



## Clinical trial results:

### An Open-label, Phase II Study of Vemurafenib in Patients with BRAF V600 Mutation-positive Cancers

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2011-004426-10  |
| Trial protocol           | GB ES DE        |
| Global end of trial date | 27 October 2016 |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v2 (current)      |
| This version publication date  | 04 November 2017  |
| First version publication date | 07 September 2017 |
| Version creation reason        |                   |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | MO28072 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01524978 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | F. Hoffmann-La Roche AG  |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070   |
| Public contact               | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |
| Scientific contact           | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.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                       | 27 October 2016 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 27 October 2016 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study is to assess the efficacy of vemurafenib in subjects with BRAF V600 mutation-positive cancers (solid tumors and multiple myeloma, except melanoma and papillary thyroid cancer) and for whom vemurafenib is deemed the best treatment option in the opinion of the investigator.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 11 April 2012    |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Efficacy, Safety |
| Long term follow-up duration                              | 1 Years          |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 103 |
| Country: Number of subjects enrolled | France: 63         |
| Country: Number of subjects enrolled | Spain: 24          |
| Country: Number of subjects enrolled | Germany: 13        |
| Country: Number of subjects enrolled | United Kingdom: 5  |
| Worldwide total number of subjects   | 208                |
| EEA total number of subjects         | 105                |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |

|                           |     |
|---------------------------|-----|
| Adolescents (12-17 years) | 0   |
| Adults (18-64 years)      | 134 |
| From 65 to 84 years       | 71  |
| 85 years and over         | 3   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

One participant with breast cancer was screened shortly after Cohort 5 (Breast Cancer) had been closed. This participant was allowed to enter the study in Cohort 7: Other BRAF V600-positive tumors. For analysis purposes Cohort 7 was split into sub-cohorts for indications with sufficient participants.

### 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>             | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib |

Arm description:

Subjects with NSCLC were treated with vemurafenib monotherapy.

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

Dosage and administration details:

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Cohort 2: Ovarian Cancer - vemurafenib |
|------------------|--|

Arm description:

Subjects with ovarian cancer were treated with vemurafenib monotherapy.

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

Dosage and administration details:

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Cohort 3a: Colorectal Cancer - vemurafenib |
|------------------|--|

Arm description:

Subjects with colorectal cancer were treated with vemurafenib monotherapy.

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

**Dosage and administration details:**

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab |
|------------------|--|

**Arm description:**

Subjects with colorectal cancer were treated with vemurafenib and cetuximab combination therapy.

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

**Dosage and administration details:**

Escalating doses were given orally twice a day starting on Day 2 of Cycle 1. The escalating doses were as follows: Dose Level 1: 720 mg of vemurafenib; Dose Level 2: 720 mg of vemurafenib; Dose Level 3: 960 mg of vemurafenib.

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | cetuximab             |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Escalating doses were administered on Day 1 and then once weekly by intravenous infusion. The escalating doses were as follows: Dose Level 1: 300 milligrams per square meter (mg/m<sup>2</sup>) loading dose of cetuximab and then 200 mg/m<sup>2</sup> weekly; Dose Level 2: 400 mg/m<sup>2</sup> loading dose of cetuximab and then 250 mg/m<sup>2</sup> weekly; Dose Level 3: 400 mg/m<sup>2</sup> loading dose of cetuximab and then 250 mg/m<sup>2</sup> weekly.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Cohort 4: Cholangiocarcinoma - vemurafenib |
|------------------|--|

**Arm description:**

Subjects with cholangiocarcinoma were treated with vemurafenib monotherapy.

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

**Dosage and administration details:**

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Cohort 6: Multiple Myeloma - vemurafenib |
|------------------|--|

**Arm description:**

Subjects with multiple myeloma were treated with vemurafenib monotherapy.

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

**Dosage and administration details:**

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

|  |   |
|--|---|
| <b>Arm title</b>   | Cohort 7a: ECD/LCH - vemurafenib                    |
| Arm description:<br>Subjects with Erdheim-Chester disease (ECD) or Langerhans cell histiocytosis (LCH) were treated with vemurafenib monotherapy.                    |   |
| Arm type   | Experimental  |
| Investigational medicinal product name   | vemurafenib   |
| Investigational medicinal product code   |   |
| Other name   | Zelboraf  |
| Pharmaceutical forms   | Tablet  |
| Routes of administration   | Oral use  |
| Dosage and administration details:<br>960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent. |   |
| <b>Arm title</b>   | Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib  |
| Arm description:<br>Subjects with anaplastic thyroid cancer were treated with vemurafenib monotherapy.   |   |
| Arm type   | Experimental  |
| Investigational medicinal product name   | vemurafenib   |
| Investigational medicinal product code   |   |
| Other name   | Zelboraf  |
| Pharmaceutical forms   | Tablet  |
| Routes of administration   | Oral use  |
| Dosage and administration details:<br>960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent. |   |
| <b>Arm title</b>   | Cohort 7c: Advanced Stage Astrocytoma - vemurafenib |
| Arm description:<br>Subjects with advanced stage astrocytoma were treated with vemurafenib monotherapy.  |   |
| Arm type   | Experimental  |
| Investigational medicinal product name   | vemurafenib   |
| Investigational medicinal product code   |   |
| Other name   | Zelboraf  |
| Pharmaceutical forms   | Tablet  |
| Routes of administration   | Oral use  |
| Dosage and administration details:<br>960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent. |   |
| <b>Arm title</b>   | Cohort 7d: Early Stage Astrocytoma - vemurafenib    |
| Arm description:<br>Subjects with early stage astrocytoma were treated with vemurafenib monotherapy.   |   |
| Arm type   | Experimental  |
| Investigational medicinal product name   | vemurafenib   |
| Investigational medicinal product code   |   |
| Other name   | Zelboraf  |
| Pharmaceutical forms   | Tablet  |
| Routes of administration   | Oral use  |
| Dosage and administration details:<br>960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent. |   |
| <b>Arm title</b>   | Other BRAF V600-positive Tumors - vemurafenib       |
| Arm description:<br>Subjects with other BRAF V600-positive tumors were treated with vemurafenib monotherapy.   |   |

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

**Dosage and administration details:**

960 milligrams (mg) vemurafenib orally twice a day until disease progression, unacceptable toxicity, or withdrawal of consent.

| <b>Number of subjects in period 1</b> | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib | Cohort 2: Ovarian Cancer - vemurafenib | Cohort 3a: Colorectal Cancer - vemurafenib |
|---------------------------------------|--|--|--|
| Started                               | 62   | 4                                      | 10   |
| Completed                             | 0  | 0                                      | 0  |
| Not completed                         | 62   | 4                                      | 10   |
| Adverse event, serious fatal          | 34   | 2                                      | 5  |
| Consent withdrawn by subject          | 12   | -                                      | 1  |
| Unspecified                           | 16   | 2                                      | 1  |
| Lost to follow-up                     | -  | -                                      | 3  |

| <b>Number of subjects in period 1</b> | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab | Cohort 4: Cholangiocarcinoma - vemurafenib | Cohort 6: Multiple Myeloma - vemurafenib |
|---------------------------------------|--|--|--|
| Started                               | 27   | 9  | 9  |
| Completed                             | 0  | 0  | 0  |
| Not completed                         | 27   | 9  | 9  |
| Adverse event, serious fatal          | 24   | 4  | 4  |
| Consent withdrawn by subject          | 1  | 3  | 1  |
| Unspecified                           | 2  | 1  | 3  |
| Lost to follow-up                     | -  | 1  | 1  |

| <b>Number of subjects in period 1</b> | Cohort 7a: ECD/LCH - vemurafenib | Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib | Cohort 7c: Advanced Stage Astrocytoma - vemurafenib |
|---------------------------------------|----------------------------------|--|---|
| Started                               | 26                               | 12   | 12  |
| Completed                             | 0                                | 0  | 0   |
| Not completed                         | 26                               | 12   | 12  |
| Adverse event, serious fatal          | 1                                | 9  | 5   |
| Consent withdrawn by subject          | 6                                | 2  | 4   |
| Unspecified                           | 17                               | 1  | 2   |
| Lost to follow-up                     | 2                                | -  | 1   |

| <b>Number of subjects in period 1</b> | Cohort 7d: Early Stage Astrocytoma - | Other BRAF V600-positive Tumors - |
|---------------------------------------|--------------------------------------|-----------------------------------|
|---------------------------------------|--------------------------------------|-----------------------------------|

|                              | vemurafenib | vemurafenib |
|------------------------------|-------------|-------------|
| Started                      | 9           | 28          |
| Completed                    | 0           | 0           |
| Not completed                | 9           | 28          |
| Adverse event, serious fatal | 6           | 17          |
| Consent withdrawn by subject | -           | 5           |
| Unspecified                  | 2           | 5           |
| Lost to follow-up            | 1           | 1           |



## Baseline characteristics

| Reporting groups  |  |
|---|--|
| Reporting group title   | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib |
| Reporting group description:  |  |
| Subjects with NSCLC were treated with vemurafenib monotherapy.  |  |
| Reporting group title   | Cohort 2: Ovarian Cancer - vemurafenib                     |
| Reporting group description:  |  |
| Subjects with ovarian cancer were treated with vemurafenib monotherapy.   |  |
| Reporting group title   | Cohort 3a: Colorectal Cancer - vemurafenib                 |
| Reporting group description:  |  |
| Subjects with colorectal cancer were treated with vemurafenib monotherapy.  |  |
| Reporting group title   | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab     |
| Reporting group description:  |  |
| Subjects with colorectal cancer were treated with vemurafenib and cetuximab combination therapy.                              |  |
| Reporting group title   | Cohort 4: Cholangiocarcinoma - vemurafenib                 |
| Reporting group description:  |  |
| Subjects with cholangiocarcinoma were treated with vemurafenib monotherapy.   |  |
| Reporting group title   | Cohort 6: Multiple Myeloma - vemurafenib                   |
| Reporting group description:  |  |
| Subjects with multiple myeloma were treated with vemurafenib monotherapy.   |  |
| Reporting group title   | Cohort 7a: ECD/LCH - vemurafenib                           |
| Reporting group description:  |  |
| Subjects with Erdheim-Chester disease (ECD) or Langerhans cell histiocytosis (LCH) were treated with vemurafenib monotherapy. |  |
| Reporting group title   | Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib         |
| Reporting group description:  |  |
| Subjects with anaplastic thyroid cancer were treated with vemurafenib monotherapy.  |  |
| Reporting group title   | Cohort 7c: Advanced Stage Astrocytoma - vemurafenib        |
| Reporting group description:  |  |
| Subjects with advanced stage astrocytoma were treated with vemurafenib monotherapy.   |  |
| Reporting group title   | Cohort 7d: Early Stage Astrocytoma - vemurafenib           |
| Reporting group description:  |  |
| Subjects with early stage astrocytoma were treated with vemurafenib monotherapy.  |  |
| Reporting group title   | Other BRAF V600-positive Tumors - vemurafenib              |
| Reporting group description:  |  |
| Subjects with other BRAF V600-positive tumors were treated with vemurafenib monotherapy.                                      |  |

| Reporting group values | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib | Cohort 2: Ovarian Cancer - vemurafenib | Cohort 3a: Colorectal Cancer - vemurafenib |
|------------------------|--|--|--|
| Number of subjects     | 62   | 4                                      | 10   |
| Age categorical        |  |  |  |
| Units: Subjects        |  |  |  |
| Adults (18-64 years)   | 30   | 4                                      | 10   |
| From 65-84 years       | 30   | 0                                      | 0  |
| 85 years and over      | 2  | 0                                      | 0  |

|   |                |               |               |
|---|----------------|---------------|---------------|
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 65.4<br>± 10.2 | 45.8<br>± 5.3 | 57.3<br>± 5.4 |
| Gender, Male/Female<br>Units: Subjects                                  |                |               |               |
| Female  | 27             | 4             | 5             |
| Male  | 35             | 0             | 5             |

| <b>Reporting group values</b>   | Cohort 3b:<br>Colorectal Cancer -<br>vemurafenib +<br>cetuximab | Cohort 4:<br>Cholangiocarcinoma<br>- vemurafenib | Cohort 6: Multiple<br>Myeloma -<br>vemurafenib |
|---|---|--|--|
| Number of subjects  | 27  | 9  | 9  |
| Age categorical<br>Units: Subjects                                      |   |  |  |
| Adults (18-64 years)  | 15  | 8  | 7  |
| From 65-84 years  | 12  | 1  | 2  |
| 85 years and over   | 0   | 0  | 0  |
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 64.3<br>± 8.8   | 53.2<br>± 9.7                                    | 62.1<br>± 4.3                                  |
| Gender, Male/Female<br>Units: Subjects                                  |   |  |  |
| Female  | 18  | 5  | 3  |
| Male  | 9   | 4  | 6  |

| <b>Reporting group values</b>   | Cohort 7a: ECD/LCH<br>- vemurafenib | Cohort 7b:<br>Anaplastic Thyroid<br>Cancer -<br>vemurafenib | Cohort 7c: Advanced<br>Stage Astrocytoma -<br>vemurafenib |
|---|-------------------------------------|---|---|
| Number of subjects  | 26                                  | 12  | 12  |
| Age categorical<br>Units: Subjects                                      |                                     |   |   |
| Adults (18-64 years)  | 15                                  | 6   | 12  |
| From 65-84 years  | 11                                  | 6   | 0   |
| 85 years and over   | 0                                   | 0   | 0   |
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 60.8<br>± 13.3                      | 66.8<br>± 9.2   | 41.6<br>± 12.2  |
| Gender, Male/Female<br>Units: Subjects                                  |                                     |   |   |
| Female  | 14                                  | 3   | 8   |
| Male  | 12                                  | 9   | 4   |

| <b>Reporting group values</b>      | Cohort 7d: Early<br>Stage Astrocytoma -<br>vemurafenib | Other BRAF V600-<br>positive Tumors -<br>vemurafenib | Total |
|------------------------------------|--|--|-------|
| Number of subjects                 | 9  | 28   | 208   |
| Age categorical<br>Units: Subjects |  |  |       |
| Adults (18-64 years)               | 8  | 19   | 134   |

|                   |   |   |    |
|-------------------|---|---|----|
| From 65-84 years  | 1 | 8 | 71 |
| 85 years and over | 0 | 1 | 3  |

|                     |        |        |     |
|---------------------|--------|--------|-----|
| Age Continuous      |        |        |     |
| Units: years        |        |        |     |
| arithmetic mean     | 34.3   | 53.7   |     |
| standard deviation  | ± 20.7 | ± 17.5 | -   |
| Gender, Male/Female |        |        |     |
| Units: Subjects     |        |        |     |
| Female              | 9      | 15     | 111 |
| Male                | 0      | 13     | 97  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib |
| Reporting group description:<br>Subjects with NSCLC were treated with vemurafenib monotherapy.  |  |
| Reporting group title   | Cohort 2: Ovarian Cancer - vemurafenib                     |
| Reporting group description:<br>Subjects with ovarian cancer were treated with vemurafenib monotherapy.   |  |
| Reporting group title   | Cohort 3a: Colorectal Cancer - vemurafenib                 |
| Reporting group description:<br>Subjects with colorectal cancer were treated with vemurafenib monotherapy.  |  |
| Reporting group title   | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab     |
| Reporting group description:<br>Subjects with colorectal cancer were treated with vemurafenib and cetuximab combination therapy.                              |  |
| Reporting group title   | Cohort 4: Cholangiocarcinoma - vemurafenib                 |
| Reporting group description:<br>Subjects with cholangiocarcinoma were treated with vemurafenib monotherapy.   |  |
| Reporting group title   | Cohort 6: Multiple Myeloma - vemurafenib                   |
| Reporting group description:<br>Subjects with multiple myeloma were treated with vemurafenib monotherapy.   |  |
| Reporting group title   | Cohort 7a: ECD/LCH - vemurafenib                           |
| Reporting group description:<br>Subjects with Erdheim-Chester disease (ECD) or Langerhans cell histiocytosis (LCH) were treated with vemurafenib monotherapy. |  |
| Reporting group title   | Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib         |
| Reporting group description:<br>Subjects with anaplastic thyroid cancer were treated with vemurafenib monotherapy.  |  |
| Reporting group title   | Cohort 7c: Advanced Stage Astrocytoma - vemurafenib        |
| Reporting group description:<br>Subjects with advanced stage astrocytoma were treated with vemurafenib monotherapy.   |  |
| Reporting group title   | Cohort 7d: Early Stage Astrocytoma - vemurafenib           |
| Reporting group description:<br>Subjects with early stage astrocytoma were treated with vemurafenib monotherapy.  |  |
| Reporting group title   | Other BRAF V600-positive Tumors - vemurafenib              |
| Reporting group description:<br>Subjects with other BRAF V600-positive tumors were treated with vemurafenib monotherapy.                                      |  |

### Primary: Confirmed Best Overall Response Rate (BORR)

|  |  |
|--|--|
| End point title  | Confirmed Best Overall Response Rate (BORR) <sup>[1]</sup> |
| End point description:<br>Confirmed BORR: percentage of subjects with an objective response (OR) (complete response [CR], partial response [PR], stringent CR [sCR] or very good PR [VGPR]) on 2 occasions $\geq$ 4 weeks apart as assessed by the Investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. or International Myeloma Working Group (IMWG) criteria. RECIST v1.1: CR: disappearance of all target lesions; PR: $\geq$ 30% decrease in the sum of diameters of target lesions. IMWG: CR: negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas and $\leq$ 5% plasma cells in bone marrow; PR: $\geq$ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by $\geq$ 90% or to $<$ 200 mg per 24 hours. VGPR: serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq$ 90% reduction in serum M-protein plus urine M-protein level $<$ 100 mg per 24 hour; sCR: CR plus normal free light chain (FLC) ratio and no |  |

clonal cells in bone marrow.

|                             |         |
|-----------------------------|---------|
| End point type              | Primary |
| End point timeframe:        |         |
| Up to approximately 3 years |         |

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: Primary efficacy results were summarized by cohort each representing specific cancer types. No statistical analyses were done, since all cohorts received vemurafenib treatment.

|                                  |  |  |  |  |
|----------------------------------|--|--|--|--|
| <b>End point values</b>          | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib | Cohort 2: Ovarian Cancer - vemurafenib | Cohort 3a: Colorectal Cancer - vemurafenib | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab |
| Subject group type               | Reporting group  | Reporting group                        | Reporting group                            | Reporting group  |
| Number of subjects analysed      | 62 <sup>[2]</sup>  | 4                                      | 10   | 27   |
| Units: percentage of subjects    |  |  |  |  |
| number (confidence interval 95%) | 37.1 (25.16 to 50.31)                                      | 50.0 (6.76 to 93.24)                   | 0 (0.00 to 30.85)                          | 7.4 (0.91 to 24.29)                                    |

Notes:

[2] - Intent-to-Treat (ITT) population included all subjects enrolled in the study.

|                                  |  |  |                                  |  |
|----------------------------------|--|--|----------------------------------|--|
| <b>End point values</b>          | Cohort 4: Cholangiocarcinoma - vemurafenib | Cohort 6: Multiple Myeloma - vemurafenib | Cohort 7a: ECD/LCH - vemurafenib | Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib |
| Subject group type               | Reporting group                            | Reporting group                          | Reporting group                  | Reporting group                                    |
| Number of subjects analysed      | 9  | 9  | 26                               | 12   |
| Units: percentage of subjects    |  |  |                                  |  |
| number (confidence interval 95%) | 22.2 (2.81 to 60.01)                       | 22.2 (2.81 to 60.01)                     | 61.5 (40.57 to 79.77)            | 25.0 (5.49 to 57.19)                               |

|                                  |   |  |   |  |
|----------------------------------|---|--|---|--|
| <b>End point values</b>          | Cohort 7c: Advanced Stage Astrocytoma - vemurafenib | Cohort 7d: Early Stage Astrocytoma - vemurafenib | Other BRAF V600-positive Tumors - vemurafenib |  |
| Subject group type               | Reporting group                                     | Reporting group                                  | Reporting group                               |  |
| Number of subjects analysed      | 12  | 9  | 28  |  |
| Units: percentage of subjects    |   |  |   |  |
| number (confidence interval 95%) | 16.7 (2.09 to 48.41)                                | 33.3 (7.49 to 70.07)                             | 17.9 (6.06 to 36.89)                          |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Confirmed Clinical Benefit

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects with Confirmed Clinical Benefit |
|-----------------|--|

# End point description:

Confirmed clinical benefit rate: percentage of subjects with confirmed PR or CR or Stable Disease (SD) that have lasted at least 6 months according to RECIST v1.1 or confirmed CR, PR, VGPR, sCR or SD for at least 6 months according to IMWG criteria. RECIST v1.1: PR:  $\geq 30\%$  decrease in the sum of diameters of target lesions; CR: disappearance of all target lesions; SD: not meeting criteria for CR, PR or progressive disease (PD). IMWG: CR: negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas and  $\leq 5\%$  plasma cells in bone marrow; PR:  $\geq 50\%$  reduction of serum M-protein and reduction in 24-hour urinary M-protein by  $\geq 90\%$  or to  $<200$  mg per 24 hours. VGPR: serum and urine M-protein detectable by immunofixation but not on electrophoresis or  $\geq 90\%$  reduction in serum M-protein plus urine M-protein level  $< 100$  mg per 24 hour; sCR: CR plus normal FLC ratio and no clonal cells in bone marrow; SD: not meeting criteria for CR, VGPR, PR or PD.

|                             |           |
|-----------------------------|-----------|
| End point type              | Secondary |
| End point timeframe:        |           |
| Up to approximately 3 years |           |

| End point values                 | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib | Cohort 2: Ovarian Cancer - vemurafenib | Cohort 3a: Colorectal Cancer - vemurafenib | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group  | Reporting group                        | Reporting group                            | Reporting group  |
| Number of subjects analysed      | 62 <sup>[3]</sup>  | 4                                      | 10   | 27   |
| Units: percentage of subjects    |  |  |  |  |
| number (confidence interval 95%) | 48.4 (35.50 to 61.44)                                      | 50.0 (6.76 to 93.24)                   | 0 (-9999 to 9999)                          | 18.5 (6.30 to 38.08)                                   |

Notes:

[3] - ITT population: all subjects enrolled. (-)9999 = not estimable due to insufficient number of events

| End point values                 | Cohort 4: Cholangiocarcinoma - vemurafenib | Cohort 6: Multiple Myeloma - vemurafenib | Cohort 7a: ECD/LCH - vemurafenib | Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib |
|----------------------------------|--|--|----------------------------------|--|
| Subject group type               | Reporting group                            | Reporting group                          | Reporting group                  | Reporting group                                    |
| Number of subjects analysed      | 9  | 9  | 26                               | 12   |
| Units: percentage of subjects    |  |  |                                  |  |
| number (confidence interval 95%) | 44.4 (13.70 to 78.80)                      | 22.2 (2.81 to 60.01)                     | 76.9 (56.35 to 91.03)            | 25.0 (5.49 to 57.19)                               |

| End point values                 | Cohort 7c: Advanced Stage Astrocytoma - vemurafenib | Cohort 7d: Early Stage Astrocytoma - vemurafenib | Other BRAF V600-positive Tumors - vemurafenib |  |
|----------------------------------|---|--|---|--|
| Subject group type               | Reporting group                                     | Reporting group                                  | Reporting group                               |  |
| Number of subjects analysed      | 12  | 9  | 28  |  |
| Units: percentage of subjects    |   |  |   |  |
| number (confidence interval 95%) | 33.3 (9.92 to 65.11)                                | 44.4 (13.70 to 78.80)                            | 17.9 (6.06 to 36.89)                          |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Response Rate (ORR)

|  |                             |
|--|-----------------------------|
| End point title  | Overall Response Rate (ORR) |
| End point description:   |                             |
| <p>ORR: percentage of subjects with an objective response (OR) (CR, PR, sCR or VGPR) on 2 occasions <math>\geq</math> 4 weeks apart as assessed by the Investigator using RECIST v1.1. or IMWG criteria. RECIST v1.1: CR: disappearance of all target lesions; PR: <math>\geq</math> 30% decrease in the sum of diameters of target lesions. IMWG: CR: negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas and <math>\leq</math> 5% plasma cells in bone marrow; PR: <math>\geq</math> 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by <math>\geq</math> 90% or to <math>&lt;</math>200 mg per 24 hours. VGPR: serum and urine M-protein detectable by immunofixation but not on electrophoresis or <math>\geq</math> 90% reduction in serum M-protein plus urine M-protein level <math>&lt;</math> 100 mg per 24 hour; sCR: CR plus normal free light chain (FLC) ratio and no clonal cells in bone marrow. ITT population: all subjects enrolled in the study.</p> |                             |
| End point type   | Secondary                   |
| End point timeframe:   |                             |
| Up to approximately 3 years  |                             |

| End point values                 | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib | Cohort 2: Ovarian Cancer - vemurafenib | Cohort 3a: Colorectal Cancer - vemurafenib | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group  | Reporting group                        | Reporting group                            | Reporting group  |
| Number of subjects analysed      | 62 <sup>[4]</sup>  | 4                                      | 10   | 27   |
| Units: percentage of subjects    |  |  |  |  |
| number (confidence interval 95%) |  |  |  |  |
| CR                               | 0 (0.00 to 5.78)   | 0 (0.00 to 60.24)                      | 0 (0.00 to 30.85)                          | 0 (0.00 to 12.77)                                      |
| PR                               | 37.1 (25.16 to 50.31)                                      | 50.0 (6.76 to 93.24)                   | 0 (0.00 to 30.85)                          | 7.4 (0.91 to 24.29)                                    |
| VGPR                             | 9999 (9999 to 9999)  | 9999 (9999 to 9999)                    | 9999 (9999 to 9999)                        | 9999 (9999 to 9999)                                    |
| sCR                              | 9999 (9999 to 9999)  | 9999 (9999 to 9999)                    | 9999 (9999 to 9999)                        | 9999 (9999 to 9999)                                    |

Notes:

[4] - 9999 = not evaluated (only in Cohort 6)

| End point values                 | Cohort 4: Cholangiocarcinoma - vemurafenib | Cohort 6: Multiple Myeloma - vemurafenib | Cohort 7a: ECD/LCH - vemurafenib | Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib |
|----------------------------------|--|--|----------------------------------|--|
| Subject group type               | Reporting group                            | Reporting group                          | Reporting group                  | Reporting group                                    |
| Number of subjects analysed      | 9  | 9  | 26                               | 12   |
| Units: percentage of subjects    |  |  |                                  |  |
| number (confidence interval 95%) |  |  |                                  |  |
| CR                               | 0 (0.00 to 33.63)                          | 0 (0.00 to 33.63)                        | 7.7 (0.95 to 25.13)              | 8.3 (0.21 to 38.48)                                |
| PR                               | 22.2 (2.81 to 60.01)                       | 11.1 (0.28 to 48.25)                     | 53.8 (33.37 to 73.41)            | 16.7 (2.09 to 48.41)                               |
| VGPR                             | 9999 (9999 to 9999)                        | 11.1 (0.28 to 48.25)                     | 9999 (9999 to 9999)              | 9999 (9999 to 9999)                                |

|     |                     |                   |                     |                     |
|-----|---------------------|-------------------|---------------------|---------------------|
| sCR | 9999 (9999 to 9999) | 0 (0.00 to 33.63) | 9999 (9999 to 9999) | 9999 (9999 to 9999) |
|-----|---------------------|-------------------|---------------------|---------------------|

| End point values                 | Cohort 7c:<br>Advanced Stage<br>Astrocytoma -<br>vemurafenib | Cohort 7d:<br>Early Stage<br>Astrocytoma -<br>vemurafenib | Other BRAF<br>V600-positive<br>Tumors -<br>vemurafenib |  |
|----------------------------------|--|---|--|--|
| Subject group type               | Reporting group  | Reporting group   | Reporting group  |  |
| Number of subjects analysed      | 12   | 9   | 28   |  |
| Units: percentage of subjects    |  |   |  |  |
| number (confidence interval 95%) |  |   |  |  |
| CR                               | 8.3 (0.21 to 38.48)  | 0 (0.00 to 33.63)   | 3.6 (0.09 to 18.35)                                    |  |
| PR                               | 8.3 (0.21 to 38.48)  | 33.3 (7.49 to 70.07)                                      | 14.3 (4.03 to 32.67)                                   |  |
| VGPR                             | 9999 (9999 to 9999)  | 9999 (9999 to 9999)                                       | 9999 (9999 to 9999)                                    |  |
| sCR                              | 9999 (9999 to 9999)  | 9999 (9999 to 9999)                                       | 9999 (9999 to 9999)                                    |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response (DOR)

|                 |                            |
|-----------------|----------------------------|
| End point title | Duration of Response (DOR) |
|-----------------|----------------------------|

End point description:

DOR was defined as the period from the date of initial PR or CR for solid tumors according to RECISTv1.1 and CR, PR, VGPR or sCR for multiple myeloma according to IMWG criteria, until the date of PD or death from any cause. RECIST v1.1: PD: At least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm. IMWG: PD: increase of  $\geq 25\%$  from lowest response value in serum or urine M-protein or bone marrow plasma cell percentage or development of new or increase in size of bone lesions or soft tissue plasmacytomas. ITT population included all subjects enrolled in the study irrespective of whether they had received study medication or not. 9999 = not estimable due to insufficient number of subjects with events.

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

End point timeframe:

Up to approximately 3 years

| End point values                 | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib | Cohort 2: Ovarian Cancer - vemurafenib | Cohort 3a: Colorectal Cancer - vemurafenib | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group  | Reporting group                        | Reporting group                            | Reporting group  |
| Number of subjects analysed      | 62   | 4                                      | 10   | 27   |
| Units: months                    |  |  |  |  |
| median (confidence interval 95%) | 7.16 (5.49 to 18.43)                                       | 8.16 (3.88 to 12.45)                   | 9999 (9999 to 9999)                        | 6.54 (5.68 to 7.39)                                    |



| <b>End point values</b>          | Cohort 4:<br>Cholangiocarcinoma - vemurafenib | Cohort 6:<br>Multiple Myeloma - vemurafenib | Cohort 7a:<br>ECD/LCH - vemurafenib | Cohort 7b:<br>Anaplastic Thyroid Cancer - vemurafenib |
|----------------------------------|---|---|-------------------------------------|---|
| Subject group type               | Reporting group                               | Reporting group                             | Reporting group                     | Reporting group                                       |
| Number of subjects analysed      | 9   | 9   | 26                                  | 12  |
| Units: months                    |   |   |                                     |   |
| median (confidence interval 95%) | 12.86 (3.58 to 22.14)                         | 9999 (9999 to 9999)                         | 9999 (9999 to 9999)                 | 9.95 (8.31 to 30.98)                                  |

| <b>End point values</b>          | Cohort 7c:<br>Advanced Stage Astrocytoma - vemurafenib | Cohort 7d:<br>Early Stage Astrocytoma - vemurafenib | Other BRAF V600-positive Tumors - vemurafenib |  |
|----------------------------------|--|---|---|--|
| Subject group type               | Reporting group  | Reporting group                                     | Reporting group                               |  |
| Number of subjects analysed      | 2  | 9   | 28  |  |
| Units: months                    |  |   |   |  |
| median (confidence interval 95%) | 9999 (13.08 to 9999)                                   | 3.42 (2.40 to 7.49)                                 | 9.92 (3.48 to 21.22)                          |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Response

|                 |                  |
|-----------------|------------------|
| End point title | Time to Response |
|-----------------|------------------|

End point description:

Time to response was defined as the time from the first day of study treatment to the date of first CR, or PR for solid tumors according to RECISTv1.1 and CR, PR, VGPR or sCR for multiple myeloma according to IMWG criteria. RECIST v1.1: CR: disappearance of all target lesions; PR: at least a 30% decrease in the sum of diameters of target lesions. IMWG criteria: CR: negative immunofixation on serum and urine and disappearance of any soft tissue plasmacytomas and  $\leq$  5% plasma cells in bone marrow; PR:  $\geq$  50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by  $\geq$  90% or to  $<$  200 mg per 24 hours. VGPR: serum and urine M-protein detectable by immunofixation but not on electrophoresis or  $\geq$  90% reduction in serum M-protein plus urine M-protein level  $<$  100 mg per 24 hour; sCR: CR plus normal FLC ratio and no clonal cells in bone marrow. ITT population: all subjects enrolled in the study. (-)9999 = not estimable due to insufficient number of subjects with events.

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

End point timeframe:

Up to approximately 3 years

| End point values                 | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib | Cohort 2: Ovarian Cancer - vemurafenib | Cohort 3a: Colorectal Cancer - vemurafenib | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group  | Reporting group                        | Reporting group                            | Reporting group  |
| Number of subjects analysed      | 62   | 4                                      | 10   | 27   |
| Units: months                    |  |  |  |  |
| median (confidence interval 95%) | 7.26 (3.68 to 9999)  | 9999 (1.64 to 9999)                    | 9999 (9999 to 9999)                        | 9999 (9999 to 9999)                                    |

| End point values                 | Cohort 4: Cholangiocarcinoma - vemurafenib | Cohort 6: Multiple Myeloma - vemurafenib | Cohort 7a: ECD/LCH - vemurafenib | Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib |
|----------------------------------|--|--|----------------------------------|--|
| Subject group type               | Reporting group                            | Reporting group                          | Reporting group                  | Reporting group                                    |
| Number of subjects analysed      | 9  | 9  | 26                               | 12   |
| Units: months                    |  |  |                                  |  |
| median (confidence interval 95%) | 9999 (3.52 to 9999)                        | 5.75 (-9999 to 9999)                     | 5.49 (3.68 to 13.73)             | 9999 (1.68 to 9999)                                |

| End point values                 | Cohort 7c: Advanced Stage Astrocytoma - vemurafenib | Cohort 7d: Early Stage Astrocytoma - vemurafenib | Other BRAF V600-positive Tumors - vemurafenib |  |
|----------------------------------|---|--|---|--|
| Subject group type               | Reporting group                                     | Reporting group                                  | Reporting group                               |  |
| Number of subjects analysed      | 12  | 9  | 28  |  |
| Units: months                    |   |  |   |  |
| median (confidence interval 95%) | 9999 (1.74 to 9999)                                 | 9999 (2.33 to 9999)                              | 9999 (3.68 to 9999)                           |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Tumor Progression (TTP)

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Time to Tumor Progression (TTP) |
|-----------------|---------------------------------|

End point description:

TTP was defined as time from the first day of study treatment to the first occurrence of progressive disease (PD). RECIST v1.1: PD: at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm. IMWG: PD: increase of  $\geq 25\%$  from lowest response value in serum or urine M-protein or bone marrow plasma cell percentage or development of new or increase in size of bone lesions or soft tissue plasmacytomas. ITT population included all subjects enrolled in the study irrespective of whether they had received study medication or not. 9999 = not estimable due to insufficient number of subjects with events.

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

End point timeframe:

Up to approximately 3 years

| End point values                 | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib | Cohort 2: Ovarian Cancer - vemurafenib | Cohort 3a: Colorectal Cancer - vemurafenib | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group  | Reporting group                        | Reporting group                            | Reporting group  |
| Number of subjects analysed      | 62   | 4                                      | 10   | 27   |
| Units: months                    |  |  |  |  |
| median (confidence interval 95%) | 7.33 (5.29 to 9.66)  | 6.44 (1.87 to 14.29)                   | 3.88 (1.84 to 5.52)                        | 3.68 (3.45 to 5.39)                                    |

| End point values                 | Cohort 4: Cholangiocarcinoma - vemurafenib | Cohort 6: Multiple Myeloma - vemurafenib | Cohort 7a: ECD/LCH - vemurafenib | Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib |
|----------------------------------|--|--|----------------------------------|--|
| Subject group type               | Reporting group                            | Reporting group                          | Reporting group                  | Reporting group                                    |
| Number of subjects analysed      | 9  | 9  | 26                               | 12   |
| Units: months                    |  |  |                                  |  |
| median (confidence interval 95%) | 3.02 (1.64 to 9.00)                        | 4.63 (2.89 to 9999)                      | 9999 (9999 to 9999)              | 2.83 (1.77 to 5.49)                                |

| End point values                 | Cohort 7c: Advanced Stage Astrocytoma - vemurafenib | Cohort 7d: Early Stage Astrocytoma - vemurafenib | Other BRAF V600-positive Tumors - vemurafenib |  |
|----------------------------------|---|--|---|--|
| Subject group type               | Reporting group                                     | Reporting group                                  | Reporting group                               |  |
| Number of subjects analysed      | 12  | 9  | 28  |  |
| Units: months                    |   |  |   |  |
| median (confidence interval 95%) | 5.62 (1.81 to 14.85)                                | 5.36 (3.02 to 9.10)                              | 3.65 (1.68 to 5.75)                           |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression free Survival (PFS)

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

End point description:

PFS was defined as the time from the first day of study treatment, until the first documented PD or death from any cause, whichever occurs first. RECIST v1.1: PD: at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm. IMWG criteria: PD: increase of  $\geq 25\%$  from lowest response value in serum or urine M-protein or bone marrow plasma cell percentage or development of new or increase in size of bone lesions or soft tissue plasmacytomas. ITT population included all subjects enrolled in the study irrespective of whether they had received study medication or not. 9999 = not estimable due to insufficient number of subjects with events.

|                             |           |
|-----------------------------|-----------|
| End point type              | Secondary |
| End point timeframe:        |           |
| Up to approximately 3 years |           |

| End point values                 | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib | Cohort 2: Ovarian Cancer - vemurafenib | Cohort 3a: Colorectal Cancer - vemurafenib | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group  | Reporting group                        | Reporting group                            | Reporting group  |
| Number of subjects analysed      | 62   | 4                                      | 10   | 27   |
| Units: months                    |  |  |  |  |
| median (confidence interval 95%) | 6.51 (5.16 to 8.97)  | 6.44 (1.87 to 14.29)                   | 3.88 (1.84 to 5.52)                        | 3.68 (1.81 to 5.39)                                    |

| End point values                 | Cohort 4: Cholangiocarcinoma - vemurafenib | Cohort 6: Multiple Myeloma - vemurafenib | Cohort 7a: ECD/LCH - vemurafenib | Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib |
|----------------------------------|--|--|----------------------------------|--|
| Subject group type               | Reporting group                            | Reporting group                          | Reporting group                  | Reporting group                                    |
| Number of subjects analysed      | 9  | 9  | 26                               | 12   |
| Units: months                    |  |  |                                  |  |
| median (confidence interval 95%) | 3.02 (1.64 to 9.00)                        | 4.63 (2.89 to 9999)                      | 9999 (9999 to 9999)              | 2.83 (1.77 to 5.49)                                |

| End point values                 | Cohort 7c: Advanced Stage Astrocytoma - vemurafenib | Cohort 7d: Early Stage Astrocytoma - vemurafenib | Other BRAF V600-positive Tumors - vemurafenib |  |
|----------------------------------|---|--|---|--|
| Subject group type               | Reporting group                                     | Reporting group                                  | Reporting group                               |  |
| Number of subjects analysed      | 12  | 9  | 28  |  |
| Units: months                    |   |  |   |  |
| median (confidence interval 95%) | 9.59 (1.81 to 14.78)                                | 5.26 (3.02 to 5.72)                              | 3.12 (1.64 to 5.55)                           |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS)

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

End point description:

OS was defined as time between the first day of study treatment and date of death of any cause. ITT population included all subjects enrolled in the study irrespective of whether they had received study medication or not. 9999 = not estimable due to insufficient number of subjects with events.

|                             |           |
|-----------------------------|-----------|
| End point type              | Secondary |
| End point timeframe:        |           |
| Up to approximately 3 years |           |

| End point values                 | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib | Cohort 2: Ovarian Cancer - vemurafenib | Cohort 3a: Colorectal Cancer - vemurafenib | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group  | Reporting group                        | Reporting group                            | Reporting group  |
| Number of subjects analysed      | 62   | 4                                      | 10   | 27   |
| Units: months                    |  |  |  |  |
| median (confidence interval 95%) | 15.38 (9.56 to 22.77)                                      | 9999 (2.56 to 9999)                    | 9.30 (7.82 to 12.88)                       | 7.16 (5.49 to 11.73)                                   |

| End point values                 | Cohort 4: Cholangiocarcinoma - vemurafenib | Cohort 6: Multiple Myeloma - vemurafenib | Cohort 7a: ECD/LCH - vemurafenib | Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib |
|----------------------------------|--|--|----------------------------------|--|
| Subject group type               | Reporting group                            | Reporting group                          | Reporting group                  | Reporting group                                    |
| Number of subjects analysed      | 9  | 9  | 26                               | 12   |
| Units: months                    |  |  |                                  |  |
| median (confidence interval 95%) | 17.94 (11.20 to 9999)                      | 24.54 (4.96 to 9999)                     | 9999 (9999 to 9999)              | 5.88 (2.17 to 16.79)                               |

| End point values                 | Cohort 7c: Advanced Stage Astrocytoma - vemurafenib | Cohort 7d: Early Stage Astrocytoma - vemurafenib | Other BRAF V600-positive Tumors - vemurafenib |  |
|----------------------------------|---|--|---|--|
| Subject group type               | Reporting group                                     | Reporting group                                  | Reporting group                               |  |
| Number of subjects analysed      | 12  | 9  | 28  |  |
| Units: months                    |   |  |   |  |
| median (confidence interval 95%) | 40.11 (9.59 to 40.11)                               | 12.75 (6.70 to 9999)                             | 11.56 (3.71 to 28.16)                         |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum Tolerated Dose for Vemurafenib in Combination with Cetuximab

|                 |  |
|-----------------|--|
| End point title | Maximum Tolerated Dose for Vemurafenib in Combination with Cetuximab |
|-----------------|--|

End point description:

Cohort 3b included subjects with colorectal cancer treated with escalating doses of vemurafenib and

cetuximab. The escalating doses were as follows: Dose Level 1: 720 milligrams (mg) of vemurafenib orally twice daily starting on Day 2 of Cycle 1 and 300 milligrams per square meter (mg/m<sup>2</sup>) loading dose of cetuximab by infusion and then 200 mg/m<sup>2</sup> weekly; Dose Level 2: 720 mg of vemurafenib twice daily starting on Day 2 of Cycle 1 and 400 mg/m<sup>2</sup> loading dose of cetuximab and then 250 mg/m<sup>2</sup> weekly; Dose Level 3: 960 mg of vemurafenib twice daily starting on Day 2 of Cycle 1 and 400 mg/m<sup>2</sup> loading dose of cetuximab and then 250 mg/m<sup>2</sup> weekly. Reported here are the maximum tolerated doses for each vemurafenib and cetuximab. The safety population included all subjects who received at least one dose of study medication.

|                             |           |
|-----------------------------|-----------|
| End point type              | Secondary |
| End point timeframe:        |           |
| Up to approximately 3 years |           |

| End point values            | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib | Cohort 2: Ovarian Cancer - vemurafenib | Cohort 3a: Colorectal Cancer - vemurafenib | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab |
|-----------------------------|--|--|--|--|
| Subject group type          | Reporting group  | Reporting group                        | Reporting group                            | Reporting group  |
| Number of subjects analysed | 0 <sup>[5]</sup>   | 0 <sup>[6]</sup>                       | 0 <sup>[7]</sup>                           | 14   |
| Units: milligrams (mg)      |  |  |  |  |
| vemurafenib                 |  |  |  | 960  |
| cetuximab                   |  |  |  | 400  |

Notes:

[5] - Endpoint only applies to combination therapy in cohort 3b.

[6] - Endpoint only applies to combination therapy in cohort 3b.

[7] - Endpoint only applies to combination therapy in cohort 3b.

| End point values            | Cohort 4: Cholangiocarcinoma - vemurafenib | Cohort 6: Multiple Myeloma - vemurafenib | Cohort 7a: ECD/LCH - vemurafenib | Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib |
|-----------------------------|--|--|----------------------------------|--|
| Subject group type          | Reporting group                            | Reporting group                          | Reporting group                  | Reporting group                                    |
| Number of subjects analysed | 0 <sup>[8]</sup>                           | 0 <sup>[9]</sup>                         | 0 <sup>[10]</sup>                | 0 <sup>[11]</sup>                                  |
| Units: milligrams (mg)      |  |  |                                  |  |
| vemurafenib                 |  |  |                                  |  |
| cetuximab                   |  |  |                                  |  |

Notes:

[8] - Endpoint only applies to combination therapy in cohort 3b.

[9] - Endpoint only applies to combination therapy in cohort 3b.

[10] - Endpoint only applies to combination therapy in cohort 3b.

[11] - Endpoint only applies to combination therapy in cohort 3b.

| End point values            | Cohort 7c: Advanced Stage Astrocytoma - vemurafenib | Cohort 7d: Early Stage Astrocytoma - vemurafenib | Other BRAF V600-positive Tumors - vemurafenib |  |
|-----------------------------|---|--|---|--|
| Subject group type          | Reporting group                                     | Reporting group                                  | Reporting group                               |  |
| Number of subjects analysed | 0 <sup>[12]</sup>                                   | 0 <sup>[13]</sup>                                | 0 <sup>[14]</sup>                             |  |
| Units: milligrams (mg)      |   |  |   |  |
| vemurafenib                 |   |  |   |  |
| cetuximab                   |   |  |   |  |

Notes:

[12] - Endpoint only applies to combination therapy in cohort 3b.

[13] - Endpoint only applies to combination therapy in cohort 3b.

[14] - Endpoint only applies to combination therapy in cohort 3b.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Dose-limiting Toxicities of Vemurafenib in Combination with Cetuximab

|                 |   |
|-----------------|---|
| End point title | Number of Dose-limiting Toxicities of Vemurafenib in Combination with Cetuximab |
|-----------------|---|

End point description:

Cohort 3b included subjects with colorectal cancer treated with escalating doses of vemurafenib and cetuximab. The escalating doses were as follows: Dose Level 1: 720 milligrams (mg) of vemurafenib orally twice daily starting on Day 2 of Cycle 1 and 300 milligrams per square meter (mg/m<sup>2</sup>) loading dose of cetuximab by infusion and then 200 mg/m<sup>2</sup> weekly; Dose Level 2: 720 mg of vemurafenib twice daily starting on Day 2 of Cycle 1 and 400 mg/m<sup>2</sup> loading dose of cetuximab and then 250 mg/m<sup>2</sup> weekly; Dose Level 3: 960 mg of vemurafenib twice daily starting on Day 2 of Cycle 1 and 400 mg/m<sup>2</sup> loading dose of cetuximab and then 250 mg/m<sup>2</sup> weekly. Reported here are type and number of dose limited toxicities observed. The safety population included all subjects who received at least one dose of study medication.

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

End point timeframe:

Up to 28 days

| End point values                | Cohort 1: Non-Small Cell Lung Cancer (NSCLC) - vemurafenib | Cohort 2: Ovarian Cancer - vemurafenib | Cohort 3a: Colorectal Cancer - vemurafenib | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab |
|---------------------------------|--|--|--|--|
| Subject group type              | Reporting group  | Reporting group                        | Reporting group                            | Reporting group  |
| Number of subjects analysed     | 0 <sup>[15]</sup>  | 0 <sup>[16]</sup>                      | 0 <sup>[17]</sup>                          | 14   |
| Units: dose-limiting toxicities |  |  |  |  |
| Grade 3 amylase increased       |  |  |  | 1  |
| Grade 4 lipase increased        |  |  |  | 1  |

Notes:

[15] - Endpoint only applies to combination therapy in cohort 3b.

[16] - Endpoint only applies to combination therapy in cohort 3b.

[17] - Endpoint only applies to combination therapy in cohort 3b.

| End point values                | Cohort 4: Cholangiocarcinoma - vemurafenib | Cohort 6: Multiple Myeloma - vemurafenib | Cohort 7a: ECD/LCH - vemurafenib | Cohort 7b: Anaplastic Thyroid Cancer - vemurafenib |
|---------------------------------|--|--|----------------------------------|--|
| Subject group type              | Reporting group                            | Reporting group                          | Reporting group                  | Reporting group                                    |
| Number of subjects analysed     | 0 <sup>[18]</sup>                          | 0 <sup>[19]</sup>                        | 0 <sup>[20]</sup>                | 0 <sup>[21]</sup>                                  |
| Units: dose-limiting toxicities |  |  |                                  |  |
| Grade 3 amylase increased       |  |  |                                  |  |
| Grade 4 lipase increased        |  |  |                                  |  |

Notes:

[18] - Endpoint only applies to combination therapy in cohort 3b.

[19] - Endpoint only applies to combination therapy in cohort 3b.

[20] - Endpoint only applies to combination therapy in cohort 3b.

[21] - Endpoint only applies to combination therapy in cohort 3b.

| End point values                | Cohort 7c:<br>Advanced<br>Stage<br>Astrocytoma -<br>vemurafenib | Cohort 7d:<br>Early Stage<br>Astrocytoma -<br>vemurafenib | Other BRAF<br>V600-positive<br>Tumors -<br>vemurafenib |  |
|---------------------------------|---|---|--|--|
| Subject group type              | Reporting group   | Reporting group   | Reporting group  |  |
| Number of subjects analysed     | 0 <sup>[22]</sup>   | 0 <sup>[23]</sup>   | 0 <sup>[24]</sup>                                      |  |
| Units: dose-limiting toxicities |   |   |  |  |
| Grade 3 amylase increased       |   |   |  |  |
| Grade 4 lipase increased        |   |   |  |  |

Notes:

[22] - Endpoint only applies to combination therapy in cohort 3b.

[23] - Endpoint only applies to combination therapy in cohort 3b.

[24] - Endpoint only applies to combination therapy in cohort 3b.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Safety: Percentage of Subjects with Adverse Event

|                 |   |
|-----------------|---|
| End point title | Safety: Percentage of Subjects with Adverse Event |
|-----------------|---|

End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. The safety population included all subjects who received at least one dose of study medication.

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

End point timeframe:

Up to approximately 3 years

| End point values              | Cohort 1: Non-<br>Small Cell Lung<br>Cancer<br>(NSCLC) -<br>vemurafenib | Cohort 2:<br>Ovarian Cancer<br>- vemurafenib | Cohort 3a:<br>Colorectal<br>Cancer -<br>vemurafenib | Cohort 3b:<br>Colorectal<br>Cancer -<br>vemurafenib +<br>cetuximab |
|-------------------------------|---|--|---|--|
| Subject group type            | Reporting group   | Reporting group                              | Reporting group                                     | Reporting group  |
| Number of subjects analysed   | 62  | 4  | 10  | 27   |
| Units: percentage of subjects |   |  |   |  |
| number (not applicable)       | 100   | 100  | 100   | 100  |

| End point values | Cohort 4:<br>Cholangiocarci | Cohort 6:<br>Multiple | Cohort 7a:<br>ECD/LCH - | Cohort 7b:<br>Anaplastic |
|------------------|-----------------------------|-----------------------|-------------------------|--------------------------|
|------------------|-----------------------------|-----------------------|-------------------------|--------------------------|



|                               | noma -<br>vemurafenib | Myeloma -<br>vemurafenib | vemurafenib     | Thyroid Cancer<br>- vemurafenib |
|-------------------------------|-----------------------|--------------------------|-----------------|---------------------------------|
| Subject group type            | Reporting group       | Reporting group          | Reporting group | Reporting group                 |
| Number of subjects analysed   | 9                     | 9                        | 26              | 12                              |
| Units: percentage of subjects |                       |                          |                 |                                 |
| number (not applicable)       | 100                   | 100                      | 100             | 91.7                            |

| <b>End point values</b>       | Cohort 7c:<br>Advanced<br>Stage<br>Astrocytoma -<br>vemurafenib | Cohort 7d:<br>Early Stage<br>Astrocytoma -<br>vemurafenib | Other BRAF<br>V600-positive<br>Tumors -<br>vemurafenib |  |
|-------------------------------|---|---|--|--|
| Subject group type            | Reporting group   | Reporting group   | Reporting group  |  |
| Number of subjects analysed   | 12  | 9   | 28   |  |
| Units: percentage of subjects |   |   |  |  |
| number (not applicable)       | 100   | 100   | 100  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From baseline up to approximately 3 years

Adverse event reporting additional description:

The safety population included all subjects who received at least one dose of study medication.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Pooled arm - vemurafenib |
|-----------------------|--------------------------|

Reporting group description:

Subjects with a variety of cancer types, who were treated with vemurafenib monotherapy, were combined into this arm.

|                       |  |
|-----------------------|--|
| Reporting group title | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab |
|-----------------------|--|

Reporting group description:

Subjects with colorectal cancer were treated with vemurafenib and cetuximab combination therapy.

| Serious adverse events  | Pooled arm - vemurafenib | Cohort 3b: Colorectal Cancer - vemurafenib + cetuximab |  |
|---|--------------------------|--|--|
| Total subjects affected by serious adverse events                   |                          |  |  |
| subjects affected / exposed   | 91 / 181 (50.28%)        | 11 / 27 (40.74%)                                       |  |
| number of deaths (all causes)                                       | 87                       | 25   |  |
| number of deaths resulting from adverse events                      |                          |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                          |  |  |
| Squamous cell carcinoma of skin                                     |                          |  |  |
| subjects affected / exposed   | 25 / 181 (13.81%)        | 3 / 27 (11.11%)  |  |
| occurrences causally related to treatment / all                     | 38 / 39                  | 3 / 3  |  |
| deaths causally related to treatment / all                          | 0 / 0                    | 0 / 0  |  |
| Keratoacanthoma   |                          |  |  |
| subjects affected / exposed   | 18 / 181 (9.94%)         | 2 / 27 (7.41%)   |  |
| occurrences causally related to treatment / all                     | 28 / 28                  | 2 / 2  |  |
| deaths causally related to treatment / all                          | 0 / 0                    | 0 / 0  |  |
| Basal cell carcinoma  |                          |  |  |
| subjects affected / exposed   | 7 / 181 (3.87%)          | 1 / 27 (3.70%)   |  |
| occurrences causally related to treatment / all                     | 11 / 13                  | 1 / 1  |  |
| deaths causally related to treatment / all                          | 0 / 0                    | 0 / 0  |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| Squamous cell carcinoma                         |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Bowen's disease                                 |                 |                |  |
| subjects affected / exposed                     | 4 / 181 (2.21%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Chronic myelomonocytic leukaemia                |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Papillary thyroid cancer                        |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Paraganglion neoplasm                           |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Skin cancer                                     |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Squamous cell carcinoma of lung                 |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Vascular disorders                              |                 |                |  |
| Jugular vein thrombosis                         |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| General disorders and administration            |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| site conditions                                 |                 |                |  |
| Non-cardiac chest pain                          |                 |                |  |
| subjects affected / exposed                     | 0 / 181 (0.00%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Pyrexia   |                 |                |  |
| subjects affected / exposed                     | 2 / 181 (1.10%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Fatigue   |                 |                |  |
| subjects affected / exposed                     | 2 / 181 (1.10%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Chest pain                                      |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Hyperthermia                                    |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Immune system disorders                         |                 |                |  |
| Hypersensitivity                                |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Reproductive system and breast disorders        |                 |                |  |
| Prostatitis                                     |                 |                |  |
| subjects affected / exposed                     | 2 / 181 (1.10%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Benign prostatic hyperplasia                    |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Uterine haemorrhage                             |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Vaginal haemorrhage                             |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                 |                |  |
| Pulmonary thrombosis                            |                 |                |  |
| subjects affected / exposed                     | 0 / 181 (0.00%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Dyspnoea  |                 |                |  |
| subjects affected / exposed                     | 3 / 181 (1.66%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Pulmonary embolism                              |                 |                |  |
| subjects affected / exposed                     | 3 / 181 (1.66%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0          |  |
| Respiratory failure                             |                 |                |  |
| subjects affected / exposed                     | 2 / 181 (1.10%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0          |  |
| Laryngeal dyspnoea                              |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Pleural effusion                                |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Pneumothorax                                    |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Psychiatric disorders                           |                 |                |  |
| Delirium  |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Depression                                      |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Investigations                                  |                 |                |  |
| Gamma-glutamyltransferase increased             |                 |                |  |
| subjects affected / exposed                     | 0 / 181 (0.00%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Body temperature increased                      |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                 |                |  |
| Femoral neck fracture                           |                 |                |  |
| subjects affected / exposed                     | 0 / 181 (0.00%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Fracture  |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Limb injury                                     |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Subdural haematoma                              |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| Cardiac disorders                               |                 |                |  |
| Acute coronary syndrome                         |                 |                |  |
| subjects affected / exposed                     | 2 / 181 (1.10%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Pericarditis                                    |                 |                |  |
| subjects affected / exposed                     | 2 / 181 (1.10%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Dressler's syndrome                             |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Myocardial infarction                           |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Pericardial effusion                            |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Nervous system disorders                        |                 |                |  |

|  |   |                 |                |  |
|--|---|-----------------|----------------|--|
| Aphasia                                      | subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
|  | occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
|  | deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Brain oedema                                 | subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
|  | occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
|  | deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Haemorrhagic stroke                          | subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
|  | occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
|  | deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Partial seizures                             | subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
|  | occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
|  | deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Peripheral motor neuropathy                  | subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
|  | occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
|  | deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Posterior reversible encephalopathy syndrome | subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
|  | occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
|  | deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Seizure                                      | subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
|  | occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
|  | deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Transient ischaemic attack                   | subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (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         |   |                 |                |  |



|   |                 |                |  |
|---|-----------------|----------------|--|
| Pseudolymphoma                                  |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Splenic infarction                              |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Eye disorders                                   |                 |                |  |
| Iridocyclitis                                   |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Gastrointestinal disorders                      |                 |                |  |
| Upper gastrointestinal haemorrhage              |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Subileus  |                 |                |  |
| subjects affected / exposed                     | 0 / 181 (0.00%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Duodenal perforation                            |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Dysphagia                                       |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Gastric ulcer                                   |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| Stomatitis                                      |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Hepatobiliary disorders                         |                 |                |  |
| Cholestasis                                     |                 |                |  |
| subjects affected / exposed                     | 0 / 181 (0.00%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Bile duct obstruction                           |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Drug-induced liver injury                       |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Skin and subcutaneous tissue disorders          |                 |                |  |
| Acute febrile neutrophilic dermatosis           |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Rash  |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Skin lesion                                     |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Renal and urinary disorders                     |                 |                |  |
| Acute kidney injury                             |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 4 / 181 (2.21%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Bladder dilatation                              |                 |                |  |
| subjects affected / exposed                     | 0 / 181 (0.00%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Obstructive uropathy                            |                 |                |  |
| subjects affected / exposed                     | 0 / 181 (0.00%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Renal failure                                   |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders |                 |                |  |
| Back pain                                       |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Infections and infestations                     |                 |                |  |
| Sepsis  |                 |                |  |
| subjects affected / exposed                     | 6 / 181 (3.31%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 6           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          |  |
| Pneumonia                                       |                 |                |  |
| subjects affected / exposed                     | 5 / 181 (2.76%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Lung infection                                  |                 |                |  |
| subjects affected / exposed                     | 4 / 181 (2.21%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| Bronchitis                                      |                 |                |  |
| subjects affected / exposed                     | 3 / 181 (1.66%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Lower respiratory tract infection               |                 |                |  |
| subjects affected / exposed                     | 2 / 181 (1.10%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Abdominal abscess                               |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Bacteraemia                                     |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Cellulitis                                      |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Diverticulitis                                  |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Furuncle  |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Septic shock                                    |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Soft tissue infection                           |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Staphylococcal sepsis                           |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Urinary tract infection                         |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Metabolism and nutrition disorders              |                 |                |  |
| Diabetes mellitus                               |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Glucose tolerance impaired                      |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Hypercalcaemia                                  |                 |                |  |
| subjects affected / exposed                     | 1 / 181 (0.55%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Dehydration                                     |                 |                |  |
| subjects affected / exposed                     | 3 / 181 (1.66%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                                   | <b>Pooled arm -<br/>vemurafenib</b> | <b>Cohort 3b:<br/>Colorectal Cancer -<br/>vemurafenib +<br/>cetuximab</b> |  |
|---|-------------------------------------|---|--|
| Total subjects affected by non-serious adverse events               |                                     |   |  |
| subjects affected / exposed   | 177 / 181 (97.79%)                  | 26 / 27 (96.30%)  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                     |   |  |
| Acrochordon   |                                     |   |  |
| subjects affected / exposed   | 0 / 181 (0.00%)                     | 2 / 27 (7.41%)  |  |
| occurrences (all)   | 0                                   | 3   |  |
| Melanocytic naevus  |                                     |   |  |
| subjects affected / exposed   | 41 / 181 (22.65%)                   | 4 / 27 (14.81%)   |  |
| occurrences (all)   | 67                                  | 4   |  |
| Seborrhoeic keratosis   |                                     |   |  |
| subjects affected / exposed   | 36 / 181 (19.89%)                   | 3 / 27 (11.11%)   |  |
| occurrences (all)   | 49                                  | 3   |  |
| Skin papilloma  |                                     |   |  |
| subjects affected / exposed   | 50 / 181 (27.62%)                   | 7 / 27 (25.93%)   |  |
| occurrences (all)   | 86                                  | 8   |  |
| Papilloma   |                                     |   |  |
| subjects affected / exposed   | 17 / 181 (9.39%)                    | 0 / 27 (0.00%)  |  |
| occurrences (all)   | 21                                  | 0   |  |
| Vascular disorders  |                                     |   |  |
| Hypertension  |                                     |   |  |
| subjects affected / exposed   | 28 / 181 (15.47%)                   | 3 / 27 (11.11%)   |  |
| occurrences (all)   | 38                                  | 3   |  |
| General disorders and administration site conditions                |                                     |   |  |
| Asthenia  |                                     |   |  |
| subjects affected / exposed   | 39 / 181 (21.55%)                   | 10 / 27 (37.04%)  |  |
| occurrences (all)   | 44                                  | 13  |  |
| Chest pain  |                                     |   |  |
| subjects affected / exposed   | 0 / 181 (0.00%)                     | 2 / 27 (7.41%)  |  |
| occurrences (all)   | 0                                   | 2   |  |
| Chills  |                                     |   |  |
| subjects affected / exposed   | 10 / 181 (5.52%)                    | 2 / 27 (7.41%)  |  |
| occurrences (all)   | 10                                  | 2   |  |
| Fatigue   |                                     |   |  |

|   |                         |                       |  |
|---|-------------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)                      | 60 / 181 (33.15%)<br>68 | 6 / 27 (22.22%)<br>8  |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all) | 21 / 181 (11.60%)<br>25 | 4 / 27 (14.81%)<br>4  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)           | 26 / 181 (14.36%)<br>30 | 5 / 27 (18.52%)<br>11 |  |
| Cyst<br>subjects affected / exposed<br>occurrences (all)              | 21 / 181 (11.60%)<br>26 | 0 / 27 (0.00%)<br>0   |  |
| Xerosis<br>subjects affected / exposed<br>occurrences (all)           | 16 / 181 (8.84%)<br>18  | 0 / 27 (0.00%)<br>0   |  |
| Respiratory, thoracic and mediastinal disorders                       |                         |                       |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)             | 31 / 181 (17.13%)<br>42 | 2 / 27 (7.41%)<br>4   |  |
| Dysphonia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 181 (0.00%)<br>0    | 2 / 27 (7.41%)<br>2   |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)          | 22 / 181 (12.15%)<br>27 | 5 / 27 (18.52%)<br>7  |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)  | 10 / 181 (5.52%)<br>11  | 0 / 27 (0.00%)<br>0   |  |
| Psychiatric disorders   |                         |                       |  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)           | 14 / 181 (7.73%)<br>14  | 2 / 27 (7.41%)<br>2   |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)        | 10 / 181 (5.52%)<br>10  | 3 / 27 (11.11%)<br>5  |  |
| Insomnia  |                         |                       |  |

|  |                         |                       |  |
|--|-------------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 18 / 181 (9.94%)<br>19  | 0 / 27 (0.00%)<br>0   |  |
| Investigations   |                         |                       |  |
| Amylase increased<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 181 (0.00%)<br>0    | 6 / 27 (22.22%)<br>6  |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 15 / 181 (8.29%)<br>15  | 2 / 27 (7.41%)<br>2   |  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)            | 10 / 181 (5.52%)<br>14  | 3 / 27 (11.11%)<br>3  |  |
| Electrocardiogram QT prolonged<br>subjects affected / exposed<br>occurrences (all)       | 37 / 181 (20.44%)<br>52 | 4 / 27 (14.81%)<br>4  |  |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)           | 0 / 181 (0.00%)<br>0    | 3 / 27 (11.11%)<br>6  |  |
| Lipase increased<br>subjects affected / exposed<br>occurrences (all)                     | 10 / 181 (5.52%)<br>21  | 9 / 27 (33.33%)<br>10 |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                     | 20 / 181 (11.05%)<br>20 | 6 / 27 (22.22%)<br>6  |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 15 / 181 (8.29%)<br>17  | 0 / 27 (0.00%)<br>0   |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 11 / 181 (6.08%)<br>12  | 0 / 27 (0.00%)<br>0   |  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)           | 19 / 181 (10.50%)<br>26 | 0 / 27 (0.00%)<br>0   |  |
| Injury, poisoning and procedural complications   |                         |                       |  |



|                                      |                   |                  |  |
|--------------------------------------|-------------------|------------------|--|
| Fall                                 |                   |                  |  |
| subjects affected / exposed          | 0 / 181 (0.00%)   | 2 / 27 (7.41%)   |  |
| occurrences (all)                    | 0                 | 3                |  |
| Sunburn                              |                   |                  |  |
| subjects affected / exposed          | 22 / 181 (12.15%) | 4 / 27 (14.81%)  |  |
| occurrences (all)                    | 27                | 4                |  |
| Nervous system disorders             |                   |                  |  |
| Headache                             |                   |                  |  |
| subjects affected / exposed          | 26 / 181 (14.36%) | 4 / 27 (14.81%)  |  |
| occurrences (all)                    | 30                | 5                |  |
| Dysgeusia                            |                   |                  |  |
| subjects affected / exposed          | 24 / 181 (13.26%) | 0 / 27 (0.00%)   |  |
| occurrences (all)                    | 25                | 0                |  |
| Peripheral sensory neuropathy        |                   |                  |  |
| subjects affected / exposed          | 27 / 181 (14.92%) | 0 / 27 (0.00%)   |  |
| occurrences (all)                    | 27                | 0                |  |
| Blood and lymphatic system disorders |                   |                  |  |
| Anaemia                              |                   |                  |  |
| subjects affected / exposed          | 30 / 181 (16.57%) | 3 / 27 (11.11%)  |  |
| occurrences (all)                    | 40                | 3                |  |
| Eye disorders                        |                   |                  |  |
| Dry eye                              |                   |                  |  |
| subjects affected / exposed          | 11 / 181 (6.08%)  | 0 / 27 (0.00%)   |  |
| occurrences (all)                    | 11                | 0                |  |
| Gastrointestinal disorders           |                   |                  |  |
| Abdominal pain                       |                   |                  |  |
| subjects affected / exposed          | 12 / 181 (6.63%)  | 12 / 27 (44.44%) |  |
| occurrences (all)                    | 13                | 18               |  |
| Abdominal pain upper                 |                   |                  |  |
| subjects affected / exposed          | 0 / 181 (0.00%)   | 4 / 27 (14.81%)  |  |
| occurrences (all)                    | 0                 | 4                |  |
| Constipation                         |                   |                  |  |
| subjects affected / exposed          | 26 / 181 (14.36%) | 5 / 27 (18.52%)  |  |
| occurrences (all)                    | 30                | 6                |  |
| Diarrhoea                            |                   |                  |  |
| subjects affected / exposed          | 49 / 181 (27.07%) | 13 / 27 (48.15%) |  |
| occurrences (all)                    | 67                | 30               |  |

|  |                   |                 |  |
|--|-------------------|-----------------|--|
| Dyspepsia                              |                   |                 |  |
| subjects affected / exposed            | 0 / 181 (0.00%)   | 2 / 27 (7.41%)  |  |
| occurrences (all)                      | 0                 | 3               |  |
| Flatulence                             |                   |                 |  |
| subjects affected / exposed            | 0 / 181 (0.00%)   | 2 / 27 (7.41%)  |  |
| occurrences (all)                      | 0                 | 5               |  |
| Nausea                                 |                   |                 |  |
| subjects affected / exposed            | 54 / 181 (29.83%) | 9 / 27 (33.33%) |  |
| occurrences (all)                      | 80                | 13              |  |
| Rectal haemorrhage                     |                   |                 |  |
| subjects affected / exposed            | 0 / 181 (0.00%)   | 2 / 27 (7.41%)  |  |
| occurrences (all)                      | 0                 | 3               |  |
| Stomatitis                             |                   |                 |  |
| subjects affected / exposed            | 19 / 181 (10.50%) | 4 / 27 (14.81%) |  |
| occurrences (all)                      | 20                | 5               |  |
| Vomiting                               |                   |                 |  |
| subjects affected / exposed            | 41 / 181 (22.65%) | 8 / 27 (29.63%) |  |
| occurrences (all)                      | 55                | 10              |  |
| Dry mouth                              |                   |                 |  |
| subjects affected / exposed            | 12 / 181 (6.63%)  | 0 / 27 (0.00%)  |  |
| occurrences (all)                      | 16                | 0               |  |
| Dysphagia                              |                   |                 |  |
| subjects affected / exposed            | 14 / 181 (7.73%)  | 0 / 27 (0.00%)  |  |
| occurrences (all)                      | 16                | 0               |  |
| Hepatobiliary disorders                |                   |                 |  |
| Hyperbilirubinaemia                    |                   |                 |  |
| subjects affected / exposed            | 11 / 181 (6.08%)  | 0 / 27 (0.00%)  |  |
| occurrences (all)                      | 14                | 0               |  |
| Skin and subcutaneous tissue disorders |                   |                 |  |
| Actinic keratosis                      |                   |                 |  |
| subjects affected / exposed            | 28 / 181 (15.47%) | 4 / 27 (14.81%) |  |
| occurrences (all)                      | 51                | 4               |  |
| Alopecia                               |                   |                 |  |
| subjects affected / exposed            | 57 / 181 (31.49%) | 2 / 27 (7.41%)  |  |
| occurrences (all)                      | 58                | 2               |  |
| Dermatitis acneiform                   |                   |                 |  |

|                             |                   |                  |
|-----------------------------|-------------------|------------------|
| subjects affected / exposed | 0 / 181 (0.00%)   | 2 / 27 (7.41%)   |
| occurrences (all)           | 0                 | 2                |
| Dermatitis bullous          |                   |                  |
| subjects affected / exposed | 0 / 181 (0.00%)   | 2 / 27 (7.41%)   |
| occurrences (all)           | 0                 | 2                |
| Dry skin                    |                   |                  |
| subjects affected / exposed | 39 / 181 (21.55%) | 2 / 27 (7.41%)   |
| occurrences (all)           | 42                | 2                |
| Hyperkeratosis              |                   |                  |
| subjects affected / exposed | 58 / 181 (32.04%) | 4 / 27 (14.81%)  |
| occurrences (all)           | 102               | 9                |
| Erythema                    |                   |                  |
| subjects affected / exposed | 24 / 181 (13.26%) | 7 / 27 (25.93%)  |
| occurrences (all)           | 34                | 11               |
| Pruritus                    |                   |                  |
| subjects affected / exposed | 42 / 181 (23.20%) | 5 / 27 (18.52%)  |
| occurrences (all)           | 47                | 5                |
| Photosensitivity reaction   |                   |                  |
| subjects affected / exposed | 39 / 181 (21.55%) | 5 / 27 (18.52%)  |
| occurrences (all)           | 44                | 5                |
| Rash                        |                   |                  |
| subjects affected / exposed | 44 / 181 (24.31%) | 10 / 27 (37.04%) |
| occurrences (all)           | 60                | 16               |
| Rash generalised            |                   |                  |
| subjects affected / exposed | 0 / 181 (0.00%)   | 2 / 27 (7.41%)   |
| occurrences (all)           | 0                 | 2                |
| Rash maculo-papular         |                   |                  |
| subjects affected / exposed | 42 / 181 (23.20%) | 3 / 27 (11.11%)  |
| occurrences (all)           | 59                | 5                |
| Skin fissures               |                   |                  |
| subjects affected / exposed | 0 / 181 (0.00%)   | 2 / 27 (7.41%)   |
| occurrences (all)           | 0                 | 2                |
| Toxic skin eruption         |                   |                  |
| subjects affected / exposed | 0 / 181 (0.00%)   | 2 / 27 (7.41%)   |
| occurrences (all)           | 0                 | 2                |
| Dermal cyst                 |                   |                  |

|  |                   |                  |  |
|--|-------------------|------------------|--|
| subjects affected / exposed                            | 18 / 181 (9.94%)  | 0 / 27 (0.00%)   |  |
| occurrences (all)                                      | 24                | 0                |  |
| <b>Dermatitis</b>                                      |                   |                  |  |
| subjects affected / exposed                            | 10 / 181 (5.52%)  | 0 / 27 (0.00%)   |  |
| occurrences (all)                                      | 10                | 0                |  |
| <b>Keratosis pilaris</b>                               |                   |                  |  |
| subjects affected / exposed                            | 33 / 181 (18.23%) | 0 / 27 (0.00%)   |  |
| occurrences (all)                                      | 33                | 0                |  |
| <b>Milia</b>   |                   |                  |  |
| subjects affected / exposed                            | 16 / 181 (8.84%)  | 0 / 27 (0.00%)   |  |
| occurrences (all)                                      | 18                | 0                |  |
| <b>Palmar-plantar erythrodysesthesia syndrome</b>      |                   |                  |  |
| subjects affected / exposed                            | 48 / 181 (26.52%) | 0 / 27 (0.00%)   |  |
| occurrences (all)                                      | 57                | 0                |  |
| <b>Papule</b>  |                   |                  |  |
| subjects affected / exposed                            | 13 / 181 (7.18%)  | 0 / 27 (0.00%)   |  |
| occurrences (all)                                      | 18                | 0                |  |
| <b>Rash papular</b>                                    |                   |                  |  |
| subjects affected / exposed                            | 21 / 181 (11.60%) | 0 / 27 (0.00%)   |  |
| occurrences (all)                                      | 26                | 0                |  |
| <b>Skin lesion</b>                                     |                   |                  |  |
| subjects affected / exposed                            | 11 / 181 (6.08%)  | 0 / 27 (0.00%)   |  |
| occurrences (all)                                      | 18                | 0                |  |
| <b>Renal and urinary disorders</b>                     |                   |                  |  |
| <b>Haematuria</b>                                      |                   |                  |  |
| subjects affected / exposed                            | 0 / 181 (0.00%)   | 2 / 27 (7.41%)   |  |
| occurrences (all)                                      | 0                 | 3                |  |
| <b>Micturition urgency</b>                             |                   |                  |  |
| subjects affected / exposed                            | 0 / 181 (0.00%)   | 2 / 27 (7.41%)   |  |
| occurrences (all)                                      | 0                 | 2                |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                   |                  |  |
| <b>Arthralgia</b>                                      |                   |                  |  |
| subjects affected / exposed                            | 79 / 181 (43.65%) | 14 / 27 (51.85%) |  |
| occurrences (all)                                      | 123               | 21               |  |
| <b>Back pain</b>                                       |                   |                  |  |

|                                    |                  |                 |  |
|------------------------------------|------------------|-----------------|--|
| subjects affected / exposed        | 18 / 181 (9.94%) | 4 / 27 (14.81%) |  |
| occurrences (all)                  | 21               | 4               |  |
| Muscle spasms                      |                  |                 |  |
| subjects affected / exposed        | 0 / 181 (0.00%)  | 2 / 27 (7.41%)  |  |
| occurrences (all)                  | 0                | 3               |  |
| Myalgia                            |                  |                 |  |
| subjects affected / exposed        | 18 / 181 (9.94%) | 3 / 27 (11.11%) |  |
| occurrences (all)                  | 23               | 4               |  |
| Pain in extremity                  |                  |                 |  |
| subjects affected / exposed        | 13 / 181 (7.18%) | 2 / 27 (7.41%)  |  |
| occurrences (all)                  | 14               | 5               |  |
| Musculoskeletal pain               |                  |                 |  |
| subjects affected / exposed        | 14 / 181 (7.73%) | 0 / 27 (0.00%)  |  |
| occurrences (all)                  | 15               | 0               |  |
| Infections and infestations        |                  |                 |  |
| Conjunctivitis                     |                  |                 |  |
| subjects affected / exposed        | 0 / 181 (0.00%)  | 3 / 27 (11.11%) |  |
| occurrences (all)                  | 0                | 3               |  |
| Folliculitis                       |                  |                 |  |
| subjects affected / exposed        | 18 / 181 (9.94%) | 3 / 27 (11.11%) |  |
| occurrences (all)                  | 24               | 3               |  |
| Oral candidiasis                   |                  |                 |  |
| subjects affected / exposed        | 0 / 181 (0.00%)  | 2 / 27 (7.41%)  |  |
| occurrences (all)                  | 0                | 2               |  |
| Rash pustular                      |                  |                 |  |
| subjects affected / exposed        | 0 / 181 (0.00%)  | 3 / 27 (11.11%) |  |
| occurrences (all)                  | 0                | 3               |  |
| Skin infection                     |                  |                 |  |
| subjects affected / exposed        | 0 / 181 (0.00%)  | 2 / 27 (7.41%)  |  |
| occurrences (all)                  | 0                | 2               |  |
| Urinary tract infection            |                  |                 |  |
| subjects affected / exposed        | 0 / 181 (0.00%)  | 3 / 27 (11.11%) |  |
| occurrences (all)                  | 0                | 6               |  |
| Metabolism and nutrition disorders |                  |                 |  |
| Decreased appetite                 |                  |                 |  |

|                             |                   |                  |  |
|-----------------------------|-------------------|------------------|--|
| subjects affected / exposed | 50 / 181 (27.62%) | 10 / 27 (37.04%) |  |
| occurrences (all)           | 56                | 15               |  |
| Dehydration                 |                   |                  |  |
| subjects affected / exposed | 0 / 181 (0.00%)   | 2 / 27 (7.41%)   |  |
| occurrences (all)           | 0                 | 2                |  |
| Hyperglycaemia              |                   |                  |  |
| subjects affected / exposed | 0 / 181 (0.00%)   | 2 / 27 (7.41%)   |  |
| occurrences (all)           | 0                 | 3                |  |
| Hypoalbuminaemia            |                   |                  |  |
| subjects affected / exposed | 0 / 181 (0.00%)   | 2 / 27 (7.41%)   |  |
| occurrences (all)           | 0                 | 2                |  |
| Hypokalaemia                |                   |                  |  |
| subjects affected / exposed | 18 / 181 (9.94%)  | 5 / 27 (18.52%)  |  |
| occurrences (all)           | 20                | 7                |  |
| Hyponatraemia               |                   |                  |  |
| subjects affected / exposed | 0 / 181 (0.00%)   | 2 / 27 (7.41%)   |  |
| occurrences (all)           | 0                 | 4                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 09 August 2012  | Cohort 3 was split into two – the pre-existing Cohort 3a - vemurafenib only, and a new Cohort 3b - combination therapy with vemurafenib and cetuximab. The protocol was amended to include rationale for vemurafenib and cetuximab treatment in this cohort.  |
| 18 March 2014   | Additional subjects (up to 70 subjects in total) were allowed to be recruited into a study cohort if a promising response rate was demonstrated in Stage II of that cohort. The exploratory objectives for the study were revised.  |
| 16 January 2015 | The secondary objectives were changed to include the evaluation of tumor assessment scans by an independent review committee (IRC) for Cohort 1 (NSCLC) and other cohorts that demonstrate clinically meaningful efficacy per investigator assessment. The presence of BRAF V600 mutations could be retrospectively confirmed. Inclusion criteria for all subjects were changed to include male or female $\geq 16$ years of age. Inclusion criteria for solid tumors and multiple myeloma were changed so that in order for the subject to be eligible, they must be able to provide a tumor sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation by a central laboratory. IRC assessment of response rates was added a secondary efficacy endpoint focusing on Week 8, Week 16 and BOR for Cohort 1 (NSCLC) and other cohorts that demonstrate clinically meaningful efficacy per investigator assessment. |
| 24 March 2016   | Prior to the closure of the trial or should the study be closed due to Sponsor decision, it was added that the Sponsor may offer subjects who have completed the protocol-mandated minimum 12-month safety follow-up and who continue to benefit from vemurafenib therapy, the opportunity to receive continued vemurafenib via enrollment in the GO28399 extension trial. The interim analysis was changed to add efficacy analysis at 9 months for expanded cohorts. In case a cohort/indication is expanded up to 70 subjects, the primary analysis for efficacy will occur once all subjects have been followed up for 9 months after last subject had been enrolled in that cohort, or the subject develops progressive disease, withdraws consent, or is lost to follow-up, whichever occurred first.   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported