

Journal Club Spotlights: Current Advancements in Non-Small Cell Lung Cancer



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Lorlatinib versus crizotinib as first-line treatment for advanced ALK-positive non-small-cell lung cancer: 7-year update from the phase III CROWN study

Dr. Alice Shaw & Dr. Jamie Chافت

Jamie Chافت: Welcome, everyone. I am Dr. Jamie Chافت from Memorial Sloan Kettering Cancer Center. In this accredited webinar, we are going to discuss the article "Lorlatinib versus crizotinib as first-line treatment for advanced ALK-positive non-small-cell lung cancer: 7-year update from the phase III CROWN study." It was published concurrently with the American Society of Clinical Oncology (ASCO) meeting on May 29, 2026, in the *Annals of Oncology*.

I am joined today by Dr. Alice Shaw from Dana-Farber Cancer Institute, who is not only the lead author of the CROWN study, but she wears the crown as the "Queen of ALK." So, I am very happy and honored to speak with you today, Alice. Welcome. Thank you for joining us.

Alice Shaw: Well, thank you so much, Jamie, and thank you for that nice compliment.

Jamie Chافت: Definitely a compliment. We are all in awe. I am going to ask you to start by providing an overview of first, very briefly, why this study was conducted so long ago and why you and your coauthors chose to update it at 7 years.

Alice Shaw: Thank you so much, Jamie, for having me today, and I am really excited to talk about this 7-year follow-up of CROWN. Just to remind everyone, because I know not everyone is thinking about ALK-positive lung cancer every moment of the day, but I think everyone does appreciate that the treatment landscape for ALK-positive lung cancer really has evolved incredibly rapidly since ALK was first discovered in lung cancer back in 2007. We have multiple generations of ALK inhibitors, from first-all the way out to fourth-generation inhibitors, and with really the idea that each generation of ALK inhibitors is improving on the last generation.

Lorlatinib, which of course is the focus today, is our third-generation ALK inhibitor, and it really was rationally designed by the medicinal chemists at Pfizer to be more potent than first- and second-generation ALK inhibitors, to cover all single ALK resistance mutations, and also to be highly brain penetrant, recognizing that ALK-positive patients are really prone to brain metastases. Jamie, you remember that we did these early phase testings of lorlatinib, which looked really compelling in patients who had been previously treated with ALK inhibitors. We had some initial data, early data, with lorlatinib in ALK-tyrosine kinase inhibitor- (TKI-) naïve patients and all of that together looked really compelling, so that we wanted to test lorlatinib as first-line therapy in patients with advanced ALK-positive lung cancer. In 2020, we actually reported the first planned interim analysis of this CROWN trial, and so CROWN was a randomized phase 3 study comparing lorlatinib vs crizotinib, the first-generation ALK inhibitor, as first-line therapy in advanced ALK-positive lung cancer.

Journal Club Spotlights: Current Advancements in Non-Small Cell Lung Cancer



Back in 2020, we already showed that this was a positive study. At that time, the median follow-up, though, was just 18 months, and median progression-free survival with lorlatinib had not yet been reached. With crizotinib, it was, as expected, at just 9 months. That was an important first analysis. It has led to lorlatinib being fully approved and approved in the first-line setting, but we did not have a median progression-free survival (PFS) [PFS was not reached for lorlatinib], and so we continued to follow those patients. We reported data at 3 years, and then at 5 years, and still did not have a median progression-free survival with first-line lorlatinib. Given the benefit that we were seeing in all of these subsequent analyses, we decided to perform yet another analysis of even longer-term outcomes from CROWN, and as you said, is now after a median follow-up of 7 years.

Jamie Chافت: Amazing, and we will get into those data. You told us already that the primary objective of the CROWN study was progression-free survival. What were your key secondary endpoints?

Alice Shaw: The primary objective was PFS, but we had the typical secondary objectives as well, such as response rate, duration of response, importantly, intracranial efficacy, also overall survival, which I will come back to in just a moment, safety, and correlatives. With regard to overall survival, because everyone always asks about the overall survival data, at the time of this data cutoff, overall survival within CROWN was still immature, so we do not have the required number of overall survival events for the protocol-specified second interim analysis, so we do not actually have the overall survival yet to share. But we do have basically all of the other endpoints that have been updated.

Jamie Chافت: Walk us through the methods. This study enrolled patients with *ALK*-positive non-small cell lung cancer. First, how was *ALK*-positive defined, and what were the other key inclusion criteria?

Alice Shaw: Yes, so patients had to have *ALK* based on an FDA-approved diagnostic test, fluorescence in situ hybridization (FISH) or immunohistochemistry (IHC), as an example. Some of the key eligibility, as you mentioned, so locally advanced stage IIIB or metastatic. Most of the patients had metastatic stage IV disease. Importantly, this was a first-line trial, so patients could not have received prior systemic treatment for metastatic disease. Then another important point around these patients is that they were allowed to enroll with untreated asymptomatic brain metastases. Then the last thing I will note about these patients is that, just as with other trials, they had to have measurable disease.

Jamie Chافت: That could be a challenge in this population, actually, with the infiltrative nature of it, and I applaud you for enrolling patients with untreated brain metastasis. We all aspire to do that in trials and often are not permitted to. Were there any key exclusion criteria?

Alice Shaw: Not really. I mean, beyond the normal ones, again, for the brain metastases, patients had to be asymptomatic, so they could be untreated, but they could not be symptomatic. The main thing is that they could not have received prior treatment, so this really is a treatment-naïve setting.

Jamie Chافت: This was a phase 3 global randomized trial, 104 sites, 23 countries. This is a rare patient population, so tough to enroll. How were the treatments given?

Alice Shaw: Yes, we enrolled almost 300 patients, like you said, across 100 sites, and we had to have that many sites because *ALK* rearrangements are really only in about 4% to 5% of our patients. Almost

Journal Club Spotlights: Current Advancements in Non-Small Cell Lung Cancer



300 patients were randomized 1:1 to receive either lorlatinib, the standard dose of 100 mg once a day, as their first-line therapy, or the other half of patients received crizotinib, the first-generation *ALK* inhibitor, at the standard dose.

Jamie Chaff: I am going to ask you an atypical question here. If you were to rewrite this study today, would you allow crossover?

Alice Shaw: I think we knew going in that there was going to be crossover outside the study. We already knew there was so much availability of second-generation *ALK* inhibitors, and of course, lorlatinib was already approved in the previously treated setting in many regions of the world, so I think we were expecting that there would be inevitably some confounding, in which case then you might as well have crossover in the study, and that way you can at least control and study it more so, possibly. I think the more common question I get, Jamie, is should we really have randomized patients to alectinib as the comparator instead of crizotinib? Back in the time, we planned the study in 2016, and it opened in 2017, and that is before we even had the global ALEX trial results back, which was comparing alectinib to crizotinib, alectinib was not even standard first-line therapy when we started CROWN. We could have anticipated that, and been more forward-thinking, and that would have helped a lot, but at the time, we just wanted to go as fast as possible, and hence we used crizotinib as a comparator.

Jamie Chaff: Right, and I think for that reason, the drug did not get immediate uptake when the first interim analysis was presented, but after 5 and 7 years, perhaps things are changing. Tell me a little about the results, starting with the patients.

Alice Shaw: As I mentioned, we had already presented the data after 18 months of follow-up, 3 years, 5 years. This is a longer-term, 7-year follow-up. Many people have heard this, that after this median follow-up of 7 years, we still do not have a median progression-free survival with first-line lorlatinib. We know what the median progression-free survival is with crizotinib. We previously reported just 2 years ago that the 5-year PFS rate with first-line lorlatinib was 60%, which is quite striking. Now in the 7-year analysis, the PFS rate at 7 years is 55%. In fact, pretty similar rates, and I think that is really reflected in the PFS curve, where you can see that there is this very clear plateauing in the PFS with first-line lorlatinib over this period of years, actually, at this point. I thought, Jamie, what was helpful to present in both the publication and the presentation was really to look at the PFS rate in yearly intervals, and I thought it was notable that really the risk of progression for patients treated with first-line lorlatinib is really highest in the first year or 2. At 2 years, about 30% of patients have had a progression event, but then when you look at subsequent years, the yearly rate really does drop down, so you go down to 5% at year 3, and then your rate of progression becomes about 2% to 3% per year in subsequent years. It really does, again, speak to that plateauing. I think what was helpful for many of us, and actually for patients, is that we could estimate, just using simple math, that if you do not have a progression event after 2 years of first-line lorlatinib, then you have an almost 80% chance of still being progression-free at 7 years, and I think that really helps patients to really think about risk, to think about timing of lorlatinib.

Then the last thing I will say is, I thought it was really important to continue focusing on efficacy outcomes related to central-nervous system (CNS) disease. In the 7-year update of CROWN, we showed that the median time to intracranial progression with first-line lorlatinib was still not reached, and in fact, the vast majority of patients, 92% of patients who were treated with first-line lorlatinib, were still free of intracranial progression, even at 7 years. That is pretty remarkable. The other fact that

Journal Club Spotlights: Current Advancements in Non-Small Cell Lung Cancer



we saw from the study is that once you got past 2½ years of lorlatinib, we did not see any other CNS progression events out to 7 years, so that really speaks to lorlatinib's activity in the brain and really the ability of lorlatinib to prevent brain metastases.

Jamie Chافت: You just answered all of the questions I was going to ask you, and I will echo that in my clinic, it is that if you are okay at 2 years, you are likely to be fine at 5 and 7 years. That has been the most common topic of conversation, and patients are really reassured by that.

Alice Shaw: It is really powerful, right?

Jamie Chافت: It is very powerful. All right, let us talk about the dirty stuff, the safety here. Many were not early adopters of lorlatinib in the front line due to its unique toxicity profile. Walk us through the most relevant toxicities and how you manage them.

Alice Shaw: Yes, I think you described it really well. Lorlatinib does have a unique safety profile compared to other targeted therapies, *ALK* inhibitors and other targeted therapies. Importantly for the 7-year analysis, we did not see any new safety signals, so it is all the same [toxicities], but now seen over a longer period of time. The most common side effects that we saw in CROWN and that we see in our patients who are on long-term lorlatinib include hyperlipidemia, so that is elevated cholesterol and oftentimes elevated triglycerides. We also frequently see edema, often it is peripheral edema, neuropathy, weight gain over time, and I would say that does gradually worsen over time. Then notably for lorlatinib, which I do think really influenced its sort of lack of uptake early on, is that lorlatinib can cause neurocognitive and mood side effects. Those, in my experience, tend to persist or even slightly worsen over time. I would say that all of these are fairly manageable as long as both the provider, as well as the patients, are aware of them. I do a lot of counseling before patients start lorlatinib to review each of these and how we manage each of these. Obviously, something like hyperlipidemia tends to be almost predominantly just a laboratory abnormality that we are testing, following with labs, and of course, we can manage hyperlipidemia. We have a whole array of therapies that we can use, statins, ezetimibe, we can go out to PCSK9, and we have specialists who can help us in case there are challenges there. Some of the other side effects are a little more difficult to manage, the edema, for example, is one that does not tend to happen right away, but it does start a couple of months in, and it can really persist and just gradually worsen over time, requiring diuretic therapy, and even then, can be somewhat difficult to manage. I mentioned already weight gain, which also does not start immediately, but once it starts, it can just keep going, and we have patients who will gain 40, 50 lb over a several year period, which is quite significant. Oftentimes, it is definitely in that grade 3 range of weight gain.

I would say that overall, in terms of managing side effects, I think the most important thing for oncologists to recognize is that these are all dose-dependent side effects, and if there is something really bothering a patient, like the neurocognitive or mood side effects or the neuropathy that can happen with lorlatinib dose modifications, so holding the drug and actually going down on the dose of the drug can be really, really helpful. Yes, we can talk through all the different management we could do, but I also think a really important lever to pull to manage some of these side effects is actually dose reducing lorlatinib.

Jamie Chافت: You did present with this update that dose reduction and previously that the dose reduction does not impact efficacy. But I will ask you the more complicated, nuanced question of what is your starting dose? Do you start with 100 mg?

Journal Club Spotlights: Current Advancements in Non-Small Cell Lung Cancer



Alice Shaw: Exactly. This has been a very controversial topic. Having worked with lorlatinib for so long, I have to say my comfort zone is to start most patients at 75 mg. I have had enough experience at 100 mg, including in the context of trials, but also initially when it was first approved to see that at least in

the patients I treat, the majority of them will really struggle at 100 mg, and I remember I had looked at this early on, Jamie, that every one of my patients who had gone on 100 mg after we had been testing lorlatinib in the clinic for a few years, every single one of them had dose reduced within the first 6 months. I had some really tough challenges in those patients who started at 100 mg. My general practice is I will start most patients at 75 mg. If they do great, I will offer the option to go to 100 mg. I have only had literally 1 or 2 patients who have wanted to go to 100 mg, but that is an option. Oftentimes, patients are happy at 75 mg. Even at 75 mg, though, a lot of patients do need to go further down, and then we do go to 50 mg.

Jamie Chافت: I have had the same experience. Are you integrating GLP-1 [agonists] at all for the weight gain?

Alice Shaw: Well, absolutely, that is a hot topic of conversation, I am sure, with you and your patients, as well, on lorlatinib. Everyone wants to know. I do have a number of patients, actually not just on lorlatinib, but a lot of our therapies that can cause some weight gain, who are interested in GLP-1 agonists, and I have had quite a few go on. Typically, I am comanaging, though, with their primary care doctor or their endocrinologist. I am not the one prescribing. Curious if you do that? I have had patients on, and some have found a lot of benefit from being on a GLP-1.

Jamie Chافت: It is the first space where I have found comfort prescribing when there is limited access to other specialists, but I think it is going to become a bigger part of our practices moving forward.

Alice Shaw: For sure.

Jamie Chافت: Well, this has been a great discussion. I will just end with a last question about unmet needs. What is unanswered and where are we going from here?

Alice Shaw: I worry a little bit because everyone thinks, wow, look, data with lorlatinib is so amazing. We really do not need much more in the *ALK* space, and of course, we do. First of all, I already mentioned that we do not even have the overall survival results back yet from lorlatinib, so I would love to see that. In the future, Jamie, you asked a great question about managing toxicities, and when we use GLP-1 [agonists], I think all of that still could use further refinement. I also think some of the main questions have to do with what ultimately does drive resistance to lorlatinib. Unfortunately, many patients still will relapse on lorlatinib. It is over an extended period of time, which is awesome, but we still do have resistance to first-line lorlatinib that will emerge in quite a number of our patients. In fact, remember, 30% of patients progress in the first 2 years. So far, from the CROWN study and from some anecdotal reports, we really do not see *ALK* resistance mutations emerging to first-line lorlatinib, and that is very compatible with its mechanism of action. What we do see, though, are what we call *ALK*-independent mechanisms, so off-target activation, for example, amplification or other off-targets that can be activated, and unfortunately not always through genetic means, so we cannot easily identify them. I do think a huge unmet need is around patients who have been on first-line lorlatinib. What is the next best therapy for them, and do we fully understand resistance to inform the next line of treatments? I do not think we have an answer to that yet.

Journal Club Spotlights: Current Advancements in Non-Small Cell Lung Cancer



Jamie Chافت: I think early progression on any of our next generation *ALK* inhibitors is a huge struggle in the clinic. Well, thank you for all of your work in this space. Patients are lucky to have you at the helm here, and we thank you for joining us today.

Alice Shaw: Thank you so much, Jamie. It was a pleasure.