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INVESTIGATING THE ROLE OF PARP INHIBITORS IN THE TREATMENT OF OVARIAN CANCER

Ph.D. Thesis

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Budapest

2025

„Wherever the art of Medicine is loved, there is also a love of Humanity.”

Hippocrates

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1 LIST OF ABBREVIATIONS

AAA	anti-angiogenic agents
AE	adverse events
CI	confidence interval
ESMO	European Society for Medical Oncology
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HGSC	high-grade serous carcinoma
HR	hazard ratio
HRD	homologous recombination deficiency
HRP	homologous recombination proficient
HRR	homologous recombination repair
ITT	intention-to-treat
LOH	loss of heterozygosity
MDS/AML	myelodysplastic syndrome and acute myeloid leukemia
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OC	ovarian cancer
OS	overall survival
PARP	poly (ADP-ribose) polymerase
PARPi	poly (ADP-ribose) polymerase inhibitor
PFS	progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	risk ratio

2 STUDENT PROFILE

2.1 Vision and mission statement, specific goals

During my Ph.D. studies my vision was, and still, is that molecular targeted therapy holds a huge potential to completely change oncological treatment forever.

I have a mission of learning on the possibilities that are offered by individualized therapy of gynecological malignant diseases and to make it widespread and get them to the bedside.

My specific goals were the following: to examine the safety and efficacy of PARPi therapy in advanced OC cases and to examine the safety and efficacy the combination of PARPi and AAA in OC cases.

2.2 Scientometrics

Number of all publications:	4
Cumulative IF:	10.3
Av IF/publication:	2.58
Ranking (SCImago):	Q1: 3, Q3: 1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	6.8
Av IF/publication:	3.4
Ranking (Sci Mago):	Q1:2
Number of citations on Google Scholar:	22
Number of citations on MTMT (independent):	16
H-index:	2

The detailed bibliography of István Baradács MD can be found on page 53.

2.3 Future plans

In the near future my plans include to improve my skills in the field of obstetrics and gynecology, especially in the field of gynecological surgeries.

Moreover, in the meantime of my clinical improvement I want to carry out new studies and scientific papers as well.

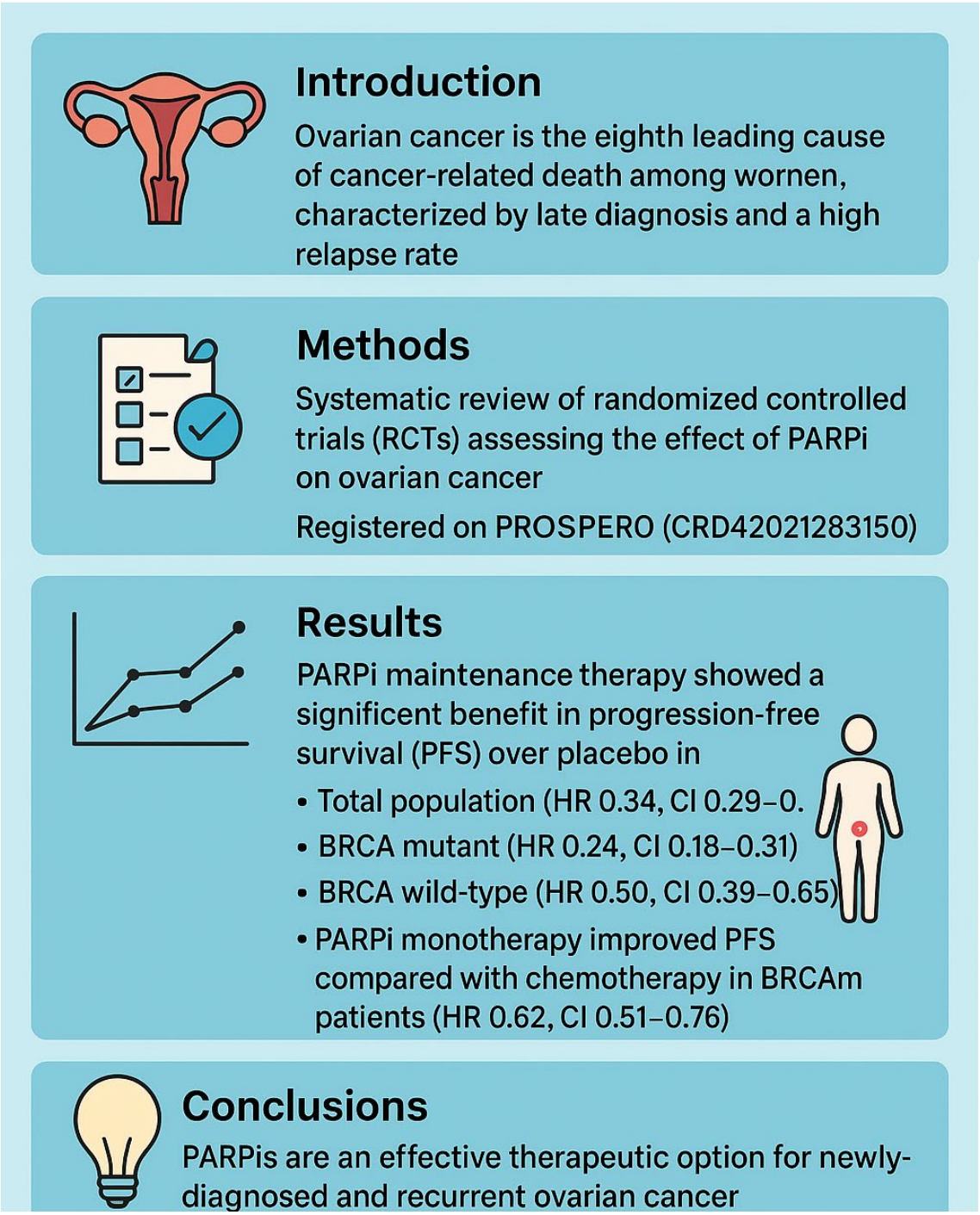
3 SUMMARY OF THE THESIS

The object of the first study was to evaluate the survival benefits and potential adverse effects of PARPis across different patient subgroups based on RCT data. The second study aimed to assess the efficacy and safety of combining PARPis with AAAs compared to monotherapy and chemotherapy. Both systematic reviews followed PRISMA and Cochrane guidelines, with protocols registered on PROSPERO. Comprehensive literature searches were conducted across MEDLINE, EMBASE, and Cochrane Library, without language restrictions. Eligibility criteria focused on RCTs involving advanced OC, with data on PFS, OS, and adverse events. Quality and bias assessments were performed using the Cochrane RoB 2 tool and GRADE methodology. Statistical analyses used random-effects models and software tools including R and Stata, with subgroup and heterogeneity analyses included for robust interpretation.

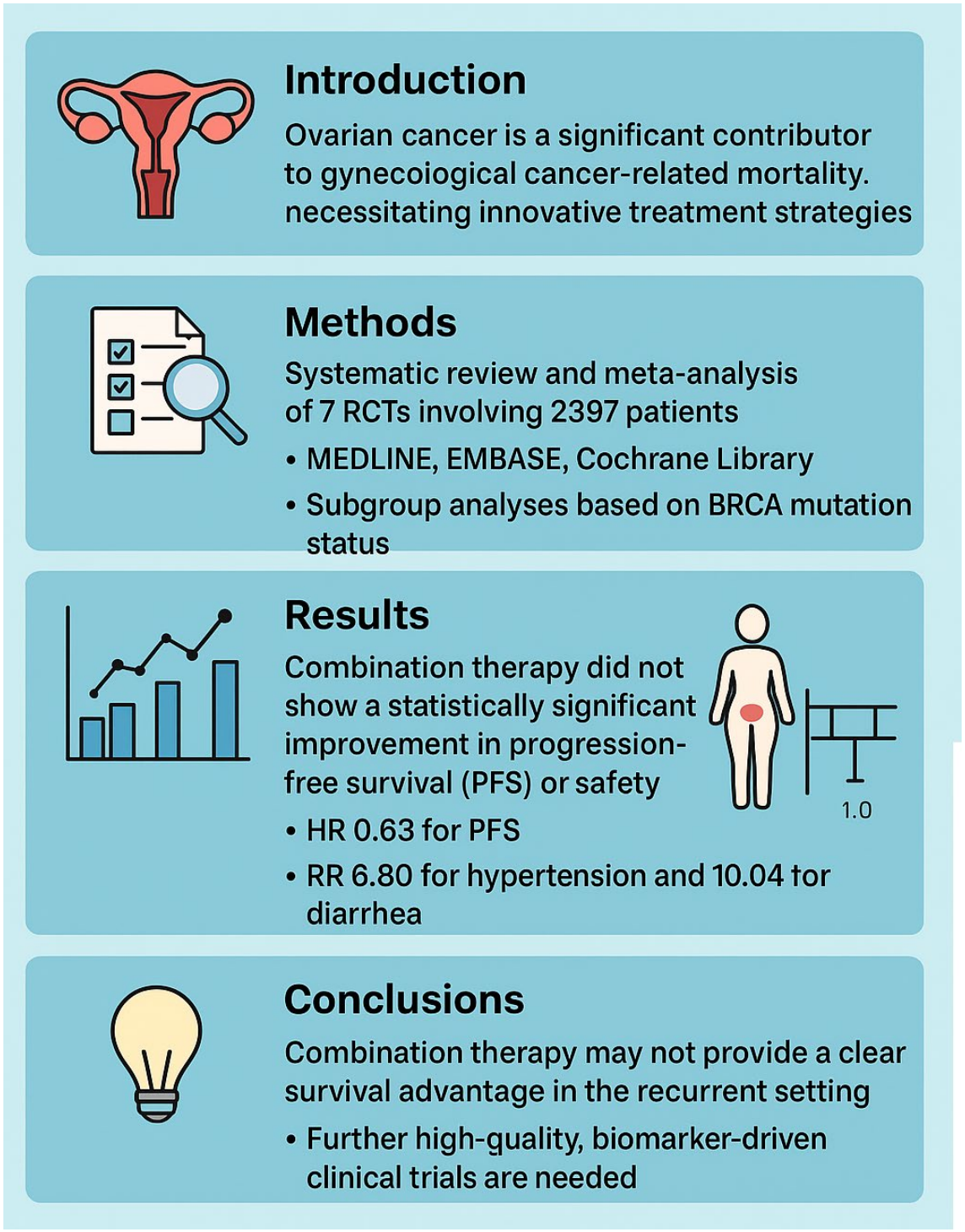
My Ph.D. studies found that PARP inhibitors (PARPis), particularly as maintenance therapy, significantly improve progression-free survival (PFS) in both recurrent and newly diagnosed ovarian cancer (OC), with the most benefit seen in BRCA-mutated populations. However, PARPis showed less efficacy when used as monotherapy or in combination with chemotherapy compared to standard chemotherapy. While maintenance PARPi therapy increased the risk of grade 3–4 adverse events—especially hematological toxicities—most were manageable, and overall safety was comparable to chemotherapy. Overall survival (OS) benefits remain unclear due to immature data and limited long-term follow-up. The addition of anti-angiogenic agents (AAAs) to PARPis did not significantly improve PFS in recurrent OC, though it showed potential in newly diagnosed HRD-positive cases, as seen in the PAOLA-1 trial. Genetic profiling, particularly BRCA and HRD status, appears critical for optimizing patient selection and predicting treatment response. Limitations include clinical heterogeneity, open-label designs, and reliance on aggregate data rather than individual patient data. Despite these, the study provides strong evidence supporting PARPi use in maintenance therapy and highlights the need for further research on HRD status, long-term outcomes, and personalized treatment strategies.

4 GRAPHICAL ABSTRACT

Study I.



Study II.


Introduction
Ovarian cancer is a significant contributor to gynecoiogical cancer-related mortality. necessitating innovative treatment strategies
Methods
Systematic review and meta-analysis of 7 RCTs involving 2397 patients
• MEDLINE, EMBASE, Cochrane Library
• Subgroup analyses based on BRCA mutation status
Results
Combination therapy did not show a statistically significant improvement in progression-free survival (PFS) or safety
1.0
• HR 0.63 for PFS
• RR 6.80 for hypertension and 10.04 for diarrhea
Conclusions
Combination therapy may not provide a clear survival advantage in the recurrent setting
• Further high-quality, biomarker-driven clinical trials are needed

5 INTRODUCTION

5.1 Overview of the topic

5.1.1 What is the topic?

Ovarian cancer (OC) is the third most frequent gynecological malignancy, the second leading cause of death of gynecologic cancers worldwide, and the eighth leading cause of cancer-related deaths among women, with a five-year survival rate of less than 50% in advanced stages. In 2020, globally, there were 313,959 new cases registered and 207,252 deaths attributed to the disease in 2020 (1).

5.1.2 What is the problem to solve?

Epithelial ovarian cancers (EOC) represent 90% of ovarian cancer cases, as around 75% classified as high-grade serous carcinoma (HGSC) (2). Current research indicate that the primary site of HGSC origin is the fallopian tube fimbriae, this fact enables rapid peritoneal dissemination (3,4). Due to its asymptomatic progression and lack of effective screening methods, approximately 75% of HGSC cases are diagnosed at advanced stages (Grade III or IV) (5).

5.1.3 What is the importance of the topic?

Standard treatment for advanced OC typically, cytoreductive surgery followed by systemic chemotherapy. Although, this approach often elicits a strong initial response, over 70% of advanced-stage patients eventually experience recurrence and/or develop resistance to chemotherapy (6,7).

5.1.4 What would be the impact of our research results?

Advances in cancer biology have seriously underlined the significance of BRCA1/2 mutations and homologous recombination deficiency (HRD) in ovarian cancer, paving the way for targeted therapies such as poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi). According to the data of The Cancer Genome Atlas, approximately 50% of HGSC patients exhibit HRD, with germline and somatic BRCA1/2 mutations are presented in 11–15% and 7% of cases, respectively (8). PARP enzymes play a key role in DNA repair by resolving single-strand breaks. Inhibiting PARP leads to the accumulation of double-strand breaks, which require homologous recombination repair (HRR). In cancer cells with BRCA1/2 mutations or other forms of HRD, the HRR pathway is

compromised, making these cells highly susceptible to PARPi-induced cell death - a process known as synthetic lethality. Globally, three PARP inhibitors (olaparib, rucaparib, and niraparib) have been approved for the treatment of ovarian cancer, including cases originating in the fallopian tubes or peritoneum (9).

Another crucial point, in the treatment of ovarian cancer is to target the vascularization of the tumor and trying to act against it this way. Angiogenesis is an essential mechanism for tumor growth and survival, as it provides tumor cells with blood supply. Anti-angiogenic agents (AAAs) such as bevacizumab act on the VEGF pathway and are proven to be effective in solid tumors, which ovarian cancer is one (10,11).

The combination of PARPis and AAAs for ovarian cancer shows potential due to their synergistic mechanisms of action and beneficial effects. Preclinical studies suggest that AAA therapy can enhance the DNA damage response and improve the efficacy of PARP inhibition (12). AAAs induce hypoxia, which downregulates key homologous recombination repair proteins such as BRCA1/2 and RAD51. This shift increases tumor dependence on PARP-mediated DNA repair pathways, thereby enhancing synthetic lethality (13). Furthermore, this therapeutic combination alters the tumor immune microenvironment: PARP inhibitors enhance tumor immunogenicity, while antiangiogenic agents mitigate VEGF-mediated immunosuppression, collectively strengthening anti-tumor immune responses (14). PARPis and AAAs have demonstrated increased PFS and overall survival (OS) in individuals with OC. However, despite these encouraging findings, current guidelines, such as those from the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), continue to prioritize monotherapy with PARP inhibitors or chemotherapy over combination therapy (13,15).

6 OBJECTIVES

6.1 Study I.

The object of my first study was to evaluate the survival benefits and potential adverse effects of PARP inhibitors by analyzing data from randomized controlled trials (RCTs), with a focus on outcomes across different patient subgroups.

6.2 Study II.

The object of my second study was to evaluate the efficacy and safety of combining PARP inhibitors with anti-angiogenic agents (AAAs) in the treatment of ovarian cancer, in comparison to PARP inhibitor monotherapy and standard chemotherapy.

7 METHODS

7.1 Study I.

7.1.1 Study design

The study followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement (16). It was conducted in accordance with the recommendations for systematic reviews of interventions detailed in the Cochrane Handbook (17). Additionally, the review protocol was registered on PROSPERO with the registration number CRD42021283150.

7.1.2 Literature search and eligibility criteria

A systematic literature search was performed from inception till April 13, 2022: during the process the electronic databases of MEDLINE (via PubMed), EMBASE, and Cochrane Library were used. The search terms included all types of PARPis and ovarian cancer-related terms. The reference lists of the eligible articles were manually reviewed to identify any additional potentially relevant trials.

During the process no language or other type of restrictions were applied.

7.1.3 Study selection and data extraction

All RCTs were marked as eligible which: (1) investigated patients who were diagnosed with advanced OC, peritoneum, or fallopian tube; (2) provided data on newly-diagnosed or recurrent cases in terms of OS, progression-free survival (PFS), or adverse events (AEs) (e.g. anaemia, thrombocytopenia, neutropenia, leukopenia, vomiting, fatigue, and nausea); (3) utilized PARP inhibitors as an intervention in monotherapy, maintenance therapy, or in combination with standard-of-care treatments. Studies got excluded that were: (1) phase I RCTs; (2) conference abstracts which did not show reliable data on study design; and (3) tested PARPis in a combination with other targeted therapeutic agents.

After duplicate removal, two authors independently selected the articles while respecting the eligibility criteria. Cohen’s kappa coefficient was calculated after each selection phase (18). All the occurring discrepancies were resolved by the involvment of a third reviewer.

Study and outcome data were extracted into a pre-defined data collection form by the two reviewers. Disagreements were resolved by the involvement of a third reviewer. The following data were collected from each of the selected articles: name of the first author, year of publication, study design, trial name, number of patients, ages of patients, outcomes (PFS, OS, and AE) and the related data, risk ratios (RRs) or hazard ratios (HRs) with 95% confidence intervals (CI), therapy settings, the number of different mutations, and the incidence of all recorded adverse events (AEs) along with their grades were evaluated on a 5-level scale based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). For each outcome, data were taken exclusively from a single article that met the inclusion criteria and provided the longest follow-up. Statistical analyses were conducted solely on published data, without directly contacting the authors for additional information.

7.1.4 Quality Assessment

Two authors independently assessed the quality of all the included studies with the help of the Revised Cochrane risk-of-bias tool for RCTs (RoB 2) (19). Bias were evaluated in five primary domains: randomization process, deviations from intended interventions, missing output data, outcome measurement, and selection of reported results. Any ocurring disagreements were resolved by the involvement of a third author.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method was used during the process to evaluate the reliability of the evidence (20). Two independent authros examined each assessment criterion for each outcome and comparison. Any disagreements were resolved by the involvement of a third reviewer.

7.1.5 Data synthesis and analysis

In the case of PFS and OS, HRs got pooled with 95% CI using random effects models with the inverse variance method based on estimates of log HRs and their standard errors. In order to estimate the between-study variance tau2, restricted maximum-likelihood estimator was applied (21). For binary outcome data (Ae), random effects estimates of risk ratios (RRs) with 95% CI were calculated using the exact Mantel-Haenszel method (22–24); hence, we did not apply continuity correction to handle zero cell counts (25,26). Following the recommendation of Veroniki et al. (27), the Paule-Mandel method (28) was used for the estimation of heterogeneity variance measure tau2. For the outcomes where

the study number was larger than 5, a Hartung-Knapp adjustment (29,30) was utilized. Adjustments were not used if the study number was 5 or smaller. Where applicable, the prediction intervals got reported (i.e., the expected range of effects of future studies) of results per the recommendations of IntHout et al. 2016 (31).

The statistical analysis of the data was conducted with the help of the R programming language (32) with the use of the meta (33) and dmetar (34) packages. The results were illustrated with forest plots, and with aggregated-forest plots. The results were deemed statistically significant if the p-value was less than 0.05. Heterogeneity was evaluated using I^2 statistics and χ^2 tests, where a p-value less than 0.1 indicated significant heterogeneity (35).

A minimum of three studies were required for each outcome to conduct a meta-analysis.

To ensure maximum homogeneity among the study groups, the two major categories of recurrent and newly diagnosed tumors were further divided based on therapy settings and BRCA mutation status.

7.2 Study II.

7.2.1 Literature search and eligibility criteria

To find eligible articles, a systematic search was performed using 3 online databases: MEDLINE (via PubMed), EMBASE, and Cochrane Library. The databases got searched through from their inception until November 28, 2022. The search strategy used a combination of relevant keywords and Medical Subject Headings (MeSH) terms, including the likes of "ovarian cancer," "PARP inhibitors," "anti-angiogenic agents," and "combination therapy". The reference lists of the eligible articles were manually reviewed to identify any additional potentially relevant trials.

This time again, no language or other type of restrictions were applied.

7.2.2 Study selection and data extraction

This study also followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement (16). It was also conducted in accordance with the recommendations for systematic reviews of interventions detailed in the Cochrane Handbook (17). This review protocol was also registered on PROSPERO under the registration number of CRD42022319461.

7.2.3 Quality assessment

Two authors independently assessed the quality of all the included studies with the help of the Revised Cochrane risk-of-bias tool for RCTs (RoB 2) (19). In this section, once again, bias were evaluated in five primary domains: randomization process, deviations from intended interventions, missing output data, outcome measurement, and selection of reported results. Any ocurring disagreements were resolved by the involvement of a third author.

In the meta-analysis that evaluated the PARPi and antiangiogenic agents' combination, again, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method was used during the process to evaluate the reliability of the evidence (20). Two independent authors examined each assessment criterion for each outcome and comparison. Any disagreements were resolved by the involvement of a third reviewer.

7.2.4 Data synthesis and analysis

As the purpose of the current meta-analysis was to synthetize the data and estimate the combined effect of PARP inhibitors and combination therapy on clinical outcomes, PFS was chosen as the primary outcome of interest. Using the inverse variance method, HRs with 95% CIs were calculated based on estimates of log HRs and by counting their standard errors. AEs were analyzed using RRs with 95% confidence intervals.

Forest plots and aggregated-forest plots were utilized in order to visualize the pooled effect sizes and their corresponding CIs. Statistical significance was defined as a p-value less than 0.05.

To compute pooled HRs, the natural logarithms of the HRs and their corresponding standard errors (SEs) were calculated, following the method described by Tierney et al. (36). The inverse variance weighting method was then applied on the log scale to estimate the pooled HR. Confidence intervals were derived using the restricted maximum-likelihood estimator and the Q-profile method (27,37).

For AE binary outcomes, RRs with 95% CIs were used as the effect size measure.

Study-specific and pooled RRs were computed by extracting the number of patients and the number of events of interest in each treatment group (i.e., raw data) from eligible studies. These RRs reflect the relative risk of events occurring in the experimental group

compared to the control group. When studies reported zero-cell counts, a continuity correction of 0.5 was applied to calculate individual study RRs and their 95% CIs. The pooled RR was estimated using the inverse variance method, with the restricted maximum-likelihood estimator and Q-profile method also used to construct the corresponding confidence intervals (27,37).

Statistical significance was assessed based on whether the pooled CI excluded the null value, or by applying a predefined alpha level of 0.05. Results from the meta-analysis were presented using individual and aggregated forest plots.

When at least three RCTs were available, between-study heterogeneity was evaluated using the I^2 statistic proposed by Higgins and Thompson (38). Interpretation of I^2 followed the Cochrane Handbook guidelines: 0–40% may indicate unimportant heterogeneity; 30–60% may reflect moderate heterogeneity; 50–90% suggests substantial heterogeneity; and values greater than 75% imply considerable heterogeneity.

All statistical analyses were performed using R (32), employing the meta package (39).

8 RESULTS

8.1 Study I.

8.1.1 Search and selection

As a result of our search strategy, we identified 9,144 records, after performing rigorous selection, 23 articles reporting on 16 trials were found eligible for the utilization of a systematic review and meta-analysis. The PRISMA flowchart of the selection process is presented on **Figure 1**.

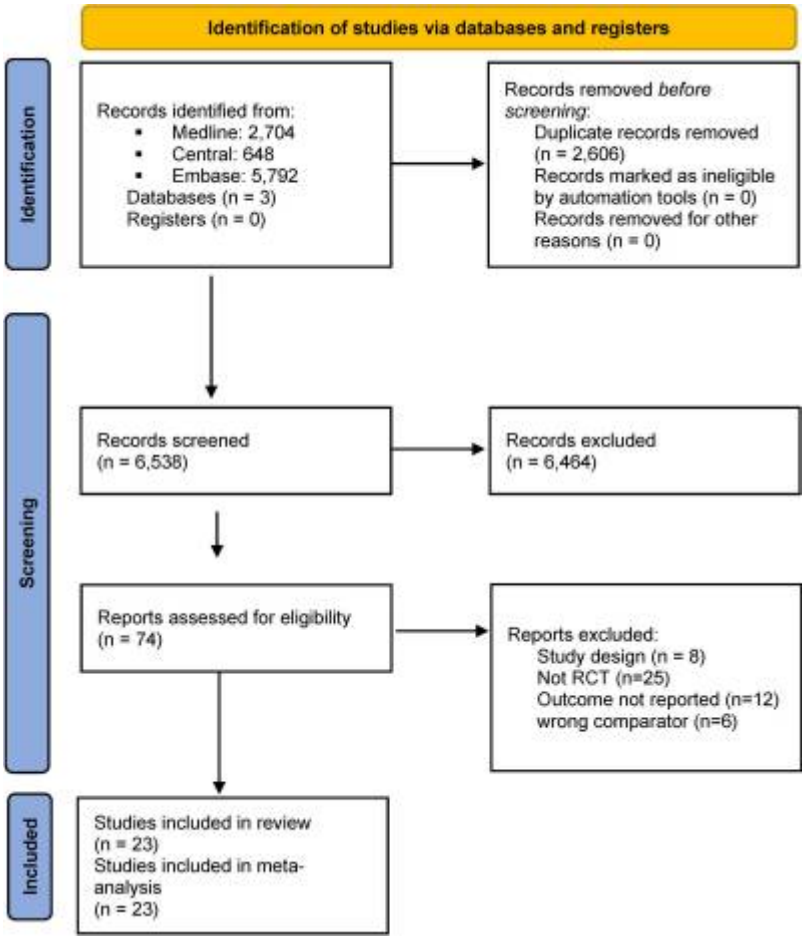


Figure 1 - the PRISMA flowchart of the selection process this Figure was published in *Baradács, I., Teutsch, B., Váradi, A., Bilá, A., Vincze, Á., Hegyi, P., Fazekas, T., Komoróczy, B., Nyirády, P., Ács, N., Bánhidy, F., & Lintner, B. (2024). PARP inhibitor era in ovarian cancer treatment: a systematic review and meta-analysis of randomized controlled trials. Journal of ovarian research, 17(1), 53. https://doi.org/10.1186/s13048-024-01362-y*

8.1.2 The included studies and their basic characteristics

From all the included studies 5,815 patients were pooled to our meta-analysis.

8.1.3 Survival Analysis of Recurrent OC cases

Of all the selected studies 12 evaluated the impact of PARPis in patients with recurrent OC.

8.1.4 PARPis used as a maintenance therapy, compared with a placebo group

Seven clinical studies concluded to the results that PARPis improvePFS comparing them with placebo groups (HR 0.34, CI 0.29–0.40). We also observed statistically significant improvement with PARPis among the BRCAm (HR 0.24, CI 0.18–0.31), and the gBRCAm (HR 0.23, CI 0.18–0.30), and BRCA wild-type (HR 0.50, CI 0.39–0.65) subgroups (40–51) (**Figure 2**).

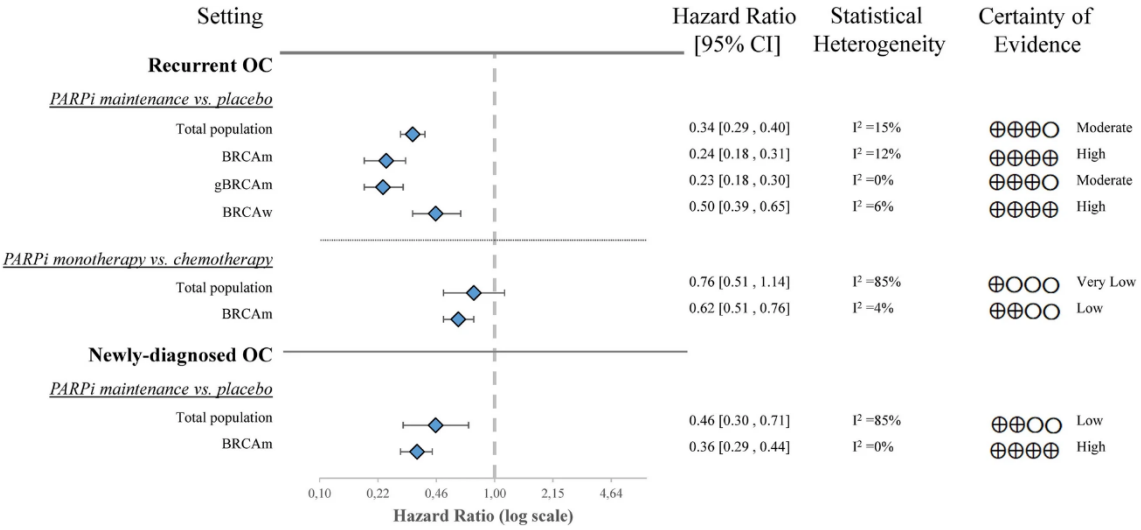


Figure 2 presenting the forest plot of aggregated data representing the hazard ratios of disease progression in recurrent OC and newly-diagnosed OC. OC-ovarian cancer, PARPi-poly ADP ribose polymerase inhibitor, BRCAm-breast cancer gene mutation, gBRCAm-germline breast cancer gene mutation, sBRCAm-somatic breast cancer gene mutation, BRCAw- breast cancer gene wild-type, CI-confidential interval. **Figure 2** was originally published in *Baradács, I., Teutsch, B., Váradi, A., Bilá, A., Vincze, Á., Hegyi, P., Fazekas, T., Komoróczy, B., Nyirády, P., Ács, N., Bánhidy, F., & Lintner, B. (2024). PARP inhibitor era in ovarian cancer treatment: a systematic review and meta-analysis*

of randomized controlled trials. Journal of ovarian research, 17(1), 53. https://doi.org/10.1186/s13048-024-01362-y

Only two studies published reports on the OS, both finding favorable outcomes with PARPis (44,49) but neither time was the result statistically significant (Study 19 (HR 0.73 CI 0.55–0.95) SOLO 2 (HR 0.74 CI 0.54-1.0)).

8.1.5 PARPis used as monotherapy, compared with a chemotherapy group

The currently presented section involves 1,056 patients whose data were presented in four separate RCTs (52–55). There was no significant increase reported with PARPis in terms of PFS in the total population (HR 0.76, CI 0.51–1.14). However, it is important to mention that PARPi impact on the PFS of mBRCA patients was more evident (HR 0.6, CI 0.51–0.76). The results are also presented on **Figure 2**.

It is also important to mention that PARPi monotherapy, compared with a chemotherapy group, did not result in increased OS in ICEBERG 3 (HR 1.01, CI 0.44–2.27) and SOLO 3 (HR 1.07, CI 0.65–1.76) trials (52,53).

8.1.6 PARPis used combined with cemotherapy, compared with a chemotherapy group

There was only one RCT (56) which reported on this therapeutic setting, with the result that the PFS was similar in the two groups - HR 1.02, CI 0.69–1.50.

8.1.7 PARPi used combined with chemotherapy plus using a PARPi maintenance therapy, compared with a chemotherapy group

Again, there was only one RCT which reported on this therapeutic setting (57). Iti is important to note that PARPi treatment combined with chemotherapy and continued as maintenance treatment significantly increased PFS compared to chemotherapy (HR 0.51, CI 0.34–0.77). In mBRCA group, the benefit from the intervention was even more substantial for PFS (HR 0.21, CI 0.08–0.55).

To mention OS, neither the total population (HR 1.17, CI 0.79–1.73) nor mBRCA group (HR 1.28, CI 0.39–4.18) showed a significant difference compared with chemoterapy usage alone.

8.1.8 Newly diagnosed OCs

Four trials reported on the usage and the efficacy of PARPis in newly diagnosed advanced OC cases (58–61).

8.1.9 PARPis used as maintenance therapy, compared with a placebo group (after chemotherapy usage)

PARPis as a maintenance therapy showed a significant PFS in three RCTs (HR 0.46, CI 0.30–0.71). This reported benefit was even more significant in mBRCA group (HR 0.36, CI 0.29–0.44). PRIMA trial reported results on 150 patients with BRCA wild-type cases and reported on a significant PFS advantage among the patients involved in the intervention group (HR 0.50, CI 0.31–0.83) (58–61). The results are again presented on **Figure 2**.

Two studies reported on OS: neither the PRIMA study (HR 0.7, CI 0.44–1.11) nor SOLO 1 study (HR 0.95, CI 0.6–1.53) reported a significant results regarding OS.

8.1.10 PARPis used as combination therapy with chemotherapy and placebo used as a maintenance therapy compared with a placebo group (after placebo usage)

The VELIA trial (40), where the involved patients were randomly assigned to 3 groups; the 2nd and 3rd groups compared PARPi plus chemotherapy combination to chemotherapy, examining their results. Regarding PFS there was no difference in the ITT (intention-to-treat) group (HR 1.07, CI 0.90–1.29), BRCAm group (HR 1.22, CI 0.82–1.80), and BRCAw group (HR 1.04, CI 0.84–1.29).

8.1.11 PARPis used as combination therapy with chemotherapy and PARPi used as a maintenance therapy compared with a placebo group (after placebo usage)

In the 1st and 3rd arm of the VELIA trial (40), patients were treated with PARPi and chemotherapy combination therapy and PARPi was used as a maintenance therapy: statistically significant PFS results were reported on all 3 groups, including the ITT group (HR 0.68, CI 0.56–0.83), the BRCAm group (HR 0.44, CI 0.28–0.68), and the BRCAw group (HR 0.80, CI 0.64–1.00).

8.1.12 Severe AEs

To comply the safety part of the meta-analysis, the total number of AEs, the 4 most common hematologic, the 3 most common toxicity, AEs that lead to the modification of dosage, dosage interruption, the discontinuation of the treatment, and the aggregate incidence of MDS/AML (myelodysplastic syndrome and acute myeloid leukemia). Grade 3 or 4 (severe) AEs and their evaluation are detailed below. The risk of the AEs was evaluated in three therapeutic settings of PARPi.

8.1.13 Grade 3 or 4 AEs in recurrent cases of OC

8.1.14 PARPis used as a maintenance therapy, compared with placebo (after chemotherapy usage)

The above-mentioned therapeutic setting significantly increased the risk of AEs compared to the placebo group: RR 2.98, CI 1.82–4.87. All the 4 examined hematological AEs, anemia (RR 14.26, CI 5.33–38.12), thrombocytopenia (RR 6.86, CI 1.45–32.35), neutropenia (RR 4.33, CI 1.58–11.86), and leukopenia (RR 4.69; C: 1.43–15.37), occurred at a higher risk on the intervention arm. The risks for the 3 most frequent adverse events, nausea (RR 4.65, CI 1.17–18.51), fatigue (RR 2.92, CI 1.53–5.55), vomiting (RR 3.05, CI 1.82–5.13), and the MDS/AML (RR 2.17, CI 1.50–3.15) were all significantly elevated in the intervention arm. To add, the risk of AEs that lead to the modification of the dosages (RR 6.68, CI 3.70–12.07), interruption of the treatment (RR 5.57, CI 2.39–12.98), and the discontinuation of the treatment (RR 3.24, CI 1.20–8.77) were all also increased on the intervention arm (41,45,46,49–51). The results are presented on **Figure 3**.

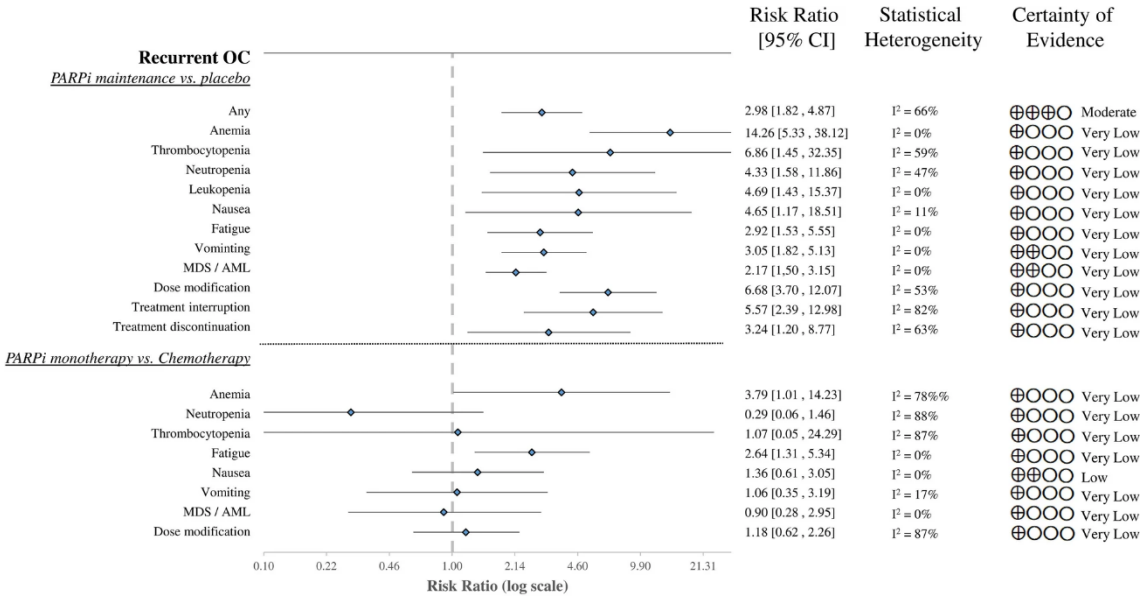


Figure 3 is presenting the forest plot of aggregated data representing the risk ratios of Grade 3 ≤ adverse events in recurrent OC. OC-ovarian cancer, PARPi-poly ADP ribose polymerase inhibitor, MDS/AML CI. Figure 3 was originally published in *Baradács, I., Teutsch, B., Váradi, A., Bilá, A., Vincze, Á., Hegyi, P., Fazekas, T., Komoróczy, B., Nyirády, P., Ács, N., Bánhidy, F., & Lintner, B. (2024). PARP inhibitor era in ovarian cancer treatment: a systematic review and meta-analysis of randomized controlled trials. Journal of ovarian research, 17(1), 53. https://doi.org/10.1186/s13048-024-01362-y*

8.1.15 PARPis used as monotherapy, compared with chemotherapy group

In patients who were treated with PARPi in monotherapy comparing their result to a group who received chemotherapy we can say that the regarding haematological toxicities that there was no significant difference regarding neutropenia (RR 0.29, CI 0.06–1.46) and thrombocytopenia (RR 1.07, CI 0.05–24.29) between the groups. However, the risk of severe anemia (RR 3.79, CI 1.01–14.23) was significantly higher among those who received PARPis compared to those who received conventional chemotherapeutic agents. The risk of fatigue (RR 2.64, CI 1.31–5.34) increased significantly in the PARPi group but regarding nausea (RR 1.36, CI 0.61–3.05) and vomiting (RR 1.06, CI 0.35–3.19) the difference was not deemed significant. The intervention resulted in no difference in AEs that lead to the modifications of the dosages (RR 1.18, CI 0.62–2.26). The difference to the risk of developing MDS and AML was also not significant between the groups (RR 0.90, CI 0.28–2.95) (52–55). The results are again presented on Figure 3.

8.1.16 Grade 3 or 4 AEs in newly diagnosed cases of OC

8.1.17 The usage of PARPis as a maintenance therapy compared to a placebo group (after the usage of chemotherapy)

First line PARPi therapy increased the overall RR of severe (grade 3 or 4) AEs compared to the placebo group: RR 3.46, CI 1.21–9.92. Even though regarding the risk of developing thrombocytopenia there was no significant difference between the groups (RR 2.83, CI 0.12–64.33) the risk of developing anemia (RR 17.05, CI 7.89–36.84) and neutropenia (RR 4.51, CI 1.40–14.58) was increased in the PARPi groups. We found that PARPis did not increase the risk of nausea (RR 1.63, CI 0.45–5.91), the reported cases of fatigue (RR 2.60, CI 0.81–8.28), or vomiting (RR 0.66, CI 0.13–3.51). Although, with the usage of PARPi the risk was higher for AEs that lead to the modification of the dosages (RR 7.51, CI 4.26–13.24), that severe AEs that treatment had to be interrupted (RR 3.23, CI 2.06–5.05), and even that severe AEs that the treatment had to be stopped (RR 4.33, CI 2.31–8.11). The reported cases of MDS/AML were relatively low in both of the groups and there were no significant differences between the two groups (RR 1.61, CI 0.24–10.70) (58–61). The results are presented on **Figure 4**.

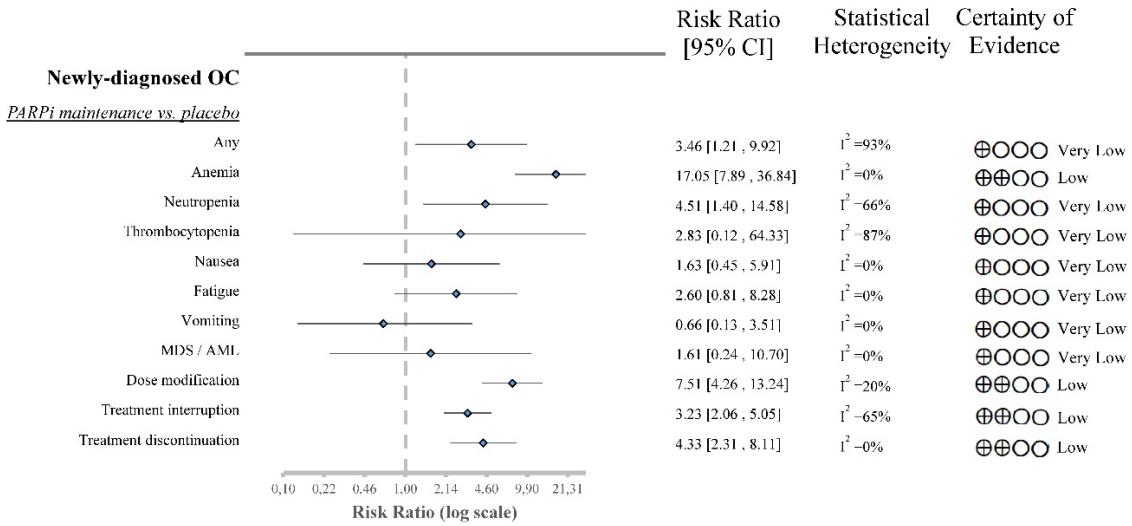


Figure 4 – Forest plot of aggregated data representing the risk ratios of grade 3 ≤ adverse events in newly-diagnosed OC., originally published in *Baradács, I., Teutsch, B., Váradi, A., Bilá, A., Vincze, Á., Hegyi, P., Fazekas, T., Komoróczy, B., Nyirády, P., Ács, N., Bánhidy, F., & Lintner, B. (2024). PARP inhibitor era in ovarian cancer treatment: a*

systematic review and meta-analysis of randomized controlled trials. Journal of ovarian research, 17(1), 53. https://doi.org/10.1186/s13048-024-01362-y

8.1.18 Risk of bias assessment

The results of the risk of bias evaluation are presented on **Figure 5**. Overall, the risk of bias was assessed as low. However, it is important to note the inclusion of six open-label trials in the analysis.

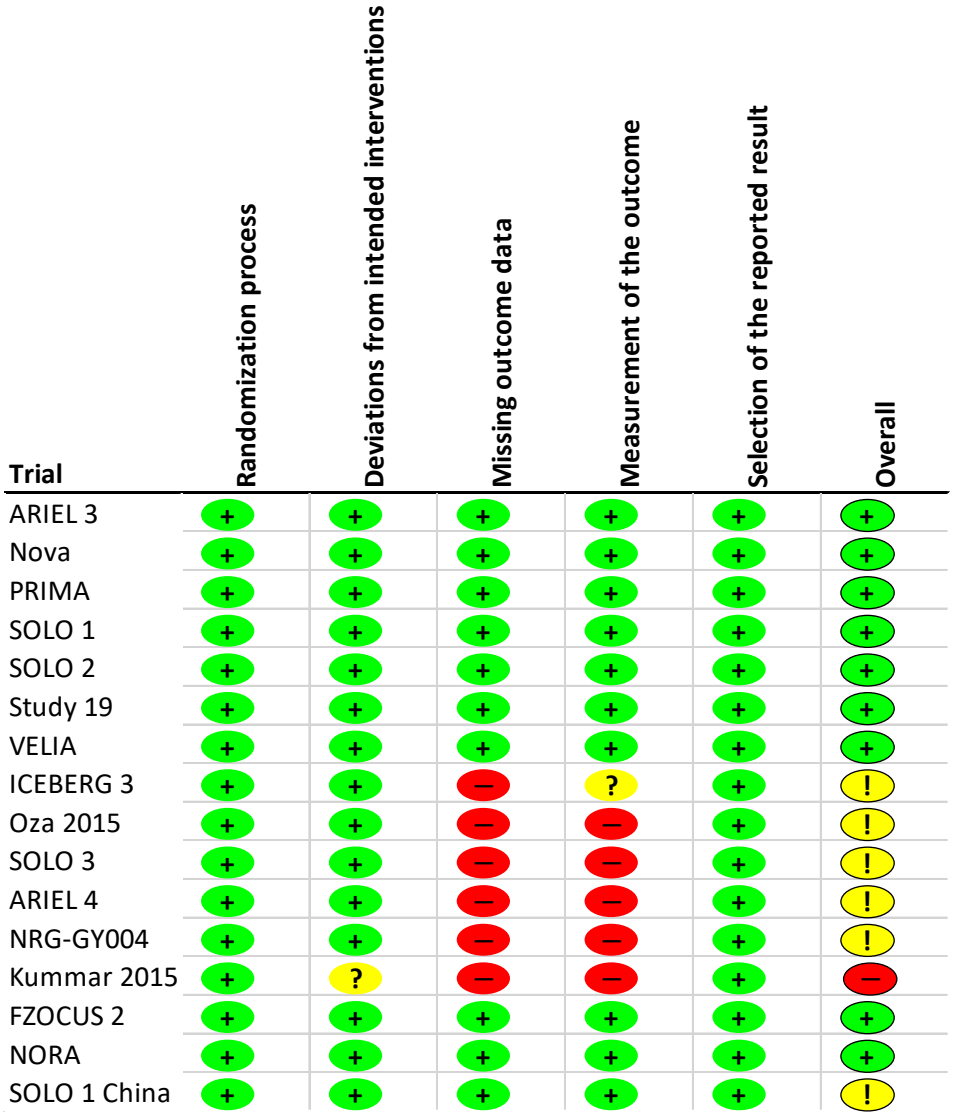


Figure 5 – Risk of bias – Originally published in the supplementary material of *Baradács, I., Teutsch, B., Váradi, A., Bilá, A., Vincze, Á., Hegyi, P., Fazekas, T., Komoróczy, B., Nyirády, P., Ács, N., Bánhidy, F., & Lintner, B. (2024). PARP inhibitor era in ovarian cancer treatment: a systematic review and meta-analysis of randomized*

controlled trials. Journal of ovarian research, 17(1), 53. https://doi.org/10.1186/s13048-024-01362-y

8.1.19 Heterogeneity and Quality of Evidence

The assessment of heterogeneity is illustrated in the figures corresponding to the evaluated outcomes (**Figures 2, 3, and 4**).

8.2 Study II.

8.2.1 Search and selection

As a result of our search strategy, we identified 4,723 records, after performing rigorous selection, 7 RCTS were found eligible for the utilization of a systematic review and meta-analysis. The PRISMA flowchart of the selection process is presented on **Figure 6**.

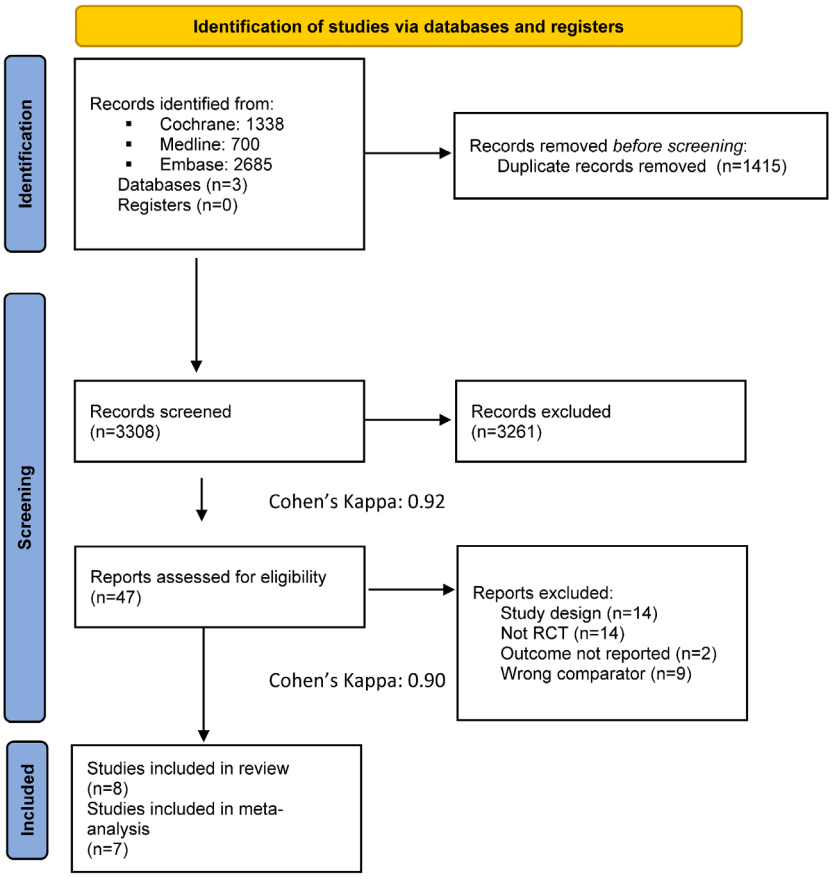


Figure 6 – PRISMA flow chart representing the selection process, originally published in *Baradács, I., Teutsch, B., Vincze, Á., Hegyi, P., Szabó, B., Nyirády, P., Ács, N., Melczer, Z., Bánhidy, F., & Lintner, B. (2025). Efficacy and Safety of Combination Therapy with*

PARP Inhibitors and Anti-Angiogenic Agents in Ovarian Cancer: A Systematic Review and Meta-Analysis. Journal of clinical medicine, 14(5), 1776. https://doi.org/10.3390/jcm14051776

8.2.2 The included studies and their basic characteristics

From all the included studies, 2,157 patients were pooled for our meta-analysis.

8.2.3 Survival analysis

We found 4 studies that evaluated the comparison of PARPi and AAA combination and PARPi therapy only (55,62–64). The results suggest that combination therapy did not yield a statistically significant improvement in progression-free survival (PFS) compared to PARP inhibitor monotherapy in the overall population (HR 0.63, 95% CI 0.37–1.06). Notably, substantial and statistically significant heterogeneity was observed ($I^2 = 67.3\%$, $p = 0.0272$). In the subgroup of patients with BRCA mutations, combination therapy also did not confer a significant PFS benefit (HR 0.70, 95% CI 0.30–1.63), with no evidence of heterogeneity ($I^2 = 0\%$, $p = 0.5325$). Similarly, among BRCA wild-type patients, no statistically significant improvement in PFS was observed (HR 0.39, 95% CI 0.14–1.07), and heterogeneity was low and not statistically significant ($I^2 = 22.1\%$, $p = 0.2772$). Results are presented in **Figure 7**.

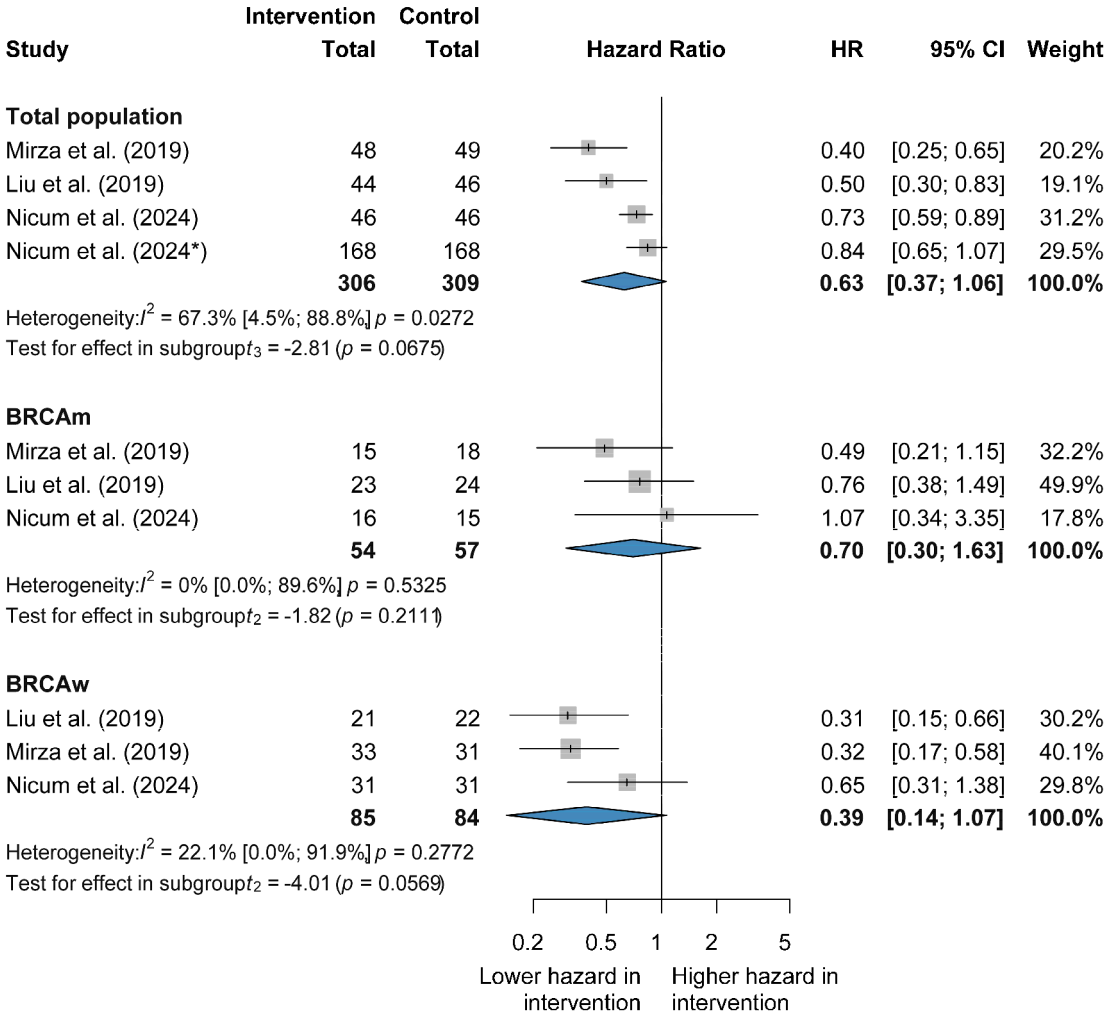


Figure 7 - Forest plot representing the efficacy of combination therapy vs. PARP inhibitor alone in recurrent ovarian cancer. The asterisk (*) indicates that this is the second publication by the same author in the same year. Originally published in *Baradács, I., Teutsch, B., Vincze, Á., Hegyi, P., Szabó, B., Nyirády, P., Ács, N., Melczer, Z., Bánhidy, F., & Lintner, B. (2025). Efficacy and Safety of Combination Therapy with PARP Inhibitors and Anti-Angiogenic Agents in Ovarian Cancer: A Systematic Review and Meta-Analysis. Journal of clinical medicine, 14(5), 1776. https://doi.org/10.3390/jcm14051776*

8.2.4 Comparing combination therapy with chemotherapy

2 RCTs (65,66) were analyzed, and the results indicate that there was no significant improvement in PFS in the observed populations (HR 0.83, CI 0.42-1.63). No significant improvement could be detected in the mBRCA subgroup (HR 0.96, CI 0.00-9126.38), nor

in the wBRCA (HR 0.85, CI 0.08-9.40) subgroup. Results are presented once again in **Figure 8**.

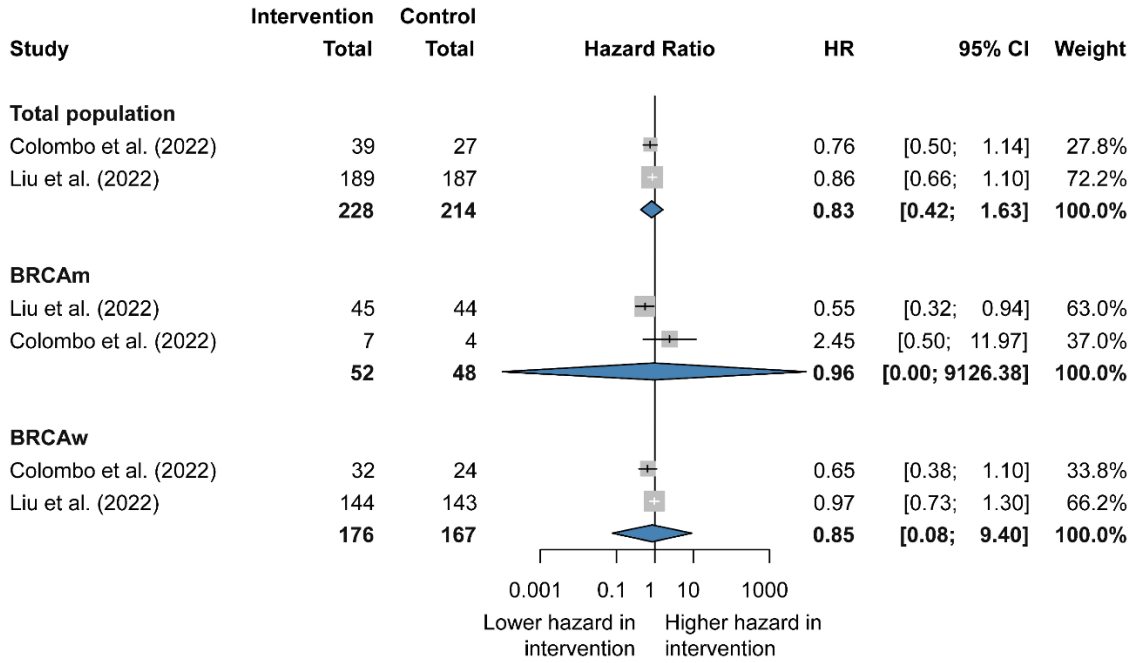


Figure 8 - Forest plot representing the efficacy of combination therapy vs. chemotherapy alone in recurrent ovarian cancer, originally published in *Baradács, I., Teutsch, B., Vincze, Á., Hegyi, P., Szabó, B., Nyirády, P., Ács, N., Melczer, Z., Bánhidy, F., & Lintner, B. (2025). Efficacy and Safety of Combination Therapy with PARP Inhibitors and Anti-Angiogenic Agents in Ovarian Cancer: A Systematic Review and Meta-Analysis. Journal of clinical medicine, 14(5), 1776. https://doi.org/10.3390/jcm14051776*

8.2.5 PARPi and AAA combination in newly diagnosed OC cases

One RCT evaluated the role of PARPi and AAA combination in newly diagnosed cases (12) the results of Ray-Coquard demonstrated that that combination therapy significantly improved PFS in the total population (HR 0.59, CI 0.49–0.72) and the BRCA-mutated (HR 0.31 CI 0.20–0.47) and BRCA wild-type groups (HR 0.63 CI 0.51–0.77).

8.2.6 PARPi and AAA combination compared with AAA only

The results of the above-mentioned study indicate that PARPi and AAA combination, compared to AAA therapy only has a beneficial role in newly diagnosed OC cases. The therapy significantly improved PFS in all the analyzed groups: in the total population (HR

0.59, CI 0.49-0.72), the BRCA mutated (HR 0.31 CI 0.20-0.47) and BRCA wild-type group (HR 0.63 CI 0.51-0.77).

8.2.7 Safety in recurrent OC cases

8.2.8 Combination therapy (PARPi and AAA) compared with PARPi therapy alone

According to the data there was no significant difference between the two therapies in terms of severe (grade 3 or 4) anemia (RR 0.48 CI 0.15-1.50), nausea (RR 0.97 CI 0.18-5.34), vomiting (RR 1.57 CI 0.61-4.08), diarrhea (RR 11.27 CI 0.93-136.40), and MDS/AML (RR 2.39 CI 0.18-32.53). However, there is an increased risk of malignant and severe hypertension with the usage of combination therapy compared with single PARPi therapy (RR 7.82 CI 1.21-50.76) (62–65). Results are presented in **Figure 9**.

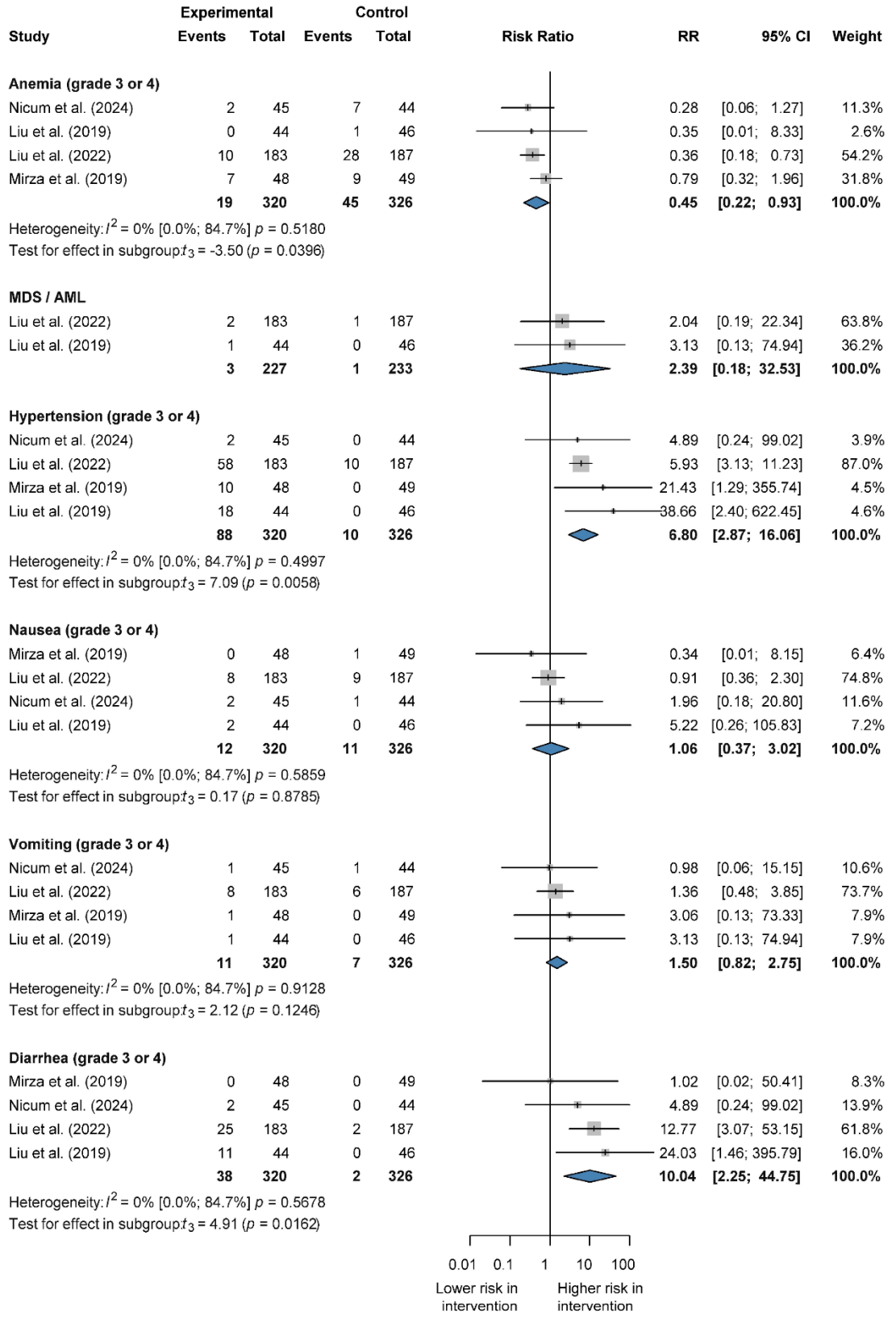


Figure 9 - Forest plot representing risk ratios of grade 3 ≤ adverse events for combination therapy vs. PARP inhibitors alone in recurrent ovarian cancer. It was originally published

in *Baradács, I., Teutsch, B., Vincze, Á., Hegyi, P., Szabó, B., Nyirády, P., Ács, N., Melczer, Z., Bánhidy, F., & Lintner, B. (2025). Efficacy and Safety of Combination Therapy with PARP Inhibitors and Anti-Angiogenic Agents in Ovarian Cancer: A Systematic Review and Meta-Analysis. Journal of clinical medicine, 14(5), 1776. https://doi.org/10.3390/jcm14051776*

8.2.9 Combination therapy (PARPi and AAA) compared with chemotherapy

Our data suggest that there is no significant difference between PARPi and AAA theapy compared with chemotherapy in terms of the following adverse effects: severe anemia (RR 1.08 CI 0.00-21389562.15), nausea (RR 1.28 CI 0.18-9.28), diarrhea (RR 6.84 CI 0.22-213.32), vomiting (RR 1.17 CI 0.19-7.15), severe, malignant hypertension (RR 15.70 CI 0.38-644.19), and MDS/AML (RR 1.91 CI 0.91-4.00) (Liu, Mirza, Colombo). Results are presented once again in **Figure 10**.

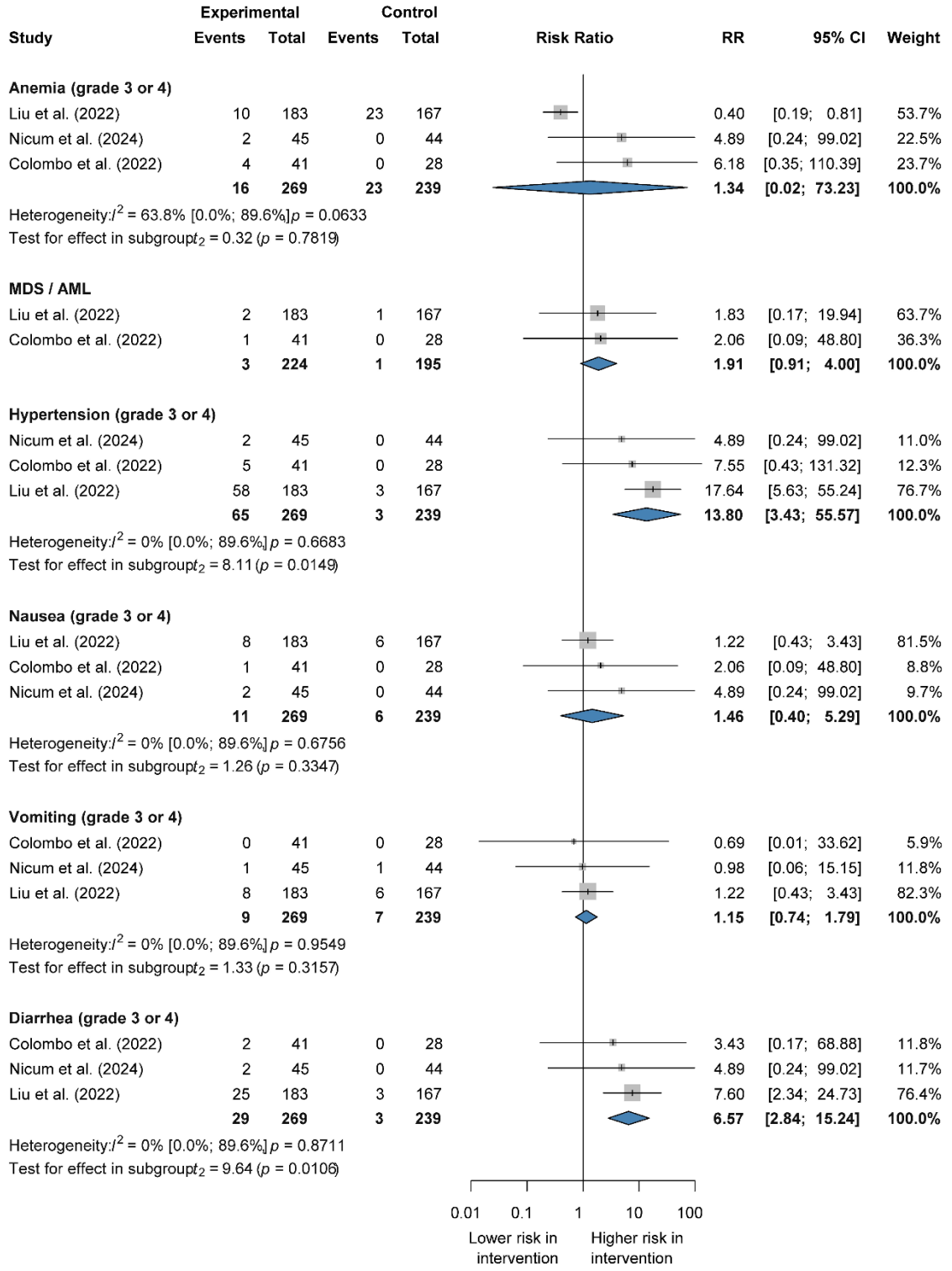


Figure 10 - Forest plot representing risk ratios of grade 3 ≤ adverse events for combination therapy vs. chemotherapy alone in recurrent ovarian cancer. It was originally published in *Baradács, I., Teutsch, B., Vincze, Á., Hegyi, P., Szabó, B., Nyirády, P., Ács, N., Melczer, Z., Bánhidy, F., & Lintner, B. (2025). Efficacy and Safety of Combination*

Therapy with PARP Inhibitors and Anti-Angiogenic Agents in Ovarian Cancer: A Systematic Review and Meta-Analysis. Journal of clinical medicine, 14(5), 1776. https://doi.org/10.3390/jcm14051776

8.2.10 Risk of bias assessment

The results of the assessment of the risk of bias are being presented on **Figure 11**.

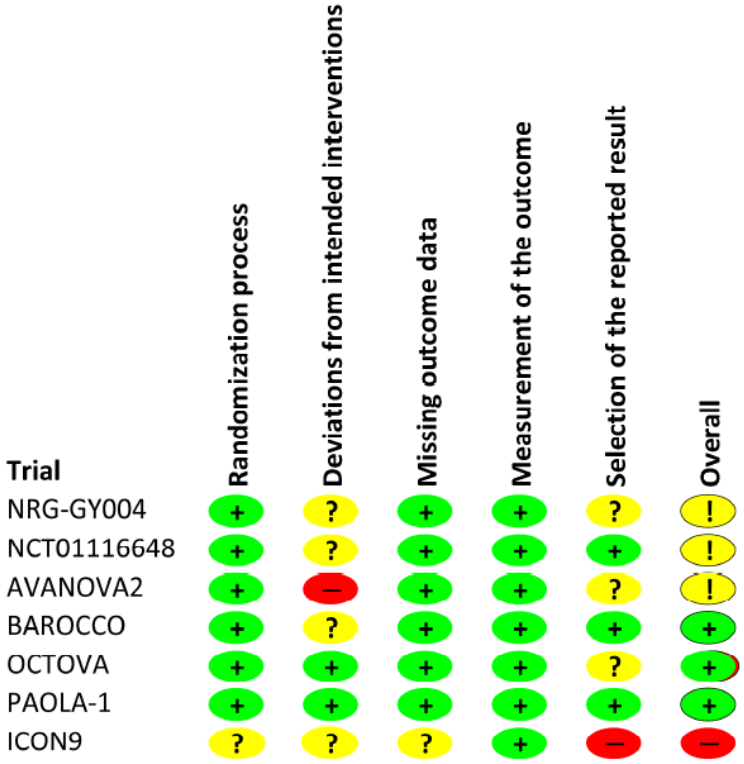


Figure 11 – Risk of bias assessment. Was originally published at the supplementary material part of *Baradács, I., Teutsch, B., Vincze, Á., Hegyi, P., Szabó, B., Nyirády, P., Ács, N., Melczer, Z., Bánhidy, F., & Lintner, B. (2025). Efficacy and Safety of Combination*

Therapy with PARP Inhibitors and Anti-Angiogenic Agents in Ovarian Cancer: A Systematic Review and Meta-Analysis. Journal of clinical medicine, 14(5), 1776. https://doi.org/10.3390/jcm14051776

It is important to mention that out of the analyzed studies, 5 were conducted in an open-label manner, and in one case, they extracted data from conference abstract well. This fact raises concerns about its possible impact on the reported results. Overall, risk of bias are unclear because of the above-mentioned circumstances.

8.2.11 Quality of evidence

The summarization of the findings for each of the outcomes is available in the column called “certainty of evidence” in Figures 2 and 3. Overall, we rated the certainty of evidence as low, mainly because of the observed inconsistencies in the pooled results.

9 DISCUSSION

9.1 Summary of findings, international comparisons

The first meta-analyses of my Ph.D. work demonstrated that PARPi maintenance therapy offers significant PFD benefits over placebo in both recurrent and newly diagnosed advanced OC.

However, these benefits diminish in therapeutic (non-maintenance) settings when PARPis are compared directly to chemotherapy.

It is also important to highlight that while maintenance therapy leads to increased rates of grade 3 and 4 AEs, PARPis do not demonstrate significantly worse toxicity profiles than chemotherapeutic agents. To add, most AEs were manageable through dose adjustments, and relatively low number of cases required treatment discontinuation.

Among patients who received PARPi maintenance, disease progression occurred significantly later comparing to placebo groups. The greatest benefit was observed in those with germline BRCA mutations, although BRCA wild-type patients also experienced measurable PFS improvement. However, we have to note that these findings should be interpreted cautiously, as many individuals classified as BRCA wild-type may have tumors with HRD, which is also predictive of PARPi sensitivity.

We were unable to conduct a meta-analysis for HRD subgroups due to the limited number of studies (fewer than three per treatment setting).

Only four trials (40,46,58,67) included HRD data, and their definitions of HRD varied significantly. For example, the NOVA trial (46) defined HRD as somatic BRCA mutation (sBRCAm) plus other forms of non-BRCA HRD, while ARIEL3 (40) included tumors with high loss of heterozygosity (LOH). The PRIMA study (58) defined HRD based on the presence of BRCA mutations or a minimum score on the myChoice HRD test, although this cut-off does not guarantee HR proficiency outside the threshold.

It is very important to note that niraparib still improved PFS (HR 0.68, CI 0.49–0.94) in the homologous recombination proficient (HRP) subgroup. In the HRD population, niraparib extended median PFS to 21.9 months compared to 10.4 months with placebo (58). This underlines the importance of further investigation in the field of HRD as a predictive biomarker.

OS data remain immature across most trials, limiting our conclusions if PARPi therapy extends life or merely delays progression (68). PFS is typically the primary endpoint due to its faster and more cost-effective assessment. A notable exception is the SOLO-1 trial (60), which reported that investigating a five-year follow-up, 48% of patients in the olaparib group had no disease progression compared to 21% in the placebo group, with a median PFS of 56 months vs. 13.8 months.

Olaparib, niraparib, and rucaparib are the three FDA- and EMA-approved PARPis that are in clinical use, as of the May of 2025.

For recurrent OC, they are approved as maintenance therapy if the disease is proven to be platinum-sensitive.

Olaparib does not require biomarker testing, as shown in Study 19 (43), which demonstrated a significant PFS benefit (HR 0.35, CI 0.25–0.49) across the overall population. Niraparib is approved for gBRCAm cases based on findings from NOVA (46) (HR 0.26, CI 0.17–0.41), while rucaparib is indicated for sBRCAm or gBRCAm cases, as supported by ARIEL3 (40) (HR 0.23, CI 0.16–0.34).

In first-line treatment settings, olaparib (alone or either in combination with bevacizumab) and niraparib are approved for maintenance therapy following a partial or complete response to platinum-based chemotherapy. SOLO-1 study (59) supports olaparib use in sBRCAm or gBRCAm patients (HR 0.30, CI 0.23–0.41). The PAOLA-1 study (12) demonstrated that combining olaparib with bevacizumab significantly improved PFS in HRD/BRCAm (HR 0.33, CI 0.25–0.45) and HRD/BRCA wild-type (HR 0.43, CI 0.28–0.66) subgroups. Niraparib is used regardless of biomarker status, as supported by PRIMA (58), which showed PFS benefits in both the overall (HR 0.62, CI 0.50–0.76) and HRD-positive populations (HR 0.43, CI 0.31–0.59).

Regarding safety, anemia, neutropenia, fatigue, vomiting, and nausea were the most frequently reported AEs, consistent across studies. Most toxicities were mild to moderate, and overall, PARPi treatment was well tolerated. However, high-grade AEs were more frequent compared to placebo in both newly diagnosed and recurrent cases, though differences with chemotherapy were minimal in recurrent disease. Hematological toxicities, particularly myelosuppression, are a known risk with PARPis (69), likely due to the role of PARP2 in hematopoiesis (70). Currently, there are no established predictive

markers for identifying patients at higher risk of severe toxicity, making regular blood monitoring essential. MDS and AML were more commonly reported in recurrent settings, although their incidence remains low, possibly due to limited follow-up periods. The long-term risks of secondary malignancies warrant further investigation (71).

This meta-analysis is notable for evaluating the efficacy of PARPis across all potential clinical settings in ovarian cancer. To ensure validity, we formed homogeneous subgroups by treatment context and applied a random-effects model. However, our analysis is limited by clinical heterogeneity across trials (e.g., different PARPis, prior treatments, surgical outcomes) and reliance on aggregated rather than individual patient data. Additionally, the relatively short follow-up periods limited our ability to assess OS comprehensively.

For future research, it is important to recognize that trial populations tend to be younger, fitter, and have fewer comorbidities than real-world ovarian cancer patients. The PRIMA trial (58) is a notable exception, enrolling a higher-risk population (e.g., 35–36% had stage IV disease, 67% received neoadjuvant chemotherapy) yet still achieving significant PFS improvements—38% in the overall group and 57% in HRD patients. Tolerability in real-world settings may differ from that observed in RCTs. Differences in efficacy and safety across PARPis have been suggested, but direct comparative evidence is limited. While some attempts to compare PARPis exist, like LaFargue CJ et al.'s 2019 study (72), more head-to-head trials are needed. To date, olaparib has been used in seven trials, niraparib in four, rucaparib in two, veliparib in two, and fuzuloparib in one—limiting the comparability of existing meta-analyses due to data heterogeneity.

As maintenance PARPi therapy is associated with increased toxicity, efforts should focus on minimizing treatment discontinuations. Personalized dosing strategies or predictive markers for adverse events may help improve tolerability. Long-term safety remains uncertain, especially concerning secondary malignancies like MDS and AML (71). Although PARPis significantly extend PFS, most tumors ultimately progress. Understanding the mechanisms behind PARPi resistance is a key challenge, particularly regarding the feasibility of retreatment and resistance prevention. Advancing knowledge in this area may lead to optimized combination therapies and more durable responses (73,74).

In conclusion, PARPi therapy significantly improves PFS in advanced ovarian cancer across various clinical contexts but is associated with an increased risk of high-grade adverse events. BRCA and HRD status are valuable predictive markers for treatment benefit. While maintenance therapy offers clear advantages for many patients, OS benefits remain uncertain due to limited long-term data. This meta-analysis provides critical insights to aid clinicians in patient selection and therapeutic planning.

Due to their complementary mechanisms of action, combination therapy involving PARP inhibitors and AAAs have shown promising potential in the treatment of ovarian cancer. However, our meta-analysis found no statistically significant improvement in PFS for combination therapy compared to PARPis or chemotherapy alone in the overall patient population. Similarly, no significant PFS benefit was observed in patients with BRCA mutations or in the BRCA wild-type subgroup. These findings suggest that, despite being explored as an alternative treatment strategy, combination therapy has not demonstrated superiority over monotherapy in the recurrent setting (12,64).

The variability in treatment response based on genetic factors such as BRCA mutation status underscores the importance of genetic profiling in ovarian cancer management. Although our pooled data did not show a statistically significant difference in PFS outcomes by BRCA mutation status, numerical trends hinted at possible differences between BRCA-mutated and BRCA wild-type patients. Previous studies, including AVANOVA2 (62) and NRG-GY004 (64), have reported outcome variations between these subgroups, suggesting that genetic characteristics may influence therapeutic efficacy. Nevertheless, in the absence of statistical significance in our analysis, further research is warranted to establish the role of genetic profiling in guiding the use of combination therapy.

Angiogenesis plays a critical role in tumor growth and survival, and anti-angiogenic agents have demonstrated efficacy in treating ovarian and other solid tumors. Preclinical research suggests that combining PARP inhibitors with AAAs may potentiate the DNA damage response and enhance PARP inhibition (11). This synergistic effect may result from agents like cediranib downregulating genes involved in homologous recombination, thereby improving the efficacy of drugs such as olaparib (75). Despite these proposed mechanistic benefits, our findings indicate that combination therapy did not significantly

improve PFS compared to chemotherapy alone in the general population. Furthermore, no statistically significant PFS benefit was observed in either BRCA-mutated or BRCA wild-type subgroups. This suggests that in the recurrent disease setting, combination therapy may not offer a clear survival advantage over standard chemotherapy.

In contrast, in the first-line treatment of newly diagnosed ovarian cancer, the PAOLA-1 trial (12) showed a significant PFS benefit with the combination of olaparib and bevacizumab, regardless of BRCA mutation status. This benefit was particularly notable in patients with homologous recombination deficiency (HRD)-positive tumors, including those without BRCA mutations. These results suggest that PARP inhibitor and AAA combination therapy may be effective across a broader patient population in the front-line setting.

Safety remains a key consideration when evaluating combination therapies. The incidences of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), serious anemia, nausea, and vomiting did not differ significantly between combination therapy and monotherapy (with either PARP inhibitors or chemotherapy). However, hypertension and diarrhea were notably more common with combination therapy. Hypertension is a well-recognized adverse effect of VEGF inhibitors, as VEGF blockade reduces nitric oxide production, leading to increased vascular resistance (76). Additionally, PARP inhibitors may contribute to vascular dysfunction by increasing oxidative stress, potentially compounding this effect (77). Therefore, proactive blood pressure monitoring and early use of antihypertensive agents are essential for patient safety. Diarrhea may result from the combined effects of VEGF inhibition—compromising intestinal microvascular integrity—and the impact of PARP inhibition on rapidly proliferating epithelial cells (78,79). Supportive measures such as hydration and dietary adjustments are critical for effective symptom management.

In light of these observations, individualized toxicity management strategies are vital, especially for patients with an elevated risk of cardiovascular or gastrointestinal side effects. Future studies should aim to identify biomarkers predictive of adverse events, enabling more personalized and safer application of combination therapies.

9.2 Strengths (including all studies)

Strengths of the first study include the exclusive use of phase II and III RCTs and the ability to analyze clinically meaningful subgroups. furthermore, the overall risk of bias was low.

The strengths of the second study, that was involved in my Ph.D. work, lies in its comprehensive analysis of randomized controlled trials, enabling a thorough assessment of both efficacy and safety outcomes. Additionally, the inclusion of subgroup analyses based on BRCA mutation status strengthens the clinical relevance and applicability of our findings.

9.3 Limitations (including all studies)

The overall certainty of the evidence is limited due to inconsistencies observed in the pooled outcomes. Five of the included trials were open-label, introducing a potential risk of bias. Furthermore, one study was included based solely on data from a conference abstract, restricting access to comprehensive methodological information. Variations in study design, treatment regimens, and control arms also hinder straightforward comparisons between trials.

10 CONCLUSIONS

Study I.

PARPi's therapy showed superior PFS outcomes compared to control groups in the treatment of advanced OC cases across various settings. However, it is also associated with an increased risk of high-grade AEs. I would also like to emphasize that evaluating BRCA mutation and HRD status is crucial in guiding PARPi use. Patients with these genetic deficiencies tend to derive significant benefit from the maintenance PARPi usage.

Study II.

The combination therapy of PARPis and AAAs did not demonstrate a statistically significant benefit in the investigated populations when they were compared to PARPis or chemotherapy alone. The safety analysis indicated that although the combination therapy was generally well tolerated, it was associated with a significantly higher incidence of severe hypertension and diarrhea compared to both PARPi monotherapy and standard chemotherapy.

11 IMPLEMENTATION FOR PRACTICE

As I demonstrated that PARPi therapy showed superior PFS outcomes compared to control groups in the treatment of advanced OC cases I hope that PARPi therapy can be widespread and will be used in the near future in more and more diagnosed advanced OC cases. Even though, that I noted that PARPi therapy is associated with a more severe risk of advanced AEs, I hope that in the near future both with individualized medicine (more precise dosages of chemotherapeutic agents) and both with future studies trying to minimalize these AEs it will not be a burden for their usage in gynecologic oncology.

As I already talked about the importance of individualized medicine I want to highlight how important it is to examine a patients HRD and BRCA status, as according my results the patients with these genetic deficiencies tend to have the most benefits from PARPi usage.

During my Ph.D. years I also studied the combination therapy of AAA and PARPi therapy compared to chemotherapeutics and single PARPi therapy.

As my results were not reassuring as the therapy did not demonstrate benefits compared to the above mentioned therapies I do not think that PARPi and AAA combination should be used in the near future in OC cases, however if future researches would appear it would form a clearer picture of PARPi and AAA combination.

12 IMPLEMENTATION FOR RESEARCH

12.1 Methodology issues

Future research should aim to standardize the definition and assessment of HRD as current variability limits comparability across studies.

Individual patient data meta-analyses could provide more precise insights into the efficacy and safety of PARPis across different subgroups. Longer follow-up periods are also essential to accurately evaluate OS and long-term AEs, such as secondary malignancies.

12.2 Study design

More head-to-head randomized controlled trials are needed to directly compare different PARP inhibitors, as current evidence is largely indirect. Study populations should better reflect real-world diversity, including older patients and those with comorbidities. Beyond placebo-controlled comparisons, combination treatment strategies (e.g., PARPi + anti-angiogenic agents) require rigorous evaluation in well-powered trials to confirm added benefit.

12.3 New aspects

Understanding the molecular mechanisms behind PARPi resistance is crucial for developing retreatment strategies and achieving more durable responses. Identifying biomarkers that predict efficacy or toxicity would support more personalized treatment approaches.

Additionally, novel therapeutic combinations—such as PARPis with immunotherapy or epigenetic agents—represent promising avenues for future investigation.

To summarize, I hope that my research can be a basement of other studies, even clinical studies and I hope that it inspires other researchers to study this, or similar topics to get more pieces of information on the treatment of advanced OC cases.

13 IMPLEMENTATION FOR POLICYMAKERS

To optimize outcomes in ovarian cancer care, policymakers should ensure equitable access to PARPis for eligible patients, particularly for maintenance therapy following platinum-based chemotherapy. Given the stronger PFS in BRCA-mutated and HRD-positive patients, national guidelines should mandate routine genetic and genomic profiling as part of standard care. Reimbursement policies must reflect the clinical value of PARPis across both BRCA-mutated and BRCA wild-type populations, particularly in the light of benefits observed even among HRP patients.

Investment in local infrastructure for HRD testing is essential, as varying definitions and inconsistent availability limit precise patient stratification. Safety monitoring frameworks should be strengthened through standardized protocols for hematologic toxicity screening, especially considering the risks of myelodysplastic syndrome and acute myeloid leukemia.

Policymakers should also promote funding for clinical and follow-up studies to evaluate long-term outcomes and tolerability, especially in older or comorbid populations underrepresented in clinical trials. Given the unclear OS impact, health technology assessments must incorporate PFS and quality-of-life measures when evaluating cost-effectiveness. While combination therapies involving PARPis and AAAs show promise in front-line settings, broader implementation should await confirmatory evidence of superiority over monotherapy. Research funding should prioritize predictive biomarkers for toxicity and resistance to personalize treatment further.

Lastly, centralized databases and interdisciplinary collaboration will be key in refining treatment algorithms and ensuring sustainable, evidence-based integration of PARPis into routine oncology care.

14 FUTURE PERSPECTIVES

In my project and the meta-analyses that I carried out during my Ph.D. years can be a basement and a support for future clinical trials that are experimenting PARPi therapy both individually and both in a combination therapy.

In the future, hopefully, during my active career years individualized therapy can gain a large space in medicine in general, and especially in the treatment of gynecological malignant diseases.

I also hope that the therapies this work experienced in OC cases both PARPi single therapy and both PARPi and AAA combinations can be and will be used widespread and will help a lot of patients overall PFS.

I also hope that in the future there will be new and new therapeutic agents and studies carried out in gynecologic oncology.

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16.1 Publications related to the thesis

Baradács I, Teutsch B, Váradi A, Bilá A, Vincze Á, Hegyi P, Fazekas T, Komoróczy B, Nyirády P, Ács N, Bánhidy F, Lintner B. PARP inhibitor era in ovarian cancer treatment: a systematic review and meta-analysis of randomized controlled trials. J Ovarian Res. 2024 Feb 26;17(1):53. doi: 10.1186/s13048-024-01362-y. PMID: 38409030; PMCID: PMC10895809.

Baradács I, Teutsch B, Vincze Á, Hegyi P, Szabó B, Nyirády P, Ács N, Melczer Z, Bánhidy F, Lintner B. Efficacy and Safety of Combination Therapy with PARP Inhibitors and Anti-Angiogenic Agents in Ovarian Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 2025 Mar 6;14(5):1776. doi: 10.3390/jcm14051776. PMID: 40095926; PMCID: PMC11901299.

16.2 Publications not related to the thesis

Komoróczy B, Váncsa S, Váradi A, Hegyi P, Vágási V, **Baradács I**, Szabó A, Nyirády P, Benkő Z, Ács N. Optimal Aspirin Dosage for the Prevention of Preeclampsia and Other Adverse Pregnancy Outcomes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Clin Med. 2025 Mar 21;14(7):2134. doi: 10.3390/jcm14072134. PMID: 40217586; PMCID: PMC11989913.

Póka R, **Baradács I**. A laparoszkópos és a nyitott műtéti technikával operált méhtestrák progressziómentes és teljes túlélési eredményeinek összehasonlítása [Comparison of progression-free and overall survival between endometrial cancer patients treated with laparoscopic and open surgical techniques]. Orv Hetil. 2020 Mar;161(10):382-388. Hungarian. doi: 10.1556/650.2020.31675. PMID: 32115990.

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