Clinical trial results:
Randomized, Non-comparative Neoadjuvant Phase II Study in Patients with ER+/HER2- Breast Cancer 2 cm with Safety Run-in, Assessing Nivolumab + Palbociclib + Anastrozole (CheckMate 7A8: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 7A8)

Summary

EudraCT number	2019-001334-34
Trial protocol	FR DE BE ES
Global end of trial date	27 July 2021

Results information

Result version number	v1 (current)
This version publication date	30 July 2022
First version publication date	30 July 2022

Trial information

Trial identification

Sponsor protocol code	CA209-7A8

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04075604
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	03 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 July 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine the number of participants with occurrence of DLTs in the Safety Run-in Phase and to estimate the RCB (0-I) rate per central assessment in participants in each randomized arm during the Randomized phase.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 October 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Spain: 5
Worldwide total number of subjects	23
EEA total number of subjects	9

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)	13

From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

23 participants were randomized and treated during the study

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Dose level 1

Arm description:

Nivolumab: 480 mg every 4 weeks (Q4W) intravenously (IV) Abemaciclib: 150 mg twice daily (BID) per os (by mouth) Anastrozole: 1 mg once daily (QD) per os (by mouth) Participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks)

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

480 mg every 4 weeks

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 mg once daily

Investigational medicinal product name	Abemaciclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg twice daily

Arm title	Cohort 2: Dose level 1

Arm description:

Nivolumab: 480 mg every 4 weeks (Q4W) intravenously (IV) Palbociclib: 125 mg once daily (QD) per os (by mouth) for 3 weeks of each cycle (1 week off) Anastrozole: 1 mg once daily (QD) per os (by mouth) Participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks)

Arm type	Experimental

Investigational medicinal product name	Palbociclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

125 mg once daily

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 mg once daily

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

Dosage and administration details:

480 mg every 4 weeks

Arm title	Cohort 2: Dose level 2

Arm description:

Nivolumab: 480 mg every 4 weeks (Q4W) intravenously (IV) Palbociclib: 100 mg once daily (QD) per os (by mouth) for 3 weeks of each cycle (1 week off) Anastrozole: 1 mg once daily (QD) per os (by mouth) Participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks)

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

480 mg every 4 weeks

Investigational medicinal product name	Palbociclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100 mg once daily

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 mg once daily

Number of subjects in period 1	Cohort 1: Dose level 1	Cohort 2: Dose level 1	Cohort 2: Dose level 2
Started	2	9	12
Completed	1	3	6
Not completed	1	6	6
Disease progression	-	1	-
Participant withdrew consent	-	-	1
Study drug toxicity	-	5	1
Adverse event, non-fatal	-	-	3
Other reasons	1	-	-
Participant request to discontinue study treatment	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Dose level 1
Reporting group description:	
Nivolumab: 480 mg every 4 weeks (Q4W) intravenously (IV) Abemaciclib: 150 mg twice daily (BID) per os (by mouth) Anastrozole: 1 mg once daily (QD) per os (by mouth) Participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks)	
Reporting group title	Cohort 2: Dose level 1
Reporting group description:	
Nivolumab: 480 mg every 4 weeks (Q4W) intravenously (IV) Palbociclib: 125 mg once daily (QD) per os (by mouth) for 3 weeks of each cycle (1 week off) Anastrozole: 1 mg once daily (QD) per os (by mouth) Participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks)	
Reporting group title	Cohort 2: Dose level 2
Reporting group description:	
Nivolumab: 480 mg every 4 weeks (Q4W) intravenously (IV) Palbociclib: 100 mg once daily (QD) per os (by mouth) for 3 weeks of each cycle (1 week off) Anastrozole: 1 mg once daily (QD) per os (by mouth) Participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks)	

Reporting group values	Cohort 1: Dose level 1	Cohort 2: Dose level 1	Cohort 2: Dose level 2
Number of subjects	2	9	12
Age Categorical Units: Participants			
< 65	1	7	5
>= 65 AND < 75	1	1	3
>= 75 AND < 85	0	1	4
Age Continuous Units: Years			
arithmetic mean	63	60.3	67.4
standard deviation	± 2.8	± 9.3	± 10.2
Sex: Female, Male Units: Participants			
Female	2	9	12
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	1
White	1	9	11
More than one race	0	0	0
Unknown or Not Reported	1	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	2	2
Not Hispanic or Latino	2	5	7
Unknown or Not Reported	0	2	3

Reporting group values	Total		
Number of subjects	23		
Age Categorical Units: Participants			
< 65	13		
>= 65 AND < 75	5		
>= 75 AND < 85	5		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	23		
Male	0		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	21		
More than one race	0		
Unknown or Not Reported	1		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4		
Not Hispanic or Latino	14		
Unknown or Not Reported	5		

End points

End points reporting groups

Reporting group title	Cohort 1: Dose level 1
Reporting group description:	
Nivolumab: 480 mg every 4 weeks (Q4W) intravenously (IV) Abemaciclib: 150 mg twice daily (BID) per os (by mouth) Anastrozole: 1 mg once daily (QD) per os (by mouth) Participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks)	
Reporting group title	Cohort 2: Dose level 1
Reporting group description:	
Nivolumab: 480 mg every 4 weeks (Q4W) intravenously (IV) Palbociclib: 125 mg once daily (QD) per os (by mouth) for 3 weeks of each cycle (1 week off) Anastrozole: 1 mg once daily (QD) per os (by mouth) Participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks)	
Reporting group title	Cohort 2: Dose level 2
Reporting group description:	
Nivolumab: 480 mg every 4 weeks (Q4W) intravenously (IV) Palbociclib: 100 mg once daily (QD) per os (by mouth) for 3 weeks of each cycle (1 week off) Anastrozole: 1 mg once daily (QD) per os (by mouth) Participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks)	

Primary: The Number of Participants with Dose Limiting Toxicities (DLT) in the Safety Run-in Phase

End point title	The Number of Participants with Dose Limiting Toxicities (DLT) in the Safety Run-in Phase[1]
End point description:	
The number of participants with dose limiting toxicities (DLTs) during the safety run-in phase. DLTS are defined as treatment emergent adverse events (TEAE) graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 that occurs during the first 4 weeks (1 cycle) after treatment. Participants who withdraw from the study during the DLT evaluation period or have received less than 1 dose of nivolumab and 75% of accumulative doses of palbociclib of the cycle for reasons other than a DLT will not be considered as DLT-evaluable participants.	
End point type	Primary
End point timeframe:	
From first dose to 4 weeks after first dose	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only summary statistics planned for this endpoint	

End point values	Cohort 1: Dose level 1	Cohort 2: Dose level 1	Cohort 2: Dose level 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	9	12	
Units: Participants	0	2	0	

Statistical analyses

No statistical analyses for this end point

Primary: Residual Cancer Burden (RCB) 0-1 Rate in the Randomized Phase

End point title	Residual Cancer Burden (RCB) 0-1 Rate in the Randomized

	Phase[2]

End point description:

RCB 0-I rate is defined as the percentage of randomized participants who achieve RCB 0: no residual disease or RCB-I: minimal residual disease. RCB is a continuous index combining pathological measurements of primary tumor (size and cellularity) and nodal metastases (number and size) defined by a point system at surgery.

End point type	Primary

End point timeframe:

From randomization phase up to 5 treatment cycles (up to approximately 20 weeks)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics planned for this endpoint

End point values	Cohort 1: Dose level 1	Cohort 2: Dose level 1	Cohort 2: Dose level 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[3]	0[4]	0[5]	
Units: Percent of Participant				

Notes:

[3] - Trial closed after completion of the Safety Run-in.

[4] - Trial closed after completion of the Safety Run-in.

[5] - Trial closed after completion of the Safety Run-in.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR is defined as the percentage of participants with a best overall response (BOR) of complete response (CR) or partial response (PR) per investigator radiographic assessment. Complete response is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. Partial response (PR) is defines as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

From first dose up to approximately 6 months after first dose

End point values	Cohort 1: Dose level 1	Cohort 2: Dose level 1	Cohort 2: Dose level 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	9	12	
Units: Percentage of Participants				
number (confidence interval 95%)	0.0 (0.0 to 84.2)	66.7 (29.9 to 92.5)	75.0 (42.8 to 94.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Breast Conserving Surgery (BCS) Rate

End point title	Breast Conserving Surgery (BCS) Rate

End point description:

The percentage of participants who undergo breast conserving surgery (BCS) after completing the study treatments. Confidence interval based on the Clopper and Pearson method.

End point type	Secondary

End point timeframe:

From first dose up to approximately 6 months after first dose

End point values	Cohort 1: Dose level 1	Cohort 2: Dose level 1	Cohort 2: Dose level 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	9	12	
Units: Percentage of Participants				
number (confidence interval 95%)	50.0 (1.3 to 98.7)	55.6 (21.2 to 86.3)	50.0 (21.1 to 78.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pathological Complete Response (pCR) Rate

End point title	Pathological Complete Response (pCR) Rate

End point description:

The percentage of participants with an absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy. Confidence interval based on the Clopper and Pearson method.

End point type	Secondary

End point timeframe:

From first dose up to approximately 6 months after first dose

End point values	Cohort 1: Dose level 1	Cohort 2: Dose level 1	Cohort 2: Dose level 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	9	12	
Units: Percentage of Participants				
number (confidence interval 95%)	0.0 (0.0 to 84.2)	0.0 (0.0 to 33.6)	8.3 (0.2 to 38.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Experiencing Adverse Events (AEs)

End point title	The Number of Participants Experiencing Adverse Events (AEs)

End point description:

The number of participants experiencing adverse events (AEs). An AE is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

From first dose to 30 days after last dose of study therapy (up to approximately 6 months)

End point values	Cohort 1: Dose level 1	Cohort 2: Dose level 1	Cohort 2: Dose level 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	9	12	
Units: Participants	2	9	12	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Experiencing Serious Adverse Events (SAEs)

End point title	The Number of Participants Experiencing Serious Adverse Events (SAEs)

End point description:

The number of participants experiencing serious adverse events (SAEs). A SAE is defined as any untoward medical occurrence that, at any dose: results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event.

End point type	Secondary

End point timeframe:

From first dose to 30 days after last dose of study therapy (up to approximately 6 months)

End point values	Cohort 1: Dose level 1	Cohort 2: Dose level 1	Cohort 2: Dose level 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	9	12	
Units: Participants	0	5	2	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Experiencing Adverse Events (AEs) Leading to Discontinuation

End point title	The Number of Participants Experiencing Adverse Events (AEs) Leading to Discontinuation

End point description:

The number of participants experiencing adverse events (AEs) that lead to discontinuation of study treatment. An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

From first dose to 30 days after last dose of study therapy (up to approximately 6 months)

End point values	Cohort 1: Dose level 1	Cohort 2: Dose level 1	Cohort 2: Dose level 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	9	12	
Units: Participants	0	5	4	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Experiencing Immune-Related Adverse Events (AEs)

End point title	The Number of Participants Experiencing Immune-Related Adverse Events (AEs)

End point description:

The number of participants experiencing adverse events that are immune-related. An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

From first dose to 100 days after last dose of study therapy (up to approximately 8 months)

End point values	Cohort 1: Dose level 1	Cohort 2: Dose level 1	Cohort 2: Dose level 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	9	12	
Units: Participants				
Hypothyroidism	1	0	0	
Hyperthyroidism	0	0	1	

Immune-mediated lung disease	0	1	0	
Pneumonitis	0	0	1	
Hepatitis	0	3	2	
Rash	0	2	0	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Deaths

End point title	The Number of Participants Deaths

End point description:

The number of participants that have died during the study.

End point type	Secondary

End point timeframe:

From first dose up to approximately 8 months

End point values	Cohort 1: Dose level 1	Cohort 2: Dose level 1	Cohort 2: Dose level 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	9	12	
Units: Participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Experiencing Laboratory Abnormalities in Specific Thyroid Tests - SI Units

End point title	The Number of Participants Experiencing Laboratory Abnormalities in Specific Thyroid Tests - SI Units

End point description:

The number of participants with laboratory abnormalities in specific thyroid tests based on SI conventional units.

TSH = Thyroid Stimulating Hormone LLN = Lower Limit of Normal ULN = Upper Limit of Normal

End point type	Secondary

End point timeframe:

From first dose to 30 days after last dose of study therapy (up to approximately 6 months)

End point values	Cohort 1: Dose level 1	Cohort 2: Dose level 1	Cohort 2: Dose level 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	9	12	
Units: Participants				
TSH > ULN	1	3	2	
TSH > ULN WITH TSH <= ULN AT BASELINE	1	2	1	
TSH >ULN WITH ATLEAST ONE FT3/FT4 TEST VALUE <LLN	0	1	2	
TSH >ULN WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN	0	2	2	
TSH > ULN WITH FT3/FT4 TEST MISSING	1	0	0	
TSH < LLN	0	3	4	
TSH <LLN WITH TSH >= LLN AT BASELINE	0	2	4	
TSH <LLN WITH ATLEAST ONE FT3/FT4 TEST VALUE > ULN	0	1	1	
TSH <LLN WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN	0	1	3	
TSH < LLN WITH FT3/FT4 TEST MISSING	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Experiencing Laboratory Abnormalities in Specific Liver Tests

End point title	The Number of Participants Experiencing Laboratory Abnormalities in Specific Liver Tests

End point description:

The number of participants with laboratory abnormalities in specific liver tests based on SI conventional units.

ALT = Alanine Aminotransferase AST = Aspartate Aminotransferase ULN = Upper Limit of Normal

End point type	Secondary

End point timeframe:

From first dose to 30 days after last dose of study therapy (up to approximately 6 months)

End point values	Cohort 1: Dose level 1	Cohort 2: Dose level 1	Cohort 2: Dose level 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	9	12	
Units: Participants				
ALT OR AST > 3XULN	0	4	3	
ALT OR AST > 5XULN	0	3	3	
ALT OR AST > 10XULN	0	2	2	
ALT OR AST > 20XULN	0	1	2	
TOTAL BILIRUBIN > 2XULN	0	0	0	

ALP > 1.5XULN	0	3	1	
ALT/AST ELEV>3XULN;TOTAL BILIRUBIN>1.5XULN-1 DAY	0	1	1	
ALT/AST ELEV>3XULN;TOTAL BILIRUBIN>1.5XULN-30 DAYS	0	1	1	
ALT/AST ELEV>3XULN;TOTAL BILIRUBIN>2XULN-1 DAY	0	0	0	
ALT/AST ELEV>3XULN;TOTAL BILIRUBIN>2XULN-30 DAYS	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs assessed from first dose to 100 days after last dose (up to 8 months). SAEs assessed from first dose to 30 days after last dose (Up to 6 months). All-Cause Mortality assessed from first dose to study completion (up to 21 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Cohort 1: Dose level 1

Reporting group description:

Nivolumab: 480 mg every 4 weeks (Q4W) intravenously (IV) Abemaciclib: 150 mg twice daily (BID) per os (by mouth) Anastrozole: 1 mg once daily (QD) per os (by mouth) Participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks)

Reporting group title	Cohort 2: Dose level 2

Reporting group description:

Nivolumab: 480 mg every 4 weeks (Q4W) intravenously (IV) Palbociclib: 100 mg once daily (QD) per os (by mouth) for 3 weeks of each cycle (1 week off) Anastrozole: 1 mg once daily (QD) per os (by mouth) Participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks)

Reporting group title	Cohort 2: Dose level 1

Reporting group description:

Nivolumab: 480 mg every 4 weeks (Q4W) intravenously (IV) Palbociclib: 125 mg once daily (QD) per os (by mouth) for 3 weeks of each cycle (1 week off) Anastrozole: 1 mg once daily (QD) per os (by mouth) Participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks)

Serious adverse events	Cohort 1: Dose level 1	Cohort 2: Dose level 2	Cohort 2: Dose level 1
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	3 / 12 (25.00%)	5 / 9 (55.56%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and			

unspecified (incl cysts and polyps)			
Second primary malignancy			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (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			
Atrial fibrillation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
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			
Hepatitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (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
Immune-mediated lung disease			

subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
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	Cohort 1: Dose level 1	Cohort 2: Dose level 2	Cohort 2: Dose level 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	12 / 12 (100.00%)	8 / 9 (88.89%)
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hot flush			
subjects affected / exposed	0 / 2 (0.00%)	2 / 12 (16.67%)	2 / 9 (22.22%)
occurrences (all)	0	2	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 2 (0.00%)	4 / 12 (33.33%)	0 / 9 (0.00%)
occurrences (all)	0	4	0
Axillary pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Fatigue			
subjects affected / exposed	1 / 2 (50.00%)	5 / 12 (41.67%)	2 / 9 (22.22%)
occurrences (all)	1	8	2
Mucosal inflammation			
subjects affected / exposed	0 / 2 (0.00%)	2 / 12 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			

subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Xerosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Dyspnoea			
subjects affected / exposed	0 / 2 (0.00%)	2 / 12 (16.67%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Pneumonitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Investigations			
Amylase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 12 (16.67%)	4 / 9 (44.44%)
occurrences (all)	0	2	4

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 12 (16.67%)	4 / 9 (44.44%)
occurrences (all)	0	2	4
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood bilirubin increased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 12 (16.67%)	1 / 9 (11.11%)
occurrences (all)	0	3	1
Blood creatinine increased			
subjects affected / exposed	0 / 2 (0.00%)	2 / 12 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Lymphocyte count decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Neutrophil count decreased			
subjects affected / exposed	0 / 2 (0.00%)	5 / 12 (41.67%)	1 / 9 (11.11%)
occurrences (all)	0	8	2
Platelet count decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	3	1
Transaminases increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
White blood cell count decreased			
subjects affected / exposed	0 / 2 (0.00%)	3 / 12 (25.00%)	2 / 9 (22.22%)
occurrences (all)	0	3	4
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Radiation skin injury			

subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Vascular access site pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Dysgeusia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Sinus headache			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	2 / 9 (22.22%)
occurrences (all)	0	1	3
Leukopenia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 12 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Macrocytosis			

subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Neutropenia			
subjects affected / exposed	0 / 2 (0.00%)	3 / 12 (25.00%)	3 / 9 (33.33%)
occurrences (all)	0	3	4
Thrombocytopenia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Thrombocytosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Ocular discomfort			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	1 / 2 (50.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 2 (50.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Diarrhoea			
subjects affected / exposed	1 / 2 (50.00%)	1 / 12 (8.33%)	2 / 9 (22.22%)
occurrences (all)	1	1	2
Dyspepsia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 12 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Nausea			

subjects affected / exposed	1 / 2 (50.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Odynophagia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 2 (50.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Stomatitis			
subjects affected / exposed	0 / 2 (0.00%)	2 / 12 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Oral pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 12 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Eczema			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	2 / 2 (100.00%)	3 / 12 (25.00%)	1 / 9 (11.11%)
occurrences (all)	2	3	1
Rash			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	1 / 2 (50.00%)	1 / 12 (8.33%)	3 / 9 (33.33%)
occurrences (all)	1	1	4
Skin toxicity			

subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Rash pruritic			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hypothyroidism			
subjects affected / exposed	1 / 2 (50.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 2 (50.00%)	2 / 12 (16.67%)	0 / 9 (0.00%)
occurrences (all)	1	2	0
Back pain			
subjects affected / exposed	0 / 2 (0.00%)	2 / 12 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Bone pain			
subjects affected / exposed	1 / 2 (50.00%)	0 / 12 (0.00%)	2 / 9 (22.22%)
occurrences (all)	1	0	2
Muscle spasms			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Musculoskeletal pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Infections and infestations			

COVID-19			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Diverticulitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 2 (50.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 2 (50.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 12 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	1 / 2 (50.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	1	2	0
Hypomagnesaemia			

subjects affected / exposed	0 / 2 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hyponatraemia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 12 (16.67%)	0 / 9 (0.00%)
occurrences (all)	0	3	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2019	Decreased and clarified the frequency of assessments and sample collections, clarified participant eligibility and stratification, and reduced the dose-limiting toxicity period.
24 July 2019	Added men, additional dose-limiting toxicity (DLT) criteria, and early study termination criteria. Updated definition of DLT, inclusion/exclusion criteria, and dose modifications.
13 May 2020	Closed the abemaciclib safety run-in Cohort 1 and removed the abemaciclib-containing combinations from the randomization phase.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Enrollment/dosing in Cohort 1 was discontinued due to risk of serious interstitial lung disease/pneumonitis in patients receiving abemaciclib with pembrolizumab. The trial closed after completion of the Safety Run-in.

Notes: