



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/m²) on Day 1 of each 28-day cycle or Paclitaxel 80 mg/m² on Days 1, 8, and 15 of each 28-day cycle or, Topotecan 1.25 mg/m² 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/m²) on Day 1 of each 28-day cycle or Paclitaxel 80 mg/m² on Days 1, 8, and 15 of each 28-day cycle or, Topotecan 1.25 mg/m² 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 (\geq) 5 millimeter (mm). Appearance of new lesions \geq 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: 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: 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: 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 \pm 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 \pm 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/m²) on Day 1 of each 28-day cycle or Paclitaxel 80 mg/m² on Days 1, 8, and 15 of each 28-day cycle or, Topotecan 1.25 mg/m² 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 occurrences (all) | 8 / 106 (7.55%) 10 | 4 / 227 (1.76%) 5 | |
| Memory impairment subjects affected / exposed occurrences (all) | 6 / 106 (5.66%) 6 | 3 / 227 (1.32%) 3 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia subjects affected / exposed occurrences (all) | 14 / 106 (13.21%) 27 | 5 / 227 (2.20%) 11 | |
| Anaemia subjects affected / exposed occurrences (all) | 21 / 106 (19.81%) 72 | 38 / 227 (16.74%) 135 | |
| Eye disorders | | | |
| Vision blurred subjects affected / exposed occurrences (all) | 8 / 106 (7.55%) 9 | 41 / 227 (18.06%) 51 | |
| Retinal detachment subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 37 / 227 (16.30%) 59 | |
| Dry eye subjects affected / exposed occurrences (all) | 7 / 106 (6.60%) 7 | 25 / 227 (11.01%) 29 | |
| Eyelid oedema subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 16 / 227 (7.05%) 23 | |
| Detachment of retinal pigment epithelium subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 15 / 227 (6.61%) 19 | |
| Periorbital oedema subjects affected / exposed occurrences (all) | 1 / 106 (0.94%) 1 | 17 / 227 (7.49%) 21 | |
| Retinal disorder subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 12 / 227 (5.29%) 29 | |
| Conjunctivitis | | | |

| | | | |
|--|----------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 106 (2.83%) 3 | 12 / 227 (5.29%) 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 occurrences (all) | 2 / 106 (1.89%) 2 | 12 / 227 (5.29%) 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: