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Editorial

Improving Outcomes with Chemoradiotherapy 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), which comprise 20% of 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 papillomaviruses (HPV) [2] or chronic inflammation and tobacco exposure. They typically present with locally advanced disease and are treated with radical chemoradiotherapy (CRT) as they are relatively radiosensitive 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, although 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 while 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]. They 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 ICIs 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 standard of care. A number of trials then embarked on combining ICIs 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 ICIs 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%

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confidence interval 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. In total, 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 was not statistically different between arms (hazard ratio 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 ($n = 685$), event-free survival just met significance (hazard ratio 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 (hazard ratio 0.84; 95% confidence interval 0.65–1.08; $P = 0.174$. Again, overall survival data are 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. Chemoimmunotherapy 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).

Although 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 60 Gy/30 fractions 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 reanalysis 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 chemoimmunotherapy in patients with locally advanced ASCC. Any future studies in this area will require rigorous radiotherapy quality assurance to ensure lymph node doses are prescribed and recorded. Retrospective review of reported mucosal SCC trials with high-quality radiotherapy quality assurance, 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 (≥25% tumour proportion score in JAVELIN, ≥1% combined positive score in Keynote 412, ≥1% tumour proportion score 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 at diagnosis are 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 while 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 ICIs. Scheduling should consider different immunotherapeutic drug targets; PD-1 inhibitors have a different mechanism of action to

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Table 1
Phase III trials in human papillomavirus (HPV)-associated squamous cell carcinomas investigating radiotherapy–immunotherapy combinations

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-IIIB Anal Cancer	Stage IIB-III anal cancer	Anti-PD-1 Nivolumab	Adjuvant	344	31/4/2024
Cervical						
NCT05173272	Induction Chemotherapy Combined With Immunotherapy Followed by Concurrent Chemoradiation in Advanced Cervical Cancer	Cervical cancer FIGO 2018 stage 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
Head and neck squamous cell carcinoma						
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-positive 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-positive 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	01/01/2025
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-positive OP/SCC of unknown head/neck primary cancer or stage III-IVB p16-negative laryngeal, HP, and oral cavity cancer	Anti-PD-L1 Durvalumab	Concurrent and adjuvant	493	31/12/2025

(*continued on next page*)

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Table 1 (*continued*)

Trial identifier	Title	Inclusion criteria	Immunotherapy	Immunotherapy regimen in relation to CRT	*n*	Estimated completion
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 Ipilumumab	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

HP, hypopharynx; OP, oropharynx.

drugs targeting CTLA-4 and it is likely optimal scheduling may differ too [23]. Preclinical 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.

While we await outcomes from the ongoing trials in anal cancer, the promise of ICI/CRT combinations for

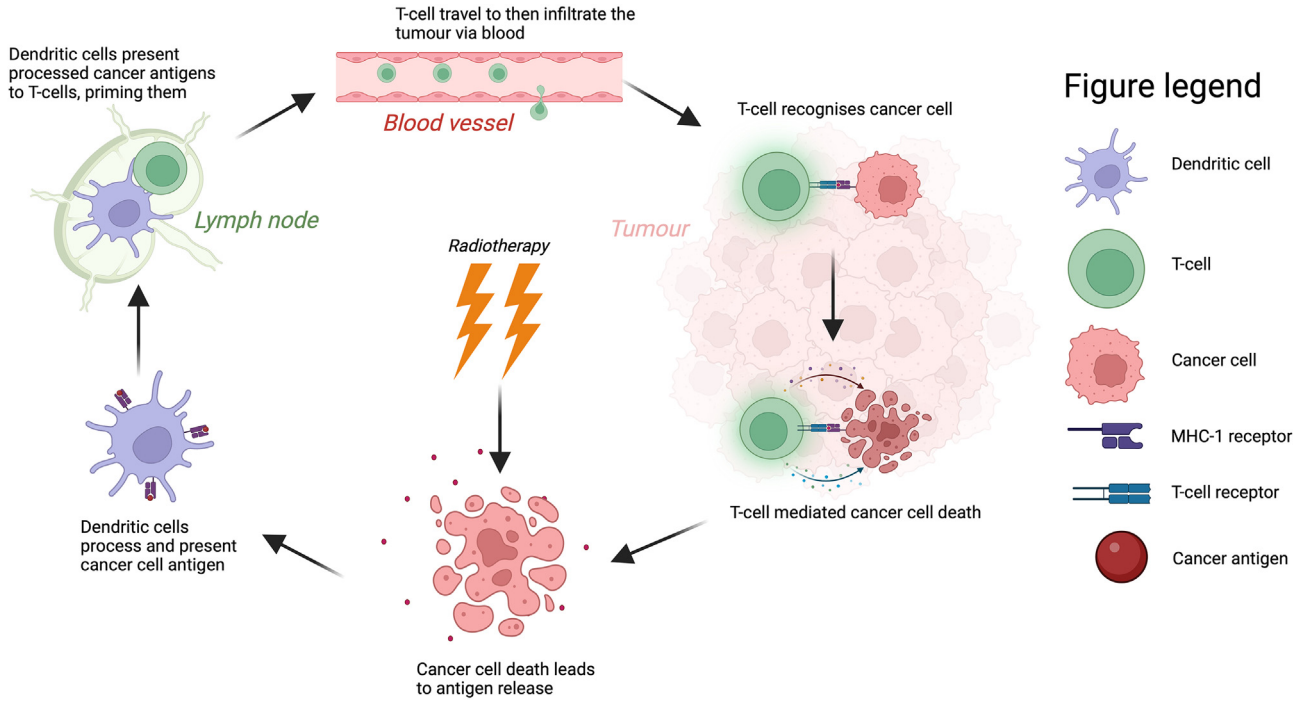

Fig 1. The cancer–immunity cycle.

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.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] India State-Level Disease Burden Initiative Cancer Collaborators. The burden of cancers and their variations across the states of India: the Global Burden of Disease Study 1990–2016. *Lancet Oncol* 2018;19(10):1289–1306.

[2] de Sanjosé S, Serrano B, Tous S, Alejo M, Lloveras B, Quirós B, *et al*. Burden of human papillomavirus (HPV)-related cancers attributable to HPVs 6/11/16/18/31/33/45/52 and 58. *JNCI Cancer Spectr* 2018;2(4):pky045.

[3] Harper DM, Nieminen P, Donders G, Einstein MH, Garcia F, Huh WK, *et al*. The efficacy and safety of Tipapkinogen Sovacivec therapeutic HPV vaccine in cervical intraepithelial neoplasia grades 2 and 3: randomized controlled phase II trial with 2.5 years of follow-up. *Gynecol Oncol* 2019;153(3):521–529.

[4] Garg MK, Zhao F, Sparano JA, Palefsky J, Whittington R, Mitchell EP, *et al*. Cetuximab plus chemoradiotherapy in immunocompetent patients with anal carcinoma: a phase II Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Cancer Research Group Trial (E3205). *J Clin Oncol* 2017;35(7):718–726.

[5] Howitt BE, Sun HH, Roemer MG, Kelley A, Chapuy B, Aviki E, *et al*. Genetic basis for PD-L1 expression in squamous cell carcinomas of the cervix and vulva. *JAMA Oncol* 2016;2(4):518–522.

[6] Yoneda K, Kuwata T, Kanayama M, Mori M, Kawanami T, Yatera K, *et al*. Alteration in tumoural PD-L1 expression and stromal CD8-positive tumour-infiltrating lymphocytes after concurrent chemo-radiotherapy for non-small cell lung cancer. *Br J Cancer* 2019;121(6):490–496.

[7] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, *et al*. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2019;381(16):1535–1546.

[8] Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med* 2017;377(25):2500–2501.

[9] Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, *et al*. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol* 2016;17(7):956–965.

[10] Morris VK, Salem ME, Nimeiri H, Iqbal S, Singh P, Ciombor K, *et al*. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. *Lancet Oncol* 2017;18(4):446–453.

[11] Rao S, Anandappa G, Capdevila J, Dahan L, Evesque L, Kim S, *et al*. A phase II study of retifanlimab (INCMGA00012) in patients with squamous carcinoma of the anal canal who have progressed following platinum-based chemotherapy (POD1UM-202). *ESMO Open* 2022;7(4):100529.

[12] Naumann RW, Hollebecque A, Meyer T, Devlin MJ, Oaknin A, Kerger J, *et al*. Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: results from the phase I/II CheckMate 358 trial. *J Clin Oncol* 2019;37:2825–2834.

[13] Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, *et al*. PACIFIC Investigators. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med* 2018;379(24):2342–2350.

[14] Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, *et al*. CheckMate 577 Investigators. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. *N Engl J Med* 2021;384(13):1191–1203.

[15] Lee NY, Ferris RL, Psyrri A, Haddad RI, Tahara M, Bourhis J, *et al*. Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol* 2021;22(4):450–462.

[16] ESMO Congress. Presidential Symposium II. LBA5 - Primary results of the phase III KEYNOTE-412 study: pembrolizumab (pembro) with chemoradiation therapy (CRT) vs placebo plus CRT for locally advanced (LA) head and neck squamous cell carcinoma (HNSCC). Available at: https://oncologypro.esmo.org/meeting-resources/esmo-congress/primary-results-of-the-phase-iii-keynote-412-study-pembrolizumab-pembro-with-chemoradiation-therapy-crt-vs-placebo-plus-crt-for-locally-advanc.

[17] Monk B, Toita T, Wu X, Limón JC, Zhou Q, Tarnawski R, *et al*. O001/#504 Durvalumab, in combination with and following chemoradiotherapy, in locally advanced cervical cancer: results from the phase 3 international, randomized, double-blind, placebo-controlled Calla trial. *Int J Gynecol Cancer* 2022;32:A2–A3.

[18] Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 2013;39(1):1–10. https://doi.org/10.1016/j.immuni.2013.07.012. PMID: 23890059.

[19] Marciscano AE, Ghasemzadeh A, Nirschl TR, Theodros D, Kochel CM, Francica BJ, *et al*. Elective nodal irradiation attenuates the combinatorial efficacy of stereotactic radiation therapy and immunotherapy. *Clin Cancer Res* 2018;24(20):5058–5071.

[20] Saddawi-Konefka R, O'Farrell A, Faraji F, Clubb L, Allevato MM, Jensen SM, *et al*. Lymphatic-preserving treatment sequencing with immune checkpoint inhibition unleashes cDC1-dependent antitumor immunity in HNSCC. *Nat Commun* 2022;13(1):4298.

[21] Dovedi SJ, Cheadle EJ, Popple AL, Poon E, Morrow M, Stewart R, *et al*. Fractionated radiation therapy stimulates antitumor immunity mediated by both resident and infiltrating polyclonal T-cell populations when combined with PD-1 blockade. *Clin Cancer Res* 2017;23(18):5514–5526.

[22] Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, *et al*. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res* 2014;74(19):5458–5468.

[23] Demaria S, Guha C, Schoenfeld J, Morris Z, Monjazeb A, Sikora A, *et al*. Radiation dose and fraction in immunotherapy: one-size regimen does not fit all settings, so how does one choose? *J Immunother Cancer* 2021;9(4):e002038.

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