Imprecision Medicine: Why Keytruda (Pembrolizumab) + Chemo for PD-L1+ NSCLC isn’t Ready for Prime Time

Let me start by saying that I’m a fan of the immune checkpoint inhibitor Keytruda (pembrolizumab) and consider it the new standard of care as a single agent (monotherapy) first line treatment for the subset of about 28-30% of patients with advanced NSCLC, either squamous or non-squamous, whose cancers have high level expression of PD-L1, defined as 50% or more cancer cells staining on the companion test for Keytruda (an antibody called 22c3). It can lead to some terrific and long-lasting responses, but it works well only in a minority of patients; in fact, even in the cherry-picked population of patients with cancers that show high PD-L1 expression, the response rate is a little less than 50%, and it’s below 20% in patients with low or no PD-L1 expression. Merck just announced that the FDA has accepted a “supplemental Biologics License Application” (sBLA) that would broaden the FDA approval for Keytruda in NSCLC to all non-squamous NSCLC patients without an EGFR mutation or ALK rearrangement and without regard to PD-L1 expression, giving Keytruda in combination with chemotherapy (carboplatin and Alimta (pemetrexed)). I think the evidence we have with this combination is encouraging and worthy of further study, but it shouldn’t be enough to lead to broad use as requested in the FDA filing. I think it’s a premature money grab that isn’t necessarily better for patients and is definitely bad for broad society. Let me explain why.

The evidence behind this strategy is from a cohort of patients (cohort G) from a larger study, KEYNOTE-021) of patients randomized to various chemo combinations with or without Keytruda. This particular trial did not have a threshold requirement for PD-L1 and enrolled 123 patients with a good performance status and advanced NSCLC to receive either carboplatin/Alimta alone or the same chemo with Keytruda at a fixed dose of 200 mg IV every 3 weeks. Patients who hadn’t progressed after 4 cycles would continue to receive maintenance Alimta (for the chemo only arm) or Alimta/Keytruda (for the chemo/immunotherapy arm) until progression or prohibitive side effects.

Patients assigned to the chemo/immunotherapy combination had a higher response rate of 55% vs. 29% (p = 0.0016), though looking at the “waterfall plots” that show tumor shrinkage as downward bars and growth as upward bars, the length proportional to the degree of change, though most patients in both arms show tumor shrinkage (chemo/immunotherapy on left, chemo alone on right):
Regardless, the primary endpoint of the trial was progression-free survival (PFS), which was significantly longer for the chemo/immunotherapy group (median 13.0 vs. 8.9 months, HR 0.53, \( p = 0.01 \)). There was no difference between the two groups in overall survival (OS), though the median follow-up of patients on the trial was just 10.6 months, so the results are immature to address this question.

Side effects were largely as expected; specifically, there were greater side effects with the arm that received chemo/Keytruda in combination, but they were really just a superimposition of the expected modest side effect profile of this generally well-tolerated chemo combination with that of Keytruda, associated with very mild side effects in most patients and moderate to severe immune-related side effects in a small percentage of patients.

There was a lot of noise about this trial at the meeting at which the results were first reported (the European Society of Medical Oncology Conference, back in early October, 2016), but lung cancer specialists have been more measured in their interpretation of its importance than the media and financial industries that often serve as amplifiers of news, regardless of the quality of it. While intriguing, here’s why I think this application to the FDA does not merit approval and, in my mind, is more of a market-driven money grab by Merck than a warranted broad change in practice:

1) It is only 123 patients. Though the FDA has justifiably approved therapies based on small trials with dramatic results, that makes more sense for rare mutation subgroups like ALK and ROS1, where it is especially challenging if not infeasible to conduct the ideal trials with hundreds of patients. But this is for a very broad population of advanced NSCLC without any selection of PD-L1, and in fact the larger phase III trial is already quite far along and just awaiting further maturation of patient outcomes and presentation. It is premature to rush through an application for a broader indication based on such scant data when an avalanche of data are around the corner that will allow for a far more informed decision.
2) While the difference in response rate and PFS are clearly favorable for addition of Keytruda, those are short term endpoints. We don't have an OS difference, with a caveat that this is still very short follow up. **But the key is whether patients end up living longer with the same or less toxicity overall**, and the critical comparator of concurrent chemo/Keytruda or any chemo/immunotherapy combination should be **sequential** chemo and immunotherapy. It is immensely possible that patients with low or no PD-L1 expression would live just as long or longer, with fewer side effects over time, by starting with chemo, continuing on that until progression or prohibitive side effects, and then moving promptly to immunotherapy after that. The clearest incentive to moving all of our therapies as early as possible is to ensure that every company gets their drug paid for. Foisting all of the potential complications, including possible toxic interactions, isn’t necessarily best for the patient.

3) The low response rate to Keytruda and other immune checkpoint inhibitors in NSCLC patient populations with low or no PD-L1 expression suggests that only a relatively small minority of these patients benefit significantly from these approaches (it’s worth remembering that the positive trials of all of these agents vs. Taxotere (docetaxel) in second line included the patients with high PD-L1 expression most likely to benefit and who would now be siphoned off to get Keytruda first line — we should question whether these second line trials would be positive with the best population removed, but that’s a “don’t ask, don’t tell” question). This means that many of the patients who are moving on to maintenance Keytruda and Alimta after 4 cycles of the full combination are only actually benefiting from the chemotherapy component (and others only from Keytruda), but we can’t tell which one is the active agent. These are two of the most expensive treatments in cancer care, and while it’s arguably worth treating patients with them for a prolonged period if patients are benefiting from them, it’s insane to give both, at a price tag of over $20,000 per month, when it’s likely that one is only adding risk of cumulative side effects for patients and unfathomable cost to society (and sometimes to patients).

4) The current standards of care have changed, making the trial design obsolete. With Keytruda the current standard of care as single agent treatment for the 30% of patients with high-level PD-L1 expression. Once you take out those patients, a huge proportion of what drove the benefit in this trial goes away. The high PD-L1 patients should be studied for the combination of chemo/Keytruda vs. Keytruda alone.

Meanwhile, for the patients with lower or no PD-L1 expression, the true comparator needs to be sequential first line chemotherapy followed by immunotherapy for ALL patients as soon as possible after patients show significant disease progression — unlike in this trial, where approximately 1/3 of patients assigned to chemotherapy never received immunotherapy. The best trial would have ALL lower PD-L1 patients receive chemotherapy and immunotherapy, with the only difference being whether they are delivered concurrently or sequentially.
The fact that we’re talking about giving indefinite Keytruda to the vast majority of patients with advanced NSCLC makes it a jackpot for Merck, but the fact is that many patients will not be benefiting from it, we have no way to know which ones are, and everyone else in society will be faced with the crushing weight of paying for this money grab.

If the larger phase III trial demonstrates a survival benefit with concurrent chemo/immunotherapy compared with a sequential approach, I will be eager to declare it an appropriate standard of care. It is certainly possible that giving both chemo and Keytruda or another checkpoint inhibitor up front will be the best way to ensure that patients receive the potential benefits of both strategies. However, this small trial with limited follow-up is woefully insufficient to justify combining chemo and Keytruda for the vast majority of patients with non-squamous NSCLC, regardless of PD-L1 expression. I see it is a marketing-driven decision, not what is best for patients, and it is a deliberate move toward “imprecision medicine”: rather than identifying and prioritizing the best therapy for each patient, it is prioritizing profits by foisting an extremely expensive therapy unhelpful for many patients on everyone possible, then handing society the bill.

Thoughts? I’d love to hear people tell me if you agree or, if you disagree, why?

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