



Clinical trial results:

Estudio abierto fase II de ultra-selección de pacientes mediante tecnología de genotipado de nueva generación para el esquema FOLFIRI + Panitumumab en pacientes con cáncer colorrectal estadio IV resistentes a irinotecán sin mutaciones detectables utilizando técnicas de alta sensibilidad para la detección de mutaciones en los genes KRAS, PIK3Ca, BRAF y NRAS

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-001955-38 |
| Trial protocol | ES |
| Global end of trial date | 30 July 2016 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 02 July 2020 |
| First version publication date | 02 July 2020 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | TTD-12-03 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01704703 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Grupo de Tratamiento de los Tumores Digestivos (TTD) |
| Sponsor organisation address | C/ Téllez Nº 30 posterior 1º oficina 4.2, Madrid, Spain, 28007 |
| Public contact | TTD, Grupo de Tratamiento de los Tumores Digestivos (TTD), 0034 91 378 82 75, ttd@ttdgroup.org |
| Scientific contact | TTD, Grupo de Tratamiento de los Tumores Digestivos (TTD), 0034 91 378 82 75, ttd@ttdgroup.org |

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 | 30 May 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 July 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 July 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To estimate the effect of the combination of panitumumab with FOLFIRI on objective response rate defined as complete and partial response according RECIST criteria 1.1, in patients with metastatic colorectal cancer (mCRC) refractory to irinotecan-based chemotherapy without any mutation associated to resistance on KRAS, PIK3Ca (exon 20), BRAF and NRAS genes detected with hypersensitive techniques (Digital PCR in Fluidigm nanofluidic dPCR platform), named as molecular ultra-selected subgroup.

Protection of trial subjects:

All patients have been treated according to GCP criteria. Patients were entitled to withdraw from the study at any time and for any reason without prejudice of their future medical care on the part of the doctor or the center.

Doses of panitumumab and FOLFIRI could be reduced/delayed in case of adverse events (AEs) as per protocol. Any medication that patients needed for their correct clinical control (except prohibited therapies), according to investigator's criteria were allowed.

Background therapy:

None.

Evidence for comparator:

Not applicable.

| | |
|---|------------------|
| Actual start date of recruitment | 13 November 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Spain: 72 |
| Worldwide total number of subjects | 72 |
| EEA total number of subjects | 72 |

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) | 38 |
| From 65 to 84 years | 34 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Ninety-six patients were recruited from November 2012 to July 2015, 24 of whom were screening failures. Thus, 72 patients were finally included in the study. This was a national study conducted in the Departments of Medical Oncology at 12 Spanish hospitals.

Pre-assignment

Screening details:

Patients aged ≥ 18 years with histologically confirmed colorectal adenocarcinoma, wild-type KRAS exon 2 (KRAS and NRAS exons 2/3/4 after protocol amendment on 25 July 2013), with ≥ 1 initially measurable and unresectable metastatic lesion, Karnofsky performance status $\geq 70\%$ and adequate bone marrow, renal, hepatic and metabolic functions.

Period 1

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

Blinding implementation details:

Not applicable

Arms

| | |
|-----------|-----------------------|
| Arm title | Panitumumab + FOLFIRI |
|-----------|-----------------------|

Arm description:

Patients were treated with panitumumab plus FOLFIRI.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Panitumumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Patients received panitumumab 6mg/kg over a 60-min intravenous infusion on day 1 in 2-weeks cycles.

| | |
|--|-----------------|
| Investigational medicinal product name | FOLFIRI |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

FOLFIRI was intravenously administered on day 1 in 2-week cycles according to the following schema: irinotecan 180mg/m² over 30-90-min infusion, leucovorin 400 mg/m² over 120-min infusion, 5-fluorouracil 400mg/m² bolus, 5-fluorouracil 2400 mg/m² over 46-h infusion.

| Number of subjects in period 1 | Panitumumab + FOLFIRI |
|---------------------------------------|--------------------------|
| Started | 72 |
| Completed | 71 |
| Not completed | 1 |
| Consent withdrawn by subject | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Overall period |
|-----------------------|----------------|

Reporting group description: -

| Reporting group values | Overall period | Total | |
|---|----------------|-------|--|
| Number of subjects | 72 | 72 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 38 | 38 | |
| From 65-84 years | 34 | 34 | |
| Age continuous | | | |
| Units: years | | | |
| median | 62 | | |
| full range (min-max) | 38 to 83 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 21 | 21 | |
| Male | 51 | 51 | |
| Tumour stage at initial diagnosis | | | |
| Units: Subjects | | | |
| II | 4 | 4 | |
| III | 16 | 16 | |
| IV | 52 | 52 | |
| Karnofsky performance status | | | |
| Units: Subjects | | | |
| 70-80 | 18 | 18 | |
| 90-100 | 54 | 54 | |
| Primary tumour site | | | |
| Units: Subjects | | | |
| Right colon | 10 | 10 | |
| Left colon | 31 | 31 | |
| Rectum | 31 | 31 | |
| Primary tumour surgery | | | |
| Units: Subjects | | | |
| Yes | 53 | 53 | |
| No | 19 | 19 | |
| Number of metastatic sites | | | |
| Units: Subjects | | | |
| <3 | 49 | 49 | |
| ≥3 | 23 | 23 | |
| Previous chemotherapy for colorectal cancer: adjuvant | | | |
| Units: Subjects | | | |
| Yes | 26 | 26 | |
| No | 46 | 46 | |
| Previous chemotherapy for colorectal cancer: palliative | | | |

| | | | |
|-----------------|----|----|--|
| Units: Subjects | | | |
| Yes | 72 | 72 | |
| No | 0 | 0 | |

Subject analysis sets

| | |
|----------------------------|-----------------------|
| Subject analysis set title | RAS wild-type by qPCR |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

RAS wild-type population by qPCR. This analysis set will be used for reporting efficacy results.

| Reporting group values | RAS wild-type by qPCR | | |
|---|-----------------------|--|--|
| Number of subjects | 65 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| Age continuous | | | |
| Units: years | | | |
| median | 62 | | |
| full range (min-max) | 38 to 83 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 19 | | |
| Male | 46 | | |
| Tumour stage at initial diagnosis | | | |
| Units: Subjects | | | |
| II | 4 | | |
| III | 14 | | |
| IV | 47 | | |
| Karnofsky performance status | | | |
| Units: Subjects | | | |
| 70-80 | 14 | | |
| 90-100 | 51 | | |
| Primary tumour site | | | |
| Units: Subjects | | | |
| Right colon | 9 | | |
| Left colon | 31 | | |
| Rectum | 25 | | |
| Primary tumour surgery | | | |
| Units: Subjects | | | |
| Yes | 49 | | |
| No | 16 | | |
| Number of metastatic sites | | | |
| Units: Subjects | | | |
| <3 | 45 | | |
| ≥3 | 20 | | |
| Previous chemotherapy for colorectal cancer: adjuvant | | | |
| Units: Subjects | | | |
| Yes | 25 | | |

| | | | |
|--|----|--|--|
| No | 40 | | |
| Previous chemotherapy for colorectal cancer: palliative Units: Subjects | | | |
| Yes | 65 | | |
| No | 0 | | |

End points

End points reporting groups

| | |
|---|-----------------------|
| Reporting group title | Panitumumab + FOLFIRI |
| Reporting group description: Patients were treated with panitumumab plus FOLFIRI. | |
| Subject analysis set title | RAS wild-type by qPCR |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: RAS wild-type population by qPCR. This analysis set will be used for reporting efficacy results. | |

Primary: Tumor response in the RAS wild-type population by q-PCR (N=65): RAS (KRAS + NRAS)

| | |
|---|--|
| End point title | Tumor response in the RAS wild-type population by q-PCR (N=65): RAS (KRAS + NRAS) ^[1] |
| End point description: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. | |
| End point type | Primary |
| End point timeframe: Tumor response at the end of the study | |

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: Statistical analyses (Fisher exact) within a single analysis set (N=65) for Nanofluidic dPCR results: Cut-off 0%, p=0.843; Cut-off 0.1%, p=0.745; Cut-off 1%, p=0.624; Cut-off 2%, p= 0.362; Cut-off 3%, p= 0.850; Cut-off 4%, p= 0.850; Cut-off 5%, p= 0.549.

| End point values | RAS wild-type by qPCR | | | |
|---|-----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 65 | | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| CR: Conventional qPCR, wild-type | 0.0 | | | |
| CR: Conventional qPCR, mutation | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 0%, wild-type | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 0%, mutation | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 0.1%, wild-type | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 0.1%, mutation | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 1%, wild-type | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 1%, mutation | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 2%, wild-type | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 2%, mutation | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 3%, wild-type | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 3%, mutation | 0.0 | | | |

| | | | | |
|---|------|--|--|--|
| CR: Nanofluidic dPCR, Cut-off 4%, wild-type | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 4%, mutation | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 5%, wild-type | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 5%, mutation | 0.0 | | | |
| PR: Conventional qPCR, wild-type | 47.7 | | | |
| PR: Conventional qPCR, mutation | 0.0 | | | |
| PR: Nanofluidic dPCR, Cut-off 0%, wild-type | 49.0 | | | |
| PR: Nanofluidic dPCR, Cut-off 0%, mutation | 43.8 | | | |
| PR: Nanofluidic dPCR, Cut-off 0.1%, wild-type | 50.0 | | | |
| PR: Nanofluidic dPCR, Cut-off 0.1%, mutation | 40.0 | | | |
| PR: Nanofluidic dPCR, Cut-off 1%, wild-type | 50.0 | | | |
| PR: Nanofluidic dPCR, Cut-off 1%, mutation | 33.3 | | | |
| PR: Nanofluidic dPCR, Cut-off 2%, wild-type | 50.0 | | | |
| PR: Nanofluidic dPCR, Cut-off 2%, mutation | 28.6 | | | |
| PR: Nanofluidic dPCR, Cut-off 3%, wild-type | 48.3 | | | |
| PR: Nanofluidic dPCR, Cut-off 3%, mutation | 40.0 | | | |
| PR: Nanofluidic dPCR, Cut-off 4%, wild-type | 48.3 | | | |
| PR: Nanofluidic dPCR, Cut-off 4%, mutation | 40.0 | | | |
| PR: Nanofluidic dPCR, Cut-off 5%, wild-type | 48.4 | | | |
| PR: Nanofluidic dPCR, Cut-off 5%, mutation | 33.3 | | | |
| SD: Conventional qPCR, wild-type | 36.9 | | | |
| SD: Conventional qPCR, mutation | 0.0 | | | |
| SD: Nanofluidic dPCR, Cut-off 0%, wild-type | 36.7 | | | |
| SD: Nanofluidic dPCR, Cut-off 0%, mutation | 37.5 | | | |
| SD: Nanofluidic dPCR, Cut-off 0.1%, wild-type | 36.0 | | | |
| SD: Nanofluidic dPCR, Cut-off 0.1%, mutation | 40.0 | | | |
| SD: Nanofluidic dPCR, Cut-off 1%, wild-type | 35.7 | | | |
| SD: Nanofluidic dPCR, Cut-off 1%, mutation | 44.4 | | | |
| SD: Nanofluidic dPCR, Cut-off 2%, wild-type | 36.2 | | | |
| SD: Nanofluidic dPCR, Cut-off 2%, mutation | 42.9 | | | |
| SD: Nanofluidic dPCR, Cut-off 3%, wild-type | 36.7 | | | |
| SD: Nanofluidic dPCR, Cut-off 3%, mutation | 40.0 | | | |

| | | | | |
|---|------|--|--|--|
| SD: Nanofluidic dPCR, Cut-off 4%, wild-type | 36.7 | | | |
| SD: Nanofluidic dPCR, Cut-off 4%, mutation | 40.0 | | | |
| SD: Nanofluidic dPCR, Cut-off 5%, wild-type | 37.1 | | | |
| SD: Nanofluidic dPCR, Cut-off 5%, mutation | 33.3 | | | |
| PD: Conventional qPCR, wild-type | 13.8 | | | |
| PD: Conventional qPCR, mutation | 0.0 | | | |
| PD: Nanofluidic dPCR, Cut-off 0%, wild-type | 12.2 | | | |
| PD: Nanofluidic dPCR, Cut-off 0%, mutation | 18.8 | | | |
| PD: Nanofluidic dPCR, Cut-off 0.1%, wild-type | 12.0 | | | |
| PD: Nanofluidic dPCR, Cut-off 0.1%, mutation | 20.0 | | | |
| PD: Nanofluidic dPCR, Cut-off 1%, wild-type | 12.5 | | | |
| PD: Nanofluidic dPCR, Cut-off 1%, mutation | 22.2 | | | |
| PD: Nanofluidic dPCR, Cut-off 2%, wild-type | 12.1 | | | |
| PD: Nanofluidic dPCR, Cut-off 2%, mutation | 28.6 | | | |
| PD: Nanofluidic dPCR, Cut-off 3%, wild-type | 13.3 | | | |
| PD: Nanofluidic dPCR, Cut-off 3%, mutation | 20.0 | | | |
| PD: Nanofluidic dPCR, Cut-off 4%, wild-type | 13.3 | | | |
| PD: Nanofluidic dPCR, Cut-off 4%, mutation | 20.0 | | | |
| PD: Nanofluidic dPCR, Cut-off 5%, wild-type | 12.9 | | | |
| PD: Nanofluidic dPCR, Cut-off 5%, mutation | 33.3 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Tumor response in the RAS wild-type population by q-PCR (N=65): RAS + BRAF

| | |
|------------------------|---|
| End point title | Tumor response in the RAS wild-type population by q-PCR (N=65): RAS + BRAF ^[2] |
| End point description: | CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. |
| End point type | Primary |
| End point timeframe: | Tumor response at the end of the study |

Notes:

[2] - 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: Statistical analyses (Fisher exact) within a single analysis set (N=65): Conventional qPCR,

p= 0.067; Nanofluidic dPCR Cut-off 0%, p=0.773; Cut-off 0.1%, p=0.604; Cut-off 1%, p=0.241; Cut-off 2%, p= 0.130; Cut-off 3%, p= 0.164; Cut-off 4%, p= 0.164; Cut-off 5%, p= 0.076.

| End point values | RAS wild-type by qPCR | | | |
|---|-----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 65 | | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| CR: Conventional qPCR, wild-type | 0.0 | | | |
| CR: Conventional qPCR, mutation | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 0%, wild-type | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 0%, mutation | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 0.1%, wild-type | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 0.1%, mutation | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 1%, wild-type | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 1%, mutation | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 2%, wild-type | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 2%, mutation | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 3%, wild-type | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 3%, mutation | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 4%, wild-type | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 4%, mutation | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 5%, wild-type | 0.0 | | | |
| CR: Nanofluidic dPCR, Cut-off 5%, mutation | 0.0 | | | |
| PR: Conventional qPCR, wild-type | 50.8 | | | |
| PR: Conventional qPCR, mutation | 0.0 | | | |
| PR: Nanofluidic dPCR, Cut-off 0%, wild-type | 51.1 | | | |
| PR: Nanofluidic dPCR, Cut-off 0%, mutation | 38.9 | | | |
| PR: Nanofluidic dPCR, Cut-off 0.1%, wild-type | 52.1 | | | |
| PR: Nanofluidic dPCR, Cut-off 0.1%, mutation | 35.3 | | | |
| PR: Nanofluidic dPCR, Cut-off 1%, wild-type | 52.8 | | | |
| PR: Nanofluidic dPCR, Cut-off 1%, mutation | 25.0 | | | |
| PR: Nanofluidic dPCR, Cut-off 2%, wild-type | 52.7 | | | |
| PR: Nanofluidic dPCR, Cut-off 2%, mutation | 20.0 | | | |
| PR: Nanofluidic dPCR, Cut-off 3%, wild-type | 51.8 | | | |

| | | | | |
|---|------|--|--|--|
| PR: Nanofluidic dPCR, Cut-off 3%, mutation | 22.2 | | | |
| PR: Nanofluidic dPCR, Cut-off 4%, wild-type | 51.8 | | | |
| PR: Nanofluidic dPCR, Cut-off 4%, mutation | 22.2 | | | |
| PR: Nanofluidic dPCR, Cut-off 5%, wild-type | 51.7 | | | |
| PR: Nanofluidic dPCR, Cut-off 5%, mutation | 14.3 | | | |
| SD: Conventional qPCR, wild-type | 36.1 | | | |
| SD: Conventional qPCR, mutation | 50.0 | | | |
| SD: Nanofluidic dPCR, Cut-off 0%, wild-type | 34.0 | | | |
| SD: Nanofluidic dPCR, Cut-off 0%, mutation | 44.4 | | | |
| SD: Nanofluidic dPCR, Cut-off 0.1%, wild-type | 33.3 | | | |
| SD: Nanofluidic dPCR, Cut-off 0.1%, mutation | 47.1 | | | |
| SD: Nanofluidic dPCR, Cut-off 1%, wild-type | 34.0 | | | |
| SD: Nanofluidic dPCR, Cut-off 1%, mutation | 50.0 | | | |
| SD: Nanofluidic dPCR, Cut-off 2%, wild-type | 34.5 | | | |
| SD: Nanofluidic dPCR, Cut-off 2%, mutation | 50.0 | | | |
| SD: Nanofluidic dPCR, Cut-off 3%, wild-type | 35.7 | | | |
| SD: Nanofluidic dPCR, Cut-off 3%, mutation | 44.4 | | | |
| SD: Nanofluidic dPCR, Cut-off 4%, wild-type | 35.7 | | | |
| SD: Nanofluidic dPCR, Cut-off 4%, mutation | 44.4 | | | |
| SD: Nanofluidic dPCR, Cut-off 5%, wild-type | 36.2 | | | |
| SD: Nanofluidic dPCR, Cut-off 5%, mutation | 42.9 | | | |
| PD: Conventional qPCR, wild-type | 11.5 | | | |
| PD: Conventional qPCR, mutation | 50.0 | | | |
| PD: Nanofluidic dPCR, Cut-off 0%, wild-type | 12.8 | | | |
| PD: Nanofluidic dPCR, Cut-off 0%, mutation | 16.7 | | | |
| PD: Nanofluidic dPCR, Cut-off 0.1%, wild-type | 12.5 | | | |
| PD: Nanofluidic dPCR, Cut-off 0.1%, mutation | 17.6 | | | |
| PD: Nanofluidic dPCR, Cut-off 1%, wild-type | 11.3 | | | |
| PD: Nanofluidic dPCR, Cut-off 1%, mutation | 25.0 | | | |
| PD: Nanofluidic dPCR, Cut-off 2%, wild-type | 10.9 | | | |
| PD: Nanofluidic dPCR, Cut-off 2%, mutation | 30.0 | | | |
| PD: Nanofluidic dPCR, Cut-off 3%, wild-type | 10.7 | | | |

| | | | | |
|---|------|--|--|--|
| PD: Nanofluidic dPCR, Cut-off 3%, mutation | 33.3 | | | |
| PD: Nanofluidic dPCR, Cut-off 4%, wild-type | 10.7 | | | |
| PD: Nanofluidic dPCR, Cut-off 4%, mutation | 33.3 | | | |
| PD: Nanofluidic dPCR, Cut-off 5%, wild-type | 10.3 | | | |
| PD: Nanofluidic dPCR, Cut-off 5%, mutation | 42.9 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: KRAS mutation distribution

| | |
|-----------------|----------------------------|
| End point title | KRAS mutation distribution |
|-----------------|----------------------------|

End point description:

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

End point timeframe:

Mutations calculated in the population of patients included in the study

| End point values | Panitumumab + FOLFIRI | | | |
|--|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 72 | | | |
| Units: Subjects | | | | |
| KRAS: Conventional qPCR, wild-type | 67 | | | |
| KRAS: Conventional qPCR, mutation | 5 | | | |
| KRAS: Nanofluidic dPCR, wild-type | 52 | | | |
| KRAS: Nanofluidic dPCR, mutation | 20 | | | |
| Exon 2-codon 12–13: Conventional qPCR, wild-type | 71 | | | |
| Exon 2-codon 12–13: Conventional qPCR, mutation | 1 | | | |
| Exon 2-codon 12–13: Nanofluidic dPCR, wild-type | 62 | | | |
| Exon 2-codon 12–13: Nanofluidic dPCR, mutation | 10 | | | |
| Exon 3-codon 58–61: Conventional qPCR, wild-type | 70 | | | |
| Exon 3-codon 58–61: Conventional qPCR, mutation | 2 | | | |
| Exon 3-codon 58–61: Nanofluidic dPCR, wild-type | 65 | | | |
| Exon 3-codon 58–61: Nanofluidic dPCR, mutation | 7 | | | |
| Exon 4-codon 117: Conventional qPCR, wild-type | 72 | | | |
| Exon 4-codon 117: Conventional qPCR, mutation | 0 | | | |

| | | | | |
|--|----|--|--|--|
| Exon 4-codon 117: Nanofluidic dPCR, wild-type | 71 | | | |
| Exon 4-codon 117: Nanofluidic dPCR, mutation | 1 | | | |
| Exon 4-codon 146: Conventional qPCR, wild-type | 70 | | | |
| Exon 4-codon 146: Conventional qPCR, mutation | 2 | | | |
| Exon 4-codon 146: Nanofluidic dPCR, wild-type | 69 | | | |
| Exon 4-codon 146: Nanofluidic dPCR, mutation | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: NRAS mutation distribution

| | |
|--|----------------------------|
| End point title | NRAS mutation distribution |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Mutations calculated in the population of patients included in the study | |

| End point values | Panitumumab + FOLFIRI | | | |
|--|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 72 | | | |
| Units: Subjects | | | | |
| NRAS: Conventional qPCR, wild-type | 70 | | | |
| NRAS: Conventional qPCR, mutation | 2 | | | |
| NRAS: Nanofluidic dPCR, wild-type | 67 | | | |
| NRAS: Nanofluidic dPCR, mutation | 5 | | | |
| Exon 2-codon 12–13: Conventional qPCR, wild-type | 71 | | | |
| Exon 2-codon 12–13: Conventional qPCR, mutation | 1 | | | |
| Exon 2-codon 12–13: Nanofluidic dPCR, wild-type | 69 | | | |
| Exon 2-codon 12–13: Nanofluidic dPCR, mutation | 3 | | | |
| Exon 3-codon 59–61: Conventional qPCR, wild-type | 71 | | | |
| Exon 3-codon 59–61: Conventional qPCR, mutation | 1 | | | |
| Exon 3-codon 59–61: Nanofluidic dPCR, wild-type | 69 | | | |
| Exon 3-codon 59–61: Nanofluidic dPCR, mutation | 3 | | | |
| Exon 4-codon 117: Conventional qPCR, wild-type | 72 | | | |

| | | | | |
|--|----|--|--|--|
| Exon 4-codon 117: Conventional qPCR, mutation | 0 | | | |
| Exon 4-codon 117: Nanofluidic dPCR, wild-type | 72 | | | |
| Exon 4-codon 117: Nanofluidic dPCR, mutation | 0 | | | |
| Exon 4-codon 146: Conventional qPCR, wild-type | 72 | | | |
| Exon 4-codon 146: Conventional qPCR, mutation | 0 | | | |
| Exon 4-codon 146: Nanofluidic dPCR, wild-type | 71 | | | |
| Exon 4-codon 146: Nanofluidic dPCR, mutation | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: BRAF mutation distribution

| | |
|--|----------------------------|
| End point title | BRAF mutation distribution |
| End point description: BRAF mutational status according to Exon 15-codon 600. | |
| End point type | Secondary |
| End point timeframe: Mutations calculated in the population of patients included in the study | |

| End point values | Panitumumab + FOLFIRI | | | |
|------------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 72 | | | |
| Units: Subjects | | | | |
| BRAF: Conventional qPCR, wild-type | 68 | | | |
| BRAF: Conventional qPCR, mutation | 4 | | | |
| BRAF: Nanofluidic dPCR, wild-type | 68 | | | |
| BRAF: Nanofluidic dPCR, mutation | 4 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PIK3CA mutation distribution

| | |
|---|------------------------------|
| End point title | PIK3CA mutation distribution |
| End point description: PIK3CA mutational status according to Exon 20-codon 1043–1047 | |
| End point type | Secondary |

End point timeframe:

Mutations calculated in the population of patients included in the study

| End point values | Panitumumab + FOLFIRI | | | |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 72 | | | |
| Units: Subjects | | | | |
| PIK3CA: Conventional qPCR, wild-type | 71 | | | |
| PIK3CA: Conventional qPCR, mutation | 1 | | | |
| PIK3CA: Nanofluidic dPCR, wild-type | 70 | | | |
| PIK3CA: Nanofluidic dPCR, mutation | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS, months) in the RAS wild-type population: RAS (KRAS/NRAS)

| | |
|-----------------|--|
| End point title | Progression-free survival (PFS, months) in the RAS wild-type population: RAS (KRAS/NRAS) |
|-----------------|--|

End point description:

Statistical analysis (Log-rank test) was performed within a single analysis set (N=65). Find below the HR (95% CIs), p-value for each Nanofluidic dPCR Cut-off: Cut-off 0%, 0.9 (0.5–1.6), p=0.741; Cut-off 0.1%, 0.9 (0.5–1.7), p=0.818; Cut-off 1%, 0.8 (0.4–1.8), p=0.657; Cut-off 2%, 1.3 (0.6–2.9), p=0.513; Cut-off 3%, 1.0 (0.4–2.5), p=0.996; Cut-off 4%, 1.0 (0.4–2.5), p=0.996; Cut-off 5%, 3.3 (1.0–11.0), p=0.048.

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

End point timeframe:

Progression-free survival (PFS) was measured from study inclusion to progression or death.

| End point values | RAS wild-type by qPCR | | | |
|---|-----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 65 ^[3] | | | |
| Units: median | | | | |
| number (not applicable) | | | | |
| Conventional qPCR, wild-type | 7.4 | | | |
| Nanofluidic dPCR, Cut-off 0%, wild-type | 7.2 | | | |
| Nanofluidic dPCR, Cut-off 0%, mutation | 7.4 | | | |
| Nanofluidic dPCR, Cut-off 0.1%, wild-type | 7.6 | | | |
| Nanofluidic dPCR, Cut-off 0.1%, mutation | 7.4 | | | |
| Nanofluidic dPCR, Cut-off 1%, wild-type | 7.6 | | | |
| Nanofluidic dPCR, Cut-off 1%, mutation | 7.4 | | | |

| | | | | |
|---|-----|--|--|--|
| Nanofluidic dPCR, Cut-off 2%, wild-type | 7.6 | | | |
| Nanofluidic dPCR, Cut-off 2%, mutation | 6.7 | | | |
| Nanofluidic dPCR, Cut-off 3%, wild-type | 7.6 | | | |
| Nanofluidic dPCR, Cut-off 3%, mutation | 7.4 | | | |
| Nanofluidic dPCR, Cut-off 4%, wild-type | 7.6 | | | |
| Nanofluidic dPCR, Cut-off 4%, mutation | 7.4 | | | |
| Nanofluidic dPCR, Cut-off 5%, wild-type | 7.6 | | | |
| Nanofluidic dPCR, Cut-off 5%, mutation | 4.0 | | | |

Notes:

[3] - dPCR Cut-off, n (wt/mut): 0%, 49/16; 0.1%, 50/15; 1%, 56/9; 2%, 58/7; 3%, 60/5; 4% 60/5; 5% 62/3

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS, months) in the RAS wild-type population: RAS/BRAF

| | |
|-----------------|---|
| End point title | Progression-free survival (PFS, months) in the RAS wild-type population: RAS/BRAF |
|-----------------|---|

End point description:

Statistical analysis (Log-rank test) was performed within a single analysis set (N=65). Find below the HR (95% CIs), p-value: Conventional qPCR, 6.0 (2.0–17.7), p= 0.001; Nanofluidic dPCR Cut-off 0%, 1.0 (0.6–1.8), p=0.965; Nanofluidic dPCR Cut-off 0.1%, 1.0 (0.6–1.9), p=0.879; Nanofluidic dPCR Cut-off 1%, 1.1 (0.6–2.2), p=0.732; Nanofluidic dPCR Cut-off 2%, 1.7 (0.9–3.4), p= 0.123; Nanofluidic dPCR Cut-off 3%, 1.7 (0.8–3.4), p= 0.160; Nanofluidic dPCR Cut-off 4%, 1.7 (0.8–3.4), p= 0.160; Nanofluidic dPCR Cut-off 5%, 5 (2.1–11.7), p<0.001.

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

End point timeframe:

Progression-free survival (PFS) was measured from study inclusion to progression or death

| End point values | RAS wild-type by qPCR | | | |
|---|-----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 65 ^[4] | | | |
| Units: median | | | | |
| number (not applicable) | | | | |
| Conventional qPCR, wild-type | 7.6 | | | |
| Conventional qPCR, mutation | 1.8 | | | |
| Nanofluidic dPCR, Cut-off 0%, wild-type | 7.6 | | | |
| Nanofluidic dPCR, Cut-off 0%, mutation | 6.7 | | | |
| Nanofluidic dPCR, Cut-off 0.1%, wild-type | 7.6 | | | |
| Nanofluidic dPCR, Cut-off 0.1%, mutation | 6.7 | | | |
| Nanofluidic dPCR, Cut-off 1%, wild-type | 7.6 | | | |
| Nanofluidic dPCR, Cut-off 1%, mutation | 5.5 | | | |
| Nanofluidic dPCR, Cut-off 2%, wild-type | 8.1 | | | |
| Nanofluidic dPCR, Cut-off 2%, mutation | 4.6 | | | |
| Nanofluidic dPCR, Cut-off 3%, wild-type | 8.1 | | | |
| Nanofluidic dPCR, Cut-off 3%, mutation | 4.6 | | | |
| Nanofluidic dPCR, Cut-off 4%, wild-type | 8.1 | | | |

| | | | | |
|---|-----|--|--|--|
| Nanofluidic dPCR, Cut-off 4%, mutation | 4.6 | | | |
| Nanofluidic dPCR, Cut-off 5%, wild-type | 8.8 | | | |
| Nanofluidic dPCR, Cut-off 5%, mutation | 4.0 | | | |

Notes:

[4] - q/dPCR Cut-off, n(wt/mut): 61/4; 0%, 47/18; 0.1%, 48/17; 1%, 53/12; 2%, 55/10; 3&4%, 56/9; 5% 58/7

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS, months) in the RAS wild-type population: RAS (KRAS/NRAS)

| | |
|-----------------|--|
| End point title | Overall survival (OS, months) in the RAS wild-type population: RAS (KRAS/NRAS) |
|-----------------|--|

End point description:

Statistical analysis (Log-rank test) was performed within a single analysis set (N=65). Find below the HR (95% CIs), p-value for each Nanofluidic dPCR Cut-off: Cut-off 0%, 0.6 (0.3–1.2), p=0.142; Cut-off 0.1%, 0.7 (0.3–1.4), p=0.294; Cut-off 1%, 0.6 (0.3–1.7), p=0.367; Cut-off 2%, 0.8 (0.3–2.1), p=0.689; Cut-off 3%, 0.8 (0.3–2.2), p= 0.620; Cut-off 4%, 0.8 (0.3–2.2), p= 0.620; Cut-off 5%, 1.5 (0.4–4.7), p= 0.534.

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

End point timeframe:

Overall survival (OS) was measured from enrolment to death

| End point values | RAS wild-type by qPCR | | | |
|---|-----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 65 ^[5] | | | |
| Units: median | | | | |
| number (not applicable) | | | | |
| Conventional qPCR, wild-type | 13.9 | | | |
| Nanofluidic dPCR, Cut-off 0%, wild-type | 11.7 | | | |
| Nanofluidic dPCR, Cut-off 0%, mutation | 17.4 | | | |
| Nanofluidic dPCR, Cut-off 0.1%, wild-type | 11.8 | | | |
| Nanofluidic dPCR, Cut-off 0.1%, mutation | 16.1 | | | |
| Nanofluidic dPCR, Cut-off 1%, wild-type | 12.5 | | | |
| Nanofluidic dPCR, Cut-off 1%, mutation | 16.1 | | | |
| Nanofluidic dPCR, Cut-off 2%, wild-type | 13.9 | | | |
| Nanofluidic dPCR, Cut-off 2%, mutation | 16.1 | | | |
| Nanofluidic dPCR, Cut-off 3%, wild-type | 13.9 | | | |
| Nanofluidic dPCR, Cut-off 3%, mutation | 16.1 | | | |
| Nanofluidic dPCR, Cut-off 4%, wild-type | 13.9 | | | |
| Nanofluidic dPCR, Cut-off 4%, mutation | 16.1 | | | |
| Nanofluidic dPCR, Cut-off 5%, wild-type | 13.9 | | | |
| Nanofluidic dPCR, Cut-off 5%, mutation | 16.1 | | | |

Notes:

[5] - dPCR Cut-off, n (wt/mut): 0%, 49/16; 0.1%, 50/15; 1%, 56/9; 2%, 58/7; 3%, 60/5; 4% 60/5; 5% 62/3

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS, months) in the RAS wild-type population: RAS/BRAF

| | |
|-----------------|---|
| End point title | Overall survival (OS, months) in the RAS wild-type population: RAS/BRAF |
|-----------------|---|

End point description:

Statistical analysis (Log-rank test) was performed within a single analysis set (N=65). Find below the HR (95% CIs), p-value: Conventional qPCR, 8.1 (2.6–25.5), $p < 0.001$; Nanofluidic dPCR Cut-off 0%, 0.7 (0.4–1.4), $p = 0.349$; Nanofluidic dPCR Cut-off 0.1%, 0.8 (0.4–1.7), $p = 0.619$; Nanofluidic dPCR Cut-off 1%, 1.0 (0.5–2.2), $p = 0.951$; Nanofluidic dPCR Cut-off 2%, 1.3 (0.6–2.8), $p = 0.528$; Nanofluidic dPCR Cut-off 3%, 1.5 (0.7–3.3), $p = 0.290$; Nanofluidic dPCR Cut-off 4%, 1.5 (0.7–3.3), $p = 0.290$; Nanofluidic dPCR Cut-off 5%, 2.8 (1.3–6.4), $p = 0.012$.

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

End point timeframe:

Overall survival (OS) was measured from enrolment to death

| End point values | RAS wild-type by qPCR | | | |
|---|-----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 65 ^[6] | | | |
| Units: median | | | | |
| number (not applicable) | | | | |
| Conventional qPCR, wild-type | 16.1 | | | |
| Conventional qPCR, mutation | 6.2 | | | |
| Nanofluidic dPCR, Cut-off 0%, wild-type | 11.8 | | | |
| Nanofluidic dPCR, Cut-off 0%, mutation | 16.1 | | | |
| Nanofluidic dPCR, Cut-off 0.1%, wild-type | 12.5 | | | |
| Nanofluidic dPCR, Cut-off 0.1%, mutation | 16.1 | | | |
| Nanofluidic dPCR, Cut-off 1%, wild-type | 13.9 | | | |
| Nanofluidic dPCR, Cut-off 1%, mutation | 13.7 | | | |
| Nanofluidic dPCR, Cut-off 2%, wild-type | 15.6 | | | |
| Nanofluidic dPCR, Cut-off 2%, mutation | 8.4 | | | |
| Nanofluidic dPCR, Cut-off 3%, wild-type | 16.2 | | | |
| Nanofluidic dPCR, Cut-off 3%, mutation | 8.4 | | | |
| Nanofluidic dPCR, Cut-off 4%, wild-type | 16.2 | | | |
| Nanofluidic dPCR, Cut-off 4%, mutation | 8.4 | | | |
| Nanofluidic dPCR, Cut-off 5%, wild-type | 16.2 | | | |
| Nanofluidic dPCR, Cut-off 5%, mutation | 7.3 | | | |

Notes:

[6] - q/dPCR Cut-off, n(wt/mut): 61/4; 0%, 47/18; 0.1%, 48/17; 1%, 53/12; 2%, 55/10; 3&4%, 56/9; 5% 58/7

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Toxicity was assessed at every study visit according to the Common Toxicity Criteria for Adverse Events version 4.0

Adverse event reporting additional description:

If a patient had more than one event classified with the same preferred term, then the worst case was used

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

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 | 28 / 72 (38.89%) | | |
| number of deaths (all causes) | 52 | | |
| number of deaths resulting from adverse events | 4 | | |
| Vascular disorders | | | |
| Ictus minor | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fever | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Confusional syndrome | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lumbar pain | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Febrile syndrome | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Intestinal subocclusion | | | |
| subjects affected / exposed | 5 / 72 (6.94%) | | |
| occurrences causally related to treatment / all | 0 / 9 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Gastrointestinal toxicity | | | |
| subjects affected / exposed | 2 / 72 (2.78%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 72 (5.56%) | | |
| occurrences causally related to treatment / all | 5 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Digestive toxicity | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucositis | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enteritis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary thromboembolism | | | |
| subjects affected / exposed | 2 / 72 (2.78%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bilateral pneumonia | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Bronchoaspiration | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Obstructive jaundice | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Renal and urinary disorders | | | |
| Urinary sepsis | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle deterioration | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Urine infection | | | |
| subjects affected / exposed | 2 / 72 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| E.Coli sepsis | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheter infection | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory infection | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 72 (1.39%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Safety population | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 72 / 72 (100.00%) | | |
| Vascular disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 4 / 72 (5.56%) | | |
| occurrences (all) | 4 | | |
| Thrombosis | | | |
| subjects affected / exposed | 4 / 72 (5.56%) | | |
| occurrences (all) | 5 | | |
| General disorders and administration site conditions | | | |
| Xerosis | | | |
| subjects affected / exposed | 8 / 72 (11.11%) | | |
| occurrences (all) | 11 | | |
| Asthenia | | | |
| subjects affected / exposed | 47 / 72 (65.28%) | | |
| occurrences (all) | 129 | | |
| Fever | | | |
| subjects affected / exposed | 8 / 72 (11.11%) | | |
| occurrences (all) | 10 | | |
| Blood and lymphatic system disorders | | | |
| Edema of lower extremities | | | |
| subjects affected / exposed | 4 / 72 (5.56%) | | |
| occurrences (all) | 4 | | |
| Anaemia | | | |
| subjects affected / exposed | 17 / 72 (23.61%) | | |
| occurrences (all) | 32 | | |
| Leukopenia | | | |
| subjects affected / exposed | 7 / 72 (9.72%) | | |
| occurrences (all) | 22 | | |

| | | | |
|-----------------------------|------------------|--|--|
| Neutropenia | | | |
| subjects affected / exposed | 27 / 72 (37.50%) | | |
| occurrences (all) | 64 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 5 / 72 (6.94%) | | |
| occurrences (all) | 13 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 15 / 72 (20.83%) | | |
| occurrences (all) | 23 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 53 / 72 (73.61%) | | |
| occurrences (all) | 165 | | |
| Dysphagia | | | |
| subjects affected / exposed | 5 / 72 (6.94%) | | |
| occurrences (all) | 6 | | |
| Stomatitis | | | |
| subjects affected / exposed | 4 / 72 (5.56%) | | |
| occurrences (all) | 8 | | |
| Constipation | | | |
| subjects affected / exposed | 17 / 72 (23.61%) | | |
| occurrences (all) | 24 | | |
| Mucositis | | | |
| subjects affected / exposed | 30 / 72 (41.67%) | | |
| occurrences (all) | 114 | | |
| Nausea | | | |
| subjects affected / exposed | 30 / 72 (41.67%) | | |
| occurrences (all) | 59 | | |
| Intestinal subocclusion | | | |
| subjects affected / exposed | 5 / 72 (6.94%) | | |
| occurrences (all) | 9 | | |
| Vomiting | | | |
| subjects affected / exposed | 18 / 72 (25.00%) | | |
| occurrences (all) | 28 | | |
| Xerostomia | | | |

| | | | |
|--|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 8 / 72 (11.11%) 14 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Tracheal dryness subjects affected / exposed occurrences (all) | 7 / 72 (9.72%) 14 | | |
| Common cold subjects affected / exposed occurrences (all) | 5 / 72 (6.94%) 5 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 8 / 72 (11.11%) 12 | | |
| Skin and subcutaneous tissue disorders | | | |
| Acne subjects affected / exposed occurrences (all) | 12 / 72 (16.67%) 33 | | |
| Alopecia subjects affected / exposed occurrences (all) | 9 / 72 (12.50%) 12 | | |
| Cutaneous subjects affected / exposed occurrences (all) | 26 / 72 (36.11%) 53 | | |
| Dermatitis subjects affected / exposed occurrences (all) | 6 / 72 (8.33%) 16 | | |
| Erythema subjects affected / exposed occurrences (all) | 7 / 72 (9.72%) 8 | | |
| Finger fissure subjects affected / exposed occurrences (all) | 11 / 72 (15.28%) 16 | | |
| Skin hyperpigmentation subjects affected / exposed occurrences (all) | 5 / 72 (6.94%) 5 | | |
| Hypertrichosis | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 6 / 72 (8.33%) | | |
| occurrences (all) | 9 | | |
| Paronychia | | | |
| subjects affected / exposed | 16 / 72 (22.22%) | | |
| occurrences (all) | 27 | | |
| Pruritus | | | |
| subjects affected / exposed | 7 / 72 (9.72%) | | |
| occurrences (all) | 12 | | |
| Rash | | | |
| subjects affected / exposed | 43 / 72 (59.72%) | | |
| occurrences (all) | 141 | | |
| Hand and foot syndrome | | | |
| subjects affected / exposed | 5 / 72 (6.94%) | | |
| occurrences (all) | 7 | | |
| Cutaneous xerosis | | | |
| subjects affected / exposed | 7 / 72 (9.72%) | | |
| occurrences (all) | 8 | | |
| Periungual fissure | | | |
| subjects affected / exposed | 4 / 72 (5.56%) | | |
| occurrences (all) | 6 | | |
| Onycholysis | | | |
| subjects affected / exposed | 4 / 72 (5.56%) | | |
| occurrences (all) | 4 | | |
| Trichomalacia | | | |
| subjects affected / exposed | 4 / 72 (5.56%) | | |
| occurrences (all) | 8 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 6 / 72 (8.33%) | | |
| occurrences (all) | 9 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Lumbar pain | | | |
| subjects affected / exposed | 8 / 72 (11.11%) | | |
| occurrences (all) | 10 | | |
| Infections and infestations | | | |

| | | | |
|---|------------------------|--|--|
| Conjunctivitis subjects affected / exposed occurrences (all) | 20 / 72 (27.78%) 26 | | |
| Urine infection subjects affected / exposed occurrences (all) | 6 / 72 (8.33%) 8 | | |
| Respiratory infection subjects affected / exposed occurrences (all) | 4 / 72 (5.56%) 5 | | |
| Metabolism and nutrition disorders | | | |
| Anorexia subjects affected / exposed occurrences (all) | 20 / 72 (27.78%) 33 | | |
| Iron deficiency subjects affected / exposed occurrences (all) | 5 / 72 (6.94%) 8 | | |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 18 / 72 (25.00%) 42 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 29 January 2013 | Through this amendment the following changes were implemented: 1- Incorporation of a new exploratory objective (identification of mutation through high-sensitivity methodology in biologic fluids, i.e. blood); 2- Protocol changes in order to enhance text comprehension; 3- Update of the principal investigators and study sites. |
| 21 June 2013 | The approval of this protocol amendment was on 25th July 2013. Through this amendment the following changes were implemented: 1- Modification of a selection criteria, extension of the mutation panel for KRAS and NRAS genes (initially patients may have had no mutation in KRAS exons 2 and 3, and after protocol amendment may have had no mutation in KRAS exons 2, 3 and 4 and NRAS exons 2, 3 and 4) and review of the sample size justification; 2- Protocol changes in order to enhance text comprehension; 3- Update of the principal investigators and study sites. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The impossibility to assess the role of PIK3CA status due to the low number of mutations. In addition, initially enrolled patients may have had mutation in KRAS 3/4 exons and NRAS 2/3/4 exons.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30840064>