PD-L1 Inhibitor MPDL3280A 'Could Be First Targeted Agent in Triple-Negative Breast Cancer'

BY ROBERT H. CARLSON

"With these checkpoint inhibitors the activity signals are unequivocal, and the implications for the future treatment of people with triple-negative breast cancer are really very, very exciting."

PHILADELPHIA—A checkpoint inhibitor that targets PD-1/PD-L1 binding may be the first targeted therapy for patients with metastatic triple-negative breast cancer (TNBC). That was the conclusion of researchers reporting the results of the Phase Ia trial here at the American Association for Cancer Research Annual Meeting (***Abstract 2859***).

MPDL3280A was found to be generally safe and well tolerated, with two complete responses (CRs) and two partial responses (PRs) out of 21 patients evaluable for efficacy, said first author Leisha Ann Emens, MD, Member, Tumor Immunology Research Program and Associate Professor of Oncology at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center.

"I think it [MPDL3280A] very well could be the first targeted therapy for triple-negative breast cancer, if that bears out in a larger trial," Emens said during an AACR news conference. "These data are still early, and we need to enroll and treat a lot more patients with this agent, but I think it has great, great promise for this particular breast cancer subtype."

MPDL3280A was designed to inhibit the binding of PD-L1 to programmed death receptor 1 (PD-1) and B7.1, which can restore antitumor T-cell activity and enhance T-cell priming, she explained.

The checkpoint inhibitor received the FDA's Breakthrough Therapy designation for metastatic bladder cancer in 2014, and a second designation in non-small cell lung cancer in February of this year.

Emens called TNBC a particularly interesting target for cancer immunotherapy, particularly the PD-L1 targeted therapies. "Triple-negative breast cancer tends to have a higher mutation rate than other breast cancer subtypes lending to its ability to produce neoantigens that could be recognized as foreign by the immune system. Neoantigens could be more effective targets for the immune response than other antigens, which tend to be recognized as self," she said.

There is also an increased number of tumor-infiltrating lymphocytes in TNBCs, relative to the other breast cancer subtypes. "Typically, patients with triple-negative breast cancer who have high levels of tumor infiltrating lymphocytes associated with their tumors have improved clinical outcomes," Emens said. And triple-negative breast cancers typically have higher PD-L1 expression levels within their tumors than estrogen-receptor-positive/HER2-positive breast cancers.

LEISHA ANN EMENS, MD: "These data are still early, and we need to enroll and treat a lot more patients—but I think MPDL3280A has great, great promise for this particular breast cancer subtype."

Emens said PD-L1 expression can inhibit T cell-type tumor responses, and this is more likely to occur with triple-negative breast cancer than with either HER2-positive or ER-positive breast cancer subtypes.

SALARY SURVEY

Continued from page 29

About 25 percent of the 2,784 members of the society responded to the survey.

The participants in the survey included 28 percent who were breast fellows and 12 percent who were surgical oncologists. The remainder were not breast-specific fellows. Manahan said that fellowship-trained surgeons in the sample earned about $336,800 a year, compared with $344,000 a year for non-fellowship trained surgeons.

Conducted in 2014, Representing 2013 Data

The online, anonymous salary survey was conducted in 2014, so the figures presented represent 2013 data, he said. After exclusions, the researchers were left with 834 observations.

In response to questions from the audience, Manahan explained that statistical adjustments took into consideration years of experience and other factors. "Getting the statisticians involved really helped adjust all of these numbers," he said, noting, though, that the figures were not adjusted to reflect the cost of living in different areas of the country.

A coauthor of the study, Diana Dickson-Witmer, MD, Medical Director of the Breast Center at Helen F. Graham Cancer Center at Christiana Care Health System in Newark, Delaware, said: "When we were calculating the salaries, they did ask about various other things that are put in the formula for how your employer calculates how much they are going to reimburse you for your services. The downstream revenue, which is huge, that breast surgeons bring to a large group or a hospital was not something that people indicated was being taken into account in that calculation of what they were being paid."

Commenting from the audience, Robert Maganini, MD, Director of St. Alexius Breast Care Center in Bartlett, Illinois, said doctors should be cautious when inquiring about participation in those downstream revenues. He said he asked and got a letter from lawyers citing state and federal laws: "The hospitals get very nervous about that. Legal advice in these negotiations is typically money well spent, as most of my colleagues probably already know."

'Sadly Disappointing'

In an interview afterwards, Maganini elaborated: "I thought the salary information was highly informative. It is sadly disappointing that female breast surgeons are not paid on par with their male counterparts, even accounting for differences in practice type, production, experience, and geography.

"Ironically, most hospital organizations perceive female breast surgeons as more desirous for the female patients with breast problems. As a whole, we work very hard, long hours, with high-stress medical problems, high responsibility, and relatively high medico-legal risk," he said.

TNBC

Continued from page 30

MPL3280A is a monoclonal antibody engineered to be specific for PD-L1. It inhibits the binding of PD-L1 to its receptors PD-1.

Inhibiting the PD-1/PD-L1 interaction can enhance T cell priming for anti-tumor T cell activity, Emens said. In addition, MPDL3280A leaves the interaction between PD-1 and PD-L2 intact, thereby potentially maintaining more effectively immune homeostasis and potentially preventing some of the autoimmunity that can be associated with targeting this particular pathway.

This study began as part of a three-plus-three dose escalation trial of MPDL3280A efficacy and safety in a number of advanced solid tumors, she noted.

After the drug's safety profile and effective dose were determined, a number of expansion cohorts were undertaken in several disease types, including triple-negative breast cancer. The patients with metastatic TNBC were initially selected for the higher levels of PD-L1 expression in their tumors.

Subsequently the trial was opened to patients regardless of their level of PD-L1 expression.

> "Circulating biomarker analyses revealed pharmacodynamic responses to MPDL3280A. Clinical evaluation of the agent in metastatic PD-L1 IHC 0 or 1 TNBC is ongoing."

Emens said a proprietary assay incorporating the SP142 antibody was used to centrally evaluate PD-L1 expression, specifically on tumor infiltrating immune cells within the patients' tumors.

The drug was given every three weeks at either 15 or 20 mg/kg, or a flat dose of 1200 milligrams.

Side Effects

Safety evaluations were done on 54 patients. These patients had any level of PD-L1 expression within their tumors, Emens said.

"In general, in these patients, the drug was safe and well tolerated, with the most common treatment-related adverse events consisting of fatigue, nausea, fever, decreased appetite, and asthenia."

Grade 3 treatment-related adverse events were reported in 11 percent of patients, including a low potassium level in blood, low white blood cell count, skin rash (lichen planus), dyspnea, and adrenal insufficiency. In addition there was one event of grade 4 pneumonitis, and two deaths. "The deaths are currently being assessed as treatment related by the investigator, but are currently under further investigation by the sponsor," Emens said.

Two CRs, Two PRs among 21 TNBC Patients

Clinical activity or efficacy for MPDL3280A treatment was evaluable in 21 patients. The overall response rate was 19 percent in patients evaluable for efficacy, and the 24-week progression-free survival rate was 27 percent.

"Importantly, these responses included two complete responses and two partial responses, and also importantly, three of the four responses were ongoing at the time of data cutoff," she said. "In contrast to the safety evaluable patient population, these are patients who expressed higher levels of PD-L1 within their tumors, at levels on immune cells of five percent or greater," Emens said.

For the 21 patients with tumors that express high levels of PD-L1, responses were durable in patients who did respond.

The median duration of response has not yet been reached, with a range of 18 to 56-plus weeks. The median duration of survival follow-up is approximately 40 weeks, with a range of two to 85 weeks.

Emens said a Phase III global, randomized trial is being planned to test MPDL3280A in combination with protein-bound paclitaxel (Abraxane) as first-line therapy for patients with metastatic TNBC.

Pseudo-progression

Emens said three patients treated with MPDL3280A initially reported to have progressive disease appeared to actually have pseudo-progression, an atypical response pattern seen in some patients treated with checkpoint inhibitors such as ipilimumab.

These three patients exhibited durable shrinkage of their target lesions while at the same time developed new lesions at other sites, yet remained clinically well despite this pattern of response.

"Pseudo-progression is a new phenomenon for many physicians to manage and requires the patient's entire clinical picture be taken into account," Emens said. "If evidence of new lesions is seen on scan but the patient is doing clinically well, you continue to treat and continue to evaluate."

Another option is to biopsy the new lesions to assess the inflammatory response to determine if this is a phenomenon of response to the therapy or a new area of tumor. "It will be important to educate physicians and their patients about this phenomenon, as well as the regulators, to develop a consensus on how to evaluate the clinical activity of this class of drugs."

'Powerful Indication of Potential'

The moderator of the news conference, Louis M. Weiner, MD, Professor and Director of the Lombardi Comprehensive Cancer Center of Georgetown University, introduced the study as "another really powerful indication of the potential of targeted checkpoint strategies to influence the outcomes in diseases for which we really don't have any effective therapies."

He said that targeting non-immunogenic cancers such as triple-negative breast cancer, renal cell carcinoma, and non-small cell lung cancer "really is quite revolutionary."

"What is revolutionary is the therapeutic philosophy and the targets," Weiner continued. "We are learning that the targets matter, that if we access the targets with drugs, we change the course of disease and save lives."

Much work is still to be done to determine which drug or drug or combinations are most effective for very particular indications, he said. "And we'll get there, because the activity signals are so strong there will be an interest in the Pharma industry in figuring out how to make that happen, and physicians will be anxious to offer these exciting hew treatments and options to their patients."

Not very long ago, he said, researchers who performed Phase I clinical trials were pleased to see even a hint of activity that would justify moving forward into Phase II, with suspiciously prolonged stable disease and maybe an occasional response: "And that would be enough to trigger further evaluation of drugs.

"With these checkpoint inhibitors the activity signals are unequivocal, and the implications for the future treatment of people with triple-negative breast cancer are really very, very exciting."

> "Triple-negative breast cancer tends to have a higher mutation rate than other breast cancer subtypes lending to its ability to produce neoantigens that could be recognized as foreign by the immune system."