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The Role of Chemotherapy and Immunotherapy in *ROS1*-Rearranged NSCLC

Announcer:
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Dr. Drilon:
Welcome, everyone. I'm Dr. Alexander Drilon, and I'm joined today by Dr. Charu Aggarwal to discuss the role of chemotherapy and immunotherapy in ROS1-rearranged lung cancers.

So, Dr. Aggarwal, let's talk a little bit about your approach to giving first-line therapy for patients with a ROS1 fusion-positive lung cancer. And maybe let's start with the fact that the ROS1 fusion is already known, do you pick targeted therapy first, chemotherapy, immunotherapy, or chemoimmunotherapy?

Dr. Aggarwal:
Thank you, Alex. And if the knowledge of ROS1 fusion is already there prior to initiating treatment, in my practice, my preference has been to come in with targeted therapy. We know from other treatment settings that it may actually be harmful to come in with an immunotherapy approach, especially in case of an oncogenic driver for two reasons: lack of efficacy, for one, but also we are learning about sequencing of various drugs. We know from the EGFR literature that if you come in with an EGFR TKI after introduction of immunotherapy, there may be an exacerbation or higher reports of immunotherapy-related adverse events that may persist even after discontinuation of immunotherapy. These have been seen with ROS1 TKIs, albeit in the setting of ALK-positive lung cancer or MET-positive lung cancer, but I think probably the same principles apply. So, wherever I can, I try and come in with targeted therapies, especially if no treatment has been administered so far.

Dr. Drilon:
Yeah, that's my approach as well. And it's worth calling out for our viewers today that chemotherapy is also an active treatment. I tend to avoid giving immunotherapy because we know, as you mentioned, that the likelihood of response can be low or durability, plus there are other concerns that we'll probably talk about later on.

Dr. Aggarwal:
So, Alex, does PD-L1 or TMB influence your treatment decisions? Do you tend to look at that, or does your sequencing trump PD-L1?

Dr. Drilon:
It's really the latter. And this is my approach, and I'm sure others have adopted this as well to oncogene-positive lung cancer, is where there may be cases where you have a ROS1 fusion or EGFR or ALK, etc., but then you see something like high PD-L1. And there are several papers that have looked at this. And I think that while we can't exclude the possibility of someone having a great response, because we just can't tell, if you look at many patients together, these cohorts show that the likelihood of response, particularly with single-agent immunotherapy, is low. So, I tend not to approach PD-L1 and/or TMB the way I would somebody without a driver, which goes back to for our ROS1 fusion-positive lung cancer, I'd definitely start with targeted therapy.

Wonderful. And about sequencing, I had alluded to this a little bit, but do you think there's an effect of having previously received immunotherapy, say someone didn't know there was a ROS1 fusion, they had gotten chemoimmunotherapy, and now we're doing a TKI?

Dr. Aggarwal:
Yeah, I definitely think that in looking back at my experience, when I used crizotinib in the past without recognizing this concern of sequencing, this may not have been a patient with ROS1, but certainly I have experienced ALT/AST abnormalities, irAEs, in patients who have initiated crizotinib and who may have had previous immunotherapy. And, you know, I think this is a real concern. We must be aware that this is a true possibility for our patients. And if we can avoid this toxicity, I think firstly, benefit our patients with targeted therapy and do minimal harm.

So, do you think there's any rationale in combining chemotherapy with checkpoint inhibition and TKIs? I know this has not been a successful strategy in ALK, but what do you think about ROS1?

Dr. Drilon:
So, for ROS1, given what we just spoke about, the likelihood of toxicity with a TKI after immunotherapy, you can imagine that when you give both together, that that risk also exists. And so, mixing a checkpoint inhibitor with a TKI isn't something that I've done and there's not great data to support that. However, in patients who have had a TKI upfront and are moving to chemotherapy, this is where in practice I've heard, and certainly I approach things this way as well, that some might continue a tyrosine kinase inhibitor with the chemotherapy. I tend to do this in patients, especially that have brain metastases, particularly those where perhaps there's only extracranial progression and the brain mets look good on the TKI, I feel like the influence of the TKI in protecting the CNS compartment is still pretty important.

Dr. Aggarwal:
Thank you, Alex. That was great. And this concludes our brief session on role of chemotherapy and immunotherapy in ROS1-rearranged lung cancer.

Announcer:
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