# Case Based Panel Discussion 2019- Lung cancer Unresectable NSCLC

# Case Based Panel Discussion Stage 3 NSCLC – Does Timing of Treatment Make a Difference in Response

Dr. Millie Das specializes in the treatment of thoracic malignancies. She sees and treats patients both at the Stanford Cancer Center and at the Palo Alto VA Hospital. She is Chief of Oncology at the Palo Alto VA and also leads the VA thoracic tumor board on a biweekly basis.

Dr. Matthew Gubens is a thoracic oncologist who treats patients with lung cancer, mesothelioma and other thoracic malignancies, including thymoma and thymic carcinoma, which are rare tumors of the mediastinum. He is an Assistant Clinical Professor of Medicine at UCSF.

---

Recently the doctors sat down to discuss a series of case-based scenarios. In this video, the doctors discuss the standard treatment of chemotherapy and radiation followed by immunotherapy and if timing of the treatment makes a difference in a patient's response, as suggested in the Pacific Trial.

Dr. Jack West: In the Pacific trial, the treatment approach was chemo and radiation and then assess for response or progression. And in patients who hadn't had a marked clinical decline and hadn't progressed would start on Imfinzi, durvalumab immunotherapy within a six week window. The trial started by looking for a two week window and then had difficulty enrolling patients and broadened it to six weeks. And there was a subset analysis that suggested that the patients who started immunotherapy within two weeks got more of a benefit from immunotherapy than the patients who started at three, four, five, six weeks out. If you have a patient now who is just going through treatment and your planning, what follows, are you getting imaging in less than two weeks and planning to start them earlier? Do you think that this is a clinically significant and meaningful difference or is this an artifact of patients who were able to start within two weeks, are not the same patients who were able to start within six weeks, and we shouldn't necessarily aspire to shoehorn everyone into an earlier start?

Dr. Millie Das: Yeah, I mean, I think again, the numbers are small. The subset analysis does suggest starting earlier could provide a benefit. I think patients are in various places after they finish chemo radiation, some patients kind of sailed through it and are ready to kind of move on. It means that then there'll be done with their year of therapy sooner. Frankly,

most of my patients, especially the ones that I treat at the VA, um, do you have significant side effects, especially towards the end from their chemo radiation and they do want and need a break. And so, this is not data that I would use to kind of push people into getting it sooner if they're not fully recovered from their chemo radiation. And I, you know, would certainly offer it to people who did fine and especially because we're seeing some suggestion that they may do, do better, but it's not something that I'm using to push patients who could use a little extra time.

Dr. Jack West: So it hasn't significantly moved up the timing of everything.

Dr. Millie Das: No. And in general, I mean, I'll say, the Pacific trial, you know, there wasn't a really significant increase in the rate of pneumonitis. But I mean, again, in real world practice, I do worry about that. And especially I think the patients that I'm treating at the VA where they do have underlying lung disease, COPD, emphysema, they've just finished chemo radiation and were worried about that. Kind of sort of extra, you know, possibility of autoimmune pneumonitis, you know.

Dr. Jack West: And again, pneumonitis is inflammation in the lungs that can be caused by many things.

Dr. Millie Das: Right. And so one of the things that we worry about is the pneumonitis caused by radiation and the pneumonitis potentially caused by the durvalumab Imfinzi and there being there being an increased risk because of these two, you know, things that could be causing pneumonitis. And I think in real life clinical practice, I have seen this, I've seen patients who are more prone to developing pneumonitis from the radiation just by virtue of having not so great lungs to begin with. And then, and those are the patients that make me very nervous about, you know, starting right away on the durvalumab. So I think it depends on the patient again, kind of depends on where they're at after chemo radiation and how aggressive they want to be.

Dr. Jack West: Matt, what's your view about the timing issue with, you know, I used to routinely get scans at three to four weeks out at least because we know their radiation effect could take that long, but has the Pacific trial and they suggestion of maybe there being more of a benefit early than late change, the timing of the scans and start of subsequent treatment for you?

Dr. Matthew Gubens: Well, I agree that, I think it's part of the small data set that wasn't designed to answer this question, whether that two versus six week is a real difference and doesn't have to just do with the patients who happen to make it by two weeks. But there is something scientifically, at least in principle, about doing it sooner with the idea that, you know part of the reason we think immunotherapy may work after radiation exposures, radiation is blown that tumor to smithereens, that tumor is striculating in little fragments. It's being processed by the liver and the kidney. The immune system is kind

of attuned to it at that time, so there's some sense to doing it as soon as you reasonably can. And I don't want to do it the day after chemo radiation finishes, but I also wouldn't wait a year. I actually would say no. If it took you a year to recover from chemo radiation, I'm not sure that immunotherapy helps. Where do I actually put my foot down? I don't know. But I do try.

Dr. Jack West: It's nothing magical.

Dr. Matthew Gubens: It's all, we always have to choose. Exactly. But you know, do I, the way I've operationalized it, I've now started getting my first scan about two weeks out. I plan to start if they're not ready. I feel very good about giving, Hey, take two or four weeks off, let's reassess. And even two to three months out, I'm comfortable doing. But when I start getting past that, what was it that made them unfit to start this soon? I'm having that conversation with the patient and in my head, but that's at least there is some a reason for why I don't want to wait too long after the radiation, if I'm going to do this and have it be beneficial.

Dr. Jack West: One of the limiting factors in executing this in practice is concerned about pneumonitis. Inflammation in the lungs. We should remember that pneumonitis didn't start with immunotherapy, that we know that giving just radiation and sequential chemotherapy, there is a risk of pneumonitis in the five ish percent range or higher maybe. And it's about a quarter of patients when you give them concurrently, which is our standard. So this has been unknown risk and it doesn't occur typically during the chemo and radiation, but most commonly weeks to a few months out. So it's in this ambiguous background of knowing there's this looming risk that we are potentially giving, immunotherapy. We also know that the chance of pneumonitis is modestly higher going from about one in four to more like one in three patients. So not staggeringly higher but not the same. I have had at least a couple of patients who have had early pneumonitis developing three, four weeks after the chemo and radiation, which is not unprecedented. It's earlier than expected, but sometimes the cancer doesn't read the book. And so I'm interested in your thoughts about for a patient who has poor pulmonary function just from bad emphysema or crawling to the finish after the chemo and radiation, maybe with the early start of pneumonitis, does that make you, especially gun shy about starting durvalumab? Do you have more of a wait and see approach and give them potentially two or three months to so-called declare themselves as to whether that's going to be a major issue or not?

Dr. Matthew Gubens: I certainly do. For those patients who have significant COBD, whose oxygen levels are already in the low nineties where our normal is usually in the high nineties, those are patients where I'm not going to do the two week planned appointment. I'm going to watch them for a month or two and just be very attentive to those changes.

Dr. Millie Das: It absolutely makes me nervous. The pneumonitis risk. And yes, I absolutely wouldn't start it right then and there and would want to follow them with a few more scans, see if that pneumonitis is really evolving radiographically.

Dr. Jack West: Particularly if, say you had a scan that suggested the early start of some new markings that look like inflammation in the lungs, maybe nothing that screams you can't but enough to raise your concern.

Dr. Millie Das: Right. And so I, you know, I wouldn't necessarily be wanting to get really frequent scans, but these are the patients where you would probably want to get a shorter term interval scan, perhaps at three or four weeks to see if it's evolving and course letting patients know if they're developing symptoms. I mean that's another big thing is if they're feeling like they're getting more short of breath more easily, then those are sort of warning signs.

Dr. Jack West: Do you have a low threshold for starting steroids in this setting?

Dr. Millie Das: I do. I have a low threshold to start steroids and then again, kind of see if there's symptomatic improvement and then, you know, schedule a taper thereafter.

Dr. Jack West: Matt?

Dr. Matthew Gubens: Right. Cause I think it's important to say cause pneumonitis maybe isn't something a lot of people have heard of except in this context. Pneumonitis can range from a, something we see on a scan that has no clinical import to something that gets you in the ICU. Like pneumonitis has a broad range. So when we talk about treatment, when there's enough pneumonitis that your oxygen level goes down a couple of notches that you're coughing really significantly, or the scans look bad, we're talking about giving prednisone steroid at high doses, potentially for weeks and months. So, you know, big quality of life hit. So just to, you know, frame that in perspective. But I'm watching these folks like a hawk. We teach them what to tell us about between visits. These are all things we're looking out for.