Clinical trial results:
Multicenter, Double-Blind, Randomized, Parallel-Group Study to Assess the Efficacy and Safety of MYL-1402O Compared With Avastin®, in the First-line Treatment of Patients with Stage IV Non-Squamous Non-Small Cell Lung Cancer

Summary

EudraCT number	2015-005141-32
Trial protocol	ES HU HR BG IT
Global end of trial date	22 November 2019

Results information

Result version number	v1 (current)
This version publication date	25 June 2022
First version publication date	25 June 2022

Trial information

Trial identification

Sponsor protocol code	MYL-1402O-3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04633564
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mylan GmbH
Sponsor organisation address	1000 Mylan Boulevard, Canonsburg, PA , United States, 15317
Public contact	Keri Vaughan, Mylan GmbH, keri.vaughan@viatris.com
Scientific contact	Dr Tazeen Idris, Mylan GmbH, TazeenAamena.Idris@viatris.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	10 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare the overall response rate (ORR) of MYL-1402O with that of Avastin, in combination with CP chemotherapy during the first 18 weeks of first-line treatment in patients with Stage IV nsNSCLC.

Protection of trial subjects:

All laboratory specimens, evaluation forms, reports, and other records were identified in a manner designed to maintain patient confidentiality. All records were kept in a secure storage area with limited access. Clinical information was not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, regulatory authorities or the IRB/IEC.
The PI (or designee) and all employees and coworkers involved with this study have not disclosed or used for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Hungary: 29
Country: Number of subjects enrolled	India: 191
Country: Number of subjects enrolled	Belarus: 24
Country: Number of subjects enrolled	Bosnia and Herzegovina: 19
Country: Number of subjects enrolled	Georgia: 58
Country: Number of subjects enrolled	Russian Federation: 140
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Ukraine: 160
Country: Number of subjects enrolled	Philippines: 2
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Viet Nam: 17

Worldwide total number of subjects	671
EEA total number of subjects	55

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)	473
From 65 to 84 years	197
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 671 patients were randomized from 89 sites. Intent To Treat population was used to determine Primary outcome.
Date first patient randomized: 21 Jan 2017, Date Last Patient's Last Assessment in Period 1 (Date of data Cut-Off): 05 Jun 19
Date Last Patient's Last Assessment in Period 2 (Date of data Cut-Off): 22 Nov 20

Pre-assignment

Screening details:

This was a multicenter, randomized, double-blind, 2-arm, parallel group, equivalence study.
The study consisted of screening/baseline, Treatment Period 1 and Period 2, an extended treatment period and safety follow up. A total of 1016 patients were screened; 345 patients were screening failures. A total of 671 patients were randomized.

Period 1

Period 1 title	Period 1 (up to week 18)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	MYL-1402O

Arm description:

Patients began Period 1 by receiving bevacizumab combination therapy (MYL-1402O- 15 mg/kg IV + Carboplatin AUC 6 IV+ Paclitaxel 200 or 175 mg/m2 IV) on Day 0 of Cycle 1 for up to 6 cycles of therapy. Each cycle consisted of 3 weeks (21 days ± 3 days) and a cycle started with the administration of bevacizumab (as MYL-1402O).

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	MYL-1402O
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab as MYL-1402O 15 mg/kg IV + Carboplatin AUC 6 IV+ Paclitaxel 200 or 175 mg/m2 IV

Arm title	Avastin

Arm description:

Patients began Period 1 receiving bevacizumab combination therapy (Avastin15 mg/kg IV + Carboplatin AUC 6 IV+ Paclitaxel 200 or 175 mg/m2 IV) on Day 0 of Cycle 1 for up to 6 cycles of therapy. Each cycle consisted of 3 weeks (21 days ± 3 days) and a cycle started with the administration of bevacizumab (as Avastin).

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	Avastin
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab as Avastin 15 mg/kg IV + Carboplatin AUC 6 IV+ Paclitaxel 200 or 175 mg/m2 IV

Number of subjects in period 1	MYL-1402O	Avastin
Started	337	334
Completed	227	220
Not completed	110	114
Consent withdrawn by subject	10	8
Physician decision	4	12
Adverse event, non-fatal	28	19
Death	8	7
Study terminated sponsor	8	6
Progressive Disease	47	51
Protocol Violation	-	1
Lost to follow-up	3	5
Not treated	2	5

Period 2

Period 2 title	Period 2 (up to week 42)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	MYL-1402O

Arm description:

In Period 2, eligible patients will continue to receive bevacizumab (MYL- 1402O) every 3 weeks as monotherapy.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	MYL-1402O
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab as MYL-1402O 15 mg/kg IV

Arm title	Avastin

Arm description:

In Period 2, eligible patients will continue to receive bevacizumab (Avastin) every 3 weeks as monotherapy.

Arm type	Active comparator

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	Avastin
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab as Avastin 15 mg/kg IV

Number of subjects in period 2[1]	MYL-1402O	Avastin
Started	200	199
Completed	107	102
Not completed	93	97
Consent withdrawn by subject	5	1
Physician decision	2	4
Adverse event, non-fatal	3	4
Study terminated sponsor	9	3
Death	-	2
Progressive Disease	74	82
Lost to follow-up	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: MYL-1402O arm: 27 patients could not enter in Period 2 from Period 1 due to AE (5), Progressive disease (18), Withdrawal by subject (1), Study terminated by Sponsor (3).
Avastin arm: 21 patients could not enter in Period 2 from Period 1 due to AE (5), Progressive disease (15), Study terminated by Sponsor (1).

Baseline characteristics

Reporting groups	
Reporting group title	MYL-1402O
Reporting group description:	
Patients began Period 1 by receiving bevacizumab combination therapy (MYL-1402O- 15 mg/kg IV + Carboplatin AUC 6 IV+ Paclitaxel 200 or 175 mg/m2 IV) on Day 0 of Cycle 1 for up to 6 cycles of therapy. Each cycle consisted of 3 weeks (21 days ± 3 days) and a cycle started with the administration of bevacizumab (as MYL-1402O).	
Reporting group title	Avastin
Reporting group description:	
Patients began Period 1 receiving bevacizumab combination therapy (Avastin15 mg/kg IV + Carboplatin AUC 6 IV+ Paclitaxel 200 or 175 mg/m2 IV) on Day 0 of Cycle 1 for up to 6 cycles of therapy. Each cycle consisted of 3 weeks (21 days ± 3 days) and a cycle started with the administration of bevacizumab (as Avastin).	

Reporting group values	MYL-1402O	Avastin	Total
Number of subjects	337	334	671
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)	237	236	473
From 65-84 years	99	98	197
85 years and over	1	0	1
Age continuous			
Units: years			
least squares mean	59.3	59.2	
standard deviation	± 9.60	± 9.73	-
Gender categorical			
Units: Subjects			
Female	124	123	247
Male	213	211	424

Subject analysis sets	
Subject analysis set title	Intent to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT set consisted of all randomized patients. The ITT set consisted of a total of 671 patients (337 in the MYL-1402O arm and 334 in the Avastin arm) who were randomized into the study under Protocol.	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP set will consist of all randomized patients who complete at least one dose of MYL-1402O or	

Avastin and do not have protocol deviations having significant impact on the (study) endpoints during the study.

Reporting group values	Intent to treat	Per Protocol	
Number of subjects	671	634	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	473	443	
From 65-84 years	197	191	
85 years and over	1	0	
Age continuous Units: years			
least squares mean	59.3	59.3	
standard deviation	± 9.66	± 9.73	
Gender categorical Units: Subjects			
Female	247	240	
Male	424	394	

End points

End points reporting groups

Reporting group title	MYL-1402O

Reporting group description:

Patients began Period 1 by receiving bevacizumab combination therapy (MYL-1402O- 15 mg/kg IV + Carboplatin AUC 6 IV+ Paclitaxel 200 or 175 mg/m2 IV) on Day 0 of Cycle 1 for up to 6 cycles of therapy. Each cycle consisted of 3 weeks (21 days ± 3 days) and a cycle started with the administration of bevacizumab (as MYL-1402O).

Reporting group title	Avastin

Reporting group description:

Patients began Period 1 receiving bevacizumab combination therapy (Avastin15 mg/kg IV + Carboplatin AUC 6 IV+ Paclitaxel 200 or 175 mg/m2 IV) on Day 0 of Cycle 1 for up to 6 cycles of therapy. Each cycle consisted of 3 weeks (21 days ± 3 days) and a cycle started with the administration of bevacizumab (as Avastin).

Reporting group title	MYL-1402O

Reporting group description:

In Period 2, eligible patients will continue to receive bevacizumab (MYL- 1402O) every 3 weeks as monotherapy.

Reporting group title	Avastin

Reporting group description:

In Period 2, eligible patients will continue to receive bevacizumab (Avastin) every 3 weeks as monotherapy.

Subject analysis set title	Intent to treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT set consisted of all randomized patients.
The ITT set consisted of a total of 671 patients (337 in the MYL-1402O arm and 334 in the Avastin arm) who were randomized into the study under Protocol.

Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

The PP set will consist of all randomized patients who complete at least one dose of MYL-1402O or Avastin and do not have protocol deviations having significant impact on the (study) endpoints during the study.

Primary: ORR at Week 18

End point title	ORR at Week 18

End point description:

The primary efficacy endpoint is the ORR as assessed by an independent review during the first 18 Weeks, assessed according to RECIST 1.1.

End point type	Primary

End point timeframe:

18 Weeks

End point values	MYL-1402O	Avastin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	334		
Units: Percentage of participants				
number (confidence interval 95%)	41.5 (36.3 to 46.8)	43.1 (37.8 to 48.4)		

Statistical analyses

Statistical analysis title	Risk Difference Analysis
Comparison groups	MYL-1402O v Avastin
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	5.9

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

PFS, defined as the time from randomization to the first documentation of PD or to death due to any cause, whichever comes first; PFS rate was calculated at 42 weeks, median PFS was determined at 42 weeks.

End point type	Secondary

End point timeframe:

Week 42

End point values	MYL-1402O	Avastin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	334		
Units: Months				
median (confidence interval 95%)	7.6 (7.0 to 9.5)	9.0 (7.2 to 9.7)		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analysis
Comparison groups	MYL-1402O v Avastin

Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0906
Method	Logrank

Secondary: Duration of Response

End point title	Duration of Response

End point description:

DOR, is defined as the time from start of the first documentation of objective tumor response (CR or PR) to the first documentation of tumor progression (i.e., PD) or to death due to any cause, whichever comes first.

End point type	Secondary

End point timeframe:

42 Weeks

End point values	MYL-1402O	Avastin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	334		
Units: Months				
median (confidence interval 95%)	7.7 (6.2 to 8.3)	6.9 (5.8 to 8.5)		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analysis
Comparison groups	MYL-1402O v Avastin
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5698
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

A treatment-emergent AE is an AE that started or deteriorated after the first administration of blinded MYL-1402O or Avastin through 100 days following the last dose of blinded MYL-1402O or Avastin.

Adverse event reporting additional description:

Overall, study drug was administered to 664 patients during the study (335 in the MYL-1402O arm and 329 in the Avastin arm), who completed at least one dose or partial dose of MYL-1402O or Avastin.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	MYL-1402O
Reporting group description: -	
Reporting group title	Avastin

Reporting group description: -

Serious adverse events	MYL-1402O	Avastin	
Total subjects affected by serious adverse events			
subjects affected / exposed	59 / 335 (17.61%)	55 / 329 (16.72%)	
number of deaths (all causes)	101	82	
number of deaths resulting from adverse events	25	14	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	1 / 335 (0.30%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	2 / 335 (0.60%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous Thrombosis			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 335 (0.30%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired Healing			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (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	4 / 335 (1.19%)	4 / 329 (1.22%)	
occurrences causally related to treatment / all	4 / 4	4 / 4	
deaths causally related to treatment / all	2 / 2	0 / 0	
Pulmonary Haemorrhage			

subjects affected / exposed	4 / 335 (1.19%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	2 / 4	1 / 3	
deaths causally related to treatment / all	2 / 4	1 / 3	
Dyspnoea			
subjects affected / exposed	5 / 335 (1.49%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 335 (0.30%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	2 / 335 (0.60%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 335 (0.30%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	2 / 335 (0.60%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute Respiratory Distress Syndrome			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Aspiration			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumomediastinum			

subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Thrombosis			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Platelet Count Decreased			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur Fracture			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Angina Unstable			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial Fibrillation			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardicac Arrest			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac Failure Acute			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
COR Pulmonale Acute			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary Artery disease			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Arrhythmia			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	2 / 335 (0.60%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	1 / 2	0 / 0	
Cerebral small vessel ischaemic disease			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (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			
Febrile Neutropenia			
subjects affected / exposed	7 / 335 (2.09%)	5 / 329 (1.52%)	
occurrences causally related to treatment / all	0 / 7	3 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
Thrombocytopenia			
subjects affected / exposed	4 / 335 (1.19%)	6 / 329 (1.82%)	
occurrences causally related to treatment / all	1 / 4	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	5 / 335 (1.49%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	4 / 335 (1.19%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	1 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 335 (0.60%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coagulopathy			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Angle Closure Glaucoma			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 335 (0.30%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 335 (0.60%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Ulcer			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Perforation			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Gastric Ulcer Haemorrhage			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestine Perforation			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic Ulcer Haemorrhage			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peptic Ulcer Perforation			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute Kidney Injury			
subjects affected / exposed	0 / 335 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelocaliectasis			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Cyst Ruptured			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pathological Fracture			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	3 / 335 (0.90%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 3	2 / 2	
deaths causally related to treatment / all	0 / 2	2 / 2	
Pneumonia			
subjects affected / exposed	3 / 335 (0.90%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 335 (0.90%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infectious pleural effusion			
subjects affected / exposed	2 / 335 (0.60%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 335 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear Infection			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye Infection Fungal			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Salmonella			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Infection			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatitis C			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			

subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	0 / 335 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Abscess			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (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	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	1 / 335 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 335 (0.30%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	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	MYL-1402O	Avastin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	311 / 335 (92.84%)	304 / 329 (92.40%)	
Investigations			
Alanine Amino-tranferase Increased			
subjects affected / exposed	25 / 335 (7.46%)	29 / 329 (8.81%)	
occurrences (all)	37	45	
Aspartate aminotransferase			

increased			
subjects affected / exposed	22 / 335 (6.57%)	19 / 329 (5.78%)	
occurrences (all)	29	28	
Weight decreased			
subjects affected / exposed	22 / 335 (6.57%)	7 / 329 (2.13%)	
occurrences (all)	23	7	
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 335 (5.67%)	16 / 329 (4.86%)	
occurrences (all)	24	23	
Nervous system disorders			
Peripheral Sensory Neuropathy			
subjects affected / exposed	74 / 335 (22.09%)	66 / 329 (20.06%)	
occurrences (all)	99	91	
Headache			
subjects affected / exposed	26 / 335 (7.76%)	17 / 329 (5.17%)	
occurrences (all)	35	20	
Hypoaesthesia			
subjects affected / exposed	15 / 335 (4.48%)	20 / 329 (6.08%)	
occurrences (all)	22	25	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	111 / 335 (33.13%)	112 / 329 (34.04%)	
occurrences (all)	232	221	
Thrombocytopenia			
subjects affected / exposed	104 / 335 (31.04%)	80 / 329 (24.32%)	
occurrences (all)	225	197	
Neutropenia			
subjects affected / exposed	68 / 335 (20.30%)	76 / 329 (23.10%)	
occurrences (all)	128	144	
Leukopenia			
subjects affected / exposed	38 / 335 (11.34%)	41 / 329 (12.46%)	
occurrences (all)	67	97	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	53 / 335 (15.82%)	33 / 329 (10.03%)	
occurrences (all)	68	42	
Pyrexia			
subjects affected / exposed	31 / 335 (9.25%)	21 / 329 (6.38%)	
occurrences (all)	57	34	
Fatigue			
subjects affected / exposed	26 / 335 (7.76%)	27 / 329 (8.21%)	
occurrences (all)	31	32	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	56 / 335 (16.72%)	49 / 329 (14.89%)	
occurrences (all)	111	108	
Vomiting			
subjects affected / exposed	54 / 335 (16.12%)	38 / 329 (11.55%)	
occurrences (all)	100	59	
Diarrhoea			
subjects affected / exposed	46 / 335 (13.73%)	30 / 329 (9.12%)	
occurrences (all)	104	55	
Stomatitis			
subjects affected / exposed	22 / 335 (6.57%)	8 / 329 (2.43%)	
occurrences (all)	29	14	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	21 / 335 (6.27%)	16 / 329 (4.86%)	
occurrences (all)	30	18	
Cough			
subjects affected / exposed	15 / 335 (4.48%)	23 / 329 (6.99%)	
occurrences (all)	16	30	
Epistaxis			
subjects affected / exposed	6 / 335 (1.79%)	17 / 329 (5.17%)	
occurrences (all)	6	19	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	148 / 335 (44.18%)	168 / 329 (51.06%)	
occurrences (all)	186	198	
Renal and urinary disorders			

Proteinuria subjects affected / exposed occurrences (all)	11 / 335 (3.28%) 18	17 / 329 (5.17%) 21	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	16 / 335 (4.78%) 28	18 / 329 (5.47%) 46	
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	43 / 335 (12.84%) 54	32 / 329 (9.73%) 39	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2018	• Change in Study Design including Removal of the Survival Period from the study; every subject will be part of the study till 42 weeks (Period 2), beyond which they can receive treatment under the extension period. During Extension Period only the related AEs will be collected. • Change in sample Size; verbatim "It is estimated that approximately 864 screened patients will yield approximately 640 patients for 1:1 randomization for having at least 628 evaluable patients, taking into account the attrition rate of 2%." • Change in the Statistical consideration in the primary endpoint as per the FDA and EMA feedback. Details of Meta-analysis included. • End of Study modified to study Closure; "Study closure will occur when either all patients have discontinued the study, or 42 weeks from the date the last patient was randomized to treatment OR at the administrative closure of the study. Patients on treatment at study closure will be advised by the PI and/or their associated primary health care provider on alternate therapies as per standard for the country. All treatment provided under the auspices of this protocol will cease at study closure." • Preferred method for Urine Protein evaluation changed from UPCR to Urine dipstick; "Inclusion Criteria: Urine protein (via dipstick): 0 or 1+. Patients with ≥ 2+ can be included only if a 24-hour urine specimen yields <2g of protein." • Dose Modification Table, as recommended in the Avastin PI 2017 is included. • Editorial changes throughout the document for harmonization of the text. • Administrative changes for study conduct
19 February 2019	• Update the definition of primary endpoint "The primary efficacy endpoint Overall Response Rate (ORR) will be based on best tumor responses as assessed by an independent review at any time point during the first 18 weeks, and assessed according to RECIST 1.1 • ORR based on confirmed tumor responses will be evaluated as sensitivity analysis

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/34819997