

Expert Round Table with Drs. Tom Hensing and David Jackman: Molecular Markers and Sequencing Therapy, Case 2, with Dr. Jack West

Dr. West: Let's turn to a different case. A 51-year-old ex-smoker who has a history of a half pack a day for 25 years, quit more than a decade ago, and she has really almost no medical history before her presentation with lung cancer. She actually presented with what appeared to be locally advanced non-small cell, had some pain in her right upper chest, had been very active and sledding with her family in the last winter and had a crash and thought that her chest wall pain was from that, but it didn't improve and she ended up getting a chest x-ray that showed a right upper lobe mass.

This was followed by a CT that confirmed a 3 – 3 ½ cm. apical mass and some moderately enlarged nodes in her aorto-pulmonary window but no evidence of distant disease. She had a fine needle aspirate of a right pre-tracheal node that showed non-small cell; and did appear to possibly be a candidate for surgery; certainly great performance status and not obviously bulky disease.

She underwent a mediastinoscopy that showed adenocarcinoma in multiple stations, including on both sides of the mediastinum - seems to be a Stage 3B patient, and this is her imaging. As you can see from the PET/CT that was ultimately done, there is at least a suggestion of the involvement that was seen histologically from her mediastinoscopy.

In terms of background, she works as an administrator in a local school system; really excellent performance status and no past medical history.

Now the wrinkle is that as she had been referred to me and a radiation oncologist: she had a planning CT for radiation that showed a new rather small right pleural effusion, and that was followed by a thoracentesis that unfortunately confirmed malignant cells. So this was no longer in the realm of treating for cure with chemo and radiation and is documented as more advanced disease.

Interesting, her smoking history is kind of on the cusp of what is sometimes considered an "oligo-smoker", and I think actually that Dave and your colleagues in Boston have largely promoted this concept of smoking history **not** being just a binary "never-smoker or ever-smoker", but that people with 10 or maybe even up to 15 pack years may have a pretty reasonable chance of some of these molecular markers that we think of more reflexively for never smokers. But she's got stage IVa disease by our new staging system and a known adenocarcinoma.

I'll start with you David, and ask, it's pretty clear that you would want molecular markers, but *which ones* would you prioritize and in particular if she did not have tissue available, let's say that we had identified from her imaging that she had stage IV disease but didn't have enough tissue available, would you feel strongly

enough in favor of molecular markers to want to pursue an additional biopsy to get tissue before initiating treatment?

Dr. Jackman: A number of good question there. First is, I would prioritize *EGFR* because that's the only one that I think informs first line treatment decision making. You know *EML4-ALK* translocation is great, but the trial is only available for second line and beyond. So I think *EGFR* is really the one we want here and now.

If there was not enough tumor tissue available, we talk to patients about getting re-biopsies, and we'll do this if they're willing, only if we can do so in a reasonably non-invasive way; or when the test can otherwise be justified.

So a CT guided needle biopsy, a thoracentesis -- that I think is all fine; to put somebody through a mediastinoscopy when a mediastinoscopy is not otherwise indicated I think is a tougher issue and is something that we haven't been doing routinely. But if there's tissue that we can get without having to put patients under any form of anesthesia, it's something we would consider doing.

Dr. West: Tom, what are your thoughts here?

Dr. Hensing: You know I would agree with that. I think in our practice, on the one hand if you look at the trials that sort of justify getting *EGFR* mutation testing in a setting that largely came from the IPASS study, and therein they looked at patients who were either never-smokers or sort of your "oligo-smokers" definition of less than a 15 pack-year history and quit I believe more than 15 years ago, but I think in our practice we're certainly testing the never-smokers as well as patients who have stopped smoking and would probably go ahead and get an *EGFR* mutation.

We tend to partly for trial reasons also, but we're getting at least three markers in most people if we have enough, which is the *EGFR* mutation, the *KRAS*, and *ALK*. Although I think in terms of outside of a trial I think the *KRAS* and the *ALK* are probably less helpful in the first line setting here. So, particularly if we had limited tissue, I'd want to get an *EGFR* at least.

Dr. West: Dave, you already addressed this issue of *ALK* rearrangement being a lower priority in the first line setting because the clinical trials are really directed to more advanced setting; so that's not something that you would necessarily wait on anything for, correct?

Dr. Jackman: Exactly.

Dr. West: How does *KRAS* status affect your clinical decision making, whether it's first line or later?

Dr. Hensing: I would say, on the one hand, if you look at the prospective studies that are out there, if you were contemplating an *EGFR* inhibitor, like Tarceva, and you knew somebody had a *KRAS* mutation, for the most part those patients do not respond to *EGFR* TKIs, or drugs like Tarceva, and so from a standpoint of response, you would probably want to pick another agent. I think for survival it's been a little tougher to show a difference, I think if you look particularly at the

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SATURN maintenance trial, it appeared anyway to the extent that there was benefit, it didn't seem to matter that it was similar in the *KRAS* type as well as *KRAS* mutants. But I think for the most part, at least in our practice, if I knew somebody had a *KRAS* mutation I would look for other options other than an EGFR TKI like Tarceva.

I think in this patient, in the first line setting, I think it's probably the least helpful, because the decision point here is really between an EGFR TKI like Tarceva and chemotherapy, and the bio-marker that's really going to be most helpful is the *EGFR* mutation. And if that's present, the likelihood is that they don't have a *KRAS* mutation. So I'm not sure it helps in the first line setting.

In the second line setting and beyond from a response rate certainly it's helpful; whether it helps with survival in terms of prediction is less clear.

Dr. West: Dave, what's your take here?

Dr. Jackman: From our standpoint I think *KRAS* has been of lower clinical utility. We published data on over 200 patients who had received Tarceva or Iressa first line and had been tested for both *EGFR* and *KRAS*. Obviously the people with *EGFR* mutations did very well. What we saw with the *KRAS* data was interesting and I think is a little contradictory as to some other previous data, in that it kind of didn't matter what your *KRAS* does, it was just the fact that you were EGFR wild type that was the negative predictor.

So it's not that the *KRAS* mutants did particularly worse than those who were wild type for both *EGFR* and *KRAS*, so I'm not sure that *KRAS* affects my clinical decision making at any point right now. Looking down the line, certainly we're looking for things to inhibit along the *KRAS* pathway for clinical trials, but in terms of picking agents in a first or second line setting, I'm not sure that *KRAS* is really informing my judgment right now.

Dr. West: So at least having a *KRAS* mutation doesn't mean that a patient should not or will not get an EGFR TKI second or third line with you.

Dr. Jackman: So I'd say this: I'd say that just the fact that they are *EGFR* wild types makes it less likely that they would certainly respond, so we shouldn't think of it as they shouldn't receive an EGFR first line. If someone is *KRAS* mutant, would I be likely to use Tarceva in a second or third line setting? No. It probably would push me towards a more standard cytotoxic chemotherapy agent.

Dr. West: Now, the other thing that we've seen, although admittedly it's in not a large number of patients, is that the patients who have an *ALK* rearrangement do not have an *EGFR* or *KRAS* mutation. So if you were to get *EGFR* and *KRAS* in the first line setting or prior to first line therapy, would detecting either of these mutations lead you to not bother pursuing an *ALK* rearrangement; Dave?

Dr. Jackman: I think it's too early to tell, to be fair. I don't think we have enough data from enough patients to be able to say how mutually exclusive these things are -- especially *EGFR* and *ALK* -- because it's a similar patient group. I imagine we're going to detect a few patients that are going to have both. It's too early to say. I

think that certainly, given the percentages, we're probably going to find rare ones here and there. I think it is a very low clinical likelihood, but I wouldn't say never.

Dr. West: So early in the story, the initial view was they're mutually exclusive *period*, but the more data you get the blurrier that becomes... Tom, what's your take?

Dr. Hensing: You know, I would agree with that. We have the *ALK* studies, and we are screening people who maybe had an *EGFR* mutation or what have you, and realizing that the chances are low, but I think right now we're still, since we don't know the full story, I think it's still reasonable to try and screen somebody for a trial and see if you see the *ALK* translocation.

Dr. West: So turning back to this patient, she received carboplatin and pemetrexed with bevacizumab, just based on a trial that Tom was one of the lead investigators for and is now being studied in a much larger setting as a phase III.

She tolerated this extremely well: she had no significant adverse affects really, had just a couple of days of transient fatigue, but very little limitation in her activities. And happy to see that after two cycles, she had a good partial response -- not a complete response, but really a very gratifying response, and then no further interval change after a total of four cycles.

Her performance status remains excellent, and she really doesn't have any significant cumulative toxicities. So she's gotten four cycles, and the question is, when would you change her treatment, and what would you go to? Six cycles? Would you drop some of these agents, or would you switch, or would you just altogether stop and watch the patient?

Tom, you were involved with some of this early work, what's your take?

Dr. Hensing: It's an interesting question. I think that first of all, although our study which was -- we went up to six cycles of all three agents, and then our maintenance was a continuation maintenance where we kept both the Alimta and Avastin going as a maintenance strategy -- and as you mentioned, that's being tested now in a randomized trial to compare it to the carbo/Taxol/bev (Avastin) with maintenance Avastin. Outside of a trial, though, I still look at it as, here you are with somebody who's had four cycles of therapy, they have stable disease now after cycle four. Outside of a trial, the only patients I would go to six cycles of the standard chemotherapy would be somebody who has ongoing response and in this patient, who has stable disease after four, I probably would stop certainly the carboplatin and the Alimta here.

I think that when you look at the maintenance question, I try to look at it first from the standpoint of, is this somebody that I would want to keep on maintenance therapy, particularly if we were to consider going to maintenance setting, maintenance Alimta by itself? In that case, though, the trial was really a switch strategy and not a continuation strategy, as would be the case here.

I think short of getting the data from the randomized trial that's looking at this compared to the carbo/Taxol/Avastin combination, probably if I were to continue anything, would continue the Avastin by itself.

This is not somebody who I think I would want to continue a maintenance cytotoxic agent on like Alimta, and I don't think there's really evidence to justify, at least in this patient, continuing Alimta beyond this setting. And so if I were to go to maintenance I probably would sort of follow what they did in the ECOG trial with Avastin and keep that going.

It's a difficult decision. It's hard to say, but until we have the data from the randomized comparison, I certainly would not continue a doublet like Alimta and Avastin in a maintenance setting without the data that shows that it either prolongs survival and does so with a reasonable side effect profile.

Dr. West: So more often than not you'd stop at four cycles of the doublet rather than continue to six, yes?

Dr. Hensing: I think that's fair. In this case it's carbo/Alimta, but even with carbo/Taxol or carbo/Alimta, I probably would stop at four if you have stable disease after the fourth cycle. I think occasionally I might go to six in somebody who somebody who's got ongoing response, but here I would probably stop.

Dr. West: It's interesting that we have routinely and almost always not returned to a first line agent after stopping it at four to six cycles and then seeing progression. With Alimta we have an agent that's pretty well tolerated on a cumulative basis, and if you were to stop it after four cycles and the person progresses two or three months later, would you just move on or would you consider that the patient might go back to Alimta either alone or with -- I don't know -- either the next treatment or sometime in the future?

I guess the question is, have they exhausted their benefit with this agent or some other after four cycles, or could we maybe be discarding an agent earlier than needed?

Dr. Hensing: Another good question. I think that I will admit that in some settings, really it depends to me on how long a period of time was there disease controlled off of therapy, and I've had patients who were able to go six months or beyond where I felt that they never failed the agent, and because it's such a well tolerated drug I have tried to go back to it. And I think this is the only drug where I would consider that. I have had some people respond again, so its limited numbers and no data would really point to, but I don't think it's unreasonable to consider that.

I would say my enthusiasm for that strategy would be lower if it were two months or three months down the road, as opposed to, say, six months or beyond, but that's subjective. I think it would be reasonable in some patients to cycle back to it; the question to me is the timing.

Dr West: Dave, what's your approach here?

Dr. Jackman: Again, I think that the phase III trial of Carbo/Tax/Avastin versus Carbo/Alimta/Avastin is tremendously interesting, and as Tom mentioned, the maintenance strategy in that trial for those folks who got Carbo/Alimta/Avastin is

to continue on with both the Alimta and the Avastin. We don't have good data to support it, but it certainly is intriguing.

In general, I'm not continuing with the doublet as maintenance, though have I done it in selected patients? The answer is yes. I think for those patients who have had tremendous responses to the initial combination and who are of such good performance status even after four to six cycles, have I considered it and actually done it? The answer is yes.

Now, ultimately, I think at this point you're asking yourself the question, has the regimen been very effective? Do I think that they can tolerate it on an ongoing basis as a maintenance drug or combination? And if the answer to both of those questions is yes, I'd think about doing it. So if they've had a very good response and an ongoing response, I don't want to lose that. And if I think they can tolerate the combination Alimta and Avastin together, in a way not just for another two or four more cycles where they're gutting it out, but really can they do this for months? If indeed the disease remains stable for that period of time, then would I think about doing it? The answer is yes.

Dr. West: It's interesting that one of the trials that was presented at ASCO was the French trial by Perol and colleagues. That had everyone getting cisplatin and gemcitabine for the first four cycles and then being randomized to observation alone, continuing the gemcitabine as a continuation maintenance, or switch maintenance to Tarceva. Both of the maintenance arms had an improvement in progression free survival, a little more striking with the gemcitabine, but significant for both; and then a not that impressive improvement in overall survival although preliminary result.

What was interesting to me was there wasn't any evidence that the continuation was less effective than an FDA approved switch maintenance. And the benefit was most pronounced in the patients who had responded well to the cisplatin/gemcitabine in the first line setting. And to me it's just interesting in that it suggested that the patients who got the most benefit haven't necessarily exhausted all of their benefit after four cycles, and there may still be some life left in it. Certainly it's not going to be for everybody, but it got me scratching my head about some of our truisms about stopping after four to six cycles because you'd necessarily reached a point of diminishing returns.

And also that we have so little data on the concept of continuation maintenance, at least this suggests that it's potentially comparable to our FDA approved and a little better studied switch maintenance strategies.

Dr. Hensing: I think we've seen patients, and if this individual had a sort of ongoing response where they were clearly benefitting, I do think there's a situation where you would continue and you might in that individual drop the carboplatin just to avoid the myelosuppression. You'd like to see some -- as you sort of said -- the people who kind of get ongoing benefits, some clear evidence that they are in fact continuing to get better, to sort of justify keeping them going on a cytotoxic agent.

Jack: Thanks.