ADCs – The New Frontier

Next generation antibody-drug conjugates, like T-DM1, are meant to kill the cancer – not the patient.

BY BOB CARLSON, MHA

Important advances in oncology often make their debut at the annual meeting of the American Society of Clinical Oncology (ASCO) held each June.

What made the biggest splash at this year's meeting was Abstract LBA1 — "Primary results from EMILIA, a phase III study of trastuzumab emtansine (T-DM1) versus capecitabine (X) and lapatinib (L) in HER2-positive locally advanced or metastatic breast cancer (MBC) previously treated with trastuzumab (T) and a taxane" — authored by Kimberly L. Blackwell, MD, associate in medicine at Duke University Medical Center, and 13 other researchers from the United States, United Kingdom, Italy, Germany, South Korea, France, and Canada.

T-DM1 is an antibody-drug conjugate (ADC) consisting of two components joined by an engineered "linker." The first component, trastuzumab (Herceptin), is a monoclonal antibody that binds to tumor cells that overexpress the human epidermal growth receptor 2 (HER2) in breast and other cancers. DM1 is a tubulin-acting cytotoxic agent developed by ImmunoGen, in Waltham, Mass., for targeted delivery to cancer cells by antibodies. DM1 that attaches through the use of a thioether linker, as in T-DM1, is referred to as emtansine. T-DMI is in global development by Roche under an agreement between ImmunoGen and Genentech.

When a patient is infused with an ADC, it circulates in the bloodstream until it encounters receptors on the exterior of the target tumor cells and binds to them. An ADC compound enters a tumor cell through a process known as endocytosis. Inside the cell, the cytotoxic agent is released from the antibody and kills the tumor cell.

ADCs offer formidable theoretical advantages over conventional chemotherapy — they attach specifically to tumor cells with their target receptors while not affecting healthy cells that don't have those receptors. That means the cytotoxic agents delivered by ADCs can be much more potent than systemic chemotherapeutic agents, which do not discriminate between cancer cells and healthy cells. It also means that patients may experience fewer and less severe adverse events than they would with systemic chemotherapy.

Compared with patients in the EMILIA study treated with capecitabine (Xeloda) and lapatinib (Tykerb) (a cohort referred to as "XL"), patients given T-DM1 experienced a statistically significant improvement in progression-free survival (PFS, median 9.6 months vs. 6.4 months).

A deeper analysis, published Oct. 1 in the *New England Journal of Medicine,* showed that patients treated with T-DM1 survived a median of 5.8 months longer than those who received lapatinib plus capecitabine: 1- and 2-year overall survival (OS) rates for T-DM1 patients were 84.7 percent and 65.4 percent, respectively, compared with 77.0 percent and 47.5 percent, respectively, for the XL group.

Some 43.6 percent of patients treated with T-DM1 experienced an objective response (OR), compared with 30.8 percent of XL patients.

"We're very excited to be soon unveiling a third-generation ADC technology" says Clay B. Siegall, PhD, Seattle Genetics president and CEO.

(The FDA generally defines OR as the sum of partial responses plus complete responses.) The median duration of response was almost double in T-DM1 patients, and a comparison of serious adverse events favored T-DM1. To the lead investigator, T-DM1 did its job in a far more patient-friendly way than chemotherapy did.

"The drug worked," Blackwell wrote in a June ASCO news release. "It was significantly better than a very effective approved therapy for HER2-overexpressing metastatic breast cancer.... Patients don't lose their hair from this drug. For patients facing metastatic breast cancer, this is a breakthrough."

Brentuximab vedotin

Using antibodies to deliver toxic payloads to animal model cancer cells was first described in the literature in the 1960s. Clinical trials with murine immunoglobulin G (IgG) ADCs were conducted in the 1980s.

Pfizer and Wyeth collaborated on gemtuzumab ozogamicin for injection (Mylotarg), a humanized

IgG4 antibody that binds to the CD33 antigen, conjugated with the cytotoxic antitumor antibiotic calicheamicin. Mylotarg was approved by the FDA in 2000 for treating acute myeloid leukemia but was withdrawn after a post-approval study of Mylotarg plus chemotherapy failed to demonstrate improved survival. Study participants on Mylotarg experienced increased fatal toxicity compared with patients on chemotherapy alone.

Genentech submitted a biologics license application (BLA) for T-DM1 in August, which was accepted by the FDA and granted priority review on November 6; approval is expected in February 2013. But T-DM1 would not be the first effective ADC — that distinction belongs to brentuximab vedotin (Adcetris), developed by Seattle Genetics, in Bothell, Wash., which was granted accelerated approval in 2011. Indicated for the treatment of Hodgkin's lymphoma and systemic anaplastic large cell lymphoma, Adcetris is a CD30 antibody linked to the cytotoxin auristatin, which blocks cell division.

Like many company heads in the ADC business, Seattle Genetics president and CEO, Clay B. Siegall, PhD, has been working on ADCs for decades. Before cofounding Seattle Genetics in 1998, Siegall, coauthor of 70 publications and holder of 15 patents, was with the National Cancer Institute and the Bristol-Myers Squibb Pharmaceutical Research Institute.

"We started putting out data on Adcetris about five years ago, and we've been at ASCO's annual meeting now for four or five years, but not until August 2011 did we get Adcetris approved," says Siegall. "Once a drug is approved, people get a lot more interested."

A safe and effective ADC like Adcetris must possess many properties: antibody specificity, avidity, and affinity for the antigens expressed on the surface of a cancer cell; antibody internalization so the ADC gets inside cancer cells; cytotoxin potency so the cancer cell is killed or stops dividing; and linker stability so the antibody and the cytotoxin stay together in the bloodstream but cleave (break their chemical bond) inside a tumor cell to activate the drug payload. Each of these properties is essential, and trying to optimize one invariably means making changes to the others.

T-DM1 is Genentech's most advanced ADC. About 25 ADCs for solid tumors and hematologic malignancies are in the company's pipeline.

For example, SGN-15, a first-generation Seattle Genetics ADC, failed a clinical trial in 1999 because the cytotoxin molecule was not potent enough. But in creating a more potent and easier-to-manufacture synthetic cytotoxin (auristatin), they were also able to simplify the design of a more stable linker. Thus was born Adcetris, the second generation ADC. A new high-throughput screening process that identifies antibodies with the right properties is now driving the next generation of ADCs.

"We're very excited to be unveiling a third-generation ADC technology toward the end of 2012," says Siegall. "We have a brand new drug linker unit and a new drug. Three additional ADCs with this new technology that are wholly owned by Seattle Genetics, some for liquid cancers and some for solid cancers, should enter clinical trials the first half of 2013."

When Siegall says "wholly owned," he means that these new ADCs are not the products of collaborations with other pharmaceutical companies. Although the company has partnered with, among others, Abbott, Pfizer, Genentech, Bayer, Agensys, and Millennium, strategic partnering seems to be giving way to proprietary ADC development.

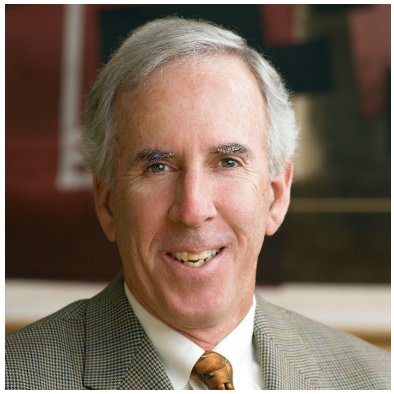
"We will continue to see a lot of partnering, but because we're a much bigger, stronger company, we're going to probably spend most of the time developing drugs on our own," says Siegall.

Conceptually very simple

Daniel M. Junius, CEO of ImmunoGen, sees it much the same way. ImmunoGen partners include Lilly, Genentech, Sanofi, Novartis, Amgen, Bayer, and Biotest. Of the 10 ImmunoGen ADCs now in the clinic, three are proprietary to ImmunoGen and seven the result of collaborations.

"We're migrating to a much more proprietary-focused strategy," says Junius. "Back in our early development days, some of the partnerships we entered into were for financial reasons, some were to access targets that we couldn't access on our own, like HER2, and some were to provide a broader base across which to demonstrate proof of concept of the technology. Now there's much greater value in developing a proprietary compound."

ImmunoGen uses targeted antibody payload (TAP) technology to create a T-DM1 linker that is "noncleavable," which means the linker does not separate from the cytotoxin but uses a different mechanism to activate the



"ImmunoGen's TAP linker technology and emtansine cytotoxin turned Genentech's trastuzumab into T-DM1," says ImmunoGen CEO Daniel M. Junius, "and generated all the buzz at the ASCO meeting."

cytotoxin inside the cancer cell. ImmunoGen's portfolio also includes two cleavable linkers and a linker that counteracts drug resistance by the cancer cell.

"Each linker is designed to convey specific properties that will allow us to optimize the configuration when going after a specific type of cancer," says Junius. "What you're dealing with on both sides is a system, and you need to understand both systems and how they interact. Each element has to be highly refined and understood when it's applied to the biology of a cancer cell. There are a lot of moving parts here — conceptually very simple, but in practice, extremely complicated."

ImmunoGen's collaboration with Genentech goes back to the late 1990s, when trastuzumab was approved for treating HER2-positive breast cancer. ImmunoGen approached Genentech with the idea of developing an ADC using its TAP technology. The license that ultimately led to T-DM1 was executed in May 2000.

One therapeutic approach

"What's unique about T-DM1 is that the antibody trastuzumab is both a therapeutic antibody targeting an over-expressed oncoprotein and something that delivers a cytotoxin," explains Stuart Lutzker, MD, PhD, Genentech vice president of oncology, early clinical development. "The naked antibodies in most other ADCs in development don't have any therapeutic benefit."

Although the ImmunoGen platform offers almost unlimited conjugation sites, the number of cytotoxic drugs linked to T-DM1 was carefully chosen, says Lutzker. "There is a 'sweet spot' drug-to-antibody ratio for T-DM1 where attaching more cytotoxin molelcules reduces antibody stability in the bloodstream and increases the rate at which circulating ADCs are metabolized by the liver." T-DM1 potentially will be an improvement over systemic chemotherapy, says Lutzker, but in and of itself, it forms one therapeutic approach to treating the cancer. The question is, he says, will an ADC overcome drug resistance?

"In oncology, be it Hodgkin's disease or diffuse large B-cell lymphoma, many of the curative regimens make use of multiple chemotherapy agents, and that's how you cure people. There aren't enough antibody-drug conjugates in the clinic right now to start combining them. But if you can determine what makes a safe and effective antibody-drug conjugate and you have multiple good targets, for a given cancer, there could ultimately be combinations of these."

T-DM1 is also being evaluated in three different lines of therapy and in combination with other medicines, including a frontline setting in combination with pertuzumab (Perjeta), a new Genentech personalized medicine approved last June. In combination with trastuzumab and chemotherapy, pertuzumab is the first medicine to improve on trastuzumab and chemotherapy for previously untreated HER2-positive metastatic breast cancer.

"We're studying T-DM1 in the front-line setting where people may be able to take the drug longer before their disease progresses, because the disease may not be as resistant at that point," Lutzker says. "We're also looking at it for adjuvant therapy. Ultimately, we'd like these drugs to be evaluated in less heavily pretreated patients with earlier disease."

T-DM1 is the most advanced Genentech ADC. About 25 ADCs for solid tumors and hematologic malignancies, including breast, ovarian, prostate, non-Hodgkin's lymphoma, colon, kidney, pancreatic, lung, liver, multiple myeloma, and melanoma are in the company pipeline. Nine of these ADCs are in clinical development, including T-DM1. Among the remaining eight is an anti-CD22 ADC, which is being investigated in a dose-escalation study, both as a single agent and in combination with rituximab (Rituxan) in non-Hodgkin's lymphoma and chronic lymphocytic leukemia. All eight of these ADCs utilize Seattle Genetics technology. Genentech is also actively collaborating with Nerviano Medical Sciences, in Milan, Italy, and Spirogen, in London.

Pyrrolobenzodiazepines

"The very early chemotherapy drugs interacted with DNA to stop the machinery that allows cancer cells to replicate," explains Christopher Martin, PhD, chief executive officer of Spirogen. But the cell's DNA repair machinery is often able to overcome that damage, Martin says. "Pyrrolobenzodiazepines (PBDs) fit very snugly into the DNA without distorting its helical geometry, so they avoid that repair machinery. Instead, they put a link across the two strands of genomic DNA, so when the cell tries to divide, it comes across this staple and finds it can't, and then the cell goes into apoptosis [programmed cell death].

These molecules are exquisitely effective at killing tumor cells."

Briefly, that's how PBDs work and why these extremely potent low molecular weight molecules could go a long way to solving the problem of cancer cell drug resistance. How potent are PBDs? Between 1,000 to 10,000 times more potent than systemic chemotherapeutics and between 100 and 1,000 times more potent than other cytotoxins used in ADCs.

Cleavable and noncleavable linkers are integral to Spirogen PBDs. The company licenses its technology to pharmaceutical companies, like Genentech, and ADC companies, like Seattle Genetics. The majority of Spirogen shares is owned by Celtic Therapeutics Management, LLLP, a private equity fund founded by biotech investment banker Stephen Evans-Freke and former Pfizer exec Peter Corr. Celtic Therapeutics is also the majority owner of ADC Therapeutics SARL, based in Lausanne, Switzerland. In collaboration with Spirogen, ADC Therapeutics will pursue clinical development of several programs within two years.

Fleximer polymer

Another linker technology is the biodegradable Fleximer polymer, developed by Cambridge, Mass.-based Mersana Therapeutics. In 2011, New Enterprise Associates (NEA), in Chevy Chase, Md., led the financing of Mersana Therapeutics, with Pfizer Venture Investments, Fidelity Biosciences, ProQuest Investments, Rho Ventures, and Harris and Harris Group. Mersana chairman David Mott, who had been CEO of MedImmune, is NEA general partner and head of the firm's healthcare investing practice.

"With the Mersana technology you can really optimize the linkers so that if you were conjugating two different chemotherapeutic agents on a Fleximer polymer backbone, you could use the perfect linker for each one," says Mott. "There's a lot more flexibility with respect to the type of targeting agents, the type of drug payload, the amount of drug payload, and the linker chemistry that you can use to attach all of those different things."

According to Mott, the Fleximer technology enables the use of antibody fragments as targeting agents in addition to full-length antibodies.

Because as many as 15 to 30 drug payloads can be delivered by one Fleximer ADC, less-toxic drugs can be used, reducing the risk of off-target toxicity. The ability to load more drug and maintain high solubility also expands the choice of toxin to those with new mechanisms of action, allowing the payload to be tailored for a given cancer type more effectively. A targeting antibody or antibody alternative and diverse drug payloads can be attached to the Fleximer backbone with different linkers to precisely control the mechanism, rate, and localization of drug release, depending on which moiety is supposed to cleave inside the cancer cell. The soluble Fleximer backbone also permits fine-tuning of the half-life of an ADC in the bloodstream and can drastically improve solubility and pharmacokinetics.

Mersana has inked deals with Endo Pharmaceuticals, the antibody technology company Adimab, and several other collaborators. Mott expects the first Mersana ADC to enter clinical trials in about two years. "The T-DM1 data that came out of the ASCO meeting earlier this year and the approval of Adcetris have catalyzed a renewed enthusiasm, credibility, and interest in this space," says Mott. "Now, we want to take it to the next level."

Grace's story

It started with a cough that wouldn't go away. An X-ray revealed a large mass in Grace's chest that turned out to be Hodgkin's lymphoma. She did six months of ABVD, a multi-drug chemotherapy, and one month of radiation treatments. Three years later, in 2005, the cancer returned and she tried natural methods such as acupuncture, nutritional supplements, Chinese herbs, and a healthier diet.

Although these methods seemed to help, they were expensive and not achieving fast results. So Grace looked to her oncologist, who referred her to the Baylor University Medical Center, in Dallas, for an autologous stem cell transplant. Three months later, the cancer returned and breathing became difficult.

Her new oncologist told Grace about a clinical trial of a new drug, SGN-35, at the MD Anderson Cancer Center in Houston. That was in February 2010. Within two months, imaging showed that her tumor had shrunk by half and by August, it was gone. That was also the month SGN-35, Seattle Genetic's Adcetris, was approved by the FDA. "This drug has truly been life-changing for me because I wouldn't be here otherwise," says Grace.

Grace (not her real name) is a 34-year-old college-educated single mother who owns and manages several properties. "Business is great and I feel wonderful," says Grace. I'm exercising every day and eating healthy. I have tons of energy. People wouldn't know that I have cancer. I look 10 years younger."

Bob Carlson, MHA, writes exclusively about healthcare. He lives near Zionsville, Ind. He can be reached at editor@biotechnologyhealthcare.com.