

## **Expert Round Table with Drs. Tom Hensing and David Jackman: Molecular Markers and Sequencing Therapy, Case 1 with Dr. Jack West**

**Dr. West:** Hi welcome, my name is Dr. Jack West; I'm a Medical Oncologist and the President and CEO of GRACE, the Global Resource for Advancing Cancer Education.

I'm here today with a couple of my colleagues and fellow experts in lung cancer, who were kind enough to join me to talk about some evolving issues in the field of lung cancer that are really quite timely; that is, the issues of testing for molecular markers that may be useful for affecting our clinical decisions, and also how to sequence treatments as we transition from first line beyond that into maintenance therapy or, if you want to think about it that way, early second line. So we'll talk about all of these issues through the lens of a few real cases.

My two guests are Dr. Tom Hensing, who is a Medical Oncologist with a particular interest in Thoracic Oncology; in fact he is the Co-Director of the Thoracic Oncology Program at the North Shore University Health System in Chicago and Evanston Illinois. Also Dr. David Jackman who is a Medical Oncologist and instructor in Medicine at Harvard Medical School and The Dana Farber Cancer Institute and he too focuses, essentially exclusively, on Thoracic Oncology there. Thank you both for joining me.

I'll mention that our program today is made possible through an educational grant from OSI Pharmaceuticals and they had no input in the development of the content for this.

These days we do run through the conflicts of interest, and both of the faculty have provided their more recent conflicts as defined as the last 12 months. Dr. Hensing has been involved with the Speakers Bureau for Lilly and Genentech although he's not done anything in that capacity in 2010, and Dr. Jackman has done consulting for Foundation Medicine.

Let's turn to a case of a 76-year-old man who is actually a retired insurance broker. He does have a significant past medical history that I'll get into a little more, but he was diagnosed with advanced non-small cell with a squamous histology. He had previously smoked a couple of packs per day of cigarettes for 40 years and he quit in 1991. He developed a cough with green sputum, and that persisted for several weeks. He mentioned that to his primary care physician, who performed a chest x-ray that showed a peripheral left lower lobe nodule.

That was followed by a chest CT that confirmed a 3.3 centimeter sub-pleural mass in the superior segment of the left lower lobe, and we'll show some of that. He also had some nodes in the pre-carinal window and AP window which were

border line and large. He then had a CT guided biopsy that showed a squamous cell non-small cell lung cancer.

He was actually referred to a thoracic surgeon, and at that point underwent a PET/CT fusion scan that showed hypermetabolism not only in the left lower lobe lesion, but also uptake in a right upper lobe and a right lung base lesion that were more potentially benign appearing, but in this case as I show you here, really concerning for abnormal uptake.

He also had an additional area in his abdomen that lit up on PET and really was concerning for potential metastatic involvement, and that's shown here. In fact, the surgeon, just to be as thorough as possible, did not rely on the imaging to confirm metastatic disease, but had an ultrasound guided biopsy of the abdominal lesion done by a gastroenterologist who did it ultrasonographically. That biopsy confirmed involvement of that lesion in the abdomen, confirming stage IV disease.

In terms of past medical history, he had a coronary artery bypass graft in 1993. He has some atherosclerosis of the carotid arteries and migraines, history of diverticulosis, some high blood pressure and high cholesterol level, but his performance status is good and he has now clear stage IV, non-small cell lung cancer in an elderly gentleman. Just to go through, this is the imaging from his chest CT and you can see at least some ambiguity in these other lesions that are perhaps more benign appearing in the right lung base here.

But the question is, you have a gentleman now with a squamous cancer and Tom, why don't I start with you, do you at this point feel that you would send for molecular markers in somebody with a defined histology that is not an adenocarcinoma and particularly is squamous?

**Dr. Hensing:** You know that's a good question. We're in this era of bio-markers -- I know there's been some nice reviews on the GRACE website about what biomarkers are -- but the ones we tend to think of most commonly, the EGFR mutation, the K-RAS mutation and the ALK translocation; all define subsets of patients who have adenocarcinoma. We really don't have good biomarkers for patients with squamous cancers, and so in this individual, at least right now, I probably would not send for any biomarkers.

I think in the future there may be some helpful biomarkers that might help us decide which chemotherapy agents to use, including maybe ERCC-1 or RRM-1, but until those are validated, I think right now there's probably not a role for biomarker testing in this individual.

**Dr. West:** And Dave, you at Dana Farber have been among the people leading the charge in molecular markers being integrated in more routine management. Perhaps you can tell us what you'd do, in terms of both algorithms for adeno versus non-adenocarcinoma and also, perhaps independent of that, if you didn't have some sort of protocol-based approach and maybe if you didn't have the test readily available, what do you think the data warrant, independent of how you guys do things, which is I think kind of forward-thinking.

**Dr. Jackman:** Sure. So in our adenocarcinomas, we are routinely right now testing for a panel of 6 or 7 different genes. We're certainly doing EGFR and EML-4/ALK translocation because we think they have therapeutic implications now. We're also looking at a number of other genes that we think a) are drivers of cancer and b) are potential druggable targets. Things like KRAS, BRAF, HER2 and PI3 kinase. So that's what we're doing for our adenocarcinomas.

We're not routinely doing any of these in squamous cells because the pre-test probability based on what we've learned so far is that it is unlikely that we're going to find these in squamous cell. We're doing a lot of basic science research right now looking for potential targets in squamous cell, but nothing that's ready for prime time clinically yet.

In terms of off trial stuff, if I were out in the community and didn't have this research protocol, certainly in the adenos that I see I would again be looking for EGFR and ALK because I think it has important therapeutic implications right now, but I certainly would not be routinely ordering these in squamous cell patients like this gentleman.

**Dr. West:** Just because the yield is so low that it's so low that it's hard to achieve that.

**Dr. Jackman:** Exactly.

**Dr. West:** And then, this is more of a grab bag, I don't think there's any right or wrong answers for this -- but if we could start with you Dave -- what treatment approach do you generally advocate for a patient with a good performance status and an advanced squamous non-small cell.

**Dr. Jackman:** I'm typically using a platinum-based doublet, something like carboplatin and paclitaxel or carboplatin and gemcitabine. In a gentleman of this age, I'd certainly be reluctant to use cisplatin, so if I felt he were of good enough performance status to tolerate a doublet, I'd certainly be using carboplatin and not cis. If I was very concerned about his performance status, I might go with mono therapy.

**Dr. West:** In a younger patient would you be more inclined to use Cisplatin then?

**Dr. Jackman:** In a younger patient, sure, I think cisplatin/gemcitabine, carboplatin/paclitaxel. In general, what we've seen is there's not a huge difference across the board. Cisplatin might be a tiny little bit better, but in a palliative setting I'm not sure that the additional toxicities are always worth it. It kind of depends patient to patient, but I think amongst the regimens I use most commonly carboplatin/paclitaxel or gemcitabine with either cis or carbo.

**Dr. West:** Tom, do you have a preferred regimen in the squamous advanced non-small cell population?

**Dr. Hensing:** I would agree with David. I think that a carboplatin based doublet typically in this setting -- I think either with taxol or gemcitabine, both of those would be reasonable to offer this patient.

**Dr. West:** Have either of you had a lot of trouble with myelosuppression and low blood counts and delays in treatment with Carboplatin and Gemcitabine in older patients particularly?

**Dr. Hensing:** We've certainly seen that. I think if we gave carboplatin and gemcitabine, we would give it on day 1 and 8 of a 21 day cycle, and certainly if we were to try the old 28 day cycle, where you got it on day 1, 8, and 15 we would have a tough time delivering it in a patient like this. But typically we do okay on the 21 day cycle.

Occasionally we find that maybe it's about 5 or 10% of the patients who really have a tough time with counts, and we either dose reduce or transition to a different regimen.

**Dr. West:** It's interesting that the data from the FLEX trial out of Europe, which looked at cisplatin and vinorelbine (Navelbine), with or without cetuximab the EGFR monoclonal antibody, had shown a very modest survival benefit, and yet that really hasn't translated to any appreciable use – though some would consider using it in someone with a squamous histology. Has that really penetrated much either in your practice or in your centers in general? Dave, why don't I start with you?

**Dr. Jackman:** I can't say that my department is using it much at all. In selected patients we're using it, but I think, just personally, I was not overwhelmed by the data. Yes, it was statistically significant in terms of an improvement in overall survival, but with two caveats: one is that the improvement was on the order of 4 to 5 weeks and then the second bit was that it comes with an increased cost, both in terms of toxicity to the patient with the addition of the Erbitux, as well as the cost to the system.

So I'm not sure that the benefits necessarily outweigh the risks to make it a commonplace piece of my practice.

**Dr. West:** Tom?

**Dr. Hensing:** You know, I would agree with that particularly if you look at the FLEX data two things would have jumped out to me. One was that they had about a 20% rate of fever and neutropenia, and that's I think too high for a palliative setting like this. And they had about a 3% mortality rate with the survival benefit they saw, which was real, but modest. It certainly hasn't penetrated here to a great extent, I think because of those issues.

One of the other things we've learned is that unfortunately the biomarkers that we do use to help us sometimes with EGFR-directed therapy really don't seem to be that predictive, at least so far, with looking at Erbitux. So we don't know yet who best to use it in. I think for a squamous patient, where we don't have a lot of other options, it's out there as an option, but I think for toxicity reasons that we don't tend to use it much either.

**Dr. West:** Dave, you at your group have looked at cetuximab and even published on the experience of looking at particular biomarkers and using it in combination with

EGFR inhibitors, but there really hasn't been a clear signal of it being especially useful in any sub group, is that correct?

**Dr. Jackman:** There has not. I think the only trial that is of interest in terms of cetuximab use in lung cancer right now -- and it's very early -- Greg Riely presented at this year's ASCO: a small phase II of Tarceva plus cetuximab in patients who were EGFR mutant had initially responded to Tarceva but then developed secondary progression, and then had cetuximab added to their Tarceva, and they did see some activity. I think that's of interest: where that goes, we'll see.

I think MSK along with William Pao at Vanderbilt are planning a trial of an irreversible inhibitor with the addition of cetuximab before such acquired resistance. and we'll see where that goes.

**Dr. West** So moving on, this gentleman did receive carboplatin and gemcitabine, and he tolerated it generally well. He had some cytopenias that required a dose reduction on the way, and he had some fatigue, which we often see, but it was nothing that he felt he couldn't handle.

And his repeat scans after a couple of cycles did demonstrate a minor response, some convincing tumor shrinkage. It did not meet criteria for an objective response, but we were all pretty happy with that, and he continued to get another couple of cycles and demonstrated stable disease.

After that point he had some cumulative myelosuppression, anemia, did not require any transfusion support, and after four cycles, with a performance status that would allow for ongoing treatment, but certainly he was receptive to thinking about a treatment break, the question is, what would you recommend? How would you approach such a situation?

We really have multiple options. You can follow someone off of treatment; we have this concept of continuation maintenance and potentially continuing the gemcitabine component, where we have a little bit of data, including some that was presented at ASCO this past year, and then the concept of switch maintenance, and moving to a completely different treatment. Tom, why don't I start with you?

**Dr. Hensing:** I think for me the starting point here after four cycles is going back to the trial that Socinski published that looked at four cycles of front line therapy versus continuing treatment. I realize that was a different regimen -- that was carbo and Taxol, and this gentleman had carbo and gemcitabine -- but based on that trial and others, it clear that there's not much of a benefit of certainly continuing the doublet beyond four cycles, especially in somebody who has stable disease.

In terms of the maintenance question, if you look at the trials that we have two FDA approved options in this setting -- one being Tarceva and the other being Alimta (pemetrexed), we know with the Alimta study that it's really not a drug that benefits patients with squamous tumors.

So for this individual in terms of a maintenance strategy, we're left with Tarceva as the main option. But I think if you look at the maintenance trials, there's a lot of

criticisms that they didn't necessarily test the timing of treatment, but more whether one had an active second line agent or not. If you look in particular at the study by Fidas, where they were looking at in this case a switch maintenance, if you will, or early second line Taxotere, that the patients who went right to it in early second line had the same survival as patients who had it at progression as long as they got the drug.

So I think for most patients, taking a break is still very reasonable. I think in this gentleman, who did have some toxicity to therapy, had some myelosuppression, at least in terms of the switch maintenance strategy out there going to Tarceva, I probably would not do it in this setting. I think he would be fine to take a break, and as long as we watch him closely both clinically and radiographically. I would probably wait until some evidence of progression before starting a second line therapy.

At ASCO this year there was this study looking at a sort of continuation therapy gemcitabine after four cycles of carbo/gem, and the main end point they were looking for there was overall survival and they did not see a benefit in terms of overall survival with sort of continuation maintenance gem. So I certainly would not do that here. I think in this gentleman I would advocate for stopping treatment at this point and watching closely.

**Dr. West:** You'd mentioned the Fidas trial, and that was not considered a positive trial looking at overall survival, but it showed a very good improvement in progression free survival. Even looking at overall survival it was a 2 ½ months difference.

In your mind, is Taxotere (docetaxel) still an option to consider in somebody who is a good candidate for switch maintenance but maybe not a candidate for Alimta, like a squamous carcinoma? Or do you think that the data with the FDA approved agents of Tarceva and Alimta was convincingly stronger?

**Dr. Hensing:** I think that for any drug to be used in the maintenance setting where we're going to have patients stay on that for an indefinite period of time, it has to be one that certainly is tolerable, and I think from the standpoint of Taxotere, I think of the drugs that are out there and have been tested in this sort of setting, I think that's the one that's the least appealing from a toxicity standpoint.

I think the other point is that certainly many of these maintenance trials showed a benefit in terms of progression free survival, which certainly can be very important for patients, but I would look more at the patient who is particularly symptomatic when they come in to their therapy. We all know patients who have a very significant disease burden and may become quite symptomatic, if they were to progress maybe they might very quickly get to a point where they couldn't get second line therapy and maybe that would be the individual we would consider a maintenance type strategy in.

But in this gentleman, I think the bulk of his issues in the course of his therapy appear to be treatment-related, not disease-related, and for that reason I wouldn't be in favor of a maintenance strategy. But if I were, if this were a more symptomatic gentleman and I wanted to do maintenance with a patient with

squamous, I would probably look more towards the Tarceva data, which did show benefit in the squamous population.

But I tend to not do a lot of maintenance therapy, particularly in a setting like this, and I probably would hold off in this individual.

**Dr. West:** I think your point is very well taken about this whole concept being predicated on having well tolerated treatments longitudinally, and certainly cisplatin-based chemo or even doublets are not that amenable for the vast majority of patients, but it's really with the handful of most tolerable agents with minimal cumulative toxicity that we can even talk about this. And yeah, you're right, Taxotere is not as appealing. Dave, what's your thought process here?

**Dr. Jackman:** To be fair -- largely similar to everything that Tom just mentioned -- I'm not overwhelmed by the maintenance data. I think that to Dr. Fidias' credit, I think his trial was particularly well designed and really kind of narrows out the question of timing, and I don't know that the Alimta and the Tarceva trials did that.

So for this particular patient, I'm always asking myself the question "*How do I help my patients live longer and feel better, and is maintenance therapy of any type going to do that?*" If we look at Panos's trial, we see from a Taxotere standpoint the answer is no, it didn't help them live longer.; from an Alimta standpoint, well certainly not in squamous cell patients. Then we're left with Tarceva and when you look at squamous cell patients specifically, at the Forest plots, it looks like there was an improvement in progression free survival, but not necessarily in overall survival for the squamous subset.

So I can't say that I'd be convinced to use a maintenance drug of any type for this patient. I think that he'd really benefit from a treatment break; both to recover his counts and enjoy a few months of being off therapy and kind of a reward for slogging through all that he already has.

**Jack:** Time served...

**Dave:** And getting stronger so that when he does need therapy and when there's a setting that therapy has been clearly shown to be of benefit in, he's more able to tolerate that.