

Gary Shelton (Moderator): Our next speaker along with Beth will be Dr. Tyler Beardslee. Tyler is a clinical pharmacist in the Department of Hematology and Oncology at Emory University Hospital. And will discuss managing ALK positive and ROS1+ metastatic non-small cell lung cancer. Tyler.

Tyler Beardslee: Appreciate that. Thanks everyone for having me. This is a subject that's pretty near and dear to my heart. So I practice in a thoracic oncology clinic. I've been there for about, I guess, total of four years now. So I'm happy to talk about this subject today. ALK and ROS1. I think it's very interesting. There's a lot happening.

So these are disclosures you've seen before. So our learning objective today is to evaluate the efficacy and safety data supporting the use of targeted and immune checkpoint therapy used to treat non-small cell lung cancer.

There we go. All right, so here's our first question. So which ALK inhibitor has the highest rate of pneumonitis?

Beth Eaby-Sandy: Read through the answers.

Tyler Beardslee: All right, so we have a brigatinib, alectinib, lorlatinib, crizotinib, or are you unsure? Which is okay.

Alrighty, so it looks like most people were unsure, which like I said is okay. So you have a 53 year old female patient with ROS1 non-small cell lung cancer who is currently on crizotinib, now develops a new brain mets. Which of the following agents would you like ... would you counsel is likely to be best? So lorlatinib, alectinib, entrectinib, brigatinib or are you unsure?

Alrighty. All right, so it looks like we have a lot to learn here today, which is great. You know, this is one of the lesser common mutations in lung cancer, ROS1 and so is ALK, which we'll see in just a moment.

So this is a little breakdown of ALK and ROS1 and non-small cell lung cancer. Looking at the different types of lung cancer and how often these mutations occur in those types of lung cancer. The majority, like our other driver mutations, EGFR are an adenocarcinoma histology. They're very rare in squamous cell, and they're typically mutually exclusive, which we talked a little bit about before. It'd be extraordinarily rare to see these along with another mutation. And these are also found in a little bit younger population, which we'll see the median ages of diagnosis a little bit later.

This is our little pie chart that every single non-small cell lung cancer talk should have in it. And like I said, these are a little bit less common than the EGFR mutations. One thing that we haven't talked about today is KRAS, which is the most common mutation.

Beth Eaby-Sandy: We're going to talk about it.

Tyler Beardslee: Oh, we are going to talk about it. Great. Yeah, so there's some cool emerging data with that, which I think is very, very helpful for these patients. But back to ROS1 is 1%, ALK is about 7%. You see these numbers vary very slightly in different literature.

So looking a little bit at the patient characteristics of ALK mutation, positive non-small cell lung cancer patients. So the median age of diagnosis for non-small cell lung cancer, I believe around 70 years old, which here we see this is data from the ALEX trial, which is a trial with alectinib. And it gives us a pretty good sense of what these patients look like. So they're about a mid fifties, fairly split between the genders. There are 45% Asian in this trial, but typically this is more in EGFR patients, not necessarily ALK, and it's definitely more common in never smokers. But we also, you know, we talked a little bit about kind of stratifying who we should test. The squamous patients who are non-smokers are definitely candidates for genetic testing.

So here we have our ROS1 characteristics, which we see are quite similar, actually. So it has median age of diagnosis around 50 again, a little bit younger, pretty even female to male split here. And also once again, associated with non-smokers and not really at all with any current smokers.

Beth Eaby-Sandy: Yeah, I can't say that I've ever seen a ROS1 smoker, I don't think. Every once in a while with ALK and EGFR, yes, but they were in that cohort of the crizotinib trial ROS1 patients, there were not any that were current smokers at the time. They were diagnosed with ROS1. So this one's just ...

Tyler Beardslee: So here we're just going to look a little bit at the dosing. I would just say the dosing is very important with these medications. With all tyrosine kinase inhibitors, I strongly recommend that you look up the administration as well because food typically can affect the absorption of some of these medications. For example, alectinib, here should be taken with food twice daily. You know, like I said, just look these things up because it can be very important, you know, it can affect the absorption, you know, 50, 60% in some of these drugs.

The interesting thing I'll mention here, which we'll talk a little bit about later, is brigatinib. You see this low dosing to start with, 90 milligrams for seven days, and then you increase up to 180 milligrams. So that's a little bit unique dosing and it's for a unique side effect that we see with brigatinib.

So talking a little bit about some of the earlier generation ALK inhibitors here, we have crizotinib, which was the first ALK inhibitor which was approved and it was the only drug that we had for quite a while. So we were really relying on this. And because this was the only drug that we had as these other more potent, and I would say better designed from a pharmacological perspective when these newer drugs got approved, a lot of them were tested first in the second line setting and then they went back and looked at them in the first line setting. So crizotinib was the only one there for a little bit. Ceritinib was second to be approved. However, we see that this one has quite a bit of toxicity, a lot of GI toxicity. And there's actually some new dosing with this one. When it was originally approved, it was 750 milligrams once daily, and that was approved based off of a phase one trial.

The new 450 milligram dosage should be taken with food and they actually found that that mitigates some of the GI toxicity with ceritinib. So the new dosing, still pretty bad GI toxicity, but it's a little bit better. Definitely go with the 450 with food.

Here we have alectinib. And this is kind of starting to really show that this is a more effective drug than crizotinib. So this was the third ALK inhibitor approved. It was originally approved a second line. Like I said, the way most of these were studied. However, the ALEX trial, they went back and they looked at this drug first line and they found that it was superior to crizotinib in a progression free survival, and I think overall survival as well now.

Beth Eaby-Sandy: Yeah.

Tyler Beardslee: Yeah. So now alectinib, based on this trial, the ALEX trial, is the preferred a first line agent.

So here we go. Here's the original PFS curve and you see this quite distinct separation between the two curves with alectinib in the blue and crizotinib in the red. And this PFS like, really blew people away when they first saw it. This is like, you know, like we said, we used to have ... this used to not even be the overall survival and now we have patients with these driver mutations and having 34 months of progression free survival, which is tremendous.

A little bit of a caveat. There were less CNS mets requiring treatment in elective arm and as we know, you know, CNS mets are poor prognostic factors. You may say the deck was slightly stacked, but I mean not enough to account for this big of a difference in the efficacy of the alectinib. Overall survival data, actually, I think is still pending. I can't remember if ...

Beth Eaby-Sandy: I didn't see it as of recently. I think it's still immature, but obviously the hazard ratio's very much in favor of alectinib.

Tyler Beardslee: Yeah. And another thing I'll say about alectinib, which we'll see a little bit later, is that the toxicities with alectinib are quite much, much better than you know, especially as crizotinib and ceritinib. In fact, it's probably one of the better tolerated TKIs that I use in my clinic. Probably the best one I would say.

So here we have the kind of a fourth drug that was approved, which is brigatinib, and this one was also approved as second line post failure for crizotinib. Also had a significant intracranial response and why we're mentioning this is, what they found in patients who were progressing on crizotinib is 60% of them had a CNS metastasis as their site of disease progression. You go back and look at the pharmacology and pharmacokinetics of crizotinib and you come to find that it only has about 5% blood brain barrier penetration. So all of these other drugs were rationally designed to have really, really good blood brain barrier penetration. And they looked at that as an endpoint in a lot of these trials and pretty much all, you know, alectinib, or brigatinib, and lorlatinib all have very good activity in the CNS.

Beth Eaby-Sandy: Yeah. And for some reason with ALK lung cancer is a much higher affinity to spread to the brain. It's literally like 60 to 70%, as opposed to the general stage four lung cancer population is more around 30%. So they have a much higher likelihood of brain metastasis. So it is important that these drugs address and are able to cross that blood brain barrier and address that need.

Tyler Beardslee: Yeah. And then we finally have, I would say it's the newest one, but now we have entrectinib. Let's see.

Beth Eaby-Sandy: Well not for ALK.

Tyler Beardslee: Not for ALK. Okay, let's stick to ALK. So lorlatinib is the most recently approved ALK inhibitor. It's approved as second line post failure of at least one or two ALK regimen. So this trial that gained this drug's approval included a lot of patients who were pretty heavily pretreated, and we saw a very, very good response rate as you can see here, about 45% response rate after failure of one or even

two regimens. So I was very impressed with the results of this trial, and I will talk a little bit later about the toxicity, like I said, which is ... this one has some unique toxicities that, you know, I only have maybe four or five patients on this, but they've all dealt with some of this stuff that we're going to talk about later, and it's a very interesting, to say the least. So there are some ongoing studies looking at this one as well in the first line setting.

All right, let's move on to talk a little bit about some of our ROS1 inhibitors. So I never started my timer. Anyway, I'll keep track.

Beth Eaby-Sandy: I'll keep track.

Tyler Beardslee: Thank you so much. So we have a crizotinib here, which is the first drug approved and it was the only drug for quite a few years. And this was based off of a pretty small study. And you know, once again going back and looking at the percentages of patients who have ROS1, it's only about 1% of patients with non-small cell lung cancer. So some of these trials are going to be quite small. So there're only 53 patients in this trial. But the median overall survival, as you can see, looking at the long-term data that's been published with this one is quite impressive. So the overall survival's over four years. You know, once again this is something that we just didn't see 10, 15 years ago.

Beth Eaby-Sandy: This was just published in the past few months and that was really exciting. But I think we know ROS1 tends to be more of a locally advancing lung cancer. Tends to be somewhat slower, but crizotinib has worked very well for it as well. So seeing these long-term median survival numbers is really good. And I think this is another one of those patients, like we were saying earlier with the certain immunotherapy patients, but it might not be unreasonable to say, you know, you could be around for years. It's likely that you would be alive for years with this disease.

Tyler Beardslee: And you know, you see the progression free survival benefit as well as the response rate, which is pretty stupendous as well.

Next we have entrectinib. So this was just a very, very recently approved, and this is for crizotinib naive patients. Excuse me. The dosage is about 600 milligrams daily, and once again, this is one of those small trials. So I had about 51 patients pooled between the three trials, and the response rate was about 78% here. And I think I looked this up, the response rate, I thought there were some patients, correct me if I'm wrong, was it ... Did they include patients in this trial who had progressed on first line crizotinib or was it all crizotinib [crosstalk]

Beth Eaby-Sandy: So it's very interesting because I just had this conversation with someone else before this. So the package insert, if you look up the package insert for entrectinib, it just says it's approved for patients with ROS1 positivity. It doesn't say what line. It doesn't say first line or second line. When I went back and did a deeper dive, because these trials, these ALKA, STARK-1, and STARK-2, were not just ROS1 non-small cell lung cancer. This was a basket trial that included several patients that were put on entrectinib. Some with entrectinib, some with ROS1, some without. It was different, and then they pooled cohorts out of them to try and get a rationalization.

So this is a good way to do a clinical trial. I liked this design very much. What I did find was they said these 51 patients, they didn't use the terminology crizotinib naive, they said they had never had a

ROS1 inhibitor. Well the only ROS1 inhibitor that's approved is crizotinib. So I would have to deduce from this that all of these patients had never had crizotinib in the past.

That being said, the drug does not say it's approved in the first line or second line setting. It just says it's approved if you have ROS1 disease. So I think, you know, the question that came up was, if you have a newly diagnosed ROS1 patient, which drug would you use? Tyler?

Tyler Beardslee: You know, I think it's ... I would lean probably more towards crizotinib at this point.

Beth Eaby-Sandy: I think absolutely.

Tyler Beardslee: You know, we have the long-term survival data and that makes me very comfortable knowing that my patient's going to live over four years. I also think, you know, both of these drugs have some toxicities that can be a little bit nasty. They're different between the two. But I think I would prefer the toxicities from crizotinib. Some of the weird ones with entrectinib [crosstalk].

Beth Eaby-Sandy: And there's just not that many patients have been treated so far. Just 51 patients in this cohort. But it's not wrong, but I think I would wait until progression on crizotinib at this point to use this. Though, what I will say, you can see that five out of seven had intercranial responses. It seems like certainly this drug probably has much better intercranial penetration than crizotinib. But I still don't think in a first line medicine, even with brain mets that I would use it. But it's not wrong. So it's interesting.

Tyler Beardslee: It's an option. Yeah.

Beth Eaby-Sandy: Yeah.

Tyler Beardslee: So talk a little bit about some other agents for ROS1. So the lorlatinib still is in trials for this. They kind of pulled out ... they kind of like you were talking about, some of those cohorts and reported on it for ALK, but they haven't reported on the ROS1 as much yet. So it has about a 50% response rate. And I think some of these patients were, and if you ... This is the one I looked at as well. If you go back and look, there are some patients that are not ... who have progressed on a first-line ALK inhibitor and the response rates are ... sorry. Our first line of crizotinib, and I think there are some response rates here. When I looked into it, I think it was like 20% or something, I found some data [crosstalk].

Beth Eaby-Sandy: It's just hard with the small numbers to make extrapolations and get FDA approval.

Tyler Beardslee: But it's nice to know that there's some activity there because what we're struggling with is finding what to do with these patients after they present, or progress on crizotinib. So we now maybe have the option of entrectinib, lorlatinib, may be an option in the future if it gets an approval.

Ceritinib, there are 28 patients in this phase two trial. It had 62% response rate. Brigatinib, very limited data. And alectinib does not work well at all on ROS1, and I very strongly encourage you to go back and look at your patient's pathology before you put them on a second line drug. I had a nightmare where I accidentally prescribed alectinib for a patient with ROS1 because I saw that he'd progressed on crizotinib, and I was like, [crosstalk 00:16:37]. He was ALK, yeah, and ... you know my attending made

the mistake, our AVP made the mistake. We were all in ... We, you know, talked about it in the circle, and we're like, yeah, all right, let's go. None of us decided to look. We caught it before the drug got to the patient. But it was just one of those things where we had to go back, talk to the patient and say, you know, "Sorry, we made a little mistake here." So that's just a little story from myself.

So there are some class effects of these drugs, but there are also some other ones that vary pretty significantly. So we'll talk about some of those class effects. The class effect that we're going to talk about is pneumonitis. So pneumonitis is pretty darn rare with these things. However, it can be fatal so you want to act pretty quickly with this one. You know I, this is one of the warnings I tell all my patients on these drugs, you know, I described to them, you know, it's a very rare thing, but if all of a sudden you have, you know, sudden changes in your breathing, a lot of shortness of breath, a lot of difficulty breathing, I want you to tell us.

Usually they come back and they say, I'm short of breath already. I go, "I know you have lung cancer, let's talk about your baselines. So you have a new baseline. This is your new baseline. If we have significant changes from here in your breathing, we want to know about it."

Permanent discontinuation is appropriate for all of the ALK inhibitors except for brigatinib. So brigatinib is a drug that they found has quite a high rate of pneumonitis, but it's reversible. So this is why they have this kind of step up dosing with this drug. Other ALK inhibitors. If you rechallenge with the drug, you're going to get pneumonitis. Again, it might be all fatal. Whereas brigatinib, you catch it early, you back off the drug depending on how bad it was or at what time in the therapy you may dose reduce versus going back to the same dose, but you can go back and do this drug with pneumonitis. But it does have a higher rate of pneumonitis.

So you see those rates here. So crizotinib, the other ALK inhibitors, you know, 1 or 2%, maybe less. Brigatinib, you know, 9 or 10% of patients can have pneumonitis. But once again, this is reversible pneumonitis-

Beth Eaby-Sandy: And the onset is in two to three days.

Tyler Beardslee: Yeah, it's quick.

Beth Eaby-Sandy: So it literally happens right away, but it's not quite as severe, and then usually it's reversible, treat it, you know, treat it as you would with steroids.

Tyler Beardslee: Yep. So, yeah, that's just a little bit of difference between these is pneumonitis with Brigatinib.

Beth Eaby-Sandy: The reason I included this case study, you can see this goes back to 2012 and this was a very young patient of mine. She was, I think, 31 years old and she ... we had just figured out ALK, we didn't know as much about it, and this was after two weeks on crizotinib. So that is a pretty diffuse bilateral. You can see on the left is her pre crizotinib, CAT scan. Clear lungs. And on the right just ground glass opacities everywhere. Pretty bad pneumonitis.

So this was really upsetting for her because she was very young, stage four lung cancer and now we couldn't use the only drugs that could give her four years of, you know, years and years of

progression free survival or overall survival. We treated her with chemotherapy for many years and when she was dying she wanted to go back on an ALK inhibitor, and we told her that this would likely, you know, be fatal.

And she said, I don't care, I need to try something. So at the time, the only other one was ceritinib, I believe. I'm trying to remember what it was.

Tyler Beardslee: That sounds right.

Beth Eaby-Sandy: I don't think alectinib was approved. Oh no, I know because she couldn't get on the Alectinib trial because she had a history of pneumonitis. So we prescribed her ceritinib or crizotinib. I don't remember. We prescribed it again and loaded her with a hundred milligrams of prednisone daily and she got pneumonitis and died. So it doesn't matter if you rechallenge them. It is pretty much always fatal. So this is not, except for the brigatinib, which is like immunotherapy pneumonitis. The rest of them it is severe.

Tyler Beardslee: Yeah. And I'm glad that you went over the images because they don't quite teach pharmacists how to read images in pharmacists-

Beth Eaby-Sandy: Oh, come on, that's obvious.

Tyler Beardslee: No, no, no, no.

Beth Eaby-Sandy: There's clouds in her lungs.

Tyler Beardslee: I was like even I know that's ... usually that's what I say in clinic. I go, that doesn't look good, when we're looking at scans together.

So talking a little bit about the toxicities of these drugs is what we're going to move into now. So what you see with crizotinib, like I said earlier, is a lot of GI toxicity. You can get edema, which happens with a few of these ALK inhibitors. Kind of an interesting side effect that you get that's not that worrisome for us, but it can be bothersome for patients are these visual changes. So this is very, very common. They're typically low grade in nature and resolve with time. However, I have some patients that have been on them for years that still have them but typically resolves with time.

So I usually describe for patients, some patients see flashing lights, some people see kind of halos around lights at night. So usually we recommend that they be careful or not drive at night at least until some of these things are resolved. There can be very, very rarely with this ... down here. Severe vision loss. However, most patients, like I said, have very low grade visual disturbances that are self resolving. I usually counsel patients if you have any vision ... you need to call us if you have any vision loss. But some of these other types of, you know, flashing lights and halos and things. Those are okay.

What else do I want to say about this one? Not too terribly much. Oh, the other one I want to mention is the potential for bradycardia. So this is one of those things that can happen with this drug. I've seen some mechanisms proposed that there might be some ALK involvement in the essay node of the heart, so that's kind of the mechanism of how this slows the heart rate. I would just say that you know, if you have a patient who's getting dizzy when standing up or something, you want to review their

med list, see if they're on something like a beta blocker and stop that first before you go on to kind of dose adjusting the crizotinib.

Beth Eaby-Sandy: I would say this bradycardia is a class effect, some more with other ALK inhibitors, but we see it with all of them. I'm talking like heart rates of 48 to 52 at rest. Our cardio oncologist at Penn has told us that as long as that patient exerts and their heart rate goes up, then it's fine. It's so ... He said, tell your patient to go walk down the hall, put the pulse ox on them and walk fast, like not slow, like walk them, exert them, and if their heart rate is 50 at rest and it goes up to 70, and then they go back to 50 when they rest, then fine. You just need to make sure. It's the problem patient that if they exert and their heart rate stays at 50 that you are in trouble because now your heart's not meeting its workload. So that's what ... that was his quick and easy way.

Tyler Beardslee: Yeah. I think symptomatic bradycardia [crosstalk].

Beth Eaby-Sandy: Oh, definitely get an EKG.

Tyler Beardslee: Yeah. So I think that's all I'll say about crizotinib right there for now. So this is the dosing I was talking about with ceritinib and some of the side effects. So ceritinib originally was approved at 750 milligrams daily and now is approved at 450 milligrams daily, with food, which helps with the absorption. The side effects, as I said, are some pretty nasty GI side effects. So I mean, you see, you know almost 90% of patients have diarrhea. This is like on afatinib's level. The other thing, I mean, this is nasty nausea. I mean, this is like cisplatin without antiemetics level nausea.

Beth Eaby-Sandy: Yeah, I mean we don't use this drug anymore.

Tyler Beardslee: We just don't use it. And I have had a very, very tough time for the patients when we used to use this, keeping them on treatment. You know a lot of dose reduction and eventually they just said I'm done.

What else would this one? I tell you, a unique side effects you get with this one is hyperglycemia. I haven't seen a ton of it but it kind of has a unique mechanism. So there's some off target effects of ceritinib on insulin, like growth factor 1, which is why we have the hyperglycemia with this one. Pancreatitis is a little bit unique with this one, but we see it with a, I think one more of these other ones. I think that's all I'll say about it and as we mentioned earlier, hepatotoxicity is a potential, you know, warning on all of these TKIs.

So we have alectinib here, which I would say is probably the most, the best tolerated. I mean some of these things here are pretty manageable. Fatigue, you know, you see that in pretty much all of our patients, you know with cancer. Constipation, we can deal with that. The edema I would say is probably the most troubling side effect for my patients. The unique one here is the potential for myalgias. So about 30% of patients can have myalgias and the package insert actually recommends that you test for CPK at least two times within the first month.

What else will I say? I think that's about it. Anything else you want to say about this drug?

Beth Eaby-Sandy: Just multiple capsules. You know the dosing on these is so obnoxious.

Tyler Beardslee: And it's actually 600 milligrams twice daily.

Beth Eaby-Sandy: Yeah. I'm sorry. You're right. That's a ... that is a typo. It is 600 twice daily, I believe. But it's just a lot of pills, a lot of times a day and ...

Tyler Beardslee: Yeah, it kind of freaks patients out. So 150 milligrams. You're telling me you're going to take four in the morning and four at night. They're like, "Eight pills a day?"

Beth Eaby-Sandy: it's not great for adherence because ... did I take three or four? I don't know.

Tyler Beardslee: Yeah. Yeah. But like I said, this is one of the better tolerated ones, and as we saw earlier, it has the efficacy data showing us that it's better than crizotinib. This is typically the go to in the first line setting for ALK.

And then we have brigatinib, which as I mentioned, has a little bit different dosing and this is due to that potential for pneumonitis very early in treatment. So they start you off at a low dose of 90 milligrams for seven days, and if they don't have any pneumonitis then you bumped them up to 180 milligrams daily. So this comes as 90s and 180s, so you can manage that pretty easily as far as the tablets.

As far as side effects with this one. This one has a couple of unique side effects kind of in the warning. So we already mentioned the ILD. The other one that I've seen is ... Where is it? Oh the hypertension. So the first patient I put on this was a like little old like, 86 year old lady and she ended up having a blood pressure of like, systolics over 200. So this is a real thing that can happen. I've seen it and it's kind of unique to this drug. This one also has the CPK elevation and hyperglycemia warning. What else do I want to say?

Beth Eaby-Sandy: Five minutes left.

Tyler Beardslee: What's that?

Beth Eaby-Sandy: Five minutes left.

Tyler Beardslee: Okay, thank you.

So the lorlatinib, this is the one that I said has some interesting side effects and what I'm talking about is this neurological changes. So 37% of patients can have cognitive or mood effects. I've seen stuff anywhere from full on hallucinations to people becoming very irritable and mean, cognitive changes, almost what it looks like dementia, and I've had to dose reduce the majority of my patients on this drug from the a hundred milligram dosage down to 75 milligrams.

Besides that, the other kind of unique side effect is the potential for a neuropathy.

Beth Eaby-Sandy: Cholesterol.

Tyler Beardslee: You know ... There you go. That's the other one. I forgot about hypercholesterolemia.

Beth Eaby-Sandy: We're not big on statins in oncology, but now you've got to be.

Tyler Beardslee: You do. So they go really high. I would say most of my patients get pretty nasty, and I've had to put people on like statins and like a fibrate to get their triglycerides down because their triglycerides are like 3-400 range. So those are the unique things about lorlatinib. So drug's pretty toxic, actually with some of these weird side effects.

And then we have entrectinib. So this is our newest ROS1 approval. So this one also has CNS effects and I think this is probably related to the fact that entrectinib is in the brain, so that's why we have some of these CNS effects. You see the cognitive impairment again, as well as the potential for mood disorders.

This is a very interesting side effect. The increased risk for fractures. In pediatric patients, they all had no trauma. Whereas some of the adult patients, they weren't sure whether or not there were some falls involved or it might've been the disease involved. But I think it's still concerning the fact that we almost have 25% of patients who are [inaudible] to have fractures. So it's something to take into account, for sure.

Lab abnormalities, LFTs. CHF is a pretty rare side effect, but it can be serious if it happens. So, you know, prior to starting I would recommend doing, you know, an echo.

So we're just going to talk a little bit ... concluding here. So ALK and ROS1 are generally uncommon, but you know, definitely test for them in our adenocarcinoma and definitely non-smoker squames. Most commonly in never smokers. We have, you know, many different drugs that we just went over and we have some pretty long-term survival, especially in, you know, both of these settings, ALK and ROS1 now. You know, obviously compliance is an issue with some of these drugs with multiple pills, I would say.

Beth Eaby-Sandy: All right, so we should do our questions again?

Tyler Beardslee: Yes.

Beth Eaby-Sandy: So, which ALK inhibitor has the highest rate of pneumonitis? Is it brigatinib, alectinib, lorlatinib, crizotinib, or I'm unsure?

Tyler Beardslee: Excellent. Look at how good you guys did.

Beth Eaby-Sandy: Yay. Brigatinib is ... Yep.

Tyler Beardslee: Great improvement. All right, sorry, next one.

Beth Eaby-Sandy: You're a 53 year old female with ROS1+ non-small cell lung cancer who is currently on crizotinib, now develops new brain mets. Which of the following agents would you counsel is likely to be best? lorlatinib, alectinib, entrectinib, brigatinib, or I'm unsure?

Very good. Yeah. Entrectinib is the only other one now that's approved for ROS1 and had the better brain penetration. So, okay.

Tyler Beardslee: Yeah, that's the key point there. All right. Thank you so much y'all.