FROM THE ANALYST'S COUCH

Bispecific antibodies in oncology

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Bispecific antibodies (bsAbs) are a diverse family of antibodies or antibody constructs that recognize two epitopes or antigens. Most bsAbs are bispecific T-cell-engagers (BiTEs), designed to redirect and/or activate CD3-expressing cytotoxic T cells (CTLs) against a specific tumour target on malignant cells. Other bsAb classes include therapies that target immune checkpoints, oncogenic signalling pathways and cytokines. Bifunctional fusion proteins are a subset of bsAbs that are typically devoid of an Fc region.

Approved bispecific antibodies

In 2014, blinatumomab (Blincyto; Amgen) became the first bsAb to gain FDA approval. This CD19×CD3 BiTE is indicated for relapsed/refractory (R/R) B cell precursor acute lymphoblastic leukaemia (ALL), and for B cell precursor ALL in first or second remission with minimal residual disease. The drug is also approved in Europe, Japan and China.

In 2021, amivantamab (Rybrevant; Janssen), an EGFR×c-MET bsAb, was granted accelerated and conditional approval in the United States and Europe for previously treated metastatic non-small-cell lung cancer (NSCLC) with *EGFR* exon 20 insertion mutations (~1–2% of NSCLC cases). Based on encouraging early-phase efficacy data, amivantamab's combination regimens with the EGFR inhibitor lazertinib (Leclaza; Yuhan/Janssen) and/or chemotherapy are also in phase III trials for first-line and previously treated *EGFR*$^{+}$ metastatic NSCLC.

Tebentafusp (Kimmtrak; Immunocore), a gp100×CD3 bispecific fusion protein, secured FDA approval in January 2022. It is indicated for the treatment of HLA-A*02:01-positive patients with unresectable or metastatic uveal melanoma. Tebentafusp recognizes a peptide fragment of gp100, expressed on uveal melanoma cells via HLA-A*02:01, and engages CD3^{+} CTLs to kill cancer cells.

Late-phase pipeline

The late-phase pipeline for bsAbs is diverse and key targets are CD20 and BCMA in haematological malignancies and CTLA4, PD1/PDL1, LAG3, EGFR and HER2/HER3 in solid tumours (TABLE 1).

Haematological malignancies. Three CD20×CD3 bsAbs, glofitamab and mosunetuzumab (Roche/Genentech/Chugai/Biogen), and epcoritamab (Genmab/AbbVie), are in phase III trials for treatment of non-Hodgkin's lymphoma (NHL). Glofitamab combined with rituximab (Rituxan/MabThera; Roche/Genentech/Chugai) and chemotherapy is being evaluated for treatment of R/R diffuse large B cell lymphoma (DLBCL) in the STARGLO trial. Epcoritamab monotherapy is also being investigated for R/R DLBCL in the EPCORE DLBCL-1 trial. Mosunetuzumab's combination regimens with lenalidomide (Revlimid; Bristol Myers Squibb) and polatuzumab vedotin (Polivy; Roche/Genentech/Chugai) are in two trials (CELESTIMO and SUNMO) for the treatment of indolent (follicular lymphoma) and aggressive B cell NHL subtypes, respectively. All three agents are in registrational phase I/II studies; regulatory submissions have been made to the FDA and EMA for mosunetuzumab.

Elranatamab (Pfizer) and teclistamab (Janssen) are BCMA×CD3 bsAbs in phase III trials for treatment of R/R multiple myeloma (MagnetisMM-5 and MajesTEC-3). In both trials, these molecules are being evaluated in combination with the anti-CD38 monoclonal antibody daratumumab (Darzalex Faspro; Janssen). Janssen has made regulatory submissions to the FDA and EMA for teclistamab monotherapy based on phase I/II data from the MajesTEC-1 trial.

Table 1 | **Select bispecific antibodies in phase III trials in oncology**

Drug	Company	Targets	Key indications
Glofitamab	Roche/Genentech/Chugai	CD20 ×CD3	DLBCL
Mosunetuzumab	Roche/Genentech/ Chugai/Biogen	CD20 ×CD3	Indolent and aggressive NHL
Epcoritamab	Genmab/AbbVie	CD20 ×CD3	DLBCL
Elranatamab	Pfizer	BCMA ×CD3	Multiple myeloma
Teclistamab	Janssen	BCMA ×CD3	Multiple myeloma
Erfonrilimab	Alphamab Oncology	PDL1 ×CTLA4	NSCLC, PDAC
Cadonilimab	Akeso Biopharma	PD1 ×CTLA4	GOJ adenocarcinoma, cervical cancer
Tebotelimab*	MacroGenics	PD1 ×LAG3	Gastric/GOJ cancer
Ivonescimab	Akeso Biopharma	PD1 ×VEGF	NSCLC
Navicixizumab	OncXerna Therapeutics/ Mereo Biopharma	DLL4 ×VEGF	Ovarian cancer
SI-B001*	SystImmune/Sichuan Baili Pharmaceutical	EGFR ×HER3	NSCLC
Zanidatamab	Zymeworks	HER2 ×HER2	Gastro-oesophageal adenocarcinoma
Catumaxomab	LintonPharma	EpCAM ×CD3	Gastric adenocarcinoma
Bintrafusp alfa	Merck KGaA	PDL1 ×TGFβ	NSCLC, biliary tract cancer
SHR-1701	Jiangsu Hengrui Medicine/ Suzhou Suncadia Biopharmaceuticals	PDL1 ×TGFβ	NSCLC, cervical cancer, gastric/GOJ cancer

BCMA, B-cell maturation antigen; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DLBCL, diffuse large B-cell lymphoma; DLL4, delta-like ligand 4; EGFR, epidermal growth factor receptor; EpCAM, epithelial cellular adhesion molecule; GOJ, gastro-oesophageal junction; HER2/3, human epidermal growth factor receptor 2/3; LAG3, lymphocyte-activation gene 3; PDAC, pancreatic ductal adenocarcinoma; PD1, programmed cell death protein 1; PDL1, programmed death-ligand 1; NHL, non-Hodgkin's lymphoma; NSCLC, non-small-cell lung cancer; TGFβ, transforming growth factor beta; VEGF, vascular endothelial growth factor. *In phase II/III.

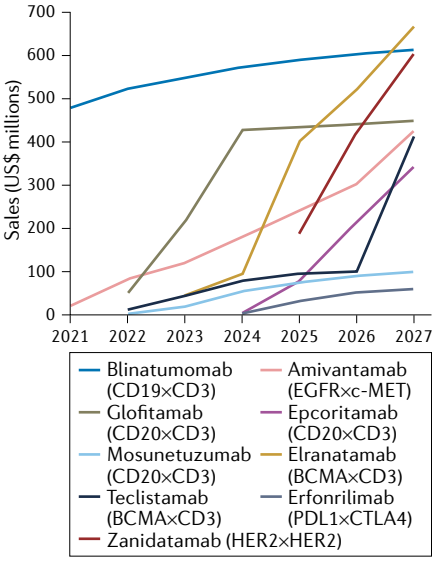

Fig. 1 | **Forecast global sales of select bispecific antibodies.** Sales of blinatumomab reflect global sales. Sales of epcoritamab, mosunetuzumab, elranatamab and zanidatamab reflect the following markets only: United States, France, Germany, Italy, Spain, United Kingdom and Japan. Sales of amivantamab, glofitamab and teclistamab reflect the following markets only: United States, France, Germany, Italy, Spain, United Kingdom, Japan and China. Sales of enfonrilimab reflect China only. Drugs with a sales forecast <US$50 million are not shown. Source: Clarivate.

Solid tumours. Most bsAbs in late-phase development for solid tumours target immune checkpoint molecules or tumour antigens. The PDL1×CTLA4 bsAb, erfonrilimab (Alphamab Oncology), and the PD1×CTLA4 bsAb, cadonilimab (Akeso Biopharma), are in phase III trials in China. Erfonrilimab is being investigated for treatment of metastatic NSCLC and advanced pancreatic ductal adenocarcinoma in the KN046-301, KN046-302 and KN046-303 trials; it has also been granted orphan drug designation (ODD) by the FDA for thymic epithelial tumours. Cadonilimab is being tested for the treatment of gastric or gastro-oesophageal junction (GOJ) adenocarcinoma and cervical cancer in the AK104-302 and AK104-303 trials, and has been granted fast-track designation and ODD by the FDA. Tebotelimab (MacroGenics), a dual affinity re-targeting molecule targeting PD1 and LAG3, is in a phase II/III trial (MAHOGANY) in combination with margetuximab (Margenza; Macrogenics) and chemotherapy for HER2$^+$ gastric/GOJ cancer.

Akeso Biopharma is also conducting a phase III trial (AK112-302) in China of a PD1×VEGF bsAb, ivonescimab, in combination with chemotherapy, for the treatment of *EGFR*$^+$ metastatic NSCLC patients who have failed prior EGFR inhibitor treatment. Navicixizumab (OncXerna Therapeutics/Mereo Biopharma) simultaneously inhibits VEGF and delta-like ligand 4 (DLL4), involved in proangiogenic Notch signalling. Navicixizumab is in a phase III trial (ONCX-NAV-G301) for the treatment of platinum-resistant ovarian cancer and has fast-track designation from the FDA.

EGFR and HER3 heterodimerize and activate downstream oncogenic AKT signalling, and inhibition of both receptors is of therapeutic value in malignancies that are dependent on these signalling cascades. The EGFR×HER3 bsAb, SI-B001 (SystImmune/Sichuan Baili Pharmaceutical), is in two phase II/III NSCLC trials (SI-B001-201 and SI-B001-208). Zanidatamab (Zymeworks) is a HER2×HER2 biparatopic bsAb, designed to have high avidity by targeting two non-overlapping epitopes on the same antigen. A phase III trial (HERIZON-GEA-01) is assessing zanidatamab in combination with chemotherapy with or without tislelizumab (Baizean; BeiGene) for the treatment of HER2$^+$ gastro-oesophageal adenocarcinoma. The EpCAM×CD3 bsAb, catumaxomab (Removab; LintonPharm), is in a phase III trial for gastric adenocarcinoma in China. Catumaxomab was approved in Europe for malignant ascites in 2009, but was voluntarily withdrawn by the company in 2017.

Two bifunctional fusion proteins targeting PDL1 and the immunosuppressive cytokine TGFβ are in phase III trials: bintrafusp alfa (Merck KGaA) with chemotherapy for treatment of biliary tract cancer and SHR-1701 (Jiangsu Hengrui Medicine/Suzhou Suncadia Biopharmaceuticals) for NSCLC, cervical cancer and gastric/GOJ cancer.

Early-phase pipeline

A plethora of bsAbs directed at both existing and novel targets are in early-phase clinical development (Supplementary Table 1). For haematological malignancies, registrational trials are underway or planned for agents targeting BCMA×CD3 (REGN5458; Regeneron, TNB-383B; AbbVie), GPRC5D×CD3 (talquetamab; Janssen) and CD20×CD3 (odronextamab; Regeneron), CD123×CD3 for acute myeloid leukaemia (flotetuzumab; MacroGenics), and CD30×CD16A for peripheral T cell lymphoma (AFM13; Affimed). For solid tumours, potentially registrational phase I/II trials are ongoing for agents targeting HER2×HER3 (zenocutuzumab; Merus), HER2×HER2 (KN026; Alphamab Oncology) and DLL3×CD3 (tarlatamab; AbbVie/Amgen).

Market indicators

The global bsAb oncology market is expected to expand rapidly, with sales forecast to approach US$3.7 billion in 2027 (FIG. 1). However, most approved or emerging bsAbs are anticipated to compete in fragmented and competitive oncology markets. Among these therapies, elranatamab is anticipated to be the top-selling bsAb ($665 million in 2027), driven by robust uptake in R/R multiple myeloma. Teclistamab sales are expected to lag behind as a result of later label expansions in multiple myeloma ($410 million in 2027). Sales of blinatumomab are expected to remain high and plateau by the end of the forecast ($615 million in 2027), primarily because blinatumomab is entrenched in the ALL treatment algorithm.

Sales of CD20×CD3-targeting agents in B cell NHL are estimated to contribute nearly 25% of bsAb market share in 2027. Glofitamab is forecast to be the best-selling of the three CD20×CD3 bsAbs ($450 million), followed by epcoritamab ($345 million). These two agents' sales will be driven by their approval in DLBCL, which has a large patient population. Mosunetuzumab is forecast to garner $100 million sales in follicular lymphoma, limited by fewer treatment opportunities and competition from existing drugs. The three agents will face competition from already approved and emerging targeted therapies and CAR-T cell therapies.

Zanidatamab is forecast to be the sales-leading bsAb in solid tumours, garnering $605 million in 2027 (two years after anticipated market entry) for HER2$^+$ gastro-oesophageal adenocarcinoma, with sales growth fuelled by its entry into the large previously untreated metastatic population. NSCLC has one of the largest treatment opportunities in oncology and amivantamab's sales are forecast to reach $425 million in 2027. Sales will be limited initially to patients with *EGFR* exon 20 insertion mutations, but label expansions from 2024 based on combination regimens could drive sales growth. Sales of erfonrilimab are forecast to be modest ($62 million) given the challenge of competing with standard-of-care immunotherapy regimens in the NSCLC treatment algorithm.

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