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**Citation:** Li X, Dai D, Chen B, Tang H, Xie X, Wei W (2018) Efficacy of PI3K/AKT/mTOR pathway inhibitors for the treatment of advanced solid cancers: A literature-based meta-analysis of 46 randomised control trials. PLoS ONE 13(2): e0192464. https://doi.org/10.1371/journal. pone.0192464

Editor: Marco Falasca, Queen Mary University of London, UNITED KINGDOM

Received: October 27, 2017

Accepted: January 23, 2018

Published: February 6, 2018

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**Data Availability Statement:** All relevant data are within the paper and its Supporting Information files.

**Funding:** The authors received no specific funding for this work.

**Competing interests:** The authors have declared that no competing interests exist.

**RESEARCH ARTICLE** 

# Efficacy of PI3K/AKT/mTOR pathway inhibitors for the treatment of advanced solid cancers: A literature-based meta-analysis of 46 randomised control trials

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# Abstract

# Background

The phosphatidylinositol-3- kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway (PI3K/AKT/mTOR pathway) plays a key role in cancer. We performed this metaanalysis to assess the clinical effect of using PI3K/AKT/mTOR pathway inhibitors on advanced solid tumours.

# Methods

All the randomised controlled trials (RCT) that compared the therapy with PI3K/AKT/mTOR pathway inhibitors with other therapies were included. The main end-point was progression-free survival (PFS); other end-points included overall survival (OS) and objective response rate (ORR). A subgroup analysis was performed mainly for PFS.

## Results

In total, 46 eligible RCT were included. The pooled results showed that PI3K/AKT/mTOR pathway inhibitor-based regimens significantly improved the PFS of patients with advanced solid tumours (hazard ratios (HR) = 0.79; 95% confidence intervals (CI): 0.71–0.88) and PI3K pathway mutations (HR = 0.69; 95% CI: 0.56–0.85). All single PI3K/AKT/mTOR pathway inhibitor therapies were compared with other targeted therapies (HR = 0.99; 95% CI: 0.93–1.06) and dual targeted therapies, including PI3K/AKT/mTOR pathway inhibitors and other targeted therapies (HR = 1.04; 95% CI: 0.62–1.74), which showed no significant differences in the PFS. Additional PI3K/AKT/mTOR pathway inhibitors showed no advantage with respect to the OS (HR = 0.98; 95% CI: 0.90–1.07) or ORR (risk ratio (RR) = 1.02; 95% CI: 0.87–1.20).

# Conclusion

Our meta-analysis results suggest that the addition of the PI3K pathway inhibitors to the therapy regiment for advanced solid tumours significantly improves PFS. The way that

patients are selected to receive the PI3K pathway inhibitors might be more meaningful in the future.

## Introduction

The PI3K/AKT/mTOR pathway plays a key role in the promotion of cell survival and proliferation in cancers[1, 2], and elevated PI3K pathway signalling seems to be a hallmark of cancer. Three classes of PI3K enzymes (Class I, II, III PI3K) are expressed in human cells, and the lipid product of class I PI3Ks activates the downstream kinase AKT (AKT1, AKT2, AKT3). The mTOR protein has two cellular complexes (mTORC1 and mTORC2), one of which (mTORC1) is a key node in cell growth that can be activated by PI3K/AKT signals or signals from other pathways[3, 4]. Activating mutations in the PI3K pathway are commonly found in solid cancers; in advanced cancers, this mutation rate can increase by 30% -60% in different tumour types, such as breast cancer, gastric cancer and colorectal cancer[5–8].

In solid cancers, preclinical tests have shown that a hyperactive PI3K pathway treated by PI3K or mTOR inhibitors results in the restoration of sensitivity of cancer cell lines to restore sensitivity to hormone therapy, chemotherapy or other targeted therapies[9–12]. With the discovery of the tumourigenesis function of the PI3K pathway, many PI3K pathway inhibitors have been generated and tested in clinical trials. Many phase I trials of PI3K pathway inhibitors have assessed their anti-tumour activity alone or combined with other therapies, but the dose-limited toxicities have still halted some trials early and have prevented further testing[13–15]. Those phase II and III trials that have tested the anti-tumour effects of PI3K pathway inhibitors are disputed, and some actual clinical results are apparently lower than expected. Multiple pathways activated together with the PI3K pathway, mutations in specific genes and dose-limited toxicities prevent drugs from achieving the best inhibitory effects and are the major factors that may weaken the effects of PI3K inhibitors effects. The results from some well-designed clinical trials that have attempted to solve the aforementioned problems must be summarized.

In this study, we have analyzed the RCTs of PI3K/AKT/mTOR pathway inhibitors to assess their efficacy in all advanced solid cancers and whether they exhibit more efficient anti-tumour properties when combined with other targeted regimens or in cancers with PI3K mutations.

#### Materials and methods

#### Data retrieval strategies

We have conducted this meta-analysis in accordance with the PRISMA statement (S1 Table). Relevant publications from PubMed, Web of Science and Embase were identified. The following medical subject heading terms were searched for: 'Tumours OR Neoplasm OR Cancer OR Solid tumour' AND 'PI3K inhibitor OR AKT inhibitor OR mTOR inhibitor OR PI3K/AKT/ mTOR inhibitor OR PI3K/mTOR inhibitor' AND 'random OR clinical OR control OR randomised control trial OR RCT'. We have also manually searched for the drug names of PI3K pathway inhibitors provided by Fruman[2] and crosschecked the references to complete the results from the searches of the databases for publications up to September 01, 2017. Only those studies that definitively indicated that their results were from a phase II or III randomized controlled trial (RCT) and those that enrolled more than 10 patients in each arm were used. When utilizing results from the same trial were considered, we screened for the most complete and recent data.

# **Inclusion criteria**

The following study inclusion criteria were used: (1) participants with advanced or metastatic solid tumours; (2) a clearly defined therapy with PI3K/AKT/mTOR pathway inhibitors in the experimental arm; (3) inclusion of placebo or other anti-tumour agents but not PI3K/AKT/mTOR pathway inhibitors in the control arm; and (4) the outcomes of progression-free survival (PFS), time to progression (TTP) and overall survival (OS) expressed as hazard ratios (HRs) or objective response rates (ORRs) could be extracted. The exclusion criteria were as follows: (1) studies including non-solid tumours; (2) insufficient data; (2) the number of patients in an arm was < 10; and (3) non-randomised studies.

# Data extraction

Two authors (XL and BC) independently screened and selected the data independently. Any disputed results were reviewed by a third author (DD). Relevant data included the name of the first author, publication year, trial name (if available), tumour types, the trial phase, the chemical properties of the experimental and control arms, the number of subjects in each arm, specific protocols, survival outcomes of PFS (as HRs), TTP and OS and the number of patients who experienced a complete or partial response in each arm. Considering the definition of TTP, we included the TTP results as part of in the PFS. For each trial, an arm was considered the experimental arm if it included a treatment with PI3K/AKT/mTOR pathway inhibitors, while the arm with placebo or other anti-tumour agents was considered the control. A PI3K mutational analysis was performed by PCR or gene sequencing. The five-item Jadad scale, which accounts for randomisation, blinding and withdrawals or dropouts, was used to assess the quality of each study[16]; scores ranged from 0 to 5.

# Statistical analysis

The Q-test and the I<sup>2</sup> statistic were used to assess statistical heterogeneity. I<sup>2</sup> values lower than 25% and P > 0.1 were considered to indicate low heterogeneity according to a fixed-effects model (Mantel-Haenszel method). I<sup>2</sup> values higher than 50% or I<sup>2</sup> < 50% but P < 0.1 were considered to indicate moderate or high heterogeneity, according to a random-effects model. Survival outcomes, including OS and PFS, were expressed as HRs with 95% confidence intervals (CIs) for each study. The RRs with 95% CIs were calculated as the result of the dichotomous variable of the objective response rate for each study. Subgroup analyses were performed for the different tumour types, treatment protocols and gene statuses. Egger's test was used to assess the publication bias by Stata and P>|t| > 0.05 indicates no significant publication bias. All statistical tests were two-sided, and the value of P < 0.05 was considered significant. The statistical tests were mostly performed primarily in Revman 5.3.

# Results

This study found 3579 potentially relevant articles, but 559 studies were excluded because they were duplicate reports. After a carefully review of the remaining studies, the full texts of 46 RCT studies were included in the final analysis (Fig 1). All included studies focused on advanced or metastatic solid tumours. Twelve studies focused on breast cancer[17–28], 13 on renal cancer[29–41], 4 on lung cancer[42–45], 4 on neuroendocrine tumors[46–49], 3 on gastrointestinal cancer[50–52], 3 on head and neck squamous cell cancer[53–55], 2 on sarcomas [56, 57], 1 on liver cancer[58], 1 on pancreatic cancer[59], 1 on endometrial cancer[60], 1 on glioblastoma[61] and 1 on melanoma[62]. The basic characteristics of the studies are outlined in Table 1. A total of 15511 cases were included in the meta-analysis, namely, 8478 cases in the



https://doi.org/10.1371/journal.pone.0192464.g001

experimental groups and 7033 cases in the control groups. Nineteen phase III RCT studies and 27 phase II RCT studies were analysed. A total of 32 studies reported mTOR inhibitors, 9 reported PI3K inhibitors, 4 reported AKT inhibitors and 1 reported PI3K/AKT/mTOR pathway inhibitors. The Egger's test results were P > |t| = 0.230 for PFS and P > |t| = 0.957 for OS showing no significant publication bias in this analysis. The Jadad score of the studies included in the meta-analysis ranged from 4 to 5. Thus, all studies were of good quality (Table 1 and S2 Table).

## **Progression-free survival**

All 46 studies reported PFS data, and 4 of these reported TTP results. Three studies reported more than 1 comparison. Thus, 50 pairs of control arms were included in this analysis. The pooled analysis showed an improvement in the PFS when using the PI3K/AKT/mTOR pathway inhibitor-based therapies were used, but with high heterogeneity (HR = 0.79; 95% CI: 0.71-0.88; I<sup>2</sup> = 87%, random-effects model; Fig 2). A subgroup analysis showed that PI3K/AKT/mTOR pathway inhibitor-based therapy significantly improved the PFS in all solid tumour types except glioblastoma. Significant differences in the PFS between the experimental and control arms were found in breast cancer, neuroendocrine tumours, endometrial cancer and melanoma. An analysis of the results according to the type of PI3K/AKT/mTOR pathway inhibitors showed that mTOR inhibitors, pan-PI3K inhibitors and AKT inhibitors all improved the PFS (data not shown). Six studies reported PFS data on patients with or without

Study	Publish	Tumor type	Trial	Experiment arm	Control arm or	General protocol	Patients numbers	Patients	Primary	Other	Reported the	aded
	year		phase	targeted reagents type	experiment arm combined targeted reagents type		in experimental arm	numbers in control arm	end-point	end- point	PI3K mutant data (yes/no)	core
Andre (BOLERO-3)	2014	Breast cancer	Ш	mTORC1	HER2	Everolimus+ Vinorelbine+ trastuzumab vs placebo +Vinorelbine+ trastuzumab	284	285	PFS	NA	yes	s.
Bachelot (GINECO)	2012	Breast cancer	п	mTORC1	NA	Everolimus+ tamoxifen vs tamoxifen	54	57	CBR	TTP, OS	ou	4
Baselga (BOLERO-2)	2012	Breast cancer	Ш	mTORC1	NA	Everolimus + exemestane vs placebo+ exemestane	485	239	PFS	os	ou	5
Baselga (BELLE-2)	2017	Breast cancer	Ш	Pan-PI3K	NA	Buparlisib+ fulvestrant vs placebo+ fulvestrant	576	571	PFS	NA	yes	5
Baselga*	2017	Breast cancer	п	mTORC1	NA	Ridaforolimus+ dalotuzumab+ exemestane vs exemestane	29	33	PFS	so	ou	4
Hurvitz (BOLERO-1)	2015	Breast cancer	I	mTORC1	HER2	Everolimus+ Trastuzumab+ Paclitaxel vs placebo + Trastuzumab+ Paclitaxel	480	239	PFS	NA	ou	5
Kim (LOTUS)	2017	Breast cancer	п	AKT	NA	Ipatasertib+ paclitaxel vs placebo+ paclitaxel	62	62	PFS	NA	yes	5
Krop (FERGI)	2016	Breast cancer	п	Pan-PI3K	NA	Pictilisib+ fulvestrant vs placebo+ fulvestrant	89	62	PFS	NA	yes	5
Martin (BELLE-4)	2016	Breast cancer	Ш	Pan-PI3K	NA	Buparlisib+ paclitaxel vs placebo+ paclitaxel	207	209	PFS	NA	yes	5
Vuylsteke (PEGGY)	2016	Breast cancer	п	Pan-PI3K	NA	Pictilisib+ paclitaxel vs placebo+ paclitaxel	16	92	PFS	NA	yes	4
Wolff (HORIZON)	2013	Breast cancer	Ш	mTORC1	NA	Temsirolimus+letrozole vs placebo+letrozole	555	555	PFS	os	ou	5
Yardley	2015	Breast cancer	п	mTORC1	VEGF inhibitor	Everolimus +Paclitaxel+ Bevacizumab vs placebo + Paclitaxel+ Bevacizumab	56	57	PFS	so	ou	4
Armstrong (ASPEN)	2016	Renal cell cancer	-	mTORC1	VEGFR inhibitor	everolimus vs sunitinib	57	51	PFS	SO	ou	4
Choueiri (METEOR)	2016	Renal cell cancer	Ш	mTORC1	VEGFR inhibitor	Everolimus vs cabozantinib	328	330	PFS	so	ou	4
Cirkel (ROPETAR)	2016	Renal cell cancer	п	mTORC1	VEGFR inhibitor	Everolimus+ pazopanib vs pazopanib	52	49	PFS	NA	ou	4
Dutchet#a; b	2009	Renal cell cancer(a: clear cell cancer; b: no clear cell cancer)	Ш	mTORC1	NA	Temsirolimus vs interferon	a: 169; b: 37	a: 170; b: 18	so	PFS	оп	4
Flaherty#a; b; c (ECOG2804)	2015	Renal cell cancer	п	mTORC1	VEGF inhibitors	(a) Bevacizumab plus temsirolimus vs bevacizumab alone (b) Bevacizumab plus temsirolimus vs bevacizumab plus sorafenib (c) Sorafenib plus temsirolimus vs bevacizumab plus sorafenib	a: 80; b: 80; c: 84	a: 84; b: 83; c: 83	PFS	NA	ou	4
Hudes#a; b	2007	Renal cell cancer	Ш	mTORC1	NA	<ul> <li>(a) Temsirolimus vs interferon (b) Temsirolimus</li> <li>+ interferon vs interferon</li> </ul>	a: 210; b: 209	a&b: 207	SO	PFS	ou	4
Hutson	2013	Renal cell cancer	Ш	mTORC1	VEGF inhibitor	Temsirolimus vs sorafenib	259	253	PFS	os	ou	4
Motzer (RECORD-1)	2010	Renal cell cancer	Ш	mTORC1	NA	Everolimus vs placebo	277	139	PFS	os	ou	5
Motzer (RECORD-3)	2014	Renal cell cancer	п	mTORC1	VEGF inhibitor	Everolimus vs sunitinib	238	233	PFS	NA	ou	4
Motzer	2015	Renal cell cancer	Ш	mTORC1	PD-1 inhibitor	Everolimus vs Nivolumab	410	411	os	PFS	ou	4
Negrier (TORAVA)	2011	Renal cell cancer	п	mTORC1	VEGF inhibitor	Temsirolimus+ bevacizumab vs interferon alfa + bevacizumab	88	40	PFS	NA	ou	4
Rini (INTORACT)	2013	Renal cell cancer	Ш	mTORC1	VEGF inhibitor	Temsirolimus+ bevacizumab vs IFN+ bevacizumab	400	391	PFS	os	no	4
Tannir	2015	Renal cell cancer	п	mTORC1	VEGFR inhibitor	Temsirolimus vs sunitinib	35	33	PFS	NA	no	4
Besse	2014	Lung cancer	п	mTORC1	EGFR inhibitor	Everolimus+ erlotinib vs erlotinib	66	67	DCR	PFS; OS	no	4
Levy	2014	Lung cancer	п	Pan-PI3K	NA	PX-866+ docetaxel vs docetaxel	48	47	PFS	os	no	4
Papadimitrakopoulou (BATTLE-2)	2016	Lung cancer	п	AKT	EGFR inhibitor	MK-2206+erlotinib vs erlotinib	42	22	DCR	PFS; OS	ou	4
Socinski (TAX 326)	2010	Lung cancer	п	AKT	NA	Enzastaurin+ carboplatin vs carboplatin	72	74	TTP	os	no	4
Zhu (EVOLVE-1)	2014	Liver cancer	Ш	mTORCI	NA	Everolimus vs placebo	362	184	os	TTP	no	5
Bendell	2011	Colorectal Cancer	п	P13K/ Akt/ mTOR signaling inhibitor	NA	Perifosine+ capecitabine vs placebo + capecitabine	20	18	dIT	os	оц	ŝ
Bowles	2016	Colorectal Cancer	п	Pan-PI3K	EGFR inhibitor	PX-866 + cetuximab vs placebo+ cetuximab	42	38	PFS	os	ou	4
Ohtsu (GRANITE-1)	2013	Gastric cancer	H	mTORCI	NA	Everolimus vs placebo	439	217	os	PFS	no	5
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Table 1. Characteristics of the included studies.

Study	Publish year	Tumor type	Trial phase	Experiment arm targeted reagents type	Control arm or experiment arm combined targeted reagents type	General protocol	Patients numbers in experimental arm	Patients numbers in control arm	Primary end-point	Other end- point	Reported the PI3K mutant data (yes/no)	Jaded Score
Jimeno	2015	Head and neck squamous cell cancer	п	Pan-PI3K	EGFR inhibitor	PX-866+cetuximab vs cetuximab	42	41	PFS	so	ou	4
Jimeno	2016	Head and neck squamous cell cancer	п	Pan-PI3K	NA	PX-866 + docetaxel vs docetaxel	42	43	PFS	so	ou	4
Soulieres (BERIL-1)	2017	Head and neck squamous cell cancer	п	Pan-PI3K	NA	Buparlisib + paclitaxel vs placebo + paclitaxel	62	79	PFS	so	ou	w
Rachards	2011	Pancreatic cancer	п	AKT	NA	Enzastaurin+ gemcitabine vs gemcitabine	86	44	os	PFS	no	4
Pavel (RADIANT-2)	2011	Neuroendocrine tumours	П	mTORC1	NA	Everolimus + octreotide LAR vs placebo+ octreotide LAR	216	213	PFS	SO	ou	5
Yao (RADIANT-3)	2011	Neuroendocrine tumours	Ш	mTORC1	NA	Everolimus vs placebo	207	203	PFS	SO	ou	5
Yao (RADIANT-3)	2014	Neuroendocrine tumours	н	mTORC1	NA	Everolimus vs placebo	44	35	PFS	SO	ou	ŝ
Yao (RADIANT-4)	2016	Neuroendocrine tumours	Π	mTORC1	NA	Everolimus vs placebo	205	67	PFS	so	ou	ŝ
Eroglu	2015	Sarcoma	п	mTORC1	RAF/MEK/ERK (MEK1) inhibitor	Temsirolimus + selumetinib vs selumetinib	35	34	PFS	NA	ou	4
Demetri	2013	Sarcoma	III	mTORC1	NA	Redaforolimus vs placebo	347	364	PFS	OS	ou	5
Oza	2015	Endometrial cancer	п	mTORC1	NA	Ridaforolimus vs progestin or chemotherapy	64	66	PFS	OS	ou	4
Wick (EORTC 26082)	2016	Glioblastoma	п	mTORC1	NA	Temsirolimus vs temozolomide	56	55	OS	PFS	no	4
Margolin (S0438)	2012	Melanoma	п	mTORC1	VEGFR inhibitor and/or RAF/MEK/ ERK inhibitor	Temsirolimus+ sorafenib vs tiplfarnib+ sorafenib	63	39	PFS	os	оц	4

Abbreviation: NR: not reported; NA: not available; PFS: progression-free survival; OS: overall survival; IFN: interferon; ORR: objective response rate; TTP: time to progression; CBR: clinical benefit rate; DCR: Disease control rate; EGFR: epidermal growth factor receptor; VEGFR: vascular endothelial growth factor receptor; mTORC1: mammalian target of rapamycin complex 1. Reported a different trial by the previous author in the same year.

# Reported more than one comparation in a trial. Lowercase letter a, b,c means different trial arm in the same study.

https://doi.org/10.1371/journal.pone.0192464.t001

Table 1. (Continued)

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Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Andre 2014	-0.2485	0.093	2.4%	0.78 [0.65, 0.94]	-
Bachelot 2012	-0.6162	0.2069	1.9%	0.54 [0.36, 0.81]	
Baselga 2012 Baselga 2017	-0.2485	0.0776	2.4%	0.78 [0.67, 0.91]	
Baselga* 2017	0.0037	0.3981	1.1%	1.00 [0.46, 2.19]	
Kim 2017	-0.5108	0.2467	2.4%	0.60 [0.37, 0.97]	
Krop 2016	-0.3011	0.18	2.0%	0.74 [0.52, 1.05]	
Vuylsteke 2016	-0.0513	0.1857	2.0%	0.95 [0.62, 1.46]	
Wolff 2013	-0.1054	0.0863	2.5%	0.90 [0.76, 1.07]	
Subtotal (95% CI)	-0.0305	0.2451	24.4%	0.77 [0.65, 0.91]	•
Heterogeneity: $Tau^2 = 0.06$ ;	$Chi^2 = 47.68, df = 1$	1 (P < 0)	00001);	$1^2 = 77\%$	
Test for overall effect. 2 = 5	.07 (P = 0.002)				
Renal cell carcinoma	0 3365	0 2395	1 7%	1 40 [0 88 2 24]	<b></b>
Choueiri 2016	-0.6733	0.1114	2.4%	0.51 [0.41, 0.63]	-
Cirkel 2016 Dutcher#1 2009	-0.2107	0.2461	1.7%	0.81 [0.50, 1.31]	
Dutcher#2 2009	-0.9676	0.2562	1.6%	0.38 [0.23, 0.63]	
Flaherty#a 2015 Flaherty#b 2015	0.01	0.1384	2.2%	1.01 [0.77, 1.32]	<b>—</b>
Flaherty#c 2015	0.3001	0.1634	2.1%	1.35 [0.98, 1.86]	<b>↓</b> •-
Hudes#a 2007 Hudes#b 2007	-0.2446	0.099	2.4%	0.67 [0.55, 0.81]	
Hutson 2013	-0.1393	0.1037	2.4%	0.87 [0.71, 1.07]	<b>•</b>
Motzer 2010 Motzer 2014	0.3365	0.0786	2.2%	1.40 [1.20, 1.63]	
Motzer 2015	0.131	0.0824	2.5%	1.14 [0.97, 1.34]	<u>+</u>
Rini 2013	0.0953	0.0486	2.6%	1.10 [1.00, 1.21]	- <sup>-</sup>
Tannir 2015 Subtotal (95% CI)	0.0392	0.2639	1.6%	1.04 [0.62, 1.74] 0.88 [0.73, 1.07]	
Heterogeneity: Tau <sup>2</sup> = 0.13;	; Chi <sup>2</sup> = 175.27, df =	16 (P < 0	0.00001);	$l^2 = 91\%$	
Test for overall effect: $Z = 1$	.29 (P = 0.20)				
Lung cancer					
Besse 2014	-0.2627	0.2136	1.9%	0.77 [0.51, 1.17]	
Papadimitrakopoulou 2016	-0.5745	0.271	1.6%	0.56 [0.33, 0.96]	_ <b>-</b> -
Socinski 2010 Subtotal (95% CI)	0.0677	0.1679	2.1%	1.07 [0.77, 1.49] 0.92 [0.64, 1.31]	<b>*</b>
Heterogeneity: Tau <sup>2</sup> = 0.08	$Chi^2 = 7.96, df = 3$	(P = 0.05	); $l^2 = 62$	%	1
Test for overall effect: $Z = 0$	1.47 (P = 0.64)				
Gastrointestinal can	er				
Bowles 2016	0.1062	0.3955	1.1%	1.11 [0.69, 1.78]	
Ohtsu 2013 Subtotal (95% CI)	-0.4155	0.0838	2.5%	0.66 [0.56, 0.78]	<u>+</u>
Heterogeneity: $Tau^2 = 0.20$ ;	Chi <sup>2</sup> = 10.48, df = 2	(P = 0.0)	05); l <sup>2</sup> =	81%	
Test for overall effect: $Z = 1$	.60 (P = 0.11)				
Head and neck cance	r				
Jimeno 2015	-0.0101	0.2388	1.7%	0.99 [0.62, 1.58]	
Soulieres 2017	-0.4308	0.1876	2.0%	0.65 [0.45, 0.94]	
Heterogeneity: $Tau^2 = 0.01$ :	$Chi^2 = 2.45$ , df = 2 (	P = 0.29	5.3%	0.81 [0.61, 1.08]	-
Test for overall effect: $Z = 1$	.43 (P = 0.15)				
Pancreatic cancer					
Rachards 2011 Subtotal (95% CI)	-0.0212	0.2331	1.8%	0.98 [0.62, 1.55]	*
Heterogeneity: Not applicab	le		21070	0.00 (0.02) 2.00)	Ť
Test for overall effect: Z = 0	.09 (P = 0.93)				
Neuroendocrine tum	our				
Pavel 2011 Yao 2011	-0.2485	0.1171	2.3%	0.78 [0.62, 0.98]	<sup>-</sup>
Yao 2014	-1.3093	0.3729	1.2%	0.27 [0.13, 0.56]	
Subtotal (95% CI)	-0.734	0.1612	Z.1% 7.9%	0.45 [0.28, 0.72]	→
Heterogeneity: $Tau^2 = 0.19$ ; Tast for overall offect: $7 = 3$	$Chi^2 = 24.95, df = 3$	(P < 0.0	001); I <sup>2</sup> =	= 88%	
Test for overall effect: $z = 3$	.30 (P = 0.0010)				
Sarcomas Demetri 2013	-0.3711	0.0886	2 4%	0 69 (0 58 0 87)	-
Eroglu 2015	0.0862	0.2797	1.5%	1.09 [0.63, 1.89]	
Heterogeneity: $Tau^2 = 0.06$ :	$Chi^2 = 2.43$ , df = 1 (	P = 0.12	4.0%	0.80 [0.53, 1.22] %	-
Test for overall effect: $Z = 1$	.02 (P = 0.31)				
Endometrial cancer					
Oza 2015 Subtotal (95% CI)	-0.6349	0.2736	1.6%	0.53 [0.31, 0.91]	
Heterogeneity: Not applicab	le		1.070	0.55 [0.51, 0.51]	
Test for overall effect: $Z = 2$	.32 (P = 0.02)				
Glioblastoma					
Wick 2016 Subtotal (95% CI)	0.2311	0.1949	2.0% 2.0%	1.26 [0.86, 1.85] 1.26 [0.86, 1.85]	
Heterogeneity: Not applicab	le lo (b. o. T. );				-
Test for overall effect: $Z = 1$	.19 (P = 0.24)				
Melanoma Massalla 2012	0.5200	0.2005	1.00	0.50.00.20.0.003	
Margolin 2012 Subtotal (95% CI)	-0.5209	0.2095	1.9% 1.9%	0.59 [0.39, 0.90] 0.59 [0.39, 0.90]	★
Heterogeneity: Not applicab	le				
rest for overall effect: Z = 2					
Liver cancer Zbu 2014	-0.0736	0.1098	2 494	0.93 (0.75 1.15)	<b>_</b>
Subtotal (95% CI)	-0.0726	3.1098	2.4%	0.93 [0.75, 1.15]	4
Heterogeneity: Not applicable Test for overall effect: 7 = 0	P = 0.51				
			100.0%	0.79 [0.71, 0.00]	
Heterogeneity: $Tau^2 = 0.11$ ;	Chi <sup>2</sup> = 363.33, df =	49 (P < )	0.00001);	$ l^2 = 87\%$	
Test for overall effect: Z = 4 Test for subgroup difference	.30 (P < 0.0001) es: Chi <sup>2</sup> = 20.22, df =	11 (P =	0.04), l <sup>2</sup>	= 45.6%	0.01 1 10 100

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Fig 2. Forest plots of hazard ratios (HRs). Progression-free survival (PFS) comparing PI3K/AKT/mTOR inhibitors with the control arm. A random-effects model was used.

https://doi.org/10.1371/journal.pone.0192464.g002

PI3K pathway mutations, and 1 of them included the pooled results of 2 RCT studies. The use of PI3K/AKT/mTOR pathway inhibitor-based therapies improved the PFS of patients with PI3K pathway mutations, as shown by the significant differences in PFS (HR = 0.69; 95% CI: 0.56–0.85;  $I^2 = 23\%$ , fixed-effects model; Fig 3 (A)). The PFS of patients without PI3K pathway mutations improved slightly, albeit with no significant differences (HR = 0.99; 95% CI: 0.85–1.16;  $I^2 = 0\%$ , fixed-effects model; Fig 3 (B)). Eight studies compared PI3K/AKT/mTOR pathway inhibitors with other targeted therapies, all of which were VEGF/VEGF receptor inhibitors. A subgroup analysis revealed no significant differences in the PFS of these patients (HR = 0.98; 95% CI: 0.72–1.33;  $I^2 = 90\%$ , random-effects model; Fig 3 (C)). Six studies compared

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а				Hazard Ratio			Hazard Ratio		
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI		IV	, Fixed, 95% CI		
Andre 2016	-0.4005	0.2031	26.2%	0.67 [0.45, 1.00]					
Baselga 2017	-0.5447	0.177	34.5%	0.58 [0.41, 0.82]					
Kim 2017	-0.821	0.4023	6.7%	0.44 [0.20, 0.97]			•		
Krop 2016	-0.3147	0.282	13.6%	0.73 [0.42, 1.27]			-+		
Martin 2016	0.157	0.3158	10.8%	1.17 [0.63, 2.17]					
Vuylsteke 2016	0.0583	0.3634	8.2%	1.06 [0.52, 2.16]					
Total (95% CI)			100.0%	0.69 [0.56, 0.85]			•		
Heterogeneity: $Chi^2 =$	6.47. df = 5 (P = 0.	26): $ ^2 =$	23%			-	•	-	
Test for overall effect:	Z = 3.55 (P = 0.000)	04)			0.01	0.1	1	10	100
h				Usered Basis			Userand Datis		
C Study or Subgroup	log[Hazard Patio]	CE.	Woight	Hazard Katio		IN/	Hazard Ratio		
Andre 2016		0 1437	weight	1 10 (0 82 1 46)		IV	, Fixed, 95% CI		
Andre 2016 Racolaa 2017	0.0953	0.1437	29.9%	1.10 [0.83, 1.46]			<b>T</b>		
Kim 2017	-0.2744	0.1304	6.2%	0.76 [0.41 1.41]			<b>I</b>		
Krop 2016	-0.3285	0.275	8.2%	0.72 [0.42 1.23]			<b>_</b>		
Martin 2016	0.1655	0.2245	12.2%	1.18 [0.76, 1.83]			<b>_</b>		
Vuvlsteke 2016	-0.2744	0.2906	7.3%	0.76 [0.43, 1.34]					
		0.2000							
Total (95% CI)			100.0%	0.99 [0.85, 1.16]			+		
Heterogeneity: Chi <sup>2</sup> =	4.07, df = 5 (P = 0.	54); l <sup>2</sup> =	0%		0.01	01		10	100
Test for overall effect:	Z = 0.10 (P = 0.92)	)			0.01	0.1	1	10	100
С				Hazard Ratio			Hazard Ratio		
Study or Subgroup	log[Hazard Ratio]	SE	Weight I	V, Random, 95% C	1	IV.	Random, 95% CI		
Armstrong 2016	0.3365	0.2395	11.0%	1.40 [0.88, 2.24	]		+		
Choueiri 2016	-0.6733	0.1114	13.7%	0.51 [0.41, 0.63	i		+		
Flaherty#b 2015	0.1823	0.1664	12.6%	1.20 [0.87, 1.66	1				
Flaherty#c 2015	0.3001	0.1634	12.7%	1.35 [0.98, 1.86	1		-		
Hutson 2013	-0.1393	0.1037	13.8%	0.87 [0.71, 1.07	]				
Margolin 2012	-0.5209	0.2095	11.7%	0.59 [0.39, 0.90	]				
Motzer 2014	0.3365	0.0786	14.2%	1.40 [1.20, 1.63	]		+		
Tannir 2015	0.0392	0.2639	10.4%	1.04 [0.62, 1.74					
Total (95% CI)			100.0%	0.98 [0.72, 1.33	1		•		
Heterogeneity: Tau <sup>2</sup> =	0.17; Chi <sup>2</sup> = 69.41,	df = 7 (P	< 0.0000	01); $I^2 = 90\%$	0.01			10	100
Test for overall effect:	Z = 0.14 (P = 0.89)				0.01	0.1	1 .	10	100
d				Userand Datis			Userand Datis		
Study or Subgroup	log[Hazard R:	atiol	SF Weir	Hazard Katio	CL		Hazard Katio		
with EGFR	log[nazara na	atioj	JE Weig	Jit 14, 11Xed, 55%			1, 11, 20, 35% CI		
Andre 2014	-0.2	485 0.0	093 14.	2% 0.78 [0.65, 0.9	941		-		
Besse 2014	-0.2	614 0.2	102 2.	8% 0.77 [0.51, 1.1	16]		-+		
Bowles 2016	0.1	044 0.24	426 2.	1% 1.11 [0.69, 1.7	79]		+		
Hurvitz 2015	-0.1	165 0.1	011 12.	0% 0.89 [0.73, 1.0	09]		-		
Jimeno 2015	-0.0	101 0.2	388 2.	2% 0.99 [0.62, 1.5	58]		-		
Papadimitrakopoulou 2 Subtotal (95% CI)	016 -0.5	798 0.2	598 1. 35.	.7% 0.56 [0.33, 0.9 0% 0.83 [0.74, 0.9	95] 93]		•		
Heterogeneity: $Chi^2 = 5$ Test for overall effect:	1.16, df = 5 (P = 0.40) 2 = 3.11 (P = 0.002)	)); I <sup>2</sup> = 3%							
with VECEP									
Cirkel 2016	-0.2	107 0 2	461 2	0% 0.81 (0.50 1.3	311		_ <b>+</b> _		
Flaherty#a 2015	-0.2	0.01 0.1	384 6	4% 1.01 [0.77 1	321		+		
Negrier 2011	0.5	365 0.2	251 2.	4% 1.71 [1.10, 2.6	56)		<b></b>		
Rini 2013	0.0	953 0.0	486 52.	1% 1.10 [1.00, 1.2	21]		•		
Yardley 2015 Subtotal (95% CI)	-0.0	305 0.24	457 2. 65.	0% 0.97 [0.60, 1.5 0% 1.09 [1.00, 1.5	57] 19]		-		
Heterogeneity: $Chi^2 = 6$	df = 4 (P = 0.20)	); $I^2 = 33$	%		-		ľ		
rest for overall effect: a	L = 2.07 (P = 0.04)								
Total (95% CI)			100.	0% 0.99 [0.93, 1.0	06]		•		
Heterogeneity: $Chi^2 = 2$	5.07, df = 10 (P = 0	.005); l <sup>2</sup> =	60%		0.01	0 1		10	100
Test for overall effect: 2	Z = 0.17 (P = 0.86) represe: $Chi^2 = 13.90$	df = 1 (P	= 0.0002	$(2)   l^2 = 92.8\%$	0.01	0.1	_ *	10	100

**Fig 3. Subgroup analyses for PFS.** Forest plots of hazard ratios (HRs) for PFS when PI3K/AKT/mTOR inhibitors were compared with the control arm. (a) PI3K mutant cancer; (b) PI3K non-mutant cancer; (c) single PI3K/AKT/mTOR inhibitor compared with other target therapy (VEGF/VEGF receptor inhibitors); (d) PI3K/AKT/mTOR inhibitors combined with another targeted reagent therapy compared with single targeted therapy without PI3K/AKT/mTOR inhibitors.

https://doi.org/10.1371/journal.pone.0192464.g003

dual-targeted therapies including PI3K/AKT/mTOR pathway inhibitors and EGFR inhibitors with EGFR inhibitors alone. The pooled results showed significant improvement as a result of dual-targeted therapies with an HR = 0.83 (95% CI: 0.74-0.93; I<sup>2</sup> = 3%, fixed-effects model Fig 3 (D)). However, the comparison of dual-targeted therapies including PI3K/AKT/mTOR pathway inhibitors and VEGF/VEGF receptor inhibitors with VEGF/VEGF receptor inhibitors alone showed a poorer PFS for patients treated with dual-targeted therapies (HR = 1.09; 95%

CI: 1.00–1.19;  $I^2 = 33\%$ , fixed-effects model; Fig 3 (D)). The pooled results of dual-targeted therapies including PI3K/AKT/mTOR pathway inhibitors compared with single-targeted therapies showed no significant differences and high heterogeneity, which may be partly due to the drugs used together with the PI3K/AKT/mTOR pathway inhibitors (HR = 0.99; 95% CI: 0.93–1.06;  $I^2 = 60\%$ ; Fig 3 (D)).

#### **Overall survival**

Data were obtained on the OS of 34 compared arms. The pooled analysis of these studies showed that PI3K/AKT/mTOR pathway inhibitor-based therapies slightly improved the OS of patients with solid tumours compared with that of the control arms, but differences were not significant (HR = 0.98; 95% CI: 0.90–1.07;  $I^2 = 55\%$ , random-effects model; Fig 4). A subgroup analysis showed that PI3K/AKT/mTOR pathway inhibitor-based therapies improved the OS of the patients with breast cancer, renal cancer, gastrointestinal cancer, head and neck squamous cell cancer, pancreatic cancer, neuroendocrine tumour and sarcomas but the differences were not statistically. In other types of cancer, the PI3K/AKT/mTOR pathway inhibitor-based therapies apparently failed to improve the OS.

#### **Objective response rate**

An objective response rate was found in 1288/7842 (16.4%) and 1078/6497 (16.6%) patients from the experimental and control arms, respectively. The risk ratio (RR) pooled from combined trials using the Mantel-Haenszel method was 1.02 (95% CI: 0.87-1.20;  $I^2 = 68\%$ , random-effects model; <u>Fig 5</u>), which thus favours the therapeutic regimen without PI3K/AKT/ mTOR pathway inhibitors. The ORR of renal cancer, lung cancer and sarcomas favoured the experimental arm, although they did not all reach statistical significance.

#### **Discontinued rate**

The use of PI3K/AKT/mTOR inhibitors was associated with a higher rate of discontinuation because of toxic and adverse effects (OR = 2.16; 95% CI: 1.59–2.95;  $I^2 = 72\%$ , random-effects model; S1 Fig). A subgroup analysis according to PI3K/AKT/mTOR inhibitors showed that the patients who received a therapy regimen consisting of mTOR inhibitors (OR = 2.35; 95% CI: 1.66–3.31;  $I^2 = 76\%$ , random-effects model; S1 Fig) or AKT inhibitors (OR = 2.61; 95% CI: 1.06–6.45;  $I^2 = 0\%$ , random-effects model; S1 Fig) showed more than a 2-fold ratio of study discontinuation because of adverse events; these differences were statistically significant. The use of pan-PI3K inhibitors also resulted in a higher ratio of adverse events, which led to study discontinuation, but the differences were not statistically significant (OR = 1.47; 95% CI: 0.53–4.13;  $I^2 = 73\%$ , random-effects model; S1 Fig).

#### Discussion

This systematic review and meta-analysis, which included 46 randomized controlled trials with a total of 15511 patients and more than 100 arms, was conducted to fully assess the effect of PI3K pathway inhibitors on solid tumours. Our analysis showed that the addition of PI3K pathway inhibitors significantly improves the PFS of subjects with in advanced solid cancers, although their efficacy differed among tumour types. We found that most trials focused on breast cancer, renal cancer, lung cancer, gastrointestinal cancer, head and neck squamous cell cancer and neuroendocrine tumours. Our analysis results suggest that the PI3K/AKT/mTOR inhibitors added to the therapy regimen significantly improved the PFS especially among patients with breast cancer and neuroendocrine tumours. Patients with mutations in the PI3K

Church and Curb and an	la affilia and Basial	Hazard Ratio	Hazard Ratio
Breast cancer	log[Hazard Ratio] St	weight TV, Random, 95% CI	I IV, Kandom, 95% CI
Bachelot 2012	-0.7985 0.3207	1.5% 0.45 [0.24, 0.84]	
Baselga 2012	-0.1165 0.1011	4.8% 0.89 [0.73, 1.09]	-+
Baselga* 2017	0.2469 0.3457	1.3% 1.28 [0.65, 2.52]	i —
Wolff 2013	-0.1165 0.1603	3.5% 0.89 [0.65, 1.22]	
Yardley 2015 Subtotal (95% CI)	0.2231 0.2539	2.1% 1.25 [0.76, 2.06] 13.1% 0.90 [0.71, 1.15]	
Heterogeneity: $Tau^2 = 0.03$ :	$Chi^2 = 7.40, df = 4 (P = 0.1)$	2); $I^2 = 46\%$	· •
Test for overall effect: $Z = 0$ .	83 (P = 0.41)		
Renal call consinence			
Armstrong 2016	0 1122 0 2161	2 5% 1 12 (0 73 1 71)	
Choueiri 2016	-0.4155 0.1119	4.5% 0.66 [0.53, 0.82]	- <b>-</b>
Dutcher#1 2009	-0.1985 0.1264	4.2% 0.82 [0.64, 1.05]	i <del>-  </del>
Dutcher#2 2009	-0.7133 0.2676	1.9% 0.49 [0.29, 0.83]	
Hudes#b 2007	-0.0408 0.1192	4.4% 0.96 [0.76, 1.21]	
Motzer 2010	-0.1393 0.1487	3.7% 0.87 [0.65, 1.16]	
Motzer 2015	0.3148 0.1214	4.3% 1.37 [1.08, 1.74]	j
Rini 2013	0.0785 0.0938	5.0% 1.08 [0.90, 1.30]	
Heterogeneity: $T_{2}u^{2} = 0.06$ :	$Chi^2 = 37.56 df = 8 (P < 0)$	33.1% $0.93[0.79, 1.14]$	' <b>T</b>
Test for overall effect: $Z = 0$ .	56 (P = 0.58)	00001), 1 = 79%	
Lung cancer			
Besse 2014	0.2469 0.3153	1.5% 1.28 [0.69, 2.37]	
Papadimitrakopoulou 2016	0.2231 0.3054	1.5% 1.51 [0.62, 2.76]	
Socinski 2010	0.3646 0.181	3.1% 1.44 [1.01, 2.05]	i –
Subtotal (95% CI)		7.8% 1.39 [1.08, 1.78]	• ◆
Heterogeneity: $Tau^2 = 0.00$ ;	$Chi^2 = 0.30, df = 3 (P = 0.9)$	6); $I^2 = 0\%$	
resctor overall effect: $Z = Z$ .	36 (F = 0.010)		
Gastrointestinal canc	er		
Bendell 2011	-0.9943 0.3676	1.2% 0.37 [0.18, 0.76]	
Bowles 2016	0.2616 0.2668	1.9% 1.30 [0.77, 2.19]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)	-0.1054 0.093	8.1% 0.81 [0.48, 1.37]	-
Heterogeneity: $Tau^2 = 0.15$ :	$Chi^2 = 7.72$ , $df = 2$ (P = 0.0	2): $I^2 = 74\%$	
Test for overall effect: $Z = 0$ .	78 (P = 0.43)		
limeno 2015	0.0396 0.397	1 7% 1 03 (0 58 1 85)	
limeno 2016	-0.1416 0.2897	1.7% 0.87 [0.49, 1.53]	
Soulieres 2017	-0.3285 0.1964	2.8% 0.72 [0.49, 1.06]	
Subtotal (95% CI)		6.2% 0.82 [0.62, 1.08]	1 🔶
Heterogeneity: Tau <sup>2</sup> = 0.00;	$Chi^2 = 1.06, df = 2 (P = 0.5)$	9); $I^2 = 0\%$	
Test for overall effect: $z = 1$ .	+1 (P = 0.16)		
Pancreatic cancer			
Rachards 2011	-0.0161 0.1938	2.9% 0.98 [0.67, 1.44]	
Subtotal (95% CI)		2.9% 0.98 [0.67, 1.44]	▲
Heterogeneity: Not applicable	e = 0.03		
Test for overall effect. $z = 0$ .	08 (F = 0.93)		
Neuroendocrine tumo	or		
Pavel 2011	0.1989 0.1496	3.7% 1.22 [0.91, 1.64]	! <b>+</b> −
Yao 2011	0.0488 0.1996		
Yao 2014	-0.4463 0.2526	2.1% 0.64 [0.39, 1.05]	
Subtotal (95% CI)		9.2% 0.99 [0.74, 1.32]	i 🔶
Heterogeneity: Tau <sup>2</sup> = 0.03;	$Chi^2 = 4.88, df = 3 (P = 0.1)$	8); I <sup>2</sup> = 39%	
Test for overall effect: $Z = 0$ .	.09 (P = 0.93)		
Sarcomas			
Demetri 2013	-0.0726 0.0948	4.9% 0.93 [0.77, 1.12]	· · ·
Subtotal (95% CI)		4.9% 0.93 [0.77, 1.12]	•
Heterogeneity: Not applicable	P = 0.44		
Test for overall effect. $z = 0$ .	// (F = 0.44)		
Endometrial cancer			
Oza 2015 Subtotal (95% CI)	0.0583 0.2069	2.7% 1.06 [0.71, 1.59]	
Heterogeneity: Not applicable	0	2.7% 1.00 [0.71, 1.55]	
Test for overall effect: $Z = 0$ .	28 (P = 0.78)		
Glioblastoma			
Subtotal (95% CI)	0.1484 0.2091	2.6% 1.16 [0.77, 1.75]	•
Heterogeneity: Not applicable	e		
Test for overall effect: $Z = 0$ .	71 (P = 0.48)		
Melanoma			
Margolin 2012	0,1906 0.2137	2.6% 1.21 (0.80. 1.84)	ı –
Subtotal (95% CI)		2.6% 1.21 [0.80, 1.84]	i 🔶
Heterogeneity: Not applicable	e		
Test for overall effect: $Z = 0$ .	89 (P = 0.37)		
Liver cancer			
Zhu 2014	0.0488 0.1018	4.8% 1.05 [0.86, 1.28]	ı +
Subtotal (95% CI)		4.8% 1.05 [0.86, 1.28]	1 ♦
Heterogeneity: Not applicable	e 48 (B - 0.63)		
rest for overall effect: $Z = 0$ .	+0 (r' = 0.03)		
Total (95% CI)		100.0% 0.98 [0.90, 1.07]	1 <b>4</b>
Heterogeneity: Tau <sup>2</sup> = 0.03;	$Chi^2 = 73.33, df = 33 (P < 0)$	$(0.0001); I^2 = 55\%$	0.01 0.1 1 10 100
Test for subgroup difference	s; $Chi^2 = 12.46$ , $df = 11$ (P -	$(0.33),  ^2 = 11.7\%$	

Fig 4. Forest plots of hazard ratios (HRs). Overall survival (OS) when PI3K/AKT/mTOR inhibitors were compared with the control arm. The random-effects model was used.

https://doi.org/10.1371/journal.pone.0192464.g004

pathway may benefit more from treatment with PI3K pathway inhibitors than patients without mutations based on the PFS. The pooled results showed no improvement in OS inhibitors or in ORR as a result of the treatment of advanced solid tumours with PI3K pathway inhibitors.

In this study, we focused on PI3K pathway inhibitors, particularly mTORC1 inhibitors, Pan-PI3K inhibitors and a few AKT and multiple-target inhibitors (Table 1). The mTOR pathway functions primarily through the PI3K/AKT pathway to activate the tumour cells; members of the PI3K pathway family are frequently altered in human cancers, which leads to cell survival and proliferation, metastasis and activation of some secretion functions[2, 63]. The

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	Experime	ental	Contr	01		Risk Ratio	Risk Ratio
Study of Subgroup	Events	Total	Events	Total	weight	M-H, Random, 95% CI	M-H, Kandom, 95% CI
Andro 2014	116	284	106	295	4.0%	1 10 (0 80 1 35)	L
Rachelot 2013	110	204	100	203	1.4%	1.06 [0.33, 1.33]	
Baselga 2012	46	485	ĩ	239	0.6%	22.67 [3.15, 163.37]	
Baselga 2017	68	576	44	571	4.2%	1.53 [1.07, 2.20]	
Baselga* 2017	2	29	1	33	0.4%	2.28 [0.22, 23.82]	
Hurvitz 2015	322	480	165	239	5.2%	0.97 [0.87, 1.08]	+
Kim 2017	25	62	20	62	3.7%	1.25 [0.78, 2.00]	+
Krop 2016	7	89	5	79	1.5%	1.24 [0.41, 3.76]	
Martin 2016	38	168	46	170	4.1%	0.84 [0.58, 1.21]	
Vuylsteke 2016	20	91	18	92	3.2%	1.12 [0.64, 1.98]	
Wolff 2013	151	555	149	555	4.9%	1.01 [0.84, 1.23]	Ť
Yardley 2015 Subtotal (95% CI)	35	2929	32	2439	4.5%	1.11 [0.82, 1.51]	T
Total augusts	0.7.5	2323	503	2435	30.070	1.10 [0.55, 1.20]	ľ
Hotorogeneity Tau? - 0.02	Chil - 21	04 45-	- 11 (8 -	0.031	12 - 4 994		
Test for overall effect: $Z = 1$	26(P = 0)	21)		0.03),			
	2010 - 011						
Renal cell carcinoma							
Armstrong 2016	5	57	9	51	1.7%	0.50 [0.18, 1.39]	
Choueiri 2016	11	328	57	330	2.9%	0.19 [0.10, 0.36]	
Dutcher#1 2009	16	169	13	170	2.7%	1.24 [0.61, 2.49]	<b>-</b>
Dutcher#2 2009	2	37	3	36	0.7%	0.65 [0.12, 3.66]	
Flaherty#a 2015	25	79	11	83	2.9%	2.39 [1.26, 4.52]	
Flaherty#b 2015	25	79	25	82	3.7%	1.04 [0.66, 1.64]	
Flanerty#c 2015	17	300	25	307	3.4%	0.66 [0.39, 1.13]	
Hudes#a 2007	10	209	10	207	2.5%	1.78 [0.84, 3.77]	
Hutton 2012	20	250	20	257	2.3%	0.08 [0.54, 1.77]	
Motzer 2010	20	274	20	137	0.3%	5.52 [0.31, 99,11]	
Motzer 2014	19	238	62	233	3.6%	0.30 [0.19, 0.49]	I
Motzer 2015	11	215	46	183	2.9%	0.20 [0.11, 0.38]	
Negrier 2011	24	88	17	40	3.5%	0.64 [0.39, 1.05]	
Rini 2013	108	400	107	391	4.8%	0.99 [0.79, 1.24]	+
Tannir 2015	1	35	3	33	0.5%	0.31 [0.03, 2.87]	
Subtotal (95% CI)		2761		2518	41.7%	0.75 [0.51, 1.09]	-
Total events	324		418				
Heterogeneity: Tau* = 0.41;	$Chi^2 = 85.$	20, df =	= 15 (P <	0.000	(01); F =	82%	
Test for overall effect: $Z = 1$ .	53 (P = 0.1)	13)					
Lung cancer							
Besse 2014	8	66	7	67	1.9%	1.16 (0.45, 3.02)	
100/2014	3	48	ó	47	0.3%	6 86 [0 36 129 23]	
Papadimitrakopoulou 2016	õ	42	ŏ	22	0.370	Not estimable	
Socinski 2010	ğ	66	16	72	2.5%	0.61 [0.29, 1.29]	
Subtotal (95% CI)		222		208	4.6%	0.95 [0.42, 2.16]	-
Total events	20		23				
Heterogeneity: Tau <sup>2</sup> = 0.20;	$Chi^2 = 3.1$	6, df =	2 (P = 0.	21); I <sup>2</sup>	= 37%		
Test for overall effect: Z = 0.	13 (P = 0.9)	90)					
Gastrointestinal cance	er						
Bendell 2011	4	20	1	18	0.5%	3.60 [0.44, 29.30]	
Bowles 2016	1	42	3	38	0.5%	0.30 [0.03, 2.78]	
Ontsu 2013 Subtotal (95% CI)	20	439	5	217	1.8%	1.98 [0.75, 5.20]	
Total events	25	501		2.1.5	21070	1.55 [0.45] 4.66]	
Heterogeneity: $Tau^2 = 0.35$	$Chi^2 = 2.9$	2 df -	2 (P = 0	23)-12	- 31%		
Test for overall effect: $Z = 0$	74 (P = 0)	46)	2 (F = 0.	23), 1	- 31/0		
Test for overall effect. 2 = 0.	/4 (/ = 0.						
Head and neck cancer							
limeno 2015	4	42	3	41	1.0%	1.30 [0.31, 5.46]	
Jimeno 2016	6	42	2	43	0.9%	3.07 [0.66, 14.37]	
Soulieres 2017	31	79	11	79	3.0%	2.82 [1.53, 5.20]	
Subtotal (95% CI)		163		163	4.9%	2.56 [1.51, 4.35]	
Total events	41		16				
Heterogeneity: Tau <sup>2</sup> = 0.00;	$Chi^2 = 1.0$	0, df =	2 (P = 0.	.61); I <sup>2</sup>	= 0%		
Test for overall effect: Z = 3.	48 (P = 0.0)	0005)					
-							
Pancreatic cancer	_		_				
Rachards 2011	7	86	2	44	0.9%	1.79 [0.39, 8.26]	
Subtotal (93% CI)	-	80			0.9%	1.79 [0.39, 8.20]	
Total events			2				
Heterogeneity: Not applicable	: 75 (0 - 0						
Test for overall effect: $z = 0$ .	75(P = 0.4)	40)					
Neuroendocrine tumo	ur						
Pavel 2011	5	216	4	213	1.2%	1.23 [0.34, 4.53]	
Yao 2011	10	207	4	203	1.5%	2.45 [0.78, 7.69]	
Yao 2014	2	44	1	35	0.4%	1.59 [0.15, 16.83]	
Yao 2016	4	205	1	97	0.5%	1.89 [0.21, 16.71]	
Subtotal (95% CI)		672		548	3.6%	1.80 [0.85, 3.84]	-
Total events	21		10	-			
Heterogeneity: $Tau^2 = 0.00$ ;	$Chi^2 = 0.6$	2, df =	3 (P = 0.	.89); I²	= 0%		
lest for overall effect: $Z = 1$ .	52 (P = 0.1)	13)					
Sarcomas							
Erechu 201E	0	25	2	24	0.3%	0.10 (0.01.3.01)	
Subtotal (95% CI)	0	35	~	34	0.3%	0.19 [0.01, 3.91]	
Total events	0		2				
Heterogeneity: Not applicable			-				
Test for overall effect: $Z = 1$ .	$O_7 (P = 0.3)$	28)					
Endometrial cancer							
Oza 2015	4	48	2	47	0.8%	1.96 [0.38, 10.19]	
Subtotal (95% CI)		48		47	0.8%	1.96 [0.38, 10.19]	
Total events	4		2				
Heterogeneity: Not applicable		4.23					
rest for overall effect: $Z = 0$ .	80 (P = 0.4)	4Z)					
Liver cancer							
Zbu 2014	9	362	3	184	1.2%	1 36 (0 36 5 05)	
Subtotal (95% CI)		362	3	184	1.2%	1.36 [0.36, 5.05]	
Total events	8		3				
Heterogeneity: Not applicable							
Test for overall effect: $Z = 0$ .	45 (P = 0.0)	65)					
Melanoma							
Margolin 2012	3	63	1	39	0.5%	1.86 [0.20, 17.23]	
Subtotal (95% CI)	-	63		39	0.5%	1.86 [0.20, 17.23]	
Total events	3		1				
Heterogeneity: Not applicable		500					
test for overall effect: $Z = 0$ .	54 (P = 0.9)	59)					
Total (95% CI)		7842		6497	100.0%	1.02 [0.87, 1.20]	▲
Total events	1288	42	1078	3-97		1.02 [0.67, 1.20]	Ť
Heterogeneity: $Tau^2 = 0.13$	$Chi^2 = 147$	2.12. df	= 45 (P	< 0.00	001): I <sup>2</sup> =	68%	<u>k</u>
Test for overall effect: $Z = 0$ .	22 (P = 0.1	82)	10.00	0.00			0.01 0.1 1 10 100
Test for subgroup differences	$: Chi^2 = 14$	8.32. di	f = 10 (P)	- 0.05	b), $l^2 = 45$	.4%	

Fig 5. Forest plots of the risk ratio (RR) for the objective response rate (ORR) comparing PI3K/AKT/mTOR inhibitors with the control arm. A random-effects model was used.

https://doi.org/10.1371/journal.pone.0192464.g005

inhibition of one or more markers in this pathway can induce anti-tumour effects in preclinical studies[64]. Some meta-analyses studies have reported the treatment of some tumours with everolimus (a mTOR inhibitor) and found it to be associated with a lower risk of poor PFS, but no significant differences were observed in any of the tests[65, 66]. In this study, the PFSrelated benefit was highest when mTOR inhibitors (HR 0.78; 95% CI: 0.68–0.89) were used, followed by AKT inhibitors (HR 0.81; 95% CI: 0.59–1.11) and pan-PI3K inhibitors (HR 0.91; 95% CI: 0.77–1.06). The direct comparison between AKT inhibitors and mTORC dual inhibitors or pan-PI3K and mTOR dual inhibitors with isolated mTORC1 inhibitors in some phase

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II trials showed no improvement in PFS[67–69], most likely because mTORCI is located at the centre of the PI3K/AKT/mTOR pathway, and parallel, but not linear, pathway inhibition may increase the clinical efficacy.

The comparison between PI3K pathway inhibitors and other targeted inhibitors, such as PD-1 inhibitors, MAPK pathway inhibitors and VEGFR inhibitors, showed no benefits in PFS. In our subgroup analysis, single mTOR inhibitors compared with VEGFR inhibitors resulted in a similar risk in terms of PFS. Many axes or molecular targets were activated along with the PI3K pathway, such as the RAS/RAF/MEK/ERK pathway, which is known to directly activate PI3K and cause cross-inhibition and cross-activation of PI3K pathways[70]. Other molecular targets, such as HER-2, VEGF and EGFR, have also been associated with PI3K pathways in cancers. The combination of PI3K pathway inhibitors with other targeted inhibitors has shown promising results in bypassing resistance mechanisms in many cancers, although their clinical effects are still contradictory. Our subgroup results showed that dual-targeted therapies that included a PI3K inhibitor showed inconsistent results in the PFS compared with single targeted reagents. The combination of VEGFR and mTORC1 targeted treatments showed no improvement in the PFS of patients, which may be due to the redundant angiogenic pathways or drug resistance, but novel PI3K inhibitors and mTORC2 inhibitors may help resolve this problem[71, 72]. These results may also be attributed to the failure to pre-select suitable patients by molecular analysis and to the unbearable toxic or side effects from dual-targeted therapies.

Our results showed no significant differences in OS between the experimental arm and the control arm. These results may be explained by the finding that most trials included in this analysis used PFS as the primary end point with a relatively short follow-up time, and many of them were phase II trials with a limited number of participants. Thus, the data were inadequate to detect differences in OS. Other factors, such as additional lines in the treatment arm and subsequent drug crossover, different combination therapies (chemotherapy or targeted therapy) with PI3K inhibitors, and the heterogeneity of cancer subtypes can all affect the results of OS. Therefore, the use of PFS instead of OS as an end point is adequate in PI3K pathway inhibitor trials.

We also analyzed the toxicity of PI3K pathway inhibitors compared with the controls. We found that toxicity is an important barrier to the use of these reagents in clinical settings. A meta-analysis conducted by Kenya on everolimus in hepatocellular carcinoma reported that everolimus significantly increased the incidence of liver injury (higher alanine aminotransferase), stomatitis, anaemia, hyperglycaemia and pneumonitis[73]. Hess compared two doses of temsirolimus (a mTOR inhibitor) with investigator choice in mantle cell lymphoma and found that the higher dose of temsirolimus significantly improved the PFS compared with the tumour response rate of the lower dose of temsirolimus but significantly increased the number of grade 3 and 4 adverse events[74]. After a rough review of the studies included in our analysis, it was found that the toxicity that induced trial discontinuation was obviously higher in the PI3K pathway inhibitors from achieving their effective anti-tumour effects, which thus weakens their effects and limiting their broad use in clinical settings. Therefore, the circumvention of this problem is crucial for PI3K inhibitors.

Our meta-analysis has some limitations. Differences in the treatment line, the combination of chemotherapeutic regimens, dose and treatment circles among these trials were difficult to fully balance, although we performed some subgroup analyses. For some types of cancers, such as endometrial cancer, glioblastoma and melanoma, the power of the analysis of the effect of PI3K pathway inhibitors was insufficient because only one trial was available for each of these cancers. Lastly, although all studies included in this analysis were randomised controlled trials,

most of them were phase II trials with a limited number of participants, and the assessment criteria and methods differed among trials, which are also limitations of our study.

#### Conclusions

Our meta-analysis results suggest that the addition of PI3K pathway inhibitors to the therapy regimens for advanced solid tumours significantly improved the PFS, especially among patients with breast cancer and neuroendocrine tumours and those with PI3K mutations. However, this study was unable to observe improvements in the OS and ORR as a result of PI3K pathway inhibitors. Considering the side effects of PI3K pathway inhibitors when these drugs are used, the risk-benefit analysis must be carefully performed. In the future, more studies that are focused on selected types of cancers will be required to identify suitable patients who will benefit the most from therapies with PI3K pathway inhibitors.

## **Supporting information**

**S1 Fig. Forest plots of odds ratio (OR) for adversed event induced the study discontinue.** Experimental arm included different kinds of PI3K/AKT/mTOR inhibitors. The randomeffects model was used. (TIF)

**S1 Table. PRISMA checklist.** (DOC)

**S2 Table. Supplement information of the included studies.** Abbreviation: NR: not reported; NA: not available; PFS: progression-free survival; OS: overall survival; IFN: interferon; ORR: objective response rate; TTP: time to progression; CBR: clinical benefit rate; DCR: Disease control rate; EGFR: epidermal growth factor receptor; VEGFR: vascular endothelial growth factor receptor; mTORC1: mammalian target of rapamycin complex 1. \* Reported a different trial by the previous author in the same year. # Reported more than one comparation in a trial. Lowercase letter a, b,c means different trial arm in the same study. (XLS)

## **Author Contributions**

Conceptualization: Xuan Li, Weidong Wei. Data curation: Xuan Li, Danian Dai, Bo Chen. Formal analysis: Xuan Li, Danian Dai, Hailin Tang. Funding acquisition: Hailin Tang, Xiaoming Xie. Methodology: Bo Chen. Project administration: Weidong Wei. Software: Bo Chen. Supervision: Xiaoming Xie. Validation: Hailin Tang, Xiaoming Xie. Visualization: Weidong Wei. Writing – original draft: Xuan Li. Writing – review & editing: Xiaoming Xie, Weidong Wei.

#### References

- Cantley LC. The phosphoinositide 3-kinase pathway. Science (New York, NY). 2002; 296(5573):1655– 7. Epub 2002/06/01. https://doi.org/10.1126/science.296.5573.1655 PMID: 12040186.
- Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K Pathway in Human Disease. Cell. 2017; 170(4):605–35. doi: 10.1016/j.cell.2017.07.029. WOS:000407445700005. PMID: 28802037
- Dibble CC, Cantley LC. Regulation of mTORC1 by PI3K signaling. Trends in cell biology. 2015; 25 (9):545–55. Epub 2015/07/15. https://doi.org/10.1016/j.tcb.2015.06.002 PMID: 26159692; PubMed Central PMCID: PMCPMC4734635.
- Saxton RA, Sabatini DM. mTOR Signaling in Growth, Metabolism, and Disease. Cell. 2017; 168 (6):960–76. Epub 2017/03/12. https://doi.org/10.1016/j.cell.2017.02.004 PMID: 28283069; PubMed Central PMCID: PMCPMC5394987.
- Maruyama N, Miyoshi Y, Taguchi T, Tamaki Y, Monden M, Noguchi S. Clinicopathologic analysis of breast cancers with PIK3CA mutations in Japanese women. Clinical cancer research: an official journal of the American Association for Cancer Research. 2007; 13(2 Pt 1):408–14. Epub 2007/01/05. https:// doi.org/10.1158/1078-0432.ccr-06-0267 PMID: 17202311.
- Kalinsky K, Jacks LM, Heguy A, Patil S, Drobnjak M, Bhanot UK, et al. PIK3CA mutation associates with improved outcome in breast cancer. Clinical cancer research: an official journal of the American Association for Cancer Research. 2009; 15(16):5049–59. Epub 2009/08/13. https://doi.org/10.1158/ 1078-0432.ccr-09-0632 PMID: 19671852.
- Lang SA, Gaumann A, Koehl GE, Seidel U, Bataille F, Klein D, et al. Mammalian target of rapamycin is activated in human gastric cancer and serves as a target for therapy in an experimental model. International journal of cancer. 2007; 120(8):1803–10. Epub 2007/01/19. https://doi.org/10.1002/ijc.22442 PMID: 17230506.
- Jehan Z, Bavi P, Sultana M, Abubaker J, Bu R, Hussain A, et al. Frequent PIK3CA gene amplification and its clinical significance in colorectal cancer. The Journal of pathology. 2009; 219(3):337–46. Epub 2009/08/22. https://doi.org/10.1002/path.2601 PMID: 19697359.
- Miller TW, Hennessy BT, Gonzalez-Angulo AM, Fox EM, Mills GB, Chen H, et al. Hyperactivation of phosphatidylinositol-3 kinase promotes escape from hormone dependence in estrogen receptor-positive human breast cancer. The Journal of clinical investigation. 2010; 120(7):2406–13. Epub 2010/06/ 10. https://doi.org/10.1172/JCI41680 PMID: 20530877; PubMed Central PMCID: PMCPMC2898598.
- Oki E, Baba H, Tokunaga E, Nakamura T, Ueda N, Futatsugi M, et al. Akt phosphorylation associates with LOH of PTEN and leads to chemoresistance for gastric cancer. International journal of cancer. 2005; 117(3):376–80. Epub 2005/05/19. https://doi.org/10.1002/ijc.21170 PMID: 15900596.
- Brognard J, Clark AS, Ni Y, Dennis PA. Akt/protein kinase B is constitutively active in non-small cell lung cancer cells and promotes cellular survival and resistance to chemotherapy and radiation. Cancer research. 2001; 61(10):3986–97. Epub 2001/05/19. PMID: 11358816.
- La Monica S, Galetti M, Alfieri RR, Cavazzoni A, Ardizzoni A, Tiseo M, et al. Everolimus restores gefitinib sensitivity in resistant non-small cell lung cancer cell lines. Biochemical pharmacology. 2009; 78 (5):460–8. Epub 2009/05/12. https://doi.org/10.1016/j.bcp.2009.04.033 PMID: 19427302.
- Patel PH, Senico PL, Curiel RE, Motzer RJ. Phase I study combining treatment with temsirolimus and sunitinib malate in patients with advanced renal cell carcinoma. Clinical genitourinary cancer. 2009; 7 (1):24–7. Epub 2009/02/14. https://doi.org/10.3816/CGC.2009.n.004 PMID: 19213664; PubMed Central PMCID: PMCPMC3740755.
- Feldman DR, Baum MS, Ginsberg MS, Hassoun H, Flombaum CD, Velasco S, et al. Phase I trial of bevacizumab plus escalated doses of sunitinib in patients with metastatic renal cell carcinoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2009; 27(9):1432–9. Epub 2009/02/20. https://doi.org/10.1200/jco.2008.19.0108 PMID: 19224847; PubMed Central PMCID: PMCPMC3655420.
- Molina AM, Feldman DR, Voss MH, Ginsberg MS, Baum MS, Brocks DR, et al. Phase 1 trial of everolimus plus sunitinib in patients with metastatic renal cell carcinoma. Cancer. 2012; 118(7):1868–76. Epub 2011/09/08. https://doi.org/10.1002/cncr.26429 PMID: 21898375; PubMed Central PMCID: PMCPMC3609026.
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled clinical trials. 1996; 17(1):1–12. Epub 1996/02/01. PMID: 8721797.
- Andre F, O'Regan R, Ozguroglu M, Toi M, Xu B, Jerusalem G, et al. Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial. The Lancet Oncology. 2014; 15(6):580–91. Epub 2014/04/20. https:// doi.org/10.1016/S1470-2045(14)70138-X PMID: 24742739.

- Yardley DA, Bosserman LD, O'Shaughnessy JA, Harwin WN, Morgan SK, Priego VM, et al. Paclitaxel, bevacizumab, and everolimus/placebo as first-line treatment for patients with metastatic HER2-negative breast cancer: a randomized placebo-controlled phase II trial of the Sarah Cannon Research Institute. Breast cancer research and treatment. 2015; 154(1):89–97. Epub 2015/10/13. https://doi.org/10. 1007/s10549-015-3599-5 PMID: 26456573.
- Baselga J, Im SA, Iwata H, Cortes J, De Laurentiis M, Jiang Z, 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. 2017; 18(7):904–16. Epub 2017/06/04. https://doi.org/10.1016/S1470-2045(17)30376-5 PMID: 28576675; PubMed Central PMCID: PMCPMC5549667.
- Baselga J, Campone M, Piccart M, Burris HA, 3rd, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. The New England journal of medicine. 2012; 366(6):520–9. Epub 2011/12/14. https://doi.org/10.1056/NEJMoa1109653 PMID: 22149876.
- Wolff AC, Lazar AA, Bondarenko I, Garin AM, Brincat S, Chow L, et al. Randomized phase III placebocontrolled trial of letrozole plus oral temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2013; 31(2):195–202. Epub 2012/12/13. https://doi.org/10. 1200/jco.2011.38.3331 PMID: 23233719; PubMed Central PMCID: PMCPMC3532391.
- 22. Kim S-B, Dent R, Im S-A, Espie M, Blau S, Tan AR, et al. Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, ran-domised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncology. 2017; 18(10):1360–72. doi: 10.1016/S1470-2045(17)30450-3. WOS:000411843500052. PMID: 28800861
- Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, Ferrero JM, Freyer G, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: A GINECO study. Journal of Oncology. 2012; 30(22):2718–24. https://doi.org/10.1200/JCO. 2011.39.0708 PMID: 22565002
- Krop IE, Mayer IA, Ganju V, Dickler M, Johnston S, Morales S, et al. Pictilisib for oestrogen receptorpositive, aromatase inhibitor-resistant, advanced or metastatic breast cancer (FERGI): a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet Oncology. 2016; 17(6):811–21. Epub 2016/ 05/09. https://doi.org/10.1016/S1470-2045(16)00106-6 PMID: 27155741; PubMed Central PMCID: PMCPMC5524539.
- Martín M, Chan A, Dirix L, O'Shaughnessy J, Hegg R, Manikhas A, et al. A randomized adaptive phase II/III study of buparlisib, a pan-class I PI3K inhibitor, combined with paclitaxel for the treatment of HER2advanced breast cancer (BELLE-4). Annals of Oncology. 2017; 28(2):313–20. <u>https://doi.org/10.1093/</u> annonc/mdw562 PMID: 27803006
- 26. Hurvitz SA, Andre F, Jiang Z, Shao Z, Mano MS, Neciosup SP, et al. Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): A phase 3, randomised, double-blind, multicentre trial. The Lancet Oncology. 2015; 16(7):816–29. https://doi.org/10.1016/S1470-2045(15)00051-0 PMID: 26092818
- 27. Vuylsteke P, Huizing M, Petrakova K, Roylance R, Laing R, Chan S, et al. Pictilisib PI3Kinase inhibitor (a phosphatidylinositol 3-kinase PI3K inhibitor) plus paclitaxel for the treatment of hormone receptorpositive, HER2-negative, locally recurrent, or metastatic breast cancer: interim analysis of the multicentre, placebo-controlled, phase II randomised PEGGY study. Annals of Oncology. 2016; 27(11):2059– 66. doi: 10.1093/annonc/mdw320. WOS:000388528900013. PMID: 27573562
- 28. Baselga J, Morales SM, Awada A, Blum JL, Tan AR, Ewertz M, et al. A phase II study of combined ridaforolimus and dalotuzumab compared with exemestane in patients with estrogen receptor-positive breast cancer. Breast cancer research and treatment. 2017; 163(3):535–44. Epub 2017/03/23. https:// doi.org/10.1007/s10549-017-4199-3 PMID: 28324268; PubMed Central PMCID: PMCPMC5448790.
- Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. New England Journal of Medicine. 2015; 373(19):1803– 13. https://doi.org/10.1056/NEJMoa1510665 PMID: 26406148
- 30. Cirkel GA, Hamberg P, Sleijfer S, Loosveld OJL, Dercksen MW, Los M, et al. Alternating Treatment With Pazopanib and Everolimus vs Continuous Pazopanib to Delay Disease Progression in Patients With Metastatic Clear Cell Renal Cell Cancer: The ROPETAR Randomized Clinical Trial. JAMA Oncol. 2017; 3(4):501–8. Epub 2016/12/06. https://doi.org/10.1001/jamaoncol.2016.5202 PMID: 27918762.
- Rini BI, Bellmunt J, Clancy J, Wang K, Niethammer AG, Hariharan S, et al. Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. Journal of Oncology. 2014; 32(8):752–9. https://doi.org/10.1200/JCO.2013.50. 5305

- 32. Flaherty KT, Manola JB, Pins M, McDermott DF, Atkins MB, Dutcher JJ, et al. BEST: A Randomized Phase II Study of Vascular Endothelial Growth Factor, RAF Kinase, and Mammalian Target of Rapamycin Combination Targeted Therapy With Bevacizumab, Sorafenib, and Temsirolimus in Advanced Renal Cell Carcinoma—A Trial of the ECOG-ACRIN Cancer Research Group (E2804). Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2015; 33(21):2384–91. Epub 2015/06/17. https://doi.org/10.1200/jco.2015.60.9727 PMID: <u>26077237</u>; PubMed Central PMCID: PMCPMC4500832.
- Motzer RJ, Barrios CH, Kim TM, Falcon S, Cosgriff T, Harker WG, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and secondline everolimus in patients with metastatic renal cell carcinoma. Journal of Oncology. 2014; 32 (25):2765–72. https://doi.org/10.1056/NEJM197608192950809 PMID: 10.1200/JCO.2013.54.6911.
- Armstrong AJ, Halabi S, Eisen T, Broderick S, Stadler WM, Jones RJ, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. The Lancet Oncology. 2016; 17(3):378–88. Epub 2016/01/23. https://doi.org/10. 1016/S1470-2045(15)00515-X PMID: 26794930.
- Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. The Lancet Oncology. 2016; 17(7):917–27. Epub 2016/06/10. <u>https://doi.org/10.1016/S1470-</u> 2045(16)30107-3 PMID: 27279544.
- Hutson TE, Escudier B, Esteban E, Bjarnason GA, Lim HY, Pittman KB, et al. Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2014; 32(8):760–7. Epub 2013/12/04. https://doi.org/10.1200/jco.2013.50.3961 PMID: 24297950.
- Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer. 2010; 116 (18):4256–65. Epub 2010/06/16. https://doi.org/10.1002/cncr.25219 PMID: 20549832.
- Negrier S, Gravis G, Perol D, Chevreau C, Delva R, Bay JO, et al. Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TOR-AVA): a randomised phase 2 trial. The Lancet Oncology. 2011; 12(7):673–80. Epub 2011/06/15. https:// doi.org/10.1016/S1470-2045(11)70124-3 PMID: 21664867.
- Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. The New England journal of medicine. 2007; 356(22):2271–81. Epub 2007/06/01. https://doi.org/10.1056/NEJMoa066838 PMID: 17538086.
- 40. Dutcher JP, de Souza P, McDermott D, Figlin RA, Berkenblit A, Thiele A, et al. Effect of temsirolimus versus interferon-alpha on outcome of patients with advanced renal cell carcinoma of different tumor histologies. Medical oncology (Northwood, London, England). 2009; 26(2):202–9. Epub 2009/02/21. https://doi.org/10.1007/s12032-009-9177-0 PMID: 19229667.
- Tannir NM, Jonasch E, Albiges L, Altinmakas E, Ng CS, Matin SF, et al. Everolimus Versus Sunitinib Prospective Evaluation in Metastatic Non-Clear Cell Renal Cell Carcinoma (ESPN): A Randomized Multicenter Phase 2 Trial. European Urology. 2016; 69(5):866–74. https://doi.org/10.1016/j.eururo. 2015.10.049 PMID: 26626617
- 42. Levy B, Spira A, Becker D, Evans T, Schnadig I, Camidge DR, 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. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2014; 9(7):1031–5. Epub 2014/06/14. https://doi.org/10.1097/jto.0000000000183 PMID: 24926548.
- Besse B, Leighl N, Bennouna J, Papadimitrakopoulou VA, Blais N, Traynor AM, et al. Phase II study of everolimus-erlotinib in previously treated patients with advanced non-small-cell lung cancer. Annals of Oncology. 2014; 25(2):409–15. https://doi.org/10.1093/annonc/mdt536 PMID: 24368400
- 44. Socinski MA, Raju RN, Stinchcombe T, Kocs DM, Couch LS, Barrera D, et al. Randomized, phase II trial of pemetrexed and carboplatin with or without enzastaurin versus docetaxel and carboplatin as first-line treatment of patients with stage IIIB/IV non-small cell lung cancer. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer. 2010; 5(12):1963–9. Epub 2010/11/26. https://doi.org/10.1097/JTO.0b013e3181fd42eb PMID: 21102260.
- 45. Papadimitrakopoulou V, Lee JJ, Wistuba II, Tsao AS, Fossella FV, Kalhor N, et al. The BATTLE-2 Study: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer. Journal of Clinical Oncology. 2016; 34(30):3638-+. doi: 10.1200/jco. 2015.66.0084. WOS:000385972600010. PMID: 27480147
- 46. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, 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. The Lancet. 2016; 387(10022):968–77. https://doi.org/ 10.1016/S0140-6736(15)00817-X

- Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. The New England journal of medicine. 2011; 364(6):514–23. Epub 2011/ 02/11. https://doi.org/10.1056/NEJMoa1009290 PMID: 21306238; PubMed Central PMCID: PMCPMC4208619.
- Pavel ME, Hainsworth JD, Baudin E, Peeters M, Horsch D, Winkler RE, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet (London, England). 2011; 378(9808):2005–12. Epub 2011/11/29. https://doi.org/10.1016/s0140-6736(11)61742-x PMID: 22119496.
- 49. Yao J, Wang JY, Liu Y, Wang B, Li YX, Zhang R, et al. A randomized phase II study of everolimus for advanced pancreatic neuroendocrine tumors in Chinese patients. Medical oncology (Northwood, London, England). 2014; 31(12):251. Epub 2014/11/15. https://doi.org/10.1007/s12032-014-0251-x PMID: 25395378.
- Bowles DW, Kochenderfer M, Cohn A, Sideris L, Nguyen N, Cline-Burkhardt V, 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. Clinical colorectal cancer. 2016; 15(4):337– 44.e2. Epub 2016/04/28. https://doi.org/10.1016/j.clcc.2016.03.004 PMID: 27118441.
- Bendell JC, Nemunaitis J, Vukelja SJ, Hagenstad C, Campos LT, Hermann RC, et al. Randomized Placebo-Controlled Phase II Trial of Perifosine Plus Capecitabine As Second- or Third-Line Therapy in Patients With Metastatic Colorectal Cancer. Journal of Clinical Oncology. 2011; 29(33):4394–400. doi: 10.1200/JCO.2011.36.1980. WOS:000297257400016. PMID: 21969495
- Ohtsu A, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, et al. Everolimus for previously treated advanced gastric cancer: Results of the randomized, double-blind, phase III GRANITE-1 study. Journal of Oncology. 2013; 31(31):3935–43. https://doi.org/10.1200/JCO.2012.48.3552 PMID: 24043745
- Soulieres D, Faivre S, Mesia R, Remenar E, Li SH, Karpenko A, et al. Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): a randomised, double-blind, placebo-controlled phase 2 trial. The Lancet Oncology. 2017; 18(3):323–35. Epub 2017/01/31. <u>https://doi.org/10.1016/S1470-2045(17)30064-5</u> PMID: 28131786.
- Jimeno A, Bauman JE, Weissman C, Adkins D, Schnadig I, Beauregard P, 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 oncology. 2015; 51 (4):383–8. Epub 2015/01/17. https://doi.org/10.1016/j.oraloncology.2014.12.013 PMID: 25593016; PubMed Central PMCID: PMCPMC4857706.
- 55. Jimeno A, Shirai K, Choi M, Laskin J, Kochenderfer M, Spira 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. Annals of oncology: official journal of the European Society for Medical Oncology. 2015; 26(3):556–61. Epub 2014/12/20. https://doi.org/10. 1093/annonc/mdu574 PMID: 25524478.
- 56. Demetri GD, Chawla SP, Ray-Coquard I, Le Cesne A, Staddon AP, Milhem MM, 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. Journal of Clinical Oncology. 2013; 31(19):2485-+. doi: 10.1200/JCO.2012.45.5766. WOS:000330520600029. PMID: 23715582
- Eroglu Z, Tawbi HA, Hu J, Guan M, Frankel PH, Ruel NH, et al. A randomised phase II trial of selumetinib vs selumetinib plus temsirolimus for soft-tissue sarcomas. British Journal of. 2015; 112(10):1644– 51. https://doi.org/10.1038/bjc.2015.126 PMID: 25897676
- 58. Zhu AX, Kudo M, Assenat E, Cattan S, Kang YK, Lim HY, et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: The EVOLVE-1 randomized clinical trial. JAMA—Journal of the American Medical Association. 2014; 312(1):57–67. <u>https://doi.org/10.1001/jama.2014.7189 PMID: 25058218</u>
- 59. Richards DA, Kuefler PR, Becerra C, Wilfong LS, Gersh RH, Boehm KA, et al. Gemcitabine plus enzastaurin or single-agent gemcitabine in locally advanced or metastatic pancreatic cancer: Results of a Phase II, randomized, noncomparative study. Investigational New Drugs. 2011; 29(1):144–53. https:// doi.org/10.1007/s10637-009-9307-8 PMID: 19714296
- Oza AM, Pignata S, Poveda A, McCormack M, Clamp A, Schwartz B, et al. Randomized Phase II Trial of Ridaforolimus in Advanced Endometrial Carcinoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2015; 33(31):3576–82. Epub 2015/06/17. https://doi.org/10. 1200/jco.2014.58.8871 PMID: 26077241.

- Wick W, Gorlia T, Bady P, Platten M, Van Den Bent MJ, Taphoorn MJB, et al. Phase II study of radiotherapy and temsirolimus versus radiochemotherapy with temozolomide in patients with newly diagnosed glioblastoma without MGMT promoter hypermethylation (EORTC 26082). Research. 2016; 22 (19):4797–806. https://doi.org/10.1158/1078-0432.CCR-15-3153 PMID: 27143690
- Margolin KA, Moon J, Flaherty LE, Lao CD, Akerley IWL, Othus M, et al. Randomized phase II trial of sorafenib with temsirolimus or tipifarnib in untreated metastatic melanoma (S0438). Research. 2012; 18 (4):1129–37. https://doi.org/10.1158/1078-0432.CCR-11-2488 PMID: 22228638
- Courtney KD, Corcoran RB, Engelman JA. The PI3K pathway as drug target in human cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2010; 28(6):1075–83. Epub 2010/01/21. https://doi.org/10.1200/jco.2009.25.3641 PMID: 20085938; PubMed Central PMCID: PMCPMC2834432.
- Cho DC, Cohen MB, Panka DJ, Collins M, Ghebremichael M, Atkins MB, et al. The efficacy of the novel dual PI3-kinase/mTOR inhibitor NVP-BEZ235 compared with rapamycin in renal cell carcinoma. Clinical cancer research: an official journal of the American Association for Cancer Research. 2010; 16 (14):3628–38. Epub 2010/07/08. https://doi.org/10.1158/1078-0432.ccr-09-3022 PMID: 20606035; PubMed Central PMCID: PMCPMC2905505.
- 65. Generali D, Venturini S, Rognoni C, Ciani O, Pusztai L, Loi S, et al. A network meta-analysis of everolimus plus exemestane versus chemotherapy in the first- and second-line treatment of estrogen receptor-positive metastatic breast cancer. Breast cancer research and treatment. 2015; 152(1):95–117. Epub 2015/06/06. https://doi.org/10.1007/s10549-015-3453-9 PMID: 26044370.
- Ravaud A, Urva SR, Grosch K, Cheung WK, Anak O, Sellami DB. Relationship between everolimus exposure and safety and efficacy: meta-analysis of clinical trials in oncology. European journal of cancer (Oxford, England: 1990). 2014; 50(3):486–95. Epub 2013/12/18. https://doi.org/10.1016/j.ejca.2013.11. 022 PMID: 24332451.
- Jonasch E, Hasanov E, Corn PG, Moss T, Shaw KR, Stovall S, et al. A randomized phase 2 study of MK-2206 versus everolimus in refractory renal cell carcinoma. Annals of oncology: official journal of the European Society for Medical Oncology. 2017; 28(4):804–8. Epub 2017/01/04. <u>https://doi.org/10.1093/</u> annonc/mdw676 PMID: 28049139.
- Powles T, Wheater M, Din O, Geldart T, Boleti E, Stockdale A, et al. A Randomised Phase 2 Study of AZD2014 Versus Everolimus in Patients with VEGF-Refractory Metastatic Clear Cell Renal Cancer. European urology. 2016; 69(3):450–6. Epub 2015/09/15. <u>https://doi.org/10.1016/j.eururo.2015.08.035</u> PMID: 26364551.
- 69. Powles T, Lackner MR, Oudard S, Escudier B, Ralph C, Brown JE, 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. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2016; 34(14):1660–8. Epub 2016/03/10. https://doi.org/10.1200/jco.2015.64.8808 PMID: 26951309.
- Mendoza MC, Er EE, Blenis J. The Ras-ERK and PI3K-mTOR pathways: cross-talk and compensation. Trends in biochemical sciences. 2011; 36(6):320–8. Epub 2011/05/03. https://doi.org/10.1016/j.tibs. 2011.03.006 PMID: 21531565; PubMed Central PMCID: PMCPMC3112285.
- Tamaskar I, Dhillon J, Pili R. Resistance to angiogenesis inhibitors in renal cell carcinoma. Clinical advances in hematology & oncology: H&O. 2011; 9(2):101–10. Epub 2011/12/17. PMID: 22173604.
- 72. Figlin RA, Kaufmann I, Brechbiel J. Targeting PI3K and mTORC2 in metastatic renal cell carcinoma: new strategies for overcoming resistance to VEGFR and mTORC1 inhibitors. International journal of cancer. 2013; 133(4):788–96. Epub 2013/01/16. https://doi.org/10.1002/ijc.28023 PMID: 23319457.
- 73. Yamanaka K, Petrulionis M, Lin S, Gao C, Galli U, Richter S, et al. Therapeutic potential and adverse events of everolimus for treatment of hepatocellular carcinoma—systematic review and meta-analysis. Cancer medicine. 2013; 2(6):862–71. Epub 2014/01/10. https://doi.org/10.1002/cam4.150 PMID: 24403259; PubMed Central PMCID: PMCPMC3892390.
- 74. Hess G, Herbrecht R, Romaguera J, Verhoef G, Crump M, Gisselbrecht C, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2009; 27(23):3822–9. Epub 2009/07/08. <u>https://doi.org/10.1200/jco.2008.20.7977</u> PMID: 19581539.