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Rational Categorization of the Pipeline of New Treatments for Advanced Cancer – Prostate Cancer as an Example

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1. Introduction

1.1. The problem

Whilst improvements in patient survival have been realized for a number of haematological and solid malignancies in the last 30 years, new efficacious systemic anti-cancer treatments are still needed. The current, widely used drug development paradigm is often associated with a poor conversion rate from experimental to licensed drug. This process involves a significant investment of resources from sponsors, investigators and patients and to date has only lead to a limited chance of success. At present there are in excess of 800 anti-cancer agents in development and less than 10 new FDA approvals each year [1]. In order to address this problem there has been considerable debate concerning the best trial methodology to rationalize this process, with discussion of the timing, sequence and design of appropriate trials [2]. At present in many tumour types including breast, lung, renal cell and prostate cancer, the pipeline of new agents is crowded. In order therefore to use the available financial and patient resource wisely, it is crucial to identify the key important pathways in oncogenesis that in turn may help and prioritize the drugs with the most promise.

1.2. A promising future

In recent years advances in molecular biology have aided our understanding of the pathogenesis of cancer. This has occurred concurrently with technological advances allowing rational drug design and development (such as tyrosine kinase inhibitors, monoclonal

antibodies and anti-sense oligonucleotides). Combining these two advances has been very beneficial in the drug development process such that we now have a wealth of opportunities. The challenge now is how to rationally categorize and prioritize the many strategies that can be deployed. In the discussion below, we propose a rational process to evaluate the merits of different strategies and use prostate cancer as an example. The different strategies include focusing on cytotoxic agents, synthetic lethality strategies, angiogenesis, oncogene addiction pathways and activated survival pathways such as those driven by systems of inflammation and/or metabolism.

2. Building on past successes – Cytotoxics and agents targeting key biological pathways

2.1. Cytotoxic agents

Cytotoxic chemotherapy has had an established role for many cancer types for many decades with the ability to eradicate some cancers, prevent relapse from micrometastatic disease in others and offer life prolonging or palliative benefit in other cancers. With respect to prostate cancer, a role for cytotoxic chemotherapy in the treatment of metastatic castrate refractory prostate cancer (CRPC) was first established using mitoxantrone in 1996, when it was shown to provide effective palliation of pain symptoms compared to prednisolone alone without prolongation of overall survival [3]. This was not associated with a survival benefit and to date the only class of cytotoxic agents to improve survival in metastatic prostate cancer are the taxanes [4]. Docetaxel was licensed in metastatic CRPC patients in 2004 following a phase III study of docetaxel plus prednisone versus mitoxantrone plus prednisone. The taxanes block cells in the G2/M phase of the cell cycle by stabilizing microtubules in the mitotic spindle thereby rendering them unable to separate during mitosis. Cancer cells sensitivity to taxanes is often short lived and resistance develops. The mechanism of this is poorly understood, although over expression of P-glycoprotein and mutations in the tubulin gene have been described [5]. Whilst the non-specific targeting of cycling cells by cytotoxic agents is not classed as targeted therapy, ongoing efforts do exist to introduce new cytotoxic agents to the prostate cancer arena. The aim of improving efficacy and delivery whilst minimizing toxicity underlies this development. In this era of personalized medicine, cytotoxic agents may continue to have a role especially where tumours do not harbour an obvious upregulated or mutated pathway to target. This approach has already led to the development and approval of the synthetic taxane - cabazitaxel for use in the second line metastatic CRPC setting. In the international multicentre phase III TROPIC trial, patients who had progressed on docetaxel were randomized to receive cabazitaxel plus prednisone or mitoxantrone plus prednisone. An improvement in overall survival of 2.4 months was seen (15.1 months versus 12.7 months HR=0.7 $p<0.001$) [6].

In addition to new members of existing cytotoxic drug classes, new mechanisms of drug delivery continue to be developed. Nanoparticle albumin bound (nab) paclitaxel and docetaxel use albumin as a vehicle to improve drug delivery to the tumour. This approach has proven to be successful using nab-paclitaxel (Abraxane®) in metastatic breast cancer where it deliv-

ered a 49% higher dose of drug to patients than a conventional solvent based approach. In addition, higher response rates were seen with an overall response rate of 33% (versus 19% for standard paclitaxel) and increased time to progression from 16.9 to 22 weeks [7]. Both agents are also in development in prostate cancer, where phase II trials are currently evaluating nab-paclitaxel and nab-docetaxel in the CRPC population. Other novel drug delivery strategies include water soluble biodegradable polyglutamate polymer with linked chemotherapeutic molecules (e.g. paclitaxel poligumex, Opaxio®) [8,9] and a nanoparticle bound docetaxel agent (BIND014) has also recently entered phase I clinical trials [10] (Table 1)

Drug	Class	Study Design	Results	Current phase of clinical development	Reference
Androgen receptor blockers					
Abiraterone	CYP 17 lyase inhibitor	Randomised placebo controlled phase III trial in post-docetaxel and chemo naïve CRPC pts.	Overall survival adv 3.9 months in post chemo population Chemo naïve study stopped early. Median OS not yet reached for Abiraterone	Licensed in post-docetaxel pts Awaiting license in chemo naïve pts	[26, 28, 29]
Enzalutamide /MDV3100	Androgen receptor antagonist	Phase III randomized placebo controlled AFFIRM study	Overall survival adv 4.8 months. Favourable toxicity profile. 0.6% seizure rate	Phase III trials in chemo-naïve setting completed accrual	[33, 34]
Orteronel/ TAK700	17,20 lyase inhibitor	Phase I-II dose escalation study in metastatic CRPC pts accrued.	RPIID is 400mg BID, no DLTs	Phase II trial accruing in asymp CRPC pts, pts without mets but rising PSA & in combination with docetaxel in met CRPC pts.	[30, 31]
TOK-001	AR antagonist, CYP 17 lyase inhibitor, ↓AR levels			Phase I-II in CRPC pts (ARMOR1) currently accruing	[113]
Histone deacetylase (HDAC) inhibitors					
Panobinostat	HDAC inhibitor	Phase I completed in combination with docetaxel/pred and phase II completed as single agent in CRPC pts	Safe as single agent and in combination. IV formulation going forward	Phase I-II with Bicalutamide in CRPC pts accruing	[37]

Vorinostat	HDAC 6 inhibitor	Phase I with safety study with docetaxel q21 days and vorinostat q1-14 days Phase II in post chemo CRPC pts receiving 400mg vorinostat orally	12 pts enrolled but 5 DLTs reported. Trials suspended due to excess toxicity 27 pts but terminated due to excess toxicity. Significant toxicity seen. 44% G3 AE's	Phase I in combination with temsirolimus planned	[38, 39]
SB939	HDAC inhibitor (multiple classes)	Phase I dose escalation trial in solid malignancies	MTD 80mg, RPIID 60mg, DLTs were fatigue, troponin elevation & QTc prolongation	Phase II single agent study in recurrent/met prostate cancer accruing	[114]
Romidepsin	Depsipeptide HDAC inhibitor	Phase II in chemo naïve met CRPC pts. 13 mg/m ² q1,8,15 every 28 days	35 pts enrolled. 2 pts had PR "/>6months. 11 pts stopped due to toxicity. N&V, fatigue & anorexia	Combination studies with cytotoxic agents planned	[115]
HSP90 inhibitors					
IPI-504 (Retaspmycin)	17-AAG analogue HSP90 inhibitor	Phase II study in CRPC patients stratified by prior chemotherapy at 400mg/m ²	No PSA or RECIST responses seen. G5 ketoacidosis and hepatic failure observed	Clinical development ongoing in NSCLC	[43]
STA9090	2 nd gen HSP90 inhibitor	Phase I dose escalation studies with IV wkly and twice wkly admin	Wkly admin - MTD 216mg/m ² DLTs due to amylase elevation, diarrhoea & fatigue Twice weekly – MTD as yet not reached	Phase II prostate trials planned	[44]
17AAG (Tanespimycin)	1 st gen HSP90 inh	Phase II in metastatic CRPC pts. 300mg/m ² weekly for ¾ weeks	Trial stopped after 1 st phase due to lack of PSA response. G3 fatigue	No further prostate trials	[41, 42]
siRNA against AR	Nanoparticle technology	In pre-clinical development			[10]

Table 1. The Androgen Receptor pathway

New classes of cytotoxic agents are also in development in prostate cancer. These are members of the epothilone family and the halichondrin B analogue - eribulin. The epothilones are macrolide antibiotics that also act by stabilizing microtubules. They are water soluble and as such

do not have to be administered in a lipophilic solution, therefore reducing the allergic reaction rate compared to taxanes. To date the epothilone - ixabepilone is licensed for use in metastatic chemo-refractory breast cancer, although it has also shown activity and acceptable toxicity in a phase II study in a mixed chemo naïve and post chemotherapy CRPC population [11]. Clinical development of several members of this family in prostate cancer continues. Patupilone or naturally occurring Epothilone B and sagopilone (a fully synthetic compound) have also shown activity in post docetaxel and chemo naïve CRPC patients respectively [12, 13].

Eribulin mesylate (or Halaven, Eisai Co.) is a synthetic analogue of the marine sponge natural product Halichondrin B that is a potent naturally occurring mitotic inhibitor. Eribulin binds predominantly with high affinity to the ends of microtubules leading to mitotic arrest and ultimately apoptosis. Eribulin is also licensed for use in metastatic chemotherapy refractory breast cancer patients although a phase II study in both chemotherapy naïve and pretreated prostate cancer patients has been performed. Most activity was demonstrated in the chemotherapy naïve cohort with a 22.4% PSA response rate and 8.8% overall response rate [14].

Another successful cytotoxic strategy for targeting prostate cancer metastases with radiation has been the studies using the alpha-emitter Radium 223. This radiopharmaceutical that acts as a calcium mimic can selectively target bone lesions from prostate cancer whilst its low penetration alpha-emissions are cytotoxic to cancer cells. Its half life of 11.4 days also favours its use as a cancer treatment. Having proven its safety in phase I and II trials [15], the phase III AL-SYMPCA trial was stopped early after a pre-planned efficacy interim analysis following recommendations from the independent data monitoring committee on the basis of a significant improvement in overall survival and favourable toxicity profile. In this large study of 922 patients, Radium-223 significantly improved overall survival in patients by 2.8 months (HR 0.695 95% CI 0.552-0.875) in addition to delaying the time to first skeletal-related event by 5.2 months (HR 0.610 95% CI 0.461-0.807) [16].

2.2. Targeting key biological pathways

A leading premise for the treatment for advanced prostate cancer is to target the androgen receptor (AR) axis or to identify cases where a single pathway mutation is thought to drive carcinogenesis. It is proposed that triaging the current pipeline of agents can be directed by building on prior successes. In light of recent advances in our knowledge of AR pathway signaling, further exploration of this pathway is warranted. Moreover, since molecular interrogation of distinct clones driving individual prostate cancers is now possible, treatment of these tumours with agents targeting these mutations would also be desirable. In the past the prostate cancer treatment paradigm has been to expose the patient to an established sequence of agents in a 'one size fits all' approach – which may have missed identifying a drug with major activity in a few patients. A strategy that is being increasingly more recognized is the need to characterize a patient's cancer and select the most appropriate treatment for that cancer phenotype. It is also important to ensure that critical appraisal of pre-clinical and clinical research continues to help guide these endeavors to identify oncogene addiction pathways.

3. Extinguishing the AR axis

The androgen dependence of prostate cancer on testosterone was first observed as early as 1941 when the effect of castration on androgen levels in prostate cancer was studied [17]. This led to the introduction of androgen deprivation therapy and the generation of the castrate state where serum levels of testosterone are reduced to <50ng/dl or 1.7nmol/l. This treatment is initially effective in 80-90% of patients and results in PSA or radiological responses and clinical improvement in the patient's symptoms. Eventually, the patient's cancer progresses despite serum testosterone levels continuing to be low. The current term used to describe this state is 'castrate resistant prostate cancer' which has replaced the misleading term 'hormone-refractory prostate cancer'. CRPC more accurately describes the ongoing dependence of the cancer on AR signaling despite low measurable testosterone levels.

Ligand independent AR signaling is thought to occur in the majority of CRPC tumours via activation of oncogenes such as ERBB2 or H-*ras* and through MAP kinase signaling [18, 19]. A small proportion of CRPC tumours will also harbour amplifications or point mutations in the ligand-binding domain of the androgen receptor gene leading to altered responsiveness to ligands [20]. A third mechanism of action bypasses androgen receptor in favour of an alternative signaling pathway [21].

The evidence for ongoing androgen sensitivity is also strengthened by the observation of up regulation of AR protein levels in hormone resistant versus hormone sensitive paired xenografts [21] as well as in patient tumour samples [22, 23]. Maintained intra-tumoural levels of testosterone and dihydrotestosterone are also observed despite castrate serum androgen levels [24].

In addition to testicular androgen production, extragonadal sites of androgen synthesis also contribute to testosterone levels. These *de novo* adrenal and intra-tumoural pathways utilize the 17 α -hydroxylase and C17, 20-lyase activity of the CYP17A1 enzyme involved in the steroid biosynthesis pathway. The importance of this pathway was initially clinically exploited with the use of ketoconazole, a weak reversible inhibitor of CYP17. Anti-tumour activity was demonstrated with a PSA response rate of 20-62% in phase II trials and a median duration of response of 3-7 months [25]. However its use was associated with significant toxicity and up to 20% of patients discontinued treatment. This toxicity profile has not been observed with the more potent CYP17 inhibitor abiraterone acetate. This agent has successfully reawakened interest in further manipulation of the AR axis in CRPC patients. After successful phase I and II clinical trial development [26, 27] randomized double blind placebo controlled phase III trials of abiraterone plus prednisolone versus placebo plus prednisolone in chemotherapy naïve and post docetaxel patients were conducted. Results in post docetaxel patients revealed a statistically significant increase in median overall survival of 3.9 months in favour of abiraterone as well as improvements in time to PSA progression, radiological PFS and PSA response rate [28]. More recent results from the interim analysis of chemotherapy naïve patients have also shown significant activity in favour of abiraterone with the interim data monitoring committee recommending unblinding and crossover for patients receiving prednisone alone [29]. Abiraterone was also well tolerated with the predominant

toxicities being hypertension, hypokalaemia and fluid retention. These are the expected consequences of the mineralocorticoid excess resulting from the accumulation of precursors upstream of CYP17. These have subsequently been managed with the concomitant use of steroids or the mineralocorticoid antagonist eplerenone.

Orteronel (or TAK 700, Takeda Pharmaceuticals) is another 17,20 lyase inhibitor which has also advanced to phase III CRPC trials after successful phase I and II development [30, 31]. This inhibitor is now in phase III trials as a single agent in asymptomatic CRPC patients and in patients with a rising PSA but no detectable metastatic disease as well as in phase I/II trials in a number of prostate cancer settings including in combination with docetaxel in metastatic CRPC patients.

In addition to steroid biosynthesis inhibitors, further manipulation of the AR axis in castrate patients has been demonstrated using MDV3100 or enzalutamide. First generation anti-androgens such as bicalutamide, flutamide and nilutamide competitively inhibit the AR ligand binding domain. This response is often transient as castration resistance develops which may in part be a consequence of the partial agonist activity of this class [21]. These observations led to the rational design of enzalutamide, an orally available anti-androgen with superior AR binding compared to bicalutamide, and no AR agonist activity in bicalutamide-resistant and AR-over expressing cell lines [32]. A phase I/II study of enzalutamide in 140 post-chemotherapy metastatic CRPC patients demonstrated a PSA response rate of 56% (78/140 patients), soft tissue responses in 22% (13/59 patients), and a median time to progression of 47 weeks. enzalutamide was well tolerated with the most common grade 3 or 4 adverse events being fatigue that resolved with a dose reduction [33]. This activity was confirmed in the multicentre double blind placebo controlled phase III AFFIRM trial comparing enzalutamide against placebo. This trial of 1199 docetaxel pre-treated patients was also stopped early due to a 4.8 months overall survival benefit for enzalutamide compared to placebo with all subgroups benefiting [34].

Other agents in development that manipulate the androgen receptor axis are shown in table 1. In addition to agents intrinsic to the androgen receptor pathway, inhibitors of chaperone proteins may also be important targets. Histone deacetylases (HDAC) are enzymes which remove acetyl groups from proteins and in so doing modulate the protein-protein interactions of co-activators associated with AR binding. HDAC enzymes are over expressed in certain solid tumours including prostate cancer, where high expression levels are associated with poor outcome [35]. HDAC over expression in prostate cancers is also often co-existent with genetic rearrangements in the ETS (E-twenty six) gene family. These genetic alterations have been found in up to 70% of prostate cancers and may interact with HDAC's already known to be upstream regulators and downstream transducers of the ETS transcription factors family [36]. The preclinical rationale for HDAC inhibition in prostate cancer has led to early phase clinical development of several HDAC inhibitors. Phase I/II studies of panobinostat both as a single agent and in combination with docetaxel confirmed the safety of this approach [37]. In the single arm study, all patients developed progressive disease despite evidence of acetylated histones in peripheral

blood mononuclear cells, however 5 out of 8 (63%) patients in the combination study had a $\geq 50\%$ reduction in PSA value. At present a study in combination with bicalutamide in CRPC patients is recruiting. However trials involving single agent vorinostat (an HDAC6 inhibitor known to acetylate tubulin and stabilize microtubules) have been terminated early due to excess toxicity with no significant activity [38, 39].

The other major group of agents that are involved in post-translational modification of the AR axis are heat shock proteins. These are proteins that ensure the maintenance of oncogenic protein homeostasis in the presence of stress factors such as hypoxia or acidotic conditions. Heat shock protein 90 (HSP 90) is an ATP-dependent multi-chaperone complex implicated in the function of the AR. The AR is stabilized by the interaction with HSP 90 that allows it to interact with androgens [40]. Pre-clinical models have shown HSP 90 inhibition leads to decreased AR expression and function and a phase I trial of 17-AAG both as a single agent and in combination with cytotoxic chemotherapy demonstrated drug safety [41]. The subsequent phase II study however failed to reach its primary endpoint and was terminated [42]. Significant toxicity was observed with the 17-AAG analogue retaspmycin (or IPI-504) [43] although clinical development of the second generation HSP90 inhibitor STA9090 has confirmed safety in phase I trials and is proceeding [44]. Studies are planned to determine whether the newer HSP90 agents can hit target and decrease activity with a suitable toxicity profile or whether the therapeutic window is too narrow for safe use of these agents.

In addition, small interfering RNA's (siRNA's) are a class of double stranded RNA molecules that are now known to exist as important gene regulatory factors in both plant and animal systems. Selective targeting of the androgen receptor by siRNA molecules may further silence the AR signaling pathway in prostate cancer. This may be made viable by nanoparticle technology being able to facilitate use of otherwise undeliverable agents. The development of these agents is currently hampered by the need for safe systemic delivery of these agents without the off target and immune stimulation problems encountered with other nucleic acid medicines such as plasmid DNA and anti-sense oligonucleotide [45].

4. An advanced understanding of cancer biology comes of age

4.1. Specific targeting of DNA repair mechanisms

In recent years one successful targeted approach has been to exploit the vulnerability of tumors with an impaired DNA damage repair mechanism by inhibiting a second DNA repair pathway and as such commit the cancer cell to die. This concept of synthetic lethality has been most successfully demonstrated in patients bearing tumors with *BRCA-1/-2* mutations where homologous recombination (HR) mechanisms are already known to be inadequate. This hypothesis has reactivated the development of poly (ADP-ribose) polymerase (PARP) inhibitors. PARP is an enzyme that is crucial in the base excision repair pathway. When this repair mechanism is inhibited in the presence of pre-existing impaired HR then efficient

DNA repair is prevented and apoptosis occurs. Following pre-clinical and more recently proof of concept clinical trials in patients with *BRCA* mutated breast and ovarian carcinoma, the PARP inhibitor olaparib has demonstrated significant activity [46]. Whilst it is hoped that the application of these agents may broaden to include sporadic tumours in which mutations in DNA pathways may also be found, there has also been considerable interest in other tumours types where these mutations may be found. The inherited *BRCA-2* mutation is associated with a 20% lifetime risk of developing prostate cancer that often occurs before 65 years of age. The subsequent tumors are often of high Gleason score, more advanced stage at diagnosis and patients have a shorter survival than patients with sporadic prostate cancers [47]. One of three prostate cancer patients with germ-line *BRCA* variant had a prolonged response to olaparib in a phase 1 trial [48]. In addition to *BRCA* mutated cancers, pre-clinical evidence has also demonstrated a sensitivity of tumours with phosphatase and tensin homolog (*PTEN*) deficiency to PARP inhibition [49]. This is one of the most commonly mutated genes in human cancers where it has a role in genome stability. *PTEN* deficiency is associated with an HR defect that sensitizes tumours cells to PARP inhibition using the same mechanism as *BRCA* mutated cancers.

At present, the clinical development of olaparib has been focused on breast and ovarian cancer. Studies in prostate cancer are underway with the PARP inhibitor veliparib (or ABT888) in combination with temozolamide in a phase I study recruiting patients with metastatic prostate cancer. In addition a phase I study using the Merck PARP inhibitor - MK4827 is currently recruiting to a prostate cancer enriched second stage following encouraging phase I study data in advanced solid malignancies [50].

4.2. Oncogene addiction pathways

The development of drugs targeting tumours driven by so-called ‘oncogene addictions’ has lead to some success. Examples include imatinib targeting the *bcr-abl* translocation in CML and mutated *c-kit* in GIST, trastuzumab and lapatinib in HER-2 positive breast cancers BRAF inhibitors in melanomas with BRAF mutations. Molecular studies in prostate cancer have to date identified mutations of this type in less than 20% of all sporadically occurring prostate cancers. Analysis of a cohort of 206 prostate cancer cases found the common BRAF mutation V600E in 10.2% (or 21/206 cases) [51], whilst PI3 kinase mutations were found in only 3% of a separate cohort [52]. Drugs inhibiting BRAF as well as PI3 kinase mutations may lead to meaningful responses in patients with tumors been driven by these mutations. It is hoped that further “oncogene addiction” pathways will be uncovered and be able to be drugged.

4.3. Ligand and transcription factor driven survival pathways

Whilst it is often hoped that mutations in a single molecular pathway will be uncovered as the crucial oncogenic event in tumour development and its abrogation lead to meaningful anticancer activity, to date this has been rarely found to be the case for sporadic tumours. Another approach is to consider the factors that cause and/or are associated with the development as well as the survival of cancer. The role of androgens and androgen receptor is clear for prostate cancer. Other biological approaches associated with cancer development

and survival include the metabolism and inflammatory systems. In both cases, there is epidemiological, preclinical and pathological data implicating these systems in the development of prostate cancer. In comparison to the “oncogene addiction” phenomenon, these cancers are driven by altered expression of ligands and control mechanisms (such as transcription factors). Knowledge of these pathways has provided valuable clues for the treatment of cancer.

5. Targeting the metabolism system

Incidence and disease specific mortality in prostate cancer exhibit marked global variation with the highest levels seen in Western Europe, North America and the lowest in Asia [53]. It is assumed that whilst this is accounted for by a significant genetic component, that diet and lifestyle factors may also contribute. Epidemiological studies also support an association between dietary fat intake, poor prognosis and risk of relapse [54]. In order to identify new pathways that are important in prostate cancer pathogenesis, evaluating a role for the metabolism system and its key components is crucial.

Cancer cells are already known to differ from normal cells in some of the fundamental metabolic pathways they employ. Most cancer cells generate energy by primarily metabolizing glucose by glycolysis followed by lactate production. This occurs in contrast to normal cells in which glucose is catabolised by oxidative phosphorylation, a primarily aerobic process. Proliferating cancer cells also exhibit increased glucose uptake compared to normal cells. This results in tumour cells with glycolytic rates over 200 times higher than those of normal tissues and allows efficient generation of macromolecules needed for new cancer cell production. This so-called Warburg hypothesis was initially thought to be the fundamental cause of cancer, however it is now thought to explain how tumours may flourish in low oxygen environments [55]. These observations suggest that differences in metabolism between normal tissues and cancer cells may be important in oncogenesis.

Insulin and insulin-like growth factors (IGF-1) are extracellular hormones and growth factors that regulate important metabolic pathways such as fatty acid and sterol synthesis as well as growth factor signaling via the PI3 kinase and MAP kinase pathways. Their activation may stimulate tumourigenesis by activating one or both of these mitogenic pathways and disrupting fat metabolism.

IGF-I and IGF-II bind to the IGF-1 receptor, a tyrosine kinase receptor that is known to be upregulated following castration in animal models [56]. It has been implicated in the development of the castrate resistant state with evidence that inhibition of the IGF-1 receptor may enhance the effect of castration in xenograft models [57]. Targeting the IGF-1 receptor is therefore an attractive therapeutic target in CRPC. Several IGF-1 receptor inhibitors are currently being evaluated in clinical trials and candidates include both monoclonal antibodies and small molecule tyrosine kinase inhibitors. Cixutumumab (or IMC-A12) is a fully human IgG1 subclass monoclonal antibody that has reached phase II of clinical development. A single agent study of chemotherapy naïve asymptomatic patients noted that the drug was well

tolerated with grade 3 fatigue and hyperglycaemia the worst toxicity seen and 29% of patients had stable disease [58]. Future trials with this agent are planned or ongoing including in the first line metastatic setting with androgen deprivation therapy (SWOG S0925) based on supporting preclinical data [57].

Drug	Class	Study Design	Results	Current phase of clinical development	Reference
Insulin-like growth factor receptor inhibitors					
Cixitumumab /IMC-A12	IGF-1 R inh	Phase II study in chemo naïve CRPC Asx pts 10mg/kg q2 wkly or 20mg/kg q3 wkly	29% disease stab >6 mths. Worst toxicity G3 fatigue & ↑glycaemia	Phase II Neoadj +ADT in high risk pts + Tamsiro in met CRPC + 1 st line met+ADT	[58]
Figitumumab /CP-751871	IGF-1 R inh	Phase Ib in adv solid tumours in comb with docetaxel 75mg/m ²	46 pts - MTD not reached. 4PR and 12 pts with disease stab >6months. G3/4 febrile neutropenia, fatigue 10/18 CRPC pts had >5 CTC with 60% response	Phase III studies recruiting in NSCLC (ADVIGO 1016). Phase II in breast, prostate, colorectal & Ewings sarcoma	[59, 60]
Ganitumab/ AMG 479	IGF-1 R inh	Phase I dose escalation study in adv solid malign of IV q2 wkly	53 pts - 1DLT – G3 ↓plts & transminitis. MTD not reached – maxdose 20mg/kg. ↑ in serum IGF-1	Phase II studies recruiting in Ex Stage small cell with platinum, +Everolimus in colorectal, in carcinoid & pNETs	[61]
Lisitinib/ OSI-906	Dual kinase inhibitor of Insulin & IGF-1 R	Phase I continuous dose escalation study in adv solid tumours using BID & QD dosing Phase I intermittent dosing in adv solid tumours	57 pts – MTD reached 400mg QD, 150mg BID. DLTs were ↑ QTc & G3 hyperglycaemia SD >12 weeks seen in 18/43 pts MTD 600 mg	Phase III recruiting in Adrenocortical Ca Phase II + Erlotinib in Breast	[62, 116]
AMP Kinase activators					
AICAR (Aminoimidazole-4-carboxamide-1-β-ribose)	AMP mimetic	Preclinical studies show inhibition of prostate cancer cell proliferation	Inhibition of tumour growth in prostate cancer xenograft models		[78, 117]

A-769662	AMP K subunit act.	Delay tumour development & decrease tumour incidence in PTEN def mice			[79]
Metformin	Indirect	44% reduction in prostate cancer cases compared to Caucasian controls		Phase II recruiting in loc adv or met CRPC and in loc disease as prevention against MS with ADT	[80]
Resveratrol	Indirect	Phase I single dose safety study in colon ca pts with hepatic metastases	Results are awaited	Phase I/II currently recruiting as neoadj in colon carcinoma pts	[82]
mTOR inhibitors					
Temsirolimus	mTOR inhibitor	Phase II study in CRPC patients post first line docetaxol chemotherapy. Pts receive maintenance temsirolimus 25mg/m2 weekly	Currently recruiting	Phase II recruiting in chemo naïve CRPC pts, in comb with cixutumumab in met CRPC, in CRPC after no response to chemo with bevacizumab & PI/II with docetaxel	[118]
Everolimus	mTOR inhibitor via mTORC1	Phase II study in castrate resistant prostate cancer of bicalutamide and everolimus compared to bicalutamide alone	<i>In vivo</i> evidence of synergy between mTOR and AR pathways. Study ongoing but 8 pts enrolled. 6/8 responses in PSA. Well tolerated with no unexpected toxicity	Phase I/II in met CRPC with docetaxel & bevacizumab, in post chemo pts with carbo/pred, in neoadj setting in int/high risk localized disease & in first line met/locally adv setting	[72, 73, 74]
PI3 kinase inhibitors					
XL-147	Class I PI3K isoform inhibitor	Phase I dose escalation study in adv solid malig of continuous daily dosing or d1-21 of 28 day cycle	68pts – DLT G3 rash. Inhibition of PI3K & ERK demonstrated. Prolonged stable disease observed	Recruiting to Phase I study in solid tumours and Phase I/II in breast & endometrial carcinoma	[65]

GDC-0941	Pan PI3K inhibitor	Phase I dose escalation study. GDC-0941 given QD for 21 out of 28 day cycle. BID cohorts also recruited	36 pts enrolled, dose escalation ongoing. QD dosing safe up to 254mg, BID dosing safe up to 180mg. 3 DLTs – headache, pl eff and red TLCO	Phase I study recruiting in NSCLC & Met breast cancer in comb. With paclitaxel or carbo +/- bevacizumab	[66]
BKM120 BEZ235	Pan class I PI3K inhibitor	Phase I dose escalation study. BKM120 PO QD	30 pts enrolled from 12.5-150mg. MTD 100mg. PD data suggests active drug at 100mg. 8/10 PR on FDG-PET	Phase I/II currently accruing in HER2+ Met breast ca. Also recruiting in combination with GSK 1120212	[67]
Akt inhibitors					
GSK 2141795 GSK 2110183	Akt inhibitor			First-in-human phase I study of GSK 2141795 in advanced solid malig, also recruiting in combination with GSK 1120212	
Perifosine	Oral Akt inhibitor	CRPC pts with rising PSA but no detectable mets. 900mg loading dose then 100mg daily	20% pts had a PSA reduction but did not meet PSA response criteria. DLTs included hypoNa, arthritis, photophobia, hyperuricaemia	Recruiting phase III in multiple myeloma with bortezomib +/- dex , phase I in recurrent paediatric solid tumours	[70]
MK2206	Highly selective non ADP comp Akt inhibitor	Phase I dose escalation study 30-90mg QOD in 28 day cycles in tx-refractory solid tumours	MTD established at 60mg QOD. PD efficacy confirmed with dec pAKT levels. SD seen in 6/19 pts	Phase II bicalutamide +/- MK2206 in pts after local therapy + rising PSA, Phase I in com with docetaxel is recruiting	[71]

Table 2. The Metabolic Syndrome

A second IGF-1 receptor antibody is the human IgG2 subclass antibody figitumumab. This was evaluated in a phase I dose escalation trial during which the maximum feasible dose was established as 20mg/kg intravenously every 21 days [59]. A phase Ib dose escalation study in combi-

nation with docetaxel then enrolled 46 predominantly metastatic CRPC patients. This combination was well tolerated with no MTD reached and the toxicity profile included nausea, febrile neutropenia, anorexia, fatigue and hyperglycaemia. A 22% response rate was observed with a disease stabilization rate of 44% for ≥ 6 months [60]. A phase II study of this combination has completed accrual and results are awaited. A third monoclonal antibody ganitumumab (or AMG478, Amgen) is also in clinical development and whilst safe in phase I dose escalation studies, its focus for ongoing development is in lung and colorectal carcinoma [61]. OSI-906 or linsitinib is a first in class inhibitor of both the insulin and IGF-1 receptors. It has been evaluated in phase I dose escalation safety studies where MTDs of 400mg QD and 150 mg BID were reached. The dose limiting toxicities were the known class effects hyperglycaemia and prolongation of the QTc interval. Whilst further development of this compound continues in adrenocortical and breast carcinomas [62], a phase II study of linsitinib in asymptomatic or mildly symptomatic CRPC patients has completed accrual and results are awaited.

An important downstream intracellular signaling pathway that has been implicated in prostate cancer pathogenesis, progression and the development of castration resistance is the PI3K/Akt/mTOR pathway. Phosphatidylinositol-3 kinase (PI3K) activation results in the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2) to generate the second messenger phosphatidylinositol 3-5triphosphate (PIP3) that activates the Akt signal transduction cascade. Reports suggest that PI3K signaling may play a critical role in castration resistance allowing prostate cancers to maintain continued proliferation in low androgen environments [63]. In addition, the PI3K isoforms p85 and p110b appear to have a role in regulating AR-DNA interactions and the assembly of the AR based transcriptional complex [64]. There are numerous PI3K inhibitors in clinical development, XL147 (Exelixis) is a class I isoform inhibitor whilst SF1126 (Semafore), GDC0941 (Genentech) and BEZ234 (Novartis) are pan PI3K inhibitors. All agents have successfully completed phase I dose escalation studies and preliminary results suggest that these agents are well tolerated and have favourable pharmacokinetic-pharmacodynamic profiles [65 - 67]. Further tumour specific phase I/II studies are ongoing, although at present no prostate specific studies are in progress.

The Akt's are a family of three serine/threonine kinases – AKT-1, AKT-2, & AKT-3. Phosphorylation of AKT modulates multiple downstream cellular functions including apoptosis, metabolism and proliferation. Enhanced pAKT correlates with more aggressive histological and pathological prostate cancer stage, and a worse prognosis underlining its importance as a druggable target and possible role as a prognostic biomarker [68, 69]. There are several classes of Akt inhibitors currently in clinical development including those inhibiting the catalytic and the pleckstrin homology (PH) domains. Perifosine, an alkylphospholipid inhibiting the PH domain has reached phase II in CRPC patients. Unfortunately although well tolerated this agent did not exhibit significant activity [70]. The pan-AKT inhibitors GSK2141795 and MK2206 with simultaneous targeting of both AKT-1 and AKT-2 are considered potentially superior to single isoform inhibitors. MK2206 was well tolerated in a phase II dose escalation study with an observed MTD of 60mg. Pharmacodynamic endpoints were met with a measurable reduction in pAKT levels. In addition, 6 of 19 patients achieved stable disease [71]. Further development continues in a number of tumour types

both as single agent and in combination with chemotherapy. Of note a phase I study in combination with docetaxel is currently recruiting, as is a randomized phase II study of bicalutamide +/- MK2206 in prostate cancer patients with a rising PSA after definitive local therapy. GSK2141795 and GSK 2110183 also entered phase I development with results of first in human safety studies pending.

Mammalian target of rapamycin (mTOR) is also a serine/threonine kinase downstream of PI3K which interacts with the mTOR complexes mTORC1 and mTORC2 to regulate cell proliferation and inhibit apoptosis. Proof of principle that the PI3K pathway can be successfully targeted for clinical use in cancer has been demonstrated by the development of the rapamycin analogs - temsirolimus and everolimus that inhibit the mTORC1 kinase. Temsirolimus is an intravenous formulation which was the first compound in this class to be approved by the FDA for first line treatment in poor risk patients with advanced renal cell cancer. Everolimus an oral formulation is also approved for use in advanced renal cell cancer but in the second line setting. Single agent studies of these agents in the prostate cancer setting have been performed but were considered disappointing with a short time to progression (2.5 months) and no radiographic or PSA responses [72]. Everolimus has also been evaluated in combination with docetaxel in CRPC patients. The recommended phase II dose was 10mg everolimus and 70mg/m² docetaxel, 3 patients had a PSA response and the combination was well tolerated with fatigue and haematological toxicities the most common [73]. Further studies with both agents in prostate cancer continue with a similar study involving temsirolimus in combination with docetaxel, as well as studies with cixitumumab and bevacizumab. A randomized study in hormone responsive patients of bicalutamide +/- everolimus is currently recruiting with early results suggesting the combination was well tolerated with PSA responses observed in six of eight patients [74]. Studies in the neoadjuvant and localized disease setting are also ongoing.

Finally, AMP kinase is a serine/threonine kinase that is activated by metabolic stressors that deplete ATP and increase AMP levels. Its activity is also under the control of hormones such as adiponectin and leptin as well as cytokines [75]. The activation of AMP kinase reduces insulin levels, as well as increasing ATP producing activities (glucose uptake, fatty acid oxidation) and suppressing ATP-consumption (synthesis of fatty acids, sterols, glycogen and proteins). AMP kinase therefore acts as a metabolic switch controlling glucose and lipid metabolism. Decreased AMP kinase activity is thought to contribute to the metabolic abnormalities involved in the metabolic syndrome [76]. In addition polymorphisms in a gene locus encoding one of the AMPK subunits correlates with prostate cancer risk [77].

Activators of AMP kinase activity may be direct or indirect. Several direct AMP kinase activators act either by allosteric binding to AMP kinase subunits or as an AMP mimetic. These agents aminoimidazole-4-carboxamide-1- β -ribose (AICAR), A-769662 and PT1 are at an early stage of clinical development. AICAR has been shown to inhibit prostate cancer cell proliferation and tumour growth in xenograft models [78]. However its further development may be limited by its poor specificity for AMPK and low oral bioavailability. To date no interventional oncology studies have been undertaken. The recent publication of the crystal structure of AMP kinase subunits has allowed rational drug design of A-769662 and

PT1. A769662 has been shown to delay tumour development and decrease tumour incidence in PTEN deficient mice [79].

The indirect activator metformin is a well established treatment for type II diabetes mellitus. Its use is associated with a 44% risk reduction in prostate cancer cases compared with controls in Caucasian men [80]. The mechanism of metformin's antitumour effect is not completely understood, although it is hypothesized that metformin may decrease circulating glucose, insulin and IGF-1 levels by inhibiting hepatic gluconeogenesis resulting in increased signaling through the insulin/IGF-1 pathway [81]. Its action in prostate cancer is currently under evaluation in a number of clinical trials, these include as a preventative treatment for metabolic syndrome in men on androgen deprivation therapy and as first line therapy in locally advanced or metastatic prostate cancer patients. Finally, resveratrol is a phytoalexin produced by plants when under attack by pathogens. It is found in the skin of grapes, grape products, red wine and mulberries and is thought to have anticancer properties. These were first identified when it was shown to inhibit tumourigenesis in a mouse skin cancer model [82]. Its indirect action on AMP kinase remains to be elucidated although its anticancer action has been explored in a number of tumour types. Clinical trials using resveratrol have explored potential roles in preventing and treating diabetes, Alzheimers disease and weight loss. In addition safety studies of its use in colorectal carcinoma patients with liver metastases have been conducted and the results are awaited. As yet no studies in prostate cancer are planned.

6. Inflammation

Numerous studies have implicated inflammation in the development of prostate cancer and its metastases. Pathologists have recognized focal areas of epithelial atrophy in the periphery of the prostate (proliferative inflammatory atrophy - PIA), where prostate cancers typically arise and these areas are associated with acute or chronic inflammation and can show morphological transitions in continuity with high grade PIN [83]. This could indicate a role of PIA as a cancer precursor [84]. Putative causes of these lesions are infection or dietary oxidants. To date, the identification of an infectious agent directly involved in prostate carcinogenesis has been elusive. However, it is possible that one or more infectious agents may be indirectly involved in prostate carcinogenesis by being initiators of the inflammatory lesion (PIA). Interesting data includes serologic evidence of *T. vaginalis* infection being associated with a higher prostate cancer risk overall, and an almost two-fold risk for poorly differentiated disease [85] as well as greater prostate cancer specific mortality (HR: 1.5; 95% CI: 1.0, 2.2) [86]. It is also of note that hereditary susceptibility genes which encode proteins with infectious response function: RNASEL and MSR1 (macrophage scavenger receptor 1) have been associated with prostate cancer [83]. Single nucleotide polymorphism's of anti-oxidant genes have also been associated with prostate cancer and include OGG1 (repair from oxidized DNA), MnSOD [88]. Also the incidence of prostate cancer has been decreased with anti-oxidants such as lycopene and NSAIDs [87].

One possible mediator of the inflammation that leads to cancer and is instigated by oxidative stress from a diverse arrays of causes is NFκB activation. Specifically, it has been shown that a vicious cycle of oxidative stress causing DNA damage and consequent influx of inflammatory cytokines into the microenvironment results in further production of proteases, angiogenic factors, growth factors and immunosuppressive cytokines. Examples of NFκB controlled proteins found in prostate cancer include COX-2, XIAP, CXCR4, macrophage inhibitory cytokine-1 (MIC-1), IL-6, IL-8, IL-1, CXCL12, and the CXCR4 [89].

NFκB is a protein complex that controls DNA transcription and is activated by numerous factors including cytokines, free radicals, receptor activator of nuclear factor kappa-B (RANK), and microbial pathogens [90]. Upon activation, the NFκB dimers translocate to the nucleus with activation of numerous genes controlling cell growth, differentiation, inflammatory responses and apoptosis. Aberrant regulation of NFκB has previously been linked to inflammatory states and cancer. Moreover, NFκB controls many of the hallmarks of cancer including: invasion (IL-6); angiogenesis (IL-8, VEGF); propagation through the cell cycle (cyclin D1); and evasion of apoptosis (cIAP-1, TRAF-2, Bcl-X_L) [91 - 95]. As such, NFκB activation has clear-cut biological plausibility as a driver of cancer progression and CRPC. In tumor cells, NFκB is constitutively active either due to mutations in genes encoding the NFκB transcription factors themselves or in genes that control NFκB activity (such as IκB genes) or due to tumor cells secreting activation factors (e.g. IL-1). Constitutive NFκB activation in prostate cancer is found in both tumor and its associated stroma and occurs early in the disease process [96 - 100]. It is of note that preclinical work has mechanistically connected NFκB activation to development of prostate cancer with a metastatic phenotype [97]. Specifically, loss of the Ras GTPase-activating protein (RasGAP) gene DAB2IP lead to increased EZH2 and in turn induced NFκB activation which in turn resulted in metastatic prostate cancer in an orthotopic mouse tumor model.

Drugs targeting the inflammatory system are in preclinical and clinical development. The agents can be classified as upstream or direct inhibitors of nuclear factor kappa B or inhibitors of products of NFκB activation Table 3. This is a very new area but one which may lead to significant improvements.

Drug	Class	Study Design	Results	Current phase of clinical development	Reference
Upstream agents					
EZH2inhibitor (Enhancer of Zeste protein)	Polycomb grp protein	Pre-clinical studies only Ectopic expression of miRNAs impt in EZH2 action inhibit cell growth & tumourigenesis			[119]

Custirsen OGX-011	Clusterin Inhibitor (antisense oligo)	Randomised phase II in mCRPC with PD on or within 6m docetaxel (D) D/Pred/C or Mito/ Pred/C	42 pts – 3/23pts with PR in D/P/C OS 15.8 mths M/P/C OS 11.5 mths Toxicity similar in both arms	Phase III Docetaxel +/- Custirsen in mCRPC as 1 st & 2 nd line recruiting	[120]
Bortezomib	Proteasome inhibitor	Phase II study of bortezomib with addition of MAB on progression. Bortezomib given d1,4,8,11 for 3 cycles	No activity in addition to docetaxel or paclitaxel (phase I) and high rates of PN observed. When given as single agent or MAB – 11/15 CR with TTP 5.5 months	Results awaited for phase I study with mitoxanthrone	[121, 122, 123]
Carfilzomib	Selective proteasome inhibitor	Phase I trial in relapsed or refractory haem malig, d1-5 IV 1.2-20mg/m2	MTD 15mg/m2 – DLT of feb neutropenia & G4 thrombocytopenia. 2/29 responses	No prostate specific trials recruiting	[124]
Denosumab (bone)	Anti-RANKL antibody	Randomised phase III trial denosumab vs zoledronic acid in mCRPC with bone mets	Median time to first SRE 20.7m denosumab vs 17.1m zoledronic acid HR 0.82 p=0.00002	Phase III study investigating lens opacification in men on demosumab and ADT	[125]
Direct agents					
Silibinin (derived from Milk Thistle)	Via down regulation of epithelial- mesenchymal transition regulators	Phase II single arm study in PC pts with localized disease prior to prostatectomy. Pts given 13g/day	Transient high blood concentration observed but low tissue concentration. Response results awaited		[126]
Flavopiridol (Alvocidib)	Cyclin dependent kinase inhibitor	Phase II single agent study in met CRPC pts. 72 hour IV infusion at 40-60 mg/m2/day	36 pts enrolled. No objective responses. 14% pts met 6 month PFS endpoint.	Further development in germ cell tumours & gastric/GOJ ca	[127]
Thalidomide	IκB kinase inhibitor	Phase II studies docetaxel (75mg/m2) and docetaxel/ bevacizumab (15mg/m2) +/- thalidomide (200mg/m2)	60 pts enrolled. 90% PSA decline of >50%. Median TTP 18.3 months, median OS 28.2 months. Manageable toxicity but all pts had G3/4 neutropenia	Phase III placebo controlled trial in recurrent hormone sensitive non metastatic PC	[128, 129]

Lenolidamide		Phase II trial after biochemical relapse with LHRH agonists & phase I/II trial as single agent 5mg or 25 mg	159 pts enrolled. Med TTP PSA 15 vs 9.6 mths. Thalidomide well tolerated, 47% DR. 60 pts enrolled, 25mg ass with greater change in PSA slope but higher toxicity	Phase III in met CRPC pts, docetaxel/ prednisone +/- lenolidamide	[130, 131]
Parthenolide analogue (derived from <i>Tanacetum parthenium</i>)	NFκB inhibitor	Dimethylamino-parthenolide (DAMPT) with superior solubility & bioavailability	DAMPT inhibited NFκB DNA binding & expression of NFκB regulated anti-apoptotic proteins	Phase I dose escalation trial currently recruiting in pts with haem malign	[132]
Downstream agents					
Siltuximab	αIL-6 Ab	Phase II study in met CRPC pts post docetaxel. 6mg/kg IV q14d for 12 cycles	53 pts enrolled. PSA response rate 3.8%, RECIST SD rate 23%. High baseline IL-6 levels ass with poor prognosis	Phase I study in combination with docetaxel in met CRPC pts	[133]
Celecoxib	NSAID				
CNTO888	α-chemokine ligand 2 Ab	Preclinical studies of CNTO888 2mg/kg twice weekly ip in vivo prostate cancer model	Reduced tumour burden by 96% at 5 weeks also synergistic with docetaxel	Phase II in met CRPC pts post docetaxel results awaited	[134]
Plerixafor BKT140	αCXCR4			Focus of clinical dvpt in AML, phase I/II studies recruiting	

Table 3. The Inflammatory System

7. Other key pathways

With time, it is anticipated that more pathways and targets key to prostate cancer growth will be identified. Angiogenesis inhibition has been successful in other cancers but minimal activity was seen in trials with Sunitinib [101] and Bevacizumab [102]. Similarly, targeting the HGF-MET axis is supported by preclinical work [103] and some activity has been seen with MET inhibition. However, Cabozantinib – a tyrosine kinase inhibitor that inhibits multiple receptor tyrosine kinases (RTKs) with growth-promoting and angiogenic properties (MET (IC₅₀ in enzymatic assays= 1.8nM), VEGFR2 (0.035nM), RET (3.8nM), and KIT (4.6nM) has significant and intriguing clinical activity in bony disease and some activity in soft tissue disease. This suggests the effect may be due to concurrent inhibition of two relevant pathways.

Cabozantinib has been studied in multiple solid tumors and has shown a broad spectrum of activity with tumour regression in patients with a variety of diseases. Its activity in medullary thyroid cancer is based on RET inhibition [104]. Of particular relevance to prostate cancer, a phase II discontinuation study of 168 men with progressive metastatic CRPC received Cabozantinib initially for 12 weeks [105]. Patients with PR continued open-label cabozantinib, patients with stable disease were randomized to cabozantinib or placebo, whilst patients with progression were discontinued. Trial accrual was halted after enrollment of 168 patients due to the significant activity observed. 78% patients had bone metastasis and significantly 86% of these had a complete or partial response on bone scan as early as week 6. 64% patients had improved pain and 46% patients reported lower narcotic analgesia use. To date the median PFS has not been reached. Most common related Grade 3/4 AEs were fatigue (11%), HTN (7%), and hand-foot syndrome (5%). Osteoclast and osteoblast effects were observed: 55% had declines of $\geq 50\%$ in plasma C-Telopeptide; 56% of patients with elevated tALP had declines of $\geq 50\%$.

Interestingly numerous lines of preclinical and clinical evidence implicate MET and VEGFR activation in bone metastases as well as prostate cancer, especially castration resistant disease. Specifically, androgen deprivation increases MET expression in prostate cancer cells [106, 107] and c-met has been shown to be upregulated in CRPC and may be a factor that supports CRPC cells in the castrate state [106, 108]. Androgen deprivation also increases expression of c-met's ligand, Hepatocyte Growth Factor (HGF) in the stroma. Increased expression of MET and HGF may contribute to disease progression following androgen deprivation therapy. This may be a compensatory mechanism as HGF/cMET activity enhances Leydig cell steroidogenetic activity [109]. It is also of note that increased expression of MET and/or HGF correlate with prostate cancer metastasis and disease recurrence [110, 111]. In addition, VEGF has been shown to activate MET signaling via neuropilin-1. Osteoblasts and osteoclasts also express MET and VEGFRs and osteoclasts secrete HGF. This supports the notion that MET signaling not only supports the tumor, but also bone turnover which provides a fertile microenvironment for prostate cancer growth [112]. These observations provide a strong rationale for dual inhibition of VEGFR2 and MET as a therapeutic strategy in men with CRPC and bone metastases. As such, cabozantinib may not only have single agent activity but also enhance abiraterone activity by simultaneously blocking a putative resistance/survival mechanism to hormonal therapy and abrogating bone turnover and making the microenvironment less hospitable for cancer growth. Given these many reasons, it is logical to hypothesize that combining these two active agents against CRPC will result in even more substantial clinical benefit.

8. Conclusion & future directions

It is clear from the foregoing discussion that increased biological knowledge and drug development technologies has resulted in a vast number of agents for clinical trial testing. However, it is paramount that judicious trial designs are employed and match the drug to the tumor by ensuring that the target is present. It is also quite certain that no single drug

will work given the inherent multiple redundant survival pathways. This is probably more apparent for castration resistant disease. Therefore, one can argue that waiting for metastatic disease or castrate resistant disease to assess a new drug is a defeatist approach, and that an assessment earlier in the disease spectrum to prevent the emergence of resistance is a more proactive and promising approach to improve outcomes in prostate cancer. The conduct of a study in patients with a biochemical relapse after definitive localized therapy provides a major opportunity for drug development. This approach allows the analysis of a drug in isolation and as well as an assessment and effective triage of the numerous new agents that are now available for testing. Also the primary pathology can be interrogated to look for activation of the pathway and provides an opportunity to biologically direct the evaluation of drugs relevant to a given pathway in an individual's cancer. Ultimately, key combinations simultaneously targeting the essential and multiply redundant pathways driving cancer survival and resistance mechanisms can be developed. This has been a successful strategy for treatment of HIV and AIDS where the early use of Highly Active Anti-retroviral Therapy (HAART) has made major advances. With time and judicious clinical development, it is possible to develop a similar strategy such as Highly Effective Early Prostate Cancer Therapy (HEEPT) for patients with rapidly progressive PSA rises after definitive local therapy and have a long life expectancy. Early use of a highly effective combination therapy will hopefully eradicate the disease and prevent patients from dying from recurrent disease that may otherwise have been lethal and more difficult to treat if waited until later in the disease

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