



Clinical trial results:

A randomized phase IIb study evaluating immunogenic chemotherapy combined with ipilimumab and nivolumab in patients with metastatic hormone receptor positive breast cancer

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-000220-10 |
| Trial protocol | NO BE |
| Global end of trial date | 11 May 2022 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 30 October 2024 |
| First version publication date | 30 October 2024 |
| Summary attachment (see zip file) | Published article (Andresen et al. JITC 2024.pdf) |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | ICON-CA209-9FN |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03409198 |
| 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 | Jon Amund Kyte , Oslo University Hospital, Department of Oncology, +47 97569619, jonky@ous-hf.no |
| Scientific contact | Jon Amund Kyte , Oslo University Hospital, Department of Oncology, +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 | 20 January 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 11 May 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 May 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Co-primary objectives:

Assessment of toxicity of combined treatment with ipilimumab, nivolumab, pegylated liposomal doxorubicin and cyclophosphamide (ipi/nivo plus chemotherapy).

Assessment of clinical response: Progression-free survival (PFS) in ipi/nivo-chemo group compared to the chemo-only group.

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 | 21 February 2018 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Scientific research, Safety |
| Long term follow-up duration | 4 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Belgium: 16 |
| Country: Number of subjects enrolled | Norway: 66 |
| Worldwide total number of subjects | 82 |
| EEA total number of subjects | 82 |

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) | 65 |
| From 65 to 84 years | 17 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Eighty-two subjects were recruited at 5 academic hospitals in Norway and Belgium; Oslo University Hospital (n= 48), CHU UCL Namur (n= 13), Stavanger University Hospital (n= 9), Kristiansand Hospital (n= 9) and Institut Jules Bordet (n= 3).

Pre-assignment

Screening details:

A total of 106 patients were assessed for eligibility in the trial. Eighty-two patients were randomized and started allocated therapy and was included in the full analysis set population.

Period 1

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

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | No |
| Arm title | Chemotherapy-only |

Arm description:

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/m2 i.v. every 2nd week. An upper limit of 44mg per dose was applied to patients with a body surface area >2.2 m2.

| | |
|--|------------------|
| 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 every 2nd cycle (i.e. first 2 weeks of each 4 week period)

| | |
|------------------|----------------------------|
| Arm title | Ipi/nivo plus chemotherapy |
|------------------|----------------------------|

Arm description:

Ipilimumab plus nivolumab plus pegylated liposomal doxorubicin plus cyclophosphamide

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Nivolumab 240 mg administered intravenously every 2nd week until disease progression or for a maximum of 24 months

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

Dosage and administration details:

Ipilimumab 1mg/kg administered intravenously every 6th week until disease progression or for a maximum of 24 months

| | |
|--|---------------------------------|
| 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/m2 i.v. every 2nd week. An upper limit of 44mg per dose was applied to patients with a body surface area >2.2 m2.

| | |
|--|------------------|
| 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 every 2nd cycle (i.e. first 2 weeks of each 4 week period)

| | |
|------------------|----------------------------|
| Arm title | Ipi/nivo-only (cross-over) |
|------------------|----------------------------|

Arm description:

Ipilimumab plus nivolumab without chemotherapy (cross-over from chemo-only)

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Nivolumab 240 mg administered intravenously every 2nd week until disease progression or for a maximum of 24 months

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

Dosage and administration details:

Ipilimumab 1mg/kg administered intravenously every 6th week until disease progression or for a maximum of 24 months

| Number of subjects in period 1 | Chemotherapy-only | Ipi/nivo plus chemotherapy | Ipi/nivo-only (cross-over) |
|---------------------------------------|-------------------|----------------------------|----------------------------|
| Started | 33 | 49 | 16 |
| Completed | 1 | 1 | 0 |
| Not completed | 32 | 48 | 16 |
| Adverse event, serious fatal | - | 1 | - |
| Patient withdrawal | 1 | - | - |
| Adverse event, non-fatal | 1 | 6 | - |
| Sponsors decision | 1 | 1 | - |
| Lack of efficacy | 29 | 40 | 16 |

Baseline characteristics

| Reporting groups | |
|--|----------------------------|
| Reporting group title | Chemotherapy-only |
| Reporting group description: Pegylated liposomal doxorubicin plus cyclophosphamide | |
| Reporting group title | Ipi/nivo plus chemotherapy |
| Reporting group description: Ipilimumab plus nivolumab plus pegylated liposomal doxorubicin plus cyclophosphamide | |
| Reporting group title | Ipi/nivo-only (cross-over) |
| Reporting group description: Ipilimumab plus nivolumab without chemotherapy (cross-over from chemo-only) | |

| Reporting group values | Chemotherapy-only | Ipi/nivo plus chemotherapy | Ipi/nivo-only (cross-over) |
|---|-------------------|----------------------------|----------------------------|
| Number of subjects | 33 | 49 | 16 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 26 | 39 | 15 |
| From 65-84 years | 7 | 10 | 1 |
| Age continuous Units: years | | | |
| median | 55 | 53 | 56 |
| full range (min-max) | 37 to 74 | 36 to 75 | 39 to 73 |
| Gender categorical Units: Subjects | | | |
| Female | 33 | 48 | 16 |
| Male | 0 | 1 | 0 |
| ECOG performance status Units: Subjects | | | |
| ECOG 0 | 18 | 19 | 11 |
| ECOG 1 | 15 | 30 | 5 |
| De novo metastatic disease Units: Subjects | | | |
| Yes | 9 | 9 | 4 |
| No | 24 | 40 | 12 |
| Bone metastases Units: Subjects | | | |
| Yes | 28 | 45 | 14 |
| No | 5 | 4 | 2 |
| Liver metastases Units: Subjects | | | |
| Yes | 28 | 36 | 15 |
| No | 5 | 13 | 1 |
| Lung metastases Units: Subjects | | | |
| Yes | 6 | 18 | 3 |
| No | 27 | 31 | 13 |
| > 3 sites of metastases | | | |

| | | | |
|---|----|----|----|
| Units: Subjects | | | |
| Yes | 9 | 14 | 4 |
| No | 24 | 35 | 12 |
| Previous CDK4/6 inhibitor | | | |
| Units: Subjects | | | |
| Yes | 30 | 44 | 15 |
| No | 3 | 5 | 1 |
| PD-L1 expression | | | |
| PD-L1 expression was assessed by immunohistochemistry on prestudy formalin-fixed paraffin-embedded (FFPE) sections by the VENTANA SP142 assay (Roche Diagnostics, Rotkreuz, Switzerland). Forty-five patients had more than one biopsy assessed and were categorized as PD-L1+ if any of the biopsies were positive. | | | |
| Units: Subjects | | | |
| Positive | 10 | 19 | 5 |
| Negative | 20 | 28 | 11 |
| Missing | 3 | 2 | 0 |
| PAM50 subtype | | | |
| Gene expression data were used to determine the intrinsic molecular subtype using the nCounter BC360 assay (NanoString Technologies, Seattle, USA). Analysis was performed on bulk RNA isolated from prestudy FFPE sections. In patients with more than one sample analyzed, the profile was based on the most recent sample. | | | |
| Units: Subjects | | | |
| Luminal A | 6 | 9 | 3 |
| Luminal B | 21 | 34 | 11 |
| HER2 enriched | 3 | 4 | 1 |
| Basal | 0 | 1 | 0 |
| Missing | 3 | 1 | 1 |

| | | | |
|-------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 82 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 65 | | |
| From 65-84 years | 17 | | |
| Age continuous | | | |
| Units: years | | | |
| median | | | |
| full range (min-max) | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 81 | | |
| Male | 1 | | |
| ECOG performance status | | | |
| Units: Subjects | | | |
| ECOG 0 | 37 | | |
| ECOG 1 | 45 | | |
| De novo metastatic disease | | | |
| Units: Subjects | | | |
| Yes | 18 | | |
| No | 64 | | |
| Bone metastases | | | |
| Units: Subjects | | | |
| Yes | 73 | | |

| | | | |
|---|----|--|--|
| No | 9 | | |
| Liver metastases Units: Subjects | | | |
| Yes | 64 | | |
| No | 18 | | |
| Lung metastases Units: Subjects | | | |
| Yes | 24 | | |
| No | 58 | | |
| >3 sites of metastases Units: Subjects | | | |
| Yes | 23 | | |
| No | 59 | | |
| Previous CDK4/6 inhibitor Units: Subjects | | | |
| Yes | 74 | | |
| No | 8 | | |
| PD-L1 expression | | | |
| PD-L1 expression was assessed by immunohistochemistry on prestudy formalin-fixed paraffin-embedded (FFPE) sections by the VENTANA SP142 assay (Roche Diagnostics, Rotkreuz, Switzerland). Forty-five patients had more than one biopsy assessed and were categorized as PD-L1+ if any of the biopsies were positive. | | | |
| Units: Subjects | | | |
| Positive | 29 | | |
| Negative | 48 | | |
| Missing | 5 | | |
| PAM50 subtype | | | |
| Gene expression data were used to determine the intrinsic molecular subtype using the nCounter BC360 assay (NanoString Technologies, Seattle, USA). Analysis was performed on bulk RNA isolated from prestudy FFPE sections. In patients with more than one sample analyzed, the profile was based on the most recent sample. | | | |
| Units: Subjects | | | |
| Luminal A | 15 | | |
| Luminal B | 55 | | |
| HER2 enriched | 7 | | |
| Basal | 1 | | |
| Missing | 4 | | |

Subject analysis sets

| | |
|--|--|
| Subject analysis set title | Chemo-only per-protocol population |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Patients evaluated for response and received the equivalent of ≥ 2 treatment cycles | |
| Subject analysis set title | Ipi/nivo plus chemotherapy per-protocol population |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Patients evaluated for tumor response and received the equivalent of ≥ 2 treatment cycles | |

| Reporting group values | Chemo-only per-protocol population | Ipi/nivo plus chemotherapy per-protocol population | |
|------------------------|------------------------------------|--|--|
| Number of subjects | 31 | 47 | |

| | | | |
|--|----------|----------|--|
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 25 | 37 | |
| From 65-84 years | 6 | 10 | |
| Age continuous | | | |
| Units: years | | | |
| median | 55 | 53 | |
| full range (min-max) | 37 to 74 | 36 to 75 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 31 | 46 | |
| Male | 0 | 1 | |
| ECOG performance status | | | |
| Units: Subjects | | | |
| ECOG 0 | 17 | 18 | |
| ECOG 1 | 14 | 29 | |
| De novo metastatic disease | | | |
| Units: Subjects | | | |
| Yes | 9 | 8 | |
| No | 22 | 39 | |
| Bone metastases | | | |
| Units: Subjects | | | |
| Yes | 27 | 43 | |
| No | 4 | 4 | |
| Liver metastases | | | |
| Units: Subjects | | | |
| Yes | 27 | 34 | |
| No | 4 | 13 | |
| Lung metastases | | | |
| Units: Subjects | | | |
| Yes | 4 | 17 | |
| No | 27 | 30 | |
| >3 sites of metastases | | | |
| Units: Subjects | | | |
| Yes | 9 | 13 | |
| No | 22 | 34 | |
| Previous CDK4/6 inhibitor | | | |
| Units: Subjects | | | |
| Yes | 29 | 42 | |
| No | 2 | 5 | |
| PD-L1 expression | | | |
| PD-L1 expression was assessed by immunohistochemistry on prestudy formalin-fixed paraffin-embedded (FFPE) sections by the VENTANA SP142 assay (Roche Diagnostics, Rotkreuz, Switzerland). Forty-five patients had more than one biopsy assessed and were categorized as PD-L1+ if any of the biopsies were positive. | | | |
| Units: Subjects | | | |
| Positive | 10 | 19 | |
| Negative | 18 | 26 | |
| Missing | 3 | 2 | |
| PAM50 subtype | | | |
| Gene expression data were used to determine the intrinsic molecular subtype using the nCounter BC360 assay (NanoString Technologies, Seattle, USA). Analysis was performed on bulk RNA isolated from | | | |

prestudy FFPE sections. In patients with more than one sample analyzed, the profile was based on the most recent sample.

| | | | |
|-----------------|----|----|--|
| Units: Subjects | | | |
| Luminal A | 6 | 9 | |
| Luminal B | 19 | 32 | |
| HER2 enriched | 3 | 4 | |
| Basal | 0 | 1 | |
| Missing | 3 | 1 | |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Chemotherapy-only |
| Reporting group description: Pegylated liposomal doxorubicin plus cyclophosphamide | |
| Reporting group title | Ipi/nivo plus chemotherapy |
| Reporting group description: Ipilimumab plus nivolumab plus pegylated liposomal doxorubicin plus cyclophosphamide | |
| Reporting group title | Ipi/nivo-only (cross-over) |
| Reporting group description: Ipilimumab plus nivolumab without chemotherapy (cross-over from chemo-only) | |
| Subject analysis set title | Chemo-only per-protocol population |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Patients evaluated for response and received the equivalent of ≥ 2 treatment cycles | |
| Subject analysis set title | Ipi/nivo plus chemotherapy per-protocol population |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Patients evaluated for tumor response and received the equivalent of ≥ 2 treatment cycles | |

Primary: Progression-free survival, per-protocol population

| | |
|---|--|
| End point title | Progression-free survival, per-protocol population |
| End point description: PFS in the per-protocol population. PFS is, defined as the time from randomization to the occurrence of disease progression 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. Comparison between treatment arms will also be given by HR for disease progression or death using a Cox proportional hazards model. | |
| End point type | Primary |
| End point timeframe: Until data cut-off 20 JAN 2023 | |

| End point values | Chemo-only per-protocol population | Ipi/nivo plus chemotherapy per-protocol population | | |
|----------------------------------|------------------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 31 | 47 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 3.6 (1.8 to 9.0) | 5.1 (3.4 to 6.5) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Cox proportional hazards model |
| Comparison groups | Ipi/nivo plus chemotherapy per-protocol population v Chemo-only per-protocol population |
| Number of subjects included in analysis | 78 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 1.51 |

Secondary: Progression-free survival, full analysis set population

| | |
|--|--|
| End point title | Progression-free survival, full analysis set population ^[1] |
| End point description: | |
| PFS in the full analysis set population. PFS is, defined as the time from randomization to the occurrence of disease progression 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. Comparison between treatment arms will also be given by HR for disease progression or death using a Cox proportional hazards model. | |
| End point type | Secondary |
| End point timeframe: | |
| Until data cut-off 20 JAN 2023 | |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Progression-free survival for the ipi/nivo-only cross-over arm is reported separately.

| End point values | Chemotherapy-only | Ipi/nivo plus chemotherapy | | |
|----------------------------------|-------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 49 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 3.6 (1.8 to 9.0) | 5.1 (3.4 to 6.5) | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Cox proportional hazards model |
| Comparison groups | Chemotherapy-only v Ipi/nivo plus chemotherapy |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 1.51 |

Secondary: Overall survival, per-protocol population

| | |
|--|---|
| End point title | Overall survival, per-protocol population |
| End point description: | |
| Overall survival (OS) in the per-protocol population. OS will be calculated from time of randomization until death. Patients alive at the time of data analysis will be treated as censored. OS will be estimated by the Kaplan Meier method. | |
| End point type | Secondary |
| End point timeframe: | |
| Until data cut-off 20 JAN 2023 | |

| End point values | Chemo-only per-protocol population | Ipi/nivo plus chemotherapy per-protocol population | | |
|----------------------------------|------------------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 31 | 47 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 19.9 (13.8 to 28.7) | 19.7 (12.5 to 24.9) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Cox proportional hazards model |
| Comparison groups | Chemo-only per-protocol population v Ipi/nivo plus chemotherapy per-protocol population |
| Number of subjects included in analysis | 78 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 1.67 |

Secondary: Overall survival, full analysis set population

| | |
|-----------------|---|
| End point title | Overall survival, full analysis set population ^[2] |
|-----------------|---|

End point description:

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

End point timeframe:

Until data cut-off 20 JAN 2023.

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Overall survival for the ipi/nivo-only cross-over arm is reported separately.

| End point values | Chemotherapy-only | Ipi/nivo plus chemotherapy | | |
|----------------------------------|---------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 49 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 19.7 (13.8 to 28.7) | 19.5 (10.4 to 24.8) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Cox proportional hazards model |
|----------------------------|--------------------------------|

Statistical analysis description:

Overall survival (OS) in the full analysis set population.

OS will be calculated from time of randomization until death. Patients alive at the time of data analysis will be treated as censored. OS will be estimated by the Kaplan Meier method.

| | |
|-------------------|--|
| Comparison groups | Chemotherapy-only v Ipi/nivo plus chemotherapy |
|-------------------|--|

| | |
|---|----|
| Number of subjects included in analysis | 82 |
|---|----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

| | |
|--------------------|-------------------------|
| Parameter estimate | Cox proportional hazard |
|--------------------|-------------------------|

| | |
|----------------|------|
| Point estimate | 1.05 |
|----------------|------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|------|
| lower limit | 0.64 |
|-------------|------|

| | |
|-------------|------|
| upper limit | 1.71 |
|-------------|------|

Secondary: Objective tumor response rate, per-protocol population

| | |
|-----------------|--|
| End point title | Objective tumor response rate, per-protocol population |
|-----------------|--|

End point description:

The number of patients with an objective response (CR or PR) in the per-protocol population of each treatment arm assessed by RECIST v1.1.

| | |
|---------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Until data cut-off 20 JAN 2023. | |

| End point values | Chemo-only per-protocol population | Ipi/nivo plus chemotherapy per-protocol population | | |
|------------------------------|------------------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 31 | 47 | | |
| Units: Subjects | | | | |
| Complete or partial response | 9 | 15 | | |
| Non-response | 22 | 32 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective tumor response rate, full analysis set population

| | |
|---|--|
| End point title | Objective tumor response rate, full analysis set population ^[3] |
| End point description: | |
| The number of patients with an objective response (CR or PR) in the full analysis set population of each treatment arm assessed by RECIST v1.1. | |
| End point type | Secondary |
| End point timeframe: | |
| Until data cut-off 20 JAN 2023. | |

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Objective tumor response rate for the ipi/nivo-only cross-over arm is reported separately.

| End point values | Chemotherapy-only | Ipi/nivo plus chemotherapy | | |
|------------------------------|-------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 49 | | |
| Units: Subjects | | | | |
| Complete or partial response | 9 | 15 | | |
| Non-response | 24 | 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: | |
| Durable response rate (DRR) in the per protocol population, defined as the proportion of patients with an objective tumor response lasting at least 6 months, according to RECIST v1.1. | |
| End point type | Secondary |
| End point timeframe: | |
| Until data cut-off 20 JAN 2023. | |

| End point values | Chemo-only per-protocol population | Ipi/nivo plus chemotherapy per-protocol population | | |
|-----------------------------|------------------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 31 | 47 | | |
| Units: Subjects | | | | |
| Durable response | 6 | 6 | | |
| Non-durable response | 25 | 41 | | |

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 ^[4] |
| End point description: | |
| Durable response rate (DRR) in the full analysis set population, defined as the proportion of patients with an objective tumor response lasting at least 6 months, according to RECIST v1.1. | |
| End point type | Secondary |
| End point timeframe: | |
| Until data cut-off 20 JAN 2023. | |

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Durable response rate for the ipi/nivo-only cross-over arm is reported separately.

| End point values | Chemotherapy-only | Ipi/nivo plus chemotherapy | | |
|-----------------------------|-------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 49 | | |
| Units: Subjects | | | | |
| Durable response | 6 | 6 | | |
| Non-durable response | 27 | 43 | | |

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:

Clinical benefit (CB) is defined as the proportion of patients in the analyzed population with best overall response "PR" or "CR", or with stable disease (SD) lasting at least until the 6 month evaluation (performed at week 24 +/- 10 days). This means that patients where PD was first recorded at the 6 month evaluation will be considered to have clinical benefit.

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

End point timeframe:

Until data cut-off 20 JAN 2023.

| End point values | Chemo-only per-protocol population | Ipi/nivo plus chemotherapy per-protocol population | | |
|-----------------------------|------------------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 31 | 47 | | |
| Units: Subjects | | | | |
| CB | 15 | 26 | | |
| Non-CB | 16 | 21 | | |

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 ^[5] |
|-----------------|--|

End point description:

Clinical benefit (CB) is defined as the proportion of patients in the analyzed population with best overall response "PR" or "CR", or with stable disease (SD) lasting at least until the 6 month evaluation (performed at week 24 +/- 10 days). This means that patients where PD was first recorded at the 6 month evaluation will be considered to have clinical benefit.

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

End point timeframe:

Until data cut-off 20 JAN 2023.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Clinical benefit rate for the ipi/nivo-only cross-over arm is reported separately.

| End point values | Chemotherapy-only | Ipi/nivo plus chemotherapy | | |
|-----------------------------|-------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 49 | | |
| Units: Subjects | | | | |
| CB | 15 | 26 | | |
| Non-CB | 18 | 23 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response, per-protocol population

| | |
|--|---|
| End point title | Duration of response, per-protocol population |
| End point description: | |
| Duration of response is defined as the interval from response was first documented (CR or PR) to either progression of disease or death from any cause, whichever comes first. | |
| End point type | Secondary |
| End point timeframe: | |
| Until data cut-off 20 JAN 2023. | |

| End point values | Chemo-only per-protocol population | Ipi/nivo plus chemotherapy per-protocol population | | |
|---------------------------------------|------------------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 31 | 47 | | |
| Units: Months | | | | |
| median (inter-quartile range (Q1-Q3)) | 7.4 (3.7 to 11.3) | 5.5 (2.8 to 10.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response, full analysis set population

| | |
|--|---|
| End point title | Duration of response, full analysis set population ^[6] |
| End point description: | |
| Duration of response is defined as the interval from response was first documented (CR or PR) to either progression of disease or death from any cause, whichever comes first. | |
| End point type | Secondary |
| End point timeframe: | |
| Until data cut-off 20 JAN 2023. | |

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Duration of response for the ipi/nivo-only cross-over arm is reported separately.

| End point values | Chemotherapy-only | Ipi/nivo plus chemotherapy | | |
|---------------------------------------|-------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 49 | | |
| Units: Months | | | | |
| median (inter-quartile range (Q1-Q3)) | 7.4 (3.7 to 11.3) | 5.5 (2.8 to 10.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival, ipi/nivo-only (cross-over)

| | |
|-----------------|--|
| End point title | Progression-free survival, ipi/nivo-only (cross-over) ^[7] |
|-----------------|--|

End point description:

PFS in the cross-over arm is, defined as the time from "Day 1/Cycle 1" to the occurrence of disease progression 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 start of therapy, data will be censored at the "Day 1/Cycle 1" date +1 day. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression.

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

End point timeframe:

Until data cut-off 20 JAN 2023

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Progression-free survival for the ipi/nivo-chemo and chemo-only arms in the main trial is reported separately.

| End point values | Ipi/nivo-only (cross-over) | | | |
|---------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: Months | | | | |
| median (inter-quartile range (Q1-Q3)) | 1.9 (1.6 to 5.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival, ipi/nivo-only (cross-over)

| | |
|--|---|
| End point title | Overall survival, ipi/nivo-only (cross-over) ^[8] |
| End point description: | |
| Overall survival (OS) will be calculated from time of "Day 1/Cycle 1"until death. Patients alive at the time of data analysis will be treated as censored. | |
| End point type | Secondary |
| End point timeframe: | |
| Until data cut-off 20 JAN 2023 | |

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Overall survival for the ipi/nivo-chemo and chemo-only arms in the main trial is reported separately.

| | | | | |
|---------------------------------------|----------------------------|--|--|--|
| End point values | Ipi/nivo-only (cross-over) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: Months | | | | |
| median (inter-quartile range (Q1-Q3)) | 22.9 (16.5 to 28.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective tumor response rate, ipi/nivo-only (cross-over)

| | |
|---|--|
| End point title | Objective tumor response rate, ipi/nivo-only (cross-over) ^[9] |
| End point description: | |
| The number of patients with an objective response (CR or PR) assessed by RECIST v1.1. | |
| End point type | Secondary |
| End point timeframe: | |
| Until data cut-off 20 JAN 2023 | |

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Objective tumor response rate for the ipi/nivo-chemo and chemo-only arms in the main trial is reported separately.

| | | | | |
|------------------------------|----------------------------|--|--|--|
| End point values | Ipi/nivo-only (cross-over) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: Subjects | | | | |
| Complete or partial response | 3 | | | |
| Non-response | 13 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Durable response rate, ipi/nivo-only (cross-over)

End point title Durable response rate, ipi/nivo-only (cross-over)^[10]

End point description:

Durable response rate, defined as the proportion of patients with an objective tumor response lasting at least 6 months, according to RECIST v1.1.

End point type Secondary

End point timeframe:

Until data cut-off 20 JAN 2023.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Durable response rate for the ipi/nivo-chemo and chemo-only arms in the main trial is reported separately.

| End point values | Ipi/nivo-only (cross-over) | | | |
|-----------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: Subjects | | | | |
| Durable response | 2 | | | |
| No durable response | 14 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate, ipi/nivo-only (cross-over)

End point title Clinical benefit rate, ipi/nivo-only (cross-over)^[11]

End point description:

Clinical benefit (CB) is defined as the proportion of patients in the analyzed population with best overall response "PR" or "CR", or with stable disease (SD) lasting at least until the 6 month evaluation (performed at week 24 +/- 10 days). This means that patients where PD was first recorded at the 6 month evaluation will be considered to have clinical benefit.

End point type Secondary

End point timeframe:

Until data cut-off 20 JAN 2023

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Clinical benefit rate for the ipi/nivo-chemo and chemo-only arms in the main trial is reported separately.

| | | | | |
|-----------------------------|----------------------------|--|--|--|
| End point values | Ipi/nivo-only (cross-over) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: Subjects | | | | |
| Clinical benefit | 4 | | | |
| No clinical benefit | 12 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response, ipi/nivo-only (cross-over)

| | |
|-----------------|--|
| End point title | Duration of response, ipi/nivo-only (cross-over) ^[12] |
|-----------------|--|

End point description:

Duration of response is defined as the interval from response was first documented (CR or PR) to either progression of disease or death from any cause, whichever comes first.

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

End point timeframe:

Until data cut-off 20 JAN 2023.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The arms are not mutually exclusive because of cross-over for a subset of patients (16/33) from the chemo-only arm to the separate ipi/nivo-only arm. Duration of response for the ipi/nivo-chemo and chemo-only arms in the main trial is reported separately.

| | | | | |
|---------------------------------------|----------------------------|--|--|--|
| End point values | Ipi/nivo-only (cross-over) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: Months | | | | |
| median (inter-quartile range (Q1-Q3)) | 7.0 (3.7 to 10.8) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From 21 FEB 2018 until data cut-off 20 JAN 2023.

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Chemotherapy-only |
|-----------------------|-------------------|

Reporting group description: -

| | |
|-----------------------|----------------------------|
| Reporting group title | Ipi/nivo plus chemotherapy |
|-----------------------|----------------------------|

Reporting group description: -

| | |
|-----------------------|----------------------------|
| Reporting group title | Ipi/nivo-only (cross-over) |
|-----------------------|----------------------------|

Reporting group description: -

| Serious adverse events | Chemotherapy-only | Ipi/nivo plus chemotherapy | Ipi/nivo-only (cross-over) |
|--|-------------------|----------------------------|----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 13 / 33 (39.39%) | 31 / 49 (63.27%) | 5 / 16 (31.25%) |
| number of deaths (all causes) | 28 | 39 | 12 |
| number of deaths resulting from adverse events | 0 | 2 | 0 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 6 / 49 (12.24%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 2 | 5 / 7 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Dyspnea | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 49 (4.08%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 49 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Fracture | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 49 (4.08%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 49 (4.08%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|----------------|----------------|----------------|
| Procedural pneumothorax subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Conduction disorder | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 49 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 49 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 49 (4.08%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peroneal nerve palsy | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 49 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 49 (4.08%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 49 (4.08%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 3 / 49 (6.12%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Rash | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Nephritis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophysitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 49 (4.08%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Secondary adrenocortical insufficiency | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 3 / 49 (6.12%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thyroiditis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 6 / 49 (12.24%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 3 / 49 (6.12%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 49 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 49 (4.08%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 4 %

| Non-serious adverse events | Chemotherapy-only | Ipi/nivo plus chemotherapy | Ipi/nivo-only (cross-over) |
|---|-------------------|----------------------------|----------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 33 / 33 (100.00%) | 49 / 49 (100.00%) | 15 / 16 (93.75%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 49 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 0 | 1 |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 49 (4.08%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 49 (4.08%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 16 / 33 (48.48%) | 27 / 49 (55.10%) | 6 / 16 (37.50%) |
| occurrences (all) | 21 | 28 | 6 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 49 (4.08%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 2 | 1 |
| Oedema | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 4 / 49 (8.16%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| Pyrexia | | | |

| | | | |
|---|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 2 / 49 (4.08%) 2 | 3 / 16 (18.75%) 3 |
| Immune system disorders Immunisation reaction subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 49 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Mycotic allergy subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 49 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Reproductive system and breast disorders Vulvovaginal discomfort subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | 2 / 49 (4.08%) 3 | 0 / 16 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | 4 / 49 (8.16%) 4 | 1 / 16 (6.25%) 1 |
| Dyspnoea subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 3 / 49 (6.12%) 3 | 0 / 16 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | 0 / 49 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Pleural effusion subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 2 / 49 (4.08%) 5 | 0 / 16 (0.00%) 0 |
| Pneumonitis subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 3 / 49 (6.12%) 3 | 1 / 16 (6.25%) 1 |
| Rhinitis subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 3 | 0 / 49 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 4 | 0 / 49 (0.00%) 0 | 0 / 16 (0.00%) 0 |

| | | | |
|--|------------------------|------------------------|----------------------|
| Insomnia subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | 7 / 49 (14.29%) 7 | 1 / 16 (6.25%) 1 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 2 / 49 (4.08%) 2 | 2 / 16 (12.50%) 2 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 1 / 49 (2.04%) 1 | 1 / 16 (6.25%) 1 |
| Ejection fraction decreased subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | 3 / 49 (6.12%) 4 | 0 / 16 (0.00%) 0 |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 5 / 33 (15.15%) 9 | 4 / 49 (8.16%) 5 | 0 / 16 (0.00%) 0 |
| Lipase increased subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 2 / 49 (4.08%) 2 | 0 / 16 (0.00%) 0 |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 15 / 33 (45.45%) 23 | 32 / 49 (65.31%) 35 | 0 / 16 (0.00%) 0 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 10 / 33 (30.30%) 29 | 11 / 49 (22.45%) 20 | 1 / 16 (6.25%) 1 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 4 / 49 (8.16%) 4 | 0 / 16 (0.00%) 0 |
| Weight decreased subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | 2 / 49 (4.08%) 2 | 1 / 16 (6.25%) 1 |
| Injury, poisoning and procedural complications | | | |
| Infusion related reaction subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 3 | 3 / 49 (6.12%) 4 | 0 / 16 (0.00%) 0 |
| Procedural pain | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | 1 / 49 (2.04%) 1 | 1 / 16 (6.25%) 1 |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 49 (4.08%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Headache | | | |
| subjects affected / exposed | 4 / 33 (12.12%) | 3 / 49 (6.12%) | 0 / 16 (0.00%) |
| occurrences (all) | 4 | 3 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 6 / 33 (18.18%) | 3 / 49 (6.12%) | 0 / 16 (0.00%) |
| occurrences (all) | 6 | 3 | 0 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 49 (4.08%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Ear and labyrinth disorders | | | |
| Ear discomfort | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 3 / 49 (6.12%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 49 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Vertigo | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 8 / 49 (16.33%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 9 | 1 |
| Eye disorders | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 2 / 49 (4.08%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 2 | 1 |
| Periorbital oedema | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 49 (4.08%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 0 / 49 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Gastrointestinal disorders | | | |

| | | | |
|----------------------------------|------------------|------------------|-----------------|
| Abdominal pain | | | |
| subjects affected / exposed | 7 / 33 (21.21%) | 8 / 49 (16.33%) | 1 / 16 (6.25%) |
| occurrences (all) | 10 | 10 | 1 |
| Colitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 49 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Constipation | | | |
| subjects affected / exposed | 18 / 33 (54.55%) | 16 / 49 (32.65%) | 0 / 16 (0.00%) |
| occurrences (all) | 20 | 21 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 13 / 49 (26.53%) | 3 / 16 (18.75%) |
| occurrences (all) | 1 | 14 | 6 |
| Dysphagia | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 7 / 49 (14.29%) | 0 / 16 (0.00%) |
| occurrences (all) | 3 | 10 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 49 (4.08%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Nausea | | | |
| subjects affected / exposed | 16 / 33 (48.48%) | 25 / 49 (51.02%) | 2 / 16 (12.50%) |
| occurrences (all) | 20 | 29 | 2 |
| Stomatitis | | | |
| subjects affected / exposed | 12 / 33 (36.36%) | 20 / 49 (40.82%) | 2 / 16 (12.50%) |
| occurrences (all) | 18 | 35 | 3 |
| Toothache | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 49 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 3 / 49 (6.12%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Hepatobiliary disorders | | | |
| Hepatitis | | | |

| | | | |
|--|------------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 49 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Hepatocellular injury subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | 1 / 49 (2.04%) 2 | 0 / 16 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 4 / 33 (12.12%) 4 | 8 / 49 (16.33%) 8 | 0 / 16 (0.00%) 0 |
| Nail disorder subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | 2 / 49 (4.08%) 3 | 0 / 16 (0.00%) 0 |
| Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) | 10 / 33 (30.30%) 11 | 16 / 49 (32.65%) 16 | 0 / 16 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | 3 / 49 (6.12%) 3 | 5 / 16 (31.25%) 5 |
| Rash subjects affected / exposed occurrences (all) | 13 / 33 (39.39%) 17 | 28 / 49 (57.14%) 33 | 6 / 16 (37.50%) 7 |
| Skin fissures subjects affected / exposed occurrences (all) | 3 / 33 (9.09%) 4 | 1 / 49 (2.04%) 2 | 0 / 16 (0.00%) 0 |
| Xeroderma subjects affected / exposed occurrences (all) | 2 / 33 (6.06%) 2 | 1 / 49 (2.04%) 1 | 2 / 16 (12.50%) 2 |
| Renal and urinary disorders | | | |
| Dysuria subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 4 / 49 (8.16%) 5 | 0 / 16 (0.00%) 0 |
| Endocrine disorders | | | |
| Hyperthyroidism subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 10 / 49 (20.41%) 10 | 1 / 16 (6.25%) 1 |
| Hypophysitis | | | |

| | | | |
|--|----------------|------------------|-----------------|
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 49 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 23 / 49 (46.94%) | 2 / 16 (12.50%) |
| occurrences (all) | 1 | 23 | 2 |
| Secondary adrenocortical insufficiency | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 49 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 49 (4.08%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Back pain | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 1 / 49 (2.04%) | 0 / 16 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 3 / 49 (6.12%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 11 / 49 (22.45%) | 5 / 16 (31.25%) |
| occurrences (all) | 5 | 14 | 6 |
| Neck pain | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 49 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 49 (0.00%) | 2 / 16 (12.50%) |
| occurrences (all) | 1 | 0 | 2 |
| Infections and infestations | | | |
| Epstein-Barr virus infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 49 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 3 / 49 (6.12%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Oral candidiasis | | | |

| | | | |
|------------------------------------|-----------------|------------------|----------------|
| subjects affected / exposed | 0 / 33 (0.00%) | 3 / 49 (6.12%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 5 / 49 (10.20%) | 0 / 16 (0.00%) |
| occurrences (all) | 3 | 8 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 3 / 49 (6.12%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 6 / 33 (18.18%) | 7 / 49 (14.29%) | 1 / 16 (6.25%) |
| occurrences (all) | 8 | 8 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 10 / 49 (20.41%) | 0 / 16 (0.00%) |
| occurrences (all) | 3 | 16 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 4 / 49 (8.16%) | 1 / 16 (6.25%) |
| occurrences (all) | 3 | 4 | 1 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 2 / 49 (4.08%) | 0 / 16 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 4 / 49 (8.16%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 13 December 2019 | Adjustment of inclusion and excusion criteria. Adjustment of the per-protocol population criteria including specification of the full analysis set population. Specification of planned statistical analyses. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/38242720>