



Clinical trial results:

A Phase 1/2 Study on the Safety of Rovalpituzumab Tesirine Administered in Combination with Nivolumab or Nivolumab and Ipilimumab for Adults with Extensive-Stage Small Cell Lung Cancer.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2016-003686-26 |
| Trial protocol | DE ES IT |
| Global end of trial date | 03 July 2019 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 17 July 2020 |
| First version publication date | 15 May 2020 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set Editorial change to clarify age ranges and an outcome measure description. |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | M16-300 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03026166 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Abbvie Deutschland GmbH & Co.KG |
| Sponsor organisation address | AbbVie House, Vanwall Business Park, Maidenhead, Berkshire, United Kingdom, SL6-4UB |
| Public contact | Global Medical Services, AbbVie, 011 800-633-9110, |
| Scientific contact | Philip Komarnitsky, MD, PhD, AbbVie, philip.komarnitsky@abbvie.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 03 July 2019 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 July 2019 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the safety of rovalpituzumab tesirine when administered in combination with nivolumab or nivolumab and ipilimumab in adult subjects with extensive-stage small cell lung cancer (SCLC).

Protection of trial subjects:

All subjects entering the study had to sign an informed consent that was explained to them and questions encouraged.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 30 March 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | France: 10 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | Italy: 3 |
| Country: Number of subjects enrolled | United States: 28 |
| Worldwide total number of subjects | 42 |
| EEA total number of subjects | 14 |

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) | 26 |
| From 65 to 84 years | 16 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 17 clinical study sites in 4 countries: United States, France, Italy, and Germany.

Pre-assignment

Screening details:

Three study cohorts were planned to enroll approximately 30 subjects in each, including a dose-limiting toxicity (DLT) evaluation phase (the first 12 weeks of any treatment for all subjects) and an expansion phase. However, Cohort 2 was limited to 12 subjects and Cohort 3 was not opened.

Period 1

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

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1: Rovalpituzumab Tesirine and Nivolumab |

Arm description:

Participants received 2 doses of 0.3 mg/kg rovalpituzumab tesirine by intravenous (IV) infusion 6 weeks apart (Day 1 of Cycles 1 and 3), and 2 doses of 360 mg nivolumab IV 3 weeks apart beginning on Cycle 2 (Day 1 of Cycles 2 and 3).

Participants then received maintenance therapy with 480 mg nivolumab IV once every 4 weeks from Cycle 4 until disease progression.

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Rovalpituzumab Tesirine) |
| Investigational medicinal product code | SC16LD6.5 |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered by intravenous infusion 0.3 mg/kg, every 6 weeks (q6wk) × 2

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Nivolumab |
| Investigational medicinal product code | |
| Other name | Opdivo® |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered by intravenous infusion

| | |
|------------------|--|
| Arm title | Cohort 2: Rovalpituzumab Tesirine and Nivolumab + Ipilimumab |
|------------------|--|

Arm description:

Participants received 2 doses of 0.3 mg/kg rovalpituzumab tesirine IV 6 weeks apart (Day 1 of Cycles 1 and 3), nivolumab 1 mg/kg every 3 weeks for 4 cycles beginning on Cycle 2 (Day 1 of Cycles 2-5), and ipilimumab 1 mg/kg IV every 3 weeks for 4 cycles beginning on Cycle 2 (Day 1 of Cycles 2-5).

After a 6-week washout, participants then received maintenance therapy with 480 mg nivolumab IV once every 4 weeks from Cycle 6 until disease progression.

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

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Rovalpituzumab Tesirine |
| Investigational medicinal product code | SC16LD6.5 |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Administered by intravenous infusion 0.3 mg/kg, every 6 weeks (q6wk) × 2 | |
| Investigational medicinal product name | Nivolumab |
| Investigational medicinal product code | |
| Other name | Opdivo® |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Administered by intravenous infusion | |
| Investigational medicinal product name | Ipilimumab |
| Investigational medicinal product code | |
| Other name | Yervoy® |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Administered by intravenous infusion 1 mg/kg once every 3 weeks | |

| Number of subjects in period 1 | Cohort 1: Rovalpituzumab Tesirine and Nivolumab | Cohort 2: Rovalpituzumab Tesirine and Nivolumab + Ipilimumab |
|--------------------------------|--|--|
| | | |
| Started | 30 | 12 |
| Completed | 0 | 0 |
| Not completed | 30 | 12 |
| Physician decision | 2 | - |
| Consent withdrawn by subject | 1 | 2 |
| Death | 22 | 7 |
| Other | 1 | - |
| Study Terminated by Sponsor | 3 | 3 |
| Lost to follow-up | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Cohort 1: Rovalpituzumab Tesirine and Nivolumab |
|-----------------------|---|

Reporting group description:

Participants received 2 doses of 0.3 mg/kg rovalpituzumab tesirine by intravenous (IV) infusion 6 weeks apart (Day 1 of Cycles 1 and 3), and 2 doses of 360 mg nivolumab IV 3 weeks apart beginning on Cycle 2 (Day 1 of Cycles 2 and 3).

Participants then received maintenance therapy with 480 mg nivolumab IV once every 4 weeks from Cycle 4 until disease progression.

| | |
|-----------------------|--|
| Reporting group title | Cohort 2: Rovalpituzumab Tesirine and Nivolumab + Ipilimumab |
|-----------------------|--|

Reporting group description:

Participants received 2 doses of 0.3 mg/kg rovalpituzumab tesirine IV 6 weeks apart (Day 1 of Cycles 1 and 3), nivolumab 1 mg/kg every 3 weeks for 4 cycles beginning on Cycle 2 (Day 1 of Cycles 2-5), and ipilimumab 1 mg/kg IV every 3 weeks for 4 cycles beginning on Cycle 2 (Day 1 of Cycles 2-5).

After a 6-week washout, participants then received maintenance therapy with 480 mg nivolumab IV once every 4 weeks from Cycle 6 until disease progression.

| Reporting group values | Cohort 1: Rovalpituzumab Tesirine and Nivolumab | Cohort 2: Rovalpituzumab Tesirine and Nivolumab + Ipilimumab | Total |
|---|--|--|-------|
| Number of subjects | 30 | 12 | 42 |
| Age categorical Units: Subjects | | | |
| < 40 years | 0 | 1 | 1 |
| ≥ 40 to < 60 years | 11 | 5 | 16 |
| ≥ 60 years | 19 | 6 | 25 |
| Age continuous Units: years arithmetic mean standard deviation | 61.87 ± 8.195 | 57.25 ± 14.085 | - |
| Gender categorical Units: Subjects | | | |
| Female | 14 | 5 | 19 |
| Male | 16 | 7 | 23 |
| Race Units: Subjects | | | |
| White | 29 | 10 | 39 |
| Black or African American | 1 | 1 | 2 |
| Not Reported | 0 | 1 | 1 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 2 | 0 | 2 |
| Not Hispanic or Latino | 28 | 11 | 39 |
| Not Reported | 0 | 1 | 1 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Cohort 1: Rovalpituzumab Tesirine and Nivolumab |
| Reporting group description: Participants received 2 doses of 0.3 mg/kg rovalpituzumab tesirine by intravenous (IV) infusion 6 weeks apart (Day 1 of Cycles 1 and 3), and 2 doses of 360 mg nivolumab IV 3 weeks apart beginning on Cycle 2 (Day 1 of Cycles 2 and 3). Participants then received maintenance therapy with 480 mg nivolumab IV once every 4 weeks from Cycle 4 until disease progression. | |
| Reporting group title | Cohort 2: Rovalpituzumab Tesirine and Nivolumab + Ipilimumab |
| Reporting group description: Participants received 2 doses of 0.3 mg/kg rovalpituzumab tesirine IV 6 weeks apart (Day 1 of Cycles 1 and 3), nivolumab 1 mg/kg every 3 weeks for 4 cycles beginning on Cycle 2 (Day 1 of Cycles 2-5), and ipilimumab 1 mg/kg IV every 3 weeks for 4 cycles beginning on Cycle 2 (Day 1 of Cycles 2-5). After a 6-week washout, participants then received maintenance therapy with 480 mg nivolumab IV once every 4 weeks from Cycle 6 until disease progression. | |

Primary: Number of Participants with Dose-limiting Toxicities (DLTs)

| | |
|--|--|
| End point title | Number of Participants with Dose-limiting Toxicities (DLTs) ^[1] |
| End point description: Dose-limiting toxicities were defined as any of the following in the 12-week DLT-evaluation period, graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03: <ul style="list-style-type: none">• Grade 4 thrombocytopenia (or Grade 3 thrombocytopenia with bleeding) lasting more than 7 days and/or requiring platelet transfusion• Grade 4 neutropenia lasting more than 7 days, and/or requiring hematopoietic growth factor rescue, or any febrile neutropenia (Grade 3 or 4 neutropenia with concurrent fever $\geq 38.3^{\circ}\text{C}$)• Grade 4 anemia unrelated to underlying disease• Clinically significant Grade 3 or 4 non-hematologic laboratory abnormality that did not resolve to Grade 0/1 or baseline within 7 days• Grade 3 or 4 non-laboratory adverse event (AE), except fatigue, asthenia, nausea, or other manageable constitutional symptom DLT-evaluable participants were those who completed 4 cycles treatment during the DLT period or stopped treatment earlier due to DLT. | |
| End point type | Primary |
| End point timeframe: 12 weeks | |

Notes:

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

Justification: Comparisons between cohorts were not conducted.

| End point values | Cohort 1: Rovalpituzumab Tesirine and Nivolumab | Cohort 2: Rovalpituzumab Tesirine and Nivolumab + Ipilimumab | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 ^[2] | 6 ^[3] | | |
| Units: participants | 1 | 3 | | |

Notes:

[2] - DLT-evaluable

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Adverse Events (AEs)

| End point title | Number of Participants with Adverse Events (AEs) ^[4] |
|-----------------|---|
|-----------------|---|

End point description:

The investigator rated the severity of each AE according to the NCI CTCAE Version 4.03 and according to the following:

Grade 1: The AE is transient and easily tolerated by the subject (mild).

Grade 2: The AE causes the subject discomfort and interrupts the subject's usual activities (moderate).

Grade 3/4: The AE causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening (severe).

Grade 5: The AE resulted in death of the subject (severe).

The maximum severity of AEs are reported.

A serious adverse event was defined as an AE meeting any of the following:

- Death
- Life-threatening
- Resulted in hospitalization or prolongation of hospitalization
- Resulted in congenital abnormality
- Resulted in persistent or significant disability or incapacity
- Was an important medical event requiring medical intervention to prevent a serious outcome.

Relationship to study drug was assessed by the Investigator.

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

End point timeframe:

From the first dose of study drug until 100 days after the last dose of study drug; median duration of treatment was 65 days and 53 days in each cohort respectively.

Notes:

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

Justification: Comparisons between cohorts were not conducted.

| End point values | Cohort 1: Rovalpituzuma b Tesirine and Nivolumab | Cohort 2: Rovalpituzuma b Tesirine and Nivolumab + Ipilimumab | | |
|------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 12 | | |
| Units: participants | | | | |
| Any adverse event | 30 | 12 | | |
| Drug-related adverse event | 29 | 12 | | |
| Serious adverse event | 23 | 9 | | |
| Drug-related serious adverse event | 13 | 6 | | |
| Grade 3 adverse event | 11 | 7 | | |
| Grade 4 adverse event | 1 | 1 | | |
| Grade 5 adverse event | 14 | 4 | | |
| Drug-related Grade 3 adverse event | 9 | 10 | | |

| | | | | |
|---|----|---|--|--|
| Drug-related Grade 4 adverse event | 3 | 1 | | |
| Drug-related Grade 5 adverse event | 4 | 0 | | |
| AE leading to study drug withdrawal | 12 | 6 | | |
| AE leading to treatment interruption | 18 | 8 | | |
| AE leading to dose reduction | 0 | 1 | | |
| Drug-related AE leading to study drug withdrawal | 9 | 4 | | |
| Drug-related AE leading to treatment interruption | 17 | 8 | | |
| Drug-related AE leading to dose reduction | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

| | |
|-----------------|-------------------------|
| End point title | Objective Response Rate |
|-----------------|-------------------------|

End point description:

Treatment response was assessed by radiographic tumor evaluations conducted by a central radiology review.

Objective response rate (ORR) is defined as the percentage of participants whose best overall response is either a confirmed complete response (CR) or partial response (PR) according to Response Evaluation Criteria for Solid Tumors (RECIST) v1.1.

Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.

Partial response (PR): A \geq 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

CR or PR must have been confirmed at least 4 weeks (28 days) from the initial determination per RECIST v 1.1.

The Efficacy Analysis Set includes participants who received at least one dose of study drug, had a target lesion identified at baseline, and either had at least 1 post-dose tumor assessment or discontinued treatment due to AE, progressive disease (PD) or death.

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

End point timeframe:

Cohort 1: at Week 6, Week 13, and every 8 weeks thereafter; Cohort 2: at Week 6, Week 12, Week 18, and every 8 weeks thereafter, up to the end of follow-up; median duration on follow-up was 31.7 and 48.0 weeks in each cohort respectively.

| End point values | Cohort 1: Rovalpituzumab b Tesirine and Nivolumab | Cohort 2: Rovalpituzumab b Tesirine and Nivolumab + Ipilimumab | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 ^[5] | 11 ^[6] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 27.6 (12.7 to 47.2) | 36.4 (10.9 to 69.2) | | |

Notes:

[5] - Efficacy Analysis Set

[6] - Efficacy Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

| | |
|-----------------|----------------------|
| End point title | Duration of Response |
|-----------------|----------------------|

End point description:

Duration of overall response is defined as the time from the date of first documented CR or PR, assessed by central radiology review and based on RECIST v. 1.1, to the documented date of progressive disease (PD) or death, whichever occurred first. Participants who neither progressed nor died were censored at the last evaluable disease assessment. Based on Kaplan-Meier estimate.

Progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, with an absolute increase of at least 0.5 cm, or the unequivocal progression of non-target lesions, or the appearance of one or more new lesions.

The analysis includes participants in the Efficacy Analysis Set with a best overall response of unconfirmed CR or PR.

"99999" indicates a value that could not be estimated.

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

End point timeframe:

Cohort 1: at Week 6, Week 13, and every 8 weeks thereafter; Cohort 2: at Week 6, Week 12, Week 18 and every 8 weeks thereafter, up to the end of follow-up; median duration on follow-up was 31.7 and 48.0 weeks in each cohort respectively.

| End point values | Cohort 1: Rovalpituzuma b Tesirine and Nivolumab | Cohort 2: Rovalpituzuma b Tesirine and Nivolumab + Ipilimumab | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 ^[7] | 6 ^[8] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 3.8 (1.6 to 5.6) | 3.3 (1.4 to 99999) | | |

Notes:

[7] - Efficacy analysis set participants with unconfirmed CR or PR

[8] - Efficacy analysis set participants with unconfirmed CR or PR

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

| | |
|-----------------|---------------------------|
| End point title | Progression-Free Survival |
|-----------------|---------------------------|

End point description:

Progression-free survival is defined as the time from the first dose date to the documented date of PD or death, whichever occurred first, based on central radiology review according to RECIST v 1.1.

Participants who neither progressed nor died were censored at the last evaluable disease assessment. Based on Kaplan-Meier estimates.

Progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, with an absolute increase of at least 0.5 cm, or the unequivocal progression of non-target lesions, or the appearance of one or more new lesions.

Efficacy Analysis Set.

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

End point timeframe:

From first dose of study drug up to the end of follow-up; median duration on follow-up was 31.7 and 48.0 weeks in each cohort respectively.

| End point values | Cohort 1: Rovalpituzuma b Tesirine and Nivolumab | Cohort 2: Rovalpituzuma b Tesirine and Nivolumab + Ipilimumab | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 ^[9] | 11 ^[10] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.8 (3.2 to 5.3) | 4.1 (1.3 to 6.0) | | |

Notes:

[9] - Efficacy Analysis Set

[10] - Efficacy Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

Overall survival is defined as the time from the first dose date to death for any reason. Participants who were still alive were censored at the last known alive date. Based on Kaplan-Meier estimates. The Full Analysis Set includes participants who received at least one dose of study drug.

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

End point timeframe:

From first dose of study drug up to the end of follow-up; median duration on follow-up was 31.7 and 48.0 weeks in each cohort respectively.

| End point values | Cohort 1: Rovalpituzuma b Tesirine and Nivolumab | Cohort 2: Rovalpituzuma b Tesirine and Nivolumab + Ipilimumab | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 ^[11] | 12 ^[12] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 7.4 (5.0 to 9.1) | 11.0 (2.3 to 17.0) | | |

Notes:

[11] - Full analysis set

[12] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug until 100 days after the last dose of study drug; median duration of treatment was 65 days and 53 days in each cohort respectively.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 20.1 |

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Cohort 2: Rovalpituzumab Tesirine and Nivolumab + Ipilimumab |
|-----------------------|--|

Reporting group description:

Participants received 2 doses of 0.3 mg/kg rovalpituzumab tesirine IV 6 weeks apart (Day 1 of Cycles 1 and 3), nivolumab 1 mg/kg every 3 weeks for 4 cycles beginning on Cycle 2 (Day 1 of Cycles 2-5), and ipilimumab 1 mg/kg IV every 3 weeks for 4 cycles beginning on Cycle 2 (Day 1 of Cycles 2-5). After a 6-week washout, participants then received maintenance therapy with 480 mg nivolumab IV once every 4 weeks from Cycle 6 until disease progression.

| | |
|-----------------------|---|
| Reporting group title | Cohort 1: Rovalpituzumab Tesirine and Nivolumab |
|-----------------------|---|

Reporting group description:

Participants received 2 doses of 0.3 mg/kg rovalpituzumab tesirine by intravenous (IV) infusion 6 weeks apart (Day 1 of Cycles 1 and 3), and 2 doses of 360 mg nivolumab IV 3 weeks apart beginning on Cycle 2 (Day 1 of Cycles 2 and 3). Participants then received maintenance therapy with 480 mg nivolumab IV once every 4 weeks from Cycle 4 until disease progression.

| Serious adverse events | Cohort 2: Rovalpituzumab Tesirine and Nivolumab + Ipilimumab | Cohort 1: Rovalpituzumab Tesirine and Nivolumab | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 12 (75.00%) | 23 / 30 (76.67%) | |
| number of deaths (all causes) | 8 | 26 | |
| number of deaths resulting from adverse events | 4 | 14 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| MALIGNANT NEOPLASM PROGRESSION | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 8 / 30 (26.67%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 2 | 1 / 8 | |
| Vascular disorders | | | |
| HYPOTENSION | | | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| CONDITION AGGRAVATED | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FACE OEDEMA | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FATIGUE | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GENERALISED OEDEMA | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| ACUTE RESPIRATORY DISTRESS SYNDROME | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ACUTE RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 30 (6.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPNOEA | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 30 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOXIA | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 8 / 30 (26.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 11 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONITIS | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 3 / 30 (10.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | |
| PNEUMOTHORAX | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 30 (6.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| FEMORAL NECK FRACTURE | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Cardiac disorders | | | |
| ACUTE MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 30 (6.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC ARREST | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| CARDIAC TAMPONADE | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERICARDIAL EFFUSION | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 30 (6.67%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TACHYCARDIA | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (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 | | | |
| ISCHAEMIC STROKE | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| PERONEAL NERVE PALSY | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| DISSEMINATED INTRAVASCULAR COAGULATION | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| ASCITES | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COLITIS | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| AUTOIMMUNE HEPATITIS | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DRUG-INDUCED LIVER INJURY | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEPATOCELLULAR INJURY | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| RASH MACULO-PAPULAR | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| MUSCULAR WEAKNESS | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| EMPHYSEMA | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFLUENZA | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| PNEUMONIA | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 30 (6.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA FUNGAL | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| RESPIRATORY TRACT INFECTION BACTERIAL | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| SEPSIS | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPTIC SHOCK | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metabolism and nutrition disorders | | | |
| DEHYDRATION | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 30 (6.67%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Cohort 2: Rovalpituzumab Tesirine and Nivolumab + Ipilimumab | Cohort 1: Rovalpituzumab Tesirine and Nivolumab | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 12 (100.00%) | 30 / 30 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| TUMOUR PAIN | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vascular disorders | | | |

| | | | |
|--|-----------------|------------------|--|
| FLUSHING | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| HYPERTENSION | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 4 / 30 (13.33%) | |
| occurrences (all) | 0 | 5 | |
| HYPOTENSION | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 4 / 30 (13.33%) | |
| occurrences (all) | 2 | 5 | |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 5 / 30 (16.67%) | |
| occurrences (all) | 5 | 14 | |
| CHEST PAIN | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| FACE OEDEMA | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 6 / 30 (20.00%) | |
| occurrences (all) | 2 | 8 | |
| FATIGUE | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 11 / 30 (36.67%) | |
| occurrences (all) | 5 | 14 | |
| LOCALISED OEDEMA | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| NON-CARDIAC CHEST PAIN | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 12 / 30 (40.00%) | |
| occurrences (all) | 4 | 18 | |
| PAIN | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 30 (10.00%) | |
| occurrences (all) | 0 | 4 | |
| PYREXIA | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 5 / 30 (16.67%) | |
| occurrences (all) | 3 | 7 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 30 (10.00%) | |
| occurrences (all) | 0 | 4 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 5 / 12 (41.67%) | 11 / 30 (36.67%) | |
| occurrences (all) | 5 | 17 | |
| DYSPNOEA EXERTIONAL | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| HICCUPS | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 2 | |
| HYPOXIA | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| OROPHARYNGEAL PAIN | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 5 / 12 (41.67%) | 7 / 30 (23.33%) | |
| occurrences (all) | 7 | 13 | |
| PRODUCTIVE COUGH | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 2 / 30 (6.67%) | |
| occurrences (all) | 2 | 2 | |
| PULMONARY HYPERTENSION | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| RHINORRHOEA | | | |

| | | | |
|---|---|---|--|
| subjects affected / exposed occurrences (all) WHEEZING subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 2 0 / 12 (0.00%) 0 | 1 / 30 (3.33%) 1 2 / 30 (6.67%) 2 | |
| Psychiatric disorders ANXIETY subjects affected / exposed occurrences (all) CONFUSIONAL STATE subjects affected / exposed occurrences (all) DEPRESSION subjects affected / exposed occurrences (all) INSOMNIA subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 1 / 12 (8.33%) 2 0 / 12 (0.00%) 0 | 3 / 30 (10.00%) 3 2 / 30 (6.67%) 2 0 / 30 (0.00%) 0 4 / 30 (13.33%) 6 | |
| Investigations ALANINE AMINOTRANSFERASE INCREASED subjects affected / exposed occurrences (all) AMYLASE INCREASED subjects affected / exposed occurrences (all) ASPARTATE AMINOTRANSFERASE INCREASED subjects affected / exposed occurrences (all) BLOOD ALKALINE PHOSPHATASE INCREASED subjects affected / exposed occurrences (all) BLOOD BILIRUBIN INCREASED subjects affected / exposed occurrences (all) BLOOD CREATINE PHOSPHOKINASE | 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 | 3 / 30 (10.00%) 6 2 / 30 (6.67%) 3 4 / 30 (13.33%) 5 2 / 30 (6.67%) 5 2 / 30 (6.67%) 4 | |

| | | | |
|--|----------------|-----------------|--|
| INCREASED | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 30 (6.67%) | |
| occurrences (all) | 1 | 2 | |
| BLOOD LACTATE DEHYDROGENASE INCREASED | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| BLOOD THYROID STIMULATING HORMONE DECREASED | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| Injury, poisoning and procedural complications | | | |
| CONTUSION | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| FALL | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Cardiac disorders | | | |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 30 (10.00%) | |
| occurrences (all) | 0 | 3 | |
| PALPITATIONS | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| PERICARDIAL EFFUSION | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 7 / 30 (23.33%) | |
| occurrences (all) | 2 | 8 | |
| SINUS TACHYCARDIA | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 30 (10.00%) | |
| occurrences (all) | 0 | 3 | |
| TACHYCARDIA | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 30 (6.67%) | |
| occurrences (all) | 2 | 2 | |

| | | | |
|--------------------------------------|-----------------|------------------|--|
| Nervous system disorders | | | |
| DIZZINESS | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 30 (6.67%) | |
| occurrences (all) | 1 | 2 | |
| DYSGEUSIA | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 3 | |
| HEADACHE | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 6 / 30 (20.00%) | |
| occurrences (all) | 0 | 6 | |
| HEMIPARESIS | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| HYPERAESTHESIA | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| NEURALGIA | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 6 / 12 (50.00%) | 10 / 30 (33.33%) | |
| occurrences (all) | 6 | 17 | |
| LEUKOCYTOSIS | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| LYMPHOPENIA | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 5 / 12 (41.67%) | 9 / 30 (30.00%) | |
| occurrences (all) | 7 | 14 | |
| Eye disorders | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| CATARACT | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| DRY EYE | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| EYE PRURITUS | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| EYELID OEDEMA | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| OCULAR HYPERAEMIA | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| PERIORBITAL OEDEMA | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 30 (6.67%) | |
| occurrences (all) | 1 | 2 | |
| RETINOPATHY | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| VISION BLURRED | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| VISUAL IMPAIRMENT | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| XEROPHTHALMIA | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| ABDOMINAL DISTENSION | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| ABDOMINAL PAIN | | | |

| | | |
|----------------------------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 12 (16.67%) | 7 / 30 (23.33%) |
| occurrences (all) | 2 | 7 |
| ABDOMINAL PAIN UPPER | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 30 (6.67%) |
| occurrences (all) | 0 | 2 |
| ASCITES | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 30 (3.33%) |
| occurrences (all) | 4 | 1 |
| COLITIS | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 |
| CONSTIPATION | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 8 / 30 (26.67%) |
| occurrences (all) | 3 | 9 |
| DIARRHOEA | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 4 / 30 (13.33%) |
| occurrences (all) | 4 | 4 |
| DRY MOUTH | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 30 (0.00%) |
| occurrences (all) | 2 | 0 |
| ERUCTATION | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 |
| GASTROOESOPHAGEAL REFLUX DISEASE | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 30 (6.67%) |
| occurrences (all) | 1 | 2 |
| LIP DRY | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 |
| NAUSEA | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 5 / 30 (16.67%) |
| occurrences (all) | 1 | 6 |
| RETCHING | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 |

| | | | |
|--|----------------------|-----------------------|--|
| VOMITING subjects affected / exposed occurrences (all) | 3 / 12 (25.00%) 3 | 7 / 30 (23.33%) 10 | |
| Hepatobiliary disorders HEPATIC FUNCTION ABNORMAL subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 30 (0.00%) 0 | |
| HEPATOCELLULAR INJURY subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 30 (0.00%) 0 | |
| LIVER INJURY subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 30 (6.67%) 2 | |
| Skin and subcutaneous tissue disorders BLISTER subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 1 / 30 (3.33%) 1 | |
| DRY SKIN subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 3 / 30 (10.00%) 3 | |
| ERYTHEMA subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 6 / 30 (20.00%) 8 | |
| PHOTOSENSITIVITY REACTION subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 4 | 7 / 30 (23.33%) 10 | |
| PRURITUS subjects affected / exposed occurrences (all) | 3 / 12 (25.00%) 4 | 1 / 30 (3.33%) 1 | |
| PRURITUS GENERALISED subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 30 (0.00%) 0 | |
| RASH subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 2 | 1 / 30 (3.33%) 1 | |
| RASH MACULAR | | | |

| | | | |
|---|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 30 (0.00%) 0 | |
| RASH MACULO-PAPULAR subjects affected / exposed occurrences (all) | 4 / 12 (33.33%) 6 | 5 / 30 (16.67%) 5 | |
| SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 30 (0.00%) 0 | |
| Renal and urinary disorders PROTEINURIA subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 30 (6.67%) 2 | |
| Endocrine disorders HYPERTHYROIDISM subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 1 / 30 (3.33%) 2 | |
| HYPOTHYROIDISM subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 3 / 30 (10.00%) 3 | |
| Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 2 | 5 / 30 (16.67%) 7 | |
| BACK PAIN subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 30 (6.67%) 2 | |
| FLANK PAIN subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 2 / 30 (6.67%) 3 | |
| MUSCULOSKELETAL PAIN subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 4 / 30 (13.33%) 4 | |
| MYALGIA subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 1 / 30 (3.33%) 1 | |
| NECK PAIN | | | |

| | | | |
|------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 30 (6.67%) | |
| occurrences (all) | 1 | 2 | |
| Infections and infestations | | | |
| BRONCHITIS | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 30 (10.00%) | |
| occurrences (all) | 0 | 3 | |
| CONJUNCTIVITIS | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| HORDEOLUM | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| ORAL CANDIDIASIS | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 3 / 30 (10.00%) | |
| occurrences (all) | 1 | 3 | |
| PNEUMONIA BACTERIAL | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| SINUSITIS | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| SKIN BACTERIAL INFECTION | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 4 / 30 (13.33%) | |
| occurrences (all) | 2 | 5 | |
| VIRAL INFECTION | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |

| | | |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 5 / 12 (41.67%) | 9 / 30 (30.00%) |
| occurrences (all) | 6 | 11 |
| DEHYDRATION | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 30 (0.00%) |
| occurrences (all) | 2 | 0 |
| HYPERCALCAEMIA | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 |
| HYPERGLYCAEMIA | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 4 / 30 (13.33%) |
| occurrences (all) | 1 | 4 |
| HYPERKALAEMIA | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 |
| HYPERLIPASAEMIA | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 30 (6.67%) |
| occurrences (all) | 0 | 3 |
| HYPERPHOSPATAEMIA | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 30 (0.00%) |
| occurrences (all) | 1 | 0 |
| HYPOALBUMINAEMIA | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 6 / 30 (20.00%) |
| occurrences (all) | 2 | 10 |
| HYPOCALCAEMIA | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 30 (3.33%) |
| occurrences (all) | 1 | 1 |
| HYPOKALAEMIA | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 5 / 30 (16.67%) |
| occurrences (all) | 0 | 5 |
| HYPOMAGNESAEMIA | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 4 / 30 (13.33%) |
| occurrences (all) | 1 | 4 |
| HYPONATRAEMIA | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 3 / 30 (10.00%) |
| occurrences (all) | 6 | 3 |
| HYPOPHOSPATAEMIA | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 30 (10.00%) | |
| occurrences (all) | 0 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 16 December 2016 | Defined target level of activity based on overall response rate (ORR) that would help inform decisions on program development; clarification of contraception recommendations; recommendations provided in the Study May Proceed Memorandum dated 08 December 2016 were added, including updated Day 2 assessments for PK and additional PK and anti-therapeutic antibody-related analytes of rovalpituzumab tesirine; and other administrative corrections and clarifications. |
| 01 December 2017 | Most amendment changes were revisions to enhance recruitment; these included clarifications to the prior therapy eligibility requirements and simultaneous cohort enrollment. Additionally, the following items were clarified: dosing schedules; required premedication and post-medication; blood tumor markers and biomarkers collection; the DLT evaluation period; dose delay criteria; washout period and telephone follow-up procedures; radiographic assessment; and permanent treatment discontinuation criteria including treatment continuation beyond progression and dosing interruption; and other administrative corrections and clarifications. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported