Clinical trial results:
The MILO Study (MEK Inhibitor in Low-grade Serous Ovarian Cancer): A Multinational, Randomized, Open-Label Phase 3 Study of MEK162 vs. Physician's Choice Chemotherapy in Patients with Recurrent or Persistent Low-grade Serous Carcinomas of the Ovary, Fallopian Tube or Primary Peritoneum

Summary

EudraCT number	2013-000277-72
Trial protocol	HU GB AT BE IT CZ DE IE FI NO NL SE PL ES DK
Global end of trial date	23 August 2022

Results information

Result version number	v1 (current)
This version publication date	18 June 2023
First version publication date	18 June 2023

Trial information

Trial identification

Sponsor protocol code	C4211003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01849874
WHO universal trial number (UTN)	-
Other trial identifiers	MILO: ARRAY-162-311

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.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	23 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 August 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Demonstrate superior efficacy (increased PFS) of binimetinib vs. physician’s choice of selected chemotherapies (liposomal doxorubicin, paclitaxel and topotecan).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 June 2013
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	Australia: 12
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Canada: 40
Country: Number of subjects enrolled	Czechia: 7
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	United States: 99
Worldwide total number of subjects	333
EEA total number of subjects	147

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)	263
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	333
Number of subjects completed	333

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	MEK162

Arm description:

Subjects received an oral dose of 45 milligram (mg) of MEK162 tablets (3 tablets of 15 mg) twice daily for each 28-day treatment cycle until disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, lost to follow-up or death, whichever occurred first. Subjects were followed up to 30 days after last dose of study intervention.

Arm type	Experimental
Investigational medicinal product name	MEK162 15 mg film-coated tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

15 mg, oral

Arm title	Physician's Choice

Arm description:

Subjects received chemotherapies as per treating physician’s choice in accordance to the institutional standard of care. Subjects received one of the three intravenous (IV) infusion therapies: Liposomal doxorubicin 40 milligram per meter square (mg/m^2) on Day 1 of each 28-day cycle or Paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle or, Topotecan 1.25 mg/m^2 on Days 1 through 5 of each 21-day cycle. Subjects were followed up to 30 days after last dose of study intervention.

Arm type	Placebo
Investigational medicinal product name	Liposomal doxorubicin 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

20 mg, IV

Investigational medicinal product name	Topotecan 4 mg
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:
4 mg, IV

Investigational medicinal product name	Paclitaxel 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:
100 mg, IV

Number of subjects in period 1	MEK162	Physician's Choice
Started	227	106
Treated	227	106
Completed	0	0
Not completed	227	106
Adverse event, serious fatal	89	40
Consent withdrawn by subject	16	11
Physician decision	7	1
Completed as per protocol amendment 6	3	-
Not specified	16	4
Study Termination By Sponsor	93	48
Lost to follow-up	3	2

Baseline characteristics

Reporting groups	
Reporting group title	MEK162

Reporting group description:

Subjects received an oral dose of 45 milligram (mg) of MEK162 tablets (3 tablets of 15 mg) twice daily for each 28-day treatment cycle until disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, lost to follow-up or death, whichever occurred first. Subjects were followed up to 30 days after last dose of study intervention.

Reporting group title	Physician's Choice

Reporting group description:

Subjects received chemotherapies as per treating physician’s choice in accordance to the institutional standard of care. Subjects received one of the three intravenous (IV) infusion therapies: Liposomal doxorubicin 40 milligram per meter square (mg/m^2) on Day 1 of each 28-day cycle or Paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle or, Topotecan 1.25 mg/m^2 on Days 1 through 5 of each 21-day cycle. Subjects were followed up to 30 days after last dose of study intervention.

Reporting group values	MEK162	Physician's Choice	Total
Number of subjects	227	106	333
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)	173	90	263
From 65-84 years	54	16	70
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	52.26	50.12	
standard deviation	± 14.64	± 13.35	-
Sex: Female, Male Units: Participants			
Female	227	106	333
Male	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	18	9	27
Not Hispanic or Latino	200	95	295
Unknown or Not Reported	9	2	11

End points

End points reporting groups

Reporting group title	MEK162

Reporting group description:

Subjects received an oral dose of 45 milligram (mg) of MEK162 tablets (3 tablets of 15 mg) twice daily for each 28-day treatment cycle until disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, lost to follow-up or death, whichever occurred first. Subjects were followed up to 30 days after last dose of study intervention.

Reporting group title	Physician's Choice

Reporting group description:

Subjects received chemotherapies as per treating physician’s choice in accordance to the institutional standard of care. Subjects received one of the three intravenous (IV) infusion therapies: Liposomal doxorubicin 40 milligram per meter square (mg/m^2) on Day 1 of each 28-day cycle or Paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle or, Topotecan 1.25 mg/m^2 on Days 1 through 5 of each 21-day cycle. Subjects were followed up to 30 days after last dose of study intervention.

Subject analysis set title	MEK162
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who were randomized into MEK162 arm.

Subject analysis set title	Physician's Choice
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who were randomized into Physician's Choice arm.

Primary: Progression-free Survival (PFS) as Assessed by Blinded Independent Central Review (BICR)

End point title	Progression-free Survival (PFS) as Assessed by Blinded Independent Central Review (BICR)[1]

End point description:

PFS was defined as the time from randomization to the earliest documented disease progression date or death due to any cause whichever occurred first. Disease progression was defined as at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including Baseline) and an absolute increase of greater than or equal to (>=) 5 millimeter (mm). Appearance of new lesions >=10 mm in diameter also constituted PD. If a subject did not have an event at the time of the analysis cutoff or at the start of any new therapy, PFS was censored at the date of last adequate tumor assessment. The full analysis set included all randomized subjects. Here "Number of Subjects Analyzed" included all randomized subjects as of primary completion date (PCD). Updated efficacy data were not analyzed at study completion date due to study early termination.

End point type	Primary

End point timeframe:

From randomization until documented progressive disease (PD) or death, whichever occurred first, for censored subjects at the date of last adequate tumor assessment (up to 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: Analysis was planned only for the arms specified.

End point values	MEK162	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	102		
Units: months				
median (confidence interval 95%)	9.10 (7.29 to 11.30)	10.58 (9.20 to 14.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization to death due to any cause. Subjects who were alive at the data cutoff date were censored for overall survival at their last contact date. The full analysis set included all randomized subjects. Here "Number of Subjects Analyzed" included all randomized subjects as of PCD. Updated efficacy data were not analyzed at study completion date due to study early termination.

End point type	Secondary

End point timeframe:

From randomization date to the date of death, for censored subjects at their last contact date (up to 24 months)

End point values	MEK162	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201[2]	102[3]		
Units: months				
median (confidence interval 95%)	25.33 (18.46 to 999999)	20.83 (17.45 to 999999)		

Notes:

[2] - Upper limit of 95% CI was not estimable due to low number of subjects with events.

[3] - Upper limit of 95% CI was not estimable due to low number of subjects with events.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (RECIST V1.1)

End point title	Objective Response Rate per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (RECIST V1.1)

End point description:

ORR was defined as the percentage of subjects achieving an overall best response of complete response (CR) or partial response (PR) (responders). CR was defined as disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures less than (<) 10 mm, PR was defined as at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the Baseline sum of diameters. Non-target lesions must be non-progressive disease. Analysis population included all randomized subjects with measurable disease at baseline per BICR. Here "Number of Subjects Analyzed" included all randomized subjects with measurable disease at baseline per BICR as of PCD. Updated efficacy data were not analyzed at study completion date due to study early termination.

End point type	Secondary

End point timeframe:

From randomization until disease progression or death (up to 24 months)

End point values	MEK162	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	101		
Units: percentage of subjects	16	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was defined as the time from first radiographic evidence of response to the earliest documented progression date or death due to any cause, and was calculated on responders only. Responders with no PD or death date or subsequent anticancer therapy by the data cutoff date, were censored for DOR at their last radiological assessment. Responders who received subsequent anticancer therapy prior to PD or death were censored at their last radiological assessment prior to initiation of subsequent anticancer therapy. Analysis population included all randomized subjects with measurable disease at baseline per BICR. Here, 'Number of Subjects Analyzed' signifies number of subjects evaluable for this outcome measure as of PCD. Updated efficacy data was not analyzed at study completion date due to study early termination.

End point type	Secondary

End point timeframe:

From the first radiographic evidence of response to the first documentation of PD or death, for censored subjects at their last radiological assessment (up to 24 months)

End point values	MEK162	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	8		
Units: months				
median (full range (min-max))	8.05 (0.03 to 11.99)	6.67 (0.03 to 9.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events

	(AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study intervention without regard to possibility of causal relationship. SAE: an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial/prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. The safety set included all subjects who received at least 1 dose of study intervention and had at least 1 post-treatment assessment, including death.

End point type	Secondary

End point timeframe:

From the first dose of study intervention until 30 days after the last dose (up to 9 years)

End point values	MEK162	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	106		
Units: subjects				
AEs	227	105		
SAEs	126	31		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

Disease control was defined as a best response of CR or PR, or stable disease (SD) documented at Week 24 or later. CR was defined as disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures <10 mm, and PR is defined as at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the Baseline sum of diameters. Non-target lesions must be non-progressive disease. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study. Due to the lack of follow-up data at the time of PCD, data reported for this outcome measure was not collected as of PCD. Updated efficacy data was not analyzed at study completion date due to study early termination.

End point type	Secondary

End point timeframe:

Week 24

End point values	MEK162	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: percentage of subjects				

Notes:

[4] - Due to the lack of follow up data at the time of data cutoff, data was not collected.

[5] - Due to the lack of follow up data at the time of data cutoff, data was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift Greater Than or Equal to Grade 3 From Baseline in Laboratory Parameter Values Based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03

End point title	Number of Subjects With Shift Greater Than or Equal to Grade 3 From Baseline in Laboratory Parameter Values Based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03

End point description:

Number of subjects with shifts from normal Baseline (Grade 0) to abnormal post-baseline on-study (shift to greater than or equal to Grade 3) were reported as per NCI-CTCAE, V4.03 from Grade 1 to 5. Grade 1: Mild; asymptomatic/mild symptoms; clinical/diagnostic observations only; intervention not indicated. Grade 2: Moderate; minimal, local/noninvasive intervention indicated. Grade 3: Severe/medically significant but not immediately life-threatening; hospitalization/prolongation of hospitalization indicated. Grade 4: Life-threatening consequences; urgent intervention indicated. Grade 5: Death. Shifts in lab parameter from Grade 0 to 3, Grade 0 to 4 and Grade 0 to Low 3 and 4 and Grade 0 to High 3 and 4 (for parameters total hemoglobin, lymphocytes, white blood cells, calcium, magnesium, potassium, and sodium) were reported. The safety set included all subjects who received at least 1 dose of study intervention and had at least 1 post-treatment assessment, including death.

End point type	Secondary

End point timeframe:

From the first dose of study intervention until 30 days after the last dose (up to 9 years)

End point values	MEK162	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	106		
Units: subjects				
International Normalized Ratio: Grade 0 to 3	0	0		
International Normalized Ratio: Grade 0 to 4	0	0		
Neutrophils: Grade 0 to 3	3	7		
Neutrophils: Grade 0 to 4	0	1		
Platelet Count: Grade 0 to 3	0	0		
Platelet Count: Grade 0 to 4	1	0		
Partial Thromboplastin Time: Grade 0 to 3	4	2		
Partial Thromboplastin Time: Grade 0 to 4	0	0		
Total Hemoglobin: Grade 0 to Low 3	10	2		
Total Hemoglobin: Grade 0 to Low 4	0	0		
Total Hemoglobin: Grade 0 to High 3	0	0		
Total Hemoglobin: Grade 0 to High 4	0	0		
Lymphocytes: Grade 0 to Low 3	8	3		

Lymphocytes: Grade 0 to Low 4	1	0		
Lymphocytes: Grade 0 to High 3	0	0		
Lymphocytes: Grade 0 to High 4	0	0		
White Blood Cells: Grade 0 to Low 3	0	1		
White Blood Cells: Grade 0 to Low 4	0	1		
White Blood Cells: Grade 0 to High 3	0	0		
White Blood Cells: Grade 0 to High 4	0	0		
Albumin: Grade 0 to 3	1	1		
Albumin: Grade 0 to 4	0	0		
Alkaline Phosphatase: Grade 0 to 3	4	1		
Alkaline Phosphatase: Grade 0 to 4	0	0		
ALT/SGPT: Grade 0 to 3	7	1		
ALT/SGPT: Grade 0 to 4	0	0		
AST/SGOT: Grade 0 to 3	7	1		
AST/SGOT: Grade 0 to 4	0	0		
Creatine Kinase: Grade 0 to 3	52	0		
Creatine Kinase: Grade 0 to 4	12	0		
Serum Creatinine: Grade 0 to 3	1	0		
Serum Creatinine: Grade 0 to 4	0	0		
Total Bilirubin: Grade 0 to 3	1	0		
Total Bilirubin: Grade 0 to 4	0	0		
Calcium: Grade 0 to Low 3	0	1		
Calcium: Grade 0 to Low 4	1	1		
Calcium: Grade 0 to High 3	1	0		
Calcium: Grade 0 to High 4	0	0		
Magnesium: Grade 0 to Low 3	2	1		
Magnesium: Grade 0 to Low 4	0	0		
Magnesium: Grade 0 to High 3	1	0		
Magnesium: Grade 0 to High 4	0	0		
Potassium: Grade 0 to Low 3	10	4		
Potassium: Grade 0 to Low 4	0	0		
Potassium: Grade 0 to High 3	3	2		
Potassium: Grade 0 to High 4	0	0		
Sodium: Grade 0 to Low 3	5	2		
Sodium: Grade 0 to Low 4	1	0		
Sodium: Grade 0 to High 3	3	0		
Sodium: Grade 0 to High 4	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment by the Quality of Life (QOL) Questionnaires European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30

End point title	Assessment by the Quality of Life (QOL) Questionnaires European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30

End point description:

The global health status/QOL scale score of the QLQ-C30 was identified as the primary patient-reported outcome variable of interest. Physical functioning, emotional functioning and social functioning scale

scores of the QLQ-C30 were considered as secondary. Higher scores for a functional or global QOL scale (Global health status/QOL, Physical functioning, Emotional functioning, and Social functioning) indicate higher QOL. The full analysis set included all randomized subjects.

End point type	Secondary

End point timeframe:

Screening, every 8 weeks from randomization date to Week 72, treatment discontinuation visit, 30-day safety follow-up visit

End point values	MEK162	Physician's Choice		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[6]	0[7]		
Units: Scale (0-100)				
arithmetic mean (standard deviation)	()	()		

Notes:

[6] - Patient-reported outcome data were not analyzed due to the early stopping of the trial.

[7] - Patient-reported outcome data were not analyzed due to the early stopping of the trial.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment by the QOL Questionnaires EORTC QLQ-OV28

End point title	Assessment by the QOL Questionnaires EORTC QLQ-OV28

End point description:

Analyses on the QLQ-OV28 was considered as secondary patient-reported outcome variable of interest. The parameters included Abdominal/gastrointestinal (GI), Peripheral neuropathy, Hormonal, Body image, Attitude to disease/treatment, Chemotherapy side effects, Other, and Sexuality. Higher scores for Sexuality indicate higher QOL. For all others, higher scores indicate lower QOL. The full analysis set included all randomized subjects.

End point type	Secondary

End point timeframe:

Screening, every 8 weeks from randomization date to Week 72, treatment discontinuation visit, 30-day safety follow-up visit

End point values	MEK162	Physician's Choice		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[8]	0[9]		
Units: Scale (0-100)				
arithmetic mean (standard deviation)	()	()		

Notes:

[8] - Patient-reported outcome data were not analyzed due to the early stopping of the trial.

[9] - Patient-reported outcome data were not analyzed due to the early stopping of the trial.

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment by the QOL Questionnaires FACT/GOG-NTX

End point title	Assessment by the QOL Questionnaires FACT/GOG-NTX

End point description:

Analyses on the FACT/GOG-NTX was considered as secondary patient-reported outcome variable of interest. The parameters included Physical well-being, Social well-being, Emotional well-being, Functional well-being, Neurotoxicity subscale, and Trial outcome index. Higher scores indicate higher QOL. The full analysis set included all randomized subjects.

End point type	Secondary

End point timeframe:

Screening, every 8 weeks from randomization date to Week 72, treatment discontinuation visit, 30-day safety follow-up visit

End point values	MEK162	Physician's Choice		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[10]	0[11]		
Units: Scale (0-100)				
arithmetic mean (standard deviation)	()	()		

Notes:

[10] - Patient-reported outcome data were not analyzed due to the early stopping of the trial.

[11] - Patient-reported outcome data were not analyzed due to the early stopping of the trial.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration-time Profiles of MEK162

End point title	Plasma Concentration-time Profiles of MEK162

End point description:

Plasma concentrations of MEK162 were determined using validated assays. The pharmacokinetics (PK) set consisted of all subjects who received at least 1 dose of MEK162 and had at least 1 postdose PK blood collection with associated bioanalytical results.

End point type	Secondary

End point timeframe:

Predose and 2 hours ± 10 minutes postdose on Study Days 1, 57, and 113.

End point values	MEK162	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: nanograms per millilitre (ng/mL)				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[12] - Due to the study early termination, PK data were not analyzed due to the small number of subjects.

[13] - Due to the study early termination, PK data were not analyzed due to the small number of subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Model-based PK Parameters of MEK162

End point title	Model-based PK Parameters of MEK162

End point description:

No noncompartmental PK parameters were estimated due to sparse sampling in this study. PK parameters were determined for MEK162 as appropriate using a model-based approach to determine appropriate model-based PK parameters and variability, if deemed appropriate. The PK set consisted of all subjects who received at least 1 dose of MEK162 and had at least 1 postdose PK blood collection with associated bioanalytical results.

End point type	Secondary

End point timeframe:

Predose and 2 hours ± 10 minutes postdose on Study Days 1, 57, and 113.

End point values	MEK162	Physician's Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[14] - Due to the study early termination, PK data were not analyzed due to the small number of subjects.
[15] - Due to the study early termination, PK data were not analyzed due to the small number of subjects.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study intervention until 30 days after the last dose (up to 9 years)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Physician's Choice

Reporting group description:

Subjects received chemotherapies as per treating physician’s choice in accordance to the institutional standard of care. Subjects received one of the three intravenous (IV) infusion therapies: Liposomal doxorubicin 40 milligram per meter square (mg/m^2) on Day 1 of each 28-day cycle or Paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle or, Topotecan 1.25 mg/m^2 on Days 1 through 5 of each 21-day cycle. Subjects were followed up to 30 days after last dose of study intervention.

Reporting group title	MEK162

Reporting group description:

Subjects received an oral dose of 45 milligram (mg) of MEK162 tablets (3 tablets of 15 mg) twice daily for each 28-day treatment cycle until disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, lost to follow-up or death, whichever occurred first. Subjects were followed up to 30 days after last dose of study intervention.

Serious adverse events	Physician's Choice	MEK162	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 106 (29.25%)	126 / 227 (55.51%)	
number of deaths (all causes)	28	92	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Papillary thyroid cancer			

subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (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	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 106 (1.89%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 106 (0.94%)	3 / 227 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	

Asthenia			
subjects affected / exposed	1 / 106 (0.94%)	2 / 227 (0.88%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 106 (0.94%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 106 (0.94%)	3 / 227 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pain			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (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			
Pulmonary embolism			
subjects affected / exposed	1 / 106 (0.94%)	6 / 227 (2.64%)	
occurrences causally related to treatment / all	1 / 1	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	3 / 106 (2.83%)	6 / 227 (2.64%)	
occurrences causally related to treatment / all	0 / 3	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea			
subjects affected / exposed	2 / 106 (1.89%)	3 / 227 (1.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 106 (0.00%)	2 / 227 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis allergic			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 106 (0.94%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Hallucination			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic reaction			

subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 106 (0.00%)	4 / 227 (1.76%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 106 (0.94%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 106 (0.00%)	2 / 227 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin I increased			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration pleural cavity			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Feeding tube complication			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
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 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured coccyx			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 106 (0.00%)	2 / 227 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 106 (0.94%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 106 (0.00%)	2 / 227 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dropped head syndrome			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 106 (1.89%)	9 / 227 (3.96%)	
occurrences causally related to treatment / all	2 / 2	15 / 29	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	0 / 106 (0.00%)	4 / 227 (1.76%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Choroiditis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal oedema			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein thrombosis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	8 / 106 (7.55%)	12 / 227 (5.29%)	
occurrences causally related to treatment / all	0 / 15	1 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 106 (1.89%)	16 / 227 (7.05%)	
occurrences causally related to treatment / all	2 / 3	8 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	4 / 106 (3.77%)	15 / 227 (6.61%)	
occurrences causally related to treatment / all	0 / 4	0 / 19	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			

subjects affected / exposed	1 / 106 (0.94%)	7 / 227 (3.08%)	
occurrences causally related to treatment / all	0 / 1	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 106 (0.00%)	10 / 227 (4.41%)	
occurrences causally related to treatment / all	0 / 0	7 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 106 (1.89%)	8 / 227 (3.52%)	
occurrences causally related to treatment / all	1 / 2	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	4 / 106 (3.77%)	7 / 227 (3.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic obstruction			
subjects affected / exposed	0 / 106 (0.00%)	4 / 227 (1.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 106 (0.00%)	3 / 227 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)	3 / 227 (1.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 106 (0.94%)	3 / 227 (1.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	2 / 106 (1.89%)	7 / 227 (3.08%)	
occurrences causally related to treatment / all	0 / 2	1 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)	2 / 227 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)	2 / 227 (0.88%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis ulcerative			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal ulcer			

subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal ulcer			

subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal discomfort			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal hypomotility			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal fistula			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 106 (0.00%)	2 / 227 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 106 (0.00%)	2 / 227 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal pain			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 106 (0.00%)	6 / 227 (2.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain in extremity			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 106 (0.94%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 106 (0.94%)	9 / 227 (3.96%)	
occurrences causally related to treatment / all	1 / 1	2 / 9	
deaths causally related to treatment / all	0 / 0	1 / 3	
Urinary tract infection			
subjects affected / exposed	1 / 106 (0.94%)	8 / 227 (3.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 106 (0.00%)	3 / 227 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cystitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	2 / 106 (1.89%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 106 (0.00%)	4 / 227 (1.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site cellulitis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 106 (0.00%)	2 / 227 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 106 (1.89%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			

subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal sepsis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal bacteraemia			

subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection fungal			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node tuberculosis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 106 (0.94%)	2 / 227 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			

subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoas abscess			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 106 (0.94%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 106 (0.00%)	4 / 227 (1.76%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			

subjects affected / exposed	1 / 106 (0.94%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 227 (0.44%)	
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: 5 %

Non-serious adverse events	Physician's Choice	MEK162	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 106 (99.06%)	226 / 227 (99.56%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	3 / 106 (2.83%)	15 / 227 (6.61%)	
occurrences (all)	3	15	
Hypertension			
subjects affected / exposed	4 / 106 (3.77%)	46 / 227 (20.26%)	
occurrences (all)	9	135	
General disorders and administration site conditions			

Non-cardiac chest pain			
subjects affected / exposed	7 / 106 (6.60%)	11 / 227 (4.85%)	
occurrences (all)	7	12	
Chills			
subjects affected / exposed	5 / 106 (4.72%)	16 / 227 (7.05%)	
occurrences (all)	6	21	
Face oedema			
subjects affected / exposed	1 / 106 (0.94%)	28 / 227 (12.33%)	
occurrences (all)	1	40	
Asthenia			
subjects affected / exposed	7 / 106 (6.60%)	29 / 227 (12.78%)	
occurrences (all)	11	64	
Pyrexia			
subjects affected / exposed	17 / 106 (16.04%)	42 / 227 (18.50%)	
occurrences (all)	26	59	
Oedema peripheral			
subjects affected / exposed	16 / 106 (15.09%)	120 / 227 (52.86%)	
occurrences (all)	19	238	
Fatigue			
subjects affected / exposed	54 / 106 (50.94%)	120 / 227 (52.86%)	
occurrences (all)	100	232	
Pain			
subjects affected / exposed	2 / 106 (1.89%)	14 / 227 (6.17%)	
occurrences (all)	2	17	
Oedema			
subjects affected / exposed	2 / 106 (1.89%)	15 / 227 (6.61%)	
occurrences (all)	7	23	
Malaise			
subjects affected / exposed	4 / 106 (3.77%)	13 / 227 (5.73%)	
occurrences (all)	4	15	
Influenza like illness			
subjects affected / exposed	2 / 106 (1.89%)	12 / 227 (5.29%)	
occurrences (all)	3	16	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	17 / 106 (16.04%)	45 / 227 (19.82%)	
occurrences (all)	29	75	
Cough			
subjects affected / exposed	23 / 106 (21.70%)	26 / 227 (11.45%)	
occurrences (all)	39	35	
Oropharyngeal pain			
subjects affected / exposed	7 / 106 (6.60%)	24 / 227 (10.57%)	
occurrences (all)	8	34	
Epistaxis			
subjects affected / exposed	4 / 106 (3.77%)	17 / 227 (7.49%)	
occurrences (all)	4	22	
Dysphonia			
subjects affected / exposed	2 / 106 (1.89%)	13 / 227 (5.73%)	
occurrences (all)	2	14	
Dyspnoea exertional			
subjects affected / exposed	0 / 106 (0.00%)	12 / 227 (5.29%)	
occurrences (all)	0	14	
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 106 (2.83%)	18 / 227 (7.93%)	
occurrences (all)	3	22	
Anxiety			
subjects affected / exposed	6 / 106 (5.66%)	21 / 227 (9.25%)	
occurrences (all)	11	28	
Insomnia			
subjects affected / exposed	12 / 106 (11.32%)	32 / 227 (14.10%)	
occurrences (all)	20	37	
Investigations			
Weight decreased			
subjects affected / exposed	12 / 106 (11.32%)	15 / 227 (6.61%)	
occurrences (all)	19	20	
Weight increased			
subjects affected / exposed	3 / 106 (2.83%)	18 / 227 (7.93%)	
occurrences (all)	4	31	
Alanine aminotransferase increased			

subjects affected / exposed	4 / 106 (3.77%)	28 / 227 (12.33%)	
occurrences (all)	4	88	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 106 (1.89%)	33 / 227 (14.54%)	
occurrences (all)	2	84	
Ejection fraction decreased			
subjects affected / exposed	11 / 106 (10.38%)	66 / 227 (29.07%)	
occurrences (all)	15	103	
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 106 (1.89%)	120 / 227 (52.86%)	
occurrences (all)	3	644	
Neutrophil count decreased			
subjects affected / exposed	9 / 106 (8.49%)	6 / 227 (2.64%)	
occurrences (all)	26	13	
Blood creatinine increased			
subjects affected / exposed	2 / 106 (1.89%)	14 / 227 (6.17%)	
occurrences (all)	2	25	
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 106 (20.75%)	48 / 227 (21.15%)	
occurrences (all)	33	75	
Dysgeusia			
subjects affected / exposed	12 / 106 (11.32%)	28 / 227 (12.33%)	
occurrences (all)	15	41	
Dizziness			
subjects affected / exposed	9 / 106 (8.49%)	33 / 227 (14.54%)	
occurrences (all)	9	44	
Neuropathy peripheral			
subjects affected / exposed	14 / 106 (13.21%)	20 / 227 (8.81%)	
occurrences (all)	20	24	
Paraesthesia			
subjects affected / exposed	4 / 106 (3.77%)	13 / 227 (5.73%)	
occurrences (all)	5	18	
Peripheral sensory neuropathy			

subjects affected / exposed	8 / 106 (7.55%)	4 / 227 (1.76%)	
occurrences (all)	10	5	
Memory impairment			
subjects affected / exposed	6 / 106 (5.66%)	3 / 227 (1.32%)	
occurrences (all)	6	3	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	14 / 106 (13.21%)	5 / 227 (2.20%)	
occurrences (all)	27	11	
Anaemia			
subjects affected / exposed	21 / 106 (19.81%)	38 / 227 (16.74%)	
occurrences (all)	72	135	
Eye disorders			
Vision blurred			
subjects affected / exposed	8 / 106 (7.55%)	41 / 227 (18.06%)	
occurrences (all)	9	51	
Retinal detachment			
subjects affected / exposed	0 / 106 (0.00%)	37 / 227 (16.30%)	
occurrences (all)	0	59	
Dry eye			
subjects affected / exposed	7 / 106 (6.60%)	25 / 227 (11.01%)	
occurrences (all)	7	29	
Eyelid oedema			
subjects affected / exposed	0 / 106 (0.00%)	16 / 227 (7.05%)	
occurrences (all)	0	23	
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 106 (0.00%)	15 / 227 (6.61%)	
occurrences (all)	0	19	
Periorbital oedema			
subjects affected / exposed	1 / 106 (0.94%)	17 / 227 (7.49%)	
occurrences (all)	1	21	
Retinal disorder			
subjects affected / exposed	0 / 106 (0.00%)	12 / 227 (5.29%)	
occurrences (all)	0	29	
Conjunctivitis			

subjects affected / exposed	3 / 106 (2.83%)	12 / 227 (5.29%)	
occurrences (all)	3	19	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	39 / 106 (36.79%)	160 / 227 (70.48%)	
occurrences (all)	59	369	
Vomiting			
subjects affected / exposed	32 / 106 (30.19%)	129 / 227 (56.83%)	
occurrences (all)	58	286	
Abdominal pain			
subjects affected / exposed	27 / 106 (25.47%)	77 / 227 (33.92%)	
occurrences (all)	50	139	
Constipation			
subjects affected / exposed	31 / 106 (29.25%)	66 / 227 (29.07%)	
occurrences (all)	49	91	
Nausea			
subjects affected / exposed	55 / 106 (51.89%)	135 / 227 (59.47%)	
occurrences (all)	98	263	
Abdominal pain upper			
subjects affected / exposed	6 / 106 (5.66%)	23 / 227 (10.13%)	
occurrences (all)	8	33	
Abdominal distension			
subjects affected / exposed	6 / 106 (5.66%)	25 / 227 (11.01%)	
occurrences (all)	9	32	
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 106 (6.60%)	23 / 227 (10.13%)	
occurrences (all)	9	25	
Dry mouth			
subjects affected / exposed	9 / 106 (8.49%)	37 / 227 (16.30%)	
occurrences (all)	13	39	
Dyspepsia			
subjects affected / exposed	11 / 106 (10.38%)	32 / 227 (14.10%)	
occurrences (all)	13	40	
Stomatitis			
subjects affected / exposed	35 / 106 (33.02%)	54 / 227 (23.79%)	
occurrences (all)	77	88	

Ascites			
subjects affected / exposed	6 / 106 (5.66%)	15 / 227 (6.61%)	
occurrences (all)	9	24	
Rectal haemorrhage			
subjects affected / exposed	6 / 106 (5.66%)	10 / 227 (4.41%)	
occurrences (all)	6	14	
Flatulence			
subjects affected / exposed	2 / 106 (1.89%)	17 / 227 (7.49%)	
occurrences (all)	3	18	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	6 / 106 (5.66%)	110 / 227 (48.46%)	
occurrences (all)	8	267	
Alopecia			
subjects affected / exposed	28 / 106 (26.42%)	57 / 227 (25.11%)	
occurrences (all)	38	63	
Rash maculo-papular			
subjects affected / exposed	17 / 106 (16.04%)	57 / 227 (25.11%)	
occurrences (all)	34	140	
Dry skin			
subjects affected / exposed	14 / 106 (13.21%)	77 / 227 (33.92%)	
occurrences (all)	17	110	
Skin fissures			
subjects affected / exposed	1 / 106 (0.94%)	34 / 227 (14.98%)	
occurrences (all)	1	65	
Rash			
subjects affected / exposed	10 / 106 (9.43%)	36 / 227 (15.86%)	
occurrences (all)	15	51	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	36 / 106 (33.96%)	11 / 227 (4.85%)	
occurrences (all)	104	27	
Pruritus			
subjects affected / exposed	11 / 106 (10.38%)	51 / 227 (22.47%)	
occurrences (all)	16	78	
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	1 / 106 (0.94%)	15 / 227 (6.61%)	
occurrences (all)	1	21	
Dysuria			
subjects affected / exposed	4 / 106 (3.77%)	16 / 227 (7.05%)	
occurrences (all)	4	16	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 106 (0.94%)	20 / 227 (8.81%)	
occurrences (all)	3	29	
Muscular weakness			
subjects affected / exposed	3 / 106 (2.83%)	21 / 227 (9.25%)	
occurrences (all)	3	30	
Pain in extremity			
subjects affected / exposed	7 / 106 (6.60%)	25 / 227 (11.01%)	
occurrences (all)	9	36	
Arthralgia			
subjects affected / exposed	8 / 106 (7.55%)	38 / 227 (16.74%)	
occurrences (all)	11	50	
Myalgia			
subjects affected / exposed	14 / 106 (13.21%)	44 / 227 (19.38%)	
occurrences (all)	15	75	
Back pain			
subjects affected / exposed	11 / 106 (10.38%)	31 / 227 (13.66%)	
occurrences (all)	12	51	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	13 / 106 (12.26%)	43 / 227 (18.94%)	
occurrences (all)	24	84	
Upper respiratory tract infection			
subjects affected / exposed	8 / 106 (7.55%)	20 / 227 (8.81%)	
occurrences (all)	11	26	
Rash pustular			
subjects affected / exposed	2 / 106 (1.89%)	15 / 227 (6.61%)	
occurrences (all)	4	24	
Paronychia			

subjects affected / exposed	2 / 106 (1.89%)	12 / 227 (5.29%)	
occurrences (all)	2	22	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	6 / 106 (5.66%)	23 / 227 (10.13%)	
occurrences (all)	10	38	
Hypomagnesaemia			
subjects affected / exposed	6 / 106 (5.66%)	28 / 227 (12.33%)	
occurrences (all)	13	56	
Decreased appetite			
subjects affected / exposed	21 / 106 (19.81%)	55 / 227 (24.23%)	
occurrences (all)	24	79	
Dehydration			
subjects affected / exposed	1 / 106 (0.94%)	13 / 227 (5.73%)	
occurrences (all)	1	15	
Hypocalcaemia			
subjects affected / exposed	1 / 106 (0.94%)	12 / 227 (5.29%)	
occurrences (all)	1	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2017	Protocol Amendment 6 was issued on 15 March 2017. Any subjects still receiving binimetinib/MEK162 at the time Protocol Amendment 6 was implemented were allowed to continue at the discretion of the investigator until any treatment discontinuation criteria were met. After treatment withdrawal, all subjects were discontinued from the study after their 30-day Safety Follow-up Visit. No further survival follow up were performed and BICR scans were no longer being collected or read. Crossover from physician's choice chemotherapy treatment to binimetinib treatment was no longer permitted. Subjects receiving physician's choice chemotherapy were transitioned to standard of care therapy according to institutional standards.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 April 2016	Per recommendation of the Data Monitoring Committee, enrollment into the study was discontinued in April 2016 after the planned interim efficacy analysis showed the hazard ratio for PFS crossed the predefined futility boundary. As such, screening and randomization was discontinued.	-

Notes:

Limitations and caveats

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

Additional efficacy data after PCD and PRO data were not analyzed due to study early termination. PK data were not analyzed due to the small number of subjects. Analysis was not performed due to the low number of subjects in the crossover set.

Notes: