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# ASCO GU update on tivozanib in advanced clear cell renal cancer

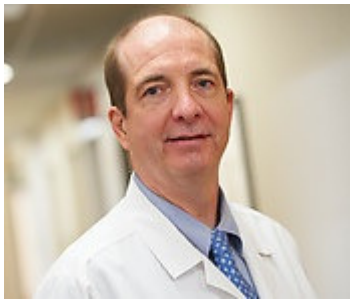
By MaverickNY on February 21, 2013



AVEO presented the phase 3 clinical trial data for tivozanib in renal cancer at the American Society of Clinical Oncology Genitourinary Cancer Symposium (ASCO GU) in Orlando last week.

The TIVO-1 data (PDF download), presented by Dr Robert Motzer (New York), showed a significant improvement in progression free survival (PFS) of 11.9 vs 9.1 months (P=0.042), but not median overall survival (MOS) i.e. 28.8 vs 29.3 months (P=0.105, HR 1.25). The lack of a significant MOS difference between the sorafenib and tivozanib treatment arms has received a lot of commentary recently, especially in light of the crossover clinical trial design.

To put the clinical trial results in context, last week at ASCO GU, I interviewed Dr Motzer, (Attending Physician, Genitourinary Oncology Service, Memorial Sloan-Kettering Cancer Center, and Professor of Medicine, Weill Medical College, Cornell University) for his perspective on the data.



*Source: MSKCC*

**PSB: I am very interested in the tivozanib data from AVEO/Astellas. What are your reactions to the results, bearing in mind that the overall survival was not significantly different from sorafenib?**

**Dr Motzer:** The TIVO-1 study was a randomized trial of tivozanib versus sorafenib and the primary endpoint was progression free survival (PFS). Since the patients were all hoping to get tivozanib, we included in the trial design for those patients who were on the sorafenib arm, if they progressed, then we would be able to switch them over to the new promising anti-cancer drug tivozanib. What we found was that most of the patients that were progressing on sorafenib, were able to switch over and get tivozanib.

**We feel that the survival being about the same on each of the two arms is maybe the result of the fact the patients on the sorafenib arm were able to receive tivozanib upon progression.**

In fact, the survival was a little bit longer on the arm that got the sorafenib followed by the tivozanib, and the reason for that is that many of the patients were treated in Eastern Europe, in Russia, Ukraine, and the only access they had targeted therapies was through this study. So if they were on the sorafenib arm they were able to get both sorafenib and tivozanib, but if they were on the tivozanib arm most of them weren't able to get any in second or third line therapy.

**I think it's important that patients get access to multiple lines of targeted therapies for kidney cancer, that is a very important thing.**

**PSB: Do you think, based on this data, that the drug is approvable by the FDA?**

**Dr Motzer:** I think it should be. I think it is a very good drug, it's effective, it has very little in the way of side effects. I think it should be an option. I think it should be approved and people should have it as an option.

Sorafenib is not one of commonly used first line agents in the United States, it has been sunitinib and now pazopanib may be the preferred agent. I would very much like to see a phase 3 trial that compares tivozanib to one of those two agents. I think that would probably provide the best information we have on how to make a choice for our patients.

**PSB: What did you like about the side effect profile of this agent?**

**Dr Motzer:** This drug is very selective for VEGF receptor, which we think is the most important target for kidney cancer response, and it has very little effects on other kinases. Many of the other drugs, they are all multi-targeted tyrosine kinases, but this one is more selective than the other ones.

Most of the side effects we see with the other drugs are from the drug hitting targets other than the VEGF receptor. So things like diarrhoea, skin sores, fatigue and so forth, that we see with the other drugs, we see very little with this one.

**PSB: One of things that is noticeable in GU medicine over the last few years is the emergence of translational medicine and biomarkers, is there anything new going on in renal cancer that might**

**help to better select patients, I think you have 8 or 9 different drugs available now, how do you choose going about which of these patients should get which of these therapies?**

**Dr Motzer:** For the most part it is based on the evidence for efficacy and what setting the drug was studied on and it is also based on the safety profile. So if it looks like one drug is safer than another or better tolerated, then that's often the choice to the patients.

What we don't have is any kind of genetic profiling that can say this drug would be better for this patient and so forth. I think that is some of the work that needs to be done. There was actually one of the posters from AVEO, to try and develop some of this, like a signature for response to tivozanib. That was a poster shown here, done in a small number of patients, more kind of a pilot study. We need more of that in kidney cancer.

**PSB: Do you think biomarkers will be more to the fore in renal cancer in the next couple of years?**

**Dr Motzer:** Yes, I think the one thing is there are now a number of different medications that are similar class, they have the same mechanism of action, so I think it's probably harder to find a biomarker to distinguish who will do better with one than another since they are related. I think the biomarkers would be important to see which patients does better with a VEGF targeted therapy like tivozanib, which one does better with an mTOR inhibitor like Torisel.

There are exciting new immunotherapies, the PD-1 antibody is very exciting in kidney cancer, for example. I think if we can identify drugs with different mechanism of action, then a biomarker might be of more use in terms of determining what is the best treatment, but when they are closely related it makes it more difficult.

**The PD-1 antibody is being studied in a big global phase 3 trial by Bristol Myers Squibb compared to everolimus. There is a lot of excitement over that one. It is more of a targeted immunotherapy.**

**My perspective – some additional thoughts…**

One of the things that got lost in the media hullabaloo when the final analysis was announced recently, was that the primary endpoint for the TIVO-1 trial was actually PFS, with median overall survival as the secondary endpoint, as Dr Motzer correctly noted.

Since tivozanib showed superior efficacy over sorafenib in the primary endpoint and a more tolerable side effect profile, then the chances of approval are higher than had both endpoints been not significant.

OS is always nice, but in this disease competition is high and distinguishing between broadly equivalent agents a little harder.

In the poster, a subset analysis was presented of the North American/Western European data demonstrating MOS had not yet been reached in either arm, but 2-year survival rates were trending in tivozanib's favour over sorafenib (75% vs. 60%). We will have to wait a little longer for the 50% point to be hit, but I thought this was encouraging. An update at ASCO in June may well be very timely.

The crossover trial design conundrum is one that other companies may well learn from – if the control arm has the potential to receive more therapy on progression that the test arm, then this will confound OS results in a global study. It's not the first time it's happened, but it does speak to addressing this issue more upfront in the study design. If PFS is the primary endpoint, then the issue is less of a problem but if companies need to demonstrate a clear differentiation in overall survival then a different approach might be necessary.

Several VEGF inhibitors are already approved by the FDA for the treatment of RCC (i.e. sorafenib, sunitinib, pazopanib, bevacizumab, axitinib) and in different lines of therapy, so the proof of concept for hitting the target in this disease is well established. Where they differ is that patients may well find some more tolerable than others or pricing/reimbursement may come into play as the competition heats up.

Presently, we have no valid biomarker for any of the VEGF inhibitors as a way of selecting a drug that a patient is most likely to respond to. Genentech/Roche have spent millions on biomarker research for Avastin with very little to show for it so far, proving how difficult this task really is.

**Check back tomorrow for an update on tivozanib and biomarkers**

Following the discussion with Dr Motzer, I followed up with Dr Murray Robinson, the Chief Scientific Officer at AVEO and will post our discussion on their fascinating research with biomarkers here on PSB. Although this research is unlikely to impact the registration trial data that is being reviewed by the FDA (the PDUFA deadline is July 28th for the TIVO-1 study), prospective inclusion of biomarkers in new studies may be very illuminating going forward.

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