Neoadjuvant and adjuvant nivolumab as **I**mmune **C**heckpoint inhibition in **O**ral cavity cancer

Eudract No.: 2017-005015-13

Trial registration No.: ISRCTN17428671

Final Statistical Analysis Report

Version 1.0 28/10/2024

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Date	28/10/2024		
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Report Shell Version and Date	N/A – V2.0 of the SAP followed the legacy LCTU template so the shell tables were included within the SAP. The tables and figures have been moved from the SAP to the current LCTC report template.		

1 Table of Contents

2 List of Tables and Figures

3 Protocol Amendments

For protocol amendments, please refer to section 18 of the NICO protocol.

4 Trial Milestones

Table 4-1 Trial Milestones

First patient was registered on:	19/08/2019
Last patient was registered on:	25/11/2020
Total number registered:	23
Total number screened:	57

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5 Recruitment

5.1 Recruitment by centre and arm

Table 5-1 Recruitment by centre

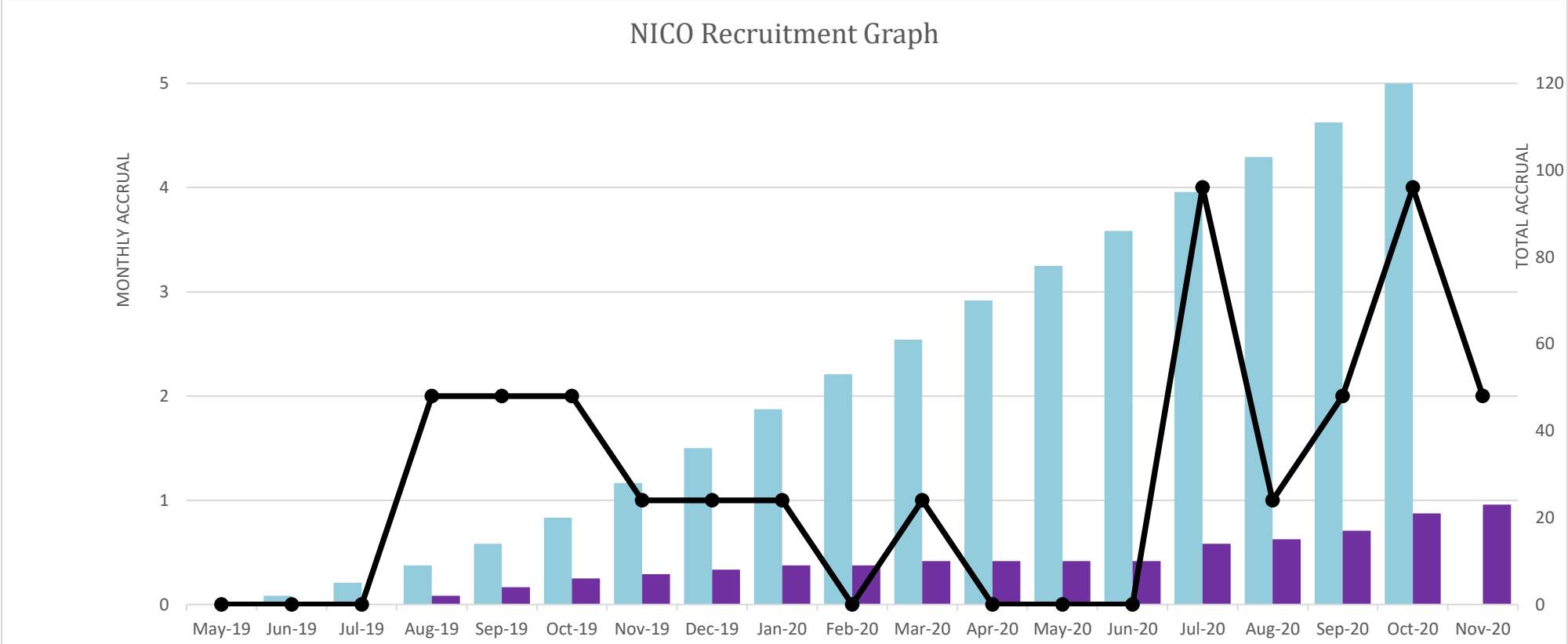
Site name	Date of greenlight	Date of first registration	Date of last registration	N screened	Not registered			N registered[1]	N allocated to RT	N allocated to CRT
					N ineligible	N declined	N other [N missing]			
University Hospital Aintree	08/05/2019	19/08/2019	25/11/2020	41	11	6	4 [1]	19	8	6
Greater Glasgow & Clyde	06/08/2019	27/12/2019	01/10/2020	16	0	5	4 [3]	4	1	2
The Clatterbridge Cancer Centre (Wirral)[2]	08/05/2019	NA	NA	0	0	0	0 [0]	0	0	0
University College Hospital (London)	11/09/2020	NA	NA	0	0	0	0 [0]	0	0	0
			Total	**57**	**11**	**11**	**8 [4]**	**23**	**9**	**8**

[1] 6 registered patients were not allocated to either RT or CRT.
[2] The Clatterbridge Cancer Centre was not a recruiting centre.

Created using: "S:\Statistical Documents\Trials\NICO\Closed\3.Final Analysis\Version 1.0\Update July 2024\Programs\03 - Recruitment by Centre V1.0.sas"

5.2 Recruitment graph

Figure 5-1 Recruitment graph



	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20
Target Accrual	0	2	5	9	14	20	28	36	45	53	61	70	78	86	95	103	111	120	
Actual Accrual	0	0	0	2	4	6	7	8	9	9	10	10	10	10	14	15	17	21	23
Montly Accrual	0	0	0	2	2	2	1	1	1	0	1	0	0	0	4	1	2	4	2

Created using: "S:\Statistical Documents\Trials\ NICO\Closed\3.Final Analysis\Version 1.0\Update July 2024\Programs\04 - Recruitment Graph Numbers V1.0.sas" and "S:\Statistical Documents\Trials\NICO\Closed\3.Final Analysis\Version 1.0\Programs\05 - Recruitment Forecast V1.0.R"

5.3 Number of sites opened per month

Table 5-2 Sites opened per month

Number of months since greenlight	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Number of sites opened*	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3

* The Clatterbridge cancer centre has not been included in this table as it was not a recruiting centre.

Created using: "S:\Statistical Documents\Trials\NICO\Closed\3.Final Analysis\Version 1.0\Update July 2024\Programs\06 - Sites Opened per Month V2.0.sas"

5.4 Recruitment problems

A) Regulatory delays – there were no regulatory delays.
B) Local trust R&D approvals – the trial was halted by the funder during site opening phase, 3 sites opened (as recruiting sites) and 2 sites recruited.
C) Local funding issues – there were no local funding issues.
D) Other – early trial termination by funder.

5.5 Recruitment rate

Table 5-3 Observed recruitment rate

Mean number of patients per site*	7.67
Mean number of patients per site, per month*^	0.42

* The Clatterbridge cancer centre has not been included in this table as it was not a recruiting centre.
^ Accounting for the number of months each site was open.

Created using: "S:\Statistical Documents\Trials\NICO\Closed\3.Final Analysis\Version 1.0\Update July 2024\Programs\07 - Observed Recruitment Rate V2.0.sas"

6 Assessment of Study Quality

Table 6-1 Missing CRFs by site

Missing data are captured in outcome tables.

Table 6-2 Missing CRFs by form

Missing data are captured in outcome tables.

Table 6-3 Summary of protocol deviations (identified and recorded)

Type	Description	Post-(C)RT allocation		Pre- and post-(C)RT allocation n deviations
		RT n deviations	CRT n deviations	
Minor	Protocol deviations not expected to have an impact on defined endpoints of the trial	3	2	5

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Table 6-4 Number of patients with major deviations

No patients had any major deviations identified and recorded.

Table 6-5 Registration checks

Check	Result
Are registration numbers[3] in correct date order?	No
Are there missing registration trial numbers?	No

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Table 6-6 Registration errors discovered

Error	Action taken
One patient's registration number is out of order	No action was taken as this was noticed retrospectively

[3] Patient numbers were assigned at screening.

7 Serious Breaches

There were no serious breaches.

8 Patient Allocation Progress

Table 8-1 Patient allocation progress by site

Site name	N registered	N not allocated to (C)RT	N allocated to RT	N allocated to CRT
University Hospital Aintree	19	5	8	6
Greater Glasgow & Clyde	4	1	1	2
The Clatterbridge Cancer Centre (Wirral)[2]	0	0	0	0
University College Hospital (London)	0	0	0	0
Total	**23**	**6**	**9**	**8**

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Table 8-2 CRT/RT allocation based on patient risk level

High risk cohort	RT allocation	CRT allocation
No	9	0
Yes*	0	8

* High risk patients will have at least one of the following:

- Cervical lymph node metastasis with extra-capsular spread.
- Surgical margins: Margins ≤ 1mm, or Close Margins (1-5mm), if in the presence of additional high-risk features such as perineural invasion, adverse pattern of invasion, multiple lymph nodes involved by metastasis, vascular emboli of tumour.

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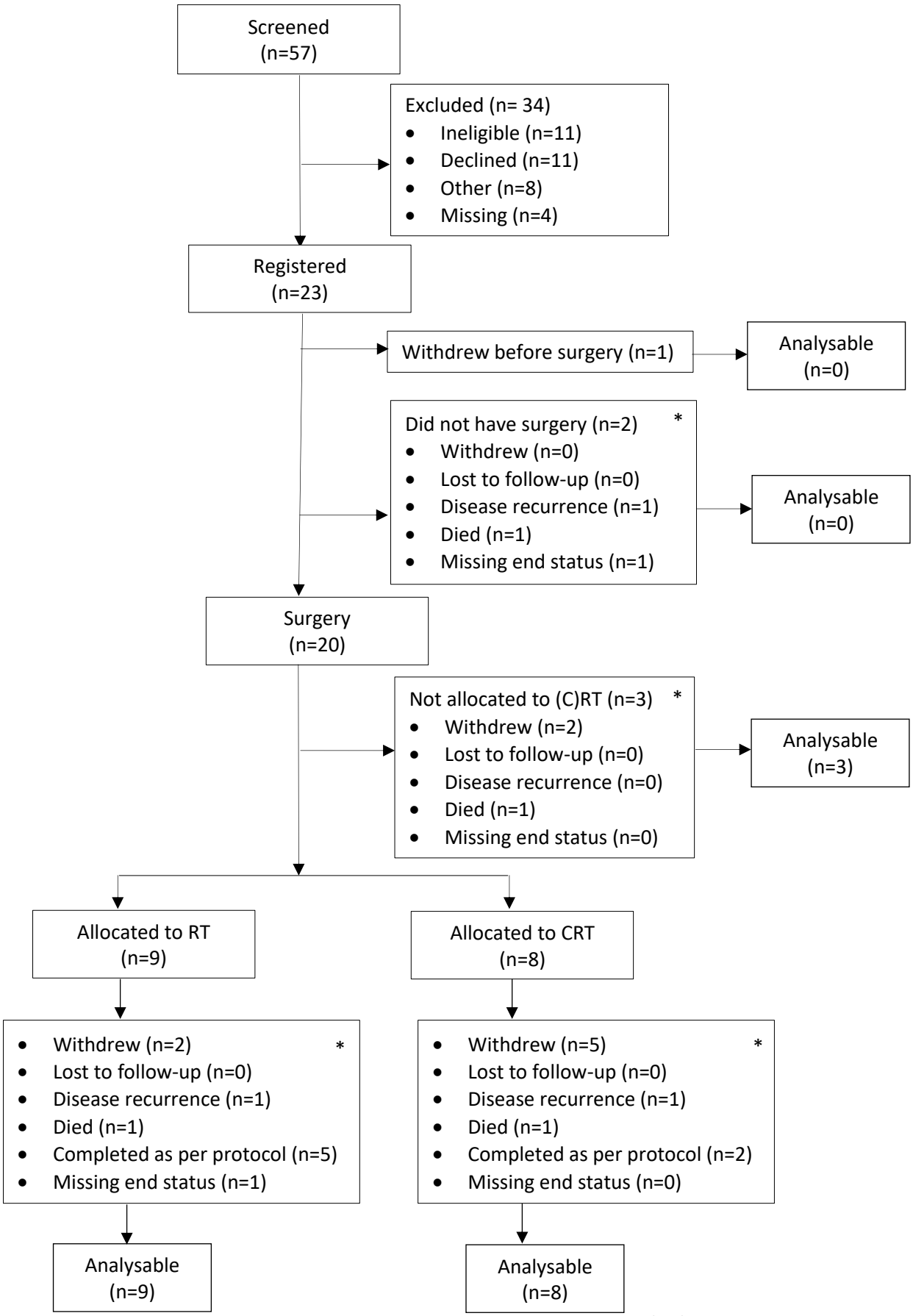
9 Completeness of follow-up

Figure 8-1 Patient disposition



* Patients may have experienced more than one study end status.

Created using: "S:\Statistical Documents\Trials\NICO\Closed\3.Final Analysis\Version 1.0\Update July 2024\Programs\11 - Completeness of Follow-up V2.0.sas"

Table 9-1 Premature withdrawals from treatment

		Post-(C)RT allocation (n=17)		Pre- and post-(C)RT allocation (n=23)
		RT (n=9)	CRT (n=8)	
Withdrawal status: n (%)	Completed as per protocol	5 (55.6)	2 (25.0)	7 (30.4)
	Prematurely withdrew	4 (44.4)	6 (75.0)	15 (65.2)
	Missing	0 (0.0)	0 (0.0)	1 (4.3)
Reason for withdrawal: n (%)		(N=4)	(N=6)	(N=15)
	Intolerable toxicity (treatment related)	2 (50.0)	2 (33.3)	4 (26.7)
	Disease recurrence	1 (25.0)	0 (0.0)	1 (6.7)
	Clinician decision (not Adverse Event)	0 (0.0)	0 (0.0)	2 (13.3)
	Patient decision (not Adverse Event)	1 (25.0)	4 (66.7)	6 (40.0)
	Death	0 (0.0)	0 (0.0)	1 (6.7)
	Withdrawn after first nivolumab dose but prior to surgical resection as condition deemed no longer amenable to surgery	0 (0.0)	0 (0.0)	1 (6.7)
Stage of withdrawal[4]: n (%)		(N=4)	(N=6)	(N=15)
	Did not commence treatment	0 (0.0)	0 (0.0)	1 (6.7)
	Pre-surgery Nivolumab dose	0 (0.0)	0 (0.0)	1 (6.7)
	Surgery	0 (0.0)	0 (0.0)	3 (20.0)

[4] Stage of withdrawal is the stage of treatment received.

CRT/RT allocation	1 (25.0)	2 (33.3)	3 (20.0)
Post CRT/RT allocation, Nivolumab dose 3-5	2 (50.0)	3 (50.0)	5 (33.3)
Post CRT/RT allocation, Nivolumab dose 6-7	1 (25.0)	1 (16.7)	2 (13.3)

Created using: "S:\Statistical Documents\Trials\NICO\Closed\3.Final Analysis\Version 1.0\Update July 2024\Programs\12 - Withdrawal from Treatment V1.0.sas"

Table 9-2 Premature withdrawals from study

		Post-(C)RT allocation (n=17)		**Pre- and post-(C)RT allocation (n=23)**
		RT (n=9)	**CRT (n=8)**	
Withdrawal status: n (%)	Completed as per protocol	5 (55.6)	2 (25.0)	7 (30.4)
	Prematurely withdrew	3 (33.3)	6 (75.0)	14 (60.9)
	Missing	1 (11.1)	0 (0.0)	2 (8.7)
Reason for withdrawal: n (%)		(N=3)	(N=6)	(N=14)
	Death	1 (33.3)	1 (16.7)	4 (28.6)
	Disease status downstaged post operatively, adjuvant treatment not indicated, patient withdrawn from study	0 (0.0)	0 (0.0)	1 (7.1)
	Drop in performance status, prolonged recovery from radiotherapy, patient declined more immunotherapy	0 (0.0)	1 (16.7)	1 (7.1)
	Fatigue and frustrated with ongoing adjuvant treatment. Patient declined final cycle	0 (0.0)	1 (16.7)	1 (7.1)
	G1 pneumonitis on imaging, patient did not wish to continue treatment due to this	0 (0.0)	1 (16.7)	1 (7.1)
	Immunotherapy related colitis	1 (33.3)	0 (0.0)	1 (7.1)
	Intolerable Toxicity - colitis	0 (0.0)	1 (16.7)	1 (7.1)

	Patient Non-compliance. PI felt continuing treatment would not be safe or feasible.	0 (0.0)	1 (16.7)	1 (7.1)
	Patient withdrawn following decision not to have adjuvant treatment	0 (0.0)	0 (0.0)	1 (7.1)
	Withdrawal from treatment, due to moving to different location	1 (33.3)	0 (0.0)	1 (7.1)
	unacceptable blood results prior to first nivolumab - therefore no nivolumab given	0 (0.0)	0 (0.0)	1 (7.1)
Stage of withdrawal[5]: n (%)		(N=3)	(N=6)	(N=14)
	Did not commence treatment	0 (0.0)	0 (0.0)	1 (7.1)
	Pre-surgery Nivolumab dose	0 (0.0)	0 (0.0)	1 (7.1)
	Surgery	0 (0.0)	0 (0.0)	1 (7.1)
	CRT/RT allocation	0 (0.0)	2 (33.3)	2 (14.3)
	Post CRT/RT allocation, Nivolumab dose 3-5	1 (33.3)	0 (0.0)	1 (7.1)
	Follow-up	2 (66.7)	4 (66.7)	8 (57.1)

Created using: "S:\Statistical Documents\Trials\NICO\Closed\3.Final Analysis\Version 1.0\Update July 2024\Programs\13 - Withdrawal from Study V1.0.sas"

[5] Stage of treatment received. If patients were followed up after they prematurely withdrew from treatment their stage of withdrawal for withdrawal from study is follow-up.

10 Baseline characteristics

Table 10-1 Baseline characteristics

		Post-(C)RT allocation (n=17)		Pre- and post-(C)RT allocation (n=23)
		RT (n=9)	CRT (n=8)	
Demographics				
Sex: n (%)	Male	4 (44.4)	7 (87.5)	14 (60.9)
	Female	5 (55.6)	1 (12.5)	9 (39.1)
Age (years)	Median (IQR)	64.0 (55.0-66.0)	56.0 (43.0-62.5)	62.0 (47.0-66.0)
Age: n (%)	18 to 64 years	5 (55.6)	7 (87.5)	15 (65.2)
	65 to 84 years	4 (44.4)	1 (12.5)	8 (34.8)
Smoking: n (%)	Non-smoker	5 (55.6)	3 (37.5)	10 (43.5)
	Current smoker	2 (22.2)	3 (37.5)	7 (30.4)
	Ex-smoker	2 (22.2)	2 (25.0)	6 (26.1)
Alcohol (units per week): n (%)	0-14 units	6 (66.7)	5 (62.5)	15 (65.2)
	15-35 units	2 (22.2)	2 (25.0)	4 (17.4)
	>35 units	1 (11.1)	1 (12.5)	4 (17.4)
Physical Assessment				
ECOG: n (%)	0	7 (77.8)	8 (100.0)	19 (82.6)
	1	2 (22.2)	0 (0.0)	4 (17.4)
Clinical Characteristics				
Tumour: n (%)	T2	0 (0.0)	2 (25.0)	2 (8.7)
	T3	1 (11.1)	2 (25.0)	5 (21.7)
	T4	2 (22.2)	0 (0.0)	3 (13.0)
	T4a	6 (66.7)	3 (37.5)	12 (52.2)
	T4b	0 (0.0)	1 (12.5)	1 (4.3)
Tumour size (mm^2)	Median (IQR)	900.0 (476.0-1352.0)	567.0 (296.0-1022.5)	705.0 (391.0-1352.0)
Nodes: n (%)	N0	2 (22.2)	1 (12.5)	5 (21.7)
	N1	5 (55.6)	2 (25.0)	8 (34.8)
	N2b	0 (0.0)	3 (37.5)	6 (26.1)
	N2c	1 (11.1)	2 (25.0)	3 (13.0)
	N3b	1 (11.1)	0 (0.0)	1 (4.3)
Metastases: n (%)	M0	9 (100.0)	8 (100.0)	23 (100.0)
Radiological evidence of extra capsular spread: n (%)	No	8 (88.9)	8 (100.0)	19 (82.6)
	Yes	1 (11.1)	0 (0.0)	4 (17.4)

Haematology				
Haemoglobin (g/L)	Median (IQR)	136.0 (117.0-144.0)	151.0 (132.5-153.0)	136.0 (128.0-152.0)
WBC (10^9/L)	Median (IQR)	8.1 (6.9-10.8)	9.0 (7.5-10.6)	8.6 (6.6-10.4)
Neutrophils (10^9/L)	Median (IQR)	6.2 (4.3-6.9)	6.0 (5.0-7.6)	5.7 (4.3-7.7)
Lymphocytes (10^9/L)	Median (IQR)	1.4 (1.1-2.6)	1.9 (1.5-2.0)	1.8 (1.3-2.2)
Platelets (10^9/L)	Median (IQR)	289.0 (259.0-312.0)	320.0 (272.0-408.5)	295.0 (259.0-365.0)
Thyroid Function Tests				
TSH (mU/L)	Median (IQR)	1.6 (1.4-3.2)	2.1 (1.8-3.0)	2.2 (1.6-3.5)
FT4 (pmol/L)	Median (IQR)	NA	NA	NA
	Missing	9	8	23
FT3 (pmol/L)	Median (IQR)	NA	NA	NA
	Missing	9	8	23
Lipase and Amylase				
Lipase (U/L)	Median (IQR)	25.0 (NA)	34.0 (NA)	29.5 (25.0-34.0)
	Missing	8	7	21
Amylase (U/L)	Median (IQR)	42.0 (40.0-44.0)	78.0 (NA)	58.0 (42.0-75.0)
	Missing	7	7	19
Biochemistry				
Blood glucose (mmol/L)	Median (IQR)	5.9 (5.8-6.7)	5.4 (5.0-5.8)	5.6 (5.1-5.9)
Sodium (mmol/L)	Median (IQR)	139.0 (135.0-140.0)	140.0 (139.0-140.5)	140.0 (136.0-140.0)
Potassium (mmol/L)	Median (IQR)	4.6 (4.4-4.7)	4.3 (4.2-4.9)	4.4 (4.2-4.9)
Calcium (unadjusted) (mmol/L)	Median (IQR)	2.4 (2.3-2.4)	2.4 (2.4-2.5)	2.4 (2.3-2.5)
Calcium (adjusted) (mmol/L)	Median (IQR)	2.3 (2.3-2.3)	2.4 (2.3-2.4)	2.3 (2.2-2.4)
Magnesium (mmol/L)	Median (IQR)	0.8 (0.8-0.9)	0.9 (0.8-0.9)	0.8 (0.8-0.9)
Urea (mmol/L)	Median (IQR)	5.4 (3.6-5.7)	4.5 (3.8-5.2)	4.9 (3.7-5.6)
Creatinine (µmol/L)	Median (IQR)	75.0 (70.0-81.0)	84.0 (77.0-90.0)	80.0 (70.0-85.0)
Creatinine clearance (ml/min)	Median (IQR)	84.7 (71.2-110.0)	118.3 (86.2-121.7)	97.3 (74.3-119.0)
Total bilirubin (µmol/L)	Median (IQR)	5.0 (5.0-10.0)	10.0 (6.5-12.0)	8.0 (5.0-11.0)
Albumin (g/L)	Median (IQR)	45.0 (42.0-46.0)	44.0 (43.0-44.0)	44.0 (42.0-45.0)
ALP (U/L)	Median (IQR)	71.0 (65.0-79.0)	88.0 (71.0-103.5)	73.0 (69.0-103.0)
AST (U/L)	Median (IQR)	17.0 (16.0-20.0)	22.5 (17.0-39.5)	18.0 (16.0-44.0)
ALT (U/L)	Median (IQR)	16.0 (13.0-17.0)	22.0 (14.5-50.5)	18.0 (13.0-38.0)
YGT (U/L)	Median (IQR)	42.5 (18.0-107.5)	68.5 (20.0-164.0)	44.5 (19.0-138.5)
	Missing	1	2	3

11 Exposure to Treatment and Compliance

Note: One patient has no Treatment CRFs but their SAE CRF indicates that they received Nivolumab - 22 patients were exposed to Nivolumab. However, the exposure to Nivolumab tables in this section are based on the Treatment CRFs.

Table 11-1 Exposure to treatment (Nivolumab)

		Post-(C)RT allocation (n=17)		Pre- and post-(C)RT allocation (n=23)
		RT (n=9)	CRT (n=8)	
Phase of treatment received: n (%)	0	9 (100.0)	8 (100.0)	23 (100.0)
	1 – Pre-surgery dose	9 (100.0)	8 (100.0)	21 (91.3)
	2 – Between surgery and CRT/RT dose	7 (77.8)	7 (87.5)	14 (60.9)
	3 – Post CRT/RT dose 1	8 (88.9)	6 (75.0)	14 (60.9)
	4 – Post CRT/RT dose 2	7 (77.8)	5 (62.5)	12 (52.2)
	5 – Post CRT/RT dose 3	5 (55.6)	4 (50.0)	9 (39.1)
	6 – Post CRT/RT dose 4	6 (66.7)	3 (37.5)	9 (39.1)
	7 – Post CRT/RT dose 5	6 (66.7)	3 (37.5)	9 (39.1)
	8 – Post CRT/RT dose 6	5 (55.6)	2 (25.0)	7 (30.4)
Number of phases	Median	8.0	4.0	4.0
	IQR	(4.0-8.0)	(2.5-7.5)	(1.0-8.0)
	Range	(1.0-8.0)	(2.0-8.0)	(0.0-8.0)
Time from start to end of treatment (days)	Median	239.0	150.5	140.0
	IQR	(140.0-251.0)	(79.0-249.5)	(38.0-245.0)
	Range	(0.0-261.0)	(38.0-274.0)	(0.0-274.0)

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Table 11-2 Treatment dose received (Nivolumab)

Phase of treatment received		Nivolumab (mg)
1 - Pre-surgery dose	N	21
	Median (IQR)	240.0 (240.0-240.0)
	Missing	0
2 - Between surgery and CRT/RT dose	N	14
	Median (IQR)	240.0 (240.0-240.0)
	Missing	0

3 - Post CRT/RT dose 1	N	14
	Median (IQR)	480.0 (480.0-480.0)
	Missing	0
4 - Post CRT/RT dose 2	N	12
	Median (IQR)	480.0 (480.0-480.0)
	Missing	0
5 - Post CRT/RT dose 3	N	9
	Median (IQR)	480.0 (480.0-480.0)
	Missing	0
6 - Post CRT/RT dose 4	N	9
	Median (IQR)	480.0 (480.0-480.0)
	Missing	0
7 - Post CRT/RT dose 5	N	9
	Median (IQR)	480.0 (480.0-480.0)
	Missing	0
8 - Post CRT/RT dose 6	N	7
	Median (IQR)	480.0 (480.0-480.0)
	Missing	0

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Table 11-3 Treatment missed/ delayed (Nivolumab)

		Phase of treatment							
		Pre-surgery dose (n=22)	**Between surgery and CRT/RT dose (n=15)**	**Post CRT/RT dose 1 (n=14)**	**Post CRT/RT dose 2 (n=13)**	**Post CRT/RT dose 3 (n=10)**	**Post CRT/RT dose 4 (n=10)**	**Post CRT/RT dose 5 (n=9)**	**Post CRT/RT dose 6 (n=8)**
Completed treatment as scheduled: n (%)	Yes	20 (90.9)	14 (93.3)	11 (78.6)	12 (92.3)	8 (80.0)	9 (90.0)	9 (100.0)	7 (87.5)
	No	2 (9.1)	1 (6.7)	3 (21.4)	1 (7.7)	2 (20.0)	1 (10.0)	0 (0.0)	1 (12.5)
Treatment missed: n (%)		1 (4.5)	1 (6.7)	0 (0.0)	1 (7.7)	1 (10.0)	1 (10.0)	0 (0.0)	1 (12.5)
Reason missed treatment: n (%)	Toxicity	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
	Consultant decision	1 (4.5)	1 (6.7)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Patient Choice	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)
Treatment delayed: n (%)		1 (4.5)	0 (0.0)	3 (21.4)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Reason treatment delayed: n (%)	Toxicity	0 (0.0)	0 (0.0)	2 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Consultant decision	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Patient choice	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Dose delay due to product expiry	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of days delayed	N (Missing)	1 (0)	-	3 (0)	-	1 (0)	-	-	-
	Median (IQR)	1 (NA)	-	15.0 (7.0-20.0)	-	1 (NA)	-	-	-

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Table 11-4 Exposure to treatment and dosage received (Radiotherapy)

			Post-(C)RT allocation (n=17)	
			RT (n=9)	**CRT (n=8)**
Completed as per protocol: n (%)		Yes	8 (88.9)	5 (62.5)
		No	0 (0.0)	2 (25.0)
		Missing	1 (11.1)	1 (12.5)
Time from start to end of treatment (days)		N (Missing)	8 (1)	8 (0)
		Median (IQR)	39.0 (39.0-39.0)	39.0 (39.0-40.5)
		Range	(39.0-39.0)	(37.0-58.0)
Dose administered (gy)	High risk	N (Missing)	-	8 (0)
		Median (IQR)	-	65.0 (65.0-65.0)
		Range	-	(0.0-65.0)
	Intermediate risk	N (Missing)	8 (0)	7 (0)
		Median (IQR)	60.0 (60.0-60.0)	60.0 (60.0-60.0)
		Range	(60.0-60.0)	(0.0-60.0)
	Low risk	N (Missing)	8 (0)	7 (0)
		Median (IQR)	54.0 (54.0-54.0)	54.0 (54.0-54.0)
		Range	(54.0-54.0)	(54.0-66.0)
Total treatment time (days)	High risk	N (Missing)	-	8 (0)
		Median (IQR)	-	42.0 (42.0-42.0)
		Range	-	(0.0-58.0)
	Intermediate risk	N (Missing)	8 (0)	7 (0)
		Median (IQR)	42.0 (42.0-42.0)	42.0 (42.0-42.0)
		Range	(42.0-42.0)	(0.0-42.0)
	Low risk	N (Missing)	8 (0)	7 (0)
		Median (IQR)	42.0 (42.0-42.0)	42.0 (42.0-42.0)
		Range	(42.0-42.0)	(30.0-42.0)
Dose interrupted: n (%)			0 (0.0)	2 (25.0)

		Post-(C)RT allocation (n=17)	
		RT (n=9)	**CRT (n=8)**
Reason dose interrupted: n (%)	Adverse Event : Event not specified	0 (0.0)	2 (25.0)
Number of days missed	N (Missing)	-	2 (0)
	Median (IQR)	-	2.0 (1.0-3.0)
	Range	-	(1.0-3.0)

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Table 11-5 Exposure to treatment and dosage received (Chemotherapy)

		CRT (n=8)	
		Chemotherapy day 1	**Chemotherapy day 22**
Completed as per protocol: n (%)	Yes	5 (62.5)	2[6] (25.0)
	No	1 (12.5)	4 (50.0)
	Missing	2 (25.0)	2 (25.0)
Treatment given: n (%)		6 (75.0)	3 (37.5)
Dose administered (mg)	N (Missing)	6 (0)	3 (0)
	Median (IQR)	199.0 (185.0-209.0)	145.0 (130.0-150.0)
	Range	(145.0-209.0)	(130.0-150.0)
Treatment not given: n (%)		0 (0.0)	3 (37.5)
Reason treatment not given: n (%)	Adverse Event : Event not specified	0 (0.0)	3 (37.5)
Dose delayed: n (%)		0 (0.0)	1 (12.5)
Reason dose delayed: n (%)	Adverse Event : Mucositis	0 (0.0)	1 (12.5)
Dose reduced: n (%)		1 (12.5)	2 (25.0)
Reason dose reduced: n (%)	Adverse Event : Mucositis	0 (0.0)	1 (12.5)
	Adverse Event : Mucositis G2, fatigue G2	0 (0.0)	1 (12.5)

[6] One patient's Chemotherapy Day 22 CRF said that they completed treatment as per protocol but they had a dose reduction.

	Previous treatment with chemotherapy for breast cancer, dose reduced	1 (12.5)	0 (0.0)
Reduced dose (mg/ml)	N (Missing)	1 (0)	2 (0)
	Median (IQR)	80.0 (NA)	69.5 (59.0-80.0)
	Range	(NA)	(59.0-80.0)

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12 Outcome Data

12.1 Primary outcome 1 – One Year Disease-Free Survival Rate

Table 12-1 One-year disease-free survival (DFS) rate by cohort

Cohort		N surgery	N experienced recurrence or death[7]	One-year DFS* probability (95% confidence interval)
Post-(C)RT allocation	RT	9	1	0.86 (0.33, 0.98)
	CRT	8	1	0.89 (0.43, 0.98)
Pre and post-(C)RT allocation		20	3	0.84 (0.59, 0.95)

* Did not experience disease recurrence or death at 12 months following surgery.

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12.2 Primary outcome 2 – Feasibility of the Study to Recruit

The feasibility to recruit to both cohorts has been covered by Table 5-2 and Table 5-3.

12.3 Secondary outcome 1 – Disease-Free Survival

Table 12-2 Disease-free survival by cohort

Cohort		N surgery	N experienced recurrence or death	Disease-free survival time* (months)	
				Range	Median (95% confidence interval)
Post-(C)RT allocation	RT	9	1	(5.42-14.95)	NA^
	CRT	8	2	(3.55-13.17)	13.17 (10.55, 13.17)
Pre and post-(C)RT allocation		20	4	(0.69-15.14)	NA^

* Measured as time from surgery until disease recurrence or death.

^ The survival probability never goes below 0.5.

[7] Participants who withdrew from the study before reaching 12 months post-surgery (without experiencing disease recurrence or death) have been assumed to have not experienced disease recurrence or death at 12 months following surgery.

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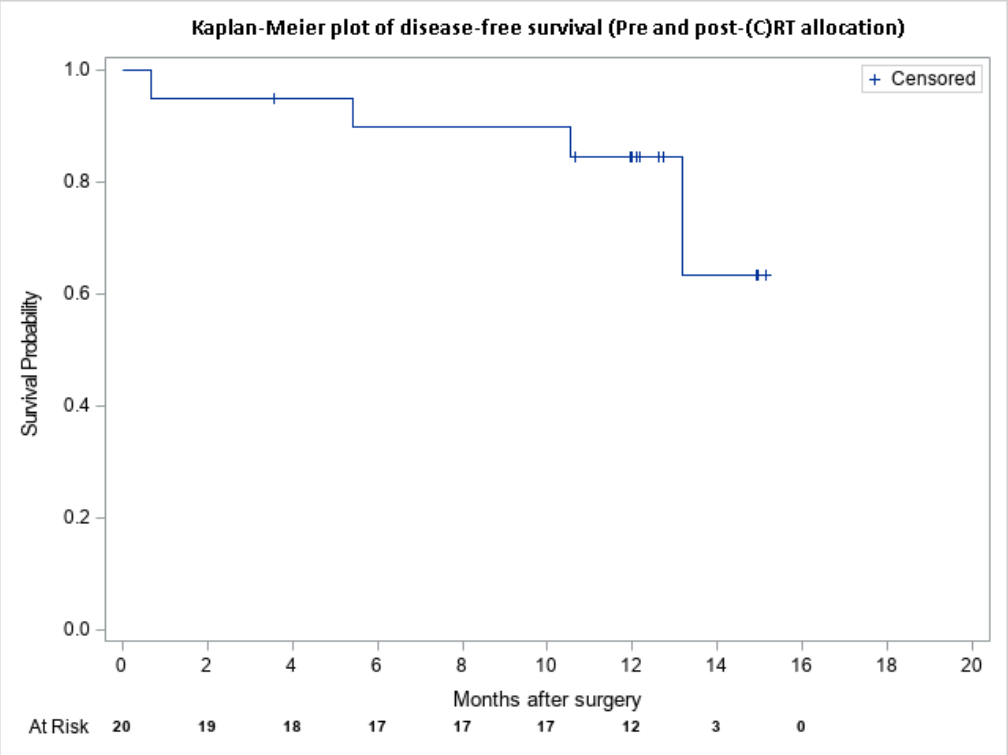
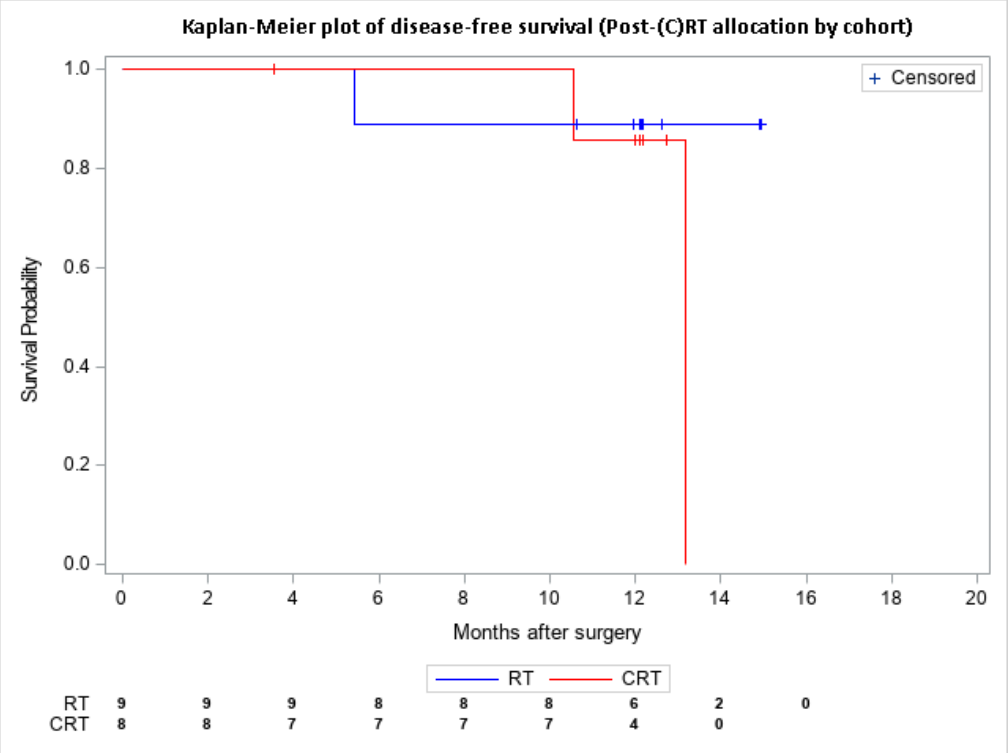
Figure 12-1 Kaplan-Meier plots of disease-free survival





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12.4 Secondary outcome 2 – Overall Survival

Table 12-3 Overall survival by cohort

Cohort		N registered	N experienced death	Overall survival time* (months)	
				Range	Median (95% confidence interval)
Post-(C)RT allocation	RT	9	1	(8.44-15.31)	NA^
	CRT	8	1	(3.94-13.50)	13.50 (NA~)
Pre and post-(C)RT allocation		23	4	(0.13-15.57)	NA^

* Measured as time from recruitment until death.

^ The survival probability never goes below 0.5.

~ Only one participant died and this was at the maximum survival time for this cohort so there is no confidence interval produced for the median survival time.

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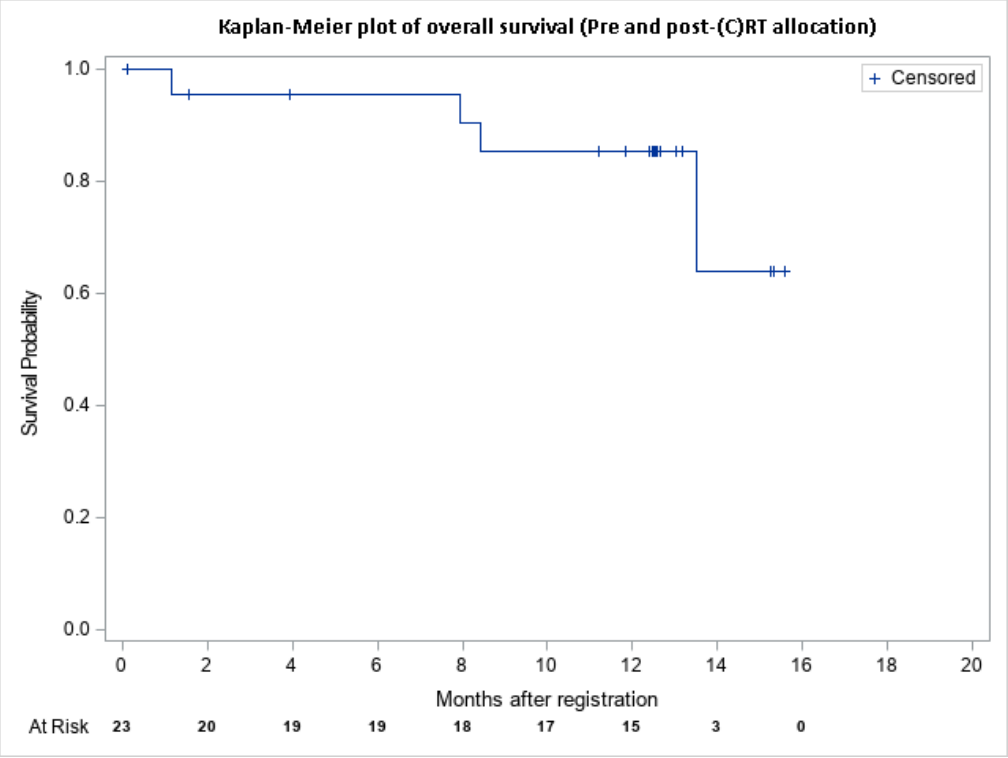
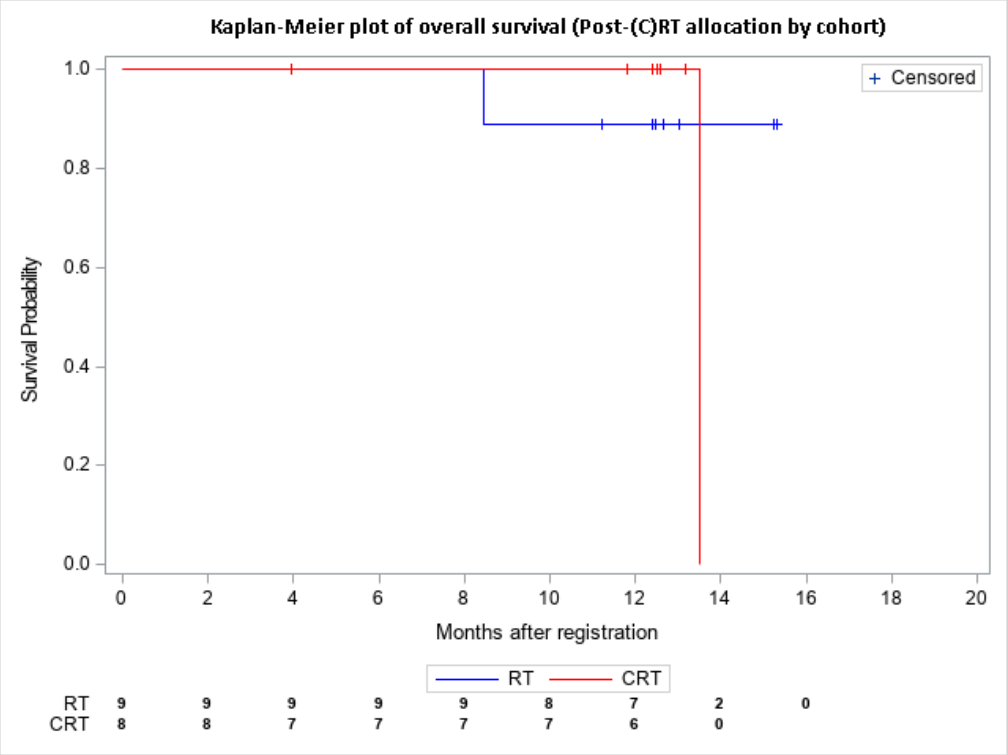
Figure 12-2 Kaplan-Meier plots of overall survival





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12.5 Secondary outcome 3 – Toxicity

Toxicity information is provided in Section 13.

12.6 Secondary outcome 4 – Surgical complications

Table 12-4 Summary of surgical complications by cohort

		Post-(C)RT allocation (n=17)		Pre- and post-(C)RT allocation (n=20)
		RT (n=9)	CRT (n=8)	
Surgical site infection: n (%)	None	7 (77.8)	6 (75.0)	14 (70.0)
	Grade I	0 (0.0)	1 (12.5)	1 (5.0)
	Grade II	1 (11.1)	0 (0.0)	1 (5.0)
	Grade IIIa	0 (0.0)	0 (0.0)	2 (10.0)
	Grade IIIb	1 (11.1)	0 (0.0)	1 (5.0)
	Missing	0 (0.0)	1 (12.5)	1 (5.0)
Other infection: n (%)	None	6 (66.7)	5 (62.5)	13 (65.0)
	Grade II	2 (22.2)	1 (12.5)	4 (20.0)
	Grade IIIa	1 (11.1)	0 (0.0)	1 (5.0)
	Grade missing	0 (0.0)	1 (12.5)	1 (5.0)
	Missing	0 (0.0)	1 (12.5)	1 (5.0)

Length of hospital admission (days)	Median (IQR)	13.0 (9.0-16.0)	9.0 (8.0-11.0)	11.0 (9.0-16.0)
	Missing	1	0	1
Free flap compromise &/ or failure: n (%)	No	8 (88.9)	7 (87.5)	17 (85.0)
	Yes	1 (11.1)	0 (0.0)	2 (10.0)
	Missing	0 (0.0)	1 (12.5)	1 (5.0)
Perioperative 30-day mortality: n (%)	Alive	9 (100.0)	8 (100.0)	19 (95.0)
	Death	0 (0.0)	0 (0.0)	1 (5.0)

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12.6.1 Infection

Table 12-5 Surgical site infection rate by cohort

Cohort		N surgery	N experienced surgical site infection (N missing)	Surgical site infection rate (95% confidence interval)
Post-(C)RT allocation	RT	9	2 (0)	0.22 (0.03, 0.60)
	CRT	8	1 (1)	0.14 (0.00, 0.58)
Pre and post-(C)RT allocation		20	5 (1)	0.26 (0.09, 0.51)

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Table 12-6 Other infection rate by cohort

Cohort		N surgery	N experienced other infection (N missing)	Other infection rate (95% confidence interval)
Post-(C)RT allocation	RT	9	3 (0)	0.33 (0.07, 0.70)
	CRT	8	2 (1)	0.29 (0.04, 0.71)
Pre and post-(C)RT allocation		20	6 (1)	0.32 (0.13, 0.57)

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12.6.2 Length of hospital admission

Table 12-7 Length of hospital admission (in days) by cohort

Cohort		N surgery (N missing discharge date)	Length of hospital admission	
			Range	Mean (95% confidence interval)
Post-(C)RT allocation	RT	9 (1)	(7-19)	12.75 (9.27, 16.23)
	CRT	8 (0)	(4-25)	10.63 (5.43, 15.82)

Pre and post-(C)RT allocation	20 (1)	(4-29)	13.21 (10.05, 16.37)

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12.6.3 Free flap failure &/or compromise

Table 12-8 Free flap failure &/or compromise rate by cohort

Cohort		N surgery	N experienced free flap failure &/or compromise (N missing)	Free flap failure &/or compromise rate (95% confidence interval)
Post-(C)RT allocation	RT	9	1 (0)	0.11 (0.00, 0.48)
	CRT	8	0 (1)	0.00 (NA)
Pre and post-(C)RT allocation		20	2 (1)	0.11 (0.01, 0.33)

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12.6.4 Perioperative (30-day) mortality

Table 12-9 Perioperative (30-day) mortality rate by cohort

Cohort		N surgery	N experienced perioperative (30-day) mortality (N missing)	Perioperative (30-day) mortality rate (95% confidence interval)
Post-(C)RT allocation	RT	9	0 (0)	0.00 (NA)
	CRT	8	0 (0)	0.00 (NA)
Pre and post-(C)RT allocation		20	1 (0)	0.05 (0.00, 0.25)

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12.7 Secondary outcome 5 – Quality of Life

The mean differences between baseline and end of study treatment measures are presented with the associated 95% confidence intervals. Data are available for 11 (EORTC QLQ-C30) and 10 (EORTC QLQ-H&N35) patients who have returned Quality of Life questionnaires at baseline and end of study treatment visits.

Table 12-10 Quality of life: completion data - forms received

Missing data are captured in change in quality of life tables.

Table 12-11 Change in quality of life from baseline to end of treatment (EORTC QLQ-C30)

EORTC QLQ-C30		Post-(C)RT allocation (n=17)		Pre- and post-(C)RT allocation (n=23)
		RT (n=9)	CRT (n=8)	
Global health status/QoL	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	4.17 (-13.97, 22.30)	-5.56 (-50.00-25.00)*	-0.76 (-18.72, 17.20)

Physical Functioning	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	-3.33 (-11.90, 5.24)	-28.89 (-53.33-0.00)*	-13.33 (-27.78, 1.11)
Role Functioning	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	-11.11 (-37.44, 15.22)	-16.67 (-50.00-0.00)*	-12.12 (-35.12, 10.88)
Emotional Functioning	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	19.44 (-1.00, 39.89)	-2.78 (-8.33-0.00)*	11.36 (-0.45, 23.18)
Cognitive Functioning	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	-5.56 (-23.62, 12.51)	-5.56 (-16.67-0.00)*	-6.06 (-15.12, 3.00)
Social Functioning	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	-16.67 (-38.79, 5.46)	-16.67 (-33.33-0.00)*	-12.12 (-27.22, 2.98)
Fatigue	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	3.70 (-24.54, 31.95)	29.63 (-11.11-66.67)*	12.12 (-11.12, 35.36)
Nausea and Vomiting	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	0.00 (-22.12, 22.12)	-5.56 (-16.67-0.00)*	-1.52 (-13.21, 10.18)
Pain	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	-11.11 (-43.68, 21.45)	-11.11 (-50.00-33.33)*	-12.12 (-34.00, 9.76)
Dyspnoea	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	0.00 (0.00-0.00)*	22.22 (0.00-33.33)*	9.09 (-8.52, 26.70)
Insomnia	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	0.00 (-54.19, 54.19)	22.22 (0.00-66.67)*	6.06 (-21.94, 34.06)
Appetite Loss	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	-11.11 (-63.78, 41.55)	44.44 (0.00-100.00)*	6.06 (-26.88, 39.00)
Constipation	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	11.11 (-31.25, 53.48)	22.22 (0.00-66.67)*	9.09 (-15.63, 33.81)
Diarrhoea	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	5.56 (-8.73, 19.84)	-11.11 (-33.33-0.00)*	3.03 (-9.05, 15.11)
Financial Difficulties	N included (N missing)	6 (3)	3 (5)	11 (12)
	Mean (95% CI)/(Range)*	-5.56 (-31.89, 20.78)	22.22 (0.00-33.33)*	3.03 (-15.58, 21.64)

* When 'N included' is 5 or less or there is no variance in scores, the range has been presented instead of a confidence interval.

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Table 12-12 Change in quality of life from baseline to end of treatment (EORTC QLQ-H&N35)

	Post-(C)RT allocation (n=17)		**Pre- and post-(C)RT allocation (n=23)**
EORTC QLQ-H&N35	**RT (n=9)**	**CRT (n=8)**	

Pain	N included (N missing)	6 (3)	2 (6)	10 (13)
	Mean (95% CI)/(Range)*	-12.50 (-37.08, 12.08)	-12.50 (-41.67-16.67)*	-13.33 (-29.53, 2.86)
Swallowing	N included (N missing)	6 (3)	2 (6)	10 (13)
	Mean (95% CI)/(Range)*	0.00 (-37.10, 37.10)	16.67 (-16.67-50.00)*	-0.83 (-25.56, 23.90)
Senses problems	N included (N missing)	6 (3)	2 (6)	10 (13)
	Mean (95% CI)/(Range)*	0.00 (-19.16, 19.16)	50.00 (50.00-50.00)*	10.00 (-7.95, 27.95)
Speech problems	N included (N missing)	6 (3)	2 (6)	10 (13)
	Mean (95% CI)/(Range)*	7.41 (-4.64, 19.45)	11.11 (-22.22-44.44)*	8.89 (-4.52, 22.29)
Trouble with social eating	N included (N missing)	6 (3)	2 (6)	10 (13)
	Mean (95% CI)/(Range)*	8.33 (-20.93, 37.60)	54.17 (25.00-83.33)*	18.33 (-6.13, 42.80)
Trouble with social contact	N included (N missing)	6 (3)	2 (6)	10 (13)
	Mean (95% CI)/(Range)*	10.00 (0.36, 19.64)	46.67 (40.00-53.33)*	22.67 (7.39, 37.95)
Less sexuality	N included (N missing)	6 (3)	2 (6)	10 (13)
	Mean (95% CI)/(Range)*	5.56 (-54.70, 65.81)	25.00 (16.67-33.33)*	10.00 (-21.39, 41.39)
Teeth	N included (N missing)	6 (3)	2 (6)	10 (13)
	Mean (95% CI)/(Range)*	11.11 (-25.02, 47.24)	0.00 (-33.33-33.33)*	10.00 (-12.62, 32.62)
Opening mouth	N included (N missing)	6 (3)	2 (6)	10 (13)
	Mean (95% CI)/(Range)*	-16.67 (-53.36, 20.02)	16.67 (0.00-33.33)*	-3.33 (-31.88, 25.21)
Dry mouth	N included (N missing)	6 (3)	2 (6)	10 (13)
	Mean (95% CI)/(Range)*	11.11 (-25.02, 47.24)	0.00 (0.00-0.00)*	13.33 (-6.77, 33.44)
Sticky saliva	N included (N missing)	6 (3)	2 (6)	10 (13)
	Mean (95% CI)/(Range)*	-5.56 (-39.95, 28.84)	16.67 (0.00-33.33)*	0.00 (-19.47, 19.47)
Coughing	N included (N missing)	6 (3)	2 (6)	10 (13)
	Mean (95% CI)/(Range)*	5.56 (-8.73, 19.84)	50.00 (33.33-66.67)*	16.67 (-6.51, 39.84)
Felt ill	N included (N missing)	6 (3)	2 (6)	10 (13)
	Mean (95% CI)/(Range)*	0.00 (-22.12, 22.12)	33.33 (-33.33-100.00)*	6.67 (-22.65, 35.98)

* When 'N included' is 5 or less or there is no variance in scores, the range has been presented instead of a confidence interval.

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Table 12-13 Change in quality of life from baseline to end of treatment (EORTC QLQ-H&N35) – binary items

EORTC QLQ-H&N35	Baseline - End of treatment n (%)	Post-(C)RT allocation (n=17)		Pre- and post-(C)RT allocation (n=23)
		RT (n=9)	CRT (n=8)	
Painkillers	Yes - Yes	2 (22.2)	1 (12.5)	5 (21.7)
	Yes - No	4 (44.4)	1 (12.5)	5 (21.7)

	Missing	3 (33.3)	6 (75.0)	13 (56.5)
Nutritional supplements (excluding vitamins)	Yes - Yes	2 (22.2)	1 (12.5)	3 (13.0)
	No - Yes	2 (22.2)	1 (12.5)	3 (13.0)
	No - No	2 (22.2)	0 (0.0)	4 (17.4)
	Missing	3 (33.3)	6 (75.0)	13 (56.5)
Feeding tube	No - Yes	1 (11.1)	0 (0.0)	1 (4.3)
	No - No	5 (55.6)	2 (25.0)	9 (39.1)
	Missing	3 (33.3)	6 (75.0)	13 (56.5)
Lost weight	Yes - Yes	0 (0.0)	1 (12.5)	1 (4.3)
	Yes - No	2 (22.2)	0 (0.0)	2 (8.7)
	No - Yes	1 (11.1)	1 (12.5)	2 (8.7)
	No - No	3 (33.3)	0 (0.0)	5 (21.7)
	Missing	3 (33.3)	6 (75.0)	13 (56.5)
Gained weight	Yes - Yes	0 (0.0)	0 (0.0)	2 (8.7)
	Yes - No	1 (11.1)	0 (0.0)	1 (4.3)
	No - Yes	4 (44.4)	0 (0.0)	4 (17.4)
	No - No	1 (11.1)	2 (25.0)	3 (13.0)
	Missing	3 (33.3)	6 (75.0)	13 (56.5)

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13 Safety Data

13.1 Non-serious adverse events

There were a total of 177 non-serious adverse events reported by 19 (86.4%) of the 22 patients in the safety population (all patients who received at least one dose of Nivolumab)[8]. 39 (22.0%) of the 177 non-serious adverse events were grade 3+.

Table 13-1 Non-serious adverse events by severity

	Post-(C)RT allocation (n=17)		Pre- and post-(C)RT allocation (n=22)
	RT (n=9)	CRT (n=8)	
AE Severity	Events n (%)	Events n (%)	Events n (%)
1	25 (26.3)	15 (22.1)	43 (24.3)
2	53 (55.8)	34 (50.0)	95 (53.7)
3	17 (17.9)	19 (27.9)	39 (22.0)
Total	95	68	177

Note: The denominator for this table is the total number of events.

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[8] The safety populations for Radiotherapy (RT) and Chemoradiotherapy (CRT) are all patients who were allocated to receive (C)RT and received at least one dose of Nivolumab, regardless of if they actually started (C)RT.

Table 13-2 Non-serious adverse events by System Organ Class and Lower Level Term

Adverse Event			Post-(C)RT allocation (n=17)				Pre- and post-(C)RT allocation (n=22)	
			RT (n=9)		CRT (n=8)			
Onset	**System Organ Class**	**Lower Level Term**	**Events n**	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**	**Patients n (%)**
Onset before date of operation:	Cardiac disorders	Left bundle branch block	0	0 (0.0)	0	0 (0.0)	1	1 (4.5)
		Right bundle branch block	0	0 (0.0)	1	1 (12.5)	1	1 (4.5)
		Sinus tachycardia	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
	Gastrointestinal disorders	Constipation	2	2 (22.2)	0	0 (0.0)	2	2 (9.1)
		Mucositis oral	0	0 (0.0)	0	0 (0.0)	1	1 (4.5)
		Oral pain	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
	General disorders and administration site conditions	Pain	3	3 (33.3)	0	0 (0.0)	3	3 (13.6)
	Infections and infestations	Lower respiratory tract infection	0	0 (0.0)	0	0 (0.0)	1	1 (4.5)
	Metabolism and nutrition disorders	Anorexia	1	1 (11.1)	0	0 (0.0)	2	2 (9.1)
	Psychiatric disorders	Insomnia	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
	Vascular disorders	Hypertension	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
	Total		10	5 (55.6)	1	1 (12.5)	15	8 (36.4)
	Blood and lymphatic system disorders	Anaemia	1	1 (11.1)	1	1 (12.5)	2	2 (9.1)

Onset from date of operation*:	Ear and labyrinth disorders	Ear pain	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
	Endocrine disorders	Adrenal insufficiency	1	1 (11.1)	0	0 (0.0)	2	2 (9.1)
		Hyperthyroidism	0	0 (0.0)	2	1 (12.5)	2	1 (4.5)
		Hypothyroidism	1	1 (11.1)	1	1 (12.5)	2	2 (9.1)
	Gastrointestinal disorders	Abdominal pain	2	2 (22.2)	0	0 (0.0)	2	2 (9.1)
		Colitis	2	2 (22.2)	0	0 (0.0)	2	2 (9.1)
		Constipation	2	2 (22.2)	1	1 (12.5)	4	4 (18.2)
		Diarrhoea	0	0 (0.0)	1	1 (12.5)	2	2 (9.1)
		Dry mouth	1	1 (11.1)	5	5 (62.5)	6	6 (27.3)
		Dysphagia	0	0 (0.0)	1	1 (12.5)	1	1 (4.5)
		Mucositis oral	10	6 (66.7)	6	6 (75.0)	16	12 (54.5)
		Nausea	3	3 (33.3)	4	4 (50.0)	8	8 (36.4)
		Oral pain	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
		Proctitis	0	0 (0.0)	1	1 (12.5)	1	1 (4.5)
		Vomiting	3	1 (11.1)	4	4 (50.0)	7	5 (22.7)
	General disorders and administration site conditions	Chills	0	0 (0.0)	1	1 (12.5)	1	1 (4.5)
		Fatigue	2	2 (22.2)	3	3 (37.5)	5	5 (22.7)
		Fever	4	2 (22.2)	0	0 (0.0)	4	2 (9.1)
		Mucositis	0	0 (0.0)	1	1 (12.5)	1	1 (4.5)
		Oedema	0	0 (0.0)	2	2 (25.0)	2	2 (9.1)
		Pain	4	4 (44.4)	5	5 (62.5)	10	10 (45.5)
	Infections and infestations	Lower respiratory tract infection	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)

		Lung infection	1	1 (11.1)	0	0 (0.0)	2	2 (9.1)
		Throat infection	0	0 (0.0)	1	1 (12.5)	1	1 (4.5)
		Upper respiratory infection	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
		Urinary tract infection	1	1 (11.1)	1	1 (12.5)	2	2 (9.1)
		Wound infection	0	0 (0.0)	0	0 (0.0)	2	2 (9.1)
	Injury, poisoning and procedural complications	Dermatitis radiation	6	5 (55.6)	5	5 (62.5)	11	10 (45.5)
		Incisional hernia	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
	Investigations	Creatinine increased	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
		Thyroid stim. hormone increased	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
		WBC decreased	0	0 (0.0)	1	1 (12.5)	1	1 (4.5)
		Weight loss	7	6 (66.7)	5	5 (62.5)	12	11 (50.0)
	Metabolism and nutrition disorders	Anorexia	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
		Dehydration	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
		Hyperkalemia	2	2 (22.2)	0	0 (0.0)	2	2 (9.1)
		Hypocalcaemia	2	2 (22.2)	0	0 (0.0)	3	3 (13.6)
		Hypoglycaemia	0	0 (0.0)	1	1 (12.5)	1	1 (4.5)
		Hypomagnesemia	2	1 (11.1)	0	0 (0.0)	2	1 (4.5)
		Hyponatraemia	2	2 (22.2)	0	0 (0.0)	2	2 (9.1)
		Hypophosphatemia	3	3 (33.3)	0	0 (0.0)	3	3 (13.6)
	Nervous system disorders	Dysgeusia	4	4 (44.4)	2	2 (25.0)	6	6 (27.3)
		Lethargy	1	1 (11.1)	1	1 (12.5)	2	2 (9.1)

		Peripheral sensory neuropathy	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
	Psychiatric disorders	Insomnia	0	0 (0.0)	1	1 (12.5)	2	2 (9.1)
	Renal and urinary disorders	Acute kidney injury	0	0 (0.0)	2	2 (25.0)	2	2 (9.1)
		Chronic kidney disease	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
	Respiratory thoraic and mediastinal disorders	Sore throat	2	2 (22.2)	4	4 (50.0)	6	6 (27.3)
	Respiratory, thoracic and mediastinal disorders	Pneumonia	0	0 (0.0)	1	1 (12.5)	1	1 (4.5)
		Pneumonitis	0	0 (0.0)	1	1 (12.5)	1	1 (4.5)
	Skin and subcutaneous tissue disorders	Alopecia	1	1 (11.1)	1	1 (12.5)	2	2 (9.1)
		Erythema	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
		Maculopapular rash	2	2 (22.2)	0	0 (0.0)	2	2 (9.1)
		Skin disorder	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
	Vascular disorders	Hypertension	0	0 (0.0)	1	1 (12.5)	1	1 (4.5)
	Total		85	9 (100.0)	67	7 (87.5)	162	19 (86.4)

* Including onset on date of operation.

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13.2 Serious adverse events

There were a total of 14 serious adverse events reported by 8 (36.4%) of the 22 patients in the safety population (all patients who received at least one dose of Nivolumab). 9 (64.3%) of the 14 serious adverse events were grade 3+.

Table 13-3 Line listing of serious adverse events (all events within double lines were experienced by the same patient)

(Chemo)radiotherapy treatment	First Nivolumab treatment date	Onset date	System Organ Class	Lower Level Term	Relationship to Nivolumab		Expectedness (MR assessment)
					Site assessment	MR assessment	
RT	20/08/2019	28/01/2020	Psychiatric disorders	Confusion[9]	Probably	Probably	Not expected
RT	20/08/2019	10/02/2020	Psychiatric disorders	Confusion[9]	Unrelated	Unlikely	NA
RT	20/08/2019	09/03/2020	Musculoskeletal and connective tissue disorders	Head soft tissue necrosis	Unlikely	Unrelated	NA
RT	10/09/2019	13/12/2019	Infections and infestations	Bronchial infection	Unlikely	Unlikely	NA
NA	20/07/2020	19/08/2020	Cardiac disorders	Heart failure	Unlikely	Unlikely	NA
NA	27/07/2020	11/08/2020	Gastrointestinal disorders	Oral haemorrhage	Unlikely	Unrelated	NA
CRT	26/10/2020	30/03/2021	Gastrointestinal disorders	Colitis	Almost Certainly	Almost Certainly	Expected
CRT	26/10/2020	20/05/2021	Gastrointestinal disorders	Colitis	Almost Certainly	Almost Certainly	Expected

[9] The second event was a continuation of the first but the patient was admitted to hospital multiple times so it was recorded as two events. As more information became available, it became clear that the confusion was related to disease relapse and not the IMP. There was no follow-up form for the first serious adverse event so it was not downgraded prior to database lock. LCTC has a database unlock process that is usually determined by consideration on study results. In this case, it is expected that one occurrence being downgraded would not overturn conclusions.

CRT	26/10/2020	21/06/2021	Gastrointestinal disorders	Colitis	Almost Certainly	Almost Certainly	Expected
CRT	26/10/2020	20/07/2021	Gastrointestinal disorders	Colitis	Almost Certainly	Almost Certainly	Expected
CRT	25/11/2020	19/10/2021	General disorders and administration site conditions	Disease progression	Unlikely	Unrelated	NA
RT	31/07/2020	11/08/2020	Gastrointestinal disorders	Diarrhoea	Almost Certainly	Almost Certainly	Expected
NA	05/10/2020	11/10/2020	Infections and infestations	Diverticulitis intestinal perforated	Unrelated	Unlikely	NA
NA	05/10/2020	17/11/2020	Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis	Probably	Possibly	Expected

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Table 13-4 Serious adverse events by severity

SAE Severity	**Post-(C)RT allocation (n=17)**		**Pre- and post-(C)RT allocation (n=22)**
	RT (n=9)	**CRT (n=8)**	
	Events n (%)	**Events n (%)**	**Events n (%)**
2	4 (80.0)	1 (20.0)	5 (35.7)
3	1 (20.0)	3 (60.0)	6 (42.9)
4	0 (0.0)	1 (20.0)	2 (14.3)
5	0 (0.0)	0 (0.0)	1 (7.1)
Total	5	5	14

Note: The denominator for this table is the total number of events.

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Table 13-5 Serious adverse events by System Organ Class and Lower Level Term

Serious Adverse Event			Post-(C)RT allocation (n=17)				Pre- and post-(C)RT allocation (n=22)	
			RT (n=9)		CRT (n=8)			
Onset	**System Organ Class**	**Lower Level Term**	**Events n**	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**	**Patients n (%)**
Onset before date of operation:	Gastrointestinal disorders	Diarrhoea	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
		Oral haemorrhage	0	0 (0.0)	0	0 (0.0)	1	1 (4.5)
	Infections and infestations	Diverticulitis intestinal perforated	0	0 (0.0)	0	0 (0.0)	1	1 (4.5)
	Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis	0	0 (0.0)	0	0 (0.0)	1	1 (4.5)
	Total		1	1 (11.1)	0	0 (0.0)	4	3 (13.6)
Onset from date of operation*:	Cardiac disorders	Heart failure	0	0 (0.0)	0	0 (0.0)	1	1 (4.5)
	Gastrointestinal disorders	Colitis	0	0 (0.0)	4	1 (12.5)	4	1 (4.5)
	General disorders and administration site conditions	Disease progression	0	0 (0.0)	1	1 (12.5)	1	1 (4.5)
	Infections and infestations	Bronchial infection	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)

	Musculoskeletal and connective tissue disorders	Head soft tissue necrosis	1	1 (11.1)	0	0 (0.0)	1	1 (4.5)
	Psychiatric disorders	Confusion	2	1 (11.1)	0	0 (0.0)	2	1 (4.5)
	Total		4	2 (22.2)	5	2 (25.0)	10	5 (22.7)

* Including onset on date of operation.

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13.3 TAME Guidelines

Table 13-6 Distribution of grade 3 or 4 adverse events

Score	Cohort		N	Number of grade 3 or 4 adverse events: Patients n (%)							
				0	1	2	3	5	7	8	11
T [a]	Post-(C)RT allocation	RT	9	4 (44.4)	1 (11.1)	1 (11.1)	2 (22.2)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
		CRT	8	4 (50.0)	2 (25.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
	Pre- and post-(C)RT allocation		22	10 (45.5)	5 (22.7)	3 (13.6)	2 (9.1)	1 (4.5)	0 (0.0)	1 (4.5)	0 (0.0)
A [b]	Post-(C)RT allocation	RT	9	7 (77.8)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		CRT	8	5 (62.5)	1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
	Pre- and post-(C)RT allocation		22	15 (68.2)	4 (18.2)	0 (0.0)	2 (9.1)	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)
T or A	Post-(C)RT allocation	RT	9	2 (22.2)	2 (22.2)	1 (11.1)	3 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
		CRT	8	3 (37.5)	1 (12.5)	2 (25.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (12.5)
	Pre- and post-(C)RT allocation		22	6 (27.3)	5 (22.7)	5 (22.7)	3 (13.6)	1 (4.5)	1 (4.5)	0 (0.0)	1 (4.5)

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[a] T scores correspond to acute events (those occurring during treatment and within 30 days of the last dose of Nivolumab).
[b] A scores correspond to late events (those occurring more than 30 days after the last dose of Nivolumab).

The distribution of individual T scores shows that for the pre- and post-(C)RT allocation cohort, 7 (31.8%) patients reported two or more high-grade acute events while 2 (9.1%) patients reported four or more high-grade acute events. The distribution of individual A scores shows that for the pre- and post-(C)RT allocation cohort, 3 (13.6%) patients reported two or more high-grade late events while 1 (4.5%) patient reported four or more high-grade late events.

Table 13-7 Average T and A scores

Cohort		**N**	**Average T score**	**Average A score**
Post-(C)RT allocation	RT	9	1.56	0.444
	CRT	8	1.50	1.38
Pre- and post-(C)RT allocation		22	1.36	0.773

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For the pre- and post-(C)RT allocation cohort, a patient is expected to experience 1.36 high-grade acute (those occurring during treatment and within 30 days of the last dose of Nivolumab) adverse events on average. For late events (those occurring more than 30 days after the last dose of Nivolumab), a patient is expected to experience 0.773 high-grade events on average.

13.4 Deaths

Table 13-8 Deaths (all causes) and deaths resulting from serious adverse events

Cause of death	**Pre- and post-(C)RT allocation n (%)**
Deaths (all causes):	4
Primarily due to disease progression	2 (50.0)
Cardiac Arrest	1 (25.0)
Death due to secondary malignancy in lungs, unrelated to primary.	1 (25.0)
Deaths resulting from serious adverse events:	1
Cardiac Arrest	1 (100.0)

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14 Lay Summary of Study Results

Cancers of the inside of the mouth are usually treated initially with surgery and, if more advanced with additional radiotherapy. The radiotherapy is given in combination with chemotherapy if there are indications of the cancer being more aggressive. However, recently there has been increasing interest in the use of drugs that can stimulate the immune system and help gain better and longer control over the cancer if it has spread. This kind of treatment is called immunotherapy. The NICO study was set up to see if the use of nivolumab (a form of immunotherapy) used before surgery, after surgery, but before radiotherapy, and after surgery for 6 months can improve outcomes for patients. We had intended to enrol 120 patients to the study, but had to stop the study early due a decision on the part of the funder. Recruitment to the study had been slower than expected partly due to the COVID pandemic. At the end of recruitment we had only enrolled 23 patients (14 male/9 female) and had opened 3 sites. Of the 23 patients, 1 withdrew before surgery, and two did not proceed with surgery; with a further three patients withdrawing after surgery and before radiotherapy. Of the remaining 17 patients, nine underwent radiotherapy only and 8 both radiotherapy and chemotherapy, and then went onto start adjuvant nivolumab. Seven patients completed all treatment doses with nivolumab. Of the 20 patients who remained on study and had surgery, 17 (85%) had no evidence of cancer at one year. In those who had radiotherapy the percentage was 89% (8/9), and 88% (7/8) in those who had chemotherapy and radiotherapy. This was one of the main endpoints of the study (that is, the main things we were looking to understand). From previous trials we expected the one year disease free survival to be only around 65% in the patients who needed chemotherapy and radiotherapy; and the outcome we observed suggests that the addition of nivolumab increases disease free survival. However, the number of patients was too small to be sure of this. We also looked at side effects from the nivolumab which were similar to what we would expect with this drug, Complications of surgery were not higher than expected so we don't think that the nivolumab pre-treatment led to more difficult surgery. Cancer and blood samples were collected which are being analysed further and will hopefully help us understand the role of immunotherapy in this setting.

15 Mapping between report shell and SAP

The trial was stopped early and given the sample size it would not be appropriate to conduct the specified statistical analyses in the current protocol and statistical analysis plan. An addendum to the SAP, which details the changes to the analyses specified in the SAP, was approved by both the Lead Statistician and Chief Investigator and was reviewed by sponsor before the database locked.

In the MHRA Good Clinical Practice Guide it says:
"As it is a legal requirement to comply with the trial protocol, the SAP should be consistent with the protocol and any analyses in the SAP that are not supported by the protocol should lead to an assessment by the sponsor of whether a protocol amendment is required".

Sponsor reviewed the changes to the analysis specified in the protocol and felt that a protocol amendment was not required as long as a full explanation was provided in the statistical analysis report.

This report has been created following the NICO Statistical Analysis Plan V2.0 (dated 15/06/2020) and NICO Final Statistical Analysis Plan Addendum V1.0 (dated 28/02/2023).

The following table lists changes from the SAP that are applicable to multiple items within the report.

Section/subsection of SAP	Changes from SAP
N/A	• 'Overall' in the header in shell tables has been replaced with 'Pre- and post-(C)RT allocation' and a grouped header of 'Post-(C)RT allocation' over RT and CRT has been added. This makes the flow of patients clearer as not all patients were allocated to RT or CRT – the RT and CRT columns will not add up to the overall column. • Wording of some headers in tables and captions has been updated to be more consistent, e.g. 'N' has been used throughout instead of a combination of 'Number' and 'N'.
Section 4.7 Sensitivity Analyses	Analysis of the data was conducted using an intention to treat approach and no per-protocol analyses were conducted (see addendum).
Section 4.2 Handling of Dropouts	SAP says that only patients who have received at least one dose will be included in the primary analysis. Since this contradicts 'Section 4.1 Patient Groups for Analysis'*, all patients have been included in the analysis. * This states that all analysis will be carried out on an intention to treat basis other than analysis of toxicity which will be carried out on those who received the study drug.
Section 4.3 Identification and Handling of outliers	The methods described in this section have not been performed (see addendum).
Section 4.6 Missing Data	No multiple imputation has been performed (see addendum).
Section 4.8 Prespecified Subgroup Analyses	No subgroup analyses have been performed (see addendum).

The following table lists each item (tables, figures and section when applicable) in this report and maps each to the relevant SAP section that describes the methods used to compute it.

Table 15-1 Mapping between report shell and SAP

Section/subsection of SAP	Item within report	Additional details (if required)
Section 3.3 Trial Milestones	Table 4-1	Changes from SAP: SAP says date of final extraction for this report, total number screened to data extract and total number registered to data extract will be presented too. Since this is the final analysis, the date of the

		extract and number to data extract is not applicable - these rows will not be presented but the total number screened has been added as an additional row.
Section 5.1 Recruitment by Centre and Arm	Table 5-1 and Figure 5-1	Changes from SAP: An additional column for screened but not registered patients has been added for those with other reasons (not ineligible or declined) or missing reasons for not being registered - there are some participants with reasons for not being registered that are not ineligible or declined. A column for the number registered has also been added as not all participants were allocated to (C)RT.
Section 4.9.1 Primary Outcomes and Section 5.2 Number of Sites Opened per Month	Table 5-2	
Section 4.9.1 Primary Outcomes and Section 5.4 Recruitment Rate	Table 5-3	
Section 6 Assessment of Study Quality	Table 6-1 to Table 6-6	Changes from SAP: Registration check table in SAP says 'Are registration numbers in MACRO database in correct date order?'. Patient numbers were assigned at screening and should be in order in the screening data from Portal not in the MACRO database so this has been changed to 'Are registration numbers in correct date order?' and a footnote added to explain that they were assigned at screening.
Section 7 Patient Allocation Progress	Table 8-1 and Table 8-2	Changes from SAP: In the SAP, patient allocation progress by site table has a column that says 'Number of patients not yet allocated to RT/CRT'. Since this is the final analysis, this has been changed to 'N not allocated to (C)RT'. Since this table is about patient allocation, the columns for 'Number of patients on RT/CRT' have been reworded to 'N allocated to RT/CRT' as some patients were allocated to (C)RT but did not actually start it.

Section 8 Withdrawals and Losses to Follow-Up	Figure 9-1, Table 9-1 and Table 9-2	Changes from SAP:
		• Patient disposition flow diagram:
		  ○ For those who were registered but did not have surgery and who had surgery but were not allocated to (C)RT, the total number has been presented in the box to make the diagram easier to understand.
		  ○ For those screened and excluded and all end status boxes, the number with missing reasons has been presented so all patients have a reason.
		  ○ For all end status boxes, progressed has been changed to disease recurrence as that is what is collected for NICO.
		  ○ For those registered but did not have surgery and had surgery but were not allocated to (C)RT the number who are analysable for the primary outcome has been presented - not just those allocated to (C)RT have been included in the analysis for the primary outcome.

		Rows for withdrawal status (completed as per protocol, prematurely withdrew and missing) have been added to both premature withdrawal tables to show the flow of patients more clearly. The following categories: 'Did not commence treatment', 'Surgery' and 'CRT/RT allocation' have been added for stages of withdrawal as some patients did not fall into any of the categories in the shell table. The other categories (other than 'Follow-up') have been reworded slightly to clarify that it is the stage with regards to the Nivolumab dose.
Section 9 Description of Subject Characteristics	Table 10-1	Changes from SAP: • Categorial age added (see addendum). • Units for tumour size added. • Units for FT4, FT3, ALP, AST, ALT and YGT updated to what they are on the CRF.
Section 10 Exposure to treatment and compliance	Table 11-1 to Table 11-5	Changes from SAP: • For the treatment missed/ delayed (Nivolumab) table, the completed treatment as scheduled row has been moved to the top of the table and the number of patients with treatment CRFs for each phase of treatment has been presented in the header for each column to show the flow of patients more clearly. • The exposure to treatment and dosage received table for radiotherapy and chemoradiotherapy has been split into separate tables with the chemotherapy table being presented split by day 1 and day 22. The information presented in both tables has been updated to reflect what is collected on the CRFs.
Section 4.9.1 Primary Outcomes and Section 11.1.2 One Year Disease Free Survival Rate	Table 12-1	Changes from SAP: • No subgroup analyses using logistic regression models. • The Kaplan-Meier 12 month disease-free survival probability has been presented.
Section 4.9.2 Secondary Outcomes, Section 4.12 Test of Assumptions and Section 11.2.1 Disease Free Survival	Table 12-2 and Figure 12-1	Changes from SAP: • No hazard ratios and p-values have been presented (see addendum). • No log rank tests (see addendum). • No subgroup analyses using Cox Proportional Hazards models and therefore not testing of the proportional hazard assumption using Schoenfeld residuals (see addendum).
Section 4.9.2 Secondary Outcomes, Section 4.12 Test of Assumptions and Section 11.2.2 Overall Survival	Table 12-3 and Figure 12-2	As above. Additionally, in the SAP overall survival is defined as the time from recruitment to death by any cause but the formula in the SAP to calculate overall survival uses date of surgery instead of date of registration. Date of registration has been used to calculate overall survival in this report.
Section 4.9.2 Secondary Outcomes and Section 11.2.5 Surgical Complications	Table 12-4 to Table 12-9	Changes from SAP: • Infection rate has been split up into surgical site infection and other infections so they can be differentiated between.

		• Free flap failure &/or compromise is presented instead of free flap failure as this is how it is collected on the CRF. • No subgroup analyses using logistic or Poisson regression models have been performed (see addendum). Instead infection (both surgical and other), free-flap failure &/or compromise and peri-operative mortality rates and 95% confidence intervals have been presented for each cohort separately. For length of hospital admission, the mean length and 95% confidence interval has been presented.
Section 4.4 Adjustment for Covariates, Section 4.9.2 Secondary Outcomes and Section 11.3 Quality of Life	Table 12-10 to Table 12-13	Changes from SAP: • No analyses that required adjustment for covariates has been performed (see addendum). • The mean and 95% confidence interval for the change from baseline to end of treatment for the non-binary symptom scales/ items of the EORTC QLQ-H&N35 (see addendum). For the binary items (i.e. yes/ no items), the change from baseline to end of treatment, e.g. 'yes-no', has been presented using frequencies and percentages. • No joint modelling of quality of life and disease-free survival has been performed (see addendum).
Section 12 Analysis of Safety & Tolerability	Table 13-1 to Table 13-8	Changes from SAP: • No statistical testing has been performed (see addendum). • AEs and SAEs have been presented using MedDRA coding rather than CTCAE short term (see addendum). • All AEs not just those that are Grade 3+ have been presented. All SAEs have been presented not just those that are the worst SAE for each type for each patient. Additionally, the number of patients affected by and occurrences of each AE and SAE have been reported (see addendum). • In the addendum, it said that the number of occurrences that are related to Nivolumab for each SAE will be presented. Due to the small number of SAEs, this has been presented in a line listing which details the site and MR assessment of relatedness for each SAE. This line listing also includes the expectedness assessment for related SAEs as this is clearer than the expectedness column in the SAE table proposed in the SAP. • The IDSMC recommended that onset date and date of first Nivolumab treatment be added to the SAE line listing following the July 2023 IDSMC so these have both been added. • T and A scores refer to grade 3 and 4 events but the SAP says grade 3+ events. Only grade 3 and 4 events have been used when calculating T and A scores so the number of grade 3+ AEs table has been changed to the number of grade 3 and 4 AEs. This table has also been split by score (T, A and T or A) and by cohort (RT, CRT and Pre- and post-(C)RT allocation), rather than just by RT and CRT.

		• Summary sentence for the distribution of T scores has been presented for the pre- and post-(C)RT allocation cohort rather than for the RT and CRT cohorts, and the distribution of A scores has also been summarised for the pre- and post-(C)RT allocation cohort. • Average T and A score table also presents them for the pre- and post-(C)RT allocation cohort rather than just by RT and CRT. • Summary sentence for average T and A scores has been presented for the pre- and post-(C)RT allocation cohort rather than for the RT and CRT cohorts. • Total number of deaths (all causes and resulting from SAEs) has been added (see addendum).

16 Version history

Table 16-1 Version history

Updated shell version no.	Shell section changed	Description of change	Date changed	Initials