Clinical trial results:
A parallel group phase I/II marker lesion study to assess the safety, tolerability and efficacy of intravenous or intravesical pembrolizumab in intermediate risk recurrent non-muscle invasive bladder cancer

Summary

EudraCT number	2016-002267-33
Trial protocol	GB
Global end of trial date	26 June 2019

Results information

Result version number	v1 (current)
This version publication date	01 January 2020
First version publication date	01 January 2020

Trial information

Trial identification

Sponsor protocol code	OCTO-089

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03167151
WHO universal trial number (UTN)	-
Other trial identifiers	ClinicalTrials.gov : NCT03167151

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Joint Research Office, 1st floor, Boundary Brook House, Churchill Drive, Headington, Oxford, United Kingdom, OX3 7GB
Public contact	Linda Collins, Oncology Clinical Trials Office, +44 01865227162, octo-pembla@oncology.ox.ac.uk
Scientific contact	Linda Collins, Oncology Clinical Trials Office, +44 01865227162, octo-pembla@oncology.ox.ac.uk

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	24 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 March 2019
Global end of trial reached?	Yes
Global end of trial date	26 June 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To test the safety, tolerability and side effects of a drug called pembrolizumab in patients with recurrent bladder cancer.

Protection of trial subjects:

The trial received ethical and regulatory approval, and was run in compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004, and amendments thereafter, the guidelines for Good Clinical Practice, and the applicable policies of the Sponsor, the University of Oxford. The protocol complied with all current applicable Regulatory Authority, Research Ethics Committee and Sponsor reporting requirements. Safety reporting will continue for 90 days post end of treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	6
EEA total number of subjects	6

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)	1
From 65 to 84 years	4
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Initially, the plan was to recruit the 6 participants for the safety run-in phase of the study within 6 months. 9 patients, of which 6 were evaluable, were recruited at the Oxford Churchill Hospital site from 17 July 2017 until 31 Jan 2019. Due to the issues with slow recruitment, the steering committee decided to end recruitment on 31 Jan 2019

Pre-assignment

Screening details:

16 patients were assessed for eligibility, 7 of whom were excluded; 1 because they were ineligible (Hep C positive in past) and 6 declined to participate.

Period 1

Period 1 title	Safety run-in phase (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not a blinded study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Cohort 1 in the safety run-in phase.
Day 1 starting dose 50mg intravesical pembrolizumab

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intravesical solution
Routes of administration	Intravesical use

Dosage and administration details:

Day 1 - 50mg
Day 8 - 50mg
Day 15 - 100mg
Day 22 - 100mg
Day 29 - 200mg
Day 36 - 200mg

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intravesical solution
Routes of administration	Intravesical use

Dosage and administration details:

Day 1 - 50mg
Day 8 - 50mg
Day 15 - 100mg
Day 22 - 100mg
Day 29 - 200mg
Day 36 - 200mg

Arm title	Cohort 2

Arm description:

Cohort 2 in the safety run-in phase.

Day 1 starting dose 100mg intravesical pembrolizumab

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intravesical solution
Routes of administration	Intravesical use

Dosage and administration details:

Day 1 - 100mg
Day 8 - 100mg
Day 15 - 200mg
Day 22 - 200mg
Day 29 - 200mg
Day 36 - 200mg

Arm title	Cohort 3

Arm description:

Cohort 3 in the safety run-in phase.
Day 1 starting dose 200mg intravesical pembrolizumab

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intravesical solution
Routes of administration	Intravesical use

Dosage and administration details:

Day 1 - 200mg
Day 8 - 200mg
Day 15 - 200mg
Day 22 - 200mg
Day 29 - 200mg
Day 36 - 200mg

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	2	2	2
Completed	2	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
Cohort 1 in the safety run-in phase. Day 1 starting dose 50mg intravesical pembrolizumab	
Reporting group title	Cohort 2
Reporting group description:	
Cohort 2 in the safety run-in phase. Day 1 starting dose 100mg intravesical pembrolizumab	
Reporting group title	Cohort 3
Reporting group description:	
Cohort 3 in the safety run-in phase. Day 1 starting dose 200mg intravesical pembrolizumab	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	2	2	2
Age categorical Units: Subjects			
Adults (18-64 years)	0	1	0
From 65-84 years	2	1	1
85 years and over	0	0	1
Age continuous Units: years			
arithmetic mean	73	66	81
standard deviation	± 0	± 10.6	± 7.8
Gender categorical Units: Subjects			
Female	0	1	0
Male	2	1	2
Race/Ethnicity Units: Subjects			
White British	2	2	2
Smoking status Units: Subjects			
Current	0	1	0
Ex-smoker	2	1	1
Never smoker	0	0	1
ECOG Performance Status Units: Subjects			
Performance Status 0	2	2	2
Site of primary tumour Units: Subjects			
Bladder	1	2	1
Left renal pelvis	0	0	1
Urothelial	1	0	0
Prior chemotherapy Units: Subjects			

Yes	2	2	2
Prior surgery Units: Subjects			
Yes	2	2	2

Reporting group values	Total		
Number of subjects	6		
Age categorical Units: Subjects			
Adults (18-64 years)	1		
From 65-84 years	4		
85 years and over	1		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	1		
Male	5		
Race/Ethnicity Units: Subjects			
White British	6		
Smoking status Units: Subjects			
Current	1		
Ex-smoker	4		
Never smoker	1		
ECOG Performance Status Units: Subjects			
Performance Status 0	6		
Site of primary tumour Units: Subjects			
Bladder	4		
Left renal pelvis	1		
Urothelial	1		
Prior chemotherapy Units: Subjects			
Yes	6		
Prior surgery Units: Subjects			
Yes	6		

Subject analysis sets

Subject analysis set title	Safety run-in
Subject analysis set type	Safety analysis

Subject analysis set description:

Population for (DLT and tolerability) safety run-in analysis: six patients received at least 5 out of 6 scheduled treatments, or withdrew early due to drug-related toxicity, and hence these six patients will contribute to the DLT and tolerability analysis.

Reporting group values	Safety run-in		
Number of subjects	6		
Age categorical Units: Subjects			
Adults (18-64 years)	1		
From 65-84 years	4		
85 years and over	1		
Age continuous Units: years arithmetic mean standard deviation	 ±		
Gender categorical Units: Subjects			
Female			
Male			
Race/Ethnicity Units: Subjects			
White British			
Smoking status Units: Subjects			
Current			
Ex-smoker			
Never smoker			
ECOG Performance Status Units: Subjects			
Performance Status 0	6		
Site of primary tumour Units: Subjects			
Bladder			
Left renal pelvis			
Urothelial			
Prior chemotherapy Units: Subjects			
Yes			
Prior surgery Units: Subjects			
Yes			

End points

End points reporting groups

Reporting group title	Cohort 1

Reporting group description:

Cohort 1 in the safety run-in phase.
Day 1 starting dose 50mg intravesical pembrolizumab

Reporting group title	Cohort 2

Reporting group description:

Cohort 2 in the safety run-in phase.
Day 1 starting dose 100mg intravesical pembrolizumab

Reporting group title	Cohort 3

Reporting group description:

Cohort 3 in the safety run-in phase.
Day 1 starting dose 200mg intravesical pembrolizumab

Subject analysis set title	Safety run-in
Subject analysis set type	Safety analysis

Subject analysis set description:

Population for (DLT and tolerability) safety run-in analysis: six patients received at least 5 out of 6 scheduled treatments, or withdrew early due to drug-related toxicity, and hence these six patients will contribute to the DLT and tolerability analysis.

Primary: The Incidence and Severity of Adverse Events to Assess the Safety, Tolerability and Toxicities of Intravesical Pembrolizumab After TURBT in Patients With Intermediate Risk NMIBC

End point title	The Incidence and Severity of Adverse Events to Assess the Safety, Tolerability and Toxicities of Intravesical Pembrolizumab After TURBT in Patients With Intermediate Risk NMIBC[1]

End point description:

Patients will be assessed for dose limiting toxicities (DLT) as well as for overall tolerability of the treatment. A DLT is defined as a clinically significant, drug related, grade 4 haematological or > grade 3 non-haematological toxicity occurring within 7 days of administration of the first treatment at a given dose for that patient. If more than 1 patient experiences a DLT at a certain dose, this dose will be declared non-tolerated and further escalation will cease.

No DLTs were seen in any of the three cohorts, and based on this, we can confirm the safety and tolerability of the highest pembrolizumab dose (200mg).

End point type	Primary

End point timeframe:

Patients were assessed for dose limiting toxicity (DLTs) occurring within 7 days of administration of the first treatment at a given dose for that patient.

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 was only a safety run-in study, so no statistical analyses were carried out.

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	2	2	
Units: Dose Limiting Toxicities (DLTs)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event monitoring starts on the day of the TURBT procedure (Day -14) until 90 days post treatment, or 30 days following administration of the last dose of study medication if the subject initiates a new anticancer therapy.

Adverse event reporting additional description:

The Investigator will monitor each patient for clinical and laboratory evidence of adverse events on a routine basis throughout the study

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Cohort 1
Reporting group description: -	
Reporting group title	Cohort 2
Reporting group description: -	
Reporting group title	Cohort 3

Reporting group description: -

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Urosepsis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 2 (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

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

Non-serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	1 / 2 (50.00%)	2 / 2 (100.00%)
Vascular disorders			
Hot flush			

subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Rigors			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	1	0	1
Fever			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Itching			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Rash	Additional description: Rash over bilateral shins		
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Urgency-Frequeny Syndrome			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	3
Dysuria			

subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	1	0	1
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	2 / 2 (100.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	2	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
24 June 2019	The temporary halt was requested by the Chief Investigator. The safety cohort completed LPLV on 26Mar2019 and the decision was taken to close the study at this stage (as per protocol). However, the funder was keen to evaluate whether or not it would be possible to complete the expansion cohort of the study. The temporary halt allowed time to consider the feasibility of completeing the expansion cohort. However, it was determined that this was not feasible and the study was closed 26Jun2019.	-

Notes:

Limitations and caveats

None reported