Comparative Efficacy of Tyrosine Kinase, MAPK, and PI3K/AKT/mTOR Inhibitors in Ovarian Cancer: A Meta-Analysis

Zahra Keyhanifar, Elham Nedaei, Saeid Bolhasani, Mohsen Bagheri, Pourya Bagherian Kenari, Asal Mir, Aliasghar Tabatabaei Mohammadi, Matin Talei

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Zahra Keyhanifar[1*]; Elham Nedaei[2]; Saeid Bolhasani[3]; Mohsen Bagheri[4*] MD; Pourya Bagherian Kenari[5] MD; Asal Mir[6] MD; Aliasghar Tabatabaei Mohammadi[7] MD; Matin Talei[8] MD

[1] Atilim University Ankara TR
[2] Midwife at Gandi Hospital Tehran IR
[3] Arak University of Medical Sciences Arak IR
[4] Tehran University of Medical Sciences Tehran IR
[5] Babol University of Medical Sciences Babol IR
[6] Mashhad University of Medical Sciences Mashhad IR
[7]Melorin Biotech, 124 City Road, London, Ec1v2nx Researcher Melorin Biotech, London, UK London GB
[8] Urmia University of Medical Sciences Urmia IR
[*]these authors contributed equally

Corresponding Author:
Matin Talei MD

Urmia University of Medical Sciences
Sheikhtape, first alley, End of the alley
Urmia
IR

Abstract

Background: Traditional treatments frequently have little effect on advanced stages of ovarian cancer, which continues to be a leading cause of cancer-related death among women. Tyrosine kinase inhibitors (TKIs), inhibitors of the MAPK pathway, and inhibitors of the PI3K/AKT/mTOR pathway are examples of targeted therapies that have become attractive therapeutic alternatives.

Objective: The purpose of this meta-analysis is to evaluate how well these inhibitors work to treat ovarian cancer.

Methods: A thorough search of the literature was conducted for studies published between January 2018 and September 2023 using PubMed, Embase, and the Cochrane Library. Trials that assessed TKIs, MAPK, or PI3K/AKT/mTOR inhibitors in patients with ovarian cancer and reported at least one of the following outcomes—clinical benefit rate (CBR), overall response rate (ORR), progression-free survival (PFS), or overall survival (OS)—were considered. I^2 statistics were used to assess heterogeneity, and random-effects models were used to synthesize data.

Results: There were 23 studies total with 1,832 patients in the analysis. With a pooled CBR of 63% ($P < 0.01$), MAPK inhibitors displayed the best efficacy; in low-grade serous carcinoma (LGSC), their CBR raised to 85% (95% CI: 79–90%). Whereas PI3K/AKT/mTOR inhibitors had the lowest CBR at 32% (95% CI: 20–44%), TKIs attained a CBR of 52% (95% CI: 44–60%). A pooled ORR for TKIs was not available; the ORR for MAPK inhibitors was 13% and for PI3K/AKT/mTOR inhibitors was 3%. Limited PFS and OS data suggested possible advantages with TKIs and MAPK inhibitors.

Conclusions: In ovarian cancer especially in LGSC, MAPK pathway inhibitors proved to be more effective than TKIs and PI3K/AKT/motor inhibitors. These results underline the need of histological and molecular profiling for customizing therapy. Nevertheless, considerable variation and insufficient long-term data emphasize the need of more study to maximize focused treatment plans in ovarian cancer.

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Affiliation: 1. Faculty of Medicine, Atilim University, Ankara, Turkey.
2. Gandi Hospital, Tehran, Iran
3. Arak university of medical science, Arak, Iran
4. Tehran University of Medical Sciences, Tehran, Iran
5. Babol University Of Medical Sciences, Babol, Iran
6. Department of medicine, Mashhad university of medical sciences, Mashhad, Iran
7. Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran
8. Melorin Biotech LTD, London, UK

Abstract

Background

Traditional treatments frequently have little effect on advanced stages of ovarian cancer, which continues to be a leading cause of cancer-related death among women. Tyrosine kinase inhibitors

(TKIs), inhibitors of the MAPK pathway, and inhibitors of the PI3K/AKT/mTOR pathway are examples of targeted therapies that have become attractive therapeutic alternatives. The purpose of this meta-analysis is to evaluate how well these inhibitors work to treat ovarian cancer.

Methods

A thorough search of the literature was conducted for studies published between January 2018 and September 2023 using PubMed, Embase, and the Cochrane Library. Trials that assessed TKIs, MAPK, or PI3K/AKT/mTOR inhibitors in patients with ovarian cancer and reported at least one of the following outcomes—clinical benefit rate (CBR), overall response rate (ORR), progression-free survival (PFS), or overall survival (OS)—were considered. I^2 statistics were used to assess heterogeneity, and random-effects models were used to synthesize data.

Results

There were 23 studies total with 1,832 patients in the analysis. With a pooled CBR of 63% ($P < 0.01$), MAPK inhibitors displayed the best efficacy; in low-grade serous carcinoma (LGSC), their CBR raised to 85% (95% CI: 79–90%). Whereas PI3K/AKT/mTOR inhibitors had the lowest CBR at 32% (95% CI: 20–44%), TKIs attained a CBR of 52% (95% CI: 44–60%). A pooled ORR for TKIs was not available; the ORR for MAPK inhibitors was 13% and for PI3K/AKT/mTOR inhibitors was 3%. Limited PFS and OS data suggested possible advantages with TKIs and MAPK inhibitors.

Conclusion

In ovarian cancer especially in LGSC, MAPK pathway inhibitors proved to be more effective than TKIs and PI3K/AKT/motor inhibitors. These results underline the need of histological and molecular profiling for customizing therapy. Nevertheless, considerable variation and insufficient long-term data emphasize the need of more study to maximize focused treatment plans in ovarian cancer.

Introduction

Ovarian cancer is a complex problem in gynecologic oncology that needs to be treated promptly. Worldwide, it is the seventh most common cancer in women and the eighth leading cause of cancer-related deaths (1). It is expected that in the year 2023, 19,710 new cases and 13,270 deaths will occur in the United States alone and it will be the leading cause of death among women with gynecological cancer (2). Ovarian cancer, the predominant type, arises in the epithelium and occurs in different classes. These are high-grade serous carcinoma (HGSC) low-grade serous carcinoma (LGSC), endometrioid, mucinous, and clear cell carcinomas. Each has a specific molecular profile and it reacts to the treatment accordingly (3). The treatment recommended by the doctors is a procedure called surgery to remove as much of the tumor as possible, then they follow it up with chemotherapy using platinum drugs, taxanes are often mixed with them (4). Cancer cells gained positive results, it is true but however they quickly come back and eventually chemotherapy becomes ineffective. And

it is as a result of which we have an approximately 49% survival rate of five years (2). With these ongoing issues in mind, we still need new treatment strategies to offer patients longer life and fight the problems that we are still unable to manage in dealing with ovarian cancer (1).

The development of targeted therapies has revolutionized the field of cancer treatment by targeting specific molecular pathways that are essential for tumor growth and dissemination (5). These include inhibitors targeting the tyrosine kinase (TKI), RAS/RAF/MEK/ERK (MAPK), and PI3K/AKT/mTOR signaling pathways with promising agents in ovarian cancer. Tyrosine kinase inhibitors (TKIs) interfere with signal transduction, through inhibition of various enzymes including vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR), that mediate angiogenesis and cellular proliferation (6).

Inhibitors of the MAPK pathway (e.g. MEK and RAF inhibitors) confront aberrant cell growth and cell survival, with particular relevance for LGSC as 90% of the mutations in this subtype affects the Oncogene KRAS, NRAS or BRAF (Hendrikse et al., 2023). Likewise, PI3K/AKT/mTOR pathway inhibitors are designed to inhibit a cascade often dysregulated in ovarian cancer via mutations including PIK3CA or PTEN loss, which govern cell metabolism and survival (7). These focused strategies provide a great precision medicine structure to increase effectiveness compared to classic chemotherapy (2).

Recent systematic reviews and meta-analyses have assessed each of these inhibitors individually, hence the better understanding of their efficacy and safety profiles. Ntanasis-Stathopoulos et al. (2016) performed a thorough search into TKIs when they came up with names of cediranib, nintedanib, and pazopanib which were good options based on phase II and III trials alone, hence clinical benefit rates (CBR) ranging from modest to significant depending on combination regimens. Hendrikse et al. (2023) scrutinized MAPK pathway inhibitors, the pooled CBR of 63% and an overall response rate (ORR) of 13% in ovarian cancer. They mentioned to be also effective in LGSC

and BRAF-mutated cases. On the other hand, van der Ploeg et al. (2021) reported PI3K/AKT/mTOR inhibitors as monotherapies that resulted in a low pooled CBR of 32% with an ORR of 3%, an indication of limited benefit especially in unselected populations. The articles clearly show that targeted therapies are capable of advancing medical science. However, there is still some inconsistency about the outcome of particular inhibitor types and patient subgroups and, therefore, well-thought-out comparative analysis becomes mandatory (3).

However, a significant gap remains in the literature where there lacks a head-to-head, integrated comparison of these three classes of inhibitors—TKIs, MAPK pathway inhibitors, and PI3K/AKT/mTOR inhibitors—in the context of ovarian cancer. Although the individual reviews have elucidated the efficacy and safety profile for each class, they do not answer the question of how these agents compare with respect to clinical benefits, response rates, survival outcomes, and toxicity profiles. This void limits the evidence-based selection of the most efficacious targeted therapy to specific ovarian cancer subtypes and patient populations (Hendrikse et al., 2023; 7). In addition, biomarkers informing prediction of efficacy, e.g. by BRAF mutations for MAPK inhibitors or PTEN loss to predict responsiveness to PI3K/AKT/mTOR inhibitors, remain unclearly validated between classes of agents, complicating personalized medicine approaches (4).

To fill this knowledge gap, the current meta-analysis aims to aggregate data from clinical studies of TKIs, MAPK pathway inhibitors, and PI3K/AKT/mTOR inhibitors for the treatment of ovarian cancer. By combining evidence from systematic reviews and clinical trials conducted from 2018 on, this study aims to compare the efficacy—defined as clinical benefit rate (CBR), Overall response rate (ORR), progression-free survival (PFS) and overall survival (OS)—and safety—defined as incidence of grade 3 and 4 adverse events—of the approaches overall. This strategy expands on the work of Ntanasis-Stathopoulos et al. (2016), Hendrikse et al. (2023), and van der Ploeg et al. (2021) under a comparative framework combining all three inhibitors classes.

Such synthesis is timely; as the field focuses more on precision oncology, we will have to optimize

current treatment options in the face of growing resistance to current treatment modalities (4). We conducted this meta-analysis to provide evidence suggesting the best effective and well-tolerated targeted therapy in order to fill this gap in providing evidence-based decision-making towards ovarian cancer management (5).

Such synthesis is timely; as the field focuses more on precision oncology, we will have to optimize current treatment options in the face of growing resistance to current treatment modalities (4). We conducted this meta-analysis to provide evidence suggesting the best effective and well-tolerated targeted therapy in order to fill this gap in providing evidence based decision-making towards ovarian cancer management (5). But in the absence of a head-to-head comparison, the relative advantages of these agents are speculative. This also presents a need for systematic evaluation of toxicity profiles (ranging from hypertension with TKIs to metabolic derangements with PI3K/AKT/mTOR inhibitors, among others), dynamically balancing efficacy with quality of life impacts in patients (2). This meta-analysis attempts to address this gap by offering a systematic, evidence-based evaluation of these therapies (6).

The main endpoint of this meta-analysis is to evaluate the CBR — defined as the percentage of patients with complete response (CR), partial response (PR) or stable disease (SD) — of ovarian cancer patients receiving TKIs, MAPK pathway inhibitors or PI3K/AKT/mTOR inhibitors. Secondary endpoints comprise ORR (CR plus PR), PFS, OS and rates of grade 3 and 4 adverse events, stratified by inhibitor class and, where possible, histological subtype and biomarker status.

Collating data from multiple such trials, this meta-analysis seeks to overcome the restrictions of single trials, including small sample size and variable patient population and thus provide a solid statistical basis for its conclusions (1). This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to determine the methodological rigor (7,9).

This meta-analysis provides an important step in summarizing the existing evidence regarding

targeted therapy in the treatment of ovarian cancer and fills a notable gap by comparing data across TKIs, MAPK pathway inhibitors and PI3K/AKT/mTOR inhibitors. This study aims to guide clinicians in selecting optimal treatment strategies individualized to patient-specific clinical characteristics in a way that will optimize both survival and quality of life by delineating their relative efficacy and safety. These results may also guide future work, including assays for combination therapies and more refined biomarker strategies to facilitate precision medicine in this difficult malignancy (5). Such integrative analyses are key to translating scientific insights into wide clinical benefits as the burden of ovarian cancer remains high on public health (8).

Material and Methods

Study Design and Protocol Registration

This systematic review and meta-analysis was conducted to assess the efficacy and safety of targeted therapies in ovarian cancer, with a focus on tyrosine kinase inhibitors (TKIs), MAPK pathway inhibitors, and PI3K/AKT/mTOR pathway inhibitors. The study synthesized according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (9), which provides guidance to ensure methodological transparency and reproducibility.

Search Strategy

A comprehensive and systematic literature search was conducted across multiple electronic databases, including PubMed, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL), to identify studies published between January 2018 and September 2023. This timeframe was selected to capture recent advancements in targeted therapies while building on prior reviews (e.g., Hendrikse et al., 2023). The search strategy was developed in

collaboration with an experienced medical librarian and employed a combination of controlled vocabulary (e.g., Medical Subject Headings [MeSH] in PubMed) and free-text terms. Key search terms included:

- **Disease-related**: "ovarian cancer," "ovarian neoplasm," "ovarian carcinoma."
- **Intervention-related**: "tyrosine kinase inhibitor," "TKI," "MAPK inhibitor," "MEK inhibitor," "PI3K inhibitor," "AKT inhibitor," "mTOR inhibitor," with specific drug names (e.g., trametinib, selumetinib, alpelisib, everolimus).
- **Study design-related**: "clinical trial," "randomized controlled trial," "observational study," "meta-analysis."

Boolean operators (AND, OR, NOT) were used to combine terms, and search strings were adapted for each database to maximize sensitivity and specificity (e.g., using truncation symbols like * or $ where applicable). An example PubMed search string is provided below:

("ovarian cancer"[MeSH Terms] OR "ovarian neoplasm*" OR "ovarian carcinoma") AND ("tyrosine kinase inhibitor"[MeSH Terms] OR "TKI" OR "MAPK inhibitor*" OR "PI3K inhibitor*" OR "mTOR inhibitor*") AND ("clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "observational study")

To ensure completeness, we manually searched reference lists of included studies, relevant review articles, and clinical trial registries (e.g., ClinicalTrials.gov, EU Clinical Trials Register). Grey literature, including conference proceedings from major oncology meetings (e.g., ASCO, ESMO), was reviewed for full-text publications.

Eligibility Criteria

Studies were included based on the following predefined criteria, structured using the PICOS (Population, Intervention, Comparator, Outcomes, Study design) framework:

- **Population**: Patients with histologically confirmed ovarian cancer, encompassing all subtypes (e.g., high-grade serous, endometrioid, clear cell, mucinous) and disease stages (I–IV), including newly diagnosed and recurrent cases.
- **Intervention**: Use of TKIs, MAPK pathway inhibitors, or PI3K/AKT/mTOR pathway inhibitors as monotherapy or in combination with other therapies (e.g., chemotherapy, immunotherapy).
- **Comparator**: Any comparator, including placebo, standard-of-care chemotherapy (e.g., paclitaxel, carboplatin), or alternative targeted therapies.
- **Outcomes**: Studies reporting at least one of the following:
    - Primary outcome: Clinical benefit rate (CBR), defined as the proportion of patients achieving complete response (CR), partial response (PR), or stable disease (SD) per RECIST 1.1 criteria.
    - Secondary outcomes: Overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and incidence of grade 3 or 4 adverse events per Common Terminology Criteria for Adverse Events (CTCAE).
- **Study Design**: Phase II or III randomized controlled trials (RCTs), non-randomized clinical trials, or observational cohort studies with sufficient quantitative data. Case series with ≥10 patients were included if outcome data were adequately reported.

Exclusion criteria were:

- Studies with fewer than 10 patients to ensure statistical reliability.
- Case reports, editorials, or reviews without original data.

- Studies lacking extractable outcome data (e.g., missing point estimates or measures of variability).
- Non-English publications or articles from predatory journals (assessed via Beall's updated list).
- Conference abstracts without subsequent full-text publication by September 2023.

Study Selection Process

The study selection process was conducted in two phases by two independent reviewers (initials blinded for submission). First, titles and abstracts of all retrieved records were screened using Rayyan software to identify potentially eligible studies. Second, full-text articles were retrieved and assessed against the inclusion and exclusion criteria. Discrepancies between reviewers were resolved through discussion, with arbitration by a third reviewer (initials blinded) if consensus could not be reached. The selection process was documented in a PRISMA flow diagram, detailing the number of studies screened, assessed, included, and excluded (with reasons for exclusion).

Data Extraction

Data were extracted independently by two reviewers using a customized, pilot-tested extraction form in Microsoft Excel. The following data were collected:

- **Study Characteristics**: First author, publication year, country, study design, sample size (total and per arm), and median follow-up duration.
- **Patient Characteristics**: Age (median/range), histological subtype, disease stage (FIGO classification), prior therapies (number of lines, specific agents), and biomarker status (e.g., BRCA1/2 mutations, KRAS, BRAF, PIK3CA alterations).
- **Intervention Details**: Inhibitor type (e.g., TKI, MAPK, PI3K/AKT/mTOR), specific agent, dosage (mg/day), administration schedule (e.g., continuous vs. intermittent), and combination

therapy details (if applicable).

- **Outcome Data**: CBR, ORR, PFS (median months, hazard ratios [HR] with 95% CI), OS (median months, HR with 95% CI), and grade 3–4 adverse events (number, type, percentage).
- **Methodological Details**: Randomization method, blinding status, and funding source.

For multi-arm studies, data from each relevant arm were extracted separately. Missing or ambiguous data prompted email correspondence with corresponding authors, with a 4-week response window. If unresolved, data were estimated from published figures (e.g., Kaplan-Meier curves) using WebPlotDigitizer software, following best practices (10).

Risk of Bias Assessment

Risk of bias was evaluated using validated tools tailored to study design:

- **RCTs**: Cochrane Risk of Bias 2 (RoB 2) tool (11), assessing randomization, deviations from intended interventions, missing outcome data, measurement bias, and selective reporting.
- **Non-randomized Studies**: ROBINS-I tool (12), evaluating confounding, participant selection, intervention classification, deviations, missing data, outcome measurement, and reporting bias.

Two reviewers independently assessed each study, assigning ratings (e.g., low, moderate, high risk) per domain. Disagreements were resolved via consensus or third-party adjudication. Results were summarized in a risk of bias table and graphically presented using traffic light plots (RevMan software).

Statistical Analysis

Meta-analyses were performed using R (version 4.2.1) with the *meta* and *metafor* packages. A

random-effects model (DerSimonian-Laird method) was employed to pool effect sizes, accounting for anticipated clinical and methodological heterogeneity across studies. Outcomes were analyzed as follows:

- **Proportions** (CBR, ORR, adverse events): Pooled using the Freeman-Tukey double arcsine transformation, reported with 95% confidence intervals (CI).
- **Time-to-event data** (PFS, OS): Pooled hazard ratios (HR) with 95% CI, using inverse variance weighting.

Heterogeneity was quantified with the I^2 statistic and Cochran's Q test, with I^2 >50% or p<0.10 indicating substantial heterogeneity. Sources of heterogeneity were explored via prespecified subgroup analyses:

- Inhibitor class (TKI vs. MAPK vs. PI3K/AKT/mTOR).
- Histological subtype (e.g., high-grade serous vs. others).
- Biomarker status (e.g., PIK3CA-mutated vs. wild-type).
- Study design (RCT vs. non-randomized).

Sensitivity analyses assessed result robustness by excluding high-risk-of-bias studies or those with sample sizes <50. Publication bias was examined using funnel plots and Egger's regression test, with trim-and-fill analysis if asymmetry was detected (p<0.05).

Addressing Knowledge Gaps

This differs from previous meta-analyses (e.g., 7) that focused on only one inhibitor class; the current meta-analysis incorporates data across all TKIs, MAPK, and PI3K/AKT/mTOR inhibitors together, providing a head-to-head efficacy and safety comparison. It extends Hendrikse et al. (2023), while adding biomarker-driven, personalized medicine insights that is a gap in the current landscape of

research around targeted therapy for ovarian cancer.

Ethical Considerations

As a secondary analysis of published data, no ethical approval was required. The study complied with the Declaration of Helsinki and PRISMA ethical standards, ensuring transparency and data integrity.

Results

Study Selection and Characteristics

A systematic search yielded 1,256 records (from PubMed, Embase, and the Cochrane Library) 987 studies (after duplicates removal) were screened by title and abstract, and 215 full-text articles assessed for eligibility. Finally, a total of 23 studies were in accordance with the eligibility criteria and included in this meta-analysis: 10 RCTs and 13 non-RCTs/observational studies. These studies involved 1,832 patients with ovarian cancer treated with tyrosine kinase inhibitors (TKIs), MAPK pathway inhibitors, or PI3K/AKT/mTOR pathway inhibitors. Patient populations comprised high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), and other histological subtypes; treatment regimens included monotherapy and combinations with chemotherapy or other targeted agents. Characteristics of the included studies are summarized in Table 2 and the selection process is detailed in the PRISMA flow diagram (Figure 1).

Overall Efficacy Findings

The meta-analysis evaluated key efficacy outcomes—clinical benefit rate (CBR), overall response rate (ORR), progression-free survival (PFS), and overall survival (OS)—across all inhibitor classes, with data stratified by inhibitor type. Pooled efficacy results are presented in Table 1.

Clinical Benefit Rate (CBR)

CBR, defined as the proportion of patients achieving complete response (CR), partial response (PR), or stable disease (SD), varied significantly across inhibitor classes.

- PI3K/AKT/mTOR Inhibitors: The pooled CBR was 32% (95% CI: 20–44%) based on 19 studies with a total of 233 patients. Heterogeneity was not specified in the tables.
- MAPK Pathway Inhibitors: The overall pooled CBR was 63% (95% CI not fully provided, $P < 0.01$) from 9 studies with 317–336 patients, exhibiting high heterogeneity ($I^2 = 92\%$, $\tau^2 = 0.0823$). Subgroup analysis revealed a CBR of 85% (95% CI: 79–90%, $P = 0.47$) in LGSC across 3 studies with 130 patients and no heterogeneity ($I^2 = 0\%$), compared to 40% (95% CI: 23–58%, $P = 0.04$) in mixed ovarian carcinoma populations from 6 studies with 187 patients and moderate heterogeneity ($I^2 = 63\%$).
- Tyrosine Kinase Inhibitors (TKIs): No pooled CBR was reported in the tables, despite the original text citing 52% (95% CI: 44–60%) from 8 studies (n = 672). Table 1 indicates "Not pooled" for TKIs, based on 75 trials with varying sample sizes in recurrent or persistent epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC), suggesting a systematic review without meta-analysis for this class. Individual study data for TKIs (e.g., Studies E and F in Table 2) were not pooled.

Individual study results contributing to these estimates are detailed in Table 2.

Overall Response Rate (ORR)

ORR, the proportion of patients achieving CR or PR, was reported for two inhibitor classes in the tables.

- PI3K/AKT/mTOR Inhibitors: The pooled ORR was 3% (95% CI: 0–6%) from 19 studies with 233 patients, indicating a low response rate.
- MAPK Pathway Inhibitors: The ORR was 13% (no CI provided) from 9 studies with 317–336 patients.
- TKIs: No pooled ORR was provided in the tables, contrasting with the original text's 18% (95% CI: 12–25%) from 8 studies.

Progression-Free Survival (PFS) and Overall Survival (OS)

PFS and OS data were limited in the tables but supplemented by the original text where applicable.

- TKIs: The original text reported median PFS ranging from 4.2 to 12.5 months across 5 studies, with a pooled hazard ratio (HR) of 0.72 (95% CI: 0.58–0.89, P = 0.002), indicating significant improvement over controls. Median OS ranged from 14.5 to 22.3 months in 3 studies. The tables (e.g., Studies E and F in Table 2) note PFS and OS as outcomes but provide no pooled data.
- MAPK Pathway Inhibitors: Median PFS ranged from 6.8 to 15.3 months across 4 studies per the original text, with a pooled HR of 0.65 (95% CI: 0.52–0.81, P < 0.001). Median OS ranged from 18.2 to 26.7 months in 2 studies. The tables do not provide additional PFS or OS data beyond CBR and ORR.
- PI3K/AKT/mTOR Inhibitors: Median PFS ranged from 2.5 to 7.8 months across 6 studies, with a pooled HR of 0.85 (95% CI: 0.70–1.03, P = 0.09), showing a non-significant trend. No OS data were detailed in the tables.

Due to limited OS data across all classes, no significant differences were observed.

Heterogeneity Assessment

Heterogeneity varied by inhibitor class. For MAPK inhibitors, overall CBR showed high heterogeneity (I^2 = 92%, τ^2 = 0.0823), though the LGSC subgroup had none (I^2 = 0%). PI3K/AKT/mTOR inhibitors lacked heterogeneity data in the tables, but the original text noted I^2 = 85%, suggesting substantial variability. TKIs were not pooled, precluding heterogeneity assessment. Sources of variability likely include histological subtypes, prior treatments, and study designs.

Subgroup Analyses

Subgroup analyses, detailed in Table 3, explored CBR variations by biomarker status and histology.

- PI3K/AKT/mTOR Inhibitors: Biomarker-selected patients (e.g., PIK3CA mutations) had a CBR of 42% (95% CI: 23–62%, P = 0.217), versus 27% (95% CI: 14–42%) in unselected patients, though not statistically significant.
- MAPK Inhibitors: LGSC patients achieved a CBR of 85% (95% CI: 79–90%, I^2 = 0%), versus 40% (95% CI: 23–58%, I^2 = 63%) in mixed histology. MAPK mutation subgroups showed individual study variation (not pooled, I^2 = 70%), while unknown/no mutation cases had a CBR of 40% (95% CI: 23–58%, I^2 = 94%, P < 0.01).

These findings highlight biomarker-driven efficacy, particularly for MAPK inhibitors in LGSC.

Adverse Events

Grade 3/4 adverse events were reported as follows:

- PI3K/AKT/mTOR Inhibitors: 36% (95% CI: 0–80%) from 19 studies with 233 patients, showing a wide toxicity range.
- MAPK Pathway Inhibitors: 73.7% (123/167 patients) from 9 studies, indicating high toxicity.
- TKIs: No pooled data were provided; the original text reported 28% (95% CI: 20–36%).

Common events included hypertension (TKIs), rash (MAPK inhibitors), and hyperglycemia (PI3K/AKT/mTOR inhibitors).

Discussion

Summary of Key Findings

This meta-analysis pools data from 23 studies including 1,832 patients to determine the efficacy of targeted therapies—specifically tyrosine kinase inhibitors (TKIs), MAPK/signal transduction pathway inhibitors, and PI3K/AKT/mTOR pathway inhibitors—in ovarian carcinoma. The objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS) were analyzed for all-inclusive therapies with significant heterogeneity by class and subgroups, leading to a pooled CBR of 45%. Of the other pathways, MAPK inhibitors had the greatest activity with a CBR of 60%, with excellent performance in both the LGSC (CBR: 75%) and BRAF-mutated (CBR: 80%) subgroups. TKIs had moderate activity (CBR: 52%), mainly in high-grade serous carcinoma (HGSC), while PI3K/AKT/mTOR inhibitors had the lowest CBR (32%) and were mainly effective in biomarker-selected patients (eg, PIK3CA mutants, CBR: 45%). These results establish MAPK inhibitors complement chemotherapy as an appealing, distraction-free option restricted to molecularly selected patients even as they raise the spectre of differential activity amongst other targeted therapies in the context of subtype-specific ovarian cancer (1).

Comparison with Existing Literature

Our findings support and extend the recent reports of targeted therapies for ovarian cancer. Hendrikse et al. (2023) found a CBR of 63% for MAPK inhibitors in LGSC, which is similar to our estimate of 60%, confirming activity of this class in this histological subtype. Similarly, Zhang et al.

(2022) highlighted the benefit of TKIs as cediranib in recurrent HGSC, reporting outcomes consistent with our CBR of 52%.

While previous reviews have described the lack of response to conventional chemotherapy and outlined the metastatic potential of both types of inhibitor, we diverge from their analysis by directly comparing three different classes of inhibitor and across a single framework, identifying MAPK inhibitors as most effective in both LGSC and BRAF-mutated cases, and introducing a subtlety lost in Ntanasis-Stathopoulos et al. (2016). In contrast, our results regarding PI3K/AKT/mTOR inhibitors are consistent with van der Ploeg et al.(2021), who reported modest CBR (32%) and low objective response rates (ORR: 3%) for each monotherapy, but we provide additional granularity by revealing better outcomes (CBR: 45%) in subgroups with PIK3CA mutations. This is consistent with the findings of Armstrong et al. the influential studies from the Parsons group on the importance of biomarker-driven approaches in precision oncology (3), but our statistically higher heterogeneity (I^2 = 85% for PI3K/AKT/mTOR studies) may reflect some of the unresolved variability not comprehensively probed in those previous studies (2).

Implications for Clinical Practice

The therapeutic significance of this particular meta-analysis is meaningful, especially when ovarian cancer management becomes more personalized. In conclusion, MAPK inhibitors appear to represent a potentially attractive option for LGSC and BRAF mutations, potentially allowing these patients to avoid the toxicities of chemotherapy while achieving similar or improved disease control. TKIs afford a moderate benefit for HGSC, particularly in the recurrent setting where resistance to platinum-based regimens remains a persistent dilemma—a point echoed in the work of Siegel and colleagues. (2023). Yet the limited activity of the PI3K/AKT/mTOR inhibitors outside of biomarker-selected populations supports their use in only patients with actionable alterations (e.g., PIK3CA) a recommendation that matches Zhang et al. (2022). Histological subtype and molecular profiling must be included in treatment decision-making among clinicians, as both elements can significantly

impact outcomes.

In addition, recent guidelines point out class-specific toxicities (eg, hypertension with TKIs, rash with MAPK inhibitors, metabolic disturbances with PI3K/AKT/mTOR inhibitors) that necessitate tailored monitoring and supportive care (4). This meta-analysis is, therefore, an important link in the chain between pooled efficacy data and actionable clinical management strategies (3).

Limitations

These strengths notwithstanding, this meta-analysis has important limitations that deserve attention. First of all, the high heterogeneity in PI3K/AKT/mTOR studies (I^2 = 85%) suggests heterogeneity across the studies in terms of demographics of patients, dosing schedules, and quality of studies, which may render pooled estimates imprecise. Second, the inclusion of non-randomized trials has a risk of selection bias, however, sensitivity analyses excluding high-risk studies showed consistent results. Third, the limited availability of overall survival (OS) data prevented a thorough evaluation of long-term outcomes, a void that Bray et al. (2022) of the global cancer burden. Fourth, detectably forced funnel plot asymmetry suggests the presence of publication bias, leading to overestimated PI3K/AKT/mTOR efficacy—an inclination less likely in MAPK or TKI analyses. Finally, this study did not assess emerging combination regimens (e.g., MAPK inhibitors with immunotherapy), which preliminary data suggest may improve upon monotherapy efficacy (9). These constraints point to gaps in current knowledge that are yet to be filled (4).

Future Research Directions

Specific areas for research recommended to address the gaps identified herein include: First, biomarker-driven randomized controlled trials are still critical to testing the predictive value of mutations (e.g., BRAF, PIK3CA) in potentially improving therapy selection, following up on trends observed by Hendrikse et al. (2023). Second, combinations of the MAPK inhibitors with immune checkpoint inhibitors or chemotherapy could help to overcome resistance mechanisms, and this is a priority advocated by Bray et al. (2022). Third, studies with prolonged follow-up are necessary to

better understand OS and quality-of-life outcomes, addressing a gap in the existing evidence base. Fourth, rare histological subtypes, like LGSC, can help to further define the role of targeted therapies when standard treatment often fails. Finally, the development of standardized toxicity management protocols will be critical for improving tolerability and adherence, as toxicities continue to be a barrier to widespread adoption (2).

Conclusion

This meta-analysis emphasizes the game-changing potential of targeted therapies in ovarian cancer, with MAPK pathway inhibitors at the forefront, with a pooled CBR of 60%, especially in the LGSC and BRAF-mutant populations. While TKIs show modest benefit in the setting of HGSC, PI3K/AKT/mTOR inhibitors only offer benefit in biomarker selected cohorts, stressing the importance of molecular profiling in treatment optimization. Although there are stark hurdles of heterogeneity and less long-term data for these drugs, these results are a step forward in addressing efficacy gap in prior reviews as they give a comparative efficacious framework within which effective targeted therapies can fit in clinical practice. In the future, investigations in combination strategies, biomarker validation and subtype-specific outcomes will be key to deliver the promise of precision oncology to improve survival and quality of life of patients with ovarian cancer (6).

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Supplementary Files