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Emerging EGFR-Targeted Therapy in Head and Neck Cancer
A Review

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IMPORTANCE Head and neck squamous cell carcinoma (HNSCC) represents a significant global health burden with limited therapeutic options for patients with recurrent or metastatic disease. Epidermal growth factor receptor (EGFR) is overexpressed in most patients with HNSCC and represents a biologically compelling target, yet current EGFR-directed therapies have demonstrated only modest clinical benefit.

OBSERVATIONS This review describes the evolving landscape of EGFR-targeted therapeutics in HNSCC, including cetuximab-based combination regimens as well as novel agents, such as bispecific antibodies, antibody-drug conjugates, immune cell engagers, and adaptive cell therapies. The biological rationale behind these approaches, and the results of early-phase trials, are presented in this review. Notably, cetuximab and other EGFR-targeted therapies have demonstrated inferior efficacy in patients with human papillomavirus (HPV)–positive disease.

CONCLUSIONS AND RELEVANCE The emerging data of combinatorial approaches and novel EGFR-targeting therapeutic agents offer renewed optimism for patients with advanced HNSCC who have limited treatment options. Future progress will depend on novel agents leveraging a deeper understanding of tumor biology, innovative approaches to reduce on-target off-tumor toxic effects of targeting EGFR, and improving efficacy in the growing population of patients with HPV-positive HNSCC.

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Head and neck cancer is the seventh most common cancer worldwide, responsible for more than 660 000 new diagnoses and 325 000 deaths each year.[1-3] Approximately 90% of these cancers are classified as head and neck squamous cell carcinoma (HNSCC), which originates from the epithelial lining of the oral cavity, pharynx, and larynx. The incidence of HNSCC varies by region, with higher prevalence in areas of high tobacco, alcohol, and areca nut use. Recent epidemiological trends indicate a rising incidence of human papillomavirus (HPV)–related oropharyngeal cancers, while tobacco-related HNSCC has been declining consistently. HPV-positive (or p16-positive) HNSCC has a distinct molecular profile and a better prognosis compared to HPV-negative HNSCC.

Despite significant advances in the management of locally advanced HNSCC, treatment options for recurrent or metastatic (R/M) HNSCC are limited, and the prognosis remains poor. The lack of dominant driver molecular pathways and modest immune responses poses a great challenge in new drug development for HNSCC. The current standard therapeutic options for R/M HNSCC include cytotoxic chemotherapy, programmed cell death 1 (PD-1) immune checkpoint blockade therapy, and epidermal growth factor receptor (EGFR) blockade therapy. EGFR overexpression is observed in the majority of patients with HNSCC, particularly when the disease is not associated with HPV, and plays a crucial role in promoting tumor cell proliferation, survival, and metastasis, making it an ideal target for therapeutic intervention.[4] While traditional EGFR-targeted therapies have shown only modest efficacy and are typically used after standard chemotherapy and immune checkpoint inhibitors (ICIs), EGFR-targeted strategies have garnered renewed interest due to the emergence of novel therapeutic modalities. This review provides a comprehensive overview of the evolving landscape of EGFR-targeted therapies in HNSCC, ranging from established traditional treatments, novel combination strategies, and emerging EGFR-targeting agents under clinical investigation.

Discussion

EGFR Pathways in Head and Neck Cancer

The EGFR, also referred to as ERBB1, serves as the prototype of the EGFR family, which also includes ERBB2, ERBB3, and ERBB4. Structurally, EGFR consists of the extracellular domain, the transmembrane domain, the intracellular juxtamembrane region, the intracellular tyrosine kinase domain, and the C-terminal regulatory region.

EGFR-ligand binding triggers a conformational change exposing dimerization domains. The resulting homodimerization or heterodimerization (with other ERBB receptors) activates intracellular tyrosine kinase domains through transautophosphorylation, where each receptor phosphorylates tyrosine residues on the other. These phosphorylated residues act as docking sites for

downstream signaling molecules that activate multiple signaling cascades, including the RAS/RAF/MEK/ERK (MAPK), PI3K/AKT/mTOR, PLCγ/PKC, and JAK/STAT pathways.

EGFR overexpression occurs in 80% to 100% of patients with HNSCC, based on elevated messenger RNA, resulting from dysregulated p53, polymorphisms in intron 1 of *EGFR*, and *EGFR* amplification.[5] EGFR expression level is an independent negative prognostic factor in HNSCC.[6,7] Other pathogenic alterations include point variants, found in less than 3% of patients, with the majority occurring in exon 19, and rarely EGFRvIII, which is a variant that removes exons 2 to 7 of the extracellular domain, causing constitutive activation.[8,9]

Traditional EGFR Monotherapy

Conventional therapeutics targeting EGFR, such as monoclonal antibodies and small-molecule tyrosine kinase inhibitors (TKIs), have been evaluated in patients with HNSCC. Cetuximab is a chimeric IgG1 monoclonal antibody against the ligand-binding domain of EGFR, inhibiting ligand-induced downstream signaling activation and promoting internalization and degradation of the receptor. It also induces immune-mediated cytotoxic pathways through antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) via Fcγ engagement on natural killer (NK) cells and macrophages.[10]

The study by Bonner et al[11] led to cetuximab's 2006 approval for treating patients with locally advanced HNSCC as a radiosensitizing agent, demonstrating improved locoregional control (hazard ratio [HR], 0.68 [95% CI, 0.52-0.89]; *P* = .005), overall survival (OS) (HR, 0.74 [95% CI, 0.57-0.97]; *P* = .03), and progression-free survival (PFS) (HR, 0.70 [95% CI, 0.54-0.90]; *P* = .006) compared to radiation therapy alone. Cetuximab monotherapy later gained approval as a second-line option after platinum-based chemotherapy, based on a phase 2 study that demonstrated a modest objective response rate (ORR) of 13%.[12] In 2008, the EXTREME regimen, a combination of cetuximab with platinum-based doublet chemotherapy, received approval for R/M HNSCC based on OS (HR, 0.80 [95% CI, 0.64-0.99]; *P* = .04) and PFS (HR, 0.54 [95% CI, 0.43-0.67]; *P* < .001) improvement over chemotherapy alone.[13] Grade 3 skin reactions were observed in 20 of 219 patients (9%) who received the EXTREME regimen compared with 1 of 215 of those who received chemotherapy alone (*P* < .001).

Panitumumab is another EGFR-targeting monoclonal antibody but lacks ADCC activity owing to its IgG2-based structure. It demonstrated a modest efficacy as second-line monotherapy with an ORR of 4% (2 of 51) and a median (IQR) PFS of 1.4 (95% CI, 1.3-2.4) months.[14] The addition of panitumumab to platinum-based chemotherapy in the first-line setting failed to improve OS for patients with R/M HNSCC.[15]

Small-molecule TKIs competitively inhibit adenosine triphosphate binding at the kinase's active site in the intracellular domain, preventing the phosphorylation of downstream proteins. EGFR-targeting TKIs have been extensively evaluated in HNSCC. First-generation reversible EGFR-targeting TKIs, such as gefitinib and erlotinib, showed limited efficacy with a low ORR and no survival benefit.[16,17] Afatinib, a second-generation irreversible inhibitor targeting multiple ERBB family receptors (EGFR, ERBB2, ERBB4), achieved a modest ORR of 10.2% but failed to improve OS over standard chemotherapy in patients with disease refractory to platinum-based chemotherapy.[18] Notably, efficacy was restricted to HPV-negative tumors. Despite lacking formal regulatory approval for treating patients with HNSCC, afatinib is endorsed in the National Comprehensive Cancer Network guideline (category B).

HPV Status and Anti-EGFR Therapy

While anti-EGFR therapies are indicated regardless of HPV status, multiple studies have reported reduced efficacy in patients with HPV-positive HNSCC.[15,19,20] This disparity may be partly attributed to differences in the underlying molecular characteristics. HPV-positive tumors harbor higher rates of genetic alterations in EGFR downstream pathways, including *PIK3CA* variants and *KRAS* variants.[21-23] Additionally, *EGFR* amplification was exclusively observed in HPV-negative tumors within the Cancer Genome Atlas dataset. Emerging EGFR-targeted treatments are exploring innovative strategies to enhance the efficacy and overcome resistance in patients with both HPV-positive and HPV-negative HNSCC.

Emerging Approaches in EGFR-Targeted Treatments

This review highlights recent advances in EGFR-directed therapies, focusing on (1) combination regimens with existing EGFR agents (**Figure 1**; **Table 1**) and (2) novel EGFR-targeting therapeutics with innovative mechanisms (**Figure 2** and **Figure 3**; **Table 2**).

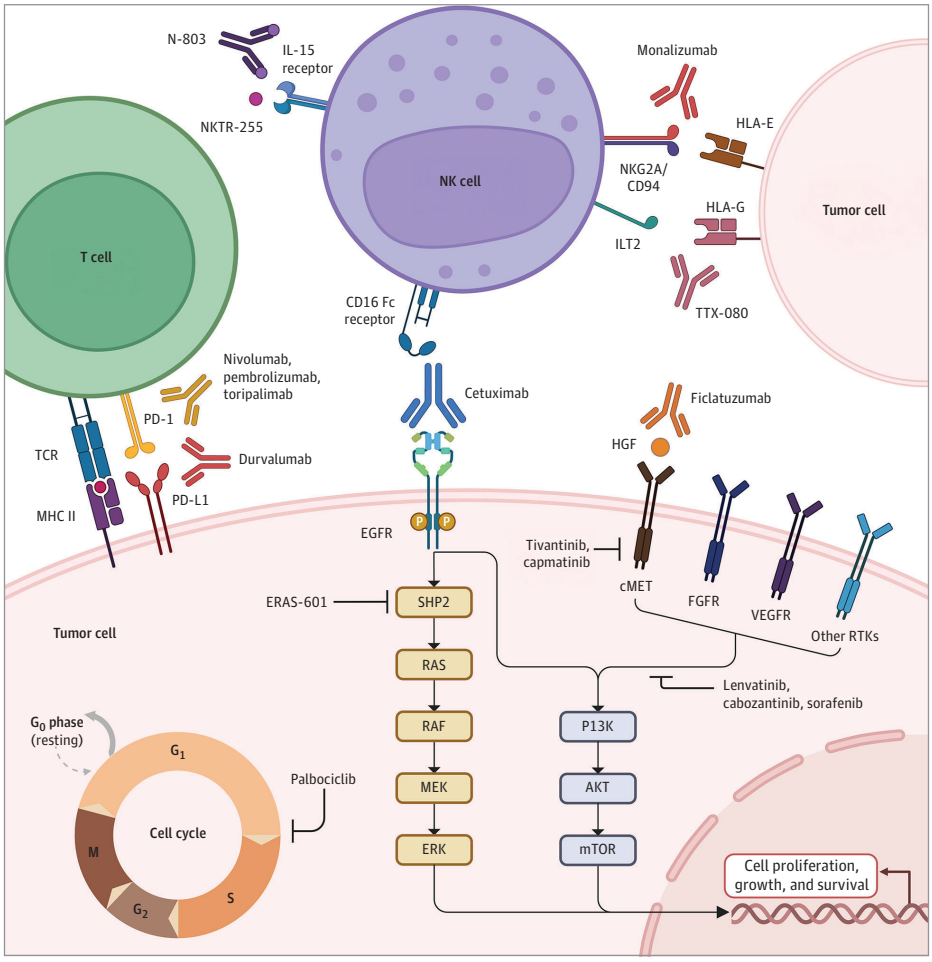
Cetuximab-Based Combination Regimens

PD-1/Programmed Cell Death Ligand 1 Inhibitors | PD-1/programmed cell death 1 ligand 1 (PD-L1) inhibitors are recommended as first-line therapy for patients with R/M HNSCC, either alone or in combination with platinum-based chemotherapy, which function by blocking T-cell exhaustion. These agents may have a synergistic effect with cetuximab through promoting antigen presentation and NK cell engagement. This interaction provides a solid rationale for combining PD-1/PD-L1 inhibitors with cetuximab to potentiate antigen-specific T-lymphocyte responses and improve therapeutic efficacy.

Cetuximab plus nivolumab showed promising results with an ORR of 22% and a median (IQR) PFS of 3.4 months in the second-line cohort and an ORR of 37% and a median (IQR) PFS of 6.1 months in the first-line cohort.[24] Biomarker analysis showed that p16/HPV negativity correlated with higher response rates (19 [41%] vs 7 [18%]; *P* = .02). Similarly, promising results were seen when cetuximab was combined with pembrolizumab, resulting in an ORR of 45%, median PFS of 6.5 (95% CI, 2.1 to NR) months, and median OS of 18.4 (95% CI, 11.0 to NR) months from mainly treatment-naive patients.[25] Again, most responses were seen in patients with HPV-negative disease, with an ORR of 57% (12 of 21).

The combination of cetuximab and other PD-1/PD-L1 ICIs, such as durvalumab and toripalimab, demonstrated similar efficacy, further supporting the hypothesis of an immune-based anticancer mechanism of cetuximab.[26,27] Consistent with other observational reports, a meta-analysis of multiple anti-PD-1–based HNSCC trials demonstrated that adding cetuximab to PD-1 inhibitors significantly improved ORR (15% [95% CI, 12%-18%] vs 46% [95% CI, 34%-58%]; *P* < .001) and 1-year OS rate (36% [95% CI, 32%-41%] vs 59% [95% CI, 47%-71%]; *P* < .001) in HPV-negative HNSCC but offered no advantage in HPV-positive disease.[46] A phase 3 randomized trial (NCT06589804) of pembrolizumab with or without

Figure 1. Cetuximab-Based Combination Regimens and Their Molecular Targets



EGFR indicates epidermal growth factor receptor; IL-15, interleukin 15; MHC, major histocompatibility; NK, natural killer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; RTK, receptor tyrosine kinase; TCR, T-cell receptor;

cetuximab has recently started enrollment and may provide data supporting the findings.

NK Cell Activators | NK cells play a crucial role in tumor immunosurveillance, with their activity regulated by a balance of activating and inhibitory receptors. Many solid tumors, including HNSCC, upregulate nonclassical major histocompatibility (MHC) molecules, such as HLA-E and HLA-G, which interact with inhibitory receptors NKG2A and ILT2/ILT4 on immune cells, respectively, allowing them to escape immune surveillance. Targeting these inhibitory axes can restore NK cell function and improve the antitumor immunity of cetuximab through enhanced ADCC.

The potential synergy between cetuximab and NK cell activators has been explored clinically through monalizumab, an anti-NKG2A antibody, which blocks the interaction with HLA-E. Despite the encouraging results from early phase trials, the phase 3 INTERLINK-1 study, which evaluated cetuximab with or without monalizumab, failed to meet the primary end point of OS in patients with R/M HNSCC after platinum chemotherapy and ICI therapy.[20,47] Interestingly, the response rate of 19% reported for cetuximab monotherapy was higher than the previously reported ORR of 13% in the pre-ICI era, which may be due to the effect of prior ICI exposure.[12]

Another strategy to restore NK cell function in HNSCC is targeting the ILT-HLA-G axis. TTX-080, a monoclonal antibody that neutralizes HLA-G, in combination with cetuximab, showed a preliminary efficacy signal in HPV-negative HNSCC, with an ORR of 57%, while patients with HPV-positive disease experienced an ORR of 0%.[28]

Interleukin 15 (IL-15) has a role in supporting NK cell proliferation and tumor killing through JAK/STAT and MAPK signaling, which provides the rationale for combining with monoclonal antibodies with ADCC effect. An ongoing study is investigating engineered NK cells, PD-L1 tumor-targeted high-affinity NK, combined with an IL-15 superagonist (N-803), along with cetuximab, in patients with advanced HNSCC (NCT06239220). Similarly, NKTR-255, a recombinant human IL-15 agonist, is being explored in combination with cetuximab.[29]

NK cell activators enhance cetuximab efficacy primarily by improving NK cell cytotoxicity, but they can also indirectly boost ADCP through the secretion of interferon-γ and tumor necrosis factor–α, which increases the phagocytic capacity of macrophages. However, tumors frequently evade ADCP through the CD47–SIRPα axis, where CD47 on tumor cells functions as a "do not eat me" signal, protecting them from macrophage-mediated phagocytosis. This makes the combination of cetuximab with an anti-CD47 agent an appealing approach.

Table 1. Key Clinical Trials of Cetuximab-Based Combination Regimens for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

Agent	Description	Study design (ClinicalTrials.gov identifier)	Intervention	Evaluable patients with R/M HNSCC, No. and characteristics	Efficacy	Participants with grade ≥3 TRAEs (discontinuation rate)
PD-1/PD-L1 inhibitors						
Nivolumab[24]	Anti-PD-1 IgG4 mAb	Phase 2 single-arm study (NCT03370276)	Cetuximab plus nivolumab	Overall cohort (N = 88) grouped into prior-therapy cohort (n = 45) (22 with HPV-positive disease) and treatment-naive cohort (n = 43) (18 with HPV-positive disease)	Prior-therapy cohort: median OS,[a] 11.4 mo; ORR, 22%; median PFS, 3.4 mo; treatment-naive cohort: median OS,[a] 20.2 mo; ORR, 37%; PFS, 6.1 mo	Prior-therapy cohort: NA; treatment-naive cohort: 23.3% (NA)
Pembrolizumab[25]	Anti-PD-1 IgG4 mAb	Phase 2 multiarm nonrandomized trial (NCT03082534)	Cetuximab plus pembrolizumab	Patients resistant to platinum-based chemotherapy (n = 33); other arms not reported to date	ORR,[a] 45%; PFS, 6.5 mo; DOR, 13.1 mo; OS, 18.4 mo	42.4% (15% discontinued)
		Phase 3 randomized clinical trial (NCT06589804)	Pembrolizumab with or without cetuximab	NA	NA	NA
Durvalumab[26]	Anti-PD-L1 IgG1 mAb	Phase 2 single-arm study (NCT03691714)	Cetuximab plus durvalumab	All patients resistant to platinum-based chemotherapy (N = 33) (10 received prior ICI, 1 prior cetuximab)	ORR,[a] 39%; median PFS, 5.8 mo; median OS, 9.6 mo	48.6% (NA)
Toripalimab[27]	Anti-PD-1 IgG4 mAb	Phase 1b/2 single-arm study (NCT04856631)	Cetuximab plus toripalimab	All patients resistant to platinum-based chemotherapy (N = 12) (9 with PD-L1 CPS ≥1)	ORR, 50%	0% (0% discontinued)
NK cell activators						
Monalizumab[20]	Anti-NKG2A IgG1 mAb	Phase 3 INTERLINK-1 randomized clinical trial (NCT04590963)	Cetuximab with or without monalizumab	All patients received prior platinum-based chemotherapy and ICI and no prior cetuximab (N = 264) (216 with HPV-unrelated disease)	Overall study population OS: HR, 1.03; *P* = .89; HPV-unrelated cohort OS[a]: HR, 1.00; *P* = .99	Monalizuamb: 38.6% (5.7% discontinued); placebo: 30.3% (1.6% discontinued)
TTX-080[28]	Anti-HLA-G IgG1 mAb	Phase 1a/1b study (NCT04485013)	Cetuximab plus TTX-080	All patients received prior ICI (N = 17) (7 with HPV-negative and 10 with HPV-positive disease)	HPV-negative cohort: ORR,[a] 57% (1 CR, 3 PR); median PFS, 23.9 mo; HPV-positive cohort: ORR,[a] 0%; median PFS, 9.1 mo	NA
N-803	IL-15 superagonist antibody cytokine fusion protein	Phase 1 study (NCT06239220)	Cetuximab plus PD-L1 tumor-targeted high-affinity NK plus N-803	NA	NA	NA
NKTR-255[29]	Recombinant IL-15 agonist	Phase 1b/2 study (NCT04616196)	Cetuximab plus NKTR-255	All patients received prior therapy (N = 3) (2 prior ICI, 1 prior cetuximab)	ORR, 0%; DCR, 66%	NA
Multireceptor TKIs						
Lenvatinib[30]	TKI against VEGFR/FGFR/PDGFRα	Phase 1/1b study (NCT03524326)	Cetuximab plus lenvatinib	Patients with R/M HNSCC or skin cancer (N = 9)	ORR, 67%; median PFS, 3.6 mo	NA
Cabozantinib[31]	TKI against AXL/c-MET/VEGFR	Phase 1 study (NCT03667482)	Cetuximab plus cabozantinib	Patients may have received prior therapy (N = 20) (19 received prior ICI, 19 prior platinum-based chemotherapy, 16 prior cetuximab)	Overall study population: ORR, 20%; DCR, 75%; median PFS, 3.4 mo; median OS, 8.1 mo; cetuximab-naive cohort: ORR, 50%	65% (NA)
Sorafenib[32]	TKI against VEGFR/PDGFR/RAF	Phase 2 randomized clinical trial (NCT00939627)	Cetuximab with or without sorafenib	Patients naive to sorafenib or cetuximab (N = 43)	Both arms: ORR, 8%; OS, NS; PFS, NS	NA

(continued)

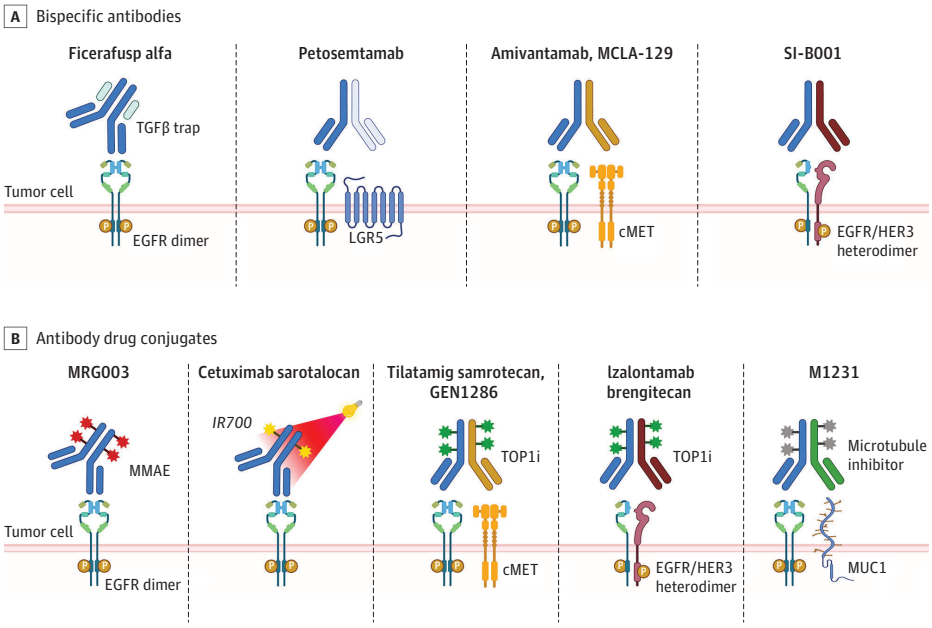
Table 1. Key Clinical Trials of Cetuximab-Based Combination Regimens for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC) (continued)

Agent	Description	Study design (ClinicalTrials.gov identifier)	Intervention	Evaluable patients with R/M HNSCC, No. and characteristics	Efficacy	Participants with grade ≥3 TRAEs (discontinuation rate)
c-MET/HGF inhibitors						
Ficlatuzumab[33]	Anti-HGF IgG1 mAb	Phase 2 randomized clinical trial (NCT03422536)	Ficlatuzumab with or without cetuximab	Patients resistant to cetuximab (N = 58); randomized to monotherapy (n = 26) or combination therapy (n = 32) (in combination therapy cohort, 16 had HPV-positive disease, 16 had HPV-negative disease)	Monotherapy closed early for futility; combination therapy cohort: ORR, 19%; median PFS, 3.7 mo; HPV positive: ORR, 0%; median PFS, 2.3 mo; HPV negative: ORR, 38% (2 CR, 4 PR), median PFS, 4.1 mo	NA
		Phase 3 FIERCE-HN randomized clinical trial (NCT06064877)	Cetuximab with or without ficlatuzumab	NA	NA	NA
Tivantinib[34]	TKI against c-MET	Phase 2 randomized clinical trial (NCT01696955)	Cetuximab with or without tivantinib	All patients received prior platinum-based chemotherapy and were cetuximab naive (N = 78); randomized to combination therapy (n = 40) or monotherapy (n = 38)	Combination therapy: ORR, 7.5% (1 CR); monotherapy: ORR, 7.9%; overall study population: median PFS, 4 mo; NS; median OS, 8 mo; NS; HPV-positive cohort ORR, 0%	NA
Capmatinib (INC280)	TKI against c-MET	Phase 1b study; terminated (NCT02205398)	Cetuximab plus capmatinib	NA	NA	NA
Other targeting agents						
ERAS-601	SHP2 inhibitor	FLAGSHP-1 phase 1 study (NCT04670679)	Cetuximab plus ERAS-601	NA	NA	NA
Palbociclib[35-37]	CDK 4/6 inhibitor	Phase 1 study (NCT03498378)	Cetuximab plus palbociclib plus avelumab	Patients with no prior therapy using EGFR inhibitor or PD-1 or PD-L1 inhibitor in the recurrent or metastatic setting (N = 12) (5 with HPV-positive disease)	ORR, 41.7% (3 CR, 2 PR); DCR, 75%; median PFS, 6.5 mo; median OS, NA	75% (NA)
		Phase 2 nonrandomized clinical trial (NCT02101034)	Cetuximab plus palbociclib	Patients may or may not have received prior therapy (N = 55); grouped into patients who are cetuximab-naive (n = 28) and cetuximab-resistant (n = 27)	HPV-unrelated disease: ORR,[a] 39%; median PFS, 5.4 mo, median OS, 9.5 mo; cetuximab naive: Median ORR,[a] 19%; median PFS, 3.7 mo; median OS, 6.3 mo	HPV-unrelated disease: 60% (NA); cetuximab naive: 44% (NA)
		PALATINUS phase 2 randomized clinical trial (NCT02499120)	Cetuximab with or without palbociclib	Patients received prior platinum-based chemotherapy and were cetuximab naive with HPV-unrelated disease (N = 125); grouped into monotherapy (n = 65) and combination therapy (n = 60)	Combination therapy: median OS,[a] 9.7 mo; median PFS, 3.9 mo; monotherapy: median OS,[a] 7.8 mo, median PFS, 4.6 mo	Combination therapy: 54.7% (NA); monotherapy: 15% (NA)
		Phase 3 randomized clinical trial (NCT04966481)	Cetuximab with or without palbociclib	All patients had CDK inhibitor 2A-altered, HPV-unrelated disease and received prior ICI (N = NA)	NA	NA

Abbreviations: CDK, cyclin-dependent kinase; CPS, combined positive score; CR, complete response; DCR, disease control rate; DOR, duration of response; HPV, human papillomavirus; HR, hazard ratio; ICI, immune checkpoint inhibitor; IL-15, interleukin 15; NA, not available; NS, not significant; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PR, partial response; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse events.

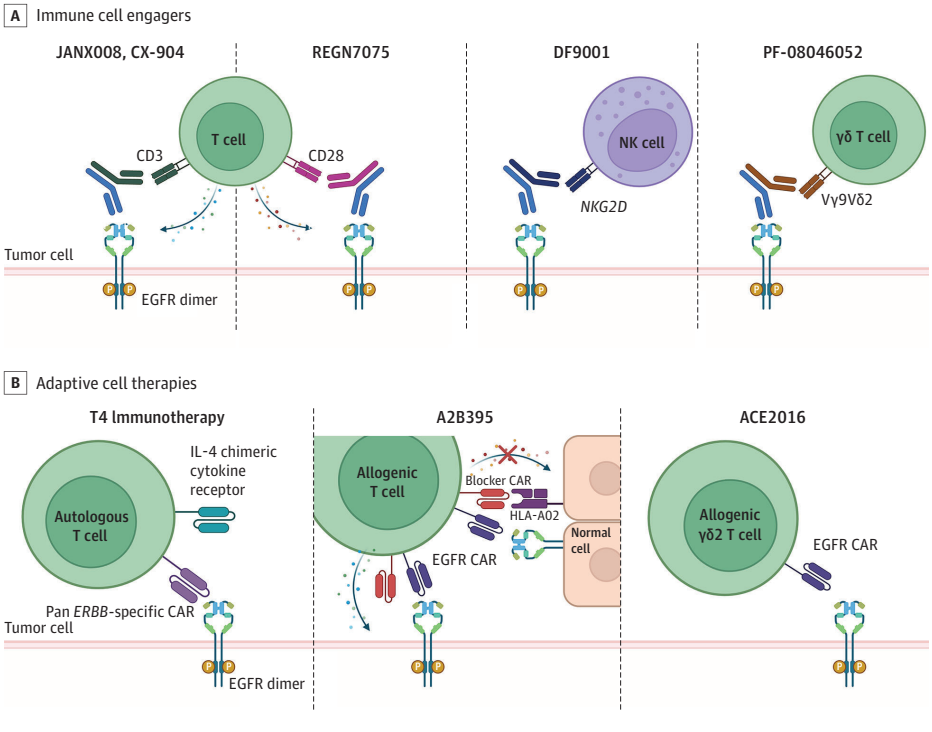
[a] Primary end point.

Figure 2. Bispecific Antibodies and Antibody-Drug Conjugates Targeting EGFR



EGFR indicates epidermal growth factor receptor; MMAE, monomethyl auristatin E; MUC1, mucin 1; TGF-β, transforming growth factor β; TOP1i, topoisomerase 1 inhibitor.

Figure 3. Immune Cell Engagers and Adaptive Cell Therapies Targeting EGFR



CAR indicates chimeric antigen receptor; EGFR, epidermal growth factor receptor; IL-4, interleukin 4; NK, natural killer.

Multireceptor TKIs | The rationale for combining multireceptor TKIs with cetuximab to treat patients with R/M HNSCC is based on the recognized role of alternative receptor tyrosine kinase activation in both intrinsic and acquired resistance to cetuximab.

Lenvatinib, a multireceptor TKI with activity against the VEGFR 1, 2, and 3; FGFR 1, 2, 3, and 4; PDGFRα; KIT; and RET pathways, was evaluated in combination with cetuximab. The unique activity of lenvatinib against FGFR 1, 2, 3, and 4, a recognized resistance mechanism for EGFR inhibition, seemed promising based on the initial responses from 9 evaluable patients. However, extensive thromboembolic events and atherosclerosis were observed in some patients, which are well-established adverse events of VEGF TKIs.[30]

Table 2. Key Clinical Trials of Novel Therapeutics Targeting Epidermal Growth Factor Receptor (EGFR) in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

Agent	Description	Study design (ClinicalTrials.gov identifier)	Intervention	Evaluable patients with R/M HNSCC, No. and characteristics	Efficacy	Participants with grade ≥3 TRAEs (discontinuation rate)
Bispecific antibodies						
Ficerafusp alfa (BCA-101)[38]	Bifunctional anti-EGFR mAb with TGF-β trap	Phase 1/1b study (NCT04429542)	Ficerafusp alfa plus pembrolizumab	All patients received first-line therapy for R/M HNSCC and had PD-L1 CPS ≥1 (N = 39)	ORR, 46%; HPV-negative disease: ORR, 57%	40% (14% discontinued)
		Phase 2/3 randomized clinical trial (NCT06788990)	Pembrolizumab with or without ficerafusp alfa	All patients received first-line therapy for R/M HNSCC, had PD-L1 CPS ≥1, and had HPV-negative disease (N = NA)	NA	NA
Petosemtamab[39]	Targets EGFR, LGR5	Single-arm phase 2 study (NCT03526835)	Petosemtamab plus pembrolizumab	All patients received first-line therapy for R/M HNSCC and had PD-L1 CPS ≥1 (N = 24) (4 had HPV-positive disease, 20 had HPV-negative disease)	ORR,[a] 67%; HPV-positive disease: ORR, 75%; HPV-negative disease: ORR, 65%	24% (4% discontinued)
		LiGeR-HN1 phase 3 randomized clinical trial (NCT06525220)	Pembrolizumab with or without petosemtamab	All patients received first-line therapy for R/M HNSCC and had PD-L1 CPS ≥1	NA	NA
		LiGeR-HN2 phase 3 randomized clinical trial (NCT06496178)	Petosemtamab vs investigator's choice of cetuximab, methotrexate, or docetaxel	All patients received prior ICI and platinum-based chemotherapy (N = NA)	NA	NA
Amivantamab	Targets EGFR, c-MET	OrigAMI-4 phase 1b/2 study (NCT06385080)	NA	NA	NA	NA
MCLA-129[40]	Targets EGFR, c-MET	Phase 1/2 study (NCT04868877)	MCLA-129	Patients whose prior treatment failed (N = 12)	ORR,[a] 17% (unconfirmed); DCR, 67%	NA
SI-B001[41]	Targets EGFR, ERBB3	S209 single-arm phase 2 study (NCT05044897)	SI-B001	All patients received prior ICI plus platinum-based chemotherapy (N = 9)	ORR,[a] 22.2%; DCR, 77.8%; median PFS, 2.7 mo	NA
		S206 single-arm phase 2 study (NCT05054439)	SI-B001 (plus paclitaxel if patients were paclitaxel naive)	All patients received prior ICI with or without platinum-based chemotherapy (N = 22)	ORR,[a] 45.5%; DCR, 81.8%; median PFS, 5.1 mo	NA
Antibody-drug conjugates						
MRG003[42]	EGFR targeting ADC with MMAE payload via valine-citrulline linker	Phase 2 study (NCT04868162)	MRG003, 2.0 mg/kg (DL1), or MRG003, 2.3 mg/kg (DL2)	Patients with EGFR-positive disease (N = 62) grouped into DL1 dosage (n = NA) and DL2 dosage (n = 14) (95.6% received prior platinum-based chemotherapy,76.1% prior ICI, 47.8% prior cetuximab)	DL1 dosage: data NA; DL2 dosage: ORR,[a] 43% (1 CR); DCR, 86%; median PFS, 4.2 mo; median OS, 11.3 mo	NA
		Phase 3 randomized clinical trial (NCT05751512)	MRG003 vs cetuximab/methotrexate	NA	NA	NA
Cetuximab sarotalocan (RM-1929)[43]	Cetuximab with IRDye700DX payload	Phase 1/2a study (NCT02422979)	Cetuximab sarotalocan	Patients received prior platinum-based chemotherapy unless contraindicated (N = 30) (21 received prior chemotherapy, 10 received prior ICI, 7 received prior cetuximab)	ORR, 26.7%; DCR, 80%	63.3% (NA)
		ECLIPSE phase 3 randomized clinical trial (NCT06699212)	Cetuximab sarotalocan plus pembrolizumab	First-line setting	NA	NA

(*continued*)

Table 2. Key Clinical Trials of Novel Therapeutics Targeting Epidermal Growth Factor Receptor (EGFR) in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC) (continued)

Agent	Description	Study design (ClinicalTrials.gov identifier)	Intervention	Evaluable patients with R/M HNSCC, No. and characteristics	Efficacy	Participants with grade ≥3 TRAEs (discontinuation rate)
Tilatamig samrotecan (AZD9592)	Bispecific ADC targeting EGFR and c-MET with TOP1i inhibitor payload	EGRET phase 1 study (NCT05647122)	Tilatamig samrotecan	NA	NA	NA
GEN1286 (PRO1286)	Bispecific ADC targeting EGFR and c-MET with TOP1i inhibitor payload	Phase 1/2 study (NCT06685068)	GEN1286	NA	NA	NA
Izalontamab brengitecan (BL-B01D1)[44]	Bispecific ADC targeting EGFR and ERBB3 with TOP1i inhibitor payload via cathepsin B cleavable linker	Phase 1 study (NCT05194982)	Izalontamab brengitecan	Patients received prior platinum-based chemotherapy (N = 20) (1 with disease progression on standard of care; 1 received prior TKI, 18 received prior ICI)	ORR, 15%; DCR 80%	36% (3% discontinued)
M1231	Bispecific ADC targeting EGFR and MUC1 with microtubule inhibitor payload	Phase 1 study (NCT04695847)	M1231	NA	NA	NA
Immune cell engagers						
JANX008	T-cell engager targeting EGFR and CD3	Phase 1 study (NCT05783622)	JANX008	NA	NA	NA
CX-904	T-cell engager targeting EGFR and CD3	Phase 1 study (NCT05387265)	CX-904	NA	NA	NA
REGN7075	T-cell engager targeting EGFR and CD28	COMBINE-EGFR-1 phase 1/2 study (NCT04626635)	REGN7075 plus cemiplimab	NA	NA	NA
DF9001	NK cell engager targeting EGFR and NKG2D	Phase 1 study (NCT05597839)	DF9001 with or without pembrolizumab	NA	NA	NA
PF-08046052 (SGN-EGFRd2)	T-cell engager targeting EGFR and T-cell receptor δ2	Phase 1 study (NCT05983133)	PF-08046052	NA	NA	NA
Adaptive cell therapies						
T4 immunotherapy[45]	Autologous panERBB-specific CAR T cells	Phase 1 study (NCT01818323)	T4 immunotherapy	Patients for whom no standard therapy remains or is suitable (N = 15)	ORR, 0%; DCR, 60%	0% (NA)
A2B395	Allogenic logic-gated EGFR CAR T cell	DENALI-1 phase 1/2 study (NCT06682793)	A2B395	NA	NA	NA
ACE2016	Allogenic EGFR targeting γδ2 T cells	Phase 1 study (NCT06415487)	ACE2016	NA	NA	NA

Abbreviations: ADC, antibody-drug conjugate; CAR, chimeric antigen receptor; CPS, combined positive score; CR, complete response; DCR, disease-control rate; HPV, human papillomavirus; ICI, immune checkpoint inhibitor; mAB, monoclonal antibody; MMAE, monomethyl auristatin E; MUC1, mucin 1; NA, not available; NK, natural killer; ORR, objective response rate; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; OS, overall survival; TGF-β, transforming growth factor β; TKI, tyrosine kinase inhibitor; TOP1i, topoisomerase 1 inhibitor; TRAE, treatment-related adverse events.

[a] Primary end point.

Cabozantinib, a TKI blocking the VEGFR 1, 2, and 3; cMET; AXL; and RET pathways, and sorafenib, a TKI blocking the VEGFR 1, 2, and 3; PDGFRβ; KIT; and RET pathways, were also evaluated in combination with cetuximab. But further development was hampered by the lack of robust efficacy or the high rate of treatment-related adverse events, including skin rash, fatigue, and liver toxic effects.[31,32]

c-MET/HGF Inhibitors | The c-MET receptor tyrosine kinase has been implicated in HNSCC progression, with c-MET overexpression being linked to advanced disease stage. Given the role of abnormal c-MET/HGF pathway activation in EGFR TKI resistance and the success of combined c-MET/HGF inhibition in lung cancers, similar combination strategies are being explored in HNSCC.

Ficlatuzumab, a monoclonal antibody inhibiting the HGF pathway, showed a potential signal of synergy with cetuximab with an ORR of 19% in patients with platinum and ICI-refractory R/M HNSCC.[33] All responses were seen in the HPV-negative subgroup with an ORR of 38%. A randomized phase 3 trial (FIERCE-HN) is ongoing to further evaluate the efficacy of this combination compared to cetuximab monotherapy in HPV-negative disease refractory to ICI and platinum chemotherapy.

Despite the appealing mechanism, not all combinations of cetuximab and HGF/c-MET targeting agents have been successful. A phase 2 randomized clinical trial of cetuximab with or without tivantinib, a MET TKI, reported an increase in toxic effects, especially myelosuppression, without improvement in response rate or survival.[34] Notably, all responses were seen in patients with HPV-negative disease in both treatment arms.

Other Targeting Agents | SHP2, an oncogenic nonreceptor tyrosine phosphatase, links receptor tyrosine kinase activation to RAS-MAPK signaling. This pathway activates through EGFR and alternative receptor tyrosine kinases involved in cetuximab resistance. The combination of ERAS-601, an allosteric SHP2 inhibitor, with cetuximab is under investigation in the FLAGSHP-1 trial.[48]

Cell-cycle dysregulation in HNSCC occurs through cyclin D1 (*CCND1*), cyclin-dependent kinase (CDK) inhibitor 2A (*CDKN2A*), or RB transcriptional corepressor 1 (*RB1*) alterations and may cause EGFR inhibition resistance. Palbociclib, a CDK 4/6 inhibitor, combined with cetuximab showed promising response rates in HPV-negative disease but failed to show OS improvement over cetuximab monotherapy in biomarker-unselected patients.[35,36] An ongoing phase 3 study (NCT04966481) is investigating cetuximab with or without palbociclib in patients with *CDKN2A*-altered, HPV-negative HNSCC.

Novel Agents Targeting EGFR

Bispecific Antibodies | Bispecific antibodies offer the advantage of engaging multiple targets, potentially enhancing antitumor activity and overcoming resistance mechanisms. Ficerafusp alfa (BCA101) is a bifunctional antibody targeting the EGFR and TGF-β1 pathways through the extracellular domain of transforming growth factor β (TGF-β) receptor 2. TGF-β promotes cancer progression via epithelial-mesenchymal transition and immune suppression, with epithelial-mesenchymal transition being implicated as a mechanism of cetuximab resistance in patients with HNSCC.[49] In an ongoing phase 1/1b study, ficerafusp alfa plus pembrolizumab demonstrated a response rate of 46% in treatment-naive R/M HNSCC. Notably, the response rate was higher in HPV-negative compared to HPV-positive disease (57% vs 18%).[38] A randomized phase 2/3 clinical trial (NCT06788990) comparing the efficacy of ficerafusp alfa plus pembrolizumab to pembrolizumab alone as first-line therapy in HPV-negative R/M HNSCC is ongoing.

Petosemtamab is a bispecific antibody targeting the EGFR and leucine-rich repeat 16 containing G protein-coupled receptor 5 (LGR5) pathways. LGR5 is a cancer stem cell marker with expression in 52% to 89% of patients with HNSCC and association with tumor self-renewal, metastasis, and resistance to chemotherapy.[50] Petosemtamab is thought to inhibit tumor growth by blocking EGFR-dependent signaling, promoting LGR5-mediated cointernalization and degradation of EGFR, and enhancing ADCC and ADCP through its low-fucose Fc domain. Petosemtamab demonstrated a robust monotherapy activity with an ORR of 36%, median (IQR) PFS of 5.0 (3.2-6.8) months, and median (IQR) OS of 11.5 (7.2-20.6) months in patients with R/M HNSCC whose disease progressed following treatment with platinum-based chemotherapy and ICI therapy.[51] The combination of petosemtamab with pembrolizumab in the first-line setting resulted in a response rate of 67%.[39] Notably, responses were seen in patients with both HPV-positive and HPV-negative disease. Two phase 3 randomized clinical trials that include patients with HPV-positive and HPV-negative disease are underway: petosemtamab monotherapy vs standard single-agent in the second-line or third-line setting (LiGeR-HN2) and pembrolizumab with or without petosemtamab as first-line therapy in R/M HNSCC (LiGeR-HN1).

Amivantamab is a bispecific antibody targeting the EGFR and c-MET pathways. An ongoing phase 1b/2 clinical trial (NCT06385080) is investigating amivantamab alone and in combination with standard-of-care treatments. MCLA-129 is another EGFR and c-MET bispecific antibody, which reported a preliminary efficacy but a high infusion-related reaction rate, leading to discontinuation of further development.[40]

SI-B001 is a bispecific antibody that targets the EGFR and ERBB3 pathways. While ERBB3 lacks intrinsic kinase activity, it forms heterodimers with other ERBB family members, particularly ERBB2, and activates downstream signaling involved in cell proliferation and survival. Given its suggested role in EGFR-directed therapy resistance, ERBB3 has emerged as an important target, and SI-B001 combined with taxane therapy has demonstrated an encouraging efficacy in HNSCC refractory to platinum chemotherapy and ICI therapy.[41]

Antibody-Drug Conjugates | Antibody-drug conjugates (ADCs) combine an antibody, linker, and payload to deliver cytotoxic drug payloads with high specificity to target cells. ADCs have seen immense success in solid tumors with multiple new approvals in recent years, yet none have been approved to treat patients with R/M HNSCC. While various antigens are being explored for ADCs in HNSCC, we will focus on a few key examples that target EGFR.

MRG003 is an ADC with an IgG1 monoclonal antibody with an affinity to EGFR higher than that of cetuximab, a valine-citrulline cleavable linker, and monomethyl auristatin E (MMAE), a highly toxic antimicrotubule payload. In a phase 2 study, MRG003 demonstrated a single-agent response rate of 30.6% in heavily pretreated patients with EGFR-positive HNSCC.[42] A randomized phase 3 study (NCT05751512) evaluating MRG003 in comparison with standard cetuximab or methotrexate as second-line and third-line therapy is ongoing.

The development of EGFR-targeting ADCs to treat patients with HNSCC faces the challenge of overcoming on-target off-tumor toxic effects. While many ADCs in clinical development use tubulin or topoisomerase 1 inhibitors (TOP1i) as their payloads, some use novel approaches using noncytotoxic payloads to tackle this issue. For example, cetuximab sarotalocan combines cetuximab with IRDye700DX, a unique payload activated by near-infrared light illumination at the tumor site.[43] A phase 3 trial (ECLIPSE, NCT06699212) for cetuximab sarotalocan plus pembrolizumab as first-line treatment for patients with locoregional recurrent HNSCC is ongoing.

To enhance the efficacy of conventional single antigen–targeting ADCs, a multiantigen targeting strategy is being explored. Tilatamig samrotecan (AZD9592) and GEN1286 (PRO1286) are bispecific ADCs targeting EGFR and c-MET, designed to deliver TOP1i payloads. Tilatamig samrotecan was engineered with a higher affinity for c-MET compared to EGFR (greater than 15-fold) to reduce EGFR-driven toxic effects.[52] It is under investigation in a phase 1 study (EGRET).[53] GEN1286 is also in early-phase clinical investigation (NCT06685068) and comprises a monovalent IgG1 fine-tuned affinity for EGFR and c-MET, conjugated with a TOP1i by a hydrophilic linker.

Other targets are also being explored for bispecific ADCs. Izalontamab brengitecan (BL-B01D1) is a bispecific tetravalent ADC targeting EGFR with a high affinity and ERBB3 with a low affinity, delivering a TOP1i payload.[44] M1231is a bispecific ADC targeting the EGFR and mucin 1 (MUC1), a transmembrane glycoprotein coexpressed with EGFR in HNSCC.

Immune Cell Engagers | Immune cell engagers are bispecific molecules that redirect T cells or NK cells to kill cancer cells by binding both a tumor-associated antigen and an immune receptor (eg, CD3, CD28, or CD16). The dual-targeting ensures specificity, limits off-target effects, and can trigger a bystander effect, allowing immune cells to eliminate nearby tumor cells lacking the tumor-associated antigen.[54]

T-cell engagers (TCEs) are a subclass of immune cell engagers that redirect cytotoxic T cells by binding both the tumor-associated antigen and CD3, enabling MHC-independent activation. Early-generation TCEs often caused cytokine release syndrome, necessitating step-up dosing. JANX008 and CX-904 are conditionally activated bispecific TCEs targeting EGFR and CD3 with protease-cleavable masking domains, remaining inactive in circulation until activated by tumor-associated proteases. This enables localized T-cell engagement and reduces the risk of cytokine release syndrome.[55,56] Both are being investigated in phase 1 clinical trials (NCT05783622, NCT05387265) with results yet to be reported.

While CD3-directed TCEs rely primarily on T-cell receptor–mediated T-cell redirection, REGN7075 targets CD28, which provides a costimulatory signal crucial for full T-cell activation, expansion, and sustained antitumor activity. An ongoing phase 1/2 study is evaluating REGN7075 in combination with cemiplimab, a PD-1 inhibitor (NCT04626635).

NK cells and γδ T cells are alternative targets for immune cell engagers that offer the advantage of allogenic compatibility without the risk of graft-vs-host disease. DF9001 targets EGFR and NKG2D, a receptor expressed on NK cells, CD8-positive T cells, and γδ T cells, and is being evaluated as monotherapy and in combination with pembrolizumab (NCT05597839).[57] PF-08046052 (SGN-EGFRd2) is a bispecific antibody that targets EGFR and the γ9δ2 T-cell receptor on γδ T cells, directing their intrinsic antitumor activity to EGFR-expressing cancer cells while requiring a secondary phosphoantigen stress signal to minimize off-target effects. It also binds to EGFR extracellular domain epitopes distinct from cetuximab's to address cetuximab-induced escape variants. A phase 1 clinical trial (NCT05983133) is evaluating PF-08046052 in selected EGFR-expressing tumors.

Adaptive Cell Therapies | Adaptive cell therapy is a type of immunotherapy using immune cells engineered to target specific cells of interest, typically involving isolation of immune cells from patients (autologous) or donors (allogeneic), ex vivo expansion with or without genetic manipulation, and reinfusion of manufactured cells. While chimeric antigen receptor (CAR) T-cell therapy has transformed treatment for hematologic cancers, applications in solid tumors remain limited due to manufacturing complexity, lack of tumor-specific antigens, inefficient cell trafficking and infiltration, and an immunosuppressive tumor microenvironment.[58] Next-generation CAR T cells use a variety of strategies to overcome these challenges.

The T4 immunotherapy study (NCT01818323) evaluates autologous CAR T cells targeting ERBB receptors in HNSCC. Patient-derived T cells are engineered to express 2 synthetic peptides: T1E28ζ (pan-ERBB chimeric peptide derived from the epidermal growth factor [EGF] protein) and 4αβ (IL-2/IL-15 signaling on IL-4 binding), enabling selective expansion in the presence of IL-4 during manufacturing. To enhance local activity and reduce systemic toxic effects, T4 CAR T cells are delivered intratumorally. Preliminary phase 1 data demonstrated feasibility, safety, and undetectable peripheral T4 CAR T cells.[45]

Logic-gated CAR T cells require 2 or more signals for activation, improving specificity and reducing off-tumor toxic effects. A2B395 is an allogeneic, logic-gated CAR T-cell therapy targeting EGFR with an HLA-binding inhibitory receptor creating an "AND-NOT" logic gate. EGFR-expressing cells lacking HLA-A02, through loss of heterozygosity in approximately 30% of solid tumors, are targeted while normal cells expressing HLA-A02 are protected. The DENALI-1 trial (NCT06682793) is enrolling patients with EGFR-expressing solid tumors and HLA-A02 loss of heterozygosity.

While αβ T-cell therapies often require MHC knockout and T-cell receptor removal to prevent graft-vs-host disease or rejection for allogeneic use, γδ2 T cells recognize antigens independently of HLA, potentially lowering these risks.[59] ACE2016, an allogeneic γδ2 T-cell therapy with conjugated anti-EGFR antibodies, is under investigation in the first human trial (NCT06415487).[60]

Conclusions

Recent advances have revitalized EGFR as a therapeutic target in HNSCC, with encouraging results from cetuximab-immunotherapy combinations and novel bispecific antibodies now progressing to registration trials. Despite this promise, significant challenges remain, including on-target off-tumor toxic effects from EGFR expression in normal tissues and limited efficacy in the growing population of patients with HPV-positive disease. The path forward will require a deeper understanding of tumor biology, resistance mechanisms, and tailored strategies for distinct tumor subtypes to meaningfully improve outcomes in this challenging cancer.

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