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### ReachMD

www.reachmd.com

info@reachmd.com

(866) 423-7849

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## The Importance of PD-L1 Testing: Shaping the Future of Treatment in ESCC

### Announcer:

Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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### Dr. Yoon:

This is CME on ReachMD, and I'm Dr. Yoon. I'm going to review the importance of PD-L1 testing in esophageal squamous cell carcinoma and its impact on treatment decisions.

First, it's important to try to have sufficient tissue to perform biomarker testing. For oncologists, this is usually not something we have a great deal of control over, but I think most of the time, there is sufficient tissue for PD-L1 testing, usually from the EGD biopsy that made the diagnosis. There are a few cases where the existing tissue is inadequate, and in those situations, I consider targeting a metastatic lesion or even repeat EGD. And in the biopsy order, I typically request six to eight forceps biopsies for EGD and four to six core biopsies of a parenchymal target lesion.

The second question is, which biomarker should be tested? The most important one in esophageal squamous cancer is PD-L1 by IHC. Now, I also order MMR mismatch repair.

But if tissue is scant, MMR is less important than PD-L1, because the incidence of deficient MMR in true esophageal squamous cancer is extremely low.

Now, testing for PD-L1 is particularly relevant now, given the recent FDA ODAC recommendation in September to withdraw the existing FDA approval in the frontline setting for patients with esophageal squamous cancer who have a PD-L1 CPS less than 1. So if the FDA accepts this ODAC recommendation, the FDA approval for IO in the first-line setting is expected to include only squamous patients with a PD-L1 CPS 1 or higher.

So the FDA recommendation was based on their own analysis of the three first-line global trials of esophageal squamous cancer. There was CheckMate-648 for nivolumab, KEYNOTE-590 for pembrolizumab, and RATIONALE-306 for tislelizumab. Now, in all these studies, patients were enrolled regardless of PD-L1 status, and they were randomized to receive IO plus chemo versus chemo alone. And because each study improved overall survival in the overall PD-L1 agnostic population, the FDA initially approved IO regardless of PD-L1 status.

But as time went on and as the initial results were analyzed further, it was getting clear that the efficacy of IO was greater in patients who had PD-L1 expression. And the pattern wasn't just noise or a byproduct of subgroup analysis, but it appeared to be real, particularly for adenocarcinomas, as we showed in a paper that Dr. Ajani and I published in *Journal of Oncology* a few years ago.

So to help really clarify which PD-L1 cutoff benefits from IO, the FDA performed their own meta-analysis using individual patient data of about 1,800 patients from those three global trials. And according to the FDA's meta-analysis, there was no meaningful benefit from immunotherapy in the PD-L1 less than 1 subgroup. That subgroup had a hazard ratio for overall survival of 1.1 and the median overall

survival was actually 1 month shorter in the IO plus chemo group compared with the chemo alone group.

And by contrast, in the PD-L1 1 or higher group, the hazard ratio for OS was very favorable at 0.68, and there was a 4.5-month benefit in overall survival. Now, although the greatest benefit was in the PD-L1 10 or higher subgroup, there was also meaningful benefit in the PD-L1 1 to 4, and PD-L1 5 through 9.

Now, usually when I see a patient in clinic for the first time and we have to make a treatment decision, the PD-L1 results are not available. And so before the FDA's recent disclosure of all the meta-analysis results, I tended to give anti-PD-1 in all squamous patients, different from the situation with adenocarcinomas. And I did this in squamous cancers, particularly since the PD-L1-negative subgroup is a minority. It's only about 9% of squamous patients in the first-line setting. But now, after the ODAC decision, I'll be starting with chemotherapy alone. And usually the PD-L1 results return about 1 to 2 weeks, in my experience, after we order those results. And if the CPS is 1 or higher, I'll add an anti-PD-1 antibody.

And we expect that in the future that reflex testing for PD-L1 will become faster, kind of like HER2 and MMR adenocarcinoma patients right now. So we'll have the PD-L1 results much sooner at the time of clinical decision-making.

Thank you for listening. I hope this discussion will be helpful in your clinical practice.

**Announcer:**

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