



## Clinical trial results:

### Phase I trial of stereotactic body radiotherapy with concurrent pembrolizumab in metastatic urothelial cancer.

#### Summary

EudraCT number	2016-001263-37
Trial protocol	BE
Global end of trial date	18 December 2018

#### Results information

Result version number	v1 (current)
This version publication date	06 June 2024
First version publication date	06 June 2024
Summary attachment (see zip file)	Final Study Report (2016-001263-37_final study report.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	2016-001263-37
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02826564
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	UZ Ghent
Sponsor organisation address	C. Heymanslaan 10, Ghent, Belgium, 9000
Public contact	HIRUZ CTU, UZ Gent, +32 9332 05 00, hiruz.ctu@uzgent.be
Scientific contact	HIRUZ CTU, UZ Gent, +32 9332 05 00, hiruz.ctu@uzgent.be

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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	12 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 April 2018
Global end of trial reached?	Yes
Global end of trial date	18 December 2018
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

To determine the SBRT-schedule associated with DLT in 20% of patients

Protection of trial subjects:

: Ethics review and approval, informed consent, supportive care and routine monitoring.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Belgium: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

Notes:

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**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)	12
From 65 to 84 years	11
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

30 patients were screened from 14/11/2016 and 2/1/2018. 23 patients were enrolled, 18 patients were randomized. End of trial notification was 27/12/18 (last patient last visit) and submitted to EC and CA on dd-mm-yyyy. There were 6 dropouts, 1 patient was excluded due to CNS lesion, 5 patients died during treatment

### Pre-assignment

Screening details:

Inclusion Criteria:

≥ 18 years of age

Have measurable disease based on RECIST 1.1.

Have had any prior treatment more than 2 weeks prior to study day 1, treatment naive patients are allowed

Histologically confirmed diagnosis of urothelial carcinoma

Willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion

### Pre-assignment period milestones

Number of subjects started	23
Number of subjects completed	18

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	drop-out before start of treatment: 4

### Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline Arm T1

Arm description:

4 cycles of pembrolizumab with SBRT applied before the first cycle

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

Dosage and administration details:

200 mg per day 1 of each 3 week cycle

Investigational medicinal product name	Radio therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radionuclide generator
Routes of administration	Other use

Dosage and administration details:

8 Gy day 1, 3, 5

<b>Arm title</b>	Baseline Arm T2
Arm description: 4 cycles of pembrolizumab with SBRT applied before the third cycle	
Arm type	Experimental
Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 200 mg per day one of each 3 week cycle	
Investigational medicinal product name	Radio therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radionuclide generator
Routes of administration	Other use
Dosage and administration details: 8 Gy day 38, 40, 42	

Number of subjects in period 1 <sup>[1]</sup>	Baseline Arm T1	Baseline Arm T2
Started	9	9
Completed	9	9

#### 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: 23 patients were enrolled, 5 patients dropped out before start of treatment hereby only 18 patients were treated.

See attachment Final Study Report

#### Period 2

Period 2 title	Overall Trial
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

#### Blinding implementation details:

Randomized - non controlled - open label

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

#### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Arm T1
Arm description: 4 cycles of pembrolizumab with SBRT applied before the first cycle	
Arm type	Experimental
Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 200 mg per day 1 of each 3 week cycle	
<b>Arm title</b>	Arm T2
Arm description: 4 cycles of pembrolizumab with SBRT applied before the third cycle	
Arm type	Experimental
Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 200 mg per day one of each 3 week cycle	

<b>Number of subjects in period 2</b>	Arm T1	Arm T2
Started	9	9
Completed	9	3
Not completed	0	6
Adverse event, serious fatal	-	5
Consent withdrawn by subject	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline Arm T1
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Reporting group description:

4 cycles of pembrolizumab with SBRT applied before the first cycle

Reporting group title	Baseline Arm T2
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Reporting group description:

4 cycles of pembrolizumab with SBRT applied before the third cycle

Reporting group values	Baseline Arm T1	Baseline Arm T2	Total
Number of subjects	9	9	18
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	58	71	
full range (min-max)	54 to 75	50 to 84	-
Gender categorical			
Units: Subjects			
Female	1	1	2
Male	8	8	16
ECOG performance-status score			
Units: Subjects			
score 0	4	6	10
score 1	5	3	8
Previous systemic treatments			
Units: Subjects			
value: 0	2	3	5
value: 1	4	5	9
value: 2	1	1	2
value: 3	2	0	2
Modified proportion score of PD-L1 $\geq 1\%$			
Units: Subjects			
PD-L1 $\geq 1\%$ : yes	3	6	9
PD-L1 $\geq 1\%$ : no	6	3	9
Modified proportion score of PD-L1 $\geq 10\%$			
Units: Subjects			

PD-L1 ≥10% : yes	2	5	7
PD-L1 ≥10% : no	7	4	11
Modified proportion score of PD-L1 ≥95%			
Units: Subjects			
PD-L1 ≥95%: yes	1	2	3
PD-L1 ≥95%: no	8	7	15
Visceral disease			
Units: Subjects			
yes	5	6	11
no	4	3	7
Liver metastases			
Units: Subjects			
yes	2	1	3
no	7	8	15
Hemoglobin concentration <10g/dL			
Units: Subjects			
<10g/dL	0	1	1
>10g/dL	9	8	17

## End points

### End points reporting groups

Reporting group title	Baseline Arm T1
Reporting group description: 4 cycles of pembrolizumab with SBRT applied before the first cycle	
Reporting group title	Baseline Arm T2
Reporting group description: 4 cycles of pembrolizumab with SBRT applied before the third cycle	
Reporting group title	Arm T1
Reporting group description: 4 cycles of pembrolizumab with SBRT applied before the first cycle	
Reporting group title	Arm T2
Reporting group description: 4 cycles of pembrolizumab with SBRT applied before the third cycle	

### Primary: Dose limiting toxicity between start of SBRT and 12 weeks after completion of SBRT

End point title	Dose limiting toxicity between start of SBRT and 12 weeks after completion of SBRT <sup>[1]</sup>
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End point description:

End point type	Primary
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End point timeframe:

dosing cycle dependent

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: DLT was assessed using the Common Terminology Criteria for Adverse Events. No DLTs occurred. No statistical analysis available.

See attachment Final Study Report

End point values	Arm T1	Arm T2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: number of patients				
AE grade 1-2	6	9		
AE grade 3	0	1		
AE grade 4-5	0	0		
DLT	0	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: determination of local control of the irradiated metastases

End point title	determination of local control of the irradiated metastases
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End point description: local response of the irradiated lesion	
End point type	Secondary
End point timeframe: N/A	

End point values	Arm T1	Arm T2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: type of response				
complete response	2	4		
partial response	1	0		
stable disease	4	4		
progressive disease	1	1		

### Statistical analyses

No statistical analyses for this end point

### Secondary: assessment of progression-free survival

End point title	assessment of progression-free survival
End point description:	
End point type	Secondary
End point timeframe: time from inclusion to documented disease progression according to irRC or death from any cause	

End point values	Arm T1	Arm T2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: months				
median (full range (min-max))	3.3 (0 to 18)	3.5 (0 to 18)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: assessment response of the combination treatment in non-irradiated metastases (evaluated as per RECIST v1.1)

End point title	assessment response of the combination treatment in non-irradiated metastases (evaluated as per RECIST v1.1)
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End point description:

End point type	Secondary
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End point timeframe:

12 weeks

End point values	Arm T1	Arm T2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: number	0	4		

### Statistical analyses

No statistical analyses for this end point

### Post-hoc: assessment of overall survival

End point title	assessment of overall survival
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End point description:

End point type	Post-hoc
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End point timeframe:

12 weeks

End point values	Arm T1	Arm T2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: months				
median (full range (min-max))	4.5 (0 to 18)	12.1 (0 to 18)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Adverse events will be reported between the first dose administration of trial medication and the last trial related activity.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	23

### Reporting groups

Reporting group title	Arm T1
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Reporting group description: -

Reporting group title	Arm T2
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Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: See attachment Final Study Report

Serious adverse events	Arm T1	Arm T2	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)	2 / 9 (22.22%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Auto-immune adrenalinitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
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			
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Lower back pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
fever			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (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 %

<b>Non-serious adverse events</b>	Arm T1	Arm T2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2016	amendment 1: Use of liquid formulation of the IMP pembroluzimab in stead of the powder for solution for infusion formulation
31 January 2017	Amendment 2: Protocol adjustment to conform to recent scientific findings
26 April 2017	Amendment 3: Inclusion of phase II trial information in the protocol. Addition of recent findings concerning rare side effects of the IMP pembrolizumab to the ICF as provided by the manufacturer.
20 June 2017	Amendment 4: Adjustment to the number of participant from 20 to 25 patients to account for potential drop-outs.
23 October 2017	Amendment 5: Adjustments to EudraCT form sections D2.3 and D.9

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30665814>

<http://www.ncbi.nlm.nih.gov/pubmed/28662677>