



## Clinical trial results:

### A Phase II, Multicenter, Single-Arm Study of Atezolizumab in Patients With Locally Advanced or Metastatic Urothelial Bladder Cancer

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-005486-39 |
| Trial protocol           | DE IT ES NL FR |
| Global end of trial date |                |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 28 July 2016 |
| First version publication date | 28 July 2016 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | GO29293 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02108652 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                             |
|------------------------------|-------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | F. Hoffmann-La Roche AG                                                                                     |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070                                                          |
| Public contact               | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com |
| Scientific contact           | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 61 6878333, 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                                       | Interim     |
| Date of interim/final analysis                       | 05 May 2015 |
| Is this the analysis of the primary completion data? | Yes         |
| Primary completion date                              | 05 May 2015 |
| Global end of trial reached?                         | No          |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective for this study was to evaluate the efficacy of atezolizumab in participants with locally advanced or metastatic urothelial carcinoma.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

|                                                           |             |
|-----------------------------------------------------------|-------------|
| Actual start date of recruitment                          | 13 May 2014 |
| Long term follow-up planned                               | Yes         |
| Long term follow-up rationale                             | Efficacy    |
| Long term follow-up duration                              | 1 Years     |
| Independent data monitoring committee (IDMC) involvement? | Yes         |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 21          |
| Country: Number of subjects enrolled | Canada: 20         |
| Country: Number of subjects enrolled | France: 6          |
| Country: Number of subjects enrolled | United Kingdom: 17 |
| Country: Number of subjects enrolled | Germany: 7         |
| Country: Number of subjects enrolled | Italy: 19          |
| Country: Number of subjects enrolled | Netherlands: 11    |
| Country: Number of subjects enrolled | United States: 210 |
| Worldwide total number of subjects   | 311                |
| EEA total number of subjects         | 81                 |

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)      | 126 |
| From 65 to 84 years       | 181 |
| 85 years and over         | 4   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Only Cohort 2 primary analysis data are included with cutoff date 5 May 2015. Per planned analysis, the primary analysis of Cohort 2 was performed approximately 6 months after the last participant in Cohort 2 had been enrolled. Cohort 1 data will be posted later, anticipated posting date 14 Sep 2016.

### Period 1

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

### Arms

|           |                                                              |
|-----------|--------------------------------------------------------------|
| Arm title | Cohort 2: Participants With Second-line or Beyond Treatments |
|-----------|--------------------------------------------------------------|

Arm description:

Participants who had disease progression during or following treatment with at least one platinum-containing chemotherapy regimen in the metastatic setting received atezolizumab 1200 milligrams (mg) via intravenous (IV) infusion on Day 1 of 21-day cycles until loss of clinical benefit or unmanageable toxicity.

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Atezolizumab          |
| Investigational medicinal product code | MPDL3280A             |
| Other name                             | Tecentriq             |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Participants were administered 1200 mg atezolizumab by IV infusion by trained medical staff at the clinical site. The initial dose of atezolizumab was delivered over 60 ( $\pm$  15) minutes. If the first infusion was tolerated without infusion-associated adverse events, the second infusion could be delivered over 30 ( $\pm$  10) minutes. If the 30-minute infusion was well tolerated, all subsequent infusions could be delivered over 30 ( $\pm$  10) minutes.

| Number of subjects in period 1 | Cohort 2:<br>Participants With<br>Second-line or<br>Beyond Treatments |
|--------------------------------|-----------------------------------------------------------------------|
| Started                        | 311                                                                   |
| Completed                      | 0                                                                     |
| Not completed                  | 311                                                                   |
| Physician decision             | 1                                                                     |
| Consent withdrawn by subject   | 9                                                                     |
| Progression of Disease         | 5                                                                     |
| Death                          | 141                                                                   |
| Unspecified                    | 2                                                                     |
| Lost to follow-up              | 1                                                                     |

|                                   |     |
|-----------------------------------|-----|
| Ongoing at data cutoff 5 May 2014 | 152 |
|-----------------------------------|-----|

## Baseline characteristics

### Reporting groups

|                       |                                                              |
|-----------------------|--------------------------------------------------------------|
| Reporting group title | Cohort 2: Participants With Second-line or Beyond Treatments |
|-----------------------|--------------------------------------------------------------|

Reporting group description:

Participants who had disease progression during or following treatment with at least one platinum-containing chemotherapy regimen in the metastatic setting received atezolizumab 1200 milligrams (mg) via intravenous (IV) infusion on Day 1 of 21-day cycles until loss of clinical benefit or unmanageable toxicity.

| Reporting group values                                                  | Cohort 2:<br>Participants With<br>Second-line or<br>Beyond Treatments | Total |  |
|-------------------------------------------------------------------------|-----------------------------------------------------------------------|-------|--|
| Number of subjects                                                      | 311                                                                   | 311   |  |
| Age categorical<br>Units: Subjects                                      |                                                                       |       |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 65.7<br>± 10.1                                                        | -     |  |
| Gender categorical<br>Units: Subjects                                   |                                                                       |       |  |
| Female                                                                  | 69                                                                    | 69    |  |
| Male                                                                    | 242                                                                   | 242   |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                         |                                                              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                   | Cohort 2: Participants With Second-line or Beyond Treatments |
| Reporting group description:<br>Participants who had disease progression during or following treatment with at least one platinum-containing chemotherapy regimen in the metastatic setting received atezolizumab 1200 milligrams (mg) via intravenous (IV) infusion on Day 1 of 21-day cycles until loss of clinical benefit or unmanageable toxicity. |                                                              |

### Primary: Percentage of Participants With a Confirmed Objective Response of Complete Response (CR) or Partial Response (PR) as Assessed by the Independent Review Facility (IRF) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

|                 |                                                                                                                                                                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With a Confirmed Objective Response of Complete Response (CR) or Partial Response (PR) as Assessed by the Independent Review Facility (IRF) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) <sup>[1]</sup> |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### End point description:

Tumor response was assessed by the IRF according to RECIST v1.1. CR was defined as disappearance of all target and non-target lesions and (if applicable) normalization of tumor marker levels. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than (<) 10 millimeters (mm). PR was defined as greater than or equal to (≥) 30 percent (%) decrease in sum of longest diameter (LD) of target lesions in reference to Baseline sum LD. Response was to be confirmed ≥4 weeks after the initial assessment of CR or PR. The percentage of participants with a confirmed objective response of CR or PR was reported. The exact 95% confidence interval (CI) was calculated using the Clopper-Pearson method. Cohort 2 objective response-evaluable population included Intent-to-treat (ITT) participants who had measurable disease per RECIST v1.1 at baseline. Cohort 2 ITT population included all participants from Cohort 2 who received any amount of study drug.

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

#### End point timeframe:

Baseline, every 9 weeks for the first 12 months, until confirmed disease progression or death, whichever occurred first (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 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 was planned for this end point.

|                                   |                                                                           |  |  |  |
|-----------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type                | Reporting group                                                           |  |  |  |
| Number of subjects analysed       | 311                                                                       |  |  |  |
| Units: percentage of participants |                                                                           |  |  |  |
| number (confidence interval 95%)  | 15.1 (11.3 to 19.6)                                                       |  |  |  |

## Statistical analyses

**Primary: Percentage of Participants With a Confirmed Objective Response of CR or PR as Assessed by the Investigator According Modified RECIST**

|                 |                                                                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With a Confirmed Objective Response of CR or PR as Assessed by the Investigator According Modified RECIST <sup>[2]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

Tumor response was assessed by the investigator according to modified RECIST. CR was defined as disappearance of all target and non-target lesions and no new measurable or unmeasurable lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR was defined as  $\geq 30\%$  decrease in sum of LD of target lesions in reference to Baseline sum LD. Response was to be confirmed  $\geq 4$  weeks after the initial assessment of CR or PR. The percentage of participants with a confirmed objective response of CR or PR was reported. The exact 95% CI was calculated using the Clopper-Pearson method. Cohort 2 objective response-evaluable population.

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

## End point timeframe:

Baseline, every 9 weeks for the first 12 months, until confirmed disease progression or death, whichever occurred first (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 months)

## Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this end point.

|                                   |                                                                           |  |  |  |
|-----------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type                | Reporting group                                                           |  |  |  |
| Number of subjects analysed       | 311                                                                       |  |  |  |
| Units: percentage of participants |                                                                           |  |  |  |
| number (confidence interval 95%)  | 18.3 (14.2 to 23.1)                                                       |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Duration of Response as Assessed by the IRF According to RECIST v1.1**

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Duration of Response as Assessed by the IRF According to RECIST v1.1 |
|-----------------|----------------------------------------------------------------------|

## End point description:

Duration of response was defined as the time from the initial occurrence of documented CR or PR (whichever occurred first) until documented disease progression or death due to any cause on study, whichever occurred first. Tumor response was assessed by the IRF according to RECIST v1.1. CR was defined as disappearance of all target and non-target lesions and (if applicable) normalization of tumor marker levels. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR was defined as  $\geq 30\%$  decrease in sum of LD of target lesions in reference to Baseline sum LD. Response was to be confirmed  $\geq 4$  weeks after the initial assessment of CR or PR. Cohort 2 objective response-evaluable population. Here, '2.99999' signifies that median duration of response was not reached at a median follow up of 7.1 months on study. Full range values are censored.

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

## End point timeframe:

Baseline, every 9 weeks for the first 12 months, until confirmed disease progression or death, whichever occurred first (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 months)

|                               |                                                                           |  |  |  |
|-------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>       | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type            | Reporting group                                                           |  |  |  |
| Number of subjects analysed   | 311                                                                       |  |  |  |
| Units: months                 |                                                                           |  |  |  |
| median (full range (min-max)) | 2.99999 (2.1<br>to 8.3)                                                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response as Assessed by the Investigator According to RECIST v1.1

|                 |                                                                               |
|-----------------|-------------------------------------------------------------------------------|
| End point title | Duration of Response as Assessed by the Investigator According to RECIST v1.1 |
|-----------------|-------------------------------------------------------------------------------|

End point description:

Duration of response was defined as the time from the initial occurrence of documented CR or PR (whichever occurred first) until documented disease progression or death due to any cause on study, whichever occurred first. Tumor response was assessed by the investigator according to modified RECIST. CR was defined as disappearance of all target and non-target lesions and no new measurable or unmeasurable lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR was defined as  $\geq 30\%$  decrease in sum of LD of target lesions in reference to Baseline sum LD. Cohort 2 ITT population. Here, "2.99999" signifies that the median duration of response was not reached at a median follow up of 7.1 months on study. Full range values are censored values.

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

End point timeframe:

Baseline, every 9 weeks for the first 12 months, until confirmed disease progression or death, whichever occurred first (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 months)

|                               |                                                                           |  |  |  |
|-------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>       | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type            | Reporting group                                                           |  |  |  |
| Number of subjects analysed   | 311                                                                       |  |  |  |
| Units: months                 |                                                                           |  |  |  |
| median (full range (min-max)) | 2.99999 (1.6<br>to 8.3)                                                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response as Assessed by the Investigator According to Modified RECIST

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Duration of Response as Assessed by the Investigator According to Modified RECIST |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

Duration of response was defined as the time from the initial occurrence of documented CR or PR (whichever occurred first) until documented disease progression or death due to any cause on study, whichever occurred first. Tumor response was assessed by the investigator according to modified RECIST. CR was defined as disappearance of all target and non-target lesions and no new measurable or unmeasurable lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR was defined as  $\geq 30\%$  decrease in sum of LD of target lesions in reference to Baseline sum LD. Cohort 2 objective response-evaluable population. Here, "2.99999" signifies that the median duration of response was not reached at a median follow up of 7.1 months on study. Full range values are censored.

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

End point timeframe:

Baseline, every 9 weeks for the first 12 months, until confirmed disease progression or death, whichever occurred first (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 months)

|                               |                                                                           |  |  |  |
|-------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>       | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type            | Reporting group                                                           |  |  |  |
| Number of subjects analysed   | 311                                                                       |  |  |  |
| Units: months                 |                                                                           |  |  |  |
| median (full range (min-max)) | 2.99999 (1.6<br>to 8.3)                                                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Death or Disease Progression as Assessed by the IRF According to RECIST v1.1

|                 |                                                                                                              |
|-----------------|--------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With Death or Disease Progression as Assessed by the IRF According to RECIST v1.1 |
|-----------------|--------------------------------------------------------------------------------------------------------------|

End point description:

Tumor response was assessed by the IRF according to RECIST v1.1. Disease progression or PD was defined as  $\geq 20\%$  increase in sum LD in reference to the smallest on-study sum LD, or the appearance of new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The percentage of participants who died or experienced PD was reported. Cohort 2 ITT population.

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

End point timeframe:

Baseline, every 9 weeks for the first 12 months, until confirmed disease progression or death, whichever occurred first (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 months)

|                                   |                                                                           |  |  |  |
|-----------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type                | Reporting group                                                           |  |  |  |
| Number of subjects analysed       | 311                                                                       |  |  |  |
| Units: percentage of participants |                                                                           |  |  |  |
| number (not applicable)           | 77.5                                                                      |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-Free Survival (PFS) as Assessed by the IRF According to RECIST v1.1

|                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                     | Progression-Free Survival (PFS) as Assessed by the IRF According to RECIST v1.1 |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                 |
| PFS was defined as the time from start of treatment to the first event of death or PD. Tumor response was assessed by the IRF according to RECIST v1.1. Disease progression or PD was defined as ≥20% increase in sum LD in reference to the smallest on-study sum LD, or the appearance of new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Cohort 2 ITT population. |                                                                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                      | Secondary                                                                       |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                 |
| Baseline, every 9 weeks for the first 12 months, until confirmed disease progression or death, whichever occurred first (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 months)                                                                                                                                                                                                                                           |                                                                                 |

|                                  |                                                                           |  |  |  |
|----------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>          | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type               | Reporting group                                                           |  |  |  |
| Number of subjects analysed      | 311                                                                       |  |  |  |
| Units: months                    |                                                                           |  |  |  |
| median (confidence interval 95%) | 2.1 (2.07 to 2.14)                                                        |  |  |  |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Percentage of Participants With Death or Disease Progression as Assessed by the Investigator According to RECIST v1.1**

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|                 |                                                                                                                       |
|-----------------|-----------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With Death or Disease Progression as Assessed by the Investigator According to RECIST v1.1 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------|

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. Disease progression or PD was defined as  $\geq 20\%$  increase in sum LD in reference to the smallest on-study sum LD, or the appearance of new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The percentage of participants who died or experienced PD was reported. Cohort 2 ITT population.

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

End point timeframe:

Baseline, every 9 weeks for the first 12 months, until confirmed disease progression or death, whichever occurred first (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 months)

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|                                   |                                                                           |  |  |  |
|-----------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type                | Reporting group                                                           |  |  |  |
| Number of subjects analysed       | 311                                                                       |  |  |  |
| Units: percentage of participants |                                                                           |  |  |  |
| number (not applicable)           | 78.1                                                                      |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: PFS as Assessed by the Investigator According to RECIST v1.1**

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|                 |                                                              |
|-----------------|--------------------------------------------------------------|
| End point title | PFS as Assessed by the Investigator According to RECIST v1.1 |
|-----------------|--------------------------------------------------------------|

End point description:

PFS was defined as the time from start of treatment to the first event of death or PD. Tumor response was assessed by the investigator according to RECIST v1.1. Disease progression or PD was defined as  $\geq 20\%$  increase in sum LD in reference to the smallest on-study sum LD, or the appearance of new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Cohort 2 ITT population.

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

End point timeframe:

Baseline, every 9 weeks for the first 12 months, until confirmed disease progression or death, whichever occurred first (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 months)

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|                               |                                                                           |  |  |  |
|-------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>       | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type            | Reporting group                                                           |  |  |  |
| Number of subjects analysed   | 311                                                                       |  |  |  |
| Units: months                 |                                                                           |  |  |  |
| median (full range (min-max)) | 2.1 (2.07 to<br>2.23)                                                     |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Death or Disease Progression as Assessed by the Investigator According to Modified RECIST

|                 |                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With Death or Disease Progression as Assessed by the Investigator According to Modified RECIST |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|

End point description:

Tumor response was assessed by the investigator according to modified RECIST. Disease progression or PD was defined as  $\geq 20\%$  increase in sum LD in reference to the smallest on-study sum LD. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The percentage of participants who died or experienced PD was reported. Cohort 2 ITT population.

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

End point timeframe:

Baseline, every 9 weeks for the first 12 months, until confirmed disease progression or death, whichever occurred first (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 months)

|                                   |                                                                           |  |  |  |
|-----------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type                | Reporting group                                                           |  |  |  |
| Number of subjects analysed       | 311                                                                       |  |  |  |
| Units: percentage of participants |                                                                           |  |  |  |
| number (not applicable)           | 73.3                                                                      |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: PFS as Assessed by the Investigator According to Modified RECIST

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | PFS as Assessed by the Investigator According to Modified RECIST |
|-----------------|------------------------------------------------------------------|

End point description:

PFS was defined as the time from start of treatment to the first event of death or PD. Tumor response was assessed by the investigator according to modified RECIST. Disease progression or PD was defined

as  $\geq 20\%$  increase in sum LD in reference to the smallest on-study sum LD. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Cohort 2 ITT population.

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

End point timeframe:

Baseline, every 9 weeks for the first 12 months, until confirmed disease progression or death, whichever occurred first (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 months)

|                               |                                                                           |  |  |  |
|-------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>       | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type            | Reporting group                                                           |  |  |  |
| Number of subjects analysed   | 311                                                                       |  |  |  |
| Units: months                 |                                                                           |  |  |  |
| median (full range (min-max)) | 2.73 (2.14 to<br>3.94)                                                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With a Confirmed Objective Response of CR or PR as Assessed by the Investigator According RECIST v1.1

|                 |                                                                                                                                  |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With a Confirmed Objective Response of CR or PR as Assessed by the Investigator According RECIST v1.1 |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. CR was defined as disappearance of all target and non-target lesions and (if applicable) normalization of tumor marker levels. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to  $< 10$  mm. PR was defined as  $\geq 30\%$  decrease in sum of LD of target lesions in reference to Baseline sum LD. Response was to be confirmed  $\geq 4$  weeks after the initial assessment of CR or PR. The percentage of participants with a confirmed objective response of CR or PR was reported. The exact 95% CI was calculated using the Clopper-Pearson method. Cohort 2 ITT population.

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

End point timeframe:

Baseline, every 9 weeks for the first 12 months, until confirmed disease progression or death, whichever occurred first (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 months)

|                                   |                                                                           |  |  |  |
|-----------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type                | Reporting group                                                           |  |  |  |
| Number of subjects analysed       | 311                                                                       |  |  |  |
| Units: percentage of participants |                                                                           |  |  |  |
| number (confidence interval 95%)  | 16.1 (12.2 to                                                             |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Who Died

|                 |                                     |
|-----------------|-------------------------------------|
| End point title | Percentage of Participants Who Died |
|-----------------|-------------------------------------|

End point description:

The percentage of participants who died from any cause was reported. Cohort 2 ITT population.

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

End point timeframe:

Baseline until death (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 months)

| End point values                  | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
|-----------------------------------|---------------------------------------------------------------------------|--|--|--|
| Subject group type                | Reporting group                                                           |  |  |  |
| Number of subjects analysed       | 311                                                                       |  |  |  |
| Units: percentage of participants |                                                                           |  |  |  |
| number (not applicable)           | 45.3                                                                      |  |  |  |

## 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 start of treatment to the time of death from any cause on study. Cohort 2 ITT population. Here, "99999" signifies that the upper limit of the 95% CI was not calculable because an insufficient number of participants reached the event at the final time point for assessment.

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

End point timeframe:

Baseline until death (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 months)

|                                  |                                                                           |  |  |  |
|----------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>          | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type               | Reporting group                                                           |  |  |  |
| Number of subjects analysed      | 311                                                                       |  |  |  |
| Units: months                    |                                                                           |  |  |  |
| median (confidence interval 95%) | 7.89 (6.7 to<br>99999)                                                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Alive at 1-year

|                                                                                                                                                                                                                                        |                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| End point title                                                                                                                                                                                                                        | Percentage of Participants Alive at 1-year |
| End point description:<br>Cohort 2 ITT population. Here, "99999" signifies that 1-year overall survival was not evaluable because it was not yet reached. Participants had not yet been on the study for a year as of the data cutoff. |                                            |
| End point type                                                                                                                                                                                                                         | Secondary                                  |
| End point timeframe:<br>1-year                                                                                                                                                                                                         |                                            |

|                                   |                                                                           |  |  |  |
|-----------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type                | Reporting group                                                           |  |  |  |
| Number of subjects analysed       | 311                                                                       |  |  |  |
| Units: percentage of participants |                                                                           |  |  |  |
| number (not applicable)           | 99999                                                                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum Serum Concentration (Cmax) of Atezolizumab

|                                                                                                                                                                                                                 |                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| End point title                                                                                                                                                                                                 | Maximum Serum Concentration (Cmax) of Atezolizumab |
| End point description:<br>Per planned analysis, the pharmacokinetic data will be analyzed and reported for all participants (Cohorts 1 and 2 combined). Data have not been analyzed separately for each cohort. |                                                    |
| End point type                                                                                                                                                                                                  | Secondary                                          |
| End point timeframe:<br>Cycle 1 Day 1 (Cycle length = 21 days)                                                                                                                                                  |                                                    |

|                                         |                                                                           |  |  |  |
|-----------------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>                 | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type                      | Reporting group                                                           |  |  |  |
| Number of subjects analysed             | 0 <sup>[3]</sup>                                                          |  |  |  |
| Units: microgram(s)/milliliter (mcg/mL) |                                                                           |  |  |  |
| arithmetic mean (standard deviation)    | ( )                                                                       |  |  |  |

Notes:

[3] - PK data will be analyzed for all participants (Cohorts 1 and 2 combined), anticipated date Sep 2016.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Minimum Serum Concentration (Cmin) of Atezolizumab

|                                                                                                                                                                                                                 |                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| End point title                                                                                                                                                                                                 | Minimum Serum Concentration (Cmin) of Atezolizumab |
| End point description:<br>Per planned analysis, the pharmacokinetic data will be analyzed and reported for all participants (Cohorts 1 and 2 combined). Data have not been analyzed separately for each cohort. |                                                    |
| End point type                                                                                                                                                                                                  | Secondary                                          |
| End point timeframe:<br>Predose on Day 1 of Cycles 1, 2, 4, 8 (Cycle length = 21 days)                                                                                                                          |                                                    |

|                                      |                                                                           |  |  |  |
|--------------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>              | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type                   | Reporting group                                                           |  |  |  |
| Number of subjects analysed          | 0 <sup>[4]</sup>                                                          |  |  |  |
| Units: mcg/mL                        |                                                                           |  |  |  |
| arithmetic mean (standard deviation) | ( )                                                                       |  |  |  |

Notes:

[4] - PK data will be analyzed for all participants (Cohorts 1 and 2 combined), anticipated date Sep 2016.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Positive for Anti-therapeutic Antibodies (ATA) to Atezolizumab

|                                                                                                                                 |                                                                                           |
|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| End point title                                                                                                                 | Percentage of Participants Positive for Anti-therapeutic Antibodies (ATA) to Atezolizumab |
| End point description:<br>Cohort 2 Safety Evaluable Population included all participants who received any amount of study drug. |                                                                                           |

Here, number of participants analyzed = participants for whom ATA samples were available.

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

End point timeframe:

Day 1 of all cycles and at treatment discontinuation (data cutoff date 05 May 2015, up to maximum length of follow-up of 10.61 months)

|                                   |                                                                           |  |  |  |
|-----------------------------------|---------------------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | Cohort 2:<br>Participants<br>With Second-<br>line or Beyond<br>Treatments |  |  |  |
| Subject group type                | Reporting group                                                           |  |  |  |
| Number of subjects analysed       | 275                                                                       |  |  |  |
| Units: percentage of participants |                                                                           |  |  |  |
| number (not applicable)           | 41.5                                                                      |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

First dose of study drug until data cutoff date 05 May 2015 (up to maximum length of follow-up of 10.61 months)

Adverse event reporting additional description:

Cohort 2 Safety Evaluable Population.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |                                                              |
|-----------------------|--------------------------------------------------------------|
| Reporting group title | Cohort 2: Participants With Second-line or Beyond Treatments |
|-----------------------|--------------------------------------------------------------|

Reporting group description:

Participants who had disease progression during or following treatment with at least one platinum-containing chemotherapy regimen in the metastatic setting received atezolizumab 1200 mg via IV infusion on Day 1 of 21-day cycles until loss of clinical benefit or unmanageable toxicity.

| Serious adverse events                                              | Cohort 2:<br>Participants With<br>Second-line or<br>Beyond Treatments |  |  |
|---------------------------------------------------------------------|-----------------------------------------------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                                                                       |  |  |
| subjects affected / exposed                                         | 141 / 311 (45.34%)                                                    |  |  |
| number of deaths (all causes)                                       | 141                                                                   |  |  |
| number of deaths resulting from adverse events                      |                                                                       |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                                                       |  |  |
| Tumour associated fever                                             |                                                                       |  |  |
| subjects affected / exposed                                         | 1 / 311 (0.32%)                                                       |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                                                                 |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                                                 |  |  |
| Tumour pain                                                         |                                                                       |  |  |
| subjects affected / exposed                                         | 1 / 311 (0.32%)                                                       |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                                                                 |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                                                 |  |  |
| Vascular disorders                                                  |                                                                       |  |  |
| Deep vein thrombosis                                                |                                                                       |  |  |
| subjects affected / exposed                                         | 3 / 311 (0.96%)                                                       |  |  |
| occurrences causally related to treatment / all                     | 0 / 3                                                                 |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                                                 |  |  |

|                                                      |                 |  |  |
|------------------------------------------------------|-----------------|--|--|
| Hypotension                                          |                 |  |  |
| subjects affected / exposed                          | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all      | 1 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Vascular compression                                 |                 |  |  |
| subjects affected / exposed                          | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Asthenia                                             |                 |  |  |
| subjects affected / exposed                          | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all      | 1 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Chest pain                                           |                 |  |  |
| subjects affected / exposed                          | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Chills                                               |                 |  |  |
| subjects affected / exposed                          | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Fatigue                                              |                 |  |  |
| subjects affected / exposed                          | 3 / 311 (0.96%) |  |  |
| occurrences causally related to treatment / all      | 1 / 3           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Haemorrhagic cyst                                    |                 |  |  |
| subjects affected / exposed                          | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Oedema peripheral                                    |                 |  |  |
| subjects affected / exposed                          | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Pain                                            |                 |  |  |
| subjects affected / exposed                     | 3 / 311 (0.96%) |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Performance status decreased                    |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pyrexia                                         |                 |  |  |
| subjects affected / exposed                     | 8 / 311 (2.57%) |  |  |
| occurrences causally related to treatment / all | 2 / 8           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Social circumstances                            |                 |  |  |
| Immobile                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Reproductive system and breast disorders        |                 |  |  |
| Pelvic pain                                     |                 |  |  |
| subjects affected / exposed                     | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vaginal haemorrhage                             |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Bronchial obstruction                           |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemoptysis                                     |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hiccups                                         |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypoxia                                         |                 |  |  |
| subjects affected / exposed                     | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pleural effusion                                |                 |  |  |
| subjects affected / exposed                     | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonitis                                     |                 |  |  |
| subjects affected / exposed                     | 3 / 311 (0.96%) |  |  |
| occurrences causally related to treatment / all | 3 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumothorax                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 6 / 311 (1.93%) |  |  |
| occurrences causally related to treatment / all | 1 / 6           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dyspnoea                                        |                 |  |  |
| subjects affected / exposed                     | 7 / 311 (2.25%) |  |  |
| occurrences causally related to treatment / all | 0 / 7           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Confusional state                               |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 3 / 311 (0.96%) |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Delirium                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hallucination                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Investigations                                  |                 |  |  |
| Alanine aminotransferase increased              |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Aspartate aminotransferase increased            |                 |  |  |
| subjects affected / exposed                     | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood alkaline phosphatase increased            |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood bilirubin increased                       |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood creatinine increased                      |                 |  |  |
| subjects affected / exposed                     | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Brain natriuretic peptide increased             |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Platelet count decreased                        |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Troponin increased                              |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| White blood cell count decreased                |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Hip fracture                                    |                 |  |  |
| subjects affected / exposed                     | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ilium fracture                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lower limb fracture                             |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Post procedural haemorrhage                     |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal compression fracture                     |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Stoma site haemorrhage                          |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Toxicity to various agents                      |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular pseudoaneurysm ruptured                |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Atrial fibrillation                             |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Coronary artery disease                         |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pericardial effusion                            |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Cerebral haemorrhage                            |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebrovascular accident                        |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diplegia                                        |                 |  |  |
| subjects affected / exposed                     | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Encephalopathy                                  |                 |  |  |
| subjects affected / exposed                     | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemorrhage intracranial                        |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Paraplegia                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Posterior reversible encephalopathy syndrome    |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Syncope                                         |                 |  |  |
| subjects affected / exposed                     | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Anaemia                                         |                 |  |  |
| subjects affected / exposed                     | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Leukocytosis                                    |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lymph node pain                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Abdominal pain                                  |                 |  |  |
| subjects affected / exposed                     | 6 / 311 (1.93%) |  |  |
| occurrences causally related to treatment / all | 0 / 7           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Abdominal pain lower                            |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Colitis                                         |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diarrhoea                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Faecal incontinence                             |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal haemorrhage                    |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ileus                                           |                 |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intestinal obstruction                          |                 |  |  |
| subjects affected / exposed                     | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Large intestinal obstruction                    |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nausea                                          |                 |  |  |
| subjects affected / exposed                     | 4 / 311 (1.29%) |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Retroperitoneal haemorrhage                     |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Small intestinal obstruction                    |                 |  |  |
| subjects affected / exposed                     | 5 / 311 (1.61%) |  |  |
| occurrences causally related to treatment / all | 0 / 7           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Subileus                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Vomiting                                        |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Cholestasis                                     |                 |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 311 (0.32%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatitis                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%)  |  |  |
| 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                     | 7 / 311 (2.25%)  |  |  |
| occurrences causally related to treatment / all | 1 / 7            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Chronic kidney disease                          |                  |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haematuria                                      |                  |  |  |
| subjects affected / exposed                     | 10 / 311 (3.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 10           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hydronephrosis                                  |                  |  |  |
| subjects affected / exposed                     | 4 / 311 (1.29%)  |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hydroureter                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Obstructive uropathy                            |                  |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal failure                                   |                  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ureteric obstruction                            |                 |  |  |
| subjects affected / exposed                     | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary retention                               |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary tract obstruction                       |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Endocrine disorders                             |                 |  |  |
| Hypothyroidism                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Arthralgia                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Back pain                                       |                 |  |  |
| subjects affected / exposed                     | 6 / 311 (1.93%) |  |  |
| occurrences causally related to treatment / all | 0 / 8           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bone pain                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Muscular weakness                               |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Abdominal abscess                               |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bacteraemia                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bronchitis                                      |                 |  |  |
| subjects affected / exposed                     | 2 / 311 (0.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cellulitis                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cellulitis of male external genital organ       |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Device related infection                        |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastroenteritis                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Kidney infection                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lobar pneumonia                                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lung infection                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia                                       |                 |  |  |  |
| subjects affected / exposed                     | 5 / 311 (1.61%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pulmonary sepsis                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Pyelonephritis                                  |                 |  |  |  |
| subjects affected / exposed                     | 3 / 311 (0.96%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Sepsis                                          |                 |  |  |  |
| subjects affected / exposed                     | 6 / 311 (1.93%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 6           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Spinal cord infection                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Urinary tract infection                         |                 |  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 19 / 311 (6.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 19           |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary tract infection pseudomonal             |                  |  |  |
| subjects affected / exposed                     | 1 / 311 (0.32%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urosepsis                                       |                  |  |  |
| subjects affected / exposed                     | 3 / 311 (0.96%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Metabolism and nutrition disorders              |                  |  |  |
| Dehydration                                     |                  |  |  |
| subjects affected / exposed                     | 6 / 311 (1.93%)  |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypercalcaemia                                  |                  |  |  |
| subjects affected / exposed                     | 4 / 311 (1.29%)  |  |  |
| occurrences causally related to treatment / all | 1 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hyponatraemia                                   |                  |  |  |
| subjects affected / exposed                     | 3 / 311 (0.96%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |

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

|                                                       |                                                                       |  |  |
|-------------------------------------------------------|-----------------------------------------------------------------------|--|--|
| <b>Non-serious adverse events</b>                     | Cohort 2:<br>Participants With<br>Second-line or<br>Beyond Treatments |  |  |
| Total subjects affected by non-serious adverse events |                                                                       |  |  |
| subjects affected / exposed                           | 263 / 311 (84.57%)                                                    |  |  |
| Investigations                                        |                                                                       |  |  |
| Weight decreased                                      |                                                                       |  |  |

|                                                         |                        |  |  |
|---------------------------------------------------------|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)        | 22 / 311 (7.07%)<br>24 |  |  |
| Nervous system disorders                                |                        |  |  |
| Dizziness                                               |                        |  |  |
| subjects affected / exposed                             | 16 / 311 (5.14%)       |  |  |
| occurrences (all)                                       | 17                     |  |  |
| Headache                                                |                        |  |  |
| subjects affected / exposed                             | 24 / 311 (7.72%)       |  |  |
| occurrences (all)                                       | 28                     |  |  |
| Blood and lymphatic system disorders                    |                        |  |  |
| Anaemia                                                 |                        |  |  |
| subjects affected / exposed                             | 41 / 311 (13.18%)      |  |  |
| occurrences (all)                                       | 56                     |  |  |
| General disorders and administration<br>site conditions |                        |  |  |
| Asthenia                                                |                        |  |  |
| subjects affected / exposed                             | 17 / 311 (5.47%)       |  |  |
| occurrences (all)                                       | 28                     |  |  |
| Chills                                                  |                        |  |  |
| subjects affected / exposed                             | 26 / 311 (8.36%)       |  |  |
| occurrences (all)                                       | 29                     |  |  |
| Fatigue                                                 |                        |  |  |
| subjects affected / exposed                             | 143 / 311 (45.98%)     |  |  |
| occurrences (all)                                       | 182                    |  |  |
| Oedema peripheral                                       |                        |  |  |
| subjects affected / exposed                             | 36 / 311 (11.58%)      |  |  |
| occurrences (all)                                       | 43                     |  |  |
| Pain                                                    |                        |  |  |
| subjects affected / exposed                             | 23 / 311 (7.40%)       |  |  |
| occurrences (all)                                       | 29                     |  |  |
| Pyrexia                                                 |                        |  |  |
| subjects affected / exposed                             | 58 / 311 (18.65%)      |  |  |
| occurrences (all)                                       | 69                     |  |  |
| Gastrointestinal disorders                              |                        |  |  |
| Abdominal pain                                          |                        |  |  |
| subjects affected / exposed                             | 33 / 311 (10.61%)      |  |  |
| occurrences (all)                                       | 39                     |  |  |

|                                                                                                              |                         |  |  |
|--------------------------------------------------------------------------------------------------------------|-------------------------|--|--|
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                             | 63 / 311 (20.26%)<br>70 |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                                | 55 / 311 (17.68%)<br>68 |  |  |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)                                                | 16 / 311 (5.14%)<br>16  |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                                   | 71 / 311 (22.83%)<br>87 |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                 | 50 / 311 (16.08%)<br>67 |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 38 / 311 (12.22%)<br>47 |  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                                 | 42 / 311 (13.50%)<br>53 |  |  |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all)       | 39 / 311 (12.54%)<br>49 |  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                                                     | 30 / 311 (9.65%)<br>37  |  |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                        | 16 / 311 (5.14%)<br>16  |  |  |
| Renal and urinary disorders<br>Haematuria                                                                    |                         |  |  |

|                                                  |                         |  |  |
|--------------------------------------------------|-------------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 35 / 311 (11.25%)<br>45 |  |  |
| Musculoskeletal and connective tissue disorders  |                         |  |  |
| Arthralgia                                       |                         |  |  |
| subjects affected / exposed                      | 43 / 311 (13.83%)       |  |  |
| occurrences (all)                                | 49                      |  |  |
| Back pain                                        |                         |  |  |
| subjects affected / exposed                      | 39 / 311 (12.54%)       |  |  |
| occurrences (all)                                | 47                      |  |  |
| Muscular weakness                                |                         |  |  |
| subjects affected / exposed                      | 20 / 311 (6.43%)        |  |  |
| occurrences (all)                                | 26                      |  |  |
| Pain in extremity                                |                         |  |  |
| subjects affected / exposed                      | 21 / 311 (6.75%)        |  |  |
| occurrences (all)                                | 24                      |  |  |
| Infections and infestations                      |                         |  |  |
| Urinary tract infection                          |                         |  |  |
| subjects affected / exposed                      | 42 / 311 (13.50%)       |  |  |
| occurrences (all)                                | 47                      |  |  |
| Metabolism and nutrition disorders               |                         |  |  |
| Decreased appetite                               |                         |  |  |
| subjects affected / exposed                      | 79 / 311 (25.40%)       |  |  |
| occurrences (all)                                | 93                      |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 11 March 2014     | The protocol was amended to clarify the dose modification guidelines as to the management of immune-related adverse events (e.g., dermatologic toxicity, endocrine toxicity). Additionally, the protocol was modified to discontinue Cohort 1 participants (first-line cisplatin ineligible) from the study who develop RECIST v1.1 progression because of the possibility that they may benefit from non-cisplatin based regimens (e.g., carboplatin-based regimens).                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 27 September 2014 | The protocol was amended in order to detail changes in the duration of treatment for participants receiving atezolizumab. Participants in Cohort 1 would receive treatment with atezolizumab until progression. Participants in Cohort 2 would receive treatment with atezolizumab until lack of clinical benefit. Participants would no longer stop treatment at 16 cycles. The re-treatment period and related text were removed.                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 06 February 2015  | The protocol was amended to specify a longer washout period for participants who received prior anti-cytotoxic T lymphocyte-associated antigen 4 (anti-CTLA-4) treatment. Additionally, primary efficacy analysis was updated: activity in participants in Cohorts 1 and 2 will be analyzed separately with separate alpha spending for each cohort. The analysis of data from Cohort 1 participants will analyze overall response rate RECIST v1.1 in a hierarchical fashion on the basis of programmed death–ligand 1 (PD-L1) immunohistochemistry (IHC) and will not include the modified RECIST v1.1. In Cohort 2, the hierarchical fixed-sequence testing procedure on the three populations will be sequentially performed and alternate between the IRF–assessed objective response rate (ORR) according to RECIST v1.1 and the investigator-assessed ORR according to modified RECIST. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported