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# Recent Advances and Emerging Approaches in the Treatment of Recurrent/Metastatic SCCHN: Matching the Patient to the Optimal Therapy

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Welcome to CME on ReachMD. This activity, entitled “Recent Advances and Emerging Approaches in the Treatment of Recurrent/Metastatic SCCHN: Matching the Patient to the Optimal Therapy” is provided by Agile.

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**Dr. Cohen:**
This is CME on ReachMD, and I'm Dr. Ezra Cohen. Today, Dr. Petr Szturz and I will be discussing recent advances in the management of recurrent or metastatic squamous cell carcinoma of the head and neck, or SCCHN.

Dr. Szturz, welcome to the show.

**Dr. Szturz:**
Thank you, Dr. Cohen. I'm glad to be here.

**Dr. Cohen:**
Petr, let's begin by focusing on how to select the best first-line treatment strategy for patients with recurrent or metastatic SCCHN. Key trials, starting with the inclusion of cetuximab in the EXTREME trial, have informed our selection strategies since 2008. Can you elaborate on the key findings from those trials?

**Dr. Szturz:**
Sure. So there are 3 randomized trials impacting on our decision-making in the first-line setting. They include EXTREME, KEYNOTE-048, and TPExtreme, published in 2008, 2019, and 2021, respectively.

Let's start with the EXTREME regimen consisting of platinum, 5-fluorouracil, and cetuximab. It became the first treatment schedule to improve overall survival, progression-free survival, response rate, and symptom control in comparison with a control arm containing platinum and fluorouracil only. Importantly, this benefit came without compromising quality of life. However, the outcomes were still unsatisfactory, with less than 5% of patients being alive at 5 years. Moreover, severe acute adverse events occurred in the majority of patients, and no predictive biomarker could be identified. But it took more than 10 years to change the paradigm.

The KEYNOTE-048 trial showed that adding the immune checkpoint inhibitor pembrolizumab to platinum fluorouracil doublet or giving it as monotherapy significantly improved overall survival and response duration in comparison with EXTREME. Another breakthrough finding from KEYNOTE-048 was validation of PD-L1 expression as a predictive biomarker. It is measured as CPS, combined positive score, and higher values help us identify patients deriving benefit from immunotherapy, while a low value indicate the necessity of using schedules with chemotherapy or even chemotherapy alone as is in the case of PD-L1-negative cases.

The third trial, TPExtreme, explored the substitution of a fluorouracil for docetaxel in the EXTREME regimen. Four cycles of the


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experimental TPEx regimen were slightly better tolerated than six cycles of EXTREME. The improvement of median overall survival was not statistically significant. Nevertheless, TPEx can be considered an alternative to EXTREME in selected patients.

**Dr. Cohen:**
Petr, I would completely agree with you with respect to the impact that KEYNOTE-048 has had on our treatment paradigms. Moreover, what's really impressive is the duration of response in those patients who have a response secondary to pembrolizumab. The median duration of response was almost 2 years with almost 1 in 5 patients being alive 5 years in now the updated analysis.

**Dr. Szturz:**
And with these trials as background, what are the disease and patient-related factors that we need to consider as part of our treatment decision for the first-line setting?

**Dr. Cohen:**
Well, you alluded to what I think is one of the more important ones, and that is PD-L1 status or PD-L1 expression in a tumor.

Moreover, I think the aggressiveness of the tumor and the entire tumor burden do influence our choice of therapy. We do understand that the addition of chemotherapy to pembrolizumab does deliver a higher objective response rate, in fact, almost a doubling of the response rate.

The sites of disease is also an important factor and that plays into symptoms and tumor burden. But in addition to that, we are also mindful of patient choices and the patient's overall health status.

And the last thing to consider, of course, is the prior therapies. For instance, in a patient who has just recurred after receiving cisplatin in the curative-intent setting, I would likely be reluctant to rechallenge with cisplatin, especially if the curative-intent therapy ended just a few months prior.

**Dr. Szturz:**
Yeah, I agree. And I think that one of the key issues here is also to elaborate on how to make these factors work together because, as you mentioned, Ezra, they should all be included in our decision-making, but some of them have to be prioritized while others brought to the background.

**Dr. Cohen:**
Absolutely.

Well, let's tie this together into a potential algorithm for selecting a first-line approach for patients with recurrent and/or metastatic head and neck cancer. Petr, what would that look like?

**Dr. Szturz:**
Well, this is a complex issue, as algorithms can provide us with some guidance, but the actual decision has to be tailored to individual patient needs. Moreover, there are differences between recommendations of different societies or working groups, and also between local drug policies.

Patients' health status and platinum eligibility are probably our first considerations. In those with contraindications to cisplatin, we can still consider carboplatin. But if the patient presents with a recurrence within 6 months after previous platinum administered in the curative setting, then this treatment should be abandoned, and we typically opt for single-agent immunotherapy.

Patients with poor performance status were not included in the 3 large randomized trials, so the level of evidence to support our decision is lower. They are usually offered less intensive treatment with fewer agents, palliative radiotherapy or surgery, or supportive care alone.

It is also of note that advanced chronological age is not a contraindication for a full-dose standard of care treatment, which can therefore be administered in elderly patients who are deemed fit according to a geriatric assessment. But in the following steps, some guidelines differ.

According to KEYNOTE-048, PD-L1 expression should guide us either towards chemotherapy alone in CPS-negative cases or to immunochemotherapy in the remaining cases with CPS of 20 being often regarded as the lowest value to allow single-agent pembrolizumab as well.

And last but not the least, we should take into account the need to induce tumor shrinkage and also potential differences in approaching a local regional recurrence only versus distant metastases. We know that in comparison with chemotherapy, immunotherapy is associated with lower response rates, but may be more active in cases with a distant metastasis.

**Dr. Cohen:**


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I think that the biggest area of controversy is likely in the CPS 1 to 19 group where single-agent pembrolizumab does provide a lower response rate but probably equal overall survival, at least in the subgroup analysis, when compared to the EXTREME regimen, and meanwhile, is going to be fairly well tolerated with a very low, long duration of response. And so I think for that CPS low- to moderate-expression tumor in the patient in front of you there is some controversy with respect to whether to use single-agent pembrolizumab versus chemotherapy and pembrolizumab.

**Dr. Szturz:**
Thank you, Ezra.

**Dr. Cohen:**
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Ezra Cohen, and here with me today is Dr. Petr Szturz. Our focus is on achieving a better clinical understanding of the management of patients with recurrent or metastatic squamous cell carcinoma of the head and neck.

**Dr. Szturz:**
So now that we've discussed first-line treatment for recurrent and/or metastatic squamous cell carcinoma of the head and neck, let's focus on previously treated patients. What issues do they bring to the table? Let's break this down first for patients who have failed a first-line immunotherapy treatment.

**Dr. Cohen:**
I think the first thing that we have to understand and realize is that now many patients whose tumor has progressed on first-line therapy are good candidates for second-line therapy.

And then the other thing to consider is that there really is not a well-defined standard of care for patients who have become refractory to first-line therapy, especially for those patients who've received prior anti-PD-1 therapy.

But let's go over what the options are and what some of the considerations will be. Many of them are the same as we talked about already in the first line, that is the performance status, the comorbidities, patient preference, the tumor burden. However, because the tumor had just progressed on anti-PD-1 therapy, further anti-PD-1 therapy is usually not part of the consideration. And what one looks at is a different type of therapy, and that usually will include some sort of cytotoxic chemotherapy, allowing for patient performance status.

What I like to use in these patients is often a taxane because I usually have not used a taxane in first-line treatment. Cetuximab comes into play, other agents like methotrexate or even other cytotoxic drugs like capecitabine, if 5-FU hasn't been used in the first line, or gemcitabine. And then of course, there's opportunities to combine them. One of my most preferred combinations is a taxane and cetuximab with what I think is reasonable, single-arm phase 2 data from a few different trials demonstrating not only fairly well-tolerated regimens, but also fairly effective, at least with respect to response rate.

**Dr. Szturz:**
Yes, I fully agree and indeed second-line treatment after immunotherapy is a relevant question. And almost half or maybe even more will receive subsequent anti-cancer therapy. And I also prefer taxane with cetuximab. But we know that some patients, and these are indeed rare cases, they can be successfully rechallenged with immunotherapy.

**Dr. Cohen:**
Absolutely, and let's go to the other side of the coin and look at how we might approach a patient with recurrent and/or metastatic head and neck cancer who has received a cisplatin regimen in the first line, but not anti-PD-1.

**Dr. Szturz:**
So after platinum failure in the recurrent and/or metastatic setting, the standard of care is to give an immune checkpoint inhibitor, either nivolumab, according to the CheckMate 141 trial published in 2016, or pembrolizumab according to Keynote-040 published in 2019. And in these trials, they were tested against single-agent methotrexate, docetaxel, or cetuximab. Nivolumab was administered in patients presenting with tumor progression within 6 months after the last dose of platinum. It significantly improved median overall survival and response rate while maintaining patients' quality of life and causing less toxicity and even yielding long-term survivors. On the other hand, this benefit was not reflected in progression-free survival, and a minority of patients had to deal with autoimmune side effects. The inclusion criteria in the pembrolizumab trial were more liberal because patients could have progressed at any time point during or after platinum-containing treatment for recurrent and/or metastatic disease. This trial, KEYNOTE-040, confirmed the results seen with nivolumab and also introduced a new predictive biomarker, albeit originating from an exploratory analysis. It was high PD-L1 expression corresponding to tumor proportion score, TPS, of at least 50% which was associated with improved outcomes.

**Dr. Cohen:**


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I completely agree. Now I do still look at PD-L1 expression in those second-line patients. I tend to only use nivolumab or pembrolizumab in patients whose tumors do express PD-L1 and look for something else in those tumors that don't express PD-L1.

Thank you for that excellent discussion. And that wraps up our second topic today. This has been a great discussion. To finish up, is there anything you think we've missed that our listeners need to know, or perhaps you have one key take-home message to share?

**Dr. Szturz:**
I think we'll surely agree that immunotherapy has changed the therapeutic landscape of recurrent and/or metastatic head and neck cancer and has been approved for both first- and second-line settings. It has also introduced PD-L1 expression as a new and long-awaited predictive biomarker. However, it has also shown that there is still work to be done in terms of refining our prediction tools, optimizing treatment sequencing, but also further decreasing toxicity.

**Dr. Cohen:**
I think you just provided an excellent summary of the entire discussion. And I think we touched upon, very nicely, the need for a standard of care in patients who are refractory or whose tumors are refractory to anti-PD-1. We certainly would like to see further improvement in efficacy in first-line recurrent metastatic patients. And we do need methods to further stratify patients and better select which patients go on which therapies. And so with that in mind, I'll thank you Petr, for an excellent discussion.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank you again, Petr, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

**Dr. Szturz:**
Thank you very much, Ezra, and have a great day.

**Announcer:**
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