



Clinical trial results:

monarchHER: A Phase 2, Randomized, Multicenter, 3-Arm, Open-Label Study to Compare the Efficacy of Abemaciclib plus Trastuzumab with or without Fulvestrant to Standard-of-Care Chemotherapy of Physician's Choice plus Trastuzumab in Women with HR+, HER2+ Locally Advanced or Metastatic Breast Cancer

Summary

EudraCT number	2015-003400-24
Trial protocol	ES GR BE GB DE IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	24 April 2020
First version publication date	24 April 2020

Trial information

Trial identification

Sponsor protocol code	I3Y-MC-JPBZ
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02675231
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 15804

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559,

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	Interim
Date of interim/final analysis	08 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 April 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the effectiveness of abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus physicians choice standard of care chemotherapy in women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 positive (HER2+) locally advanced or metastatic breast cancer after prior exposure to at least two HER2-directed therapies for advanced disease.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 May 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 19
Country: Number of subjects enrolled	United States: 45
Country: Number of subjects enrolled	United Kingdom: 28
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Korea, Republic of: 30
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Germany: 7
Worldwide total number of subjects	237
EEA total number of subjects	111

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)	185
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In the Subject disposition, participants who completed were those who died due to any cause or were alive and on study at conclusion but off treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant

Arm description:

150 milligram (mg) abemaciclib given orally every 12 hours (Q12H) of a 21-day cycle; plus 8 milligram per kilogram (mg/kg) trastuzumab intravenous (IV) infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle; plus 500 mg fulvestrant intramuscularly (IM) on day 1, 15 and 29 and then once every 4 weeks thereafter.

Arm type	Experimental
Investigational medicinal product name	Abemaciclib
Investigational medicinal product code	
Other name	LY2835219
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

150 milligram (mg) abemaciclib given orally every 12 hours (Q12H) of a 21-day cycle.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 milligram per kilogram (mg/kg) trastuzumab intravenous (IV) infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg fulvestrant intramuscularly (IM) on day 1, 15 and 29 and then once every 4 weeks thereafter.

Arm title	150 mg Abemaciclib + 8 mg/kg Trastuzumab
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Arm description:

150 mg abemaciclib given orally Q12H of a 21-day cycle; plus 8 mg/kg trastuzumab IV infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle.

Arm type	Experimental
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Investigational medicinal product name	Abemaciclib
Investigational medicinal product code	
Other name	LY2835219
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

150 mg abemaciclib given orally Q12H of a 21-day cycle.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 mg/kg trastuzumab IV infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle.

Arm title	8 mg/kg Trastuzumab + Standard of Care Chemotherapy
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Arm description:

8 mg/kg trastuzumab IV infusion on Day 1 of a 21-day cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle plus standard of care single agent chemotherapy of physician's choice administered according to product label.

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 mg/kg trastuzumab IV infusion on Day 1 of a 21-day cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle.

Investigational medicinal product name	Standard of Care Single Agent Chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Standard-of-care single-agent chemotherapy of physician's choice administered according to product label

Number of subjects in period 1	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Started	79	79	79
Received at Least One Dose of Drug	78	77	72
Completed	53	43	53
Not completed	26	36	26
On study treatment/follow up	23	31	23
Consent withdrawn by subject	1	3	1
Lost to follow-up	2	2	2

Baseline characteristics

Reporting groups

Reporting group title	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant
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Reporting group description:

150 milligram (mg) abemaciclib given orally every 12 hours (Q12H) of a 21-day cycle; plus 8 milligram per kilogram (mg/kg) trastuzumab intravenous (IV) infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle; plus 500 mg fulvestrant intramuscularly (IM) on day 1, 15 and 29 and then once every 4 weeks thereafter.

Reporting group title	150 mg Abemaciclib + 8 mg/kg Trastuzumab
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Reporting group description:

150 mg abemaciclib given orally Q12H of a 21-day cycle; plus 8 mg/kg trastuzumab IV infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle.

Reporting group title	8 mg/kg Trastuzumab + Standard of Care Chemotherapy
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Reporting group description:

8 mg/kg trastuzumab IV infusion on Day 1 of a 21-day cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle plus standard of care single agent chemotherapy of physician's choice administered according to product label.

Reporting group values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects	79	79	79
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	54.34 ± 10.25	54.99 ± 11.08	56.77 ± 12.37
Gender categorical Units: Subjects			
Female	79	79	79
Male	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	14	11	12
Not Hispanic or Latino	58	52	56
Unknown or Not Reported	7	16	11
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	15	10	10
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	2	4
White	55	53	55
More than one race	0	0	1
Unknown or Not Reported	6	13	8
Region of Enrollment			

Units: Subjects			
Argentina	9	7	3
United States	20	8	17
United Kingdom	9	9	10
Spain	6	8	3
Greece	1	1	2
Canada	2	4	4
South Korea	11	9	10
Belgium	5	7	7
Brazil	3	1	4
Italy	2	5	2
Mexico	2	1	3
Australia	2	4	2
France	6	13	8
Germany	1	2	4

Reporting group values	Total		
Number of subjects	237		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	237		
Male	0		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	37		
Not Hispanic or Latino	166		
Unknown or Not Reported	34		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	2		
Asian	35		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	9		
White	163		
More than one race	1		
Unknown or Not Reported	27		
Region of Enrollment			
Units: Subjects			
Argentina	19		
United States	45		
United Kingdom	28		
Spain	17		
Greece	4		

Canada	10		
South Korea	30		
Belgium	19		
Brazil	8		
Italy	9		
Mexico	6		
Australia	8		
France	27		
Germany	7		

End points

End points reporting groups

Reporting group title	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant
Reporting group description: 150 milligram (mg) abemaciclib given orally every 12 hours (Q12H) of a 21-day cycle; plus 8 milligram per kilogram (mg/kg) trastuzumab intravenous (IV) infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle; plus 500 mg fulvestrant intramuscularly (IM) on day 1, 15 and 29 and then once every 4 weeks thereafter.	
Reporting group title	150 mg Abemaciclib + 8 mg/kg Trastuzumab
Reporting group description: 150 mg abemaciclib given orally Q12H of a 21-day cycle; plus 8 mg/kg trastuzumab IV infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle.	
Reporting group title	8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Reporting group description: 8 mg/kg trastuzumab IV infusion on Day 1 of a 21-day cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle plus standard of care single agent chemotherapy of physician's choice administered according to product label.	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description: PFS time was measured from the date of randomization to the date of investigator-determined objective progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, or death from any cause. Progressive Disease (PD) was at least a 20% increase in sum of the diameters of target lesions, with reference being the smallest sum on study and an absolute increase of at least 5 mm, or unequivocal progression of non-target lesions, or 1 or more new lesions. If a participant does not have a complete baseline disease assessment, then the PFS time was censored at the date of first dose, regardless of whether or not objectively determined disease progression or death has been observed for the participant. If a participant was not known to have died or have objective progression as of data inclusion cutoff date for the analysis, the PFS time was censored at the last adequate tumor assessment date. Analysis Population Description (APD) included all enrolled participants.	
End point type	Primary
End point timeframe: Baseline to Progressive Disease or Death from Any Cause (Up To 36 Months)	

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79 ^[1]	79 ^[2]	79 ^[3]	
Units: Months				
median (confidence interval 95%)	8.3 (5.9 to 12.6)	5.7 (4.2 to 7.2)	5.7 (5.4 to 6.9)	

Notes:

[1] - Censored participants: =23

[2] - Censored participants: =18

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
PFS analysis was planned after approximately 165 PFS events occurred in the enrolled population, yielding greater than or equal to (\geq) 80% power assuming a Hazard ration (HR) of 0.667 at an experiment-wise 2-sided alpha level of 0.2.	
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.0506 ^[5]
Method	Logrank

Notes:

[4] - PFS analysis was planned after approximately 165 PFS events occurred in the enrolled population, yielding greater than or equal to (\geq) 80% power assuming a Hazard ration (HR) of 0.667 at an experiment-wise 2-sided alpha level of 0.2.

[5] - This is statistically significant at the pre-specified 2-sided alpha of 0.2

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
PFS analysis was planned after approximately 165 PFS events occurred in the enrolled population, yielding greater than or equal to (\geq) 80% power assuming a Hazard ration (HR) of 0.667 at an experiment-wise 2-sided alpha level of 0.2.	
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.7695
Method	Logrank

Notes:

[6] - PFS analysis was planned after approximately 165 PFS events occurred in the enrolled population, yielding greater than or equal to (\geq) 80% power assuming a Hazard ration (HR) of 0.667 at an experiment-wise 2-sided alpha level of 0.2.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS defined as the time from first dose date to the date of death due to any cause. For each participant who is not known to have died as of the data-inclusion cutoff date for overall survival analysis, OS time was censored on the last date the participant is known to be alive.	
End point type	Secondary
End point timeframe:	
Baseline to Death from Any Cause (Estimated up to 48 Months)	

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79 ^[7]	79 ^[8]	79 ^[9]	
Units: Months				
number (not applicable)	99999	99999	99999	

Notes:

[7] - Results will be reported after last patient visit (LPV). 99999=NA

[8] - Results will be reported after LPV. 99999=NA

[9] - Results will be reported after LPV. 99999=NA

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Complete Response (CR) or Partial Response (PR): Objective Response Rate (ORR)

End point title	Percentage of Participants Achieving Complete Response (CR) or Partial Response (PR): Objective Response Rate (ORR)
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End point description:

ORR was the percentage of participants achieving a best overall response (BOR) of complete response (CR) or partial response (PR) as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. CR defined as the disappearance of all target and non-target lesions and no appearance of new lesions. PR defined as at least a 30% decrease in the sum of the longest diameters (LD) of target lesions (taking as reference the baseline sum LD), no progression of non-target lesions, and no appearance of new lesions. APD included all enrolled participants.

End point type	Secondary
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End point timeframe:

Baseline to Objective Disease Progression (Up To 36 Months)

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	79	79	
Units: Percentage of participants				
number (confidence interval 95%)	32.9 (22.5 to 43.3)	13.9 (6.3 to 21.6)	13.9 (6.3 to 21.6)	

Statistical analyses

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)
End point description:	
DoR was the time from the date of first evidence of complete response or partial response to the date of objective progression or the date of death due to any cause, whichever is earlier. CR and PR were defined using the RECIST v1.1. CR defined as the disappearance of all target and non-target lesions and no appearance of new lesions. PR defined as at least a 30% decrease in the sum of the LD of target lesions (taking as reference the baseline sum LD), no progression of non-target lesions, and no appearance of new lesions. If a responder was not known to have died or have objective progression as of the data inclusion cutoff date, duration of response was censored at the last adequate tumor assessment date. APD included all enrolled participants who received at least one dose of study drug and achieved CR or PR. 99999=NA because for 8 mg/kg Trastuzumab + Standard of Care Chemotherapy, the median and upper limit of the 95% CI was not calculated due to the high censoring rate.	
End point type	Secondary
End point timeframe:	
Date of CR or PR to Date of Objective Disease Progression or Death from Any Cause (Up To 36 Months)	

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26 ^[10]	11 ^[11]	11 ^[12]	
Units: Months				
median (confidence interval 95%)	12.5 (6.5 to 23.5)	9.5 (2.8 to 22.7)	99999 (4.1 to 99999)	

Notes:

[10] - Censored participants: =12

[11] - Censored participants: =3

[12] - Censored participants: =11

99999 = NA.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Best Overall Response of CR, PR, or Stable Disease (SD): Disease Control Rate (DCR)

End point title	Percentage of Participants with a Best Overall Response of CR, PR, or Stable Disease (SD): Disease Control Rate (DCR)
End point description:	
Disease Control Rate (DCR) was the percentage of participants with a best overall response of CR, PR, or Stable Disease (SD) as per Response using RECIST v1.1 criteria. CR defined as the disappearance of all target and non-target lesions and no appearance of new lesions. PR defined as at least a 30% decrease in the sum of the LD of target lesions (taking as reference the baseline sum LD), no progression of non-target lesions, and no appearance of new lesions. SD was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD for target lesions, no progression of non-target lesions, and no appearance of new lesions. APD included all enrolled participants.	
End point type	Secondary
End point timeframe:	
Baseline to Objective Disease Progression (Up To 36 Months)	

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	79	79	
Units: Percentage of participants				
number (confidence interval 95%)	78.5 (69.4 to 87.5)	74.7 (65.1 to 84.3)	67.1 (56.7 to 77.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Best Overall Response of CR, PR, or SD with Duration of SD for at Least 6 Months: Clinical Benefit Rate (CBR)

End point title	Percentage of Participants with Best Overall Response of CR, PR, or SD with Duration of SD for at Least 6 Months: Clinical Benefit Rate (CBR)
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End point description:

Clinical benefit rate defined as percentage of participants with best overall response of CR, PR, or SD with a duration of at least 6 months. CR, PR, or SD were defined using RECIST, v1.1 criteria. CR defined as the disappearance of all target and non-target lesions and no appearance of new lesions. PR defined as at least a 30% decrease in the sum of the LD of target lesions (taking as reference the baseline sum LD), no progression of non-target lesions, and no appearance of new lesions. SD was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD for target lesions, no progression of non-target lesions, and no appearance of new lesions. Percentage of participants = (participants with CR+PR+SD with a duration of at least 6 months /number of participants enrolled) *100. APD included all enrolled participants.

End point type	Secondary
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End point timeframe:

Date of CR, PR or SD to 6 Months Post CR, PR or SD (Up To 36 Months)

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	79	79	
Units: Percentage of participants				
number (confidence interval 95%)	58.2 (47.4 to 69.1)	45.6 (34.6 to 56.6)	38.0 (27.3 to 48.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pain and Symptom Burden Assessment on the Modified Brief Pain Inventory-Short Form (mBPI-sf)

End point title	Change from Baseline in Pain and Symptom Burden Assessment on the Modified Brief Pain Inventory-Short Form (mBPI-sf)
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End point description:

The mBPI-sf is an 11-item instrument used as a multiple-item measure of cancer pain intensity. In addition to pain intensity (4 items), the mBPI-sf is designed for participants to record the presence of pain in general, pain relief, and pain interference with function (general activity, mood, ability to walk, ability to perform normal work, relations with others, sleep, enjoyment of life). Responses for the mBPI-sf items are captured through the use of 11-point numeric rating scales anchored at 0 (no pain or does not interfere) and 10 (pain as bad as you can imagine or completely interferes). The mBPI-sf recall period is 24 hours and typical completion time for this instrument is less than 5 minutes. Mean Interference Score data is reported here. Least square (LS) Mean value was controlled for Treatment, visit, Treatment*Visit and baseline. APD included all enrolled participants.

End point type	Secondary
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End point timeframe:

Baseline, 30 Days After Treatment Discontinuation (Up To 36 Months)

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	79	79	
Units: units on a scale				
least squares mean (standard error)	0 (± 0.18)	0.20 (± 0.18)	0.31 (± 0.19)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.232 ^[13]
Method	MMRM Model

Notes:

[13] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Secondary: Change from Baseline in Symptom Burden on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30)

End point title	Change from Baseline in Symptom Burden on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30)
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End point description:

EORTC QLQ-C30 v3.0 was a self-administered questionnaire with multidimensional scales that measures 5 functional domains (physical, role, cognitive, emotional, and social), global health status, and symptom scales of fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation and diarrhea, and financial difficulties. A linear transformation is applied to standardize the raw scores to range between 0 and 100 per developer guidelines. For functional domains and global health status, higher scores represent a better level of functioning. For symptoms scales, higher scores represented a greater degree of symptoms. LS Mean value was controlled for Treatment, visit, Treatment*Visit and baseline. APD included all randomized participants who received at least one dose of study drug with baseline and post-baseline EORTC QLQ-C30 data for each EORTC QLQ-C30 items.

End point type	Secondary
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End point timeframe:

Baseline, 30 Days After Treatment Discontinuation (Up To 36 Months)

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	72	69	
Units: units on a scale				
least squares mean (standard error)				
Global health status	-2.9 (± 1.6)	-5.9 (± 1.7)	-1.9 (± 1.8)	
Functional scale: Physical functioning	-1.0 (± 1.6)	-4.4 (± 1.6)	-4.5 (± 1.7)	
Functional scale: Role functioning	-2.7 (± 2.2)	-5.0 (± 2.3)	-8.2 (± 2.4)	
Functional scale: Emotional functioning	2.4 (± 1.7)	-0.4 (± 1.8)	1.1 (± 1.8)	
Functional scale: Cognitive functioning	-1.8 (± 1.4)	-1.1 (± 1.5)	-1.6 (± 1.6)	
Functional scale: Social functioning	-0.9 (± 1.9)	-0.9 (± 1.9)	-2.4 (± 2.0)	
Symptom scale: Fatigue	1.8 (± 1.9)	7.0 (± 2.0)	4.7 (± 2.1)	
Symptom scale: Nausea and vomiting	6.3 (± 1.4)	5.6 (± 1.4)	2.2 (± 1.5)	
Symptom scale: Pain	-2.5 (± 2.1)	3.1 (± 2.1)	4.3 (± 2.2)	
Symptom scale: Dyspnoea	0.7 (± 1.9)	2.9 (± 2.0)	3.7 (± 2.1)	
Symptom scale: Insomnia	-4.4 (± 2.1)	-1.6 (± 2.2)	2.0 (± 2.3)	
Symptom scale: Appetite loss	6.3 (± 2.3)	5.5 (± 2.4)	2.4 (± 2.5)	
Symptom scale: Constipation	-6.3 (± 1.9)	-10.5 (± 1.9)	-3.4 (± 2.0)	
Symptom scale: Diarrhoea	21.5 (± 2.2)	25.3 (± 2.3)	2.2 (± 2.4)	
Symptom scale: Financial difficulties	0.8 (± 2.0)	-1.9 (± 2.1)	-3.2 (± 2.2)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1: Global health status
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.689 ^[14]
Method	MMRM Model

Notes:

[14] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 2: Functional scale: Physical
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.141 ^[15]
Method	MMRM Model

Notes:

[15] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 3: Functional scale: Role
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.095 ^[16]
Method	MMRM Model

Notes:

[16] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical analysis 4: Functional scale: Emotional
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.591 ^[17]
Method	MMRM Model

Notes:

[17] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 5: Functional scale:Cognitive
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.935 ^[18]
Method	MMRM Model

Notes:

[18] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical analysis 6: Functional scale: Social
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.578 ^[19]
Method	MMRM Model

Notes:

[19] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 7: Symptom scale: Fatigue
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.308 ^[20]
Method	MMRM Model

Notes:

[20] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 8 : Symptom: Nausea, vomiting
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043 ^[21]
Method	MMRM Model

Notes:

[21] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 9: Symptom scale: Pain
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026 ^[22]
Method	MMRM Model

Notes:

[22] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 10: Symptom scale: Dyspnoea
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276 ^[23]
Method	MMRM Model

Notes:

[23] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 11: Symptom scale: Insomnia
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041 ^[24]
Method	MMRM Model

Notes:

[24] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 12: Symptom: Appetite loss
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.262 ^[25]
Method	MMRM Model

Notes:

[25] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 13: Symptom scale: Constipation
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority ^[26]
P-value	= 0.285
Method	MMRM Model

Notes:

[26] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 14: Symptom scale: Diarrhoea
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[27]
Method	MMRM Model

Notes:

[27] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 15: Symptom scale: Financial
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18 ^[28]
Method	MMRM Model

Notes:

[28] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM):
Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Secondary: Change From Baseline on the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Index Score

End point title	Change From Baseline on the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Index Score
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End point description:

The EQ-5D-5L is a standardized instrument for use as a measure of self-reported health status. Participants completed the 5-level (no problem, slight problem, moderate problem, severe problem, and inability or extreme problem), 5-dimension (mobility, self-care, usual activities, pain/discomfort, and

anxiety/depression) questionnaire concerning their current health state. Five dimensions of health status are each assessed with 5 response options and scored as a composite index which were anchored on a scale of 0 to 1 with a higher score representing better health status. LS Mean value was controlled for Treatment, visit, Treatment*Visit and baseline. APD included all enrolled participants who received at least one dose of study drug with baseline and post-baseline EQ-5D 5L data.

End point type	Secondary
End point timeframe:	
Baseline, 30 Days After Treatment Discontinuation (Up To 36 Months)	

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	72	68	
Units: units on a scale				
least squares mean (standard error)	0.01 (± 0.02)	-0.01 (± 0.02)	-0.04 (± 0.02)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033 ^[29]
Method	MMRM Model

Notes:

[29] - p-values are from Type 3 sums of squares mixed models repeated measures model: Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 2
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.275 ^[30]
Method	MMRM Model

Notes:

[30] - p-values are from Type 3 sums of squares mixed models repeated measures model: Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Secondary: Change From Baseline on the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Visual Analogue Scale (VAS)

End point title	Change From Baseline on the EuroQol 5-Dimension, 5-Level
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End point description:

European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L) is a standardized measure of health status of the participant. The EQ-5D-5L is assessed using a visual analog scale (VAS) that ranged from 0 to 100 millimeter (mm), where 0 is the worst health you can imagine and 100 is the best health you can imagine. A higher score indicates better health state. LS Mean value was controlled for Treatment, visit, Treatment*Visit and baseline. APD included all enrolled participants who received at least one dose of study drug with baseline and post-baseline EQ-5D 5L VAS data.

End point type

Secondary

End point timeframe:

Baseline, 30 Days After Treatment Discontinuation (Up To 36 Months)

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	71	70	
Units: millimeter (mm)				
least squares mean (standard error)	0.61 (± 1.4)	-1.64 (± 1.4)	-0.61 (± 1.5)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.546
Method	MMRM Model

Statistical analysis title	Statistical Analysis 2
Comparison groups	8 mg/kg Trastuzumab + Standard of Care Chemotherapy v 150 mg Abemaciclib + 8 mg/kg Trastuzumab
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority ^[31]
P-value	= 0.62
Method	MMRM Model

Notes:

[31] - EQ 5D-5L Visual Analog Scale Score

Secondary: Pharmacokinetics (PK): Minimum Steady State Concentration (Cmin,ss)

of Abemaciclib and its Metabolites (M2 and M20)

End point title	Pharmacokinetics (PK): Minimum Steady State Concentration (C _{min,ss}) of Abemaciclib and its Metabolites (M2 and M20) ^[32]
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End point description:

Minimum Steady State Concentration (C_{min,ss}) of Abemaciclib and Its Metabolites (M2 and M20) was evaluated. M2 and M20 are 2 major active metabolites of abemaciclib.

End point type	Secondary
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End point timeframe:

Cycle(C)1 Day(D)1,C1D15, C2D1, C2D8, C3D1,C3D15, C4D1, C5D1:pre-dose; C1D1, C2D1, C3D1, C4D1, C5D1:post-dose

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No inferential statistics were planned or conducted for this endpoint.

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	71		
Units: nanogram/milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Abemaciclib	134 (± 77)	155 (± 53)		
M2	72.0 (± 120)	96.5 (± 120)		
M20	136 (± 120)	181 (± 130)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up To 36 Months

Adverse event reporting additional description:

All enrolled participants who received at least one dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant
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Reporting group description:

150 mg abemaciclib given orally every 12 hours (Q12H) of a 21-day cycle; plus 8mg/kg trastuzumab intravenous (IV) infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle; plus 500mg fulvestrant intramuscularly (IM) on day 1, 15 and 29 and then once every 4 weeks thereafter.

Reporting group title	150 mg Abemaciclib + 8 mg/kg Trastuzumab
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Reporting group description:

150 mg abemaciclib given orally Q12H of a 21-day cycle; plus 8 mg/kg trastuzumab IV infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle.

Reporting group title	8 mg/kg Trastuzumab + Standard of Care Chemotherapy
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Reporting group description:

8 mg/kg trastuzumab IV infusion on Day 1 of a 21-day cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle plus standard of care single agent chemotherapy of physician's choice administered according to product label.

Serious adverse events	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 78 (26.92%)	15 / 77 (19.48%)	11 / 72 (15.28%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (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
pyrexia			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	3 / 78 (3.85%)	1 / 77 (1.30%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
drug hypersensitivity			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
vaginal haemorrhage			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
acute respiratory distress syndrome			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
dyspnoea			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 77 (1.30%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
epistaxis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (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
interstitial lung disease			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (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
pleural effusion			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	2 / 72 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumothorax			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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
pulmonary embolism			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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
respiratory failure			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Psychiatric disorders			
confusional state			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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			
neutrophil count decreased			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
white blood cell count decreased			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
femur fracture			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (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
hip fracture			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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
radiation pneumonitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
cardio-respiratory arrest			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
pericardial effusion alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
cerebral haemorrhage alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
dizziness alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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
headache alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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
Blood and lymphatic system disorders			
anaemia alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
febrile neutropenia alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	3 / 72 (4.17%)
occurrences causally related to treatment / all	1 / 1	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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
ascites			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (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			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	2 / 77 (2.60%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
faecaloma			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ileus			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (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
intestinal obstruction			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nausea			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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
stomatitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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
vomiting			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 77 (1.30%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
bile duct stone			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (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
cholangitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	2 / 78 (2.56%)	1 / 77 (1.30%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
urinary retention			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
urinary tract obstruction			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
musculoskeletal chest pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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
musculoskeletal pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (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
osteonecrosis of jaw			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (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
Infections and infestations			
cellulitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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
fungal infection			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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
gastroenteritis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastroenteritis viral			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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
herpes zoster			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (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
influenza			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lower respiratory tract infection alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lung infection alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (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
lymphangitis alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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
otitis media alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 77 (1.30%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sepsis alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

soft tissue infection alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
urinary tract infection alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 77 (1.30%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
decreased appetite alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 72 (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
hypokalaemia alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 72 (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

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

Non-serious adverse events	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 78 (97.44%)	75 / 77 (97.40%)	68 / 72 (94.44%)
Vascular disorders			
hot flush alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	5 / 78 (6.41%)	3 / 77 (3.90%)	2 / 72 (2.78%)
occurrences (all)	7	4	2
hypertension			

alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	3 / 78 (3.85%) 4	4 / 77 (5.19%) 7	2 / 72 (2.78%) 3
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	11 / 78 (14.10%) 17	12 / 77 (15.58%) 16	7 / 72 (9.72%) 14
fatigue			
alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	33 / 78 (42.31%) 58	29 / 77 (37.66%) 52	26 / 72 (36.11%) 30
influenza like illness			
alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	2 / 78 (2.56%) 2	6 / 77 (7.79%) 12	0 / 72 (0.00%) 0
mucosal inflammation			
alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	1 / 78 (1.28%) 1	3 / 77 (3.90%) 4	4 / 72 (5.56%) 6
non-cardiac chest pain			
alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	5 / 78 (6.41%) 6	0 / 77 (0.00%) 0	1 / 72 (1.39%) 1
oedema peripheral			
alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	4 / 78 (5.13%) 6	6 / 77 (7.79%) 9	7 / 72 (9.72%) 9
pyrexia			
alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	11 / 78 (14.10%) 15	4 / 77 (5.19%) 7	10 / 72 (13.89%) 16
Respiratory, thoracic and mediastinal disorders			

cough alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	18 / 78 (23.08%) 25	11 / 77 (14.29%) 14	8 / 72 (11.11%) 12
dyspnoea alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	14 / 78 (17.95%) 21	7 / 77 (9.09%) 9	12 / 72 (16.67%) 14
epistaxis alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	6 / 78 (7.69%) 8	7 / 77 (9.09%) 11	5 / 72 (6.94%) 5
Psychiatric disorders anxiety alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	2 / 78 (2.56%) 2	3 / 77 (3.90%) 3	4 / 72 (5.56%) 4
insomnia alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	4 / 78 (5.13%) 5	6 / 77 (7.79%) 12	5 / 72 (6.94%) 5
Investigations alanine aminotransferase increased alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	6 / 78 (7.69%) 12	6 / 77 (7.79%) 12	8 / 72 (11.11%) 20
aspartate aminotransferase increased alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	9 / 78 (11.54%) 13	7 / 77 (9.09%) 12	8 / 72 (11.11%) 24
blood alkaline phosphatase increased alternative dictionary used: MedDRA 22.0 subjects affected / exposed occurrences (all)	6 / 78 (7.69%) 11	1 / 77 (1.30%) 1	2 / 72 (2.78%) 4
blood bilirubin increased			

alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	5 / 78 (6.41%)	2 / 77 (2.60%)	4 / 72 (5.56%)
occurrences (all)	6	3	8
blood creatinine increased			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	10 / 78 (12.82%)	11 / 77 (14.29%)	0 / 72 (0.00%)
occurrences (all)	14	16	0
lymphocyte count decreased			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 78 (2.56%)	4 / 77 (5.19%)	4 / 72 (5.56%)
occurrences (all)	2	5	26
neutrophil count decreased			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	24 / 78 (30.77%)	19 / 77 (24.68%)	13 / 72 (18.06%)
occurrences (all)	65	73	61
platelet count decreased			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	19 / 78 (24.36%)	16 / 77 (20.78%)	5 / 72 (6.94%)
occurrences (all)	58	42	36
weight decreased			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	6 / 78 (7.69%)	5 / 77 (6.49%)	1 / 72 (1.39%)
occurrences (all)	7	5	1
white blood cell count decreased			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	12 / 78 (15.38%)	7 / 77 (9.09%)	8 / 72 (11.11%)
occurrences (all)	32	26	46
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	4 / 78 (5.13%)	8 / 77 (10.39%)	2 / 72 (2.78%)
occurrences (all)	6	10	2
dysgeusia			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	4 / 78 (5.13%)	4 / 77 (5.19%)	2 / 72 (2.78%)
occurrences (all)	4	4	2
headache			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	12 / 78 (15.38%)	10 / 77 (12.99%)	13 / 72 (18.06%)
occurrences (all)	17	14	15
neuropathy peripheral			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	3 / 78 (3.85%)	0 / 77 (0.00%)	4 / 72 (5.56%)
occurrences (all)	3	0	4
peripheral sensory neuropathy			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 78 (2.56%)	5 / 77 (6.49%)	9 / 72 (12.50%)
occurrences (all)	2	6	15
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	27 / 78 (34.62%)	20 / 77 (25.97%)	16 / 72 (22.22%)
occurrences (all)	85	43	42
leukopenia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	6 / 78 (7.69%)	2 / 77 (2.60%)	3 / 72 (4.17%)
occurrences (all)	16	2	24
neutropenia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	17 / 78 (21.79%)	9 / 77 (11.69%)	15 / 72 (20.83%)
occurrences (all)	54	28	51
thrombocytopenia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	3 / 78 (3.85%)	8 / 77 (10.39%)	0 / 72 (0.00%)
occurrences (all)	6	13	0
Eye disorders			
lacrimation increased			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	6 / 78 (7.69%)	4 / 77 (5.19%)	2 / 72 (2.78%)
occurrences (all)	12	6	2
vision blurred			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	4 / 78 (5.13%)	3 / 77 (3.90%)	1 / 72 (1.39%)
occurrences (all)	4	3	1
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	5 / 78 (6.41%)	3 / 77 (3.90%)	0 / 72 (0.00%)
occurrences (all)	5	3	0
abdominal pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	16 / 78 (20.51%)	13 / 77 (16.88%)	12 / 72 (16.67%)
occurrences (all)	21	14	14
abdominal pain upper			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	10 / 78 (12.82%)	3 / 77 (3.90%)	4 / 72 (5.56%)
occurrences (all)	12	7	4
constipation			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	9 / 78 (11.54%)	8 / 77 (10.39%)	14 / 72 (19.44%)
occurrences (all)	11	10	18
diarrhoea			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	61 / 78 (78.21%)	60 / 77 (77.92%)	18 / 72 (25.00%)
occurrences (all)	191	179	40
dry mouth			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	4 / 78 (5.13%)	4 / 77 (5.19%)	4 / 72 (5.56%)
occurrences (all)	5	5	6
dyspepsia			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	8 / 78 (10.26%)	6 / 77 (7.79%)	5 / 72 (6.94%)
occurrences (all)	15	9	5
gastroesophageal reflux disease			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	5 / 78 (6.41%)	1 / 77 (1.30%)	1 / 72 (1.39%)
occurrences (all)	5	1	1
nausea			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	36 / 78 (46.15%)	32 / 77 (41.56%)	25 / 72 (34.72%)
occurrences (all)	58	47	36
stomatitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	3 / 78 (3.85%)	7 / 77 (9.09%)	8 / 72 (11.11%)
occurrences (all)	6	10	17
vomiting			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	20 / 78 (25.64%)	22 / 77 (28.57%)	11 / 72 (15.28%)
occurrences (all)	31	29	13
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	6 / 78 (7.69%)	7 / 77 (9.09%)	8 / 72 (11.11%)
occurrences (all)	6	8	10
dry skin			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	5 / 78 (6.41%)	4 / 77 (5.19%)	4 / 72 (5.56%)
occurrences (all)	5	4	4
nail disorder			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 78 (2.56%)	4 / 77 (5.19%)	1 / 72 (1.39%)
occurrences (all)	3	4	2
onychoclasia			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	4 / 78 (5.13%)	1 / 77 (1.30%)	0 / 72 (0.00%)
occurrences (all)	4	1	0
palmar-plantar erythrodysaesthesia syndrome			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	12 / 72 (16.67%)
occurrences (all)	0	2	19
pruritus			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	11 / 78 (14.10%)	9 / 77 (11.69%)	3 / 72 (4.17%)
occurrences (all)	18	10	3
rash			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	5 / 78 (6.41%)	8 / 77 (10.39%)	6 / 72 (8.33%)
occurrences (all)	7	12	8
rash maculo-papular			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	5 / 78 (6.41%)	6 / 77 (7.79%)	2 / 72 (2.78%)
occurrences (all)	6	9	4
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	10 / 78 (12.82%)	8 / 77 (10.39%)	8 / 72 (11.11%)
occurrences (all)	13	9	9
back pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	5 / 78 (6.41%)	11 / 77 (14.29%)	5 / 72 (6.94%)
occurrences (all)	6	12	7
bone pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	3 / 77 (3.90%)	7 / 72 (9.72%)
occurrences (all)	1	3	7
musculoskeletal pain			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	2 / 78 (2.56%)	5 / 77 (6.49%)	3 / 72 (4.17%)
occurrences (all)	2	7	3
myalgia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	7 / 78 (8.97%)	7 / 77 (9.09%)	10 / 72 (13.89%)
occurrences (all)	9	7	12
pain in extremity			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	5 / 77 (6.49%)	8 / 72 (11.11%)
occurrences (all)	2	7	9
Infections and infestations			
gastroenteritis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	5 / 78 (6.41%)	0 / 77 (0.00%)	2 / 72 (2.78%)
occurrences (all)	5	0	3
influenza			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	4 / 78 (5.13%)	5 / 77 (6.49%)	2 / 72 (2.78%)
occurrences (all)	6	6	2
nasopharyngitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	5 / 78 (6.41%)	3 / 77 (3.90%)	2 / 72 (2.78%)
occurrences (all)	5	3	2
rhinitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	4 / 78 (5.13%)	2 / 77 (2.60%)	1 / 72 (1.39%)
occurrences (all)	4	2	1
upper respiratory tract infection			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	8 / 78 (10.26%)	2 / 77 (2.60%)	8 / 72 (11.11%)
occurrences (all)	15	2	12
urinary tract infection			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed occurrences (all)	6 / 78 (7.69%) 9	8 / 77 (10.39%) 21	5 / 72 (6.94%) 8
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	16 / 78 (20.51%)	16 / 77 (20.78%)	13 / 72 (18.06%)
occurrences (all)	27	24	15
dehydration			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	3 / 78 (3.85%)	2 / 77 (2.60%)	4 / 72 (5.56%)
occurrences (all)	4	2	4
hyperglycaemia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 77 (1.30%)	4 / 72 (5.56%)
occurrences (all)	1	3	9
hyperkalaemia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	5 / 78 (6.41%)	3 / 77 (3.90%)	1 / 72 (1.39%)
occurrences (all)	6	3	1
hypokalaemia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	6 / 78 (7.69%)	7 / 77 (9.09%)	4 / 72 (5.56%)
occurrences (all)	16	15	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2015	- Added the safety lead-in portion for Arm A due to no data around the triplet combination
23 January 2019	- Updated the safety language regarding hepatic monitoring, assessment of renal function, and venous thromboembolic events (VTEs) for ongoing patients and align with the updated label of abemaciclib.
10 February 2020	- Added dose modification table for interstitial lung disease (ILD)/pneumonitis and updated guidance for management of ILD/pneumonitis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported