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TARGETS & MECHANISMS

New paths for a bispecific road less traveled

BY KAREN TKACH TUZMAN, SENIOR EDITOR

As bispecifics against two tumor antigens win their first approval and gain traction at ASCO, drug developers are also eyeing the opportunities this class of compounds could open up for ADCs.

Bispecific antibodies are steadily becoming a must-have for cancer drug developers. The modality has surpassed both mAbs and cell therapies as the focus of pharma oncology deals, and has been a consistent bright spot at cancer meetings, generating clinical data in new target spaces of immuno-oncology that CAR Ts haven't yet touched.

Although the lion's share of development in the class has focused on immune cell engagers — compounds that target tumor cells with one arm, and use the other arm to kill them via immune effectors — only one has reached the market, the T cell engager Blincyto blinatumomab from Amgen Inc. (NASDAQ:AMGN), approved by FDA in 2014.

Friday's approval of Rybrevant amivantamab-vmjw from the Janssen unit of Johnson & Johnson (NYSE:JNJ) reflects the bispecifics field's growing footprint beyond T cell engagers, and marks a breakthrough for the modality in targeted cancer therapies. It continues a trend for recent cancer approvals which skewed last year to targeted therapies, and highlights the clinical progress made by bispecifics against two tumor antigens.

Rybrevant, which targets EGFR and c-MET, was granted accelerated approval by FDA for use in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations. It is the third bispecific antibody to gain approval, after Hemlibra, emicizumab-kxwh from Roche (SIX:ROG; OTCQX:RHHBY) was approved in 2017 to treat hemophilia.

In Rybrevant's case, the approval says more about the unmet need in the rare NSCLC patient population than the likelihood

of success for tumor-targeting bispecifics overall. Because these patients' tumors are not thought to co-express c-MET, they are not benefitting directly from the bispecific properties of the drug.

Rather, the advantage is in Rybrevant's extracellular EGFR targeting strategy, since EGFR exon 20 insertions render patients resistant to intracellular tyrosine kinase inhibitors (TKIs). Having recruited patients with a broad range of EGFR mutations for its NSCLC trials, the company serendipitously identified the compound's benefit for this patient subset.

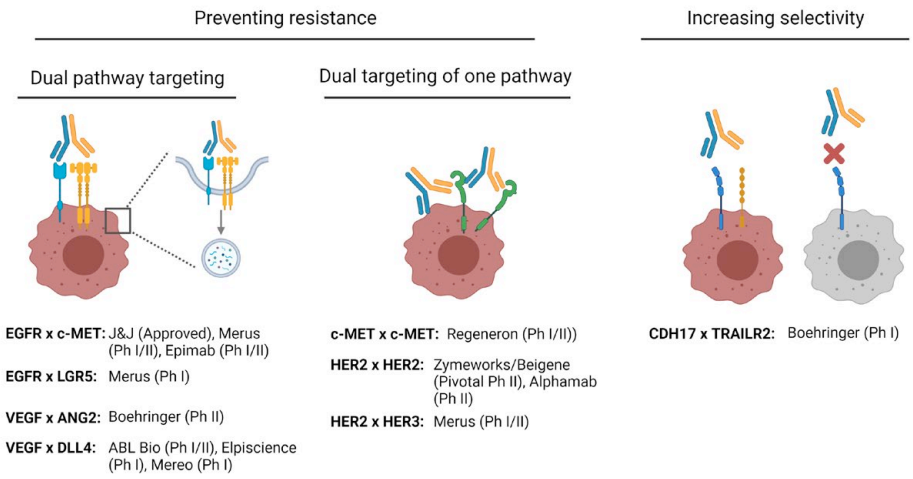
"If you look at the current standard of care, it almost doubled the survival, and almost tripled the progression-free survival," Mark Wildgust, VP of global medical affairs/oncology at Janssen, told BioCentury. "The fact that it hits MET at the same time may not be necessarily important there, the more important part is that it's targeting EGFR effectively."

Still, data to be presented at the 2021 meeting of the American Society for Clinical Oncology (ASCO) suggests multiple bispecifics against two tumor antigens, including amivantamab, are producing clinical benefit as a result of their two-pronged design, particularly in biomarker-defined patient populations.

And growing understanding of how bispecifics against two proteins on the same cell surface trigger receptor internalization is giving a clearer picture of these compounds' effects, and creating new opportunities for a separate modality that is critically dependent on receptor internalization: antibody-drug conjugates (ADCs).

"Bispecifics can make non-internalizing receptors become internalizing ones, which opens up a lot of new settings for ADCs where they couldn't work before," said EpimAb Biotherapeutics Inc. CEO and founder Chengbin Wu. In addition, he said, a bispecific scaffold targeting two tumor antigens is likely to increase the selectivity of ADCs, widening their therapeutic window.

"We think this type of targeted therapy with bispecifics can offer something immuno-oncology may not be able to offer," said Wu.



Select tumor-targeted bispecific antibody data at ASCO 2021

Company	Compound	Targets	Combo	Phase	Indication	No. pts	ORR	SD	Abstract
Janssen	Amivantamab	EGFR x c-MET	TKI	Ph I	Osi-relapsed EGFR-mutant NSCLC	45	36%	NA	9006
Alphamab	KN026	HER2 x HER2	None	Ph II	HER2-overexpressing GC/GEJC	18	56%	17%	e16005
Zymeworks/Beigene	Zanidatamab	HER2 x HER2	Chemo, anti-PD-1	Ph II	HER2+ breast cancer or GC/GEJC	50	NA	NA	TPS2656
Merus	Zenocutuzumab	HER2 x HER3	None	Ph I/II	NRG1 fusion-positive pancreatic cancer	10	40%	50%	3003
Boehringer	BI 936880	VEGF x ANG2	Anti-PD-1	Ph Ib	Solid tumors	145	6%	60%	2579

ORR - overall response rate; SD - stable disease; NSCLC- non-small cell lung cancer; GC/GEJC - gastric and gastroesophageal junction cancer; TKI - tyrosine kinase inhibitor

"Many ADC companies have come to us hoping to collaborate. It's a very interesting proposition that we intend to pursue."

Two birds in the same bush

The landscape of clinical bispecifics targeting two tumor antigens is clustered around a handful of target pairs, with EGFR, HER2 and VEGF taking center stage.

The products can also be grouped according to whether their design is primarily geared to improve efficacy by preventing resistance, or improve safety by increasing specificity.

Which strategy a company chooses will be reflected in both its choice of target antigens, and the way it tunes affinity. For example, a company whose primary goal is to hit a widely expressed target on a narrow set of cells will give the arm against its cell type-specific target a higher affinity than the arm against its functional target, Wu said.

Boehringer Ingelheim GmbH has disclosed a Phase I candidate, BI 905711, whose bispecific format is designed for selectivity. By anchoring onto the gastrointestinal tumor marker CDH17, it spares liver cells from the cell-killing activity of TRAILR2.

For resistance prevention, strategies are a split between hitting tumor cells through two separate pathways, and those aiming to completely shut down signaling through a single pathway.

Bispecific candidates against two different receptors on the same cell are among those that have been shown to induce receptor internalization and degradation.

"We realized there was this interesting and powerful mechanism of receptor co-

degradation that was triggered by bispecifics, but not combinations of mAbs," Wu said, adding the company has also seen the phenomenon with other target pairs. "This could be a more general type of mechanism, and that could have a profound impact."

J&J and EpimAb have both reported the effect for their EGFR x c-MET bispecifics; Merus N.V. (NASDAQ:MRUS) declined to disclose whether its compound triggered receptor internalization.

Compounds that hit two different pathways on the same cell generally also have a secondary benefit of increasing tumor selectivity.

A separate type of bispecific, known as biparatopic antibodies, hits the same target via two non-overlapping epitopes. This strategy prevents tumor escape via mutations to one domain and promotes receptor aggregation at the cell surface, which also increases internalization.

Merus' lead candidate Zenocutuzomab, while not biparatopic, is also designed to shut down a single pathway in two different ways. The HER3-targeted arm prevents the receptor from opening up to interact with its ligand NRG1, while the HER2-targeted arm prevents the HER2-HER3 interaction required for downstream signaling.

The company has designed its tumor-targeting bispecifics to also engage immune cell killing by incorporating engineered Fc domains. President and CEO Bill Lundberg told BioCentury such domains are not used in bispecifics designed to be immune cell engagers because they would induce undesirable antibody-dependent cellular cytotoxicity (ADCC) against effector cells.

Wildgust said that in addition to blocking EGFR and c-MET signaling and inducing the receptors' degradation, amivantamab also recruits macrophages and NK cells via engineered Fc domains.

In a *Molecular Cancer Therapeutics* study published in October, the company showed tumor cell killing was dependent on immune cell activity, including trogocytosis — a process by which immune cells transfer antigens from other cells onto their own cell surfaces.

Pairing off at ASCO

Among the take-homes from ASCO presentations on tumor-targeting bispecifics is the importance of biomarkers to determine which patients are most likely to benefit.

Janssen's ASCO presentations include an update on what it believes will be the major indication for amivantamab: patients with common EGFR mutations who develop resistance to TKIs.

"In patients with common EGFR mutations, one of the primary tyrosine kinase inhibitor resistance pathways is MET," Wildgust said. "We believe the antibody targets both the primary driver of the cancer, and also the primary mechanism of resistance."

The company's strategy is to completely shut down EGFR signaling by combining the extracellularly acting bispecific with an intracellularly targeted TKI.

Janssen is combining amivantamab with the company's Phase III-stage EGFR inhibitor lazertinib in NSCLC patients with EGFR exon 19 deletions or L858R mutations who progressed after treatment with the TKI osimertinib. The company showed the amivantamab/lazertinib combo had an ORR of 36% in 45 osimertinib-relapsed, EGFR-mutant NSCLC patients, with a median duration of response of 9.6 months.

Among 20 patients where tumor tissue was available to perform immunohistochemistry (IHC) testing for EGFR and c-MET, the company observed responses in nine out of ten patients with high expression of both markers, versus one out of ten patients who were IHC low.

Wu said biomarker-defined patient populations will also be key for EpimAb's EGFR x c-MET bispecific EMB01; the company is honing its undisclosed biomarker strategy via the dose escalation portion of its Phase I/II study.

He believes EMB01 will be effective as a monotherapy in this patient population, but would consider layering on an EGFR inhibitor, c-MET inhibitor or immunotherapy for more challenging patient populations.

Similarly, Alphamab Oncology Ltd. (HKEX:9966) showed an ORR of 56% in 18 HER2-overexpressing patients treated with its biparatopic HER2 x HER2 antibody KN026, versus an ORR of 22% in nine patients with low HER2 expression.

Merus' Lundberg said the company had initially tested Zenocutuzumab in breast cancer patients, but found the signal was not robust enough to move forward. A major breakthrough came in 2019 when the company's collaborators at Memorial Sloan Kettering Cancer Center showed initial proof-of-concept for the compound in patients with NRG1 fusions, which promote hyperactive HER3 signaling.

"Without selecting patients, you'll dilute out your signal," he said.

Ahead of ASCO, the company showed the HER2 x HER3 bispecific had an ORR of 40% in 10 pancreatic cancer patients with NRG1 fusions, and an overall ORR of 27% across all 33 NRG1 fusion-positive solid tumor patients in the study, who had a median of three prior lines of therapy.

Lundberg thinks the clinical data emerging for tumor-targeted bispecifics could revive interest in the approach.

"A few years ago, this approach was more in fashion, but it was difficult to do," he said. "If we continue to see success with c-MET x EGFR, and as we see success with HER2 x HER3, it will add a lot of momentum to the idea of targeting tumor antigens purely again."

TARGETS

ANG2 (ANGPT2) - Angiopoietin 2
CDH17 - Cadherin 17
c-MET (MET; HGFR) - c-Met receptor tyrosine kinase
DLL4 - Delta like canonical Notch ligand 4
HER2 (EGFR2; ErbB2; neu) - Epidermal growth factor receptor 2
HER3 (ERBB3; EGFR3) - Erb-b2 receptor tyrosine kinase 3
LGR5 (GPR49) - Leucine-rich repeat-containing G protein-coupled receptor 5
NRG1 (HRG1) - Neuregulin 1
TRAILR2 - (TNFRSF10B; DR5; CD262) - Tumor necrosis factor (TNF) receptor superfamily member 10b
VEGF - Vascular endothelial growth factor

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