PD-L1 Expression for Immunotherapy Agents in Lung Cancer? Vital or “Don’t Ask, Don’t Tell”? 

In the span of a week, we’ve just had new FDA approvals of Keytruda (pembrolizumab) for previously treated advanced non-small cell lung cancer (NSCLC) patients with tumors that express PD-L1, followed by a broadened approval for Opdivo (nivolumab) for previously treated patients with advanced non-squamous NSCLC, without a requirement for PD-L1 expression testing. This second approval for Opdivo complements the prior lung cancer approval for Opdivo, for patients with advanced squamous NSCLC, without restriction by PD-L1 expression.

So now what? Do we test for PD-L1 and use that to decide between Keytruda and Opdivo? Do we use PD-L1 testing to determine when to give an immune checkpoint inhibitor, or even if we should give it at all? Or do we just decide that if we can give one checkpoint inhibitor without restriction by PD-L1 expression, it’s not worth the time, cost, or effort of doing a test to make things more restrictive?

This is a controversial question, and my own views have been evolving as I carefully consider the treatment landscape. I’ll present why I think we SHOULD be doing PD-L1 expression testing, why it doesn’t necessarily matter which of these treatments you give, and how I see this debate shifting as new data emerge and our treatment approaches are likely to change in the next few years.

First, I’ll clarify a few background points. Prior presentations of randomized trial data comparing Opdivo to standard second line Taxotere (docetaxel) chemotherapy in patients with either previously chemotherapy-treated squamous NSCLC (in the so-called CheckMate 017 trial) or non-squamous NSCLC (in the so-called CheckMate 057) trial both showed a significant improvement in median overall survival (OS) of about 3 months favoring Opdivo. One critical difference between these two parallel studies was that in the squamous patients, the benefit of Opdivo was comparable whether patients’ tumors had more or less or no PD-L1 expression, while in the non-squamous patients, the benefit in survival was confined to the patients with PD-L1 expression (about half of the patients). Keytruda was approved based on the results in a very large phase I trial that showed a 46% response rate and very favorable survival in the 1/3 of patients with >50% PD-L1 expression on a particular version of PD-L1 testing. Patients with lower level PD-L1 testing on this study fared no better than the patients with no PD-L1 expression. Though there is some ambiguity in the approval language for Keytruda, the actual test approved as a “companion diagnostic test” for Keytruda uses 50% as the cut-off value for what is considered a positive test, so it appears that this is consistent with what is likely the intent behind the FDA approval, though it is possible that centers will do different versions of PD-L1 testing and use different thresholds to consider a patient as PD-L1 positive or not. Whether payers will cover a more liberal interpretation of PD-L1 positivity is unknown.

Though the response rate with Keytruda in the high PD-L1 expressing patients is 45%, more than double the response rate of 19% in the broader population of unselected previously treated patients with advanced non-squamous NSCLC who received Opdivo in the CheckMate
057 trial, this doesn't mean that there are significant differences between the two agents or perhaps among any of the PD-1 or PD-L1 inhibitors (all working on the same pathway/receptor interaction). In fact, the vast majority of specialists in lung cancer and/or immunotherapy strongly suspect that Opdivo and Keytruda are remarkably similar in efficacy and tolerability if evaluated in the same population. Instead, the main difference we've seen in results is very likely to be a product of the focus of Keytruda being on a more selected population very likely to do well with any immune checkpoint inhibitor. In other words, if you were to study Opdivo in the same population of patients with >50% PD-L1 expression, you'd see the same result. One difference between Keytruda and Opdivo is that the former is administered IV every 3 weeks, the latter every 2 weeks, so the greater convenience of less frequent administration is a modest benefit for Keytruda. This may also translate to a lower cost if the cost is per infusion rather than per month — I hope to learn more about whether Keytruda costs significantly less over a 3 month period because only 4 treatments are given in that interval, rather than 6 (any good insight on this question is very welcome — please comment below).

But with Opdivo approved for any previously treated patient with no PD-L1 restriction, and Keytruda approved only for the minority of patients who have surpassed the hurdle of PD-L1 positivity (most appropriately with a >50% threshold based on the likely intent of the approval, perhaps more liberally interpreted), should we bother with the cost, time, and effort of PD-L1 testing, or should we simply pursue a strategy of Opdivo as second line therapy for everyone with advanced NSCLC?

My reflexive answer to this, just moments after learning of Keytruda’s approval, was “why bother with PD-L1 testing?”, and there are many thoughtful people who share this view. But I now believe that we should learn from our more mature thought processes in a different field, that of EGFR inhibition for patients with vs. without an activating EGFR mutation, and specifically what we learned based on the very important IPASS trial published by Mok and colleagues in 2009 (full discussion here).

Why would a study about EGFR inhibitor therapy inform us about the strategy for immunotherapy agents? Because IPASS underscored the importance of selecting optimal therapy on the basis of the presence or absence of a biomarker, and that not having the biomarker could be the difference between being helped or harmed by a default strategy of the new treatment for everyone. Specifically, the study randomized about 1200 Asian never- or light prior smoking patients with an adenocarcinoma to either standard chemotherapy or the oral EGFR tyrosine kinase inhibitor (TKI) Iressa (gefitinib), and this patient population was selected because the lung cancer world knew that lots of Asians with little or no smoking history and an adenocarcinoma were the patients especially likely to respond to drugs like Iressa. This trial was designed before EGFR mutation testing became a standard of care, but the trial specifically looked for EGFR mutations in as many patients as they could obtain tissue from and compared results of the trial in patients who did vs. did not have an activating EGFR mutation (60% had an EGFR mutation, 40% did not). The trial found that the results of the overall trial was rather muddled, and the pattern of the progression-free survival (PFS) curve suggested that there were actually two distinct populations. In fact, when the investigators looked at the results based on whether patients had an EGFR mutation, they saw completely opposite results in the two groups: those with an EGFR mutation did far better with first line
Iressa, and those without an EGFR mutation did far better with first line chemotherapy.

These results ushered in sea changes in our approach to clinical vs. biomarker selection of a targeted therapy. They showed two things:

1) Molecular selection for EGFR mutation trumped clinical selection by features associated with benefit from Iressa.

2) There were major consequences to selecting incorrectly, since PFS was much worse with Iressa if treated someone without an EGFR mutation with an EGFR TKI.

Mind you, I realize that PD-L1 is not EGFR and that immunotherapy is not EGFR TKI therapy, but the situation is actually remarkably similar. Instead of potentially selecting patients for first line EGFR inhibitor therapy with a potential biomarker, we’re considering how to select patients for second line immunotherapy with a potential biomarker. The key is the PFS curve for the CheckMate 057 trial of Opdivo vs. Taxotere in non-squamous NSCLC:

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Distinct Populations within One Curve
Progression-free Survival

Fast progression with either
Do better with chemo
Do better with Opdivo

<table>
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<tr>
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<th>Nivolumab (n = 292)</th>
<th>Docetaxel (n = 290)</th>
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<td>mPFS, mo</td>
<td>2.3</td>
<td>4.2</td>
</tr>
<tr>
<td>HR</td>
<td>0.92 (95% CI: 0.77, 1.11); P=0.3932</td>
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West, on Paz-Ares, 2015
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The key point here is that there are a few segments of this curve. The first drop, at the far left, is a group of about 40% of the population that progress rapidly on either arm. The second portion, about 30% of the patients, shows the chemotherapy group outperforming Opdivo. You can see that where the two lines cross 50% PFS, which is the median PFS, the chemo arm is in front, which corresponds to the Taxotere median PFS of 4.2 months vs. 2.3 months with Opdivo (we haven’t really focused on that statistic, have we?!). It’s only the bottom 25-30%, at most, who do far better with Opdivo. It certainly matters that a minority of patients do very well for a long time on Opdivo, but that’s only a small segment of the treated population and likely remarkably few who are PD-L1 negative.

We’ve seen overall survival curves by PD-L1 expression with Opdivo, which clearly show that the patients with PD-L1 expression do better with Opdivo than with Taxotere, while there are no significant differences between the two for patients without PD-L1 expression. However, the PFS curve really indicates that a large proportion of patients are likely rescued by getting subsequent effective non-immunotherapy treatment, and they end up with a comparable survival after starting with Opdivo despite starting with Opdivo, not because of it. The “hazard ratio” for Opdivo vs. Taxotere among PD-L1 negative with a PD-L1 expression (cutoff of 1%) is 1.19, which wasn’t statistically significant but suggests a better result with chemotherapy. Cutoffs of 5% and 10% expression were highly significant at discriminating major differences in PFS between those who tested positive vs. negative. There were also major differences in response rate by PD-L1 status at any cutoff between 1% and 10%; the response rate was ~10% with nivolumab among PD-L1 negative, vs. ~15% for docetaxel in these patients.

Given the difference in efficacy for Opdivo between PD-L1 positive and PD-L1 negative patients, I am reminded of how we approach the EGFR mutation negative patients with first line EGFR inhibitors. The National Comprehensive Cancer Network (NCCN) committee judgment concluded with a consensus as early as 2010 that the IPASS data and a couple of <200 patient trials from Japan with Iressa in first line treatment of EGFR mutation-positive patients were all that was necessary to make it an inviolable truth as early as 2010 that all advanced non-squamous NSCLC patients MUST have EGFR mutation as early as possible, that all patients with an identified EGFR mutation MUST receive first line EGFR TKI therapy, and that it would be a crime against humanity to give first line EGFR TKI therapy to a patient who either hadn’t been tested or has been found to not have an EGFR mutation. We also have data from the more or less forgotten but still instructive TORCH trial that the order of therapy matters and that the better therapy should be given first if there’s a significant difference in efficacy between the. Since we came to these conclusions, we’ve never looked back. Of course, very few trials of first line EGFR TKI therapy have demonstrated a survival benefit because we know that nearly all patients who started with chemo could go on to get an EGFR TKI later and end up doing just as well in terms of survival over time.

So let’s take a moment and review the situation for PD-L1 testing and selecting immunotherapy or chemotherapy. It’s not really the case that patients who are PD-L1 negative do just as well with Opdivo second line. They actually seem to fare a shade better with second line Taxotere but then end up doing the same, likely from being “rescued” from subsequent therapies.
Some have raised the point that even if responses in PD-L1 negative patients are uncommon, they do occur in about 10% of patients, and when they do, they can be dramatic and prolonged. That’s true, but in the treatment approach I’ve outlined, I would still favor PD-L1 negative patients getting Opdivo, just later than second line. Here again, it’s analogous to the EGFR story: Tarceva (erlotinib) was demonstrated to have a proven benefit in previously treated patients with advanced NSCLC, including in mutation-negative patients, but the benefit is modest. Even so, a rare patient has a much better, potentially prolonged response beyond what we’d expect for EGFR wild type (no mutation), which may be because of tissue heterogeneity (the cancer is actually EGFR mutation positive at least in some areas, but the biopsy missed it) or the test otherwise being incorrect. So I definitely favor having just about all patients eventually get an immunotherapy, which in the current clinical world would be Opdivo.

And while you can say that there’s a chance that someone will occasionally miss their chance with immunotherapy, I would contend that the optimism for and good tolerability of immunotherapy will mean that few will miss their chance. And it would be worse to have people miss their chance with a treatment that costs about 5% as much and is MORE likely to help them.

The future of immunotherapy will make PD-L1 testing even more compelling. First, there are multiple trials of immunotherapies in first line treatment of NSCLC. **Spoiler alert:** though they haven’t been completed, they will show that patients who exceed a certain threshold of PD-L1 positivity do better with immunotherapy alone or, perhaps in some cases, added to standard chemotherapy compared with chemotherapy alone. However, NSCLC patients who have little or no PD-L1 expression will not benefit greatly from substitution with or addition of immunotherapy in the first line setting. As for testing for EGFR, ALK, and ROS1, we’ll need to do initial PD-L1 testing to determine which patients should receive this strategy and which ones shouldn’t.

And then there are immunotherapy combinations. Though in the world of melanoma, work presented in the Plenary Session of ASCO 2015 showed that patients who received a combination of the PD1 inhibitor Opdivo with the CTLA-4 inhibitor Yervoy (ipilimumab) demonstrated a significantly longer PFS than patients who received either treatment alone, but the benefit was entirely in patients who were negative for PD-L1 expression. Those who were positive for PD-L1 did just as well with Opdivo alone. So along with the other reasons to test for PD-L1 in lung cancer, I think there’s an excellent chance we’ll be using it to help determine which patients are likely to do well with a single agent vs. combined immunotherapy approach.

All in all, it remains a debatable question, but I think that the PFS data on CheckMate 057 are very much like the data on IPASS and should lead us to the same conclusion: that it makes the most sense, in terms of the best efficacy for patients and also the most cost-effective strategy, to determine the optimal therapy at that particular time rather than “treating blind” and giving everyone the same treatments over time.

**Addendum (10/13):**

After having had further discussions with colleagues about the data and the challenges in
interpreting the optimal treatment in this setting, I am inclined to soften my view that Taxotere is quite likely to be the superior second line therapy for most patients without PD-L1 expression. Specifically, I/we should bear in mind that response rate and PFS probably make Opdivo look less favorable than the actual reality, because at least some true beneficiaries in terms of survival may fail to have a response or even have progression by our standard (so called RECIST) criteria but actually have “pseudoprogression” of immune cells infiltrating around the cancer and making measurable disease look bigger or even have new nodules appear, an appearance that will technically be called progression on scans and not a response, but which precedes a real benefit for the patient. The OS curves on the Opdivo vs. Taxotere trial in non-squamous NSCLC still show the “IPASS-like” pattern of two populations within — one doing somewhat better with chemotherapy and one doing better with Opdivo — but PD-L1 isn’t necessarily optimal to discriminate between them.

I still believe that the goal should be to try to give the best and ideally most cost-effective therapy at a given time to every patient, and PD-L1 status can help with that. I also think it's important to ensure that every patient, regardless of PD-L1 status, gets their opportunity with an immune checkpoint inhibitor, ideally while they have a pretty good performance status. I wouldn’t come down saying that it’s critical for patients to undergo PD-L1 testing, at least not now. But I think it will very likely become necessary before these checkpoint inhibitors move into the first line setting, which I anticipate will only for PD-L1 positive patients.

A final point to make: It was only just called to my attention that the FDA-approved dose for Keytruda is 2 mg/kg IV every 3 weeks, which is established for melanoma but was NOT the dose in which the 45% response rate was demonstrated in patients with NSCLC. In fact, all of those patients (actually only 61 with PD-L1 staining >50%) received 10 mg/kg IV every 2 or 3 weeks (no difference in efficacy between 2 and 3 week administration). So we’re left either taking on faith that it’s just as good to give 1/5th the dose that was actually tested and looked so favorable in NSCLC patients, or we prescribe the evidence-based dose for lung cancer at a cost that is 5 times the already high price for Keytruda (matched at 2 mg/kg every 3 weeks to be comparable to that for Opdivo at 3 mg/kg every 2 weeks). THAT'S A BIG PROBLEM: I’m not going to be inclined to charge a patient or insurer $60,000/month giving Keytruda at the dose that actually showed a benefit, nor am I going to give the FDA approved dose that doesn’t have the evidence to support strong activity in lung cancer. This is a situation that isn’t tenable, so I expect something will change soon.