

Dr. Nathan Pennell

Question & Answer Session from
“The Emerging Role of Molecular Markers in the
Management of Non-Small Cell Lung Cancer”

Dr. West: Thanks for a great run through of a lot of topics, all fitting in this broad change in how we’re approaching lung cancer.

Has the KRAS mutation been shown to correlate with response to the EGFR monoclonal antibodies, cetuximab or panitumumab in non-small cell? Maybe you can speak to both KRAS and EGFR as well as can we predict who will or won’t be a beneficiary of those drugs?

Dr. Pennell: That’s an excellent question, and its one that I didn’t focus on because for now I don’t think the EGFR antibodies are necessarily going to play a huge role in treatment of non-small cell lung cancer; at least for 2010.

We know that the EGFR antibodies, cetuximab and panitumumab, play a big role in treatment of other malignances—in particular colorectal cancer. KRAS mutation status has been a very important predictor and in this case it is a negative predictor of benefit from these antibodies. It’s been very clearly shown, and even the FDA label for these drugs has been changed. Patients who have KRAS mutations in colorectal cancer should not receive these drugs, because they just don’t work.

Now, everyone suspected that when the Phase III trials of cetuximab came out that they would find the same thing. And for that reason they did their best to get as much tissue to determine KRAS status as they could.

The FLEX trial was the large Phase III European trial of chemotherapy with or without cetuximab for non-small cell lung cancer, it did show a statistically significant overall survival benefit in the overall population.

It appeared that there was no hint of a negative effect of KRAS mutation versus KRAS wild-type in these tumors.

In fact, there didn’t appear to be much of a benefit to any of the markers that they looked at — EGFR mutations, EGFR gene copy number by FISH had all been promising potential markers for benefit. And in fact it didn’t appear that any of them predicted a benefit from cetuximab. It could be just that there is not enough of a signal of activity with these molecules in lung cancer to be able to piece it out. I think more than likely whatever benefit is coming from these drugs, these simply aren’t the right markers.

Dr. West: Would any of these tests be of value in somebody who's already received a couple lines of chemotherapy and an EGFR inhibitor? Is there any role for people who have been on treatment for a couple or three years right now?

Dr. Pennell: Well, that's a good question. I would say certainly EGFR mutation testing is most useful when you have a brand new patient in front of you who has never received treatment because Tarceva is approved and you can give it to people in second and third-line anyway. I will say that for clinical trials of second-generation EGFR inhibitors, or those who are trying to overcome resistance, it certainly makes sense to perhaps do EGFR mutation testing again to see if there is perhaps some mechanisms of resistance that have developed that might target them towards a particular program.

In patients who are non-smokers on the Pfizer trial, I think it would be reasonable to consider looking for an ALK translocation and finding a place where the trial would be available, because if you are a non-smoker or a very light smoker and you don't have an EGFR mutation, again, probably one out of three people will have an ALK translocation and this is something that's fairly exciting.

For now in the metastatic setting, there's no reason to look for any of the other markers. Probably the short answer is no, other than potentially looking for ALK translocation.

Dr. West: But this is a changing field where more and more of our treatments are potentially becoming target-based. I think ALK is an interesting proof of concept of what you can see when you give a targeted therapy to a targeted population and see a 60% response rate. It's impressive.

Dr. Pennell: It is, and I envision a time when this will be done on a much more continuous basis where patients will come in, get a molecular characterization of their tumor, come up with a cocktail of drugs that inhibits particular targets that are identified, but if patients progress perhaps a year or two later on, a new biopsy in order to try to see what changed and then do it again, perhaps with a different cocktail of drugs. I think that that is the future that hopefully is not too far away.

Dr. West: As we move toward much more individualized or segmented breakdown of treatments based on these characteristics, how is that going to impact the development of new treatments for non-small cell lung cancer? Are we done doing large trials of carboplatin, paclitaxel or any standard chemo plus new drug X?

Dr. Pennell: That is a great question. The Cleveland Clinic held something they called the Innovation Summit in 2009. They had the CEOs of most of the big

pharmaceutical companies such as AstraZeneca, Genentech, Pfizer were there, and someone stood up and asked that question to the CEO of AstraZeneca, "Do you support moving towards more targeted trial designs?" because many people perceive that as not being in the interest of these companies to develop drugs that may only benefit a thousand or two thousand patients a year. He stood up there in front of the entire room and said "yes, this is the future of treatment. We understand that the era of the blockbuster drug that's going to help everyone maybe ending and we're supporting that."

Now, whether that is true or not, I don't know if that's the case. I do know that I very much hope that the era of the multiple-thousand patient trials of carboplatin and paclitaxel with or without drug X is ending and we're moving towards more targeted drugs.

Dr. West: I think that the development of the Pfizer drug (PF)-02341066 is interesting because it's emblematic of a change in approach. This is a drug where we probably wouldn't have seen an impressive effect if you just gave it to everybody.

Dr. Pennell: Absolutely, in fact, it probably would have had, just so that everyone out there in the audience realizes, chemotherapy trials or targeted drug trials that had response rates in the single digits are considered bad drugs that failed historically. They were dropped. There's probably been lots of drugs that have been dropped and abandoned because they had a 5% response rate. How many of those of those "one patient in that 20-patient" trial who responded actually had a specific target that that drug was hitting? Dr. West's point is excellent. The Pfizer trial is a sign that companies like Pfizer are willing to actually invest in this. They anticipate that there's probably going to be only 6,000 patients a year, that's 4% of non-small cell lung cancer. Yet they are investing in the registration Phase III trial for this drug.

Dr. West: 01:05:33 And, we'll see how that fares, because certainly there's been a huge interest in if you can test people and find a target and then you now have a 60-70-80% probability of responding with EGFR inhibitors. This is just not the world we've operated in an advanced lung cancer before.

So, it's an exciting proposition, though it does bring challenges of collecting tissue and sending that off and we're still working that through. It's been an exasperating experience. Its true, the science is a little ahead of the practical aspects of this, but it's very much a work in progress.

Do you know of any treatments that are still early in research, maybe pre-clinical or Phase I or II that are looking promising for their association with molecular markers?

Dr. Pennell: I would say for my own particular area of research there is an intensive amount of investigation in Phase I programs trying to identify mechanisms of resistance to EGFR inhibitors. For the group of patients with EGFR mutations who respond, as most of you are probably aware, almost everyone develops resistance and eventually progresses. While a two-year median survival might sound great to Dr. West and me because it's twice what we would expect, it doesn't sound all that great to the 45-year old mother at home.

The important thing is though these are still cancers that are driven by an EGFR mutation in many cases; or perhaps it required a second change. There are lots of trials going on perhaps combining it with a pathway inhibitor farther down in the cascade.

So if we go back to our little diagram that I showed you here, if the EGFR something down here has changed that has made this cancer resistant, there are inhibitors that are being developed to all sorts of different proteins that are farther down here inside the cell that are being combined with EGFR inhibitors and at least preclinically are able to overcome certain mechanisms of resistance.

In addition, there are drugs that are next generation EGFR inhibitors that are designed specifically to target the most common resistance which is a mutation called the T790 mutation, which I'm hopeful will end up being slightly better than the current generation of EGFR inhibitors. So I think this is a promising and active area of research that I'm not sure if I could pick out one particular one that I thought was most promising. I would say there are a half a dozen that show significant promise.

Dr. West: Can you speak to any data with sorafenib or sunitinib in lung cancer, any sense that these are associated with any molecular markers at this point?

Dr. Pennell: That's an excellent question. Certainly every trial that has tested these vascular endothelial growth factor receptor inhibitors has attempted to identify biomarkers that predict this, such as VEGF levels in the blood, soluble VEGF receptor levels in the blood. As of right now, I don't think anyone has ever shown a particular molecular marker that has shown any benefit.

In the breast cancer world, Avastin, which is an antibody against VEGF and is also approved for non-small cell lung cancer has been approved in breast cancer, and there was a large trial of patients who received chemotherapy and Avastin that showed that you could identify something called a genetic polymorphism, which is not a mutation; it's actually a normal variation of a certain gene that is present in a certain percentage of

people out there. Everyone's genes are slightly different and work in slightly different ways. But there are some polymorphisms that were relatively common in women who were being treated with Avastin, and based on certain polymorphisms they had a dramatically better survival when treated with Avastin compared to those who had a different genotype.

To my knowledge, this has not yet been tested and certainly hasn't been published in lung cancer, but I would be very curious to see if perhaps is something as simple as a genotype analysis of a patient's blood could indicate who would benefit from Avastin. As far as Sorafenib and Sunitinib, I'm not aware of anything that's been shown yet.

Dr. West: If someone was tested early on and is found to have EGFR wild-type, is it possible, have you heard of anybody who has ever acquired that or is that something you have at the beginning or if you don't have it, you probably will not?

Dr. Pennell: I have to say I don't that I've heard of that. Most likely this is a very early genetic change in the development of someone's cancer so you would expect it to be present in all of the cancer cells that are present as opposed to developing later on. I don't see why this wouldn't be possible; however, what I would worry about is if an EGFR mutation was detected later on that it probably wouldn't have been the underlying cause that caused the cancer, so inhibiting it might not be all that effective.

Dr. West: You had said that in an ideal world, you'd test all tissue. If someone has a squamous cell carcinoma is there a value that you can see in doing EGFR mutation testing?
Or as another question, any value in extending the search for, say, ALK to groups like squamous?

Dr. Pennell: There have been squamous cell carcinomas where ALK inhibitors have been identified. From that standpoint, right now I think because it's so infrequent, people are trying to look for the non-smokers and the adenocarcinomas and whatnot, but I know that Dr. Shaw at Mass General Hospital is in Phase I trials there's at least one squamous cell patient in ALK rearrangement and did respond to the treatment.

From the EGFR mutation standpoint, I don't think that it's going to be terribly cost-effective to do EGFR mutation testing on squamous cells. I'm working with a pathologist at my own institution to try to do blanket EGFR mutation testing of all adenocarcinomas because even rarely patients who were heavy smokers will still have an EGFR mutation. I'm not aware of described EGFR mutation in squamous cell and Dr. West you can help me on that if you've heard of that.

Dr. West: I think that's one of the issues that you really struggle with. I have heard of patients with squamous tumors who have had a response and/or a mutation, but I think the real question is if it's an appropriate second-line therapy anyway and you're going to give it, how critical is it? I think that the real great value of it is sequencing it early on and making sure that someone with a mutation definitely has their chance to get it when their performance status is favorable. Or, if they maybe are a high probability but don't have the mutation, reserving it for a later therapy and ensuring that they get a chemo-based treatment early on, which is something we've learned about from IPASS.

Dr. Pennell: Right. Also a setting where perhaps a serum test such as the proteomic profiling might be useful because it's clear that that is not identifying EGFR mutations. Its identifying populations of patients who don't have EGFR mutations who may do better than others or more usefully perhaps, though some who do worse than others, that might guide you later on in your lines of treatment about who might benefit from an EGFR TKI or not.

Let's close it out. I want to thank everyone for their participation. I especially want to thank Dr. Pennell for a great presentation and for taking the time to answer these questions.

Have a good night everyone.