



Clinical trial results:

A double-blind, placebo-controlled, randomized, multicenter phase II trial to assess the efficacy of temsirolimus added to standard primary therapy in elderly patients with newly diagnosed AML

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-002365-37 |
| Trial protocol | DE |
| Global end of trial date | 26 April 2017 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 06 October 2021 |
| First version publication date | 06 October 2021 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | 3066K1-1165 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01611116 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Goethe University |
| Sponsor organisation address | Theodor-Stern-Kai 7, Frankfurt am Main, Germany, 60590 |
| Public contact | Prof Christian Brandts, MD, Lead PI, J.W. Goethe University Hospital, 0049 69 6301 7104, Christian.brandts@kgu.de |
| Scientific contact | Prof Christian Brandts, MD, Lead PI, J.W. Goethe University Hospital, 0049 69 6301 7104, Christian.brandts@kgu.de |

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 | 21 September 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 November 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 April 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Run-in part; To determine the optimal temsirolimus dose and schedule for the main part of the study
Main part: To compare the median Event Free Survival (EFS) And the EFS probability of all AML patients between the temsirolimus and the control group

* EFS defined as: Time interval from day 1 of study treatment until treatment failure, relapse from CR or CRi, or death from any cause, whichever occurs first. The time point at which the patient is resistant to therapy or survives induction without a CR, CRi or morphologic leukemia-free state will be recorded.

Protection of trial subjects:

Data safety monitoring board to decide on optimal dose for main part as well as on serious adverse events with unclear relation to the study drug

Background therapy:

Induction I (7+3):

| | | |
|--------------|----------------------------------|---------|
| Cytarabine | 100mg/m ² /24hrs i.v. | day 1-7 |
| Daunorubicin | 60mg/m ² i.v. | day 3-5 |

Induction II (HAM elderly) for patients with PR or treatment failure:

| | | |
|----------------------|--|-------------|
| Cytarabine (HD-AraC) | 1g/m ² /3hrs i.v. (2 x daily) | day 1, 3, 5 |
| Mitoxantrone | 10mg/m ² i.v. | day 3-5 |

Consolidation I (high-dose cytarabine):

Cytarabine (HD-AraC) 1g/m²/3hrs i.v. (2 x daily) day 1, 3, 5

Consolidation II (high-dose cytarabine):

Cytarabine (HD-AraC) 1g/m²/3hrs i.v. (2 x daily) day 1, 3, 5

Evidence for comparator:

Not applicable

| | |
|---|--------------|
| Actual start date of recruitment | 22 June 2012 |
| 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 | Germany: 33 |
| Worldwide total number of subjects | 33 |
| EEA total number of subjects | 33 |

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) | 9 |
| From 65 to 84 years | 24 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patient were recruited by treating physician/investigator upon relevant diagnosis at the hospital

Pre-assignment

Screening details:

additional screening procedures compared to standard diagnostics: informed consent,
laboratory test: troponin T / troponin I, CK, CK-MB, NT-proBNP

Period 1

| | |
|------------------------------|------------------------------|
| Period 1 title | Run-in part (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Randomized not controlled, 3 experiemental arms with different doselevels (cohort 1; cohort 2; cohort 3)

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1 |

Arm description:

temsirolimus 12.5mg on day -1 of each chemotherapy cycle

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Temsirolimus |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cohort 1: temsirolimus 12.5mg on day -1 of each chemotherapy cycle

Cohort 2: temsirolimus 12.5mg on day -1 and day 8 of each chemotherapy cycle

Cohort 3: temsirolimus 25mg on day -1 and day 8 of each chemotherapy cycle

| | |
|------------------|----------|
| Arm title | Cohort 2 |
|------------------|----------|

Arm description:

temsirolimus 12.5mg on day -1 and day 8 of each chemotherapy cycle

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Temsirolimus |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cohort 1: temsirolimus 12.5mg on day -1 of each chemotherapy cycle

Cohort 2: temsirolimus 12.5mg on day -1 and day 8 of each chemotherapy cycle

Cohort 3: temsirolimus 25mg on day -1 and day 8 of each chemotherapy cycle

| | |
|------------------|----------|
| Arm title | Cohort 3 |
|------------------|----------|

Arm description:

temsirolimus 25mg on day -1 and day 8 of each chemotherapy cycle

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Temsirolimus |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cohort 1: temsirolimus 12.5mg on day -1 of each chemotherapy cycle

Cohort 2: temsirolimus 12.5mg on day -1 and day 8 of each chemotherapy cycle

Cohort 3: temsirolimus 25mg on day -1 and day 8 of each chemotherapy cycle

| Number of subjects in period 1 | Cohort 1 | Cohort 2 | Cohort 3 |
|--|----------|----------|----------|
| Started | 5 | 17 | 11 |
| DLT (cohort 1; cohort 2; cohort 3) | 3 | 9 | 7 |
| Completed | 3 | 9 | 7 |
| Not completed | 2 | 8 | 4 |
| Consent withdrawn by subject | 1 | 2 | - |
| Physician decision | 1 | 2 | - |
| pt died before 1st dose was administered | - | - | 1 |
| Lost to follow-up | - | 1 | - |
| Lack of efficacy | - | 1 | 3 |
| Protocol deviation | - | 2 | - |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|-------------|
| Reporting group title | Run-in part |
| Reporting group description: - | |

| Reporting group values | Run-in part | Total | |
|---|-------------|-------|--|
| Number of subjects | 33 | 33 | |
| Age categorical | | | |
| All patients enrolled in the run-in part regardless of evaluability | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 9 | 9 | |
| From 65-84 years | 24 | 24 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 14 | 14 | |
| Male | 19 | 19 | |

Subject analysis sets

| | |
|---|--------------|
| Subject analysis set title | Run-in part |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| All patients enrolled in the run-in part regardless of evaluability | |

| Reporting group values | Run-in part | | |
|---|-------------|--|--|
| Number of subjects | 33 | | |
| Age categorical | | | |
| All patients enrolled in the run-in part regardless of evaluability | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 9 | | |
| From 65-84 years | 24 | | |
| 85 years and over | 0 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 14 | | |
| Male | 19 | | |

End points

End points reporting groups

| | |
|--|--------------|
| Reporting group title | Cohort 1 |
| Reporting group description: temsirolimus 12.5mg on day -1 of each chemotherapy cycle | |
| Reporting group title | Cohort 2 |
| Reporting group description: temsirolimus 12.5mg on day -1 and day 8 of each chemotherapy cycle | |
| Reporting group title | Cohort 3 |
| Reporting group description: temsirolimus 25mg on day -1 and day 8 of each chemotherapy cycle | |
| Subject analysis set title | Run-in part |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All patients enrolled in the run-in part regardless of evaluability | |

Primary: Optimal temsirolimus dose and schedule

| | |
|---|---|
| End point title | Optimal temsirolimus dose and schedule ^[1] |
| End point description: According to the definition in the protocol, dose level / mode of application in cohort I and cohort II could be evaluated as being safe. Eleven patients were enrolled in cohort III. Due to a simultaneous patient screening, seven evaluable patients were eventually included. Two DLTs were observed: Mucositis oral grade 3 and Mucositis/colitis grade 3 with suspected relationship. Multiple incidences of mucositis grade 3 both in cohort II (1 DLT and 1 not evaluable patient with SAE mucositis oral grade 3 with suspected relationship to study drug) and cohort III suggest that temsirolimus may cause increased mucosal toxicity when administered in combination with 7+3 standard therapy. After reassessing the risk benefit ratio, the co-ordinating investigator in line with the data safety monitoring board decided not to enroll any additional patients in cohort III thus giving priority to the patients' safety over formal requirements of the 3+3 design. | |
| End point type | Primary |
| End point timeframe: Run-in part | |
| 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: Only descriptive analysis! | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|-----------------------------|------------------|------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 4 ^[2] | 9 ^[3] | 7 ^[4] | |
| Units: ng | 12500 | 12500 | 25000 | |

Notes:

[2] - Dose: 12,5 mg

[3] - Dose: 12,5 mg

[4] - Dose: 25 mg

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From enrolment until 30 days following last dose of study treatment or 42 days after last dose of study treatment (for neutropenia and thrombocytopenia)

Adverse event reporting additional description:

Not applicable

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

| | |
|--------------------|------|
| Dictionary version | 4.03 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Run-in part |
|-----------------------|-------------|

Reporting group description: -

| Serious adverse events | Run-in part | | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 29 (48.28%) | | |
| number of deaths (all causes) | 6 | | |
| number of deaths resulting from adverse events | 3 | | |
| Cardiac disorders | | | |
| Heart failure | Additional description: Not applicable | | |
| subjects affected / exposed | 4 / 29 (13.79%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Nervous system disorders | | | |
| Intracranial hemorrhage | Additional description: Epidural hematoma | | |
| subjects affected / exposed | 1 / 29 (3.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Allergic reaction | Additional description: dyspnea, facial rash, fever + shivering | | |
| subjects affected / exposed | 1 / 29 (3.45%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Small intestinal mucositis | Additional description: Not applicable | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower gastrointestinal hemorrhage | Additional description: Peranal bleeding | | |
| subjects affected / exposed | 1 / 29 (3.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | Additional description: Not applicable | | |
| subjects affected / exposed | 1 / 29 (3.45%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspiration | Additional description: Not applicable | | |
| subjects affected / exposed | 1 / 29 (3.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Infections and infestations | | | |
| Lung infection | Additional description: Not applicable | | |
| subjects affected / exposed | 3 / 29 (10.34%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | Additional description: Sepsis in neutropenia | | |
| subjects affected / exposed | 1 / 29 (3.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Metabolism and nutrition disorders | | | |
| Hypernatremia | Additional description: Not applicable | | |
| subjects affected / exposed | 1 / 29 (3.45%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Run-in part | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 29 / 29 (100.00%) | | |
| Vascular disorders | | | |
| Hematoma | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 29 (17.24%) | | |
| occurrences (all) | 7 | | |
| Phlebitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 3 | | |
| Edema face | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | | |
| occurrences (all) | 3 | | |
| Edema limbs | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | | |
| occurrences (all) | 17 | | |
| Fatigue | | | |
| subjects affected / exposed | 5 / 29 (17.24%) | | |
| occurrences (all) | 5 | | |
| Fever | | | |
| subjects affected / exposed | 17 / 29 (58.62%) | | |
| occurrences (all) | 26 | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | | |
| occurrences (all) | 2 | | |
| Infusion site extravasation | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Injection site reaction | | | |

| | | | |
|--|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Localized edema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Multi-organ failure</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 29 (13.79%)</p> <p>6</p> <p>5 / 29 (17.24%)</p> <p>5</p> <p>2 / 29 (6.90%)</p> <p>2</p> <p>3 / 29 (10.34%)</p> <p>3</p> | | |
| <p>Immune system disorders</p> <p>Allergic reaction</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>8 / 29 (27.59%)</p> <p>18</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pleural effusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pneumonitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pulmonary edema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sore throat</p> | <p>7 / 29 (24.14%)</p> <p>9</p> <p>10 / 29 (34.48%)</p> <p>12</p> <p>16 / 29 (55.17%)</p> <p>18</p> <p>2 / 29 (6.90%)</p> <p>2</p> <p>4 / 29 (13.79%)</p> <p>4</p> <p>2 / 29 (6.90%)</p> <p>2</p> | | |

| | | | |
|--|--------------------------------------|--|--|
| subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 6 | | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | | |
| occurrences (all) | 4 | | |
| Confusion | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Delirium | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | | |
| occurrences (all) | 2 | | |
| Depression | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Investigations | | | |
| Investigations - Other, specify (CRP) | Additional description: CRP increase | | |
| subjects affected / exposed | 5 / 29 (17.24%) | | |
| occurrences (all) | 5 | | |
| Investigations - Other, specify (TPZ) | Additional description: TPZ decrease | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | | |
| occurrences (all) | 3 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | | |
| occurrences (all) | 8 | | |
| Weight loss | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| White blood cell decreased | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 3 | | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|--|--|
| Fall subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 12 / 29 (41.38%) 12 1 / 29 (3.45%) 2 | | |
| Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Thrombotic thrombocytopenic purpura subjects affected / exposed occurrences (all) | 8 / 29 (27.59%) 8 12 / 29 (41.38%) 20 1 / 29 (3.45%) 2 | | |
| Eye disorders Vitreous hemorrhage subjects affected / exposed occurrences (all) Dry eye subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 2 / 29 (6.90%) 2 | | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Bloating | 4 / 29 (13.79%) 5 | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Colitis | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | | |
| occurrences (all) | 3 | | |
| Constipation | | | |
| subjects affected / exposed | 8 / 29 (27.59%) | | |
| occurrences (all) | 11 | | |
| Diarrhea | | | |
| subjects affected / exposed | 19 / 29 (65.52%) | | |
| occurrences (all) | 22 | | |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 3 | | |
| Mucositis oral | | | |
| subjects affected / exposed | 21 / 29 (72.41%) | | |
| occurrences (all) | 23 | | |
| Nausea | | | |
| subjects affected / exposed | 8 / 29 (27.59%) | | |
| occurrences (all) | 10 | | |
| Oral hemorrhage | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 3 | | |
| Oral pain | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Stomach pain | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | | |
| occurrences (all) | 6 | | |
| Vomiting | | | |
| subjects affected / exposed | 11 / 29 (37.93%) | | |
| occurrences (all) | 19 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | | |
| occurrences (all) | 3 | | |

| | | | |
|--|---------------------------------------|--|--|
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | | |
| occurrences (all) | 2 | | |
| Purpura | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | | |
| occurrences (all) | 5 | | |
| Skin ulceration | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 3 | | |
| Urinary incontinence | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations | | | |
| Infections and infestations - Other, specify (CRP) | Additional description: CRP increased | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Bladder infection | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Catheter related infection | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | | |
| occurrences (all) | 6 | | |
| Lip infection | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | | |
| occurrences (all) | 7 | | |
| Lung infection | | | |

| | | | |
|------------------------------------|------------------|--|--|
| subjects affected / exposed | 7 / 29 (24.14%) | | |
| occurrences (all) | 7 | | |
| Mucosal infection | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | | |
| occurrences (all) | 7 | | |
| Papulopustular rash | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | | |
| occurrences (all) | 3 | | |
| Skin infection | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Tooth infection | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | | |
| occurrences (all) | 4 | | |
| Hyperglycemia | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | | |
| occurrences (all) | 3 | | |
| Hyperkalemia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | | |
| occurrences (all) | 2 | | |
| Hypokalemia | | | |
| subjects affected / exposed | 18 / 29 (62.07%) | | |
| occurrences (all) | 25 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|--|
| 15 May 2013 | <p>Study design</p> <ul style="list-style-type: none">• Increase of number of patients in run-in part• Implementation of dose-escalating study design with three consecutive cohorts• Definition of Dose Limiting Toxicity• Changes in definition of non-hematological DLT• Changes in definition of evaluability for DLT assessment <p>Definition of Dose Limiting Toxicity</p> <ul style="list-style-type: none">• Changes in definition of non-hematological DLT• Changes in definition of evaluability for DLT assessment <p>Treatment</p> <ul style="list-style-type: none">• Modification of scheme of run-in part• Modification of treatment schedule for induction chemotherapy• Modification of treatment schedule for induction II chemotherapy• Modification of treatment schedule for consolidation chemotherapy I and II <p>Dose modification and delays of temsirolimus / placebo</p> <ul style="list-style-type: none">• Dose modifications for non-hematological toxicity• Instructions for safety evaluations and dose modification in patients with cardiac disorders• Instructions for dose modification in patients with mucositis |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|--------------|--|-------------------|
| 21 July 2012 | Interruption of accrual after two SUSAR (Heart failure) in order to re-evaluate patient safety | 05 September 2013 |

Notes:

Limitations and caveats

None reported