TABLE 103e-6 ANTIBODIES USED IN CANCER TREATMENT

Drug	Target	Indications and Features of Use
Tumor Regulatory Antibodies		
Rituximab	CD20	B cell neoplasms (also emerging role in autoimmune disease); chimeric antibody with frequent mouse-derived sequences; frequent infusion reactions, particularly on initial doses; reactivation of infections, particularly hepatitis; progressive multifocal leukoencephalopathy; tumor lysis syndrome
Ofatumumab	CD20	active in CLL; fully human antibody with distinct binding site compared to rituximab; decreased intensity infusion reactions;
Trastuzumab	HER2/neu	Active in breast cancer and GI cancers expressing HER2/neu; cardiotoxicity, particularly in setting of prior anthracyclines, requires monitoring; infusion reactions
Pertuzumab	HER2/neu	Breast cancer; targets distinct binding site from trastuzumab, inhibiting dimerization of HER2 family members; infusion reactions; cardiac toxicity
Cetuximab	EGFR	Colorectal cancers with wild-type Ki-ras oncoprotein; head and neck cancers with radiation; rash, diarrhea, infusion reactions
Panitumumab	EGFR	Colorectal cancers with wild-type Ki-ras oncoprotein; fully humanized; decreased infusion reactions; different IgG subtype than cetuximab
Bevacizumab	VEGF	Metastatic colorectal cancer and non-small-cell lung cancer (nonsquamous) with chemotherapy; renal cancer and glioblastoma as single agents; prominent HBP, proteinuria, GI perforations, hemorrhage, thrombosis (venous and arterial)
Immunoregulatory Antibodies		
Alemtuzumab	CD52	CLL, T cell lymphomas; activates complement after binding to cell surface; infusion reactions, hypersensitivity, tumor lysis, activation of infections, cytopenias
Ipilimumab	CTLA4	Melanoma; inhibits the negative proliferative signal to T cells acting through CTLA4, resulting in prominent T cell activation; side effects include immune-mediated toxicity to liver, skin, pituitary, gut, which if severe calls for steroids, which inhibit antineoplastic effect
Pembrolizumab	PD-1	Melanoma unresectable or metastatic and if B-RAF V600 mutated, refractory to a B-RAF inhibitor; also can cause immune related colitis, hepatitis, hypophysitis, nephritis, and altered thyroid function; also consider steroids for treatment of severe adverse events

Abbreviations: CLL, chronic lymphocytic leukemia; EGFR, epidermal growth factor receptor; GI, gastrointestinal; HBP, high blood pressure; VEGF, vascular endothelial growth factor.

human immunoglobulin gene loci. Three general strategies have emerged using antibodies. *Tumor-regulatory antibodies* target tumor cells directly or indirectly to modulate intracellular functions or attract immune or stromal cells. *Immunoregulatory antibodies* target antigens expressed on the tumor cells or host immune cells to modulate primarily the host's immune responsiveness to the tumor. Finally, *antibody conjugates* can be made with the antibody linked to drugs, toxins, or radioisotopes to target these "warheads" for delivery to the tumor. Table 103e-6 lists features of currently used or promising antibodies for cancer treatment.

TUMOR-REGULATORY ANTIBODIES Humanized antibodies against the CD20 molecule expressed on B cell lymphomas (rituximab and ofatumumab) are exemplary of antibodies that affect both signaling events driving lymphomagenesis as well as activating immune responses against B cell neoplasms. They are used as single agents and in combination with chemotherapy and radiation in the treatment of B cell neoplasms. Obinutuzumab is an antibody with an altered glycosylation that enhances its ability to fix complement; it is also directed against CD20 and is of value in chronic lymphocytic leukemia. It seems to be more effective in this setting than rituximab.

The HER2/neu receptor overexpressed on epithelial cancers, especially breast cancer, was initially targeted by trastuzumab, with noteworthy activity in potentiating the action of chemotherapy in breast cancer as well as some evidence of single-agent activity. Trastuzumab also appears to interrupt intracellular signals derived from HER2/neu and to stimulate immune mechanisms. The anti-HER2 antibody pertuzumab, specifically targeting the domain of HER2/neu responsible for dimerization with other HER2 family members, is more specifically directed against HER2 signaling function and augments the action of trastuzumab.

EGF receptor (EGFR)-directed antibodies (such as cetuximab and panitumumab) have activity in colorectal cancer refractory to chemotherapy, particularly when used to augment the activity of an additional chemotherapy program, and in the primary treatment of head and neck cancers treated with radiation therapy. The mechanism of action is unclear. Direct effects on the tumor may mediate an antiproliferative effect as well as stimulate the participation of host mechanisms involving immune cell or complement-mediated response to tumor cell–bound antibody. Alternatively, the antibody may alter the release of paracrine factors promoting tumor cell survival.

The anti-VEGF antibody bevacizumab shows little evidence of antitumor effect when used alone, but when combined with chemotherapeutic agents, it improves the magnitude of tumor shrinkage and time to disease progression in colorectal and nonsquamous lung cancers. The mechanism for the effect is unclear and may relate to the capacity of the antibody to alter delivery and tumor uptake of the active chemotherapeutic agent. Ziv-aflibercept is not an antibody, but a solubilized VEGF receptor VEGF binding domain, and therefore may have a distinct mechanism of action with comparable side effects.

Unintended side effects of any antibody use include infusion-related hypersensitivity reactions, usually limited to the first infusion, which can be managed with glucocorticoid and/or antihistamine prophylaxis. In addition, distinct syndromes have emerged with different antibodies. Anti-EGFR antibodies produce an acneiform rash that poorly responds to glucocorticoid cream treatment. Trastuzumab (anti-HER2) can inhibit cardiac function, particularly in patients with prior exposure to anthracyclines. Bevacizumab has a number of side effects of medical significance, including hypertension, thrombosis, proteinuria, hemorrhage, and gastrointestinal perforations with or without prior surgeries; these adverse events also occur with small-molecule drugs modulating VEGFR function.

IMMUNOREGULATORY ANTIBODIES Purely immunoregulatory antibodies stimulate immune responses to mediate tumor-directed cytotoxicity. First-generation approaches sought to activate complement and are exemplified by antibodies to CD52; these are active in chronic lymphoid leukemia and T cell malignancies. A more refined understanding of the tumor–host interface has defined that cytotoxic tumor-directed T cells are frequently inhibited by ligands upregulated in the tumor cells. The programmed death ligand 1 (PD-L1; also known as B7-homolog 1) was initially recognized as an entity that induced T cell death through a receptor present on T cells, termed the PD receptor (Fig 103e-5), which physiologically exists to regulate the intensity of the immune response. The PD family of ligands and receptors also regulates macrophage function, present in tumor stroma. These actions raised the hypothesis that antibodies directed against the PD signaling axis (both anti-PD-L1 and anti-PD) might be useful in cancer treatment by allowing reactivation of the immune response against tumors. Indeed, nivolumab and lambrolizumab, both anti-PD antibodies, have shown evidence of important immune-mediated actions against certain solid tumors, including melanoma and lung cancers.