Interview with Dr. Suresh Ramalingam:
First Line and Maintenance Therapy for Advanced NSCLC

by Dr. Howard (Jack) West
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Dr. West: Hi, I’m Dr. Jack West, medical oncologist at Swedish Cancer Institute in Seattle, and the President and CEO of GRACE, the Global Resource for Advancing Cancer Education. I’m here with Suresh Ramalingam, who is the Director of Lung Cancer Program at the Winship Cancer Institute at Emory University in Atlanta and one of the leaders in the field of Thoracic Oncology, so thanks for joining us.

Dr. Ramalingam: Thank you, Jack.

Dr. West: In the setting of advanced non-small cell, are you now routinely sending tissue for molecular markers?

Dr. Ramalingam: I’m not routinely sending markers, but there are selected patients that I have relied upon the markers to guide therapy. We have chemotherapeutic agents, a number of good active chemotherapy regimens that are available. We now have at least two targeted drugs that are approved for treatment of non-small cell lung cancer primarily the EGFR inhibitors are Tarceva is the drug for which we now have some molecular markers that would help us select who might benefit from this drug. And we’re still in the early days of using molecular markers to choose therapy for somebody and not give Tarceva to another patient. So we’ve not routinely started sending those molecular markers, but certainly if there was a certain patient who was not an ideal candidate for chemotherapy or who had some of the markers like having had never smoked cigarettes, a female adenocarcinoma, some of those subsets where EGFR mutations are common in the tumors, then we send those patients’ tissues out for the EGFR mutation analysis.

Dr. West: Can you tell us a bit about the IPASS trial that was just presented in the last few months and whether that had any effect on your thinking about molecular markers and potentially giving an EGFR inhibitor as a first-line therapy?

Dr. Ramalingam: Sure, the IPASS trial, I think, is a very important trial that has really helped us learn a lot more about molecular markers, in particular EGFR mutations. The study basically enrolled patients who had never smoked cigarettes in their lifetime primarily or had very minimal smoking history, and randomized them to treatment with either chemotherapy combination Carboplatin and Taxol or Iressa as a single agent. These were all advanced stage non-small cell lung cancer patients, and the study was conducted in the Far East.

And what they reported was that for patients with that never smoking or light smoking category, Iressa was associated with similar progression-free survival benefit actually turned out to be superior to chemotherapy in those subset of patients. What impact it’s had on survival, we have to wait and see.

But the most intriguing part of this study was that they had tumor tissues in close to 30% of their patients. When they looked at the presence of EGFR mutation, they showed that those patients who had the EGFR mutation did well with Iressa, whereas those patients without the mutation did better with chemotherapy in terms of
progression-free survival, which really makes us think that the mutation may be perhaps one of the most important determinants of outcome with treatment with EGFR inhibitors.

Now there are other studies that are ongoing that will hopefully confirm these results and put us firmly on a path to where we are testing tumors for these mutations and perhaps other markers to identify who would benefit even in the first-line setting. So we are in the early part of understanding how to use these effectively in the clinic, and this is why we don’t still recommend routine practice, but certainly this is becoming to be a more important factor to keep in mind.

Dr. West: To me it was interesting just to see that even among never-smoking -- and it was mostly never-smokers -- never smoking Asian women which were 80% of the patients in that trial, if you didn't have the mutation, you did not do especially well with an EGFR inhibitor. So it seemed to me that this was the most compelling evidence that molecular markers trump the clinical factors.

Dr. Ramalingam: I completely agree with you. I think one issue I would like to point out is this, as we talk about first-line therapy. The impact of this on second-line therapy may not be quite the same as first-line therapy, and that needs to be evaluated further. There is an ongoing study being participated (in) by the national cooperative groups that is evaluating whether in a second-line therapy setting, use of molecular markers select who should benefit from chemotherapy versus Tarceva. So I would encourage patients to consider participation in the trial for second-line setting.

In the first-line setting, I would agree with you that the current evidence seem to be leading up to a road where presence of mutation are the molecular markers appear to be better suited to select therapy more so than the clinical markers.

Dr. West: It’s important though to keep in mind, as you were alluding to, that there’s a difference between the threshold to override a standard like first line doublet chemotherapy versus using it in the second or third line setting where it’s otherwise indicated and not just discarding it and saying it will not be useful. The data don’t show that absence of an EGFR mutation gives you no benefit from an EGFR inhibitor; it just suggests that it’s not of the same magnitude as standard chemo.

What would you consider to be your preferred chemotherapy backbone in the first-line setting for advanced non-small cell these days?

Dr. Ramalingam: So this used to be an easier answer a few months ago. I think the approval of Cisplatin/Alimta for first-line therapy of non-squamous tumors has really given us a new regimen which in a selected subset of non-small cell lung cancer patients appears to be a preferred backbone. So if I had a patient with non-squamous, particularly adenocarcinoma or large cell carcinoma, I have started preferring the Alimta/Cisplatin regimen for a suitable patient with good renal function and good functional status.

For squamous cell carcinoma, I think a Carboplatin-based doublet, any one of the other agents such as Taxol, Taxotere, Gemcitabine are all appropriate in that setting. So that’s sort of how I view my first line practice at this point.

Dr. West: And you do routinely distinguish between histology types, then?

Dr. Ramalingam: I have started paying more attention to histology just like other groups now with the emerging evidence that histology may determine sensitivity to specific chemotherapy regimens.
So, yes, I look at the histology. If that information is not available which happens available, which happens in about 20%-30% of the patients, I go back to the pathologists and ask them if they could guide me on what the specific subtype is. If I know for sure that the patient has non-squamous subtype, then I prefer an Alimta-based regimen.

Dr. West: In the patients who you can’t get a good answer for that and perhaps there was just a very small amount of tissue for the diagnosis, do you recommend obtaining another biopsy and perhaps getting more tissue for clarifying histology and perhaps sending off molecular studies, or are you content with a diagnosis of non-small cell “not otherwise specified”?

Dr. Ramalingam: Well at this point because of the risks associated with additional biopsies, though we discuss them, we don’t tell a patient that you need to have another biopsy. There have been some patients who wanted that information so we have done that, but if we are going to get other lines of information such as looking of molecular markers or for a patient to participate in a clinical trial that the patient is interested in that it requires more tissue for doing some of the biological studies, may be situations where we might consider a biopsy. But, just because the tissue is inadequate, but we have a diagnosis of non-small cell lung cancer, we haven’t started going for a re-biopsy at this time.

Dr. West: You have been a long-time member of ECOG, the East Cooperative Oncology Group, that ran the pivotal trial with Avastin in a design of Carbo and Taxol with or without Avastin for a subset of patients and showed a survival benefit with it; that included patients who had non-small cell that couldn’t have a clarification of histology. Are you okay with giving Avastin to patients with non-small cell that can’t be specified by histology?

Dr. Ramalingam: Sure. The ECOG 4599 study by definition included patients who did not have predominant squamous histology. So in other words, if the pathologist said this is non-small cell lung cancer, but there’s nothing to believe that there a predominant squamous component, those patients were allowed in the study. And we have plenty of safety data on those patients who got bevacizumab, or Avastin, with chemotherapy. So in a patient with unspecified non-small cell lung cancer, I am comfortable using Avastin in combination with chemotherapy.

Dr. West: Can you tell us a bit about the AVAiL trial done in Europe that also tested the role of Avastin and whether that had any effect on your approach with Avastin now?

Dr. Ramalingam: Sure. The ECOG 4599 showed (a) clear survival benefit with the addition of Avastin to chemotherapy and the primary end point of the study was to look for survival advantage. The AVAiL trial, which was done in Europe primarily, was designed to look at progression-free survival and it had more patients than the ECOG 4599 trial.

What it showed was that the progression-free survival was improved as per the statistical criteria, but at best a very modest benefit. But the survival advantage that was seen in the ECOG trial was not shown in the AVAiL trial.

There could be many reasons behind why these two trials could have given us these slightly different results, and we can certainly take the whole day talking about those differences. But what this tells us is that Avastin provides perhaps a modest benefit and it is very useful given to the right patient. For example, even in the AVAiL trial, the response rate was higher with the addition of Avastin, the progression-free survival was higher just like it was in the ECOG trial. So I think what this tells us is
that identifying subset of patients who would benefit from these drugs using markers would really be the way forward in terms of using Avastin. We know it benefits some patients, perhaps not all patients, and perhaps not to the extent we would like for a variety of non-small cell lung cancer patients.

Dr. West: What do you think of the argument that Avastin may be beneficial with some chemo combinations, but not with others?

Dr. Ramalingam: Well that argument, unfortunately, has not been answered and it’s going to be difficult to hypothesize that if you give one chemo it works; if you give another chemo it does not work without any clear biological underpinnings. We are beginning to see some pre-clinical studies that suggest that say when you us the gemcitabine-based regimen, the use Avastin in addition may have some pre-clinical or biological reasons why the effectiveness may (not) be quite as much as with using chemotherapy including Carboplatin and Taxol. Again, these are very early data coming out.

At this point, I don’t think we can say that we know which chemotherapy regimens we can work with to enhance the effectiveness with Avastin and which will not.

Dr. West: You did an important subset analysis by age of the ECOG trial looking at how patients did if they were elderly versus younger. Can you tell us about that and how that has changed your practice?

Dr. Ramalingam: Sure. So the subset analysis was part of the ECOG 4599 study, and when the study started, we had no intention of performing such an analysis based on age. But over the course of the past few years, we’ve learned that the majority of the patients we were seeing in our clinic now are those over the age of 70, or at least 50% of the patients. And it became important that as we establish or develop new treatment paradigms that we make sure that our elderly patients are suited to receive that.

So when we looked at the ECOG 4599 trial and assessed the impact of being over the age of 70 versus less than the age of 70, what we found was that the benefit with chemotherapy in combination with Avastin was trending along the same lines as the overall study, though we could not see a survival benefit -- again, the study was not powered subset analysis to show such a benefit. What was more important to us was that there were certain toxicities or side effects that happened more commonly in older patients compared to younger patients. And this included hypertension, certain bleeding events, and neutropenia, and fever with neutropenia.

What that tells us or suggests to us is that for elderly patients there is a higher price to pay when you use the regimen of Carboplatin/Taxol and Avastin. And the survival benefit may not be quite as much as you see in younger patients.

So we are interpreting these results very cautiously because it’s a unplanned subset analysis. However, the safety signals are not trivial enough to ignore. So if I have an elderly patient in my clinic, especially if the patient has multiple other medical issues, medical illnesses then I tend not to use the Carboplatin/Taxol/Avastin, just to be on the safe side. If I have a patient who is even older than 70, close to the 80s or higher, then I tell them that we really did not have too many patients over the age of 80 in the ECOG 4599 trial even to comment on the potential safety of the combination.

On the other hand, if I have a patient in the low 70s who has an outstanding functional status, who has no other medical illnesses, I don’t hesitate as much to give them Carboplatin/Taxol/Avastin. What I would say is we clearly need more data, more prospective perhaps evaluation of the safety regimen in older patients with the
use of a targeted drug in combination with chemotherapy as we do with new regimens.

Dr. West: The ECOG trial didn’t include patients with a marginal performance status. What is your approach for these patients who are pretty common in our practice?

Dr. Ramalingam: So, in the performance status we rank the patients as being from zero to five depending on how fit and functional they are and the majority of the patients that we treat with combination regimens are those who have an excellent performance status, which we call zero or one. The optimal way of managing patients with performance status two is still a controversial one. There are many approaches; a combination regimen with, say, Carboplatin/Taxol or Carboplatin/Gemcitabine is certainly an acceptable regimen. A targeted drug in an unselected group of patients with marginal performance status perhaps may not be a appropriate based on the randomized study that we learned of a couple of years ago.

So the way I look at these subgroup of patients is I ask the question, why is their functional status poor? Is this because of the cancer or is this because of something else they’ve had for a while. If a patient was relatively well until they got diagnosed with cancer or they developed symptoms from cancer and have experienced a decline in their functional status because of their lung cancer, then I tend to be more aggressive with treating those patients. On the other hand, a patient who has already had some medical problems that had caused a decline in their functional status, then regardless of how aggressively you go after the cancer, you’re not going to be able to fix those underlying problems; and therefore I tend to be more cautious and use single agent chemotherapy in those patient groups. I certainly do not recommend the use of three-drug combinations in patients with a marginal performance status.

Dr. West: The ECOG trial also excluded patients with brain metastases and patients who were on full-doses of blood thinners, and these are pretty common in our practice. We’ve also gotten more experience that suggests that it probably is safe. Do you feel comfortable giving Avastin now to patients with treated asymptomatic brain metastases and/or patients who are on Coumadin?

Dr. Ramalingam: I would say cautiously yes, because what we’ve seen in the last one year are data that suggest that in a group of patients with brain metastases following radiation therapy to the brain, administration of Avastin in combination with chemotherapy appears to be safe. There were no undue bleeding events in the brain. Again, the best data we have now are in a group of about 100-odd patients who received this kind of a treatment. So this is reassuring that these patients tolerate Avastin-based chemotherapy without excessive bleeding episodes. So I think it is certainly it adds to our comfort level and we recommend this combination.

Now I would be cautious if a patient had a metastasis in the brain that had bled inside, which suggests already that there is a bleeding tendency for that particular tumor; then I would probably not use it. And I’m certainly looking forward to the upcoming meetings to learn more about the safety of Avastin in patients with brain metastases, as such studies are ongoing.

In terms of full-dose anticoagulation, once again in the AVAL trial, 10% of the patients had received Avastin in the context of full-dose anticoagulation and they did not experience any undue bleeding. So I feel more comfortable using this, though I tend to watch their coagulation parameters very closely while they are receiving the combination.
Dr. West: All of the trials with Avastin have included a maintenance portion after the initial 4 or 6 cycles of chemotherapy and then continuing on the Avastin. There’s also been a growing tendency to perhaps continue a chemo drug such as Alimta. Do you routinely do that? do you think it is valuable and important to continue one or more agents from the first-line setting after 4-6 cycles until some progresses or do you feel comfortable stopping and watching patients off of treatment for a while?

Dr. Ramalingam: That’s a great question because we are experiencing, or we have seen recently data that suggest, a role for earlier institution of an new agent or perhaps continuation of the same agent. So in the ECOG 4599 trial, the way the study was designed was that all patients who got the three drugs in combination, Carbo/Taxol and Avastin, after six cycles their tumor was still under control, they received the Avastin as maintenance therapy. And we did see the survival benefit in that trial.

Now if one were to play out the scenario where if those patients did not receive the maintenance therapy, “Would the survival benefit have been seen?” The answer is, “We don’t know.” So I think the evidence-based approach at this point is to use the Avastin as maintenance until their disease progresses or if they develop some major side effect.

We’ve also seen with Alimta now in the Phase 3 trial that after giving two-drug combinations, not including Avastin, after four cycles, when these patients were switched to treatment with Alimta, there was a progression-free survival advantage and a trend toward survival benefit compared to no maintenance or placebo maintenance.

So what is coming around based on these studies and some of the other recent trials that have been reported, including the trial with early versus delayed Taxotere, earlier administration of an active agent or continuing a targeted agent is the new direction where we’re heading is my own personal feeling.

If I use a Carboplatin-Taxol-Avastin regimen, I continue Avastin as maintenance. If I use a two-drug combination in the front-line setting, I strongly consider use of Alimta as a maintenance in that setting.

Dr. West: Is that going to be Alimta as a second-line agent after a different two-drug combination or would you be giving a platinum with Alimta and then continuing the single agent Alimta after 4-6 cycles?

Dr. Ramalingam: So far what I have done is typically a patient who gets Cisplatin-Alimta, I’ve continued Alimta for a longer duration. Now, we are awaiting the results of the survival on the Alimta maintenance trial, and if it does show a survival benefit, I will be more inclined to switch from a two-drug combination to Alimta as maintenance as we move forward.

Dr. West: We have seen now a couple trials that show a clear progression-free survival benefit with Taxotere as an early second-line therapy or Alimta, and we’ve seen some press releases that the same trends seem to hold true with adding Tarceva early after four cycles of chemotherapy alone, or in Avastin-receiving patients having them continue on Avastin with Tarceva added appears to improve progression-free survival compared to just Avastin alone.

How important do you think progression-free survival is or do you need to see an improvement in overall survival to really consider it to be of clinically significant value?
Dr. Ramalingam: I think this is a very controversial area at this point, to say the least. We have always used survival as the most important end point for clinical trials. And the reasons are very simple: if you have a new drug and adding the drug does not result in any improvement in survival, then maybe you can get to the same milestone with some combination or sequencing of existing drugs. So the standard has been a new drug to be approved has to have a survival benefit.

Now what we’re talking about in the maintenance setting is a little different, because what you’re trying to do is a patient has done well with a standard regimen and hopefully those benefits were associated with the improvement in the patient’s well being and the symptoms, then delaying the progression would mean maintaining the patient in a relatively symptom-free period for a longer length of time. So I think in that instance the progression-free survival becomes a clinically very meaningful end point.

So I would say that we should not ignore a significant progression-free survival advantage if there was not a statistical survival benefit; perhaps even a trend towards a survival benefit with a strong statistical significance and meaningful progression-free survival would be compelling enough for me to consider using it in my practice.

Dr. West: Well thank you very much for taking the time today.