Targeting the PI3K pathway in cancer: are we making headway?

Filip Janku, Timothy A. Yap and Funda Meric-Bernstam*

Abstract | The PI3K–AKT–mTOR pathway is one of the most frequently dysregulated pathways in cancer and, consequently, more than 40 compounds that target key components of this signalling network have been tested in clinical trials involving patients with a range of different cancers. The clinical development of many of these agents, however, has not advanced to late-phase randomized trials, and the antitumour activity of those that have been evaluated in comparative prospective studies has typically been limited, or toxicities were found to be prohibitive. Nevertheless, the mTOR inhibitors temsirolimus and everolimus and the PI3K inhibitors idelalisib and copanlisib have been approved by the FDA for clinical use in the treatment of a number of different cancers. Novel compounds with greater potency and selectivity, as well as improved therapeutic indices owing to reduced risks of toxicity, are clearly required. In addition, biomarkers that are predictive of a response, such as *PIK3CA* mutations for inhibitors of the PI3K catalytic subunit α isoform, must be identified and analytically and clinically validated. Finally, considering that oncogenic activation of the PI3K–AKT–mTOR pathway often occurs alongside pro-tumorigenic aberrations in other signalling networks, rational combinations are also needed to optimize the effectiveness of treatment. Herein, we review the current experience with anticancer therapies that target the PI3K–AKT–mTOR pathway.

The PI3K–AKT–mTOR signalling pathway is one of the most frequently dysregulated pathways in human cancers[1–6]. This pathway controls key cellular processes, such as metabolism, motility, growth, and proliferation, that support the survival, expansion and dissemination of cancer cells[7]; the pathway can be aberrantly activated in these cells through multiple mechanisms, including diverse genomic alterations involving *PIK3CA*, *PIK3R1*, *PTEN*, *AKT*, *TSC1*, *TSC2*, *LKB1* (also known as *STK11*), *MTOR*, and other oncogenes or tumour suppressor genes[8–18] (FIG. 1). These alterations are frequently detected in a range of tumour types (TABLE 1) and offer opportunities for therapeutic targeting of the PI3K–AKT–mTOR pathway. In addition, the results of preclinical and early clinical experiments have supported the potential efficacy of such approaches[8,9,19–24]. Investigations involving therapeutic targeting of the PI3K–AKT–mTOR pathway have resulted in the development of several distinct classes of drugs, including PI3K and AKT inhibitors, as well as allosteric mTOR and catalytic mTOR kinase inhibitors[1], Indeed, >40 different inhibitors of these proteins have reached various stages of clinical development, but only a few — the mTOR inhibitors temsirolimus and everolimus and the PI3K inhibitors idelalisib and copanlisib — have been approved by the FDA for clinical use in the treatment of patients with cancer[25–29] (TABLE 2). Many questions relating to the use of PI3K–AKT–mTOR pathway inhibitors remain unanswered, including which drugs or classes of drugs should be used in specific cancer contexts and whether the development of rational combination strategies will provide improved clinical benefit and lead to further regulatory approval of such compounds. Notably, novel inhibitors with increased specificity for individual isoforms of aberrant proteins, particularly PI3K, seem to have better therapeutic efficacy and improved toxicity profiles compared with non-isoform-selective agents[30]. Furthermore, the optimization of dosing schedules remains challenging, and robust predictive biomarkers of therapeutic activity or resistance have not been identified[1]. In this Review, we describe the key discoveries and challenges in the clinical development of antitumour therapies targeting the PI3K–AKT–mTOR pathway and discuss potential strategies to improve the clinical translation of such treatments in the future.

mTOR inhibitors

mTOR is a serine and threonine protein kinase that is the catalytic subunit of two multiprotein complexes, mTOR complex 1 (mTORC1) and mTORC2, that function as

Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), The University of Texas MD Anderson Cancer Center, Houston, TX, USA.
**e-mail: fjanku@mdanderson.org*

doi:10.1038/nrclinonc.2018.28
Published online 6 Mar 2018

Key points

- The PI3K–AKT–mTOR signalling pathway, which controls multiple cellular processes including metabolism, motility, proliferation, growth, and survival, is one of the most frequently dysregulated pathways in human cancers.
- The PI3K–AKT–mTOR pathway can be aberrantly activated by multiple factors, including diverse oncogenic genomic alterations in *PIK3CA*, *PIK3R1*, *PTEN*, *AKT*, *TSC1*, *TSC2*, *LKB1*, *MTOR*, and other critical genes, which can serve as targets for anticancer therapy.
- More than 40 inhibitors of the PI3K–AKT–mTOR signalling pathway have reached different stages of clinical development, but few — temsirolimus, everolimus, idelalisib, and copanlisib — have been approved for clinical use.
- Limited single-agent activity, problematic levels of toxicity, and a lack of predictive biomarkers for treatment selection have all been major barriers to the clinical translation of agents that target components of the PI3K–AKT–mTOR pathway.
- Novel compounds and dosing schedules that have fewer off-target effects need to be developed; efforts to identify biomarkers associated with clinical activity also need to be expanded beyond *PIK3CA* or *PTEN* alterations.
- Finally, as demonstrated in patients with metastatic hormone-receptor-positive breast cancer, combination strategies might open viable paths to advancing PI3K–AKT–mTOR inhibitors from clinical studies to new standard-of-care treatments.

nutrient, energy, and redox sensors involved in controlling cellular metabolism and growth[31]. Activation of mTORC1 downstream of PI3K and AKT increases the production of proteins, lipids, and nucleotides while downregulating autophagy, which supports cell survival, growth, and proliferation; mTORC2 also increases cellular proliferation and survival through the regulation of protein kinases, including AKT, which collectively provides the rationale for therapeutic targeting of mTOR complexes in cancer[32,33] (FIG. 2). Indeed, mTOR inhibitors were the first compounds that target the PI3K–AKT–mTOR pathway to advance to the clinic[25,26].

Allosteric mTOR inhibitors

Temsirolimus is an intravenously administered prodrug form of the allosteric mTORC1 inhibitor rapamycin (sirolimus), which forms a complex with the peptidyl-prolyl *cis*-trans isomerase FKBP1A that is incorporated into mTORC1, but not mTORC2, and inhibits mTOR. In 2007, this drug was approved by the FDA for the treatment of patients with advanced-stage renal cell carcinoma (RCC) based on the results of the phase III Global ARCC trial[25]. In this trial, temsirolimus monotherapy was associated with prolonged overall survival versus that observed with IFNα in treatment-naive patients with metastatic RCC (10.9 months versus 7.3 months; HR 0.73, 95% CI 0.58–0.92; $P = 0.008$); however, only 8.6% of patients had an objective response according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria[25].

Everolimus, another derivative of rapamycin that is administered orally, is currently approved by the FDA for the treatment of numerous cancers, including advanced-stage RCC; hormone receptor-positive, HER2-negative breast cancer in postmenopausal women; pancreatic neuroendrocrine tumours (NETs) and other selected NETs; adult renal angiomyolipoma associated with tuberous sclerosis complex; and paediatric or adult subependymal giant cell astrocytoma (SEGA) with tuberous sclerosis complex[14,26,27,34–36]. In the phase III RECORD-1 trial[26], everolimus monotherapy for previously treated patients with advanced-stage RCC was associated with prolonged progression-free survival (PFS) compared with that observed with placebo (median PFS 4.0 months versus 1.9 months; HR 0.30, 95% CI 0.22–0.40; $P < 0.0001$). This prolonged PFS did not, however, translate into a statistically significant improvement in overall survival, probably owing to patient crossover from the placebo arm to receive everolimus upon disease progression[26]. Notably, the reported overall response rates (ORRs) with everolimus in patients with RCC are consistently very low, ranging from 1% to 5%[26,37,38]. Everolimus has also been demonstrated to prolong the PFS of patients with advanced-stage pancreatic NETs in the randomized, phase III RADIANT-3 trial[34] (median PFS 11.0 months versus 4.6 months; HR 0.35, 95% CI 0.27–0.45; $P < 0.001$), but the ORR among patients in the everolimus arm did not exceed 5%. In addition, results of the phase III RADIANT-4 trial[39] in patients with progressive, well-differentiated, non-functional gastrointestinal or lung NETs demonstrated prolonged PFS in those treated with everolimus compared with in those treated with placebo (11.0 months versus 3.9 months; HR 0.48, 95% CI 0.35–0.67; $P < 0.00001$). In another randomized trial (BOLERO-2) enrolling patients with advanced-stage hormone receptor-positive, HER2-negative breast cancer previously treated with the aromatase inhibitors (AIs) letrozole or anastrozole[27], everolimus plus the AI exemestane was associated with a significantly higher ORR (9.5% versus 0.5%; $P < 0.001$) and a longer median PFS duration (6.9 months versus 2.8 months; HR 0.43, 95% CI 0.35–0.54; $P < 0.001$) than placebo plus exemestane, according to investigators' assessments. The findings of BOLERO-2 validated the hypothesis that activation of PI3K–AKT–mTOR signalling contributes to the development of resistance to hormone therapy.

In the phase III SUCCEED trial[40], ridaforolimus — another orally administered analogue of rapamycin — prolonged PFS compared with that observed using placebo in patients with previously treated metastatic soft-tissue sarcomas (median PFS 17.7 weeks versus 14.6 weeks; HR 0.72, 95% CI 0.61–0.85; $P = 0.001$). Objective responses were infrequent, however, with a mean decrease in target lesion size of only 1.3%. Moreover, median overall survival was not significantly improved with ridaforolimus (90.6 weeks versus 85.3 weeks; HR 0.93, 95% CI 0.78–1.12; $P = 0.46$)[40]. Further development of this compound for the treatment of cancer has not been pursued owing to a lack of therapeutic activity.

Finally, intravenously administered nanoparticle albumin-bound (nab)-rapamycin (ABI-009), which has improved bioavailability compared with oral rapamycin, was tested in 26 patients with advanced-stage nonhaematological malignancies in a dose-escalation study[41]. Grade 3 or 4 adverse events (AEs) were infrequent and were mostly laboratory findings, such as anaemia (8%), hypophosphataemia (8%), thrombocytopenia (12%), and transaminitis (8%). A partial response (PR) was observed in a patient with RCC, and a patient with

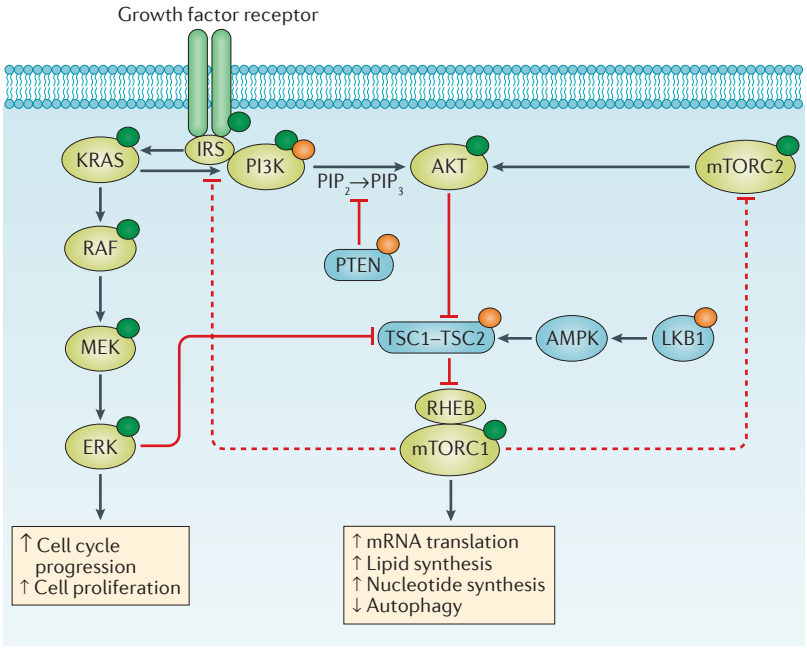

Figure 1 | **Intracellular signalling via the PI3K–AKT–mTOR pathway.** The PI3K–AKT–mTOR pathway is triggered by the activation of various growth factor receptor tyrosine kinases or G protein-coupled receptors (not shown). The class I PI3K proteins are recruited to the plasma membrane by adaptor proteins, such as insulin receptor substrate (IRS) family members, that interact with these activated cell-surface receptors, leading to phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP_2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP_3). PIP_3 is a second messenger that activates the AKT kinases, which are able to phosphorylate tuberous sclerosis protein 1 (TSC1) and TSC2, and thereby dissociate the TSC1–TSC2 complex. The TSC1–TSC2 complex negatively regulates the activity of the kinase mTOR; therefore, AKT results in the activation of mTOR complex 1 (mTORC1) and ultimately in increased protein and lipid synthesis and decreased autophagy, which supports cell growth and proliferation. Notably, mTORC1 is involved in a negative feedback loop that serves to prevent the overactivation of AKT (dashed red lines). The PI3K–AKT–mTOR pathway can be upregulated by activating molecular alterations in the PI3K subunits (such as PI3K catalytic subunit α isoform, encoded by *PIK3CA*), AKT, and mTOR (depicted by green circles) or by loss-of-function alterations in the PI3K regulatory subunits (such as PI3K regulatory subunit-α, encoded by *PIK3R1*), PTEN, TSC1, TSC2, and LKB1 (also known as STK11) (depicted by orange circles). In parallel, activation of the growth factor receptor tyrosine kinases and G protein-coupled receptors induces KRAS–RAF–MEK–ERK signalling, and ERK activation can further contribute to mTORC1 activation through dissociation of the TSC1–TSC2 complex. KRAS can also reinforce the activation of PI3K. Notably, the KRAS–RAF–MEK–ERK pathway can also be activated constitutively by gain-of-function alterations in the component kinases or cell-surface receptors (green circles).

mesothelioma and another with NET remained on study for 238 days and 365 days, respectively. Nab-rapamycin is currently being evaluated in phase II studies (TABLE 2).

mTOR kinase inhibitors

Competitive (non-allosteric) inhibitors of mTOR kinase are effective against both mTORC1 and mTORC2 (FIG. 2). These agents have the potential to prevent the feedback-loop-based activation of AKT caused by inhibition of mTORC1 but not mTORC2 (REFS 33,42–44) (FIG. 1). Thus, mTOR kinase inhibitors might result in a greater level of inhibition of PI3K–AKT–mTOR signalling than mTORC1-selective allosteric mTOR inhibitors, resulting in improved anticancer activity.

The mTORC1 and mTORC2 (mTORC1/2) inhibitor vistusertib (AZD2014) has been tested in patients with advanced-stage cancers in a phase I study; fatigue and mucositis were dose-limiting toxicities (DLTs), consistent with the expected safety profile of mTOR inhibitors, and one patient with pancreatic acinar cell carcinoma had a PR[45]. In the phase II MANTA study[46], 333 postmenopausal women with advanced-stage hormone receptor-positive, HER2-negative breast cancer were randomized to receive the selective oestrogen receptor degrader fulvestrant plus either daily vistusertib, intermittent vistusertib, everolimus, or fulvestrant alone; the median PFS durations were 7.6 months, 8.0 months, 12.3 months, and 5.4 months, respectively. A comparison of the fulvestrant plus daily vistusertib and the fulvestrant only groups demonstrated a hazard ratio of 0.88 (95% CI 0.63–1.24; $P = 0.42$), and a comparison of the fulvestrant plus everolimus and fulvestrant plus daily vistusertib arms demonstrated a hazard ratio of 0.63 (95% CI 0.45–0.90; $P = 0.01$)[46]. The results with vistusertib are disappointing, although this agent is under continued investigation in multiple phase I and II trials involving patients with glioblastoma, meningioma, prostate cancer, or tumours harbouring *RICTOR* amplification or *TSC* mutations (TABLES 2,3), which result in hyperactivation of mTORC1 and/or mTORC2 and are, therefore, hypothesized to increase sensitivity to the drug[13,15]. Vistusertib is also being clinically evaluated in rationally designed combinations with other therapies, such as paclitaxel, olaparib, palbociclib, and selumetinib, in order to overcome intrinsic and acquired resistance mechanisms and improve patient outcomes.

AZD8055, another mTORC1/2 inhibitor, has been evaluated in 49 patients with advanced-stage solid cancer or lymphoma[47]; no responses were reported. The most frequent grade 3 or 4 AE was transaminitis, and this toxicity, as well as a lack of clinical activity, impeded the advancement of AZD8055 to phase II trials; no clinical studies are currently investigating this drug.

In two independent phase I dose-escalation studies[48,49], the safety and efficacy of sapanisertib was examined in 115 patients with advanced-stage solid tumours and in 39 patients with refractory multiple myeloma, non-Hodgkin lymphoma (NHL), or Waldenström macroglobulinaemia. In the latter study, the results of which have been reported in a full publication[48], grade 3 or 4 drug-related AEs were reported in 31% of patients treated on continuous dosing schedules and in 77% of patients receiving treatment on intermittent dosing schedules and were mostly consistent with those of other drugs in this class. Objective responses were infrequent (two PRs in the solid tumour study[49] and one PR in the haematological malignancies study[48]). Nevertheless, sapanisertib has been advanced to further clinical testing across a diverse range of tumour types and in multiple combinations. In addition, owing to previous reports of the increased efficacy of mTOR inhibitors based on the presence of certain PI3K–AKT–mTOR-pathway aberrations[11], sapanisertib is currently being tested in patients with tumours harbouring *TSC1* or *TSC2* mutations as part of the National Cancer Institute (NCI) MATCH

Table 1 | **Potential directly and indirectly druggable alterations in the PI3K–AKT–mTOR pathway**

Gene	Type of alteration	Expected consequence	Cancer type	Frequency of mutation[a] (%)
PIK3CA	Mutation	Gain of function	Endometrial	35–53
			Breast	26–41
			Squamous cervical	27
			Bladder	20–23
			Squamous head and neck	18–21
			Colorectal	15–21
			Gastric	2–17
			Squamous lung	15–16
			Ampullary	13
			Glioblastoma	9–11
			Oesophageal	10
	Amplification	Gain of function	Squamous lung	38–47
			Ovarian	18–29
			Oesophageal	23
			Neuroendocrine prostate	22
			Squamous head and neck	21
			Squamous cervical	20
PIK3CB	Amplification	Gain of function	Neuroendocrine prostate	22
			Squamous lung	9–16
			Ovarian	4–11
			Squamous cervical	10
			Squamous head and neck	10
			Oesophageal	10
PIK3R1	Mutation	Loss of function	Endometrial	33
			Glioblastoma	11
			Low-grade glioma	5
PTEN	Mutation or deletion	Loss of function	Endometrial	65
			Glioblastoma	31–41
			Prostate	7–39
			Squamous lung	11–18
			Neuroendocrine prostate	17
			Melanoma	12–13
			Gastric	12
			Breast	5–10
AKT	Mutation	Gain of function	Breast	2–6
			Oesophageal	3
			Bladder	2
	Amplification	Gain of function	Neuroendocrine prostate	21
			Pancreatic	10
			Ovarian	5
TSC1	Mutation	Loss of function	Bladder	6–9
			Gastric	6
			Oesophageal	5
TSC2	Mutation	Loss of function	Gastric	6
			Colorectal	5
			Melanoma	5

Table 1 (cont.) | **Potential directly and indirectly druggable alterations in the PI3K–AKT–mTOR pathway**

Gene	Type of alteration	Expected consequence	Cancer type	Frequency of mutation[a] (%)
LKB1	Mutation	Loss of function	Adenocarcinoma lung	15–17
			Pancreatic	2–3
			Oesophageal	3
MTOR	Mutation	Gain of function	Endometrial	11
			Colorectal	8
			Melanoma	7
RICTOR	Amplification	Gain of function	Neuroendocrine prostate	18
			Squamous lung	8–16
			Lung adenocarcinoma	10

[a]As reported in cBioPortal on 18 November 2017; data sets with ≥100 patients and cancer types with a frequency of alteration ≥10% or the three cancer types with the highest prevalence of alteration are included in this table.

trial, in which groups of patients with advanced-stage cancers carrying specific genetic aberrations are matched with various targeted therapies, according to the precision medicine paradigm (TABLE 3).

A different mTORC1/2 inhibitor, CC-223, has been investigated in a dose-escalation study involving 28 patients with advanced-stage solid tumours or multiple myeloma[50]. One patient with breast cancer had a PR, equating to a disappointing ORR of 4%[50]. Accordingly, plans to further develop CC-223 seem to be limited.

Finally, OSI-027 has been tested in a dose-escalation, dose-expansion study involving 128 patients with various advanced-stage solid tumours or lymphomas[51]. The investigators examined intermittent (3 days on then 4 days off), weekly, and daily dosing schedules. The intermittent and weekly schedules were tested in dose-expansion cohorts, and the daily schedule was associated with the highest number of treatment discontinuations owing to drug-related AEs, with 17% of patients experiencing grade 3 or 4 AEs including fatigue and diarrhoea[51]. No patients had an objective response; however, six patients had stable disease for >6 months[51]. Notably, correlative studies revealed that the dose required for proper target engagement was above the tolerable limit[51]. To our knowledge, this drug has not been advanced to testing in other clinical trials, except for one phase I/II study investigating multiple combinations of the drug with chemotherapy or biologic agents in patients with advanced-stage head and neck squamous cell carcinoma (HNSCC).

In summary, although mTOR inhibitors are generally well tolerated, they have only modest clinical activity when used as single agents. The inhibitors of mTORC1, temsirolimus and everolimus, are currently approved for clinical use as single agents for indications in which therapeutic options were lacking at the time of approval (RCC, pancreatic NET, non-functional lung or gastrointestinal NET, and SEGA) or in combination with hormone therapy to overcome endocrine resistance in women with hormone receptor-positive, HER2-negative breast cancer[14,25–27,34–36,39]. Whether or not catalytic mTOR kinase (mTORC1/2) inhibitors offer any clinically relevant advantage over allosteric mTORC1 inhibitors remains unclear, and drugs of both classes continue to be tested in phase I and II studies, including — perhaps importantly — trials involving rationally designed combinations and studies that include biomarker-based patient selection strategies (TABLE 3).

Pan-PI3K inhibitors

Pan-PI3K inhibitors inhibit, to some degree, the catalytic activity of all four PI3K class I isoforms: PI3Kα (encoded by *PIK3CA*), PI3Kβ (encoded by *PIK3CB*), PI3Kγ (encoded by *PIK3CG*), and PI3Kδ (encoded by *PIK3CG*). Theoretically, therefore, these agents should be effective against cancers with elevated production of phosphatidylinositol 3,4,5-trisphosphate (PIP_3) irrespective of the type of PI3K or PTEN alterations involved. These inhibitors offer a potentially broader spectrum of activity by encompassing a wide range of molecular targets (FIG. 3), although with an increased risk of on-target and off-target effects and toxicities[3]. With the exception of copanlisib, no pan-PI3K inhibitors have been approved for clinical use outside of trials owing to either a lack of activity or to safety concerns, as outlined below.

Buparlisib is one of the most extensively tested pan-PI3K inhibitors to date, with data available from three randomized trials[52–54]. In the phase III BELLE-2 trial[52], 1,147 patients with advanced-stage hormone receptor-positive breast cancer who had disease progression on AI therapy were randomly assigned to receive fulvestrant with either placebo or buparlisib. The primary end point of the study was met, with the addition of buparlisib prolonging PFS compared with placebo, albeit by a modest amount of time (median PFS 6.9 months versus 5.0 months; HR 0.78, 95% CI 0.67–0.89; $P = 0.00021$)[52]. Of note, patients with *PIK3CA* mutations detected in plasma-derived cell-free DNA had a longer median PFS duration with buparlisib therapy than with placebo (7.0 months versus 3.2 months)[52]. Up to 25% of patients treated with buparlisib had severe (grade ≥3) AEs, such as on-target hyperglycaemia and liver toxicities[52]. In BELLE-3 (REF. 53), another phase III trial, 432 postmenopausal women who had previously received AIs and mTOR inhibitors were randomly assigned to receive treatment with fulvestrant plus either buparlisib or placebo. In comparison with the patients who received placebo, those who received buparlisib

Table 2 | **Selected PI3K–AKT–mTOR inhibitors that are approved for clinical use or are under clinical development**

Drug class	Drug	Stage of clinical development
mTORC1 inhibitors	Temsirolimus[a]	Approved for the treatment of advanced-stage renal cancer
	Everolimus	Approved for the treatment of advanced-stage renal cancer, advanced-stage HR$^+$ breast cancer in postmenopausal women in combination with exemestane, well-differentiated neuroendocrine tumours, renal angiomyolipoma and tuberous sclerosis complex, and subependymal giant cell astrocytoma and tuberous sclerosis complex
	Ridaforolimus	Phase III trial in patients with advanced-stage soft-tissue sarcoma completed; no further development
	Nab-rapamycin[a]	Phase II studies ongoing in patients with *MTOR*-mutated advanced-stage cancers, perivascular epithelioid cell tumours, and other sarcomas
mTORC1 and mTORC2 inhibitors	Vistusertib	Phase II studies ongoing in patients with *RICTOR*-amplified tumours and in those with a variety of advanced-stage cancers
	AZD8055	Phase I study in patients with advanced-stage solid tumours and lymphoma completed; no further development
	Sapanisertib	Phase II studies ongoing in patients with advanced-stage cancers; also evaluated in the NCI-MATCH trial
	CC-223	Phase II study ongoing in patients with lymphoma
	OSI-027	Phase II study ongoing in patients with HNSCC in combination with chemotherapy or biologic agents
Pan-PI3K inhibitors	Buparlisib	Phase III studies completed in patients with advanced-stage breast cancer
	Pictilisib	Randomized phase II studies completed in patients with breast cancer; no further development
	Pilaralisib	Phase II studies completed in patients with breast or endometrial cancers; no further development
	Copanlisib[a]	Approved for the treatment of relapsed follicular lymphoma
	PX-866	Phase II studies completed in patients with solid tumours; no further development
	CH5132799	Phase I study completed in patients with advanced-stage solid tumours; no further development
	ZSTK474	Phase I studies completed in patients with solid tumours; no further development
	SF1126[a]	Phase II study in patients with HNSCC harbouring a PI3K alteration
Dual pan-PI3K and mTORC1–mTORC2 inhibitors	BGT226	Phase I studies completed in patients with advanced-stage cancers; no further development
	Dactolisib	Phase II studies completed in renal cell carcinoma and prostate cancer; no further development
	Apitolisib	Randomized phase II study completed in patients with renal cell carcinoma; no further development
	Gedatolisib[a]	Phase I/II studies ongoing in patients with advanced-stage NSCLC or breast cancer
	PF-04691502	Phase I study completed in patients with solid tumours; no further development
	LY3023414	Phase II studies ongoing in patients with diverse cancers
	PQR309	Studies ongoing in patients with lymphoma or breast cancer in combination with chemotherapy
PI3Kα inhibitors	Alpelisib	Phase I and phase II studies ongoing in patients with diverse cancers
	Taselisib	Phase III trials ongoing in patients with breast cancer or NSCLC
	TAK-117	Phase II studies ongoing in patients with breast cancer or renal cancer
	ASN003	Phase I study ongoing in patients with solid tumours
PI3Kβ inhibitors	GSK2636771	Phase II studies ongoing in patients with diverse cancers
	AZD8186	Phase I study ongoing in patients with solid tumours
	SAR260301	Phase I study completed in patients with solid tumours; no further development
PI3Kγ inhibitor	IPI-549	Phase I study ongoing in patients with carcinoma or melanoma
PI3Kδ inhibitors	Idelalisib	Approved for the treatment of CLL, follicular lymphoma, and SLL
	Duvelisib	Phase III trial ongoing in patients with CLL or SLL
	AMG319	Phase II study ongoing in patients with HNSCC
AKT inhibitors	MK-2206	Biomarker-driven randomized phase II studies ongoing in patients with NSCLC or breast cancer
	BAY 1125976	Phase I study ongoing in patients with solid tumours
	Uprosertib	Phase I/II studies ongoing in patients with solid tumours
	Ipatasertib	Phase II and phase III studies ongoing in patients with breast or prostate cancer
	AZD5363	Phase II studies ongoing in patients with a diverse range of cancers
	Miransertib	Phase I studies ongoing in patients with solid tumours
	ARQ 751	Phase I study ongoing in patients with solid tumours
	MSC2363318A	Phase I study ongoing in patients with solid tumours
	TAS-117	Phase I study ongoing in patients with solid tumours

CLL, chronic lymphocytic leukaemia; HNSCC, head and neck squamous cell carcinoma; HR, hormone receptor; mTORC, mTOR complex; NCI, US National Cancer Institute; NSCLC, non-small-cell lung cancer; SLL, small lymphocytic leukaemia. [a]Administered intravenously; all other agents are administered orally.

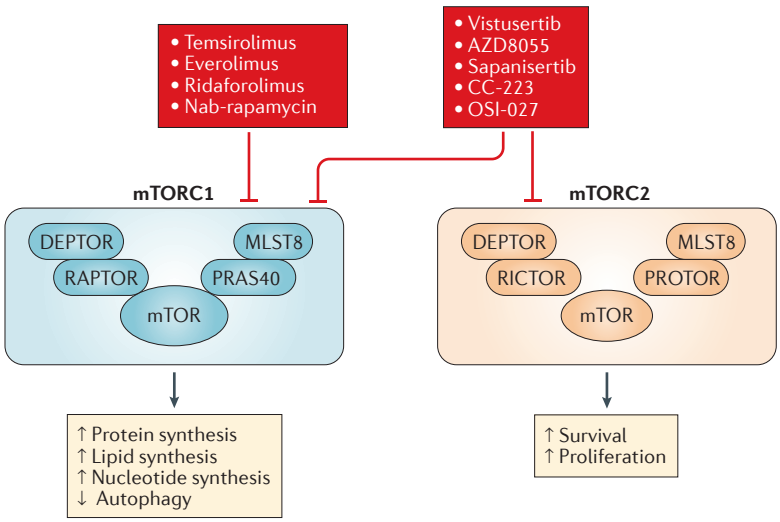

Figure 2 | **Summary of pharmacological agents that target various components of the PI3K–AKT–mTOR pathway.** Inhibitors of mTOR complex 1 (mTORC1) and/or mTORC2 can interfere with the tumour-promoting cellular functions regulated by PI3K–AKT–mTOR signalling. Specific inhibitors of mTORC1 do not inhibit mTORC2, and their effectiveness can be limited by paradoxical suppression of an mTORC1-mediated negative feedback loop that normally regulates the degree of mTORC2 and AKT activation. DEPTOR, DEP domain-containing mTOR-interacting protein; MLST8, mammalian lethal with SEC13 protein 8; nab-rapamycin, nanoparticle albumin-bound rapamycin; PRAS40, proline-rich AKT1 substrate 1; PROTOR, protein observed with RICTOR (also known as PRR5); RAPTOR, regulatory-associated protein of mTOR; RICTOR, rapamycin-insensitive companion of mTOR.

had a longer median PFS duration (3.9 months versus 1.8 months; HR 0.67, 95% CI 0.53–0.84; $P < 0.0001$)[53]. A total of 349 patients had a known *PIK3CA* mutation on the basis of analysis of plasma cell-free DNA in liquid biopsy samples; buparlisib was associated with a greater prolongation of median PFS among the 147 (42%) patients with *PIK3CA* mutations (4.7 months versus 1.6 months with placebo; HR 0.50, 95% CI 0.33–0.76) than in patients without *PIK3CA* mutations (3.7 months versus 2.7 months with placebo; HR 0.73, 95% CI 0.52–1.01)[53]. Unfortunately, >20% of patients had grade 3 or 4 transaminitis, and several patients had severe anxiety and depression leading to suicide attempts[53]. These mood alterations might reflect the effects of broad PI3K inhibition in the brain because buparlisib is expected to cross the blood–brain barrier (BBB) and shrinkage of brain metastasis has been observed in patients treated with this drug[55]. Finally, in the randomized phase II BELLE-4 study[54], 416 patients with advanced-stage HER2-negative breast cancer were assigned to receive either buparlisib or placebo in combination with paclitaxel. The result of an interim analysis after ≥125 PFS events had occurred did not demonstrate a statistically significant difference in PFS between the two treatments in the intention-to-treat population (median PFS 8.0 months versus 9.2 months, HR 1.18), nor in the subgroup of patients with PI3K-pathway activation owing to *PIK3CA* mutations or *PTEN* loss (median PFS 9.1 months versus 9.2 months, HR 1.17). Notably, a phase I study[56,57] has revealed the promising activity of a combination comprising buparlisib and the MEK inhibitor trametinib — designed to target the PI3K and MAPK pathways in order to combat adaptive and innate resistance — in patients with low-grade serous ovarian cancer with *RAS* or *RAF* mutations refractory to standard therapies, as reflected by an ORR of 29%. This response rate compares favourably with an ORR of 15% observed in a phase II study involving MEK inhibitor monotherapy with selumetinib in unselected patients with recurrent low-grade serous ovarian cancer[56,57]. However, 65% of patients had grade 3 or 4 AEs, including stomatitis, transaminitis, creatinine kinase elevation, and rash, which might impede the future clinical development of this combination therapy[56,57].

Pictilisib is another pan-PI3K inhibitor that has been evaluated in randomized clinical trials[58,59]. In the two-part, phase II FERGI study[58], 229 postmenopausal women with advanced-stage, AI-resistant, hormone receptor-positive, HER2-negative breast cancer were randomly assigned to receive either pictilisib or placebo in combination with fulvestrant. The first part of this study involved 168 patients with or without *PIK3CA* mutations, among whom the median PFS durations were not significantly different between the pictilisib and placebo arms (6.6 months versus 5.1 months; HR 0.74, 95% CI 0.52–1.06; $P = 0.096$), even after stratification of data by *PIK3CA* status[58]. A similar result was reported for the second part of the study, which involved a separate group of 61 patients with *PIK3CA* mutations (median PFS 5.4 months with pictilisib versus 10 months with placebo; HR 1.07, 95% CI 0.53–2.18; $P = 0.87$)[58]. Notably, the pictilisib dose was reduced owing to toxicities in up to 24% of patients, and an additional 22–24% of patients in the pictilisib arm discontinued treatment owing to AEs[58]. Similarly, in the PEGGY study[59], investigators randomly assigned 183 patients with hormone receptor-positive, HER2-negative metastatic breast cancer to receive pictilisib or placebo in combination with paclitaxel. The primary end point of the study was not met: irrespective of *PIK3CA* mutation status, the median PFS durations of patients who received pictilisib (8.2 months) and those who received placebo (7.8 months) did not differ significantly (HR 0.95, 95% CI 0.62–1.46; $P = 0.83$), which might be at least partially attributable to more frequent dose modifications in the pictilisib arm[59].

The pan-PI3K inhibitor pilaralisib has been evaluated in 69 patients with advanced-stage solid tumours in a phase I dose-escalation study[60]. The most frequent AEs included rash, diarrhoea, nausea, and anorexia. One patient with non-small-cell lung cancer (NSCLC) had a PR (ORR 1.4%), although eight patients (11.6%) were progression-free at 6 months[60]. Similarly, in a subsequent phase II study[61], pilaralisib had only modest levels of clinical activity in 67 patients with previously treated advanced-stage endometrial carcinoma, with 2 patients having an objective response (ORR 6%) and a 6-month PFS rate of 11.9%. Of note, no significant association between the presence of specific molecular alterations and clinical activity was detected[61]. Pilaralisib has also been tested in combination with other agents, including carboplatin and paclitaxel in patients with advanced-stage solid tumours, letrozole in patients with hormone

Table 3 | **Ongoing clinical trials of PI3K–AKT–mTOR inhibitors with biomarker-based selection of patients**

Class	Drug	Biomarker	Disease setting	Study phase	ClinicalTrials.gov registration
mTORC1 inhibitor	Everolimus	Mutations in the genes encoding proteins in the PI3K–AKT–mTOR pathway	Neuroendocrine tumours	II	NCT02315625
	Everolimus	*TSC1* or *TSC2* mutation	Advanced-stage cancers	II	NCT02201212
	Sirolimus	*PIK3CA* mutation and/or amplification	Advanced-stage solid cancers	II	NCT02449564
mTORC1 and mTORC2 inhibitor	Vistusertib	*RICTOR* amplification	Advanced-stage non-small-cell lung cancer	II	NCT03106155
	Vistusertib and selumetinib (MEK inhibitor)	*KRAS* mutation	Advanced-stage cancers	I/II	NCT02583542
	Sapanisertib	*TSC1* or *TSC2* mutation	Advanced-stage bladder cancer	II	NCT03047213
	Sapanisertib	*TSC1* or *TSC2* mutation	Advanced-stage solid cancers, lymphoma, or myeloma (NCI-MATCH)	II	NCT02465060
Pan-PI3K inhibitors	Copanlisib	*PIK3CA* mutation or amplification and/or *PTEN* loss	Advanced-stage squamous head and neck cancer	I/II	NCT02822482
Dual pan-PI3K and mTORC1–mTORC2 inhibitors	LY3023414	Mutations in the genes encoding proteins in the PI3K–AKT–mTOR pathway	Advanced-stage solid tumours, non-Hodgkin lymphoma, or histiocytic disorders (Pediatric MATCH)	II	NCT03213678
	PQR309	*RICTOR* amplification	Advanced-stage cancers	I	NCT02483858
PI3Kα inhibitors	Alpelisib and fulvestrant (anti-oestrogen) or placebo	*PIK3CA* mutation (present or absent)	Advanced-stage HR^+HER2^- breast cancer	III	NCT02437318
	Alpelisib and fulvestrant or letrozole (aromatase inhibitor)	*PIK3CA* mutation	Advanced-stage HR^+HER2^- breast cancer	II	NCT03056755
	Taselisib	*PIK3CA* mutation	Advanced-stage squamous cell lung cancer (Lung-MAP)	II	NCT02154490
Dual PI3Kα and BRAF inhibitor	ASN003	*PIK3CA* and/or *BRAF* mutations	Advanced-stage solid cancers	I	NC02961283
PI3Kβ inhibitors	GSK2636771 and enzalutamide (anti-androgen)	*PTEN* loss	CRPC	I	NCT02215096
	GSK2636771 and pembrolizumab (anti-PD-1 antibody)	*PTEN* loss	Advanced-stage melanoma	I/II	NCT03131908
	GSK2636771	*PTEN* loss, mutation, or deletion	Advanced-stage solid cancers, lymphoma, or myeloma (NCI-MATCH)	II	NCT02465060
	GSK2636771 and paclitaxel (chemotherapy)	*PTEN* loss or mutation, or alterations in *PIK3CB* or *PIK3R1*	Advanced-stage gastric carcinoma	I/II	NCT02615730
	AZD8186 (± the anti-androgen abiraterone for metastatic CRPC or vistusertib for TNBC)	*PTEN* loss or mutation, or *PIK3CB* mutation	Selected advanced-stage cancers	I	NCT01884285
AKT inhibitors	MK-2206	*PIK3CA*, *AKT*, or *PTEN* mutation	Advanced-stage lung and thymus cancers	II	NCT01306045
	Ipatasertib and paclitaxel or placebo	*PIK3CA*, *AKT*, or *PTEN* alteration	Advanced-stage breast cancer	III	NCT03337724
	AZD5363	*AKT* mutation	Advanced-stage solid cancers, lymphoma, or myeloma (NCI-MATCH)	II	NCT02465060
	AZD5363 (plus enzalutamide for prostate cancer or fulvestrant for HR^+ breast cancer)	*AKT* mutation	Advanced-stage solid tumours	I	NCT03310541

Table 3 (cont.) | **Ongoing clinical trials of PI3K–AKT–mTOR inhibitors with biomarker-based selection of patients**

Class	Drug	Biomarker	Disease setting	Study phase	ClinicalTrials.gov registration
AKT inhibitors (cont.)	AZD5363 and paclitaxel (chemotherapy)	*PIK3CA* mutation or amplification	Advanced-stage gastric cancer	II	NCT02451956
	Miransertib plus carboplatin and/or paclitaxel chemotherapy (or with the aromatase inhibitor anastrozole for ovarian or endometrial cancer)	*PIK3CA* or *AKT* mutation	Selected advanced-stage solid cancers	I	NCT02476955
	ARQ 751	*PI3K* mutations, *PTEN* mutations, or *PTEN* loss	Advanced-stage solid tumours	I	NCT02761694
	TAS-117	*PI3K* and *AKT* alterations	Advanced-stage solid tumours	I	NCT03017521
	BAY 1125976	*AKT* mutation	Advanced-stage solid tumours	I	NCT01915576
Dual AKT and S6K1 inhibitors	MSC2363318A (plus the anti-HER2 antibody trastuzumab for $HER2^+$ breast cancer or the anti-oestrogen tamoxifen for HR^+HER2^- breast cancer)	PI3K pathway alterations	Advanced-stage cancers	I	NCT01971515

CRPC, castration-resistant prostate cancer; HR, hormone receptor; Lung-MAP, Lung Cancer Master Protocol study; mTORC, mTOR complex; NCI, US National Cancer Institute; PD-1, programmed cell death protein 1; TNBC, triple-negative breast cancer.

receptor-positive advanced-stage breast cancer, and trastuzumab with or without paclitaxel in patients with HER2-positive metastatic breast cancer[62–66]. However, none of these efforts ultimately supported subsequent clinical development, and pilaralisib is not currently being actively studied.

Unlike the aforementioned pan-PI3K inhibitors, copanlisib is administered intravenously. This agent has been evaluated in a dose-escalation study involving 57 patients with advanced-stage cancers[67]. Hyperglycaemia and nausea were the most frequent AEs[67]. The study revealed encouraging levels of clinical activity: one patient with endometrial cancer harbouring *PIK3CA* and *PTEN* mutations and another patient with NHL had complete responses (CRs), and two patients with breast cancer and six patients with NHL had PRs[67]. In the subsequent phase II CHRONOS-1 trial[68], 142 patients with relapsed and/or refractory indolent B cell NHL or lymphoplasmocytoid or Waldenström macroglobulinaemia were treated with copanlisib, resulting in an ORR of 59% (CR rate 12%; PR rate 47%) and a median PFS duration of 11.2 months. In September 2017, copanlisib received accelerated approval from the FDA for the treatment of refractory follicular lymphoma on the basis of data from this phase II study[68]. Copanlisib is now being compared with placebo in patients with rituximab-refractory indolent B cell NHL or lymphoplasmocytoid or Waldenström macroglobulinaemia in multiple randomized phase III trials and in trials of rational combinations with chemotherapy, hormone therapy, targeted agents, or immunotherapies in patients with various advanced-stage solid tumours and lymphomas, including a biomarker-based phase I/II study in patients with recurrent and/or metastatic head and neck cancer (TABLE 3).

PX-866 is an orally administered irreversible pan-PI3K inhibitor that has been tested in an unselected population of 84 patients with advanced-stage solid tumours in a first-in-human dose-escalation study[69]. The main treatment-related toxicities were predominantly gastrointestinal AEs, such as diarrhoea; no patient had an objective response[69]. Subsequently, PX-866 was combined with docetaxel in a dose-escalation study involving 43 patients with advanced-stage solid tumours[70]. Two patients had PRs, with no association detected between *PIK3CA*-mutant and *KRAS*-wild-type status versus *PIK3CA*-wild-type and *KRAS*-wild-type status and treatment outcomes[70]. In addition, PX-866 was combined with the BRAF inhibitor vemurafenib in a dose-escalation study involving 22 patients with *BRAF*-mutant melanoma and two patients with *BRAF*-mutant gastrointestinal stromal tumours[71]. The ORR was 29% in all patients (29% among 14 patients naive to BRAF–MEK-targeted therapy and 30% among 10 patients previously treated with BRAF–MEK-targeted therapy)[71], which is substantially lower than the rate reported for single-agent vemurafenib in the front-line setting in melanoma[72]. PX-866 has also been evaluated in several other phase I and II studies[73–78]; however, development of this agent was ultimately terminated owing to modest antitumour activity.

CH5132799 is another oral pan-PI3K inhibitor that has been tested in 38 unselected patients with metastatic solid tumours in a phase I study[79]. The most common toxicities were transaminitis, diarrhoea, nausea, and stomatitis[79]. One patient with *PIK3CA*-mutant ovarian cancer had an antitumour response on the basis of changes in serum CA125 levels[79]. Nevertheless, this compound has not been advanced to later stages of drug development. Likewise, gastrointestinal toxicities were common among 24 patients with advanced-stage solid tumours treated with the oral pan-PI3K inhibitor ZSTK474 in a phase I study[80]; no patient had an

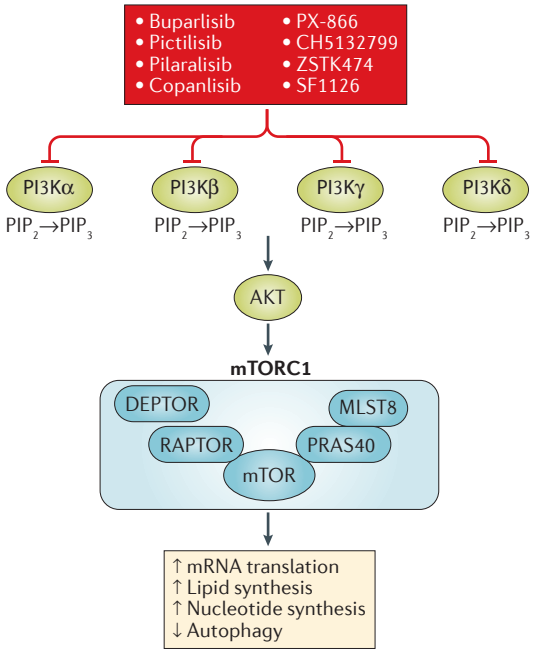

Figure 3 | **Pan-PI3K inhibitors.** Pan-PI3K inhibitors inhibit all four major isoforms of PI3K: PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ. These agents can suppress PI3K signalling across diverse cancers, irrespective of the predominant PI3K isoform, but with important consequences for a range of nonmalignant cell types, including those that promote the supportive cancer microenvironment. For example, PI3Kα has roles in angiogenesis, PI3Kβ and PI3Kγ mediate inflammation, and PI3Kδ regulates the adaptive immune response. DEPTOR, DEP domain-containing mTOR-interacting protein; MLST8, mammalian lethal with SEC13 protein 8; mTORC1, mTOR complex 1; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; PRAS40, proline-rich AKT1 substrate 1; RAPTOR, regulatory-associated protein of mTOR.

objective response, and the compound is not currently being tested in further clinical studies.

Finally, the clinical activity of the intravenous pan-PI3K inhibitor SF1126 has been examined in 44 patients with various advanced-stage solid tumours or B cell malignancies, none of whom had an objective response[81]; gastrointestinal toxicities were the most frequent AEs. SF1126 is now being tested in phase I and II studies in patients with relapsed neuroblastoma (NCT02337309) or advanced-stage hepatocellular carcinoma (NCT03059147).

Overall, the clinical development of most pan-PI3K inhibitors has been discontinued owing to insufficient efficacy, problematic toxicities, and the absence of biomarkers that are reliably associated with clinical activity (TABLE 2). The notable exception is the intravenous inhibitor copanlisib, which is currently approved for clinical use in selected patients with lymphoma. Plausibly, weekly pulsatile administration, as opposed to daily dosing, could lead to more on-target and fewer off-target effects, which might contribute to the generally favourable therapeutic index of copanlisib[82]. The development of buparlisib, which was proved to be efficacious in two phase III studies[52,53], has been complicated by the emergence of psychiatric AEs, including suicide attempts, that might be related to the penetration of the drug through the BBB.

Dual pan-PI3K and mTOR inhibitors

Dual pan-PI3K and mTOR inhibitors are active against either all or most of the four PI3K isoforms and mTORC1 and mTORC2, resulting in inhibition of the three most critical nodes in the PI3K–AKT–mTOR pathway (FIG. 4). These drugs have a toxicity profile similar to that of the pan-PI3K inhibitors, and perhaps accordingly, none of these dual inhibitors have yet been approved for clinical use (TABLE 2).

BGT226 is a dual pan-PI3K and mTOR inhibitor that has been tested in a phase I study involving 57 unselected patients with advanced-stage cancer[83]. Unsurprisingly, gastrointestinal toxicities were the most frequent AEs. The compound elicited no objective responses, and overall pharmacodynamic effects on the PI3K pathway in biopsy samples were inconsistent[83]. Thus, this compound has not advanced beyond phase I trials.

Dactolisib is another such agent that has been investigated both as a single agent or as part of a combination in multiple phase I and II studies[84–86]. Overall, dactolisib as a monotherapy was found to have limited levels of clinical activity and inconsistent pharmacokinetic characteristics[86]; therefore, the clinical development of this compound has been discontinued.

The safety and efficacy of apitolisib, another oral agent of this class, was tested in 120 unselected patients with advanced-stage solid tumours who were enrolled in a phase I study[87]. Grade 3 or 4 AEs included hyperglycaemia, rash, liver dysfunction, diarrhoea, and pneumonitis. Notably, apitolisib inhibited the PI3K pathway by ≥90%, as indicted by measurements of AKT activity in platelet-rich plasma, and 10 patients with mesothelioma or *PIK3CA*-mutant head and neck cancer had PRs[87]. Apitolisib has also been tested both as a single agent and in combinations in multiple clinical studies[88,89]. The most important of these studies was a randomized phase II study with results demonstrating that patients receiving apitolisib had a shorter median PFS duration than those receiving everolimus (3.7 months versus 6.1 months; $P < 0.01$), which might be explained by poor tolerance of apitolisib, resulting in high levels of treatment discontinuation owing to AEs in the apitolisib arm (31% versus 12%)[89]. Currently, no studies involving apitolisib are ongoing, suggesting that further development of this compound will not be pursued.

Gedatolisib is an intravenous dual pan-PI3K and mTOR inhibitor. In a first-in-human study, this agent was tested in 78 patients with various advanced-stage solid tumours[90]. The most frequent grade 3 AEs included stomatitis and transaminitis; no grade 4 or 5 AEs were observed, and severe hyperglycaemia was infrequent, although the overall frequency of this toxicity was 26%[90]. Two patients, one with *PTEN*-deficient NSCLC and another with *PTEN*-deficient granulosa cell tumours of the ovary, had PRs[90]. Additionally, a third patient with endometrial cancer and low levels

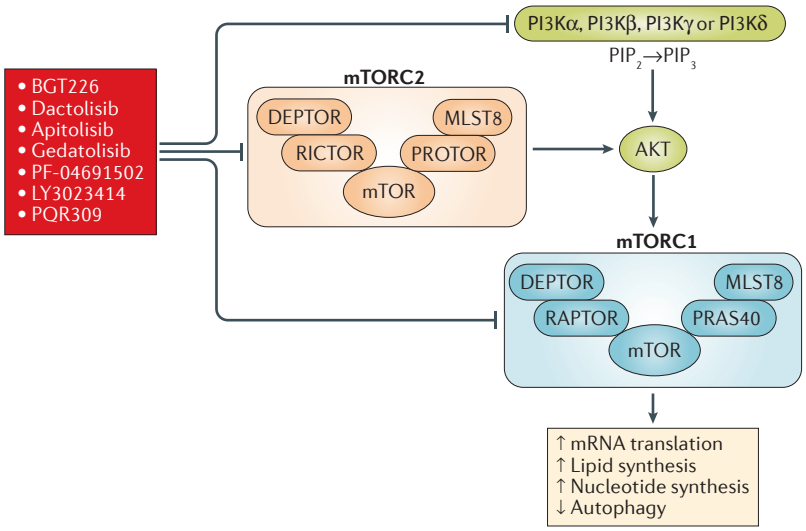

Figure 4 | **Dual pan-PI3K and mTORC1–mTORC2 inhibitors.** Dual PI3K–mTOR kinase inhibitors have activity against all four PI3K isoforms, mTOR complex 1 (mTORC1), and mTORC2 and therefore have the potential to suppress the pro-tumorigenic functions of PI3K–AKT–mTOR signalling across all tumour types. DEPTOR, DEP domain-containing mTOR-interacting protein; MLST8, mammalian lethal with SEC13 protein 8; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; PRAS40, proline-rich AKT1 substrate 1; PROTOR, protein observed with RICTOR (also known as PRR5); RAPTOR, regulatory-associated protein of mTOR; RICTOR, rapamycin-insensitive companion of mTOR.

of PTEN protein expression had an unconfirmed PR[90]. Furthermore, 8 patients had stable disease for at least 6 months[90]. At present, gedatolisib is currently under investigation in combination with chemotherapies and other targeted therapies, such as CDK4 and CDK6 (CDK4/6) inhibitors, predominantly in patients with NSCLC (NCT02920450, NCT03065062) or breast cancer (NCT01920061, NCT02626507, NCT02684032, NCT03243331).

Daily dosing of the oral PI3K–mTOR inhibitor PF-04691502 has been tested in 37 patients with advanced-stage solid tumours[91]. DLTs included grade 3 fatigue, intolerable grade 2 fatigue, and grade 3 rash. No objective responses were noted[91]; therefore, the clinical development of this compound has been discontinued.

Treatment with LY3023414 using once-daily or twice-daily schedules has been investigated in 47 patients with advanced-stage tumours[92]. Grade 3 or 4 AEs were recorded in >25% patients and included nausea, fatigue, mucositis, and thrombocytopenia[92]. One patient with endometrial cancer and *PIK3R1* and *PTEN* mutations had a PR[92]. This compound is currently being tested in phase I and II studies as a monotherapy for patients with endometrial cancer (NCT02549989) and in combination with chemotherapy or hormone therapies in patients with other cancers, including breast cancer (NCT02057133), NSCLC (NCT02079636), and prostate cancer (NCT02407054). LY3023414 is also being investigated in paediatric patients with *TSC* mutations or other PI3K–AKT–mTOR pathway aberrations in the Pediatric MATCH trial (TABLE 3).

Another oral pan-PI3K and mTORC1/2 inhibitor, PQR309, was initially tested in 28 patients with advanced-stage solid tumours using a daily administration schedule[93]. As with similar agents, grade 3 or 4 hyperglycaemia, rash, and fatigue were the most frequent AEs[93]. Preliminary signals of anticancer activity included a PR in one patient with thymic carcinoma and *RICTOR* amplification and tumour shrinkage of 24% in a patient with *PIK3CA*-mutated sinonasal undifferentiated carcinoma[93]. In addition, studies involving preclinical models suggest that the compound has activity in HNSCC with inactivating *NOTCH1* mutations[94]. Owing to its ability to cross the BBB, PQR309 has also been advanced to multiple phase II studies in patients with central nervous system lymphomas; this agent has also been investigated in patients with refractory lymphomas and in combination with eribulin in patients with metastatic breast cancer (TABLE 2). In addition, PQR309 is being assessed in a separate phase I study using alternative intermittent dosing schedules (NCT02483858).

Dual inhibitors of PI3K and mTOR kinases continue to be actively investigated in early phase clinical trials, either as single agents in studies with or without biomarker selection or in combination with other therapies. Data regarding the role of alterations in *PIK3CA* and *PTEN* remain conflicting, and some novel biomarkers, such as alterations in *TSC* and *RICTOR*, are being investigated (TABLE 3).

Isoform-specific PI3K inhibitors

Isoform-specific inhibitors have been developed to target cancers that are addicted to one of the PI3K isoforms. These compounds are expected to have a wider therapeutic index and fewer off-target AEs owing to the restricted expression of the different PI3K isoforms in nonmalignant cells. Whereas PI3Kα and PI3Kβ are expressed ubiquitously, PI3Kγ and PI3Kδ are mostly restricted to leukocytes[2,95].

PI3Kα inhibitors

PI3Kα inhibitors selectively inhibit the class I PI3K catalytic subunit α isoform, which is often activated owing to molecular alterations in *PIK3CA*, the gene encoding this protein (FIG. 5). However, molecular alterations in other downstream components of the PI3K pathway can negate the requirement for PI3K activity (FIG. 1) and lead to the emergence of resistance to these inhibitors[7,30,96]. A number of oral PI3Kα-specific inhibitors have been investigated in clinical trials.

In an initial phase I study of alpelisib[97], 134 patients with advanced-stage solid tumours harbouring *PIK3CA* alterations were treated using once-daily and twice-daily schedules. Grade 3 or 4 AEs occurred in ~42% of patients; twice-daily dosing seemed to be less tolerable[97]. As expected, hyperglycaemia, which is an on-target AE of PI3Kα inhibitors, accounted for more than half of the grade 3 or 4 treatment-related toxicities[97]. Nevertheless, alpelisib had promising clinical activity, with one patient with endometrial cancer having a CR and seven patients with cervical, breast, endometrial, or colorectal cancers having PRs[97]. Given the emergence of increasing evidence of synergy between agents targeting oestrogen receptors and the PI3K–AKT–mTOR pathway[27,98–100], the

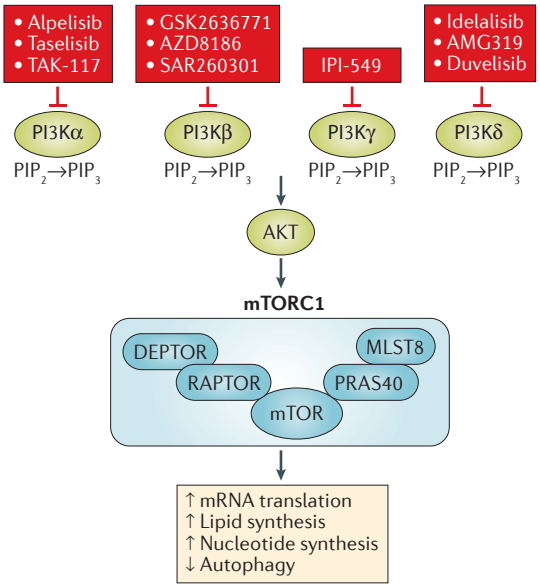

Figure 5 | **Isoform-specific PI3K inhibitors.** Multiple agents with selective activity against or a high degree of specificity for either PI3Kα, PI3Kβ, PI3Kγ, or PI3Kδ have been developed. PI3Kα inhibitors selectively inhibit the class I PI3K catalytic subunit α isoform, which is often activated owing to molecular alterations in *PIK3CA*. However, alterations in other downstream components of the PI3K pathway can negate the requirement for PI3K activity and lead to resistance to PI3Kα inhibitors. PI3Kβ inhibitors selectively inhibit the class I PI3K catalytic subunit β isoform, which is often activated owing to loss of inhibitory function of PTEN. PI3Kγ inhibitors selectively inhibit the class I PI3K catalytic subunit γ isoform, which is expressed in leukocytes and has key roles in chemokine-dependent leukocyte chemotaxis and mast cell activation[114,115]. PI3Kγ is highly expressed in tumour-associated macrophages and can contribute to resistance to immune-checkpoint inhibitors[116]. PI3Kδ is an important mediator of B cell receptor signalling, which has crucial roles in the pathogenesis of haematological malignancies such as chronic lymphocytic leukaemia[114]. DEPTOR, DEP domain-containing mTOR-interacting protein; MLST8, mammalian lethal with SEC13 protein 8; mTORC1, mTOR complex 1; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; PRAS40, proline-rich AKT1 substrate 1; RAPTOR, regulatory-associated protein of mTOR.

study was amended to include a dose-escalation cohort comprising 87 patients with hormone receptor-positive metastatic breast cancer with or without *PIK3CA* alterations who received a combination of alpelisib and the oestrogen receptor downregulator fulvestrant[98]. As observed in the monotherapy cohort, grade 3 or 4 hyperglycaemia was the most frequent toxicity associated with the combination therapy[98]. Notably, the ORR among patients with *PIK3CA* alterations was 26.5%, whereas no patient without *PIK3CA* alterations had a response. In addition, the median PFS duration of patients with *PIK3CA*-altered tumours was longer than that of patients with *PIK3CA*-wild-type tumours (6.1 months versus 4.7 months)[98]. In a separate phase I study[24], alpelisib was tested in combination with the AI letrozole in 26 patients with hormone receptor-positive, HER2-negative metastatic breast cancer. Except for maculopapular rash, which tended to appear early in the course of therapy, grade 3 or 4 AEs associated with alpelisib (predominantly hyperglycaemia and gastrointestinal disturbances) were uncommon and generally cumulative[24]. Among all patients receiving alpelisib and letrozole, the ORR was 19%[24]. Interestingly, four of five (80%) patients with tumours harbouring the $PIK3CA^{H1047R}$ mutation had a PR or stable disease lasting ≥6 months, whereas only two of seven (28%) patients with tumours harbouring *PIK3CA* exon 9 mutations had durable PRs or stable disease lasting >6 months[24]. Two patients with primary tumours harbouring both a *PIK3CA* alteration and a known activating *ESR1* mutation (Y537S or D538G) had stable disease or a PR. Notably, among the patients evaluable for response, all those with cancers harbouring *FGFR1* or *FGFR2* amplifications and/or *KRAS* and *TP53* mutations had progressive disease on treatment.

On the basis of preclinical data indicating that activation of EGFR and PI3K contributes to resistance to BRAF inhibitors in *BRAF*-mutated colorectal cancer[101–103], alpelisib has also been evaluated in combination with the BRAF inhibitor encorafenib and the anti-EGFR monoclonal antibody cetuximab in a phase I study involving 28 patients with this disease[101]. Most patients (79%) had grade 3 or 4 toxicities, most frequently hyperglycaemia (11%); however, the ORR was 18%, which compares favourably with an ORR of 4% observed with another BRAF inhibitor, vemurafenib, in combination with cetuximab in a separate trial involving a similar patient population[104]. Alpelisib is undergoing continued testing in combination with a range of targeted therapies and chemotherapies in multiple phase I and phase II studies involving patients with a diverse range of cancers, including cohorts with or without stratification according to *PIK3CA* mutation status (TABLES 2,3).

The first-in-human study of taselisib involved 34 patients with various advanced-stage cancers[105]. The types of AEs seen were consistent with those observed with other PI3K inhibitors, including hyperglycaemia, diarrhoea, rash, and stomatitis; the most frequent grade 3 or 4 AEs were hyperglycaemia (15%) and rash (12%)[105]. The ORRs were 36% for patients with *PIK3CA*-mutant tumours and 0% for those without known activating *PIK3CA* mutations[105]. Taselisib has since been advanced to testing in a phase III clinical trial involving postmenopausal patients with *PIK3CA*-mutated, hormone receptor-positive metastatic breast cancer in combination with either fulvestrant or placebo (SANDPIPER study[106]). As of February 2017, >300 of the 600 planned patients had been enrolled[106]. In addition, neoadjuvant treatment with taselisib in combination with letrozole has been compared with letrozole plus placebo in a randomized phase II study involving 334 patients with hormone receptor-positive, HER2-negative early stage breast cancer[107]. The addition of taselisib to AI therapy was found to increase the ORR in all patients (50% versus 39%, $P = 0.049$) and even more so in 152 patients with *PIK3CA* mutations (56% versus 38%; $P = 0.033$)[107].

Taselisib is also being investigated as a second-line treatment of advanced-stage squamous cell lung cancer in the biomarker-driven S1400 Lung-MAP study (TABLE 3).

TAK-117 (also known as MLN1117 or INK1117) is another oral PI3Kα inhibitor. In the first-in-human study of this agent[82], 71 patients with advanced-stage solid tumours were treated using either a daily dosing schedule or one of two different intermittent dosing schedules (Monday–Wednesday–Friday or Monday–Tuesday–Wednesday); patients on the daily dosing schedule had a higher rate of grade 3 or 4 off-target toxicities, such as transaminitis, than patients receiving treatment on either of the intermittent schedules (21% versus 15% and 5%, respectively) but had a lower rate of grade 3 or 4 on-target toxicities, such as hyperglycaemia (0% versus 7% and 15%, respectively). Perhaps correspondingly, both intermittent schedules resulted in higher total weekly areas under the curve than the daily schedule did (470,000 ng/h/ml versus 105,000 ng/h/ml)[82]. Among 61 patients evaluated for response, 53 patients had tumours with *PIK3CA* mutations and 4 patients (3 with breast cancer and 1 with gastric cancer) had PRs; notably, all these patients had *PIK3CA*-mutant disease[82]. TAK-117 is now being tested in combination with targeted therapies or chemotherapy in patients with diverse advanced-stage solid cancers.

PI3Kα inhibitors have progressed to the advanced stages of clinical testing after demonstrating encouraging efficacy, mostly in patients with *PIK3CA* mutations, and favourable toxicity profiles, with fewer off-target effects than pan-PI3K inhibitors. The results of ongoing randomized phase III studies have determined the utility of adding these agents to existing standard-of-care hormone treatments in patients with metastatic breast cancer (TABLE 3). Interestingly, a dual PI3Kα and $BRAF^{V600E/K}$ inhibitor, ASN003, entered clinical testing in patients with advanced-stage solid tumours, and data from dose-escalation studies are expected in 2018 (REF. 108).

PI3Kβ inhibitors

PI3Kβ inhibitors selectively inhibit the class I PI3K catalytic subunit β isoform (FIG. 5), which is often activated owing to loss of the inhibitory function of PTEN[96,109,110]. One such agent, GSK2636771, has been tested in 65 patients with advanced-stage solid tumours with PTEN deficiency as determined using immunohistochemistry (H-score ≤30, with a maximum of 30% of cells at a 1+ staining intensity)[111]. Grade 3 or 4 treatment-related AEs were reported in 23% of patients, including hypophosphataemia (7%), rash (5%), fatigue (3%), and hypocalcaemia (3%)[111]. One patient with castration-resistant prostate cancer (CRPC) had a durable PR[111]. A total of 10 other patients, including two with CRPC, five with colorectal cancer, one with endometrial cancer, one with gastric cancer, and one with NSCLC, remained on therapy for at least 24 weeks[111]. Two of seven patients with *PIK3CB* aberrations (29%) derived clinical benefit from GSK2636771, including the patient with CRPC who had a PR and another patient with CRPC who had prolonged stable disease[111]. GSK2636771 is now being tested as a monotherapy in patients with advanced-stage cancers with *PTEN* loss or mutations as part of the NCI-MATCH precision medicine study, as well as in combination with pembrolizumab in patients with PTEN-deficient melanoma, with enzalutamide in patients with PTEN-deficient CRPC, and with paclitaxel in patients with gastric cancers harbouring *PTEN*, *PIK3CB*, or *PIK3R1* aberrations (TABLES 2,3).

AZD8186 is another PI3Kβ-selective inhibitor, which also has some activity against PI3Kδ. This compound is currently being tested using continuous and intermittent dosing schedules in a first-in-human dose-escalation study in patients with advanced-stage prostate cancer, squamous cell lung cancer, triple-negative breast cancer (TNBC), or other solid malignancies with known *PTEN* or *PIK3CB* aberrations (TABLE 3). Preliminary safety and efficacy data for AZD8186 obtained from 87 patients have been presented[112]; DLTs included grade 3 rash and grade ≥2 fever and/or chills, and one patient with colorectal cancer had a PR. The ongoing study has been expanded to test AZD8186 in combination with the mTORC1 and mTORC2 inhibitor vistusertib in patients with TNBC harbouring *PTEN* or *PI3KCB* aberrations or with the cytochrome P450 17A1 (CYP17; also known as CYP17A1) inhibitor abiraterone in patients with metastatic CRPC harbouring *PTEN* or *PI3KCB* aberrations.

Findings from the first-in-human study of a different PI3Kβ-selective inhibitor, SAR260301, have also been presented[113]. Among 21 patients with various advanced-stage solid tumours, the most worrisome grade 3 toxicity was pneumonitis, which also constituted a DLT[113]. No patient had an objective response; however, only three patients with PTEN-deficient tumours were included in this study[113]. Pharmacokinetics data suggest that the rapid clearance of SAR260301 precludes the possibility of sustained pathway inhibition[113], and therefore, the development of this compound has not advanced further towards the clinic.

Overall, PI3Kβ inhibitors seem to be well tolerated and continue to be investigated in early stage clinical trials. Importantly, biomarker-driven patient selection, typically based on *PTEN* status and an absence of activating alterations in the PI3Kα catalytic subunit, is being incorporated into many of these trials (TABLE 3).

PI3Kγ inhibitors

PI3Kγ inhibitors selectively inhibit the class I PI3K catalytic subunit γ isoform (FIG. 5), which is expressed in leukocytes and has key roles in chemokine-dependent leukocyte chemotaxis and mast cell activation[114,115]. Preclinical studies have demonstrated that PI3Kγ is highly expressed in tumour-associated macrophages and can contribute to resistance to immune-checkpoint inhibitors[116]. Notably, blockade of PI3Kγ signalling causes reprogramming of macrophages in the tumour microenvironment from an M2-like, pro-tumour phenotype to an M1-like, antitumour phenotype, resulting in increased production of pro-inflammatory cytokines and greater numbers and activity levels of antitumour T cells, thereby restoring the sensitivity of tumours to immune-checkpoint inhibition[116].

IPI-549 is an orally administered selective inhibitor of PI3Kγ that is being tested as a monotherapy and in combination with immune-checkpoint inhibitor nivolumab in a dose-escalation study in patients with various advanced-stage carcinomas or melanoma[117]. Preliminary data have been presented in abstract form and encompass 15 evaluable patients treated with IPI-549 as a monotherapy (6 of whom remained on study for at least 24 weeks) and 6 evaluable patients who received IPI-549 in combination with nivolumab[117]. In both arms, treatment seemed to be well tolerated, and patient enrolment continues.

PI3Kδ inhibitors

Compounds that selectively inhibit the PI3K catalytic subunit δ isoform have also been developed (FIG. 5; TABLE 2). PI3Kδ is an important mediator of B cell receptor signalling, which has crucial roles in the pathogenesis of certain haematological malignancies such as chronic lymphocytic leukaemia (CLL)[114]. Indeed, the PI3Kδ-selective inhibitor idelalisib is approved, in combination with rituximab, for the treatment of patients with CLL and was, in fact, the first PI3K inhibitor approved for clinical use outside of clinical trials. The FDA approved idelalisib on the basis of the results of a phase III trial involving 220 patients with relapsed CLL[28], which demonstrated that the addition of idelalisib to rituximab increased the ORR (81% versus 13% with rituximab plus placebo; $P < 0.001$), improved PFS at 24 weeks (93% versus 46%; $P < 0.001$), and, importantly, improved 1-year overall survival (92% versus 80%; $P = 0.02$). Nevertheless, grade 3 or 4 AEs were reported in 56% of patients in the idelalisib arm, compared with in 48% of patients in the placebo arm[28]. In the idelalisib arm, four patients had grade 3 or 4 diarrhoea, and two patients had grade 3 or 4 rash[28]. In addition, idelalisib has been shown to confer a risk of serious immune-mediated hepatotoxicity, pneumonitis, infection, and intestinal perforation, which are now reflected on the FDA drug label[118,119]. Idelalisib has also been approved as a monotherapy for patients with relapsed follicular B cell NHL or relapsed small lymphocytic leukaemia (SLL) who have received at least two prior systemic therapies[120]. This approval was based on the results of a multicentre, single-arm trial[29], in which 125 patients with relapsed indolent NHL received idelalisib orally twice daily. The ORR among patients with follicular lymphoma was 54% and was 58% in patients with SLL[29]. Approximately 50% of patients had serious AEs that included pneumonia, pyrexia, sepsis, febrile neutropenia, diarrhoea, and pneumonitis. Other common AEs included abdominal pain, nausea, fatigue, cough, dyspnoea, rash, and treatment-emergent laboratory-detected abnormalities, such as elevations in the activity of liver enzymes, absolute lymphocyte counts, and serum triglyceride levels. More recently, idelalisib has been tested in combination with bendamustine and rituximab in 416 patients with relapsed or refractory CLL, and compared with the addition of placebo to the bendamustine and rituximab regimen, increased the ORR (70% versus 45%; $P < 0.0001$) and prolonged the median PFS (20.8 months versus 11.1 months; $P < 0.0001$) and overall survival durations (not reached versus 31.6 months; $P = 0.031$)[121]. In March 2016, the FDA issued an alert[122] that patient enrolment into six clinical trials of idelalisib in combination with other cancer agents had been halted owing to safety concerns, including an increased risk of death from respiratory infections.

Duvelisib, a potent and selective inhibitor of both PI3Kδ and PI3Kγ, has mainly been tested in clinical trials involving patients with haematological malignancies, such as CLL, B cell NHL, cutaneous T cell lymphoma, and peripheral T cell lymphoma, although only limited data from these studies are in the public domain[123–127] (TABLE 2). Currently, duvelisib is being compared with ofatumumab for the treatment of patients with CLL or SLL in a phase III trial (NCT02004522), the results of which are expected to be reported soon.

AMG319 is another PI3Kδ-selective inhibitor. The drug was first tested clinically in patients with relapsed lymphoid malignancies[128]. Early safety data from 28 patients have been presented; the most frequent grade 3 or 4 treatment-related AEs were colitis and anaemia, each of which occurred in 3 patients[128]. Some preliminary evidence of therapeutic activity in patients with CLL was noted[128]. Outside of haematological malignancies, a randomized phase II study designed to compare neoadjuvant AMG319 with placebo in patients with HNSCC is currently ongoing (NCT02540928).

AKT inhibitors

Multiple drugs can selectively inhibit AKT proteins, preventing activation of mTORC1 and thereby modulating the downstream effects of PI3K–AKT–mTOR signalling (FIG. 6). Targeting of AKT prevents aberrant activation of the PI3K–AKT–mTOR pathway by AKT itself and other sources such as PI3K, PTEN, and mTORC2.

MK-2206 is an allosteric inhibitor with activity against AKT1, AKT2, and, to a lesser extent, AKT3. In the initial dose-finding study of this agent, which involved 33 patients with advanced-stage solid tumours, no patient had an objective response, although one patient with pancreatic cancer that lacked PTEN expression had tumour shrinkage of 23.3% and a reduction in the serum level of the tumour marker CA19.9 of approximately 60%[129]. Subsequently, MK-2206 has been tested either as a monotherapy or in combination with other anticancer agents in ~50 phase I or II studies. For example, MK-2206 has been tested in the adaptive phase II I-SPY 2 trial, a neoadjuvant precision medicine trial designed to evaluate the efficacy of novel potential therapies for patients with stage II or III breast cancer[130–132]. In this study, MK-2206 was found to improve the pathological CR rate of patients with subtypes of breast cancer characterized by three different MammaPrint gene-expression signatures, which were mostly associated with hormone receptor-positive and HER2-negative tumours. MK-2206 has also been tested in combination with the EGFR inhibitor erlotinib or the MEK inhibitor selumetinib in patients

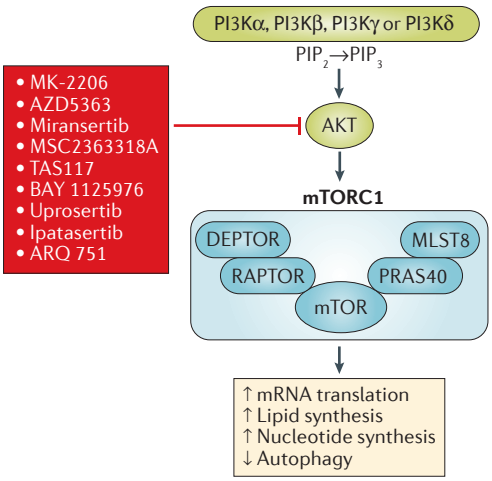

Figure 6 | **AKT inhibitors.** AKT inhibitors downregulate the PI3K–AKT–mTOR signalling by preventing the activation of mTOR complex 1 (mTORC1). Targeting AKT prevents aberrant activation of the PI3K–AKT–mTOR pathway by AKT itself and other factors, such as PI3K, PTEN and mTORC2. DEPTOR, DEP domain-containing mTOR-interacting protein; MLST8, mammalian lethal with SEC13 protein 8; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; PRAS40, proline-rich AKT1 substrate 1; RAPTOR, regulatory-associated protein of mTOR.

with advanced-stage NSCLC previously treated with platinum-based chemotherapy in a phase II study with adaptive randomization using biomarker-based assessments, which included mutation testing and gene-expression analyses[133]. The primary end point was the disease control rate at 8 weeks, which did not differ between the adaptively randomized treatment arms. In general, preclinical and early clinical data suggest that MK-2206 has increased efficacy in patients with tumours harbouring *PIK3CA* and *PTEN* alterations, but the predictive value of these alterations as biomarkers has not been confirmed in subsequent clinical trials[134–136].

Miransertib is another allosteric pan-AKT inhibitor, which has been tested using continuous and intermittent dose schedules in patients with advanced-stage solid tumours, including lymphomas[137]. The most frequent AEs included hyperglycaemia, rash, nausea, and diarrhoea[137]. One patient with endometrial cancer and one patient with lymphoma, both with activating *PIK3CA* mutations, had PRs[137]. Miransertib is now being tested in combination with chemotherapy or hormone therapy in a biomarker-driven phase I trial in patients with advanced-stage solid tumours (TABLE 3).

ARQ 751 is a next-generation allosteric pan-AKT inhibitor with properties that are distinct from those of miransertib[138], and is now being tested in a dose-escalation study involving patients with advanced-stage solid tumours harbouring AKT, PI3K, and/or PTEN aberrations (TABLE 3). Preclinical evidence of the sensitivity of cancer cells with *PIK3CA*, *PIK3R1*, $AKT1^{E17K}$, or *PTEN* mutations to both miransertib and ARQ 751 supports the use of this biomarker-driven approach[138].

TAS-117, another non-ATP-competitive inhibitor of AKT, is being tested in a phase I study in Japan involving patients with advanced-stage solid tumours with genetic aberrations affecting PI3K and AKT (TABLE 3). Finally, BAY 1125976 is a selective allosteric inhibitor of AKT1 and AKT2 that has shown activity in a diverse range of preclinical cancer models, including $PIK3CA^{H1074R}$-mutant breast cancer and AKT^{E17K}-mutant prostate cancer xenografts[139]. This agent has been tested clinically in an initial dose-escalation study in patients with advanced-stage solid tumours, with a planned dose-escalation cohort consisting of patients with metastatic breast cancer (irrespective of mutation status) or with $AKT1^{E17K}$-mutant tumours (TABLE 3), although results have not yet been presented.

Uprosertib is an ATP-competitive AKT inhibitor that has been evaluated in a phase I study involving patients with various advanced-stage solid tumours[140]. Preliminary safety and efficacy data from 66 patients have been published in abstract form[140]; the most frequent grade 3 or 4 drug-related AEs were hyperglycaemia (11%) and rash (3%), and a PR was reported in one patient with anal cancer. Subsequently, multiple early phase clinical trials of uprosertib have been initiated, including studies of this drug in combination with other targeted therapies, such as BRAF or MEK inhibitors; however, none of these studies is active at the time of this Review.

Ipatasertib is another ATP-competitive AKT inhibitor. The first-in-human study of this agent included a dose-escalation cohort and two dose-expansion cohorts[141], comprising a total of 52 patients with advanced-stage solid tumours. The most frequent treatment-related AEs of grade 2 or higher were nausea, diarrhoea, asthenia, and hyperglycaemia[141]. The best clinical response was stable disease in 16 patients, lasting >6 months in 6 of them[141]. Interestingly, none of the 7 patients with tumours harbouring a *KRAS* mutation had stable disease, suggesting — in agreement with preclinical and early clinical data[9,19–21,23] — a mechanism of therapy resistance. More recently, ipatasertib in combination with paclitaxel was compared with placebo plus paclitaxel in a randomized phase II study involving 124 patients with previously untreated advanced-stage TNBC[142]. The results demonstrated a longer median PFS duration in the ipatasertib arm than in the placebo arm (6.2 months versus 4.9 months; $P = 0.037$)[142]. Ipatasertib is currently being investigated further in phase II and III studies involving patients with breast or prostate cancer (TABLES 2,3).

A different pan-AKT inhibitor, AZD5363, was initially examined in a phase I study using one continuous and two intermittent dosing schedules[143]. In a cohort of patients with various advanced-stage solid tumours, the major grade 3 or 4 toxicities were diarrhoea and rash in the continuous-schedule arm and hyperglycaemia in the intermittent-schedule arms[144]. The study included five dose-expansion cohorts — in which patients received AZD5363 at the recommended phase II dose on a 4-days-on and 3-days-off schedule — comprising patients with either *PIK3CA*-mutant

breast cancer, *PIK3CA*-mutant gynaecological cancer, *AKT*-mutant breast cancer, *AKT*-mutant gynaecological cancer, or other *AKT*-mutant solid tumours. In the *PIK3CA*-mutant breast cancer cohort, 1 of 28 patients (4%) had confirmed PRs, and in the *PIK3CA*-mutant gynaecological cancer cohort, 2 of 26 patients (8%) had confirmed PRs[143]. Among the 58 patients with *AKT*-mutant disease, 52 had AKT^{E17K} mutations[10], 7 of whom had PRs to AZD5363, including patients with breast cancer, endometrial cancer, cervical cancer, or lung adenocarcinoma[144].

MSC2363318A is a novel inhibitor of both S6K1 and AKT that was designed to achieve a greater degree of pathway inhibition by targeting these two important nodes in the PI3K–AKT–mTOR signalling cascade. This compound has been evaluated in a phase I study incorporating biomarker selection (TABLE 3), with data from 15 patients currently available; grade 3 lipase elevation was the only DLT, but no patient had an objective response[145]. Patients continue to be enrolled into dose-expansion cohorts of this study, including one comprising patients with hormone receptor-positive breast cancer who will receive the drug in combination with tamoxifen and one comprising patients with HER2-positive breast cancer who will receive MSC2363318A and trastuzumab.

In general, AKT inhibitors are well tolerated and continue to be investigated in early phase clinical trials. Encouraging levels of activity have been reported in patients with cancers harbouring AKT^{E17K} mutations in particular, which supports the use of biomarker-driven strategies in the future clinical development of these agents (TABLE 3).

Future directions

Despite the considerable amount of effort invested in the preclinical and clinical development of compounds targeting the PI3K–AKT–mTOR pathway, only a handful of agents have been approved for clinical use. Several possible reasons exist for this lack of progress.

First, most inhibitors of the oncogenically activated PI3K–AKT–mTOR pathway, including FDA-approved allosteric mTORC1 inhibitors, are associated with low ORRs when used as monotherapies[25,26]. The modest activity of single-agent mTORC1 inhibitors is often explained by disruption of the mTORC1–S6K1-mediated negative feedback loop, which paradoxically results in activation of AKT1 through PI3K and mTORC2 signalling[33,42–44,146] (FIG. 1). Early clinical data suggest that combinations of inhibitors targeting the PI3K–AKT–mTOR pathway are more effective than monotherapy with such agents, plausibly owing to the inhibition of compensatory mechanisms involved in intrinsic and adaptive resistance[9,23]. Moreover, in addition to the few PI3K or mTOR inhibitors approved as monotherapies, rational combinations — such as everolimus and exemestane, which is an approved combination treatment for hormone receptor-positive breast cancer — have demonstrated the greatest potential for translation into routine clinical practice[27]. For example, two randomized trials provided promising results with the pan-PI3K inhibitor buparlisib in combination with fulvestrant; however, a problematic safety profile halted further testing of this combination therapy[52,53].

Second, as emphasized by the example of buparlisib, PI3K–AKT–mTOR pathway inhibitors often have common on-target and off-target toxicities that are dose limiting, leading to the establishment of subtherapeutic maximum-tolerated doses, which often result in inadequate pathway inhibition. The safety profiles of these compounds, as well as the depth and duration of target inhibition, could potentially be improved through the use of alternative intermittent dosing schedules, which often facilitate better durations of drug exposure with more on-target, but fewer off-target, toxicities than continuous dosing strategies[82]. Isoform-specific PI3K inhibitors might also lead to more effective target inhibition, with fewer off-target AEs.

Third, a biomarker that enables the reliable prediction of sensitivity to PI3K–AKT–mTOR inhibitors has not been identified to date. Anecdotal and early clinical data suggest that oncogenic mutations in *PIK3CA* are predictive of a response and/or a prolonged PFS duration in patients treated with selected PI3K–AKT–mTOR pathway inhibitors, but these findings are in conflict with those other studies[8,22,27,52,53]. In general, PI3Kα-specific inhibitors seem to elicit higher ORRs and longer PFS durations in patients with *PIK3CA* mutations than in those without such aberrations, but even patients with *PIK3CA* mutations can have short response durations[97,98]. The duration and depth of patients' responses can potentially be limited by other molecular alterations in related signalling pathways, such as mutations in *KRAS* for PI3K–AKT–mTOR-pathway inhibitors in general, or aberrations in *PTEN* for PI3Kα-specific inhibitors[9,96]. In addition, even among patients with similar *PIK3CA*-mutation profiles, outcomes associated with therapeutic targeting of the PI3K–AKT–mTOR pathway are dismal in patients with certain cancers (such as colorectal cancer), but promising in patients with other cancers (gynaecological or breast malignancies, for example)[22,147,148]. These observations suggest that the level of addiction to PI3K–AKT–mTOR activation varies in different cancers and that the presence or absence of additional simultaneous molecular or other alterations needs to be further defined. Furthermore, studies of tumour heterogeneity in breast, lung, and other cancers suggest that *PIK3CA* mutations are subclonal driver mutations, at least in some tumours[149–151], which might limit the therapeutic effectiveness of PI3K pathway inhibitors, especially if they are used as single agents. The AKT^{E17K} mutation is one promising biomarker, with early clinical data suggesting an association between the presence of this aberration and a response to the ATP-competitive AKT inhibitor AZD5363 (REF. 10). Furthermore, responses to PI3K–AKT–mTOR-pathway inhibitors in patients with *RICTOR* amplifications have been reported anecdotally, and preclinical evidence indicates that such inhibitors have activity in patients with inactivating mutations in *NOTCH1* (REFS 15,93,94).

Conclusions

In summary, aberrant PI3K–AKT–mTOR signalling contributes to development of the vast majority of cancers and a multitude of available drugs inhibit this pathway. Unfortunately, however, limited progress has been made to date in targeting the PI3K–AKT–mTOR pathway for anticancer therapy — with notable exceptions in certain malignancies. An improved understanding of the complexities of this signalling pathway and the interconnecting cascades has led to the development of novel agents with greater target specificity, which might result in an improved therapeutic index and facilitate their clinical translation. In order to bring new PI3K–AKT–mTOR inhibitors to the clinic, we also need to develop new dosing schedules that are more effective and better tolerated, assess new rational combinations that overcome redundancies in the PI3K–AKT–mTOR pathway itself and/or other simultaneously activated signalling pathways, and identify predictive biomarkers of clinical activity. We must also understand the effects of the various pathway inhibitors on the tumour microenvironment, which might provide supporting evidence for the use of specific combinations, in particular, with immunotherapies.

1. Polivka, J. Jr & Janku, F. Molecular targets for cancer therapy in the PI3K/AKT/mTOR pathway. *Pharmacol. Ther.* **142**, 164–175 (2014).
2. Engelman, J. A. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. *Nat. Rev. Cancer* **9**, 550–562 (2009).
3. Liu, P., Cheng, H., Roberts, T. M. & Zhao, J. J. Targeting the phosphoinositide 3-kinase pathway in cancer. *Nat. Rev. Drug Discov.* **8**, 627–644 (2009).
4. Fruman, D. A. & Rommel, C. PI3K and cancer: lessons, challenges and opportunities. *Nat. Rev. Drug Discov.* **13**, 140–156 (2014).
5. Janku, F. Phosphoinositide 3-kinase (PI3K) pathway inhibitors in solid tumors: from laboratory to patients. *Cancer Treat. Rev.* **59**, 93–101 (2017).
6. Yap, T. A., Bjerke, L., Clarke, P. A. & Workman, P. Drugging PI3K in cancer: refining targets and therapeutic strategies. *Curr. Opin. Pharmacol.* **23**, 98–107 (2015).
7. Thorpe, L. M., Yuzugullu, H. & Zhao, J. J. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. *Nat. Rev. Cancer* **15**, 7–24 (2015).
8. Janku, F. et al. *PIK3CA* mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitors. *Mol. Cancer Ther.* **10**, 558–565 (2011).
9. Janku, F. et al. Assessing PIK3CA and PTEN in early-phase trials with PI3K/AKT/mTOR inhibitors. *Cell Rep.* **6**, 377–387 (2014).
10. Hyman, D. M. et al. AKT inhibition in solid tumors with *AKT1* mutations. *J. Clin. Oncol.* **35**, 2251–2259 (2017).
11. Iyer, G. et al. Genome sequencing identifies a basis for everolimus sensitivity. *Science* **338**, 221 (2012).
12. Kwiatkowski, D. J. et al. Mutations in TSC1, TSC2, and MTOR are associated with response to rapalogs in patients with metastatic renal cell carcinoma. *Clin. Cancer Res.* **22**, 2445–2452 (2016).
13. Wagle, N. et al. Response and acquired resistance to everolimus in anaplastic thyroid cancer. *N. Engl. J. Med.* **371**, 1426–1433 (2014).
14. Krueger, D. A. et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. *N. Engl. J. Med.* **363**, 1801–1811 (2010).
15. Cheng, H. et al. *RICTOR* amplification defines a novel subset of patients with lung cancer who may benefit from treatment with mTORC1/2 inhibitors. *Cancer Discov.* **5**, 1262–1270 (2015).
16. Grabiner, B. C. et al. A diverse array of cancer-associated *MTOR* mutations are hyperactivating and can predict rapamycin sensitivity. *Cancer Discov.* **4**, 554–563 (2014).
17. Moulder, S. et al. Inhibition of the phosphoinositide 3-kinase pathway for the treatment of patients with metastatic metaplastic breast cancer. *Ann. Oncol.* **26**, 1346–1352 (2015).
18. Moulder, S. et al. Responses to liposomal doxorubicin, bevacizumab, and temsirolimus in metaplastic carcinoma of the breast: biologic rationale and implications for stem-cell research in breast cancer. *J. Clin. Oncol.* **29**, e572–e575 (2011).
19. Ihle, N. T. et al. Mutations in the phosphatidylinositol-3-kinase pathway predict for antitumor activity of the inhibitor PX-866 whereas oncogenic Ras is a dominant predictor for resistance. *Cancer Res.* **69**, 143–150 (2009).
20. Di Nicolantonio, F. et al. Deregulation of the PI3K and KRAS signaling pathways in human cancer cells determines their response to everolimus. *J. Clin. Invest.* **120**, 2858–2866 (2010).
21. Engelman, J. A. et al. Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. *Nat. Med.* **14**, 1351–1356 (2008).
22. Janku, F. et al. PI3K/AKT/mTOR inhibitors in patients with breast and gynecologic malignancies harboring *PIK3CA* mutations. *J. Clin. Oncol.* **30**, 777–782 (2012).
23. Janku, F. et al. *PIK3CA* mutation H1047R is associated with response to PI3K/AKT/mTOR signaling pathway inhibitors in early-phase clinical trials. *Cancer Res.* **73**, 276–284 (2013).
24. Mayer, I. A. et al. A phase Ib study of alpelisib (BYL719), a PI3Kα-specific inhibitor, with letrozole in ER + /HER2- metastatic breast cancer. *Clin. Cancer Res.* **23**, 26–34 (2017).
25. Hudes, G. et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N. Engl. J. Med.* **356**, 2271–2281 (2007).
26. Motzer, R. J. et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* **372**, 449–456 (2008).
27. Baselga, J. et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N. Engl. J. Med.* **366**, 520–529 (2012).
28. Furman, R. R. et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N. Engl. J. Med.* **370**, 997–1007 (2014).
29. Gopal, A. K. et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N. Engl. J. Med.* **370**, 1008–1018 (2014).
30. Rodon, J., Dienstmann, R., Serra, V. & Tabernero, J. Development of PI3K inhibitors: lessons learned from early clinical trials. *Nat. Rev. Clin. Oncol.* **10**, 143–153 (2013).
31. Saxton, R. A. & Sabatini, D. M. mTOR signaling in growth, metabolism, and disease. *Cell* **168**, 960–976 (2017).
32. Janku, F., McConkey, D. J., Hong, D. S. & Kurzrock, R. Autophagy as a target for anticancer therapy. *Nat. Rev. Clin. Oncol.* **8**, 528–539 (2011).
33. Sarbassov, D. D., Guertin, D. A., Ali, S. M. & Sabatini, D. M. Phosphorylation and regulation of Akt/PKB by the rictor–mTOR complex. *Science* **307**, 1098–1101 (2005).
34. Yao, J. C. et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N. Engl. J. Med.* **364**, 514–523 (2011).
35. Bissler, J. J. et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* **381**, 817–824 (2013).
36. Franz, D. N. et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet* **381**, 125–132 (2013).
37. Motzer, R. J. et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N. Engl. J. Med.* **373**, 1803–1813 (2015).
38. Choueiri, T. K. et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol.* **17**, 917–927 (2016).
39. Yao, J. C. et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* **387**, 968–977 (2016).
40. Demetri, G. D. et al. Results of an international randomized phase III trial of the mammalian target of rapamycin inhibitor ridaforolimus versus placebo to control metastatic sarcomas in patients after benefit from prior chemotherapy. *J. Clin. Oncol.* **31**, 2485–2492 (2013).
41. Gonzalez-Angulo, A. M. et al. Weekly nab-rapamycin in patients with advanced nonhematologic malignancies: final results of a phase I trial. *Clin. Cancer Res.* **19**, 5474–5484 (2013).
42. Sabatini, D. M. mTOR and cancer: insights into a complex relationship. *Nat. Rev. Cancer* **6**, 729–734 (2006).
43. Hsu, P. P. et al. The mTOR-regulated phosphoproteome reveals a mechanism of mTORC1-mediated inhibition of growth factor signaling. *Science* **332**, 1317–1322 (2011).
44. Yu, Y. et al. Phosphoproteomic analysis identifies Grb10 as an mTORC1 substrate that negatively regulates insulin signaling. *Science* **332**, 1322–1326 (2011).
45. Banerji, U. et al. First-in-human phase I trial of the dual mTORC1 and mTORC2 inhibitor AZD2014 in solid tumors [abstract]. *J. Clin. Oncol.* **30** (Suppl.), 3004 (2012).
46. Schmid, P. et al. in *San Antonio Breast Cancer Symposium* GS2-07 (San Antonio, Texas, 2017).
47. Naing, A. et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of AZD8055 in advanced solid tumours and lymphoma. *Br. J. Cancer* **107**, 1093–1099 (2012).
48. Ghobrial, I. M. et al. TAK-228 (formerly MLN0128), an investigational oral dual TORC1/2 inhibitor: a phase I dose escalation study in patients with relapsed or refractory multiple myeloma, non-Hodgkin lymphoma, or Waldenstrom's macroglobulinemia. *Am. J. Hematol.* **91**, 400–405 (2016).
49. Infante, J. R. et al. A phase 1, dose-escalation study of MLN0128, an investigational oral mammalian target of rapamycin complex 1/2 (mTORC1/2) catalytic inhibitor, in patients (pts) with advanced non-hematologic malignancies [abstract]. *Mol. Cancer Ther.* **12** (Suppl.), C252 (2013).
50. Bendell, J. C. et al. A phase I dose-escalation study to assess safety, tolerability, pharmacokinetics, and preliminary efficacy of the dual mTORC1/mTORC2 kinase inhibitor CC-223 in patients with advanced solid tumors or multiple myeloma. *Cancer* **121**, 3481–3490 (2015).
51. Mateo, J. et al. A first in man, dose-finding study of the mTORC1/mTORC2 inhibitor OSI-027 in patients with advanced solid malignancies. *Br. J. Cancer* **114**, 889–896 (2016).
52. Baselga, J. et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* **18**, 904–916 (2017).
53. Di Leo, A. et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* **19**, 87–100 (2018).
54. Martin, M. et al. A randomized adaptive phase II/III study of buparlisib, a pan-class I PI3K inhibitor, combined with paclitaxel for the treatment of HER2$^-$ advanced breast cancer (BELLE-4). *Ann. Oncol.* **28**, 313–320 (2017).

55. Bendell, J. C. et al. Phase I, dose-escalation study of BKM120, an oral pan-Class I PI3K inhibitor, in patients with advanced solid tumors. *J. Clin. Oncol.* **30**, 282–290 (2012).
56. Bedard, P. L. et al. A phase Ib dose-escalation study of the oral pan-PI3K inhibitor buparlisib (BKM120) in combination with the oral MEK1/2 inhibitor trametinib (GSK1120212) in patients with selected advanced solid tumors. *Clin. Cancer Res.* **21**, 730–738 (2015).
57. Farley, J. et al. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. *Lancet Oncol.* **14**, 134–140 (2013).
58. Krop, I. E. et al. Pictilisib for oestrogen receptor-positive, aromatase inhibitor-resistant, advanced or metastatic breast cancer (FERGI): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol.* **17**, 811–821 (2016).
59. Vuylsteke, P. et al. Pictilisib PI3Kinase inhibitor (a phosphatidylinositol 3-kinase [PI3K] inhibitor) plus paclitaxel for the treatment of hormone receptor-positive, HER2-negative, locally recurrent, or metastatic breast cancer: interim analysis of the multicentre, placebo-controlled, phase II randomised PEGGY study. *Ann. Oncol.* **27**, 2059–2066 (2016).
60. Shapiro, G. I. et al. Phase I safety, pharmacokinetic, and pharmacodynamic study of SAR245408 (XL147), an oral pan-class I PI3K inhibitor, in patients with advanced solid tumors. *Clin. Cancer Res.* **20**, 233–245 (2014).
61. Matulonis, U. et al. Phase II study of the PI3K inhibitor pilaralisib (SAR245408; XL147) in patients with advanced or recurrent endometrial carcinoma. *Gynecol. Oncol.* **136**, 246–253 (2015).
62. Tolaney, S. et al. Phase I/II study of pilaralisib (SAR245408) in combination with trastuzumab or trastuzumab plus paclitaxel in trastuzumab-refractory HER2-positive metastatic breast cancer. *Breast Cancer Res. Treat.* **149**, 151–161 (2015).
63. Soria, J. C. et al. Phase I dose-escalation study of pilaralisib (SAR245408, XL147), a pan-class I PI3K inhibitor, in combination with erlotinib in patients with solid tumors. *Oncologist* **20**, 245–246 (2015).
64. Brown, J. R. et al. Phase I trial of the pan-PI3K inhibitor pilaralisib (SAR245408/XL147) in patients with chronic lymphocytic leukemia (CLL) or relapsed/refractory lymphoma. *Clin. Cancer Res.* **21**, 3160–3169 (2015).
65. Abramson, V. G. et al. Phase Ib study of safety and pharmacokinetics of the PI3K inhibitor SAR245408 with the HER3-neutralizing human antibody SAR256212 in patients with solid tumors. *Clin. Cancer Res.* **23**, 3520–3528 (2017).
66. Wheler, J. et al. Phase I dose-escalation study of pilaralisib (SAR245408, XL147) in combination with paclitaxel and carboplatin in patients with solid tumors. *Oncologist* **22**, 377–e37 (2017).
67. Patnaik, A. et al. First-in-human phase I study of copanlisib (BAY 80–6946), an intravenous pan-class I phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors and non-Hodgkin's lymphomas. *Ann. Oncol.* **27**, 1928–1940 (2016).
68. Dreyling, M. et al. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. *J. Clin. Oncol.* **35**, 3898–3905 (2017).
69. Hong, D. S. et al. A multicenter phase I trial of PX-866, an oral irreversible phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors. *Clin. Cancer Res.* **18**, 4173–4182 (2012).
70. Bowles, D. W. et al. A multicenter phase 1 study of PX-866 in combination with docetaxel in patients with advanced solid tumours. *Br. J. Cancer* **109**, 1085–1092 (2013).
71. Yam, C. et al. A multicenter phase I study evaluating dual PI3K and BRAF inhibition with PX-866 and vemurafenib in patients with advanced BRAF V600 mutant solid tumors. *Clin. Cancer Res.* **24**, 22–32 (2017).
72. Flaherty, K. T. et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N. Engl. J. Med.* **363**, 809–819 (2010).
73. Levy, B. et al. A randomized, phase 2 trial of docetaxel with or without PX-866, an irreversible oral phosphatidylinositol 3-kinase inhibitor, in patients with relapsed or metastatic non-small-cell lung cancer. *J. Thorac Oncol.* **9**, 1031–1035 (2014).
74. Bowles, D. W. et al. A multicenter phase 1 study of PX-866 and cetuximab in patients with metastatic colorectal carcinoma or recurrent/metastatic squamous cell carcinoma of the head and neck. *Invest. New Drugs* **32**, 1197–1203 (2014).
75. Jimeno, A. et al. A randomized, phase II trial of cetuximab with or without PX-866, an irreversible oral phosphatidylinositol 3-kinase inhibitor, in patients with relapsed or metastatic head and neck squamous cell cancer. *Ann. Oncol.* **26**, 556–561 (2015).
76. Jimeno, A. et al. A randomized, phase 2 trial of docetaxel with or without PX-866, an irreversible oral phosphatidylinositol 3-kinase inhibitor, in patients with relapsed or metastatic head and neck squamous cell cancer. *Oral Oncol.* **51**, 383–388 (2015).
77. Pitz, M. W. et al. Phase II study of PX-866 in recurrent glioblastoma. *Neuro Oncol.* **17**, 1270–1274 (2015).
78. Bowles, D. W. et al. A randomized, phase II trial of cetuximab with or without PX-866, an irreversible oral phosphatidylinositol 3-kinase inhibitor, in patients with metastatic colorectal carcinoma. *Clin. Colorectal Cancer* **15**, 337–344.e2 (2016).
79. Blagden, S. et al. First-in-human study of CH5132799, an oral class I PI3K inhibitor, studying toxicity, pharmacokinetics, and pharmacodynamics, in patients with metastatic cancer. *Clin. Cancer Res.* **20**, 5908–5917 (2014).
80. Lockhart, A. C. et al. A first-in-human phase I study of ZSTK474, an oral pan-PI3K inhibitor, in patients with advanced solid malignancies [abstract]. *Mol. Cancer Ther.* **12**, B271 (2013).
81. Mahadevan, D. et al. Phase I pharmacokinetic and pharmacodynamic study of the pan-PI3K/mTORC vascular targeted pro-drug SF1126 in patients with advanced solid tumours and B-cell malignancies. *Eur. J. Cancer* **48**, 3319–3327 (2012).
82. Juric, D. et al. A first-in-human, phase I, dose-escalation study of TAK-117, a selective PI3Kα isoform inhibitor, in patients with advanced solid malignancies. *Clin. Cancer Res.* **23**, 5015–5023 (2017).
83. Markman, B. et al. Phase I safety, pharmacokinetic, and pharmacodynamic study of the oral phosphatidylinositol-3-kinase and mTOR inhibitor BGT226 in patients with advanced solid tumors. *Ann. Oncol.* **23**, 2399–2408 (2012).
84. Bendell, J. C. et al. A phase 1 study of the sachet formulation of the oral dual PI3K/mTOR inhibitor BEZ235 given twice daily (BID) in patients with advanced solid tumors. *Invest. New Drugs* **33**, 463–471 (2015).
85. Carlo, M. I. et al. A phase Ib study of BEZ235, a dual inhibitor of phosphatidylinositol 3-kinase (PI3K) and mammalian target of rapamycin (mTOR), in patients with advanced renal cell carcinoma. *Oncologist* **21**, 787–788 (2016).
86. Massard, C. et al. Phase Ib dose-finding study of abiraterone acetate plus buparlisib (BKM120) or dactolisib (BEZ235) in patients with castration-resistant prostate cancer. *Eur. J. Cancer* **76**, 36–44 (2017).
87. Dolly, S. O. et al. Phase I study of apitolisib (GDC-0980), dual phosphatidylinositol-3-kinase and mammalian target of rapamycin kinase inhibitor, in patients with advanced solid tumors. *Clin. Cancer Res.* **22**, 2874–2884 (2016).
88. Makker, V. et al. A multicenter, single-arm, open-label, phase 2 study of apitolisib (GDC-0980) for the treatment of recurrent or persistent endometrial carcinoma (MAGGIE study). *Cancer* **122**, 3519–3528 (2016).
89. Powles, T. et al. Randomized open-label phase II trial of apitolisib (GDC-0980), a novel inhibitor of the PI3K/mammalian target of rapamycin pathway, versus everolimus in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* **34**, 1660–1668 (2016).
90. Shapiro, G. I. et al. First-in-human study of PF-05212384 (PKI-587), a small-molecule, intravenous, dual inhibitor of PI3K and mTOR in patients with advanced cancer. *Clin. Cancer Res.* **21**, 1888–1895 (2015).
91. Britten, C. D. et al. Phase I study of PF-04691502, a small-molecule, oral, dual inhibitor of PI3K and mTOR, in patients with advanced cancer. *Invest. New Drugs* **32**, 510–517 (2014).
92. Moore, K. N. et al. A phase I, first-in-human dose study of the dual PI3K/mTOR inhibitor LY3023414 (LY) in patients (pts) with advanced cancer. *J. Clin. Oncol.* **33**, 11075–11075 (2015).
93. Kristeleit, R. S. et al. A phase 1 first-in-human (FIH) dose-escalation (DE) study of the oral dual PI3K/mTOR inhibitor PQR309 in patients (pts) with advanced solid tumors: final DE results [abstract]. *J. Clin. Oncol.* **33** (Suppl.), 2592 (2015).
94. Sambandam, V. et al. Identification of NOTCH1 inactivating mutation as a therapeutic vulnerability to PI3K/mTOR pathway inhibition in head and neck squamous cell carcinoma (HNSCC) [abstract]. *Cancer Res.* **77** (Suppl.), 2992 (2017).
95. Okkenhaug, K. & Vanhaesebroeck, B. PI3K in lymphocyte development, differentiation and activation. *Nat. Rev. Immunol.* **3**, 317–330 (2003).
96. Juric, D. et al. Convergent loss of PTEN leads to clinical resistance to a PI(3)Kα inhibitor. *Nature* **518**, 240–244 (2015).
97. Juric, D. et al. Phosphatidylinositol 3-kinase α-selective inhibition with alpelisib (BYL719) in *PIK3CA*-altered solid tumors: results from the first-in-human study. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.2017.72.7107 (2018).
98. Janku, F. et al. Phase I study of the PI3K alpha inhibitor BYL719 plus fulvestrant in patients with *PIK3CA*-altered and wild type ER$^+$/HER2$^-$ locally advanced or metastatic breast cancer [abstract]. *Cancer Res.* **75** (Suppl.), PD5-5 (2015).
99. Miller, T. W., Balko, J. M. & Arteaga, C. L. Phosphatidylinositol 3-kinase and antiestrogen resistance in breast cancer. *J. Clin. Oncol.* **29**, 4452–4461 (2011).
100. Bosch, A. et al. PI3K inhibition results in enhanced estrogen receptor function and dependence in hormone receptor-positive breast cancer. *Sci. Transl Med.* **7**, 283ra51 (2015).
101. van Geel, R. et al. A phase Ib dose-escalation study of encorafenib and cetuximab with or without alpelisib in metastatic *BRAF*-mutant colorectal cancer. *Cancer Discov.* **7**, 610–619 (2017).
102. Prahallad, A. et al. Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. *Nature* **483**, 100–103 (2012).
103. Mao, M. et al. Resistance to BRAF inhibition in BRAF-mutant colon cancer can be overcome with PI3K inhibition or demethylating agents. *Clin. Cancer Res.* **19**, 657–667 (2013).
104. Hyman, D. M. et al. Vemurafenib in multiple nonmelanoma cancers with *BRAF* V600 mutations. *N. Engl. J. Med.* **373**, 726–736 (2015).
105. Juric, D. et al. Phase I dose-escalation study of taselisib, an oral PI3K inhibitor, in patients with advanced solid tumors. *Cancer Discov.* **7**, 704–715 (2017).
106. Baselga, J. et al. SANDPIPER: phase III study of the PI3-kinase (PI3K) inhibitor taselisib (GDC-0032) plus fulvestrant in patients (pts) with estrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer (BC) enriched for pts with PIK3CA-mutant tumors [abstract]. *J. Clin. Oncol.* **35** (Suppl.), TPS1119 (2017).
107. Saura, C. et al. Primary results of LORELEI: a phase II randomized, double-blind study of neoadjuvant letrozole (LET) plus taselisib versus LET plus placebo (PLA) in postmenopausal patients (pts) with ER$^+$/HER2-negative early breast cancer (EBC) [abstract]. *Ann. Oncol.* **28** (Suppl.), LBA9 (2017).
108. Thompson, S. K. et al. ASN003, a unique B-RAF inhibitor with additional selective activity against PI3K and mTOR kinases, shows strong antitumor activity in multiple xenograft models [abstract]. *Mol. Cancer Ther.* **14** (Suppl. 2), B100 (2015).
109. Jia, S. et al. Essential roles of PI(3)K-p110β in cell growth, metabolism and tumorigenesis. *Nature* **454**, 776–779 (2008).
110. Ni, J. et al. Functional characterization of an isoform-selective inhibitor of PI3K-p110β as a potential anticancer agent. *Cancer Discov.* **2**, 425–433 (2012).
111. Mateo, J. et al. A first-time-in-human study of GSK2636771, a phosphoinositide 3 kinase beta-selective inhibitor, in patients with advanced solid tumors. *Clin. Cancer Res.* **23**, 5981–5992 (2017).
112. Hansen, A. R. et al. A first in human phase I study of AZD8186, a potent and selective inhibitor of PI3K in patients with advanced solid tumours as monotherapy and in combination with the dual mTORC1/2 inhibitor vistusertib or abiraterone acetate [abstract]. *J. Clin. Oncol.* **35** (Suppl.), 2570 (2017).
113. Bédard, P. L. et al. First-in-human trial of the PI3Kβ-selective inhibitor SAR260301 in patients with advanced solid tumors. *Cancer* **124**, 315–324 (2018).
114. Randis, T. M., Puri, K. D., Zhou, H. & Diacovo, T. G. Role of PI3Kδ and PI3Kγ in inflammatory arthritis and tissue localization of neutrophils. *Eur. J. Immunol.* **38**, 1215–1224 (2008).
115. Barbi, J. et al. PI3Kgamma (PI3Kγ) is essential for efficient induction of CXCR3 on activated T cells. *Blood* **112**, 3048–3051 (2008).

116. De Henau, O. et al. Overcoming resistance to checkpoint blockade therapy by targeting PI3Kγ in myeloid cells. *Nature* **539**, 443–447 (2016).
117. Tolcher, A. et al. IPI-549-01 — a phase 1/1b, first-in-human study of IPI-549, a PI3K-γ inhibitor, as monotherapy and in combination with nivolumab in patients with advanced solid tumors [abstract]. *Cancer Res.* **77** (Suppl.), CT089 (2017).
118. Lampson, B. L. et al. Idelalisib given front-line for treatment of chronic lymphocytic leukemia causes frequent immune-mediated hepatotoxicity. *Blood* **128**, 195–203 (2016).
119. Barr, P. M. et al. Phase 2 study of idelalisib and entospletinib: pneumonitis limits combination therapy in relapsed refractory CLL and NHL. *Blood* **127**, 2411–2415 (2016).
120. Miller, B. W. et al. FDA approval: idelalisib monotherapy for the treatment of patients with follicular lymphoma and small lymphocytic lymphoma. *Clin. Cancer Res.* **21**, 1525–1529 (2015).
121. Zelenetz, A. D. et al. Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* **18**, 297–311 (2017).
122. US Food and Drug Administration. FDA alerts healthcare professionals about clinical trials with Zydelig (idelalisib) in combination with other cancer medicines [online]. https://www.fda.gov/Drugs/DrugSafety/ucm490618.htm (2016).
123. O'Brien, S. et al. Duvelisib (IPI-145), a PI3K-δ,γ inhibitor, is clinically active in patients with relapsed/refractory chronic lymphocytic leukemia. *Blood* **124**, 3334–3334 (2014).
124. Porcu, P. et al. Clinical activity of duvelisib (IPI-145), a phosphoinositide-3-kinase-δ,γ inhibitor, in patients previously treated with ibrutinib. *Blood* **124**, 3335–3335 (2014).
125. Flinn, I. et al. A phase 1 evaluation of duvelisib (IPI-145), a PI3K-δ,γ inhibitor, in patients with relapsed/refractory iNHL. *Blood* **124**, 802–802 (2014).
126. Horwitz, S. M. et al. Duvelisib (IPI-145), a phosphoinositide-3-kinase-δ,γ inhibitor, shows activity in patients with relapsed/refractory T-cell lymphoma. *Blood* **124**, 803–803 (2014).
127. Flinn, I. et al. An open-label, phase Ib study of duvelisib (IPI-145) in combination with bendamustine, rituximab or bendamustine/rituximab in select subjects with lymphoma or chronic lymphocytic leukemia. *Blood* **124**, 4422–4422 (2014).
128. Glenn, M. et al. First-in-human study of AMG 319, a highly selective, small molecule inhibitor of PI3Kδ, in adult patients with relapsed or refractory lymphoid malignancies. *Blood* **122**, 678–678 (2013).
129. Yap, T. A. et al. First-in-man clinical trial of the oral pan-AKT inhibitor MK-2206 in patients with advanced solid tumors. *J. Clin. Oncol.* **29**, 4688–4695 (2011).
130. Rugo, H. S. et al. Adaptive randomization of veliparib-carboplatin treatment in breast cancer. *N. Engl. J. Med.* **375**, 23–34 (2016).
131. Park, J. W. et al. Adaptive randomization of neratinib in early breast cancer. *N. Engl. J. Med.* **375**, 11–22 (2016).
132. Tripathy, D. et al. Adaptively randomized trial of neoadjuvant chemotherapy with or without the Akt inhibitor MK-2206: graduation results from the I-SPY 2 trial [abstract]. *J. Clin. Oncol.* **33**, 524 (2015).
133. Papadimitrakopoulou, V. et al. The BATTLE-2 study: a biomarker-integrated targeted therapy study in previously treated patients with advanced non-small-cell lung cancer. *J. Clin. Oncol.* **34**, 3638–3647 (2016).
134. Sangai, T. et al. Biomarkers of response to Akt inhibitor MK-2206 in breast cancer. *Clin. Cancer Res.* **18**, 5816–5828 (2012).
135. Gonzalez-Angulo, A. M. et al. SU2C phase Ib study of paclitaxel and MK-2206 in advanced solid tumors and metastatic breast cancer. *J. Natl Cancer Inst.* **107**, dju493 (2015).
136. Yap, T. A. et al. Interrogating two schedules of the AKT inhibitor MK-2206 in patients with advanced solid tumors incorporating novel pharmacodynamic and functional imaging biomarkers. *Clin. Cancer Res.* **20**, 5672–5685 (2014).
137. Tolcher, A. et al. Results from a phase 1 study of ARQ 092, a novel pan AKT-inhibitor, in subjects with advanced solid tumors or recurrent malignant lymphoma [abstract]. *Eur. J. Cancer* **51** (Suppl. 3), 338 (2015).
138. Yu, Y. et al. Targeting AKT1-E17K and the PI3K/AKT pathway with an allosteric AKT inhibitor, ARQ 092. *PLoS ONE* **10**, e0140479 (2015).
139. Politz, O. et al. BAY 1125976, a selective allosteric AKT1/2 inhibitor, exhibits high efficacy on AKT signaling-dependent tumor growth in mouse models. *Int. J. Cancer* **140**, 449–459 (2017).
140. Burris, H. A. et al. Safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of the oral AKT inhibitor GSK2141795 (GSK795) in a phase I first-in-human study [abstract]. *J. Clin. Oncol.* **29** (Suppl.), 3003 (2011).
141. Saura, C. et al. A first-in-human phase I study of the ATP-competitive AKT inhibitor ipatasertib demonstrates robust and safe targeting of AKT in patients with solid tumors. *Cancer Discov.* **7**, 102–113 (2017).
142. Kim, S. B. et al. Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol.* **18**, 1360–1372 (2017).
143. Banerji, U. et al. A phase 1 open-label study to identify a dosing regimen of the pan-AKT inhibitor AZD5363 for evaluation in solid tumors and in PIK3CA-mutated breast and gynecologic cancers. *Clin. Cancer Res.* https://doi.org/10.1158/1078-0432.CCR-17-2260 (2017).
144. Banerji, U. et al. A pharmacokinetically (PK) and pharmacodynamically (PD) driven phase I trial of the pan-AKT inhibitor AZD5363 with expansion cohorts in *PIK3CA* mutant breast and gynecological cancers [abstract]. *J. Clin. Oncol.* **33** (Suppl.), 2500 (2015).
145. Tsimberidou, A. M. et al. A first in human, dose escalation trial of MSC2363318A — a dual p70S6K/Akt inhibitor, for patients with advanced malignancies [abstract]. *Ann. Oncol.* **26** (Suppl. 2), P5.01 (2015).
146. Janku, F. et al. *PIK3CA* mutations frequently coexist with *RAS* and *BRAF* mutations in patients with advanced cancers. *PLoS ONE* **6**, e22769 (2011).
147. Ganesan, P. et al. Target-based therapeutic matching in early-phase clinical trials in patients with advanced colorectal cancer and *PIK3CA* mutations. *Mol. Cancer Ther.* **12**, 2857–2863 (2013).
148. Dienstmann, R. et al. Molecular profiling of patients with colorectal cancer and matched targeted therapy in phase 1 clinical trials. *Mol. Cancer Ther.* **11**, 2062–2071 (2012).
149. McGranahan, N. et al. Clonal status of actionable driver events and the timing of mutational processes in cancer evolution. *Sci. Transl Med.* **7**, 283ra54 (2015).
150. Yates, L. R. et al. Subclonal diversification of primary breast cancer revealed by multiregion sequencing. *Nat. Med.* **21**, 751–759 (2015).
151. Jamal-Hanjani, M. et al. Tracking the evolution of non-small-cell lung cancer. *N. Engl. J. Med.* **376**, 2109–2121 (2017).

Acknowledgements
The work of the authors has been supported by the Sheikh Khalifa Al Nahyan Ben Zayed Institute for Personalized Cancer Therapy, by the US National Institutes of Health (NIH) through the National Center for Advancing Translational Sciences (grant UL1 TR000371), and by an MD Anderson Cancer Center Support Grant (P30 CA016672). The authors thank J. Munch of the MD Anderson Department of Scientific Publications for editing the manuscript before submission.

Author contributions
F.J. researched data for the article. All authors contributed to discussions of content and to writing, review, and editing of the manuscript.

Competing interests
F.J. has received research support from Genentech, Novartis, and Piqur and has served on scientific advisory boards for Novartis. T.A.Y. has been a member of the scientific advisory boards of AstraZeneca, Bristol-Myers Squibb, Clovis Oncology, EMD Serono, Ignyta, and Pfizer, has received research funding from AstraZeneca, Clearbridge BioMedics, and Vertex, and has received travel support from AstraZeneca, Bristol-Myers Squibb, EMD Serono, Janssen-Cilag, MSD Oncology, and Vertex. F.M.-B. has received research funding from Aileron, AstraZeneca, Bayer, Calithera, Curis, CytomX, Debiopharm, Effective Pharmaceuticals, Genentech, Jounce, Novartis, Pfizer, PUMA, Taiho, and Zymeworks and has served on advisory boards for ClearLight Diagnostics, Darwin Health, GRAIL, and Pieris.

Reviewer information
Nature Reviews Clinical Oncology thanks D. Sarker and the other anonymous reviewers for their contribution to the peer review of this work.

FURTHER INFORMATION
cBioPortal: http://www.cbioportal.org/
ClinicalTrial.gov: http://clinicaltrials.gov/

ALL LINKS ARE ACTIVE IN THE ONLINE PDF