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Released: 12/30/2024
Valid until: 12/30/2025
Time needed to complete: 1h 14m

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First-line Treatment of MSI-H/dMMR mCRC: The Role of Immunotherapy

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Parikh:
Hi, this is CME on ReachMD. I'm Dr. Aparna Parikh, a GI oncologist at the Mass General Cancer Center. Today, I'm going to review the role of immunotherapy as a first-line treatment for metastatic colorectal cancer that is mismatch repair high or mismatch repair deficient.

So there's been a lot of excitement in terms of the landscape of first-line immune checkpoint blockades for patients with colorectal cancer that harbor the mismatch repair deficiency. I think first of all, just highlighting the fact that mismatch repair deficiency can be tested by many modalities, including IHC, PCR, and NGS. And it is still a small portion of the overall patients that are metastatic, so around 5% to 10% of patients that have colorectal cancer are actually found to be microsatellite unstable.

Over the last several years, we've really seen a burgeoning of immunotherapies and a tremendous response allowing many more options for patients that are found to be MSI-high. This started over 5 years ago with data with a tumor-agnostic indication for patients that were MSI-high in the refractory setting. But over the last several years, we've had more and more data in the first-line setting that has really changed the landscape of how we treat these patients.

So the first study to note is a study of pembrolizumab. This was the KEYNOTE-177 study. This was a phase 3 study looking at pembrolizumab versus investigator's choice chemotherapy. Over 300 patients in this randomized phase 3 study. And this study was the first study to demonstrate head-to-head checkpoint inhibitors versus chemotherapy with the response rate of 44% and initially reported a hazard ratio of 0.60 with the study meeting its primary endpoint of PFS. So really was the first study that, outside of a tumor-agnostic study in refractory settings, that really gave us insight into how effective checkpoint inhibitors would be for these patients.

In parallel, we also started to see some data of dual checkpoint inhibitors, so with CTLA-4 ipilimumab, as well as nivolumab and anti-PD-1 therapy. And the first data that we saw to speak to this was the CheckMate 142 data. And this is a phase 2 study. Over 100 patients, around 120 patients. And what we saw with this was slightly higher toxicity but a response rate that seemed to be better. So around a 69% response rate for these patients with the use of dual checkpoint inhibitors.

And we are very much awaiting the most recent data from the CheckMate 8HW study, which is a randomized study, a phase 3 study. And we've seen the readouts of some of the arms, but not all the arms, and I'll talk you through this study. So 8HW was a study of, again, dual checkpoint inhibitors, nivolumab and ipilimumab, in the first-line metastatic MSI-high setting. And patients were randomized 2:2:1 to several different options.

And the study actually had dual primary endpoints, and noting that in this study that MSI-high testing had to be centrally confirmed. And the dual primary endpoints was looking at PFS in the nivo and ipi versus chemo arm, and that was the first primary endpoint that was reported and we're waiting for the other endpoint any day now, which is looking at the monotherapy arm.

And in the, again, the combination arm which was reported, remarkable data in terms of PFS. So a 24-month PFS rate of 72% with nivo and ipi, compared to 14% with chemotherapy.

So when we're thinking about first-line options, in the NCCN Guidelines we have both the option of nivo and ipi as well as monotherapy as well as just PD-1 alone. But I think seeing the data from the monotherapy arm from 8HW will give us a better sense of how monotherapy performs compared to combination therapy.

Thank you for your attention, and I hope this discussion will be useful in your practice.

Announcer:
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