PD-1 x VEGF and PD-L1 x VEGF bispecific antibodies:

a business, pipeline and competitor analysis from an industry perspective

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aims to offer a wider therapeutic window regardless of tumor levels. Most of the PD-1xVEGF antibodies have a VEGF-targeted IgG monoclonal antibody as backbone which in three published cases is bevacizumab (Avastin) except JS207 which uses the anti-PD-1 antibody toripalimab as backbone. Bevacizumab is a VEGF-A specific antibody.

The second specificity is added to the backbone IgG via fusion with the second targeting moiety. Anti-PD-1 scFv are typically fused at the C-terminus to the anti-VEGF IgG in contrast to SSGJ-707 which consists of anti-PD-1 Fabs N-terminally fused to the anti-VEGF IgG. LM-299 uses VHH domains for PD-1 targeting, while JS207 adds single domain antibodies targeting VEGF to the anti-PD-1 antibody toripalimab. As far as disclosed, the Fc part of the IgG backbone is silenced to avoid effector functions.

CR-001 was designed as a follower of ivonescimab with the only difference of engineered anti-PD-1 scFvs. Crescent Biopharma claims them to be highly potent and stable. CR-001 as well as ivonescimab have native FcRn binding for IgG typical distribution and elimination.

The cooperativity between PD-1 and VEGF binding is shown by the fact that VEGF binding to ivonescimab increases affinity to PD-1 by about 18-fold and vice versa (about 4-fold), enhancing both T-cell activation and VEGF-signaling blockade. This helps explain the cross-trial outperformance of ivonescimab vs. an anti-PD-L1 + anti-VEGF combination. The PD-1 arm concentrates VEGF inhibition in the tumor microenvironment (TME), potentially sparing healthy tissue and reducing adverse events (AEs).

In preclinical studies, the tetravalent structure of ivonescimab allowed the formation of large complexes with dimeric VEGF, resulting in improved avidity to PD-1 and an increase in functional valency and potency. PD-1 binding to ivonescimab also enhanced its binding affinity to VEGF and the enhanced potency in depleting VEGF. This mutual **cooperativity** elicited the potent anti-tumor efficacy in mice.

3.2 Pipeline of bispecific PD-L1xVEGF antibodies

Six PD-L1xVEGF antibodies have been identified with five of them in clinical development (Table 4). Clinical readouts have been published for three of them (HB0025; IMM2510 and PM8002) which are described in detail in the Drug Profiles chapter of this report and discussed in the Clinical Experience chapter.

Minghui is “looking forward to exploring strategic partnerships to facilitate this development”.

5.1.8 NY-500

In January 2025, NAYA Biosciences announced that it is expanding its bifunctional antibody pipeline to include a novel PD-1 x VEGF tetravalent bifunctional antibody for the treatment of hepatocellular carcinoma (HCC) and other solid tumors (Press Release Jan 06, 2025). NAYA is leveraging its proprietary FLEX antibody platform and further optimizing its design through a partnership with MabSilico, an artificial intelligence & deep technology-focused company, to accelerate the development of new best-in-class candidates for validated therapeutic targets.

Source: NAYA Biosciences Presentation Jan 06, 2024

The PD-1 x VEGF antibody NY-500 will target hepatocellular carcinoma (HCC) and other solid tumors with high unmet medical needs. NY-500 has a differentiated molecular design, leveraging both NAYA’s proprietary FLEX format and AI-optimization, and is expected to enter monotherapy phase 1/2a clinical trials in early 2026 in the US for the first-line treatment of hepatocellular carcinoma (HCC) & other solid tumors. Other potential indications include lung, colorectal and renal cancers (NAYA Biosciences Presentation Jan 06, 2024).

5.1.9 RC148

In July 2023, China’s Center for Drug Evaluation (CDE) approved RemeGen’s Phase I clinical trial of the novel bispecific antibody **RC148** (PD-1/VEGF) as monotherapy for the treatment of advanced malignant solid tumors. The multi-center, open-label Phase I clinical study of RC148 is being conducted in China at more than 30 centers. In September 2023, the first patient was enrolled (RemeGen Interim Report Sep 25, 2024).

RemeGen developed the novel humanized IgG1 silenced bispecific antibody RC148 to target VEGF and PD-1 (Fang, 2024). RC148 allows dimeric VEGF crosslinking and gradually enhances PD-1 binding activity, potentially reduces systemic toxicity of anti-VEGF therapy and

entire upfront payment equivalent to US$ 500 million from SUMMIT Therapeutics, which included US$ 474.9 million cash and the consideration of shares with value equivalent to US$ 25.10 million.

On June 3, 2024, Akeso entered into an amendment to the license agreement with Summit Therapeuitcs, pursuant to which Summit's license territory for ivonescimab was expanded to include Central America, South America, the Middle East and Africa. In exchange for these rights, the total deal value is worth up to $70 million. Akeso reported revenue of license income of RMB85.3 million (about US$ 12 mln) in H1/2024.

7.3 AP Biosciences

Based in Taipei, Taiwan, AP Biosciences was founded in 2013 to develop technology for construction of the fully human Omni-Mab Naïve Antibody Phage Display Library and for development & validation of the T-cube bispecific antibody platform. In 2018, OBI Pharma acquired a majority (67%) stake in AP Biosciences. In several financing rounds, the company raised a total of more than $ 85 mln up to series D. In addition, AP Biosciences is listed on the Emerging Stock market in Taiwan.

In July 2019, AP Biosciences signed a cooperative development and licensing agreement with Tasly Biopharmaceuticals Co. for the development of new bispecific antibodies aimed at cancer treatment. This partnership grants Tasly exclusive rights for clinical development, manufacturing, and sales of APBio's new antibody drugs across Greater China, including mainland China, Hong Kong, and Macao (Press Release July 29, 2019). Tasly made an upfront payment of USD $4.5 million to APBio, with additional milestone payments upon achieving predefined objectives, as well as royalties based on a percentage of the product's net sales.

The agreement covers several antibodies, including AP505, a bispecific antibody that simultaneously inhibits PD-L1 and VEGF. Tasly Pharmaceutical Group Co. initiated a clinical phase I trial in China in 2023 and received China NMPA phase II clinical trial approval in December 2024.

In parallel, AP Biosciences initiated a phase I clinical trial in Taiwan which is active, but not recruiting. An US IND approval for a phase I study was obtained in January 2023, but no clinical trial is registered in the US (AP Biosciences Homepage Jan 13, 2025).

8.3 PD-L1 Antibody Market

Tecentriq and Imfinzi were the two best selling anti-PD-L1 antibodies in 2023 with sales of US$ 4,358 mln and US$ 4,019 mln, respectively (Table 17).

Table 17: 2023 Individual Sales of Monospecific PD-L1 Antibodies

Product Name	Target / Mechanism of Action	Class of Compound	Company	2023 Sales & Source of Information
Tecentriq; atezolizumab	Programmed Death Ligand-1 (PD-L1)	Rec human IgG1 mAb	Roche	Roche 2023 Finance Report Feb 01, 2024 - 2023 sales of CHF 3,766 mln (+9% at CER vs 2022) = **US$ 4,358 mln**
Imfinzi; durvalumab	PD-L1	Rec fully human IgG1 mab with triple Fc mutation	AstraZeneca	AstraZeneca PR Feb 08, 2024 - Combined 2023 sales of Imfinzi and Imjudo of US$ 4,237 mln (+52% vs 2022) of which **US$ 4,019 mln** are Imfinzi sales
Bavencio; avelumab	PD-L1	Rec fully human IgG1 mAb	Merck KGaA (EMD Serono)	Merck KGaA PR Mar 07, 2024 - Merck reports 2023 sales of € 716 mln (+16.6% vs 2022) = **US$ 773 mln** (Merck took over from Pfizer global commercialization effective June 30, 2023)
Enweida; envafolimab; (China)	PD-L1	Rec fusion protein of anti-PD-L1 sdAb with Fc of IgG	3D Medicines (from Jiangsu Alphamab Biopharma-ceuticals)	3D Medicines Announcement Mar 28, 2024 - 2024 full year sales of RMB 634.9 mln (+11.9% vs 2022) = **US$ 88.8 mln**
Cejemly; sugemalimab (China)	PD-L1	Rec human, full length IgG4 mAb (OMT transgenic animal platform)	CStone Phar-maceuticals (originator) & Pfizer (mainland China)	CStone Announcement Mar 27, 2024 - Pfizer did not disclose 2023 sales in China. CStone reports full year 2023 royalty income of RMB 31.4 mln for estimated sales of RMB 310 mln based on assumed 10% royalties = **US$ 43.4 mln**
				Sub-Total: **US$ 9,282 mln**

Sales reported for the year 2024 were CHF 3,640 mln or **US$ 4,093 mln** (+/-0% at CER vs 2023) for Roche`s Tecentriq (Press Release Jan 30, 2025). AstraZeneca's Imfinzi posted 2024 sales of **US$ 4,771 mln** (+16% vs 2023) (Press Release Feb 06, 2025).

The STRIDE (Single Tremelimumab Regular Interval Durvalumab) regimen added additional sales to Imfinzi in 2023, but was excluded in 2024 (Table 18).

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