Clinical trial results:
A phase II randomised feasibility study of chemoresection and surgical management in low risk non muscle invasive bladder cancer.

Summary

EudraCT number	2013-005095-18
Trial protocol	GB
Global end of trial date	21 February 2022

Results information

Result version number	v1 (current)
This version publication date	01 February 2023
First version publication date	01 February 2023

Trial information

Trial identification

Sponsor protocol code	ICR-CTSU/2013/10041

Additional study identifiers

ISRCTN number	ISRCTN24855462
ClinicalTrials.gov id (NCT number)	NCT02070120
WHO universal trial number (UTN)	-
Other trial identifiers	NIHR Reference Number: PB-PG-0712-28112, Sponsor Identifier Number: CCR4134

Notes:

Sponsors

Sponsor organisation name	Institute of Cancer Research
Sponsor organisation address	15 Cotswold Road, Sutton, United Kingdom, SM2 5NG
Public contact	Steven Penegar, Institute of Cancer Research, 44 02087224238, caliber-icrctsu@icr.ac.uk
Scientific contact	Steven Penegar, Institute of Cancer Research, 44 02087224238, caliber-icrctsu@icr.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	12 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 October 2018
Global end of trial reached?	Yes
Global end of trial date	21 February 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Can chemotherapy in the bladder (chemoresection) enable the avoidance of surgery for those diagnosed with a recurrence of low risk non-muscle invasive bladder cancer?

CALIBER is a two stage phase II, multicentre, randomised (2:1) non-comparative trial (RCT) powered to demonstrate that chemoablation will achieve at least 60% complete response (CR) at 3 months under a Simon 2-stage design (p0=0.45, p1=0.60, alpha=0.10). A control group was included in stage1 to provide prospective data about surgical management and outcomes and assess feasibility of recruitment to a randomised study.
Trial did not met its pre-sopecified threshold at Stage 1 (at least 26 CR/51pts needed), and the IDMC advised that the trial should stop for futility.

Protection of trial subjects:

For trial entry and optional tissue donation, patients were given a verbal explanation, discussion and written information.
The Principal Investigator at each site was responsible for ensuring written informed consent was obtained for each patient.
Eligible patients were given as much time as they needed to consider and come to a decision about entering the trial, prior to giving consent for registration.
The patient information sheet, described fully which parties would have access to their identifiable personal information and patients were asked to
give consent to this.
The trial was overseen by an Independent Data Monitoring Committee, who reviewed the accumulating trial data and could recommend stopping the trial if there was any cause for concern about patient safety and if this were the case the patient's oncologist would be notified.

Background therapy:

Bladder cancer is the ninth most common cancer worldwide, and most frequently presents as non-muscle-invasive bladder cancer (NMIBC). Approximately 50% of patients with bladder cancer have low-risk NMIBC, with a 0.8–6% risk of progression to muscle-invasive disease or bladder cancer death within 5 years and a relatively high rate of local recurrence, 46–62%. Half of recurrences occur within the first year of follow-up. The discomfort and inconvenience of managing NMIBC recurrence, combined with cost, are the key issues for patients and healthcare providers managing low-risk NMIBC.

Guidelines recommend annual cystoscopy for 5 years for low-risk NMIBC. Treatments for local recurrence include transurethral resection and cystodiathermy under general anaesthesia, laser ablation under local anaesthesia and watchful waiting. This variety reflects the indolent nature of low-risk NMIBC and lack of high-quality evidence about the optimal management.

Evidence for comparator:

Several small studies have demonstrated promising results for intravesical chemotherapy alone (chemoablation) as an alternative to surgical management for NMIBC. The optimal schedule and its effectiveness in achieving a complete response in low-risk NMIBC are unclear. Reviews of chemoablation (including >1200 patients with varying risk and different chemotherapy regimens) suggest the complete response rate is ~50%, with the therapeutic effect sustained for at least 2 years. These data suggest chemoablation may be a viable treatment for low-risk NMIBC.

Surgical intervention is the standard of care within this patient population.

Actual start date of recruitment	01 October 2014
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: 82
Worldwide total number of subjects	82
EEA total number of subjects	0

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)	14
From 65 to 84 years	62
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Between February 2015 and August 2017 82 patients with visual diagnosis of recurrent low risk NMIBC were enrolled from 24 UK hospitals (54 chemoablation, 28 surgical management).

Pre-assignment

Screening details:

Patients that met the eligibility criteria were recruited into the study.
Eligible patients had previously diagnosed, histologically confirmed, low risk NMIBC with visual diagnosis of recurrence.
Patients were over 16, with an EORTC risk of recurrence score ≤6 with no history of high grade/≥T1 or non-urothelial transitional cell carcinoma.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Chemoablation

Arm description:

Chemoablation participants received four once weekly intravesical instillations of 40mg mitomycin-C (MMC) as outpatients, in accordance with local policy. No dose reductions were permitted.

Arm type	Experimental
Investigational medicinal product name	mitomycin C
Investigational medicinal product code	ATC Code: L01D
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravesical use

Dosage and administration details:

Four once weekly intravesical instillations of 40mg mitomycin-C (MMC) as outpatients, in accordance with local policy.

Arm title	Surgical Management

Arm description:

Participants assigned to surgical management had the local standard technique for treatment of recurrence; a single instillation of 40mg MMC within 24 hours post-operatively was permitted.

Arm type	Surgery

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Chemoablation	Surgical Management
Started	54	28
Complete response rate stage 1 accrual	54	26
Completed	54	26
Not completed	0	2
Consent withdrawn by subject	-	1

Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Chemoablation
Reporting group description:	
Chemoablation participants received four once weekly intravesical instillations of 40mg mitomycin-C (MMC) as outpatients, in accordance with local policy. No dose reductions were permitted.	
Reporting group title	Surgical Management
Reporting group description:	
Participants assigned to surgical management had the local standard technique for treatment of recurrence; a single instillation of 40mg MMC within 24 hours post-operatively was permitted.	

Reporting group values	Chemoablation	Surgical Management	Total
Number of subjects	54	28	82
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			
arithmetic mean	73.4	69.3	
standard deviation	± 7.6	± 11.5	-
Gender categorical Units: Subjects			
Female	14	5	19
Male	40	23	63

End points

End points reporting groups

Reporting group title	Chemoablation

Reporting group description:

Chemoablation participants received four once weekly intravesical instillations of 40mg mitomycin-C (MMC) as outpatients, in accordance with local policy. No dose reductions were permitted.

Reporting group title	Surgical Management

Reporting group description:

Participants assigned to surgical management had the local standard technique for treatment of recurrence; a single instillation of 40mg MMC within 24 hours post-operatively was permitted.

Subject analysis set title	Evaluable population - chemoablation
Subject analysis set type	Per protocol

Subject analysis set description:

This population includes all randomised patients with 3 months assessment available and who have received their allocated treatment regardless of whether they were later found to be ineligible or a protocol violator.
Because the primary endpoint is non-comparative, the patients in the chemoablation group define the chemoablation population as defined in the SAP v1.0.

Subject analysis set title	Evaluable population - surgery
Subject analysis set type	Per protocol

Subject analysis set description:

This population includes all randomised patients with 3 months assessment available and who have received their allocated treatment regardless of whether they were later found to be ineligible or a protocol violator.
Because the primary endpoint is non-comparative, the patients in the chemoablation group define the chemoablation population as defined in the SAP v1.0.

Primary: Complete response

End point title	Complete response[1]

End point description:

Complete response (CR) to chemoablation 3 months post-treatment, defined as an absence of any tumour following chemoablation. Response will be assessed visually at check cystoscopy by patients' urologists and a biopsy of the tumour bed will take place to confirm visual assessment of CR.

End point type	Primary

End point timeframe:

3 months post-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: CALIBER is a two stage phase II, multicentre, randomised (2:1) non-comparative trial (RCT) powered to demonstrate that chemoablation will achieve at least 60% complete response (CR) at 3 months under a Simon 2-stage design. A control group was included in stage1 to provide prospective data about surgical management and outcomes and assess feasibility of recruitment to a randomised study. Trial did not met its pre-specified threshold at Stage 1 (at least 26 CR needed) and stopped accrual.

End point values	Evaluable population - chemoablation			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: Percentage				
number (confidence interval 95%)	37 (24 to 51)			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment compliance in the chemoablation group

End point title	Treatment compliance in the chemoablation group

End point description:

Patients who receive 4 MMC instillations with no more than 14 days between each instillation will be described as fully compliant

End point type	Secondary

End point timeframe:

While on treatment

End point values	Evaluable population - chemoablation			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: patients				
Compliant	53			
Not compliant	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to recurrence

End point title	Time to recurrence

End point description:

Time to recurrence: defined as time from end of treatment to first occurrence of subsequent disease (local or distant recurrence or death due to bladder cancer) by response status (with and without CR) at 3 months

End point type	Secondary

End point timeframe:

Proportion free to subsequent recurrence at 12 months

End point values	Evaluable population - chemoablation	Evaluable population - surgery		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	26		
Units: Months				
number (confidence interval 95%)	82.7 (69.4 to 90.6)	75.4 (53.2 to 88.2)		

Statistical analyses

Statistical analysis title	Comparison time to recurrence
Comparison groups	Evaluable population - chemoablation v Evaluable population - surgery
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.089
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	1.15

Secondary: Subsequent TURBT /biopsy rate

End point title	Subsequent TURBT /biopsy rate
End point description:	
Subsequent TURBT /biopsy rate by response status (with and without CR) at 3 months	
End point type	Secondary
End point timeframe:	
3 months	

End point values	Evaluable population - chemoablation	Evaluable population - surgery		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	28		
Units: number recurrences				
median (inter-quartile range (Q1-Q3))	0.00 (0.00 to	0.00 (0.00 to		

0.49)	0.00)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

Time to progression is defined as time from randomisation to the first of muscle invasive bladder recurrence, recurrence in the pelvic nodes, distant metastatic recurrence or death from any cause

End point type	Secondary

End point timeframe:

12 months

End point values	Evaluable population - chemoablation	Evaluable population - surgery		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	28		
Units: progression or death events				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in EORTC QLQ-C30 Global Health

End point title	Change from baseline in EORTC QLQ-C30 Global Health

End point description:

High score represents high quality of life
Positive change from baseline represents improvement.

End point type	Secondary

End point timeframe:

Six months

End point values	Evaluable population - chemoablation	Evaluable population - surgery		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	18		
Units: score points				
arithmetic mean (confidence interval 99%)	-4.8 (-11.8 to 2.2)	1.4 (-8.2 to 10.9)		

Statistical analyses

Statistical analysis title	Difference in change from baseline

Statistical analysis description:

Treatment effect chemoablation vs surgery and its 99% confidence intervals are obtained from an analysis of covariance (ANCOVA) model, using change from baseline as the outcome measure and adjusting treatment effect for baseline score on the same subscale. A p-value of <0.01 will be deemed statistically significant to acknowledge that some adjustment be made for multiple testing

Comparison groups	Evaluable population - chemoablation v Evaluable population - surgery
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Median difference (net)
Point estimate	-5.8
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-17.9
upper limit	6.3

Secondary: Change from baseline in EORTC QLQ-NMIBC24 Urinary Symptoms

End point title	Change from baseline in EORTC QLQ-NMIBC24 Urinary Symptoms

End point description:

End point type	Secondary

End point timeframe:

6 months

End point values	Evaluable population - chemoablation	Evaluable population - surgery		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	19		
Units: score units				
arithmetic mean (confidence interval 99%)	-3.2 (-7.4 to 0.9)	2.5 (-7.2 to 12.3)		

Statistical analyses

Statistical analysis title	Diffewrence in mean change form baseline

Statistical analysis description:

Treatment effect chemoablation vs surgery and its 99% confidence intervals are obtained from an analysis of covariance (ANCOVA) model, using change from baseline as the outcome measure and adjusting treatment effect for baseline score on the same subscale. A p-value of <0.01 will be deemed statistically significant to acknowledge that some adjustment be made for multiple testing

Comparison groups	Evaluable population - chemoablation v Evaluable population - surgery
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-4.5
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-12
upper limit	3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation until 3 months after treatment

Adverse event reporting additional description:

Treatment-emergent adverse events are reported; these are defined as an event not present prior to the initiation of trial treatment or an event already present that worsens at end of treatment or at 3 month follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	pre-specified+Meddra
Dictionary version	20.1

Reporting groups

Reporting group title	Safety population - chemoablation
Reporting group description: -	
Reporting group title	Safety population - surgery

Reporting group description: -

Serious adverse events	Safety population - chemoablation	Safety population - surgery	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)	0 / 28 (0.00%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Safety population - chemoablation	Safety population - surgery	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 54 (51.85%)	16 / 28 (57.14%)	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	2 / 54 (3.70%)	4 / 28 (14.29%)	
occurrences (all)	2	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 54 (7.41%)	1 / 28 (3.57%)	
occurrences (all)	4	1	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	4 / 54 (7.41%)	0 / 28 (0.00%)	
occurrences (all)	4	0	
Renal and urinary disorders			
Bladder spasm			
subjects affected / exposed	2 / 54 (3.70%)	5 / 28 (17.86%)	
occurrences (all)	2	5	
Haematuria			
subjects affected / exposed	4 / 54 (7.41%)	9 / 28 (32.14%)	
occurrences (all)	4	9	
Urinary incontinence			
subjects affected / exposed	0 / 54 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Urinary retention			
subjects affected / exposed	3 / 54 (5.56%)	3 / 28 (10.71%)	
occurrences (all)	3	3	
Urinary tract pain			
subjects affected / exposed	5 / 54 (9.26%)	7 / 28 (25.00%)	
occurrences (all)	5	7	
Micturition urgency			
subjects affected / exposed	7 / 54 (12.96%)	8 / 28 (28.57%)	
occurrences (all)	7	8	
Pollakiuria			
subjects affected / exposed	10 / 54 (18.52%)	10 / 28 (35.71%)	
occurrences (all)	10	10	
Infections and infestations			
Bladder infection			
subjects affected / exposed	0 / 54 (0.00%)	3 / 28 (10.71%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2016	Inclusion of 2004 WHO classification of low grade tumour for sites where grade is no longer reported using 1973 WHO classification. Clarification of the time period over which patients' prior recurrence rate should be calculated. This has been limited to five years where lengthy disease history is present to ensure that these patients' most recent recurrence rate is used to calculate risk of further recurrence. Clarification that patients with any history of non-TCC bladder cancer should be excluded. Clarification that patients are excluded if the trial entry recurrence is within 11.5 months of the original diagnosed tumour. Trial entry tumours seen within this period would have an ineligible recurrence rate of >1 recurrence per year. 11.5 months (rather than 12) has been used as a cut off to account for variation in patients' annual follow up visits. Removal of exclusion criterion following Trial Management Group review. This criterion was deemed not relevant as the primary endpoint is local tumour response at three months post treatment. Detail of the collection of additional translational samples within the CALIBER-T sub study following funding by Cancer Research UK.
03 March 2016	Change in eligibility criteria. The criteria was clarified to state that patients with a history of intermediate/high risk NMIBC features were excluded from CALIBER.
02 November 2016	Change in eligibility criteria. The criteria was widened to include patients with a risk of recurrence score of 6 (previously 5). Clarification that patients presenting with any stage of transitional cell carcinoma greater than Ta would be ineligible. Patients are eligible with visually diagnosed recurrent low risk NMIBC at outpatient cystoscopy. Clarification that any residual/recurrent tumour found at cystoscopy at 3 months post treatment may be treated by biopsy and cystodiathermy where clinically appropriate. Clarification that complete response would be evaluated in relation to patients in the chemoresection treatment group. Clarification that further investigation would be demonstrated if adequate activity was assessed in the chemoresection group.
23 June 2017	Change of trial design and accrual target. In order to complete recruitment within a reasonable timeframe, whilst also providing an estimate of the control rate with chemoresection, revisions are proposed such that the power of the trial is reduced from 90% to 85% and the significance level increased from 5% to 10%. Stage 1 will complete as originally planned. If the stop/go activity criteria at the end of stage 1 indicate that recruitment should continue, the second stage will recruit 9 additional chemoresection patients. As the trial is non-comparative and patient acceptance of randomisation has been demonstrated during stage 1 (acceptance rate of 56% to March 2017 reported on screening) the surgical management control group will be dropped following completion of stage 1. The overall target sample size (including stage 1 controls and a 5% allowance for drop outs) will therefore be amended to 89 patients (from 174).

29 September 2017	Notification of closure to recruitment.

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 trial was not powered for direct comparison of response rate between randomised groups.
The population reflects a group of patients with intermediate, rather than low-risk NMIBC.
There was relatively poor compliance with the biopsy at 3 months.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32124514