



Clinical trial results:

An open label, randomized controlled prospective multicenter two arm phase IV trial to determine Patient preference for everolimus in combination with exemestane or capecitabine in combination with bevacizumab for advanced (inoperable or metastatic) HER2 -negative hormone receptor positive breast cancer

Summary

EudraCT number	2013-005329-22
Trial protocol	DE
Global end of trial date	30 September 2017

Results information

Result version number	v1 (current)
This version publication date	14 October 2018
First version publication date	14 October 2018
Summary attachment (see zip file)	IMPROVE_CSR_Synopsis (IMPROVE_CSR_E3_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	iOM-12293
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02248571
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	iOMEDICO AG
Sponsor organisation address	Hanferstr. 28, Freiburg i.Br., Germany, 79108
Public contact	Contract Research Organisation, iOMEDICO AG, 0049 761152420, info@iomedico.com
Scientific contact	Contract Research Organisation, iOMEDICO AG, 0049 761152420, info@iomedico.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	25 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2017
Global end of trial reached?	Yes
Global end of trial date	30 September 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial is to compare patients' preferences of the two treatment combinations everolimus plus exemestane or capecitabine in combination with bevacizumab after failure of standard antihormonal therapy in patients with advanced (inoperable or metastatic) Her2/neu-negative hormone receptor positive breast cancer

Protection of trial subjects:

The study was conducted in accordance with all relevant laws and regulations relating to clinical studies and the protection of patients. Each participating site had to maintain appropriate records for this trial, in compliance with ICH E6 GCP, and regulatory requirements for the protection of confidentiality of patients. The investigator ensured pseudonymity of the patients; signed patient informed consent and patient enrollment log were kept strictly confidential to enable patient identification at the site.

Background therapy:

N/A

This is a crossover phase IV-trial to determine patients' preference for everolimus in combination with exemestane or capecitabine in combination with bevacizumab for advanced breast cancer patients. This design was chosen to assess the patient reported preference for either treatment.

Evidence for comparator:

N/A

Actual start date of recruitment	17 October 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 77
Worldwide total number of subjects	77
EEA total number of subjects	77

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)	37
From 65 to 84 years	39
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients will be randomized in a 1:1 fashion to receive capecitabine in combination with bevacizumab (Arm A) or everolimus in combination with exemestane (Arm B).

Pre-assignment

Screening details:

Eligibility of the patient has to be assessed within 28 days prior to randomization with the exception of Patient reported outcomes (PRO) questionnaires, which must be completed within 14 days before randomization. Randomization has strictly to be performed within 7 days prior to the first study treatment. In total, 86 patients were screened.

Pre-assignment period milestones

Number of subjects started	77
Number of subjects completed	77

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - Cap/Bev followed by Eve/Exe

Arm description:

Arm A - 1st-line: Capecitabine/Bevacizumab (Cap/Bev); 2nd-line: Everolimus/Exemestane (Eve/Exe)

Arm type	Experimental
Investigational medicinal product name	Capecitabine/ Bevacizumab followed by Everolimus/ Exemestane
Investigational medicinal product code	L01BC06/ L01XC07 followed by L01XE10/ L02BG06
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Capecitabine: 1000 mg/m² orally applied twice daily as combined 150 mg and 500 mg tablets on days 1 to 14 of each 21-day cycle, followed by a seven day rest period.

Bevacizumab: 15 mg/kg intravenously applied once every three weeks.

Everolimus: 10 mg/day orally applied tablet.

Exemestane: 25 mg/day orally applied tablet.

Arm title	Arm B - Eve/Exe followed by Cap/Bev
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Arm description:

Arm B - 1st line: Everolimus/Exemestane (Eve/Exe); 2nd line: Capecitabine/Bevacizumab (Cap/Bev)

Arm type	Experimental
Investigational medicinal product name	Everolimus/ Exemestane followed by Capecitabine/ Bevacizumab
Investigational medicinal product code	L01XE10/ L02BG06 followed by L01BC06/ L01XC07
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Everolimus: 10 mg/day orally applied tablet.

Exemestane: 25 mg/day orally applied tablet.

Capecitabine: 1000 mg/m² orally applied twice daily as combined 150 mg and 500 mg tablets on days 1 to 14 of each 21-day cycle, followed by a seven day rest period.

Bevacizumab: 15 mg/kg intravenously applied once every three weeks.

Number of subjects in period 1	Arm A - Cap/Bev followed by Eve/Exe	Arm B - Eve/Exe followed by Cap/Bev
Started	39	38
Completed	37	37
Not completed	2	1
Did not receive allocated intervention	2	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment period - overall period
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Reporting group description: -

Reporting group values	Treatment period - overall period	Total	
Number of subjects	77	77	
Age categorical			
Units: Subjects			
Adults (18-64 years)	37	37	
From 65-84 years	39	39	
85 years and over	1	1	
Age continuous			
Age			
Units: years			
median	65.5		
full range (min-max)	47.0 to 86.0	-	
Gender categorical			
Units: Subjects			
Female	77	77	
Male	0	0	
Menopausal Status			
Menopausal Status			
*postmenopausal			
*premenopausal			
Units: Subjects			
Postmenopausal	77	77	
Premenopausal	0	0	
ECOG Performance Status at baseline			
ECOG Performance Status at baseline			
Units: Subjects			
ECOG 0	36	36	
ECOG 1	39	39	
ECOG 2	2	2	
missing	0	0	
Location of primary tumor			
Localisation of primary tumor			
*left			
*right			
*unknown			
Units: Subjects			
left	40	40	
right	36	36	
unknown	1	1	
HER2 status			
HER2/neu status			
*positive			
*negative			
Units: Subjects			

positive	0	0	
negative	77	77	
Hormone receptor status			
Hormone receptor status *positive *negative			
Units: Subjects			
negative	0	0	
positive	77	77	
Histology at primary diagnosis			
Histology at primary diagnosis			
Units: Subjects			
invasive ductal	51	51	
invasive lobular	19	19	
inflammatory Ca	1	1	
not otherwise specified	6	6	
DFI - non-visceral metastases only/ visceral metastases or local relapse			
Intervall groups comprise: * non-visceral metastases only / visercal metastases or local relaps * anthracycline-/taxane pretreated / non-anthracycline-/taxane pretreated *0-1 prior antihormonal therapies / >1 antihormonal therapies. (Analysis for mITT not available)			
Units: Subjects			
non-visceral metastases only <=2	7	7	
non-visceral metastases only >2	17	17	
visceral metastases or local relapse <=2	17	17	
visceral metastases or local relapse >2	36	36	
DFI - anthracycline/taxane pretreated / not anthracycline/taxane pretreated			
Intervall groups comprise: * non-visceral metastases only / visercal metastases or local relaps * anthracycline-/taxane pretreated / non-anthracycline-/taxane pretreated *0-1 prior antihormonal therapies / >1 antihormonal therapies. (Analysis for mITT not available)			
Units: Subjects			
anthracycline/taxane pretreated <=2	9	9	
anthracycline/taxane pretreated >2	39	39	
not anthracycline/taxane pretreated <=2	15	15	
not anthracycline/taxane pretreated >2	14	14	
DFI - 0-1 prior antihormonal therapies / >1 prior antihormonal therapies			
Intervall groups comprise: * non-visceral metastases only / visercal metastases or local relaps * anthracycline-/taxane pretreated / non-anthracycline-/taxane pretreated *0-1 prior antihormonal therapies / >1 antihormonal therapies. (Analysis for mITT not available)			
Units: Subjects			
0-1 prior antihormonal therapies <=2	13	13	
0-1 prior antihormonal therapies >2	42	42	

>1 prior antihormonal therapies <=2	11	11	
>1 prior antihormonal therapies >2	11	11	
Prior endocrine therapies by stratification variables			
Number of prior palliative endocrine therapies in subgroups Stratification variable: *non-visceral metastases only / visceral metastases or local relapse Number of prior palliative antihormonal therapies: *0-1 *>1 (Analysis for mITT not available)			
Units: Subjects			
non-visceral metastases only 0-1	17	17	
non-visceral metastases only >1	7	7	
visceral metastases or local relapse 0-1	38	38	
visceral metastases or local relapse >1	15	15	
Prior endocrine therapies by stratification variables			
Number of prior palliative endocrine therapies in subgroups Stratification variable: *AT / non-AT pretreatment Number of prior palliative antihormonal therapies: *0-1 *>1 (Analysis for mITT not available)			
Units: Subjects			
anthracycline/taxane pretreated 0-1	41	41	
anthracycline/taxane pretreated >1	7	7	
not anthracycline/taxane pretreated 0-1	14	14	
not anthracycline/taxane pretreated >1	15	15	
Prior endocrine therapies by stratification variables			
Number of prior palliative endocrine therapies in subgroups Stratification variable: *DFI <= 2 years / >2 years Number of prior palliative antihormonal therapies: *0-1 *>1 (Analysis for mITT not available)			
Units: Subjects			
disease free interval <=2 years 0-1	13	13	
disease free interval <=2 years >1	11	11	
disease free interval >2 years 0-1	42	42	
disease free interval >2 years >1	11	11	
Weight			
Weight at baseline			
Units: kg			
median	69.0		
full range (min-max)	42.0 to 113.0	-	
Body Mass Index			

Units: kg/m ² median full range (min-max)	25.5 18.0 to 43.1	-	
DFI Disease-free interval			
Disease-free interval [years] (Data for reporting group 1 were not analysed; therefore data fields were completed with "0").			
Units: years median full range (min-max)	0 0 to 0	-	
Time from initial diagnosis to start of treatment			
Times were calculated using the date of randomization as end date. (Data for reporting group 1 were not analysed; therefore data fields were completed with "0").			
Units: years median full range (min-max)	0 0 to 0	-	
Time from relapse to start of treatment			
Times were calculated using the date of randomization as end date. (Data for reporting group 1 were not analysed; therefore data fields were completed with "0").			
Units: months median full range (min-max)	0 0 to 0	-	
Number of metastatic sites at inclusion			
(Data for reporting group 1 were not analysed; therefore data fields were completed with "0").			
Units: number median full range (min-max)	0 0 to 0	-	

Subject analysis sets

Subject analysis set title	Arm A - ITT (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analysed according to the study arm they have been assigned to during the randomization procedure.

The ITT population is the relevant population for the efficacy evaluation including demographic and other baseline characteristics as well as study treatment evaluations. It serves as additional analysis population for all patient reported outcomes.

Subject analysis set title	Arm B - ITT (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analysed according to the study arm they have been assigned to during the randomization procedure.

The ITT population is the relevant population for the efficacy evaluation including demographic and other baseline characteristics as well as study treatment evaluations. It serves as additional analysis population for all patient reported outcomes.

Subject analysis set title	Arm A - modified ITT (mITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified ITT (MITT) population comprises all patients who qualify for analysis of the primary endpoint, i.e. all patients who

- receive at least 12 weeks of first-line treatment or less for other reasons than PD
- cross over to second-line treatment within 12 weeks after termination of first-line treatment

- receive at least 12 weeks of second-line treatment or less for other reasons than PD
- answer preference question on patients' preference questionnaire

The modified ITT population is the relevant population for the analysis of the primary outcome and all patient reported outcomes. All secondary efficacy endpoints as well as the description of baseline characteristics will be repeated with the modified ITT population.

Subject analysis set title	Arm B - modified ITT (mITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified ITT (MITT) population comprises all patients who qualify for analysis of the primary endpoint, i.e. all patients who

- receive at least 12 weeks of first-line treatment or less for other reasons than PD
- cross over to second-line treatment within 12 weeks after termination of first-line treatment
- receive at least 12 weeks of second-line treatment or less for other reasons than PD
- answer preference question on patients' preference questionnaire

The modified ITT population is the relevant population for the analysis of the primary outcome and all patient reported outcomes. All secondary efficacy endpoints as well as the description of baseline characteristics will be repeated with the modified ITT population.

Reporting group values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)
Number of subjects	39	38	5
Age categorical			
Units: Subjects			
Adults (18-64 years)	20	17	3
From 65-84 years	19	20	2
85 years and over	0	1	0
Age continuous			
Age			
Units: years			
median	64.4	65.9	59.8
full range (min-max)	47.0 to 83.6	49.8 to 86.0	56.4 to 77.1
Gender categorical			
Units: Subjects			
Female	39	38	5
Male	0	0	0
Menopausal Status			
Menopausal Status			
*postmenopausal			
*premenopausal			
Units: Subjects			
Postmenopausal	39	38	5
Premenopausal	0	0	0
ECOG Performance Status at baseline			
ECOG Performance Status at baseline			
Units: Subjects			
ECOG 0	19	17	4
ECOG 1	19	20	1
ECOG 2	1	1	0
missing	0	0	0
Location of primary tumor			
Localisation of primary tumor			
*left			
*right			
*unknown			

Units: Subjects			
left	18	22	1
right	21	15	4
unknown	0	1	0
HER2 status			
HER2/neu status			
*positive			
*negative			
Units: Subjects			
positive	0	0	0
negative	39	38	5
Hormone receptor status			
Hormone receptor status			
*positive			
*negative			
Units: Subjects			
negative	0	0	0
positive	39	38	5
Histology at primary diagnosis			
Histology at primary diagnosis			
Units: Subjects			
invasive ductal	27	24	3
invasive lobular	7	12	1
inflammatory Ca	1	0	0
not otherwise specified	4	2	1
DFI - non-visceral metastases only/ visceral metastases or local relapse			
Intervall groups comprise: * non-visceral metastases only / visceral metastases or local relaps * anthracycline-/taxane pretreated / non-anthracycline-/taxane pretreated *0-1 prior antihormonal therapies / >1 antihormonal therapies.			
(Analysis for mITT not available)			
Units: Subjects			
non-visceral metastases only <=2	4	3	0
non-visceral metastases only >2	8	9	0
visceral metastases or local relapse <=2	8	9	0
visceral metastases or local relapse >2	19	17	0
DFI - anthracycline/taxane pretreated / not anthracycline/taxane pretreated			
Intervall groups comprise: * non-visceral metastases only / visceral metastases or local relaps * anthracycline-/taxane pretreated / non-anthracycline-/taxane pretreated *0-1 prior antihormonal therapies / >1 antihormonal therapies.			
(Analysis for mITT not available)			
Units: Subjects			
anthracycline/taxane pretreated <=2	5	4	0
anthracycline/taxane pretreated >2	17	22	0
not anthracycline/taxane pretreated <=2	7	8	0
not anthracycline/taxane pretreated >2	10	4	0
DFI - 0-1 prior antihormonal therapies /			

>1 prior antihormonal therapies			
Intervall groups comprise: * non-visceral metastases only / visceral metastases or local relaps * anthracycline-/taxane pretreated / non-anthracycline-/taxane pretreated *0-1 prior antihormonal therapies / >1 antihormonal therapies. (Analysis for mITT not available)			
Units: Subjects			
0-1 prior antihormonal therapies <=2	6	7	0
0-1 prior antihormonal therapies >2	21	21	0
>1 prior antihormonal therapies <=2	6	5	0
>1 prior antihormonal therapies >2	6	5	0
Prior endocrine therapies by stratification variables			
Number of prior palliative endocrine therapies in subgroups Stratification variable: *non-visceral metastases only / visceral metastases or local relapse Number of prior palliative antihormonal therapies: *0-1 *>1 (Analysis for mITT not available)			
Units: Subjects			
non-visceral metastases only 0-1	7	10	0
non-visceral metastases only >1	5	2	0
visceral metastases or local relapse 0-1	20	18	0
visceral metastases or local relapse >1	7	8	0
Prior endocrine therapies by stratification variables			
Number of prior palliative endocrine therapies in subgroups Stratification variable: *AT / non-AT pretreatment Number of prior palliative antihormonal therapies: *0-1 *>1 (Analysis for mITT not available)			
Units: Subjects			
anthracycline/taxane pretreated 0-1	19	22	0
anthracycline/taxane pretreated >1	3	4	0
not anthracycline/taxane pretreated 0-1	8	6	0
not anthracycline/taxane pretreated >1	9	6	0
Prior endocrine therapies by stratification variables			
Number of prior palliative endocrine therapies in subgroups Stratification variable: *DFI <= 2 years / >2 years Number of prior palliative antihormonal therapies: *0-1 *>1 (Analysis for mITT not available)			
Units: Subjects			

disease free interval <=2 years 0-1	6	7	0
disease free interval <=2 years >1	6	5	0
disease free interval >2 years 0-1	21	21	0
disease free interval >2 years >1	6	5	0
Weight			
Weight at baseline			
Units: kg			
median	69.0	68.5	80.0
full range (min-max)	45.0 to 113.0	42.0 to 103.0	62.0 to 113.0
Body Mass Index			
Units: kg/m ²			
median	25.6	24.9	27.0
full range (min-max)	18.0 to 43.1	19.2 to 36.9	22.3 to 43.1
DFI Disease-free interval			
Disease-free interval [years] (Data for reporting group 1 were not analysed; therefore data fields were completed with "0").			
Units: years			
median	4.7	5.0	5.2
full range (min-max)	0.0 to 18.9	0.0 to 12.3	0.0 to 8.6
Time from initial diagnosis to start of treatment			
Times were calculated using the date of randomization as end date. (Data for reporting group 1 were not analysed; therefore data fields were completed with "0").			
Units: years			
median	9.6	6.6	5.4
full range (min-max)	0.9 to 22.7	0.8 to 19.1	2.1 to 9.6
Time from relapse to start of treatment			
Times were calculated using the date of randomization as end date. (Data for reporting group 1 were not analysed; therefore data fields were completed with "0").			
Units: months			
median	8.4	5.1	0.6
full range (min-max)	0.1 to 206.4	0.6 to 158.9	0.4 to 10.6
Number of metastatic sites at inclusion			
(Data for reporting group 1 were not analysed; therefore data fields were completed with "0").			
Units: number			
median	2.0	2.0	1.0
full range (min-max)	1.0 to 4.0	1.0 to 5.0	1.0 to 2.0
Reporting group values	Arm B - modified ITT (mITT)		
Number of subjects	8		
Age categorical			
Units: Subjects			
Adults (18-64 years)	3		
From 65-84 years	5		
85 years and over	0		
Age continuous			
Age			
Units: years			
median	65.9		
full range (min-max)	51.1 to 77.6		

Gender categorical			
Units: Subjects			
Female	8		
Male	0		
Menopausal Status			
Menopausal Status *postmenopausal *premenopausal			
Units: Subjects			
Postmenopausal	8		
Premenopausal	0		
ECOG Performance Status at baseline			
ECOG Performance Status at baseline			
Units: Subjects			
ECOG 0	3		
ECOG 1	5		
ECOG 2	0		
missing	0		
Location of primary tumor			
Localisation of primary tumor *left *right *unknown			
Units: Subjects			
left	4		
right	4		
unknown	0		
HER2 status			
HER2/neu status *positive *negative			
Units: Subjects			
positive	0		
negative	8		
Hormone receptor status			
Hormone receptor status *positive *negative			
Units: Subjects			
negative	0		
positive	8		
Histology at primary diagnosis			
Histology at primary diagnosis			
Units: Subjects			
invasive ductal	6		
invasive lobular	2		
inflammatory Ca	0		
not otherwise specified	0		
DFI - non-visceral metastases only/ visceral metastases or local relapse			
Intervall groups comprise: * non-visceral metastases only / visceral metastases or local relaps * anthracycline-/taxane pretreated / non-anthracycline-/taxane pretreated *0-1 prior antihormonal therapies / >1 antihormonal therapies.			

(Analysis for mITT not available)			
Units: Subjects			
non-visceral metastases only <=2	0		
non-visceral metastases only >2	0		
visceral metastases or local relapse <=2	0		
visceral metastases or local relapse >2	0		
DFI - anthracycline/taxane pretreated / not anthracycline/taxane pretreated			
Intervall groups comprise: * non-visceral metastases only / visceral metastases or local relaps * anthracycline-/taxane pretreated / non-anthracycline-/taxane pretreated *0-1 prior antihormonal therapies / >1 antihormonal therapies.			
(Analysis for mITT not available)			
Units: Subjects			
anthracycline/taxane pretreated <=2	0		
anthracycline/taxane pretreated >2	0		
not anthracycline/taxane pretreated <=2	0		
not anthracycline/taxane pretreated >2	0		
DFI - 0-1 prior antihormonal therapies / >1 prior antihormonal therapies			
Intervall groups comprise: * non-visceral metastases only / visceral metastases or local relaps * anthracycline-/taxane pretreated / non-anthracycline-/taxane pretreated *0-1 prior antihormonal therapies / >1 antihormonal therapies.			
(Analysis for mITT not available)			
Units: Subjects			
0-1 prior antihormonal therapies <=2	0		
0-1 prior antihormonal therapies >2	0		
>1 prior antihormonal therapies <=2	0		
>1 prior antihormonal therapies >2	0		
Prior endocrine therapies by stratification variables			
Number of prior palliative endocrine therapies in subgroups Stratification variable: *non-visceral metastases only / visceral metastases or local relapse Number of prior palliative antihormonal therapies: *0-1 *>1			
(Analysis for mITT not available)			
Units: Subjects			
non-visceral metastases only 0-1	0		
non-visceral metastases only >1	0		
visceral metastases or local relapse 0-1	0		
visceral metastases or local relapse >1	0		
Prior endocrine therapies by stratification variables			
Number of prior palliative endocrine therapies in subgroups Stratification variable:			

*AT / non-AT pretreatment			
Number of prior palliative antihormonal therapies:			
*0-1			
*>1			
(Analysis for mITT not available)			
Units: Subjects			
anthracycline/taxane pretreated 0-1	0		
anthracycline/taxane pretreated >1	0		
not anthracycline/taxane pretreated 0-1	0		
not anthracycline/taxane pretreated >1	0		
Prior endocrine therapies by stratification variables			
Number of prior palliative endocrine therapies in subgroups			
Stratification variable:			
*DFI ≤ 2 years / >2 years			
Number of prior palliative antihormonal therapies:			
*0-1			
*>1			
(Analysis for mITT not available)			
Units: Subjects			
disease free interval ≤2 years 0-1	0		
disease free interval ≤2 years >1	0		
disease free interval >2 years 0-1	0		
disease free interval >2 years >1	0		
Weight			
Weight at baseline			
Units: kg			
median	67.5		
full range (min-max)	60.0 to 90.0		
Body Mass Index			
Units: kg/m ²			
median	24.1		
full range (min-max)	21.5 to 31.1		
DFI Disease-free interval			
Disease-free interval [years]			
(Data for reporting group 1 were not analysed; therefore data fields were completed with "0").			
Units: years			
median	5.0		
full range (min-max)	0.0 to 10.2		
Time from initial diagnosis to start of treatment			
Times were calculated using the date of randomization as end date.			
(Data for reporting group 1 were not analysed; therefore data fields were completed with "0").			
Units: years			
median	6.5		
full range (min-max)	2.0 to 19.1		
Time from relapse to start of treatment			
Times were calculated using the date of randomization as end date.			
(Data for reporting group 1 were not analysed; therefore data fields were completed with "0").			
Units: months			
median	2.0		
full range (min-max)	0.7 to 100.7		

Number of metastatic sites at inclusion			
(Data for reporting group 1 were not analysed; therefore data fields were completed with "0").			
Units: number			
median	2.0		
full range (min-max)	1.0 to 3.0		

End points

End points reporting groups

Reporting group title	Arm A - Cap/Bev followed by Eve/Exe
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Reporting group description:

Arm A - 1st-line: Capecitabine/Bevacizumab (Cap/Bev); 2nd-line: Everolimus/Exemestane (Eve/Exe)

Reporting group title	Arm B - Eve/Exe followed by Cap/Bev
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Reporting group description:

Arm B - 1st line: Everolimus/Exemestane (Eve/Exe); 2nd line: Capecitabine/Bevacizumab (Cap/Bev)

Subject analysis set title	Arm A - ITT (ITT)
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The ITT population comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analysed according to the study arm they have been assigned to during the randomization procedure.

The ITT population is the relevant population for the efficacy evaluation including demographic and other baseline characteristics as well as study treatment evaluations. It serves as additional analysis population for all patient reported outcomes.

Subject analysis set title	Arm B - ITT (ITT)
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The ITT population comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analysed according to the study arm they have been assigned to during the randomization procedure.

The ITT population is the relevant population for the efficacy evaluation including demographic and other baseline characteristics as well as study treatment evaluations. It serves as additional analysis population for all patient reported outcomes.

Subject analysis set title	Arm A - modified ITT (mITT)
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The modified ITT (MITT) population comprises all patients who qualify for analysis of the primary endpoint, i.e. all patients who

- receive at least 12 weeks of first-line treatment or less for other reasons than PD
- cross over to second-line treatment within 12 weeks after termination of first-line treatment
- receive at least 12 weeks of second-line treatment or less for other reasons than PD
- answer preference question on patients' preference questionnaire

The modified ITT population is the relevant population for the analysis of the primary outcome and all patient reported outcomes. All secondary efficacy endpoints as well as the description of baseline characteristics will be repeated with the modified ITT population.

Subject analysis set title	Arm B - modified ITT (mITT)
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The modified ITT (MITT) population comprises all patients who qualify for analysis of the primary endpoint, i.e. all patients who

- receive at least 12 weeks of first-line treatment or less for other reasons than PD
- cross over to second-line treatment within 12 weeks after termination of first-line treatment
- receive at least 12 weeks of second-line treatment or less for other reasons than PD
- answer preference question on patients' preference questionnaire

The modified ITT population is the relevant population for the analysis of the primary outcome and all patient reported outcomes. All secondary efficacy endpoints as well as the description of baseline characteristics will be repeated with the modified ITT population.

Primary: Rates of Patient Preference

End point title	Rates of Patient Preference
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End point description:

The primary objective of the study is to compare patients' preferences of the two treatment combinations everolimus plus exemestane or capecitabine in combination with bevacizumab after failure of standard antihormonal therapy in patients with advanced (inoperable or metastatic) Her2/neu-negative hormone receptor positive breast cancer.

The preference will be ascertained using the patient preference questionnaire, assessed after 12 weeks of second line therapy.

End point type	Primary
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End point timeframe:

Assessed at week 12 of second-line therapy, or - in case of early (<12 weeks) treatment discontinuation of second-line - assessed two weeks after discontinuation for any other reason than PD.

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	38	5	8
Units: number / %				
number (confidence interval 95%)				
Cap-Bev	7.7 (1.6 to 20.9)	26.3 (13.4 to 43.1)	40.0 (5.3 to 85.3)	75.0 (34.9 to 96.8)
Eve-Exe	12.8 (4.3 to 27.4)	5.3 (0.6 to 17.7)	20.0 (0.5 to 71.6)	12.5 (0.3 to 52.7)
Cannot decide	7.7 (1.6 to 20.9)	10.5 (2.9 to 24.8)	40.0 (5.3 to 85.3)	12.5 (0.3 to 52.7)
not evaluable	5.1 (0.6 to 17.3)	5.3 (0.6 to 17.7)	0 (0 to 0)	0 (0 to 0)
missing	10.3 (2.9 to 24.2)	2.6 (0.1 to 13.8)	0 (0 to 0)	0 (0 to 0)
no second-line	56.4 (39.6 to 72.2)	50.0 (33.4 to 66.6)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	Asymptotic chi-square test
Comparison groups	Arm A - modified ITT (mITT) v Arm B - modified ITT (mITT)
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	≤ 0.05 ^[2]
Method	Chi-squared

Notes:

[1] - p-value of Chi-square test according to Prescott's approach

[2] - p-value of Chi-square test according to Prescott's approach

Secondary: PFS first-line

End point title	PFS first-line
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End point description:

Progression free survival is defined as the time between start of therapy and first documented tumor progression or death of any cause, whatever comes first.

End point type	Secondary
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End point timeframe:

The time from start of first-line therapy to progression or death of any cause before start of a new therapy. The PFS rate in first-line will be assessed after 12 weeks of therapy.

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	38	5	8
Units: months				
median (confidence interval 95%)	11.1 (7.8 to 18.0)	3.5 (2.7 to 5.5)	13.1 (8.3 to 18.0)	3.1 (1.6 to 7.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference ... less tired and exhausted

End point title	Reason for preference ... less tired and exhausted
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to all patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to all patients with preference for Eve/Exe [n= 7].*****

End point type	Secondary
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End point timeframe:

After 12 weeks of second line therapy

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[3]	7 ^[4]		
Units: Patients				
Yes	7	5		
No	3	1		
I didn't have this symptom	3	1		
missing	0	0		

Notes:

[3] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[4] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference ...less pain

End point title	Reason for preference ...less pain
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for Eve/Exe [n= 7].*****

End point type	Secondary
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End point timeframe:

After 12 weeks of second line therapy

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[5]	7 ^[6]		
Units: Patients				
Yes	5	3		
No	3	3		
I didn't have this symptom	4	1		
missing	1	0		

Notes:

[5] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[6] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference ...less irritation of taste

End point title	Reason for preference ...less irritation of taste
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for

End point type	Secondary
End point timeframe:	
After 12 weeks of second line therapy	

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[7]	7 ^[8]		
Units: Patients				
Yes	3	3		
No	6	3		
I didn't have this symptom	4	1		
missing	0	0		

Notes:

[7] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[8] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference ...less taking of blood samples

End point title	Reason for preference ...less taking of blood samples
End point description:	
The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively. *****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for Eve/Exe [n= 7].*****	
End point type	Secondary
End point timeframe:	
After 12 weeks of second line therapy	

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[9]	7 ^[10]		
Units: Patients				
Yes	3	2		
No	10	3		
I didn't have this symptom	0	1		
missing	0	1		

Notes:

[9] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[10] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference ...less infections

End point title	Reason for preference ...less infections
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for Eve/Exe [n= 7].*****

End point type	Secondary
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End point timeframe:

After 12 weeks of second line therapy

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[11]	7 ^[12]		
Units: Patients				
Yes	4	2		
No	0	2		
I didn't have this symptom	8	2		
missing	1	1		

Notes:

[11] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[12] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference ...less skin problems

End point title	Reason for preference ...less skin problems
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for

End point type	Secondary
End point timeframe:	
After 12 weeks of second line therapy	

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[13]	7 ^[14]		
Units: Patients				
Yes	7	1		
No	3	4		
I didn't have this symptom	3	2		
missing	0	0		

Notes:

[13] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[14] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference ...less sleeping disorders

End point title	Reason for preference ...less sleeping disorders
End point description:	
The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively. *****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for Eve/Exe [n= 7].*****	
End point type	Secondary
End point timeframe:	
After 12 weeks of second line therapy	

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[15]	7 ^[16]		
Units: Patients				
Yes	4	3		
No	4	3		
I didn't have this symptom	4	1		
missing	1	0		

Notes:

[15] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[16] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference ...less loss of appetite

End point title	Reason for preference ...less loss of appetite
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for Eve/Exe [n= 7].*****

End point type	Secondary
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End point timeframe:

After 12 weeks of second line therapy

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[17]	7 ^[18]		
Units: Patients				
Yes	5	4		
No	4	1		
I didn't have this symptom	2	2		
missing	2	0		

Notes:

[17] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[18] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference ...other reasons

End point title	Reason for preference ...other reasons
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for

End point type	Secondary
End point timeframe:	
After 12 weeks of second line therapy	

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[19]	7 ^[20]		
Units: Patients				
No other reasons specified	10	6		
heavy fatigue "starke Müdigkeit"	1	0		
less toxicity "weniger Nebenwirkungen"	1	0		
Infusion more effective "Infusion wirkungsvoller"	1	0		
less alopecia, skin and nail problems	0	1		

Notes:

[19] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[20] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference ...did not spend so much time in practice

End point title	Reason for preference ...did not spend so much time in practice
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for Eve/Exe [n= 7].*****

End point type	Secondary
End point timeframe:	
After 12 weeks of second line therapy	

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[21]	7 ^[22]		
Units: Patients				
Yes	3	5		
No	8	2		
missing	2	0		

Notes:

[21] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[22] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference ...quality of life generally better

End point title	Reason for preference ...quality of life generally better
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for Eve/Exe [n= 7].*****

End point type	Secondary
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End point timeframe:

After 12 weeks of second line therapy

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[23]	7 ^[24]		
Units: Patients				
Yes	11	3		
No	2	4		
missing	0	0		

Notes:

[23] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[24] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference ...main reasons

End point title	Reason for preference ...main reasons
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for Eve/Exe [n= 7].*****

End point type	Secondary
End point timeframe:	
After 12 weeks of second line therapy	

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[25]	7 ^[26]		
Units: Patients				
less numbness on hands and feet	0	1		
less tired and exhausted	1	0		
Quality of life generally better	9	3		
other reasons	2	1		
less sleeping disorders	1	0		
less diarrhea	0	1		
less time in the oncological practice	0	1		

Notes:

[25] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[26] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS second-line

End point title	PFS second-line
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End point description:

Progression free survival is defined as the time between start of therapy and first documented tumor progression or death of any cause, whatever comes first.

(Please note: 95% CI upper values marked as N/A in the statistical analysis were set to "100" in the data entry fields due to data base entry requirements).

End point type	Secondary
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End point timeframe:

The time from start of second-line therapy to progression or death of any cause before start of a new therapy. The PFS rate in second-line will be assessed after 12 weeks of therapy in the second-line treatment.

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	19	5	8
Units: months				
median (inter-quartile range (Q1-Q3))	3.7 (2.4 to 7.8)	3.6 (2.3 to 5.5)	7.8 (3.7 to 100)	4.6 (2.3 to 13.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

(Please note: 95% CI upper values marked as N/A in the statistical analysis were set to "100" in the data entry fields due to data base entry requirements).

End point type	Secondary
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End point timeframe:

Time from randomization to death of any cause

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	38	5	8
Units: months				
median (confidence interval 95%)	28.8 (19.7 to 100)	24.7 (13.9 to 28.8)	100 (28.8 to 100)	28.8 (16.6 to 100)

Statistical analyses

No statistical analyses for this end point

Secondary: Best Response first-line

End point title	Best Response first-line
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End point description:

Best Response for patients with measurable disease and non-measurable disease

End point type	Secondary
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End point timeframe:

Time from start of study treatment until the end of treatment

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	38	5	8
Units: Percentage of patients				
number (confidence interval 95%)				
CR	7.7 (1.6 to 20.9)	2.6 (0.1 to 13.8)	0 (0 to 0)	0 (0 to 0)
PR	15.4 (5.9 to 30.5)	7.9 (1.7 to 21.4)	0 (0 to 0)	12.5 (0.3 to 52.7)
PD	20.5 (9.3 to 36.5)	42.1 (26.3 to 59.2)	0 (0 to 0)	50.0 (15.7 to 84.3)
SD	48.7 (32.4 to 65.2)	39.5 (24.0 to 56.6)	100.0 (47.8 to 100.0)	37.5 (8.5 to 75.5)
missing	7.7 (1.6 to 20.9)	7.9 (1.7 to 21.4)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate - First-line (ORR-1)

End point title	Objective Response Rate - First-line (ORR-1)
End point description:	Overall response rate (ORR=CR+PR) for patients with measurable disease.
End point type	Secondary
End point timeframe:	Time from start of 1st line study treatment until the end of 1st line treatment

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	38	5	8
Units: Percentage of patients				
number (confidence interval 95%)				
Yes	23.1 (11.1 to 39.3)	10.5 (2.9 to 24.8)	0 (0 to 0)	12.5 (0.3 to 52.7)
missing	7.7 (1.6 to 20.9)	7.9 (1.7 to 21.4)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) - First-line

End point title	Disease Control Rate (DCR) - First-line
End point description:	
Disease control rate (DCR=CR+PR+SD) for all patients	
End point type	Secondary
End point timeframe:	
Time from start of study treatment until the end of treatment	

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	38	5	8
Units: Percentage of patients				
number (confidence interval 95%)				
Yes	71.8 (55.1 to 85.0)	50.0 (33.4 to 66.6)	100.0 (47.8 to 100.0)	50.0 (15.7 to 84.3)
missing	7.7 (1.6 to 20.9)	7.9 (1.7 to 21.4)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) - Second-line

End point title	Disease Control Rate (DCR) - Second-line
End point description:	
Disease control rate (DCR=CR+PR+SD) for all patients	
End point type	Secondary
End point timeframe:	
Time from start of study treatment until the end of treatment	

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	38	5	8
Units: Percentage of patients				
number (confidence interval 95%)				
Yes	17.9 (7.5 to 33.5)	26.3 (13.4 to 43.1)	100.0 (47.8 to 100.0)	62.5 (24.5 to 91.5)
missing	66.7 (49.8 to 80.9)	57.9 (40.8 to 73.7)	0 (0 to 0)	12.5 (0.3 to 52.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Best Response second-line

End point title Best Response second-line

End point description:

Best Response for patients with measurable disease and non-measurable disease

End point type Secondary

End point timeframe:

Time from start of study treatment until the end of treatment

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	38	5	8
Units: Percentage of patients				
number (confidence interval 95%)				
CR	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
PR	0 (0 to 0)	7.9 (1.7 to 21.4)	0 (0 to 0)	12.5 (0.3 to 52.7)
PD	15.4 (5.9 to 30.5)	15.8 (6.0 to 31.3)	0 (0 to 0)	25.0 (3.2 to 65.1)
SD	17.9 (7.5 to 33.5)	18.4 (7.7 to 34.3)	100.0 (47.8 to 100.0)	50.0 (15.7 to 84.3)
missing	66.7 (49.8 to 80.9)	57.9 (40.8 to 73.7)	0 (0 to 0)	12.5 (0.3 to 52.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate - Second-line (ORR-2)

End point title Overall Response Rate - Second-line (ORR-2)

End point description:

Overall response rate (ORR=CR+PR) for patients with measurable disease

End point type Secondary

End point timeframe:

Time from start of study treatment until the end of treatment

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	38	5	8
Units: Percentage of patients				
number (confidence interval 95%)				
Yes	0 (0 to 0)	7.9 (1.7 to 21.4)	0 (0 to 0)	12.5 (0.3 to 52.7)
missing	66.7 (49.8 to 80.9)	57.9 (40.8 to 73.7)	0 (0 to 0)	12.5 (0.3 to 52.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Treatment Satisfaction First-line

End point title	Overall Treatment Satisfaction First-line
End point description:	
A satisfaction with therapy questionnaire will be administered 12 weeks after Day 1 of first cycle of Treatment Phase 1 and 12 weeks after Day 1 of first cycle of Treatment Phase 2 (or 2 weeks after early stopping in each phase).	
Missing: Item not answered or not evaluable. Discrepancies between the sum of answers and the total n reported are due to patients who did not answer the whole questionnaire. Answers 'correct' and 'rather correct' were classified as 'satisfied', answers 'rather not correct' and 'not correct at all' were classified as 'not satisfied'.	
End point type	Secondary
End point timeframe:	
12 weeks after start of Treatment Phase 1	

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	38	5	8
Units: number				
satisfied	30	24	4	5
not satisfied	5	7	1	3
missing	0	2	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Treatment Satisfaction Second-line

End point title	Overall Treatment Satisfaction Second-line
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End point description:

A satisfaction with therapy questionnaire will be administered 12 weeks after Day 1 of first cycle of Treatment Phase 1 and 12 weeks after Day 1 of first cycle of Treatment Phase 2 (or 2 weeks after early stopping in each phase).

Missing: Item not answered or not evaluable. Discrepancies between the sum of answers and the total n reported are due to patients who did not answer the whole questionnaire. Answers 'correct' and 'rather correct' were classified as 'satisfied', answers 'rather not correct' and 'not correct at all' were classified as 'not satisfied'.

End point type	Secondary
End point timeframe:	
12 weeks after start of Treatment Phase 2	

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	19	5	8
Units: number				
satisfied	10	11	3	8
not satisfied	3	5	2	0
missing	1	2	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Physician Preference

End point title	Rate of Physician Preference
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End point description:

Physicians' preference for therapy combination EE or CB or no preference will be assessed using the same questions as used in the patients' preference questionnaire. Physicians additionally have the opportunity to say "I treat the patient for a short time and have no preference" in case they didn't attend the whole study with the patient.

End point type	Secondary
End point timeframe:	
Time from start of study treatment until the end of treatment. Assessed at week 12 of second-line therapy, or - in case of early (<12 weeks) treatment discontinuation of second-line - assessed two weeks after discontinuation for any other reason than PD.	

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	38	5	8
Units: number (%)				
number (confidence interval 95%)				
Cap-Bev	25.6 (13.0 to 42.1)	26.3 (13.4 to 43.1)	60.0 (14.7 to 94.7)	37.5 (8.5 to 75.5)
Eve-Exe	12.8 (4.3 to 27.4)	13.2 (4.4 to 28.1)	40.0 (5.3 to 85.3)	25.0 (3.2 to 65.1)
I cannot decide	5.1 (0.6 to 17.3)	10.5 (2.9 to 24.8)	0 (0 to 0)	37.5 (8.5 to 75.5)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS-rate 1 (week 12)

End point title PFS-rate 1 (week 12)

End point description:

(Please note: 95% CI upper values marked as N/A in the statistical analysis were set to "100" in the data entry fields due to data base entry requirements).

End point type Secondary

End point timeframe:

Progression free survival rate after 12 weeks of 1st line therapy

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	38	5	8
Units: Percentage of patients				
number (confidence interval 95%)	11.1 (7.8 to 18.0)	3.5 (2.7 to 5.5)	13.1 (8.3 to 18.0)	3.1 (1.6 to 7.6)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS-rate 2 (week 12)

End point title PFS-rate 2 (week 12)

End point description:

(Please note: 95% CI upper values marked as N/A in the statistical analysis were set to "100" in the data entry fields due to data base entry requirements).

End point type Secondary

End point timeframe:

Progression free survival rate after 12 weeks of 2nd line therapy

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)	Arm A - modified ITT (mITT)	Arm B - modified ITT (mITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	19	5	8
Units: Percentage of patients				
number (confidence interval 95%)	3.7 (2.4 to 7.8)	3.6 (2.3 to 5.5)	7.8 (3.7 to 100)	4.6 (2.3 to 13.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference...less burning sensation on hands or feet

End point title	Reason for preference...less burning sensation on hands or feet
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for Eve/Exe [n= 7].*****

End point type	Secondary
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End point timeframe:

After 12 weeks of second line therapy

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[27]	7 ^[28]		
Units: Patients				
yes	2	2		
no	5	3		
I didn't have this symptom	6	2		
missing	0	0		

Notes:

[27] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[28] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

Secondary: Reason for preference...less numbness on hands or feet

End point title	Reason for preference...less numbness on hands or feet
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for Eve/Exe [n= 7].*****

End point type	Secondary
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End point timeframe:

After 12 weeks of second line therapy

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[29]	7 ^[30]		
Units: Patients				
yes	2	1		
no	4	4		
I didn't have this symptom	7	2		
missing	0	0		

Notes:

[29] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[30] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference.....less inflamed mucosa, e.g. orally

End point title	Reason for preference.....less inflamed mucosa, e.g. orally
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for Eve/Exe [n= 7].*****

End point type	Secondary
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End point timeframe:

After 12 weeks of second line therapy

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[31]	7 ^[32]		
Units: Patients				
yes	4	0		
no	3	6		
I didn't have this symptom	6	1		
missing	0	0		

Notes:

[31] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[32] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference...less diarrhea

End point title	Reason for preference...less diarrhea
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for Eve/Exe [n= 7].*****

End point type	Secondary
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End point timeframe:

After 12 weeks of second line therapy

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[33]	7 ^[34]		
Units: Patients				
yes	4	2		
no	3	1		
I didn't have this symptom	5	4		
not evaluable	1	0		

Notes:

[33] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[34] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Reason for preference...less nausea and/or vomiting

End point title	Reason for preference...less nausea and/or vomiting
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End point description:

The patient preference questionnaire asks not only for the preference itself but also for the reasons, if a clear preference was stated. Additionally, patients are asked to name one of the reasons the main reason for the preference. The reasons for patient's preference (Cap/Bev or Eve/Exe) are shown for all patients with relevant information available (ITT population). In total, 13 patients and 7 patients reported Cap/Bev and Eve/Exe as their preferred treatment regimen, respectively.

*****PLEASE NOTE: For this endpoint, subject analysis set named "Arm A - ITT (ITT)" refers to patients with preference for Cap/Bev [n=13], and "Arm B - ITT (ITT)" refers to patients with preference for Eve/Exe [n= 7].*****

End point type	Secondary
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End point timeframe:

After 12 weeks of second line therapy

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13 ^[35]	7 ^[36]		
Units: Patients				
yes	2	2		
no	5	0		
I didn't have this problem	6	4		
not evaluable	0	1		

Notes:

[35] - (All patients with preference for Cap/Bev treatment (ITT); n=13)

[36] - (All patients with preference for Eve/Exe treatment (ITT); n=7)

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQC30 global health score - Treatment phase 1 (Baseline and week 12)

End point title	EORTC QLQC30 global health score - Treatment phase 1 (Baseline and week 12)
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End point description:

The EORTC QLQ-C30 questionnaire provides five functional scales, three symptom scales two global items and several single items. Each item is answered with "not at all", "a little", "quite a bit" and "very much", rated as 1 (not at all), 2, 3 or 4 (very much).

End point type	Secondary
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End point timeframe:

Baseline (before start of Treatment Phase 1) and at week 12 of Treatment Phase 1

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38 ^[37]	38 ^[38]		
Units: score value (0-100)				
median (full range (min-max))				
Baseline	50 (16.7 to 83.3)	50 (16.7 to 100)		
Week 12	50 (0.0 to 91.7)	50 (0.0 to 91.7)		

Notes:

[37] - N = 38 refers to the number of questionnaires available at baseline (week 12: n = 36)

[38] - N = 38 refers to the number of questionnaires available at baseline (week 12: n = 32)

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC QLQC30 global health score - Treatment phase 2 (Baseline and week 12)

End point title	EORTC QLQC30 global health score - Treatment phase 2 (Baseline and week 12)
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End point description:

The EORTC QLQ-C30 questionnaire provides five functional scales, three symptom scales two global items and several single items. Each item is answered with "not at all", "a little", "quite a bit" and "very much", rated as 1 (not at all), 2, 3 or 4 (very much).

End point type	Secondary
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End point timeframe:

Baseline (before start of Treatment Phase 2) and at week 12 of Treatment Phase 2

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[39]	19 ^[40]		
Units: score value (0-100)				
median (full range (min-max))				
Baseline	41.7 (0.0 to 83.3)	50.0 (25.0 to 66.7)		
Week 12	50.0 (0.0 to 66.7)	50.0 (16.7 to 66.7)		

Notes:

[39] - N = 17 refers to the number of questionnaires available at baseline (week 12: n = 13)

[40] - N = 19 refers to the number of questionnaires available at baseline (week 12: n = 18)

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC-QLQ-FA13 Treatment Phase 1 (Baseline and week 12)

End point title	EORTC-QLQ-FA13 Treatment Phase 1 (Baseline and week 12)
End point description: The EORTC QLQ-FA13 provides three subscales. Each item is answered with “not at all”, “a little”, “quite a bit” and “very much”, rated as 1 (not at all), 2, 3 or 4 (very much).	
End point type	Secondary
End point timeframe: Baseline (before start of Treatment Phase 1) and at week 12 of Treatment Phase 1	

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38 ^[41]	38 ^[42]		
Units: units on a scale				
median (full range (min-max))				
Cognitive Fatigue - Baseline	22.2 (0.0 to 77.8)	11.1 (0.0 to 100)		
Cognitive Fatigue - Week 12	11.1 (0.0 to 66.7)	11.1 (0.0 to 100)		
Emotional Fatigue - Baseline	45.5 (0.0 to 100)	33.3 (0.0 to 100)		
Emotional Fatigue - Week 12	33.3 (0.0 to 100)	41.7 (0.0 to 100)		
Physical Fatigue - Baseline	58.3 (0.0 to 100)	45.8 (0.0 to 100)		
Physical Fatigue - Week 12	54.2 (16.7 to 100)	58.3 (0.0 to 100)		

Notes:

[41] - N = 38 refers to the number of questionnaires available at baseline (week 12: n = 36)

[42] - N = 38 refers to the number of questionnaires available at baseline (week 12: n = 33)

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC-QLQ-FA13 Treatment Phase 2 (Baseline and week 12)

End point title	EORTC-QLQ-FA13 Treatment Phase 2 (Baseline and week 12)
End point description: The EORTC QLQ-FA13 provides three subscales. Each item is answered with “not at all”, “a little”, “quite a bit” and “very much”, rated as 1 (not at all), 2, 3 or 4 (very much).	
End point type	Secondary
End point timeframe: Baseline (before start of Treatment Phase 2) and at week 12 of Treatment Phase 2	

End point values	Arm A - ITT (ITT)	Arm B - ITT (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[43]	19 ^[44]		
Units: units on a scale				
median (full range (min-max))				
Cognitive Fatigue - Baseline	33.3 (0.0 to 77.8)	16.7 (0.0 to 88.9)		
Cognitive Fatigue - Week 12	22.2 (0.0 to 100)	16.7 (0.0 to 100)		
Emotional Fatigue - Baseline	58.3 (0.0 to 100)	41.7 (0.0 to 91.7)		
Emotional Fatigue - Week 12	50.0 (16.7 to 100)	50.0 (0.0 to 100)		
Physical Fatigue - Baseline	66.7 (8.3 to 100)	66.7 (0.0 to 100)		
Physical Fatigue - Week 12	66.7 (25.0 to 100)	58.3 (0.0 to 100)		

Notes:

[43] - N = 17 refers to the number of questionnaires available at baseline
(week 12: n = 13)

[44] - N = 19 refers to the number of questionnaires available at baseline
(week 12: n = 16)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall trial (Arm A vs. Arm B; per treatment line)

Adverse event reporting additional description:

(S)AE are reported per Arm and treatment line.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.4
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Reporting groups

Reporting group title	Arm A - Cap/Bev (1st Line)
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Reporting group description:

Arm A Cap/Bev (1st line): 4 SAR (Capecitabine) and 2 SAR (Bevacizumab) were observed; no SAR with fatal outcome was reported.

Total number of deaths (all causes, n=13) represent all fatalities occurred in Arm A (1st + 2nd line) until LPLV.

Reporting group title	Arm A - Eve/Exe (2nd Line)
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Reporting group description:

Arm A Eve/Exe (2nd line): 4 SAR (Everolimus) and no SAR (Exemestane) were observed; no SAR with fatal outcome was reported.

Total number of deaths (all causes; n = 13) represent all fatalities occurred in Arm A (1st + 2nd line) until LPLV.

Reporting group title	Arm B - Eve/Exe (1st line)
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Reporting group description:

Arm B Eve/Exe (1st line): 6 SAR (Everolimus) and 2 SAR (Exemestane) occurred; no SAR with fatal outcome was reported.

Total number of deaths (all causes, n=18) represent all fatalities occurred in Arm A (1st + 2nd line) until LPLV.

Reporting group title	Arm B - Cap/Bev (2nd line)
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Reporting group description:

Arm B Cap/Bev (2nd line): No SAR (Capecitabine) and 3 SAR (Bevacizumab) were observed; no SAR with fatal outcome was reported.

Total number of deaths (all causes, n=18) represent all fatalities occurred in Arm A (1st + 2nd line) until LPLV.

Serious adverse events	Arm A - Cap/Bev (1st Line)	Arm A - Eve/Exe (2nd Line)	Arm B - Eve/Exe (1st line)
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 37 (35.14%)	9 / 17 (52.94%)	17 / 37 (45.95%)
number of deaths (all causes)	13	13	18
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Malignant neoplasm progression subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to meninges			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Neoplasm progression			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood test abnormal			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Overdose			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation oesophagitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paralysis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastric perforation			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 37 (2.70%) 0 / 1 0 / 0	0 / 17 (0.00%) 0 / 0 0 / 0	0 / 37 (0.00%) 0 / 0 0 / 0
Bacterial sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 37 (0.00%) 0 / 0 0 / 0	0 / 17 (0.00%) 0 / 0 0 / 0	1 / 37 (2.70%) 0 / 1 0 / 0
Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 37 (0.00%) 0 / 0 0 / 0	0 / 17 (0.00%) 0 / 0 0 / 0	1 / 37 (2.70%) 1 / 1 0 / 0
Clostridium difficile colitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 37 (0.00%) 0 / 0 0 / 0	1 / 17 (5.88%) 0 / 1 0 / 0	0 / 37 (0.00%) 0 / 0 0 / 0
Device related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 37 (0.00%) 0 / 0 0 / 0	0 / 17 (0.00%) 0 / 0 0 / 0	1 / 37 (2.70%) 0 / 1 0 / 0
Diverticulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 37 (5.41%) 1 / 2 0 / 0	0 / 17 (0.00%) 0 / 0 0 / 0	0 / 37 (0.00%) 0 / 0 0 / 0
Erysipelas subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 37 (2.70%) 0 / 1 0 / 0	0 / 17 (0.00%) 0 / 0 0 / 0	1 / 37 (2.70%) 0 / 1 0 / 0
Oesophageal candidiasis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 37 (0.00%) 0 / 0 0 / 0	0 / 17 (0.00%) 0 / 0 0 / 0	1 / 37 (2.70%) 1 / 1 0 / 0
Peritonitis			

subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 17 (11.76%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm B - Cap/Bev (2nd line)		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 19 (42.11%)		
number of deaths (all causes)	18		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to meninges			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neoplasm progression			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Impaired healing			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			

subjects affected / exposed	3 / 19 (15.79%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood test abnormal			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Fall			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligament sprain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radiation oesophagitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiomyopathy			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus node dysfunction			

subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paralysis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Diverticulum intestinal haemorrhagic subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enteritis subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric perforation subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileus subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders Cholecystitis acute subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrotic syndrome			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacterial sepsis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erysipelas			

subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal candidiasis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			

subjects affected / exposed	0 / 19 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Arm A - Cap/Bev (1st Line)	Arm A - Eve/Exe (2nd Line)	Arm B - Eve/Exe (1st line)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 37 (97.30%)	12 / 17 (70.59%)	36 / 37 (97.30%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	1 / 37 (2.70%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 37 (29.73%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences (all)	14	0	6
Lymphoedema			
subjects affected / exposed	2 / 37 (5.41%)	1 / 17 (5.88%)	2 / 37 (5.41%)
occurrences (all)	2	1	2
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	13 / 37 (35.14%)	2 / 17 (11.76%)	6 / 37 (16.22%)
occurrences (all)	15	2	7
General physical health deterioration			
subjects affected / exposed	3 / 37 (8.11%)	0 / 17 (0.00%)	2 / 37 (5.41%)
occurrences (all)	3	0	2
Mucosal inflammation			
subjects affected / exposed	4 / 37 (10.81%)	2 / 17 (11.76%)	7 / 37 (18.92%)
occurrences (all)	4	2	7
Non-cardiac chest pain			

subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	2 / 37 (5.41%)	0 / 17 (0.00%)	6 / 37 (16.22%)
occurrences (all)	2	0	7
Pain			
subjects affected / exposed	2 / 37 (5.41%)	1 / 17 (5.88%)	1 / 37 (2.70%)
occurrences (all)	2	1	1
Peripheral swelling			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	5
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	2 / 37 (5.41%)	2 / 17 (11.76%)	1 / 37 (2.70%)
occurrences (all)	2	2	1
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	5 / 37 (13.51%)	3 / 17 (17.65%)	6 / 37 (16.22%)
occurrences (all)	5	4	6
Dysphonia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences (all)	3	0	1
Dyspnoea			
subjects affected / exposed	6 / 37 (16.22%)	3 / 17 (17.65%)	4 / 37 (10.81%)
occurrences (all)	7	3	5
Dyspnoea exertional			

subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Epistaxis			
subjects affected / exposed	1 / 37 (2.70%)	2 / 17 (11.76%)	4 / 37 (10.81%)
occurrences (all)	1	2	4
Oropharyngeal pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	5 / 37 (13.51%)
occurrences (all)	0	0	5
Pneumonitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Pulmonary embolism			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Insomnia			
subjects affected / exposed	3 / 37 (8.11%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences (all)	3	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Blood creatine increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	2
C-reactive protein increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	4 / 37 (10.81%)
occurrences (all)	0	0	4
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	0 / 17 (0.00%) 0	1 / 37 (2.70%) 1
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 17 (0.00%) 0	1 / 37 (2.70%) 1
Weight decreased subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 4	1 / 17 (5.88%) 1	5 / 37 (13.51%) 6
Injury, poisoning and procedural complications Rib fracture subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	0 / 17 (0.00%) 0	2 / 37 (5.41%) 2
Cardiac disorders Cyanosis subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 17 (0.00%) 0	0 / 37 (0.00%) 0
Tachyarrhythmia subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 17 (0.00%) 0	1 / 37 (2.70%) 1
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2	1 / 17 (5.88%) 1	4 / 37 (10.81%) 4
Headache subjects affected / exposed occurrences (all)	6 / 37 (16.22%) 7	0 / 17 (0.00%) 0	6 / 37 (16.22%) 10
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	6 / 37 (16.22%) 6	0 / 17 (0.00%) 0	1 / 37 (2.70%) 1
Polyneuropathy subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2	0 / 17 (0.00%) 0	0 / 37 (0.00%) 0
Somnolence subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 2	0 / 17 (0.00%) 0	0 / 37 (0.00%) 0
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	4 / 17 (23.53%) 4	5 / 37 (13.51%) 5
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2	0 / 17 (0.00%) 0	1 / 37 (2.70%) 1
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2	0 / 17 (0.00%) 0	2 / 37 (5.41%) 2
Eye disorders Eyelid oedema subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 17 (0.00%) 0	2 / 37 (5.41%) 2
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 4	0 / 17 (0.00%) 0	2 / 37 (5.41%) 2
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 3	0 / 17 (0.00%) 0	4 / 37 (10.81%) 4
Aphthous ulcer subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	1 / 17 (5.88%) 1	4 / 37 (10.81%) 4
Constipation subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	1 / 17 (5.88%) 1	2 / 37 (5.41%) 2
Diarrhoea subjects affected / exposed occurrences (all)	12 / 37 (32.43%) 20	2 / 17 (11.76%) 2	10 / 37 (27.03%) 15
Dry mouth subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 3	1 / 17 (5.88%) 1	4 / 37 (10.81%) 4
Dyspepsia subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 17 (0.00%) 0	2 / 37 (5.41%) 2
Flatulence			

subjects affected / exposed	2 / 37 (5.41%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences (all)	2	0	1
Nausea			
subjects affected / exposed	15 / 37 (40.54%)	1 / 17 (5.88%)	8 / 37 (21.62%)
occurrences (all)	20	1	8
Stomatitis			
subjects affected / exposed	9 / 37 (24.32%)	1 / 17 (5.88%)	4 / 37 (10.81%)
occurrences (all)	11	1	6
Toothache			
subjects affected / exposed	3 / 37 (8.11%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences (all)	3	0	0
Vomiting			
subjects affected / exposed	5 / 37 (13.51%)	1 / 17 (5.88%)	5 / 37 (13.51%)
occurrences (all)	7	1	5
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	3 / 37 (8.11%)	0 / 17 (0.00%)	3 / 37 (8.11%)
occurrences (all)	3	0	3
Erythema			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	3
Hyperhidrosis			
subjects affected / exposed	1 / 37 (2.70%)	1 / 17 (5.88%)	1 / 37 (2.70%)
occurrences (all)	1	1	1
Onychoclasia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 17 (0.00%)	3 / 37 (8.11%)
occurrences (all)	1	0	3
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	21 / 37 (56.76%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences (all)	26	0	1
Pruritus			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	3 / 37 (8.11%)
occurrences (all)	0	1	3
Rash			

subjects affected / exposed	2 / 37 (5.41%)	1 / 17 (5.88%)	5 / 37 (13.51%)
occurrences (all)	2	1	6
Rash pruritic			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Skin atrophy			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Skin discolouration			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Skin fissures			
subjects affected / exposed	2 / 37 (5.41%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences (all)	3	1	0
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	1 / 37 (2.70%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Proteinuria			
subjects affected / exposed	2 / 37 (5.41%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 37 (13.51%)	0 / 17 (0.00%)	4 / 37 (10.81%)
occurrences (all)	5	0	5
Back pain			
subjects affected / exposed	4 / 37 (10.81%)	1 / 17 (5.88%)	2 / 37 (5.41%)
occurrences (all)	4	1	2
Bone pain			
subjects affected / exposed	3 / 37 (8.11%)	0 / 17 (0.00%)	6 / 37 (16.22%)
occurrences (all)	3	0	7
Musculoskeletal chest pain			
subjects affected / exposed	2 / 37 (5.41%)	1 / 17 (5.88%)	1 / 37 (2.70%)
occurrences (all)	2	1	1
Musculoskeletal pain			

subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	4 / 37 (10.81%)
occurrences (all)	0	1	4
Myalgia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Neck pain			
subjects affected / exposed	1 / 37 (2.70%)	1 / 17 (5.88%)	1 / 37 (2.70%)
occurrences (all)	1	1	1
Pain in extremity			
subjects affected / exposed	2 / 37 (5.41%)	0 / 17 (0.00%)	2 / 37 (5.41%)
occurrences (all)	5	0	2
Polyarthrititis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Rotator cuff syndrome			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Spinal pain			
subjects affected / exposed	2 / 37 (5.41%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences (all)	2	0	1
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Gastrointestinal infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Infection			
subjects affected / exposed	1 / 37 (2.70%)	2 / 17 (11.76%)	1 / 37 (2.70%)
occurrences (all)	1	2	1
Oral herpes			
subjects affected / exposed	2 / 37 (5.41%)	0 / 17 (0.00%)	2 / 37 (5.41%)
occurrences (all)	2	0	2
Parotitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	3

Pneumonia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	1 / 37 (2.70%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	4 / 37 (10.81%)	1 / 17 (5.88%)	2 / 37 (5.41%)
occurrences (all)	4	1	2
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 37 (16.22%)	1 / 17 (5.88%)	2 / 37 (5.41%)
occurrences (all)	6	1	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 37 (16.22%)	1 / 17 (5.88%)	5 / 37 (13.51%)
occurrences (all)	6	1	5
Hypoalbuminaemia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 17 (5.88%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Selenium deficiency			
subjects affected / exposed	0 / 37 (0.00%)	0 / 17 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1

Non-serious adverse events	Arm B - Cap/Bev (2nd line)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 19 (78.95%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Lymphoedema			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
General physical health deterioration			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Peripheral swelling			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Chronic obstructive pulmonary			

disease			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Dysphonia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Dyspnoea exertional			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Pneumonitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Pulmonary embolism			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Investigations			

Aspartate aminotransferase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood creatine increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Cyanosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Tachyarrhythmia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nervous system disorders			

Dysgeusia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2		
Polyneuropathy subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Somnolence subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Eye disorders Eyelid oedema subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		

Aphthous ulcer			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	5		
Dry mouth			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	5		
Stomatitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Erythema			

subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Onychoclasia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	6 / 19 (31.58%)		
occurrences (all)	6		
Pruritus			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Rash pruritic			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Skin atrophy			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin discolouration			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin fissures			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Proteinuria			

subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Bone pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Polyarthrititis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Rotator cuff syndrome			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Spinal pain			

subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastrointestinal infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Parotitis			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	0 / 19 (0.00%)		
occurrences (all)	0		
Selenium deficiency			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2014	Amendment 1 - substantial (Amendment date is the favourable opinion of the EC or the approval of the relevant CA)
17 February 2015	Amendment 2 - substantial (Amendment date is the favourable opinion of the EC or the approval of the relevant CA)
24 April 2015	Amendment 3 - substantial (Amendment date is the favourable opinion of the EC or the approval of the relevant CA)
06 November 2015	Amendment 4 - substantial (Amendment date is the favourable opinion of the EC or the approval of the relevant CA)
23 March 2016	Amendment 5 - substantial (Amendment date is the favourable opinion of the EC or the approval of the relevant CA)
05 September 2016	Amendment 6 - substantial (Amendment date is the favourable opinion of the EC or the approval of the relevant CA)
02 August 2017	Amendment 7 - substantial (Amendment date is the favourable opinion of the EC or the approval of the relevant CA)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 February 2016	Specification of safety references (SmPC capecitabine) for the occurrence of adverse events for known DPD-deficiency. The genetic assessment for the exclusion of an (unknown) DPD-deficiency was demanded to be a requirement for patient recruitment by the central ethics committee. During the clarification process with the ethics committee patient recruitment was temporarily stopped. The official requirements of the ethics committee have been taken back.	23 March 2016

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The primary endpoint was not reached when considering the small analytical population (mITT) (due to low number of evaluable patients and premature termination of study) used for evaluation of the primary endpoint.)

Notes: