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REVIEW

Role of Akt signaling in resistance to DNA-targeted therapy

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Abstract

The Akt signal transduction pathway controls most hallmarks of cancer. Activation of the Akt cascade promotes a malignant phenotype and is also widely implicated in drug resistance. Therefore, the modulation of Akt activity is regarded as an attractive strategy to enhance the efficacy of cancer therapy and irradiation. This pathway consists of phosphatidylinositol 3 kinase (PI3K), mammalian target of rapamycin, and the transforming serine-threonine kinase Akt protein isoforms, also known as protein kinase B. DNA-targeted agents, such as platinum agents, taxanes, and antimetabolites, as well as radiation have had a significant impact on cancer treatment by affecting DNA replication, which is aberrantly activated in malignancies. However, the caveat is that they may also trigger the activation of repairing mechanisms, such as upstream and downstream cascade of Akt survival pathway. Thus, each target can theoretically be inhibited in view of improving the potency of conventional treatment. Akt inhibitors, *e.g.*, MK-2206 and perifosine, or PI3K modulators, *e.g.*, LY294002 and Wortmannin, have shown some promising results in favor of sensitizing the cancer cells to the therapy *in vitro* and *in vivo*, which have provided the rationale for incorporation of these novel agents into multimodality treatment of different malignancies. Nevertheless, despite the acceptable safety profile of some of these agents in the clinical studies, with regard to the efficacy, the results are still too preliminary. Hence, we need to wait for the upcoming data from the ongoing trials before utilizing them into the standard care of cancer patients.

Key words: Phosphatidylinositol 3 kinase/Akt; Platinum; Taxane; Antimetabolite; Radiation

Core tip: The Akt pathway plays an important role in resistance to several cytotoxic agents, targeted drugs and radiation. Exposure to these drugs will stimulate the Akt survival pathway leading to a decreased response to these drugs. In model systems inhibition of the Akt pathway enhanced the cytotoxicity of drugs like taxanes, antimetabolites, platinum analogs, several targeted drugs

and radiation. Akt inhibitors offer a new opportunity to increase the efficacy of currently used drugs and of radiotherapy.

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AKT PATHWAY SIGNALING OVERVIEW

The Akt signal transduction pathway controls most hallmarks of cancer, including metabolism, cell survival, cell cycle progression, regulation of apoptosis, protein synthesis, motility, and genomic instability by phosphorylation of the substrates[1]. Aberrant loss or gain of Akt activation has been associated with the development of various diseases, *e.g.,* diabetes, autoimmune diseases, and cancer[2-5].

The Akt pathway consists of phosphatidylinositol 3 kinase (PI3K), mammalian target of rapamycin (mTOR), and the transforming serine-threonine kinase Akt protein isoforms (further referred to as Akt), also known as protein kinase B (PKB) and phosphate and tensin homologue (PTEN) as a critical tumor suppressor. PI3K enzymes phosphorylate phosphatidylinositol-4,5-biphosphate (PIP2) to generate phosphatidylinositol-3,4,5-triphosphate (PIP3) at the cell membrane that are required for the recruitment and activation of Akt[6,7] (Figure 1). These phospholipids are constitutively elevated in most cancer cells. Docking of Akt to the cell membrane causes a conformational change, which in turn leads to phosphorylation of the two critical amino acid residues, threonine 308 and serine 473, and finally leads to the activation of Akt[8]. After the activation, Akt is translocated to intracellular compartments where it phosphorylates several substrate proteins. The downstream targets of Akt are numerous due to the multiple interactions with its consensus sequence[1]. In summary, the most important effects of Akt activation are: (1) cell survival through inhibition of BAD, caspase-9, and FOX[9-11]; (2) cell proliferation and gluconeogenesis through inhibition of GSK3, P21, P27, *etc.*[12]; and (3) protein synthesis and cell growth through activation of mTOR[13] (Figure 1).

To date, 3 Akt family members have been identified in mammals, *i.e.,* Akt1 (also known as PKBα), Akt2 (PKBβ) and Akt3 (PKBγ). Having shown highly conserved properties, these homologues may be activated by the same mechanism[14]. However, being encoded by three different regions at 14q32, 19q13, and 1q44, respectively, these three isoforms are distinct substrates with distinct physiological outcomes, and also opposing to each other. Accumulating evidence casts Akt1 and Akt2 function almost in contrary to each other in modulating phenotypes associated with migration and invasion. Akt isoforms contain an N-terminal pleckstrin homology (PH) domain, a central catalytic domain, and a C-terminal regulatory region. The PH domain can bind phosphatidylinositol lipids (*e.g.,* PIP3) with high affinity and targets Akt to the cell membrane[15].

Regulation of Akt, on the other hand, is mainly achieved through PTEN, which antagonizes PI3K. *PTEN* is a tumor suppressor gene that is frequently mutated in different types of cancer, and loss of PTEN leads to elevation of PI3K lipid products and thus activating the Akt pathway[16]. Thus, PTEN negatively regulates the Akt pathway, while loss of PTEN results in overactive Akt, which induces proliferation and promotes survival by inhibiting apoptosis[10,17]. Among the three Akt isoforms, Akt2, is exclusively having carcinogenic properties in PTEN-deficient solid tumors[18].

Despite many breakthroughs in elucidating the cancer behavior and possible mechanisms leading to developing different treatments, resistance is still a problem. The main goal of cytotoxic cancer therapy is to eliminate irregularly dividing cancer cells by targeting DNA synthesis or the mitotic apparatus. Different molecules, genes, proteins and signal transduction pathways are involved in this complicated process[1,19,20]. Resistance is often related to uptake, metabolism or alterations in the target. Besides, many studies demonstrated the modulation of key signaling pathways by the DNA-targeted therapies (reviewed in the following sections). The PI3K/Akt signaling pathway being mutated in a high percentage of malignancies[20] is widely implicated in tumor growth, which may also render tumor cells resistant to chemotherapeutic drugs[5]. Thus, inhibition of this pathway should foil local tumor growth. Many trials are underway to investigate whether adding inhibitors targeting PI3K/Akt pathway may improve the efficacy of the conventional regimen by reducing the apoptotic threshold[21]. Here, we review the literature on the potential value of modulating Akt pathway in view of improving the cytotoxicity of DNA-targeted anticancer drugs and radiotherapy.

METHODS: A SYSTEMATIC BEST EVIDENCE REVIEW

We looked for publications studying the effects of the approved or tested DNA-targeted cytotoxic agents on the Akt signaling using the Medline *via* PubMed database. The inclusion criteria consisted of studies on modulation of Akt signaling by DNA-targeted cytotoxic agents, *i.e.,* platinum agents (cisplatin, carboplatin, oxaliplatin), taxanes (paclitaxel, docetaxel), antimetabolites (gemcitabine, fluorouracil, pemetrexed), and radiation in glioblastoma, mesothelioma and lung, ovary, and pancreas cancers, including their synonyms, with no language restriction as of September 2014. Search terms related to the Akt modulation were "p-Akt" OR "pAkt" OR "phospho-Akt"

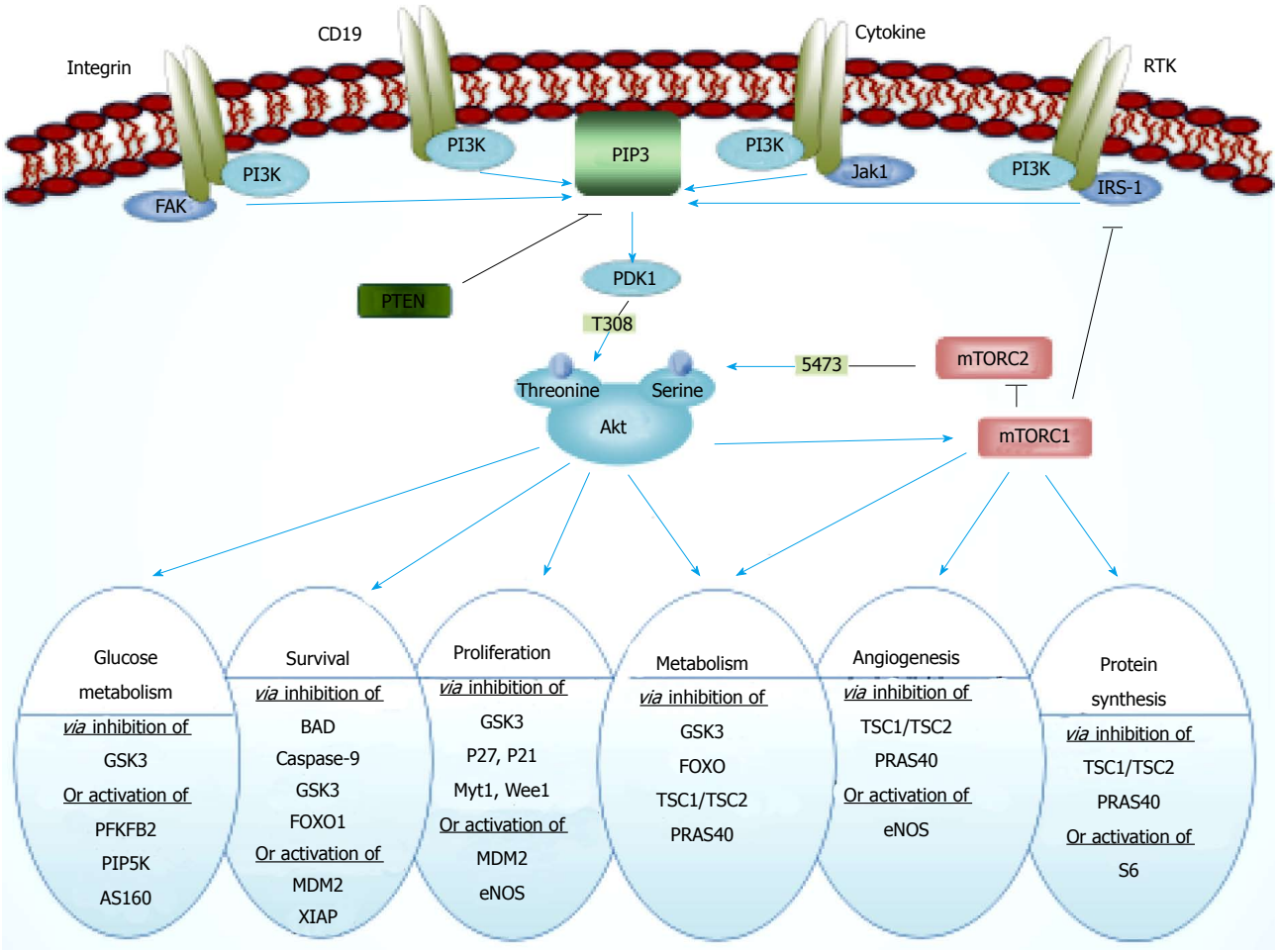

Figure 1 Phosphatidylinositol 3 kinase/Akt pathway. Activated RTKs activate PI3K through direct binding or through tyrosine phosphorylation of scaffolding adaptors, such as IRS1, which then bind and activate PI3K. PI3K phosphorylates PIP2 to generate PIP3, in a reaction that can be reversed by the PIP3 phosphatase PTEN. Activation of PI3K results in membrane recruitment and thus activation of Akt protein. Akt regulates cell growth and many other cellular processes through its effects on mTOR pathways and thus regulates glucose metabolism, protein synthesis, mitochondrial metabolism, lipid metabolism, adipogenesis, lipogenesis, angiogenesis, autophagy, proliferation and cell growth. Other targets of Akt include insulin receptor substrate-1 (IRS-1), glycogen synthase kinase 3 (GSK3), phosphodiesterase-3B (PDE-3), B cell lymphoma-2-associated death promoter (BAD), human caspase-9, Forkhead box (FOX) and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) transcription factors, endothelial nitric oxide synthase (eNOS), Rapidly Accelerated Fibrosarcoma (Raf) kinases, P21CIP1/WAF1 (P21; a potent cyclin-dependent kinase inhibitor), P27Kip1, Tuberous Sclerosis Complex 2 (TSC2; also known as Tuberin), X-linked inhibitor of apoptosis protein (XIAP; also known as inhibitor of apoptosis protein 3 and baculoviral IAP repeat-containing protein 4), and Mouse Double Minute 2. Following the activation, Akt phosphorylates and blocks the molecules involved in the apoptotic pathway, including FOX, Caspase-9 and BAD. In addition to the inhibition of proapoptotic factors, Akt can activate the transcription of antiapoptotic genes through the activation of the transcription factor Rel/NFκB. Akt also phosphorylates and activates IκB, which results in IκB degradation by the proteasome. This allows NFκB to translocate from the cytoplasm to the nucleus and activate transcription of a variety of substrates including anti-apoptotic IAP genes, such as the *c-IAP1* and *c-IAP2*. IRS1: Insulin receptor substrate 1; PI3K: Phosphatidylinositol 3-kinase; PIP3: Phosphatidylinositol-3,4,5-trisphosphate; PTEN: Phosphate and tensin homologue; RTK: Receptor tyrosine kinase.

OR "phosphorylat* Akt" OR "Akt phosphorylation" OR "Akt inhibition" OR "Akt modulation" OR "inhibit* Akt" OR "inactivation of Akt" OR "Akt inactivation" OR "activation of Akt" OR "inactivating Akt". Because of a large body of data on this subject, here we narrowed the scope of the current review down to the preclinical and clinical data on the simultaneous administration of cisplatin, paclitaxel, gemcitabine, or pemetrexed with some of the most clinically relevant PI3K/Akt modulators, *i.e.,* PI3K inhibitors, (*e.g.,* LY294002, Wortmannin), PI3K/mTOR inhibitors (*e.g.,* BEZ235), or Akt inhibitors (*e.g.,* perifosine, MK2206), which were tested in combinations with DNA-targeted agents in any of the five types of cancers. We excluded papers not meeting the inclusion criteria as well as retracted publications, duplicates, or non-original papers, *i.e.,* review articles, letters and editorials, comments, and case reports.

For clinical data, we searched for all the registered trials, being planned or performed to study the effect of PI3K/Akt inhibitors, *i.e.,* MK2206, perifosine, LY294002, Wortmannin, BEZ235, in combination with any of the nine DNA-targeted modalities discussed above, *i.e.,* carboplatin, cisplatin, oxaliplatin, paclitaxel, docetaxel, fluorouracil, gemcitabine, pemetrexed, and radiation. All published full text papers or abstracts as well as those with preliminary results in any languages fulfilling selection criteria were

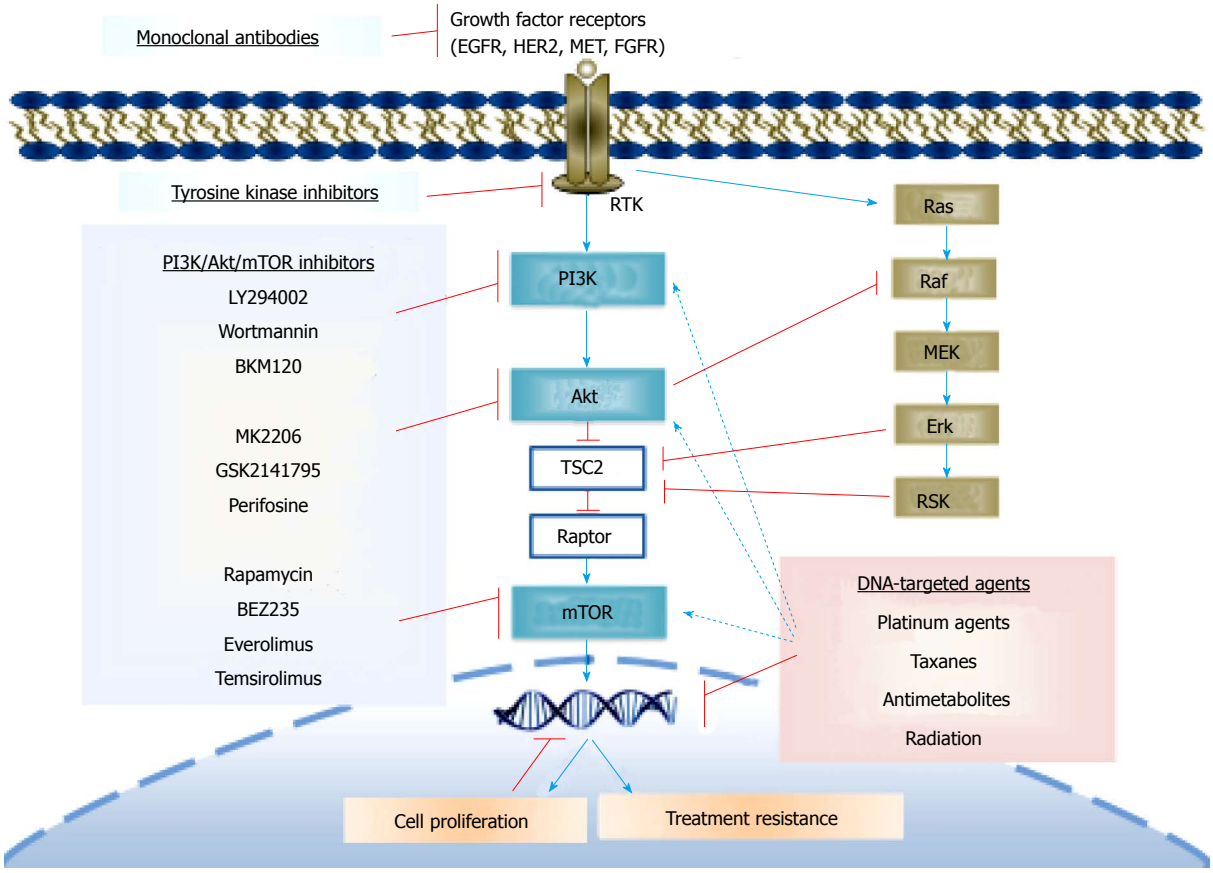

Figure 2 A schematic figure showing the complementary effects of phosphatidylinositol 3-kinase/Akt inhibitors with platinum agents, taxanes, antimetabolites, tumor antibiotics, and radiation resulting in a better cytotoxic profile.

included with no time period restriction. Studies with prior administration of anticancer medications, or combination of drugs targeting other signaling pathways other than Akt, PI3K, and mTOR were excluded. The databases that were used in this phase included the US clinical trials registry (clinicaltrials.gov), NIH clinical research studies (clinicalstudies.info.nih.gov), worldwide clinical trials listings (www.clinicaltrialssearch.org/5-cancer-clinical-trials.html), and the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch). The latter included 13 registries (Nationalities: Australian, New Zealand, Chinese, American, Canadian, European, Dutch, Brazilian, Indian, Korean, Cuban, German, Iranian, Japanese, Pan African, Sri Lankean, and Thai clinical trials).

AN OVERVIEW ON PI3K/AKT INHIBITORS

Many compounds have been developed to inhibit PI3K, Akt, and mTOR signaling, among which only few were tested in clinical settings (Figure 2). However, they did not yet have significant clinical benefit, except for idelalisib (GS-1101, a p110δ-selective inhibitor), which is the first Food and Drug Administration approved PI3K inhibitor[22], and some mTOR inhibitors, *e.g.,* rapamycin and its analogs. There are six general classes of these agents targeting the Akt network: Pan-class Ⅰ PI3K inhibitors, isoform-selective PI3K inhibitors, rapamycin analogues (rapalogues), active-site mTOR inhibitors, pan-PI3K-mTOR inhibitors and Akt inhibitors[23] (Table 1). Isoformspecific PI3K inhibitors targeting PI3Kβ, inhibitors of ribosomal protein S6 kinase β1 (S6K), PDK1 inhibitors and isoform-selective Akt kinase inhibitors (Akt1 and 2) are also under investigations soon to be tested in the clinic[23].

PI3K is upstream of Akt pathway, and with its inhibition all the subsequent signaling will potentially be down-regulated. Emerging clinical data show limited single-agent activity of inhibitors targeting PI3K. However, the drugs targeting PI3K pathway usually modulate the myriad substrates, including Akt and/or mTOR. LY294002, Wortmannin, and perifosine as PI3K/Akt inhibitors, BEZ235 as dual PI3K/mTOR inhibitor, and MK2206 as a specific Akt inhibitor are some of the commonly used drugs in this category that modulate Akt signaling. LY294002 is a morpholine-containing chemical compound that is a potent reversible inhibitor of PI3K signaling. Wortmannin is a steroid metabolite of the fungi Penicillium funiculosum with an irreversible inhibitory effect on PI3K. Perifosine is an orally active alkylphospholipid analog, which targets cell membrane and modulates different

Table 1 Drugs targeting phosphatidylinositol 3 kinase/Akt/mammalian target of rapamycin pathway

PI3K/Akt/mTOR subgroups	Agents	Clinical Stage
Pan-PI3K inhibitors	XL147	Phase Ⅱ
	BKM120	Phase Ⅲ
	GDC0941	Phase Ⅱ
Rapalogues (mTORC1 inhibitors)	Sirolimus	Phase Ⅲ
	Everolimus	Approved
	Temsirolimus	Approved
	Ridaforolimus	Phase Ⅲ
mTORC1/2 inhibitors	INK128	Phase Ⅱ
	AZD8055	Phase Ⅰ
	OSI027	Phase Ⅰ
PI3K–mTOR inhibitors	BEZ235	Phase Ⅱ
	XL765	Phase Ⅱ
	GSK1059615	Phase Ⅰ
Isoform-specific PI3K inhibitors	CAL-101 (p110δ)	Phase Ⅲ
	INK1117 (p110α)	Phase Ⅰ
	BYL719 (p110α)	Phase Ⅱ
Akt inhibitors	Perifosine	Phase Ⅲ
	MK-2206	Phase Ⅱ
	GDC0068	Phase Ⅱ
	GSK690693	Phase Ⅰ

PI3K: Phosphatidylinositol 3 kinase; mTOR: Mammalian target of rapamycin.

signaling pathways, and Akt in particular[24,25].

INDIRECT ALTERATION OF AKT SIGNALING AND ITS MODULATION

We finally selected 65 papers being suited to this review (Figure 3; Table 2) by which combination of a PI3K/Akt inhibitor with any of cisplatin, paclitaxel, gemcitabine, or pemetrexed was studied. The results are precisely discussed in the following sections.

Effect of platinum analogs on Akt signaling

Cisplatin, carboplatin and oxaliplatin are the 3 most commonly used anticancer platinum analogs. The main antitumor properties of cisplatin are attributed to the formation of platinum-DNA adducts causing DNA bending[26], which interferes with DNA replication, transcription and other nuclear functions leading to the inhibition of cellular proliferation and tumor growth. Intrinsic and acquired resistance limits the efficacy of platinum drugs in cancer treatment. Decreased drug uptake along with increased influx or inactivation by sulfhydryl molecules, such as glutathione, or increased DNA adduct repair can result in platinum resistance[27,28]. Wang and Lippard[29] suggested that induction of signaling pathways might be an alternative mechanism of resistance to platinum analogs.

Some data suggest that cell death induced by cisplatin may occur through regulation of cell cycle[30-32]. Mitsuuchi *et al*[32] demonstrated that PI3K, Akt1, and Akt2 are required for p53 protein expression and the full induction of p21 in ovarian cancer cells treated with cisplatin. Liu *et al*[33] suggested that Akt1 expression regulates cisplatin resistance in lung cancer cells through mTOR pathway, and its inhibition may sensitize cells to cisplatin. Moreover, amplification of a catalytic subunit of PI3K (PIK3CA) was also found to be associated with the risk of resistance to platinum-based chemotherapy in a group of patients with ovarian cancer, but not with the overall survival[34]. Thus vailable data support the probable role of Akt amplification/overexpression in platinum-resistance *in vitro* and *in vivo*[33,35-43].

The PTEN (encoding PIP3 phosphatase) and PIK3CA (encoding the PI3K catalytic isoform p110α) are the two most frequently altered mutated tumor suppressor and oncogenes, respectively[23]. Moreover, a low level of the PTEN expression is associated with amplified PIK3CA expression and finally PI3K/Akt activity[42]. Other data suggest that loss of the FHIT (fragile histidine triad; an inhibitor of Akt signaling) and overexpression of Redd1 (an inhibitor of mTOR signaling) are associated with cisplatin resistance in lung cancer cell lines[44-46]. Furthermore, overexpression of ADAM17 (a disintegrin and metalloproteinase-17) has been found to be associated with hypoxia-induced cisplatin resistance in hepatocellular carcinoma cells through activation of EGFR/PI3K/Akt pathway *in vitro*[47]. ADAM17 is a member of the metalloproteinase superfamily involved in the cleavage of ectodomain of many transmembrane proteins. Besides, prostate apoptosis response-4 (a proapoptotic tumor suppressor protein) downregulation was associated with cisplatin resistance in pancreatic cancer cells through upregulation of PI3K/Akt signaling *in vivo*[31]. Given that cisplatin activates PI3K/Akt signaling, downregulation of this pathway may bypass cisplatin-resistance. Akt pathway overactivation may decrease cisplatin sensitivity and cause treatment resistance even in platinum sensitive cells, whereas downregulation of Akt can boost the drug sensitivity and resistance to platinum compounds like cisplatin[36,39].

Effect of Akt-inhibition on platinum sensitivity

Some studies did not find treatment sensitization by adding LY294002 to cisplatin[48,49]. However, the PI3K/Akt inhibitors, LY294002, Wortmannin, or BEZ235 in combination with cisplatin showed synergistic or additive effects against malignant mesothelioma and lung cancer[44,50-55], pancreatic cancer[30], ovarian cancer[41-43,56-61], as well as glioblastoma[62,63] *in vitro* and *in vivo* (Table 3).

Perifosine increased the antineoplastic activity of cisplatin in ovarian[25,87], endometrial[91], and lung[44,54,55,92] cancer cells by activating apoptotic pathways and thus enhancing the cytotoxicity of cisplatin. Likewise, the specific Akt inhibitor MK-2206 showed synergism when combined with cisplatin in lung cancer[51,55], gastric cancer[93], and nasopharyngeal carcinoma cells[94] *in vitro* and *in vivo*. It can be concluded that activation of the Akt survival pathway plays a pivotal role in platinum resistance, and inhibition of Akt may enhance the effect of this type of anticancer drug.

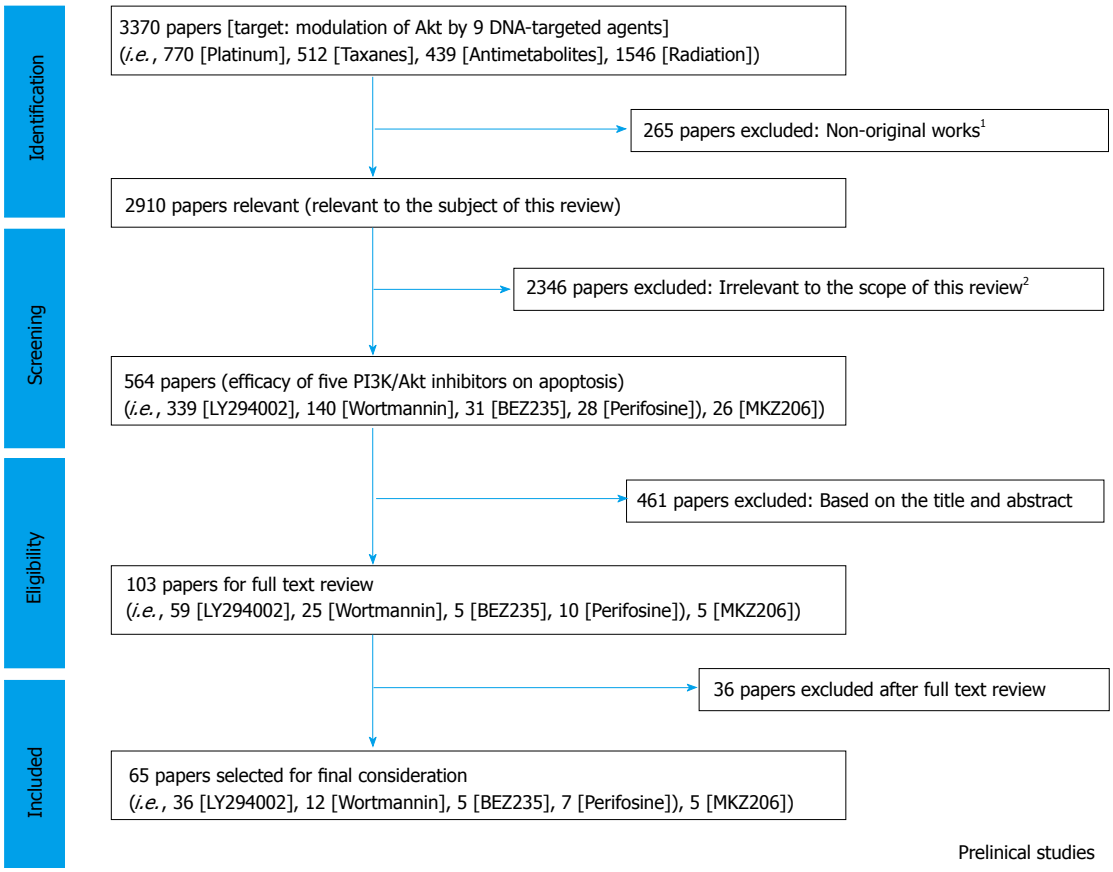

Figure 3 Review flow diagram of the publication selection in preclinical category. [1]Exclusion criteria include the retracted publication, duplicate publication or non-original papers, including review articles, letters and editorials, comments, case reports, *etc.*; [2]According to the scope of the current review: Efficacy of Akt modulation by 9 DNA-targeted agents in 5 types of cancer, including lung cancer, malignant mesothelioma, pancreatic cancer, ovarian cancer, and malignant glioma. PI3K: Phosphatidylinositol 3 kinase; EGFR: Epidermal growth factor receptor; mTOR: Mammalian target of rapamycin.

Table 2 Systematic chart of searching methodology and the results based on PubMed

DNA-targeted therapies	Agents	Akt modulation							
		All papers[1]	Non-original[2]	Relevant papers[3]	PI3K/Akt inhibitors[4]				
					LY294002	Wortmannin	BEZ235	Perifosine	MK2206
Platinum	Carboplatin	68	6	51	3	1	0	0	4
	Cisplatin	631	15	589	85	22	8	9	5
	Oxaliplatin	71	5	59	5	2	0	0	0
Taxane	Docetaxel	149	13	127	9	2	3	1	3
	Paclitaxel	363	18	331	47	15	4	2	5
Antimetabolite	Fluorouracil	191	5	174	18	6	0	2	3
	Gemcitabine	213	14	191	16	8	3	1	1
	Pemetrexed	35	3	32	5	2	1	0	0
Radiation	Irradiation/ radiation	1649	186	1356	151	82	12	13	5
Total articles	(9 agents)	3370	265	2910	339	140	31	28	26

[1]Terms used in the search: Query agent/radiation, and Akt, within whole the article with no language limitation, as of September, 2014; [2]Including the retracted publication, duplicate publication or non-original papers, including Review articles, Letters and Editorials, Comments, Case Reports, *etc.*; [3]Relevant with regard to the modulation of Akt by the query agent. [p-Akt OR pAkt OR "phospho-Akt" OR (phosphorylat* Akt) OR "Akt phosphorylation" OR "Akt inhibition" OR "Akt modulation" OR (inhibit* Akt) OR "inactivation of Akt" OR "Akt inactivation" OR "activation of Akt" OR "inactivating Akt"]; [4]Suppressing Akt cascade by a PI3K/Akt inhibitor to sensitize the query agent. PI3K: Phosphatidylinositol 3 kinase.

Effect of taxanes on Akt signaling

Taxanes, *e.g.*, paclitaxel and docetaxel, are frontline therapy for several cancers. They stabilize microtubules, leading to cell cycle arrest through centrosomal impairment, induction of abnormal spindles and suppression of spindle microtubule dynamics, finally triggering apoptosis[95]. Microtubules are critical for the integrity of the segregated DNA during mitosis. However, inherent or acquired resistance to taxanes

Table 3 Studies evaluating the efficacy of phosphatidylinositol 3 kinase phosphatidylinositol 3 kinase/Akt modulators on the apoptotic profile of cisplatin, paclitaxel, gemcitabine and pemetrexed

PI3K/Akt inhibitor and DNA-targeted agent combination	Akt modulation (phosphorylation)							
	Lung cancer and mesothelioma		Pancreatic cancer		Ovarian cancer		Malignant glioma	
	Synergistic	Antagonistic	Synergistic	Antagonistic	Synergistic	Antagonistic	Synergistic	Antagonistic
LY294002/Cisplatin	1[51]a	1[50]	2[30,31]	-	6[42,56-60]	1[49]	2[62,63]b	1[48]
LY294002/Paclitaxel	2[64,65]	2[50,66]	-	-	7[32,56,67-71]b	-	1[63]	-
LY294002/Gemcitabine	1[72]	1[73]	4[74-77]b	1[78]	1[56]	-	-	-
LY294002/Pemetrexed	1[79]	1[50]	-	-	-	-	-	-
Wortmannin/Cisplatin	1[52]		-	-	3[41-43]	-	-	-
Wortmannin/Paclitaxel	1[80]	-	-	-	1[70]	-	1[80]	-
Wortmannin/Gemcitabine	-	-	5[74,81-84]	-	-	-	-	-
Wortmannin/Pemetrexed	1[79]	-	-	-	-	-	-	-
BEZ235/Cisplatin	1[53]	-	-	-	1[61]	-	-	-
BEZ235/Paclitaxel	-	-	-	-	1[61]	-	-	-
BEZ235/Gemcitabine	-	-	1[85]	-	-	-	-	-
BEZ235/Pemetrexed	1[86]	-	-	-	-	-	-	-
Perifosine/Cisplatin	2[44,54]	-	-	-	2[25,87]	-	-	-
Perifosine/Paclitaxel	-	-	-	-	1[88]	-	-	-
Perifosine/Gemcitabine	1[54]b	-	-	-	1[89]	-	-	-
Perifosine/Pemetrexed	-	-	-	-	-	-	-	-
MK2206/Cisplatin	2[51,55]	-	-	-	-	-	-	-
MK2206/Paclitaxel	-	-	-	-	-	-	-	-
MK2206/Gemcitabine	2[54,90]b	-	-	-	-	-	-	-
MK2206/Pemetrexed	-	1[54]c	-	-	-	-	-	-
Total	17	6	12	1	24	1	4	1

[a]Chowdhry *et al*[51]. Reporting an increased sensitivity, but synergism not evaluated; [b]Shingu *et al*[62,63], Kawaguchi *et al*[69], Pinton *et al*[54] additive enhancement of proliferative inhibition; [c]Holcomb *et al*[76] LY294002 combination with gemcitabine showed additive effects on proliferative inhibition in PANC-1 and synergistic in $PaCa^{2+}$ pancreatic cancer cell lines. However, pAkt levels rebounded at later time points. PI3K: Phosphatidylinositol 3 kinase.

may compromise their therapeutic efficacy[96,97].

Resistance to taxanes includes increased efflux, and modification in tubulins. Akt pathway activation contributed to an increased resistance to paclitaxel or docetaxel in epithelial ovarian cancer, prostate cancer, and breast cancer cells[98-101]. Activation of Akt1 by HER2/PI3K may also lead to taxane resistance in breast adenocarcinoma cells[102]. Moreover, *PIK3CA* gene, encoding a catalytic subunit of the PI3K, is mutated and/or amplified in various neoplasms, such as ovarian cancer. Its amplification strongly decreased the sensitivity and thus response to platinum with/without taxanes in patients with ovarian carcinoma[34].

There are also crosstalks between PI3K/Akt pathway with BAD and ERK[41,68], and inhibition of these cascades sensitized ovarian cancer cells to taxanes. Therefore, in order to sensitize taxane treatment, PI3K/Akt cascade can be considered as a suitable target.

Effect of Akt-inhibition on taxane sensitivity

LY294002, Wortmannin, BEZ235, or perifosine-mediated inhibition of the PI3K/Akt-dependent survival pathway enhanced paclitaxel cytotoxicity in various cancers, *e.g.*, malignant glioma[63,80], lung[50,64-66,80], esophageal[64,80], and ovarian cancer cells[32,56,61,67-70,88] (Table 3). However, there are some data not in favor of the combination. LY294002 did not potentiate cisplatin, pemetrexed, or paclitaxel in A549 lung adenocarcinoma cells harboring K-ras mutation and wild-type EGFR[50]. Likewise, inactivation of PI3K/Akt signaling by LY294002 did not result in significant alteration of sensitivity of human ovarian carcinoma A2780 cells to paclitaxel[48]. Similarly, the combination of paclitaxel with LY294002 was antagonistic *in vitro* when dexamethasone was also administered; although dexamethasone did not alter the Akt activity[66].

Activation of NFκB is linked to Akt-dependent transcription of pro-survival genes[103]. Thus, LY294002-mediated suppression of the PI3K/Akt survival pathway with secondary inhibition of NFκB transcriptional activity is associated with enhancement of paclitaxel cytotoxicity in lung, esophageal and ovarian cancer cells[64,104,105], which indicates that NFκB may be the crucial intermediary step connecting Akt to the intrinsic susceptibility of cancer cells to paclitaxel.

Additionally, the Akt inhibitor MK-2206 augmented the efficacy of paclitaxel and carboplatin combination in gastric cancer[106], breast cancer[107], and melanoma cells[108]. However, addition of MK-2206 to paclitaxel alone had no additive inhibitory effect on growth of nasopharyngeal carcinoma cells *in vitro*[90]. Furthermore, Hirai *et al*[90] found that synergy of MK-2206 with docetaxel was dependent on the treatment sequence, in which a schedule of MK-2206 before docetaxel was not effective in terms of growth inhibition. Dual inhibition of PI3K and mTORC1/2 by BEZ235 may overcome docetaxel resistance in human castration resistant prostate cancer *in vitro* and *in vivo*[109]. Thus, modulation of the PI3K/Akt signaling may increase the efficacy and potency of taxanes according

to *in vitro* and *in vivo* data. However, the effect may have been masked by inclusion of platinum in several studies, indicating that in some studies, the effect might be *via* platinum.

Effect of antimetabolites on Akt signaling

Antimetabolites are a large group of anticancer drugs widely used in combination therapy of various leukemias and solid tumors. They interfere with DNA and RNA synthesis and therefore the growth of tumor[110]. Antimetabolites are categorized as pyrimidine analogs [*e.g.,* 5-fluorouracil (5-FU), gemcitabine], purine analogs (*e.g.,* azathioprine, mercaptopurine), and antifolates (*e.g.,* methotrexate, pemetrexed). In the present review, we mainly focused on two commonly used antimetabolites gemcitabine and 5-FU, as well as the novel anti-folate pemetrexed.

Effect of gemcitabine on Akt signaling and effect of Akt inhibition: Gemcitabine is used in the treatment of various carcinomas, such as lung cancer, bladder cancer, breast cancer, pancreatic cancer, and lymphomas[111]. A substantial number of potential biomarkers for sensitivity or resistance to gemcitabine have been characterized, including ribonucleotide reductase, deoxycytidine kinase, cytidine deaminase and human equilibrative transporter-1[112,113]. Additional mechanisms of resistance may exist, possibly not involving metabolism and direct targets[74,75,112,114].

Gemcitabine resistance in breast cancer cells may also be mediated by activation of the PI3K/Akt signaling pathway through phosphorylated Akt[115], so that inhibitors of PI3K/Akt might reverse the resistance to gemcitabine. Moreover, involvement and overexpression of PI3K and phosphorylated Akt in pancreatic carcinoma tissues has been reported in gemcitabine-resistant cells *in vitro*[73,78,84]. Rad51 overexpression may also mediate gemcitabine resistance through Akt or ERK1/2 activation in non-small cell lung cancer (NSCLC) cells, which could be overcome by downregulation of Rad51 or inhibition of Akt and ERK1/2 proteins[72]. Although Akt phosphorylation status is tailored as a predictive biomarker for gemcitabine resistance in NSCLC patients[116], gemcitabine may also reduce Akt phosphorylation without affecting the Akt overall expression[117]. Wilson *et al*[73] reported a weak correlation between phosphorylated S6K and phosphorylated Akt, suggesting the existence of Akt-independent regulation of mTOR-mediated resistance to apoptosis. Overall, inhibition of PI3K/Akt signaling may enhance the gemcitabine cytotoxic profile.

Wortmannin enhanced the efficacy of gemcitabine by a 5-fold increase of apoptosis in murine pancreatic xenografts[81]. A synergistic effect of Wortmannin, LY29 4002, and BEZ235 with gemcitabine was also reported in ovarian cancer[56] and pancreatic carcinoma[74-77,81-85] *in vitro* and *in vivo* (Table 3). Although gemcitabine induces cell cycle arrest at the G1 and early S phases, PI3K/Akt activation does not seem to influence gemcitabine-induced cell cycle arrest[84]. Likewise, perifosine has shown additivity in combination with gemcitabine by inhibiting Akt1 and Akt3 axis, and interfering Akt upstream, EGFR, and MET phosphorylation[54]. Perifosine also enhanced the gemcitabine-mediated antitumor effect on pancreatic cancer cells through blocking p70S6K1 (S6K1) activation, and thus disrupting S6K1-Gli1 association and subsequent Gli1 activation[89]. Besides, Akt[118], mTOR[119], and MAPK[120] may also activate Gli1. Likewise, the Akt inhibitor MK2206 enhanced the effect of gemcitabine on growth inhibition *in vitro* and *in vivo*[90]. In the contrary, Arlt *et al*[78] found that NFκB, rather than PI3K/Akt, activity conferred resistance to gemcitabine in a panel of five pancreatic carcinoma cell lines, which was strongly diminished by NFκB inhibitors, and not by LY294002. Overall, the PI3K/Akt inhibitors have been efficacious in improving gemcitabine cytotoxicity.

Effect of FU on Akt signaling and effect of Akt inhibition: 5-FU is an antimetabolite that acts by inhibition of thymidylate synthase (TS) and can be incorporated into RNA and DNA altering the cancer cell replication and proliferation[121]. 5-FU-based regimens are often used in adjuvant chemotherapy regimens and treatment of various advanced malignancies, such as colon cancer, head and neck cancer, breast cancer, but depending on the disease and stage of the tumor, intrinsic resistance to 5-FU can be as high as 50%[122]. Resistance to 5-FU has often been associated with an increased TS expression, both transient and permanent[123]. Other factors, such as enzymes involved in pyrimidine metabolism, *i.e.,* increased dihydropyrimidine dehydrogenase, decreased orotate phosphoribosyltransferase, or altered folate metabolism have been associated with 5-FU resistance[121,124,125]. Moreover, 5-FU has major effects on glycosylation pathways as well[126], which may indirectly have effects on signaling pathways. Hence, evidence is accumulating that 5-FU resistance is associated with altered signaling.

Smad4 deficiency may also contribute to 5-FU resistance through upregulation of vascular endothelial growth factor expression, which is associated with increased vascular density[127,128]. Zhang *et al*[129] found that loss of Smad4 in colorectal cancer patients may induce resistance to 5-FU through activation of Akt pathway. Akt can interact with Smad molecules to regulate transforming growth factor beta (TGF-β) signaling that is involved in transmitting chemical signals from the cell surface to the nucleus[130-132]. In summary, suppression of PI3K/Akt signaling may potentiate 5-FU.

The combination of LY294002 with 5-FU was synergistic *via* downregulation of PI3K/Akt signaling in Smad4-deficient colorectal cancer cells[129]. Likewise, sequential combination of 5-FU and LY294002 induced synergistic cytotoxicity and overcame intrinsic and acquired resistance of 5-FU *via* downregulation of Akt and mitochondria-dependent apoptosis in an Epstein-Barr virus positive gastric cancer cell line[133]. Wortmannin also promoted 5-FU antitumor activity in oral squamous cell carcinoma[134] and breast cancer cells[135]. In colorectal cancer cell lines, preclinical

studies indicate that perifosine and BEZ235 may enhance the cytotoxic effects of 5-FU, likely through the NFκB and thus PI3K/Akt pathway[136]. As a result, PI3K/Akt pathway is a rational target for sensitizing the tumor cells to 5-FU.

Effect of pemetrexed on Akt signaling and effect of Akt inhibition: Pemetrexed (Alimta; formerly known as LY231514), a multitargeted antifolate, inhibits thymidylate synthase (TS), dihydrofolate reductase, and the de novo purine nucleotide synthesis[137]. Pemetrexed is currently used as a single agent, but more often in combination with cisplatin for first line treatment of non-squamous NSCLC and malignant pleural mesothelioma[138-140]. Resistance to pemetrexed has been associated with TS upregulation in a colon cancer cell line[123,141], a transport deficiency, decreased activation by folylpolyglutamate synthetase and increased efflux[139]. Members of the ATP-binding cassette (ABC) transporters including P-glycoprotein (Pgp/ABCB1), multidrug resistance proteins (MRPs/ABCC) as well as breast cancer resistance protein (BCRP/ABCG2) as ATP-dependent drug efflux transporters may play roles in pemetrexed resistance[142]. The PI3K/Akt pathway regulates ABCG2-mediated drug efflux, which induces drug resistance[86,143-145].

Pemetrexed can also activate Akt signaling[79,143,146,147], although its molecular mechanisms is not completely understood. Chen *et al*[79] have observed a pemetrexed-induced cell apoptosis and a parallel increase in sustained Akt phosphorylation and nuclear accumulation in the NSCLC A549 cell line, and postulated that the activated Akt may play a proapoptotic role, while Giovannetti *et al*[147] observed that pemetrexed increased EGFR phosphorylation and slightly reduced Akt phosphorylation and enhanced apoptosis in six NSCLC cell lines[143,146] and malignant pleural mesothelioma (MPM) cells, particularly when combined with EGFR inhibitor erlotinib or carboplatin.

Adding a PI3K/Akt inhibitor may further increase pemetrexed antineoplastic effect. LY294002 and Wortmannin decreased the pemetrexed-stimulated Akt and GSK3β phosphorylated activation in the NSCLC A549 cell line[79] (Table 3). Perifosine antagonized the effect of pemetrexed in MPM cells by interfering upstream of Akt, affecting EGFR and MET phosphorylation[54]. Likewise, BEZ235 enhanced the antineoplastic effect of pemetrexed in malignant pleural mesothelioma by decreasing ABCG2-mediated drug efflux at the cell surface[86], which may be of therapeutic value in combination regimens. These data suggest that combining pemetrexed with a PI3K/Akt inhibitor may result in a better antineoplastic effect in various tumors.

Effects of irradiation and chemoradiation on Akt signaling: The combination of radiation with cytotoxic chemotherapy has become a standard treatment option for the majority of inoperable, locally advanced cancers, including brain, head and neck, lung, and gastrointestinal malignancies[148]. However, resistance to irradiation compromises therapeutic efficacy leading to tumor recurrence or metastasis. Tumors that recur after a successful radiation are often associated with radioresistance[149]. Resistance to radiotherapy is predominantly related to efficient repair of the DNA damage induced by X-ray. Both normal and neoplastic cells have several types of repair pathways, usually starting with the recognition and excision of the lesion, and then insertion of a new nucleotide. Regulation of several of these repair enzymes is mediated through methylation of the gene or activation of various protein kinases[150]. Given the complex biology underlying the interactions between the targeted agent and chemoradiation, comprehensive preclinical investigations are critical to design the rational combination[148].

Different combinations of drugs and radiation have been studied to improve efficacy and lessen toxicity. Chemotherapeutic drugs that perturb nucleotide metabolism have the potential to produce substantial sensitization of tumor cells to radiation treatment. Redistribution of cells into S-phase of the cell cycle and depletion of deoxynucleotide pools are probable mechanisms for gemcitabine and 5-FU, which made them potent radiosensitizers[151,152].

Radiation can activate multiple signaling pathways in cells[153], such as EGFR and several downstream proteins, *i.e.,* PI3K/Akt, MAPK JNK, p38, NFκB, *etc.,* stimulating DNA repair and thus causing radioresistance and survival of tumor cells. Loss of PTEN[154], as well as *KRAS* mutations[155,156] and NF-κB activation[157,158] also are associated with radioresistance, making the DNA less susceptible to ionizing radiation. Additionally, the ability of radiation to activate signaling pathways may depend on the expression of growth factor receptors, *RAS* mutation, and autocrine or paracrine ligands such as TGF-α, TGF-β, HB-EGF, neuregulins, and interleukin 6[153].

Effect of Akt-inhibition on radiation sensitivity: Alkylphosphocholines may potentiate the effect of radiation if given before or together with radiotherapy[159]. Targeting the PI3K pathway by LY294002 led to radiosensitization in glioblastoma[154] and human bladder cancer cell xenografts[160] *in vivo.* BEZ235 has also shown a modest antitumor response *in vivo*, while the combination of BEZ235 and ionizing radiation provided a longer survival and led to a smaller tumor volume when compared to radiation alone[161]. Likewise, the PI3K inhibitor BKM120 inhibited the radiation-induced activation of Akt[162]. This induced suppression of DNA-double-strand breaks repair and increased apoptosis, which resulted in increased sensitivity of liver cancer cells to irradiation[162]. Perifosine showed some radiosensitization in squamous cell carcinoma[163-165], malignant glioma[166], lymphoma[167], and prostate cancer[168]. In contrast, one study failed to show any favorable results with perifosine in terms of increasing its anticancer potency, despite a significant reduction in the level of phosphorylated Akt as well as Akt activity *in vitro* and *in vivo*[169]. Overall, given the activation of PI3K/Akt pathway by radiation, addition of a PI3K/Akt inhibitor may potentiate the therapeutic index of the conventional

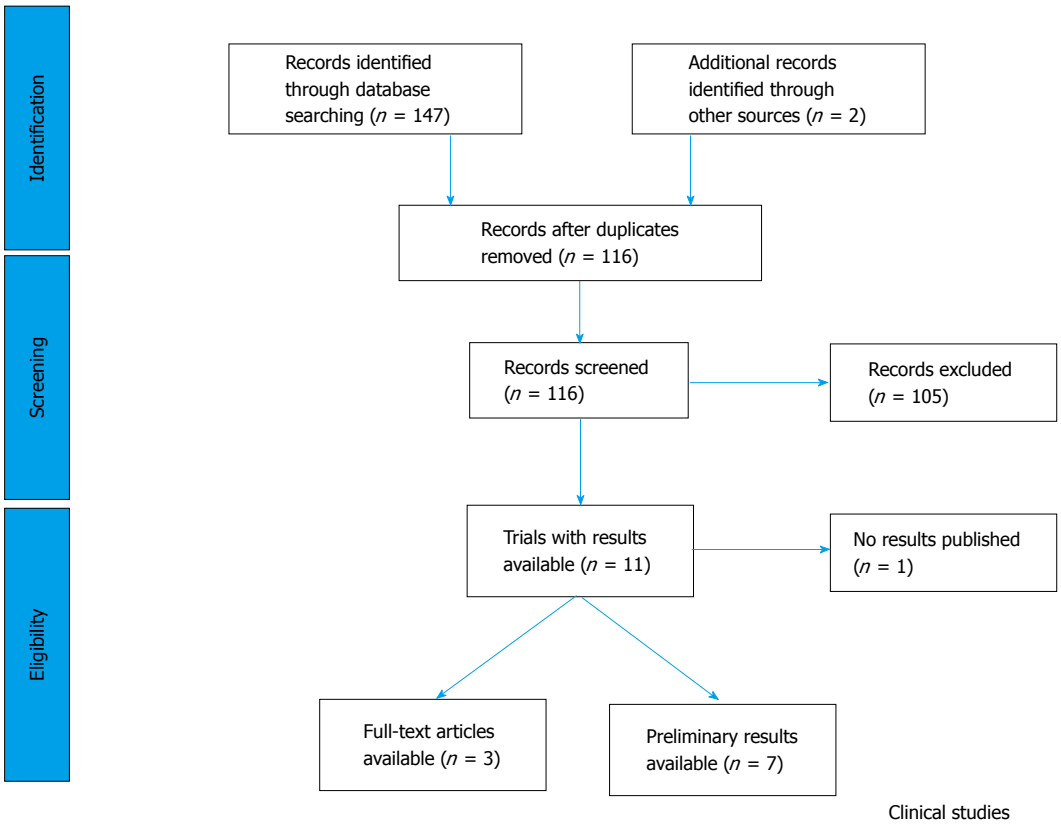

Figure 4 Review flow diagram of the publication selection in clinical category.

chemoradiation therapy.

PI3K/AKT INHIBITORS IN THE CLINIC

In the trial databases, we found 147 studies (Figure 4), which were designed to test the clinical profile of the six PI3K/Akt inhibitors. Only 11 trials - three published - were planned to assess the efficacy and safety of any of the PI3K/Akt inhibitors in combination with DNA-targeted agents (Table 4). We could not find any clinical trials being reported or registered to study the safety and efficacy of LY294002 or Wortmannin.

MK-2206

From 36 trials on MK-2206, registered between April 2008 (the first trial) and May 2013 (the last trial), to evaluate the safety and efficacy of MK-2206; only three suited our selection criteria (Table 4).

In a phase Ⅰ study with 72 patients with advanced solid tumor, Molife *et al*[170] (clinicaltrials.gov; NCT00848718) demonstrated that MK-2206 (45 or 60 mg every other day) plus carboplatin [area under the curve 6.0 mg/mL (AUC 6)] and paclitaxel (200 mg/m^2), docetaxel (75 mg/m^2), or erlotinib (100 or 150 mg daily) was well-tolerated, with early evidence of antitumor activity. The main dose-limiting toxicities included skin rash, febrile neutropenia, tinnitus, and stomatitis. Common drug-related toxicities included fatigue, nausea, and rash.

In a phase Ⅰ trial (NCT01235897) on 17 patients[171], MK2206 in combination with weekly paclitaxel (80 mg/m^2 weekly) with or without trastuzumab (2 mg/kg weekly after a 1-time loading dose of 4 mg/kg) has been tested in patients with human epidermal growth factor receptor 2 (HER2)-overexpressing solid tumor malignancies (11 breast, 3 gastric, 1 esophageal). The highest safe dose of MK-2206 was found to be 135 mg weekly [The Best Disease Response by Response Evaluation Criteria in Solid Tumor (RECIST) scoring was used for evaluation of the treatment toxicity in 15 patients]. Two patients experienced dose-limiting toxicities, while 64% showed tumor response and 29% had no disease progression[171]. Although all patients experienced different adverse events due to the treatment, serious or life threatening adverse events were reported in 5/17 (29.41%) participants. Based on these results, the authors concluded that MK2206 weekly at a dose of 135 mg in combination with weekly paclitaxel and trastuzumab was safe and well tolerated.

A phase Ⅰ trial (NCT01263145) is ongoing to determine the maximum tolerated dose, safety and antitumor activity of MK2206 and paclitaxel combination in patients with locally advanced or metastatic solid tumors or metastatic breast cancer. Thus, based on this scant evidence, we cannot conclude for or against administration of MK-2206 in combination with the available DNA-targeted agents.

Perifosine

From 42 trials on perifosine, registered between June

Table 4 Clinical trials on phosphatidylinositol 3 kinase/Akt inhibitors in combination with DNA-targeted agents

PI3K/Akt inhibitor	Target(s)	Combination arm(s)	Condition	Trial phase/status	Trial/registration
MK-2206	Akt	Carboplatin + paclitaxel, docetaxel, erlotinib	Locally advanced, metastatic solid tumors	Ⅰ/completed (published)	NCT00848718/February 2009[170]
		Paclitaxel, trastuzumab	HER2-overexpressing advanced solid tumors	Ⅰ/completed (abstract is published)	NCT01235897/ November 2010[171]
		Paclitaxel	Adult solid neoplasm, recurrent or metastatic breast cancer	Ⅰ/ongoing (unpublished)	NCT01263145/ December 2010
Perifosine	PI3K/Akt	Docetaxel, prednisone	Neoplasms	Ⅰ/completed (abstract is published)	NCT00399087/ November 2006[172]
		Docetaxel	Recurrent ovarian cancer	Ⅰ/completed (abstract is published)	NCT00431054/February 2007[173]
		Paclitaxel	Neoplasms	Ⅰ/completed (abstract is published)	NCT00399126/ November 2006[174]
		Gemcitabine	Neoplasms	Ⅰ/completed (abstract is published)	NCT00398697/ November 2006[175]
		Radiation	Solid tumors	Ⅰ/published	Vink *et al*[176]
		Radiation	Biochemically recurrent, hormone-sensitive prostate cancer with previous prostatectomy and/or radiation therapy	Ⅱ/published	Chee *et al*[177]
BEZ235	PI3K/ mTOR	BEZ235 + paclitaxel, BKM120 + paclitaxel, BEZ235 + paclitaxel + trastuzumab, BKM120 + paclitaxel + trastuzumab	Metastatic or locally advanced solid tumors	Ⅰ/completed (abstract is published)	NCT01285466/January 2011[178]
		Paclitaxel	Inoperable locally advanced breast cancer, metastatic breast cancer	Ⅰ and Ⅱ/completed (abstract is published)	NCT01495247/ September 2011[179]

HER2: Human epidermal growth factor receptor 2; PI3K: Phosphatidylinositol 3 kinase; mTOR: Mammalian target of rapamycin.

2000 (first trial) and August 2014 (last trial), only four studies as well as two published papers met our selection criteria for the current review.

Three trials evaluated the safety and efficacy of docetaxel or paclitaxel with perifosine (50, 100, and 150 mg/d). However, the results, despite the completion of the studies, have not yet been published (Table 4). In the first open-label study (NCT00399087) on 39 patients[172], daily doses up to 150 mg perifosine in combination with 75 mg/m^2 per 3 wk docetaxel with/without prednisolone was tolerated. Furthermore, the maximum tolerated dose for the weekly perifosine was 1200 mg. In the second trial (NCT00431054)[173] the safety and efficacy of the combination of docetaxel and perifosine were studied on 22 patients with epithelial cancer of the ovary, fallopian tube cancer or gynecologic primary peritoneal cancer, which were platinum resistant or refractory. The third phase Ⅰ trial (NCT00399126)[174] studied the gastrointestinal toxicity and cancer progression on the combination of daily perifosine with weekly or every 3-wk paclitaxel in 12 cancer patients. The preliminary results showed that the combination was well tolerated without increasing the toxicities being expected from using each drug alone.

Perifosine in combination with gemcitabine has also been studied in a non-randomized open-label phase Ⅰ trial (NCT00398697) on 22 patients[175]. The preliminary results showed that 150 mg daily perifosine might have some manageable toxicities without affecting the pharmacokinetic of perifosine.

The feasibility and tolerability of daily perifosine and radiation combination have also been studied in two independent successive trials. Vink *et al*[176] tested this combination in 21 radio-naive patients with solid tumors, of which 17 had NSCLC. Dysphasia and pneumonitis were the main complications of radiotherapy, and nausea, fatigue, vomiting, diarrhea, and anorexia as major drug-related toxicities in the population. One hundred and fifty milligram daily perifosine combined with fractionated radiotherapy was considered a safe modality. Chee *et al*[177] conducted a phase Ⅱ trial in 25 patients with biochemically recurrent, hormone-sensitive prostate cancer with previous prostatectomy and/or radiation therapy. However, only 20% of patients met the primary endpoint of prostate-specific antigen reduction, defined as a decrease by $\geqslant$ 50% from the pretreatment value. Accordingly, we should wait for the results of ongoing and future studies before coming to the conclusion if perifosine may add to the potency of DNA-targeted therapies.

BEZ235

From 23 trials on BEZ235, registered between February 2008 (first trial) and December 2013 (last trial), only two met our selection criteria for the final review, evaluating the safety and efficacy of the combination with any of the named DNA-targeted agents.

A phase Ⅰ multi-center, open-label, 4-arm dose-escalation study (NCT01285466)[178] is ongoing to evaluate the safety and efficacy of oral BEZ235 and

BKM120 in combination with weekly paclitaxel in patients with advanced solid tumors and weekly paclitaxel/trastuzumab in patients with HER2$^+$ metastatic breast cancer. The preliminary results[178] showed that of 35 patients who received BEZ235 at 400-800 mg/d and paclitaxel at 70-80 mg/m^2 per week dose-limiting toxicities occurred in 5 patients, 29% discontinued due to adverse effects and 63% due to progressive disease. Thus, they concluded that the safety over efficacy of this regimen would be questionable.

Additionally, a dose-finding phase Ⅰ followed by an open-label, randomized phase Ⅱ trial (NCT01495247)[179] of oral BEZ235 given twice daily (bid) with paclitaxel in patients with HER2 negative, locally advanced or metastatic breast cancer have recently been completed. The preliminary results with 18 patients showed that the determined maximum tolerated dose of BEZ235 (200 mg bid) in combination with paclitaxel (80 mg/m^2 per week) was not reached, and the trial has been terminated[179]. Thus, based on these two preliminary results, BEZ235 seems not safe in combination with paclitaxel for patients with solid tumors.

CONCLUSION

The Akt pathway is clearly important for the regulation of cell proliferation and survival. Its activation is an additional resistance mechanism for current chemoradiotherapy. Therefore, modulation of Akt activity is an attractive strategy to enhance the efficacy of treatment. However, insight in the mechanism of protection is incomplete and warrants further research. This lack of knowledge hampers to properly evaluate combinations in clinic, while current clinical trials are too preliminary to draw conclusions, despite having several drugs that are relatively safe and efficacious. Thus, the Akt modulation is an attractive target to improve the toxicity and safety profile of classical antitumor compounds and irradiation. Nevertheless, studies were inadequate and therefore inconclusive regarding the additive effect of PI3K/Akt inhibitors to the standard regimens. Accordingly, more in-depth preclinical and clinical studies as well as a critical appraisal are warranted to find congruent rational avenues to designing solid studies on any of the combinations.

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