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Practicing Precision in *ALK* and *ROS1* Rearrangement Positive NSCLC:

Testing, Targets, and Treatments

This transcript has been edited for style and clarity and includes all slides from the presentation.

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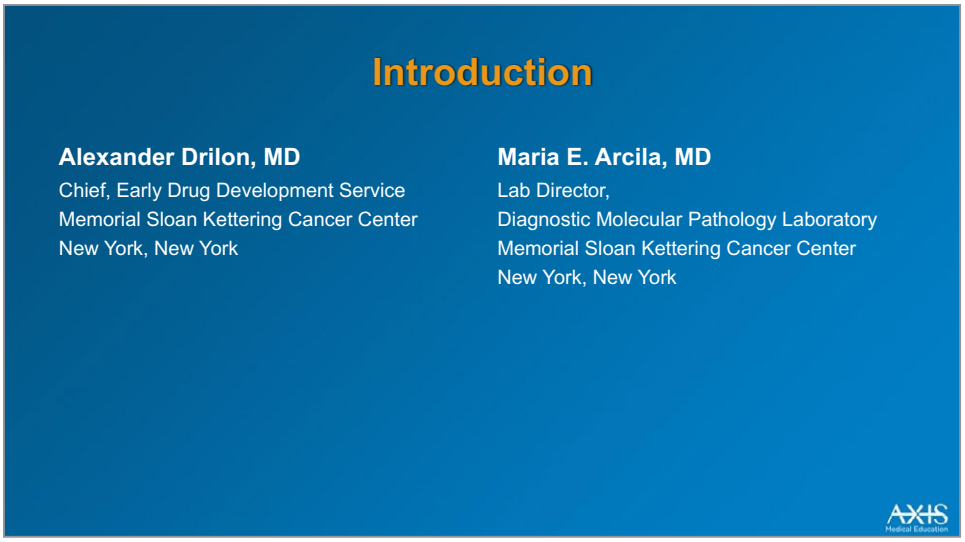
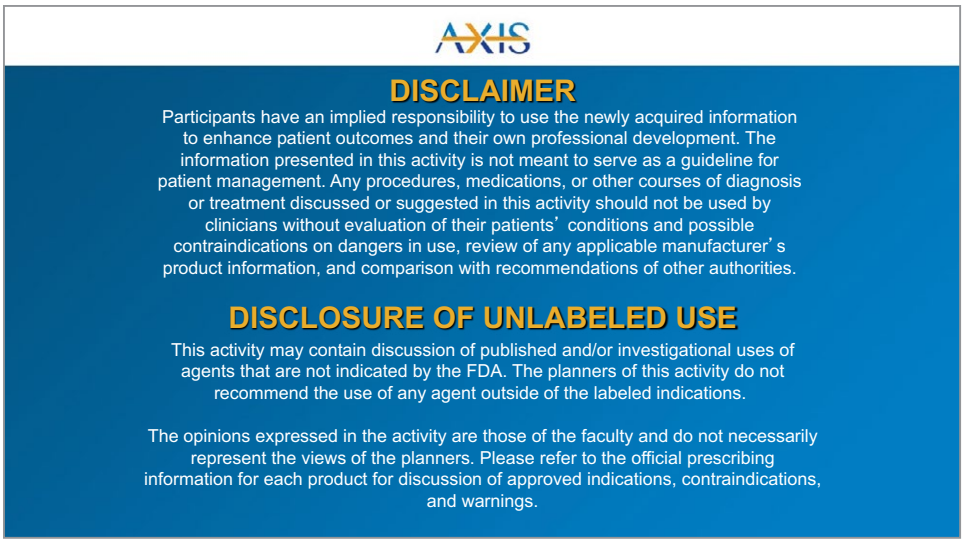
Practicing Precision in *ALK* and *ROS1* Rearrangement Positive NSCLC: Testing, Targets, and Treatments

Maria E. Arcila, MD; Alex Drilon, MD

Maria E. Arcila, MD: Hello, everyone, and welcome to this educational activity *Practicing Precision in ALK and ROS1 Rearrangement-Positive Non–Small Cell Carcinomas: Testing, Targets, and Treatments*.



I am Maria Arcila, and I am the lab director at Memorial Sloan Kettering Cancer Center in the Diagnostic Molecular Pathology Laboratory. I am joined today by Dr. Alexander Drilon, who is the chief in the Early Drug Development Service, also at Memorial Sloan Kettering.



- To start with, we have a few disclaimers and disclosures indicating that we may be discussing off-label usage of approved agents or agents that are in development.

- And also, we have our financial disclosure information for you to review.

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Evaluate the evolving science and guideline recommendations for molecular testing in NSCLC, including testing for *ALK* and *ROS1* rearrangements
- Apply appropriate treatment selection of *ALK* and *ROS1* targeted agents based upon efficacy data, recommended guidelines, and biomarker testing results to improve patient outcomes
- Implement strategies to incorporate best practices for molecular testing, and biomarker-guided personalized treatment decision-making, and sequencing across the continuum of NSCLC care
- Identify factors that act as barriers or challenges to appropriate use of biomarker testing and strategies to address and optimize treatment outcomes for patients with NSCLC who harbor actionable mutations

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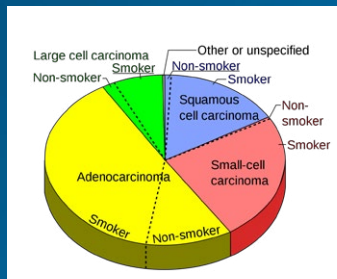
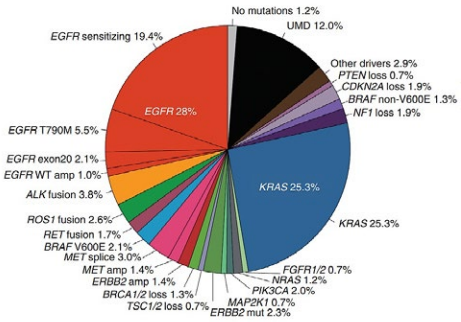
And here are the learning objectives for this activity.

Lung Cancer: Molecular Heterogeneity

NSCLC is Heterogenous



Biomarker Distribution in Adenocarcinoma



Häggström M. 2014. https://upload.wikimedia.org/wikiversity/en/7/7b/Medical_gallery_of_Mikael_H%C3%A4ggstr%C3%B6m_2014.pdf; Jordan et al. *Cancer Discov*. 2017;7(6):596-609.

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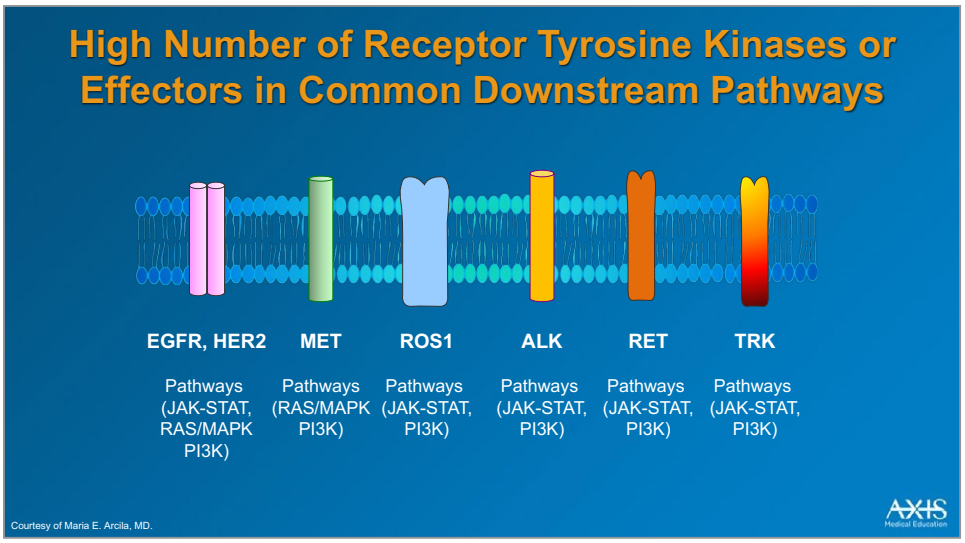
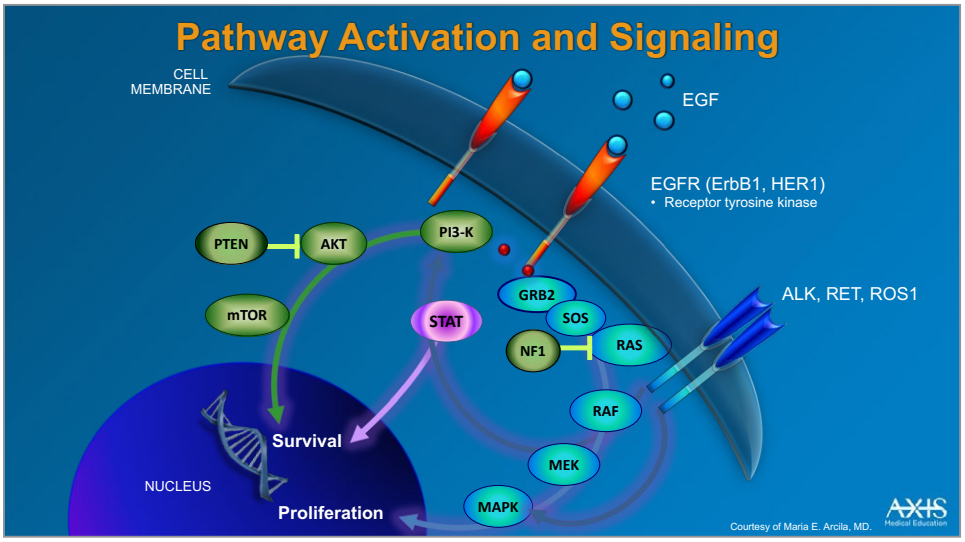
All right, so, as you all know, lung cancer is a highly heterogeneous disease that historically has been classified based on the morphologic and immunophenotypic attributes of the cancer. Non–small cell carcinoma constitutes the largest proportion of lung cancers, and within this category, adenocarcinoma is the largest subtype. However, in the past decade, there have been major advances in molecular biology and diagnostics that have enabled a more precise classification now based on molecular attributes of the tumor. So, on the right of this slide, what you see is this subclassification of adenocarcinoma tumors based on the genetic alterations.

While there are numerous genetic abnormalities that have been reported in recent years, only a proportion of these constitute the well-characterized driver oncogenes. It is these drivers, the ones that have moved the science forward, that are the key targets that may be treated with alteration-specific therapies. Common genetic alterations in lung cancer include *EGFR* and *KRAS*, and those together constitute about 50% of the alterations that are identified in adenocarcinoma. However, after these, there are several alterations that each correspond to about 1% to 3% of the alterations in lung cancer, but these are equally targetable. So it is, of course, very important to test for them.



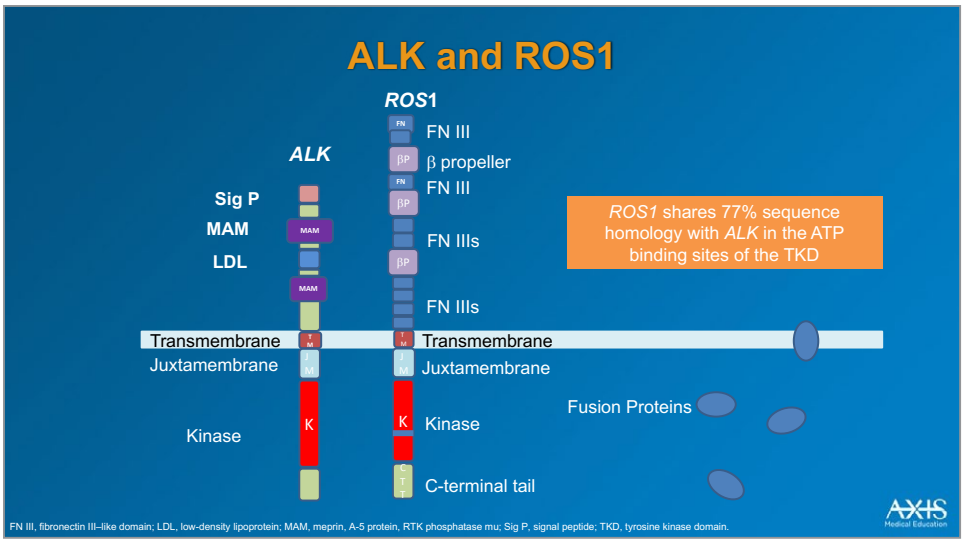
- A high number of the alterations that are targetable in lung cancer happened to be in receptor tyrosine kinases, and the remaining are identified in the effectors of common downstream pathways that are associated with those kinases. Mutations in *EGFR* have been well known for over a decade. But more recently, fusions and rearrangements involving genes such as *ROS1* and *ALK, RET*, and *NTRK* and rearrangements in *MET* as well have been identified. So that's going to be the topic for us today.



- So very briefly, as far as biology is concerned, all of the genes that I've mentioned have common signaling pathways where alterations that dysregulate their function can have a major impact on the cells. Very briefly, starting in this diagram with the pathway and activation and signaling that is associated with the mutations and the fusions that we're going to talk about, we can start with the EGFR pathway, which is common for all of them.

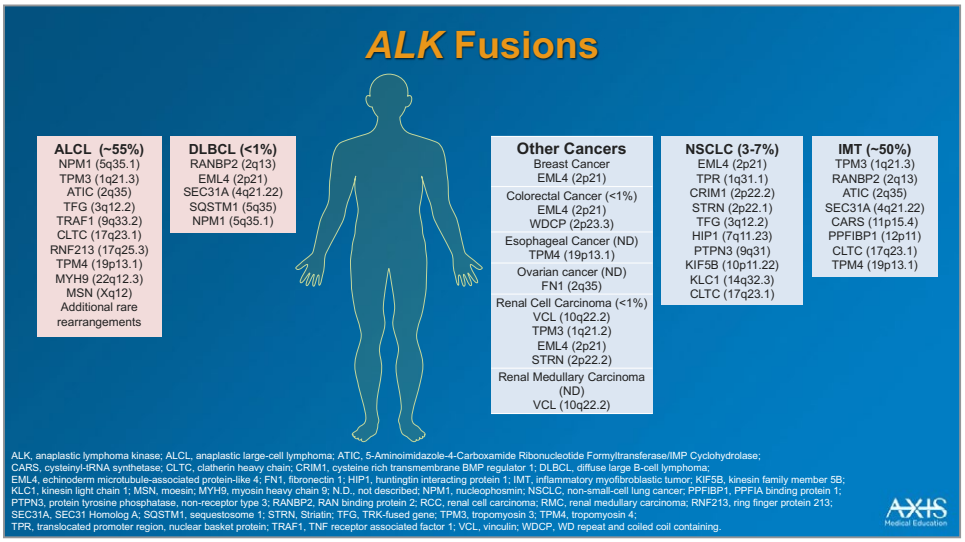
EGFR is a kinase that is bound to the cell membrane and in normal cell function dimerizes after it is bound to its ligand. Following dimerization and phosphorylation of these dimers, this activates several downstream pathways, primarily three pathways: PI3 kinase, STAT, and RAS/MAPK. And the signals from these three different pathways travel to the nucleus where they promote the survival and proliferation of the cells. This is, of course, a very highly regulated type of pathway–or these three pathways are highly regulated, and any mutation or fusion can cause disorganized proliferation and the development of a neoplastic process.

ALK, RET, and ROS are similar membrane-bound proteins or receptors that dimerize and after ligand binding physiologically, they can activate exactly the same pathways as EGFR.

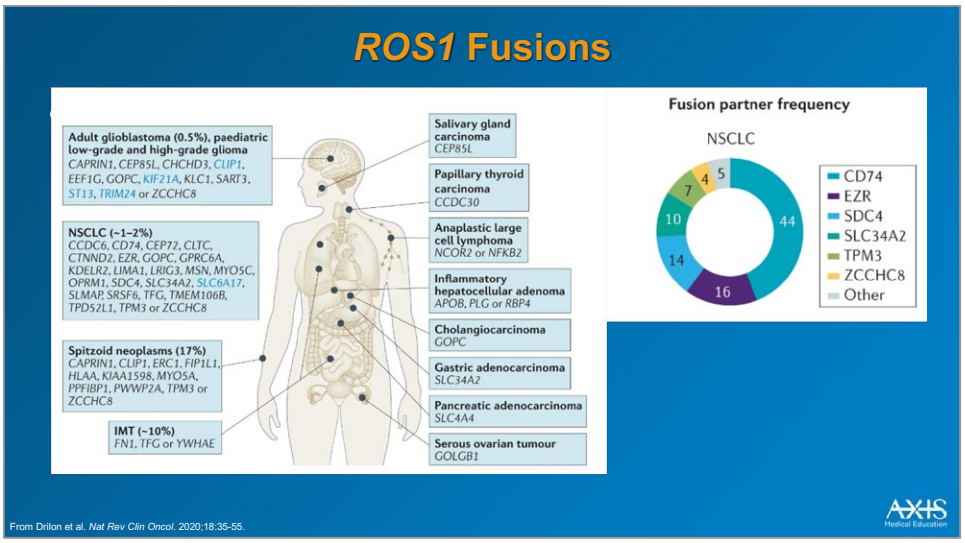


So today, again, we're going to be concentrating on ALK and ROS, and both of these receptors happen to be in the insulin family of receptors. They both have a number of domains in the extracellular compartment of the cell and a very large kinase domain in the intracellular compartment and also a transmembrane domain that maintains the molecule stably bound to the membrane. Importantly, *ROS1* shares about 77% to 80% sequence homology to ALK in the ATP binding site of the tyrosine kinase domain, and this is actually responsible for the observation that some ALK inhibitors may profoundly inhibit ROS1 kinase activity and lead to tumor progression.

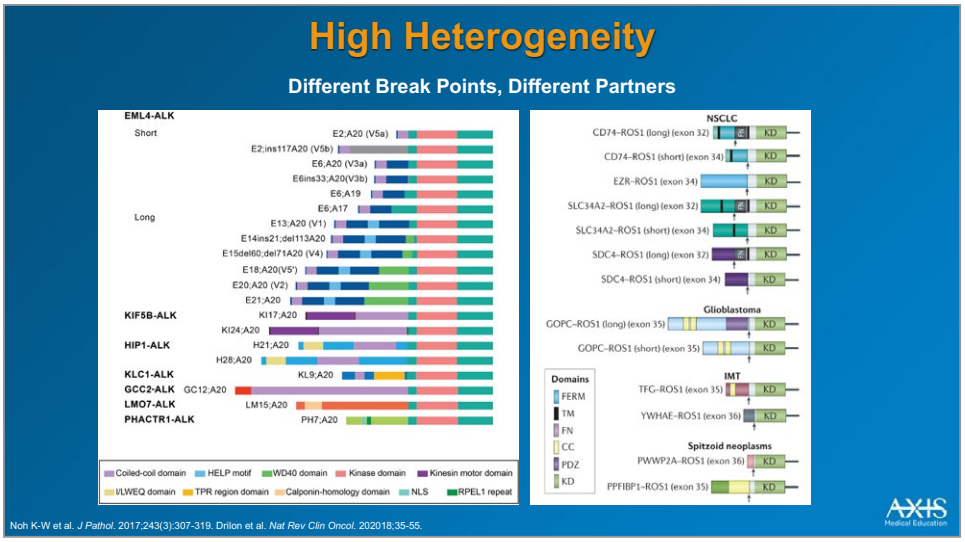
Both of these genes may be rearranged, and in the process of rearrangement they actually lose the attachment to the cell membrane, so that the fusion is now a fusion protein that now lives in the cytoplasm or even in various other compartments of the cell, depending on the partner, and the function of that fusion changes depending on the partner that they are bound to.



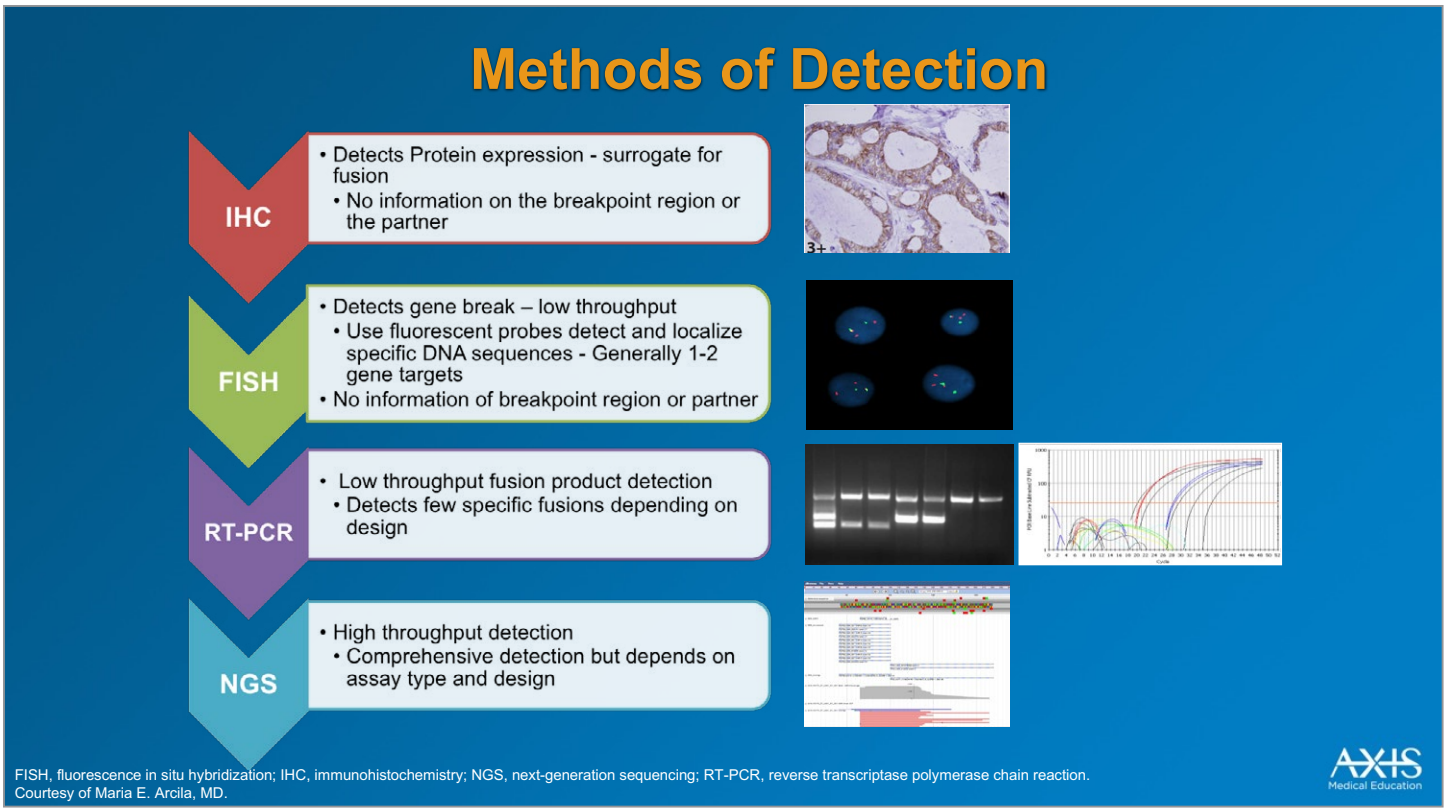
ALK fusions are not only found in lung carcinomas, but also first described in anaplastic large cell lymphomas and hence the name ALK, which stands for anaplastic lymphoma kinase. Fusions involving this gene may be identified in several malignancies and some with predilection for specific partners. They may be identified in lymphomas of different kinds, they could be identified in several solid tumors, and are particularly prevalent in inflammatory myofibroblastic tumors, for example.



- *ROS1* fusions may be identified in several solid tumors, and the highest number of partners has been reported in non–small cell cancers, which actually makes the biology and the detection of these fusions within lung cancer quite difficult, which we're going to talk about a little bit more in the next few slides.



- So *ROS1* and *ALK* fusions and their accompanying proteins end up being highly heterogeneous because of all of the partners that they can associate with. The most important thing, however, is that in all of the rearrangements, it actually requires that the fusion protein has a kinase domain that remains functional. So while the kinase domain remains functional and remains intact, then the associated portion of the different genes that become the partners of these fusions are the ones that add the heterogeneity to these tumors.

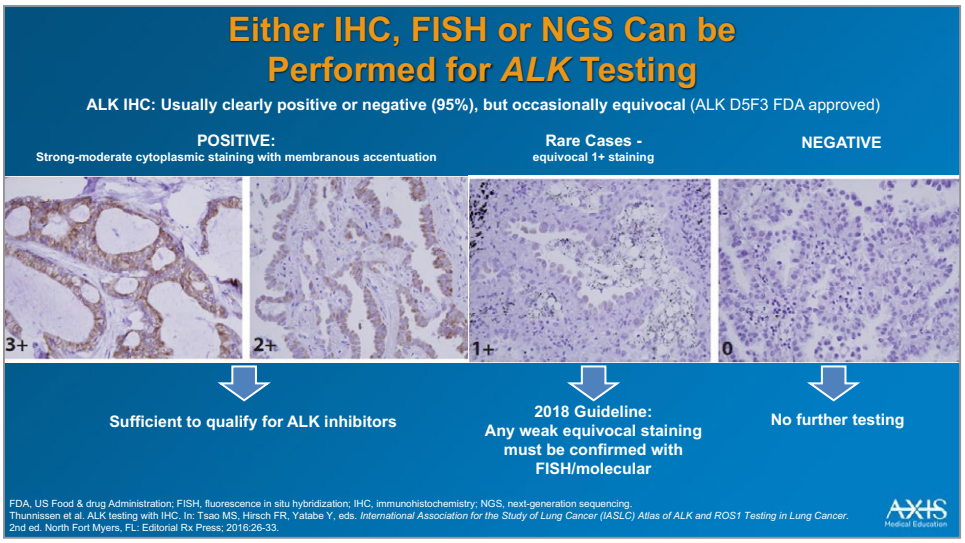


So given the very high heterogeneity that these tumors have and the location of the fusion within the cell and whether they in the cytoplasm or remain bound to the cell membrane, testing actually may not be as simple as one would think. There are four main methods that are used right now to test this in clinical laboratories, one of them being immunohistochemistry and which does not test for the genetic fusion, but tests for expression of the protein, either on the cell membrane or within the cytoplasm. So it is used as a surrogate for the presence of a genetic fusion, but this provides no information on the partner or the breakpoint region.

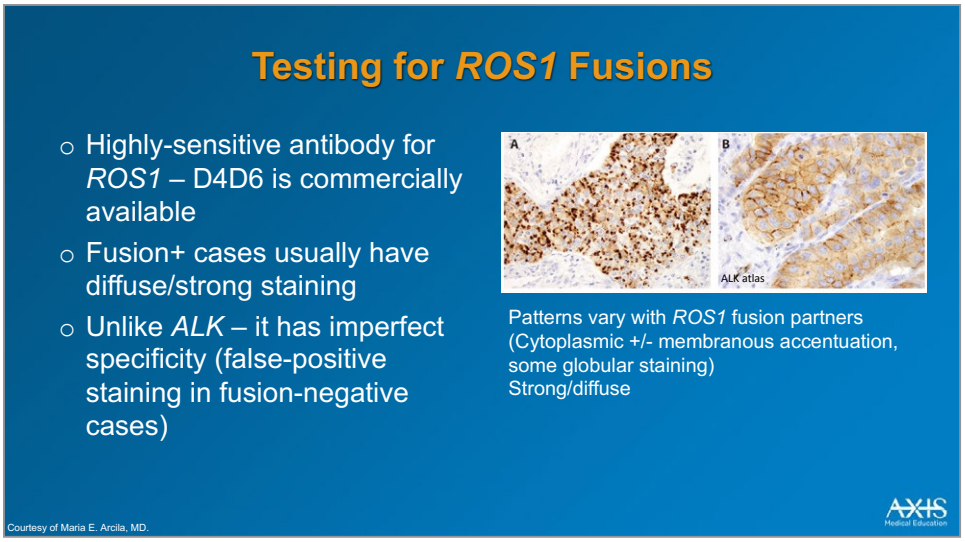
On the other hand, you could use fluorescent in situ hybridization (FISH). This is a molecular method that is very good, but is very low throughput, and it detects the gene break, but it doesn't detect what the partner is. So, with no information on the partner of the breakpoint region, it may not necessarily reflect the entire biology or whether the fusion itself or the break is a functional break or not.

And then on the other hand, you can have assays that test with polymerase chain reaction (PCR) or with amplification and sequencing, and those will be real-time PCR and the next-generation sequencing methods. Both methods are good, except that one of them is low throughput. So real-time PCR or quantitative PCR is a low-throughput method that is designed to be specific for the fusion that is known. As I already explained, sometimes you just do not know the partner. So it decreases the sensitivity of the assay to detect every single fusion that is present.

On the other hand, you could do next-generation sequencing, which is the preferred method because it can detect many of the fusions very broadly, some of them not necessarily knowing the partner. But the identification of the fusions fully depends on the design of the assay, and not all next-generation sequencing assays are created equal. So, when testing for fusions, it is very important to understand the pros and cons of the specific assay that is being performed either in a local lab or in a laboratory that you're sending out to.

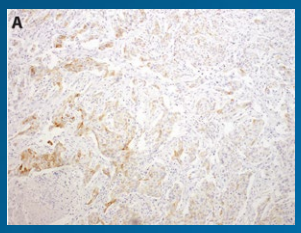


- Very quickly, either immunohistochemistry, FISH, or next-generation sequencing can be performed for all testing. Immunohistochemistry (IHC) is very rapid and provides an excellent assessment for fusions with nearly 100% sensitivity and specificity. Cases that are positive by IHC, they are either truly positive or truly negative, and there are only rare cases that have a weak positivity; however, these must be confirmed with another method, either FISH or a molecular assay from the ones that I just explained.



- On the other hand, *ROS1* is not as easy to test with IHC. IHC usually would show if you have a fusion, a very strong staining, and it is highly sensitive, but the specificity is not as high. So unlike ALK IHC, you can have many false-positive results. And then depending on the partner, you can have a distribution of staining that may be either membranous or cytoplasmic or globular, and it could be very strong or diffuse. And this is actually reflecting the biology of these tumors and which one is the partner that that *ROS1* gene is associating with.

ROS1: Nonspecific Staining in Fusion-Negative Cases



- Nonspecific staining is typically patchy and weak
- Rate of nonspecific staining reported as 5%-10% (higher if focal staining is included)

IASLC Guidelines	
ROS1 testing must be performed on all lung adenocarcinoma patients, irrespective of clinical characteristics	Strong recommendation
ROS1 IHC may be used as a screening test in lung adenocarcinoma patients; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method.	Expert consensus opinion

IASLC, International Association for the Study of Lung Cancer; IHC, immunohistochemistry.
Tsao et al eds. *International Association for the Study of Lung Cancer (IASLC) Atlas of ALK and ROS1 Testing in Lung Cancer*. 2nd ed. North Fort Myers, FL: Editorial Rx Press; 2016:26-33.

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- Many cases can actually have nonspecific staining, and this is associated with a very high intrinsic expression of wild type *ROS1*. So for these reasons, the current guidelines recommend that *ROS1* should only be used as a screening method, but any type of positive result must be confirmed with a molecular or cytogenetic method.

  So, I am happy to welcome Dr. Alex Drilon to help us with the next session.

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Faculty Roundtable Discussion 1:

The Roadmap to Best Practices for Biomarker Testing

- **Alexander Drilon, MD:** Thanks very much, Dr. Arcila, for a really wonderful talk. I will very briefly go through a few questions, which I'm sure our listeners will be interested in. So the first, of course, would be which testing platform is preferred to interrogate these cancers genomically, not just for *ROS1* and *ALK*, of course, but considering the broader landscape of other oncogenes that might be actionable.

  Arcila: So usually the testing platform, because it's lung carcinoma, you have so many genes that you have to test for, a next-generation sequencing assay is the best way to go so that you can test everything up front. And because you need tissue for the initial diagnosis, it is preferred that you test tissue first, because you can have a morphologic correlate to the diagnosis that you're making.

  But, of course, if you do not have tissue, plasma-based testing could be performed, but the assay has to be created in such a way that you can detect fusions, which may not necessarily be the case, because you have to flank specific regions, and you have to target those intronic regions as well as detect them.

  As far as the next-generation sequencing test itself, you can do this with either DNA or RNA. And some fusions can be detectable by a DNA assay when it is very well targeted, and it also has a design that will detect most of these fusions. In the absence of a fusion by DNA, my recommendation would be that you reflex that to an RNA assay, where you may be able to find a fusion that perhaps didn't have a partner that was targeted by the DNA assay.

  RNA assays can come in many flavors, and there are some assays that will detect the fusions regardless of the

partner that they have. There are three, four different types of assays that you could use. So again, to reiterate what I said, it is very important that you actually know when you're testing these that the assay is created to detect the fusions and in a broad and sensitive way.

So, Dr. Drilon, as you know, turnaround times for testing have historically been very challenging. In your clinical practice, what are some of the strategies that you integrate to improve the receipt of testing results, or what do you typically do while you wait for these results when you know that they're going to take a long time?

Drilon: Yeah, it really takes a more global view of what's going on with a patient. If it's someone that's very sick, then obviously we rely on rapid tests. You mentioned the turnaround time of plasma-based testing, but then there are also the ALK D5F3 stain, which you mentioned, where you can get an answer very quickly. In those cases, if you identify a driver, you move to targeted therapy.

But in cases where you can't wait, then you will want a systemic therapy like chemotherapy plus/minus immunotherapy that can be very active. However, if a patient can't wait for more comprehensive testing, then that's always the preferred route because you can choose the best first therapy to start. And if you identify an oncogene that can't be identified in early testing, then you at least triage your patient to the best possible treatment up front.

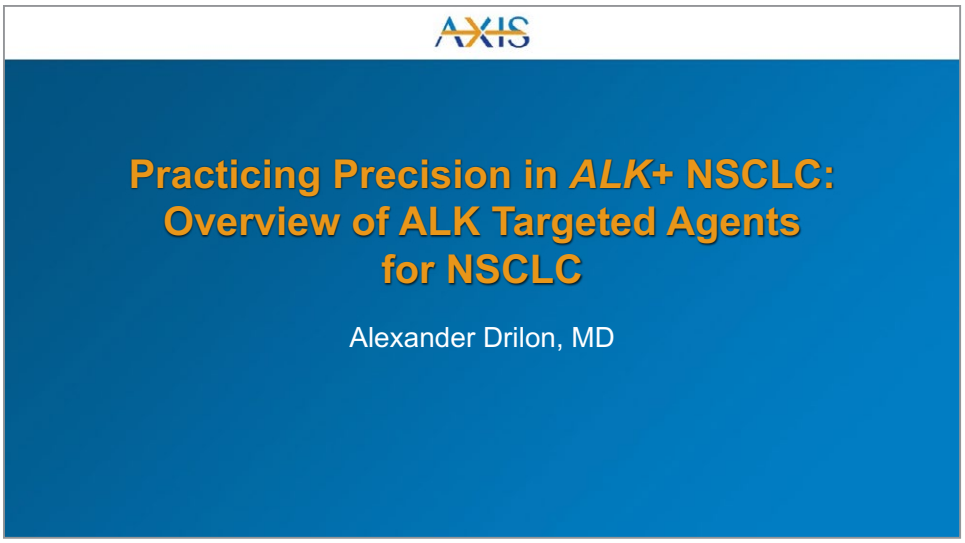
Arcila: Alex, what do you do when a patient presents with suspected resistance? We know that there are some fusions that can actually appear at the time of resistance. How does this impact your approach in retesting the patient?

Drilon: The first thing I'll say is that this hasn't found its way into the guidelines and with very strong language. Definitely, a lot of the guidelines revolve around early testing to identify these drivers. But we know the utility of interrogating the genome, again, of these cancers in the setting of resistance, because especially if you find on-target mechanisms like acquired kinase domain mutations, there are next-generation agents designed to be active against these mutations. And we've seen clinical proof of principle across different fusion types of patients responding when they hop from one pill to another. So my personal approach is to resequence a biopsy and/or do plasma circulating cell-free DNA to see which of these resistance mechanisms can help triage your patient to one therapy over another.

Arcila: What are the challenges, if any, that you face when it comes to navigating the insurance coverage for things that are not getting the guidelines and reimbursement with regards to molecular testing in this setting?

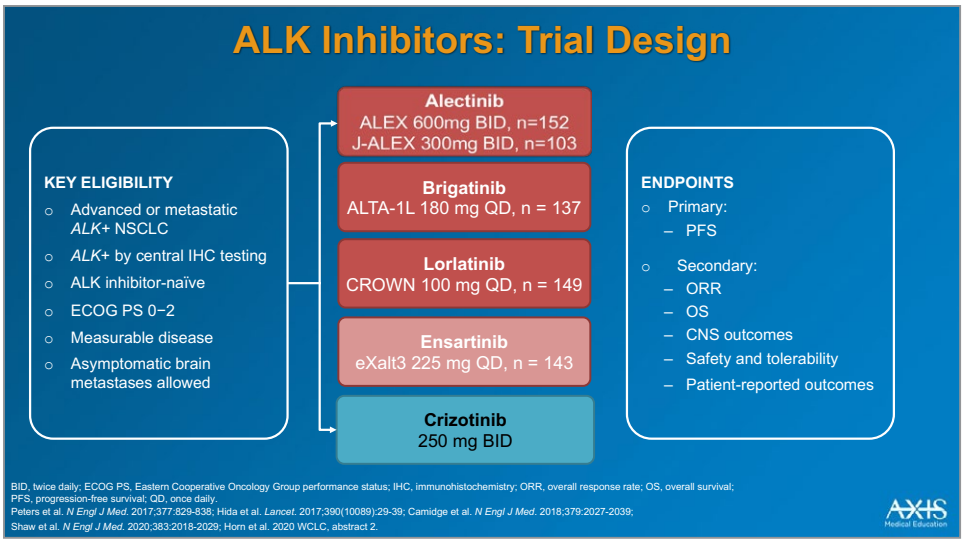
Drilon: Thankfully, we've seen a trend toward less of that. Less and less we've had to deal with challenging insurance denial. But of course, there are situations where certain payers don't provide coverage, and often we have to write letters of medical necessity, etc. I think that if despite all of that you're unable to get coverage for molecular testing, thankfully, a lot of clinical trials offer testing. Many of these are being done in the metastatic state, but some are even doing it for earlier stage disease for the neoadjuvant or adjuvant therapy. So there are other channels or avenues to potentially explore if you can't get coverage by insurance.

Arcila: Great, thank you so much.



Drilon: All right. So now we move into the treatment section where we're going to first focus on targeted therapy for *ALK* fusion positive lung cancers.

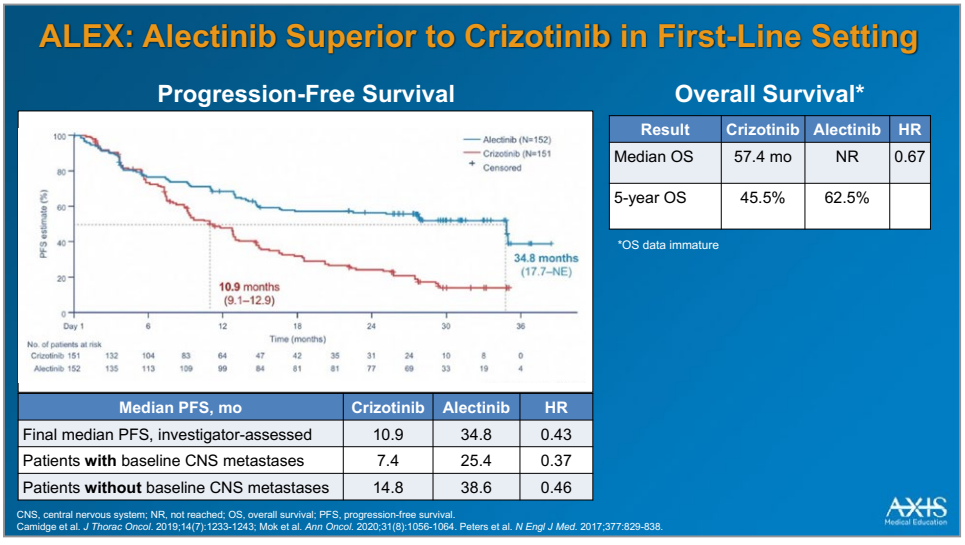
And the first major section deals with first-line tyrosine kinase inhibitor (TKI) therapy. Here, we're going to examine the design of the regulatory data sets that led to the approval or the presentation of the first major data sets for many of these agents.



So here we have on this slide a summary, a schema of many different trials put together. This really highlights that there's a common or shared study design among these regulatory trials. And you'll note on the left that we have patients obviously with a bona fide *ALK* fusion–positive, non–small cell lung cancer, good functional capacity, and who are treatment-naive with measurable disease.

And you have the different trials here seen in dark or light red. In the dark red, you have the trials that led to the FDA approval of these TKIs. In the light red, you have a trial of a drug that's been reported but does not yet have approval within the United States. For alectinib, you have the ALEX and J-ALEX trials; and brigatinib, ALTA-1L; lorlatinib the CROWN trial; and for ensartinib you have eXalt3. And each of these TKIs was randomized, so patients were randomized either to this next-generation TKI or to the former standard of care, which is the first-generation TKI crizotinib.

Another shared feature would be the primary endpoint, on the right, of progression-free survival, with the typical secondary endpoints of response survival, CNS outcomes, and safety, that we're going to go through in the next couple of slides.



So starting first with alectinib in the ALEX trial, the topline result here is that if you look at the progression-free survival, alectinib in the blue versus crizotinib in the red, you can drive a truck through these Kaplan-Meier curves, showing that there are meaningful improvements in progression-free survival with alectinib, where you have a median of almost 35 months compared to a median progression-free survival of almost 11 months with crizotinib. Now that occurred in patients with and without CNS metastases, the benefit where you saw the difference or the divergence.

J-ALEX: Progression-Free Survival

PFS (IRF-assessed)	Crizotinib	Alectinib
Median PFS, mo	10.2	Not reached
HR	0.34	
P	<.0001	
Final median PFS, mo	10.2	34.1
HR	0.37	

IRF, independent review facility; PFS, progression-free survival.
Hida et al. *Lancet* 2017;390(10089):29-39; Nakagawa et al. *Lung Cancer* 2020;139:195-199.

- And here you see in the Japanese trial, called J-ALEX, a similar result, where you see that the hazard ratio for alectinib versus crizotinib was a very nice number at 0.34 and 0.37 for the IRF-assessed median progression-free survival, and actually the final median progression-free survival in this trial, just showing again that next-generation ALK TKI therapy beats early generation TKI therapy with crizotinib.

ALTA-1L: Progression-Free Survival
Brigatinib Superior to Crizotinib in First-Line Setting

PFS	Crizotinib	Brigatinib
First prespecified interim analysis BIRC-assessed estimated 12-month PFS, %	43%	67%
HR	0.49	
P	<.001	
Second interim analysis BIRC-assessed median PFS, mo	11.0	24.0
HR	0.49	
P	<.0001	
Second interim analysis investigator-assessed median PFS, mo	9.2	29.4
HR	0.43	

BIRC, blinded independent review committee; PFS, progression-free survival.
Camidge et al. *N Engl J Med*. 2018;379:2027-2039; *J Clin Oncol*. 2020;38:3592-3603.

- Moving through different TKIs, we're next going to look at the data for brigatinib, and this was the ALTA-1L trial. And while this table looks different, the punch line here is the same, that brigatinib did beat out crizotinib in terms of progression-free survival in several other outcomes on this study. And here you see a hazard ratio of 0.49 marching through the different prespecified interim analyses.

CROWN: Progression-Free Survival

PFS	Crizotinib	Lorlatinib
BIRC-assessed median PFS, mo	9.3	NR
HR	0.28	
P	<.001	
12-month PFS, %	39%	78%
HR	0.28	
P	<.001	
Investigator-assessed 12-month PFS, %	35%	80%
HR	0.21	

BIRC, blinded independent review committee; NR, not reached; PFS, progression-free survival.
Shaw et al. *N Engl J Med.* 2020;383:2018-2029.

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- Now we move to the third drug, lorlatinib, on the CROWN trial. And this was obviously a more recent presentation following on the heels of the alectinib and brigatinib presentations and publications. But again here, you see that with this third-generation ALK TKI lorlatinib, the hazard ratio is even lower at 0.28 compared to crizotinib. Again, with the smarter design of these next-generation TKIs, which were built to include CNS coverage and activity against certain resistance mutations, we know that the preferred strategy is to reach for one of these next-generation TKIs.

ALK+ NSCLC: First-Line ALK Inhibitor Summary

	Alectinib		Brigatinib	Lorlatinib	Ceritinib	Crizotinib
Trial	ALEX	J-ALEX	ALTA-1	CROWN	ASCEND-4	PROFILE 1014
Comparator	crizotinib		crizotinib	crizotinib	chemotherapy	chemotherapy
Median PFS, months	34.8 (HR 0.43)	34.1 (HR 0.37)	24.0 (HR 0.49)	NR (HR 0.28)	16.6 (HR 0.55)	10.9 (HR 0.45)

Mok et al. *Ann Oncol.* 2020;31:P1056-1064; Nakagawa et al. *Lung Cancer* 2020;139:195-199; Camidge et al. *J Clin Oncol.* 2020;38:3592-3603; Shaw et al. *N Engl J Med.* 2020;383:2018-2029; Soria et al. *Lancet* 2017;389:917-929; Solomon et al. *N Engl J Med.* 2014;371:2167-2177.

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- This next slide shows you all of the TKIs stacked side by side. On the far right you have the first-generation drug crizotinib in the PROFILE 1014 study, and then moving from right to left you have ceritinib in the ASCEND-4 study—we didn't discuss that today. As you can see here, this is an agent with intermediate activity between crizotinib and the three other drugs we discussed previously.

  But if you look at the FDA-approved agents alectinib, brigatinib, and lorlatinib, you'll see very nice hazard ratios that are well below 0.5. In fact, with lorlatinib you're seeing the hazard ratio go to 0.28. So the punch line for practitioners is that these TKIs are available for use, and maybe in the questions we can get into how to choose these agents or choose from these different agents.

eXalt3: Progression-Free Survival

PFS	Crizotinib	Ensartinib
ITT population BIRC-assessed median PFS, mo	12.7	25.8
HR	0.51	
P	<.0001	
Modified ITT population BIRC-assessed median PFS, mo	12.7	NR
HR	0.51	
P	.001	

- ITT population: patients with locally tested ALK+ NSCLC
- Modified ITT population: all centrally ALK+ patients by Abbott FISH test

BIRC, blinded independent review committee; ITT, intention to treat; PFS, progression-free survival; NR, not reached.
Horn et al. 2020 World Conference on Lung Cancer. Presidential Symposium. Abstract 2.

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- We shouldn't forget also the eXalt3 trial which looked at ensartinib, also a next-generation TKI with similar results or better than crizotinib.

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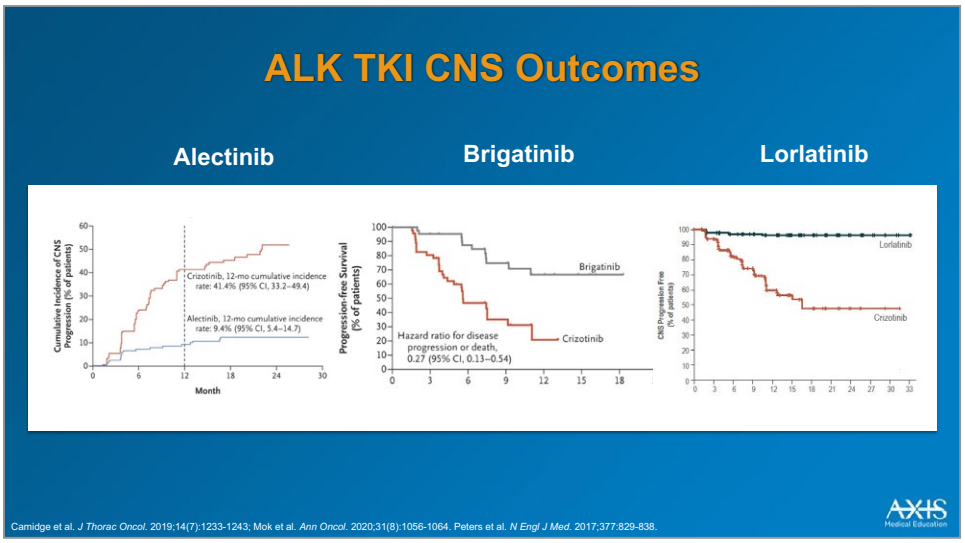
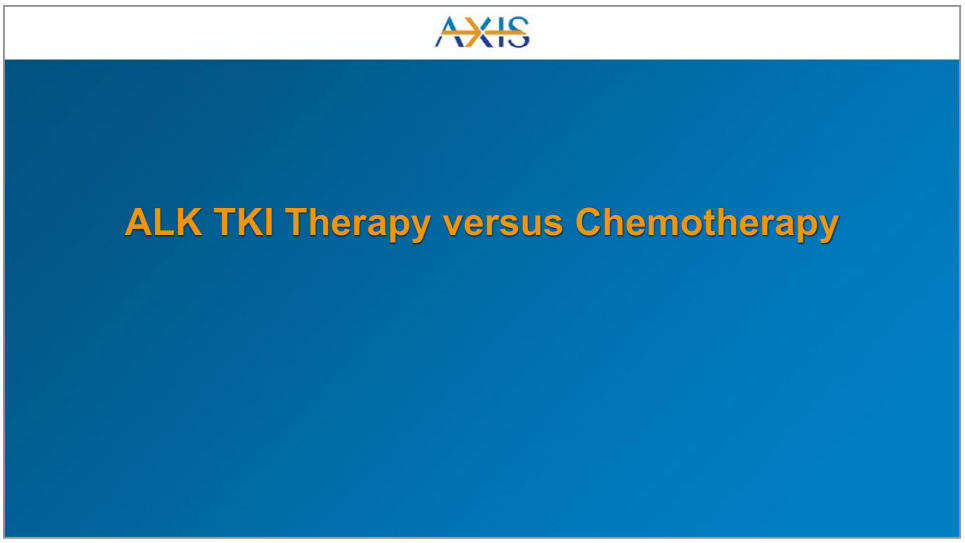
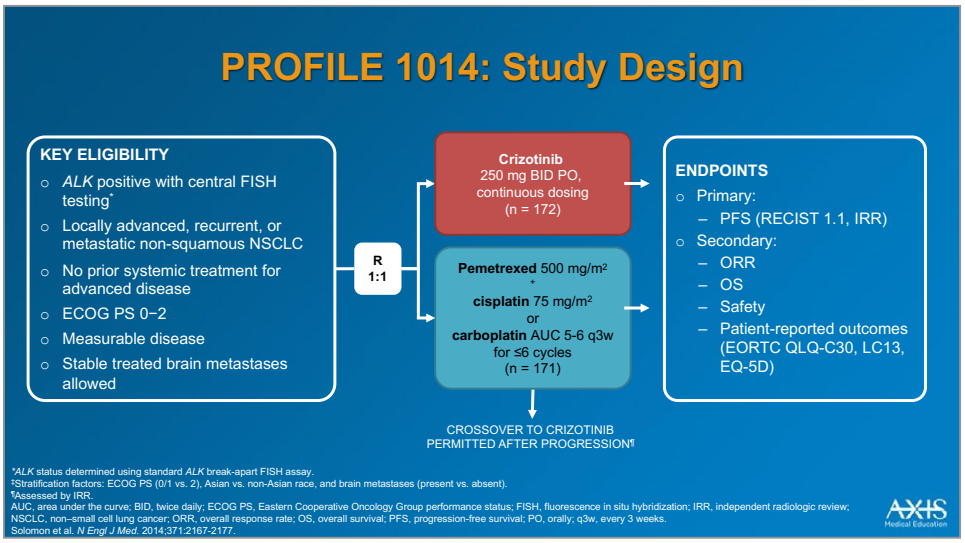
CNS Activity of Next-Generation ALK Inhibitors

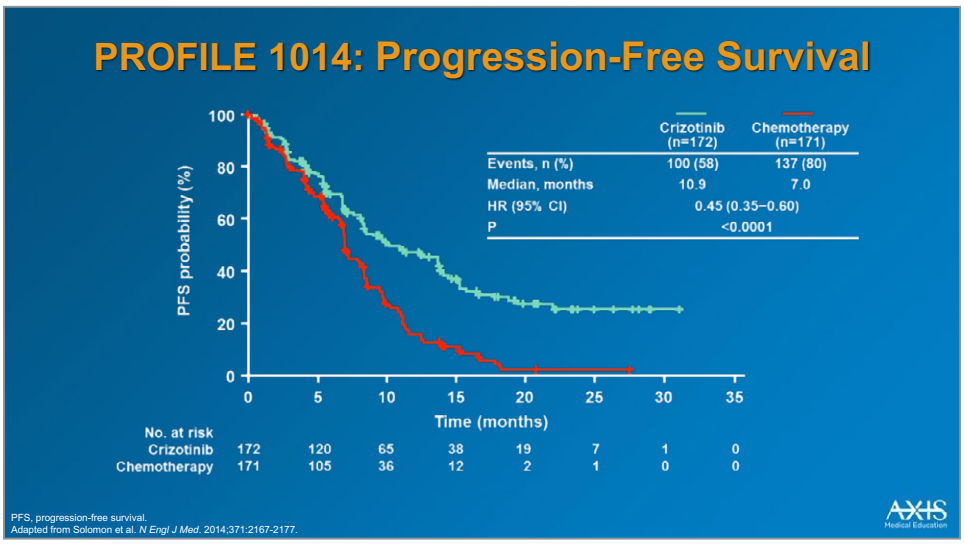
- Now one feature that's important that was baked into these next-generation TKIs is coverage of the CNS.



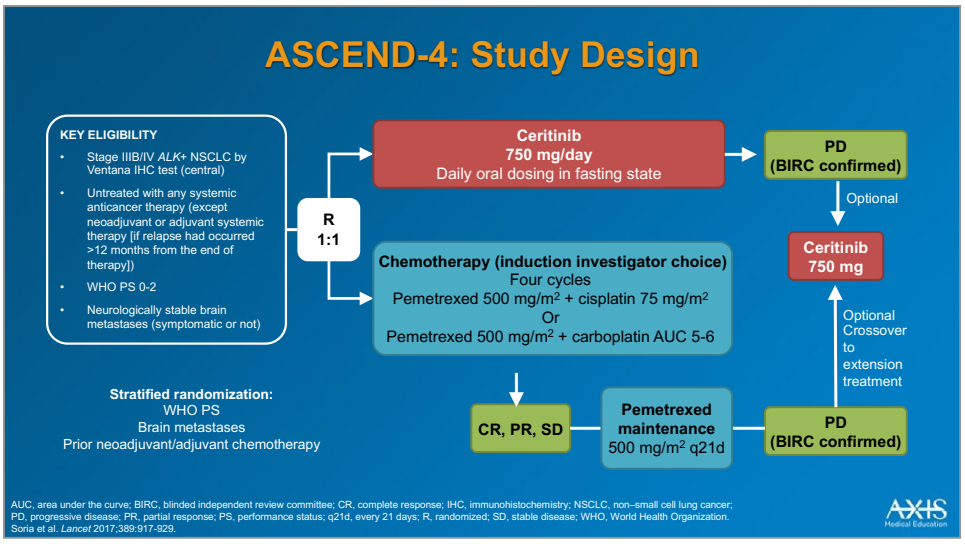
- We know that if you look at the cumulative incidence of CNS progression or intracranial progression-free survival, that again the curves diverge between crizotinib in red and the later-generation TKIs alectinib, brigatinib, and lorlatinib. And this is good for patients. You have protection of the sanctuary site from the acquisition of metastases, and this serves as an opportunity to treat intracranial disease, knowing that these cancers do have a proclivity for CNS spread.



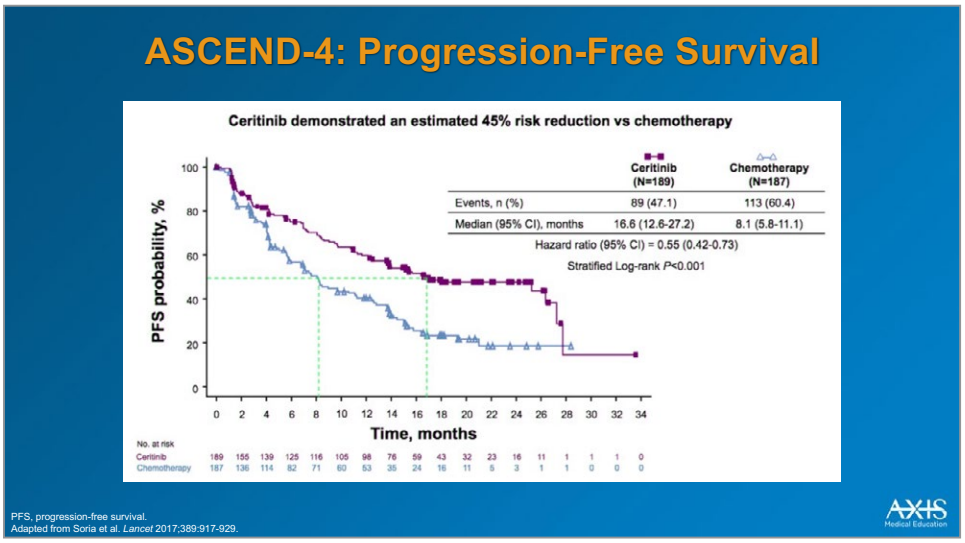


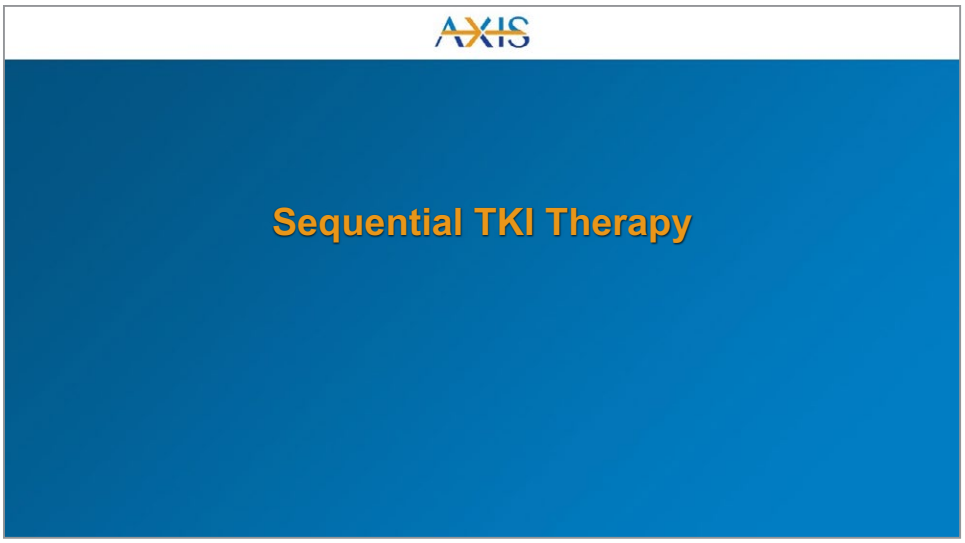


- Now ALK TKI therapy versus chemo, in case you are to ask, this has been explored with crizotinib randomization to crizotinib versus pemetrexed, cisplatin, or carboplatin was done on that PROFILE 1014 study we mentioned, and TKI therapy beat out chemotherapy. So of course, now we know that targeted therapy is the preferred approach over cytotoxic chemotherapy.



- This was echoed in ASCEND-4, a ceritinib study where, again, randomizing patients to ceritinib versus chemotherapy, you have improvement in progression-free survival with targeted therapy versus chemotherapy, just really summarizing that when an *ALK* fusion is identified and that's known, the targeted therapy should be used first, preferably with one of the three drugs that we mentioned earlier: alectinib, brigatinib, or lorlatinib.





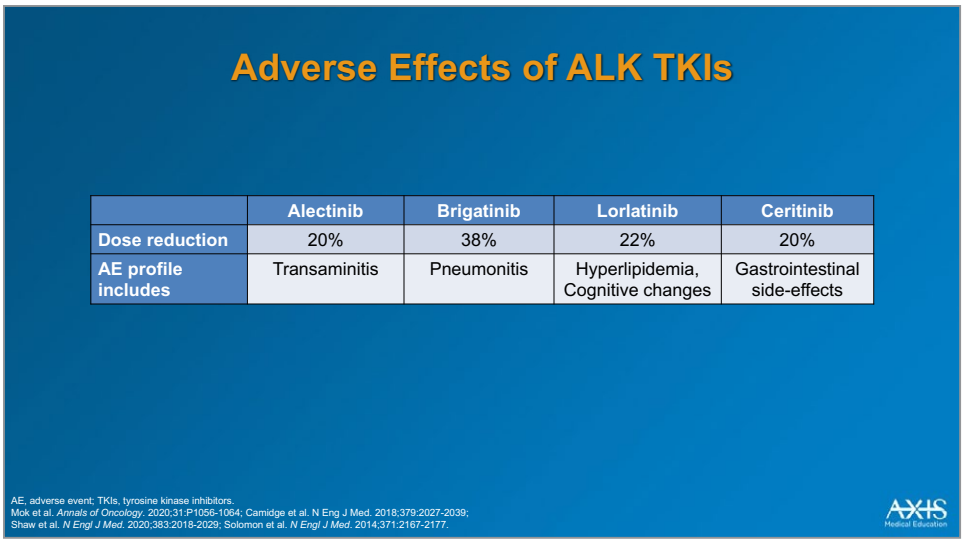
- Is there a role, however, for sequential TKI therapy?

ALK Rearrangement–Positive Advanced/Metastatic NSCLC: Subsequent Therapy Options

ALK Inhibitor	Trial(s)	Reference(s)
Alectinib	NP28673 Phase 2	Ou et al. *J Clin Oncol*. 2016;34:661-668. Shaw et al. *Lancet Oncol*. 2016;17:234-242.
Brigatinib	Phase 2 ALTA	Kim et al. *J Clin Oncol*. 2017;35:2490-2498.
Ceritinib	ASCEND-5	Shaw et al. *Lancet Oncol*. 2017;18:874-886.
Lorlatinib	Phase 2	Solomon et al. *Lancet Oncol*. 2018;19:1654-1667.

Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 5.2021.

- And the answer is yes, especially in patients who might get a drug like alectinib or brigatinib, for example, who develop acquired on-target or kinase-intrinsic resistance. We know that agents like lorlatinib have FDA approval in the second- or third-line space, and we've seen substantial activity in patients with acquired kinase domain mutations that render resistance to the earlier-generation agents, but for which lorlatinib has activity. And there are newer generation agents that are currently in development that may add to the list that we currently have on clinical trials.



- Finally, a brief word on safety. Many of these TKIs are amenable to chronic administration and are tolerable. And here in this slide you will see, however, that there is a somewhat different profile of adverse events. If you look across the TKIs, you might see a little more transaminitis with alectinib, pulmonary events with brigatinib, which is why you do a step-up dose by way of the recommended dose of the drug. Lorlatinib, you see hypercholesterolemia, cognitive changes. And of course with ceritinib at the full dose, you can see gastrointestinal side effects.

- **Arcila:** Thank you so much, Dr. Drilon. Would you mind providing a brief recap of the current clinical practice guideline recommendations for ALK-targeted agents in the first and subsequent lines of therapy including the recent addition of lorlatinib and the CROWN trial?

  Drilon: When you know a patient has an *ALK* fusion and they're treatment naive, the preferred initial strategy is targeted therapy. Of the targeted therapies, alectinib, brigatinib, and lorlatinib currently have regulatory approval, and any of those would be a reasonable choice for a patient who is TKI naive.

  In subsequent lines of therapy, my personal preference is to consider the genomics of the cancer, and if you're seeing off-target resistance or polyclonal resistance, perhaps reach for chemotherapy, plus or minus immunotherapy. However, if you're clearly seeing on-target resistance, then going from a drug like alectinib or brigatinib to lorlatinib that covers a wider swath of resistance mutations is something that I would do.

  Arcila: Great. And for patients who are *ALK* positive, can you share your approach for treatment selection and how you differentiate among the currently available ALK targeted agents and both for front and subsequent lines of therapy?

  Drilon: No one has really put down their penny and said you must do this one pill, and it's a bit of an art deciding in

clinic. So it comes down to the tolerability and comorbidities that patients have. If someone has very bad lungs and you're worried about the pulmonary events that might occur with brigatinib, I might use alectinib. If you start out with a drug like alectinib and see the transaminitis, then it's reasonable to switch to one of the other TKIs.

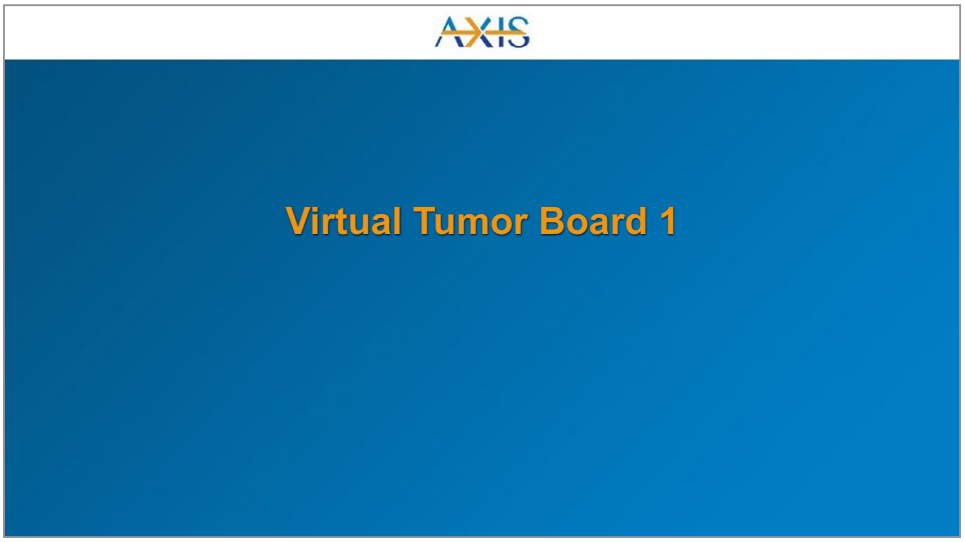
Many have talked about the utility of lorlatinib, and certainly it has the best hazard ratio of the three, however, we do see a very high frequency of hyperlipidemia, and you have cognitive changes. And so there's the argument that has been made that tolerability might not be as great as with alectinib or brigatinib, but still if you want to be aggressive in someone who you may have started the lorlatinib without tolerability issues, you know, it certainly bodes well for them to possibly stay on the treatment for longer, even though we have no head-to-head comparisons.

Arcila: What about the challenges with brain metastases in lung cancer? Can you share your perspective about the intracranial responses across the available TKIs?

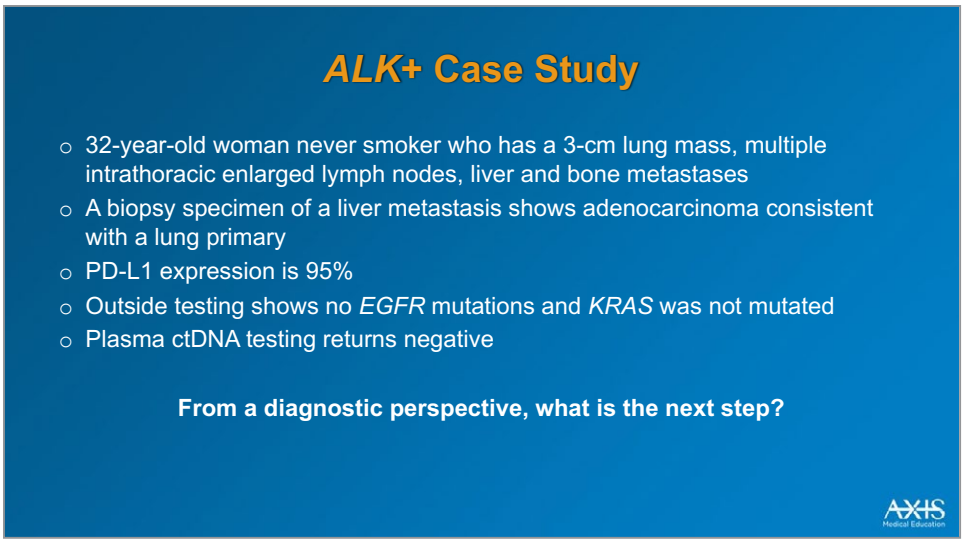
Drilon: I'm very happy that drug design has caught up with this question of sanctuary site coverage. And we've seen the data that these drugs can work very well in the CNS, both against existing disease and for the prevention of metastatic disease. So unlike crizotinib, which you would argue could be suboptimal, I think the alectinib, brigatinib, and lorlatinib give you the extra confidence that you're covering the CNS compartment.

Arcila: Great, thank you.

Drilon: You're welcome.



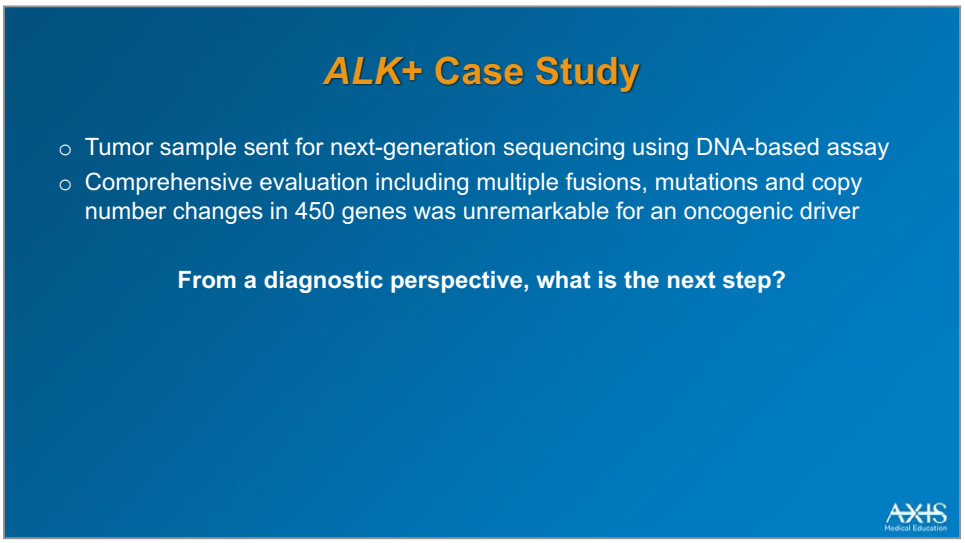
▶ All right let's move right in our virtual tumor board, and we'll try to go through one case study. I'll ask you some questions, and you'll ask me some questions as we go along.



For the audience, we have a 32-year-old woman never smoker, presents with a 3-cm lung mass, widespread disease with multiple intrathoracic lymph nodes, liver and bone metastases. A biopsy of the liver met shows adenocarcinoma, consistent with a lung primary. High PD-L1 expression at 95%, and outside molecular testing shows no *EGFR* mutations. *KRAS* wild-type, and plasma ctDNA testing returns "negative."

Dr. Arcila, from a diagnostic perspective, what do you think is the best next step?

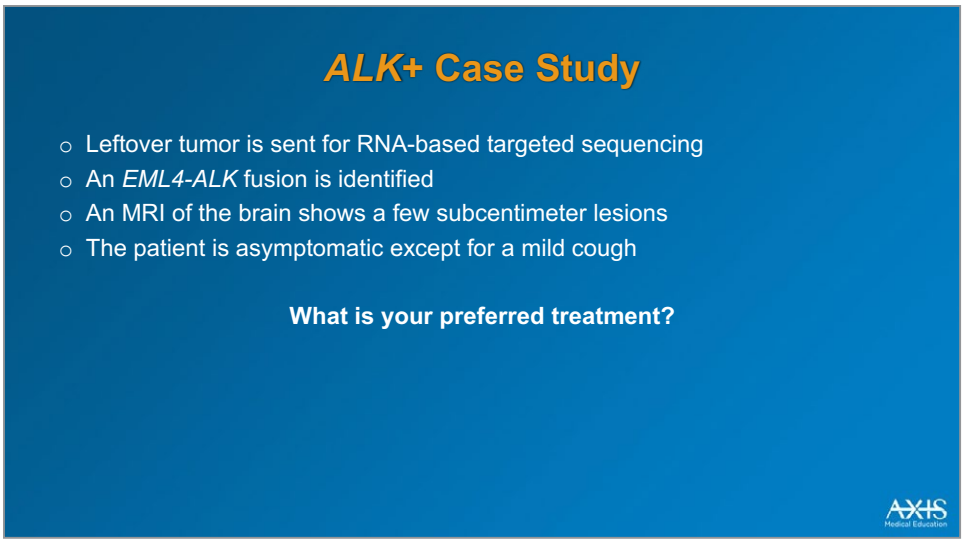
Arcila: So for a patient that has been tested with a very targeted assay, so in this case just *EGFR* and *KRAS*, then the best next step is to do next-generation sequencing to be able to profile that broadly. The plasma ctDNA testing, even though it came back negative, as you know, there is just a very large biological difference on how differently patients with lung cancers shed cell-free DNA in circulation. So any negative results should be interpreted as a false negative until proven otherwise.



Drilon: Wonderful, and that's exactly what they did. The tumor was sent for next-generation sequencing using a DNA-based assay, and a comprehensive evaluation including fusion interrogation, mutations, copy number changes in hundreds of genes was unremarkable for an oncogenic driver.

Dr. Arcila, what should someone consider doing in this situation?

Arcila: So given that this was a next-generation sequencing assay that was DNA-based, depending on the assay, of course, my next approach would be to test RNA to ensure that we didn't miss any type of fusions.

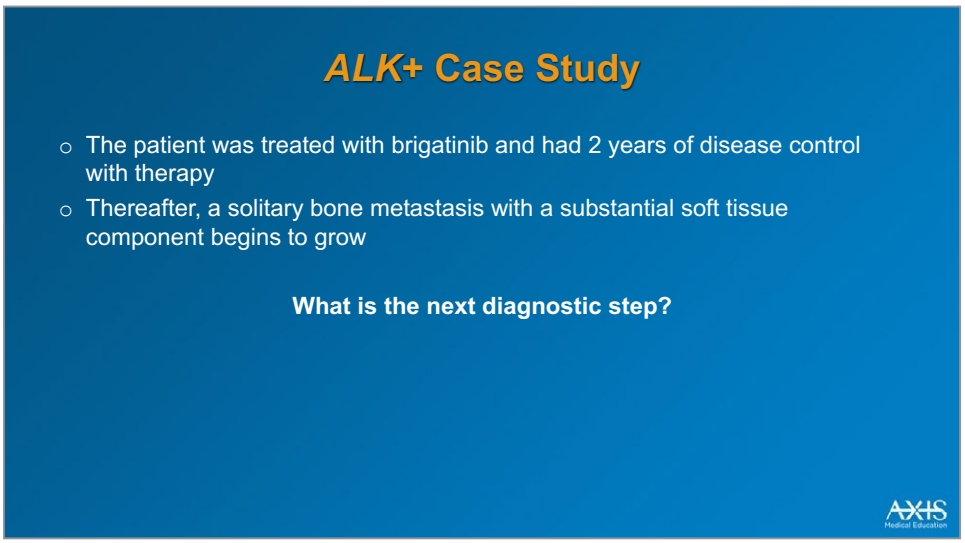


Drilon: Great, and that's also exactly what they did.

Leftover tumor was sent for RNA-based targeted sequencing. They then found an EML4-ALK canonical fusion, and an MRI of the brain showed a few subcentimeter lesions.

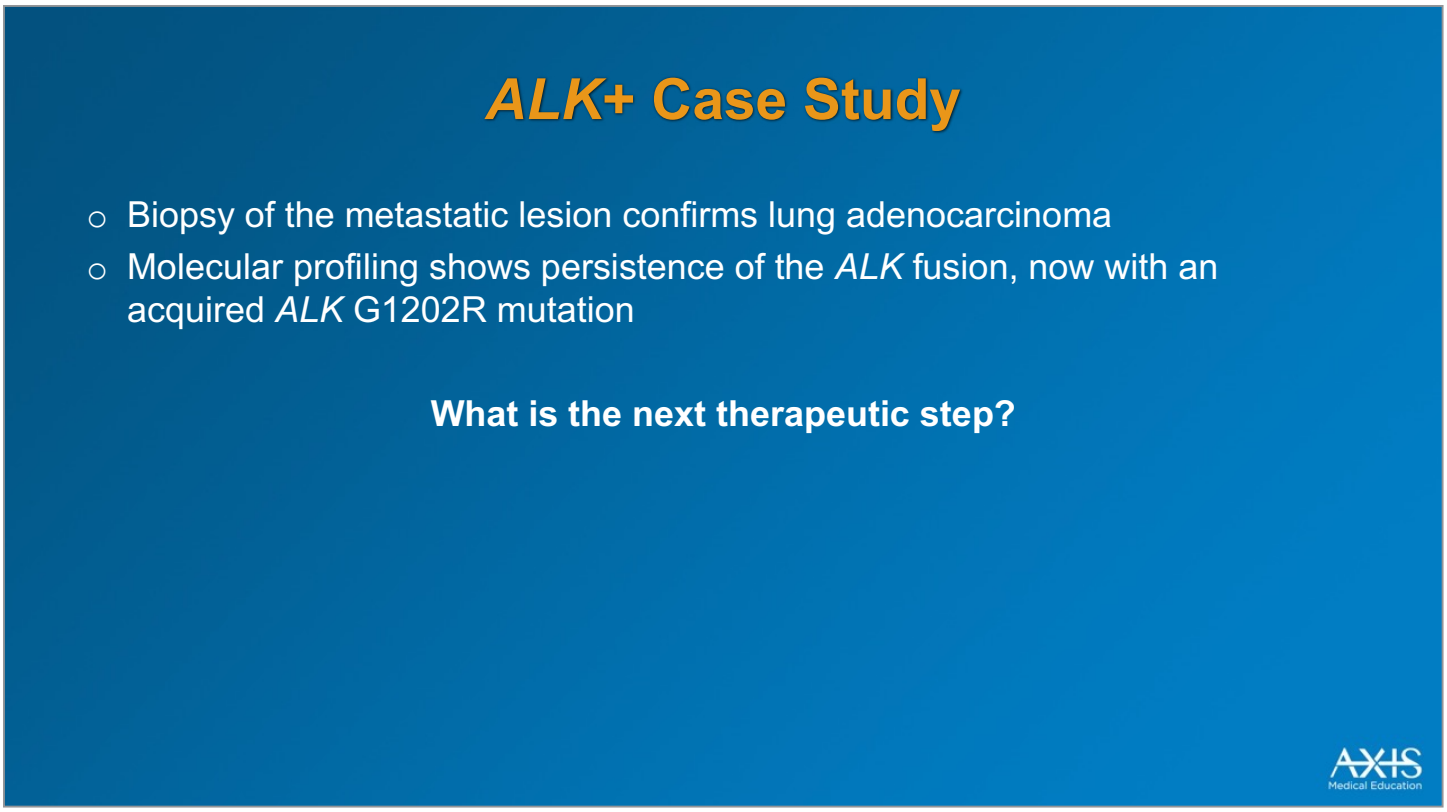
Arcila: So, Dr. Drilon, the patient is asymptomatic except for a mild cough. In a patient like this, what is your preferred treatment?

Drilon: I would really reach for targeted therapy first, and we discussed the three options: alectinib, brigatinib, and lorlatinib. There's currently no correct answer, but for a patient like this, I might start with alectinib, which we know would cover the extracranial disease and cover the intracranial disease.



Arcila: This patient was treated and had 2 years of disease control with therapy. But then thereafter, a solitary bone metastasis with a substantial soft tissue component begins to grow. What do we do with a patient like this?

Drilon: I'll ask you what you think, as well, but I would prefer to do a biopsy of that soft tissue component, and then I would send it your way.

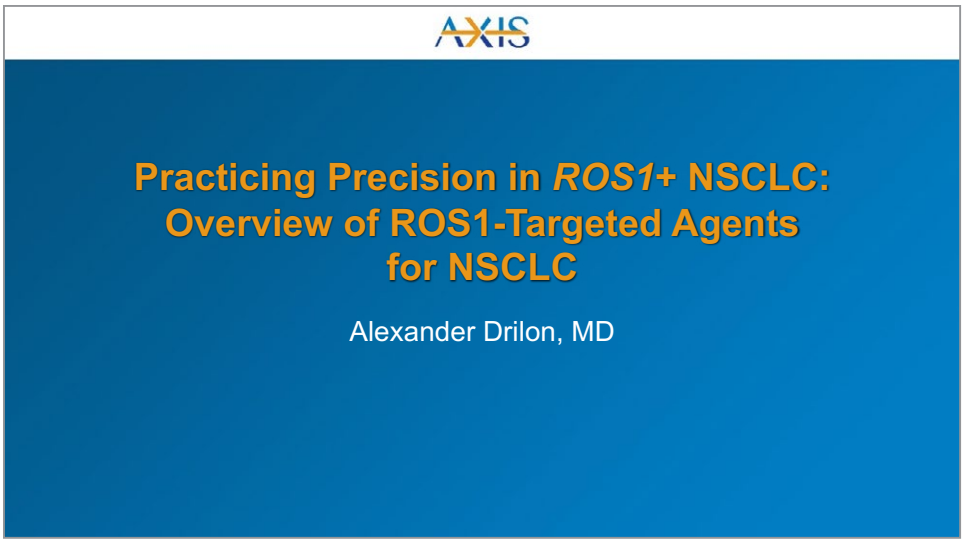


Arcila: So the key thing here is the fact that it's a bone metastasis. From the testing perspective, testing bone metastasis is a difficult thing, because usually these lesions tend to be decalcified, and they end up having either a failure of testing or they have a false negative, which is associated with some of the fibroblast or the fibrous component of the biopsy being the one that provides the DNA component for the testing.

So, when testing bone lesions, it is very important to ensure that the biopsy is obtained and that there is explicit information for the lab to ensure that it doesn't get decalcified and that the testing gets done in tissue that is either fresh or decalcified without acid, such as EDTA, for example.

Drilon: To end the story, the biopsy confirmed lung adenocarcinoma, and molecular profiling showed that the *ALK* fusion was still there but now with the acquired *ALK* G1202R mutation. And the final question is, what's the next therapeutic step? And of course, we know, as has been mentioned, lorlatinib has activity against resistance mutations including G1202R, so I would sequence this patient on the lorlatinib on progression.

The last thing I'll say is that if this were true solitary site progression I would probably radiate that met first and continue the brigatinib until more widespread progression, after which I would consider switching to lorlatinib, just highlighting the utility of local therapy in the face of solitary or oncoprogression.



Drilon: In the last section, we're going to switch to *ROS1* fusion–positive lung cancers and tell you the data surrounding targeted therapy in this space.

ROS1 Rearrangement–Positive Advanced/Metastatic NSCLC

NCCN® Recommendation	Drug	Trial(s)	Reference(s)
First-Line Therapy			
Preferred	Entrectinib*	ALKA-372-001 STARTRK-1 STARTRK-2	Drilon et al. *Lancet Oncol*. 2020;21:261-270.
	Crizotinib	PROFILE 1001	Shaw et al. *N Engl J Med*. 2014;371:1963-1971.
Other recommended	Ceritinib	Phase 2	Lim et al. *J Clin Oncol*. 2017;35:2613-2618.
Subsequent Therapy			
	Lorlatinib	Phase 2	Solomon et al. *Lancet Oncology*. 2018;19:1654-1667. Shaw et al. *J Clin Oncol*. 2019;37:1370-1379.
	Entrectinib (CNS PD)**	ALKA-372-001 STARTRK-1 STARTRK-2	Drilon et al. *Lancet Oncol*. 2020;21:261-270.

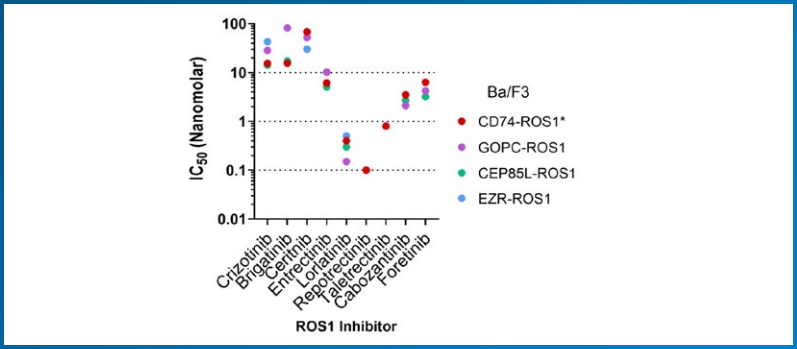
*Entrectinib may be better for patients with brain metastases.
**Entrectinib is primarily for patient with CNS progression after crizotinib.
Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 5.2021.

We'll start with this first table that shows you different ROS1 TKIs that have been explored in different trials that are listed in the third column there for patients with *ROS1* fusion–positive lung cancers. For your reference, the publications are listed off to the right, so you can check them out.

But we'll start by walking back to the definition of generation. And as you've heard in the last section, crizotinib was thought to be a first-generation ALK TKI. Then you have second-generation drugs like alectinib, for example. And then you have later-generation agents like lorlatinib. It doesn't quite work out like that in the ROS1 space, so don't equate the generation that you attribute in the ALK space to the ROS1-TKI space.

Early- and Next-Generation ROS1 TKIs have Varying Potencies

Inhibitory activity of ROS1 TKIs against different *ROS1* fusions in Ba/F3 cell assays



Drilon et al. *Nat Rev Clin Oncol*. 2021;18:35-55.

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And here in this slide, you'll see actually that drugs have different potencies. So we'll call out brigatinib, which is not a first-generation drug, but you see here that the IC-50s against ROS1 are in the same range as crizotinib. So it really challenges our view of generation when we move from oncogenic driver to oncogenic driver.

And here you'll see that lorlatinib is still considered a later-generation drug along with repotrectinib, but everything else the IC-50s seemed to drift above that, meaning be higher or less potent against ROS1. So keep that in mind.

Early-Generation ROS1 TKIs Are Active in TKI-Naïve Patients

ROS1 TKI	Study (phase)	ORR	Median DoR, mo	Median PFS, mo	Median OS, mo
Crizotinib	PROFILE 1001 (1b)	72%	24.7	19.3	51.4
	OxOnc (2)	72%	19.7	15.9	-
	EUCROSS (2)	70%	19.0	20.0	-
	AcSe (2)	69%	-	5.5	17.2
	METROS (2)	65%	21.4	22.8	-
Entrectinib	Drilon et al. (1/2)	77%	24.6	19.0	-
Ceritinib	Lim et al. (2)	67%	21.0	19.3	24.0
Brigatinib	Gettinger et al. (1)	100%	-	-	-

DoR, duration of response; ORR, overall response rate; OS, overall survival; TKI, tyrosine kinase inhibitor.
Adapted from Drilon et al. *Nat Rev Clin Oncol*. 2021;18:35-55.

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With that being said, the early-generation ROS1 TKIs, and we're going to call those crizotinib, entrectinib, ceritinib, and brigatinib, have been explored in prospective clinical trials. You see here that, very interestingly, the objective response rates seem to cluster right around the high 60s to the 70s across many of these programs. The other thing also is that the median progression-free survival, the numbers for many of these trials are in the order again of around 16 to a little over 22 months.

And so what we haven't seen quite yet here that you saw earlier with ALK is that any of these early generation TKIs have really exceeded dramatically the activity that we see with crizotinib. But in terms of selection, of course, there are certain features such as CNS coverage, that we'll get to in a later slide, that might make you pick one of these drugs over another. Before we leave the slide, just a quick reminder that only crizotinib and entrectinib have regulatory approval for *ROS1* fusion–positive lung cancers, and the others, as yet, do not.

Early-Generation ROS1 TKIs Achieve Improved Outcomes Compared to Chemotherapy

Study (n)	Efficacy Measure	Crizotinib	Platinum-based chemotherapy	*P*
Shen et al (77)	ORR	86.7%	44.7%	<.001
	Median PFS	18.4 mo	8.6 mo	<.001
Xu et al (102)	ORR	83.9%	56.5%	.002
	Median PFS	14.9 mo	8.5 mo	.001
Zhang et al (51)	ORR	80.0%	40.8%	<.05
	Median PFS	9.4 mo	3.5 mo	<.05

Series	Chemotherapy	ORR	Median PFS
Xu et al	Platinum-based, first-line (n = 46) Non-platinum agents were: pemetrexed (n = 35), paclitaxel (n = 5), docetaxel (n = 2) or gemcitabine (n = 4)	–	8.5 mo (95% CI 6.8-10.3)
	Platinum-pemetrexed (n = 35; subset analysis of the above)	–	8.8 mo (95% CI 6.8-10.8)
Shen et al	Platinum-pemetrexed, first-line (n = 47)	44.7% (95% CI 29.8–57.4)	8.6 mo (95% CI 6.9-10.3)
	With bevacizumab	–	9.0 mo
	Without bevacizumab	–	8.1 mo
Park et al	Pemetrexed-based (n = 90)	53.3%	8.0 mo (95% CI 6.4-11.7)
Drilon et al	Pemetrexed-based (n = 10) Alone or combination with a platinum agent ± bevacizumab	–	23 mo
Mazieres et al (EUROS1)	Pemetrexed-based chemotherapy (n = 31) Pemetrexed alone or in combination with a platinum agent	57.5%	7.2 mo (95% CI 4.8-9.6)

ORR, overall response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
Adapted from Drilon et al. *Nat Rev Clin Oncol.* 2021;18:35-55.

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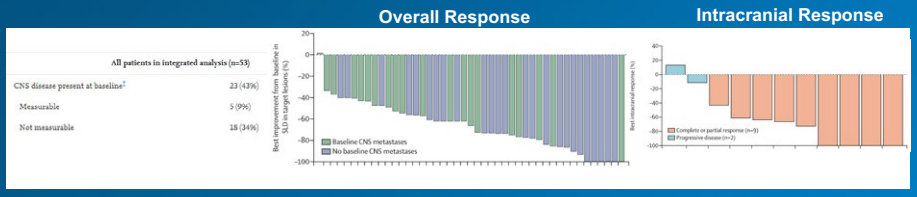
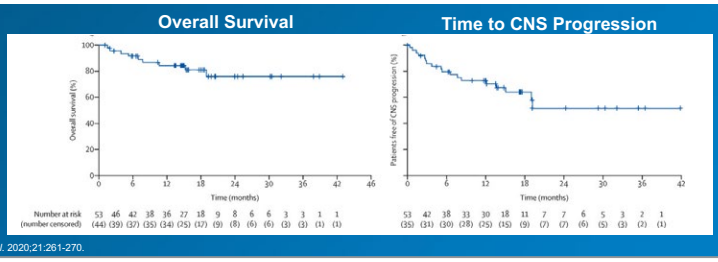
So here in the next slide, echoing what we saw with ALK, you see the comparison of ROS1 TKIs against chemotherapy. And as opposed to the prospective studies that you saw earlier, here you'll see retrospective series, knowing that *ROS1* is a less frequent event compared to *ALK*, that I've shown that if you compare crizotinib to platinum-based chemotherapy, that again you see an improvement with targeted therapy, underlining that we should choose targeted therapy in this space, when we know that a *ROS1* fusion is present, rather than chemotherapy.

Entrectinib Trial Enriched for Patients With Baseline Brain Metastases





Drilon et al. *Lancet Oncol.* 2020;21:261-270.

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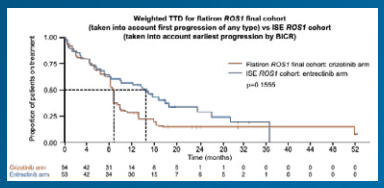
But like I said in the last slide, one thing to keep in mind when we choose between these targeted therapies is coverage for the CNS. And arguably one of the most developed data sets for CNS coverage of the early-generation TKIs is entrectinib. And you see that this trial was enriched for patients with baseline brain metastases—43% had known brain metastases at trial entry, compared to much lower frequencies for crizotinib and the other drugs. And even though those top line results seem to be comparable, if you look at certain series, knowing that the entrectinib trial was enriched for bad actors with CNS disease but still the report card was comparable to the other agents, I tend to prefer this drug over crizotinib for a ROS1-TKI–naive patient.

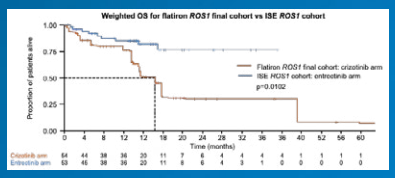
And you see the intracranial response on the upper right, as well as the time to CNS progression on the lower right.

Early-Generation ROS1 TKIs Active in *ROS1*-rearranged Lung Cancers

Time to Treatment Discontinuation



Overall Survival



	Crizotinib	Entrectenib
TTD	8.8 months	14.6 months
OS	~20 months	Not reached

Doebele et al. *J Clin Oncol*. 2019;15:9070.

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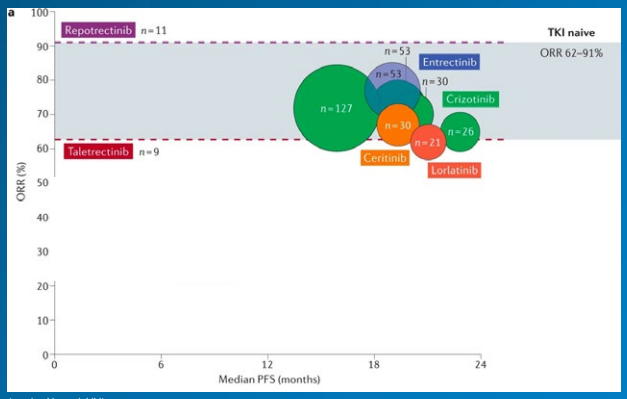
- And this is one retrospective series that showed that when you look at real-world evidence, if you compare crizotinib to entrectinib, that you do see a divergence in the curves for time, the treatment discontinuation, and also an overall survival, providing a substrate again for making the decision to potentially choose entrectinib as the TKI of choice in the TKI-naive space. Now, the guidelines aren't concrete about choosing entrectinib over crizotinib, but these are the things I think about when I choose one of these TKIs for my patients.

Next-Generation ROS1 TKIs Yet to Achieve Much Longer PFS Compared to Early-Generation TKIs



PFS, progression-free survival; TKIs, tyrosine kinase inhibitors.
Drilon et al. *Nat Rev Clin Oncol*. 2021;18:35-55.

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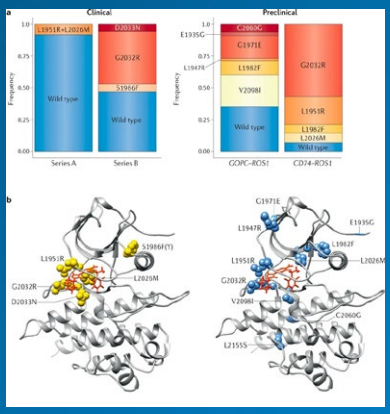
- This is a summative slide where you see graphically in the bubble plot all of the early-generation TKIs against ROS1 stacked up against the next-generation drugs like repotrectinib and taletrectinib in the purple and the blue. And the point here that we're trying to make is, especially if you include lorlatinib in the orange, when you look at objective response rate, things again seem to cluster, but they do so as well for median progression-free survival.

  The bar for the approval of one of these later-generation agents, as a replacement for crizotinib or entrectinib, will really be contingent on a meaningful improvement in progression-free survival, which we have yet to see with the next-generation agents. We hope that with more mature data you'll see that the Ns here are very low for the next-generation drugs that we might see that divergence that we saw with ALK, but we need to sit tight and wait to see how the data mature in this space.

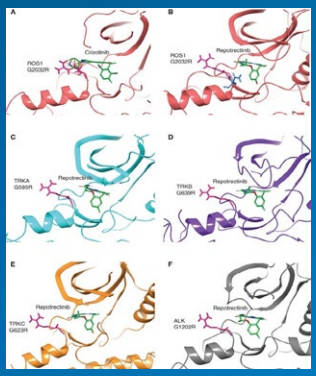
On-Target Resistance to ROS1 TKI Therapy Occurs in Form of Acquired *ROS1* Kinase Domain Mutations



TKI, tyrosine kinase inhibitors.
Drilon et al. *Nat Rev Clin Oncol*. 2021;18:35-55.

- Thankfully, there are things that the next-generation drugs still remain good for, if you don't use them in the TKI-naive space. And that again parallels what we spoke about in ALK, that on-target resistance can be acquired with ROS1-TKI therapy. This is in the form of acquired ROS1 kinase domain mutations that are displayed here.

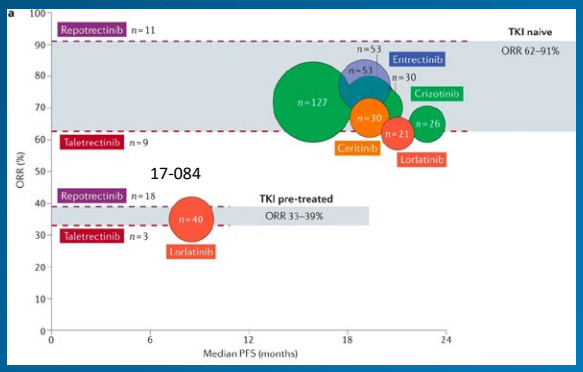
Common Design Parameter of Next-Generation ROS1 TKIs: Smaller Compared to First-Generation Drugs and Macrocyclics



TKIs, tyrosine kinase inhibitors.
Drilon et al. *Cancer Discov*. 2018;8:1227-1236.

- Thankfully, these next-generation agents like repotrectinib, for example, taletrectinib, have been designed with a shared feature of a smaller macrocycle that avoids the steric penalties of these substitutions that occur as a result of these mutations. And so you effectively re-engage the kinase domain and shut down the oncogenic signal.

Response to Next-Generation ROS1 TKIs in ROS1 TKI Pretreated NSCLCs Occurs in a Subset of Patients



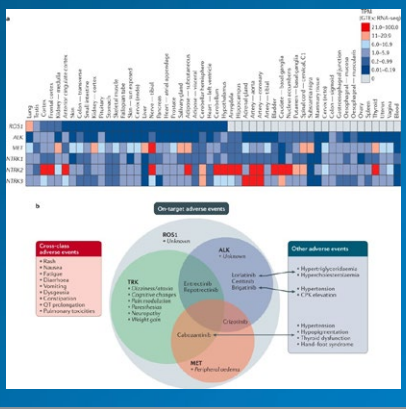
Repotrectinib

- FDA fast-track designation 8/2020 (prior chemo and 1-2 prior ROS1 TKIs)

ORR, overall response rate; TKIs, tyrosine kinase inhibitors.
Drilon et al. *Nat Rev Clin Oncol*. 2021;18:35-55.

- And as such here in the next slide, you are seeing on the lower left, this time, overlaid on the data that we saw in the prior slide, that we are seeing activity in TKI-pretreated cases with repotrectinib and lorlatinib, including taletrectinib, there in the red. So there is a potential for us to do sequential TKI therapy, as is the case with *ALK* fusion–positive lung cancers.

Consequences of ROS1 Inhibition in Non-Neoplastic Cells Remain Unclear: AEs Defined by Concurrent Kinase Inhibition



AEs, adverse events.
Drilon et al. *Nat Rev Clin Oncol*. 2021;18:35-55.

- Finally, a word on safety, before we end this section. It's currently unclear what the consequences are of ROS1 inhibition in non-neoplastic cells. So in simple terms, we don't quite know what the side effects are of pure ROS1 inhibition. If you look at the preclinical studies, there are a few things that are called out that don't really make their way into a side-effect profile of these drugs.

  And the other reason we don't really know is that all of the drugs that are currently available in clinical trials that we know about are multikinase agents that also inhibit other kinases. So you have the confounding effect of inhibiting TRK that can give you a certain profile of adverse events, MET that can do the same thing, and ALK. So just something to keep in mind. That's an interesting nugget about the biology and as it relates to safety in the clinic.

Arcila: Thank you so much, Dr. Drilon. Can you provide a recap of the clinical practice guidelines for *ROS1* testing and the recommended use of ROS1-targeted agents?

Drilon: Thankfully, a lot of the learnings in ALK can directly be applied to ROS1, and it's the same shebang. If you know that a *ROS1* fusion is present, the recommendation is to start with targeted therapy. There are two FDA-approved agents, crizotinib and entrectinib.

I've shared my personal preference, even though there is no strong recommendation in the guidelines. I tend to choose entrectinib because of that potential element of CNS coverage. I would certainly do it if someone had a brain metastasis at diagnosis, just leveraging the data that we've seen.

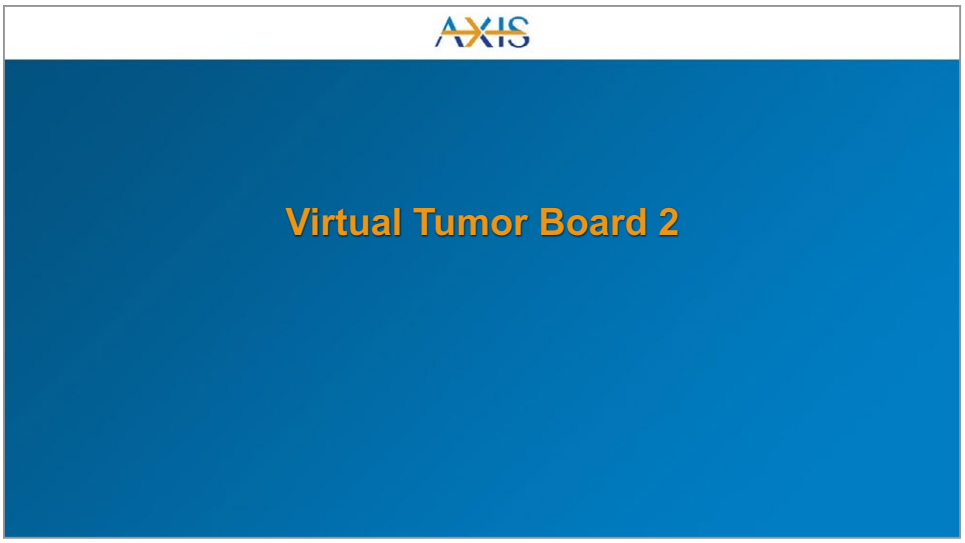
In the subsequent post-TKI space where patients have progressed, I would think about resequencing the cancer, looking to see if certain mutations are acquired, because now we have clinical trials of repotrectinib, taletrectinib, and actually in the NCCN Guidelines, we have the potential use of lorlatinib in the TKI refractory setting where we've seen proof of concept that patients have responded to a second pill after progressing on a first pill.

Arcila: So, Dr. Drilon, is there a role for other treatments, such as chemo for these patients?

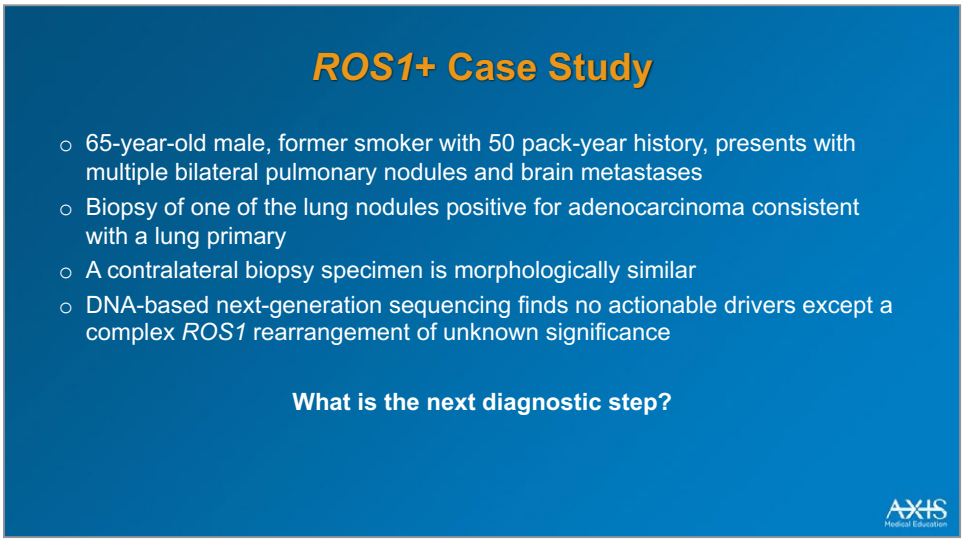
Drilon: Yes, absolutely. And we've shown that pemetrexed-containing chemotherapy that may be platinum-doublet inclusive can work very well for ROS1. So if you've exhausted your TKI options, going to platinum pemetrexed backbone, with or without a third agent, is something that I would certainly do, and we've seen it work.

Immunotherapy I would hesitate to give it by itself, because we've seen that these cancers tend to be TMB low, and when you look at responses to new checkpoint inhibitors, the batting average is also very low. So if I were to consider immunotherapy, I would probably consider a chemotherapy and immunotherapy together, rather than giving immunotherapy by itself.

Arcila: Okay, great. Thank you.



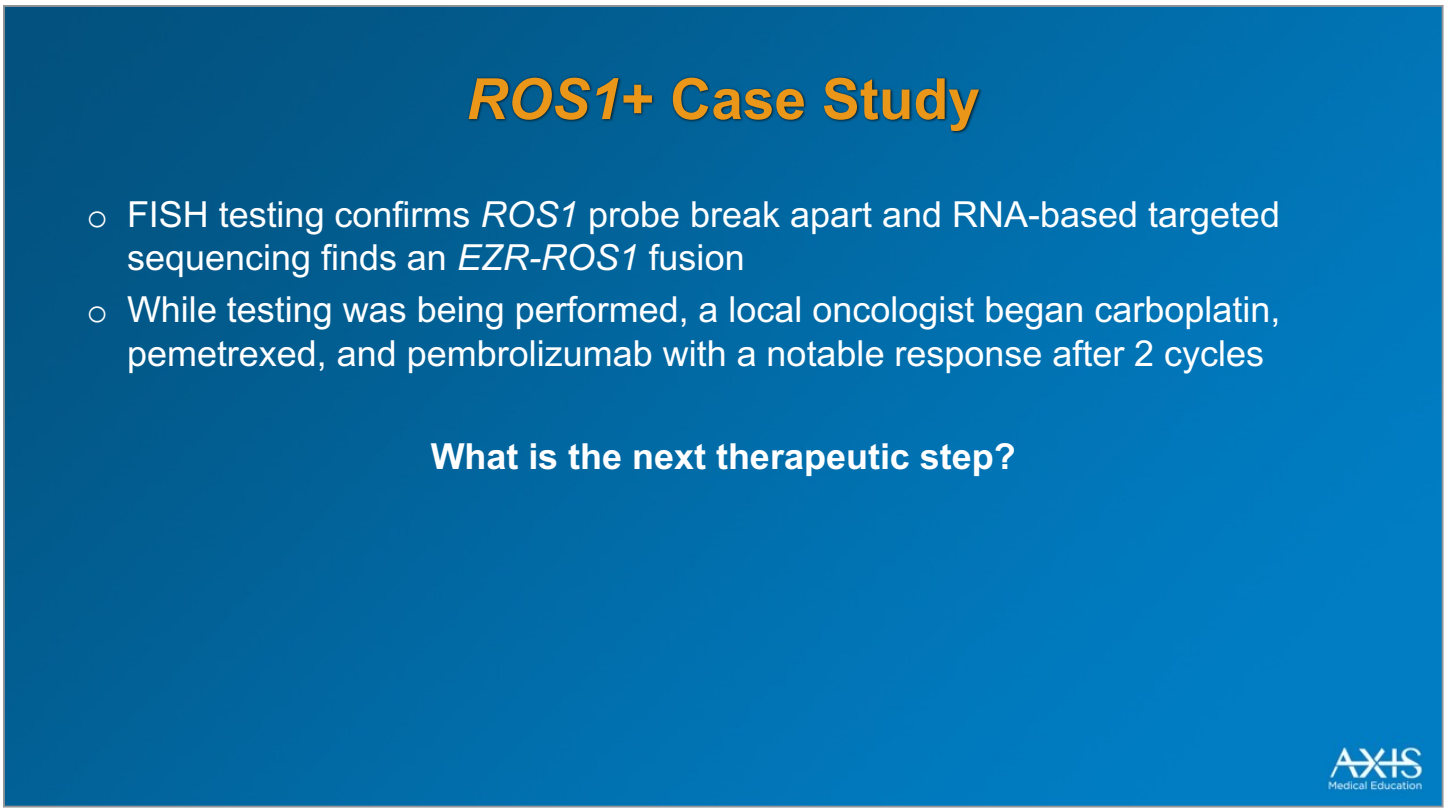
Drilon: Now we move on to the final section of this presentation where we have a virtual tumor board 2, and we have a ROS1 case for you.



A 65-year-old man former 50 pack-year smoker presents with multiple bilateral pulmonary nodules and brain metastases. A biopsy of a lung nodule shows adenocarcinoma consistent with a lung primary, and a contralateral nodule biopsy is morphologically similar. DNA-based next-generation sequencing finds no actionable drivers except unequivocal complex *ROS1* rearrangement of unknown significance.

Dr. Arcila, what would you do in this situation?

Arcila: So in this case, I think that you can do an RNA-based assay, would be my next thing for testing. So the fact that if you do find the fusion, then that means that the fusion has been transcribed and is more likely to be something that is productive and perhaps actionable. And I think that you could of course test as well by immunohistochemistry, but I think that the role of immunohistochemistry for something like this would not be as helpful. I would say the RNA assay would be the best thing to do.



It so happened that this patient actually had a FISH testing, which confirmed the *ROS1*. And just to mention that you can also do, of course, FISH testing, but FISH testing does not necessarily provide what the partner is going to be.

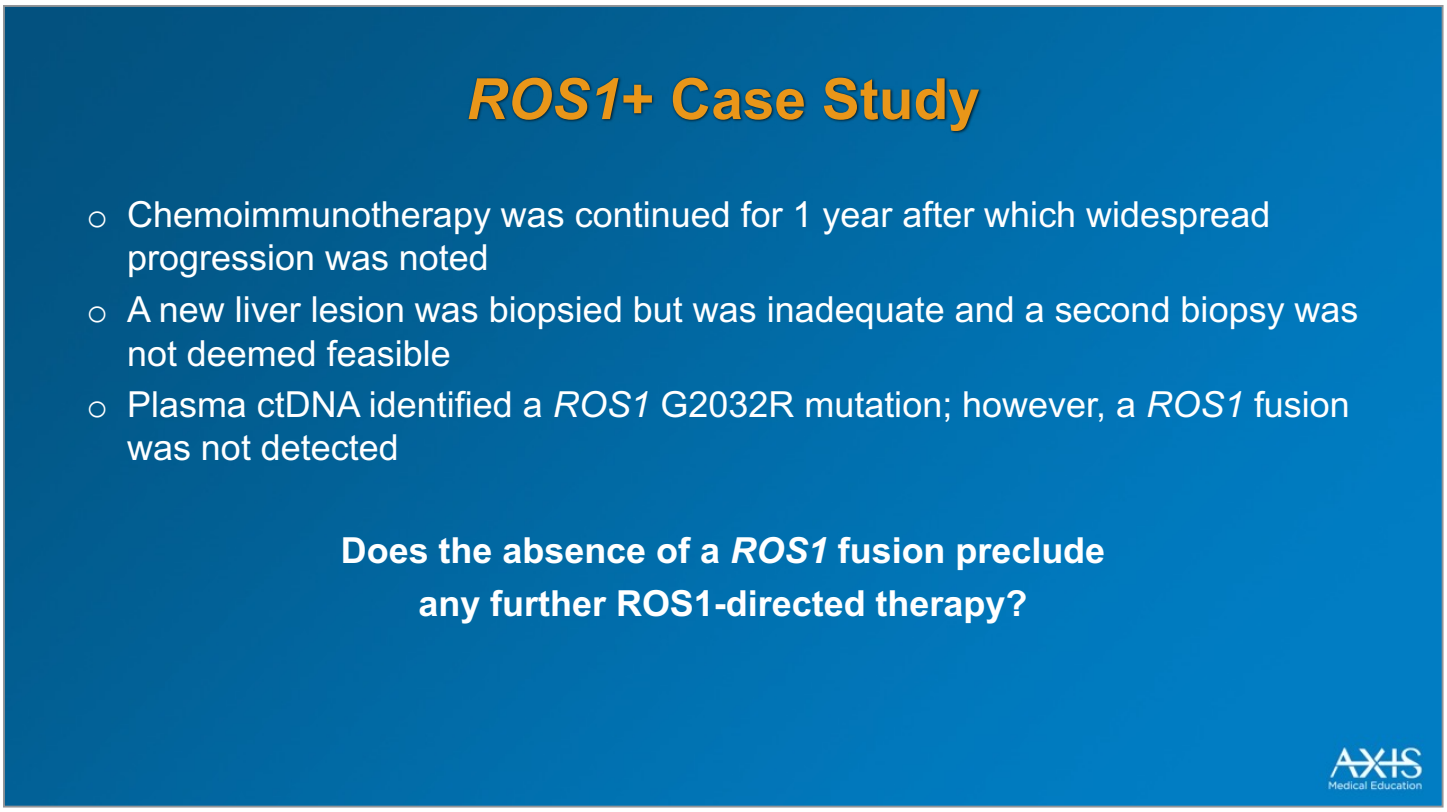
And then of course, this patient not only had the *ROS*1 break-apart probe by FISH, but also had the RNA-based targeted sequencing. And these actually found a fusion involving *EZR* and *ROS1*.

So while testing was being performed, a local oncologist began carboplatin, pemetrexed, and pembrolizumab, with a notable response after two cycles.

So, Dr. Drilon, now that you have these results of the molecular testing, what is the next therapeutic approach?

Drilon: This is a very common question, because sometimes the molecular findings come back after you've started therapy, and my answer is always if it works very well and you do a scan showing that the chemoimmunotherapy achieved an optimal response, I would just continue through until progression or intolerability, and then consider switching the targeted therapy.

However, if you do a scan and the response is suboptimal from the get-go, I would very quickly switch to targeted therapy. And as I mentioned, my preference would be to use entrectinib.



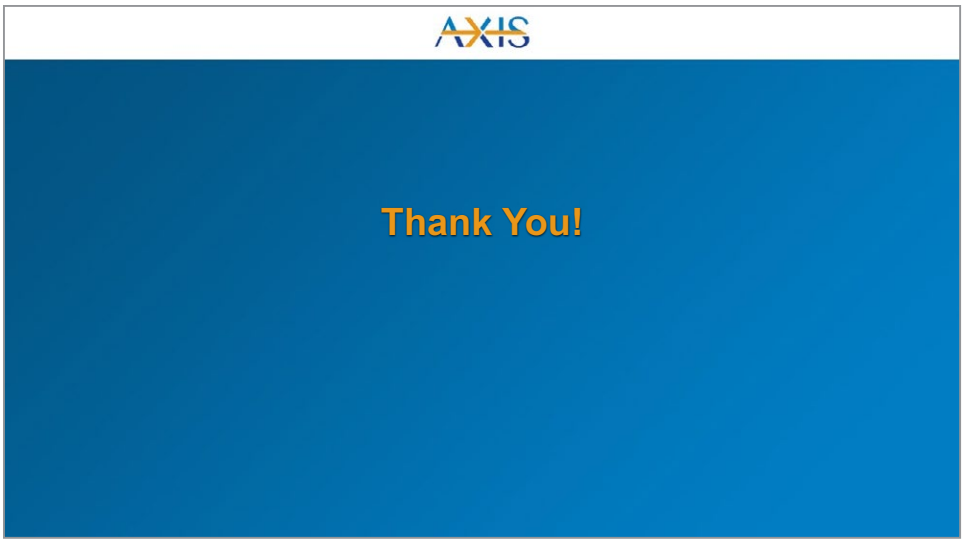
Arcila: So that's exactly what happened with this patient. The chemoimmunotherapy was continued for 1 year, after which widespread progression was noted. And the patient developed a new liver lesion that was biopsied but was inadequate, and a second biopsy was not being feasible.

So in this case, plasma was tested for circulating tumor DNA, and this identified a *ROS1-G2032R* mutation. However, the *ROS1* fusion was not detected. So does the absence of a *ROS1* fusion preclude any further ROS1-directed therapy?

Drilon: Not at all, and I'm going to throw this back to you in a second to see what your thoughts are. But in this case, the *ROS1* fusion is likely there but possibly not detected on the blood test. And so I would take the *G2032R* mutation as evidence of on-target resistance and consider next-generation TKI like repotrectinib or taletrectinib has been shown in the laboratory to have activity against this.

But Dr. Arcila, I'm curious if you see this situation where plasma may not pick up a fusion, but something else pops up.

Arcila: Yes, actually, this is a very common finding. So as you know, the fragments of tumor that are circulating in plasma are very small fragments. And designing an assay to target very fragmented DNA is extremely difficult, and you may end up with a false negative because the template is just very low and fusions are just difficult to characterize with a cell-free DNA assay. So the fact that this resistance mutation is there, it basically tells you that the *ROS1* fusion is still there, it's just not detected by the assay, and that's purely due to the limitations of the technology.

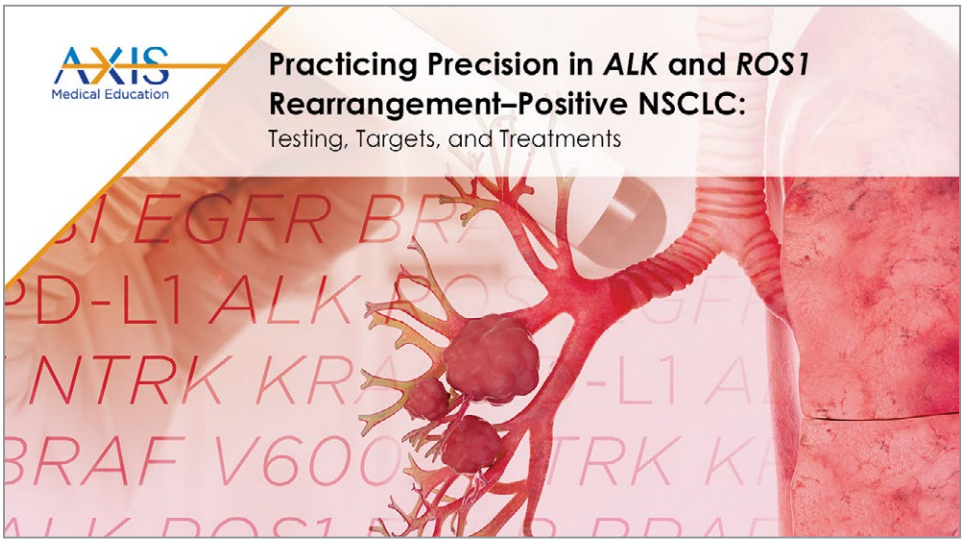


Drilon: Thanks, Dr. Arcila. And thanks to everyone for joining this program, we're going to end with a few takeaways. And I'm going to ask you, Dr. Arcila, to give your diagnostic takeaway on the fusions, and I'll end with my therapeutic takeaway for our listeners.

Arcila: So from the testing perspective, it is extremely important to recognize what the limitations are for testing. And because there are so many fusions, so many partners, and there is high biologic variability, it is important to choose an assay that can provide a broad assessment up front. If you have a very small biopsy, it is better to just utilize a next-generation sequencing assay that can detect these as fast as possible and in a broad manner. From the testing, I think that that is the very key feature.

Drilon: And of course, once you find these fusions, it's very important to highlight that targeted therapy is the way to go. And you've seen the data on many of these TKIs that are highly active, higher response rates, long progression-free and overall survival and activity in the brain. So that would be my preference.

And finally, in the resistance setting, because of intelligent drug design, we have next-generation pills that are able to overcome the penalties of resistance mutations that might be acquired with the earlier-generation agents.



And with that we end our program. Thank you so much for joining us again, and I hope this was helpful to all of you. Thank you, Dr. Arcila.

Arcila: Thank you.

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