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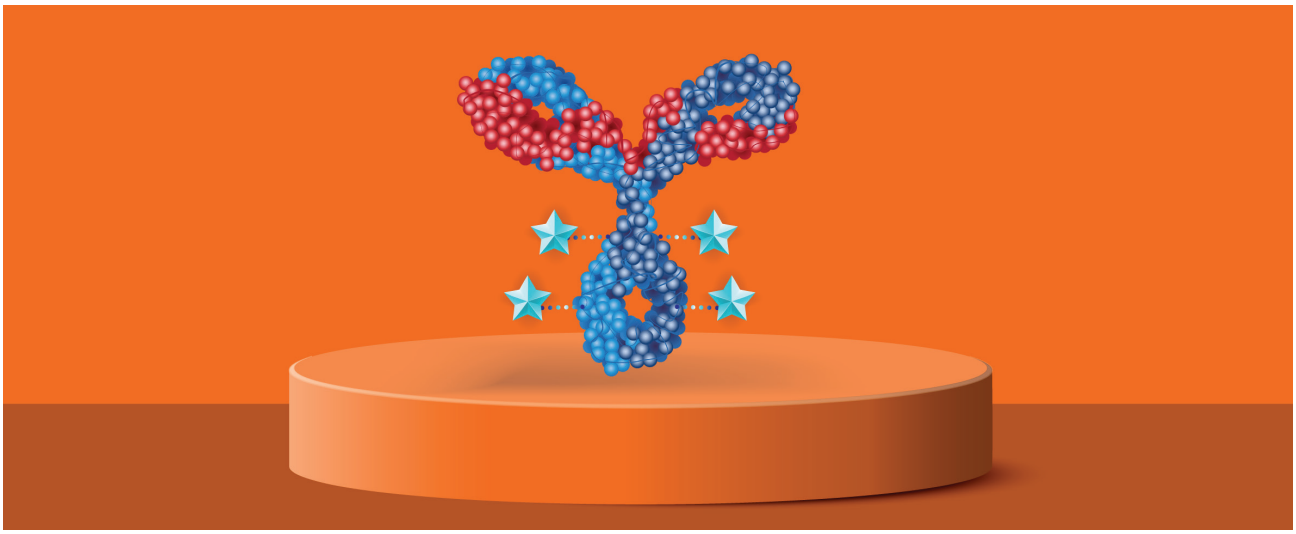
How Alphamab is differentiating in crowded cancer targets

BY LAUREN MARTZ, EXECUTIVE DIRECTOR, BIOPHARMA INTELLIGENCE



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Bringing technology twists to crowded but high-value cancer targets is the strategy that has propelled Alphamab from an antibody start-up to a multimodality, commercial oncology company with global ambitions.

Suzhou-China based Alphamab Oncology Ltd. (HKEX:9966), which launched in 2008, became the first company to gain regulatory approval of a subcutaneous PD-L1 mAb with the 2021 marketing authorization of Enweida envafolimab in China.

Now, it's advancing toward a second approval after anbenitamab (KN026), a biparatropic HER2 bispecific, reported standout Phase III data at this year's ESMO Congress. Second-line treatment with anbenitamab led to a 75% reduction in the risk of disease progression or death (PFS HR=0.25) and a 71% reduction in the risk of death (OS HR=0.29) in patients with HER2-positive gastric cancer. The company submitted an NDA to China's NMPA in September.

What those two programs have in common is their fresh take on a popular target. Much of the rest of Alphamab's pipeline follows the same format.

A decade ago, when the first PD-1 and PD-L1 therapies were beginning to live up to their commercial promise, Alphamab made its entry into the arena by bypassing an intravenous formulation and going directly to a subcutaneous one. The decision was a deviation from what was becoming the standard mAb development strategy, which typically puts IV first. Companies often introduce a subcutaneous version later, a move that can reset the intellectual property clock.

The subcutaneous formulation of market-leading Keytruda pembrolizumab from Merck & Co. Inc. (NYSE:MRK) was approved this September, more than 11 years after the IV therapy first reached the market.

Alphamab founder, Chairman and CEO Ting Xu told BioCentury that the opportunity to differentiate on delivery, and possibly efficacy, drove Alphamab's decision.

"I had the belief that for immunotherapy, delivery through subcutaneous [injection] may help boost efficacy because it would be distributed through the lymphatic system," Xu said.

Envafolimab was approved in China in 2021 to treat solid tumors with genomic instability as indicated by MSI-high or dMMR status. Alphamab is also developing the product in the

U.S., where it has orphan drug designation for biliary tract cancer and soft tissue sarcoma.

Alphamab's second program also brings a technology twist to a well-validated target: HER2. As many HER2 programs shifted toward emulating the success of antibody-drug conjugate Enhertu trastuzumab deruxtecan, Alphamab chose a different route: designing a bispecific antibody that targets two non-overlapping epitopes on HER2, known as a biparatropic design. The goal was to induce more efficient receptor internalization than therapies that bind one site on HER2, thereby durably blocking receptor signaling.

Anbenitamab is the most advanced biparatropic HER2 bispecific in development for gastric cancers, but another is on the market for a different indication. Ziihera zanidatamab from partners Jazz Pharmaceuticals plc (NASDAQ:JAZZ) and BeOne Medicines Ltd. (NASDAQ:ONC; HKEX:6160) was the first to market, with a 2024 FDA approval to treat biliary tract cancer.

Alphamab is now looking to build on anbenitamab's clinical success with a next-generation therapy that incorporates the biparatropic antibody into an ADC to deliver a topoisomerase inhibitor alongside HER2 inhibition. The bispecific ADC, JSKN003, is designed for stable payload attachment via site-specific conjugation to the antibody's Fc glycans. It is being evaluated in a Phase III trial in second-line, HER2-positive breast cancer, with an NDA submission possible next year.

ADC strategy

JSKN003 reflects Alphamab's broader ADC strategy, which Xu believes could yield therapies with safety advantages over other ADCs in development. The company's pipeline is increasingly centered on ADCs — especially bispecific ADCs.

Seven of the nine additional clinical assets in Alphamab's disclosed pipeline are bispecific ADCs.

The company's glycan conjugation is the foundation of its safer ADC design, according to Xu.

Site-specific payload conjugation has gained traction across the ADC field because it yields more stable and homogeneous products. Several strategies are used to achieve this, each with distinct tradeoffs.

Alphamab's approach of conjugating the payload to Fc glycans preserves the antibody's binding activity because the linkage is made at the non-binding end of the molecule, where it is unlikely to interfere with antigen engagement. By contrast, conjugation to cysteines found throughout the antibody sequence — a standard approach — can make receptor binding less efficient. "Our ADCs are really antibody-driven," Xu added.

"OUR ADCS ARE REALLY ANTIBODY-DRIVEN."

TING XU, ALPHAMAB

Because the glycan structure is partly shielded by the Fc chain, Fc-glycan conjugation may also provide better payload protection than cysteine conjugation. "The release of free toxin is very little," said Xu.

Xu highlighted manufacturing advantages as well. Alphamab uses the native glycan structure and a glycotransferase to attach the payload in a single-step click reaction. The glycan itself functions as a hydrophilic linker, which Xu said confers greater stability than cysteine conjugation. The same system can generate dual-payload ADCs by simply adding a second enzyme. The process is simpler than approaches that rely on incorporating non-natural amino acids into the antibody.

The trade-off is that fewer conjugation sites are available on Fc glycans than on cysteines, which limits the achievable drug-antibody ratio (DAR) and may reduce potency. However, Xu believes the safety and manufacturability profile offsets this constraint.

He pointed to JSKN016, a TROP2 x HER3 ADC, as an example of the safety profile, noting the therapy has led to lower rates of Grade 3 adverse events than most ADCs. He cited a 17% Grade 3 treatment-related adverse event rate in a Phase I study of about 200 patients vs. about 40-50% for "the majority of ADCs."

Lower toxicity means more opportunities to dose the ADCs in combination, an emerging trend in early-line cancer settings. "The safety can be translated to a lot of open space for combinations. Our thing from the very beginning was that we wanted a very safe ADC," said Xu.

It was the prospect of overcoming safety-imposed limitations on efficacy that guided Alphamab to its bispecific ADC focus.

"We do safe ADCs two ways," Xu said. "The first is a reduced DAR. We believe DAR 8 is too much. DAR 4 is enough, but the efficacy can be compromised a little bit. Then we increase function from the antibody side by making a bispecific." With the HER2 biparatropic, he noted, the internalization is "much faster and more extensive," which translates to greater efficacy.

PD-1 x VEGF differentiation

Alphamab's approach to the PD-1 x VEGF bispecific frenzy is another example of the forward-looking design strategy.

Rather than developing a bispecific against the target pair, the biotech is approaching the field with its bispecific ADC

strategy. The reason, said Xu, is that the PD-1 x VEGF bispecifics will likely need to be combined with chemotherapy in many settings, and conjugating a chemotoxic payload to a bispecific could be safer.

"In lung cancer, if it's not PD-L1 over 50%, it has to be a combination with chemo," Xu said. By incorporating a functional PD-L1 x VEGFR2 bispecific into an ADC design, it creates a more targeted, slow-releasing vehicle for the chemotherapy component, he noted.

Xu believes that specifically targeting VEGFR2, which most bispecifics in the class do not, could lead to efficacy in colorectal cancer, where unmet need is high. VEGFR2 is often highly expressed in colorectal cancers, which are responsive to VEGF blockade. Although ADCs have not been effective in the indication, the hope is that using the right antibody target for an ADC could change that.

He told BioCentury that the company is screening for payloads that synergize with topoisomerase inhibitors, including molecular glues, to create dual-payload therapies for the company's next wave of ADCs.

Alphamab, which is partnered with Simcere Pharmaceutical Group Ltd. (HKEX:2096) on marketed drug envafolimab and with CSPC Pharmaceutical Group Ltd. (HKEX:1093) on its other advanced programs, is actively seeking partners to support global development of its later-stage pipeline and to support multi-indication development programs for its earlier-stage programs, such as JSKN022, a PD-L1 x ITGB6 ADC in Phase I testing.

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NEWSROOM
news@biocentury.com

SAN CARLOS, CA
+1 650-595-5333; Fax: +1 650-595-5589

CHICAGO
+1 312-755-0798; Fax: +1 650-595-5589

WASHINGTON, DC
+1 202-462-9582; Fax: +1 202-667-2922

UNITED KINGDOM
+44 (0)1865-512184; Fax: +1 650-595-5589