Clinical trial results:
A Phase III Randomized Study Evaluating the Efficacy and Safety of Continued and Re-induced Bevacizumab in Combination with Chemotherapy for Patients with Locally Recurrent or Metastatic Breast Cancer After First-Line Chemotherapy and Bevacizumab Treatment

Summary

EudraCT number	2010-020998-16
Trial protocol	ES SK HU AT DE GR IT
Global end of trial date	30 March 2015

Results information

Result version number	v1 (current)
This version publication date	14 February 2016
First version publication date	14 February 2016

Trial information

Trial identification

Sponsor protocol code	MO22998

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a Phase III, open-label, randomized, 2-arm study evaluating the efficacy and safety of continued and re-introduced bevacizumab in combination with chemotherapy for participants with locally recurrent (LR) or metastatic breast cancer (mBC) that had progressed during/ following first-line chemotherapy and bevacizumab treatment. Participants whose disease had progressed following previous therapy with bevacizumab plus chemotherapy were randomized on a 1:1 basis to receive standard of care chemotherapy (CT Arm) or standard of care chemotherapy plus bevacizumab (CT+BV Arm).
The primary objective was to determine the clinical benefit of continued or re-introduced bevacizumab treatment in combination with second-line chemotherapy for participants with locally recurrent or mBC whose disease progressed after treatment with first-line chemotherapy combined with bevacizumab, as measured by second-line progression-free survival (PFS).

Protection of trial subjects:

This study was conducted in accordance with the principles of the "Declaration of Helsinki" and "Good Clinical Practice" (GCP) and in compliance with the applicable laws and regulations. The investigators were trained according to applicable standard operating procedures (SOPs) and was documented by the investigator's signature on the protocol agreeing to carry out all of its terms in accordance with the applicable regulations and law and to follow International Conference on Harmonization (ICH) GCP guidelines. Approval from the independent ethics committees (IECs)/institutional review boards (IRBs) was obtained before study start and was documented in a letter to the investigator specifying the date on which the committee met and granted the approval. Approval from the relevant Competent Authority was also obtained prior to starting the study. No modifications were made to the protocol after receipt of the IEC approval. Protocol amendments were prepared by the Sponsor, and were submitted to the IRB/IEC and to regulatory authorities in accordance with local regulatory requirements. Approval was also obtained from the IRB/IEC and regulatory authorities (as locally required) before implementation of any changes.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 February 2011
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	Slovakia: 8
Country: Number of subjects enrolled	Spain: 85
Country: Number of subjects enrolled	Austria: 19
Country: Number of subjects enrolled	France: 142
Country: Number of subjects enrolled	Germany: 86
Country: Number of subjects enrolled	Greece: 8

Country: Number of subjects enrolled	Hungary: 31
Country: Number of subjects enrolled	Italy: 72
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Switzerland: 12
Country: Number of subjects enrolled	Croatia: 6
Country: Number of subjects enrolled	Argentina: 3
Worldwide total number of subjects	494
EEA total number of subjects	457

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)	379
From 65 to 84 years	115
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 556 participants were screened and of these, 494 participants were randomized.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Chemotherapy (CT) Arm

Arm description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Chemotherapy Plus Bevacizumab (CT+BV) Arm

Arm description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 milligrams per kilogram (mg/kg), intravenously (IV), every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 mg/kg, IV, every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was either given as 10 mg/kg given every 2 weeks, or 15 mg/kg given every 3 weeks.

Number of subjects in period 1	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm
Started	247	247
Completed	45	54
Not completed	202	193
Physician decision	11	3
Consent withdrawn by subject	32	20
Death	141	148
Not specified	-	4
Adverse event	5	4
Lost to follow-up	9	6
Participant non-compliance	2	-
Protocol deviation	2	8

Baseline characteristics

Reporting groups

Reporting group title	Chemotherapy (CT) Arm

Reporting group description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

Reporting group title	Chemotherapy Plus Bevacizumab (CT+BV) Arm

Reporting group description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 milligrams per kilogram (mg/kg), intravenously (IV), every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 mg/kg, IV, every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

Reporting group values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm	Total
Number of subjects	247	247	494
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 54.7 ± 10.83	 55.8 ± 11.17	 -
Gender categorical Units: Subjects			
Female Male	247 0	247 0	494 0

End points

End points reporting groups

Reporting group title	Chemotherapy (CT) Arm

Reporting group description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

Reporting group title	Chemotherapy Plus Bevacizumab (CT+BV) Arm

Reporting group description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 milligrams per kilogram (mg/kg), intravenously (IV), every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 mg/kg, IV, every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

Primary: Percentage of Participants With Second-Line Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1

End point title	Percentage of Participants With Second-Line Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1[1]

End point description:

Second-line PFS was defined as the time from randomization to progressive disease (PD) or death due to any cause during their second-line of treatment with bevacizumab and/or chemotherapy, whichever occurred first. For target lesions (TLs), PD was defined as at least a 20 percent (%) increase in the sum of the largest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For non-target lesions (NTLs), PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented.
Analysis population (AP): Intent-to-treat (ITT) population - all randomized participants.

End point type	Primary

End point timeframe:

Baseline [less than or equal to (≤) 28 days after randomization], every 8-9 weeks thereafter according to the standard of care of treatment site until approximately 3 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was planned only for PFS duration and reported in the respective endpoint.

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	247		
Units: percentage of participants				
number (not applicable)	88.7	93.9		

Statistical analyses

No statistical analyses for this end point

Primary: Second-Line PFS

End point title	Second-Line PFS

End point description:

The median time, in months, from randomization to second-line PFS event. For TLS, PD was defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented.
AP: ITT population.

End point type	Primary

End point timeframe:

Baseline (≤28 days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 3 years

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	247		
Units: months				
median (confidence interval 95%)	4.2 (3.9 to 5.3)	6.3 (5.5 to 7.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0204
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.97

Notes:

[2] - The 95% confidence interval (CI) was estimated using Cox proportional hazards methodology. The stratification factors used in the analysis were hormone receptor status, first-line PFS, choice of chemotherapy,and lactate dehydrogenase (LDH) level.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0245
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	0.97

Notes:

[3] - Unstratified analysis.

Primary: Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 6

End point title	Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 6[4]

End point description:

Second-line PFS was defined as the time from randomization to PD or death due to any cause during their second-line of treatment with bevacizumab and/or chemotherapy, whichever occurred first. For TLS, PD was defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented.
AP: ITT population.

End point type	Primary

End point timeframe:

Month 6

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was planned only for PFS duration and reported in the respective endpoint.

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	247		
Units: percentage of participants				
number (confidence interval 95%)	40.7 (34.3 to 47)	54.2 (47.7 to 60.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 12

End point title	Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 12[5]

End point description:

Second-line PFS was defined as the time from randomization to PD or death due to any cause during their second-line of treatment with bevacizumab and/or chemotherapy, whichever occurred first. For TLs, PD was defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from BL or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented.
AP: ITT population.

End point type	Primary

End point timeframe:

Month 12

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was planned only for PFS duration and reported in the respective endpoint.

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	247		
Units: percentage of participants				
number (confidence interval 95%)	16.9 (12.3 to 22.2)	24.2 (19 to 29.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 18

End point title	Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 18[6]

End point description:

Second-line PFS was defined as the time from randomization to PD or death due to any cause during their second-line of treatment with bevacizumab and/or chemotherapy, whichever occurred first. For TLS, PD was defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented.
AP: ITT population.

End point type	Primary

End point timeframe:

Month 18

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was planned only for PFS duration and reported in the respective endpoint.

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	247		
Units: percentage of participants				
number (confidence interval 95%)	9.9 (6.4 to 14.3)	11 (7.4 to 15.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 24

End point title	Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 24[7]

End point description:

Second-line PFS was defined as the time from randomization to PD or death due to any cause during their second-line of treatment with bevacizumab and/or chemotherapy, whichever occurred first. For TLS, PD was defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented.
AP: ITT population.

End point type	Primary

End point timeframe:

Month 24

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was planned only for PFS duration and reported in the respective endpoint.

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	247		
Units: percentage of participants				
number (confidence interval 95%)	6.4 (3.6 to 10.2)	6.5 (3.7 to 10.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Second-Line PFS by Baseline Risk Factor (Data Cutoff 20 December 2013)

End point title	Second-Line PFS by Baseline Risk Factor (Data Cutoff 20 December 2013)

End point description:

The median time in months from randomization to second-line PFS event according to following baseline risk factors: hormone receptor negative, HER2 negative (triple negative), hormone receptor positive/HER-2 negative (HR-pos/HER-neg), first-line PFS < 6 months, first-line PFS ≥ 6 months, taxane chemotherapy (chemo), non-taxane chemo, vinorelbine chemo, LDH ≤ 1.5 upper limit of normal (ULN), LDH > 1.5 ULN, < 65 and <70 years of age, ≥ 65 and ≥ 70 years of age, < 3 and ≥ 3 metastatic organ sites, bevacizumab-free (B-free) interval ≤ 6 weeks and > 6 weeks, disease-free (D-free) interval ≤ 24 months, > 24 months, ≤ 12 months, and > 12 months. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented. The 95% CI was estimated using Kaplan-Meier methodology.
AP: ITT population. Here, Number of participants analyzed= participants evaluable for this end point and n= participants included for specified risk factor.

End point type	Secondary

End point timeframe:

Baseline (≤28 days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 3 years

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	219		
Units: months				
median (confidence interval 95%)				
HR-neg (n=60,56)	2.1 (2 to 3.9)	4.9 (3.4 to 6.1)		
HR-pos/HER-neg (n=187,191)	4.7 (4.2 to 6.2)	6.7 (6 to 7.8)		
PFS <6 months (n=69,68)	3.9 (2.3 to 4.3)	5.1 (4.1 to 6.9)		
PFS ≥6 months (n=178,179)	4.6 (3.9 to 6.1)	6.4 (5.8 to 7.6)		
Taxane chemo (n=32,32)	3.2 (1.7 to 5.3)	6.9 (4.9 to 9.8)		
Non-taxane chemo (n=191,188)	4.4 (3.9 to 5.8)	6 (4.9 to 6.8)		
Vinorelbine chemo (n=24,27)	2.4 (1.8 to 4.3)	6.5 (4.2 to 11.1)		
LDH ≤ 1.5 ULN (n=207,210)	4.4 (3.9 to 6)	6.3 (5.5 to 7.6)		

LDH > 1.5 ULN (n=40,37)	2.1 (1.7 to 3.9)	5.8 (2.5 to 7.3)		
< 65 years of age (n=196,183)	4.2 (3.9 to 4.7)	6.1 (4.7 to 6.9)		
≥ 65 years of age (n=51,64)	4.2 (2.2 to 7.8)	6.7 (5.5 to 8)		
< 70 years of age (n=226,219)	4.2 (3.7 to 4.6)	6.2 (5.3 to 7.3)		
≥ 70 years of age (n=21,28)	7.8 (2.2 to 11.9)	6.7 (4.1 to 11.2)		
< 3 metastatic organ sites (n=158,167)	4.2 (3.9 to 6.1)	6.9 (6 to 8.2)		
≥ 3 metastatic organ sites (n=88,80)	4 (2.1 to 4.9)	4.7 (4.1 to 6.2)		
B-free ≤ 6 weeks (n=165,149)	4.2 (3.6 to 4.6)	5.8 (4.4 to 6.6)		
B-free > 6 weeks (n=81,98)	4.4 (3.3 to 6.3)	7.6 (6 to 9.5)		
D-free ≤ 24 months (n=58,53)	2.8 (2 to 3.9)	5.8 (4.2 to 6.3)		
D-free > 24 months (n=138,156)	4.9 (4 to 6.1)	6.5 (5.5 to 8.1)		
D-free ≤ 12 months (n=24,18)	2.1 (1.3 to 5.8)	5.8 (3.9 to 9.7)		
D-free > 12 months (n=172,191)	4.3 (3.9 to 5.7)	6.3 (5.3 to 7.6)		

Statistical analyses

Statistical analysis title	Subgroup analysis: HR-neg
Comparison groups	Chemotherapy Plus Bevacizumab (CT+BV) Arm v Chemotherapy (CT) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0088
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.88

Statistical analysis title	Subgroup analysis: HR-pos/ HER-neg
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1196
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.05

Statistical analysis title	Subgroup analysis PFS < 6 months
Comparison groups	Chemotherapy Plus Bevacizumab (CT+BV) Arm v Chemotherapy (CT) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.9

Statistical analysis title	Subgroup analysis: PFS ≥ 6 months
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0816
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.03

Statistical analysis title	Subgroup analysis: taxane chemo
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0395
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.98

Statistical analysis title	Subgroup analysis: nontaxane chemo
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1385
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.06

Statistical analysis title	Subgroup analysis: vinorelbine chemo
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.75

Statistical analysis title	Subgroup analysis: LDH ≤ 1.5 ULN
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm

Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0171
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.96

Statistical analysis title	Subgroup analysis: LDH > 1.5 ULN
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1797
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.16

Statistical analysis title	Subgroup analysis: < 65 years of age
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0229
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.97

Statistical analysis title	Subgroup analysis: ≥ 65 years of age
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2139
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.16

Statistical analysis title	Subgroup analysis: < 70 years of age
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.89

Statistical analysis title	Subgroup analysis: ≥ 70 years of age
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5216
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	2.39

Statistical analysis title	Subgroup analysis: < 3 metastatic organ sites
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0148
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.94

Statistical analysis title	Subgroup analysis: ≥ 3 metastatic organ sites
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3102
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.17

Statistical analysis title	Subgroup analysis: B-free ≤ 6 weeks
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0967
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.04

Statistical analysis title	Subgroup analysis: B-free > 6 weeks
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0489
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1

Statistical analysis title	Subgroup analysis: D-free ≤ 24 months
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0176
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.92

Statistical analysis title	Subgroup analysis: D-free > 24 months
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm

Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2318
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.11

Statistical analysis title	Subgroup analysis: D-free ≤ 12 months
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0568
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.03

Statistical analysis title	Subgroup analysis: D-free > 12 months
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1143
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.05

Secondary: Percentage of Participants With a Second-Line Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) According to RECIST v1.1 (Data Cutoff 20 December 2013)

End point title	Percentage of Participants With a Second-Line Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) According to RECIST v1.1 (Data Cutoff 20 December 2013)

End point description:

BOR was defined as a confirmed CR or PR during second-line treatment. For TLs, CR was defined as the disappearance of all TLs, and PR was defined as at least a 30% decrease in the SLD of the TLs, taking as a reference the baseline SLD. For NTLs, CR was defined as the disappearance of all NTLs and normalization of tumor marker levels. The 95% CI was determined using the Pearson-Clopper method. AP: ITT population; only randomized participants with measurable disease at baseline were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (≤28 days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 3 years

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	182		
Units: percentage of participants				
number (confidence interval 95%)	16.8 (11.7 to 22.9)	20.9 (15.2 to 27.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.3457 [9]
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	12.4

Notes:

[8] - The 95% CI was estimated using Hauck-Anderson methodology.

[9] - P-value was calculated using two-sided chi-square test using Schouten correction.

Secondary: Percentage of Participants With a Second-Line CR, PR, Stable Disease

(SD), and PD According to RECIST v1.1 (Data Cutoff 20 December 2013)

End point title	Percentage of Participants With a Second-Line CR, PR, Stable Disease (SD), and PD According to RECIST v1.1 (Data Cutoff 20 December 2013)

End point description:

For TLs, CR was defined as the disappearance of all TLs; PR was defined as at least a 30% decrease in the SLD of the TLs, taking as a reference the baseline SLD; SD was defined as neither sufficient decrease in SLD to qualify for PR nor sufficient increase in SLD to qualify for PD; and PD was defined as at least a 20% increase in the SLD of TLs, taking as reference the smallest SLD recorded since the treatment started. For NTLs, CR was defined as the disappearance of all NTLs and normalization of tumor marker levels; SD was defined as the persistence of 1 or more NTLs and/or maintenance of tumor marker levels above normal limits; and PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing NTLs. The 95% CI was determined using the Pearson-Clopper method.
AP: ITT population; only randomized participants with measurable disease at baseline were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (≤28 days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 3 years

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	182		
Units: percentage of participants				
number (confidence interval 95%)				
CR	1.1 (0.1 to 3.9)	0.5 (0 to 3)		
PR	15.7 (10.8 to 21.7)	20.3 (14.7 to 26.9)		
SD	33.5 (26.8 to 40.8)	48.9 (41.4 to 56.4)		
PD	41.1 (33.9 to 48.5)	24.2 (18.1 to 31.1)		
Unable to assess	8.6 (5 to 13.7)	6 (3.1 to 10.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Second-Line Objective Response (Data Cutoff 20 December 2013)

End point title	Duration of Second-Line Objective Response (Data Cutoff 20 December 2013)

End point description:

The median time in months from the date of the first second-line documentation of CR or PR according to RECIST v1.1 to the date of the first second-line documentation of PD or death due to any cause. For TLs, CR was disappearance of all TLs; PR was as at least a 30% decrease in the SLD of the TLs, taking as reference the baseline SLD; and PD was at least a 20% increase in the SLD of TLs, taking as reference the smallest SLD recorded since the treatment started. For NTLs, CR was disappearance of all NTLs and normalization of tumor marker levels, and PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing NTLs. Participants with CR or PR who had experienced

neither disease progression nor died were censored at the date of the last available tumor assessment when the participant was known to be progression free.
AP: ITT population; only randomized participants with a CR or PR were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline (≤ 28 days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 3 years

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	38		
Units: months				
median (confidence interval 95%)	10.6 (4.4 to 16.7)	8.3 (6.1 to 10.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The 95% CI was estimated using Cox proportional hazards methodology. The stratification factors used in stratified analysis were hormone receptor status, first-line PFS, choice of chemotherapy, and LDH level.

Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9825
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.99

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Unstratified analysis.

Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3601
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	2.34

Secondary: Percentage of Participants With a Second-Line Documented CR or PR According to RECIST v1.1 Estimated to be Alive and Free of Disease Progression at Months 3, 6, and 9 (Data Cutoff 20 December 2013)

End point title	Percentage of Participants With a Second-Line Documented CR or PR According to RECIST v1.1 Estimated to be Alive and Free of Disease Progression at Months 3, 6, and 9 (Data Cutoff 20 December 2013)

End point description:

Duration of objective response was median time in months from date of first second-line documentation of CR or PR to date of first second-line documentation of PD or death due to any cause. For TLs, CR was disappearance of all TLs; PR was at least a 30% decrease in SLD of TLs, taking as a reference the baseline SLD; and PD was as at least a 20% increase in SLD of TLs, taking as reference smallest SLD recorded since treatment started. For NTLs, CR was disappearance of all NTLs and normalization of tumor marker levels, and PD was appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants with CR or PR who had experienced neither disease progression nor died were censored at date of last available tumor assessment when the participant was known to be progression free.
AP: ITT population - only randomized participants with CR or PR included in analysis. "99.9 and 999.9": data unavailable as all participants were alive and free of PD at Month 3.

End point type	Secondary

End point timeframe:

Months 3, 6, and 9

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	38		
Units: percentage of participants				
number (confidence interval 95%)				
Month 3	96.7 (78.6 to 99.5)	100 (99.9 to 999.9)		
Month 6	69 (48.9 to 82.5)	72.8 (55.3 to 84.4)		
Month 9	60.9 (40.4 to 76.3)	40.8 (24.6 to 56.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Third-Line PFS According to RECIST v1.1

End point title	Percentage of Participants With Third-Line PFS According to RECIST v1.1

End point description:

Third-line PFS was defined as the time from the date of first dose of third-line bevacizumab and/or chemotherapy to the date of third-line PD or death due to any cause. For TLs, PD was defined at least a 20% increase in the SLD, taking as reference the smallest SLD recorded frombaseline or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing NTLs. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented. Participants without third-line PD or death were censored at the date of last tumor assessment where non-progression was documented.
AP: Third line ITT population: all randomized participants who received third-line treatment.

End point type	Secondary

End point timeframe:

First dose of third-line treatment until PD or death due to any cause (assessed every 8-9 weeks, over a period of approximately 14 months)

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	129		
Units: percentage of participants				
number (not applicable)	94.3	96.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Third-Line PFS

End point title	Third-Line PFS

End point description:

The median time, in months, from the first dose of third-line bevacizumab and/or chemotherapy to third-line PD or death, due to any cause. For TLs, PD was defined as at least a 20% increase in SLD, taking as reference the smallest SLD recorded from baseline or the appearence of 1 or more new lesions. For NTLs, PD was defined as the appearence of 1 or more new lesions and/or unequivocal progression of NTLs. Participants without third-line PD or death were censored at the date of last tumor assessment where non-progression was documented.
AP: Third line ITT population.

End point type	Secondary

End point timeframe:

First dose of third-line treatment until PD or death due to any cause (assessed every 8-9 weeks, over a period of approximately 14 months)

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	129		
Units: months				
median (confidence interval 95%)	2.9 (2.2 to 3.9)	3.8 (2.4 to 5.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The 95% CI was estimated using Cox proportional hazards methodology. The stratification factors used in stratified analysis were hormone receptor status, first-line PFS, choice of chemotherapy, and LDH level.

Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.108
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.06

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The 95% CI was estimated using unstratified analysis.

Comparison groups	Chemotherapy Plus Bevacizumab (CT+BV) Arm v Chemotherapy (CT) Arm

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0625
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.02

Secondary: Percentage of Participants With Second- and Third-Line PFS According to RECIST v1.1

End point title	Percentage of Participants With Second- and Third-Line PFS According to RECIST v1.1

End point description:

Second- and third-line PFS was defined as the time from the date randomization to the date of third-line PD or death due to any cause. For TLs, PD was defined at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing NTLs. Participants without third-line PD or death were censored at the date of last tumor assessment where non-progression was documented.
AP: ITT population.

End point type	Secondary

End point timeframe:

Baseline (≤28 days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 4 years

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	247		
Units: percentage of participants				
number (not applicable)	71.7	83.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Second- and Third-Line PFS

End point title	Second- and Third-Line PFS

End point description:

The median time, in months, from randomization to third-line PFS event. For TLS, PD was defined as at

least a 20% increase in SLD, taking as reference the smallest SLD recorded from the baseline or the appearence of one or more lesions. For NTLs, PD was defined as the appearence of one or more lesions and/or unequivocal progression of existing NTLs. Participants without third-line PD or death were censored at the date of last tumor assessment where non-progression was documented.
AP: ITT population.

End point type	Secondary

End point timeframe:

Baseline (≤28 days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 4 years

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	247		
Units: months				
median (confidence interval 95%)	10.7 (9.2 to 12.5)	12.8 (10.7 to 14.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The 95% CI was estimated using Cox proportional hazards methodology. The stratification factors used in stratified analysis were hormone receptor status, first-line PFS, choice of chemotherapy, and LDH level.

Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1349
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.05

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The 95% CI was estimated using unstratified analysis.

Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm

Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0863
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.03

Secondary: Percentage of Participants With Second- and Third-Line Tumor Progression

End point title	Percentage of Participants With Second- and Third-Line Tumor Progression

End point description:

Second- and third-line tumor progression was defined as the time from the date of randomization to the date of third-line PD according to RECIST v1.1 or death due to progression of disease. For TLs, PD was defined at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without third-line PD or death due to progression of disease were censored at the date of last tumor assessment where non-progression was documented.
AP: ITT population.

End point type	Secondary

End point timeframe:

Baseline (≤28 days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 4 years

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	247		
Units: percentage of participants				
number (not applicable)	67.2	75.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Second- and Third-Line Tumor Progression

End point title	Time to Second- and Third-Line Tumor Progression

End point description:

Time to second- and third-line tumor progression was defined as the interval from the date of randomization until the earlier date of the third-line disease progression or death due to progression of disease. For TLs, PD was defined as at least a 20% increase in SLD, taking as reference the smallest SLD recorded from baseline or the appearence of one or more lesions. For NTLs, PD was defined as the appearence of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without third-line PD or death were censored at the date of last tumor assessment where non-progression was documented.
AP: ITT population.

End point type	Secondary

End point timeframe:

Baseline (≤28 days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 4 years

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	247		
Units: months				
median (confidence interval 95%)	11.2 (9.4 to 12.7)	13.3 (12 to 15.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The 95% CI was estimated using Cox proportional hazards methodology. The stratification factors used in stratified analysis were hormone receptor status, first-line PFS, choice of chemotherapy, and LDH level.

Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0744
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.02

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The 95% CI was estimated using unstratified analysis.

Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0503
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1

Secondary: Percentage of Participants Who Died

End point title	Percentage of Participants Who Died

End point description:

Percentage of participants who died due to any reason were reported.
AP: ITT population.

End point type	Secondary

End point timeframe:

Baseline until death (up to approximately 4 years)

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	247		
Units: percentage of participants				
number (not applicable)	63.2	66		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the median time, in months, from the date of randomization to the date of death, due to any cause. Participants who had not died were censored at the date the patient was last known to be alive.
AP: ITT population.

End point type	Secondary

End point timeframe:

Baseline until death (up to approximately 4 years)

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	247		
Units: months				
median (confidence interval 95%)	18.7 (15.4 to 21.2)	19.7 (17.6 to 21)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The 95% CI was estimated using Cox proportional hazards methodology. The stratification factors used in stratified analysis were hormone receptor status, first-line PFS, choice of chemotherapy, and LDH level.

Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm
Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7253
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.21

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The 95% CI was estimated using unstratified analysis

Comparison groups	Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm

Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5332
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.16

Secondary: Percentage of Participants Estimated to be Surviving at Months 6, 12, 18, and 24

End point title	Percentage of Participants Estimated to be Surviving at Months 6, 12, 18, and 24

End point description:

OS was defined as the median time, in months, from the date of randomization to the date of death, due to any cause. Participants who had not died were censored at the date the participant was last known to be alive.
AP: ITT population.

End point type	Secondary

End point timeframe:

Months 6, 12, 18, and 24

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	247		
Units: percentage of participants				
number (confidence interval 95%)				
Month 6	85.2 (79.9 to 89.2)	90.4 (85.9 to 93.5)		
Month 12	68.6 (62 to 74.3)	72.4 (66.2 to 77.7)		
Month 18	52.8 (46 to 59.3)	54.9 (48.2 to 61)		
Month 24	38.4 (31.8 to 44.9)	37.6 (31.3 to 43.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Problems by European Quality of Life Instrument (EQ-5D) Category (Data Cutoff 20 December 2013)

End point title	Percentage of Participants Experiencing Problems by European Quality of Life Instrument (EQ-5D) Category (Data Cutoff 20 December 2013)

End point description:

EQ-5D is composed of 5 single-item measures and participants (pts) responded to questions assessing health status by responding with either 'no problems', 'some problems', or extreme problems' in the following categories: mobility (M) ('no problems'='I have no problems in walking about' to 'extreme problems'='I am confined to bed'), self-care (SC) ('no problems'='I have no problems with SC' to 'extreme problems'='I am unable to wash or dress myself”), usual activities (UA) ('no problems'= 'I have no problems performing my UA' to 'extreme problems'='I am unable to perform my UA'), pain/discomfort (P/D) ('no problems'='I have no P/D' to 'extreme problems'='I have extreme P/D', and anxiety/depression (A/D) ('no problems'='I am not anxious or depressed' to 'extreme problems'=I am extremely anxious or depressed').
AP: ITT population. Here, Number of pts analyzed = pts evaluable for this end point and n= number of pts completing questionaires at specified time point.

End point type	Secondary

End point timeframe:

Baseline (BL), during second-line treatment at Weeks 8 and 16 (4-week cycles) or Weeks 9 and 18 (3-week cycles) and at second-line PD (up to approximately 3 years)

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	214	224		
Units: percentage of participants				
number (not applicable)				
BL: M, no problems (n=214,224)	60.3	64.3		
BL: M, some problems (n=214,224)	36.4	34.8		
BL: M, extreme problems (n=214,224)	0.5	0.4		
BL: SC, no problems (n=214,224)	82.7	85.7		
BL: SC, some problems (n=214,224)	12.6	11.2		
BL: SC, extreme problems (n=214,224)	0.5	1.8		
BL: UA, no problems (n=214,224)	53.7	46.4		
BL: UA, some problems (n=214,224)	40.2	48.7		
BL: UA, extreme problems (n=214,224)	2.8	4		
BL: P/D, no problems (n=214,224)	24.3	27.7		
BL: P/D, some problems (n=214,224)	68.7	66.1		
BL: P/D, extreme problems (n=214,224)	4.2	5.4		
BL: A/D, no problems (n=214,224)	33.6	34.8		
BL: A/D, some problems (n=214,224)	56.5	58.5		
BL: A/D, extreme problems (n=214,224)	5.6	5.8		
Week 8/9: M, no problems (n=133,141)	61.7	51.8		
Week 8/9: M, some problems (n=133,141)	34.6	43.3		
Week 8/9: M, extreme problems (n=133,141)	1.5	2.1		
Week 8/9: SC, no problems (n=133,141)	82	75.9		

Week 8/9: SC, some problems (n=133,141)	13.5	17		
Week 8/9: SC, extreme problems (n=133,141)	1.5	3.5		
Week 8/9: UA, no problems (n=133,141)	53.4	40.4		
Week 8/9: UA, some problems (n=133,141)	40.6	51.8		
Week 8/9: UA, extreme problems (n=133,141)	3	5		
Week 8/9: P/D, no problems (n=133,141)	29.3	23.4		
Week 8/9: P/D, some problems (n=133,141)	61.7	68.1		
Week 8/9: P/D, extreme problems (n=133,141)	5.3	6.4		
Week 8/9: A/D, no problems (n=133,141)	49.6	46.8		
Week 8/9: A/D, some problems (n=133,141)	40.6	48.2		
Week 8/9: A/D, extreme problems (n=133,141)	6.8	2.8		
Week 16/18: M, no problems (n=84,123)	66.7	49.6		
Week 16/18: M, some problems (n=84,123)	29.8	47.2		
Week 16/18: M, extreme problems (n=84,123)	0	2.4		
Week 16/18: SC, no problems (n=84,123)	81	78.9		
Week 16/18: SC, some problems (n=84,123)	14.3	17.1		
Week 16/18: SC, extreme problems (n=84,123)	0	3.3		
Week 16/18: UA, no problems (n=84,123)	50	36.6		
Week 16/18: UA, some problems (n=84,123)	42.9	56.1		
Week 16/18: UA, extreme problems (n=84,123)	3.6	4.1		
Week 16/18: P/D, no problems (n=84,123)	34.5	19.5		
Week 16/18: P/D, some problems (n=84,123)	59.5	76.4		
Week 16/18: P/D, extreme problems (n=84,123)	1.2	3.3		
Week 16/18: A/D, no problems (n=84,123)	51.2	49.6		
Week 16/18: A/D, some problems (n=84,123)	44	43.1		
Week 16/18: A/D, extreme problems (n=84,123)	0	5.7		
Second-line PD: M, no problems (n=82,76)	59.8	47.4		
Second-line PD: M, some problems (n=82,76)	34.1	48.7		
Second-line PD: M, extreme problems (n=82,76)	2.4	3.9		
Second-line PD: SC, no problems (n=82,76)	76.8	75		
Second-line PD: SC, some problems (n=82,76)	15.9	18.4		

Second-line PD: SC, extreme problems (n=82,76)	1.2	6.6		
Second-line PD: UA, no problems (n=82,76)	39	30.3		
Second-line PD: UA, some problems (n=82,76)	50	59.2		
Second-line PD: UA, extreme problems (n=82,76)	6.1	10.5		
Second-line PD: P/D, no problems (n=82,76)	19.5	18.4		
Second-line PD: P/D, some problems (n=82,76)	67.1	69.7		
Second-line PD: P/D, extreme problems (n=82,76)	8.5	11.8		
Second-line PD: A/D, no problems (n=82,76)	36.6	26.3		
Second-line PD: A/D, some problems (n=82,76)	50	61.8		
Second-line PD: A/D, extreme problems (n=82,76)	7.3	11.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life Assessed As an Index Score Using the EQ-5D (Data Cutoff 20 December 2013)

End point title	Quality of Life Assessed As an Index Score Using the EQ-5D (Data Cutoff 20 December 2013)

End point description:

EQ-5D is composed of 5 single-item measures where participants responded to questions assessing health status by responding with either "no problems", "some problems", or "extreme problems" in the following categories: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Based on large population surveys, an algorithm was used to combine the responses to each of these 5 measures into 1 single EQ-5D index score ranging from -0.59 (extreme problems) to +1 (no problems). AP: ITT population. Here, Number of participants analyzed = participants evaluable for this end point and n= number of participants completing questionnaires at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, during second-line treatment at Weeks 8 and 16 (4-week cycles) or Weeks 9 and 18 (3-week cycles) and at second-line PD (up to approximately 3 years)

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	219		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				

Baseline (n= 202, 219)	0.6806 (0.6489 to 0.7122)	0.6725 (0.6389 to 0.7061)		
Week 8/9 (n=127,135)	0.6953 (0.647 to 0.7437)	0.6515 (0.6057 to 0.6973)		
Week 16/18 (n=80,118)	0.7496 (0.7114 to 0.7879)	0.6534 (0.6058 to 0.701)		
Second•line PD (n=77,76)	0.629 (0.5642 to 0.6938)	0.5553 (0.4736 to 0.637)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EQ-5D Index Scores (Data Cutoff 20 December 2013)

End point title	Change From Baseline in EQ-5D Index Scores (Data Cutoff 20 December 2013)

End point description:

EQ-5D is composed of 5 single-item measures where participants responded to questions assessing health status by responding with either "no problems", "some problems", or "extreme problems" in the following categories: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Based on large population surveys, an algorithm was used to combine the responses to each of these 5 measures into 1 single EQ-5D index score ranging from -0.59 (extreme problems) to +1 (no problems) where a negative value indicated a worsening of perceived quality of life and a positive value indicated an improvement of perceived quality of life.
AP: ITT population. Here, Number of participants analyzed = participants evaluable for this end point and n=number of participants completing the questionnaires at the specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, during second-line treatment at Weeks 8 and 16 (4-week cycles) or Weeks 9 and 18 (3-week cycles) and at second-line PD (up to approximately 3 years)

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	122		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Week 8/9 (n=107,122)	-0.0103 (-0.0482 to 0.0276)	-0.037 (-0.0868 to 0.0127)		
Week 16/18 (n=68,110)	0.0387 (-0.0025 to 0.08)	-0.0508 (-0.1038 to 0.0021)		
Second-line PD (n=69,71)	-0.0884 (-0.1398 to -0.0371)	-0.087 (-0.1649 to -0.0107)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life Assessed Using the EQ-5D Visual Analogue Scale (VAS) Scores (Data Cutoff 20 December 2013)

End point title	Quality of Life Assessed Using the EQ-5D Visual Analogue Scale (VAS) Scores (Data Cutoff 20 December 2013)

End point description:

The participant was asked to rate their overall health on a 0-100 millimeter (mm) vertical scale, where the lowest endpoint=0 (labeled as worst imaginable health state) and the highest endpoint =100 (labeled as the best imaginable health state). The participant marked the line corresponding to their assessment and the distance from the bottom was measured in mm. A higher value indicated a better health state.
AP: ITT population. Here, Number of participants analyzed = participants evaluable for this end point and n=number of participants completing the questionnaires at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, during second-line treatment at Weeks 8 and 16 (4-week cycles) or Weeks 9 and 18 (3-week cycles) and at second-line PD (up to approximately 3 years)

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	212		
Units: millimeters (mm)				
arithmetic mean (confidence interval 95%)				
BL (n=200,212)	66.5 (64.1 to 69)	63.4 (60.8 to 65.9)		
Week 8/9 (n=123,135)	69.3 (66.4 to 72.1)	66.5 (63.7 to 69.2)		
Week 16/18 (n=75,119)	67.3 (63.3 to 71.3)	66.4 (63.2 to 69.5)		
Second-line PD (n=78,75)	63.7 (59.5 to 68)	61.7 (57 to 66.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in VAS Scores (Data Cutoff 20 December 2013)

End point title	Change From Baseline in VAS Scores (Data Cutoff 20

	December 2013)

End point description:

The participant was asked to rate their overall health on a 0-100 mm vertical scale, where the lowest endpoint =0 (labeled as worst imaginable health state) and the highest endpoint =100 (labeled as the best imaginable health state). The participant marked the line corresponding to their assessment and the distance from the bottom was measured in mm. A negative value indicated a worsening of perceived quality of life and a positive value indicated an improvement of perceived quality of life.
AP: ITT population. Here, Number of participants analyzed = participants evaluable for this end point and n=number of participants completing the questionnaires at the corresponding timepoint.

End point type	Secondary

End point timeframe:

Baseline, during second-line treatment at Weeks 8 and 16 (4-week cycles) or Weeks 9 and 18 (3-week cycles) and at second-line PD (up to approximately 3 years)

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	118		
Units: millimeters (mm)				
arithmetic mean (confidence interval 95%)				
Week 8/9 (n=106,118)	-2 (-4.8 to 0.9)	2 (-1.4 to 5.3)		
Week 16/18 (n=66,107)	-0.2 (-4.7 to 4.3)	2 (-1.6 to 5.5)		
Second-line PD (n=70,69)	-5.1 (-9.1 to -1)	-1.3 (-5.5 to 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Cancer Therapy-Breast (FACT-B) Scores (Data Cutoff 20 December 2013)

End point title	Functional Assessment of Cancer Therapy-Breast (FACT-B) Scores (Data Cutoff 20 December 2013)

End point description:

FACT-B is composed of 5 multi-item sections and pts responded to questions assessing symptoms (scale: 0-4; 0='not at all' and 4='very much'): physical well-being (PWB; 7 items, total score 0-28), social/family well-being (SWB; 7 items, total score 0-28), emotional well-being (EWB; 6 items, total score 0-24), functional well-being (FWB; 7 items, total score 0-28); and breast cancer score based on the additional concerns section of FACT-B (10 items, total score 0-40). FACT-B Trial Outcomes Index (TOI)= sum of PWB, FWB, and breast cancer score subscale scores (total score 0-96). FACT-B total score=sum of PWB, SWB, EWB, FWB, and breast cancer score subscales scores (total score 0-148). A higher value indicated a better quality of life.
ITT population. No of pts analyzed = pts evaluable for this OM and n=no of pts completing the questionnaires at specified timepoint.
The data 9.99, 99.9, 999.9, 999, 9999, 99999 signifies data not available.

End point type	Secondary

End point timeframe:

BL (≤28 days after randomization), every 8-9 weeks thereafter until second-line PD (up to approximately 3 years)

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	224		
Units: scores on a scale				
median (confidence interval 95%)				
BL: PWB (n=215,222)	20.621 (19.9 to 21.342)	20.253 (19.5 to 21.006)		
BL: SWB (n=214,223)	20.722 (20.028 to 21.416)	20.674 (19.923 to 21.425)		
BL: EWB (n=215,224)	14.847 (14.176 to 15.519)	15.062 (14.419 to 15.704)		
BL: FWB (n=215,224)	16.091 (15.289 to 16.894)	15.726 (14.951 to 16.502)		
BL: Breast Cancer Score (n=210,224)	24.986 (24.103 to 25.869)	24.388 (23.578 to 25.198)		
BL: FACT-B TOI (n=204,219)	61.677 (59.658 to 63.696)	60.277 (58.365 to 62.189)		
BL: Total FACT-G Score (n=207,218)	72.169 (69.919 to 74.419)	71.864 (69.786 to 73.942)		
BL: Total FACT-B Score (n=201,218)	96.908 (94.063 to 99.753)	96.115 (93.485 to 98.746)		
Week 8/9: PWB (n=129,138)	20.413 (19.413 to 21.413)	19.156 (18.158 to 20.153)		
Week 8/9: SWB (n=127,135)	20.833 (19.888 to 21.779)	21.116 (20.245 to 21.987)		
Week 8/9: EWB (n=129,139)	15.943 (15.07 to 16.815)	16.671 (15.9 to 17.441)		
Week 8/9: FWB (n=129,139)	16.662 (15.609 to 17.715)	16.169 (15.18 to 17.158)		
Week 8/9: Breast Cancer Score (n=128,139)	26.276 (25.188 to 27.364)	25.884 (24.928 to 26.839)		
Week 8/9: FACT-B TOI (n=126,136)	63.547 (60.975 to 66.118)	61.279 (58.811 to 63.747)		
Week 8/9: Total FACT-G Score (n=122,134)	74.255 (71.212 to 77.299)	73.393 (70.603 to 76.184)		
Week 8/9: Total FACT-B Score (n=123,134)	100.375 (96.582 to 104.169)	99.213 (95.667 to 102.76)		

Week 16/18: PWB (n=83,107)	21.733 (20.721 to 22.744)	19.629 (18.571 to 20.688)		
Week 16/18: SWB (n=80,105)	20.93 (19.855 to 22.006)	20.843 (19.829 to 21.857)		
Week 16/18: EWB (n=80,107)	17.33 (16.26 to 18.4)	16.806 (15.961 to 17.65)		
Week 16/18: FWB (n=81,106)	17.055 (15.818 to 18.291)	15.92 (14.787 to 17.053)		
Week 16/18: Breast Cancer (n=81,106)	26.923 (25.493 to 28.354)	25.755 (24.63 to 26.88)		
Week 16/18: FACT-B TOI (n=78,105)	65.628 (62.539 to 68.717)	61.107 (58.309 to 63.905)		
Week 16/18: Total FACT-G (n=78,102)	76.794 (73.269 to 80.318)	73.269 (70.116 to 76.421)		
Week 16/18: Total FACT-B (n=76,103)	103.503 (98.819 to 108.187)	98.906 (94.865 to 102.948)		
Week 24/27: PWB (n=48,80)	21.94 (20.599 to 23.282)	18.965 (17.515 to 20.416)		
Week 24/27: SWB (n=47,78)	20.84 (19.468 to 22.211)	21.399 (20.192 to 22.606)		
Week 24/27: EWB (n=45,78)	17.098 (15.719 to 18.477)	16.438 (15.411 to 17.436)		
Week 24/27: FWB (n=45,79)	18.244 (16.754 to 19.734)	16.051 (14.861 to 17.241)		
Week 24/27: Breast Cancer (n=46,79)	26.067 (24.146 to 27.988)	24.632 (23.231 to 26.033)		
Week 24/27: FACT-B TOI (n=44,77)	65.882 (61.991 to 69.653)	60.014 (56.548 to 63.48)		
Week 24/27: Total FACT-G (n=44,77)	78.305 (74.166 to 82.443)	73.083 (69.365 to 76.801)		
Week 24/27: Total FACT-B (n=43,77)	104.011 (98.433 to 109.588)	97.795 (92.995 to 102.595)		
Week 32/36: PWB (n=26,44)	22.949 (21.427 to 24.471)	19.686 (18.121 to 21.25)		
Week 32/36: SWB (n=25,43)	22.14 (20.433 to 23.847)	21.222 (19.645 to 22.798)		
Week 32/36: EWB (n=26,44)	18.385 (16.69 to 20.079)	16.755 (15.481 to 18.028)		
Week 32/36: FWB (n=26,44)	19.615 (17.875 to 21.356)	17.195 (15.585 to 18.805)		
Week 32/36: Breast Cancer (n=26,43)	29.568 (27.722 to 31.415)	26.163 (24.457 to 27.869)		

Week 32/36: FACT-B TOI (n=26,42)	72.132 (68.549 to 75.716)	63.017 (59.199 to 66.836)		
Week 32/36: Total FACT-G (n=25,42)	83.087 (78.178 to 87.995)	74.879 (70.566 to 79.191)		
Week 32/36: Total FACT-B (n=25,42)	112.904 (107.315 to 118.494)	100.904 (95.302 to 106.506)		
Week 40/45: PWB (n=20,27)	22.215 (20.583 to 23.847)	20.63 (18.82 to 22.44)		
Week 40/45: SWB (n=21,26)	19.658 (17.955 to 21.361)	20.915 (19.146 to 22.685)		
Week 40/45: EWB (n=20,27)	17.56 (15.708 to 19.412)	16.067 (13.875 to 18.259)		
Week 40/45: FWB (n=20,27)	18.45 (16.12 to 20.78)	16.519 (13.901 to 19.136)		
Week 40/45: Breast Cancer (n=21,27)	29.386 (27.156 to 31.616)	23.819 (21.013 to 26.625)		
Week 40/45: FACT-B TOI (n=19,27)	68.75 (63.981 to 73.518)	60.967 (55.065 to 66.87)		
Week 40/45: Total FACT-G (n=19,26)	76.955 (71.48 to 82.43)	75.235 (68.901 to 81.568)		
Week 40/45: Total FACT-B (n=19,26)	105.54 (98.512 to 112.568)	99.072 (90.613 to 107.531)		
Week 48/54: PWB (n=13,24)	23.308 (21.283 to 25.333)	20.033 (18.124 to 21.943)		
Week 48/54: SWB (n=13,23)	20.74 (18.953 to 22.527)	20.45 (18.31 to 22.59)		
Week 48/54: EWB (n=13,23)	19.308 (17.522 to 21.093)	17.27 (15.494 to 19.045)		
Week 48/54: FWB (n=13,23)	18.538 (16.586 to 20.491)	16.268 (13.949 to 18.587)		
Week 48/54: Breast Cancer (n=13,23)	28.912 (26.879 to 30.945)	26.237 (22.842 to 29.632)		
Week 48/54: Fact-B TOI (n=13,23)	70.758 (66.403 to 75.114)	62.679 (55.941 to 69.418)		
Week 48/54: Total FACT-G (n=13,23)	81.894 (76.424 to 87.363)	74.162 (67.865 to 80.458)		
Week 48/54: Total FACT-B (n=13,23)	110.806 (104.704 to 116.908)	100.399 (91.294 to 109.503)		
Week 56/63: PWB (n=8,14)	21.792 (18.958 to 24.626)	20.298 (17.412 to 23.184)		
Week 56/63: SWB (n=8,14)	19.583 (15.598 to 23.569)	20.817 (17.629 to 24.004)		
Week 56/63: EWB (n=7,14)	17.143 (13.389 to 20.897)	15.714 (12.606 to 18.823)		

Week 56/63: FWB (n=7,14)	17.143 (13.876 to 20.41)	16.476 (12.633 to 20.319)		
Week 56/63: Breast Cancer (n=8,14)	28.24 (23.931 to 32.548)	25.459 (21.407 to 29.512)		
Week 56/63: FACT-B TOI (n=7,14)	66.179 (55.888 to 76.469)	62.233 (53.524 to 70.942)		
Week 56/63: Total FACT-G (n=6,14)	73.667 (58.381 to 88.952)	73.305 (62.863 to 83.746)		
Week 56/63: Total FACT-B (n=6,14)	101.042 (81.841 to 120.242)	98.764 (85.368 to 112.16)		
Week 64/72: PWB (n=7,9)	21.857 (17.376 to 26.338)	21.889 (19.569 to 24.209)		
Week 64/72: SWB (n=7,9)	18.976 (16.352 to 21.6)	22.685 (19.417 to 25.953)		
Week 64/72: EWB (n=7,9)	18.143 (13.758 to 22.527)	17.889 (14.274 to 21.503)		
Week 64/72: FWB (n=7,9)	18.429 (14.658 to 22.199)	16.037 (12.89 to 19.184)		
Week 64/72: Breast Cancer (n=7,9)	27.464 (22.941 to 31.988)	26.889 (22.584 to 31.194)		
Week 64/72: FACT-B TOI (n=7,9)	67.75 (56.306 to 79.194)	64.815 (56.516 to 73.114)		
Week 64/72: Total FACT-G (n=7,9)	77.405 (63.847 to 90.963)	78.5 (68.852 to 88.148)		
Week 64/72: Total FACT-B (n=7,9)	104.869 (87.586 to 122.152)	105.389 (92.415 to 118.363)		
Week 72/81: PWB (n=6,7)	23.083 (18.906 to 27.26)	21 (16.407 to 25.593)		
Week 72/81: SWB (n=5,7)	19.667 (16.238 to 23.095)	20.043 (14.019 to 26.067)		
Week 72/81: EWB (n=6,7)	17.5 (13.476 to 21.524)	18.114 (14.13 to 22.098)		
Week 72/81: FWB (n=6,7)	17.333 (14.316 to 20.351)	16.429 (11.339 to 21.518)		
Week 72/81: Breast Cancer (n=6,6)	28.597 (24.421 to 32.774)	25.333 (20.25 to 30.417)		
Week 72/81: FACT-B TOI (n=6,6)	69.014 (59.566 to 78.462)	60.833 (47.031 to 74.635)		
Week 72/81: Total FACT-G (n=5,7)	76.467 (62.045 to 90.889)	75.586 (57.141 to 94.03)		
Week 72/81: Total FACT-B (n=5,6)	106.117 (88.146 to 124.087)	97.211 (73.196 to 121.226)		
Week 80/90: PWB (n=2,3)	19.25 (-32.634 to 71.134)	18 (2.487 to 33.513)		

Week 80/90: SWB (n=2,3)	18.375 (7.257 to 29.493)	19.944 (3.434 to 36.455)		
Week 80/90: EWB (n=2,3)	14 (-49.531 to 77.531)	15.733 (-3.285 to 34.752)		
Week 80/90: FWB (n=2,3)	15 (-35.825 to 65.825)	12.333 (-1.348 to 26.015)		
Week 80/90: Breast Cancer (n=2,3)	21.667 (0.49 to 42.844)	25 (14.172 to 35.828)		
Week 80/90: FACT-B TOI (n=2,3)	55.917 (-67.969 to 179.802)	55.333 (20.085 to 90.581)		
Week 80/90: Total FACT-G (n=2,3)	66.625 (-110.732 to 243.982)	66.011 (2.191 to 129.831)		
Week 80/90: Total FACT-B (n=2,3)	88.292 (-110.243 to 286.826)	91.011 (20.313 to 161.709)		
Week 88/99: PWB (n=0,1)	9999 (999 to 99999)	22 (9.99 to 99.9)		
Week 88/99: SWB (n=0,1)	9999 (999 to 99999)	23.333 (9.99 to 99.9)		
Week 88/99: EWB (n=0,1)	9999 (999 to 99999)	20 (9.99 to 99.9)		
Week 88/99: FWB (n=0,1)	9999 (999 to 99999)	21 (9.99 to 99.9)		
Week 88/99: Breast Cancer (n=0,1)	9999 (999 to 99999)	35 (9.99 to 99.9)		
Week 88/99: FACT-B TOI (n=0,1)	9999 (999 to 99999)	78 (9.99 to 99.9)		
Week 88/99: Total FACT-G (n=0,1)	9999 (999 to 99999)	86.333 (9.99 to 99.9)		
Week 88/99: Total FACT-B (n=0,1)	9999 (999 to 99999)	121.333 (99.9 to 999.9)		
Week 96/108: PWB (n=2,1)	26 (9.99 to 99.9)	22 (9.99 to 99.9)		
Week 96/108: SWB (n=2,1)	24.383 (-3.782 to 52.549)	21 (9.99 to 99.9)		
Week 96/108: EWB (n=2,2)	22 (9.294 to 34.706)	18 (-7.412 to 43.412)		
Week 96/108: FWB (n=2,2)	21.083 (7.318 to 34.848)	10.5 (-46.678 to 67.678)		
Week 96/108: Breast Cancer (n=2,2)	30.389 (-2.788 to 63.566)	24.5 (-7.266 to 56.266)		
Week 96/108: FACT-B TOI (n=2,1)	77.472 (58.06 to 96.884)	59 (9.99 to 99.9)		
Week 96/108: Total FACT-G (n=2,1)	93.467 (38.83 to 148.103)	74 (9.99 to 999.9)		
Week 96/108: Total FACT-B (n=2,1)	123.856 (102.396 to 145.315)	96 (9.99 to 999.9)		
Week 104/117: PWB (n=1,3)	27 (9.99 to 99.9)	21.333 (17.539 to 25.128)		
Week 104/117: SWB (n=1,2)	26.6 (9.99 to 99.9)	20.5 (14.147 to 26.853)		
Week 104/117: EWB (n=1,3)	22 (9.99 to 99.9)	18 (6.616 to 29.384)		
Week 104/117: FWB (n=1,3)	22 (9.99 to 99.9)	11 (-1.908 to 23.908)		
Week 104/117: Breast Cancer (n=1,3)	27.143 (9.99 to 99.9)	28 (19.395 to 36.605)		

Week 104/117: FACT-B TOI (n=1,3)	76.143 (9.99 to 99.9)	60.333 (45.778 to 74.889)		
Week 104/117: Total FACT-G (n=1,2)	97.6 (9.99 to 99.9)	70.5 (-50.209 to 191.209)		
Week 104/117: Total FACT-B (n=1,2)	124.743 (99.9 to 999.9)	100.5 (-20.209 to 221.209)		
Week 112/126: PWB (n=0,1)	9999 (999 to 99999)	14 (9.99 to 99.9)		
Week 112/126: SWB (n=0,1)	9999 (999 to 99999)	15.4 (9.99 to 99.9)		
Week 112/126: EWB (n=0,1)	9999 (999 to 99999)	15 (9.99 to 99.9)		
Week 112/126: FWB (n=0,1)	9999 (999 to 99999)	11 (9.99 to 99.9)		
Week 112/126: Breast Cancer (n=0,1)	9999 (999 to 99999)	20 (9.99 to 99.9)		
Week 112/126: FACT-B TOI (n=0,1)	9999 (999 to 99999)	45 (9.99 to 99.9)		
Week 112/126: Total FACT-G (n=0,1)	9999 (999 to 99999)	55.4 (9.99 to 99.9)		
Week 112/126: Total FACT-B (n=0,1)	9999 (999 to 99999)	75.4 (9.99 to 99.9)		
Second-Line PD: PWB (n=89,81)	19.086 (17.873 to 20.299)	17.412 (15.977 to 18.846)		
Second-Line PD: SWB (n=88,79)	20.623 (19.456 to 21.79)	21.487 (20.335 to 22.639)		
Second-Line PD: EWB (n=88,80)	15.111 (14.102 to 16.121)	14.175 (12.872 to 15.478)		
Second-Line PD: FWB (n=88,80)	15.447 (14.122 to 16.772)	15.235 (13.877 to 16.593)		
Second-Line PD: Breast Cancer (n=85,81)	24.978 (23.602 to 26.354)	24.445 (22.989 to 25.901)		
Second-Line PD: FACT-B TOI (n=84,80)	59.23 (56.033 to 62.428)	57.002 (53.234 to 60.77)		
Second-Line PD: Total FACT-G (n=86,78)	69.829 (66.264 to 73.393)	68.485 (64.384 to 72.586)		
Second-Line PD: Total FACT-B (n=82,78)	94.93 (90.24 to 99.619)	92.983 (87.645 to 98.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in FACT-B Scores (Data Cutoff 20 December 2013)

End point title	Change From Baseline in FACT-B Scores (Data Cutoff 20 December 2013)

End point description:

FACT-B is composed of 5 multi-item sections where pts responded to questions assessing symptoms (scale: 0-4; 0='not at all' and 4='very much'), as follows: PWB (7 items, total score 0-28), SWB (7

items, total score 0-28), EWB (6 items, total score 0-24), FWB (7 items, total score 0-28), and breast cancer score based on the additional concerns section of FACT-B (10 items, total score 0-40). FACT-B TOI score=sum of PWB, FWB, and breast cancer score subscale scores (total score 0-96). FACT-G total score=sum of PWB, SWB, EWB, and FWB subscales scores (total score 0-108). FACT-B total score=sum of PWB, SWB, EWB, FWB, and breast cancer score subscale scores (total score 0-148). Higher value indicated better perceived quality of life.
ITT population. No of pts analyzed = pts evaluable for end point and n=no of pts completing the questionnaires at specified timepoint.
The data -9.99, -99.9, 9.99, 99.9, 999, 9999, 99999 signifies data not available.

End point type	Secondary

End point timeframe:

Baseline (≤28 days after randomization), every 8-9 weeks thereafter until second-line PD (up to approximately 3 years)

End point values	Chemotherapy (CT) Arm	Chemotherapy Plus Bevacizumab (CT+BV) Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	128		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Week 8/9: PWB (n=118,125)	-1.281 (-2.219 to -0.344)	-1.289 (-2.239 to -0.338)		
Week 8/9: SWB (n=116,125)	0.356 (-0.283 to 0.994)	0.707 (-0.226 to 1.64)		
Week 8/9: EWB (n=116,128)	0.408 (-0.274 to 1.089)	1.024 (0.314 to 1.734)		
Week 8/9: FWB (n=117,128)	-0.226 (-1.043 to 0.591)	-0.24 (-1.027 to 0.548)		
Week 8/9: Breast Cancer Score (n=113,128)	0.228 (-0.659 to 1.116)	0.95 (0.121 to 1.78)		
Week 8/9: FACT-B TOI (n=110,122)	-1.361 (-3.295 to 0.573)	-0.357 (-2.407 to 1.693)		
Week 8/9: Total FACT-G Score (n=110,122)	-0.76 (-2.92 to 1.399)	0.369 (-1.945 to 2.684)		
Week 8/9: Total FACT-B Score (n=108,120)	-0.728 (-3.332 to 1.876)	1.342 (-1.544 to 4.229)		
Week 16/18: PWB (n=77,97)	0.294 (-0.733 to 1.322)	-1.823 (-2.871 to -0.775)		
Week 16/18: SWB (n=74,97)	-0.443 (-1.411 to 0.525)	0.359 (-0.678 to 1.397)		
Week 16/18: EWB (n=73,98)	1.197 (0.415 to 1.979)	0.921 (0.186 to 1.657)		
Week 16/18: FWB (n=75,98)	-0.548 (-1.666 to 0.57)	-0.517 (-1.422 to 0.389)		
Week 16/18: Breast Cancer (n=72,97)	0.578 (-0.658 to 1.815)	0.546 (-0.423 to 1.514)		
Week 16/18: FACT-TOI (n=68,95)	-0.483 (-3.149 to 2.183)	-1.732 (-4.049 to 0.586)		
Week 16/18: Total FACT-G (n=71,93)	-0.019 (-2.97 to 2.931)	-0.836 (-3.494 to 1.821)		
Week 16/18: Total Fact-B (n=66,93)	-0.007 (-3.744 to 3.73)	-0.127 (-3.421 to 3.167)		
Week 24/27: PWB (n=44,73)	0.181 (-1.236 to 1.598)	-1.996 (-3.306 to -0.685)		

Week 24/27: SWB (n=44,72)	-0.193 (-1.49 to 1.104)	1.375 (-0.001 to 2.75)		
Week 24/27: EWB (n=42,72)	0.867 (-0.101 to 1.834)	1.217 (0.366 to 2.067)		
Week 24/27: FWB (n=42,72)	0.119 (-1.405 to 1.643)	0.056 (-1.053 to 1.166)		
Week 24/27: Breast Cancer (n=40,72)	-0.038 (-1.723 to 1.647)	0.078 (-1.106 to 1.262)		
Week 24/27: FACT-B TOI (n=38,70)	0.221 (-3.411 to 3.853)	-1.573 (-4.383 to 1.238)		
Week 24/27: Total FACT-G (n=40,70)	0.764 (-3.066 to 4.595)	0.817 (-2.497 to 4.131)		
Week 24/27: Total FACT-B (n=37,70)	0.793 (-4.106 to 5.693)	1.157 (-2.828 to 5.142)		
Week 32/36: PWB (n=25,39)	0.88 (-0.913 to 2.673)	-1.235 (-2.799 to 0.329)		
Week 32/36: SWB (n=24,40)	-0.388 (-1.754 to 0.979)	1.036 (-1.209 to 3.281)		
Week 32/36: EWB (n=25,40)	1.064 (-0.298 to 2.426)	1.555 (0.204 to 2.906)		
Week 32/36: FWB (n=25,40)	1.38 (-0.103 to 2.863)	1.635 (-0.201 to 3.471)		
Week 32/36: Breast Cancer (n=23,40)	0.928 (-1.916 to 3.771)	1.278 (-0.435 to 2.99)		
Week 32/36: FACT-B TOI (n=23,38)	3.123 (-1.39 to 7.637)	1.471 (-2.522 to 5.464)		
Week 32/36: Total FACT-G (n=24,39)	2.617 (-1.313 to 6.547)	3.197 (-1.346 to 7.74)		
Week 32/36: Total FACT-B (n=22,38)	3.529 (-2.074 to 9.132)	3.896 (-1.579 to 9.37)		
Week 40/45: PWB (n=18,25)	0.137 (-2.051 to 2.325)	-0.68 (-2.93 to 1.57)		
Week 40/45: SWB (n=19,24)	-0.589 (-2.436 to 1.259)	0.951 (-1.59 to 3.492)		
Week 40/45: EWB (n=18,25)	0.2 (-1.598 to 1.998)	1.048 (-0.658 to 2.754)		
Week 40/45: FWB (n=18,25)	1.417 (-0.562 to 3.395)	0.857 (-0.893 to 2.608)		
Week 40/45: Breast Cancer (n=18,25)	1.395 (-1.268 to 4.058)	0.444 (-2.358 to 3.247)		
Week 40/45: FACT-B TOI (n=16,25)	2.432 (-2.496 to 7.36)	0.622 (-4.688 to 5.932)		
Week 40/45: Total FACT-G (n=17,24)	1.444 (-3.342 to 6.231)	2.432 (-3.035 to 7.899)		
Week 40/45: Total FACT-B (n=16,24)	1.916 (-3.95 to 7.782)	2.673 (-4.258 to 9.603)		
Week 48/54: PWB (n=13,20)	1.295 (-2.037 to 4.627)	-1.833 (-3.721 to 0.055)		
Week 48/54: SWB (n=13,20)	1.529 (-0.316 to 3.375)	2.008 (-1.083 to 5.099)		
Week 48/54: EWB (n=13,20)	1.492 (0.492 to 2.492)	1.71 (-0.183 to 3.603)		
Week 48/54: FWB (n=13,20)	2.269 (0.174 to 4.365)	1.592 (-0.872 to 4.055)		
Week 48/54: Breast Cancer (n=12,20)	0.599 (-1.714 to 2.912)	1.897 (-0.463 to 4.258)		
Week 48/54: FACT-B TOI (n=12,20)	4.044 (-2.832 to 10.919)	1.656 (-3.691 to 7.002)		
Week 48/54: Total FACT-G (n=13,20)	6.586 (1.392 to 11.78)	3.477 (-2.596 to 9.55)		
Week 48/54: Total FACT-B (n=12,20)	7.067 (0.241 to 13.894)	5.374 (-2.391 to 13.139)		

Week 56/63: PWB (n=8,13)	-2.063 (-6.094 to 1.969)	-0.526 (-3.996 to 2.944)		
Week 56/63: SWB (n=8,13)	-1.5 (-5.699 to 2.699)	3.033 (-1.729 to 7.796)		
Week 56/63: EWB (n=7,13)	0.857 (-2.781 to 4.495)	0.954 (-2.19 to 4.097)		
Week 56/63: FWB (n=7,13)	0 (-4.835 to 4.835)	5.654 (0.511 to 10.797)		
Week 56/63: Breast Cancer (n=8,13)	-0.83 (-6.133 to 4.474)	1.675 (-1.291 to 4.641)		
Week 56/63: FACT-B TOI (n=7,13)	-3.591 (-17.803 to 10.621)	6.803 (1.093 to 14.699)		
Week 56/63: Total FACT-G (n=6,13)	-4.083 (-22.93 to 14.764)	9.115 (-3.82 to 22.05)		
Week 56/63: Total FACT-B (n=6,13)	-5.301 (-29.74 to 19.138)	10.791 (-3.114 to 24.695)		
Week 64/72: PWB (n=7,9)	0 (-6.733 to 6.733)	0.926 (-1.491 to 3.342)		
Week 64/72: SWB (n=7,9)	-2.014 (-5.182 to 1.154)	3.57 (-1.034 to 8.174)		
Week 64/72: EWB (n=7,9)	-0.057 (-3.537 to 3.423)	3.667 (-0.63 to 7.964)		
Week 64/72: FWB (n=7,9)	0.214 (-4.531 to 4.959)	3.222 (-2.143 to 8.588)		
Week 64/72: Breast Cancer (n=7,9)	-2.298 (-7.507 to 2.912)	3.086 (-1.361 to 7.534)		
Week 64/72: FACT-B TOI (n=7,9)	-2.083 (-17.13 to 12.963)	7.235 (-3.624 to 18.093)		
Week 64/72: Total FACT-G (n=7,9)	-1.857 (-17.855 to 14.14)	11.385 (-3.116 to 25.886)		
Week 64/72: Total FACT-B (n=7,9)	-4.155 (-24.302 to 15.993)	14.472 (-4.192 to 33.135)		
Week 72/81: PWB (n=5,7)	2.133 (-6.045 to 10.311)	-0.429 (-3.965 to 3.108)		
Week 72/81: SWB (n=4,7)	-1.208 (-5.126 to 2.71)	6.829 (-3.189 to 16.846)		
Week 72/81: EWB (n=5,7)	-0.6 (-5.042 to 3.842)	4.686 (-0.608 to 9.979)		
Week 72/81: FWB (n=5,7)	0 (-5.341 to 5.341)	7.381 (-1.169 to 15.931)		
Week 72/81: Breast Cancer (n=5,6)	-0.461 (-6.531 to 5.609)	3.667 (-3.41 to 10.743)		
Week 72/81: FACT-B TOI (n=5,6)	1.672 (-12.563 to 15.907)	8.278 (-7.45 to 24.005)		
Week 72/81: Total FACT-G (n=4,7)	-0.167 (-22.161 to 21.828)	18.467 (-1.867 to 38.801)		
Week 72/81: Total FACT-B (n=4,6)	1.174 (-23.085 to 25.432)	16.906 (-9.207 to 43.018)		
Week 80/90: PWB (n=2,3)	-3.75 (-30.221 to 22.721)	3 (-11.605 to 5.605)		
Week 80/90: SWB (n=2,3)	-0.875 (-34.229 to 32.479)	7.344 (-9.614 to 24.303)		
Week 80/90: EWB (n=2,3)	-4 (-42.119 to 34.119)	4.733 (-18.466 to 27.932)		
Week 80/90: FWB (n=2,3)	-1 (-64.531 to 62.531)	2.556 (-9.165 to 14.276)		

Week 80/90: Breast Cancer (n=2,3)	-5.833 (-29.128 to 17.461)	3.667 (-11.512 to 18.845)		
Week 80/90: FACT-B TOI (n=2,3)	-10.583 (-77.291 to 56.124)	3.222 (-30.212 to 36.657)		
Week 80/90: Total FACT-G (n=2,3)	-9.625 (-171.1 to 151.85)	11.633 (-41.554 to 64.821)		
Week 80/90: Total FACT-B (n=2,3)	-15.458 (-153.638 to 122.722)	15.3 (-48.177 to 78.777)		
Week 88/99: PWB (n=0,1)	9999 (999 to 99999)	-6 (-9.99 to 9.99)		
Week 88/99: SWB (n=0,1)	9999 (999 to 99999)	23.333 (9.99 to 99.9)		
Week 88/99: EWB (n=0,1)	9999 (999 to 99999)	0 (-9.99 to 9.99)		
Week 88/99: FWB (n=0,1)	9999 (999 to 99999)	21 (9.99 to 99.9)		
Week 88/99: Breast Cancer (n=0,1)	9999 (999 to 99999)	3 (-9.99 to 9.99)		
Week 88/99: FACT TOI (n=0,1)	9999 (999 to 99999)	18 (9.99 to 99.9)		
Week 88/99: Total FACT-G (n=0,1)	9999 (999 to 99999)	38.333 (9.99 to 99.9)		
Week 88/99: Total FACT-B (n=0,1)	9999 (999 to 99999)	41.333 (9.99 to 99.9)		
Week 96/108: PWB (n=2,1)	7.333 (-51.962 to 66.629)	-3 (-9.99 to 9.99)		
Week 96/108: SWB (n=2,1)	2.183 (-23.441 to 27.808)	1.4 (-9.99 to 9.99)		
Week 96/108: EWB (n=2,1)	0 (-12.706 to 12.706)	6 (-9.99 to 9.99)		
Week 96/108: FWB (n=2,1)	6.583 (-13.535 to 26.701)	-1.333 (-9.99 to 9.99)		
Week 96/108: Breast Cancer (n=2,1)	3.167 (-41.305 to 47.638)	-3 (-9.99 to 9.99)		
Week 96/108: FACT-B TOI (n=2,1)	17.083 (11.789 to 22.378)	-7.333 (-9.99 to 9.99)		
Week 96/108: Total FACT-G (n=2,1)	16.1 (15.253 to 16.947)	3.067 (-9.99 to 9.99)		
Week 96/108: Total FACT-B (n=2,1)	19.267 (-24.358 to 62.891)	0.067 (-9.99 to 9.99)		
Week 104/117: PWB (n=1,2)	3.667 (-9.99 to 9.99)	-2 (-40.119 to 36.119)		
Week 104/117: SWB (n=1,1)	4.2 (-9.99 to 9.99)	8.8 (-9.99 to 9.99)		
Week 104/117: EWB (n=1,2)	0 (-9.99 to 9.99)	10 (-28.119 to 48.119)		
Week 104/117: FWB (n=1,2)	8 (-9.99 to 9.99)	2.333 (-56.962 to 61.629)		
Week 104/117: Breast Cancer (n=1,2)	6.032 (-9.99 to 9.99)	4 (-59.531 to 67.531)		
Week 104/117: FACT-B TOI (n=1,2)	17.698 (9.99 to 99.9)	4.333 (-156.612 to 165.279)		
Week 104/117: Total FACT-G (n=1,1)	15.867 (9.99 to 99.9)	29.8 (9.99 to 99.9)		
Week 104/117: Total FACT-B (n=1,1)	21.898 (9.99 to 99.9)	38.8 (9.99 to 99.9)		

Week 112/126: PWB (n=0,1)	9999 (999 to 99999)	-11 (-99.9 to 9.99)		
Week 112/126: SWB (n=0,1)	9999 (999 to 99999)	-4.2 (-9.99 to 9.99)		
Week 112/126: EWB (n=0,1)	9999 (999 to 99999)	5 (-9.99 to 9.99)		
Week 112/126: FWB (n=0,1)	9999 (999 to 99999)	-5.333 (-9.99 to 9.99)		
Week 112/126: Breast Cancer (n=0,1)	9999 (999 to 99999)	-5 (-9.99 to 9.99)		
Week 112/126: FACT-B TOI (n=0,1)	9999 (999 to 99999)	-21.333 (-99.9 to 9.99)		
Week 112/126: Total FACT-G (n=0,1)	9999 (999 to 99999)	-15.533 (-99.9 to 9.99)		
Week 112/126: Total FACT-B (n=0,1)	9999 (999 to 99999)	-20.533 (-99.9 to 9.99)		
Second-Line PD: PWB (n=81,77)	-0.871 (-1.916 to 0.174)	-2.507 (-3.783 to -1.231)		
Second-Line PD: SWB (n=80,75)	-0.106 (-0.902 to 0.69)	-0.766 (-1.788 to 0.256)		
Second-Line PD: EWB (n=80,76)	-0.44 (-1.553 to 0.673)	-0.508 (-1.562 to 0.546)		
Second-Line PD: FWB (n=80,76)	-1.415 (-2.59 to -0.239)	-0.773 (-1.809 to 0.263)		
Second-Line PD: Breast Cancer (n=77,77)	0.12 (-1.182 to 1.421)	0.241 (-0.878 to 1.36)		
Second-Line PD: FACT-B TOI (n=74,76)	-2.311 (-5.07 to 0.447)	-3.003 (-5.734 to -0.273)		
Second-Line PD: Total FACT-G (n=76,74)	-2.771 (-5.902 to 0.361)	-4.702 (-7.941 to -1.462)		
Second-Line PD: Total FACT-B (n=72,74)	-2.719 (-6.633 to 1.195)	-4.44 (-8.515 to -0.366)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to approximately 4 years

Adverse event reporting additional description:

All randomized participants who received at least 1 dose of bevacizumab and/or chemotherapy were included in the analysis.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	CT Arm

Reporting group description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

Reporting group title	CT+BV Arm

Reporting group description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 mg/kg, IV, every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 mg/kg, IV, every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

Serious adverse events	CT Arm	CT+BV Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 238 (23.11%)	89 / 245 (36.33%)	
number of deaths (all causes)	6	8	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metastases to liver			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism venous			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	3 / 245 (1.22%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism arterial			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infarction			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Salpingo-oophorectomy			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth extraction			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine anastomosis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 238 (0.84%)	4 / 245 (1.63%)	
occurrences causally related to treatment / all	2 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 238 (0.84%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	3 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	3 / 245 (1.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pain			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Patient-device incompatibility			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menstrual disorder			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 238 (0.84%)	6 / 245 (2.45%)	
occurrences causally related to treatment / all	2 / 2	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 238 (0.42%)	3 / 245 (1.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Gamma-glutamyltransferase increased			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 238 (0.42%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biopsy liver			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium increased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 238 (0.42%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Acute coronary syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 238 (0.42%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure congestive			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiotoxicity			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Congestive cardiomyopathy			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Left ventricular failure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sinus tachycardia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 238 (0.84%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Convulsion			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor dysfunction			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Partial seizures			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured cerebral aneurysm			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Blood and lymphatic system disorders			
Febrile neutropenia			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 238 (2.10%)	12 / 245 (4.90%)	
occurrences causally related to treatment / all	5 / 5	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 238 (2.52%)	10 / 245 (4.08%)	
occurrences causally related to treatment / all	7 / 7	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 238 (0.00%)	5 / 245 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 238 (0.84%)	4 / 245 (1.63%)	
occurrences causally related to treatment / all	2 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 238 (0.42%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Melaena			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Subileus			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
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			
Skin ulcer			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Obstructive uropathy			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postrenal failure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
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			
Bone pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 238 (0.84%)	3 / 245 (1.22%)	
occurrences causally related to treatment / all	2 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	3 / 245 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device related infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site infection			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 238 (0.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urosepsis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 238 (0.42%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 238 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CT Arm	CT+BV Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	181 / 238 (76.05%)	218 / 245 (88.98%)	
Vascular disorders			
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	55 / 238 (23.11%)	90 / 245 (36.73%)	
occurrences (all)	91	181	
Haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 238 (2.94%)	29 / 245 (11.84%)	
occurrences (all)	7	51	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	10 / 238 (4.20%)	15 / 245 (6.12%)	
occurrences (all)	12	15	
Blood and lymphatic system disorders			
Neutropenia			
alternative assessment type: Systematic			
subjects affected / exposed	55 / 238 (23.11%)	64 / 245 (26.12%)	
occurrences (all)	112	158	
Leukopenia			
alternative assessment type: Systematic			
subjects affected / exposed	18 / 238 (7.56%)	30 / 245 (12.24%)	
occurrences (all)	30	71	
Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	13 / 238 (5.46%)	22 / 245 (8.98%)	
occurrences (all)	19	29	
Thrombocytopenia			
subjects affected / exposed	4 / 238 (1.68%)	16 / 245 (6.53%)	
occurrences (all)	8	30	
General disorders and administration site conditions			
Fatigue			
alternative assessment type: Systematic			

subjects affected / exposed	33 / 238 (13.87%)	49 / 245 (20.00%)	
occurrences (all)	39	67	
Mucosal inflammation			
alternative assessment type: Systematic			
subjects affected / exposed	9 / 238 (3.78%)	26 / 245 (10.61%)	
occurrences (all)	9	38	
Asthenia			
subjects affected / exposed	5 / 238 (2.10%)	14 / 245 (5.71%)	
occurrences (all)	5	16	
Pyrexia			
subjects affected / exposed	11 / 238 (4.62%)	14 / 245 (5.71%)	
occurrences (all)	17	18	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	27 / 238 (11.34%)	35 / 245 (14.29%)	
occurrences (all)	35	44	
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	31 / 238 (13.03%)	33 / 245 (13.47%)	
occurrences (all)	35	45	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	22 / 238 (9.24%)	16 / 245 (6.53%)	
occurrences (all)	28	20	
Abdominal pain			
subjects affected / exposed	3 / 238 (1.26%)	15 / 245 (6.12%)	
occurrences (all)	4	18	
Constipation			
subjects affected / exposed	9 / 238 (3.78%)	13 / 245 (5.31%)	
occurrences (all)	13	14	
Respiratory, thoracic and mediastinal disorders			
epistaxis			
subjects affected / exposed	3 / 238 (1.26%)	18 / 245 (7.35%)	
occurrences (all)	3	19	

Skin and subcutaneous tissue disorders Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	 58 / 238 (24.37%) 76	 72 / 245 (29.39%) 103	
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	 70 / 238 (29.41%) 103	 133 / 245 (54.29%) 247	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 2 / 238 (0.84%) 2	 16 / 245 (6.53%) 16	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 4 / 238 (1.68%) 4	 21 / 245 (8.57%) 23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 January 2011	• Exclusion criteria regarding participants not using effective contraception were updated to specify time limits (during the study and for 6 months after the last bevacizumab administration). • Time limit for reporting pregnancies after the completion of bevacizumab was updated from 90 days to 6 months. • AEs to be collected were updated from all AEs to all SAEs and/or Grade 3-5 AEs and all adverse event of special interest (AESI). • AESI were added; all grades of AESI were to be reported; any treatment for AESI was to be captured. • Clinically significant laboratory test results to be captured in the electronic CRF (eCRF) were specified as Grade 3-5 only. • Specification added that information on anti-cancer treatments given post third-line progression should be collected. • Clarification added that second-line progression, and not toxicity, would result in third-line treatment. • Clarification added that in the CT Arm after second-line disease progression participants had to receive third-line standard of care chemotherapy. • Clarification added that tumor assessment would only be performed post-study treatment in the absence of confirmation of disease progression. • Clarification added that plasma (not serum) assays would be used for genetic analysis and that 2 x 2.5 mL blood instead of 6 mL blood samples would be collected for RCR sampling. • Clarification added that chemotherapy at the investigator's discretion must be approved.
03 September 2013	•List of reasons for participants finishing treatment in second-line was updated to include 'maximum cumulative dose of anthracycline.' • Clarification added regarding the treatment options available to participants who discontinued chemotherapy due to toxicity during second- and third-line treatment. • End of study and length of study were defined and aligned and the different analysis time points were differentiated. • Post-trial provision of care with bevacizumab was clarified. • Clarification added that both second- and third-line chemotherapy options permitted for this study must be one of those listed in the protocol. • In response to queries from countries where the local SmPC was not aligned with the protocol-defined chemotherapy dose, chemotherapy dosing was allowed as per local label (on approval from the study sponsor team or its representative). • The vinorelbine dose was updated to include the 60 mg/m2/week induction dose to be consistent with the starting dose stated in the SmPC. • To avoid any misinterpretation by investigators, it was clarified that cross-over from the CT Arm to CT+BV Arm was not permitted after second-line therapy. • Further to a request of the steering committee, eribulin was included as a chemotherapy option for third-line treatment only. • Randomization was defined as the baseline for tumor assessments. • It is standard clinical practice to use endocrine therapy in combination with chemotherapy. Therefore in cases of bevacizumab toxicity where the patient continued with chemotherapy only (CT+BV Arm), the use of endocrine therapy in combination with chemotherapy was permitted. • In line with updated European Commission guidelines, the reporting period for SAEs was amended from 'within 1 working day' to 'within 24 hours'.Text updated to provide the correct information regarding SAE reporting after database lock. • Additional information was added to explain why bevacizumab should not be used during pregnancy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported