

Improving outcomes with chemo-radiotherapy in the mucosal squamous cell carcinomas – immune checkpoint inhibition and broken promises.

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Cancers arising at mucosal surfaces include cancers of worldwide significance (cancer of the cervix and head and neck squamous cell carcinomas (HNSCC) comprise 20% cancers in India [1]), anal squamous cell cancer (ASCC - rising in incidence in high income countries) and rare tumours where evidence-based approaches to treatment are limited (vulval, vaginal and penile cancers). They share biology and epidemiology, associated with high-risk subtypes of Human Papilloma Viruses (HPV) [2] or chronic inflammation and tobacco exposure. They typically present with locally advanced disease and are treated with radical chemo-radiotherapy (CRT) as they are relatively radio-sensitive and surgery brings significant morbidity and mortality (e.g., colostomy or tracheostomy). Relapses are not infrequent in patients presenting with locally advanced disease, typically at the primary site though metastatic disease is increasingly seen. Although comprehensive prophylactic HPV vaccination and tobacco control programmes would be expected to significantly reduce their incidence (and vaccines are in development to help patients already affected with HPV [3]), incidence is likely to increase over the next 20 years before a reduction is seen. Improving outcomes for the locally advanced mucosal SCCs then presents a major challenge of global importance.

CRT continues to undergo technical refinement - advances in radiotherapy planning increase doses to the tumour whilst sparing normal tissues. However, CRT is close to the ceiling of toxicity and previous attempts to add further drugs resulted in increased toxicity without improving outcomes [4]. Importantly after CRT the tumour remains in situ, cleared over a

number of months by the immune system. Immune checkpoints (PD-1/PD-L1) that inhibit tumour immune recognition are thought to play an important role in facilitating tumorigenesis [5] and resistance to CRT [6]. Immune checkpoint inhibitors (ICI) have revolutionised the treatment of cancer during the last decade [7]. ICIs appear to be particularly effective in cancers with frequent mutations and those of viral aetiology [8] and have efficacy across the mucosal SCCs in the metastatic setting, with studies reporting efficacy in HNSCC [9], anal [10, 11] and cervical, vulval and vaginal cancers [12].

There has therefore been significant interest in the addition of ICI to CRT across these cancers, supported by results of the PACIFIC trial in non-small cell lung cancer where durvalumab improved overall survival following CRT [13] and Checkmate 577 testing nivolumab after CRT for oesophageal cancer [14], where both have become a standard of care. A number of trials then embarked on combining ICI with CRT across the mucosal tumours, typically testing a block of adjuvant treatment +/- a concurrent component. However, the first tranche of these are now reporting and to date, somewhat unexpectedly, results are disappointing.

Two large phase III trials tested the addition of ICI to CRT in patients with HNSCC and have reported primary outcomes. Javelin head and neck 100 [15] randomised 697 patients undergoing radical CRT for locally advanced HNSCC to +/- avelumab (anti PD-L1) with patients in the experimental arm receiving a single infusion pre-CRT, then concurrent Avelumab during CRT and continuing for 12 months. There was no improvement in progression-free survival, the primary outcome measure (hazard ratio 1.21 [95% CI 0.93–1.57] favouring the placebo group). Keynote 412 (NCT03040999) tested the same approach (neoadjuvant, concurrent and then adjuvant) this time with the PD-1 inhibitor pembrolizumab [16], again in patients with locally advanced HNSCC. 804 patients were randomised between the two arms; with a median follow up of 47.7 months (range, 37.0–61.4) the primary outcome measure of event-free survival (EFS) was not statistically different between arms (HR 0.83 [0.68–1.03], $p=0.0429$) although the trend did favour the Pembrolizumab arm. In the cohort of patients with high levels of PD-L1 expression in the pre-treatment biopsy specimen ($n=685$), EFS just met significance (HR 0.80 [0.64–1.00]). Information on overall survival is awaited. Moving to cervical cancer, the phase III CALLA trial (NCT03830866) randomised 770 patients undergoing CRT (+ brachytherapy) for locally

advanced disease to +/- concurrent durvalumab, with patients in the experimental arm continuing adjuvant treatment for up to 2 years. With a median follow up of 18.5 months [17], the addition of durvalumab did not improve the primary outcome measure of progression-free survival (HR 0.84 [95% CI, 0.65–1.08]; p=0.174. Again, overall survival data is awaited.

Although there are no randomised trial results published in ASCC there are multiple ongoing studies. RADIANCE (Germany), CORINTH (UK), NCI-EA2165 (USA) and NCT05374252 (China) are all combining PD-1 inhibitors with standard CRT, with neoadjuvant, concurrent and adjuvant immunotherapy schedules all being investigated. Chemo-immunotherapy followed by CRT is being used in the INTER-ION trial (France) for locally advanced disease. There are no current immunotherapy studies for the other rare HPV-driven tumours (vulval, vaginal and penile).

Whilst the results from trials in anal cancer and further trials in HNSCC and cervical cancer might yet buck the trend (Table 1), it is pertinent to consider these unexpected results. Radiotherapy technique, the choice and schedules of immunotherapeutic drug(s) and patient selection, are potential reasons why these first CRT-ICI combination trials may have failed to improve outcomes in mucosal SCCs.

The generation of T-cell anti-tumour responses to cancer is a cyclic process that can be enhanced with radiotherapy (Figure 1) that might be amplified by immunotherapeutic drugs, and in theory produce synergistic efficacy [18]. For T-cells to be primed against cancer antigens, functional draining lymph nodes are important. Preclinical models suggest that radiotherapy to the draining lymph node dampens this adaptive immune response, reducing cytotoxic T-cell and dendritic cell signalling [19, 20]. Treatment of mucosal SCCs typically includes elective doses to uninvolved locoregional lymph nodes and lymphatic drainage. Elective doses may be as high as 60Gy/30# for HNSCC in “intermediate risk” areas, which could impact anti-tumour T-cell priming. In contrast, lung and oesophageal treatment guidelines do not involve elective doses to local lymph nodes to the same extent.

Volume and length of treatment may also impact the efficacy of ICI. Radiotherapy volumes in the pelvis can be large, in some instances including para-aortic nodes and metabolically active bone marrow. The standard fractionation regimen for mucosal SCCs produces

ongoing lymphopenia during and immediately after a 5-7 week treatment regimen. Given the inherent sensitivity of leukocytes to radiotherapy and the significant neutropenia and lymphopenia associated with pelvic irradiation, a careful re-analysis of the benefits and drawbacks of pelvic treatment volumes is required in the age of immunotherapy. These issues are addressed in the INTERACT-ION study (NCT04719988), where a reduced radiotherapy field is prescribed following an objective complete response to chemo-immunotherapy in patients with locally advanced ASCC. Any future studies in this area will require rigorous radiotherapy quality assurance (RTQA) to ensure lymph node doses are prescribed and recorded. Retrospective review of reported mucosal SCC trials with high quality RTQA such as JAVELIN may allow us to see if elective dose volumes have impacted immunotherapy efficacy. Before testing reduced elective volumes in the curative setting, with the attendant risks of reduced rates of cure, these concepts could initially be explored in fractionated palliative radiotherapy, where lower doses and volumes are frequently utilised and could be combined with the (relatively) modest ICI toxicities.

Although survival stratified by PD-L1 expression was investigated in CALLA (secondary endpoint), Keynote 412 and JAVELIN (both exploratory), none of these trials used any biomarker to select or stratify patient selection. Furthermore, PD-L1 positive definitions varied across all studies making comparison even within HNSCC difficult ($\geq 25\%$ tumour proportion score (TPS) in JAVELIN, $\geq 1\%$ combined positive score (CPS) in Keynote 412, $\geq 1\%$ TPS in CALLA). There are many other potential biomarkers that could be investigated using existing samples from trials and compared with standard of care biobank samples. Simplistically, tumour infiltrating lymphocytes (TILs) at diagnosis is prognostic in cervical, ASCC and HNSCC. Although outcomes vary for radical CRT across these cancers, there are certain groups of patients with locally advanced disease who do well. Five year locoregional failure rates for locally advanced ASCC are 20-30% - three quarters of unselected patients would get no benefit from immunotherapy whilst exposed to potential side-effects of additional treatment.

The timing of immunotherapy in relation to CRT is another barrier to success, with discordant approaches across different preclinical models and clinical trials. Many of the mucosal SCC trials discussed reference the same preclinical papers showing that concurrent or sequential immunotherapy (starting within 7 days of finishing radiotherapy) was superior

to adjuvant immunotherapy [21, 22]. However many of these trials investigated combinations of neoadjuvant, concurrent and adjuvant regimens together and teach us little about the scheduling of ICI. Scheduling should consider different immunotherapeutic drug targets; PD-1 inhibitors have a different mechanism of action to drugs targeting CTLA-4 and it is likely optimal scheduling may differ too [23]. Pre-clinical data most relevant to mucosal SCCs should inform future trials, many preclinical models use radiotherapy alone rather than CRT or have fractionation regimens completely different to those used in mucosal SCCs.

Whilst we await outcomes from the ongoing trials in anal cancer, the promise of ICI/CRT combinations for mucosal cancers remains unfulfilled. With many unknowns, it should be a fertile time for exploration of the underlying immunobiology of the CRT response. Importantly these findings should inform future trials across the mucosal SCCs – also incorporating studies that include the rarer subtypes with the appropriate biological rationale (e.g. basket protocols that might incorporate Bayesian designs). In short, better science, better biomarkers and better radiotherapy are needed to improve outcomes for these patients.

Figure 1: the cancer-immunity cycle

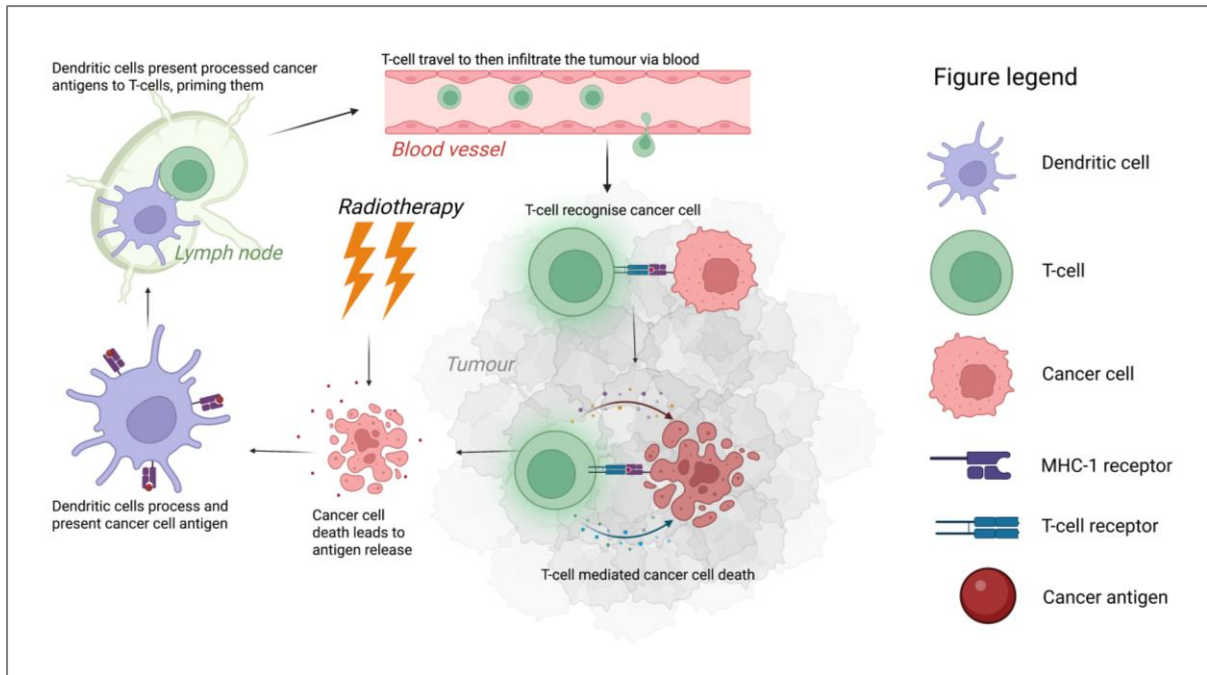


Table 1: Phase III trials in HPV-associated SCCs investigating RT-IO combinations. (OP – oropharynx, HP – hypopharynx)

Trial identifier	Title	Inclusion criteria	Immunotherapy	Immunotherapy regimen in relation to CRT	N	Estimated completion
Anal						
NCT05374252	Chemoradiotherapy Combined With or Without PD-1 Blockade in Anal Canal Squamous Carcinoma Patients	Stage III Anal Cancer	Anti-PD-1 Sintilimab	Adjuvant	102	31/12/2025
NCT03233711	Nivolumab After Combined Modality Therapy in Treating Patients With High Risk Stage II-III Anal Cancer	Stag IIB-III Anal	Anti-PD-1 Nivolumab	Adjuvant	344	31/4/24
Cervical						
NCT05173272	Induction Chemotherapy Combined With Immunotherapy Followed by Concurrent Chemoradiation in Advanced Cervical Cancer	Cervical Cancer FIGO 2018 Ib3-IIIc2	Anti-PD-1 Slulimumab	Neoadjuvant with chemotherapy	286	28/12/2028
NCT05235516	A Study of AK104/Placebo Combined With Chemoradiotherapy For The Treatment of Locally Advanced Cervical Cancer (AK104-305)	Cervical Cancer FIGO 2018 Stage IIIA-IVA	Anti-PD-1/CTLA-4 bi-specific antibody Cadonilimab	Concurrent	636	01/05/2029
NCT04221945	Study of Chemoradiotherapy With or Without Pembrolizumab (MK-3475) For The Treatment of Locally Advanced Cervical Cancer (Keynote A-18)	Cervical Cancer FIGO 2014 Stages IB2–IIB with N+ or III–IVA	Anti-PD-1 Pembrolizumab	Concurrent and adjuvant	980	07/12/2024
HNSCC						
NCT03765918	Study of Pembrolizumab Given Prior to Surgery and in Combination With Radiotherapy Given Post-surgery for Advanced Head and Neck Squamous Cell Carcinoma (MK-3475-689)	Stage III OP HPV +ve cancer, Stage III/IVA OP HPV negative cancer, Stage III/IVA larynx/HP/oral cavity cancer	Anti-PD-1 Pembrolizumab	Neoadjuvant and concurrent	704	30/07/2026
NCT03576417	A Trial Evaluating the Addition of Nivolumab to Cisplatin-RT for Treatment of Cancers of the Head and Neck (NIVOPOSTOP)	Oral cavity, OP, HP or larynx cancer with high risk of relapse	Anti-PD-1 Nivolumab	Neoadjuvant, concurrent and adjuvant	680	01/09/2027
NCT03952585	De-intensified Radiation Therapy With Chemotherapy (Cisplatin) or Immunotherapy (Nivolumab) in Treating Patients With Early-Stage, HPV-Positive, Non-Smoking Associated Oropharyngeal Cancer	p16 +ve T1-2N1M0 or T3N0M0 OP cancer	Anti-PD-1 Nivolumab	Neoadjuvant, concurrent and adjuvant	711	28/02/2025

NCT03700476	Sintilimab (PD-1 Antibody) and Chemoradiotherapy in Locoregionally-advanced Nasopharyngeal Carcinoma (CONTINUUM)	Stage III/IVA Nasopharyngeal Cancer	Anti-PD-1 Sintilimab	Neoadjuvant, concurrent and adjuvant	425	01/0125
NCT01810913	Testing Docetaxel-Cetuximab or the Addition of an Immunotherapy Drug, Atezolizumab, to the Usual Chemotherapy and Radiation Therapy in High-Risk Head and Neck Cancer	Stage III/IV p16 negative oral cavity, OP, larynx, HP cancer	Anti-PD-L1 Atezolizumab	Neoadjuvant, concurrent and adjuvant	613	01/01/2027
NCT03258554	Radiation Therapy With Durvalumab or Cetuximab in Treating Patients With Locoregionally Advanced Head and Neck Cancer Who Cannot Take Cisplatin	Stage III p16 +ve OP/SCC of unknown head/neck primary cancer or Stage III-IVB p16 -ve laryngeal, HP, and oral cavity cancer	Anti-PD-L1 Durvalumab	Concurrent and adjuvant	493	31/12/2025
NCT02999087	Randomized Trial of Avelumab-cetuximab-radiotherapy Versus SOCs in LA SCCHN (REACH)	Stage III/IVA/IVB Oral cavity, OP, HP or larynx cancer	Anti-PD-1 Avelumab	Concurrent and adjuvant	707	01/12/2027
NCT03427827	PD-1 Antibody Versus Best Supportive Care After Chemoradiation in Locoregionally Advanced Nasopharyngeal Carcinoma (PACIFIC-NPC)	Stage III/IVA Nasopharyngeal Cancer	Anti-PD-1 Camrelizumab	Adjuvant	442	01/02/2026
NCT03452137	A Study of Atezolizumab (Anti-Pd-L1 Antibody) as Adjuvant Therapy After Definitive Local Therapy in Patients With High-Risk Locally Advanced Squamous Cell Carcinoma of the Head and Neck	Squamous Cell Carcinoma of the Head and Neck, not nasopharynx or paranasal sinuses	Anti-PD-L1 Atezolizumab	Adjuvant	406	01/06/2027
NCT03700905	Study of Nivolumab Alone or in Combination With Ipilimumab as Immunotherapy vs Standard Follow-up in Surgical Resectable HNSCC After Adjuvant Therapy (IMSTAR-HN)	Stage III-IVB HPV negative OP, oral cavity, HP, and larynx cancer	Anti-PD-1 Nivolumab, Anti-CTLA4 Ipilimumab	Adjuvant	276	01/05/2024
NCT03811015	Testing Immunotherapy Versus Observation in Patients With HPV Throat Cancer	p16 positive OP cancer	Anti-PD-1 Nivolumab	Adjuvant	636	01/01/2027

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