

Expert Round Table with Drs. Tom Hensing and David Jackman: Molecular Markers and Sequencing Therapy, Case 3, with Dr. Jack West

Dr. West: The last patient is a 60-year-old Chinese never-smoking woman who was ultimately diagnosed with an advanced adenocarcinoma of the lung, and her symptoms also began with some right shoulder problems. She had some escalation of this pain over months, actually starting last year, and was in the process of a workup for adhesive capsulitis and developed some increasing shortness of breath. She had a chest x-ray a few months ago that demonstrated a large right pleural effusion, and she had a large volume thoracentesis, cytology positive for an adenocarcinoma, was positive for TTF1 and CK7, negative for cytokeratin 20, and her CT imaging also showed some pleural nodules in several areas in her right chest; and not evidence of more distant disease.

She has no past medical history to speak of and a good performance status, though recently she has some symptoms, both the pain and the shortness of breath related to her disease.

Here you can see the CT done, that shows a really very large effusion on the right side, really compressing the right lung. Her PET/CT shows a little better that there's focal areas of disease involvement. Even with this, you can't completely appreciate the pleural involvement that was seen in some other imaging that was done.

Now she doesn't have adequate tissue to send off for molecular markers, and so really the question is, this is a never-smoking Asian woman: would you pursue an additional intervention to obtain tissue and wait on it before starting first line therapy? And if so, what would be the highest priority for you. Tom, why don't I start with you here?

Dr. Hensing: I think for this patient, even before we got to the era of biomarkers, her dominant issue is the malignant effusion, and I probably would have sent her to a thoracic surgeon for a VATS pleurodesis. In somebody like this, these days that would also give you the opportunity to both palliate the pleural effusion, but get additional tissue for biomarker testing. So I think from a clinical standpoint, you can justify taking the time to do the pleurodesis to deal with her dominant issue, and that would also buy some additional time to get your biomarker. If you're able to do that, I think the issue is do you wait for the result before moving forward or not? I think a lot of that depends on how symptomatic the patient is.

But I think in this case, particularly if you were to proceed with a pleurodesis first, at least our surgeons would want us to wait a week or two before starting cytotoxic therapy to let the pleurodesis sort of take hold. In which case, you would have that time to get the biomarker results, so I don't know that it's necessarily delaying therapy, but in this patient I would want to get a VATS pleurodesis done quickly to get more tissue but also to help with the effusion.

Dr. West: And in fact, that's what she did have. She had a VATS, both to control this large and symptomatic effusion and at the same time to get additional tissue. And the surgeon did send for EGFR and KRAS mutations from the tumor tissue at that time. The problem was the lab that the hospital used took weeks to get that back.

Occasionally this is an issue: there's a huge amount of heterogeneity within the practice community about the time required to get these molecular markers back. It's great if you're at a place that runs these tests, but if you have to get tissue sent from your pathology department to some outside place, waiting two or more weeks can be challenging sometimes for the patient, the doctor, or both.

She ultimately decided that she didn't want to wait to start on treatment, and in this setting, if somebody fits the criteria for the greatest probability of having an EGFR mutation, would that lead you to treat with an EGFR inhibitor off protocol, or would you be most inclined to use a chemo-based approach? Dave, why don't I start with you?

Dr. Jackman: So given her demographic, Asian woman never-smoker adenocarcinoma, I think that her chance of having EGFR mutation, if we look at the mutation analysis from things like the IPASS trial or other Asian trials, her EGFR mutation is probably upwards of 60 or 70% -- so it's pretty high. I would probably give her an EGFR inhibitor. We know that clinical demographic predictors are not nearly as good as the molecular markers. However, in a few rare cases, including one like this where the demographic data is so strong, and knowing that if she does have an EGFR mutation her chance of responding to an agent like Tarceva would be really high, I'd probably give it to her.

Dr. West: Tom, would you have the same approach?

Dr. Hensing: I think that I, if you look at the IPASS data, I was struck by, if this was the same population that we're dealing with this patient and if somebody in fact was wild type, that there was a potential for harm, where the outcome was poor. And I think if you look even at the initial survival curves, or progression-free survival curve, and even patients that were mutants respond better to chemotherapy than if they were wild type. For me, if I know somebody has a mutation in this setting clearly, I would start with Tarceva.

If I either don't have enough tissue to test or if I have and I don't have the result, I would typically start with chemotherapy and then get the result and then decide what to do in either a maintenance setting or beyond. But I'm not routinely starting based on demographic data alone; I would want to get the biomarker first.

Dr. West: You know, it's interesting the IPASS data have certainly had an enormous impact, and we think about that, and Dave, you already alluded to the fact that demographic data, though important, are inferior to molecular marker data -- that's pretty clear. But the question is really whether if everyone ends up getting the treatment over time are they going to end up doing just as well? In other words, if you do capture progression on an EGFR inhibitor and then give them chemo after that will they end up getting the same benefit? And perhaps the same could be said for EGFR mutation patients getting it in the maintenance or second line setting instead of first line.

The TORCH trial was presented at ASCO this year, and this was in a molecularly unselected population, presumably the clear majority of these European patients not selected for smoking status or anything else, do not have an EGFR mutation. The design of the TORCH trial was half the patients getting chemo followed by an EGFR inhibitor and the other half of patients starting with the EGFR inhibitor, in this case Tarceva, followed by chemo. It was I think impressive and somewhat surprising to me that there was a clear difference both in progression-free survival and even overall survival that favored initial chemotherapy.

For you Dave, does that dissuade you at all about the upfront EGFR inhibitor concept, or is this just primarily a byproduct of it being a 90% EGFR negative group instead of a 70% EGFR positive group?

Dr. Jackman: I think you're right to bring up that data. I think that this is particularly in a Caucasian population. I think I would be more leery about proceeding with an EGFR TKI. I think all the data we have so far, you're right, is that there doesn't seem to be a clear benefit even in our known EGFR mutants for getting Tarceva first versus Tarceva second; that is in terms of overall survival. Even in the IPASS trial, there was no difference in overall survival, likely due to crossover.

That having been said, I think that because it's an Asian patient, I look at it a little differently. I think that if she just had no tissue available, if you looked at the IPASS data without regard to mutation status, we saw that randomized Iressa versus carbo/Taxol, the Iressa was just as good if not even a little better in terms of overall survival, without respect to EGFR mutation testing. So I think it's because it's an Asian patient that I look at it just a little differently; and not just Asian but again, Asian never-smoker adeno female. I think it's strong enough for me to think about doing it, but that's the only population I'd really think about doing it without having molecular data.

Dr. West: So she actually ended up having chemo-based therapy with carbo and paclitaxel, and Avastin as well. She tolerated it generally well -- had some myalgias and decreased blood counts, but she did have a minor response on the scan after a second cycle. In the meantime, we did get marker studies back that show an exon 19 deletion, so an activating mutation associated with a higher probability, not complete, but about a 70% probability of a very good response.

So with this information, how would you use it? Dave, I'll start with you. Do you transition her immediately? Would you give her up to 4 cycles and integrate the Tarceva with Avastin along the lines of the ATLAS trial, or how would you pursue it?

Dr. Jackman: Well at this point she's started on a regimen, she's had clinical benefit to it and when I think about settings like this, I think ultimately we're in it for the long haul. And if she's on a therapy that's working for her, I wouldn't switch off it prematurely to switch to another agent. I would save that agent for when we need it; that is, at progression.

So I'd be inclined to treat her as on the ECOG 4599 trial -- do the carbo/Tax/Avastin, and the Avastin maintenance. If she's benefitting from and tolerating it, it just prolongs things that much longer and allows us to keep Tarceva in our back pocket and use it when we need to, when she's progressing.

Dr. West: Tom, what would you do?

Dr. Hensing: You know, I would agree with that. I think of the cases you've had, this particular decision point I think was the toughest. I mean, you do have a therapy where she's tolerating it and benefitting from it, and you don't want to cycle through things too quickly.

I think certainly, even though she has a mutation, because she's benefitting from her current regimen and treating her like the ECOG trial, I think is certainly very reasonable. I think when I used Tarceva as a switch maintenance strategy, it's largely been in the patients with the EGFR mutations. Had I not started sort of the regimen carbo/Taxol/Avastin, had it been a doublet alone, I may have considered using it as a switch maintenance strategy. But I think in this case, keeping her on a therapy that's working makes sense.

Dr. West: So even at the time of discontinuing chemo, just continuing that Avastin rather than adding in the Tarceva with it along the lines of the ATLAS trial, you'd kind of leave it in your back pocket as a highly likely effective second line therapy?

Dr. Hensing: I think that if I were to go to Tarceva as switch maintenance here, I probably honestly would stop the Avastin. I think if you look at the ATLAS data, where you gave the combination, keeping both Avastin and Tarceva going as a maintenance strategy, at least in that study, there was not a survival benefit. Obviously, they're not just doing it in the patients with EGFR mutations, but there was fairly significant toxicity as well with the combination. So I think I would either stick with the regimen she's on, based on the ECOG trial, or switch her to Tarceva by itself -- I'm not sure I would keep her on a doublet as a maintenance strategy.

Dr. West: And then finally, this is not for this particular patient, but we all have patients who have received an EGFR inhibitor and have done extremely well, do have a good partial response or maybe even a complete response for a year or 18 months, or longer, and then begin to show progression.

Dave, you and your group have really been doing a lot of work on acquired resistance and potential molecular markers: Are you routinely trying to obtain tissue from patients when they progress after a good response? And whether you have that or not, what kind of approach are you using? Are you adding chemo to the EGFR inhibitor and continuing it, or are you just switching entirely to a different approach?

Dr. Jackman: We are trying to biopsy all of our patients who initially respond to but then secondarily acquire resistance, to try to determine if we can the reason for that resistance; that is, do they have a second mutation in their EGFR, the T790M? Or do they have amplification of a different gene -- MET --that can be another source of EGFR resistance? Because if we have that information, we can hopefully direct them to an appropriate clinical trial that tries to overcome that particular mechanism of resistance.

In the absence of either having that information or in the absence of having available such a trial, what are we doing? Well, what am I doing? I'm generally keeping patients on the Tarceva and adding chemotherapy on top of it. Why? Well, we know that patients who are EGFR mutants and who's tumors are really addicted to that particular oncogene, when Tarceva is taken away for whatever reason, whether it's progression, slight progression, or toxicity -- whatever -- when we take it away their disease certainly can flare. And there was a small trial from Greg Riely that really quantified this nicely, looking radiographically at these patients; and that when we restart the Tarceva in these patients we can often get secondary responses. And so for that reason, I'm keeping the Tarceva on and adding chemotherapy on top of it.

Dr. West: Tom, what's your approach here?

Dr. Hensing: I've been doing the same thing, based also largely on the Memorial data, I think, to avoid a disease flare. If somebody either I know had a mutation or just that we put them on it and they benefited for an extended period of time, I would generally keep the Tarceva going and add whatever my second line agent would be and typically kind of keep the doublet going as long as we can. I have occasionally, after a period of overlap, if they were having a lot of toxicity to the EGFR inhibitor, I potentially drop it out. I haven't seen any flares as long as there's been an overlap, but I think for the most part I try to keep it going and add in a second line agent.

Dr. West: When you do this, either of you, do you use a pharmacodynamic separation approach of stopping the Tarceva for a couple of days before and after the chemo or are you not concerned about that?

Dr. Jackman: I generally haven't been. I know the data from Angela Davies looking at those strategies, stopping before doing the Tarceva essentially from days 2 to 15 out of a 21 day cycle, giving space for the chemotherapy. It's certainly of interest, but I think that in patients

with known EGFR mutations, with sensitivity to the Tarceva, I feel like the notion for pharmacodynamic separation came out of concern that the patients who got chemo plus Tarceva in the TRIBUTE trial looked like they did worse. However, in the non-smoking subset of those trials, those patients did just fine. So I'm not sure that there's any clear signal that we should go through the trouble of the pharmacodynamic separation; and if our goal is to prevent a flare anyway, that's all the more reason I think not to stop the Tarceva.

Dr. West: Tom, what's your approach?

Dr. Hensing: I agree. I understand the concerns and maybe the desire to try to schedule it differently, but I'm not sure how clinically relevant that is, and I've tended to keep it going. I think even if you look at the CALGB trial that, albeit, it was a first line study in minimal smokers, but it was, that was Tarceva versus chemotherapy plus Tarceva. There really wasn't a signal that there was any worse outcome if you gave them in combination, and so I've generally just found it easier to kind of keep it going in combination without trying to change the schedule.

Dr. West: Great. Well, thank you both very much. It's really interesting -- these are all situations where there is no right answer, and we're all struggling to do our best in interpreting data that are coming out in real time. So it's great for all of us to hear what other people are doing and it's great for the patients and caregivers out there to know that there's really a wide range of approaches, that there isn't any clear right or wrong answer. Lung cancer is becoming a much more individualized approach than any one size fits all.

So thank you all for taking the time: it's been great.