Clinical trial results:
A phase II study of durvalumab (MEDI4736) plus tremelimumab for the treatment of patients with advanced neuroendocrine neoplasms of gastroenteropancreatic or lung origin (the DUNE trial).

Summary

EudraCT number	2016-002858-20
Trial protocol	ES
Global end of trial date	06 March 2023

Results information

Result version number	v1 (current)
This version publication date	14 December 2023
First version publication date	14 December 2023
Summary attachment (see zip file)	DUNE- Final CSR ICH synopsis 2022 (DUNE- Final CSR ICH synopsis 2022.pdf)

Trial information

Trial identification

Sponsor protocol code	ESR-15-11561-61/DUNE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03095274
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo Espanol de Tumores Neuroendocrinos
Sponsor organisation address	Balmes 24, Escalera A , Barcelona, Spain, 08006
Public contact	Federico Nepote, MFAR Clinical Research, 34 910616228, investigacion@mfar.net
Scientific contact	Federico Nepote, MFAR Clinical Research, 34 934344412, investigacion@mfar.net

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	14 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Cohorts 1 to 3: Clinical benefit rate by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1, which is defined as the percentage of patients achieving complete response, partial response, or stable disease at month 9 after durvalumab plus tremelimumab was started.
Cohort 4: Overall survival rate, which is defined as the percentage of patients alive at month 9 after durvalumab plus tremelimumab was started.

Protection of trial subjects:

This assignment will designate the user as the primary user for the listed clinical trial in regards to result related information. It will enable them to prepare and post result related information for this trials on behalf of the sponsor in accordance with Commission Guideline 2012/C 302/03 and its technical guidance on the format of the data fields of result-related information on clinical trials submitted in accordance with article 57(2) of Regulation (EC) No 726/2004 and article 41(2) of Regulation (EC) No 1901/2006.

Background therapy:

Well-differentiated gastroenteropancreatic and lung neuroendocrine tumors are generally malignancies with a prolonged natural history. However, clinical behavior is heterogeneous and when tumor progression is observed, treatment options are limited. The most used therapy for neuroendocrine tumors management are somatostatin analogs, with clear evidence of antitumor activity demonstrated by two phase III clinical trials in gastroenteropancreatic neuroendocrine tumors. However, even the use in lung carcinoids is quite usual, no antitumoral activity has been demonstrated in prospective clinical trials. In recent years, targeted therapies as sunitinib and everolimus have been approved for pancreatic neuroendocrine tumors and recently everolimus have showed a significant reduction in the risk of progression or death in patients with non-functional neuroendocrine tumors of lung and gastrointestinal origin. After the failure of these therapies, no drugs have demonstrated efficacy. Only Interferon alpha-2b is an option for these patients who have worsening symptoms of carcinoid syndrome while on treatment with somatostatin analogs and have showed some evidence of antitumoral activity in neuroendocrine tumors. The efficacy of Interferon alpha 2-b is not fully understood, but one of its antitumoral mechanisms of action could be related via stimulation of T cells. Tremelimumab and Durvalumab combination could be more efficient drugs to improve immune system activation and could obtain a significantly higher clinical benefit in these patients. We have analyzed presence of tumor-infiltrating lymphocytes (TILS) in these tumor types.

Evidence for comparator:

Tremelimumab and Durvalumab
combination could be more efficient drugs to improve immune system activation and could obtain a significantly higher clinical benefit in these patients. We have analyzed presence of tumor-infiltrating lymphocytes (TILS) in these tumor types. We found a high number of TILS that could be activated through Tremelimumab and Durvalumab. In cases of advanced high-grade G3 neuroendocrine carcinomas (NEC), regardless of the site of the primary tumor, combination chemotherapy using cisplatin/etoposide is recommended in first-line setting (provided that the patient has adequate organ function and performance status). There is no establishedsecond-line therapy for poorly differentiated neuroendocrine carcinomas of the gastroenteropancreatic origin.
Tremelimumab and Durvalumab would be the first immune combination agents showing efficacy in neuroendocrine neoplasms of different origins.

Actual start date of recruitment	02 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 123
Worldwide total number of subjects	123
EEA total number of subjects	123

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)	123
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This is a prospective, multi-center, open label, stratified, exploratory phase II study evaluating the efficacy and safety of durvalumab plus tremelimumab in different cohorts of patients with neuroendocrine neoplasms.

Pre-assignment

Screening details:

Cohort 1: Well-moderately differentiated lung neuroendocrine tumors (classically known as typical and atypical carcinoids) after progression to somatostatin analogs and one prior targeted therapy or chemotherapy.
Cohort 2: G1/G2 (WHO grade 1 and 2) gastrointestinal neuroendocrine tumors after progression to somatostatin analogs and one prior targ

Period 1

Period 1 title	Treatment and follow-up
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Expeimental: Durvalumab+Tremelimumab

Arm description:

Patients will receive 1500 mg durvalumab via IV infusion q4w for up to 4 doses/cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles, and then continue 1500 mg durvalumab q4w starting on Week 16 for up to 8 months (9 doses). Dosing outside the window should be discussed with the Study Physician. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator’s discretion

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	MEDI4736I
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

Patients will receive 1500 mg durvalumab via IV infusion q4w for up to 4 doses/cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles, and then continue 1500 mg durvalumab q4w starting on Week 16 for up to 8 months (9 doses). Dosing outside the window should be discussed with the Study Physician. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator’s discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

Number of subjects in period 1	Expeimental: Durvalumab+Tremelimumab
Started	123
Completed	123

Period 2

Period 2 title	Baseline
Is this the baseline period?	Yes[1]
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	PATIENTS WITH ADVANCED NEUROENDOCRINE NEOPLASMS OF GASTROENTER

Arm description:

Screening will occur between Day -28 and Day -1. The purpose of the screening period is to establish protocol eligibility. Informed consent will be obtained up to 4 weeks prior to Cycle 1 Day 1 and after the study has been fully explained to each subject and prior to the conduct of any screening procedures or assessments.
The purpose of the baseline visit is to establish disease characteristics prior to allocation and treatment and to confirm protocol eligibility as specified in the inclusion/exclusion criteria. Results of baseline assessments must be obtained prior to the first dose of study drug (Cycle 1/Day 1). Baseline assessments may be performed on Day -1 or on Cycle 1/Day 1 prior to dosing. Clinical laboratory tests including pregnancy test (where applicable) can be performed within 72 hours of the first dose of study drug. Subjects who complete the baseline visit and continue to meet the criteria for inclusion/exclusion will begin the treatment phase of this study.

Arm type	Experimental
Investigational medicinal product name	Not treatment period
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Patients will receive 1500 mg durvalumab via IV infusion q4w for up to 4 doses/cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles, and then continue 1500 mg durvalumab q4w starting on Week 16 for up to 8 months (9 doses). Dosing outside the window should be discussed with the Study Physician. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator’s discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 include all study states

Number of subjects in period 2	PATIENTS WITH ADVANCED NEUROENDOCRINE NEOPLASMS OF GASTROENTER
Started	123
Completed	123

Baseline characteristics

Reporting groups

Reporting group title	PATIENTS WITH ADVANCED NEUROENDOCRINE NEOPLASMS OF GASTROENTER

Reporting group description:

Screening will occur between Day -28 and Day -1. The purpose of the screening period is to establish protocol eligibility. Informed consent will be obtained up to 4 weeks prior to Cycle 1 Day 1 and after the study has been fully explained to each subject and prior to the conduct of any screening procedures or assessments.
The purpose of the baseline visit is to establish disease characteristics prior to allocation and treatment and to confirm protocol eligibility as specified in the inclusion/exclusion criteria. Results of baseline assessments must be obtained prior to the first dose of study drug (Cycle 1/Day 1). Baseline assessments may be performed on Day -1 or on Cycle 1/Day 1 prior to dosing. Clinical laboratory tests including pregnancy test (where applicable) can be performed within 72 hours of the first dose of study drug. Subjects who complete the baseline visit and continue to meet the criteria for inclusion/exclusion will begin the treatment phase of this study.

Reporting group values	PATIENTS WITH ADVANCED NEUROENDOCRINE NEOPLASMS OF GASTROENTER	Total	
Number of subjects	123	123	
Age categorical			
Age, Continuous Mean (Standard Deviation) Unit of measure: years Age (years at informed consent signed)			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	123	123	
From 65-84 years	0	0	
85 years and over	0	0	
Age (years at informed consent signed)	0	0	
Age continuous			
Age, Continuous Mean (Standard Deviation) Unit of measure: years Age (years at informed consent signed)			
Units: years			
geometric mean	61.54		
standard deviation	± 11.56	-	
Gender categorical			
Sex: Female, Male			
Units: Subjects			
Female	51	51	
Male	72	72	

Race/Ethnicity, Customized			
Measure Type: Count of Participants Unit of measure: participants			
Units: Subjects			
Caucasic	122	122	
African	1	1	
Race/Ethnicity, Customized			
MeasureType: Count of Participants Unit of measure: participants			
Units: Subjects			
Caucasic	122	122	
African	1	1	

Subject analysis sets

Subject analysis set title	Cohort 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Well-moderately differentiated lung neuroendocrine tumors (classically known as typical and atypical carcinoids) after progression to somatostatin analogs and one prior targeted therapy or chemotherapy.

Subject analysis set title	Cohort 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Well-moderately differentiated G1/G2 (WHO grade 1 and 2) gastrointestinal neuroendocrine tumors after
progression to somatostatin analogs and one targeted therapy (prior targeted therapy could be everolimus or a
multikinase inhibitor). Prior therapies with interferon alpha-2b or radionucleotide therapy are allowed.

Subject analysis set title	Cohort 3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Well-moderately differentiated neuroendocrine tumors G1/G2 (WHO grade

1 and 2) from pancreatic origin after progression to standard therapies (chemotherapy, somatostatin analogs
and target therapy); patients must be treated with at least two prior systemic treatment lines and a maximum of
four previous treatment lines.

Subject analysis set title	Cohort 4
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Neuroendocrine neoplasms (WHO grade 3) of gastroenteropancreatic origin or unknown primary site

(excluding lung primary tumors), patients will be treated in second line only, after

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	27	31	32
Age categorical			
Age, Continuous Mean (Standard Deviation) Unit of measure: years Age (years at informed consent signed)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0

Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	27	31	32
From 65-84 years	0	0	0
85 years and over	0	0	0
Age (years at informed consent signed)	0	63	0
Age continuous			
Age, Continuous Mean (Standard Deviation) Unit of measure: years Age (years at informed consent signed)			
Units: years			
geometric mean	62.32	62.77	65.06
standard deviation	± 11.40	± 10.7	± 11.29
Gender categorical			
Sex: Female, Male			
Units: Subjects			
Female	9	13	18
Male	18	18	14
Race/Ethnicity, Customized			
Measure Type: Count of Participants Unit of measure: participants			
Units: Subjects			
Caucasic	26	31	32
African	1	0	0
Race/Ethnicity, Customized			
MeasureType: Count of Participants Unit of measure: participants			
Units: Subjects			
Caucasic	26	31	32
African	1	0	0

Reporting group values	Cohort 4		
Number of subjects	33		
Age categorical			
Age, Continuous Mean (Standard Deviation) Unit of measure: years Age (years at informed consent signed)			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	33		
From 65-84 years	0		
85 years and over	0		
Age (years at informed consent signed)	0		

Age continuous			
Age, Continuous Mean (Standard Deviation) Unit of measure: years Age (years at informed consent signed)			
Units: years			
geometric mean	56.33		
standard deviation	± 11.97		
Gender categorical			
Sex: Female, Male			
Units: Subjects			
Female	11		
Male	22		
Race/Ethnicity, Customized			
Measure Type: Count of Participants Unit of measure: participants			
Units: Subjects			
Caucasic	32		
African	0		
Race/Ethnicity, Customized			
MeasureType: Count of Participants Unit of measure: participants			
Units: Subjects			
Caucasic	33		
African	0		

End points

End points reporting groups

Reporting group title	Expeimental: Durvalumab+Tremelimumab

Reporting group description:

Patients will receive 1500 mg durvalumab via IV infusion q4w for up to 4 doses/cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles, and then continue 1500 mg durvalumab q4w starting on Week 16 for up to 8 months (9 doses). Dosing outside the window should be discussed with the Study Physician. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion

Reporting group title	PATIENTS WITH ADVANCED NEUROENDOCRINE NEOPLASMS OF GASTROENTER

Reporting group description:

Screening will occur between Day -28 and Day -1. The purpose of the screening period is to establish protocol eligibility. Informed consent will be obtained up to 4 weeks prior to Cycle 1 Day 1 and after the study has been fully explained to each subject and prior to the conduct of any screening procedures or assessments.
The purpose of the baseline visit is to establish disease characteristics prior to allocation and treatment and to confirm protocol eligibility as specified in the inclusion/exclusion criteria. Results of baseline assessments must be obtained prior to the first dose of study drug (Cycle 1/Day 1). Baseline assessments may be performed on Day -1 or on Cycle 1/Day 1 prior to dosing. Clinical laboratory tests including pregnancy test (where applicable) can be performed within 72 hours of the first dose of study drug. Subjects who complete the baseline visit and continue to meet the criteria for inclusion/exclusion will begin the treatment phase of this study.

Subject analysis set title	Cohort 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Well-moderately differentiated lung neuroendocrine tumors (classically known as typical and atypical carcinoids) after progression to somatostatin analogs and one prior targeted therapy or chemotherapy.

Subject analysis set title	Cohort 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Well-moderately differentiated G1/G2 (WHO grade 1 and 2) gastrointestinal neuroendocrine tumors after
progression to somatostatin analogs and one targeted therapy (prior targeted therapy could be everolimus or a
multikinase inhibitor). Prior therapies with interferon alpha-2b or radionucleotide therapy are allowed.

Subject analysis set title	Cohort 3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Well-moderately differentiated neuroendocrine tumors G1/G2 (WHO grade

1 and 2) from pancreatic origin after progression to standard therapies (chemotherapy, somatostatin analogs
and target therapy); patients must be treated with at least two prior systemic treatment lines and a maximum of
four previous treatment lines.

Subject analysis set title	Cohort 4
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Neuroendocrine neoplasms (WHO grade 3) of gastroenteropancreatic origin or unknown primary site

(excluding lung primary tumors), patients will be treated in second line only, after

Primary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)[1]

End point description:

Clinical Benefit Rate (CBR) by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, which is defined as the percentage of patients
achieving complete response (CR), partial response (PR), or stable disease (SD) at month 9 after durvalumab plus
tremelimumab was started.

End point type	Primary

End point timeframe:

9 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Clinical Benefit Rate (CBT) according to the Evaluation Criteria of
response in solid tumors (RECIST 1.1), which was defined as the percentage of patients
who achieved a complete response (CR), partial response (PR) or stable disease (SE)
at month 9 after starting durvalumab plus tremelimumab.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	29	29	29
Units: patients				
CR	0	0	1	1
PR	1	0	0	1
SD	6	11	2	0
PD	18	16	6	27
Follow-up less than 9m (without previous PD/ Death	0	2	20	0

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Response Rate by immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) criteria

End point type	Secondary

End point timeframe:

9 months

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	21	23	11
Units: months				
median (confidence interval 95%)	00 (00 to 00)	29.49 (21.86 to 37.11)	24.83 (15.33 to 34.32)	7.04 (4.08 to 10.01)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate

End point description:

Overall Response Rate by immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) criteria

End point type	Secondary

End point timeframe:

9 months

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	31	32	33
Units: patients				
CR or PR	3	0	2	3
No response	24	31	30	30

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of Response by immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) criteria

End point type	Secondary

End point timeframe:

9 months

End point values	Cohort 1	Cohort 3	Cohort 4	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	2	3	
Units: months				
median (confidence interval 95%)	2.98 (2.68 to 15.50)	16.31 (10.64 to 21.98)	10.08 (3.90 to 24.26)	

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 by immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) criteria

End point type	Secondary

End point timeframe:

9 months

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	27	29	33
Units: months				
median (confidence interval 95%)	5.55 (4.94 to 6.17)	5.79 (3.12 to 8.45)	5.52 (2.38 to 8.66)	2.41 (2.08 to 2.75)

Statistical analyses

No statistical analyses for this end point

Secondary: Response Status 12 months

End point title	Response Status 12 months

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	31	32	33
Units: Overall Number of Participants Analyzed				
CR or PR	1	0	1	2
No response	26	31	31	31

Statistical analyses

No statistical analyses for this end point

Secondary: Response Status 9 months

End point title	Response Status 9 months

End point description:

by irRECIST criteria, at 6, 9 and 12 months after start of study treatment.

End point type	Secondary

End point timeframe:

9 months

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	31	32	33
Units: patient				
CR or PR	1	0	2	2
No response	26	31	30	31

Statistical analyses

No statistical analyses for this end point

Secondary: Response Status 6 months

End point title	Response Status 6 months

End point description:

Response Status 6 monthsby irRECIST criteria, at 6, 9 and 12 months after start of study treatment.

End point type	Secondary

End point timeframe:

6 months

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	31	32	33
Units: patients number				
CR or PR	1	0	2	2
No response	26	31	30	31

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

5 years

Adverse event reporting additional description:

CTCAE Common Terminology Criteria for Adverse Events;

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE, v4.03
Dictionary version	4.03

Reporting groups

Reporting group title	Cohort 1

Reporting group description:

Well-moderately differentiated lung neuroendocrine tumors (classically known as typical and atypical carcinoids) after progression to somatostatin analogs and one prior targeted therapy or chemotherapy.

Reporting group title	cohort 2

Reporting group description:

Well-moderately differentiated G1/G2 (WHO grade 1 and 2) gastrointestinal neuroendocrine tumors after
progression to somatostatin analogs and one targeted therapy (prior targeted therapy could be everolimus or a
multikinase inhibitor). Prior therapies with interferon alpha-2b or radionucleotide therapy are allowed.

Reporting group title	cohort 3

Reporting group description:

Well-moderately differentiated neuroendocrine tumors G1/G2 (WHO grade
1 and 2) from pancreatic origin after progression to standard therapies (chemotherapy, somatostatin analogs
and target therapy); patients must be treated with at least two prior systemic treatment lines and a maximum of
four previous treatment lines.

Reporting group title	Cohort 4

Reporting group description:

Cohort 4 : Neuroendocrine neoplasms (WHO grade 3) of gastroenteropancreatic origin or unknown primary site

(excluding lung primary tumors), p atients will be treated in second line only, after

Serious adverse events	Cohort 1	cohort 2	cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 27 (62.96%)	9 / 31 (29.03%)	16 / 32 (50.00%)
number of deaths (all causes)	13	19	23
number of deaths resulting from adverse events			
Vascular disorders			
Cellulitis G3			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (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

Flushing			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (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
Hypotension - G2			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leg edemas			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (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
Thromboembolic event - G3			
subjects affected / exposed	2 / 27 (7.41%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Abdominal pain - G2			
subjects affected / exposed	2 / 27 (7.41%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death NOS - G5			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pain - G2			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
clinical deterioration			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Alanine aminotransferase increased G1			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (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
Alanine aminotransferase increased - G2			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	2 / 32 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased - G3			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased - G1			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (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
Aspartate aminotransferase increased - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	3 / 32 (9.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Creatinine increased - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GGT increased G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serum amylase increased - G3			

subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight loss - G1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
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			
Infusion related reaction - G1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury to superior vena cava - G3			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (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
Cardiac disorders			
Atrial fibrillation G3			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	0 / 32 (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
Heart failure			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	0 / 32 (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
Myocardial infarction G4			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myositis G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (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
Myasthenia gravis G5			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Seizure - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stroke			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood and lymphatic system disorders			
Anemia G3			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia G4			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Eye disorders_diplopia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites - G3			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (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
Ascites - G5			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis - G2			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhea - G2			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhea - G3			
subjects affected / exposed	1 / 27 (3.70%)	3 / 31 (9.68%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 1	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1

Diarrhea - G4			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	3 / 32 (9.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhea - G5			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Duodenal ulcer - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction - G3			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	0 / 32 (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
Small intestinal obstruction - G5			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal hemorrhage - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visceral arterial ischemia - G5			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting - G2			

subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting - G3			
subjects affected / exposed	2 / 27 (7.41%)	0 / 31 (0.00%)	2 / 32 (6.25%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Edema limbs - G2			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	2 / 32 (6.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	0 / 32 (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
Acute kidney injury - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis G4			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure G5			

subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Hepatobiliary disorders - Other, specify - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cholangitis G2			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hepatitis G4			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	0 / 32 (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
trasnaminitis G2			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	0 / 32 (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
Skin and subcutaneous tissue disorders			
Skin hypopigmentation			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	0 / 32 (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
Renal and urinary disorders			
Acute kidney injury - G1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury - G5			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Acute renal injury G5			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Rectal hemorrhage - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure G3			
subjects affected / exposed	2 / 27 (7.41%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency G3			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	0 / 32 (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
Hyperthyroidism - G2			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	0 / 32 (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
Hypothyroidism - G3			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myositis G2			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Encephalitis infection - G5			

subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Sepsis-G2			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory infection - G5			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Urinary tract infection - G2			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hepatitis G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory infection G2			
subjects affected / exposed	1 / 27 (3.70%)	0 / 31 (0.00%)	0 / 32 (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
Upper respiratory infection G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis G3			
subjects affected / exposed	1 / 27 (3.70%)	1 / 31 (3.23%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycemia-G3			

subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycemia - G4			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatremia - G3			
subjects affected / exposed	0 / 27 (0.00%)	0 / 31 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 4		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 33 (48.48%)		
number of deaths (all causes)	23		
number of deaths resulting from adverse events			
Vascular disorders			
Cellulitis G3			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Flushing			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension - G2			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leg edemas			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thromboembolic event - G3			

subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Abdominal pain - G2				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Death NOS - G5				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain - G2				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
clinical deterioration				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased G1				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Alanine aminotransferase increased - G2				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Alanine aminotransferase increased - G3				

subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased - G1				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased - G3				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Creatinine increased - G3				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GGT increased G3				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Serum amylase increased - G3				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Weight loss - G1				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Infusion related reaction - G1				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Injury to superior vena cava - G3			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation G3			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Heart failure			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction G4			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocarditis G3			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myositis G3			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myasthenia gravis G5			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Seizure - G3				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Somnolence - G3				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stroke				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anemia G3				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia G4				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Eye disorders_diplopia				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain - G3				
subjects affected / exposed	3 / 33 (9.09%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Ascites - G3				

subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites - G5				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis - G2				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis - G3				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhea - G2				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhea - G3				
subjects affected / exposed	2 / 33 (6.06%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhea - G4				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhea - G5				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer - G3				

subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia - G3				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction - G3				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction - G5				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal hemorrhage - G3				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Visceral arterial ischemia - G5				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting - G2				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting - G3				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Edema limbs - G2				

subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue - G3				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute kidney injury - G3				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Autoimmune hepatitis G4				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis - G3				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure G5				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders - Other, specify - G3				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
cholangitis G2				

subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
hepatitis G4				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
trasnaminitis G2				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Skin hypopigmentation				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury - G1				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute kidney injury - G5				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute renal injury G5				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal hemorrhage - G3				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure G3				

subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency G3			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperthyroidism - G2			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypothyroidism - G3			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Myositis G2			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Encephalitis infection - G5			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis-G2			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory infection - G5			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Urinary tract infection - G2			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
hepatitis G3			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory infection G2			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory infection G3			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis G3			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycemia-G3			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycemia - G4			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatremia - G3			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Cohort 1	cohort 2	cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)	31 / 31 (100.00%)	32 / 32 (100.00%)
Vascular disorders			
Flushing Grade			
subjects affected / exposed	1 / 27 (3.70%)	8 / 31 (25.81%)	0 / 32 (0.00%)
occurrences (all)	1	8	0
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	0 / 27 (0.00%)	2 / 31 (6.45%)	3 / 32 (9.38%)
occurrences (all)	2	2	3
Fatigue			
subjects affected / exposed	13 / 27 (48.15%)	16 / 31 (51.61%)	20 / 32 (62.50%)
occurrences (all)	13	16	20
Flu like symptoms			
subjects affected / exposed	2 / 27 (7.41%)	4 / 31 (12.90%)	1 / 32 (3.13%)
occurrences (all)	2	4	1
General disorders and administration site conditions			
subjects affected / exposed	2 / 27 (7.41%)	3 / 31 (9.68%)	1 / 32 (3.13%)
occurrences (all)	2	3	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 27 (11.11%)	2 / 31 (6.45%)	2 / 32 (6.25%)
occurrences (all)	3	2	2
Dyspnea			
subjects affected / exposed	4 / 27 (14.81%)	3 / 31 (9.68%)	1 / 32 (3.13%)
occurrences (all)	4	3	1
Respiratory, thoracic and mediastinal disorders - Other, specify Grade			
subjects affected / exposed	3 / 27 (11.11%)	2 / 31 (6.45%)	0 / 32 (0.00%)
occurrences (all)	3	2	0
Psychiatric disorders			
Insomnia			

subjects affected / exposed	1 / 27 (3.70%)	5 / 31 (16.13%)	2 / 32 (6.25%)
occurrences (all)	1	5	2
Investigations			
GGT increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	3 / 32 (9.38%)
occurrences (all)	0	1	3
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 27 (11.11%)	3 / 31 (9.68%)	3 / 32 (9.38%)
occurrences (all)	3	3	3
Somnolence			
subjects affected / exposed	1 / 27 (3.70%)	2 / 31 (6.45%)	2 / 32 (6.25%)
occurrences (all)	1	2	2
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 27 (3.70%)	4 / 31 (12.90%)	3 / 32 (9.38%)
occurrences (all)	1	4	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 27 (7.41%)	11 / 31 (35.48%)	5 / 32 (15.63%)
occurrences (all)	2	11	5
Ascites			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Constipation Grade			
subjects affected / exposed	4 / 27 (14.81%)	3 / 31 (9.68%)	9 / 32 (28.13%)
occurrences (all)	4	3	9
Diarrhea			
subjects affected / exposed	14 / 27 (51.85%)	15 / 31 (48.39%)	12 / 32 (37.50%)
occurrences (all)	14	15	12
Gastrointestinal disorders - Other, specify Grade			
subjects affected / exposed	4 / 27 (14.81%)	7 / 31 (22.58%)	2 / 32 (6.25%)
occurrences (all)	4	7	2
Gastrointestinal pain			
subjects affected / exposed	2 / 27 (7.41%)	3 / 31 (9.68%)	1 / 32 (3.13%)
occurrences (all)	2	3	1

Mucositis oral			
subjects affected / exposed	2 / 27 (7.41%)	3 / 31 (9.68%)	6 / 32 (18.75%)
occurrences (all)	2	3	6
Nausea			
subjects affected / exposed	2 / 27 (7.41%)	7 / 31 (22.58%)	3 / 32 (9.38%)
occurrences (all)	2	7	3
Pain			
subjects affected / exposed	3 / 27 (11.11%)	5 / 31 (16.13%)	4 / 32 (12.50%)
occurrences (all)	3	5	4
Vomiting psychogenic			
subjects affected / exposed	2 / 27 (7.41%)	7 / 31 (22.58%)	3 / 32 (9.38%)
occurrences (all)	2	7	3
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 27 (0.00%)	4 / 31 (12.90%)	2 / 32 (6.25%)
occurrences (all)	0	4	2
Pruritus Grade			
subjects affected / exposed	5 / 27 (18.52%)	11 / 31 (35.48%)	11 / 32 (34.38%)
occurrences (all)	5	11	11
Rash acneiform			
subjects affected / exposed	0 / 27 (0.00%)	5 / 31 (16.13%)	4 / 32 (12.50%)
occurrences (all)	0	5	4
Rash maculo-papular			
subjects affected / exposed	1 / 27 (3.70%)	1 / 31 (3.23%)	2 / 32 (6.25%)
occurrences (all)	1	1	2
Skin and subcutaneous tissue disorders - Other, specify Grade			
subjects affected / exposed	4 / 27 (14.81%)	4 / 31 (12.90%)	2 / 32 (6.25%)
occurrences (all)	4	4	2
Renal and urinary disorders			
Renal and urinary disorders - Other, specify Grade			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 27 (0.00%)	1 / 31 (3.23%)	2 / 32 (6.25%)
occurrences (all)	0	1	2

Hypothyroidism			
subjects affected / exposed	0 / 27 (0.00%)	3 / 31 (9.68%)	6 / 32 (18.75%)
occurrences (all)	0	3	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 27 (7.41%)	4 / 31 (12.90%)	7 / 32 (21.88%)
occurrences (all)	2	4	7
Back pain			
subjects affected / exposed	1 / 27 (3.70%)	1 / 31 (3.23%)	2 / 32 (6.25%)
occurrences (all)	1	1	2
Bone pain			
subjects affected / exposed	2 / 27 (7.41%)	2 / 31 (6.45%)	2 / 32 (6.25%)
occurrences (all)	2	2	2
Generalized muscle weakness			
subjects affected / exposed	3 / 27 (11.11%)	3 / 31 (9.68%)	0 / 32 (0.00%)
occurrences (all)	3	3	0
Musculoskeletal and connective tissue disorder			
subjects affected / exposed	3 / 27 (11.11%)	3 / 31 (9.68%)	1 / 32 (3.13%)
occurrences (all)	3	3	1
Myalgia			
subjects affected / exposed	1 / 27 (3.70%)	4 / 31 (12.90%)	1 / 32 (3.13%)
occurrences (all)	1	4	1
Pain in extremity			
subjects affected / exposed	2 / 27 (7.41%)	0 / 31 (0.00%)	2 / 32 (6.25%)
occurrences (all)	2	0	2
Infections and infestations			
Upper respiratory infection Grade			
subjects affected / exposed	4 / 27 (14.81%)	3 / 31 (9.68%)	4 / 32 (12.50%)
occurrences (all)	4	3	4
Urinary tract infection			
subjects affected / exposed	1 / 27 (3.70%)	1 / 31 (3.23%)	1 / 32 (3.13%)
occurrences (all)	1	1	1
Alanine aminotransferase increased			
subjects affected / exposed	2 / 27 (7.41%)	3 / 31 (9.68%)	6 / 32 (18.75%)
occurrences (all)	2	3	6
Aspartate aminotransferase			

increased			
subjects affected / exposed	2 / 27 (7.41%)	4 / 31 (12.90%)	5 / 32 (15.63%)
occurrences (all)	2	4	5
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	6 / 27 (22.22%)	9 / 31 (29.03%)	0 / 32 (0.00%)
occurrences (all)	6	9	0

Non-serious adverse events	Cohort 4		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)		
Vascular disorders			
Flushing Grade			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	18 / 33 (54.55%)		
occurrences (all)	18		
Flu like symptoms			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
General disorders and administration site conditions			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Dyspnea			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders - Other, specify Grade			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Investigations			
GGT increased			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	5		
Ascites			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Constipation Grade			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	5		
Diarrhea			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	7		
Gastrointestinal disorders - Other, specify Grade			

subjects affected / exposed occurrences (all) Gastrointestinal pain subjects affected / exposed occurrences (all) Mucositis oral subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Vomiting psychogenic subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1 2 / 33 (6.06%) 2 3 / 33 (9.09%) 3 7 / 33 (21.21%) 7 1 / 33 (3.03%) 1 7 / 33 (21.21%) 7		
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all) Pruritus Grade subjects affected / exposed occurrences (all) Rash acneiform subjects affected / exposed occurrences (all) Rash maculo-papular subjects affected / exposed occurrences (all) Skin and subcutaneous tissue disorders - Other, specify Grade subjects affected / exposed occurrences (all)	 1 / 33 (3.03%) 1 6 / 33 (18.18%) 6 1 / 33 (3.03%) 1 4 / 33 (12.12%) 4 1 / 33 (3.03%) 1		
Renal and urinary disorders			

Renal and urinary disorders - Other, specify Grade			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Hypothyroidism			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Generalized muscle weakness			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorder			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Infections and infestations			
Upper respiratory infection Grade			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2020	• Cambios de seguridad debido a la actualización de los manuales del investigador de la versión 14 de Durvalumab a la versión 15 y de la versión 9 de Tremelimumab a la versión 10. Estos cambios se deben recoger en el protocolo del ensayo así como en la Hoja de Información al Paciente. • Cambio de presentacion del Tremelimumab, hecho que repercute en su etiquetado.
04 August 2021	Cambios de seguridad debido a la actualización de los manuales del investigador de la versión 15 de Durvalumab a la versión 16 y 16.1. Estos cambios se deben recoger en el protocolo del ensayo así como en la Hoja de Información al Paciente.

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/37221181