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COMMENTARY

Podcast on Lorlatinib as a First-Line Treatment Option for Patients with *ALK*-Positive Metastatic NSCLC with Brain Metastasis

Geoffrey Liu · Vincent K. Lam

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ABSTRACT

Brain metastases are especially common in anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer (NSCLC), with a cumulative incidence of over 50% and associated with a poor prognosis, high symptom burden, and decreased quality of life. Lorlatinib is a brain-penetrant, third-generation ALK tyrosine kinase inhibitor (TKI), which has a high potency against resistance mutations seen with earlier generation ALK TKIs. In 2018, lorlatinib was granted accelerated approval in second- and third-line treatment for use in patients with *ALK*-positive metastatic NSCLC on the basis of phase 1/2 study results. This initial approval was expanded for first-line treatment of patients with *ALK*-positive metastatic NSCLC on the basis of the interim analysis of the phase 3 CROWN study showing longer progression-free survival, time to intracranial progression, duration of response, and objective response rate compared with crizotinib. This manuscript is a transcript of our podcast, in which we discuss the clinical significance of controlling the onset of brain metastases, considerations in selecting a first-line therapy option, efficacy and safety observed in patients with and without brain metastases, and rationales for using lorlatinib upfront versus reserving for a later line in therapy.

Keywords: Lorlatinib; ALK-positive; Non-small cell lung cancer; Brain metastases

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G. Liu
Princess Margaret Cancer Centre, Toronto, ON, Canada

V. K. Lam (✉)
Johns Hopkins Medicine, 201 N. Broadway, Baltimore, MD 21287, USA
e-mail: vklam@jhmi.edu

Key Summary Points

Brain metastases are frequently observed at diagnosis and upon progression in patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (mNSCLC) and are associated with a poor prognosis, high symptom burden, and decreased quality of life.

Lorlatinib is a potent, brain-penetrant, third-generation ALK tyrosine kinase inhibitor (TKI), and is approved for the treatment of patients with ALK-positive mNSCLC.

This podcast discusses the clinical significance of brain metastases and impact on treatment selection.

The authors discuss the efficacy and safety of second- and third-generation ALK TKIs for patients with and without brain metastasis to explore considerations for selecting a first-line therapy.

DIGITAL FEATURES

This article is published with digital features, including podcast audio, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.23549364.

PODCAST TRANSCRIPT

Podcast Attendees:

Geoffrey Liu (GL): Princess Margaret Cancer Centre, Toronto, Canada.

Vincent Lam (VL): Johns Hopkins Medicine, Baltimore, USA.

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GL: Hello. My name is Geoffrey Liu. I'm a professor at the University of Toronto and the Alan Brown Chair and also a medical oncologist at the Princess Margaret Cancer Centre.

VL: Hi there. My name is Vincent Lam. I'm a thoracic medical oncologist at Johns Hopkins with a clinical and translational focus on *ALK*-positive lung cancer. Really delighted to be here today with you, Geoff, to discuss the emerging data for lorlatinib in *ALK*-positive lung cancer.

We will be reviewing the importance of treating or delaying the onset of brain metastases. Geoff, can you give a brief overview of brain metastases in *ALK*-positive lung cancer?

GL: I would love to, Vincent. Lung cancer can spread to the brain through the bloodstream and the central nervous system causing these brain metastases [1]. These metastases are common in patients with *ALK*-positive non-small cell lung cancer. These patients tend to be relatively young and have a more favorable prognosis than those with other forms of non-small cell lung cancer [2–5]. They can experience a significant increase in symptoms, including fatigue, shortness of breath, nausea, vomiting, and, of course, headaches [6]. Approximately a third of patients are diagnosed with brain metastases at the time of diagnosis [7]. It's actually quite a high figure. In patients without baseline brain metastases, delay of the onset of brain metastases is critically important since brain metastases are associated with poor prognosis, including decreased PFS [progression-free survival] [8–10], and can lead to neurocognitive dysfunction [6, 11–13]. And that can then impact patient quality of life. While we can treat brain metastases with a variety of tools, including radiotherapy, surgery, chemotherapy, and with symptom relief through steroids, these treatments can be associated with unwanted side effects [14–17]. They're not always effective and, in some cases, can be particularly highly invasive. And so, it makes treating brain metastases complex. Advances in targeted therapy have shown promising intracranial efficacy, and this may offer an additional therapeutic approach. Vincent, would you like to discuss the role of lorlatinib in patients with *ALK*-positive metastatic non-small cell lung cancer?

VL: Absolutely. Lorlatinib is a third-generation ALK TKI that was designed particularly to be brain penetrant with broad spectrum potency against ALK resistance mutations [18–20]. It attained accelerated second-line or third-line approval for use in patients with *ALK*-positive metastatic non-small cell lung cancer in the US in 2018, I believe, based on the phase 1/2 study results [21, 22]. Interim results from a subsequent phase 3 study, the so-called CROWN study, comparing lorlatinib and crizotinib in treatment-naive patients with *ALK*-positive metastatic non-small cell lung cancer [23], led to expanded approval to include front-line patients [22]. Initially, in the CROWN study, at 18 months of follow-up, lorlatinib significantly reduced the risk of disease progression or death by 72% based on a hazard ratio of 0.28 versus crizotinib [23]. Then we got longer-term data from the CROWN study that were recently presented with 3 years of follow-up showing that lorlatinib continued to show superior efficacy over crizotinib [24]. The median PFS assessed by independent review remained unreached for lorlatinib with a hazard ratio of 0.27 and a landmark 3-year PFS of 64%. Median time to intracranial progression was also not reached for lorlatinib with a hazard ratio of 0.08, which is really striking. So together, these data show unprecedented overall and intracranial PFS with lorlatinib in the front-line setting with no new safety signals.

But there remains a question of how best to choose an ALK inhibitor in the front line. The difficulty here is that there are no head-to-head studies between lorlatinib and these second-generation TKIs. Due to differences in study design, analyses, and patient populations, comparisons across these trials, as you know, have significant limitations. And so, doing these sorts of cross-trial comparisons is fraught with danger at times. Geoff, in your clinical practice, what is your preferred front-line treatment approach for patients with metastatic *ALK*-positive, non-small cell lung cancer and brain metastases?

GL: This is an important question and one that does not have a singular answer. But as I mentioned before, these brain metastases significantly impact our patients with *ALK*-positive non-small cell lung cancer. And in patients who have brain metastases at baseline, control of the disease is critical. So, this is an area of major discussion for our newly diagnosed patients. Typically, I do discuss the first-line ALK TKI options, including alectinib, brigatinib, and lorlatinib. In the recent publication that included data from 3 years of follow-up, the patients with brain metastases at diagnosis who received lorlatinib continue to benefit with a longer median progression-free survival, a longer time to intracranial progression, and an improved intracranial response rate compared to patients who received crizotinib [24]. There were 37 patients in the lorlatinib group and 39 patients in the crizotinib group in this analysis, and this is in line with the proportion of patients we typically observe having brain metastases at baseline with *ALK*-positive non-small cell lung cancer.

What is important to note is the median progression-free survival by blinded assessment was not reached in the lorlatinib group and the hazard ratio was 0.21. The intracranial objective response was a very high 83% with lorlatinib and the median duration of intracranial response, again, has not been reached yet. The median time to intracranial progression was also not reached with lorlatinib with a hazard ratio of 0.10. So, with that in mind, what data are available for the second-generation ALK TKIs, Vincent?

VL: For context, if we look at the latest data for lorlatinib, alectinib, and brigatinib, the results appear to favor lorlatinib in the front-line setting, particularly in patients with baseline brain metastases.

Let me briefly summarize these data for alectinib and brigatinib. For example, in the phase 3 ALEX study, alectinib showed a benefit compared to crizotinib. With a 3-year follow-up, median PFS, as assessed by investigators, and not independent review, was 25.4 months with alectinib and a hazard ratio of 0.37 [9]. Intracranial response with alectinib was 81% and median duration of intracranial response was 17.3 months [25].

Similarly, for brigatinib in the phase 3 ALTA-1L study, brigatinib showed superior efficacy versus crizotinib [8]. Now, with a follow-up of

about 40 months, median PFS there, as assessed by independent review was 24 months, with a hazard ratio of 0.29. The median duration of intracranial response in this study was 27.9 months with brigatinib. So, in patients with baseline brain metastases, looking at the data available for these three trials, the hazard ratios of the study drug versus crizotinib again were 0.21 for lorlatinib, 0.37 for alectinib, and 0.29 for brigatinib. With those data in mind, Geoff, what's your approach for front-line treatment in patients with brain metastases?

GL: Vincent, I always believe that numbers, by themselves, are only a part of the picture. In general, I tend to discuss with my patients the three options. I give them the information with the idea that my gut feeling is that lorlatinib, and with the data that's been presented, is probably the best in class amongst or between these three options. However, there are other considerations as well that need to be taken into account. Each of these drugs have different toxicities, and patients should have an option to actually select and choose not only on the basis of efficacy but also on the basis of toxicity as well, too. So, in general, I try to give the information to the patients in terms of both the expected benefit but also the potential side effects. And then we enter into a dialogue and sometimes some patients will basically say, "Why don't you choose?" And then I'm happy to do so.

In that case, over the last few months, I would have to say I've been leaning more and more towards lorlatinib in that setting. However, I also am cognizant of the fact that I've become more comfortable with the toxicities and side effects of lorlatinib, making it a little easier for me to choose it as an option. I think in the past, my tendency to choose the other drugs is because of the fact that I was more comfortable with their toxicities as well. Vincent, how do you approach the same question with your patients?

VL: Well, Geoff, I think you put it extremely well. It really encapsulates my approach as well in the front-line setting in these patients with brain metastases. Given its particular potency in the CNS, I do favor lorlatinib in this setting. Though, as you mentioned, we do discuss the specific pros and cons of each of these three drugs. In particular, the potential side effect profile differences. But it's pretty clear, I think, again, cross-trial caveats aside, that lorlatinib has particular potency in the brain. And so, we do give that strong consideration.

Interestingly, though, it's the neurocognitive side effects, which we'll talk about in detail later, it's these side effects that really are primary in our discussion about the toxicity of lorlatinib. And interestingly, and ironically, it's actually patients with brain metastases and potentially patients who've had prior radiation for their brain metastases that may be at increased risk for these neurotoxicities. And this is based on a retrospective analysis that was recently published. That's just one consideration that needs to be taken into account as we consider lorlatinib for these patients with baseline brain metastases. But what about patients without baseline brain metastases? We mentioned that brain metastasis is really a significant and major problem, particularly for this subtype of non-small cell lung cancer with a baseline CNS prevalence of about 30%. But what about the majority of patients that don't already present with brain metastases? What about those patients, Geoff?

GL: Well, I actually think that the data supports the idea that if you could delay the onset of brain metastases in this subset of patients, it will do a lot of good, particularly since they didn't start off with brain metastases. So, the longer you delay development of brain metastases, the more functional they are, the fewer symptoms and side effects that they have. I think it's really important to take into consideration the fact that we really need to be delaying brain metastases. That's why I've been really excited about the CROWN study in this particular population, because the data showed efficacy with lorlatinib compared to crizotinib in patients without brain metastases, with a progression-free survival that remains unreached in the lorlatinib group and a 3-year PFS of 68% [24]. The median time to intracranial progression was also not reached in the lorlatinib group with only one of 112 patients developing brain lesions. That's very remarkable. In other words, over 99% of patients were

alive and event free in the lorlatinib group versus 50% in the crizotinib group. So, these data suggest that lorlatinib may improve outcomes compared to crizotinib in patients without baseline brain metastases. Vincent, maybe you can also, despite the cross-trial comparisons, which we've heard all the caveats about, maybe you can talk a little bit about alectinib and brigatinib?

VL: Yeah. So, in the ALEX study, alectinib showed excellent activity in the brain as well, with a survival benefit compared to crizotinib in patients without baseline brain metastasis, as I mentioned. At the 3-year follow-up, median PFS was 38.6 months with alectinib [9] and at about 18 months of follow-up in the intent-to-treat population, time to intracranial progression was significantly longer with alectinib compared to crizotinib with a hazard ratio of 0.16 [25]. Now for brigatinib, in the phase 3 ALTA-1L study with about 40 months of follow-up, the brigatinib group had a hazard ratio for disease progression or death of 0.62 [8]. In these studies, the hazard ratio for progression or death of the study drug versus crizotinib, to summarize, were 0.29 for lorlatinib, 0.46 for alectinib, and 0.62 for brigatinib suggesting that they all have better efficacy in this population than crizotinib. Though, again, lorlatinib with what appears to be most favorable efficacy in these patients without brain metastasis, again, cross-trial caveats apply.

GL: Yeah. I'm curious to know what you would do, how you would approach patients without brain metastases in the setting, then?

VL: I'm with you. I think you emphasized that the effect is remarkable with lorlatinib. And in many ways, I think that that's the most compelling indication for the use of lorlatinib in the front-line setting in patients without brain metastasis. I mean, only one of 112 patients who did not have brain metastases eventually got brain metastases in the 3-year follow-up [24]. That is indeed remarkable. And that's something that we've seen with the second-generation TKIs. It remains to be seen how that may translate to overall survival, for example. But the quality of life and other clinical factors really makes a compelling case for prioritizing lorlatinib in the front-line setting. And, as I had mentioned earlier, conveniently it's actually patients without brain metastases that may actually end up having less of the neurocognitive side effects, based on a very exploratory, retrospective analysis. What are your thoughts about that approach, Geoff?

GL: I think that this is the group of patients that may potentially benefit the most. But my concern and questions still relate to the fact that neurocognitive side effects do occur, even if they occur less frequently, in this population with lorlatinib. So, I still need to have that discussion with my patients in that setting because there may be some neurocognitive side effects seen with this drug that you won't necessarily see with alectinib or brigatinib. So again, I would emphasize the fact that regardless of whether they have brain metastases or not, that central discussion with the patient, even if it is only 5 min or 10 min to find out what their feeling is towards these side effects and the potential benefits, is really important.

VL: Yeah, I would agree. As you know, one of the key things and active areas of investigation in this space is to try to identify which patients may be more predisposed to brain metastases, as opposed to those patients who may do just fine with potentially a less brain-penetrant drug and thus be able to be okay with taking a TKI that has less side effects. It's pretty clear, Geoff, that lorlatinib is quite effective and quite a potent ALK TKI but as we've touched upon on several instances now already, one factor in why everybody is not quite getting lorlatinib in the front line is its unique side effect profile. How does that safety profile impact your treatment decisions? I know you touched upon it a little bit in terms of the shared decision, and that's quite important.

GL: I'll give some data first and then I'll talk a little bit about my own feelings towards this. With 3 years of follow-up in the CROWN trial, lorlatinib had a similar safety profile compared to the 18-month interim analysis. Grade 3 or 4 adverse events (AEs) occurred in three-quarters of patients in the lorlatinib group versus 57% in the crizotinib group [24], a bit higher. Despite this higher incidence of grade 3 or 4 adverse events with lorlatinib, discontinuations were similar with 7% of patients discontinuing

lorlatinib and 10% discontinuing crizotinib due to adverse events.

But there's some unique aspects to these toxicities. For example, hypercholesterolemia and hypertriglyceridemia are the most common adverse events that occur within the first weeks of treatment with lorlatinib [24, 26]. And the grade 3 or 4 hypercholesterolemia occurred in roughly one in five patients, or 19% [24]. Similarly, with the hypertriglyceridemia, which occurred in 23% of patients. These events can usually be managed without the need for lorlatinib dose interruptions or reductions [24]. It is important, in that case, to monitor the cholesterol and triglycerides and to use lipid-lowering agents such as pitavastatin, pravastatin, or rosuvastatin, which should be initiated or increased to manage these lipid levels [22, 26]. And if you can't control it that way, you might need, at that point, to add in dose interruptions and perhaps even dose reductions, although that may very well be a fairly rare event that's necessary once you start the lipid-lowering agents [26]. So, I've talked a little bit about the cholesterol issues. Vincent, maybe you can talk a little bit about the CNS toxicities, which is kind of the thing that we and others are most concerned about or in the forefront of our minds when we're dealing with our patients.

VL: Yeah, that's correct. It is definitely the constellation of side effects that gets the most visibility. Rightfully so. The phase 1/2 study raised some of these concerns in terms of CNS toxicity, such as cognitive side effects, difficulty multitasking, slowed speech, short-term memory deficits, and mood effects [18, 22]. So, for example, 72% of the patients in the phase 1/2 study had brain metastases at baseline and 52% had two or more prior TKI treatments [18]. That may play a role in terms of the potential neurocognitive side effects that the patients in that study experienced. And, as I mentioned earlier, a recent retrospective study identified potentially brain metastases, prior radiation, baseline psychiatric diagnoses, or use of neurotropic medications as potential risk factors for these neurocognitive side effects on lorlatinib [27].

Based on the longer-term data from the CROWN study, again, with about 3 years of follow-up, the reported rate of CNS adverse events was 39% in patients treated with lorlatinib [24]. And the majority of these were low grade, as in grade 1 and 2. So, that was reassuring. Among the 103 treatment-emergent CNS adverse events, 59% of those patients required no intervention, 15% only required dose reduction, and an additional 14% required the addition of a concurrent medication to manage the side effect. Reassuringly, only 2% of CNS adverse events led to treatment discontinuation. Overall, 15% required dose reduction to 75 mg and 15% required dose reduction to 50 mg. So, that's definitely one of the strategies that we employ most often to manage these neurocognitive side effects. In a fairly small exploratory analysis, it did appear that these dose reductions do not compromise the efficacy [28]. But again, that was exploratory analysis. But it does provide some confidence that these dose reductions should be okay in terms of efficacy. Geoff, what are the adverse events for alectinib and brigatinib that you often discuss with your patients?

GL: Actually, that's a good point. Because each of these drugs has unique side effects and toxicities. None of these drugs are perfect by any means. I will comment just a little bit about what you've just said. When you hear the words, 39% have CNS adverse events and then majority are grade 1 or 2, I never understand what that means. What really matters to patients is not what grade of toxicity, but how it interferes with their function. I'm way more interested in the proportion of patients that required dose interruption and that is about one in seven, or 15%. So, I'm way more quoting that 15% than I am that 39%. I find that when you warn patients about these things, oftentimes they can compensate because they're aware of what's going on. And functionally, it doesn't bother them as much. And I think that's an important thing because I never understand what grade 1 or 2 CNS adverse events means. And my patients complain that they can't add things or they forget a few things, but it doesn't bother them very much. They use other tools to help them with memory and so forth. I think that part is an important aspect.

VL: Yeah, that's a great point, Geoff.

GL: As for what do I tell my patients about these other drugs? Well, I'll start off with the data. In the ALEX study, with the alectinib treatment, the most common grade 3 or greater adverse events were anemia, increased AST [aspartate transaminase], increased ALT [alanine transaminase], and pneumonia [9]. However, I do need to comment on the fact that sometimes it's the grade 1 side effects that bother the patients the most. Most of them are not bothered by the anemia. They get annoyed if I have to stop the drug because of elevated LFTs [liver function tests] or have to have dose interruptions, but it doesn't bother them. So, even though we're quoting grade 3–5 adverse events were similar between alectinib and crizotinib, roughly about 52–56%, and the AEs led to treatment discontinuation in 14% of patients in the alectinib group, the reality of the situation is that, for that drug, I often have to comment and warn patients about the weight gain, the peripheral edema, the muscle aches and pains, because those are the things that bother patients much more than the common grade 3 or greater adverse events, which many of them are paper toxicities.

With brigatinib treatment there is a grade 3–5 treatment-emergent AE in about 78% of patients in the brigatinib group compared with 64% in the crizotinib group [8]. And the most common grade 3 or greater treatment-related adverse events in the brigatinib group were, again, elevated CPK [creatine phosphokinase], increased lipase, and hypertension. And the adverse events led to treatment discontinuations in a very similar 13% versus 9% in the crizotinib patients. So, the concern that we almost always have to tell our patients about is the early onset pulmonary events—that shortness of breath and coughing that occurs within 1 or 2 days, typically, and up to 7 days after initiation of brigatinib that has to be monitored; there has to be warnings associated with it, but it's also manageable in that setting. It is important to note that interstitial lung disease or pneumonitis did occur in 6% of brigatinib patients versus 2% of crizotinib. So, I do warn my patients of not only the grade 3 or greater types of side effects but often the niggly side effects, the ones that are chronically difficult to manage because the patient is on the drug for months to years, that's often grade 1. And sometimes we forget to mention that. I think that's an important aspect. Vincent, what are your thoughts about that, as well? And then maybe you could talk a little bit about what you think is a rationale for using lorlatinib either immediately or maybe saving it for later line.

VL: I agree with the fact that the lower-grade, chronic side effects are just as important as the more visible or higher-grade side effects that often get mentioned the most. We talk a lot about the neurocognitive side effects. Again, for good reason. But in many ways, it's actually the longer-term, chronic, potential side effects of high cholesterol, edema, weight gain that also need to be discussed with the patients because those can have a longer impact and a potentially significant quality of life impact as well. And again, these side effects, like weight gain and edema are not necessarily exclusive only to lorlatinib. Some of these are class effects for the ALK TKIs.

But in terms of the rationale for using lorlatinib upfront in general in cancer, but specifically, oncogenic-driven, non-small cell lung cancer like ALK, we would love to and prefer using our best drug first—our most potent drug first. Because we have data that show that sequential use of TKIs does increase the risk of resistant, in the case of ALK, compound *ALK* mutations. So, if possible, we try to use our best drug first. Now, when patients progress on one ALK inhibitor, they may be able to receive another like alectinib then lorlatinib. But, as I just mentioned, that sort of sequence may increase patients' risk for difficult acquired resistance mutations. And then it's also important to note that not everybody that progresses, for example, on alectinib or brigatinib will do best with lorlatinib in the second line. If they do not have an actual acquired resistance mutation within the ALK kinase domain, lorlatinib may not be the best choice. It does make a compelling case for using lorlatinib upfront, with the toxicity concerns aside. And of course, we talked a lot about the efficacy data that supports the use of lorlatinib upfront as opposed to saving it for later, and especially the intracranial efficacy of lorlatinib with a time to intracranial

progression of just remarkable hazard ratios [24]. So, given these results, I think it really is compelling to prioritize lorlatinib upfront. Geoff, what are the efficacy results when used in the later lines?

GL: I think one of the important things to keep in mind is exactly what you said. If you can prevent something from occurring, if you can actually keep people going because you're using the most effective drug, then there's really a difficult argument to make why you want to save that drug for later and use something that may not be quite as effective. In this case, toxicity is something that, as we said, needs to be discussed with our patients. But, even then, I find that most of my patients, with a few exceptions, tend to favor really good, strong efficacy with the idea that we can manage the toxicities as we go along.

Evidence from the CROWN and the phase 1 and 2 trial for lorlatinib both demonstrated an incremental decrease in efficacy once you start adding more previous lines of ALK TKI before you get to lorlatinib [21, 24]. And so that is something that is important to keep in mind. That this is a bit of evidence to suggest that maybe, again, you should use your best drug first. And so, to summarize, the objective response rates and median PFS were higher with lorlatinib in the first-line setting compared to those who had one or more prior ALK TKIs. And similarly, the intracranial ORR [objective response rate] in patients with brain metastases at baseline started to decrease with the addition of more lines of prior ALK TKI therapy. So, these data from these studies support, in my mind, the fact that, exactly what you said, Vincent, that you really should go forward with your best foot forward first and your best drug, in this case. So, in summary, Vincent, what treatment would you suggest if a member of your family calls having just received a diagnosis of *ALK*-positive, advanced non-small cell lung cancer with brain metastases? I know that's completely an unfair question, but anyway.

VL: Well, I would point them to this podcast where we have highlighted the trade-offs in terms of efficacy and toxicity between the three different first-line agents and highlight the fact that this is a shared decision-making process. I do admit I am inclined for many patients now towards lorlatinib because as you said at the outset, as we get more and more comfortable with managing the toxicity, that is something that I'm more strongly considering. And then again, based on exploratory and emerging data, it may be even more compelling for instance, for patients with variant 3 *ALK* fusions. So, this is still an active area of research. But based on the data we have in front of us, the long-term data from the phase 3 CROWN study really do add to the body of evidence supporting robust intracranial efficacy of lorlatinib in patients both with and without brain metastases at diagnosis [24]. And also keeping in mind that alectinib and brigatinib also have demonstrated improved efficacy versus crizotinib in this patient population. So, definitely, those are all worth discussing.

GL: Well, thank you, Vincent. Ultimately, it is probably going to be important for us to continue discussing with our patients the risk/benefit profile of each of these options, and to take into consideration disease and patient-related factors, everything from performance status, extent of disease, tumor burden, comorbidities, degree of things like shortness of breath. If you're worried about use of it in a drug like brigatinib, for instance, or in patients who are already quite hefty in size, you may be worried about weight gain as well. Regardless, I would say that we've had a wonderful talk today and it's been a pleasure discussing the various treatment options for patients with or without brain metastases with you, Vincent.

VL: Likewise, Geoff.

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