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Released: 12/30/2021
Valid until: 12/30/2022
Time needed to complete: 15 minutes

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Keeping Pace in Lung Cancer: Integration of Immune Checkpoint Inhibitors as Initial Therapy for Advanced Disease

Announcer:
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Dr. Socinski:
Hello, and welcome to this lung cancer education series. Immunotherapy has become a new pillar of treatment for patients with non-small cell lung cancer whose cancer does not have an actionable mutation. Today we’re going to discuss the selection and management of immune checkpoint inhibitors for these patients with advanced disease.

This is CME on ReachMD, and I’m Dr. Mark Socinski.

Dr. Patel:
And I’m Dr. Sandip Patel.

Dr. Socinski:
So, Sandip, let’s get started. It seems that new targets are being identified in this disease every day, and we, you know, have to identify them. We’re going to focus not necessarily on the actionable targets, but what’s the population today that does not have an actionable target?

Dr. Patel:
In my opinion, all metastatic lung cancer patients have an actionable target, whether that target relates to a specific small molecule inhibitor, for example, for EGFR, ALK. Whether it be immunotherapy for PD-L1 high or the absence of those biomarkers, indicating chemoimmunotherapy may be a patient’s best option. I think all patients have a, quote/unquote, actionable target, but in terms of a bona fide small molecule inhibitor, it’s probably about 40% to 50% depending on your patient population, of which the most common mutations you’ll see will be EGFR and KRAS G12C, followed by ALK.

So the most common actionable target for lung adenocarcinoma, especially never-smokers, is EGFR. KRAS G12C tends to be more common in former smokers. And it’s really critical to understand if a patient has a targetable driver mutation, because not only do we know that patients, for example, EGFR and ALK rearrangements, who were not part of the early immunotherapy frontline studies, but if they get immunotherapy and then receive targeted therapy, they’re likely to get toxicities in addition to lack of benefit from their prior immunotherapy, which can be severe pneumonitis or immune hepatitis, for example. And so as patients become refractory to these targeted therapies, at that juncture, consideration of chemoimmunotherapy regimens is very reasonable. One of the ones that’s most commonly utilized and studied is the IMpower150 regimen, looking at chemotherapy, anti-VEGF, and anti-PD-L1-containing combination therapy.

Dr. Socinski:
So let's assume you've done your comprehensive genomic testing, and, you know, assume it's on tissue and blood, which is what we both do, and there is no actionable target. In that setting, what factors do you consider when selecting initial therapy for a patient with advanced disease, stage 4?

Dr. Patel:
And so there are 2 ways to get a negative test, I think, in molecular medicine, right? One is you don't get any drivers at all to explain what's going on in their cancer, and then doing either repeat liquid, repeat tissue, I think, can make sense. And if you have to do something while you're waiting, this is a good time to do radiation. You could do chemotherapy by itself and add immunotherapy in cycle 2. But let's say they have a non-actionable KRAS, or they have a driver that's not targetable. I think these are patients where immunotherapy can play a role. I do test for PD-L1 in those patients that have tissue available that's amenable for PD-L1 testing. And these are great candidates for chemoimmunotherapy approaches or if their PD-L1 status is high, immunotherapy alone.

Dr. Socinski:
So how do you deal with the issue that PD-L1 is an immunohistochemical test? We get it back in 48 hours or so; you have that result. Should we act on it before you know the genomics, or what's your advice?

Dr. Patel:
Yeah, it's a great question. I think one key point about PD-L1 is it's not a direct biomarker, meaning your PD-L1 can be high and you can, for example, have an EGFR exon 19 deletion. That can happen, 30%, 40% of the time. You can have an ALK or ROS1 rearrangement over half the time, potentially, with a high PD-L1.

And so PD-L1 can be a red herring, and it can actually really lead you astray by itself, but in conjunction with the molecular sequencing, really place the patients on their right path. And so what I'll typically do is, you don't have the PD-L1 back, I'll wait for the remainder of the molecular sequencing to make sure they don't have an EGFR, ALK, ROS1 or any other targetable mutation. Because in all these scenarios, we know targeted therapy works better, and we also know that you can get unusual kind of pseudosynergistic side effects when we do immunotherapy before a targeted therapy that we really want to limit for these patients.

Dr. Socinski:
Dr. Patel, can you give us an overview of how you think about immunotherapies when you are trying to match the right initial treatment to the right patient with advanced disease – kind of what's going through your mind? And why don't we start with the high expressers, the greater than 50% PD-L1 positive?

Dr. Patel:
Well, I think one key concept with the greater than 50% PD-L1 population is to avoid the red herring of the PD-L1 coming back and the genomics not yet coming back. For example, patients with EGFR, ALK, ROS1, and so on, can be PD-L1 greater than 50%. So after you've done the genomics and found that there's no targetable driver for those patients, I think symptomatic burden probably plays the biggest role in determining whether they receive chemoimmunotherapy or immuno-monotherapy in the form of drugs like pembrolizumab and atezolizumab and cemiplimab. For those patients with lower volume disease who have high PD-L1 status, I – and whether this is through a 22C3 Dako, or an SP142, which looks both at tumor immune cells – I think this represents a very attractive option for these patients. We do have the additional data that at 2 years, there is the option to discontinue frontline therapy, otherwise these patients are coming in every couple weeks, and those patients can benefit from rechallenge. But now we're starting to see data out to 5 years, meaning 3 years after their last dose of protocol-mandated therapy, that a third of these patients are still alive in metastatic lung cancer, which is a drastic difference from the era in which we were debating the bark of which U-tree was the superior anticancer agent.

Dr. Socinski:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Mark Socinski, and here with me today is Dr. Sandip Patel. We're discussing immune checkpoint inhibitors for advanced non-small cell lung cancer.

Yeah, I'd like to get your perspective. If you look at the data from KEYNOTE-024, IMpower110, and EMPOWER-Lung 1, in the results of those data, realizing that KEYNOTE-024 is certainly the most mature of all those trials, in some ways, it kind of looks like, Coke, Pepsi, Dr. Pepper. You know, we all have our favorites there. The data looks very convincingly similar. Do you have any thoughts or preferences, or do you think they all offer roughly the same benefit?

Dr. Patel:
I think they're all similar. Of course, you mentioned the earliest data we have is for pembrolizumab, and so we have the most mature data there. But there's scenarios in which, you know, atezolizumab, for example, someone with high immune cell – meaning greater

than 10% PD-L1 expression – that may be their only opportunity for immuno-monotherapy. If you're a patient with a history of HIV, hepatitis, or active brain mets, the data would be more along the lines of cemiplimab. But your point, that by and large, the pembrolizumab data – and it's every-6-week dosing, which for many patients because they're going to do so well for so long, may be an advantage – is well taken. But like you, I view these very similarly, and whichever button on the vending machine I press, I'm going to be happy with any of these choices.

Dr. Socinski:
Yeah, and then I do think we should touch on this a bit. There are patients with a heavy symptom burden, a high tumor volume when you look at their scans and stuff, where you know you can get a 20%-25% higher response rate with chemo IO, so even if their PD-L1 expression is very high but they're symptomatic or have a great tumor burden, where you really feel like you need to get control of the disease, get a response, I use chemo IO in this setting and do not necessarily trust immuno-monotherapy as much as I do adding in the cytotoxic chemotherapy.

The 1 to 49s or the negative – is this the land of, kind of, chemo-IO combinations?

Dr. Patel:
I think so. I think chemo-IO or dual immunotherapy – PD-1, CTLA4 – is very reasonable here. I tend to go with chemoimmunotherapy whether it's, you know, chemotherapy plus pembrolizumab, chemotherapy-nivolumab, ipilimumab. These are all reasonable choices. I think it relates to specific patient factors. For example, for me, if patients have brain metastasis or squamous histology, these are patients I may preferentially consider a CTLA4-based chemo, PD-1-containing regimen, for example.

Dr. Socinski:
Yeah, are there patients with lower expression in which you would use immuno-monotherapy? We know we have the indication for pembrolizumab, greater than 1%, but we had a nice analysis from the FDA at ASCO this year that didn't really shine a very bright light on that strategy.

Dr. Patel:
Yeah, it's definitely an option to use, you know, pembrolizumab, for example, per KEYNOTE-42. You could use nivolumab plus ipilimumab, CHECKMATE 227 here, as well. I think, for the 1%-49% patients, and even the PD-L1 0% patients, there is a benefit to chemotherapy, and – if the patients can tolerate it. But if they have an absolute contraindication or it's one of these scenarios where if you try to do perfect, they won't do anything, right? Meaning if you do chemo, they'll walk away from the whole regimen. You do as much as you can. And, you know, if a patient has the right molecular signature, right, you know, even though their PD-L1 may be intermediate, if they have, for example, very high TMB [tumor mutational burden], they lack STK11, KEAP1, they may still respond. But I think that's a personalized issue, and I think if you had to pick a default, chemoimmunotherapy would be my go-to here.

Dr. Socinski:
So let me ask you one other question, and that is, we haven't touched on the role of bevacizumab. Is there a role for IMpower150?

Dr. Patel:
I think so. in my practice, IMpower150, has a couple niches that I think are particularly interesting and worthy of discussion. I think in patients, for example, post-EGFR ALK, this is the only regimen with really any data that we have that contains an immunologic, and so I think it's a clear choice there. There is some data for patients with liver metastasis and CNS metastasis. There may be some attractive features to anti-angiogenic inhibition. I actually think anti-VEGF strategies are really excellent. I think the hesitation one may find may be with the chemotherapy backbone. Many prefer pemetrexed over paclitaxel when given the option due to, you know, alopecia, neuropathy, and other side effects. But in terms of anti-angiogenics and unlocking that potential, I think there's certain niches that make a lot of sense.

Dr. Socinski:
So, yeah, I agree with those comments. You know, one of the more frustrating clinical situations we find ourself in more often is relapse following IO therapy, and of course, we don't necessarily have a good sense of what the mechanism of action may be for progression. But how do you approach these patients who relapse after a kind of a chemo IO or IO-alone strategy in the first-line setting?

Dr. Patel:
Yes, it's a tough question. I think some of it depends on the nature of their relapse. There are patients who have kind of primary refractory disease that, you know, basically within their first 6 months, or right around there, of even chemoimmunotherapy, their cancer really doesn't respond to either the chemo component or the IO component. And I think for those patients, aggressive therapy doublets, you know, docetaxel-ramucirumab, outside of a clinical trial, make a lot of sense. There are some patients that, for example, after induction chemoimmunotherapy, maybe about a year and a half in, we've let their maintenance pemetrexed go; they're on IO by itself.

Sometimes you can reintroduce the pemetrexed; sometimes you just move on to next line of therapy. It really depends. I think radiation's a really good tool in our arsenal.

As we've improved our systemic control, I actually think the ability for SBRT [stereotactic body radiation therapy] to be offered to more patients with benefit for oligoprogression is something I'm really keen on. And obviously, the work you do, and others, on clinical trials, right? The next generations of therapies, I think that really, to me, is the most attractive option amongst the 3. But it's good to have multiple options where we used to have, you know, just docetaxel alone.

Dr. Socinski:
Yeah, that brings me to, you know, we know the highest concentrations of crystal balls are in Southern California, so how do you see this field over the next 3 to 5 years? What are some of the promising new strategies? We have a generation of trials, of anti-TIGIT trials. Are you excited about those, or what are your thoughts?

Dr. Patel:
Yeah, I think anti-TIGIT is one of the many really interesting and novel targets we've seen in IO. I think the other opportunity we had that I think was less obvious is targeting immunogenic drivers, right? Like KRAS G12C. KRAS was historically untargetable, and I think monotherapy is really just the floor, not the ceiling of what we'll see in terms of combinations. And so they'll be slow molecule inhibitors and other KRAS and immunosensitive phenotypes. I think TIGITs are very reasonable. I think the other approach that is a little more nuanced is TILT – tumor infiltrating lymphocyte therapy, right, where you resect the tumor, harvest the TILs, reinfuse. And so we don't know which of these is the best option. There are many active clinical trials ongoing, and there're also novel targets outside of these that are being investigated, drugs that target NK cells and macrophages. And so I think the future is really bright for patients. We've already seen an improvement in mortality in all cancers driven by improvements in lung cancer, and these novel therapeutics will hopefully add to that further.

Dr. Socinski:
I couldn't agree more. This is a fascinating conversation. Before we wrap up, what would be your one take-home message for the audience?

Dr. Patel:
I think now that we have so many good options, the question on how we select the best option for a given patient, what's our map, so to speak, in terms of taking patients on the best path? I really think it's this biomarker selected strategies. I think the era of one-size-fits-all chemotherapy is really a relic of the past at this juncture, and that adequate molecular testing tells you not only what you need to do if they have a targetable driver mutation, but what also not to do with expensive, ineffective, and toxic therapies.

Dr. Socinski:
Yeah, my take-home message is that the gains we are seeing in lung cancer have really changed this or should be changing any level of therapeutic nihilism that patients had with lung cancer or physicians had with lung cancer to a disease that's become quite complex, and your point that one size does not fit all in this setting.

So that's all the time we have today, so I want to thank our audience for listening in and thank you, Dr. Patel, for joining me. It was great speaking with you today, and so be sure to tune in to our other episodes of Keeping Pace series for additional discussions on non-small cell lung cancer.

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