



ASCO 2011 Highlights: Advanced Non-Small Cell Lung Cancer, by Dr. Nasser Hanna

Dr. West:

Hello and welcome. My name is Dr. Jack West, and I'm a Medical Oncologist in Seattle, Washington and also the President and CEO of GRACE, the Global Resource for Advancing Cancer Education. Today, we're doing a program on the Lung Cancer Highlights from ASCO, the Annual Conference of the American Society for Clinical Oncology, held in June of each year. This live webinar, as well as the podcast materials to be produced from it, are the product of a partnership between GRACE and the LUNGeVity Foundation.

Let's move to the second half of the program. This will focus on the metastatic advanced non-small cell setting where there a lot of activity. Dr. Nasser Hanna is Associate Professor of Medical Oncology and a particular expert in thoracic oncology: lung cancer and mesothelioma. With that, I'll turn it over to him.

Dr. Hanna:

Well thank you Jack. I really appreciate having the opportunity to participate in tonight's webinar. I'd like to go over metastatic non-small cell lung cancer. I'm going to highlight just a hand full of studies over the next 15 to 20 minutes.

These are my disclosures. I always have a hard time knowing exactly what to say and here I don't think I have any conflict of interest, but I never quite know. So I just list things that I'm not sure about. So there you go.

OK, so this is my overview slide. I think the most exciting thing that I'm going to talk about today are the first two presentations, which is ALK inhibition, which is a true breakthrough. This is a really big deal and a major discovery in lung cancer that will have an impact on tens of thousands of people's lives. Mark Kris presented an elegant presentation on driver mutations which I think is going to set up the big breakthroughs in the next 5 to 10 years. Then I'm going to talk about a new target, MET. Then I'm going to just review very briefly three abstracts looking at more refined strategies with existing tools rather than the really new age and new targets.

So I'm going to start with the most exciting data, and that's with crizotinib. So, at the preliminary session at ASCO in 2010, this phase one/ phase two study was presented. It was published in the *New England Journal of Medicine*. Crizotinib was assessed in the classic phase one study once the phase one dose and toxicities were best defined, the patients who had ALK positive tumors and the patients who had MET positive tumors were then enrolled on separate clinical trials with crizotinib. So this trial looked at patients with non small cell lung cancer who were positive for the ALK gene rearrangement as tested by FISH. They had 1,500 patients that they screened and the identified 82 eligible patients. These patients were all positive by fluorescence *in situ* hybridization. There were two other methods for which you could test for this ALK gene; one is polymerase chain reaction and 31 of those patients were tested. Nine of the 31 were negative for the finding in ALK partner. So, it was not the way that patients were screened, but it was an important observation.

Twenty-five patients who were tested who were FISH-positive -- were all positive by immunohistochemistry as well. This is a very heavily pretreated patient population. Most of the patients were 1, 2, 3, or 4 prior regimens. They were given crizotinib, and they were all ALK positive by FISH. The typical response rate in this patient population would be expected to be about 5%, with about 15 to 20% of patients with brief stable disease, with the whole number of available regimens. But amazingly, 57% of the patients achieved an objective response. An additional 33% of patients achieved stable disease. So, at ASCO this year, Dr. Camidge updated this data and recorded progression free survival of this phase one study with 119 patients.

These were the characteristics of these 119 patients. Half are men, and half were women. 72% of the patients were never-smokers, but it's important to note that 28% of the patients were former or current smokers. It really had been thought that ALK gene rearrangements were seen almost exclusively in never smokers. That's clearly not true: 28% of patients in this series were former or current smokers. Almost all of the patients on this trial had adenocarcinoma and, as you can see, the majority of the patients have received multiple prior therapeutic regimens.

Despite the heavily pretreated group of patients, the response rate for the 116 patients for whom response was evaluable was 61%, and 31% of patients had stable disease. This is really remarkable: 92% of the patients given the single agent oral medicine had control or response in their disease. The response was much longer than one would expect with chemotherapy agents.

The median duration of response was almost a year, meaning half of the patients responded far greater than a year. And the responses were quick: these patients knew it soon. The first disease evaluation, they had found a response. And the progression-free survival which, in these trials, is typically 1-3 months, the median was 10 months on this trial. The overall survival of the median had not been reached at the time of this report. But 81% of the patients were alive at 1 year. Again, if you look at historical controls of many agents, this number would be expected to be more like 20 to 25%.

There were some adverse events, and one of the more unique ones is this visual field effect that the patients experienced. It's like a stream of lights that they see, sort of like the effect that you have when you're staring at a light bulb and then suddenly you turn the lights off and you move your head to the left and the right. And the light sort of streams left and right, and it's kind of an interesting side effect that most patients get. It's thought to be due to the fact that ALK is important in the development of the circuitry of the visual system.

There is a little bit of nausea and vomiting, generally grade I and grade II with this drug. That's because ALK is thought to be important in development of the gut as well.

So, there were a few comments that I had, other than the fact that this is really a big deal, and a remarkably active drug. The authors were not able to provide us any information on various fusion subsets. We know that EML4-ALK is the most common fusion partner with ALK, EML4 is. But there are other partners. There are several variants of EML4 that partner with ALK. We know that preclinically, they have variable responses to ALK inhibitors. So, there is more room to refine this information. We know preclinically that ALK inhibitors are more active than chemotherapy in patients with ALK positive disease. And retrospective data does appear to support this as well. There was some recent interesting data that suggest that pemetrexed is also quite active in patients who have an ALK gene rearrangement. But ultimately the company has recently completed a brief study.

This is a second or third line trial. Patients who have ALK gene rearrangements randomized to either docetaxel or pemetrexed versus receiving crizotinib. And hopefully we'll get the answer to that trial this year.

Now, I'd like to move on to a very important presentation that Mark Kris provided on behalf of the new organization called the Lung Cancer Mutation Consortium. This is a group of investigators who receive federal money to help train their individual pathology labs to run molecular profiling on patients with adenocarcinoma in their institutions. So the objective was to take 1,000 tumor samples from patients with adenocarcinoma. They assessed them for what we call "drug-able" targets. In other words, mutations that can be found for which there are available drugs, either on a clinical trials or commercially available to treat patients. These are listed on the slide. This did include EML4-ALK, EGFR, and the others listed here.

Ultimately, they wanted to use this information to try and figure out what clinical trial to place these patients on. Many of these institutions had phase I studies, for instance with MEK inhibitors. So, if you had a MEK mutation identified in this series, you'd be preferentially placed on that clinical trial. So this was the overall design.

They took 1,000 patients who had Stage IV disease with the adenocarcinoma. Of course they had to have sufficient tissue for testing. This was confirmed by a central biopsy of the adenocarcinoma. Then they did the mutational analysis testing in CLIA certified labs at 14 different institutions. That information was reported to a database in a virtual way, so they can each see them and also reported to the individual physicians. If patients were found to have EGFR mutations, they were treated with erlotinib. If they were found to have the other targets, they were then routed towards individual clinical trials.

This is the really important slide here. This is the entire population of patients that they've tested thus far, which is 516 patients. More than half of the patients were found to have a "drug-able" gene mutation: 54%. The majority of those were patients who had KRAS mutations, 17% had EGFR mutation, 17% had the EML4-ALK gene rearrangement, which is the target for crizotinib. But you can see there were a variety of other targets, which, by themselves, are not in large numbers. But when you add them up, you'll find that a majority of patients had at least one target that could be looked at.

When you have a target, you usually have no other targets. So 97% of all the mutations that were discovered were mutually exclusive. So if you had an ALK gene rearrangement, you really didn't appear to have any other hits in EGFR or KRAS and so forth. This was occasionally not true but, again, only 3% of patients had more than one gene mutation found. That's 14 out of 516 patients. So, I really think that type of data, which has been generated by this Lung Cancer Mutation group and is being generated by other groups, such as the one at MD Anderson, is really building the back bone of how we're going to treat our patients in the future and how we're going to select

Now, Dr. Spigel looked at a new class of agents called MET inhibitors. He reported the final results of a randomized phase II study of a drug called MetMab, in combination with erlotinib versus placebo in combination with erlotinib.

This is the background with MetMab. MET is apparently an important target in non-small cell lung cancer. By itself, it's implicated in driving the growth of some cancers. But it also appears to be a mechanism to resistance of EGFR inhibitor activating mutations such as, there are a group of patients who have an EGFR mutation who response very well to erlotinib and then eventually develop resistance. When those patients have their tumors re-biopsied, about a third of them

have MET amplification, which appears to be the mechanism of resistance for either erlotinib or gefitinib. And so MetMab is an antibody to the MET oncogene.

This is the design of the trial. This was the second or third line non-small cell lung cancer trial. Patients were randomized in a one to one fashion to either MetMab plus erlotinib or placebo plus erlotinib. They were primarily looking at progression-free survival. They did perform immunohistochemistry on the available tumor samples to determine if the patients were MET positive by immunohistochemistry or MET negative.

Now when the trial results were reported, there was no difference in progression-free survival between the two groups. But what was significant about this study is the patients who were positive for MET appeared to have an improvement in progression-free survival when they were treated with the MET inhibitor combined with erlotinib, versus erlotinib and placebo. The hazard rate for progression free survival was 0.53, which is a number we don't typically see in patients treated on non-small cell lung cancer trials. But more importantly, the hazard rate for improved survival favoring the MetMab arm was 0.37. That is really unprecedented in non-small cell lung cancer. That is in only the patients who had MET positive tumors.

Now they looked at various subpopulations to discern if it was the MET positivity by immunohistochemistry, perhaps it was the MET positivity by FISH analysis. But perhaps other factors played a role, such as EGFR mutation status. So these numbers get pretty small. But I think we can see that at least there are some trend lines. If patients were MET FISH positive, there did appear to be a slight improvement for patients that received the MET antibody. But if patients were FISH negative, they still appeared to have an improved MET with the MET antibody as long as they were immunohistochemistry positive. So this upper panel suggests that the FISH status is not the key, but perhaps simply being immunohistochemistry positive.

Now we look at EGFR mutation status: this is a group of patients who are MET positive, but have EGFR non mutations versus MET positive FISH negative and EGFR non mutations. Once again, the driver of this was MET positivity by immunohistochemistry. It was not driven by EGFR mutation status or by MET FISH status either.

This is a look at the side effects of the MET inhibitor, which you can see there is one unique side effect and that is peripheral edema. That was more than double in the group of patients that received MetMab plus erlotinib versus placebo plus erlotinib.

Now I'd like to turn our attention to this study. This is called the EURTAC trial.

Just to give you a little bit of background about this trial, about two years ago, a group from Asia reported the results of a trial called IPASS. IPASS was a trial of Asian patients who had adenocarcinoma and were primarily never smokers. Those patients were randomized in the first line setting to the EGFR inhibitor gefitinib versus carboplatin/paclitaxel. That group reported no difference in survival in the Asian population regardless of whether they got an EGFR inhibitor or they got carboplatin and paclitaxel.

Again, this is a group of never smokers with adenocarcinoma. They had preplanned subset analysis though, looking at this never smoking group. They divided them by EGFR mutation status. It turns out that about 60% of patients had EGFR mutation, and 40% did not. When you look specifically in the group of patients who were never smokers who had EGFR mutations, their progression free survival was substantially better if they received gefitinib. The converse was true if they were never smokers that did not have EGFR mutation -- the progression-free survival far favored the chemotherapy group. This was prospectively assessed in a second Asian study

confirming those results: those with EGFR mutation benefited from the EGFR inhibitor. Those who were EGFR wild type benefited with the chemotherapy. The EURTAC trial is really replicating these data in prospective fashion, but not in an Asian group of patients, but rather a European group of patients.

This is the design of the study. The patients were chemotherapy naïve. This was first line treatment. They all had an EGFR mutation. They were randomized to platinum based chemotherapy versus erlotinib.

This is the progression-free survival, significantly favoring the erlotinib group. So this data has now been replicated in a non-Asian population which is something that is very important to do, because of the Asian population frequently has the outcomes on the trials can differ sometimes from North America and European populations. This may be due to pharmacogenomic issues or biologic characteristics of the tumor.

When they looked at overall survival, there was no difference in overall survival. But this is probably attributed to cross-over, whereby those patients who were randomized to the chemotherapy arm eventually were treated with erlotinib. That occurred in the majority of patients, therefore blunting any difference that one might find in overall survival.

This is the second study that I'd like to look at looking at strategy, and it's called the PARAMOUNT study. This study was a phase III study assessing the role of maintenance pemetrexed in patients who had previously received cisplatin and pemetrexed as an induction therapy. The idea behind this is to see if we can improve progression-free survival by continuing pemetrexed after having already receiving pemetrexed as induction therapy. This study -- again these patients were chemotherapy-naïve. They all received cisplatin and pemetrexed for four cycles of therapy. If they had not progressed, they were then randomized to either maintenance pemetrexed plus best supportive care versus placebo with best supportive care. Again, the primary end point of this trial was progression-free survival.

Indeed, the investigators met their primary end point. Those patients that continued on pemetrexed after the initial four cycles of cisplatin and pemetrexed had an improvement in progression-free survival compared to those who stopped their pemetrexed and went on placebo alone.

Now this type of result has been seen in other trials with other drugs, showing that if you prolong therapy with the same drugs in the first line study, you can improve progression-free survival. However, those studies using the same drugs in the maintenance setting as were given in the front line setting have largely not shown inability to improve overall survival. We have not seen the results of overall survival on this trial. We've only seen the results of progression-free survival and quality of life. So the question remains, "What is the relevance in the improvement of progression free survival?" Certainly, if one can demonstrate that your symptoms remain under better control or you have fewer complications from your cancer as a result of longer disease control, or if you have an improvement in other quality of life parameters, that this by itself would warrant the use of maintenance therapy even if you weren't able to demonstrate an improvement in overall survival.

Well, this quality of life analysis was performed on this trial. If you look at the very bottom of this slide what you'll see is that there is no statistical difference in the quality of life scores between the two arms. We do know that those patients who receive maintenance pemetrexed did have more adverse events as a result of receiving pemetrexed. Most of these were not serious adverse

events, but nevertheless, some of them were things like fatigue, there can be some low grade nausea, occasional diarrhea, and sometimes rash. So, this is the data that we have at this point. I think it's too premature to utilize maintenance pemetrexed after having received induction pemetrexed as the first line setting.

I believe this is my last slide. This was, I thought a very intriguing study. I had mentioned earlier that patients who have EGFR mutations have a very high likelihood of responding to EGFR inhibitors. But invariably, patients eventually progress. In those patients who progress, repeat biopsies have demonstrated at least two main mechanisms of resistance. One of them is called a T790 mutation and the other I have already referred to, which is the MET amplification. The T790 mutation represents a change in the conformation of where the EGFR inhibitor binds against the tumor. It doesn't allow it to bind where it had previously been binding before.

One strategy to overcome resistance based upon this mechanism is to use what we call an irreversible EGFR inhibitor. The EGFR inhibitors that we use now, gefitinib and erlotinib, are reversible inhibitors. They bind to their site, they inhibit their tumor, but they also come off the site as well. The irreversible inhibitors bind and then they don't release. It shouldn't make any difference if you change the conformation of the binding site if the drug is already bound.

So this is something that has been well demonstrated preclinically. The EGFR inhibitors that are irreversible are active in the T790 mutation cell lines. There is nice preclinical evidence that shows when you combine one of the irreversible inhibitors, such as the drug afatanib, with an EGFR antibody, you can further overcome the resistance than just the irreversible inhibitor alone. So, the investigators on abstract 7525 took a look at this. They had treated patients with EGFR tyrosine kinase inhibitors and then the patients had progressed, and the patients were rebiopsied.

All of the patients were then treated with afatanib, which is an irreversible EGFR inhibitor combined with cetuximab, which is an EGFR antibody. They were all treated, regardless of whether they had the T790 mutation or not. What they reported was that more than half of the patients who did *not* have the T790 mutations were able to achieve a response with the utilization of these two drugs. About a third of the patients who *did* have a T790 mutation were able to achieve a response with the combination of these two drugs. This is very provocative because we know that patients who are treated with EGFR antibodies by themselves don't appear to have much activity in either of these patient populations. So if you combine the antibody with an irreversible inhibitor, it seems to be able to overcome resistance both through the T790 mechanism as well as other mechanisms that haven't been described at this point. I think this is very interesting data and will certainly lead to further study.

So I'm going to end there, Jack, and hopefully we'll have some questions and I'll be happy to field those.

Dr. West:

We'll continue with a question and answer session in a later podcast.

Thanks for listening, and thanks to our co-sponsor, LUNGeVity Foundation, for helping to make the live program and these enduring podcast materials possible.