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Frontline Insights: Emerging Therapeutic Strategies in HNSCC

Dr. Harrington:
In 2025, we have seen exciting new data on novel therapeutic approaches in head and neck cancer. Are you up to date on the latest clinical findings?

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

Dr. Le Tourneau:
And I'm Dr. Christophe Le Tourneau.

Dr. Harrington:
Christophe, what new data and therapeutic approaches are you most excited about in locally advanced disease?

Dr. Le Tourneau:
So I guess that the 2025 year has been a successful year for locally advanced head and neck squamous cell carcinoma, with two randomized phase 3 trials that have established immunotherapy.

The first one is the KEYNOTE-689, with a scale that is a perioperative, starting with immunotherapy before surgery and then continuing with radiotherapy or chemoradiation and immunotherapy, followed by an adjuvant phase. And that study was positive in terms of event-free survival.

The NIVOPOSTOP trial was another randomized phase 3 trial that evaluated nivolumab in the adjuvant setting after surgery. Patients were randomized between chemoradiation and nivolumab, one injection, followed by chemoradiation and nivolumab and nivolumab in the adjuvant phase. And that trial was also positive in terms of disease-free survival.

In the definitive setting, there is a study that is quite interesting evaluating a very new class of agent, which is a radioenhancer. These are actually nanoparticles of hafnium that are being injected in the tumor of patients, and then patients get radiation radiotherapy.

Results of the phase 1 trial in NBTXR3-102 were presented and are going to be published very soon. And in this patient population that is not eligible for concomitant chemoradiation, we see outcomes that are quite encouraging. Usually, overall survival is around 12 months, and we have here overall survival around 20 months. So this is the rationale for the ongoing phase 3 randomized trial, NANORAY-312.

In that trial, patients can be injected in the primary tumor, but also in the cervical lymph nodes, which wasn't the case in the phase 1 trial. So this trial is ongoing and we're really looking forward to the results.

Kevin, what are your thoughts on these new approaches actually?

Dr. Harrington:
Well, Christophe, I think it's a fantastically exciting time to be a head and neck oncologist. So looking first at the KEYNOTE-689 and the NIVOPOSTOP data, we've got 2 randomized clinical trial data sets that point the direction towards new approaches in managing patients with locally advanced disease, which is operable. And I think that is going to change the way we address this disease.

And then you touched upon, I think, really interesting data coming from the JNJ-1900 molecule and the old nanobiotics, as it was. This agent, I think, is a really fascinating drug. So as a radioenhancing agent that can increase doses of radiation within local tumors receiving curative-intent radiation, this is potentially a drug that can be used in the platinum-ineligible population. But of course, we see big opportunities to bring that forward also for patients with a platin-eligible disease, where it may add even further benefit.

So I think there are big chances for really exciting new work to be done in this space.

Dr. Le Tourneau:
Yeah, I have to say that I agree with you. And the beauty, also, of this radioenhancer is actually that it could work in many cancer types, actually. And there are data that have been presented in some GI tumors, but also ongoing data in lung cancer, and this is really exciting.

There were also some new data on novel approaches in recurrent or metastatic disease. Kevin, what do our listeners need to know about these studies?

Dr. Harrington:
Well, Christophe, there's been huge developments in this area. I mean, I think there's a lot to cover, but I'd like to maybe highlight some of what I think are potentially going to be studies that can change practice in the future.

So the first—I hope you'll forgive me if I touch upon the OrigAMI-4 cohort 1 data that I was lucky enough to present at the recent ESMO meeting in Berlin. So in the Cohort 1, patients with IO and platin pre-treated relapsed metastatic disease received amivantamab as a single agent as a subcutaneous injection. Patients with HPV-unrelated disease were eligible for this treatment, and this was given as a 3-weekly schedule. We reported data for 86 patients in the safety cohort. Generally speaking, the drug was well tolerated. Anticipated MET side effects as well as EGFR side effects were seen, but these were manageable.

The infusion-related reactions, which we've seen so commonly with the intravenous formulations, were only at 7% with the subcutaneous administration, none greater than grade 2. Importantly, in this second- and third-line treatment population, IO and platin exposed, we saw a response rate of 45% and a further 45% of patients with stable disease. We saw that the responses were durable. We saw that the median duration of response was in excess of 7 months, and the median progression-free survival was around about 7 months, and the median overall survival was not yet reached. So this is really important data.

We also saw, at the same meeting, an amivantamab plus paclitaxel study presented, again, in patients with previous IO and platin exposure. And in a small cohort of 11 patients, we saw a response rate of 64%.

So a lot to build on there with amivantamab combinations. And of course, really excitingly for me, those have pointed the way towards a newly opened phase 3 registrational study in the first-line setting, OrigAMI-5, in which amivantamab will be combined with carboplatin and pembrolizumab in comparison to the chemo-pembrolizumab combination arm from KEYNOTE-048.

Lots of interesting work with amivantamab.

For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Kevin Harrington, and here with me today is Dr. Christophe Le Tourneau. We're discussing recent data on novel therapeutic approaches in head and neck cancer.

I think it would be remiss not to talk about other EGFR-targeted strategies. So petosemtamab, a bispecific antibody targeting EGFR and LGR5, has presented really impressive data in the second- and third-line setting as a monotherapy, and also now as a combination with pembrolizumab in the first-line setting in phase 2 data with a response rate of 63%.

So, remarkable data that now has gone forward into phase 3 clinical trials, the LiGeR-HN1 study in the first-line setting and the LiGeR-HN2 study in the second- and third-line setting.

Another agent which I think is going to make a lot of impact in this disease is ficerafusp alfa, a bispecific antibody targeting EGFR, but also able to bind TGF beta and take it out of play within the tumor microenvironment. Again, we've seen really impressive phase 1/1b data for ficerafusp alfa and pembrolizumab with a response rate of 54% in that study. Again, that's gone into a phase 2/phase 3 study with dose optimization, the FORTIFY-HN01 study.

And I guess finally, just coming back to the JNJ-1900 agent, that is also being tested alongside stereotactic body radiotherapy, followed by immunotherapy in patients with a range of advanced solid cancers. And those data were presented recently in an abstract form. So I think lots to build on, lots to be interested in. And I'd really be interested, Christophe, to hear your take on these novel approaches.

Dr. Le Tourneau:
Yeah, thanks, Kevin. I guess this is really the revival of EGFR targeting with novel approaches that are really interesting. I mean, these

bispecific agents, they produce substantial efficacy and efficacy that is much higher than what we see with cetuximab, which is a single EGFR-targeting agent. So it's very likely, actually, that these drugs come in the first-line combination with pembrolizumab in the recurrent/metastatic setting. So obviously we'll need to wait for the phase 3 trial results, but this is a very encouraging result so far.

Dr. Harrington:
Christophe, what are the safety profiles of these novel therapeutic approaches that we've just been discussing?

Dr. Le Tourneau:
So in terms of immunotherapy that we will probably use in the locally advanced setting, I have to say that the safety is not very different than the one that we have experienced in the recurrent/metastatic setting. And we are now very used to using immunotherapy in that setting. So I'm not very worried about that.

Now, in terms of the local injection with the NBTXR3 radioenhancer, so we have quite an extensive experience since I launched that program in France. And I have to say that right now we haven't seen a lot of toxicities except a little bit of pain or a little bit of swelling. But nothing that is important and obviously all that is very transient.

For bispecific antibodies, I mean, we needed to get used with this new CRS and we now have a premedication and we know how to handle that. The rashes also, that is not that different from the one we knew with cetuximab. So I would say these are new drugs with new safety profiles, but now we know how to deal with these new drugs.

Dr. Harrington:
Yeah, it's a really interesting and important point, Christophe. So we are seeing with the novel agents that are coming to the clinic, they challenge us and they challenge the team with novel forms of toxicity.

So anticipation is key. Interaction with colleagues who are experts in various fields. So, for instance, relearning and reacquainting ourselves with things including hepatology, dermatology, neurology, gastroenterology, all of these disciplines now are things that we need to make contacts with specialties, but also, I think, re-skill ourselves in knowing what the toxicities can be and how to manage them.

I think the key to all of this, as we have always known in head and neck, is multidisciplinarity. I think if we get a good team together, we can give the best benefits for our patients.

Dr. Le Tourneau:
Yeah, I cannot agree more with you, Kevin. I mean, we have been used to working with surgeons and radiation oncologists, medical oncologists, and all the rehabilitation, etc. But working with other specialties has become now necessary for using these new drugs, especially immunotherapy. And I guess this is the key, I agree, for successfully treating our patients.

Dr. Harrington:
Well, this was a great conversation. But before we conclude, Christophe, what's your one take-home message for our audience today?

Dr. Le Tourneau:
So what I would like to say is that in the locally advanced setting, in patients who will undergo surgery, immunotherapy will become standard of care for many patients, actually, which is great news because it improves survival. We are lucky enough in head and neck cancer, also, to have new drugs, and I was very lucky to lead the intratumoral injections of JNJ and therapeutic vaccination as well. And hopefully, this will be novel modalities in the future for our patients.

Dr. Harrington:
Yeah, I agree. That's really exciting work. And I think in the setting of relapsed metastatic disease, I think I would echo your comments about the rebirth of EGFR-targeted therapies, especially in HPV-negative disease. I think there are other agents, including the antibody-drug conjugates and the therapeutic vaccines, which I hope are going to move the dial for HPV-positive disease, as well. But overall, the take-home message is this is a time of great optimism for change for patients with head and neck cancer and to provide better outcomes for them and their families.

And that's all the time we have today. So I want to thank our audience for listening in and thank you, Dr. Christophe Le Tourneau, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Le Tourneau:
Thank you, Dr. Kevin Harrington. It was great speaking with you today.