

## Special Growth Factor Mab: Cancer Therapies Approved by FDA

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The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that is commonly up regulated by various mechanism, including common mutations and truncations to its extracellular domain, such as in the EGFRvIII truncations, as well as to its kinase domain, such as the L858R and T790M mutations, or the exon 19 truncation. These EGFR aberrations over-activate downstream pro-oncogenic signaling pathways, including the RAS-RAF-MEK-ERK MAPK and AKT-PI3K-mTOR pathways. Blocking EGF-EGFR activities is developed to solid tumor since EGFR is overexpressed in cancers such as in non-small-cell lung cancer, metastatic colorectal cancer, glioblastoma, head and neck cancer, pancreatic cancer, and breast cancer (ERBITUX, VECTIBIX, PORTRAZZA, RYBREVANT)

Platelet-derived growth factor receptor alpha (PDGFR- $\alpha$ ) is also a receptor tyrosine kinase expressed on cells of mesenchymal origin. Signaling through this receptor plays a role in cell growth, chemotaxis, and mesenchymal stem cell differentiation. The receptor has also been detected on some tumor and stromal cells, including sarcomas, where signaling can contribute to cancer cell proliferation, metastasis, and maintenance of the tumor microenvironment. Blocking PDGFR- $\alpha$  prevents binding of the receptor by the PDGF-AA and -BB ligands as well as PDGF-AA, -BB, and -CC-induced

receptor activation and downstream PDGFR- $\alpha$  pathway signaling (LARTRUVO).

Vascular endothelial growth factor (VEGF) with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. In xenotransplant models of colon cancer in nude (athymic) mice, Blocking VEGF and its receptor reduces microvascular growth and inhibits metastatic disease progression (AVASTIN, CYRAMZA, MVASI, ZIRABEV)

In 1975, the monoclonal antibody (mAb) technique was created by Georges Köhler, César Milstein, and Niels Kaj Jerne by using a mouse x mouse hybridoma. They shared the Nobel Prize in Physiology of Medicine in 1984 for the discovery. Eight years later, in 1992 US FDA approved the first therapeutic mAb muromonab-CD3 (trade name Orthoclone OKT3) to reduce acute rejection in patients with organ transplants. Since then, as of November 30, 2021, FDA has approved 133 therapeutic mAbs (not including two diagnostic mAb). (1) Each year FDA approved up to 17 therapeutic antibodies (2017). (2-7) This mini review focuses briefly on the characteristics of 12 anti-HER2 therapeutic antibodies approved by FDA for the treatment of solid cancer (Table 1) (8-16).

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Table 1. Special Growth Factor Mab: Cancer Therapies Approved By FDA

Approval on	MAH	Drug Name	Active Ingredients	Indication	Warning and Precaution	Adverse Events
2/12/2004	IM CLO-NE	ERBITUX	cetuximab (epidermal growth factor receptor (EGFR) antagonis)	Squamous Cell Carcinoma of the Head and Neck (SCCHN); K-Ras Wild-type, EGFR-expressing Colorectal Cancer(CRC); BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)	fatal infusion reactions and Cardiopulmonary arrest (Boxed); Pulmonary Toxicity; Dermatologic Toxicity; Hypomagnesemia and Accompanying Electrolyte Abnormalitie; Increased tumor progression, increased mortality, or lack of benefit observed in patients with Ras-mutant mCRC; Embryo-Fetal Toxicity	cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection
2/26/2004	GENEN TECH	AVASTIN	bevacizumab (vascular endothelial growth factor inhibitor)	Metastatic Colorectal Cancer; First-Line Non-Squamous Non-Small Cell Lung Cancer; Recurrent Glioblastoma; Metastatic Renal Cell Carcinoma ; Persistent, Recurrent, or Metastatic Cervical Cancer; Epithelial Ovarian, Fallopian Tube, or Primary; Peritoneal Cancer; Hepatocellular Carcinoma	Gastrointestinal Perforations and Fistula; Surgery and Wound Healing Complications; Hemorrhage; Thromboembolic Events; Hypertension; Posterior Reversible Encephalopathy Syndrome (PRES); Renal Injury and Proteinuria; Infusion-Related Reactions; Embryo-Fetal Toxicit; Ovarian Failure; Congestive Heart Failure (CHF)	>10% epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis.
9/27/2006	AMGEN	VECTIBIX	panitumumab (EGFR)	metastatic colorectal cancer (mCRC): wild-type RAS (KRAS and NRAS) determined by an FDA-approved test	Dermatologic and Soft Tissue Toxicity; Electrolyte Depletion; Infusion Reactions; Interstitial Lung Disease (ILD); Ocular Toxicities; Embryo-fetal Toxicity	skin rash with variable presentations, paronychia, fatigue, nausea, and diarrhea
4/21/2014	ELI LILLY	CYRAMZA	ramuciruma (vascular endothelial growth factor receptor 2 (VEGFR2) antagonis)	Gastric Cancer; Non-Small Cell Lung Cancer; Colorectal Cance; Hepatocellular Carcinoma	Same as AVASTIN, plus Worsening of Pre-existing Hepatic Impairmen; Proteinuria Including Nephrotic Syndrome; Thyroid Dysfunction	hypertension and diarrhe fatigue/asthenia, neutropenia, diarrhea, and epistaxi
11/24/2015	ELI LILLY	PORTRAZAZA	necitumumab (EGFR)	Squamous Non-Small Cell Lung Cancer (NS-CLC)	Cardiopulmonary arrest and Hypomagnesemia (Boxed) plus	
10/19/2016	ELI LILLY	LAR TRUVO	olaratumab (platelet-derived growth factor receptor alpha PDGFR- $\alpha$ )	soft tissue sarcoma (STS)	Infusion-Related Reactions; Embryo-Fetal Toxicity	nausea, fatigue, musculoskeletal pain, mucositis, alopecia, vomiting, diarrhea, decreased appetite, abdominal pain, neuropathy, and headach
9/14/2017	AMGEN	MVASI	bevacizumab-awwb (VEGF)	Similar to AVASTIN	Similar to AVASTIN	Similar to AVASTIN

6/27/2019	PFIZER	ZIRABEV	bevacizumab-bvzr (VEGF)	Similar to AVASTIN	Similar to AVASTIN	Similar to AVASTIN
5/21/2021	JAN SSEN	RYBRE VANT	amivantamab-vmjw (EGF+MET bispecific)	NSCLC (EGFR exon 20 insertion mutations, as detected by an FDA-approved test)	Infusion-Related Reactions (IRRO; nterstitial Lung Disease (ILD)/Pneumonitis; Dermatologic Adverse Reactions; Ocular Toxicity; Embryo-Fetal Toxicity	rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting

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