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 meta-analysis 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 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 $I^2$ statistic were used to assess statistical heterogeneity. $I^2$ values lower than 25% and $P > 0.1$ were considered to indicate low heterogeneity according to a fixed-effects model (Mantel-Haenszel method). $I^2$ values higher than 50% or $I^2 < 50\%$ 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...
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; $I^2 = 87\%$, 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...
Table 1. Characteristics of the included studies.

| Study                  | Tumor type                  | Trial phase | Experimental 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) | Judged Score |
|------------------------|-----------------------------|-------------|----------------------------------------|-------------------------------------------------------------|------------------|-------------------------------------|-----------------------|------------------|----------------|----------------------------------------|---------------|
| Andre (BOLERO-3)       | Breast cancer               | III         | mTORC1 HER2                            | Everolimus + Vinorelbine + trastuzumab vs placebo + Vinorelbine + trastuzumab | 284              | 285                                 | PFS                  | NA               | yes            | 5                                      |               |
| Baselga (BOLEO-2)      | Breast cancer               | III         | mTORC1 NA                              | Everolimus + exemestane vs placebo + exemestane             | 485              | 239                                 | PFS                  | OS               | no             | 5                                      |               |
| Baselga (BELLE-2)      | Breast cancer               | III         | Pan-Pi3K NA                            | Buparlisib + fulvestrant vs placebo + fulvestrant          | 576              | 571                                 | PFS                  | NA               | yes            | 5                                      |               |
| Baselga                | Breast cancer               | II          | mTORC1 NA                              | Radifromolimus + dolutumumb + exemestane vs exemestane     | 29               | 33                                  | PFS                  | OS               | no             | 4                                      |               |
| Baselga (BOLEO-1)      | Breast cancer               | III         | mTORC1 HER2                            | Everolimus + Trastuzumab + Paclitaxel vs placebo + Trastuzumab + Paclitaxel | 480              | 239                                 | PFS                  | NA               | no             | 5                                      |               |
| Kim (LOTUS)            | Breast cancer               | II          | AKT NA                                 | Ipatasertib + paclitaxel vs placebo + paclitaxel          | 62               | 62                                  | PFS                  | NA               | yes            | 5                                      |               |
| Krop (FERGI)           | Breast cancer               | III         | mTORC1 NA                              | Everolimus + tamoxifen vs tamoxifen                        | 89               | 79                                  | PFS                  | NA               | yes            | 5                                      |               |
| Martin (BELLE-4)       | Breast cancer               | III         | Pan-Pi3K NA                            | Buparlisib + paclitaxel vs placebo + paclitaxel          | 207              | 209                                 | PFS                  | NA               | yes            | 5                                      |               |
| Yapinker (PEGGY)       | Breast cancer               | III         | Pan-Pi3K NA                            | Buparlisib + Paclitaxel vs placebo + Paclitaxel          | 91               | 92                                  | PFS                  | NA               | no             | 4                                      |               |
| Wolfl (HORIZON)        | Breast cancer               | III         | mTORC1 NA                              | Temsirolimus + letrozole vs placebo + letrozole            | 555              | 555                                 | PFS                  | OS               | no             | 5                                      |               |
| Yardley                | Breast cancer               | III         | mTORC1 VEGF inhibitor                  | Everolimus + Paclitaxel + Bevacizumab vs placebo + Paclitaxel + Bevacizumab | 56               | 57                                  | PFS                  | OS               | no             | 4                                      |               |
| Armstrong (ASPIN)      | Renal cell cancer           | III         | mTORC1 VEGFR inhibitor                 | Everolimus + sunitinib                                      | 57               | 51                                  | PFS                  | OS               | no             | 4                                      |               |
| Choueiri (METEOR)      | Renal cell cancer           | III         | mTORC1 VEGFR inhibitor                  | Everolimus + sunitinib                                      | 328              | 330                                 | PFS                  | OS               | no             | 4                                      |               |
| Cirkel (ROPETAR)       | Renal cell cancer           | III         | mTORC1 VEGFR inhibitor                  | Everolimus + pazopanib vs pazopanib                        | 52               | 49                                  | PFS                  | NA               | no             | 4                                      |               |
| Dutcher,b                 | Renal cell cancer (a: clear cell cancer; b: no clear cell cancer) | III         | mTORC1 NA                              | Temsirolimus vs interferon                                 | a: 169; b: 37   | a: 170; b: 18                       | OS                   | PFS              | no             | 4                                      |               |
| Flaherty,a; c (ECOG2884) | Renal cell cancer            | III         | mTORC1 VEGF inhibitor                   | (a) Bevacizumab + temsirolimus vs bevacizumab alone (b) Bevacizumab + temsirolimus vs bevacizumab + sunitinib (c) Sorafenib vs temsirolimus + bevacizumab + sorafenib | a: 80; b: 80; c: 84 | a: 84; b: 83; c: 85                 | PFS                  | NA               | no             | 4                                      |               |
| Hudes,a; b              | Renal cell cancer           | III         | mTORC1 NA                              | (a) Temsirolimus vs interferon (b) Temsirolimus vs interferon vs interferon | a: 210; b: 209 | ab: 207                             | OS                   | PFS              | no             | 4                                      |               |
| Hutson                  | Renal cell cancer           | III         | mTORC1 VEGF inhibitor                   | Temsirolimus vs sorafenib                                  | 259              | 253                                 | PFS                  | OS               | no             | 4                                      |               |
| Motzer (RECORD-1)      | Renal cell cancer           | III         | mTORC1 NA                              | Everolimus vs placebo                                      | 277              | 139                                 | PFS                  | OS               | no             | 5                                      |               |
| Motzer (RECORD-3)      | Renal cell cancer           | III         | mTORC1 VEGF inhibitor                   | Everolimus vs sorafenib                                    | 238              | 233                                 | PFS                  | OS               | no             | 4                                      |               |
| Motzer                  | Renal cell cancer           | III         | mTORC1 PD-1 inhibitor                   | Everolimus vs Nivolumab                                     | 410              | 411                                 | OS                   | PFS              | no             | 4                                      |               |
| Nequist (TORAVA)       | Renal cell cancer           | III         | mTORC1 VEGF inhibitor                   | Temsirolimus + bevacizumab vs interferon alfa + bevacizum   | 88               | 40                                  | PFS                  | NA               | no             | 4                                      |               |
| Rini (INTACT)          | Renal cell cancer           | III         | mTORC1 VEGF inhibitor                   | Temsirolimus + bevacizumab vs IFN + bevacizumab            | 400              | 391                                 | PFS                  | OS               | no             | 4                                      |               |
| Tamitir                | Renal cell cancer           | III         | mTORC1 VEGF inhibitor                   | Temsirolimus vs sorafenib                                  | 35               | 33                                  | PFS                  | NA               | no             | 4                                      |               |
| Bessis                 | Lung cancer                 | II          | mTORC1 EGFR inhibitor                   | Everolimus vs doxorubic                                    | 66               | 67                                  | DCR                  | PFS; OS          | no             | 4                                      |               |
| Levy                   | Lung cancer                 | II          | Pan-Pi3K NA                            | PS-866 + docetaxan vs doxorubic                           | 48               | 47                                  | PFS                  | OS               | no             | 4                                      |               |
| Papadimitrakopoulos     | Lung cancer                 | II          | AKT EGFR inhibitor                      | MK-2206 + Erlotinib vs Erlotinib                          | 42               | 22                                  | DCR                  | PFS; OS          | no             | 4                                      |               |
| Socinski (TAX 326)     | Lung cancer                 | II          | AKT NA                                 | Estramustine + carboplatin vs carboplatin                  | 72               | 74                                  | TTP                  | OS               | no             | 4                                      |               |
| Zhu (EOLIVELL-1)       | Liver cancer                | III         | mTORC1 NA                              | Everolimus vs placebo                                     | 362              | 184                                 | OS                   | TTP              | no             | 5                                      |               |
| Bendell                | Colorectal Cancer           | III         | PIK/Akt/mTOR signaling inhibitor NA     | Perifosine + capecitabine vs placebo + capecitabine        | 20               | 18                                  | TTP                  | OS               | no             | 5                                      |               |
| Bowles                 | Colorectal Cancer           | III         | PIK-Pi3K EGFR inhibitor                 | PS-866 + otezumab vs placebo + otezumab                    | 42               | 38                                  | PFS                  | OS               | no             | 4                                      |               |
| Ohnna (GRANITE-1)      | Gastric cancer              | III         | mTORC1 NA                              | Everolimus vs placebo                                     | 439              | 217                                 | OS                   | PFS              | no             | 5                                      |               |

(Continued)
| 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 | II          | Pan-PI3K EGFR inhibitor PX-866+cetuximab vs cetuximab | PX-866 + docetaxel vs docetaxel | PFS OS no 4       | 42 41                               |                               |                 |               |                                       |             |
| Jimeno                      | 2016         | Head and neck squamous cell cancer | II          | Pan-PI3K NA PX-866 + docetaxel vs docetaxel | NA                                             | PFS OS no 4       | 42 43                               |                               |                 |               |                                       |             |
| Soulieres (BERIL-1)         | 2017         | Head and neck squamous cell cancer | II          | Pan-PI3K NA Buparlisib + paclitaxel vs placebo + paclitaxel | NA                                             | PFS OS no 5       | 79 79                               |                               |                 |               |                                       |             |
| Rachards                    | 2011         | Pancreatic cancer            | II          | AKT NA Enzastaurin+ gemcitabine vs gemcitabine | NA                                             | PFS OS no 4       | 86 44                               |                               |                 |               |                                       |             |
| PSELF (RADIANT-2)           | 2011         | Neuroendocrine tumours       | III         | mTORC1 NA Everolimus + octreotide LAR vs placebo + octreotide LAR | NA                                             | PFS OS no 5       | 216 213                              |                               |                 |               |                                       |             |
| Yao (RADIANT-3)             | 2011         | Neuroendocrine tumours       | III         | mTORC1 NA Everolimus vs placebo          | NA                                             | PFS OS no 5       | 207 203                              |                               |                 |               |                                       |             |
| Yao (RADIANT-4)             | 2014         | Neuroendocrine tumours       | II          | mTORC1 NA Everolimus vs placebo          | NA                                             | PFS OS no 5       | 44 35                                |                               |                 |               |                                       |             |
| Yao (RADIANT-5)             | 2016         | Neuroendocrine tumours       | III         | mTORC1 NA Everolimus vs placebo          | NA                                             | PFS OS no 5       | 205 97                               |                               |                 |               |                                       |             |
| Eroglu                      | 2015         | Sarcoma                     | II          | mTORC1 RAF/MEK/ERK (MEK1) inhibitor Temsirolimus + selumetinib vs selumetinib | NA                                             | PFS NA no 4       | 35 34                                |                               |                 |               |                                       |             |
| Demetri                     | 2013         | Sarcoma                     | III         | mTORC1 NA Redafoxolimus vs placebo        | NA                                             | PFS OS no 5       | 347 364                              |                               |                 |               |                                       |             |
| Oza                         | 2013         | Endometrial cancer          | II          | mTORC1 NA Redafoxolimus vs progesterone or chemotherapy | NA                                             | PFS OS no 5       | 64 66                                |                               |                 |               |                                       |             |
| Wick (EORTC 26082)          | 2016         | Glioblastoma                | II          | mTORC1 NA Temsirolimus vs temozolomide    | NA                                             | PFS OS no 4       | 56 55                                |                               |                 |               |                                       |             |
| Margolin (SO438)            | 2012         | Melanoma                    | II          | mTORC1 RAF/MEK/ERK inhibitor and/or RAF/MEK/ERK inhibitor Temsirolimus + sorafenib vs sorafenib | NA                                             | PFS OS no 4       | 63 39                                |                               |                 |               |                                       |             |

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 comparison in a trial. Lowercase letter a, b, c means different trial arm in the same study.

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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...
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; I² = 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%
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; I² = 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; I² = 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; I² = 68%, random-effects model; Fig 5), 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; I² = 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; I² = 76%, random-effects model; S1 Fig) or AKT inhibitors (OR = 2.61; 95% CI: 1.06–6.45; I² = 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; I² = 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
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].

Efficacy of PI3K/AKT/mTOR pathway inhibitors in advanced solid cancers

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.

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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 PFS-related 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
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 arms (16.7%) than in the control arms (9.8%). Serious toxicity may prevent 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 adverse event induced the study discontinue. Experimental arm included different kinds of PI3K/AKT/mTOR inhibitors. The random-effects model was used.

**S1 Table.** PRISMA checklist.

**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 comparison in a trial. Lowercase letter a, b, c means different trial arm in the same study.

**Author Contributions**

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