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Retifanlimab Across POD1UM-303 Subgroups in Squamous Cell Carcinoma of the Anal Canal

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Incyte. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me today to review data from subgroup analyses of the POD1UM-303 trial, which focused on the impact of retifanlimab in patients with squamous cell carcinoma of the anal canal, is lead author Dr. Marwan Fakih. Not only is he a Professor in the Department of Medical Oncology and Therapeutics Research, but he's also the Judy and Bernard Briskin Distinguished Director of Clinical Research at City of Hope Comprehensive Cancer Center. Dr. Fakih, welcome to the program.

Dr. Fakih:
Thank you, Charles. Thank you for having me. Happy to be here.

Dr. Turck:
Well, why don't we start with some background, Dr. Fakih. The phase 3 POD1UM-303/INTERAACT2 study demonstrated a statistically significant and clinically meaningful improvement in progression-free survival with retifanlimab plus carboplatin-paclitaxel versus chemotherapy alone. In a less common disease like advanced squamous cell carcinoma of the anal canal where phase 3 data have historically been limited, how do you see these findings shaping clinical practice?

Dr. Fakih:
Squamous cell cancer of anal canal is a rare disease, and the majority of cases present with localized disease or regional disease. The percentage of patients who have metastatic disease at presentation or who relapse is still a small fraction of that overall number of patients and represents probably somewhere around 25 to 30 percent of the population eventually.

So far, there had been no randomized phase 3 clinical trials to really guide us as to what is the best path for the treatment of advanced squamous cell cancer of the anal canal. We have historically used data from phase 2 trials, whether it's single arm or randomized. The standard of care had been carboplatin and paclitaxel until the POD1UM-303 trial reported recently. And that study showed that adding retifanlimab, a PD-1 inhibitor, to carboplatin and paclitaxel substantially improves the progression-free survival of the patient population receiving this treatment. Indeed, the hazard ratio is 0.63. So we know that adding retifanlimab, a PD-1 inhibitor, to carboplatin paclitaxel in the first-line treatment of metastatic, recurrent after chemoradiation, and unresectable squamous cell cancer of the anal canal improves the PFS by approximately 37 percent. That's a 37 percent delay in time to progression.

This is highly meaningful, and what makes it even more meaningful is that in metastatic squamous cell cancer of the anal canal, when we use carboplatin and paclitaxel, we typically cap the treatment, and indeed in this study, the treatment was capped at six months. And so to have a median progression-free survival of 9.3 months and a substantial number of the patient population still without progression at the two-year mark is really remarkable and I think sets a new standard of care in the management of squamous cell cancer of the anal canal that is metastatic or recurrent.

Dr. Turck:
And with that in mind, let's turn our attention to the subgroup analyses. Across all the predefined subgroups, including PD-L1 expression, region of enrollment, liver metastases, extent of disease, and HPV and HIV status, the progression-free survival benefit was consistent. Were you surprised by that consistency, and what does it suggest about this regimen's potential applicability to real-world practice?

Dr. Fakih:
I wouldn't say I was surprised, but I had my eyes on PD-L1 expression in this patient population. Earlier studies with anti-PD-1, such as pembrolizumab and other agents, had suggested a difference in the outcome in patients who are PD-L1 positive and PD-L1 negative. For example, pembrolizumab monotherapy after progression on first-line treatment for advanced squamous cell cancer of the anal canal had a substantial difference in response rate with approximately 2 to 3 percent of the PD-L1 negative patient population only having objective response. Hence, the expectation was that patients with PD-L1 expression of less than 1 percent—meaning zero —would not be deriving a benefit from adding PD-1-targeted agents. And in POD1UM-303, we see no difference in hazard ratios between the PD-L1 negative and the PD-L1 positive. Now, I want to say, however, that there was a small number of patients with PD-L1 expression of zero in this study—only 28 patients. So it's really not enough to answer this question, but it's really comforting to see the same benefit or the same trend in benefits across the subgroups.

As far as the rest of the variables, it's also the same story, particularly for liver metastases. We've always worried that patients with liver metastatic disease have an unfavorable tumor microenvironment, and there are some studies across different tumor types, such as melanoma, non-small cell lung cancer, and colorectal cancer, with MSS population where liver metastases have been associated with a relatively lower benefit from PD-1-targeted agents. And in POD1UM-303, the hazard ratio for patients with liver metastatic disease was 0.48 in favor of adding retifanlimab, and in patients without liver metastasis, it was 0.75. So clearly no hint here that patients with liver metastatic disease do not benefit.

As far as HIV goes, it's really hard to comment here because it was only 11 patients, and so I think it's hard to answer that question based on 11 patients in a large phase 3 trial.

But all in all, the trends have been very consistent here across the overall population, and at this point, I have to say that based on the data, retifanlimab is indicated across the board in the first-line treatment of metastatic squamous cell cancer of the anal canal, unless there is a contraindication for immunotherapy such as patients with autoimmune diseases.

Dr. Turck:
Now I'd like to look more closely at the PD-L1 expression subgroup with the retifanlimab plus chemotherapy arm. Median progression-free survival differed numerically by PD-L1 category, yet the hazard ratios favored retifanlimab over chemotherapy alone regardless of PD-L1 status. So how should clinicians think about PD-L1 testing in this setting, and are we moving toward a more biomarker agnostic approach?

Dr. Fakih:
I think the data speaks for itself, and at this point, if we are to apply the POD1UM-303 data, PD-L1 should not be a decision maker. Now, saying that, my opinion is that we really need more information, and we need to collect more data to guide us in the future. We cannot set standards of care based on 28 patients, and this is a small subgroup of patients. And given the fact that the trends are consistent, I think I would not really prohibit therapy with PD-1 therapy to a patient who is PD-L1 negative.

However, in answer to your question, I think we need more information in the first-line setting. I think in a refractory setting, it does appear to be a predictive biomarker, not a perfect predictive biomarker. Even PD-L1 negative patients can respond to PD-1 monotherapy in squamous cell cancer of anal canal. But in the first-line setting at this point, we cannot say that it has a predictive value, so more data is needed in this particular setting.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Marwan Fakih about research on the impact of retifanlimab in patients with advanced squamous cell carcinoma of the anal canal.

Now that we've discussed the frontline data and subgroup findings from POD1UM-303, let's review what happened in the crossover phase. In that part of the study, 45 percent of patients in the placebo plus chemotherapy arm crossed over to receive open-label retifanlimab after confirmed progression. With the caveat that these analyses are exploratory in nature, overall survival was numerically longer in patients who received retifanlimab upfront. So, Dr. Fakih, what do these exploratory findings suggest about the impact of delaying immunotherapy until after progression?

Dr. Fakih:
Thank you, Charles, for the question. First, let's discuss the overall survival with carboplatin-paclitaxel and retifanlimab in the study. The primary endpoint was progression-free survival, and as I mentioned earlier, the study met the primary endpoint. Now, anytime you have a crossover design, crossover can affect your overall survival because you're getting the active agent in the subsequent line of therapy. Hence, it's appropriate for this study to focus on the PFS as a primary endpoint. However, the overall survival was also one of the endpoints of the study, and the median overall survival in an updated analysis recently for the carboplatin paclitaxel group was 32.8

months versus 22.2 months for carboplatin paclitaxel plus placebo. Now, this is a 10 month-difference in overall survival in patients who received retifanlimab; that is very clinically meaningful, even if it did not meet a statistically significant secondary endpoint result.

So I want to stress that the PFS difference here did translate in overall survival, and I think this is really remarkable because it really highlights the durable benefit that we see in the population that received retifanlimab in the first-line setting. And I think the credit here goes to a very long duration of response that we see with carboplatin-paclitaxel and retifanlimab—14 months versus 7 months with carboplatin-paclitaxel and placebo.

We looked at the impact of crossover, so we looked at the population that received carboplatin-paclitaxel and retifanlimab first line and then another group of patients that received carboplatin-paclitaxel and placebo but then did not receive the crossover, meaning they progressed but did not receive further retifanlimab. And then the group that received carboplatin-paclitaxel and placebo and then received retifanlimab was roughly about 50 percent of the patients who enrolled in the control arm. And when we look at the population that received retifanlimab monotherapy after carboplatin-paclitaxel and placebo, their overall survival wasn't really as good as the population that received retifanlimab as the first-line therapy. Actually, it was almost as good as carboplatin-paclitaxel and placebo without further retifanlimab.

This really suggests to me a synergistic potential for PD-1 therapy in the first-line setting that cannot be made up for with subsequent salvage with PD-1. In other words, carboplatin-paclitaxel followed by retifanlimab does not appear to be as good as carboplatin-paclitaxel plus retifanlimab. This is very important. It tells us that we have a window where the incorporation of PD-1 targeting with retifanlimab results in the best outcome for our patients. And that window is in the first-line treatment, and that window is with the initiation of PD-1 targeting with retifanlimab and with carboplatin-paclitaxel in the first-line setting. So this data is important, and I think it really highlights the need of incorporating retifanlimab early on in the management of our patients with advanced squamous cell cancer of the anal canal.

Dr. Turck:
Now we're almost out of time for today, so I have one final question for you before we close, Dr. Fakih. Putting it all together and considering the primary results of the trial, subgroup consistency, and exploratory crossover findings, how are you thinking about treatment sequencing in your own practice today? And what factors should clinicians weigh when making first-line decisions?

Dr. Fakih:
There's no question that we have a new standard of care in the management of squamous cell cancer of the anal canal. That's why NCCN guidelines now have carboplatin-paclitaxel plus retifanlimab as a level one evidence recommendation for the management of squamous cell cancer of the anal canal with metastasis. That is what I use for my patients; that is the standard of care. And unless there's a contraindication for immunotherapy in those patients, I think there is really no space anymore for systemic chemotherapy alone in the first-line treatment of anal cancer that is metastatic or recurrent.

Dr. Turck:
Well, as those comments bring us to the end of today's program, I want to thank my guest, Dr. Marwan Fakih, for joining me to review the data from the POD1UM-303 subgroup analyses. Dr. Fakih, it was great having you on the program.

Dr. Fakih:
Charles, thank you for having me.

Announcer:
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