5 Key Points on Immune Checkpoint Inhibitors for Lung Cancer: Game Changer or Just Leveling Up?

Just last week, I ranked the development of immunotherapies as the leading development in lung cancer in 2013. I don’t consider 2013 to be the clear turning point for immunotherapies in lung cancer: they have been the subject of interest and research for many years, and ASCO 2012 really marks their breakout from niche idea to more widespread credibility. But if 2012 was the real launchpad, 2013 saw the rocket really take off. The question is where is it really going?

I’ve had the opportunity to put more than a dozen patients on immune checkpoint inhibitors (anti-PD1, anti-PDL1) over the past 12-18 months, and in that time I’ve been able to combine my real life clinical experience with more data from other agents. At this point, I’d like to offer some preliminary projections on what we should expect from immunotherapies.

1) They work very well for a few patients. As is seemingly always the case, the first patient you try on a new therapy does remarkably well, and that has been the case with me putting my first patient on the trial of nivolumab, the anti-PD1 therapy from BMS, vs. Taxotere (docetaxel) as second line therapy. Clinically, her symptoms improved so quickly I had trouble believing it was from the treatment (within days), and the response has lasted a year and is still ongoing.

2) Immunotherapies are not going to replace conventional chemotherapy and fundamentally overhaul all lung cancer treatment. I mentioned that this phenomenal response was in my first patient, but I haven’t seen that kind of benefit in patients after my first. The phase I/II trial results we’ve seen thus far have indicated a response rate of 20-25% for immune checkpoint inhibitors, but frankly, I expect the objective response rate in the larger phase III studies with nivolumab, for instance, to be below 15%, and very possibly below 10%. That’s just the pattern of what happens with drugs that go from very limited testing in one or a few centers to widespread testing in a multicenter national or international trial. The currently plain Jane combination of carboplatin and Taxol (paclitaxel) had a response rate as high as 50% reported in initial phase II testing for first line treatment of advanced NSCLC, and now we know to expect more like 20-25% at most in a big phase III experience. Second line Taxotere (docetaxel) had a response rate initially reported at 25% in phase II research, then settled in at the 5-10% response rate we have seen in study after study over the past decade.

With broad study, I expect that we’ll find that immune checkpoint inhibitors are very far from a replacement for current standard therapies. The 25-35% response rate we typically see from standard chemotherapy +/- Avastin (bevacizumab) in the first line setting is likely to eclipse the response rate with a single immune checkpoint inhibitor given in a broad, unselected population.

3) Immune checkpoint inhibitors can lead to prolonged responses. A major appeal of immunotherapies is that they can lead to very sustained responses. As I alluded to earlier, my best responding patient on nivolumab is continuing to do well for a year after the start of treatment. Dr. Julie Brahmer reported that many of the responding patients on her initial
landmark study presented at ASCO 2012 continue to respond as of ASCO 2013. We don’t know how long they will respond, but it appears that immunotherapies do hold a realistic promise of a treatment that can lead to a benefit that is at least in the range of what we see with targeted therapies like EGFR and ALK inhibitors in patients with these respective driver mutations, well exceeding the typical duration of benefit from standard chemotherapy.

We don’t know how long their benefit might last, but it looks as if it’s feasible to see years of benefit. My best responding patient needed to come off of treatment for a couple of months due to side effects (more on this below), during which time her scans continued to look good, with no progression of her cancer, which had previously progressed at a rapid pace through standard chemotherapy, so it isn’t just a very indolent cancer. The folks from BMS informed me that in some of their trials of nivolumab in other cancer settings, patients continued to do very well for a long time after a fixed duration of treatment, without further infusions of the inhibitory antibody. This pattern suggests that the immune system continues to exert an inhibitory effect on the cancer, so it may well be possible for some patients to do very well with immune checkpoint inhibitors for a very long time (how long? indefinitely? we don’t know yet) without requiring ongoing infusions.

4) We are still working on identifying which patients are the major beneficiaries of these treatments. While the early nivolumab research and subsequent phase III trials do not restrict by expression of PDL1 protein (overexpressed in somewhere in the range of 40-50% of people with advanced NSCLC), some work with MPDL3280A, an anti-PDL1 immune checkpoint inhibitor from Genentech/Roche suggests that response rates are particularly high for those with PDL1 overexpression (~80% vs. <20% in those without it). Some studies being conducted with various immune checkpoint inhibitors are now restricting enrollment to those patients with PDL1 overexpression, though there isn’t any standard assay for defining this as a binary result of high expression or not. Presumably, this is because the companies want to get a fast approval for a drug if it shows a response rate over 50% in a defined population. That may work, but it’s clear that the potential benefit of these agents is not restricted to just a subgroup with any biomarker being used right now.

There have also been some early findings that efficacy of immune checkpoint inhibitors may be particularly favorable in those with squamous NSCLC and smokers or ex-smokers (as opposed to never-smokers who are far more likely to have a cancer harboring a driver mutation like EGFR, ALK, or ROS1), but we definitely need to learn more about these preliminary leads before using them to guide enrollment or treatment recommendations.

5) Immunotherapies are not non-toxic. They have different side effects than standard chemotherapy, but it would be a grave mistake to oversimplify and presume that immune-based treatments, including immune checkpoint inhibitors, will let us treat cancer effectively while sparing the patient treatment-related complications.

We'll require a careful assessment of the results from a large pool of patients to see what patterns emerge, but my patient sailing along on nivolumab had a scary period of months in which she was experiencing very high fevers, up to 104F, and low blood pressure that landed her briefly in an ICU. She had persistently low lymphocyte counts that could leave her
vulnerable to some infections. She developed newly enlarged lymph nodes in her chest and under her arms that were biopsied to determine whether they represented progressing cancer, a new lymphoma, or some other process, and the biopsy showed what seemed to be an overly dramatic immune response killing off the nodes. She’s doing remarkably better since I worked with BMS and followed a recommendation from one of their immunotherapy experts and put her on Celebrex (celecoxib), but I’ve had several conversations with other colleagues who have treated a growing number of patients with immune checkpoint inhibitors and who have developed a greater respect for the potentially significant curve ball side effects we might see with them. Pneumonitis has been reported in up to about 3% of patients receiving nivolumab (seemingly more prevalent among those with squamous NSCLC), and we may well see other significant auto-immune mediated side effects as we learn more.

In fact, most of my patients haven’t had significant side effects from immune checkpoint inhibitors, but we can’t presume that immunotherapies will represent a freebie in terms of effective cancer treatment that is free of side effects.

I’m very happy to see these agents tested not only in previously treated patients with advanced NSCLC but also in other settings, alone or in combinations. I stand by my earlier designation of the momentum of immunotherapies as the most significant development in lung cancer over the past year, but we won’t move to a new era in which our world of treatments before immunotherapy is considered the dark ages of cancer care. As much as I believe that not one but several immune-based treatments will likely find their way into treatment of lung cancer, they will add to but not fundamentally replace everything that came before them.