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Research Article

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

Wuzhi Zhong[1], Tao Yan1, Lehui Li[1], Xinguang Zhang[1], Ru Zhang[1], Dijia Li[1], Lijie Ma[1], Jinli Yan[1], Chunfa Zhang[1], Ya Wang[1], Xiaodong Cao[1], Nan Zhang[1], and Ziying Zhang[1,2*]

[1]Department of Medical Oncology, Basic Medicine College, Inner Mongolia Medical University, Hohhot, Inner Mongolia, China

[2]Medical Experiment Center, Inner Mongolia Medical University, Hohhot, 010110, China

***Correspondence:** Ziying Zhang, Department of Medicine, Tongrun Tang Traditional Chinese Medicine Clinic, Nanchong City, Sichuan, China

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

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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 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)

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 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 $SD = n^{0.5} \times (UCL - LCL)$ was used. Conversion to SE involved using the formula $SE = \frac{SD}{2}$ 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.

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)andHR+/HER2-breastcancerpatients(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).

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%;) (Figure5e) 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).

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).

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 STATEMEN

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.

REFERENCES

1) Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, et al. (2021) Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3):209-249.

2) Sivaganesh V, Promi N, Maher S, Peethambaran B (2021) Emerging immunotherapies against novel molecular targets in breast cancer. Int J Mol Sci 22(5).

3) Waks AG, Winer EP (2019) Breast cancer treatment: A review. Jama 321(3):288-300.

4) Lau KH, Tan AM, Shi Y (2022) New and emerging targeted therapies for advanced breast cancer. Int J Mol Sci 23(4).

5) Raheem F, Karikalan SA, Batalini F, El Masry A, Mina L (2023) Metastatic ER+ breast cancer: Mechanisms of resistance and future therapeutic approaches. Int J Mol Sci 24(22).

6) Engebraaten O, Vollan HKM, Børresen-Dale AL (2013) Triple-negative breast cancer and the need for new therapeutic targets. Am J Pathol 183(4):1064-1074.

7) Lebert JM, Lester R, Powell E, Seal M, McCarthy J (2018) Advances in the systemic treatment of triple-negative breast cancer. Curr Oncol 25:S142-S150.

8) Haffty BG, Yang Q, Reiss M, Kearney T, Higgins SA, et al. (2006) Locoregional relapse and distant metastasis in conservatively managed triple negative early- stage breast cancer. J Clin Oncol 24(36):5652-5657.

9) Li Y, Zhang H, Merkher Y, Chen L, Liu N, et al. (2022) Recent advances in therapeutic strategies for triple-negative breast cancer. J Hematol Oncol 15(1):121.

10) Brufsky AM, Dickler MN (2018) Estrogen receptor-positive breast cancer: Exploiting signaling pathways implicated in endocrine resistance. Oncologist 23(5):528-539.

11) Andrikopoulou A, Chatzinikolaou S, Panourgias E, Kaparelou M, Liontos M, et al. (2022) "The emerging role of capivasertib in breast cancer". Breast (Edinburgh, Scotland) 63:157-167.

12) Martorana F, Motta G, Pavone G, Motta L, Stella S, et al. (2021) AKT Inhibitors: New weapons in the fight against breast cancer? Frontiers in pharmacology 12:662232.

13) Wisinski KB, Tevaarwerk AJ, Burkard ME, Rampurwala M, Eickhoff J, et al. (2016) Phase I study of an akt inhibitor (mk-2206) combined with lapatinib in adult solid tumors followed by dose expansion in advanced HER2+ breast cancer. Clin Cancer Res 22(11):2659-2667.

14) Toson B, Fortes IS, Roesler R, Andrade SF (2022) Targeting Akt/PKB in pediatric tumors: A review from preclinical to clinical trials. Pharmacol Res 183:106403.

15) Uko NE, Güner OF, Matesic DF, Bowen JP (2020) Akt pathway inhibitors. Curr Top Med Chem 20(10):883-900.

16) Kaboli PJ, Salimian F, Aghapour S, Xiang S, Zhao Q, et al. (2020) Akt-targeted therapy as a promising strategy to overcome drug resistance in breast cancer-A comprehensive review from chemotherapy to immunotherapy. Pharmacol Res 156:104806.

17) Bahrami A, Khazaei M, Hasanzadeh M, ShahidSales S, Joudi Mashhad M, et al. (2018) Therapeutic potential of targeting PI3K/AKT pathway in treatment of colorectal cancer: Rational and progress. J Cell Biochem 2018;119(3):2460-2469.

18) Xu J, Yu X, Martin TC, Bansal A, Cheung K, et al. (2021) AKT Degradation Selectively Inhibits the Growth of PI3K/PTEN Pathway-Mutant Cancers with Wild-Type KRAS and BRAF by Destabilizing Aurora Kinase B. Cancer discovery 11(12):3064-3089.

19) Sobhani N, Roviello G, Corona SP, Scaltriti M, Ianza A, et al. (2018) The prognostic value of PI3K mutational status in breast cancer: A meta-analysis. J Cell Biochem 119(6):4287-4292.

20) Miller TW, Balko JM, Arteaga CL (2011) Phosphatidylinositol 3-kinase and antiestrogen resistance in breast cancer. J Clin Oncol 29(33):4452-4461.

21) Gonzalez-Angulo AM, Ferrer-Lozano J, Stemke-Hale K, Sahin A, Liu S, et al. (2011) PI3K pathway mutations and PTEN levels in primary and metastatic breast cancer. Mol Cancer Ther 10(6):1093-1101.

22) Mittendorf EA, Philips AV, Meric-Bernstam F, Qiao N, Wu Y, et al. (2014) PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res 2(4):361-370.

23) Di Cosimo S, Baselga J (2010) Management of breast cancer with targeted agents: Importance of heterogeneity. Nat Rev Clin Oncol 7(3):139-147.

24) Zhu K, Wu Y, He P, Fan Y, Zhong X, et al. (2022) PI3K/AKT/mTOR-targeted therapy for breast cancer. Cells 11(16).

25) Yuan Y, Yost SE, Cui Y, Ruel C, Murga M, et al. (2023) Phase I trial of ipatasertib plus carboplatin, carboplatin/paclitaxel, or capecitabine and atezolizumab in metastatic triple-negative breast cancer. Oncologist 28(7):e498-e507.

26) Schmid P, Abraham J, Chan S, Wheatley D, Brunt AM, et al. (2020) Capivasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer: The PAKT trial. J Clin Oncol 38(5):423-433.

27) Kim SB, Dent R, Im SA, Espié M, Blau S, et al.(2018) Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): A multicentre, randomised, double-blind, placebo- controlled, phase 2 trial. Lancet Oncol (10):1360-1372.

28) Davies BR, Greenwood H, Dudley P, Crafter C, Yu DH, Zhang J, Li J, et al. (2012) Preclinical pharmacology of AZD5363, an inhibitor of AKT: Pharmacodynamics, antitumor activity, and correlation of monotherapy activity with genetic background. Mol Cancer Ther (4):873-887.

29) Turner NC, Alarcón E, Armstrong AC, Philco M, Chuken, et al. (2019) BEECH: A dose-finding run-in followed by a randomised phase II study assessing the efficacy of AKT inhibitor capivasertib (AZD5363) combined with paclitaxel in patients with estrogen receptor-positive advanced or metastatic breast cancer, and in a PIK3CA mutant sub-population. Ann Oncol (5):774-780.

30) Robertson JF, Coleman RE, Cheung KL, Evans A, Holcombe C, et al. (2020) Proliferation and akt activity biomarker analyses after capivasertib (AZD5363) treatment of patients with ER(+) invasive breast cancer (stakt). Clin Cancer Res 26(7):1574-1585.

31) Lin J, Sampath D, Nannini MA, Lee BB, Degtyarev M, et al. (2013) Targeting activated Akt with GDC-0068, a novel selective Akt inhibitor that is efficacious in multiple tumor models. Clin Cancer Res 19(7):1760-1772.

32) Turner N, Dent RA, O'Shaughnessy J, Kim SB, Isakoff SJ, et al. (2022) Ipatasertib plus paclitaxel for PIK3CA/AKT1/PTEN-altered hormone receptor- positive HER2-negative advanced breast cancer: Primary results from cohort B of the IPATunity130 randomized phase 3 trial. Breast Cancer Res Treat 191(3):565-576.

33) Lu H, Zha S, Zhang W, Wang Q, Jiang D, et al. (2021) A systematic review and meta-analysis of nab-paclitaxel mono-chemotherapy for metastatic breast cancer. BMC cancer 21(1):830.

34) Turner NC, Oliveira M, Howell SJ, Dalenc F, Cortes J, et al. (2023) Capivasertib in hormone receptor-positive advanced breast cancer. N Engl J Med 388(22):2058-2070.

35) Clusan L, Ferrière F, Flouriot G, Pakdel F. (2024) A basic review on estrogen receptor signaling pathways in breast cancer. Int J Mol Sci 24(7).

36) Rugo HS, Rumble RB, Macrae E, Barton DL, Connolly HK, et al. (2016) Endocrine therapy for hormone receptor-positive metastatic breast cancer. J Clin Oncol 34(25):3069-3103.

37) Rugo HS, Rumble RB, Macrae E, Barton DL, Connolly HK, et al.(2022) Genetic heterogeneity, tumor microenvironment and immunotherapy in triple-negative breast cancer. Int J Mol Sci 23(23).

38) Rasha F, Sharma M, Pruitt K (2021) Mechanisms of endocrine therapy resistance in breast cancer. Future Oncol 532:111322.

39) Heeke AL, Tan AR (2021) Checkpoint inhibitor therapy for metastatic triple- negative breast cancer. Cancer metastasis reviews.

Cancer Metastasis Rev 40(2):537-547.

40) Herzog SK, Fuqua SAW (2022) ESR1 Mutations and therapeutic resistance in metastatic breast cancer: Progress and remaining challenges. Br J Cancer 126(2):174-186.

41) Vasan N, Toska E, Scaltriti M (2019) Overview of the relevance of PI3K pathway in HR-positive breast cancer. Ann Oncol 30(10):3-11.

42) Altomare DA, Testa JR (2005) Perturbations of the AKT signaling pathway in human cancer. Oncogene 24(50):7455-7464.

43) Dong C, Wu J, Chen Y, Nie J, Chen C (2021) Activation of PI3K/AKT/mTOR pathway causes drug resistance in breast cancer. Front pharmacol 12:628690.

44) Ribas R, Pancholi S, Guest SK, Marangoni E, Gao Q, et al. (2015) AKT antagonist AZD5363 influences estrogen receptor function in endocrine- resistant breast cancer and synergizes with fulvestrant (ICI182780) in vivo. Mol Cancer Ther 14(9):2035-2048.

45) Wu Q, Nie DY, Ba-Alawi W, Ji Y, Zhang Z, et al (2022) PRMT inhibition induces a viral mimicry response in triple-negative breast cancer. Nat Chem Biol 18(8):821-830.

46) Zhang Z, Richmond A, Yan C (2022) Immunomodulatory properties of PI3K/ AKT/mTOR and MAPK/MEK/ERK inhibition augment response to immune checkpoint blockade in melanoma and triple-negative breast cancer. Int J Mol Sci 23(13):7353.

47) Schmid P, Im SA, Armstrong A, Park YH, Chung WP, et al. (2021) BEGONIA: Phase 1b/2 study of Durvalumab (D) combinations in locally advanced/metastatic Triple-Negative Breast Cancer (TNBC)-initial results from arm 1, d+ Paclitaxel (P), and arm 6, d+ Trastuzumab Deruxtecan (T-DXd). Clin Oncol 39(15):1023.

48) Rose S (2023) Capivasertib doubles pfs in some breast cancers. Cancer discov 13(2):250.

49) Howell SJ, Casbard A, Carucci M, Ingarfield K, Butler R, et al. (2022) Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive, HER2-negative breast cancer (FAKTION): Overall survival, updated progression-free survival, and expanded biomarker analysis from a randomised, phase 2 trial. Lancet Oncol 23(7): 851-864.

50) Oliveira M, Saura C, Nuciforo P, Calvo I, Andersen J, et al. (2019) FAIRLANE, a double-blind placebo-controlled randomized phase II trial of neoadjuvant ipatasertib plus paclitaxel for early triple-negative breast cancer. Ann Oncol 30(8):1289-1297.

51) Ludmir EB, McCaw ZR, Kim DH, Tian L, Wei LJ (2020) Fulvestrant plus capivasertib for metastatic breast cancer. Lancet Oncol 21(5):e233.

52) Jones RH, Casbard A, Carucci M, Foxley A, Howell SJ (2020) Fulvestrant plus capivasertib for metastatic breast cancer-Authors' reply. Lancet Oncol. 21(5):e234.

53) Abushanab AK, Mousa MT, Mustafa MA, Qawaqzeh RA (2023) The efficacy and safety of Capivasertib (AZD5363) in the treatment of patients with solid tumor: A systematic review and meta-analysis of randomized clinical trials. Drug Saf 22(9):799-805.

54) Shapiro GI, LoRusso P, Cho DC, Musib L, Yan Y, et al. (2021) A phase Ib open-label dose escalation study of the safety, pharmacokinetics, and pharmacodynamics of cobimetinib (GDC-0973) and ipatasertib (GDC-0068) in patients with locally advanced or metastatic solid tumors. Invest New Drugs 39:163-174