



Clinical trial results:

A Phase II trial to assess FOLFIRI + aflibercept efficacy in patients with oxaliplatin-pretreated metastatic colorectal cancer with or without ACE polymorphisms

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2016-001508-45 |
| Trial protocol | ES |
| Global end of trial date | 11 December 2018 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 26 June 2020 |
| First version publication date | 26 June 2020 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | TTD-16-02 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02970916 |
| 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 | 04 September 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 11 December 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 December 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess FOLFIRI + aflibercept efficacy in patients with or without angiotensin converting enzyme (ACE) polymorphisms in terms of progression-free survival (PFS).

Protection of trial subjects:

All patients included in the clinical trial received the combination of aflibercept + FOLFIRI regimen in 2-week cycles. Treatment was given until disease progression, unacceptable toxicity or patient withdrawal (investigator or patient decision, death, appearance of any of the exclusion criteria clinically relevant, significant non-compliance with protocol, development of a second cancer, addition of an anti-neoplastic drug other than study drugs or pregnancy).

All patients that discontinued the study treatment were followed up every 3 months to document progression (If patients withdraw from the treatment before progression), treatment-related adverse events (AE), further cancer treatments and survival, except for those who withdrew their informed consent, were lost to follow-up or died.

Background therapy:

Not applicable

Evidence for comparator: -

| | |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment | 23 November 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 12 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Spain: 101 |
| Worldwide total number of subjects | 101 |
| EEA total number of subjects | 101 |

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) | 57 |
| From 65 to 84 years | 44 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

One hundred and fifteen patients were recruited, 14 of whom were considered screening failures (noncompliance with selection criteria, n=11; withdrawal of consent n=2 and not possible to evaluate RECIST criteria due to patient's weight, n=1). Therefore, 101 patients were finally included in this national study conducted in 15 Spanish hospitals.

Pre-assignment

Screening details:

Patients aged ≥ 18 years, with histologically proven colorectal adenocarcinoma, metastatic disease and ≥ 1 measurable unidimensional lesion using CT or MRI according to RECIST criteria. The mCRC had to be resistant to or progressive on an oxaliplatin-containing regimen. WHO performance status 0-2 and adequate bone marrow, renal and liver functions.

Period 1

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

Blinding implementation details:

Not applicable.

Arms

| | |
|-----------|-----------------------|
| Arm title | Aflibercept + FOLFIRI |
|-----------|-----------------------|

Arm description:

All patients included in the clinical trial received the combination of aflibercept + FOLFIRI regimen in 2-week cycles. Treatment was given until disease progression, unacceptable toxicity or patient withdrawal (investigator or patient decision, death, appearance of any of the exclusion criteria clinically relevant, significant non-compliance with protocol, development of a second cancer, addition of an anti-neoplastic drug other than study drugs or pregnancy).

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

Dosage and administration details:

Aflibercept was administered at a dose of 4 mg/kg by intravenous infusion on day 1 of each 2-week cycle.

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

Dosage and administration details:

FOLFIRI regimen was administered immediately after aflibercept:

Irinotecan: was administered at a dose of 180 mg/m²

Folinic acid: was administered at a dose of 400 mg/m² (400 mg/m² [racemic] or 200 mg/m² [L-form]) by i.v. infusion followed by

5-Fluorouracil (5-FU) bolus: was administered at a dose of 400 mg/m² as a bolus followed by

5-FU infusion: was administered at a dose of 2400 mg/m² over 46 hours by continuous i.v. infusion.

| Number of subjects in period 1 | Aflibercept + FOLFIRI |
|---------------------------------------|--------------------------|
| Started | 101 |
| Completed | 101 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Baseline |
|-----------------------|----------|

Reporting group description: -

| Reporting group values | Baseline | Total | |
|------------------------------------------------------|---------------|-------|--|
| Number of subjects | 101 | 101 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 57 | 57 | |
| From 65-84 years | 44 | 44 | |
| Age continuous | | | |
| Units: years | | | |
| median | 63.8 | | |
| inter-quartile range (Q1-Q3) | 57.7 to 71.3 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 41 | 41 | |
| Male | 60 | 60 | |
| ACE polymorphisms | | | |
| The genotype frequencies of the ACE polymorphisms. | | | |
| Units: Subjects | | | |
| IN/DEL | 47 | 47 | |
| IN/IN | 14 | 14 | |
| DEL/DEL | 40 | 40 | |
| AGTR1 polymorphisms | | | |
| The genotype frequencies of the AGTR1 polymorphisms. | | | |
| Units: Subjects | | | |
| A/A | 54 | 54 | |
| A/C | 38 | 38 | |
| C/C | 9 | 9 | |
| RAS status | | | |
| Units: Subjects | | | |
| Mutant | 60 | 60 | |
| Wild-type | 34 | 34 | |
| Unknown | 7 | 7 | |
| ACE serum levels | | | |
| Units: ng/ml | | | |
| median | 161.2 | | |
| inter-quartile range (Q1-Q3) | 82.5 to 320.6 | - | |
| VEGF-A serum levels | | | |
| Units: ng/ml | | | |
| median | 1.6 | | |
| inter-quartile range (Q1-Q3) | 0.3 to 15.8 | - | |

End points

End points reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Aflibercept + FOLFIRI |
|-----------------------|-----------------------|

Reporting group description:

All patients included in the clinical trial received the combination of aflibercept + FOLFIRI regimen in 2-week cycles. Treatment was given until disease progression, unacceptable toxicity or patient withdrawal (investigator or patient decision, death, appearance of any of the exclusion criteria clinically relevant, significant non-compliance with protocol, development of a second cancer, addition of an anti-neoplastic drug other than study drugs or pregnancy).

| | |
|----------------------------|-----|
| Subject analysis set title | ITT |
|----------------------------|-----|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Intention to treat (ITT) population: included all patients receiving at least one dose of study treatment and with quality DNA sample available for biomarker determination (N=101).

| | |
|----------------------------|----|
| Subject analysis set title | PP |
|----------------------------|----|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Per protocol (PP) population: included all patients who met all the inclusion criteria and none of the exclusion criteria who received the study treatment as per the protocol, had at least one assessment of efficacy and/or safety post-baseline and without major protocol deviations that entailed patient's withdrawal from the study (N=89).

| | |
|----------------------------|--------|
| Subject analysis set title | IN/DEL |
|----------------------------|--------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

ACE polymorphism IN/DEL

| | |
|----------------------------|-------|
| Subject analysis set title | IN/IN |
|----------------------------|-------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

ACE polymorphism IN/IN

| | |
|----------------------------|---------|
| Subject analysis set title | DEL/DEL |
|----------------------------|---------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

ACE polymorphism DEL/DEL

| | |
|----------------------------|--------------|
| Subject analysis set title | <1.941 ng/ml |
|----------------------------|--------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

VEFG-A levels <1.941 ng/ml

| | |
|----------------------------|--------------|
| Subject analysis set title | ≥1.941 ng/ml |
|----------------------------|--------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

VEFG-A levels ≥1.941 ng/ml

Primary: Progression-free survival (PFS)

| | |
|-----------------|------------------------------------------------|
| End point title | Progression-free survival (PFS) ^[1] |
|-----------------|------------------------------------------------|

End point description:

The primary study endpoint was PFS, defined as the time from inclusion to disease progression (observed radiologically) or death from any cause.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From inclusion to disease progression or death from any cause.

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: Absolute and relative frequency distributions were presented for qualitative variables, as well as measures of central tendency and dispersion for quantitative variables. The Kaplan–Meier method was used to analyse the primary and secondary time-to-event endpoints.

| End point values | ITT | PP | | |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 101 | 89 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 7.5 (6.0 to 8.9) | 8.4 (6.9 to 9.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

| | |
|---------------------------------------------------------------|-----------------------|
| End point title | Overall survival (OS) |
| End point description: | |
| OS was defined as time from inclusion to death from any cause | |
| End point type | Secondary |
| End point timeframe: | |
| From inclusion to death from any cause. | |

| End point values | ITT | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 101 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 12.6 (8.4 to 16.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP)

| | |
|---------------------------------------------------------------------|---------------------------|
| End point title | Time to progression (TTP) |
| End point description: | |
| Time from inclusion to disease progression or death for progression | |
| End point type | Secondary |
| End point timeframe: | |
| From inclusion to disease progression or death for progression | |

| End point values | ITT | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 101 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 8.3 (7.1 to 9.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure (TTF)

| | |
|------------------------------------------------------------------|---------------------------------|
| End point title | Time to treatment failure (TTF) |
| End point description: | |
| Time from inclusion to treatment discontinuation for any reason. | |
| End point type | Secondary |
| End point timeframe: | |
| From inclusion to treatment discontinuation. | |

| End point values | ITT | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 101 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 6.1 (4.8 to 7.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR)

| | |
|----------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title | Overall response rate (ORR) |
| End point description: | |
| Percentage of patients with either a complete response (CR) or partial response (PR) according to RECIST criteria (version 1.1). | |
| End point type | Secondary |
| End point timeframe: | |
| From the beginning until the end of the study. | |

| End point values | ITT | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 101 ^[2] | | | |
| Units: Percentage of patients | | | | |
| number (confidence interval 95%) | 15.8 (9.6 to 24.8) | | | |

Notes:

[2] - PR was reported in 15.8% (n=16).

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR)

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| End point title | Disease control rate (DCR) |
| End point description: Percentage of patients with either a complete response (CR), partial response (PR) or stable disease (SD) according to RECIST criteria (version 1.1). | |
| End point type | Secondary |
| End point timeframe: From the beginning until the end of the study. | |

| End point values | ITT | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 101 ^[3] | | | |
| Units: Percentage of patients | | | | |
| median (confidence interval 95%) | 69.3 (59.2 to 77.9) | | | |

Notes:

[3] - PR and SD were reported in 15.8% (n=16) and 53.5% (n=54) respectively.

Statistical analyses

No statistical analyses for this end point

Secondary: ORR according to ACE polymorphisms

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| End point title | ORR according to ACE polymorphisms |
| End point description: Percentage of patients with either a complete response (CR) or partial response (PR) according to RECIST criteria (version 1.1) and classified according to ACE polymorphisms. | |
| End point type | Secondary |
| End point timeframe: From the beginning until the end of the study. | |

| End point values | IN/DEL | IN/IN | DEL/DEL | |
|-----------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 47 | 14 | 40 | |
| Units: Subjects | 9 | 3 | 7 | |

Statistical analyses

| | |
|-----------------------------------------|--------------------------|
| Statistical analysis title | Fisher`s exact test |
| Comparison groups | IN/DEL v IN/IN v DEL/DEL |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.941 |
| Method | Fisher exact |

Secondary: DCR according to ACE polymorphisms

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| End point title | DCR according to ACE polymorphisms |
| End point description: Percentage of patients with either a complete response (CR), partial response (PR) or stable disease (SD) according to RECIST criteria (version 1.1) and classified according ACE polymorphisms. | |
| End point type | Secondary |
| End point timeframe: From the beginning until the end of the study. | |

| End point values | IN/DEL | IN/IN | DEL/DEL | |
|-----------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 47 | 14 | 40 | |
| Units: Subjects | 33 | 9 | 28 | |

Statistical analyses

| | |
|-----------------------------------------|--------------------------|
| Statistical analysis title | Fisher`s exact test |
| Comparison groups | IN/DEL v IN/IN v DEL/DEL |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.913 |
| Method | Fisher exact |

Secondary: PFS according to ACE polymorphisms

| | |
|-----------------|------------------------------------|
| End point title | PFS according to ACE polymorphisms |
|-----------------|------------------------------------|

End point description:

PFS was defined as the time from inclusion to disease progression (observed radiologically) or death from any cause. Results are presented here according to ACE polymorphisms.

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

End point timeframe:

From inclusion to disease progression or death from any cause.

| End point values | IN/DEL | IN/IN | DEL/DEL | |
|----------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 47 | 14 | 40 | |
| Units: months | | | | |
| median (confidence interval 95%) | 9.0 (6.9 to 11.0) | 4.3 (0.0 to 9.4) | 7.4 (5.4 to 9.3) | |

Statistical analyses

| | |
|-----------------------------------------|--------------------------|
| Statistical analysis title | Log-Rank |
| Comparison groups | IN/DEL v IN/IN v DEL/DEL |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.854 |
| Method | Logrank |

Secondary: OS according to ACE polymorphisms

| | |
|-----------------|-----------------------------------|
| End point title | OS according to ACE polymorphisms |
|-----------------|-----------------------------------|

End point description:

Time from inclusion to death from any cause according to ACE polymorphisms.

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

End point timeframe:

From inclusion to death from any cause.

| End point values | IN/DEL | IN/IN | DEL/DEL | |
|----------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 47 | 14 | 40 | |
| Units: months | | | | |
| median (confidence interval 95%) | 15.5 (11.0 to 20.0) | 8.6 (0.7 to 16.5) | 10.4 (7.3 to 13.4) | |

Statistical analyses

| | |
|-----------------------------------------|--------------------------|
| Statistical analysis title | Log-Rank |
| Comparison groups | IN/DEL v IN/IN v DEL/DEL |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.689 |
| Method | Logrank |

Secondary: TTP according to ACE polymorphisms

| | |
|-------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| End point title | TTP according to ACE polymorphisms |
| End point description: Time from inclusion to disease progression or death for progression according to ACE polymorphisms. | |
| End point type | Secondary |
| End point timeframe: From inclusion to disease progression or death for progression. | |

| | | | | |
|----------------------------------|----------------------|----------------------|----------------------|--|
| End point values | IN/DEL | IN/IN | DEL/DEL | |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 47 | 14 | 40 | |
| Units: months | | | | |
| median (confidence interval 95%) | 9.0 (6.8 to 11.2) | 4.3 (0.0 to 9.4) | 7.4 (4.4 to 10.4) | |

Statistical analyses

| | |
|-----------------------------------------|--------------------------|
| Statistical analysis title | Log-Rank |
| Comparison groups | IN/DEL v IN/IN v DEL/DEL |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.828 |
| Method | Logrank |

Secondary: TTF according to ACE polymorphisms

| | |
|-----------------|------------------------------------|
| End point title | TTF according to ACE polymorphisms |
|-----------------|------------------------------------|

End point description:

Time from inclusion to treatment discontinuation for any reason according to ACE polymorphisms.

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

End point timeframe:

From inclusion to treatment discontinuation.

| End point values | IN/DEL | IN/IN | DEL/DEL | |
|----------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 47 | 14 | 40 | |
| Units: months | | | | |
| median (confidence interval 95%) | 7.1 (5.1 to 9.2) | 4.5 (2.1 to 7.0) | 5.4 (3.9 to 7.0) | |

Statistical analyses

| | |
|-----------------------------------------|--------------------------|
| Statistical analysis title | Log-Rank |
| Comparison groups | IN/DEL v IN/IN v DEL/DEL |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.477 |
| Method | Logrank |

Secondary: OS according to VEGF-A levels

| | |
|-----------------|-------------------------------|
| End point title | OS according to VEGF-A levels |
|-----------------|-------------------------------|

End point description:

Time from inclusion to death from any cause according to VEGF-A levels.

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

End point timeframe:

From inclusion to death from any cause.

| End point values | <1.941 ng/ml | ≥1.941 ng/ml | | |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 53 | 47 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 18.9 (14.8 to 23.0) | 7.6 (4.5 to 10.7) | | |

Statistical analyses

| Statistical analysis title | Log-Rank |
|-----------------------------------------|-----------------------------|
| Comparison groups | <1.941 ng/ml v ≥1.941 ng/ml |
| Number of subjects included in analysis | 100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.001 |
| Method | Logrank |

Other pre-specified: PFS according to VEGF-A levels

| | |
|------------------------|--------------------------------------------------------------------------------------------------------------------------|
| End point title | PFS according to VEGF-A levels |
| End point description: | Time from inclusion to disease progression (observed radiologically) or death from any cause according to VEGF-A levels. |
| End point type | Other pre-specified |
| End point timeframe: | From inclusion to disease progression or death from any cause. |

| End point values | <1.941 ng/ml | ≥1.941 ng/ml | | |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 53 | 47 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9.2 (8.4 to 10.0) | 4.2 (2.7 to 5.6) | | |

Statistical analyses

| Statistical analysis title | Log-Rank |
|----------------------------|-----------------------------|
| Comparison groups | <1.941 ng/ml v ≥1.941 ng/ml |

| | |
|-----------------------------------------|---------------|
| Number of subjects included in analysis | 100 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.001 |
| Method | Logrank |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The treatment safety profile was a secondary endpoint, assessed according to AEs recorded throughout the study and the incidence of dose adjustments and compliance of study treatment.

Adverse event reporting additional description:

The variables evaluated to characterize the AE profile of the treatment were their incidence and severity as per the NCI-CTCAE criteria (version 4.03).

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

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 | 37 / 101 (36.63%) | | |
| number of deaths (all causes) | 65 | | |
| number of deaths resulting from adverse events | 11 | | |
| Injury, poisoning and procedural complications | | | |
| Chemical peritonitis | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Ventricular dysfunction | Additional description: Left ventricular systolic dysfunction | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| General disorders and administration site conditions | | | |

| | | | | |
|---------------------------------------------------------------------------|-------------------------------------------------|-----------------|--|--|
| Asthenia | subjects affected / exposed | 4 / 101 (3.96%) | | |
| | occurrences causally related to treatment / all | 3 / 4 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| Death | subjects affected / exposed | 1 / 101 (0.99%) | | |
| | occurrences causally related to treatment / all | 1 / 1 | | |
| | deaths causally related to treatment / all | 1 / 1 | | |
| Additional description: Febrile syndrome of persistent respiratory focus. | | | | |
| Pyrexia | subjects affected / exposed | 1 / 101 (0.99%) | | |
| | occurrences causally related to treatment / all | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | subjects affected / exposed | 6 / 101 (5.94%) | | |
| | occurrences causally related to treatment / all | 1 / 6 | | |
| | deaths causally related to treatment / all | 0 / 5 | | |
| Pain | subjects affected / exposed | 2 / 101 (1.98%) | | |
| | occurrences causally related to treatment / all | 0 / 2 | | |
| | deaths causally related to treatment / all | 0 / 1 | | |
| Blood and lymphatic system disorders | | | | |
| Febrile neutropenia | | | | |
| | subjects affected / exposed | 1 / 101 (0.99%) | | |
| | occurrences causally related to treatment / all | 1 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | | |
| Abdominal pain | | | | |
| | subjects affected / exposed | 4 / 101 (3.96%) | | |
| | occurrences causally related to treatment / all | 0 / 4 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | | |
| | subjects affected / exposed | 1 / 101 (0.99%) | | |
| | occurrences causally related to treatment / all | 1 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|-------------------------------------------------|-----------------|--|--|--|
| Diarrhoea | | | | |
| subjects affected / exposed | 3 / 101 (2.97%) | | | |
| occurrences causally related to treatment / all | 3 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dysphagia | | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enterocolitis | | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal toxicity | | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Intestinal obstruction | | | | |
| subjects affected / exposed | 8 / 101 (7.92%) | | | |
| occurrences causally related to treatment / all | 0 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Large intestine perforation | | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Female genital tract fistula | | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vomiting | | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 101 (0.99%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 101 (1.98%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 101 (1.98%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephritic syndrome | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 101 (1.98%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| Infections and infestations | | | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 101 (0.99%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

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 | 101 / 101 (100.00%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 37 / 101 (36.63%) | | |
| occurrences (all) | 76 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 22 / 101 (21.78%) | | |
| occurrences (all) | 40 | | |
| Neurotoxicity | | | |
| subjects affected / exposed | 6 / 101 (5.94%) | | |
| occurrences (all) | 7 | | |
| Blood and lymphatic system disorders | | | |

| | | | |
|------------------------------------------------------|-------------------|--|--|
| Anaemia | | | |
| subjects affected / exposed | 13 / 101 (12.87%) | | |
| occurrences (all) | 18 | | |
| Neutropenia | | | |
| subjects affected / exposed | 45 / 101 (44.55%) | | |
| occurrences (all) | 136 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 8 / 101 (7.92%) | | |
| occurrences (all) | 27 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 75 / 101 (74.26%) | | |
| occurrences (all) | 282 | | |
| Fatigue | | | |
| subjects affected / exposed | 7 / 101 (6.93%) | | |
| occurrences (all) | 11 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 6 / 101 (5.94%) | | |
| occurrences (all) | 7 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 58 / 101 (57.43%) | | |
| occurrences (all) | 162 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 8 / 101 (7.92%) | | |
| occurrences (all) | 8 | | |
| Pyrexia | | | |
| subjects affected / exposed | 15 / 101 (14.85%) | | |
| occurrences (all) | 30 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 6 / 101 (5.94%) | | |
| occurrences (all) | 6 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 29 / 101 (28.71%) | | |
| occurrences (all) | 52 | | |
| Abdominal pain upper | | | |

| | | | |
|---------------------------------------|-------------------|--|--|
| subjects affected / exposed | 10 / 101 (9.90%) | | |
| occurrences (all) | 11 | | |
| Constipation | | | |
| subjects affected / exposed | 19 / 101 (18.81%) | | |
| occurrences (all) | 22 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 78 / 101 (77.23%) | | |
| occurrences (all) | 283 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 14 / 101 (13.86%) | | |
| occurrences (all) | 18 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 7 / 101 (6.93%) | | |
| occurrences (all) | 9 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 6 / 101 (5.94%) | | |
| occurrences (all) | 8 | | |
| Nausea | | | |
| subjects affected / exposed | 34 / 101 (33.66%) | | |
| occurrences (all) | 72 | | |
| Odynophagia | | | |
| subjects affected / exposed | 8 / 101 (7.92%) | | |
| occurrences (all) | 9 | | |
| Proctalgia | | | |
| subjects affected / exposed | 10 / 101 (9.90%) | | |
| occurrences (all) | 23 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 8 / 101 (7.92%) | | |
| occurrences (all) | 12 | | |
| Stomatitis | | | |
| subjects affected / exposed | 7 / 101 (6.93%) | | |
| occurrences (all) | 13 | | |
| Vomiting | | | |
| subjects affected / exposed | 30 / 101 (29.70%) | | |
| occurrences (all) | 46 | | |
| Respiratory, thoracic and mediastinal | | | |

| | | | |
|-------------------------------------------------|-------------------|--|--|
| disorders | | | |
| Aphonia | | | |
| subjects affected / exposed | 9 / 101 (8.91%) | | |
| occurrences (all) | 10 | | |
| Dysphonia | | | |
| subjects affected / exposed | 24 / 101 (23.76%) | | |
| occurrences (all) | 37 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 7 / 101 (6.93%) | | |
| occurrences (all) | 11 | | |
| Epistaxis | | | |
| subjects affected / exposed | 31 / 101 (30.69%) | | |
| occurrences (all) | 50 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 10 / 101 (9.90%) | | |
| occurrences (all) | 10 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 9 / 101 (8.91%) | | |
| occurrences (all) | 12 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 22 / 101 (21.78%) | | |
| occurrences (all) | 29 | | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 6 / 101 (5.94%) | | |
| occurrences (all) | 9 | | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 9 / 101 (8.91%) | | |
| occurrences (all) | 10 | | |
| Proteinuria | | | |
| subjects affected / exposed | 10 / 101 (9.90%) | | |
| occurrences (all) | 16 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |

| | | | |
|------------------------------------|-------------------|--|--|
| subjects affected / exposed | 10 / 101 (9.90%) | | |
| occurrences (all) | 12 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 7 / 101 (6.93%) | | |
| occurrences (all) | 10 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 31 / 101 (30.69%) | | |
| occurrences (all) | 48 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

| |
|------------------------------------------------------------------------------|
| These preliminary results are exploratory and further analysis are required. |
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Notes: