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Precision medicine for advanced prostate cancer

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Abstract

Purpose of review—Precision cancer medicine, the use of genomic profiling of patient tumors at the point-of-care to inform treatment decisions, is rapidly changing treatment strategies across cancer types. Precision medicine for advanced prostate cancer may identify new treatment strategies and change clinical practice. In this review, we discuss the potential and challenges of precision medicine in advanced prostate cancer.

Recent findings—Although primary prostate cancers do not harbor highly recurrent targetable genomic alterations, recent reports on the genomics of metastatic castration-resistant prostate cancer has shown multiple targetable alterations in castration-resistant prostate cancer metastatic biopsies. Therapeutic implications include targeting prevalent DNA repair pathway alterations with PARP-1 inhibition in genomically defined subsets of patients, among other genomically stratified targets. In addition, multiple recent efforts have demonstrated the promise of liquid tumor profiling (e.g., profiling circulating tumor cells or cell-free tumor DNA) and highlighted the necessary steps to scale these approaches in prostate cancer.

Summary—Although still in the initial phase of precision medicine for prostate cancer, there is extraordinary potential for clinical impact. Efforts to overcome current scientific and clinical barriers will enable widespread use of precision medicine approaches for advanced prostate cancer patients.

Keywords

BRCA2; castration-resistant prostate cancer; DNA repair; genomics; precision medicine; prostate cancers

INTRODUCTION

Precision cancer medicine, the use of genomic profiling at the point-of-care to inform treatment decisions (Fig. 1), is changing cancer care by enabling more accurate and efficient

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Conflicts of interest

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prediction of therapies for individual cancer patients. This revolution is the result of numerous studies identifying key cancer drivers, their alterations, and therapies to specifically target these alterations [1]. More recently, multiple cancer landscape studies have provided further insight into the alterations within and between tumor types [2]. That success, along with the increased affordability and reliability of sequencing, and development of computational tools for clinical genomic analysis, has led to the integration of genome science directly into clinical practice. Tight networks and collaboration between clinicians, genome scientists, and pharmaceuticals companies will continue to advance precision medicine [3–5].

Prostate cancer is the most common solid tumor in men in the USA [6]. Prostate cancer is a hormone-dependent tumor, demonstrated by recurrent alterations in the androgen receptor and its pathway [7]. Castration-resistant prostate cancer (CRPC) is a lethal clinical state in which the tumor has developed resistance to androgen deprivation therapy. This occurs in the majority of advanced or metastatic prostate cancer patients. The genomic landscape of localized prostate cancer has been well defined [8–11,12■■,13–15]. Multiple studies have highlighted the lack of highly recurrent clinically actionable alterations, as well as the high level of tumor intraheterogeneity even in the primary setting [15,16]. In contrast with the primary prostate cancer genome, the extensive mutational landscape of metastatic CRPC lesions has exposed the possibility of targeted therapies and precision medicine in CRPC [17■■]. In this review, we discuss the potential of genomics to impact the clinical management of CRPC, and consider the challenges that must be overcome to enable wide implementation in the clinic.

CURRENT THERAPEUTIC APPROACHES FOR CASTRATION-RESISTANT PROSTATE CANCER

In the CRPC setting, the primary successful therapeutic target remains the androgen receptor. The discovery of androgen receptor, along with the persistent unearthing of androgen receptor resistance mechanisms, has enabled additional effective treatments in CRPC patients [7,18–21]. Approved therapies in this space include new androgen synthesis pathway agents, such as abiraterone, and direct inhibitors of androgen receptor, such as enzalutamide [22–28]. However, the majority of CRPC patients ultimately develop resistance to androgen receptor-focused therapies, despite multiple new agents reaching the clinic. Furthermore, there are many patients who never respond to these therapies and manifest intrinsic resistance to this therapeutic approach. Generally, almost all patients with CRPC ultimately succumb to the disease.

Genomics and lethal prostate cancer

Studies examining the genomic alterations involved in lethal prostate cancer from autopsy cohorts revealed the underlying biology behind the disease and the evolutionary processes driving advanced disease [29,30■■,31,32■■]. Despite these crucial insights, these studies did not have clinical cohorts to explore the landscape of potential clinically actionable targets. Recently, a study examined 150 metastatic site biopsies from living patients with CRPC through integrative whole-exome sequencing (WES) and whole transcriptome

sequencing [17■■]. A high number of targetable mutations, defined as predicting response or resistance to a therapy, or having a diagnostic or prognostic utility, were found in these patients, in contrast to localized prostate cancer. Not including androgen receptor, 65% of patients had a targetable mutation, many of which have been linked to ongoing clinical trials (Table 1). The details of these findings are described below.

Androgen receptor

Numerous studies have addressed the androgen receptor and its pathway alterations in metastatic CRPC [7,29,30■■,31,32■■]. Despite reduced androgen circulation in CRPC, androgen receptor is still activated through various mechanisms, including androgen receptor amplification or overexpression, activating androgen receptor mutations, alterative androgen production, androgen receptor coactivator overexpression, and indirect androgen receptor activation [33]. Robinson *et al.* presented that 34% of CRPC patients still have only androgen receptor as a clinically relevant mutation, indicating they may be differentially sensitive to existing and novel androgen receptor-directed therapies. However, the clinical significance of these androgen receptor mutations for predicting response or resistance to these agents remains to be determined. Although several drugs have shown promise targeting androgen receptor in this space, including abiraterone and enzalutamide, most patients eventually develop resistance to these agents [23,25,26]. Recently, it was reported that patients with androgen receptor-V7 splice variant, in the transcriptomic data, may be resistant to enzalutamide but respond to galeterone, a novel androgen receptor therapy currently in phase III trials [34■,35], potentially demonstrating the first genomically driven therapy in CRPC. Furthermore, there are numerous experimental agents that target androgen receptor or its pathway in novel ways (Table 1) that may augment the ability to effectively inhibit this dominant pathway in patients with tumors that are still wholly dependent on androgen receptor signaling.

DNA repair pathway

Beyond the androgen receptor pathway, the most striking result from clinical genomic profiling of CRPC patients was that 19% of patients have a DNA repair pathway alterations, including 12.7% of patients with a putative pathogenic *BRCA2* germ line mutation [36,37]. Additional somatic and germ line DNA repair alterations were found in *ATM, BRCA1, CDK12, FANCA, RAD51B*, and *RAD51C*. Many of these alterations are associated with platinum response in other cancer types [38–40]. In addition, PARP inhibition demonstrated great efficacy in patients with *BRCA2* mutations and other DNA repair alterations in CRPC and other tumor types [41■■]. Mateo *et al.* conducted a phase II trial of olaparib plus genomic correlates in 50 CRPC patients. A total of 16 of the 50 patients harbored DNA repair gene inactivation alterations, and 14 out of those 16 patients responded to olaparib [41■■], highlighting another potential genomically driven therapy in CRPC. Based on these findings there are currently multiple clinical trials testing the effects of PARP inhibitors with or without androgen receptor-targeted therapies in CRPC patients, demonstrating the rapid impact of this DNA repair genomic discovery on realizing precision medicine for prostate cancer.

Phosphoinositide 3-kinase pathway

The phosphoinositide 3-kinase (*PI3K*) pathway is recurrently mutated in CRPC, commonly through loss of *PTEN*, amplification of *PIK3CA/B*, and activating mutation of *PIK3CA/B* and *AKT1* [42]. In Robinson *et al., PI3K* pathway was altered in 49% of patients, making it the second most frequently altered pathway after androgen receptor. In the past, many *PI3K* monotherapies have had a lack of efficacy, thought to be because of lack of specificity, coexisiting alterations, and signaling feedback [43■]. Recently, multiple inhibitors of specific *PI3K* isoforms have begun testing in clinical trials, potentially increasing the specificity of these agents. In CRPC, there are recurrent mutations in *PIK3CB* and frequent loss of *PTEN*, which may activate *PIK3CB* over *PIK3CA* [44], emphasizing the need for these specific *PI3K* isoforms inhibitors [45,46] to effectively clinically target this pathway. There has also been evidence that there is cross-pathway interaction between *PI3K* and homologous recombination pathway, indicating that patients with *PI3K* pathway alterations may respond to PARP inhibitors as well [47–49].

WNT pathway

In Robinson *et al.,* 18% of metastatic CRPC patient are presented with mutation in WNT pathway, including activating *CTNNB1, APC, RNF43, RSPO2*, and *ZNRF3* mutations. Furthermore, a recent study of CRPC patients' circulating tumor cells demonstrated an upregulation of WNT signaling in this clinical setting [50]. Historically, the WNT pathway has been extremely difficult to target because of the multitude of receptors, ligands, and downstream pathways [51]. The WNT pathway has many imperative biologic functions from embryonic development to tissue homeostasis and is activated by proteins secreted by tumor cells as part of an autocrine loop, or they may be produced by surrounding stromal cells, increasing the difficulty of targeting this pathway. The WNT pathway is also thought to be activated in cancer stem cells, which are thought to drive resistance to many therapies [52■]. Although it is known that the WNT signaling pathway is altered in CRPC, it is unknown whether an antagonist or agonist would work better to inhibit growth. There is contradicting evidence in multiple tumor types whether activation or repression of the pathway increases survival. Evidence also supports β-catenin signaling in dictating tissue-specific predisposition to *APC*-driven tumorigenesis [53], helping to indicate whether a repressor or activator would work best. This is again demonstrated by the contradicting therapeutics currently in clinical trials (Table 1): Foxy-5 activates the WNT pathway, whereas OMP-54F28 inhibits the pathway. Efficacy data will inform their utility in this clinical setting. Additional preclinical and clinical studies are needed to determine how to best target this pathway in CRPC. It is also known that all of the WNT pathway therapeutics have had significant toxicities associated because of the wide range of functions of the WNT pathway [54].

Cell cycle pathway

Loss of *RB1* was seen in 21% of metastatic biopsies versus 1% in localized prostate cancer [15,17■■]. Less common cell cycle pathway alterations including mutations in *CDKN2A/B, CDKN1B*, and amplifications of *CCND1*, were seen. The major role of the cell cycle pathway is to stop mitosis to allow for DNA repair via the inhibition of cyclin-dependent

kinases (CDKs) and *RB1* phosphorylation [55]. *CDK4/6* inhibition can induce cell cycle arrest and cancer cell senescence. Currently, there is one *CDK4/6* inhibitor approved in breast cancer, and multiple other *CDK4/6* and pan-CDK inhibitors in clinical trials [56]. In CRPC, there are multiple trials for *CDK4/6* inhibitors (Table 1). There are known resistance to these drugs, including Rb-negativity and a lack of codeletion of *CDKN2A/CDKN2B* in glioblastoma, indicating any trial with these compounds must be genomically driven and may be relevant in CRPC [57].

Immunotherapy

The most mature effort for CRPC immunotherapy is sipuleucel-T, a cell-based immunotherapy, which is Federal Drug Administration approved [22]. It is created using mature, autologous antigen-presenting cells obtained from patients. However, this approach has thus far not resulted in clinical benefit in stratified patient subsets. In order to expand immunotherapy approaches in the setting of success in other tumor types, multiple checkpoint inhibitors have been testing in CRPC, although thus far, these therapies have had limited clinical results [58]. Notably, multiple studies have recently demonstrated a correlation between response to immune checkpoint inhibitors and mutational burden [59■■–61■■]. A subset of CRPC patients has a high mutation load because of alterations in mismatch repair genes, *MLH1* and *MSH2.* Thus, CRPC patients with a high mutational burden may benefit greatly from immunotherapy, such as a checkpoint inhibitor, and future efforts geared toward determining whether this relationship holds across CRPC patients may inform the clinical utility of checkpoint inhibitors in the CRPC setting.

TECHNOLOGIES FOR ENHANCING PRECISION MEDICINE IN CASTRATION-RESISTANT PROSTATE CANCER

Despite continuous advances in high-throughput genomic sequencing technologies and their utilization in cancer, there are several challenges in successful implementation of precision medicine in CRPC (Table 2). For example, access to tumor tissue for profiling is especially complicated because of the need to obtain metastatic biopsies, including bone metastasis [62] and the low percentage of cancer cells in many of these samples. Although it has been demonstrated that sequencing tumor from bone biopsies is feasible, these approaches are difficult and require much expertise [63■]. There is also the reality that not all patients can get a biopsy or that the capacity of interventional radiology facilities will permit biopsy sampling in all patients. Moreover, a single biopsy may not capture the extent of disease. As demonstrated in localized prostate cancer and by studying multiple metastatic sites from individual patients, there is significant intra-tumor heterogeneity in prostate cancer [30■■]. If a patient has multiple metastatic sites, only sampling one, may not demonstrate the biology of the whole tumor. In addition, one must also consider the possibility of not finding any targetable genetic alteration in a patient’s tumor. With additional genomics research and novel therapeutics, this possibility will decrease.

A potential technology that may address difficulty in obtaining biopsies, and tumor heterogeneity in CRPC is the use of liquid biopsy techniques. One such approach involves the use of circulating tumor cells (CTCs) to identify genomic alterations of CRPC. CTCs

have been demonstrated to have a reasonable readout of the tumor genomic landscape in patients with CRPC [64]. Circulating tumor DNA (ctDNA) is another novel way to identify genomic alterations and track patient's genomic landscape over time [65■]. In other tumor types, WES has been performed from ctDNA [66■■], indicating metastatic biopsies may not be needed in the future. These technologies may also help us identify patients who are developing resistance earlier than a radiological scan [64,67,68]. As seen in multiple other cancer types, the genomic profile of tumors after treatment is often very different [69■,70■]. From a clinical standpoint, early detection of resistance is crucial to optimizing therapy, and the use of ultradeep sequencing in multiple regions of a biopsy, together with monitoring of tumor evolution using ctDNA could provide this information [71■].

CLINICAL STRATEGIES TO IMPLEMENT PRECISION MEDICINE

A major logistical challenge toward implementing precision medicine in CRPC and across cancer types is building an infrastructure for genomic sequencing in cancer, including collecting tissue, genomic alterations testing, genomic analysis, and reporting results back to patients [72■■,73■■,74–77]. Another limitation to genomic sequencing is cost. Although the cost of genomic sequencing is continuously decreasing, it is rarely covered by insurance [78], causing limited access to many patients [79]. In addition, once genomic alterations are identified, it is often difficult for patients to get access to affordable medication [80]. Finally, owing to the small percentage of patients with particular genomic alterations, new clinical trial schemas have been developed to support ongoing precision medicine therapeutics.

Two efficient ways to test the effects of multiple drugs is through a basket or umbrella trial (Fig. 2a and b). These trial schemas have been well demonstrated in lung cancer [81] and are currently a declared initiative of the National Institutes of Health (NIH). The National Cancer Institute program, a large basket trial initiative, will include 3000 patients with different types of cancer to find early signals of a response to targeted therapies. Basket trials test the effect of a single drug targeting a specific molecular alteration in a variety of cancers. This design not only allows for a faster identification of candidate patient, but also to assess the potential value of this targeted therapy across different tumor types. An umbrella trial assesses the effect of different drugs in different molecular alterations either in one or several tumors. This would involve sequencing the tumors of all men with CRPC, and placed in the appropriate slot based on the genomic profile. One additional challenge to umbrella trials is identifying the correct driver mutation. Ongoing efforts to identify and rank known driver mutations [72■■] should help place patients in the appropriate slot. These trial schemas will also help drug development for less common alterations. Implementing either of these trial schemas for CRPC will allow expedited identification of targeted therapies that work well in this setting.

CONCLUSION

The concept of precision medicine driven by genomics for CRPC is appealing; however, it is in its infancy. We must continue to obtain additional genomic information and correlate this with therapeutic response. Developing catalogues of CRPC cancer-related genes, together assessments of pathway activation could enable a better identification of additional driver in

the future. The characterization of the genomic landscape of tumors and of the activated protein network will guide combination therapies to optimize therapeutic effects. Finally, logistics and operational challenges need to be addressed.

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KEY POINTS

- Precision medicine shows great promise in advanced prostate cancer, but it is still in the initial stages.
- Advancement in prostate cancer precision medicine is dependent on continuous research in prostate cancer genomics and correlation with response to current and novel therapies.
- Expansion of liquid biopsy techniques, such as circulating tumor cells or cell-free DNA, may be especially impactful in precision medicine for CRPC.

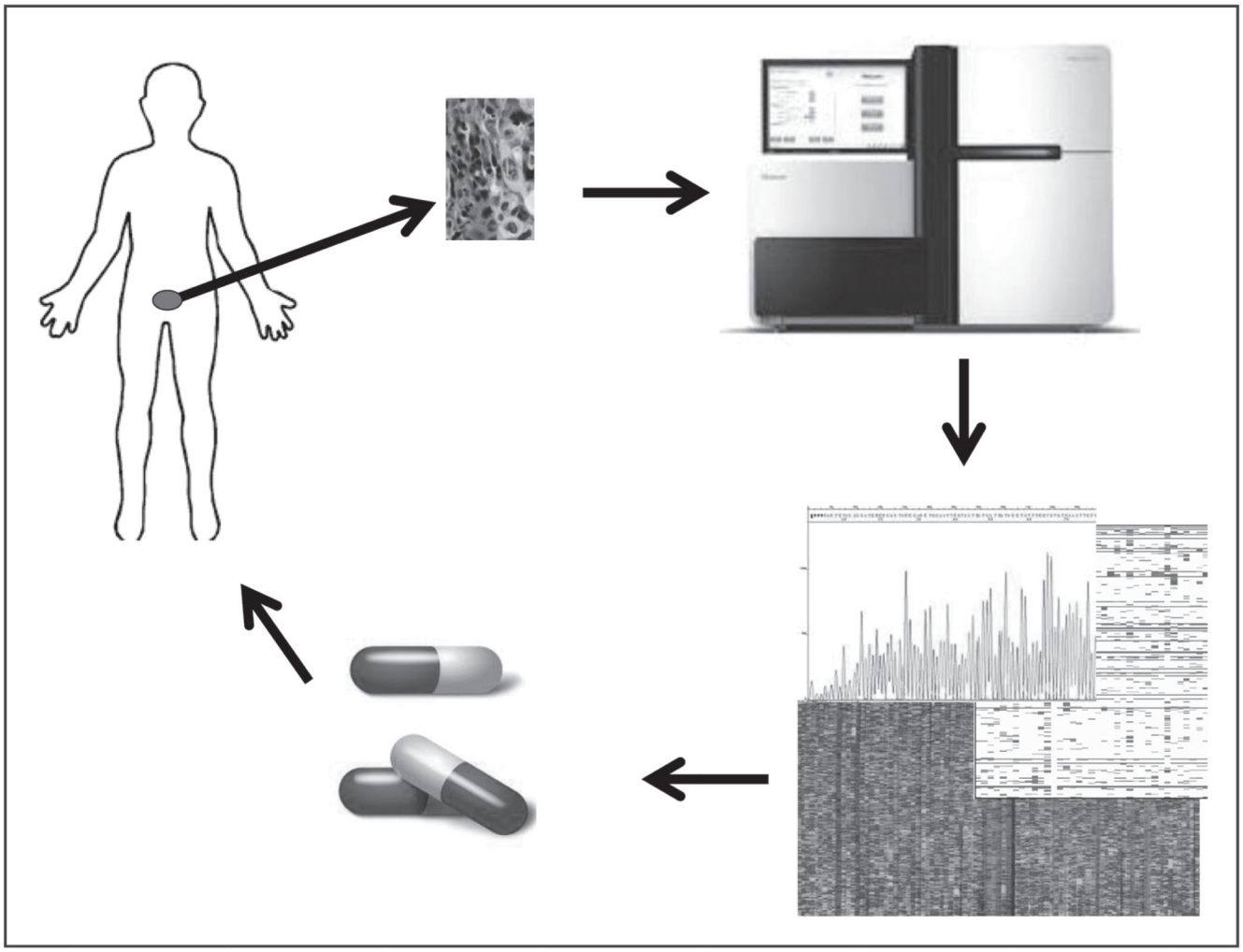

FIGURE 1.

Precision medicine in advanced prostate cancer revolves around the ability to take a tumor sample, ideally metastatic tumor, sequence the tumor, and assign therapy to the patient. This involves biopsy of tumor tissue, DNA/RNA extraction, WES/WGS/Transcriptome sequencing, bioinformatics interpretation of results, and assignment of treatment based on therapeutic profile. This process may be repeated as needed when patients progress. WES, whole-exome sequencing; WGS, whole genome sequencing.

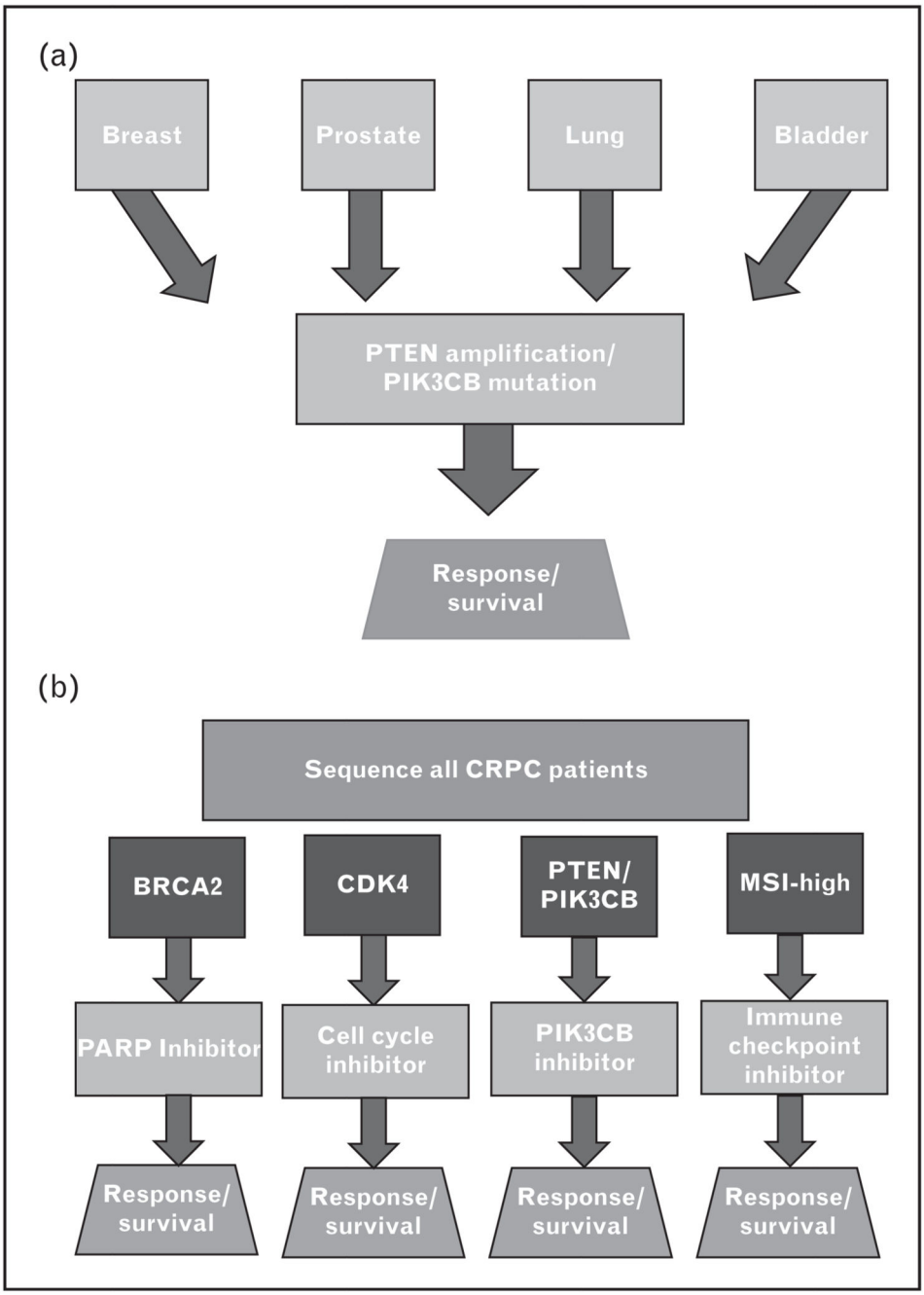

FIGURE 2.

Basket trials (a) and umbrella trials (b) are two approaches to precision medicine with novel therapeutics in advanced prostate cancer. (a) Basket trials take patients with multiple different tumor types with the same genetic alteration to test a single therapeutic. This allows for fast identification of potential patients and tests the drug/alteration across different diseases quickly. (b) Umbrella trials test the effect of different drugs on different genetic

alterations within the same disease type. This allows for increase accrual of all advanced prostate patients and tests multiple drug/genomic alteration combinations at the same time.

Table 1

Ongoing clinical trials in advanced CRPC with potential precision medicine applications

	Gene	Potential therapeutic	Current clinical trials/therapies*	Phase
Androgen receptor	Androgen receptor	Mifepristone (RU-486)	NCT00140478	Phase 2
		Mifepristone/enzalutamide	NCT02012296	Phases 1, 2
		Galeterone	NCT02438007	Phase 3
		GTx-758	NCT01615120	Phase 2
		VT-464	NCT02445976	Phase 2
		Trilostane	NCT00181597	Phase 2
		AZD3514	NCT01162395	Phase 1
		Orteronel (TAK-700)	NCT00569153, NCT01809691, NCT01809691	Phases 1, 2, 3
		Triamcinalone	NCT00186108	Phase 1
Immunotherapy		Ipilimimab + ADT	NCT01377389	Phase 2
		AR DNA Vaccine	NCT02411786	Phase 1
		Ipilimimab	NCT00170157	Phase 2
		BNIT-PR-001		Phase 1
PIK3CA	PIK3CA	Buparlisib (BKM120)	NCT02487823	Phase 1
	PIK3CB	AZD8186	NCT01884285	Phase 1
	PIK3CB	GSK2636771/enzalutamide	NCT02215096	Phase 1
	PIK3CB	GDC-0068/abiraterone	NCT01485861	Phase 2
Cell Cycle	BCL-2	Navitoclax/abiraterone	NCT01828476	Phase 2
	CDK4/6	Ribociclib	NCT02555189	Phases 1, 2
	CDK4/6	PD 0332991	NCT02059213	Phase 2
DNA damage	PARP	Niraparib/enzalutamide	NCT02500901, NCT00749502	Phase 1
		Olaparib/enzalutamide	NCT01972217	Phase 2
		BMN 673	NCT01286987	Phase 1
		Veliparib	NCT00892736	Phase 1
WNT	WNT	Foxy-5	NCT02020291	Phase 1
		OMP-54F28	NCT01608867	Phase 1

* List collected October 2015.

Table 2

Logistical and scientific challenges in CRPC precision medicine initiatives

	Challenge	Description	Potential solutions
Logistical challenges	Genomic testing infrastructure	Setting up genomic testing in a hospital requires infrastructure with pathology, clinician, bioinformatics, information systems, and many more	Have key academic centers for testing and distribute results to community centers
	Cost of genomic testing	In nonacademic centers, genomic testing is run by private companies	Allow testing to be covered by insurance or make low cost testing available
	Metastatic biopsies	Biopsy is not feasible in all patients	Collection and sequencing of CTCs
	Testing target therapeutics in CRPC	Although we know there are therapeutics that work with many of these targets in other diseases, these therapeutics must be testing in CRPC	Designing basket and bucket trials to test multiple targets or therapeutics at the same time
Scientific challenges	Tumor intraheterogeneity	CRPC is known to have a lot of heterogeneity in the primary specimen, by biopsying one metastatic lesion, it is unknown if we see the entire genomic picture.	Future studies should focus on heterogeneity in the metastatic setting
	Lack of targetable mutations	Not all patients will have an oncogenic driver because of a low number of genes screened	Perform WES, RNA or protein based assays on these patients
	Secondary resistance	Although patients may respond to a targeted therapy, most will develop resistance. Posttreatment biopsy tumor samples may have a different genomic profile than pretreatment	Track patient progress using ctDNA or CTCs. Test and provide combination therapy for patients
	Identification of driver mutation	Some patients may present with multiple targetable mutations	Use heuristic and predictive modeling to determine which mutation is best to initially target.

CRPC, castration-resistant prostate cancer; CTCs, circulating tumor cells; ctDNA, Circulating tumor DNA; WES, whole-exome sequencing.