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OLAPARIB VERSUS BEVACIZUMAB IN PLATINUM-RESISTANT OR RECCURENT OVARIAN/FALLOPIAN TUBE/PERITONEAL CANCER.CLINICAL BENEFITS AND RISK (META-ANALYSIS)

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ABSTRACT

Objective: This paper which aimed at comparing clinical outcomes of Olaparib and Bev in women who developed ovarian carcinoma. These trials outcomes included, first Overall Survival second Progression free Survival then the third is development of Adverse Events. **Methods:** Search strategies: randomized trial AND (Olaparib OR bevacizumab) AND (peritoneal cancer OR tubal cancer OR ovarian cancer) all advanced search. There after, data were extracted data from selected studies. Data extracted was entered on Excel and thereafter exported to SPSS and R for analysis. We used three random models for three outcomes separately as stated in the objective section. Statistical fit tests were performed and analyzed. **Results:** BEV exhibited longer PFS than OLA although the statistic difference was not significant was not statistically (es, 4.360 ([95% CI] -1.335 - 10.055), *p>.05* in Bev; 0.149 (95% CI -2.234 to 2.531) *p>.05* in Ola). On the other hand, Ola significantly reduced OS as compared with Bev (es, -0.775 (95% CI -1.115 to 5.716) *p<.001* in Ola and 1.199 ([95% CI]-1.638 to 4.036) *p>.05 in Bev.*). Bev resulted into lower AEs than Ola although the modification was not significant according to statistics performed (es, 0.491 ([95% CI] -3.156 to 4.137), *p>.05*) in Ola and -0.035 (95% CI -4.880 to 4.809), *p>.05*). **Limitations:** Our study used data that were reported in other studies. This is because meta-analyses have secondary reliability because they depend on the level of accuracy and truthfulness of previous studies. Moreover, the study did not account for confounding variables including BRCA mutation; a fact that has the potential to reduce the strength of evidence. **Conclusions:** The study shows that Olaparib might be statistically effective at the same level of therapeutic approach with Bevacizumab with PFS and OS. Adverse events risk in Olaparib and bevacizumab are almost similar in cases with resistance to platinum, recurrent cancer, fallopian tube or peritoneal cancer.

KEYWORDS: Ovarian cancer, Tubal cancer**,** Bevacizumab, Peritoneal cancer, Olaparib and randomized clinical trial.

CHAPTER 1: INTRODUCTION/BACKGROUND

In our case, we conducted a meta-analysis on the way to compare the effectiveness of bevacizumab or Olaparib therapy for women with sensitive recurrent or platinum-resistant OC, fallopian tube, peritoneal cancer, regardless of BRCA gene status or HRD.

The combination of a PARPi agent is a new therapeutic method that seems promising in first-line treatment recurrent ovarian carcinoma and advanced desease management, while its relevance in recurrent illness remains unknown. It is critical to define which patients are elligible for monotherapy treatment or combination therapy, according to the case, while also considering the safety and risk profiles of drugs alone or giving in combination, as well as how these therapies should be sequenced and follow in clinical practice.

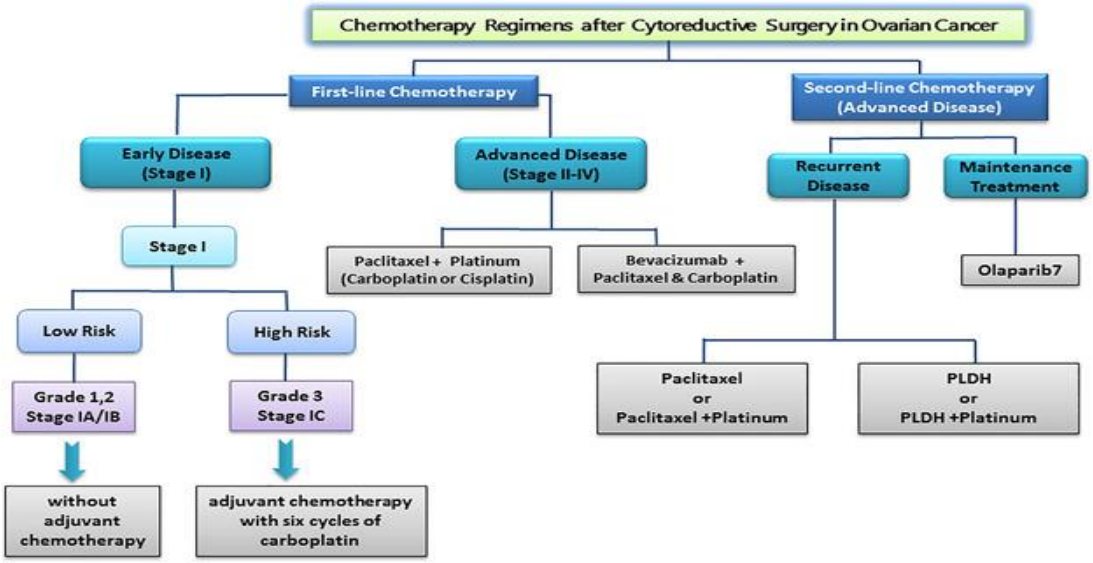
Whereas both antiangiogenic medicines and PARP inhibitors have shown effectiveness as monotherapies in recurrent ovarian cancer. combining these treatments has been of interest, especially because they have mainly limited overlapping toxicities. Combining antiangiogenic therapy with PARP inhibition could theoretically result in greater anticancer activity.

However, This study looked at the effectiveness, pharmacokinetics, safety of bevacizumab versus Olaparib specifically not in combination with four chemotherapy agents commonly used in patients with platinum-resistant ovarian cancer: carboplatin, PLD, topotecan and gemcitabine both taking place for chemotherapy cure.

Initial cure management intended for fallopian, ovarian, or peritoneal cancer normally consists of appropriate surgical according to the stage of desease, followed by standard chemotherapy procedure in most case (but not all) patients.

Surgery treatment alone (followed by regular checking) may be enough as initial treatment for some people with early-stage of disease. Furthermore, for some histologic subtypes, adjuvant therapy with hormonal drugs may be recommended with good outcomes.[1-3] Old age, frailty, low performance level, disease coupled with comorbidities, or condition that is unlikely to be adequately reduced. Individuals with advanced-stage ovarian cancer are reasons why many patients do not have first primary debulking surgery (PDS) for that they should be treat with neoadjuvant chemotherapy (NACT) with interval debulking surgery (IDS).[4,5]

Patient range, dose choice, therapy time duration, and various combinations of different medication indicated will all be important factors to reach good outcome after the effective treatments. focusing on single pathway, the epigenetic, the immunogenetic and mutation, changed platinum resistant in ovarian carcinoma type HGSOC phenotype should be used to solve resistance when novel treatments are created.[6]



Ovarian cancers (OC) are a deadly malignancy due to the fact Patients suffer from recurrent desease and face resistance during treatment. Patients with platinum-resistant OC have poor prognosis, with low response rates to comparable treatment and a median survival not superiorto 12 months approximately. The complexity of platinum-resistant OC, includes a diverse range of illnesses is certainly a long way from being absolutely understood.

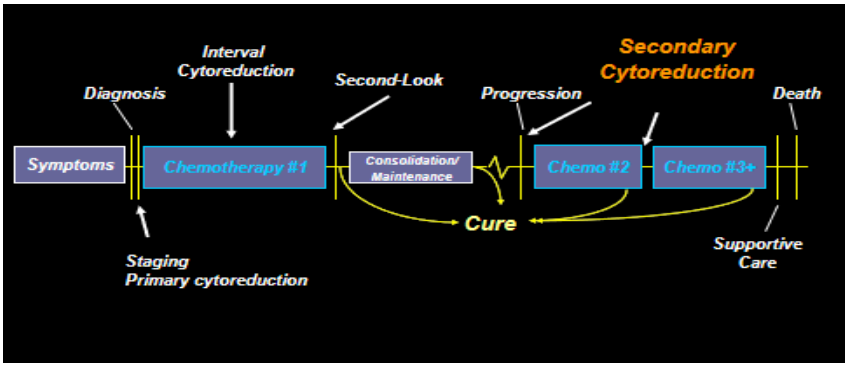
Therefore, understanding tumors organic, determine dependable biomarkers, might also predict responses to therapies. Claudia Marchetti, Khalid El Bairi.

Moreover, BRCA m is regarded as a predictive issue for PARPi benefit.

Currently for the mainstream of cancer cases with a BRCA wild type (BRCAwt) status, no prognostic biomarkers is determine to guide the doctor preference between the two therapies either PARPi or bevacizumab.

In the other hand Angiogenesis agent is a crucial mechanism growth of cells in cancer. Several studies are currently focusing and involving on anti-angiogenic medications, bevacizumab is well studied anti-angiogenesis.[7] The European Medicines Agency has approved it for the first line cure of progressive and epithelial resistant ovarian carcinoma, fallopian tube cancer, or peritoneal carcinoma along with carboplatin and paclitaxel, as well as the first recurrence of platinum sensitive ovarian carcinoma mixt with carboplatin and gemcitabine.[8]

Most of the time, recurrent ovarian carcinoma is a chemo-sensitive condition that is manageable applying some few treatment procedures, treatment strategy is now a difficult area for onco-gynecology. Among those new agents, for example niraparib and veliparib, proved amazing anti-tumoral undertaking additionally in patients and, at a decreased dose, should be given along with radiotherapy or chemotherapy.



ADVANCED OVARIAN CANCER, PLATINUM RESISTANT AND PLATINUM SENSITIVE

The platinum-free gap, or the duration between the previous platinum-based cycle and the onset of illness, is a guidance for chemotherapy selection for recurrent epithelial ovarian carcinoma(EOC). Platinum-refractory cases reverse within six months of receiving platinum therapy; platinum-resistant women relapse between one and three months.

Women who relapse after six months of platinum cure are labeled platinum-resistant, while women who relapse after a period of time superior to six months of platinum therapy are considered platinum-sensitive. Cancer cases who relapsed between six and twelve months after starting platinum therapy (partially sensitive to platinum) are separated from those who decline after twelve months.[9]

Mechanisms of resistance and biomarkers

Epithelial mesenchymal transition

Through EMT process cells go in to long series of alterations that induce formation of mesenchymal cell phenotype from an epithelial cell phenotype.[10]

Several research focused on involving in EMT, which leads to cancer development and therapy resistance. EMT is an important element of understanding cancer development, predominantly ovarian carcinoma HGSOCs.[11]

Cancer stem cells

CSCs are a assemblage of cancer cells that renew themselves indefinitely, they also initiate and maintain tumor growth, can help to remain dormant for lengthy period of time.[12] The cancer stem cell (CSC) of disease progression is still contentious because the process is still mostly unknown. they are associated to platinum resistance and illness in ovarian carcinoma.[13] The mechanism of CSC connected to platinum resistance is mainly unknown, latency during treatment remains the most expected.[14]

miRNAs

Various strategies for targeting miRNAs for cancer treatment are now being developed, including expression vector 'miRNA sponges,[15] antisense or mimic oligos.[16] and small molecule inhibitors (SMIRs).[17] The most potential therapeutic goal for miRNAs are SMIRs, but severe hurdles to deliver and pharmacologic and pharmacokinetic features remain critical difficulties to solve.[18]

MicroRNAs are (eighty to twenty-five nucleotides) non coding rubbles of RNA with a length of about ninety to twenty-five nt that inhibit mRNA. Most of them are associated with regulation of mRNA during progression disease, including the formation and development of cancer.

Table 2: miRNA and Drug Resistant/Oc.[6]

miRNA	Action	Effect on platinum chemotherapy	Reference
Let-7b	Overexpression in HGSOC	Poor survival and resistance to chemotherapy	Tang *et al.* (2014)
miR-9	Downregulates BRCA1 High levels in SOC	Sensitizes to cisplatin Better response and longer PFS	Sun *et al.* (2013)
miR-21	Over expression in HGSOC from the TGCA Over expression in A2780 cisplatin-resistant cells regulates Programmed cell death 4, c-IAP2 and NAV3	Shorter PFS Cisplatin resistance	Chan *et al.* (2014) Pink *et al.* (2015)
miR-27a miR-23a miR-30c Let-7g miR-199a-3p	Overexpression in stage I and stage III HGSOC	Cisplatin resistance	Eitan *et al.* (2009)
miR-141-3p	Overexpression in OC cell lines	Cisplatin resistance	Ying *et al.* (2015)
miR-146a	Overexpression in SOC omental lesions	Cisplatin resistance	Vang *et al.* (2013)
miR-150	Overexpression in SOC omental lesions	Cisplatin resistance	Vang *et al.* (2013)
miR-181a	Over expression in SOC Suppresses Smad7 and mediates EMT	Cisplatin resistance, shorter OS and PFS	Pink *et al.* (2015)
miR-484	Low expression in SOC, targets VEGFB and VEGFR2 pathways and tumour vasculature	Poor chemotherapy response (stable or progressive disease) Does not mediate chemoresistance *in vitro*	Vecchione *et al.* (2013)
miR-622	Targets the Ku pathway and downregulates NHEJ	Mediates chemoresistance	Choi *et al.* (2016)
Profile of 9 miRNAs	Regulation of EMT and TGF/WNT signaling	Mediates chemoresistance	Boac *et al.* (2016)

CHEMOTHERAPY

Pegylated liposomal doxorubicin

Because of side effects observed traditional treatment with doxorubicin, there was a demand for the creation of a liposomal preparation with equivalent efficacy and less side effects. the primary benefits is adopting liposomes as delivery mechanism including fact that the phospholipids produce vesicles derived from natural sources safe for the body such as egg yolks and soybeans. Furthermore, the inundation of the phospholipid bilayer lead to his alteration and induce change of drug releasing**.** Various polymers, for example polyethylene glycol (PEG), and cerebroside sulfate have the ability to suppress the opsonization of liposomes by plasma proteins and increase liposome stability. Liposomal half-life medicines regnited interest in mechanism of liposomal drug liberation. Longer liposome is linked to the improvement of therapeutic efficacy of anthracyclines liposomal, which may be due to higher accumulation of liposomes drug-loaded in tumor tissue.

Pegylated liposomal doxorubicin (for example Doxil®/Caelyx®), was a further advancement in this area of treatment72. PEGylating is the process through which materials are coated with PEG. This inhibits drug uptake by the RES, extending circulation duration (3-4 days[22] vs. 30 hours for standard doxorubicin) this duration allow the drug to remain encapsulated until it will be release in the tumor location.[23,24]

Topotecan

[25,26] In advanced ovarian cancer, topotecan therapy is very successful in suppressing tumor development.[27] Although comparable to MTD dose, this regimen reduces tumor vascularity and proliferation cell with minimum reported damage. The improved sensitivity of topotecan therapy on human endothelial cells in vitro also exhibited anti-angiogenic characteristics of metronomic topotecan. Additionally, in vitro and in vivo, topotecan markedly reduced the expression of potent pro-angiogenic cytokines VEGF and Hif-1, implying indirect influence on the tumor micro-environment.[28,29]

1.4 MAINTENANCE TREATEMENT

Medicines like PARPi, angiogenesis inhibitors, and various medecines with cytotoxic effect are being studied as an adjuvant maintenace therapy therapy to increase platinum free period after induction chemotherapy and ideal OS.[30]

Selecting Patients for Maintenance Remedy

The NCCN suggested alternatives for supervision of patients who have completed main therapy, including maintenance therapy options, after completion of first surgery followed by systematic medication. The recommended options are determined by disease stage, primary systemic therapy agents utilized, with good outcome to initial treatment, and BRCA1/2 mutation status.

FDE	NCCN
accepted procedure for maintenance cure with bevacizumab is not competent founded on *BRCA1/2* m condition in Ovarian carcinoma.	bevacizumab sustaining cure is restricted to the cases that are deprived of a *BRCA1/2* m only.
Maintenance regiment with bevacizumab is restricted to cases with grade III-IV sickness of OC.	contain this as an option for stage II of Ovarian cancer.
Olaparib, and bevacizumab associated maintenance cure does not specify that bevacizumab should be taken in first line treatment.	limit this possibility to those with prior bevacizumab.
approved Olaparib and bevacizumab mixt sustaining therapy is restricted to cancer case with *BRCA1/2* m or genomic variability, recombination deficiency (HRD).	Olaparib and bevacizumab grouping maintenance regiment as a choice regardless status (HRD), selecting as an alternative to emphasis on the PFS advantage detected for the bigger subcategory of cases without *BRCA1/2.*
niraparib maintenance is not restricted according to *BRCA1/2* mutation status or bevacizumab was given in combination with platinum-based chemotherapy during OC.	but, for patients who used bevacizumab as part of primary therapy, niraparib is a maintenance optional treatement only for those with a *BRCA1/2* mutation.

three PARPi (olaparib, niraparib, rucaparib) are agreed for single-agent maintenance therapy currently accepted by the FDA for maintenance cure after result to prior line chemotherapy in cases with newly diagnosed advanced illness. cases belong to advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who had a total or partial response to prior line platinum based chemotherapy are eligible for the FDA-approved indications. The FDA suggestion for single-agent olaparib concerned individuals with a gene deleterious BRCA, while the FDA suggestion for bevacizumab plus Olaparib cure in this situation is restricted to persons with a deleterious mutation or suspected gene BRCA m.

Table 1 also illustrates whether NCCN suggested options for cancer are consistent with FDA agreed suggestion, and possibilities that are dependable with an administration of food and drug approved recommandation but are not suggested in NCCN Rules. There are some significant differences concerning maintenance treatment requirement between FDA labeling and NCCN guidelines.

2.2 Olaparib (PARPi)
Olaparib (Lynparza, formerly AZD2281) oral cancer treatment.

Breaks in ssDNA.[31] Olaparib has undergone the most extensive examination to date because it was the first PARP inhibitor to be explored.

Many PARPi (poly ADP ribose polymerase inhibitors) have been proven their effectiveness for recurrent and advanced ovarian cancer and have been licensed by the FDA for a variety of applications in cancer.[32],[30]

PARP (PARP 1, PARP 2, PARP3) involve during a variety of DNA reparation pathways, and abnormalities in these restoration systems have been linked to certain cancers. PARP interacts toward a solitary molecule.[33,34]

Chemistry
Olaparib which is recognize by the formula $C_{24}H_{23}FN_4O_3$; belong to PARPi with a molecular mass of 434.47 DAa in addition IC 50 of 0.005 micronM for PARP1.

Human metabolism and pharmacokinetics
Peak olaparib concentrations are reached in 1-3 hours of initial dose. Drug contact proportionally with cumulative dose up to 100 mg twice a day.; the capsule formulation is inferior then the oral bio-availability of drug contein in tablet.

Pharmacokinetic studies revealed that acquaintance (zone under time required the plasma concentration curve [AUC]) after three hundred milligram tablet twice a day was 77% higher after 400 milligram capsule two times during a day. The calculated maximum concentration at fixed at prescribed 300 mg twice a day.

The stable state AUC fluctuated from 7.7 to 49.0 g/milliliter, and the Cmax ss vacillated from 5.8 to 42.0 g/milliliter. With numerous doses of olaparib, steady-state clearance reduced by 15%. Olaparib excreted in urine (35-50% of the time) and feces (from12 to 60% of the time).[35,36]

Pharmacodynamics in preclinical studies
In clinical research, variety of tumor cell were tested to be sensitive to PARPi utilizing colony formation assays.[37,38] In BRCA1 and BRCA2 mutations line cells or poor homologous recombination appearance.

It was discovered that genes increased olaparib sensitivity. These findings were reliable through the proposed mechanism of PARP i, which HRD causes DNA to be unable to fix double strand DNA interruptions caused by PARP inhibitor treatment.[38]

Olaparib has been revealed to be anticancer in BRCA deficient mouse cancers. A BRCA1 and 2 mouse mammary tumor type besides a BRCA 1 and 2 mouse model treated with Olaparib 50 milligram per kg during twenty-eight days had significant anticancer efficacy.[39,40] Further research has shown that Using BRCA mouse mammary models, olaparib enhances the effectiveness of platinum treatments.

Evers et al. demonstrated that combining cisplatin with olaparib in BRCA2-defective mouse mammary cell lines, has an improver impact has been observed in a BRCA competent control group.[41] Hay and Rottenberg demonstrated this by combining platinum drugs with olaparib, which raised both PFS and OS.

Toxicity
Olaparib as first-line maintenance has an acceptable toxicity outline (stage one or stage two). Serious treatment evolving different adverse events (AEs) represent 20.8%. Olaparib cases and 12.3% for placebo group. Nausea, diarrhea, asthenia, vomiting, and anemia, were the greatest prevalent treatment related AEs of all stage linked to olaparib. lymphocytopenia appeared at stage 3 or stage 4.

The olaparib treatment
Treatment with a single agent as a monotherapy
research on olaparib capsules monotherapy discovered a extreme tolerated dose (MTD) of 400 milligram twice a day. An incomplete response was observed in 19 cases with gBRCA-associated breast,prostate and ovarian cancer.[36] An expanded group of 39 patients having gBRCA was then included. Participants received dose of 200 mg per day, with 40% achieving a RECIST or CA125 response over a 28-week period. This investigation uncovered a significant link among platinum sensitivity and experimental advantage provided by olaparib. The higher the sensitivity of platinum is, the higher outcomes rate to olaparib (estimated twenty-three% in platinum refractory patients, fourty-five% belong to resistant platinume case patients, and sixty-nine% in platinum sensitive case), most likely when HRD increases action of both PARP inhibitors in addition platinum chemo as well.[32] Audeh et al. studied BRCA gene along with recurrent EOC and found that olaparib had a dose-response relationship. Participants were divided into two cohorts (100 and 400 milligram) it was discovered that individuals getting 400 milligram twice a day olaparib cure had a result of 33 percent beside to 13 percent received 100 milligram. olaparib capsules twice a day. These findings point to a measure dependent response; nonetheless should be regarded with precaution.

Maintenance treatment with platinum
As earlier stated, vast majority of cases identified with progressive EOC will experience recurrence. While the common cases are platinum-sensitive at the time of their first recurrence, the therapy-free interval frequently decreases with successive relapse.[32,42]

Olaparib for maintenancy front-line treatment
The expansion knowlegde of PARPi provided new

avenue for improving oncologic treatment in gynaecology. As previously stated, olaparib has monotherapy indications. Treatment for BRCA mutation, recurrent desease in fourth line cure and elsewhere for recurrent[43], platinum sensitive in treatment of ovarian carcinoma succeeding response to reinduction platinum founded remedy nonetheless BRCA status. Recently, in maintenance treatment after front line initiation therapy in cases with a BRCA gene mutation.[42]

Near future

With the first line agreement of olaparib, BRCA-associated Ovarian cancer, is in a position to move forward. where women may recur with prior PARPi exposure possibly advancement. This leads to next stage of research, which focuses on solving intrinsic and acquired resistance to PARP inhibitor. The evidence that advanced grade EOC evolves during treatment, and patients with BRCA mutated gene gain acquired resistance due to gBRCA.[44]

PARPi resistance is classified into three categories: renewal of homologous recombination deficiency, replication stress mutilation by delaying the cell sequence to enable long period for DNA repair, and additional (damage PARP1 protein, and export PARPi inhibitor via P glycoprotein).

Other resistance biomarkers pathway.[45] The mechanism determines how resistance to PARPi is tackled. For example, the reading frame can be restored by the occurrence of reversion mutations and result during transcription BRCA gene, may justify the amount of PARPi resistance but may remain irreversible when it happens. Lin et al. observed the presence of these degeneration modifications in circulating tumor DNA (cfDNA) predicted abscence of outcome to the PARPi rucaparib in both visible PARPi individuals.[46] Combination therapy, on the other hand, target mechanisms induce to homologous recombination deficiency. Their inhibition and utilizing PARPi, lead to overcome some forms of natural resistance.

2.3 bevacizumab

It was also one of the first and most extensively studied antiangiogenic agents for the treatment of ovarian tumors, and there is adequate indication to support its use. The outcomes of randomized clinical controlled Phase III trials led to its approval for the initial line cure of advanced cancer, fallopian tube cancer, and peritoneal cancercinoma. The International Collaborative Ovarian Neoplasm controlled Trial 7 (ICON-7) and the Gynecologic Oncology Group protocol (GOG 0218) both confirmed improved progression free survival (PFS), primarily in high risk ovarian carcinoma patients.[47] FIGO phase III tumor, sub optimal surgery cytoreduced disease (remaining disease after intermission debulking surgery >1 centimeter), or grade IV disease were considered high risk.

Mechanism

As an angiogenesis inhibitor, bevacizumab binds to vascular endothelial growth factor (VEGF) to prevents it from attaching to receptors on the endothelial surface cells. Neutralizing VEGF reduces neo-vascularization and causes apoptosis of tumor cells as well and reduction interstitial fluid pression in tumors, what is allowing chemotherapeutic medicines to reach specific targeted locations more effectively and successfully. In general, bevacizumab shown significant and meaningful treatment benefits in numerous randomized clinical trials when used with chemotherapy for advanced ovarian cancer.[7,8]

Bevacizumab treatment

Dosage

The GOG-0218 dose regimen was determined according to half life of twenty days when administered in the vein and the dosage accepted in non small cell pulmonary carcinoma.[48] ICON7 took 7.5 milligram/kg every three week. In Europe, the dosage for metastatic colorectal cancer is approved. The FDA has approved dosage for recurrent ovarian carcinoma related to trials for AURELIA, OCEANS, and GOG-0213; for platinum sensitive disease, bevacizumab is agreed fifteen milligram/ kg every three week. Bevacizumab fifteen milligram/ kg is given every three week with topotecan in platinum resistant cancer, while bevacizumab ten milligram/kg is administered each 2 weekly paclitaxel, PLD, and topotecan.

Because both timetables are 5 milligram/kg per week, the option to administer bevacizumab each three weeks or every two week take into account the dosage schedule of the concurrent chemo for simplicity of supervising drug.[49] While high quality research is scarce, there appears not to be. There is a variance in effectiveness observe by the high dosage (5 milligram/kg per week) and small dose (2.5 milligram/kg each week) regimens, small dosage may have fewer dose related to adverse reaction.

In combination NACT, bevacizumab

NACT is a therapy selection for case with progressive ovarian carcinoma that aims to less morbidity of disease. IDS improve the chances to full cytoreduction.[50] There is a lot of hope for neoadjuvant therapy.

The improved efficacy demonstrated with bulky disease, bevacizumab may boost cytoreduction at IDS even further, although this must be balanced against the known risks of significant Gastrointestinal problems and poor wound healing.[51] Bevacizumab has a number of adverse effect.

Bevacizumab is used to treat platinum-sensitive EOC.

Three carboplatin-based chemotherapy regimens provided for platinum-sensitive ovarian cancer are similarly effective: carboplatin versus paclitaxel[51], carboplatin versus gemcitabine, and carboplatin versus

pegylated liposomal doxorubicin (PLD)[52], with therapy cure porcedure tailored to the specific cases. Furthermore, the FDA has approved maintenance therapy with PARP inhibitors for the cure of recurrent platinum sensitive chemotherapy.[53]

Bevacizumab for ROC

In overall, platinum based chemotherapy are used to cure platinum-sensitive and recurrent of ovarian carcinoma, while mono-agent chemotherapy is used for platinum-resistant recurrence of ovarian carcinoma. Bevacizumab has been studied in three Phase III trials for persistent platinum sensitive ROC.[54]

resistant ovarian carcinoma to platinum shows lower response percentage to chemo (usually 10 to 20%) than those with platinum sensitive cancer (ORR classically 50 to 60%), have worse prognosis. Following enough recurrences, it is expected that all patients would progress to platinum-resistant illness.[55] Standard therapy for ovarian carcinoma resistant to platinum.

For ovarian carcinoma a single agent cytotoxic therapy that is often used along with paclitaxel, PLD, gemcitabine, topotecan. Bevacizumab has been approved by the administration of food and drug as a combination therapy for platinum-resistant EOC in addition to mono-agent therapy.[47,48,56]

Study limitation

The application of the current study focus in comparison of effects of bevacizumab and Olaparib patient resistant, advanced ovarian carcinoma.

However, due to the diverse designs of the included research, the study has significant limitations.

OBJECTIVES

1. To Compare PFS in overall population.
2. To Compare OS in overall population
3. Adverse event will be compared in Olaparib group, bevacizumab group, and placebo (or chemotherapy group)

Regardless BRCAm statut.

CHAPTER 2: MATERIALS AND APPROACHES

SEARCH STRATEGY

Investigation was done in PUBMED, COCHRANE, and SCIENCE DIRECT databases. From 1st January 2019 to 15 Oct 2022 for appropriate trials using the next keywords: randomized trial AND (Olaparib OR bevacizumab) AND (peritoneal cancer OR tubal cancer OR ovarian cancer). all advanced search.

SELECTION CRITERIA

The study inclusion criteria

Studies related to platinum-resistant, recurrence desease, advanced ovarian cancer, fallopian tube, peritoneal cancer. trials used bevacizumab or olaparib, and randomized controlled studies, type of chemotherapy received (carboplatin, PLD, gemcitabine, topotecan, or other platinum regiments).

The non elligible criteria

Non case corresponding controlled study, non comparative trials, newly diagnosed ovarian cancer, review articles, letters or news papers, abstracts only, protocols, in vitro survey and irrelevant outcomes in papers.

Because of the lack of a control group, phase I and single-arm phase II randomized controlled trials were excluded from the meta-analysis. Additionally, two-arm phase II randomized controlled trials were also excluded due to insufficient sample sizes.

PRISMA

After the selection procedure, we recruited four randomized trials. The use of bevacizumab was explored in two papers, among which the trial by Shoji T. and Pignata S beyond progression., in cases earlier exposed to bevacizumab in the prior line setting. The other two studies concerned maintenance cure with Olaparib specifically. These two trials by Vander A. and Penson R. in association to chemo, and then as maintenance remedy. Designated studies are briefed on table bellow.

DATA PRESENTATION

AUTHORS	DESIGN	POPULATION	EFFECTIFS	TREATEMENT	PFS	OS	ADVERS EV
S PIGNATA.	RCT	overall population with platinum-resistant/ advanced OC/fallopian tube/peritoneal cancer	bevacizumab: 201/control:200	« carboplatin-based doublet intravenously (carboplatin area under the concentration curve [AUC] 5 on day 1 plus paclitaxel 175 mg/m² on day 1, every 21 days; carboplatin AUC 4 on day 1 plus gemcitabine 1000 mg/m² on days 1 and 8, every 21 days; or carboplatin AUC 5 on day 1 plus pegylated liposomal doxorubicin 30 mg/m² on day 1, every 28 days), or a carboplatin-based doublet plus bevacizumab (10 mg/kg intravenous every 14 days combined with pegylated liposomal doxorubicin–carboplatin, or 15 mg/kg every 21 days combined with gemcitabine–carboplatin or paclitaxel–carboplatin) »[57]	« Median progression-free survival was 8·8 months (95% CI 8·4–9·3) in the standard chemotherapy group and 11·8 months (10·8–12·9) in the bevacizumab group (hazard ratio 0·51, 95% CI 0·41–0·65; log-rank p<0·0001) »[57]	« Hazard ratio 0·99 (95% CI 0·73–1·39), stratified log-rank p<0·98 » [57]	

T SHOJI.	RCT	advanced epithelial ovarian cancer		« the dosing schedule for each chemotherapy regimen was as follows and each cycle was repeated until disease progression: PLD was administered intravenously at 40 mg/m2 or 50 mg/m2, 1 mg/min on Day 1 with a cycle equal to 28 d; topotecan was administered intravenously at 1.25 mg/m2 for more than 30 min on Days 1, 2, 3, 4, and 5 with a cycle equal to 21 d; paclitaxel was administered intravenously at 80 mg/m2 for 60 min on Days 1, 8, and 15 with a cycle equal to 21 d; and GEM was administered intravenously at 1000 mg/m2 for 30 min on Days 1 and 8 with a cycle equal to 21 d. »[58]	« The median investigator-assessed PFS (primary endpoint) was 3.1 mo (95% CI: 2.5-4.6) in the chemotherapy group and 4.0 mo (95% CI: 3.0-5.7) in the chemotherapy + bevacizumab group (HR = 0.54, 95% CI: 0.32-0.90, 1-sided *P* = .0082) »[58]	« The median OS was 11.3 mo (95% CI: 8.8-12.6) in the chemotherapy group and 15.3 mo (95% CI: 10.0-17.4) in the chemotherapy + bevacizumab group (HR = 0.67, 95% CI: 0.38-1.17, *P* =.1556) »[58]	
PENSON R.	RCT	Platinum resistant or partially resistant. Platinum sensitive relapsed ovarian carcinoma.	Olaparib:178/Chemotherapy+placebo:88	« olaparib tablets 300 mg twice a day or physician's choice of single-agent chemotherapy: PLD 50 mg/m2 on day 1 every 4 weeks; paclitaxel 80 mg/m2 on days 1, 8, 15, and 22 every 4 weeks; gemcitabine 1,000 mg/m2 on days 1, 8, and 15 every 4 weeks; or topotecan 4 mg/m2 on days 1, 8, and 15 every 4 weeks. »[59]	« Olaparib versus chemotherapy (HR, 0.62 [95% CI 0.43 to 0.91]; P = .013), with a median PFS of 13.4 months for Olaparib versus 9.2 months for chemotherapy » [59]		« 23.6% of patients in the olaparib group (most commonly anemia [2.8% of patients]) versus 18.4% of patients in the chemotherapy group (most commonly vomiting [3.9%]) »[59]
ANDRIAAN VANDERSTICHELE		PSOC and PROC	OLAPARIB:107/CT+PLACEBO:53	« OLA was given as tablets at a starting dose of 300 mg BID (2 × 150mg tablets) continuously, beginning on day 1 and every cycle of 28 days thereafter until study discontinuation. Dose interruptions were allowed if required for a maximum of 28 days. Dose reductions to 250 mg BID and 200 mg BID were done according to dose modification guidelines. Patients with PSOC disease randomized to CT were treated with one of the following regimens: Carboplatin (AUC 4; on day 1) + Gemcitabine (1000 mg/m2 on day 1 and 8) in 21-day cycles; Carboplatin (AUC 5; on day 1) + Paclitaxel (175 mg/m2 on day 1) in 21-day cycles; Carboplatin (AUC 5; on day 1) + Pegylated Liposomal Doxorubicin (PLD; 30 mg/m2 on day 1) in 28-day cycles. For PROC disease, the following regimens were possible: PLD (40 mg/m2 on day 1) in 28-day cycles; Topotecan (1.25 mg/m2 on day 1–5) in 21-day cycles; Paclitaxel (80 mg/m2 on day 1, 8 and 15) in 28-day cycles; Gemcitabine (1000 mg/m2 on day 1, 8 and 15) in 28-day cycles. »[60]	« Median PFSwas 4.8months (95% CI 3.2–6.1) in theOLA group versus 5.7months (95% CI 4.0–8.0) in the CT group (hazard ratio [HR] 1.07 [95% CI 0.66–1.32]; log-rank p=0.700) »	« 12.5 months (95% CI 9.0–17.2) in the OLA group versus 14.4 months (95% CI 11.2–24.0) in the CT group (hazard ratio [HR] 1.14 [95% CI 0.61–1.28]; log-rank p=0.500 »	

STATISTICAL ANALYSIS

We performed these meta-analyses for three different outcomes separately. We performed meta-analyses using random effects models for all the meta-analyses. Firstly, we examined the effects of OLA and BEV on progression-free survival (PFS). Then, we investigated the effects of OLA and BEV on overall survival (OS) and finally on their effects on the development of adverse

events (AEs). Therefore, we had three outcomes of interest: PFS, OS, and AEs. PFS was the primary and principal outcome while OS was the secondary outcome. On the other hand, AEs were considered as an auxiliary outcome. Ideally, we were supposed to use means and standard deviations for us to measure PFS and OS. However, all the papers that were extracted had not reported means and standard deviations. Consideration was given to see if it were possible to extract means and standard deviations from the papers through supplementary files. However, this did not help. Therefore, using an application of several theoretical underpinnings under a normal distribution and conceptual features of means, medians, standard deviations and confidence intervals, we treated medians as means for all medians reported in the papers. Standard deviations were calculated by dividing the 95% confidence intervals of medians (means as considered in this paper) by 3.92. We then performed meta-analyses for against these outcomes treating means as summary estimates of effect sizes for PFS and OS. On the other hand, success and failure rates, as used under binomial assumptions, were used to measure AEs such that the proportion of patients who developed AEs in the treatments (OLA or BEV) was compared to proportion of patients who developed AEs in controls. In all the three models, we only factored treatment type (OLA or BEV) alongside adjustment with BRCA. I square statistic program and Cochran's Q was used as indexes of heterogeneity in order to allow for assessment of dispersion. We used R software (version 4.1.1, "meta" and "metasens"), Statistical Package for Social Sciences (SPSS version 29) and MS Excel to analyze data.

CHAPTER 3: RESULTS

Table 1 below presents the outcomes of the meta analysis for PFS, OS, in addition AE. BEV revealed longer PFS than OLA although the modification was not statistically significant (es, 4.360 (95% CI -1.335 to 10.055), *p>.05* in Bev; 0.149 (95% CI -2.234 to 2.531) *p>.05* in Ola). On the other hand, Ola significantly reduced OS as compared with Bev (es, -0.775 (95% CI -1.115 to 5.716) *p<.001* in Ola and 1.199 (95% CI -1.638 to 4.036) *p>.05.*). Bev resulted into lower AEs than Ola although the modification was not statistically significant (es, 0.491 (95% CI -3.156 to 4.137), *p>.05*) in Ola and -0.035 (95% CI -4.880 to 4.809), *p>.05*). Forest plots for PFS, OS, and AE are labelled figures 1, 3 and 5 respectively. Funnel plots for PFS, OS, and AE are labeled 2, 4 and 6 respectively.

Table 1: Effect Size Estimates for Subgroup Analysis.

Outcome	Treatment	ES	SE	Z	Sig. (2-tailed)	95% CI	
						Lower	Upper
PFS	OLA	.149	1.2154	.122	.903	-2.234	2.531
	BEV	4.360	2.9057	1.500	.134	-1.335	10.055
	Overall	2.250	1.7680	1.273	.203	-1.215	5.716
OS	OLA	-.775	.1735	-4.467	<.001	-1.115	-.435
	BEV	1.199	1.4476	.828	.408	-1.638	4.036
	Overall	.538	1.0600	.507	.612	-1.540	2.615
AE	OLA	.491	1.8605	.264	.792	-3.156	4.137
	BEV	-.035	2.4718	-.014	.989	-4.880	4.809
	Overall	.300	1.4865	.202	.840	-2.613	3.214

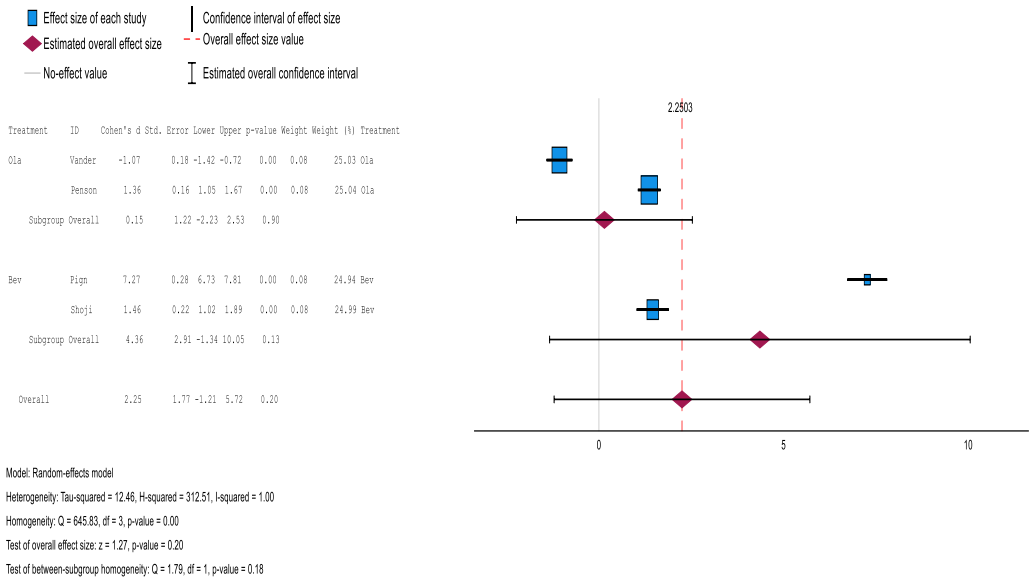


Figure 1: Forest Plot for PFS.

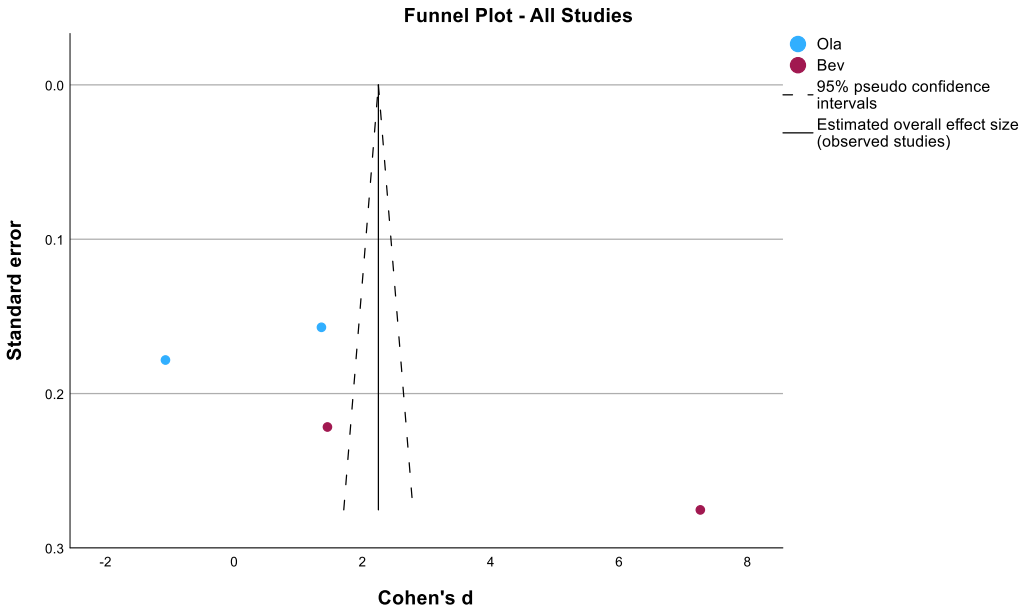


Figure 2: Funnel Plot for PFS.

VEV

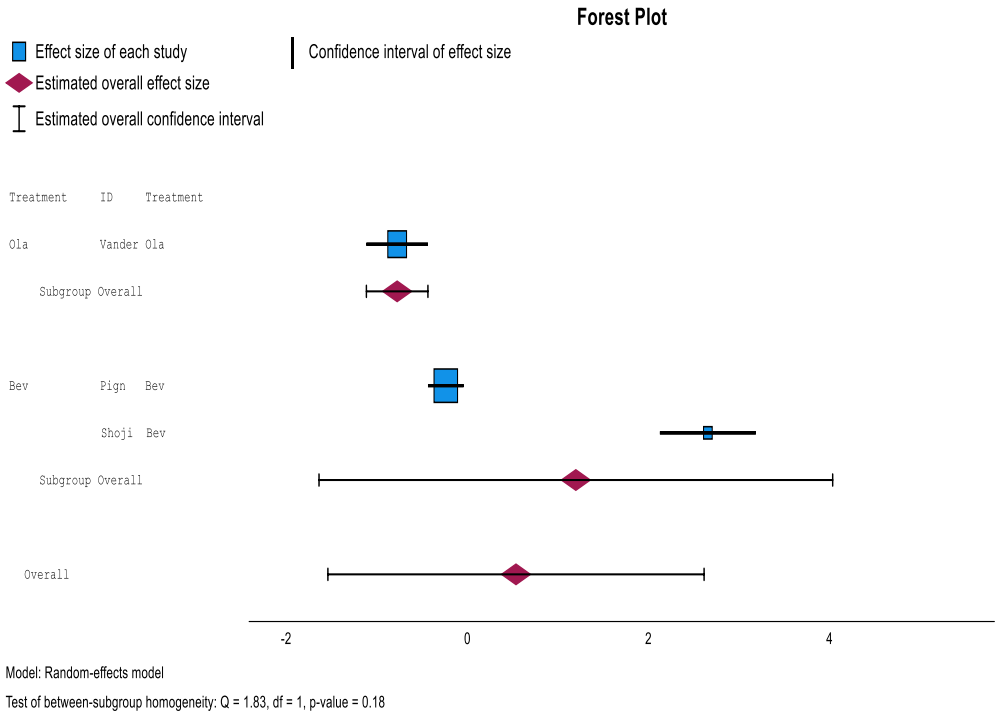


Figure 3: Forest Plot for OS.

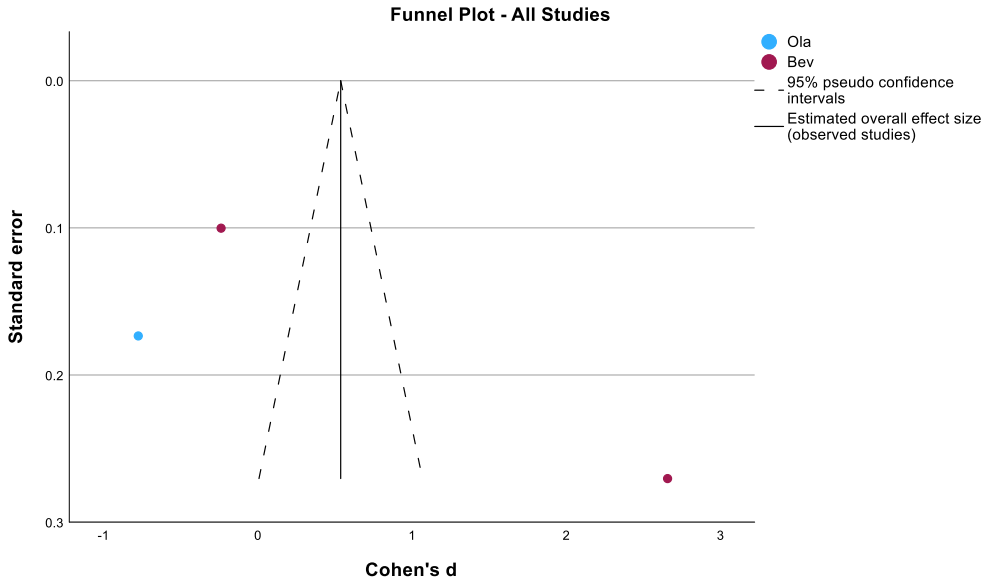


Figure 4: Funnel Plot for OS.

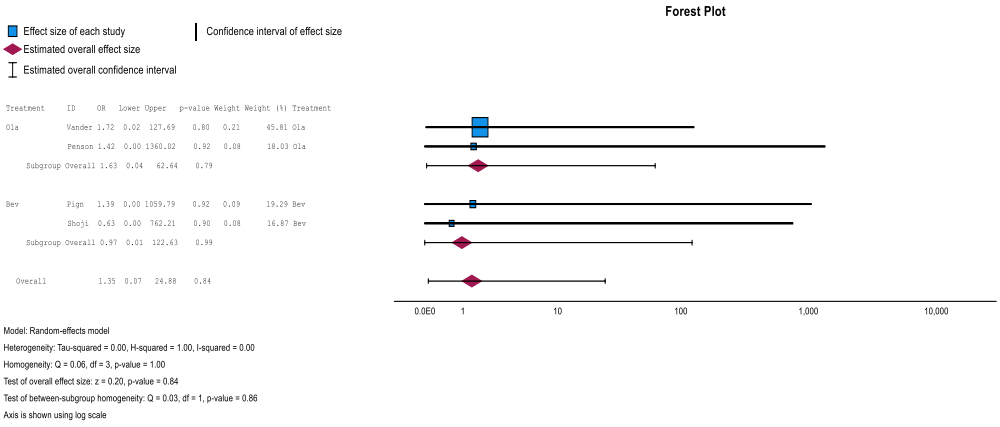


Figure 5: Forest Plot for AEs.

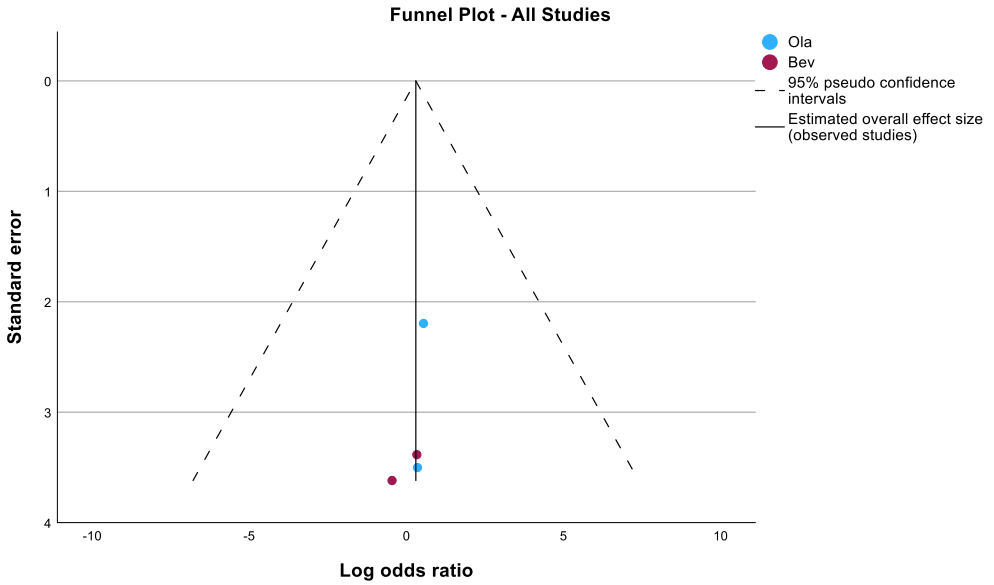


Figure 6: Funnel Plot for AEs.

CHAPTER 4: DISCUSSION

Our study has found that there is no difference in the effects of bev and ola on PFS. This shows that both drugs equally improve the PFS. This finding is supported by wide range of clinical trial studies. Several studies have been conducted to evaluate effects of bev and ola on PFS and OS in various types of cancer. For example, in advanced gastric cancer, a phase III study known as AVAGAST trial found that the combination of bevacizumab with standard chemotherapy improved PFS compared to chemotherapy alone.[61] This was supported by another phase III trial known as AVAil trial which was conducted on patients with advanced non-squamous non-small cell lung cancer, showed that the addition of bevacizumab to the chemotherapy improved PFS.[62] Overall, the results of these studies suggest that the addition of bevacizumab to standard chemotherapy or radiation improves PFS for patients with various types of cancer.

- On the other hand, in ovarian cancer, several studies have been conducted to evaluate the effects of olaparib on progression-free survival (PFS). A phase III study known as SOLO-2 found that olaparib monotherapy improved PFS compared to placebo, platinum-sensitive and platinum relapsed ovarian cancer.[63] Another phase III study found that olaparib monotherapy improved PFS compared to chemotherapy in patients with germline BRCA-mutated, HER2-negative metastatic breast cancer.[64] Another study in prostate cancer, a phase III study known as profound trial found that olaparib monotherapy improved PFS compared to enzalutamide or abiraterone in men with homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer.[65] These studies have generally suggested that olaparib monotherapy can improve PFS in patients with ovarian and breast cancer with certain genetic mutations and prostate cancer with HRR gene mutations. Young ju suh at all, in the overall population with ovarian cancer, no significant difference in PFS was observed between women treated with PARPi and those treated with bevacizumab. however PARPi improved PFS significantly more than bevacizumab in women with a BRCAm (HR 0.47; 95% CI0.36–0.60) and with HRD (HR 0.66; 95% CI 0.50–0.87). However Yaling feng at all studies: PARPis showed significant improvement in PFS compared to AIs (HR 0.73; 95% CrI 0.63–0.86) and CTA (HR 0.64; 95% CrI 0.52–0.78).

These findings are consistent with the findings with our metanalysis. This synthesis proves that the use of bev and ola based on the PFS should be an option of the doctor considering other patient factors and issues to do with drug availability and/or economical considerations.

Although studies have not sufficiently evaluated which, between bev and ola, has greater effect on PFS, available evidence shows that the combination of bevacizumab and olaparib improved PFS compared to olaparib alone in cases with BRCA-mutated ovarian cancer who received three prior lines therapy. However, this contradicts to the findings of other two studies in breast cancer and colorectal cancer found that the combination of bevacizumab and olaparib did not improve PFS compared to bevacizumab alone.

It's important to note that these studies were conducted on specific subgroups of patients and the results may not be generalizable to other patient populations. It's also worth noting that more recent studies are being conducted and the results are not yet available.

Our meta-analysis further found that Ola significantly reduced OS than PFS. This implies that OS is shorter in Ola than in Bev suggesting that Bev improved OS. However, this finding contradicts with most of the available literature.

Bevacizumab was reported to have improved OS when it was combined with standard chemotherapy over the use of chemotherapy alone in colorectal cancer (AVAGAST phase III study).[61] However, other studies reported that the use of bev did not improve OS lung cancer (AVAil phase III trial study[62]); glioblastoma (RTOG 0825 study[66]); and in cell carcinoma (AVOREN phase III trial[67]). This is unlike the findings for Olaparib which has widely been reported to have improved OS among cancer patients. Studies in ovarian cancer (SOLO-2[63] and ENGOT-OV16/NOVA[68]), in breast cancer (OlympiAD trial[69]) and prostate cancer (PROfound trial)[65] have reported that the use of Olaparib improved OS among patients over the use of standard chemotherapy. Findings from these strongly studies suggest that olaparib monotherapy can improve OS in patients with ovarian and breast cancer with certain genetic mutations and prostate cancer with HRR gene mutations. On the other hand, Bev has limited scope for improving OS among cancer patients. This is seeming contradiction to the findings of our meta analysis.

The inconsistencies in the effects of Bev and Ola on PFS and OS is attributed to levels of endpoint between the two. This is because OS is a more robust endpoint than PFS, as it takes into account both the duration of response and death from any cause. Therefore, it is not always expected that a drug that improves PFS will also improve OS. Additionally, OS can be affected by many factors including the type and stage of cancer, patient's overall health, and other treatments received. Therefore, contextual discrepancies and differences in the target populations might also have affected the results produced by these studies.

In terms of adverse events, both drugs are associated with different adverse events. Therefore, comparing the adverse events for these two drugs was not robust and

reliable enough to compare these two drugs head to head in terms of efficacy or safety, as they are used in different patient population and for different purposes.

Overall, three treatment arms reflecting diverse maintenance methods were selected: bevacizumab with PARPi, and post chemo monitoring (CT). In this review of prospective trials, the indirect comparisons offered the first data confirming PARPi advantage maintenance cure over bevacizumab maintenance treatment for platinum-sensitive recurrent EOC. According to our findings, PARPi therapy should be the first line of treatment for platinum-sensitive ovarian carcinoma patients. Michele Bartoletti 1.

Adverse events

According to the case adverse events can lead to the choice of which maintenance is applicable either bevacizumab or eirther PARPi.

In research trial on BEV, common adverse events (grade ≥ 3) were high blood pressur, thromboembolic situation, neutropenia, and non-CNS hemorrhage [vander and penso]. In trials experimentation on OLA, anemia, thrombocytopenia, neutropenia, lethargy, and nausea were common adverse events observed (grade ≥ 3) [pignata and shoji]. Our research demonstrate that dangers of adverse events did not change for bevacizumab either for Olaparib used for ovarian carcinoma (grade ≥ 3).

AEs that are frequently associated with bevacizumab, such as hypertension (43% versus 4%), although the highest incidence of hypertension was seen with bevacizumab alone. ignace vergote. https://www.ejcancer.com/article/S0959-8049(21)00550-5/fulltext#

CONCLUSION

Although this study focused in evaluations among studies with different designs, the indirect comparisons an analysis approach indicate that Ola reduces OS more than Bev; Bev has longer PFS than Ola and Bev lower the AEs than Ola. On the other hand, the study shows that olaparib might be statistically effective at the same level of therapeutic procedures with bevacizumab respectevely to PFS and OS and that the risk of thoughtful adverse events posed by Olaparib and bevacizumab are similar in women with platinum-resistant or recurrent ovarian/fallopian tube/peritoneal cancer ovarian carcinoma. However, new evidence has shown that the prolongation of PFS does not continuously directly correlate with the upgrading of OS due to the development of multiple effective anti-cancer therapy options following the prior line treatment which have considerably influenced the progression.

ABREVIATION LIST

PFS =progression free survival
OS =overall survival
PLD = pegylated liposomal doxorubicin;
HR = hazard ratio
AEs= adverse events
RCT= randomized controlled trial
EMT= epithelial mesenchymal transition
NACT= neoadjuvant chemotherapy treatment
PARPi= poly adenosine diphosphate-ribose polymerase
VEFGi= vascular endothelial growth factor
FIGO= international federation of gynaecology and obstetrics
NCCN= national comprehensive cancer network**.**

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