Clinical trial results:
A Phase 2, Multicenter, Randomized, Double-Blind Study of Ficlatuzumab Plus Erlotinib Versus Placebo Plus Erlotinib in Subjects who have Previously Untreated Metastatic, EGFR-Mutated Non-Small Cell Lung Cancer (NSCLC) and BDX004 Positive Label

Summary

EudraCT number	2014-003443-35
Trial protocol	IT
Global end of trial date	14 September 2016

Results information

Result version number	v1 (current)
This version publication date	25 August 2021
First version publication date	25 August 2021

Trial information

Trial identification

Sponsor protocol code	AV-299-14-206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02318368
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AVEO Pharmaceuticals, Inc.
Sponsor organisation address	30 Winter Street, Boston, United States, MA 02108
Public contact	Chief Medical Officer, AVEO Pharmaceuticals, Inc., 857 400-0101, Clinical@aveooncology.com
Scientific contact	Chief Medical Officer, AVEO Pharmaceuticals, Inc., 857 400-0101, Clinical@aveooncology.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	17 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 September 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of ficlatuzumab plus erlotinib versus placebo plus erlotinib in terms of progression-free survival (PFS) in subjects who have previously untreated metastatic Epidermal growth factor receptor (EGFR)-mutated Non-small cell lung cancer (NSCLC) and a BDX004 Positive Label.

Protection of trial subjects:

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the Good Clinical Practice guidelines of the International Conference on Harmonization (ICH), and of the Declaration of Helsinki. The study also carried out in keeping with local legal requirements. Before the start of the study, the study protocol and/or other relevant documents was approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB)/Competent Authorities, in accordance with local legal requirements. Any protocol amendment or revised informed consent form are reviewed and approved by the appropriate IEC/IRB, and signed by all subjects subsequently enrolled in the study as well as those who were already enrolled in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 November 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Singapore: 1
Worldwide total number of subjects	10
EEA total number of subjects	1

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)	6
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who met all the inclusion and none of the exclusion criteria were enrolled in 9 sites in the United States, Australia, Hong Kong, Italy, Singapore, Korea, and Taiwan. The Sponsor terminated Study AV-299-14-206, effective 14-Sep-2016, after determining that enrollment of subjects was much lower than expected.

Pre-assignment

Screening details:

If not alreday done as standard of care, subjects were screened for sensitizing EGFR mutation to determine eligibility for treatment with erlotinib. All subjects underwent inclusion exclusion criteria assessment and all eligible subjects signed the informed consent before undergoing any study-related procedures.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

The study subjects, investigator, study coordinator(s), and the Sponsor study team and its representatives were blinded to the identity of the assigned treatment in the main study from the time of randomization until database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ficlatuzumab Plus Erlotinib

Arm description:

Subjects received 150 mg Erlotinib orally once daily starting on Day 1 of Cycle 1 with 20 mg/kg Ficlatuzumab administered intravenously once every 2 weeks on Day 1 and Day 15 of each 28 day cycle.

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

Dosage and administration details:

Subjects received intravenous (IV) infusion of 20 mg/kg as an admixture with normal saline, over 30-60 minutes once every 2 weeks (Day 1 and Day 15) of each 28-day cycle.

Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 150 mg orally daily, starting on Day 1 of Cycle 1.

Arm title	Placebo Plus Erlotinib

Arm description:

Subjects received 150 mg Erlotinib orally once daily starting on Day 1 of Cycle 1 with Placebo administered intravenously once every 2 weeks on Day 1 and Day 15 of each 28 day cycle.

Arm type	Experimental
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Administered 150 mg orally daily, starting on Day 1 of Cycle 1.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Administered IV infusion of placebo (saline) over 30-60 minutes once every 2 weeks (Day 1 and Day 15) of each 28-day cycle.

Number of subjects in period 1	Ficlatuzumab Plus Erlotinib	Placebo Plus Erlotinib
Started	7	3
Completed	0	0
Not completed	7	3
Consent withdrawn by subject	2	-
Death	-	1
Study terminated by the sponsor	5	2

Baseline characteristics

Reporting groups	
Reporting group title	Ficlatuzumab Plus Erlotinib
Reporting group description:	
Subjects received 150 mg Erlotinib orally once daily starting on Day 1 of Cycle 1 with 20 mg/kg Ficlatuzumab administered intravenously once every 2 weeks on Day 1 and Day 15 of each 28 day cycle.	

Reporting group title	Placebo Plus Erlotinib
Reporting group description:	
Subjects received 150 mg Erlotinib orally once daily starting on Day 1 of Cycle 1 with Placebo administered intravenously once every 2 weeks on Day 1 and Day 15 of each 28 day cycle.	

Reporting group values	Ficlatuzumab Plus Erlotinib	Placebo Plus Erlotinib	Total
Number of subjects	7	3	10
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	2	6
From 65-84 years	3	1	4
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	2	2	4
Male	5	1	6

End points

End points reporting groups

Reporting group title	Ficlatuzumab Plus Erlotinib

Reporting group description:

Subjects received 150 mg Erlotinib orally once daily starting on Day 1 of Cycle 1 with 20 mg/kg Ficlatuzumab administered intravenously once every 2 weeks on Day 1 and Day 15 of each 28 day cycle.

Reporting group title	Placebo Plus Erlotinib

Reporting group description:

Subjects received 150 mg Erlotinib orally once daily starting on Day 1 of Cycle 1 with Placebo administered intravenously once every 2 weeks on Day 1 and Day 15 of each 28 day cycle.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)[1]

End point description:

Progression Free Survival is defined as the time from the date of randomization to the date of the first objective documentation of radiographic disease progression or death due to any cause, whichever occurs first. The study was terminated prior to completing enrollment; after determining that enrollment of subjects was much lower than expected, no data was collected for this outcome measure.

End point type	Primary

End point timeframe:

Approximately 24 months

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 study was terminated prior to completing enrollment; after determining that enrollment of subjects was much lower than expected, no data was collected for this outcome measure.

End point values	Ficlatuzumab Plus Erlotinib	Placebo Plus Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Subjects				
number (not applicable)				

Notes:

[2] - No subjects were analyzed as the study was terminated.

[3] - No subjects were analyzed as the study was terminated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects With Adverse Events

End point title	Number of subjects With Adverse Events

End point description:

To evaluate Safety and tolerability of ficlatuzumab plus erlotinib versus placebo plus erlotinib in subjects who have previously untreated metastatic EGFR-mutated NSCLC and a BDX004 Positive Label.

End point type	Secondary

End point timeframe:

Approximately 24 months

End point values	Ficlatuzumab Plus Erlotinib	Placebo Plus Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	3		
Units: Count of Subjects				
number (not applicable)				
Patients with Treatment-Emergent Adverse Events	7	3		
Patients with Serious Adverse Events	3	1		
Patients with grade 5 TEAEs	0	0		
Patients with grade 3 or 4 TEAEs	4	1		
Patients permanently discontinued	2	0		
Patients with dose reduction or interruption	3	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 24 months

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Ficlatuzumab Plus Erlotinib

Reporting group description:

Subjects received 150 mg Erlotinib orally once daily starting on Day 1 of Cycle 1 with 20 mg/kg Ficlatuzumab administered intravenously once every 2 weeks on Day 1 and Day 15 of each 28 day cycle.

Reporting group title	Placebo Plus Erlotinib

Reporting group description:

Subjects received 150 mg Erlotinib orally once daily starting on Day 1 of Cycle 1 with Placebo administered intravenously once every 2 weeks on Day 1 and Day 15 of each 28 day cycle.

Serious adverse events	Ficlatuzumab Plus Erlotinib	Placebo Plus Erlotinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	1 / 3 (33.33%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Spinal compression fracture			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (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			
Pulmonary embolism			

subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
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: 2 %

Non-serious adverse events	Ficlatuzumab Plus Erlotinib	Placebo Plus Erlotinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	3 / 3 (100.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Ejection fraction decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Vascular disorders			

Venous thrombosis limb			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Leukopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	3 / 3 (100.00%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	2 / 7 (28.57%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Mouth ulceration			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Abdominal distension			

subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Epigastric discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Pelvic fluid collection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Respiratory gas exchange disorder			

subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 7 (71.43%)	2 / 3 (66.67%)	
occurrences (all)	7	2	
Dermatitis acneiform			
subjects affected / exposed	2 / 7 (28.57%)	2 / 3 (66.67%)	
occurrences (all)	5	3	
Pruritus			
subjects affected / exposed	2 / 7 (28.57%)	1 / 3 (33.33%)	
occurrences (all)	4	1	
Dry skin			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Eczema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hyperkeratosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nail disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Papule			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Skin exfoliation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Skin hyperpigmentation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Alopecia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	

Infections and infestations			
Paronychia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	
occurrences (all)	2	3	
Nail infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Vaginal infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 7 (28.57%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2015	Study eligibility requirements were revised. Inclusion criteria were updated: #4 referring to EGFR mutation status was updated, #6 expanded to include subset of subjects who were currently on Cycle 1 of EGFR tyrosine kinase inhibitors therapy (erlotinib, gefitinib, afatinib) as first-line treatment for NSCLC such that they would discontinue their EGFR TKI therapy at the end of Cycle 1 within 4 days of randomization. Exclusion criteria were updated: # 2 expanded the eligibility criteria to include subjects with asymptomatic brain metastases, #5 updated the text to clarify which subjects with cardiovascular disease were eligible for the study, #7 revised timing of prior malignancy per input from investigators, #8 defined eligibility status of subjects after major surgery, exclusion criterion #13 was added regarding usage of CYP3A4 inducers and strong CYP3A4 inhibitor prior to randomization. Clarified how modifications to study treatment may occur. Revised to distinguish CYP3A4 inducers from "strong" CYP3A4 inhibitors. Revised the text to include that EGFR mutation status is part of baseline characteristics. Clarified subject assessment medical history. Clarified/corrected pharmacokinetic (PK) time points, per schedule of PK sample collection during study treatment , also included weight and dosing, per schedule of procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 September 2016	Sponsor determined that enrollment of subjects were much lower than expected and that timely completion of the study was not feasible.	-

Notes:

Limitations and caveats

None reported