

**Questions and Answer Session following,
“Maintenance Therapy for Advanced NSCLC:
Who, What, Why, & What’s Left after Post-Maintenance Relapse?”
By Dr. Mark Socinski
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Dr. West: Hi, I'm Dr. Jack West, medical oncologist and President and CEO of GRACE, the Global Resource for Advancing Cancer Education. The following podcast is the continuation of the presentation by Dr. Mark Socinski, Professor at the University of North Carolina at Chapel Hill and leader of the Thoracic Oncology Program there, on the Timing and Selection of Treatment after First Line for patients with advanced non-small cell lung cancer.

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Here is the question and answer session that followed his presentation, which is available as a separate podcast.

I'm going to ask a question to you, Mark, and that is, you had listed Taxotere among the agents that would be a strong consideration. The trial with it was negative for a survival benefit, at least statistically, but obviously many patients, particularly those with a squamous tumor, are not going to be eligible for pemetrexed because that agent is really not effective in that setting. Would you hesitate at all to apply these principles to Taxotere, or would you really say that there's really no clear difference among the agents that have been tested?

Dr. Socinski: Well, yeah, that's a good point that you make. Even though I believe that the message from the Fidas Taxotere trial is consistent with the other trials that we've talked about, it is the smallest trial, it is the one that did not have a survival advantage. Although I think there was a strong trend there.

In my practice, I think the squamous histology patients obviously are not going to benefit from Alimta. I didn't show the slide with regard to the SATURN trial, but the squamous histology patients in that trial got significant benefit from the use of Tarceva as a maintenance drug, and I happen to think that a once-a-day pill that's fairly well tolerated is a fairly attractive maintenance sort of approach, if you will, than is an IV approach.

So I think the way that I've done it in my practice with squamous cell is [that] I typically treat them in the first-line setting with either carboplatin and gemcitabine or carboplatin and taxane, and then when I have done the maintenance or early second-line therapy, I've actually used Tarceva as the maintenance drug and reserved the Taxotere for, whether you call it second-line or third-line therapy, say therapy after maintenance Tarceva, in that particular setting, because I think although the impact of Taxotere in the Fidas trial was similar, it wasn't as quite as robust a conclusion that we can draw from that trial.

I find that, of these agents, that Taxotere probably has the least attractive toxicity profile for this kind of setting as a maintenance drug. So that's kind of how I've done it or thought about it in my practice.

Dr. West: Yeah, it's interesting that if we track back to several years ago when Alimta and Taxotere were compared head to head as second-line agents, and found to be essentially completely identical in their efficacy, we saw a major shift over time toward Alimta use (this is before we even knew about histology), and that was really based on a perception of the tolerability difference favoring Alimta and challenges with Taxotere, and that may be especially so in patients who haven't had a break after four cycles or six cycles of first-line treatment and that are jumping right into the next line of therapies. So it's a good point that it's important to be mindful of the toxicity challenges.

There are a couple of questions that have come in already. One is, is there a quality of life difference for those who delay treatment and are on a break?

Dr. Socinski: I don't know that we know enough about these particular studies in terms of the quality of life components of them or whether they actually really did have modified quality of life aspects of them.

They did have some data suggesting that there were benefits and symptom relief sorts of things, but I think at least my personal opinion is that is if your cancer is controlled and you can have safely a treatment break, that there's a quality of life advantage as long as your cancer's controlled of having some time off treatment where you're not having toxicity or complications of treatment. So the quality of life may be in favor of a treatment break, assuming that there's good evidence that the cancer seems to be under good control.

Dr. West: And certainly that's part of why this has been such a heated discussion, is that there's been an open question of whether if we can deliver the treatment more reliably later, that you wouldn't be able to achieve the same benefit but still maximize quality of life by that.

Dr. Socinski: Right. And my concern, Jack, is that, what I'm hesitant to do is to keep patients on kind of continuous treatment that they're always getting treatment, which is what this essentially is, because you get your first-line therapy, you sequence right to maintenance therapy, and then you progress, you would go to whether you call it second-line or third-line therapy. But you're kind of always on treatment, and to me I think there's a risk. Because although some of these therapies we consider *well tolerated*, they still on a day-to-day basis can have low-grade side effects that on any given day can make your day worse than if you weren't getting treatment. Again, assuming your cancer's under control.

So I think there's a lot to be learned about that, and lots to be learned about patients. One of the most gratifying things in my practice is if you have a patient who has a very robust response to first-line therapy and you give them a treatment break and you see them back 4 to 6 or 8 weeks later, and they actually feel significantly better getting away from treatment than they were at the end of their treatment and enjoy some time where they actually feel like

doing things and have some level of energy and so on and so forth, and I think that that's very beneficial in selected patients.

Dr. West: We have not really tackled the question of continuation versus switch maintenance therapy, and that's because the data that we have are really with the concept of switching from one thing to another, but you presented early on that we pretty much by default do a lot of continuation Avastin because that was the way it was built into one of the original trials.

Dr. Socinski: Right.

Dr. West: And we often will do that for patients who are on Alimta in the first-line setting and if they're on both, Avastin or Alimta with platinum we will often continue both of them.

Dr. Socinski: Right.

Dr. West: You had done one of the most pivotal trials of fixed treatment with four cycles of carbo and Taxol versus ongoing treatment until progression, so with that work in the back of your mind, how are you approaching the question of switching to a new agent versus continuing one or two agents from the first-line setting?

Dr. Socinski: Yeah and I think that this is an area where we need more data. I'm afraid that we'll probably never have data on this issue of maintenance Avastin. I think we're kind of stuck with the paradigm that when we're using Avastin, we'll continue it after chemotherapy and continue it till progression. I think the question there is going to be, do you add something to it, do you do continuous maintenance with Avastin and then switch, or add an agent like either Tarceva or maybe Alimta? Maybe that's the right thing to do, and maybe it's not the right thing to do. Maybe you would get as much or more benefit by simply stopping Avastin and switching to Alimta if you did use Alimta in the first-line setting.

Likewise, in my practice I think all of us are seeing or using Alimta in the first-line setting. All of the information we have about Alimta as a maintenance drug is in patients who did not receive Alimta in the first-line setting, and so I don't think we can extrapolate that this means that prolonging the exposure to Alimta has the same impact as this switch maintenance to Alimta in patients who hadn't received it yet.

I think that there's some confusion about the optimal way to manage patients in this particular setting, and we're going to have a couple of trials that are going to address some of these points, and I think these are important and we should put a plug in for clinical trials: they're very important, because as you can see in this discussion, we've answered some questions, but often when you answer a question, it creates two or three other important questions that need to be addressed. I think these are some of the things that need to be addressed.

Dr. West: And they're also predicated on having agents that you can continue on a longitudinal basis without developing prohibitive toxicities, which is better than what we've had historically.

Dr. Socinski: Right.

Dr. West: Other questions have come in. One is, you mentioned that in some of the trials, like for instance the Fidas trial, that the threshold for starting therapy at the delay point is different from what people would do clinically necessarily. Can you elaborate on actual practice versus the trial and how that would maybe...

Dr. Socinski: Well, yeah I think that's a very insightful question. If we just kind of set the example of managing a patient on the placebo arm of this trial: As an example, obviously physicians didn't know whether they were receiving placebo or active treatment, but let's say Mrs. Jones comes in and you don't know whether she's on placebo or not, but she says to you "I don't feel as well, I've lost a couple pounds, my appetite is not what it was three or four weeks ago. My pain seems to be a little bit worse, I'm taking more Percocet or more narcotics to control it." Then you think, "*Well this doesn't sound good, let me go look at Mrs. Jones' CT scan*", and you look at her CT scan and her tumor is a little bit worse but maybe it's only 5-10% worse.

On the clinical trial you couldn't necessarily do anything different with Mrs. Jones, because she didn't necessarily meet the criteria for calling her cancer officially being worse. So you had to say to Mrs. Jones, well you know it looks a little worse but not that much, and so we'll repeat the scan in six weeks, and then Mrs. Jones gets worse and she has a problem, and she ends up never getting treatment because she got too sick to get treatment.

Now outside of a clinical trial, in my practice, if Mrs. Jones comes in and says "I'm not feeling as well", she tells you all the same things I just mentioned, and her CAT scan looks 5-10% worse, I'm going to treat that patient, right then. I'm going to make sure that she gets sequential treatment. If she was on placebo, I'd make sure she goes something then. If she wasn't -- if she was on the active agent -- we would consider a different type of therapy for her.

So you know in a way you could make the argument that the placebo arm of these trials did in a way kind of set up a patient for perhaps getting or being at risk of getting less treatment, obviously than we might in our practices, because I think those of us who do lung cancer for a living, as I say, we don't think that we lose 40% of our patients. It's certainly not my experience, and in my practice that if I treat 10 patients in the first-line, I only treat 6 patients in the second-line, which is essentially what these trials did. That's not my sense and I think, Jack, you would agree with that.

Dr. West: Yeah.

Somebody has a question about: aside from the question of symptoms after four or six cycles of first-line chemo, are there other factors that you would use in deciding to recommend maintenance therapy versus observation, and particularly is tumor burden a factor that you'd think about?

Dr. Socinski: Well, tumor burden to me is only relevant if it's causing symptoms. So symptoms are a big thing to me, what your CT scan looks like. The other big thing to me is what sort of side effects you've had from your initial treatment.

Some people have a lot of fatigue, they develop anemia and those sorts of things, and that does influence me in terms of wanting to give people a little bit of a treatment break, because I want them to recover from their first-line toxicities and get them feeling better before we actually jump into, whether they call it maintenance or second-line therapy, but just give them some time to recover from the toxicities of first-line treatment.

So those are the three things, symptoms, what your CT looks like, and then your residual side effects from the first four cycles of treatment.

Dr. West: I'd add the issue of the underlying natural history, or the pace of the disease. We can often get a flavor for whether a cancer is very fulminant or whether it has a more indolent pace from our scans, and this is related to a person's symptoms and physiology, but we're all probably more inclined to feel comfortable with observation for somebody who seems to have the characteristics of a more indolent cancer, where we feel comfortable that we're going to detect something by scans long before they're going to have a significant clinical decline.

Dr. Socinski: Yeah, and I think I would agree with that, and I would add a fifth measure and that would be patient preference.

Dr. West: Of course.

Dr. Socinski: If someone feels strongly that they want a treatment break and they're appropriate for it, and vice versa, and on the other hand if patients are aware of the potential impact of maintenance and they feel like it's in their best interests, I think that does factor into our decision making.

Dr. West: A sophisticated question that I've scratched my head about, but none of us has really talked about to my knowledge, and that is: in that comparison in the Fidas trial that shows equivalent survival in the two thirds of the patients in the placebo arm who ended up getting the treatment, it's actually not the same population exactly as the ones who were assigned the maintenance active drug, and the question is do you think it might be significant that the people who actually got it that may have had more indolent disease and that the maintenance arm with the active drug includes a broader population, potentially with a more aggressive physiology that could be the one third who dropped out?

Dr. Socinski: Well yeah, I think that's kind of what I was getting at when I was alluding to try to identify patients who are going to progress early, have more aggressive disease, are going to have disease-related problems early and you're going to miss that opportunity. That's exactly what I was referring to. I do think that if you look at the Fidas trial, the main reason patients didn't get delayed docetaxel, they had disease related decline in their performance status and were thought to be not good candidates for treatment.

So I think the issue is, how do you identify someone with aggressive disease? You were just referring to this, too, and I think that obviously some clinical judgment needs to go into that.

Dr. West: Well with that we're at the end of the hour and I just want to express my extreme gratitude to Dr. Socinski for taking the time to walk us through such a challenging and ongoing topic and thanks to everyone who added their comments.

With that I'll say good night and thanks to everyone. Take care.

Dr. Socinski: Thank you.

Dr. West: Bye.