HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Durvalumab Plus Tremelimumab for First-Line Treatment of Hepatocellular Carcinoma

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G&H What is the rationale for using durvalumab and tremelimumab in combination for the treatment of hepatocellular carcinoma?

RK Durvalumab (Imfinzi, AstraZeneca) and tremelimumab (Imjudo, AstraZeneca) are both immune checkpoint inhibitors, but different ones. Durvalumab is an inhibitor of the programmed death ligand 1 (PD-L1) checkpoint, whereas tremelimumab is an inhibitor of the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) immune checkpoint. Other tumor types, as well as preclinical models, have shown that targeting 2 different pathways in the cancer immune microenvironment can help a patient's immune system, including T cells and other immune effector cells, avoid inhibition by the tumor and, instead, recognize and hopefully elicit an effective antitumor immune response.

G&H What are the key efficacy data on the use of durvalumab plus tremelimumab for hepatocellular carcinoma treatment?

RK The HIMALAYA trial was a phase 3 randomized international trial that studied the combination of durvalumab plus tremelimumab, compared with a control arm of durvalumab alone and the standard control arm of sorafenib alone. The tyrosine kinase inhibitor sorafenib had been the standard of care since the SHARP trial in 2008. For the primary comparison of durvalumab plus tremelimumab vs the standard control arm of sorafenib in the HIMALAYA trial, the combination significantly improved the primary endpoint of overall survival. The median overall survival was 16.4 months in the combination arm, compared with 13.8 months in the sorafenib arm, resulting in a significant hazard ratio of 0.78.

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Beyond that improvement in survival and the significant hazard ratio, what clinicians also likely find important is the durability and robustness of these outcomes over time. Immune-mediated responses can be the deepest and most durable of the systemic and nonsurgical treatments used in oncology. In fact, when looking at follow-up data from the HIMALAYA trial (at 1, 1.5, 2, 3, and now 4 years), the responses that were achieved were ongoing and extremely durable. This translates to prolonged survival over time, now out to 48 months. Twenty-five percent of patients with advanced or metastatic hepatocellular carcinoma (HCC) who were treated with durvalumab plus tremelimumab were alive at 4 years, compared with only 15% for those treated with standard sorafenib. This

is a clinically meaningful difference between the 2 arms, especially in light of the fact that many of these patients are still alive receiving treatment even now. This durability of treatment benefit is historic in HCC and a huge accomplishment that clinicians are excited about.

G&H Are there any other recent data on this combination that you would like to highlight?

RK One of the most important issues involving dual immune checkpoint inhibitor combinations is the balance between efficacy and toxicity. A recent presentation that I found very encouraging as a clinician was an analysis of immune-mediated adverse events from the HIMALAYA trial in relationship to clinical outcomes and efficacy. Dr George Lau and colleagues presented these findings at last year's annual meeting of the American Society of Clinical Oncology. Immune-mediated adverse events, including those requiring corticosteroids, tended to occur in the first 3 months of treatment (ie, soon after patients received their single dose of tremelimumab as part of this regimen), and events after 3 months were much rarer. In addition, patients who experienced such events, even if corticosteroid immunosuppression was required, tended to have more robust efficacy outcomes. This might be intuitively expected with the thinking that patients' immune systems were activated enough not only to cause an immune-related toxicity but also enough to achieve a better immune response. Therefore, although the analysis was not powered for comparisons between response rate or survival according to immune-related toxicity, trends were seen toward a higher proportion with survival at 3 years for patients who had immune-related toxicity compared with those who did not, as well as higher rates of objective response for patients who had immune-related toxicity compared with those who did not. It was encouraging to see that the onset of immune-related toxicity most commonly occurred during a limited time window during the first 3 months of treatment, and that it did not interfere with efficacy but was, in fact, associated with a trend toward improved outcomes.

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G&H How was the dosing regimen determined?

RK Before the durvalumab and tremelimumab combination was studied in the HIMALAYA trial, my colleagues and I conducted a large, randomized phase 2 trial to examine several different dosing regimens. These included a sequential dose regimen very similar to the ipilimumab (Yervoy, Bristol Myers Squibb) plus nivolumab (Opdivo, Bristol Myers Squibb) historical precedent in which durvalumab was used with 4 doses of tremelimumab, as well as a single, higher-dose tremelimumab regimen followed by sequential dosing of durvalumab. Intriguingly, the single, higher-dose tremelimumab regimen showed the highest rates of objective response and the longest median overall survival in this phase 2 trial. A pharmacodynamic biomarker analysis also showed that the single, higher-dose tremelimumab plus sequential durvalumab arm produced the highest counts of an activated T-cell population in the peripheral blood, which correlated with radiographic response. Based upon these data from the phase 2 study, single-dose tremelimumab followed by sequential durvalumab moved forward as the experimental arm in the HIMALAYA trial.

This regimen is now the US Food and Drug Administration (FDA)-approved combination known as STRIDE, which stands for single-dose tremelimumab with regular interval durvalumab. The STRIDE regimen consists of tremelimumab at a flat dose of 300 mg given once on day 1, accompanied by the PD-L1 inhibitor durvalumab at a 1500-mg flat dose given at the same time on day 1 and then continued once a month thereafter as long as the patient is benefiting and does not have prohibitive toxicity. Thus, this is an easy regimen to give from an oncologist's perspective.

G&H What are the most common toxicities or adverse events with this combination?

RK The durvalumab plus tremelimumab STRIDE regimen has favorable high-level toxicity metrics in comparison with, for example, a tyrosine kinase inhibitor or even the combination of atezolizumab (Tecentriq, Genentech) plus bevacizumab. A little less than 14% of patients required discontinuation owing to toxicity, which compares favorably with other combination regimens. The rate of grade 3 or 4 immune-mediated events was a little less than 13%, which is also favorable

compared with a prolonged ipilimumab dosing combination. Systemic corticosteroids were required to manage immune-related adverse events in 20% of patients treated with the STRIDE regimen in the HIMALAYA trial. Although this is a lower proportion than what has been reported in most studies of the combination of ipilimumab plus nivolumab—which is another CTLA-4 inhibitor–based combination used in multiple tumor types, including HCC—the potential for serious immune-related toxicity on the STRIDE regimen requires vigilance on the part of clinicians as well as patients and their caregivers.

One of the most common immune-related adverse events associated with durvalumab plus tremelimumab was diarrhea, but only around 4% was grade 3 or 4. Another common class of adverse events expected with most immune checkpoint inhibitor regimens involved skin-related events such as rash or itching. These occurred in over 20% of patients, but only 1.5% of the events were grade 3 or higher. Beyond these diarrhea and skin events, approximately 5% of patients had elevated aspartate aminotransferase and/or alanine aminotransferase liver enzyme levels in the grade 3 or 4 range, and most resolved within the first 3 months, as with the other immune-related toxicities.

G&H Where does the combination of durvalumab plus tremelimumab fit in the current treatment algorithm for HCC?

RK This combination has been approved by the FDA, as well as regulatory agencies in multiple countries, as an option for first-line treatment for patients with unresectable, advanced stages of HCC, including locally advanced unresectable HCC as well as metastatic HCC. This space is where atezolizumab plus bevacizumab is also approved, so clinicians now have the option to use either one of these 2 combinations for first-line HCC therapy. Generally, I make the decision based on the comorbidity profile of the individual patient before me, coupled with the known adverse-event profile of each of these first-line immunotherapy-based combinations. For example, patients who have a higher risk of immune-related toxicity, such as patients with underlying autoimmune disease, might be a better choice for atezolizumab plus bevacizumab combination therapy. Conversely, the patients I triage toward the durvalumab-tremelimumab STRIDE regimen include those who are at high risk for bleeding or blood clots, those who have a preexisting arterial vascular disease such as claudication or prior strokes, or those who are on anticoagulation, as these patients would be at risk for vascular complications with bevacizumab.

G&H How should patients receiving durvalumab plus tremelimumab combination therapy be followed?

RK Dosing is monthly, so I generally like to see patients or schedule a telehealth visit after the first 2 weeks as a midcycle check, although that is not always necessary. Thereafter, I will see patients before their infusions every month and check for any immune-related toxicity with blood tests, including a comprehensive metabolic panel and complete blood counts. Thyroid function is also monitored, as hypothyroidism is a common immune-mediated endocrinopathy with all immune checkpoint inhibitors. Symptoms such as nausea, vomiting, and abdominal pain should prompt checking for pancreatitis, which is a rare but reported immune-mediated adverse event. Low blood pressure or electrolyte abnormalities should prompt checking for other endocrinopathies. Oncologists are now very familiar with monitoring for immune-mediated toxicity with immune checkpoint inhibitors owing to the ubiquitousness of this class of drugs across solid tumor oncology treatment.

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In addition, before treatment is started, patients should come in for an education session with a provider in the oncology clinic and receive patient education materials for review and future reference. We ask patients to bring a family member or friend to this meeting so someone else can hear this advice as well. We let them know about the potential for sudden-onset immune-related toxicity, which is not specific to the STRIDE regimen but applies to all solid tumor patients treated with immune checkpoint inhibitors. Symptoms such as sudden-onset diarrhea in which the patient suddenly has many (eg, 20) bowel movements over a few hours, or likewise suddenly has an extremely bad cough and shortness of breath, could be an immune-mediated process that might need urgent initiation of high-dose corticosteroids or immunosuppression. Essentially, we counsel patients to watch for anything out of the ordinary that progresses quickly. When that occurs, patients should call their doctors or go to the emergency room immediately because if their

immune system is ramping up, it can escalate an immune response inappropriately in a dangerous part of the body rapidly. If treated quickly, most of these immune-related toxicities are manageable and reversible.

G&H What are the priorities of research in this area?

RK It is a promising new step forward to have multiple treatment options in the first line for HCC and multiple immune-mediated combinations in that line. One of the priorities is attaining the elusive goal of biomarkers that can help determine which patient should receive which therapy. Right now, decisions are often based on toxicity, not on any biomarkers. Identifying biologic or clinical features of a tumor that can predict, for better or worse, response to a given regimen is always our holy grail to help spare patients toxicity they do not need, avoid the opportunity cost of a treatment that does not work, and achieve a faster response.

Another goal is to acknowledge that although the STRIDE regimen and the combination of atezolizumab plus bevacizumab are both enormous advances that are leading to prolonged survival worldwide in HCC, only a subset of patients respond to either regimen. New combinations are needed that can achieve durable immune responses in a higher proportion of patients. New studies have been looking at adding novel immunomodulatory agents to durvalumab plus tremelimumab, as well as examining new immune checkpoint inhibitors in different combinations.

Disclosures

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Suggested Reading

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