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[BLINCYTO TOXIC UNDERTOW SOON TO GO?](#)

Terrific bispecifics crash CAR T party: Watch data mature, says Xencor CEO

By Randy Osborne, Staff Writer

Enthusiasm for bispecific antibodies has anything but abated since late 2014, when the FDA granted accelerated approval of Amgen Inc.'s Blincyto (blinatumomab) for Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (ALL).

Bispecifics are tougher to manufacture, since they call for the modification, by various creative means, of an antibody to target two antigens. But that hasn't deterred major players from continuing to enter the fray. Increasingly, pundits are trying to stack up bispecifics' prospects against another hot zone in oncology: chimeric antigen receptor (CAR) T-cell therapies.

It's complicated. Since, unlike bispecific antibodies, they're used along with chemotherapy, CAR T approaches must somehow be measured for efficacy in the presence of the knockdown of lymphocytes and T cells that chemo brings. That also makes harder the chore of stacking up CAR T prospects' profiles against each other.

'GIVE IT A COUPLE OF YEARS'

"I think the comparison is going to be even more direct," said Bassil Dahiyat, CEO of Monrovia, Calif.-based [Xencor Inc.](#), an early stage player. "It's going to be, 'OK, CAR T with the conditioning chemo, compare that to bispecifics,' absolutely. But there are going to be many areas where you're not going to be able to compare, because there are segments where you're not going to try a CAR T. You're not going to try a CAR T in combination with, say, a kinase inhibitor in second-line lymphoma. The niche for CAR Ts is going to be extraordinarily narrower than that of antibodies generally. Even in the exact same space, relapsed/refractory adult ALL – where CD19 CAR Ts have made the biggest impact, pretty much the only impact, and where Blincyto's approved – look at the response-rate data for minimum residual disease conversion using Blincyto. Look at the data they're publishing now with Blincyto, where they've been treating for a couple more cycles. The differences between the CAR T response rates and durability [and Blincyto], with the exception of a few patients that go out really long, is not profound."

Data with bispecifics are just starting to mature. "I don't see the magic [of CAR Ts]" when laid alongside them, Dahiyat said. "It's not like the CAR Ts are 100 percent. It's not [even] like they're 90

percent. The initial headline numbers you see are exciting. Clearly this mechanism is working, and it's working in a lot of patients. But you shouldn't think of [the situation] as, 'If we compare bispecifics to CAR Ts, it's always going to be an uphill battle.' The problem is, there's not enough data out there yet for bispecifics. Give it a couple of years. We'll see where things stand then."

Drawn forward by the major benefits (and profits) that bispecifics promise, not only in cancer but in other indications such as hemophilia and immunotherapy, Xencor – which plans to start trials with two bispecifics this year – and other developers forge ahead. "The technology that we've used to build [our] portfolio of candidates is based on our longstanding work in Fc engineering," Dahiyat said. The company has built "a new Fc domain that spontaneously and very stably assembles into an Fc domain that has two different halves," he said. "You can then have anything you want at the top of each of those sides binding different stuff, using standard antibody engineering tools we've known and loved for years." A deal with Thousand Oaks, Calif.-based Amgen, struck in September of last year, gives the latter access to Xencor's technology, which Amgen will "plug into" five ongoing programs, he said.

FRENCH CONNECTION: MERUS TARGETS HER2

The first-ever bispecific antibody to gain marketing clearance in the world was Removab (catumaxomab) from Bad Homburg, Germany-based Fresenius SE & Co. KGaA, given the nod in 2009 by the European Commission for the treatment of malignant ascites (fluid build-up in the abdomen caused by cancer). Most common in ovarian, pancreatic and gastric tumors, with an incidence of 20 percent to 50 percent of all cases, malignant ascites (like the indication for which Amgen, of Thousand Oaks, Calif., won Blincyto approval in the U.S.) represents a relatively small market. Coming down the pike, though, is the bispecific ACE910 from Basel, Switzerland-based Roche AG and Chugai Pharmaceutical Co. Ltd., of Tokyo, for hemophilia A. The FDA in September of last year

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granted breakthrough therapy designation to ACE910 (RG6013, RO5534262) for the prophylactic treatment of people who are 12 years or older with hemophilia A with factor VIII inhibitors, and a phase III trial is under way. The batch of other larger firms with bispecific programs in the works include Amgen, Celgene Corp., Eli Lilly and Co., Regeneron Pharmaceuticals Inc., not to mention small- to midcap, pure-play outfits in the mix, such as Affimed Therapeutics AG, MacroGenics Inc. and Xencor.

A recent, 215-page report by Piper Jaffray on bispecifics found more than 60 constructs reported in the scientific literature and about 40 in clinical development. "Conceptually, altering an antibody to target two (or more) antigens instead of one is straightforward, but the mechanics of actually accomplishing this at scale is far from easy," noted the report. "A number of companies have created innovative solutions and the field is now exploding with activity."

Cambridge, U.K.-based F-star Alpha Ltd. kicked off the year with a deal under which it will work with Abbvie Inc., of North Chicago, to research and develop bispecifics in immunology. Terms were not disclosed, though the firms said F-star's Modular Antibody Technology, which introduces an antigen binding site into the constant region of an antibody to create an "Fcab," will be used against two targets and generate several candidates.

Also as 2016 began, Merus BV, of Utrecht, the Netherlands, and France's Institut Gustave Roussy joined forces to design and conduct basic, preclinical and translational research studies and early clinical studies with Merus' portfolio of bispecific antibody candidates, including those in early development with combinations of immunomodulatory molecules.

Gustave Roussy will take part in clinical trials with Merus' MCLA-128, a HER2xHER3 bispecific antibody candidate that is designed for the treatment of patients with HER2-expressing solid tumors, and Merus' MCLA-117, a CLEC12AxCD3 bispecific antibody candidate that is designed to recruit and activate T cells for the treatment of patients with acute myeloid leukemia.

CHECKPOINT INSPECTION

For its part, Xencor has XmAb14045 targeting CD123 and CD3, which could offer an alternative to CAR Ts in acute myeloid leukemia. XmAb13676 targets CD20 and CD3 and will be developed for B-cell malignancies. Xencor's strategy of T-cell engagement is also used by Amgen's anti-CD19 Blincyto – the drug puts CD19 with CD3, which is expressed by T cells – and has been taken up by others due for data reports in the next year or so, Piper Jaffray pointed out in the report.

Those include Roche's RG7828, Amgen's AMG330, REGN1979 from Regeneron, of Tarrytown, N.Y., and Rockville, Md.-based MacroGenics' MGD006, while "the list continues to grow as additional programs advance through and into the clinic." CD20 is a validated target for B-cell malignancies and Rituxan

(rituximab, Roche AG), when paired with chemotherapy, has greatly improved outcomes for patients with B-cell lymphoma and chronic lymphocytic leukemia (CLL).

"Nevertheless, disease relapse or recurrence occurs in virtually all patients with follicular lymphoma and CLL, and [in] about half of patients with aggressive B-cell lymphoma (e.g., diffuse large B-cell lymphoma). Thus, bispecific anti-CD20/CD3 may offer an attractive alternative with a distinct mechanism of action to increase cure rates in B-cell malignancies," in Piper Jaffray's view. "CD33 and CD123 are interesting targets for acute myeloid [leukemia], but [have] yet to be validated in clinic." On a similar note, Heidelberg, Germany-based Affimed's AFM13, an NK cell engager that targets CD16 and CD30, has shown cause for optimism in Hodgkin's lymphoma, but the dosing regimen is still up in the air. The compound may turn out to be synergistic with anti-PD-1 antibodies.

Dahiyat predicted Xencor's technology platform "is going to be a leader [in bispecifics], but even if I'm wrong about that, the molecular engineering approaches have finally gotten to the point where the promise of bispecific antibodies can start to bear fruit. We're just entering the clinic with this new generation. Regeneron and Roche just put some things in, and [during] the next year or two years, we'll start seeing real data emerge. Imagine if you had molecules that had the kind of activity profile of a Blincyto but didn't have the acute toxicity, that didn't have the need for an infusion pump, [and] that could be given every week or two, like Rituxan."

Regeneron and Roche bear "strength because of their scale and capability," he said. "The approach they're taking is a good one. Make [the drug candidates] behave like antibodies, build them like antibodies, go to the trouble of having antibody-like structures. That will pay off in the good pharmaceutical properties and the flexibility of how you can engineer the molecule."

Engineering is "another problem that people don't recognize with CAR Ts, when they think about comparing them to antibodies," he said. With the latter, "you can engineer and prototype and fiddle with them. You can try things preclinically very easily. Many candidates can be tried, even with a small company like Xencor."

As biology is better understood, engineering of antibodies will grow still more complex. "In a decade, we're not going to talk about a bispecific or trispecific antibody," Dahiyat said. "It's just going to be an antibody, and whether it's a bi- or tri- as a mono- [is something] you'll ask as the second question. That's how the field's going to have to go, because there have not been that many new, exciting targets that have emerged for a regular antibody to impact in the last decade. You've got PCSK9s, you've got CGRPs for migraine." PD-1, he noted, "is a much older target. People have just been trying for years and they finally got it over the finish line."

Combination therapies with checkpoint inhibitors “are part of the future” as well, Dahiyat said.

“Hopefully, we can start doing that sooner rather than later, but we’re not quite at that step yet.” Solid tumors eventually will be attacked with greater success. “The potential is certainly there for tumor-associated antigen CD3 bispecifics,” he said, though solid tumors are less selectively expressed and pose special difficulties. “They can be expressed in healthy tissues that you

don’t want to ablate. Your body is incredibly tolerant if, in the process of blasting a hematological tumor, you also blast a bunch of the healthy blood cells. But your body might not be as tolerant if, in the process of blasting a solid tumor, you blast the intestines.”

Dahiyat predicted “an explosion in the diversity of biologies we can hit” as work continues with bispecifics, and said researchers are only “in the infancy of exploiting” the approach.