

**Clinical trial results:****A Phase II open-label multicenter exploratory study to assess efficacy of Pembrolizumab re-challenge as second or further line in patients with advanced non - small cell lung cancer****Summary**

EudraCT number	2017-003947-39
Trial protocol	ES
Global end of trial date	09 March 2023

Results information

Result version number	v1 (current)
This version publication date	26 February 2025
First version publication date	26 February 2025
Summary attachment (see zip file)	Summary final report_REPLAY (Resumen informe final REPLAY_v.1.0_03Jul2023.pdf) REPLAY_PRotocol Summary (REPLAY_Protocol Summary v 3.0_14.01.2019.pdf)

Trial information**Trial identification**

Sponsor protocol code	GECP17/02
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03526887
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fundación GECP
Sponsor organisation address	Avda. Meridiana nº 258, 6th floor, Barcelona, Spain, 08027
Public contact	Eva Pereira, Fundación GECP, 34 934302006205, epereira@gecp.org
Scientific contact	Eva Pereira, Fundación GECP, 34 934302006205, epereira@gecp.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	Final
Date of interim/final analysis	03 May 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 March 2023
Global end of trial reached?	Yes
Global end of trial date	09 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Pembrolizumab re-challenge administered 200 mg iv every 21 days in second or further line for advanced NSCLC after progression to monotherapy check point PD1 / PDL1 inhibitors measured by Overall Response Rate (ORR) per RECIST v1.1 and per modified RECIST (irRC).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2018
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	Spain: 73
Worldwide total number of subjects	73
EEA total number of subjects	73

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)	3
From 65 to 84 years	60
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

Between October 2018 and May 2021, a total of 73 patients were enrolled in the study from 17 different sites.

Pre-assignment

Screening details:

Patients who are advanced non-small cell lung cancer with prior documented benefit (stable disease, partial response, complete response) in controlling the PD1/PDL1 inhibitor (Nivolumab, Pembrolizumab, Durvalumab, Atezolizumab, Avelumab, or others) during at least 16 weeks will be enrolled in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Experimental: Cohort 1
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Arm description:

Patients who experienced progression disease while on treatment progression disease < 12 weeks after stopping treatment. After that the patients took chemotherapy \geq 4 cycles and progressed again. After the last progression the patient is included in the study to be retreated with Pembrolizumab 200mg. The treatment will continue until progression, unacceptable toxicity, consent withdraw, or until the treatment is administered during 24 months, whichever occurs first.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	Keytruda
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

All trial treatments will be administered on an outpatient basis. Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

Arm title	Experimental: Cohort 2
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Arm description:

Stop treatment and progression > 12 weeks after stopping treatment. After the last progression the patient is included in the study to be retreated with Pembrolizumab 200mg. All trial treatments will be administered on an outpatient basis. Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

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

Dosage and administration details:

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

Number of subjects in period 1	Experimental: Cohort 1	Experimental: Cohort 2
Started	55	18
Completed	55	18

Baseline characteristics

Reporting groups

Reporting group title	Experimental: Cohort 1
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Reporting group description:

Patients who experienced progression disease while on treatment progression disease < 12 weeks after stopping treatment. After that the patients took chemotherapy ≥ 4 cycles and progressed again. After the last progression the patient is included in the study to be retreated with Pembrolizumab 200mg. The treatment will continue until progression, unacceptable toxicity, consent withdraw, or until the treatment is administered during 24 months, whichever occurs first.

Reporting group title	Experimental: Cohort 2
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Reporting group description:

Stop treatment and progression > 12 weeks after stopping treatment. After the last progression the patient is included in the study to be retreated with Pembrolizumab 200mg.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

Reporting group values	Experimental: Cohort 1	Experimental: Cohort 2	Total
Number of subjects	55	18	73
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	63.5	69.8	
full range (min-max)	41 to 80	55 to 83	-
Gender categorical Units: Subjects			
Female	39	15	54
Male	16	3	19
Performance Status			
ECOG Performance Status Scale: It describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability GRADES: ECOG 0: Fully active. ECOG 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature ECOG 2: Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours ECOG 3: Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours ECOG 4: Completely disabled ECOG 5: Dead			
Units: Subjects			
ECOG 0	15	8	23
ECOG 1	39	10	49

ECOG 2	0	0	0
ECOG 3	0	0	0
ECOG 4	0	0	0
Not recorded	1	0	1
Cigarette Smoking History			
Units: Subjects			
Never smoker	7	1	8
Former smoker	39	15	54
Smoker	8	2	10
Not recorded	1	0	1
Clinical Stage			
Units: Subjects			
Stage III	3	1	4
Stage IV	52	17	69
Histological diagnosis			
Units: Subjects			
Adenocarcinoma	32	8	40
Squamous	19	8	27
Large Cell Carcinom	1	1	2
Adenosquamous	2	0	2
Other	1	1	2
Body Mass Index			
Units: units on a scale			
median	26	28	
full range (min-max)	17.1 to 35.3	20.2 to 34.8	-

End points

End points reporting groups

Reporting group title	Experimental: Cohort 1
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Reporting group description:

Patients who experienced progression disease while on treatment progression disease < 12 weeks after stopping treatment. After that the patients took chemotherapy ≥ 4 cycles and progressed again. After the last progression the patient is included in the study to be retreated with Pembrolizumab 200mg. The treatment will continue until progression, unacceptable toxicity, consent withdraw, or until the treatment is administered during 24 months, whichever occurs first.

Reporting group title	Experimental: Cohort 2
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Reporting group description:

Stop treatment and progression > 12 weeks after stopping treatment. After the last progression the patient is included in the study to be retreated with Pembrolizumab 200mg.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

Primary: Overall survival

End point title	Overall survival
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End point description:

Overall survival: Defined as the length of time from either the date of diagnosis or the start of the treatment that patients diagnosed with the disease are still alive.

End point type	Primary
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End point timeframe:

From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 50 months.

End point values	Experimental: Cohort 1	Experimental: Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	18		
Units: month				
median (full range (min-max))	9.4 (1 to 18)	19.1 (3 to 55)		

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	Experimental: Cohort 1 v Experimental: Cohort 2
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	Logrank
Parameter estimate	Median difference (final values)
Point estimate	9.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	9.4
upper limit	19.1

Secondary: Progression Free Survival

End point title	Progression Free Survival
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End point description:

PFS: Defined as the length of time from the date of randomization to the date of the first documented progression of disease. "Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0), 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
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End point timeframe:

From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 50 months.

End point values	Experimental: Cohort 1	Experimental: Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	18		
Units: month				
median (full range (min-max))	1.6 (0 to 11)	4.1 (0.2 to 18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Global Response

End point title	Best Global Response
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End point description:

To evaluate the best global response of the treatment as measured by investigator-assessed overall response rate (ORR) according to RECIST v1.1. Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; Progression 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
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End point timeframe:

From the date of randomization until end of follow up, up to 30 months

End point values	Experimental: Cohort 1	Experimental: Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	18		
Units: Participant				
Complete response	0	0		
Partial response	1	3		
Stable disease	24	11		
Progression disease	25	3		
Not evaluable	5	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

30 months

30 months

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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Reporting groups

Reporting group title	Cohort 1
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Reporting group description: -

Reporting group title	Cohort 2
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Reporting group description: -

Serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 55 (3.64%)	1 / 18 (5.56%)	
number of deaths (all causes)	44	5	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Alkaline phosphatase increased			
subjects affected / exposed	1 / 55 (1.82%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 55 (1.82%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	0 / 55 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 55 (47.27%)	11 / 18 (61.11%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 55 (5.45%)	1 / 18 (5.56%)	
occurrences (all)	3	1	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 55 (5.45%)	2 / 18 (11.11%)	
occurrences (all)	3	2	
Blood bilirubin increased			
subjects affected / exposed	3 / 55 (5.45%)	1 / 18 (5.56%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 55 (12.73%)	4 / 18 (22.22%)	
occurrences (all)	7	4	
Anorexia			
subjects affected / exposed	3 / 55 (5.45%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	8 / 55 (14.55%)	8 / 18 (44.44%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	4 / 55 (7.27%)	1 / 18 (5.56%)	
occurrences (all)	4	1	
Stomach pain			
subjects affected / exposed	1 / 55 (1.82%)	0 / 18 (0.00%)	
occurrences (all)	1	0	

Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	5 / 55 (9.09%) 5	3 / 18 (16.67%) 3	
Rash subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3	1 / 18 (5.56%) 1	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	0 / 18 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3	1 / 18 (5.56%) 1	
Metabolism and nutrition disorders Hypomagnesemia subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3	0 / 18 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2019	Change of Sponsor: The Spanish Lung Cancer Group (GECP), sponsor of the REPLAY study, has recently established the GECP Foundation

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

NA

Notes: