



## 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). “PANGAEA-Breast”**

### Summary

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

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1            |
| This version publication date  | 18 March 2022 |
| First version publication date | 18 March 2022 |

### 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:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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                       |
| <b>Arm title</b>             | 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/m<sup>2</sup> (Dose Level 0) or 1,000mg/m<sup>2</sup> (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/m<sup>2</sup> 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.

|                  |          |
|------------------|----------|
| <b>Arm title</b> | 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/m<sup>2</sup> (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/m<sup>2</sup> 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.

| <b>Number of subjects in period 1</b> | 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/m<sup>2</sup> (Dose Level 0) or 1,000mg/m<sup>2</sup> (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/m<sup>2</sup> (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.<br>0 - Asymptomatic<br>1 - Symptomatic but completely ambulatory<br>2 - Symptomatic, <50% in bed during the day<br>3 - Symptomatic, >50% in bed, but not bedbound<br>4 - Bedbound<br>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  |    |    |    |
| <p>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.</p> <p>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.</p> <p>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.</p> |    |    |    |
| Units: Subjects  |    |    |    |
| Triple negative  | 9  | 12 | 21 |
| Luminal A+B  | 5  | 10 | 15 |
| Ki67 cut off 20%   |    |    |    |
| <p>Ki67 is a protein found in the nucleus of cells when they divide. Ki67 determines the proliferation rate. Tumors with high proliferation rates (&gt; 20%) have a worse prognosis.</p>   |    |    |    |
| 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   |    |    |    |
| <p>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.</p> <p>G1 or well differentiated (score 3, 4, or 5): cells are slower-growing, and look more like normal breast tissue.</p> <p>G2 or moderately differentiated (score 6, 7): cells are growing at a speed of and look like cells somewhere between G1 and 3.</p> <p>G3 or poorly differentiated (score 8, 9): cells look very different from normal and will probably grow and spread faster.</p>                    |    |    |    |
| 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/m<sup>2</sup> (Dose Level 0) or 1,000mg/m<sup>2</sup> (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/m<sup>2</sup> (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) <sup>[1]</sup> |
|-----------------|---|

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 have been performed as only one patient experienced a DLT.

| 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 <sup>[2]</sup> <sup>[3]</sup> |
|-----------------|---|

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: RP2D of Gemcitabine in Combination With Pembrolizumab was calculated as follows: The RP2D was decided by the internal committee taken into consideration the information obtained in the study and based on the number of DLT.

[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: RP2D of Gemcitabine in Combination With Pembrolizumab was calculated as follows: The RP2D was decided by the internal committee taken into consideration the information obtained in the study and based on the number of DLT. Also, RP2D is only measured in the Run-in Phase a per protocol.

|                             |                              |  |  |  |
|-----------------------------|------------------------------|--|--|--|
| End point values            | Run-in Phase<br>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  $\geq 30\%$  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<br>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 <sup>[4]</sup>                 |
| 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<br>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  $\geq 30\%$  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<br>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  $\geq 30\%$  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<br>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  $\geq 30\%$  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<br>Dose Level 0 | Phase II          |  |  |
|----------------------------------|------------------------------|-------------------|--|--|
| Subject group type               | Reporting group              | Reporting group   |  |  |
| Number of subjects analysed      | 14 <sup>[5]</sup>            | 22 <sup>[6]</sup> |  |  |
| 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 |
|----------------|-----------|

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End point timeframe:

Through study

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| <b>End point values</b>          | Run-in Phase<br>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<br>11.7)         | 10.1 (7.3 to<br>17.7) |  |  |

### **Statistical analyses**

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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 | 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/m<sup>2</sup> (Dose Level 0) or 1,000mg/m<sup>2</sup> (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/m<sup>2</sup> (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.

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

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

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



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

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

| <b>Non-serious adverse events</b>                     | Run-in Phase Dose Level 0 | Phase II         |  |
|---|---------------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                           |                  |  |
| subjects affected / exposed                           | 8 / 14 (57.14%)           | 17 / 22 (77.27%) |  |
| Investigations  |                           |                  |  |
| Neutrophil count decreased                            |                           |                  |  |
| subjects affected / exposed                           | 3 / 14 (21.43%)           | 12 / 22 (54.55%) |  |
| occurrences (all)                                     | 3                         | 12               |  |
| Platelet count decreased                              |                           |                  |  |
| subjects affected / exposed                           | 2 / 14 (14.29%)           | 1 / 22 (4.55%)   |  |
| occurrences (all)                                     | 2                         | 1                |  |
| Alanine aminotransferase increased                    |                           |                  |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)            | 0 / 22 (0.00%)   |  |
| occurrences (all)                                     | 1                         | 0                |  |
| Aspartate aminotransferase increased                  |                           |                  |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)            | 0 / 22 (0.00%)   |  |
| occurrences (all)                                     | 1                         | 0                |  |
| Lymphocyte count decreased                            |                           |                  |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)            | 0 / 22 (0.00%)   |  |
| occurrences (all)                                     | 1                         | 0                |  |
| White blood cell count decreased                      |                           |                  |  |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 14 (7.14%)<br>1  | 0 / 22 (0.00%)<br>0  |  |
| Vascular disorders<br>Hot flush<br>subjects affected / exposed<br>occurrences (all)   | 0 / 14 (0.00%)<br>0  | 1 / 22 (4.55%)<br>1  |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 0 / 14 (0.00%)<br>0  | 2 / 22 (9.09%)<br>2  |  |
| General disorders and administration<br>site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Pyrexia<br>subjects affected / exposed<br>occurrences (all)<br><br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all) | 2 / 14 (14.29%)<br>2<br><br>0 / 14 (0.00%)<br>0<br><br>0 / 14 (0.00%)<br>0 | 12 / 22 (54.55%)<br>12<br><br>2 / 22 (9.09%)<br>2<br><br>1 / 22 (4.55%)<br>1 |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)   | 4 / 14 (28.57%)<br>4<br><br>0 / 14 (0.00%)<br>0                            | 6 / 22 (27.27%)<br>6<br><br>2 / 22 (9.09%)<br>2                              |  |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting   | 0 / 14 (0.00%)<br>0<br><br>2 / 14 (14.29%)<br>2                            | 5 / 22 (22.73%)<br>5<br><br>1 / 22 (4.55%)<br>1                              |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 14 (0.00%)<br>0 | 1 / 22 (4.55%)<br>1 |  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)                | 0 / 14 (0.00%)<br>0 | 2 / 22 (9.09%)<br>2 |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 0 / 14 (0.00%)<br>0 | 1 / 22 (4.55%)<br>1 |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)      | 0 / 14 (0.00%)<br>0 | 1 / 22 (4.55%)<br>1 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 27 June 2017     | <ul style="list-style-type: none"><li>• 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 biopsable.</li><li>• Modify in the inclusion criteria number 8, the alkaline phosphatase limit for patients with hepatic, bone or disease metastases.</li><li>• Update the information described in the biomarker analyses.</li><li>• 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.</li><li>• Change the population by protocol for population effectiveness and clarify its definition.</li><li>• Add the definition of what is considered an overdose of Gemcitabine.</li><li>• 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.</li><li>• Minor typographic changes</li></ul>  |
| 27 November 2017 | <ul style="list-style-type: none"><li>• Add the possibility of analysing FT3 instead of only T3</li><li>• Minor typographic errors</li></ul>   |
| 19 March 2018    | <ul style="list-style-type: none"><li>• 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.</li><li>• 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.</li><li>• 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.</li><li>• 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.</li><li>• 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.</li><li>• 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.</li><li>• Minor typographic changes</li></ul> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------|--------------|--------------|
|------|--------------|--------------|

|               |  |   |
|---------------|--|---|
| 17 April 2018 | <p>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.</p> <p>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.</p> | - |
|---------------|--|---|

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, which is an adverse scenario for immunotherapy .

Notes:

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## Online references

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