

# Advances in Advanced Prostate Cancer Therapies– A Review by a Patient-Scientist

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## Abstract

**Background:** Prostate cancer (PCa) affects one in six men, and of these, for one in six it will be fatal. Most cases are indolent, yet for many it is aggressive and metastasizes to bone, lymph nodes or to soft tissue organs. PCa has many similarities with breast cancer, and with only a slightly lower mortality rate.

**Aim & Objectives:** Many new therapies have been developed in recent years for advanced PCa, and far more are under development. The objective is to review these developments (proven and unproven) and to assess the practical impact they have on patients. The author is both a scientist and the patient.

**Methods/Study Design:** A review of recent literature was conducted to evaluate the potential of approved therapies (in the USA) on advanced prostate cancer. A historical search was made of earlier developments as well to determine how they have influenced current thinking and advances.

**Results/Findings:** There are at least three major therapy classifications for advanced PCa.

They are (1) Interference within the androgen axis, (2) attacking cancer by using, or modifying, the patient's immune system (immunotherapy), and (3) killing the cancer directly by chemotherapeutic drugs, or targeted drugs.

(1) The androgen axis focuses on disabling the androgen receptor (AR) from translocating the nuclear membrane and activating genes within DNA for growth and reproduction of PCa cells. Androgens (testosterone, DHT) activates the AR by binding in a pocket within the AR. Strategies for interfering with the androgen axis include inhibiting androgen production (GnRH agonist or antagonists, castration), altering the pathway of cholesterol to androgen transformation by enzyme inhibition (Abiraterone Acetate, AA), inhibiting the binding of androgen (Enzalutamide, ENZ), or inhibiting the binding of the AR with DNA (Bromodomain

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inhibitor, experimental IQ1).

(2) The immune system is used to attack PCa cells with therapeutic vaccines generally by modifying dendritic cells (DCs). The Sipuleucel-T (ST) therapy exposes patient's DCs to non-patient PAP antigens. Other variations include engineered viruses that express prostate cancer related antigens like PSA (Prostvac). Attempts have also been made to use checkpoint inhibitors CTLA-4 and PD-1, and to directly engineer T-cells.

(3) Finally there are drug therapies directed to kill cancer cells. Taxanes alter the dynamics of microtubules, which interpret cell mitosis and enhance apoptosis (Docetaxel or Cabazitaxel). Platins, especially used for neuroendocrine PCa, binds to DNA interfering with cell division.

## Advances in Advanced Prostate Cancer Therapies: A Review by a Patient-Scientist

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**Roadmap:**

- Background
- I. Androgen axis
- II. Immunotherapy
- III. Attack cancer directly

### I. The Androgen axis

Androgens: Testosterone and **dihydrotestosterone (DHT)**

Protein, Androgen receptor (AR)

1. Androgen binds to the AR.
2. AR-androgen translocates into nucleus.
3. ARs pair up (dimer) and bind to DNA.

Human androgens consist of three steroid hormones

Androgen Deprivation Therapy (first line therapy used today)  
Remove androgens (primarily testosterone). This can extend survival by many years.

Discover: Charles Huggins 1941. Almost 75 years ago.  
Charles Huggins received the Nobel Prize in Physiology/Medicine in 1966 "for his discoveries concerning hormonal treatment of prostatic cancer."

"the importance of this discovery (androgen deprivation) far transcends its practical implications; for it means that thought and endeavor in cancer research have been **misdirected in consequence of the belief that tumor cells are anarchic**." Peyton Rous

The work of Huggins showed us what some of the rules of Prostate Cancer are.

Studies on prostate cancer: I. The effect of castration, androgen and androgen receptor on tumor development in metastatic carcinoma of the prostate. Huggins and C. Huggins. Cancer Research 1, 469-490 (1966).

### ADT: Chemical reduction of testosterone by agonist (Leuprolide) or an antagonist (Degarelix) of Gonadotropin Releasing Hormone (GnRH), also known as LH-RH. GnRH works on the pituitary via the hypothalamus to inhibit testosterone production in the testes.

ADT in advanced prostate cancer. Results of the C321 trial showing the probability of progression free survival vs. time upon taking Degarelix or Leuprolide as the first line ADT. After 1 year (vertical dashed line), those on Leuprolide could change to Degarelix, and the curve shows the results of those changing, after a Tosthal et al., European Urology 57, 838-842 (2010).

### Castrate resistant prostate cancer

Enzalutamide (MDV3100, Xtandi): Stop [1], the binding of Androgen to the AR. Fill the AR binding pocket.

### II Immunotherapy strategies:

Therapeutic Vaccines must often "boost" Dendritic Cells

Dendritic cells: Cells that digest foreign (cancerous) antigens and display them on MHC complexes on their surface to activate T-cells.

Ralph Steinman created a revolution in immunology when he discovered a beautiful cell for just looking through a microscope... he showed that dendritic cells are critical for initiating the most important immune responses.

Michel C. Bassermann, Nobel Prize lecture 2011.

**Sipuleucel-T (FDA approved).**

Therapeutic vaccine.

Patient's Dendritic cells exposed to antigen (in laboratory) then reinfused into patient.

Antigen (generic, not from patient) + Prostatic Acid Phosphatase (PAP) + granulocyte-macrophage colony stimulating factor (GM-CSF) from recombinant fusion gene. Should be given early, but not FDA approved until castrate resistance. Cost ~ \$120,000

Survival curve in phase IIIb and placebo. The median survival time across all 50% probability (Miller PM, Bassett et al., New England Journal of Medicine 365, 411-422 (2011)).

Notes:

1. Extended Overall survival 4.1 months.
2. No effect for 6 months.

Immunotherapy takes time to work. Start early.

### Immune Checkpoint Inhibitors

CTLA-4, PD-1 Not much progress in Prostate Cancer \$100,000 - \$250,000

... suppressing the immune system, but unhelping it to attack whatever is most going to attack. An Alton (see CTLA-4 checkpoint inhibitors)

(A) Activate (B) Inactivate (C) Activate

(How CTLA-4 inhibition works. (Left panel) A dendritic cell with a cancer antigen presented on its MHC binds to the T cell receptor (TCR) of a T cell. A second signal is needed to fully activate the T cell, and that is the binding of a CD28 or CTLA-4 to a B7 cell. (Center Panel) The second signal causes the T cell to express CTLA-4. But CTLA-4 binds better to CD80 or 86 than CD28, thus shutting down further activation. Right Panel: An antibody, CTLA-4 inhibitor, binds to CTLA-4 so that CD80/86 can again bind to CD28 to fully activate the T cell so that it is happy to attack tumors. See e.g. A. Sznol et al., Proteins in Biotechnology 44(7), 1-14 (2015)).

### Engineered T-cells

A great idea that almost no one is pursuing for prostate cancer. Idea is to modify a patient's T-cells so that they attack prostate cancer cells. The modification is a chimeric antigen receptor built to bind to antigens on Prostate Cancer cells.

A comparison of normal T-cell activation with that of T-cell attack of cancer cells using chimeric antigen receptors, CARs. (A) The natural activation of T-cells by binding of the T-cell receptor to an antigen presented on the MHC of an antigen presenting cell (APC). The activated T-cell has its own repertoire and has to find the tumor cell. (B) A first generation CAR that by itself is capable of providing Signal 1. Signal 2 requires binding to an APC. (C) A 2nd generation CAR that has co-stimulatory proteins in the CAR. But does present both Signal 1 and Signal 2. Adding proteins to the CAR creates 3rd generations that produce Signal 3 as well. (D) CARs that the tumor cell is directly involved in expressed CAR T-cells. In contrast to the natural process (A), (D) are details in the Lee et al., Clinical Cancer Research 16, 2786-2796 (2010).

### III. Direct targeting to kill cancer cells: Chemotherapy, radiation, R01231

**Chemotherapy**

Taxanes Docetaxel FDA approved 2004 for metastatic PCa.

Original source the Yew Plant.

Has benefit in about 1% of patients. Serious side effects.

**Major classes of drugs:**

| Class        | Effect                                                                                                                            |
|--------------|-----------------------------------------------------------------------------------------------------------------------------------|
| Chemotherapy | A primary source for a class of antineoplastic drugs.                                                                             |
| Chemotherapy | A class of drugs that kill or damage the genetic material, DNA, of the dividing tumor cells.                                      |
| Chemotherapy | The first class of drugs discovered.                                                                                              |
| Chemotherapy | No early chemotherapy drug was a success. As yet no DNA topoisomerase II inhibitor has been successful in killing tumor cells.    |
| Chemotherapy | A class of drugs that kill or damage the genetic material, DNA, of the dividing tumor cells.                                      |
| Chemotherapy | Also the primary source. Taxanes are a class of drugs that kill or damage the genetic material, DNA, of the dividing tumor cells. |
| Chemotherapy | A primary source for a class of antineoplastic drugs.                                                                             |
| Chemotherapy | A class of drugs that kill or damage the genetic material, DNA, of the dividing tumor cells.                                      |
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### Taxanes lose their effectiveness - Chemo Resistance

Popular explanations include:

1. Change in tubulin isotypes (not all tubulin is the same).
2. Efflux mechanisms (removal of taxanes).
3. Alteration of cell death pathways.
4. Mutations of tubulin that affect the polymerization and dynamics of microtubules.

### Summary

- Great opportunities for advancement.
- Genomics still plays a minor role (outside the laboratory).
- Modern improvements have been incremental.
- Our understanding has greatly improved, but advances in therapies are modest.
- Immunology holds promise, but so far has not delivered significantly to the treatment of advanced prostate cancer.
- The 1941 work (Huggins) still provides more benefit to prostate cancer patients than any of the modern developments.

Patients don't turn down the modern improvements. A starving man will eat what is available.

General Reference: [TroubleWithTheNewGland.com](http://TroubleWithTheNewGland.com) ISBN 9780986131540 [troublewiththegland@gmail.com](mailto:troublewiththegland@gmail.com) [www.troublewiththegland.com](http://www.troublewiththegland.com)

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