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Personalizing the Treatment of Recurrent/Metastatic HNSCC: *A Multifactorial Path*

Announcer:
Welcome to CME on ReachMD. This activity, titled “Personalizing the Treatment of Recurrent/Metastatic HNSCC: A Multifactorial Path” is provided by Prova Education.

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Dr. Burtness:
The use of anti-PD-1 monoclonal antibodies has led to a paradigm change in our frontline approach to recurrent or metastatic head and neck squamous cell carcinoma, but there are still uncertainties over optimal disease management.

This is CME on ReachMD, and I’m Dr. Barbara Burtness. I’d like to welcome my colleague, Dr. Nabil Saba, to our discussion, where we’ll address this medical challenge.

Dr. Saba:
Thank you very much, Dr. Burtness.

Dr. Burtness:
Let’s dive right in. Dr. Saba, let’s look at what led to this paradigm shift where we now use anti-PD-L1 monoclonal antibodies in the front line for most patients with recurrent metastatic head and neck cancer. What can you tell us about key clinical trial data, specifically around efficacy, safety, and outcomes?

Dr. Saba:
So it has been really an exciting past decade. We started with KEYNOTE-012, which was a trial looking at pembrolizumab and different tumor types, and what caught the attention is really the response rate that was observed on this trial, even in the heavily pretreated population. Moving to the first randomized phase 3 trial that led to an approval of nivolumab in recurrent metastatic disease, CheckMate 141, which was a 2:1 randomization between the PD-1 inhibitor nivolumab versus either methotrexate, docetaxel, and cetuximab. The patients who received nivolumab had a significantly better overall survival, leading to the FDA approval. There’s also evidence that the quality of life for patients on nivolumab was maintained more than patients on chemotherapy. A very similar trial, KEYNOTE-040, also randomized patients in the same manner to pembrolizumab as single agent or investigators’ choice, as the same agents that I mentioned earlier, and led to initially not so significant improvement in survival. But upon further analysis the trial did meet its endpoint in terms of overall survival improvement, and the overall survival was enriched with a higher PD-L1.

So two phase 3 trials in head and neck recurrent metastatic disease changed our standard of care. Now, the first-line therapy, even after these trials, still remained the EXTREME regimen, which has been the standard of care. Basically, both the 040 and CheckMate 141 selected patient populations that had failed either the EXTREME regimen or progressed within 6 months of platinum-based therapies.

Then came KEYNOTE-048, which looked at the first-line approach, and perhaps, Dr. Burtness, since you led the study, it would be great if you can talk to us about 048.

Dr. Burtness:
So in the wake of CheckMate 141 and KEYNOTE-040 and single-agent data in KEYNOTE-012, there was a clear indication that PD-1 inhibition was active in head and neck cancer, but the response rates were in the 16% to 22% range across those studies. And so the question was: How could you put that sort of therapy up against the historic standard of the EXTREME regimen with its approximately 36% response rate in symptomatic patients? So the design of KEYNOTE-048 was that the control arm was either carboplatin or cisplatin with 5-FU and cetuximab, and then there were 2 experimental arms: either pembrolizumab alone or pembrolizumab together with the same 2 chemo drugs but without cetuximab. And there was a staged statistical plan that allowed the analysis first of patients who had PD-L1 expression in their tumors, as these were known to have higher response rate from the prior trials. And so there were a lot of analyses for overall survival and progression-free survival in pembrolizumab versus EXTREME and pembrolizumab plus chemotherapy versus EXTREME across the different biomarker-defined populations. So starting with the CPS 20 or higher population, here there was a survival benefit for pembrolizumab compared to the EXTREME regimen. The response rate was higher with the EXTREME regimen, progression-free survival was longer with the EXTREME regimen, but for those patients with a response, the duration of response was remarkable – almost 2 years – and the survival benefit has now continued to the 4-year mark. Similarly for the CPS 1 population the use of pembrolizumab monotherapy was superior to the EXTREME regimen [OS: 30% vs 19%], and that has again continued to the 4-year mark [OS: 16.7% vs 5.9%]. For the total population, the use of pembrolizumab was non-inferior to chemotherapy and cetuximab.

And then if you turn to pembrolizumab plus chemotherapy compared to the EXTREME regimen, here there was clear superiority for the experimental arm. So in CPS 20 or higher, in CPS 1 or higher, and in the total population, pembrolizumab plus chemotherapy was superior to the EXTREME regimen. The response rate was comparable, progression-free survival was comparable, but median survival and 4-year survival were far superior with pembrolizumab plus chemotherapy. And so this really led to the inclusion of pembrolizumab either as monotherapy for PD-L1-expressing cancers or in combination with chemotherapy to become the standard first-line treatment for recurrent metastatic head and neck cancer.

Dr. Saba:
Thank you for this very nice review of KEYNOTE-048. There has been a number of efforts to compare immunotherapy with the EXTREME regimen in the first-line setting. It's important to mention the CheckMate 651 trial, which looked at the combination of nivolumab and ipilimumab, a CTLA-4 inhibitor, with a PD-1 inhibitor and compared it head-to-head with the EXTREME regimen. The trial did not meet its primary endpoint, and looking more into the results of this trial, it seems that the patients on the EXTREME regimen in the overall population did perform better compared to the traditional outcome with EXTREME regimen and the outcome that we observed also in KEYNOTE-048. What was important, though, is that the nivo plus ipilimumab did seem to compare very favorably – of course, we're not supposed to compare head-to-head with other trials – but did compare favorably with the 048 data. I have to say, though, that in general, the CTLA-4 inhibitors and the PD-L1 inhibitors have not really had much proven efficacy compared to PD-1 inhibitors in recurrent metastatic head and neck cancer. Recently, the KESTREL trial was also reported, and this was a negative study. And what's interesting is that when you look at the magnitude of difference between the EXTREME regimen and durvalumab or durvalumab and tremelimumab, this does not reach the same level of difference that you see with nivolumab and ipilimumab.

There have been other trials as well, but those were in the second-line setting, like EAGLE and CONDOR, and did not read positively in favor of immunotherapy, even though they had the same design as the CheckMate 141 and the KEYNOTE-048. So at the moment, our standard of care consists of what was reported in the 040 trial and CheckMate 141 for the second-line setting. The 048 has been such an important study that taught us so much, and maybe we can look at, Dr. Burtness, at the different factors that lead us to use these anti-PD-1 therapeutic agents in patients.

Announcer:
For those just tuning in, you're listening to CME on ReachMD with Dr. Barbara Burtness and Dr. Nabil Saba, while they focus is on identifying clinical strategies to optimize outcomes for patients with recurrent or metastatic head and neck squamous cell cancer.

Dr. Burtness:
The first thing to say is that PD-L1 has proved to be a very reliable and reproducible biomarker for the use of anti-PD-1 therapy in recurrent metastatic head and neck cancer. This has been validated now in the CheckMate 651 trial, as we were just discussing, and in neoadjuvant trials, we're seeing that the CPS 20 population has a higher response rate to PD-1 inhibition or to immunotherapy combinations than the other groups. We did go back in KEYNOTE-048 and do an analysis of the PD-L1 low and PD-L1 non-expressing cases because, as you remember, the initial analysis started with the most PD-L1-enriched group and then all PD-L1 expressers and then the total population, which included both PD-L1 negative and PD-L1 expressing. So we went back and looked at these subsets, and so if you looked in the PD-L1 1 to 19 group – so PD-L1 expressing but not in the richest subset – for both of those comparisons, pembrolizumab appeared superior to the EXTREME regimen, and pembrolizumab plus chemotherapy appeared superior to the

EXTREME regimen. If you looked at the PD-L1 non-expressing cases – so CPS <1 – there, pembrolizumab monotherapy did appear not to be as good as the EXTREME regimen with shorter numeric overall survival. It was a small subset of patients and didn't have a great deal of power. The confidence intervals were wide, but quite concerning that pembrolizumab alone should not be given to those patients. Pembrolizumab plus chemotherapy appeared quite comparable to the EXTREME regimen in those patients, and I think we probably still have something to learn about whether starting with the EXTREME regimen and crossing over to pembrolizumab is appropriate. In our practice, we tend to think about immunotherapy combinations for those patients that might amplify the benefit of pembrolizumab.

It was clear from early studies, like the KEYNOTE-012, that higher tumor burden was an adverse predictor of response to pembrolizumab monotherapy. So I would also think about pembrolizumab/chemotherapy combination for patients with bulkier disease, for those with lower PD-L1 expression, obviously, and for those who are most symptomatic because they'll benefit the most from a higher response. One of the things that I think remains somewhat unclear is whether or not HPV status ought to be something that drives us towards pembrolizumab/chemotherapy. If you look at the forest plots from KEYNOTE-048 for pembrolizumab versus the EXTREME regimen in p16-positive cases that are PD-L1 expressing, the hazard ratio approaches 1, whereas if you look at pembrolizumab plus chemotherapy, the hazard ratio is about 0.39. Obviously, you start with a great deal of sensitivity to platinum-based chemotherapy in these patients, but it does appear for survival as if that synergy or interaction between chemotherapy and pembrolizumab may be particularly beneficial in the HPV-positive patients. That was a small subset, and I think that those data were initially sort of thought of as maybe a fluke, but when you look in CheckMate 651, again, that's a group of patients where the median survival was actually lower for nivolumab plus ipilimumab than it was for the EXTREME regimen. So I think we still have more to learn about that HPV-positive subset. Certainly, patient health status, a patient who's not a candidate for chemotherapy but is a candidate for pembrolizumab; and a final consideration is obviously how recently the patient has had cisplatin chemotherapy. So for those patients who progress shortly after cisplatin/radiation, we would move straight on to immunotherapy.

I'd like to close our discussion today with a look into the future. Dr. Saba, what clinical trials are underway in recurrent metastatic head and neck cancer and some maybe recent phase 2 data that may suggest better outcomes may be coming in the future?

Dr. Saba:
These studies that we discussed really have revolutionized our care for patients, but we're still not really reaching the benefit for the majority of these patients, and let's not forget that the majority of these patients actually progress. And so over the last several years, there has been efforts to try to find what would be the best partner to combine with the PD-1 inhibitor, given that these agents are well tolerated. And so, you know, VEGF inhibitors came as a very attractive class of agents given that VEGF inhibitors are immunomodulatory. There have been also a lot of focus and interest on EGFR inhibitors, because let's not forget that those were the standard of care with cetuximab in the recurrent metastatic setting. So there's a couple of trials that are worth mentioning. Certainly, we did, in collaboration with Moffitt Cancer Center, a trial of pembrolizumab and cabozantinib, and the responses in this trial really were encouraging. The trial did have a distribution as far as CPS score that is similar to or comparable – of course, the numbers are much smaller than 048, but really when we looked at the response rate, we have observed a [objective] response that reached about 54% for these patients using the combination. I have to say the combination was fairly well tolerated. Many patients required dose reductions, so I think that opens the door for exploring similar combinations in recurrent metastatic disease.

A second trial that is important is the phase 3 pembrolizumab/lenvatinib trial, which is the LEAP-10 study. It's a placebo-controlled trial comparing pembro/lenvatinib versus pembro/placebo in the first-line recurrent metastatic setting. The results are awaited with a lot of expectations to see if the standard of care can be once more changed.

The question that we're trying to tackle is not just which agent we combine, but also the appropriate sequence of therapy. And so I think, you know, for patients who fail PD-1 inhibitors, is it more plausible to go straight to chemotherapy? Or is it more plausible to go, for example, to a non-chemotherapy combination that would be targeted therapy?

We ought to mention that other efforts are ongoing, as well, in terms of combinations of different targeted agents – some of them not so promising. Unfortunately, the press release for the INTERLINK-1 trial did not seem to indicate that this is a positive study. It's a monalizumab plus cetuximab versus cetuximab and placebo, as well.

However, there are multiple trials and multiple agents that could be candidates for good partnership, if you like, with pembrolizumab or with any PD-1 inhibitor here in head and neck cancer.

Dr. Burtness:
This has been a great discussion. Unfortunately, that's all the time we have today, so I want to thank our audience for listening in, and thank you, Dr. Nabil Saba, for joining me and for sharing all your valuable insights. It was great speaking with you today.

Dr. Saba:
It was a great pleasure as well, Dr. Burtness. Thank you.

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