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Keeping Pace in GI Cancer: Advances in Immunotherapy in MSI-H/dMMR Metastatic Colorectal Cancer

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Keeping Pace in GI Cancer: Advances in Immunotherapy in Microsatellite-instability High or Mismatch Repair Deficient Metastatic Colorectal Cancer." is provided by PROVA EDUCATION and is supported by an independent educational grant from Merck.

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Here is Dr. Edward Chu.

Dr. Chu:
Colorectal cancer is a leading cause of cancer-related deaths worldwide and has a 5-year survival rate of only 14% in patients with metastatic disease. Patients whose metastatic disease is microsatellite instability-high/mismatch repair deficient demonstrate poor outcomes compared with patients who are not microsatellite instable/mismatch repair deficient. The issue to be discussed today is how we can improve patient outcomes for this particular subset of patients.

This is CME on ReachMD, and I’m Dr. Edward Chu from the Albert Einstein Cancer Center.

Dr. Overman:
And I’m Dr. Michael Overman from the MD Anderson Cancer Center.

Dr. Chu:
Okay, Mike, let’s go ahead and get started. So what’s the underlying mechanism that causes microsatellite instability-high/mismatch repair deficient disease, also known as MSI-high/dMMR? Further, how is this mutation detected, and why do patients with this mutation have poor outcomes with standard chemotherapy?

Dr. Overman:
I think that’s a really great question for us to start because, you know, it is a bit confusing. We use these terms, mismatch repair and microsatellite instability, and they really are similar phenomenons that are occurring. But the fundamental underlying issue at hand is that you have a deficiency in one mechanism of DNA repair. And so that’s kind of the mismatch repair system. And that’s really involved in correcting, kind of, single-base pair insertion and deletions, and so that’s really the fundamental thing that’s occurring. And so one obvious way is you look at just protein loss of these mismatch repair proteins, and that’s a very common way of looking at a immunochemical testing. The other way is you can look for the outcome of this loss of mismatch repair, and the outcome, if you’re not repairing mistakes in DNA, is that you develop multiple mutations through DNA replication that are not fixed. So generating multiple mutations, kind of high mutation load, and that can be picked up in a mechanism that we call, kind of, microsatellite instability-high. And the reason that works is that these mutations tend to occur at areas of microsatellites or at DNA repeats, and so you can look at variation in the length of these DNA repeats.

And now we’re really talking about the identification of patients that would be appropriate for immunotherapy-based treatment, and that

really occurs more in the metastatic space, and there is this really interesting relationship where MSI-high or deficiency mismatch repaired has better outcomes in earlier stage patients, but then when metastatic disease happened, it really kind of changes. That escape from, kind of, immune surveillance generates this metastatic deficiency mesentery MSI-high situation, where they have worse outcomes and there does appear to be kind of less benefit from chemotherapy.

Let's turn to the emerging role of immunotherapy and the management of this colorectal cancer subset. And I think a good place to start with this discussion is really probably with the findings of the KEYNOTE-164. And so I wonder, Ed, if you want to kind of take us into that clinical trial and implications and results from that.

Dr. Chu:
So KEYNOTE-164 was an international, phase 2, nonrandomized study that was conducted in 9 different countries around the world. So this study enrolled a total of 124 patients with locally advanced or metastatic MSI-high or defective mismatch repair colorectal cancer. And patients had received prior fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy. And for this study, patients received pembrolizumab at a fixed dose of 200 mg IV every 3 weeks for up to 2 years. I think it's important to note that there were 2 different cohorts in this study. Cohort A included patients who had been treated with more than 2 prior lines of standard systemic therapy with chemotherapy with or without biologic therapy, either anti-VEGF or an anti-EGFR antibody treatment. And Cohort B was patients who had not been as heavily pretreated, and they had received more than 1 prior line of systemic therapy. Primary endpoint of KEYNOTE-164 was objective response rate as determined by an independent central review. And I think, you know, what was impressive about this study was that the overall response rates for both cohorts was 33%. The median time to response was about 4.3 months, and I think what was most impressive was that the time of analysis – the median duration of response – had not been reached. Also the responses were really durable. So 95% of the patients had a duration of response more than 12 months, which really is, I think, very, very impressive for this group of patients who had been previously treated with systemic therapy. In terms of median PFS for Cohort A, that was 2.3 months, and the overall survival was 31.4 months. As one might expect, in Cohort B where patients were not as heavily pretreated, the median PFS was 4.1 months, and the median overall survival had not yet been reached. I think another important point to note, Mike, is that the responses were observed in patients with BRAF mutant tumors, as well as in patients who had mutations in KRAS and/or NRAS.

So I think KEYNOTE-164 is an important study as it confirms the clinical activity of pembrolizumab and shows that there's really durable clinical activity with a manageable safety profile in this patient group with previously-treated MSI-high/defective mismatch repair advanced or metastatic colorectal cancer. And I think, certainly, the outcomes from this study are consistent with and provide further support to the earlier studies that led to the accelerated approval of pembrolizumab for MSI-high/defective mismatch repair colorectal cancer and other non-colorectal cancer types in the United States in May of 2017.

Dr. Overman, we've been discussing the use of immunotherapy in patients who had failed prior therapy for their MSI-high/defective mismatch repair metastatic colorectal cancer. A logical next step is to look at the outcomes from CheckMate 142 with nivolumab. And you were obviously the lead investigator in that study; you know that study well. So perhaps you can tell us how these data in CheckMate 142 helped to advance our understanding of how immunotherapy can impact outcomes for these patients.

Dr. Overman:
Yes. Thanks, Ed. No, this was a large, you know, clinical trial, the CheckMate 142 study, looking at really this microsatellite instability-high/deficient mismatch repair population that we initiated back, you know, 2013, actually. And has multiple cohorts in it. It's all single-arm cohorts, so there's no randomization here, but has multiple different cohorts. And probably the first cohort that went forward was the monotherapy with nivolumab cohort, and that's a cohort that we published back in 2017. And in that cohort, we enrolled 74 patients that were refractory metastatic colorectal cancer with this genetic abnormality, so microsatellite instability-high and deficient mismatch repair. And out of those 74 patients, we had, again, 31% response rates. And again, that point I like to really make with this population is the 24-month progression-free survival was close to about 50%. And I think that really gets at this, you know, clear benefit we see with these patients where you really have, kind of, responses that appear durable.

I think the outcomes are very similar to what we see, what we just discussed with the KEYNOTE-164 in regards to pembrolizumab. And fairly similar, kind of, population base that were targeted again at different times and at different studies. Also within the CheckMate 142, there was a cohort that was treated with nivolumab and ipilimumab, so combination anti-PD-1 and anti-CTLA-4. Initially, that was, again, a very similar refractory kind of population that was 119 patients. And in that kind of a cohort, we saw a response rate of 55%, and the 24-month progression-free survival rate was around 70%. So numerically, it appeared a little bit higher than the monotherapy cohort, though, again, not designed to be compared and not randomized cohorts here, but conducted within the same study. And this really led – those two cohorts led to the FDA approval that exists for nivolumab and nivolumab and ipilimumab in this population.

And then I think I'll briefly just mention, within the CheckMate 142, there was even another cohort that looked at nivolumab and

ipilimumab in the frontline therapy for metastatic colorectal cancer that was microsatellite instability-high or deficient in mismatch repair. And this enrolled a smaller 45-patient frontline, so untreated metastatic patients. And in the frontline population, this 45 population, we saw a response rate of 60% and a 24-month PFS approximately about 74%. So again, very robust, kind of consistent benefits that appeared similar from frontline to refractory line.

Dr. Chu:
Great. For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Edward Chu of the Albert Einstein Cancer Center, and here with me today is Dr. Michael Overman from the MD Anderson Cancer Center. We're just about to continue our discussion on advances in immunotherapy and MSI-high/defective mismatch repair metastatic colorectal cancer.

Dr. Overman:
So Ed, the next question is for you. And we've discussed at length the findings related to CheckMate 142. However, there is new data now with KEYNOTE-177 that's emerged in the microsatellite instability-high/deficient mismatch repair metastatic colorectal cancer frontline population that was pembrolizumab versus standard of care. And so I wonder if you can kind of discuss that study with us?

Dr. Chu:
So as you know, KEYNOTE-177 really, I think, represents a true landmark study. So this was an international, phase 3, randomized, multicenter study that enrolled 307 treatment-naïve patients. So this was metastatic colorectal cancer in the frontline setting, and patients had MSI-high or defective mismatch repair disease. And so in this study, patients were randomized to receive either pembrolizumab at a fixed dose of 200 mg every 3 weeks for up to 2 years or to investigators' choice of standard systemic chemotherapy using either modified FOLFOX6 or FOLFIRI, plus either the anti-VEGF antibody bevacizumab or the anti-EGFR antibody cetuximab. I think also, it's important to note that there was an optional crossover design incorporated in this study, where patients who progressed on the standard systemic chemotherapy arm could then receive pembrolizumab at the same dose and schedule, of 200 mg IV every 3 weeks for up to 35 cycles. Of note, the study had 2 primary endpoints – progression-free survival and overall survival – but I think also important to note that as part of the study design, pembrolizumab needed to demonstrate superiority over systemic chemotherapy for only 1 of the 2 endpoints for this trial to be considered positive. And the secondary endpoints are what we typically consider overall response rate and safety.

And so at the virtual ASCO meeting this year, Dr. André presented the results of the PFS analysis. And these results were really remarkable in that the median progression-free survival for patients treated with pembrolizumab was 16.5 months as compared to a median PFS of 8.2 months for those treated with standard systemic therapy. So this represents a doubling of the progression-free survival, and for someone who's been in the colorectal cancer field as long as I have, I mean this is truly a remarkable result that we've just not observed over the past 15-20 years of clinical studies that have focused on the treatment of metastatic colorectal cancer. And when one looks at the hazard ratio, pembrolizumab therapy resulted in a highly statistically significant 40% reduction in the risk of disease progression. Again, a result that we just haven't seen in any previous clinical study.

And as Dr. Overman has noted in our previous discussion, when one looks at the durability of the response, at the 12- and 24-month follow-up, the PFS was significantly higher for patients treated with pembrolizumab. And when we look at 2 years, the PFS rate was 48.3% for those treated with pembrolizumab versus only 18.6% for patients treated with systemic chemotherapy. And if one looks at the forest plot that also confirms the benefit of single-agent pembrolizumab, really across all of the main subgroups, which include age, gender, ECOG, performance status, geographic region, and site of primary tumor. Overall response rates were higher with pembrolizumab therapy, but again, I think as we've noted previously, what's really impressive with pembrolizumab therapy is the complete response rate. And so in KEYNOTE-177, the complete response rate seen with pembrolizumab therapy was 11% as compared to only 3.9% for patients treated with chemotherapy. So this is nearly a 3-fold difference in the complete response rate seen with pembrolizumab therapy. And again, the duration of response, significantly longer in patients treated with pembrolizumab. So 83% of the patients treated with pembrolizumab had a response lasting longer than 2 years, in contrast to only 35% of patients receiving chemotherapy had a response for more than 2 years.

So I think, you know, for me, KEYNOTE-177 is really a landmark study in that it's the first study to show the clear benefit of single-agent pembrolizumab in the frontline treatment of MSI-high/defective mismatch repair metastatic colorectal cancer. And really, I think the findings from this study are truly practice-changing. And based on the results of this historic study, pembrolizumab was approved by the US Food and Drug Administration at the end of June of this year, 2020, for the first-line treatment of patients with unresectable or metastatic MSI-high or defective mismatch repair colorectal cancer.

So this has certainly been a terrific conversation and discussion, but before we wrap up, Mike, can you share your one take-home message with our audience?

Dr. Overman:

Yeah, thanks, Ed. I mean, I think the one take-home message would really be that, you know, we need to test all of our colorectal cancer patients for this underlying abnormality, so mismatch repair deficiency or microsatellite instability-high. And in part, really, you know, related to that, the idea of identifying Lynch patients and then potentially preventing cancers. And now, you know, with the secondarily idea of identifying patients that are eligible for immunotherapy with the potential there for durable, maybe even curable kind of outcomes from immune therapy. Really too, just amazing potential benefits from testing that emerge, and so really just stresses the need for us to really consistently in every colorectal cancer patient be testing for this.

Dr. Chu:
Yeah, it's critically important that we test all of our patients with metastatic colorectal cancer for their MSI-high/defective mismatch repair status, because clearly then – if they are in that group, then they should receive immunotherapy with pembrolizumab either in the disease refractory setting or now, based on the landmark KEYNOTE-177 study, they actually can receive pembrolizumab monotherapy as their frontline treatment of choice. But also, to expand that to patients who have non-colorectal cancer disease and who have progressed on whatever treatments they've received, that also one should also assess for the MSI-high/defective mismatch repair status because they also could benefit pretty significantly from pembrolizumab monotherapy.

Unfortunately, that's all the time we have today, so I would like to thank our audience for listening in and thank you, Dr. Overman, for joining me and for sharing all of your valuable and terrific insights. It was great speaking with you today.

Dr. Overman:
Thank you, Dr. Chu. It was really a pleasurable podcast.

Announcer:
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