Clinical trial results:
A randomized parallel group phase III trial of OSE 2101 as 2nd or 3rd line compared with standard treatment (docetaxel or pemetrexed) in HLA-A2 positive patients with locally advanced (IIIB) unsuitable for radiotherapy or metastatic (IV) Non-Small-Cell Lung Cancer. (OSE2101C301)

Summary

EudraCT number	2015-003183-36
Trial protocol	CZ HU DE ES PL SI IT
Global end of trial date	15 January 2021

Results information

Result version number	v1 (current)
This version publication date	27 September 2023
First version publication date	26 November 2022

Trial information

Trial identification

Sponsor protocol code	0OSE2101C301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02654587
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	OSE Immunotherapeutics
Sponsor organisation address	22, boulevard Benoni Goullin, Nantes, France, 44200
Public contact	Clinical Development, OSE Immunotherapeutics, +33 143 29 78 57, contact@ose-immuno.com
Scientific contact	Clinical Development, OSE Immunotherapeutics, +33 143 29 78 57, contact@ose-immuno.com

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	15 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 January 2021
Global end of trial reached?	Yes
Global end of trial date	15 January 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Step 1 (phase II) 2:1 randomized non-comparative one stage Fleming phase II
Primary objective
To evaluate the overall survival (OS) rate at 12 months in HLA-A2 positive patients with locally advanced (IIIB) or metastatic (IV) NSCLC as 2nd or 3rd line therapy after failure of checkpoint-inhibitor regimens.

Step 2 (conditional phase III) comparative randomized phase III
Primary objective
To demonstrate that OSE2101 is superior to control treatment with respect to overall survival (OS) in HLA-A2 positive patients with locally advanced (IIIB) or metastatic (IV) NSCLC as 2nd or 3rd line therapy after failure of checkpoint-inhibitor regimens.

Protection of trial subjects:

Patients were completely free to refuse to enter the study or to withdraw from it at any time for any reason.
Patients with recognized immunodeficiency disease including human immunodeficiency virus (HIV) infection and other cellular immunodeficiencies, hypogammaglobulinemia or dysgammaglobulinemia; subjects who have hereditary, congenital or acquired immunodeficiencies, patients with auto-immune disease, with the exception of type I diabetes or treated hypothyroidism, and patients with severe acute or chronic medical or psychiatric conditions, or laboratory abnormalities that would impart, in the judgment of the investigator and/or sponsor, excess risk associated with study participation or study drug administration, were excluded from the study.
Female patients had to be surgically sterile or be postmenopausal, or had to agree to use effective contraception during the period of the trial and for at least 90 days after completion of treatment. Male patients sexually active with a woman of childbearing potential had to be surgically sterile or had to agree to use effective contraception during the period of the trial and for at least 90 days after completion of treatment.
Pregnant and breastfeeding women were also excluded from the trial.

Background therapy:

Patients in Arm B required premedication as per product information. Unless started earlier for other reasons, the premedication started before day 1 of each cycle (i.e. day 1 of each cycle will be injection day for chemotherapy).
- Patients in Arm B with docetaxel:
Patients were required to take dexamethasone, 8 mg orally, twice daily, the day before, the day of and the day after docetaxel dosing. Intramuscular or intraperitoneal administration of dexamethasone with the same total dose as oral dexamethasone, or equivalent corticosteroids, were allowed per country regulations. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities.
- Patients in Arm B with Pemetrexed
Patients were required to take folic acid, 350-1000 µg orally daily beginning approximately 1 to 2 weeks before the first dose of pemetrexed and continuing daily until 3 weeks after the last dose of pemetrexed. Vitamin B12, 1000 µg, was injected intramuscularly approximately 1 to 2 weeks before the first dose of pemetrexed and was repeated approximately every 9 weeks until discontinuation. Patients were also be required to take dexamethasone, 4 mg orally, twice daily, the day before, the day of and the day after pemetrexed dosing. Intramuscular or intraperitoneal administration of dexamethasone with the same total dose as oral dexamethasone was allowed per country regulations.

Evidence for comparator:

Reference therapy was available and approved alike in the US and Europe as the trial extent needed to reach these 2 regions and thus only docetaxel and pemetrexed meet this criterion. Docetaxel was reference therapy in squamous cancer and pemetrexed was reference therapy in non-squamous NSCLC, due to having a better safety profile combined with proven efficacy in this indication.

Actual start date of recruitment	12 February 2016
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	Poland: 4
Country: Number of subjects enrolled	Spain: 48
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	France: 82
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Italy: 48
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	219
EEA total number of subjects	189

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)	108
From 65 to 84 years	110
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

First Patient First Visit: February 12, 2016
Last Patient Last Visit: January 15, 2021
The study was discontinued on April 1st, 2020 because of the COVID-19 pandemic at the recommendations of the IDMC and Steering Committee when 219 patients had been enrolled.

Pre-assignment

Screening details:

Pre-screening: HLA-A2 testing (using PCR methods) can be done at any time before inclusion (a specific consent form is available).
Screening: 1 to 35 days before treatment administration.

Pre-assignment period milestones

Number of subjects started	312[1]
Number of subjects completed	219

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not eligible (did not receive ICI as prior therapy: 93

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: No data were analysed for patients who were not eigible.

Period 1

Period 1 title	Treatment period step 1 & 2 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - OSE2101

Arm description:

OSE2101: Day 1 each 21-day cycle for 6 cycles, then every 8 weeks for the remainder of year one and, finally every 12 weeks beyond year one.

Arm type	Experimental
Investigational medicinal product name	OSE2101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients randomized to OSE2101 received 1 mL of OSE2101 administered subcutaneously on Day 1 every three weeks for six cycles, then every eight weeks for the remainder of year one and, finally every twelve weeks beyond year one until unequivocal RECIST 1.1-defined disease progression as determined by the investigator, unacceptable toxicity, or consent withdrawal.

Arm title	Arm B - docetaxel or pemetrexed

Arm description:

Docetaxel (patients with squamous cancer) or pemetrexed (patients with non-squamous NSCLC): Day 1 each 21-day cycle (i.e. every 3 weeks)

Arm type	Active comparator

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Patients randomized to docetaxel received standard approved NSCLC dose: 75 mg/m2 in 1 hour infusion every 3 weeks. Docetaxel was prepared as per the manufacturer's recommendations. Patients were also be required to take dexamethasone, 8 mg orally, twice daily, the day before, the day of and the day after docetaxel dosing. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities at the discretion of the investigator.

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Patients randomized to pemetrexed received standard approved NSCLC dose: 500 mg/m2 in 10-minute infusion every 3 weeks. Pemetrexed was prepared as per the manufacturer's recommendations. Patients were also be required to take folic acid, 350-1000 µg orally daily beginning approximately 1 to 2 weeks before the first dose of pemetrexed and continuing daily until 3 weeks after the last dose of pemetrexed. Vitamin B12, 1000 µg, was injected intramuscularly approximately 1 to 2 weeks before the first dose of pemetrexed and was repeated approximately every 9 weeks until discontinuation. Patients were also be required to take dexamethasone, 4 mg orally, twice daily, the day before, the day of and the day after pemetrexed dosing.

Number of subjects in period 1	Arm A - OSE2101	Arm B - docetaxel or pemetrexed
Started	139	80
Completed	2	1
Not completed	137	79
Adverse event, serious fatal	5	6
Consent withdrawn by subject	1	2
Disease progression	109	49
Adverse event, non-fatal	17	14
Other	4	2
Not treated	1	6

Baseline characteristics

Reporting groups	
Reporting group title	Arm A - OSE2101
Reporting group description:	
OSE2101: Day 1 each 21-day cycle for 6 cycles, then every 8 weeks for the remainder of year one and, finally every 12 weeks beyond year one.	
Reporting group title	Arm B - docetaxel or pemetrexed
Reporting group description:	
Docetaxel (patients with squamous cancer) or pemetrexed (patients with non-squamous NSCLC): Day 1 each 21-day cycle (i.e. every 3 weeks)	

Reporting group values	Arm A - OSE2101	Arm B - docetaxel or pemetrexed	Total
Number of subjects	139	80	219
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			
arithmetic mean	65.3	63.6	
standard deviation	± 8.77	± 7.89	-
Gender categorical			
Units: Subjects			
Female	40	24	64
Male	99	56	155

End points

End points reporting groups

Reporting group title	Arm A - OSE2101

Reporting group description:

OSE2101: Day 1 each 21-day cycle for 6 cycles, then every 8 weeks for the remainder of year one and, finally every 12 weeks beyond year one.

Reporting group title	Arm B - docetaxel or pemetrexed

Reporting group description:

Docetaxel (patients with squamous cancer) or pemetrexed (patients with non-squamous NSCLC): Day 1 each 21-day cycle (i.e. every 3 weeks)

Subject analysis set title	Patients of Interest
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Population of Interest (PoI) was defined as patients with secondary resistance to ICI monotherapy administered as last line.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

This analysis set included all patients included who were randomized and received at least one dose of randomized study treatment. Patients will be analyzed in the group according to the treatment they received. All safety data analyses were analyzed using the safety set.

Primary: Overall Survival (OS) in ITT

End point title	Overall Survival (OS) in ITT

End point description:

To demonstrate that OSE2101 was superior to control treatment with respect to OS in HLA-A2 positive patients with advanced NSCLC as 2nd or 3rd line therapy after failure of checkpoint-inhibitor regimens in the primary population consisting of the Population of Interest (PoI) defined as patients with secondary resistance to ICI monotherapy administered as last line. A sensitivity analysis was to be done in all randomized patients.
OS was summarized using the Kaplan-Meier method and displayed graphically.

End point type	Primary

End point timeframe:

OS was defined as time from randomization to death, expressed in months, and was censored at the analysis cut-off date (15JAN2021).

End point values	Arm A - OSE2101	Arm B - docetaxel or pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	80		
Units: months				
median (confidence interval 95%)	8.80 (7.622 to 10.842)	8.34 (6.472 to 9.791)		

Attachments (see zip file)	Kaplan-Meier Plot of Overall Survival /ose2101c301-study-

Statistical analyses

Statistical analysis title	Hazard Ratio Cox Regression

Statistical analysis description:

A 2-sided log-rank test stratified for the randomization stratification factors was used to compare OS between the two treatment arms. The Cox regression model, stratified for the same stratification factors, was fitted, and the estimated hazard ratio and 2-sided 95% confidence interval was provided. The hazard ratio, as estimated in this Cox regression model, was provided with its 2-sided 95% CI.

Comparison groups	Arm B - docetaxel or pemetrexed v Arm A - OSE2101
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.19

Primary: Overall survival (OS) in PoI

End point title	Overall survival (OS) in PoI

End point description:

To demonstrate that OSE2101 was superior to control treatment with respect to OS in HLA-A2 positive patients with advanced NSCLC as 2nd or 3rd line therapy after failure of checkpoint-inhibitor regimens in the primary population consisting of the Population of Interest (PoI) defined as patients with secondary resistance to ICI monotherapy administered as last line.

End point type	Primary

End point timeframe:

OS was defined as time from randomization to death, expressed in months, and was censored at the analysis cut-off date (15JAN2021).

End point values	Arm A - OSE2101	Arm B - docetaxel or pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80[1]	38[2]		
Units: months				
median (confidence interval 95%)	11.07 (8.575 to 13.503)	7.47 (4.731 to 10.283)		

Notes:

[1] - Only Patients of Interest

[2] - Only Patients of Interest

Attachments (see zip file)	Kaplan-Meier Plot of Overall Survival in PoI/ose2101c301-

Statistical analyses

Statistical analysis title	Hazard Ratio Cox Regression

Statistical analysis description:

A 2-sided log-rank test stratified for the randomization stratification factors was used to compare OS between the two treatment arms. The Cox regression model, stratified for the same stratification factors, was fitted, and the estimated hazard ratio and 2-sided 95% confidence interval was provided.

Comparison groups	Arm A - OSE2101 v Arm B - docetaxel or pemetrexed
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.587
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.377
upper limit	0.913

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time that the subject/patient provided informed consent through the study treatment period until the last injection and including 28 calendar days after the final administration of the investigational medicinal product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	OSE2101

Reporting group description:

Patient who had received OSE2101

Reporting group title	SoC (Doc/Pem)

Reporting group description:

Patients treated with comparator (Docetaxel or Pemetrexed)

Serious adverse events	OSE2101	SoC (Doc/Pem)	
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 138 (34.06%)	33 / 74 (44.59%)	
number of deaths (all causes)	10	11	
number of deaths resulting from adverse events	10	11	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	3 / 138 (2.17%)	3 / 74 (4.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Metastases to central nervous system			

subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic syndrome0			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	4 / 138 (2.90%)	5 / 74 (6.76%)	
occurrences causally related to treatment / all	0 / 4	1 / 5	
deaths causally related to treatment / all	0 / 3	0 / 3	
Influenza like illness			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 138 (1.45%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	6 / 138 (4.35%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	12 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Giant cell arteritis			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchial obstruction			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 138 (2.17%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Haemoptysis			

subjects affected / exposed	1 / 138 (0.72%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 138 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Wheezing			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			

subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 138 (0.00%)	3 / 74 (4.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 138 (0.72%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 138 (0.72%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			

subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 138 (1.45%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 138 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 138 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal haematoma			

subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 138 (1.45%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Endocarditis			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 138 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 138 (0.72%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 138 (1.45%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 138 (1.45%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	OSE2101	SoC (Doc/Pem)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	131 / 138 (94.93%)	74 / 74 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 138 (2.90%)	4 / 74 (5.41%)	
occurrences (all)	5	5	
General disorders and administration site conditions			
Injection site induration			
subjects affected / exposed	16 / 138 (11.59%)	0 / 74 (0.00%)	
occurrences (all)	17	0	
Injection site pain			
subjects affected / exposed	10 / 138 (7.25%)	0 / 74 (0.00%)	
occurrences (all)	14	0	
Injection site reaction			
subjects affected / exposed	13 / 138 (9.42%)	0 / 74 (0.00%)	
occurrences (all)	15	0	
Asthenia			
subjects affected / exposed	32 / 138 (23.19%)	32 / 74 (43.24%)	
occurrences (all)	36	67	
Chest pain			
subjects affected / exposed	13 / 138 (9.42%)	2 / 74 (2.70%)	
occurrences (all)	13	2	
Chills			
subjects affected / exposed	9 / 138 (6.52%)	0 / 74 (0.00%)	
occurrences (all)	10	0	
Fatigue			
subjects affected / exposed	13 / 138 (9.42%)	12 / 74 (16.22%)	
occurrences (all)	13	15	
General physical health deterioration			
subjects affected / exposed	4 / 138 (2.90%)	6 / 74 (8.11%)	
occurrences (all)	4	6	
Oedema			
subjects affected / exposed	2 / 138 (1.45%)	4 / 74 (5.41%)	
occurrences (all)	2	4	
Oedema peripheral			

subjects affected / exposed	7 / 138 (5.07%)	7 / 74 (9.46%)	
occurrences (all)	8	9	
Pain			
subjects affected / exposed	7 / 138 (5.07%)	5 / 74 (6.76%)	
occurrences (all)	8	11	
Pyrexia			
subjects affected / exposed	26 / 138 (18.84%)	10 / 74 (13.51%)	
occurrences (all)	37	11	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	10 / 138 (7.25%)	0 / 74 (0.00%)	
occurrences (all)	21	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 138 (9.42%)	8 / 74 (10.81%)	
occurrences (all)	17	10	
Dyspoea			
subjects affected / exposed	22 / 138 (15.94%)	16 / 74 (21.62%)	
occurrences (all)	27	20	
Haemoptysis			
subjects affected / exposed	6 / 138 (4.35%)	5 / 74 (6.76%)	
occurrences (all)	8	5	
Investigations			
Weight decreased			
subjects affected / exposed	6 / 138 (4.35%)	8 / 74 (10.81%)	
occurrences (all)	6	8	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 138 (2.17%)	4 / 74 (5.41%)	
occurrences (all)	3	4	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 138 (5.07%)	2 / 74 (2.70%)	
occurrences (all)	16	2	
Neuropathy peripheral			

subjects affected / exposed	0 / 138 (0.00%)	7 / 74 (9.46%)	
occurrences (all)	0	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 138 (6.52%)	14 / 74 (18.92%)	
occurrences (all)	11	15	
Febrile neutropenia			
subjects affected / exposed	0 / 138 (0.00%)	4 / 74 (5.41%)	
occurrences (all)	0	4	
Leukopenia			
subjects affected / exposed	0 / 138 (0.00%)	4 / 74 (5.41%)	
occurrences (all)	0	5	
Neutropenia			
subjects affected / exposed	1 / 138 (0.72%)	14 / 74 (18.92%)	
occurrences (all)	1	15	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 138 (0.00%)	4 / 74 (5.41%)	
occurrences (all)	0	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 138 (5.07%)	1 / 74 (1.35%)	
occurrences (all)	8	1	
Constipation			
subjects affected / exposed	9 / 138 (6.52%)	11 / 74 (14.86%)	
occurrences (all)	10	13	
Diarrhoea			
subjects affected / exposed	12 / 138 (8.70%)	22 / 74 (29.73%)	
occurrences (all)	15	28	
Nausea			
subjects affected / exposed	20 / 138 (14.49%)	14 / 74 (18.92%)	
occurrences (all)	23	17	
Stomatitis			
subjects affected / exposed	2 / 138 (1.45%)	4 / 74 (5.41%)	
occurrences (all)	2	5	
Vomiting			

subjects affected / exposed	14 / 138 (10.14%)	11 / 74 (14.86%)	
occurrences (all)	18	14	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 138 (0.72%)	21 / 74 (28.38%)	
occurrences (all)	1	26	
Nail toxicity			
subjects affected / exposed	0 / 138 (0.00%)	4 / 74 (5.41%)	
occurrences (all)	0	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	20 / 138 (14.49%)	6 / 74 (8.11%)	
occurrences (all)	26	6	
Back pain			
subjects affected / exposed	14 / 138 (10.14%)	9 / 74 (12.16%)	
occurrences (all)	17	9	
Myalgia			
subjects affected / exposed	7 / 138 (5.07%)	4 / 74 (5.41%)	
occurrences (all)	8	5	
Pain in extremity			
subjects affected / exposed	4 / 138 (2.90%)	4 / 74 (5.41%)	
occurrences (all)	6	5	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 138 (0.72%)	5 / 74 (6.76%)	
occurrences (all)	1	6	
Pneumonia			
subjects affected / exposed	2 / 138 (1.45%)	4 / 74 (5.41%)	
occurrences (all)	2	4	
Respiratory tract infection			
subjects affected / exposed	3 / 138 (2.17%)	5 / 74 (6.76%)	
occurrences (all)	4	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	28 / 138 (20.29%)	14 / 74 (18.92%)	
occurrences (all)	31	23	

Hyperglycaemia			
subjects affected / exposed	1 / 138 (0.72%)	4 / 74 (5.41%)	
occurrences (all)	1	5	
Hypoalbuminaemia			
subjects affected / exposed	5 / 138 (3.62%)	5 / 74 (6.76%)	
occurrences (all)	5	5	
Hypokalaemia			
subjects affected / exposed	1 / 138 (0.72%)	4 / 74 (5.41%)	
occurrences (all)	2	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2015	Exclusion criteria n°9 added to exclude patients treated with corticosteroids within 3-weeks before inclusion (except if low dose)
30 November 2015	Exclusion criteria n°1 modified to exclude patients with Large Cell Carcinoma; Inclusion criterion n°5 clarified to authorize patients as 2nd line after failure of prior platinum-based chemotherapy or as 3rd line after failure of platinum-based chemotherapy then immune checkpoint inhibitor (ICI)
14 February 2017	Inclusion criterion n°5 modified to authorize patients as 2nd line or 3rd line after failure of platinum-based chemotherapy and/or failure of ICI (sequential or combined with chemo) as ICIs may be used either as 1st or 2nd line therapy; PDL-1 expression on tumor biopsy not further mandatory for inclusion; clarification on inclusion criteria n°9 to authorize only patients with asymptomatic brain metastases.
21 December 2017	Inclusion criterion n°5 modified to only authorize the subgroup of patients previously treated with ICI and who have progressed after ICI (as 2nd line after ICI + chemotherapy first line or as 3rd line after platinum-based chemotherapy in first line then ICI in second line); Study design modified for a Phase II (Step-1) / Phase III (Step-2) design with a first step Fleming non comparative Phase II design and randomization 2:1; First secondary criterion modified for disease control rate instead of progression-free survival; Clarification on population for analysis for Step-1 and Step-2 (in version 4.1 per request after the voluntary harmonized procedure (VHP) in the European Union) Per IDMC request, the recruitment was temporarily halted from June 2017 to November 2017 before the decision to restart the recruitment only in the subgroup of patients who progressed after ICI was taken based on the IDMC independent analysis of data (safety and death events) reported in the first 131 patients randomized until June 2017; This analysis was blinded from the investigators and the Sponsor.
29 March 2019	• Implementation of the 8th edition of TNM instead of 7th edition leading to modify the study title with no modification of the target study population; • Inclusion criterion n°7 modified to authorize patient with progression during or within 12 months after the end of ICI as sequential or concomitant platinumbased chemotherapy ± radiation for locally advanced disease (stage III); • Study design modified to to remove the possibility of a sample size reassessment of Step-2 based on the Step-1 Phase II results, o to continue with the 2:1 randomization ratio in Step-2 and, as a consequence, o to increase the number of events in Step-2 from 250 to 278 and to increase accordingly the number of patients, o to not consider for the final analysis the 38 patients with previous ICI treatment randomized before the recruitment hold; • Implementation of NCI CTCAE version 5.0 instead of CTCAE version 4.0 leading to clarifying the definition of cytokine release syndrome (CRS) as well as the management of CRS still per Lee recommendation; • A translational study has been added for patients/sites who agreed, in order to assess immunogenicity before and under treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 March 2020	On March 25, 2020 due to the COVID-19 pandemic, the Independent Data Monitoring Committee (IDMC) and Steering Committee recommended to discontinue the ATALANTE-1 study, to complete the analysis of Step-1 and to continue the treatment and follow-up of the 219 patients already randomized in Step-2 until the death of remaining patients.	-

Notes:

Limitations and caveats

None reported