



Clinical trial results:

Phase 1/2 Study of anti-PD-L1 in Combination with Chemo(radio)therapy for Oesophageal Cancer

Summary

EudraCT number	2015-005298-19
Trial protocol	GB
Global end of trial date	17 June 2022

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	LUD2015-005
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02735239
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ludwig Institute for Cancer Research Ltd
Sponsor organisation address	600 3rd Avenue 32nd Floor, New York, United States, 10016
Public contact	Jonathan Skipper, Ludwig Institute for Cancer Research Ltd, 001 2124501539, jskipper@lcr.org
Scientific contact	Jonathan Skipper, Ludwig Institute for Cancer Research Ltd, 001 2124501539, jskipper@lcr.org

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	28 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 June 2022
Global end of trial reached?	Yes
Global end of trial date	17 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives are (1) to assess the safety and tolerability of durvalumab alone and tremelimumab + durvalumab in combination with oxaliplatin/capecitabine chemotherapy in metastatic or locally advanced oesophageal cancer (OC), and then (2) to assess the safety and tolerability of durvalumab in combination with neoadjuvant chemo(radio)therapy before surgery in operable oesophageal cancer. Secondary objectives are (1) to assess the clinical efficacy of durvalumab alone and tremelimumab + durvalumab in combination with oxaliplatin/capecitabine chemotherapy in metastatic or locally advanced OC. (Endpoints: Tumor Response by irRECIST, progression-free survival [PFS] and overall survival [OS]) and (2) to assess the clinical efficacy of durvalumab in combination with neoadjuvant chemo(radio)therapy (oxaliplatin/capecitabine, FLOT, and paclitaxel/carboplatin/radiotherapy) in operable OC. (Endpoints: PFS after surgery, 1-year survival rate, OS, response rate)

Protection of trial subjects:

Subjects were given full and adequate written information about the nature, purpose and possible risks and benefits of the study. Dose adjustments, delays and discontinuation criteria were included in the protocol in the form of dose adjustment and management guidelines for toxicity related to study treatment.

Phase 1 of the study (Cohorts A1 and A2) evaluated the feasibility/safety of administering durvalumab or tremelimumab + durvalumab pre-operatively to OC subjects. Once safety was established in these cohorts, the additional cohorts were open for enrollment.

In addition, safety monitoring and study stopping rules were implemented in the protocol.

The assessment of safety and tolerability was performed by the internal data safety monitoring panel on an ongoing basis, based on data review and regular conference calls with the investigators.

Standard safety evaluation and reporting for early phase trials were used for Cohorts B, C/C-FLOT, and D/D2. In addition, for Cohorts C/C-FLOT and D/D2, subjects undergoing surgery were closely monitored for post-operative complications to evaluate the possibility of an impact.

Laboratory tests, vital sign measurements, physical exams (including neurological exams) and subject interviews were performed to detect new abnormalities and deteriorations of any pre-existing conditions. The investigator evaluated any laboratory abnormalities for clinical significance, and clinically significant abnormalities were recorded as adverse events. All clinically significant abnormalities and deteriorations from time of signing of informed consent to the end of study visit were to be recorded in the Case Report Forms as adverse events and graded according to the National Cancer Institute Common Terminology for Adverse Events (CTCAE), version 4.03.

Background therapy:

The fluoropyrimidine-platinum (traditionally 5FU-cisplatin) based CRT regimen has long been a standard of care in the pre-operative management of oesophageal cancer. The use of this combination was largely historic, with only one small positive trial, and several meta-analyses supporting its use over surgery alone. The oxaliplatin-capecitabine based CRT regimen was selected over the cisplatin-fluoropyrimidine regime for Cohorts A, B & C based on several factors including maintaining the same chemotherapy backbone in the metastatic or locally advanced OC Cohorts A & B as in the Cohort C neoadjuvant chemotherapy arm of the trial. This decision was based on a randomized Phase 2 study in definitive chemoradiation showing comparable efficacy and less toxicity of oxaliplatin-5FU combination in comparison to cisplatin-5FU combination, emerging Phase 1b/2 data suggesting feasibility and activity of oxaliplatin-fluoropyrimidine based CRT regimens in the pre-operative setting and use of this regimen in the NEOSCOPE trial, a randomized Phase 2 trial that was ongoing in the UK at the time when this protocol was being developed.

While the trial was ongoing, two additional background treatments were added for subjects with operable OC based on emerging data.

In Cohort C-FLOT, oxaliplatin and capecitabine as neoadjuvant chemotherapy was replaced with the FLOT regimen to run concurrently with durvalumab treatment, and introducing post-operative chemotherapy, also with FLOT. This was to run concurrently with durvalumab immunotherapy.

In Cohort D, 2 doses of durvalumab were to be given during a 4-week immunotherapy period, followed by neoadjuvant chemoradiotherapy (5 weekly doses of paclitaxel + carboplatin + radiotherapy) without concurrent durvalumab. Cohort D2 is a subset of Cohort D subjects for whom durvalumab doses were to continue during chemoradiotherapy, after the initial 4-week immunotherapy.

Evidence for comparator: -

Actual start date of recruitment	22 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 73
Worldwide total number of subjects	73
EEA total number of subjects	0

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)	47
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was from 22 April 2016 to 31 December 2019. Seventy-nine subjects were assessed for eligibility, 6 were excluded and 73 were recruited for treatment.

The study included 2 phases, a safety run-in Phase 1 (Cohorts A1 and A2) and an expansion Phase 2, Cohorts B, C, C-FLOT and D/D2.

Pre-assignment

Screening details:

Screening was completed within 28 days of the start of therapy.

Subjects must have had a histological diagnosis of oesophageal or gastroesophageal cancer and have not received prior chemotherapy.

Cohorts A and B - metastatic/locally advanced cancer.

Cohorts C, C-FLOT and D/D2 - deemed suitable for surgery with curative intent.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A1

Arm description:

Metastatic/locally Advanced Oesophageal Cancer, Durvalumab + Oxaliplatin/Capecitabine Chemotherapy

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	MEDI4736
Other name	Imfinzi
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Durvalumab (750 mg every two weeks [Q2W]) was to be given for up to 11 doses.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	Eloxatin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Oxaliplatin (130 mg/m²) was administered by intravenous infusion in six three-week cycles starting on the day of the third dose of durvalumab.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine (1250 mg/m²/day) was given orally in two divided doses for six three-week cycles starting on the day of the first oxaliplatin infusion.

Arm title	Cohort A2
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Arm description:

Metastatic/locally Advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capecitabine Chemotherapy

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	MEDI4736
Other name	Imfinzi
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Durvalumab (750 mg every two weeks [Q2W]) was to be given for up to 11 doses.

Investigational medicinal product name	Tremelimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

One dose of tremelimumab (37.5 mg) was given by intravenous infusion on the same day as the first dose of durvalumab.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	Eloxatin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Oxaliplatin (130 mg/m²) was administered by intravenous infusion in six three-week cycles starting on the day of the third dose of durvalumab.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine (1250 mg/m²/day) was given orally in two divided doses for six three-week cycles starting on the day of the first oxaliplatin infusion.

Arm title	Cohort B
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Arm description:

Metastatic/locally Advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capecitabine Chemotherapy

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	MEDI4736
Other name	Imfinzi
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Durvalumab (750 mg every two weeks [Q2W]) was to be given for up to 11 doses.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:	
Capecitabine (1250 mg/m ² /day) was given orally in two divided doses for six three-week cycles starting on the day of the first oxaliplatin infusion.	
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	Eloxatin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Oxaliplatin (130 mg/m ²) was administered by intravenous infusion in six three-week cycles starting on the day of the third dose of durvalumab.	
Investigational medicinal product name	Tremelimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
One dose of tremelimumab (75 mg) was given by intravenous infusion on the same day as the first dose of durvalumab.	
Arm title	Cohort C
Arm description:	
Operable Oesophageal Cancer, Durvalumab + Oxaliplatin/Capecitabine Chemotherapy	
Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	MEDI4736
Other name	Imfinzi
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Durvalumab (750 mg every two weeks [Q2W]) was given for 11 doses.	
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	Eloxatin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Oxaliplatin (130 mg/m ²) was administered by intravenous infusion in six three-week cycles starting on the day of the third dose of durvalumab.	
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Capecitabine (1250 mg/m ² /day) was given orally in two divided doses for six three-week cycles starting on the day of the first oxaliplatin infusion.	
Arm title	Cohort C-FLOT
Arm description:	
Operable Oesophageal Cancer, Durvalumab + Neoadjuvant 5-fluorouracil (5-FU), Leucovorin, Oxaliplatin, and Docetaxel (FLOT) Chemotherapy	
Arm type	Experimental

Investigational medicinal product name	Durvalumab
Investigational medicinal product code	MEDI4736
Other name	Imfinzi
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Durvalumab (750 mg every two weeks [Q2W]) was to be given for 6 doses prior to surgery. Optional durvalumab for up to a total of 12 doses was allowed after recovery from surgery provided this was within 3 months of surgery.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	Eloxatin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

As part of two cycles of neoadjuvant FLOT chemotherapy, oxaliplatin (85 mg/m²) was administered by intravenous infusion before surgery starting on the day of the third dose of durvalumab. Subjects were to undergo surgery 6 to 8 weeks after completing chemotherapy or according to institutional policies for surgery; and would be eligible to resume durvalumab dosing (to a maximum of 12 infusions), FLOT or durvalumab plus FLOT at the discretion of the Investigator once recovered from surgery, provided that this was within 3 months of surgery.

Investigational medicinal product name	5-Flourouracil
Investigational medicinal product code	
Other name	5-FU
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

As part of two cycles of neoadjuvant FLOT chemotherapy, 5-fluorouracil (5-FU) (2600 mg/m²) was administered as a 24-hr infusion before surgery starting on the day of the third dose of durvalumab. Subjects were to undergo surgery 6 to 8 weeks after completing chemotherapy or according to institutional policies for surgery; and would be eligible to resume durvalumab dosing (to a maximum of 12 infusions), FLOT or durvalumab plus FLOT at the discretion of the Investigator once recovered from surgery, provided that this was within 3 months of surgery.

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

As part of two cycles of neoadjuvant FLOT chemotherapy, leucovorin (200 mg/m² IV), was administered before surgery starting on the day of the third dose of durvalumab. Subjects were to undergo surgery 6 to 8 weeks after completing chemotherapy or according to institutional policies for surgery; and would be eligible to resume durvalumab dosing (to a maximum of 12 infusions), FLOT or durvalumab plus FLOT at the discretion of the Investigator once recovered from surgery, provided that this was within 3 months of surgery.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

As part of two cycles of neoadjuvant FLOT chemotherapy, docetaxel (50 mg/m²) was administered before surgery starting on the day of the third dose of durvalumab. Subjects were to undergo surgery 6 to 8 weeks after completing chemotherapy or according to institutional policies for surgery; and would be eligible to resume durvalumab dosing (to a maximum of 12 infusions), FLOT or durvalumab plus FLOT at the discretion of the Investigator once recovered from surgery, provided that this was within 3

months of surgery.

Arm title	Cohort D/D2
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Arm description:

Operable Oesophageal Cancer, Durvalumab + Neoadjuvant Chemo(radio)therapy with Paclitaxel, Carboplatin and Radiotherapy.

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	MEDI4736
Other name	Imfinzi
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Durvalumab (750 mg every two weeks [Q2W]) was to be given for 2 doses (Cohort D) or 5 doses (Cohort D2) prior to surgery. Optional durvalumab dosing was allowed after recovery from surgery for up to 12 total doses provided that this was within 3 months of surgery.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	Taxol
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Five weekly doses of paclitaxel (50 mg/m²) by intravenous infusion as part of neoadjuvant chemoradiotherapy (41.4 Gy radiotherapy given over 23 fractions) were administered before surgery. In Cohort D2, subjects continued durvalumab for 3 additional doses while receiving chemoradiation. Subjects were to undergo surgery 6 to 8 weeks after completing chemo(radio)therapy or according to institutional policies for surgery; and would be eligible to resume durvalumab dosing (to a maximum of 12 infusions) once recovered from surgery, provided that this was within 3 months of surgery.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	Paraplatin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Five weekly doses of carboplatin (AUC 2) by intravenous infusion as part of neoadjuvant chemoradiotherapy (41.4 Gy radiotherapy given over 23 fractions) were administered before surgery. In Cohort D2, subjects continued durvalumab for 3 additional doses while receiving chemoradiation. Subjects were to undergo surgery 6 to 8 weeks after completing chemo(radio)therapy or according to institutional policies for surgery; and would be eligible to resume durvalumab dosing (to a maximum of 12 infusions) once recovered from surgery, provided that this was within 3 months of surgery.

Number of subjects in period 1	Cohort A1	Cohort A2	Cohort B
Started	12	5	21
Completed	8	2	13
Not completed	4	3	8
Adverse event, serious fatal	1	1	-
Consent withdrawn by subject	-	1	-

Physician decision	-	-	1
Adverse event, non-fatal	-	-	4
Progressive disease	3	1	3

Number of subjects in period 1	Cohort C	Cohort C-FLOT	Cohort D/D2
Started	11	9	15
Completed	11	9	13
Not completed	0	0	2
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	-	-	-
Physician decision	-	-	-
Adverse event, non-fatal	-	-	-
Progressive disease	-	-	2

Baseline characteristics

Reporting groups

Reporting group title	Cohort A1
Reporting group description: Metastatic/locally Advanced Oesophageal Cancer, Durvalumab + Oxaliplatin/Capecitabine Chemotherapy	
Reporting group title	Cohort A2
Reporting group description: Metastatic/locally Advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capecitabine Chemotherapy	
Reporting group title	Cohort B
Reporting group description: Metastatic/locally Advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capecitabine Chemotherapy	
Reporting group title	Cohort C
Reporting group description: Operable Oesophageal Cancer, Durvalumab + Oxaliplatin/Capecitabine Chemotherapy	
Reporting group title	Cohort C-FLOT
Reporting group description: Operable Oesophageal Cancer, Durvalumab + Neoadjuvant 5-fluorouracil (5-FU), Leucovorin, Oxaliplatin, and Docetaxel (FLOT) Chemotherapy	
Reporting group title	Cohort D/D2
Reporting group description: Operable Oesophageal Cancer, Durvalumab + Neoadjuvant Chemo(radio)therapy with Paclitaxel, Carboplatin and Radiotherapy.	

Reporting group values	Cohort A1	Cohort A2	Cohort B
Number of subjects	12	5	21
Age categorical Units: Subjects			
Adults (18-64 years)	7	3	16
From 65-84 years	5	2	5
Age continuous Units: years			
median	59.5	55.0	58.0
full range (min-max)	23 to 75	29 to 67	42 to 78
Gender categorical Units: Subjects			
Female	2	1	4
Male	10	4	17

Reporting group values	Cohort C	Cohort C-FLOT	Cohort D/D2
Number of subjects	11	9	15
Age categorical Units: Subjects			
Adults (18-64 years)	8	6	7
From 65-84 years	3	3	8

Age continuous Units: years median full range (min-max)	57.0 46 to 71	56.0 33 to 72	65.0 50 to 72
Gender categorical Units: Subjects			
Female	0	1	3
Male	11	8	12

Reporting group values	Total		
Number of subjects	73		
Age categorical Units: Subjects			
Adults (18-64 years)	47		
From 65-84 years	26		
Age continuous Units: years median full range (min-max)	-		
Gender categorical Units: Subjects			
Female	11		
Male	62		

End points

End points reporting groups

Reporting group title	Cohort A1
Reporting group description: Metastatic/locally Advanced Oesophageal Cancer, Durvalumab + Oxaliplatin/Capecitabine Chemotherapy	
Reporting group title	Cohort A2
Reporting group description: Metastatic/locally Advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capecitabine Chemotherapy	
Reporting group title	Cohort B
Reporting group description: Metastatic/locally Advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capecitabine Chemotherapy	
Reporting group title	Cohort C
Reporting group description: Operable Oesophageal Cancer, Durvalumab + Oxaliplatin/Capecitabine Chemotherapy	
Reporting group title	Cohort C-FLOT
Reporting group description: Operable Oesophageal Cancer, Durvalumab + Neoadjuvant 5-fluorouracil (5-FU), Leucovorin, Oxaliplatin, and Docetaxel (FLOT) Chemotherapy	
Reporting group title	Cohort D/D2
Reporting group description: Operable Oesophageal Cancer, Durvalumab + Neoadjuvant Chemo(radio)therapy with Paclitaxel, Carboplatin and Radiotherapy.	

Primary: Number of Subjects With Best Overall Tumor Response by the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

End point title	Number of Subjects With Best Overall Tumor Response by the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) ^[1]
End point description: Tumor responses were evaluated using appropriate imaging and categorized according to irRECIST at Screening (up to 28 days before the first dose of study treatment), and in Cycles 1, 3, 5 and 6 in Cohorts A1, A2 and B. In the other cohorts, tumor response was assessed at baseline, post-surgery and 14 days after the last dose. In Cohort C-FLOT, an additional assessment was done prior to surgery and in Cohorts C and D, an additional assessment was done in Cycle 3. Per irRECIST, measurable lesions are categorized as follows: Immune-related Complete Response (irCR): Complete disappearance of all target lesions; Immune-related Partial Response (irPR): $\geq 30\%$ decrease from baseline in the total measurable tumor burden (TMTB); Immune-related Progressive Disease (irPD): $\geq 20\%$ increase from nadir in TMTB; Immune-related Stable Disease (irSD): not meeting above criteria; irNon-CR/Non-PD: not evaluable.	
End point type	Primary
End point timeframe: up to 1 year	
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: In this study where different regimens are being studied in each Cohort, the primary objective was to assess the safety of the different regimens and sample sizes were determined based on this. While secondary objectives were to obtain preliminary efficacy of each regimen, the intent was not to compare the regimens and as a results no statistical comparisons were made between cohorts.	

End point values	Cohort A1	Cohort A2	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	5	20	9
Units: subjects				
irCR	2	0	0	3
irPR	3	3	10	1
irSD	5	1	4	0
irPD	1	1	5	1
irNon-CR/Non-PD	0	0	1	1
Not Evaluable	0	0	0	3

End point values	Cohort C-FLOT	Cohort D/D2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: subjects				
irCR	1	2		
irPR	0	0		
irSD	0	0		
irPD	0	1		
irNon-CR/Non-PD	0	0		
Not Evaluable	4	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Metastatic/locally Advanced Oesophageal Cancer (OC) Who Had a Response at Cycle 6 by irRECIST

End point title	Number of Subjects With Metastatic/locally Advanced Oesophageal Cancer (OC) Who Had a Response at Cycle 6 by irRECIST ^[2]
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End point description:

Tumor responses were evaluated using appropriate imaging and categorized according to irRECIST at Screening (up to 28 days before the first dose of study treatment), and in Cycles 1, 3, 5 and 6 in Cohorts A1, A2 and B. Per irRECIST, measurable lesions are categorized as follows: irCR: Complete disappearance of all target lesions; irPR: $\geq 30\%$ decrease from baseline in the total measurable tumor burden (TMTB); irPD: $\geq 20\%$ increase from nadir in TMTB; irSD: not meeting above criteria; irNon-CR/Non-PD: not evaluable.

End point type	Secondary
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End point timeframe:

Up to 23 weeks.

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: In this study where different regimens are being studied in each Cohort, the primary objective was to assess the safety of the different regimens and sample sizes were determined based on this. While secondary objectives were to obtain preliminary efficacy of each regimen, the intent was not to compare the regimens and as a results no statistical comparisons were made between cohorts.

End point values	Cohort A1	Cohort A2	Cohort B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	3	14	
Units: Number of subjects				
irCR	2	0	0	
irPR	2	2	7	
irSD	3	1	4	
irPD	1	0	1	
irNonCR/Non-PD	0	0	1	
Not evaluable	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Median Progression-free Survival (PFS) by irRECIST as Estimated Using the Kaplan-Meier Method

End point title	Median Progression-free Survival (PFS) by irRECIST as Estimated Using the Kaplan-Meier Method
End point description:	
In Cohorts A1, A2 and B, PFS was measured from the date of the first dose of study treatment to the date of earliest disease progression according to irRECIST or to the date of death, if disease progression did not occur.	
For subjects in Cohorts C/C-FLOT and D/D2 undergoing successful surgery, post-operative PFS was measured with time origin at the day of surgery until the first occurrence of confirmed progression by irRECIST or date of death if the subject dies from any causes before progression.	
Per irRECIST, irPD was defined as a $\geq 20\%$ increase from nadir in the TMTB.	
The median was not reached in Cohort C-FLOT, this is indicated by 999. The upper 95% confidence interval limit was not reached in Cohorts A2, C, C-FLOT and D, this has been indicated by 999.	
End point type	Secondary
End point timeframe:	
Up to 1 year	

End point values	Cohort A1	Cohort A2	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	5	21	11
Units: Months				
median (confidence interval 95%)	8.7 (0.9 to 29.1)	5.2 (1.4 to 999)	11.9 (3.9 to 15.6)	25.40 (6.47 to 999)

End point values	Cohort C-FLOT	Cohort D/D2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	14		
Units: Months				
median (confidence interval 95%)	32.03 (2.10 to 999)	999 (9.59 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Overall Survival (OS) as Estimated Using the Kaplan-Meier Method

End point title	Median Overall Survival (OS) as Estimated Using the Kaplan-Meier Method
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End point description:

After completion of treatment, all subjects were followed for survival every 6 months for up to 3 years from start of treatment. OS was measured from the date of the first dose of study treatment to the date of death or last follow-up. Subjects lost to follow-up were censored on the date when they were last known to be alive. Per protocol amendment 8.0, all post study follow-up for the collection of survival data was discontinued as of 30 June 2022.

The medians were not estimable for Cohorts C, C-FLOT and D/D2, this has been indicated by a median which is indicated as 999. The upper 95% confidence interval limit was not reached in Cohorts A, A2, C, C-FLOT and D/D2, this has been indicated by 999.

End point type	Secondary
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End point timeframe:

Up to 30 June 2022

End point values	Cohort A1	Cohort A2	Cohort B	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	5	21	11
Units: Months				
median (confidence interval 95%)	11.8 (3.1 to 999)	8.6 (2.7 to 999)	15.6 (9.3 to 33.5)	999 (18.46 to 999)

End point values	Cohort C-FLOT	Cohort D/D2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	15		
Units: Months				
median (confidence interval 95%)	999 (8.02 to 999)	999 (13.14 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: One Year Survival Rate in Subjects with Operable OC

End point title	One Year Survival Rate in Subjects with Operable OC ^[3]
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End point description:

After completion of treatment, all subjects were followed for survival every 6 months for up to 3 years from start of treatment. OS was measured from the date of the first dose of study treatment to the date of death or last follow-up. Subjects lost to follow-up were censored on the date when they were last known to be alive. Per protocol amendment 8.0, all post study follow-up for the collection of survival data was discontinued as of 30 June 2022.

In Cohort C, both the upper and lower limits of the 95% confidence interval were not reached, this has been indicated by 0 and 999 respectively.

End point type	Secondary
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End point timeframe:

Up to 1 year

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: In this study where different regimens are being studied in each Cohort, the primary objective was to assess the safety of the different regimens and sample sizes were determined based on this. While secondary objectives were to obtain preliminary efficacy of each regimen, the intent was not to compare the regimens and as a results no statistical comparisons were made between cohorts.

End point values	Cohort C	Cohort C-FLOT	Cohort D/D2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	9	15	
Units: Percent				
number (confidence interval 95%)	100 (0 to 999)	89.0 (43.3 to 98.4)	86.7 (56.4 to 96.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Prior to Surgery in Operable OC (Cohorts C, C-FLOT and D/D2) using Positron Emission Tomography (PET) Response Criteria in Solid Tumors (PERCIST)

End point title	Overall Response Prior to Surgery in Operable OC (Cohorts C, C-FLOT and D/D2) using Positron Emission Tomography (PET) Response Criteria in Solid Tumors (PERCIST) ^[4]
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End point description:

18 fluorodeoxyglucose (18F-FDG) PET scans were conducted at baseline and in Cycle 3 in Cohorts C and D, and after completion of therapy in Cohort C-FLOT and D2. Complete metabolic response: 18F-FDG-avid lesions revert to background of normal tissues in which they are located; Partial metabolic response: 30% or greater reduction in measurable tumors; Stable Metabolic Response: no visible change in metabolic activity of tumor; Progressive metabolic disease: increase in intensity or extent of tumor metabolic activity or new sites of activity.

All operable OC patients in Cohorts C, C-FLOT and D/D2 who had a baseline PET scan and a PET scan prior to surgery were included in the analyses.

End point type	Secondary
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End point timeframe:

After completion of therapy and prior to surgery.

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: In this study where different regimens are being studied in each Cohort, the primary objective was to assess the safety of the different regimens and sample sizes were determined based on this. While secondary objectives were to obtain preliminary efficacy of each regimen, the intent was not

to compare the regimens and as a results no statistical comparisons were made between cohorts.

End point values	Cohort C	Cohort C-FLOT	Cohort D/D2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	6	13	
Units: Subjects				
Complete Metabolic Response	2	1	3	
Partial Metabolic Response	5	3	7	
Stable Disease	1	2	1	
Progressive Disease	3	0	2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occurring between the signing of informed consent and the off-study date (i.e., through 110 days after the last dose of study treatment) were documented, regardless of a causal relationship to study drug.

Adverse event reporting additional description:

AE documentation included onset/resolution dates, severity using NCI CTCAE (version 4.03), seriousness, relationship to study drug, study drug action taken, treatment and outcome. Preferred terms were counted once per subject at the maximum reported grade.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Cohort A1
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Reporting group description:

Metastatic/locally advanced Oesophageal Cancer, Durvalumab + Oxaliplatin/Capcitabine Chemotherapy

Reporting group title	Cohort A2
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Reporting group description:

Metastatic/locally advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capcitabine Chemotherapy

Reporting group title	Cohort B
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Reporting group description:

Metastatic/locally advanced Oesophageal Cancer, Durvalumab, Tremelimumab + Oxaliplatin/Capcitabine Chemotherapy

Reporting group title	Cohort C
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Reporting group description:

Operable Oesophageal Cancer; Durvalumab + Oxaliplatin/Capcitabine Chemotherapy

Reporting group title	Cohort C-FLOT
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Reporting group description:

Operable Oesophageal Cancer, Durvalumab + FLOT (5-fluorouracil, leucovorin, oxaliplatin, docetaxel) Chemotherapy

Reporting group title	Cohort D/D2
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Reporting group description:

Operable Oesophageal Cancer, Durvalumab + Neoadjuvant Chemo(radio)therapy with Paclitaxel, Carboplatin and radiotherapy.

Serious adverse events	Cohort A1	Cohort A2	Cohort B
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)	4 / 5 (80.00%)	12 / 21 (57.14%)
number of deaths (all causes)	9	5	16
number of deaths resulting from adverse events	3	2	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			

subjects affected / exposed	2 / 12 (16.67%)	1 / 5 (20.00%)	4 / 21 (19.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 4
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (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
Surgical and medical procedures			
Jejunostomy refashioning			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Oesophagectomy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (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
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (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
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (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
Pleural effusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Pneumonia aspiration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Pneumonitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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, poisoning and procedural complications			
Postoperative wound complication			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalitis autoimmune			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 21 (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
Seizure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 21 (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	1 / 12 (8.33%)	0 / 5 (0.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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			
subjects affected / exposed	2 / 12 (16.67%)	0 / 5 (0.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Enteritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Odynophagia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	2 / 5 (40.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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 and urinary disorders			
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary retention			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (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
Acute kidney injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Musculoskeletal and connective tissue disorders			
Pain in jaw			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
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			
Appendicitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Bacteraemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Liver abscess			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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

Lower respiratory tract infection subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (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
Neutropenic sepsis subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Orchitis subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Postoperative wound infection subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Respiratory tract infection subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Sepsis subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 21 (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
Urinary tract infection			

subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 12 (16.67%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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
Hyperglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (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

Serious adverse events	Cohort C	Cohort C-FLOT	Cohort D/D2
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 11 (63.64%)	6 / 9 (66.67%)	10 / 15 (66.67%)
number of deaths (all causes)	5	2	6
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Surgical and medical procedures			
Jejunostomy refashioning			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagectomy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Mucosal inflammation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Pleural effusion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (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

Pneumonitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Postoperative wound complication			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (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			
Angina pectoris			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Nervous system disorders			
Encephalitis autoimmune			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Seizure			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (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			
Anaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Neutropenia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Diarrhoea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Dysphagia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	3 / 15 (20.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Haematemesis			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Nausea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Odynophagia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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			
Cholecystitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Urinary retention			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Acute kidney injury			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (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
Musculoskeletal and connective tissue			

disorders			
Pain in jaw			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Herpes simplex			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (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
Infection			
subjects affected / exposed	0 / 11 (0.00%)	2 / 9 (22.22%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Neutropenic sepsis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (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

Orchitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (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 tract infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (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
Electrolyte imbalance			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort A1	Cohort A2	Cohort B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	5 / 5 (100.00%)	21 / 21 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Skin papilloma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Tumour pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Flushing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Orthostatic hypotension			

subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Phlebitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Chest discomfort			
subjects affected / exposed	1 / 12 (8.33%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences (all)	3	1	1
Chest pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	3
Chills			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Early satiety			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	10 / 12 (83.33%)	5 / 5 (100.00%)	13 / 21 (61.90%)
occurrences (all)	16	10	23
Feeling cold			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	2 / 21 (9.52%)
occurrences (all)	0	2	2
Infusion site reaction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			

subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	3
Oedema peripheral			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Pyrexia			
subjects affected / exposed	2 / 12 (16.67%)	2 / 5 (40.00%)	0 / 21 (0.00%)
occurrences (all)	3	2	0
Temperature intolerance			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 12 (33.33%)	2 / 5 (40.00%)	4 / 21 (19.05%)
occurrences (all)	4	2	5
Dyspnoea			
subjects affected / exposed	2 / 12 (16.67%)	2 / 5 (40.00%)	4 / 21 (19.05%)
occurrences (all)	2	3	6
Dyspnoea exertional			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Laryngospasm			
subjects affected / exposed	1 / 12 (8.33%)	2 / 5 (40.00%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Nasal congestion			

subjects affected / exposed	1 / 12 (8.33%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences (all)	1	2	1
Productive cough			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Rhinorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 12 (0.00%)	2 / 5 (40.00%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Confusional state			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	2 / 12 (16.67%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Insomnia			
subjects affected / exposed	3 / 12 (25.00%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences (all)	3	1	1
Irritability			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	4 / 21 (19.05%)
occurrences (all)	0	0	8
Amylase increased			

subjects affected / exposed	3 / 12 (25.00%)	1 / 5 (20.00%)	2 / 21 (9.52%)
occurrences (all)	5	1	10
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	5 / 21 (23.81%)
occurrences (all)	0	0	8
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	5
Blood creatinine increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Blood iron decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Blood magnesium decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Blood urea increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	6 / 12 (50.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	10	0	1
Neutrophil count decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Platelet count decreased			

subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	2 / 21 (9.52%)
occurrences (all)	2	0	4
Transaminases increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	5	0	4
Weight decreased			
subjects affected / exposed	2 / 12 (16.67%)	3 / 5 (60.00%)	4 / 21 (19.05%)
occurrences (all)	5	3	6
White blood cell count decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 12 (16.67%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Dumping syndrome			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Tooth fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Wound complication			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Wound haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			

Palpitations			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Dizziness postural			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dysaesthesia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	3 / 21 (14.29%)
occurrences (all)	1	0	3
Dysgeusia			
subjects affected / exposed	4 / 12 (33.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	4	0	0
Head discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 12 (8.33%)	1 / 5 (20.00%)	2 / 21 (9.52%)
occurrences (all)	2	1	2
Lethargy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Muscle contractions involuntary			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Neuropathy peripheral			
subjects affected / exposed	3 / 12 (25.00%)	2 / 5 (40.00%)	6 / 21 (28.57%)
occurrences (all)	6	2	10
Paraesthesia			

subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 6	1 / 5 (20.00%) 1	3 / 21 (14.29%) 3
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 9	1 / 5 (20.00%) 1	5 / 21 (23.81%) 5
Poor quality sleep subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 5 (0.00%) 0	0 / 21 (0.00%) 0
Presyncope subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Sciatica subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 5 (0.00%) 0	0 / 21 (0.00%) 0
Syncope subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 5 (0.00%) 0	0 / 21 (0.00%) 0
Tremor subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2	0 / 5 (0.00%) 0	0 / 21 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	5 / 12 (41.67%) 10	1 / 5 (20.00%) 6	4 / 21 (19.05%) 12
Neutropenia subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 9	1 / 5 (20.00%) 1	3 / 21 (14.29%) 9
Thrombocytopenia subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 12	1 / 5 (20.00%) 2	3 / 21 (14.29%) 8
Ear and labyrinth disorders			
Ear pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 5 (0.00%) 0	0 / 21 (0.00%) 0
Eye disorders			

Blepharospasm subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Dry eye subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Eye pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Vision blurred subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	0 / 5 (0.00%) 0	2 / 21 (9.52%) 3
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	2 / 5 (40.00%) 2	2 / 21 (9.52%) 2
Abdominal distension subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Abdominal pain subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 5	1 / 5 (20.00%) 1	3 / 21 (14.29%) 3
Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 5 (0.00%) 0	0 / 21 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Colitis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Constipation subjects affected / exposed occurrences (all)	5 / 12 (41.67%) 7	4 / 5 (80.00%) 5	5 / 21 (23.81%) 7
Diarrhoea			

subjects affected / exposed	7 / 12 (58.33%)	2 / 5 (40.00%)	11 / 21 (52.38%)
occurrences (all)	14	3	22
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	3 / 12 (25.00%)	3 / 5 (60.00%)	4 / 21 (19.05%)
occurrences (all)	6	5	5
Epigastric discomfort			
subjects affected / exposed	2 / 12 (16.67%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Eructation			
subjects affected / exposed	2 / 12 (16.67%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Gastritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Melaena			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Nausea			

subjects affected / exposed	10 / 12 (83.33%)	4 / 5 (80.00%)	12 / 21 (57.14%)
occurrences (all)	17	7	24
Lip pruritus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Malabsorption			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Oesophageal fistula			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Oesophageal ulcer			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Oesophagitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Pancreatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Retching			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Salivary hypersecretion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Sensitivity of teeth			

subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Steatorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Tongue coated			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	11 / 12 (91.67%)	2 / 5 (40.00%)	8 / 21 (38.10%)
occurrences (all)	15	11	14
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Hyperbilirubinaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Dermatitis psoriasiform			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	2 / 12 (16.67%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences (all)	5	1	1
Erythema			

subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Onycholysis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	5 / 21 (23.81%)
occurrences (all)	2	0	8
Pigmentation disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	5 / 21 (23.81%)
occurrences (all)	0	0	7
Pruritus generalised			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Rash			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	3 / 21 (14.29%)
occurrences (all)	0	1	3
Rash generalised			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Rash macular			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Rash maculo-papular			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Rash pruritic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1

Swelling face subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 5 (0.00%) 0	0 / 21 (0.00%) 0
Systemic lupus erythematosus rash subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 5 (0.00%) 0	0 / 21 (0.00%) 0
Endocrine disorders			
Hyperthyroidism subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 5 (20.00%) 1	0 / 21 (0.00%) 0
Hypothyroidism subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	1 / 5 (20.00%) 1	0 / 21 (0.00%) 0
Adrenal insufficiency subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 5 (0.00%) 0	2 / 21 (9.52%) 2
Arthritis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 5 (0.00%) 0	0 / 21 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 4	0 / 5 (0.00%) 0	2 / 21 (9.52%) 2
Flank pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 5 (0.00%) 0	0 / 21 (0.00%) 0
Jaw disorder subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 5 (0.00%) 0	1 / 21 (4.76%) 1
Limb discomfort subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 5 (0.00%) 0	0 / 21 (0.00%) 0
Muscle spasms			

subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	1 / 12 (8.33%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences (all)	1	2	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	2 / 21 (9.52%)
occurrences (all)	0	1	3
Musculoskeletal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Myopathy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pain in jaw			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Balanitis candida			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1

Cystitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Localised infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	4 / 21 (19.05%)
occurrences (all)	0	0	4
Medical device site infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nail infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Oesophageal candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	3 / 12 (25.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	3	0	1
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1

Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Rhinitis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 5 (40.00%)	1 / 21 (4.76%)
occurrences (all)	0	2	2
Skin infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	3
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Wound infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 12 (16.67%)	3 / 5 (60.00%)	3 / 21 (14.29%)
occurrences (all)	2	6	4
Dehydration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Diabetes mellitus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Gout			

subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	2
Hypocalcaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	2 / 12 (16.67%)	1 / 5 (20.00%)	1 / 21 (4.76%)
occurrences (all)	4	1	1
Hypomagnesaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Hypophosphataemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Iron deficiency			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1

Non-serious adverse events	Cohort C	Cohort C-FLOT	Cohort D/D2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)	9 / 9 (100.00%)	15 / 15 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			

subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 2
Skin papilloma subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Tumour pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Vascular disorders			
Deep vein thrombosis subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Flushing subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Hypotension subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Orthostatic hypotension subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Phlebitis subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Chest discomfort subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Chest pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	2 / 15 (13.33%) 2
Chills			

subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Early satiety			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	7 / 11 (63.64%)	6 / 9 (66.67%)	8 / 15 (53.33%)
occurrences (all)	17	11	18
Feeling cold			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Influenza like illness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Infusion site reaction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Mucosal inflammation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 9 (22.22%)	0 / 15 (0.00%)
occurrences (all)	0	3	0
Temperature intolerance			
subjects affected / exposed	3 / 11 (27.27%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	3	0	0
Respiratory, thoracic and mediastinal			

disorders			
Cough			
subjects affected / exposed	6 / 11 (54.55%)	2 / 9 (22.22%)	5 / 15 (33.33%)
occurrences (all)	6	2	6
Dyspnoea			
subjects affected / exposed	3 / 11 (27.27%)	1 / 9 (11.11%)	3 / 15 (20.00%)
occurrences (all)	3	1	3
Dyspnoea exertional			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	2
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Laryngospasm			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	2
Productive cough			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Upper-airway cough syndrome			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Confusional state			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	3
Irritability			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	2
Amylase increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Blood iron decreased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Blood magnesium decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Blood thyroid stimulating hormone decreased			

subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Blood urea increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 9 (22.22%) 2	0 / 15 (0.00%) 0
C-reactive protein increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	0 / 15 (0.00%) 0
Lipase increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 2	0 / 15 (0.00%) 0
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Transaminases increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 3	0 / 9 (0.00%) 0	4 / 15 (26.67%) 8
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Dumping syndrome subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	3 / 15 (20.00%) 4
Fall			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Infusion related reaction			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	2
Tooth fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Wound complication			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Wound haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	0	1	2
Dizziness postural			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	3	1	1
Dysaesthesia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	2 / 11 (18.18%)	3 / 9 (33.33%)	1 / 15 (6.67%)
occurrences (all)	4	3	1
Head discomfort			

subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	1	1	2
Lethargy			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Muscle contractions involuntary			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	6 / 11 (54.55%)	4 / 9 (44.44%)	0 / 15 (0.00%)
occurrences (all)	11	6	0
Paraesthesia			
subjects affected / exposed	3 / 11 (27.27%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	3	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Poor quality sleep			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Presyncope			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Sciatica			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	2 / 11 (18.18%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	2	0	1
Tremor			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	3 / 9 (33.33%) 3	5 / 15 (33.33%) 6
Neutropenia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 9 (22.22%) 3	3 / 15 (20.00%) 3
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	2 / 15 (13.33%) 2
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Eye disorders Blepharospasm subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Dry eye subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Eye pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Abdominal distension subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 9 (11.11%) 2	2 / 15 (13.33%) 3
Abdominal pain lower			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	2 / 11 (18.18%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	2	2	2
Colitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 11 (9.09%)	4 / 9 (44.44%)	5 / 15 (33.33%)
occurrences (all)	1	5	5
Diarrhoea			
subjects affected / exposed	5 / 11 (45.45%)	7 / 9 (77.78%)	10 / 15 (66.67%)
occurrences (all)	13	11	27
Dyspepsia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 9 (22.22%)	4 / 15 (26.67%)
occurrences (all)	0	4	5
Dry mouth			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	3	1	1
Dysphagia			
subjects affected / exposed	1 / 11 (9.09%)	3 / 9 (33.33%)	3 / 15 (20.00%)
occurrences (all)	2	4	4
Epigastric discomfort			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Eructation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	3
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 11 (36.36%)	3 / 9 (33.33%)	3 / 15 (20.00%)
occurrences (all)	5	4	4
Haemorrhoidal haemorrhage			

subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Melaena			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	5 / 11 (45.45%)	5 / 9 (55.56%)	9 / 15 (60.00%)
occurrences (all)	6	6	17
Lip pruritus			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Malabsorption			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Odynophagia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Oesophageal fistula			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Oesophageal ulcer			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Oesophagitis			
subjects affected / exposed	0 / 11 (0.00%)	2 / 9 (22.22%)	5 / 15 (33.33%)
occurrences (all)	0	2	6
Oral pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Pancreatitis			

subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Retching			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Salivary hypersecretion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Sensitivity of teeth			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Steatorrhoea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Tongue coated			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	1 / 11 (9.09%)	3 / 9 (33.33%)	6 / 15 (40.00%)
occurrences (all)	1	3	8
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Dermatitis acneiform			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Dermatitis psoriasiform			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Onycholysis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Pigmentation disorder			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	2 / 11 (18.18%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	2	1	4
Pruritus generalised			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 11 (0.00%)	4 / 9 (44.44%)	5 / 15 (33.33%)
occurrences (all)	0	4	6

Rash generalised subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Rash macular subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	0 / 15 (0.00%) 0
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Rash pruritic subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Swelling face subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Systemic lupus erythematosus rash subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Endocrine disorders			
Hyperthyroidism subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 9 (11.11%) 1	1 / 15 (6.67%) 1
Hypothyroidism subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 9 (11.11%) 2	1 / 15 (6.67%) 2
Adrenal insufficiency subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 15 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 9 (11.11%) 1	1 / 15 (6.67%) 1
Arthritis subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 15 (6.67%) 1
Back pain			

subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Flank pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Jaw disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Limb discomfort			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Muscle spasms			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 11 (0.00%)	2 / 9 (22.22%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	2 / 15 (13.33%)
occurrences (all)	0	3	2
Musculoskeletal stiffness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Myopathy			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Osteoporosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			

subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	3	1	0
Pain in jaw			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Infections and infestations			
Balanitis candida			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Localised infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Lower respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Medical device site infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Nail infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

Nasopharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Oesophageal candidiasis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	1 / 11 (9.09%)	2 / 9 (22.22%)	2 / 15 (13.33%)
occurrences (all)	1	2	2
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	2 / 11 (18.18%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Urinary tract infection			
subjects affected / exposed	2 / 11 (18.18%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	2	1	1
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Wound infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 11 (18.18%)	5 / 9 (55.56%)	5 / 15 (33.33%)
occurrences (all)	2	6	12
Dehydration			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Diabetes mellitus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Gout			
subjects affected / exposed	1 / 11 (9.09%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Hypoglycaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 9 (11.11%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 9 (22.22%)	3 / 15 (20.00%)
occurrences (all)	0	2	3
Hypomagnesaemia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 9 (11.11%)	1 / 15 (6.67%)
occurrences (all)	1	1	1
Hyponatraemia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 9 (22.22%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Hypophosphataemia			

subjects affected / exposed	1 / 11 (9.09%)	2 / 9 (22.22%)	2 / 15 (13.33%)
occurrences (all)	1	2	2
Iron deficiency			
subjects affected / exposed	0 / 11 (0.00%)	0 / 9 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2017	Change to treatment regimen in Cohort D (neoadjuvant chemoradiotherapy before surgery in operable oesophageal cancer): The oxaliplatin-capecitabine backbone of the CRT regimen was replaced with a paclitaxel/carboplatin regimen.
08 September 2017	<p>Additional requirements for carboplatin and paclitaxel treatment.</p> <p>Women of childbearing potential should avoid becoming pregnant while taking carboplatin and paclitaxel; they should notify the treating physician immediately if pregnancy occurs. Female and male subjects of fertile age and/or their partners should use contraceptives during and for at least 6 months after treatment with these drugs.</p> <p>Male subjects should also avoid sperm donation during and for at least 6 months after treatment with these drugs.</p> <p>Breastfeeding should be discontinued for the duration of treatment with these drugs.</p> <p>Male subjects should be advised regarding cryoconservation of sperm prior to treatment because of the possibility of irreversible infertility due to the treatment.</p> <p>CYP2C8 or CYP3A4 inhibitors/inducers: Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.</p> <p>Nephrotoxic/ototoxic drugs: Auditory defects have been reported during carboplatin therapy. Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin and diuretics is not recommended as they may increase or exacerbate toxicity, particularly in renal failure patients, due to carboplatin induced changes in renal clearance.</p>
10 March 2018	<p>The eligibility criteria have been amended to exclude patients who have received prior full dose chemotherapy, this enables collection of a pre-treatment biopsy for the planned biomarker analysis (tertiary endpoint). This eligibility criteria was originally included in the protocol and was removed from the protocol in error during a previous protocol amendment.</p> <p>Elevations of amylase and lipase are expected adverse events for durvalumab or the combination of durvalumab and tremelimumab and the study requires regular testing of both as potential indicators of pancreatitis. The dose limiting toxicity definitions have been clarified to exclude grade 3+ asymptomatic increases in amylase or lipase, which show no clinical evidence of pancreatitis. Grade 3+ pancreatitis remains a dose limiting toxicity.</p> <p>Expected adverse events have been added to the protocol, based on the durvalumab and tremelimumab dose modifications guidelines (updated Nov 2017). The events added are myocarditis (previously listed under 'other inflammatory responses'), myositis/polymyositis and some new events added to 'other inflammatory responses'.</p> <p>Clarification has been added to indicate that surgery timing is according to institutional policies. The study was initially set-up as a single site study and the 6-8 weeks post treatment timeframe for surgery was as per standard of care at that site alone. Surgery may be delayed at any site as per clinical need.</p>

20 July 2018	<p>The chemotherapy backbone administered in Cohort C was updated due to changes in standard of care treatment in the UK. The new cohort was referred to as Cohort C-FLOT which is a regimen combining 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and docetaxel.</p> <p>Based on emerging data, a proposal was made to add Cohort C-FLOT to the study, in addition to Cohort C. The proposal for Cohort C-FLOT includes the following:</p> <ol style="list-style-type: none"> 1. Replace Oxaliplatin and capecitabine as neoadjuvant chemotherapy with the FLOT regimen to run concurrently with durvalumab treatment. 2. Introduce post-operative chemotherapy, also with FLOT. This will run concurrently with durvalumab immunotherapy. 3. Subjects allocated to oxaliplatin and capecitabine in Cohort C before the introduction of Cohort C-FLOT will not be replaced and will be included in the total 20 Subjects for Cohort C + Cohort C-FLOT. <p>The protocol will now include the collection of saliva samples for translational research at the same time point as the research biopsy (3 timepoints, baseline, immunotherapy only D22 and at end of treatment/day of surgery).</p> <p>Patients will be asked to consent to use of photographs of their alimentary tract taken during the biopsy procedure.</p> <p>Videos are taken as standard of care of the biopsy for quality improvement and still pictures may also be taken as part of this procedure. These pictures will not be identifiable. Current patients may also be reconsented. This is an optional consent.</p>
26 April 2019	<p>The Investigator(s) had the option to approach subjects with long-term survival (PFS > 1 year, still in remission) from the metastatic cohorts (A and B) of the trial to request blood (up to 300 mL) for additional testing.</p> <p>Introduction of Cohort D2</p> <p>Cohort D2 is a subset of Cohort D subjects for whom durvalumab doses will continue during chemoradiotherapy, after the initial 4-week immunotherapy period. Enrollment was to proceed to Cohort D2, unless there was a medical reason to enroll a specific subject to Cohort D.</p>
11 January 2022	<p>The Post Study Follow-up for the collection of survival data was discontinued as of 30 June 2022. As of 30 June 2022, all subjects had completed treatment and On Study Follow-up and all but up to 8 subjects had completed the 3-year Post Study Follow-up, which would have occurred by December 2022 for the remaining subjects.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported