Translational and clinical implications of the genetic landscape of prostate cancer

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Abstract

Over the past several years, analyses of data from high-throughput studies have elucidated many fundamental insights into prostate cancer biology. These insights include the identification of molecular alterations and subtypes that drive tumour progression, recurrent aberrations in signalling pathways, the existence of substantial intertumoural and intratumoural heterogeneity, Darwinian evolution in response to therapeutic pressures and the complicated multidirectional patterns of spread between primary tumours and metastatic sites. However, these concepts have not yet been fully translated into clinical tools to improve prognostication, prediction and personalization of treatment of patients with prostate cancer. The current and future clinical implications of 'omics' level knowledge is not only revolutionizing our understanding of prostate cancer biology, but is also shaping ongoing, and future clinical investigations and practice. In this Review, these advances are summarized, and the remaining challenges surrounding tumour heterogeneity and the ability to overcome treatment resistance are described.

Historically, the decision-making processes regarding the prognosis of patients with prostate cancer, and the optimal therapeutic approach have been driven by clinical and pathological variables such as tumour stage, Gleason score and serum PSA levels(1, 2). However, new insights into the genomic aberrations underlying prostate cancer are rapidly transforming the diagnosis and treatment of patients with this disease, from early detection through to treatment of late-stage tumours. Characterizing the molecular landscape of prostate cancer through 'omics' level analyses has, historically, been technically challenging owing to the small size of the available diagnostic specimens (usually core biopsy samples), the difficulties in identifying tumours grossly at the time of resection (for procurement of fresh tissue for high-quality nucleic acid isolation) and the difficulties in obtaining highly pure samples of the tumour population, owing to the presence of large amounts of stroma and normal tissue within cancer foci.

Characterizing the genomic landscape of metastatic prostate cancer that has progressed despite castration levels of serum testosterone, as induced by gonadotrophin-releasing hormone agonists (a form of androgen deprivation therapy; ADT), termed castration-resistant prostate cancer (CRPC), has been even more challenging given the lack of biopsy sampling of metastases in routine clinical practice and the difficulties in obtaining quantitatively and qualitatively adequate tissue from metastatic sites, such as bone. Nevertheless, data from multiple rigorous, large, whole genome, exome and/or transcriptome sequencing studies have revolutionized our understanding of the genomic processes underlying the development and evolution of prostate cancer(3-11). For example, DNA copy-number alterations (CNAs) and chromosomal rearrangements, compared with point mutations or small insertion and/or deletion (indel) mutations, are more frequently observed alterations in patients with prostate cancer(3). Importantly, higher burdens of CNAs and other mutations have been observed in patients with more-aggressive prostate tumours in numerous studies, and correlate with clinical outcomes(3-6, 10, 12).

Despite these advances, application of these insights into clinical decision making, particularly for patients with metastatic disease, remains in its infancy and therapeutic strategies are largely driven by the presence, and extent of routine clinical and pathological factors. Over the next decade, insights from genomics are likely to have a much more prominent role in drug development, prognostication, patient selection, monitoring treatment response and/or resistance, and clinical practice as a whole. In this Review, we outline a selected number of important genomic alterations in prostate cancer, and the clinical implications of these discoveries (Table 1).

Molecular subtypes

Findings of gene expression profiling, exome sequencing and candidate gene-based studies have provided robust evidence supporting the existence of a range of molecular subtypes of prostate cancer, based largely on the presence or absence of gene fusions involving members of the ETS gene family of transcriptional regulators (most commonly *ERG*, *ETV1*, *ETV4*, *ETV5* and *FLI1*). Fusions juxtaposing the non-coding androgen-driven promoter elements of the transmembrane protease gene *TMPRSS2* to nearly full length *ERG* (*TMPRSS2–ERG*

fusions) are the most common ETS gene fusions observed in prostate cancer biopsy samples, occurring in approximately 40–50% of all tumours in PSA-screened, predominantly white populations. Alterations occurring exclusively in the approximately 50-60% of prostate tumours that are *ETS* fusion-negative (*ETS⁻*) include overexpression of the serine peptidase inhibitor gene *SPINK1*, recurrent point mutations in the transcriptional repressor gene *SPOP*, loss and/or mutation of the DNA-binding protein *CHD1*, and RAS/RAF family gene fusions or mutations(10, 11, 13, 14). Data from gene expression profiling studies support the distinction of ETS fusion-positive (*ETS⁺*) and *ETS⁻* tumours; furthermore, findings of several studies[15–17], including those from the The Cancer Genome Atlas (TCGA) multi-omics profiling study[17], support the distinction of *ETS⁺* tumours into those with *ERG* fusions (*ERG⁺*, comprising approximately 90% of all *ETS⁺* tumours) and those with fusions involving non-*ERG* members of the ETS family (occurring in approximately 5–10% of all *ETS⁺* tumours)(15-17).

Other than *TMPRSS2–ERG* fusions, the development and progression of most prostate cancers seems to be driven by a variety of diverse, low-frequency oncogenic events. Owing in part to this genetic diversity, research by the TCGA has resulted in a large number of primary prostate cancer molecular classes being described (seven in total). These subtypes are defined by the presence of genetic alterations that are, essentially, mutually exclusive: *ERG* fusions (46%), *ETV1* fusions (8%), *ETV4* fusions (4%), *FLI1* fusions (1%), *SPOP* mutations (11%), *FOXA1* mutations (3%) and *IDH1* mutations (1%)(17). However, even within these subgroups, marked genetic diversity exists in terms of mutations, copy number alterations, gene expression and DNA methylation, and several common alterations can occur across different molecular classes (for example, chromosome 8q gain or *PTEN* deletion). Moreover, 26% of prostate cancers could not be classified into one of these seven subgroups[17], suggesting that even more genetically distinct molecular subtypes are likely to be uncovered in the future.

Androgen signaling

The androgen receptor

Androgen signalling has been the principle focus of medical treatment of prostate cancer since the discovery by Huggins and Hodges that surgical castration of men with advanced-stage prostate cancer resulted in tumour regression(18). The androgen receptor (AR) signalling axis is the most clinically targeted pathway in patients with both untreated prostate cancer (who are castration-sensitive) and in those with CRPC. Lowering serum testosterone levels, or more specifically, dihydrotestosterone (DHT) levels, activates a feedback loop that increases transcription of the *AR* in prostate cancer cells(19, 20). This paradoxical increase in AR expression and signalling is hypothesized to lead to DNA strand breaks, which might be responsible for the resulting *AR* amplifications seen in 20–55% of CRPC samples, which is the most common mechanism of developing CRPC(21, 22). In the majority of patients with newly diagnosed CRPC, *AR* overexpression is driven by these DNA strand breaks, resulting in X chromosome rearrangement and subsequent focal *AR* copy number gain(5). High-level, focal *AR* amplifications are almost never (in <1% of patients) identified in patients with untreated, localized prostate cancer, but as described

above, are much more common in those with CRPC, usually after prolonged exposure to ADT(3-5, 10, 11, 23-27). Mutations in the *AR* itself are less common than amplifications of the *AR* and are found in 2–18% of prostate cancer specimens in mCRPC(28, 29). The resulting overexpression and mutation of *AR* has important clinical implications for treatment resistance, promiscuous effects of other adrenal steroids, and even the conversion of first-generation AR antagonists to agonists(30).

Owing to the dependency of prostate cancer on AR signalling, multiple clinical attempts to further suppress AR signaling activity have been made. Most notably, CYP17A1 inhibitors (such as abiraterone) and second-generation anti-androgens (such as enzalutamide) that reduce ligand availability or compete for the ligand-binding domain (LBD) of the AR, respectively, have been developed and shown to confer survival benefits in patients with CRPC(31-35). The added benefit derived from use of second-generation anti-androgens is not only the more complete blockade of the AR compared with first-generation anti-androgens , but also the prevention of nuclear translocation of the AR and the subsequent downstream activation of AR-target genes(36, 37). Enzalutamide, the first FDA-approved, second-generation anti-androgen has demonstrated improvement in overall survival in both the pre-docetaxel and post-docetaxel setting in patients with CRPC, and is currently being tested as a treatment of patients with early-stage prostate cancer(31, 32). A structurally similar compound, ARN-509, has also shown promise in early-phase clinical trials and is current being tested in a phase III randomized clinical trial (NCT01946204)[167] in patients with non-metastatic CRPC (TABLE 2)(34, 37). A third, structurally distinct, second-generation AR antagonist, ODM-201 has also shown promise in phase I clinical trials as a treatment of both metastatic and non-metastatic CRPC(38, 39). Similar to ARN-509, ODM-201 is currently being evaluated in a phase III trial in patients with non-metastatic CRPC (NCT02200614)[168].

Despite widespread clinical use of CYP17A1 inhibitors or second-generation AR antagonists in patients with CRPC, no prospectively validated clinical biomarkers that enable accurate prediction of a response to treatment currently exist. *AR* amplifications and/or mutations detected in circulating cell-free DNA are associated with resistance to abiraterone and enzalutamide in patients with metastatic CRPC(40). Additionally, data from transcriptome analysis has revealed that acquired resistance to ARN-509 or enzalutamide correlates with glucocorticoid receptor (GR) upregulation(41), and high levels of GR expression have been associated with resistance to neoadjuvant androgen deprivation(42). The effectiveness of combined AR and GR inhibition is being testing in an early phase clinical trial combining enzalutamide with the GR antagonist mifepristone (NCT02012296)[169]. The identification of truncated *AR* transcript isoforms, referred to as AR splice variants, or AR-Vs is a particularly exciting discovery with high relevance to predicting a response to AR-targeted therapy(43). These isoforms are missing an LBD, but retain the ablty to code for the DNA binding and transactivation domains. Furthermore, the presence of specific AR-Vs, in comparison to the full-length *AR*, appears to drive the development of distinct transcriptional profiles in patients with CRPC. For example, AR-V7 has been shown to upregulate a set of cell-cycle genes independent of full-length AR signalling, whereas the full-length AR induces upregulation of gene sets related to biosynthesis, metabolism and secretion that are largely not upregulated by AR-V7(44).

Furthermore, these AR-V splice variants are constitutively active and are not inhibited by standard first-generation or second-generation anti-androgens. As such, AR-V expression is associated with progression to CRPC(45, 46), resistance to anti-androgen therapy(47), and poor cancer-specific outcomes(48) compared with patients who do not express AR-Vs. For example, the presence of AR-V7 in circulating tumour cells (CTCs) is associated with resistance to abiraterone and enzalutamide, as demonstrated in a small clinical cohort study(47). These findings have demonstrated that the presence of AR-Vs in CTCs is a potentially powerful biomarker for the identification of patients that are unlikely to respond to therapies targetting the full-length AR protein. Assessments of clinical grade assays, performed prospectively in Clinical Laboratory Improvement Amendment-approved laboratories will be of critical importance to determining the predictive validity of AR-V7 detection. Likewise, whether AR-V7 expression is responsible for resistance to AR-targeted therapies, or is an indicator of other processes associated with resistance (for example, AR-V7 expression is often highest in patients with *AR* amplification) is unclear, and AR-V7 transcripts can be detected at low levels in both benign prostate tissue biopsy specimens, and those from patients with untreated prostate cancer(3).

Following the discovery of AR-Vs that could potentially confer treatment resistance owing to constitutive activity with a lack of a LBD, a series of new compounds that target other domains of the truncated AR protein have been developed. For instance, compounds that target the N-terminal domain (EPI-001; ESSA Pharma, Vancouver, Canada, ASO EZN-4167; Enzon pharmaceuticals, Florida, USA) and the DNA-binding domain (ISIS-ARRx, Ionis pharmaceuticals, California, USA) of the AR have demonstrated early potential as viable therapies in preclinical models(49-53) and in a phase I clinical trial[49]. These experimental therapies will need to demonstrate an acceptable level of specificity for the AR, with few, or no off-target effects; however, tremendous hope exists that these therapies could provide clinical benefits for patients whose tumors are no longer reliant on the LBD of the AR and are therefore resistant to anti-androgen therapy. Likewise, AR-directed therapies with combined mechanisms of action might enable targetting of both the full-length AR and AR-Vs. For example, based on data demonstrating efficacy in a small number of patients with AR-V7 expression in CTCs, a phase III randomized trial (NCT02438007)[170] has been initiated to test galeterone—a CYP17A1 inhibitor that also acts as a direct AR antagonist and degrades full-length and truncated AR versus enzalutamide in men with CRPC and AR-V7 expression, as confirmed by analysis of CTCs. Importantly, this trial is the first phase III trial in patients with prostate cancer to use the presence of a molecular biomarker as an inclusion criterion.

AR co-factors

A host of co-factors modulate the expression of downstream targets of the AR(54, 55). These include, but are not limited to, the forkhead protein FOXA1, the transcription factor GATA2, and the P160 steroid receptor co-activator proteins, NCoA-1, NCoA-2 and NCoA-3. Unlike *AR* mutations which are almost exclusively found in CRPC biopsy samples, mutations of these *AR* cofactors have been detected in both primary and metastatic tumours(3, 5, 11). When combining *AR* alterations and AR co-factor aberrations, 71% of patients with CRPC harbour AR signalling pathway aberrations(3).

FOXA1 interacts with the AR and serves as a pioneer co-factor that is capable of specifying unique AR binding sites(56). Additionally, FOXA1 is also able to a regulate metastatic potential in an AR-independent manner(57), thus development of an inhibitor of FOXA1 might hold some promise(58). GATA2 co-localizes with FOXA1 and AR on chromatin, and a complex feedback mechanism exists between AR and GATA2 whereby GATA2 promotes expression of AR and conversely, GATA2 expression is repressed by androgen and AR(59). Furthermore, preclinical data support the efficacy of Bromodomain and Extra-Terminal motif (BET) protein inhibitors, which have been shown to downregulate AR by disrupting the AR–BRD4 interaction at the N-terminal domain of the AR, thus altering gene expression by preventing interactions of this complex with chromatin(60). These results have led to the clinical assessment of BET inhibitors as a treatment of CRPC, including a phase I trial of the BET inhibitor OTX015 (Merck, New Jersey, USA) in men with CRPC (NCT02259114)[171].

The P160 SRC family genes, *NCOA1*, *NCOA2* and *NCOA3* which function as steroid receptor co-activators, are recognized as important cofactors in CRPC. Even in the absence of circulating androgens, overexpression of NCOA1 or NCOA2 can drive increased AR transactivation(61). NCOA2 is amplified in approximately 6% of patients with advanced-stage prostate cancer, and increased NCOA2 function amplifies AR pathway activity(10, 62). NCOA3 overexpression is associated with tumour proliferation in patients prostate cancer, and notably, is a key target of the ubiquitin ligase SPOP(11, 63). Targeting P160 SRC proteins might prove beneficial as a treatment of CRPC and might resensitize patients to the standard treatments of CRPC. Promisingly, 65% of patients with metastatic CRPC have a potentially targetable genetic aberration through established agents, even excluding those with alteration of the AR signalling axis(3).

TMPRSS2–ETS fusions

Stimulation of the AR can bring the *TMPRSS2* and the *ERG* gene loci into close proximity, an effect thought to be critical for the development of the *TMRPSS–ERG* gene fusion(64-66). Younger men (**~55% in men <50 vs. ~35% in men >75**) have higher incidences of structural rearrangements and *ERG* gene fusions than older men, resulting in the hypothesis that androgen-activated transcription might be an early driver of prostate cancer(67).

The translational relevance of *TMPRSS2–ERG* fusions has been demonstrated by the introduction of a urine-based early detection test (in combination with urine levels of PCA3, which is a non-coding RNA transcript) and a diagnostic, tissue-based test (using antibodies directed against *ERG*)(68-71). Thus, the first clinical applications of *ETS* fusions are as diagnostic tools, exploiting the specificity of this gene fusion to prostate cancer, rather than as a prognostic biomarker post-treatment. The prognostic utility of *ERG* fusions has been extensively investigated in various contexts, particularly after radical prostatectomy, with the largest published series to date indicating no utility of the presence of these fusions or ERG overexpression for prediction of biochemical recurrence(72, 73). No clinically available methods of directly inhibiting *TMPRSS2–ERG* signalling currently exist; although, inducible knockdown of *ERG*, which is endogenously expressed in the VCaP CRPC cell line has shown that *ERG* drives cellular proliferation and blocks differentiation of these cells to

neuroendocrine or luminal cell types, supporting the clinical utility of targeting these early, driving alterations(74). Likewise, in preclinical studies investigating targetted deletion of *TMPRSS2*, this protein was found to promote cancer cell invasion and metastasis(75).

Inhibition of *ETS* cofactors, rather than the fusion product itself, has attracted increased interest as a potential therapeutic strategy. In preclinical studies, *ETS*-positive tumours have been shown to be more sensitive to pharmacological inhibition of targetable cofactors, including PARP1, HDAC1, and DNAPK.(72, 76). Multiple phase I and II studies have focused on the inhibition of PARP1 in patients with CRPC, most notably a randomized study, in which patients were stratified patients based on *ETS* fusion status (NCT01576172)[172]. Likewise, two phase II studies designed to investigate the effectiveness of HDAC inhibitors in patients with CRPC have been attempted, however these have yielded disappointing results(77, 78). Several other trials assessing HDAC inhibitors in patients with CRPC are still in progress, or have been completed, with results currently pending (NCT01075308, NCT00878436 and NCT01174199). Thus, prognostic and predictive relevance of *ETS* fusions continues to be investigated, and the results of ongoing clinical trials are highly anticipated.

Signal transduction pathways

Molecularly targeted therapies for the treatment of prostate cancer have, historically, and given the importance and ubiquity of androgen axis signalling in the pathogenesis of this malignancy, largely focused on androgen signalling pathways. Nevertheless, the importance of other signal transduction cascades has been increasingly elucidated from the findings of genomic analyses. For example, in the setting of metastatic CRPC, nearly 50% of tumours carry *PI3K* abnormalities, and 18% have *MAPK* or *WNT* alterations(3). Furthermore, 100% and 90% of metastatic tumours have upregulated PI3K and MAPK signalling, respectively, according to gene expression analyses(10).

PI3K Pathway

Outside of the androgen signalling axis, the PI3K signalling cascade is the most commonly dysregulated signal transduction pathway in patients with prostate cancer. The PI3K pathway is a critical regulator of proliferation, survival, metabolism, angiogenesis, and immune function. Hyperactivation of the pathway through loss of *PTEN*, which encodes a lipid phosphatase that acts as a negative regulator of PI3K signalling is by far the most common PI3K aberration observed in patients with prostate cancer(3, 10). Homozygous *PTEN* deletions were present in 15% of primary prostate cancers in the TCGA dataset, which is one of the highest incidences of this deletion among any tumour type, and *PTEN* mutations were present in another 2%[17]. *PTEN* alterations are even more common in the setting of metastatic disease, with over 40% of tumours having *PTEN* mutation or loss(3, 5, 10, 17). *PTEN* loss has been associated with a poor clinical outcome in numerous studies compared with patients whose tumours express wild-type *PTEN*(79-83), with some(82), but not all(83), suggesting that the prognostic value of *PTEN* loss is dependent on *ERG*-fusion status. PI3K signalling and androgen signalling have been suggested to be reciprocally regulated(84), and treatment with combination therapy is, therefore, likely to be necessary to

overcome intrinsic and acquired resistance to single-agent therapy, given that the findings of trials designed to investigate the efficacy of both pan-PI3K and dual PI3K–mTOR inhibitors have been disappointing to date(85, 86).

Wnt pathway

Alterations in the Wnt signalling pathway are also common in prostate cancer, both in the primary setting and in patients with metastatic CRPC, where it is present in approximately 18% of patients(3, 5, 17). Canonical Wnt signalling is an evolutionarily conserved pathway that has been implicated in cancer stem-cell maintenance, epithelial-to-mesenchymal transition, embryonic development and homeostasis in adults(87). Alterations have been observed in multiple nodes of the Wnt-signaling pathway in patients with prostate cancer, including recurrent mutations in *CTNNB1*, the gene encoding the central mediator of the Wnt-pathway β-catenin(3, 17), and APC, which forms part of the multiprotein deconstruction complex that regulates β-catenin levels(3, 5, 88). Also, mutations in the ubiquitin ligases *RNF43*, *ZNRF3*, and in *RSPO2*, an activator of Wnt signalling via LGR4-6 activation were observed in 6% of patients with mCRPC in a study published in 2015(3). The presence of mutations in these genes in patients with metastatic CRPC was mutually exclusive of *APC* alterations(3). By profiling paired pre-treatment and post-treatment prostate cancer biopsy samples, investigators have demonstrated that Wnt-pathway activating alterations (such as *CTNNB1* mutation or amplification) are adaptive responses to therapy, similar to AR mutations/amplifications(88, 89).

Multiple Wnt-pathway targeting agents are currently in clinical development, although none are being specifically studied as treatments of prostate cancer, to date(90). These agents include the small molecule PRI-724, an inhibitor of the interaction between β-catenin and one of its co-activators in the nucleus, CREB binding protein(91), (NCT01302405, NCT01764477, NCT01606579) and LGK-974 (Novartis, Basel, Switzerland), a small molecule that inhibits PORCN, a key regulatory protein in the Wnt signalling pathway, thereby impairing Wnt ligand secretion (NCT01351103). Prostate cancers with mutations in *RNF43*, *ZNRF3*, and *RSPO2* would be expected to respond to these agents(92). Several molecular therapies targeted to the Wnt-ligand-binding Frizzled receptor are also being investigated in various cancers (NCT01973309, NCT01957007, NCT02005315, NCT02069145, NCT02092363, NCT02050178, and NCT01469975).

MAPK Pathway

The MAPK/ERK pathway, which is implicated in cell survival, cell-cycle progression, tumour dissemination, and resistance to therapy in multiple cancers(93), also seems to have a role in a subset of prostate cancers, and data from preclinical research suggests an association with more aggressive disease in certain genetic contexts(94). *BRAF* is the most commonly altered MAPK gene in prostate cancer, with gene fusions or activating mutations present in 2–3% of tumours(3, 5, 17). Interestingly, canonical *BRAF*[V600E] mutation was not observed in prostate cancer specimens analyzed in the TCGA dataset, although this mutation has been described, rarely, in other studies(10, 17). Additionally, no activating *BRAF* rearrangements were found in the TCGA study[17], despite these having been described

previously in prostate cancer(95). Given the rarity of *BRAF*^{V600E} mutations in prostate cancer, less specific *BRAF* or *MEK* inhibitors might prove to have more clinical utility in patients with prostate cancer than the currently available mutant *BRAF* inhibitors such as vemurafenib.

IDH1 Signaling

Approximately 1% of primary prostate cancers are defined by the presence of isocitrate dehydrogenase 1 (*IDH1*) ArgR132His hotspot mutations(17), this critical finding from the TCGA prostate cancer study represents a novel prostate cancer molecular subtype and confirms previous observations of these mutations in prostate cancer(88, 96-98). These *IDH1* gene mutations generally result in a loss of function, owing to the conversion of isocitrate to 2-ketoglutarate. Instead, the altered enzyme adopts an abnormal function: production of D-2-hydroxyglutarate(99). These genetic changes have been found to inhibit the enzymatic function of many α-ketoglutarate-dependent dioxygenases, including histone and DNA demethylases, resulting widespread changes in the epigenome.

The presence of these *IDH1* mutations appears to define a rare, unique subset of early onset prostate cancer, with relatively few copy number alterations and even higher levels of genomic hypermethylation than *IDH1*-mutant glioblastoma or acute myelocytic leukaemia (AML)(100, 101). Notably, in both AML and glioblastoma, patients with *IDH1* mutations have a markedly better prognosis than those with wild-type *IDH1*(102, 103). Whether or not the presence of *IDH1* mutations also portends an improved prognosis for patients with prostate cancer is worthy of future investigation, given the significant potential implications for active surveillance and treatment recommendations in men harbouring tumours with this alteration. Additionally, patients with *IDH1* mutations might be candidates for treatment with one of the various *IDH1*-specific therapies that are currently being developed(103, 104).

Cell cycle/proliferation

Similar to many other cancers, alterations in genes encoding proteins involved in regulation of the cell cycle have an important role in prostate cancer. For example, *TP53* is mutated or deleted in 8% of primary prostate cancers and up to 53% of metastatic CRPCs(3, 5, 10, 17, 88). *TP53* encodes the p53 transcription factor that, in response to DNA damage, activates the G1–S cell-cycle checkpoint and the apoptotic signalling cascade(105). Furthermore, other genes encoding important inhibitors of cell-cycle progression at G1–S, including *CDKN2A*, *CDKN2B* and *CDKN1B,* are each lost in about 2–3% of primary prostate cancers(17). *RB1*, another critical negative regulator of the G1–S checkpoint that is responsible for repressing the E2F family of transcription factors(106), is also commonly lost in metastatic CRPC(3, 10, 88) (most specifically in small-cell carcinoma); whereas *CCND1*, the gene encoding cyclin D1, which is an activator of cell-cycle progression through G1–S transition, is recurrently amplified(3, 88). Thus, dysfunction of the G1–S checkpoint, potentially owing to a variety of different genetic aetiologies, is a frequently ocurring molecular event in patients with prostate cancer, particularly in those with metastatic CRPC.

Despite being perhaps the most commonly altered set of genes across all cancers, clinical therapeutic strategies targeting cancer cells harbouring deficiencies in cell-cycle regulation (besides non-selective chemotherapy) have been lacking . However, multiple new agents are moving into the clinic and have shown promising results in the metastatic setting. For example, the cyclin-dependent kinase (CDK) 4/6 inhibitor palbociclib in combination with anti-oestrogen therapy has demonstrated impressive activity in patients with hormone-receptor positive breast cancer(107, 108). CDK4/6 inhibitors are expected to be particularly effective in tumours harbouring inactivating *CDKN2A/B* mutations or *CCND1* amplification, both of which are recurrent alterations present in primary and, more commonly, metastatic CRPC. Three registered clinical trials currently exist to investigate the effectiveness of these agents in patients with prostate cancer: ribociclib in combination with docetaxel in patients with metastatic CRPC (NCT02494921), enzalutamide +/− ribociclib in patients with metastatic CRPC (NCT02555189), and ADT +/− paclociclib in patients with hormone-sensitive prostate cancer, in which patients with RB1 wild-type tumours were pre-selected for recruitment, which is the first example of biomarker-driven recruitment of patients with hormone-sensitive prostate cancer (NCT02059213).

Targeting cells with p53 deficiency has long been a goal of oncologists, but has proven difficult in clinical practice(109). Given that p53 is a fundamental regulator of the G1–S checkpoint, one strategy for targeting cells with this deficiency could be to exploit their hypothesized increased reliance on the G2–M checkpoint for DNA damage repair. Inhibitors of the G2–M regulatory proteins ATR(110, 111), Wee1(112, 113) and Chk1(114, 115) have been shown to have increased activity when used as single agents, and also promote sensitization of p53-deficient cancer cells to DNA-damaging agents. Inhibitors of each of these molecules have entered early phase clinical testing in various cancer types(116, 117) (NCT02223923) and might be promising in patients with metastatic CRPC.

In addition to G1–S checkpoint aberrations, localized prostate cancers might also harbour amplification of one of the three *MYC* isoforms that also promote progression from G_1–S phase: MYC (also known as c-MYC), MYCL, or MYCN(8)ꞏ(17). Like p53, MYC has long been considered undruggable, and direct targeting is challenging with standard pharmaceutical approaches(118). Nevertheless, in a novel approach to this challenge, DCR-MYC, a first-in-class Dicer substrate small interfering double-stranded RNA targeted to the *MYC* oncogene in a lipid nanoparticle suspension is currently being tested in early phase clinical trials (NCT02110563, NCT02314052). Thus far, this therapy has been well tolerated and showed some patients have had promising responses to treatment in early clinical testing(119). In addition to this direct therapeutic targeting strategy, several indirect experimental therapies have shown promising results in preclinical testing in patients with MYC-driven tumours, such as PIM inhibition(120), inhibition of the bromodomain-protein BET(121), exploiting replication stress in MYC-expressing cancer cells via ATR inhibition(122), targeting MYC-upregulating STAT proteins via an antisense nucleotide to STAT3 (NCT01563302) or direct inhibition the STAT5–SH2 binding domain(123).

DNA damage repair/heredity

DNA Repair

The DNA damage repair (DDR) response is governed by input from a diverse array of signalling cascades that are integral to the maintenance of genomic integrity(124). Many proteins involved in DDR act as tumour suppressors, thus preventing the formation and propagation of both mutations and copy number alterations. Genomic instability via loss of DDR proteins is common in prostate cancers compared with many other types of cancer, owing to both somatic and germline alterations. For example, approximately 19% of primary prostate cancers and 23% of patients with mCRPC have been reported to harbour inactivating mutations in DDR genes(3, 5, 17, 88). Notably, certain DDR deficiencies appear to be much more common in patients with meatastatic CRPC than in those with primary prostate cancer. For example, approximately 20% of meatastatic CRPC primary tumour samples have been reported to harbour germ-line and/or somatic aberrations in *BRCA2*, *BRCA1*, or *ATM*(3, 5, 88, 125), whereas only ~3% of tumours from those with primary prostate cancer had germline or somatic alterations in *BRCA1* and *BRCA2*(17).

Losses or mutations of *BRCA2, ATM,* and *BRCA1* are the most commonly reported mutations in DDR genes in patients with prostate cancer(3, 5, 17, 88). The wild-type forms of these genes are important components of homologous recombination, a high fidelity DDR process that utilizes the sister chromatid as a template during G2/M to excise and replace defective stretches of DNA in an error-free manner. Mutations in other components of the homologous recombination response have also been described, including those in *PALB2*, *RAD51B* and *RAD51C*(3, 17). Thus, defective homologous recombination is a recurrent motif in the development of prostate cancer, particularly in the advanced-stage or castration-resistant setting. Furthermore, data from a large pan-cancer analysis revealed a mutational signature correlating with mismatch repair deficiency in a subset of prostate cancers(126), and loss-of-function genomic lesions in mismatch repair proteins (most frequently somatic mutations and deletions in *MSH2*) have been described in several datasets(3, 5, 127-129). Given the high mutation load of their tumours, patients that have prostate cancer with mismatch repair deficiencies might be good candidates for investigation of immunotherapeutic approaches such as CTLA-4 or PD-1 inhibition(130, 131).

Currently, defective or lost DDR proteins cannot be directly targeted pharmacologically; although, these aberrations might create tumour specific vulnerabilities that can be exploited via the principal of synthetic lethality. This process occurs when two cellular pathways are inhibited simultaneously resulting in cell death, but inhibition of either pathway by itself is not lethal. When DNA repair function is intact, single-strand DNA breaks are repaired through the base excision repair pathway. Poly (ADP-ribose) polymerase (PARP) is a key component of the base excision repair pathway, and inhibition of this protein results in an increased frequency of single-strand DNA breaks and eventually the creation of double-strand DNA breaks during replication. Normally, these double-strand breaks are repaired by homologous recombination. However, if cells have mutations in genes that encode proteins that control homologous recombination (such as *BRCA*) then DNA replication is likely to

fail. The combination of PARP inhibition in the presence of *BRCA* mutations impairs these two damage repair pathways, thus causing selective synthetic lethality(132).

The clinical relevance of synthetic lethality was originally demonstrated by the discovery that breast and ovarian cancers with BRCA deficiencies are exquisitely sensitive to PARP inhibition(133-135). These findings might have relevance for prostate cancer as well. Data from a phase II trial with a cohort that contained eight patients with germline *BRCA1* or *BRCA2* mutations and recurrent cancer demonstrated that half of these patients with advanced-stage prostate cancer had responses(136). Even more promisingly, following the TOPARP-A trial, investigators reported that 14 of 16 (87.5%) patients with mCRPC and homozygous deletions or deleterious mutations in DNA-damage repair genes such as *BRCA1* or *BRCA2*, *ATM*, *CHEK2*, *FANCA* and *PALB2* responded to olaparib, in comparison to two of 33 (6%) without these aberrations(137). This high level of specificity of genomic alterations to a targeted therapy is unprecedented in patients with prostate cancer. Serious (grade 3) treatment-related adverse events included anaemia (in 10 patients), fatigue (in six patients), leukopenia (in three patients), thrombocytopenia (in two patients) and neutropenia (in two patients). Multiple other trials designed to investigate the effectiveness of PARP inhibitors in patients with prostate cancer are currently underway or have been completed in the past 5 years (NCT01576172, NCT01085422, NCT01972217) and a complete response in a patient with deficiencies in DDR genes who was treated with a PARP inhibitor (with or without other therapies) has also been described(138).

In addition to predicting a response to targeted DDR inhibition, tumours with genomic deficiencies in homologous recombination or Fanconi anaemia proteins might also be more responsive to platinum-based chemotherapy(139, 140). Platinum-based chemotherapy is currently rarely used in patients with prostate cancer (except in those with small-cell or neuroendocrine carcinoma) given the lack of benefit derived from this treatment by unselected patients. However, this might be a promising approach for patients with mCRPC harbouring genetic DDR pathway alterations, thus an evaluation of the effectiveness of PARP inhibitors compared with that of chemotherapy might be warranted.

The existence of a novel interplay between DNA repair and AR signalling was described in 2013(141). Inhibition of the AR seems to supress non-homologous end joining, and to reduce the functional ability of the DNA-dependent protein kinase catalytic subunit(142). Furthermore, genotoxic stress (such as radiotherapy) not only causes DNA damage, but also upregulates AR signalling and pro-survival pathways to mediate treatment resistance(143). Further research is ongoing to better characterize how to optimally utilize this information to enable the rational combination of radiotherapy with ADT (NCT02297386). Additionally, an important interplay exists between PARP and the AR given that PARP-1 is recruited to sites of AR function and supports AR transcriptional function, suggesting that PARP should be further investigated as an treatment target in patients with prostate cancer(141, 142).

[H3] Heredity

Data from genomic studies have confirmed that, in addition to the somatic mutations present in prostate cancer, germline aberrations in DDR genes also have a critical influence on genetic predisposition to prostate cancer(3, 144). *BRCA2* was one of the first mutated genes

to be associated with an increased risk of prostate cancer(145-147). Furthermore, the presence of *BRCA1* mutations also increases the risk of prostate cancer, albeit to a lesser extent than the presence of *BRCA2* aberrations(148). Additionally, men with germline mutations in mismatch repair genes have approximately twice the risk of developing prostate cancer as unaffected individuals, with a cumulative risk of approximately 30% by the age of 80, compared with around 18% in the age-matched general population [142]. Other genetic alterations have been identified that confer an increased familial risk of prostate cancer (such as *HOXB13* mutations), however, these mutations usually occur at low frequencies(149).

Identifying men who have a strong genetic predisposition to prostate cancer has important clinical implications. For example, these men might be eligible for more intense screening, or lowering the serum PSA threshold that indicates a need for biopsy sampling. Unfortunately, no reliable evidence exists that pharmacological prevention, such as use of finasteride, selenium, and/or vitamins can prevent, or reduce the risk of developing high grade cancers(150)·(151). Thus, no pharmacological strategy for prostate cancer prevention can currently be recommended. The role of even more aggressive risk reduction, such as prophylactic prostatectomy, is also unclear. Further study of screening and prevention of prostate cancer in men with a high genetic predisposition to prostate cancer is an important avenue for future investigation.

Tumour heterogeneity and evolution

The substantial interpatient tumour heterogeneity observed among patients with prostate cancer is highlighted by the variety of different molecular aberrations present across different cancers (FIG 1)(3, 10). This interpatient heterogeneity has been a major challenge in identifying effective therapies in 'all-comers' in randomized trials, given that the potential benefit derived from use of a targeted treatment in selected patients harbouring a predictive genomic alteration might be masked if the alteration is only present in a small subset of those enrolled. Nevertheless, intra-patient heterogeneity might also pose hurdles to the personalization of treatment. In patients with localized prostate cancer, the majority of prostate cancers are known to be multifocal(152, 153). Furthermore, although these multifocal tumours have often been identified, using either single-gene and/or whole-exome sequencing, to be genetically distinct, suggesting an independent origin, non-driving somatic mutations might be shared between tumor foci and even among histologically 'normal' prostate tissue samples(7, 8, 154). Moreover, lethal metastases have been reported to arise from a minor population of subclones, including dissemination from an organ-confined, low-grade area of a bulky, high-grade primary tumour(155). Likewise, data from sequential profiling of circulating cell-free DNA has demonstrated that the basic prostate cancer molecular subtype (defined by *ERG*-fusion status) might change in response to selective pressure induced by anti-androgen therapy(156). Therefore, the use of targeted biopsy sampling using image guided techniques (CT, MRI, and/or ultrasound guided), both in patients with localized, and mCRPC will need to be carefully evaluated to determine whether or not this approach can capture the dominant biology of any one patient's cancer. Additionally, the delivery of focal therapy to the prostate gland, such as focal brachytherapy or cryotherapy, might be unwise until a method to readily detect the driver foci that are responsible for metastatic spread is developed.

Given the extensive intratumoural and intertumoural heterogeneity observed in patients with prostate cancer, in line with Darwinian theories of evolution, certain subclones containing a selective growth or survival advantage in comparison to others are likely to proliferate and form the majority of the tumour population throughout the natural history of the disease, and in response to selective pressures. Eventually, in most patients with lethal prostate cancer, a subset of tumour subclones gains the ability to disseminate to distant organs. Furthermore, the introduction of therapeutic interventions, which provide new pressures on tumour selection, can radically reshape the subclonal composition of a tumour(156). Thus, the tumour genome and epigenome are in a dynamic state of selection pressure and evolutionary drift as the tumour continually divides and new mutations arise.

Some of the most interesting insights to emerge from genome sequencing projects involve tracking the evolution of prostate cancer from a locally invasive process into a disseminated malignancy. For example, data from several copy number analyses and genome sequencing studies from individual patients have suggested that, despite the multifocal and multiclonal nature of primary prostate cancers, lethal metastases might arise from a single subclone(155, 157). However, studies published in the past 2 years, with data from multiple patients, suggest that prostate cancer metastases can arise from either a single, or several subclones within the primary tumour (6, 156). Furthermore, the complexity of metastatic spread patterns of prostate cancer has been highlighted by the findings of genomic studies. In addition to the classical primary-to-metastasis model, high rates of metastasis-to-metastasis, and even metastasis-to-surgical bed, spread have been observed in heavily treated patients(6, 158). In summary, these data support the hypothesis that, rather than only unidirectional seeding from the primary to metastatic sites, metastatic CRCP is truly a systemic disease arising from a subclone or subclones with multidirectional spread of subclones between all sites of malignancy(159). This hypothesis has clinical implications for treating both the primary, as well as metastatic sites in order to limit the extent of any further metastatic progression. Given that not all metastatic spread arises from the primary tumour, ablation of oligometastases in patients in whom the primary tumour is eradicated might, in theory, decrease the reservoir of subclones containing the ability to disseminate, thereby slowing the progresion of metastatic spread.

Multiple lines of evidence suggest that tumours evolve in response to treatment(156, 158). For example, certain aberrations such as AR mutations and amplifications that are common in prostate biopsy samples from patients with mCRPC are almost never detected in similar samples from patients with hormone-naïve prostate cancer(3, 5, 6, 160). Additionally, the relative proportions of circulating DNA from the various tumour subclones markedly changes over time in response to treatment, with those containing mutations that are known to confer treatment resistance emerging during progression, whereas others regress during treatment responses, thus revealing a complex dynamic of temporal and spatial heterogeneity[150] . In many cases these resistant clones are already extant in small numbers prior to treatment, rather than arising *de novo*, and eventually become the dominant population under selection pressure. For example, in the TCGA study, researchers detected AR splice variants, including the AR-V7 splice variant that is associated with resistance to anti-androgen therapy, and is present at low levels in biopsy samples from normal prostate tissue and from androgen-naïve prostate cancers(17). Given that diversity often exists with

respect to therapeutic resistance mechanisms across different metastatic sites, a challenge can occur when a targeted therapy is adequately controlling the majority of the patient's disease, but one or more foci are discordantly progressing. One potential method that is of clinical interest, but needs to be rigorously tested in context of clinical trials, is to maintain patients on targeted therapies whilst also controlling the emergence of metastatic tumour clones that harbour acquired resistance using ablative treatments. Stereotactic body radiotherapy (SBRT) is one form of ablative therapy that allows high doses of radiotherapy to be delivered to the tumour and avoids exposing normal tissue to radiation. This technique holds promise for treatment of patients in the metastatic setting that should be tested prospectively.

The dynamic intratumoural heterogeneity observed in patients with prostate cancer, along with its fundamental intertumoural diversity, is a fundamental challenge to the personalized management of patients with this disease. Of particular relevance, targeting early driving ('truncal') alterations in prostate cancer, such as *ERG* gene fusions or *SPOP* mutations, is currently not possible. Given the assumption that prostate cancer metastases might arise from a minor subclonal population, attempting to utilize molecular sequencing to improve prognostication will be extremely challenging. Hence, determining both common and rare patterns of tumour progression is a critical area of need for clinicians treating patients with prostate cancer. Such studies, which must track the emergence lethal clones from the primary tumour to ADT-refractory CRPC, through to disease that is refractory to second-line anti-androgen therapies, are complicated by the long follow-up duration that is required to obtain such samples. Likewise, studies assessing tumour tissue histology, circulating tumour cells and circulating DNA are required to determine the most informative (and clinically relevant) approaches.

The molecular diversity of metastatic prostate cancer generally indicates that achieving long-term remission from treatment with agents targeted to a single pathway is unlikely, and the clinical effectiveness of combination strategies, possibly using orthogonal targets or synergistic combinations, should be investigated(161). In addition, the dynamic nature of prostate cancer genomics supports the repeated, longitudinal evaluation of the genomic characteristics of a patient's tumour over time, and during treatment(156). For example, all rapid autopsy studies conducted on heavily treated patients with mCRPC in the pre second-generation antiandrogen therapy era demonstrate uniform *ETS* fusion status within an individual patient's metastases(5, 6, 157, 162), assessment of cell-free DNA supports dynamic *ETS* fusion status upon treatment with second generation anti-androgens(156). Hence, non-invasive methods (coupled with tissue-based assessments) are being actively investigated in order to capture the spectrum of a patient's tumour heterogeneity in response to treatment in real-time through assessment of circulating tumour cells, cell-free DNA, urine and serum biomarkers, and molecular imaging.

Neuroendocrine prostate cancer

Small-cell carcinoma of the prostate can exist *de novo* within the prostate and patients with this type of prostate cancer typically have a shorter overall survival compared with those who have prostate adenocarcinoma(163). Additionally, prostate adenocarcinomas can also

progress to lose expression of active AR signalling markers (such as serum PSA) with, or without small-cell carcinoma differentiation, thus likely reflecting a truly AR-independent phenotype and a terminally differentiated state (3, 5, 128, 164). Clinically, patients with this type of prostate cancer have metastases in atypical visceral sites, and abnormally low serum PSA levels(125, 164-166). The terminology of neuroendocrine prostate cancer (NEPC) is evolving and this type of prostate cancer is clearly a heterogeneous spectrum of de-differentiation, particularly as patients are increasingly being treated with therapies designed to target androgen signalling(125, 164, 167). The exact incidence of NEPC is unclear, and ranges from 1–32% after treatment with enzalutamide or abiraterone(3, 168).

Distinct genomic alterations are likely required to enable prostate cancer to transition from an AR-dependent adenocarcinoma to an AR-independent disease state (with or without overt neuroendocrine differentiation, as defined by marker expression). Some of the proposed and identified aberrations include loss of *TP53* and *RB1*, and gain of *AURKA*, *MYCN*, *MYCL* and *PEG10*, a gene that encodes an anti-apoptotic signalling protein(88, 125, 164, 169-172). Co-amplification of the genes *AURKA* and *MYCN*, although not consistently observed, has been reported in up to 40% of patients with NEPC(164). Based on these findings, a phase II trial of an AURKA inhibitor MLN8237 in patients with NEPC (NCT01799278) is underway. With the continued understanding of neuroendocrine/small-cell prostate cancer, and the process of de-differentiation, the current list of target genes (such as *MYCN*, *AURKA* and *PEG10*) will likely expand. Owing to a lack of functional reliance on AR signalling, typical AR-based therapies are largely ineffective in patients who exclusively harbour these aggressive disease variants, and novel treatments are desperately needed.

Conclusions

In summary, improvements in multiplatform sequencing technologies have revolutionized research into prostate cancer genetics, enabling unprecedented insight into the biology of this disease. This knowledge has elucidated promising opportunities for personalized treatment interventions, and has also highlighted the formidable hurdles in managing a dynamically evolving heterogeneous disease. Developing novel avenues for applying this knowledge regarding genomics to the clinical care of patients with prostate cancer in order to increase therapeutic effectiveness while limiting adverse treatment sequelae is, undoubtedly, a major challenge to clinical oncology over the coming years. To overcome these hurdles, continued multidisciplinary integration of basic science, genomics, bioinformatics, industry research and clinical practice will be necessary in order to advance the clinical science of prostate cancer.

Acknowledgements

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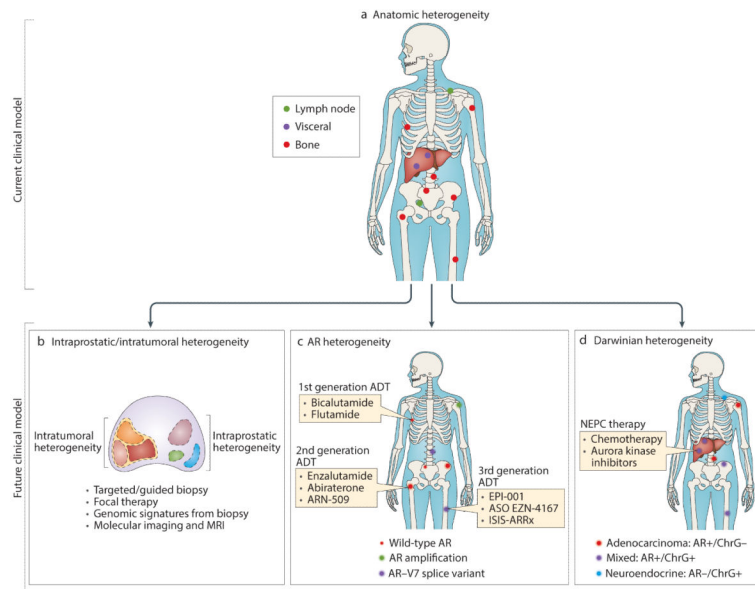
Figure 1. Types and implications of prostate cancer heterogeneity
a | The clinical and anatomical heterogeneity of metastatic prostate cancer fails to capture the immense biological heterogeneity of prostate cancer. **b** | Intraprostatic/intratumoral heterogeneity, **c** | Androgen receptor heterogeneity, and **d** | Darwinian heterogeneity demonstrate clinical strategies and obstacles regarding treatment and diagnosis.

Table 1

Select genomic alterations and their future clinical implications

Pathway process	Targets	Drug development	Potential prognostic or predictive biomarkers
AR signalling	AR NCOR1/2 FOXA1 ZBTB16 SPOP	N-terminal domain AR inhibitors; Dual AR/GR inhibitors	AR-V7 spice variants; AR amplification
Cell cycle	P53 MYC CDKN2A RB1 AURKA	DNA-binding domain AR inhibitors; CDK4/6 inhibitors; AURKA inhibitors	RB1 status; AR lo/independence; AURKA amplification
DNA repair	BRCA ATM RAD51 MSH2/6 SPOP DNAPK	PARP inhibitors, PD-L1 inhibitors	DNA repair defects
ETS Fusion	ERG ETV1	HDAC inhibitors, PARP inhibitors	ETS gene fusion status
MAPK pathway	BRAF RAF1 HRAS	BRAF inhibitors; MEK inhibitors	Mutations or gene fusions
Wnt pathway	CTNNB1 APC ZNRF3 RNF43 RSPO2	Porcupine inhibitors	Mutations or gene fusions
PI3K pathway	PTEN PIK3CA PI3KCB AKT1	pan-PI3K and dual PI3K–mTOR inhibitors; PI3KCB inhibitors	Mutations or copy number alterations

AKT, v⁻akt murine thymoma viral oncogene homologue; APC, adenomatous polyposis coli; AR, androgen receptor; BRAF, B-Raf proto-oncogene, serine/threonine kinase; BRCA, breast cancer; CTNNB1, catenin β 1; ERG, v⁻ets avian erythroblastosis virus E26 oncogene homologue; ETS variant 1; FOXA1, forkhead box A1; GR, glucocorticoid receptor; HDAC, histone deacetylases; HRAS, Harvey rat sarcoma viral oncogene homologue; MSX, msh homeobox; MYC, MYC proto-oncogene protein; NCOR, nuclear receptor co-repressor; PARP, poly(ADP-ribose) polymerase; PD-L1, programmed cell death 1 ligand 1; PIK3C, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit; PTEN, phosphatase and tensin homologue; RAD51, RAD51 recombinase; RAF1, Raf-1 proto-oncogene, serine/threonine kinase; RB1, retinoblastoma 1; RNF43, ring finger protein 43; RSPO2, R-spondin 2; SPOP, speckle type BTB/POZ protein; ZBTB16, zinc finger and BTB domain containing 16; ZNRF3, zinc and ring finger 3.

Table 2

Select clinical trials of novel therapies in prostate cancer

Therapy	Mechanism of action	ClinicalTrials.gov identifier
AR signalling		
ARN-509	Second-generation AR antagonist	NCT01946204, NCT02200614
ARN-509 + abiraterone	Second-generation AR antagonist, CYP17 inhibitor	NCT01792687
Enzalutamide + abiraterone	Second-generation AR antagonist, CYP17 inhibitor	NCT01650194, NCT01949337
Galeterone (TOK-001)	Dual CYP17 inhibitor and AR antagonist	NCT01709734
ODM-201	Second-generation AR antagonist	NCT02200614
VT-464	Lyase-selective inhibitor of CYP17	NCT02012920
EPI-001/EPI-506	N-terminal domain AR inhibitor	NCT2606123
ISIS-ARRx	AR mRNA inhibitor	NCT02144051
ASO EZN-4176	Antisense oligonucleotide	NCT01337518
PI3K		
GDC-0068 + abiraterone	Pan-AKT inhibitor; CYP17 inhibitor	NCT01485861
BEZ235 + abiraterone	Dual PI3K and mTOR inhibitor; CYP17 inhibitor	NCT01634061
BKM120 + abiraterone	Pan PI3K inhibitor; CYP17 inhibitor	NCT01634061
AZD8186	PI3Kβ and PI3Kδ inhibitor	NCT01884285
GSK2636771	PI3Kβ inhibitor	NCT01458067
Temsirolimus + vorinostat	mTOR inhibitor, HDAC inhibitor	NCT01174199
DNA repair		
Olaparib	PARP 1 inhibitor	NCT01682772
Olaparib + Abiraterone	PARP 1 inhibitor, CYP17 inhibitor	NCT01972217
Abiraterone +/− veliparib	PARP inhibitor, CYP17 inhibitor	NCT01576172
ABT-888 + temozolamide	PARP inhibitor, DNA alkylating agent	NCT01085422
Neuroendocrine		
Alisertib (MLN8237)	AURKA inhibitor	NCT01799278
Alisertib + abiraterone	AURKA inhibitor; CYP17 inhibitor	NCT01848067
Cell cycle		
Ribociclib (LEE011) + docetaxel	CDK 4/6 inhibitor	NCT02494921
AZD6738	ATR inhibitor	NCT02223923
MYC		

Therapy	Mechanism of action	ClinicalTrials.gov identifier
DCR–MYC	MYC inhibitor	NCT02110563
ISIS–STAT3Rx	STAT3 antisense oligonucleotide inhibitor	NCT01563302
Other		
SB939	HDAC inhibitor	NCT01075308
Panobinostat + bicalutamide	HDAC inhibitor; 1st generation antiandrogen	NCT00878436
Abiraterone +/− vemurafenib	CYP17 inhibitor; RAF inhibitor	NCT01085422

AR, androgen receptor; HDAC, histone deacetylase; PARP, Poly [ADP-ribose] polymerase; MYC, MYC proto-oncogene protein; STAT3, Signal transducer and activator of transcription 3.