FROM THE ANALYST'S COUCH

The prostate cancer drug market

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Prostate cancer is the most common cancer in men and accounts for the second most cancer deaths among men globally. Most patients with prostate cancer are diagnosed with localized disease and treated with curative intent, so survival rates are high (nearly 100%). However, almost 10% of patients will present with metastatic disease; these patients have a poor prognosis and a 5-year survival of approximately 30%.

Current treatments

Hormonal agents are the mainstay of prostate cancer treatment and are routinely used at all stages, from early-stage localized disease to distant metastatic disease. Androgen deprivation therapy (ADT) is the most common form of hormonal treatment; it can be achieved pharmacologically with luteinizing hormone-releasing hormone agonists or antagonists, and/or antiandrogens, or surgically with orchiectomy.

Most patients will, however, eventually develop castrate-resistant prostate cancer (CRPC), defined as disease progression despite castrate levels of serum testosterone, obtained by ADT. Because the androgen receptor (AR) remains active in CRPC, novel agents that inhibit AR signalling have been developed. Abiraterone (Zytiga, Johnson & Johnson) and enzalutamide (Xtandi, Pfizer/Astellas), the first AR-directed therapies to receive approval for metastatic CRPC (mCRPC; in 2011 and 2012, respectively), are the first-line standards of care. In 2018, the use of AR-directed therapies was expanded to nonmetastatic CRPC; combined with ADT, apalutamide (Erleada, Janssen), enzalutamide, and then darolutamide (Nubeqa, Bayer HealthCare) were approved in this population. These agents are also being assessed in late-phase trials for earlier-stage disease. Abiraterone, enzalutamide and apalutamide (all in combination with ADT) are also standards of care for metastatic hormone-sensitive prostate cancer (mHSPC). Darolutamide is also in phase III development for mHSPC.

Other therapeutic agents are used to treat mCRPC, although their use is dependent upon specific clinical characteristics. The chemotherapeutic agents docetaxel and cabazitaxel (Jevtana, Sanofi) are traditionally reserved for symptomatic disease in the second-line and, for cabazitaxel, also in the third-line after docetaxel. Docetaxel may also be used to treat mHSPC with a high volume of disease or asymptomatic patients with mCRPC who are rapidly progressing. Radium-223 (Xofigo, Bayer HealthCare), an α-particle-emitting radiopharmaceutical, is indicated for CRPC with symptomatic bone metastases, but not visceral metastases. This narrow label restricts its use. Sipuleucel-T (Provenge, Sanpower Group/Dendreon) is an autologous therapeutic vaccine that is approved in the United States for asymptomatic or minimally symptomatic chemotherapy-naive mCRPC; however, it sees minimal use.

In 2020, two poly (ADP-ribose) polymerase (PARP) inhibitors were approved by the FDA for mCRPC that has progressed following AR-directed therapy. Olaparib (Lynparza, AstraZeneca/Merck & Co.) was approved for patients with deleterious germline or somatic homologous recombination repair gene mutations (~20–30% of cases) and rucaparib (Rubraca, Clovis Oncology) for patients with germline or somatic *BRCA* mutations (~12% of cases); for rucaparib, patients must have received prior chemotherapy. Both olaparib and rucaparib are being tested in phase III trials in combination with AR-directed therapies for first line mCRPC.

The PD1 inhibitor pembrolizumab (Keytruda, Merck & Co.) is not specifically approved in prostate cancer, but it is recommended as a treatment for mCRPC based on its tumour-agnostic approval. Patients must be microsatellite instability-high or mismatch repair deficient and progressed through docetaxel and/or an AR-directed therapy. The prevalence of mismatch repair deficiency in mCRPC is very low (2–5% of cases).

Emerging therapies

The prostate cancer phase III pipeline is diverse and includes molecules in approved drug classes as well as drugs with novel mechanisms of action, including radioligands targeted to prostate-specific membrane antigen (PSMA), kinase inhibitors and immune checkpoint inhibitors (TABLE 1).

Table 1 | **Select therapies in the phase III pipeline for prostate cancer**

Product	Companies	Target or MOA
Talazoparib (Talzenna)	Pfizer	PARP
Niraparib (Zejula)	Janssen	PARP
^{177}Lu-PSMA-617	Novartis	PSMA
TLX591 (^{177}Lu-DOTA-rosopatamab)	Telix Pharmaceuticals	PSMA
Ipatasertib	Roche/Genentech/Chugai	AKT
Capivasertib	AstraZeneca	AKT
Masitinib	AB Science	KIT
Cabozantinib (Cabometyx/Cometriq)	Exelixis/Takeda/Ipsen	TKI
Pembrolizumab (Keytruda)	Merck & Co.	PD1
Nivolumab (Opdivo)	Bristol Myers Squibb/Ono Pharmaceutical	PD1
Sabizabulin (VERU-111)	Veru	Tubulin inhibitor
CAN-2409	Candel Therapeutics	Oncolytic viral therapy

MOA, mechanism of action; PARP, poly (ADP-ribose) polymerase; PSMA, prostate-specific membrane antigen; TKI, tyrosine kinase inhibitor.

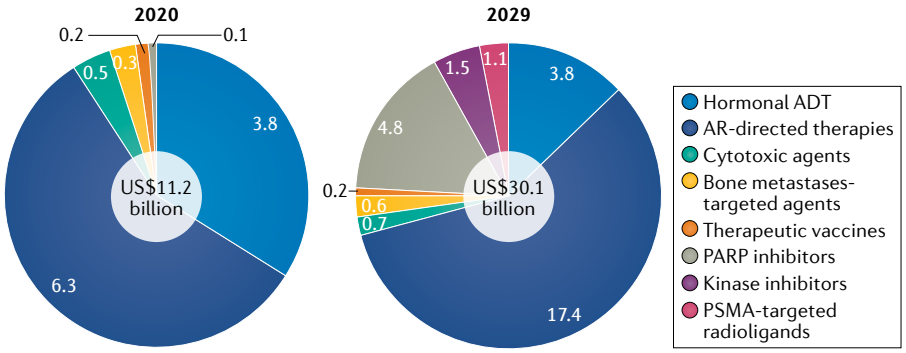

Fig. 1 | **Estimated major-market sales of key therapies for prostate cancer, by drug class.** The 2020 sales and 2029 forecast for the seven major markets: the United States, France, Germany, Italy, Spain, the United Kingdom and Japan. ADT, androgen deprivation therapy; AR, androgen receptor; PARP, poly (ADP-ribose) polymerase; PSMA, prostate-specific membrane antigen. Source: Clarivate.

Based on the proven efficacy of olaparib and rucaparib in prostate cancer, PARP inhibitors are one of the most promising drug classes in the phase III pipeline. Like olaparib and rucaparib, talazoparib (Talzenna, Pfizer) and niraparib (Zejula, Janssen) are being developed in combination with an AR-directed therapy for first-line treatment of mCRPC (TALAPRO-2 and MAGNITUDE, respectively). However, unlike olaparib and rucaparib, talazoparib and niraparib are also in phase III trials (TALAPRO-3 and AMPLITUDE) for mHSPC.

There are two PSMA-targeted radiopharmaceutical therapies in phase III trials for patients with PSMA$^+$ prostate cancer (more than 80% of advanced prostate cancers express this protein). ^{177}Lu-PSMA-617 (Novartis), a radioligand therapy, is being evaluated in three phase III trials; two trials in mCRPC (VISION and PSMAfore) and a third trial in mHSPC (PSMAddition). In March 2021, Novartis announced that VISION met both primary end points, overall survival and radiographic progression-free survival (rPFS), with US and European regulatory submission anticipated in 2021. TLX591 (^{177}Lu-DOTA-rosopatamab, Telix Pharmaceuticals), an antibody-based radiopharmaceutical targeted to PSMA, entered phase III development in May 2021. This agent will be assessed in combination with the best standard of care for second-line mCRPC in a trial known as PROSTACT.

Two AKT inhibitors, ipatasertib (Roche/Genentech/Chugai) and capivasertib (AstraZeneca), are being investigated in combination with abiraterone for metastatic prostate cancer. Ipatasertib is being assessed in asymptomatic or minimally symptomatic mCRPC in a trial known as IPATential150; primary results from IPATential150 showed a statistically significant improvement in rPFS in patients with mCRPC and *PTEN* deficiency, but not in all patients. Capivasertib is being assessed for the treatment of patients with mHSPC with *PTEN* deficiency in a trial known as CAPItello-281.

Other kinase inhibitors in phase III development for mCRPC are masitinib (AB Science) and cabozantinib (Cabometyx/Cometriq, Exelixis/Takeda/Ipsen). In April 2021, AB Science announced that the trial evaluating masitinib plus docetaxel met its primary end point, rPFS, in chemotherapy-naive mCRPC. Following promising data from the phase Ib trial mCRPC cohort, cabozantinib is now being evaluated in a phase III trial (CONTACT-01) in combination with the PDL1 inhibitor atezolizumab (Tecentriq, Roche/Genentech/Chugai) compared with AR-directed therapy in patients with mCRPC who have received one AR-directed therapy. Notably, single-agent cabozantinib for mCRPC failed in phase III trials in 2015.

The PD1 inhibitors pembrolizumab and nivolumab (Opdivo, Bristol Myers Squibb/Ono Pharmaceutical) are being evaluated in combination with therapies already approved for prostate cancer. Three trials are recruiting patients with mCRPC to receive pembrolizumab in combination with enzalutamide, docetaxel or olaparib, while a fourth is evaluating pembrolizumab plus enzalutamide in mHSPC. Nivolumab is being assessed in combination with docetaxel in chemotherapy-naive mCRPC with patients who have received prior AR-directed therapy. Sabizabulin (VERU-111, Veru), an oral tubulin inhibitor, is also being tested in mCRPC in a phase III trial (VERACITY). It could be an alternative to intravenous taxane chemotherapy in patients with advanced disease.

An intratumorally administered oncolytic viral therapy, aglatimagene besadenovec (CAN-2409, Candel Therapeutics), is also in phase III development. It is being investigated in combination with radiation for intermediate-risk and high-risk localized prostate cancer; it is the only therapy that has advanced to phase III for early-stage disease.

Market indicators

In 2020, the prostate cancer market totalled US$11.2 billion and was dominated by sales of AR-directed therapies (57% of sales). Despite the patent expiry and ensuing competition from generic agents during our 2020–2029 forecast period, the prostate cancer market is forecast to increase 11.6% annually to $30.1 billion in 2029 (FIG. 1). The continued uptake and label expansions of existing therapies, coupled with the forecast approval of premium-priced emerging agents, are anticipated to fuel this growth.

In 2029, AR-directed therapies are expected to remain the dominant drug class, capturing 58% of the total prostate cancer market ($17.4 billion). We forecast that apalutamide and enzalutamide will be the best-selling agents in the overall prostate cancer market by 2029; these agents will collectively capture sales of approximately $14.2 billion across the major markets. The strong uptake of apalutamide and enzalutamide in currently approved settings and anticipated label expansions in the hormone-sensitive settings will help drive the growth of the prostate cancer market.

PARP inhibitors are expected to be the second sales-leading drug class, capturing 16% of the total major-market sales. We anticipate significant sales from niraparib in combination with abiraterone in the mHSPC setting by 2029 ($2.6 billion); its sales will not reflect a high uptake, but rather its high cost and long duration of treatment. The expected approval of kinase inhibitors as well as PSMA-targeted radioligands should also boost major-market sales in 2029. However, sales of some therapies will likely be constrained by their biomarker-defined populations and high costs, as well as strong competition between current and emerging therapies across multiple patient populations.

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Competing interests
The authors declare no competing interests.