mCRPC:Here is a comprehensive analysis of the immunotherapy landscape for androgen receptor (AR)–resistant metastatic castration-resistant prostate cancer (mCRPC) in the US and EU, based on the provided tool use results.

**Executive Summary**

As of October 2025, the immunotherapy landscape for androgen receptor (AR)–resistant metastatic castration-resistant prostate cancer (mCRPC) is characterized by a robust and diverse clinical pipeline, yet a notable absence of recent regulatory approvals in the US and EU. The only approved immunotherapy remains the cancer vaccine Sipuleucel-T [[24](https://www.urotoday.com/conference-highlights/interdisciplinary-genitourinary-cancer-forum-2025/161411-interdisciplinary-gu-cancer-forum-2025-meeting-advances-in-immunotherapy.html)]. The field is dominated by investigational agents across five key modalities: checkpoint inhibitors (CPIs), cellular therapies (CAR-T/TCR), cancer vaccines, oncolytic viruses (OVs), and bispecific antibodies.

Development efforts are increasingly focused on overcoming the intrinsically "cold," or non-immunogenic, tumor microenvironment (TME) of prostate cancer through biomarker-driven patient selection and rational combination strategies. While radioligand therapies like Pluvicto currently set a high efficacy bar in the mCRPC setting, the most promising near-term immunotherapeutic advances are expected from bispecific antibodies and next-generation cellular therapies targeting antigens like PSMA and STEAP1 [[3](https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-pluvictos-metastatic-castration-resistant-prostate-cancer-indication)][[6](https://www.prnewswire.com/news-releases/metastatic-castration-resistant-prostate-cancer-clinical-trial-pipeline-appears-robust-with-90-key-pharma-companies-actively-working-in-the-therapeutics-segment--delveinsight-302272429.html)].

**1. Regulatory Status and Key Approval Milestones**

As of late 2025, the regulatory landscape for novel immunotherapies in mCRPC is defined by a lack of new approvals.

* **No New Approvals (2024-2025):** A review of FDA and EMA activity reveals no new approvals for checkpoint inhibitors, CAR-T therapies, cancer vaccines, or bispecific antibodies specifically for AR-resistant mCRPC during this period [[44](https://www.urologytimes.com/view/2024-urology-times-pipeline-report)][[45](https://www.targetedonc.com/view/fda-s-july-2024-roundup-breakthroughs-and-milestones-in-cancer-treatment)].
* **Checkpoint Inhibitors:** Pembrolizumab (Keytruda®) holds tissue-agnostic FDA approvals for tumors that are microsatellite instability-high (MSI-H), DNA mismatch repair deficient (dMMR), or have a high tumor mutational burden (TMB-high, ≥10 mut/Mb). These apply to a small subset (~5-10%) of mCRPC patients but do not represent a broad approval for the indication [[24](https://www.urotoday.com/conference-highlights/interdisciplinary-genitourinary-cancer-forum-2025/161411-interdisciplinary-gu-cancer-forum-2025-meeting-advances-in-immunotherapy.html)][[52](https://www.sciencedirect.com/science/article/pii/S2588931123000640)].
* **Cancer Vaccines:** Sipuleucel-T (Provenge®) remains the only FDA and EMA-approved immunotherapy for prostate cancer, indicated for asymptomatic or minimally symptomatic mCRPC [[24](https://www.urotoday.com/conference-highlights/interdisciplinary-genitourinary-cancer-forum-2025/161411-interdisciplinary-gu-cancer-forum-2025-meeting-advances-in-immunotherapy.html)].
* **Regulatory Designations:** The FDA has granted special designations to accelerate development for some promising candidates, including a Regenerative Medicine Advanced Therapy (RMAT) designation for the cancer vaccine CAN-2409 and a Fast Track designation for the radiopharmaceutical 225Ac-FL-020, highlighting agency interest in novel modalities for prostate cancer [[6](https://www.prnewswire.com/news-releases/metastatic-castration-resistant-prostate-cancer-clinical-trial-pipeline-appears-robust-with-90-key-pharma-companies-actively-working-in-the-therapeutics-segment--delveinsight-302272429.html)][[7](https://ir.candeltx.com/news-releases/news-release-details/candel-therapeutics-receives-fda-regenerative-medicine-advanced)].

The absence of recent approvals underscores that most immunotherapy programs remain in clinical development, with pivotal data and regulatory submissions anticipated in the coming years.

**2. Analysis by Immunotherapy Modality**

The mCRPC immunotherapy pipeline is diverse, with over 100 assets in active development across more than 90 companies [[6](https://www.prnewswire.com/news-releases/metastatic-castration-resistant-prostate-cancer-clinical-trial-pipeline-appears-robust-with-90-key-pharma-companies-actively-working-in-the-therapeutics-segment--delveinsight-302272429.html)].

**A. Checkpoint Inhibitors (CPIs)**

* **Mechanism of Action:** CPIs, such as anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies, work by blocking inhibitory signals on T-cells, thereby "releasing the brakes" on the immune system to enable T-cell-mediated tumor killing [[13](https://pubmed.ncbi.nlm.nih.gov/40563393)].
* **Development Status & Pipeline:** Single-agent CPIs have shown limited efficacy in unselected mCRPC populations due to the "cold" TME, which has low TMB and an abundance of suppressive myeloid cells [[13](https://pubmed.ncbi.nlm.nih.gov/40563393)]. Consequently, the current strategy has shifted towards:
  + **Biomarker-Selected Trials:** Focusing on patient subsets more likely to respond, such as those with CDK12 biallelic loss, which generates immunogenic fusion neoantigens [[28](https://aacrjournals.org/clincancerres/article/30/15/3200/746585/Evaluating-Immune-Checkpoint-Blockade-in)][[49](https://www.sciencedirect.com/science/article/pii/S1525157821002890)]. The PERSEUS-1 trial, initiated in June 2025, is prospectively enrolling mCRPC patients with MMRd and other immune-sensitive subtypes to receive pembrolizumab [[47](https://www.sciencedirect.com/science/article/pii/S2588931125001221)].
  + **Combination Therapies:** Combining CPIs with other agents to "heat up" the TME. The Phase 2 LORIKEET trial, which fully enrolled in March 2025, is studying the PD-1xCTLA-4 bispecific antibody **lorigerlimab** with docetaxel [[46](https://www.globenewswire.com/news-release/2025/03/20/3046698/0/en/MacroGenics-Provides-Update-on-Corporate-Progress-and-2024-Financial-Results.html)]. Other combinations under investigation include CPIs with PARP inhibitors, bipolar androgen therapy (BAT), and radioligand therapy [[29](https://actr.amegroups.org/article/view/10098/html)][[50](https://www.sciencedirect.com/science/article/pii/S2211383521000083)][[51](https://www.sciencedirect.com/science/article/pii/S022352342500594X)].
* **Mechanisms of Resistance:** Resistance is primarily driven by the immunosuppressive TME. Key factors include the accumulation of tumor-associated macrophages (TAMs) that produce adenosine to blunt T-cell responses, low neoantigen load, and activation of alternative resistance pathways like STAT3 [[11](https://pubmed.ncbi.nlm.nih.gov/39633050)][[12](https://pubmed.ncbi.nlm.nih.gov/40427227)].

**B. CAR-T/TCR Cellular Therapies**

* **Mechanism of Action:** These are "living drugs" where a patient's T-cells are genetically engineered to express either a Chimeric Antigen Receptor (CAR) or a T-Cell Receptor (TCR) that recognizes a specific tumor antigen. Key targets in mCRPC include PSMA, STEAP1, and PSCA [[14](https://www.nature.com/articles/s41591-024-02979-8)][[15](https://www.nature.com/articles/s41467-023-37874-2)].
* **Development Status & Pipeline:** All programs are in preclinical or early-phase clinical development. The pipeline is robust, with 47 cell therapy programs identified in the US and EU [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Neuroendocrine%20cancer%20of%20the%20prostate%20metastatic%22%2C%20%22Prostate%20cancer%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22United%20Kingdom%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)].

| **Key Candidate** | **Target** | **Developer** | **Phase** | **Key Highlights from Searched Data** |
| --- | --- | --- | --- | --- |
| **TmPSMA-02** | PSMA | Kite Pharma | Phase II | An advanced PSMA-targeted CAR-T therapy [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Neuroendocrine%20cancer%20of%20the%20prostate%20metastatic%22%2C%20%22Prostate%20cancer%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22United%20Kingdom%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. |
| **AZD-0754** | STEAP1 | AstraZeneca | Phase II | A leading CAR-T candidate targeting STEAP1 [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Neuroendocrine%20cancer%20of%20the%20prostate%20metastatic%22%2C%20%22Prostate%20cancer%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22United%20Kingdom%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. A Phase I/II trial of a STEAP1-CAR-T in combination with enzalutamide began dosing in late 2024 [[32](https://www.fredhutch.org/en/research/clinical-trials/trial-details.fh_trial_id_15047.cell-therapy-steap1-cart-with-enzalutamide-for-the-treatment-of-patients-with-metastatic-castration-resistant-prostate-cancer.html)]. |
| **BPX-601 (rimiducid)** | PSCA | Bellicum (now Anixa) | Phase I | Published Phase I data showed that 4 of 14 patients achieved a PSA decline of ≥50%, with manageable toxicity [[14](https://www.nature.com/articles/s41591-024-02979-8)]. |
| **PSMA-CAR-T** | PSMA | City of Hope | Phase I | Ongoing trial reported an early imaging-based complete response in one patient and is now exploring an IL-15 arm to improve persistence [[31](https://www.urotoday.com/conference-highlights/2025-ucsf-ucla-psma-conference/159354-psma-and-beyond-2025-car-t-and-bispecific-antibodies-targeting-psma.html)]. |

* **Mechanisms of Resistance:** Challenges include limited in-vivo persistence of CAR-T cells, T-cell exhaustion, and antigen loss on tumor cells. The hostile TME, with its dense stroma and suppressive myeloid cells, can also restrict CAR-T cell trafficking and function [[11](https://pubmed.ncbi.nlm.nih.gov/39633050)][[14](https://www.nature.com/articles/s41591-024-02979-8)][[15](https://www.nature.com/articles/s41467-023-37874-2)].
* **Recent Patents:** Recent patent filings focus on improving efficacy and safety, such as a Fred Hutchinson patent for a STEAP1-CAR designed to be effective even at low antigen densities, a feature relevant for tumors post-AR inhibition [[39](https://patents.google.com/patent/WO2023154890A2/en)].

**C. Cancer Vaccines**

* **Mechanism of Action:** Cancer vaccines aim to stimulate a patient's own immune system to recognize and attack cancer cells by presenting tumor-associated antigens (e.g., Prostatic Acid Phosphatase, PSA) [[16](https://pubmed.ncbi.nlm.nih.gov/38101860)].
* **Development Status & Pipeline:** This is the most populated category in the pipeline, with 89 programs identified [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Neuroendocrine%20cancer%20of%20the%20prostate%20metastatic%22%2C%20%22Prostate%20cancer%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22United%20Kingdom%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. Sipuleucel-T is the only approved product.

| **Key Candidate** | **Type** | **Developer** | **Phase** | **Key Highlights from Searched Data** |
| --- | --- | --- | --- | --- |
| **Stapuldencel-T** | Dendritic Cell | Sotio | Phase III | An advanced dendritic cell vaccine in late-stage trials across multiple EU countries [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Neuroendocrine%20cancer%20of%20the%20prostate%20metastatic%22%2C%20%22Prostate%20cancer%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22United%20Kingdom%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. |
| **Rilimogene galvacirepvec (Prostvac)** | Viral Vector | Bavarian Nordic | Phase II | Targets PSA and incorporates immune costimulatory molecules [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Neuroendocrine%20cancer%20of%20the%20prostate%20metastatic%22%2C%20%22Prostate%20cancer%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22United%20Kingdom%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. |
| **CAN-2409** | Adenoviral Vector | Candel Therapeutics | Phase II/III | Received RMAT designation from the FDA for treating localized high-risk prostate cancer, keeping the vaccine category on the radar [[7](https://ir.candeltx.com/news-releases/news-release-details/candel-therapeutics-receives-fda-regenerative-medicine-advanced)]. |
| **SYNC-T** | In-situ Vaccine | Syncromune | Phase II | An intratumoral therapy designed to create a personalized vaccine in-situ. Early data showed a ≥30% ctDNA drop in 6 of 18 mCRPC patients [[33](https://www.urotoday.com/conference-highlights/asco-2025/asco-2025-prostate-cancer/161019-asco-2025-clinical-responses-to-sync-t-therapy-in-situ-personalized-cancer-vaccination-with-intratumoral-immunotherapy-in-patients-with-mcrpc.html)]. |

* **Mechanisms of Resistance:** A key challenge is that vaccine-primed T-cells often face the same inhibitory hurdles within the TME, such as PD-1/PD-L1 expression, necessitating combination with checkpoint inhibitors [[16](https://pubmed.ncbi.nlm.nih.gov/38101860)].

**D. Oncolytic Viruses (OVs)**

* **Mechanism of Action:** OVs are viruses engineered to selectively replicate within and kill cancer cells. This process causes immunogenic cell death (ICD), releasing tumor antigens and danger signals that can trigger a systemic anti-tumor immune response, effectively acting as an in-situ vaccine [[17](https://www.sciencedirect.com/science/article/pii/S237277052030067X)][[26](https://www.labiotech.eu/in-depth/oncolytic-virus-therapy-cancer-2025/)].
* **Development Status & Pipeline:** All programs are in early-stage development. The focus is on improving delivery and overcoming resistance.
  + **Systemic Delivery:** Research is shifting from direct intratumoral injection to systemic (intravenous) delivery using "cloaking" technologies like lipid nanocarriers or capsid shielding to protect the virus from neutralizing antibodies and prolong circulation [[25](https://www.sciencedirect.com/science/article/pii/S2950329925000190)][[27](https://www.cancerbiomed.org/content/21/12/1104)].
  + **"Armed" Viruses:** OVs are being engineered to carry "cargo," such as IL-12, to help convert the "cold" TME into a "hot," T-cell-inflamed environment, making it more susceptible to other immunotherapies like CPIs [[26](https://www.labiotech.eu/in-depth/oncolytic-virus-therapy-cancer-2025/)].
* **Mechanisms of Resistance:** Resistance can be intrinsic, where tumor cells activate antiviral interferon programs that block viral replication, or adaptive, where the immune system rapidly clears the virus [[17](https://www.sciencedirect.com/science/article/pii/S237277052030067X)][[18](https://www.sciencedirect.com/science/article/abs/pii/B9780443160325000105)].
* **Recent Patents:** A 2024 patent from the University of Minnesota describes an adenovirus engineered to selectively bind to PSMA, enabling systemic delivery with reduced off-tumor effects and positioning it for AR-resistant disease where PSMA is often upregulated [[42](https://patents.google.com/patent/WO2024226921A1/en)].

**E. Bispecific Antibodies**

* **Mechanism of Action:** These antibodies have two binding sites: one for a tumor antigen (e.g., PSMA, STEAP1) and one for a receptor on an immune cell (typically CD3 on T-cells). They act as a bridge, physically bringing T-cells to the tumor to induce killing [[19](https://www.cancer.gov/research/participate/clinical-trials-search/v?id=NCI-2021-11596)].
* **Development Status & Pipeline:** This is one of the most rapidly advancing modalities, with 31 programs in the pipeline and several in or entering late-stage trials [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Neuroendocrine%20cancer%20of%20the%20prostate%20metastatic%22%2C%20%22Prostate%20cancer%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22United%20Kingdom%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)].

| **Key Candidate** | **Target** | **Developer** | **Phase** | **Key Highlights from Searched Data** |
| --- | --- | --- | --- | --- |
| **Xaluritamig (AMG 509)** | STEAP1 x CD3 | Amgen | Phase III | The most advanced STEAP1-targeted bispecific. Phase I data showed a PSA50 response rate of 30% at the recommended dose [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Neuroendocrine%20cancer%20of%20the%20prostate%20metastatic%22%2C%20%22Prostate%20cancer%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22United%20Kingdom%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)][[37](https://www.urotoday.com/center-of-excellence/mcrpc-treatment/from-the-editor/156268-advancing-mcrpc-treatment-new-approaches-approvals-and-emerging-therapies.html)]. |
| **Pasritamig (JNJ-78278343)** | KLK2 x CD3 | Johnson & Johnson | Phase I | A first-in-class T-cell engager targeting KLK2. Phase I data showed a 19% objective response rate (ORR) and 63% disease control rate (DCR) [[36](https://ascopubs.org/doi/10.1200/JCO-25-00678)]. |
| **Vudalimab (XmAb20717)** | PD-1 x CTLA-4 | Xencor | Phase II | Though not a T-cell engager, this dual checkpoint-blocking bispecific showed a promising 33% ORR and 25% PSA90 response rate in a small cohort of heavily pre-treated mCRPC patients [[2](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Metastatic%20brain%20cancer%22%2C%20%22Cancer%22%5D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Cell-based%20Therapies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)]. |
| **REGN-4336** | PSMA x CD3 | Regeneron | Phase II | A key PSMA-targeted bispecific in mid-stage development [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Neuroendocrine%20cancer%20of%20the%20prostate%20metastatic%22%2C%20%22Prostate%20cancer%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22United%20Kingdom%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)]. |

* **Mechanisms of Resistance:** Resistance can emerge through T-cell exhaustion and upregulation of alternative checkpoint molecules like PD-L1 on tumor cells. Cytokine Release Syndrome (CRS) is a common toxicity that requires careful management, often through step-up dosing protocols [[19](https://www.cancer.gov/research/participate/clinical-trials-search/v?id=NCI-2021-11596)][[38](https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.2536)][[40](https://patents.google.com/patent/WO2023152581A1/en)].

**3. Competitive Market Analysis**

* **Market Size and Key Players:** The global mCRPC treatment market was valued at approximately $11.99 billion in 2024 and is projected to grow at a CAGR of 8.1% through 2032. The US market is dominant, accounting for over 60% of revenues in the seven major markets [[9](https://www.databridgemarketresearch.com/reports/global-metastatic-castrate-resistant-prostate-cancer-treatment-market?srsltid=AfmBOopMCNI5LSpbjMr8H2jS4Ae_Tt1UFOw_HPp728peFYmBsFEr__2s)][[10](https://finance.yahoo.com/news/metastatic-castration-resistant-prostate-cancer-180000604.html)]. Key players in the immunotherapy space include **Amgen, Regeneron, Johnson & Johnson, Kite Pharma (Gilead), AstraZeneca, Sotio, and CureVac** [[1](https://www.noahai.co/tool/drug-compete/?search_param=%7B%22indication_name%22%3A%20%5B%22Neuroendocrine%20cancer%20of%20the%20prostate%20metastatic%22%2C%20%22Prostate%20cancer%22%5D%2C%20%22phase%22%3A%20%5B%22Preclinical%22%2C%20%22IND%22%2C%20%22I%22%2C%20%22II%22%2C%20%22III%22%2C%20%22BLA%2FNDA%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Cell-based%20Therapies%22%2C%20%22Vaccine%22%2C%20%22Bi-specific%20Antibodies%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22location%22%3A%20%5B%22USA%22%2C%20%22European%20Union%22%2C%20%22EU%22%2C%20%22Germany%22%2C%20%22France%22%2C%20%22United%20Kingdom%22%2C%20%22Italy%22%2C%20%22Spain%22%2C%20%22UK%22%5D%2C%20%22top_n%22%3A%201000%7D)][[6](https://www.prnewswire.com/news-releases/metastatic-castration-resistant-prostate-cancer-clinical-trial-pipeline-appears-robust-with-90-key-pharma-companies-actively-working-in-the-therapeutics-segment--delveinsight-302272429.html)].
* **Competitive Dynamics:** The approval and success of the radioligand therapy **Pluvicto (lutetium-177 vipivotide tetraxetan)** has significantly impacted the landscape. It has set a high efficacy benchmark that new immunotherapies must meet or exceed [[3](https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-pluvictos-metastatic-castration-resistant-prostate-cancer-indication)][[6](https://www.prnewswire.com/news-releases/metastatic-castration-resistant-prostate-cancer-clinical-trial-pipeline-appears-robust-with-90-key-pharma-companies-actively-working-in-the-therapeutics-segment--delveinsight-302272429.html)]. The expansion of Pluvicto into the pre-chemotherapy setting in 2025 will further solidify its position and force immunotherapy developers to demonstrate clear additive benefit, likely in combination regimens [[3](https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-pluvictos-metastatic-castration-resistant-prostate-cancer-indication)].
* **Partnerships and M&A:** The searched materials for 2024-2025 indicate a relative lull in major partnerships or acquisitions specifically for mCRPC immunotherapy assets, suggesting that potential partners may be awaiting more mature mid-phase data before committing significant capital [[46](https://www.globenewswire.com/news-release/2025/03/20/3046698/0/en/MacroGenics-Provides-Update-on-Corporate-Progress-and-2024-Financial-Results.html)]. This contrasts with the active deal-making seen in the radiopharmaceutical space [[6](https://www.prnewswire.com/news-releases/metastatic-castration-resistant-prostate-cancer-clinical-trial-pipeline-appears-robust-with-90-key-pharma-companies-actively-working-in-the-therapeutics-segment--delveinsight-302272429.html)].

**4. Biomarker-Based Patient Stratification**

To overcome the low response rates in unselected populations, a major trend is the use of biomarkers to identify patients most likely to benefit from immunotherapy.

| **Biomarker** | **Prevalence in mCRPC** | **Rationale & Clinical Relevance** |
| --- | --- | --- |
| **MSI-H / dMMR** | ~5% | Generates high neoantigen load. Pembrolizumab has a tissue-agnostic FDA approval for this biomarker [[52](https://www.sciencedirect.com/science/article/pii/S2588931123000640)]. |
| **TMB-High (≥10 mut/Mb)** | ~5% | Correlates with higher neoantigen load. Pembrolizumab has a tissue-agnostic FDA approval [[52](https://www.sciencedirect.com/science/article/pii/S2588931123000640)]. |
| **CDK12 Biallelic Loss** | ~4-5% | Creates a unique "focal tandem duplication" signature, leading to highly immunogenic fusion neoantigens. Enriches for response to CPIs [[28](https://aacrjournals.org/clincancerres/article/30/15/3200/746585/Evaluating-Immune-Checkpoint-Blockade-in)][[49](https://www.sciencedirect.com/science/article/pii/S1525157821002890)]. |
| **DDR Gene Mutations (e.g., BRCA2)** | ~20-25% | Impaired DNA damage repair can increase genomic instability and activate the cGAS-STING pathway, potentially sensitizing tumors to CPIs, especially in combination with PARP inhibitors [[50](https://www.sciencedirect.com/science/article/pii/S2211383521000083)]. |
| **PSMA Expression** | >80% | Essential target for PSMA-directed CAR-Ts, bispecifics, and radioligands. PSMA-PET imaging is used to select patients with high, uniform target expression [[51](https://www.sciencedirect.com/science/article/pii/S022352342500594X)]. |
| **Immune Gene Signatures (e.g., T-cell inflamed GEP)** | ~25-30% | A composite score of immune-related gene expression that identifies tumors with a pre-existing, albeit suppressed, immune infiltrate. May predict response to CPIs [[53](https://www.sciencedirect.com/science/article/pii/S2588931122000608)]. |

This has led to a tiered testing strategy in clinical trials and for future practice: first, screening for genomic markers (MSI, TMB, CDK12, DDR), followed by target expression imaging (PSMA-PET) to guide therapy selection [[49](https://www.sciencedirect.com/science/article/pii/S1525157821002890)][[50](https://www.sciencedirect.com/science/article/pii/S2211383521000083)][[51](https://www.sciencedirect.com/science/article/pii/S022352342500594X)][[52](https://www.sciencedirect.com/science/article/pii/S2588931123000640)][[53](https://www.sciencedirect.com/science/article/pii/S2588931122000608)].

**5. Future Outlook: Trends, Catalysts, and Challenges**

* **Emerging Trends:**
  1. **Rational Combinations:** The future is in combining modalities with non-overlapping mechanisms and toxicities (e.g., OV + CPI, radioligand + CPI, bsAb + CPI) to create a multi-pronged attack on the tumor and its microenvironment [[26](https://www.labiotech.eu/in-depth/oncolytic-virus-therapy-cancer-2025/)][[33](https://www.urotoday.com/conference-highlights/asco-2025/asco-2025-prostate-cancer/161019-asco-2025-clinical-responses-to-sync-t-therapy-in-situ-personalized-cancer-vaccination-with-intratumoral-immunotherapy-in-patients-with-mcrpc.html)][[51](https://www.sciencedirect.com/science/article/pii/S022352342500594X)].
  2. **Target Diversification:** While PSMA remains a key target, there is growing interest in novel antigens like STEAP1, PSCA, and KLK2 to overcome antigen-loss resistance and expand treatment options [[14](https://www.nature.com/articles/s41591-024-02979-8)][[36](https://ascopubs.org/doi/10.1200/JCO-25-00678)][[37](https://www.urotoday.com/center-of-excellence/mcrpc-treatment/from-the-editor/156268-advancing-mcrpc-treatment-new-approaches-approvals-and-emerging-therapies.html)].
  3. **Novel Engineering and Delivery:** Innovations include "armored" CAR-Ts that resist the TME, IgG-based bispecifics with longer half-lives, and systemically deliverable oncolytic viruses [[27](https://www.cancerbiomed.org/content/21/12/1104)][[38](https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.2536)][[39](https://patents.google.com/patent/WO2023154890A2/en)].
* **Anticipated Catalysts (2025-2026):** While no major PDUFA dates for mCRPC immunotherapies are on the immediate horizon, several key clinical data readouts are expected:
  1. **JANX007 (Janux Therapeutics):** Updated results for this PSMA-targeted T-cell engager are expected in H2 2025 [[23](https://www.noahai.co/tool/catalyst/?search_param=%7B%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Prostate%20tumor%22%5D%2C%20%22catalyst_type%22%3A%20%5B%22PDUFA%20Approval%22%2C%20%22Top-Line%20Results%22%2C%20%22Trial%20Data%20Update%22%5D%2C%20%22custom_impact%22%3A%20true%2C%20%22details%22%3A%20true%2C%20%22top_n%22%3A%2030%7D)].
  2. **BT5528 + Nivolumab (Bicycle Therapeutics):** Combination data is anticipated in Q4 2025 [[23](https://www.noahai.co/tool/catalyst/?search_param=%7B%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Prostate%20tumor%22%5D%2C%20%22catalyst_type%22%3A%20%5B%22PDUFA%20Approval%22%2C%20%22Top-Line%20Results%22%2C%20%22Trial%20Data%20Update%22%5D%2C%20%22custom_impact%22%3A%20true%2C%20%22details%22%3A%20true%2C%20%22top_n%22%3A%2030%7D)].
  3. **ORIC-944 (ORIC Pharmaceuticals):** Data from combination studies of this EZH1/2 inhibitor with immune effects are expected through H2 2025 and early 2026 [[23](https://www.noahai.co/tool/catalyst/?search_param=%7B%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Prostate%20tumor%22%5D%2C%20%22catalyst_type%22%3A%20%5B%22PDUFA%20Approval%22%2C%20%22Top-Line%20Results%22%2C%20%22Trial%20Data%20Update%22%5D%2C%20%22custom_impact%22%3A%20true%2C%20%22details%22%3A%20true%2C%20%22top_n%22%3A%2030%7D)].
  4. **Phase III Readouts:** Top-line results for trials like TALAPRO-3 (PARP inhibitor) and PSMAddition (Pluvicto) in 2025 will continue to shape the treatment landscape into which new immunotherapies must fit [[23](https://www.noahai.co/tool/catalyst/?search_param=%7B%22indication_name%22%3A%20%5B%22Cancer%22%2C%20%22Prostate%20tumor%22%5D%2C%20%22catalyst_type%22%3A%20%5B%22PDUFA%20Approval%22%2C%20%22Top-Line%20Results%22%2C%20%22Trial%20Data%20Update%22%5D%2C%20%22custom_impact%22%3A%20true%2C%20%22details%22%3A%20true%2C%20%22top_n%22%3A%2030%7D)].
* **Potential Challenges:**
  1. **Overcoming the TME:** The primary biological hurdle remains converting the "cold" prostate TME to a "hot" one.
  2. **Toxicity Management:** Managing CRS and neurotoxicity for cellular therapies and bispecifics is critical, especially in an older patient population.
  3. **Cost and Accessibility:** The high cost and complex manufacturing of cellular therapies pose significant barriers to widespread adoption.
  4. **High Efficacy Bar:** New agents must demonstrate a compelling benefit over existing and emerging standards of care, including potent AR-pathway inhibitors and radioligand therapies.