

## Dr. Jared Weiss, Medical Oncologist, University of Pennsylvania: The Debatable Role of Adjuvant Therapy with an EGFR Inhibitor in Resected Non-Small Cell Lung Cancer

### Dr. West:

*Hello and welcome to everyone who is joining us for our webinar with Dr. Jared Weiss from the University of Pennsylvania. Dr. Weiss is a medical oncologist with a particular expertise in lung cancer as well as head and neck cancer. He's also known to many of you as a leading faculty member on the GRACE website, but today he's kind enough to join us to give his perspective on an open question and an area that has really been one where we have an idea that is compelling but arguably a little ahead of the data that we have to support it. That question is whether there is a role for postoperative EGFR inhibitor therapy with a drug like erlotinib, a.k.a. Tarceva. With that I'll turn it over to Dr. Weiss to give his perspective on this topic. Thanks.*

### Dr. Weiss:

Thank you Dr. West and thanks for this topic. It's kind of a fun topic to talk about today because this is a question that does not yet have answer. What I'd like to try to do today is to talk about what we know and what we're doing to get that answer.

We'll start by going over the general goals of adjuvant chemotherapy and then we'll go into a perspective on how adjuvant therapies have been historically developed. We'll use that as a transition to whether these old methods really still apply to biologic agents such as Tarceva and Iressa. We'll talk about the data that does exist, some retrospective non-study data at Memorial Sloan Kettering and a small amount of data that exists after chemoradiation. We'll spend the bulk of our time discussing the most important ongoing trials given that this is an unanswered question. Finally, we'll address who should have molecular testing at the time of surgery.

So in any cancer decision, I think we need to come back like a broken record to two key questions: whether the therapy is in the metastatic setting or whether it's in the curative adjuvant setting.

1. Will the proposed therapy improve duration of life?
2. Will this therapy improve quality of life?

All other measures, even curing disease, are surrogates for those key measures. This point is important when we get into the biologics for adjuvant therapy.

Traditionally, the primary and perhaps only goal of adjuvant chemotherapy has been to increase the cure rate. The idea was that a few cells could be left behind after surgery or even have spread somewhere else, like say five cells to the liver by the time of surgery. The chemotherapy would get everywhere in the body and try to cleanup those last few cells rendering a patient cured who was not cured before. I agree with this goal. I think the most important goal of adjuvant chemotherapy is cure. We'd ideally like to cure everybody.

However, I would like to propose that there maybe some patients who get adjuvant chemotherapy who are not cured by the therapy, but nonetheless get some benefit. There may be a population of patients whose cancer cells are knocked down increasing the time to recurrence and yielding those two benefits that we talked about—increased duration of life and increased quality of life while not

quite reaching the point of cure. Essentially these will be patients for whom adjuvant therapy is essentially equivalent to their first-line metastatic therapy just given early.

A long time ago, a series of trials demonstrated a survival advantage for chemotherapy for metastatic or stage IV disease—the incurable patients. Patients lived longer and they had an increased time until additional symptoms developed. This led many investigators to hypothesize that if chemotherapy could knock down cancer in the metastatic setting, maybe in patients with local disease who had gotten good surgery, chemotherapy could increase the cure rate by cleaning up those last few cells. Originally, the first several trials were negative; they used older, less effective, sometimes more toxic chemotherapy regimens. But as we got better chemotherapy, we eventually showed the survival advantage shown here, combining the results of many trials.

In fact, more modern third-generation regimens such as cisplatin and vinorelbine generally show a bigger survival advantage than the older the regimens.

I mentioned that the general paradigm is to extrapolate from the metastatic setting to the adjuvant setting. Indeed, many therapies that have been proven to be better in the metastatic setting have then been brought over to the adjuvant setting. Some lung cancer oncologists are willing to even do so without a trial. If a drug looks better in the metastatic setting, they move it over to the adjuvant setting saying that it may also be better there.

You're looking at data from the TAC326 study which showed better survival with cisplatin and docetaxel compared to the older but then standard regimen of cisplatin/Vinorelbine. Many, many oncologists suggested that if patients lived longer in the metastatic setting with docetaxel and they got more cycles in, perhaps the same would be true in the adjuvant setting and this became a commonly used regimen.

Others of us, including myself, were skeptical. We say just because its better in the metastatic setting, it's not necessarily better also in the adjuvant setting. It could be exactly the same or even worse; we just don't know.

An ongoing discussion about this issue between myself and Dr. Tracey Evans, who by coincidence was a residency classmate of Dr. West, led us to look back at the U Penn tumor database and see what the results actually were with treatment of cisplatin/ docetaxel. I had to eat crow: I was wrong. Certainly the regimen was extremely feasible. In this small series of patients it was actually more feasible than the best published results with cisplatin/ vinorelbine.

As for survival, you can't entirely compare a retrospective series to large randomized trials. However, what we can say is that although the patients were sicker and more advanced than those reported in the trials, survival results were at least comparable. So call me pigheaded, but even after disproving this idea myself of cisplatin/docetaxel, I'm still skeptical about applying the same idea to biologic therapy. These drugs work by different mechanisms of action and the rules may be different.

The first hint that I may have a point came this past summer at ASCO. This is NSABP-CO8; the standard adjuvant chemotherapy regimen for colon cancer is FOLFOX, a combination of 5-FU and oxaliplatin. The investigators randomized patients to get the standard regimen (shown in yellow) versus to get the standard regimen plus the addition of Avastin. As you can see there is some separation of the curves, but by 3 ½ years the curves have totally come together indicating that there is no increase in long-term cure rate from the addition of Avastin. The astute will note that there was in fact a separation of those curves for a time. We talked earlier that there may be benefits beyond just cure to adjuvant chemotherapy.

Here, at one year when the Avastin was still being given, there was a dramatic benefit to Avastin therapy as shown in the hazard ratio of .6. But as you go over time, 1½, 2, 2½ years, we see that magnitude of benefit shrinking until it loses statistical significance at 3 years and essentially disappears by 3 ½ years. So a patient was more likely to be alive and without cancer at 1 year, 1½, 2, even 2½ years but ultimately the patients who are destined to have their disease recur had some recurrence.

Colon cancer is not lung cancer and Avastin is not Tarceva. However, this study raises a flag of warning to say that the rules may have changed.

This audience is mostly familiar with Tarceva, but let's just be sure. There are two similar drugs: erlotinib or Tarceva; and Iressa otherwise known as gefitinib, that are once a day pills active against lung cancer with major side effects of rash and diarrhea, but generally greater tolerability than chemotherapy.

The drugs are targeted particularly to the epidermal growth factor receptor and effect downstream cascades as shown in simplified form at the bottom right. We've reviewed on GRACE many times before survival data from multiple trials with these agents. I'm showing a survival advantage versus placebo.

Here it's particularly the patients with the EGFR mutations (shown in green) who seem to benefit from Iressa more than chemotherapy and patients without the mutation seeming to better with chemotherapy; at least in the first-line. This raises the hypothesis that in the adjuvant setting, too, there maybe differential benefit for patients with or without mutations.

As I see it, here are the key questions we're left with: Can Tarceva increase the cure rate after surgery? If not, can it at least provide some benefit, delay the time until the cancer comes back? Can it do this in everyone or just patients with mutations? And finally, if we do buy into Tarceva, how should we give it? Should we give chemotherapy first in the same fashion we're doing? Or should it be used instead of chemotherapy? Should it be used after chemotherapy?

We have some small amount of data and a number of major ongoing trials. This year at ASCO, the group from New York — Memorial Sloan Kettering — showed us some retrospective data. This was not a study. They didn't randomize patients to therapy or not, but they did give a lot of patients therapy with Iressa or Tarceva in the adjuvant setting and they looked back at their results. The simplified results show that at two years there was a strong trend that was not statistically significant towards better survival with the adjuvant Tarceva or Iressa; and a number that I think is clinically meaningful, an 8% improvement.

Here are those curves shown graphically. This is disease-free survival, meaning that to stay on the curve you have to be both alive and without evidence of your cancer coming back. If you follow the curve from the 24-month time at the bottom of the curve and follow those numbers upwards, you can see those same numbers that were reflected on the summary slide. You can see that between a year and about three years, there's a clear benefit to having received the adjuvant therapy.

But you can also see that in this retrospective data that at about 3 ½ years those curves seem to come together. So, again, we're seeing at least a suggestion that these drugs may delay time until recurrence just like in the colon cancer trial, but there does not seem to be an increase in long-term cure; at least in this data. Overall survival numbers are fairly similar.

Here's an interesting analysis looking at the patients who were not treated with either Iressa or Tarceva. On the black curve at the top, the people who did best had EGFR mutations. They did better even without getting Iressa or Tarceva. In the middle, we have patients with neither of the

major mutations and at the bottom we have patients with the KRAS mutation. This data is similar to data we've seen before and that we've reviewed at GRACE before.

This trial was one of the biggest shockers in lung therapy in a while. This was trial that randomized patients with stage IIIB disease to either the standard of care or the standard of care plus Iressa. Standard of care here is chemoradiotherapy; all patients on this trial got standard chemoradiotherapy. The patients in the yellow group also got Iressa following that therapy.

Some of us hypothesized that the Iressa would help. Others hypothesized that it would help only in patients with EGFR mutations and at the signal would thus be small. The biggest skeptics hypothesized that there'd be no benefit and that curves would be essentially superimposed, or on top of each other.

What was incredibly surprising was that there was meaningful and statistically significant difference favoring the placebo group. Gefitinib actually harmed patients. It wasn't just some new side effect of the gefitinib: it was actually cancer recurrence that was the biggest determinant of this.

I hate to tell this to you, but I have no idea why this happened or what this meant. I'm with the majority who's still scratching our heads. However, it does certainly make me pause and consider the possibility once again that the rules could have changed here compared to standard adjuvant therapies, that although gefitinib and Tarceva have benefit in the metastatic setting, we have to be very cautious as we design our adjuvant trials.

This is the schema for the RADIANT Trial, one of the largest trials going on to answer the question of Tarceva's benefit. All patients get full standard therapy. What this means is that patients have to have a good surgery and they are then allowed to discuss with their doctor whether to get traditional adjuvant chemotherapy following that. The patient will complete all of the therapy they decide together with their doctor, their surgery and then the chemo if they're going to get it. They are then randomized in a two to one fashion meaning twice as many people go on the experimental arm to either get two years of Tarceva or to get placebo. The end point here I think is the right one—disease-free survival—meaning you need to be alive and without evidence of our cancer. I think this is the right end point given that we're going for cure here. This trial is ongoing at many institutions including my own. You may notice that this trial does not require you to have an EGFR mutation although EGFR status is checked, patients with or without the mutation can enter.

Some oncologists hypothesize that the benefit of Tarceva in the adjuvant setting maybe restricted just to people with the EGFR mutation; that population that we seen does particularly well in the metastatic setting with these agents. This is a study out of the Massachusetts General Hospital that evaluates this question. There's no randomization here. This is a phase II trial. To get on the trial, you have to have full appropriate lung cancer surgery and you have to have an EGFR mutation. Much like RADIANT, you're then allowed to get adjuvant chemotherapy if together with your doctor you think that's the right thing. Then everybody on this trial will get two years of adjuvant Tarceva.

A similar trial to the RADIANT trial was done with Iressa, with some data supposedly being presented at ASCO this coming summer.

Finally, I have one particularly novel study to show you that looks at a control arm of cisplatin/pemetrexed; and I should say here that these are all patients with an adenocarcinoma and the trial randomized these patients to either that control arm that authors considered their best regimen for adenocarcinoma or this customized experimental arm. The customized experimental arm uses a pair of biomarkers to determine what therapy should be.

So the first decision point is whether you have the EGFR mutation. Patients with the EGFR mutation get Tarceva alone, no chemotherapy -- that's your adjuvant therapy. If you don't have the EGFR mutation, you then have analysis for ERCC1. We've seen some retrospective data that shows us a hypothesis that it maybe just the patients who are ERCC1 negative who benefit from cisplatin adjuvant therapy.

So what happens here is if you're in that group, the group that we think benefits, the ERCC1 negative group, you get the cisplatin-based chemotherapy — cisplatin/ pemetrexed. But if you have that ERCC1 marker, that may indicate a lack of responsive-ness to chemotherapy, you get observation alone. The idea here being that if you're not going to benefit, we'll spare you the toxicity and side effects of the chemotherapy.

This study opened in the spring of 2009 and is currently enrolling patients. The hypothesis is to increase three-year disease-free survival by 8%, from 50% projected in the control to 58% in the experimental arm. It is ongoing.

So I was asked to specifically address the question of who should have EGFR testing at the time of surgery. There is no definite answer to this question either and I will admit that my opinion falls towards perhaps the extreme end of the curve. But I think almost everybody with adenocarcinoma should be tested. The first and most immediate reason is to determine adjuvant trial eligibility. Some of the ongoing trials require an EGFR mutation.

The much more commonly available SATURN trial does not require an EGFR mutation; however, when I'm counseling my patients about whether to consider this or similar trial, I'm much more excited about it if they have an EGFR mutation and I think that this does play into the decision-making for both doctor and patient.

Finally, and unfortunately, lung cancer often recurs. These tests take a fair amount of time. At my institution, we're waiting on an approximately three-week average turnaround to get EGFR and KRAS testing, with EML4-ALK sometimes taking longer. I'd rather know in advance if my patient has any of these changes so that should we be unfortunate enough that the patient recurs, I'll know immediately what to do instead of needing to send out the tests and potentially wait on therapy.

Many of us are collecting tumor databases of our patients. This has been a long-established means to generate hypotheses and try to improve care. I believe that these tumor databases will be better armed to give us new knowledge if they include molecular information and I think that's good enough reason alone.

Who can avoid testing? First, patients with squamous cell carcinoma. Squamous cell carcinoma does not seem to ever bear these mutations. In fact my first thought if I were to get back an EGFR mutation on a squamous cell carcinoma would be to send the slides back to the pathologist and ask the question is this really squamous cell carcinoma.

Perhaps heavy smokers can forego testing. They're very unlikely to bear a sensitizing mutation to the EGFR or an activating mutation. The very smallest of stage I cancers are unlikely to recur and for that reason can probably defer testing.

I thank you for your interest and attention and I'd be happy to take questions.

Dr. West: Thanks very much. That's great. We do have a few questions that have come in. One is really is a rubber hits the road type question and that is if you have a patient who has gotten mutation testing and they find that they do have the mutation after surgery for

stage II non-small cell lung cancer and they come to you asking about receiving Tarceva in the adjuvant setting, either in addition to or instead of chemo, independent of a clinical trial which is always an appealing and easy answer, if you don't have the trial available or the patient isn't eligible, what would you say about your enthusiasm for doing erlotinib, Tarceva as an adjuvant therapy off protocol if we know they have an EGFR mutation? Would you recommend it? Would you be comfortable with pursuing it after a thorough discussion or would you recommend against it?

Dr. Weiss: You won't let me hide behind the clinical trial. I think this is the kind of situation where I have to have a long conversation with my patient because there's no right answer here and I don't know the answer to this. I'm not going to totally cop out, I will give you my bias which is that I'm not recommending adjuvant Tarceva or Iressa outside of the context of a clinical protocol.

I would have a conversation with the patient about it and I would certainly not criticize someone who was doing this; especially in patients with a mutation. The benefit of these therapies has not been proven and we've had reasons that we just explored to have pause and think that there maybe no benefit. There maybe a restricted benefit, or there could even be harm.

The Memorial data that we reviewed we saw that there really is not clear evidence of an increase in long-term cure, but maybe some benefit in patients with mutation. The SWOG data, which I really have no idea how to interpret even after having a year to look at it, at least raised the hypothesis that there maybe patients that we're harming with these therapies. These drugs, in addition to potential lack of benefit in preventing tumor recurrence or potential harm as seen in the SWOG trial, while they're more mild than chemotherapy, there are real side effects to these drugs.

Most of these trials look at a year or two of Tarceva and there's a real rate of significant diarrhea, significant rash, occasional pulmonary toxicity, that makes this not an entirely innocent thing to do.

So again, I'm not recommending it off protocol, but I think that there are others who have a very strong opinion in the other direction and I see it as at least reasonable to consider together with the patient.

Dr. West: Yeah, it is a very difficult question which is why I talked with you about doing this webinar because its so current and its frustrating to be in the situation where we have the reality of EGFR mutation testing becoming increasingly widespread and our enthusiasm about using molecular markers to tailor therapy in a non-curative setting and yet we just don't have the data to tell us what to do in a higher stakes setting of potentially curing more patients, but also the higher stakes situation of potentially harming patients and the SWOG trial that you highlighted with the maintenance Iressa being so sobering and that not only was it not neutral, it was harmful and nobody expected this which should make us fearful about what we might also not expect, but could be detrimental. So, its tough, I really overall agree with you that its something to have a careful discussion with patients about, certainly not something I'd want to be heavy-handed about dismissing because you could be doing benefit.

Another question that I would have is even if it is beneficial, at least in terms of disease-free survival, if it is not curative it maybe harmful to burn and induce resistance a treatment that could be really effective when a patient is symptomatic later on, but you've

induced resistance long before they would have any evidence of the disease. I think that's an unknown question.

Dr. Weiss: And then looking at the two pieces of data showing that aim of potentially delaying recurrence but not improving cure, even if you totally buy into that, and I don't think that that data should let us totally buy into anything. Even if that idea turns out to be true, that there's a substantial portion of people who may delay recurrence, what we don't know is whether you could get that same benefit later. Or perhaps as you suggest, even greater benefit in doing it later, at the time of a clear recurrence. You may get that same benefit at a later point and there maybe a large portion of people you're giving this therapy to who are never going to recur that have side effects without benefit. So I think there are a lot of reasons for pause here.

Dr. West: Another question is along the same lines: if Tarceva does work for somebody, presumably this is in the advanced disease setting, if Tarceva works and a patient develops acquired resistance and progression, are there any treatments that we have either increasing the dose or adding a new agent that is able to restore activity that you know about?

Dr. Weiss: I think there are two answers to this question. First is no, I'm not increasing the dose. There are two approaches for the patient who was previously sensitive and derives benefit who then recurs. The first one is simple: chemotherapy. There's nothing about the EGFR mutation that makes chemotherapy not work; in fact, those patients maybe more sensitive to chemotherapy. The second question I'm now going to solidly stand behind my cop out of clinical trials because there are a number of clinical trials going on that address just this question of second-line tyrosine kinase inhibitors that look at just this population and say can we somehow overcome that resistance, be it an irreversible inhibitor or a T790M inhibitor or a MEK inhibitor, there are a variety of hypotheses and very exciting trials. I'm very hopeful that one of them will hit.

Dr. West: I agree that right now we don't have any commercially available known answer for this in terms of raising dose or adding another agent to restore activity, but the hope is that as we focus a lot on the molecular causes of acquired resistance and there are increasing numbers of clinical trials that that may lead us to a way to get the genie back in the bottle and see activity again in these people who have had great benefit that unfortunately hasn't seemed to last forever.

Another question is, if someone is tested for the EGFR mutation, say after surgery, and their tissue does not show an EGFR mutation, does it make sense to have the tissue retested if someone develops a recurrence? In other words, to have a biopsy of a recurrent patient to look for the EGFR mutation if we already knew from the operative pathology that they don't have the EGFR mutation?

Dr. Weiss: A number of small series have looked at this question of whether the primary tumor, the original cancer in the lung and the metastases (spread sites) can be different on the variety of markers. We've looked at this in a number of cancers and we've looked at in a number of markers, and there have been several series that have shown discordance between EGFR mutation status in the primary and the met. In particular, you phrased your question to ask about if the primary was negative, if it ever happens that the mets can be positive. That actually has been shown before. It's not a terribly common phenomenon, but in a minority of patients this can happen. We see this phenomenon where they're either through out treatment or between the primary and the met where the EGFR mutation status is different and that you can have some clones that are therefore

very responsive to Tarceva, and some that seem less responsive. To my mind, this is sometimes a valuable thing to do and is something that I sometimes consider.

I'd like to also note, though, that if the primary is negative, my most common practice is to initiate therapy with chemo. I'm not going to do a repeat biopsy when I already know that the primary was once negative and wait that three weeks from when that biopsy is done to start a therapy. If I consider a biopsy, it's for later lines of therapy.

So by the time you've done one or more lines of chemotherapy, you're also thinking about Tarceva anyway, even if you don't have evidence of an EGFR mutation. So I think the answer to this question sometimes becomes more practical than theoretical, that if I'm going to be doing Tarceva anyway at that point, then I might think to spare my patient the small risks and discomfort of the biopsy.

Dr. West: I think that's a really good point, that whatever we might say about the theoretical possibility of someone having a different genetic profile of recurrence later on, being tested and having EGFR wild type (no mutation) certainly doesn't make it likely that you're going to have the mutation, and that that would make chemotherapy a very strong leading option, which it would otherwise be as your default choice for first-line treatment in the advanced setting.

I agree with you that as we talk more and more about EGFR mutations and molecular testing, it would be a mistake to get too far ahead of ourselves, because I think one of the mistakes that I'm often seeing is that people who are tested and found to not have the EGFR mutation are sometimes not being offered an EGFR inhibitor at all, whether it's first, second, third, or later line -- and that's just not what the data suggests. The data show that from the IPASS trial, for instance, you're better served by getting chemo *initially* if you don't have an EGFR mutation. But larger studies like the BR21 trial that led to the approval of Tarceva as a second and third-line therapy showed a benefit in a much broader population that may not have been dramatic and long lasting benefits like we sometimes see in patients with an EGFR mutation, but a benefit nonetheless in a group that wasn't just the minority of patients who have a mutation. So if you're going to very appropriately be using Tarceva as a second or third-line agent, you don't need to do mutation testing to justify that idea.

Dr. Weiss: I agree with that. Along similar lines, I've found the SATURN data shown at World Lung to be very sobering. So we're in the middle of a conference that's all about molecular markers and personalized therapy. That trial, which I'll remind our audience, was looking at Tarceva as a maintenance therapy. When they did the subgroup analysis, it seem to benefit all of the subgroups regardless of however they tried to break it down. So, as fancy as we like to get, this often comes down to the simple practical questions.

Dr. West: Another is we've been talking about molecular markers and EGFR mutations in particular, all in the setting of non-small cell lung cancer. So the question comes in, "What about patients with small cell? Is there any value in doing this mutation testing or using Tarceva, Iressa or other molecular agents right now in small cell lung cancer?"

Dr. Weiss: It's a great question that embarrasses me, because it demonstrates just how little advance we've made in molecular treatment of small cell lung cancer. Small cell lung cancer doesn't seem to bear these mutations to be worth testing, and there doesn't seem to be activity of these drugs in small cell lung cancer. Small cell lung cancer is a much more genetically complex cancer than non-small cell, particularly the non-smoking type non-small cell that tends to bear the EGFR mutation.

In the non-smoking, EGFR mutation-driven lung cancers, we're talking about a series of mutations that the cancer seems very dependent on. There was a recent [Nature](#) paper that came out looking at small cell lung cancer and how many genetic changes there were in one particular cell line, and I forget the number, but it was something on the order of 20,000. This may have a lot to do with cigarette smoke that the more heavily cigarette-dependent small cell lung cancer may create a lot more genetic changes, and so its been harder as a scientific target to nail down one or two that are really important that we can then drug to benefit the patient. I suspect and hope that as our understanding of the molecular biology of our small cell lung cancer improves that we may ultimately at some point in the future see that translate into real therapeutic advances like Tarceva in non-small cell. But to be honest, I think we're awhile off.

Dr. West: I really agree that unfortunately for all the enthusiasm in our real improvements in understanding and treating non-small cell more effectively, small cell lung cancer has been a maddeningly difficult nut to crack. So I think that right now where we have tested it or looked for mutations, it hasn't been as fruitful as we'd have wanted.

With that I'm going to say thank you very much to Dr. Weiss for joining us today. We really appreciate your help and we also appreciate your ongoing commentary and great thoughts on the website. So, thanks so much for being part of all of it.

Dr. Weiss: Thank you. It's been a wonderful opportunity and a privilege to be a part of this community.