Clinical trial results:
NICO - CA209-891: Neoadjuvant and adjuvant nivolumab as Immune Checkpoint inhibition in Oral cavity cancer

Summary

EudraCT number	2017-005015-13
Trial protocol	GB
Global end of trial date	01 November 2021

Results information

Result version number	v1 (current)
This version publication date	13 March 2025
First version publication date	13 March 2025
Summary attachment (see zip file)	NICO Final SAR V1.0.pdf (NICO Final Statistical Analysis Report V1.0 20241028.pdf)

Trial information

Trial identification

Sponsor protocol code	C0947

Additional study identifiers

ISRCTN number	ISRCTN17428671
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Clatterbridge Cancer Centre NHS Foundation Trust
Sponsor organisation address	Clatterbridge Road, Bebington, Wirral, United Kingdom, CH63 4JY
Public contact	Dr Maria Maguire, Head of Research Governance and Sponsorship, The Clatterbridge Cancer Centre , +44 7824609720, maria.maguire2@nhs.net
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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	01 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2021
Global end of trial reached?	Yes
Global end of trial date	01 November 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess whether Nivolumab in addition to standard therapy (Surgery followed by radiotherapy or radiotherapy with chemotherapy) leads to a reduction of disease recurrence.

Feasibility of recruitment into both cohorts.

Protection of trial subjects:

Central and site monitoring is conducted to ensure protection of patients participating in the trial, and that trial procedures, trial intervention administration, and laboratory and data collection processes are of high quality and meet sponsor and, when appropriate, regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 May 2019
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: 23
Worldwide total number of subjects	23
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)	15

From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial opened to recruitment on 08/05/2019. Four centres were opened (one was not a recruiting centre), three in England and one in Scotland.

Pre-assignment

Screening details:

Potentially eligible patients were assessed at the earliest opportunity following referral of patients with locally advanced oral cavity cancer to trial clinicians.

Period 1

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

Arms

Arm title	Nivolumab

Arm description:

Single dose of nivolumab (240mg flat dose) will be delivered pre-surgery and then between surgery and chemoradiotherapy/radiotherapy. The latter will be followed by six months of adjuvant nivolumab (480mg flat dose every 4 weeks, total of 6 doses). Resection of the tumour, and radiotherapy or chemoradiotherapy will follow standard practice, with patients with high risk features on pathological section (presence of extracapsular spread, involved or positive margins) being assigned to chemoradiation.

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

A single dose of nivolumab (240mg flat dose) will be delivered pre-surgery and then between surgery and chemoradiotherapy/radiotherapy. The latter will be followed by six months of adjuvant nivolumab (480mg flat dose every 4 weeks, total of 6 doses).

Number of subjects in period 1	Nivolumab
Started	23
Completed	7
Not completed	16
Intolerable Toxicity - colitis	1
G1 pneumonitis on imaging, pat didn't wish to cont	1
Decision not to have adjuvant treatment	1
Immunotherapy related colitis	1
Disease status downstaged post operatively	1
Moved to different location	1

Patient non-compliance	1
Fatigue/frustrated with treatment, pat declined	1
Perform stat drop, prolonged recovery, pat decline	1
Died	4
Missing	2
Unacceptable blood results prior to first niv	1

Baseline characteristics

Reporting groups	
Reporting group title	Main Trial (overall period)

Reporting group description: -

Reporting group values	Main Trial (overall period)	Total	
Number of subjects	23	23	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	15	15	
From 65-84 years	8	8	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	9	9	
Male	14	14	
Smoking status Units: Subjects			
Non-smoker	10	10	
Current smoker	7	7	
Ex-smoker	6	6	
Alcohol (units per week) Units: Subjects			
0-14 units	15	15	
15-35 units	4	4	
>35 units	4	4	
ECOG Units: Subjects			
Zero	19	19	
One	4	4	
Tumour Units: Subjects			
T2	2	2	
T3	5	5	
T4	3	3	
T4a	12	12	
T4b	1	1	
Nodes Units: Subjects			
N0	5	5	

N1	8	8	
N2b	6	6	
N2c	3	3	
N3b	1	1	
Metastases Units: Subjects			
M0	23	23	
Radiological evidence of extra capsular spread Units: Subjects			
No	19	19	
Yes	4	4	
Tumour size Units: mm^2			
median	705.0		
inter-quartile range (Q1-Q3)	391.0 to 1352.0	-	
Haemoglobin Units: g/L			
median	136.0		
inter-quartile range (Q1-Q3)	128.0 to 152.0	-	
WBC Units: 10^9/L			
median	8.6		
inter-quartile range (Q1-Q3)	6.6 to 10.4	-	
Neutrophils Units: 10^9/L			
median	5.7		
inter-quartile range (Q1-Q3)	4.3 to 7.7	-	
Lymphocytes Units: 10^9/L			
median	1.8		
inter-quartile range (Q1-Q3)	1.3 to 2.2	-	
Platelets Units: 10^9/L			
median	295.0		
inter-quartile range (Q1-Q3)	259.0 to 365.0	-	
TSH Units: mU/L			
median	2.2		
inter-quartile range (Q1-Q3)	1.6 to 3.5	-	
Lipase Units: U/L			
median	29.5		
inter-quartile range (Q1-Q3)	25.0 to 34.0	-	
Amylase Units: U/L			
median	58.0		
inter-quartile range (Q1-Q3)	42.0 to 75.0	-	
Blood glucose Units: mmol/L			
median	5.6		
inter-quartile range (Q1-Q3)	5.1 to 5.9	-	

Sodium Units: mmol/L median inter-quartile range (Q1-Q3)	 140.0 136.0 to 140.0	 -	
Potassium Units: mmol/L median inter-quartile range (Q1-Q3)	 4.4 4.2 to 4.9	 -	
Calcium (unadjusted) Units: mmol/L median inter-quartile range (Q1-Q3)	 2.4 2.3 to 2.5	 -	
Calcium (adjusted) Units: mmol/L median inter-quartile range (Q1-Q3)	 2.3 2.2 to 2.4	 -	
Magnesium Units: mmol/L median inter-quartile range (Q1-Q3)	 0.8 0.8 to 0.9	 -	
Urea Units: mmol/L median inter-quartile range (Q1-Q3)	 4.9 3.7 to 5.6	 -	
Creatinine Units: µmol/L median inter-quartile range (Q1-Q3)	 80.0 70.0 to 85.0	 -	
Creatinine clearance Units: ml/min median inter-quartile range (Q1-Q3)	 97.3 74.3 to 119.0	 -	
Total bilirubin Units: µmol/L median inter-quartile range (Q1-Q3)	 8.0 5.0 to 11.0	 -	
Albumin Units: g/L median inter-quartile range (Q1-Q3)	 44.0 42.0 to 45.0	 -	
ALP Units: U/L median inter-quartile range (Q1-Q3)	 73.0 69.0 to 103.0	 -	
AST Units: U/L median inter-quartile range (Q1-Q3)	 18.0 16.0 to 44.0	 -	
ALT Units: U/L median inter-quartile range (Q1-Q3)	 18.0 13.0 to 38.0	 -	

YGT Units: U/L median inter-quartile range (Q1-Q3)	 44.5 19.0 to 138.5	 -	
Age continuous Units: Years median inter-quartile range (Q1-Q3)	 62.0 47.0 to 66.0	 -	

End points

End points reporting groups

Reporting group title	Nivolumab

Reporting group description:

Single dose of nivolumab (240mg flat dose) will be delivered pre-surgery and then between surgery and chemoradiotherapy/radiotherapy. The latter will be followed by six months of adjuvant nivolumab (480mg flat dose every 4 weeks, total of 6 doses). Resection of the tumour, and radiotherapy or chemoradiotherapy will follow standard practice, with patients with high risk features on pathological section (presence of extracapsular spread, involved or positive margins) being assigned to chemoradiation.

Primary: One year disease-free survival rate

End point title	One year disease-free survival rate[1]

End point description:

End point type	Primary

End point timeframe:

Probability of disease-free survival at 12 months following surgery

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: Due to the trial being stopped early, there was no statistical analyses conducted.

End point values	Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	20[2]			
Units: Probability				
number (confidence interval 95%)	0.84 (0.59 to 0.95)			

Notes:

[2] - All participants who had surgery

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical complications - surgical site infection

End point title	Surgical complications - surgical site infection

End point description:

End point type	Secondary

End point timeframe:

Surgical site infection following trial surgery

End point values	Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	20[3]			
Units: Surgical site infection rate				
number (confidence interval 95%)	0.26 (0.09 to 0.51)			

Notes:

[3] - All participants who had surgery

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical complications - other infection

End point title	Surgical complications - other infection

End point description:

End point type	Secondary

End point timeframe:

Other infection post trial surgery

End point values	Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	20[4]			
Units: Other infection rate				
number (confidence interval 95%)	0.32 (0.13 to 0.57)			

Notes:

[4] - All participants who had surgery

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical complications - length of hospital admission

End point title	Surgical complications - length of hospital admission

End point description:

End point type	Secondary

End point timeframe:

Length of hospital admission post trial surgery

End point values	Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	19[5]			
Units: Days				
arithmetic mean (confidence interval 95%)	13.21 (10.05 to 16.37)			

Notes:

[5] - All participants who had surgery and are not missing discharge dates

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical complications - free flap failure &/or compromise

End point title	Surgical complications - free flap failure &/or compromise

End point description:

End point type	Secondary

End point timeframe:

Free flap failure &/or compromise post trial surgery

End point values	Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	20[6]			
Units: Free flap failure &/or compromise rate				
number (confidence interval 95%)	0.11 (0.01 to 0.33)			

Notes:

[6] - All participants who had surgery

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical complications - perioperative (30-day) mortality

End point title	Surgical complications - perioperative (30-day) mortality

End point description:

End point type	Secondary

End point timeframe:

Perioperative (30-day) mortality post surgery

End point values	Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	20[7]			
Units: Perioperative (30-day) mortality rate				
number (confidence interval 95%)	0.05 (0.00 to 0.25)			

Notes:

[7] - All participants who had surgery

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life - EORTC QLQ-C30

End point title	Quality of life - EORTC QLQ-C30

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to end of treatment

End point values	Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	11[8]			
Units: Change from baseline in score				
arithmetic mean (confidence interval 95%)				
Global health status/QoL	-0.76 (-18.72 to 17.20)			
Physical Functioning	-13.33 (-27.78 to 1.11)			
Role Functioning	-12.12 (-35.12 to 10.88)			
Emotional Functioning	11.36 (-0.45 to 23.18)			
Cognitive Functioning	-6.06 (-15.12 to 3.00)			
Social Functioning	-12.12 (-27.22 to 2.98)			
Fatigue	12.12 (-11.12 to 35.36)			
Nausea and Vomiting	-1.52 (-13.21 to 10.18)			
Pain	-12.12 (-34.00 to 9.76)			
Dyspnoea	9.09 (-8.52 to 26.70)			
Insomnia	6.06 (-21.94 to 34.06)			
Appetite Loss	6.06 (-26.88 to 39.00)			

Constipation	9.09 (-15.63 to 33.81)			
Diarrhoea	3.03 (-9.05 to 15.11)			
Financial Difficulties	3.03 (-15.58 to 21.64)			

Notes:

[8] - All participants with both baseline and end of treatment questionnaires

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life - EORTC QLQ-H&N35

End point title	Quality of life - EORTC QLQ-H&N35

End point description:

End point type	Secondary

End point timeframe:

Change in quality of life from baseline to end of treatment

End point values	Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	10[9]			
Units: Change from baseline score				
arithmetic mean (confidence interval 95%)				
Pain	-13.33 (-29.53 to 2.86)			
Swallowing	-0.83 (-25.56 to 23.90)			
Senses problems	10.00 (-7.95 to 27.95)			
Speech problems	8.89 (-4.52 to 22.29)			
Trouble with social eating	18.33 (-6.13 to 42.80)			
Trouble with social contact	22.67 (7.39 to 37.95)			
Less sexuality	10.00 (-21.39 to 41.39)			
Teeth	10.00 (-12.62 to 32.62)			
Opening mouth	-3.33 (-31.88 to 25.21)			
Dry mouth	13.33 (-6.77 to 33.44)			
Sticky saliva	0.00 (-19.47 to 19.47)			
Coughing	16.67 (-6.51 to 39.84)			
Felt ill	6.67 (-22.65 to 35.98)			

Notes:
[9] - All participants with baseline and end of treatment questionnaires

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life - EORTC QLQ-H&N35 binary items

End point title	Quality of life - EORTC QLQ-H&N35 binary items

End point description:

End point type	Secondary

End point timeframe:
Change in quality of life from baseline to end of treatment

End point values	Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	10[10]			
Units: Participants				
Painkillers Yes-Yes	5			
Painkillers Yes-No	5			
Nutritional supplements (exc vitamins) Yes-Yes	3			
Nutritional supplements (exc vitamins) No-Yes	3			
Nutritional supplements (exc vitamins) No-No	4			
Feeding tube No-Yes	1			
Feeding tube No-No	9			
Lost weight Yes-Yes	1			
Lost weight Yes-No	2			
Lost weight No-Yes	2			
Lost weight No-No	5			
Gained weight Yes-Yes	2			
Gained weight Yes-No	1			
Gained weight No-Yes	4			
Gained weight No-No	3			

Notes:
[10] - All participants with baseline and end of treatment questionnaires

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free survival

End point title	Disease-free survival

End point description:

End point type	Secondary

End point timeframe:

Measured as time from surgery until disease recurrence or death. The survival probability never goes below 0.5 so no median is able to be presented.

End point values	Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	20[11]			
Units: Participants				
Experienced disease recurrence or death	4			
Did not experience disease recurrence or death	16			

Notes:

[11] - All participants who had surgery

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Measured as time from recruitment until death. The survival probability never goes below 0.5 so a median is not presented.

End point values	Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	23[12]			
Units: Participants				
Experienced death	4			
Did not experience death	19			

Notes:

[12] - All participants

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

New AEs that occurred following consent and up to 100 days post last dose of trial treatment needed to be recorded. In other situations, medical and scientific judgement were exercised to decide if expedited reporting was appropriate.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Safety

Reporting group description:

Participants had to have had at least once dose of Nivolumab.

Serious adverse events	Safety		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 22 (36.36%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	1		
Cardiac disorders			
Heart failure			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Oral haemorrhage			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Toxic epidermal necrolysis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusion			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Head soft tissue necrosis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis intestinal perforated			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 22 (86.36%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	5		
Fever			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	2		
Mucositis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	13 / 22 (59.09%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Sore throat			
subjects affected / exposed	6 / 22 (27.27%)		
occurrences (all)	6		
Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		

Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 3 / 22 (13.64%) 3		
Investigations Creatinine increased subjects affected / exposed occurrences (all) Thyroid stim. hormone increased subjects affected / exposed occurrences (all) WBC decreased subjects affected / exposed occurrences (all) Weight loss subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 12 / 22 (54.55%) 11		
Injury, poisoning and procedural complications Dermatitis radiation subjects affected / exposed occurrences (all) Incisional hernia subjects affected / exposed occurrences (all)	 11 / 22 (50.00%) 10 1 / 22 (4.55%) 1		
Cardiac disorders Left bundle branch block subjects affected / exposed occurrences (all) Right bundle branch block subjects affected / exposed occurrences (all) Sinus tachycardia subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1		
Nervous system disorders			

Dysgeusia subjects affected / exposed occurrences (all)	6 / 22 (27.27%) 6		
Lethargy subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Colitis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Constipation subjects affected / exposed occurrences (all)	6 / 22 (27.27%) 6		
Diarrhoea subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Dry mouth subjects affected / exposed occurrences (all)	6 / 22 (27.27%) 6		
Dysphagia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Mucositis oral			

subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Oral pain subjects affected / exposed occurrences (all) Proctitis subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	17 / 22 (77.27%) 13 8 / 22 (36.36%) 8 2 / 22 (9.09%) 2 1 / 22 (4.55%) 1 7 / 22 (31.82%) 5		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Maculopapular rash subjects affected / exposed occurrences (all) Skin disorder subjects affected / exposed occurrences (all)	 2 / 22 (9.09%) 2 1 / 22 (4.55%) 1 2 / 22 (9.09%) 2 1 / 22 (4.55%) 1		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) Chronic kidney disease subjects affected / exposed occurrences (all)	 2 / 22 (9.09%) 2 1 / 22 (4.55%) 1		
Endocrine disorders			

Adrenal insufficiency			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Hyperthyroidism			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	1		
Hypothyroidism			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Lung infection			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Throat infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Upper respiratory infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Wound infection			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Dehydration			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hyperkalemia			

subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Hypoglycaemia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hypomagnesemia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Hypophosphatemia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2019	Update of PIs at sites. Addition of new sites. Update of RSI and IB
08 August 2019	Addition of 4 new sites
29 July 2020	Dear Patient and Dear Investigator Letters prepared in response to NICO re-opening and lifting the pause in recruitment due to COVID-19 NIHR issued guidance for consideration towards restarting projects (see Annex A https://www.nihr.ac.uk/documents/restart-framework/24886) NICO re-start followed this framework.
13 August 2020	Substantial amendment to the Protocol, PIS and ICF to include: 1. Update to Reference Safety Information following Investigator Brochure update. 2. Trial Treatment: Time to adjuvant Nivolumab extended from 6 weeks to 10 weeks 3. Change to follow up scan times from 4 months to 6, 9, 12 to ensure scans are outside of treatment window 4. Chemo/Radiotherapy updated to clarify any patient experiencing an 8 week or greater interval between surgery and commencement of radiotherapy/chemoradiotherapy will be withdrawn from the trial. 5. Translational Research Sub-studies: a) faecal and oral microbiome samples and b) imaging 6. Translational samples: increase amount of blood sample as original bloods insufficient for testing / maximise opportunities 7. Ethical Considerations: Update to include GDPR requirements Luton & Dunstable Site added
06 November 2020	Addition 3 New sites: The Walton Centre (MRI sub-study site) East Lancashire Hospital Trust (ELHT) (Royal Blackburn Teaching Hospital) Cambridge University Hospital Trust (Addenbrooke's Hospital)
11 February 2021	Early Termination by funder (MS) Protocol update & Dear Patient Letter/reconsent

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 October 2020	On 26/10/2020, the study funder wrote to the Chief Investigator and Study Sponsor to terminate the Investigator-Sponsor Research Agreement. The termination allowed the continued registration of new patients up to 30 days from the date of the letter of termination. All study recruitment was ceased by 25/11/2020.	-

Notes:

Limitations and caveats

None reported