Five Key Insights from the Targeted Therapies in Lung Cancer Meeting

I’m just now returning from the International Association for the Study of Lung Cancer’s “12th Annual Targeted Therapies in Lung Cancer Conference”, which consisted of about 170 very brief talks about several classes of agents, as I described in my last post. Some of these are likely to emerge as viable, truly beneficial therapies for patients; many others will fall by the wayside. Because it's really not feasible to discuss such a broad range of agents that we only get a snapshot view of, I thought I’d try to convey what emerged as five core takeaway points from the 2012 iteration of this important meeting.

1) Molecularly-defined treatments are only becoming more important, and treatment approaches for clinical groups are becoming more narrow. The days of trials designed as “chemo backbone X with or without new agent Y for everyone with advanced NSCLC” are going away. (Though they still exist in earlier stage NSCLC and SCLC, some insights will encroach on new treatment designs and more tailored approaches for these populations as well.) There is growing concern that by lumping patient groups together that are simply too broad and are really distinct groups, we are going to miss valuable benefits for small groups that are diluted in large populations of others far less likely to benefit. Just as one clear example among many, if XALKORI (crizotinib) were tested first in everyone and not focused on the 4% of NSCLC patients with an ALK rearrangement, we’d likely see a 3% response rate and probably pass over it, rather than recognize it as a 60% response rate in a narrow population. In fact, we also run the risk of missing the fact that we could be simultaneously helping a subpopulation of patients while simultaneously harming another subpopulation, as is suggested by the phase II MetMAb trial and the overall results of the IPASS trial if you don’t do the important next step of looking at the results divided by biomarker status.

2) Unfortunately, the very encouraging results we’re seeing in some smaller, biomarker-defined groups won’t apply to everyone, or even the majority of people with lung cancer. It’s not a coincidence that so many of these biomarkers, ranging from EGFR and ALK to ROS1, HER2, and others, are most commonly seen in adenocarcinomas, and especially in patients who are never-smokers or have a light and remote prior smoking history. These are the more genetically simple cancers, which are most likely to have a single driver mutation that can be brought to its knees to finding the right key for that lock. But the cancers developing in longtime smokers, even with adenocarcinoma but particularly the cancers with squamous or large cell or SCLC histology, are far more likely to have dozens of mutations each contributing a bit. We aren’t likely to see dramatic benefits from addition of one new therapy in these far more genetically complex cancers that likely comprise at least 70-75% of the lung cancers out there, at least outside of Asia (where lung cancer in never-smokers and a unique driver mutation in the cancer are clearly more common).

3) Combinations of targeted therapies are likely to gain more traction. Dr. Tom Lynch from Yale gave the keynote speech at the opening of the conference, in which he made the compelling point that the more difficult problems may require a multi-pronged attack. The now very effective treatments for AIDS, tuberculosis, and many lymphomas are predicated on
combinations of effective agents all given together, rather than sequential administration of single agents that are each associated with subsequent relapses. Dr. Lynch is quite optimistic about combinations of targeted therapies for patients with particular driver mutations leading to situations we can consider a cure, but I'm more wary: we need to determine whether these cancers will still circumvent the combinations, leaving us with no further effective therapies as arrows in our quiver. It may be that giving two or three effective therapies at once will kill the last cancer cell in a treatment-sensitive metastatic lung cancer; it also might just exhaust our treatment options much sooner than applying several effective therapies serially. I wouldn’t want to presume the answer but absolutely agree that we’re now at a time when studies should move from single agents to testing combinations.

4) **We know less than we thought we did. Many truisms aren’t holding up under scrutiny.** Seeing things like biopsied EGFR mutation-positive adenocarcinoma being re-biopsied after acquired resistance and now emerging as an EGFR mutation-positive SCLC, different mutational profiles in biopsies from different areas of a person’s cancer (such as the primary lung tumor and liver or adrenal metastases), and responses when “re-challenging” a patient with a targeted therapy after a period off of it are leading oncologists to step back and revisit some of our central tenets. We’re less and less confident that the molecular markers from a resected lung cancer from 2009 will represent the biomarker profile for a recurrence 2-3 years later, or even that the metastases that emerge after a year on Tarceva (erlotinib) represent the same biology as the initial cancer. Continuing an agent on which someone is even showing progression, or returning to it later, makes some sense now. And perhaps we can actually cure some patients with metastatic disease, even if the principles of cancer have long dictated otherwise.

5) **The incentive for a highly specialized evaluation in lung cancer is only increasing.** In the days when the differences between seeing a general oncologist and someone with a major focus in lung cancer and clinical research was primarily which chemotherapy doublet you’d get, I don’t think there was a huge incremental value to getting a specialist opinion. It doesn’t matter much whether you have your appendectomy done by the local general surgeon or by the Chief of Surgery at the Mayo Clinic: there’s a ceiling to how well you can do. For a very long time, our limited understanding of the biology of lung cancer created a low ceiling, and the treatments available at the closest broadly capable oncologist’s office were really functionally equivalent to what was available at the most renowned academic centers. But now, new trials for rare mutations like ROS-1 or clinical situations like acquired resistance to an EGFR tyrosine kinase inhibitor may only be available at 3 or 5 centers around the country, or if you’re lucky, at one or two centers in your state. But with the incentive that these novel treatments could be highly valuable and not just marginally useful, I now find myself, for the first time, recommending that some patients (at least those with the highest “pre-test probability” for a clinically actionable biomarker) consider a consultation at one of a very small number of centers where their cancer can be tested for some markers that right now can’t be tested for commercially, or that they consider a trial that might require them to get on a plane to participate.

It’s not something that is feasible for everyone, but the value proposition between standard, competent general oncology management and a very specialized perspective, with the
additional clinical research opportunities that often come with that, has never been greater.

I’m interested in your thoughts about these take-aways. I’m also sure there will be much more to add, and quickly, as we continue to refine our understanding of these molecular targets, and our clinical experience with targeted agents grows.

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