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Innovations in the Treatment of Locally Advanced Squamous Cell Carcinoma of Head and Neck: Enhancing Antitumor Activity Through Inhibitor of Apoptosis Protein Antagonism

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Innovations in the Treatment of Locally Advanced Squamous Cell Carcinoma of Head and Neck: Enhancing Antitumor Activity Through Inhibitor of Apoptosis Protein Antagonism” is provided by Agile.

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Dr. Harrington:
This is CME on ReachMD, and I’m Dr. Kevin Harrington. Today I’m joined by Dr. Barbara Burtness and Dr. Ari Rosenberg, and we will be discussing locally advanced squamous cell carcinoma of the head and neck. We’ll look at the challenges, current treatment landscape, and some exciting new data for a novel approach to treatment using an inhibitor of apoptosis protein antagonists. Welcome.

Dr. Burtness:
Thank you, Dr. Harrington. Glad to be here.

Dr. Rosenberg:
Thank you. Good to be here with both of you.

Dr. Harrington:
So let’s get started. Dr. Burtness, first and foremost, what are the unmet needs associated with managing locally advanced squamous cell carcinoma? And what are some of the more interesting data from recent clinical trials?

Dr. Burtness:
Well, many patients who are treated with combined modality therapy for locally advanced head and neck squamous cell carcinoma are cured and for those patients, I think our highest need is for therapies that are less toxic. But it’s also the case that many patients, and particularly those with HPV-negative disease, are not cured. Although they have initial disease control, there’s disease recurrence, and many patients succumb to head and neck cancer. So I think the most pressing need is for advances that will increase the cure rate and that will do so in the difficult, treatment-resistant, HPV-negative population. I think we had been full of hope that the answer to that question would come from immunotherapy, and there have been some randomized trials that looked at immune checkpoint inhibition integrated with chemoradiation or with radiation in the locally advanced setting. Unfortunately, they haven’t provided the step forward that we anticipated. The first trial that was reported was the JAVELIN trial, and this looked at cisplatin radiation, either with the PD-L1 inhibitor avelumab or with placebo, and in that trial, not only did avelumab not improve outcome, there was actually a non-statistically but numerically apparent worsening in both progression-free survival and overall survival with the hazard ratio for progression of 1.21 for the avelumab arm.

A very similar, large, randomized phase 3 study was done with the PD-1 inhibitor, pembrolizumab, and so this is an agent that’s better validated in head and neck cancer. Standard of care in recurrent metastatic disease.

The addition of pembrolizumab to chemoradiation in the Keynote-412 trial improved 36-month event-free survival from 52% to 57%, which was not a statistically significant difference. The hazard ratio for event-free survival was 0.83, and the P value was not significant. And even in the patients who had a PD-L1 CPS 20 or higher where the hazard ratio for overall survival was 0.67, this difference was not statistically significant. There's also been a small trial from NRG, looking at the use of the PD-L1 inhibitor durvalumab in platinum-ineligible patients. So this randomized patients between radiation/cetuximab and radiation with durvalumab, and here again there was a slight numerical disadvantage for the use of durvalumab compared with cetuximab. If you looked at locoregional failure, this was 32% in the durvalumab arm compared with 15% in the cetuximab arm. So at this point we do not have any standard of care that incorporates immunotherapy, immune checkpoint inhibitors, into the standard management of locally advanced disease.

Dr. Harrington:
Dr. Rosenberg, perhaps you could have your perspective.

Dr. Rosenberg:
I completely agree with Dr. Burtness about some of the disappointment related to the challenges in translating the clear benefit that we see with anti-PD-1 inhibitors in the recurrent metastatic setting and bringing them into even the highest risk locoregionally advanced setting, in combination with chemoradiation.

Dr. Harrington:
Really, really excellent points, both. And I think for me, one of the big opportunities now is what could we do, what could we potentially add in that concomitant phase of chemoradiation that may be able to deliver a benefit? And that's something that we're going to discuss through the rest of this presentation.

Dr. Burtness:
Dr. Rosenberg, now that we have a clearer picture of the burden faced by our patients, what can you tell us about the apoptotic pathway as it relates to locally advanced squamous cell head and neck cancer?

Dr. Rosenberg:
I think for locoregionally advanced head and neck squamous cell carcinoma we've known for a number of decades that when we combined cytotoxic chemotherapy with radiation in the definitive setting for locoregionally advanced disease, that really through the radio-sensitizing properties of cytotoxic chemotherapy we can actually reduce the local failure rate, and that this is ultimately what drives the benefit in terms of a survival advantage with chemoradiation versus radiation alone, certainly. And so both chemotherapy and radiation really work through multiple different mechanisms of cell death to lead to those improved outcomes, but one of the important mechanisms is through programmed cell death, through apoptosis, through multiple downstream of factors. And not only that, but also inducing immunogenic cell death, a type of cell death that also drives, we hope, within the tumor microenvironment some specific antitumor immunity as well. We know that apoptosis induced by chemotherapy and radiation, there's 2 pathways in particular. The first one is called the intrinsic pathway. This is initiated through chemotherapy and radiation-induced disruption of the mitochondrial membrane that then leads to release of cytochrome c, the development of an apoptosome, and then through downstream caspase activation, ultimately leading to a cascade that drives apoptosis and cell death. And this intrinsic pathway, under normal cellular circumstances, is actually regulated by an inhibitor of apoptosis proteins which is an X-linked IAP. And so this inhibits the intrinsic pathway in particular.

The other pathway that's important to mention is the extrinsic pathway. This pathway can also be induced by initiators of apoptosis, including chemotherapy and radiation, and are driven by – or initiated by death ligands and death receptors which leads also to a downstream cascade of caspase activation, and ultimately leading to apoptosis. And this pathway, the extrinsic pathway, is actually regulated by cellular IAPs – so cellular IAP1, cellular IAP2 – of course IAP standing for inhibitor of apoptosis proteins. And so these negative inhibitors of both the intrinsic and extrinsic pathways of apoptosis, both the X-linked IAP and the cellular IAP can be inhibited by IAP inhibitors, which we have an endogenous form called SMAC, which stands for secondary mitochondrial-derived activator of caspases. We also have been developing therapeutic manipulation of this mechanism of action through a SMAC mimetic. So SMAC mimetics are able to inhibit both the X-linked IAP as well as the cellular IAP, which are the regulators of both the intrinsic and the extrinsic pathways. And one other important thing mechanistically to mention as, well, is that the cellular IAP1, cellular IAP2 also regulates immune modulation through NF-κB, both canonical and non-canonical downstream effectors. Non-canonical NF-κB signaling actually has an important immunomodulatory role, it seems, with activation of CD8-positive and CD4-positive T cell activation, ultimately leading to activation of tumor cytomacrophages and increased phagocytic destruction of tumor. And so we hypothesize that it may be that an additional mechanism, in addition to the impact on the apoptotic pathways, may have an important immunogenic role in terms of driving increased immunogenic cell death.

We also have an animation video that also demonstrates the mechanism of action of IAP inhibitors in the context of overcoming

resistance to apoptosis.

Announcer:
Anticancer cellular stress in the intrinsic apoptotic tumor pathway leads to the release of various proteins from mitochondria. These proteins form a regulatory apoptosome that activates caspase-9, leading to the activation of caspases-3, 7, and subsequent tumor apoptosis. The extrinsic apoptotic pathway also drives apoptosis, but this happens through the activation of caspase-8, then 3, 7, and subsequent tumor apoptosis. Both apoptotic pathways are downregulated by IAPs, or "inhibitor of apoptosis proteins." SMAC* is also released from mitochondria during cellular stress. This protein antagonizes IAPs and frees caspases from IAP downregulation. Exogenous small molecule SMAC mimetics are now being assessed in cancer therapy. Like endogenous SMAC, these agents antagonize IAPs, resulting in an increased apoptotic signal. SMAC mimetics may also support heightened inflammatory antitumor responses from immune cells in the tumor microenvironment. This occurs by activating noncanonical NF-KB** signaling, with release of IAP inhibition downstream of the TNF receptor.

Dr. Rosenberg:
So that video hopefully gives a sense about a mechanism of IAP inhibitors and why we're excited about the potential of this new target in terms of improving outcomes for locoregionally advanced head and neck squamous cell carcinoma with combined modality chemoradiation.

Dr. Harrington:
For those of you just tuning in, you're listening to CME on ReachMD. I'm Dr. Kevin Harrington, and here with me today are Drs. Barbara Burtness and Ari Rosenberg. Our focus is on the exciting data for IAP antagonists in improving survival outcomes in our patients with locally advanced squamous cell carcinomas of the head and neck.

Dr. Rosenberg:
Dr. Harrington, do you have any thoughts on that that you'd like to share?

Dr. Harrington:
Well, Ari, for me, I think one of the big areas of excitement is the fact that we now have a class of drugs where we can fine-tune the mechanism by which a cancer cell is killed, and in particular, we can try to modulate that death to ensure that it occurs in a fashion that is most visible to the immune system and can potentially trigger antitumor immunity that may attribute to locoregional control, but also in a durable sense, prevent systemic metastatic relapse.

Barbara, you have some other thoughts to share on this?

Dr. Burtness:
I think that we have been aware of overexpression of the IAP's mutation in caspase genes as being associated with a worse prognosis in head and neck cancer for a long time. So it makes good sense that they would be appropriate targets in this disease.

Dr. Rosenberg:
Yeah, and just building on that very critical point, I'm wondering, Dr. Harrington, can you explain why there's so much excitement over the role of IAP antagonists in treating patients with locoregionally advanced squamous cell carcinoma of the head and neck?

Dr. Harrington:
I think there is genuine excitement about these drugs. I guess I'll just reiterate the point: Not only can we kill more cancer cells by triggering apoptosis, but we can fine-tune that mechanism of death, potentially to act in the favor of the patient and generate curable remissions and potentially anti-cancer immunity. So just like to rehearse with the audience some of the data that has led to this excitement within the community, and of course, this comes in the first instance from the randomized, phase 2 study of the SMAC mimetic Xevinapant, or previously called Debio 1143.

This was a study led by Jean Bourhis and his colleagues. Initially, with the Part A, which was essentially a safety run-in, combining the drug alongside chemoradiation, looking for tolerability of the agent, and subsequently the drug going into a randomized clinical trial in which patients were treated with either Xevinapant or placebo during a course of radical chemoradiation. So in the part A of this study, which was essentially a dose-finding phase 1, patients were treated with single-agent Xevinapant, leading to the recommendation of a recommended phase 2 dose of 200 mg every day.

Now this was a phase 2 study, so only 96 patients in the intention-to-treat population. Standard of care chemoradiation – 70 Gy of radiation with IMRT [intensity-modulated radiation therapy]. So-called "high-dose cisplatin," so 100 mg/m2 every 3 weeks for 3 cycles. Xevinapant was given for 14 days out of every 21 days, for 3 cycles. And the primary endpoint of this study was a novel endpoint, which was the locoregional control measured at 18 months. Now, in this study what the investigators demonstrated was at this primary

endpoint they showed an uplift of more than 20%. In fact 54% versus 33%, roughly, in terms of the 18-month improvement in locoregional control. So the study met its primary endpoint. Subsequent analyses have shown at the 3-year follow-up we have seen durable locoregional control. So rates of locoregional control of 22% improvement – 78% versus 56% – so again, impressive data. And then, more recently, at the ESMO meeting that has taken place just in the last few months, we have seen the 5-year data, and in particular I'd like to draw the audience's attention to the 5-year overall survival data from this phase 2 study, with a near-doubling of survival at 5 years, for overall survival – so 53% versus 28%. And it is these data, really, that has led to the level of excitement within the community. Subsequent to that, of course this agent has progressed into further randomized evaluation in the phase 3 clinical trial, the TrilynX study. This is a large, randomized, phase 3 study. The design broadly similar to the phase 2 study, but again, the importance here is that there is an increased duration of exposure to the Xevinapant drug, so in addition to the concomitant phase, there are 3 cycles of adjuvant Xevinapant, or placebo, given in that study, and that comes from the observation that some of the responders in the phase 2 study, the response was generated as a late event, and we think that maybe the drug continues to act after the completion of chemoradiation.

In addition, there is another study – a phase 3 study called the XRAY VISION study, in patients with resected head and neck cancer who are not eligible for platin, looking at the addition of Xevinapant to radiation versus no additional drug. And of course, in addition to survival and locoregional control endpoints, we will be capturing quality of life data to see whether or not either the omission of a platin-based therapy or the addition of Xevinapant to a platin-based therapy is associated with improved control and, as such, improved quality of life. I would hope that we'll begin to see these data emerging from these studies in the course of the next 2 to 3 years and that we will begin to then have an understanding of whether or not these drugs are going to change practice.

And again, Barbara, just going to turn to you and see. Any additional comments that you'd like to make about this subject?

Dr. Burtness:
I think seeing the 5-year overall survival data matching the locoregional control and PFS data is very striking. The thing I wanted to highlight for the audience is that the phase 2 trial was done in a predominantly HPV-negative population with very high median number of pack-years of tobacco exposure. The phase 3 study is going to be done entirely in the HPV-negative population, so this will be a very clear test of restoring apoptosis as a mechanism of radiation-induced cell death.

Ari, do you have anything to add?

Dr. Rosenberg:
I completely agree. I share both of your enthusiasm about the potential, and I look forward to seeing the TrilynX results in particular. And the other thing that strikes me about the phase 2 results is that the survival benefits that we've made thus far in locoregionally advanced multi-modality therapy has really been driven by that improvement in locoregional control. And so I am encouraged by the fact that while it is only a randomized phase 2, as an important caveat, that the improvement in locoregional control seems to also be what drives what we hope will turn out to be a survival advantage in the upcoming trial.

Dr. Harrington:
Well, I thank you both. I think we've found now that simply adding immunotherapy to chemoradiation is not the solution, neither, in fact, in HPV-negative nor in HPV-positive disease, and I think we need to look at the options of novel classes of drugs. And therefore, this option with SMAC mimetics really gives us a new perspective on how to treat this disease.

But unfortunately, with that, that's all the time that we have today. So, I want to thank our audience for listening and in particular, of course, I want to thank you, Dr. Barbara Burtness and Dr. Ari Rosenberg, for joining me and for sharing all of your valuable insights and wisdom. It was great speaking with both of you today.

Dr. Burtness:
Likewise. Thank you very much, and good-bye.

Dr. Rosenberg:
Thanks very much. It was a pleasure. Talk soon.

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