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Integrating Novel Therapeutic Monoclonal Antibodies into the Management of Head and Neck Cancer

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Abstract

Head and neck squamous cell carcinoma (HNSCC) is an immunosuppressive malignancy. Interest in developing novel immunotherapies in HNSCC has been reawakened by the success of cetuximab, a therapeutic monoclonal antibody (mAb) against the epidermal growth factor receptor which likely relies on immune as well as anti-signaling mechanisms. We focus on novel therapeutic mAb in current clinical development against established mechanisms of immune evasion in HNSCC, targeting: tumor antigens (TA), with resultant potential to induce antibody-dependent cell-mediated cytotoxicity and T cell activation; immunosuppressive cytokines; co-stimulatory Tumor Necrosis Factor (TNF)-family receptors; and co-inhibitory immune checkpoint receptors. Clinical trials of immunotherapeutic mAb as monotherapy, in combination with cytolytic standard therapies exposing TA or in combination with other immunomodulatory mAb, are urgently needed in HNSCC.

Introduction

Head and neck squamous cell carcinoma (HNSCC), the sixth leading incident cancer worldwide[1], has been recognized as an immunosuppressive disease. HNSCC induces a tumor-permissive cytokine profile[2, 3], qualitative and quantitative lymphocyte deficiencies[4–6], anergy in major immune effector cells[7–10], and poor antigen-presentation.[11–13] An increasing proportion of HNSCC in North America and Europe is caused by oral infection with human papillomavirus (HPV)[14–16], rather than the classic exposures of tobacco and alcohol. Whether caused by environmental carcinogenesis or transformation by HPV oncogenes, HNSCC thwarts immune surveillance, recognition and destruction, which must be reversed to maximize therapeutic efficacy.

Early clinical trials in HNSCC exploited available immunostimulatory cytokines, which faltered clinically due to disinterest in local delivery or prohibitive systemic toxicity.[17–19] Three parallel advancements have reawakened enthusiasm for the development of novel immunotherapies in HNSCC: 1) realization of the contribution of immune mechanisms to the clinical activity of cetuximab[20, 21], the monoclonal antibody (mAb) against the

epidermal growth factor receptor (EGFR) approved in HNSCC by the U.S. Food and Drug Administration (FDA) in 2006; 2) progressive preclinical insights into specific, targetable immune escape mechanisms important to the survival of HNSCC tumors; 3) previously unimagined clinical responses in non-small cell lung cancer (NSCLC), a non-immunogenic solid tumor similar to HNSCC, to phase I therapy with an immune checkpoint mAb.[22, 23] In the interest of prioritizing rational clinical investigations, this review will examine the immunotherapeutic mAb currently in human trials for cancer patients, in the specific context of immune escape mechanisms in HNSCC. Immunotherapeutic mAbs will be conceptually divided into those which target tumor antigens (TA), immunosuppressive cytokines, TNF receptor (TNFR) costimulatory molecules, or immune checkpoint receptors (Table 1).

TA-Targeted mAbs

Although cytotoxic T lymphocytes (CTL) specific for p53, EGFR, or the HPV E7 oncoprotein have been detected in HNSCC patients,[24–26] the nascent adaptive immune response is ineffective. Due to selective loss of human leukocyte antigen (HLA) I and functional deficiency in antigen processing machinery, HNSCC tumor cells avoid recognition and destruction by extant TA-specific CTLs.[11, 27] Recent evidence confirms that cetuximab, a chimeric, IgG1-isotype mAb which blocks the extracellular domain of EGFR, potentiates both innate and adaptive immune responses against endogenous TAs[20] – indicating that TA-targeted mAb have broader immunogenic potential than is currently being exploited.

In HNSCC, cetuximab development was compelled by the frequent finding of over-expression of EGFR correlating with advanced stage, radiation resistance, and poor survival.[28, 29] Indeed, cetuximab increased response rate and overall survival combined with radiation in locally advanced HNSCC, or with platinum-based chemotherapy in recurrent HNSCC, ultimately gaining FDA approval for both indications.[30, 31] Cetuximab is frequently described as the first molecularly targeted agent in HNSCC, a deserved appellation; yet certain conundrums prompted the search for additional, immunologic mechanisms of action. First, despite over-expression of EGFR in more than 90% of HNSCC[32], cetuximab monotherapy demonstrates a response rate of only 10–15% in recurrent disease.[33] Moreover, over-expression or amplification of EGFR does not predict clinical benefit from cetuximab, and activating EGFR mutations are not found in HNSCC, underscoring the absence of a predictive molecular marker.[34, 35] Second, non-immunogenic small molecule inhibitors of the intracellular tyrosine kinase domain of EGFR have not demonstrated clinical benefit in randomized trials in HNSCC.[36, 37] Third, despite rapid abrogation of EGFR phosphorylation and tumor proliferation upon mAb exposure in preclinical models[38], *in vitro* tumor cell apoptosis or lysis requires the presence of lymphocytes.[11]

Dissection of the immunologic actions of cetuximab provides guidance for further development of TA-targeted mAb in HNSCC. Specifically, cetuximab-coated HNSCC tumor cells activate the antibody-binding receptor (FcγR IIIa) on natural killer (NK) cells, the major effector cell of innate immunity. Binding between the constant Fc component of the IgG mAb and FcγR IIIa instigates antibody-dependent cellular cytotoxicity

(ADCC).[21, 39, 40] Moreover, activation of FcγR IIIa upregulates NK cell secretion of IFN-γ, an immunostimulatory cytokine which promotes maturation of dendritic cells (DC). NK-DC cross-priming enhances antigen processing and presentation by DCs, ultimately promoting activation of TA-specific CTL. Of interest, the repertoire of TA-specific CTLs induced by cetuximab is not restricted to EGFR. Preclinical modeling also demonstrates cross-priming of CTLs specific for MAGE-3, a second TA.[20] These findings suggest three broad and interacting strategies to augment the therapeutic potential of cetuximab and other TA-targeted mAb: 1) potentiating ADCC; 2) promoting DC maturation; 3) releasing suppression of CTLs.

Fundamentally, ADCC requires binding between FcγR IIIa on NK cells and the IgG Fc region on the mAb-coated tumor cell, an interaction which may be influenced by an intrinsic patient factor, FcγR polymorphisms, or a drug factor, the IgG isotype subclass. Differential patient response to mAb including rituximab in lymphoma (anti-CD20), trastuzumab in breast cancer (anti-HER2), and cetuximab in colorectal cancer has been correlated with FcγR IIIa polymorphisms, thought to reflect Fc binding affinities.[41–43] While these findings raise the possibility of patient selection for mAb therapy by ADCC capacity, a similar preclinical correlation in HNSCC was not validated in patients. The VV FcγR IIIa genotype favorably influenced NK cytolysis of HNSCC tumor cells in ADCC assays[44], but was not associated with cetuximab outcome in HNSCC patients where it was found in only 5% of cases.[20] Thus, enhancing mAb activity by patient selection for favorable polymorphisms is not currently suitable for the clinic.

The FcγR binding partner, the IgG Fc subclass of the mAb itself, appears increasingly important to the efficacy of TA-targeted mAb. In HNSCC, the case in point is panitumumab. Panitumumab is a fully humanized IgG2 mAb specific for the same EGFR epitope as cetuximab. In contrast to IgG1, the IgG2 isotype has a low binding affinity for FcγR IIIa, and is ineffective at mediating ADCC by NK cells.[20, 21, 45] IgG2 does bind FcγR IIa on myeloid-lineage lytic cells, triggering ADCC, however the clinical importance of this mechanism is unclear.[45] Of note, panitumumab does not induce the NK-DC cross-priming underlying the adaptive immune response.[20] Unlike cetuximab, panitumumab did not improve survival when combined with platinum-based chemotherapy in recurrent HNSCC, although a secondary analysis noted improvement in patients with p-16 negative tumors, a surrogate marker for HPV within the oropharynx.[46] In a phase II trial in the locally advanced setting, panitumumab-radiotherapy was inferior to cisplatin-radiotherapy for the primary endpoint of 2-year locoregional control.[47] The failure of panitumumab to make therapeutic inroads in HNSCC, despite identical anti-signaling properties to cetuximab, has further elevated the hypothesis that immune mechanisms are critical to cetuximab's activity. This insight should inform development of subsequent TA-targeted mAb in HNSCC, with prioritization of IgG1 subclass drugs.

Innate or acquired resistance to cetuximab is frequently associated with compensatory signaling by alternate growth factor receptors, e.g. HER2, HER3, cMet, and insulin growth factor receptor (IGFR).[48] In this light, TA-specific mAb targeting parallel growth factor receptors are rational candidates for investigation in HNSCC. Representative IgG1-isotype mAb are in clinical development. Trastuzumab and pertuzumab target HER2-overexpressing

breast cancer; co-targeting HER2 with both drugs in a HER2-expressing xenograft model augmented ADCC.[49] Thus, combinatorial mAb strategies are desirable, and investigation of immune correlates will be critical to guiding development. For example, AV-203, an anti-HER3mAb, is under phase I evaluation in combination with cetuximab (NCT01603979). This trial includes a cetuximab-resistant HNSCC cohort, a setting where both signaling and immune resistance mechanisms may occur. While cixutumumab, an anti-IGFR mAb failed to improve PFS alone or in combination with cetuximab as compared to cetuximab monotherapy[50], it is now under investigation in a window-of-opportunity trial in patients with operable HNSCC (NCT00957853). In this model, both signaling and immune mechanisms could be investigated in paired tumor specimens.

While FcγR-Fc binding is required for ADCC, the NK cell's capacity for cytolysis is significantly amplified by the immunostimulatory cytokines IL-12 and TNFα, secreted by activated DCs following TA uptake and presentation. In the development of IgG1-isotype mAb in HNSCC, judicious co-investigation of two ADCC adjuncts would appear rational: exogenous cytokines, such as IL-12, or toll-like receptor (TLR) agonists. Intravenous IL-12 has been studied in phase I combination with paclitaxel and trastuzumab in HER2-expressing cancers, exploiting the ADCC mechanism.[51] In operable HNSCC, neoadjuvant tumoral injections of IL-12 resulted in migration of NK cells to the primary tumor and draining lymph nodes, and increased IFN-γ secretion[52]; these promising immunomodulatory findings underpin an ongoing phase II study of cetuximab and subcutaneous IL-12 in recurrent HNSCC (NCT01468896). VTX-2337, a TLR8 agonist, activates innate immunity, amplifying phagocytosis, immunostimulatory cytokine secretion, and antigen presentation by DCs.[53–56, 57] Randomized trials evaluating cetuximab with/without VTX-2337 (NCT01334177) or platinum-based chemotherapy and cetuximab, with/without VTX-2337 (NCT01836029), are recruiting.

Cytokine-Targeted mAbs

The immunosuppressive cytokine profile of the HNSCC microenvironment is driven by aberrant regulation of the signal transducer and activator of transcription (STAT) family. HNSCC tumors and immune cells demonstrate deficient immunostimulatory STAT1 signaling, and excess immunosuppressive STAT3 signaling.[3, 58, 59] The STAT1/STAT3 activation imbalance results in dominant production of TGF-β1, IL-6, IL-10 and vascular endothelial growth factor (VEGF) by HNSCC tumors and tumor-associated macrophages.[60] These cytokines inhibit NK cell cytolysis, DC maturation, and CTL activation while inducing regulatory T cells (Treg).[7, 58, 61–63] Tumor-associated fibroblasts reinforce immunosuppression through secretion of hepatocyte growth factor (HGF), a paracrine cytokine which promotes HNSCC proliferation and metastasis through cMet signaling while inhibiting DC maturation.[64, 65] As immunosuppressive cytokines in sera of HNSCC patients correlate longitudinally with poor response and relapse[2], cytokine-neutralizing mAb may be particularly relevant therapeutic adjuncts. Specifically, mAb targeting VEGF and HGF are in clinical development in HNSCC, whereas mAb neutralizing TGF-β1 and IL-6 are under study in other malignancies.

Bevacizumab is an anti-VEGF IgG1 subclass mAb which increased survival when combined with carboplatin-paclitaxel chemotherapy in advanced NSCLC,[66] and VEGF and microvascular density are negative prognostic indicators in HNSCC.[67, 68] While the phase II combination of bevacizumab-cetuximab had disappointing efficacy in recurrent HNSCC[69], a randomized phase III ECOG trial testing frontline platinum-based chemotherapy with/without bevacizumab is ongoing (NCT00588770).

Ficlatuzumab (IgG1) and rilotumumab (IgG2) are humanized mAb which neutralize HGF, preventing ligation of the oncogenic cMet receptor. As HGF/cMet signaling is implicated in resistance to standard HNSCC therapies[70–72], trials combining these agents with cetuximab, cisplatin and/or radiation are in development. Bearing in mind that HGF inhibits DC maturation, companion immune biomarkers should be incorporated into early phase design.

Fresolimumab is an IgG4 subclass mAb which neutralizes all TGF-β isoforms, under phase I study in myeloproliferative disorders, kidney cancer and melanoma (NCT01291784; NCT00356460). In a HNSCC xenograft model, adding a preclinical TGF-β mAb to cetuximab prevented resistance to NK cell cytolysis mediated by TGF-β1.[73] Siltuximab is an IgG1 chimeric mAb against IL-6, under phase II evaluation in kidney cancer[74], prostate cancer and multiple myeloma (NCT00385827; NCT01484275). As TGF-β1 and IL-6 are key immunosuppressive STAT3 cytokines, and no direct STAT3 inhibitors are available, both agents are of significant interest in HNSCC.

TNFR-Family Targeted mAbs

Ultimately, effective immune eradication of tumor requires priming of the TA-specific, HLA-I restricted, CD8(+) CTL by APCs. Binding of the T cell receptor (TCR) by its cognate TA-HLA I complex is insufficient for differentiation of the naïve CTL. TA recognition can be followed by anergy vs. activation, depending upon the balance of co-inhibitory vs. co-stimulatory intercellular signaling across the lymphocyte-APC “immune synapse” (Figure 1). Priming, cytolytic capacity, and memory cell differentiation require predominance of co-stimulatory signaling by the TNFR superfamily of accessory surface receptors. Agonist mAb to TNFR co-stimulatory members including CD40, OX40, and CD137 are in early clinical development.[75] In most cases, these mAb demonstrate synergy with other immunomodulatory therapies including the cytolytic modalities of chemotherapy and radiation; TA-targeted mAb; or T cell checkpoint inhibitors.

Signaling by CD40, a TNFR expressed by APCs, dramatically magnifies APC priming capacity. Binding of CD40 on DCs by its ligand CD40L, present solely on activated CD4(+) T helper cells, triggers immunostimulatory cytokine secretion, upregulation of antigen processing machinery, and CTL priming. In HNSCC, CD40/CD40L expression on APCs/lymphocytes decreases with advancing stage. Moreover, monocytic CD40 expression increases post-operatively, suggesting this pathway is actively suppressed during HNSCC immune evasion.[76] Agonist CD40 mAb have been developed to substitute for the critical role of the T helper cell in licensing DC.[77] A point of theoretical controversy is that HNSCC cell lines and human tumors express CD40, where ligation promotes proliferation and angiogenesis in preclinical models.[78, 79] Nonetheless, in the first clinical trial evaluating CD40 agonism with recombinant human CD40L, a patient with refractory HNSCC

sustained a long-term complete response.[80] CP-870,893, a humanized IgG2 mAb with CD40 agonist activity, demonstrated efficacy in melanoma during phase I evaluation.[81] CP-870,893 may be more active when added to treatments which release TA, such as cytotoxic chemotherapy or radiation. Phase I combinations with carboplatin-paclitaxel or gemcitabine showed immunologic and clinical responses.[82, 83]

Tumor-infiltrating lymphocytes (TILs) in HNSCC display an anergic phenotype associated with low expression of the co-stimulatory TNFRs, OX40 and CD137.[10] OX40 signaling supports survival, clonal expansion, inflammatory cytokine production, and memory function in T helper cells; conversely, suppression by T regulatory cells (Tregs) is relieved.[84, 85] Although not explicitly evaluated in HNSCC preclinical models, OX40 agonism has arrested both immunogenic and non-immunogenic solid tumors[86]; however as with CD40, more robust responses were seen upon combination with cytolytic treatments.[87] An OX40 agonist mAb is under phase I study in combination with radiation in breast and prostate cancers (NCT01642290; NCT01303705). CD137 signaling enhances proliferation, inflammatory cytokine production, cytolytic capacity and survival of CTLs[88]; like OX40, ligation of CD137 on Tregs can paradoxically release immunosuppression.[89] CD137 on NK cells also co-stimulates ADCC. A significant proportion of HNSCC patients receiving cetuximab demonstrate upregulation of CD137 on NK cells, which correlating with the VV and VF FcγR IIIa polymorphisms.[90] In HNSCC preclinical models, cetuximab induces CD137 upregulation on NK cells; sequential treatment with a CD137 mAb enhances cytolytic activity.[90] Urelumab is a humanized IgG4 agonist mAb against CD137 which has been evaluated in dose-finding trials in melanoma, NSCLC and lymphoma. As serious hepatotoxicity limited dose-escalation, lower-dose phase I studies have resumed, including a combination trial with rituximab (NCT01471210; NCT01775631). Similarly, PF-05082566 is an IgG2 CD137 agonist mAb under evaluation in combination with rituximab (NCT01307267). In HNSCC, combinatorial trials with cetuximab, chemotherapy or radiation are warranted.

Immune Checkpoint-Targeted mAbs

The therapeutic complement to agonism of co-stimulatory TNFRs is blockade of co-inhibitory receptors. HNSCC TILs are characterized by high expression of the co-inhibitory receptors cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed-death 1 (PD-1), so-called “immune checkpoints.”[10, 91] CTLA-4 is a surface glycoprotein progressively expressed by CTLs following TCR ligation. CTLA-4 down-modulates immune response to chronic antigen stimulation, preventing autoimmunity; however in the case of cancer, CTLA-4 promotes inappropriate tolerance and immune escape. Tregs in the HNSCC microenvironment constitutively express CTLA-4.[92] CTLA-4 and the major co-stimulatory receptor CD28 compete for B7 ligands, CD80 and CD86 (Figure 1). Thus, mAb blockade of CTLA-4 frees CD28 to bind B7 and propagate the necessary TCR co-stimulatory signal. Inhibition of Treg CTLA-4 signaling also releases CTL suppression, potentiating TA-targeted cytolysis.[93] This novel therapeutic paradigm culminated in the first FDA approval of an immune checkpoint inhibitor for melanoma, an IgG4 anti-CTLA-4 mAb, ipilimumab.[94] Ipilimumab has intriguing potential to reverse immunosuppression in HNSCC, alone or in combination with other immunogenic therapies. Of particular interest to

trial design, CTLA-4 inhibition potentiates the abscopal effect when combined with fractionated radiotherapy: in breast and colon cancer radiation experiments, a preclinical CTLA-4 mAb inhibited out-of-field secondary tumor growth.[95] A phase I trial of cetuximab, ipilimumab and intensity modulated radiotherapy in the management of locally advanced HNSCC is now accruing (NCT01860430).

Like CTLA-4, PD-1 is an inhibitory member of the B7-CD28 family of co-receptors. Following TCR activation, PD-1 is expressed by multiple immune cells including CTLs, NK cells, B lymphocytes, monocytes and DCs. The PD-1 ligand, PD-L1, is expressed broadly on non-hematopoietic tissue in response to IFN-γ; thus PD-1 ligation is thought to broadly protect against autoimmunity and immune destruction of normal tissue during infection.[96] PD-L1 is also expressed in the majority of HNSCC, and is explicitly linked to the immune-privileged, invasive front of HPV-transformed HNSCC.[97–99] Infiltration by PD-1 expressing T cells is associated with favorable prognosis in HPV-associated disease; this paradox highlights the importance of prior immune response and the therapeutic potential of restoring it by PD-1 blockade.[91] Therapeutic targeting of PD-1 or PD-L1 block the co-inhibitory signal at the immune synapse. Nivolumab, a humanized IgG4 anti-PD-1 mAb, was investigated in advanced solid tumors.[23] Objective response rates in this heavily treated population were notable in renal cell carcinoma (27%), melanoma (28%), and NSCLC (18%). An important preliminary observation correlated objective response with PD-L1^{+} tumors. BMS-936559, a humanized IgG4 mAb which inhibits binding of PD-L1 to both PD-1 and CD80, also resulted in objective responses in a phase I study for patients with pretreated, advanced solid tumors – including NSCLC (10%). Anti-PD-1 and PD-L1 mAb are of pressing interest for therapeutic development in HPV-positive and HPV-negative HNSCC.

Conclusion

Successful development of novel immunotherapeutic mAb in HNSCC can be guided by recent insights into the immune mechanisms of cetuximab, the first FDA-approved immunotherapy in HNSCC, as well as dissection of immune evasion by HNSCC. In addition to blocking EGFR signaling, cetuximab induces ADCC, DC maturation, and cross-priming of EGFR-specific CTLs – immune mechanisms which could be augmented by co-treatment with other TA-targeted mAb, exogenous IL-12 or TLR stimulation, mAb to neutralize immunosuppressive cytokines, mAb to enhance antigen presentation, or mAb favorably influencing co-stimulatory vs. co-inhibitory receptor signaling. However, the strategic vision for novel therapeutic mAb should not be limited to co-administration with cetuximab. HNSCC exploits numerous redundant and mutually reinforcing immune escape mechanisms, including an imbalanced STAT1/STAT3 cytokine profile, downregulation of antigen processing and presentation, underexpression of co-stimulatory receptors and overexpression of co-inhibitory receptors in TILs. Targeting these nodes of immunosuppression may be of independent therapeutic value, and holds the promise of synergy with standard cytotoxic modalities exposing TA – including chemotherapy and radiation. Clinical trials evaluating monotherapeutic and combinatorial mAb strategies, including combinations with cytolytic therapy, are of urgent priority.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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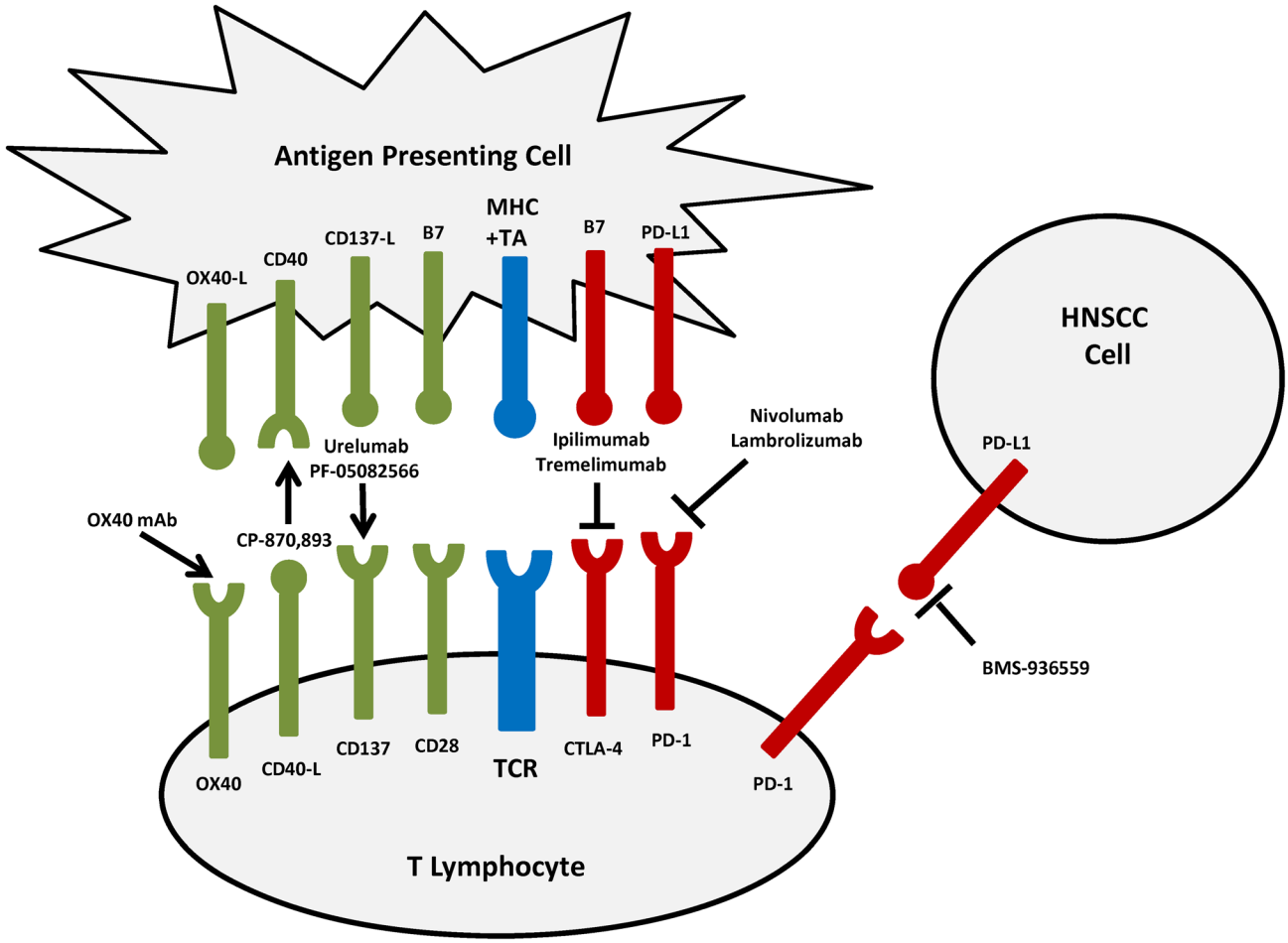

Figure 1.

Table 1

Therapeutic Monoclonal Antibodies to Overcome Immune Escape in HNSCC

Drug (Company)	Target	IgG subclass	Phase of development, human cancer	HNSCC development
Tumor Antigen Targeted Monoclonal Antibodies				
Cetuximab (Bristol-Myers Squibb, Eli Lilly)	EGFR antagonist	IgG1	III/IV (FDA-approved HNSCC, NSCLC, colon cancer)	Phase III/IV
Panitumumab (Amgen)	EGFR antagonist	IgG2	III/IV (FDA-approved colon cancer)	Phase II/III
Onartuzumab (Genentech)	cMet antagonist (single-arm Fab)	IgG1	II/III	---
Pertuzumab (Genentech)	HER2 antagonist	IgG1	III	---
AV-203 (Aveo)	HER3 antagonist	IgG1	I	Phase I (monotherapy; cetuximab combination)
MM-121 (Merck)	HER3 antagonist	IgG2	I/II	---
RO5479599 (Roche)	HER3 antagonist	Glyco-engineered	I/II	---
Cixutumumab (Eli Lilly)	IGFR antagonist	IgG1	II	Phase 0-II (neoadjuvant monotherapy; cetuximab combination)
Cytokine Targeted Monoclonal Antibodies				
Bevacizumab (Genentech)	VEGF neutralizer	IgG1	III/IV (FDA approved in NSCLC, colon)	Phase III (platinum chemotherapy +/−)
Ficlatuzumab (Aveo)	HGF neutralizer	IgG1	I/II	Phase I (cetuximab combination; cisplatin-radiation combination)
AMG 102 (Amgen)	HGF neutralizer	IgG2	I/II	---
Fresolimumab (Genzyme)	TGF-β neutralizer	IgG4		---
Siltuximab (Janssen Biotech)	IL-6 neutralizer	IgG1	I/II	---
TNF Receptor Targeted Monoclonal Antibodies				
CP-870,893 (Pfizer)	CD40 agonist	IgG2	I	---
OX40 mAb (AgonOx, Providence Health)	OX40 agonist	IgG2	I	---
Urelumab (Bristol-Myers Squibb)	CD137 agonist	IgG4	I	---
PF-05082566 (Pfizer)	CD137 agonist	IgG2	I	---
Immune Checkpoint Targeted Monoclonal Antibodies				
Ipilimumab (Bristol-Myers Squibb)	CTLA4	IgG1	III/IV (FDA approved in melanoma	Phase I (cetuximab-radiation combination)
Tremelimumab (Pfizer)	CTLA4	IgG2	III	---
Nivolumab (Bristol-Myers Squibb)	PD-1	IgG4	I/II/III	---
Lambrolizumab (Merck)	PD-1	IgG4	I/II	---
BMS-936559 (Bristol-Myers Squibb)	PD-L1	IgG4	I	---