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Released: 12/20/2024
Valid until: 12/20/2025
Time needed to complete: 15 minutes

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Advancing ALK Inhibition Into Early-Stage NSCLC: Integrating Biomarker-Driven Therapies to Reduce Recurrence Risk Post Resection

Announcer:
Welcome to CME on ReachMD. This activity, titled "Advancing ALK Inhibition Into Early-Stage NSCLC: Integrating Biomarker-Driven Therapies to Reduce Recurrence Risk Post Resection" is provided by AXIS Medical Education.

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Dr. Socinski:
Hello, and welcome to this podcast. I'm Dr. Mark Socinski, a thoracic medical oncologist and the Executive Medical Director of the Advent Health Cancer Institute in Orlando, Florida. Today, I will be discussing strategies for ALK inhibition in early-stage non-small cell lung cancer. So let's begin.

I'm showing on this slide the common genomic alterations in non-small cell, it's become quite complex. We have 5 mutations and 4 fusions that are really part of the diagnosis. We're going to focus on ALK fusions or rearrangements highlighted in the box to the right. And you can see that depending upon what population of study that you might look at, the occurrence of this, or the incidence of this, can be anywhere from 4 to 8%. Of course, that will depend upon the population that you're testing.

If we look at the NCCN guidelines for perioperative systemic therapy, and this really is the guidelines looking at systemic therapy following surgical resection, the NCCN guidelines call out testing for PD-L1, EGFR mutations, and ALK rearrangements in stage IB, through IIIA, up to IIIB, the T3, N2 category. And we'll talk a little bit about the rationale for this when we talk about the ALINA trial in a couple of slides.

Now, how should that testing be done? This is a table looking at the molecular methods for a biomarker testing. You can see there are a number of techniques shown to the left. I've highlighted what I think is the standard of care, and that's next-generation sequencing. The advantages here, this is high throughput. It has great sensitivity and specificity. It can cover all of these targets. We're focusing on ALK fusions today, but again, there are other mutations and other fusions that are important in the assessment of early-stage non-small as well as late stage non-small cell. So this is important. It does require a lot of bioinformatics support. It does have a bit longer turnaround time. It's really not an issue in the surgical population, because obviously these patients have to recover from surgery. Tissue issues are not as great in the early-stage population, because you have resected tissue or biopsies that are adequate for testing.

And the reason we're testing is because the results of the ALINA trial shown here, this is a global, open-label, phase 3, randomized clinical trial. And this is using the 7th Edition. It included using stage IB; these were the larger stage 1B greater than 4 cm to IIIA, ALK-positive, non-small cell lung cancer. Other key eligibility criteria were good performance status. You were eligible to receive platinum-based therapy, you had good end-organ function, and had no prior therapy. The patients were stratified by stage as shown, as well as by race, Asian versus non-Asian.

The randomization was to platinum-based chemotherapy vs alectinib. Now, this is different than other trials, because this was a

comparison of targeted therapy to our standard guideline-endorsed platinum-based chemotherapy for 4 cycles. The primary endpoint of this trial was disease-free survival by the investigator. There was a hierarchical testing method looking at the stage II to IIIA, so essentially the node-positive population, as well as the intent-to-treat population, which included the stage IB patients. Other endpoints included CNS disease-free survival, overall survival, and safety.

Now, it's important to note that disease assessments, including brain MRI, were conducted every 12 weeks for years 1 to 2, and every 24 weeks for years 3 to 5, and then annually.

Now, looking at the primary endpoint of disease-free survival in the stage II to IIIA patients, you can clearly see that these curves separate early. The disease-free survival hazard ratio is 0.24, so a significant reduction in either the risk of recurrence or death. In looking at the 3-year time point, the difference is 53% for the chemotherapy control arm vs 88% for the alectinib arm on this trial.

When one adds in the stage IB, or this would be the intent-to-treat population, you can see that the hazard ratio remains stable at 0.24, highly statistically significant. It's very early in the follow-up. Obviously, the median follow-up for survival was just over 2 years in both arms of this particular trial. So at this data cutoff, there were only about 2% of overall survival events that had been reported. So we will have to stay tuned for the impact on overall survival in this setting.

Now, I mentioned in the design slide the frequent assessment of the CNS. This looks at the CNS disease-free survival. Again, in the intent-to-treat population, we see here a CNS disease-free survival hazard ratio of 0.22. Very significant in this particular setting. Again, chemotherapy at 3 years, about 80% of patients are free of CNS occurrence, whereas in the alectinib arm, which has very good CNS activity, about 95% in this setting.

So we also recently had some information on a trial referred to as the ALNEO trial. This is perioperative alectinib in resectable stage III disease. There are about 25 patients in this presentation that we saw recently at the World Conference on Lung Cancer. Patients received perioperative alectinib at 600 mg BID. The primary endpoint is shown here with major pathologic response in 39% pathologic CR in 17%. The perioperative alectinib did not impact the percentage of patients undergoing surgery; 86% underwent surgery, R0 resection in all of those patients, and about 81% had a lobectomy. The overall response rate to preoperative portion of alectinib was 80%. And there were no grade 3 or greater adverse events during the neoadjuvant portion – of the alectinib.

Now, we do have data with other agents. This is a very small trial. Only 7 patients reported, but this was neoadjuvant ceritinib in the same population of ALK-positive locally advanced disease. I think the take-home message here is similar to what we saw in the ALNEO trial, again, small number of patients, the overall response rate was 100%, 6 of 7 patients went to resection, 5 had R0 resections. Pathologic response, 2 pathologic CRs and 4 major pathologic response. And again, the most common adverse events were related to GI toxicity, which we know are certainly there with ceritinib.

Now, other agents in this category of patients are being studied. This is the ensartinib trial. Again, this is a trial of adjuvant therapy in ALK-positive resected non-small cell patients. Again, double-blind, a placebo-controlled, phase 3 trial. This is a slightly different design, more like ADAURA, if you will. Again, this is in the stage IB greater than 4 centimeters up to IIIB ALK-positive patients. Again, good performance status, eligible to receive platinum-based chemotherapy. The chemotherapy was optional and was per the investigators discretion. If chemotherapy is given, or maybe the investigator will opt not to give chemotherapy, patients are randomized to ensartinib at the standard dose for 2 years vs placebo for 2 years. This is more similar to the ADAURA trial, very different than the ALINA trial design. The primary endpoint is disease-free survival, and the other endpoints are overall survival as well as safety.

So getting back to the alectinib story again, this is now a guideline standard by the NCCN. But just some issues about toxicity and adherence. Here we see a slide from a recent publication looking at the cardiac toxicity with alectinib; most of this is centered around bradycardia. You can see this is a very nice study by a cardio-oncology group from the Netherlands, 53 patients with ALK-positive disease, treated with alectinib. They were followed with serial echocardiograms. They also looked at echocardiograms and showed no significant changes in left ventricular ejection fraction. You can see that the median heart rate decreased by about 17 beats per minute, 42% developed a bradycardia, 17% required dose reduction, 13% developed edema. This was, of course, edema not associated with a change in left ventricular ejection fraction. And you can see to the right that the higher mean plasma exposure in patients correlated with more severe toxicity. You can see that compared to patients without severe toxicity, that the mean alectinib trough concentrations were higher in those patients with severe toxicity. And no difference between patients with no severe toxicity or those with severe that had dose reduction.

They do offer a management strategy shown here. Obviously, in the bottom part of this, if you have no clinically significant adverse events or asymptomatic bradycardia, try to continue at the maintain dose level. If you get into the symptomatic areas, particularly if you have symptomatic bradycardia with exercise, they suggest a role for therapeutic drug monitoring. And that might lead to a dose reduction in these sorts of patients. And then certainly, if patients have grade 2 adverse events or have unacceptable complaints or

higher-grade toxicity, obviously this would be a reason for dose reduction or other measures. Obviously, the cardiologist will need to be involved with these sorts of decisions.

Now, there is some literature in the field in the area of adherence. Obviously, it's important that patients adhere to treatment to get the effect. This is a retrospective cohort, sort of the Optum Clinformatics data, a commercial claims database, if you will. Almost 38,000 patients. You can see the overall adherence rate was about 52%. The adherence was worse with increased out-of-pocket cost, hospitalization in Medicare, low-income subsidy. They broke it down by tumor site, and you can see we've highlighted lung cancer here. So about 2/3 of patients that maintained a adherence of at least 80% or so in this particular dataset.

Now, we know there are adherence barriers. These include low health literacy, limited patient knowledge, they have a complex administration schedule. Certainly, the two probably that drive most of it are adverse effects, as well as out-of-pocket costs. There are a number of tools that have been used over the years, pill diaries, pill counts, electronic monitors, cellphone apps, refill rates, obviously direct observation, as well as drug monitoring. There are some data with exposure response with alectinib. This is again in an observational study of about 52 patients, standard dose of 600 mg BID. Progression-free survival is prolonged in patients that have a higher median. Shown here to the right, you see the patients with a higher than 435 ng/mL concentration vs the lower. This is statistically significant. And so the implication here is, would monitoring levels make a difference in patients that really have no or minimal toxicity? And should that be part of routine clinical management in this particular setting?

Lastly, a few comments about endpoints in operable non-small cell lung cancer. Typically, as you've seen in the trials that I've mentioned, disease-free survival has been the primary endpoint. This has been demonstrated to be a valid surrogate endpoint for overall survival in trials of adjuvant chemotherapy. And we do have precedent in the ADAURA trial that that initial DFS benefit translated into an overall survival benefit. I think other clinically meaningful endpoints here include CNS disease-free survival. This is a very common problem in the ALK population to have brain metastases, so protection of the CNS is important. Patient-related outcomes, what is the impact of toxicity? As well as adherence, so you can get the long-term benefit from these treatments.

So our key takeaways here. Targeted therapies are now part of the standard of care in molecularly defined subsets of early-stage resectable non-small cell lung cancer. Molecular profiling is the standard of care. Ideally, it should be done by next-generation sequencing, and should be performed in all these patients with stage IB through IIIB disease.

Now in the ALINA trial, we saw the adjuvant alectinib improved disease-free survival, as well as CNS disease-free survival in stage IB through IIIA ALK fusion-positive resected non-small cell. Again, the disease-free survival has been a valid surrogate endpoint for OS, although we don't yet have OS in the adjuvant setting in this population of patients.

We should develop strategies that ensure adherence for patients. And certainly, what we've seen in data thus far is that the side effect profile of alectinib in the post-surgical setting appears to be manageable, just like it is in advanced-stage disease.

So with that, we will conclude today's activity. Thank you for your participation.

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