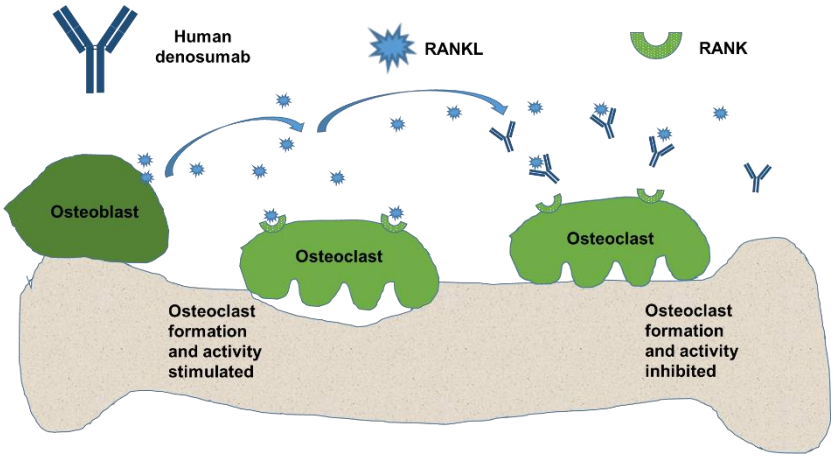
Denosumab – Fact Sheet

Molecule

Denosumab (Prolia®, Xgeva®) is a fully human IgG2 monoclonal antibody and has a molecular weight of 147 kDa. It consists of 2 heavy and 2 light chains. Each light chain has 215 and each heavy chain 448 amino acids with 4 intramolecular disulfide bridges.

Mode of Action

Bone remodeling is driven most notably by osteoblasts secreting new bone and osteoclasts breaking down bone. Pre-osteoclasts express on their surface the receptor activator of nuclear factor-kappa B (RANK), a member of the tumor necrosis factor receptor (TNFR) superfamily. RANK is activated by RANKL (RANK-Ligand), which exists as cell surface molecule on osteoblasts. Activation of RANK by RANKL promotes the maturation of pre-osteoclasts into osteoclasts. Denosumab inhibits maturation of osteoclasts by binding to and inhibiting RANKL similar to the natural function of the endogenous RANKL inhibitor osteoprotegerin. This Mode-of-Action thus counters the progression of osteoporosis.



Indication

Denosumab is indicated for the treatment of patients with osteoporosis at high risk for fracture (Prolia®), giant cell tumor of bone, hypercalcemia in malignancy and for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

Patent Situation

Expiry dates of basic Prolia® patents related to the antibody and treatment of patients range from 2017 to 2023 in US and from 2017 to 2021 in EU.

Market and Competitive Field

Denosumab was first approved as Prolia® by EMA in 2010, and then approved as Xgeva® and Prolia® by FDA in 2010 (as the first RANKL inhibitor). It was developed and is marketed by Amgen. In 2018, Amgen´s sales were 2.09 billion € (Prolia®) and 1.63 billion € (Xgeva®), which increased in 2019 to 2.44 and 1.77 million €, respectively.

VelaLabs GmbH
Brunner Straße 69 / Obj. 3, A-1230 Vienna / Austria
Phone: +43 1 890 5979 11, Fax: +43 1 890 5979 10
E-Mail: office@vela-labs.at

VelaLabs Portfolio

		Denosumab
		Prolia®, Pralia®, Ranmark®, Xgeva®
	Clone selection/ comparability	
HPLC	Separation based on **size** (SE-HPLC)	
HPLC	Separation based on **hydrophobicity** (RP-HPLC)	
HPLC	Detection of **charge variants** (CEX-HPLC)	
Binding	Binding to **cell surface** expressed target (Flow cytometry)	c.l.d.
Binding	Binding to **soluble target** (ELISA)	
Binding	Binding to specific **antibody or antigen** (SPR-BIACORE, ELISA)	
Binding	**Affinity/ kinetic** to recombinant target (SPR-BIACORE)	
Effector function	Binding to C1q, [1]**CDC surrogate** (ELISA)	
Effector function	**Affinity** to recombinant Fc-receptors (SPR-BIACORE)	
Effector function	Reporter gene assays, [2]**ADCC surrogate** (Luminescence)	
Effector function	[1]**CDC** (Flow cytometry)	n.a.
Effector function	[2]**ADCC** (DELFIA, Fluorescence)	n.a.
Effector function	Additional **bioassays** (Luminescence, fluorescence)	Potency assay
Gly	Glyco-pattern with **Lectin Microarray** (45 different lectins)	
	(Pre)clinical application	
Clinics	Pharmacokinetics – **PK** (ECL, ELISA)	
Clinics	Pharmacodynamics – **PD** (ECL, ELISA, flow cytometry, bioassay)	
Clinics	Immunogenicity - [3]**ADAs** (ECL, Biacore, ELISA, neutr. assay)	

[1]CDC = Complement Dependent Cytotoxicity
[2]ADCC = Antibody Dependent Cellular Cytotoxicity
[3]ADA = Anti-Drug-Antibody

	Vela portfolio
	Vela planned
	c.l.d. = cell line dependent
	n.a. = not applicable
	In development

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