jpg

Statistical analyses

Statistical analysis title	HR of Arm B vs. Arm A for PFS (stratified).

Statistical analysis description:

HR is the hazard rate of Arm B divided by hazard rate of Arm A.
Based on Cox proportional hazards model adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of age)

Comparison groups	Arm B v Arm A
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0094 [36]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	1.61

Notes:

[36] - Two-sided log-rank test adjusted by stratification factors at randomization

Secondary: Time to treatment failure (ITT population)

End point title	Time to treatment failure (ITT population)

End point description:

Time to treatment failure (TTF) was defined as time from first drug intake to progression, death or withdrawal from study treatment, whichever occurred first. Patients without an event were censored at the date of the last tumor assessment or last treatment administration, whichever occurred last.

End point type	Secondary

End point timeframe:

Median TTF, associated stratified Hazard Ratio (HR).

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285[37]	279[38]		
Units: months				
median (confidence interval 95%)	8.4 (8.0 to 9.7)	7.2 (6.0 to 8.1)		

Notes:

[37] - ITT population

[38] - ITT population

Attachments (see zip file)	KM Plot TTF (ITT population)/gkmettf_tg_i.jpg

Statistical analyses

Statistical analysis title	HR of Arm B vs. Arm A for TTF (stratified)

Statistical analysis description:

HR is the hazard rate of Arm B divided by hazard rate of Arm A.
Based on Cox proportional hazards model adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of Age)

Comparison groups	Arm B v Arm A
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1957 [39]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.35

Notes:

[39] - Two-sided log-rank test adjusted by stratification factors at randomization

Secondary: Time to treatment failure (PP population)

End point title	Time to treatment failure (PP population)

End point description:

Time to treatment failure (TTF) was defined as time from first drug intake to progression, death or withdrawal from study treatment, whichever occurred first. Patients without an event were censored at the date of the last tumor assessment or last treatment administration, whichever occurred last.

End point type	Secondary

End point timeframe:

Median TTF, associated stratified Hazard Ratio (HR).

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266[40]	265[41]		
Units: months				
median (confidence interval 95%)	8.3 (8.0 to 9.4)	7.3 (5.9 to 8.2)		

Notes:

[40] - PP population

[41] - PP population

Attachments (see zip file)	KM plot for TTF (PP population)/gkmettf_tg_p.jpg

Statistical analyses

Statistical analysis title	HR of Arm B vs. Arm A for TTF (stratified)

Statistical analysis description:

HR is the hazard rate of Arm B divided by hazard rate of Arm A.
Based on Cox proportional hazards model adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of Age)

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2583 [42]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.34

Notes:

[42] - Two-sided log-rank test adjusted by stratification factors at randomization

Secondary: Time to response (ITT population)

End point title	Time to response (ITT population)

End point description:

Time to Response (TR) was defined as time from randomization until occurrence of response (CR or PR) according to RECIST criteria. Patients without response were censored after the longest time actually observed. Since the median TR was not observed, the number of subjects with a response at given timepoints were reported.

End point type	Secondary

End point timeframe:

Median TR, associated stratified Hazard Ratio (HR).

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285[43]	279[44]		
Units: subjects				
Month 3	83	57		
Month 6	111	69		
Month 9	121	74		
Month 12	123	75		
Month 15	123	75		

Notes:

[43] - ITT population

[44] - ITT population

Attachments (see zip file)	KM Plot TR (ITT population)/gkmettr_tg_i.jpg

Statistical analyses

Statistical analysis title	HR of Arm B vs. Arm A for TR (stratified)

Statistical analysis description:

HR is the hazard rate of Arm B divided by hazard rate of Arm A.
Based on Cox proportional hazards model adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of Age)

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [45]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.77

Notes:

[45] - Two-sided log-rank test adjusted by stratification factors at randomization

Secondary: Time to response (PP population)

End point title	Time to response (PP population)

End point description:

Time to Response (TR) was defined as time from randomization until occurrence of response (CR or PR) according to RECIST criteria. Patients without response were censored after the longest time actually

observed. Since the median TR was not observed, the number of subjects with a response at given timepoints were reported.

End point type	Secondary

End point timeframe:

Median TR, associated stratified Hazard Ratio (HR).

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266[46]	265[47]		
Units: subjects				
Month 3	81	56		
Month 6	108	68		
Month 9	118	72		
Month 12	119	73		
Month 15	119	73		

Notes:

[46] - PP population

[47] - PP population

Attachments (see zip file)	KM plot for TR (PP population)/gkmettr_tg_p.jpg

Statistical analyses

Statistical analysis title	HR of Arm B vs. Arm A for TR (stratified)

Statistical analysis description:

HR is the hazard rate of Arm B divided by hazard rate of Arm A.
Based on Cox proportional hazards model adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of Age)

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [48]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.75

Notes:

[48] - Two-sided log-rank test adjusted by stratification factors at randomization

Secondary: Duration of response (ITT population)

End point title	Duration of response (ITT population)

End point description:

Duration of response (DR) was defined as time from date of first occurrence of any response (CR or PR) until the occurrence of progression of disease or death. Patients with response who neither progressed nor died were censored at the date of their last tumor assessment.

End point type	Secondary

End point timeframe:

Median DR, associated stratified Hazard Ratio (HR).

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125[49]	76[50]		
Units: months				
median (confidence interval 95%)	11.2 (10.1 to 14.0)	10.3 (8.6 to 12.4)		

Notes:

[49] - ITT population restricted to patients who experienced a partial or complete response

[50] - ITT population restricted to patients who experienced a partial or complete response

Attachments (see zip file)	KM Plot DR /gkmedr_tg_i.jpg

Statistical analyses

Statistical analysis title	HR of Arm B vs. Arm A for DR (stratified)

Statistical analysis description:

HR is the hazard rate of Arm B divided by hazard rate of Arm A.
Based on Cox proportional hazards model adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of Age)

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0582 [51]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	2.02

Notes:

[51] - Two-sided log-rank test adjusted by stratification factors at randomization

Secondary: Duration of response (PP population)

End point title	Duration of response (PP population)

End point description:

Duration of response (DR) was defined as time from date of first occurrence of any response (CR or PR) until the occurrence of progression of disease or death. Patients with response who neither progressed nor died were censored at the date of their last tumor assessment.

End point type	Secondary

End point timeframe:

Median DR, associated stratified Hazard Ratio (HR).

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121[52]	74[53]		
Units: months				
median (confidence interval 95%)	11.2 (9.5 to 14.2)	10.3 (8.4 to 12.4)		

Notes:

[52] - PP population restricted to patients who experienced a partial or complete response

[53] - PP population restricted to patients who experienced a partial or complete response

Attachments (see zip file)	KM Plot DR/gkmedr_tg_p.jpg

Statistical analyses

Statistical analysis title	HR of Arm B vs. Arm A for DR (stratified)

Statistical analysis description:

HR is the hazard rate of Arm B divided by hazard rate of Arm A.
Based on Cox proportional hazards model adjusted by stratification factors at randomization:
1) estrogen and/or progesterone status (positive vs. other)
2) country
3) menopausal status (premenopausal or male <=50 years of age vs. postmenopausal or male >50 years of Age)

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0429 [54]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	2.1

Notes:

[54] - Two-sided log-rank test adjusted by stratification factors at randomization

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events recording for a patient was started with the first dose of any of the study drugs until the 28-day post-treatment follow up visit. Pre-existing conditions which worsened during the study were reported as Adverse Events.

Adverse event reporting additional description:

After the 28-day follow up visit only new and ongoing serious adverse events considered to be related to study drug or protocol procedures were recorded by the investigator

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Arm A

Reporting group description:

Patients in this arm received a combination of bevacizumab plus paclitaxel in cycles of 28 days as first-line treatment. Treatment continued until first progression of disease (PD), unacceptable toxicity or withdrawal of patients consent. For patients who stopped chemotherapy for any reason before PD, bevacizumab was to be given as monotherapy until PD.
Bevacizumab 10mg/kg i.v., days 1 and 15, every 4 weeks
Paclitaxel 90mg/m², days 1, 8 and 15, every 4 weeks

The safety population comprised all patients randomized who received at least one dose of study medication. For the purpose of safety analyses, patients were included in the treatment groups of their actually received treatment. However, if patients received only one component of the assigned combination treatment (e.g. only paclitaxel in group A), then they were analyzed under the treatment group randomized.

Reporting group title	Arm B

Reporting group description:

Patients in Arm B received combination treatment with bevacizumab plus capecitabine as first-line treatment in cycles of 21 days, until first progression of disease (PD), unacceptable toxicity or withdrawal of patient consent. For patients who stopped chemotherapy for any reason before PD, bevacizumab was to be given as montherapy until PD.
Bevacizumab 15 mg/kg i.v. on day 1 every 3 weeks
Capecitabine 1000 mg/m² twice-daily on days 1-14, every 3 weeks

The safety population comprised all patients randomized who received at least one dose of study medication. For the purpose of safety analyses, patients were included in the treatment groups of their actually received treatment. However, if patients received only one component of the assigned combination treatment (e.g. only paclitaxel in group A), then they were analyzed under the treatment group randomized.

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	65 / 284 (22.89%)	68 / 277 (24.55%)	
number of deaths (all causes)	196	209	
number of deaths resulting from adverse events	9	10	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			

subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 284 (0.35%)	5 / 277 (1.81%)	
occurrences causally related to treatment / all	0 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 284 (0.35%)	2 / 277 (0.72%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic thrombosis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			

subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	2 / 284 (0.70%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheterisation venous			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast lump removal			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 284 (0.70%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 284 (1.06%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chest pain			
subjects affected / exposed	1 / 284 (0.35%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain			
subjects affected / exposed	1 / 284 (0.35%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site pain			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gait disturbance			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 284 (0.70%)	6 / 277 (2.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pulmonary embolism			
subjects affected / exposed	2 / 284 (0.70%)	4 / 277 (1.44%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 284 (0.00%)	3 / 277 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	2 / 284 (0.70%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, olfactory			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizoaffective disorder			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			

subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			

subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Systolic dysfunction			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 284 (0.70%)	2 / 277 (0.72%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			
subjects affected / exposed	1 / 284 (0.35%)	2 / 277 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 284 (0.35%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain hypoxia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain oedema			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve root compression			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 284 (0.00%)	4 / 277 (1.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	2 / 284 (0.70%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 284 (0.35%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 284 (0.35%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 284 (0.35%)	4 / 277 (1.44%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 284 (0.00%)	2 / 277 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 284 (0.35%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 284 (0.00%)	2 / 277 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 284 (0.00%)	2 / 277 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			

subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			

subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Dermatitis bullous			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 284 (0.35%)	3 / 277 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			

subjects affected / exposed	0 / 284 (0.00%)	2 / 277 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	2 / 284 (0.70%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Catheter site infection			
subjects affected / exposed	3 / 284 (1.06%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 284 (1.06%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			

subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin infection			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 284 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			

subjects affected / exposed	0 / 284 (0.00%)	2 / 277 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	264 / 284 (92.96%)	240 / 277 (86.64%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	102 / 284 (35.92%)	83 / 277 (29.96%)	
occurrences (all)	192	130	
Nervous system disorders			
Dizziness			
subjects affected / exposed	33 / 284 (11.62%)	17 / 277 (6.14%)	
occurrences (all)	39	19	
Dysgeusia			
subjects affected / exposed	17 / 284 (5.99%)	10 / 277 (3.61%)	
occurrences (all)	19	14	
Headache			
subjects affected / exposed	37 / 284 (13.03%)	27 / 277 (9.75%)	
occurrences (all)	46	32	

Neuropathy peripheral			
subjects affected / exposed	86 / 284 (30.28%)	9 / 277 (3.25%)	
occurrences (all)	105	9	
Paraesthesia			
subjects affected / exposed	17 / 284 (5.99%)	12 / 277 (4.33%)	
occurrences (all)	18	12	
Peripheral sensory neuropathy			
subjects affected / exposed	23 / 284 (8.10%)	5 / 277 (1.81%)	
occurrences (all)	25	5	
Polyneuropathy			
subjects affected / exposed	27 / 284 (9.51%)	6 / 277 (2.17%)	
occurrences (all)	35	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	35 / 284 (12.32%)	17 / 277 (6.14%)	
occurrences (all)	59	20	
Leukopenia			
subjects affected / exposed	46 / 284 (16.20%)	6 / 277 (2.17%)	
occurrences (all)	127	8	
Neutropenia			
subjects affected / exposed	87 / 284 (30.63%)	13 / 277 (4.69%)	
occurrences (all)	204	24	
Thrombocytopenia			
subjects affected / exposed	9 / 284 (3.17%)	19 / 277 (6.86%)	
occurrences (all)	12	26	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	44 / 284 (15.49%)	34 / 277 (12.27%)	
occurrences (all)	50	37	
Fatigue			
subjects affected / exposed	97 / 284 (34.15%)	76 / 277 (27.44%)	
occurrences (all)	127	89	
Mucosal inflammation			
subjects affected / exposed	23 / 284 (8.10%)	13 / 277 (4.69%)	
occurrences (all)	29	13	
Oedema peripheral			

subjects affected / exposed	27 / 284 (9.51%)	11 / 277 (3.97%)	
occurrences (all)	28	13	
Pyrexia			
subjects affected / exposed	23 / 284 (8.10%)	17 / 277 (6.14%)	
occurrences (all)	27	20	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	20 / 284 (7.04%)	18 / 277 (6.50%)	
occurrences (all)	26	21	
Abdominal pain upper			
subjects affected / exposed	18 / 284 (6.34%)	14 / 277 (5.05%)	
occurrences (all)	24	17	
Constipation			
subjects affected / exposed	27 / 284 (9.51%)	25 / 277 (9.03%)	
occurrences (all)	32	32	
Diarrhoea			
subjects affected / exposed	58 / 284 (20.42%)	59 / 277 (21.30%)	
occurrences (all)	83	83	
Dyspepsia			
subjects affected / exposed	17 / 284 (5.99%)	15 / 277 (5.42%)	
occurrences (all)	24	17	
Nausea			
subjects affected / exposed	57 / 284 (20.07%)	70 / 277 (25.27%)	
occurrences (all)	82	94	
Stomatitis			
subjects affected / exposed	22 / 284 (7.75%)	20 / 277 (7.22%)	
occurrences (all)	27	24	
Vomiting			
subjects affected / exposed	29 / 284 (10.21%)	34 / 277 (12.27%)	
occurrences (all)	40	46	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	3 / 284 (1.06%)	16 / 277 (5.78%)	
occurrences (all)	3	18	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	32 / 284 (11.27%)	20 / 277 (7.22%)	
occurrences (all)	37	22	
Dysphonia			
subjects affected / exposed	35 / 284 (12.32%)	10 / 277 (3.61%)	
occurrences (all)	37	11	
Dyspnoea			
subjects affected / exposed	32 / 284 (11.27%)	24 / 277 (8.66%)	
occurrences (all)	39	27	
Epistaxis			
subjects affected / exposed	89 / 284 (31.34%)	39 / 277 (14.08%)	
occurrences (all)	122	46	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	87 / 284 (30.63%)	5 / 277 (1.81%)	
occurrences (all)	88	5	
Nail disorder			
subjects affected / exposed	48 / 284 (16.90%)	10 / 277 (3.61%)	
occurrences (all)	50	10	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	8 / 284 (2.82%)	155 / 277 (55.96%)	
occurrences (all)	8	197	
Rash			
subjects affected / exposed	17 / 284 (5.99%)	11 / 277 (3.97%)	
occurrences (all)	20	14	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	10 / 284 (3.52%)	16 / 277 (5.78%)	
occurrences (all)	13	16	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	30 / 284 (10.56%)	18 / 277 (6.50%)	
occurrences (all)	58	20	
Back pain			
subjects affected / exposed	27 / 284 (9.51%)	29 / 277 (10.47%)	
occurrences (all)	35	29	

Bone pain			
subjects affected / exposed	28 / 284 (9.86%)	29 / 277 (10.47%)	
occurrences (all)	33	31	
Musculoskeletal pain			
subjects affected / exposed	3 / 284 (1.06%)	14 / 277 (5.05%)	
occurrences (all)	5	15	
Myalgia			
subjects affected / exposed	20 / 284 (7.04%)	9 / 277 (3.25%)	
occurrences (all)	26	9	
Pain in extremity			
subjects affected / exposed	25 / 284 (8.80%)	24 / 277 (8.66%)	
occurrences (all)	32	28	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	24 / 284 (8.45%)	14 / 277 (5.05%)	
occurrences (all)	29	18	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	35 / 284 (12.32%)	33 / 277 (11.91%)	
occurrences (all)	38	38	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported