Lung Cancer Library

Case Based Panel Discussion

Timing and Treatment 48 YO Male with EGFR NSCLC, High PD-L1 with Lung Mass & Disseminated Cancers Across Both Lungs & No Real Comorbidities

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Dr. Benjamin Levy: 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, 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. Benjamin Levy: That's great. A pleasure to have you both here and again, we'll, we'll try to get to three or four cases and these are real cases. So I think the relevance here will resonate with all of us. So we'll start with patient one here. This is a 48 year old male. He's a hedge fund manager. He's married, he's a never smoker. And has two siblings and no history of any malignancies. His past medical history is consistent with hypertension and hyperthyroidism. His surgical history is just significant for work for wisdom tooth extraction. And he has no allergies only on Synthroid and hydrochlorothiazide. And his initial presentation to us was in March of 2018. When he presented with to the emergency room with worsening, shortness of breath and cough, and a 10 pound weight loss. His examination showed decreased breath sounds bilaterally. He did have a right supraclavicular node or a enlargement above his right clavicle, which was a palpable, so we could feel it.

And a CT scan in the ER demonstrated what we see here. And, you know, what we're seeing here is a cut of the lungs. And we can see here on the left image a mass roughly two centimeters in the right upper lobe, that's that white speculated spot there, but then what we see across both lungs, in other cuts, we see a lot of white here and that white is really disseminated lung cancer across both lungs. So you know, clearly this patient has lung cancer, not only in his right lung but his left lung as well. The patient does get some initial blood work. That's not that abnormal. He has a slight anemia or low red blood cell count and he's admitted to the hospital for management, he's placed on oxygen. And as part of all of our lung cancer workups, or the presumed lung cancer workups, he does get an MRI of the brain. We need to be mindful that lung cancer can go to the brain. And he does get an MRI of the brain that is negative.

His patient, we often have to decide what's the best way to get tissue on patients. And maybe this will be my first stopping point to ask the panelists, you know, so this decision on where to get tissue and how to get tissue, I think we now know that tissue is critical and we can talk about other ways that we get information for lung cancer patients, not just off tissue, but potentially liquid or blood. But maybe I'll start with Stephen. You know, some of the considerations you have when you see a patient like this and some of your thought processes on, you know, what's the best way to get tissue. And is there a thought process, and is this a discussion you have with your multidisciplinary team?

Dr. Stephen Liu: It really is. And I think that's changed a lot during our careers. In the past, I think a lot of oncologists wouldn't be called until the diagnosis was already established, but we are encouraging our colleagues, our internists, our referring doctors to really involve us pretty early, if there's a suspicion because how and what you biopsy, it makes a big difference. I think in the past, you wanted to make a diagnosis and a diagnosis of cancer is made with a biopsy. We'll talk a bit about liquid biopsy during these sessions, but today to make a diagnosis of cancer, we need a tissue biopsy, a needle biopsy, a surgical biopsy to really look under the microscope and establish that this is indeed cancer. I think we've all been fooled where we saw something that really looked like a cancer, but ended up being an inflammatory lesion, sarcoidosis infection, something different. We need to prove that it is a cancer. And we used to do that in the safest possible way, the smallest needle, the most accessible lesion to really minimize any risk from that biopsy.

Now, though we realize that what your biopsy and how much tissue you get from that biopsy can have major implications on the treatment course. Lung cancer really is managed by molecular testing. We have to keep that in mind, when we do this biopsy, then making a diagnosis of carcinoma or lung cancer or non-small cell lung cancer, even adenocarcinoma. That is not enough of a diagnosis that does not give us enough information. We need more tissue. So we want to biopsy an area that will yield enough tissue to do the types of tests. We need lymph nodes, lung organs. Those are all lesions that can be biopsied. Bone can be biopsied, but when we decalcify the bone for the processing, that can sometimes damage the DNA and make subsequent molecular testing a little more difficult. And I'll end with one more thing. We still want to minimize the number of procedures. So if I have a suspicious lesion outside of the chest, if I can make the diagnosis and establish the stage of that cancer in one process, in one procedure, then I'd prefer to do that.

Dr. Benjamin Levy: Yeah, that's well stated. I think encapsulates all the things that I think we think about when we see these patients, Julie, you know, do you talk, if you see these patients, are you talking to both the interventional pulmonologist and the interventional radiologist? Who's making the decision? Is it the medical oncologist here? Stephen talked about how important it is and how critical it is to get tissue who makes this decision for you, or is it who makes decision your team? Is it you, is it your colleagues?

Dr. Julie Brahmer: Yeah, I think that you know, to Stephen's point, you know, the tissue is really needed when we want to look at PD-L1 as well as the diagnosis. And thus far blood has not yet been great about picking up PD-L1 expression on tumor cells, but I'm sure that's coming. But from a diagnosis standpoint, to decide where to biopsy a lot, depends on who's

ordering that biopsy. So, it potentially could be an internist. It could be a pulmonologist, it could be the floor team, and that's who ends up deciding obviously it's great to be involved early on to best decide where the biopsy is done in order to be able to get the largest amount of tissue safely, as well as established stage if needed.

Dr. Benjamin Levy: So, this patient, a lot of the things that you guys so eloquently stated, the conversations did go down and, you know, I think in a never smoker, and we now know that 20% of lung cancer is never smokers. And this is something we're seeing more commonly. The need for tissue is important. We can talk about why that is. This patient had a CT guided biopsy of that big note on top of his clavicle, and it did reveal the most common type of lung cancer was non-small cell lung cancer. And the subtype that we see, which is about 70 to 75, 80% of non-small cell was adenocarcinoma. As you mentioned, Stephen and Julie, this tissue was sent off for molecular testing, otherwise known as NGS or next generation sequencing. So we all know that may take some time, and maybe we can talk about the importance of that in a few slides down. But clearly all the right steps were put in here and we got enough tissue. The PD-L1 was 80%.

Remember we do to try to capture both what type of lung cancer it is, but also additionally, two separate things PD-L1, which is important to drive immunotherapy decisions, but also more importantly, potentially is molecular testing and next generation sequencing. And that takes a little more time sometimes than the PD-L1. So this is what we have right now. We have a patient, you saw the scan, the patient's a little bit symptomatic. The patient has a biopsy and the patients, you know, sent out on four liters of oxygen. And I guess the question is, is what should be done next for this patient? And, you know, I don't know if there's a right answer here. You have a patient with lung cancer in both lungs with an adenocarcinoma diagnoses. We have the PD-L1 back the is a little bit symptomatic, and we don't know yet about the molecular testing, which we know can drive treatment decisions. So Stephen, no right answer here. But what would you do in this setting, in a patient like this?

Dr. Stephen Liu: You know, you mentioned that he was stabilized was sent home. I will sort of also in the same breath mentioned that this person is fairly, I think, symptomatic. He's on oxygen now. He wasn't before. And when I see CT scans like that, and, you know, I think we've all seen our share gets my attention. There's a lot of disease there. And in someone who's already hypoxic, I think a little more progression and this person can really be in trouble. So this is not an elective process, and this is a workup that needs to go fairly quickly. This person needs to start treatment pretty soon. And so I think that our next steps really need to be figuring out what treatment we need and sort of what the optimal sequence of therapy is.

Dr. Benjamin Levy: Right. So, a good framework to start. Julia, I'll put you on here. So, Stephen said maybe starting treatment. What would you start with? Would you start with chemotherapy, would you start with immunotherapy? We know the PD-L1 is 80%, and we've learned from you that PD-L1 greater than 50%. Those patients derive a meaningful benefit with immunotherapy. So, this is a patient that may need treatment. We know the next generation sequencing; the molecular testing may take two to four weeks to come back to tailor that treatment. What would you do in this case?

Dr. Julie Brahmer: Well, I think this is a great case. I think at this point while we're waiting, I would order an additional test to be drawn doing cell-free DNA or CT DNA in the blood to see if we can by chance pick up tumor DNA circulating in the blood. This is not tumor cells, but DNA that shed in the blood and the hope is that the data would come back more quickly compared to the tissue NGS in order to be able to direct therapy. But I agree with Stephen, I don't know if I feel comfortable waiting at all for treatment. Now with this patient, who's a never smoker. You're tempted with a high PD-L1 to do a pembrolizumab, but the fact that he's a never smoker gives me pause in the fact that there is a fair chance that this gentleman would have a targetable gene change that we can use a pill for. And if we give them or these types of patients pembrolizumab first, and then try to give a targeted therapy, there's a higher chance of side effects. So honestly, I may start, if for some reason I'm worried that I can't do a cell-free DNA test for some reason or another. I would consider giving them just chemotherapy first while I'm waiting for the NGS. So that's fine.

Dr. Benjamin Levy: All right. You both are right. So this patient got chemotherapy and at the same time prior to chemotherapy, we ordered a liquid biopsy and Stephen, maybe you can talk just briefly about liquid biopsies and why we're using them. And this whole idea of capturing 10 CCs off of a patient or 10 CCs of blood off a patient that may allow us to decide which treatment sounds like science fiction 10 years ago, but it's reality for our clinic patients now briefly just a bit on liquid biopsies

Dr. Stephen Liu: We all know that when tumor cells die, they break and release their DNA into the bloodstream. And we have now the technology to capture that DNA and to look for cancer associated mutations. These tests are commercially often done, and there are several different vendors out there. The turnaround has better and better. And I think that years ago, it took a couple of weeks. Now we will often have those results back within a week. And a lot of times we'll get the results back before we can even schedule our next dose of chemotherapy so they can come back quite quickly. But it's important to interpret them in the right way. They are fairly specific meaning if we do a blood test and we find an actionable driver mutation, we see this change that we can target. We believe it. We act on it. We move. If we, however get nothing back, there could still be something there it's not always picked up in the blood. Some tumors are not shedders

meaning they don't release their DNA. And so, you may miss a lot of them. If you see a positive test, we believe it. If it's a negative test, you have to wait for the tissue.

Dr. Benjamin Levy: Yeah, I think it's been a pleasure to see the advancements in this happen so quickly. It's been such a win for our patient. Julie, Stephen talked about actionable mutations, and maybe we can just step back like 10 steps here. What are actionable mutations, and why is it so important to order these liquid biopsies? I mean, what's this whole idea of targeted therapy and how is it different than immunotherapy?

Dr. Julie Brahmer: Targeted therapy is specifically designed to target a specific gene change. And so most of the drugs that are currently approved for these type of changes have a very high response rate, and our tumor shrinkage rate and how also have a long disease, a long time where the cancer can be controlled just on a pill. And so most of these drugs have that data behind it, and some of the drugs actually have been directly compared to chemotherapy. And so we want to be able to get the best type of therapy for each patient. Now, target therapy is different than immunotherapy in the fact that if you aren't on the targeted therapy, the therapy doesn't continue to work. Immunotherapy. We're trying to take the brakes off of patient's immune system in order to get the immune system to target the cancer.

And then that case, if we have to stop the therapy for one reason or another, we can speed prolonged immune effects, where we train the immune system to target the cancer. Typically interestingly, for those patients with targeted genes associated, or excuse me, changes in their genes, more associated with never smoking, these patients tend to do not quite as well with immunotherapy. And so this is why another reason why we think that these patients may not do as well, just in the fact there's typically one, or just a couple of changes in their tumors where the immune system cannot target very well.

Dr. Benjamin Levy: Yeah. But build on, sorry, go ahead and.

Dr. Stephen Liu: Just to sort of build on what Julie said. You can't guess, right? Because it's not like there's one mutation where there isn't, and we can just try a pill because now there are so many different mutations and different pills. And if we line up that mutation, that genetic vulnerability with the right pill, we're so confident, right. We know that this is going to work. It almost always works. And it works fairly quickly. Patients can feel better within days, much faster than radiation. Then chemotherapy responses are very fast and they they're very frequent, but if we give the wrong targeted treatment, the chance of response is zero. It won't work. And so, you can't guess you really need to know sort of what specific mutation is there.

Dr. Benjamin Levy: Yeah. As a former mentor of mine once said, test don't guess. You've got to have, you can't get the drug unless you, you know, you know, the target. And as you mentioned, there's a growing list of targets that can be wedded to all these new therapies. And some of them older therapies that are still around, but certainly targeted therapies that have brisk responses. So, this patient for the sake of time has an EGFR mutation, which is one of the more common mutations we see, this is not a gene that the patient was born with. I talk to patients about this. This is a gene only inherent in the lung cancer. People get a little confused or patients get a little confused about genetic testing and what that means. And when we're mentioning this, we're talking about genes only inherent in the lung cancer that governed the lung cancer's growth. So this patient has an EGFR mutations, this is one of the most common genes that we see. And we see here, this is just six weeks of a drug called Osimertinib. And we see, you know, a lot of white on both of these lungs here, that's lung cancer that has completely resolved after six weeks. Is this atypical? Or is this what we generally see? Stephen Is this what you're seeing in your clinic with patients with targeted therapy, these types of responses?

Dr. Stephen Liu: Yeah, it really is, you know, it's you know, we're in a specialty where you can't make promises or guarantees, but if things line up, right, you know, we're very confident where we really expect a response, not a situation where we're hoping something works. We really expect it to work. And if it doesn't work, we really are scratching our head and trying to figure out why. So seeing responses, complete responses, or even dramatic responses is fairly common. And, you know, patients will call back and say within days they're feeling better. And then it can be very rewarding when we line it up. Right.

Dr. Julie Brahmer: Ben, you might want to just note on the garden testing, there was data for gefitinib or erlotinib as well as gefitinib. But now we have data, at least in this particular where as you chose the osimertinib does outperform erlotinib and the gefitinib based on a clinical trial. And so, you know, osimertinib would be our typical go-to drug right now for the first-line treatment or in patients with no prior treatment for this particular EGFR mutation.

Dr. Benjamin Levy: Yeah. I think that osimertinib certainly has become the standard of care based on that phase three flora study. I'd love to spend time on the longitudinal assessment of liquid as you see down here, but we're going to move on. Because there has been some data that intuitively if the level of the mutation in the blood drops, that's a good indicator that the drug is working very well. And we saw that in this case, I want to end this case with unfortunately what we know about these drugs is that they work very well for a period of time. But resistance can occur. The cancer cells can start figuring out ways to

grow and there's different ways they can do this. And we call this resistance in that we see these patients will start to experience more symptoms. And then we see that the cancer can grow again. And that's hard for patients. It's hard to relay that, that we've got this great drug, but unfortunately at some point it may start, the cancer may start growing again on that drug.

So, the patient here, unfortunately after two years of being on osimertinib, which is not atypical I don't think, that's right in the range of what I generally see does start experiencing worsening, shortness of breath and some shoulder pain. And we see that there is some pleural fluid there that's built up and to save the suspense, essentially this is tapped or removed and it's cancerous, and there's worsening cancer below that, underneath that pleural fluid. And so I guess the question is, you know, a lot of patients ask, well, you started me on a great targeted therapy. It's worked for a while. What's next? What do we do next? And what's the plan. And so Stephen, I know you work a lot in the genotype space. You've led a lot of the efforts in the resistance setting and identifying novel genes in lung cancer. What do you tell patients when we get or if you get to that point?

Dr. Stephen Liu: Right. Well, I try to prepare patients early and, you know, I'll also say there's no limit as to how long a drug osimertinib can work. I think we've all had patients. We care patients that have been known for extremely long periods of time. But as you said, these aren't cures. And eventually for most patients, we will encounter resistance. And the way I look at it, if you know, something's changed, we gave a drug, we had a good response, the cancer got a lot smaller and a lot better, and now it's growing again. So something has changed here. If we haven't changed our treatment, then it means the cancer has changed in some way. If we can pinpoint exactly how the cancer has changed, and then we can overcome that change, adapt our treatment to really overcome it and counter that resistance. So, I would repeat a biopsy. I would send a liquid biopsy, I would send a tissue biopsy and really try to understand what's different about this cancer. And can we very easily adapt our treatment to overcome that resistance.

Dr. Benjamin Levy: A great point. Julie, you've been intimately involved in the immunotherapy field and led a lot of the efforts. Is this where immunotherapy comes in? Is there a time where Immunotherapy comes in these patients?

Dr. Julie Brahmer: Well, obviously it depends on the patient and how they're doing. But outside of a clinical trial that matches a patient resistance mechanism. The next standard treatment is really chemotherapy or chemotherapy plus immunotherapy. And for patients with EGFR mutations, the only study that included patients like this in chemotherapy and immunotherapy trial was a study called Empower 150. And that trial combined chemotherapy plus a something called anti-VEG F antibody that was Susamab also

known as Avastin, and then added Atezolizmuab, which is an immunotherapy drug. And that four-drug regimen seemed to do better compared to chemotherapy, plus just the bevacizumab or better than chemotherapy itself. So, in patients that I think can tolerate those four drugs, that's what I consider. I don't think single agent immunotherapy at this point would be the next best thing. I think really chemotherapy in some type of combination would be the best place to go outside of a clinical trial, that specifically is for mechanism of resistance that can occur.