



## Clinical trial results:

**Ensayo clínico fase II de un solo brazo, multicéntrico y prospectivo para la validación de biomarcadores en pacientes con cáncer colorrectal avanzado y/o metastásico con gen KRAS no mutado tratados con quimioterapia más cetuximab bisemanal como terapia de primera línea.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2010-019236-12 |
| Trial protocol           | ES             |
| Global end of trial date | 20 June 2017   |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 02 June 2021 |
| First version publication date | 02 June 2021 |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | GEMCAD-1002 |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01276379 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Grupo Español Multidisciplinar en Cáncer Digestivo (GEMCAD)  |
| Sponsor organisation address | Ronda General Mitre 200, entresuelo 3a, Barcelona, Spain,  |
| Public contact               | Joan Maurel Santasusana, Grupo Español Multidisciplinar en Cáncer Digestivo (GEMCAD), jmaurel@clinic.cat |
| Scientific contact           | Joan Maurel Santasusana, Grupo Español Multidisciplinar en Cáncer Digestivo (GEMCAD), jmaurel@clinic.cat |

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                       | 29 January 2019 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 15 March 2017   |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 20 June 2017    |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

Validación de los biomarcadores BRAF, IGF1P/MMp7 (DP) y PI3K-PTEN para predecir la SLP en pacientes con cáncer colorrectal avanzado y/o metastásico con KRAS no mutado tratados con quimioterapia estándar más cetuximab bisemanal como terapia de primera línea.

Identificar nuevos biomarcadores que puedan predecir la supervivencia libre de progresión (SLP) en pacientes KRAS no mutado tratados con quimioterapia (QT) y cetuximab bisemanal en terapia de primera línea.

La necesidad de identificar biomarcadores adicionales de la eficacia de cetuximab proviene del pequeño valor predictivo de la clasificación actual, basada en el estado mutacional de KRAS, de la eficacia de la administración de cetuximab bisemanal en el grupo de pacientes de la enfermedad a estudio.

Los biomarcadores propuestos son:

- 1.Mutaciones BRAF
- 2.IGF-1Rp/MMP-7 (DP)
- 3.PIK3CA-PTEN.

Protection of trial subjects:

The protocol provided all measures needed to grant the integrity of human patients enrolled and the conservation of their rights.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 27 June 2011 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Spain: 221 |
| Worldwide total number of subjects   | 221        |
| EEA total number of subjects         | 221        |

Notes:

### Subjects enrolled per age group

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

|                           |     |
|---------------------------|-----|
| months)                   |     |
| Children (2-11 years)     | 0   |
| Adolescents (12-17 years) | 0   |
| Adults (18-64 years)      | 221 |
| From 65 to 84 years       | 0   |
| 85 years and over         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

221 recruited, 40 do not comply with all protocol specifications, total of 181 patients enrolled and evaluable

### Pre-assignment

Screening details:

221 recruited, 40 do not comply with all protocol specifications, total of 181 patients enrolled and evaluable

### Period 1

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

Blinding implementation details:

Single-arm

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| Arm title                    | BRAF WT |

Arm description:

FOLFIRI (m): FOLFIRI (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:

- Irinotecan 180 mg/m<sup>2</sup> in infusion i.v., 120 minutes, on day 1 of each cycle.
- I-Leucovorin 200 mg/m<sup>2</sup> (or d,l-leucovorin 400 mg/m<sup>2</sup>), in infusion i.v., 120 minutes, on day 1.
- One bolus i.v. (2-4 minutes) of 400 mg/m<sup>2</sup> of 5-FU on day 1.
- 5-FU in continuous infusion (2400 mg/m<sup>2</sup>) administered through an ambulatory pump during 46-48 hours.

FOLFOX-6 (m): FOLFOX6 (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:

- Oxaliplatin 85 mg/m<sup>2</sup> in infusion i.v., 120 minutes, on day 1 of each cycle.
- I-Leucovorin 200 mg/m<sup>2</sup> (or d,l-leucovorin 400 mg/m<sup>2</sup>) in infusion i.v., 120 minutes, on day 1.
- One bolus i.v. (2-4 minutes) of 400 mg/m<sup>2</sup> of 5-FU on day 1.
- 5-FU in continuous infusion (2400 mg/m<sup>2</sup>) administered through an ambulatory pump during 46-48 hours.

Cetuximab: - 500 mg/m<sup>2</sup> i.v. Every 2 weeks.

|  |   |
|--|---|
| Arm type                               | Experimental                            |
| Investigational medicinal product name | FOLFIRI                                 |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate for solution for infusion   |
| Routes of administration               | Intravenous bolus use , Intravenous use |

Dosage and administration details:

administered on day 1 of each 14-days-cycle. The administered doses will be: - Irinotecan 180 mg/m<sup>2</sup> in infusion i.v., 120 minutes, on day 1 of each cycle. - I-Leucovorin 200 mg/ m<sup>2</sup> (or d,l-leucovorin 400 mg/m<sup>2</sup>), in infusion i.v., 120 minutes, on day 1.- One bolus i.v. (2-4 minutes) of 400 mg/m<sup>2</sup> of 5-FU on day 1. - 5-FU in continuous infusion (2400 mg/m<sup>2</sup>) administered through an ambulatory pump during 46-48 hours

|  |  |
|--|--|
| Investigational medicinal product name | FOLFOX                                 |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Concentrate for solution for infusion  |
| Routes of administration               | Intravenous use, Intravenous bolus use |

**Dosage and administration details:**

Administered on day 1 of each 14-days-cycle. The administered doses will be: -Oxaliplatin 85 mg/m<sup>2</sup> in infusion i.v., 120 minutes, on day 1 of each cycle. - I-Leucovorin 200 mg/m<sup>2</sup> (or d,l-leucovorin 400 mg/m<sup>2</sup>) in infusion i.v., 120 minutes, on day 1. -One bolus i.v. (2-4 minutes) of 400 mg/m<sup>2</sup> of 5-FU on day 1. -5-FU in continuous infusion (2400 mg/m<sup>2</sup>) administered through an ambulatory pump during 46-48 hours

|  |                       |
|--|-----------------------|
| 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:**

500 mg/m<sup>2</sup> i.v. Every 2 weeks.

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Mutant BRAF |
|------------------|-------------|

**Arm description:**

FOLFIRI (m): FOLFIRI (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:

- Irinotecan 180 mg/m<sup>2</sup> in infusion i.v., 120 minutes, on day 1 of each cycle.
- I-Leucovorin 200 mg/m<sup>2</sup> (or d,l-leucovorin 400 mg/m<sup>2</sup>), in infusion i.v., 120 minutes, on day 1.
- One bolus i.v. (2-4 minutes) of 400 mg/m<sup>2</sup> of 5-FU on day 1.
- 5-FU in continuous infusion (2400 mg/m<sup>2</sup>) administered through an ambulatory pump during 46-48 hours.

FOLFOX-6 (m): FOLFOX6 (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:

- Oxaliplatin 85 mg/m<sup>2</sup> in infusion i.v., 120 minutes, on day 1 of each cycle.
- I-Leucovorin 200 mg/m<sup>2</sup> (or d,l-leucovorin 400 mg/m<sup>2</sup>) in infusion i.v., 120 minutes, on day 1.
- One bolus i.v. (2-4 minutes) of 400 mg/m<sup>2</sup> of 5-FU on day 1.
- 5-FU in continuous infusion (2400 mg/m<sup>2</sup>) administered through an ambulatory pump during 46-48 hours.

Cetuximab: - 500 mg/m<sup>2</sup> i.v. Every 2 weeks.

|  |  |
|--|--|
| Arm type                               | Experimental                           |
| Investigational medicinal product name | FOLFIRI                                |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Concentrate for solution for infusion  |
| Routes of administration               | Intravenous use, Intravenous bolus use |

**Dosage and administration details:**

administered on day 1 of each 14-days-cycle. The administered doses will be: - Irinotecan 180 mg/m<sup>2</sup> in infusion i.v., 120 minutes, on day 1 of each cycle. - I-Leucovorin 200 mg/m<sup>2</sup> (or d,l-leucovorin 400 mg/m<sup>2</sup>), in infusion i.v., 120 minutes, on day 1.- One bolus i.v. (2-4 minutes) of 400 mg/m<sup>2</sup> of 5-FU on day 1. - 5-FU in continuous infusion (2400 mg/m<sup>2</sup>) administered through an ambulatory pump during 46-48 hours

|  |   |
|--|---|
| Investigational medicinal product name | FOLFOX                                  |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate for solution for infusion   |
| Routes of administration               | Intravenous bolus use , Intravenous use |

**Dosage and administration details:**

Administered on day 1 of each 14-days-cycle. The administered doses will be: -Oxaliplatin 85 mg/m<sup>2</sup> in infusion i.v., 120 minutes, on day 1 of each cycle. - I-Leucovorin 200 mg/m<sup>2</sup> (or d,l-leucovorin 400 mg/m<sup>2</sup>) in infusion i.v., 120 minutes, on day 1. -One bolus i.v. (2-4 minutes) of 400 mg/m<sup>2</sup> of 5-FU on day 1. -5-FU in continuous infusion (2400 mg/m<sup>2</sup>) administered through an ambulatory pump during 46-48 hours

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

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Dosage and administration details:

500 mg/m<sup>2</sup> i.v. Every 2 weeks.

| Number of subjects in period<br>1 <sup>[1]</sup> | BRAF WT | Mutant BRAF |
|--|---------|-------------|
|  |         |             |
| Started  | 161     | 20          |
| Completed  | 161     | 20          |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 221 recruited, 40 do not comply with all protocol specifications, total of 181 patients enrolled and evaluable

## Baseline characteristics

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | BRAF WT |
|-----------------------|---------|

Reporting group description:

FOLFIRI (m): FOLFIRI (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:

- Irinotecan 180 mg/m<sup>2</sup> in infusion i.v., 120 minutes, on day 1 of each cycle.
- I-Leucovorin 200 mg/m<sup>2</sup> (or d,l-leucovorin 400 mg/m<sup>2</sup>), in infusion i.v., 120 minutes, on day 1.
- One bolus i.v. (2-4 minutes) of 400 mg/m<sup>2</sup> of 5-FU on day 1.
- 5-FU in continuous infusion (2400 mg/m<sup>2</sup>) administered through an ambulatory pump during 46-48 hours.

FOLFOX-6 (m): FOLFOX6 (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:

- Oxaliplatin 85 mg/m<sup>2</sup> in infusion i.v., 120 minutes, on day 1 of each cycle.
- I-Leucovorin 200 mg/m<sup>2</sup> (or d,l-leucovorin 400 mg/m<sup>2</sup>) in infusion i.v., 120 minutes, on day 1.
- One bolus i.v. (2-4 minutes) of 400 mg/m<sup>2</sup> of 5-FU on day 1.
- 5-FU in continuous infusion (2400 mg/m<sup>2</sup>) administered through an ambulatory pump during 46-48 hours.

Cetuximab: - 500 mg/m<sup>2</sup> i.v. Every 2 weeks.

|                       |             |
|-----------------------|-------------|
| Reporting group title | Mutant BRAF |
|-----------------------|-------------|

Reporting group description:

FOLFIRI (m): FOLFIRI (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:

- Irinotecan 180 mg/m<sup>2</sup> in infusion i.v., 120 minutes, on day 1 of each cycle.
- I-Leucovorin 200 mg/m<sup>2</sup> (or d,l-leucovorin 400 mg/m<sup>2</sup>), in infusion i.v., 120 minutes, on day 1.
- One bolus i.v. (2-4 minutes) of 400 mg/m<sup>2</sup> of 5-FU on day 1.
- 5-FU in continuous infusion (2400 mg/m<sup>2</sup>) administered through an ambulatory pump during 46-48 hours.

FOLFOX-6 (m): FOLFOX6 (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:

- Oxaliplatin 85 mg/m<sup>2</sup> in infusion i.v., 120 minutes, on day 1 of each cycle.
- I-Leucovorin 200 mg/m<sup>2</sup> (or d,l-leucovorin 400 mg/m<sup>2</sup>) in infusion i.v., 120 minutes, on day 1.
- One bolus i.v. (2-4 minutes) of 400 mg/m<sup>2</sup> of 5-FU on day 1.
- 5-FU in continuous infusion (2400 mg/m<sup>2</sup>) administered through an ambulatory pump during 46-48 hours.

Cetuximab: - 500 mg/m<sup>2</sup> i.v. Every 2 weeks.

| Reporting group values                                | BRAF WT | Mutant BRAF | Total |
|---|---------|-------------|-------|
| Number of subjects                                    | 161     | 20          | 181   |
| Age categorical<br>Units: Subjects                    |         |             |       |
| In utero  |         |             | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) |         |             | 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)                                  |         |             | 0     |
| From 65-84 years                                      |         |             | 0     |
| 85 years and over                                     |         |             | 0     |
| Age continuous<br>Units: years                        |         |             |       |
| arithmetic mean                                       | 62      | 67          |       |
| standard deviation                                    | ± 10.5  | ± 7.4       | -     |

|  |     |    |     |
|--|-----|----|-----|
| Gender categorical   |     |    |     |
| Units: Subjects  |     |    |     |
| Female   | 46  | 7  | 53  |
| Male   | 115 | 13 | 128 |
| Stage  |     |    |     |
| Measure Description: The stage of a cancer describes the size and spread of a tumour:<br>stage I – The cancer has grown through the mucosa and has invaded the muscular layer of the colon or rectum.<br>stage II – The cancer has grown through the wall of the colon or rectum stage III – The cancer has grown through the inner lining or into the muscle layers of the intestine. It has spread to lymph nodes stage IV – The cancer has spread to a distant part of the body |     |    |     |
| Units: Subjects  |     |    |     |
| Stage I  | 1   | 0  | 1   |
| Stage II   | 13  | 0  | 13  |
| Stage III  | 30  | 5  | 35  |
| Stage IV   | 117 | 15 | 132 |
| Primary location   |     |    |     |
| Measure Description: Part of the colon where the primary tumor was located   |     |    |     |
| Units: Subjects  |     |    |     |
| Ascending colon  | 23  | 9  | 32  |
| Transverse colon   | 12  | 2  | 14  |
| Descending colon   | 10  | 4  | 14  |
| Sigmoid colon  | 73  | 3  | 76  |
| Rectum   | 43  | 2  | 45  |
| Surgery of the primary tumor   |     |    |     |
| Percentage of patients that had surgery for their primary colorectal tumor   |     |    |     |
| Units: Subjects  |     |    |     |
| Yes  | 91  | 10 | 101 |
| No   | 70  | 10 | 80  |
| ECOG PS  |     |    |     |
| Eastern Cooperative Oncology Group (ECOG) performance status (PS). ECOG scale measures the performance status of a patients. It ranges from 0 (fully active, able to carry on all pre-disease performance without restriction) to 5 (death).   |     |    |     |
| Units: Subjects  |     |    |     |
| ECOG 0   | 112 | 7  | 119 |
| ECOG 1   | 49  | 13 | 62  |
| Number of metastatic organs  |     |    |     |
| Percentage of patients presenting metastasis in one or more distant organs. The number of patients with 1,2, 3 or more than 4 affected organs are reported   |     |    |     |
| Units: Subjects  |     |    |     |
| 1 organ  | 87  | 7  | 94  |
| 2 organs   | 58  | 11 | 69  |
| 3 organs   | 15  | 2  | 17  |
| 4 or higher organs   | 1   | 0  | 1   |



## End points

### End points reporting groups

|   |             |
|---|-------------|
| Reporting group title   | BRAF WT     |
| Reporting group description:  |             |
| FOLFIRI (m): FOLFIRI (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:  |             |
| <ul style="list-style-type: none"><li>• Irinotecan 180 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.</li><li>• I-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2), in infusion i.v., 120 minutes, on day 1.</li><li>• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.</li><li>• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.</li></ul> |             |
| FOLFOX-6 (m): FOLFOX6 (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:   |             |
| <ul style="list-style-type: none"><li>• Oxaliplatin 85 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.</li><li>• I-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2) in infusion i.v., 120 minutes, on day 1.</li><li>• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.</li><li>• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.</li></ul>  |             |
| Cetuximab: - 500 mg/m2 i.v. Every 2 weeks.  |             |
| Reporting group title   | Mutant BRAF |
| Reporting group description:  |             |
| FOLFIRI (m): FOLFIRI (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:  |             |
| <ul style="list-style-type: none"><li>• Irinotecan 180 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.</li><li>• I-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2), in infusion i.v., 120 minutes, on day 1.</li><li>• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.</li><li>• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.</li></ul> |             |
| FOLFOX-6 (m): FOLFOX6 (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:   |             |
| <ul style="list-style-type: none"><li>• Oxaliplatin 85 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.</li><li>• I-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2) in infusion i.v., 120 minutes, on day 1.</li><li>• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.</li><li>• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.</li></ul>  |             |
| Cetuximab: - 500 mg/m2 i.v. Every 2 weeks.  |             |

### Primary: Progression free survival (PFS)

|   |                                 |
|---|---------------------------------|
| End point title   | Progression free survival (PFS) |
| End point description:  |                                 |
| Measurements according to RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors). Main techniques: CTscan. Two groups will be defined based on the score built from the proposed clinical variables and biomarkers. Instead of a binomial distribution, a Log-rank method has been used to calculate the sample size in order to include all the incidents during the follow-up. Expecting a minimum 20% difference (60 vs. 40%) on PFS at 12 months between groups and with the following assumptions: Alpha error (bilateral): 5% Beta error: 20% |                                 |
| End point type  | Primary                         |
| End point timeframe:  |                                 |
| 4 years   |                                 |

| End point values                 | BRAF WT            | Mutant BRAF      |  |  |
|----------------------------------|--------------------|------------------|--|--|
| Subject group type               | Reporting group    | Reporting group  |  |  |
| Number of subjects analysed      | 161                | 20               |  |  |
| Units: Months                    |                    |                  |  |  |
| median (confidence interval 95%) | 11.4 (9.9 to 13.1) | 5.9 (3.3 to 7.8) |  |  |

## Statistical analyses

| Statistical analysis title              | Log rank               |
|---|------------------------|
| Comparison groups                       | BRAF WT v Mutant BRAF  |
| Number of subjects included in analysis | 181                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.004 <sup>[1]</sup> |
| Method                                  | Logrank                |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 2.01                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 1.23                   |
| upper limit                             | 3.29                   |

Notes:

[1] - If pvalue <0.05 the null hypothesis is discarded and we assume there are statistically significant differences between groups

## Secondary: Overall Survival (OS)

| End point title                                  | Overall Survival (OS) |
|--|-----------------------|
| End point description:                           |                       |
| Proportion of patients alive at the end of study |                       |
| End point type                                   | Secondary             |
| End point timeframe:                             |                       |
| 4 years  |                       |

| End point values                 | BRAF WT             | Mutant BRAF     |  |  |
|----------------------------------|---------------------|-----------------|--|--|
| Subject group type               | Reporting group     | Reporting group |  |  |
| Number of subjects analysed      | 161                 | 20              |  |  |
| Units: Months                    |                     |                 |  |  |
| median (confidence interval 95%) | 32.6 (27.5 to 38.8) | 9.3 (5.3 to 22) |  |  |

## Statistical analyses

|   |                         |
|---|-------------------------|
| <b>Statistical analysis title</b>       | Log rank                |
| Comparison groups                       | BRAF WT v Mutant BRAF   |
| Number of subjects included in analysis | 181                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.0001 <sup>[2]</sup> |
| Method                                  | Logrank                 |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 2.29                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 1.33                    |
| upper limit                             | 3.96                    |

Notes:

[2] - If p-value was lower than  $P < 0.05$  the null hypothesis was discarded and it is assumed that there are statistically significant differences among the groups

### Secondary: Duration of response

|   |                      |
|---|----------------------|
| End point title   | Duration of response |
| End point description:  |                      |
| Duration of the partial or total response to the treatment. Evaluation and classification according to RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors) |                      |
| End point type  | Secondary            |
| End point timeframe:  |                      |
| 4 years   |                      |

| End point values              | BRAF WT              | Mutant BRAF          |  |  |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type            | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed   | 161                  | 20                   |  |  |
| Units: months                 |                      |                      |  |  |
| median (full range (min-max)) | 8.66 (1.16 to 53.49) | 8.66 (1.16 to 53.49) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Tumoral response

|  |                  |
|--|------------------|
| End point title  | Tumoral response |
| End point description:   |                  |
| Measurements according to RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors). Main techniques: CT scan |                  |
| End point type   | Secondary        |
| End point timeframe:   |                  |
| 4 years  |                  |

| <b>End point values</b>     | BRAF WT         | Mutant BRAF     |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 161             | 20              |  |  |
| Units: Patients             |                 |                 |  |  |
| Complete response (CR)      | 16              | 1               |  |  |
| Partial response (PR)       | 106             | 6               |  |  |
| Stable disease (SD)         | 25              | 6               |  |  |
| Pogression disease (PD)     | 8               | 4               |  |  |
| Not evaluable (NE)          | 6               | 3               |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

4 years

Adverse event reporting additional description:

Safety assessments included patient history and physical examinations, vital signs, ECOG PS, AEs, blood chemistry, and blood counts at each visit.

AE severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0. Relation to cetuximab or chemotherapy assessed by PI

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

### Dictionary used

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

|                    |     |
|--------------------|-----|
| Dictionary version | 3.0 |
|--------------------|-----|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Safety population |
|-----------------------|-------------------|

Reporting group description: -

| Serious adverse events                               | Safety population  |  |  |
|--|--------------------|--|--|
| Total subjects affected by serious adverse events    |                    |  |  |
| subjects affected / exposed                          | 173 / 218 (79.36%) |  |  |
| number of deaths (all causes)                        | 136                |  |  |
| number of deaths resulting from adverse events       | 12                 |  |  |
| Vascular disorders                                   |                    |  |  |
| Vascular disorders NOS                               |                    |  |  |
| subjects affected / exposed                          | 10 / 218 (4.59%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 10             |  |  |
| deaths causally related to treatment / all           | 0 / 4              |  |  |
| General disorders and administration site conditions |                    |  |  |
| Asthenia   |                    |  |  |
| subjects affected / exposed                          | 19 / 218 (8.72%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 19             |  |  |
| deaths causally related to treatment / all           | 0 / 0              |  |  |
| Edema  |                    |  |  |
| subjects affected / exposed                          | 1 / 218 (0.46%)    |  |  |
| occurrences causally related to treatment / all      | 0 / 1              |  |  |
| deaths causally related to treatment / all           | 0 / 0              |  |  |
| Fever  |                    |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 218 (0.46%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| General site reactions NOS                      |                 |  |  |
| subjects affected / exposed                     | 2 / 218 (0.92%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pain  |                 |  |  |
| subjects affected / exposed                     | 2 / 218 (0.92%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hand foot syndrome                              |                 |  |  |
| subjects affected / exposed                     | 1 / 218 (0.46%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| multiorgan failure                              |                 |  |  |
| subjects affected / exposed                     | 2 / 218 (0.92%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 2           |  |  |
| Immune system disorders                         |                 |  |  |
| Allergic reaction to excipient                  |                 |  |  |
| subjects affected / exposed                     | 7 / 218 (3.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 7           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Respiratory disorders NOS                       |                 |  |  |
| subjects affected / exposed                     | 6 / 218 (2.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 6           |  |  |
| deaths causally related to treatment / all      | 0 / 3           |  |  |
| Cardiac disorders                               |                 |  |  |
| Cardiac disorders NOS                           |                 |  |  |
| subjects affected / exposed                     | 2 / 218 (0.92%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| Nervous system disorders                        |                   |  |  |
| Neuropathy                                      |                   |  |  |
| subjects affected / exposed                     | 5 / 218 (2.29%)   |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Paresthesia                                     |                   |  |  |
| subjects affected / exposed                     | 5 / 218 (2.29%)   |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Blood and lymphatic system disorders            |                   |  |  |
| Febrile neutropenia                             |                   |  |  |
| subjects affected / exposed                     | 5 / 218 (2.29%)   |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Leucocytopenia                                  |                   |  |  |
| subjects affected / exposed                     | 4 / 218 (1.83%)   |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Neutropenia                                     |                   |  |  |
| subjects affected / exposed                     | 53 / 218 (24.31%) |  |  |
| occurrences causally related to treatment / all | 0 / 53            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Thrombocytopenia                                |                   |  |  |
| subjects affected / exposed                     | 3 / 218 (1.38%)   |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Eye disorders                                   |                   |  |  |
| Ocular alterations                              |                   |  |  |
| subjects affected / exposed                     | 1 / 218 (0.46%)   |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Ocular disorders                                |                   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 3 / 218 (1.38%)   |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastrointestinal disorders                      |                   |  |  |
| Abdominal pain                                  |                   |  |  |
| subjects affected / exposed                     | 3 / 218 (1.38%)   |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Ascites   |                   |  |  |
| subjects affected / exposed                     | 1 / 218 (0.46%)   |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Constipation                                    |                   |  |  |
| subjects affected / exposed                     | 2 / 218 (0.92%)   |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Diarrhoea                                       |                   |  |  |
| subjects affected / exposed                     | 28 / 218 (12.84%) |  |  |
| occurrences causally related to treatment / all | 0 / 28            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Fistula   |                   |  |  |
| subjects affected / exposed                     | 7 / 218 (3.21%)   |  |  |
| occurrences causally related to treatment / all | 0 / 7             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastrointestinal disorders NOS                  |                   |  |  |
| subjects affected / exposed                     | 5 / 218 (2.29%)   |  |  |
| occurrences causally related to treatment / all | 0 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Intestinal obstruction                          |                   |  |  |
| subjects affected / exposed                     | 10 / 218 (4.59%)  |  |  |
| occurrences causally related to treatment / all | 0 / 10            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Mucoitis  |                   |  |  |



|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 11 / 218 (5.05%)  |  |  |
| occurrences causally related to treatment / all | 0 / 11            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Nausea  |                   |  |  |
| subjects affected / exposed                     | 9 / 218 (4.13%)   |  |  |
| occurrences causally related to treatment / all | 0 / 9             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Rectal bleeding                                 |                   |  |  |
| subjects affected / exposed                     | 1 / 218 (0.46%)   |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hepatobiliary disorders                         |                   |  |  |
| hepatic toxicity                                |                   |  |  |
| subjects affected / exposed                     | 3 / 218 (1.38%)   |  |  |
| occurrences causally related to treatment / all | 0 / 3             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Transaminitis                                   |                   |  |  |
| subjects affected / exposed                     | 2 / 218 (0.92%)   |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Skin and subcutaneous tissue disorders          |                   |  |  |
| Alopecia  |                   |  |  |
| subjects affected / exposed                     | 4 / 218 (1.83%)   |  |  |
| occurrences causally related to treatment / all | 0 / 4             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Skin reaction                                   |                   |  |  |
| subjects affected / exposed                     | 29 / 218 (13.30%) |  |  |
| occurrences causally related to treatment / all | 0 / 29            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Xerosis   |                   |  |  |
| subjects affected / exposed                     | 8 / 218 (3.67%)   |  |  |
| occurrences causally related to treatment / all | 0 / 8             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Renal and urinary disorders                     |                   |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Urinary disorders NOS                           |                 |  |  |
| subjects affected / exposed                     | 4 / 218 (1.83%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Musculoskeletal disorders NOS                   |                 |  |  |
| subjects affected / exposed                     | 5 / 218 (2.29%) |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Infections                                      |                 |  |  |
| subjects affected / exposed                     | 9 / 218 (4.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 9           |  |  |
| deaths causally related to treatment / all      | 0 / 3           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Anemia  |                 |  |  |
| subjects affected / exposed                     | 4 / 218 (1.83%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Anorexia  |                 |  |  |
| subjects affected / exposed                     | 2 / 218 (0.92%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolic disorders NOS                         |                 |  |  |
| subjects affected / exposed                     | 6 / 218 (2.75%) |  |  |
| occurrences causally related to treatment / all | 0 / 6           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

|   |                    |  |  |
|---|--------------------|--|--|
| <b>Non-serious adverse events</b>                     | Safety population  |  |  |
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 198 / 218 (90.83%) |  |  |
| Vascular disorders                                    |                    |  |  |

|  |  |  |  |
|--|--|--|--|
| Vascular disorders NOS<br>subjects affected / exposed<br>occurrences (all)   | 12 / 218 (5.50%)<br>12   |  |  |
| General disorders and administration<br>site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Fever<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain NOS<br>subjects affected / exposed<br>occurrences (all) | 101 / 218 (46.33%)<br>101<br><br>25 / 218 (11.47%)<br>25<br><br>21 / 218 (9.63%)<br>21 |  |  |
| Respiratory, thoracic and mediastinal<br>disorders<br>Respiratory disorders NOS<br>subjects affected / exposed<br>occurrences (all)  | 29 / 218 (13.30%)<br>29  |  |  |
| Psychiatric disorders<br>Psychiatric disorders NOS<br>subjects affected / exposed<br>occurrences (all)   | 12 / 218 (5.50%)<br>12   |  |  |
| Congenital, familial and genetic<br>disorders<br>Trichomegaly<br>subjects affected / exposed<br>occurrences (all)  | 11 / 218 (5.05%)<br>11   |  |  |
| Nervous system disorders<br>Dysgeusia<br>subjects affected / exposed<br>occurrences (all)<br><br>Neuropathy<br>subjects affected / exposed<br>occurrences (all)<br><br>Paresthesia<br>subjects affected / exposed<br>occurrences (all)                       | 22 / 218 (10.09%)<br>22<br><br>72 / 218 (33.03%)<br>72<br><br>45 / 218 (20.64%)<br>45  |  |  |
| Blood and lymphatic system disorders   |  |  |  |

|  |                         |  |  |
|--|-------------------------|--|--|
| Anemia<br>subjects affected / exposed<br>occurrences (all)                                       | 34 / 218 (15.60%)<br>34 |  |  |
| Leucopenia<br>subjects affected / exposed<br>occurrences (all)                                   | 16 / 218 (7.34%)<br>16  |  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                                  | 37 / 218 (16.97%)<br>37 |  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                             | 22 / 218 (10.09%)<br>22 |  |  |
| Eye disorders<br>Ocular disorders NOS<br>subjects affected / exposed<br>occurrences (all)        | 24 / 218 (11.01%)<br>24 |  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all) | 28 / 218 (12.84%)<br>28 |  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                 | 40 / 218 (18.35%)<br>40 |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                    | 80 / 218 (36.70%)<br>80 |  |  |
| Fistula<br>subjects affected / exposed<br>occurrences (all)                                      | 47 / 218 (21.56%)<br>47 |  |  |
| Mucosa dryness<br>subjects affected / exposed<br>occurrences (all)                               | 13 / 218 (5.96%)<br>13  |  |  |
| Mucositis<br>subjects affected / exposed<br>occurrences (all)                                    | 87 / 218 (39.91%)<br>87 |  |  |
| Nausea   |                         |  |  |

|  |                           |  |  |
|--|---------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)   | 60 / 218 (27.52%)<br>60   |  |  |
| Gastrointestinal disorders NOS<br>subjects affected / exposed<br>occurrences (all)   | 40 / 218 (18.35%)<br>40   |  |  |
| Hepatobiliary disorders<br>Transaminitis<br>subjects affected / exposed<br>occurrences (all)   | 13 / 218 (5.96%)<br>13    |  |  |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all)                               | 29 / 218 (13.30%)<br>29   |  |  |
| Cutaneous reaction<br>subjects affected / exposed<br>occurrences (all)   | 134 / 218 (61.47%)<br>134 |  |  |
| Xerosis<br>subjects affected / exposed<br>occurrences (all)  | 36 / 218 (16.51%)<br>36   |  |  |
| Renal and urinary disorders<br>Urinary disorders NOS<br>subjects affected / exposed<br>occurrences (all)                             | 13 / 218 (5.96%)<br>13    |  |  |
| Musculoskeletal and connective tissue disorders<br>Musculoskeletal disorders NOS<br>subjects affected / exposed<br>occurrences (all) | 20 / 218 (9.17%)<br>20    |  |  |
| Infections and infestations<br>Infections NOS<br>subjects affected / exposed<br>occurrences (all)                                    | 17 / 218 (7.80%)<br>17    |  |  |
| Metabolism and nutrition disorders<br>Anorexia and bulimia syndrome<br>subjects affected / exposed<br>occurrences (all)              | 27 / 218 (12.39%)<br>27   |  |  |
| Metabolic disorders NOS  |                           |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 36 / 218 (16.51%) |  |  |
| occurrences (all)           | 36                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment |
|------------------|-----------|
| 24 February 2011 | NA        |
| 13 July 2011     | NA        |
| 15 December 2011 | NA        |
| 17 April 2012    | NA        |
| 14 December 2012 | NA        |
| 18 April 2013    | NA        |
| 15 May 2013      | NA        |
| 04 July 2014     | NA        |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported