



Clinical trial results:

Randomised phase 2 trial of stereotactic body radiation therapy, SBRT, in combination with checkpoint inhibitors in metastatic castration-resistant prostate cancer

Summary

EudraCT number	2018-003461-34
Trial protocol	DK
Global end of trial date	30 August 2024

Results information

Result version number	v1 (current)
This version publication date	06 August 2025
First version publication date	06 August 2025

Trial information

Trial identification

Sponsor protocol code	UR1840
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05655715
WHO universal trial number (UTN)	-
Other trial identifiers	BMS study number: CA209-8TY

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 Rikke Løvendahl Eefsen, Department of Oncology, Herlev & Gentofte Hospital, +45 3868 9381, rikke.helene.loevendahl.eefsen@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	19 November 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2024
Global end of trial reached?	Yes
Global end of trial date	30 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the response rate of immune checkpoint inhibition, ipilimumab and nivolumab in combination with SBRT and compare to combination immunotherapy with ipilimumab and nivolumab.

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	25 November 2019
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: 91
Worldwide total number of subjects	91
EEA total number of subjects	91

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)	19
From 65 to 84 years	72
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was open for recruitment of patients from November 2019 to Jan 2024. 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 castration-resistant prostate cancer Evidence of disease progression after prior therapy for mCRPC, ECOG PS 0-1, adequate organ and hematologic function.

(Pre-assignment section used to depicture patients initially included and randomised, but not started intervention)

Pre-assignment period milestones

Number of subjects started	91
Number of subjects completed	81

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Clinical deterioration: 10
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Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - SBRT + nivolumab and ipilimumab

Arm description:

Stereotactic body radiotherapy of 8 Gray (Gy) x 3 on one soft tissue or bone metastasis and immunotherapy

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 3 mg/kg every 3 weeks (q3w) for 4 cycles and in absence of disease progression continued with flat dosing 480 mg every 4 weeks (q4w).

Treatment in the trial continued until disease progression, unacceptable toxicity, withdrawal of consent or completion of 12 months of treatment, whichever occurred first.

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 (1mg/kg) was given every 3 weeks for a maximum of four cycles.

Arm title	Arm B - nivolumab and ipilimumab
Arm description: Immunotherapy	
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 3 mg/kg every 3 weeks (q3w) for 4 cycles and in absence of disease progression continued with flat dosing 480 mg every 4 weeks (q4w).

Treatment in the trial continued until disease progression, unacceptable toxicity, withdrawal of consent or completion of 12 months of treatment, whichever occurred first.

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 (1mg/kg) was given every 3 weeks for a maximum of four cycles.

Number of subjects in period 1^[1]	Arm A - SBRT + nivolumab and ipilimumab	Arm B - nivolumab and ipilimumab
Started	37	44
Completed	30	41
Not completed	7	3
Adverse event, non-fatal	7	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The difference in subjects is due to the fact that 10 subjects, that had been randomised (8 in arm A, 2 in arm B), did not start treatment - those are listed as non-completion in the pre-assignment period section.

Baseline characteristics

Reporting groups

Reporting group title	Arm A - SBRT + nivolumab and ipilimumab
Reporting group description: Stereotactic body radiotherapy of 8 Gray (Gy) x 3 on one soft tissue or bone metastasis and immunotherapy	
Reporting group title	Arm B - nivolumab and ipilimumab
Reporting group description: Immunotherapy	

Reporting group values	Arm A - SBRT + nivolumab and ipilimumab	Arm B - nivolumab and ipilimumab	Total
Number of subjects	37	44	81
Age categorical			
Units: Subjects			
Adults (18-64 years)	8	8	16
From 65-84 years	29	36	65
Age continuous			
Units: years			
median	72	73	
full range (min-max)	58 to 81	46 to 82	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	37	44	81
ECOG Performance status			
Units: Subjects			
PS 0	18	21	39
PS 1	19	23	42
Bone lesions at baseline			
Units: Subjects			
None	1	6	7
Less than 5	2	2	4
At least 5	34	36	70
Mesurable disease at baseline			
Mesurable disease as defined by RECIST version 1.1			
Units: Subjects			
Yes	24	36	60
No	13	8	21
Number of prior lines of systemic therapy for metastatic disease			
Units: Subjects			
< 3 lines	0	3	3
≥ 3 lines	37	41	78

End points

End points reporting groups

Reporting group title	Arm A - SBRT + nivolumab and ipilimumab
Reporting group description: Stereotactic body radiotherapy of 8 Gray (Gy) x 3 on one soft tissue or bone metastasis and immunotherapy	
Reporting group title	Arm B - nivolumab and ipilimumab
Reporting group description: Immunotherapy	

Primary: PSA response

End point title	PSA response ^[1]
End point description: Percentage of subjects achieving a $\geq 50\%$ decline in PSA from baseline at any time from treatment start (confirmed by another measurement after ≥ 3 weeks)	
End point type	Primary
End point timeframe: at any time from treatment start to end of treatment within study or prior to any further anti cancer treatment.	

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: See co-primary endpoint ORR . With PSA response achieved for $n \geq 8$ subjects in each of the treatment arms and a difference between arms is < 5 , both treatments pass the testing procedure. Both treatments have at least a certain number of responses, and the difference in response is small. Therefore, no claim can be made that one treatment is more efficacious than the other.

End point values	Arm A - SBRT + nivolumab and ipilimumab	Arm B - nivolumab and ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	44 ^[2]		
Units: percent				
number (confidence interval 95%)	21.6 (9.8 to 38.2)	20.5 (9.8 to 35.3)		

Notes:

[2] - 2 subjects with baseline PSA < 1

Statistical analyses

No statistical analyses for this end point

Primary: ORR

End point title	ORR ^[3]
End point description: Objective response-rate per modified RECIST1.1/PCWG3 for patients with measurable disease	
End point type	Primary
End point timeframe: Assessments were done every 8 weeks from treatment start to confirmation of progression of disease	

Notes:

[3] - 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 is not designed to directly compare arms, but based on a two-stage design for randomized phase II trials with two experimental treatment arms, with the following features: (1) the type I error rate and power within each arm are controlled in a fashion similar to that of a typical single-arm phase II anticancer trial; and (2) the probability of mistakenly selecting an inferior arm and the probability of correctly selecting a superior arm are controlled at prespecified levels.

End point values	Arm A - SBRT + nivolumab and ipilimumab	Arm B - nivolumab and ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24 ^[4]	36 ^[5]		
Units: percent				
number (confidence interval 95%)	16.7 (4.7 to 37.4)	22.2 (10.1 to 39.2)		

Notes:

[4] - subjects with measurable disease only

[5] - subjects with measurable disease only

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA progression

End point title	Time to PSA progression
End point description:	
Time to PSA progression is the time from treatment initiation until PSA progression defined as $\geq 25\%$ increase and $\geq 2\text{ng/ml}$ above the nadir 12 weeks after initiation of study treatment, confirmed ≥ 3 weeks later if there is a PSA decline from baseline	
End point type	Secondary
End point timeframe:	
PSA measurements were done every cycle (q3w or q4w) until end of study	

End point values	Arm A - SBRT + nivolumab and ipilimumab	Arm B - nivolumab and ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	42 ^[6]		
Units: months				
median (confidence interval 95%)	2.63 (1.94 to 3.81)	2.5 (1.97 to 2.99)		

Notes:

[6] - 2 patients not evaluable for PSA

Statistical analyses

No statistical analyses for this end point

Secondary: rPFS

End point title	rPFS
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End point description:

Time from treatment initiation to radiographic progression according to PCWG3 modified RECIST 1.1 or death.

End point type	Secondary
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End point timeframe:

Tumor assessments will be performed by CT scans/18F-NaF PET/CT scans every 8 weeks from treatment start to progression of disease

End point values	Arm A - SBRT + nivolumab and ipilimumab	Arm B - nivolumab and ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	44		
Units: month				
median (confidence interval 95%)	2.10 (1.91 to 3.81)	1.87 (1.84 to 2.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: OS

End point title	OS
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End point description:

End point type	Secondary
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End point timeframe:

from treatment initiation to death (includes at least 1 year of follow up for each subject without event)

End point values	Arm A - SBRT + nivolumab and ipilimumab	Arm B - nivolumab and ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	44		
Units: month				
median (confidence interval 95%)	10.2 (7.13 to 14.1)	9.2 (7.06 to 14.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: CBR

End point title	CBR
End point description:	
For patients with measurable disease, Clinical Benefit rate (CBR) is defined as CR, PR, stable disease (SD) for more than 6 months. For patients with evaluable disease based on bone lesions (non-measurable disease), CBR includes those patients that had non-progressive disease documented in 3 or more assessments.	
End point type	Secondary
End point timeframe:	
Assessments were done every 8 weeks from treatment start to confirmation of progression of disease.	

End point values	Arm A - SBRT + nivolumab and ipilimumab	Arm B - nivolumab and ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	44		
Units: percent				
number (confidence interval 95%)	21.6 (9.8 to 38.2)	22.7 (11.5 to 37.8)		

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:

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
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Dictionary used

Dictionary name	NCI-CTCAE
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Dictionary version	5
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Reporting groups

Reporting group title	Arm A - SBRT + nivolumab and ipilimumab
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Reporting group description:

Stereotactic body radiotherapy of 8 Gray (Gy) x 3 on one soft tissue or bone metastasis and immunotherapy

Reporting group title	Arm B - nivolumab and ipilimumab
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Reporting group description:

Immunotherapy

Serious adverse events	Arm A - SBRT + nivolumab and ipilimumab	Arm B - nivolumab and ipilimumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 37 (56.76%)	29 / 44 (65.91%)	
number of deaths (all causes)	30	37	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Thromboembolic event	Additional description: Includes terms: Pulmonary embolism and Deep vein thrombosis		
subjects affected / exposed	2 / 37 (5.41%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 37 (5.41%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain	Additional description: includes terms: pain in groin, back pain		

subjects affected / exposed	1 / 37 (2.70%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Phimosi			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	2 / 37 (5.41%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 37 (2.70%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Stroke			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischemia cerebrovascular			

subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 37 (2.70%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	1 / 37 (2.70%)	3 / 44 (6.82%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	6 / 37 (16.22%)	3 / 44 (6.82%)	
occurrences causally related to treatment / all	8 / 9	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraperitoneal hemorrhage			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Hepatitis			
subjects affected / exposed	2 / 37 (5.41%)	3 / 44 (6.82%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria acuta			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 37 (0.00%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematuria			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 37 (0.00%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	1 / 37 (2.70%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	1 / 37 (2.70%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Covid-19			
subjects affected / exposed	1 / 37 (2.70%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 37 (5.41%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 37 (5.41%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 37 (2.70%)	6 / 44 (13.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection - unknown focus			
subjects affected / exposed	2 / 37 (5.41%)	7 / 44 (15.91%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 37 (2.70%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	1 / 37 (2.70%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Ketoacidosis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A - SBRT + nivolumab and ipilimumab	Arm B - nivolumab and ipilimumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 37 (100.00%)	44 / 44 (100.00%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 37 (27.03%)	8 / 44 (18.18%)	
occurrences (all)	15	8	
Alanine aminotransferase increased			
subjects affected / exposed	8 / 37 (21.62%)	6 / 44 (13.64%)	
occurrences (all)	10	8	
Nervous system disorders			

Myasthenia gravis subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2	9 / 44 (20.45%) 11	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2	8 / 44 (18.18%) 15	
Eye disorders Dry Eyes subjects affected / exposed occurrences (all)	7 / 37 (18.92%) 7	2 / 44 (4.55%) 2	
Gastrointestinal disorders Colitis subjects affected / exposed occurrences (all) Diarrhea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Mucositis oral subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all)	9 / 37 (24.32%) 15 9 / 37 (24.32%) 13 3 / 37 (8.11%) 3 0 / 37 (0.00%) 0 6 / 37 (16.22%) 6 4 / 37 (10.81%) 4	6 / 44 (13.64%) 10 7 / 44 (15.91%) 13 5 / 44 (11.36%) 8 5 / 44 (11.36%) 6 6 / 44 (13.64%) 6 2 / 44 (4.55%) 3	
Hepatobiliary disorders Hepatitis subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3	3 / 44 (6.82%) 3	
Respiratory, thoracic and mediastinal disorders			

Pneumonitis subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 8	3 / 44 (6.82%) 3	
Dyspnea subjects affected / exposed occurrences (all)	5 / 37 (13.51%) 8	5 / 44 (11.36%) 5	
Cough subjects affected / exposed occurrences (all)	5 / 37 (13.51%) 8	5 / 44 (11.36%) 5	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	13 / 37 (35.14%) 18	19 / 44 (43.18%) 30	
Rash maculo-papular subjects affected / exposed occurrences (all)	11 / 37 (29.73%) 25	18 / 44 (40.91%) 25	
Dry skin subjects affected / exposed occurrences (all)	8 / 37 (21.62%) 9	15 / 44 (34.09%) 17	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	5 / 37 (13.51%) 5	11 / 44 (25.00%) 14	
Hyperthyroidism subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3	10 / 44 (22.73%) 10	
Adrenal Insufficiency subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 3	5 / 44 (11.36%) 7	
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	7 / 37 (18.92%) 11	8 / 44 (18.18%) 12	
Athralgia subjects affected / exposed occurrences (all)	5 / 37 (13.51%) 6	7 / 44 (15.91%) 7	

Myositis subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 2	4 / 44 (9.09%) 4	
Metabolism and nutrition disorders			
Anorexia subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 4	9 / 44 (20.45%) 13	
Hyperglycemia subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 6	4 / 44 (9.09%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2020	- Scanning modality for tumor assessments amended from CT-scan to 18F-NaF PET/CT scan. - Clarification of timing of SBRT - Added cortisol, creatine kinase, troponin to safety laboratory assessments
01 December 2021	- removal of inclusion criteria that requires presence of at least two soft tissue metastases, hence patients with both predominant bone metastases AND/OR soft tissue metastases were subsequently allowed to be recruited to the trial - primary endpoint has been changed to co-primary endpoints where clinical beneficial rate (CBR) has been replaced by: - Objective response rate (complete and partial response, ORR) per RECIST 1.1 (for patients with measurable disease) - Prostate-specific antigen (PSA) response-rate of $\geq 50\%$ decline from baseline at any time from treatment start (confirmed after ≥ 4 weeks, all patients with measurable and non-measurable disease) - added the secondary endpoints of radiographic progression-free survival (rPFS), PSA progression-free survival (PSA-PFS) and transferred the initial primary endpoint (CBR) to the secondary - added PSA assessment q4w (instead of simultaneously with scans) - translational analyses extended with single-cell sequencing on T cells. - adjustment of study time lines

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported