Crowds ASPIRE to Hear Myeloma Report

BY ROBERT H. CARLSON

"When patients are potentially eligible for lenalidomide and dexamethasone treatment, physicians would be thinking that it wouldn't add a lot of toxicity to add carfilzomib and they could give their patients almost a year of additional progression-free survival."

SAN FRANCISCO—The session on "Myeloma Therapy, Excluding Transplantation" here at the American Society of Hematology Annual Meeting was so popular that one of the largest halls in the Moscone Convention Center immediately filled to capacity as soon as the doors opened. An "overflow room" was designated, but that too filled up fast, so the crowd in the hallway was directed to a second overflow room on the next floor. Then that room filled up as well, leaving about 200 attendees standing in the hallway watching the proceedings on a large television screen.

What attendees heard first was the much anticipated interim results from the ASPIRE trial, a randomized, open-label Phase III trial of KRd (carfilzomib [Kyprolis]-lenalidomide [Revlimid]-low dose dexamethasone) versus Rd (lenalidomide-low dose dexamethasone) in patients with relapsed multiple myeloma following treatment with one to three prior regimens (***Abstract 79***).

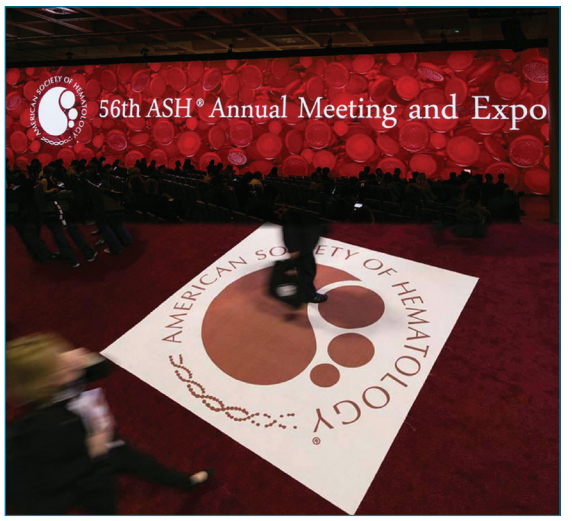
A. Keith Stewart, MD, Dean for Research and Professor of Cancer Research at the Mayo Clinic in Arizona, presented the data on 792 patients in the U.S., Europe, and Israel. The trial was sponsored by the maker of carfilzomib, Onyx, an Amgen subsidiary.

Stewart reported that the primary endpoint, progression-free survival, favored the three-drug combination: median progression-free survival was 26.3 months versus 17.6 months for the two-drug arm.

"Progression-free survival of over two years is unprecedented in myeloma," Stewart said.

Overall response was also impressive for carfilzomib-lenalidomide-dexamethasone: The mean time to response was 1.6 months for KRd versus 2.3 months for Rd.

The rate of complete response was 31.8 percent for KRd—three times the 9.3 percent for Rd. And the rate of very good partial response was 69.9 percent for KRd versus 40.4 percent for Rd. Median duration of response was 28.6 vs. 21.2 months, respectively.



Stewart said at this time the median overall survival has not been met, although there is a trend toward superiority for the triplet combination.

American Society of Hematology

A. KEITH STEWART, MD: "Progression-free survival of over two years is unprecedented in myeloma."

Adverse Events Manageable

Adverse events were manageable, he said. "Despite adding a third drug to the cocktail treatment the patients were taking, adverse events were virtually the same for both study arms," Stewart noted.

He said cardiac and renal events were reported at rates consistent with or lower than prior studies of single-agent carfilzomib.

At a news conference earlier in the meeting, Stewart was asked about peripheral neuropathy, a concern with bortezomib. He said there was no increase in peripheral neuropathy with the triplet combination containing carfilzomib, confirming that carfilzomib does not cause that side effect.

Stewart said there had been speculation about cardiac toxicity with carfilzomib, but what was seen in ASPIRE was only an increase in hypertension—14 percent for KRd versus eight percent for Rd.

"KRd should be the standard of care for relapsed myeloma as of today," Stewart said.

'New Standard'

"Dr. Steward's study will establish a new standard of care in multiple myeloma," agreed the moderator of the news

continued on page 39

AETHERA

Continued from page 37

"A 20-month improvement in progression-free survival at two years is extraordinary."

On the placebo arm, 85 percent of patients crossed over to receive brentuximab, and 16 percent of patients on brentuximab received subsequent brentuximab.

Moskowitz said that in 2009 researchers at his institution estimated that median overall survival of Hodgkin patients in whom stem cell transplant failed was between 24 and 28 months.

"But in 2015, it's 42 to 48 months, primarily because of all the new agents available," he said, mentioning HDAC inhibitors and check-point inhibitors as well as brentuximab vedotin.

He highlighted two aspects of patient characteristics in the trial: First, half of the patients needed more than one salvage regimen to achieve chemotherapy-sensitive disease before they could qualify for transplant—"Patients who need more than one salvage regimen usually have only a 20 to 30 percent chance of long-term survival," he said.

Second, some patients in the study had primary refractory disease—60 percent of patients did not achieve remission with the upfront chemotherapy comprising the ABVD or BEACOPP regimens.

Side effects included peripheral neuropathy of any grade at 87 percent in brentuximab vedotin versus 19 percent with placebo. There were no grade 4 adverse events, but two deaths did occur within 40 days, both in the brentuximab vedotin arm.

The outcome of the study demonstrates that early consolidation treatment with brentuximab vedotin in Hodgkin lymphoma patients at high risk of relapse can result in a substantial improvement in progression-free survival versus placebo, he said.

"In my opinion, for patients in remission less than a year, with disease outside the lymph nodes, or with primary refractory disease, this should be the standard of care."

Big Question

After the session, Kahl elaborated on his remarks, saying that this is the first study that has shown a big benefit for a post-transplant strategy for any aggressive lymphoma trial. "But the big question in my mind here is whether the application of maintenance brentuximab vedotin is just delaying inevitable relapse—will they relapse later—or has the treatment taken patients who are destined to relapse and turned them into a cured patient?

"We don't know the answer, but we hope that will be become apparent over time."

FDA's Fast Track Designation to DPX-Survivac for Ovarian Cancer

The Food and Drug Administration has granted Fast-Track status to DPX-Survivac as maintenance therapy for patients with advanced ovarian, fallopian tube, and peritoneal cancer who have no measurable disease following surgery and front-line platinum/taxane chemotherapy to improve their progression-free survival.

DPX-Survivac, made by Immunovaccine Inc., is a novel cancer immune therapy that stimulates the immune system to produce T cell responses targeting the tumor associated antigen survivin.

The Fast Track designation, established under the FDA Modernization Act of 1997, is designed to facilitate frequent interactions with the FDA review team to expedite clinical development and submission of a New Drug Application for medicines with the potential to treat serious or life-threatening conditions and address unmet medical needs. The designation permits the drug developer the opportunity to submit sections of an NDA on a rolling basis as data become available, allowing the FDA to review those materials on a rolling basis as well.

The design of a large randomized Phase II trial in ovarian cancer is being finalized, following reports of positive results from earlier Phase I trials for the drug in patients with ovarian cancer, according to a news release from the manufacturer.

ASPIRE

Continued from page 38

conference, Brad S. Kahl, MD, Associate Professor of Medicine at the University of Wisconsin and Director of the UW Lymphoma Service and Clinical Research Director for Hematologic Malignancies at the University of Wisconsin Carbone Cancer Center.

'One of the Easier Drugs'

Asked for 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 in Charlotte, N.C., said one consideration when using two versus three drugs in a heavily pretreated population is whether toxicity will increase. "What we see with this combination, however, is that the toxicity profile is really good, very comparable to lenalidomide-dexamethasone," he said.

Usmani also noted that in the past there have been concerns about unusual cardiac toxicities with carfilzomib, but these were not reported in significant numbers in ASPIRE, Usmani noted. "They were slightly increased in the carfilzomib arm, but in the three to four percent range compared with one-and-a-half percent on the standard arm."

> "I can tell you that clinical practice will be impacted by the ASPIRE study."

He said he has used carfilzomib to treat many patients on clinical trials, "and I think it's one of the easier drugs in myeloma therapy today.

"Clinical practice will be impacted by the ASPIRE study," Usmani said. "When patients are potentially eligible for lenalidomide and dexamethasone treatment, physicians would be thinking that it wouldn't add a lot of toxicity to add carfilzomib and they could give their patients almost a year of additional progression-free survival."