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Studying Carboplatin-Paclitaxel + Retifanlimab for 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. Here with me today to review a Phase 3 study of retifanlimab in combination with carboplatin/paclitaxel in patients with inoperable, locally recurrent, or metastatic squamous cell anal carcinoma is Dr. Richard Kim. He's a Service Chief of Medical Gastrointestinal Oncology and a senior member in the Gastrointestinal Oncology Department at Moffitt Cancer Center. He's also a Professor of Oncology at the University of South Florida, College of Medicine. Dr. Kim, welcome to the program.

**Dr. Kim:**
Thank you for having me.

**Dr. Turck:**
Well, if we start with some background, Dr. Kim, would you walk us through the therapeutic landscape for advanced squamous cell anal carcinoma and why there's such a need to explore new treatment strategies?

**Dr. Kim:**
Sure. We know that anal cancer is mostly a subtype of anal cancer is squamous, and that is usually driven by the HPV. And in the past decade or so, there has been a steady rise in incidents, particularly among HIV-positive patients and in the men-who-have-sex-with-men population as well. And I know that despite this, treatment options have lagged behind compared to other HPV-associated cancers, such as head and neck. In the past for at least advanced disease, the treatment that we typically used was the backbone of cisplatin/5-FU. But more recently, based on some of the randomized Phase 2 data, we found that carboplatin/paclitaxel is as good as cisplatin/5-FU in the first-line setting and much better tolerated. Since then, carboplatin/paclitaxel has become the standard of care in the treatment of advanced anal cancer.

However, most recently, the breakthrough came with the use of immune checkpoint inhibitors, particularly PD-1 inhibitors such as nivolumab, pembrolizumab, and, more recently, retifanlimab, which is the new PD-1 inhibitor on board. So we know that at least in the refractory setting, those single agents had a modest response rate of 15 to 20 percent, with some of them showing very durable response.

So I think this hinted at an opportunity to build upon immunotherapy in combination with chemotherapy in the frontline setting. And I think this is an area where some breakthrough trials were presented last year at ESMO.

**Dr. Turck:**
Now, if we zero in on the POD1UM-303 trial, I was wondering if you could tell us a little bit more about the rationale for evaluating retifanlimab with carboplatin/paclitaxel and what the methods were that the investigators used?

**Dr. Kim:**
Sure. I think the rationale for using checkpoint inhibitors, such as retifanlimab, in anal cancer is very strong because we know that squamous cell anal cancer is driven by HPV, a virus that induces immune invasion via T cell exhaustion. And we know that PD-1 blockade could potentially restore immune surveillance.

We also know that as I mentioned, single agents have some activity in the refractory setting. So the question that we asked in POD1UM-303 is, can we improve the first-line outcome in advanced cancer by combining immunotherapy with chemotherapy? That is now the question.

So the trial was a randomized Phase 3 study looking at patients with unresectable, locally recurrent, or metastatic squamous cell anal cancer. And these patients were basically randomized to carboplatin/paclitaxel plus retifanlimab or placebo. And this was a trial that included a diverse population, including HIV patients. And after 6 months of chemotherapy, the patients would continue on with retifanlimab or placebo for up to 12 months. The primary endpoint of the study was PFS, and they looked at overall survival and response rate as secondary endpoints. Also, it's interesting to note that in this study, the crossover was allowed.

**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. Richard Kim about new findings on retifanlimab with carboplatin/paclitaxel in patients with previously untreated, locally recurrent, or metastatic squamous cell anal carcinoma.

So let's dive into the efficacy results, Dr. Kim. What can you tell us about the progression-free survival and overall response rates for retifanlimab and carboplatin/paclitaxel in patients with this disease?

**Dr. Kim:**
Yeah. So the POD1UM study demonstrated that by adding retifanlimab to carboplatin and paclitaxel, there was an improvement in PFS—improvement from 7.4 months for chemo alone to 9.3 months for the combination of retifanlimab plus chemotherapy, with a hazard ratio of 0.64. Beyond PFS, the objective response rate was much higher as well; it improved from 44 percent to 56 percent, including complete response rate that doubled. This indicates a deeper tumor shrinkage compared to chemotherapy alone.

Furthermore, I think that the disease control rate was also improved, and the response rates were noted to be more durable in the arm of immunotherapy. And so taken together, this suggests that the addition of retifanlimab not only delays progression, but it delivers more profound and lasting response.

Having said that, OS data was premature. Even though there was a separation of curve favoring the arm of chemoimmunotherapy, the P value was not significant. But with longer follow-up, it may change. Not only that, but as I mentioned before, in this trial, they did allow crossover, which may muddy up the water a little bit.

**Dr. Turck:**
Now, as you suggested, we're still collecting overall survival data. So what are the next steps for confirming long-term benefits?

**Dr. Kim:**
Yeah. So at the interim analysis, the median overall survival was about 29 months in the arm of retifanlimab versus about 23 months in the chemotherapy arm, with a hazard ratio of 0.70. Even though the P value didn't meet the predefined threshold, it showed a strong signal, showing that there is a benefit of adding immunotherapy. And obviously, more mature data will answer that question.

But more importantly, because the patients in the placebo arm were allowed to crossover to immunotherapy upon progression, there's a possibility that the survival difference would've been even greater if the crossover was not allowed. And furthermore, the exploratory analysis adjusting the crossover suggests that the true OS benefit could be more pronounced.

So we're hoping that with long-term follow-up, we will see OS data that is significant. But even without the OS being significant at this time, I do believe that, based on the PFS data and the response rate, this combination of chemoimmunotherapy will become standard of care.

**Dr. Turck:**
Now, are there any safety concerns we should know about?

**Dr. Kim:**
Yeah. Overall, adding a checkpoint inhibitor—retifanlimab—to chemotherapy was very well tolerated with no new safety signals. I think the adverse events were consistent with the known profile that's out there with chemotherapy and PD-1.

While Grade 3 adverse events were maybe a little bit higher, as expected because you're adding immunotherapy, the most notable immune-related adverse event seen was hypothyroidism, which we know how to manage, in about 14 percent of the patients. But the discontinuation rate was very low in both arms. Also, this trial included patients with HIV, and those patients did very well as well. So I think based on the safety data, I see no concern.

**Dr. Turck:**

Now, as we approach the end of our program, Dr. Kim, do you have any final thoughts you'd like to share on how combining retifanlimab with chemotherapy could impact the future of squamous cell anal carcinoma care?

**Dr. Kim:**
Based on the study, the combination of retifanlimab plus chemotherapy showed improvement in PFS, a higher response rate, and durable responses as well. We have to wait for a longer follow-up to see if the OS trends hold up, but because the trial allowed crossover, I think you have to take that into consideration. And beyond the numbers that I shared, I do think that this trial is important because it did, once again, involve patients who are HIV. I think that is very important. And I think that by using this combination, I think we're delivering a better quality response, opening doors for possible future combinations, and reshaping the expectation of a cancer that desperately needs progress.

**Dr. Turck:**
Well, those final insights in mind, I want to thank my guest, Dr. Richard Kim, for joining me to review the efficacy and safety of retifanlimab and carboplatin/paclitaxel in patients with inoperable, locally recurrent, or metastatic squamous cell anal carcinoma. Dr. Kim, it was great having him on the program.

**Dr. Kim:**
Thank you very much for having me. Appreciate it.

**Announcer:**
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