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## Practical Considerations on the Use of Immune Checkpoint Inhibitors & Chemotherapy in mNSCLC

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Here's your host, Dr. Mark Socinski.

Dr. Socinski:

As immunotherapies continue to change, the treatment landscape of advanced non-small cell lung

cancer has left many of us wondering whether or not a patient's PD-L1 status still matters when it comes to determining therapy, which is the exact question we'll be exploring in our discussion today.

This the CME on ReachMD, and I'm Dr. Mark Socinski. Joining me to discuss the use of immune checkpoint inhibitors and chemotherapy in metastatic non-small cell lung cancer are Dr. Benjamin Levy and Dr. Jyoti Patel.

Dr. Patel, Dr. Levy, welcome to both of you.

Dr. Patel:  
Thank you.

Dr. Levy:  
Thank you, Mark.

Dr. Patel:  
Great to be here.

Dr. Socinski:  
So, let's jump in. It's been about 3 years now when we saw the results of KEYNOTE-024 in the patients that had high expression of PD-L1, in this case greater than 50%. Tell us about that trial and tell us how you incorporated that into practice and the use of PD-L1.

Dr. Patel:  
Sure. This was a revolutionary trial for us. In the frontline setting, patients were selected if they had high PD-L1 expressions, so greater than 50%. That ends up being about a third of patients. And, in fact, the trial screened over a thousand patients. And then about 30% of all patients were enrolled and randomized to pembrolizumab in the frontline setting versus chemotherapy. Multiple regimens were tested. There was a significant and sort of breathtaking and practice-changing difference in how patients did, so patients who were high PD-L positive and received pembrolizumab had a doubling of response rate, had improvement in progression-free survival and in overall survival. Over the years we've looked and parsed this data, and it's reassuring and I think even more gratifying to see how well this data has held up, and the overall survival now in high PD-L1 patients receiving frontline pembrolizumab is over 30 months at this juncture. Certainly, I think this is now an option that is backed by level 1 evidence. There are fewer toxicities for our patients in getting immunotherapy up front, and generally, I think that's a preferred regimen for my patients who are mutation negative and high PD-L1.

Dr. Socinski:  
And, of course, the obvious question then is: If this is an option for patients greater than 50%, can you

extend a monotherapy strategy to those less than, we saw the KEYNOTE-042 recently and that readout. Ben, walk us through that.

Dr. Levy:

Yeah, very similar design as 024, just flip the numbers, 042. Very large trial including patients with both adeno and squamous cell. Patients were randomized. In this case the cutoff for entry was greater than 1% rather than greater than 50%, and patients were randomized to histology-directed chemotherapy versus single-agent pembrolizumab. Question being asked is: Is single-agent pembrolizumab superior to chemotherapy as standard of care for patients with greater than 1%? And this is where the data gets a little nuanced.

Dr. Socinski:

Yeah.

Dr. Patel:

So, generally, I would urge patients under 50% to think about combination therapy. My sense is that the survival benefit, symptomatic benefit, tends to be quite modest. Certainly, these concerns are patients who are unfit for chemotherapy or something else is happening at the initial juncture in which I may treat with monotherapy. But the curves cross. There's no doubt.

Dr. Socinski:

Yeah.

Dr. Patel:

Patients fall off, and that can be a critical time for patients at first diagnosis, that if disease is moving rapidly, you may never get to the benefit at the tail end.

Dr. Socinski:

Actually, that brings up the point I wanted to ask you, getting back to 024, and that obviously created single-agent pembrolizumab as an option, but there certainly are those patients that are 90% PD-L1 positive, they are very symptomatic, but they have a high disease burden. In general, I've been advocating and recommending combination therapy. We'll get to KEYNOTE-189 in a moment, but certainly KEYNOTE-189 did show in the greater than 50% a much higher response rate than monotherapy.

Dr. Levy:

Right.

Dr. Patel:

I'd agree with you. And I think if we put it in the landscape of other cancers that have had great success with immunotherapies, cancer bulk and tumor burden play a significant role.

Dr. Levy:  
Matter, yeah.

Dr. Socinski:  
Yeah.

Dr. Patel:  
Right? And so the cytotoxicity up front may be more advantageous and make immunotherapy that much more effective.

Dr. Socinski:  
So, Ben, getting back to KEYNOTE-189, we had a recent update in the survival of that trial. Do you want to tell us about that?

Dr. Levy:  
Yeah, so KEYNOTE-189, just as review, landmark trial, practice-changing, patients with nonsquamous non-small cell lung cancer randomized to carboplatin/pemetrexed versus carboplatin/pemetrexed with the addition of pembrolizumab. All PD-L1s were allowed. There's no cutoff here. And we saw a benefit initially in terms of response, in terms of progression-free survival, and importantly in terms of overall survival for all patients independent of PD-L1. We've had an update now at ASCO showing that the median—a

3-year update showing that the median overall survival in the experimental arm, the triplet therapy, which is now standard of care, 22 to 23 months, hazard ratio of 0.56, almost a doubling of overall survival compared to the control arm which underperformed in 10.6, 10.7 months. So the trends remain there. I think this doesn't add anything new other than reinforces the importance of this regimen for patients with nonsquamous non-small cell lung cancer.

Dr. Socinski:  
One thing to note though is we do have IMpower 132, which was essentially the same trial design, carbo/pemetrexed plus or minus atezolizumab. That was a negative trial.

Dr. Levy:  
Yeah.

Dr. Socinski:  
It did show a PFS modest benefit but no overall survival benefit.

Dr. Levy:

You know, there's a lot of questions. This is not the only circumstance or only scenario where we saw differences between 1 immunotherapy versus another by the same trial design.

Dr. Socinski:

Right.

Dr. Levy:

It does beg the question: Are these drugs different, or is it just hard to consistently show survival advantages trial after trial given that...

Dr. Socinski:

Right. And to build on that, we also had IMpower 130, which was the use of carbo/nab-paclitaxel plus or minus atezo in nonsquamous non-small cell.

Dr. Levy:

Yeah, that did show a survival advantage.

Dr. Socinski:

It did show a survival advantage, and so it's...

Dr. Levy:

Yeah, so is this luck, serendipity? Are these drugs different?

Dr. Socinski:

And there are certainly patients in which the pemetrexed probably shouldn't be given, the borderline renal function where nab-paclitaxel would be an option.

Dr. Levy:

Yeah.

Dr. Patel:

However these trials are tough when you enroll broad populations of people, so we cut and dice at greater than 50%, 1 to 49, those that don't express any PD-L1 and try to make inferences, but in actuality, these patients have different biology. They are never smokers in this population. We're still exploring TMV or other factors that could change outcome.

Dr. Socinski:

Getting back to defining appropriate strategies, the use of anti-angiogenic agents in this paradigm, we have the results of IMpower 151 which grafted atezolizumab on to the FDA-approved regimen of

carbo/paclitaxel/bevacizumab, and there's certainly a lot of preclinical rationale and model rationale for why anti-VEGF and anti-PD-L1 should work. We had a positive trial. How do you see this being integrated into practice?

Dr. Patel:

So, certainly, having the trial that incorporated bevacizumab showing improvements in PFS and OS and response rate without increased toxicity was exciting. The magnitude of benefit, again with these cross-trial comparisons, is a little bit tougher. There are toxicities that are unique to paclitaxel that patients may have problems with: alopecia, the neuropathy, also time. So the quad regimen or the kitchen sink or whatever we call the 4-drug regimen comes with, I think, a price, but certainly, the area that I've been using it in primarily are patients with borderline renal function in which pemetrexed would be difficult. Also, there's a very interesting subset in these patients. So this was a large trial, over 1,000 patients. About 10% of patients were patients with EGFR and ALK mutations.

Dr. Levy:

Which were excluded from all the other trials.

Dr. Patel:

Which were excluded from the other trials. Martin Reck had an update that you were also an author on that really sort of did a deep dive into these patients. It's not, I think, as straightforward as we had hoped. Some patients had TKIs. The majority had had TKIs, but if you didn't...

Dr. Socinski:

And they weren't all sensitizing EGFR mutations.

Dr. Patel:

Right, right, so it's a small number of patients, but at least there's some data. It's about 50 patients that we have some data, and it seems that that regimen is appropriate. And, certainly, those patients also had a benefit from immune checkpoint inhibitors. We traditionally felt that the benefit was quite small.

Dr. Socinski:

One of the other subgroups we looked at in that is the rather poor prognostic group of liver metastases, and there may be tumor microenvironment arguments as to the combination of the VEGF inhibition, and PD-L1 may have a particular advantage in that regimen. How is the liver met resonating? Ben, do you want to...

Dr. Levy:

Thank you for the biological rationale.

(Laughter)

Dr. Levy:

I was trying to figure this out. You know, I haven't... Like Jyoti, I tend to use this regimen for patients potentially post TKI, even though the approval is not there for EGFR patients.

Dr. Socinski:

Yeah.

Dr. Levy:

But the liver met story I'm still trying to learn about. We had some update from 189 showing a benefit with immunotherapy in that subset of patients with liver met, from 189 as well. I don't know if anti-angiogenesis in combination with immunotherapy is particularly advantageous specifically for patients with liver mets.

Dr. Socinski:

Well, there is historical data from ECOG 4599 that shows a very positive effect in liver met, so my thinking is that anti-VEGF adds to the liver met story, and immunotherapy adds, but it seems like them being together gets you additional gain in that population.

Dr. Levy:

Yeah. I don't know if I'm routinely... I think it's a compelling story and something to continue to look at. I'm not sure if I'm selecting out my patients with liver mets and using the quad regimen.

Dr. Patel:

And I'd agree.

Dr. Socinski:

And I'm not doing... Yeah, I'm not doing that either. I think this is a regimen... To me it's more are you a believer in anti-angiogenic theory and are you going to use bev, and if you're going to use bev, then use the IMpower 150.

Dr. Levy:

Sure.

Dr. Socinski:

You know, there are lots of reasons not to use bev.

Dr. Levy:

Yeah.

Dr. Socinski:

So I find myself using more KEYNOTE-189.

Dr. Levy:

Yeah.

Dr. Socinski:

Let's switch gears.

Dr. Patel:

So, Mark, as you say, I think there is great acceptance within the medical oncology community for the triplet regimen, so carboplatin/pemetrexed/pembrolizumab for all-comers. Certainly, that third of patients, 25% of patients, theoretically they could get pembrolizumab alone. That's a period of chemotherapy I think is there, but in practice, that might be a smaller number.

Dr. Socinski:

It might be, but it's the primary reason to check PD-L1—

Dr. Patel:

Absolutely.

Dr. Socinski:

—as you find those patients in which monotherapy would be their best treatment.

Dr. Patel:

I think we'll get some additional clarity with the INSIGNIA trial, the NCI trial from Hossein Borghaei. It's a 3-arm study looking at patients who have greater than 1 PD-L1 expression and essentially randomizing them to the triplet versus pembrolizumab and 2 other arms either with continuation chemotherapy or the triplet regimen and progression.

Dr. Socinski:

Yeah.

Dr. Patel:

Certainly then I think we'll be able to tease out who benefits the most and what that appropriate time is to rechallenge a patient.

Dr. Socinski:

Yeah. Let's switch gears, Ben, in squamous.

Dr. Levy:



Yeah.

Dr. Socinski:

We have had some impressively positive data from KEYNOTE-407.

Dr. Levy:

Yeah, mirroring the 189 data. Why let science get in the way of progress? Just add the pembro to the platinum doublet and compare it to platinum doublet alone. So this was a large squamous cell study trial randomizing patients to carboplatin and a taxane, either nab-paclitaxel or paclitaxel, versus carboplatin/taxane and adding pembro into that. And similar to 189 we saw improvements in response rates, we saw improvements in progression-free survival, and we saw improvements in overall survival.

Dr. Socinski:

Regardless of PD-L1 status.

Dr. Levy:

And again, mirroring 189, independent of PD-L1, so I think this firmly cements this regimen as an option for patients with squamous cell. I think the question, as is in the adenocarcinoma patient population: What do you do for your patients greater than 50?

Dr. Socinski:

Right.

Dr. Levy:

Do you give them carboplatin/taxane/pembro, or do you give them pembro alone? Because remember, 024 included all histologies.

Dr. Socinski:

Right.

Dr. Levy:

So very exciting data and certainly practice-changing.

Dr. Patel:

So, what do you do for your squamous cell patients now? There's really no difference in the outcome of patients treated with nab-paclitaxel or paclitaxel in that study. How do you approach it?

Dr. Socinski:

Now, when we did the original nab-paclitaxel trial, we did not know prospectively that there would be a

much higher response rate in squamous. We did not power it in the squamous subset for survival outcomes, so that's always been an open question, but I wonder... Because I do think it's a more active drug, I tend to use it more, because I find most of my squamous patients are more symptomatic, higher volume of disease, and may be a little sicker and they just need a response, so that's what I tend to use, although not universally.

Dr. Patel:  
Right.

Dr. Levy:  
Yeah, I would agree. I tend to use nab-pac just based on a chance for higher response rate.

Dr. Socinski:  
Right.

Dr. Levy:  
I think the question becomes how to time the nab-pac on day 8 and day 21 and adding in the pembro. I tend to admit... Excuse me, day 15. I'll do a day 1, day 8 every 21 days with a nab-pac and give the pembro up front on day 1 with a carboplatin nab-pac, but I think there's a lot of questions on how often the nab-pac should be given in between the cycles.

Dr. Socinski:  
Well, yeah, when I talk to a patient about the plan to give 12 consecutive weeks of nab-paclitaxel, I say, "I can guarantee you you're going to miss 3 of them or so."

Dr. Socinski:  
Well, this has been great. Thank you both for doing this. I just want to give you an opportunity to give our listeners just some final thoughts about how you think our field has changed. And I assume we're all kind of bought in that PD-L1 testing is still kind of a standard part of our initial workup. Jyoti?

Dr. Patel:  
Absolutely, these drugs have changed how we approach our standard of care for patients, so certainly, although immunotherapy is exciting for almost all patients, we still have to test, so you have to test PD-L1, you have to check for mutations, because we know that there can be significant toxicity in patients in whom you mix drugs, so buyer beware.

Dr. Socinski:  
Right. And also, as a general rule, the immunotherapies have really not performed well in patients with driver mutations, so it's not the best therapy for them.

Dr. Patel:

Right, right. Again, my sense is it's a lot of conversation and individual patient decision, but there are opportunities for some patients to do extraordinarily well with monotherapy.

Dr. Socinski:

Ben?

Dr. Levy:

I would say that immunotherapy is not for everybody, and remember to genotype your patients.

Dr. Socinski:

Right.

Dr. Levy:

That's really important. And often times we'll get the PD-L1 back before we have molecular interrogation, and we need to be mindful to follow up on that molecular interrogation result.

Dr. Socinski:

PD-L1 means nothing until you know the molecular results.

Dr. Levy:

That's exactly right.

Dr. Patel:

Exactly.

Dr. Levy:

And, unfortunately, immunotherapy doesn't work for everyone. As much excitement and enthusiasm we have for these drugs, we need to be mindful that we need to work on clinical trial designs that are rooted in scientific rationale for the resistant setting and come up with options for patients in which first-line treatment with either monotherapy or triplet therapy is not working for them.

Dr. Socinski:

Well, again, thank you both. This has been great. I hope our listeners gained some knowledge and wisdom from this discussion, so I want to thank you both for joining today.

Dr. Levy:

Thanks, Mark.

Dr. Patel:

Thank you.

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