



## Clinical trial results:

### Phase II study of ageadjusted RBAC (Rituximab, Bendamustine, Cytarabine) as induction therapy in older patients with Mantle Cell Lymphoma (MCL)

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2011-005739-23    |
| Trial protocol           | IT                |
| Global end of trial date | 11 September 2017 |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 25 August 2022 |
| First version publication date | 25 August 2022 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | FIL-RBAC500 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01662050 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                               |
|------------------------------|-----------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Fondazione Italiana Linfomi (FIL) ONLUS                                                       |
| Sponsor organisation address | Piazza Turati 5, Alessandria, Italy,                                                          |
| Public contact               | Segreteria, Fondazione Italiana Linfomi ONLUS, +39 0131/033151, segreteriadirezione@filinf.it |
| Scientific contact           | Segreteria, Fondazione Italiana Linfomi ONLUS, +39 0131/033151, segreteriadirezione@filinf.it |

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                       | 15 January 2019   |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 29 August 2014    |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 11 September 2017 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to determine the activity (complete remission rate according to Cheson 2007 criteria) and safety of ageadjusted RituximabBendamustineCytarabine (RBAC500) regimen at the end of treatment in older untreated patients with MCL.

Protection of trial subjects:

- 1) Occurrence of relevant toxicity for two subsequent or consecutive cycles (the protocol allows for a 25% reduction of drugs dosage when an episode of relevant toxicity occurs for the first time)
- 2) Grade 3-4 hematological or nonhematological toxicity on day +28 of a cycle not resolving within two weeks (+28 days+14 days since last cycle)
- 3) Grade 3-4 hematological or nonhematological toxicity on day +28 of a cycle after the 25% dose reduction
- 4) Patient refusal to procede with further cycles due to perceived excessive toxicity
- 5) Any unpredictable drug related event that suggests against study continuation

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 20 March 2012 |
| 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 | Italy: 57 |
| Worldwide total number of subjects   | 57        |
| EEA total number of subjects         | 57        |

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) | 5  |
| From 65 to 84 years  | 52 |
| 85 years and over    | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Fifty-seven patients recruited in Italy from 03/20/2012 , with date of last completed at 09/11/2017. We adopted the Bryant and Day two-stage design for calculating the sample size. At the end of the first stage, 19 pts, the trial will be stopped if there are  $\leq 8/19$  responses and  $\geq 7/19$  toxicities. Otherwise, further 38 pts will be enrolled.

### Pre-assignment

Screening details:

Patients with an established histological diagnosis of MCL on lymph-node biopsy, bone marrow biopsy, or extranodal tissue are eligible for entry into the study.

All patients must satisfy all the inclusion criteria and none of exclusion criteria.

### Period 1

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

### Arms

|           |            |
|-----------|------------|
| Arm title | Single arm |
|-----------|------------|

Arm description:

Patients will be treated with at least two cycles of RBAC500, recycling every 28 days.

Patients with PD after 2 cycles will stop treatment, while all other patients will continue treatment. After 4 cycles patients that had SD after 2 cycles will be reevaluated for response and they will stop treatment if still in SD or PD. Responsive patients (CR, CRu, PR after 2 cycles; SD after 2 cycles that improved their response at the end of cycle 4) will receive a total of 6 cycles. Patients experiencing at least one episode of relevant toxicity during any of the first 4 cycles will be treated with a total of four cycles (end of treatment after 4 cycles) regardless of response to treatment.

|                                        |                  |
|----------------------------------------|------------------|
| Arm type                               | Single arm study |
| Investigational medicinal product name | Rituximab        |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Infusion         |
| Routes of administration               | Intravenous use  |

Dosage and administration details:

Dose administered: 375 mg/m<sup>2</sup>

The amount (in mg) of Rituximab to be administered will be determined based on body surface area (BSA) using a standard calculation.

Patients presenting with high lymphocyte count in the peripheral blood, defined as total lymphocytes  $>20000/\text{mmc}$  will receive the dose of Rituximab postponed after chemotherapy, 4 days after the completion of the last dose of Ara-C (+8 from the start of therapy). Patients that still have elevated lymphocyte count at that time point will avoid Rituximab for the first cycle, maintaining the same measures for subsequent cycles.

|                                        |                      |
|----------------------------------------|----------------------|
| Investigational medicinal product name | Bendamustine         |
| Investigational medicinal product code |                      |
| Other name                             |                      |
| Pharmaceutical forms                   | Powder for injection |
| Routes of administration               | Intravenous use      |

Dosage and administration details:

Bendamustine will be administered intravenously at a dose of 70 mg/m<sup>2</sup> and as a 30-60 minute infusion on Days 2 and 3.

Following the first cycle, if no major complication has followed rituximab infusion, bendamustine and ara-C will be administered on day 1 following rituximab, and the complete cycle will last for 3 days, in

order to facilitate an outpatient approach.

|                                        |                 |
|----------------------------------------|-----------------|
| Investigational medicinal product name | Cytarabine      |
| Investigational medicinal product code |                 |
| Other name                             | Ara-C           |
| Pharmaceutical forms                   | Injection       |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Ara-C will be administered intravenously at the dose of 500 mg/m<sup>2</sup> as a 2-hour infusion, 2 hours after Bendamustine on Day 2 and 3, and once on Day 4.

Following the first cycle, if no major complication has followed rituximab infusion, bendamustine and ara-C will be administered on day 1 following rituximab, and the complete cycle will last for 3 days, in order to facilitate an outpatient approach.

| <b>Number of subjects in period 1</b> | Single arm |
|---------------------------------------|------------|
| Started                               | 57         |
| Completed                             | 38         |
| Not completed                         | 19         |
| Adverse Event                         | 14         |
| Medical Decision                      | 4          |
| Lack of efficacy                      | 1          |

## Baseline characteristics

### Reporting groups

|                                                                                                                       |          |
|-----------------------------------------------------------------------------------------------------------------------|----------|
| Reporting group title                                                                                                 | Baseline |
| Reporting group description:                                                                                          |          |
| Fifty-seven patients recruited in Italy from 03/20/2012 , with date of last completed (last follow-up) at 09/11/2017. |          |

| Reporting group values                                | Baseline | Total |  |
|-------------------------------------------------------|----------|-------|--|
| Number of subjects                                    | 57       | 57    |  |
| Age categorical                                       |          |       |  |
| Units: Subjects                                       |          |       |  |
| Adults (18-64 years)                                  | 5        | 5     |  |
| From 65-84 years                                      | 52       | 52    |  |
| Age continuous                                        |          |       |  |
| Units: years                                          |          |       |  |
| median                                                | 71       |       |  |
| inter-quartile range (Q1-Q3)                          | 67 to 75 | -     |  |
| Gender categorical                                    |          |       |  |
| Units: Subjects                                       |          |       |  |
| Female                                                | 14       | 14    |  |
| Male                                                  | 43       | 43    |  |
| Ann Arbor stage                                       |          |       |  |
| Units: Subjects                                       |          |       |  |
| II                                                    | 5        | 5     |  |
| III-IV                                                | 52       | 52    |  |
| Bone marrow involvement                               |          |       |  |
| Units: Subjects                                       |          |       |  |
| Yes                                                   | 36       | 36    |  |
| No                                                    | 21       | 21    |  |
| Eastern Cooperative Oncology Group performance status |          |       |  |
| Units: Subjects                                       |          |       |  |
| ECOG 0-1                                              | 54       | 54    |  |
| ECOG 2                                                | 3        | 3     |  |
| Morphological variants                                |          |       |  |
| Units: Subjects                                       |          |       |  |
| Classical                                             | 43       | 43    |  |
| Pleomorphic                                           | 8        | 8     |  |
| Blastoid                                              | 6        | 6     |  |
| Ki67 index                                            |          |       |  |
| Units: Subjects                                       |          |       |  |
| <30%                                                  | 35       | 35    |  |
| ≥30%                                                  | 16       | 16    |  |
| NA                                                    | 6        | 6     |  |
| MIPI                                                  |          |       |  |
| Units: Subjects                                       |          |       |  |
| Low risk                                              | 9        | 9     |  |
| Intermediate risk                                     | 23       | 23    |  |

|           |    |    |  |
|-----------|----|----|--|
| High risk | 25 | 25 |  |
|-----------|----|----|--|

|                              |         |   |  |
|------------------------------|---------|---|--|
| Ki67 index                   |         |   |  |
| Only 51 patients             |         |   |  |
| Units: percent               |         |   |  |
| median                       | 20      |   |  |
| inter-quartile range (Q1-Q3) | 8 to 33 | - |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Single arm       |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                  |
| Patients will be treated with at least two cycles of RBAC500, recycling every 28 days. Patients with PD after 2 cycles will stop treatment, while all other patients will continue treatment. After 4 cycles patients that had SD after 2 cycles will be reevaluated for response and they will stop treatment if still in SD or PD. Responsive patients (CR, CRu, PR after 2 cycles; SD after 2 cycles that improved their response at the end of cycle 4) will receive a total of 6 cycles. Patients experiencing at least one episode of relevant toxicity during any of the first 4 cycles will be treated with a total of four cycles (end of treatment after 4 cycles) regardless of response to treatment. |                  |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Subject analyzed |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Full analysis    |
| Subject analysis set description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                  |
| Fifty-seven patients recruited in Italy from 03/20/2012 , with date of last completed (last follow-up) at 09/11/2017.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                  |

### Primary: Complete response rate (CR)

|                                                                                                                                                     |                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title                                                                                                                                     | Complete response rate (CR) |
| End point description:                                                                                                                              |                             |
| Primary efficacy end point of the study is the proportion of CR defined according to Cheson criteria (2007) at the end of treatment (6 or 4 cycles) |                             |
| End point type                                                                                                                                      | Primary                     |
| End point timeframe:                                                                                                                                |                             |
| At the end of treatment (6 or 4 cycles)                                                                                                             |                             |

| End point values            | Single arm      | Subject analyzed     |  |  |
|-----------------------------|-----------------|----------------------|--|--|
| Subject group type          | Reporting group | Subject analysis set |  |  |
| Number of subjects analysed | 57              | 57                   |  |  |
| Units: subject              |                 |                      |  |  |
| CR                          | 52              | 52                   |  |  |

### Statistical analyses

|                                         |                               |
|-----------------------------------------|-------------------------------|
| Statistical analysis title              | Complete Response (CR) Rate   |
| Comparison groups                       | Single arm v Subject analyzed |
| Number of subjects included in analysis | 114                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | other                         |
| Parameter estimate                      | CR proportion                 |
| Point estimate                          | 91                            |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 1-sided                       |
| lower limit                             | 85                            |



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**Primary: Patients with at least a relevant one episode of relevant toxicities**

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|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Patients with at least a relevant one episode of relevant toxicities |
|-----------------|----------------------------------------------------------------------|

End point description:

Relevant toxicity was defined as grade 4 cytopenia lasting for more than 6 days, grade 3–4 non haematological toxicity, or febrile neutropenia lasting for more than 3 consecutive days.

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

End point timeframe:

6 months

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| End point values                  | Single arm      | Subject analyzed     |  |  |
|-----------------------------------|-----------------|----------------------|--|--|
| Subject group type                | Reporting group | Subject analysis set |  |  |
| Number of subjects analysed       | 57              | 57                   |  |  |
| Units: Subject                    |                 |                      |  |  |
| Patients with relevant toxicities | 23              | 23                   |  |  |

**Statistical analyses**

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | Patients with relevant toxicities |
| Comparison groups                       | Single arm v Subject analyzed     |
| Number of subjects included in analysis | 114                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | other                             |
| Parameter estimate                      | Proportion                        |
| Point estimate                          | 40                                |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 1-sided                           |
| upper limit                             | 53                                |

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**Secondary: Progression Free Survival (PFS)**

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|                 |                                 |
|-----------------|---------------------------------|
| End point title | Progression Free Survival (PFS) |
|-----------------|---------------------------------|

End point description:

PFS is measured from the time of enrollment until disease progression, relapse or death from any cause.

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

End point timeframe:

30 months. The reported value corresponds to PFS% at 2-years.

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| End point values                 | Single arm      | Subject analyzed     |  |  |
|----------------------------------|-----------------|----------------------|--|--|
| Subject group type               | Reporting group | Subject analysis set |  |  |
| Number of subjects analysed      | 57              | 57                   |  |  |
| Units: Probability               |                 |                      |  |  |
| number (confidence interval 95%) | 81 (68 to 89)   | 81 (68 to 89)        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

|                                                                                      |                       |
|--------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                      | Overall Survival (OS) |
| End point description:<br>OS is measured from enrollment until death from any cause. |                       |
| End point type                                                                       | Secondary             |
| End point timeframe:<br>30 months. The reported value corresponds to OS% at 2-years. |                       |

| End point values                 | Single arm      | Subject analyzed     |  |  |
|----------------------------------|-----------------|----------------------|--|--|
| Subject group type               | Reporting group | Subject analysis set |  |  |
| Number of subjects analysed      | 57              | 57                   |  |  |
| Units: Probability               |                 |                      |  |  |
| number (confidence interval 95%) | 86 (74 to 93)   | 86 (74 to 93)        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of responses (DOR)

|                                                                                                                                                       |                             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title                                                                                                                                       | Duration of responses (DOR) |
| End point description:<br>DOR is measured from the first assessment that documents response (CR or PR) to the date of disease relapse or progression. |                             |
| End point type                                                                                                                                        | Secondary                   |
| End point timeframe:<br>30 months. The reported value corresponds to DOR% at 2-years.                                                                 |                             |

| End point values                 | Single arm      | Subject analyzed     |  |  |
|----------------------------------|-----------------|----------------------|--|--|
| Subject group type               | Reporting group | Subject analysis set |  |  |
| Number of subjects analysed      | 57              | 57                   |  |  |
| Units: Probability               |                 |                      |  |  |
| number (confidence interval 95%) | 90 (85 to 94)   | 90 (85 to 94)        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Rate of molecular response

|                                                                                                                                                                                 |                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| End point title                                                                                                                                                                 | Rate of molecular response |
| End point description:                                                                                                                                                          |                            |
| Molecular response is the proportion of patients with molecular rearrangements at baseline that become negative during treatment, measured by qualitative and quantitative PCR. |                            |
| End point type                                                                                                                                                                  | Secondary                  |
| End point timeframe:                                                                                                                                                            |                            |
| 6 months                                                                                                                                                                        |                            |

| End point values            | Single arm        | Subject analyzed     |  |  |
|-----------------------------|-------------------|----------------------|--|--|
| Subject group type          | Reporting group   | Subject analysis set |  |  |
| Number of subjects analysed | 45 <sup>[1]</sup> | 45 <sup>[2]</sup>    |  |  |
| Units: Patients             |                   |                      |  |  |
| Bone Marrow                 | 24                | 24                   |  |  |
| Peripheral Blood            | 35                | 35                   |  |  |

Notes:

[1] - Of 57 patients, 45 (79%) had a molecular marker

[2] - Of 57 patients, 45 (79%) had a molecular marker

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

30 months

Adverse event reporting additional description:

All subjects will be monitored for adverse events throughout the study and for 30 days after the end of treatment.

During the follow-up, patients will be monitored for adverse events every 3 months.

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

### Dictionary used

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

|                    |   |
|--------------------|---|
| Dictionary version | 4 |
|--------------------|---|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Single arm |
|-----------------------|------------|

Reporting group description:

Patients will be treated with at least two cycles of RBAC500, recycling every 28 days.

Patients with PD after 2 cycles will stop treatment, while all other patients will continue treatment. After 4 cycles patients that had SD after 2 cycles will be reevaluated for response and they will stop treatment if still in SD or PD. Responsive patients (CR, CRu, PR after 2 cycles; SD after 2 cycles that improved their response at the end of cycle 4) will receive a total of 6 cycles. Patients experiencing at least one episode of relevant toxicity during any of the first 4 cycles will be treated with a total of four cycles (end of treatment after 4 cycles) regardless of response to treatment.

| Serious adverse events                            | Single arm       |  |  |
|---------------------------------------------------|------------------|--|--|
| Total subjects affected by serious adverse events |                  |  |  |
| subjects affected / exposed                       | 21 / 57 (36.84%) |  |  |
| number of deaths (all causes)                     | 12               |  |  |
| number of deaths resulting from adverse events    | 1                |  |  |
| Cardiac disorders                                 |                  |  |  |
| Atrial fibrillation                               |                  |  |  |
| subjects affected / exposed                       | 2 / 57 (3.51%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 2            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Blood and lymphatic system disorders              |                  |  |  |
| Anaemia G4, Thrombocytopenias G3                  |                  |  |  |
| subjects affected / exposed                       | 1 / 57 (1.75%)   |  |  |
| occurrences causally related to treatment / all   | 1 / 1            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Neutropenia                                       |                  |  |  |

|                                                      |                |  |  |
|------------------------------------------------------|----------------|--|--|
| subjects affected / exposed                          | 2 / 57 (3.51%) |  |  |
| occurrences causally related to treatment / all      | 3 / 3          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Febrile neutropenia                                  |                |  |  |
| subjects affected / exposed                          | 3 / 57 (5.26%) |  |  |
| occurrences causally related to treatment / all      | 4 / 4          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Severe Leukopenia and Thrombocytopenias              |                |  |  |
| subjects affected / exposed                          | 1 / 57 (1.75%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Pancytopenia                                         |                |  |  |
| subjects affected / exposed                          | 2 / 57 (3.51%) |  |  |
| occurrences causally related to treatment / all      | 2 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Cough and fever                                      |                |  |  |
| subjects affected / exposed                          | 1 / 57 (1.75%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Epistaxis and fever                                  |                |  |  |
| subjects affected / exposed                          | 1 / 57 (1.75%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Fever                                                |                |  |  |
| subjects affected / exposed                          | 3 / 57 (5.26%) |  |  |
| occurrences causally related to treatment / all      | 3 / 3          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Fever and cutaneous rash                             |                |  |  |
| subjects affected / exposed                          | 1 / 57 (1.75%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Febrile neutropenia and Temperature                  |                |  |  |

|                                                 |                |  |  |  |
|-------------------------------------------------|----------------|--|--|--|
| max 38° C                                       |                |  |  |  |
| subjects affected / exposed                     | 1 / 57 (1.75%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Febrile neutropenia and Temperature max 38.2° C |                |  |  |  |
| subjects affected / exposed                     | 1 / 57 (1.75%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Fever, CMV reactivation and pancytopenia        |                |  |  |  |
| subjects affected / exposed                     | 1 / 57 (1.75%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pneumonitis with fever and cough                |                |  |  |  |
| subjects affected / exposed                     | 1 / 57 (1.75%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Melaena, with findings of severe anemia         |                |  |  |  |
| subjects affected / exposed                     | 1 / 57 (1.75%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Left cheek lesion and Melaena                   |                |  |  |  |
| subjects affected / exposed                     | 1 / 57 (1.75%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Neutropenia and fever                           |                |  |  |  |
| subjects affected / exposed                     | 1 / 57 (1.75%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Fever, Dehydration, Hypoalbuminaemia            |                |  |  |  |
| subjects affected / exposed                     | 1 / 57 (1.75%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |

|                                                         |                |  |  |
|---------------------------------------------------------|----------------|--|--|
| Chest pain                                              |                |  |  |
| subjects affected / exposed                             | 1 / 57 (1.75%) |  |  |
| occurrences causally related to treatment / all         | 1 / 1          |  |  |
| deaths causally related to treatment / all              | 0 / 0          |  |  |
| Myocardial infarction and pseudomonas aeruginosa sepsis |                |  |  |
| subjects affected / exposed                             | 1 / 57 (1.75%) |  |  |
| occurrences causally related to treatment / all         | 1 / 1          |  |  |
| deaths causally related to treatment / all              | 1 / 1          |  |  |
| Pancytopenia and Epistaxis                              |                |  |  |
| subjects affected / exposed                             | 1 / 57 (1.75%) |  |  |
| occurrences causally related to treatment / all         | 1 / 1          |  |  |
| deaths causally related to treatment / all              | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders         |                |  |  |
| Severe bone pain                                        |                |  |  |
| subjects affected / exposed                             | 1 / 57 (1.75%) |  |  |
| occurrences causally related to treatment / all         | 1 / 1          |  |  |
| deaths causally related to treatment / all              | 0 / 0          |  |  |
| Infections and infestations                             |                |  |  |
| CMV Reactivation                                        |                |  |  |
| subjects affected / exposed                             | 1 / 57 (1.75%) |  |  |
| occurrences causally related to treatment / all         | 1 / 1          |  |  |
| deaths causally related to treatment / all              | 0 / 0          |  |  |
| Infection                                               |                |  |  |
| subjects affected / exposed                             | 1 / 57 (1.75%) |  |  |
| 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 %

|                                                       |                  |  |  |
|-------------------------------------------------------|------------------|--|--|
| <b>Non-serious adverse events</b>                     | Single arm       |  |  |
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 55 / 57 (96.49%) |  |  |
| Vascular disorders                                    |                  |  |  |

|                                                                                 |                         |  |  |
|---------------------------------------------------------------------------------|-------------------------|--|--|
| Other hemorrhage<br>subjects affected / exposed<br>occurrences (all)            | 2 / 57 (3.51%)<br>5     |  |  |
| Cardiac disorders                                                               |                         |  |  |
| Supraventricular arrhythmia<br>subjects affected / exposed<br>occurrences (all) | 2 / 57 (3.51%)<br>2     |  |  |
| Ventricular arrhythmia<br>subjects affected / exposed<br>occurrences (all)      | 1 / 57 (1.75%)<br>2     |  |  |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 57 (1.75%)<br>1     |  |  |
| Nervous system disorders                                                        |                         |  |  |
| Motor neuropathy<br>subjects affected / exposed<br>occurrences (all)            | 1 / 57 (1.75%)<br>2     |  |  |
| Sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)          | 1 / 57 (1.75%)<br>1     |  |  |
| Blood and lymphatic system disorders                                            |                         |  |  |
| Platelets<br>subjects affected / exposed<br>occurrences (all)                   | 51 / 57 (89.47%)<br>217 |  |  |
| Leucocytes<br>subjects affected / exposed<br>occurrences (all)                  | 52 / 57 (91.23%)<br>209 |  |  |
| Haemoglobin<br>subjects affected / exposed<br>occurrences (all)                 | 49 / 57 (85.96%)<br>190 |  |  |
| Granulocytes<br>subjects affected / exposed<br>occurrences (all)                | 53 / 57 (92.98%)<br>205 |  |  |
| Febrile neutropenia<br>subjects affected / exposed<br>occurrences (all)         | 15 / 57 (26.32%)<br>20  |  |  |
| General disorders and administration                                            |                         |  |  |



|                                                                                                                                                                                                                                                       |                                                                      |  |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|--|--|
| site conditions<br>Other toxicities<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                               | 33 / 57 (57.89%)<br>111                                              |  |  |
| Gastrointestinal disorders<br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br>Mucositis<br>subjects affected / exposed<br>occurrences (all)                      | 5 / 57 (8.77%)<br>6<br>4 / 57 (7.02%)<br>4<br>3 / 57 (5.26%)<br>4    |  |  |
| Hepatobiliary disorders<br>Liver dysfunction<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                      | 1 / 57 (1.75%)<br>1                                                  |  |  |
| Renal and urinary disorders<br>Renal failure<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                      | 3 / 57 (5.26%)<br>11                                                 |  |  |
| Infections and infestations<br>Viral infection<br>subjects affected / exposed<br>occurrences (all)<br>Bacterial infection<br>subjects affected / exposed<br>occurrences (all)<br>Fungal infection<br>subjects affected / exposed<br>occurrences (all) | 4 / 57 (7.02%)<br>4<br>10 / 57 (17.54%)<br>12<br>2 / 57 (3.51%)<br>3 |  |  |
| Metabolism and nutrition disorders<br>Hyperglycemia<br>subjects affected / exposed<br>occurrences (all)<br>Hyperbilirubinemia                                                                                                                         | 1 / 57 (1.75%)<br>4                                                  |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 57 (1.75%) |  |  |
| occurrences (all)           | 1              |  |  |
| Hyperuricemia               |                |  |  |
| subjects affected / exposed | 2 / 57 (3.51%) |  |  |
| occurrences (all)           | 5              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27927586>