

**Clinical trial results:****A PROSPECTIVE RANDOMIZED, OPEN-LABEL PHASE 2 STUDY OF IMMUNE CHECKPOINT INHIBITION, NIVOLUMAB WITH OR WITHOUT IPIILIMUMAB IN COMBINATION WITH RADIATION THERAPY IN PRETREATED PATIENTS WITH METASTATIC PANCREATIC CANCER OR BILIARY TRACT CANCER****Summary**

EudraCT number	2016-001883-12
Trial protocol	DK
Global end of trial date	09 November 2022

Results information

Result version number	v1 (current)
This version publication date	08 November 2023
First version publication date	08 November 2023

Trial information**Trial identification**

Sponsor protocol code	GI1616
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02866383
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Herlev and Gentofte Hospital, Department of Oncology
Sponsor organisation address	Borgmester Ib Juuls Vej 1, Herlev, Denmark, 2730
Public contact	Principal investigator Inna Chen, Oncology dept. Herlev & Gentofte Hospital, +45 38682898, inna.chen@regionh.dk
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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	09 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 November 2022
Global end of trial reached?	Yes
Global end of trial date	09 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical benefit rate of immune checkpoint inhibition, ipilimumab and/or nivolumab in combination with RT

Protection of trial subjects:

Patients that signed informed consent and fulfilling eligibility criteria were included. Continued monitoring of standard safety parameters during treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 November 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	Denmark: 145
Worldwide total number of subjects	145
EEA total number of subjects	145

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)	75
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was open for recruitment of patients with pancreatic cancer from November 2016 to November 2019. Recruitment of patients with biliary tract cancer was open from September 2018 to January 2022. All patients are recruited at a single site: Copenhagen University Hospital - Herlev and Gentofte in Denmark

Pre-assignment

Screening details:

Eligible patients were ≥ 18 years with metastatic pancreatic or biliary tract cancer, who had received ≥ 1 line of prior systemic chemotherapy, ECOG PS 0-1, mGPS ≥ 1 , with at least two tumor lesions (one amenable to radiotherapy and one qualified as measurable per RECIST 1.1) and adequate organ and hematologic function

Period 1

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

Blinding implementation details:

NB separate randomisation to one of the treatment arms for the 2 patient groups, i.e. pancreatic cancer (PC) and biliary tract cancer (BTC). For each arm Simon 2 stage design was used to decide if arm should continue recruitment. For PC both arms continued recruitment in stage 2, whereas for BTC treatment in arm A (SBRT + Nivolumab) was discontinued at stage 1 -thereafter recruitment continued for BTC arm B (SBRT + Nivolumab+ Ipilimumab) without randomisation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pancreatic Cancer Arm A: SBRT + Nivolumab

Arm description:

Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab was administered at 3 mg/kg over 60 minutes as an IV infusion on day 1 just after RT and then every 2 weeks (q2w), for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment

Arm title	Pancreatic Cancer Arm B: SBRT + Nivolumab + Ipilimumab
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Arm description:

Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w and ipilimumab 1 mg/kg q6w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment

Arm type	Experimental
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Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab was administrated at 3 mg/kg over 60 minutes as an IV infusion on day 1 just after RT and then every 2 weeks (q2w), for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab was administrated at 1 mg/kg over 90 minutes as an IV infusion on day 1 (30 min after completion of nivolumab infusion) and then every 6 weeks (q6w), for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment

Arm title	Biliary Tract Cancer Arm A: SBRT + Nivolumab
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Arm description:

Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab was administrated at 3 mg/kg over 60 minutes as an IV infusion on day 1 just after RT and then every 2 weeks (q2w), for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment

Arm title	Biliary Tract Cancer Arm B: SBRT + Nivolumab +Ipilimumab
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Arm description:

Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w and ipilimumab 1 mg/kg q6w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab was administrated at 3 mg/kg over 60 minutes as an IV infusion on day 1 just after RT and then every 2 weeks (q2w), for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion

Routes of administration	Intravenous use
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Dosage and administration details:

Ipilimumab was administered at 1 mg/kg over 90 minutes as an IV infusion on day 1 (30 min after completion of nivolumab infusion) and then every 6 weeks (q6w), for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment

Number of subjects in period 1	Pancreatic Cancer Arm A: SBRT + Nivolumab	Pancreatic Cancer Arm B: SBRT + Nivolumab + Ipilimumab	Biliary Tract Cancer Arm A: SBRT + Nivolumab
	Started	41	43
Completed	38	38	19
Not completed	3	5	0
Adverse event, serious fatal	-	-	-
Adverse event, non-fatal	1	3	-
Death from malignant disease under study	2	2	-

Number of subjects in period 1	Biliary Tract Cancer Arm B: SBRT + Nivolumab +Ipilimumab
Started	42
Completed	35
Not completed	7
Adverse event, serious fatal	2
Adverse event, non-fatal	5
Death from malignant disease under study	-

Baseline characteristics

Reporting groups

Reporting group title	Pancreatic Cancer Arm A: SBRT + Nivolumab
Reporting group description: Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment	
Reporting group title	Pancreatic Cancer Arm B: SBRT + Nivolumab + Ipilimumab
Reporting group description: Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w and ipilimumab 1 mg/kg q6w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment	
Reporting group title	Biliary Tract Cancer Arm A: SBRT + Nivolumab
Reporting group description: Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment	
Reporting group title	Biliary Tract Cancer Arm B: SBRT + Nivolumab +Ipilimumab
Reporting group description: Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w and ipilimumab 1 mg/kg q6w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment	

Reporting group values	Pancreatic Cancer Arm A: SBRT + Nivolumab	Pancreatic Cancer Arm B: SBRT + Nivolumab + Ipilimumab	Biliary Tract Cancer Arm A: SBRT + Nivolumab
Number of subjects	41	43	19
Age categorical Units: Subjects			
Adults (18-64 years)	25	18	8
From 65-84 years	16	25	11
Age continuous Units: years			
median	63	66	66
full range (min-max)	37 to 80	35 to 79	46 to 76
Gender categorical Units: Subjects			
Female	19	21	11
Male	22	22	8
ECOG Performance status Units: Subjects			
PS 0	21	20	9
PS 1	20	23	10
Prior resection of primary tumor Units: Subjects			
Yes	10	9	4
No	31	34	15

Number of metastatic sites Units: Subjects			
=1	13	11	7
=2	17	17	4
>=3	11	15	8
Number of previous treatment lines Units: Subjects			
=1	19	21	17
=>2	22	22	2

Reporting group values	Biliary Tract Cancer Arm B: SBRT + Nivolumab +Ipilimumab	Total	
Number of subjects	42	145	
Age categorical Units: Subjects			
Adults (18-64 years)	24	75	
From 65-84 years	18	70	
Age continuous Units: years			
median	59		
full range (min-max)	34 to 81	-	
Gender categorical Units: Subjects			
Female	23	74	
Male	19	71	
ECOG Performance status Units: Subjects			
PS 0	24	74	
PS 1	18	71	
Prior resection of primary tumor Units: Subjects			
Yes	9	32	
No	33	113	
Number of metastatic sites Units: Subjects			
=1	6	37	
=2	14	52	
>=3	22	56	
Number of previous treatment lines Units: Subjects			
=1	30	87	
=>2	12	58	

End points

End points reporting groups

Reporting group title	Pancreatic Cancer Arm A: SBRT + Nivolumab
Reporting group description: Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment	
Reporting group title	Pancreatic Cancer Arm B: SBRT + Nivolumab + Ipilimumab
Reporting group description: Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w and ipilimumab 1 mg/kg q6w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment	
Reporting group title	Biliary Tract Cancer Arm A: SBRT + Nivolumab
Reporting group description: Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment	
Reporting group title	Biliary Tract Cancer Arm B: SBRT + Nivolumab +Ipilimumab
Reporting group description: Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w and ipilimumab 1 mg/kg q6w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment	

Primary: Clinical Benefit Rate

End point title	Clinical Benefit Rate ^[1]
End point description: clinical benefit rate (CBR), defined as the percentage of patients with stable disease (SD), partial response (PR), or complete response (CR) according to RECIST 1.1	
End point type	Primary
End point timeframe: Tumor assessments were performed every 8 weeks until progression	

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: The study includes 2 patient populations analysed independently. Within each population, the study was not designed to compare treatment arms A and B, but each arm had the same Simon two-stage design to evaluate efficacy/recommendation for further investigation of the treatment.

End point values	Pancreatic Cancer Arm A: SBRT + Nivolumab	Pancreatic Cancer Arm B: SBRT + Nivolumab + Ipilimumab	Biliary Tract Cancer Arm A: SBRT + Nivolumab	Biliary Tract Cancer Arm B: SBRT + Nivolumab +Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	43	19	42
Units: percent				
number (confidence interval 95%)	17.1 (8 to 30.6)	37.2 (24 to 52.1)	10.5 (1.3 to 33.1)	31 (17.6 to 47.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title | Objective response rate

End point description:

Objective response rate (ORR), defined as the percentage of patients with partial response (PR), or complete response (CR) according to RECIST 1.1

End point type | Secondary

End point timeframe:

Tumor assessments were done every 8 weeks until progression of disease

End point values	Pancreatic Cancer Arm A: SBRT + Nivolumab	Pancreatic Cancer Arm B: SBRT + Nivolumab + Ipilimumab	Biliary Tract Cancer Arm A: SBRT + Nivolumab	Biliary Tract Cancer Arm B: SBRT + Nivolumab + Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	43	19	42
Units: percent				
number (confidence interval 95%)	2.4 (0.3 to 10.8)	14 (6 to 26.5)	0 (0 to 17.6)	11.9 (4 to 25.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response

End point title | Best overall response

End point description:

End point type | Secondary

End point timeframe:

Tumor assessments were done every 8 weeks until progression of disease

End point values	Pancreatic Cancer Arm A: SBRT + Nivolumab	Pancreatic Cancer Arm B: SBRT + Nivolumab + Ipilimumab	Biliary Tract Cancer Arm A: SBRT + Nivolumab	Biliary Tract Cancer Arm B: SBRT + Nivolumab + Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	43	19	42
Units: subjects				
Partial response	1	6	0	5
Stable disease	6	10	2	8
Progressive disease	28	23	17	23
Not evaluable/no post-baseline assessment	6	4	0	6

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival
End point description:	PFS is the time from randomisation to radiological progression or death
End point type	Secondary
End point timeframe:	time from randomisation to radiological progression or death

End point values	Pancreatic Cancer Arm A: SBRT + Nivolumab	Pancreatic Cancer Arm B: SBRT + Nivolumab + Ipilimumab	Biliary Tract Cancer Arm A: SBRT + Nivolumab	Biliary Tract Cancer Arm B: SBRT + Nivolumab + Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	43	19	42
Units: months				
median (confidence interval 95%)	1.7 (1.7 to 1.8)	1.6 (1.6 to 2.8)	1.7 (1.6 to 1.9)	1.7 (1.6 to 1.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
End point description:	
End point type	Secondary

End point timeframe:
Time from randomisation to death

End point values	Pancreatic Cancer Arm A: SBRT + Nivolumab	Pancreatic Cancer Arm B: SBRT + Nivolumab + Ipilimumab	Biliary Tract Cancer Arm A: SBRT + Nivolumab	Biliary Tract Cancer Arm B: SBRT + Nivolumab + Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	43	19	42
Units: months				
median (confidence interval 95%)	3.8 (3.1 to 5.8)	3.8 (2.8 to 6.5)	4.7 (3.8 to 8.5)	5.4 (3.8 to 8.8)

Statistical analyses

No statistical analyses for this end point

Secondary: OS rate at 1 year

End point title OS rate at 1 year

End point description:

End point type Secondary

End point timeframe:

1 year from randomisation

End point values	Pancreatic Cancer Arm A: SBRT + Nivolumab	Pancreatic Cancer Arm B: SBRT + Nivolumab + Ipilimumab	Biliary Tract Cancer Arm A: SBRT + Nivolumab	Biliary Tract Cancer Arm B: SBRT + Nivolumab + Ipilimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	43	19	42
Units: percent				
number (confidence interval 95%)	7.3 (2.5 to 21.8)	14 (6.6 to 29.3)	5.1 (0.4 to 21.4)	16.7 (7.3 to 29.3)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE were collected from initiation of study treatment until 100 days after discontinuation of dosing or until starting a new anti-neoplastic therapy (whichever occurred first)

Adverse event reporting additional description:

For non-serious AE section, only AEs with causal relationship to treatment (AR) are listed (numbers includes subjects/occurrences reported as SARs as well).

Assessment type	Systematic
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Dictionary used

Dictionary name	NCI-CTCAE
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Dictionary version	4
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Reporting groups

Reporting group title	Pancreatic Cancer Arm A: SBRT + Nivolumab
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Reporting group description:

Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment

Reporting group title	Pancreatic Cancer Arm B: SBRT + Nivolumab + Ipilimumab
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Reporting group description:

Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w and ipilimumab 1 mg/kg q6w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment

Reporting group title	Biliary Tract Cancer Arm A: SBRT + Nivolumab
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Reporting group description:

Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment

Reporting group title	Biliary Tract Cancer Arm B: SBRT + Nivolumab +Ipilimumab
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Reporting group description:

Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle, followed by nivolumab 3 mg/kg q2w and ipilimumab 1 mg/kg q6w for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or clear clinical deterioration, according to investigator's judgment

Serious adverse events	Pancreatic Cancer Arm A: SBRT + Nivolumab	Pancreatic Cancer Arm B: SBRT + Nivolumab + Ipilimumab	Biliary Tract Cancer Arm A: SBRT + Nivolumab
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 41 (43.90%)	24 / 43 (55.81%)	4 / 19 (21.05%)
number of deaths (all causes)	40	40	19
number of deaths resulting from adverse events	0	1	0
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 19 (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
thromboembolic event			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 19 (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			
Back pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 19 (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
Fever			
subjects affected / exposed	0 / 41 (0.00%)	2 / 43 (4.65%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tumor fever			
subjects affected / exposed	0 / 41 (0.00%)	0 / 43 (0.00%)	0 / 19 (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
Pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 43 (0.00%)	0 / 19 (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, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 41 (4.88%)	0 / 43 (0.00%)	0 / 19 (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
Pneumonia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 43 (4.65%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Haematoma	Additional description: liver haematoma after biopsy		
subjects affected / exposed	0 / 41 (0.00%)	0 / 43 (0.00%)	0 / 19 (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			
Cardiac failure			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 19 (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
Myocarditis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 19 (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
Myocardial infarction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 43 (0.00%)	0 / 19 (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			
Cerebral infarction			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 19 (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
Syncope			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 19 (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
Cerebral ischaemia			

subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 19 (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
Guillain-Barre syndrome			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 19 (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
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 19 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 41 (12.20%)	1 / 43 (2.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 19 (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
Colitis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 43 (4.65%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 41 (2.44%)	1 / 43 (2.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	1 / 41 (2.44%)	3 / 43 (6.98%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	2 / 43 (4.65%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 19 (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
Vomiting			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 19 (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
Oesophageal varices			
subjects affected / exposed	0 / 41 (0.00%)	0 / 43 (0.00%)	0 / 19 (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			
Biliary tract infection			
subjects affected / exposed	2 / 41 (4.88%)	0 / 43 (0.00%)	0 / 19 (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
Cholestasis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 19 (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
Hepatitis			

subjects affected / exposed	0 / 41 (0.00%)	0 / 43 (0.00%)	0 / 19 (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
Skin and subcutaneous tissue disorders			
erythroderma			
subjects affected / exposed	0 / 41 (0.00%)	0 / 43 (0.00%)	0 / 19 (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			
Hydronephrosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 43 (0.00%)	0 / 19 (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
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 41 (0.00%)	2 / 43 (4.65%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 19 (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
Infections and infestations			
Liver abscess			
subjects affected / exposed	1 / 41 (2.44%)	1 / 43 (2.33%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection unknown focus			
subjects affected / exposed	0 / 41 (0.00%)	2 / 43 (4.65%)	3 / 19 (15.79%)
occurrences causally related to treatment / all	0 / 0	0 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine abscess			

subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 19 (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
Endocarditis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 19 (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
Sepsis			
subjects affected / exposed	4 / 41 (9.76%)	3 / 43 (6.98%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 7	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 19 (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 / 41 (2.44%)	2 / 43 (4.65%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	0 / 41 (0.00%)	0 / 43 (0.00%)	0 / 19 (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
myelomeningoradiculitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 43 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 19 (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
Hypoglycaemia			

subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	0 / 19 (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

Serious adverse events	Biliary Tract Cancer Arm B: SBRT + Nivolumab +Ipilimumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 42 (38.10%)		
number of deaths (all causes)	38		
number of deaths resulting from adverse events	2		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
thromboembolic event			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Back pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fever			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
tumor fever			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Haematoma		Additional description: liver haematoma after biopsy	
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocarditis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Guillain-Barre syndrome			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric perforation			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal varices			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary tract infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholestasis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Skin and subcutaneous tissue disorders			
erythroderma			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypophysitis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Liver abscess			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection unknown focus			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Uterine abscess			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis bacterial			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
myelomeningoradiculitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pancreatic Cancer Arm A: SBRT + Nivolumab	Pancreatic Cancer Arm B: SBRT + Nivolumab + Ipilimumab	Biliary Tract Cancer Arm A: SBRT + Nivolumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 41 (100.00%)	41 / 43 (95.35%)	19 / 19 (100.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 41 (4.88%)	4 / 43 (9.30%)	0 / 19 (0.00%)
occurrences (all)	5	9	0
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 41 (9.76%)	4 / 43 (9.30%)	0 / 19 (0.00%)
occurrences (all)	9	10	0

Alkaline phosphatase increased subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 5	3 / 43 (6.98%) 4	0 / 19 (0.00%) 0
Hyperbilirubinaemia subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	0 / 43 (0.00%) 0	0 / 19 (0.00%) 0
Blood TSH increased subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	1 / 43 (2.33%) 1	0 / 19 (0.00%) 0
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	9 / 41 (21.95%) 13	8 / 43 (18.60%) 13	2 / 19 (10.53%) 2
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3	6 / 43 (13.95%) 11	1 / 19 (5.26%) 1
Headache subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3	4 / 43 (9.30%) 12	1 / 19 (5.26%) 1
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	12 / 41 (29.27%) 19	14 / 43 (32.56%) 25	5 / 19 (26.32%) 8
Fever subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 3	10 / 43 (23.26%) 13	2 / 19 (10.53%) 2
Chills subjects affected / exposed occurrences (all)	8 / 41 (19.51%) 9	6 / 43 (13.95%) 7	0 / 19 (0.00%) 0
Pain subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 4	2 / 43 (4.65%) 3	0 / 19 (0.00%) 0
Flu like symptoms subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	1 / 43 (2.33%) 2	0 / 19 (0.00%) 0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 41 (4.88%)	3 / 43 (6.98%)	0 / 19 (0.00%)
occurrences (all)	2	3	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 41 (2.44%)	3 / 43 (6.98%)	1 / 19 (5.26%)
occurrences (all)	3	6	1
Dry mouth			
subjects affected / exposed	1 / 41 (2.44%)	3 / 43 (6.98%)	1 / 19 (5.26%)
occurrences (all)	1	6	1
Nausea			
subjects affected / exposed	9 / 41 (21.95%)	14 / 43 (32.56%)	4 / 19 (21.05%)
occurrences (all)	11	26	6
Vomiting			
subjects affected / exposed	2 / 41 (4.88%)	7 / 43 (16.28%)	1 / 19 (5.26%)
occurrences (all)	2	9	1
Diarrhoea			
subjects affected / exposed	16 / 41 (39.02%)	15 / 43 (34.88%)	4 / 19 (21.05%)
occurrences (all)	18	38	5
Colitis			
subjects affected / exposed	2 / 41 (4.88%)	5 / 43 (11.63%)	1 / 19 (5.26%)
occurrences (all)	2	12	1
Pancreatitis			
subjects affected / exposed	3 / 41 (7.32%)	0 / 43 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 41 (2.44%)	1 / 43 (2.33%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			

Dry skin subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	3 / 43 (6.98%) 5	1 / 19 (5.26%) 1
Pruritus subjects affected / exposed occurrences (all)	10 / 41 (24.39%) 11	14 / 43 (32.56%) 25	2 / 19 (10.53%) 3
Rash subjects affected / exposed occurrences (all)	8 / 41 (19.51%) 11	9 / 43 (20.93%) 19	0 / 19 (0.00%) 0
Endocrine disorders			
Adrenal insufficiency subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 2	5 / 43 (11.63%) 8	0 / 19 (0.00%) 0
Hypothyroidism subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	3 / 43 (6.98%) 3	0 / 19 (0.00%) 0
Thyroiditis subjects affected / exposed occurrences (all)	7 / 41 (17.07%) 10	13 / 43 (30.23%) 18	7 / 19 (36.84%) 7
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 7	12 / 43 (27.91%) 25	5 / 19 (26.32%) 5
Myalgia subjects affected / exposed occurrences (all)	5 / 41 (12.20%) 7	7 / 43 (16.28%) 13	1 / 19 (5.26%) 1
Back pain subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 3	3 / 43 (6.98%) 4	2 / 19 (10.53%) 2
Metabolism and nutrition disorders			
Anorexia subjects affected / exposed occurrences (all)	6 / 41 (14.63%) 9	11 / 43 (25.58%) 13	2 / 19 (10.53%) 2

Non-serious adverse events	Biliary Tract Cancer Arm B: SBRT + Nivolumab +Ipilimumab		
Total subjects affected by non-serious			

adverse events			
subjects affected / exposed	42 / 42 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	12		
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 42 (19.05%)		
occurrences (all)	12		
Alkaline phosphatase increased			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	9		
Hyperbilirubinaemia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Blood TSH increased			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	4		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	5		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 42 (45.24%)		
occurrences (all)	30		
Fever			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		

Chills			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	7		
Pain			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Flu like symptoms			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	6		
Dry mouth			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	12 / 42 (28.57%)		
occurrences (all)	14		
Vomiting			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	10		
Diarrhoea			
subjects affected / exposed	13 / 42 (30.95%)		
occurrences (all)	18		
Colitis			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	8		
Pancreatitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 5		
Hepatobiliary disorders Hepatitis subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 3		
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 5 19 / 42 (45.24%) 35 19 / 42 (45.24%) 28		
Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all) Hypothyroidism subjects affected / exposed occurrences (all) Thyroiditis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1 0 / 42 (0.00%) 0 9 / 42 (21.43%) 13		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Back pain	12 / 42 (28.57%) 18 6 / 42 (14.29%) 10		

subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2016	Added biopsy at time of progressive disease, if feasible
26 March 2018	- expansion of the trial to patients with metastatic biliary tract cancer. Both target population to have their separate Arm A and Arm B, and Simon 2-stage design for each arm. Analyses for the two target populations to be done independently from each other.
04 December 2018	- Added fecal samples for translational research - Adjustment of study time lines
03 November 2019	Added Olink analysis in translational research.
12 March 2021	-Arm A for biliary tract cancer discontinued at the end of stage 1 according to Simon-2 stage design. - added intratumor microbiome and immune cell gene-expression profiling for translational research

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/35476508>