

Question & Answer Session: Exploring Personalized Therapy for First Line Treatment of Advanced Non-small Cell Lung Cancer

by Dr. Suresh Ramalingam

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- Dr. West:** There is a question that came in and I would invite other people through the chat function to add a question if they have them. The question is, are there any treatments specifically at this point directed for people who have an identified K-RAS mutation?
- Dr. Ramalingam:** Sure that's a great question. K-RAS mutations are seen in about 20-30% of Adenocarcinoma patients and we have not had a strong track record in targeting K-RAS. There've been a number of agents that have been developed as "K-RAS inhibitors" that did not live up to their promise. This a hot area of research, there is nothing at this point that's available in the market but there are certainly some experimental K-RAS inhibitors that are being developed, so stay tuned. If we can break the K-RAS enigma we would be making a very major contribution to lung cancer outcomes.
- Dr. West:** And what about for patients with squamous carcinomas at this point? Are you testing any of those people either as standard practice or on request or mutations or is the probability low enough that, that's not your approach?
- Dr. Ramalingam:** Right, I mean from a mass screening, in other words in order to pick an EGFR mutation in one patient with squamous cell cancer, you would probably have to test about 80-90, and that really becomes not practical. So at this point we're not routinely testing, but if there was a special circumstance where you see squamous cell in a patient with some of the other features such as a female who had never smoked, again we don't see too many squamous patients with a no-smoking history. It's not something that's common so we're not routinely testing for it.
- Dr. West:** What would you say at this point is the role for Cetuximab, Erbitux? Is this something that you're seeing commonly used or is it still being really just individualized?
- Dr. Ramalingam:** Yes I see it used sporadically. If the drug is approved by the FDA that might change its usage pattern, but at this point I see this being used sporadically for some patients with squamous cell cancer but not to the same extent it's used in colon cancer or in head and neck cancer.
- Dr. West:** Then there's the question of patients with histological diagnosis of non-small cell lung cancer, not otherwise specified. The question is really if you get that diagnosis from the pathologist, first are you going to try to get more tissue for that? And secondly .if that's the most information you can get, are you disinclined to use both Avastin and Alimta, or how do you think about that?

Dr. Ramalingam: When the pathologist says I cannot tell you what subtype this is, I typically give them a call and ask them is the fact that you cannot specify because you don't have enough tissue, or the fact that the tumor has de-differentiated so much that no matter how much tissue you have you will not be able to say what it is.

If the pathologist says, "listen I don't have enough tissue to make a more accurate call", then if necessary we even go back and re-biopsy. In instances where the pathologist says, "You know what? You can give me the whole tumor out, I still may not be able to tell you", then there is no point in going for another biopsy.

For those patients who have *not otherwise specified* lung cancer, at this point it is not clear to what extent pemetrexed, or Alimta, would work. It's definitely approved in non squamous, so one could make the case and use this drug. I, for one, tend to reserve Alimta for second line for those patients, or third line, and give them other drugs in the first time setting.

With regards to Avastin, if they have a tumor that is centrally located or has cavitation and they have this NOS type then I don't use the Avastin because the risk of bleeding there may be higher. But if the tumor is located peripherally I still feel comfortable using Avastin in those patients.

Dr. West: Now you were actually pretty modest in your coverage of the issue of age and Avastin, because you published a paper that has really gotten a lot of us thinking about this, that showed that in the large ECOG trial that led to the FDA approval of Avastin with carbo and Taxol, the benefit was much clearer in younger patients and actually wasn't seen in patients who were over 70.

So as the person who wrote about this and thinks about it a lot, what is your approach for an older patient who is otherwise a candidate for Avastin?

Dr. Ramalingam: The analysis that you referred to, Jack, was done on the ECOG trial. There were about 26% of the 800 patients on the ECOG trial that we looked at and for patients over the age of 70 there was a trend towards higher side effects and less benefit with the addition of Avastin to chemotherapy.

Because this is retrospective analysis, it's not a good idea to draw lasting conclusions, but the results were compelling enough for us to take a step back and make sure that if we are dealing with an elderly patient, particularly who is over the age of 75 or so, then we really need to be careful about what other medical conditions does the patient have. What is the functional status of the patient? Are there other risk factors for bleeding?

So the older the age of the patient, I tend less and less to give them Avastin in combination with chemotherapy. Certainly there are some

patients who are in their low 70s who have perfect functional status, who have no other medical problems where I have felt more comfortable using it. This is an area where we really need more specific studies looking at whether this combination of Avastin with chemotherapy can be given or if they need to be dose reduced or so forth.

Dr. West: Are there any particular molecular testing factors that you perceive as being different for patients with BAC, the bronchioloalveolar carcinoma subtype now or in the next few years?

Dr. Ramalingam: Actually Jack did the first prospective trial in BAC patients with Iressa several years ago. It showed that these patients actually respond to BAC better with Iressa than potentially what they could have done with chemotherapy. EGFR seems to be an important pathway in patients with BAC, so I would definitely check them for EGFR mutations. At this point, we don't have any other markers in the BAC subtype yet for other groups of agents, but that's only because BAC is a rare kind of cancer: it's only about 3-5% percent of all lung cancer patients that have BAC.

Dr. West: Another question is about how reliable EGFR mutation testing is and are we confident enough about the reproducibility to use it for testing? It might be related to the test itself, it might be related to heterogeneity of the tumor tissue in different parts of the tumor or one metastasis versus the primary. Do you have any sense of that and how confident you'd be about a result and would you ever be inclined to retest it?

Dr. Ramalingam: The labs that do the EGFR mutation testing have to be "CLIA certified", which stands for an approval that is given for labs that meet certain preset qualifications and criteria. If a tumor is reported as having an EGFR mutation – now there are many different kinds of EGFR mutations, we didn't get into the different types, there are various sites on the gene where the mutation can be – and not all of them have the same relevance for EGFR inhibitor therapy. So we need to know exactly where the mutation is and if a lab reports the tumor as having EGFR mutation, I would take it for the face value of it because it comes from a CLIA certified lab.

Sometimes when you don't have good quality specimens or if the patients' surgery was done 5 years ago and the tumor specimen that's available is from what was there 5 years ago not now, that might impair our ability to see whether the patient has a mutation now or not. So in some instances if we have compelling characteristics, like if a person is a never-smoker and female and adenocarcinoma, the more these kind of clinical selection factors, if we don't think we had enough tissue, we actually talk to patients about their willingness to undergo a second biopsy.

Dr. West: What about the people who have an EGFR mutation and don't respond, or the occasional patient who doesn't have the tested mutation or is found to be wild type but has a phenomenal response. Do you have a sense of whether those are related to, say, a non representative part of the tissue being sampled?

Dr. Ramalingam: That's probably the case, because if you look at all patients with EGFR mutation, we don't see 100% response with Tarceva, we would expect 100% response, but we see somewhere in the 60-80% ballpark. So the question comes up for those 20% who don't respond, is it because the mutation they had was present erroneously, or was reported erroneously, or whether the method used was not right and they picked up some secondary event that was not really relevant.

Those are all questions that come up, or the tissue that the test is run on may have been obtained before the patient had been exposed to several other agents, and what was present at the original time of diagnosis is no longer present because the patient has already received two different kinds of chemotherapy: the tumor cells have gone on to become more resistant and to develop secondary events.

So why those 20% don't respond may have a lot to do with how you test them and when you test them and how much sample you had and what part of the tumor was tested.

Dr. West: Another question came in about whether a 1.5 cm tumor is enough to test for EGFR, and I think that we can both safely say that's a huge amount of tissue: that's a dream. If you've got that, we can do everything.

But I think it brings up the issue of getting enough tissue because so much of this exciting work that Ram had mentioned is predicated on tumor tissue testing, and historically in lung cancer we have often relied on getting a diagnosis from a very thin tiny needle biopsy that yields just a few cells, enough to tell us that it's a cancer and tell us it's a non-small cell lung cancer or small cell, but really wouldn't be enough to do the molecular testing studies.

We are sometimes now in a situation of having to recommend or at least discuss doing additional biopsies and basic procedures that are minimal, but not zero-risk in order to get more tissue and now I think -- and I'll invite Ram to comment on this -- but I think that we need to, as a lung cancer community, work to get core biopsies which is a more significant amount of tissue as a regular standard approach for all sorts of reasons: for the greater confidence of knowing what particular subtype of lung cancer someone has, and also to have a reasonable amount of tumor tissue available for the molecular markers that we've been talking about today but also potential future markers down the road.

Dr. Ramalingam: That is a great point, Jack. I think the time where we just stuck a small needle and got a few cells and said, "Okay, this is lung cancer -- let's go...what can we treat the patient with?" are history. We clearly need more tissue: more and more radiologists and pulmonologists are using core needles, which allows for more tissue to be available. I would say that we need to increase the awareness and educate not only our colleagues but the patient community, as well as to the need for sometimes a second biopsy.

What is also becoming an issue is if somebody had a biopsy and has been on an EGFR inhibitor, say Tarceva, for a few years and the cancer is now getting worse, we are now starting to get a second biopsy on that patient to get a snapshot of the status of the tumor at that point; What has changed in the tumor that it has become resistant? And can we use that information to select specific therapy for that patient? Even though that information is used for experimental purposes at this time, I think more and more we're going to have to start thinking about a second biopsy at the time of progression for patients.

Dr. West: If you had a surgery in 2005 and someone has a relapse in 2009, are you comfortable using tissue from that far back, or would you say that time has potentially changed and the molecular profile has changed and you'd recommend a more contemporary tumor tissue?

Dr. Ramalingam: If it's been more than at least 1-5 years since the cancer has been previously treated and cancer has recurred, it's clearly a situation where we would want additional tissue at the present to see whether there is a new abnormality or what exactly is this? Is this even the same cancer? Could this be a different primary? Are there changes in this that are entirely different from the previous tumor?

I would say that anything more than a year or two since the original biopsy was obtained, we would always think about getting a second tissue. But that is only in situations where a patient has had a curative treatment and now this is the first time there is evidence of something else is happening.

If a patient has already been diagnosed 2 years ago, with, say, advanced stage disease and has been on multiple treatment regimens since that time, then we wouldn't pursue biopsy unless it was linked to a specific clinical trial and the patient was willing to do it.

Dr. West: Well thanks, yeah, I think you bring up a really good point and that is if someone has gone a few years from their initial presentation, one of the things that we are often inclined to do is to get another biopsy to confirm that we are really dealing with a recurrence of that cancer. It could be a separate process going on, especially if it's been a long time, and the longer that time has gone by, the more possibility that it is a genetically different process.

There is one other question that has come in, and it is related to people who are on Tarceva and experiencing problematic side effects, and this is specifically asking about diarrhea, but it often applies to the side effects like rash. The question's really how much do you persevere with trying to manage side effects versus giving up on that, because I think that there is a lot of variability in both patient and physician tolerance of side effects from some of these potentially more chronic drugs, and sometimes giving up on treatments like Tarceva if they are associated with problematic rash or diarrhea over a period of weeks to months.

Dr. Ramalingam: For these patients the first question is, is that patient someone who has an EGFR mutation? If they have a mutation, my inclination to persist and try various other options is much greater. For EGFR mutated tumor, or even for other patients, common steps initially would be to first use supportive measures like anti-diarrhea medicines, topical creams, antibiotics, or steroids, and so forth to try to see if that would help ameliorate the symptoms.

If those don't work then one could start reducing the doses of Tarceva to see if a lower dose than the 150 mg that is FDA approved could be better tolerated. If even with dose reductions one does not experience improvement in side effects, which is only about in 5-10% of all patients, then I stop them. But if they have an EGFR mutation, I try to keep going down on the dose until I find a tolerable dose that which they can take the drug, because I think for a patient with EGFR mutation to give up on Tarceva early on would not be right.

Dr. West: Well I think that really raises several issues. One is that the patients who have an EGFR mutation appear to be exquisitely sensitive to the drug, in potentially the negative ways as well, but that also means that they may be able to derive great benefit even from much lower doses, and that's one of the things that's been found in lab-based work and suggests that it's one of the reasons that I think Iressa is still a very effective drug for patients with an EGFR mutation but maybe not for patients who don't have one.

Dr. Ramalingam: Right.

Dr. West: It is also a great point that for the people who have the potential to benefit quite a bit, it's worth trying to persevere with managing side effects even if that means dropping the dose and being pretty aggressive about all the other medications. Because I certainly see sometimes even patients with an EGFR mutation who come off of an EGFR inhibitor early because of a rash, and it's a real shame because these are agents that can be beneficial for not just months but sometimes even years for people.

Dr. Ramalingam: Agreed.

Dr. West: Well I would like to express my sincere thanks to Dr. Ramalingam for a great presentation. Have a great night.

Dr. Ramalingam: Thank you, goodbye.