



## Clinical trial results:

**ALICE: A randomized placebo-controlled phase II study evaluating atezolizumab combined with immunogenic chemotherapy in patients with metastatic triple-negative breast cancer.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-003570-40 |
| Trial protocol           | DK             |
| Global end of trial date | 25 April 2023  |

### Results information

|                                   |                                                               |
|-----------------------------------|---------------------------------------------------------------|
| Result version number             | v1 (current)                                                  |
| This version publication date     | 18 October 2024                                               |
| First version publication date    | 18 October 2024                                               |
| Summary attachment (see zip file) | Published article (Røssevold et al. Nature Medicine 2022.pdf) |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | ML39079_ALICE |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03164993 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                                      |
|------------------------------|------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Oslo University Hospital, Department of Oncology                                                     |
| Sponsor organisation address | Ullernchausseen 70, Oslo, Norway, 0379                                                               |
| Public contact               | Dr. Jon Amund Kyte (Principal Investigator), Oslo University Hospital, +47 97569619, jonky@ous-hf.no |
| Scientific contact           | Dr. Jon Amund Kyte (Principal Investigator), Oslo University Hospital, +47 97569619, jonky@ous-hf.no |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |              |
|------------------------------------------------------|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 05 July 2022 |
| Is this the analysis of the primary completion data? | No           |

|                                  |               |
|----------------------------------|---------------|
| Global end of trial reached?     | Yes           |
| Global end of trial date         | 25 April 2023 |
| Was the trial ended prematurely? | Yes           |

Notes:

## General information about the trial

Main objective of the trial:

Co-primary objectives:

Assessment of toxicity of combined treatment with atezolizumab, pegylated liposomal doxorubicin and cyclophosphamide.

Assessment of clinical response: Progression-free survival; descriptive comparison of the PFS rates in the total per protocol population, and the PD-L1+ PP population

Protection of trial subjects:

The trial was conducted according to the guidelines of Good Clinical Practice and the principles of the World Medical Association's Declaration of Helsinki. All patients provided written informed consent.

Background therapy: -

Evidence for comparator: -

|                                                           |                             |
|-----------------------------------------------------------|-----------------------------|
| Actual start date of recruitment                          | 24 August 2017              |
| Long term follow-up planned                               | Yes                         |
| Long term follow-up rationale                             | Safety, Scientific research |
| Long term follow-up duration                              | 3 Months                    |
| Independent data monitoring committee (IDMC) involvement? | Yes                         |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Norway: 47  |
| Country: Number of subjects enrolled | Denmark: 21 |
| Worldwide total number of subjects   | 68          |
| EEA total number of subjects         | 68          |

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) | 53 |
| From 65 to 84 years  | 15 |
| 85 years and over    | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The trial enrolled 68 patients at 5 academic hospitals in Norway (n = 47) and Denmark (n = 21): Oslo University Hospital (Oslo, NO), Stavanger University Hospital (Stavanger, NO), St.Olavs Hospital (Trondheim, NO), Vejle Hospital (Vejle, DK) and Rigshospitalet (Copenhagen, DK).

### Pre-assignment

Screening details:

Eligible patients were adult women and men with metastatic or incurable locally advanced, histologically confirmed triple-negative breast cancer who had received a maximum of one previous line of chemotherapy in the metastatic setting.

### Period 1

|                              |                                       |
|------------------------------|---------------------------------------|
| Period 1 title               | Overall study (overall period)        |
| Is this the baseline period? | Yes                                   |
| Allocation method            | Randomised - controlled               |
| Blinding used                | Double blind                          |
| Roles blinded                | Subject, Investigator, Monitor, Carer |

Blinding implementation details:

Placebo treatment consisted of an identical-looking intravenous infusion of NaCl 0.9% administered in the same manner. The preparation of active drug dilution/placebo, according to the respective randomization code, was facilitated by the hospital pharmacy, in order to maintain the double blind.

### Arms

|                              |                      |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes                  |
| <b>Arm title</b>             | Placebo-chemotherapy |

Arm description:

Placebo plus pegylated liposomal doxorubicin plus cyclophosphamide

|                                        |                                 |
|----------------------------------------|---------------------------------|
| Arm type                               | Active comparator               |
| Investigational medicinal product name | Pegylated liposomal doxorubicin |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Injection/infusion              |
| Routes of administration               | Intravenous use                 |

Dosage and administration details:

Pegylated liposomal doxorubicin 20 mg/m<sup>2</sup> i.v. every 2nd week. An upper limit of 44 mg per dose will be applied to patients with a body surface area >2.2 m<sup>2</sup>

|                                        |                  |
|----------------------------------------|------------------|
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

Cyclophosphamide tablets 50 mg per day, daily as continuous treatment for the first 2 weeks in each 4 week period (i.e. every second 2-week cycle)

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | Atezolizumab-chemotherapy |
|------------------|---------------------------|

Arm description:

Atezolizumab plus pegylated liposomal doxorubicin plus cyclophosphamide

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|                                        |                    |
|----------------------------------------|--------------------|
| Investigational medicinal product name | Atezolizumab       |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Injection/infusion |
| Routes of administration               | Intravenous use    |

Dosage and administration details:

Atezolizumab will be administered intravenously 840 mg every 2nd week

|                                        |                                 |
|----------------------------------------|---------------------------------|
| Investigational medicinal product name | Pegylated liposomal doxorubicin |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Injection/infusion              |
| Routes of administration               | Intravenous use                 |

Dosage and administration details:

Pegylated liposomal doxorubicin 20 mg/m<sup>2</sup> i.v. every 2nd week. An upper limit of 44 mg per dose will be applied to patients with a body surface area >2.2 m<sup>2</sup>

|                                        |                  |
|----------------------------------------|------------------|
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

Cyclophosphamide tablets 50 mg per day, daily as continuous treatment for the first 2 weeks in each 4 week period (i.e. every second 2-week cycle)

| <b>Number of subjects in period 1</b> | Placebo-<br>chemotherapy | Atezolizumab-<br>chemotherapy |
|---------------------------------------|--------------------------|-------------------------------|
| Started                               | 28                       | 40                            |
| Completed                             | 0                        | 2                             |
| Not completed                         | 28                       | 38                            |
| Physician decision                    | 1                        | 1                             |
| Adverse event, non-fatal              | 1                        | 2                             |
| Still on treatment at data lock       | -                        | 2                             |
| Lack of efficacy                      | 26                       | 33                            |

## Baseline characteristics

### Reporting groups

|                                                                         |                           |
|-------------------------------------------------------------------------|---------------------------|
| Reporting group title                                                   | Placebo-chemotherapy      |
| Reporting group description:                                            |                           |
| Placebo plus pegylated liposomal doxorubicin plus cyclophosphamide      |                           |
| Reporting group title                                                   | Atezolizumab-chemotherapy |
| Reporting group description:                                            |                           |
| Atezolizumab plus pegylated liposomal doxorubicin plus cyclophosphamide |                           |

| Reporting group values                                   | Placebo-chemotherapy | Atezolizumab-chemotherapy | Total |
|----------------------------------------------------------|----------------------|---------------------------|-------|
| Number of subjects                                       | 28                   | 40                        | 68    |
| Age categorical                                          |                      |                           |       |
| Units: Subjects                                          |                      |                           |       |
| Adults (18-64 years)                                     | 24                   | 29                        | 53    |
| From 65-84 years                                         | 4                    | 11                        | 15    |
| Age continuous                                           |                      |                           |       |
| Units: years                                             |                      |                           |       |
| median                                                   | 52.5                 | 58.5                      |       |
| full range (min-max)                                     | 28 to 74             | 31 to 77                  | -     |
| Gender categorical                                       |                      |                           |       |
| Units: Subjects                                          |                      |                           |       |
| Female                                                   | 28                   | 39                        | 67    |
| Male                                                     | 0                    | 1                         | 1     |
| PD-L1 status                                             |                      |                           |       |
| Programmed death ligand 1 expression by the SP-142 assay |                      |                           |       |
| Units: Subjects                                          |                      |                           |       |
| Positive                                                 | 10                   | 21                        | 31    |
| Negative                                                 | 17                   | 19                        | 36    |
| Missing                                                  | 1                    | 0                         | 1     |
| ECOG performance status                                  |                      |                           |       |
| Eastern Oncology Group Performance status                |                      |                           |       |
| Units: Subjects                                          |                      |                           |       |
| ECOG 0                                                   | 21                   | 27                        | 48    |
| ECOG 1                                                   | 7                    | 13                        | 20    |
| De novo metastatic disease                               |                      |                           |       |
| Units: Subjects                                          |                      |                           |       |
| Yes                                                      | 8                    | 10                        | 18    |
| No                                                       | 20                   | 30                        | 50    |
| Bone metastases                                          |                      |                           |       |
| Units: Subjects                                          |                      |                           |       |
| Yes                                                      | 16                   | 17                        | 33    |
| No                                                       | 12                   | 23                        | 35    |
| Liver metastases                                         |                      |                           |       |
| Units: Subjects                                          |                      |                           |       |
| Yes                                                      | 13                   | 12                        | 25    |
| No                                                       | 15                   | 28                        | 43    |
| Lung metastases                                          |                      |                           |       |

|                                  |    |    |    |
|----------------------------------|----|----|----|
| Units: Subjects                  |    |    |    |
| Yes                              | 10 | 18 | 28 |
| No                               | 18 | 22 | 40 |
| Lymph node metastases            |    |    |    |
| Units: Subjects                  |    |    |    |
| Yes                              | 13 | 22 | 35 |
| No                               | 15 | 18 | 33 |
| CNS metastases                   |    |    |    |
| Units: Subjects                  |    |    |    |
| Yes                              | 1  | 1  | 2  |
| No                               | 27 | 39 | 66 |
| Number of metastatic sites       |    |    |    |
| Units: Subjects                  |    |    |    |
| ≤2                               | 15 | 27 | 42 |
| >2                               | 13 | 13 | 26 |
| Line of chemotherapy             |    |    |    |
| Units: Subjects                  |    |    |    |
| 1st                              | 16 | 24 | 40 |
| 2nd                              | 12 | 16 | 28 |
| Previous anthracycline treatment |    |    |    |
| Units: Subjects                  |    |    |    |
| Yes                              | 20 | 28 | 48 |
| No                               | 8  | 12 | 20 |
| Intrinsic breast cancer subtype  |    |    |    |
| Units: Subjects                  |    |    |    |
| Lum A                            | 2  | 0  | 2  |
| Lum B                            | 1  | 1  | 2  |
| HER2E                            | 2  | 4  | 6  |
| Basal                            | 12 | 22 | 34 |
| Missing                          | 11 | 13 | 24 |
| BRCA mutation status             |    |    |    |
| Units: Subjects                  |    |    |    |
| BRCA1 mutation                   | 1  | 2  | 3  |
| Normal variant                   | 12 | 22 | 34 |
| Missing                          | 15 | 16 | 31 |

### Subject analysis sets

|                                                                                                                                                                                                |                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Subject analysis set title                                                                                                                                                                     | Placebo-chemo per-protocol population      |
| Subject analysis set type                                                                                                                                                                      | Per protocol                               |
| Subject analysis set description:                                                                                                                                                              |                                            |
| Patients in placebo-chemotherapy arm evaluated for tumor response and received a minimum of 4 doses of atezolizumab/placebo and a minimum of 3 doses with pegylated liposomal doxorubicin      |                                            |
| Subject analysis set title                                                                                                                                                                     | Atezolizumab-chemo per-protocol population |
| Subject analysis set type                                                                                                                                                                      | Per protocol                               |
| Subject analysis set description:                                                                                                                                                              |                                            |
| Patients in atezolizumab-chemotherapy arm evaluated for tumor response and received a minimum of 4 doses of atezolizumab/placebo and a minimum of 3 doses with pegylated liposomal doxorubicin |                                            |

| Reporting group values                                   | Placebo-chemo per-protocol population | Atezolizumab-chemo per-protocol population |  |
|----------------------------------------------------------|---------------------------------------|--------------------------------------------|--|
| Number of subjects                                       | 23                                    | 36                                         |  |
| Age categorical                                          |                                       |                                            |  |
| Units: Subjects                                          |                                       |                                            |  |
| Adults (18-64 years)                                     | 19                                    | 25                                         |  |
| From 65-84 years                                         | 4                                     | 11                                         |  |
| Age continuous                                           |                                       |                                            |  |
| Units: years                                             |                                       |                                            |  |
| median                                                   | 52                                    | 59                                         |  |
| full range (min-max)                                     | 28 to 74                              | 31 to 77                                   |  |
| Gender categorical                                       |                                       |                                            |  |
| Units: Subjects                                          |                                       |                                            |  |
| Female                                                   | 23                                    | 35                                         |  |
| Male                                                     | 0                                     | 1                                          |  |
| PD-L1 status                                             |                                       |                                            |  |
| Programmed death ligand 1 expression by the SP-142 assay |                                       |                                            |  |
| Units: Subjects                                          |                                       |                                            |  |
| Positive                                                 | 8                                     | 19                                         |  |
| Negative                                                 | 14                                    | 17                                         |  |
| Missing                                                  | 1                                     | 0                                          |  |
| ECOG performance status                                  |                                       |                                            |  |
| Eastern Oncology Group Performance status                |                                       |                                            |  |
| Units: Subjects                                          |                                       |                                            |  |
| ECOG 0                                                   | 16                                    | 25                                         |  |
| ECOG 1                                                   | 7                                     | 11                                         |  |
| De novo metastatic disease                               |                                       |                                            |  |
| Units: Subjects                                          |                                       |                                            |  |
| Yes                                                      | 6                                     | 9                                          |  |
| No                                                       | 17                                    | 27                                         |  |
| Bone metastases                                          |                                       |                                            |  |
| Units: Subjects                                          |                                       |                                            |  |
| Yes                                                      | 13                                    | 14                                         |  |
| No                                                       | 10                                    | 22                                         |  |
| Liver metastases                                         |                                       |                                            |  |
| Units: Subjects                                          |                                       |                                            |  |
| Yes                                                      | 9                                     | 10                                         |  |
| No                                                       | 14                                    | 26                                         |  |
| Lung metastases                                          |                                       |                                            |  |
| Units: Subjects                                          |                                       |                                            |  |
| Yes                                                      | 9                                     | 16                                         |  |
| No                                                       | 14                                    | 20                                         |  |
| Lymph node metastases                                    |                                       |                                            |  |
| Units: Subjects                                          |                                       |                                            |  |
| Yes                                                      | 13                                    | 20                                         |  |
| No                                                       | 10                                    | 16                                         |  |
| CNS metastases                                           |                                       |                                            |  |
| Units: Subjects                                          |                                       |                                            |  |
| Yes                                                      | 1                                     | 1                                          |  |
| No                                                       | 22                                    | 35                                         |  |
| Number of metastatic sites                               |                                       |                                            |  |



|                                  |    |    |  |
|----------------------------------|----|----|--|
| Units: Subjects                  |    |    |  |
| ≤2                               | 12 | 26 |  |
| >2                               | 11 | 10 |  |
| Line of chemotherapy             |    |    |  |
| Units: Subjects                  |    |    |  |
| 1st                              | 12 | 23 |  |
| 2nd                              | 11 | 13 |  |
| Previous anthracycline treatment |    |    |  |
| Units: Subjects                  |    |    |  |
| Yes                              | 17 | 25 |  |
| No                               | 6  | 11 |  |
| Intrinsic breast cancer subtype  |    |    |  |
| Units: Subjects                  |    |    |  |
| Lum A                            | 2  | 0  |  |
| Lum B                            | 1  | 1  |  |
| HER2E                            | 2  | 4  |  |
| Basal                            | 11 | 20 |  |
| Missing                          | 7  | 11 |  |
| BRCA mutation status             |    |    |  |
| Units: Subjects                  |    |    |  |
| BRCA1 mutation                   | 1  | 2  |  |
| Normal variant                   | 11 | 22 |  |
| Missing                          | 11 | 12 |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                |                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Reporting group title                                                                                                                                                                          | Placebo-chemotherapy                       |
| Reporting group description:                                                                                                                                                                   |                                            |
| Placebo plus pegylated liposomal doxorubicin plus cyclophosphamide                                                                                                                             |                                            |
| Reporting group title                                                                                                                                                                          | Atezolizumab-chemotherapy                  |
| Reporting group description:                                                                                                                                                                   |                                            |
| Atezolizumab plus pegylated liposomal doxorubicin plus cyclophosphamide                                                                                                                        |                                            |
| Subject analysis set title                                                                                                                                                                     | Placebo-chemo per-protocol population      |
| Subject analysis set type                                                                                                                                                                      | Per protocol                               |
| Subject analysis set description:                                                                                                                                                              |                                            |
| Patients in placebo-chemotherapy arm evaluated for tumor response and received a minimum of 4 doses of atezolizumab/placebo and a minimum of 3 doses with pegylated liposomal doxorubicin      |                                            |
| Subject analysis set title                                                                                                                                                                     | Atezolizumab-chemo per-protocol population |
| Subject analysis set type                                                                                                                                                                      | Per protocol                               |
| Subject analysis set description:                                                                                                                                                              |                                            |
| Patients in atezolizumab-chemotherapy arm evaluated for tumor response and received a minimum of 4 doses of atezolizumab/placebo and a minimum of 3 doses with pegylated liposomal doxorubicin |                                            |

### Primary: PFS, per-protocol population

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | PFS, per-protocol population |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                              |
| PFS in the per-protocol population.<br>PFS is defined as the time from randomization to the occurrence of disease progression, as determined by investigators from tumor assessments per immune-modified RECIST (iRECIST), or death from any cause, whichever occurs first. Data for patients without disease progression or death will be censored at the last tumor assessment date. Data for patients with a PFS event who missed two or more assessments scheduled immediately prior to the date of the PFS event will be censored at the last tumor assessment prior to the missed visits. If no tumor assessment was performed after randomization, data will be censored at the date of randomization +1 day. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. The HR for disease progression or death (atezo-chemo versus placebo-chemo) will be estimated using a Cox proportional hazards model. |                              |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Primary                      |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                              |
| Until data cutoff 5 th of July 2022                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                              |

| End point values                 | Placebo-chemo per-protocol population | Atezolizumab-chemo per-protocol population |  |  |
|----------------------------------|---------------------------------------|--------------------------------------------|--|--|
| Subject group type               | Subject analysis set                  | Subject analysis set                       |  |  |
| Number of subjects analysed      | 23 <sup>[1]</sup>                     | 36 <sup>[2]</sup>                          |  |  |
| Units: Months                    |                                       |                                            |  |  |
| median (confidence interval 95%) | 3.5 (2.6 to 5.5)                      | 4.3 (3.5 to 7.3)                           |  |  |

Notes:

[1] - Per-protocol population Placebo-chemo

[2] - Per-protocol population Atezo-chemo

### Statistical analyses

|                                         |                                                                                    |
|-----------------------------------------|------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Cox proportional hazards model                                                     |
| Comparison groups                       | Placebo-chemo per-protocol population v Atezolizumab-chemo per-protocol population |
| Number of subjects included in analysis | 59                                                                                 |
| Analysis specification                  | Pre-specified                                                                      |
| Analysis type                           | superiority                                                                        |
| P-value                                 | = 0.047                                                                            |
| Method                                  | Logrank                                                                            |
| Parameter estimate                      | Cox proportional hazard                                                            |
| Point estimate                          | 0.57                                                                               |
| Confidence interval                     |                                                                                    |
| level                                   | 95 %                                                                               |
| sides                                   | 2-sided                                                                            |
| lower limit                             | 0.33                                                                               |
| upper limit                             | 0.99                                                                               |

### Primary: PFS, PD-L1 positive per-protocol population

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | PFS, PD-L1 positive per-protocol population |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                             |
| <p>PFS in the PD-L1 positive patients (SP142 assay) of the PP population.</p> <p>PFS is defined as the time from randomization to the occurrence of disease progression, as determined by investigators from tumor assessments per immune-modified RECIST (iRECIST), or death from any cause, whichever occurs first. Data for patients without disease progression or death will be censored at the last tumor assessment date. Data for patients with a PFS event who missed two or more assessments scheduled immediately prior to the date of the PFS event will be censored at the last tumor assessment prior to the missed visits. If no tumor assessment was performed after randomization, data will be censored at the date of randomization +1 day. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. The HR for disease progression or death will be estimated using a Cox proportional hazards model.</p> |                                             |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Primary                                     |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                             |
| Until data cutoff 5th July 2022                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                             |

| <b>End point values</b>          | Placebo-chemo per-protocol population | Atezolizumab-chemo per-protocol population |  |  |
|----------------------------------|---------------------------------------|--------------------------------------------|--|--|
| Subject group type               | Subject analysis set                  | Subject analysis set                       |  |  |
| Number of subjects analysed      | 8 <sup>[3]</sup>                      | 19 <sup>[4]</sup>                          |  |  |
| Units: Months                    |                                       |                                            |  |  |
| median (confidence interval 95%) | 3.9 (3.6 to 99)                       | 5.5 (2.9 to 9.6)                           |  |  |

Notes:

[3] - PD-L1 pos PP-population

[4] - PD-L1 pos PP population

### Statistical analyses

|                                   |                                                                                    |
|-----------------------------------|------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b> | Cox proportional hazards model                                                     |
| Comparison groups                 | Placebo-chemo per-protocol population v Atezolizumab-chemo per-protocol population |

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 27                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.33                  |
| Method                                  | Logrank                 |
| Parameter estimate                      | Cox proportional hazard |
| Point estimate                          | 0.65                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.27                    |
| upper limit                             | 1.54                    |

## Secondary: PFS, full analysis set population

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | PFS, full analysis set population |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                   |
| <p>Progression-free survival in the full analysis set population (n = 68).</p> <p>PFS is defined as the time from randomization to the occurrence of disease progression, as determined by investigators from tumor assessments per immune-modified RECIST (iRECIST), or death from any cause, whichever occurs first. Data for patients without disease progression or death will be censored at the last tumor assessment date. Data for patients with a PFS event who missed two or more assessments scheduled immediately prior to the date of the PFS event will be censored at the last tumor assessment prior to the missed visits. If no tumor assessment was performed after randomization, data will be censored at the date of randomization +1 day. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. The HR for disease progression or death (atezo-chemo versus placebo-chemo) will be estimated using a Cox proportional hazards model.</p> |                                   |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Secondary                         |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                   |
| Until data cutoff 5th of July                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                   |

| End point values                 | Placebo-chemotherapy | Atezolizumab-chemotherapy |  |  |
|----------------------------------|----------------------|---------------------------|--|--|
| Subject group type               | Reporting group      | Reporting group           |  |  |
| Number of subjects analysed      | 28                   | 40                        |  |  |
| Units: Months                    |                      |                           |  |  |
| median (confidence interval 95%) | 3.1 (1.8 to 5.4)     | 3.9 (3.5 to 5.9)          |  |  |

## Statistical analyses

|                            |                                                  |
|----------------------------|--------------------------------------------------|
| Statistical analysis title | Cox proportional hazards model                   |
| Comparison groups          | Placebo-chemotherapy v Atezolizumab-chemotherapy |

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 68                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.033                 |
| Method                                  | Logrank                 |
| Parameter estimate                      | Cox proportional hazard |
| Point estimate                          | 0.56                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.33                    |
| upper limit                             | 0.95                    |

## Secondary: OS, full analysis set population

|                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                     | OS, full analysis set population |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |
| Overall survival in the full analysis set population (n = 68).<br>Overall survival (OS) will be calculated from the time of randomization until death. Patients alive at the time of data analysis will be treated as censored. The HR for OS will be estimated using a Cox proportional hazards model. The CI for the HR will be provided. Kaplan-Meier methodology will be used to estimate the median OS for each treatment arm. |                                  |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                      | Secondary                        |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                |                                  |
| Until data cutoff 5th of July 2022                                                                                                                                                                                                                                                                                                                                                                                                  |                                  |

| End point values                 | Placebo-chemotherapy | Atezolizumab-chemotherapy |  |  |
|----------------------------------|----------------------|---------------------------|--|--|
| Subject group type               | Reporting group      | Reporting group           |  |  |
| Number of subjects analysed      | 28 <sup>[5]</sup>    | 40 <sup>[6]</sup>         |  |  |
| Units: Months                    |                      |                           |  |  |
| median (confidence interval 95%) | 14.6 (8.1 to 21.3)   | 15.3 (10.9 to 25.5)       |  |  |

Notes:

[5] - Full analysis set

[6] - Full analysis set

## Statistical analyses

|                                                                                                                                                                                                                                       |                                                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Statistical analysis title                                                                                                                                                                                                            | Cox proportional hazards model                   |
| Statistical analysis description:                                                                                                                                                                                                     |                                                  |
| Overall survival (OS) will be calculated from the time of randomization until death. Patients alive at the time of data analysis will be treated as censored. The HR for OS will be estimated using a Cox proportional hazards model. |                                                  |
| Comparison groups                                                                                                                                                                                                                     | Placebo-chemotherapy v Atezolizumab-chemotherapy |

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 68                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| Parameter estimate                      | Cox proportional hazard |
| Point estimate                          | 0.75                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.43                    |
| upper limit                             | 1.3                     |

### Secondary: OS, per-protocol population

|                                                                                                                                                                                                                                                                                                                                                                                                                                |                             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                | OS, per-protocol population |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                         |                             |
| Overall survival in the per-protocol population (n = 59).<br>Overall survival (OS) will be calculated from the time of randomization until death. Patients alive at the time of data analysis will be treated as censored. The HR for OS will be estimated using a Cox proportional hazards model. The CI for the HR will be provided. Kaplan-Meier methodology will be used to estimate the median OS for each treatment arm. |                             |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                 | Secondary                   |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                           |                             |
| Until data cutoff 5th of July 2022                                                                                                                                                                                                                                                                                                                                                                                             |                             |

| End point values                 | Placebo-chemo per-protocol population | Atezolizumab-chemo per-protocol population |  |  |
|----------------------------------|---------------------------------------|--------------------------------------------|--|--|
| Subject group type               | Subject analysis set                  | Subject analysis set                       |  |  |
| Number of subjects analysed      | 23 <sup>[7]</sup>                     | 36 <sup>[8]</sup>                          |  |  |
| Units: Months                    |                                       |                                            |  |  |
| median (confidence interval 95%) | 15.6 (8.1 to 21.3)                    | 15.3 (11.2 to 27.0)                        |  |  |

Notes:

[7] - Per-protocol population

[8] - Per protocol population

### Statistical analyses

|                                                                                                                                                                                                                                       |                                                                                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Statistical analysis title                                                                                                                                                                                                            | Cox proportional hazards model                                                     |
| Statistical analysis description:                                                                                                                                                                                                     |                                                                                    |
| Overall survival (OS) will be calculated from the time of randomization until death. Patients alive at the time of data analysis will be treated as censored. The HR for OS will be estimated using a Cox proportional hazards model. |                                                                                    |
| Comparison groups                                                                                                                                                                                                                     | Placebo-chemo per-protocol population v Atezolizumab-chemo per-protocol population |

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 59                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| Parameter estimate                      | Cox proportional hazard |
| Point estimate                          | 0.71                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.39                    |
| upper limit                             | 1.3                     |

### Secondary: ORR, full analysis set population

|                        |                                                                                                                                         |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | ORR, full analysis set population                                                                                                       |
| End point description: | The proportion of patients in each arm with best overall response either "iPR" or "iCR" by iRECIST in the full analysis set population. |
| End point type         | Secondary                                                                                                                               |
| End point timeframe:   |                                                                                                                                         |
| Until data cutoff      | 5th of July 2022                                                                                                                        |

| End point values            | Placebo-<br>chemotherapy | Atezolizumab-<br>chemotherapy |  |  |
|-----------------------------|--------------------------|-------------------------------|--|--|
| Subject group type          | Reporting group          | Reporting group               |  |  |
| Number of subjects analysed | 28 <sup>[9]</sup>        | 40 <sup>[10]</sup>            |  |  |
| Units: Objective responders |                          |                               |  |  |
| iPR/iCR                     | 5                        | 11                            |  |  |
| Non-iPR/iCR                 | 23                       | 29                            |  |  |

Notes:

[9] - Full analysis set

[10] - Full analysis set

### Statistical analyses

No statistical analyses for this end point

### Secondary: ORR, per-protocol population

|                        |                                                                                                                                   |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| End point title        | ORR, per-protocol population                                                                                                      |
| End point description: | The proportion of patients in each arm with best overall response either "iPR" or "iCR" by iRECIST in the per-protocol population |
| End point type         | Secondary                                                                                                                         |
| End point timeframe:   |                                                                                                                                   |
| Until                  | 5th of July 2022                                                                                                                  |

| End point values            | Placebo-chemo per-protocol population | Atezolizumab-chemo per-protocol population |  |  |
|-----------------------------|---------------------------------------|--------------------------------------------|--|--|
| Subject group type          | Subject analysis set                  | Subject analysis set                       |  |  |
| Number of subjects analysed | 23                                    | 36                                         |  |  |
| Units: Objective responders |                                       |                                            |  |  |
| iCR/iPR                     | 5                                     | 11                                         |  |  |
| Non-iCR/iPR                 | 18                                    | 25                                         |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical benefit rate, full analysis set population

|                                                                                                                                                                                                                                                                                                                      |                                                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                      | Clinical benefit rate, full analysis set population |
| End point description:<br>The proportion in each arm of the full analysis set population with clinical benefit (CBR). CBR was defined as the proportion of patients who had either an objective response (iPR/iCR) by iRECIST or stable disease lasting at least until the radiological evaluation at 24weeks±7days. |                                                     |
| End point type                                                                                                                                                                                                                                                                                                       | Secondary                                           |
| End point timeframe:<br>Until data cutoff 5th of July 2022                                                                                                                                                                                                                                                           |                                                     |

| End point values            | Placebo-chemotherapy | Atezolizumab-chemotherapy |  |  |
|-----------------------------|----------------------|---------------------------|--|--|
| Subject group type          | Reporting group      | Reporting group           |  |  |
| Number of subjects analysed | 28                   | 40                        |  |  |
| Units: Subjects             |                      |                           |  |  |
| CB                          | 10                   | 20                        |  |  |
| Non-CB                      | 18                   | 20                        |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical benefit rate, per-protocol population

|                                                                                                                                                                                                                                                                                                                 |                                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                 | Clinical benefit rate, per-protocol population |
| End point description:<br>The proportion in each arm of the per-protocol population with clinical benefit (CBR). CBR was defined as the proportion of patients who had either an objective response (iPR/iCR) by iRECIST or stable disease lasting at least until the radiological evaluation at 24weeks±7days. |                                                |
| End point type                                                                                                                                                                                                                                                                                                  | Secondary                                      |
| End point timeframe:<br>Until data cutoff 5th July 2022                                                                                                                                                                                                                                                         |                                                |



| <b>End point values</b>     | Placebo-chemo<br>per-protocol<br>population | Atezolizumab-<br>chemo per-<br>protocol<br>population |  |  |
|-----------------------------|---------------------------------------------|-------------------------------------------------------|--|--|
| Subject group type          | Subject analysis set                        | Subject analysis set                                  |  |  |
| Number of subjects analysed | 23                                          | 36                                                    |  |  |
| Units: Subjects             |                                             |                                                       |  |  |
| CB                          | 10                                          | 19                                                    |  |  |
| Non-CB                      | 13                                          | 17                                                    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Durable response rate, full analysis set population

|                                                                                                                                                                                                                     |                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| End point title                                                                                                                                                                                                     | Durable response rate, full analysis set population |
| End point description:                                                                                                                                                                                              |                                                     |
| The number of subjects in each arm of the full analysis set population with durable response. Durable response rate (DRR) was defined as the proportion of patients with a duration of response of $\geq 6$ months. |                                                     |
| End point type                                                                                                                                                                                                      | Secondary                                           |
| End point timeframe:                                                                                                                                                                                                |                                                     |
| Until data cutoff 5th of July 2022                                                                                                                                                                                  |                                                     |

| <b>End point values</b>     | Placebo-<br>chemotherapy | Atezolizumab-<br>chemotherapy |  |  |
|-----------------------------|--------------------------|-------------------------------|--|--|
| Subject group type          | Reporting group          | Reporting group               |  |  |
| Number of subjects analysed | 28                       | 40                            |  |  |
| Units: Subjects             |                          |                               |  |  |
| Durable response            | 1                        | 6                             |  |  |
| Non-durable response        | 27                       | 34                            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Durable response rate, per-protocol population

|                                                                                                                                                                                                                |                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| End point title                                                                                                                                                                                                | Durable response rate, per-protocol population |
| End point description:                                                                                                                                                                                         |                                                |
| The number of subjects in each arm of the per-protocol population with durable response. Durable response rate (DRR) was defined as the proportion of patients with a duration of response of $\geq 6$ months. |                                                |

|                                     |           |
|-------------------------------------|-----------|
| End point type                      | Secondary |
| End point timeframe:                |           |
| Until data cut-off 5th of July 2022 |           |

| End point values            | Placebo-chemo per-protocol population | Atezolizumab-chemo per-protocol population |  |  |
|-----------------------------|---------------------------------------|--------------------------------------------|--|--|
| Subject group type          | Subject analysis set                  | Subject analysis set                       |  |  |
| Number of subjects analysed | 23                                    | 36                                         |  |  |
| Units: Subjects             |                                       |                                            |  |  |
| Durable response            | 1                                     | 6                                          |  |  |
| Non-durable response        | 22                                    | 30                                         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Median duration of response, full analysis set population

|                                                                                                                                                                                                                                                   |                                                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| End point title                                                                                                                                                                                                                                   | Median duration of response, full analysis set population |
| End point description:                                                                                                                                                                                                                            |                                                           |
| The median duration of response (iPR/iCR by iRECIST) in each arm of the full analysis set population. The duration of response was defined as the time from the first documentation of an objective response to the time of progression or death. |                                                           |
| End point type                                                                                                                                                                                                                                    | Secondary                                                 |
| End point timeframe:                                                                                                                                                                                                                              |                                                           |
| Until 5th of July 2022                                                                                                                                                                                                                            |                                                           |

| End point values                      | Placebo-chemotherapy | Atezolizumab-chemotherapy |  |  |
|---------------------------------------|----------------------|---------------------------|--|--|
| Subject group type                    | Reporting group      | Reporting group           |  |  |
| Number of subjects analysed           | 28                   | 40                        |  |  |
| Units: Months                         |                      |                           |  |  |
| median (inter-quartile range (Q1-Q3)) | 3.7 (1.6 to 4.8)     | 7.3 (2.1 to 19.6)         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Median duration of response, per-protocol population

|                 |                                                      |
|-----------------|------------------------------------------------------|
| End point title | Median duration of response, per-protocol population |
|-----------------|------------------------------------------------------|

---

End point description:

The median duration of response (iPR/iCR by iRECIST) in each arm of the per-protocol population. The duration of response was defined as the time from the first documentation of an objective response to the time of progression or death.

---

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

---

End point timeframe:

Until data cutoff 5th of July 2022

---

| End point values                      | Placebo-chemo per-protocol population | Atezolizumab-chemo per-protocol population |  |  |
|---------------------------------------|---------------------------------------|--------------------------------------------|--|--|
| Subject group type                    | Subject analysis set                  | Subject analysis set                       |  |  |
| Number of subjects analysed           | 23                                    | 36                                         |  |  |
| Units: Months                         |                                       |                                            |  |  |
| median (inter-quartile range (Q1-Q3)) | 3.7 (1.6 to 4.8)                      | 7.3 (2.1 to 19.6)                          |  |  |

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From 24th AUG 2017 until data lock 5th of JUL 2022.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Placebo-chemotherapy |
|-----------------------|----------------------|

Reporting group description: -

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Atezolizumab-chemotherapy |
|-----------------------|---------------------------|

Reporting group description: -

| Serious adverse events                            | Placebo-chemotherapy | Atezolizumab-chemotherapy |  |
|---------------------------------------------------|----------------------|---------------------------|--|
| Total subjects affected by serious adverse events |                      |                           |  |
| subjects affected / exposed                       | 8 / 28 (28.57%)      | 19 / 40 (47.50%)          |  |
| number of deaths (all causes)                     | 23                   | 28                        |  |
| number of deaths resulting from adverse events    | 0                    | 0                         |  |
| Injury, poisoning and procedural complications    |                      |                           |  |
| Infusion related reaction                         |                      |                           |  |
| subjects affected / exposed                       | 0 / 28 (0.00%)       | 1 / 40 (2.50%)            |  |
| occurrences causally related to treatment / all   | 0 / 0                | 1 / 1                     |  |
| deaths causally related to treatment / all        | 0 / 0                | 0 / 0                     |  |
| Cardiac disorders                                 |                      |                           |  |
| Atrioventricular block complete                   |                      |                           |  |
| subjects affected / exposed                       | 1 / 28 (3.57%)       | 0 / 40 (0.00%)            |  |
| occurrences causally related to treatment / all   | 1 / 1                | 0 / 0                     |  |
| deaths causally related to treatment / all        | 0 / 0                | 0 / 0                     |  |
| Nervous system disorders                          |                      |                           |  |
| Headache                                          |                      |                           |  |
| subjects affected / exposed                       | 1 / 28 (3.57%)       | 0 / 40 (0.00%)            |  |
| occurrences causally related to treatment / all   | 0 / 1                | 0 / 0                     |  |
| deaths causally related to treatment / all        | 0 / 0                | 0 / 0                     |  |
| Syncope                                           |                      |                           |  |

|                                                      |                |                |  |
|------------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                          | 0 / 28 (0.00%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| Pyrexia                                              |                |                |  |
| subjects affected / exposed                          | 1 / 28 (3.57%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                           |                |                |  |
| Nausea                                               |                |                |  |
| subjects affected / exposed                          | 0 / 28 (0.00%) | 2 / 40 (5.00%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 2          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Abdominal pain                                       |                |                |  |
| subjects affected / exposed                          | 1 / 28 (3.57%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Hepatobiliary disorders                              |                |                |  |
| Cholecystitis                                        |                |                |  |
| subjects affected / exposed                          | 0 / 28 (0.00%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Hepatic haemorrhage                                  |                |                |  |
| subjects affected / exposed                          | 1 / 28 (3.57%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Hepatic pain                                         |                |                |  |
| subjects affected / exposed                          | 1 / 28 (3.57%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders      |                |                |  |
| Pleural effusion                                     |                |                |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 28 (3.57%) | 5 / 40 (12.50%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 9           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pneumonitis                                     |                |                 |  |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 4 / 40 (10.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Dyspnoea                                        |                |                 |  |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 2 / 40 (5.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pneumothorax                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 1 / 40 (2.50%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pulmonary embolism                              |                |                 |  |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 1 / 40 (2.50%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Renal and urinary disorders                     |                |                 |  |
| Urinary tract obstruction                       |                |                 |  |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 1 / 40 (2.50%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                |                 |  |
| Musculoskeletal pain                            |                |                 |  |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 1 / 40 (2.50%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Infections and infestations                     |                |                 |  |
| Urinary tract infection                         |                |                 |  |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 3 / 40 (7.50%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Infection                                       |                |                |  |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 2 / 40 (5.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lung infection                                  |                |                |  |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 2 / 40 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Upper respiratory tract infection               |                |                |  |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 2 / 40 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Corona virus infection                          |                |                |  |
| subjects affected / exposed                     | 0 / 28 (0.00%) | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |
| Hypokalaemia                                    |                |                |  |
| subjects affected / exposed                     | 1 / 28 (3.57%) | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 3 %

| <b>Non-serious adverse events</b>                     | Placebo-<br>chemotherapy | Atezolizumab-<br>chemotherapy |  |
|-------------------------------------------------------|--------------------------|-------------------------------|--|
| Total subjects affected by non-serious adverse events |                          |                               |  |
| subjects affected / exposed                           | 27 / 28 (96.43%)         | 40 / 40 (100.00%)             |  |
| Vascular disorders                                    |                          |                               |  |
| Thrombosis                                            |                          |                               |  |
| subjects affected / exposed                           | 1 / 28 (3.57%)           | 2 / 40 (5.00%)                |  |
| occurrences (all)                                     | 1                        | 2                             |  |
| Hypotension                                           |                          |                               |  |
| subjects affected / exposed                           | 1 / 28 (3.57%)           | 0 / 40 (0.00%)                |  |
| occurrences (all)                                     | 1                        | 0                             |  |
| General disorders and administration                  |                          |                               |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| site conditions                                 |                  |                  |  |
| Fatigue                                         |                  |                  |  |
| subjects affected / exposed                     | 12 / 28 (42.86%) | 20 / 40 (50.00%) |  |
| occurrences (all)                               | 15               | 23               |  |
| Pyrexia                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 28 (3.57%)   | 3 / 40 (7.50%)   |  |
| occurrences (all)                               | 3                | 5                |  |
| Malaise                                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 28 (0.00%)   | 2 / 40 (5.00%)   |  |
| occurrences (all)                               | 0                | 2                |  |
| Oedema                                          |                  |                  |  |
| subjects affected / exposed                     | 2 / 28 (7.14%)   | 2 / 40 (5.00%)   |  |
| occurrences (all)                               | 3                | 2                |  |
| Pain                                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 28 (0.00%)   | 2 / 40 (5.00%)   |  |
| occurrences (all)                               | 0                | 2                |  |
| Thirst                                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 28 (3.57%)   | 0 / 40 (0.00%)   |  |
| occurrences (all)                               | 1                | 0                |  |
| Immune system disorders                         |                  |                  |  |
| Hypersensitivity                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 28 (0.00%)   | 3 / 40 (7.50%)   |  |
| occurrences (all)                               | 0                | 3                |  |
| Reproductive system and breast disorders        |                  |                  |  |
| Vulvovaginal dryness                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 28 (0.00%)   | 4 / 40 (10.00%)  |  |
| occurrences (all)                               | 0                | 4                |  |
| Vaginal haemorrhage                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 28 (3.57%)   | 0 / 40 (0.00%)   |  |
| occurrences (all)                               | 1                | 0                |  |
| Vulvovaginal pain                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 28 (3.57%)   | 0 / 40 (0.00%)   |  |
| occurrences (all)                               | 1                | 0                |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| Cough                                           |                  |                  |  |



|                                                                                                                                 |                        |                        |  |
|---------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                                | 4 / 28 (14.29%)<br>4   | 5 / 40 (12.50%)<br>5   |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                                                    | 3 / 28 (10.71%)<br>3   | 4 / 40 (10.00%)<br>8   |  |
| Painful respiration<br>subjects affected / exposed<br>occurrences (all)                                                         | 1 / 28 (3.57%)<br>1    | 0 / 40 (0.00%)<br>0    |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                                           | 1 / 28 (3.57%)<br>1    | 0 / 40 (0.00%)<br>0    |  |
| Investigations<br>Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)                                | 10 / 28 (35.71%)<br>16 | 18 / 40 (45.00%)<br>19 |  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)                                                  | 4 / 28 (14.29%)<br>5   | 4 / 40 (10.00%)<br>9   |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                                                            | 0 / 28 (0.00%)<br>0    | 3 / 40 (7.50%)<br>3    |  |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)                                                    | 1 / 28 (3.57%)<br>2    | 1 / 40 (2.50%)<br>1    |  |
| Pancreatic enzymes increased<br>subjects affected / exposed<br>occurrences (all)                                                | 1 / 28 (3.57%)<br>2    | 1 / 40 (2.50%)<br>2    |  |
| Injury, poisoning and procedural complications<br>Infusion related reaction<br>subjects affected / exposed<br>occurrences (all) | 1 / 28 (3.57%)<br>1    | 3 / 40 (7.50%)<br>3    |  |
| Fracture<br>subjects affected / exposed<br>occurrences (all)                                                                    | 0 / 28 (0.00%)<br>0    | 2 / 40 (5.00%)<br>2    |  |
| Nervous system disorders                                                                                                        |                        |                        |  |

|                                      |                 |                 |  |
|--------------------------------------|-----------------|-----------------|--|
| Dizziness                            |                 |                 |  |
| subjects affected / exposed          | 1 / 28 (3.57%)  | 4 / 40 (10.00%) |  |
| occurrences (all)                    | 1               | 4               |  |
| Headache                             |                 |                 |  |
| subjects affected / exposed          | 4 / 28 (14.29%) | 4 / 40 (10.00%) |  |
| occurrences (all)                    | 4               | 4               |  |
| Neuropathy peripheral                |                 |                 |  |
| subjects affected / exposed          | 3 / 28 (10.71%) | 2 / 40 (5.00%)  |  |
| occurrences (all)                    | 3               | 2               |  |
| Dysgeusia                            |                 |                 |  |
| subjects affected / exposed          | 0 / 28 (0.00%)  | 2 / 40 (5.00%)  |  |
| occurrences (all)                    | 0               | 2               |  |
| Parosmia                             |                 |                 |  |
| subjects affected / exposed          | 0 / 28 (0.00%)  | 2 / 40 (5.00%)  |  |
| occurrences (all)                    | 0               | 2               |  |
| Amnesia                              |                 |                 |  |
| subjects affected / exposed          | 1 / 28 (3.57%)  | 0 / 40 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Dysarthria                           |                 |                 |  |
| subjects affected / exposed          | 1 / 28 (3.57%)  | 0 / 40 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Syncope                              |                 |                 |  |
| subjects affected / exposed          | 1 / 28 (3.57%)  | 0 / 40 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Blood and lymphatic system disorders |                 |                 |  |
| Anaemia                              |                 |                 |  |
| subjects affected / exposed          | 1 / 28 (3.57%)  | 1 / 40 (2.50%)  |  |
| occurrences (all)                    | 1               | 1               |  |
| Leukopenia                           |                 |                 |  |
| subjects affected / exposed          | 1 / 28 (3.57%)  | 0 / 40 (0.00%)  |  |
| occurrences (all)                    | 1               | 0               |  |
| Eye disorders                        |                 |                 |  |
| Dry eye                              |                 |                 |  |
| subjects affected / exposed          | 0 / 28 (0.00%)  | 2 / 40 (5.00%)  |  |
| occurrences (all)                    | 0               | 2               |  |
| Gastrointestinal disorders           |                 |                 |  |

|                                            |                  |                  |  |
|--------------------------------------------|------------------|------------------|--|
| Nausea                                     |                  |                  |  |
| subjects affected / exposed                | 15 / 28 (53.57%) | 21 / 40 (52.50%) |  |
| occurrences (all)                          | 16               | 25               |  |
| Mucosal inflammation                       |                  |                  |  |
| subjects affected / exposed                | 6 / 28 (21.43%)  | 19 / 40 (47.50%) |  |
| occurrences (all)                          | 6                | 25               |  |
| Constipation                               |                  |                  |  |
| subjects affected / exposed                | 12 / 28 (42.86%) | 18 / 40 (45.00%) |  |
| occurrences (all)                          | 12               | 19               |  |
| Dyspepsia                                  |                  |                  |  |
| subjects affected / exposed                | 3 / 28 (10.71%)  | 8 / 40 (20.00%)  |  |
| occurrences (all)                          | 3                | 9                |  |
| Diarrhoea                                  |                  |                  |  |
| subjects affected / exposed                | 6 / 28 (21.43%)  | 4 / 40 (10.00%)  |  |
| occurrences (all)                          | 6                | 4                |  |
| Dry mouth                                  |                  |                  |  |
| subjects affected / exposed                | 2 / 28 (7.14%)   | 6 / 40 (15.00%)  |  |
| occurrences (all)                          | 2                | 6                |  |
| Abdominal pain                             |                  |                  |  |
| subjects affected / exposed                | 2 / 28 (7.14%)   | 5 / 40 (12.50%)  |  |
| occurrences (all)                          | 2                | 6                |  |
| Dysphagia                                  |                  |                  |  |
| subjects affected / exposed                | 0 / 28 (0.00%)   | 2 / 40 (5.00%)   |  |
| occurrences (all)                          | 0                | 2                |  |
| Vomiting                                   |                  |                  |  |
| subjects affected / exposed                | 0 / 28 (0.00%)   | 2 / 40 (5.00%)   |  |
| occurrences (all)                          | 0                | 2                |  |
| Skin and subcutaneous tissue disorders     |                  |                  |  |
| Rash                                       |                  |                  |  |
| subjects affected / exposed                | 11 / 28 (39.29%) | 26 / 40 (65.00%) |  |
| occurrences (all)                          | 14               | 36               |  |
| Palmar-plantar erythrodysesthesia syndrome |                  |                  |  |
| subjects affected / exposed                | 3 / 28 (10.71%)  | 21 / 40 (52.50%) |  |
| occurrences (all)                          | 3                | 22               |  |
| Pruritus                                   |                  |                  |  |

|                                                                                                                             |                      |                        |  |
|-----------------------------------------------------------------------------------------------------------------------------|----------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                            | 2 / 28 (7.14%)<br>2  | 7 / 40 (17.50%)<br>7   |  |
| Hair growth abnormal<br>subjects affected / exposed<br>occurrences (all)                                                    | 1 / 28 (3.57%)<br>1  | 0 / 40 (0.00%)<br>0    |  |
| Nail ridging<br>subjects affected / exposed<br>occurrences (all)                                                            | 1 / 28 (3.57%)<br>1  | 0 / 40 (0.00%)<br>0    |  |
| Pigmentation disorder<br>subjects affected / exposed<br>occurrences (all)                                                   | 1 / 28 (3.57%)<br>1  | 0 / 40 (0.00%)<br>0    |  |
| Skin hyperpigmentation<br>subjects affected / exposed<br>occurrences (all)                                                  | 1 / 28 (3.57%)<br>1  | 0 / 40 (0.00%)<br>0    |  |
| Skin ulcer<br>subjects affected / exposed<br>occurrences (all)                                                              | 1 / 28 (3.57%)<br>1  | 1 / 40 (2.50%)<br>1    |  |
| Renal and urinary disorders<br>Cystitis noninfective<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 28 (3.57%)<br>1  | 1 / 40 (2.50%)<br>1    |  |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)                                   | 2 / 28 (7.14%)<br>2  | 5 / 40 (12.50%)<br>5   |  |
| Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)                                                         | 2 / 28 (7.14%)<br>2  | 1 / 40 (2.50%)<br>1    |  |
| Cushingoid<br>subjects affected / exposed<br>occurrences (all)                                                              | 1 / 28 (3.57%)<br>1  | 0 / 40 (0.00%)<br>0    |  |
| Musculoskeletal and connective tissue disorders<br>Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all) | 6 / 28 (21.43%)<br>9 | 11 / 40 (27.50%)<br>17 |  |
| Infections and infestations                                                                                                 |                      |                        |  |

|                                    |                 |                 |  |
|------------------------------------|-----------------|-----------------|--|
| Skin infection                     |                 |                 |  |
| subjects affected / exposed        | 2 / 28 (7.14%)  | 7 / 40 (17.50%) |  |
| occurrences (all)                  | 2               | 8               |  |
| Upper respiratory tract infection  |                 |                 |  |
| subjects affected / exposed        | 0 / 28 (0.00%)  | 6 / 40 (15.00%) |  |
| occurrences (all)                  | 0               | 9               |  |
| Urinary tract infection            |                 |                 |  |
| subjects affected / exposed        | 1 / 28 (3.57%)  | 5 / 40 (12.50%) |  |
| occurrences (all)                  | 3               | 16              |  |
| Oral fungal infection              |                 |                 |  |
| subjects affected / exposed        | 1 / 28 (3.57%)  | 3 / 40 (7.50%)  |  |
| occurrences (all)                  | 1               | 3               |  |
| Gastroenteritis                    |                 |                 |  |
| subjects affected / exposed        | 0 / 28 (0.00%)  | 2 / 40 (5.00%)  |  |
| occurrences (all)                  | 0               | 2               |  |
| Conjunctivitis                     |                 |                 |  |
| subjects affected / exposed        | 1 / 28 (3.57%)  | 0 / 40 (0.00%)  |  |
| occurrences (all)                  | 1               | 0               |  |
| Mastitis                           |                 |                 |  |
| subjects affected / exposed        | 1 / 28 (3.57%)  | 1 / 40 (2.50%)  |  |
| occurrences (all)                  | 1               | 1               |  |
| Metabolism and nutrition disorders |                 |                 |  |
| Decreased appetite                 |                 |                 |  |
| subjects affected / exposed        | 3 / 28 (10.71%) | 7 / 40 (17.50%) |  |
| occurrences (all)                  | 3               | 7               |  |
| Hyperglycaemia                     |                 |                 |  |
| subjects affected / exposed        | 0 / 28 (0.00%)  | 2 / 40 (5.00%)  |  |
| occurrences (all)                  | 0               | 2               |  |
| Hypokalaemia                       |                 |                 |  |
| subjects affected / exposed        | 1 / 28 (3.57%)  | 1 / 40 (2.50%)  |  |
| occurrences (all)                  | 1               | 1               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                          |
|------------------|------------------------------------------------------------------------------------------------------------------------------------|
| 29 June 2020     | Updated inclusion/exclusion criteria. Specification of endpoints and hypotheses.                                                   |
| 12 February 2021 | Update in primary objectives and efficacy measures, and inclusion/exclusion criteria. Interim analysis of PD-L1 negative patients. |
| 22 February 2022 | Premature end of patient recruitment. Update in planned statistical analyses.                                                      |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36482103>