**Integration of Checkpoint Inhibitors into the Management of Locally Advanced Head and Neck Cancer – future perspectives**

**Abstract**

Immune checkpoint inhibitors (ICI) are finding increasing roles in the management of solid tumours in the metastatic setting, raising the potential for durable disease control in at least a proportion of cases. Unsurprisingly, clinical investigation is now turning to the neo-adjuvant and adjuvant setting. Locally advanced squamous cell cancer of the head and neck (LASCCHN) is an obvious target for the introduction of immunotherapy, with 5 year survival remaining in the region of 50% despite multimodality treatment. However, with an already gruelling treatment regime in patients who often have multiple comorbidities, intensification of therapy with the addition of checkpoint inhibitors will need to be carefully balanced against potential increases in toxicity and the ability of patients to complete a multimodality treatment course. Here we review recent evidence in the use of checkpoint inhibitors in SCCHN and look to the future challenges of integrating this therapy into the management of LASCCHN.

**Key Words**

Head and neck cancer; immunotherapy; checkpoint inhibitors; PDL1/PD1; CTLA4; chemoradiotherapy; surgery; multimodality.

**Abbreviations**

LASCCHN – Locally advanced squamous cell carcinoma of the head and neck

SCCHN – Squamous cell carcinoma head and neck

HPV – Human Papillomavirus

NSCLC – Non small cell lung cancer

ICI - Immune checkpoint inhibitors

PD-1 - Programmed death 1

PD-L1 – Programmed death ligand 1

CRT - Chemoradiotherapy

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**Introduction**

Radical treatment strategies for LASCCHN are centred on a multidisciplinary approach with options ranging from primary chemoradiotherapy (CRT) to surgical resection, followed by radiotherapy or CRT depending upon pathological risk factors. Such intensive regimes have reduced recurrence rates, often at the cost of organ dysfunction and reduced quality of life [1, 2]. Indeed, there have been moves to de-escalate treatment in those with human papillomavirus (HPV) positive tumours which have better prognosis [3], with trials geared towards reducing toxicities while maintaining cure rates. De-escalation strategies including less invasive surgical techniques, tailored dose radiotherapy/chemotherapy and substitution of alternative agents for cisplatin are being investigated [4, 5]. De-ESCALaTE and RTOG 1016 are the first to report after substituting cetuximab for cisplatin and describe inferior survival in the cetuximab arm with no benefit in terms of adverse events [6, 7]. Despite this, upwards of 50% of patients with LASCCHN relapse, and there is thus a need for intensification of therapy in some patient groups.

Immune checkpoint inhibitors (ICI) are a relatively new class of agent that have activity in metastatic SCCHN. Most evidence around their use involves Programmed Death 1 (PD-1) and PD Ligand 1 (PD-L1) inhibitors, which are generally well tolerated and are associated with better quality of life compared to chemotherapy [8]. These agents may be ideal candidates for intensification in radical therapy for LASCCHN.

**ICI in recurrent/metastatic head and neck cancer**

Until recently, standard of care for patients with relapsed/metastatic SCCHN had remained first line platinum and 5-fluorouracil chemotherapy with or without cetuximab (following the EXTREME study) and taxane/methotrexate or single agent cetuximab in the second line [9,10, 11]. There is increasing evidence that ICI such as the PD-1 inhibitors (e.g. pembrolizumab and nivolumab) and PD-L1 inhibitors (e.g. durvalumab) have activity in this setting. These agents target and abrogate key immune evasion mechanisms in turn activating the immune response against malignant cells [12]. The Keynote-012 trial demonstrated response rates of 18% for pembrolizumab in patients whose tumours were PD-L1 positive, whilst retaining tolerable side effect profile (grade >/= 3 adverse events (AEs) 17%) [13]. These findings were echoed in the Keynote-055 study with similar response rates and toxicity [14]. Durvalumab has also proven to be efficacious and safe in a heavily pre-treated population [15].

The CheckMate 141 study subsequently demonstrated a survival benefit for nivolumab in patients with recurrent/metastatic SCCHN previously treated with cisplatin, compared to single agent methotrexate, docetaxel or cetuximab. Median OS was 7.5 months (95% CI 5.5-9.1) in the nivolumab group versus 5.1 months (95% CI 4.0-6.0) on standard therapy with fewer grade 3/4 side effects along with delayed time to deterioration in quality of life [8, 16]. Updated follow up data reported a maintained benefit for nivolumab with estimated 24 month OS rate of 16.9% (95% CI 12.4%–22.0%) [17]. Outcomes were also analysed by HPV status and expression of PDL1; high expression of which has been shown to enrich for response to PD1/PDL1 agents in different tumour groups. Both HPV positive and negative patients gained benefit from nivolumab in the 2 year analysis (hazard ratio (HR) 0.60 and 0.59 respectively). Expression of PDL1 was more strongly associated with positive outcome; HR 0.55 (95% CI- 0.39-0.78) and 0.73 (CI 0.49-1.09) with PDL1 expression >1% and <1% respectively [17]. A further phase III study (Keynote-040) in the same setting examined pembrolizumab versus investigators choice chemotherapy and showed similar results with updated survival analysis reporting an improvement in median OS (8.4 vs. 6.9 months; HR 0.8 95% CI 0.65-0.98) [18, 19]. Recently, Keynote-048 has provided early evidence for the use of first line pembrolizumab alone or in combination with cisplatin and 5-fluorouracil when compared to EXTREME regime. These regimens demonstrated non-inferiority and improved OS respectively in interim analysis [20]. While final analysis is awaited these promising results suggest Keynote-048 will be practice changing.

**Adjuvant and neoadjuvant ICI in other solid malignancies**

Preclinical studies have shown that combining ICI and radiotherapy can alter the balance within the tumour microenvironment in an immunostimulatory direction, promote auto-immunisation and subsequent immunogenic cell death [21, 22, 23]. In addition, potential synergies have been reported between immunotherapy and chemotherapy [24]. These findings, and the flattening of survival curves often seen in ICI trials (which suggest cure in a proportion of cases) has underpinned a move towards utilising ICI in earlier disease i.e. neo/adjuvant setting. While trials set in this context are yet to report in SCCHN, proof of concept has been provided in melanoma and lung cancer.

The EORTC 18071 trial investigated patients with stage III melanoma who received up to 3 years adjuvant ipilimumab (anti CTLA-4 monoclonal antibody) and reported 5 year OS rates of 65.4% in the treatment arm compared to 54.4% in placebo (HR for death, 0.72; P=0.001) [25]. Subsequently CheckMate 238 randomised 906 patients to either adjuvant nivolumab or ipilimumab for up to 12 months. Nivolumab proved superior; with recurrence free survival rates of 70.5% (95% CI, 66.1-74.5) compared to 60.8% (95% CI, 56.0-65.2) [26]. As adjuvant PD-1 inhibitors become standard of care [27, 28] there is emerging evidence that ICI in the neo-adjuvant setting is beneficial in stage III melanoma with early results from OpACIN (NCT02437279) and NCT 02519322 reporting a reduction in tumour burden with nivolumab plus ipilimumab prior to lymph node resection [29, 30].

Evidence is also accumulating in non-small cell lung cancer (NSCLC) with the PACIFIC trial using 12 months of durvalumab versus placebo in patients with stage III NSCLC who had complete response following CRT. Progression free survival was dramatically improved by 11.2 months (HR for disease progression/death, 0.52; p 0.001) [31]. Results of other trials examining alternative PD-1/PD-L1 agents in the adjuvant setting (e.g. PEARLS NCT02504372) are eagerly awaited [32]. As in melanoma, there is evidence that neoadjuvant ICI have activity and in a small trial Chaft et al used 2 doses of nivolumab prior to surgical resection in patients with stage IB-IIIA NSCLC. There were no delays to surgery and 86% of patients were alive without recurrence at 9 months [33]. Whilst there are similarities between NSCLC and SCCHN patient demographics and disease course, the presence of key differences (role of viruses etc.) should invoke a degree of caution when drawing comparisons.

**Adjuvant, neoadjuvant and concurrent ICI in LAHNSCC- which agents, when and for how long?**

There are many questions to be answered with regards to the ideal approach for integrating ICI into the management of LASCCHN, namely treatment duration and timing. The wide range of regimes applied within clinical trials reflects this uncertainty; some encourage immune priming with (neo)adjuvant ICI (e.g. CompARE, CRUK/13/026 [34]), whilst others seek to test concurrent ICI with CRT and varying lengths of adjuvant therapy (e.g. 6 months in Keynote-412 NCT03040999 and 12 months in JAVELIN NCT02952586 [35, 36]) (see table 1). In addition, studies such as NICO (neo-adjuvant and adjuvant nivolumab for surgically managed locally advanced oral cavity cancer) seek to exploit potential adjuvant benefit whilst utilising the surgical window of opportunity (and its rich bio-resource) in search of biomarkers for response capable of guiding future clinical decision making [37]. Although this could revolutionise the treatment of SCCHN specific barriers cannot be ignored; particularly whether adding further systemic anti-cancer drugs to CRT could induce intolerable side effects, or in the case of neoadjuvant treatment prevent commencement of standard of care therapy. Preliminary trial results (NCT02586207) have however reported manageable toxicities. Out of 27 patients with LASCCHN treated with pembrolizumab in conjunction with primary CRT, three stopped pembrolizumab due to side effects and all completed their radiotherapy without significant delay [38].

On the other hand (neo)adjuvant ICI has the advantage of reducing the chances of adverse interactions with CRT, and has shown survival benefit, albeit in NSCLC rather than HNSCC [31]. Ferris et al presented data from CheckMate 358, which is examining neoadjuvant nivolumab in virus associated solid tumours. They focused upon 29 patients with SCCHN all of whom received 2 cycles of nivolumab prior to surgery. Two patients suffered adverse events of grade 3/4 without delays to resection, leading to the presumption that neoadjuvant ICI is unlikely to impact adversely on current standard of care [39].

**Conclusions**

While considerable work is needed to define the best approach, integration of ICI in this setting holds great possibilities. We are within an era where there is potential to improve outcomes for patients who would ordinarily have had high rates of recurrence [1], however this must be balanced with a new list of toxicities. If trial results confirm a survival benefit from adding ICI into the management of LASCCHN we will be faced with the challenge of ensuring these new therapies are incorporated safely, which will only be achieved by careful patient selection, clinician education and close collaboration within the head and neck MDT and acute medical departments [40, 41]. In a patient population where previous attempts at escalation of therapeutic intensity have failed to achieve significant survival benefit, an opportunity remains to determine what additional benefit might be derived from the inclusion of ICI in treatment paradigms.

**Conflict of Interest Statement**

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 Dr 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. They 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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