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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Advancing Care in HNSCC: Evolving Strategies Across the Disease Continuum

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Dr. Harrington:
Exciting data on new therapeutic approaches in head and neck cancer were presented at the ESMO Congress this year. Are you up to date with the latest clinical findings?

This is CE on ReachMD, and I'm Dr. Kevin Harrington.

Dr. Rodriguez:
And I'm Dr. Cristina Rodriguez.

Dr. Harrington:
There were some interesting abstracts on new approaches using immunotherapy as perioperative or adjuvant treatment in resectable locally advanced disease. Tina, can you review these studies for us, please?

Dr. Rodriguez:
Sure, I'm happy to. So there have been quite a few developments focused on incorporating the immune checkpoint inhibitors into curative-intent strategies in head and neck cancer. And I think we could talk about 4 notable studies.

I think the first of these is obviously the landmark trial, KEYNOTE-689, recently published in *The New England Journal*. This demonstrated a superior EFS in patients with resectable mucosal head and neck cancer who received pembrolizumab before and after surgery compared to patients who were receiving standard surgery followed by appropriate postoperative treatment.

This trial enrolled mostly oral cavity cancer, so a predominantly HPV-negative population, and this resulted in the approval of pembrolizumab for use in the perioperative setting in both the US and Europe, and it's approved only for patients who are CPS 1 or higher.

At ESMO, we saw secondary analyses presented, particularly focused on patient-reported quality of life outcomes. There was no significant change in baseline versus preoperative quality of life in the patients in the experimental arm. And not surprisingly, there was a quality of life reduction during the postoperative treatment phase for patients in both arms, which improved after they recovered from treatment.

The second trial I thought that was very interesting was the CAMORAL trial presented by our colleagues from Shanghai. This was a very similar trial to KEYNOTE-689. However, the experimental arm used a chemoimmunotherapy triplet combination. This was a randomized phase 2 study, about 60 patients in each arm, but it showed a very impressive improvement in event-free survival in the

experimental arm.

Notably, the objective responses and the major pathologic responses in the experimental arm were a lot higher than what we observed in KEYNOTE-689. Now, we know cross-trials comparisons being what they are, are limited. But this observation of a higher response rate is something we've also observed in the recurrent metastatic setting, and it may indicate that through this approach, we might have an impact on the extent of surgery that these patients require and may have an impact on their long-term quality of life.

Of course, the downside to this approach is we anticipate a higher rate of toxicity in chemoimmunotherapy combinations, which also raises the concern, are we losing the window to operate on these patients? But reassuringly, in both arms, about 90% of patients in this trial went on to curative-intent surgery.

Finally, I would be remiss not to mention 2 randomized trials that also used immunotherapy in curative-intent treatment but did not meet their endpoints of interest. The first one was the CompARE trial, where patients with unresectable head and neck cancer were randomized to durvalumab prior to and after definitive chemoradiation, compared to chemoradiation alone. The other was an ADRISK trial, where patients who had high-risk pathologic features after resection were randomized either to pembrolizumab with chemoradiation followed by maintenance versus chemoradiation alone.

Both trials didn't meet their primary endpoints, and I think the underlying cause is that the population was different. These trials enrolled a predominant p16-positive HPV-associated population, where we've seen in prior trials that the magnitude of benefit to pembrolizumab just has not been seen.

So there have been positive and negative trials in the perioperative and adjuvant setting in locally advanced disease.

What's your take on these studies, Kevin?

Dr. Harrington:
Well, I think the data are remarkable. We've seen, I think, practice-changing, practice-defining data emerging from KEYNOTE-689. I think that has already led to a change in global standard of care for patients with resectable locally advanced head and neck cancer, particularly oral cavity cancer. The data from the CAMORAL study, I think, are really intriguing and point the way to future studies. I think we're absolutely obliged now to address this question: Would we get more for our patients if we gave chemo IO combinations as the induction phase?

The data from the HPV-positive patients, and particularly from the CompARE study, perhaps, which is more in line with the negative studies that we've seen from JAVELIN Head and Neck 100 and the KEYNOTE-412, those, I think, really answer the question that delivering induction immunotherapy followed by radical chemoradiation with immunotherapy is probably not the way to go. The German study, the ADRISK study, the number of patients there with HPV-positive disease receiving operations for locally advanced disease is probably out of kilter with much of the rest of the world. And I think those data have to be reviewed with some caution.

Dr. Rodriguez:
Yeah, I think it's pretty clear that these approaches really benefit the p16-negative population. I mean, I think we'd have an incomplete discussion if we didn't mention the NIVOPOSTOP data that was presented at ASCO coming out of GORTEC, where nivolumab was included in postoperative therapy and showed a benefit. That was also a primarily p16-negative population.

It's interesting, too, that there may be differences in outcome benefit in terms of event-free survival when immunotherapy is given before or after surgery. Because in KEYNOTE-689, the event-free survival was really driven by a reduction in distant metastatic failure, while in NIVOPOSTOP, it was really a local-regional control benefit.

Dr. Harrington:
No, I agree with you, Tina. I think for me, the real conundrum about the difference between the KEYNOTE-689 data set and the NIVOPOSTOP data set is this difference between protection against metastatic failure with KEYNOTE-689, which I regard as really one of the hallmarks of what a bona fide immunotherapy approach should achieve, versus an improvement in locoregional control for NIVOPOSTOP.

And I think understanding where that difference is coming from will tell us a great deal about the differences in the treatment strategies. And from my mind, I think that that immunization event that occurs perioperatively before removal of the tumor looks to me to be the best candidate that we have for a priming event that leads to this protection against systemic failure. And I think further studies, I hope, will build upon those data.

Dr. Rodriguez:
There were some interesting abstracts on novel approaches in recurrent or metastatic disease. Kevin, what do our listeners need to

know about these studies?

Dr. Harrington:
Well, thanks, Tina. I'm happy to share my thoughts. And I agree, there have been a number of really interesting developments. So I think, again, looking at the ESMO data set, I'd like to draw upon 3 key contributions to our understanding, which I think add a great deal to how we contemplate how we manage patients with relapsed and/or metastatic disease.

So first of all, perhaps, I'd like to review the data from the phase 2 EV-202 trial. So this is a combination study of enfortumab vedotin plus pembrolizumab in patients with recurrent/metastatic head and neck cancer. Now, this study builds upon the original Cohort 5 of the 202 study, in which patients who had received previous immunotherapy and had also received chemotherapy, those patients had received monotherapy treatment with enfortumab vedotin. And we'd seen a remarkable response rate of about 24% in those patients. So that led to Cohort 9, in which the combination of enfortumab vedotin was given alongside pembrolizumab, and the primary endpoint of this study was confirmed overall response rate.

So we saw data from 41 patients, predominantly a US population, 78% of patients recruited from United States centers, 54% of the patients with oral cavity cancers. We saw that a large number of the patients had PD-L1 relatively high tumors at CPS greater than or equal to 20. We saw a confirmed overall response rate of 39% in this group of patients, 10% of whom achieved a complete remission of their disease.

The median time to achieving a response was relatively rapid. This was a confirmed response at about 2.3 months median, and the duration of response was very positive at about 82% of patients still in response at 6 months.

We saw median progression-free survival of about 5 months, and the median overall survival data have not yet been reached. This was achieved with relatively modest toxicity, and so this to me looks like a really promising chemotherapy plus pembrolizumab combination in the first-line setting.

We also saw data, again in the first-line setting, trying to combine the treatment of patients with disease that could be addressed with radiation therapy, pembrolizumab plus radiation versus pembrolizumab alone. There were a number of patients recruited into that study who were being treated after platin or after second- or third-line chemotherapy, and this was to increase patient recruitment.

We saw that patients receiving radiation who had lesions that were amenable to radiation, who were receiving first-line pembrolizumab, would actually have radiotherapy commencing, then start the pembrolizumab. They would complete a course of 36 Gy and 12 fractions to 1, 2, or 3 irradiatable lesions while continuing with pembrolizumab for up to 12 months. And the control arm received just pembrolizumab on its own on a 3-weekly schedule.

There were stipulations about the bulk of disease that needed to be present in order to qualify to the study, and this was more than 2 mL of disease. The majority of patients had metastatic disease below the clavicle, and many of them had prior radiotherapy for their primary treatment.

When we look at the outcome of the study, which was based around response in the unirradiated lesions, we saw that there was a difference between those who received radiation plus pembrolizumab versus those who just received pembrolizumab. And this was true both of the intention-to-treat population and also of the per-protocol population. And in the per-protocol population, we saw a difference of 43% versus about 24%. So that was very interesting data.

The third study I'd like to discuss are the data from Cohort 1 of the OrigAMI-4 study. This was the amivantamab monotherapy study in second and third line, and I was fortunate enough to present those data. This agent, amivantamab, is a tri-functional agent, if you like. It targets both EGF receptor, MET, but also it has a functional FC receptor that allows immune activation.

What we saw in this study was with single-agent subcutaneous amivantamab on a 3-weekly schedule in patients who had received prior immunotherapy and platin-based chemotherapy, treated in second- and third-line settings, we saw that this was very tolerable. So in a toxicity population of 86 patients, we saw that this was highly manageable. Notably, we saw that the infusion-related reactions that we see with intravenous amivantamab were very low at 7% with the subcutaneous formulation and all at grade 1 or grade 2.

We saw in the efficacy population of 38 patients, we saw a response rate of 45%, with a further 45% of patients achieving stable disease. We saw that this was achievable with durability of response, so that we saw that a number of patients remained in response well beyond 6 months, so a median duration of response exceeding 7 months. A median progression-free survival again approaching 7 months.

So overall, this agent looks very promising. So I think we've seen movement in the first line and also in the second and third line with novel therapeutic agents.

So, Tina, I'd be really interested to see what your thoughts are around these new data emerging in the early phase in relapsed and/or metastatic disease.

So for those just tuning in, you're listening to CE on ReachMD. I'm Dr. Kevin Harrington, and here with me today is Dr. Cristina Rodriguez. We're discussing new data on head and neck cancer that were presented at this year's ESMO Congress.

Dr. Rodriguez:
Well, Kevin, we've been doing this a long time and we've seen a lot of early phase, maybe, encouraging data sets. But I think increasingly in the recent years, we've been really observing much better response rates that could potentially change practice in larger trials.

In particular, what I'm most intrigued about are the novel EGFR inhibitors in combination with pembro in the first-line setting. To me, I think these early-phase response rates are pretty encouraging. And they're pretty encouraging in the HPV-negative population. So similarly, in the recurrent metastatic setting, there just seems to be a split between what works for the HPV negatives and the HPV positives, which makes sense. You know, they're 2 different diseases. So I'm very encouraged by that because it's consistently been shown even with other novel EGFR inhibitors, and there's ongoing phase 3 trials that might provide practice change in this population.

Dr. Harrington:
Yeah, I agree with you. And I think, for me, we discussed the data there with amivantamab, but we didn't discuss agents such as petosemtamab and ficerafusp alfa, which are effectively targeting the EGF receptor access. And I think there are big opportunities there now, largely in the HPV-negative space, albeit with petosemtamab, also including patients with p16-positive HPV-related cancers in their pivotal phase 3 study.

I think it's encouraging with the antibody-drug conjugate, the EV plus pembrolizumab approach, that we see that there are such profound responses in the HPV-positive population. Because as yet, we're not seeing major changes in the vaccine space, although we're still optimistic about that. So it's good to know that maybe the ADCs bring something to the mix there that give us opportunities for this group of patients.

Dr. Rodriguez:
Yeah. I think the other thing to think about with the ADC combinations is that the toxicities are non-trivial, and I think that's what we've learned running these trials. We've also learned that toxicity is important in recurrent metastatic head and neck trials. For example, one large study, the LEAP trial that included lenvatinib, had better response rates but didn't improve overall survival, largely because most patients couldn't take the medication. So it's a very important balance that we have to strike when designing these regimens. They have to be tolerable for patients.

Dr. Harrington:
Perioperative pembrolizumab was approved by the FDA earlier this year for resectable, locally advanced head and neck squamous cell carcinoma. What do we need to keep in mind when incorporating this regimen into clinical practice?

Dr. Rodriguez:
Well, Kevin, I think these recent developments have really underscored the importance of a multidisciplinary evaluation for our patients and diagnosis. So at our center, we have multidisciplinary clinics where I, the medical oncologist, my colleagues from radiation oncology and head and neck surgery, all see the patients together. I think this really allows us to provide a cohesive plan for the patient that involves all the various areas of expertise at the time they set foot in the clinic.

And the other really important component that, to be completely honest we're still working on, is really having that CPS data available at the time of seeing the patient.

Because it's really important to kind of be able to offer this new standard of care of KEYNOTE-689 right up front. And you can't really do that. You can't get approval for pembrolizumab if you don't have the CPS score.

I think the other thing that is, to me, very critical is to always remember the eligibility criteria for this study. Because I think we start not doing our patients a service if we start extrapolating this data into settings where it's not studied. For example, I think the biggest takeaway from KEYNOTE-689 is this is a population that has resectable disease and that we saw the benefit mainly in the reduction of distant metastasis.

What this means is the patients with borderline resectable disease or a patient with unresectable disease, that's probably not the best candidate for this KEYNOTE-689 approach. The response rates, the objective response rates and the pathologic response rates were low, and you can't really expect to convert someone with unresectable disease to resectable disease with this type of approach. Maybe

in future trials with chemo IO, that might be a good thing to study, but not for the current data as it stands.

Dr. Harrington:
Yeah, I think that's a really important point, a number of important points.

So I think we've known for some time that multidisciplinarity in our practice is to the benefit of our patients, but that's going to become even more important now we're in the era of the perioperative immunotherapy management. The surgeon, the pathologist, the radiologist are all playing even greater roles, and as a team, we have to be more cohesive and, I guess, less competitive with one another in order to develop the best treatment approaches for our patients. I think this is really going to be one of the key challenges as a team, as a group that we have in this field.

But I think the opportunities for our patients are absolutely enormous.

Dr. Rodriguez:
It's exciting times. So the field is moving very rapidly, Kevin. What does your crystal ball tell you about the future of managing this disease?

Dr. Harrington:
So I think that certainly in terms of the role of neoadjuvant immunotherapy perioperative treatment, I think that paradigm has now changed, and I think we are now in a new era where for patients with resectable disease, especially for those, I see, really, oral cavity cancer and laryngeal cancer as being the areas where we're going to develop this strategy most strongly.

I think the big opportunities lie with, as you reviewed the CAMORAL data, looking at chemotherapy plus immunotherapy in induction. I think that offers big opportunities. We've known for some time that in larynx cancer, chemo selection of patients for organ preservation is appropriate, and I think we're going to build upon those data both in oral cavity and in laryngeal cancer.

But we also need to bear in mind that there will be opportunities, I hope, for IO-IO combinations. Just because they've failed in relapsed metastatic disease doesn't mean that they're actually doomed to fail in this setting, in treatment-naïve, intact immune systems. And then, of course, there are the novel agents that we're seeing gain traction in relapsed metastatic disease in first, second, and third lines. So I think in particular the EGFR-targeting agents with immunotherapy in a neoadjuvant approach, and also they lend themselves potentially to durable treatment in an adjuvant setting. I think these really demand clinical trial activity.

So I think one of the other challenges that we will face is defining how long patients should remain on immunotherapy in the adjuvant setting. So we know that from KEYNOTE-689, that was targeting a 12-month adjuvant phase, but we don't yet know really how long people need to be in that adjuvant treatment phase. And I think certainly, in terms of healthcare burden and burden to the patients, we need to try to see can we bring that down or at least examine the possibility of bringing that down. And then, as we've discussed in the recurrent and/or metastatic space, I think there are huge opportunities in the HPV-negative space. I think the excitement around EGFR-targeted therapies is real and I hope will lead to practice change and approvals.

And in the HPV-positive space, as we've touched upon, drugs such as the ADCs are offering us a hope there. But again, I really strongly believe that the vaccine strategies are the way that we're going to move the dial in that group of patients. So I think there's the opportunity.

And I'm really interested to hear, Tina, what your views are on that, what other perspectives you have.

Dr. Rodriguez:
I think, like I mentioned earlier, we are now seeing that distinguishing between the HPV-positive and the HPV-negative population is important, even in the recurrent/metastatic setting. We've known this for a long time, but it's increasingly clear that we need to have different therapeutic strategies for each of them.

I do think, as you said, I agree with you that we need to be careful about the p16-negative population. In the real world, outside of clinical trials, this is a population that has limited resources, that has comorbidity, so thinking about strategies that are well tolerated, that are not financially toxic to the patient, I think, is going to be very important.

I'd be so interested to look at real-world data after these all kind of roll out and try to see how these things really are carried out when outside of a clinical trial.

So, yeah, I think there's a lot of reasons to be excited about the future, very promising data in both these patients. I think it also underscores the importance of putting these patients in clinical trials. The only way we can improve outcomes for these patients is to put them on trials and learn about what works and what doesn't work.

Dr. Harrington:
Amen to that. Absolutely. Well, this was a great conversation. And before we conclude, Tina, I'd like maybe just to hear one final take-home message from you for our audience, please.

Dr. Rodriguez:
Well, I think that in the locally advanced setting, there's been a marked paradigm shift with the approval of pembrolizumab to be given before and after surgery. This effect is really most noted in the HPV-negative population, and the event-free survival benefit is really mostly in the observance of lower risk of distant metastasis. And lots of ongoing trials, so we anticipate more developments in the locally advanced head and neck space.

Dr. Harrington:
And maybe I could add just some thoughts finally on the relapsed metastatic space. Because, again, I think that since the publication of the KEYNOTE-048 data set, where we have tried, I think, repeatedly to improve upon chemo-free regimens in the first-line relapse metastatic setting, I think for the first time in a while, I think there's great optimism that we're going to see some positive studies in the next 2 or 3 years. I'm very hopeful that that is the case.

I think also in second and third line, we have some very credible agents that may be benefiting patients who don't receive such drugs in the first- and second-line settings. So I think we've really got a chance now to improve not just locoregionally advanced disease, but also patients who come back with recurrent and/or metastatic head and neck cancer, and we can improve outcomes for those patients.

So I share your optimism. It's a great time, I think, to be a head and neck oncologist. Lots of new developments for our patients, hopefully lots of things for our patients to benefit from.

Dr. Rodriguez:
For sure.

Dr. Harrington:
And sadly, that's all the time we have today. So I want to thank our audience for listening in, and I want to thank you especially, Dr. Cristina Rodriguez, for joining me and for sharing all of your valuable insights. It's been really great speaking with you today.

Dr. Rodriguez:
It was my pleasure. Thank you so much for having me.

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