Lung Cancer Library

Case Based Panel Discussion

Stage IV ALK+ 74 YO Male with Brain Metastasis

Outcomes of Genomic Profiling: FISH Testing vs. NGS

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Dr. Benjamin Levy: Hello. I'm Dr. Benjamin Levy. I'm an associate professor at Johns Hopkins School of Medicine. And it's a pleasure for me to have two fabulous faculty members, one from Georgetown and one from Johns Hopkins as well for this GRACE discussion. And it's a pleasure for us to have a forum where we can discuss cases and work through how we would manage these cases. And so we'll be doing that over the next 30 to 45 minutes. We'll be looking over separate cases and talking about how we would manage these and maybe even taking a step back and talking about some of the treatment or diagnostic implications of these cases. But before we get started, I just want to turn it over and have each of the panelists introduce themselves before we get to the cases. So, Stephen, I'll start with you.

Dr. Stephen Liu: Thanks, Ben. Happy to be here. My name is Stephen Liu. I'm a medical oncologist at Georgetown University in Washington, DC.

Dr. Benjamin Levy: And Julie.

Dr. Julie Brahmer: Hi, thanks for having me. I'm Dr. Julie Brahmer, I'm a medical oncologist at Johns Hopkins.

Dr. Stephen Liu: That's great. A pleasure to have you both here. All right. So I have a shorter case to go over that I think has some interesting points. This is one of my patients. Although I think they did see you once Julie early on in their course is a 74 year old gentlemen who presented way back in 2016 with dyspnea. This has been going on for a few months. He was prescribed let's see, Bronchodilators for, I guess, adult onset asthma. He was given multiple courses of antibiotics. He's given a proton pump inhibitor, but the shortness of breath kept getting worse. I finally got a chest x-ray, which showed a large left pleural effusion. We sent him for a thoracentesis that's where we remove that fluid, and it did reveal cancer in that fluid that makes this a stage four cancer. His full CT scan showed mediastinal lymph nodes and spread to the bone. An MRI did show multiple brain metastases as well. He had no symptoms from those.

He had molecular testing done at his local community hospital that showed a normal or negative EGFR, ALK, KRAS, ROS, and BRAF. And so when he was seen at the outside facility he was recommended to start immunotherapy, and that would either be standard immunotherapy or as part of a clinical trial, but because there were multiple brain metastases they decided to treat that first. In fact, he had opted for the clinical trial, the trial required that those brain be radiated. So he was being radiated that he was getting a stereotactic radiation to the brain metastases, I guess my first question is you know, what should we do next? What would you recommend maybe if a trial wasn't available? Ben What do you think?

Dr. Benjamin Levy: So, this is a patient with unfortunately advanced adenocarcinoma of the lung. The cytology from the fluid was positive. He doesn't unfortunately have anything molecularly that could allow us to give a targeted treatment off of the trial. I didn't see his PD-L1, do we have a PD-L1?

Dr. Stephen Liu: Let's say it's unknown because this was back in 2016, but let's say the PD-L1 is unknown.

Dr. Benjamin Levy: Okay. I think off of a clinical trial, I would probably offer this patient chemotherapy with immunotherapy. I would offer three drugs, carboplatin, Alimta, and Keytruda similar to the last case. And at least offer four treatments as long as the brain is also being addressed or has been addressed.

Dr. Stephen Liu: So that's a good point there. Maybe I'll ask Julie is it always necessary to treat those brain metastases with radiation or sometimes can you watch those?

Dr. Julie Brahmer: So a lot depends on the patient's symptoms and size and how much swelling is around someone's brain metastasis. Certainly if they're very tiny and their patients are not having any symptoms from them, you can consider with either immunotherapy or certainly for sure, with targeted therapies, you can consider starting with treatment without doing radiation, but if someone's having a lot of swelling around a mass or a very big mass, even if it's not symptomatic than we usually like to do some treatment. But I guess I'd probably, I mean, this is in 2016, but if they presented today, I would want to thumb through the molecular testing that was done to look, to see which genes were tested to make sure that they're testing everything that I can think of that has a targeted drug available. Obviously this changes almost on a at least every six month basis which is exciting these days. But it's just something to always look at as a physician to see which mutations have been tested for, or other things that could be targeted with targeted therapies.

Dr. Stephen Liu: I think that's such an important point. I think a medical oncologist in 2021, especially in lung cancer really needs to be a molecular biologist or a pathologist. They really need to understand not just what genes to look for, but what tests to run. These are some of his original images we see on that left panel, the large left pleural effusion. That's also shown that middle panel. And on the left panel, we see an image of one of the brain metastases there in the top, right corner of that scan. If you go to the next slide because he was getting this radiation. He was able to seek out second opinions and he saw some other oncologists myself included that recommended that he really get full next generation sequencing. I did not share those details. The original tests were all PCR and fish based tests. We sent him for a full DNA and RNA sequencing. And if we click the next slide, we see that there was EML4/ALK fusion. The most common fusion, not a rare variant, not a rare alteration, one that we actually tested for. But it was tested with FISH, which is not as sensitive as a test. Let me go back to you, Julie, do you see this a lot where the first test is negative and then the second test is positive? Did they do the test wrong?

Dr. Julie Brahmer: No, I think it's the sensitivity of the test. So FISH based testing is not as sensitive as the RNA seek test. So if you have a high index of suspicion it's definitely worth going in and doing the full NGS, test results. And we typically recommend that this is done.

Dr. Stephen Liu: This patient found an ALK fusion. He was started on a drug called alectinib or Alisenza, can you tell us a little bit about that drug? Is that similar to osimertinib and EGFR?

Dr. Benjamin Levy: I think the data we seen it looks as good if not better than osimertinib in the EGFR space. So this is a tyrosine kinase inhibitor, similar to osimertinib, but works differently. It works for patients without fusions. The data that we have just briefly that has been kind of the Seminole work that has led to the approval and the clinical implementation of this drug is the Alex Trial looking at this drug in comparison to a prior ALK directed therapy called crizotnib. Head to head comparison, showing improvements in outcomes with alectinib versus crizotinib and importantly improvements in intracranial responses as well, which we know is ALK lung cancer has a proclivity go to the brain. And this drug seems to be better in the brain than crizotnib. And you know, the median time on drug updated analysis or what we call median progression-free survival is close to three years that is incredible to be on a drug that long in this day and age, and it really has pushed the envelope. So that is my preferred drug for, for out fusion patients. There's other drugs that are out there but clearly alectinib has, I think I have the most experience with, and we have the most data on.

Dr. Stephen Liu: Do we have other reasonable first-line options here if you know, if a doctor suggested a different drug, are there other drugs we think of here?

Dr. Julie Brahmer: Well, certainly we had an older drug called crizotnib. But that was particularly for this patient with brain metastasis, that drug did not give into the brain very well. There's Ceritinib as well as alectinib. And then there's also a newer drug called forgatinib for the first-line treatment. And that certainly would be an option as well. I think lorlatinib may be the next drug to come into the first line space because that drug also gets into the brain and is very good at targeting some resistance mechanisms. But I think from my standpoint, alectinib is still my go-to drug because it seems, and for most patients pretty easy to tolerate.

Dr. Stephen Liu: I think about this particular patient a lot, still very close to this patient. If we go to the next slide. I often play, and here's the images of that scan. We can see that left effusion really cleared up. The brain metastases, granted they were radiated, but he's had pretty much a complete response and we're coming up on about five years still on the same drugs, still with a complete response, doing really, really quite well. But I think about it a lot because I think we were very close to things going in a different direction. If we click that next slide you know, I'd like to play the, what if game, what if we had not done next gen sequencing, which I don't think anyone would have faulted anyone for 2016, those are most of the genes we were looking for. He had an FDA approved test you know, FISH is a standard test. There's nothing wrong with that test. If we had not done NGS, he would have enrolled onto that immunotherapy trial. And that was immunotherapy

alone at the time. And you know, Julia, what do you think would have happened if this ALK positive test?

Dr. Julie Brahmer: Yeah. For immunotherapy alone in ALK positive patients right now, a single agent such as Keytruda or Opdivo or some of the other PD1 or PD-L1 antibodies, we don't think that these drugs work very well for these patients, particularly in the first line treatment setting where they've never had treatment before. But I would say that while chemotherapy doesn't work, as well as these targeted ALK drugs, Alimpta plus carboplatinum has worked well for some patients before we had these types of drugs available and they can work well for a long period of time. But certainly when compared head to head that ALK targeting drugs work hands down better and longer than the chemotherapy does.

Dr. Stephen Liu: Yeah, that's been my experience to me in a therapy has been largely ineffective here. And I think that the sequences is important. And we've talked a bit about this before, but Ben, if this gentleman had enrolled onto an immunotherapy trial, which would have been probably ineffective we would not have treated that cancer really with an effective drug for at least a few months. Now he comes back to see us. And if we detect the ALK fusion, then after immunotherapy, can you tell us a little bit about that situation and the challenges there?

Dr. Benjamin Levy: It's a double whammy you've given first of all, a drug frontline that like immunotherapy, that we know just doesn't work all that well. And in this type of molecular niche without, so that's one way, I mean, and then the second whammy that you're alluding to is that if you then discover the ALK and this patient then needs to go onto a drug like alectinib. And if we know there's a real chance for toxicity, we are learning that there is overlapping toxicity when you start a patient on immunotherapy first, and then you have to sequence them to a tyrosine kinase inhibitor, like alectinib. There's a chance that could develop inflammation of the lung or inflammation of other organs. And we've seen that in other datasets, there's a real chance of pneumonitis and other toxicities. So we have to be careful.

And this is the importance of, I think, what you were getting at before of, you know, dotting the I's and crossing the T's, and truly searching for molecular underpinnings of the tumor leave, no gene behind. And so I think that's really, you know, the challenge here is the patient starts on immunotherapy, then that's, it gets sequenced afterwards to a targeted therapy. One, they should have gotten the targeted therapy first. Two, if you do give the targeted therapy, you may need to space it out and give a tincture of time and be patient somehow some way before giving them that drug, maybe giving them chemo first or another chemo first, and then giving them the tyrosine kinase

inhibitor, like alectinib maybe eight, 12 weeks down the road, which would delay treatment, but which is sometimes what we have to do.

Dr. Stephen Liu: These are great points, and I know we're at time, but just to sort of close this case, I think that lung cancer is very complex and there's a lot of thought that goes into this. Each case is so individual. And when we see a patient you know, it's not always the fastest treatment, we really need to get the right treatment and we don't want to guess we want to get it right the first time. So I know great points, thanks for your input, both Julie, Ben.

Dr. Benjamin Levy: Yeah. These were great cases, a robust discussion. I learned a lot and I really do appreciate both of your expert insight and really leveraging your research and clinical expertise into this because the field is evolving so quickly. It's always nice to hit the pause button. Look at these cases, see where we are and discuss them and move the field forward. So Stephen and Julie, thank you for joining for this panel discussion. It's been a great one. Hopefully we can do it again soon.

Dr. Julie Brahmer: Thank you.

Dr. Stephen Liu: Thanks.