Anti-CD38 Monoclonal Antibodies Called Next 'Blockbuster' Drug Class for Myeloma

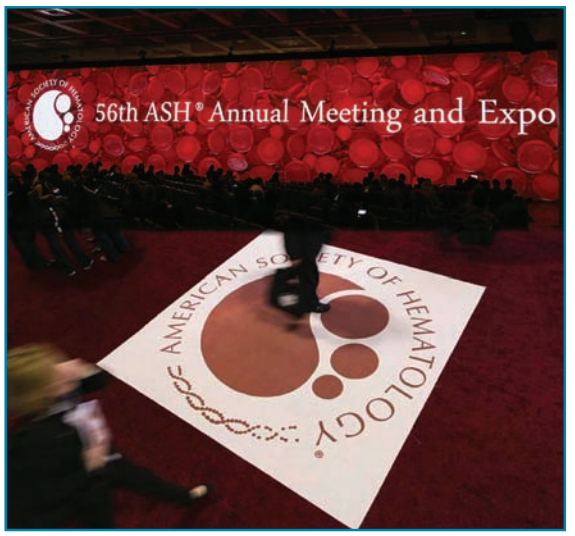
BY ROBERT H. CARLSON

SAN FRANCISCO—Are anti-CD38 monoclonal antibodies the next blockbusters in treating multiple myeloma? That was one investigator's appraisal here at the American Society of Hematology Annual Meeting.

"I think these CD38 antibodies are the new blockbuster drugs for multiple myeloma," said Thomas G. Martin III, MD, Clinical Professor of Medicine in the Adult Leukemia and Bone Marrow Transplantation Program and Associate Director of the Myeloma Program at the University of California, San Francisco.

"Antibodies have worked very well with drugs like rituximab in lymphoma, but in myeloma we're 10 years behind. Finally we have some that work."

Martin presented trial data on the anti-CD38 agent SAR650984; and data from another anti-CD38 agent, daratumumab, were reported by Philippe Moreau, MD, Head of the Hematology Department at University Hospital of Nantes, France.



Daratumumab, SAR650984, & MOR202

Martin explained that there are currently three anti-CD38 antibodies under investigation for multiple myeloma—daratumumab, SAR650984, and MOR202. All bind to a different part of the CD38 receptor, "but whether that makes any clinical difference we don't know at this time."

He said the humanized IgG1 monoclonal antibodies bind selectively to the CD38 receptor and "flag down the immune system."

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THOMAS G. MARTIN III, MD: "Antibodies have worked very well with drugs like rituximab in lymphoma, but in myeloma we're 10 years behind. Finally we have some that work."

A blockbuster would be an agent with significant single-agent activity in the front-line setting that also combines effectively with proven agents in the relapsed/refractory setting, he said. "With the two 'blockbuster' classes of drugs we have now, the immunomodulators [IMiDs] and the proteosome inhibitors, we have advanced the overall survival of patients with myeloma, from potentially three years to seven to 10 years, although in a more heavily pretreated population, such as the patients in these two trials, the average survival is less than one year."

Martin presented Phase Ib data from the TCD11863 dose-escalation trial of SAR650984 combined with lenalidomide and dexamethasone (***Abstract 83***), which was funded by Sanofi. At nine months' follow-up the overall median progression-free survival time was 6.2 months, and median progression-free survival had been not reached.

He said this was a promising combination because SAR650984 stimulates the immune system while lenalidomide is an immunomodulator.

Preclinical studies showed synergy between SAR650984 and lenalidomide, he said, and use of the former as a single agent in a similar group of patients produced an overall response rate of approximately 30 percent.

This was a heavily pretreated population, with no upper limit on prior therapies, Martin pointed out. The median number of prior regimens was seven with four median prior lines of therapy, and all patients did have adequate bone marrow reserve at study entry.

A total of 94 percent of patients had received prior lenalidomide; 94 percent, prior bortezomib; 29 percent, prior pomalidomide; and 48 percent had prior carfilzomib.

"Many of these patients were what we consider 'double refractory'—i.e., refractory to our most potent blockbuster drugs," he said.

PHILIPPE MOREAU, MD: "By targeting a simple molecule expressed by the cancer cells, this therapy has the potential to become a potent addition to conventional treatment."

The starting regimen was 3 mg/kg every other week with standard doses of lenalidomide and dexamethasone, increasing to 10 mg/kg every other week.

The regimen was well tolerated with no unexpected toxicities, Martin said, although there were infusion reactions often seen with antibody agents. Those led two patients to discontinue treatment—one with a serious anaphylactic reaction and the other with non-serious maculopapular rash.

Most infusion reactions were seen in cycle 1, and none after cycle 2. The response rate in the 31 patients treated was 58 percent at nine months follow-up, with a clinical benefit rate of 65 percent (including minor responses).

> The pharmacokinetics of SAR650984 and lenalidomide appear to be independent of each other.

Overall response in the 24 patients who received the highest dose (10 mg/kg) was 63 percent, which Martin pointed out was double the single-agent response rate. These included two stringent complete responses.

The overall response rates were 50 percent in the 26 patients who were relapsed or refractory to IMiDs, 40 percent in the 15 patients refractory to

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> SAR650984 stimulates the immune system and lenalidomide is an immunomodulator, making the combination promising.

Accelerated Approval for Olaparib for Advanced Ovarian Cancer, along with Companion Diagnostic Test

The Food and Drug Administration has granted accelerated approval to olaparib (Lynparza, made by AstraZeneca) to treat women with advanced ovarian cancer associated with defective BRCA genes, as detected by an FDA-approved test—i.e., in this case, Myriad's BRACAnalysis CDx, which was approved at the same time.

Lynparza is a poly ADP-ribose polymerase (PARP) inhibitor that blocks enzymes involved in repairing damaged DNA. It is intended for women with heavily pretreated ovarian cancer that is associated with defective BRCA genes.

"The approval constitutes the first of a new class of drugs for treating ovarian cancer," said Richard Pazdur, MD, Director of the FDA's Office of Hematology and Oncology Products. "Lynparza is approved for patients with specific abnormalities in the BRCA gene and is an example of how a greater understanding of the underlying mechanisms of disease can lead to targeted, more personalized treatment.

The approval was accompanied by approval of the companion BRACAnalysis CDx diagnostic to detect the presence of mutations in BRCA genes in blood samples from patients with ovarian cancer. The BRCA genes are involved with repairing damaged DNA and normally work to suppress tumor growth. Women with mutations resulting in defective BRCA genes are more likely to get ovarian cancer, and an estimated 10 to 15 percent of all ovarian cancer is thought to be associated with hereditary BRCA mutations.

As explained in an FDA news release, the agency evaluated BRACAnalysis CDx's safety and efficacy under the premarket approval pathway used for high-risk medical devices. Until now, the manufacturer, a clinical laboratory, had been marketing the test—although not specifically as a companion diagnostic—without FDA approval as a laboratory-developed test (LDT)—i.e., a test designed, manufactured, and used in a single laboratory.

"The approval of safe and effective companion diagnostic tests and drugs continue to be important developments in oncology," said Alberto Gutierrez, PhD, Director of the FDA's Office of In Vitro Diagnostics and Radiological Health. "We are very excited that the BRACAnalysis CDx is the FDA's first approval of an LDT under a premarket approval application and is the first approval of an LDT companion diagnostic. The use of companion diagnostics helps bring to market safe and effective treatments specific to a patient's needs."

Common side effects of Lynparza included nausea, fatigue, vomiting, diarrhea, distorted taste (dysgeusia), indigestion, headache, decreased appetite, common cold-like symptoms, cough, arthralgia, musculoskeletal pain, myalgia, back pain, dermatitis, and abdominal pain. Serious side effects included the development of myelodysplastic syndrome, acute myeloid leukemia, and lung inflammation.

The most common laboratory abnormalities were increased creatinine, increased average volume of red blood cells, decreased red blood cell count, decreased white blood cell count, and decreased platelet levels.

In June, Lynparza was reviewed by the FDA's Oncologic Drugs Advisory Committee for potential use as maintenance therapy, but the vote was 11 to 2 that the data did not support accelerated approval for this use. After the meeting, the company submitted additional information supporting Lynparza's use for a different use: in patients with mutated BRCA genes (gBRCAm)-associated ovarian cancer who have received three or more chemotherapy treatments.

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carfilzomib; and 33 percent in the nine patients relapsed/refractory to pomalidomide. Median progression-free survival was 6.2 months.

Martin said the pharmacokinetics of SAR650984 and lenalidomide appear to be independent of each other.

"This combination was well tolerated, and in my mind had a fairly dramatic response with two-thirds of the patients having responses.

"The next five years are going to be really interesting, moving these drugs from the refractory setting to the less refractory setting to front line. It's going to be really exciting."

The next step will be a randomized trial of SAR650984-lenalidomide-dexamethasone versus lenalidomide-dexamethasone to compare outcomes, he said.

> The challenge with monoclonal antibodies is the infusion time and the schedule.

"It could well be you'll see a really striking PFS advantage overall," Richardson said.

Martin said he thought the progression-free survival may not change very much but that the duration of response may indeed improve. Richardson suggested that an IMiD might be the best to combine with SAR650984, for a co-immune-stimulatory effect, and Martin agreed.

Martin was asked to comment on the SAR650984 maximum tolerated dose (MTD), which had not been reached.

"I don't know what Sanofi has planned, but I would love to increase the dose of SAR—double or even triple it," he answered. "That may help with progression-free survival and duration of response."

SAAD USMANI, MD: "Anti-CD38 monoclonal antibodies are by far the most exciting drugs that are in development in multiple myeloma."

Paul Richardson: 'Remarkable Results'

After Martin's presentation, session co-moderator Paul G. Richardson, MD, Clinical Director of the Jerome Lipper Myeloma Center at Dana-Farber Cancer Institute, called the results remarkable, especially given the short follow-up of nine months "and already seeing a progression-free survival of 6.2 months."

Daratumumab Tested with Backbone Regimens

European researchers in the MMY1001 trial hypothesized they could potentially improve response rates for the anti-CD38 antibody daratumumab by combining it with a standard regimen, so they combined it with four standard regimens: bortezomib-dexamethasone (received by six patients), bortezomib-thalidomide-dexamethasone (also six patients), bortezomib-melphalan-prednisone (also six patients), and pomalidomide-dexamethasone (seven patients) (***Abstract 176***).

The 25 patients in this four-arm, open-label Phase Ib trial, which was sponsored by Jansen Research & Development, had newly diagnosed, relapsed, or refractory disease. The dose of daratumumab for all patients was 16 mg/kg.

Moreau reported safety data in the trial of 17 patients in the three bortezomib

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arms. At a median of 44 days there were infusion-related reactions, which did not interrupt treatment, but no unexpected adverse events. Although this was a safety trial, he was able to report overall response rates of 100 percent in the newly diagnosed group and 50 percent in the relapsed group.

No patients receiving front-line treatment achieved a complete response, but there was one complete response in the pomalidomide arm. All responses were seen in cycle 1, and median time to first response was approximately 25 days.

Because of the small size of this study, the response rates are probably underestimated, Moreau said. "By targeting a simple molecule expressed by the cancer cells, this therapy has the potential to become a potent addition to conventional treatment."

Patients Eager to Enroll

At a news conference at the meeting highlighting newsworthy lymphoma and myeloma abstracts, Martin was asked what these trial results might mean to community oncologists. He said it should encourage them to refer appropriate patients to clinical trials—if their patients haven't already called the researchers themselves: "Most of the time patients were calling us, because they know about these trials," he said.

"We finished our trial in record time, about 10 months, because doctors were literally on the line fighting to get their patients on the trial. This is where it's at."

Also at the news conference, the moderator, Brad Kahl, MD, Clinical Research Director of Hematologic Malignancies at the University of Wisconsin Carbone Cancer Center, was asked whether the data on the anti-CD38 agents supported their "blockbusterness."

"These are small trials, and it's too early to plant the victory flag in the ground, but all that's been said about them is totally justified regarding bringing them to front-line setting," he replied.

'Phenomenal Responses in Small Expansion Cohort'

Asked his opinion for this article, Saad Usmani, MD, Director of Clinical Research in Hematologic Malignancies and Head of the Myeloma Program at Levine Cancer Institute, said that both SAR650984 and daratumumab appear to be quite effective in the relapsed/refractory myeloma setting as single agents and in combination with some of the other approved myeloma drugs, but the SAR650984 trial was unique in that all patients enrolled were refractory to lenalidomide.

"They're trying to tease out the effect of the anti-CD38 in this patient population—whether adding the SAR drug will help potentiate that somehow,"

> "The next five years are going to be very exciting, moving these drugs from the refractory setting to the less refractory setting to front line."

he said. "And that's what the study shows. In a small expansion cohort of 18 patients they are seeing phenomenal responses with this combination, with an overall response rate somewhere in the 63 percent range for a very refractory patient population.

"Anti-CD38 monoclonal antibodies are by far the most exciting drugs that are in development in multiple myeloma.

The challenge with monoclonal antibodies is the infusion time and the schedule, he noted. "It takes several hours to give them—the first time it may take up to six hours, although the subsequent infusions can be reduced to three-and-a-half to four hours. That's the challenge for these drugs, to figure out the schedule—once a week, every other week?—and how long to give it.

"The Phase I study with daratumumab was essentially a safety-generating study to justify using daratumumab with other available anti-myeloma therapies, the common backbones we utilize for myeloma. This was a safety not efficacy trial, but it does add to the efficacy of the combination."