

BioCentury

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PRODUCT DEVELOPMENT

INTERMITTENT MOVE BEYOND BLINCYTO

BY ERIN MCCALLISTER, SENIOR EDITOR

A swath of data at ASH shows that companies have been able to move beyond the 28-day continuous dosing of Amgen Inc.'s first-generation BiTE, Blincyto, to build next-generation antibodies with more convenient, intermittent dosing and a better safety profile.

Companies expect that these advantages, and the modality's relative lack of logistical baggage, will position the products to compete with CAR T cells as well.

Multispecific antibodies represented the third largest class of clinical cancer modality abstracts presented at the American Society of Hematology (ASH) meeting in San Diego, with several studies building on the first-generation bispecific T cell engager (BiTE), Blincyto blinatumomab (see "[Cell Therapy Momentum at ASH](#)").

While Blincyto, which targets CD19 and CD3, showed impressive efficacy, its commercial success has been hobbled by the need for continuous dosing and a black box warning for cytokine release syndrome (CRS) and neurotoxicity.

"This has been a significant impediment and makes it hard to do the basic logistics of delivering clinical care," said Bassil Dahiyat, president and CEO of Xencor Inc.

The challenges are due to Blincyto's structure, which lacks key domains that confer the stability and half-life of mAbs. As a result, companies have spent the last few years tinkering with ways to make the next generation of immune cell-engaging bispecifics more mAb-like.

Four of the companies with data at ASH have engineered human mAbs with two different antigen-targeting domains and showed that these new structures could overcome Blincyto's shortcomings. When combined with a stepped dosing regimen, these antibodies offer weekly dosing or better, and in some cases, reduced toxicity.

Efficacy comparisons are limited because the compounds were tested in different indications or subgroups of patients,

and none was tested in the same indication for which Blincyto is approved.

However, Roche's mosunetuzumab stood out on safety and convenience, with a competitive response rate from a 21-day treatment cycle, and CRS rates not exceeding grade 3 (see "[Table: Bispecific Data at ASH](#)").

Still, even if successful, many of these next-generation programs will have to compete with CAR T cell therapies, which have shown impressive response rates but are complicated to deliver. Companies believe that the lack of complex clinical preparation and delivery protocols for their multispecific antibodies will give them an advantage.

In the meantime, companies are increasing their options by running combination studies with other immunotherapies to boost efficacy and improve response durability.

BUILDING ON BLINCYTO

Since early clinical data for Blincyto showed response rates far exceeding standard of care (SOC), companies have focused on how to build a better multispecific antibody.

Blincyto was developed by Micromet Inc., which Amgen acquired in 2012 (see "[Amgen Swallows BiTEs](#)").

It was approved in 2014 to treat Philadelphia chromosome-negative relapsed or refractory B cell precursor acute lymphoblastic leukemia (ALL) based on a complete response rate (CRR) of 32% in 185 patients compared with 13% for historical controls.

But toxicity is a major drawback. In its clinical trials, Blincyto produced CRS rates of 7-15%, including events of grade 3 or higher in 3% of patients with relapsed/refractory ALL and 5% in the minimal residual disease (MRD)-positive setting. Also, 65% of patients experienced neurotoxicity, including 13% with grade 3 or higher toxicities.



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Uptake of Blinicyto has been slow. Amgen reported nine-month sales of \$167 million for Blinicyto as of Sept. 30, up 30% from \$129 million during the same period in 2017.

The molecule was constructed as two single-chain variable fragment (scFv) domains of an antibody joined with a synthetic linker. Each scFv domain is specific for a different antigen. Blinicyto's two scFv domains recognize CD3 on T cells and CD19 on the surface of B cells. The idea is that the bispecific molecules bring T cells physically to the cancer cells to stimulate an immune response.

However, Blinicyto lacks an Fc domain, which confers the stability of mAbs. As a result, Blinicyto has a half-life of only two hours, necessitating the continuous four-week dosing schedule. Patients must stay in the hospital for the first three to nine days of the initial cycle, with a shorter stay during the second cycle and no hospitalization requirements thereafter.

"Blinicyto was really pioneering in what it did to engage the T cells and the tumor antigen but what it lacked was all of the natural properties that antibodies have that make them wonderful drugs," said Dahiyat.

At ASH, Roche and its Genentech Inc. unit, Xencor and Regeneron Pharmaceuticals Inc. each presented data on multispecific T cell antibodies that have two different scFv domains, but otherwise incorporate all the domains of standard mAbs.

"When we saw the more interesting clinical data for Blinicyto emerge, we said 'we have to make bispecifics because they're very powerful,'" but it has to have more of the inherent drug-like properties of an antibody," Dahiyat told BioCentury. "What we're seeing at ASH is the first wave of clinical data now from a protein engineering effort that started around that time at Roche, Xencor, MacroGenics Inc., Amgen and many places to improve upon this first-generation technology."

Roche's mosunetuzumab, Regeneron's REGN1979, Xencor's XmAb14045 and Pfizer Inc.'s PF-06863135 are full-length antibodies in which each arm binds a different target. Roche also presented data for a second T cell bispecific, CD20-TCB (RG6026), which is a full-length mAb that has two CD20 binding sites and one CD3 domain to confer activity, even in the presence of anti-CD20s from previous lines of therapy.

HITTING THE MARKS

Roche's mosunetuzumab and Affimed N.V.'s AFM13 showed the clearest evidence yet that the tweaks to first-generation BiTEs are yielding improvements in tolerability and dosing.

Mosunetuzumab targets CD20 and CD3. CD20 is a much-used target in non-Hodgkin lymphoma (NHL) and is found on the surface of B cells. In the Phase I trial in patients with relapsed/refractory NHL, mosunetuzumab was given weekly for the first three weeks and every 21 days thereafter. To minimize the number and severity of CRS events, Roche used a stepped dosing regimen during the weekly administration, in which the dose was steadily increased until it reached its target level at week three. This week three dose strength was maintained for each of the 21-day dosing cycles.

The treatment led to an ORR of 34% in 47 patients with diffuse large B cell lymphoma (DLBCL), and 69% in 26 patients with relapsed, refractory follicular lymphoma. There were also no cases of grade 3 or worse CRS, and a 22.9% rate of lower grades of CRS. The pharma showed similarly high responses and low adverse events for its other CD20/CD3 T cell multispecific mAb, also in NHL.

"I really feel that this is a paradigm shift in lymphoma," said Nancy Valente, VP of global product development for hematology/oncology at Genentech/Roche. "We've got very promising efficacy and safety for both of these molecules and it's the kind of safety and efficacy that could provide a transformational benefit."

In the Phase I trial of CD20-TCB, instead of a stepped dosing regimen, patients were pretreated with Roche's anti-CD20 therapy Gazyva obinutuzumab, which reduces the number of B cells circulating in the body, in order to mitigate the potential risk of immune-mediated side effects such as CRS, the pharma told BioCentury.

Following treatment with Gazyva, the full dose of CD20-TCB was administered every two weeks, with no grade 3 or worse CRS events.

Affimed improved tolerability and dosing by constructing a larger molecule with greater binding affinity for its targets, rather than recapitulating a complete mAb. Unlike the other competitors, Affimed is harnessing NK cells rather than T cells by using the NK-cell marker Fcγ receptor IIIa (CD16a; FCGR3A; FcγRIIIa).

AFM13 was engineered from Affimed's ROCK platform to have a longer serum half-life than Blincyto by more than doubling its size, putting it above the threshold for renal clearance. As a tetravalent molecule, it has longer residence times in contact with immune effector cells, the biotech told BioCentury in a written response.

At ASH, Affimed presented data from a Phase I trial in nine patients with CD30-positive cutaneous lymphomas, in which AFM13 was administered weekly in six patients and continuously for five days in the other three. There were no cases of CRS.

"The CD16a engagement of innate immune cells allows the retargeting of NK cells and macrophages and thereby actualizes innate immunity to eliminate cancer cells. Such an approach appears to show a much better safety profile compared to T cell engagement," the company told BioCentury.

Affimed said it plans to use the weekly dosing regimen in a registrational study of AFM13 to treat peripheral T cell lymphoma (PTCL).

WEEKLY FOR THE WIN

Xencor and Regeneron also demonstrated efficacy and a better dosing regimen for their next-generation compounds. But both are still trying to optimize the dose to tamp down the CRS rates seen in early cohorts.

Regeneron presented data at ASH for its CD20/CD3 mAb REGN1979, which showed high response rates in a small cohort of relapsed/refractory follicular lymphoma patients. It reported one case of grade 3 or greater CRS, but this was mitigated in future patients through stepped dosing in which patients were first exposed to a lower dose, according to Israel Lowy, VP of clinical sciences and head of translational science and oncology.

"We're very excited about that," Lowy told BioCentury. "As we continue to dose up, we may be able to spread that out a bit more. Right now, we don't know if the one-week half-life we're seeing is intrinsic to the antibody or if it's a function of it being eaten up by the tumor via target-mediated clearance. It could be once we get past that then maybe the half-life approaches two weeks, which would be more typical of an antibody," Lowy said.

The response rate for REGN1979 was lower in the DLBCL population of 36 patients, where Regeneron said it would continue to test higher doses.

"We're thrilled about the data not only because it looks like a great, promising treatment for B cell lymphoma, but it's also validation of our whole approach," said Lowy.

Xencor's XmAb14045 targets CD3 and interleukin-3 receptor α (CD123), a marker on leukemic stem cells that is correlated with worse outcomes in patients with acute myelogenous leukemia (AML).

CONTINUOUSLY OPTIMISTIC

Among the new data for immune cell bispecific programs at ASH were four agents that rely on first-generation technology and continuous dosing. Nonetheless, the companies are optimistic their treatments could at the very least demonstrate POC ahead of longer-acting agents that are coming down the pike.

Amgen Inc. presented first-in-human data two bispecific T cell engager (BiTE) programs at the American Society of Hematology (ASH) meeting: AMG 420 and AMG 330. Both use the platform from which first-in-class Blincyto blinatumomab was developed, requiring continuous dosing. Data at ASH showed both produced grade 3 or worse cytokine release syndrome (CRS), like their predecessor.

However, AMG 330, which targets CD33 (SIGLEC3) and CD3, showed the highest response rates among four other first- and next-generation bispecific immune antibody programs presented at ASH to treat acute myelogenous leukemia (AML) (see "Table: Bispecific Data at ASH").

"The data we've released clearly demonstrate an anti-leukemic effect of the product as well as its safety and tolerability," said Elliott Levy, Amgen's SVP of global development.

Levy was similarly optimistic about AMG420, which targets BCMA (TNF receptor superfamily member 17; TNFRSF17; CD269). In a Phase I trial in multiple myeloma (MM), the BiTE resulted in responses in 7 of 10 patients (70%) treated with the same dose that will be tested in Phase II.

Amgen expects Phase I data next year for analogs of these BiTEs that use half-life extending technology, aiming for dosing at weekly or longer intervals.

Amphivena Therapeutics Inc. showed a 14-day continuous treatment cycle for its CD33/CD3 bispecific antibody AMV564, with no severe CRS events among the 26 patients with relapsed/refractory AML.

Jeanmarie Guenot, president and CEO, said the biotech would explore higher doses over the 14-day cycle and extend its initial duration. "We will go up in dose based on the promising safety and activity profile."

If Amphivena can improve responses and maintain the safety advantage with a higher dose over 14 days, Guenot believes AMV564 will have an advantage over longer continuous regimens.

The Phase I study also revealed the product had a half-life of two days, which could make it amenable to intermittent dosing. Based on this, "we started plans to explore different dosing regimens," Guenot said.

MacroGenics Inc. presented data at ASH for flotetuzumab, its first-generation bispecific antibody against CD3 and interleukin-3 receptor α (CD123) developed using the biotech's Dual-Affinity Re-Targeting (DART) technology program. The antibody was delivered via continuous dosing over 14-28 days. MacroGenics also has a next-generation version of the molecule in preclinical testing that incorporates the Fc domain, conferring a longer half-life. The biotech declined to give a timeline on when it might enter the clinic.

— Erin McCallister

Among 18 patients with relapsed/refractory AML, the mAb produced an ORR of 28%, comprising all CRs or complete responses with incomplete hematologic recovery (CRis). While 55% of patients experienced CRS, including 6% with grade 3 or greater at the active dose, the effect was more severe on the initial dose and usually resolved within one to four hours, the biotech said.

“This is very promising data and we are still dose escalating to optimize the dosing schedule,” said Dahiyat.

However, the AML population tends to be more frail because the patients are about 10 years older than NHL patients, making them more susceptible to treatment side effects. Still, Xencor plans to optimize the dose to see what the data show. “I don’t think it’s the case that just because it’s a bispecific and they’re so profoundly toxic that they can’t be used in a frail population. Those data are not in yet and we have to let it play out,” Dahiyat said.

He said the biotech will evaluate a stepped dosing regimen to help avoid or reduce the severity of CRS.

Pfizer presented early safety data for a weekly dosing regimen of its PF-06863135, a humanized IgG bispecific targeting CD3 and BCMA (tumor necrosis factor receptor superfamily member 17; TNFRSF17; CD269). In the ongoing Phase I trial of five patients, there were no cases of CRS reported. Efficacy data from the trial have not yet been reported and Pfizer couldn’t respond to questions in time for publication.

CARVING A NICHE

The next-generation immune cell bispecifics will also have to compete with CAR Ts, given the convergence around NHL.

Companies in the space think that the off-the-shelf delivery of their products should give them an edge, even if combination strategies are needed to match or exceed CART efficacy.

Roche and Regeneron presented data in relapsed/refractory NHL where there are two CAR Ts already approved — Yescarta axicabtagene ciloleucel from Gilead Sciences Inc. and Kymriah tisagenlecleucel from Novartis AG.

In clinical trials, the CAR Ts produced ORRs of 50-80% in patients with DLBCL — well above the rates reported for either of the Roche molecules or Regeneron’s REGN1979 in this patient population.

But the CAR Ts are burdened by much higher rates of CRS, cumbersome delivery and lack of availability at most hospitals. Less than 100 centers in the U.S. are certified to extract and subsequently infuse the personalized treatments.

CAR Ts are also making a splash in multiple myeloma (MM) trials, with products targeting BCMA (see “[Weekend ASH Presentations Hint at Future of BCMA CARs](#)”).

Amgen is aiming to compete with its BiTE technology, and presented data for a continuously dosed BiTE that targets BCMA.

Regeneron, Roche and Amgen are optimistic that their multispecific antibody programs will be able to find a niche.

“Bispecifics have a clear advantage because these are off-the-shelf products that would be ready when the patient needs them,” said Roche’s Valente. She added that this is particularly important in the heavily pretreated population included in the pharma’s trials of mosunetuzumab and CD20-TCB.

PROMISING BUT EARLY

Two oncologists who spoke with BioCentury were largely split on the early data for next-generation bispecific immune engager programs presented at ASH, with one declaring Roche’s mosunetuzumab an early leader and the other wanting more data.

Amitkuman Mehta and Amir Fathi’s differing opinions largely came down to the strength of the evidence. Mehta is an assistant professor in the lymphoma program at the University of Alabama at Birmingham, and Fathi is an assistant professor of medicine at Harvard Medical School.

Mehta, who specializes in non-Hodgkin lymphoma (NHL), was impressed by the robustness of the mosunetuzumab data and the responses across the different disease subtypes. “What impressed me in the data was the single activity in all of the patients. All had failed prior CD20 therapy and they still responded. Whether it was follicular, mantle cell, DLBCL or transformed follicular, they all had a response,” he said.

Mosunetuzumab targets CD20 and CD3 and was tested in patients with relapsed/refractory NHL who had failed a median of three prior therapies. The trial enrolled 131 patient and reported response rates of 34-69% across different disease subtypes (see “[Table: Bispecific Data at ASH](#)”).

Regeneron Pharmaceuticals Inc. also posted high response rates for its REGN1979 in relapsed/refractory follicular lymphoma but the population size was smaller at 17 patients and the ORR was lower in other disease subtypes.

“The effect was rather limited to follicular lymphoma and I didn’t see much activity in the other lymphomas, so I’d like to see more mature data on that to see if we’re seeing activity across the different types,” said Mehta, an investigator on the mosunetuzumab trial.

Fathi specializes in acute myelogenous leukemia (AML), where there were fewer patients studied in the data sets presented at ASH. As a result, he was more circumspect about the data presented for four different bispecific programs in this indication.

“On average the composite remission rates were 20-30%, which is promising, but I think that these modalities still require additional study in larger clinical trials. Also there are some challenges with certain agents in terms of cytokine release syndrome and logistically, with the continuous dosing of the drug,” he said.

The programs presented at ASH used one of two tumor antigens on their bispecific antibodies — CD33 (SIGLEC3) or interleukin-3 receptor α (CD123) — both of which are found on leukemic cells, but there was no consistent difference in efficacy or tolerability based on the tumor antigen targeted.

Fathi said it was too soon to know which strategy might be better. “We need more time to see which populations to study with these different targeted antigens to know which patients will benefit optimally.”

— Erin McCallister

BISPECIFIC DATA AT ASH

Data presented at the **American Society for Hematology** (ASH) meeting show that at least five companies have figured out how to build next-generation antibodies that avoid the continuous dosing of the first-generation BiTE, Blincyto blinatumomab from **Amgen Inc.** (NASDAQ:AMGN). Eight companies presented data from 10 different multispecific immune cell antibody programs at ASH, and six of the programs use next-generation technology to provide intermittent dosing, with four reducing cases of cytokine release syndrome (CRS) that were grade 3 or higher, compared to Blincyto.

Roche (SIX:ROG; OTCQX:RHHBY) and its Genentech Inc. unit reported the longest duration between treatments, with a 21-day gap between doses. Three other companies showed response rates in various cancers for multispecific antibodies that were administered weekly. **Pfizer Inc.** (NYSE:PFE) also reported safety data for its weekly regimen, but not efficacy results. The Roche, Pfizer and **Affimed N.V.** (NASDAQ:AFMD) programs showed no evidence of grade 3 or greater cytokine release syndrome (CRS).

Three other companies reported response data for four programs that rely on continuous dosing. Only one of the companies, **Amphivena Therapeutics Inc.**, was able to show a benefit of no grade 3 or worse CRS events. However, Amgen and **MacroGenics Inc.** (NASDAQ:MGNX) are developing next-generation programs that could be dosed weekly, and Amphivena said it will explore intermittent dosing for its program, AMV564.

ORR = overall response rate; CR = complete response; CRi = complete response with incomplete hematologic recovery; CRS = cytokine release syndrome; FL = follicular lymphoma; DLBCL = diffuse large B-cell lymphoma; trFL = transformed follicular lymphoma; B-NHL = B cell non-Hodgkin lymphoma; NR = not reported; (A) Blincyto label used; Amgen trial used complete response with partial hematologic recovery; Source: *BCIQ: BioCentury Online Intelligence, ASH abstracts and presentations, company announcements, Blincyto label*

Company	Program	Targets	Indication	Patients	ORR	CR or CRi	CRS	CRS ≥ grade 3	Dosing frequency
Amgen Inc. (NASDAQ:AMGN)	Blincyto blinatumomab	CD19/CD3	Relapsed/ refractory acute lymphoblastic leukemia (ALL)	NA	NR	32-42% (A)	7-15%	3-5%	Continuous 28 days
Intermittent									
Affimed N.V. (NASDAQ:AFMD)	AFM13	CD30/Fcy receptor IIIa (CD16a; FCGR3A; FcyRIIIa)	CD30-positive cutaneous lymphoma	9	44%	11%	0%	0%	Weekly and five-day continuous
Pfizer Inc. (NYSE:PFE)	PF-06863135	BCMA (tumor necrosis factor receptor superfamily member 17; TNFRSF17; CD269)/CD3	Multiple myeloma (MM)	5	NR	NR	0%	0%	Weekly
Regeneron Pharmaceuticals Inc. (NASDAQ:REGN)	REGN1979	CD20/CD3	Relapsed/ refractory non- Hodgkin lymphoma (NHL)	68; 17 w/FL; 36 w/DLBCL	FL: 65%; DLBCL: 31%	FL: 53%; DLBCL: 8%	47%	6%	Weekly
Genentech Inc. / Roche (SIX:ROG; OTCQX:RHHBY)	Mosunetuzumab (RG7828)	CD20/CD3e (CD3E)	Relapsed/ refractory NHL	131; 26 w/FL; 47 with DLBCL or trFL	FL: 69%; DLBCL/ trFL: 34%	FL: 39%; DLBCL/ trFL: 19%	23%	0%	Every 21 days or every 7 days for 3 weeks, then every 21 days
Genentech Inc. / Roche (SIX:ROG; OTCQX:RHHBY)	RG6026	CD20/CD3	Relapsed/ refractory NHL	64; 5 w/FL; 24 with B-NHL	FL: 60%; B-NHL: 25%	FL: 60%; B-NHL: 25%	22%	0%	Every 14 or 21 days
Xencor Inc. (NASDAQ:XNCR)	XmAb14045	Interleukin-3 receptor α (CD123)/CD3	Relapsed/ refractory acute myelogenous leukemia (AML)	66	NR	28% at 2 highest doses (n=18)	55%	6%	Weekly
Continuous									
Amgen Inc. (NASDAQ:AMGN)	AMG 330	CD33 (SIGLEC3)/CD3	Relapsed/ refractory AML	40	10%	10%	28%	10%	Continuous 14-28 days
Amgen Inc. (NASDAQ:AMGN)	AMG 420	BCMA/CD3	MM	42	31%	17%	38%	2%	Continuous for 4 weeks, then 2 weeks off
Amphivena Therapeutics Inc.	AMV564	CD33/CD3	Relapsed/ refractory AML	26	8%	8%	4%	0%	Continuous 14 days
MacroGenics Inc. (NASDAQ:MGNX) / Servier	Flotetuzumab	CD123/CD3	Relapsed/ refractory AML	27	26%	19%	93%	13%	Continuous for first 28 days, then 4 days on, 3 off

Amgen's SVP of Global Development Elliott Levy agreed. "Patients can be treated with a BiTE as soon as a seat is available in the infusion center," he said, adding that "to receive a CART, patients have to be stable enough to wait out the production period," which can take over two weeks.

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BASSIL DAHIYAT, XENCOR

The companies believe that the greatest value for the next-generation compounds will be in their tolerability profile, allowing them to be combined with other agents.

"The safety and efficacy we're seeing, particularly the safety, allows us the opportunity to combine with other therapies and we've already started those trials," Valente said. Roche has a Phase Ib/II trial of mosunetuzumab

plus its PD-L1 inhibitor Tecentriq atezolizumab, and a Phase I trial of mosunetuzumab plus the antibody-drug conjugate polatuzumab vedotin, which targets CD79b molecule immunoglobulin-associated β (CD79B; B29). Polatuzumab vedotin is in Phase III testing for first-line DLBCL.

Regeneron has also started a Phase I trial of REGN1979 plus its marketed anti-PD-1 inhibitor Libtayo cemiplimab-rwlc. The trial in patients with relapsed/refractory B cell lymphomas was started in 2016 and is expected to have data in 2021, according to ClinicalTrials.gov.

While CAR Ts have yet to make inroads in AML, the treatment landscape has seen six new drugs approved to treat the disease in the last two years. Most recent was AbbVie Inc.'s Venclexta venetoclax, a small molecule B cell lymphoma 2 (BCL-2; BCL2) inhibitor. 

COMPANIES AND INSTITUTIONS MENTIONED

AbbVie Inc. (NYSE:ABBV), Chicago, Ill.
Affimed N.V. (NASDAQ:AFMD), Heidelberg, Germany
American Society of Hematology (ASH), Washington, D.C.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Amphivena Therapeutics Inc., South San Francisco, Calif.
Genentech Inc., South San Francisco, Calif.
Gilead Sciences Inc. (NASDAQ:GILD), Foster City, Calif.
Harvard Medical School, Boston, Mass.
MacroGenics Inc. (NASDAQ:MGNX), Rockville, Md.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Regeneron Pharmaceuticals Inc. (NASDAQ:REGN), Tarrytown, N.Y.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
University of Alabama at Birmingham, Birmingham, Ala.
Xencor Inc. (NASDAQ:XNCR), Monrovia, Calif.

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