Clinical trial results:
Phase II non-randomized study of Atezolizumab (MPDL3280A) in combination with Carboplatin Plus Pemetrexed in patients who are chemotherapy-naïve and have stage IV non-squamous non-small cell lung cancer with asymptomatic brain metastases (ATEZO-BRAIN)

Summary

EudraCT number	2017-005154-11
Trial protocol	ES
Global end of trial date	31 March 2022

Results information

Result version number	v1 (current)
This version publication date	13 September 2023
First version publication date	13 September 2023
Summary attachment (see zip file)	ATEZO_BRAIN final report (ATEZO-BRAIN CSR_final report summary_v.1.0_03Dec2022.pdf)

Trial information

Trial identification

Sponsor protocol code	GECP17/05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03526900
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fundación GECP
Sponsor organisation address	Avda. Meridiana 358, Barcelona, Spain, 08027
Public contact	Eva Pereira, Fundación GECP, +34 934302006, epereira@gecp.org
Scientific contact	Eva Pereira, Fundación GECP, +34 934302006, 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	08 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2022
Global end of trial reached?	Yes
Global end of trial date	31 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of atezolizumab combined with CBDCA and pemetrexed in patients with NSCLC and asymptomatic BM based on PFS according to RANO and RECIST v1.1 criteria for brain and systemic disease respectively

To evaluate the safety of atezolizumab combined with CBDCA and pemetrexed in patients with NSCLC and asymptomatic BM based on the NCI CTCAE v4.0

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	15 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: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	30
From 65 to 84 years	10

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between November 2018 and Desember 2018, a total of 43 patients were enrolled in the study from 15 different sites.

Pre-assignment

Screening details:

Screening details:Patients who are chemotherapy naïve and have Stage IV non-squamous NSCLC with untreated brain metastases will be enrolled in this study.

Period 1

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

Blinding implementation details:

Not Blinded

Arms

Arm title	Experimental

Arm description:

Induction phase: atezolizumab will be given intravenously (iv) at a dose of 1200 mg for 60 minutes on day 1 of each cycle. Subsequent atezolizumab cycles may be administered for 30 minutes, if there were no perfusion-related toxicity. Pemetrexed will be administered at a dose of 500 mg/m2 IV for 15 minutes on day 1 of each cycle. In addition, folic acid, vitamin B12, and dexamethasone 4 mg will be given the day before and the day after treatment with pemetrexed. Carboplatin will be given at a dose with an area under the 5 curve for 30 minutes on day 1 of each cycle, approximately 30 minutes after the pemetrexed infusion is complete. After completing 4 to 6 cycles of Carboplatino plus pemetrexed and atezolizumab, patients will continue with pemetrexed in combination with atezolizumab (maintenance phase) until they have an unacceptable toxicity, progression of the disease, decision of the patient/physician or have Completed 2 years of treatment.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Induction (four or six 21-day cycles) : Atezolizumab 1200 mg / iv + carboplatin 5 AUCs + pemetrexed 500 mg/m2
Maintenance (21-day cycles): atezolizumab 1200 mg/iv + pemetrexed 500 mg/m2.

Number of subjects in period 1	Experimental
Started	40
Completed	40

Baseline characteristics

Reporting groups	
Reporting group title	Overall study (overall period)

Reporting group description: -

Reporting group values	Overall study (overall period)	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
Age continuous Units: years			
median	66.75		
standard deviation	± 14.2	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	29	29	
Performance Status Units: Subjects			
ECOG 0	14	14	
ECOG 1	26	26	
Cigarrette Smoking History Units: Subjects			
Never Smoke	6	6	
Former Smoke	11	11	
Smoker	23	23	
Unknown	0	0	
Histology Units: Subjects			
Adenocarcinoma	39	39	
Adenosquamous	0	0	
Squamous	0	0	
Large Cell Carcinoma	0	0	
NOS/Undifferentiated	1	1	
Other	0	0	
PD-L1 expression Units: Subjects			
> 50%	10	10	
1-49%	10	10	
0%	18	18	
Unknown	2	2	
Baseline corticosteroids Units: Subjects			
Yes	22	22	
No	18	18	
Diagnosis of brain metastases			

Units: Subjects			
Synchronous	37	37	
Metachronous	3	3	

Inclusion T- Clinical Stage			

Staging is a classification where cancer is located, if or where it has spread and whether it's affecting other parts of the body.
In the TNM system:
Primary tumor (T)
- TX means that there is no information about the tumor or it cannot be measured.
- T0 means that there is no evidence of a tumor.
- Tis refers to a tumor "in situ." This means that the tumor is only found in the cells where it started. It has not spread to any surrounding tissue.
- T1-T4 describe the size and location of the tumor, on a scale of 1 to 4. A larger tumor or a tumor that has grown deeper into nearby tissue

Units: Subjects			
Tx	3	3	
T0	0	0	
Tis	0	0	
T1a	2	2	
T1b	2	2	
T1c	2	2	
T2a	4	4	
T2b	1	1	
T3	7	7	
T4	19	19	

Inclusion N Clinical Stage			

Regional lymph nodes (N) NX: Cancer in nearby lymph nodes cannot be measured. N0: No regional lymph node metastases N1: Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension N2: Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s) N3: Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Units: Subjects			
Nx	3	3	
N0	5	5	
N1	2	2	
N2	17	17	
N3	13	13	

Inclusion M Clinical Stage			

Proposed M descriptors for the 8th edition of TNM for Lung Cancer
M - Distant Metastasis:
- M0 No distant metastasis.
- M1 Distant metastasis present.
- M1a Separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion.
M1b Single extrathoracic metastasis.
- M1c Multiple extrathoracic metastases in one or several organs.

Units: Subjects			
M0	0	0	
M1a	1	1	
M1b	5	5	
M1c	34	34	

Total number of brain lesions per patient			
Units: Number			
median	5		
full range (min-max)	1 to 20	-	

Total number of target brain lesions per patient			
Units: Number			
median	1		
full range (min-max)	1 to 4	-	

End points

End points reporting groups

Reporting group title	Experimental

Reporting group description:

Induction phase: atezolizumab will be given intravenously (iv) at a dose of 1200 mg for 60 minutes on day 1 of each cycle. Subsequent atezolizumab cycles may be administered for 30 minutes, if there were no perfusion-related toxicity. Pemetrexed will be administered at a dose of 500 mg/m2 IV for 15 minutes on day 1 of each cycle. In addition, folic acid, vitamin B12, and dexamethasone 4 mg will be given the day before and the day after treatment with pemetrexed. Carboplatin will be given at a dose with an area under the 5 curve for 30 minutes on day 1 of each cycle, approximately 30 minutes after the pemetrexed infusion is complete. After completing 4 to 6 cycles of Carboplatino plus pemetrexed and atezolizumab, patients will continue with pemetrexed in combination with atezolizumab (maintenance phase) until they have an unacceptable toxicity, progression of the disease, decision of the patient/physician or have Completed 2 years of treatment.

Primary: Progression Free Survival at 12 weeks

End point title	Progression Free Survival at 12 weeks[1]

End point description:

Rate of PFS at 12 weeks after enrollment defined as the rate of patients free of disease progression (intracranial or systemic) or death from any cause whichever occurs first at 12 weeks as determined by the investigator according to RANO and RECIST v1.1. criteria for brain and systemic disease respectively.

End point type	Primary

End point timeframe:

At 12 weeks from initiation of treatment

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: Safety and efficacy were assessed in the intention-to-treat population cohort of 40 patients using the Bayesian Multc Lean design.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Subjects				
number (confidence interval 95%)				
Global	62.2 (47.1 to 76.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best response (Intracranial)

End point title	Best response (Intracranial)

End point description:

End point type	Secondary

End point timeframe:

Defined as a complete response or partial response, stable response or progression, on two consecutive evaluations 6 weeks apart, as determined by the investigator according to RANO and RECIST v1.1 criteria for brain and systemic disease respectively.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	40[2]			
Units: Subjects				
Complete Response	5			
Partial response	12			
Stable response	17			
Progression response	5			
No evaluated	1			

Notes:

[2] - Intracranial

Statistical analyses

No statistical analyses for this end point

Secondary: Best response (Systemic)

End point title	Best response (Systemic)

End point description:

End point type	Secondary

End point timeframe:

Defined as a complete response , partial response, stables response, progression on two consecutive evaluations 6 weeks apart, as determined by the investigator according to RANO and RECIST v1.1 criteria for systemic disease respectively.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Subjects				
Complete response	1			
Partial response	17			
Progression response	16			
Stable response	4			
No evaluated	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survivall (OS)

End point title	Overall Survivall (OS)

End point description:

End point type	Secondary

End point timeframe:

Overall Survival (OS) is defined as the time, in months, from the inclusion date to the death date. A patient is censored at the last contact date if he/she does not die.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: month				
median (full range (min-max))	11.8 (7.6 to 16.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event or breakdown occurring during the course of the study.
The investigator will have to collect all adverse events once they have signed informed consent, during treatment and 30 days after the last dose study treatment administration.

Adverse event reporting additional description:

The severity of AE will be determined using CTCAE version 4.0.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Subjects per protocol

Reporting group description: -

Serious adverse events	Subjects per protocol		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 40 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nephritis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Subjects per protocol		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 40 (75.00%)		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
Platelet count decreased			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Alanine aminotransferase increased			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	7		
Lipase increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 40 (25.00%)		
occurrences (all)	10		

Anorexia subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 5		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Mucositis oral subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Diarrhea subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Serum amylase increased subjects affected / exposed occurrences (all)	 9 / 40 (22.50%) 9 6 / 40 (15.00%) 6 7 / 40 (17.50%) 7 3 / 40 (7.50%) 3 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2		
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all) Rash acneiform subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2 4 / 40 (10.00%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2019	Changes in the protocol: due to the new version of the IB of Atezolizumab v15. The management guidelines for immune-mediated effects are changed. In addition, other changes are made to the protocol to update different aspects of study management.
12 March 2021	Changes in the protocol: The information contained in the protocol regarding the analyzes to be carried out in the brain magnetic resonance imaging (MRI) of the patients included in the study is reviewed. A new translational analysis of the study MRIs is added to identify neuroimaging radiomic markers that predict intracranial response to study systemic anticancer therapy. This new analysis may contribute to a better understanding of the clinical evolution of patients with lung cancer by obtaining predictions of the results of possible treatments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37603816