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Efficacy and Safety of AKT Inhibitors in HR+/HER2- Breast Cancer or Metastatic TNBC: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Abstract

Background: This study aims to investigate the impact of AKT inhibitors (Capivasertib and Ipatasertib) on the efficacy and safety of patients with HR+/HER2- breast cancer or metastatic TNBC.

Methods: A comprehensive search for relevant Randomized Clinical Trials (RCTs) of AKT inhibitors were conducted through PubMed, Embase, and Cochrane Library. The meta-analysis included five studies with a total of 1304 patients. Outcome indicators such as Progression-Free Survival (PFS), Adverse Events (AEs), Overall Survival (OS), Duration of Response (DOR), Objective Response Rate (ORR), and Clinical Benefit Rate (CBR) were analyzed using Review Manager 5.4.1.

Results: Patients treated with AKT inhibitors showed a significant improvement in PFS compared to those without (MD=2.39; 95% CI: 1.06, 3.73; p=0.0005; I2=55%). However, the incidence of some dangerous AEs increased, including infection (OR=1.72; 95% CI: 1.09, 2.72; p=0.02; I2=0%) and hyperglycemia (OR=3.07; 95% CI: 1.36, 6.93; p=0.007; I2=63%).

Conclusion: AKT inhibitors significantly prolonged the survival of patients with metastatic TNBC and HR+/HER2- breast cancer. Nevertheless, the occurrence of AEs, such as infection and hyperglycemia, during AKT inhibitor treatment suggests the need for careful and rational drug usage based on specific patient conditions.

Keywords: HR+/HER2- breast cancer; Triple negative breast cancer; Capivasertib, Ipatasertib; Meta-analysis

Abbreviations: WHO: World Health Organization; HER2: Human Epidermal Growth Factor Receptor 2; BC: Breast Cancer; ER: Estrogen Receptor; TNBC: Triple-Negative Breast Cancer; AKT: Serine-Threonine Kinase; RCT: Randomized Clinical Trial; ASCO: American Society of Clinical Oncology; ESMO: European Society of Medical Oncology; SABCS: San Antonio Breast Cancer Symposium; PFS: Progression-Free Survival; AEs: Adverse Events; OS: Overall Survival; ORR: Objective Response Rate; DOR: Duration of Response; CBR: Clinical Benefit Rate; NR: Not Recorded; TNBC: Triple Negative Breast Cancer; HR: Hormone Receptor; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PFS: Progression-Free Survival

Introduction

In 2020, the World Health Organization (WHO) reported a shift in the prevalence of cancer types, with breast cancer surpassing lung cancer as the most predominant form among females [1]. Breast cancer is classified into three distinct types based on the status of Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2): Hormone Receptor (HR, including ER or PR) positive/human epidermal growth factor receptor-2 negative (HR+/HER2-), human epidermal growth factor receptor-2 positive/hormone receptor negative or hormone receptor positive (HER2+/HR- or HR+), and triple-negative (HR-/HER2-) [2,3]. For HR+ breast cancer, endocrine therapy serves as a common and effective adjuvant treatment [4]. However, given the heterogeneity of breast cancer, the treatment paradigm has shifted towards molecular targeting [5]. Conversely, Triple-Negative Breast Cancer (TNBC) typically undergoes surgery and chemotherapy due to its specific molecular pattern, rendering endocrine therapy or HER2-targeted therapy ineffective [6,7]. Despite this, chemotherapy resistance often leads to frequent metastasis [8]. Thus, there is an urgent need for a novel treatment strategy that is both safer and more effective, particularly for HR+/HER2- breast cancer or metastatic TNBC. Research has shown a close association between the metastasis and progression of breast cancer and the activation of signaling pathways [9,10]. Among these, the Phosphoinositide 3-Kinase (PI3K)/Serine-threonine Kinase (AKT) pathway is the most commonly mutated pathway in breast cancer [11]. Approximately 50% of HR+ breast cancer and 25% of TNBC exhibit concurrent activation of the AKT pathway during the transition [12]. Additionally, AKT inhibitors have been identified as influential in impacting the progression of breast cancer by modulating HER2 status, thereby playing a pivotal role in the efficacy and safety of cancer treatment [11,13]. Consequently, the study of AKT inhibitors is indispensable for advancing breast cancer treatment.

As a central node of the PI3K/AKT signaling pathway, the activation of AKT is closely associated with the invasion and metastasis of tumor cells [14,15]. Furthermore, it is related to chemotherapy resistance in tumor cell therapy [16-18]. In breast cancer with mutations in the PI3K/AKT signaling pathway, approximately 40% are HR+ subtypes, and patients in treatment often develop resistance to endocrine therapy [19-21]. Simultaneously, AKT inhibitors delaying tumor progression by affecting the expression of Programmed Death Ligand 1 (PD-L1)

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in TNBC have attracted more attention [16,22,23]. As an emerging anti-breast cancer drug, AKT inhibitors have shown promise in the treatment of metastatic TNBC and HR+/HER2- breast cancer through continuous research and development [24-27].

Capivasertib (AZD5363) is an effective and highly selective AKT 1-3 subtype oral active small molecule kinase inhibitor [28]. A Randomized Clinical Trial (RCT) found no significant change in the dose intensity and tolerance of paclitaxel in patients with ER+/HER2- metastatic breast cancer treated with Capivasertib [29]. Furthermore, studies indicated that Capivasertib can decrease the expression of Ki67, a proliferation marker of ER+ breast cancer, and has a potential association with tumor progression [30]. Ipatasertib (GDC-0068), another highly selective ATP competitive small molecule oral AKT inhibitor, also exhibits the same inhibitory effect on the three subtypes of AKT [31]. A phase III clinical trial evaluated the safety and efficacy of Ipatasertib in breast cancer patients [32]. The results showed that taking Ipatasertib had no effect on the efficacy of breast cancer patients, contrary to the evaluation results of another phase II clinical trial (LOTUS trial) [27].

In summary, the clinical efficacy of these two AKT inhibitors for HR+/HER2- breast cancer or metastatic TNBC patients is controversial. Therefore, a systematic and comprehensive analysis of the results of clinical studies using AKT inhibitors is necessary.

Materials and Methods

Literature retrieval strategy

A thorough search of relevant RCTs was conducted through PubMed, Embase, and the Cochrane Library databases, spanning from the database to December 2023. To avoid any omission of pertinent literature, the abstracts of ClinicalTrials.gov, the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), and the San Antonio Breast Cancer Symposium (SABCS) manually searched and supplemented using similar search terms to enhance the analysis. The search terms included "breast cancer" and "AKT inhibitor" (Ipatasertib or Capivasertib). The search strategy is detailed in supplementary material 1.

Eligibility criteria

Inclusion criteria: (1) Standard phase II and phase III RCTs; (2) Patients diagnosed with HR+/HER2- or TNBC; (3) The experimental group, among trial participants, received a regimen containing AKT inhibitors, while the control group was treated with paclitaxel or other drugs plus a corresponding placebo regimen; (4) Inclusion of survival indicators (progression-free survival) and safety indicators (adverse events), with complete and available data; (5) English-language research.

Exclusion criteria: (1) Repetitive publication of the same studies in different journals (e.g. same clinical registration number); (2) Studies with significant bias in data conversion or analysis.

Outcome measures

The primary outcomes included Progression-Free Survival (PFS) and Adverse Events (AEs) assessed by investigators. Specific adverse events (such as infection, rash, neuropathy, and neutropenia) were detailed in supplementary material 2. Secondary outcomes included Overall Survival (OS), Objective Response Rate (ORR), Duration of Response (DOR), and Clinical Benefit Rate (CBR). For subgroup analysis, this study primarily analyzed the PFS of patients based on AKT pathway status, the use of (neo) adjuvant chemotherapy, breast cancer type, and AKT inhibitor type. Subgroup analysis results for secondary outcomes are available in the supplementary materials.

Data extraction and risk of bias assessment

Two authors independently extracted detailed information from the included experimental articles. The extracted included: (1) Basic information of articles: First author, publication time, type of experimental design, research stage, and median follow-up time; (2) Details of the experimental and control groups: Sample size (total and AKT subgroups), treatment plan (dosage and administration time), breast cancer type, age and ethnic composition, tumor metastasis and metastatic site, number of previous chemotherapy lines, and chemotherapy regimens; (3) Survival indicators, including PFS and OS; (4) Disease control rate, including ORR, CBR, and DOR; (5) AEs, including the incidence of all grades, grade 3/4, and grade ≥ 3 AEs. The extracted information is derived from the most recent and comprehensive evaluation data included in the article.

The Cochrane Collaboration bias assessment tool was used to assess potential risks in included articles across seven areas: Random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and any other potential sources of bias. Assessment levels in all fields are categorized as "low risk", "high risk", or "unclear". Tests with more than four "low risk" classifications are identified as low risk and high-quality tests [33].

Data extraction and bias assessment were conducted independently by two system reviewers. Disagreements were resolved through consultation between both parties or with a third reviewer.

Statistical analysis

The data were analyzed using Review Manager 5.4.1, evaluating extracted data by 95% Confidence Intervals (CI) Hazard Ratio (HR), 95% CI Mean Difference (MD), and 95% CI Odds Ratio (OR).

When literature did not report Standard Deviation (SD) or Standard Error (SE) but presented 95% CI, conversion was done using RevMan Calculator (https://training.cochrane.org/resource/revman-calculator). If n ≤ 60, direct conversion from the table was employed; for n>60, the formula $SD = n^{0.5} * \frac{UCL - LCL}{3.92}$ was used. Conversion to SE involved using the formula $SE \frac{\frac{UCL - LCL}{2}}{1.96}$ for n>60 and direct table conversion for n ≤ 60.

During the evaluation, this study used OR to reflect the difference in exposure between the AKT inhibitor group and the control group, indicating the ratio of exposed to non-exposed individuals in the AKT inhibitor group compared to the control group. The study also used HR to express the likelihood of illness in the AKT inhibitor group compared with the control group, reflecting the risk of events in the two groups. Additionally, when combining results, the heterogeneity between studies was measured using the I^2 test. For I^2<50%, the fixed-effect model was applied; for I^2>50%, the random-effect model was used for analysis. A significance level of $p \leq 0.05$ was considered statistically significant.

Results

Literature retrieval and quality assessment

The initial search strategy yielded 787 articles, with 163 studies excluded due to duplication in the search results, followed by the exclusion of 220 retrospective studies. Among the remaining 404 articles, 292 were excluded based on titles or abstracts not meeting the requirements. A comprehensive review of the remaining 112

articles resulted in the exclusion of 107 articles. Ultimately, this paper incorporates five studies: Three focusing on Capivasertib and two on Ipatasertib inhibitors [26,27,29,32,34]. One of the studies was recently published, with some data unavailable (Figure 1).

The bias assessment results for the included literature are illustrated in Figure 2. Notably, random sequence generation, allocation concealment (selection bias), and blinding of outcome assessment (detection bias) were low risk in four studies. Blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias) were deemed low risk in three studies. However, blinding of outcome assessment (detection bias) was high risk in one study. In summary, three out of the five included studies demonstrated high quality, signifying an overall high quality and low risk in the literature.

Data transformation and population baseline characteristics

The meta-analysis includes five studies, encompassing a total of 1304 patients, comprising 264 TNBC patients and 1040 HR+/HER2- patients. The AKT pathway status changed in 632 patients, while it remained unchanged in 204 patients. Except for one study, which used the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 or 5.0 to grade included Adverse Events (AEs), other characteristics are detailed in Table 1. Definitions and assessment methods are available in Supplementary Material 2.

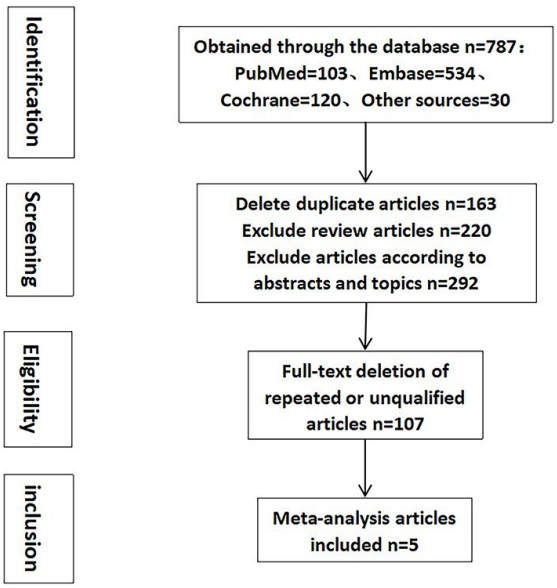

Figure 1: Article screening process.

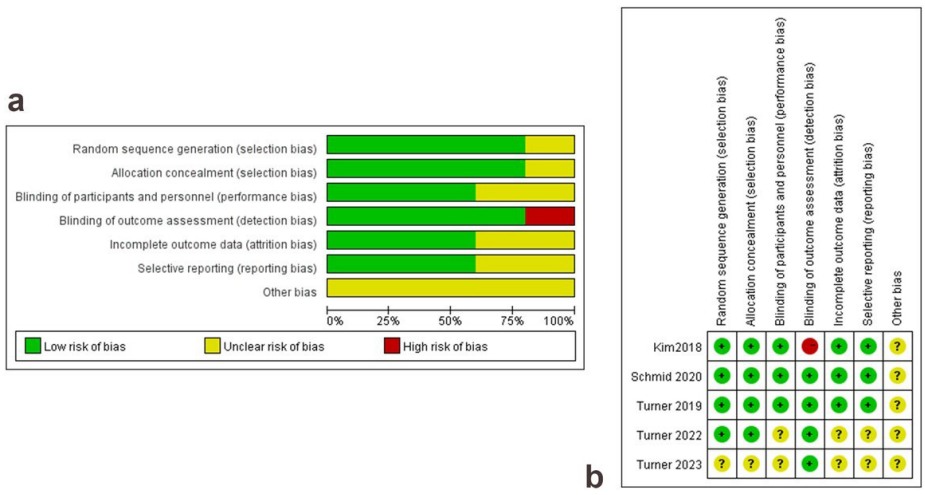

Figure 2: Literature quality bias risk map. (a) Bias risk assessment bar chart; (b) Bias risk assessment diagram. Note: +: low risk; -: high risk; ?: not clear.

First author	Year	Study design	Participants		No. of the AKT pathway				Median age (years)		Median follow-up time (months)		Stage of breast cancer	Intervention *vs* comparison		End point				Method of AEs	Version
																primary		Secondary		assessment	
			No. of patients with	No. of patients with	AKT-altered		AKT-non-altered		No. of patients with	No. of patients with	No. of patients with	No. of patients with		No. of patients with	No. of patients with	No. of patients with	No. of patients with	No. of patients with	No. of patients with		
			AKT inhibitor	placebo	No. of patients with	No. of patients with	No. of patients with	No. of patients with	AKT inhibitor	placebo	AKT inhibitor	placebo		AKT inhibitor	placebo	AKT inhibitor	placebo	AKT inhibitor	placebo		
					AKT inhibitor	placebo	AKT inhibitor	placebo													
Peter Schmid	2020	Phase II, RCT	70	70	17	11	42	42	55.5	51.9	18.2		Metastatic TNBC	Paclitaxel plus Capivasertib	Paclitaxel plus Placebo	PFS, AEs	PFS, AEs	OS, ORR, CBR, DOR	OS, ORR, CBR, DOR	NR	NR
Prof Sung-Bae Kim	2018	Phase II, RCT	62	62	26	16	28	33	54	53	10.4	10.2	Metastatic TNBC	Paclitaxel plus Ipatasertib	Paclitaxel plus Placebo	PFS, AEs	PFS, AEs	OS, ORR, CBR, DOR	OS, ORR, CBR, DOR	NCI CTCAE	version 4.0
Nicholas Turner	2022	Phase III, RCT	146	76	146	76	NR		57.5	56	12.9		HR+/ HER2- advanced BC	Paclitaxel plus Ipatasertib	Paclitaxel plus Placebo	PFS, AEs	PFS, AEs	OS, ORR, CBR, DOR	OS, ORR, CBR, DOR		version 4.0
Nicholas Turner	2019	Phase II, RCT	54	56	26	25	28	31	53	60	16.9	15.2	Metastatic ER+/ HER2- advanced BC	Paclitaxel plus Capivasertib	Paclitaxel plus Placebo	PFS, AEs	PFS, AEs	OS, ORR, DOR	OS, ORR, DOR		version 4.0
Nicholas Turner	2023	Phase III, RCT	355	353	155	134	NR		59	58	NR		HR+/ HER2- advanced BC	Fulvestrant plus Capivasertib	Fulvestrant plus Placebo	PFS, AEs	PFS, AEs	OS	OS		version 5.0

Table 1: Basic characteristics of included studies.

Progression-Free Survival (PFS)

In these five randomized controlled trials, 687 patients (52.68%) received Capivasertib or Ipatasertib. The PFS of patients in the AKT inhibitor group was significantly improved compared to the control group (MD=2.39; 95% CI: 1.06, 3.73; p=0.0005; I^2=55%;) (Figure 3a).

Subgroup analysis based on AKT pathway status change revealed a significant prolongation of PFS in patients receiving AKT inhibitors (SMD=0.33; 95% CI: 0.11, 0.55; p=0.003; I^2=49%;) (Figure 3b). Whether the AKT pathway status changed (SMD=0.34; 95% CI: 0, 0.69; p=0.05; I^2=69%;) (Figure 3b) or remained unchanged (SMD=0.31; 95% CI: 0.04, 0.59; p=0.03; I^2=0%;) (Figure 3b), the use of AKT inhibitors improved PFS.

Subgroup analysis of (neo) adjuvant chemotherapy showed significantly improved PFS with combined AKT inhibitors (HR=0.8; 95% CI: 0.65, 0.98; p=0.03; I2=0%;) (Figure S1a).

Subgroup analysis of breast cancer type indicated prolonged PFS in TNBC patients (MD=1.63; 95% CI: -0.03, 3.29; p=0.05; I^2=0%;) (Figure S1b) and HR+/HER2- breast cancer patients (MD=2.75; 95% CI: 1.07, 4.43; p=0.001; ICI: 1.6, 4.16; p<0.0001; I^2=55%;) (Figure S1c), with =53%;) (Figure S1b) after AKT inhibitor use.

AKT inhibitor type subgroup analysis demonstrated significantly improved PFS in patients using Capivasertib (MD=2.88; 95% CI: 1.6, 4.16; p<0.0001; I^2=55%;) (Figure S1c), with a trend towards improvement in patients using Ipatasertib (MD=0.62; 95% CI: -2.07, 3.31; p=0.65; I^2=0%;) (Figure S1c).

Overall Survival (OS)

Although no significant difference was observed, the AKT inhibitor group exhibited a tendency to prolong patient OS compared to the control group (HR=0.86; 95% CI: 0.73, 1.01; p=0.06; I^2=0%;) (Figure 4a). Similar results were obtained in AKT pathway subtype analysis (Figure S2a).

Duration of Response (DOR)

Three studies reporting patient DOR indicated no significant difference in the effect of AKT inhibitor treatment (MD=0.11; 95% CI: -2.03, 2.26; p=0.92; I^2=0%;) (Figure 4b).

Objective Response Rate (ORR) and Clinical Benefit Rate (CBR)

The use of AKT inhibitors did not impact ORR (OR=1.22; 95% CI: 0.87, 1.72; p=0.24; I^2=0%;) (Figure 4c) or CBR (OR=1.31; 95% CI: 0.9, 1.91; p=0.16; I^2=0%;) (Figure 4d). Although not statistically significant, there was a tendency for patient status improvement (Figure S2b, 2c).

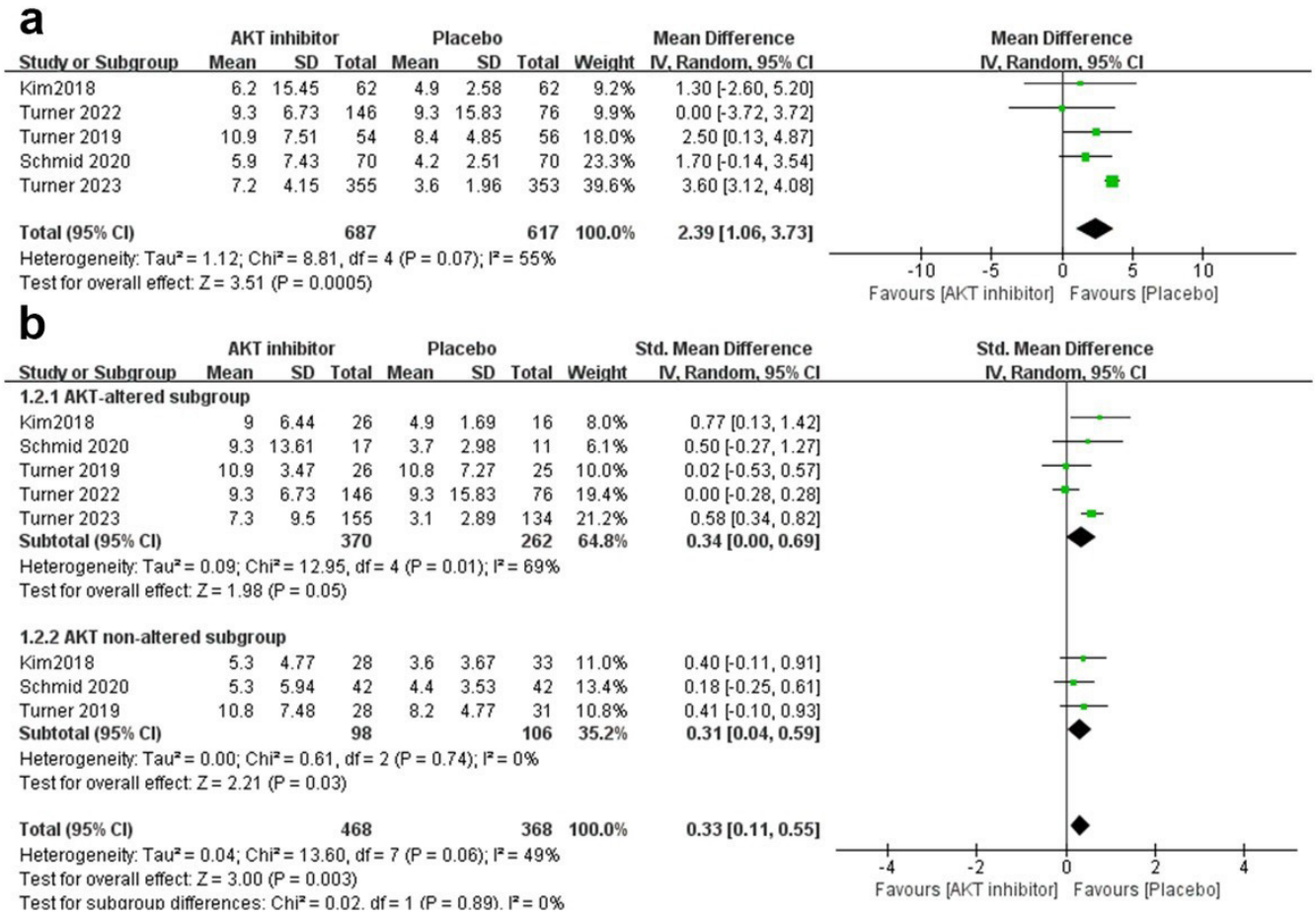

Figure 3: PFS-related evaluation results. (a) PFS of total population; (b) PFS of total population associated with AKT pathway subgroup. AKT, serine-threonine kinase; PFS, progression-free survival.

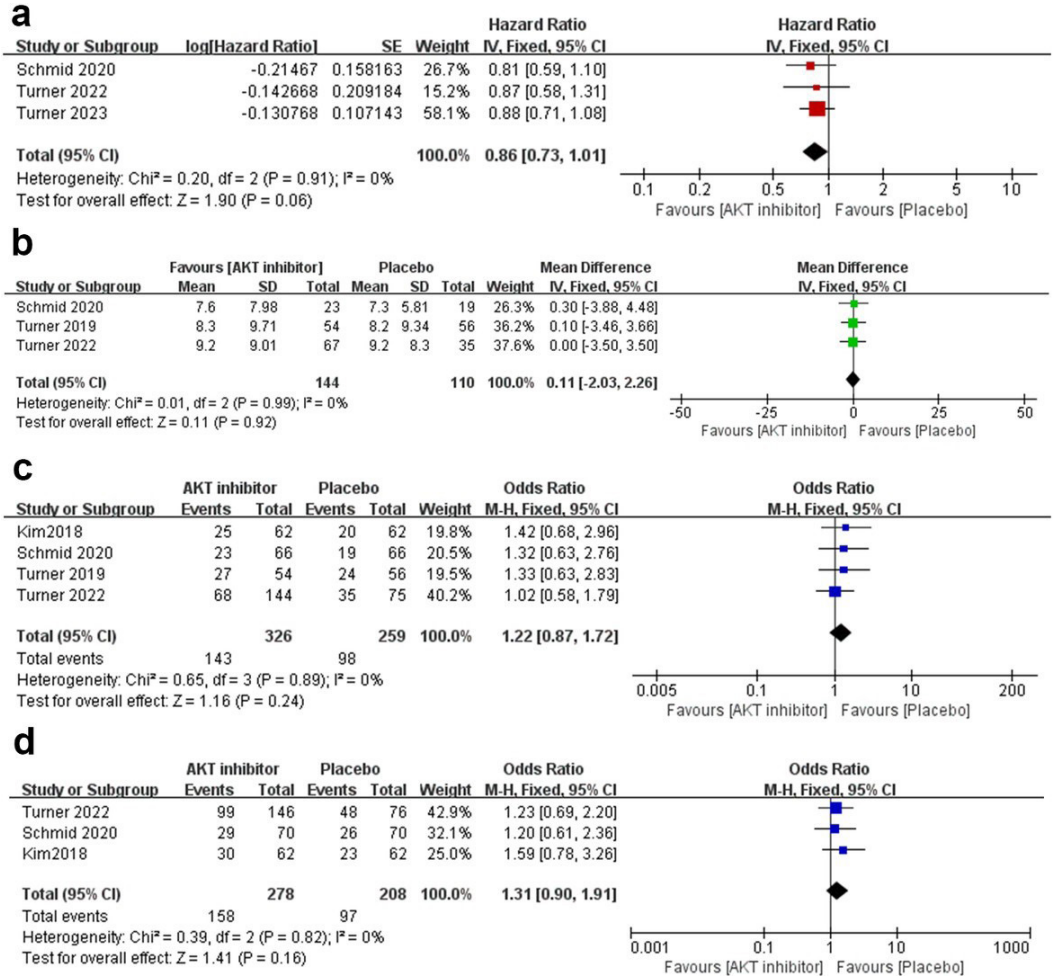

Figure 4: Related evaluation results of secondary indicators. (a) OS of total population; (b) DOR of total population; (c) ORR of total population; (d) CBR of total population.

Adverse Events (AEs)

In this meta-analysis, all studies assessed Adverse Events (AEs) across multiple levels, encompassing all/any grades, grade 3/4, and grade ≥ 3. This study specifically presents the findings related to all/any grades of total AEs, specific general AEs (diarrhea, fatigue, nausea, rash, and vomiting), and certain severe AEs (neuropathy, infection, hyperglycemia, neutropenia, hypertension, and alanine aminotransferase reduction). The outcomes for the remaining grades, not explicitly discussed in the article, will be detailed in the supplementary materials.

Total Adverse Events

For all/any grades of total AEs, the evaluation results indicated a higher incidence in patients treated with AKT inhibitors than those without (OR=4.78; 95% CI: 2.84, 8.07; p<0.00001; I^2=1%;) (Figure 5a). Additionally, the incidence of grade 3/4 and grade ≥ 3 total AEs in the AKT inhibitor group was higher than the control group (Figure S3).

General AEs

All/any grades of general AEs showed a higher incidence of diarrhea (OR=11.06; 95% CI: 6.83, 17.9; p<0.00001; I^2=59%;) (Figure 5b), nausea (OR=2.35; 95% CI: 1.82, 3.03; p<0.00001; I^2=37%;) (Figure 5c), rash (OR=3.62; 95% CI: 1.68, 7.83; p=0.001; I^2=78%;) (Figure 5d), and vomiting (OR=2.93; 95% CI: 1.63, 5.27; p=0.0003; I^2=59%;) (Figure 5e) in patients treated with AKT inhibitors compared to the control group. Fatigue showed no significant difference (OR=1.31; 95% CI: 0.81, 2.1; p=0.27; I^2=60%;) (Figure 5f). Incidence of fatigue, nausea, and vomiting in general AEs of grade 3/4 and grade ≥ 3 did not change due to treatment; however, diarrhea and rash were more likely to occur in patients after AKT inhibitor use (Figure S4).

Dangerous AEs

Evaluation of six dangerous AEs indicated an increased probability, in patients using AKT inhibitors, of all/any grades, grade 3/4, or/and grade ≥ 3 infection (OR=1.72; 95% CI: 1.09, 2.72; p=0.02; I^2=0%;) (Figure 6a) and hyperglycemia (OR=3.07; 95% CI: 1.36, 6.93; p=0.007; I^2=63%;) (Figure 6c). No significant difference was observed in the incidence of the other four dangerous AEs between the AKT inhibitor and the control group (Figures S5 and S6). Interestingly, the incidence of neutropenia of all/any grades and grade ≥ 3 hypertension showed a decreasing trend after AKT inhibitor use (Figures S6b and S6c).

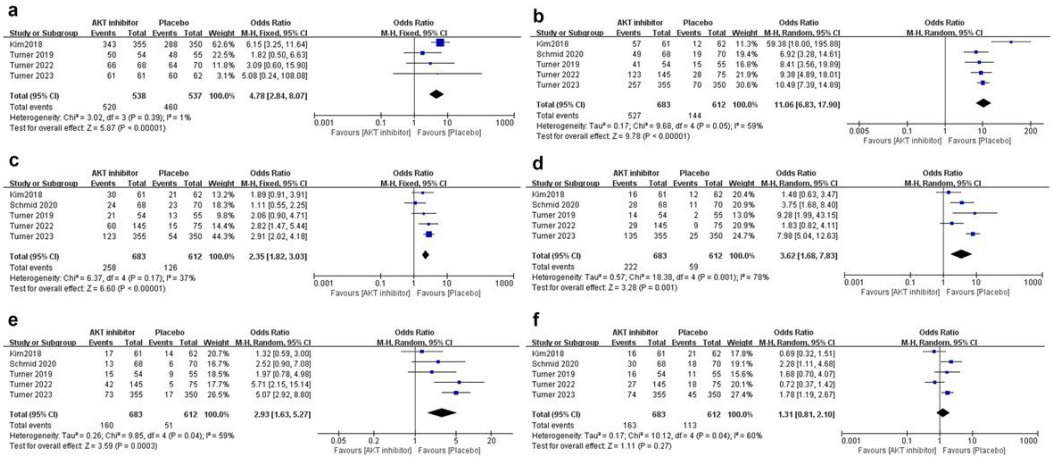

Figure 5: Evaluation results of all/any grades total AEs and general AEs. (a) Total AEs; (b) Diarrhea; (c) Nausea; (d) Rash; (e) Vomiting; (f) Fatigue.

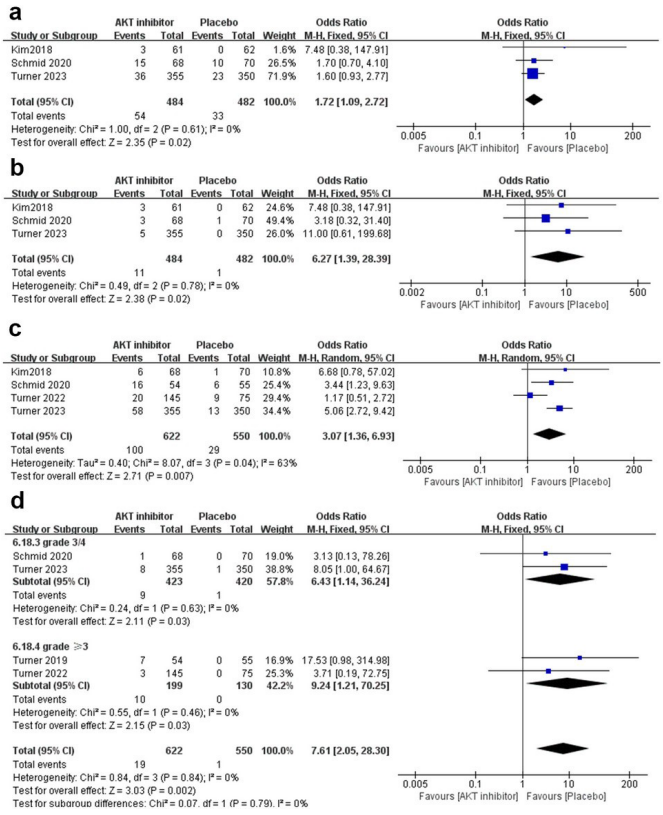

Figure 6: Evaluation of infection and hyperglycemia. (a) All/any grades of infection; (b) Grade 3/4 infection; (c) All/any grades of hyperglycemia; (d) Grade 3/4 and grade ≥ 3 hyperglycemia.

Discussion

Breast cancer stands out as the most prevalent and fatal cancer among women globally [35]. For patients grappling with advanced or metastatic breast cancer, conventional treatments involving endocrine and surgical interventions encounter reduced efficacy owing to the absence of therapeutic targets, drug resistance, or tumor metastasis [36,37]. Employing diverse combinations of inhibitors emerges as a viable strategy to identify potential treatment targets [38,39]. Notably, HR+/HER2- breast cancer, the most common subtype [40], exhibits an interdependence between HR+ breast cancer and the PI3K pathway [41]. The PI3K/AKT pathway, frequently mutated in breast cancer, holds a pivotal role in tumor progression, chemotherapy resistance, and poor prognosis [11,42,43]. Clinical trials underscore the efficacy of AKT inhibitors as a promising treatment modality [27,28,44]. Similarly, TNBC, the most malignant subtype [9,45], often features activation of the PI3K/AKT/mTOR pathway, contributing to resistance to MAPK inhibitor therapy and tumor progression [46]. Clinical

studies demonstrate that AKT inhibitors, when combined with other drugs, enhance the survival of TNBC patients [26,47]. Consequently, a systematic analysis of AKT inhibitors' efficacy in TNBC and HR+/HER2- breast cancer patients is imperative.

This study primarily assessed the impact of AKT inhibitors on PFS in breast cancer patients. The findings indicate a significant extension of PFS when AKT inhibitors are combined with other treatments. Further analysis reveals improved PFS across the AKT pathway subgroup, irrespective of the AKT pathway state. Recent research highlights Capivasertib's potential to double the PFS of breast cancer patients [48], particularly those with altered AKT pathway (PIK3CA or MTOR) [11], aligning with the study's evaluation results. In the AKT inhibitor type subgroup analysis, Capivasertib notably prolongs patient PFS, while Ipatasertib exhibits a potential, though not statistically significant, extension of PFS. A phase I clinical trial underscores Ipatasertib's efficacy in combination with other chemotherapy drugs for TNBC treatment [25]. Future clinical trials are warranted to validate Ipatasertib's effectiveness. AKT inhibitors (Capivasertib and Ipatasertib) hold promise in breast cancer treatment, particularly in conjunction with paclitaxel and fulvestrant [30,49-52].

The PFS evaluation results in breast cancer patients align with the latest meta-analysis of Capivasertib in solid tumor treatment. However, the AKT pathway subgroup PFS results differ, showcasing improvement regardless of the AKT pathway state [53]. This discrepancy with Abushanab's meta-analysis could stem from its inclusion of two tumor types (breast cancer and prostate cancer), unlike this study's exclusive focus on breast cancer. The study's comprehensive evaluation, considering two AKT inhibitors (Capivasertib and Ipatasertib), contributes to the divergence in results. Despite the small sample size of studies, the study calls for additional clinical investigations to bolster the analysis's credibility.

Moreover, the study provides AEs during AKT inhibitor treatment. Total AEs exhibit a significant rise following AKT inhibitor treatment compared to chemotherapy or hormone therapy alone. Individual AE analysis indicates increased incidence for most AEs with AKT inhibitors, such as diarrhea, rash, vomiting, and hyperglycemia. Consistent safety outcomes in clinical studies on AKT inhibitors (Capivasertib and Ipatasertib) in solid tumor patients validate these findings [11,25,54]. Notably, infection risk elevation after AKT inhibitor intake, unmentioned in other studies, underscores the importance of cautious use in patients with infection or hyperglycemia history.

Conclusion

The study boasts several strengths, such as double-blind, RCT inclusion, ensuring overall study reliability. AKT inhibitors' efficacy and safety in HR+/HER2- and metastatic TNBC breast cancer subtypes further underscores its significance. Standardized analysis of indicators measured using different methods enhances the study's robustness. However, limitations include the transformation of evaluation data and potential bias risks. Inaccessibility of supplementary materials from one study might introduce analysis deviations. The small number of clinical studies contributes to limited sample size, heightening study heterogeneity and impacting evaluation result accuracy.

AKT inhibitors significantly enhance breast cancer patients' PFS, particularly in the AKT pathway status change subgroup. While improvements in OS, DOR, ORR, and CBR lack statistical significance, a discernible trend towards improvement exists. However, potential AEs induced by AKT inhibitors, such as infection and hyperglycemia, necessitate cautious use based on individual patient conditions in subsequent treatments.

Author contributions

Wuzhi Zhong, Tao Yan and Lehui Li designed this study; Ziying Zhang, Nan Zhang and Xiaodong Cao contributed to the writing of the first draft; Wuzhi Zhong and Lehui Li carried out literature retrieval and data extraction, and Tao Yan, Chunfa Zhang and Ya Wang analyzed the data. Xingguang Zhang, Lijie Ma and Jinli Yan made statistical analysis and revised the manuscript. Ru Zhang and Dijia Li wrote the manuscript. All the authors read and approved the final submission.

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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