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The Role of Immunotherapy in the Treatment of Recurrent or Metastatic HNSCC: The Evidence

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Dr. Saba:
Hello, this is CME on ReachMD, and I'm Dr. Nabil Saba. Here with me today is my friend and colleague, Dr. Barbara Burtness.

And, Dr. Burtness, let's dive right in and look at the KEYNOTE-048 data. What do the results of this study tell us about when to consider pembrolizumab monotherapy versus pembrolizumab plus chemotherapy.

Dr. Burtness:
It's great to be here with you today. And what we saw from the study was that for all comers, pembrolizumab plus chemotherapy was superior to cetuximab plus chemotherapy. And we saw that for pembrolizumab monotherapy, it was not inferior in all comers, but it was superior to chemotherapy and cetuximab if PD-L1 was expressed either with CPS [combined positive score] greater than or equal to 1 or CPS greater than or equal to 20.

Subsequently, we went back and we have published unplanned subset analyses, looking at the CPS 1 to 19 and the CPS less than 1. And there, we saw clear evidence that pembro mono was superior to chemotherapy and cetuximab for 1 to 19. And it looked, at least numerically, to be inferior in those with CPS less than or equal to 1. If you look at response rate, that's higher when you give chemotherapy together with pembrolizumab. Five-year survivals coming out just a few percent higher, maybe, with the addition of chemotherapy.

I think the power, though, to really answer that question was not present in that study. And I think it is something that maybe prospectively ought to still be studied. But you know, there have been other trials in the first-line setting.

Dr. Saba:
If you recall very well, the very initial studies were basically focused on single-agent PD-1 inhibitors. KEYNOTE-012, 055, and then were followed by KEYNOTE-040 and CheckMate 141, which basically established the superiority and overall survival [OS] with single-agent, and those were without specific guidance as far as biomarker positivity, which really came with 048.

But the newer generations of trials that attempted to change the standard of care in the first-line setting both focused on adding a CTLA4 inhibitor to the PD-1 backbone and compared it to EXTREME. As you know, both KESTREL and CheckMate 651 followed that design. And KESTREL, unfortunately, the median PFS [progression-free survival] was longer with EXTREME compared to the other 2 arms, including the CTLA4 arm. And that suggested that subsequent immunotherapy used by many patients on the EXTREME arm contributed to probably similar overall survival outcomes between these different arms.

For the same reasons, and despite the generous duration of response in 651 that we observed, especially in the biomarker-positive group, and despite the trend and improved overall survival, actually, in this group this did not really translate into a statistically significant

difference. And when we look further at the KEYNOTE-714, which compared to the nivo single agent to nivo plus ipilimumab, the data really refuted, I think, any possible benefit to adding a CTLA4 inhibitor to an anti-PD-1 therapy.

Barbara, what do you think about the more recent data with chemo immunotherapy? We know that 5-FU is not a very commonly appreciated drug, I guess, if I can say, in North America, and so the KEYNOTE-B10 was really interesting.

Dr. Burtness:
KEYNOTE-B10, which used a regimen of a platinating agent together with paclitaxel, were 2 different ways to schedule the taxane together with pembro that had just over 100 patients in it and showed a response rate of 49% and very comparable progression-free survival and overall survival results to KEYNOTE-048. And so I think for a situation where the patient isn't enthusiastic about infusional 5-FU, that provides I think, you know, real support for substituting a taxane-based regimen.

And then the FRAIL-IMMUNE trial was used, again, a taxane, platinating agent, and in this case durvalumab, an agent that's not approved for head and neck cancer but clearly has activity. And this also had a very high response rate.

Dr. Saba:
Yeah, certainly very exciting times.

I think it's important also to mention the other phase 3 trials and combinations that are attempting to you know, remove chemotherapy altogether. We know the VEGF TKIs have had a certain success rate. And when you look at overall response rate and progression-free survival, certainly the LEAP-010 trial was positive as far as these 2 endpoints; however, unfortunately it did not translate to an improved overall survival or duration of response, raising the question of whether treatment discontinuation on this trial or toxicity played a role in these observations.

Similarly, yet with a different compound, cabozantinib and pembrolizumab combinations have resulted in encouraging overall response, PFS, and OS. And the phase 2/3 STELLAR-305 trial is currently enrolling, and we'll see whether zanzalintinib, which is a similar agent to cabozantinib, will have a better chance in improving the outcome for these patients.

So this has been a great discussion. I think the takeaways, I guess, is that immunotherapy has clearly transformed the landscape and therapy in recurrent metastatic disease. And we expect this field to continue evolving rapidly, hopefully with novel combinations. And this has been, I guess, a great bite-sized discussion. Unfortunately, our time is up. Thank you for listening.

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