

PROSTATE CANCER: IMMUNOTHERAPY

IMMUNOTHERAPY IN PROSTATE CANCER

10 QUESTIONS TO ASK YOUR DOCTOR ABOUT IMMUNOTHERAPY AND PROSTATE CANCER

- 1. What is “Immunotherapy”?**

Immunotherapy refers to a class of treatments that takes advantage of a person’s own immune system to identify and help kill cancer cells. However, tumors often find ways to evade the immune system, which allows them to continue to grow and spread. Immunotherapy is designed to circumvent the ability of tumors to evade the body’s immune system.
- 2. What is the “Tumor Microenvironment”?**

The “tumor microenvironment” is composed of molecules, cells, tissue and blood vessels that surround the tumor. Tumors can often change their microenvironment and the microenvironment can influence how a cancer tumor grows. Tumors and their microenvironment interact with each other so it is important to consider both in treatment plans.
- 3. What types of Immunotherapy are used to treat cancers?**

There are different types of Immunotherapy, but not all types are effective against all cancers. Some examples of Immunotherapy are Cancer Vaccines; Immune Checkpoint Inhibitors; Immunomodulators; CAR-T Cell Therapy; and Cytokines.
- 4. Does Immunotherapy work in Prostate Cancer?**

Traditionally, the immune “microenvironment” around prostate cancer has been thought to be “cold” (unresponsive to most immunotherapy). There are currently limited immunotherapy options for metastatic CRPC: (1) Therapeutic Vaccines for those patients with metastatic CRPC who are asymptomatic or minimally symptomatic; and (2) Immune Checkpoint Inhibitors for a small number of patients with certain genetic mutations.
- 5. Are there any approved Immunotherapy Vaccines?**

Yes, in 2010 Sipuleucel-T (Provenge) was approved as a dendritic cell-based therapeutic vaccine for men with asymptomatic or minimally-symptomatic metastatic castrate-resistant prostate cancer. Sipuleucel-T is the first and currently the only autologous cellular therapeutic vaccine approved for solid tumors.
- 6. How Is Sipuleucel-T (Provenge) prepared and administered?**

Sipuleucel-T is prepared from a patient’s own cells, removed through leukapheresis and combined with a fusion protein of GM-CSF (granulocyte-macrophage colony stimulating factor) plus prostatic acid phosphatase (PAP) at a central manufacturing facility. The fused product is sent back to the physician and re-infused into the patient. This process from leukapheresis to re-infusion takes about three to four days. The procedure is repeated twice more, at two-week intervals, totaling 3 infusions over 4 weeks.
- 7. Are there objective findings that demonstrate benefit of Sipuleucel-T?**

Sipuleucel-T (Provenge) does not lead to significant declines in PSA or to radiographically-shown antitumor response. Clinical factors such as tumor growth and patient preference may be used to assess benefit, but the objective of Provenge is to extend life, which was shown in the trials.
- 8. How does Genetic and Genomic Testing improve chances for successful treatment with Immunotherapy?**

The other approved Immunotherapy option for prostate cancer, Immune Checkpoint Inhibitors, are only effective in a small subset of metastatic CRPC patients, so it is very important to carry out germline (inherited) and somatic (tumor) testing to determine suitability for that therapy.
- 9. What is Mismatch Repair, Microsatellite Instability, Tumor Mutational Burden, and DNA Homologous Recombination Repair?**

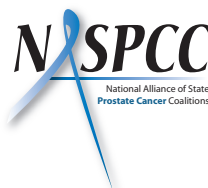
Mismatch Repair proteins fix mistakes in a person’s genetic material. A loss of one of these proteins (dMMR) means that mistakes in DNA can’t be fixed properly. Microsatellite Instability (MSI) results from defects in DNA repair; the presence of MSI-High is evidence that Mismatch Repair proteins are not functioning normally. Tumor Mutational Burden (TMB) is the level of genetic mutations in a tumor. Defective DNA Homologous Recombination Repair (dHRR) is a faulty mechanism of repairing double-strand breaks in DNA. These all act as biomarkers for selection of appropriate patients for Immune Checkpoint Inhibitors (ICIs).
- 10. Are there any approved Immune Checkpoint Inhibitors (ICI’s) based upon these genetic mutations? What are future directions?**

Two ICI’s, pembrolizumab and dostarlimab, have been approved as “tissue agnostic” or “pan-cancer” for treatment of refractory solid tumors (including prostate cancer) with dMMR (or, in the case of pembrolizumab, with high TMB) that have no other satisfactory treatment choices. However, those two mutations do not appear frequently in prostate cancer. On the other hand, dHRR is seen in almost a quarter of metastatic CRPC’s, making them susceptible to PARP Inhibitors and perhaps a better immune response. Future possible immunotherapy mechanisms include PD-1 Pathway Inhibition, CAR-T Cell Therapy, other monoclonal antibodies, Bispecific Antibodies, or combinations of the above drugs.

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PROSTATE CANCER: IMMUNOTHERAPY FOR PHYSICIANS

Effective
Immunotherapy in
mCRPC includes a
Vaccine and limited use
of Checkpoint Inhibitors
for a subset of Patients

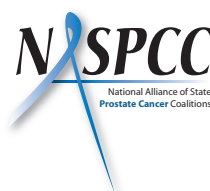
PLEASE REVIEW THE 10 PATIENT QUESTIONS AND ANSWERS ON THE REVERSE SIDE

1. The premise of “Immunotherapy” to treat cancer is that a patient’s own immune system can be trained to find and eradicate cancer in the body. However, tumors and their “microenvironment” often elude the immune system. Immunotherapy involves both a stimulation of the immune response and, conversely, inactivation of the unrestrained T-cell function (through the binding of PD-1 with PD-L1) which prevents the T-cells from attacking normal cells as well as cancer cells. Immune Checkpoint Inhibitors (ICI’s) unleash the power of the T-cells to kill tumor cells. Another form of immunotherapy is a Cancer Vaccine that boosts the immune system.
2. The “Tumor Microenvironment” harbors tumor cells that interact with surrounding cells using the circulatory and lymphatic systems, that then influence cancer progression. Even nonmalignant cells in the microenvironment play important roles by stimulating and aiding uncontrolled cell proliferation. Manipulating these cancer stem cells and molecules in the tumor microenvironment can help control cancer.
3. There are several types of Immunotherapy that treat various cancers, including Cancer Vaccines that help prevent or treat cancer; Checkpoint Inhibitors, such as PD-1 Inhibitors, that remove the brakes from the immune system; Chimeric Antigen Receptor (CAR)T-cell Therapy, combining T-cells with a special virus to train them to kill cancer cells; Cytokines, that stimulate T-cells to attack cancer; Immunomodulators, that boost part of the immune system; Monoclonal Antibodies, that can bind to a specific part of a cancer cell; and Oncolytic Viruses, designed in the lab to kill certain tumor cells.
4. Immunotherapy has become an important option in many advanced cancers, but has had only moderate success in metastatic CRPC. This could be because the patient’s immune system doesn’t recognize the cancer cells as foreign; or because the immune system response isn’t strong enough to destroy the cancer; or because the cancer cells are able to keep the immune system from locating or attacking them. Immune Checkpoint Inhibitors (ICI’s) have had some success when given to patients whose tumors harbor certain genetic mutations, such as deficient Mismatch Repair (dMMR), high Microsatellite Instability (MSI-H), or high Tumor Mutational Burden (TMB).
5. In 2010, after three clinical trials showed benefit, an autonomous vaccine, Sipuleucel-T (Provenge) was approved for early metastatic CRPC in men with asymptomatic or minimally symptomatic disease. Provenge does not significantly reduce PSA or result in disease regression, so men who are heavily symptomatic or require opioids for pain relief are not suitable candidates.
6. Sipuleucel-T (Provenge) is created and administered in several steps after removal of a patient’s peripheral blood mononuclear cells through leukapheresis. The cells are sent to a central manufacturing facility where they are mixed with a fusion protein of GM-CSF plus prostatic acid phosphatase (PAP). The product is sent back to the patient’s physician for reinfusion. The entire procedure is repeated two more times, with three total infusions over 4 weeks.
7. The mechanism of action for Sipuleucel -T is unknown. However, in the third clinical trial before approval, results showed that in the Sipuleucel-T arm, OS was improved by a clinically meaningful 4.1 months. Since PSA reflects disease burden in prostate cancer, baseline PSA was a strong indicator of outcome; and those men who had the lowest quartile in terms of baseline PSA showed the best outcomes compared to placebo. And in the PROCEED prospective registry trial of patients treated with Sipuleucel-T, the best results in median OS were in the lowest quartile of baseline PSA. [There is some evidence that black men had a greater reduction in risk of death than similarly matched white men, but this has not been proven.]
8. Combined genetic and genomic testing for all advanced prostate cancer patients is strongly recommended, because Immune Checkpoint Inhibitors (ICI’s) have shown good activity in the small subset of mCRPC patients with potentially actionable mutations.
9. Checkpoint Inhibitors are approved for mCRPC patients whose tumors harbor specific genetic mutations such as high levels of PD-L1, deficient Mismatch Repair (dMMR)/ high levels of Microsatellite Instability (MSI-H), DNA homologous recombination repair (HRR) defects, and/or high levels of Tumor Mutational Burden (TMB). However, dMMR/MSI-H is fairly rare in prostate cancer. [On the other hand, HRR gene alterations have been observed in almost 25% of mCRPC; and these tumors seem to have greater TMB and be more immune-responsive.]
10. Pembrolizumab and dostarlimab have been approved as tissue-agnostic options for refractory solid tumors, including prostate cancer, in men with dMMR and high TMB whose disease has progressed on prior treatment and who have no other satisfactory options. Pembrolizumab has also shown durable and synergistic activity in mCRPC when added to enzalutamide; clinical trials are underway to evaluate combination therapies that combine pembrolizumab and other therapies such as Olaparib and talabostat. Pembrolizumab is also appropriate as part of therapy for small cell neuroendocrine prostate cancer. Future immunotherapy options for prostate cancer may include Car-T cell therapy, Bi-specific antibodies, and other monoclonal antibodies.

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