Patents

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A shifting market environment and strategies fueling innovation in prostate cancer treatment

Blockbuster drug patent expiration, advances in enabling technology, and the emergence of personalized medicine for prostate cancer treatment create a landscape worth examining.

Despite being well managed for most patients, prostate cancer (PC) continues to be of major interest for leading pharmaceutical companies because of the poor prognosis of advanced disease. There has been a flurry of transactional activity in the space among startup biotech companies and leading pharmas in recent years. Industry dynamics swirling around patent expiration of blockbuster drugs, advances in enabling technology, and the emergence and seeming omnipotence of personalized medicine in all things biopharma have created a landscape worth examining as a prime example of the intersection of technological innovation and opportunism all aimed at improving patient care.

Disease landscape and biology

Before delving into the market dynamics behind innovation in PC, it is important to understand the biology driving the large unmet need and the demographics of the patient population. Overall, PC is the second most common cancer among men and represents 7% of newly diagnosed cancers in men globally[1]. This totals more than 1.2 million new cases diagnosed annually, with an associated 350,000 deaths[2]. As with most cancers, the risk of PC increases with age, and correspondingly, 85% of newly diagnosed cases are in individuals greater than 60 years old, with increased risk attributed to an accumulation of genetic mutations[3].

There is a high degree of inter- and intratumoral heterogeneity that makes cancer profiling difficult[4]. Despite this, the general mechanism of tumorigenesis and disease progression is well established. In general, as cellular homeostasis is disrupted and growth becomes irregular, mutations occur in both oncogenes and tumor suppressors, leading to progressively worse disease driven by aberrant androgen receptor function[5].

Disease staging is well defined in PC. It begins locally in the prostate, where mutations drive disease initiation leading to malignant cell transformation. Disease is usually diagnosed at this stage and treated with radiotherapy and/or prostatectomy if patient history suggests high risk of metastasis[6]. Patients whose disease is diagnosed early enough have a 99% survival rate over 10 years[3]. Unfortunately, many patients miss this early diagnostic window and present with metastatic lesions in lymph nodes and bones. These patients can be characterized as having castration-sensitive or castration-resistant prostate cancer (mCSPC or mCRPC, respectively), reflecting the sensitivity of tumor growth to androgen deprivation therapy (ADT)[6]. It is these two patient populations, comprising about 80,000 cases per year in the United States, that drive much of the dynamics of the PC transactional landscape[2,7,8]. Existing ADT-based therapies, including blockbuster standard of care Xtandi (enzalutamide) and abiraterone, eventually all fail. In fact, the median survival time for patients diagnosed with mCRPC is approximately two years[9]. It is ultimately for this reason that novel therapies and diagnostic solutions are so highly valued. The resulting PC market is characterized by high pharma interest at each phase of disease treatment — from diagnosis to surgery to therapy — all driven by the unmet need faced by patients with metastatic disease.

Market dynamics

We are witness to a confluence of landscape-shifting events in this $11 billion segment, including pharma inflection points for companies responding to patent expiration and generic entry, segment leader displacement, and novel technology introduction[10]. Overall, we have seen pharma transactions centered around PC assets (to include mergers and acquisitions, licensing, partnership and private equity deals) total over $17 billion since 2017 (Fig. 1). Concomitantly, we have seen investment into the space trend upwards as investors are enticed by the possibility of large financial gains following a series of high-profile transactions with leading pharmas in the space (for example, Eli Lilly, Novartis, AstraZeneca, Lantheus and Astellas). To put this into context, it is helpful to understand the dynamics of the sector and transaction landscape in the context of the patient treatment paradigm, which we will explore here.

Detection and diagnosis

Overall, PC detection is well managed with longitudinal tracking of prostate-specific antigen (PSA), as the cancer itself is slow growing and never causes problems for most[6]. However, PSA-based tracking is not without downsides, as there is a lack of any correlation between elevated PSA levels and the necessity to provide radical treatment for disease. In fact, the US Food and Drug Administration recommends against PSA-based screening in men over 70 (ref. 11). As such, industry generally relies on imaging-based approaches such as magnetic resonance imaging and biopsy to determine severity of disease. Although there are many approaches in the pipeline and available commercially through laboratory-developed testing that claim enhanced PC detection, including gene expression profiling and elucidation of novel biomarkers, perhaps more interesting in this category is the application of precision medicine approaches to inform treatment of disease once it is diagnosed. The PC segment

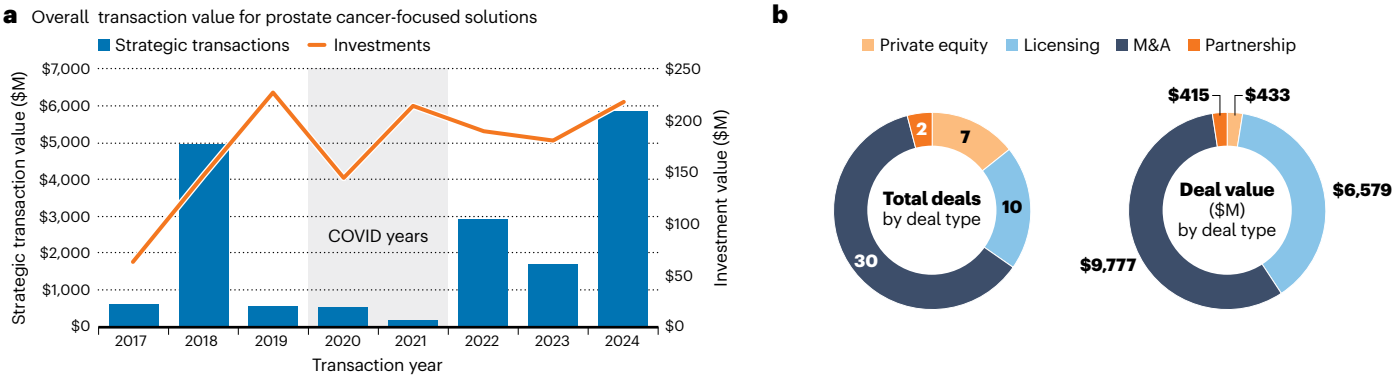

Fig. 1 | Summary of transactions surrounding prostate cancer–focused companies and assets. a, Non-venture capital-based deal activity (M&A, partnership, licensing and private equity deals), with total deal value in bars corresponding to the left vertical axis. Venture capital-based investments are highlighted by the line corresponding to the right vertical axis. The timeline is filled with multiple billion-dollar transactions from AstraZeneca and Merck (2024), Eli Lilly (2023), Lantheus (2022) and Novartis (2018). There is a notable dip in investment from venture capital firms and pharmas alike during the COVID-19 years (2020–2021), when resources were focused elsewhere. **b**, Transactional activity by both value and deal type. M&A transactions led the way in both frequency and value, reaching nearly $10 billion in total deal value. Licensing also played a large role in dealmaking, as it allows pharmas to mitigate risk by staging large payments behind achievement of clinical and commercial milestones.

represents a microcosm of the embrace of personalized medicine.

Tumor microenvironments and patients alike are very heterogeneous, with differing sensitivities and responses to cancer therapies[4,5]. Recent improvements in cost-effectiveness and in sensitivity and specificity of molecular diagnostic assays assessing patient genomic and proteomic backgrounds have allowed large companies to focus on targeted populations within indications to optimize therapeutic pipelines[12]. This approach reduces clinical risk while improving patient care, as trials can be designed around medications with a higher likelihood of reaching patients where they will have an effect. One such leader in the field, MDxHealth, is attempting to capture the entire PC patient diagnostic pathway from detection to confirmation and risk assessment. In 2022, MDxHealth acquired Exact Science's Genomic Prostate Cancer Score test from their Oncotype DX franchise for up to $100 million to bolster their PC screening and confirmatory tests, creating a one-stop shop for PC testing needs[13]. Additionally, the industry has seen the entrance of patient population stratification by homologous recombination repair (HRR) gene mutations via companion diagnostics, as well as the emergence of a new biomarker, prostate-specific membrane antigen (PSMA)[14]. Telix Pharmaceuticals and Lantheus Pharmaceuticals lead the space for detection of PSMA via positron emission tomography (PET) imaging. Lantheus acquired rights to its now US Food and Drug Administration (FDA)-approved Pylarify PSMA-PET imaging probe through a merger completed in 2020, before FDA authorization, that was fueled by clinical data and commercial promise of the then-emerging biomarker[15]. Capitalizing on this deal, Pylarify generated an estimated $800 million in revenues in 2023 (ref. 16). This singular asset in the PC space has transformed the growth profile of Lantheus — a fact noticed by competitors and partners alike as PSMA detection through PET imaging alone has enabled novel therapeutic approaches (PSMA-radioligand therapy) and combinations for patients with PC (detailed later) and has spurred an additional $1.5 billion in revenues annually.

Surgical

Surgical approaches are a common choice to treat PC if it has not spread outside the prostate gland (up to grade 2 PC)[6]. The rise in surgical robotics devices produced by companies like Intuitive Surgical with their da Vinci robotic systems has shown the effectiveness and success of minimally invasive robotic-assisted surgeries, particularly with prostatectomies[17]. The growth in urologic surgeries performed with robotic surgical systems is likely to increase as Intuitive Surgical acquired further FDA approval for their single-incision system for radical prostatectomy in early 2023 (ref. 18). As interest in robotic approaches to PC treatment rise, there has been a concomitant decline in the use of ablative procedures, either cold or heat-inducing, to kill cancer cells in treatment of PC. Cryotherapy and high-frequency ultrasound approaches are relatively new techniques for treating PC, and physicians remain unsure of the long-term efficacy of these approaches or whether recurrence rates will be higher than with simple removal of the diseased prostate early[19,20]. Despite this preference, the investment history surrounding the underlying and supporting technologies is remarkably similar. In the last five years, there has been approximately $4 billion invested in ablation technologies and surgical robotics through both private equity and pharma transactions. Much of the enthusiasm for both approaches lies outside of PC treatment, as ablation techniques are pursued heavily in cardiovascular conditions and robotic procedure growth has recently been driven by increased use in general surgery applications. In any event, much of the PC market dynamic is driven by cases wherein surgery is no longer an option and pharmaceuticals must be used.

Hormone therapy and combination approaches

Beyond surgery, often the first line of treatment for PC is ADT. A longtime leader in this class of PC treatment, Johnson & Johnson Innovative Medicine (J&J, formerly Janssen Pharmaceuticals) has seen a drastic erosion in US product sales since the entrance of generic versions of its blockbuster drug Zytiga (abiraterone acetate). US product sales in 2023 were just $50 million, down nearly 96% since their peak of $1.77 billion in 2018 (ref. 21). Further, despite an increase in volumes of sales of abiraterone globally, J&J has seen marked sales

erosion following generic introduction. To combat market share erosion from the once blockbuster drug, J&J is attempting to expand the pool of patients eligible for treatment. This can be done in several ways, but in the PC market, the approval of combination therapies, in addition to moving upstream in the disease progression pathway to treat non-metastatic and castration-sensitive forms of the disease, is frequently pursued.

Illustrating how value can also be added to a company's pipeline by expanding the number of patients eligible for therapeutics contained within that pipeline, we will be sticking with J&J's overall strategy in the segment. Their pipeline decisions showcase this strategy clearly. After achieving approvals for Zytiga in patients with mCRPC, mCSPC and high-risk mCSPC, it appears this total patient population is the upper limit in whom Zytiga given as a sole agent will be effective considering the mechanism of action[22–24]. J&J has since introduced Erleada (apalutamide), which has a different mechanism of action, to expand the patient population that can be treated with J&J drugs. This now includes mCSPC and non-metastatic castration-resistant prostate cancer, representing a gain of more than 250,000 patients eligible for monthly doses[7].

Exploring novel combinations to expand the utility and efficacy of existing drugs presents an opportunity for pharmas to enter partnerships with other global leaders in a way that spreads clinical risk among partners while also creating sizeable shared upside. J&J has explored and executed this strategy with combination clinical trials using new steroid approaches in new patient populations (Zytiga plus prednisone in patients with mCSPC), as well as joining AstraZeneca (and Merck) in a combination therapy using its poly(ADP-ribose) polymerase (PARP) inhibitor Lynparza (olaparib) alongside Zytiga as a first line treatment for mCRPC.

With J&J's fall from the top of the US PC market by revenue, we have seen the establishment of the Astellas and Pfizer drug Xtandi (enzalutamide) as the industry leader in sales, with $5 billion globally in 2023 (ref. 25). Similarly, Xtandi is facing a patent cliff in 2027 and is likely to see market share erosion as generic forms of Xtandi enter. Like Zytiga, Xtandi is indicated for use in patients with both mCRPC and mCSPC. Similarly, Pfizer, who owns rights to US sales of Xtandi, is seeking novel combinations to expand the eligible patient population, with FDA approvals for its own PARP inhibitor combination treatment of Xtandi plus Talzenna (talazoparib) for a subset of patients with certain HRR mutations. To further defend its position, Astellas acquired Propella Therapeutics for $175 million for its phase 1 abiraterone-based asset (abiraterone decanoate), diversifying the clinical mechanisms for which its drugs work while encroaching on territory of its biggest competitor globally, J&J[26]. Astellas has added PRL-02, a CYP17 inhibitor competing with Zytiga, to complement its androgen receptor inhibitor, thus combining the two most common treatment approaches into one therapeutic pipeline. This targeted approach aimed at a defined patient population not only showcases an attempt at expanding the eligible patient population, but also highlights how global pharmas are leveraging advances in molecular diagnostic technology to put personalized medicine approaches into clinical practice.

Next-generation therapies

While existing therapies benefit patients by enhancing overall survival and progression-free survival for a period, ADTs eventually all fail, leaving patients without options. To meet this need, there has been a flurry of transactional activity among industry leaders for both new treatment modalities as well as new drug targets. As previously mentioned, a major area of interest surrounds the exploitation of the PSMA, which is overexpressed in PC cells, to target various therapeutic agents specifically to tumor sites[14]. To unlock value in PSMA-targeting therapeutics, pharmas are developing and acquiring technologies to both visualize and treat PC. Radiolabeled therapies and imaging agents present ideal solutions to both effectively visualize and treat disease, but also introduce a novel modality to offer alternatives to ADTs that may overcome some common resistance mechanisms that plague the industry. These technologies work in tandem to both diagnose PSMA elevation and immediately follow up with an α-emitting radionuclide to kill cancerous cells. This approach is being seized upon by industry leaders such as Lantheus and Novartis. Lantheus is following up on their PSMA imaging capabilities to offer a therapeutic candidate via their exclusive licensing transaction with Point Biopharma for $260 million up front in cash considerations[27]. Eli Lilly later doubled down on Point Biopharma's promise in the radiotherapeutic space following the transaction with Lantheus by buying out all outstanding shares of Point Biopharma for roughly $1.4 billion[28]. Similarly, Novartis is expecting about $800 million in sales in 2024 (peak sales estimated at over $2 billion) following the approval of their radionuclide therapeutic Pluvicto in 2023. Pluvicto was the centerpiece of Novartis's $2.1 billion acquisition of Endocyte in 2018, showcasing the windfall that effective therapeutics can bring, even within a relatively small patient population such as those affected by metastatic PC[29]. Similarly, Bayer is jumping into PSMA-based radiotherapy with its acquisition of Noria Therapeutics and PSMA Therapeutics[30].

Beyond the resurgence of radiotherapeutics, the PC space is seeing several small molecule drugs with varied mechanism of action enter clinical development to offer alternatives to hormone-based therapies. The utility of precision diagnostic approaches to guide therapy development and patient treatment aids in unlocking mechanisms to attack 'undruggable' targets. Bolstered by the FDA approvals of $KRAS^{G12C}$-targeted therapies sotorasib and adagrasib for use in select groups of patients with non-small cell lung cancer, companies are seeking new KRAS targeting therapies for the G12C and G12D mutants seen in PC cohorts[31].

A major market factor that is likely to change the investment strategies of venture capital groups and industry leaders alike is the Inflation Reduction Act, signed 16 August 2022 (ref. 32). For the first time in the United States, pharmaceutical manufacturers must deal with a European-style downward pricing pressure placed on new therapeutics by government payers via an assessment of a maximum fair price. The process also sets molecule class-based timelines during which drugs can avoid government pricing controls. Small molecule drugs come under the mandate of Medicare price controls 7 years after FDA approval, while large molecule therapies (including important drug classes like monoclonal antibodies and cell and gene therapies) avoid Medicare-controlled pricing for 11 years after FDA approval[33]. Depending on the indication targeted, this 5-year difference can represent a loss in billions in sales for an effective small molecule. While reduced costs for effective medications benefits the American patient, there may be downstream effects on investment decisions by venture capital groups for companies with promising early-stage small molecule clinical assets and by large pharma groups as they evaluate opportunities for mergers and acquisitions (M&A). The price protection afforded large molecule therapies has created a scenario whereby investment decisions by groups

mandated to return capital to investors or partners could be skewed away from promising small molecule drugs, which comprise the bulk of all medicines taken today, and into novel biologic therapies that may or may not reach the same patient population. As such, there may be more transactional interest in large molecule therapeutics like antibody–drug conjugates, monoclonal antibodies and cell therapies in the PC space.

Conclusions

The PC segment represents one of the most well defined and stratified patient populations among the many specific cancer indications. A defined mechanism of action and well-established clinical practices allow pharmas to develop drugs to precisely target specific patient populations. With this backdrop, we can see universally applied strategies for these companies to maintain or gain market leadership applied within this segment. Both new and old technologies are often tested in combination to gain advantageous new labels for existing products. Personalized medicine approaches to define individual patient tumor conditions are being leveraged to enable new combinations and diagnostic technologies. Additionally, pharmas are constantly seeking to introduce new treatment modalities in a market dominated by ADTs to gain a foothold in an $11 billion market. As the ebb and flow of market leadership and product revenues continue, we expect to see additional transformational acquisitions, opportunistic licenses and the entrance of more treatment modalities as pharmas aim for a majority share of a relatively small patient population.

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Competing interests

The authors declare no competing interests.