



## Clinical trial results:

### Maintenance therapy with trabectedin versus observation after first line treatment with doxorubicin of patients with advanced or metastatic soft tissue sarcoma

#### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2016-003535-38          |
| Trial protocol           | DE GB NL PL ES FR CY IT |
| Global end of trial date | 05 June 2020            |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 28 January 2021 |
| First version publication date | 28 January 2021 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | 1447-STBSG |
|-----------------------|------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02929394 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |                                                                                                                                    |
|------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | EORTC                                                                                                                              |
| Sponsor organisation address | Avenue E. Mounier 83, Bruxelles, Belgium, 1200                                                                                     |
| Public contact               | Clinical Operations Department, European Organisation for the Research and treatment of Cancer, 0032 27741013, regulatory@eortc.be |
| Scientific contact           | Clinical Operations Department, European Organisation for the Research and treatment of Cancer, 0032 27741013, regulatory@eortc.be |

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                       | 08 May 2020   |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 14 April 2020 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 05 June 2020  |
| Was the trial ended prematurely?                     | Yes           |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate whether maintenance trabectedin given after 6 cycles of doxorubicin first-line therapy for advanced or metastatic STS prolongs progression-free survival (PFS) as compared to an observational approach.

Protection of trial subjects:

The responsible investigator ensures that this study was conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (<http://www.wma.net>)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500002874.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf)).

The protocol was approved by the competent ethics committee(s) as required by the applicable national

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 17 November 2017 |
| 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 | Spain: 3   |
| Country: Number of subjects enrolled | France: 10 |
| Worldwide total number of subjects   | 13         |
| EEA total number of subjects         | 13         |

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          | 0 |

|                           |   |
|---------------------------|---|
| months)                   |   |
| Children (2-11 years)     | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years)      | 8 |
| From 65 to 84 years       | 5 |
| 85 years and over         | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 13 patients were registered by 6 institutions between 17/Nov/2017 and 29/Aug/2018.

### Pre-assignment

Screening details:

Age 18 yo WHO PS  $\leq 1$  adequate bone marrow, liver and renal function. No prior exposure to trabectedin. Histologically proven locally advanced or metastatic high grade STS (excluding histologies insensitive to chemotherapy). Non-progressive disease after 6 cycles of first-line chemotherapy with doxorubicin.

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 13 |
| Number of subjects completed | 13 |

### Period 1

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

### Arms

|                              |                                 |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes                             |
| <b>Arm title</b>             | Arm A - Trabectedin maintenance |

Arm description:

Treatment should start within 3 days from randomization. Trabectedin was administered on day 1 every 4 weeks at the dose of 1.2 mg/m<sup>2</sup> body surface area, administered as an intravenous infusion over 24 hours. Trabectedin (trade name Yondelis®) was supplied by PharmaMar free of charge. Trabectedin was provided as a sterile lyophilized powder for reconstitution in solution for infusion in strength of 1 mg.

|                                        |                                  |
|----------------------------------------|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | TRABECTEDIN                      |
| Investigational medicinal product code |                                  |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravascular use                |

Dosage and administration details:

Trabectedin was provided as a sterile lyophilized powder for reconstitution in solution for infusion in strength of 1 mg. Trabectedin was administered on day 1 every 4 weeks at the dose of 1.2 mg/m<sup>2</sup> body surface area, administered as an intravenous infusion over 24 hours.

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | Arm B - Observational |
|------------------|-----------------------|

Arm description:

Observation through clinical and radiological follow-up until disease progression (RECIST 1.1). Patients could receive commercial trabectedin after progression in Arm B as second line treatment as per investigator's decision.

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Arm type                                                  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

| <b>Number of subjects in period 1</b>        | Arm A - Trabectedin maintenance | Arm B - Observational |
|----------------------------------------------|---------------------------------|-----------------------|
| Started                                      | 7                               | 6                     |
| Completed                                    | 0                               | 1                     |
| Not completed                                | 7                               | 5                     |
| Toxicity                                     | 5                               | -                     |
| Symptomatic deterioration                    | 1                               | 1                     |
| Patient's decision (not related to toxicity) | -                               | 1                     |
| Progression of disease/death due to PD       | 1                               | 3                     |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                              | Arm A - Trabectedin maintenance |
| Reporting group description:<br>Treatment should start within 3 days from randomization. Trabectedin was administered on day 1 every 4 weeks at the dose of 1.2 mg/m <sup>2</sup> body surface area, administered as an intravenous infusion over 24 hours. Trabectedin (trade name Yondelis®) was supplied by PharmaMar free of charge. Trabectedin was provided as a sterile lyophilized powder for reconstitution in solution for infusion in strength of 1 mg. |                                 |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                              | Arm B - Observational           |
| Reporting group description:<br>Observation through clinical and radiological follow-up until disease progression (RECIST 1.1). Patients could receive commercial trabectedin after progression in Arm B as second line treatment as per investigator's decision.                                                                                                                                                                                                  |                                 |

| Reporting group values                                                                       | Arm A - Trabectedin maintenance | Arm B - Observational | Total |
|----------------------------------------------------------------------------------------------|---------------------------------|-----------------------|-------|
| Number of subjects                                                                           | 7                               | 6                     | 13    |
| Age categorical<br>Units: Subjects                                                           |                                 |                       |       |
| Adults (18-64 years)                                                                         | 5                               | 3                     | 8     |
| From 65-84 years                                                                             | 2                               | 3                     | 5     |
| Age continuous<br>Units: years                                                               |                                 |                       |       |
| median                                                                                       | 61                              | 64                    |       |
| full range (min-max)                                                                         | 34 to 70                        | 45 to 74              | -     |
| Gender categorical<br>Units: Subjects                                                        |                                 |                       |       |
| Female                                                                                       | 5                               | 2                     | 7     |
| Male                                                                                         | 2                               | 4                     | 6     |
| WHO performance status (PS)<br>Units: Subjects                                               |                                 |                       |       |
| WHO PS = 0                                                                                   | 2                               | 2                     | 4     |
| WHO PS = 1                                                                                   | 5                               | 4                     | 9     |
| A first line chemotherapy with Doxorubicin (6 cycles)<br>Units: Subjects                     |                                 |                       |       |
| Yes                                                                                          | 7                               | 6                     | 13    |
| Previous treatment - Dose of Doxorubicin (mg/m <sup>2</sup> )<br>Units: (mg/m <sup>2</sup> ) |                                 |                       |       |
| median                                                                                       | 75.0                            | 75.0                  |       |
| full range (min-max)                                                                         | 50.0 to 75.0                    | 60.0 to 75.0          | -     |

### Subject analysis sets

|                                                                            |                                   |
|----------------------------------------------------------------------------|-----------------------------------|
| Subject analysis set title                                                 | Overall - full patient population |
| Subject analysis set type                                                  | Intention-to-treat                |
| Subject analysis set description:<br>Considers all 13 patients randomised. |                                   |

|                                                               |                                   |  |  |
|---------------------------------------------------------------|-----------------------------------|--|--|
| <b>Reporting group values</b>                                 | Overall - full patient population |  |  |
| Number of subjects                                            | 13                                |  |  |
| Age categorical                                               |                                   |  |  |
| Units: Subjects                                               |                                   |  |  |
| Adults (18-64 years)                                          | 8                                 |  |  |
| From 65-84 years                                              | 5                                 |  |  |
| Age continuous                                                |                                   |  |  |
| Units: years                                                  |                                   |  |  |
| median                                                        | 62                                |  |  |
| full range (min-max)                                          | 34 to 74                          |  |  |
| Gender categorical                                            |                                   |  |  |
| Units: Subjects                                               |                                   |  |  |
| Female                                                        | 7                                 |  |  |
| Male                                                          | 6                                 |  |  |
| WHO performance status (PS)                                   |                                   |  |  |
| Units: Subjects                                               |                                   |  |  |
| WHO PS = 0                                                    | 4                                 |  |  |
| WHO PS = 1                                                    | 9                                 |  |  |
| A first line chemotherapy with Doxorubicin (6 cycles)         |                                   |  |  |
| Units: Subjects                                               |                                   |  |  |
| Yes                                                           | 13                                |  |  |
| Previous treatment - Dose of Doxorubicin (mg/m <sup>2</sup> ) |                                   |  |  |
| Units: (mg/m <sup>2</sup> )                                   |                                   |  |  |
| median                                                        | 75.0                              |  |  |
| full range (min-max)                                          | 50.0 to 75.0                      |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                              | Arm A - Trabectedin maintenance   |
| Reporting group description:<br>Treatment should start within 3 days from randomization. Trabectedin was administered on day 1 every 4 weeks at the dose of 1.2 mg/m <sup>2</sup> body surface area, administered as an intravenous infusion over 24 hours. Trabectedin (trade name Yondelis®) was supplied by PharmaMar free of charge. Trabectedin was provided as a sterile lyophilized powder for reconstitution in solution for infusion in strength of 1 mg. |                                   |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                              | Arm B - Observational             |
| Reporting group description:<br>Observation through clinical and radiological follow-up until disease progression (RECIST 1.1). Patients could receive commercial trabectedin after progression in Arm B as second line treatment as per investigator's decision.                                                                                                                                                                                                  |                                   |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                         | Overall - full patient population |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                          | Intention-to-treat                |
| Subject analysis set description:<br>Considers all 13 patients randomised.                                                                                                                                                                                                                                                                                                                                                                                         |                                   |

### Primary: Progression-free survival (PFS)

|                                                                                                                                                                                                                                                                                                                                                    |                                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                    | Progression-free survival (PFS) |
| End point description:<br>PFS was estimated by the Kaplan-Meier method. Median PFS was provided with it's 95% confidence interval.<br><br>Patients who were alive without evidence of progression and who did not start a new antitumoral treatment in the absence of progression were censored at the date of their last radiological assessment. |                                 |
| End point type                                                                                                                                                                                                                                                                                                                                     | Primary                         |
| End point timeframe:<br>Progression-free survival was measured from the date of randomization until the date of the first documented disease progression, start of new antitumoral treatment in the absence of documented disease progression, or death, whichever occurs first.                                                                   |                                 |

| End point values                 | Arm A -<br>Trabectedin<br>maintenance | Arm B -<br>Observational |  |  |
|----------------------------------|---------------------------------------|--------------------------|--|--|
| Subject group type               | Reporting group                       | Reporting group          |  |  |
| Number of subjects analysed      | 7                                     | 6                        |  |  |
| Units: Months                    |                                       |                          |  |  |
| median (confidence interval 95%) | 11.3 (6.5 to 19.0)                    | 5.4 (1.4 to 14.7)        |  |  |

|                                   |                                                           |
|-----------------------------------|-----------------------------------------------------------|
| <b>Attachments (see zip file)</b> | PFS - Since randomization/1447_PFS_from_Randomization.jpg |
|-----------------------------------|-----------------------------------------------------------|

### Statistical analyses

|                                   |              |
|-----------------------------------|--------------|
| <b>Statistical analysis title</b> | Kaplan-Meier |
|-----------------------------------|--------------|

Statistical analysis description:

There were only 13 patients available in the study (the study was closed for recruitment for poor accrual) so it is not justifiable to make statistical analysis. For the "Parameter estimate" Section, median PFS (and 95% CI) for Trabectedin Arm were described in order to avoid an error in the system.

|                                         |                                                         |
|-----------------------------------------|---------------------------------------------------------|
| Comparison groups                       | Arm A - Trabectedin maintenance v Arm B - Observational |
| Number of subjects included in analysis | 13                                                      |
| Analysis specification                  | Pre-specified                                           |
| Analysis type                           | other <sup>[1]</sup>                                    |
| Parameter estimate                      | Median PFS estimate                                     |
| Point estimate                          | 11.3                                                    |
| Confidence interval                     |                                                         |
| level                                   | 95 %                                                    |
| sides                                   | 2-sided                                                 |
| lower limit                             | 6.5                                                     |
| upper limit                             | 19                                                      |

Notes:

[1] - Progression-free survival was estimated by the Kaplan-Meier method. The median survival time and its associated 95% CI was provided. For the "Parameter estimate" Section, median PFS (and 95% CI) for Trabectedin Arm were described in order to avoid an error in the system.

### Secondary: Overall survival (OS)

|                 |                       |
|-----------------|-----------------------|
| End point title | Overall survival (OS) |
|-----------------|-----------------------|

End point description:

Overall survival was estimated by the Kaplan-Meier method. The median survival time and its associated 95% CI was provided.

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

End point timeframe:

Overall survival was measured from the date of randomization to the date of death, whatever the cause of death. Patients who were alive were censored at the date of their last follow-up.

| End point values                 | Arm A -<br>Trabectedin<br>maintenance | Arm B -<br>Observational |  |  |
|----------------------------------|---------------------------------------|--------------------------|--|--|
| Subject group type               | Reporting group                       | Reporting group          |  |  |
| Number of subjects analysed      | 7                                     | 6                        |  |  |
| Units: Months                    |                                       |                          |  |  |
| median (confidence interval 95%) | 9999 (15.3 to 9999)                   | 9999 (5.3 to 9999)       |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival (PFS) - Since Doxorubicin

|                 |                                                     |
|-----------------|-----------------------------------------------------|
| End point title | Progression-free survival (PFS) - Since Doxorubicin |
|-----------------|-----------------------------------------------------|

End point description:

PFS was estimated by the Kaplan-Meier method. Median PFS was provided with it's 95% confidence interval.

|                                                                              |           |
|------------------------------------------------------------------------------|-----------|
| End point type                                                               | Secondary |
| End point timeframe:                                                         |           |
| PFS was measured from the date of starting first-line Doxorubicin treatment. |           |

| End point values                 | Arm A -<br>Trabectedin<br>maintenance | Arm B -<br>Observational |  |  |
|----------------------------------|---------------------------------------|--------------------------|--|--|
| Subject group type               | Reporting group                       | Reporting group          |  |  |
| Number of subjects analysed      | 7                                     | 6                        |  |  |
| Units: Months                    |                                       |                          |  |  |
| median (confidence interval 95%) | 16.6 (11.0 to 24.2)                   | 10.0 (6.6 to 19.5)       |  |  |

|                                   |                                                             |
|-----------------------------------|-------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | PFS - Since Doxorubicin/1447_PFS_from_Doxorubicin_start.jpg |
|-----------------------------------|-------------------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival - since Doxorubicin start

|                                                                                                                             |                                            |
|-----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| End point title                                                                                                             | Overall survival - since Doxorubicin start |
| End point description:                                                                                                      |                                            |
| Overall survival was estimated by the Kaplan-Meier method. The median survival time and its associated 95% CI was provided. |                                            |
| End point type                                                                                                              | Secondary                                  |
| End point timeframe:                                                                                                        |                                            |
| OS was measured from the date of starting first-line Doxorubicin treatment.                                                 |                                            |

| End point values                 | Arm A -<br>Trabectedin<br>maintenance | Arm B -<br>Observational |  |  |
|----------------------------------|---------------------------------------|--------------------------|--|--|
| Subject group type               | Reporting group                       | Reporting group          |  |  |
| Number of subjects analysed      | 7                                     | 6                        |  |  |
| Units: Months                    |                                       |                          |  |  |
| median (confidence interval 95%) | 9999 (20.6 to 9999)                   | 9999 (9.9 to 9999)       |  |  |

|                                   |                                                           |
|-----------------------------------|-----------------------------------------------------------|
| <b>Attachments (see zip file)</b> | OS - since Doxorubicin/1447_OS_from_Doxorubicin_start.jpg |
|-----------------------------------|-----------------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Start from randomization up to 30 days after administration of the last dose.

Adverse event reporting additional description:

CRF for AEs contains pre-specified items. (2 AEs are reported as "other" and are not reported as not available from the list of SOC). Both AEs and SAEs are evaluated using CTC grading.

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

### Dictionary used

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

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

### Reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | Arm A |
|-----------------------|-------|

Reporting group description:

Treatment should start within 3 days from randomization. Trabectedin was administered on day 1 every 4 weeks at the dose of 1.2 mg/m<sup>2</sup> body surface area, administered as an intravenous infusion over 24 hours. Trabectedin (trade name Yondelis®) was supplied by PharmaMar free of charge. Trabectedin was provided as a sterile lyophilized powder for reconstitution in solution for infusion in strength

| Serious adverse events                            | Arm A          |  |  |
|---------------------------------------------------|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 4 / 7 (57.14%) |  |  |
| number of deaths (all causes)                     | 1              |  |  |
| number of deaths resulting from adverse events    | 0              |  |  |
| Vascular disorders                                |                |  |  |
| ARTERIAL STENOSIS                                 |                |  |  |
| alternative dictionary used: CTCAE 4              |                |  |  |
| alternative assessment type: Systematic           |                |  |  |
| subjects affected / exposed                       | 1 / 7 (14.29%) |  |  |
| occurrences causally related to treatment / all   | 0 / 1          |  |  |
| deaths causally related to treatment / all        | 0 / 0          |  |  |
| Cardiac disorders                                 |                |  |  |
| CARDIAC FAILURE                                   |                |  |  |
| alternative dictionary used: CTCAE 4              |                |  |  |
| alternative assessment type: Systematic           |                |  |  |
| subjects affected / exposed                       | 2 / 7 (28.57%) |  |  |
| occurrences causally related to treatment / all   | 0 / 2          |  |  |
| deaths causally related to treatment / all        | 0 / 0          |  |  |

|                                                                                                                                                                                                                                                                                        |                                                          |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|--|--|
| Gastrointestinal disorders<br>ABDOMINAL PAIN UPPER<br>alternative dictionary used: CTCAE 4<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                  | <br><br><br><br>1 / 7 (14.29%)<br><br>0 / 1<br><br>0 / 0 |  |  |
| Respiratory, thoracic and mediastinal disorders<br>PLEURAL EFFUSION<br>alternative dictionary used: CTCAE 4<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | <br><br><br><br>1 / 7 (14.29%)<br><br>0 / 1<br><br>0 / 0 |  |  |

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

| Non-serious adverse events                                                                                                                                                  | Arm A                           |  |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|--|--|
| Total subjects affected by non-serious adverse events                                                                                                                       |                                 |  |  |
| subjects affected / exposed                                                                                                                                                 | 7 / 7 (100.00%)                 |  |  |
| Investigations                                                                                                                                                              |                                 |  |  |
| ALANINE AMINOTRANSFERASE INCREASED<br>alternative dictionary used: CTCAE 4<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all)   | <br><br><br>1 / 7 (14.29%)<br>1 |  |  |
| ASPARTATE AMINOTRANSFERASE INCREASED<br>alternative dictionary used: CTCAE 4<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all) | <br><br><br>1 / 7 (14.29%)<br>3 |  |  |
| CPK INCREASED<br>alternative dictionary used: CTCAE 4<br>alternative assessment type:                                                                                       |                                 |  |  |

|                                                                     |                |  |  |
|---------------------------------------------------------------------|----------------|--|--|
| Systematic                                                          |                |  |  |
| subjects affected / exposed                                         | 1 / 7 (14.29%) |  |  |
| occurrences (all)                                                   | 7              |  |  |
| CREATININE INCREASED                                                |                |  |  |
| alternative dictionary used: CTCAE 4                                |                |  |  |
| alternative assessment type: Systematic                             |                |  |  |
| subjects affected / exposed                                         | 1 / 7 (14.29%) |  |  |
| occurrences (all)                                                   | 2              |  |  |
| EJECTION FRACTION DECREASED                                         |                |  |  |
| alternative dictionary used: CTCAE 4                                |                |  |  |
| alternative assessment type: Systematic                             |                |  |  |
| subjects affected / exposed                                         | 1 / 7 (14.29%) |  |  |
| occurrences (all)                                                   | 1              |  |  |
| LYMPHOCYTE COUNT DECREASED                                          |                |  |  |
| alternative dictionary used: CTCAE 4                                |                |  |  |
| alternative assessment type: Systematic                             |                |  |  |
| subjects affected / exposed                                         | 1 / 7 (14.29%) |  |  |
| occurrences (all)                                                   | 2              |  |  |
| NEUTROPHIL COUNT DECREASED                                          |                |  |  |
| alternative dictionary used: CTCAE 4                                |                |  |  |
| alternative assessment type: Systematic                             |                |  |  |
| subjects affected / exposed                                         | 1 / 7 (14.29%) |  |  |
| occurrences (all)                                                   | 8              |  |  |
| WHITE BLOOD CELL DECREASED                                          |                |  |  |
| alternative dictionary used: CTCAE 4                                |                |  |  |
| alternative assessment type: Systematic                             |                |  |  |
| subjects affected / exposed                                         | 1 / 7 (14.29%) |  |  |
| occurrences (all)                                                   | 6              |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |  |  |
| NEVROMA                                                             |                |  |  |
| alternative dictionary used: CTCAE 4                                |                |  |  |
| alternative assessment type: Systematic                             |                |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                     |                                                |  |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                    | 1 / 7 (14.29%)<br>1                            |  |  |
| Cardiac disorders<br>CARDIAC DISORDERS - OTHER,<br>ARTERIAL STENOSIS<br>alternative dictionary used: CTCAE<br>4<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>HEART FAILURE<br>alternative dictionary used: CTCAE<br>4<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 7 (14.29%)<br>1<br><br>2 / 7 (28.57%)<br>2 |  |  |
| Nervous system disorders<br>DYSGEUSIA<br>alternative dictionary used: CTCAE<br>4<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                  | 1 / 7 (14.29%)<br>1                            |  |  |
| Blood and lymphatic system disorders<br>ANEMIA<br>alternative dictionary used: CTCAE<br>4<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                         | 2 / 7 (28.57%)<br>4                            |  |  |
| General disorders and administration<br>site conditions<br>EDEMA LIMBS<br>alternative dictionary used: CTCAE<br>4<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>FATIGUE<br>alternative dictionary used: CTCAE<br>4<br>alternative assessment type:<br>Systematic                                                         | 2 / 7 (28.57%)<br>2                            |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |  |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
| <p>subjects affected / exposed</p> <p>3 / 7 (42.86%)</p> <p>occurrences (all)</p> <p>4</p> <p>FEVER</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>1 / 7 (14.29%)</p> <p>occurrences (all)</p> <p>1</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| <p>Gastrointestinal disorders</p> <p>ABDOMINAL PAIN</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>2 / 7 (28.57%)</p> <p>occurrences (all)</p> <p>3</p> <p>DIARRHEA</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>1 / 7 (14.29%)</p> <p>occurrences (all)</p> <p>1</p> <p>DRY MOUTH</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>1 / 7 (14.29%)</p> <p>occurrences (all)</p> <p>1</p> <p>MUCOSITIS ORAL</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>2 / 7 (28.57%)</p> <p>occurrences (all)</p> <p>2</p> <p>NAUSEA</p> <p>alternative dictionary used: CTCAE 4</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>3 / 7 (42.86%)</p> <p>occurrences (all)</p> <p>3</p> <p>VOMITING</p> |  |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                           |  |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|--|--|
| alternative dictionary used: CTCAE 4<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                 | 1 / 7 (14.29%)<br>1                                                       |  |  |
| Respiratory, thoracic and mediastinal disorders<br>COUGH<br>alternative dictionary used: CTCAE 4<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                     | 1 / 7 (14.29%)<br>1                                                       |  |  |
| Musculoskeletal and connective tissue disorders<br>BONE PAIN<br>alternative dictionary used: CTCAE 4<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>INFLAMMATORY LEGS<br>alternative dictionary used: CTCAE 4<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>PAIN IN EXTREMITY<br>alternative dictionary used: CTCAE 4<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 7 (14.29%)<br>1<br><br>1 / 7 (14.29%)<br>1<br><br>1 / 7 (14.29%)<br>1 |  |  |
| Metabolism and nutrition disorders<br>ANOREXIA<br>alternative dictionary used: CTCAE 4<br>alternative assessment type: Systematic<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                               | 1 / 7 (14.29%)<br>1                                                       |  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24 March 2017 | <p>The protocol and patient information sheet have been updated according to the VHP comments:</p> <ul style="list-style-type: none"><li>- Contraceptive methods considered to be highly effective, listed in the protocol, are now in line with Clinical Trial Facilitation group (CTFG) guidance.</li><li>- A definition of women of childbearing potential has been included.</li><li>- According to the Trabectedin SmPC, a note for advice on the possibility of ovules/sperm conservation has been added in the inclusion criteria.</li><li>- It has been clarified that protocol waivers are not acceptable. A new section 16.4 regarding protocol and GCP compliance has been added as well.</li><li>- Complete blood counts must be performed weekly for the first two cycles.</li></ul> <p>This amendment has been discussed and agreed by the study team and study coordinator.</p> |

Notes:

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### 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.

Despite many efforts from all the parties involved, only few patients (13 patients in total) were recruited. The study was closed for recruitment on 10/08/2018 for poor accrual but two patients were included after that because they consented earlier.

Notes: