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Editorial

Integration of Checkpoint Inhibitors into the Management of Locally Advanced Head and Neck Cancer – Future Perspectives

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Radical treatment strategies for locally advanced squamous cell carcinoma of the head and neck (LASCCHN) are centred on a multidisciplinary approach with options ranging from primary chemoradiotherapy (CRT) to surgical resection, followed by radiotherapy or CRT depending on pathological risk factors. Such intensive regimens 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 who 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 therefore 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 squamous cell carcinoma of the head and neck (SCCHN). Most evidence around their use involves programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors, which are generally well tolerated and are associated with better quality of life compared with chemotherapy [8]. These agents may be ideal candidates for intensification in radical therapy for LASCCHN.

Immune Checkpoint Inhibitors 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 [9–11]. 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 showed response rates of 18% for pembrolizumab in patients whose tumours were PD-L1 positive, while retaining a tolerable side-effect profile (grade $\geq$3 adverse events 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 pretreated population [15].

The CheckMate 141 study subsequently showed a survival benefit for nivolumab in patients with recurrent/metastatic SCCHN previously treated with cisplatin, compared with single-agent methotrexate, docetaxel or cetuximab. The median overall survival was 7.5 months (95% confidence interval 5.5–9.1) in the nivolumab group versus 5.1 months (95% confidence interval 4.0–6.0) on standard therapy, with fewer grade 3/4 side-effects together with delayed time to deterioration in quality of life [8,16]. Updated follow-up data reported a maintained benefit for nivolumab, with an estimated 24 month overall survival rate of 16.9% (95% confidence interval 12.4–22.0%)

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[17]. Outcomes were also analysed by HPV status and expression of PD-L1; high expression of which has been shown to enrich the response to PD-1/PD-L1 agents in different tumour groups. Both HPV-positive and -negative patients gained benefit from nivolumab in the 2 year analysis (hazard ratio 0.60 and 0.59, respectively). Expression of PD-L1 was more strongly associated with a positive outcome; hazard ratio 0.55 (95% confidence interval 0.39–0.78) and 0.73 (95% confidence interval 0.49–1.09) with PD-L1 expression >1% and <1%, respectively [17]. A further phase III study (Keynote-040) in the same setting examined pembrolizumab versus the investigator's choice of chemotherapy and showed similar results, with an updated survival analysis reporting an improvement in median overall survival (8.4 versus 6.9 months; hazard ratio 0.8, 95% confidence interval 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 with the EXTREME regimen. These regimens showed non-inferiority and improved overall survival, respectively, in an interim analysis [20]. Although the final analysis is awaited, these promising results suggest that Keynote-048 will be practice changing.

Adjuvant and Neoadjuvant Immune Checkpoint Inhibitors 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 [21–23]. 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. the neo/adjuvant setting. Although 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 of adjuvant ipilimumab (anti CTLA-4 monoclonal antibody) and reported 5 year overall survival rates of 65.4% in the treatment arm compared with 54.4% in placebo (hazard ratio 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% confidence interval 66.1–74.5) compared with 60.8% (95% confidence interval 56.0–65.2) [26]. As adjuvant PD-1 inhibitors become standard of care [27,28] there is emerging evidence that ICI in the neoadjuvant setting are beneficial in stage III melanoma, with early results from OpACIN (NCT02437279) and NCT02519322 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 a complete response following CRT. Progression-free survival was dramatically improved by 11.2 months (hazard ratio 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.* [33] used two 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]. Although 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 Immune Checkpoint Inhibitors in Locally Advanced Squamous Cell Carcinoma of the Head and Neck – 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 regimens applied within clinical trials reflects this uncertainty; some encourage immune priming with (neo)adjuvant ICI (e.g. CompARE, CRUK/13/026 [34]), whereas 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 (neoadjuvant and adjuvant nivolumab for surgically managed locally advanced oral cavity cancer) seek to exploit potential adjuvant benefit while utilising the surgical window of opportunity (and its rich bioresource) in search of biomarkers for a 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 anticancer drugs to CRT could induce intolerable side-effects or, in the case of neoadjuvant treatment, prevent the commencement of standard of care therapy. Preliminary trial results (NCT02586207) have, however, reported manageable toxicities. 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.* [39] presented data from CheckMate 358, which is examining neoadjuvant nivolumab in

Table 1
Listed phase II/III neoadjuvant, adjuvant and concurrent trials utilising immune checkpoint inhibitors in the management of locally advanced squamous cell carcinoma of the head and neck (SCCHN)

Clinical trial identifier	Trial name	Sponsor/collaborator	Phase	Eligibility	Treatment arms	Outcome measure
Neoadjuvant/adjuvant trials						
NCT03317327	REPORT	Oslo University Hospital/Bristol-Myers Squibb	I/II	Recurrent or second primary SCCHN following prior radiotherapy suitable for re-irradiation	Radiotherapy plus concurrent and adjuvant nivolumab (up to 12 months)	Incidence and severity of adverse events
NCT03247712		Providence Health & Services	I/II	SCCHN planned for surgical resection	Neoadjuvant radiotherapy plus nivolumab ± surgical resection then 6 months of adjuvant nivolumab	Unplanned delay to surgery, decrease in tumour size or number of involved nodes
NCT03051906	Ducro-HN	Azienda Ospedaliero-Universitaria Careggi	I/II	Locally advanced SCCHN ineligible for surgical resection	Durvalumab, cetuximab and radiotherapy plus adjuvant durvalumab (6 months)	2 year progression-free survival
NCT03003637	IMCISION	The Netherlands Cancer Institute	I/II	Locally advanced SCCHN suitable for surgical resection	Neoadjuvant nivolumab plus ipilimumab followed by surgical resection	Delay to surgery, tumour pathological response
NCT02841748	PATHWay	University of Chicago	II	Stage III–IVb SCCHN with high risk of recurrence following curative therapy	12 months of adjuvant pembrolizumab versus 12 months of adjuvant placebo	2 year progression-free survival
NCT03355560		University of Cincinnati/Bristol-Myers Squibb	II	Local recurrence of SCCHN treated with salvage surgical resection (previous curative treatment)	12 months of adjuvant nivolumab	Grade 3 or 4 adverse events
NCT02919683		Dana-Farber Cancer Institute/Bristol-Myers Squibb	II	T2 or greater and/or nodal involved oral cavity SCC planned for curative treatment	Neoadjuvant nivolumab, 1 dose versus neoadjuvant nivolumab plus Ipilimumab, 1 dose	Response rates
2017-005015-13 (EudraCT number)	NICO	Clatterbridge Cancer Centre NHS Foundation Trust/ Aintree University Hospital NHS Foundation Trust/ Liverpool Cancer Trials Unit/Bristol-Myers Squibb	II	Locally advanced SCC oral cavity planned for surgical resection	Neoadjuvant nivolumab, radical surgery and subsequent risk-stratified adjuvant radiotherapy or chemoradiotherapy, then 6 months of adjuvant nivolumab	1 year progression-free survival
NCT02777385		University of Pittsburgh/Merck Sharp & Dohme	II	Locally advanced SCCHN not undergoing surgical resection	Chemoradiotherapy with concurrent pembrolizumab versus chemoradiotherapy with 6 months of adjuvant pembrolizumab	1 year progression-free survival, 1 year failure rate, acute toxicity rate
NCT02289209		Dan Zandberg/Merck Sharp & Dohme	II	Locoregional recurrent SCCHN which is unresectable, suitable for re-irradiation	Radiotherapy plus concurrent and adjuvant pembrolizumab (3–24 months based on response)	Progression-free survival
NCT03383094		Loren Mell, University of California/Merck Sharp & Dohme	II	P16-positive SCCHN with high/intermediate risk disease	Radiotherapy with concurrent cisplatin versus radiotherapy with concurrent and adjuvant pembrolizumab (20 cycles)	Progression-free survival

Table 1 (*continued*)

Clinical trial identifier	Trial name	Sponsor/collaborator	Phase	Eligibility	Treatment arms	Outcome measure
NCT03107182	Optima-II	University of Chicago	II	HPV-positive SCCHN. No previous surgery or radiation therapy	Induction nab-paclitaxel, carboplatin, nivolumab. Following this: surgery and adjuvant radiotherapy depending on risk factors versus de-escalated chemoradiotherapy versus standard dose chemoradiotherapy. All patients 6 months of adjuvant nivolumab	Tumour shrinkage (%), deep response rate
NCT03342911		Sidney Kimmel Cancer Centre at Thomas Jefferson University/Bristol-Myers Squibb	II	Stage III–IV SCCHN surgically resectable at baseline	3 cycles of induction paclitaxel, carboplatin and nivolumab prior to surgical resection	Pathological complete response
NCT02769520		Ezra Cohen/Merck Sharp & Dohme	II	Local and/or locoregional recurrent SCCHN amenable to salvage surgery. Disease-free interval 18 months post-curative therapy	Salvage surgery with 12 months of adjuvant pembrolizumab	Disease-free survival at 12 months
NCT02296684		Washington University School of Medicine/Merck Sharp & Dohme	II	Locally advanced surgically resectable SCCHN	Neoadjuvant pembrolizumab, surgical resection with adjuvant risk-based radiotherapy or chemoradiotherapy plus 6 cycles of adjuvant pembrolizumab versus neoadjuvant pembrolizumab, surgical resection	Locoregional recurrence rates, distant failure rates, rate of major pathological treatment effect
NCT03325465	KEO	University of Chicago	II	Locally advanced SCCHN appropriate for surgical resection	Neoadjuvant pembrolizumab plus epacadostat, surgical resection with 12 months of adjuvant pembrolizumab plus epacadostat versus neoadjuvant pembrolizumab, surgical resection with 12 months of adjuvant pembrolizumab	Rate of major treatment effect, rate of complete response
NCT03174275		UNC Lineberger Comprehensive Cancer Centre/ AstraZeneca/Celgene	II	Stage III and IV SCCHN amenable to surgical resection	Risk dependent: 5 cycles of neoadjuvant carboplatin, nab-paclitaxel plus durvalumab, surgical resection with adjuvant chemoradiotherapy and subsequent 3 cycles adjuvant durvalumab	Pathological complete response rate
NCT03406247	ADJORL1	Gustave Roussy, Cancer Campus, Grand Paris	II	Recurrent or second primary SCCHN in at previously irradiated site that has received salvage surgery	6 months of adjuvant nivolumab versus 6 months of adjuvant nivolumab plus ipilimumab	2 year disease-free survival

(*continued on next page*)

Table 1 (*continued*)

Clinical trial identifier	Trial name	Sponsor/collaborator	Phase	Eligibility	Treatment arms	Outcome measure
NCT03114280	PICH	Centre Antoine Lacassagne/GORTEC	II	Untreated unresectable locally advanced SCCHN	3 cycles of induction docetaxel, cisplatin, 5-fluorouracil plus pembrolizumab followed by chemoradiotherapy with carboplatin	Progression-free survival
NCT02827838		Wake Forest University Health Sciences/National Cancer Institute	II	SCCHN suitable for surgical resection	Neoadjuvant durvalumab followed by surgical resection	Immune responses
NCT03426657		University of Erlangen-Nurnberg Medical School	II	Locally advanced SCCHN (stage III–IVB)	Neoadjuvant durvalumab, tremelimumab, cisplatin, docetaxel: stable/ decreased CD8+T cell density on biopsy = standard chemoradiotherapy Increased CD8+ = radiotherapy with concurrent durvalumab plus tremelimumab followed by 8 cycles of adjuvant durvalumab	Number of patients with increased CD8+ T cell densities. Predictive character of changes in T cell density
NCT03258554		National Cancer Institute	II/III	Locally advanced SCCHN contraindication to cisplatin	Radiotherapy plus concurrent and adjuvant durvalumab versus radiotherapy plus concurrent cetuximab	Dose-limiting toxicity, overall survival, progression-free survival
NCT02952586	JAVELIN Head and Neck 100	Pfizer	III	Locally advanced SCCHN eligible for chemoradiotherapy with curative intent	Neoadjuvant avelumab, chemoradiotherapy plus avelumab with 12 months of adjuvant avelumab Versus neoadjuvant placebo, chemoradiotherapy plus placebo with 12 months of adjuvant placebo	Progression-free survival
NCT02999087	REACH	Groupe Oncologie Radiotherapie tete et Cou/Merck KGaA/ Pfizer	III	Locally advanced SCCHN fit for cisplatin and unfit for cisplatin	Fit for cisplatin: radiotherapy plus concurrent cisplatin versus radiotherapy plus concurrent cetuximab and avelumab, 12 months of adjuvant avelumab Unfit for cisplatin: radiotherapy plus cetuximab versus radiotherapy plus concurrent cetuximab and avelumab with 12 months of adjuvant avelumab	Progression-free survival

Table 1 (*continued*)

Clinical trial identifier	Trial name	Sponsor/collaborator	Phase	Eligibility	Treatment arms	Outcome measure
NCT03040999	Keynote 412	Merck Sharp & Dohme	III	Locally advanced SCCHN eligible for definitive chemoradiotherapy	Radiotherapy plus concurrent pembrolizumab and cisplatin with 6 months of adjuvant pembrolizumab versus Radiotherapy plus placebo and cisplatin with 6 months of adjuvant placebo	Event-free survival
CRUK/13/026	CompARE	Cancer Research UK Experimental Cancer Medicine Centre (ECMC) NIHR Clinical Research Network: Cancer University of Birmingham	III	Intermediate or high risk oropharyngeal SCC suitable for chemoradiotherapy	Chemoradiotherapy versus high dose radiotherapy with concurrent cisplatin versus surgical resection followed by chemoradiotherapy versus neoadjuvant durvalumab, followed by chemoradiotherapy and 6 months of adjuvant durvalumab	Progression-free survival
Concurrent trials						
NCT02759575		Nooshin Hashemi-Sadraei, University of Cincinnati/Merck Sharp & Dohme	I/II	Locally advanced laryngeal SCC	Chemoradiotherapy with cisplatin plus pembrolizumab	Treatment-related adverse events, laryngectomy-free survival
NCT02609503		UNC Lindeberger Comprehensive Cancer Centre/Merck Sharp & Dohme	II	Locally advanced SCCHN	Radical radiotherapy plus concomitant pembrolizumab	Progression-free survival
NCT02641093		Trisha Wise-Draper, University of Cincinnati/Merck Sharp & Dohme	II	Locally advanced SCCHN suitable for resection and adjuvant radiotherapy/ chemoradiotherapy	Radiotherapy plus pembrolizumab or chemoradiotherapy plus pembrolizumab depending on pathological risk factors	Treatment-related adverse effects, disease-free survival
NCT02707588		Groupe Oncologie Radiotherapie Tete et Cou	II	Locally advanced SCCHN ineligible for cisplatin chemoradiotherapy	Radiotherapy with concurrent pembrolizumab versus radiotherapy with concurrent cetuximab	Locoregional control
NCT03349710		Bristol-Myers Squibb	III	Locally advanced unresectable SCCHN	Unfit for cisplatin: nivolumab plus placebo plus radiotherapy versus cetuximab plus placebo plus radiotherapy Fit for cisplatin: nivolumab plus cisplatin plus radiotherapy versus placebo plus cisplatin plus radiotherapy	Event-free survival

https://www.clinicaltrials.gov/.
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial.
https://eudract.ema.europa.eu/.
HPV, human papilloma virus; SCC, squamous cell carcinoma.

virus-associated solid tumours. They focused on 29 patients with SCCHN, all of whom received two cycles of nivolumab before 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

Although 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], but 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 that 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 multidisciplinary team 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.

Conflicts of Interest

J.J. Sacco has received honoraria from BMS and Immunocore, and has been consulted in an advisory role for Immunocore, BMS, MSD and Delcath. 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. J.J. Sacco has had travel, accommodation or other expenses paid or reimbursed by BMS, MSD within the last 2 years. R. Brooker and A.G. Schache certify that they have no affiliations with or involvement in any organisation 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 editorial. They are not directly receiving funding from BMS, but they are currently contributing to the set up and opening of the NICO trial, which is being funded by BMS.

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