Clinical trial results:
Phase 2 study in pretreated patients with advanced pancreatic cancer to assess efficacy of ipilimumab, nivolumab and tocilizumab in combination with radiation.

Summary

EudraCT number	2019-004438-40
Trial protocol	DK
Global end of trial date	17 November 2021

Results information

Result version number	v1 (current)
This version publication date	25 October 2022
First version publication date	25 October 2022

Trial information

Trial identification

Sponsor protocol code	GI1950

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04258150
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of Oncology, Herlev & Gentofte Hospital
Sponsor organisation address	Borgmester Ib Juuls Vej 1, Herlev, Denmark, 2730
Public contact	PI Inna Chen, Department of Oncology, Herlev & Gentofte Hospital, +45 38682898, inna.chen@regionh.dk
Scientific contact	PI Inna Chen, Department of Oncology, Herlev & Gentofte Hospital, +45 38682898, inna.chen@regionh.dk

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	07 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 November 2021
Global end of trial reached?	Yes
Global end of trial date	17 November 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

For PART A LEAD IN : To assess the efficacy of ipilimumab, nivolumab and tocilizumab in combination with SBRT in terms of objective response rate (ORR).

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	17 April 2020
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: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	15
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was opened for recruitment in april 2020 and closed for enrollment in January 2021 . Patients were included at a single site, Herlev Hospital, Denmark.

Pre-assignment

Screening details:

Eligible patients were ≥ 18 years with locally advanced or metastatic pancreatic cancer, who had progressed during or after at least 1 line of chemotherapy in the advanced setting, ECOG PS 0-1, adequate organ and hematologic functions. Key exclusion criteria were active autoimmune disease and requirement for > 10 mg/d of prednisone or equivalent.

Period 1

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

Arms

Arm title	Ipilimumab, nivolumab, tocilizumab, and SBRT 15 Gy

Arm description:

Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle. Ipilimumab (1 mg/kg) was administered intravenously on day 1 and repeated once after 6 weeks. Nivolumab (6 mg/kg) and tocilizumab (8 mg/kg) were given intravenously on day 1 and every 4 weeks for up to one year or until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or clear clinical deterioration according to the investigator's judgment.

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

Dosage and administration details:

Tocilizumab 8 mg/kg was given IV on day 1 (± 3 days) over 1-hour, repeated every 4 weeks, for up to one year or until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or clear clinical deterioration according to the investigator's judgment.

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 6 mg/kg (up to 480 mg maximum) was given IV on day 1 (± 3 days) of each 28-day treatment cycle until the progression of disease or maximum of 48 weeks, discontinuation due to toxicity, withdrawal of consent.

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 (1 mg/kg) was administered intravenously on day 1 and repeated once after 6 weeks.

Number of subjects in period 1	Ipilimumab, nivolumab, tocilizumab, and SBRT 15 Gy
Started	26
Completed	23
Not completed	3
Adverse event, non-fatal	3

Baseline characteristics

Reporting groups

Reporting group title	Protocol Treatment

Reporting group description: -

Reporting group values	Protocol Treatment	Total	
Number of subjects	26	26	
Age categorical Units: Subjects			
Adults (18-64 years)	15	15	
From 65-84 years	11	11	
Age continuous Units: years			
median	62		
inter-quartile range (Q1-Q3)	54 to 71	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	16	16	
Previous Whipple procedure Units: Subjects			
Yes	7	7	
No	19	19	
Number of previous treatment lines Units: Subjects			
=1	5	5	
>=2	21	21	
ECOG Units: Subjects			
PS 0	14	14	
PS 1	12	12	

End points

End points reporting groups

Reporting group title	Ipilimumab, nivolumab, tocilizumab, and SBRT 15 Gy

Reporting group description:

Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle. Ipilimumab (1 mg/kg) was administered intravenously on day 1 and repeated once after 6 weeks. Nivolumab (6 mg/kg) and tocilizumab (8 mg/kg) were given intravenously on day 1 and every 4 weeks for up to one year or until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or clear clinical deterioration according to the investigator's judgment.

Primary: Objective response rate

End point title	Objective response rate[1]

End point description:

End point type	Primary

End point timeframe:

Tumor assessments were done every 8 weeks until progression of disease

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: Single arm study, not to be compared with historical data.

End point values	Ipilimumab, nivolumab, tocilizumab, and SBRT 15 Gy			
Subject group type	Reporting group			
Number of subjects analysed	23[2]			
Units: percent				
number (confidence interval 95%)	0 (0 to 13)			

Notes:

[2] - 3 patients without post-baseline imaging for tumorassessment

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate

End point title	Disease control rate

End point description:

End point type	Secondary

End point timeframe:

Tumor assessements were performed every 8 weeks until progression

End point values	Ipilimumab, nivolumab, tocilizumab, and SBRT 15 Gy			
Subject group type	Reporting group			
Number of subjects analysed	23[3]			
Units: percent				
number (confidence interval 95%)	19 (7 to 39)			

Notes:

[3] - 3 patients without post-baseline imaging available for tumor assessment

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response

End point title	Best overall response

End point description:

Best overall response according to RECIST 1.1

End point type	Secondary

End point timeframe:

Tumor assessment was performed every 8 weeks until progression of disease

End point values	Ipilimumab, nivolumab, tocilizumab, and SBRT 15 Gy			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: subjects				
Complete Response	0			
Partial response	0			
Stable disease	5			
Progressive disease	18			
No assessment available	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 occured first)

Adverse event reporting additional description:

All serious AE are reported. Non serious adverse event are reported if events were assessed with causal relationship to study treatment only.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	5

Reporting groups

Reporting group title	Ipilimumab, nivolumab, tocilizumab, and SBRT 15 Gy

Reporting group description:

Patients received SBRT of 15 Gy to a single primary or metastatic lesion administered on day 1 of the first cycle. Ipilimumab (1 mg/kg) was administered intravenously on day 1 and repeated once after 6 weeks. Nivolumab (6 mg/kg) and tocilizumab (8 mg/kg) were given intravenously on day 1 and every 4 weeks for up to one year or until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or clear clinical deterioration according to the investigator’s judgment.

Serious adverse events	Ipilimumab, nivolumab, tocilizumab, and SBRT 15 Gy		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 26 (23.08%)		
number of deaths (all causes)	25		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
haemorrhage after liverbiopsy			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Ipilimumab, nivolumab, tocilizumab, and SBRT 15 Gy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 26 (96.15%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	5		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	6		
Blood bilirubin increased			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 3		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Mucositis oral subjects affected / exposed occurrences (all)	 4 / 26 (15.38%) 5 2 / 26 (7.69%) 2 2 / 26 (7.69%) 2 4 / 26 (15.38%) 4		
Skin and subcutaneous tissue disorders Rash maculo-papular subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 7 / 26 (26.92%) 10 6 / 26 (23.08%) 7		
Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all) Hyperthyroidism subjects affected / exposed occurrences (all) Hypothyroidism subjects affected / exposed occurrences (all)	 2 / 26 (7.69%) 2 9 / 26 (34.62%) 10 3 / 26 (11.54%) 4		
Musculoskeletal and connective tissue disorders Arthralgia			

subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	 2 / 26 (7.69%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2020	- Number of biopsies per timepoint increased to up to three biopsies for additional translational analyses

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was prematurely ended as the predictive probarbility to meet efficacy gate (ORR 15%) was not given. A substantiel amendment was pre-planned to expand as either non-RCT or RCT depending on ORR observed in part A.

Notes: