



## Clinical trial results:

### A Phase IIIB, Single Arm, Multicenter Study of Atezolizumab (Tecentriq) in Combination With Bevacizumab to Investigate Safety and Efficacy in Patients With Unresectable Hepatocellular Carcinoma Not Previously Treated With Systemic Therapy-AMETHISTA

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2020-001973-66 |
| Trial protocol           | IT             |
| Global end of trial date | 13 August 2024 |

#### Results information

|                                |                                                                                                                 |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Result version number          | v2 (current)                                                                                                    |
| This version publication date  | 23 October 2025                                                                                                 |
| First version publication date | 27 August 2025                                                                                                  |
| Version creation reason        | <ul style="list-style-type: none"><li>Correction of full data set</li><li>Correction to AE Time Frame</li></ul> |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | ML42243 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04487067 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                     |
|------------------------------|-----------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | F. Hoffmann-La Roche AG                                                                             |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4058                                                  |
| Public contact               | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact           | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |

Notes:

#### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                |
|------------------------------------------------------|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 26 May 2025    |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 13 August 2024 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

The primary purpose of this study was to evaluate the safety of atezolizumab in combination with bevacizumab in terms of bleeding/haemorrhage in participants with unresectable hepatocellular carcinoma (HCC) who received no prior systemic treatment.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 25 August 2020   |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 44 Months        |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Italy: 152 |
| Worldwide total number of subjects   | 152        |
| EEA total number of subjects         | 152        |

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)                      | 60 |
| From 65 to 84 years                       | 87 |
| 85 years and over                         | 5  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 152 participants with unresectable HCC and no prior systemic treatment took part in the study at 21 investigative sites in Italy from 25 August 2020 to 13 August 2024.

### Pre-assignment

Screening details:

Participants received atezolizumab in combination with bevacizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator. Of the 152 participants enrolled, three participants did not receive any 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

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | Atezolizumab + Bevacizumab |
|------------------|----------------------------|

Arm description:

Participants received atezolizumab, 1200 milligrams (mg) as intravenous (IV) infusion, along with bevacizumab, 15 milligrams/kilogram (mg/kg), also as IV infusion, every 3 weeks (Q3W) on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Bevacizumab           |
| Investigational medicinal product code | RO4876646             |
| Other name                             | Avastin               |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Bevacizumab, 15 mg/kg, IV, was administered Q3W on Day 1 of each 21-day cycle.

|                                        |                       |
|----------------------------------------|-----------------------|
| Investigational medicinal product name | Atezolizumab          |
| Investigational medicinal product code | RO5541267             |
| Other name                             | Tecentriq             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Atezolizumab, 1200 mg, IV, was administered Q3W on Day 1 of each 21-day cycle.

| Number of subjects in period 1 | Atezolizumab + Bevacizumab |
|--------------------------------|----------------------------|
| Started                        | 152                        |
| Safety analysis population     | 149                        |
| Completed                      | 21                         |
| Not completed                  | 131                        |
| Consent withdrawn by subject   | 15                         |
| Adverse Event                  | 3                          |

|                                            |    |
|--------------------------------------------|----|
| Progressive Disease                        | 1  |
| Discontinuation From Study as per Protocol | 6  |
| Lost to follow-up                          | 3  |
| Death Due To Progressive Disease           | 40 |
| Death Other Than Progressive Disease       | 60 |
| Protocol deviation                         | 3  |

## Baseline characteristics

### Reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Atezolizumab + Bevacizumab |
|-----------------------|----------------------------|

Reporting group description:

Participants received atezolizumab, 1200 milligrams (mg) as intravenous (IV) infusion, along with bevacizumab, 15 milligrams/kilogram (mg/kg), also as IV infusion, every 3 weeks (Q3W) on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

| Reporting group values | Atezolizumab + Bevacizumab | Total |  |
|------------------------|----------------------------|-------|--|
| Number of subjects     | 152                        | 152   |  |
| Age categorical        |                            |       |  |
| Units: Subjects        |                            |       |  |

|                                           |         |     |  |
|-------------------------------------------|---------|-----|--|
| Age Continuous                            |         |     |  |
| Units: years                              |         |     |  |
| arithmetic mean                           | 67.1    |     |  |
| standard deviation                        | ± 10.52 | -   |  |
| Sex: Female, Male                         |         |     |  |
| Units: participants                       |         |     |  |
| Female                                    | 31      | 31  |  |
| Male                                      | 121     | 121 |  |
| Race (NIH/OMB)                            |         |     |  |
| Units: Subjects                           |         |     |  |
| American Indian or Alaska Native          | 0       | 0   |  |
| Asian                                     | 3       | 3   |  |
| Native Hawaiian or Other Pacific Islander | 0       | 0   |  |
| Black or African American                 | 0       | 0   |  |
| White                                     | 145     | 145 |  |
| More than one race                        | 0       | 0   |  |
| Unknown or Not Reported                   | 4       | 4   |  |
| Ethnicity (NIH/OMB)                       |         |     |  |
| Units: Subjects                           |         |     |  |
| Hispanic or Latino                        | 5       | 5   |  |
| Not Hispanic or Latino                    | 141     | 141 |  |
| Unknown or Not Reported                   | 6       | 6   |  |

## End points

### End points reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Atezolizumab + Bevacizumab |
|-----------------------|----------------------------|

Reporting group description:

Participants received atezolizumab, 1200 milligrams (mg) as intravenous (IV) infusion, along with bevacizumab, 15 milligrams/kilogram (mg/kg), also as IV infusion, every 3 weeks (Q3W) on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

### Primary: Number of Participants With Grade 3-5 National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) Bleeding/Haemorrhage

|                 |                                                                                                                                                                                  |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants With Grade 3-5 National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) Bleeding/Haemorrhage <sup>[1]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Severity of AEs was graded using NCI CTCAE v5.0. Grade 3=Severe/medically significant but not immediately life-threatening, hospitalization/prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living; Grade 4=Life-threatening consequences, urgent intervention indicated; Grade 5=Death related to AE. Safety analysis population included all enrolled participants who had at least one full or partial administration of atezolizumab plus bevacizumab.

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

End point timeframe:

Up to approximately 47.6 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: No statistical analysis for this end point.

| End point values            | Atezolizumab + Bevacizumab |  |  |  |
|-----------------------------|----------------------------|--|--|--|
| Subject group type          | Reporting group            |  |  |  |
| Number of subjects analysed | 149                        |  |  |  |
| Units: participants         |                            |  |  |  |
| Grade 3                     | 17                         |  |  |  |
| Grade 4                     | 3                          |  |  |  |
| Grade 5                     | 2                          |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Response Rate (ORR)

|                 |                               |
|-----------------|-------------------------------|
| End point title | Objective Response Rate (ORR) |
|-----------------|-------------------------------|

End point description:

ORR was defined as the percentage of participants with complete or partial response (CR or PR), as

determined by the investigator according to RECIST v1.1. CR was defined as disappearance of all target lesions or any pathological lymph nodes must have reduction in short axis to < 10 mm. PR was defined as at least a 30% decrease in the SOD of all target lesions, taking as reference the baseline SOD, in the absence of CR. ITT population included all participants who signed the ICF and were enrolled in the study.

|                                 |           |
|---------------------------------|-----------|
| End point type                  | Secondary |
| End point timeframe:            |           |
| Up to approximately 47.6 months |           |

|                                   |                            |  |  |  |
|-----------------------------------|----------------------------|--|--|--|
| <b>End point values</b>           | Atezolizumab + Bevacizumab |  |  |  |
| Subject group type                | Reporting group            |  |  |  |
| Number of subjects analysed       | 152                        |  |  |  |
| Units: percentage of participants |                            |  |  |  |
| number (not applicable)           | 28.29                      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression-free Survival (PFS)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Progression-free Survival (PFS) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                 |
| PFS was defined as the time from initiation of study treatment to the first occurrence of disease progression (PD) or death from any cause (whichever occurs first), as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). PD was defined as at least a 20% increase in the sum of diameters (SOD) of target lesions, taking as reference the smallest SOD at prior timepoints (including baseline). In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of $\geq 5$ millimeters (mm). Participants alive and without any PD were censored at the last assessment date. K-M method was used to estimate the PFS. ITT population included all participants who signed the ICF and were enrolled in the study. Number analyzed is the number of participants with data available for analysis. |                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Secondary                       |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                 |
| Up to approximately 47.6 months                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                 |

|                                  |                            |  |  |  |
|----------------------------------|----------------------------|--|--|--|
| <b>End point values</b>          | Atezolizumab + Bevacizumab |  |  |  |
| Subject group type               | Reporting group            |  |  |  |
| Number of subjects analysed      | 149                        |  |  |  |
| Units: months                    |                            |  |  |  |
| median (confidence interval 95%) | 8.80 (7.89 to 11.24)       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Progression (TTP)

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

End point description:

TTP was defined as the time from initiation of study treatment to the first occurrence of PD, as determined by the investigator according to RECIST v1.1. PD was defined as at least a 20% increase in the SOD of target lesions, taking as reference the smallest SOD at prior timepoints (including baseline). In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of  $\geq 5$  mm. Participants without any PD were censored at the last assessment date. K-M method was used to estimate the TTP. ITT population included all participants who signed the ICF and were enrolled in the study. Number analyzed is the number of participants with data available for analysis.

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

End point timeframe:

Up to approximately 47.6 months

|                                  |                            |  |  |  |
|----------------------------------|----------------------------|--|--|--|
| <b>End point values</b>          | Atezolizumab + Bevacizumab |  |  |  |
| Subject group type               | Reporting group            |  |  |  |
| Number of subjects analysed      | 149                        |  |  |  |
| Units: months                    |                            |  |  |  |
| median (confidence interval 95%) | 11.24 (8.48 to 15.77)      |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| End point title | Number of Participants With Treatment-Emergent Adverse Events (TEAEs) |
|-----------------|-----------------------------------------------------------------------|

End point description:

An AE was any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. TEAEs are defined as AEs with onset date on or after the start of the first study treatment component. Safety analysis population included all enrolled participants who had at least one full or partial administration of atezolizumab plus bevacizumab. Number of participants with any TEAEs are reported here.

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

End point timeframe:

Up to approximately 47.6 months

|                             |                            |  |  |  |
|-----------------------------|----------------------------|--|--|--|
| <b>End point values</b>     | Atezolizumab + Bevacizumab |  |  |  |
| Subject group type          | Reporting group            |  |  |  |
| Number of subjects analysed | 149                        |  |  |  |
| Units: participants         | 144                        |  |  |  |

## 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 the time from initiation of study treatment to death from any cause. Kaplan-Meier (K-M) method was used to estimate the OS. ITT population included all participants who signed the ICF and were enrolled in the study. Number analyzed is the number of participants with data available for analysis. |                       |
| End point type                                                                                                                                                                                                                                                                                                            | Secondary             |
| End point timeframe:                                                                                                                                                                                                                                                                                                      |                       |
| Up to approximately 47.6 months                                                                                                                                                                                                                                                                                           |                       |

|                                  |                            |  |  |  |
|----------------------------------|----------------------------|--|--|--|
| <b>End point values</b>          | Atezolizumab + Bevacizumab |  |  |  |
| Subject group type               | Reporting group            |  |  |  |
| Number of subjects analysed      | 149                        |  |  |  |
| Units: months                    |                            |  |  |  |
| median (confidence interval 95%) | 20.76 (16.85 to 26.35)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Reporting Severe Symptoms in Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Questionnaire

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Number of Participants Reporting Severe Symptoms in Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Questionnaire |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                               |
| Participants self-reported symptomatic AEs using PRO-CTCAE, a validated item bank used to characterize presence, frequency of occurrence, severity, &/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities. PRO-CTCAE contains questions that are rated either dichotomously (for determination of presence vs. absence)/ on a 5-point Likert scale (for determination of frequency of occurrence, severity, & interference with daily function). Treatment toxicities can occur with observable signs (e.g., vomiting)/ non-observable symptoms (e.g., nausea). Subset of 14 symptoms most applicable to current treatments were selected for this study. Symptoms were selected based on toxicities associated with drug's class, mechanism of action, or mode of administration, & toxicities reported with drug in another indication. Participants reporting severe |                                                                                                                                                               |

symptoms per the PRO-CTCAE questionnaire on Day 1 of each cycle is reported here. Safety analysis population.

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

End point timeframe:

From Cycle 1 Day 1 to Cycle 63 Day 1 (1 Cycle = 21 days)

| End point values            | Atezolizumab + Bevacizumab |  |  |  |
|-----------------------------|----------------------------|--|--|--|
| Subject group type          | Reporting group            |  |  |  |
| Number of subjects analysed | 149                        |  |  |  |
| Units: participants         |                            |  |  |  |
| Cycle 1 Day 1               | 39                         |  |  |  |
| Cycle 2 Day 1               | 33                         |  |  |  |
| Cycle 3 Day 1               | 23                         |  |  |  |
| Cycle 4 Day 1               | 30                         |  |  |  |
| Cycle 5 Day 1               | 23                         |  |  |  |
| Cycle 6 Day 1               | 22                         |  |  |  |
| Cycle 7 Day 1               | 17                         |  |  |  |
| Cycle 8 Day 1               | 14                         |  |  |  |
| Cycle 9 Day 1               | 19                         |  |  |  |
| Cycle 10 Day 1              | 16                         |  |  |  |
| Cycle 11 Day 1              | 17                         |  |  |  |
| Cycle 12 Day 1              | 16                         |  |  |  |
| Cycle 13 Day 1              | 13                         |  |  |  |
| Cycle 14 Day 1              | 13                         |  |  |  |
| Cycle 15 Day 1              | 9                          |  |  |  |
| Cycle 16 Day 1              | 8                          |  |  |  |
| Cycle 17 Day 1              | 10                         |  |  |  |
| Cycle 18 Day 1              | 10                         |  |  |  |
| Cycle 19 Day 1              | 8                          |  |  |  |
| Cycle 20 Day 1              | 11                         |  |  |  |
| Cycle 21 Day 1              | 5                          |  |  |  |
| Cycle 22 Day 1              | 6                          |  |  |  |
| Cycle 23 Day 1              | 8                          |  |  |  |
| Cycle 24 Day 1              | 10                         |  |  |  |
| Cycle 25 Day 1              | 8                          |  |  |  |
| Cycle 26 Day 1              | 7                          |  |  |  |
| Cycle 27 Day 1              | 8                          |  |  |  |
| Cycle 28 Day 1              | 10                         |  |  |  |
| Cycle 29 Day 1              | 6                          |  |  |  |
| Cycle 30 Day 1              | 7                          |  |  |  |
| Cycle 31 Day 1              | 7                          |  |  |  |
| Cycle 32 Day 1              | 6                          |  |  |  |
| Cycle 33 Day 1              | 6                          |  |  |  |
| Cycle 34 Day 1              | 7                          |  |  |  |
| Cycle 35 Day 1              | 9                          |  |  |  |
| Cycle 36 Day 1              | 8                          |  |  |  |
| Cycle 37 Day 1              | 7                          |  |  |  |
| Cycle 38 Day 1              | 9                          |  |  |  |

|                |   |  |  |  |
|----------------|---|--|--|--|
| Cycle 39 Day 1 | 8 |  |  |  |
| Cycle 40 Day 1 | 8 |  |  |  |
| Cycle 41 Day 1 | 5 |  |  |  |
| Cycle 42 Day 1 | 6 |  |  |  |
| Cycle 43 Day 1 | 3 |  |  |  |
| Cycle 44 Day 1 | 3 |  |  |  |
| Cycle 45 Day 1 | 3 |  |  |  |
| Cycle 46 Day 1 | 2 |  |  |  |
| Cycle 47 Day 1 | 2 |  |  |  |
| Cycle 48 Day 1 | 3 |  |  |  |
| Cycle 49 Day 1 | 3 |  |  |  |
| Cycle 50 Day 1 | 2 |  |  |  |
| Cycle 51 Day 1 | 3 |  |  |  |
| Cycle 52 Day 1 | 2 |  |  |  |
| Cycle 53 Day 1 | 2 |  |  |  |
| Cycle 54 Day 1 | 1 |  |  |  |
| Cycle 55 Day 1 | 1 |  |  |  |
| Cycle 56 Day 1 | 1 |  |  |  |
| Cycle 57 Day 1 | 0 |  |  |  |
| Cycle 58 Day 1 | 0 |  |  |  |
| Cycle 59 Day 1 | 0 |  |  |  |
| Cycle 60 Day 1 | 0 |  |  |  |
| Cycle 61 Day 1 | 0 |  |  |  |
| Cycle 62 Day 1 | 0 |  |  |  |
| Cycle 63 Day 1 | 0 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response (DOR)

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

End point description:

DOR was defined as the time from the first occurrence of a documented objective response (CR or PR) to PD or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1. CR=disappearance of all target lesions or any pathological lymph nodes must have reduction in short axis to < 10 mm. PR=at least a 30% decrease in the SOD of all target lesions, taking as reference the baseline SOD, in the absence of CR. PD was defined as at least a 20% increase in the SOD of target lesions, taking as reference the smallest SOD at prior timepoints (including baseline). In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of  $\geq 5$  mm. Participants who were alive and without any PD were censored at the last assessment date. K-M method was used to estimate the DOR. ITT population included all participants who signed the ICF and were enrolled in the study. Number analyzed is the number of participants with CR or PR.

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

End point timeframe:

Up to approximately 47.6 months

|                                  |                            |  |  |  |
|----------------------------------|----------------------------|--|--|--|
| <b>End point values</b>          | Atezolizumab + Bevacizumab |  |  |  |
| Subject group type               | Reporting group            |  |  |  |
| Number of subjects analysed      | 43                         |  |  |  |
| Units: months                    |                            |  |  |  |
| median (confidence interval 95%) | 17.35 (13.54 to 27.24)     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Post-progression Survival (PPS)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Post-progression Survival (PPS) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                 |
| PPS was defined as the time from the first occurrence of PD as determined by the investigator according to RECIST v1.1 to death from any cause. PD was defined as at least a 20% increase in the SOD of target lesions, taking as reference the smallest SOD at prior timepoints (including baseline). In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of $\geq 5$ mm. Participants who were alive were censored at the last assessment date. K-M method was used to estimate the PPS. ITT population included all participants who signed the ICF and were enrolled in the study. Number analyzed is the number of participants with a progressive disease. |                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Secondary                       |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                 |
| Up to approximately 47.6 months                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                 |

|                                  |                            |  |  |  |
|----------------------------------|----------------------------|--|--|--|
| <b>End point values</b>          | Atezolizumab + Bevacizumab |  |  |  |
| Subject group type               | Reporting group            |  |  |  |
| Number of subjects analysed      | 97                         |  |  |  |
| Units: months                    |                            |  |  |  |
| median (confidence interval 95%) | 11.27 (8.41 to 13.80)      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Reporting Very Severe Symptoms in PRO-CTCAE Questionnaire

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Number of Participants Reporting Very Severe Symptoms in PRO-CTCAE Questionnaire |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                  |
| Participants self-reported symptomatic AEs using PRO-CTCAE, a validated item bank used to characterize presence, frequency of occurrence, severity, &/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities. PRO-CTCAE contains questions that are rated either dichotomously (for determination of presence vs. absence)/ on a 5-point Likert scale (for determination of frequency of occurrence, severity & interference with daily function). Treatment toxicities can occur with observable signs (e.g.vomiting)/ non-observable symptoms (e.g.nausea). |                                                                                  |

Subset of 14 symptoms most applicable to current treatments were selected for this study. Symptoms were selected based on toxicities associated with drug's class, mechanism of action/ mode of administration, & toxicities reported with drug in another indication. Participants reporting very severe symptoms per the PRO-CTCAE questionnaire on Day 1 of each cycle is reported here. Safety analysis population.

|                                                          |           |
|----------------------------------------------------------|-----------|
| End point type                                           | Secondary |
| End point timeframe:                                     |           |
| From Cycle 1 Day 1 to Cycle 63 Day 1 (1 Cycle = 21 days) |           |

| End point values            | Atezolizumab + Bevacizumab |  |  |  |
|-----------------------------|----------------------------|--|--|--|
| Subject group type          | Reporting group            |  |  |  |
| Number of subjects analysed | 149                        |  |  |  |
| Units: participants         |                            |  |  |  |
| Cycle 1 Day 1               | 15                         |  |  |  |
| Cycle 2 Day 1               | 18                         |  |  |  |
| Cycle 3 Day 1               | 12                         |  |  |  |
| Cycle 4 Day 1               | 12                         |  |  |  |
| Cycle 5 Day 1               | 10                         |  |  |  |
| Cycle 6 Day 1               | 11                         |  |  |  |
| Cycle 7 Day 1               | 7                          |  |  |  |
| Cycle 8 Day 1               | 11                         |  |  |  |
| Cycle 9 Day 1               | 7                          |  |  |  |
| Cycle 10 Day 1              | 7                          |  |  |  |
| Cycle 11 Day 1              | 6                          |  |  |  |
| Cycle 12 Day 1              | 5                          |  |  |  |
| Cycle 13 Day 1              | 7                          |  |  |  |
| Cycle 14 Day 1              | 7                          |  |  |  |
| Cycle 15 Day 1              | 7                          |  |  |  |
| Cycle 16 Day 1              | 8                          |  |  |  |
| Cycle 17 Day 1              | 4                          |  |  |  |
| Cycle 18 Day 1              | 5                          |  |  |  |
| Cycle 19 Day 1              | 4                          |  |  |  |
| Cycle 20 Day 1              | 4                          |  |  |  |
| Cycle 21 Day 1              | 1                          |  |  |  |
| Cycle 22 Day 1              | 4                          |  |  |  |
| Cycle 23 Day 1              | 2                          |  |  |  |
| Cycle 24 Day 1              | 3                          |  |  |  |
| Cycle 25 Day 1              | 4                          |  |  |  |
| Cycle 26 Day 1              | 4                          |  |  |  |
| Cycle 27 Day 1              | 3                          |  |  |  |
| Cycle 28 Day 1              | 3                          |  |  |  |
| Cycle 29 Day 1              | 3                          |  |  |  |
| Cycle 30 Day 1              | 2                          |  |  |  |
| Cycle 31 Day 1              | 4                          |  |  |  |
| Cycle 32 Day 1              | 3                          |  |  |  |
| Cycle 33 Day 1              | 3                          |  |  |  |
| Cycle 34 Day 1              | 5                          |  |  |  |
| Cycle 35 Day 1              | 5                          |  |  |  |
| Cycle 36 Day 1              | 3                          |  |  |  |

|                |   |  |  |  |
|----------------|---|--|--|--|
| Cycle 37 Day 1 | 6 |  |  |  |
| Cycle 38 Day 1 | 4 |  |  |  |
| Cycle 39 Day 1 | 4 |  |  |  |
| Cycle 40 Day 1 | 4 |  |  |  |
| Cycle 41 Day 1 | 4 |  |  |  |
| Cycle 42 Day 1 | 5 |  |  |  |
| Cycle 43 Day 1 | 4 |  |  |  |
| Cycle 44 Day 1 | 4 |  |  |  |
| Cycle 45 Day 1 | 2 |  |  |  |
| Cycle 46 Day 1 | 2 |  |  |  |
| Cycle 47 Day 1 | 1 |  |  |  |
| Cycle 48 Day 1 | 1 |  |  |  |
| Cycle 49 Day 1 | 0 |  |  |  |
| Cycle 50 Day 1 | 1 |  |  |  |
| Cycle 51 Day 1 | 0 |  |  |  |
| Cycle 52 Day 1 | 1 |  |  |  |
| Cycle 53 Day 1 | 1 |  |  |  |
| Cycle 54 Day 1 | 0 |  |  |  |
| Cycle 55 Day 1 | 1 |  |  |  |
| Cycle 56 Day 1 | 0 |  |  |  |
| Cycle 57 Day 1 | 1 |  |  |  |
| Cycle 58 Day 1 | 0 |  |  |  |
| Cycle 59 Day 1 | 0 |  |  |  |
| Cycle 60 Day 1 | 0 |  |  |  |
| Cycle 61 Day 1 | 0 |  |  |  |
| Cycle 62 Day 1 | 0 |  |  |  |
| Cycle 63 Day 1 | 0 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Other AEs: Up to approximately 47.6 months

SAEs and All-cause Mortality: Up to approximately 47.6 months

Adverse event reporting additional description:

Safety analysis population included all enrolled participants who had at least one full or partial administration of atezolizumab plus bevacizumab.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 27.1 |
|--------------------|------|

### Reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Atezolizumab + Bevacizumab |
|-----------------------|----------------------------|

Reporting group description:

Participants received atezolizumab, 1200 mg as IV infusion, along with bevacizumab, 15 mg/kg, also as IV infusion, Q3W on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

| Serious adverse events                                              | Atezolizumab + Bevacizumab |  |  |
|---------------------------------------------------------------------|----------------------------|--|--|
| Total subjects affected by serious adverse events                   |                            |  |  |
| subjects affected / exposed                                         | 62 / 149 (41.61%)          |  |  |
| number of deaths (all causes)                                       | 102                        |  |  |
| number of deaths resulting from adverse events                      | 3                          |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                            |  |  |
| Tumour haemorrhage                                                  |                            |  |  |
| subjects affected / exposed                                         | 1 / 149 (0.67%)            |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                      |  |  |
| deaths causally related to treatment / all                          | 0 / 0                      |  |  |
| Vascular disorders                                                  |                            |  |  |
| Haemorrhage                                                         |                            |  |  |
| subjects affected / exposed                                         | 2 / 149 (1.34%)            |  |  |
| occurrences causally related to treatment / all                     | 2 / 2                      |  |  |
| deaths causally related to treatment / all                          | 0 / 0                      |  |  |
| Deep vein thrombosis                                                |                            |  |  |
| subjects affected / exposed                                         | 1 / 149 (0.67%)            |  |  |
| occurrences causally related to treatment / all                     | 1 / 1                      |  |  |
| deaths causally related to treatment / all                          | 0 / 0                      |  |  |
| Pelvic venous thrombosis                                            |                            |  |  |

|                                                      |                 |  |  |
|------------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                          | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Shock haemorrhagic                                   |                 |  |  |
| subjects affected / exposed                          | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 1 / 1           |  |  |
| Thrombophlebitis                                     |                 |  |  |
| subjects affected / exposed                          | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Surgical and medical procedures                      |                 |  |  |
| Leg amputation                                       |                 |  |  |
| subjects affected / exposed                          | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Chest pain                                           |                 |  |  |
| subjects affected / exposed                          | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Oedema                                               |                 |  |  |
| subjects affected / exposed                          | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Oedema peripheral                                    |                 |  |  |
| subjects affected / exposed                          | 2 / 149 (1.34%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Pyrexia                                              |                 |  |  |
| subjects affected / exposed                          | 2 / 149 (1.34%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Dyspnoea                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Epistaxis                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemoptysis                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Interstitial lung disease                       |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 5 / 149 (3.36%) |  |  |
| occurrences causally related to treatment / all | 4 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Confusional state                               |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Investigations                                  |                 |  |  |
| Blood bilirubin increased                       |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Electrocardiogram abnormal                      |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Accidental exposure to product                  |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Femur fracture                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Humerus fracture                                |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infusion related reaction                       |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thermal burn                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ulna fracture                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Wound dehiscence                                |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Cardiac arrest                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Cardiac failure                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Myocardial infarction                           |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bradycardia                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Angina unstable                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Ataxia                                          |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Encephalopathy                                  |                 |  |  |
| subjects affected / exposed                     | 2 / 149 (1.34%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Headache                                        |                 |  |  |
| subjects affected / exposed                     | 2 / 149 (1.34%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatic encephalopathy                          |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 2 / 149 (1.34%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypoglycaemic coma                              |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Syncope                                         |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Transient ischaemic attack                      |                 |  |  |
| subjects affected / exposed                     | 2 / 149 (1.34%) |  |  |
| occurrences causally related to treatment / all | 2 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Iron deficiency anaemia                         |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Anaemia                                         |                 |  |  |
| subjects affected / exposed                     | 3 / 149 (2.01%) |  |  |
| occurrences causally related to treatment / all | 2 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Eye disorders                                   |                 |  |  |
| Diplopia                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Nausea                                          |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Enterovesical fistula                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |  |
| Gastric haemorrhage                             |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Gastrointestinal haemorrhage                    |                 |  |  |  |
| subjects affected / exposed                     | 3 / 149 (2.01%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Haematemesis                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Haemoperitoneum                                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Large intestinal haemorrhage                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Melaena                                         |                 |  |  |  |
| subjects affected / exposed                     | 2 / 149 (1.34%) |  |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Ascites                                         |                 |  |  |  |
| subjects affected / exposed                     | 3 / 149 (2.01%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Oesophageal varices haemorrhage                 |                 |  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 4 / 149 (2.68%) |  |  |
| occurrences causally related to treatment / all | 2 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancreatic haemorrhage                          |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rectal haemorrhage                              |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Small intestinal haemorrhage                    |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 1 / 1           |  |  |
| Upper gastrointestinal haemorrhage              |                 |  |  |
| subjects affected / exposed                     | 2 / 149 (1.34%) |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Bile duct stone                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholangitis                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholecystitis                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatic failure                                 |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Dermatitis bullous                              |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Purpura                                         |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Acute kidney injury                             |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Proteinuria                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal failure                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Infections and infestations                     |                 |  |  |
| Biliary tract infection                         |                 |  |  |
| subjects affected / exposed                     | 2 / 149 (1.34%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Brain abscess                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| COVID-19                                        |                 |  |  |
| subjects affected / exposed                     | 4 / 149 (2.68%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| COVID-19 pneumonia                              |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Gangrene                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infection                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Peri-implantitis                                |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 2 / 149 (1.34%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Sepsis                                          |                 |  |  |
| subjects affected / exposed                     | 5 / 149 (3.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Hyponatraemia                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 149 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                     | Atezolizumab +<br>Bevacizumab |  |  |
|-------------------------------------------------------|-------------------------------|--|--|
| Total subjects affected by non-serious adverse events |                               |  |  |
| subjects affected / exposed                           | 142 / 149 (95.30%)            |  |  |
| Vascular disorders                                    |                               |  |  |
| Hypertension                                          |                               |  |  |
| subjects affected / exposed                           | 51 / 149 (34.23%)             |  |  |
| occurrences (all)                                     | 99                            |  |  |
| General disorders and administration site conditions  |                               |  |  |
| Asthenia                                              |                               |  |  |
| subjects affected / exposed                           | 64 / 149 (42.95%)             |  |  |
| occurrences (all)                                     | 97                            |  |  |
| Fatigue                                               |                               |  |  |
| subjects affected / exposed                           | 26 / 149 (17.45%)             |  |  |
| occurrences (all)                                     | 30                            |  |  |
| Oedema peripheral                                     |                               |  |  |
| subjects affected / exposed                           | 12 / 149 (8.05%)              |  |  |
| occurrences (all)                                     | 14                            |  |  |
| Mucosal inflammation                                  |                               |  |  |
| subjects affected / exposed                           | 10 / 149 (6.71%)              |  |  |
| occurrences (all)                                     | 12                            |  |  |
| Pyrexia                                               |                               |  |  |
| subjects affected / exposed                           | 32 / 149 (21.48%)             |  |  |
| occurrences (all)                                     | 38                            |  |  |
| Respiratory, thoracic and mediastinal disorders       |                               |  |  |
| Cough                                                 |                               |  |  |
| subjects affected / exposed                           | 21 / 149 (14.09%)             |  |  |
| occurrences (all)                                     | 29                            |  |  |
| Epistaxis                                             |                               |  |  |
| subjects affected / exposed                           | 18 / 149 (12.08%)             |  |  |
| occurrences (all)                                     | 23                            |  |  |
| Dysphonia                                             |                               |  |  |
| subjects affected / exposed                           | 9 / 149 (6.04%)               |  |  |
| occurrences (all)                                     | 9                             |  |  |

|                                                                                          |                         |  |  |
|------------------------------------------------------------------------------------------|-------------------------|--|--|
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                             | 8 / 149 (5.37%)<br>8    |  |  |
| Investigations                                                                           |                         |  |  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)            | 13 / 149 (8.72%)<br>21  |  |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)             | 11 / 149 (7.38%)<br>19  |  |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 11 / 149 (7.38%)<br>14  |  |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 8 / 149 (5.37%)<br>10   |  |  |
| Nervous system disorders                                                                 |                         |  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                             | 18 / 149 (12.08%)<br>21 |  |  |
| Blood and lymphatic system disorders                                                     |                         |  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                     | 16 / 149 (10.74%)<br>35 |  |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                              | 15 / 149 (10.07%)<br>17 |  |  |
| Gastrointestinal disorders                                                               |                         |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                            | 42 / 149 (28.19%)<br>64 |  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                       | 25 / 149 (16.78%)<br>32 |  |  |
| Nausea                                                                                   |                         |  |  |

|                                        |                   |  |  |
|----------------------------------------|-------------------|--|--|
| subjects affected / exposed            | 22 / 149 (14.77%) |  |  |
| occurrences (all)                      | 28                |  |  |
| Ascites                                |                   |  |  |
| subjects affected / exposed            | 16 / 149 (10.74%) |  |  |
| occurrences (all)                      | 18                |  |  |
| Abdominal pain upper                   |                   |  |  |
| subjects affected / exposed            | 14 / 149 (9.40%)  |  |  |
| occurrences (all)                      | 16                |  |  |
| Constipation                           |                   |  |  |
| subjects affected / exposed            | 14 / 149 (9.40%)  |  |  |
| occurrences (all)                      | 16                |  |  |
| Vomiting                               |                   |  |  |
| subjects affected / exposed            | 14 / 149 (9.40%)  |  |  |
| occurrences (all)                      | 15                |  |  |
| Stomatitis                             |                   |  |  |
| subjects affected / exposed            | 10 / 149 (6.71%)  |  |  |
| occurrences (all)                      | 10                |  |  |
| Hepatobiliary disorders                |                   |  |  |
| Hypertransaminasaemia                  |                   |  |  |
| subjects affected / exposed            | 9 / 149 (6.04%)   |  |  |
| occurrences (all)                      | 13                |  |  |
| Hyperbilirubinaemia                    |                   |  |  |
| subjects affected / exposed            | 8 / 149 (5.37%)   |  |  |
| occurrences (all)                      | 11                |  |  |
| Skin and subcutaneous tissue disorders |                   |  |  |
| Pruritus                               |                   |  |  |
| subjects affected / exposed            | 36 / 149 (24.16%) |  |  |
| occurrences (all)                      | 46                |  |  |
| Renal and urinary disorders            |                   |  |  |
| Proteinuria                            |                   |  |  |
| subjects affected / exposed            | 28 / 149 (18.79%) |  |  |
| occurrences (all)                      | 48                |  |  |
| Endocrine disorders                    |                   |  |  |
| Hypothyroidism                         |                   |  |  |
| subjects affected / exposed            | 17 / 149 (11.41%) |  |  |
| occurrences (all)                      | 20                |  |  |
| Musculoskeletal and connective tissue  |                   |  |  |

|                                    |                   |  |  |
|------------------------------------|-------------------|--|--|
| disorders                          |                   |  |  |
| Arthralgia                         |                   |  |  |
| subjects affected / exposed        | 24 / 149 (16.11%) |  |  |
| occurrences (all)                  | 43                |  |  |
| Back pain                          |                   |  |  |
| subjects affected / exposed        | 15 / 149 (10.07%) |  |  |
| occurrences (all)                  | 16                |  |  |
| Infections and infestations        |                   |  |  |
| COVID-19                           |                   |  |  |
| subjects affected / exposed        | 13 / 149 (8.72%)  |  |  |
| occurrences (all)                  | 14                |  |  |
| Metabolism and nutrition disorders |                   |  |  |
| Decreased Appetite                 |                   |  |  |
| subjects affected / exposed        | 33 / 149 (22.15%) |  |  |
| occurrences (all)                  | 42                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 18 March 2021    | The following changes were made as per amendment 1: The number of sites were updated to comply with the actual number of investigational sites (21); The inclusion criterion on contraception was modified for better clarity; The option of 'any severe infection that in the opinion of the investigator could impact participant's safety' was added to the list of types of infections that require the exclusion of the participant from the study; Co-infection with hepatitis B virus (HBV) and hepatitis D viral infection was added as an exclusion criterion; Further specifications on exclusion due to anticoagulants or thrombolytic agents were added for better clarity. |
| 13 December 2021 | The following changes were made as per amendment 2: The second interim analysis, which was planned; A specification that live, attenuated vaccines are not permitted was added for better clarity; Specification on evaluation of post-progression tumor changes and on use of radiopharmaceutical products was added for better clarity; The RECIST v1.1 criteria for overall response at a single time point was modified to reflect the latest updated RECIST criteria.                                                                                                                                                                                                              |
| 11 January 2022  | The following changes were made as per amendment 3: A specification on childbearing potential was added for better clarity; Specification on evaluation of post-progression tumor changes and on use of radiopharmaceutical products was added for better clarity.                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 15 February 2023 | The following changes were made as per amendment 4: The list of identified risks for atezolizumab was revised to include pericardial disorders, facial paresis, and myelitis; The AE management guidelines had been updated to align with the Atezolizumab Investigator's Brochure, Version 19 and the Atezolizumab Investigator's Brochure Version 19, Addendum 1 and 2.                                                                                                                                                                                                                                                                                                               |
| 11 January 2024  | The following change was made as per amendment 5: The Risks Associated with Atezolizumab and Guidelines for Management of AEs Associated with Atezolizumab was updated to align with the Atezolizumab Investigator's Brochure, Version 20.                                                                                                                                                                                                                                                                                                                                                                                                                                              |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported