By Randy Osborne, Staff Writer

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

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.

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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
CD20 is a validated target for B-cell malignancies and Rituxan® adds another dimension, as it engages the CD3 receptor on T cells. This combination of B-cell and 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 engaged with combinations of immunomodulatory molecules. This 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 just put some things in, 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 regular antibody to impact in the last decade. You’ve got PCSK9s, you’ve got CRGRPs 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.