Topics: NSCLC/PD-1

Physician Information
Specialty: Lung Cancer
Location: VA, US

Interview NSCLC1
TL #10083
Highlights

We use to give [chemotherapy] to everybody sitting in their therapy for second line. Now for the non-EGFR or ALK mutant population, we’ve begun to check PD-L1-status up front trying to get them pembrolizumab for first line. For the 30% that are PD-L1 positive they get immunotherapy -- usually pembro at this point — and for the non-PD-L1 mutated they get regular old chemotherapy.

Everybody used to get nivolumab and the reason everybody got nivolumab was because there was no PD-L1 testing required so we pretty much gave it to everybody. That’s why we never gave pembrolizumab in second line treatment before. I don’t think the drug is any different, but the first line patients will get pembro now and second line who are PD-L1-negative will probably get nivo.

Once they progressed on a PD-1, I would not pick a different one.

I think [nivolumab/ipilimumab] is a very interesting combination. I think it’s a pretty toxic combo, which is obviously a concern. But I do think it’s very promising and I think there certainly is probably going to be some good data. I think it’s better than nivo by itself. Is it enough to warrant an increase in toxicity? I am not 100 percent sure.

Ceritinib is a very toxic drug and it’s largely fallen off the radar screen. I gave it a couple times when there’s no options at progression, but I don’t really give it in the second line setting at all.

I’m not very confident [in PD-L1 biomarker testing]. I don’t think it’s done very well. I don’t think the labs that are doing it have really mastered it very well. When you order these assays you don’t necessarily get the pembro assay still. You get whatever the lab decides that PD-L1 assay, so it’s still a challenge to get the appropriate one done. That will hopefully change in the near future, but we’re not close to having it optimized. When you ask for PD-L1, the hospital contracts with whoever’s doing the test and they decide whatever PD-L1 assay they want to do. It’s not as easy as one might think.

I’m not super enthusiastic [about PD-1 combinations with other immunotherapies] to be candid with you just because I think those are patients that are probably low mutational burden and not ones likely to respond. I think there’s going to be excellent data with chemo and if you look at some of the preliminary data with atezolizumab and chemo it’s really good. I think for lung cancer, and potentially other cancers as well, that might be a very good option. That’s to me the most exciting right now. Targeted therapy… it needs to be studied and the question answered, but I’m enthusiastic about it.

Unless there's something contracting a better price or something glaringly different... the fourth [PD-1] drug when it comes out or these other ones, it's going to be really hard to find a reason to use them.
About the Author

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Maybe we can just start with a little bit of information about your current practice. Just sort of the size of your practice, the setting, etc.

We are a private practice group. I see a large majority, probably 80 to 90% of my patients are lung cancer patients. I run our clinical trials program and have a whole slew of Phase I, II, and III clinical studies. I run a Phase I program as well. Obviously, very familiar with immunotherapy and all that.

How large is your practice? How many patients do you typically see?

I probably see 10 to 15 new lung cancers a month, probably 20 to 25 new patients a month. See 80 to 100 visits a week.

You said 80 to 90% of your patients are lung cancer patients. What other tumor types or patients do you see?

GI is the next most predominant and then I see a smattering of other stuff as well.

Do you see patients with any hematologic cancers?

Yeah. Lung is my majority but I definitely see hematologic cancers as well.

Since lung is your specialty, or the majority of your patients, I guess that is a good place to start with. Can you just describe your current treatment paradigm for new lung cancer patients that you see?

With the approval of pembrolizumab for first line, chemo's still... we use to give to everybody sitting in their therapy for second line, now for the non-EGFR or ALK mutant population, we've begun to check PD-L1-status up front trying to get them pembrolizumab for first line. For the 30% that are PD-L1-positive they get immunotherapy – usually pembro at this point – and for the non-PD-L1 mutated they get regular old chemotherapy.

So you're already prescribing pembrolizumab first line for patients who are PD-L1-positive?

We are testing, we've given it to 1 or 2 because it's literally pretty much hot off the presses that it's FDA-approved in that setting.

You're right. It's hot off the presses. What were you using before that?

Before this, everybody was getting chemotherapy first and immunotherapy second line.
I know that the paradigm is changing very quickly with the pembrolizumab in first line. So it was previously chemo and then second line would be immunotherapy like pembrolizumab or nivolumab, and now I guess there's the third atezolizumab that has been added, but that's also hot off the presses.

Right, exactly.

Can we talk a little bit about what your preferences were in the second line for PD-1 therapies?

Sure, everybody used to get nivo and the reason everybody got nivo was because there was no PD-L1 testing required so we pretty much gave it to everybody. That's why we never gave pembro in second line treatment before. I don't think the drug is any different, but the first line patients will get pembro now and second line who are PD-L1-negative will probably get nivo.

You said following pembrolizumab first line you would give nivo in the second line?

No. No, no, so patients who got chemo in first line would get nivo in second line.

Okay. I know, again, it's hot off the presses, but for patients who do get pembrolizumab in the first line, what would you use in the second line?

Chemotherapy. Standard chemotherapy.

Even in a third line, or after second line, would you give another PD-1 at any point?

No, I would not. Once they progressed on a PD-1, I would not pick a different one.

Just to make it clear, if chemotherapy is given in the first line then you would still prefer nivolumab in the second line rather than pembrolizumab because those are the patients who probably have not expressed high PD-L1, right?

Exactly.

Since you were talking a little bit about the preference for nivolumab and that it doesn't require biomarker testing, can you tell us a little bit about your experience with the biomarker testing? Is it a cumbersome process to put your patients through?

Yeah, it is because it takes a little time to get it back, you also don't have enough, and the current status is it's very tough to get them to report by what needs to be reported. I'm sure you know that technically for pembro you need more than 50% positivity, and not everybody reports it in that manner so it's a little bit challenging, although I imagine it's going to get a little bit easier now that it's become more of a standard.
What were the other ways that the results were reported besides the TPS score? I think was the standard reporting, right?

Sometimes when you get the reports back they just say positive or negative but it doesn't tell you what percent. Technically for Merck drug, 50% positivity, so when it was 50 ... They were just not reporting the data instead of reporting just plus or minus, it's not super helpful.

If you were to get an actual TPS score in the first line and it's below 50%, would you give any of those patients pembrolizumab off-label? There did seem to be a reasonable amount of efficacy I think below 50%.

Obviously there's a spectrum. One percent is different than 15 is different than 48. Part of it is, to be candid, insurance companies, especially the non-Medicare ones, may very well want a number because they don't fit the FDA’s group criteria. Somebody who's 48% or 42% I probably would give it. If it was 15%, I probably would not. And it's not a concern of efficacy, it's more of a concern of making sure it gets reimbursed.

Have you had any different experiences getting reimbursed between nivolumab and pembro?

Yeah... Nivo is a second line, it's never really mattered, right? Nivo is approved in the second line so there's no reason. Pembro's only approval is for PD-L1-positive so obviously we're always a little bit concerned that that could affect what insurance companies decide to do.

In your experience are there any other characteristic differences between nivo and pembro? I'm assuming there's probably not a whole lot of experience with atezolizumab.

I think they're all the same. I have no qualms that they're the exact same drug. It's just that you have to go by the approvals to ensure coverage.

I think that a lot of sentiment is that they essentially are the exact same drug... or at least were until ESMO and the fact that nivo didn't succeed in first line. It may not really matter in practice, but thinking about the development of nivolumab going forward maybe in other indications, do you have any thoughts about why, if they are so similar, why nivo failed in first line?

The nivo cut-off was 5% and I'm guessing that by pembro really making it a super select sub-group of patients with their test they probably got the most likely response. That's what I think personally. There's obviously always a little bit of luck in doing studies as well. You just get the right patients at the right time and 15 patients can really screw up your data, but my guess is it's probably because they picked the cut-offs the best, and that's the results they got for pembro and nivo probably picked a little too low cut-off.
Are they using the same PD-L1 assay? My understanding was they were not.

They’re now using a different assay and their assay is 5%. But whenever you cut-off for that assay, in my mind, it’s just probably not as good to pick the true PD-L1-positives, that’s my thoughts.

In other words, 5% positive for the nivo assay, which was the cut-off for the CheckMate study is probably not as good a marker as 50% by the Merck assay.

Nivolumab still has a second shot at first line with the CheckMate-227 study, which is nivolumab plus ipilimumab. Are you familiar with that study?

Very much so, yes.

How do you feel about that combination? Do you think that's a promising first line study or first line combination?

I do. I think it's a very interesting combination, I think it's a pretty toxic combo. which is obviously a concern. But I do think it’s very promising and I think there certainly is probably going to be some good data. I think it's better than nivo by itself. Is it enough to warrant an increase in toxicity? I am not 100 percent sure.

Can you talk about the toxicity? It seems like most of the toxicity is coming from ipilimumab. Can you talk about how difficult that is to deal with in general or how severe it is?

It can be severe. There’s a lot of diarrhea, diarrhea, diarrhea. And it is significantly more toxic than nivo by itself. We’ve given it for melanoma now for a long time and in clinical studies as well, and it’s a pretty... not nearly as easy combination.

That's the toxicity that ipilimumab is bringing. How much efficacy do you think it's really going to be bringing to the table? It seems to me like nivolumab might be doing a lot of the heavy lifting. Is there biochemical or molecular biological rationale for combining another checkpoint inhibitor even if there's no testing for CTLA-4 or anything like that?

There is data, the nivo/ipi combo on melanoma is better than nivo by itself. There is, I think, preliminary data that it appears to be a more active combination, so the answer is yes. I think it’s a very interesting combination for the right patients if one can overcome the toxicity and the formal lung data is positive.

Given that pembro is now already approved in first line, even if that ‘227 study was to succeed, how do you think it could compete with monotherapy pembro? What kind of efficacy would you need to see?
The nivo/ipi combo I think would be viewed very well depending on what the toxicity is and how PD-L1 plays out. I think because of the significant increase in toxicity I would be a little bit more concerned about it.

Right now I think the pembro first line study gave something around a 4 month PFS benefit over platinum chemo. Let's say the ‘227 study gives a 5 month PFS benefit... I know you can't compare between trials, but let's say it's a 5 month PFS benefit over platinum chemo.

If it's really just 1 month, it's probably not worth the toxicity for the average lung cancer patient.

I guess that's what I'm getting at. If it's just 1 month you might not favor the combo. Is there some level that you think you would? 2 months, 3 months more than pembro?

Knowing the combo, knowing the reality of what a non-trial lung cancer patient is I would probably say more 7 to 8 months because it's a pretty intense combination. I would like to see a significant increase. The problem is it's going to be very difficult to compare across studies as well. If it's 5 1/2 months you're going to say, "All right, it's 5 1/2 months across studies, is that really a difference?" You don't know. So you're going to want to see a significant increase that makes you think it's not just one study got luckier over the other one.

Okay. What about pricing? Reimbursement for two fairly expensive therapies in nivo and ipi versus the monotherapy. Is that a consideration in your setting?

It's always a consideration and it's a very bad thing and it's what makes oncologists look bad. Notwithstanding that, it's never become a factor so far so I don't think it would be although it probably should be.

We did bring up the Roche drug, atezolizumab (Tecentriq). Basically that had pretty positive data at ESMO as well. Right after the meeting, it got approval for second line. In line with what you were saying about nivo and pembro, are you considering that as essentially the same drug since that targets PD-L1 instead of PD-1?

Yeah. We all think they're the same drug, and I think as the second line it's interchangeable with the other two. Really interchangeable with nivo because they're both approved independent of PD-L1 status. They will be used interchangeably in my mind.

Did atezolizumab get approved for squamous cell as well as non-squamous patients like nivolumab?

Yup. It's approved for all non-small cell, doesn't matter the histology. So you would use it fully interchangeably with nivo in the second line?
Nivo, yes.

Even if you're considering them equivalent in the real world, since you have experience with nivo would you actually choose atezolizumab for any reason?

Yeah. I have experience with atezo in bladder as well so I would strongly use it in any situation. Which one would I use more I think would depend over time. It depends on cost, it depends on reimbursement, it would depend on profit margin. Atezo is a little nicer because it's Q3W. A lot is going to go into that and at this point tough to tell. I think a lot will come down to contracting.

Is there any other reason that you could see PD-L1 targeted inhibitors faring any differently than just the PD-1?

No.

No? Okay, that's clear enough. We touched a little bit on squamous cell treatment. Can you describe the paradigm now? What do you use first line before nivo or I guess atezo now?

The conversation for squamous is the same as non-squamous. It's the exact same paradigm. We don't treat them any differently with regards to immunotherapy. The chemo backbone is the difference. In other words, we use Alimta, we use it with carbo for non-squamous, and usually Taxol for squamous, but the paradigm for PD-L1 testing is the exact same.

What were you using before these PD-1's came into play with squamous patients? I believe there was no real standard of care in that disease population? Is it just chemotherapy?

It was chemotherapy. It was the exact same thing. Chemotherapy for first line. When nivo and pembro were approved in the second line setting we started to give them nivo usually because you don't need PDL testing in a second line setting. Before nivo, we used to give people second line chemotherapy for squamas. Usually docetaxel is what we used to give at that point.

Did you start using Opdivo after it was approved? I believe it was early October. Or did you start prescribing it to your patients when they originally got the NCCN guideline recommendation? I believe that was in June. There was a difference there.

It was approved in June. Honestly, the NCCN guidelines didn’t really differentiate from histological subtype, and nobody really thought there was any difference so we used it as soon as it was FDA approved. It was FDA approved I guess for adeno first, I don't remember honestly at this point, but as soon as we were able to use the drug in second line we used it for squamous in second line.
Maybe we can move on from NSCLC in general and ask about some specific subtypes like EGFR mutation, or ALK-positive patients. Can you describe what your current treatment paradigm is for EGFR-positive patients?

Yeah. They all get a TKI first. I think they're all the same, I usually use erlotinib and with their biopsies I look for T790M. If I have T790M, they get osimertinib. If they don't, they get chemotherapy definitely. I tend not to use immunotherapies really at all, except for when a patient's really out of options. I think the general thinking is that immuno-oncology is just not... because there's not a lot of mutational burdens and PD-L1 status tests tend to be almost always negative that I really try to shy away from immunotherapy not thinking that it really works very well.

Even if you did, could you get reimbursed for that? Since I think the labels don't include EGFR- or ALK-positive patients.

I don't think it really matters. I don't think the first line improves, I don't think it matters in the second line setting. I could be wrong, but you can get it approved. There's not an insurance issue.

It's just...

Guidelines at that level... At that level of detail nobody pays attention so I don't think it's a reimbursement issue.

It's really more just the idea that the mutational burden is low for those patients and they're likely to be PD-L1 negative anyway?

Correct.

Is there any reason you choose erlotinib as your first line TKI or have a preference for that?

I feel like it's what I've been using for the last 12 years. It's what I'm most comfortable with.

What about for ALK-positive patients? Your treatment paradigm.

Crizotinib to begin with. Alectinib at progression either in the brain or in the body. Third line, usually chemotherapy for now. Obviously we try and there are some clinical trials for some of the newer drugs out there. We go into potential clinical studies right now because it's not a focus, but it's crizotinib, alectinib, and chemotherapy in that order, and it's the same exact discussion. I usually don't give immunotherapy because it usually doesn't work.

I think at ESMO there was some new data for ceritinib...
Ceritinib is a very toxic drug and it’s largely fallen off the radar screen. I gave it a couple times when there’s no options at progression, but I don’t really give it in the second line setting at all. Is that what you’re referring to, second line data for ceritinib?

Yes, I think it was the ASCEND-5 study. It was second line and-

In the United States most of lung cancer oncologists do not give ceritinib. It’s a nasty drug.

Can you comment on what the toxicity is?

GI toxicity: nausea and vomiting.

I think they even have a study ongoing for first line.

Yeah, but alectinib is a much easier drug. Alectinib already has data first line versus crizotinib: the J-ALEX study, and the ALEX study. The J-ALEX study was positive. We’re waiting for the full ALEX study to really move alectinib into the first line setting, and once that's positive, I’m sure we’ll be moving that to the first line, but ceritinib is essentially the same drug.

My next area was exploring more about PD-1 therapies in general, although we’ve touched on a number of the issues already. You’ve already mentioned that the biomarker testing for nivo and pembro are different. You’re using at least pembro's PD-1 assay now to select patients. How confident do you feel in that assay?

I’m not very confident. I don’t think it’s done very well. I don’t think the labs that are doing it have really mastered it very well. When you order these assays you don’t necessarily get the pembro assay still. You get whatever the lab decides that PD-L1 assay, so it's still a challenge to get the appropriate one done. That will hopefully change in the near future, but we’re not close to having it optimized. When you ask for PD-L1, the hospital contracts with whoever’s doing the test and they decide whatever PD-L1 assay they want to do. It’s not as easy as one might think.

The fact that PD-L1 positivity has a fairly weak relationship with efficacy – there's enhanced efficacy in high expressers, but there's actually a fair amount of efficacy in low expressers – do you think that’s a problem with the assay? Or do you think there's more of a biological reason that even for PD-L1 low expressers some still respond to the drug?

I think it’s the assay. I think it’s the best biomarker there is out there, but it has a lot to do with tissue fixation, length of tissue... how well they’re doing the tests, all that stuff, so I personally think it’s the assay’s not very good right now. I think they’ve either got to improve on the assay or find another biomarker.

Are there any other biomarkers? If they fail to improve on the assay itself are there other promising biomarkers for PD-1 efficacy?
I think tumor mutational burden is one of the interesting things out there. I think that probably has the best options out there. Just looking at the number of mutations, that correlates pretty well from what we've seen so far. I'm sure there will be something else soon, but that's one that comes to mind currently.

What about resistance to PD-1 therapy? There was a presentation at ESMO talking about resistance to PD-L1's, I think in one of the keynotes. Are you familiar with or do you experience a lot of resistance?

I don't know what the presentation was, but these drugs do not work forever and people ultimately progress and have to find something else. I don't know what the exact presentation is that you are referring to, but as we all know, these drugs... they stop working at some point.

What about other promising tumor types for PD-1's. We know that they've gotten some approvals.

Opdivo was approved in head and neck today, triple-negative breast has data, ovarian has minimal data. I think gastric has some data. I don't think there's a cancer where it's not being studied where there's at least a hint of activity other than maybe ER-positive breast.

Are there any of those that you would out at the top of the list as the most promising? Maybe because of mutational burden or even just actual preliminary clinical efficacy data?

The ones that are approved or about to be approved are the top hits. I think esophageal/GE-junction is not far away. I think HCC is coming down the pike. I think the other ones are going to require a little bit more work for combinations just because there’s just not enough data to get them FDA-approved.

You just brought up combinations, and we've already talked a little bit about nivo and ipi as a combination and you thought that it was pretty promising. Are there other combinations besides two checkpoint inhibitors that you see as particularly promising?

There's a million different combos to study. IDL inhibitors, LAG3, OX40. There's a million different ones that people are looking at right now. If I knew which one worked I'd tell you, but I don't know which one is really going to be the one that works.

Even just from a pre-clinical data or theoretical basis, how do you feel about the combination of PD-1 or any kind of immunotherapy with a targeted therapy where the targeted therapy might be the bridge to the slow-reacting immunotherapy?
Great question. We have some studies ongoing of combinations. I'm not super enthusiastic to be candid with you just because I think those are patients that are probably low mutational burden and not ones likely to respond. I think there's going to be excellent data with chemo and if you look at some of the preliminary data with atezo and chemo it's really good. I think for lung cancer, and potentially other cancers as well, that might be a very good option. That's to me the most exciting right now. Targeted therapy... It needs to be studied and the question answered, but I'm enthusiastic about it.

I think there is a pembro plus chemo first line study going on?

There's pembro plus chemo, there's atezo plus chemo, those are the ones I'm a little bit more excited about. Targeted therapy, we have some ongoing studies. I'm not super excited about it though.

Even if we think ahead about pembro or atezo plus chemo succeeding would you be comfortable with almost any numerical benefit over pembro monotherapy?

Basically what I'm getting at is how much toxicity comes with chemo or how much difficulty comes with the combination?

I think it's a great question. I would have to see the numbers. If the response rates go from 30% to 35% with a survival benefit measured in 4 weeks? No. But if it goes from 30% to 70% and the survival benefit increases by 6 months, yes. I think it really needs to be... see the data, and obviously the individual patient as well.

Is the toxicity of chemo in first line lung pretty severe?

No. It depends on the patient. Many of our patients can do first line chemo without any problems. It really is very patient dependent.

You mentioned a couple of the other checkpoints, when we were talking about combinations. Just thinking about them individually are there other immunotherapy targets, checkpoints, that you particularly like or see as promising coming down the pipeline?

They're all kind of interesting and there are 17 different modalities. Is there one better? I honestly don't know. The jury's still out and I would be really just guessing right now.

Okay, that's fair enough. If we even just leave lung cancer or PD-1's, were there other interesting things you thought coming out of ESMO? I know that's pretty broad, but if there was another interesting topic...

Nothing that comes to mind.
I know that another area that you've been pretty interested in is personalized medicine. Can you talk a little bit about that and where you think that the future of that is?

I think there's a lot of these 1 to 3% mutations that are going to be very important for many cancers. There's the RET mutations work. ROS1 is well known in lung cancer. ALK probably works in several other cancers as well. FGFR inhibitors are very exciting. So I think there's a lot of these low number mutations that are really exciting. For me, personalized medicine and the whole concept of next-gen sequencing is really trying to figure these out and figure where they really work in. I think it's a way away from being the cure-all for a lot of these patients. I think it's going to be 1 to 5% of an individual cancer, but that's a very important number.

When we're thinking about next-gen sequencing and things like that, how do you think that'll affect trial designs going forward?

I think there's going to be trials with very small numbers of patients. You know, you're going to be looking for RET mutations... we know about RET mutations in lung cancer and there's cabozantinib that is a RET drug that is not approved. As it gets approval, you're going to be looking for this very low number of patients so you're going to have to design large studies looking at a lot of centers to get a small number of people.

Do you feel comfortable with the way the PD-1s were developed? It seems like it's becoming a trend -- these basket trials where these Phase I studies involve all tumor types and they just keep expanding.

Yeah, I think that's a great way to do them. It's nice because it's very broad. It's challenging because you have to really hunt to find the signal, but I think it's a great way to look for small numbers of patients.

Do you think though that basically a chance signal is causing companies to pursue indications where, because they have such a small number of patients, they're just relying too heavily on those basket trials and then expanding tumor types where it could be a false positive?

No. I think it's a great study, and I think the idea is if you have a basket study and you find the needle in the haystack you then have to make sure that you have two needles in the haystack and be ready to expand that and not give up on it. You have to really want to be able to push and expand that. When you find it acknowledging it's going to be a very small number of patients to begin with.

Do you have any experience with using either pembrolizumab or nivolumab in melanoma? If you had any sort of preference between those two.
So at this point for melanoma, I either give nivo + ipi or I give nivo by itself. I don’t use pembro very much just because I’m just so used to giving people nivo + ipi if they can tolerate the combo or just nivo single agent. It’s just the easy thing to do. Pembro’s a little bit easier – it’s given every three weeks and it’s a great drug – but old habits die hard so why switch this stuff around.

**Are you currently prescribing any of these PD-1 therapies off-label to other non-approved indications?**

Only compassionate. In other words, we don’t try to get insurance companies to pay for it. We only do it where we can get free drug. Hence the patients that really want to try it.

**When you were saying that you give either nivo or nivo + ipi in melanoma, when do you try the combo? Is it just patient dependent? What you think they can tolerate when you choose mono versus combo?**

Exactly.

**Okay, so it's like for a higher performance status patient you would just go with the combo or maybe try that first?**

Yes.

**Do you see a strong drop in efficacy? I know in whatever sample size you have and it's in different patients, but do you have a strong feeling about how the combo versus the monotherapy works?**

I think the combo’s better. I’ve seen probably more responses when using the combination, but obviously there’s a toxicity price for some people. The answer is I do think it’s better, but you have to pick the right patient.

**I’m wondering if maybe you just have a broader opinion about why you think Opdivo has done a lot a lot better than Keytruda... if you have any other thoughts on why you think that that is.**

It's because of second line lung cancer. You don’t need to have a PD-L1-positive test so why worry about it? That’s why everybody gave nivo, plain and simple.

**You've said a couple of times that old habits die hard. You're already comfortable with nivo. Atezolizumab is seen as essentially the same as the other ones. There are other PD-1s coming down the line for the similar indications...**

It's going to be really hard.
Barring any unique characteristics, you're pretty much comfortable with nivo and pembrolizumab?

Unless there's something contracting a better price or something glaringly different... the fourth drug when it comes out or these other ones, it's going to be really hard to find a reason to use them.