PAUL BUNN EXPANDS ON SIGNIFICANCE OF ATEZOLIZUMAB/BEVACIZUMAB REGIMEN IN NSCLC

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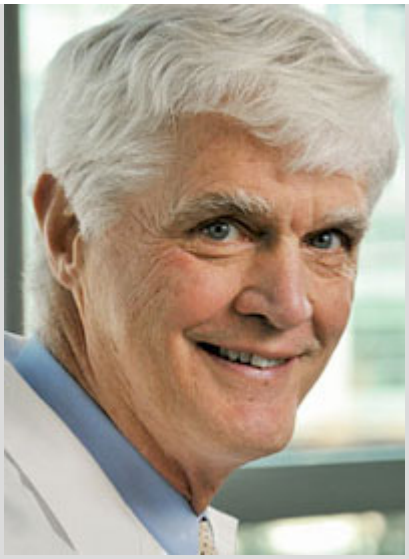

Paul A. Bunn Jr, MD

Findings from the phase III IMpower150 trial presented at the 2017 ESMO Immuno-Oncology Congress demonstrated that treatment with the combination of atezolizumab (Tecentriq), bevacizumab (Avastin), carboplatin, and paclitaxel delayed progression or death by 38% compared with bevacizumab and chemotherapy alone for patients with nonsquamous non–small cell lung cancer (NSCLC).

The IMpower150 study enrolled 1202 patients with stage IV nonsquamous NSCLC. Patients were randomized to receive atezolizumab plus carboplatin and paclitaxel (arm A), atezolizumab with bevacizumab plus carboplatin and paclitaxel (arm B), or bevacizumab plus carboplatin and paclitaxel (arm C). Progression-free survival (PFS) and overall survival (OS) were the primary endpoints.

The atezolizumab combination elicited a median PFS of 8.3 months compared with 6.8 months with bevacizumab and chemotherapy alone (HR, 0.62; 95% CI, 0.52-0.74; *P* <.0001). After a minimum follow-up of 9.5 months, the median OS was 14.4 months (95% CI, 12.8-17.1) versus 19.2 months (95% CI, 16.8-26.1), in favor of the atezolizumab group (HR,

0.775; 95% CI, 0.619-0.970; *P* = .0262).

In an interview with *OncLive,* Paul A. Bunn, Jr, MD, distinguished professor, Division of Medical Oncology/University of Colorado, James Dudley Chair in Lung Cancer Research, University of Colorado Denver, 2014 Giant of Cancer Care® in Lung Cancer, shared his expert opinion on the IMpower150 study and other immunotherapy combinations in NSCLC.

OncLive: **Can you discuss the results of the IMpower150 study?**

Bunn: One issue about immunotherapy is that a minority of patients respond to it—that is, only about 20%. Therefore, we were wondering if you combined a single-agent checkpoint inhibitor with other immunotherapies, chemotherapies, or antiangiogenic agents, would you have a higher response rate and better overall outcome?

This trial was designed to determine whether the addition of atezolizumab to chemotherapy would be better than chemotherapy alone. This is a phase III randomized trial that reported on this combination. However, cohort G of the KEYNOTE-021 trial was a randomized phase II trial that already reported on a similar combination. Additionally, there are a number of other trials that have released preliminary information, including KEYNOTE-189, MYSTIC, and CheckMate-227.

This is the first trial that looked at chemotherapy versus chemotherapy plus a checkpoint inhibitor to present randomized phase III data. It is always better to be first; however, the combination of pembrolizumab (Keytruda) with chemotherapy for nonsquamous NSCLC has already been approved by the FDA because of randomized phase II data.

How does the pembrolizumab and chemotherapy combination compare with the atezolizumab combination?

The median OS in cohort G of KEYNOTE-021 had not been reached for the combination arm. However, at 18 months, 70% of patients were alive and the OS for the chemotherapy arm was 20.9 months. The IMpower150

trial is a similar population, but the median OS for arm B was 19.2 months. In this study, at 18 months, 55% of patients were alive. The chemotherapy arm had an OS of 14.4 months. They are different trials, making it difficult to compare, but the long-term survival of the atezolizumab combination does not seem quite as good as the pembrolizumab combination.

The chemotherapy arm, arm A, in the IMpower150 study is not as good as the bevacizumab arm. Cross comparisons are complicated, but 4-drug combinations are going to be more expensive than 3-drug combinations. In general, OS tends to become more impressive as time goes on. These data were from an early time.
It is good for Genentech (the manufacturer of atezolizumab and bevacizumab) that this trial met its endpoint, but we are not sure whether it will be approved or not. I would assume with a trial like this that it would, but then the combinations will have to compete. The major disadvantage is that this combination is a more expensive regimen. However, this combination is the first one to have a phase III trial done.

What would be the optimal patient population to receive the atezolizumab and bevacizumab regimen?

The dominant biomarker that has been used so far is PD-L1 expression. Genentech is at a disadvantage because their antibody is less sensitive for PD-L1 than the [pembrolizumab] combination. In this trial, they did not use PD-L1; they used T-effector gene expression signature. In the patients with T-effector high, the differences were greater than in T-effector–low patients. I do not think that the differences were statistically significant either way or that anyone is going to be using T-effector gene expression signature since it is a more complicated biomarker. I also do not believe that anyone will decide whether to use chemotherapy plus atezolizumab or pembrolizumab based on a biomarker.

Are there any other ongoing trials with atezolizumab that are showing promise?

There are many ongoing trials in the IMpower series. Arguably, one of the more important studies would be in combination with nab-paclitaxel [which is given without steroids]. One of the concerns for [other] combinations was the fact that you have to give steroids with them. Now, the data so far do not suggest that 3 days of steroids impact anything, because with pemetrexed you also have to give 3 days of steroids.

There are many combinations. IMpower150 looked at nonsquamous tumors, but squamous tumor data will be coming soon. We will capture some first-line [data], but we are currently competing with something that is already approved and is more expensive.

Looking ahead, what could be the next steps for this combination?

Originally, I was a skeptic about the combination of all checkpoint inhibitors with chemotherapy. I thought that the combination of checkpoint inhibitors with other immune modulators might be less toxic and better overall. We do not have any immunotherapy with immunotherapy data, but there are enough data showing that giving chemotherapy with checkpoint inhibitors is better than chemotherapy alone. None of these studies have looked at the combination versus checkpoint inhibitors alone.

If you have PD-L1 expression greater than 50%, monotherapy alone does well. Again, cross trial comparisons are complicated. It is likely that in the next 6 months, all of these trials will report out. Many of them will show that a number of chemotherapy regimens plus different checkpoint inhibitors are better than chemotherapy alone. We are probably going to see an increase in first-line use of checkpoint inhibitors.

There are a lot of checkpoint inhibitors. However, we haven't seen any data from the MYSTIC trial. There are many chemotherapy trials that are likely to read out soon. There is also a big international trial using pembrolizumab versus chemotherapy, and there is a trial investigating

pembrolizumab with chemotherapy versus chemotherapy.

It is likely that in the future, there will be an increase in immunotherapy plus chemotherapy combinations in the first-line setting. Atezolizumab is going to be used, but how often it is used still needs to be determined. Most data would suggest that it is will be hard to determine, especially since OS is the best endpoint and, in the IMpower150 study, OS was still immature.

The addition of bevacizumab made a difference. There are other trials with different antiangiogenics that will be interesting to see the results of. Most of the trials are chemotherapy plus immunotherapy that have not included antiangiogenics.