Clinical trial results:
A multicenter phase II trial to evaluate the efficacy and safety of pembrolizumab and gemcitabine in patients with HER2-negative Advanced Breast Cancer (ABC). “PANGEA-Breast”

Summary

EudraCT number	2016-001779-54
Trial protocol	ES
Global end of trial date	

Results information

Result version number	v2
This version publication date	28 April 2022
First version publication date	18 March 2022
Version creation reason	• Correction of full data set AEs data correction

Trial information

Trial identification

Sponsor protocol code	GEICAM/2015-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03025880
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GEICAM (FUNDACIÓN GRUPO ESPAÑOL DE INVESTIGACIÓN EN CÁNCER DE MAMA)
Sponsor organisation address	Avenida de los Pirineos 7, San Sebastián de los Reyes / Madrid, Spain, 28703
Public contact	Clinical Operations Department, GEICAM (Fundación Grupo Español de Investigación en Cáncer de Mama), +34 916592870, inicio_ensayos@geicam.org
Scientific contact	Clinical Operations Department, GEICAM (Fundación Grupo Español de Investigación en Cáncer de Mama), +34 916592870, inicio_ensayos@geicam.org

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	03 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Run-in-phase: To determine the Recommended Phase II Dose (RP2D) of gemcitabine in combination with fixed doses of pembrolizumab.
Phase II: To assess the efficacy of pembrolizumab in combination with gemcitabine in terms of Objective Response Rate (ORR) in patients with HER2-negative ABC.

Protection of trial subjects:

Not applicable. It was not necessary to applied extra measures for protection of the subjects out of the good clinical practice environment.

Background therapy:

Available data support the hypothesis of an immune mediated antitumor activity in breast carcinoma, and several lines of research are ongoing. It is critical to understand what happens in the tumoral microenvironment in order to design biological agents and approaches that might modulate the immune response towards cancer cell destruction. At this point and due to new knowledge emerged with immune checkpoints function at immune synapses, combinatorial schedules seem to be a promising strategy. In this sense, combining chemotherapy and immunotherapy is an interesting approach in chemo-sensitive diseases that will eventually synergize and reach meaningful clinical results.
Gemcitabine is a cytotoxic drug with well-known immunostimulatory properties that include increasing antigen (neoantigens) threshold and cross-presentation (via APCs), with enhancement of T-cell response and generation of memory T cells. In addition, gemcitabine has demonstrated the ability to restore immune surveillance by reducing myeloid derived suppressor cells (MDSC) levels in murine models. Furthermore, gemcitabine-based schedules have demonstrated clinical activity in breast cancer.
Pembrolizumab is a human programmed death receptor-1 (PD-1)-blocking antibody that has gained Food and Drug Administration (FDA) approval for the
treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab treatment.
In our opinion, there is sufficient evidence to consider that advanced breast carcinoma may be sensitive to immunotherapeutic approaches. Our proposal is based on a combination strategy with two immunostimulatory agents: gemcitabine (immunogenic apoptosis and elimination of MDSC) and pembrolizumab (blocking PD1/PD-L1 interaction) in advanced breast carcinoma (ABC) that may synergize and induce responses with long term clinical benefit.

Evidence for comparator: -

Actual start date of recruitment	28 June 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	100 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	33
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From June 2017 to May 2018, 36 patients were recruited in nine Spanish sites for the first stage of the Simon minimax two-stage design, but only 5 patients presented a response, so recruitment was stopped permanently

Pre-assignment

Screening details:

From June 2017 to May 2018, 36 patients were recruited in nine Spanish sites for the first stage of the Simon minimax two-stage design, but only 5 patients presented a response, so recruitment was stopped permanently

Period 1

Period 1 title	Overall trial (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	Run-in Phase Dose Level 0

Arm description:

Eligible patients were enrolled and treated with Pembrolizumab at a dose of 200mg as an intravenous (IV) infusion on day 1 of each 21-day cycle in combination with Gemcitabine at a dose of 1,250mg/m2 (Dose Level 0) or 1,000mg/m2 (Dose Level -1) as a IV infusion on day 1 and 8 of each 21-day cycle. Treatment will be repeated on day 1 of each 21-day cycle until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first.
An initial exploratory run-in-phase will be performed to test the safety of the combination and determine the Recommended Phase II Dose (RP2D) of Gemcitabine in combination with fixed doses of Pembrolizumab .

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

Dosage and administration details:

Pembrolizumab at a dose of 200mg as an intravenous (IV) 30 minutes infusion on day 1 of each 21-day cycle. Treatment will be repeated on day 1 of each 21-day cycle until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first. Patients completing 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication will stop pembrolizumab treatment (though may continue with gemcitabine). Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional pembrolizumab treatment if they progress after stopping it.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	Gemzar
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine at a dose of 1,250mg/m2 as an intravenous (IV) 60 minutes infusion on day 1 and 8 of each 21-day cycle. Treatment will be repeated on day 1 of each 21-day cycle until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first.

Arm title	Phase II

Arm description:

Eligible patients were enrolled and treated with Pembrolizumab (P) at a dose of 200mg as an intravenous (IV) infusion on day 1 of each 21-day cycle in combination with Gemcitabine (G) at a dose of 1,250mg/m2 (Recommended Phase II Dose (RP2D) from the run-in phase) as a IV infusion on day 1 and 8 of each 21-day cycle.
Treatment will be repeated on day 1 of each 21-day cycle until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first.

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

Dosage and administration details:

Pembrolizumab at a dose of 200mg as an intravenous (IV) 30 minutes infusion on day 1 of each 21-day cycle. Treatment will be repeated on day 1 of each 21-day cycle until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first. Patients completing 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication will stop pembrolizumab treatment (though may continue with gemcitabine). Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional pembrolizumab treatment if they progress after stopping it.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	Gemzar
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine at a dose of 1,250mg/m2 as an intravenous (IV) 60 minutes infusion on day 1 and 8 of each 21-day cycle. Treatment will be repeated on day 1 of each 21-day cycle until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first.

Number of subjects in period 1	Run-in Phase Dose Level 0	Phase II
Started	14	22
Completed	12	19
Not completed	2	3
Adverse event, serious fatal	1	1
Consent withdrawn by subject	-	1
Physician decision	-	1
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups

Reporting group title	Run-in Phase Dose Level 0

Reporting group description:

Eligible patients were enrolled and treated with Pembrolizumab at a dose of 200mg as an intravenous (IV) infusion on day 1 of each 21-day cycle in combination with Gemcitabine at a dose of 1,250mg/m2 (Dose Level 0) or 1,000mg/m2 (Dose Level -1) as a IV infusion on day 1 and 8 of each 21-day cycle. Treatment will be repeated on day 1 of each 21-day cycle until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first.
An initial exploratory run-in-phase will be performed to test the safety of the combination and determine the Recommended Phase II Dose (RP2D) of Gemcitabine in combination with fixed doses of Pembrolizumab .

Reporting group title	Phase II

Reporting group description:

Eligible patients were enrolled and treated with Pembrolizumab (P) at a dose of 200mg as an intravenous (IV) infusion on day 1 of each 21-day cycle in combination with Gemcitabine (G) at a dose of 1,250mg/m2 (Recommended Phase II Dose (RP2D) from the run-in phase) as a IV infusion on day 1 and 8 of each 21-day cycle.
Treatment will be repeated on day 1 of each 21-day cycle until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first.

Reporting group values	Run-in Phase Dose Level 0	Phase II	Total
Number of subjects	14	22	36
Age categorical Units: Subjects			
Adults (18-64 years)	14	19	33
From 65-84 years	0	3	3
Age continuous Units: years			
median	48.5	56	
full range (min-max)	32 to 61	31 to 77	-
Gender categorical Units: Subjects			
Female	14	22	36
Male	0	0	0
Race Units: Subjects			
White	14	22	36
Menopause Status Units: Subjects			
Postmenopausal	10	16	26
Premenopausal	4	6	10
Eastern Cooperative Oncology Group (ECOG) status			

ECOG score runs from 0 to 5, with 0 denoting perfect health and 5 death.
0 - Asymptomatic
1 - Symptomatic but completely ambulatory
2 - Symptomatic, <50% in bed during the day
3 - Symptomatic, >50% in bed, but not bedbound
4 - Bedbound
5 - Death

Units: Subjects			
ECOG 0	7	16	23
ECOG 1	6	6	12
ECOG 2	1	0	1
Type of Disease for Cohort Purposes			
Luminal A: estrogen-receptor (ER) and/or progesterone-receptor (PR) positive, Human Epidermal Growth Factor Receptor 2 (HER2) negative, low levels of Ki67. Luminal A are low-grade, tend to grow slowly and have the best prognosis. Luminal B: ER and/or PR positive, and HER2 positive or HER2 negative with high levels of Ki67. Luminal B grow faster than luminal A and their prognosis is worse. Triple-negative (TN): negative for ER, PR, and HER2. Is more aggressive and have poorer prognosis than Luminal due to there are fewer targeted medicines that treat TN.			
Units: Subjects			
Triple negative	9	12	21
Luminal A+B	5	10	15
Ki67 cut off 20%			
Ki67 is a protein found in the nucleus of cells when they divide. Ki67 determines the proliferation rate. Tumors with high proliferation rates (> 20%) have a worse prognosis.			
Units: Subjects			
Ki67 < 20%	1	4	5
Ki67 >= 20	8	13	21
Ki67 not available or not done	5	5	10
Histopathologic Type Units: Subjects			
Ductal	13	20	33
Lobular	1	1	2
Other: Squamous Invasive Cancer	0	1	1
Histologic Grade			
Cancer cells are given a Grade (G) when they are removed from the breast and checked under a microscope. The G is based on how much the cancer cells look like normal cells. G1 or well differentiated (score 3, 4, or 5): cells are slower-growing, and look more like normal breast tissue. G2 or moderately differentiated (score 6, 7): cells are growing at a speed of and look like cells somewhere between G1 and 3. G3 or poorly differentiated (score 8, 9): cells look very different from normal and will probably grow and spread faster.			
Units: Subjects			
Grade 1	0	1	1
Grade 2	4	10	14
Grade 3	6	10	16
Unknown	1	0	1
Not done	3	1	4

End points

End points reporting groups

Reporting group title	Run-in Phase Dose Level 0

Reporting group description:

Eligible patients were enrolled and treated with Pembrolizumab at a dose of 200mg as an intravenous (IV) infusion on day 1 of each 21-day cycle in combination with Gemcitabine at a dose of 1,250mg/m2 (Dose Level 0) or 1,000mg/m2 (Dose Level -1) as a IV infusion on day 1 and 8 of each 21-day cycle. Treatment will be repeated on day 1 of each 21-day cycle until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first.
An initial exploratory run-in-phase will be performed to test the safety of the combination and determine the Recommended Phase II Dose (RP2D) of Gemcitabine in combination with fixed doses of Pembrolizumab .

Reporting group title	Phase II

Reporting group description:

Eligible patients were enrolled and treated with Pembrolizumab (P) at a dose of 200mg as an intravenous (IV) infusion on day 1 of each 21-day cycle in combination with Gemcitabine (G) at a dose of 1,250mg/m2 (Recommended Phase II Dose (RP2D) from the run-in phase) as a IV infusion on day 1 and 8 of each 21-day cycle.
Treatment will be repeated on day 1 of each 21-day cycle until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first.

Primary: Incidence rate of Dose Limiting Toxicity (DLT)

End point title	Incidence rate of Dose Limiting Toxicity (DLT)[1]

End point description:

DLT was defined as the occurrence of any of the following adverse events (AE) or abnormal laboratory value (graded according to the NCI Common Terminology Criteria for AE (CTCAE) version 4.0), assessed as possibly, probably or definitively related to study drug/medication, occurring within the first cycle of study treatment: any Grade 4 thrombocytopenia or neutropenia lasting > 7 days; episcleritis, uveitis, or iritis of Grade 2 or higher, any Grade 4 toxicity, any Grade 3 toxicity EXCLUDING: nausea, vomiting, or diarrhea controlled by medical intervention within 72 hours, grade 3 rash in the absence of desquamation, no mucosal involvement, does not require steroids, and resolves to Grade 1 by the next scheduled dose of pembrolizumab, transient Grade 3 Aspartate Transaminase (AST) or Alanine Transaminase (ALT) elevation, defined as no more than 3 days with or without steroid use, discontinuation or delay of more than 2 weeks of any study drug/medication due to treatment-related AE.

End point type	Primary

End point timeframe:

Up to cycle 1

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: No statistical analyses for this end point

End point values	Run-in Phase Dose Level 0	Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	22		
Units: Events	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: The Recommended Phase II Dose (RP2D) of gemcitabine

End point title	The Recommended Phase II Dose (RP2D) of gemcitabine[2][3]

End point description:

Up to cycle 1

End point type	Primary

End point timeframe:

The RP2D was decided by the internal committee taken into consideration the information obtained in the study and based on the number of DLT.

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: No statistical analyses for this end point

[3] - 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 statistical analyses for this end point

End point values	Run-in Phase Dose Level 0			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: mg/m2	1250			

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Tumor response was assessed using Response Evaluation Criteria In Solid Tumors Criteria (RECIST 1.1). ORR is defined as the percentage of patients with a Complete Response (CR) or Partial Response (PR) out of the patients from the efficacy population. Per RECIST, CR is defined as the disappearance of all target lesions; PR is defined as an >=30% decrease in the sum of the longest diameter of target lesions.

End point type	Primary

End point timeframe:

Through study treatment, and average of 3 months

End point values	Run-in Phase Dose Level 0	Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	20		
Units: Participants	0	5		

Statistical analyses

Statistical analysis title	ORR analysis
Comparison groups	Run-in Phase Dose Level 0 v Phase II
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	percentage
Point estimate	25
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.7
upper limit	49.1

Notes:

[4] - The rate of OR and confidence interval

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

Tumor response was assessed using Response Evaluation Criteria In Solid Tumors Criteria (RECIST 1.1). PFS is defined as the time from enrollment to the first documented progression disease (PD), or death from any cause, whichever occurs first. PD is defined using RECIST, as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions

End point type	Secondary

End point timeframe:

Through study treatment, and average of 3 months

End point values	Run-in Phase Dose Level 0	Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	20		
Units: Months				
median (confidence interval 95%)	3.1 (0.9 to 5.4)	2.6 (1.9 to 6.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

Tumor response was assessed using Response Evaluation Criteria In Solid Tumors Criteria (RECIST 1.1) criteria. CBR was defined as the percentage of patients with a Complete Response (CR) or Partial Response (PR) plus stable disease (SD) out of the efficacy population. Per RECIST, CR is defined as the disappearance of all target lesions; PR is defined as an >=30% decrease in the sum of the longest diameter of target lesions; SD is defined as a failure to meet criteria for CR or PR in the absence of progressive disease. Overall Response (OR) = CR + PR.

End point type	Secondary

End point timeframe:

Through study treatment, and average of 3 months

End point values	Run-in Phase Dose Level 0	Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	20		
Units: Events	7	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) at Least 24 Weeks

End point title	Clinical Benefit Rate (CBR) at Least 24 Weeks

End point description:

Tumor response was assessed using Response Evaluation Criteria In Solid Tumors Criteria (RECIST 1.1) criteria. CBR was defined as the percentage of patients with a Complete Response (CR) or Partial Response (PR) plus stable disease (SD) lasting at least 24 months out of the efficacy population. Per RECIST, CR is defined as the disappearance of all target lesions; PR is defined as an >=30% decrease in the sum of the longest diameter of target lesions; SD is defined as a failure to meet criteria for CR or PR in the absence of progressive disease lasting at least 24 months. Overall Response (OR) = CR + PR.

End point type	Secondary

End point timeframe:

24 Weeks

End point values	Run-in Phase Dose Level 0	Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	20		
Units: Events	1	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Response Duration (RD)

End point title	Response Duration (RD)

End point description:

Tumor response was assessed using Response Evaluation Criteria In Solid Tumors Criteria (RECIST 1.1) criteria. RD was defined as the time from the first documentation of objective tumor response (complete response (CR) or partial response (PR)) to the first documented progressive disease (PD), or to death due to any cause, whichever occurs first. Per RECIST, CR is defined as the disappearance of all target lesions; PR is defined as an >=30% decrease in the sum of the longest diameter of target lesions; PD is defined as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions

End point type	Secondary

End point timeframe:

Through study treatment, and average of 3 months

End point values	Run-in Phase Dose Level 0	Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[5]	22[6]		
Units: Months				
median (confidence interval 95%)	0 (0 to 0)	4.3 (2.3 to 7.4)		

Notes:

[5] - No patients from Run-in phase have complete partial or complete response.

[6] - 5 patients from phase II have complete partial or complete response.

Statistical analyses

Statistical analysis title	RD analysis
Comparison groups	Phase II v Run-in Phase Dose Level 0
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	survival median
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.3
upper limit	10.3

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from the date of enrollment to the date of death from any cause.

End point type	Secondary

End point timeframe:

Through study

End point values	Run-in Phase Dose Level 0	Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	20		
Units: Months				
median (confidence interval 95%)	6.1 (1.3 to 11.7)	10.1 (7.3 to 17.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE were reported after Informed Consent Document (ICD) and before study drugs until approximately 30 days following the discontinuation of study treatment

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Phase II

Reporting group description:

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Treatment will be repeated on day 1 of each 21-day cycle until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first.

Reporting group title	Run-in Phase Dose Level 0

Reporting group description:

Eligible patients were enrolled and treated with Pembrolizumab at a dose of 200mg as an intravenous (IV) infusion on day 1 of each 21-day cycle in combination with Gemcitabine at a dose of 1,250mg/m2 (Dose Level 0) or 1,000mg/m2 (Dose Level -1) as a IV infusion on day 1 and 8 of each 21-day cycle.
Treatment will be repeated on day 1 of each 21-day cycle until objective disease progression, clinical progression (under investigator criteria), unacceptable toxicity, death or withdrawal of consent, whichever occurs first.
An initial exploratory run-in-phase will be performed to test the safety of the combination and determine the Recommended Phase II Dose (RP2D) of Gemcitabine in combination with fixed doses of Pembrolizumab .

Serious adverse events	Phase II	Run-in Phase Dose Level 0	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 22 (18.18%)	8 / 14 (57.14%)	
number of deaths (all causes)	11	11	
number of deaths resulting from adverse events	0	0	
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 22 (0.00%)	2 / 14 (14.29%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte count decreased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neurological decompensation			
subjects affected / exposed	1 / 22 (4.55%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 14 (14.29%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			

subjects affected / exposed	1 / 22 (4.55%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 22 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 22 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 22 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bacterial pyelonephritis			

subjects affected / exposed	0 / 22 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Phase II	Run-in Phase Dose Level 0	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 22 (95.45%)	14 / 14 (100.00%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	2 / 22 (9.09%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Hypertension			
subjects affected / exposed	0 / 22 (0.00%)	4 / 14 (28.57%)	
occurrences (all)	0	7	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 22 (63.64%)	7 / 14 (50.00%)	
occurrences (all)	21	9	
Pyrexia			
subjects affected / exposed	6 / 22 (27.27%)	4 / 14 (28.57%)	
occurrences (all)	7	8	
Fatigue			
subjects affected / exposed	2 / 22 (9.09%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Pain			

subjects affected / exposed	0 / 22 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 22 (9.09%)	1 / 14 (7.14%)	
occurrences (all)	3	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 22 (4.55%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	15 / 22 (68.18%)	7 / 14 (50.00%)	
occurrences (all)	28	53	
Platelet count decreased			
subjects affected / exposed	11 / 22 (50.00%)	8 / 14 (57.14%)	
occurrences (all)	18	19	
Alanine aminotransferase increased			
subjects affected / exposed	11 / 22 (50.00%)	9 / 14 (64.29%)	
occurrences (all)	33	24	
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 22 (59.09%)	9 / 14 (64.29%)	
occurrences (all)	34	30	
Lymphocyte count decreased			
subjects affected / exposed	12 / 22 (54.55%)	13 / 14 (92.86%)	
occurrences (all)	89	101	
White blood cell count decreased			
subjects affected / exposed	18 / 22 (81.82%)	11 / 14 (78.57%)	
occurrences (all)	68	82	
Alkaline phosphatase increased			
subjects affected / exposed	10 / 22 (45.45%)	14 / 14 (100.00%)	
occurrences (all)	46	51	
INR increased			
subjects affected / exposed	2 / 22 (9.09%)	8 / 14 (57.14%)	
occurrences (all)	5	33	
Blood bilirubin increased			

subjects affected / exposed	2 / 22 (9.09%)	2 / 14 (14.29%)	
occurrences (all)	4	3	
Lymphocyte count increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
Weight decreased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 22 (9.09%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 22 (95.45%)	13 / 14 (92.86%)	
occurrences (all)	218	136	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 22 (27.27%)	2 / 14 (14.29%)	
occurrences (all)	7	4	
Diarrhoea			
subjects affected / exposed	2 / 22 (9.09%)	2 / 14 (14.29%)	
occurrences (all)	3	11	
Vomiting			
subjects affected / exposed	2 / 22 (9.09%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	1 / 22 (4.55%)	3 / 14 (21.43%)	
occurrences (all)	2	3	
Abdominal pain upper			
subjects affected / exposed	0 / 22 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	2 / 22 (9.09%)	1 / 14 (7.14%)	
occurrences (all)	3	2	
Pain of skin			
subjects affected / exposed	1 / 22 (4.55%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Pruritus			
subjects affected / exposed	0 / 22 (0.00%)	3 / 14 (21.43%)	
occurrences (all)	0	3	
Alopecia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Albuminuria			
subjects affected / exposed	0 / 22 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 22 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 14 (0.00%)	
occurrences (all)	3	0	
Back pain			
subjects affected / exposed	2 / 22 (9.09%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 22 (4.55%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 22 (4.55%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	3 / 22 (13.64%)	2 / 14 (14.29%)	
occurrences (all)	3	2	
Hypoalbuminemia			
subjects affected / exposed	10 / 22 (45.45%)	9 / 14 (64.29%)	
occurrences (all)	30	21	
Hyperglycemia			
subjects affected / exposed	7 / 22 (31.82%)	4 / 14 (28.57%)	
occurrences (all)	15	23	
Hypoglycemia			
subjects affected / exposed	3 / 22 (13.64%)	2 / 14 (14.29%)	
occurrences (all)	6	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2017	• Add inclusion criterion number 6 to be able to perform a biopsy in the inclusion and in the progression (if possible), for which the tumor lesions are to be biopsible. • Modify in the inclusion criteria number 8, the alkaline phosphatase limit for patients with hepatic, bone or disease metastases. • Update the information described in the biomarker analyses. • Update the information on the preparation of pembrolizumab, since before it contained the preparation of pembrolizumab in lyophilized powder, but the pembrolizumab used in this study was in solution. • Change the population by protocol for population effectiveness and clarify its definition. • Add the definition of what is considered an overdose of Gemcitabine. • Update the schedule of visits to be able to clarify if you have to recalculate the dose of gemcitabine and do not have to repeat the baseline analyses if you have done them in the 7 days before the 1 day 1 cycle. • Minor typographic changes
27 November 2017	• Add the possibility of analysing FT3 instead of only T3 • Minor typographic errors
19 March 2018	• Update the security changes collected in the new version of the Investigator Brochure v. 15 both in the protocol, updating the dose adjustment table of the pembrolizumab, as in the Informed Consent, updating the section of side effects. This new version of Consent Informed had to be signed only by new patients. • Modify inclusion criteria number 7 to restrict the inclusion of patients to those that present a functional status according to the ECOG scale of 0 or 1. • Add to the inclusion criteria number 9 a maximum number of previous lines of Chemotherapy for treatment of ABC. These two criteria are modified by their negative influence on the clinical evolution of patients impacting on the likelihood of them obtaining a benefit from the administration of treatment of the study, and therefore, in that it can carry out an adequate evaluation of the anti-tumor activity of this combination of drugs in the population in study. • Update the information on the administration of gemcitabine, as before the administration was shown in 60 minutes, but in the summary product characteristics (SmPC) is 30 minutes. • The dose adjustment section of gemcitabine has been updated to collect the assumption that there has been hematological toxicity in the previous cycle that has caused the omission of the dose of day 8. • Update the visits schedule to clarify that the peripheral blood sample which is to be taken in the end-of-treatment visit is in the case of discontinuation of pembrolizumab. • Minor typographic changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

17 April 2018	Per protocol, a Simon minimax two-stage design was employed with the possibility of stopping early due to lack of response. Per this Simon design, the first stage included 31 evaluable patients, if at least 7 presented a response, recruitment will continue to include the 53 evaluable patients. The study was interrupted on 17-Apr-2018 as per Simon minimax two-stage design, when 33 evaluable patients were included and then the recruitment was stopped. Only 5 presented a response, so recruitment was permanently stopped.	-

Notes:

Limitations and caveats

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

Patients included were heavily pretreated in most of the cases with a median of 4 previous lines. There were no patient preselection with respect to their PD-L1 positivity or TILs density, wich is an adverse scenario for immunotherapy .

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34771596