

## **Androgen Receptor Mutation – Hormone Refractory Prostate Cancer**

Compiled by Charles (Chuck) Maack – Prostate Cancer Activist/Mentor

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.

There is no absolute explanation of precisely what occurs to cause androgen receptor mutation (ARM), the effect wherein an antiandrogen, rather than blocking testosterone access to the cancer cell nucleus by way of androgen receptors on all cancer cells, eventually is unable to serve that role and like testosterone, becomes a fuel to cancer cell growth. This more often occurs as cancer cells grow in numbers that are androgen "independent" (AI) wherein the medications that had in the past been effective on reining in androgen "dependent" cancer cells no longer serve that purpose because of the increase in numbers of androgen independent cancer cells.

As explained in the conclusion of the following paper, the development of Androgen Receptor Mutation (ARM) can be the result of multitudes of variables yet to hopefully be determined in future research:

<http://www.nature.com/aja/journal/v12/n5/full/aja201089a.html>

“AR remains one of the most important nuclear transcription factors from the steroid hormone receptor superfamily of genes. Normal prostate growth and development, prostate carcinogenesis and AI progression of PCa are dependent on AR expression and function. As a brief and oversimplified statement, the prostate gland at any state of normal or neoplastic growth is addicted to AR. Alterations in AR structure, expression and signaling could have a determining role in PCa progression toward an incurable AI state. These alterations could be secondary to somatic or germline mutations, presence or absence of nonandrogenic ligands, cytoplasmic signaling crosstalk with other kinases or cross-modulation by other

nuclear transcription factors. This review provides a synopsis of the most common events, signaling and mutation that might change the benign or malignant state of the prostate. Although the focus of this review was prostate epithelial cells, we should emphasize that other cellular and acellular elements of the prostate microenvironment have important regulatory roles for AR expression and signaling. Future studies are still required to dissect AR biology, especially in HRPCa. It should be noted that the complex nature of PCa and its unique and inherent heterogeneity prevent us from predicting whether or not interference with the AR dependency of PCa can prove to be the final cure.”

When a patient has been including an antiandrogen (bicalutamide/Casodex, flutamide/Eulexin, nilutamide/Niladron) in his androgen deprivation therapy wherein his PSA levels, though previously controlled, are now showing elevation, the effect of Androgen Receptor Mutation/ARM is most often considered the cause and the antiandrogen is stopped to see if PSA elevation subsides. As explained above, ARM is usually an indication that androgen “independent” (AI) cancer cells have now multiplied in sufficient numbers wherein androgen deprivation medications for androgen “dependent” cancer cells are losing their effectiveness with both ARM and Hormone Refractory Prostate Cancer (HRPC) occurring requiring prescribing of other medications.

Medications now available at this point of prostate cancer management were Ketoconazole, either High Dose or Low Dose, accompanied by the corticosteroid Hydrocortisone (to counter cortisone depletion from ketoconazole); however, in more recent use (though currently the patient must also be experiencing metastases), are the medications Zytiga/abiraterone acetate (that requires being accompanied by Prednisone for the same reason ketoconazole requires hydrocortisone), or Xtandi/enzalutamide (with Xtandi not requiring an accompanying medication for effectiveness). My hope is that both Zytiga and Xtandi will soon be available at the time ARM/HRPC occurs even prior to metastases having already developed, since it stands to reason that if effective in this earlier time-frame metastases may be prevented or at least prolonged in occurring,

In my personal opinion, when ARM/HRPC has occurred and PSA continues elevation, Zytiga should be the next medication added to continuing LHRH agonist or antagonist prescribing (and dutasteride/Avodart if also part of previous androgen deprivation therapy). I would reserve Xtandi as the next backup medication to precede any necessity to have to move to the more toxic chemotherapy agents. This may also be a point where administration of

Provenge/sipuleucel-T may be considered to enhance effectiveness of the immune system for the foregoing medications to hopefully be even more effective when prescribed following the Provenge procedure.