



## Clinical trial results:

**A Phase II, open label, multi-center, multi-arm study of ceritinib in patients with advanced solid tumors and hematological malignancies characterized by genetic abnormalities of anaplastic lymphoma kinase (ALK)**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2015-000814-23    |
| Trial protocol           | ES DE CZ FR DK IT |
| Global end of trial date | 20 August 2018    |

### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 02 September 2019 |
| First version publication date | 02 September 2019 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CLDK378A2407 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |                         |
|------------------------------------|-------------------------|
| ISRCTN number                      | -                       |
| ClinicalTrials.gov id (NCT number) | NCT02465528             |
| WHO universal trial number (UTN)   | -                       |
| Other trial identifiers            | Eudract: 2015-000814-23 |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Novartis Pharma AG   |
| Sponsor organisation address | CH-4002, Basel, Switzerland,   |
| Public contact               | Study Director, Novartis Pharma AG, 41 613241111,<br>Novartis.email@novartis.com |
| Scientific contact           | Study Director, Novartis Pharma AG, 41 613241111,<br>Novartis.email@novartis.com |

Notes:

### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 20 August 2018 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 20 August 2018 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 20 August 2018 |
| Was the trial ended prematurely?                     | Yes            |

Notes:

## General information about the trial

Main objective of the trial:

Assess the antitumor activity of ceritinib as measured by disease control rate (DCR) determined by Investigators.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 06 May 2016 |
| 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: 8              |
| Country: Number of subjects enrolled | Czech Republic: 2     |
| Country: Number of subjects enrolled | France: 3             |
| Country: Number of subjects enrolled | Korea, Republic of: 4 |
| Country: Number of subjects enrolled | Denmark: 1            |
| Country: Number of subjects enrolled | Italy: 1              |
| Country: Number of subjects enrolled | Thailand: 2           |
| Country: Number of subjects enrolled | Israel: 1             |
| Worldwide total number of subjects   | 22                    |
| EEA total number of subjects         | 15                    |

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)      | 18 |
| From 65 to 84 years       | 4  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A minimum of 10 and a maximum of 20 subjects were to be enrolled in each arm (tumor type)

### Period 1

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

### Arms

|                              |                                       |
|------------------------------|---------------------------------------|
| Are arms mutually exclusive? | Yes                                   |
| <b>Arm title</b>             | Anaplastic large cell lymphoma (ALCL) |

Arm description:

Patients with a diagnosis of ALCL histologically or cytologically confirmed to be ALK-positive

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Ceritinib    |
| Investigational medicinal product code | LDK378       |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Ceritinib was administered orally once daily at a dose of 750 mg (5 capsules of 150 mg ceritinib) on a continuous dosing schedule. A complete treatment cycle was defined as 28 days of once daily continuous treatment with ceritinib.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Inflammatory myofibroblastic tumor (IMT) |
|------------------|--|

Arm description:

Patients diagnosed with IMT with a confirmed translocation involving the ALK gene

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Ceritinib    |
| Investigational medicinal product code | LDK378       |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Ceritinib was administered orally once daily at a dose of 750 mg (5 capsules of 150 mg ceritinib) on a continuous dosing schedule. A complete treatment cycle was defined as 28 days of once daily continuous treatment with ceritinib.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Glioblastoma (GBM) |
|------------------|--------------------|

Arm description:

Patients with GBM with a translocation involving the ALK gene

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Ceritinib    |
| Investigational medicinal product code | LDK378       |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Ceritinib was administered orally once daily at a dose of 750 mg (5 capsules of 150 mg ceritinib) on a continuous dosing schedule. A complete treatment cycle was defined as 28 days of once daily continuous treatment with ceritinib.

|                  |                              |
|------------------|------------------------------|
| <b>Arm title</b> | Any other ALK-positive tumor |
|------------------|------------------------------|

Arm description:

Patients with any other ALK-positive tumor. Patients in this arm included adenocarcinoma (n= 2), sarcoma (1) and other (2).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Ceritinib    |
| Investigational medicinal product code | LDK378       |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Ceritinib was administered orally once daily at a dose of 750 mg (5 capsules of 150 mg ceritinib) on a continuous dosing schedule. A complete treatment cycle was defined as 28 days of once daily continuous treatment with ceritinib.

| Number of subjects in period 1 | Anaplastic large cell lymphoma (ALCL) | Inflammatory myofibroblastic tumor (IMT) | Glioblastoma (GBM) |
|--------------------------------|---------------------------------------|--|--------------------|
|                                |                                       |  |                    |
| Started                        | 1                                     | 4  | 12                 |
| Completed                      | 0                                     | 0  | 0                  |
| Not completed                  | 1                                     | 4  | 12                 |
| Consent withdrawn by subject   | -                                     | -  | 2                  |
| Physician decision             | -                                     | -  | 1                  |
| Adverse event, non-fatal       | -                                     | -  | -                  |
| Study terminated by sponsor    | 1                                     | 2  | -                  |
| Progressive disease            | -                                     | 2  | 9                  |

| Number of subjects in period 1 | Any other ALK-positive tumor |
|--------------------------------|------------------------------|
| Started                        | 5                            |
| Completed                      | 0                            |
| Not completed                  | 5                            |
| Consent withdrawn by subject   | -                            |
| Physician decision             | -                            |
| Adverse event, non-fatal       | 1                            |
| Study terminated by sponsor    | -                            |
| Progressive disease            | 4                            |

## Baseline characteristics

### Reporting groups

|   |  |
|---|--|
| Reporting group title   | Anaplastic large cell lymphoma (ALCL)    |
| Reporting group description:  |  |
| Patients with a diagnosis of ALCL histologically or cytologically confirmed to be ALK-positive                              |  |
| Reporting group title   | Inflammatory myofibroblastic tumor (IMT) |
| Reporting group description:  |  |
| Patients diagnosed with IMT with a confirmed translocation involving the ALK gene   |  |
| Reporting group title   | Glioblastoma (GBM)                       |
| Reporting group description:  |  |
| Patients with GBM with a translocation involving the ALK gene   |  |
| Reporting group title   | Any other ALK-positive tumor             |
| Reporting group description:  |  |
| Patients with any other ALK-positive tumor. Patients in this arm included adenocarcinoma (n= 2), sarcoma (1) and other (2). |  |

| Reporting group values     | Anaplastic large cell lymphoma (ALCL) | Inflammatory myofibroblastic tumor (IMT) | Glioblastoma (GBM) |
|----------------------------|---------------------------------------|--|--------------------|
| Number of subjects         | 1                                     | 4  | 12                 |
| Age, Customized            |                                       |  |                    |
| Units: Subjects            |                                       |  |                    |
| 18 to <65                  | 1                                     | 4  | 10                 |
| 65 to ≤75                  | 0                                     | 0  | 2                  |
| Age Continuous             |                                       |  |                    |
| Units: years               |                                       |  |                    |
| arithmetic mean            | 36.0                                  | 42.8                                     | 49.3               |
| standard deviation         | ± 999.9                               | ± 19.41                                  | ± 15.40            |
| Sex: Female, Male          |                                       |  |                    |
| Units: Subjects            |                                       |  |                    |
| Female                     | 1                                     | 3  | 6                  |
| Male                       | 0                                     | 1  | 6                  |
| Race/Ethnicity, Customized |                                       |  |                    |
| Units: Subjects            |                                       |  |                    |
| Caucasian                  | 0                                     | 1  | 10                 |
| Asian                      | 1                                     | 1  | 1                  |
| Other                      | 0                                     | 2  | 1                  |

| Reporting group values | Any other ALK-positive tumor | Total |  |
|------------------------|------------------------------|-------|--|
| Number of subjects     | 5                            | 22    |  |
| Age, Customized        |                              |       |  |
| Units: Subjects        |                              |       |  |
| 18 to <65              | 3                            | 18    |  |
| 65 to ≤75              | 2                            | 4     |  |
| Age Continuous         |                              |       |  |
| Units: years           |                              |       |  |
| arithmetic mean        | 57.4                         | -     |  |
| standard deviation     | ± 14.64                      | -     |  |

|                            |   |    |  |
|----------------------------|---|----|--|
| Sex: Female, Male          |   |    |  |
| Units: Subjects            |   |    |  |
| Female                     | 1 | 11 |  |
| Male                       | 4 | 11 |  |
| Race/Ethnicity, Customized |   |    |  |
| Units: Subjects            |   |    |  |
| Caucasian                  | 2 | 13 |  |
| Asian                      | 3 | 6  |  |
| Other                      | 0 | 3  |  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Anaplastic large cell lymphoma (ALCL)    |
| Reporting group description:  |  |
| Patients with a diagnosis of ALCL histologically or cytologically confirmed to be ALK-positive                              |  |
| Reporting group title   | Inflammatory myofibroblastic tumor (IMT) |
| Reporting group description:  |  |
| Patients diagnosed with IMT with a confirmed translocation involving the ALK gene   |  |
| Reporting group title   | Glioblastoma (GBM)                       |
| Reporting group description:  |  |
| Patients with GBM with a translocation involving the ALK gene   |  |
| Reporting group title   | Any other ALK-positive tumor             |
| Reporting group description:  |  |
| Patients with any other ALK-positive tumor. Patients in this arm included adenocarcinoma (n= 2), sarcoma (1) and other (2). |  |

### Primary: Disease Control Rate (DCR) based on investigator assessments for participants with at least 16 weeks of treatment

|   |  |
|---|--|
| End point title   | Disease Control Rate (DCR) based on investigator assessments for participants with at least 16 weeks of treatment <sup>[1]</sup> |
| End point description:  |  |
| The DCR is defined as the percentage of patients with complete response (CR), partial response (PR) or stable disease (SD) at 16 weeks from the start of ceritinib treatment. The assessment criteria are: Solid Tumors (RECIST 1.1., Response Evaluation Criteria in Solid Tumors); GBM (RECIST 1.1 and RANO, Response Evaluation in Neuro-Oncology); Hematologic tumors (Cheson). |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| Baseline up to approximately 16 weeks   |  |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No analysis was done for this endpoint

| End point values                  | Anaplastic large cell lymphoma (ALCL) | Inflammatory myofibroblastic tumor (IMT) | Glioblastoma (GBM) | Any other ALK-positive tumor |
|-----------------------------------|---------------------------------------|--|--------------------|------------------------------|
| Subject group type                | Reporting group                       | Reporting group                          | Reporting group    | Reporting group              |
| Number of subjects analysed       | 1 <sup>[2]</sup>                      | 4 <sup>[3]</sup>                         | 12 <sup>[4]</sup>  | 5 <sup>[5]</sup>             |
| Units: percentage of participants |                                       |  |                    |                              |
| number (confidence interval 95%)  | 100.00 (2.5 to 100.0)                 | 75.00 (19.4 to 99.4)                     | 0.0 (0.0 to 26.5)  | 40.0 (5.3 to 85.3)           |

Notes:

[2] - n=1

[3] - n=3

[4] - n=0

[5] - n=2

### Statistical analyses



No statistical analyses for this end point

### Secondary: Overall Response Rate (ORR) per investigator assessment

|  |   |
|--|---|
| End point title  | Overall Response Rate (ORR) per investigator assessment |
| End point description:<br>ORR is defined as the percentage of patients with best overall response of complete response (CR) or partial response (PR) based on local assessment according to RECIST 1.1, RANO or Cheson hematological criteria. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Baseline, every 8 weeks until disease progression or end of treatment, whichever came first assessed up to approximately 84 weeks  |   |

| End point values                  | Anaplastic large cell lymphoma (ALCL) | Inflammatory myofibroblastic tumor (IMT) | Glioblastoma (GBM) | Any other ALK-positive tumor |
|-----------------------------------|---------------------------------------|--|--------------------|------------------------------|
| Subject group type                | Reporting group                       | Reporting group                          | Reporting group    | Reporting group              |
| Number of subjects analysed       | 1 <sup>[6]</sup>                      | 4 <sup>[7]</sup>                         | 12 <sup>[8]</sup>  | 5 <sup>[9]</sup>             |
| Units: percentage of participants |                                       |  |                    |                              |
| number (confidence interval 95%)  | 100.0 (2.5 to 100.0)                  | 75.0 (19.4 to 99.4)                      | 0.0 (0 to 26.5)    | 0.0 (0.0 to 52.2)            |

Notes:

[6] - n=1

[7] - n=3

[8] - n=0

[9] - n=0

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DOR) per investigator assessment

|   |  |
|---|--|
| End point title   | Duration of Response (DOR) per investigator assessment <sup>[10]</sup> |
| End point description:<br>DOR is defined as the time from date of first documented CR or PR to date of first documented disease progression or death due to any cause |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline, every 8 weeks until disease progression or end of treatment, whichever came first, assessed up to approximately 84 weeks            |  |

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No analysis was done for this endpoint

| End point values                 | Anaplastic large cell lymphoma (ALCL) | Inflammatory myofibroblastic tumor (IMT) |  |  |
|----------------------------------|---------------------------------------|--|--|--|
| Subject group type               | Reporting group                       | Reporting group                          |  |  |
| Number of subjects analysed      | 1 <sup>[11]</sup>                     | 3 <sup>[12]</sup>                        |  |  |
| Units: weeks                     |                                       |  |  |  |
| median (confidence interval 95%) | 999.9 (999.9 to 999.9)                | 999.9 (3.0 to 999.9)                     |  |  |

Notes:

[11] - n=0

[12] - n=1

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Response (TTR) per investigator assessment

|                 |  |
|-----------------|--|
| End point title | Time to Response (TTR) per investigator assessment |
|-----------------|--|

End point description:

TTR is defined as the time from date of the first dose to date of first documented response (CR or PR)

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

End point timeframe:

Baseline, every 8 weeks until disease progression or end of treatment, whichever came first, assessed up to approximately 84 weeks

| End point values                 | Anaplastic large cell lymphoma (ALCL) | Inflammatory myofibroblastic tumor (IMT) | Glioblastoma (GBM)     | Any other ALK-positive tumor |
|----------------------------------|---------------------------------------|--|------------------------|------------------------------|
| Subject group type               | Reporting group                       | Reporting group                          | Reporting group        | Reporting group              |
| Number of subjects analysed      | 1 <sup>[13]</sup>                     | 4 <sup>[14]</sup>                        | 12 <sup>[15]</sup>     | 5 <sup>[16]</sup>            |
| Units: weeks                     |                                       |  |                        |                              |
| median (confidence interval 95%) | 7.1 (0.999 to 999.9)                  | 16.4 (6.3 to 999.9)                      | 999.9 (999.9 to 999.9) | 999.9 (999.9 to 999.9)       |

Notes:

[13] - n=1

[14] - n=3

[15] - n=0

[16] - n=4

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression Free Survival (PFS) per investigator assessments

|                 |  |
|-----------------|--|
| End point title | Progression Free Survival (PFS) per investigator assessments |
|-----------------|--|

End point description:

PFS is defined as the time from the date of first dose of ceritinib to the date of first documented disease progression or death from any cause

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

End point timeframe:

Baseline, every 8 weeks until disease progression or death from any cause, assessed for up to approximately 84 weeks

| End point values                 | Anaplastic large cell lymphoma (ALCL) | Inflammatory myofibroblastic tumor (IMT) | Glioblastoma (GBM) | Any other ALK-positive tumor |
|----------------------------------|---------------------------------------|--|--------------------|------------------------------|
| Subject group type               | Reporting group                       | Reporting group                          | Reporting group    | Reporting group              |
| Number of subjects analysed      | 0 <sup>[17]</sup>                     | 2 <sup>[18]</sup>                        | 9 <sup>[19]</sup>  | 5 <sup>[20]</sup>            |
| Units: weeks                     |                                       |  |                    |                              |
| median (confidence interval 95%) | ( to )                                | 999.9 (3.7 to 999.9)                     | 1.7 (1.1 to 2.7)   | 1.7 (1.6 to 5.1)             |

Notes:

[17] - No participants met the criteria for PFS, n=0

[18] - n=2

[19] - n=9

[20] - n=5

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent of on treatment participant deaths during treatment and 30 day follow-up

|   |  |
|---|--|
| End point title   | Percent of on treatment participant deaths during treatment and 30 day follow-up |
| End point description:  |  |
| Deaths due to any cause during treatment and 30 day follow-up |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline up to approximately 84 weeks                         |  |

| End point values               | Anaplastic large cell lymphoma (ALCL) | Inflammatory myofibroblastic tumor (IMT) | Glioblastoma (GBM) | Any other ALK-positive tumor |
|--------------------------------|---------------------------------------|--|--------------------|------------------------------|
| Subject group type             | Reporting group                       | Reporting group                          | Reporting group    | Reporting group              |
| Number of subjects analysed    | 0 <sup>[21]</sup>                     | 0 <sup>[22]</sup>                        | 3                  | 1                            |
| Units: percent of participants |                                       |  |                    |                              |
| number (not applicable)        |                                       |  | 25.0               | 20.0                         |

Notes:

[21] - no deaths in this arm

[22] - no deaths in this arm

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 28 days post treatment, up to maximum duration of approximately 84 weeks

Adverse event reporting additional description:

Any sign or symptom that occurs during the study treatment plus 30 days post treatment.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

### Reporting groups

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Inflammatory Myofibroblastic Tumor |
|-----------------------|------------------------------------|

Reporting group description:

Inflammatory Myofibroblastic Tumor

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Anaplastic Large Cell Lymphoma |
|-----------------------|--------------------------------|

Reporting group description:

Anaplastic Large Cell Lymphoma

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Any other ALK+ tumor |
|-----------------------|----------------------|

Reporting group description:

Any other ALK+ tumor

|                       |              |
|-----------------------|--------------|
| Reporting group title | All Subjects |
|-----------------------|--------------|

Reporting group description:

All Subjects

|                       |              |
|-----------------------|--------------|
| Reporting group title | Glioblastoma |
|-----------------------|--------------|

Reporting group description:

Glioblastoma

| Serious adverse events                            | Inflammatory Myofibroblastic Tumor | Anaplastic Large Cell Lymphoma | Any other ALK+ tumor |
|---|------------------------------------|--------------------------------|----------------------|
| Total subjects affected by serious adverse events |                                    |                                |                      |
| subjects affected / exposed                       | 2 / 4 (50.00%)                     | 0 / 1 (0.00%)                  | 4 / 5 (80.00%)       |
| number of deaths (all causes)                     | 0                                  | 0                              | 1                    |
| number of deaths resulting from adverse events    | 0                                  | 0                              | 0                    |
| Investigations                                    |                                    |                                |                      |
| Haemoglobin decreased                             |                                    |                                |                      |
| subjects affected / exposed                       | 0 / 4 (0.00%)                      | 0 / 1 (0.00%)                  | 1 / 5 (20.00%)       |
| occurrences causally related to treatment / all   | 0 / 0                              | 0 / 0                          | 0 / 1                |
| deaths causally related to treatment / all        | 0 / 0                              | 0 / 0                          | 0 / 0                |
| Transaminases increased                           |                                    |                                |                      |

|   |               |               |               |
|---|---------------|---------------|---------------|
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Injury, poisoning and procedural complications  |               |               |               |
| Head injury                                     |               |               |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Vascular disorders                              |               |               |               |
| Embolism  |               |               |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Nervous system disorders                        |               |               |               |
| Cerebrovascular accident                        |               |               |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Depressed level of consciousness                |               |               |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Haemorrhage intracranial                        |               |               |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Hydrocephalus                                   |               |               |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |
| Hypersomnia                                     |               |               |               |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |

|  |                |               |                |
|--|----------------|---------------|----------------|
| Intracranial pressure increased                      |                |               |                |
| subjects affected / exposed                          | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| Paraesthesia   |                |               |                |
| subjects affected / exposed                          | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| Seizure  |                |               |                |
| subjects affected / exposed                          | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| Blood and lymphatic system disorders                 |                |               |                |
| Anaemia  |                |               |                |
| subjects affected / exposed                          | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| Thrombocytopenia                                     |                |               |                |
| subjects affected / exposed                          | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 2 / 5 (40.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| General disorders and administration site conditions |                |               |                |
| Asthenia   |                |               |                |
| subjects affected / exposed                          | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| Oedema peripheral                                    |                |               |                |
| subjects affected / exposed                          | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |
| Pyrexia  |                |               |                |
| subjects affected / exposed                          | 1 / 4 (25.00%) | 0 / 1 (0.00%) | 2 / 5 (40.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         | 0 / 0          |

|   |                |               |                |
|---|----------------|---------------|----------------|
| Gastrointestinal disorders                      |                |               |                |
| Stomatitis                                      |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                |               |                |
| Dermatitis allergic                             |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Dermatitis bullous                              |                |               |                |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Paraneoplastic pemphigus                        |                |               |                |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Renal and urinary disorders                     |                |               |                |
| Haematuria                                      |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Nephrotic syndrome                              |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Renal failure                                   |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Infections and infestations                     |                |               |                |
| Cellulitis                                      |                |               |                |

|   |                |               |                |
|---|----------------|---------------|----------------|
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Lung infection                                  |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Pneumonia                                       |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Pyelonephritis                                  |                |               |                |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Tooth infection                                 |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Metabolism and nutrition disorders              |                |               |                |
| Decreased appetite                              |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Hypercalcaemia                                  |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Hyperglycaemia                                  |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Hypoalbuminaemia                                |                |               |                |



|   |               |               |                |
|---|---------------|---------------|----------------|
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |
| Hyponatraemia                                   |               |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0          |

| <b>Serious adverse events</b>                     | All Subjects     | Glioblastoma     |  |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events |                  |                  |  |
| subjects affected / exposed                       | 16 / 22 (72.73%) | 10 / 12 (83.33%) |  |
| number of deaths (all causes)                     | 4                | 3                |  |
| number of deaths resulting from adverse events    | 0                | 0                |  |
| Investigations                                    |                  |                  |  |
| Haemoglobin decreased                             |                  |                  |  |
| subjects affected / exposed                       | 1 / 22 (4.55%)   | 0 / 12 (0.00%)   |  |
| occurrences causally related to treatment / all   | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| Transaminases increased                           |                  |                  |  |
| subjects affected / exposed                       | 1 / 22 (4.55%)   | 1 / 12 (8.33%)   |  |
| occurrences causally related to treatment / all   | 1 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| Injury, poisoning and procedural complications    |                  |                  |  |
| Head injury                                       |                  |                  |  |
| subjects affected / exposed                       | 1 / 22 (4.55%)   | 1 / 12 (8.33%)   |  |
| occurrences causally related to treatment / all   | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| Vascular disorders                                |                  |                  |  |
| Embolism  |                  |                  |  |
| subjects affected / exposed                       | 1 / 22 (4.55%)   | 1 / 12 (8.33%)   |  |
| occurrences causally related to treatment / all   | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            |  |
| Nervous system disorders                          |                  |                  |  |
| Cerebrovascular accident                          |                  |                  |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 22 (4.55%) | 1 / 12 (8.33%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Depressed level of consciousness                |                |                 |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 1 / 12 (8.33%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Haemorrhage intracranial                        |                |                 |  |
| subjects affected / exposed                     | 2 / 22 (9.09%) | 2 / 12 (16.67%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hydrocephalus                                   |                |                 |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 1 / 12 (8.33%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 1           |  |
| Hypersomnia                                     |                |                 |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 1 / 12 (8.33%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Intracranial pressure increased                 |                |                 |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 1 / 12 (8.33%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Paraesthesia                                    |                |                 |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 1 / 12 (8.33%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Seizure   |                |                 |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 12 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Blood and lymphatic system disorders            |                |                 |  |
| Anaemia   |                |                 |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| subjects affected / exposed                          | 1 / 22 (4.55%)  | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Thrombocytopenia                                     |                 |                |  |
| subjects affected / exposed                          | 2 / 22 (9.09%)  | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| General disorders and administration site conditions |                 |                |  |
| Asthenia   |                 |                |  |
| subjects affected / exposed                          | 1 / 22 (4.55%)  | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Oedema peripheral                                    |                 |                |  |
| subjects affected / exposed                          | 1 / 22 (4.55%)  | 1 / 12 (8.33%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Pyrexia  |                 |                |  |
| subjects affected / exposed                          | 4 / 22 (18.18%) | 1 / 12 (8.33%) |  |
| occurrences causally related to treatment / all      | 0 / 4           | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Gastrointestinal disorders                           |                 |                |  |
| Stomatitis   |                 |                |  |
| subjects affected / exposed                          | 1 / 22 (4.55%)  | 1 / 12 (8.33%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Skin and subcutaneous tissue disorders               |                 |                |  |
| Dermatitis allergic                                  |                 |                |  |
| subjects affected / exposed                          | 1 / 22 (4.55%)  | 1 / 12 (8.33%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Dermatitis bullous                                   |                 |                |  |
| subjects affected / exposed                          | 1 / 22 (4.55%)  | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Paraneoplastic pemphigus                        |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Haematuria                                      |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 1 / 12 (8.33%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nephrotic syndrome                              |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 1 / 12 (8.33%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal failure                                   |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Cellulitis                                      |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 1 / 12 (8.33%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lung infection                                  |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 1 / 12 (8.33%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pyelonephritis                                  |                |                |  |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 12 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|  |                                  |                                  |  |
|--|----------------------------------|----------------------------------|--|
| Tooth infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | 1 / 22 (4.55%)<br>0 / 1<br>0 / 0 | 1 / 12 (8.33%)<br>0 / 1<br>0 / 0 |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 1 / 22 (4.55%)<br>1 / 1<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Hypercalcaemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 22 (4.55%)<br>0 / 1<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 2 / 22 (9.09%)<br>2 / 2<br>0 / 0 | 1 / 12 (8.33%)<br>1 / 1<br>0 / 0 |  |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 22 (4.55%)<br>0 / 1<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | 1 / 22 (4.55%)<br>0 / 1<br>0 / 0 | 1 / 12 (8.33%)<br>0 / 1<br>0 / 0 |  |

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

| <b>Non-serious adverse events</b>                     | Inflammatory Myofibroblastic Tumor | Anaplastic Large Cell Lymphoma | Any other ALK+ tumor |
|---|------------------------------------|--------------------------------|----------------------|
| Total subjects affected by non-serious adverse events |                                    |                                |                      |
| subjects affected / exposed                           | 4 / 4 (100.00%)                    | 1 / 1 (100.00%)                | 5 / 5 (100.00%)      |
| General disorders and administration site conditions  |                                    |                                |                      |

|   |                |               |                |
|---|----------------|---------------|----------------|
| Asthenia  |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 4 / 5 (80.00%) |
| occurrences (all)                               | 0              | 0             | 4              |
| Fatigue   |                |               |                |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 1              | 0             | 0              |
| Gait disturbance                                |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Oedema  |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)                               | 0              | 0             | 1              |
| Oedema peripheral                               |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Pain  |                |               |                |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 1              | 0             | 0              |
| Respiratory, thoracic and mediastinal disorders |                |               |                |
| Cough   |                |               |                |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 1              | 0             | 0              |
| Dyspnoea  |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Epistaxis                                       |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Lung disorder                                   |                |               |                |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 1              | 0             | 0              |
| Respiratory disorder                            |                |               |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0              |
| Psychiatric disorders                           |                |               |                |

|  |                     |                      |                     |
|--|---------------------|----------------------|---------------------|
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 4 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0   | 1 / 5 (20.00%)<br>1 |
| Investigations   |                     |                      |                     |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 3 / 4 (75.00%)<br>4 | 1 / 1 (100.00%)<br>1 | 1 / 5 (20.00%)<br>1 |
| Amylase increased<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 4 (50.00%)<br>4 | 0 / 1 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 3 / 4 (75.00%)<br>5 | 1 / 1 (100.00%)<br>2 | 1 / 5 (20.00%)<br>4 |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 2 / 4 (50.00%)<br>3 | 1 / 1 (100.00%)<br>1 | 1 / 5 (20.00%)<br>1 |
| Blood bilirubin abnormal<br>subjects affected / exposed<br>occurrences (all)             | 1 / 4 (25.00%)<br>2 | 0 / 1 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)            | 1 / 4 (25.00%)<br>2 | 0 / 1 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)           | 2 / 4 (50.00%)<br>3 | 0 / 1 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0  |
| Creatinine renal clearance increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 4 (25.00%)<br>1 | 0 / 1 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0  |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all)  | 2 / 4 (50.00%)<br>2 | 1 / 1 (100.00%)<br>1 | 1 / 5 (20.00%)<br>1 |
| Lipase increased<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 4 (25.00%)<br>1 | 0 / 1 (0.00%)<br>0   | 1 / 5 (20.00%)<br>1 |
| Weight decreased   |                     |                      |                     |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 4 (0.00%)<br>0   | 0 / 1 (0.00%)<br>0   | 1 / 5 (20.00%)<br>1  |
| Injury, poisoning and procedural complications<br>Cartilage injury<br>subjects affected / exposed<br>occurrences (all)  | 0 / 4 (0.00%)<br>0   | 0 / 1 (0.00%)<br>0   | 1 / 5 (20.00%)<br>1  |
| Cardiac disorders<br>Bradycardia<br>subjects affected / exposed<br>occurrences (all)<br><br>Sinus bradycardia<br>subjects affected / exposed<br>occurrences (all)<br><br>Tachycardia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 4 (0.00%)<br>0<br><br>1 / 4 (25.00%)<br>1<br><br>0 / 4 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0<br><br>0 / 1 (0.00%)<br>0<br><br>0 / 1 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0<br><br>1 / 5 (20.00%)<br>1  |
| Nervous system disorders<br>Aphasia<br>subjects affected / exposed<br>occurrences (all)<br><br>Cognitive disorder<br>subjects affected / exposed<br>occurrences (all)<br><br>Depressed level of consciousness<br>subjects affected / exposed<br>occurrences (all)<br><br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Hemiparesis<br>subjects affected / exposed<br>occurrences (all)<br><br>Somnolence | 0 / 4 (0.00%)<br>0<br><br>0 / 4 (0.00%)<br>0<br><br>0 / 4 (0.00%)<br>0<br><br>0 / 4 (0.00%)<br>0<br><br>0 / 4 (0.00%)<br>0<br><br>0 / 4 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0<br><br>0 / 1 (0.00%)<br>0<br><br>0 / 1 (0.00%)<br>0<br><br>0 / 1 (0.00%)<br>0<br><br>0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0 |



|  |                    |                    |                    |
|--|--------------------|--------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Blood and lymphatic system disorders             |                    |                    |                    |
| Anaemia  |                    |                    |                    |
| subjects affected / exposed                      | 2 / 4 (50.00%)     | 0 / 1 (0.00%)      | 3 / 5 (60.00%)     |
| occurrences (all)                                | 3                  | 0                  | 3                  |
| Leukocytosis                                     |                    |                    |                    |
| subjects affected / exposed                      | 1 / 4 (25.00%)     | 0 / 1 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 2                  | 0                  | 0                  |
| Lymphopenia                                      |                    |                    |                    |
| subjects affected / exposed                      | 2 / 4 (50.00%)     | 0 / 1 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 2                  | 0                  | 0                  |
| Neutropenia                                      |                    |                    |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 1 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Thrombocytopenia                                 |                    |                    |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 1 (0.00%)      | 2 / 5 (40.00%)     |
| occurrences (all)                                | 0                  | 0                  | 2                  |
| Gastrointestinal disorders                       |                    |                    |                    |
| Abdominal pain                                   |                    |                    |                    |
| subjects affected / exposed                      | 2 / 4 (50.00%)     | 1 / 1 (100.00%)    | 2 / 5 (40.00%)     |
| occurrences (all)                                | 2                  | 1                  | 2                  |
| Abdominal pain upper                             |                    |                    |                    |
| subjects affected / exposed                      | 1 / 4 (25.00%)     | 0 / 1 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 1                  | 0                  | 0                  |
| Constipation                                     |                    |                    |                    |
| subjects affected / exposed                      | 2 / 4 (50.00%)     | 0 / 1 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 2                  | 0                  | 0                  |
| Diarrhoea  |                    |                    |                    |
| subjects affected / exposed                      | 3 / 4 (75.00%)     | 1 / 1 (100.00%)    | 2 / 5 (40.00%)     |
| occurrences (all)                                | 4                  | 2                  | 3                  |
| Eructation                                       |                    |                    |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 1 (0.00%)      | 1 / 5 (20.00%)     |
| occurrences (all)                                | 0                  | 0                  | 1                  |
| Flatulence                                       |                    |                    |                    |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                 | 0 / 4 (0.00%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)                           | 0              | 0               | 0              |
| Gastrooesophageal reflux disease            |                |                 |                |
| subjects affected / exposed                 | 0 / 4 (0.00%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)                           | 0              | 0               | 0              |
| Nausea                                      |                |                 |                |
| subjects affected / exposed                 | 3 / 4 (75.00%) | 1 / 1 (100.00%) | 3 / 5 (60.00%) |
| occurrences (all)                           | 6              | 1               | 4              |
| Stomatitis                                  |                |                 |                |
| subjects affected / exposed                 | 1 / 4 (25.00%) | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)                           | 2              | 0               | 0              |
| Vomiting                                    |                |                 |                |
| subjects affected / exposed                 | 2 / 4 (50.00%) | 1 / 1 (100.00%) | 4 / 5 (80.00%) |
| occurrences (all)                           | 2              | 1               | 6              |
| Skin and subcutaneous tissue disorders      |                |                 |                |
| Dermatitis acneiform                        |                |                 |                |
| subjects affected / exposed                 | 0 / 4 (0.00%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)                           | 0              | 0               | 0              |
| Dermatitis bullous                          |                |                 |                |
| subjects affected / exposed                 | 1 / 4 (25.00%) | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)                           | 1              | 0               | 0              |
| Palmar-plantar erythrodysaesthesia syndrome |                |                 |                |
| subjects affected / exposed                 | 1 / 4 (25.00%) | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)                           | 1              | 0               | 0              |
| Photosensitivity reaction                   |                |                 |                |
| subjects affected / exposed                 | 1 / 4 (25.00%) | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)                           | 1              | 0               | 0              |
| Pruritus                                    |                |                 |                |
| subjects affected / exposed                 | 1 / 4 (25.00%) | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)                           | 1              | 0               | 0              |
| Rash  |                |                 |                |
| subjects affected / exposed                 | 1 / 4 (25.00%) | 1 / 1 (100.00%) | 1 / 5 (20.00%) |
| occurrences (all)                           | 1              | 1               | 1              |
| Skin toxicity                               |                |                 |                |

|  |                     |                    |                    |
|--|---------------------|--------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 4 (25.00%)<br>1 | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 |
| Renal and urinary disorders                      |                     |                    |                    |
| Haematuria                                       |                     |                    |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)       | 0 / 1 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Renal failure                                    |                     |                    |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)       | 0 / 1 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Musculoskeletal and connective tissue disorders  |                     |                    |                    |
| Arthralgia                                       |                     |                    |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)       | 0 / 1 (0.00%)      | 1 / 5 (20.00%)     |
| occurrences (all)                                | 0                   | 0                  | 1                  |
| Back pain  |                     |                    |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)       | 0 / 1 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Muscular weakness                                |                     |                    |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)       | 0 / 1 (0.00%)      | 1 / 5 (20.00%)     |
| occurrences (all)                                | 0                   | 0                  | 1                  |
| Musculoskeletal pain                             |                     |                    |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)       | 0 / 1 (0.00%)      | 1 / 5 (20.00%)     |
| occurrences (all)                                | 0                   | 0                  | 1                  |
| Infections and infestations                      |                     |                    |                    |
| Bronchitis                                       |                     |                    |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)       | 0 / 1 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Candiduria                                       |                     |                    |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)       | 0 / 1 (0.00%)      | 1 / 5 (20.00%)     |
| occurrences (all)                                | 0                   | 0                  | 1                  |
| Catheter site cellulitis                         |                     |                    |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)       | 0 / 1 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Genital herpes                                   |                     |                    |                    |
| subjects affected / exposed                      | 0 / 4 (0.00%)       | 0 / 1 (0.00%)      | 0 / 5 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Influenza  |                     |                    |                    |

|                                    |                |               |                |
|------------------------------------|----------------|---------------|----------------|
| subjects affected / exposed        | 1 / 4 (25.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                  | 2              | 0             | 0              |
| Paronychia                         |                |               |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                  | 0              | 0             | 0              |
| Pyelonephritis                     |                |               |                |
| subjects affected / exposed        | 1 / 4 (25.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                  | 1              | 0             | 0              |
| Urinary tract infection            |                |               |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                  | 0              | 0             | 0              |
| Uterine infection                  |                |               |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                  | 0              | 0             | 0              |
| Metabolism and nutrition disorders |                |               |                |
| Decreased appetite                 |                |               |                |
| subjects affected / exposed        | 2 / 4 (50.00%) | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)                  | 2              | 0             | 1              |
| Dehydration                        |                |               |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                  | 0              | 0             | 0              |
| Hypercalcaemia                     |                |               |                |
| subjects affected / exposed        | 1 / 4 (25.00%) | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)                  | 1              | 0             | 1              |
| Hyperglycaemia                     |                |               |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                  | 0              | 0             | 0              |
| Hyperkalaemia                      |                |               |                |
| subjects affected / exposed        | 1 / 4 (25.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                  | 2              | 0             | 0              |
| Hypernatraemia                     |                |               |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                  | 0              | 0             | 0              |
| Hyperuricaemia                     |                |               |                |
| subjects affected / exposed        | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                  | 0              | 0             | 0              |

|                             |                |               |                |
|-----------------------------|----------------|---------------|----------------|
| Hypokalaemia                |                |               |                |
| subjects affected / exposed | 2 / 4 (50.00%) | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)           | 4              | 0             | 1              |
| Hypomagnesaemia             |                |               |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)           | 0              | 0             | 1              |
| Increased appetite          |                |               |                |
| subjects affected / exposed | 0 / 4 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |

| <b>Non-serious adverse events</b>                     | All Subjects      | Glioblastoma      |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 22 / 22 (100.00%) | 12 / 12 (100.00%) |  |
| General disorders and administration site conditions  |                   |                   |  |
| Asthenia  |                   |                   |  |
| subjects affected / exposed                           | 5 / 22 (22.73%)   | 1 / 12 (8.33%)    |  |
| occurrences (all)                                     | 5                 | 1                 |  |
| Fatigue   |                   |                   |  |
| subjects affected / exposed                           | 6 / 22 (27.27%)   | 5 / 12 (41.67%)   |  |
| occurrences (all)                                     | 6                 | 5                 |  |
| Gait disturbance                                      |                   |                   |  |
| subjects affected / exposed                           | 1 / 22 (4.55%)    | 1 / 12 (8.33%)    |  |
| occurrences (all)                                     | 1                 | 1                 |  |
| Oedema  |                   |                   |  |
| subjects affected / exposed                           | 1 / 22 (4.55%)    | 0 / 12 (0.00%)    |  |
| occurrences (all)                                     | 1                 | 0                 |  |
| Oedema peripheral                                     |                   |                   |  |
| subjects affected / exposed                           | 3 / 22 (13.64%)   | 3 / 12 (25.00%)   |  |
| occurrences (all)                                     | 3                 | 3                 |  |
| Pain  |                   |                   |  |
| subjects affected / exposed                           | 1 / 22 (4.55%)    | 0 / 12 (0.00%)    |  |
| occurrences (all)                                     | 1                 | 0                 |  |
| Respiratory, thoracic and mediastinal disorders       |                   |                   |  |
| Cough   |                   |                   |  |
| subjects affected / exposed                           | 1 / 22 (4.55%)    | 0 / 12 (0.00%)    |  |
| occurrences (all)                                     | 1                 | 0                 |  |

|                                      |                 |                 |  |
|--------------------------------------|-----------------|-----------------|--|
| Dyspnoea                             |                 |                 |  |
| subjects affected / exposed          | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                    | 1               | 1               |  |
| Epistaxis                            |                 |                 |  |
| subjects affected / exposed          | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                    | 1               | 1               |  |
| Lung disorder                        |                 |                 |  |
| subjects affected / exposed          | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Respiratory disorder                 |                 |                 |  |
| subjects affected / exposed          | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                    | 1               | 1               |  |
| Psychiatric disorders                |                 |                 |  |
| Anxiety                              |                 |                 |  |
| subjects affected / exposed          | 2 / 22 (9.09%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                    | 2               | 1               |  |
| Investigations                       |                 |                 |  |
| Alanine aminotransferase increased   |                 |                 |  |
| subjects affected / exposed          | 7 / 22 (31.82%) | 2 / 12 (16.67%) |  |
| occurrences (all)                    | 8               | 2               |  |
| Amylase increased                    |                 |                 |  |
| subjects affected / exposed          | 2 / 22 (9.09%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                    | 4               | 0               |  |
| Aspartate aminotransferase increased |                 |                 |  |
| subjects affected / exposed          | 5 / 22 (22.73%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                    | 11              | 0               |  |
| Blood alkaline phosphatase increased |                 |                 |  |
| subjects affected / exposed          | 4 / 22 (18.18%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                    | 5               | 0               |  |
| Blood bilirubin abnormal             |                 |                 |  |
| subjects affected / exposed          | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                    | 2               | 0               |  |
| Blood bilirubin increased            |                 |                 |  |
| subjects affected / exposed          | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                    | 2               | 0               |  |
| Blood creatinine increased           |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                    | 2 / 22 (9.09%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                              | 3               | 0               |  |
| Creatinine renal clearance increased           |                 |                 |  |
| subjects affected / exposed                    | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                              | 1               | 0               |  |
| Gamma-glutamyltransferase increased            |                 |                 |  |
| subjects affected / exposed                    | 4 / 22 (18.18%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                              | 4               | 0               |  |
| Lipase increased                               |                 |                 |  |
| subjects affected / exposed                    | 2 / 22 (9.09%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                              | 2               | 0               |  |
| Weight decreased                               |                 |                 |  |
| subjects affected / exposed                    | 2 / 22 (9.09%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                              | 2               | 1               |  |
| Injury, poisoning and procedural complications |                 |                 |  |
| Cartilage injury                               |                 |                 |  |
| subjects affected / exposed                    | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                              | 1               | 0               |  |
| Cardiac disorders                              |                 |                 |  |
| Bradycardia                                    |                 |                 |  |
| subjects affected / exposed                    | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                              | 1               | 1               |  |
| Sinus bradycardia                              |                 |                 |  |
| subjects affected / exposed                    | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                              | 1               | 0               |  |
| Tachycardia                                    |                 |                 |  |
| subjects affected / exposed                    | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                              | 1               | 0               |  |
| Nervous system disorders                       |                 |                 |  |
| Aphasia  |                 |                 |  |
| subjects affected / exposed                    | 2 / 22 (9.09%)  | 2 / 12 (16.67%) |  |
| occurrences (all)                              | 2               | 2               |  |
| Cognitive disorder                             |                 |                 |  |
| subjects affected / exposed                    | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                              | 1               | 1               |  |
| Depressed level of consciousness               |                 |                 |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                     | 1 / 22 (4.55%)<br>1  | 1 / 12 (8.33%)<br>1  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)        | 1 / 22 (4.55%)<br>2  | 1 / 12 (8.33%)<br>2  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)         | 3 / 22 (13.64%)<br>3 | 3 / 12 (25.00%)<br>3 |  |
| Hemiparesis<br>subjects affected / exposed<br>occurrences (all)      | 1 / 22 (4.55%)<br>1  | 1 / 12 (8.33%)<br>1  |  |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)       | 2 / 22 (9.09%)<br>2  | 2 / 12 (16.67%)<br>2 |  |
| Blood and lymphatic system disorders                                 |                      |                      |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)          | 5 / 22 (22.73%)<br>6 | 0 / 12 (0.00%)<br>0  |  |
| Leukocytosis<br>subjects affected / exposed<br>occurrences (all)     | 1 / 22 (4.55%)<br>2  | 0 / 12 (0.00%)<br>0  |  |
| Lymphopenia<br>subjects affected / exposed<br>occurrences (all)      | 3 / 22 (13.64%)<br>3 | 1 / 12 (8.33%)<br>1  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)      | 2 / 22 (9.09%)<br>2  | 2 / 12 (16.67%)<br>2 |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all) | 5 / 22 (22.73%)<br>5 | 3 / 12 (25.00%)<br>3 |  |
| Gastrointestinal disorders   |                      |                      |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)   | 5 / 22 (22.73%)<br>5 | 0 / 12 (0.00%)<br>0  |  |
| Abdominal pain upper   |                      |                      |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                 | 1 / 22 (4.55%)   | 0 / 12 (0.00%)  |  |
| occurrences (all)                           | 1                | 0               |  |
| Constipation                                |                  |                 |  |
| subjects affected / exposed                 | 4 / 22 (18.18%)  | 2 / 12 (16.67%) |  |
| occurrences (all)                           | 4                | 2               |  |
| Diarrhoea                                   |                  |                 |  |
| subjects affected / exposed                 | 13 / 22 (59.09%) | 7 / 12 (58.33%) |  |
| occurrences (all)                           | 17               | 8               |  |
| Eructation                                  |                  |                 |  |
| subjects affected / exposed                 | 1 / 22 (4.55%)   | 0 / 12 (0.00%)  |  |
| occurrences (all)                           | 1                | 0               |  |
| Flatulence                                  |                  |                 |  |
| subjects affected / exposed                 | 1 / 22 (4.55%)   | 1 / 12 (8.33%)  |  |
| occurrences (all)                           | 1                | 1               |  |
| Gastrooesophageal reflux disease            |                  |                 |  |
| subjects affected / exposed                 | 1 / 22 (4.55%)   | 1 / 12 (8.33%)  |  |
| occurrences (all)                           | 1                | 1               |  |
| Nausea                                      |                  |                 |  |
| subjects affected / exposed                 | 13 / 22 (59.09%) | 6 / 12 (50.00%) |  |
| occurrences (all)                           | 17               | 6               |  |
| Stomatitis                                  |                  |                 |  |
| subjects affected / exposed                 | 3 / 22 (13.64%)  | 2 / 12 (16.67%) |  |
| occurrences (all)                           | 5                | 3               |  |
| Vomiting                                    |                  |                 |  |
| subjects affected / exposed                 | 11 / 22 (50.00%) | 4 / 12 (33.33%) |  |
| occurrences (all)                           | 15               | 6               |  |
| Skin and subcutaneous tissue disorders      |                  |                 |  |
| Dermatitis acneiform                        |                  |                 |  |
| subjects affected / exposed                 | 1 / 22 (4.55%)   | 1 / 12 (8.33%)  |  |
| occurrences (all)                           | 1                | 1               |  |
| Dermatitis bullous                          |                  |                 |  |
| subjects affected / exposed                 | 1 / 22 (4.55%)   | 0 / 12 (0.00%)  |  |
| occurrences (all)                           | 1                | 0               |  |
| Palmar-plantar erythrodysaesthesia syndrome |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Photosensitivity reaction                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Pruritus  |                 |                 |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Rash  |                 |                 |  |
| subjects affected / exposed                     | 3 / 22 (13.64%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 3               | 0               |  |
| Skin toxicity                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Renal and urinary disorders                     |                 |                 |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                               | 1               | 1               |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                               | 1               | 1               |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 22 (9.09%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                               | 2               | 1               |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 22 (13.64%) | 3 / 12 (25.00%) |  |
| occurrences (all)                               | 3               | 3               |  |
| Muscular weakness                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Musculoskeletal pain                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Infections and infestations                     |                 |                 |  |

|                                    |                 |                 |  |
|------------------------------------|-----------------|-----------------|--|
| Bronchitis                         |                 |                 |  |
| subjects affected / exposed        | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                  | 1               | 1               |  |
| Candiduria                         |                 |                 |  |
| subjects affected / exposed        | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                  | 1               | 0               |  |
| Catheter site cellulitis           |                 |                 |  |
| subjects affected / exposed        | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                  | 1               | 1               |  |
| Genital herpes                     |                 |                 |  |
| subjects affected / exposed        | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                  | 1               | 1               |  |
| Influenza                          |                 |                 |  |
| subjects affected / exposed        | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                  | 2               | 0               |  |
| Paronychia                         |                 |                 |  |
| subjects affected / exposed        | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                  | 1               | 1               |  |
| Pyelonephritis                     |                 |                 |  |
| subjects affected / exposed        | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                  | 1               | 0               |  |
| Urinary tract infection            |                 |                 |  |
| subjects affected / exposed        | 2 / 22 (9.09%)  | 2 / 12 (16.67%) |  |
| occurrences (all)                  | 2               | 2               |  |
| Uterine infection                  |                 |                 |  |
| subjects affected / exposed        | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                  | 1               | 1               |  |
| Metabolism and nutrition disorders |                 |                 |  |
| Decreased appetite                 |                 |                 |  |
| subjects affected / exposed        | 3 / 22 (13.64%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                  | 3               | 0               |  |
| Dehydration                        |                 |                 |  |
| subjects affected / exposed        | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                  | 1               | 1               |  |
| Hypercalcaemia                     |                 |                 |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 22 (9.09%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)           | 2               | 0               |  |
| Hyperglycaemia              |                 |                 |  |
| subjects affected / exposed | 2 / 22 (9.09%)  | 2 / 12 (16.67%) |  |
| occurrences (all)           | 2               | 2               |  |
| Hyperkalaemia               |                 |                 |  |
| subjects affected / exposed | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)           | 2               | 0               |  |
| Hypernatraemia              |                 |                 |  |
| subjects affected / exposed | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)           | 1               | 1               |  |
| Hyperuricaemia              |                 |                 |  |
| subjects affected / exposed | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)           | 1               | 1               |  |
| Hypokalaemia                |                 |                 |  |
| subjects affected / exposed | 3 / 22 (13.64%) | 0 / 12 (0.00%)  |  |
| occurrences (all)           | 5               | 0               |  |
| Hypomagnesaemia             |                 |                 |  |
| subjects affected / exposed | 1 / 22 (4.55%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Increased appetite          |                 |                 |  |
| subjects affected / exposed | 1 / 22 (4.55%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)           | 1               | 1               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 30 November 2015 | <p>Clarified the inclusion criteria 2 for ALK positivity. A subject was to have a histologically or cytologically confirmed diagnosis of one of the tumors that was ALK- positive.</p> <p>The ALK test results were to be available at the Investigator site before the first dose of the study drug. The tumor types are described below: ALCL: local confirmation of diagnosis of ALK+ ALCL was sufficient for eligibility. IMT: local confirmation of translocation involving the ALK gene. GBM, IBC and any other locally documented ALK+ tumor were to carry a locally documented genetic alteration of ALK. Provided follow up evaluations for hepatic toxicities and work-up guidelines for potential Drug Induced Liver Injury (DILI) cases. Updated the exclusion criteria for contraception use. Dose guidance modification for QTcF text was updated to provide clarification on monitoring procedure.</p> |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported