Targeting the PI3K/Akt pathway in prostate cancer: Challenges and opportunities (Review)

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Abstract. The PI3K/Akt pathway is an actively pursued therapeutic target in oncology. In prostate cancer, the activation of this pathway appears to be characteristic of many aggressive prostate cancers. Further, activation of the PI3K/Akt pathway is more frequently observed as prostate cancer progresses toward a resistant, metastatic disease. Signalling from this pathway activates numerous survival, growth, metabolic and metastatic functions characteristic of aggressive cancer. Biomarkers of this pathway have correlated activation of this pathway to high grade disease and higher risk of disease progression. Therefore there is significant interest in developing effective strategies to target this pathway in prostate cancer. In this review, we discuss the pre-clinical and clinical data relevant to targeting of the PI3K/Akt pathway in prostate cancer. In particular, we review the rationale and relevance of co-targeting approaches against the PI3K/Akt pathway. It is anticipated that through an improved understanding of the biology of the PI3K/Akt pathway in prostate cancer, relevant biomarkers and rationale combination therapies will optimize targeting of this pathway to improve outcomes among patients with aggressive prostate cancer.

Contents

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1. Introduction

Prostate cancer is the second most frequent cause of cancer death in American men, with approximately 1 in 36 men dying of prostate cancer (1). Over the last several years, new therapies have emerged for treatment of castrate resistant prostate cancer (CRPC) which have improved the survival of patients with this disease (2,3). Nonetheless, cure remains elusive with resistance developing over time. With the increasing use of potent anti-androgens such as abiraterone and enzalutamide, there is renewed interest in targeting non-AR pathways in prostate cancer progression.

One of the most prominent alternate pathways in prostate cancer is the PI3K/Akt signalling pathway. Activation of this pathway is implicated in many aggressive human cancers (4). Accordingly, there has been significant investment toward developing targeted inhibitors of this pathway in various hematologic and solid cancers. In this review, we will discuss the relevance of the PI3K/Akt pathway in prostate cancer, highlighting both basic science and clinical aspects.

2. PI3K/Akt signalling pathway

The PI3K/Akt signalling pathway regulates cellular metabolism, tumour development, growth, proliferation, metastases and cytoskeletal reorganization. It is part of a complex intracellular cell signalling cascade (Fig. 1). PI3K is a plasma membrane-associated protein kinase consisting of three subunits: the regulatory subunits p85 and p55; referred by convention as collectively p85 and a catalytic subunit, p110 (5). There are three classes; it is the class IA PI3Ks which are the most clearly implicated in human cancer, including prostate cancer. Moreover, this class is usually downstream of receptor tyrosine kinases. Activation of receptor tyrosine kinases at the cell membrane results in conformational changes which removes auto-inhibition of the catalytic domain of PI3K. Three catalytic isoforms p110α, p110β and p110δ are, respectively, the product of the genes PIK3CA, PIK3CB and PIK3CD. Once activated, PI3K catalyzes the phosphorylation of PIP2 to produce PIP3. PIP3 then activates intracellular signalling through its binding to pleckstrin homology (PH) domains of many signalling proteins, including Akt. In prostate cancer, it appears that the p110β isoform is most relevant to prostate

cancer progression and resistance (6). It has been associated with basal activation of Akt in prostate cancer models (7).

The PI3K/Akt pathway functions downstream of receptor tyrosine kinases (RTKs) as well as independently of RTKs. Non-RTK activation of this pathway may be from other intracellular signalling pathways or from other membrane receptors including G-protein coupled receptors. The main upstream activators likely are context specific. In autopsy specimens of metastatic prostate lesions, various RTKs were associated with Akt activation (8). Of note, many of the RTKs which activated the PI3K/Akt pathway, including EGFR, IGF-IR, FGFR and c-MET receptors, are actively researched as targets in CRPC. Nonetheless, some *in vitro* studies in prostate cancer cells suggests that basal activation of this pathway occurs independently of RTKs (7). Notably, phospho-proteomic analysis of metastatic tumour samples collected on rapid autopsy found that Akt was the tyrosine kinase most commonly found to be active in metastastic prostate cancer (8). Activated Akt is a kinase which in turn phosphorylates and activates many oncogenic features within cancer cells. Upon recruitment to the cell membrane, it is phosphorylated by phosphoinositide-dependent kinase 1 (PDK1), a reaction catalyzed by PIP3 binding to the PH domains of both molecules (Fig. 1). Once phosphorylated at both Ser473 and Thr308 phosphosites, the activated Akt can activate many downstream functions via its kinase activity.

Mammalian target of rapamycin (mTOR) is a major downstream signalling protein involved in protein translation via the eIF4E complex and S6K which is activated by Akt. Both mTOR and S6K are found in higher levels in prostate cancer compared to benign controls (9). The proteins differentially associated with mTOR defined the TORC1 andTORC2 complexes. These have overlapping, but different functions, with TORC2 providing negative feedback regulation on the PI3K/Akt pathway via S6K (10,11). There are many other downstream oncogenic effects of Akt phosphorylation. Cell survival is promoted through anti-apoptotic effects, particularly inhibition of the pro-apoptotic Bcl-2 family members BAD and BAX (12). Transcription factor FOX01 acts as a tumour suppressor and its phosphorylation by Akt induces its ubiquitation and degradation by the proteasome. Further, inhibition of glycogen synthase kinase 3 (GSK-3) increases cellular translation of proteins as does phosphorylation of 4eBP-1. Regulation of cell growth and survival by Akt also occurs by the NF-κB pathway via activation of IκB kinase (IKK) (Fig. 1). Further, the PI3k/Akt pathway in prostate cancer appears to be involved with modulation of DNA damage repair pathway (13). More recently, the PI3K/Akt pathway has been implicated in modulating a more aggressive phenotype through modulation of cholesterol ester formation in prostate cancer cells (14). This suggests a possible relationship with metabolic pathway disturbances and the development of aggressive prostate cancer. Overall, there are a plethora of downstream cellular functions of the Akt pathway which correspond to a clinically aggressive phenotype.

3. Regulation by phosphatases

The PI3K/Akt pathway is antagonized by several phosphatases, including phosphatase and tensin homolog gene (PTEN), PH and leucine-rich repeat protein phosphatase (PHLPP), cellular prostatic acid phosphatase, PP2A and INPP4B (15-17) (Table I).

Table I. Common genomic alterations potentially involved in activation of the PI3K/Akt/mTOR pathway from the MSKCC dataset (47).

Gene	Type of alteration	Prevalence in metastatic disease (%)	Prevalence in localized disease (%)
PTEN	Loss or inactivation	4	42
INPP4B	Loss or inactivation	8	47
PIK3R1	Loss or inactivation	22	58
PIK3R3	Loss or inactivation	2	16
PIK3CA	Activating mutation	6	16
PHLPP	Loss or inactivation	11	37

Genetic loss or other inactivation of these phosphatases results in greater amounts of phospho-Akt and subsequent increased or sustained oncogenic signaling. Notably, the PTEN gene on chromosome 10q23.3 is the most-commonly deleted gene in prostate cancer (18). However, genomic loss of PTEN does not always correlate with activation of the PI3K/Akt pathway (19). Pre-clinical models and patient samples also show that loss of PTEN results in a particularly aggressive phenotype when found in combination with activation of receptor tyrosine kinases (20,21). PHLPP is regulated by the AR via FKBP5 and explains in part the upregulation of the PI3K/Akt pathway seen following androgen deprivation (17). INPP4B is decreased following androgen deprivation and may be another mechanism through which the Akt pathway is activated resulting in earlier disease recurrence (16).

4. Role of PI3K/Akt in prostate carcinogenesis and progression

The mechanisms through which the PI3K pathway may induce carcinogenesis include the activation of growth and survival pathways. Further, activation of this pathway may also alter epigenetic regulators, such as BIM1 (22). The PI3K/Akt pathway has also been shown to be important to the survival and proliferation of prostate cancer stem cells (23).

PTEN deletion is commonly used to model prostate cancer progression in mice (24,25). PTEN loss in mice has been shown to suppress androgen-responsive genes and promote cell autonomous growth (26). Activation of the P3K/Akt pathway in mice may also occur using myristolated Akt or constitutive activation of p110β. In a murine subrenal xenograft model, activation of both AR and Akt has been noted to synergize to increase prostate tumour growth (27). Nonetheless, the exact role of this pathway in carcinogenesis in humans is uncertain. On the contrary, a recent genome wide sequencing analysis suggests that PTEN loss is a late-stage feature in the progression of prostate cancer (28).

Pre-clinical studies suggest that concomitant loss of certain proteins together with PTEN loss appear to accelerate prostate cancer progression. This has been demonstrated in mice and correlated with features of aggressiveness, such as Gleason score, in patient samples for the tumour suppressors NKX3.1, EAF2/

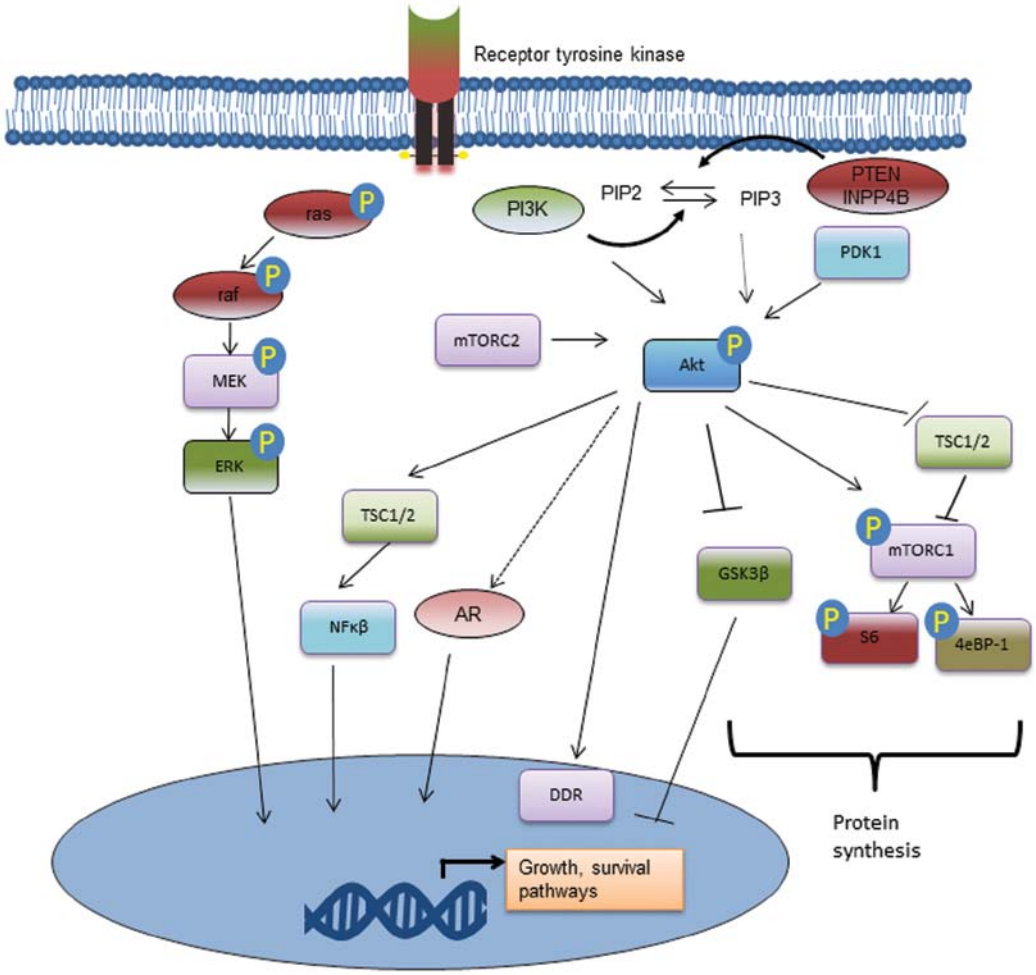

Figure 1. Schematic of some of the molecular pathways related to the PI3K/Akt pathway in prostate cancer.

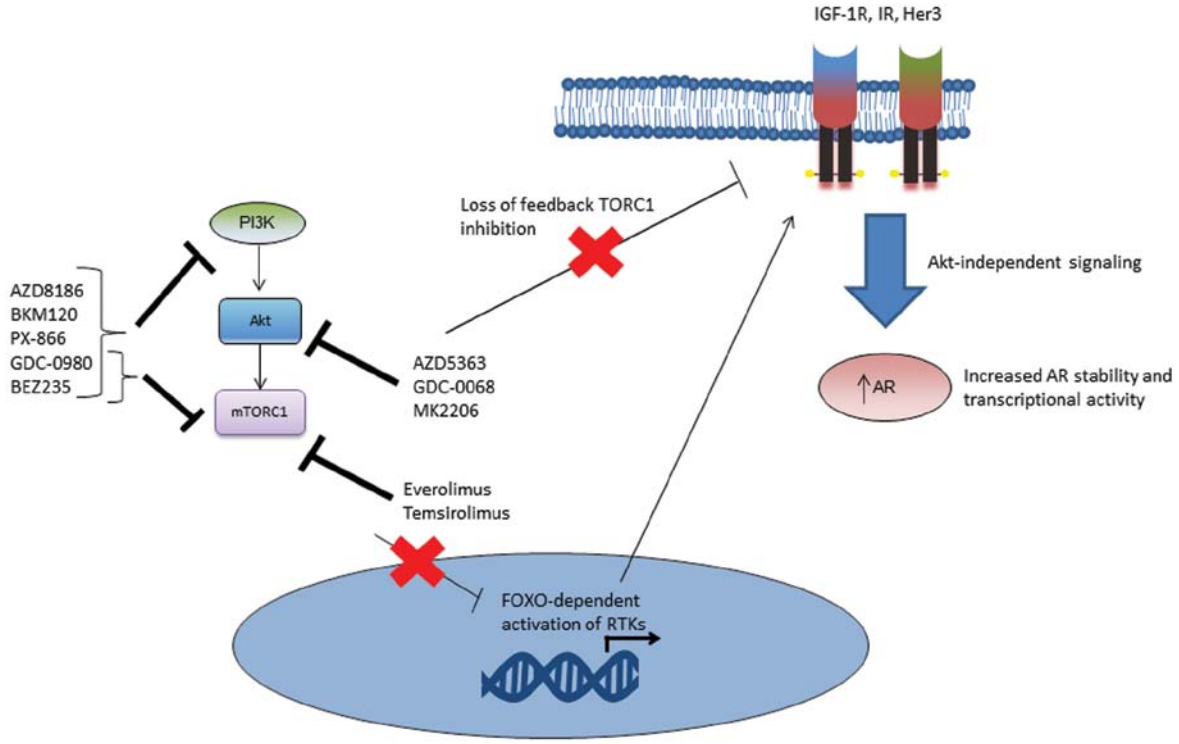

Figure 2. Schematic of selected agents targeting the PI3K/Akt pathway in being evaluated in prostate cancer with possible pathways resulting in reciprocal AR upregulation with PI3K/Akt inhibition.

Table II. Selected pre-clinical combination studies of PI3K/Akt/mTOR inhibitors.

PI3K/Akt/mTOR pathway inhibitor	Additional pathway target	Selected outcomes assessed	Author (Refs.)
ZSTK474 (Pan-PI3K inhibitor)	PSMA	*In vitro* and *in vivo* (C4-2luc) tumour growth	Baiz *et al* (83)
BEZ235 (PI3K-mTOR inhibitor)	HDAC	Attenuation of DNA damage repair protein ATM	Ellis *et al* (13)
AZD5363 (Akt inhibitor)	AR	Apoptosis, proliferation, LNCaP tumour growth	Thomas *et al* (38)
BEZ235 (PI3K/mTOR inhibitor)	Microtubules	*In vitro* and *in vivo* tumour growth	Yasumizu *et al* (84)
AZD5363 (Akt inhibitor)	Autophagy	Apoptosis, tumour growth	Lamoureux *et al* (85)
Akt inhibitors	Pim-1	Apoptosis, tumour growth	Cen *et al* (86)
Rapamycin (mTOR inhibitor)	MEK	*In vitro* and *in vivo* tumour growth	Kinkade *et al* (87)
Everolimus (mTOR inhibitor)	Propachlor (from drug screen panel)	Authophagic cell death	Tai *et al* (88)
Perifosine (Akt inhibitor)	EGFR	Apoptosis	Festuccia *et al* (89)

PSMA, prostate specific membrane antigen; HDAC, histone deacetylase; AR, androgen receptor.

U19, Gata3 and Sox9 (29-33). B-raf and Stat3 activation and loss of SMAD4 and p53 signalling have also been shown in murine models to cooperate with PTEN loss to enhance prostate cancer progression (34-37). This complex network with other pathways highlights why monotherapy against the PI3K/Akt pathway may not be an optimal strategy. Table II lists different combination strategies which have been explored targeting the PI3K/Akt/mTOR pathway in pre-clinical models of prostate cancer.

5. PI3K/Akt and the AR pathway

The relationship between the PI3K/Akt and AR pathways is of significant interest as a co-targeting strategy in prostate cancer (17,38). Reciprocal interactions between these pathways have been demonstrated in several pre-clinical studies (17,39,40). Blockade of the AR pathway results in PHLPP-mediated Akt inactivation via a decrease in androgen regulated FKBP5 (17,26). Inhibition of the PI3K/Akt pathway may result in upregulation of AR transcriptional activity via activation of membrane signalling proteins such as HER3 (Fig. 2) (17,41). Direct AR phosphorylation by Akt appears to predominantly be relevant in the low-testosterone state (i.e., during androgen deprivation) (27,42,43). Akt has been shown to phosphorylate the AR at Ser-213 and Ser-791, but the significance of these phosphosites is unclear (27). *In vitro* models suggest that Akt may regulate AR transcription (27), but that this is not by direct phosphorylation of the AR (27,44).

The combination of bicalutamide and a pan-Akt inhibitor, AZD5363 have been noted *in vitro* and *in vivo* in LNCaP models to synergize to decreased tumour growth (38). Early results suggest markedly decreased *in vivo* tumour volumes with the use of potent pan-Akt or PI3K isoform specific inhibitors in combination with potent AR inhibitors (45,46). These pre-clinical findings have supported the development of clinical trials of combination blockade of both the AR and the PI3k/Akt/mTOR pathways (Table III). Further understanding of the interactions between these pathways in pre-clinical models may aid in design of future clinical trials.

6. PI3K/Akt pathway as a biomarker in prostate cancer

With the aggressive oncogenic characteristics of the PI3K/Akt pathway, there has been significant interest to use this pathway as a biomarker to differentiate more significant, lethal prostate cancer from more indolent disease. While it does appear from the current data that this pathway does provide prognostic information, it is unclear that it provides any significant improvement over currently used clinical and pathologic markers. However, there is ongoing interest to use this pathway as a predictive biomarker for newer targeted agents of this pathway.

The challenges of using this pathway as a biomarker relate in large part to the complexity of the biology in advanced prostate cancer and tumour heterogeneity. Firstly, there is a large diversity of mutations and genomic alterations which may

Table III. PI3K/Akt inhibitors in current clinical evaluation for prostate cancer.

Drug	Inhibitors	Phase	Regimen	Population	Trial registry no.[b]
AZD8186 (AstraZeneca)	PI3Kβ and δ inhibitor	I	Monotherapy	CRPC	NCT01884285
BKM120 (Novartis)	Pan-PI3K inhibitor	I	+ abiraterone acetate	Post-abiraterone CRPC	NCT01634061
		I	+ abiraterone acetate	mCRPC	NCT01741753
		II	Monotherapy	Post-chemo	NCT01385293
PX-866 (Oncothyreon)	Pan-PI3K inhibitor	II	Monotherapy	mCRPC post ADT	NCT01331083
BEZ235 (Novartis)	PI3K/mTOR inhibitor	I	+ abiraterone acetate	Post-abiraterone CRPC	NCT01634061
GDC-0980 (Genetech)	PI3K/mTOR inhibitor	I/II	+ abiraterone acetate	Post-docetaxel	NCT01485861 2011-004126-10
AZD5363 (AstraZeneca)	Akt inhibitor	I	Monotherapy	mCRPC	NCT01692262
		II	+ enzalutamide	mCRPC	2013-004091-34
		I/II	+ docetaxel	mCRPC	NCT02121639
GDC-0068 (Genetech)	Akt inhibitor	I/II	+ abiraterone acetate	Post-docetaxel	NCT01485861 2011-004126-10
MK2206 (Merck)	Akt inhibitor	II	+ bicaluatmide	Biochemical failure after primary therapy	NCT01251861
Everolimus (Novartis)	mTORC1 inhibitor	II	+ pasireotide (somatostatin)	Chemo-naïve CRPC	NCT01313559
		I/II	+ docetaxel, bevacizumab (VEGF inhibitor)	mCRPC	NCT00574769
		I/II	+ carboplatin, everolimus, and prednisone	Post-docetaxel mCRPC	NCT01051570
		II	+ bicalutamide	Recurrent or mCRPC post ADT	NCT00814788
Temsirolimus (Wyeth)	mTORC1 inhibitor	I/II	+ bevacizumab	Post-docetaxel mCRPC	NCT01083368
		I	+ vorinostat	Post-docetaxel mCRPC	NCT01174199
		II	Monotherapy	CRPC	2011-002087-24
		I/II	+ docetaxel	CRPC	NCT01206036 2010-018370-21
		I/II	+ cixutumumab	mCRPC	NCT01026623

[a]Both abiraterone acetate and docetaxel are given in combination with low dose prednisone. [b]ClinicalTrials.gov number and/or EudraCT number.

activate this pathway, making any single marker less sensitive. Further, the context of this pathway in prostate cancer differs from other malignancies where this pathway also plays an important role. For example, while activating PI3KCA mutations are relatively common among advanced malignancies, it does not appear to be as common in prostate cancer (47). Factors in the tumour microenvironment can influence signalling of this pathway, which is downstream of various cell surface receptors. Therefore, both tumour and patient heterogeneity contribute to a complexity making biomarker evaluation and validation more challenging. For example, in circulating tumour cells PTEN allelic loss has significant heterogeneity when analyzed by fluorescent *in situ* hybridization (48). Further, on immunohistochemistry, analysis of downstream targets does not clearly correlate in patient samples with the phosphorylation of Akt. In one study, phosphorylation of downstream GSK3β and a forkhead transcription factor was noted in only 29 and 40% of cases, respectively, in localized prostate cancer samples with phospho-Akt (49). Finally, technical variation, antibody limitations, tissue acquisition and processing also present challenges to use of this pathway as a clinical biomarker.

It is estimated that genomic PTEN alterations are found in 9-45% of high grade prostate intra-epithelial neoplasia (HG-PIN), increase to 20-60% in localized prostate cancer, and are altered in up to 100% of cases of metastatic prostate cancer (47,50). Homozygous deletion of PTEN is linked with CRPC (51). Further, PTEN is the most common gene with loss of heterozygosity in circulating tumour cells CTCs (52). Similarly, mutations in the PI3K pathway occur more frequently in metastatic tissue compared to primary tumours. In the Taylor *et al* dataset, mutations in the PI3K regulatory genes PIK3R1, PIK3R3 and PIK3CS occur at a frequency of 22, 2 and 6% in primary tumours, respectively. In metastatic tissues, the frequency increases to 58, 16 and 16%, respectively (47). Mutations in PIK3CA catalytic gene of PI3K are known to be activating to the pathway and also may predict response to therapy with PI3K inhibitors, though they are not highly prevalent in prostate cancer (53). Mutations in the regulatory phosphatase PHLPP gene can also result in activation of the Akt pathway, occurring at 11 and 37% in primary and metastatic tumours, respectively (47).

On immunohistochemistry, both PTEN status and phospho-Akt are the most commonly investigated biomarkers. Akt can be phosphorylated at Thr308 and Ser473; it appears that both sites are usually phosphorylated in the active state. It does appear that Akt staining is specific to tumour cells, without any staining in adjacent stromal tissue (49). Not surprisingly given the molecular features of the activated PI3K/Akt pathway, the loss of PTEN staining in localized prostate cancer samples correlates with higher Gleason score and pathologic stage (54,55) as well as an increased risk of positive lymph nodes (56). PTEN protein loss on immunohistochemistry of the primary tumour has also been associated with shorter time to biochemical recurrence post radical prostatectomy, but not consistently (57). Levels of phospho-Akt increase with higher Gleason grade (58,59) and are associated with poorer survival in CRPC (60). However, it is unclear whether they hold any prognostic significance in low and intermediate grade disease (Gleason score 6-7) (59). Levels of phospho-Akt also predict for biochemical recurrence post radical prostatectomy, with improved prediction when used in combination with PTEN protein loss (61). Loss of INPP4B has been noted to be a good marker of aggressive breast cancer (62), but has not been explored in prostate cancer. Another area which remains to be more fully explored is the cellular localization of phospho-Akt. It is unclear whether increased nuclear staining improves prognostication, as suggested by one study which found that greater nuclear phospho-Akt staining was associated with higher Gleason grade (63).

In addition to the above mentioned studies on the use of PTEN, phospho-Akt or other related proteins as prognostic biomarkers, there is significant interest into the use of predictive biomarkers for PI3K/Akt targeting agents. Only a few studies to date have investigated predictive biomakers, but this area is expected to increase as more inhibitors of this pathway enter clinical evaluation. In unselected men with CRPC, PTEN status on immunohistochemistry did not predict response to everolimus (64). Activating mutations in mTOR were found in one patient with an excellent response to combination everolimus and pazopanib (65). Similar anecdotal responses to AZD5363, a pan-Akt inhibitor has been reported to be associated with genetic alterations, but not yet in prostate cancer patients (66). Prospected clinical investigation and validation is ongoing to identify and evaluate appropriate predictive biomarkers in patients for response to PI3K/Akt inhibitor therapy in prostate cancer patients.

7. Clinical studies of PI3K/Akt/mTOR inhibitors in prostate cancer

Several novel PI3K/Akt/mTOR pathway inhibitors are in clinical development (Table III) for advanced prostate cancer. Two studies have evaluated monotherapy with the Akt inhibitor perifosine in prostate cancer. Perifosine is an alkylphospholid with Akt inhibitor properties. Akylphospholipids are known to accumulate in cell membranes, but the exact reason for the anticancer activity is unclear, but this is presumed due to its capacity to inhibit the Akt pathway. A phase II trial of perifosine monotherapy in 25 patients with biochemical recurrence after primary therapy did not alter PSA doubling time and was ended early for lack of response (67). No significant toxicities were reported in this relatively healthy population. A second trial in 19 patients with metastatic prostate cancer also demonstrated minimal benefit (68). The median time to progression was 4 weeks, with only 4 patients having stable disease beyond 12 weeks. A recent phase III trial with perifosine in colon cancer has also found no therapeutic benefit (69).

The novel agents now in development (Table III) differ significantly from perifosine's mechanism of action and limited side effects. Most are small molecule reversible inhibitors of the catalytic function of PI3K, Akt, and/or mTOR. The common adverse effects of PI3k/Akt inhibitors reported to date include insulin resistance, hyperglycemia, nausea and mood alterations. PI3K inhibitors include non-specific and isoform-specific inhibitors. The three isoforms (p110α, β, and δ) of class IA PI3K may play relatively different roles in the progression of prostate cancer (7). Isoform-specific inhibitors in prostate cancer aim to inhibit only the PI3Kβ and δ isoforms to decrease insulin resistance and hyperglycemia associated with PI3Kα inhibition (70).

BKM120 is an oral pan-PI3K inhibitor with reported clinical data in advanced solid tumours, including prostate cancer (71). Among 31 patients in the phase I trial, one had a partial response and 12 (52%) had stable disease. Treatment-related adverse events include rash, hyperglycemia, diarrhea, anorexia, mood alteration, nausea and fatigue. Reversible neuropsychiatric adverse events may be due to BKM120 crossing the blood-brain barrier and inhibiting PI3K/Akt/mTOR signalling modulating neurotransmitter concentrations. Similarly, results with the oral pan-Akt inhibitor AZD5363 showed two partial responses out of 92 patients in two phase I trials (66). Notably, both patients had mutations in Akt1 or PI3KCA, suggesting mutations in these genes may be predictive of response.

Results to date with inhibition of downstream TORC1 or TORC2 in prostate cancer have been disappointing. Rapalogs such as everolimus, temsirolimus, and ridaforolimus have had poor results as single agents in prostate cancer clinical trials (64,72). This may be due in part to TORC2 mediated feedback on Akt (10). Dual TORC1/TORC2 inhibition has demonstrated improved inhibition of downstream effectors such as the eIF-4E protein translation complex not seen with mTORC1 inhibition (73). Dual mTORC1/mTORC2 inhibi-

tors have entered clinical testing for advanced solid tumours, including prostate cancer (74).

8. Combination targeting in prostate cancer

From pre-clinical data to date, as well as the failure of prior monotherapy trials, it appears that targeting of the PI3K/Akt pathway in prostate cancer is optimally done in combination with other agents. While monotherapy with newer agents may have some activity, the abundance of cross-talk with other pathways seen in pre-clinical studies suggests that resistance will develop as other pathways are reciprocally upregulated. In breast cancer, the combination of the aromatase inhibitor targeting the estrogen receptor with everolimus targeting mTOR demonstrated significant synergy (75). In an analogous manner in prostate cancer, rationale combination therapy may significantly improve clinical response rates and reduce the development of resistance.

Combination therapy with PI3K/Akt/mTOR inhibitors in prostate cancer can be conceptualized as vertical blockade, with inhibition of multiple nodes in the PI3K/Akt pathway or horizontal blockade, with inhibition of the PI3K/Akt pathway together with other parallel pathways. For example, pre-clinical work in transgenic mice suggests that dual targeting of the Akt and mTOR signalling (i.e., vertical blockade) has significantly more activity compared to either monotherapy (76). Dual PI3K/mTOR blockade with one molecule is facilitated by similarities of the PI3K and mTOR catalytic sites. Similarly, effective combinations of Akt or mTOR inhibition with AR blockade has been noted in other pre-clinical studies (17,38,77). Combination of Akt inhibition with receptor tyrosine kinases is another horizontal blockade strategy with good pre-clinical data (10).

Many of the ongoing clinical trials are evaluating a PI3K/Akt inhibitor in combination with an AR pathway inhibitor (Table III). A limited number of trials targeting both pathways have been reported in prostate cancer. A study in 36 patients with CRPC of the mTOR inhibitor everolimus in combination with bicalutamide has been reported (78). This study did not show any benefit for the combination, though it was well tolerated. Reasons for the lack of benefit could include a possible partial agonist effect of bicalutamide, lack of effective AR inhibition with bicalutamide as well as the activation of upstream Akt as a result of mTOR inhibition. However, another phase I/II trial found that of 13 patients treated with bicalutamide and everolimus, 9 had a partial response, one an unconfirmed partial response and 3 had stable disease. Of the 5 patients treated with placebo + bicalutamide, 1 had partial response, one unconfirmed partial response, 2 stable disease and 1 had disease progression. The mean time to relapse was 220 days for the everolimus + bicalutamide vs 109 days for placebo + bicalutamide (79). Very early results of the combination of BKM120 with abiraterone and prednisone are also promising (80).

One putative benefit of combination therapy is decreased toxicity while maintaining therapeutic efficacy. However, this has yet to be consistently observed in clinical trials in patients. Increased toxicity has been noted in some early studies to date when using combination therapy (81,82). In a clinical trial of 11 patients with CRPC treated with ridaforolimus and bicalutamide, 3 had dose-limiting toxicity, including hyperglycemia and stomatitis. It is anticipated that continued experience with these newer PI3K inhibitors will result in better dosing schedules to minimize adverse effects, while maintaining therapeutic efficacy.

9. Conclusion

Activation of the PI3K/Akt pathway clearly plays a major role in the aggressive nature of many prostate cancers. With the use of newer AR pathway inhibitors and combination therapy, this non-androgen receptor pathway may become increasingly relevant as more patients develop non-AR driven tumours. Clinical trials are now assessing the efficacy of targeting this pathway in CRPC. An improved understanding of the biology and relevant biomarkers of this pathway in prostate cancer will be important to understand which patients will benefit from PI3K/Akt/mTOR inhibitors and at what point in the disease course they should be given. The use of combination therapy has potential to substantially improve the outcome of patients, but needs to be balanced against toxicities, particularly if combination therapies are utilized earlier in the course of disease.

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