TREATING CASTRATE-RESISTANT PROSTATE CANCER

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Disclaimer: Please recognize that I am not a Medical Doctor. I have been an avid student researching and studying prostate cancer as a survivor and continuing patient since 1992. I have dedicated my retirement years to continued research and study in order to serve as an advocate for prostate cancer awareness, and, from a activist patient's viewpoint, to help patients, caregivers, and others interested develop an understanding of prostate cancer, its treatment options, and the treatment of the side effects that often accompany treatment. Readers of this paper must understand that the comments or recommendations I make are not intended to be the procedure to blindly follow; rather, they are to be reviewed as my opinion, then used for further personal research, study, and subsequent discussion with the medical professional/physician providing prostate cancer care.

ZYTIGA/ABIRATERONE ACETATE

In layman terms, by binding to CYP-17 enzymes, Zytiga blocks the production of testosterone by the three production routes of testicular, adrenal glands, and by cancer cells themselves, thus also preventing testosterone conversion to the more powerful stimulant to cancer cell growth, dihydrotestosterone/DHT. Since this binding could also cause hypertension, hypokalemia, fluid retention and liver damage as well as ameliorate increased mineralocorticoid, the corticosteroid Prednisone is prescribed to accompany Zytiga/abiraterone acetate in order to guard against these effects. Zytiga is prescribed as four 250mg tablets taken at once daily two hours following any food or drink and one hour prior to consuming any food or drink other than water. Prednisone is prescribed as one 5mg tablet to be taken twice daily. Zytiga is currently authorized for prescribing to patients experiencing failure of androgen/hormonal deprivation therapy (aka castrate resistant prostate cancer) whose cancer has already metastasized (mCRPC) and has been found to be more effective at this stage than withholding use until failure of docetaxel/Taxotere chemotherapy. Our hope is that the medication will become available to patients failing androgen/hormonal deprivation therapy BEFORE their cancer is found to have metastasized and hopefully have yet better effect in either cancer cell apoptosis or much longer term management. A difference between ketoconazole and abiraterone acetate is that though ketoconazole also binds to CYP-17, it can come unbound whereas abiraterone acetate remains bound and thus is much more effective. In a sense, abiraterone acetate/Zytiga could be considered a "super"

ketoconazole. Unfortunately, abiraterone acetate/Zytiga is an extremely expensive medication at over $5000.00 per month.

TAK-700/ORTERONEL

Based on the success of Zytiga, it is clear that CYP17A is a viable target in the treatment of mCRPC, which has generated interest in other CYP17A-inhibiting agents including TAK-700/Orteronel, which is mechanistically similar to Zytiga. TAK-700 inhibits 17, 20 lyase activity of CYP17A but does not inhibit 17-hydroxylase to the same extent, and therefore it may preclude the need for the coadministration of prednisone. A phase 3 trial of TAK-700 without prednisone is now under way for high-risk PCa patients undergoing radiation and conventional androgen deprivation (RTOG 1115). TAK-700 will also be evaluated in non-mCRPC. If as successful as Zytiga, we would again hope that the medication will become available to patients failing androgen/hormonal deprivation therapy BEFORE their cancer is found to have metastasized and would have the advantage of not requiring co-administration of prednisone as well as available with or without meals. If as effective as Zytiga, and if not requiring co-administration of a corticosteroid, we would hope this drug becomes available at less cost than Zytiga.

XTANDI/ENZALUTAMIDE

Enzalutamide is an oral high-affinity selective androgen receptor (AR) antagonist that potently binds to the AR, decreases ligand-induced nuclear translocation, inhibits AR binding to DNA, and blocks cell proliferation. Enzalutamide shows effective blocking of the AR wherein patients have earlier experienced failure of the antiandrogen bicalutamide/Casodex. In a sense, enzalutamide/Xtandi could be considered a "super" bicalutamide/Casodex. Enzalutamide/Xtandi does not require co-administration with any other medication, thus can be taken with or without food and is prescribed as four 40mg tablets taken at once daily. Again unfortunately, enzalutamide/Xtandi comes at even a higher price than Zytiga at over $7000.00 per month.

ARN-509

Building on the success of enzalutamide, ARN-509 is a novel small molecule AR antagonist. In the preclinical setting, ARN-509 has a better therapeutic index than enzalutamide that may allow the use of a lower active dose of the compound. In early studies, ARN-509 showed encouraging response rates and duration of response. ARN-509 is being evaluated in mCRPC in the pre- and postchemotherapy settings and in a phase 2 study in non-mCRPC.

TOK-001
Another approach involves maximizing androgen blockade by combining a CYP-17 inhibitor and an AR antagonist. TOK-001 combines these two properties in a single drug and is in the early phase of development. In my opinion, should this combination apparently of abiraterone acetate and enzalutamide or similar compounds be found effective, we would hope it would be approved for administration pre-metastasis at the time usual androgen/hormonal deprivation medications are showing failure.

When reviewing the activity of the foregoing medications, it would appear they would be even more effective in bringing about prostate cancer cell apoptosis as replacement therapy for the current androgen/hormonal deprivation medications. The combination of compounds with the activity of abiraterone acetate and enzalutamide as in trial with TOK-001 and found to be effective, appears to be the most promising as follow-on salvage therapy to either surgical removal of, or radiation to, the prostate gland when these treatment options show failure.

Click on http://tinyurl.com/mblzgz2 and take the time to thoroughly review information in this paper "Castration-Resistant Prostate Cancer: From New Pathophysiology to New Treatment" for a comprehensive overview of not only the forgoing medications but chemotherapy medications, immunotherapy medications, radiopharmaceuticals, novel agents, sequencing new agents, and more.