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Multifaceted and Personalized Therapy Of Advanced Prostate Cancer

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Abstract

Purpose of Review—A number of molecular and genomic biomarkers that possess the ability to guide treatment or “actionable targets,” are being reported in metastatic prostate cancer. In addition pathways of resistance to existing therapies and novel agents to overcome them are currently under active investigation. The next wave of investigations is focused on personalized therapy of prostate cancer. The focus of this review paper is to provide an update clinical developments in advanced prostate cancer and to highlight the ongoing investigations of biomarker discovery, and ways of overcoming therapeutic resistance. The next generation of clinical trials developing novel targets and compounds promises to be in populations enriched with specific marker expression.

Recent Findings—The breakthrough report, of the ability of the ARV-7 mutation, detected in circulating tumor cells, to predict lack of response to abiraterone or enzalutamide, and the remarkable responses of poly ADP ribose polymerase (PARP) inhibitors in prostate cancer with DNA repair mutations, have elevated hopes of a bright future in the biomarker driven therapeutic arena. Novel targets such as BET-1 and PI3 kinase hold promise for the possibility of overcoming resistance. Novel hormone agents are also under active study.

Summary—As the clinical application of the multifaceted therapies narrows down to enriched patient populations selected by genomic testing, the therapeutic efficiency will escalate considerably. Novel targets, resistance mechanisms, and relevant agents are being avidly tested and the dream of personalized medicine is emerging into reality.

Keywords

castrate resistant; ARV-7; PARP inhibitors; BRCA-1/2 mutations; BET-1

Introduction

With the wide range of palliative therapeutic options [1–9] the management of prostate cancer has become extremely complex and no evidence is currently available to guide selection of therapy. This has created a dire need for biomarkers to improve the efficiency of

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the therapeutic sequence, without relying solely on subjective clinical judgment. The advances in the field of genomic medicine have translated into development of techniques for comprehensive molecular profiling of tumor specimens and have enabled exploration of the genomic signature of advanced and metastatic prostate cancer subtypes. Whole-exome and transcriptome sequencing has led to recognition of novel potential driver mutations, somatic mutations and copy number alterations [10]. Importantly, some of these DNA alterations are clinically actionable, and potentially targetable and hold promise for development of personalized therapeutic options. Mutational profiling is also leading to a better understanding of the biological mechanisms of therapeutic resistance. The focus of this review paper is to give a summary of the current clinical perspectives on the indications, pros and cons of the currently approved regimens, and to delve into future investigations of novel therapies and biomarker testing.

Hormone Naïve Metastatic Prostate Cancer

Androgen deprivation therapy

Continuous (CAD) vs intermittent androgen deprivation (IAD) was studied as a non-inferiority trial in intergroup trial INT 0162 (S9346) [11]. Median overall survival (OS) was 5.8 years in the continuous as compared to 5.1 years in the intermittent arm (HR 1.10, 95% CI 0.99–1.23). This trial also studied quality of life (QoL) parameters at baseline, 3, 9, and 15 months. Only erectile function and mental health showed statistically significant improvements at three months with IAD, however this advantage was lost at later time points. The results of this trial were contrary to common belief that IAD and CAD have similar outcomes. A recent report critiques the clinical relevance of a margin of non-inferiority ranging from 7 months to 1.8 years that was considered a statistically acceptable difference between the two arms [12]. Most treating physicians would concur that a difference of greater than 7 months would be clinically significant and cannot be considered a comparable outcome. In summary, none of the randomized trials conducted have revealed that IAD was better than CAD, and the ones that claimed non inferiority, accepted fairly large differences in OS outcome that are not clinically acceptable. In fact OS was worse in the intermittent group, in some trials such as SWOG 9346, with a median OS difference of almost eight months, favoring continuous therapy as standard.

Role of early Docetaxel [Table 1]

Early docetaxel in metastatic hormone sensitive prostate cancer has recently emerged as a new standard of care in the patient population with extensive metastatic burden. [13]. The CHAARTED study randomized 790 patients to ADT with six cycles of docetaxel vs ADT alone. With a median follow up of 29 months, OS was noted to be significantly higher in the chemo-hormonal group with a difference of 14 month in median OS (HR 0.61, 95% CI 0.47–0.80). Subgroup analysis of 513 patient with extensive or high volume disease, defined as visceral metastasis and/or four or more areas of bone metastasis, showed that OS was significantly increased in the chemotherapy group (median OS 49 versus 32 months, HR 0.60, 95% CI 0.45–0.81). The subgroup analysis of low volume disease comprised of 277 showed no significant OS benefit (HR 0.60, 95% CI 0.32–1.13, $p = 0.11$). Similar results have been observed in the STAMPEDE trial that was presented at ASCO 2015 [14]. 2962

patients with metastatic or high-risk disease were randomized. The initial results demonstrated an improvement in OS in chemo-hormonal arm vs ADT alone (Median OS 77 vs 67 months, HR 0.76, 95% CI 0.63–0.91). In a subset analysis of patients with high-risk non metastatic disease, OS benefit persisted in the combined docetaxel and ADT arm. (median OS 65 versus 43 months, HR 0.73, 95% CI 0.59–0.89). A third study done by the French group (GETUG-AFU 15 trial)[15] with longer median follow up of 82.9 months, failed to show benefit in a similar patient population but predominantly comprised of patients with low volume metastatic disease. Of the 385 patients in the intention to treat population, 212 had died. Median OS was 46.5 months [39.1–60.6] in the ADT arm vs 60.9 months [46.1–71.4] in the ADT + Docetaxel arm (HR: 0.9 [95% CI: 0.7–1.2]). In a subset analysis of high volume disease patients, the median OS was 35.1 months [29.9–44.2] in the ADT alone arm vs 39 months [28–52.6] in the combination arm (HR: 0.8 [0.6–1.2]). The smaller sample size and low proportion of extensive disease patients, could have contributed to the attenuated impact of early chemotherapy. The role of early chemotherapy in non-metastatic high risk prostate cancer receiving definitive ADT and radiation, was studied in RTOG 0521[16]. 562 evaluable patients were randomized to ADT with radiation vs ADT with radiation followed by docetaxel. With a median follow up of 5.5 years, a 4 year OS was 89% (95% CI : 84–92%) and 93% (95% CI : 90–96 %) in the arms without and with docetaxel chemotherapy (HR 0.68 CI 0.44–1.03).

Role of early Abiraterone/Enzalutamide

Enzalutamide, which is a direct androgen receptor (AR) blocker, has been studied in a phase II trial in the setting of hormone sensitive prostate cancer without ADT [17]. 67 men with hormone sensitive disease, that were either metastatic or showing progression by prostate specific antigen (PSA) only, in whom ADT was indicated. 62/67 (93%) had PSA decline. Abiraterone acetate was studied in a phase II trial (SWOG 1014) in metastatic hormone sensitive patients that had PSA of 4 or greater, after being on ADT for 6–12 months [18]. Five (13%) patients achieved an undetectable PSA of 0.2ng/ml (95% CI 4%, 27%) and 9 (23%) patients had a nadir PSA level between 0.2 and 4 ng/ml. The study did not reach the protocol pre-specified response rate but it showed that few patients with suboptimal response to ADT can potentially respond to abiraterone. [18, 19].

Our group at Karmanos Cancer Institute is currently conducting a phase II randomized multicenter trial to investigate the combination of enzalutamide + luteinizing hormone releasing hormone (LHRH) analogue vs bicalutamide + LHRH analogue in metastatic hormone sensitive prostate cancer (NCT02058706). This study has utilized the PSA nadir after 7 months of ADT as the primary endpoint, that serves as a surrogate for OS outcome. A large global phase III trial with similar study design, but utilizing OS as an endpoint, is currently ongoing [20].

Current Management of Castrate Resistant Prostate Cancer Advances in Chemotherapy

ARV-7, a truncated form of androgen receptor has been postulated to predict resistance to abiraterone and enzalutamide based therapies [21]. In a recent study, ARV-7 was analyzed in

circulating tumor cells of patients with metastatic castrate resistant prostate cancer. In this study, detection of ARV-7 was not associated with primary resistance to taxane-based chemotherapy. Based on this analysis ARV-7 may represent a predictive marker for taxane sensitivity [22].

Cabazitaxel demonstrated OS benefit post docetaxel and now with the use of docetaxel in hormone sensitive metastatic prostate cancer, it will likely emerge as the default front line chemotherapy in mCRPC. A phase II trial randomized patients to cabazitaxel with or without carboplatin [23]. With a median follow up of 11.4 months, median PFS was 4.4 months in cabazitaxel alone vs 6.7 months in the combination arm (95% CI 2.8–5.7 vs 4.4 – 8.9, $p = 0.01$).

Overcoming chemotherapy resistance has been an area of active research but with disappointing clinical results. Docetaxel based combinations have failed to demonstrate an OS benefit [24]. OGX-011, an antisense inhibitor of clusterin initially demonstrated promising efficacy in combination with docetaxel based chemotherapy. [25]. Phase III trials of docetaxel and cabazitaxel with/without OGX-011 have revealed no benefit in OS. Median OS of 23.4 months was noted in custirsen arm vs 22.2 months with docetaxel and similarly lack of pain control or OS benefit in the cabazitaxel study [26].

Antibody drug conjugates are agents that utilize a combination of antibody connected by a linker to a chemotherapeutic agent, enabling efficient delivery of chemotherapy to cancer cells. A phase II trial of PSMA with monomethyl auristatin E (MMAE) showed anti-tumor activity and PSA reduction in taxane refractory population [27]. However the toxicity of ADCs, especially neuropathy, hyperglycemia and constipation, and the modest therapeutic activity has represented a challenge for rapid development of this modality in mCRPC.

Immunotherapy

Sipuleucel T has demonstrated OS benefit in the patients with minimally symptomatic/asymptomatic patients with metastatic CRPC [3]. The patients with a PSA of 22ng/ml or less had a prolonged median OS of 41.2 months as compared to 28.3 months in the placebo arm. Sipuleucel T is best applied to patients in the early or the slowly progressive phases of mCRPC. Other vaccine therapies are being investigated in placebo-controlled trials.

Immune checkpoints such as cytotoxic T-lymphocyte associated protein 4 (CTLA 4) and programmed cell death 1 (PD-1/ PDL-1) have shown modest efficacy in mCRPC [28,29].

Prostavac, a novel immunotherapy, is a PSA-targeted poxviral-based vaccine, administered with three costimulatory molecules (known as TRI-COM) to increase PSA-specific immune responses [30]. The primary endpoint of PFS was unchanged in a placebo controlled randomized trial, however a 8.5-month improvement in median OS (25.1 months versus 16.6 months) and a 44% reduction in the death rate (HR 0.56, $P = 0.0061$) was noted [31]. A randomized placebo-controlled multicenter phase III trial (PROSPECT) is currently ongoing and will evaluate three arms: ProstVac-VF plus adjuvant GM-CSF, ProstVac-VF plus placebo and placebo-only (NCT01322490). The primary endpoint of the ongoing study is

OS, which is appropriate for an immune therapy but will require prolonged follow up and maybe confounded by subsequent treatments.

ADXS-PSA (Advaix Inc.), an immunotherapy that delivers PSA antigen to the antigen presenting cells via a live attenuated gram positive bacterial vector [32] has commenced clinical trials in combination with a PD-1 inhibitor pembrolizumab (NCT02325557). PDL-1 expression was noted to be upregulated after anti-androgen and inflammatory cytokine treatment [33]. Clinical trials of pembrolizumab in combination with enzalutamide (NCT02312557) and cryosurgery (NCT02489357) are ongoing.

Bispecific antibodies are being investigated as a non-toxic targeted approach. In a phase 1 trial with Anti-CD3 and Anti-Her2 bispecific antibody in mCRPC, significant decrease in PSA and pain score was noted in three of the seven evaluable patients. [34]. The regimen had no serious treatment related adverse events. Phase II evaluation is ongoing in mCRPC; both in the pre and post chemo settings, in combination with the PD-1 inhibitor pembrolizumab. Future evaluation of vaccines and T cell therapies in combination with immune checkpoint inhibitors should be exciting for the potential of inducing durable remissions.

Androgen targeted Therapy

An attractive option at present is to use abiraterone and enzalutamide sequentially with the hope of delaying chemotherapy in metastatic CRPC. Unfortunately it appears that these two agents used in immediate sequence provide minimal benefit, with evidence of cross-resistance. Retrospective analysis of patients treated with abiraterone after progression on docetaxel followed by enzalutamide showed modest PFS of 2.7 to 3.5 months with less than 20% patients attaining > 30% decline in PSA [35, 36]. Enzalutamide after docetaxel and abiraterone, resulted in 40% of the patients with PSA decline [37]. In addition, there is a threat of encountering neuroendocrine prostate cancer at progression. Post docetaxel; the beneficial effects of either abiraterone or enzalutamide are attenuated and with the increasing use of chemotherapy in hormone naïve prostate cancer, this is a very likely future scenario in majority of mCRPC patients. This fact underlines the importance of clinical trials of early use of abiraterone and enzalutamide prior to the emergence of castrate resistance.

The non-metastatic disease state remains an unmet need in prostate cancer and to date no systemic agent has shown proven benefit. ARN-509 and ODM-201 are androgen receptor inhibitors currently in placebo controlled double blind trials. Both are androgen receptor antagonists that claim higher affinity to androgen receptor than enzalutamide and lower central nervous system penetration [38,39].

Use of enzalutamide and abiraterone combination in metastatic castrate resistant prostate cancer is of interest. This therapy mimicks complete androgen blockade as per the combination of LHRH analogue with bicalutamide. A Phase III (ALLIANCE) trial is testing the use of enzalutamide with or without abiraterone in a multicenter study within the cooperative group setting (NCT 01949337).

An AR splice variant (ARV-7) was detected to be a reliable marker in metastatic CRPC to predict for lack of response to abiraterone or enzalutamide [21]. ARV-7 detection in circulating tumor cells from men with mCRPC was noted to be associated with resistance to enzalutamide and abiraterone. The presence or acquisition of the ARV-7 mutation was associated with the resistance. The study was conducted in only 31 patients each treated with abiraterone or enzalutamide and needs validation in a larger cohort. In addition the reproducibility of the test needs to be determined and multicenter clinical trial testing is required. Currently galeterone is being compared to enzalutamide in patients expressing ARV-7 in mCRPC (NCT02438007). Similarly aldo-keto reductase family 1 member C3 (AKR1C3) has been implicated in enzalutamide resistance after treatment with enzalutamide [40]. Androgen receptor escape with expansion of cancer cells with unregulated glucocorticoid receptor [41] and also via the androstenedione pathways are some of the mechanisms of resistance to agents such as enzalutamide and abiraterone respectively.

Advances in Radiation therapy

External beam radiation therapy has been used for decades for treatment of neuropathic compression and for pain palliation in metastatic prostate cancer. Due to the extensive bone involvement in advanced prostate cancer, radiopharmaceuticals such as strontium-89 and samarium-43 were introduced to rapidly control multiple sites of pain. However the severe myelosuppressive effects of these agents limited their clinical application. Radium-223 is a therapy that mimics calcium and has selective uptake in the bones. It utilizes alpha particles to decrease the penetration into the bone marrow and limits the incidence and extent of cytopenias. Alpharadin or radium-223 was evaluated in a placebo controlled phase III trial in docetaxel pretreated or chemotherapy ineligible mCRPC patients [9]. An OS benefit was noted favoring the radium-223 treatment and minimal incidences of severe neutropenia and thrombocytopenia (Grade 3 and 4 incidence of 2% and 6% respectively) were noted. Combination studies of Radium-223 with abiraterone and enzalutamide are completed and results are awaited. A global three arm randomized trial evaluating Radium-223 at higher doses, (80 Becquerel units/kg as compared to 50 becquerel units/kg) or prolonged administration (12 months versus 6 months) is complete and will shed light on the optimal regimen of alpharadin therapy.

Novel Agents with Promising Efficacy in CRPC

VT-464, is a small molecule CYP 17 inhibitor that has shown promise in pre-clinical studies[42] and is currently in clinical trials (NCT 02445976). EPI-506 is another small molecule N-terminal domain (NTD) androgen receptor inhibitor that is being studied in Phase I/II clinical trial [43]. ASN-001 (Asana Biosciences) [44] is a CYP17 lyase inhibitor that selectively binds to and inhibits the lyase activity of CYP17A1 in both the testes and adrenal glands and is currently in phase I/II testing. Galeterone (TOK-001) has anti testosterone production and androgen receptor blockade properties and is currently being evaluated in a randomized trial comparing it to enzalutamide in ARV-7 positive mCRPC [45]. AZD3514 is a first-in-class, oral, selective androgen-receptor down-regulator (SARD) which functions as a powerful androgen receptor inhibitor with efficacy in enzalutamide resistant cell lines. Phase I study of 49 patients [46] determined the dose limiting toxicities

of nausea and emesis, and preliminary efficacy with 17% measurable disease responses and 13% PSA response rates. Insulin like growth factor receptor inhibitors showed initial promise in mCRPC however the toxicity of hyperglycemia, and modest clinical activity observed to date, are the obstacles in further development of these agents. Disappointing clinical activity was seen with the addition of IGF1R antibody to ADT in the SWOG0925 trial in hormone sensitive advanced prostate cancer [47]. The proportion of patients achieving an undetectable PSA (<0.2 ng/ml) at 28 weeks was 40% with the addition of cixutumumab and 32.3% with ADT alone [47].

Bet or bromodomains have emerged as actionable targets that play an important role in maintaining androgen receptor (AR) activity. The BET inhibitors display *in vitro* disruption of AR recruitment to target gene loci and inhibit gene transcription downstream of AR, including induction of the TMPRSS2-ERG gene fusion and its oncogenic activity [48]. The efficacy of BET bromodomain inhibition in CRPC xenograft mouse models was superior to that seen by AR antagonists such as enzalutamide. The AR can also promote c-myc upregulation that promotes tumor growth independent of the ligand and this can also be impacted by BET inhibition [49].

Selective inhibitors of nuclear exporter (SINE) is a novel class of agents with a distinct and unique mechanism of action. The target, exportin-1 (XPO1) is responsible for export of about 220 proteins including several tumor suppressor and growth regulatory proteins [50]. Many solid tumor malignancies have elevated XPO1 levels and inhibiting this exporter protein has shown inhibition of tumor growth. KPT-330 or selinexor (Karyopharm Inc) was selected for clinical trial testing as the most effective and orally bioavailable SINE. The phase I trial reported dose limiting toxicities of dehydration, anorexia and fatigue, and preliminary efficacy in mCRPC. All five patients with prostate cancer demonstrated stable disease despite being pretreated with multiple lines of chemotherapy and hormone therapies. The observation of clinical results in the phase I trial, led to a phase II trial of KPT-330 in mCRPC which is ongoing [50].

Biomarker Based Personalized Therapies in CRPC

Therapies investigating molecular pathways that are linked to the androgen receptor pathway, or independent of it, are currently in clinical trials and are summarized in Table 2.

Poly adenosine diphosphate [ADP]–ribose polymerase (PARP) inhibitors initially were reported to show activity in BRCA mutation carriers with mCRPC [51]. However recent studies have noted that DNA repair aberrations, with or without BRCA mutations are susceptible to platinum and PARP inhibitors. [52] A phase 2 clinical trial of the PARP inhibitor, olaparib was conducted in mCRPC cases pretreated with at least two prior regimens including chemotherapy [53]. 16 of 49 evaluable patients had abnormality in DNA repair gene (most commonly BRCA) detected by next-generation sequencing. 14 of these 16 patients (88%) showed response to olaparib compared to only 2 of 33 (6%) biomarker-negative patients. Radiologic PFS was 9.8 months in biomarker-positive group compared to 2.7 months in the biomarker-negative group ($P < 0.001$) Median OS was 13.8 months in the biomarker positive group and 7.5 months in the biomarker-negative group ($P = 0.05$).

The loss of PTEN in prostate cancer is associated with phosphatidylinositol-3 (PI3) kinase activity and hence clinical evaluation of single agent inhibitors of this pathway, or in combinations with enzalutamide or SARDs is ongoing [54, 55]. MTOR overexpression is another mechanism of resistance noted to chemotherapy or ADT [56]. Combinations of mTOR inhibitors and AR targeted agents are undergoing evaluation. The combination of carboplatin and MTOR inhibitor everolimus was studied. Modest activity was noted and patients with loss of Akt on archival tumor tissue had an increased likelihood of clinical benefit with the regimen [57].

Neuroendocrine prostate cancer

Neuroendocrine histology in prostate cancer usually marks the development of highly aggressive disease with a dismal prognosis. It expresses neuroendocrine markers such as chromogranin A, synaptophysin, neuron specific enolase. This disease typically lacks AR expression and has loss of the copy numbers of tumor suppressors RB1 (85% to 90%) and displays TP53 (50% to 60%) mutations [58]. Patients usually present with metastatic disease and low PSA levels. These tumors are known to lack androgen receptors. Small cell cancers of prostate are rare (<1% of prostate cancers), however the development of neuroendocrine disease is noted after treatment with androgen deprivation therapy. In a recent review, 101 pathological specimens from men treated with abiraterone or enzalutamide showed classic small cell cancer in 12% [59]. Median overall survival was noted to be 6.6 months in this group. The amplification of aurora kinase A as well as N- myc have been demonstrated in these tumors [59]. These tumors demonstrate AR positive and negative cells and demonstrate TMPRSS2-ERG gene rearrangement. The latter can also be detected in circulating tumor cells [60]. The loss of cyclin D1 seems to be unique to prostate neuroendocrine tumors. The therapeutic implications of this have not been explored at present [61]. Platinum based chemotherapy is the standard management however relapses rate are very high. Aurora kinase inhibitors and other targeted therapies are under active investigation.

Conclusions

Multiple therapies with distinct mechanisms of action are now available for the management of metastatic CRPC. Figure 1 summarizes the current and clinical trial based treatment algorithm for metastatic prostate cancer. Since most of these agents were developed in parallel, no comparison trials exist. The cumulative effect of using multiple therapies in sequence is likely to result in attenuated outcomes, and PFS and OS similar to those seen in clinic trials cannot be realistically expected. The early use of docetaxel is expected to have an impact on the efficacy of abiraterone and/or enzalutamide. Improvement in efficiency of this therapy with use of predictive biomarkers will go a long way towards improving outcomes, reducing costs and decreasing toxicities. Significant strides have been made in this field, resulting in a clinically relevant impact on the morbidity and mortality of advanced prostate cancer.

The last few years have demonstrated a switch from chemotherapy based regimens to non-chemotherapy options in metastatic CRPC. This has made systemic therapies widely

applicable and feasible, as even the elderly, or those with significant co morbidities can tolerate the treatments. Now the time is ripe to explore narrowing the use of these therapies based on predictive biomarkers exhibited by these cancers that will escalate therapeutic efficiency. Development of predictive biomarkers for each of these therapies and careful selection of an enriched patient population will reduce costs, enhance outcomes and optimize toxicities. With an exponential increase in actionable targets in metastatic CRPC, the personalized medicine dream is on the brink of turning into reality in this disease.

Acknowledgments

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Summary

- Combinations and sequences of current multifaceted therapies are under active investigation.
- Personalized therapy based on actionable targets expressed, is the future of prostate cancer management.
- Immune therapy with check point inhibitors, vaccines and T cell based regimens hold promise in CRPC.
- Neuroendocrine prostate cancer, perhaps the most lethal form of PC, needs to be tackled with dedicated effort.

Figure 1.
Contemporary Therapeutic Decision Making in Metastatic Prostate Cancer

Table 1

Randomized trials of early chemotherapy in hormone sensitive prostate cancer

Study	Sample size	Therapy arms	Endpoint OS chemo vs not	Hazard ratio (HR)	P value
CHARTED [2]	790	ADT + chemo ×6 ADT	58 mo 44mo	0.61	0.0003
STAMPEDE [3]	2962	ADT + chemo ×6 ADT	77mo 67mo	0.76	0.003
GETUG- AFU 15 [4]	385	ADT + chemo ×9 ADT	60.9mo 46.5 mo	0.9	0.444
RTOG 0521 [5] Non metastatic high risk prostate cancer	562	ADT + RT ADT + RT + Chemo × 6	89% (4 year OS) 93%	0.68	0.03

CHARTED – Chemohormonal Therapy vs Androgen Ablation Randomized Trial for Extensive Disease, STAMPEDE – Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of drug Efficacy, GETUG-AFU – French Genitourinary Tumor Group, ADT – Androgen Deprivation Therapy, R – Radiation, Chemo – Docetaxel, mo-months

Table 2

Selected ongoing Phase I, II and III Clinical Trials in Advanced Prostate Cancer

Trial	Target	Investigational Drug	Study design
SP005/VIABLE Sotio Inc	Dendritic cell based active immunotherapy	DCVAC/PCa	Phase III: Docetaxel+/- DCVAC/PCa Double Blind Placebo Controlled
Alliance	Hormone therapy	none	Phase III: enzalutamide+/- abiraterone
Galeterone	ARV-7 patients only	Galeterone/TOK-001	Phase III: enzalutamide vs galeterone
PI3 kinase inhibitors	PTEN loss	GSK20331	Phase I: enzalutamide + GSK20331
PI3 kinase inhibitors	PTEN loss	AZD 5157	Single agent and combinations
NCT02380313	AKT	Afuresertib	Abiraterone/ Enzalutamide
NCT02059213	Cyclin dependent kinase 4/6	Palbociclib	Androgen deprivation therapy
NCT02204072	Insulin like growth factor	BI 836845	Enzalutamide
NCT01120236	Insulin like growth factor	Cixutumumab	Androgen deprivation therapy
NCT02182622	Hedgehog	LDE225	Docetaxel
NCT02115828	Hedgehog	Vismodegib	
NCT02125084	MTOR	MLN0128	Enzalutamide
NCT02091531	MTOR	MLN0128	Single agent
NCT02407054	MTOR	LY3023414	Enzalutamide
NCT01385293	PI3 Kinase	BKM120	Single agent
NCT01576172	Poly-ADP-ribose polymerase (PARP)	Veliparib	Abiraterone
NCT01972217	Poly-ADP-ribose polymerase (PARP)	Olaparib	Abiraterone
NCT01885949	Vascular endothelial growth factor (VEGF)	Tivozanitib	Enzalutamide
NCT01254864	Vascular endothelial growth factor (VEGF)	Sunitinib	Abiraterone