



## Clinical trial results:

**A single arm Phase I-II multicenter trial with avelumab plus autologous dendritic cell vaccine in pre-treated mismatch repair-proficient (MSS) metastatic colorectal cancer patients.**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2016-003838-24    |
| Trial protocol           | ES                |
| Global end of trial date | 15 September 2020 |

### Results information

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)  |
| This version publication date     | 10 March 2023   |
| First version publication date    | 10 March 2023   |
| Summary attachment (see zip file) | ICH3 CSR AVEVAC<br>(AVEVAC_Clinical_Study_Report_rev_clean.pdf) |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | GEMCAD-1602 |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03152565 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | GEMCAD   |
| Sponsor organisation address | C/ Balmes 243 5º 1º, Barcelona, Spain, 08006               |
| Public contact               | Pau Doñate, MFAR Clinical Research, investigacion@mfar.net |
| Scientific contact           | Pau Doñate, MFAR Clinical Research, investigacion@mfar.net |

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                       | 26 January 2021   |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 15 September 2020 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 15 September 2020 |
| Was the trial ended prematurely?                     | Yes               |

Notes:

## General information about the trial

Main objective of the trial:

Phase I: To determine the recommended phase II dose (RP2D) of avelumab in combination with ADC vaccine in previously treated MSS CRC patients who have progressed at least to 2 chemotherapy lines.  
Phase II: To increase the percentage (from 20% to 40%) of pre-treated MSS mCRC patients free of progression at 6 months.

Protection of trial subjects:

The protocol and the patient information sheet as well as the informed consent contain all measures needed to reduce and mitigate risks for trial subjects

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 22 March 2018 |
| 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: 19 |
| Worldwide total number of subjects   | 19        |
| EEA total number of subjects         | 19        |

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)                      | 10 |
| From 65 to 84 years                       | 9  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

28 patients were screened

### Pre-assignment period milestones

|                              |                   |
|------------------------------|-------------------|
| Number of subjects started   | 28 <sup>[1]</sup> |
| Number of subjects completed | 19                |

### Pre-assignment subject non-completion reasons

|                            |                           |
|----------------------------|---------------------------|
| Reason: Number of subjects | Not eligible patient: 8   |
| Reason: Number of subjects | Apheresis not feasible: 1 |

Notes:

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

Justification: 28 patients were screened in the pre-assignment period. Only 19 comply eligibility and were enrolled in the study and allocated to receive the study treatment

### Period 1

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

### Arms

|           |                                      |
|-----------|--------------------------------------|
| Arm title | Avelumab plus dendritic cell vaccine |
|-----------|--------------------------------------|

Arm description:

Avelumab biweekly intravenous during a maximum of 12 months and biweekly 10x10<sup>6</sup> ADC vaccine (intradermal) for five doses (days 1, 14, 28, 42 and 56) followed by a maximum of 6 doses every 6 months.

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

Dosage and administration details:

Avelumab will be administered intravenously at a dose of 10 mg per kilogram of body weight, every 14 days until disease progression or unacceptable toxicity.

|  |                                     |
|--|-------------------------------------|
| Investigational medicinal product name | Dendritic cell vaccine (autologous) |
| Investigational medicinal product code |                                     |
| Other name                             |                                     |
| Pharmaceutical forms                   | Solution for injection              |
| Routes of administration               | Intramuscular use                   |

Dosage and administration details:

10x10<sup>6</sup> ADC vaccine (intradermal) for five doses (days 1, 14, 28, 42 and 56) followed by a maximum of 6 doses every 6 months

| <b>Number of subjects in period 1</b> | Avelumab plus<br>dendritic cell vaccine |
|---------------------------------------|---|
| Started                               | 19                                      |
| Completed                             | 19                                      |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall study |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values   | Overall study | Total |  |
|--|---------------|-------|--|
| Number of subjects   | 19            | 19    |  |
| Age categorical  |               |       |  |
| Units: Subjects  |               |       |  |
| In utero   | 0             | 0     |  |
| Preterm newborn infants (gestational age < 37 wks)   | 0             | 0     |  |
| Newborns (0-27 days)   | 0             | 0     |  |
| Infants and toddlers (28 days-23 months)   | 0             | 0     |  |
| Children (2-11 years)  | 0             | 0     |  |
| Adolescents (12-17 years)  | 0             | 0     |  |
| Adults (18-64 years)   | 10            | 10    |  |
| From 65-84 years   | 9             | 9     |  |
| 85 years and over  | 0             | 0     |  |
| Gender categorical   |               |       |  |
| Units: Subjects  |               |       |  |
| Female   | 9             | 9     |  |
| Male   | 10            | 10    |  |
| IMMETCOLS  |               |       |  |
| Number of patients that consume competitively inhibitors of HMG-CoA reductase, an enzyme that limits the rate of cholesterol biosynthesis, and inhibits cholesterol synthesis in the liver.                              |               |       |  |
| Units: Subjects  |               |       |  |
| Yes  | 5             | 5     |  |
| No   | 10            | 10    |  |
| Not evaluable  | 4             | 4     |  |
| GEP  |               |       |  |
| Number of patients with expression of Granulin epithelin precursor (GEP), which is reported to function as a growth factor stimulating proliferation and migration, and conferring chemoresistance in many cancer types. |               |       |  |
| Units: Subjects  |               |       |  |
| Yes  | 5             | 5     |  |
| No   | 10            | 10    |  |
| Not evaluable  | 4             | 4     |  |
| LDH  |               |       |  |
| Measure Description: Number of patients with lactate dehydrogenase (LDH) blood levels in the normal (<234) or higher (>234) range.   |               |       |  |
| Units: Subjects  |               |       |  |
| Values < 234   | 11            | 11    |  |
| Values > 234   | 8             | 8     |  |
| Local diagnosis  |               |       |  |
| Number of patients stratified according to the local region of the primary tumor   |               |       |  |
| Units: Subjects  |               |       |  |
| Rectum   | 6             | 6     |  |

|  |    |    |  |
|--|----|----|--|
| Sigma  | 13 | 13 |  |
| Local tumor surgery  |    |    |  |
| Number of patients that had their primary tumor surgically removed   |    |    |  |
| Units: Subjects  |    |    |  |
| Yes  | 13 | 13 |  |
| No   | 6  | 6  |  |
| Previous treatment lines   |    |    |  |
| Number of patients classified by the number of previous treatment lines they had received at inclusion. The patients were clustered in 1-2 previous lines or more than 2 previous lines  |    |    |  |
| Units: Subjects  |    |    |  |
| Previous lines ≤2  | 3  | 3  |  |
| Previous lines >2  | 16 | 16 |  |
| Genotype   |    |    |  |
| Number of patients with mutations in typical candidate genes for colorectal cancer   |    |    |  |
| Units: Subjects  |    |    |  |
| All native   | 5  | 5  |  |
| KRAS mutant  | 13 | 13 |  |
| BRAF mutant  | 1  | 1  |  |
| ECOG   |    |    |  |
| Number of patients stratified by their East Cooperative Oncology Group (ECOG) performance status (PS).<br>The ECOG PS measures the performance and independence of patients to develop activities of daily living. The score ranges from 0 (fully functional) to 5 (exitus)  |    |    |  |
| Units: Subjects  |    |    |  |
| Score 0  | 13 | 13 |  |
| Score 1  | 6  | 6  |  |
| Number of affected organs  |    |    |  |
| Units: Subjects  |    |    |  |
| 1 organ  | 4  | 4  |  |
| >1 organ   | 15 | 15 |  |
| Neo/adjuvant chemotherapy  |    |    |  |
| Number of patients that received a neo/adjuvant chemotherapy regimen   |    |    |  |
| Units: Subjects  |    |    |  |
| Yes  | 2  | 2  |  |
| No   | 17 | 17 |  |
| Tumor stage at diagnosis   |    |    |  |
| Tumor stage measures the level of spread of cancer.<br>Stage 0: This is called cancer in situ.<br>Stage I: The cancer has grown through the mucosa and has invaded the muscular layer of the colon or rectum.<br>Stage II: The cancer has grown through the wall of the colon or rectum but has not spread to nearby tissue or to the nearby lymph nodes.<br>Stage III: The cancer has grown through the inner lining or into the muscle layers of the intestine. It has spread.<br>Stage IV: The cancer has spread to distant part of the body. |    |    |  |
| Units: Subjects  |    |    |  |
| Stage II   | 1  | 1  |  |
| Stage III  | 2  | 2  |  |
| Stage IV   | 16 | 16 |  |

## End points

### End points reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Avelumab plus dendritic cell vaccine |
|-----------------------|--------------------------------------|

Reporting group description:

Avelumab biweekly intravenous during a maximum of 12 months and biweekly 10x10<sup>6</sup> ADC vaccine (intradermal) for five doses (days 1, 14, 28, 42 and 56) followed by a maximum of 6 doses every 6 months.

### Primary: Dose of Avelumab in Combination With Autologous Dendritic Cells

|                 |  |
|-----------------|--|
| End point title | Dose of Avelumab in Combination With Autologous Dendritic Cells <sup>[1]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

18 months

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: This is a phase I/II trial with a single arm, non randomized, open-label design. There were no control or comparison arms contemplated by the study design. Thus, statistical comparisons are not applicable

| End point values            | Avelumab plus dendritic cell vaccine |  |  |  |
|-----------------------------|--------------------------------------|--|--|--|
| Subject group type          | Reporting group                      |  |  |  |
| Number of subjects analysed | 6 <sup>[2]</sup>                     |  |  |  |
| Units: miligram / kilogram  |                                      |  |  |  |
| number (not applicable)     | 10                                   |  |  |  |

Notes:

[2] - Only those patients in the dose escalation phase

### Statistical analyses

No statistical analyses for this end point

### Primary: Progression free survival (PFS) rate

|                 |   |
|-----------------|---|
| End point title | Progression free survival (PFS) rate <sup>[3]</sup> |
|-----------------|---|

End point description:

Percentage of patients without progression of disease at 6 months

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

End point timeframe:

6 months

Notes:

[3] - 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: This is a phase I/II trial with a single arm, non randomized, open-label design. There were no control or comparison arms contemplated by the study design. Thus, statistical comparisons are not applicable

|                             |                                      |  |  |  |
|-----------------------------|--------------------------------------|--|--|--|
| <b>End point values</b>     | Avelumab plus dendritic cell vaccine |  |  |  |
| Subject group type          | Reporting group                      |  |  |  |
| Number of subjects analysed | 19                                   |  |  |  |
| Units: Patients             |                                      |  |  |  |
| Progression-free patients   | 0                                    |  |  |  |
| Progression                 | 19                                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Progression free survival

|                 |  |
|-----------------|--|
| End point title | Progression free survival <sup>[4]</sup> |
|-----------------|--|

End point description:

Estimation by kaplan meier of the median PFS. The PFS is defined as time from treatment start until radiological progression disease according to RECIST criteria

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

End point timeframe:

Throughout the study period, average 12 months

Notes:

[4] - 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: This is a phase I/II trial with a single arm, non randomized, open-label design. There were no control or comparison arms contemplated by the study design. Thus, statistical comparisons are not applicable

|                               |                                      |  |  |  |
|-------------------------------|--------------------------------------|--|--|--|
| <b>End point values</b>       | Avelumab plus dendritic cell vaccine |  |  |  |
| Subject group type            | Reporting group                      |  |  |  |
| Number of subjects analysed   | 19                                   |  |  |  |
| Units: Months                 |                                      |  |  |  |
| median (full range (min-max)) | 3.1 (2.1 to 5.3)                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: KRAS mutational status

|                 |                        |
|-----------------|------------------------|
| End point title | KRAS mutational status |
|-----------------|------------------------|

End point description:

KRAS mutation status at baseline and during treatment.

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

End point timeframe:

18 months



| End point values            | Avelumab plus dendritic cell vaccine |  |  |  |
|-----------------------------|--------------------------------------|--|--|--|
| Subject group type          | Reporting group                      |  |  |  |
| Number of subjects analysed | 19                                   |  |  |  |
| Units: Patients             |                                      |  |  |  |
| Native                      | 6                                    |  |  |  |
| Mutant                      | 13                                   |  |  |  |
| Not evaluable               | 0                                    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: NRAS mutational status

|                        |  |
|------------------------|--|
| End point title        | NRAS mutational status                                 |
| End point description: | NRAS mutation status at baseline and during treatment. |
| End point type         | Secondary  |
| End point timeframe:   | 18 months  |

| End point values            | Avelumab plus dendritic cell vaccine |  |  |  |
|-----------------------------|--------------------------------------|--|--|--|
| Subject group type          | Reporting group                      |  |  |  |
| Number of subjects analysed | 19                                   |  |  |  |
| Units: Patients             |                                      |  |  |  |
| Native                      | 17                                   |  |  |  |
| Mutated                     | 0                                    |  |  |  |
| Not evaluable               | 2                                    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: BRAF mutational status

|                        |  |
|------------------------|--|
| End point title        | BRAF mutational status                                 |
| End point description: | BRAF mutation status at baseline and during treatment. |

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 18 months            |           |

|                             |                                      |  |  |  |
|-----------------------------|--------------------------------------|--|--|--|
| <b>End point values</b>     | Avelumab plus dendritic cell vaccine |  |  |  |
| Subject group type          | Reporting group                      |  |  |  |
| Number of subjects analysed | 19                                   |  |  |  |
| Units: Patients             |                                      |  |  |  |
| Native                      | 16                                   |  |  |  |
| Mutated                     | 1                                    |  |  |  |
| Not evaluable               | 2                                    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival

|  |                  |
|--|------------------|
| End point title  | Overall survival |
| End point description:   |                  |
| Median value of overall survival estimated by kaplan meier. Defined as time from treatment start to death from any cause |                  |
| End point type   | Secondary        |
| End point timeframe:   |                  |
| Throughout the study period, average 12 months   |                  |

|                               |                                      |  |  |  |
|-------------------------------|--------------------------------------|--|--|--|
| <b>End point values</b>       | Avelumab plus dendritic cell vaccine |  |  |  |
| Subject group type            | Reporting group                      |  |  |  |
| Number of subjects analysed   | 19                                   |  |  |  |
| Units: Months                 |                                      |  |  |  |
| median (full range (min-max)) | 12.1 (3.2 to 22.9)                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Throughout the study period, up to 24 months

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

### Dictionary used

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

|                    |     |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

### Reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Avelumab plus dendritic cell vaccine |
|-----------------------|--------------------------------------|

Reporting group description:

Avelumab biweekly intravenous during a maximum of 12 months and biweekly 10x10<sup>6</sup> ADC vaccine (intradermal) for five doses (days 1, 14, 28, 42 and 56) followed by a maximum of 6 doses every 6 months.

| Serious adverse events                               | Avelumab plus dendritic cell vaccine |  |  |
|--|--------------------------------------|--|--|
| Total subjects affected by serious adverse events    |                                      |  |  |
| subjects affected / exposed                          | 8 / 19 (42.11%)                      |  |  |
| number of deaths (all causes)                        | 18                                   |  |  |
| number of deaths resulting from adverse events       | 0                                    |  |  |
| General disorders and administration site conditions |                                      |  |  |
| Clinical deterioration                               |                                      |  |  |
| subjects affected / exposed                          | 2 / 19 (10.53%)                      |  |  |
| occurrences causally related to treatment / all      | 0 / 2                                |  |  |
| deaths causally related to treatment / all           | 0 / 0                                |  |  |
| Fever  |                                      |  |  |
| subjects affected / exposed                          | 1 / 19 (5.26%)                       |  |  |
| occurrences causally related to treatment / all      | 0 / 1                                |  |  |
| deaths causally related to treatment / all           | 0 / 0                                |  |  |
| Gastrointestinal disorders                           |                                      |  |  |
| Abdominal pain                                       |                                      |  |  |
| subjects affected / exposed                          | 1 / 19 (5.26%)                       |  |  |
| occurrences causally related to treatment / all      | 0 / 1                                |  |  |
| deaths causally related to treatment / all           | 0 / 0                                |  |  |
| Diarrhoea  |                                      |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 19 (5.26%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intestinal obstruction                          |                 |  |  |
| subjects affected / exposed                     | 2 / 19 (10.53%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vomiting  |                 |  |  |
| subjects affected / exposed                     | 1 / 19 (5.26%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Pleural effusion                                |                 |  |  |
| subjects affected / exposed                     | 1 / 19 (5.26%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Acute injury                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 19 (5.26%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Muscle weakness left-sided                      |                 |  |  |
| subjects affected / exposed                     | 1 / 19 (5.26%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Port-a-cath infection                           |                 |  |  |
| subjects affected / exposed                     | 1 / 19 (5.26%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

| <b>Non-serious adverse events</b>                     | Avelumab plus dendritic cell vaccine |  |  |
|---|--------------------------------------|--|--|
| Total subjects affected by non-serious adverse events |                                      |  |  |
| subjects affected / exposed                           | 19 / 19 (100.00%)                    |  |  |
| General disorders and administration site conditions  |                                      |  |  |
| Cough   |                                      |  |  |
| subjects affected / exposed                           | 2 / 19 (10.53%)                      |  |  |
| occurrences (all)                                     | 2                                    |  |  |
| Fatigue   |                                      |  |  |
| subjects affected / exposed                           | 11 / 19 (57.89%)                     |  |  |
| occurrences (all)                                     | 11                                   |  |  |
| Fever   |                                      |  |  |
| subjects affected / exposed                           | 5 / 19 (26.32%)                      |  |  |
| occurrences (all)                                     | 5                                    |  |  |
| Infected cyst   |                                      |  |  |
| subjects affected / exposed                           | 1 / 19 (5.26%)                       |  |  |
| occurrences (all)                                     | 1                                    |  |  |
| Pain  |                                      |  |  |
| subjects affected / exposed                           | 2 / 19 (10.53%)                      |  |  |
| occurrences (all)                                     | 2                                    |  |  |
| Chills  |                                      |  |  |
| subjects affected / exposed                           | 1 / 19 (5.26%)                       |  |  |
| occurrences (all)                                     | 1                                    |  |  |
| Myalgia   |                                      |  |  |
| subjects affected / exposed                           | 1 / 19 (5.26%)                       |  |  |
| occurrences (all)                                     | 1                                    |  |  |
| Neck pain   |                                      |  |  |
| subjects affected / exposed                           | 1 / 19 (5.26%)                       |  |  |
| occurrences (all)                                     | 1                                    |  |  |
| Night sweats  |                                      |  |  |
| subjects affected / exposed                           | 1 / 19 (5.26%)                       |  |  |
| occurrences (all)                                     | 1                                    |  |  |
| Pain in extremity                                     |                                      |  |  |
| subjects affected / exposed                           | 1 / 19 (5.26%)                       |  |  |
| occurrences (all)                                     | 1                                    |  |  |
| Pelvic pain   |                                      |  |  |

|  |  |  |  |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Perineal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 19 (5.26%)</p> <p>1</p> <p>1 / 19 (5.26%)</p> <p>1</p>  |  |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>chest wall pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pneumonitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 19 (5.26%)</p> <p>1</p> <p>1 / 19 (5.26%)</p> <p>1</p>  |  |  |
| <p>Psychiatric disorders</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Memory impairment</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Mood disorder due to a general medical condition</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>1 / 19 (5.26%)</p> <p>1</p> <p>1 / 19 (5.26%)</p> <p>1</p> <p>1 / 19 (5.26%)</p> <p>1</p>                                 |  |  |
| <p>Investigations</p> <p>Hypocalcaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ALT increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>AST increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>LDH increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>bilirubin increased</p> | <p>1 / 19 (5.26%)</p> <p>1</p> <p>1 / 19 (5.26%)</p> <p>1</p> <p>1 / 19 (5.26%)</p> <p>1</p> <p>4 / 19 (21.05%)</p> <p>4</p> |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 19 (5.26%)<br>1  |  |  |
| creatinine increased<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 19 (5.26%)<br>1  |  |  |
| low hematocrit<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 19 (5.26%)<br>1  |  |  |
| Nervous system disorders<br>peripheral neuropathy<br>subjects affected / exposed<br>occurrences (all) | 3 / 19 (15.79%)<br>3 |  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 1 / 19 (5.26%)<br>1  |  |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 19 (5.26%)<br>1  |  |  |
| Blood and lymphatic system disorders<br>Erythema<br>subjects affected / exposed<br>occurrences (all)  | 1 / 19 (5.26%)<br>1  |  |  |
| platelet count decrease<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 19 (5.26%)<br>1  |  |  |
| Ear and labyrinth disorders<br>Ear pain<br>subjects affected / exposed<br>occurrences (all)           | 1 / 19 (5.26%)<br>1  |  |  |
| Eye disorders<br>decline of vision<br>subjects affected / exposed<br>occurrences (all)                | 1 / 19 (5.26%)<br>1  |  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)      | 4 / 19 (21.05%)<br>4 |  |  |

|                              |                 |  |  |
|------------------------------|-----------------|--|--|
| Constipation                 |                 |  |  |
| subjects affected / exposed  | 4 / 19 (21.05%) |  |  |
| occurrences (all)            | 4               |  |  |
| Diarrhoea                    |                 |  |  |
| subjects affected / exposed  | 3 / 19 (15.79%) |  |  |
| occurrences (all)            | 3               |  |  |
| Flank pain                   |                 |  |  |
| subjects affected / exposed  | 1 / 19 (5.26%)  |  |  |
| occurrences (all)            | 1               |  |  |
| Intestinal obstruction       |                 |  |  |
| subjects affected / exposed  | 2 / 19 (10.53%) |  |  |
| occurrences (all)            | 2               |  |  |
| Small intestinal obstruction |                 |  |  |
| subjects affected / exposed  | 2 / 19 (10.53%) |  |  |
| occurrences (all)            | 2               |  |  |
| Vomiting                     |                 |  |  |
| subjects affected / exposed  | 3 / 19 (15.79%) |  |  |
| occurrences (all)            | 3               |  |  |
| anal pain                    |                 |  |  |
| subjects affected / exposed  | 1 / 19 (5.26%)  |  |  |
| occurrences (all)            | 1               |  |  |
| Dysphagia                    |                 |  |  |
| subjects affected / exposed  | 1 / 19 (5.26%)  |  |  |
| occurrences (all)            | 1               |  |  |
| Mucositis oral               |                 |  |  |
| subjects affected / exposed  | 1 / 19 (5.26%)  |  |  |
| occurrences (all)            | 1               |  |  |
| Nausea                       |                 |  |  |
| subjects affected / exposed  | 1 / 19 (5.26%)  |  |  |
| occurrences (all)            | 1               |  |  |
| rectal hemorrhage            |                 |  |  |
| subjects affected / exposed  | 1 / 19 (5.26%)  |  |  |
| occurrences (all)            | 1               |  |  |
| Toothache                    |                 |  |  |
| subjects affected / exposed  | 1 / 19 (5.26%)  |  |  |
| occurrences (all)            | 1               |  |  |



|  |  |  |  |
|--|--|--|--|
| flu like symptoms<br>subjects affected / exposed<br>occurrences (all)  | 1 / 19 (5.26%)<br>1  |  |  |
| Hepatobiliary disorders<br>Hepatic pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 19 (5.26%)<br>1  |  |  |
| Skin and subcutaneous tissue disorders<br>Urticaria<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin toxicity<br>subjects affected / exposed<br>occurrences (all)<br><br>bollous dermatitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash<br>subjects affected / exposed<br>occurrences (all)<br><br>Pruritus<br>subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1<br><br>1 / 19 (5.26%)<br>1<br><br>1 / 19 (5.26%)<br>1<br><br>1 / 19 (5.26%)<br>1<br><br>2 / 19 (10.53%)<br>2 |  |  |
| Renal and urinary disorders<br>hematuria<br>subjects affected / exposed<br>occurrences (all)   | 1 / 19 (5.26%)<br>1  |  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Bone pain  | 2 / 19 (10.53%)<br>2<br><br>4 / 19 (21.05%)<br>4   |  |  |

|                                    |                 |  |  |
|------------------------------------|-----------------|--|--|
| subjects affected / exposed        | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| tendinitis                         |                 |  |  |
| subjects affected / exposed        | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Infections and infestations        |                 |  |  |
| upper respiratory infection        |                 |  |  |
| subjects affected / exposed        | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Urinary tract infection            |                 |  |  |
| subjects affected / exposed        | 2 / 19 (10.53%) |  |  |
| occurrences (all)                  | 2               |  |  |
| Tooth infection                    |                 |  |  |
| subjects affected / exposed        | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| ALK increased                      |                 |  |  |
| subjects affected / exposed        | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Metabolism and nutrition disorders |                 |  |  |
| Anorexia and bulimia syndrome      |                 |  |  |
| subjects affected / exposed        | 3 / 19 (15.79%) |  |  |
| occurrences (all)                  | 3               |  |  |
| hyperglycaemia                     |                 |  |  |
| subjects affected / exposed        | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Hypothyroidism                     |                 |  |  |
| subjects affected / exposed        | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                  | 1               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment                       |
|--------------|---------------------------------|
| 31 July 2019 | changes in eligibility criteria |

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 study was ended prematurely due to lack of efficacy |
|---|

Notes: