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Conference Coverage: Breaking News on Head and Neck Studies from the American Society for Radiation Oncology 58th Annual Meeting

Narrator:

Welcome to CME on ReachMD. This segment, Conference Coverage: Breaking News on Head and Neck Studies from the American Society for Radiation Oncology - 58th Annual Meeting, is sponsored by Prova Education. Your host is Dr. Jennifer Caudle, who welcomes Dr. Tanguy Seiwert, Assistant Professor of Medicine at the University of Chicago Medicine in Chicago, Illinois. Dr. Seiwert receives consulting fees from Merck/MSD, Bristol-Myers Squibb, Astra-Zeneca, Eli Lilly and Company, Amgen, Celgene, Innate Pharma, and Merck Serono.

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Dr. Caudle:
This is CME on ReachMD, and I am Dr. Jennifer Caudle. With me today is Dr. Tanguy Seiwert, who joins our program to bring us Breaking News on Head and Neck Studies from the American Society for Radiation Oncology's 58th Annual Meeting that recently took place in Boston, Massachusetts.

Dr. Seiwert, welcome to ReachMD.

Dr. Seiwert:
Hello, it's my pleasure to be here.

Dr. Caudle:
Dr. Seiwert, to begin our discussion, there is substantial excitement concerning immunotherapy in the treatment of different cancers, such as melanoma and non-small cell lung cancer, notably with agents that block checkpoint inhibition. This excitement has now come to head and neck cancer. Could you describe the mechanistic basis for checkpoint inhibition and why it's a pharmacological target?

Dr. Seiwert:
It is becoming clear that immunotherapy is likely a major pillar, probably as big as radiation or surgery or chemotherapy, and will be a major modality that affects very large parts of how we treat cancer. We have seen this in melanoma where we have three approved agents now for immunotherapy and marked benefit. We have seen this in lung cancer, also multiple approved agents and a lot of excitement in the field. And recently, and I am particularly happy about this, we've also seen positive studies and exciting data in head and neck cancer.

It's actually interesting, if you go back more than a decade, it was actually known that head and neck cancer can be an enflamed tumor type where you see immune cells infiltrating the tumor, which is, essentially a hallmark of an immunogenic cancer; however, we didn't know what to do about it. But recently, it has become clear that those cancers that are recognized by the immune system have a way of escaping that immune response, and often times those are immune checkpoints, and PD-1, PD-L1 interaction is one of those. And I think after the initial data in melanoma and then also in lung cancer, it became clear that the same phenotype that we have in lung

cancer and melanoma is also present in those head and neck cancers, meaning this inflammation.

And then, we saw exciting data with several agents in head and neck cancer. The first data was from the KEYNOTE-012 study. This was a PD-1 inhibitor, pembrolizumab, that was used for head and neck tumors that were heavily pretreated, second, third, fourth line recurrent metastatic disease, and those are patients that do not do very well, usually have a short life expectancy, and we saw activity. We saw, actually, striking activity on the order of about 18% of patients had a response, and an additional 20, 25% had stable disease. What was remarkable about this initial data was that not only was the level of activity at least as good, if not higher, than the best targeted therapy, which is cetuximab, but we also saw many patients who lived for prolonged periods of time, and that's a hallmark that we have seen with other cancer types where immunotherapy is different from chemotherapy and target therapies. So, the durability of those responses is striking. That actually led to approval of pembrolizumab in early August 2016 under accelerated approval, so we now have the first PD-1 inhibitor, that being pembrolizumab, approved for head and neck cancer.

There's another PD-1 inhibitor called nivolumab, very similar drug, that was tested in a Phase III study. That was a CheckMate-141 study, and that was a positive study. That was in the second line, in patients who have failed platinum-based therapy, and it was compared to single agent either docetaxel, methotrexate or cetuximab, and that was a positive study where I think at one year we saw an increase in surviving patients from 16 to 36%, so a marked improvement. And it is expected that nivolumab will also be approved very soon.

Making the link to the ASTRO Meeting 2016, I think it's a bit early to actually understand how these immune checkpoint inhibitors like pembrolizumab and nivolumab will integrate with standard of care treatments. We actually don't know how to interact with chemotherapy or with radiation. However, there are preclinical data suggesting that radiation may actually release antigen, kill tumor cells, and makes those antigens visible to immune cells, and so there's this idea that radiation might be an in vivo or inpatient vaccine that could actually potentiate the effect. And there are actually studies ongoing to test that. So, the reality is we actually don't have those data quite yet, but it's certainly exciting to maybe move these treatments, immune checkpoint treatments, from last line, second, third line to first-line and maybe curative intent with radiation.

Dr. Caudle:
Dr. Seiwert, how did the trial outcomes compare with current standard of care approaches to advanced head and neck cancer?

Dr. Seiwert:
So, the first point to make is that they do appear to be non cross-resistant with other treatments, so patients who are resistant to radiation, resistant to chemotherapy or targeted therapies can still respond to immunotherapy. The second difference, as I alluded to already, is that some patients have marked benefit. For some patients it really changes their lives where they have prolonged benefit, either prolonged stable disease or prolonged responses, so the durability is probably better, and that's likely why we see this impact on survival. Thirdly, it does appear that they are superior. In the Phase III study compared to single-agent chemotherapy, overall survival was superior, so while response rate on the order of 17, 18% is nice and better than, for example, compared to cetuximab, there seems to be an even larger impact on overall survival.

They have a very favorable side effect profile, so compared to radiation or cytotoxic chemotherapy, most patients have very few side effects, so Grade 1 toxicity, Grade 2 toxicity, skin itching, mild fatigue, those are the most common side effects. And then hypothyroidism occurs in about 10, 15% of patients, a side effect that's easily manageable with substitution of levothyroxine.

The one thing, though, that is unique and different are there are these more severe immune-related side effects, for example, pneumonitis. It only occurs in about 1 to 2% of patients. However, it needs to be screened for, quickly recognized and treated quickly and early, and that's really, really important.

Dr. Caudle:
Dr. Seiwert, how can patients with head and neck cancer be identified, and who will best respond to immunotherapy treatment? For example, are there useful biomarkers? And what effect does being HPV positive or having a high tumor load have on the potential outcome?

Dr. Seiwert:
The honest answer is we actually don't know for sure what the most reliable factors are, but we do have a few bits of information that give us a hint, and there are other ongoing studies. So, we do know that patients who express a protein called PD-L1, which is a ligand for PD-1, do tend to have high response rate. However, the problem is or the limitation is -- and that's true in other cancer types as well -- is that the biomarker is not perfect, so even patients who are PD-L1 negative can have benefit from these agents, PD-L1 agents, but the rate is lower. So, I always kind of summarize it saying that PD-L1 as a biomarker can enrich for patients who have more benefit, but it's not necessarily a way to select patients. And if you actually go to the approval for pembrolizumab and likely the approval that is

pending for nivolumab, both are, or will be, approved without a biomarker, and so the biomarker is more of a tool right now, and it clearly shows us that we need to do better.

With regard to clinical factors, none of them are perfect, and they're early data, but it does seem that, at least in some studies, HPV-positive patients may have somewhat more benefit. There clearly is activity and benefit in HPV-negative patients. And, in fact, in the KEYNOTE-012 study, the benefit between comparing HPV-negative and HPV-positive patients was actually very similar. However, in subsequent studies there was a trend towards more benefit in the HPV-positive patients, and, in general, we know that HPV-positive patients do better with a lot of modalities, so it's not that surprising that they also do better with immunotherapy.

Finally, it seems like some patients with larger tumors may have a lower chance of benefit, but that's very exploratory data.

There are ongoing efforts to identify better biomarkers. One of those that I'm involved in is the gamma interferon signature and inflammation signature, essentially mild tumor markers of tumor inflammation, and that looks quite promising in early theories. And again, I think we will need to validate those early data, but maybe that will be a better biomarker than PD-L1, or maybe it will be used in combination.

Dr. Caudle:
Deescalation approaches play a big role for HPV-positive head and neck cancer. Do you think immunotherapy may potentially help deescalation? And how do we best integrate immunotherapy in the curative intense setting?

Dr. Seiwert:
I think we know that we are seeing an "epidemic" of HPV-positive patients, the numbers are rising quickly, and these tumors are biologically different. And also, these patients are younger, in better shape, and we realize that our treatments are probably overtreating many patients. And we've seen a number of early studies, either ongoing or already completed, that are trying to give less treatment to minimize toxicity. And the ECOG 1308 study was maybe the first one to really provide evidence that this approach is feasible.

At the ASTRO 2016 meeting in Boston, we saw two approaches that were presented. One was actually from our institution, my colleague James Melotek, looking at giving a smaller disease radiation volume and trying to limit the toxicity to normal tissue, and then we saw another approach giving a lower dose from the group at UCLA giving a dose of 54 or 60 Gray, and both approaches, I think, are very promising with regard to lowering toxicity.

I think the second part of your question was: How about immunotherapy? And I think the honest answer is we don't know right now but, in principle, the idea that maybe immunotherapy can synergize with radiation might also allow us to decrease potentially the radiation dose. There's a study that is being run by my colleagues, Robert Ferris and Maura Gillison within the RTOG, the NRG, RTOG 3504, which integrates nivolumab, the PD-1 inhibitor, in the curative intense setting. At the same time, there are also other efforts. We have an institutional effort here trying to use immunotherapy to strengthen treatment on one hand but maybe lowering some of the doses from radiation or other side effects.

Dr. Caudle:
How might immunotherapy be used in combination or in sequence with chemotherapy or chemoradiation, even possibly surgical approaches, when treating head and neck cancer? And what options are currently being pursued in clinical trials?

Dr. Seiwert:
So, I think we don't know the answer to how best integrate immunotherapy with chemotherapy or radiation, chemoradiation and surgery. However, there are many, many studies ongoing, and I think very soon we'll probably get answers. The little that we do know is in other cancer types, it appears that PD-1 blockade seems to synergize with chemotherapy, and that seems to be consistently the case. I don't think we have published data yet, but multiple presentations using pembrolizumab, using nivolumab, using a PD-L1 agent -- atezolizumab in lung cancer -- and it seems like consistently there are higher response rates, and likely it seems at least with pembrolizumab we saw in lung cancer also an effect on progression-free survival. So, I think the early data are promising for that.

What I can point out is that one study, which is the KEYNOTE-048 study, that is currently ongoing, combines pembrolizumab in the first-line setting for head and neck cancer, combining it with chemotherapy and comparing it to standard of care EXTREME, so first-line usage, a new combination of chemotherapy plus pembrolizumab, versus EXTREME, which is a platinum, plus 5-FU, plus cetuximab, versus pembrolizumab alone, and that's a first-line study that's currently ongoing. So, I think there's high hope that soon we'll have data, and I think the early data looks promising.

What about radiation? There are studies ongoing. Again, I mentioned already one of the studies integrating nivolumab with chemoradiation run through the NRG and led by Maura Gillison and Robert Ferris. There's another study that is led by Stuart Wong and other people within the RTOG/NRG looking at SBRT, so hypofractionated, higher doses but fewer fractions, and that might by and large

be favorable, combined with pembrolizumab, and the idea is maybe that will actually boost up the effectiveness of immunotherapy.

There also may be approaches with surgery. There are adjuvant studies or new adjuvant studies, window of opportunity studies. I do believe that surgery seems like a very good modality because it's in principle not immunosuppressive and may synergize or may actually be sequential.

Dr. Caudle:
Now, what has been presented at ASTRO 2016 that you find most encouraging with regard to the use of immunotherapy, checkpoint inhibitors specifically, in head and neck cancers? And as an overlay of that, has data on expanding the types of cancers in which immunotherapy may be effective been presented at ASTRO?

Dr. Seiwert:
So, I think, ASTRO, the data on immunotherapy was relatively early. We saw some data from Duke University and Emory University combining immunotherapy with radiation for patients with melanoma and non-small cell lung cancer, and that looked promising. With head and neck cancers, the data was limited with immunotherapy and radiation. I think it was largely limited to presentation of ongoing studies. The other thing that I think is consistently shown is preclinical data that is true for head and neck cancer looking at synergy in preclinical models.

Dr. Caudle:
And lastly, is there anything that you would like to discuss concerning immunotherapy in head and neck cancer that we have not already addressed in this interview, or perhaps a topic you'd like to revisit?

Dr. Seiwert:
I do believe that PD-1 is just a first step. I think combinations with radiation, chemotherapy and surgery are promising. But also, keep in mind that new biomarkers might be helpful, and ultimately combinations. So I believe that combination approaches using maybe dual checkpoint blockade, PD-1 or PD-L1 plus CTLA-4, maybe PD-1 plus IDO, maybe other combinations are even more effective. I believe we are literally just scratching the surface of immunotherapy for head and neck cancer.

Dr. Caudle:
Great. Well, Dr. Seiwert, thank you for joining us today and sharing your insights on Breaking News on Head and Neck Studies from the American Society for Radiation Oncology's 58th Annual Meeting.

Dr. Seiwert:
Thank you so much for having me.

Dr. Caudle:
I'm Dr. Jennifer Caudle inviting our audience to access this and other CME Conference Coverage on ReachMD where you can be part of the knowledge, and thank you for listening.

Narrator:
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