The NICO Phase II clinical trial – Focus on an emerging immunotherapy strategy for the adjuvant treatment of locally advanced oral cancers

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[1]Abstract

Outcomes remain poor for patients presenting with locally advanced oral cancers and it remains imperative to re-evaluate adjuvant therapies in order to provide individuals with improved outcomes, ideally without compromising on long term quality of life. We present current available evidence supporting the use of immune checkpoint inhibitors (ICI) in squamous cell carcinoma of the head and neck (SCCHN) and discuss trials examining the integration of ICI into the locoregional management of resectable SCCHN. We focus particularly on the NICO trial which is investigating the integration of neoadjuvant and adjuvant ICI into the treatment of resectable locally advanced oral cavity cancers.

[1]
LA - Locally advanced
OSCC - Oral Squamous Cell Cancer
ICI - Immune Checkpoint Inhibitors
SCCHN - Squamous Cell Cancer of the Head and Neck
HPV - Human Papillomavirus
NICO – Neoadjuvant and adjuvant nivolumab as Immune Checkpoint inhibition in Oral cavity cancer
CT scan – Computed Tomography scan
PD1 – Programmed Cell Death Protein-1

KeyWords: Oral Cancer, squamous cell cancer, immune checkpoint inhibitors, immunotherapy, chemoradiotherapy, adjuvant.

Despite strategies to reduce local recurrence rates in individuals with locally advanced oral squamous cell carcinoma (LA OSCC), outcomes remain poor with 5 year survival rates remaining around 50% [1]. There is a clear unmet need to identify therapeutic options capable of improving cure rates without inducing significant additional long term morbidity.

The immune checkpoint inhibitors (ICI) nivolumab and pembrolizumab (which target Programmed cell death protein 1 (PD1)) have been shown to improve survival in platinum refractory metastatic squamous cell carcinoma of head and neck (SCCHN) compared with second line chemotherapy (CheckMate 141 and Keynote 040 studies), and in the case of nivolumab, delayed time to deterioration in quality of life scores [2, 3]. More recently, ICI have proven to be beneficial when used in the first line metastatic setting (Keynote 048) [4].

Naturally there has been enthusiasm to investigate the use of these drugs earlier in the disease process with the premise of priming the immune system and treating tumours when the disease burden is low and patients are physiologically fitter. The hypothesis that this treatment improves outcomes when used in the locoregional management of SCCHN has been strengthened by studies in melanoma and non-small cell lung cancer where the use of adjuvant ICI has improved recurrence free survival for patients with high risk locally advanced disease [5]. A considerable amount of work investigating the integration of ICI into the multimodality treatment of SCCHN is ongoing (table 1). Initial results from the phase I CheckMate 358 study demonstrated that neoadjuvant nivolumab in a cohort of 29 patients with resectable SCCHN did not delay standard of care surgery and 48% experienced reduction in tumour volume on CT (Computed Tomography) imaging within one month of treatment [6]. The phase II NCT02641093 study published early data on 23 patients who received neoadjuvant pembrolizumab prior to surgical resection of high risk SCCHN with subsequent (chemo)radiotherapy and concurrent/adjuvant pembrolizumab. After one neoadjuvant dose pathological responses were seen in 47% with increased tumour immune-cell infiltrate correlating to more robust responses [7]. Similarly the currently recruiting phase II NCT02296684 study reported that neoadjuvant pembrolizumab did not delay surgery or cause serious adverse events after treating 21

patients with human papillomavirus (HPV) negative stage III/IV SCCHN; 43% had pathological response after neoadjuvant treatment [8].

Building upon these initial findings, and with an expectation that benefit might be derived in the curative setting, the NICO (Neoadjuvant and adjuvant nivolumab as Immune Checkpoint inhibition in Oral cavity cancer) study was developed [9]. With a specific focus on patients with oral cavity cancers, this non-randomised phase II study explores the hypothesis that (neo)adjuvant immunotherapy works synergistically with (chemo)radiotherapy, priming and consolidating immune responses. The protocol introduces nivolumab into the patient's treatment prior to standard of care surgical ablation (+/- reconstruction), again before risk stratified (chemo)radiotherapy, and then adjuvantly (figure 1). Patients are eligible for inclusion if they have been diagnosed with LA OSCC (pre-operative staging T1-4 N1-2 or T3-4 N0) and are fit enough to be considered for platinum based concurrent chemoradiotherapy. In contrast to other trials, the specific focus upon the oral cavity sub-site will provide a cohort of patients who will benefit from intensification of therapy due to poor outcomes and where the low HPV prevalence will have little or no impact upon disease biology nor clinical outcomes [10]. This subsite also offers a rare opportunity to obtain multiple easily accessible biopsies throughout the treatment course in order to support vital translational research seeking to clarify potential biomarkers of response to ICI.

The clinical community has embarked upon an exciting era where patients at high risk for recurrence can be offered clinical trial opportunities exploring escalated adjuvant regimes seeking to achieve improved survival outcomes without adding significantly to long-term toxicities. Ongoing dynamic recruitment to studies such as NICO will enable us to come closer to this shared goal and pave the way for improved patient care.

The NICO study (supported by The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool Clinical Trials Centre, and Bristol-Myers Squibb) is currently recruiting in multiple United Kingdom centres (NicoCT@liverpool.ac.uk).

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Ethical approval and patient permissions/consent

N/a

Conflict of Interests

Dr J.J. Sacco has received honoraria from BMS and Immunocore, and has been consulted in an advisory role for Immunocore, BMS, MSD, and Delcath. Dr J.J Sacco has received research funding and/or has held roles as principal investigator / regulatory principal investigator / site principal investigator / member of a steering committee of a study that does not have a principal investigator for AZ, BMS, MSD, Immunocore, Replimmune and Amgen. Dr J.J. Sacco has had travel, accommodations, or other expenses paid or reimbursed by BMS, MSD within the last 2 years.

Dr R. Brooker and Mr A.G. Schache certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. Dr R. Brooker and Mr A.G. Schache are not directly receiving funding from BMS however they are currently contributing to the set up and opening of the NICO trial which is being funded by BMS.

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Figure 1: Schematic of NICO study design:

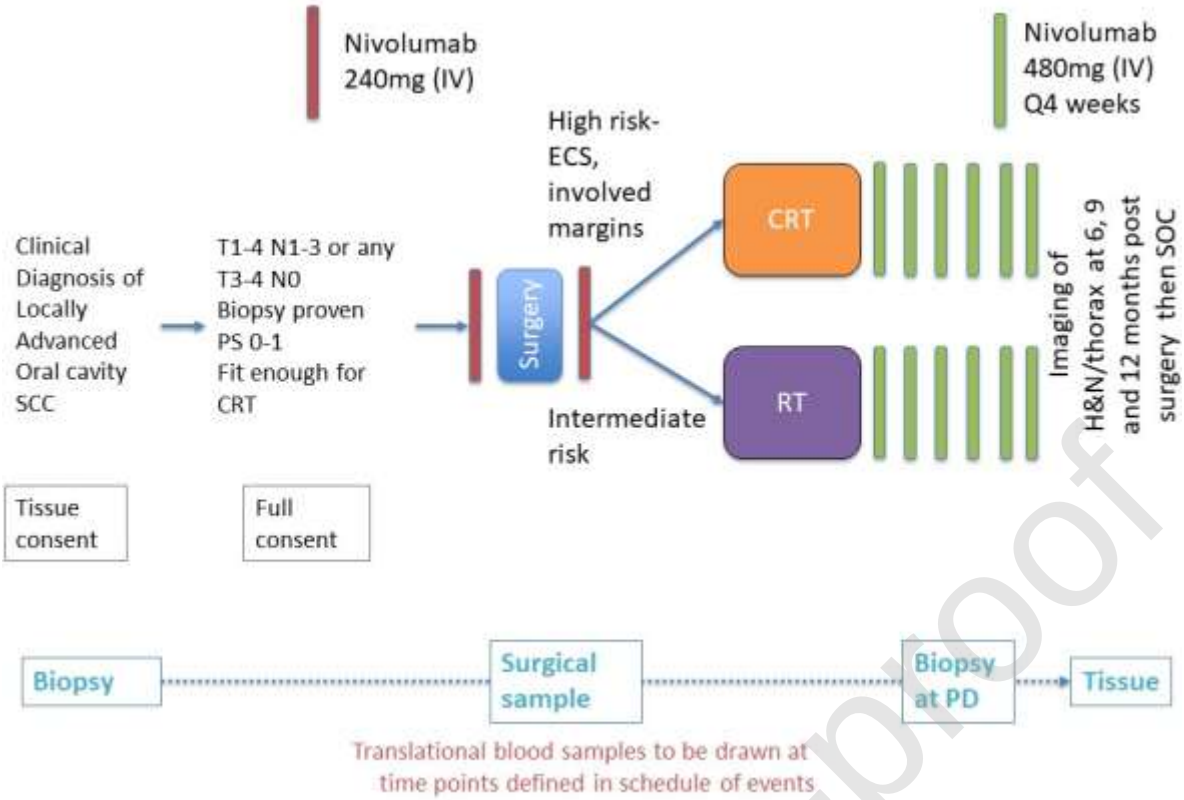

Table 1: Currently recruiting phase II/III trials investigating (neo)adjuvant checkpoint inhibitors in resectable SCCHN

Clinical trial identifier / name	Sponsor / collaborator	Inclusion	Trial Treatment Schedule
NCT No: 03721757 ***NICO***	Clatterbridge Cancer Centre NHS Foundation Trust/ Bristol-Myers Squibb	Stage III/IV SCC oral cavity	Neoadjuvant nivolumab followed by surgery. Further dose of nivolumab prior to adjuvant (C)RT. Subsequent adjuvant nivolumab x 6 (Phase II)
NCT No: 03700905 ***IMSTAR-HN***	Universitätsklinikum Hamburg-Eppendorf / University Hospital, Essen Westpfalz-Clinical Center GmbH Charite University, Berlin, Germany	Stage III/IV SCCHN (all sites).	Neoadjuvant nivolumab followed by surgery two weeks later. Adjuvant (C)RT with subsequent randomised three arms: • Adjuvant nivolumab x 6 • Nivolumab plus ipilimumab x 6 • Standard of care follow up. (Phase II)
NCT No: 03708224	Alain Algazi / Genentech, Inc.	Stage III/IV HPV negative SCCHN (all sites).	Neoadjuvant atezolizumab x 2 followed by surgery. Adjuvant (C)RT with subsequent adjuvant atezolizumab x12. (Phase II)

NCT No: 02641093	Trisha Wise-Draper / Merck Sharp & Dohme Corp.	Stage III/IV SCCHN (all sites)	Neoadjuvant pembrolizumab x 1 followed by surgery. Adjuvant (C)RT with adjuvant pembrolizumab x 6 (Phase II)
NCT No: 02296684	Washington University School of Medicine / Merck Sharp & Dohme Corp.	Stage III/IV HPV negative SCCHN (all sites).	Cohort 1: Neoadjuvant pembrolizumab x 1 followed by surgery. Adjuvant (C)RT with subsequent adjuvant pembrolizumab x 6 in those with high risk pathological features. Cohort 2: Neoadjuvant pembrolizumab x 2 followed by standard of care surgery. (Phase II)
EUDRA-CT No: 2016-004787-20 ***NadiHN***	Rheinische Friedrich-Wilhelms-Universität Bonn / Bristol-Myers Squibb	Resectable intermediate risk SCCHN (all sites).	Surgical resection followed by nivolumab x 1 and subsequent CRT. Maintenance nivolumab x 12. (Phase II)
EUDRA-CT No: 2017-002546-74 ***ADRISK***	University Leipzig / Merck Sharp & Dohme Corp.	Resectable stage III/IV SCCHN (all sites).	Surgical resection followed by adjuvant CRT or adjuvant CRT with concurrent pembrolizumab. (Phase II)
EDURA-CT No: 2017-001139-38 NCT NO: 03765918 ***KEYNOTE 689***	Merck Sharp & Dohme Corp.	Resectable stage III/IV SCCHN (all sites).	Cohort 1: Neoadjuvant pembrolizumab x 2 followed by surgery. Adjuvant (C)RT with concurrent and maintenance pembrolizumab x 15. Cohort 2: Standard of care surgery and adjuvant (C)RT. (Phase III)