CONFIDENTIAL

CA209-891: **N**eoadjuvant and adjuvant nivolumab as **I**mmune **C**heckpoint inhibition in **O**ral cavity cancer

NICO

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Protocol version:	5.0
Date:	04-Nov-2020

Study Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Authorised by the Chief Investigator:

Signature: See accompanying email confirmation **Date:** 17/11/2020

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General Information

This document describes the NICO trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Liverpool Clinical Trials Centre (LCTC)) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator Dr Joe Sacco via LCTC.

This protocol defines the patient characteristics required for study entry and the schedule of treatment and follow-up. Patient recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non–compliance are NOT permitted.

Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in sections 10 and 11.

The Liverpool Clinical Trials Centre has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

Statement of Compliance

This study is designed to comply with the guideline developed by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, LCTC Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

UK Registration

This study will undergo HRA review and approval before opening to recruitment. The HRA approval will bring together the assessment of governance and legal compliance in addition to an independent Research Ethics Committee (REC) review provided the through the UK research ethics service. Each centre will confirm they have the capability and capacity to deliver the study locally prior to being open to recruitment.

Furthermore, the study will hold a Clinical Trials Authorisation issued by the Medicines and Healthcare Products Regulatory Agency (MHRA).

Relationship Statements

The Clatterbridge Cancer Centre NHS Foundation Trust are the Sponsoring Organisation and will formally delegate specific sponsoring roles to the Chief Investigator and Clinical Trials Unit, but remains legally responsible for the trial. The Liverpool Clinical Trials Centre at the University of Liverpool in collaboration with the chief investigator Dr. Joe Sacco, will have overall management responsibility for the trial from a CTU perspective and will be responsible for the co-ordination of centres.

Liverpool Clinical Trials Centre is built upon the experience of the Liverpool Clinical Trials Collaborative which has achieved full registration with the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and core standard operating procedures.

Liverpool Clinical Trials Centre Merger

During the management of the NICO Trial the Liverpool Cancer Trials Unit (LCTU) and the Clinical Trial Research Centre (CTRC) have merged to become the Liverpool Clinical Trials Centre (LCTC). The LCTC will continue to use the LCTU PORTAL as a legacy system for the duration of this trial, for the purposes of this protocol it will be referred to as the Portal only.

TRIAL TERMINATION

On 26th October 2020 the study funder Bristol Myers Squibb (BMS) wrote to the Chief Investigator and Study Sponsor to terminate the Investigator-Sponsored Research Agreement. The termination allowed the continued registration of new patients up to 30 days from the date of the letter of termination. Therefore all study recruitment MUST cease by Wednesday 25 November 2020.

All patients on study at the point of the termination will be allowed to continue on study until they have reached the patient end of trial definition.

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Contact Details: Research Site and Principal Investigators

Principal Investigators	Details of the Principal Investigators and research sites are stored in the individual research site files held in the LCTC and on the Portal. Please contact Trial Co-ordinator for further details

Additional Contacts:

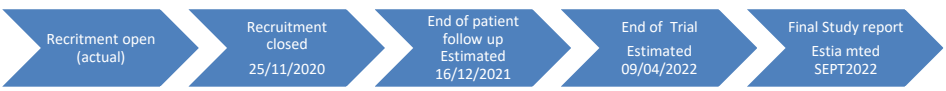
The contact details for the trial oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File

Table of Contents

Glossary

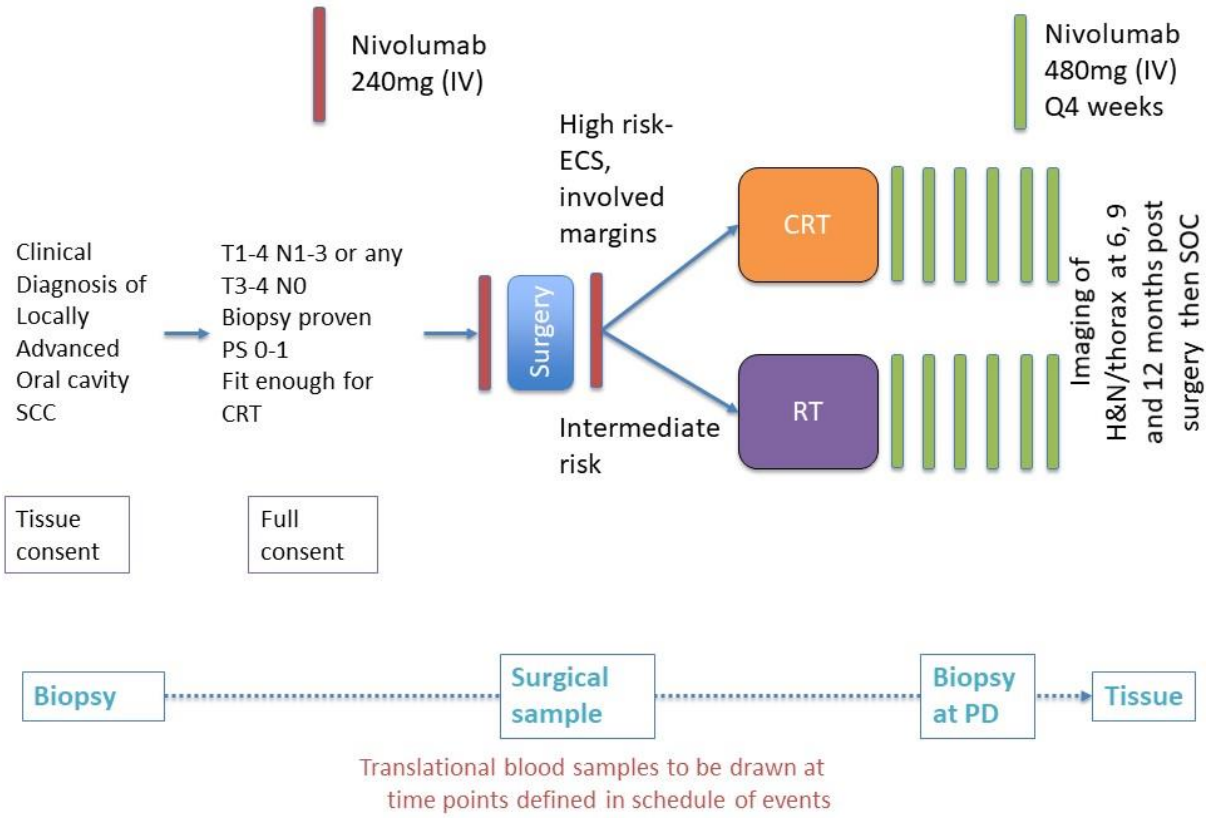
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DFS	Disease Free Survival
DILI	Drug Induced Liver Injury
GP	General Practitioner
HNSCC	Head and neck squamous cell carcinoma
IB	Investigator's Brochure
ISDMC	Independent Safety and Data Monitoring Committee
IEC	Independent Ethical Committee
IMP	Investigational Medicinal Product
IMRT	Intensity Modulated Radiation Therapy
I-O	Immuno-oncology
REC	Research Ethics Committee
LCTC	Liverpool Clinical Trials Centre
NSCLC	Non-small cell lung cancer
OS	Overall survival
PI	Principal Investigator
R&D	Research & Development
RCC	Renal cell carcinoma
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCC	Squamous cell carcinoma
SEER	Surveillance Epidemiology and End Results Programme
SmPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

1 PROTOCOL SUMMARY

Study Title:	CA209-891: Neoadjuvant and adjuvant nivolumab as Immune Checkpoint inhibition in Oral cavity cancer
Study Acronym:	NICO
Phase:	II
Target Condition:	Squamous cell carcinoma of the oral cavity
Brief Background and Importance	Despite multimodality therapy, the 5 year overall survival for locally advanced oral cavity SCC remains less than 50%. Immunotherapy agents targeting PD1 such as nivolumab have demonstrated efficacy in metastatic HNSCC, with prolonged responses in a proportion of cases. We hypothesise that the use of nivolumab as part of primary therapy is likely to improve long term outcomes with minimal additional toxicity. By including a neoadjuvant dose, this study will additionally provide a unique opportunity to investigate the biological underpinnings of response and thus contribute towards development of predictive biomarkers
Sample Size:	Maximum 30 (revised from 120 due to early termination of recruitment)
Main Inclusion Criteria (Ref: Section 3.1)	1. Histologically confirmed squamous cell carcinoma of the oral cavity (tongue (anterior 2/3), gingiva/alveolus, floor of mouth, buccal sulcus, retromolar trigone, and hard palate) 2. Clinically and/or radiologically staged* as; T1-4 N1-3 or any T3-T4 N0 (unless T4 on the basis of bone invasion only) 3. ECOG PS of 0 or 1 4. Surgery planned as primary treatment modality * AJCC/UICC TNM 8th Edition
Main Exclusion Criteria (Ref: Section 3.2)	1. Distant metastases detected, or suspected on imaging 2. Unfit for chemoradiotherapy 3. Previous active malignancy in the last 3 years 4. On immunosuppressive agents (including steroids at dose equivalent to prednisolone > 10mg/day unless used as adrenal replacement therapy) 5. Known HIV or hepatitis
Study sites and Distribution:	Patients will be recruited from 3 tertiary specialist centres across the UK
Study Timelines and overall trial duration:	18 months recruitment, 15 months follow up, 6 months close out 
Study Duration per patient:	Patients will be on study for a minimum of 12 months

Description of Agent/ Intervention:	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). 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.	
	Objective	**Endpoint Measure**
Co Primary:	1 year Disease Free Survival	The endpoint is disease recurrence at 12 months measured as a 1 for patients who have disease recurrence (or death by any cause) and 0 for those that do not.
	Feasibility of recruitment to both cohorts	Feasibility will predominantly be assessed as using the recruitment rate as the endpoint of interest measured as the number of patients/site/month
Secondary	Safety	Measured and categorised based on CTCAE (version 4). Interest will predominantly be on the number of grade 3/4 adverse events.
	Time to recurrence	Measured as the time from surgery until disease recurrence or death by any cause
	Overall survival	Measured as the time from registration until death by any cause
	Quality of life	Quality of Life Questionnaire–Core 30 module (QLQ-C30) and the head-and-neck–specific module (QLQ-H&N35)
	Surgical Complications	Infection rate, length of hospital admission, free flap failure, perioperative (30-day) mortality

Figure 1:Schematic of Study Design:



2 BACKGROUND INFORMATION

2.1 Introduction

Head and neck squamous cell carcinoma (HNSCC) comprises a group of malignancies arising from the epithelium of the upper aerodigestive tract, including the oral cavity, oropharynx, nasopharynx, hypopharynx and larynx. Together these malignancies are associated with significant morbidity and mortality internationally, with an annual incidence and mortality rate of ~ 500,000 and 300,000 respectively (1). In addition, the incidence of head and neck cancer has been rising sharply in the last few decades. This has mostly been ascribed to a rise in Human Papillomavirus (HPV) related disease, however recent data suggest that HPV negative HNSCC may also be increasing (2)

While early stage disease is generally cured with surgery and/or radiotherapy, a large proportion of locally advanced HNSCC patients (particularly HPV negative) die of their disease despite multimodality treatment. Data from the SEER database suggest a 5-year survival for 'regional disease' (stage III and IV involving nodes but not distant metastases) of 48% (tongue) and 38% (floor of mouth). This is supported by a large meta-analysis, in which concomitant chemoradiation improved 5 year survival from 38% to 46.6% (1 year OS of approximately 75%) (3), again indicating poor long term outcomes. These poor outcomes despite radical therapy highlight the need for further adjuvant therapies; however none have demonstrated improved survival in this setting to date. For example, a recent trial of lapatinib added to standard chemoradiation and as subsequent adjuvant therapy failed to show an improvement in outcome (4). While further agents are being assessed in this setting, overlapping toxicity with the significant side effects of chemoradiation are often prohibitive.

Immunotherapy, which aims to activate the host immune system rather than to act directly on cancer cells, has revolutionised the treatment of melanoma (5), and increasingly other malignancies, including squamous cell carcinoma of the lung (6, 7). This follows the development of checkpoint inhibitors; monoclonal antibodies that block key inhibitory receptors on immune or cancer cells and result in activation of the immune system. Monoclonal antibodies that target CTLA4 or PD1 receptors have now been licenced in multiple malignancies including head and neck cancer. Nivolumab, an anti-PD1 monoclonal antibody recently demonstrated an improvement in overall survival in head and neck cancer in platinum refractory recurrent/metastatic disease (8). A second anti-PD1 agent, pembrolizumab has also been licenced based on two single arm studies in recurrent/metastatic HNSCC (9, 10).

While several trials investigating the activity of checkpoint inhibitors as adjuvant or neoadjuvant therapy are underway, none have reported full results to date. However, as proof of principle, the CA184-029 trial recently demonstrated an improvement in overall survival with the use of adjuvant ipilimumab in high risk melanoma, albeit using a higher dose than currently licenced (11). In addition, use of checkpoint inhibitors earlier in the disease process poses significant theoretical advantages in terms of the ability to eradicate residual disease and the development of immune memory that may prevent later recurrence. Furthermore, checkpoint inhibitors may have higher efficacy in the adjuvant setting where the patients have less burden of disease (microscopic only) and are potentially less subject to certain factors (e.g. poor nutrition) that may reduce immune status in the metastatic setting. As outlined in section 1.2 and 1.3 below, nivolumab is generally well tolerated , making it an ideal agent for investigation in the adjuvant setting.

In this study, we aim to investigate the use of nivolumab in sequence with standard of care surgery and radiation/chemoradiation in locally advanced oral cavity SCC.

2.2 Nivolumab

Nivolumab is a human IgG4 monoclonal antibody that targets the programmed death 1 (PD-1) cell surface receptor. PD-1 (expressed on activated T-cells) interacts with PD ligand 1 (PD-L1) on tumour cells resulting in an inhibitory signal that prevents recognition of the tumour as non-self and thus target cell killing. Nivolumab disrupts this inhibitory signal and thus promotes tumour cell recognition and ultimately T-cell mediated tumour cell killing (12, 13).

Nivolumab is licenced (by the FDA, EMA or both) for the treatment of metastatic or unresectable melanoma (alone or in combination with the anti-CTLA4 monoclonal antibody, ipilimumab), as well as previously treated advanced renal cell carcinoma (RCC), previously treated non-small cell lung cancer (NSCLC), Hodgkin's lymphoma, urothelial carcinoma and previously treated recurrent/metastatic head and neck cancer. In addition, nivolumab is under investigation in several other cancer types and settings.

The safety profile of nivolumab is well established, based on data accrued following treatment of over 12,300 patients to date (Bristol-Myers Squibb, investigator brochure (IB)) with either monotherapy or in combination. Adverse events are predominantly immune related and are usually low grade, and if required, responsive to steroids and other immunosuppressants. These are listed in detail in the IB, while a summary of adverse events in head and neck cancer (checkmate 141 study) is provided in section 1.3 below. Notably, following the extensive experience with the drug, protocols for the management of toxicity are well established (Appendix B)

2.3 Immunotherapy in head and neck cancer.

The recent publication of the results of the checkmate 141 study, provide significant evidence of the activity of nivolumab in recurrent/metastatic HNSCC (8). In this randomised phase 3 study, patients with recurrent/metastatic HNSCC, whose disease had progressed within 6 months of prior platinum-based chemotherapy, were randomised 2:1 to nivolumab or investigators choice (methotrexate, docetaxel or cetuximab). Treatment continued until progression or intolerable toxicity, and the primary endpoint was overall survival (OS). The median OS in the study was 7.5 months in patients receiving nivolumab, compared to 5.1 months in the standard therapy arm, with a hazard ratio of 0.70 (p= 0.01). The 1 year survival in the nivolumab arm was 36% in the nivolumab arm versus 16.6% in the control arm. Subgroup analysis suggested lower efficacy in PDL1 low and HPV negative tumours. However, the number of patients in these subgroups were low, and although benefits were lower, the OS was numerically better in all subgroups.

Notably this improvement in survival was associated with fewer grade 3 or 4 treatment related adverse events and a stabilization in quality of life indices compared to the control arm (8). Treatment related grade 3 adverse events occurred in 13.1% of patients on nivolumab versus 35.1% in the control arm. Two treatment related deaths were reported in the nivolumab arm (out of 236 patients; one patient with a grade 5 event of hypercalcaemia and one patient with grade 3 pneumonitis who subsequently died of a grade 5 pulmonary embolism. The most common toxicity (all grades) was fatigue (14%), nausea (8.5%), rash (7.6%), decreased appetite (7.2%) and pruritus (7.2%). Gastrointestinal events occurred in 6.8% (primarily diarrhoea, with no grade 3-4 events), while pneumonitis occurred in 2.1% of patients.

The results of the CheckMate 141 study are supported by two trials of a different anti-PD1 agent-pembrolizumab (Keytruda, Merk). The Keynote 012 and 055 studies were both single arm trials of pembrolizumab in recurrent or metastatic (R/M) head and neck cancer with slightly different eligibility criteria. Keynote 012 enrolled patients with 1% or greater PD-L1 expression, with no requirement regarding prior lines of systemic therapy, although the majority of patients had received at least two prior lines of therapy (9). Keynote 055 on the other hand did not specify level of PDL1 expression

(although only 15% had lower than 1% expression), but did require patients to be refractory to both cisplatin and cetuximab(10). The overall response rates for the two trials were 18% and 15% respectively, in keeping with the results of the Checkmate 141 study. Adverse events were also similar, with no unexpected toxicity.

A wide array of other studies are currently underway which will contribute to defining the role of checkpoint inhibitors in R/M HNSCC. These include studies of nivolumab alone or in combination with ipilimumab in first line R/M HNSCC. Similarly, trials of the anti-PDL1 agent, durvalumab, alone or in combination with tremelimumab in first or second line R/M HNSCC are recruiting or in follow up.

More recently, a number of studies have opened which are investigating checkpoint inhibitors in the treatment of locally advanced disease. These include the CA209-410/RTOG 3504 study which is a phase I/III study which will investigate the addition of nivolumab to cisplatin chemoradiotherapy for intermediate/high risk locally advanced HNSCC (NCT02764593). While the current study will be the first to investigate nivolumab as both neoadjuvant and adjuvant treatment of head and neck cancer, a study of pembrolizumab in a similar setting is ongoing (NCT02296684), with early data supporting both safety and activity (14).

2.4 Rationale for choice of oral cavity subsite

Oral cavity cancer is a subsite of head and neck cancer, for which there is a desperate need for improved outcomes. UK Incidence is rising (2), despite population declines in tobacco smoking (15). While all cancers of the head and neck are likely to benefit from this approach we have chosen to perform the trial in oral cavity cancers. This is specifically aimed at ensuring homogenous outcomes from a single site given the variation in outcomes seen at different locations within the head and neck which may complicate analysis. In addition, the oral cavity is readily accessible allowing for sufficient biopsies to be obtained prior to treatment.

Rationale for dosing regimen

In this study nivolumab will be interleaved with current standard of care therapy. This will minimise the chances of delaying/preventing standard therapy, while treating early in the disease process where immune priming is most likely to have a significant effect on disease progress.

The first dose of nivolumab will be 1-2 weeks prior to surgery. We hypothesise that this will allow sufficient time for an initial priming of the immune system while not constraining the timeline for surgery. While the efficacy of this strategy has not been tested in this setting, studies in NSCLC and melanoma demonstrate that even short courses of immunotherapy pre-operatively can have significant efficacy (16, 17). The delivery of a dose in the 'window' between biopsy and surgery will further enable an assessment of the effects of nivolumab on T-cell infiltration of the tumour.

The second dose will be delivered in the interval between surgery and radiotherapy. This will again be timed to prevent any delay in standard therapy. Treatment will not continue during chemoradiation/radiation therapy, to reduce the likelihood of additive or synergistic toxicity. The combination of nivolumab and radical chemoradiotherapy is being investigated in other studies.

We further hypothesise that an adjuvant phase will consolidate and boost the immune response obtained through initial doses. While the optimal duration of adjuvant treatment remains uncertain, we have selected 6 months in line with other similar clinical trials in the area. This represents a balance between potential efficacy and tolerability/acceptability in a heavily pretreated population.

In line with other recent studies of nivolumab, we will utilise a fixed dose regimen. This follows dose-exposure modelling based on population pharmacokinetics, which has predicted equivalent efficacy and safety with flat dosing both at a 2 weekly dose of 240mg and a 480mg dose every 4 weeks

[Investigator brochure and (18)]. Four weekly dosing is generally preferable to patients as it reduces the number of hospital visits and investigations, and as such will be utilized in the adjuvant phase of this study (in keeping with most other nivolumab studies in development). The bulk of nivolumab toxicity data has however been generated using 2 weekly dosing and, while unlikely, there is a potential that the higher dose could result in increased acute toxicity. As a precautionary measure we will therefore use the 240mg dose level for the pre-surgery and pre-radiotherapy doses, to minimize any potential for delays to definitive therapy.

2.5 Risk/Benefit

Potential Risks

Nivolumab has a well-established toxicity profile, following multiple clinical trials in multiple indications including head and neck cancer. As of the latest IB, over 12,000 patients had been treated with nivolumab monotherapy. The drug is well tolerated and where toxicity occurs this is generally immune mediated and reversible through the use of steroids or other immunosuppressants.

In the setting of the trial, there are additional risks related to potential delay in definitive therapies (i.e. surgery and chemo/radiation). However, only one and two cycles of nivolumab will have been delivered prior to these therapies respectively. As adverse events following nivolumab are generally late, it is unlikely that either of these treatments will be delayed significantly. This is borne out by early results of a neoadjuvant study of pembrolizumab (NCT02296684), in which no unexpected surgical delays or complications have been observed in the first 21 patients (14).

Finally, there is the potential for synergistic toxicity with radiotherapy. In the current study, the potential for this is low as treatments will not be given concurrently. In addition, data to date do not suggest significant accentuation of toxicity due to the combination, and indeed several trials are ongoing which combine chemoradiotherapy with nivolumab, or other anti-PD1 agents as discussed above.

Known Potential Benefits

As described above, nivolumab has been shown to improve survival as second line therapy in patients with recurrent/ or metastatic head and neck cancer who have disease progression or recurrence within 6 months of platinum based therapy (including as part of chemoradiation for locally advanced disease) (8). A second antiPD1 drug, pembrolizumab, has similarly shown activity in this setting. We hypothesise that nivolumab will have at least as significant an effect in earlier disease, and that potentially a greater proportion of patients will benefit as detailed in the rationale above (section 1.2). Treatment in the adjuvant and neoadjuvant setting offers the potential for improving the cure rate of this disease, which is currently less than 50%.

Risk/Benefit

Overall, the risks of this trial relate to toxicity of the IMP and potential delays to Standard of Care (SOC) therapies. As the treatments are well tolerated and relatively unlikely to impact on standard treatments (see above), these risks are potentially outweighed by the benefits in improving cure rates. Notably toxicity will be mitigated by well established protocols for management which are detailed in Appendix B.

The risk category for the study is type B, as nivolumab is licenced in this disease, albeit not for the indication under study here.

2.6 Lay Summary

Mouth cancer is usually treated with surgery, often followed by radiation therapy with or without chemotherapy. Unfortunately despite this treatment, it recurs or spreads in about half of patients. Recently, a drug called nivolumab which is given into a vein via a drip, has been shown to be of benefit where the cancer has spread and worsened following treatment with chemotherapy. This drug stimulates the immune system and when it works, often does so for a long period of time. In this trial we aim to use this drug to reduce the chances of the cancer coming back after surgery and radiotherapy. We will give a single dose of the drug before surgery and again after surgery, but before radiotherapy. After radiotherapy has completed we will treat with 6 further doses. While the treatment does cause some side effects, these are generally quite mild and reverse on withholding the drug or giving drugs to temporarily dampen the immune system. We hope that the study will show that this treatment leads to a reduction in the cancer coming back which will be assessed by scanning three times within a year, after which follow up will be as standard for each institution.

2.7 Early Stopping of Recruitment

On 26th October 2020 the study funder Bristol Myers Squibb (BMS) wrote to the Chief Investigator and Study Sponsor to terminate the Investigator-Sponsored Research Agreement. The termination allowed the continued registration of new patients up to 30 days from the date of the letter of termination. Therefore all study recruitment MUST cease by Wednesday 25 November 2020.

All patients on study at the point of the termination will be allowed to continue on study until they have reached the patient end of trial definition. , In keeping with the revised recruitment period, the study has been amended to reflect the projected recruitment at the time of recruitment termination (maximum of 30 patients) and to maximise the study's clinical and translational endpoints. The statistical considerations have been revised in line with this (see section 9.0). The patient schedules, trial treatment and all data collection will continue as documented in this protocol.

3 TRIAL DESIGN

3.1 Overall Design

This is a non-randomised two arm study of nivolumab in high risk oral cavity cancer for whom resection is the primary treatment. Following initial biopsy and confirmation of eligibility, patients will be enrolled and treated with a single dose of nivolumab, followed by surgery within 1-2 weeks. Based on pathological risk factors, patients will be assigned to undergo adjuvant radiotherapy or chemoradiotherapy. A further (single) dose of nivolumab will be given between surgery and commencement of chemoradiotherapy or radiotherapy (1-2 weeks prior). Following completion of chemo/radiation, the patients will commence adjuvant nivolumab, with a total of 6 doses given at 4 weekly intervals. All patients will have imaging of the head & neck and chest using CT and/or MRI 6 months after surgery, further scans will be performed at 9 and 12 months post surgery, with an end of study visit after the last scan. Patients will then be followed for survival until the final study definition is reached.

3.2 End of Trial Definition

Unless early termination is required, the end of study will be once all patients have completed the minimum follow-up of 12 months or have died/come off study for other reasons, together with sufficient time to collect outstanding data or resolve queries. The final statistical analysis will not be triggered until the end of study is reached (whether this is as planned or due to early termination).

3.3 Objectives

The intention is to investigate the additional clinical activity of nivolumab when added to standard therapy for high risk oral cavity cancer in sequence. We intend to investigate the feasibility and safety of this approach, while also estimating one year survival on this regimen. This will then allow us to determine if there is reason to proceed to a randomised phase III study in this setting. Additionally we intend to collect tissue from patients before and after treatment and at relapse, which will be utilised to investigate potential predictive biomarkers as well as investigation into interactions between immune therapy and other therapeutic interventions.

3.3.1 Primary Objective.

The study includes co-primary endpoints:

- Estimation of 1 year Disease Free Survival (DFS) defined as disease recurrence or death at 12 months following surgery.
- Feasibility assessed as using the recruitment rate as the endpoint of interest measured as the number of patients/site/month

Secondary Objective(s)

Secondary endpoints include:

- Disease free survival measures as the time from surgery until disease recurrence or death by any cause.
- Overall survival measured as the time from surgery to death by any cause
- Toxicity measured based on CTCAE (Version 4) definitions
- Surgical complications

a. Infection rate measured using Clavien Dindo classifications
b. length of hospital admission measured in days
c. Free flap failure measured as a binary covariate
d. Perioperative (30-day) mortality measured as a binary covariate

- Quality of Life Questionnaire–Core 30 module (QLQ-C30) and the head-and-neck–specific module (QLQ-H&N35)

4 STUDY POPULATION

4.1 Inclusion Criteria

1. Signed, written informed consent
2. Subjects must be willing and able to comply with scheduled visits and procedures
3. Histologically confirmed squamous cell carcinoma of the oral cavity, (oral tongue (anterior 2/3), gingiva/alveolus, floor of mouth, buccal sulcus, retromolar trigone, and hard palate as defined by ICD-10 codes)
4. Subjects willing to have a fresh biopsy performed, or archival tissue available from diagnostic biopsy meeting requirements set out in laboratory manual.
5. Clinically and/or radiologically staged as T1-4 N1-3 or any T3-4 N0 (unless T4 on the basis of bone invasion only). Staging based upon the AJCC/UICC TNM 8th Edition.
6. Surgery planned as primary treatment modality with patients fit for major resection ± reconstruction surgical procedure.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
8. 18 years or over at time of provision of consent for trial inclusion.
9. Screening laboratory values must meet the following criteria

WBC ≥ 2000/µL	= WBC ≥ 2x10^9/L
Neutrophils ≥ 1500/uL	=Neutrophils ≥ 1.5 x10^9/L
Platelets ≥ 100x10^3/uL	= Platelets ≥ 100x10^9/L
Haemoglobin ≥ 9.0 g/dL	= Haemoglobin ≥ 90 g/L

   Serum creatinine ≤1.5 x ULN or calculated creatinine clearance > 40 mL/min (using the Cockcroft-Gault formula)
   AST ≤ 3.0 x ULN
   ALT ≤ 3.0 x ULN
   Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0x ULN).

10. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

11. WOCBP must agree to follow instructions for method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives. WOCBP randomized/assigned to receive nivolumab should use an adequate method to avoid pregnancy for 5 months (30 days plus the time required for nivolumab to undergo approximately five half-lives) after the last dose of investigational drug.

12. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately five half-lives

13. Males who are sexually active with WOCBP must continue contraception for 7 months (90 days plus the time required for nivolumab to undergo approximately five half-lives) after the last dose

of investigational drug. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in these sections. Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception which have a failure rate of < 1% when used consistently and correctly*.

* Highly effective methods on contraception which have a failure rate of < 1% when used consistently and correctly

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence i.e. True abstinence: When this is in line with the preferred and usual lifestyle of the subject." [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of contraception]

  The above contraceptive methods must be supplemented with a male condom

4.2 Exclusion Criteria

1. Tumours staged as T4 on the basis of bone invasion only and in the absence of nodal metastases.
2. Distant metastases detected, or suspected on imaging
3. Unfit for chemoradiotherapy, due to comorbidity.
4. Previous malignancy requiring treatment within the last 3 years (with the exception of non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, oesophageal endometrial, cervical/dysplasia, melanoma, or breast). Prior head and neck cancer within the last three years is allowed if the tumour was treated with surgery only, and did not require radiotherapy.
5. Prior head and neck radiotherapy
6. On immunosuppressive medication (including steroids at dose equivalent to prednisolone >10mg/day unless used as replacement therapy).
7. Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, lichen planus or other conditions not expected to recur in the absence of an external trigger are permitted to enrol.
8. Known human immunodeficiency virus (HIV) or viral hepatitis infection.
9. Women who are pregnant or breastfeeding

10. Known medical condition that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.

4.3 Patient Transfer and Withdrawal

In consenting to the trial, patients are consenting to trial treatment, follow-up and data collection. If withdrawal from trial treatment occurs, the patient should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable. Patients who do discontinue from the trial will be contacted for safety assessments for **100 days after the** last dose of nivolumab. The investigator must take every reasonable effort to keep patients on study for the duration of the trial. Provided consent is not withdrawn, patients will be traced through their GP and national records to assist in the collection of long term follow-up information and the closure of all SAEs. A signed withdrawal form will be completed in all cases, specifiying whether the patient consents to further follow up.

Patients who withdraw from study prior to the first dose of study drug will be replaced; patients who have received at least one dose will be included in the primary analysis.

Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient or for follow-up via GP.

A copy of the patient's CRFs should be provided to the new site. The patient will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. The LCTC should be notified in writing of patient transfers.

Withdrawal from Trial Intervention

Patients **may** be withdrawn from treatment for any of the following reasons:

a. Patient (or, where applicable, legal representative) withdraws consent.

b. Unacceptable toxicity.

c. Intercurrent illness preventing further treatment.

d. Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion.

e. Serious patient violation of the study protocol e.g. failure to attend clinic

f. Greater than 8 weeks between surgery and commencement of radiotherapy / chemoradiotherapy

g. Nivolumab not commenced within 10 weeks of completing radiotherapy or chemoradiotherapy.

h. If there is no indication for adjuvant (c)RT(pT1-2 N0) upon review of pathology report

If a patient wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be

used for trial purposes. Generally, follow-up will continue as per protocol unless the patient explicitly also withdraws consent for follow-up (see below).

Patients **MUST** be withdrawn from treatment in the event of pregnancy. This will be reported as detailed in section 9.2.3 below.

Withdrawal from Trial Completely

Patients are free to withdraw consent at any time without providing a reason. Patients who wish to withdraw consent for the trial will have anonymised data collected up to the point of that withdrawal of consent included in the analyses. The patient will not contribute further data to the study and the CTU should be informed in writing and a withdrawal CRF should be completed. Data up to the time of withdrawal will be included in the analyses unless the patient explicitly states that this is not their wish.

Co-enrolment Guidelines

Participants may not participate in another clinical trial of Investigational Medicinal Product (IMP) with any investigational drug within 30 days prior to registration until the last follow-up visit has been completed after 12 months, or following disease recurrence if this is sooner.

Recruitment into another non IMP study may be considered if this would not affect NICO trial endpoints; however this must first be discussed with the LCTC and confirmed by the CI Dr. Joe Sacco

5 SELECTION OF CENTRES/CLINICIANS

Each participating Centre (and investigator) has been identified on the basis of:

- Having a Head & Neck MDT offering the comprehensive range of treatments, both surgical (including microvascular reconstruction) and non-surgical (radiotherapy and chemotherapy).
- Included within the MDT must be an individual with an interest in, and experience of, the management of patients receiving immunotherapeutic agents
- Included within the MDT must be a further individual (Head & Neck Surgeon) able to provide evidence of a minimum of 10 surgical resections for patients with SCC of the Oral Cavity (stage comparable to inclusion criteria 5) under their care in the preceding 12 month period.
- Showing enthusiasm to participate in the study.
- Ensuring that sufficient time, staff and adequate facilities are available for the study.
- Providing information to all supporting staff members involved with the study or with other elements of the patient's management.
- Acknowledging and agreeing to conform to the administrative and ethical requirements and responsibilities of the study, including signing up to Good Clinical Practice (GCP) and other regulatory documentation.
- Suitable MDT meeting structure to identify patients and recruit a minimum of 1 patient per month
- Ability to conduct all study procedures including surgery, (chemo)radiotherapy and IMP administration

A feasibility questionnaire and assessment will be conducted prior to a centre being included in the study.

Centre/Clinician Inclusion Criteria

a. Completed site feasibility questionnaire with LCTC review and approval
b. Confirmation of capacity and capability from NHS trust via the HRA
c. Signed Research Site Agreement including material transfer clauses
d. Receipt of evidence of completion of (b) & (c) by LCTC
e. Completion and return of "Signature and Delegation Log" to LCTC
f. Curriculum Vitae (CV) including a record of International Conference for Harmonisation (ICH) of GCP training – Principal Investigator (PI)
g. CV including a record of ICH GCP training – Other personnel on the delegation log
h. Clinical Study Protocol Receipt Form
i. Investigator Brochures Receipt Form
j. Local laboratory accreditation/Quality Check
k. Completion of pharmacy practice form
l. Local laboratory reference ranges
m. Provision of approved patient information sheet, consent form and GP letter on trust headed paper

Centre/Clinician Exclusion Criteria

Sites will be required to confirm their compliance with the above criteria, with sign off by the chief investigator. Those centres that do not fulfil the above inclusion criteria will not be permitted to participate in the study.

6 ENROLMENT AND REGISTRATION

6.1 Screening Process

A screening log of patients who are assessed for eligibility but not registered will be maintained as this will provide important information for monitoring purposes.

Screening will be performed upon a patient's possible eligibility for the study and must be documented on the LCTC web Portal "Screening and Enrolment log". Screening details should be entered into the Portal and this will automatically generate a screening number and a confirmation email with these details will be sent to site staff. The screening log can be printed at any time from the Portal to allow for storage in the Investigator Site File. The screening log will not collect patient initials and DOB in order to maintain confidentiality

Step-by-step guides for the log will be issued to research site staff prior to green light and the process will also be demonstrated during site initiations.

The potential eligibility of patients will be assessed at the earliest opportunity following referral of patients with locally advanced oral cavity cancer to trial clinicians. In the event that a histological diagnosis is awaited, the patient will be provided with a Research Tissue PIS, which will enable extra research tissue to be taken at the same time as the diagnostic biopsy, and following confirmation of malignancy.

Informed Consent Procedures for Research Biopsy prior to consent onto the main trial:

Pathway 1: Patients who have already undergone a diagnostic biopsy

- Separate PIS + ICF - Additional research biopsy
- Specific visit or undergoing a procedure e.g. Planning for surgery

Pathway 2: Patients yet to undergo a diagnostic biopsy

- Separate PIS + ICF - Extra biopsy
- Taken when undergoing diagnostic biopsy

Depending on other eligibility criteria being met, the patient will then be asked to give FULL informed consent and will be registered for the study. If the patient already has a histological diagnosis, the patient will consent to the full study, and if feasible, to an additional research biopsy procedure. Patient hospital notes should be screened by the research team prior to the patient being approached to ensure no obvious ineligibility criterion are apparent.

Screening assessments must be performed within the 28 days prior to patient registration and first dose of treatment with the exception of histological confirmation and imaging (see section 5.2 Screening Assessments).

The patient`s written informed consent must be obtained before the research biopsy and before any trial related procedures are undertaken.

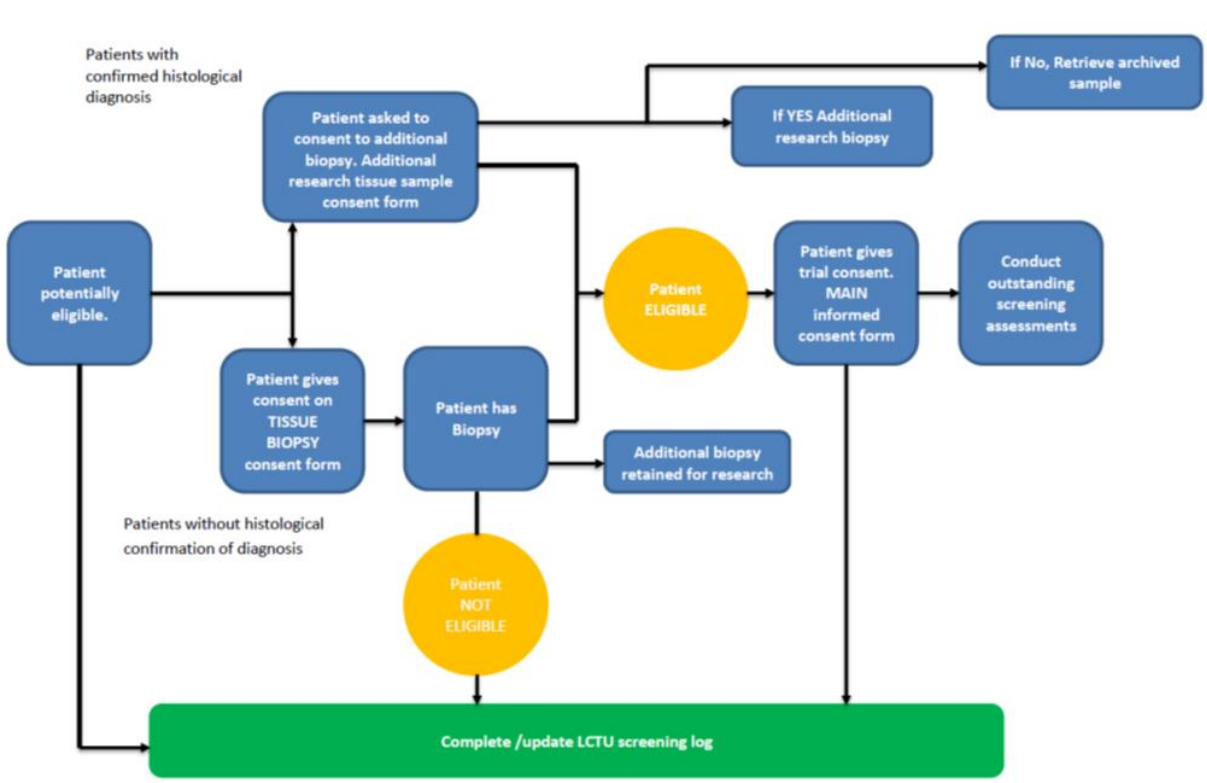


Figure 2

6.2 Screening Assessments

Study specific screening activities will be performed after patients have consented to study participation and signed the MAIN Informed consent form. Assessments can only be used for screening if performed within **28 days (or 8 days for highlighted assessments)** prior to the first dose of treatment with the exception of histological confirmation of diagnosis and imaging as detailed below. Investigations performed for the purposes of diagnosis and staging may be used as screening assessments provided they are performed within this time frame. The following screening/baseline assessments should be performed:

- MAIN TRIAL Written Informed Consent
- Complete Demography and medical history
- Concomitant medication review and check
- Physical examination and Medical Review
- ECOG Performance Status
- 12-lead ECG
- Haematological / clinical biochemistry*
- Vital signs, height and weight, O_2 stats*
- Pregnancy test (women of child-bearing potential only)*
- Thyroid Function Test

*8 Days prior to registration

A histological confirmation of the current malignancy is required but is not subject to a screening window. Imaging of head and neck (MRI or CT) and chest (CT) should be performed within the 8 weeks prior to first dose of nivolumab.

6.3 Enrolment/ Baseline

Patients who have given informed consent and have been found to comply with all inclusion and exclusion criteria will be registered for the study by trained staff at the LCTC.

To ensure essential entry criteria are fulfilled, registration can only occur following the completion and forwarding of the study registration documents by the investigators:

- Completed Registrations Forms signed by an Investigator
- A copy of the MAIN Signed Consent Form signed by both the patient and the investigator
- Anonymised copy of the histology report
- Anonymised copy of screening haematology/serum chemistry

The registration documents should be faxed or scanned and emailed to the LCTC on Monday - Friday from 09:00 to 17:00, fax number: 00 44 (0) 151 794 8931 email: nicoct@liverpool.ac.uk. Prior to sending documents, site staff should telephone 00 44 (0) 151 795 8577 to inform the LCTC staff of the incoming Registration.

Trial Registration – Tel: 00 44 (0) 151 795 8577

Fax: 00 44 (0) 151 794 8931

Email: nicoct@liverpool.ac.uk.

(Note that the LCTC is open from 09:00 – 17:00, Monday – Friday, excluding public holidays)

Personnel from the LCTC will review the documents; confirm eligibility and record essential demographic data. The LCTC will query any issues with the documents listed above. Once the documentation is complete, the LCTC trial team will register the patient using the LCTC MACRO system.

The patient will be given a unique study number by the system, which will also automatically generate a confirmation email which will be communicated to the LCTC trial team and all relevant members of the site staff and pharmacy, notifying them of the patient trial number.

This study number should then be filled in on each subsequent page of the patients CRF.

Once a patient has been enrolled onto the trial they must be provided by the clinical team with the following:

Patient contact card (SSNIC_D008)

The first dose of nivolumab should be administered 1-2 weeks prior to planned surgery.

7 TRIAL TREATMENT

7.1 Introduction

All trial patients will be enrolled and treated with a single dose of **nivolumab** (240mg flat dose), followed by **surgery** within 1-2 weeks. A further (single) 240 mg flat dose of nivolumab will be given 1 -2 weeks before commencement of **chemoradiotherapy** or **radiotherapy**. The decision as to treatment with radiotherapy (+/- chemotherapy) will be dependent on pathological risk factors as detailed in the section below. Within 4 weeks of completion of chemo/radiation, the patients will be commenced on adjuvant nivolumab. Exceptionally this may be delayed by up to a further 6 weeks post CRT/RT to allow grade 2+ toxicity to improve to grade 1 or resolve, or to allow discontinuation of steroids if utilised in management of toxicity. Adjuvant nivolumab will be given as 480 mg flat dose which will be continued 4 weekly for 6 months (6 doses), after which patients will be followed up for 1 year (with imaging every 6, 9 and 12months from the date of surgery), and then as per standard of care thereafter.

7.2 NIVOLUMAB

Formulation, Packaging, Labelling, Storage and Stability

Table 1 : Details of Nivolumab	
Generic name:	*Nivolumab (BMS – 936558)*
Formulation:	Concentrate for solution for infusion.
Method of Administration	IV
Packaging, Storage and Stability.	Store in a refrigerator (2°C to 8°C). Do not freeze. Store in the original package in order to protect from light. Stability after preparation = 24 hours Shelf life unopened vial = 60 months
Supplier's name	Bristol Myers Squibb
Distributor' s name	Quay Pharmaceuticals Ltd
Appearance	Nivolumab concentrate for solution for infusion (sterile concentrate) is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles. Investigator Brochure BMS-936558/MDX1106/ONO-4538 nivolumab 221
Dose	The amount of nivolumab given is calculated as flat dose. The protocol specified dose is 240mg flat dose for dose 1 and 2 i.e. Pre-surgery and Pre-radiotherapy (+/- Chemotherapy) 480mg flat dose for doses 3-8 i.e. post radiotherapy (+/- Chemotherapy).
Pack size	Packages will not be patient specific and will contain 3 vials in a labeled box. Both the outer package and the vial will be labelled with Annex 13 compliant labels. Each Pack contains 1 vial 40 mg/4 mL 2 vials 100 mg/10 mL

Nivolumab 240 mg patient kit

Nivolumab 100mg/10mL and 40mg/4ml vials

Drug will initially be supplied to site after they have been given the green light approval to start recruiting patients. Subsequent deliveries will be made on completion of the re-ordering process described in the trial pharmacy operating manual.

Preparation, Dosage and Administration of Study Treatment

Preparation of Nivolumab should be performed by appropriately trained personnel named on the delegation log and in accordance with good practice rules especially with respect to asepsis.

7.2.1.1 Calculating the dose

The protocol doses for the trial patients are;
240mg flat dose for dose 1 and 2 i.e. Pre-surgery and Pre-radiotherapy (+/- Chemotherapy)

480mg flat dose for doses 3-8 i.e. post radiotherapy (+/- Chemotherapy)
Route: IV infusion
Each pack contains three vials of Nivolumab;
1 vial of 40 mg/4 mL
2 vials of 100 mg/10 mL

7.2.1.2 Preparing the Infusion

Care should be taken to ensure aseptic handling when preparing the infusion. The infusion should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents.

Please use whole kits to make up doses. Kits should not be split without prior consultation with the NICO trial team.

Nivolumab can be used for intravenous administration either:

- Without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- After diluting to concentrations as low as 1 mg/mL. The final infusion concentration should range between 1 and 10 mg/mL.

Nivolumab concentrate may be diluted with either:

- sodium chloride 9 mg/mL (0.9%) solution for injection; or
- 50 mg/mL (5%) glucose solution for injection.

STEP 1
Inspect the Nivolumab concentrate for particulate matter or discoloration. Do not shake the vial. Nivolumab concentrate is a clear to opalescent, colourless to pale yellow liquid. Discard the vial if the solution is cloudy, is discoloured, or contains particulate matter other than a few translucent to- white particles. Withdraw the required volume of Nivolumab concentrate using an appropriate sterile syringe.

STEP 2
Transfer the concentrate into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin). If applicable, dilute with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. For ease of preparation, the concentrate can also be transferred directly into a pre-filled bag containing the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. Gently mix the infusion by manual rotation. Do not shake.

7.2.1.3 Administration

The Nivolumab infusion **must not** be administered as an intravenous push or bolus injection.
If administered via infusion this should be done intravenously over a period of 60 minutes. The nivolumab infusion should not be infused at the same time in the same intravenous line with other agents.

Use a separate infusion line for the infusion. Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm). The infusion is compatible with PVC and

polyolefin containers, glass bottles, PVC infusion sets and in-line filters with polyethersulfone membranes with pore sizes of 0.2 µm to 1.2 µm. In line filters are to be sourced from hospital stock.

After administration of the nivolumab dose, flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

7.2.1.4 Disposal

Do not store any unused portion of the infusion solution for reuse. Any unused medicinal product or waste material should be disposed of in accordance with procedures specified in the Pharmacy operating manual

Dose Modifications

Please refer to Appendix B for management algorithms for nivolumab drug related adverse events

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Chief investigator or Medical Monitor representing the Sponsor.
A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory aetiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology (Nivolumab) drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

Adverse events ≥ Grade 3 considered drug related but not covered by these algorithms should be referred to the Chief investigator or designated medical monitor for the trial.

Accountability Procedures for Study Treatment

The PI is fully responsible for the Investigational Medicinal Product (IMP) at the trial centre. Nivolumab is classed as an IMP for the purposes of this clinical trial. Dispensing of study treatment may be delegated to the hospital pharmacy as locally applicable.
The person responsible for dispensing the study treatment will be responsible for maintaining adequate control of the IMPs and for documenting all transactions relating to them (as a minimum batch number, expiry date and dispensing date must be documented on the Drug Accountability Log). IMPs must be stored in a safe and secure place (only accessible to authorized personnel), and applicable Standard Operating Procedures (SOPs) must be followed.

Assessment of Compliance with Study Treatment

Administration of nivolumab will be completed at the clinic visit and the dosing information will be written in the CRF.

Concomitant Medications

7.2.1.5 Medications Permitted

No premedication is required prior to nivolumab infusion.

7.2.1.6 Medications Not Permitted/Precautions Required

- No other anti-cancer therapies may be given prior to recurrence of disease.
- Systemic long term corticosteroid* therapy at dose equivalent to prednisolone >10mg/day (unless used as replacement therapy) prior to trial registration
- Immunosuppressive agents* prior to trial registration

*systemic corticosteroids and other immunosuppressants can be used after starting Nivolumab to treat immune related adverse reactions

7.2.1.7 Data on Concomitant Medication

Dose and names of all concomitant medication should be documented on the CRF at screening. This will be reassessed by the PI throughout trial participation during clinical review. Any new medications introduced or changes to medications during the trial period should be documented on the CRF.

7.2.1.8 Overdoses

No cases of overdose of Nivolumab have been reported in clinical trials. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

7.3 IMAGING

Staging imaging must include head, neck and chest to allow assessment of the primary tumour, assessment for cervical lymphnode metastases and distant metastases respectively. As is routine, such scans will also be utilised to detect evidence of inoperability or synchronous malignancies.

Either MRI or CT (or a combination of both, ie MRI head and neck, and CT chest) is acceptable, however the same modality(ies) must be used throughout the trial for consistency. At sites that routinely perform a PET-CT scan post chemoradiation, this may replace one of the per-protocol scans. Additionally, where there is clinical suspicion of recurrence or metastasis, imaging may be performed as per local standard practice.

An imaging substudy will be carried out in a subset of participating sites. Here, a single additional scan (following neoadjuvant dose and prior to surgical resection) will be performed. Such an additional scan will be MRI only and, as such, will carry no (additional) exposure to ionising radiation.

7.4 SURGERY

Surgical resection will be performed with the intention of achieving complete microscopic clearance of the primary tumour and, as a minimum, an ipsilateral selective neck dissection, should be undertaken within 7 to 14 days of the 1st Nivolumab dose. Within the constraints of tumour, site and vital adjacent anatomical structures, ablation of the primary tumour should be made with a clinical margin of 10mm as measured from the tumour-normal interface.

Surgical management of the ipsilateral neck should be undertaken in all cases by way of a selective neck dissection/modified radical neck dissection. The extent to which levels of the neck should be dissected is made at the discretion of the surgeon however should include levels I-III as a minimum. Where tumour abuts or crosses the midline a selective neck dissection of the contralateral (clinically and radiologically N0) neck should be considered. Contralateral neck dissection is required where clinical, radiological or FNAC evidence of N+ disease is apparent in contralateral nodes. Primary reconstruction following surgical resection is anticipated in most cases and is made at the discretion of the operative surgeon.

As detailed in the site selection criteria, each recruiting centre must include a Head & Neck Surgeon with experience in the surgical management of oral cavity malignancy. To ensure credentialing of these individuals the provision of evidence of having undertaken the surgical management of 10 oral cavity cancers (of comparable stage to the trial inclusion criteria) in the preceding 12 month period is required.

To ensure surgical quality assurance, the nodal yield (absolute number of lymph nodes) from each neck dissection specimen will be reported upon and provided to the Independent Safety and Data Monitoring Committee (ISDMC) Assessment. A nodal yield of >18 lymph nodes is anticipated from a level I-III selective neck dissection in accordance with published literature(18) in most instances (and comparable head & neck surgical trials (PATHOS, Best-of). Where the nodal yield for an individual surgeon or centre is consistently below the set standard, the ISDMC will highlight and recommend appropriate corrective steps via the Trial Steering Committee (TSC).

7.5 PATHOLOGY

Surgical resection pathology reporting

Surgical specimens derived from patients with oral squamous cell carcinoma (OSCC) are routinely reported by pathologists working in either Clinical Pathology Accreditation (CPA (UK) Ltd) or International Organization for Standardization (ISO 15189:2012) approved diagnostic laboratories according to evidence-based documents published by the Royal College of Pathologists: Standards and datasets for reporting cancers. Dataset for histopathology reporting of mucosal malignancies of the oral cavity (19) and dataset for histopathology reporting of nodal excisions and neck dissection specimens associated with head and neck carcinomas(20). Histopathology data will be abstracted from pathology reports generated by pathologists at the participating centres. Staging will be performed according to the UICC TNM Classification 8th Edition(21). Given the recent transition from TNM7 to TNM8 in clinical practice, recording of staging according to both systems is required. For quality assurance purposes, a centrally conducted review of pathology will be undertaken for all surgical resection specimens. Upon review of pathology report, if there is no indication for adjuvant (c)RT (pT1-2 N0) then the patient should be withdrawn from study treatment (see section 4.3).

Biomarker testing

Human papillomavirus

Tumour human papillomavirus (HPV) infection will not determine entry into the trial.
HPV infection is uncommon in oral cavity SCC and to date has not been demonstrated to have any convincing prognostic benefit (22). Nevertheless, HPV status will be determined during the post-hoc analysis of trial biopsies. HPV status will be assessed using p16 immunohistochemistry (CINtec histology, Roche MTM laboratories), high-risk HPV DNA in situ hybridisation (Inform HPV III, Ventana Medical Systems Inc.) and HPV RNAscope (Advanced Cell Diagnostics).

PD-L1

Tumour PD-L1 expression will not be used to determine entry into the trial.
PD-L1 status will be determined during the post-hoc analysis of trial biopsies and resection specimens using the recommended PD-L1 test for Nivolumab (Dako PD-L1 IHC 28-8 PharmaDx kit performed on a Dako Autostainer Link 48) (23). This utilises a rabbit antihuman PD-L1 antibody (clone 28–8, Epitomics), using prespecified expression levels as defined previously and in line with analyses performed in the Checkmate 141 study (8)
A pathologist will score the PD-L1 staining according to the manufacturer's instructions (24).

7.6 CHEMO/RADIOTHERAPY

After surgery patients will be stratified to radiotherapy or chemo-radiotherapy depending on pathological features. Patients with the following high-risk criteria will be assigned to receive chemoradiotherapy:

- Cervical lymph node metastasis with extra capsular spread
- Surgical margins ≤1mm, or close margins (1-5mm) in the presence of additional high risk features such as peri-neural invasion, adverse pattern of invasion, multiple lymph node metastases, vascular emboli of tumour.

Patients with intermediate risk features (T3-4, perineural invasion, vascular invasion and/or >1 positive nodes), but without positive margins (as defined above) and no evidence of extracapsular spread will receive radiotherapy alone.

Treatment will begin within 8 weeks (56 days) of surgical resection, equating to a cumulative treatment time of 14 weeks. Any patient experiencing an 8 week or greater interval between surgery and commencement of radiotherapy/chemoradiotherapy will be withdrawn from trial treatment (Nivolumab).

Radiotherapy

7.6.1.2 Imaging

Patients will be immobilised in a thermoplastic mask. A contrast enhanced CT (slice thickness<3mm) from vertex to carina is recommended. The use of MRI is discretional.

7.6.1.3 Target volumes

The following target volumes will be defined.
High risk CTV (CTV_6500): primary tumour bed with positive margin and positive node levels with ECS.
Intermediate risk CTV (CTV_6000): primary tumour bed with negative margin and positive nodal levels with no ECS
Low risk CTV (CTV_5400): low risk node levels.
High risk PTV (PTV_6500): CTV_6500 +3-5mm margin
Intermediate risk PTV (PTV_6000): CTV_6000 + 3-5mm margin
Low risk PTV (PTV_5400): CTV_5400 + 3-5mm margin

PTVs will be cropped up to 6mm from the skin surface to generate Plan_PTV6500, Plan_PTV6000 and Plan_PTV5400 for the purpose of the treatment planning. The use of bolus is not permitted however, when CTV/PTV is close to skin, PTV can be cropped to skin surface and optimization build up used at the discretion of individual treating clinician / local practice. When using optimisation build up PTVs should be edited back to skin surface and PlanPTV_XXXX_OPT structures created.

7.6.1.4 Organs at Risk

The mandatory set of OAR to be contoured is as follows:

Spinal cord – the spinal cord should be outlined from the slice below the level of the foramen magnum to 2 cm below the most inferior slice of the PTV. The spinal cord itself, rather than the spinal canal, should be delineated. A typical expansion of 3mm (depending on local practice) should be applied to form the Planning Organ at Risk Volume (PRV).
• **Brainstem** – the whole brainstem should be contoured from the slice above the most superior slice of the spinal cord, extending superiorly. A typical expansion of 3mm should be applied to form the PRV according to local practice.
• **Optic nerves** – to be outlined as mandatory
• **Optic chiasm** – to be outlined as mandatory .
• **Left and Right Parotid** – both superficial and deep lobes should be defined as a single organ. Where blood vessels are encased by the gland, these should be included. Where applicable, the anterior boundary should extend to incorporate either the gland or parotid duct lateral to the masseter muscle. Parotid_L/R_PC will be defined as the parotid outside the PlanPTVs with a margin of 5mm. Parotid_L/R_PC will be used for plan optimisation and both Parotid and Parotid_PC will be considered for dose reporting..
• **Mandible_*** – entire mandible bone, without teeth; the use of bone view settings is recommended; Mandible and Mandible_PC (i.e. cropped 5mm from PlanPTV) will be considered for dose reporting.
• **Larynx_*** - from superior border of the body of the hyoid bone to the inferior border of the thyroid cartilage.
• **Trachea_*** - from the inferior border of the thyroid cartilage to 2 cm below the most inferior slice of the PTV.
• **Oesophagus_*** - from the inferior border of the thyroid cartilage to 2 cm below the most inferior slice of the PTV.

* The OARs_PC (i.e. cropped 5mm from PlanPTVs) will be considered for dose reporting.

7.6.1.5 Treatment planning and dose schedule

All patients in the NICO Trial will be treated with IMRT (fixed-beam or rotational arc therapy, including volumetric modulated arc radiotherapy -VMAT- and TomoTherapy).
For fixed field therapy, a five to nine field technique for bilateral irradiation, and a 4-5 field technique for lateralised cases, are likely to be required to achieve adequate target coverage and fulfil the dose constraints outlined below.
For arc therapy, a partial arc may be required for lateralised cases to minimise dose to the contralateral side.

A dose of 65Gy (or 60Gy if intermediate risk features alone) and 54Gy in 30 fractions will be prescribed to PlanPTV_6500, PlanPTV_6000 and PlanPTV_5400 respectively.
Dose constraints for Organs at Risk and further details of the planning process are reported in the RTQA document. All the participating Centres must be accredited for the trial RTQA. Streamlined RTQA is permitted for Centres already accredited for other head and neck trials (e.g. WISTERIA, ARTDECO, NIMRAD, COMPARE, etc).

7.6.1.6 Treatment delivery

Radiotherapy will be delivered once daily from Monday to Friday for 6 consecutive weeks.

Treatment verification is required for at least the first three fractions to determine if any systematic error exists. As a minimum correction should be carried out at fraction four according to local practice, and a further check made to confirm the adjustment. Verification is then performed once weekly throughout the remainder of the treatment, tolerances are according to local practice. Planar MV, kV Pimaging or volumetric imaging (Cone-Beam Computed Tomography (CBCT)) may be used. The number of monitor units used for verification should be minimised.
If a weekly image has an out of tolerance error, verification images should be reported for the next two fractions to allow calculation of a new systematic shift. Re-planning should be according to local practice and must be reported to the NICO Trial Office and to the RTTQA contact.

7.6.1.7 Treatment breaks and compensation

Treatment breaks are only allowed for severe acute toxicity or intercurrent illness and not for social or logistical reasons. Any radiotherapy treatment break due to toxicity should be reported with documentation of reason in the CRF. Any radiotherapy treatment break/prolongation of overall treatment time for causes other than acute toxicity or inter-current illness will be considered a protocol deviation and should be reported on the Deviation Form.
Patients in the NICO trial are managed as category 1 patients. If radiotherapy is not given on a planned day as scheduled, then this will be compensated for that week or in accordance with local practice.

Chemotherapy

Patients will receive concomitant IV Cisplatin 100mg/m2 d1 and d22.
Cisplatin is classed as a non-IMP (NIMP) for this trial as it is a background treatment only

Commercially available Cisplatin will be used in the study and will be supplied from NHS stock. No additional labelling by the site pharmacy is required. No accountability is required.

Cisplatin is a platinum containing drug which causes DNA damage and will not be subject to any special packaging or labelling.

Generic Cisplatin sourced from manufacturers listed on electronic Medicines Compendium are allowed for use in this study http://emc.medicines.org.uk. For packaging, storage and stability please refer to the specific SmPC for each individual product and any local policies which may apply.

Cisplatin must be handled according to the instructions within the corresponding SmPC (Please refer to current Cisplatin SmPCs supplied by the appropriate manufacturer: https://www.medicines.org.uk/emc/search?q=cisplatin and to any local policies which may apply).

Hydration and antiemetic pre-medication should be given according to local practice.

7.6.2.1 Dose modification for concomitant Cisplatin

Any Cisplatin dose delay, modification or omission should be recorded.
If a weight change of >10% occurs during the course of the study, concomitant Cisplatin dose should be recalculated. If the BSA is >2.0 m^2, doses should be capped, at a BSA of 2.0 m^2.
If the patient's weight changes by <10% during the course of the study, the concomitant Cisplatin dose may be adjusted in accordance with local policy and at the Prinicipal Investigator's discretion, but this is not an absolute requirement.
If calculated GFR (Cockroft & Gault), immediately before any cycle of concomitant chemotherapy, isbelow 50mL/min, Cisplatin should be discontinued and consideration given to substitution of the second cycle of treatment with Carboplatin AUC5 given concomitantly with radiotherapy.
If the second dose of concomitant Cisplatin is delayed more than 28 days because of hematologic or renal adverse events, that dose must be omitted.

Dose modifications are required in the following circumstances:
Neutropenia: If on the day of scheduled treatment with Cisplatin, the ANC is ≤1.5 x 10^9/L, withhold Cisplatin until ANC ≥1.5 x 10^9/L, then treat at 100% dose.
Thrombocytopenia: platelet count on the day of scheduled treatment with Cisplatin ≤100 x 10^9/L withhold Cisplatin until platelet count ≥100 x 10^9/L, then treat at 100% dose.

In each of the following situations, Cisplatin should be modified and consideration given to substitution with Carboplatin if discontinued as per standard local practice:
Neurotoxicity: e.g. peripheral neuropathy grade 3 or greater
Ototoxicity: new tinnitus that interferes with activities of daily or clinically significant hearing loss. If the Investigator is unsure about the severity of hearing loss, an audiogram is recommended.
Allergic phenomena: Anaphylactoid reactions to cisplatin have been observed.
These reactions
can be controlled by administration of antihistamines, adrenaline and/or glucocorticoids.

8 ASSESSMENTS AND PROCEDURES

8.1 Schedule of Trial Procedures

Study procedure	Screening/ baseline 28 days*	Treatment 1: Pre-surgery	Surgery	Treatment 2: (post-surgery, pre radiotherapy),	Treatments 3- 8 (post CRT or RT)	Follow up	End of Study treatment/safety visit (confirmed recurrence, LP 1 year follow up.))
Day	≤28 days*	7- 14 days prior to planned surgery		7- 14 days prior to commencing radiotherapy	Within 4 weeks of completing RT or CRT, then every 28 days (25- 31 days)[1]	6, 9, 12 Months (+/- 7 days) from date of surgery.	100 days from date of nivolumab dose 8
Procedures							
Informed Consent	X						
Registration – LCTC	X						
Assessment of Eligibility Criteria	X						
Medical History	X						
Physical Examination and ECOG PS	X	X[2]		X	X		X
Height, Weight[3]	X			X	X		X
Imaging[4/*]	X*	X*				X[5]	
Vital signs, O2 sats	X	X[2]		X	X		X
ECG	X						
Investigations							

FBC, U&Es, LFTs, Calcium, magnesium, glucose, AST and ALT.	X	X [2]		X	X		X
Pregnancy test[6]	X						
Thyroid function tests	X	X [2]		X	X[7]		
Diagnostic Biopsy tissue sample[8]	X						
Biopsy research tissue sample[9]	X						
Tissue sample from surgical specimen (Paraffin and where available All protect and/or fresh frozen)			X				
Tissue sample from progressive disease (Paraffin and where available All protect and/or fresh frozen)							X
Translational bloods	X[10]		X[10]	X[10]	X[10]		X[10]
Faecal microbiome sample	X[15]	X[15]			X[15]		
Oral microbiome sample	X[16]	X[16]		X[16]	X[16]		X[16]
Nivolumab: 240mg Flat dose		X[11]		X[11]			
Nivolumab: 480 mg Flat dose					X[12]		
Central Analysis Investigations							
None							
Patient Questionnaire/Procedures							
EORTC (H&N module)	X[14]			X[14]	X[14]		X[14]
Data Collection							
Adverse Events Data	X	X [2]		X	X		X
Concomitant Medications[13]	X	X [2]		X	X		X

Surgical Complications (Clavien-Dindo), and Radiotherapy/ CRT related AEs				X	X		
End of Study Form							X

* With the exception of biopsy and imaging:
- Confirmation of diagnosis (Histology) – no time frame
- MRI or CT Scan of Head and Neck – within 8 weeks
- CT scan of chest – within 8 weeks

[1]Commencement of adjuvant nivolumab may be delayed up to 10 weeks (70 days) after completion of radiotherapy/chemoradiotherapy to allow grade 2+ toxicity to improve to grade 1 or resolve where this is considered likely to negatively interact with immunotherapy. Additionally, adjuvant immunotherapy may be delayed where steroids or other prohibited immunosuppressant have been instituted to control toxicity. In all cases, such delays must be prospectively discussed and confirmed with the trial centre. If immunotherapy cannot be instituted with 10 weeks (70 days), the patient will be withdrawn from the study.
[2]not required if done during screening and within 7 days.
[3]Height required at baseline only
[4]Imaging must include head, neck and chest. Either MRI or CT (or a combination of both, ie MRI head and neck, and CT chest) is acceptable, however the same modality(ies) must be used throughout. PET/CT is not required, however where this is included as standard of care locally this may substitute one of the per-protocol scans. Imaging of head and neck (MRI or CT) and chest (CT) should be performed within the 8 weeks prior to first dose of nivolumab.
*Additional MRI Scan of the head and neck will be performed in the case of individuals consented for inclusion on imaging research sub-study
[5]Months 6, 9, 12 from date of surgery (+/-7 days)
[6] females of child bearing potential only. A serum pregnancy test may be carried out instead of urine if this is preferred
[7]Thyroid function tests performed every two cycles of Nivolumab (1 cycle = 1 dose)
[8]Diagnostic tissue sample: A histological confirmation of the current malignancy is required but is not subject to a screening window
[9]Research tissue sample: Wherever possible, research tissue consent (Pathway 1/Pathway 2 ICF) should be obtained prior to diagnostic biopsy to enable collection of fresh tissue (to be collected in All protect and where resource allows also fresh frozen and/or couriered directly to research laboratory). Alternatively where diagnostic biopsy has already occurred, patients should be approached for an additional research biopsy. However, if this is not feasible, archival tissue is required from the biopsy sample. A histological confirmation of the current malignancy is required but is not subject to a screening window
[10]Translational blood samples are taken at the following time points
a) Prior to surgery and initial Nivolumab treatment

b) At surgery
c) Post surgery but pre-radiotherapy/chemoradiotherapy
d) First administration of Nivolumab post radiotherapy/chemoradiotherapy
e) Third administration of Nivolumab post radiotherapy/chemoradiotherapy
f) Sixth administration of Nivolumab post radiotherapy/chemoradiotherapy
g) End of Study treatment/Safety visit

[11] Nivolumab pre-surgery and pre-Radiotherapy/Chemoradiotherapy at 240mg flat dose

[12] Nivolumab post Radiotherapy/Chemoradiotherapy at 480mg flat dose

[13] After screening visit, changes to concomitant medications to be collected on each visit.

[14] QOL Questionnaires to be taken at the following time points time points

a) Prior to surgery and initial Nivolumab treatment
b) Post surgery but pre-radiotherapy/chemoradiotherapy
c) First administration of Nivolumab post radiotherapy/chemoradiotherapy
d) Third administration of Nivolumab post radiotherapy/chemoradiotherapy
e) Sixth administration of Nivolumab post radiotherapy/chemoradiotherapy
f) End of Study treatment/Safety visit

[15]Faecal microbiome samples to be taken at the following time points in a proportion of patients consented for inclusion in substudy

a) Prior to surgery and initial Nivolumab treatment (baseline)
b) Post 1st administration of Nivolumab prior to surgery,
c) Post CRT or RT but before administration of Nivolumab

[16]Oral microbiome samples to be taken at the following time points in a proportion of patients constented for inclusion in substudy

a) Prior to surgery and initial Nivolumab treatment (baseline)
b) Post first administration of Nivolumab prior to surgery
c) Post surgery, post second administration of Nivolumab but pre-radiotherapy/chemoradiotherapy
d) Post CRT or RT but before administration of Nivolumab
e) End of study treatment/Safety visit (confirmed recurrence)

8.2 Procedures for assessing Efficacy

Efficacy will be assessed in terms of disease relapse and survival (see section 2.3 for details of objectives and section 8.2 for details of outcome measures (endpoints)). The presence of tumour recurrence or metastasis will be assessed by imaging (CT+/-MR as defined in section 6.3) at 6, 9, and 12 months following surgery by the investigator at each site. The time of relapse will be defined as the earliest date at which relapse is identified on protocol defined imaging, clinical examination or interval scanning instituted for any reason. Where relapse is strongly suspected and then confirmed on a subsequent scan (ie suspicious lesions have further increased in size), the earlier date will be used for definition of relapse. Wherever feasible, confirmation of relapse by biopsy should be performed. This is particularly the case with local relapse as this may be difficult to discriminate from post treatment changes. Death details will be obtained from the PI at each centre.

8.3 Procedures for Assessing Safety

Safety will be assessed through the reporting of adverse events as described in Section 9. Formal toxicity assessments will be performed at each study visit as described in Section 7.1. Adverse events will be described using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4, which can be accessed at the following website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40_conversion

8.4 Other Assessments

Surgical and post-operative procedures

The following documentation and assessment records will be provided;
Surgical record of treatment (operation note)
Discharge summary (including length of admission and inpatient surgical and non-surgical complications).
Histopathology report (inc minimum dataset for reporting of Head & Neck Pathology)
Record of clinical examination and surgical complications (Clavien Dindo Classification) at post surgical followup and post (C)RT .

Quality of Life and Health Economics

Quality of life forms EORTC QLQ-C30 v3 and EORTC Module for Head and Neck Cancer QLQ-H&N35 will be completed at baseline, post surgery but prior to Radiotherapy/Chemoradiotherapy, first dose of nivolumab post Radiotherapy/Chemoradiotherapy, third dose of nivolumab post Radiotherapy/Chemoradiotherapy, sixth dose of nivolumab post Radiotherapy/Chemoradiotherapy and at the end of study treatment/Safety visit.

8.5 Translational research

The trial will provide an invaluable opportunity for translational research, which will predominantly (but not exclusively) aim to identify predictive markers of response and to explore potential mechanisms of resistance to nivolumab. All patients may consent to the collection of archival tissue

from the biopsy sample, and from the surgical specimen, and for collection of blood samples as outlined in the schedule of assessments. Where feasible, patients will additionally consent to the collection of a research specific biopsy prior to treatment with nivolumab, and for a biopsy in the event of recurrence. In centres participating in a microbiome substudy, patients will also consent to faecal and saliva samples to be collected at timepoints specified in the schedule of assessments. Sample collection, processing and distribution is outlined in the laboratory manual, while planned investigations are included in a separate translational protocol.

8.6 Substudies

An imaging substudy will be carried out in a subset of participating sites. Here, a single additional scan (following neoadjuvant dose and prior to surgical resection) will be performed. Such an additional scan will be MRI only and, as such, will carry no (additional) exposure to ionising radiation.

In those centres participating in imaging substudies, patients will additionally consent to a further MRI scan prior to the neoadjuvant dose of nivolumab and again within 3 days of planned surgical resection. The substudy has a separate MRI Patient Information Sheet and Informed Consnt Form

8.7 Loss to Follow-up

If any of the trial patients are lost to follow up, contact will initially be attempted through the PI at each centre. If the PI at the trial centre is not the patient's usual clinician responsible for their speciality care then follow-up will also be attempted through this clinician. Where all of these attempts are unsuccessful, the patient's GP will be asked to provide follow-up information to the recruiting centre.

8.8 Trial Closure

Investigators will be informed when patient recruitment is to cease. Trial enrolment may be stopped at a site when the total requested number of subjects for the trial has been obtained. The ISDMC may recommend to the TSC that the trial be stopped prematurely. Such premature termination/suspension of the trial will be notified to the MHRA and REC as required. The trial will be considered formally "closed" when all patients have been followed up for the period specified in the protocol and all outstanding data has been collected.

9 STATISTCIAL CONSIDERATIONS

9.1 Introduction

This section details the statistical methods relating to the study.

9.2 Outcome Measures

9.2.1 Primary

This study includes co-primary endpoints:

- 1-year DFS defined as disease recurrence or death at 12 months following surgery.
- Feasibility of the study to recruit to both cohorts of the study.

These endpoints are still estimable and will be presented although sub-group analyses assessing effects within the high-risk group will be infeasible due to there being a maximum of 5 patients recruited in this group.

9.2.2 Secondary

Secondary endpoints include:

- Disease free survival measures as the time from surgery until disease recurrence or death by any cause.
- Overall survival measured at the time from recruitment to death by any cause.
- Toxicity measured based on CTCAE (Version 4).
- Surgical complications (infection rate, length of hospital admission, free flap failure and perioperative (30-day) mortality).

9.3 Sample Size

Original Sample size calculation

We estimate that approximately a third of all patients with the above eligibility criteria will have high risk disease (ECS, involved margins) post-surgery and will be enrolled onto the chemoradiotherapy arm. With a total population of 120 (recruited over 18 months) we would thus anticipate recruiting 40 patients into the high-risk cohort. With an additional follow-up of 1 year, essentially all patients will be available for analysis for the primary endpoint. 12-month DFS for this patient group would be estimated at ~65% following standard treatment including adjuvant chemoradiation (see below), with confidence intervals of 53.9% - 74.2% (assuming a 40-patient cohort). Thus, an observed PFS of ≥ 75% (corresponding to a hazard ratio of 0.67), would represent a clinically relevant positive result.

Estimates for 1-year DFS are based on historical trials. In a recent trial investigating the addition of lapatinib to chemoradiation and as adjuvant therapy, the one-year DFS rate was ~70% (4). Notably this included some HPV +ve patients and earlier stage disease, and patients with stage IVA/IVB HPVve disease would be expected to have a worse survival, with a 1-year DFS of around 50-60%. This is supported by a large meta-analysis, in which concomitant chemoradiation improved 5-year survival from 38% to 46.6% (1 year OS of approximately 75%) (3), again indicating poor long term outcomes.

Revised Sample Size

Due to early closure, a maximum of 30 patients will be recruited with approximately 25 in the no-high risk group. With 1 year follow-up, estimates of DFS here will likely be based on the majority of these

patients. Estimation of the 12 months DFS rate would likely have a confidence interval of with half length of approximately 20% meaning that if a DFS of 65% is observed this will have a precision of (45% - 85%).

9.4 Recruitment

The target for recruitment is 120 patients over a period of 18 months. A total of 10 recruiting centres will initially be opened at a rate of 3 sites every 2 months. The average recruitment rate is expected to be 0.8 patients per site per month. Figure 3 below shows the anticipated recruitment rate over the course of the study.

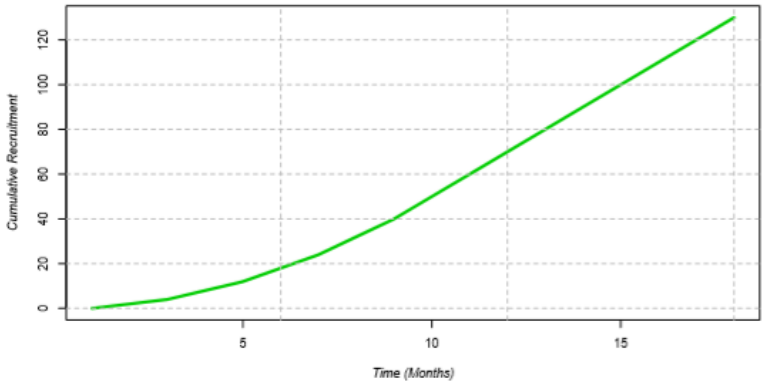


Figure 3: Planed cumulative recruitment

The actual recruitment was terminated on the 25th November 2020 with the actual greenlight data being obtained in May 2019 and 2 sites opened to recruitment. By the end of this 18 month period, an anticipated 30 patients were to be recruited which was 43% of the planned recruitment rate at this point (70).

9.5 Interim Monitoring and Analyses

There are no formal stopping rules for efficacy or toxicity in this study. Interim analyses of accumulating data will be performed at regular intervals (at least annually) for review by an Independent Safety and Data Monitoring Committee (ISDMC). These analyses will be performed at the Liverpool Clinical Trials Centre. The ISDMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the ISDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The ISDMC will make recommendations to the Trial Steering Committee (TSC, see section 16) as to the continuation of the trial.

9.6 Analysis Plan

9.6.1 Feasibility Measures

The primary measure of feasibility will be the ability of the study to recruit sufficient patients..

The target for the initial study was to recruit 120 patients over 18 months which should have reached an eventual recruitment rate of 10 patients per month. A full list of feasibility outcomes to be measured are:

- Recruitment rate: Defined as the total number of patients randomised per month.

- Site opening: Defined as the time take to open the target number of sites (initially 10 sites) in the study.
- Patient Adherence to Protocol: To determine whether patients and/or care given adhere to the conditions of the protocol. Measured using the number of minor/major protocol deviations.
- Data Collection: measured via the number of missing forms and data queries and included to demonstrate the function of the internal data collection procedures.

9.6.2 Statistical Analysis of Clinical data

Summary Statistics

Continuous data shall be summarised as medians (inter-quartile ranges). Categorical data shall be reported as frequencies of counts and percentages.

Levels of Significance

No formal testing procedures are included in this study. All relevant estimates shall be reported with 95% confidence intervals.

Missing Data

Missing data are anticipated to be small and all analyses will be carried out on a complete case basis. Should a substantial amount of missing data be observed, either in the response or key prognostic variable, then multiple imputation using chained equations shall be employed.

Data Analysis

DFS Rate: The 1-year disease recurrence rate shall be defined as a binary variable and estimated alongside a 95% confidence interval assuming a binomial distribution. No multivariable modelling will be performed.

DFS & OS: Disease Free Survival and Overall Survival estimates shall be calculated using the Kaplan-Meier method and compared across clinical subgroups using a log rank test. No further multivariable analyses will be performed.

Toxicity: Adverse events (AEs) and Serious adverse events (SAEs) shall be defined using CTCAE (version 4) definitions. All AEs and SAEs shall be compared across groups using TAME guidelines. Furthermore, the worst AE/SAE for each type for each patient shall also be retained and compared across treatment groups using a stratified Chi-Square test.

Surgical Outcome

Infection rate shall be measured based on clavien dindo classifications and analysed as a binary covariate. Infection rate, free flap failure and peri-operative mortality shall be reported as frequencies of counts and associated percentages. Further multivariable logistic regression models will be used to assess the impact of clinical covariates on response, using a maximum of 3 covariates per model.

The length of hospital admissions shall be measured as the number of days in hospital following surgery and reported with associated inter-quartile ranges. Regression analysis assuming the count of days to follow a Poisson distribution will be used to assess the impact of clinical covariates on response.

Quality of Life

Quality of Life will be measured using the Eortc-qlqc30 (+ H&N module). Data will be summarised across each QoL dimension with interest primarily on the overall quality of life scores derived from questions 29 and 30 on the eortc-qlqc30 score.

Analyses shall be carried out on the unadjusted change from baseline to the end of treatment and reported in terms of the mean (95% confidence interval) on the various components obtained from each QoL source.

10 PHARMACOVIGILANCE

10.1 Terms and Definitions

The following definitions have been adapted from European Directive 2001/20/EC and ICH GCP E6

Adverse Event (AE)
Any untoward medical occurrence (i.e. any unfavourable or unintended sign including abnormal laboratory results, symptom or disease) in a research participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)
Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR)
An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:
a) In the case of a product with a marketing authorization, in the summary of product characteristics for that product
b) In the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
Any adverse eventor adverse reaction is classified as serious if it:

a) results in death
b) is life-threatening* (subject at immediate risk of death)
c) requires in-patient hospitalisation or prolongation of existing hospitalisation**
d) results in persistent or significant disability or incapacity, or
e) consists of a congenital anomaly or birth defect
f) Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is considered an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs or in the case of pregnancy reported via trial specific measures .

10.2 Notes on Adverse Event Inclusions and Exclusions

There are trial specific inclusions and exclusions for reporting SAEs for NICO. These are detailed below;

Include

- An exacerbation of a pre-existing illness
- An event that delays planned standard of care treatment i.e. surgery, (chemo) radiotherapy
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory anomalies that require discontinuation of the study drug, clinical intervention or further investigation (unless they are associated with an already reported clinical event)
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Potential Drug Induced Liver Injury (DILI) defined as
    1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

    AND

    2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

    AND

    3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.
- Injury or accidents

Do Not Include

- Expected effects or complications of major head and neck curative surgery, radiotherapy or CRT, except where these are judged by the investigator to have been exacerbated or prolonged by the nivolumab treatment. Complications and outcomes from surgery, radiotherapy or CRT must however be collected at the appropriate visits detailed in the schedule of events.
- Extended hospital stay due to a delay in planned surgery.
- Medical or surgical procedures- the condition which leads to the procedure is the adverse event
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

Reporting of Pregnancy

Pregnancy testing should be conducted prior to study treatment. If a patient or their partner becomes pregnant during treatment, they must be withdrawn immediately.
If a patient or their partner becomes pregnant during treatment or in the seven months following treatment, a completed Pregnancy Report Form must be emailed via secure transmission to the LCTC within 24 hours of learning of its occurrence. On pregnancy outcome, the final Pregnancy Report Form should be faxed to the LCTC 30 days after the outcome. The final Pregnancy Report Form is used to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy follow-up information on this form also includes an assessment of the possible relationship to the trial medication of any pregnancy outcome. Pregnancy outcomes should also be collected for the female partners of male patient participating in the trial. Consent to report information regarding these pregnancy outcomes should be obtained from the mother prior to completion and faxing of the final Pregnancy Report Form. Any SAE experienced during pregnancy must be reported on the SAE form.

Reporting: Pregnancies must be reported
***within 24 hours of becoming aware of the event* to the**
Liverpool Clinical Trials Unit
Email: LCTCSafe@liverpool.ac.uk

Outcomes: Pregnancy outcomes must be reported
***30 days following the outcome* to the**
Liverpool Clinical Trials Unit
Email: LCTCSafe@liverpool.ac.uk

10.3 Notes Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.
Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities
Life threatening
Death

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.4 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table 2.
If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Table 2: Definitions of Causality

Relationship	Description
None	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Highly Probable	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.5 Expectedness

An AE whose causal relationship to the study drug is assessed by the investigator as "possible", "probable", or "highly probable" is an Adverse Drug Reaction.
All events judged by the investigator to be possibly, probably, or highly probably related to the IMP, graded as serious and **unexpected** for list of Expected Adverse Events (see Reference Safely Information section 10.6) should be reported as a SUSAR.

10.6 Reference Safety Information

The Reference Safety Information (RSI) to be used for this trial is as follows:

Section 5.6 Reference safety information within the IB for Nivolumab (OPDIVO), specifically adverse reactions reported in the pooled data set for patients treated with nivolumab monotherapy. Additional information is available in Appendix 1 Reference Safety Information Tables for Assessment of Expectedness of Serious Adverse Reactions. The Sponsor consults this section when determining reporting requirements for Suspected Unexpected Serious Adverse Reactions (SUSARs) from clinical studies in accordance with regional and/or local regulations.

10.7 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.
When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with

sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.8 Reporting Procedures

All new Adverse Events (AEs) that occur either following the participants written consent and up to **100 days** following the last dose of trial treatment need to be recorded in the case report form and are part of the expedited reporting procedure.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Any questions concerning adverse event reporting should be directed to the LCTC in the first instance

9.8.1 Non serious ARs/AEs

All such events, whether expected or not, should be recorded in the visit pages of the CRF or, if a field for the event is not provided there, in the AE Form which can be downloaded from the Portal within 100 days after completion of the final treatment cycle.

Instructions and training will be provided at site initiation..

9.8.2 Serious ARs/AEs/SUSARs

Investigators MUST REPORT ALL SERIOUS ADVERSE EVENTS (SAEs), including disease related as well as treatment related events that occur during and within 100 days following the last dose of trial treatment.

SAEs SARs and SUSARs must be reported **within 24 hours** of sites becoming aware of them by sending a completed SERIOUS ADVERSE EVENT FORM to the Liverpool Clinical Trials Centre as follows:

Reporting:
SAEs SARs and SUSARs must be reported
within 24 hours of becoming aware of the event **to the**
Liverpool Clinical Trials Unit
Email: LCTCSafe@liverpool.ac.uk

Blank Serious Adverse Event forms can be obtained by logging onto the Portal (www.lctc.org.uk). When submitting an SAE please contact the NICO team via phone to confirm that the SAE has been received at LCTC..

All SAEs must be emailed via secure transmission to LCTC.

If a computer system failure has occurred in order to report the SAE please contact the NICO trial team on 0151 795 8577 to verbally report the SAE information .

Steps for reporting:

i. The SAE form should be completed by the responsible investigator i.e. the consultant named on the 'signature list and delegation of responsibilities log' who is responsible for the patient's care. The investigator should assess the SAE for the likelihood that it is a response to an investigational medicine. In the absence of the responsible investigator the form should be completed and signed by a designated member of the site trial team. The responsible investigator should check the SAE form, make changes as appropriate and sign as soon as possible. The initial report shall be followed byfollow up reports as new information becomes available.
ii. The SAE form should be sent to the LCTC by secureemail (see above).
iii. The responsible investigator must notify their R&D department of the event (as per standard local procedure).
iv. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.
v. All follow-up information must be recorded on a new SAE form.
vi. The patient must be identified by trial number, date of birth and initials only. No patient identifiable information should be included in any correspondence.

The minimuminformation required for reporting is as follows:

- Valid EudraCT number
- Sponsor trial number
- One identifiable coded subject
- One identifiable reporter
- One SAE
- One suspect IMP (including active substance name)
- A causality assessment.

i.

PLEASE ENSURE THAT MULITPLE SERIOUS ADVERSE EVENTS ARE REPORTED SEPARATELY TO THE LCTC

ONE SAE REPORT SHOULD ONLY RELATE TO ONE OVERALL DIAGNOSIS.

Suspected Unexpected Serious Adverse Reaction (SUSAR)
The Chief Investigator and the Liverpool Clinical Trials Centre will ensure that all SUSARs are reported to the Sponsor, Competent Authorities (MHRA Clinical Trials Unit) and Ethical Committees within the following timelines.

- Fatal or life threatening SUSARs within 7 days after receiving the initial information.
- All other SUSARs with 15 days after receiving the information.

The Chief Investigator and the Liverpool Clinical Trials Centre will inform all investigators of SUSARs as they occur.

All SUSARs are managed in accordance with the LCTC Pharmacovigilance SOPs and the NICO Pharmacovigilance plan.

Annual Reporting to MHRA and REC
The sponsor will submit a Development Safety Update Report (DSUR).
The DSUR will present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period relating to the Investigational Medicinal Product. It will cover the following 4 areas:
(1) Examine whether the information obtained by the sponsor during the reporting period is in accordance with previous knowledge of the investigational drug's safety.
(2) Describe new safety issues that could have an impact on the protection of clinical trial subjects.
(3) Summarise the current understanding and management of identified and potential risks.
(4) Provide an update on the status of the clinical investigation/development programme and study results.

10.9 Responsibilities – Investigator

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.
All SAEs must be reported to LCTC within 24 hours of the site becoming aware unless the SAE is specified in the protocolas not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

10.10 Responsibilities – LCTC

The LCTC is undertaking duties delegated by the trial sponsor, The Clatterbridge Cancer Centre NHS Foundation Trust and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA, competent authorities of other European member states in which the trial is taking place and, if required, the research ethics committees) as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the LCTC is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the LCTC first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion
- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:
    a. A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;
    b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
    c. A major safety finding from a newly completed animal study (such as carcinogenicity).
    d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;

- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the LCTC will liaise with the Sponsor delegated Medical Reviewer who will evaluate all SAEs received for expectedness and causality.. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report. All SUSARs identified by this review wil be onward reported to regulatory authorities and REC

The LCTC will also send an annual safety report containing a list of all SARs to regulatory authorities and

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

All pregnancies and SAEs regardless of casuality will be onward reported to BMS by LCTC

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

The NICO trial will be conducted in accordance with, but not limited to, the Human Rights Act 1998, the DPA, Freedom of Information Act 2000 subject to the provisions of sections 41 and 43 thereof, the EU Clinical Trials Directive, the Medicines for Human Use (Clinical Trials) Regulations 2004, the Medicines Act 1968, the Human Tissue Act 2004, ICH GCP, the Declaration of Helsinki 1996 and the NHS Research Governance Framework for Health and Social Care, as amended from time to time. Patients will be asked to consent that data are recorded, collected, stored and processed and may be transferred to other countries, in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).

The protocol has undergone ethical review by an independent Research Ethics Committee and has received a favourable opinion. Any particular issues directly affecting participants are highlighted in the PIS/ICF to ensure consent is fully informed.

Patients will be asked to consent that data are recorded, collected, stored and processed and may be transferred to other countries, in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC) and to allow a copy of their completed signed consent form to be sent to the Liverpool Clinical Trials Centre.

This study may be terminated at the request of the CI, ISDMC, independent Research Ethics Committee (REC) or the MHRA if, during the course of the study, concerns about the safety of further dosing emerge.

The CI will update the ethics committee of any new information related to the study drug when appropriate and this will also be disseminated to the Principal Investigators at each trial centre.

11.2 Ethical Approval

The trial protocol PIS/ICF and any proposed public-facing material has received the written favourable opinion of the London Harrow Research Ethics Committee (REC) Health Research Authority and host institution(s).

Local approval to conduct the study at each NHS Trust participating will be sought from the local Research & Development (R&D). A copy of this approval including confirmation of capacity and capability will be forwarded to the LCTC. A copy of the Patient Information Sheet and Consent Form on local headed paper should be forwarded to LCTC before patients are entered.

Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in LCTC coordinated trials. In obtaining and documenting informed consent, the

investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with appropriate experience. An appropriate Patient Information and Consent forms, describing in detail the trial interventions/products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient and answer any questions that may arise. A contact point where further information about the trial may be obtained will be provided

After being given adequate time, preferably 24 hours, to consider the information, the patient will be asked to sign the informed consent document. A copy of the informed consent document will be given to the patient for their records and a copy placed in the medical records, with the original retained in the Investigator Site File.

After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient remains free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing the further treatment. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

Patients may withdraw from the trial at any time by revoking the informed consent

11.4 Study Discontinuation

The reason for discontinuation of study treatment/study should be clearly documented and the end of treatment and end of study CRFs completed.

12 REGULATORY APPROVAL

This trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA). The CTA reference is 21390/0008/001-0001

13 TRIAL MONITORING

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. A risk assessment will be carried out to determine the level of monitoring required, and a subsequent monitoring plan will be developed to document who will conduct the central (and potentially site) monitoring, at what frequency monitoring will be carried out and the level of detail at which monitoring will be conducted.

13.1 Risk Assessment

In accordance with the LCTC SOPs a risk assessment has been completed in partnership with:

- Representatives of the Trial Sponsors
- Chief Investigator
- Trial Co-ordinator
- Trial Statistician
- LCTC Operational Director

In conducting this risk assessment, the contributors considered potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.
The outcome of the risk assessment is expressed as an overall risk level as set out below, assigned according to one of the following categories:

CTIMP Type A = Comparable to the risk of standard medical care
CTIMP Type B = Somewhat higher than the risk of standard medical care
CTIMP Type C = Markedly higher than the risk of standard medical care
Non-CTIMP

The risk assessment resulted in a CTIMP Type B = Somewhat higher than the risk of standard medical care

13.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical trial.

13.3 Data Capture Methods

Trial data will be captured using remote data entry at research sites which will be entered onto the MACRO database by site staff at participating sites. AE and SAE data will be reported to the LCTC via fax on paper forms (see Section 9.8.2) . You may complete paper copies of the workbooks as an aid to

data collection, however data should be entered via eCRF on MACRO. The LCTC do not require copies of the workbooks, however a paper copy of the ICF is still required. If MACRO is not in service and the deadline for data entry completion is close you may send a paper copy of the workbook to the LCTC for data entry, however this must first be discussed with the NICO Data Manager by telephone.

Case Report Forms

The study electronic case report form (eCRF) is the primary data collection instrument for the study. All data requested on the eCRF must be recorded. All missing data must be explained. Data should be entered in a timely fashion, with all data being entered within 2 weeks of the patient's final follow-up. A guide for entering data on MACRO will be available in the Portal Investigator Site File section and training will be given to delegated staff at the Site Initiation Visit.

13.4 Monitoring at LCTC

Data stored at LCTC will be checked for missing or unusual values (range checks) and checked for consistency within patients over time. If any such problems are identified, a PDF list of queries will be emailed to the local site for checking and confirmation or correction as appropriate – data should be amended on MACRO and an email detailing changes sent in response. LCTC will send reminders for any overdue and missing data.
There are a number of monitoring features in place at the LCTC to ensure reliability and validity of the trial data.

13.5 Clinical Site Monitoring

Direct access to data

In order to perform their role effectively, monitors and persons involved in Quality Assurance and Inspection will need direct access to primary subject data, eg patient records, laboratory reports, appointment books, etc. Because this affects the patient's confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited.
Samples will be transferred to the GCLP facility and will be identifiable by the patient's unique trial number only. Consent forms sent to the LCTC as part of the registration process may contain patient identifiers for the purpose of monitoring as described in the trial risk assessment. Such information will be stored separately from clinical data in secure, locked cabinets.

Quality Assurance and Quality Control of Data

Systems of quality assurance, including all elements described in this protocol have been/will be implemented within relevant institutions with responsibility for this trial. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.
The NICO trial centres, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit and inspection by competent authorities or REC. Such audits/inspections may take place at any trial centre where the trial related activity is taking place (the Sponsor, trial centres, LCTC, or at any investigator's centre including laboratories, pharmacies etc.).

The trial centre staff should assist in all aspects of audit/inspection and be fully cognisant of the LCTC communication strategy for multicentre trials. This includes management systems such as the Green Light Process which conforms to the total Quality Management System currently operating within the LCTC.

13.6 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Trial File, until the LCTC informs the investigator that the documents are no longer to be retained. In addition, the investigator is responsible for the archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The LCTC undertakes to store original documents completed for the trial research e.g. ICF for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only.

At the point where it is decided that the trial documentation is no longer required; the investigator will be responsible for the destruction of all site trial specific documentation and the Sponsor/LCTC will be responsible for the destruction of all trial related materials retained by the Sponsor/LCTC.

Verification of appropriate informed consent will be enabled by the provision of copies of patients' signed informed consent forms being supplied to the LCTC by recruiting centres. This requires that name data will be transferred to the LCTC, which is explained in the PIS. The LCTC will preserve the confidentiality of patients taking part in the study and the University of Liverpool is a Data Controller registered with the Information Commissioners Office.

14 INDEMNITY

NICO is sponsored by The Clatterbridge Cancer Centre NHS Foundation Trust and co-ordinated by the LCTC in the University of Liverpool. The Clatterbridge Cancer Centre NHS Foundation Trust does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

The University of Liverpool has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of a clinical study, including but not limited to the authorship of the Clinical Study Protocol. The University of Liverpool has appropriate insurance in place to cover this liability.

15 FINANCIAL ARRANGEMENTS

This study is an academic lead study that has been costed in accordance with DOH guidelines: Attributing the costs of health & social care Research & Development (AcoRD). There will be a per patient payment payable to centres to cover the patient specific research costs. Details of this payment are covered in the Research Site Agreement.
The study has been adopted by the National Institute for Health Research Clinical Research Network (NIHR CRN) and UK Clinical Research Network (UKCRN).

Nivolumab will be provided free of charge by Bristol Myers Squibb for the duration of the study.

Patients will not be paid or re-imbursed expenses accrued as a result of participating in this study.

Optional Sub-studies
Additional funding has been provided for the imaging sub-study and a grant application is in progress for the microbiome sample collection (and this will not proceed until the funding is in place).

Imaging sub-study
For participating patients on the optional imaging substudy the following compensation payments will be made in acknowledgement of any inconvenience (maximum payable £50):

- 2 extra MRI scans and associated travel costs to the value of £25 per scan appointment

16 TRIAL OVERSIGHT COMMITTEES

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the Liverpool Clinical Trials Unit. The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately 6 times a year.

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson, 2/3 independent experts in the field of surgery, oncology and a biostatistician and up to seven Principal Investigators. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.
The TSC will operate under a TSC Charter, which will be agreed by all members prior to study opening.

16.3 Independent Safety and Data Monitoring Committee (IDSMC)

The independent Safety and Data Monitoring Committee (ISDMC) consists of an independent chairperson, plus 2 independent members: who are expert in the field of oncology and medical statistics.

The ISDMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The ISDMC will first convene before the study is open and will then define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in section 8.

The ISDMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the study.

17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and ISDMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

18 PROTOCOL AMENDMENTS

18.1 Version 1 (10-January-2018)

Original version submitted to REC and MHRA.

18.2 Version 2 (10-April-2018)

Original Approved version by REC and MHRA.
Changes from version 1 are available on the Summary of Amendment & Sponsor Assessment Form: Amendment (1) Substantial

18.3 Version 3 (30-September-2019)

Changes from version 2 are available on the Summary of Amendment & Sponsor Assessment Form: Amendment (4) Non-Substantial

18.4 Version 4 (01-November-2019)

Changes from version 3 are available on the Summary of Amendment & Sponsor Assessment Form: Amendment (5) Substantial

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20 APPENDICES

Appendix A: Quality of Life Questionnaires:

SSNIC_D009 – EORTC QLQ-C30 (English)
SSNIC_D010 – EORTC QLQ H&N35 (English)
SSNICD011 – EORTC QLQ-C30 (Welsh)

Appendix B: Management algorithms for immune –oncology drug related adverse events:

GI Adverse Event Management Algorithm
Renal Adverse Event Management Algorithm
Pulmonary Adverse Event Management Algorithm
Hepatic Adverse Event Management Algorithm
Endocrinopathy Management Algorithm
Skin Adverse Event Management Algorithm
Neurological Adverse Event Management Algorithm

Appendix A: Quality of Life Questionnaires

PATIENT TRIAL NUMBER __ __ __ __ __ __

ENGLISH

EORTC QLQ-C30

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

PATIENT TRIAL NUMBER __ __ __ __ __ __

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

PATIENT TRIAL NUMBER __ __ __ __ __ __

WELSH

EORTC QLQ-C30

Mae gennym ddiddordeb mewn rhai pethau sy'n berthnasol i chi a'ch iechyd. Atebwch yr holl gwestiynau eich hun trwy roi cylch am y rhif sydd yn fwyaf perthnasol i chi. Nid oes atebion "cywir" nac "anghywir". Bydd y wybodaeth a roddwch i ni yn aros yn hollol gyfrinachol.

Dyddiad heddiw (Dydd, Mis, Blwyddyn): 31 

		Dim o gwbl	Ychydig	Eithaf tipyn	Llawer iawn
1.	A ydych chi'n cael unrhyw drafferth gwneud gweithgareddau corfforol egnïol, fel cario bag siopa trwm neu gês dillad?	1	2	3	4
2.	A ydych chi'n cael unrhyw drafferth mynd am dro hir?	1	2	3	4
3.	A ydych chi'n cael unrhyw drafferth mynd am dro byr y tu allan i'r tŷ?	1	2	3	4
4.	A oes angen i chi aros yn y gwely neu mewn cadair yn ystod y dydd?	1	2	3	4
5.	A oes angen help arnoch chi i fwyta, gwisgo, ymolchi neu ddefnyddio'r toiled?	1	2	3	4

Yn ystod yr wythnos ddiwethaf:		**Dim o gwbl**	**Ychydig**	**Eithaf tipyn**	**Llawer iawn**
6.	A oeddech chi'n cael eich rhwystro wrth wneud un ai eich gwaith neu weithgareddau dyddiol eraill?	1	2	3	4
7.	A oeddech chi'n cael eich rhwystro wrth ddilyn eich diddordebau neu weithgareddau hamdden eraill?	1	2	3	4
8.	A oeddech chi'n fyr eich gwynt?	1	2	3	4
9.	A ydych chi wedi cael poen?	1	2	3	4
10.	A oedd angen gorffwys arnoch?	1	2	3	4
11.	A ydych chi wedi cael trafferth cysgu?	1	2	3	4
12.	A ydych chi wedi teimlo'n wan?	1	2	3	4
13.	A ydych chi wedi bod heb awydd bwyd?	1	2	3	4
14.	A ydych chi wedi teimlo fel taflu fyny?	1	2	3	4
15.	A ydych chi wedi taflu fyny?	1	2	3	4
16.	A ydych chi wedi bod yn rhwym (constipated)?	1	2	3	4

Ewch i'r dudalen nesaf

Appendix B: Management algorithms for immune –oncology drug related adverse events

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.
A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

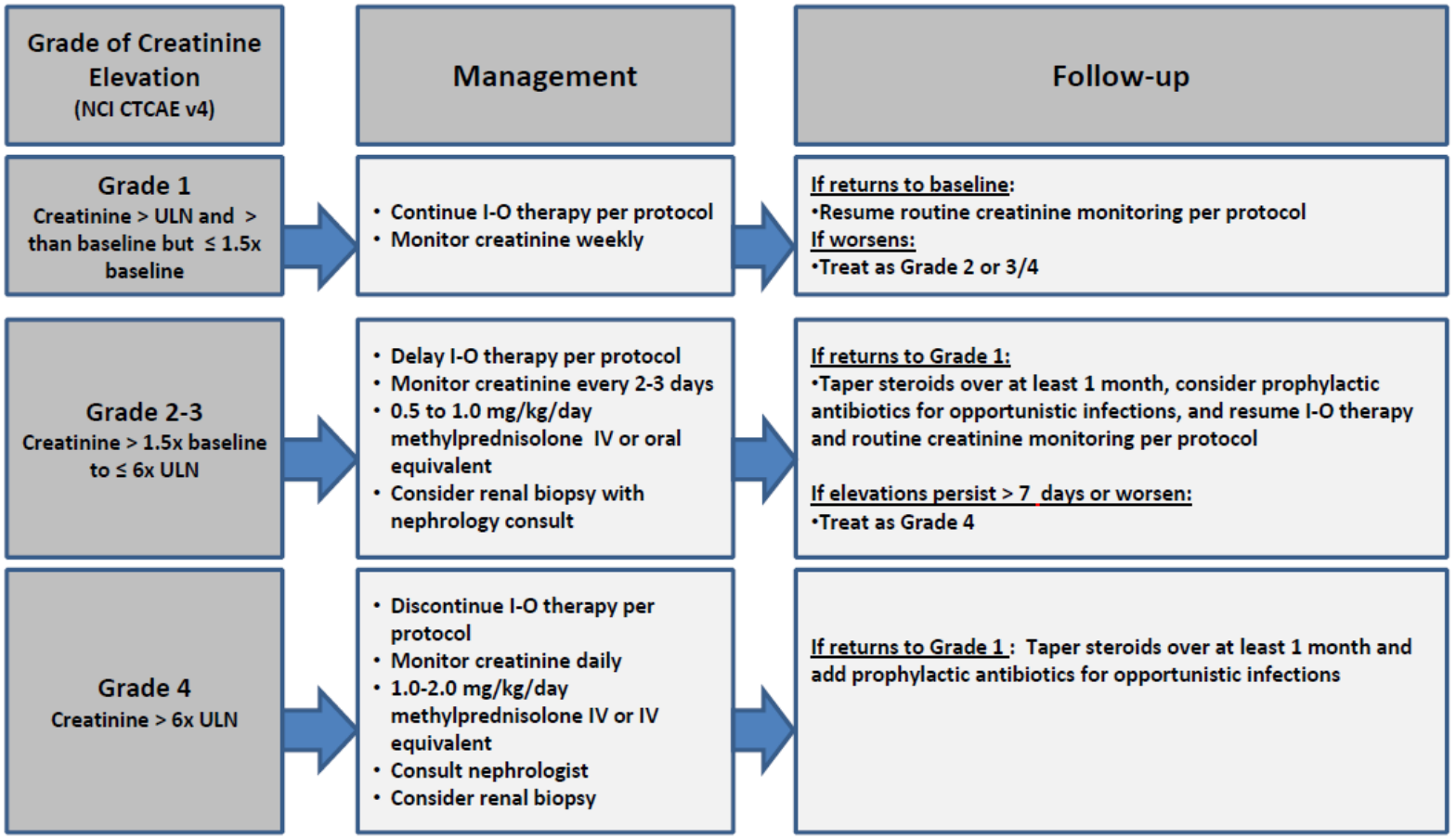
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

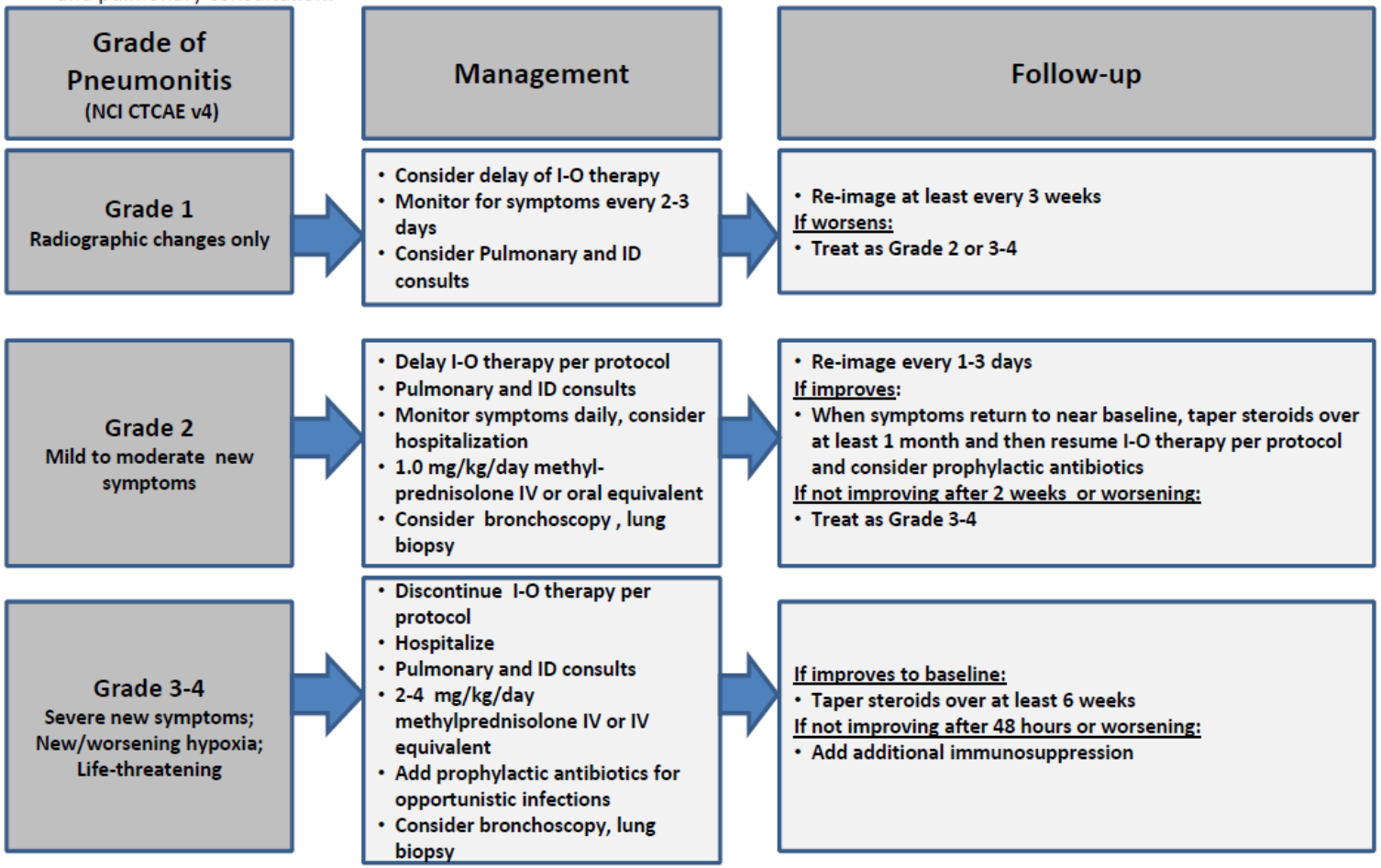
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

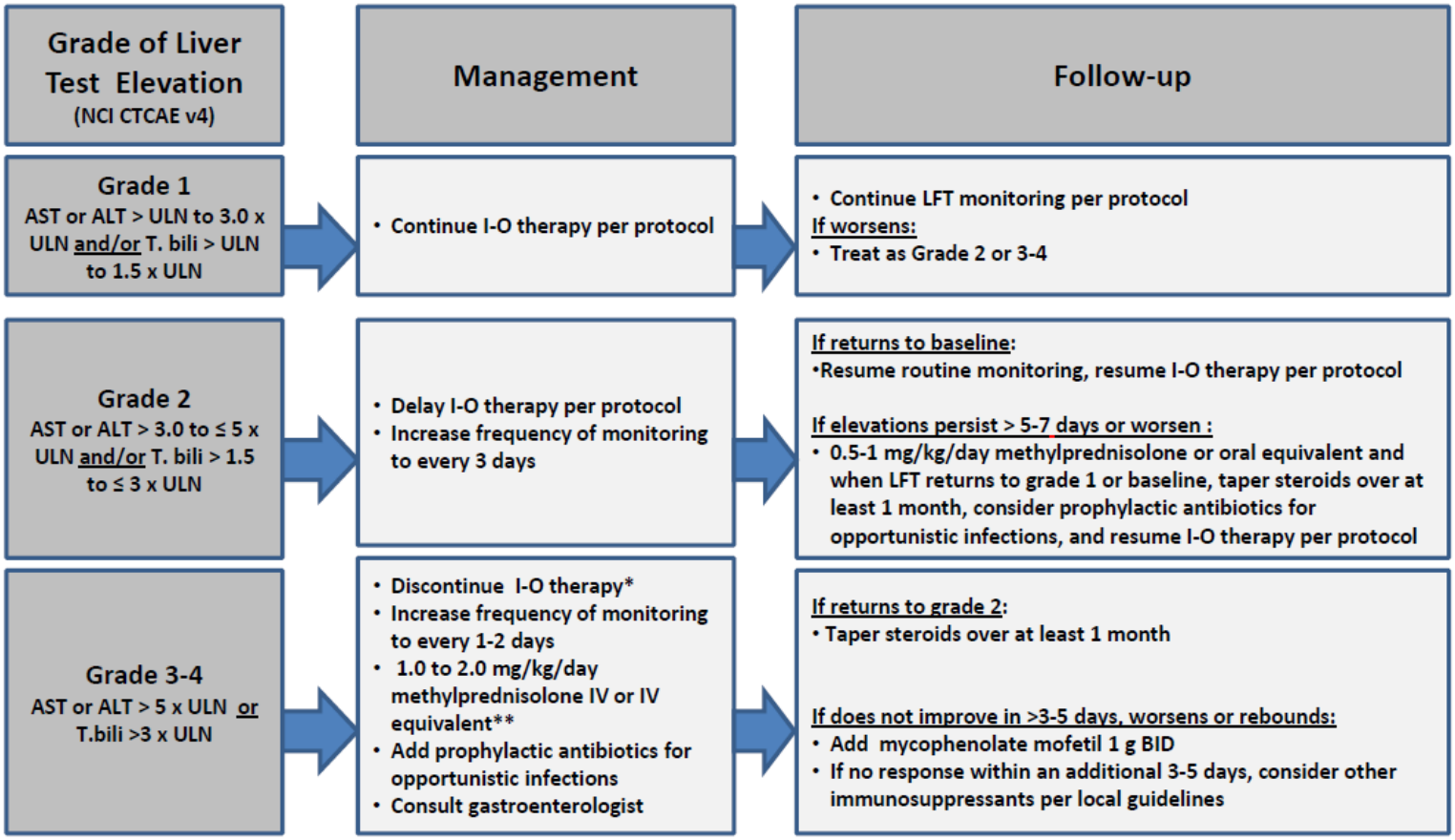
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



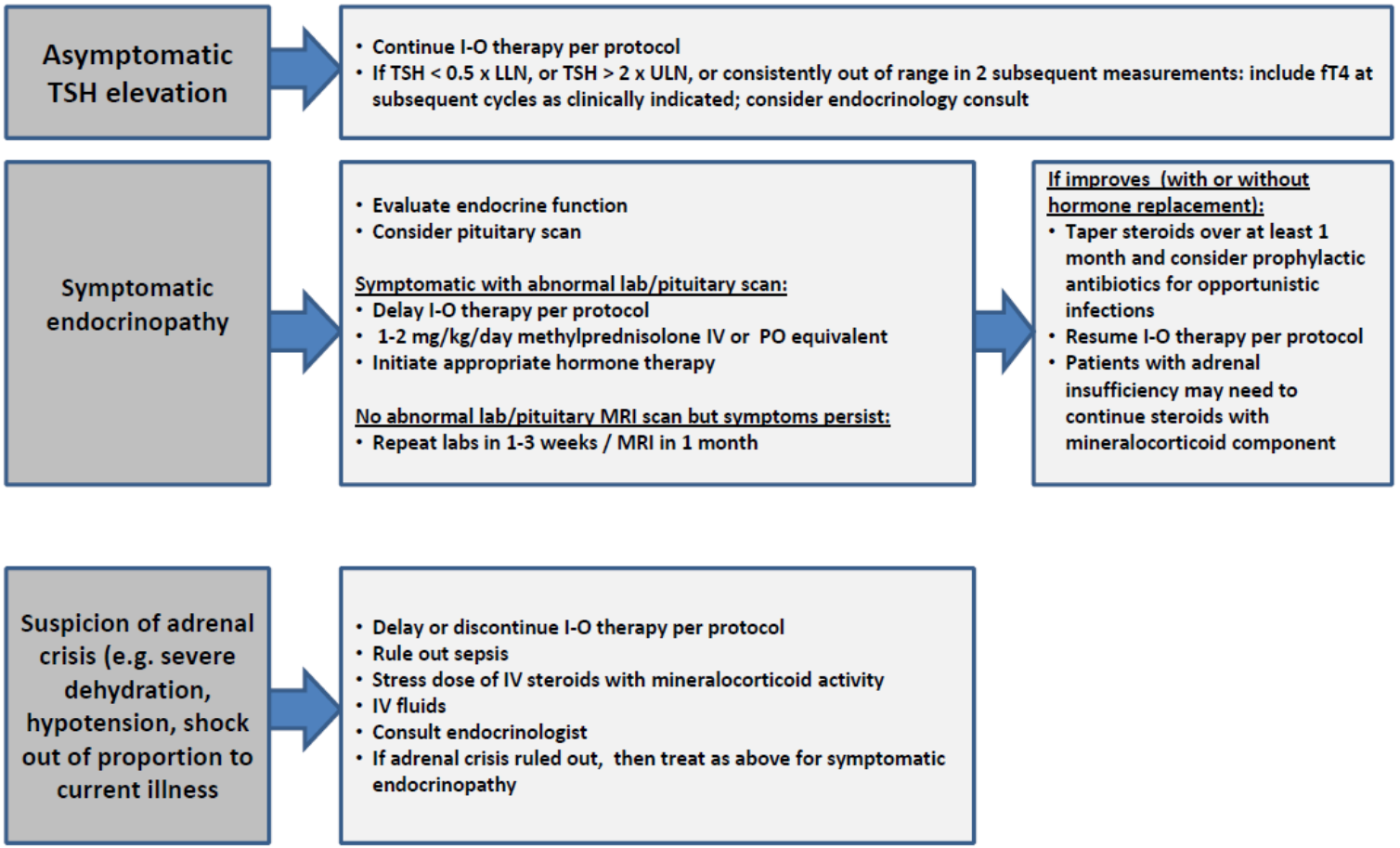
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Management Algorithm

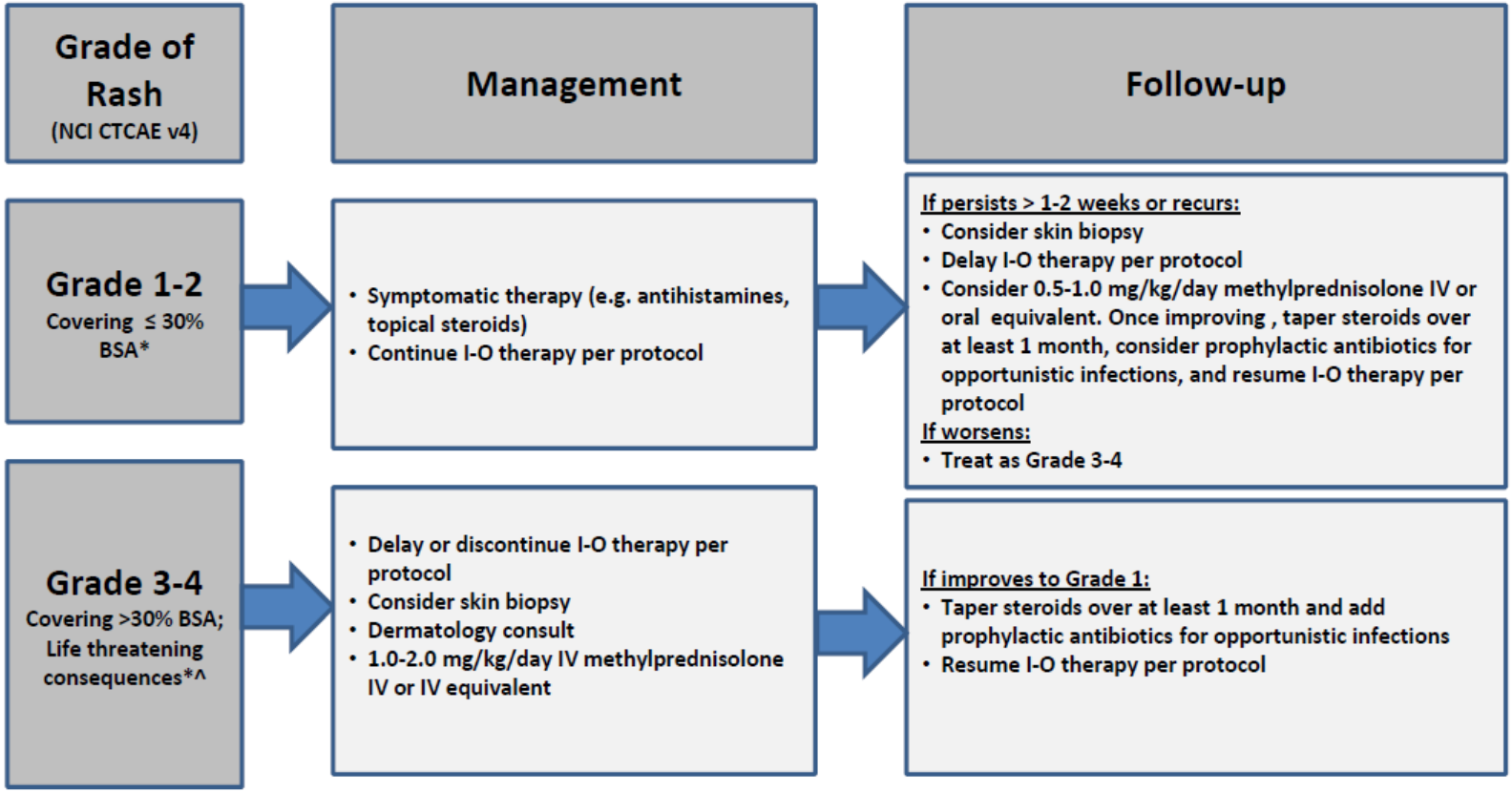
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

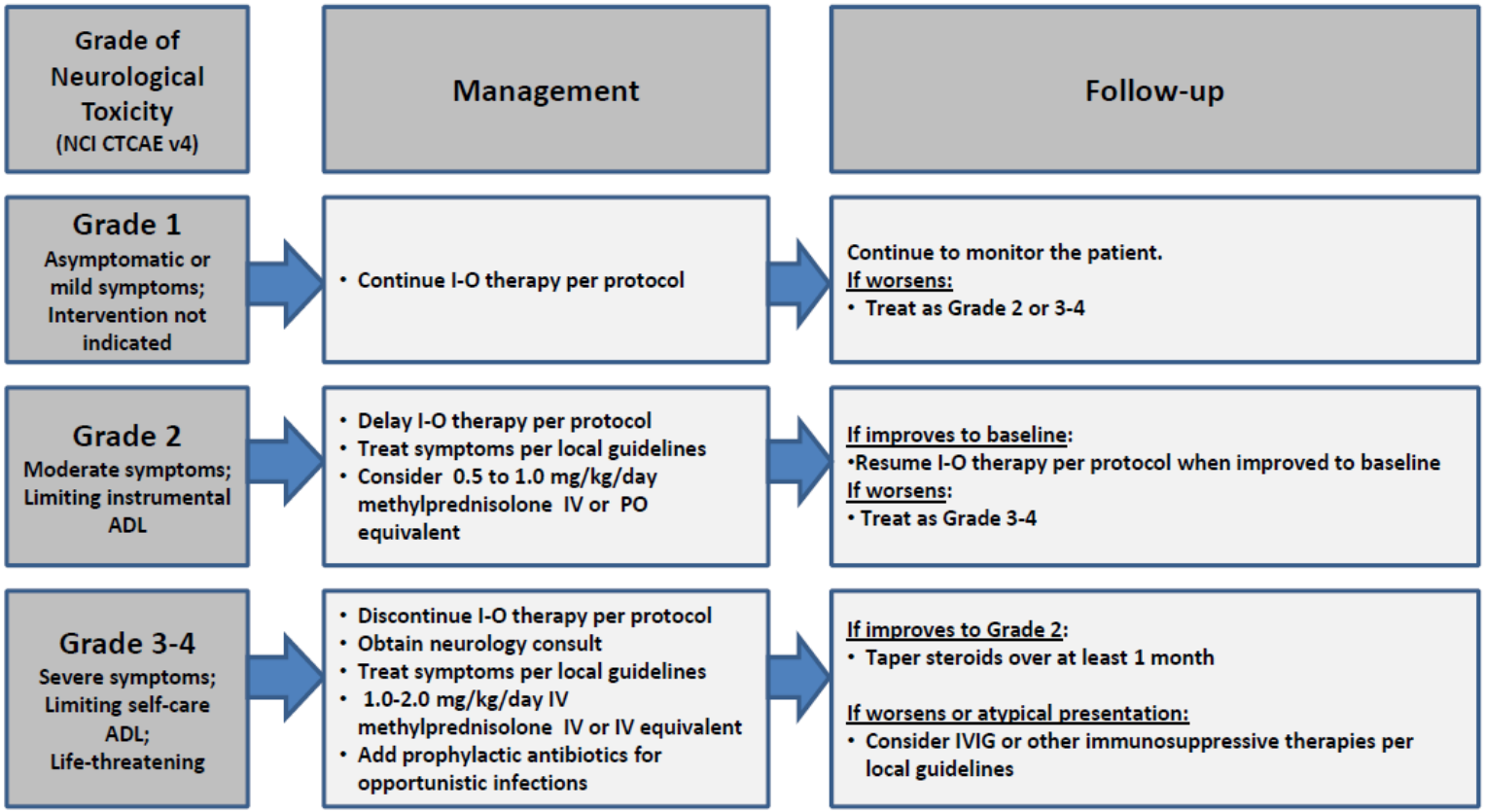
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.