TARGETING PSMA IN PROSTATE CANCER
PROSTATE CANCER IS A LEADING CAUSE OF MORTALITY IN MEN\textsuperscript{1-3}

Prostate cancer is the most frequently diagnosed non-cutaneous cancer in men in the United States and the European Union and the second most common non-cutaneous cancer in men worldwide.\textsuperscript{1,4-6}

In the United States, the median age of diagnosis is 66 years. While 71.5\% of prostate cancers are diagnosed between the ages of 55 and 74 years, only 9.5\% are diagnosed between the ages of 35 and 54 years.\textsuperscript{2}

At the time of diagnosis, 17\% of prostate cancers have spread to regional lymph nodes or metastasized.\textsuperscript{2} The most common metastatic sites include bone, distant lymph nodes, liver, and thorax.\textsuperscript{6}

Metastatic prostate cancer can lead to additional complications and increased mortality.\textsuperscript{2} Patients may experience trouble urinating, blood in semen, discomfort in the pelvic area, bone pain and fractures, erectile dysfunction, and decreased quality of life.\textsuperscript{7,8}

In 2018, 164,690 new cases and 29,430 deaths were estimated from prostate cancer in the United States; 449,800 new cases and 107,300 deaths were estimated from prostate cancer in the European Union; and 1,276,106 new cases and 358,989 deaths were estimated worldwide.\textsuperscript{1-3}

DEVELOPMENT OF METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Historically, androgen-deprivation therapy (ADT) has been the standard of care for regional or advanced prostate cancer. However, most men with advanced prostate cancer eventually stop responding to ADT and are categorized as castration-resistant (CRPC).\textsuperscript{9,10,12,\ast}

Resistance to androgen deprivation can arise through multiple mechanisms.\textsuperscript{10,12}

- Upregulation of androgen receptor, androgen receptor target genes, and genes that allow for survival in low-androgen environments allow for signaling in low levels of ligand or ligand-independent growth and survival.\textsuperscript{13}

- CRPC tissue can express testosterone and dihydrotestosterone at levels that allow prostate cancer cells to maintain androgen receptor signaling.\textsuperscript{12}

- Mutations that alter the steroid-binding specificity of the androgen receptor permit different ligands to activate signaling.\textsuperscript{14}

These and other adaptive cellular responses can allow prostate cancer cells to survive and proliferate despite ADT.\textsuperscript{10}

Metastases can occur in both men with hormone-sensitive prostate cancer and CRPC (mCRPC), and the majority of mCRPC incidence results from progression of CRPC.\textsuperscript{11} Approved treatments for mCRPC include ADT, chemotherapy, immunotherapy, radium isotope therapy (to be used for adenocarcinoma without visceral metastases in patients with symptomatic bone metastases), and palliative therapies.\textsuperscript{9} Despite advances in chemotherapy and novel hormone therapies, mCRPC remains incurable.\textsuperscript{9} The 5-year survival rate for mCRPC is 30\%, representing a high unmet medical need.\textsuperscript{2}

\textsuperscript{\ast} CRPC is prostate cancer that progresses despite castrate levels of serum testosterone (< 50 ng/dL).\textsuperscript{16}
PROSTATE-SPECIFIC MEMBRANE ANTIGEN (PSMA) IS A POTENTIAL TARGET FOR PROSTATE CANCER THERAPY

PSMA, a type II transmembrane glycoprotein composed of 750 amino acids, is expressed on the atypical surface of certain endothelial cells. PSMA expression can be found in all prostate tissues but is absent or moderately expressed in normal and benign tissues. In contrast, in advanced mCRPC, up to 80% of cancer cells are PSMA positive. High PSMA expression on biopsy is associated with increased chance of disease recurrence after treatment compared with low or absent PSMA expression. As PSMA expression increases with tumor aggressiveness, androgen independence, metastatic disease, and disease recurrence, PSMA is considered an independent indicator of poor prognosis.

A NUMBER OF MODALITIES ARE BEING INVESTIGATED TO TARGET PSMA

As PSMA expression increases with disease progression, numerous clinical trials have been initiated with modalities that target PSMA.

- Investigational radiolabeled compounds that are designed to bind to the extracellular domain of PSMA target beta-particle therapy to prostate cancer cells.
- Investigational antibody-drug conjugates specifically bind extracellular PSMA and deliver a cytotoxic drug into the cell.
- Immune cell–targeted therapies designed to selectively target PSMA on the tumor cells are also being investigated as a potential therapeutic strategy in prostate cancer.
  - Approaches that use anti-PSMA chimeric antigen receptor (CAR) natural killer (NK) cell and CAR T cell platforms are designed such that patients’ NK or T cells are isolated from their blood and genetically engineered with the goal of targeting the extracellular domain of PSMA, and infused back into patients.
  - Investigational PSMA-directed vaccines are designed to target T cells to the extracellular domain of PSMA.
  - Investigational BiTE® (bispecific T cell engager) molecules are designed to bridge the extracellular domain of PSMA on a prostate cancer cell to cytotoxic T cells.

Immunohistochemistry staining for PSMA (brown)

Gleason score (GS) is used to grade prostate cancers from GS \( \leq 6 \), overall low risk/grade 1, to GS 8–10, high risk/grade 4–5. PSMA expression correlates positively with GS and differs significantly between grades.

Since 1986, PSMA has been considered a potential molecular target for prostate cancer therapy.
KEY TAKEAWAYS

- PSMA is a well-known cell surface antigen in prostate cancer, with high extracellular expression on prostate cancer cells compared with normal cells.\(^{19,23}\)
- As PSMA levels correlate with cancer aggressiveness, it is actively being studied in several investigational prostate cancer therapies.\(^{17-21,23}\)

Abbreviations: ADT, androgen-deprivation therapy; BiTE\(^\text{®}\), bispecific T cell engager; CAR, chimeric antigen receptor; mAb, monoclonal antibody; mCRPC, metastatic castration-resistant prostate cancer; NK, natural killer; PSMA, prostate-specific membrane antigen.

References:
34. Murphy K. *Janeway’s Immunobiology*. 2012.

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