One Drug To Rule Them All: Medivation's Xtandi To Dominate Prostate Cancer Market

August 05, 2014, 08:51:23 AM EDT By Bay Area Biotech, SeekingAlpha

Comment

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The Background

Medivation (MDVN) is a clinical-stage bio-pharmaceutical company operating out of San Francisco, CA. Medivation's lead (and currently only) drug is Enzalutamide (Xtandi), an FDA-approved second-generation Androgen Receptor ("AR") inhibitor. Enzalutamide is partnered with Astellas Pharma, in which MDVN retains 50% of Xtandi profits in the US, and high-teen % royalties in the EU alongside pre-determined royalties from Astellas.

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On January 29th, MDVN presented its PhIII PREVAIL data, which showed unprecedented results for Castration-resistant Prostate Cancer ((CRPC)) patients in the "pre-chemo" setting. The stock reached highs of $85.83 as a result of this news.

In light of the PREVAIL data, we believe MDVN is one of the most compelling investments in the healthcare sector today. Xtandi represents the next step towards translating a new generation of highly selective and potent oncoprotein inhibitors to the clinic, and that will ultimately extend the lives of thousands of prostate cancer patients.

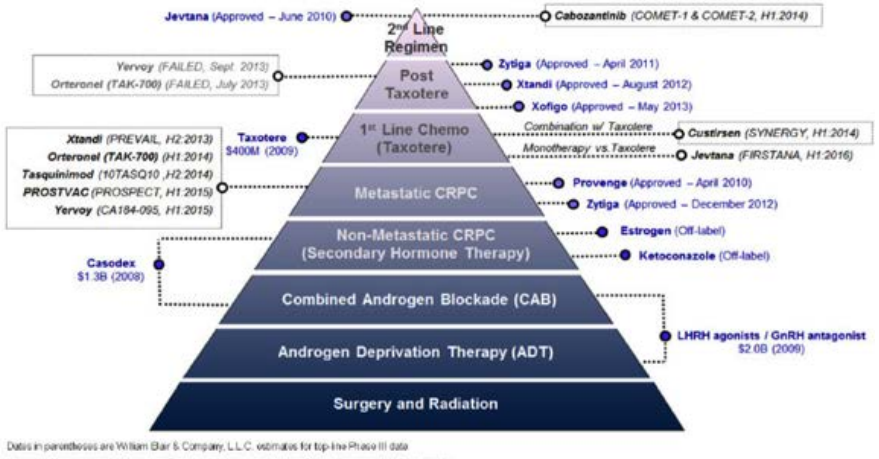
The Prostate Cancer Landscape

Prostate cancer is the leading cause of cancer death in American men. 230,000 men are diagnosed each year in the US alone, and 30,000 die each year. The progression of prostate cancer, along with the current therapeutic landscape, is outlined below.

(click to enlarge)

William Blair & Company, L.L.C.

Exhibit 2
2014 Genitourinary Cancers Symposium (ASCO-GU) Update
Current Landscape of Prostate Cancer Treatments: Approved and Phase III Agents Only



Dates in parentheses are William Blair & Company, L.L.C. estimates for top-line Phase III data
Sources: Company reports,Bloomberg, ClinicalTrials.gov and William Blair & Company, L.L.C. estimates

Importantly, there are significantly more patients in the earlier stages of prostate cancer progression

Run of Growth -- WSJ

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chemo settings are, in order, (in combo with hormones) Casodex (bicalutamide - AZN) and Zytiga (Abiraterone - JNJ). The MDVN investment thesis stands on the belief Xtandi will likely expand to the front-line settings.

Casodex (bicalutamide): This is the frontline "hormone-therapy" AR inhibitor, frequently given in combination with, or after, LHRH agonists or GnRH antagonists (testosterone deprivation) therapy in locally-advanced prostate cancer. Bicalutamide is a "first-generation" AR-inhibitor that was a >$1.3B drug for AZN in 2008, though is off-patent now. Even with generic competition since 2008, it has still sold ~$300mil last year (2013).

Zytiga (Abiraterone): Zytiga is a CYP17A inhibitor from JNJ that inhibits CYP17's ability to biosynthesize androgens, effectively serving as androgen-deprivation therapy. Thus, Zytiga targets the "ligand" presumably responsible for AR activation. Zytiga is currently approved for patients in the post hormone, pre-chemo setting. Peak sales estimates have been as high as 4.7B. Sales have been good, reaching 1.7B in just its second full year on the market in 2013 and being on track to surpass 2B this year with sales for 1H2014 reaching 1.074B. However, sales have been stagnating since Xtandi's rise to market, and will likely continue to be negatively affected by Xtandi, especially after the PREVAIL data (SEE BELOW). Two months ago, the US patent and trademark office extended a method of use patent for JNJ's Zytiga. Zytiga patent extension allows exclusivity for Zytiga until at least 2018, and maybe later. When Zytiga goes off patent, presumably cheaper generic alternatives will then be given the green light. However, Zytiga's patent extension is actually beneficial for future Xtandi revenue, because it will delay cheap generic competition in the space and delay pricing pressure on Xtandi.

Provenge (DNDN) : Dendreon's NK-cell therapy is also approved in the pre-chemo setting. However, due to its non-competing MOA and poor acceptance clinically, we will not discuss it as a direct competitor to Xtandi.

To tap into the prostate cancer market, agents typically start clinical investigation in post-chemo salvage setting, and then, once they show efficacy, work their way up with subsequent trials. In 2012, on the legs of the post-chemo AFFIRM trial, Xtandi was granted approval for the post-chemo setting, and the drug has been seeing 30% quarter-over-quarter sales growth, ultimately leading to MDVN's first positive-EPS quarter in 4Q13.

Xtandi will outcompete Zytiga in the pre-chemo CRPC setting

The major, imminent, question for MDVN is whether Xtandi can outcompete Zytiga in the pre-chemo setting. On January 2014, MDVN released the data for PREVAIL, a PhIII study evaluating Enzalutamide in the pre-chemo, mCRPC setting. The results were unprecedented, and have provided strong support for Xtandi's superiority over the already-approved Zytiga. This is key, since much of MDVN's valuation is placed on how it will fare against Zytiga's peak-sales estimates in the pre-chemo

Xtandi in the pre-chemo setting, leading to significantly higher revenues that will likely surpass the conservative FY2014 guidance. Of note, in the post-chemo setting, **Xtandi received approval approx. 9 weeks early** (9-10 weeks prior to September 18th could have been early July so decision is anticipated any time now). Ultimately, the market share question will come down to physician (both urologist and oncologist) choice and awareness. However, this choice is much more clear than MDVN's current market cap reflects. We will go over a few scientific reasons for Xtandi's superiority over Zytiga in the next section, but there are now also significant clinical data to support this point. Here's why: Physicians, when presented with two treatment options will assess two things that will dictate which to use first: 1). Safety and 2). Efficacy. Enzalutamide edges out Zytiga in both.

Effectiveness: Even though cross-trial comparisons should be taken with a grain of salt (no direct trials have been initiated comparing Zytiga and Xtandi directly in the pre-chemo setting), here is a table comparing commonly measured metrics in the respective pre-chemo Phase III trials:

	Reduced Risk of Cancer Progression (CT/MRI)	Time to initiation of chemo	PSA decline >50%	Duration of treatment
Zytiga	57% (.43HR)	8.4mo	51%	13.8
Enza	81% (.19HR)	10.8mo	80%	16.6

By all metrics, Enzalutamide outperforms. Similar retrospective cross-trial analysis has already been performed for the *post-chemo* trials. A poster presented at 2013 Genitourinary Cancers Symposium (J Clin Oncol 21, 2013 suppl 6; abstr217) compared the analysis from the respective Phase III trials and concluded in a cross-trial comparison that Enzalutamide indeed outperformed Zytiga. Their conclusion stated: "In this indirect comparative effectiveness analysis, [Enzalutamide] appears to be more effective than [Abiraterone] in time to PSA progression, rPFS, and PSA response. OS was not different". However, OS is hard to interpret since both studies had significant patient cross-over.

Safety and Convenience: Enzalutamide is more convenient (1 pill type/day) while also having a favorable safety profile to Zytiga, particularly given CRPC's patient population. Zytiga suffers two major drawbacks (i, ii), and one minor one ((

III)):

i). Steroids. Zytiga must be taken with steroids (prednisone), Enzalutamide does not. These steroids are associated with adverse events that many physicians find unfavorable.

ii). Cardiovascular risk. Zytiga may have higher cardiac (hypertension) adverse events. Enzalutamide is generally considered safer for patients with pre-existing cardiac or hypertension problems. An update from ASCO 2014 notes that Zytiga's hypertension risk is 2x higher than Enzalutamide's. The average age of a prostate cancer diagnosis is 66, so it is largely an elderly population disease. Elderly populations in the US are likely to have cardiac and/or hypertension problems, so this will likely impact physicians' prescription choices in favor of Xtandi.

iii). Diet. Zytiga comes with diet restrictions, largely due to the prednisone

Zytiga achieved worldwide sales of 1.7B in 2013, and is expected to obtain 2.5B in 2014, with peaks sales at approx. 4.6B in 2017. In JNJ's 1Q14 conference call, they reported that Zytiga was in control of 34% of the mCRPC market. If we look at US sales of Xtandi and Zytiga in the last 3 quarters of 2013, we see a 30% increase in quarter-over-quarter sales of Xtandi, yet a rather stagnating picture for Zytiga. Keep in mind, these figures are all *prior* to the PREVAIL data in January, which are likely to shift these trends in Xtandi's favor even more. Physician sentiment is skewing heavily in Xtandi's favor, with some reports placing the Xtandi/Zytiga split at 70/30 market share.

It is also important to note that there is strong rationale for the combination use of Zytiga and Xtandi together. Indeed, there is an investigator sponsored trial assessing the combination in the pre-chemo setting. When looking at Zytiga vs. Xtandi, most patients will likely end up seeing both during the course of their prostate cancer treatment. However, due to cross-resistance, the treatment given *first* will likely see a much longer duration of treatment than the second (which = significantly higher sales). We believe Xtandi will overwhelming be the frontline therapy choice, here's why:

A potential mechanism of resistance to AR inhibition is expression of AR-V7. AR-V7 promotes resistance to both Zytiga and Xtandi. However, in a small sample size of Xtandi/Zytiga naïve patients, 25% of Xtandi-resistant patients developed ARV7 whereas 51% of Zytiga-treated patients developed ARV7. Since presence of ARV7 would make a patient cross-resistant to both therapies (thus sequential therapy would not work), this data provides rationale for Xtandi use *before* Zytiga and reinforces our previous points (see above) about the rationale of using Xtandi as a superior drug to prevent cross-resistance with a potential paradigm of treatment as shown below: Xtandi -> Zytiga > Zytiga -> Xtandi. In reality, we believe that in time both drugs will be given to patients either in succession, or in combination. However, since cross-resistance does indeed occur with these two agents, whichever one is prescribed first will likely see the longer treatment duration, which will translate to higher sales.

Working its way up (STRIVE/TERRAIN) to the front-line setting

MDVNs future success vs. Zytiga in the pre-chemo setting is currently underappreciated, but this is far from where the story ends. It is currently in PhII trials assessing its utility in the front-line setting directly against bicalutamide (Casodex). These trials are TERRAIN in the EU and STRIVE in the US. Data for TERRAIN is expected mid-summer 2014 (soon), while STRIVE is seeing rapid enrollment with data expected in mid-summer 2015 and thus represent significant upcoming catalysts for MDVN.

In oncology, the mechanisms of resistance to therapy can teach us a lot about the primary drivers of disease. It is well known that the AR is the primary driver of disease in the vast majority of prostate cancers, however this is also proven by the fact that the majority of bicalutamide resistance consists of rescue of AR signaling, despite presence of drug. So, why is Xtandi clinically more effective than Casodex?

1. Xtandi was discovered in Casodex-resistant cells and the specific steps that were taken towards its discovery are nicely presented in several reviews Expert Opin Drug Discov. 2014 Jul;9(7):837-45
2. During pre-clinical development, Enzalutamide was found to be much more effective in killing AR-overexpressing cells compared to Bicalutamide
3. Mechanisms of resistance to Casodex almost always include AR-centric alterations.

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