Lung Cancer News and Updates ASCO 2020

Trial Updates-NSCLC

The ADAURA Trial-Potential Clinical Impact-Potentially Curative Setting in Adjuvant Therapy for Patients Post Surgery with EGFR Mutation

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Dr. Jack West: Hi, I'm Dr. Jack West, I'm associate clinical professor in medical oncology at the City of Hope Comprehensive Cancer Center, and also the founder and president of GRACE global resource for advancing cancer education. I'm very happy to be joined today for an ASCO highlights presentation in the field of lung cancer with two of my friends and colleagues from other parts of the country who are lung cancer experts with some different perspectives. And we're going to go through some of the key presentations and talk about what we think this means for patients. So first I have Dr. Helena Yu, who is medical oncologist at Memorial Sloan Kettering Cancer Center and Dr. David Spigel, who is chief scientific officer and director of the lung cancer program at the Sarah Cannon Cancer Center in Nashville, Tennessee. Thanks guys for joining. The first trial that I wanted to talk about is called ADAURA.

And this study was presented in the plenary session. The biggest session of the ASCO annual meeting, and really, I would say by a large margin is the one that got the most discussion about its potential clinical impact. Now, ADOURA is a trial that looked at postoperative, also known as Adjuvant therapy with a targeted therapy for EGFR mutation positive non-small cell. The drug Tagrisso, also known as Osimertinib, which is a third generation agent that is largely our go-to choice as first line treatment for patients with metastatic or advanced non small cell lung cancer if patients have an EGFR mutation. But this study looked at it in a different setting, potentially curative setting of patients who have undergone surgery and then were found to have an EGF arm mutation.

And patients were randomized. If they had stage one V, stage two, or stage three A disease and had an EGFR mutation were randomized them to up to three years of Tagrisso given at the standard dose that's used for metastatic disease, 80 milligrams,

daily or placebo for up to three years. And the trial looked at the primary endpoint. The main thing that they were looking at is disease free survival. The time before the cancer would come back, or patients might potentially die of their disease. This was a large study of nearly 700 patients, and it was actually stopped early by the so-called data safety monitoring board that reviews the trial as it's being conducted. They stopped it because they felt it was unethical to continue to randomize patients when they saw striking benefits that clearly favored the Tagrisso arm.

And you can see from this curve, this is a so-called Kaplan Meier curve where patients, the time is along the horizontal and the higher the line is as you go from left to right over time, the more patients are doing well. And the key finding from this is that there was a remarkable improvement in how long patients went before the cancer might come back, or how many patients had evidence of the cancer relapsing. This is particularly focusing on what was the primary focus, which was patients with higher risk disease, stage two or three disease. And here you could see what's called a hazard ratio. That means basically the proportion of the benefit was essentially an 83% improvement in the probability of the cancer coming back or not in the patients who were on Tagrisso versus placebo.

And otherwise there was also a breakdown when looking at the patients by stage, and you could see that the greatest benefits were really in the patients with higher risk. That makes sense. The more the risk was of it coming back, the greater, the potential benefit of this treatment. There was a benefit in the stage one B patients or in the top, right? You can clearly see a separation of the curves. It's not of the same magnitude. And so this was a well tolerated treatment on unlike some of the other drugs that inhibited GFR. This was one that patients could potentially receive for years at a time with usually just mild diarrhea or, or rash rarely anything more than that. And so there was some debate about it.

Then the main one was around whether we should be expecting an improvement in overall survival, or how happy should we be with a disease-free survival benefit with a treatment that we know can improve how well people do at least four months or a year or two. But it may or may not translate to a significant improvement in overall survival. So essentially you know, is this definitely better to give everybody the treatment upfront versus waiting, see who has the cancer come back and only treat those people if they could do potentially as well in survival. That said, we also know that for the vast majority of people, if it does come back, it's not curable at that point. So I've certainly covered a lot. And I would also add that Dr. Spigel was the person who gave the expert commentary at the actual plenary session.

Why don't I start with Dr. Yu actually for this, but we'll get Dr. Spigel's comments, but Dr. Yu, I know you, Helena, you see lots and lots of patients with the GFR mutations all the time and Memorial Sloan Kettering. I imagine that you also see quite a few either before or after a relapse for early stage disease. What do you take from this? And do you have much concern about the lack of overall survival difference yet?

Dr. Helena Yu: Yes. I think that I I've been eagerly awaiting this ADOURA data for years now. I think all of us, you know, there has not been a really good adjuvant after surgery study of the use of targeted therapy for early stage disease. So this is really kind of a seminal clinical trial in that perspective. And I think one that we were looking at to sort of extrapolate maybe to other targeted therapy, you know, sort of uses as well. I, you know, I think that there, of course, like you said, there's been a lot of debate about this. I think of course the gold standard for early stage disease should be overall survival. And I think that certainly we will get that data from this study. I think even though the study was unblinded and stopped early, it was at a time where all the patients were randomized, they'd been followed for at least a year. So I think you know, I do feel confident we'll ultimately have the survival data to better kind of judge this treatment strategy. But to be honest, I, you know, I think about especially you know, talking to patients, I think personally I think a disease free survival extension or just market benefit in this case.

I do think is clinically meaningful for our patients. You know, if you look at the, the graphs that you, that the screen is showing right now for later stage disease, stage two and stage three disease with placebo, up to 70% of people recur. So those are people that are you know, whose cancer has come back. And as Jack said are no longer curable they're metastatic. And when cancer comes back, it often comes with symptoms and morbidity. And so, you know, for me and for my patients, if there is a you know, an ability to delay the time to overt sort of metastatic disease that often comes with symptoms, I think that that is a valuable endpoint for my patients. And so although the data is the sort of final data are still pending. You know, this is something that I definitely will and have been talking to my patients about. And I think particularly for stage two and stage three disease, the more high risk disease it's something that I would certainly discuss and offer to my patients.

Dr. Jack West: And David, I know you have the high stakes role of putting this into context for the whole broader audience. Can you add for the thoughts that I'm particularly interested in how you feel about the stage differential and would you approach or speak to a patient with stage one B disease differently from stage two or three A?

Dr. David Spigel: Yeah. I mean, first of all, you both covered it really nicely. And I know we've all had a chance to dive deeply into this. You know, maybe I had an advanced period to do that, to prepare, but not much to add. The study's not perfect, right. I mean, it's got

problems. There was, you know, 45% of people with stage three cancer, don't get chemotherapy. That's kind of odd, right. You know, a patient in front of you at surgery, stage three, you'd say, how do you feel about randomizing to placebo? I mean, that's not ideal. And then as [inaudible] shows, we don't have, we don't have overall survival data. I'm not so confident we're going to get it because I just, it's a global study and there'll be access issues. But I do think there'll be patients on the control arm that want to move over.

So, so we'll see, Hey Jack, you, you know, in the discussion, I kind of towed the line of the study was designed to look at stage two and three A, but there's no way I'm not going to talk about this with my resecting one B patients where, you know, there's at least that there's some data in this group. And I think it's a spectrum. I think there's probably benefit. It's just less benefit. And I think that's a conversation with patients where you just tell them what we know, what we don't know and what the ups and downs are of that, but I do think this is going to be kind of a global strategy. So not just limited to the FDA's purview, I think this is going to be something that is going to be available for all patients. And I think it's going to be something we need to be prepared to talk about with patients. I think the patient's decision is all that matters, right? If he or she wants to do this based on approved agent and willing to kind of understand the things that come with three years of an oral therapy, you know, I'll go down that road with them, but, you know, there's still data we have to find out.

Dr. Jack West: Yeah. You know, I do think though, one of the arguments, I think one of the leading concerns is just the probability, especially as you move into the earlier stage patients, that we're going to over-treat a lot of people who are already cured and that's less of a concern for stage three A, or even a stage two patient. But, you know, there's, in most cases, especially if they were to get chemo, you would expect that about half the patients with stage two disease would have a good outcome based on other data sets. I do think that as a global trial, it's pretty concerning and almost dismaying that so many didn't get treated with standard chemotherapy that they should have gotten, but for stage one B. And also my concern is that this will mean that if everyone is getting tested and a stage, smaller then one A is found to have an EGFR mutation, you might have this discussion and then decide that people will, should maybe want to do it.

You know, for a drug that costs $20,000 a month, even if it's not costing the patient that much money, it's costing somebody. And you know, these are some of the things that I have concern about. We can simplify it by saying, well, it's just up to the patient, but I think it it's increasingly something that we need to think about when it becomes a strategy to over-treat potentially significant populations. And especially to extrapolate this to even earlier stage or treat beyond three years, because, you know, one of the other questions here is that how much confidence can you really have that you cured

these people? If it takes three years of therapy? That's not the initial idea of what we did adjuvant therapy for, which was you give a short course to kill any stray, micro, metastatic disease. You do that, or you don't, and then you move on. This is no longer that concept.

Dr. David Spigel: Yeah. I don't know. You know, Helena, I don't, if you're on, look at the three A there, if you're on that gold curve, you know, which none of us want to be on. Right. Do we think OSI can rescue you, you know, whenever, whenever you're censored on there. So when your disease comes back and hopefully these patients didn't die, but if they came back and came to the attention of their oncologist, can we then say, okay, I'll give you OSI, like flora, first line, advanced setting, recurrent setting. And you're going to do just as well as the groups that got it in the beginning. So I just think it's going to be hard to tease that out based on where this trial is. But you know, I'm looking forward to it. I think there's another trial, the ADAURA 2. I'm not mistaken. That includes even earlier like one A and one B patients, but I'm not mistaken. So we'll get some data from that.

Dr. Helena Yu: I think two things to point out too, is that, you know, there is always, when you look at the Pacific study, which Dirvalumab, there's always a dropout where, you know, people with early stage disease maybe because their recurrence is more symptomatic or they're not as, you know, in a good functional state where they're not able to get treatment for their metastatic disease. And so people sort of drop off completely and aren't able to get treatment. And then I think one other important thing to note is with the earlier not perfect adjuvant studies using Alectinib, when patients got adjuvant treatment, say they finished the course and then their disease recurred after they stopped treatment. There's kind of, at least some data that shows that their disease is still sensitive to the TKI if they were to restart. So I don't, you know, I think that's another sort of thing that I've heard, oh, you're wasting the TKI in the early stage setting, but I don't necessarily think we have data that, that would be the case. And if people recur, while they're on the treatment, that's an aggressive disease that sort of is a different story. So I think just something to bring up.

Dr. Jack West: Very good. All right. Well, we'll have to see as we can hope that we'll get more information over time, but in the meantime largely a practice changing result. Even if you acknowledge the differences between what we would have hoped to get and what was delivered. We don't often see curves that separate like this in our careers.