Dr. Tomasz Beer

Xtandi

Dr. Tomasz Beer is Professor of Medicine and Deputy Director of the Knight Cancer Institute at Oregon Health & Science University in Portland. Prostate Forum spoke with him recently about Xtandi for prostate cancer.

PROSTATE FORUM: Can explain to my readers what your role was in the development and validation of Xtandi (enzalutamide) for metastatic castration-resistant prostate cancer?

DR. TOMASZ BEER: I’ve been working with Xtandi from the very first studies in patients-the Phase I trial, which became a Phase I/II clinical trial. We initially joined Memorial Sloan-Kettering Cancer Center and the University of Washington in developing and carrying out that trial. I was the second author after Dr. Howard Scher of Memorial Sloan-Kettering in the Phase I/II paper that reported the results. The very first patients treated with that drug anywhere in the world were treated in New York and here in
Oregon.

Out of that work came two Phase III clinical trials: one examined Xtandi in metastatic castration-resistant patients that had previously received chemotherapy. Dr. Scher led that trial. Then the other trial tested Xtandi in the pre-chemotherapy setting. I led that one.

What is Xtandi's mechanism of action?

Xtandi is a potent blocker of the androgen receptor. Androgens are hormones, and so the signaling induced by androgens occurs through the binding of the ligand or androgen (typically dihydrotestosterone, but other androgens as well) to the androgen receptor.

When that happens, the androgen receptor is activated and moves into the nucleus of the cell, binds to specific sequences in the DNA, recruits relevant co-factors, and then regulates the expression of hundreds of genes. It affects all the things that testosterone does: libido, facial hair, etc.

One of the things that testosterone does is promote and develop the prostate gland, and ultimately promote the growth of prostate cancer. Xtandi binds to the androgen receptor and prevents the translocation into the nucleus, prevents the binding of the ligand, and pre-vents the recruitment of co-factors. It has several ways in which it interferes with androgen receptor action.

On June 1, 2014 you published results in the *New England Journal of Medicine* showing that Xtandi can be of use in patients on ADT who hadn't received chemotherapy yet. Can you talk a little bit about those results and what they mean?
This was a Phase III clinical trial with co-primary endpoints of overall survival and radiographically documented progression-free survival. These are very meaningful clinical end-points. 1,717 patients across the globe participated, so it was one of the largest studies in prostate cancer ever done—not the largest, but one of the largest. It might very well be the largest in castration-resistant disease. What we found was a significant reduction in the risk of death with a 29% reduction in risk of death and a very large reduction in the risk of disease progression. There was an 81% reduction in risk of progression. The drug was able to control the disease and, as a consequence, extend overall survival.

Gratifyingly, we saw a clearly positive result not just through the primary measures, but also through all the secondary and exploratory end points that we used like PSA response rate, skeletal-related complications of malignancy, quality of life deterioration, and responses in measurable disease. All of those things very strongly favored Xtandi over placebo.

What all of this really means is that, assuming the FDA concurs, we have a new oral drug that is relatively well-tolerated that can be used in patients before chemotherapy. Xtandi is more convenient and less toxic than chemotherapy (although of course the studies did not compare it directly to chemotherapy—so this is my opinion based on the sum of all available data). It doesn't take a rocket scientist to figure out that most people would prefer a non-chemotherapy option if it were effective and safe.

I believe another study is underway that is looking at Xtandi versus Casodex. Can you speak a little bit about that? Are you involved in the study?

I am not involved in that study. It is a randomized Phase II trial. It's
not as large as PRE-VAIL, but it's looking at using Xtandi even a little earlier in the course of advanced prostate cancer, right when a patient begins progressing on primary hormonal therapy.

In PREVAIL, the vast majority of patients had received Casodex and progressed on it. But this trial compares Xtandi to Casodex, which is a previous generation androgen receptor antagonist, instead of placebo as we did in PRE-VAIL. There are some design differences in the trial, but it's relatively similar in that it looks at Xtandi prior to chemotherapy but after progression on hormonal therapy.

Are some patients resistant to Xtandi?

It depends on which measure you use. If you look at the conventional 50% reduction in PSA as a marker of activity, the response rate was 78%. That means 22% of patients didn't respond to Xtandi. Many of those patients had lesser PSA decline, so I don't have an exact percentage of the patients who truly didn't respond at all. It's in the neighborhood of 10%.

Clearly resistance occurs. One of the things we're trying to do here in Oregon is understand why that is. We're obtaining tumor biopsies and collecting circulating tumor cells from patients at the beginning of Xtandi therapy and at the time of progression and then analyzing the biology. We're going to capture some of those primary refractory patients because we're enrolling them at the beginning. Some won't respond, so we'll be able to take a look and see what the mechanisms are. There are a lot of potential candidate mechanisms, but thankfully, it is an uncommon event, especially in the pre-chemotherapy setting. Some of this work is being supported by a Dream Team grant from Stand Up to Cancer and we are working with 5 other institutions on the west coast. It's a wonderful group of
collaborators.

I spoke with Dr. Emmanuel Antonarakis from Johns Hopkins University about his work with androgen receptor splice variant-7 (AR-V7). What do you think of his results?

I am certainly very interested in his results. I think that AR-V7 is one of the plausible candidate mechanisms for resistance. There are other receptor mutations that are interesting. There is also, of course, the possibility that there are other ways cancer cells can get around receptor blockade, but I think that Emanuel's work is very promising. He is expanding on it and that is what needs to be done.

The one caution that one always has to have about these things is that, particularly with diagnostics and sometimes with therapeutics, as well, is that the early results are always good because if they were bad, you wouldn't hear about them. When you see something in the first 20 patients and it has been reported, it's always good. Not all medical tests look quite as good when you examine them in an unselected larger patient population. I think there is work to be done, but I view his work as one of the most promising early investigations into a possible mechanism of resistance.

Are Xtandi’s side effects significant?

The side effect story is actually not a simple one. The simple answer would be that there aren't many downsides, though of course every treatment has some. One measure of risk from a drug is the percentage of patients who discontinue therapy due to a side effect. That is a pragmatic measure. What we saw was that 6% of patients in an Xtandi-treated arm and 6% in the placebo-treated arm discontinued treatment due to a side effect. It was reassuring that the
percentage of people who stopped treatment for a side effect was the same for both those receiving the drug and those receiving placebo.

If you look at the incidents of Grade 3 side effects, it was 43% in the Xtandi arm and 37% in the placebo arm. A little bit higher. It's worth remembering that placebo patients were observed for an average of 5 months whereas Xtandi patients were observed for an average of 17 months, which reflects the fact that the drug was working. It's a little hard to know to what extent this apparent excess of adverse effects in the Xtandi arm reflects an actual increase in toxicity versus the fact that we were looking longer at older folks who may experience unrelated medical events that are reported as possible side effects.

The thing that was clearly more common with Xtandi than with placebo was fatigue and to a small extent back pain. I'm not sure I really understand the mechanism behind the back pain. Constipation and joint pain were both a little bit more common with Xtandi than with placebo. For example, 27% on Xtandi had back pain versus 22% on placebo and 22% on Xtandi had constipation versus 17% on placebo.

What we were pretty happy about is that there was only one seizure in each arm: one in placebo and one in Xtandi. Previous studies raised concerns about rare seizures, but here we really saw no difference between Xtandi and placebo. It was a really rare event. As it turned out, both of those patients had a prior history of seizures that they didn't disclose to the investigators.

We didn't see much in the way of liver enzyme abnormalities—less than 1% for Grade 3 or higher and 1% for all grades, the same in both placebo and Xtandi arms.

When you stack all of the above against, for example,
chemotherapy, there is obviously a very large difference between the side effect profiles. Obviously, this was not a trial that compared Xtandi to chemotherapy, so scientifically, you can't say that, but still: it is appealing to have some data that Xtandi can be used before chemotherapy so patients can delay the need for chemotherapy. In fact, the median time to chemotherapy was delayed by 17 months with Xtandi.

How much time will Xtandi actually buy a prostate cancer patient, or is that really dependent on the patient?

That is a very hard question to answer correctly. When we look at things that truly measure the effect of Xtandi, like time to chemotherapy or time to radiographic progression, we're looking at differences on the order of 16 to 18 months, but radiographic progression wasn't actually reached in the initial analysis and subsequent analyses. It depends on which definition you look at, but it's around a 16-month difference. When you look at overall survival, the difference in medians is much smaller, but the medians aren't very well estimated because patients were followed for a median of 22 months and the median survival was in excess of 30 months. We hadn't really reached the median survival in the median patient, so it's a very rough estimate.

Many patients received subsequent life-extending therapy, so when you study drugs early, and there are many other subsequent therapies, they have a tendency to potentially dilute the effect on overall survival. It's a very difficult question to answer with regard to overall survival, but when you look at radiographic progression that is an uncontaminated comparison. People stayed on treatment through radiographic progression, so they either got Xtandi or placebo. The difference is almost a year and a half, so it is a
How expensive is Xtandi?

I don't know the exact price, but the new drugs are costly. Medivation believes they provide a significant benefit and a lot of value. I agree with that, but I do know that for some of my patients who have high copays, it is a challenge.

Is Xtandi not covered by insurance?

Nowadays it is almost universally covered, but it's an oral prescription drug so people have variable levels of coverage. I've prescribed the same drug to patients who have a $50 copay and others who have a $2,000 copay. Many pharmaceutical companies do donate funds to support copay assistance and so do the manufacturers of Xtandi.

Certainly if they go on to subsequent treatments, right?

It's a global challenge in cancer care now. We have some really exciting advances. The costs are high, and we as a community and as a society have some work to do on figuring out how to really balance the need for return on an investment that can be put to good use in terms of supporting research. The cost of bringing a drug to market is enormous.

I'm not here to criticize anyone. As a clinician, I see it as a challenge, and I'd like for us to think about that together as a society. How are we going to continue to make improvements while still affording the things that we're creating?

It's a good problem to have. If we weren't inventing any good new medicines, we wouldn't have this problem. It's a challenge, and it's not just in oncology. I can see all sides of it. I can see how
incredibly expensive and risky it is for folks to undertake the work that is required to develop a drug. I would not want to discourage that.

I know that capital has choices as to where it goes. Having a healthy return on investment is really important. These are very high-risk things. It's pretty easy to put up a McDonald's restaurant and make some money. It's really risky to take on a brand new cancer drug that nobody knows is going to pan out or not.

We need to remember that, but at the same time, we also need to figure out how regular patients who are on Social Security can get access to drugs, health systems can manage to function, and insurance can remain affordable. These are all important topics for society to consider.

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