Clinical trial results:
CHEMOIMMUNE - A Phase II study evaluating an anti-PD1 monoclonal antibody (pembrolizumab) in lymphopenic metastatic breast cancer patients treated with metronomic cyclophosphamide

Summary

EudraCT number	2016-002736-33
Trial protocol	FR
Global end of trial date	18 September 2019

Results information

Result version number	v1 (current)
This version publication date	18 March 2021
First version publication date	18 March 2021

Trial information

Trial identification

Sponsor protocol code	ET16-073

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03139851
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Centre Léon Bérard
Sponsor organisation address	28 rue Laennec, LYON, France, 69008
Public contact	Dr O. TREDAN, Centre Léon Bérard, 33 4 78 78 28 28, DRCIreglementaire@lyon.unicancer.fr
Scientific contact	Dr O. TREDAN, Centre Léon Bérard, 33 4 78 78 28 28, DRCIreglementaire@lyon.unicancer.fr

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 September 2019
Global end of trial reached?	Yes
Global end of trial date	18 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-Safety run-in phase:
To evaluate the safety of a combination therapy using pembrolizumab in association with metronomic cyclophosphamide.
-Phase II:
To demonstrate the efficacy of a combined treatment associating pembrolizumab with metronomic cyclophosphamide in terms of 24-week Clinical Benefit Rate (CBR24w) as per RECIST 1.1.

Protection of trial subjects:

Study treatments will continue to be administered as long as patient experiences clinical benefit in the opinion of the investigator or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status or withdrawal of consent.
The investigator will have to inform the patient of the study treatment, the objectives and the design of the study, as well as the biological samples collection, provide the patient information leaflet / Informed consent form, answer to any questions that the patient may have and ensure that she understands the potential risks and benefits of participating in the study before signing the informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

At screening, a complete physical examination should be performed as per institutional practice with a measure of weight. During the study, a limited, symptom-oriented physical examinations should be performed. PS will be measured using the ECOG Scale. Vitals signs to be recorded include blood pressure, temperature, respiratory rate and pulse rate.

Period 1

Period 1 title	Safety run-in phase
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	safety run-in phase

Arm description:

A safety run-in phase aiming to evaluate the safety of the combination therapy pembrolizumab + metronomic cyclophosphamide based on the occurrence of severe toxicities.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients will receive cyclophosphamide (50 mg/day, daily, per os) and pembrolizumab (200 mg every 3 weeks, intravenously [IV]). A cycle is defined as an interval of 21 days.

Number of subjects in period 1	safety run-in phase
Started	20
Completed	20

Period 2

Period 2 title	Two-stage phase II
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Two-stage phase II

Arm description:

A two-stage phase II aiming to evaluate the clinical activity of the combination therapy pembrolizumab + metronomic cyclophosphamide. The first 6 patients enrolled in the safety run-in phase will be part of the Phase II analysis.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients will receive cyclophosphamide (50 mg/day, daily, per os) and pembrolizumab (200 mg every 3 weeks, intravenously [IV]). A cycle is defined as an interval of 21 days.

Number of subjects in period 2	Two-stage phase II
Started	20
Completed	20

Baseline characteristics

End points

End points reporting groups

Reporting group title	safety run-in phase

Reporting group description:

A safety run-in phase aiming to evaluate the safety of the combination therapy pembrolizumab + metronomic cyclophosphamide based on the occurrence of severe toxicities.

Reporting group title	Two-stage phase II

Reporting group description:

A two-stage phase II aiming to evaluate the clinical activity of the combination therapy pembrolizumab + metronomic cyclophosphamide. The first 6 patients enrolled in the safety run-in phase will be part of the Phase II analysis.

Primary: Primary end point

End point title	Primary end point[1]

End point description:

End point type	Primary

End point timeframe:

Safety run-in phase
To evaluate the safety of a combination therapy using pembrolizumab in association with metronomic cyclophosphamide.
Phase II
To demonstrate the efficacy of a combined treatment associating pembrolizumab with metronomic cyclophospha

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: The analysis of the safety run-in phase will be performed after 6 weeks of follow-up of the first 6th patients.
Phase II: At the end of Stage INB, an interim efficacy analysis will be performed with analysis of data from the first 18 evaluable patients.

End point values	safety run-in phase	Two-stage phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	20		
Units: number toxicity	6	20		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

The investigator collects (spontaneous patient report or questionning) and immediately notifies the sponsor of all SAEs, in a written report, wether or not theay are deemed to be attributable to research and wich occur during the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: All patients experienced at least one AE: 14 patients (70%) had at least one event related to Pembrolizumab, and 16 patients (80%) had at least one event related to Cyclophosphamide. 12 patients experienced at least one AE grade ≥3, 15% of patients had at least one AE grade ≥3 related to Pembrolizumab, 40% of patients had at least one AE grade ≥3 related to Cyclophosphamide.
No Immune related AE (irAE) was reported. No toxic death was reported.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2017	Update of adverse events related to pembrolizumab (new AE including new irAE / imAE) Tumor biopsies : addition of criteria and precisions in order to perform tumor biopsies (to be performed as per investigator judgement , irradiated lesion should not be biopsied
17 January 2018	Update of dose modifications, supportive care in case of related AEs to pembrolizumab Addition of an exploratory objective: to explore the levels of TGFβ (bioactive and non-bioactive) in serum, plasma and platelets of breast cancer patients
04 June 2018	Modification of criteria I10 (ASAT and ALAT tolerated up to 5 ULN in case of liver metastases and suppression of LDH criteria)
16 January 2019	Update of adverse events related to pembrolizumab (new AE) Update of Data protection Section, following the General Data Protection Regulation (GDPR)
18 September 2019	Suppression of irRC criteria for endpoints of secondary objectives

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported