

Antibody–drug Conjugates in Head and Neck Cancer: Current and Future Perspectives

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Antibody–drug conjugates (ADCs) are a class of targeted agents composed of a monoclonal antibody directed to a target antigen, linked to a therapeutic payload. The premise of ADC design is to improve safety and widen the therapeutic window by releasing the cytotoxic payload to cancer cells upon antigen binding. Several ADCs have been approved in recent years for the treatment of both haematological and solid malignancies. Head and neck cancer (HNC) often recurs despite standard multimodality treatment, including surgery, radiotherapy and chemotherapy. Treatment options in the recurrent and/or metastatic setting are largely limited following platinum-based chemotherapy and immunotherapy. Thus, there is a substantial unmet need for improved therapeutic strategies in HNCs. Recently, ADCs have emerged as a promising therapeutic strategy in head and neck malignancies, with efficacy and safety data from several early-phase trials completed and ongoing studies suggesting promise for ADCs in HNCs. ADC composition, appropriate target antigen selection, mechanisms of resistance and combinatorial strategies for treatment optimization in HNC remain key considerations and are explored in this article.

Keywords

Antibody–drug conjugates, clinical trials, cytotoxic payloads, developmental therapeutics, head and neck cancer, head and neck squamous cell carcinomas (HNSCCs)

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Head and neck cancer (HNC), with over 946,000 new cases and 482,000 deaths in 2022, is the seventh most common cause of cancer-related deaths globally.¹ Specifically, in the USA, the number of estimated new cases in 2024 was 74,000.² Head and neck squamous cell carcinoma (HNSCC) represents approximately 90% of all HNCs and consists of a diverse group of epithelial neoplasms arising from multiple anatomic sites, including the paranasal sinuses, nasal cavity, oral cavity, pharynx and larynx.³ While carcinogens such as tobacco and alcohol exposure are implicated in HNSCC, there is a rapidly increasing incidence of human papillomavirus (HPV)-associated with HNSCC, which arises largely in the oropharynx. In patients with non-viral-mediated disease, despite multimodality treatment including radiation and chemotherapy with or without surgery, survival remains poor, with approximately half of patients developing recurrent and/or metastatic disease.⁴ Patients who develop HPV-associated disease have a more favourable prognosis compared with their carcinogen-induced counterparts; yet, approximately 15–25% of HPV-associated tumours will also recur following chemoradiotherapy-based approaches.⁵ Novel therapeutics that leverage new mechanisms for therapeutic antitumour efficacy and synergistic approaches with current treatment approaches represent an urgent unmet need within the field.

Although progress has been made in improving survival for patients with relapsed/metastatic (R/M) HNSCC, such as use of immunotherapy, outcomes remain poor.⁶ With platinum-based chemotherapy and immunotherapy, approximately a quarter of patients remain alive at 4 years; yet, patients largely ultimately develop therapeutic resistance to these therapies.⁷ Nivolumab and pembrolizumab, programmed cell death 1 antibody (anti-PD-1) immune checkpoint inhibitors, improved overall survival (OS) in patients with recurrent or metastatic HNSCC who progressed after first-line platinum-based chemotherapy and, subsequently, in front-line R/M HNSCC.⁸ However, only a minority of patients derive long-term benefits from anti-PD-1 therapy.^{9,10} Beyond immune checkpoint inhibitor therapy targeting PD-(L)1 axis and platinum-based chemotherapy, treatment options are limited. Cetuximab, an epidermal growth factor receptor (EGFR)-targeted monoclonal antibody (mAb), has limited activity with response rates ~8–10% in the pre-immunotherapy era and can be given with chemotherapy, but it appears to have higher activity after immunotherapy with response rates of ~19% or up to 24% in non-viral-mediated disease.^{11,12} The high recurrence rate following curative-intent treatment and the poor prognosis in the recurrent or metastatic setting highlight the urgent need for the development of novel treatment modalities.⁸

Antibody–drug conjugates (ADCs), previously known as immunoconjugates, represent an emerging class of treatment contributing to the field of oncology. The first ADC approved by the US Food and Drug Administration (FDA) in 2000 was the CD33-targeting agent gemtuzumab ozogomycin.^{13,14}

In the following years, the introduction of ADCs has been extensive in haematological malignancies, including acute myelogenous leukaemia, multiple myeloma and diffuse large B-cell lymphoma. Ado-trastuzumab emtansine (T-DM1) was the first FDA-approved ADC for solid malignancy (breast cancer) in 2013, and five other ADCs have since received FDA approval across multiple indications for solid malignancies, including breast, cervical, ovarian and urogenital cancer.¹⁵ Potential targets are currently being investigated to determine the role of ADCs in treating HNCs, particularly in the relapsed refractory metastatic setting.

Our review discusses the structure and function of ADCs, the need for ADC therapy in recurrent/metastatic HNC, potential targets in HNC, the latest updates regarding ongoing efforts exploring ADCs in HNC and the future direction for ADCs in the HNC landscape.

Overview of antibody–drug conjugates

ADCs are a combination of a therapeutic drug and an antibody coupled by a linker, designed to deliver a therapeutic payload to the cells expressing the target antigen.¹⁶ The binding of the antibody to the target tumour cell surface triggers antigen-mediated endocytosis, leading to internalization and release of the cytotoxic payload, which ultimately induces apoptosis and other forms of cell death. Notably, these targets do not need to be oncogenic tumour drivers, as their primary role is to serve as entry portals for the cytotoxic agent. Preferably, the ADC target is highly expressed on the outer surface of each tumour cell and undergoes internalization upon binding of the ADC. Minimal to no expression in normal tissues is essential to create a therapeutic window, allowing for effective ADC treatment with reduced on-target toxicity.¹⁷

The three essential parts of an ADC – a monoclonal antibody (mAb) targeting a specific antigen, a cytotoxic drug (the payload) and a linker connecting the payload to the antibody – determine their efficacy and toxicity profiles.¹⁸

Antibody moiety

Antibodies are a fundamental component of the ADC.¹⁶ The preferred antibody in ADC design is fully humanized or humanized IgG1. High affinity and avidity for the target antigen, efficient internalization and low immunogenicity are important properties of an ideal antibody. Fully humanized IgG1 also carries a lower risk for infusion-related reactions. IgG1 also has a prolonged serum half-life and potent Fc-mediated immune functions.¹⁹ In addition, the antibody moiety can provide synergistic anticancer action in addition to the payload's independent effect. Antibody binding to the target antigen can interrupt its downstream effects by inducing its degradation or hindering interactions with its binding partners.^{20,21} Antitumour effects can also be achieved through antibody-dependent activation of immune activation, including antibody-dependent cellular cytotoxicity, as seen with trastuzumab.²²

Linker

The linker couples the antibody and cytotoxic payload while the drug is in systemic circulation and allows the controlled delivery of the payload within the tumour microenvironment.⁸ Ideally, linkers should preserve the ADC's stability while in circulation to ensure that it reaches the target cell intact. Once internalized, the linker should readily break down to facilitate payload release.²³ There are two main types of linkers: cleavable and non-cleavable. Cleavable linkers are designed to break down through reduction, proteolysis or hydrolysis as a result of intracellular tumour physiological factors such as proteases or pH.¹⁸ They can be categorized as acid-sensitive, protease-sensitive or glutathione-sensitive. Given that these physiologic parameters are achievable without antigen

internalization, cleavable linkers, especially the acid-sensitive ones, tend to be less stable in the systemic circulation.^{23,24} They have a higher bystander effect and tumour diffusion; however, the therapeutic window is narrower due to off-target toxicity.²⁵ Non-cleavable linkers, on the other hand, create stable bonds that release the payload only when the ADC antibody undergoes internalization and complete lysosomal breakdown within target cells. This leads to reduced off-target toxicity but possibly reduced efficacy due to limited diffusion across the tumour.²⁵

Payloads

This is the chemotherapeutic component of the ADC that causes target tumour cell cytotoxicity.¹⁶ Upon entry of the ADC into the target cell cytoplasm, it is deployed. Having good stability in the systemic circulation and lysosomal environments is crucial for safe and effective activity at the target site. Chemotherapy payloads have higher cytotoxicity compared with traditional chemotherapy agents. Typically, microtubule-binding or DNA damage (DNA cleavage or alkylation)-inducing agents are used. Topoisomerase inhibitors, microtubule inhibitors and DNA-alkylating agents are examples of payloads used in ADCs. Topoisomerases assist with the unwinding of supercoiled DNA during DNA replication. Their inhibition causes the accumulation of DNA breaks with resultant cellular apoptosis. Rapid clearance and dose-related toxicity are major limitations with the use of conventional systemic topoisomerase inhibitors. Integration of topoisomerase inhibitors into ADCs potentially overcomes these barriers. Topoisomerase type 1 (TOP1) inhibitors, which cause single-strand DNA breaks, are the most frequently used topoisomerase inhibitors in ADCs. Microtubule inhibitors cause cell cycle arrest by inhibiting tubulin polymerization and destabilizing the assembly of microtubules, which assist in chromosome division during mitosis.²⁶ They include auristatin derivatives and maytansine derivatives. DNA-alkylating agents inhibit DNA replication by introducing alkyl groups to nucleobases, thereby causing cellular apoptosis.²⁷

Antibody–drug conjugation

The conjugation of an antibody to a cytotoxic payload changes the pharmacokinetics and therapeutic index of the ADC.¹⁶ The traditional method of drug conjugation involves a random process that occurs on the mAb backbone with multiple amino acid side chains, which results in a heterogeneous mixture of ADCs with varying drugs-to-antibody ratio (DAR). The DAR can range from zero to eight cytotoxic payloads per antibody, affecting the pharmacokinetics, efficacy and safety profiles of the ADC.^{23,28,29} While a higher DAR may enhance ADC potency, it can also lead to destabilization, aggregation, increased toxicity and accelerated systemic clearance.³⁰

Target antigens for antibody–drug conjugate therapy in head and neck cancer

There are limited options available for treating patients with relapsed refractory advanced HNCs after conventional chemotherapy, cetuximab and immune checkpoint inhibitors. Unlike other solid tumours such as non-small cell lung cancers, HNCs are not largely driven by oncogenic alterations.³¹ Thus, targeted therapies are not particularly efficacious in this disease. ADCs, however, target cell-surface antigens that are sometimes expressed in HNCs and are likely to impact the current treatment landscape.

Tumour antigen selection is important when investigating novel therapeutics, such as ADCs, in the treatment of solid tumours. To minimize off-tumour toxicity and broaden the drug's therapeutic window, an appropriate target antigen candidate should be highly expressed in tumours, while normal, healthy tissue should have low levels of

expression. Other considerations related to target antigens include their localization (such as cell membrane, cytoplasm and/or nucleus), as well as the degree of internalization after antibody binding.

Nectin-4 is a target molecule that mediates cell adhesion and other cellular functions such as cell differentiation, proliferation and survival. Additionally, nectin-4 appears to play an immunomodulatory role by binding to the inhibitory receptor T-cell immunoreceptor with Ig and ITIM.³² Nectin-4 is frequently expressed at low or medium levels in HNSCC.³³ Given the ubiquitous expression of nectin-4 in solid cancers, ADCs targeting nectin-4, such as enfortumab vedotin (EV), are currently being explored across solid tumours, including HNC.³⁴ The localization of nectin-4 expression is emerging as a potential biomarker for ADC targeting in advanced solid tumours.

Tissue factor is historically known as a transmembrane glycoprotein that is a key activator of the extrinsic pathway of the coagulation cascade.^{35,36} It is, however, also associated with tumorigenesis, tumour angiogenesis and metastasis.³⁶ Tissue factor is expressed in cervical cancer and similarly expressed in HNSCC (immunohistochemistry ≥ 2 in 75%), and is associated with poor prognosis.³⁷

Integrin beta 6 (ITGB6) is a part of an adhesion receptor heterodimer of alpha-v/beta-6. It is highly expressed in numerous solid tumours, particularly NSCLC and HNSCC. A study reported high protein expression

of H-270 in HNSCC.³⁸ ITGB6 contributes to tumour invasiveness and pathogenesis, and when present, it is a negative prognostic indicator.³⁹

EGFR is a pertinent target in HNCs, given its high level of expression. EGFR overexpression is seen in up to 90% of HNSCC and usually portends poor clinical outcomes.^{40,41} Cetuximab, an anti-EGFR mAb, has been an important part of the treatment of HNSCC, underscoring the importance of the EGFR pathway in these cancers. When used as a single agent or in combination with a taxane, cetuximab demonstrated about 17% objective response rate (ORR) in patients with platinum-refractory HNSCC.⁴² An important consideration in the development of novel therapeutics exploring the EGFR pathway is that EGFR is also present in healthy epithelial cells. This poses a risk for on-target, off-tumour toxicity with the use of EGFR-targeting agents, as seen with the significant skin toxicity associated with cetuximab.⁴³

Trophoblast cell surface antigen 2 (Trop-2) is another target that has been explored in ADCs. It is a cell-surface glycoprotein and is expressed by many epithelial cancers while minimally expressed in normal tissues.⁴⁴ In particular, Trop-2 is expressed in varying degrees in HNSCC. A study revealed an overexpression of Trop-2 in 89% of HNSCC.⁴⁵

CD44v6 is a variant isoform of the cell adhesion molecule CD44 and is highly expressed in HNSCC and also normal squamous epithelium, such

Figure 1: Antibody–drug conjugate components with select target antigens and payloads studied in head and neck cancers

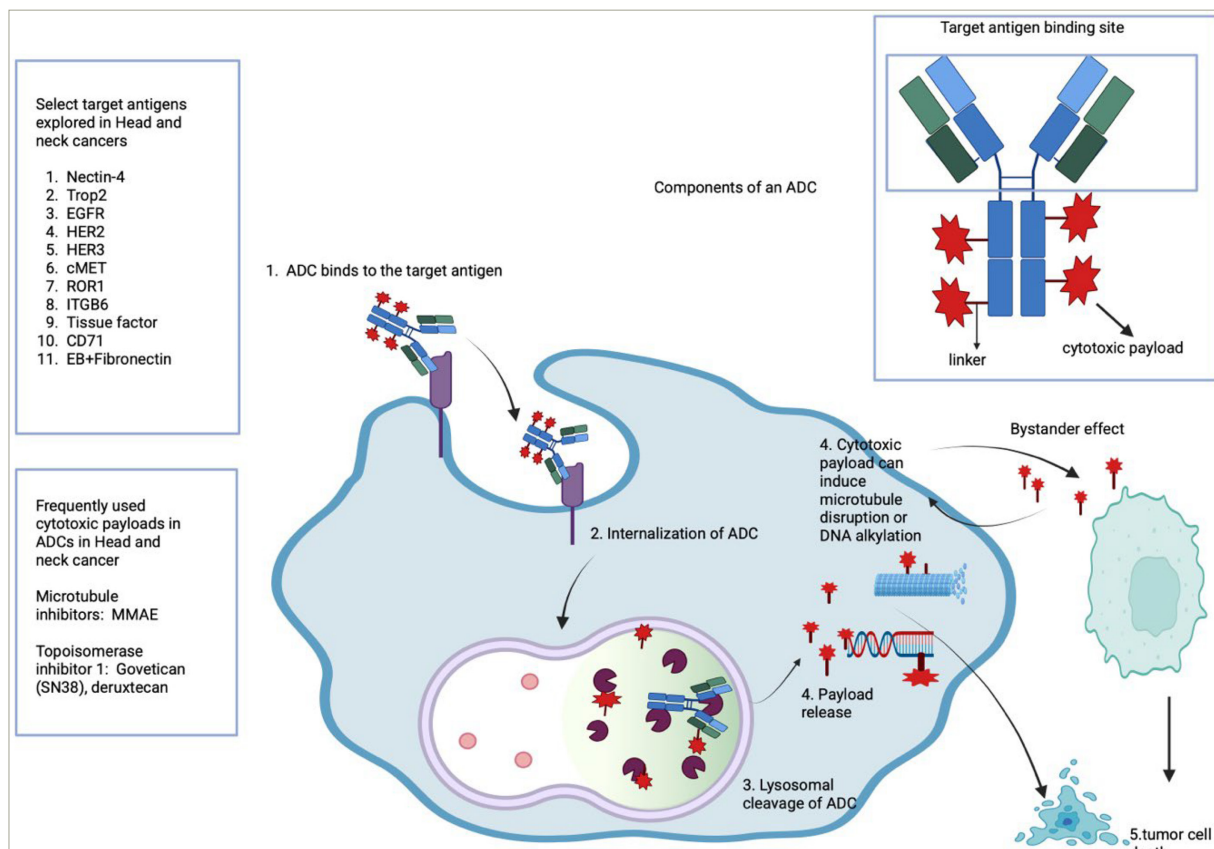


Figure created with BioRender.com⁴⁸

ADC = antibody–drug conjugate; CD71 = cluster of differentiation 71; cMET = c-mesenchymal-epithelial transition factor; EB + fibronectin = extra domain B splice variant of fibronectin; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor 2; HER3 = human epidermal growth factor 3; ITGB6 = integrin beta-6; MMAE = monomethyl auristatin E; ROR1 = receptor tyrosine kinase-like orphan receptor 1; Trop-2 = trophoblast cell-surface antigen.

as skin keratinocytes.^{46,47} This increases the risk of off-tumour/on-target toxicities. Other select target antigens are shown in *Figure 1*.⁴⁸

Review of current data on antibody–drug conjugate therapy in head and neck cancer

Herein, we evaluate current data regarding ADCs in HNCs.

EV is an ADC that binds to nectin-4 and is linked to a monomethyl auristatin E (MMAE) via a protease-cleavable linker.⁴⁹ This ADC has shown the highest activity in urothelial cancer and is now approved in the first-line setting in combination with pembrolizumab for the treatment of metastatic urothelial cell cancer. EV is currently being studied in HNCs. A multicohort phase II trial EV-202 (An Open-label, Multicenter, Multicohort, Phase 2 Study to Evaluate Enfortumab Vedotin in Subjects With Locally Advanced or Metastatic Malignant Solid Tumors; ClinicalTrials.gov identifier: NCT04225117) investigating EV included patients with HNC heavily pretreated refractory and metastatic disease.³⁵ In 46 response-evaluable patients, investigator-assessed confirmed ORR was 23.9% (95% CI: 12.6, 38.8), with a best overall response comprising a complete response of 2.2% (1/46 patients), a partial response (PR) of 21.7% (10/46 patients) and stable disease of 32.6% (15/46 patients). The reported median progression-free survival and mOS were 3.94 and 5.98 months, respectively. No new safety signals were seen in this study, and the safety profile was similar to what was seen in EV monotherapy in locally advanced or metastatic urothelial cancer. The most noteworthy treatment adverse events of any grade peripheral neuropathy, hyperglycemia and peripheral neuropathy were reported to be 33%, 4.3% and 46%, respectively. Another cohort of EV-202 investigating the addition of pembrolizumab and EV in patients with R/M HNSCC with a PD-L1 combined positive score of ≥ 1 is ongoing (ClinicalTrials.gov identifier: NCT04225117). Beyond EV, other nectin-4-directed ADCs are under investigation. LY4101174, an ADC with the cytotoxic payload, a topoisomerase inhibitor exatecan, is linked to the antibody through a cleavable linker. An early-phase study investigating LY4101174 in R/M solid tumours including HNCs is ongoing (EXCEED trial; A Phase 1 Trial Investigating LY4101174, an Antibody-Drug Conjugate Targeting Nectin-4, in Participants With Recurrent, Advanced or Metastatic Solid Tumors; ClinicalTrials.gov identifier: NCT06238479).⁵⁰ CRB-701 is a novel, third-generation, nectin-4-directed ADC currently being tested in R/M HNSCC (A Phase 1/2 Study to Investigate the Safety, Pharmacokinetics, and Efficacy of CRB-701, an Antibody-drug Conjugate Targeting Nectin-4, in Patients with Advanced Solid Tumors; ClinicalTrials.gov identifier, NCT06265727).^{51,52} It has a stable linker complex which results in site-specific payload release and, in turn, improves payload-associated toxicities.

Tisotumab vedotin (TV) is an ADC with a DAR of 4, consisting of the human anti-TF IgG1-kappa targeting tissue factor conjugated with an MMAE through a val-cit cleavable linker.⁵³ TV is currently being investigated in solid cancers in a phase II basket trial called InnovaTV 207 (Open Label Phase 2 Study of Tisotumab Vedotin for Locally Advanced or Metastatic Disease in Solid Tumors; ClinicalTrials.gov identifier: NCT03485209).⁵⁴ In this trial including pretreated and treatment-naïve patients, TV was given alone or in combination with pembrolizumab and/or platinum chemotherapy. In part A of the study, TV was given alone at 2 mg/kg once every 3 weeks and an ORR of 16% (5 PRs out of 31), disease control rate of 58.1% (18/31 patients), median PFS of 4.2 months and median OS of 9.4 months.⁵⁵ An updated analysis of part C of the InnovaTV 207 study revealed an ORR of 32.5% (13 out of 40 patients) and median duration of response (mDOR) of 5.6 months in patients who received TV at 1.7 mg/kg every 2 weeks.^{54,56}

In another part of the study, special interest treatment-related adverse events including ocular toxicity, peripheral neuropathy and bleeding events occurred in 30%, 40% and 17.5% of patients.⁵⁶ The parts of the InnovaTV 207 trial investigating TV in combination with pembrolizumab (part F) in the frontline setting for R/M HNSCC are currently under investigation (ClinicalTrials.gov identifier: NCT03485209).⁵⁷

Sacituzumab govitecan is an ADC composed of a humanized IgG1 antibody targeting Trop-2 linked by a hydrolyzable CL2A linker to a topoisomerase I inhibitor and irinotecan metabolite, SN38, with a DAR of 7.6. It is now approved in the second-line setting for the treatment of metastatic breast cancer and urothelial cancer.^{58–60} Sacituzumab govitecan was investigated in the phase I/II basket trial, IMMU-132-01, which included a few patients with HNSCC. Serious treatment-related adverse events due to the cytotoxic payload were febrile neutropenia and diarrhoea in 4% and 2.8% of treated patients.⁵⁸ A basket trial – TROPiCS-03 (A Phase 2 Open-Label Study of Sacituzumab Govitecan [IMMU-132] in Subjects With Metastatic Solid Tumors; ClinicalTrials.gov identifier: NCT03964727) – evaluating the activity of sacituzumab govitecan in multiple cancers included heavily pretreated 43 patients with HNSCC and demonstrated a 16% ORR (7 confirmed partial responses out of 43), and the mDOR, PFS OS was 4.2, 4.1 and 9 months, respectively.⁶¹ The most common adverse events reported were haematological abnormalities linked to topoisomerase I inhibition, including neutropenia, leukopenia and anaemia. Serious adverse events (i.e. grade 3 or more) were observed in 58% of patients with three reported deaths, one due to septic shock.⁶²

EGFR is a key player in tumorigenesis, tumour migration and survival.⁶³ When bound by its ligand, epidermal growth factor, several downstream signalling processes are activated. MGR003 is an EGFR-directed ADC with a DAR of 4, consisting of a fully human IgG1 mAb linked to its MMAE payload via a val-cit cleavable linker. An early-phase study investigating MGR003 in HNSCC showed a favourable toxicity profile with preliminary efficacy data from the dose expansion phase revealing an ORR of 40% (5 out of 13 patients) and median overall survival of 11.8 months. The ORR in nasopharyngeal cancer was 44% (6 out of 14 patients).⁵⁵ A phase III randomized trial (A Randomized, Open-Label, Multicenter, Phase III Study to Evaluate MRG003 vs Cetuximab/Methotrexate as Second/Third Line of Treatment in Patient With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck [RM-SCCHN]; ClinicalTrials.gov identifier: NCT05751512) is investigating MGR003 with anti-EGFR mAb cetuximab or methotrexate in refractory R/M HNSCC, following efficacy seen from an earlier study (An Open-Label, Single Arm, Multi-Center Phase II Clinical Study to Evaluate the Efficacy and Safety of MRG003 in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of Head and Neck; ClinicalTrials.gov identifier: NCT04868162).^{64,65} Losatuxizumab vedotin (ABBV-221) and depatuxizumab mafodotin are examples of EGFR-directed ADCs under investigation in HNSCC.^{66–68}

Sigvotaug vedotin (SGN-B6A) is an ITGB6-directed-ADC consisting of a humanized anti-ITGB6 antibody conjugated to an MMAE payload via a cleavable valine-citrulline linker. There is an ongoing multicohort phase I study investigating SGN-B6A in HNSCC (A Phase 1 Study of SGN-B6A in Advanced Solid Tumors; ClinicalTrials.gov identifier: NCT04389632).^{69,70} In addition to testing the ADC in patients who received prior systemic therapies, the study is also testing the activity of the ADC in the first-line setting with different cohorts investigating SGN-B6A and immunotherapy in PD-L1-positive HNSCC and SGN-B6A and chemoimmunotherapy, regardless of the PD-L1 status. Initial analyses showed a 23.2% ORR and median DoR of 5.5 months in patients included between escalation and

dose expansion. It also demonstrated a manageable safety profile with all solid cohorts with grade 3 or higher treatment-related adverse events observed in 19.5%, with neutropenia being the most frequent one (7.7%). Of note, 86% of HNSCC patients in the study received at least two lines of therapy for R/M disease.

A CD44v6-targeting ADC, bivatuzumab mertasine, was one of the first ADCs explored in HNSCC. A phase I clinical trial investigating bivatuzumab mertasine in patients with R/M HNSCC accrued 31 patients.⁷¹ The study was terminated due to a high incidence of severe dermatologic adverse events, given the high expression of CD44v6 in skin cells. Efficacy data were not fully evaluated with the early termination of the study. At least partial response was observed in three patients with regression response lasting 4–8 months.

HER2 is encoded by the *ERBB2* gene (erb-b2 receptor tyrosine kinase 2).⁷² Various genomic alterations in the *ERBB2* gene are oncogenic drivers, including *HER2* gene mutation, amplification and HER2 protein overexpression, particularly in salivary gland tumours, similar to breast cancer.⁷³ Trastuzumab deruxtecan (T-DXd) is an ADC currently explored in head and neck tumours, particularly salivary gland malignancies.^{74,75} It consists of a HER-2-directed antibody linked to deruxtecan, a topoisomerase inhibitor, by a protease-cleavable linker with a DAR of 8. Some key features of T-DXd include its high membrane permeability and high bystander effect due to the cleavable peptide linker. This ADC is currently approved for the treatment of diverse solid tumours. DESTINY-PanTumor02 (DP-02) (A Phase 2, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan [T-DXd, DS-8201a] for the Treatment of Selected HER2 Expressing Tumors [DESTINY-PanTumor02]; ClinicalTrials.gov identifier: NCT04482309) tested trastuzumab deruxtecan in pretreated patients with HER-2 positive locally advanced or metastatic solid tumours.⁷⁶ In an analysis of the cohort, including 24 patients with HNC, 19 patients were diagnosed with salivary gland cancer. About 15 out of 24 patients received at least two prior lines of therapy. The response was seen across all HER2 expressions. Confirmed OR was reported in 10 out of 24 patients (41.7%, 95% CI: 22.1, 63.4), and mDoR and mPFS were 22.1 months and 12.4 months, respectively. About 10 out of 24 patients experienced grade 3 or higher treatment-related adverse events with adjudicated interstitial lung disease/pneumonitis occurring in 3 out of 24 (12.5%) patients.⁷⁷ In the MYTHOS trial, a phase II study of trastuzumab deruxtecan in patients with recurrent/metastatic salivary gland cancer, ORR by blind independent committee review was 68.4% (13 out of 19 patients, 95% CI: 43.4, 87.4%) with a median PFS of 15.9 months (95% CI: 5.8, NE).⁷⁸

Another HER2-targeting ADC is disitamab vedotin, which is conjugated to its MMAE cytotoxic payload via its val-cit linker. It is currently being investigated in a phase II basket trial including patients with HNSCC with varying HER2 expressions (A Phase 2 Basket Study of Disitamab Vedotin in Adult Subjects With Previously Treated, Locally-Advanced Unresectable or Metastatic Solid Tumors That Express HER2; ClinicalTrials.gov identifier: NCT06003231).⁷⁹ We include selected ongoing ADC trials in head and neck cancer in Table 1.^{35,51,55,56,62,66,69,77–80}

Development of next-generation antibody–drug conjugates

The ADC landscape is fast advancing, with several approvals in the treatment of solid tumours. While ADCs show some promise in the treatment of HNCs, there are areas of potential improvement, including mitigating treatment-related toxicities, optimizing the efficacy,

understanding mechanisms of resistance and biomarker selection. The development of next-generation ADCs to tackle these issues is an important area of focus.

Target antigen heterogeneity and antigen loss are key resistance mechanisms affecting the antitumour activities of current ADCs.⁸¹ To optimize ADC binding and internalization, bispecific ADCs or biparatopic ADCs which bind to different target antigens or different epitopes of the same antigen, respectively, are being explored. For example, resistance to EGFR-targeting ADCs could be the result of crosstalk between EGFR and HER2 and HER3 pathways.⁸² A phase I study investigated the EGFR × HER3 bispecific ADC, izalontamab brengitecan (BL-B01D1) in patients with NSCLC, nasopharyngeal carcinoma and HNSCC. The efficacy was modest for patients with HNSCC, with a reported ORR of 7.7% (A Phase I Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetic Characteristics and Preliminary Efficacy of BL-B01D1 in Patients With Locally Advanced or Metastatic Solid Tumor; ClinicalTrials.gov identifier: NCT05194982).^{80,83} Another bispecific ADC, AZD9592 targeting EGFR and cMET, is currently under investigation in a phase I basket study in patients with NSCLC and HNSCC (A Phase I, Multicenter, Open-label, First-in-Human, Dose Escalation and Expansion Study of AZD9592 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Tumors; ClinicalTrials.gov identifier: NCT05647122).^{84,85} Similarly, a biparatopic ADC targeting two nonoverlapping epitopes of HER2 is currently being investigated in patients who are not responsive to HER2-directed therapies.⁸⁶

Next-generation ADCs can also help mitigate toxicities associated with current ADCs. Broadly speaking, the toxicities from ADCs are on-target off-tumour and off-target off-tumour events. An example of an on-target off-tumour effect is the severe skin toxicity seen in trials investigating bivatuzumab mertasine, given the high expression of CD44v6 in skin cells.⁶³ On-target, off-tumour side effects underscore the importance of appropriate target antigen selection. An ideal target antigen should be minimally expressed on normal tissue. On the other hand, off-target off-tumour side effects stem from the cytotoxic payloads. The most frequently used payload in ADCs in HNSCC is MMAE, which is associated with peripheral neuropathy and bone marrow suppression. Toxicities ensuing from the release of cytotoxic payloads are influenced by the type of linker (cleavable versus non-cleavable), antibody binding and histology of the cancer.⁸⁷

One strategy to reduce toxicity is to use an antibody prodrug that is only released in the tumour microenvironment. The CD71-directed ADC, CX2029, consists of a protease-activatable antibody prodrug linked to MMAE through a protease-cleavable val-cit linker and activated by tumour-associated proteases. The antibody prodrug has a masking domain which prevents antibody binding to normal tissue. An early-phase clinical trial investigating CX2029 in solid tumours included eight patients with HNSCC.⁸⁸ ORR observed across tumour subtypes was 12%, and grade 3 or 4 treatment-related events were 60% (mainly haematological abnormalities such as anaemia and neutropenia). Ozuriftamab vedotin (BA3021) is a so-called conditionally active biology ADC (CAB) and preferentially binds to the target antigen ROR1 under acidic conditions. Another strategy is using an ADC to target components within the tumour extracellular matrix rather than the tumour cells themselves.⁸⁹ PYX-201 is an ADC directed against extradomain-B fibronectin, which is found in the tumour extracellular matrix. The agent is under investigation as monotherapy and in combination with immunotherapy in the phase I PYX-201-101 trial (A First-in-Human, Open-label, Multicenter, Phase 1 Clinical Study to

Table 1: Selected ongoing trials investigating antibody–drug conjugates in head and neck squamous cell carcinoma^{35,51,55,56,62,66,69,77–80}

Study (ClinicalTrials.gov identifier)	Type of study and number of evaluable patients with HNC	Study drug	Conjugated payload and linker	Median PFS	ORR	mDOR	Common treatment-related adverse events
Nectin-4 targeting ADCs							
EV-202 (NCT04225117) ³⁵	Phase II, single-arm, tumour-specific cohort with R/M HNC n=46	Enfortumab vedotin	Monomethyl auristatin E	3.9 (2.8–4.7)	23.9%	NR	Alopecia, peripheral neuropathy, fatigue
CRB-701-01 (NCT06265727) ⁵¹	Phase II, single-arm, total pan tumour cohort n=31	CRB-701-01	Monomethyl auristatin E	–	–	–	Corneal epithelial lesions, hematuria, hypertriglyceridemia
Trop-2 targeting ADCs							
TROPiCS-03 (NCT03964727) ⁶²	Phase II, single-arm, R/M HNSCC n=43	Sacituzumab govitecan	Govitecan (SN38)/cleavable hydrazone linker	4.1 (2.6–5.8)	16%	4.2 (2.6–NR)	Neutropenia, leukopenia, anaemia
Tissue factor targeting ADCs							
InnovaTV 207 Part C (NCT03485209) ⁵⁶	Phase II, single-arm, n=43	Tisotumab vedotin	MMAE/val-cit cleavable linker	–	32.5%	5.6 (3.0–NR)	Ocular toxicity, peripheral neuropathy, bleeding events
HER2 targeting ADCs							
DESTINY-PanTumor02 (NCT04482309) ⁷⁷	Phase II, single-arm, n=24	Trastuzumab deruxtecan	Deruxtecan (TOP1 inhibitor)/ tetrapeptide cleavable linker	12.4	41.7%	22.1	Neutropenia, anaemia
MYTHOS trial ⁷⁸	Phase II, single-arm, R/M HER2+ salivary gland cancer, n=19	Trastuzumab deruxtecan	Deruxtecan (TOP1 inhibitor)/ tetrapeptide cleavable linker	15.9 (5.8–non-estimable)	68.4%	–	Neutropenia, lymphopenia, anaemia, drug-related ILD
NCT06003231 ⁷⁹	Phase II trial	Disitamab vedotin	MMAE/val-cit (cleavable)	NR	NR	NR	–
ITGB6 targeting ADCs							
SGNB6A-001 (NCT04389632) ⁶⁹	Phase Ia/Ib, single-arm, n=56	Sigvatatug vedotin	MMAE/val-cit (cleavable)	–	23.2%	5.5 (1.4–23.3)	Neutropenia
EGFR-targeting ADCs							
NCT04686834 ⁵⁵	IgG1 anti-EGFR/MMAE/cleavable	MRG003	MMAE/cleavable linker	–	40%	5.6	Leukopenia, neutropenia, hyponatremia
NCT02365662 ⁶⁶	Phase Ia, single-arm, n=5	Losatuxizumab vedotin (ABBV-221)	MMAE/cleavable	–	20%	–	Infusion-related reactions, fatigue
NCT05194982 ⁸⁰	Phase I study including NPC n=24, HNSCC n=13	BL-B01D1 (EGFRxHER3)	Ed-04, a camptothecin based alkaloid /val-cit (cleavable)	–	6.7%	–	Neutropenia, leukopenia, anaemia, thrombocytopenia

ADCs = antibody–drug conjugates; EGFR = epidermal growth factor receptor; EV = enfortumab vedotin; HER = human epidermal growth factor receptor; HNSCC = head and neck squamous cell lung cancer; IgG1 = immunoglobulin G1; ILD = interstitial lung disease; ITGB6 = integrin receptor subunit beta-6; mDOR = median duration of response; MMAE = monomethyl auristatin E; mPFS = median progression-free survival; N = number of patients; NPC = nasopharyngeal cancer; NR = no response; ORR = overall response rate; R/M = recurrent/metastatic; TOP1 = topoisomerase inhibitor 1; Trop-2 = trophoblast cell-surface antigen; val-cit = valine-citrulline.

Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of PYX-201 in Participants With Advanced Solid Tumors; ClinicalTrials.gov identifier: NCT05720117) and phase I/II PYX-201-102 trial (A Phase 1/2, Open-label, Global, Multicenter, Dose-Escalation and Dose-Expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of PYX-201 in Combination With Pembrolizumab in Participants With Advanced Solid Tumors; ClinicalTrials.gov identifier: NCT06795412), respectively.^{90,91} Preliminary data reported shows an overall favourable safety profile. Next-generation ADCs targeting nectin-4 have also been of interest, particularly those that attempt to improve efficacy and reduce treatment-related toxicities. CRB-701, for example, is a nectin-4-targeted ADC with every 3-week dosing schedule currently in clinical trials for HNSCC in addition to other tumour types such as cervical and urothelial cancers.⁵²

Other agents outside of traditional chemotherapeutic agents are being explored in the ADC design. Bacterial toxins, small molecules and immune modulators are examples of such agents under investigation in the development of next-generation ADCs.^{8,92}

Future perspectives of antibody–drug conjugate therapy in head and neck cancer

Leveraging the combination of ADCs with other pre-existing drug groups would be important for incorporating ADCs in the treatment paradigm for HNCs. One effective strategy in optimizing ADC activity, as evidenced by several studies, is the combination of immunotherapy with ADCs.^{35,52,54} It is thought that the addition of ADCs to immunotherapy may lead to increased recruitment of CD8+ effector T cells to tumour tissue. Findings from the InnovaTV 301/ENGOT-cx12/GOG-3057 study showed superior survival outcomes when TV was used in combination with anti-PD1 immunotherapy compared with the investigator's choice of chemotherapy in recurrent cervical cancer.⁹³ This ADC-immune checkpoint inhibitor strategy might result in similar outcomes in HNCs, with clinical trials investigating this strategy ongoing. The addition of chemotherapy to ADCs is another combinatorial strategy currently under investigation in HNSCC.⁹⁴ Most ADC treatment-related adverse events are related to the cytotoxic payloads.⁹⁵ Thus, the addition of chemotherapy to ADCs should be approached with caution due to the theoretically increased risk for toxicities. The combination of ADCs with other drug classes should be explored.

Another future consideration is the possibility of investigating ADCs in curative intent settings. ADC in combination with immunotherapy warrants investigation in the neoadjuvant setting, particularly as further data investigating immunotherapy in the neoadjuvant setting in locoregionally advanced HNC emerges.

Improvement in biomarker selection, particularly biomarkers predictive of ADC tumoural response, remains an important unmet need warranting further investigations. Although H-score and target expression for HNSCC thus far have not definitively demonstrated the ability to predict therapeutic response, in urothelial carcinoma, some translational studies have suggested that membrane expression may be important for

enriching therapeutic efficacy.⁹⁶ Ultimately, biomarker selection for these targeted ADCs will be critical in their development across tumour types, including HNC.

Conclusion

In conclusion, ADCs represent a new frontier in the treatment of HNSCC, with early promising efficacy signals as monotherapy in platinum- and immunotherapy-refractory disease across multiple targets, including nectin-4, tissue factor, integrin B6A and others. Studies evaluating combinations with immunotherapy and across other disease settings are ongoing. Further biomarker work to optimize patient selection is needed. □

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