



Clinical trial results:

An Open-Label, Single-arm, Phase Ib/II study of AEB071 (a Protein Kinase C Inhibitor) and Everolimus (mTOR inhibitor) in Patients with CD79-mutant or ABC subtype Diffuse Large B-Cell Lymphoma

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-001265-16 |
| Trial protocol | IT DE NL FR |
| Global end of trial date | 01 June 2016 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 08 June 2017 |
| First version publication date | 08 June 2017 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | COEB071X2103 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01854606 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | ND: ND |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharmaceuticals AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Novartis Pharmaceuticals AG, Novartis Pharmaceuticals AG, 41 613241111, |
| Scientific contact | Novartis Pharmaceuticals AG, Novartis Pharmaceuticals AG, 41 613241111, |

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 | 01 June 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 June 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The Phase Ib part of the study was to estimate the maximum tolerated dose/recommended Phase II dose (MTD/RP2D) of the combination of sotrastaurin and everolimus in patients with CD79 mutant and/or activated B-cell (ABC) subtype diffuse large B-cell lymphoma (DLBCL). The Phase II part was to assess the preliminary evidence of anti-tumor activity at the RP2D for the combination of sotrastaurin and everolimus in the same patient population (i.e. patients with a CD79 mutation and in those wild-type for the mutation but of the ABC subtype). However, due to suboptimal tolerability of the combination treatment of sotrastaurin and everolimus in the Phase Ib part of the study, the Phase II part was not initiated nor conducted.

Protection of trial subjects:

This study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 05 December 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Hong Kong: 5 |
| Country: Number of subjects enrolled | Korea, Republic of: 12 |
| Country: Number of subjects enrolled | United States: 6 |
| Country: Number of subjects enrolled | Taiwan: 1 |
| Country: Number of subjects enrolled | Netherlands: 4 |
| Country: Number of subjects enrolled | Germany: 3 |
| Worldwide total number of subjects | 31 |
| EEA total number of subjects | 7 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| 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) | 16 |
| From 65 to 84 years | 15 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

At the study termination date (01-Jun-2016), all 31 patients had discontinued study.

Pre-assignment

Screening details:

A minimum of 70 patients (at least 15 for Phase Ib and approximately 55 for Phase II) were to be enrolled. At the time of enrollment halt, a total of 31 patients were enrolled into the Phase Ib part of the study. Treatment arms were described by sotrastaurin dose and regimen only since the dose and regimen of everolimus remained constant.

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | 200mg Sotrastaurin + 2.5 mg everolimus |

Arm description:

Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | AEB071 |
| Investigational medicinal product code | |
| Other name | Sotrastaurin |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were to receive sotrastaurin orally, twice a day (at approximately 12-hour intervals). The patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

| | |
|--|------------|
| Investigational medicinal product name | Everolimus |
| Investigational medicinal product code | |
| Other name | RAD001 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were to receive 2.5mg everolimus once daily. The patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

| | |
|------------------|--|
| Arm title | 250mg Sotrastaurin + 2.5 mg everolimus |
|------------------|--|

Arm description:

Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | AEB071 |
| Investigational medicinal product code | |
| Other name | Sotrastaurin |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were to receive sotrastaurin orally, twice a day (at approximately 12-hour intervals). The

patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

| | |
|--|------------|
| Investigational medicinal product name | Everolimus |
| Investigational medicinal product code | |
| Other name | RAD001 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were to receive everolimus once daily. The patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

| | |
|------------------|--|
| Arm title | 300mg Sotrastaurin + 2.5 mg everolimus |
|------------------|--|

Arm description:

Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | AEB071 |
| Investigational medicinal product code | |
| Other name | Sotrastaurin |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were to receive sotrastaurin orally, twice a day (at approximately 12-hour intervals). The patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

| | |
|--|------------|
| Investigational medicinal product name | Everolimus |
| Investigational medicinal product code | |
| Other name | RAD001 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were to receive everolimus once daily. The patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

| | |
|------------------|--|
| Arm title | 400mg Sotrastaurin + 2.5 mg everolimus |
|------------------|--|

Arm description:

Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | AEB071 |
| Investigational medicinal product code | |
| Other name | Sotrastaurin |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were to receive sotrastaurin orally, twice a day (at approximately 12-hour intervals). The patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

| | |
|--|------------|
| Investigational medicinal product name | Everolimus |
| Investigational medicinal product code | |
| Other name | RAD001 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Patients were to receive everolimus once daily. The patient's dose of each study drug depended upon which dose level the patient was assigned to. Patients were dosed on a flat, fixed dose and not by body weight or body surface area.

weight or body surface area.

| Number of subjects in period 1 | 200mg Sotrastaurin + 2.5 mg everolimus | 250mg Sotrastaurin + 2.5 mg everolimus | 300mg Sotrastaurin + 2.5 mg everolimus |
|--|--|---|--|
| | | | |
| Started | 3 | 16 | 6 |
| Completed | 0 | 0 | 0 |
| Not completed | 3 | 16 | 6 |
| Adverse event, serious fatal | - | 4 | 1 |
| Consent withdrawn by subject | 1 | 1 | 2 |
| Physician decision | - | - | 1 |
| Adverse event, non-fatal | - | 3 | - |
| Follow-up phase completed as per protocol | 2 | 7 | 2 |
| Lost to follow-up | - | 1 | - |

| Number of subjects in period 1 | 400mg Sotrastaurin + 2.5 mg everolimus |
|--|--|
| Started | 6 |
| Completed | 0 |
| Not completed | 6 |
| Adverse event, serious fatal | 2 |
| Consent withdrawn by subject | 2 |
| Physician decision | - |
| Adverse event, non-fatal | - |
| Follow-up phase completed as per protocol | 2 |
| Lost to follow-up | - |

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | 200mg Sotrastaurin + 2.5 mg everolimus |
| Reporting group description: | |
| Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily | |
| Reporting group title | 250mg Sotrastaurin + 2.5 mg everolimus |
| Reporting group description: | |
| Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily | |
| Reporting group title | 300mg Sotrastaurin + 2.5 mg everolimus |
| Reporting group description: | |
| Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily | |
| Reporting group title | 400mg Sotrastaurin + 2.5 mg everolimus |
| Reporting group description: | |
| Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily | |

| Reporting group values | 200mg Sotrastaurin + 2.5 mg everolimus | 250mg Sotrastaurin + 2.5 mg everolimus | 300mg Sotrastaurin + 2.5 mg everolimus |
|--|--|--|--|
| Number of subjects | 3 | 16 | 6 |
| Age categorical | | | |
| Units: Subjects | | | |
| < 65 Years | 2 | 6 | 3 |
| 65 to < 85 Years | 1 | 10 | 3 |
| Age continuous | | | |
| Full Analysis Set (FAS): Consisted of all patients who received at least one full or partial dose of sotrastaurin or everolimus. Patient data were analyzed according to the planned treatment combination. Unless otherwise specified, FAS is the default set for Phase Ib data analysis. | | | |
| Units: years | | | |
| arithmetic mean | 58 | 64.8 | 59.2 |
| standard deviation | ± 7 | ± 10.62 | ± 14.06 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 1 | 4 | 0 |
| Male | 2 | 12 | 6 |

| Reporting group values | 400mg Sotrastaurin + 2.5 mg everolimus | Total | |
|--|--|-------|--|
| Number of subjects | 6 | 31 | |
| Age categorical | | | |
| Units: Subjects | | | |
| < 65 Years | 5 | 16 | |
| 65 to < 85 Years | 1 | 15 | |
| Age continuous | | | |
| Full Analysis Set (FAS): Consisted of all patients who received at least one full or partial dose of sotrastaurin or everolimus. Patient data were analyzed according to the planned treatment combination. Unless otherwise specified, FAS is the default set for Phase Ib data analysis. | | | |
| Units: years | | | |
| arithmetic mean | 55.5 | | |
| standard deviation | ± 13.52 | - | |

| | | | |
|--------------------|---|----|--|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 3 | 8 | |
| Male | 3 | 23 | |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | 200mg Sotrastaurin + 2.5 mg everolimus |
| Reporting group description: Sotrastaurin 200 mg twice daily + everolimus 2.5 mg once daily | |
| Reporting group title | 250mg Sotrastaurin + 2.5 mg everolimus |
| Reporting group description: Sotrastaurin 250 mg twice daily + everolimus 2.5 mg once daily | |
| Reporting group title | 300mg Sotrastaurin + 2.5 mg everolimus |
| Reporting group description: Sotrastaurin 300 mg twice daily + everolimus 2.5 mg once daily | |
| Reporting group title | 400mg Sotrastaurin + 2.5 mg everolimus |
| Reporting group description: Sotrastaurin 400 mg twice daily + everolimus 2.5 mg once daily | |
| Subject analysis set title | 0-0.16 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Dose determining set (DDS): The DDS consisted of all patients from the Safety Set who either met the minimum exposure criterion and had sufficient safety evaluations during Cycle 1, or experienced a DLT during Cycle 1. A patient was considered to have met the minimum exposure criterion if they received at least 21 out of the 28 planned daily combination doses of sotrastaurin (bid) and everolimus (qd) in the first 28 days of dosing. Patients who did not experience a DLT during the first cycle were considered to have sufficient safety evaluations if they were observed for at least 28 days following the first dose and were considered by both Novartis and Investigators to have had enough safety data to conclude that a DLT did not occur. | |
| Subject analysis set title | 0.16-0.35 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Dose determining set (DDS). | |
| Subject analysis set title | 0.35-1 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Dose determining set (DDS). | |
| Subject analysis set title | All Dose Cohorts |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Full Analysis Set (FAS): Consisted of all patients who received at least one full or partial dose of sotrastaurin or everolimus. Patient data were analyzed according to the planned treatment combination. Unless otherwise specified, FAS is the default set for Phase Ib data analysis. | |

Primary: Posterior Distribution of Dose Limiting Toxicities (DLTs) rates at time of last dose escalation meeting, 2.5 mg Everolimus

| | |
|--|---|
| End point title | Posterior Distribution of Dose Limiting Toxicities (DLTs) rates at time of last dose escalation meeting, 2.5 mg Everolimus ^[1] |
| End point description: Dose determining set (DDS): The DDS consisted of all patients from the Safety Set who either met the minimum exposure criterion and had sufficient safety evaluations during Cycle 1, or experienced a DLT during Cycle 1. A patient was considered to have met the minimum exposure criterion if they received at least 21 out of the 28 planned daily combination doses of sotrastaurin (bid) and everolimus (qd) in the first 28 days of dosing. Patients who did not experience a DLT during the first cycle were considered to have sufficient safety evaluations if they were observed for at least 28 days following the first dose and were considered by both Novartis and Investigators to have had enough safety data to conclude that a DLT did not occur. | |
| End point type | Primary |

End point timeframe:

Approximately 12 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: Descriptive analyses.

| End point values | 0-0.16 | 0.16-0.35 | 0.35-1 | |
|-----------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 28 ^[2] | 28 ^[3] | 28 ^[4] | |
| Units: probability | | | | |
| number (not applicable) | | | | |
| 250mg sotrastaurin | 0.37 | 0.616 | 0.014 | |
| 300mg sotrastaurin | 0.231 | 0.738 | 0.031 | |
| 350mg sotrastaurin | 0.137 | 0.783 | 0.08 | |
| 400mg sotrastaurin | 0.086 | 0.743 | 0.171 | |
| 450mg sotrastaurin | 0.061 | 0.66 | 0.279 | |

Notes:

[2] - all patients in DDS

[3] - all patients in DDS

[4] - all patients in DDS

Statistical analyses

No statistical analyses for this end point

Primary: Posterior Distribution of Dose Limiting Toxicities (DLTs) Rates at time of last dose escalation meeting, 5.0 mg Everilimus

| | |
|-----------------|---|
| End point title | Posterior Distribution of Dose Limiting Toxicities (DLTs) Rates at time of last dose escalation meeting, 5.0 mg Everilimus ^[5] |
|-----------------|---|

End point description:

Analysis done in the Dose determining set (DDS).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Approximately 12 months

Notes:

[5] - 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: Descriptive analyses.

| End point values | 0-0.16 | 0.16-0.35 | 0.35-1 | |
|-----------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 28 ^[6] | 28 ^[7] | 28 ^[8] | |
| Units: Probability | | | | |
| number (not applicable) | | | | |
| 250mg sotrastaurin | 0.155 | 0.682 | 0.162 | |
| 300mg sotrastaurin | 0.098 | 0.602 | 0.3 | |
| 350mg sotrastaurin | 0.069 | 0.488 | 0.443 | |

Notes:

[6] - All patients in the DDS

[7] - All patients in the DDS

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1

| | |
|-----------------|--|
| End point title | Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1 ^[9] |
|-----------------|--|

End point description:

Estimate the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) of the AEB071and EVEROLIMUS combination therapy in patients with DLBCL in the Dose determining set (DDS).

A patient with multiple occurrences of DLTs under one treatment is counted only once in the AE category for that treatment.

A patient with multiple DLTs within a primary system organ class is counted only once in the total row.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Approximately 12 months

Notes:

[9] - 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: Descriptive analyses.

| End point values | 200mg Sotrastaurin + 2.5 mg everolimus | 250mg Sotrastaurin + 2.5 mg everolimus | 300mg Sotrastaurin + 2.5 mg everolimus | 400mg Sotrastaurin + 2.5 mg everolimus |
|--------------------------------------|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 14 | 5 | 6 |
| Units: Participants | | | | |
| Blood and lymphatic system disorders | 0 | 1 | 0 | 0 |
| -Thrombocytopenia | 0 | 1 | 0 | 0 |
| Gastrointestinal disorders | 1 | 0 | 0 | 2 |
| -Nausea | 0 | 0 | 0 | 2 |
| -Vomiting | 0 | 0 | 0 | 2 |
| -Diarrhoea | 0 | 0 | 0 | 1 |
| -Stomatitis | 1 | 0 | 0 | 0 |
| Infections and infestations | 0 | 1 | 0 | 0 |
| -Pneumocystis jirovecii pneumonia | 0 | 1 | 0 | 0 |
| Metabolism and nutrition disorders | 0 | 1 | 1 | 0 |
| -Decreased appetite | 0 | 0 | 1 | 0 |
| -Hypertriglyceridaemia | 0 | 1 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Radiological Response

| | |
|-----------------|------------------------------------|
| End point title | Best Overall Radiological Response |
|-----------------|------------------------------------|

End point description:

Evaluate preliminary anti-tumor activity for AE071 and EVEROLIMUS in the Dose determining set (DDS).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

approximately 24 months

| End point values | All Dose Cohorts | | | |
|-------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 31 | | | |
| Units: Patients | | | | |
| Complete response | 1 | | | |
| Partial response | 4 | | | |
| Stable disease | 9 | | | |
| Progressive disease | 6 | | | |
| Unknown best overall response | 11 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Area Under Curve

| | |
|-----------------|--|
| End point title | Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Area Under Curve |
|-----------------|--|

End point description:

Pharmacokinetic Analysis Set: Consisted of all patients who had evaluable PK data. The Pharmacokinetic Analysis Set was used for summaries (tables and figures) and listings of derived PK data. Patients could be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients were identified at the time of the analyses.

Area Under Curve (AUC_{0-8h}) = Area under the concentration-time curve from time 0 to 8 hours post-dose [mass x time x volume⁻¹]

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

| End point values | 200mg Sotrastaurin + 2.5 mg everolimus | 250mg Sotrastaurin + 2.5 mg everolimus | 300mg Sotrastaurin + 2.5 mg everolimus | 400mg Sotrastaurin + 2.5 mg everolimus |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 16 | 6 | 6 |
| Units: hr*ng/mL | | | | |

| median (full range (min-max)) | | | | |
|-------------------------------|------------------------|-----------------------|------------------------|------------------------|
| Day 1 | 7660 (7660 to 7660) | 14000 (3960 to 35800) | 18600 (14100 to 23900) | 29000 (27700 to 30300) |
| Day 15 | 13200 (11500 to 17400) | 19100 (8590 to 37200) | 30100 (23400 to 81900) | 36800 (14100 to 51700) |

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Cmax

| | |
|-----------------|--|
| End point title | Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Cmax |
|-----------------|--|

End point description:

Analysis done in the Pharmacokinetic Analysis Set.

Cmax=Maximum observed concentration after drug administration [mass x volume-1].

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

| End point values | 200mg Sotrastaurin + 2.5 mg everolimus | 250mg Sotrastaurin + 2.5 mg everolimus | 300mg Sotrastaurin + 2.5 mg everolimus | 400mg Sotrastaurin + 2.5 mg everolimus |
|-------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 16 | 6 | 6 |
| Units: ng/ml | | | | |
| median (full range (min-max)) | | | | |
| Day 1 | 3420 (3420 to 3420) | 2970 (718 to 5780) | 3310 (2500 to 3640) | 7690 (7370 to 8000) |
| Day 15 | 2530 (2320 to 2870) | 3840 (1770 to 6280) | 4610 (3470 to 12900) | 5270 (3700 to 9870) |

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Tmax

| | |
|-----------------|--|
| End point title | Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Tmax |
|-----------------|--|

End point description:

Analysis done in the Pharmacokinetic Analysis Set.

Tmax=Time to reach Cmax [time]

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

| End point values | 200mg Sotrastaurin + 2.5 mg everolimus | 250mg Sotrastaurin + 2.5 mg everolimus | 300mg Sotrastaurin + 2.5 mg everolimus | 400mg Sotrastaurin + 2.5 mg everolimus |
|-------------------------------|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 16 | 6 | 6 |
| Units: hr | | | | |
| median (full range (min-max)) | | | | |
| Day 1 | 1 (1 to 1) | 2 (0.5 to 5.98) | 3.97 (0.967 to 4.17) | 0.992 (0.983 to 1) |
| Day 15 | 1.08 (1 to 1.93) | 2 (0.5 to 4.05) | 4.05 (2 to 4.25) | 1 (0.533 to 2.05) |

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Racc

| | |
|-----------------|--|
| End point title | Primary PK Parameters for Whole Blood Sotrastaurin by Treatment Group - Racc |
|-----------------|--|

End point description:

Analysis done in the Pharmacokinetic Analysis Set.

Racc = Accumulation ratio calculated as AUC0-8h or AUCtau at Day 15/AUC0-8h or AUCtau at Day 1

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

| End point values | 200mg Sotrastaurin + 2.5 mg everolimus | 250mg Sotrastaurin + 2.5 mg everolimus | 300mg Sotrastaurin + 2.5 mg everolimus | 400mg Sotrastaurin + 2.5 mg everolimus |
|-------------------------------|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 16 | 6 | 6 |
| Units: Ratio | | | | |
| median (full range (min-max)) | | | | |
| Day 15 | 1.51 (1.51 to 1.51) | 1.41 (1.04 to 4.7) | 1.26 (1.26 to 1.26) | 1.11 (0.51 to 1.71) |

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Everolimus by Treatment Group - Area Under Curve

| | |
|-----------------|--|
| End point title | Primary PK Parameters for Whole Blood Everolimus by Treatment Group - Area Under Curve |
|-----------------|--|

End point description:

Analysis done in the Pharmacokinetic Analysis Set.

Area Under Curve (AUC_{0-8h}) = Area under the concentration-time curve from time 0 to 8 hours post-dose [mass x time x volume⁻¹]

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

| End point values | 200mg Sotrastaurin + 2.5 mg everolimus | 250mg Sotrastaurin + 2.5 mg everolimus | 300mg Sotrastaurin + 2.5 mg everolimus | 400mg Sotrastaurin + 2.5 mg everolimus |
|-------------------------------|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 16 | 6 | 6 |
| Units: hr*ng/mL | | | | |
| median (full range (min-max)) | | | | |
| Day 1 | 40.7 (40.7 to 40.7) | 62.6 (51 to 152) | 57.1 (41 to 145) | 58.9 (26.1 to 132) |
| Day 15 | 98 (78 to 140) | 115 (56.6 to 181) | 221 (185 to 238) | 161 (149 to 161) |

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Everolimus by Treatment Group - C_{max}

| | |
|-----------------|--|
| End point title | Primary PK Parameters for Whole Blood Everolimus by Treatment Group - C _{max} |
|-----------------|--|

End point description:

Analysis done in the Pharmacokinetic Analysis Set.

C_{max}=Maximum observed concentration after drug administration [mass x volume⁻¹].

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

| End point values | 200mg Sotrastaurin + 2.5 mg everolimus | 250mg Sotrastaurin + 2.5 mg everolimus | 300mg Sotrastaurin + 2.5 mg everolimus | 400mg Sotrastaurin + 2.5 mg everolimus |
|-------------------------------|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 16 | 6 | 6 |
| Units: ng/ml | | | | |
| median (full range (min-max)) | | | | |
| Day 1 | 7.62 (7.62 to 7.62) | 12.5 (7.78 to 31.9) | 11.4 (7.36 to 40.6) | 11 (4.57 to 34.6) |
| Day 15 | 18.7 (12.8 to 23.6) | 17.5 (13.7 to 37.6) | 32.5 (29 to 40.9) | 27.9 (23.5 to 30.9) |

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Everolimus by Treatment Group – Tmax

| | |
|-----------------|--|
| End point title | Primary PK Parameters for Whole Blood Everolimus by Treatment Group – Tmax |
|-----------------|--|

End point description:

Analysis done in the Pharmacokinetic Analysis Set.

Tmax = Time to reach Cmax [time]

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

| End point values | 200mg Sotrastaurin + 2.5 mg everolimus | 250mg Sotrastaurin + 2.5 mg everolimus | 300mg Sotrastaurin + 2.5 mg everolimus | 400mg Sotrastaurin + 2.5 mg everolimus |
|-------------------------------|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 16 | 6 | 6 |
| Units: hr | | | | |
| median (full range (min-max)) | | | | |
| Day 1 | 4 (4 to 4) | 1.54 (0.5 to 6) | 2.48 (0.967 to 4.17) | 2 (0.967 to 6) |
| Day 15 | 1.93 (1.08 to 3.98) | 2 (0 to 4.05) | 1.64 (1.64 to 1.64) | 2.08 (1.22 to 5.7) |

Statistical analyses

No statistical analyses for this end point

Secondary: Primary PK Parameters for Whole Blood Everolimus by Treatment Group

– Racc

| | |
|-----------------|--|
| End point title | Primary PK Parameters for Whole Blood Everolimus by Treatment Group – Racc |
|-----------------|--|

End point description:

Analysis done in the Pharmacokinetic Analysis Set.

Racc = Accumulation ratio calculated as AUC0-8h or AUCtau at Day 15/AUC0-8h or AUCtau at Day 1

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Approximately 24 months (Day 1 and Day 15 of Cycle 1)

| End point values | 200mg Sotrastaurin + 2.5 mg everolimus | 250mg Sotrastaurin + 2.5 mg everolimus | 300mg Sotrastaurin + 2.5 mg everolimus | 400mg Sotrastaurin + 2.5 mg everolimus |
|-------------------------------|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 16 | 6 | 6 |
| Units: Ratio | | | | |
| median (full range (min-max)) | | | | |
| Day 15 | 2.41 (2.41 to 2.41) | 1.37 (1.19 to 2.62) | 1.64 (1.64 to 1.64) | 2.08 (1.22 to 5.07) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | AEB 200 mg bid +@ RAD 2.5 mg qd |
|-----------------------|---------------------------------|

Reporting group description:

AEB 200 mg bid +@ RAD 2.5 mg qd

| | |
|-----------------------|---------------------------------|
| Reporting group title | AEB 250 mg bid +@ RAD 2.5 mg qd |
|-----------------------|---------------------------------|

Reporting group description:

AEB 250 mg bid +@ RAD 2.5 mg qd

| | |
|-----------------------|---------------------------------|
| Reporting group title | AEB 300 mg bid +@ RAD 2.5 mg qd |
|-----------------------|---------------------------------|

Reporting group description:

AEB 300 mg bid +@ RAD 2.5 mg qd

| | |
|-----------------------|---------------------------------|
| Reporting group title | AEB 400 mg bid +@ RAD 2.5 mg qd |
|-----------------------|---------------------------------|

Reporting group description:

AEB 400 mg bid +@ RAD 2.5 mg qd

| | |
|-----------------------|--------------|
| Reporting group title | All@patients |
|-----------------------|--------------|

Reporting group description:

All@patients

| Serious adverse events | AEB 200 mg bid +@ RAD 2.5 mg qd | AEB 250 mg bid +@ RAD 2.5 mg qd | AEB 300 mg bid +@ RAD 2.5 mg qd |
|---|------------------------------------|------------------------------------|------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 11 / 16 (68.75%) | 3 / 6 (50.00%) |
| number of deaths (all causes) | 0 | 4 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasm progression | | | |

| | | | |
|--|---------------|-----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Intracardiac mass | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 4 / 16 (25.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 16 (12.50%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 16 (12.50%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |

| | | | |
|---|---------------|-----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Citrobacter infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 16 (12.50%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 16 (12.50%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|----------------|----------------|
| Septic shock | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------------------------|------------------|--|
| Serious adverse events | AEB 400 mg bid +@ RAD 2.5 mg qd | All@patients | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 6 (83.33%) | 20 / 31 (64.52%) | |
| number of deaths (all causes) | 2 | 7 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasm progression | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Intracardiac mass | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| 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 | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 4 / 31 (12.90%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| 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 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|-----------------|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 31 (6.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 4 / 31 (12.90%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Citrobacter infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 31 (6.45%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 31 (6.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 31 (6.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 31 (9.68%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | AEB 200 mg bid +@ RAD 2.5 mg qd | AEB 250 mg bid +@ RAD 2.5 mg qd | AEB 300 mg bid +@ RAD 2.5 mg qd |
|---|------------------------------------|------------------------------------|------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 15 / 16 (93.75%) | 6 / 6 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Superior vena cava occlusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Catheter site swelling | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Face oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 16 (12.50%) | 3 / 6 (50.00%) |
| occurrences (all) | 1 | 2 | 3 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oedema peripheral | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 16 (12.50%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 3 | 2 |
| Reproductive system and breast disorders | | | |
| Vaginal discharge | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 2 / 16 (12.50%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 3 / 16 (18.75%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 3 | 1 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Lung infiltration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Oropharyngeal plaque | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Pleural effusion | | | |

| | | | |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Productive cough | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 1 | 2 |
| Biopsy skin | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood cholesterol abnormal | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood potassium decreased | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eastern Cooperative Oncology Group performance status worsened | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Urine output decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |

| | | | |
|--|---------------------|-----------------------|---------------------|
| Pericardial effusion subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 6 (0.00%) 0 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 6 (0.00%) 0 |
| Dysgeusia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 16 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 6 / 16 (37.50%) 8 | 2 / 6 (33.33%) 3 |
| Leukopenia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 16 (6.25%) 3 | 0 / 6 (0.00%) 0 |
| Lymph node pain subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Neutropenia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 3 / 16 (18.75%) 3 | 1 / 6 (16.67%) 7 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 7 / 16 (43.75%) 15 | 1 / 6 (16.67%) 7 |
| Ear and labyrinth disorders | | | |
| Vertigo subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 6 (0.00%) 0 |
| Eye disorders | | | |
| Eyelids pruritus subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 6 (0.00%) 0 |

| | | | |
|---|---------------------|----------------------|---------------------|
| Periorbital oedema subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Visual acuity reduced subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 6 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 2 / 16 (12.50%) 2 | 1 / 6 (16.67%) 1 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 16 (6.25%) 1 | 1 / 6 (16.67%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 5 / 16 (31.25%) 6 | 3 / 6 (50.00%) 5 |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 3 / 16 (18.75%) 3 | 3 / 6 (50.00%) 9 |
| Dry mouth subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 6 (0.00%) 0 |
| Duodenal obstruction subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 16 (6.25%) 1 | 2 / 6 (33.33%) 3 |
| Epigastric discomfort subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Impaired gastric emptying | | | |

| | | | |
|--|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Melaena | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 9 / 16 (56.25%) | 4 / 6 (66.67%) |
| occurrences (all) | 2 | 9 | 7 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 3 / 16 (18.75%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 3 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 6 / 16 (37.50%) | 3 / 6 (50.00%) |
| occurrences (all) | 0 | 8 | 6 |
| Hepatobiliary disorders | | | |
| Hepatic pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Rash | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 3 / 16 (18.75%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin discolouration | | | |

| | | | |
|--|--------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Skin hyperpigmentation subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Skin texture abnormal subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 6 (0.00%) 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Chromaturia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 2 / 16 (12.50%) 2 | 0 / 6 (0.00%) 0 |
| Dysuria subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Enuresis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 6 (0.00%) 0 |
| Haematuria subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 2 / 16 (12.50%) 2 | 0 / 6 (0.00%) 0 |
| Oliguria subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Ureteric obstruction subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 6 (0.00%) 0 |
| Endocrine disorders | | | |
| Adrenal insufficiency subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 6 (16.67%) 1 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Back pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal discomfort | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Bacterial infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Candida infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes zoster | | | |

| | | | |
|------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumonia cytomegaloviral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 6 / 16 (37.50%) | 4 / 6 (66.67%) |
| occurrences (all) | 1 | 7 | 4 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fluid imbalance | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|-----------------------------|---------------|-----------------|----------------|
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 16 (12.50%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 4 | 1 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 4 / 16 (25.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 5 | 1 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 16 (6.25%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 1 | 2 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|------------------------------------|------------------|--|
| Non-serious adverse events | AEB 400 mg bid +@ RAD 2.5 mg qd | All@patients | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 30 / 31 (96.77%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|--|---------------------|-----------------------|--|
| Superior vena cava occlusion subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 1 | |
| General disorders and administration site conditions | | | |
| Catheter site swelling subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 1 | |
| Face oedema subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 31 (3.23%) 1 | |
| Fatigue subjects affected / exposed occurrences (all) | 3 / 6 (50.00%) 4 | 9 / 31 (29.03%) 10 | |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 1 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 2 / 31 (6.45%) 2 | |
| Pain subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 1 | |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 3 / 31 (9.68%) 5 | |
| Reproductive system and breast disorders | | | |
| Vaginal discharge subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 31 (3.23%) 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 2 | 6 / 31 (19.35%) 6 | |
| Dyspnoea | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 1 / 6 (16.67%) | 5 / 31 (16.13%) | |
| occurrences (all) | 1 | 5 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 2 | |
| Lung infiltration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences (all) | 1 | 1 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 31 (9.68%) | |
| occurrences (all) | 1 | 3 | |
| Oropharyngeal plaque | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 31 (6.45%) | |
| occurrences (all) | 0 | 2 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences (all) | 1 | 1 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 31 (6.45%) | |
| occurrences (all) | 0 | 2 | |

| | | | |
|--|----------------|-----------------|--|
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 4 / 31 (12.90%) | |
| occurrences (all) | 4 | 5 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 5 / 31 (16.13%) | |
| occurrences (all) | 2 | 5 | |
| Biopsy skin | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 31 (6.45%) | |
| occurrences (all) | 0 | 2 | |
| Blood cholesterol abnormal | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Blood potassium decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Eastern Cooperative Oncology Group performance status worsened | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 2 | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 31 (6.45%) | |
| occurrences (all) | 0 | 2 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 3 / 31 (9.68%) | |
| occurrences (all) | 5 | 6 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 31 (6.45%) | |
| occurrences (all) | 0 | 2 | |
| Urine output decreased | | | |

| | | | |
|---|---------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 1 | |
| Weight decreased subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 31 (3.23%) 1 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 1 | |
| Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 1 | |
| Procedural pain subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 31 (3.23%) 1 | |
| Cardiac disorders Pericardial effusion subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 1 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 2 | 2 / 31 (6.45%) 3 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 2 / 31 (6.45%) 2 | |
| Headache subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 31 (3.23%) 1 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 10 / 31 (32.26%) 13 | |
| Leukopenia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 3 | |

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|--|---------------------|------------------------|--|
| Lymph node pain subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 31 (3.23%) 1 | |
| Neutropenia subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 3 | 7 / 31 (22.58%) 14 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 4 | 10 / 31 (32.26%) 27 | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 1 | |
| Eye disorders Eyelids pruritus subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 31 (3.23%) 1 | |
| Periorbital oedema subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 31 (3.23%) 1 | |
| Visual acuity reduced subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 31 (3.23%) 1 | |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 2 / 31 (6.45%) 2 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 3 / 31 (9.68%) 3 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 2 / 31 (6.45%) 2 | |
| Constipation subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 2 | 10 / 31 (32.26%) 14 | |
| Diarrhoea | | | |

| | | | |
|--|-----------------|------------------|--|
| subjects affected / exposed | 6 / 6 (100.00%) | 12 / 31 (38.71%) | |
| occurrences (all) | 10 | 22 | |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Duodenal obstruction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 31 (9.68%) | |
| occurrences (all) | 0 | 4 | |
| Epigastric discomfort | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences (all) | 1 | 1 | |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Melaena | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Nausea | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 21 / 31 (67.74%) | |
| occurrences (all) | 11 | 29 | |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 8 / 31 (25.81%) | |
| occurrences (all) | 4 | 9 | |
| Vomiting | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 15 / 31 (48.39%) | |
| occurrences (all) | 9 | 23 | |
| Hepatobiliary disorders | | | |
| Hepatic pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis acneiform | | | |

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|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences (all) | 1 | 1 | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 31 (9.68%) | |
| occurrences (all) | 1 | 3 | |
| Rash | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 4 / 31 (12.90%) | |
| occurrences (all) | 1 | 6 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 31 (6.45%) | |
| occurrences (all) | 1 | 2 | |
| Rash papular | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences (all) | 1 | 1 | |
| Skin discolouration | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences (all) | 1 | 1 | |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences (all) | 1 | 1 | |
| Skin texture abnormal | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Chromaturia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 31 (9.68%) | |
| occurrences (all) | 1 | 3 | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences (all) | 1 | 1 | |
| Enuresis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|--|---------------------|---------------------|--|
| Haematuria subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 2 / 31 (6.45%) 2 | |
| Oliguria subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 31 (3.23%) 1 | |
| Ureteric obstruction subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 31 (3.23%) 1 | |
| Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 1 | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 3 / 31 (9.68%) 3 | |
| Flank pain subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 31 (3.23%) 1 | |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 1 | |
| Muscular weakness subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 1 / 31 (3.23%) 1 | |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 1 | |
| Musculoskeletal discomfort subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 1 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 2 | |
| Pain in jaw | | | |

| | | | |
|--|--------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 31 (3.23%) 1 | |
| Infections and infestations | | | |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Candida infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences (all) | 1 | 1 | |
| Herpes simplex | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences (all) | 1 | 1 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Pneumonia cytomegaloviral | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Rash pustular | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences (all) | 1 | 1 | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) | |
| occurrences (all) | 0 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences (all) | 1 | 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences (all) | 1 | 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |

| | | |
|-----------------------------|----------------|------------------|
| subjects affected / exposed | 4 / 6 (66.67%) | 15 / 31 (48.39%) |
| occurrences (all) | 6 | 18 |
| Dehydration | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) |
| occurrences (all) | 2 | 2 |
| Fluid imbalance | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) |
| occurrences (all) | 0 | 1 |
| Fluid retention | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) |
| occurrences (all) | 1 | 1 |
| Hypercholesterolaemia | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) |
| occurrences (all) | 0 | 1 |
| Hyperglycaemia | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 31 (9.68%) |
| occurrences (all) | 0 | 5 |
| Hyperkalaemia | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 31 (6.45%) |
| occurrences (all) | 0 | 2 |
| Hypertriglyceridaemia | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 31 (3.23%) |
| occurrences (all) | 0 | 1 |
| Hypocalcaemia | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 2 / 31 (6.45%) |
| occurrences (all) | 2 | 2 |
| Hypokalaemia | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 6 / 31 (19.35%) |
| occurrences (all) | 2 | 8 |
| Hyponatraemia | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 4 / 31 (12.90%) |
| occurrences (all) | 1 | 4 |
| Hypophosphataemia | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 31 (6.45%) |
| occurrences (all) | 0 | 2 |
| Tumour lysis syndrome | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 31 (3.23%) | |
| occurrences (all) | 1 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 09 August 2013 | <ul style="list-style-type: none">•Removal of the prior anthracycline treatment criterion for inclusion of patients into the study due to differences in global standard of care in elderly DLBCL patient populations.•Correction of typographical error of exclusion criterion for abnormal laboratory values (absolute neutrophil and platelet counts).•Removal of exclusion criterion of patients with significant coagulopathy or requiring long-term systemic anticoagulation since newly obtained tumor samples was not required per protocol. |
| 24 September 2014 | <ul style="list-style-type: none">•As requested by Health Authorities and to align with the everolimus IB, amend protocol exclusion criterion #12 to exclude sexually active male patients unless a condom was used during intercourse while taking study treatment and for 8 weeks after discontinuation of study treatment.•As requested by Health Authorities, include a statement that caution is necessary when administering medications which are substrates of transportation MDR1 (P-gp) and OATP1B1 because sotrastaurin may act as an inhibitor of these transporters.•Modify exclusion criterion #15 to exclude patients who received ibritumomab tiuxetan (Zevalin®) and/or tositumomab (Bexxar®) treatment less than 3 months prior to starting study drug. After 3 months of discontinuing ibritumomab or tositumomab it was expected that any bone marrow suppressive effects would have resolved. This wash-out period allowed for additional patients to be considered for the study.•Clarification of the molecular pre-screening analysis to be performed at a central Novartis-designated laboratory during the Phase Ib escalation phase and the Phase II parts of this study have been included, so it is clear to Investigators.•Allow for a CT/MRI scan that was performed prior to obtaining study informed consent, but performed per standard of care within 28 days of Cycle 1 Day 1 to be used for Screening to avoid an unnecessary repeat of this procedure. In addition, to include an EOT CT/MRI if a CT/MRI was not acquired within 6 weeks prior to the EOT visit date. This was to ensure final radiological response assessment of disease prior to patients coming off study.•Specify the required inclusion criterion for definition of measurable disease to ensure the correct radiological assessment as per non-Hodgkin's Lymphoma International Working Group criteria.•This study only required radiological response assessment, references to additional response criteria that are not applicable for this study were removed. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The trial did not progress into Phase II due to the suboptimal tolerability of the combination treatment of sotrastaurin and everolimus in the Phase Ib part of the study. There were no serious safety concerns associated with this combination.

Notes: