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The effectiveness of monotherapy with PI3K/AKT/mTOR pathway inhibitors in ovarian cancer: A meta-analysis

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HIGHLIGHTS

- Monotherapy with PI3K/AKT/mTOR inhibitors resulted in a pooled CBR of 32% and ORR of 3% in ovarian cancer patients.
- Exclusion of stable disease for a period below 6 months as a beneficial outcome measure reduced the pooled CBR to 7%.
- Drug-related grade 3 and 4 toxicities occurred in 36% (range 0–80%) of the patients.
- Current PI3K/AKT/mTOR biomarkers insufficiently predict therapy response indicating the need for improved biomarker assays.
- Combined treatments regimes targeting two signaling pathways may provide favorable outcomes over single agent therapy.

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ABSTRACT

Objective. To determine the clinical benefit of monotherapy with PI3K/AKT/mTOR inhibitors in patients diagnosed with advanced or recurrent ovarian cancer and to investigate the predictive value of current PI3K/AKT/mTOR biomarkers on therapy response.

Methods. A systematic search was conducted in PubMed, Embase and the Cochrane Library for articles reporting on treatment with PI3K/AKT/mTOR inhibitors in ovarian cancer. The primary endpoint was defined as the clinical benefit rate (CBR), including the proportion of patients with complete (CR) and partial response (PR) and stable disease (SD). Secondary endpoints included the overall response rate (ORR, including CR and PR) and drug-related grade 3 and 4 adverse events.

Results. We included 233 patients from 19 studies and observed a pooled CBR of 32% (95% CI 20–44%) and ORR of 3% (95% CI 0–6%) in advanced or recurrent ovarian cancer patients treated with PI3K/AKT/mTOR inhibitors. Subgroup analysis tended to favor the studies who selected patients based on current PI3K/AKT/mTOR biomarker criteria (e.g. genomic alterations or loss of PTEN protein expression), but the difference in CBR was not statistically significant from studies with unselected populations (respectively, CBR of 42% (95% CI 23–62%) and 27% (95% CI 14–42%), $P = 0.217$). To better reflect true patient benefit, we excluded SD <6 months as a beneficial outcome which resulted in a pooled CBR of 7% (95% CI 2–13%). The overall proportion of patients with drug-related grade 3 and 4 adverse events was 36%.

Conclusions. The efficacy of monotherapy with PI3K/AKT/mTOR inhibitors in advanced recurrent ovarian cancer patients is limited to a small subgroup and selection of patients with the use of current biomarkers did not improved the CBR significantly. Given the toxicity profile, we suggest that current treatment with PI3K/AKT/mTOR inhibitors should not be initiated unless in clinical trials. Furthermore, improved biomarkers to measure functional PI3K/AKT/mTOR pathway activity are needed to optimize patient selection.

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Contents

List of abbreviations

CBR	Clinical benefit rate
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
HER2	Human epidermal growth receptor
HRR	Homologous recombination repair
PARP	poly (ADP-ribose) polymerase
PI3K	Phosphatidylinositol-3-kinase
PIP2	Phosphatidylinositol (4, 5)-bisphosphate
PIP3	Phosphatidylinositol (3, 4, 5)-triphosphate
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PTEN	Phosphatases and tensin homolog
ROBINS-I tool	Risk Of Bias in Non-randomised Studies of Interventions
MAPK	Mitogen-activated protein kinase
MTD	Maximum-tolerated dose
mTOR	Mammalian target of rapamycin
NA	Not available
OC	Ovarian cancer
ORR	Overall response rate

1. Introduction

Ovarian cancer is the most lethal gynecological malignancy and reflects a heterogenous disease [1]. Histologically ovarian cancer can be categorized in five subtypes, namely high-grade serous, low-grade serous, endometrioid, mucinous and clear cell carcinoma [2]. First-line treatment consists predominantly of platinum-based chemotherapy and debulking surgery [1]. Despite complete remission after initial treatment, 70–80% of the patients will develop relapse of disease, which eventually becomes platinum-resistant [3]. As a result, numerous trials have been conducted to identify alternative treatment strategies. One such strategy involves inhibition of the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) growth factor signaling pathway, as this pathway is frequently activated in ovarian cancer by gain-of-function mutations and amplifications or by loss-of-function of tumor suppressor genes [4].

The PI3K/AKT/mTOR pathway is a complex signaling network which plays an essential role in survival mechanisms of the cell [5]. The pathway has many loops and branches, starting with the activation of PI3K enzymes via extracellular growth factors (Fig. 1). PI3Ks are lipid kinases including three subclasses, of which particularly class IA PI3Ks are of therapeutic importance due to frequent alterations [6]. Class IA PI3Ks consist of a regulatory (p85) and catalytic (p110) subunit [7]. The regulatory (p85) subunit of PI3K can bind and stabilize the catalytic (p110) subunit, and therefore, is functioning as an endogenous inhibitor of the pathway [4]. Isoforms of both subunits have been reported, of which the p110 isoforms result in the expression of three different genes, namely *PIK3CA*, *PIK3CB*, and *PIK3CD* [4,5]. A gain-of-function amplification or mutation in the *PIK3CA* gene, resulting in the p110α-isoform, is found in 2–20% of the high-grade serous carcinoma and 20–46% of the endometrioid, mucinous and clear cell carcinoma [4,5].

Following activation, PI3K phosphorylates phosphatidylinositol (4, 5)-bisphosphate (PIP2) to generate the second messenger phosphatidylinositol (3, 4, 5)-triphosphate (PIP3) (Fig. 1) [7]. Phosphatases and tensin homolog (PTEN) is able to dephosphorylate PIP3 and is therefore another endogenous inhibitor of the PI3K/AKT/mTOR pathway [7]. Loss-of-function mutations, deletions or silencing of the *PTEN* gene are found in 7% of the high-grade serous carcinoma and 21–45% in endometrioid and clear cell carcinoma [4,7–9]. Subsequently, PIP3 may activate AKT by specific phosphorylation to initiate several downstream effects, e.g. inhibition of apoptosis, protein synthesis, and cell growth and survival [10]. Eventually, activated AKT may directly and indirectly activate mTOR, which controls, among others, cell proliferation, metabolism, autophagy and angiogenesis [5].

Many preclinical and clinical studies have been conducted to inhibit PI3K/AKT/mTOR pathway activity with the use of targeted agents, which are classified in four categories: PI3K inhibitors, AKT inhibitors, mTOR inhibitors and dual PI3K/mTOR inhibitors (Fig. 1). Others have summarized response rates to PI3K/AKT/mTOR pathway inhibitors, either as monotherapy or in combination with other therapeutics, in advanced solid tumors [8,11–13]. However, no meta-analysis has been conducted focusing on treatment efficacy in solely ovarian cancer patients. In addition, study results have been inconclusive on the predictive value of PI3K/AKT/mTOR alterations, either defined by mutations,

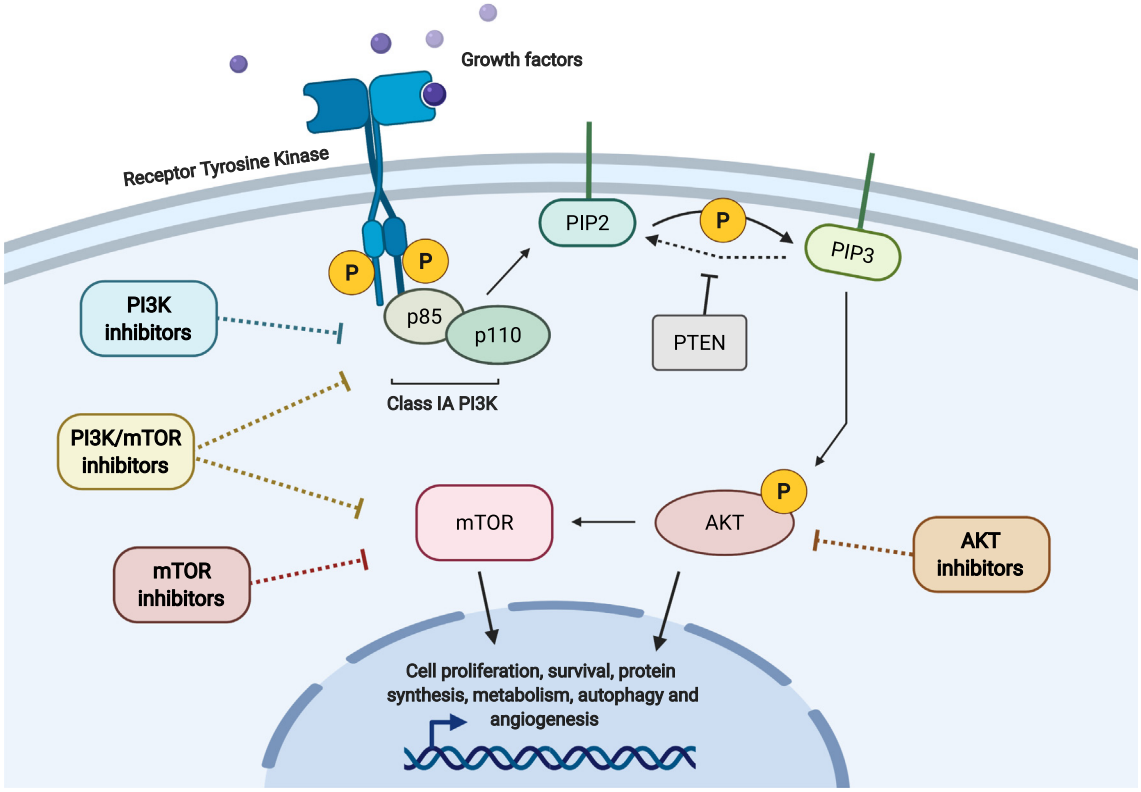

Fig. 1. Schematic overview of the major components of the PI3K/AKT/mTOR signaling pathway with different strategies for inhibition (this figure is created with BioRender.com).

amplifications or deletions by sequencing analysis or by loss of PTEN protein expression by immunohistochemistry [8,11,12]. Therefore, in this meta-analysis, we will focus on the effects of monotherapy with PI3K/AKT/mTOR inhibitors and aim to determine the clinical benefit rate, defined as complete and partial response and stable disease, in patients diagnosed with advanced or recurrent ovarian cancer. Furthermore, we aim to investigate the predictive value of current PI3K/AKT/mTOR biomarkers on therapy response by subgroup analysis of clinical benefit in studies selecting patients based on PI3K/AKT/mTOR biomarker criteria and studies with unselected populations.

2. Methods

2.1. Protocol and registration

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [14]. A study protocol was published at Prospero International prospective register of systematic reviews (CRD42020164469) [15].

2.2. Eligibility criteria

Studies were eligible for inclusion when reporting on treatment with monotherapy of PI3K/AKT/mTOR inhibitors in women with advanced or recurrent ovarian cancer. We focused on the use of drugs directly targeting the PI3K/AKT/mTOR components and excluded the use of human epidermal growth receptor (HER2) inhibitors. Phase I, II and III clinical trials, randomised controlled trials, prospective and retrospective cohort studies and case series were eligible for inclusion. To be included in the meta-analysis, study populations should at least consist of five ovarian cancer patients. Systematic reviews and meta-analysis were carefully screened for additional inclusions of individual studies. A language restriction for English was applied.

2.3. Literature search

Studies were retrieved by a literature search in the electronic databases; PubMed, Embase via Ovid and the Cochrane Library. The search consisted of free terms (several synonyms) and Mesh terms for "ovarian cancer" and "PI3K/AKT/mTOR inhibitors" and "PI3K/AKT/mTOR proteins". An example of the full search strategy is provided in Supplementary material 1. We restricted the literature search to studies published during the last 10 years (from 2010 to present). The databases were searched on January 10, 2020 and the last search was conducted on January 6, 2021.

2.4. Study selection

Titles and abstracts were independently screened by two reviewers (AU and PvdP) based on pre-defined exclusion criteria. Next, both reviewers (AU and PvdP) conducted eligibility assessment of the full-text articles. In case of disagreement, a third author was consulted (JMJP). Reasons for exclusion were documented. Authors were contacted to obtain additional data if clinical response data was not presented separately for ovarian cancer patients (for example if multiple types of cancers were included in the study).

2.5. Data extraction

For the included studies, study characteristics and outcome data were extracted according to a pre-defined data extraction template

(Supplementary materials 2). The primary outcome of this meta-analysis was clinical benefit rate (CBR) defined as the proportion of patients with best overall response of complete response (CR), partial response (PR) or stable disease (SD), as defined by RECIST 1.1 or GCIG criteria [16]. We selected this primary outcome measure over progression-free survival to allow for the inclusion of phase I clinical trials, in which antitumor activity is often defined by response rates rather than progression-free survival. Additional outcomes were overall response rate (ORR) defined as the proportion of patients with CR or PR defined by RECIST 1.1 or GCIG criteria and the proportion of patients experiencing drug-related grade 4 and 5 adverse event according to the Common Terminology Criteria for Adverse Events (CTCAE) [17].

2.6. Bias screening

The risk of bias was assessed independently by two reviewers (AU and PvdP) via the ROBINS-I tool (Risk Of Bias in Non-randomised Studies of Interventions) [18]. Any disagreements were resolved by consulting a third reviewer (JMJP). Risk of bias was judged as low, high or unclear risk for seven predefined domains of bias: confounding, selection of participants, description of intervention, deviation from intervention, missing data, measurements of outcome and selective reporting. The ROBINS-I tool requires the establishment of a 'hypothetical target trial', which we defined as a phase II or III clinical trial investigating PI3K/AKT/mTOR monotherapy in ovarian cancer patients either with or without evidence of PI3K/AKT/mTOR pathway dysregulation. The trial should meet the following requirements: 1. baseline information should include number of prior lines of treatment and histological subtype, 2. a detailed description of the selection process and the intervention, 3. deviations from intended intervention and missing data should concern ≤25% of the population and 4. therapy response should be measured by RECIST 1.1 or GCIG criteria at standardized time points. Finally, the overall risk of bias of the seven domains was considered low if none of the domains was judged as high risk of bias, moderate if one or two domains were judged as high risk of bias and high if three or more domains were judged as high risk of bias.

2.7. Statistical analysis

Meta-analysis and subgroup analysis were performed using a random-effect model with the DerSimonian-Laird estimator for between study variance τ^2 to estimate the pooled proportion of patients with clinical benefit with 95% confidence intervals (CI). To assess for heterogeneity across the included studies I^2 values of 25%, 50% and 75% were considered to indicate, respectively, low, moderate and high heterogeneity. The Freeman-Tukey Double arcsine transformation was applied to stabilize the variance of the proportions of individual studies. Confidence intervals of individual studies were estimated using the Clopper-Pearson method and Jackson method was used for the confidence intervals of τ^2. Funnel plots with Egger's tests for asymmetry were created to assess for publication bias. Additionally, a leave-one-out sensitivity analysis was conducted to investigate the influence of outliers. Statistical analysis was conducted using the 'metaprop' command of the 'meta' package in R, version 3.5.2. (Rstudio Inc.) [19].

3. Results

3.1. Study selection

We identified 2538 records through database and reference searching, of which 164 duplicates were removed (Fig. 2). Subsequent title and abstract screening resulted in the exclusion of 2117 records. After full-text screening of the remaining 257 records, we excluded an additional 238 records based on: the use of combination therapy with other targeted agents or chemotherapy (131 records); the inclusion of less than five ovarian cancer patients (58 records); the publication of a conference abstract without availability of a full-text article (17 records); the publication of a conference abstract of which the full-text article already was included (14 records); an ongoing clinical trial (four records); an unknown number of ovarian cancer patients treated with a PI3K/AKT/mTOR inhibitor (four records); the inclusion of an unknown number of ovarian cancer patients (two records); absence of the primary outcome measure (two records) and population without ovarian cancer patients (two records). In total, 23 studies complied with the inclusion criteria. However, several of the included studies did not specify therapy response for ovarian cancer patients, for which we contacted the authors to retrieve additional data. Eventually, we were unable to obtain sufficient response data of the ovarian cancer patients of four studies [20–23], resulting in the inclusion of 19 studies to conduct the meta-analysis [24–42].

3.2. Study characteristics

The included studies involved a total of 233 ovarian cancer patients. The sample size of individual studies ranged from five to 54 ovarian cancer patients treated with PI3K/AKT/mTOR inhibitors (Table 1) [24–42]. Nine phase I and six phase II studies were included, as well as one phase I/IIA study. In addition, one case report on six clear cell carcinoma patients [37] and two studies aiming to implement molecular profiling were included [30,38]. Four studies assessed the effect of PI3K inhibitors in a total of 40 patients [28,29,33,34], whereas five studies assessed the response to AKT inhibitors in a total of 61 patients [26,27,31,41,42]. The response to mTOR inhibitors was investigated in five studies including 100 patients [24,25,30,37,39], four studies assessed the effect of PI3K/mTOR inhibitors in a total of 24 patients [32,35,36,40], and one study including 8 patients assessed both AKT and mTOR inhibitors based on their molecular profile [38]. Almost all studies assessed a different type of PI3K/AKT/mTOR inhibitor, with the exception of the mTOR inhibitors temsirolimus (used in three studies) and everolimus (used in two studies) and the AKT inhibitors MK-2206 and uprosertib (both used in two studies).

3.3. Risk of bias assessment

Studies were subjected to a comprehensive quality assessment for the risk of bias on seven predefined domains. In case studies included populations consisting of different advanced solid malignancies, bias domains were applied to the study as a whole. A detailed description of the reviewers' judgements of each bias domain can be found in Supplementary material 3 and data is summarized in Table S1. The combined risk of bias assessment of the seven predefined domains is reported in Table 1.

3.4. Effectiveness of PI3K/AKT/mTOR inhibitors in ovarian cancer

Our meta-analysis revealed that treatment with PI3K/AKT/mTOR inhibitors was associated with a pooled CBR of 32% (95% CI 20–44%) in ovarian cancer patients, with moderate to high between-study heterogeneity ($I^2 = 64\%$) (Fig. 3). Consistently low response rates were observed across all studies. Although several patients achieved a PR, none of the included studies reported on complete tumor regression in ovarian cancer patients. With regard to the ORR to PI3K/AKT/mTOR inhibitors, our meta-analysis revealed a pooled ORR of 3% (95% CI 0–6%), with low between-study heterogeneity ($I^2 = 0\%$) (Fig. 4).

Subgroup analysis by type of inhibitor showed that treatment with PI3K inhibitors was associated with the highest pooled CBR of 48% (95% CI 22–75%, $I^2 = 61\%$), but this was not statistically significant from the results of other subgroups ($P = 0.331$) (Fig. 3). For mTOR inhibitors we observed a pooled CBR of 42% (95% CI 32–52%, $I^2 = 0\%$), and treatment with dual PI3K/mTOR inhibitors resulted in a pooled CBR of 30% (95% CI 1–72%, $I^2 = 72\%$). Treatment with AKT inhibitors resulted in the lowest pooled CBR of 18% (95% CI 3–41%, $I^2 = 69\%$).

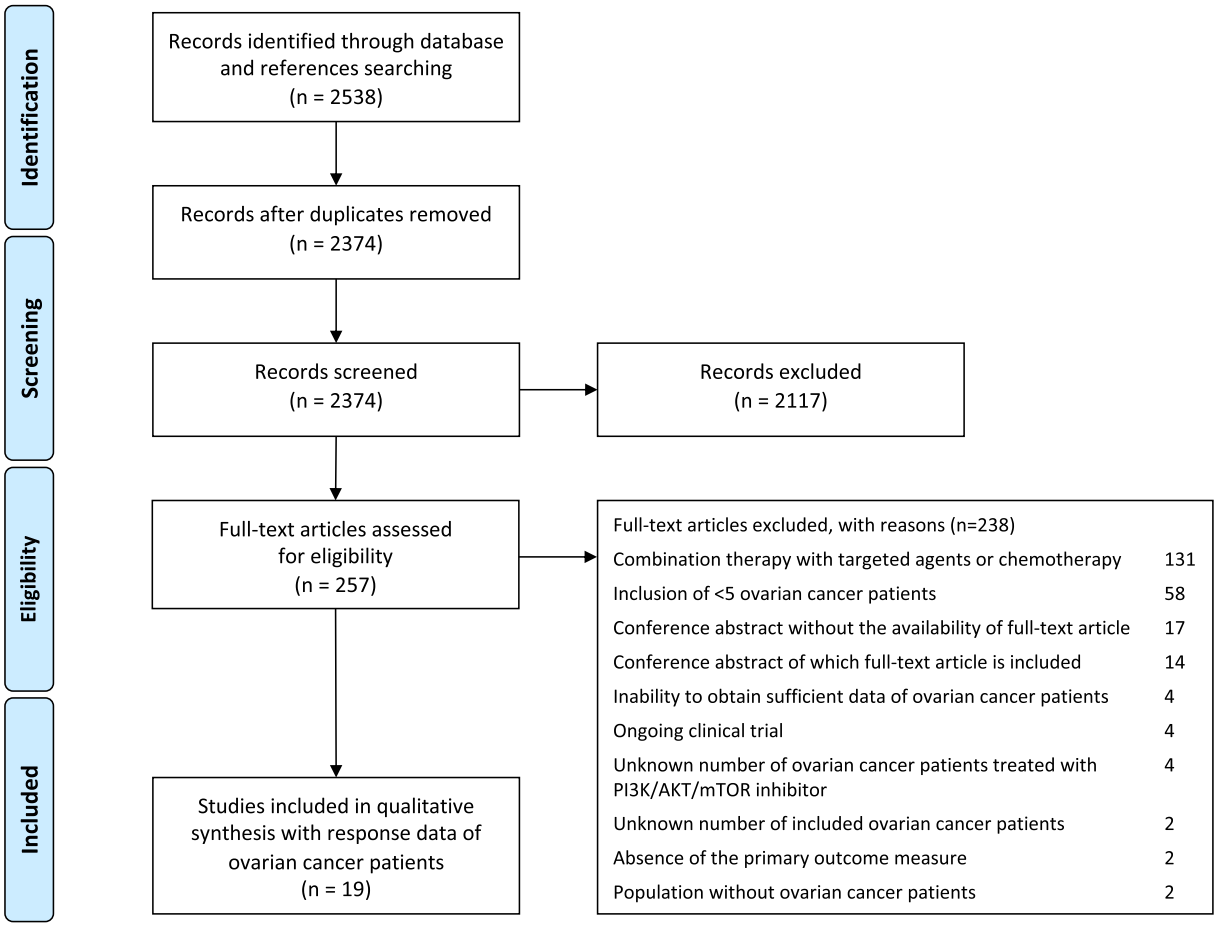

Fig. 2. PRISMA flow chart of the identified studies and the selection procedure of the included studies.

Analysis of ORR per type of inhibitor favored mTOR inhibitors with a pooled ORR of 5% (95% CI 1–11%, $I^2 = 0\%$), but this not statistically significant from the ORR of other subgroups ($P = 0.381$) (Fig. 4). For the other types of inhibitors consistent pooled ORRs were observed, namely 1% for PI3K inhibitors (95% CI 0–9%, $I^2 = 0\%$), 1% for AKT inhibitors (95% CI 0–7%, $I^2 = 0\%$) and 1% for PI3K/mTOR inhibitors (95% CI 0–14%, $I^2 = 0\%$). The study of Varnier et al. assessed both AKT and mTOR inhibitors and observed two PRs (one for both type of inhibitor) resulting in an ORR of 25% (95% CI 3–65%).

Additionally, we assessed whether small studies with small response rates were missing in our analysis. Evaluation of funnel plots for the CBR and ORR meta-analysis and analysis with Egger's tests for asymmetry did not indicate obvious publication bias (Fig. S1). Finally, we performed a sensitivity analysis based on the leave-one-out method to detect if one of the studies distorted the pooled effect. The analysis indicated two studies with high contribution to the overall heterogeneity in the CBR meta-analysis; Juric et al. and Yap et al. [29,41]. Recalculating the pooled CBR by omitting these studies resulted in a minimal pooled CBR of 28% (95% CI 18–40%, $I^2 = 56\%$) by removing Juric et al. and a maximal pooled CBR of 35% (95% CI 25–46%, $I^2 = 51\%$) by removing Yap et al. (Fig. S2) [29,41]. The leave-one-out method resulted in minimal change in pooled ORR (minimal 2%, maximal 3%).

Our meta-analysis showed that best overall response was most often defined as SD. Therefore, in terms of the CBR, the effectiveness of PI3K/AKT/mTOR inhibitors can almost completely be attributed to disease stabilization. Although SD is a valuable outcome in the advanced and recurrent disease setting, the duration of disease stabilization is of particular importance to assess meaningful clinical benefit. Therefore, we categorized SD based on the duration of <6 months or ≥6 months. Within the group of patients with a best overall response evaluation of SD ($n = 71$), progression of disease primarily occurred within 6 months after the start of therapy. To assess a better reflection of true patient benefit, we revised the pooled CBR with a longer-term measure of SD. Therefore, we excluded SD for <6 months as outcome measure from the CBR, resulting in the inclusion of PR and SD for ≥6 months. The revised analysis demonstrated a pooled CBR of 7% (95% CI 2–13%, $I^2 = 21\%$) (Fig. S3).

3.5. Effectiveness of patient selection based on current PI3K/AKT/mTOR biomarker criteria

In seven of the 19 included studies, patients were selected based on evidence of dysregulation of the PI3K/AKT/mTOR pathway ($n = 60$) [29–31,33,34,36,38]. In these studies, enrollment depended on biomarker criteria of activating genomic PI3K/AKT/mTOR alterations (e.g. mutations, amplifications or deletions) and/or loss of PTEN expression by immunohistochemistry. In addition, six studies did not apply biomarker criteria for patient selection but did performed the above-mentioned PI3K/AKT/mTOR molecular assessment during the study period, resulting in mixed populations with ($n = 20$) and without ($n = 44$) evidence of dysregulation of the PI3K/AKT/mTOR pathway [26–28,35,40,42]. Of the remaining six studies who did not apply biomarker criteria, four studies ($n = 82$) conducted immunohistochemical biomarker analysis of other downstream PI3K/AKT/mTOR proteins for instance phosphorylated-AKT [24,32,39,41], and two studies ($n = 27$) did not conduct any PI3K/AKT/mTOR molecular assessments [25,37]. Overall, studies allowed the use of both archived tumor tissue and recently taken biopsies for PI3K/AKT/mTOR molecular assessments. An

Table 1
Study characteristics, outcome data and overall risk of bias assessment of studies reporting on monotherapy with PI3K/AKT/mTOR inhibitors in ovarian cancer patients.

Study	Phase	OC patients treated (n)	Total patients treated (n)	Tumor histology	Type of treatment	CR (%)	PR (%)	SD <6 months (%)	SD ≥6 months (%)	Not evaluable OC patients (%)	ORR (%)	CBR (%)	Drug-related grade 3 and 4 adverse events according to CTCAE (total population)	Overall risk of bias assessment
PI3K inhibitors														
Piha-Paul et al. 2019 [34]	II	12	146	*N.A.*	Buparlisib	0	0	8	17	17	0	25	82% (all cause)	Moderate
Juric et al. 2018 [29]	IA	14	134	*N.A.*	Alpelisib	0	7	64	7	14	7	79	44%	High
Juric et al. 2017 [28]	I	9	71	*N.A.*	Serabelisib	0	0	22	22	*N.A.*	0	44	27%	Moderate
Mateo et al. 2017[a] [33]	I/IIA	5	65	*N.A.*	GSK2636771	0	0	40	0	0	0	40	23%	Moderate
AKT inhibitors														
Lee et al. 2020 [31]	II	6	6	6 HGSC (all platinum-resistant)	MK-2206	0	0	50	17	20	0	67	80%	Low
Aghajanian et al. 2018 [42]	I	9	77	*N.A.*	Uprosertib	0	11	0	0	11	11	11	$n = 22$[b] (all cause)	Low
Hasegawa et al. 2017[a] [27]	II	21	71	7 serous, 11 clear cell, 1 endometrioid, 1 mucinous, 1 unknown	Perifosine	0	0	19	0	14	0	19	$n = 47$[b] (all cause)	Low
Gungor et al. 2015 [26]	I	11	12	8 serous, 1 endometrioid, 1 clear cell, 1 unknown (all platinum-resistant)	Uprosertib	0	9	0	18	0	9	27	17%	Moderate
Yap et al. 2015[a] [41]	I	14	71	*N.A.*	MK-2206	0	0	0	0	*N.A.*	0	0	$n = 12$[b]	Low
mTOR inhibitors														
Voss et al. 2020[a] [39]	I	9	198	*N.A.*	Sapanisertib	0	0	22	0	*N.A.*	0	22	44%	Moderate
Emons et al. 2016 [25]	II	21	44	17 serous, 4 unknown (all platinum-resistant)	Temsirolimus	0	5	33[c]		14	5	38	98% (all cause)	Low
Le Tourneau et al. 2015[a] [30]	II	10	46	10 adenocarcinoma unspecified	Everolimus	0	0	30	0	40	0	30	*N.A.*	Moderate
Behbakht et al. 2011 [24]	II	54	54	39 serous, 8 adenocarcinoma unspecified, 4 endometrioid, 3 clear cell	Temsirolimus	0	9	41[c]		11	9	50	$n = 44$[b] (all cause)	Moderate
Takano et al. 2011 [37]	Case series	6	6	6 clear cell	Temsirolimus	0	17	17	0	0	17	33	0%	Moderate
PI3K/mTOR inhibitors														
Rodon et al. 2018[a] [35]	I/IB	8	183	*N.A.*	Dactolisib	0	0	0	0	0	0	0	44% (all cause)	Moderate
Wicki et al. 2018 [40]	I	6	28	*N.A.*	Bimiralisib	0	0	67	0	17	0	67	57%	Moderate
Shapiro et al. 2015[a] [36]	I	5	77	1 granulosa cell tumor, 1 endometrioid, 3 unknown	Gedatolisib	0	20	0	0	60	20	20	29%	Moderate
Mahadevan et al. 2012 [32]	I	5	44	5 adenocarcinoma unspecified	SF1126	0	0	40	20	*N.A.*	0	60	11%	Moderate
Combination study with AKT and mTOR inhibitors														
Varnier et al. 2017 [38]	Prospective cohort study	8	39	6 serous, 1 endometrioid, 1 germ cell tumor	LY2780301 or everolimus	0	25	0	0	0	25	25	*N.A.*	Moderate

Aberrations: OC, ovarian cancer; CR, complete response; PR, partial response; SD, stable disease; ORR, overall response rate; CBR, clinical benefit rate; CTCAE, Common Terminology Criteria for Adverse Events, PI3K, phosphatidylinositol-3-kinase; N.A., data not available; HGSC, high grade serous carcinoma; mTOR, mammalian target of rapamycin; MTD, maximum-tolerated dose.

[a] We received additional information from these authors on therapy response rates in ovarian cancer patients.

[b] Number of adverse events counted. Possibility that multiple adverse events occurred in the same patients and patients are therefore counted more than once.

[c] For these studies it was not possible to distinguish between SD < or ≥6 months. These studies results were excluded from the revised analysis of the pooled CBR (Fig. S3).

overview of the number of patients with evidence of dysregulation of the PI3K/AKT/mTOR pathway and the type of analysis used for molecular assessment is provided in Table S2.

We performed subgroup analysis to assess the predictive value of current PI3K/AKT/mTOR biomarkers (e.g. mutations, amplifications or loss of PTEN function by immunohistochemistry) on the effectiveness of PI3K/AKT/mTOR inhibitors. We stratified the studies into two groups; A. studies selecting patients based on PI3K/AKT/mTOR biomarker criteria and therefore including solely patients with evidence of dysregulation of the PI3K/AKT/mTOR pathway ($n = 60$), and B. studies who did not select patients based on biomarker criteria, resulting in mixed populations with and without dysregulated PI3K/AKT/mTOR pathway activity ($n = 173$). We observed a trend towards a better pooled CBR in studies selecting patients based on PI3K/AKT/mTOR biomarker criteria (CBR of 42%, 95% CI 23–62%, $I^2 = 51\%$) compared to studies who did not apply biomarker criteria for patient selection (CBR of 27%, 95% CI 14–42%, $I^2 = 69\%$), however, this difference was not significant ($P = 0.217$) (Fig. 5). For pooled ORR, there was no difference between the two groups (Fig. S4).

3.6. Grade 3 and 4 adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE)

Unless otherwise stated, the proportion of patients with drug-related grade 3 and 4 adverse events is reported in Table 1. Most of the included studies reported on treatment with PI3K/AKT/mTOR

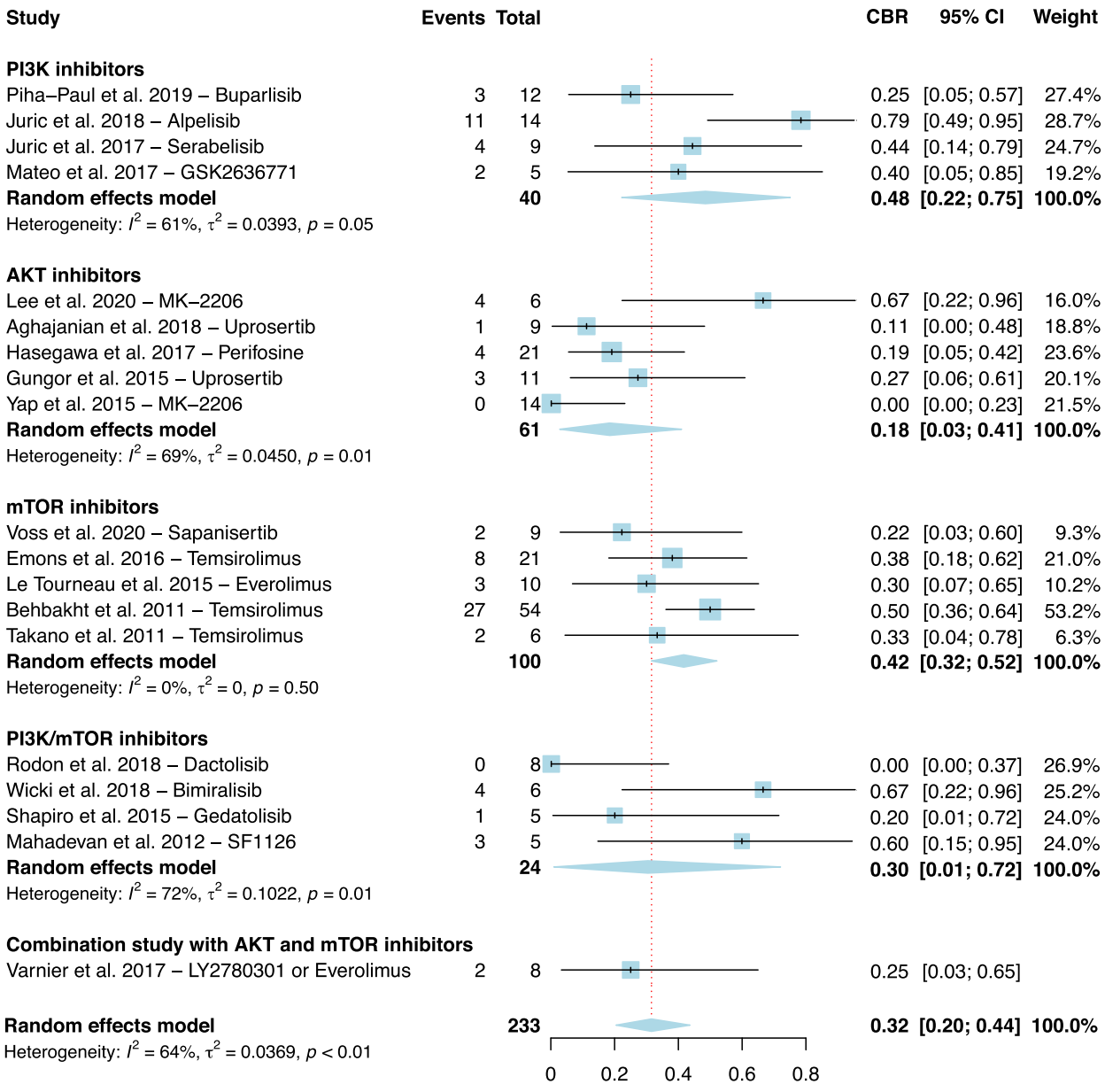

Fig. 3. Forest plot of the association between treatment with PI3K/AKT/mTOR inhibitors and clinical benefit rate (CBR) in ovarian cancer patients. CBR is defined as the proportion of patients with best overall response of complete or partial response or stable disease (both <6 and ≥6 months). The blue squares and black bars represent the CBR with 95% confidence interval (CI) of individual studies. The pooled CBR with 95% CI by type of inhibitor is represented by the blue diamonds. The final blue diamond indicates the pooled CBR with 95% CI of all studies. PI3K, phosphatidylinositol-3-kinase; mTOR, mammalian target of rapamycin.

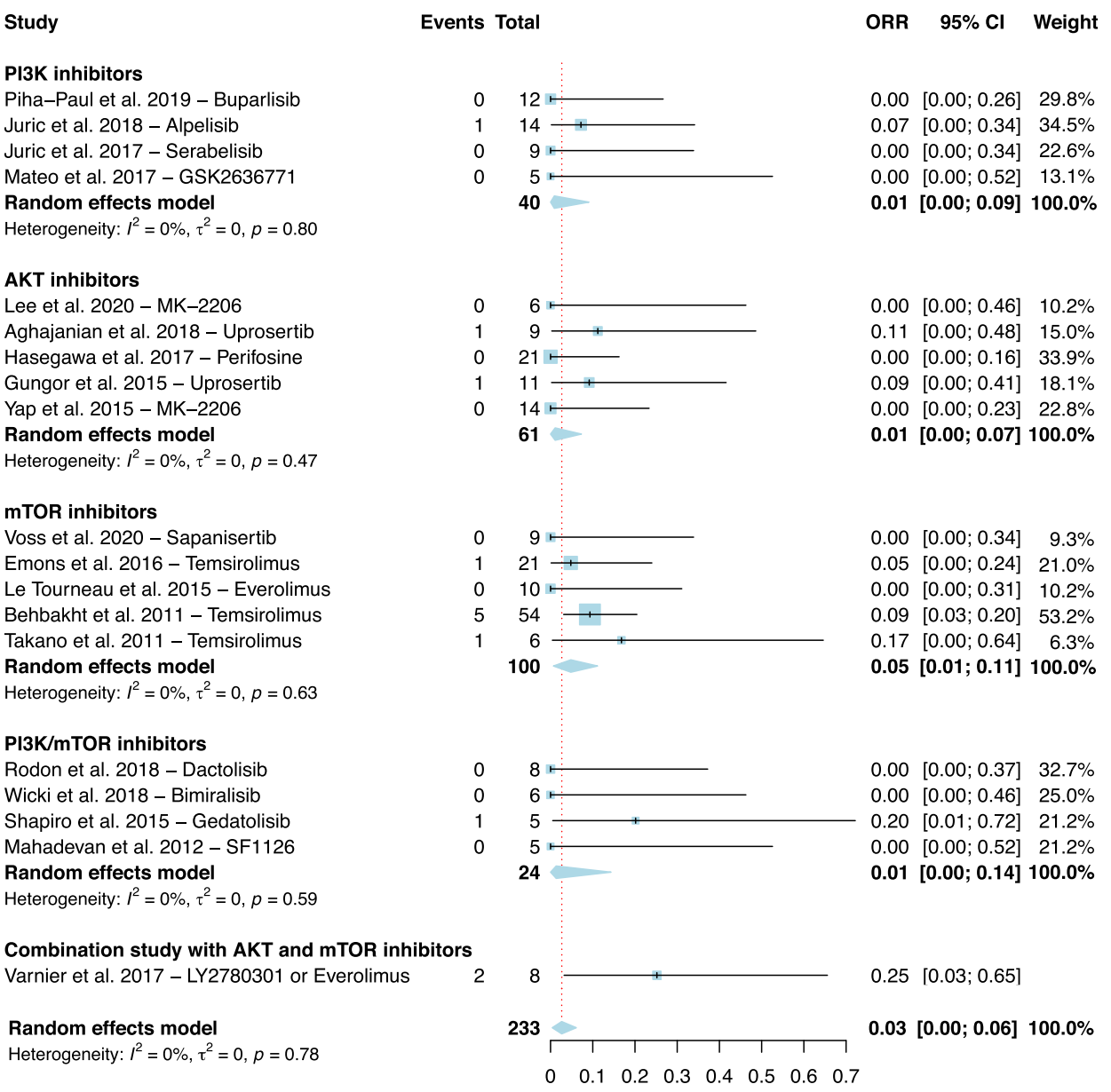

Fig. 4. Forest plot of the association between treatment with PI3K/AKT/mTOR inhibitors and overall response rate (ORR) in ovarian cancer patients. ORR is defined as the proportion of patients with best overall response of complete or partial response. The blue squares and black bars represent the ORR with 95% confidence interval (CI) of individual studies. The pooled ORR with 95% CI by type of inhibitor is represented by the blue diamonds. The final blue diamond indicates the pooled ORR with 95% CI of all studies. PI3K, phosphatidylinositol-3-kinase; mTOR, mammalian target of rapamycin.

inhibitors in populations including different advanced solid malignancies and did not specify incidence rates of adverse events per tumor type. Therefore, we reported the proportion of the total study population in Table 1. For several studies we reported the number of grade 3 or 4 adverse events counted as studies lacked information on the total proportion. In total, drug-related grade 3 or 4 adverse events occurred in 36% of the treated patients (229 of 641 patients (range 0–80%), excluding the studies reporting on all-cause adverse events and counted events). Whereby the case series of Takano et al. reported no grade 3 and 4 adverse events in their ovarian cancer population [37]. It must be noted that, due the retrospective nature of the case series, reporting bias may have distorted the documentation of adverse events. Table S3 provides additional information on the proportion of patients with all cause grade 3 and 4 adverse events, as well as the most frequently reported grade 3 and 4 adverse events, number of dose-interruptions and -reductions and number of patients with treatment discontinuation due to adverse events. Most common grade 3 and 4 adverse events included hyperglycemia, elevated liver enzymes and gastro-intestinal complaints (e.g. diarrhea, nausea, vomiting and stomatitis). The high incidence of adverse events may have resulted in suboptimal dosing in a substantial proportion of the patients. Dose-interruptions and -reductions were required in 2–62% of the patients and in 2–25% adverse events lead to early discontinuation of treatment.

4. Discussion

Our meta-analysis includes 233 patients from 19 studies and indicates that targeted therapy with PI3K/AKT/mTOR inhibitors is

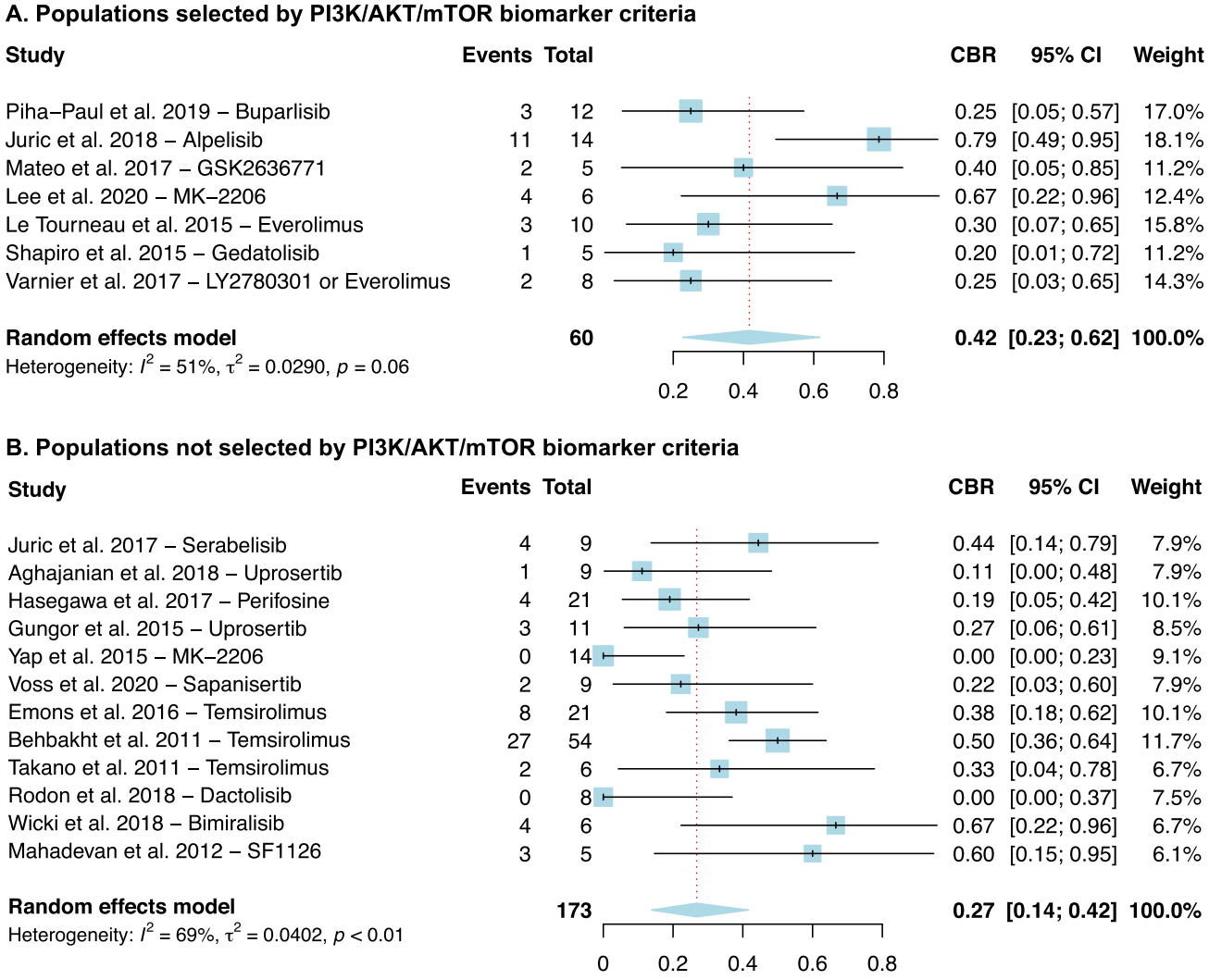

Fig. 5. Forest plot of the association between PI3K/AKT/mTOR inhibitors and clinical benefit rate (CBR) by dysregulation of PI3K/AKT/mTOR pathway activity in ovarian cancer patients. CBR is defined as the proportion of patients with best overall response of complete or partial response or stable disease. The blue squares and black bars represent the CBR with 95% confidence interval (CI) of individual studies. The pooled CBR with 95% CI per group is represented by the blue diamonds. A. Populations selected by PI3K/AKT/mTOR biomarker criteria. B. Populations not selected by PI3K/AKT/mTOR biomarker criteria. PI3K, phosphatidylinositol-3-kinase; mTOR, mammalian target of rapamycin.

associated with a pooled CBR of 32% (95% CI 20–44%) and a pooled ORR of 3% (95% CI 0–6%) in advanced or recurrent ovarian cancer patients. Dysregulation of the PI3K/AKT/mTOR pathway is considered to be one of the hallmarks of cancer development and alterations in genes associated with this pathway are commonly found in ovarian cancer. Alterations are assumed to mediate hyperactivation of the PI3K/AKT/mTOR pathway, supporting the hypothesis that targeting this signaling pathway might represent a useful treatment strategy. As a result, several PI3K/AKT/mTOR inhibitors have been developed for the treatment of cancer over the past years. To the best of our knowledge, this is the first meta-analysis investigating the effectiveness of these inhibitors solely in ovarian cancer patients.

The CBR may be criticized as outcome measure due to the inclusion of SD without any consideration of the duration of response. In order to better reflect patient benefit, we revised the pooled CBR by the exclusion of SD for <6 months as a beneficial outcome. This resulted in a pooled CBR of 7% (95% CI 2–13%, I^2 = 21%). Furthermore, in 36% of the patients (range 0–80%), treatment with PI3K/AKT/mTOR inhibitors was associated with drug-related grade 3 and 4 adverse events, including hyperglycemia, gastro-intestinal complaints and elevated liver enzymes. The incidence of severe toxicities further contributes to unsatisfactory results, which in combination with the limited clinical benefit suggests that current treatment with PI3K/AKT/mTOR inhibitors should not be initiated unless in clinical trials aimed to identify those patients who benefit from this treatment.

Overall, we observed a wide variety in efficacy among the different types of inhibitors. Our subgroup analysis tended to favor the effectiveness of PI3K and mTOR inhibitors over AKT and dual PI3K/mTOR inhibitors, but this difference was not statistically significant. Within the mTOR subgroup, a substantial proportion of the effectiveness could be attributed to temsirolimus, as the inhibitor was investigated in three individual studies. Although the intravenous administration of temsirolimus could have improved bioavailability, the highest CBR was observed in the pooled group of orally administrated PI3K inhibitors. The PI3K component of the signaling pathway is most frequently altered, which might explain the slightly improved CBR as compared to the other types of inhibitors [5,10]. In comparison, limited clinical benefit was achieved with AKT inhibitors, the component in which mutations are rare [5,10]. Potentially, dual PI3K/mTOR inhibitors could exert more inhibitory effects over single PI3K or mTOR inhibitors [43].

In case tumors harbor both PI3K and mTOR alterations, dual inhibitors have the opportunity to suppress pathway activity at both levels. In addition, simultaneous inhibition of mTOR may overcome potential mechanisms of adaptive resistance to PI3K inhibitors [44,45]. However, our results do not confirm this hypothesis as dual PI3K/mTOR inhibitors were not found to have superior efficacy over the other types of inhibitors.

Furthermore, we assessed the potential role of patient selection by current PI3K/AKT/mTOR biomarkers based on sequencing or immunohistochemical analysis (e.g. mutations, amplifications or loss of PTEN function) as a marker for sensitivity to PI3K/AKT/mTOR inhibitors. Subgroup analysis showed a trend towards an improved CBR in studies including patients solely with evidence of PI3K/AKT/mTOR pathway dysregulation compared to studies who did not apply biomarker criteria for patient selection, but this difference was not significant (respectively, pooled CBR of 42% and 27%, $p = 0.217$). The lack of support regarding the predictive value of current PI3K/AKT/mTOR biomarkers (most frequently *PIK3CA*, *PIK3R1* and *AKT2* genes and PTEN protein expression) to select responding patients might be explained by the heterogeneity of analysis techniques used, including next-generation sequencing and immunohistochemistry. A recent study by Sieuwerts et al. measured functional activity of the PI3K pathway based on mRNA expression levels of pathway-specific target genes, in addition to genomic mutation analysis, in ER positive breast cancer samples using a novel assay technology [46]. In contrast to genomic mutations, functional PI3K pathway activity was associated with shorter progression-free survival in metastatic patients treated with tamoxifen. In addition, their findings demonstrated that functional PI3K pathway activity did not correlate to *PIK3CA* mutation status, indicating that the activation state of a signaling pathway cannot simply be inferred from genomic alterations [46]. Moreover, in addition to genomic alterations, the functional phenotype of tumor cells is affected by epigenetic modifications and influenced by the tumor microenvironment. This is a possible explanation for the lack of support for a relation between genomic alterations or loss of protein expression and activity of the corresponding pathway and the limited predictive value of current biomarkers on the efficacy of pathway inhibitors. In the search for an alternative biomarker, the focus on transcriptional activation of the PI3K/AKT/mTOR pathway may provide useful information to guide patient selection for targeted therapy. Furthermore, most studies used archived tumor tissue of the primary tumor or a previous recurrence for biomarker analysis rather than recently taken biopsies of the recurrent tumor. Treatment with PI3K/AKT/mTOR inhibitors was often preceded by prior treatment regimens for multiple recurrences. The use of archived material from the primary tumor or a previous recurrence may have precluded the detection of alterations that have emerged during tumor evolution. Both platinum-based chemotherapeutics and changes in the tumor associated with recurrence have been shown to increase genetic heterogeneity in ovarian cancer [47,48]. In addition, previous research in breast cancer patients revealed substantial discordance in PTEN protein expression and *PIK3CA* mutations between primary disease and metastases [49]. Therefore, assessment of alteration status in recently taken tumor tissue might provide more useful information for therapy selection.

The PI3K/AKT/mTOR signaling pathway does not exert its function independently, as crosstalk with other signaling pathways, such as the poly (ADP-ribose) polymerase (PARP) and mitogen-activated protein kinase (MAPK) pathways, has been described [12,50]. Preclinical work has shown that PI3K-inhibitors can sensitize tumors to PARP-inhibitors via downregulation of *BRCA 1/2* genes, abrogation of intrinsic or acquired homologous recombination repair (HRR) proficiency and DNA damage [51]. In addition, previous clinical studies indicated potential mechanistic synergy of combined therapy. Konstantinopoulos et al. performed a phase IB trial in which PARP-inhibitor olaparib was combined with p110α-isoform-specific PI3K inhibitor alpelisib in 30 patients with epithelial ovarian cancer [51]. Their preliminary results are promising, with 10 patients (36%) having a RECIST 1.1 PR and 14 (50%) SD, of which eight patients had SD lasting ≥6 months. The toxicity profile was acceptable and further follow-up of patients who completed treatment is still ongoing. Furthermore, a recent study by Bardia et al. combined MEK-inhibitor binimetinib with pan-PI3K inhibitor buparlisib in a phase IB trial [52]. The expansion phase included different types of tumors, including 18 patients with *RAS*- or *BRAF*-mutant advanced ovarian cancer. The best responses were observed in this subgroup with a CBR of 61% (95% CI 36–83%), with six patients showing a PR. However, continuous dosing beyond the dose-limiting toxicity period with buparlisib was not feasible due to unacceptable toxicity. Similarly, a trial by Matulonis et al. in which olaparib and buparlisib were administered to recurrent ovarian and breast cancer patients, could not achieve meaningful dose-escalation of buparlisib due to unacceptable central nervous system toxicity and grade 3 transaminase elevation [53]. This indicates that treatment with p110α-isoform-specific inhibitors such as alpelisib with a favorable toxicity profile might be preferable in combination strategies over pan-PI3K inhibitors such as buparlisib. On the other hand, combination regimens may benefit from lower or intermittent dosing schedules to improve long-term tolerability on the premise that optimal pathway inhibition is sustained. In the near future, new drugs targeting the PI3K/AKT/mTOR signaling pathway might be developed by using bioinformatic analysis using tools such as String database [54].

The strength of this meta-analysis is the comprehensive review of the existing evidence on the effectiveness of PI3K/AKT/mTOR inhibitors in advanced or recurrent ovarian cancer, including subpopulations of larger studies with different advanced solid tumors. However, this resulted in a relatively small number of included ovarian cancer patients, which could have caused selection bias. Our meta-analysis is further limited by large heterogeneity in study designs. In comparison to the fixed drug dosage in phase II studies, phase I dose-escalation studies used a variety of dosages and schedules to obtain the maximum-tolerated dose, resulting in within-study bias. In addition, heterogeneity in histological subtype could have distorted therapy efficacy as genomic alterations are more common in endometrioid and clear cell carcinoma as compared to high-grade serous carcinoma [8].

Taken together, our findings demonstrate limited to no efficacy of monotherapy with PI3K/AKT/mTOR inhibitors in advanced or recurrent ovarian cancer patients. Best overall response was often defined by disease stabilization lasting for a short period of time (<6 months). Although SD is a valuable outcome in this highly pretreated population, the short duration of response may be insufficient to qualify as true patient benefit. Moreover, clinical evidence that current biomarkers are properly predicting response to pathway inhibitors is lacking. Given the overall toxicity rate of 36% grade 3 or 4 adverse events, we suggest that PI3K/AKT/mTOR inhibitors should only be used within clinical studies, preferably in combination with other targeted drugs, in a highly selected population based on reliable biomarkers that measure functional activity of the PI3K/AKT/mTOR pathway.

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Author's contribution

PvdP, AU and JMJ were involved in conceptualization of the study, developing the protocol, study selection and bias screening. PvdP and AU performed data extraction, data analysis and drafted the manuscript. AMJT, HMW, IAB, SL, AvdS, RLMB and JMJP participated in critical discussions and manuscript editing. All authors approved the submitted version of the manuscript.

Declaration of Competing Interest

PvdP is employed by Catharina Hospital, where her research work is co-funded by the Catharina research fund, and Molecular Pathway Dx, Philips. AvdS is employed by Molecular Pathway Dx, Philips. The other authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.07.008.

References

[1] C.G. Smith, A resident's perspective of ovarian cancer, Diagnostics (Basel) 7 (2017) 24.
[2] S.I. Labidi-Galy, E. Papp, D. Hallberg, N. Niknafs, V. Adleff, M. Noe, et al., High grade serous ovarian carcinomas originate in the fallopian tube, Nat. Commun. 8 (2017) 1093.
[3] A. du Bois, A. Reuss, E. Pujade-Lauraine, P. Harter, I. Ray-Coquard, J. Pfisterer, Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO), Cancer. 115 (2009) 1234–1244.
[4] B. Cheaib, A. Auguste, A. Leary, The PI3K/Akt/mTOR pathway in ovarian cancer: therapeutic opportunities and challenges, Chin. J. Cancer 34 (2015) 4–16.
[5] M.K. Ediriweera, K.H. Tennekoon, S.R. Samarakoon, Role of the PI3K/AKT/mTOR signaling pathway in ovarian cancer: biological and therapeutic significance, Semin. Cancer Biol. 59 (2019) 147–160.
[6] F. Janku, Phosphoinositide 3-kinase (PI3K) pathway inhibitors in solid tumors: from laboratory to patients, Cancer Treat. Rev. 59 (2017) 93–101.
[7] K.D. Courtney, R.B. Corcoran, J.A. Engelman, The PI3K pathway as drug target in human cancer, J. Clin. Oncol. 28 (2010) 1075–1083.
[8] H. Li, J. Zeng, K. Shen, PI3K/AKT/mTOR signaling pathway as a therapeutic target for ovarian cancer, Arch. Gynecol. Obstet. 290 (2014) 1067–1078.
[9] D. Bell, A. Berchuck, M. Birrer, J. Chien, D.W. Cramer, F. Dao, et al., Integrated genomic analyses of ovarian carcinoma, Nature 474 (2011) 609–615.
[10] S. Mabuchi, H. Kuroda, R. Takahashi, T. Sasano, The PI3K/AKT/mTOR pathway as a therapeutic target in ovarian cancer, Gynecol. Oncol. 137 (2015) 173–179.
[11] A. Alqahtani, H.S.K. Ayesh, H. Halawani, PIK3CA gene mutations in solid malignancies: association with clinicopathological parameters and prognosis, Cancers (Basel) 12 (2019) 93.
[12] T.T. Huang, E.J. Lampert, C. Coots, J.M. Lee, Targeting the PI3K pathway and DNA damage response as a therapeutic strategy in ovarian cancer, Cancer Treat. Rev. 86 (2020) 102021.
[13] X. Li, D. Dai, B. Chen, H. Tang, X. Xie, W. Wei, 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 (2018), e0192464.
[14] A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gøtzsche, J.P. Ioannidis, et al., The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration, BMJ (Clin. Res. Ed.) 339 (2009), b2700.
[15] A. Uittenboogaard, P. van der Ploeg, J. Piek, The effectiveness of monotherapy with PI3K/AKT/mTOR inhibitors in ovarian cancer: a systematic review (CRD42020164469), PROSPERO, 2020.
[16] G.J. Rustin, I. Vergote, E. Eisenhauer, E. Pujade-Lauraine, M. Quinn, T. Thigpen, et al., Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG), Int. J. Gynecol. Cancer 21 (2011) 419–423.
[17] National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), 2021.
[18] J.A. Sterne, M.A. Hernán, B.C. Reeves, J. Savović, N.D. Berkman, M. Viswanathan, et al., ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions, BMJ 355 (2016), i4919.
[19] N. Wang, How to Conduct a Meta-analysis of Proportions in R: A Comprehensive Tutorial, 2018.
[20] U. Banerji, E.J. Dean, J.A. Pérez-Fidalgo, G. Batist, P.L. Bedard, B. You, et al., A Phase I Open-Label Study to Identify a Dosing Regimen of the Pan-AKT Inhibitor AZD5363 for Evaluation in Solid Tumors and in *PIK3CA*, Mutat. Breast Gynecol. Cancers 24 (2018) 2050–2059.
[21] S. Blagden, A. Omlin, D. Josephs, C. Stavraka, A. Zivi, D.J. Pinato, et al., First-in-human study of CH5132799, an oral class I PI3K inhibitor, studying toxicity, pharmacokinetics, and pharmacodynamics, in patients with metastatic cancer, Clin. Cancer Res. 20 (2014) 5908–5917.
[22] D.S. Hong, D.W. Bowles, G.S. Falchook, W.A. Messersmith, G.C. George, C.L. O'Bryant, et al., A Multicenter Phase I Trial of PX-866, an Oral Irreversible Phosphatidylinositol 3-Kinase Inhibitor, in Patients with Advanced Solid Tumors, 18, 2012 4173–4182.
[23] P. Munster, R. Aggarwal, D. Hong, J.H. Schellens, R. van der Noll, J. Specht, et al., First-in-human phase I study of GSK2126458, an oral pan-class I phosphatidylinositol-3-kinase inhibitor, in patients with advanced solid tumor malignancies, Clin. Cancer Res. 22 (2016) 1932–1939.
[24] K. Behbakht, M.W. Sill, K.M. Darcy, S.C. Rubin, R.S. Mannel, S. Waggoner, et al., Phase II trial of the mTOR inhibitor, temsirolimus and evaluation of circulating tumor cells and tumor biomarkers in persistent and recurrent epithelial ovarian and primary peritoneal malignancies: a Gynecologic Oncology Group study, Gynecol. Oncol. 123 (2011) 19–26.
[25] G. Emons, C. Kurzeder, B. Schmalfeldt, P. Neuser, N. de Gregorio, J. Pfisterer, et al., Temsirolimus in women with platinum-refractory/resistant ovarian cancer or advanced/recurrent endometrial carcinoma. A phase II study of the AGO-study group (AGO-GYN8), Gynecol. Oncol. 140 (2016) 450–456.
[26] H. Gungor, A. Saleem, S. Babar, R. Dina, M.A. El-Bahrawy, E. Curry, et al., Dose-finding quantitative 18F-FDG PET imaging study with the oral pan-AKT inhibitor GSK2141795 in patients with gynecologic malignancies, J. Nuclear Med. 56 (2015) 1828–1835.
[27] K. Hasegawa, M. Kagabu, M. Mizuno, K. Oda, D. Aoki, S. Mabuchi, et al., Phase II basket trial of perifosine monotherapy for recurrent gynecologic cancer with or without PIK3CA mutations, Investig. New Drugs 35 (2017) 800–812.
[28] D. Juric, J.S. de Bono, P.M. LoRusso, J. Nemunaitis, E.I. Heath, E.L. Kwak, et al., A first-in-human, phase I, dose-escalation study of TAK-117, a selective PI3Kα isoform inhibitor, in patients with advanced solid malignancies, Clin. Cancer Res. 23 (2017) 5015–5023.
[29] D. Juric, J. Rodon, J. Tabernero, F. Janku, H.A. Burris, J.H.M. Schellens, et al., Phosphatidylinositol 3-kinase α-selective inhibition with alpelisib (BYL719) in PIK3CA-altered solid tumors: results from the first-in-human study, J. Clin. Oncol. 36 (2018) 1291–1299.
[30] C. Le Tourneau, J.P. Delord, A. Gonçalves, C. Gavoille, C. Dubot, N. Isambert, et al., Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial, Lancet Oncol. 16 (2015) 1324–1334.
[31] E.K. Lee, Z. Tan-Wasielewski, C. Aghajanian, R.L. Coleman, J. Curtis, M.S. Hirsch, et al., Results of an abbreviated phase II study of AKT inhibitor MK-2206 in the treatment of recurrent platinum-resistant high grade serous ovarian, fallopian tube, or primary peritoneal carcinoma (NCT 01283035), Gynecol. Oncol. Rep. (2020) 100546.
[32] D. Mahadevan, E. Chiorean, W. Harris, D. Von Hoff, A. Stejskal-Barnett, W. Qi, et al., Phase I pharmacokinetic and pharmacodynamic study of the pan-PI3K/mTORC vascular targeted pro-drug SF1126 in patients with advanced solid tumours and B-cell malignancies, Eur. J. Cancer (Oxford, England : 1990) 48 (2012) 3319–3327.
[33] J. Mateo, G. Ganji, C. Lemech, H.A. Burris, S.W. Han, K. Swales, et al., A first-time-in-human study of GSK2636771, a phosphoinositide 3 kinase beta-selective inhibitor, in patients with advanced solid tumors, Clin. Cancer Res. 23 (2017) 5981–5992.
[34] S.A. Piha-Paul, M.H. Taylor, D. Spitz, L. Schwartzberg, J.T. Beck, T.M. Bauer, et al., Efficacy and safety of buparlisib, a PI3K inhibitor, in patients with malignancies harboring a PI3K pathway activation: a phase 2, open-label, single-arm study, Oncotarget 10 (2019) 6526–6535.
[35] J. Rodon, A. Pérez-Fidalgo, I.E. Krop, H. Burris, A. Guerrero-Zotano, C.D. Britten, et al., Phase 1/1b dose escalation and expansion study of BEZ235, a dual PI3K/mTOR inhibitor, in patients with advanced solid tumors including patients with advanced breast cancer, Cancer Chemother. Pharmacol. 82 (2018) 285–298.
[36] G.I. Shapiro, K.M. Bell-McGuinn, J.R. Molina, J. Bendell, J. Spicer, E.L. Kwak, et al., First-in-human study of PF-05212384 (PKI-587), a Small-molecule, Intravenous, Dual Inhibitor of PI3K and mTOR in Patients with Advanced Cancer, 21, 2015 1888–1895.
[37] M. Takano, Y. Kikuchi, K. Kudoh, T. Goto, K. Furuya, R. Kikuchi, et al., Weekly administration of temsirolimus for heavily pretreated patients with clear cell carcinoma of the ovary: a report of six cases, Int. J. Clin. Oncol. 16 (2011) 605–609.
[38] R. Varnier, I. Ray-Coquard, V. Corset, C. Baudet, D. Pissaloux, V. Attignon, et al., Actionable molecular alterations in advanced gynecologic malignancies: first results from the ProfiLER program (NCT01774409) in France, Ann. Oncol. 28 (2017) v333.
[39] M.H. Voss, M.S. Gordon, M. Mita, B. Rini, V. Makker, T. Macarulla, et al., Phase 1 study of mTORC1/2 inhibitor sapanisertib (TAK-228) in advanced solid tumours, with an expansion phase in renal, endometrial or bladder cancer, Br. J. Cancer 123 (2020) 1590–1598.
[40] A. Wicki, N. Brown, A. Xyrafas, V. Bize, H. Hawle, S. Berardi, et al., First-in human, phase 1, dose-escalation pharmacokinetic and pharmacodynamic study of the oral dual PI3K and mTORC1/2 inhibitor PQR309 in patients with advanced solid tumors (SAKK 67/13), Eur. J. Cancer (Oxford, England : 1990) 96 (2018) 6–16.
[41] T.A. Yap, L. Yan, A. Patnaik, N. Tunariu, A. Biondo, I. Fearen, et al., Interrogating Two Schedules of the AKT Inhibitor MK-2206 in Patients with Advanced Solid Tumors Incorporating Novel Pharmacodynamic and Functional Imaging Biomarkers, 20, 2014 5672–5685.
[42] C. Aghajanian, K.M. Bell-McGuinn, H.A. Burris 3rd, L.L. Siu, L.A. Stayner, J.J. Wheler, et al., A phase I, open-label, two-stage study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of the oral AKT inhibitor GSK2141795 in patients with solid tumors, Investig. New Drugs 36 (2018) 1016–1025.

[43] M. Elkabets, S. Vora, D. Juric, N. Morse, M. Mino-Kenudson, T. Muranen, et al., mTORC1 inhibition is required for sensitivity to PI3K p110α inhibitors in PIK3CA-mutant breast cancer, Sci. Transl. Med. 5 (2013), 196ra99.
[44] K.E. O'Reilly, F. Rojo, Q.B. She, D. Solit, G.B. Mills, D. Smith, et al., mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt, Cancer Res. 66 (2006) 1500–1508.
[45] S.C.E. Wright, N. Vasilevski, V. Serra, J. Rodon, P.J.A. Eichhorn, Mechanisms of resistance to PI3K inhibitors in cancer, Adapt. Resp. Drug Tolerance Cell. Plasticity 13 (2021) 1538.
[46] A.M. Sieuwerts, M.A. Inda, M. Smid, H. van Ooijen, A. van de Stolpe, J.W.M. Martens, et al., ER and PI3K pathway activity in primary ER positive breast cancer is associated with progression-free survival of metastatic patients under first-line tamoxifen, Cancers (Basel) 12 (2020) 802.
[47] J.E. Fehniger, A.A. Berger, L. Juckett, J. Elvin, D.A. Levine, D.A. Zajchowski, Comprehensive genomic sequencing of paired ovarian cancers reveals discordance in genes that determine clinical trial eligibility, Gynecol. Oncol. 155 (2019) 473–482.
[48] S. Lambrechts, D. Smeets, M. Moisse, E.I. Braicu, A. Vanderstichele, H. Zhao, et al., Genetic heterogeneity after first-line chemotherapy in high-grade serous ovarian cancer, Eur. J. Cancer (Oxford, England : 1990) 53 (2016) 51–64.
[49] A.M. Gonzalez-Angulo, J. Ferrer-Lozano, K. Stemke-Hale, A. Sahin, S. Liu, J.A. Barrera, et al., PI3K pathway mutations and PTEN levels in primary and metastatic breast cancer, Mol. Cancer Ther. 10 (2011) 1093–1101.
[50] C. Perez-Juarez, F. Arechavaleta-Velasco, M. Zeferino-Toquero, L. Alvarez-Arellano, I. Estrada-Moscoso, L. Díaz-Cueto, Inhibition of PI3K/AKT/mTOR and MAPK signaling pathways decreases progranulin expression in ovarian clear cell carcinoma (OCCC) cell line: a potential biomarker for therapy response to signaling pathway inhibitors, Med. Oncol. 37 (2019) 4.
[51] P.A. Konstantinopoulos, W.T. Barry, M. Birrer, S.N. Westin, K.A. Cadoo, G.I. Shapiro, et al., Olaparib and α-specific PI3K inhibitor alpelisib for patients with epithelial ovarian cancer: a dose-escalation and dose-expansion phase 1b trial, Lancet Oncol. 20 (2019) 570–580.
[52] A. Bardia, M. Gounder, J. Rodon, F. Janku, M.P. Lolkema, J.J. Stephenson, et al., Phase Ib study of combination therapy with MEK inhibitor binimetinib and phosphatidylinositol 3-kinase inhibitor buparlisib in patients with advanced solid tumors with RAS/RAF alterations, Oncologist 25 (2020) e160–e169.
[53] U.A. Matulonis, G.M. Wulf, W.T. Barry, M. Birrer, S.N. Westin, S. Farooq, et al., Phase I dose escalation study of the PI3kinase pathway inhibitor BKM120 and the oral poly (ADP ribose) polymerase (PARP) inhibitor olaparib for the treatment of high-grade serous ovarian and breast cancer, Ann. Oncol. 28 (2017) 512–518.
[54] D. Szklarczyk, A.L. Gable, D. Lyon, A. Junge, S. Wyder, J. Huerta-Cepas, et al., STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets, Nucleic Acids Res. 47 (2019) D607–d13.