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Angiogenesis Inhibitors for the Treatment of Ovarian Cancer

An Updated Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Angiogenesis inhibitors showed activity in ovarian cancer, but preliminary data could not accurately reflect the survival benefit. We thus did a systematic review and meta-analysis of randomized controlled trials to reassess the efficacy and safety of angiogenesis inhibitors combined with chemotherapy for ovarian cancer.

Methods: We searched PubMed, EMBASE, Cochrane, and ClinicalTrials.gov for randomized controlled trials comparing angiogenesis inhibitors containing therapy with conventional chemotherapy alone or no further treatment. Our main outcomes were the progression-free survival (PFS), overall survival (OS), and common adverse events.

Results: Fifteen trials were included (N = 8721 participants). For newly diagnosed ovarian cancer, combination treatment with angiogenesis inhibitors and chemotherapy yielded a lower risk of disease progression (hazard ratio [HR], 0.83; 95% confidence interval (CI), 0.71–0.97) and no improved OS (HR, 0.95; 95% CI, 0.86–1.05). In the high-risk progression subgroup, the addition of bevacizumab significantly improved PFS (HR, 0.72; 95% CI, 0.65–0.81) and OS (HR, 0.84; 95%CI, 0.74–0.96). In recurrent patients, the combined HR was 0.58 (95% CI, 0.52–0.65) for PFS, and for OS, the combined HR was 0.86 (95% CI, 0.79–0.94). We found no significant improvement for either PFS (HR, 0.80; 95% CI, 0.63–1.01) or OS (HR, 1.06; 95% CI, 0.88–1.28) in the pure maintenance therapy.

In the overall population, angiogenesis inhibitors increased the incidence of gastrointestinal perforation (risk ratio [RR], 2.57; 95% CI, 1.66–3.97), hypertension (RR, 7.60; 95% CI, 2.79–20.70), arterial thromboembolism (RR, 2.27; 95% CI, 1.34–3.84), proteinuria (RR, 4.31; 95% CI, 2.15–8.64), and complication of wound healing (RR, 1.72, 95% CI, 1.12–2.63).

Conclusions: Combination treatment with angiogenesis inhibitors and chemotherapy significantly improved PFS and OS in both patients with high-risk of progression and recurrent ovarian cancer, with an increased incidence of common adverse events. Conversely, we detected no statistically significant survival benefit in the pure maintenance setting. The main limitation of the review is clinical heterogeneity across the studies.

Key Words: Ovarian neoplasms, Angiogenesis inhibitors, Chemotherapy, Systematic review, Meta-analysis

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Description of the Condition

Worldwide, ovarian cancer is the leading cause of gynecological cancer–associated death.¹ It is the fifth leading cause of cancer-related deaths in female patients in developed countries.² The poor prognosis is usually attributed to advanced stage at diagnosis and treatment resistance.³ Approximately 60% of women are diagnosed with late-stage disease that has already spread within the abdomen.^{1,4}

Platinum/taxane doublet chemotherapy is the upfront standard of care in advanced ovarian cancer and yields an objective response in up to 80% of patients,⁵ but almost all will experience multiple recurrences of disease, with ever shorter disease-free intervals.^{6,7}

Given the therapeutic limitations of conventional chemotherapy, recent investigations have explored molecularly guided therapies to target pathways of oncogenesis. A number of studies have shown that tumor growth and progression are partly dependent on angiogenesis.^{8,9}

Description of the Intervention

Angiogenesis is recognized as a hallmark of several types of tumors including ovarian cancer.¹⁰ One of the most important cytokines responsible for tumor-mediated angiogenesis is vascular endothelial growth factor (VEGF), which is secreted by tumor cells and binds to the VEGF receptor that is present on normal endothelial cells, stimulating new blood vessel formation.¹¹ Hence, efforts to block this pathway, either by inhibiting VEGF or its receptor, have emerged as attractive strategies for cancer treatment.^{12,13}

Why it is Important to do This Review?

The good news is that there were clinical trials suggesting that angiogenesis inhibitors showed activity in ovarian cancer. However, the survival benefit was different in these trials. It is important to establish whether the addition of these new drugs to conventional chemotherapy regimens has additional survival benefit, if so, at what cost, and additional harmful effects. Moreover, there remain a lot of controversies. Should they be used as part of first-line therapy, recurrent setting, or to maintain patients with stable disease later in the course of their disease?

The most recently published meta-analysis¹⁴ indicated that antiangiogenic therapy showed clear progression-free survival (PFS) benefit with increased toxicity, but its role in overall survival (OS) was undefined for ovarian cancer. We therefore did a systematic review and meta-analysis of RCTs comparing angiogenesis inhibitors containing therapy with conventional chemotherapy alone or no further treatment for ovarian cancer to reassess the efficacy and safety of angiogenesis inhibitors in different clinical setting, including newly diagnosed ovarian cancer, recurrent patients, and pure maintenance setting. In this present study, the final data and 3 new randomized controlled trials (RCTs)^{15–17} were included.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. We searched PubMed, EMBASE, Central (Cochrane clinical trials database) database, and clinicaltrial.gov. We searched the database from 1994 to March 2017. We sought articles in all languages and there were no translations necessary. We used the following combined text and MeSH terms: "Ovarian Neoplasms", "Angiogenesis Inhibitors", "Bevacizumab", "Avastin", "Pazopanib", "GW786034", "Votrient", "Trebananib", "AMG386", "Nintedanib", "vargatef", "BIBF1120", "cediranib", "AZD2171", "recentin", "Sorafenib", "BAY 545-9085", "BAY43-9006", "Nexavar", "NSC724772", "sunitinib", and "SU11248".

Study Selection and Data Extraction

We regarded studies as eligible for inclusion if they were RCTs in women with histologically proven epithelial ovarian cancer of any stage (age, ≥ 18 years), compared angiogenesis inhibitors plus conventional chemotherapy with conventional chemotherapy alone, or angiogenesis inhibitors to no further treatment.

Two investigators independently reviewed study titles and abstracts, and excluded those studies that clearly did not meet our inclusion criteria. We then obtained copies of the full text of potentially relevant references. Trials selected for detailed analysis and data extraction were analyzed by 2 investigators. We resolved disagreements by discussion between the 2 authors and documented the reasons for exclusion. We



FIGURE 1. Flow chart indicating the study selection procedure.

TABLE 1. Characteri	stics of	f included	d RCTs				
	Year	Stage	Patients Enrolled	Sample Size	Control Arm	Experimental Arm	Primary Endpoint
Burger et al, 2011 ³	2011	Phase 3	Newly diagnosed, FIGO stage III or IV epithelial ovarian, primary peritoneal or fallopian tube cancer GOG PS 0-2	1248	Cycles1–6: T (175 mg/m ²) + C (AUC 6) + PL, q3w Cycles 7–22: PL,q3w	Cycles 1–6: T (175 mg/m ²) + C (AUC 6) + Bev (15 mg/kg), q3w Cycles 7–22: Bev(15 mg/kg), q3w	PFS
Aghajanian et al, 2012 ²¹	2012	Phase 3	Platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma ECOG PS 0-1	484	Cycles $1-10$: G (1000 mg/m ² , days 1 and 8) + C (AUC 4, day 1) + PL (15 mg/kg, day 1), q3w	Cycles 1–10: G (1000 mg/m ² on days 1 and 8) + C (AUC 4 on day 1) + Bev (15 mg/kg on day 1), q3w	PFS
Oza et al, 2015 ²²	2015	Phase 3	Newly diagnosed, High-risk FIGO stage I–IIA or IIB–IV ovarian epithelial, fallopian tube, or primary peritoneal cavity cancer ECOG PS 0-2	1528	Cycles 1–6: T (175 mg/m²) + C (AUC 5 or 6), q3w	Cycles 1–6:T (175 mg/m ²) + C (AUC 5 or 6) + Bev (7.5 mg/kg), q3w Cycles 7–18: Bev (7.5 mg/kg), q3w	PFS
Pujade-Lauraine et al, 2014 ²³	2014	Phase 3	Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer ECOG PS 0-2	361	Cycles 1-PD: PLD (40 mg/m ² , day 1, q4w); PAC (80 mg/m ² on days 1, 8, 15, and 22, q4w); or TOP (4 mg/m ² , days 1, 8, 15, q4w or 1.25 mg/m ² , days 1-5, q3w);	Cycles 1-PD: PLD (40 mg/m ² , day 1q4w) or PAC (80 mg/m ² , days 1, 8, 15, and 22, q4w);or TOP (4 mg/m ² , days 1, 8, 15, q4w or 1.25 mg/m ² , days 1–5, q3w); + Bev (15 mg/kg, q3w or 10 mg/kg, q2w)	PFS
Coleman et al, 2015 ¹⁶	2015	Phase 3	Platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer GOG PS 0-2	748	T (175 mg/m2) + C (AUC5),q3w	T (175 mg/m ²) + C (AUC5) + Bev (15 mg/kg), q3w followed by Bev maintenance	SO

(Continued on next page)

	Year	Stage	Patients Enrolled	Sample Size	Control Arm	Experimental Arm	Primary Endpoint
Bois et al, 2016 ²⁴	2016	Phase 3	Chemotherapy-naive, FIGO stage IIB–IV epithelial ovarian cancer, fallopian tube or primary peritoneal cancer ECOG PS 0-2	1366	Cycles1-6: T (175 mg/m ²) + C (AUC5 or 6) + PL (200 mg, twice a day, days $2-21$, $q3w$) followed by PL maintenance	Cycles1-6: T (175 mg/m ²) + C (AUC5 or6) + Nintedanib (200 mg twice a day, days 2–21), q3w followed by Nintedanib maintenance	PFS
Ledermann et al, 2011 ²⁵	2011	Phase 2	Advanced ovarian carcinoma, fallopian tube carcinoma or primary peritoneal cancer of serous type with recurrent disease and who responded to second, third, or fourth line chemotherapy. ECOG PS 0-1	83	Cycles1-9: maintenance PL (250 mg, twice a day, q4w)	Cycles1-9: maintenance Nintedanib (250 mg twice a day), q4w	PFS Rate at 36 Weeks
Monk et al, 2016 ²⁶	2016	Phase 3	Recurrent partially platinum-sensitive or resistant epithelial ovarian, primary peritoneal or fallopian tube cancers GOG PS 0-1	919	Cycles1-PD: PAC (80 mg/m ² , days 1, 8, 15, q4w) + PL	Cycles1-PD: PAC(80 mg/m ² , days 1, 8, 15,q4w) + trebananib (15 mg/kg. qw)	PFS
Karlan et al, 2012 ¹⁸	2012	Phase 2	Recurrent epithelial ovarian (FIGO stage II–IV), fallopian tube or primary peritoneal cancer ECOG PS 0-1	161	PAC (80 mg/m ² , days 1, 8, 15, q4w) + AMG 386 placebo	PAC (80 mg/m ² , days 1, 8, 15, q4w) + AMG 386 (3 mg/kg, qw) or AMG386 (10 mg/kg, qw)	PFS
Pignata et al, 2015 ²⁷	2015	Phase 2	Platinum-resistant or refractory ovarian cancer ECOG PS 0-1	73	Cycles1-PD: PAC (80 mg/m ² , days 1, 8, 15, q4w)	Cycles1-PD: PAC (80 mg/m ² , days 1, 8, 15, q4w) + pazopanib(800 mg, orally, once daily)	PFS

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TABLE 1. (Continued)

PFS	PFS	PFS	PFS	led on next page)
Maintenance Pazopanib (800 mg, orally, once daily for 104 wks (24 mos)	Cycles 1–6: TOP (1.25 mg/m ² , days 1–5, q3w) + Sorafenib (400 mg orally twice a day, days 6–15, q3w) followed by sorafenib maintenance for 12 mos	Cycles1-PD: maintenance Sorafenib(400 mg orally twice a day, q4w)	Cycles 1–6: recommended chemotherapy (TC/GC/C), q3w cediranib (20 mg once daily) followed by cediranib maintenance (20 mg once daily) for 18 mos or PD	רסעזעו)
Maintenance PL (800 mg, orally, once daily), for 104 wks (24 mos).	Cycles 1–6: TOP (1.25 mg/m ² , days $1-5$, $q3w$) + PL (400 mg orally twice a day, days $6-15$, $q3w$) followed by PL maintenance for 12 mos	Cycles1-PD: maintenance PL (400 mg orally twice a day q4w)	Cycles 1–6: recommended chemotherapy (TC/GC/C), q3w + PL (20 mg once daily) followed by PL maintenance (20 mg once daily) for 18 mos or PD	
940	172	246	282	
FIGO stage II–IV epithelial ovarian, fallopian tube or primary peritoneal carcinoma who have not progressed after first line chemotherapy ECOG PS 0-1	Platinum-resistant recurrent epithelial ovarian cancer, primary peritoneal carcinomatosis or fallopian tube cancer	FIGO stage III–IV ovarian epithelial cancer or primary peritoneal cancer who have achieved a response after standard platinum/taxane containing chemotherapy (first-line therapy) ECOG PS 0-1	Platinum-sensitive relapsed epithelial ovarian cancer, primary peritoneal carcinomatosis or fallopian tube cancer after first-line platinum-based chemotherapy ECOG PS 0-1	
Phase 3	Phase 2	Phase 2	Phase 3	
2014	2016	2013	2016	
du Bois et al, 2014 ²⁸	Sehouli et al, 2016 ¹⁷	Herzog et al, 2013 ²⁹	Ledermann et al, 2016 ³⁰	

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	Year	Stage	Patients Enrolled	Sample Size	Control Arm	Experimental Arm	Primary Endpoint
Gotlieb et al, 2012 ¹⁵	2012	Phase 2	Platinum-resistant, and TOP-resistant and/or PLD-resistant disease; Advanced ovarian cancer patients with recurrent symptomatic malignant ascites ECOG PS 0-2	55	PL (4.0 mg/kg intravenous q2w)	Aflibercept(4.0 mg/kg intravenous q2w)	Time to Repeat Paracentesis
AUC, area under curv paclitaxel; PD, progressiv	e; Bev, t /e diseas	bevacizuma se; PL, plac	ab; C, carboplatin; ECOG, Ea cebo; PLD, pegylated liposon	stern Cooperative nal doxorubicin; P	Oncology Group; GOG, C S, performance status; T, J	iynaecological Oncology Group; G, paclitaxel; TOP, topotecan.	gemcitabine; PAC, weekly

extracted the following data from each selected trial: participant characteristics, study interventions, and outcomes.

Assessment of Risk of Bias in Included Studies

Cochrane Collaboration's tool was used to assess the risk of bias in included RCTs. We had presented results in both a risk of bias graph and a risk of bias summary.

Data Analysis and Statistical Methods

We assessed the effect and safety of angiogenesis inhibitors–containing therapy on 3 outcomes: OS, PFS, and incidence of adverse events. For time-to-event data (OS and PFS), we pooled the hazard ratios (HRs) and two-sided 95% confidence interval (CI) using the generic inverse variance facility of RevMan 5.3. For dichotomous outcomes (toxicity), we used the risk ratio (RR). The Karlan 2012¹⁸ trail had multiple treatment groups (3-arm trial), and so we divided the control group between the treatment groups (with different dose), and treated comparisons between each treatment group and a split control group as independent comparisons.

The χ^2 test and Cochran Q-test were used to evaluate heterogeneity among trials, and $I^2 > 50\%$ indicated a moderateto-high heterogeneity.¹⁹ We used random-effects models for PFS and toxicity based on the large heterogeneity among the different trials. We pooled OS in a fixed effect model. Subgroup analysis was adopted to determine whether there is clinical benefit for patients in the subgroup classified by prognostic factors or different response to platinum-containing therapy. The meta-analysis software RevMan 5.3 provided by the Cochrane library was used for the data analysis.

We assessed the possibility of publication bias by constructing a funnel plot. We assessed funnel plot asymmetry using Begg and Egger tests, and defined significant publication bias as a P < 0.1.²⁰ We used Stata (version 12.0) for the statistical analysis.

RESULTS

We initially identified 5440 articles from all searched database of which 15 trials (with data for 8721 participants) were retained after a full-text screening for inclusion in our review after excluding duplicates, reviews, case report, and phase I trials (Fig. 1). Two^{16,17} of the references were conference abstracts that described RCTs that met our inclusion criteria. The 15 trials were all published between 2011 and 2016.

The main characteristics of 15 RCTs were summarized in Table 1, and the data of outcomes were summarized in Table 2.

The assessment of risk of bias in the trials was shown in Figure 2. The risk of bias was unclear in the 2 studies that were published in an abstract form. Other RCTs reported sufficient information for randomization excluding 2 trials, 28,29 for which "Randomize" was used in abstract and text, but further details were not reported, and none was stopped early. Moreover, 3 studies^{22,23,27} lacked blinding to participants and personnel, the other 2 trials^{25,29} did not specify whether data collectors and outcome assessors were masked to treatment allocation, and only $4^{3,22,27,30}$ were not funded by industry.

ReferencesArmsBurger et al, 2011 $TC + PL$ $(GOG-0218)^3$ $TC + Bev + Bev(m)$ $(GOG-0218)^3$ $TC + Bev + Bev(m)$ $2012 (OCEANS)^{21}$ $GC + PL + PL(m)$ $2012 (OCEANS)^{21}$ $GC + Bev + Bev(m)$ $Oza et al, 2015$ TC $(ICON 7)^{22}$ $TC + Bev + Bev(m)$ Pujade-Lauraine et al, $2014 (AURELIA)^{23}$ $PLD/PAC/TOP + B$ Coleman et al, 2015 TC $GOG-0213)^{16}$ $TC + Bev + Bev(m)$ Bois et al, 2016 $TC + nintedanib + nintedanib (m)$	Size m) 625 m) 623 (233 (242 m) 242 764 m) 764 182 Bev 179 374 m) 374	Patients Enrolled Newly diagnosed Platinum-sensitive recurrent Newly diagnosed Platinum-resistant recurrent Platinum-sensitive recurrent	Primary Endpoint PFS PFS	Median (mo)		HR,	Median		HR, 95%CI
Burger et al, 2011TC + PL (GOG-0218) ³ TC + Bev + Bev(m) Aghajaniann et al, 2012 (OCEANS) ²¹ GC + PL + PL(m) GC + Bev + Bev(m)Aghajaniann et al, 2012 (OCEANS) ²¹ GC + Bev + Bev(m) GC + Bev + Bev(m)Oza et al, 2015TC TCDiade-Lauraine et al, 2014 (AURELIA) ²³ PLD/PAC/TOP PLD/PAC/TOP + B Coleman et al, 2015Coleman et al, 2015TC TC (GOG-0213) ¹⁶ Bois et al, 2016TC TC + Bev + Bev(m)	m) 625 () 242 (m) 242 (m) 764 m) 764 182 Bev 179 374 m) 374	Newly diagnosed Platinum-sensitive recurrent Newly diagnosed Platinum-resistant recurrent Platinum-sensitive recurrent	PFS PFS		HK	95%CI	(0M)	HR	
(UOU-0218)TC + Bev + Bev(m)Aghajaniann et al, 2012 (OCEANS)GC + PL + PL(m)2012 (OCEANS)GC + Bev + Bev(m)Oza et al, 2015TCOza et al, 2015TCPujade-Lauraine et al, 2014 (AURELIA)PLD/PAC/TOP + BColeman et al, 2015TCColeman et al, 2015TCBois et al, 2016TCAdGO-OVAR 12)TC + Bev + Bev(m)	m) 623 () 242 (m) 242 m) 764 m) 764 182 Bev 179 374 m) 374	Platinum-sensitive recurrent Newly diagnosed Platinum-resistant recurrent Platinum-sensitive recurrent	PFS	10.3	0.717	0.625-0.824	39.3	0.885	0.750-1.040
Aghajaniann et al, 2012 (OCEANS)21 $GC + PL + PL(m)$ 2012 (OCEANS)21 $GC + Bev + Bev(m)$ Oza et al, 2015 TC (ICON 7)22 $TC + Bev + Bev(m)$ Pujade-Lauraine et al, 2014 (AURELIA)23 $PLD/PAC/TOP + B$ Coleman et al, 2015 TC GOG-0213) ¹⁶ $TC + Bev + Bev(m)$ Bois et al, 2016 $TC + Bev + Bev(m)$) 242 m) 242 m) 764 m) 764 182 Bev 179 374 m) 374	Platinum-sensitive recurrent Newly diagnosed Platinum-resistant recurrent Platinum-sensitive recurrent	PFS	14.1			39.7		
DescriptionDescriptionDescriptionDescriptionOza et al, 2015TCHev + Bev (m)Oza et al, 2015TCHev (m)Pujade-Lauraine et al, 2014 (AURELIA)23PLD/PAC/TOP + BColeman et al, 2014 (AURELIA)23PLD/PAC/TOP + BColeman et al, 2015TCColeman et al, 2015TCGOG-0213)16TC + Bev + Bev (m)Bois et al, 2016TC + nintedanib +	m) 244 m) 764 Bev 179 374 m) 374	Newly diagnosed Platinum-resistant recurrent Platinum-sensitive recurrent		4. c 4. z	0.484	0.388–0.605	32.9 33.6	0.952	0.771-1.176
ConstructionTCBevBev(m)(ICON $7)^{22}$ TCBevBev(m)Pujade-Lauraine et al,PLD/PAC/TOPB.2014 (AURELIA)^{23}PLD/PAC/TOPB.Coleman et al, 2015TCBev(GOG-0213)^{16}TC<+ Bev	m) 764 182 Bev 179 374 m) 374	Platinum-resistant recurrent Platinum-sensitive recurrent	DFS	17.5	0.03	0 83-1 05	58.6	00.0	0 85-1 14
Pujade-Lauraine et al, 2014 (AURELIA)23PLD/PAC/TOP2014 (AURELIA)23PLD/PAC/TOP2014 (AURELIA)23PLD/PAC/TOPColeman et al, 2015TC(GOG-0213)16TCBois et al, 2016TCRois et al, 2016TChintedanib(AGO-OVAR 12)24nintedanib(m)	Bev 179 374 m) 374	Platinum-resistant recurrent Platinum-sensitive recurrent		19.9	CC.0	CO.1-CO.0	58.0	().n	LT.I_C0.0
2014 (AURELIA) ²³ PLD/PAC/TOP + B Coleman et al, 2015 TC (GOG-0213) ¹⁶ TC + Bev + Bev(m Bois et al, 2016 TC + nintedanib + (AGO-OVAR 12) ²⁴ nintedanib(m)	Bev 179 374 m) 374	recurrent Platinum-sensitive recurrent	PFS	3.4	0.48	0.380 - 0.600	13.3	0.85	0.66 - 1.080
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	374 m) 374	Platinum-sensitive recurrent		6.7			16.6		
$\begin{array}{ll} (GOG-0213)^{16} & TC + Bev + Bev(m) \\ Bois et al, 2016 & TC + nintedanib + \\ (AGO-OVAR 12)^{24} & nintedanib(m) \end{array}$	m) 374	recurrent	SO	10.4	0.614	0.522-0.722	37.3	0.827	0.683 - 1.005
Bois et al, 2016 TC + nintedanib + (AGO-OVAR 12) ²⁴ nintedanib(m)				13.8			42.2		
	+ 911	Newly diagnosed,	PFS	17.2	0.84	0.72–0.98	34	0.99	0.77–1.27
TC + PL + PL(m)	455			16.6			32.8		
Ledermann et al, 2011 ²⁵ BIBF1120	43	Pure maintenance	PFS rate at	NA	0.65	0.41 - 1.02	NA	0.84	0.51 - 1.39
PL	40		36 wks	NA			NA		
Monk et al, 2016 PAC + trebananib	461	Recurrent disease	PFS	7.2	0.66	0.57 - 0.77	19.3	0.95	0.81 - 1.11
$(TRINOVA-1)^{26}$ PAC + PL	458			5.4			18.3		
Karlan et al, 2012 ¹⁸ PAC + AMG386 (10 mg/kg)	53	Recurrent	PFS	7.2	0.76	0.49 - 1.18	22.5	0.60	0.34 - 1.06
PAC + PL	55			4.6			20.9		
Karlan et al, 2012 ¹⁸ PAC + AMG 386 (3 mg/kg)	53	Recurrent	PFS	5.7	0.75	0.48 - 1.17	20.4	0.77	0.45–1.31
PAC + PL	55			4.6			20.9		
Pignata et al, 2015 PAC + pazopanib	37	Platinum-resistant	PFS	6.35	0.42	0.25 - 0.69	19.1	0.6	0.32 - 1.13
(MTO-11) ²⁷ PAC	36	recurrent		3.49			13.7		
du Bois et al, 2014 ²⁸ Pazopanib	472	Pure maintenance	PFS	17.9	0.77	0.64 - 0.91	NA	1.08	0.87 - 1.33
PL	468			12.3			NA		
Sehouli et al, 2016^{17} TOP + sorafenib	86	Platinum-resistant or	PFS	6.7	0.6	0.43 - 0.83	17.1	0.65	0.45 - 0.93
TOP + PL	86	refractory recurrent		4.4			10.1		
Herzog et al, 2013 ²⁹ Sorafenib	123	Pure maintenance	PFS	12.7	1.09	0.72 - 1.63	NA	1.49	0.69 - 3.23
PL	123			15.7			NA		

						PFS			SO	
keferences	Arms	Size	Patients Enrolled	Primary Endpoint	Median (mo)	HR	HR, 95%CI	Median (mo)	HR	HR, 95%CI
edermann et al, 2016 (ICON 6) ³⁰	TC/GC/C + PL TC/GC/C + Cediranib + cediranib(m)	$\frac{118}{164}$	Platinum-sensitive relapsed	PFS	8.7 11	0.56	0.44-0.72	21 26.3	0.77	0.55-1.07
Gotlieb et al, 2012 ¹⁵	Aflibercept PL	29 26	Platinum-resistant relapsed	Time to repeat paracentesis	6.3 7.3	NA	NA	16 12.9	1.023	0.562-1.863
Bev, Bevacizumab; C, oxorubicin; TC, Paclitax	Carboplatin; GC, Gemcitabine el + Carboplatin; TOP, topotec	e + Carb can.	oplatin; m, maintenance t	herapy; NA, not ava	ilable; PA(C, weekly	/ paclitaxel; PL,	placebo; P	LD, pegy	lated liposomal

Overall Survival

Three studies (n = 4142 participants) assessed the risk of death in patients with newly diagnosed ovarian cancer, pooling the data of these studies showed no significant difference in OS when participants were treated with angiogenesis inhibitors and chemotherapy combination treatment compared with chemotherapy alone (HR, 0.95; 95% CI, 0.86–1.05; $l^2 = 0\%$). In contrast, subgroup analysis suggested antiangiogenics-containing combination therapies had a significantly better OS in the patients with a high risk of progression from 2 studies with a total of 1750 participants (HR, 0.84; 95% CI, 0.74–0.96; $l^2 = 0\%$).

Nine studies (n = 3310 participants) assessed the risk of death in the recurrent setting, pooling the data of these studies also found statistically significant lower risk of death in women who received antiangiogenics-containing combination therapies compared with those who received chemotherapy alone (HR, 086; 95% CI, 0.79–0.94; $l^2 = 0\%$).

In addition, further subgroup analysis showed angiogenesis inhibitors had significant survival benefits for both platinum-sensitive recurrent ovarian cancer from 3 trials with a total of 1514 participants (HR, 0.86; 95% CI, 0.76–0.98; $I^2 = 0\%$) and platinum-resistant recurrent ovarian cancer from 4 trials with a total of 661 participants (HR, 0.78; 95% CI, 0.65–0.94; $I^2 = 0\%$).

Conversely, no significant difference in the risk of death was observed in the pure maintenance antiangiogenics therapy who achieved a good response to before chemotherapy (HR, 1.06; 95% CI, 0.88–1.28; $I^2 = 0\%$) based on the results of 3 studies with a total of 1269 patients (Fig. 3a).

The funnel plot for OS revealed almost symmetry (Fig. 4a), and we further assessed publication bias on Egger test (P = 0.156), thus indicating no significant publication bias for OS.

Progression-Free Survival

Angiogenesis inhibitors and chemotherapy combination treatment had significantly lower risks of disease progression compared with women with chemotherapy alone in both newly diagnosed setting (HR, 0.83; 95% CI, 0.71–0.97; $I^2 = 75\%$) and the recurrent setting (HR, 0.58; 95% CI, 0.52–0.65; $I^2 = 39\%$). Subgroup analysis for newly diagnosed patients with a high risk of progression indicated the PFS was significantly improved (HR, 0.72; 95% CI, 0.65–0.81; $I^2 = 0\%$). Moreover, further subgroup analysis comparing the benefit on PFS for platinum-sensitive recurrent ovarian cancer (HR, 0.56; 95% CI, 0.48–0.64; $I^2 = 31\%$) and platinum-resistant recurrent ovarian cancer (HR, 0.50; 95% CI, 0.42–0.60; $I^2 = 0\%$) both suggested significantly lower risks of disease progression. We detected no significant heterogeneity in both subgroups.

However, although pazopanib showed a significantly improved PFS (HR, 0.76; 95% CI, 0.64–0.91) from 1 trial,²⁸ we found no significant improvement for PFS in the pure maintenance angiogenesis inhibitors therapy (HR, 0.80; 95% CI, 0.63–1.01; $I^2 = 37\%$), with no significant between-study heterogeneity (Fig. 3b).

The funnel plot for PFS revealed almost symmetry (Fig. 4b), and we further assessed publication bias on Egger test (P = 0.185), thus indicating no significant publication bias for PFS.

TABLE 2. (Continued)



FIGURE 2. Risk of bias graph A, review of authors' judgements about each risk of bias item presented as percentages across all included studies. Risk of bias summary B, review of authors' judgements about each risk of bias item for each included study.

Adverse Events

Supplementary Figure A http://links.lww.com/IGC/A709 presents 7 common adverse events that are potentially associated with angiogenesis inhibitors during treatment. Among this updated analysis, the risks of adverse events (AEs) were significantly increased as follows: gastrointestinal perforation (G \geq 3; RR, 2.57; 95% CI, 1.66–3.97; $I^2 = 63\%$), hypertension (G \geq 3; RR, 7.60; 95% CI, 2.79–20.70; $I^2 = 74\%$), arterial thromboembolism (RR, 2.27; 95% CI, 1.34–3.84; $I^2 = 0\%$), proteinuria (G \geq 3; RR, 4.31; 95% CI, 2.15–8.64; $I^2 = 0\%$), and complication of wound healing (RR, 1.72; 95% CI, 1.12–2.63; $I^2 = 1\%$).We found no significant increased risks for either neutropenia (G \geq 4; RR, 1.09; 95% CI, 0.93–1.28; $I^2 = 46\%$) or venous thromboembolism (RR, 1.08; 95% CI, 0.79–1.48; $I^2 = 26\%$).

DISCUSSION

This updated meta-analysis was derived from 3 new RCTs and final data to reassess the efficacy and safety of angiogenesis inhibitors and chemotherapy combination treatment in ovarian cancer. The conclusion is different from the previous metaanalysis, especially in the grouping of statistical analysis. Considering the clinical settings to use angiogenesis inhibitors may play a major role in the treatment benefit, we divided 15 trials into 3 groups.

For newly diagnosed ovarian cancer, the addition of angiogenesis inhibitors to chemotherapy was associated with a significant improvement on PFS with large heterogeneity, but there was no evidence of a benefit on OS. Considering the large heterogeneity, we performed further subgroup analysis in patients with a high risk of progression who were predefined in the ICON7 trial and matched all the recruited patients in the GOG-218 trial, the results of which showed bevacizumabcontaining therapy had significant improvement in both PFS and OS, with no significant between-study heterogeneity. Hence, our analysis showed that bevacizumab plus chemotherapy, followed by maintenance bevacizumab therapy, could be considered a front-line treatment option for patients with high-risk features or high-postsurgical tumor burden, with evidence of both PFS and OS benefits for this subgroup. However, because the survival benefit of angiogenesis inhibitors in highrisk patients was concluded from subgroup analysis, the results should be noted as the consistency of patient characteristics and principle of randomization were not ensured.

Although women with advanced epithelial ovarian cancer responded to many available therapeutic agents, almost all die from recurrence, which makes the treatment of recurrent ovarian cancer important. In the present study, antiangiogenics-containing therapies significantly reduced the HR of progression by 42% and risk of death by 14%, compared with chemotherapy alone with no significant between-study heterogeneity. Further analysis of 2 subgroups (ie, platinum-sensitive recurrent ovarian cancer and platinum-resistant recurrent ovarian cancer) both showed improvement on PFS and OS, with no significant between-study heterogeneity. The results were encouraging among women with recurrent ovarian cancer no matter whether responded to previous platinum-containing chemotherapy or not, demonstrating that angiogenesis inhibitors combined with chemotherapy is a great

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()			Experimental	Control		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV. Fixed, 95% CI	IV. Fixed, 95% Cl
Bois 2016(NCT01015118)	-0.0112	0.1277	911	455	16.0%	0.99 [0.77, 1.27]	+
Burger 2011(GOG-0218)	-0.1242	0.0834	623	625	37.5%	0.88 [0.75, 1.04]	1
Subtotal (95% CI)	-0.0107	0.0745	2298	1844	100.0%	0.95 [0.86, 1.05]	•
Heterogeneity: Chi ² = 1.08, df = 2 (P = 0.58); l ² = 0% Test for overall effect: Z = 1.09 (P = 0.28)							
1.1.2 first line treatment/High-risk of progression	ĩ						
Burger 2011(GOG-0218)	-0.1242	0.0834	623	625	63.5%	0.88 [0.75, 1.04]	
Oza 2015 icon7 high risk Subtotal (95% CI)	-0.2462	0.1101	248 871	254 879	36.5% 100.0%	0.78 [0.63, 0.97] 0.84 [0.74, 0.96]	•
Heterogeneity: $Chi^2 = 0.78$, $df = 1$ (P = 0.38); $I^2 = 0\%$ Text for everyal effect: $Z = 2.54$ (P = 0.04)							
Test of overall energy, z = 2.54 (P = 0.01)							
1.1.3 Recurrent ovarian cancer Achaianian 2012(OCEANS)	-0.049	0.1077	242	242	16.7%	0.95 (0.77, 1.18)	+
Coleman 2015(GOG-0213)	-0.1881	0.0985	374	374	19.9%	0.83 [0.68, 1.00]	-
Karlan 2012(NCT00479817)AMG 386 at 10mg/kg	-0.5103	0.2901	53	55	2.3%	0.60 [0.34, 1.06]	
Karlan 2012(NCT00479817)AMG 386 at 3mg/kg Ledermann 2016(NCT00532194)	-0.2642	0.2726	53	55 118	2.6%	0.77 [0.45, 1.31] 0.77 [0.55, 1.07]	
Monk 2016 (NCT01204749)	-0.0532	0.0804	461	458	29.9%	0.95 [0.81, 1.11]	
Pujade-Lauraine 2016(AURELIA)	-0.1693	0.1256	179	182	12.3%	0.84 [0.66, 1.08]	-
Sehouli 2016(NCT01047891) Subtotal (95% CI)	-0.4355	0.1852	86 1678	86 1632	5.6% 100.0%	0.65 [0.45, 0.93] 0.86 [0.79, 0.94]	•
Heterogeneity: Chi ² = 8.60, df = 9 (P = 0.47); l ² = 0%							
Test for overall effect: Z = 3.46 (P = 0.0005)							
1.1.4 Platinum-sensitive recurrent ovarian cance Adhaianian 2012(OCEANS)	n 0/79	0.1089	242	242	37 9%	0.95 (0.77 1 19)	+
Coleman 2015(GOG-0213)	-0.1928	0.0984	374	374	46.5%	0.82 [0.68, 1.00]	-
Ledermann 2016(NCT00532194) Subtotal (95% CI)	-0.2651	0.1698	164 780	118 734	15.6% 100.0%	0.77 [0.55, 1.07] 0.86 [0.76, 0.98]	٠
Heterogeneity: Chi ² = 1.53, df = 2 (P = 0.47); $I^2 = 0\%$ Test for overall effect: $Z = 2.22$ (P = 0.03)							
A & F Blother webben							
1.1.5 Platinum-resistant recurrent ovarian cancel Gotlieb 2012(NCT00327444)	0.0204	0.3062	29	26	9.5%	1.02 [0.56, 1.86]	+-
Pignata 2015 (NCT01644825)	-0.5086	0.3219	37	36	8.6%	0.60 [0.32, 1.13]	
Sehouli 2016(NCT01047891)	-0.1693 -0.4355	0.1256	179	182 86	06.2% 25.8%	0.64 (0.66, 1.08) 0.65 (0.45, 0.93)	
Subtotal (95% CI) Heterogeneity: Chi ² = 2.84, df = 3 (P = 0.42); l ² = 0%	31		331	330	100.0%	0.78 [0.65, 0.94]	•
Test for overall effect: Z = 2.65 (P = 0.008)							
1.1.6 Pure maintenance treatment							L
Dubois A 2014(NCT00866697)	0.073	0.1083	472	468	79.7%	1.08 [0.87, 1.33]	
Ledermann 2011(NCT00710762)	-0.172	0.2558	43	40	14.3%	0.84 [0.51, 1.39]	-
Subtotal (95% CI) Heterogeneity: Chi ² = 1.58, df = 2 (P = 0.45); l ² = 0%			638	631	100.0%	1.06 [0.88, 1.28]	Ť
Test for overall effect: Z = 0.60 (P = 0.55)							
						F I I I I I I I I I I I I I I I I I I I	
						0	0.01 0.1 1 10 100 Favours [experimental] Favours [control]
(B)						c	0.01 0.1 1 10 100 Favours [experimental] Favours [control]
(B) Study of Subgroup	logfileword Patio	ee	Experimental	Control	Maight	Hazard Ratio	0.01 0.1 1 10 100 Favours [experimental] Favours [control] Hazard Ratio
(B) Study or Subgroup 1.2.1 first line treatment	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	(Hazard Ratio IV. Random, 95% Ci	0.01 0.1 1 00 100 Favours [experimental] Favours [control] Hazard Ratio
(B) <u>Study or Subgroup</u> 1.2.1 first line treatment Bois 2016[NCT01015118] Burger 2011(05G.0218)	log[Hazard Ratio] -0.1744 -0.3318	SE 0.0786 0.0705	Experimental Total 911 623	Control Total 455 625	Weight 31.2% 33.1%	Hazard Ratio IV. Random, 95% Ci 0.84 (0.72, 0.98) 0.72 (0.63, 0.82)	0.01 0.1 1 10 100 Favours [experimental] Favours [control] Hazard Ratio I IV. Random, 95% CI
(B) <u>Study or Subgroup</u> 1.2.1 first line treatment Bois 2016(NC 0701015118) Barger 2011(GCG 0218) Coza 2015 (CCM 7)	log[Hazard Ratio] -0.1744 -0.3318 -0.0688	SE 0.0786 0.0705 0.08	Experimental Total 911 623 764	Control Total 455 625 764	Weight 31.2% 33.1% 35.6%	(Hazard Ratio <u>IV. Random, 95% Ci</u> 0.84 [0.72, 0.98] 0.72 [0.63, 0.82] 0.93 [0.83, 1.05]	0.01 0.1 1 10 100 Favours [experimental] Favours [control] Hazard Ratio
(B) <u>Study or Subgroup</u> 1.2.1 first line treatment Bois 2016(NC1015118) Burger 2011(GOG-0218) Oza 2015 (ICON 7) Subtotal (95% C) Heterogeneity: Tau'e 0.01; Chi ² = 8.07, df = 2 (P = C	log[Hazard Ratio] -0.1744 -0.3318 -0.0688 1.02); I ^a = 75%	SE 0.0786 0.0705 0.08	Experimental Total 911 623 764 2298	Control Total 455 625 764 1844	Weight 31.2% 33.1% 35.6% 100.0%	Hazard Ratio IV. Random, 95% Ci 0.84 [0.72, 0.98] 0.72 [0.63, 0.82] 0.93 [0.83, 1.05] 0.83 [0.71, 0.97]	0.01 0.1 1 10 100 Fevours [experimental] Favours [control] 100 Hazard Ratio I. IV. Random, 93% Cl
(B) <u>Study or Subgroup</u> 1.2.1 first line treatment Bois 2016(GC01015118) Burger 2011(GCG-0218) Oza 2015 (CCO T / Subtotal (65% CI) Heterogeneity: Trai = 0.01; Chi ² = 8.07, cf = 2 (P = (C Test for overall effect: Z = 2.35 (P = 0.02)	log[Hazard Ratio] -0.1744 -0.3318 -0.0688 1.02); I ^a = 75%	SE 0.0786 0.0705 0.06	Experimental Total 911 623 764 2298	Control Total 455 625 764 1844	Weight 31.2% 33.1% 35.6% 100.0%	Hazard Ratio IV. Random, 95% Ci 0.84 [0.72, 0.98] 0.72 [0.63, 0.82] 0.93 [0.83, 1.05] 0.83 [0.71, 0.97]	0.01 0.1 1 10 100 Favours [experimental] Favours [control] Hazard Ratio Hazard Ratio I. IV. Random. 95% Cl
(B) <u>Study or Subgroup</u> 1.2.1 first line treatment Bois 2016(070105118) Burger 2011(0G/G-Q218) Coza 2015 (CICO 7) Subtola (65% CI) Hearrogeneity: Tat' = 0.01; CH ² = 8.07, cf = 2 (P = (Test for overall effect: Z = 2.55 (P = 0.02) 1.2.2 first line treatment(High-risk of progression	log[Hazard Ratio] -0.1744 -0.3318 -0.0688 1.02]; I ^s = 75%	SE 0.0786 0.0705 0.08	Experimental Total 911 623 764 2298	Control Total 455 625 764 1844	Weight 31.2% 33.1% 35.6% 100.0%	Hazard Ratio <u>IV. Random, 95% Ci</u> 0.84 (0.72, 0.96) 0.72 (0.63, 0.82) 0.93 (0.83, 1.05) 0.83 (0.71, 0.97]	0.01 0.1 1 10 100 Favours [experimental] Favours [control] Hazard Ratio I. IV. Random, 95% Cl
(B) <u>Study or Subgroup</u> 1.2.1 first line treatment Bois 2016(0C1015118) Burger 2011(GCG-0218) Oza 2015 (ICON 7) Subtotal (95% CI) Heterogeneity: Tau ² = 0.01; Chi ² = 8.07, df = 2 (P = (Test for overal effect: Z = 2.35 (P = 0.02) 1.2.2 first line treatment(High-risk of progression Burger 2011(GCG-0218) Oza 2015(GCG-0218)	log[Hazard Ratio] -0.1744 -0.316 -0.0688 .02); I ^o = 75% -0.3316 -0.3311	SE 0.0786 0.0705 0.06 0.0705 0.0935	Experimental Total 911 623 764 2298 623 248	Control Total 455 625 764 1844 625 254	Weight 31.2% 33.1% 35.6% 100.0% 63.8% 36.2%	Hazard Ratio (V. Random, 95% Ci 0.84 (0.72, 0.98) 0.72 (0.63, 0.82) 0.93 (0.83, 0.82) 0.83 (0.71, 0.97) 0.72 (0.63, 0.82) 0.72 (0.63, 0.82) 0.73 (0.61, 0.88)	0.01 0.1 1 10 100 Favours [experimental] Favours [control]
(B) Study or Subgroup 12.1 first line treatment Boia 2019(NCT01015118), Boia 2015 (ICON 7) Subtotal (BSK C) Heterogeneity, Taa' = 0.01, CHI = 0.07, cH = 2 (P = C) Test for overall effect: Z = 2.35 (P = 0.02) 12.2 first line catament(High-risk of progression Burger 2011(GOG-0218) Subtotal (BSK C) Heterogeneity Taa' = 0.07, CHI = 0.03, cH = 4 (P = C) Restored (PSK C)	log[Hazard Ratio] -0.1744 -0.3318 -0.0688 1.02); I ² = 75% -0.3318 -0.3318 -0.3318	SE 0.0786 0.0705 0.08 0.0705 0.0935	Experimental Total 911 623 764 2298 623 249 871	Control Total 455 764 1844 625 254 879	Weight 31.2% 33.1% 35.6% 100.0% 63.8% 36.2% 100.0%	Hazard Ratio 1/V. Random. <u>95%</u> . CI 0.84 (0.72, 0.98) 0.72 (0.63, 0.82) 0.93 (0.83, 1.05) 0.83 (0.71, 0.97) 0.72 (0.63, 0.82) 0.72 (0.65, 0.81)	0.01 0.1 1 00 100 Fexours (experimental) Fexours (control) 100 Hazard Ratio
(B) <u>Study or Subgroup</u> 1.2.1 first line treatment Bois 2016(NC 101015118) Burger 2011(GCG-0218) Coza 2015 (CCN 7) Subtool (85% CI) Heterogeneity: Tau'e 0.01; Chi ² = 8.07, df = 2 (P = C Test for overall effect: Z = 2.55 (P = 0.02) 1.2.2 first line treatment(High-risk of progression Burger 2011(GCG-0218) Coza 2015 (con7 high risk Subtool (85% CI) Heterogeneity: Tau'e 0.00, Chi ² = 0.03, df = 1 (P = C Test for overall effect: Z = 5.76 (P = 0.0001)	_log[Hazard Ratio] -0, 1744 -0, 3318 -0.0688 1.02); I ^o = 75% -0.3318 -0.3111 1.86); I ^o = 0%	SE 0.0786 0.0705 0.08 0.0705 0.0935	Experimental Total 911 623 764 2298 623 623 871	Control Total 455 625 764 1844 625 254 879	Weight 31.2% 33.1% 35.6% 100.0% 63.8% 36.2% 100.0%	Hazard Ratio 17. Random, 95% Ci 0.84 (0.72, 0.98) 0.72 (0.63, 0.82) 0.83 (0.71, 0.97) 0.73 (0.63, 0.82) 0.73 (0.61, 0.88) 0.72 (0.65, 0.81)	0.01 0.1 1 10 100 Fevours [experimental] Favours [control] 100 Hazard Ratio I. IV. Random, 93% Cl
(B) <u>Study or Subgroup</u> 1.2.1 first line treatment Bois 2016(0-C0105118) Burger 2011(GOG-0218) Oza 2015 (COK 7) Subtool (85% CI) Heterogeneity: Tau ⁴ = 0.01; Ch ² = 6.07, df = 2 (P = C) Test for overall effect: Z = 2.35 (P = 0.02) 1.2.2 first line treatment(High-risk of progression Burger 2011(GOG-0218) Oza 2015 (con7 high risk Subtoola (95% CI) Heterogeneity: Tau ⁴ = 0.03, df = 1 (P = C) Test for overall effect: Z = 5.76 (P < 0.00001) 1.2.3 Recurrent ovarian cancer	log[Hazard Ratio] -0.1744 -0.3318 -0.0688 1.02); I ^a = 75% -0.3318 -0.3111 1.866); I ^a = 0%	SE 0.0786 0.0705 0.06 0.0705 0.0935	Experimental Total 911 623 764 2298 623 248 871	Control Total 455 625 764 1844 625 254 879	Weight 31.2% 33.1% 35.6% 100.0% 63.8% 36.2% 100.0%	Hazard Ratio IV. Random. 95% Cf 0.84 (0.72, 0.98) 0.72 (0.63, 0.82) 0.93 (0.83, 0.82) 0.83 (0.71, 0.97) 0.72 (0.63, 0.82) 0.72 (0.63, 0.82) 0.72 (0.68, 0.81)	0.01 0.1 1 10 100 Favours [experimental] Favours [control] 100 Hazard Ratio I. IV. Randem. 93% Cl
(B) Study or Subgroup 1.2.1 first line treatment Bois 2016(NCO1015118) Burger 2011(GOG-0218) Coz 2015 (COR 7) Subtotal (95% C) Heterogeneity: Tau ⁴ = 0.01; Chi ² = 8.07, df = 2 (P = C) Test for overal effect: Z = 2.35 (P = 0.02) 1.2.2 first line treatment(High-risk of progression Burger 2011(GOG-0218) Coz 2015 icon7 high risk Subtotal (95% C)] Heterogeneity: Tau ⁴ = 0.00; Chi ² = 0.03, df = 1 (P = C) Test for overal effect: Z = 5.76 (P < 0.00001) 1.2.3 Recurrent oversion cancer Aphaginan 2012(OCEANS)) Corrents Of CoGA D0110)	log[Hazard Ratio] -0,1744 -0,3318 -0,668 1.02); I ^a = 75% -0,3318 -0,3111 1.866); I ^a = 0% -0,7246	SE 0.0786 0.0705 0.06 0.0705 0.0935	Experimental Total 911 623 764 2298 623 248 871 248 871	Control Total 455 625 764 1844 625 254 879 242 237	Weight 31.2% 33.1% 35.6% 100.0% 63.8% 36.2% 100.0%	Hazard Ratio U. Random. 95% Cf 0.84 (0.72, 0.98) 0.72 (0.63, 0.63, 1.62) 0.93 (0.83, 1.62) 0.93 (0.83, 1.62) 0.83 (0.71, 0.97] 0.72 (0.63, 0.82] 0.72 (0.63, 0.82) 0.72 (0.65, 0.81) 0.84 (0.38, 0.60) 0.81 (0.52, 0.72)	0.01 0.1 1 0 100 Favours [experimental] Favours [control] 100 Hazard Ratio M. Random. 95% Cl
(B) <u>Study or Subgroup</u> 1.2.1 first line treatment Bois 2016(070105118) Burger 2011(GOG-0218) Coz 2015 (COR 7) Subtotal (95% CI) Hetercognerity: Trai* = 0.01; Chi* = 8.07, df = 2 (P = C) Test for overal effect: Z = 2.35 (P = 0.02) 1.2.2 first line treatment(High-risk of progression Burger 2011(GOG-0218) Coz 2015 (con7 high risk Subtotal (95% CI) Hetercognerity: Tai* = 0.00; Chi* = 0.03, df = 1 (P = C) Test for overal effect: Z = 6.76 (P < 0.00001) 1.2.3 Recurrent overain cancer Aplagiance 2012(20CE AKS) Colema 2012(20CE AKS) Colema 2012(20CE AKS)	log[Hazard Ratio] -0.1744 -0.3318 -0.6688 1.02); I ^a = 75%) -0.3318 -0.3111 1.86); I ^a = 0% -0.7246 -0.4879 0	SE 0.0786 0.0705 0.06 0.0705 0.0935 0.0935 0.0935	Experimental 911 623 764 2298 623 248 871 248 871 242 242 374 0	Control Total 455 625 764 1844 625 254 879 242 374 0	Weight 31.2% 33.1% 35.6% 100.0% 63.8% 36.2% 100.0% 13.7% 18.6%	Hazard Ratio IV. Random. 95% CI 0.84 (0.7,2,0.98) 0.72 (0.63,0.82) 0.93 (0.83,0.82) 0.83 (0.71,0.97] 0.72 (0.63,0.82) 0.72 (0.63,0.82) 0.72 (0.64,0.88) 0.72 (0.65,0.81) 0.48 (0.39,0.60) 0.48 (0.39,0.60) Not seimable	0.01 0.1 1 10 100 Favours [experimental] Favours [control] Hazard Ratio I. IV. Random. 95% Cl
(B) Study or Subgroup 12.1 first line treatment Bois 2019(NCT01015118); Burger 2011(0C60-0018) Ora 2015 (ICON 7) Subtotal (B5% C) Heterogramity: Tau" = 0.01; CH" = 6.07, cf = 2 (P = C) Test for overall effect: Z = 2.35 (P = 0.02) 12.2 first line teatment(High-risk of progression Burger 2011(0C9-0218) Caz 2015 (ICON-0218) Subtotal (B5% C) Heterogramity: Tau" = 0.00; CH" = 0.03, cf = 1 (P = C) Test for overall effect: Z = 5.76 (P < 0.00001) 12.3 Recurrent ovarian cancer Aplagianina 2012(OCEDANS) Codeman 2012(NCT00478817/MAG 386 at 10mg/kg Karian 2012(NCT00478817/MAG 386 at 10mg/kg	log[Hazard Ratio] -0.1744 -0.3318 -0.6688 1.02); I ^a = 75%) -0.3318 -0.3318 -0.3111 1.86); I ^a = 0% -0.7246 -0.4879 0.2879 -0.2739	SE 0.0786 0.0705 0.06 0.0705 0.0935 0.0935 0.1133 0.0827 0 0.2273	Experimental Total 911 623 764 2298 623 248 871 242 374 0 374 0 53 353	Control Total 455 625 764 1844 625 254 879 242 374 0 55	Weight 31.2% 33.1% 35.6% 100.0% 63.8% 36.2% 100.0% 13.7% 18.6% 5.2% 5.1%	Hazard Ratio IV. Random. 95% Cf 0.84 [0.72, 0.96] 0.72 [0.63, 0.82] 0.83 [0.83, 1.05] 0.83 [0.71, 0.87] 0.72 [0.63, 0.82] 0.72 [0.63, 0.82] 0.72 [0.64, 0.88] 0.72 [0.65, 0.81] 0.48 [0.39, 0.60] 0.61 [0.52, 0.72] Not estimable 0.76 [0.48, 1.18] 0.75 [0.48, 1.18]	0.01 0.1 1 10 100 Favours [experimental] Favours [control] Hazard Ratio I. IV. Random, 95% Cl
(B) Study on Subgroup 1.2.1 first line treatment Bois 2016(NC101015118) Barger 2011(GCG-0218) Coz 2015 (COM 7) Subtoal (BS% C) 1.2.2 first line treatment(High-risk of progression Barger 2011(GCG-0218) Coz 2015 (con7 high risk Subtoal (BS% C) Heierogeneity: Tau' = 0.01; Chi* = 0.03, cfi = 1 (P = C) Test for overal effect Z = 0.16 (P = 0.00001) Heierogeneity: Tau' = 0.00; Chi* = 0.03, cfi = 1 (P = C) Test for overal effect Z = 0.16 (P = 0.00001) 1.2.3 Recurrent ovarian cancer Aphaginan 2012(OCGA/S18) Codeman 2015(OCGA/S18) Codeman 2015(log[Hazard Ratio] -0.1744 -0.2316 -0.069 -0.069 -0.3316 -0.3111 1.86); ² = 0% -0.7246 -0.4679 -0.2685 -0.2709 -0.2709 -0.2685 -0.5747	0.0786 0.0705 0.08 0.0705 0.0935 0.0935 0.0935	Experimental Total 623 764 2298 623 248 871 248 871 374 0 53 353 53 53 53 53 53 53 53 53 53 53 53	Control Total 455 625 764 1844 625 254 879 242 374 0 55 55 118	Weight 31.2% 33.1% 35.6% 100.0% 63.8% 36.2% 100.0% 13.7% 18.6% 5.1% 12.2% 10.0%	Hazard Ratio <u>IV. Random. 95% Cf</u> 0.84 (0.72, 0.98) 0.72 (0.63, 0.82) 0.72 (0.63, 0.82) 0.73 (0.61, 0.82) 0.72 (0.63, 0.82) 0.72 (0.64, 0.72) Not estimated 0.76 (0.48, 1.8) 0.76 (0.44, 0.72) 0.56 (0.44, 0.72)	0.01 0.1 1 00 100 Favours [experimental] Favours [contro] 100 Hazard Ratio IV. Random, 93% Cl
(B) <u>Study or Subgroup</u> 1.2.1 first line treatment Bois 2016(NCT015116) Burger 2011(GCG-0218) Coz 2015 (CON 7) Subtoat (85% CI) Heterogeneity: Tau' = 0.01; Chi ² = 8.07, df = 2 (P = C) Test for overall effect: 2 = 2.51 (P = 0.02) 1.2.2 first line treatment(High-risk of progression Burger 2011(GCG-0218) Coz 2015 (con7 nigh risk Subtoat (85% CI) Heterogeneity: Tau' = 0.00; Chi ² = 0.03, df = 1 (P = C) Test for overall effect: 2 = 5.76 (P = 0.0001) 1.2.3 Recurrent ovarian cancer Aphajama 2013(CCEANS) Coleman 2015(CGC-9213) Gottleb 2012(NCT00327841) Karian 2012(NCT00378917)AMG 388 at 10mg/kg Karian 2012(NCT00378917)AMG 388 at 10mg/kg Karian 2012(NCT00478917)AMG 388 at 10mg/kg Karian 2012(NCT0164425)	log[Hazard Ratio] -0.1744 -0.2316 -0.068 -0.021; I ^a = 75%) -0.3318 -0.3111 1.86); I ^a = 0% -0.7246 -0.4879 0 0 -0.2895 -0.5787 -0.417 -0.479	0.0786 0.0705 0.06 0.0935 0.0827 0 0.2242 0.2273 0.2273 0.2273	Experimental Total 911 623 764 2298 623 248 871 242 374 374 0 53 53 164 461 37	Control Total 455 625 764 1844 879 242 254 879 242 374 0 55 55 118 8458 836	Weight 31.2% 33.1% 33.5% 100.0% 63.8% 100.0% 13.7% 18.6% 5.2% 5.1% 12.2% 19.7% 4.1%	Hazard Ratio (J. Random, 95% Cf 0.84 (0.72, 0.98) 0.72 (0.63, 0.83) 0.73 (0.63, 0.82) 0.73 (0.61, 0.83) 0.72 (0.63, 0.82) 0.73 (0.61, 0.88) 0.72 (0.65, 0.81) 0.61 (0.52, 0.72) Not estimatic 0.76 (0.49, 1.18) 0.76 (0.49, 1.18) 0.76 (0.49, 1.19) 0.76 (0.44, 1.77) 0.66 (0.57, 0.77) 0.66 (0.57, 0.72)	0.01 0.1 1 00 100 Favours [experimental] Favours [control] 100 Hazard Ratio IV. Randem, 93% Cl
(B) <u>Study or Subgroup</u> 1.2.1 first line treatment Bois 2016(NC1015116) Burger 2011(GOG 0218) Coz 2015 (COG 0218) Coz 2015 (COG 0218) Coz 2015 (COG 0218) Coz 2015 (COG 0218) Deterogramity: Tau ⁴ = 0.01; Ch ² = 6.07, df = 2 (P = C Test for overal effect: Z = 2.55 (P = 0.02) 1.2.2 first line treatment(High+risk of progression Burger 2011(GOG Co218) Coz 2015 (con7 high risk Subtotal (95% Ci) Heisrogoneity: Tau ⁴ = 0.00; Ch ² = 0.03, df = 1 (P = C Test for overal effect: Z = 6.76 (P < 0.0001) 1.2.3 Recurrent ovarian cancer Aphajana 2012(OCEANS) Coleman 2015(COG Co313) Goliteb 2012(NCT00327841/NKG 386 at 10mg/kg Karian 2012(NCT00478917/MKG 386 at 10mg/kg Karian 2012(NCT01624425) Pujsde-Laursina 2016(NCT01624425) Pujsde-Laursina 2016(NCT0164425) Pujsde-Laursina 2016(NCT01647491)	log[Hazard Ratio] -0.1744 -0.2318 -0.068 -0.02318 -0.3318 -0.3111 1.865); I [≠] = 0% -0.7246 -0.4879 0 -0.2895 -0.578	0.0786 0.0705 0.06 0.0935 0.0935 0.0935 0.0935 0.0935 0.0935 0.0272 0.2242 0.2242 0.2242 0.2242 0.2242 0.2273 0.2259 0.1678	Experimental Total 911 623 764 2298 623 248 871 248 871 0 533 164 461 377 984	Control Total 455 625 764 1844 1844 879 242 374 879 242 374 0 0 55 55 118 84 98 6 25 25 242 879 879 879 879 879 879 879 879 879 879	Weight 31.2% 33.1% 55.5% 100.0% 13.7% 18.0% 5.2% 5.1% 12.2% 19.7% 12.2% 12.2% 12.3% 2.4%	Hazard Ratio (), Random, 95%, C() 0.84 (0.72, 0.98) 0.72 (0.63, 0.63) 0.83 (0.71, 0.97) 0.72 (0.63, 0.62) 0.73 (0.61, 0.88) 0.72 (0.65, 0.81) 0.72 (0.65, 0.81) 0.64 (0.52, 0.72) Not estimate 0.76 (0.49, 1.18) 0.75 (0.44, 1.17) 0.56 (0.44, 0.73) 0.56 (0.44, 0.72) 0.56 (0.54, 0.72) 0	0.01 0.1 1 00 100 Favours [experimental] Favours [control] Hazard Ratio Hazard Ratio H.Randem, 95% Cl
(B) <u>Study or Subgroup</u> 1.2.1 first line treatment Bois 2016(NC1015118) Burger 2011(GCG-0.218) Coz 2015 (COR 7) Subtotal (85% C) Heterogeneity: Tau ⁴ = 0.01; Chi ² = 8.07, cf = 2 (P = C) Test for overal effect: Z = 2.35 (P = 0.02) 1.2.2 first line treatment(High-risk of progression Burger 2011(GCG-0.218) Coz 2015 (con7 high risk Subtotal (85% C)) Heterogeneity: Tau ⁴ = 0.00; Chi ² = 0.03, cf = 1 (P = C) Test for overal effect: Z = 5.76 (P < 0.00001) 1.2.3 Recurrent ovarian cancer Aphaginan 2012(OCGANS) Codeman 2015(CGCG-0213) Codiema 2015(RCT10032744) Karian 2012(NCT100474817/MMG 386 at 10mg/kg Karian 2012(NCT010474817/MMG 386 at 10mg/kg Karian 2012(NCT010478817/MMG 386 at 10mg/kg Karian 2012(NCT010478817) Subtotal (85% C) Figural 2015 (NCT01644625) Figural 2015 (NCT01646625) Figural 2015 (NCT01646625	log[Hazard Ratio] -0.1744 -0.3318 -0.6688 1.02); I ^a = 75% -0.3318 -0.3111 .866); I ^a = 0% -0.7246 -0.7246 -0.4879 -0.2739 -0.2759 -0.2759 -0.5151 -0.5152 -0.5151 -0.5152 -0.5151 -0.5152 -0.5151 -0.5152 -0.5151 -0.5152	0.0786 0.0705 0.08 0.0935 0.0935 0.0935 0.0935 0.0252 0.0259 0.1165 0.1678	Experimental Total 911 623 764 2298 623 248 871 242 248 871 0 33 31 64 146 146 146 166 166 166 166	Control <u>Total</u> 455 625 764 1844 1844 879 242 374 0 55 55 55 188 458 879 242 242 242 374 0 55 55 56 188 458 625 184 1845 1845 1855	Weight 31.2% 33.1% 35.8% 100.0% 63.8% 63.8% 100.0% 13.7% 5.2% 5.1% 19.2% 13.3% 62.2% 19.2% 13.2% 10.0%	Hazard Ratio U.Random. 95% Cf 0.84 (0.72, 0.89) 0.72 (0.63, 0.62) 0.93 (0.63, 1.05) 0.83 (0.71, 0.97] 0.72 (0.63, 0.82) 0.73 (0.61, 0.89) 0.72 (0.65, 0.82) 0.73 (0.61, 0.89) 0.72 (0.65, 0.81) 0.61 (0.52, 0.72) Not estimatic 0.76 (0.48, 1.17) 0.56 (0.54, 0.72) 0.66 (0.57, 0.77) 0.66 (0.57, 0.77) 0.42 (0.25, 0.68) 0.43 (0.33, 0.60) 0.65 (0.52, 0.65)	0.01 0.1 1 00 100 Favours [experimental] Favours [control] 100 Hazard Ratio Hazard Ratio Hazard Ratio
(B) Study or Subgroup 1.2.1 first line treatment Bois 2019(NCT01015118); Burger 2011(050-6018) Craz 2015 (ICON 7) Subtotal (BSK C) Heterogramity: Tau' = 0.01; Chi' = 6.07, df = 2 (P = 0) Test for overall effect: Z = 2.35 (P = 0.02) 1.2.2 first line teatment(High-risk of progression Burger 2011(050-0218); Subtotal (BSK C) Heterogramity: Tau' = 0.00; Chi' = 0.03, df = 1 (P = 0) Test for overall effect: Z = 5.76 (P < 0.00001) 1.2.3 Recurrent ovarian cancer Apolaginan 2012(NCT00478817);MMS 386 at 10mg/kg Karian 2012(NCT016478817);MMS 386 at 3mg/kg Lederman 2016(NCT016478817);MMS 386 at 3mg/kg Lederman 2016(NCT01647881); Subtotal (BSK C) Heterogeneily: Tau' = 0.01; Chi' = 13.19, df = 6 (P = 0.0001)	log[Hazard Ratio] -0, 7744 -0.2318 -0.2318 -0.2318 -0.3318 -0.3111 1.86]; I° = 0% -0.7246 -0.4879 0.2789 -0.7246 -0.4879 0.2789 -0.7246 -0.477 -0.7382 -0.5151 0.11); I° = 38%	0.0786 0.0705 0.08 0.0935 0.0935 0.0935 0.0935 0.0935 0.02242 0.0259 0.1165 0.1678	Experimental Total 911 623 764 2298 623 249 671 0 53 53 53 53 164 461 37 179 86 1649	Control Total 455 562 764 1844 879 2242 374 0 55 55 55 118 458 86 182 86 1606	Weight 31.25 33.15 33.55 35.65 100.0% 63.85 5.25 5.15 5.55 5.55 19.25 5.15 19.25 5.15 19.25 5.15 19.25 5.15 19.25 5.19 19.25 5.19 19.25 5.15 19.25 5.15 19.05 5.15 5.25 5.15 5.25 5.15 5.25 5.15 5.25 5.15 5.25 5.15 5.25 5.15 5.25 5.15 5.25 5.15 5.25 5.15 5.25 5.15 5.25 5.15 5.25 5.15 5.25 5.15 5.25 5.55 5.15 5.25 5.55 5.15 5.25 5.55 5.15 5.25 5.55 5.15 5.25 5.55 5.15 5.25 5.55 5.25 5.55 5.25 5.55 5.55 5.55 5.55 5.55 5.25 5.55 5.25 5.55 5.25 5.55 5.25 5.55 5.25 5.55 5.25 5.55 5.25 5.55 5.25 5.55 5.25 5.55 5.25 5.55 5.25 5.55	Hazard Ratio IV. Random. 95% Cf 0.84 (0.72, 0.98) 0.72 (0.63, 0.63) 0.83 (0.71, 0.97] 0.73 (0.63, 0.82) 0.73 (0.61, 0.88) 0.72 (0.63, 0.82) 0.73 (0.61, 0.88) 0.72 (0.65, 0.81) 0.48 (0.39, 0.60) 0.61 (0.52, 0.72) Not estimable 0.76 (0.49, 1.18) 0.75 (0.49, 1.18) 0.75 (0.49, 1.18) 0.75 (0.49, 1.18) 0.75 (0.49, 1.18) 0.75 (0.49, 0.38) 0.66 (0.57, 0.77) 0.42 (0.25, 0.68) 0.48 (0.25, 0.65)	0.01 0.1 1 10 100 Favours [experimental] Favours [control] Hazard Ratio I. IV. Random. 95% Cl
(B) Study or Subgroup 1.2.2 first line treatment Borger 201(NCO1015118) Borger 201(NCO0471) Subdeal (BVK) Subdeal (BVK) 1.2.2 first line treatment(High-risk of progression Subdeal (SVK) 1.2.2 first line treatment(High-risk of progression Suger 201(NCO-0218) Subdeal (SVK) 1.2.2 first line treatment(High-risk of progression Suger 201(NCO-0218) Subdeal (SVK) Hearogeneity: Tax' = 0.07; CH' = 0.03, df = 1 (P = C) Test for overall effect: Z = 5.76 (P < 0.0001) 1.2.3 Recurrent ovarian cancer Apolganian 2012(NCOEANS) Codeman 2012(NCT00478817),MK0 386 at 10mg/k8 Karian 2012(NCT00478817),MK0 386 at 10mg/k8 Karian 2012(NCT01247481) Nork 2016 (NCT01247481) Pignals 2015 (NCT01247891) Subtoal (SVK) C) Hearogeneity: Tax' = 0.07; CH' = 13.19, df = 6 (P = C) Test for overall effect: Z = 9.73 (P < 0.0001) 1.2.4 Platitum-sensitive recurrent ovarian cancer Apoles 2015(NCT01247891) Subtoal (SVK) C) Hearogeneity: Tax' = 0.01; CH' = 13.19, df = 6 (P = C) Test for overall effect: Z = 9.73 (P < 0.0001)	log[Hazard Ratio] -0.1744 -0.2318 -0.0631 -0.0631 -0.3318 -0.3111 1.86]; * = 0% -0.7246 -0.479 -0.479 -0.2739 -0.2739 -0.2739 -0.2739 -0.5747 -0.7382 -0.5151 0.11]; * = 39%	SE 0.0786 0.0705 0.080 0.0935 0.0935 0.0935 0.0935 0.0935 0.0935 0.2242 0.2242 0.2273 0.2273 0.2273 0.0259 0.1165 0.1678	Experimental Total 911 623 764 2298 623 248 871 242 374 374 375 33 353 53 353 53 53 53 53 53 53 53 53	Control Total 455 562 764 1844 879 2242 374 0 55 55 5118 458 86186 1606	Weight 31.2% 33.1% 35.6% 100.0% 63.8% 63.8% 5.3% 5.3% 5.2% 5.1% 8.2% 12.2% 12.2% 12.2% 100.0%	Hazard Ratio IV. Random. 95% Cf 0.84 (0.72, 0.96) 0.72 (0.63, 0.62) 0.83 (0.83, 10.5) 0.73 (0.63, 0.82) 0.73 (0.61, 0.88) 0.72 (0.63, 0.82) 0.72 (0.63, 0.82) 0.72 (0.64, 0.88) 0.72 (0.65, 0.81) 0.48 (0.39, 0.60) 0.61 (0.52, 0.72) Not estimable 0.76 (0.49, 1.18) 0.75 (0.49, 1.18) 0.75 (0.49, 1.18) 0.75 (0.49, 0.18) 0.66 (0.57, 0.77) 0.48 (0.25, 0.68) 0.48 (0.38, 0.60) 0.48 (0.38, 0.60) 0.48 (0.38, 0.60) 0.48 (0.38, 0.60) 0.48 (0.52, 0.65)	0.01 0.1 1 10 100 Favours [experimental] Favours [control] Hazard Ratio I. IV. Randem, 95% Cl
(B) Study on Subgroup 1.2.1 first line treatment Bois 2016(NC101015118) Burger 2011(GCG-0218) Coa 2015 (COM 7) Subtool (BS% COI 1.2.2 first line treatment(High-risk of progression Burger 2011(GCG-0218) Coa 2015 (con 7 high risk Subtool (BS% COI 2.2.2 first line treatment(High-risk of progression Burger 2011(GCG-0218) Coa 2015 (con 7 high risk Subtool (BS% COI 1.2.3 Recurrent ovarian cancer Aphagina 2013(CCGA/2015) Codeman 2012(CCGA/2014) Codeman 2014(CCGA/2014) Codeman 2014(CCGA/2014) Codeman 2014(CCGA/2014) Codeman 201	log[Hazard Ratio] -0.1744 -0.2316 -0.068 -0.068 -0.3318 -0.3111 1.86]; ² = 0% -0.7246 -0.4879 0.2885 -0.5745 -0.57	SE 0.0786 0.0705 0.080 0.0935 0.0935 0.0935 0.0935 0.0935 0.2242 0.2273 0.2242 0.2736 0.2273 0.229 0.1165 0.1678	Experimental Total 911 623 764 2298 623 248 871 623 248 871 0 53 374 0 53 374 0 53 374 0 53 374 0 53 374 0 53 374 0 53 374 0 53 376 491 1 1 49 2422 242 242 242 242 242 242 242 242	Control Total 455 625 764 1844 625 254 879 242 334 374 374 374 374 374 879 242 242 242 86 1606	Weight 31.2% 33.1% 35.6% 100.0% 63.8% 63.8% 13.7% 5.2% 5.2% 5.2% 8.2% 10.0% 30.2% 4.1% 8.2% 100.0%	Hazard Ratio H. Random, 95% Cf 0.84 (0.72, 0.98) 0.72 (0.63, 0.63) 0.93 (0.83, 10.5) 0.83 (0.71, 0.97) 0.72 (0.63, 0.82) 0.73 (0.61, 0.89) 0.72 (0.65, 0.81) 0.48 (0.39, 0.60) 0.61 (0.52, 0.72) Not estimate 0.76 (0.49, 1.18) 0.76 (0.49, 1.18) 0.76 (0.49, 1.18) 0.76 (0.49, 1.18) 0.76 (0.49, 1.18) 0.76 (0.49, 1.18) 0.76 (0.49, 1.18) 0.75 (0.48, 1.17) 0.66 (0.57, 0.77) 0.66 (0.57, 0.72) 0.66 (0.52, 0.68) 0.48 (0.38, 0.60) 0.49 (0.38, 0.60) 0.49 (0.38, 0.60) 0.49 (0.39, 0.60) 0.49 (0.50, 0.60) 0.40	0.01 0.1 1 00 100 Favours [experimental] Favours [contro] 100 Hazard Ratio IV. Random, 95% Cl
(B) <u>Study or Subgroup</u> 1.2.1 first line treatment Biol 2016(NC1015116) Burger 2011(GCG-0218) Coz 2015 (CCN 7) Subtool (BS% CI) Heterogeneity: Tau ⁴ = 0.01; Ch ² = 8.07, df = 2 (P = C Test for overal effect: Z = 2.35 (P = 0.02) 1.2.2 first line treatment(High-risk of progression Burger 2011(GCG-0218) Coz 2015 (con ⁷ nigh risk Subtool (BS% CI) Heterogeneity: Tau ⁴ = 0.00; Ch ² = 0.03, df = 1 (P = C Test for overal effect: Z = 5.76 (P = 0.0001) 1.2.3 Recurrent ovarian cancer Anhajman 2012(CCEANS) Coleman 2015(CCG-0213) Gottleb 2012(NCT00327817)/MG 386 at 10mg/kg Karian 2012(NCT00478817)/MG 386 at 10mg/kg Karian 2012(NCT00478917)/MG 386 at 10mg/kg Karian 2012(NCT00478917)/MG 386 at 10mg/kg Karian 2012(NCT016478917)/MG 386 at 10mg/kg Karian 2012(NCT016	log[Hazard Ratio] -0.1744 -0.2316 -0.068 -0.021; I° = 75% -0.3318 -0.3111 1.86); I° = 0% -0.7246 -0.4879 0 -0.2895 -0.5747 -0.7392 -0.5151 0.11); I° = 38% -0.7262 -0.5747 -0.7262 -0.5747 -0.7262 -0.5747 -0.7262 -0.5747 -0.7262 -0.5747 -0.7262 -0.5747 -0.7262 -0.5747 -0.7262 -0.5747 -0.7262 -0.5747 -0.7262 -0.5747 -0.5757 -0.5747 -0.5757 -0.	\$ \$ \$	Experimental Total 911 623 764 2298 623 248 871 242 374 0 53 3164 461 37 179 86 6 1649 242 374 164	Control Total 455 625 764 1844 625 254 879 2242 374 455 55 518 86 86 182 86 1806 812 242 2374 118	Weight 31.2% 33.1% 33.5% 35.5% 100.0% 63.8% 5.2% 100.0% 13.7% 12.2% 10.0% 12.2% 10.0% 30.7% 44.1% 30.7%	Hazard Ratio (), Random, 95%, C(), Random, Ran	101 0.1 1 10 100 Favours [experimental] Favours [control] Hazard Ratio IV. Randem, 95% Cl
(B) <u>study or Subgroup</u> 1.2.1 first line treatment Bois 2016(NC1015116) Burger 2011(GCGO218) Coz 2015 (COG 0218) Coz 2015 (COG 0218) Codema 2015(COG 0213) Codema 2015(COT 0124749) Pujsde Loursine 2016(AURELIA) Subtola(16%) Codema 2015(COG 0213) Codema 2015(COG Cod 03) Subtola(16%) Codema 2015(COG Cod 03) Codema 2015(COG Cod 03) Subtola(16%) Codema 2015(COG Cod 03) Codema 2015(COG 0213) Lederman 2015(COG Cod 03) Codema 2015(COC Cod 03) Cod	log[Hazard Ratio] -0.1744 -0.3318 -0.080 -0.080 -0.3318 -0.3111 1.86); I* = 0% -0.7246 -0.4879 0 -0.2739 -0.2739 -0.2739 -0.5151 0.11½; I* = 39% -0.5151 0.11½; I* = 39% -0.5747 -0.57	SE 0.0795 0.0705 0.068 0.02273 0.2273 0.2273 0.2273 0.1256 0.1678	Experimental Total 911 623 764 2298 623 764 249 871 9 374 374 374 374 461 377 179 966 1649 242 374 471 464 1649 780	Control Total 455 625 764 1844 625 254 879 0 0 55 55 55 55 118 145 1606 1606 242 2374 158 1606	Weight 31.2% 33.1% 35.6% 36.2% 100.0% 43.7% 5.1% 5.2% 5.2% 5.1% 2.2% 10.2% 30.7% 4.1% 13.3% 2.2% 100.0%	Hazard Ratio (), Random, 95%, C(), 0.84 (0.72, 0.98) 0.72 (0.63, 0.82) 0.93 (0.83, 1.05) 0.83 (0.71, 0.97) 0.72 (0.63, 0.82) 0.73 (0.61, 0.88) 0.72 (0.65, 0.81) 0.72 (0.65, 0.81) 0.64 (0.52, 0.72) Not estimate 0.76 (0.49, 1.18) 0.75 (0.44, 1.72) 0.66 (0.57, 0.77) 0.66 (0.57, 0.73) 0.68 (0.57, 0.68) 0.69 (0.52, 0.68) 0.69 (0.52, 0.68) 0.69 (0.52, 0.68) 0.69 (0.52, 0.68) 0.69 (0.52, 0.68)	0.01 0.1 1 00 100 Favours [experimental] Favours [control] Hazard Ratio M.Randem, 95% Cl
(B) Study or Subgroup 1.2.1 first line treatment Bois 2019(NCT01015118); Burger 2011(OCG-0218) Oraz 2015 (ICON 7) Subtotal (BSK C) Hearographic, Tau' = 0.01; Ch' = 6.07, df = 2 (P = C) Test for overall effect: Z = 2.35 (P = 0.02) 1.2.2 first line teatment(High-Fisk of progression Burger 2011(GCG-0218) Caz 2015 (ICON - 7) Subtotal (BSK C) Hearographic, Tau' = 0.00; Ch' = 0.03, df = 1 (P = C) Test for overall effect: Z = 5.76 (P < 0.00001) 1.2.3 Recurrent ovarian cancer Aplagianna 2012(OCGEANS) Coleman 2015(ICOT024744) Karian 2012(NCT010478911) Subtotal (BSK C) Hearographic, Tau' = 0.01; Ch' = 1.319, df = 8 (P = Test for overall 2016(IACTELIA) Sabutotal (BSK C) Hearographic, Tau' = 0.01; Ch' = 1.319, df = 8 (P = Test for overall 2016(IACTELIA) Sabutotal (BSK C) Hearographic, Tau' = 0.01; Ch' = 2.31, df = 8 (P = Test for overall 2016(IACTELIA) Sabutotal (BSK C) Hearographic, Tau' = 0.01; Ch' = 2.31, df = 2 (P = (Caleman 2015(IACG-0213) Ladermann 2016(IACTE0532144) Sabutotal (BSK C) Hearographic, Tau' = 0.01; Ch' = 2.31, df = 2 (P = (Test for overall effect: Z = 0.73 (C + 0.00001) 1.2.4 Platinum-sensitive recurrent ovarian cancer Aplaginan 2013(ICCG-0213) Ladermann 2016(IACTE0532144) Sabutotal (BSK C) Hearographic, Tau' = 0.01; Ch' = 2.31, df = 2 (P = (Test for overall effect: Z = 0.73 (C + 0.00001) Laderman 2016(IACTE0532144) Sabutotal (BSK C) Hearographic, Tau' = 0.01; Ch' = 2.31, df = 2 (P = (Test for overall effect: Z = 0.73 (C + 0.00001) Hearographic, Tau' = 0.01; Ch' = 2.41, df = 2 (P = (Test for overall effect: Z = 0.73 (C + 0.00001) Hearographic, Tau' = 0.01; Ch' = 2.41, df = 2 (P = (Test for overall effect: Z = 0.73 (C + 0.00001)	Log[Hazard Ratio] -0.1744 -0.3318 -0.6688 1.02); I [#] = 75% -0.3318 -0.3111 1.865); I [#] = 0% -0.7246 -0.4879 -0.2739 -0.2865 -0.5747 -0.411; -0.4797 -0.4151 0.11); I [#] = 39% -0.7242 -0.7492 -0.7592	0.0796 0.0705 0.06 0.0705 0.0935 0.0935 0.0935 0.2242 0.2273 0.1256 0.1678 0.1678 0.1099 0.083 0.1256	Experimental Total 911 623 764 2298 623 248 871 0 53 54 649 1649 1649 242 374 164 780	Control Total 455 5764 1844 879 242 374 458 806 1606 1606 1606 1606 1606 1734	Weight 31.2% 33.1% 35.6% 100.0% 63.8% 5.6% 5.4% 5.4% 5.2% 12.2% 100.0% 30.7% 4.4% 25.2% 100.0%	Hazard Ratio U. Random. 95% Cf 0.84 (0.72, 0.68) 0.72 (0.63, 0.63) 0.93 (0.63, 1.05) 0.93 (0.63, 1.05) 0.93 (0.63, 1.05) 0.73 (0.61, 0.89) 0.72 (0.65, 0.82] 0.73 (0.61, 0.88) 0.72 (0.65, 0.81) 0.61 (0.52, 0.72) Nol estimatie 0.76 (0.44, 1.72) 0.68 (0.54, 0.72) 0.68 (0.54, 1.72) 0.68 (0.54, 0.72) 0.68 (0.54, 0.83) 0.68 (0.52, 0.65] 0.48 (0.38, 0.60) 0.61 (0.52, 0.72) 0.56 (0.44, 0.72) 0.56 (0.44, 0.72) 0.56 (0.44, 0.72)	0.01 0.1 1 00 100 Favours [experimental] Favours [control] Hazard Ratio I. IV. Randem. 95% Cl
(B) Study or Subgroup 1.2.1 first line treatment Boia 2018(NCT01015118) Burger 2011(GOG 0017) Subbial (BNK 00) Heterogravity: Tau ² = 0.01; Chi ² = 0.07, cf = 2 (P = C Test for overall effect: Z = 0.25 (P = 0.02) 1.2.2 first line treatment(High-risk of progression Burger 2011(GOG-0218) Course 10 (Chi = 0.07, cf = 2 (P = C Test for overall effect: Z = 5.76 (P < 0.0001) 1.2.3 Recurrent ovarian cancer Apolyania 2012(OCEANS) Codema 2012(OCEANS) Codema 2012(OCEANS) Codema 2012(NCT0027841) Karian 2012(NCT0027841) Karian 2012(NCT0027841) Karian 2012(NCT0027841) Subtoal (BYK 0) Heterogravity: Tau ² = 0.01; Chi ² = 1.3.9, df = 6 (P = C Test for overall effect: Z = 9.73 (P < 0.0001) 1.2.4 Platform = 2016(AURELIA) Sabutoal (BYK 0) Heterogravity: Tau ² = 0.01; Chi ² = 1.3.9, df = 6 (P = C Test for overall effect: Z = 9.73 (P < 0.0001) 1.2.4 Platform = sensitive recurrent ovarian cancer Apolgania 2015(NCT01284749) Subtoal (BYK 0) Heterogravity: Tau ² = 0.01; Chi ² = 1.3.9, df = 6 (P = T Test for overall effect: Z = 9.73 (P < 0.0001) Laderman 2016(NCT0028314) Subtoal (BYK 0) Heterogravity: Tau ² = 0.01; Chi ² = 2.91, df = 2 (P = C Test for overall effect: Z = 9.77 (P < 0.0001) Laderman 2016(NCT0028714) Subtoal (BYK 0) Heterogravity: Tau ² = 0.01; Chi ² = 2.91, df = 2 (P = C Test for overall effect: Z = 8.77 (P < 0.0001) Laderman 2016(NCT0028714) Subtoal (BYK 0) Heterogravity: Tau ² = 0.01; Chi ² = 2.91, df = 2 (P = C Test for overall effect: Z = 8.77 (P < 0.0001) Laderman 2016(NCT0028714) Subtoal (BYK 0) Heterogravity: Tau ² = 0.01; Chi ² = 2.91, df = 2 (P = C Test for overall effect: Z = 8.77 (P < 0.0001) Laderman 2016(NCT0028714) Subtoal (BYK 0) Heterogravity: Tau ² = 0.01; Chi ² = 2.91, df = 2 (P = C Test for overall effect: Z = 8.77 (P < 0.0001) Laderman 2016(NCT0028714) Subtoal (BYK 0) Heterogravity: Tau ² = 0.01; Chi ² = 2.91, df = 2 (P = C Test for overall effect: Z = 8.77 (P < 0.0001) Laderman 2016(NCT0028714) Laderman 2016(NCT0028714) Lade	log[Hazard Ratio] -0.1744 -0.2318 -0.081 -0.081 -0.3318 -0.3111 -0.3111 -0.3111 -0.3111 -0.3111 -0.3111 -0.3111 -0.3111 -0.3111 -0.3219 -0.4792 -0.5747 -0.7392 -0.5151 0.11]; P = 39% -0.7286 -0.4912 -0.5747 -0.5755 -0.5747 -0.5755 -0.5747 -0.5755 -0.5757 -0.5757 -0.5757 -0.5757 -0.5757 -0.5757 -0.5757 -0.5757 -0.5757 -0.5757 -0.5757 -0.5757 -0.5757 -0.5757 -0.5757 -0.5747 -0.5757 -0.5757 -0.5757 -0.5757 -0.5747 -0.5757 -0.5757 -0.5757 -0.5757 -0.5757 -0.5747 -0.5757 -0.5757 -0.5757 -0.5747 -0.5757 -0.5757 -0.5757 -0.5747 -0.5757 -0.5757 -0.5747 -0.5757 -0.5747 -0.5757 -0.5747 -0.5747 -0.5747 -0.5757 -0.574	0.0705 0.060 0.0705 0.0835 0.0835 0.02242 0 0.2242 0.1256 0.1678 0.1678	Experimental Total 911 623 764 2298 623 248 871 242 374 374 353 164 953 164 953 164 9 1649 242 374 471 757 164 9 242 374 164 9	Control Total 455 764 1844 625 254 879 242 374 0 55 55 118 458 36 1606 1606	Weight 31.2% 33.1% 63.8% 63.8% 100.0% 5.2% 5.2% 5.2% 10.0% 13.7% 14.5% 100.0% 30.7% 100.0%	Hazard Ratio IV. Random. 95% Cf 0.84 (0.72, 0.98) 0.72 (0.63, 0.82) 0.73 (0.63, 0.82) 0.73 (0.61, 0.82) 0.73 (0.61, 0.82) 0.73 (0.61, 0.82) 0.72 (0.63, 0.82) 0.73 (0.61, 0.83) 0.72 (0.63, 0.82) 0.73 (0.61, 0.83) 0.72 (0.63, 0.82) 0.75 (0.64, 0.72) Not estimatile 0.76 (0.48, 0.72) 0.68 (0.57, 0.72) 0.68 (0.52, 0.72) 0.58 (0.44, 0.72) 0.56 (0.48, 0.64)	0.01 0.1 1 00 100 Favours [experimental] Favours [control] Hazard Ratio IV. Random, 93% Cl
(B) Study of Subgroup 1.2.1 first line treatment Bois 2016(NCD1015118) Burger 2011(GCG-0218) Coz 2015 (CCD 7) Subtool (B%5) United Team (B%5) Coz 2015 (CCD 7) Subtool (B%5) 1.2.2 first line treatment(High-risk of progression Burger 2011(GCG-0218) Coz 2015 (CCD 7) 1.2.2 first line treatment(High-risk of progression Burger 2011(GCG-0218) Coz 2015 (CCD 7) Heitrogramity, Tau' = 0.0; Ch' = 0.0; d' = 1 (P = C Test for overal effect: Z = 2.76 (P = 0.0001) 1.2.2 first line treatment(High-risk of progression Burger 2011(GCG-0218) Core 2015 (CCD 7) Heitrogramity, Tau' = 0.0; Ch' = 0.0; d' = 1 (P = C Test for overal effect: Z = 5.76 (P = 0.0001) 1.2.3 Recurrent overain cancer Aghapinen 2015(GCG-0413) Corian 2012(RCT004788)7/MIG 386 at 10mg/kg Karian 2012(RCT004788)7/MIG 386 at 3mg/kg Karian 2015(RCT01844825) Heitrogeneity, Tau' = 0.37, C P = 0.31, d = 2 (P = C Test for overal effect: Z = 3.07 (P < 0.00073)741 Ledorman 2015(RCT01844825) Heitrogeneity, Tau' = 0.37, C P = 2.91, d' = 2 (P = C Test for overal effect: Z = 3.07 (P < 0.00073)741 Heitrogeneity, Tau' = 0.07 (C + 0.00073)74 Heitrogeneity, Tau' = 0.07 (C + 0.00073)74 Heitrogeneity, Tau' = 0.07 (C + 0.00073)74 Heitrogen	log[Hazard Ratio] -0.1744 -0.2316 -0.06316 -0.06316 -0.3316 -0.3111	0.0705 0.0935 0.0935 0.0935 0.0935 0.0935 0.2242 0.2273 0.1256 0.1678 0.1099 0.11678 0.1099 0.11678	Experimental Total 911 623 764 2298 623 248 871 242 374 0 53 374 0 53 374 0 53 374 164 9 164 9 164 9 780 780	Control Total 455 625 764 1844 879 242 242 242 242 374 0 55 55 155 1606 8182 82 82 82 84 1606 242 374 118 118 734	Weight 31.2% 33.1% 55.5% 5.1% 5.1% 5.1% 5.2% 5.1% 13.7% 10.0% 13.7% 10.0% 13.2% 10.0% 13.2% 10.0% 13.2% 5.1% 10.0% 13.2% 5.2% 5.1% 10.0% 13.2% 5.4% 13.2% 5.4% 13.7% 10.0% 13.2% 5.4% 10.0% 13.2% 5.4% 10.0% 13.2% 5.4% 10.0% 13.2% 5.4% 10.0% 13.2% 5.4% 10.0% 13.2% 5.4% 10.0% 10.	Hazard Ratio H. Random, 95% Cf 0.84 (0.72, 0.98) 0.72 (0.63, 0.82) 0.73 (0.63, 0.82) 0.73 (0.61, 0.82) 0.73 (0.61, 0.82) 0.72 (0.65, 0.81) 0.74 (0.39, 0.60) 0.61 (0.52, 0.72) Not estimatic 0.76 (0.49, 1.18) 0.76 (0.49, 1.18) 0.48 (0.39, 0.60) 0.44 (0.39, 0.60) 0.61 (0.52, 0.72) 0.65 (0.54, 0.72) 0.65 (0.54, 0.72) 0.65 (0.54, 0.72) 0.55 (0.44, 0.72) 0.55 (0.44, 0.72) 0.55 (0.44, 0.72) 0.55 (0.44, 0.72) 0.56 (0.44, 0.72) 0.5	100 D.1 1 10 100 Favours [experimental] Favours [control] Hazard Ratio IV. Random, 95% Cl.
(B) <u>Study of Subgroup</u> 1.2.1 first line treatment Bois 2016(NCT01015116) Burger 2011(GCG-0218) Coa 2015 (CON 7) Subtool (BS% C0) Heterogeneity: Tau' = 0.01; Ch ² = 8.07, df = 2 (P = C) Test for overal effect: Z = 2.35 (P = 0.02) 1.2.2 first line treatment(High-risk of progression Burger 2011(GCG-0218) Coa 2015 (con7 high risk Subtool (BS% C0) Heterogeneity: Tau' = 0.00; Ch ² = 0.03, df = 1 (P = C) Test for overal effect: Z = 3.76 (P = 0.00001) 1.2.3 Recurrent ovarian cancer Aphajanna 2012(OCENAS) Coloman 2015(GCG-0213) Golieb 2012(NCT00327444) Karin 2012(NCT00479817)ANG 386 at 10mg/kg Karin 2012(NCT00479817)ANG 386 at 10mg/kg Karin 2012(NCT00479817)ANG 386 at 10mg/kg Karin 2012(NCT00479817)ANG 386 at 10mg/kg Karin 2012(NCT016478817) Subtool (BS% C1) Heterogeneity: Tau' = 0.01; Ch ² = 13.19, df = 6 (P = Test for overal effect: Z = 3.67 (P = 0.00001) 1.2.4 Plathum-seistant recurrent ovarian cancer Aphajanna 2012(OCCENAS) Coloman 2015(COCENAS) Coloman 2015(COCENAS)	Log[Hazard Ratio] -0.1744 -0.2316 -0.0681 -0.081 -0.3318 -0.3111 1.86); ² = 0% -0.7246 -0.4879 0.2855 -0.5747 -0.4879 0.2855 -0.5747 -0.7392 -0.5747 -0.7392 -0.5747 -0.7392 -0.4974 -0.4974 -0.7262 -0.4974 -0.7262 -0.5747 -0.7262 -0.5757 -0.7262 -0.5757 -0.5	0.1795 0.0705 0.0835 0.0705 0.0935 0.0935 0.0935 0.2273 0.2273 0.2273 0.2273 0.1678 0.1678 0.1678	Experimental Total 911 623 764 2298 623 764 871 242 374 0 53 3164 461 377 179 86 1649 242 374 461 779 76 7780	Control Total 455 625 75 75 879 242 242 242 242 242 242 374 879 0 55 55 55 1606 1606 242 374 186 1806 242 374 187 9 8 1806 1806 1806 1807 1807 1807 1807 1807 1807 1807 1807	Weight 31.2% 33.1% 63.8% 36.6% 100.0% 63.8% 5.2% 5.1% 5.5% 5.2% 5.1% 13.7% 13.7% 13.8% 5.2% 5.1% 13.8% 13.2% 13.2% 13.2% 13.2% 13.2% 13.2% 13.2% 13.2% 13.5% 14.5% 13.5% 14.5% 13.5% 14.5% 13.5% 14.5% 15.5% 14.5%	Hazard Ratio (), Random, 95%, C(), 0, 84 (0, 72, 0, 98), 0, 72 (0, 63, 0, 83, 10, 0), 0, 83 (0, 71, 0, 97) 0, 72 (0, 63, 0, 82), 0, 73 (0, 61, 0, 88), 0, 72 (0, 63, 0, 82), 0, 73 (0, 61, 0, 88), 0, 72 (0, 63, 0, 82), 0, 74 (0, 39, 0, 60), 0, 61 (0, 52, 0, 72), Not estimate 0, 76 (0, 49, 1, 17), 0, 56 (0, 44, 0, 18), 0, 76 (0, 49, 1, 17), 0, 56 (0, 44, 0, 17), 0, 56 (0, 44, 1, 17), 0, 56 (0, 44, 0, 18), 0, 60 (0, 43, 0, 83), 0, 60 (0, 43, 0, 83), 0, 60 (0, 43, 0, 83), 0, 64 (0, 38, 0, 60), 0, 44 (0, 43, 0, 63), 0, 44 (0, 43, 0, 64), 0, 44 (0, 43, 0, 64),\\0, 44 (0, 43, 0, 64),\\0, 44 (0, 43, 0, 64),\\0, 44 (0, 43, 0, 64),\\0, 44 (0, 43, 0, 64),\\0, 44 (0, 43, 0, 64),\\0, 44 (0, 43	100 D.1 1 10 100 Favours [control] Favours [control] Hazard Ratio IV. Randem, 93% Cl
(B) <u>Study or Subgroup</u> 1.2.1 first line treatment Bois 2016(NCT015116) Burger 2011(GCG-0218) Coza 2015 (CCN 7) Subtool (BS% CI) Heterogeneity: Tau' = 0.01; Ch' = 8.07, df = 2 (P = C) Test for overal effect: Z = 2.35 (P = 0.02) 1.2.2 first line treatment(High-risk of progression Burger 2011(GCG-0218) Coza 2015 (CoX 7) high risk Subtool (BS% CI) Heterogeneity: Tau' = 0.00; Ch' = 0.03, df = 1 (P = C) Test for overal effect: Z = 5.76 (P = 0.0001) 1.2.3 Recurrent ovarian cancer Anhajama 2012(CCEANS) Coleman 2015(CCG-0213) Gottleb 2012(NCT00327817)ANG 386 at 10mg/kg Karian 2012(NCT00478817)ANG 386 at 10mg/kg Karian 2012(NCT00478917)ANG 386 at 10mg/kg Karian 2012(NCT00478917) Subtool (BS% CI) Heterogeneity: Tau' = 0.01; Ch' = 1.3.19, df = 6 (P = Test for overal effect: Z = 9.73 (P < 0.00001) 1.2.4 Platinum-sensitive recurrent ovarian cancer Aphajama 2015(CCEANS) Coleman 2015(CCEANS) Coleman 2015(NCT01542142) Subtool (BS% CI) Heterogeneity: Tau' = 0.01; Ch' = 2.91, df = 2 (P = C) Test for overal effect: Z = 8.07 (P < 0.00001) 1.2.5 Platinum-resistant recurrent ovarian cancer Pignata 2015(NCT0164281) Subtool (BS% CI) Heterogeneity: Tau' = 0.01; Ch' = 2.91, df = 2 (P = C) Test for overal effect: Z = 8.07 (P < 0.00001) 1.2.5 Platinum-resistant recurrent ovarian cancer Pignata 2015(NCT0164281) Subtool (BS% CI) Heterogeneity: Tau' = 0.01; Ch' = 2.91, df = 2 (P = C) Subtool (BS% CI) Heterogeneity: Tau' = 0.01; Ch' = 2.91, df = 2 (P = C) Subtool (BS% CI) Heterogeneity: Tau' = 0.01; Ch' = 1.81, df = 2 (P = C) Subtool (BS% CI) Heterogeneity: Tau' = 0	log[Hazard Ratio] -0.1744 -0.2316 -0.0629 -0.3316 -0.3316 -0.3316 -0.3316 -0.3318 -0.3111 1.86); IP = 0% -0.7246 -0.4879 -0.2895 -0.5787 -0.7382 -0.5747 -0.5747 -0.5787 -0.5	0.0705 0.0835 0.0705 0.0935 0.0935 0.0935 0.0935 0.0272 0.2242 0.2736 0.259 0.1678 0.1099 0.083 0.1256 0.1678	Experimental Total 911 623 764 2298 623 248 871 242 374 0 53 3164 9 53 3164 9 1649 242 374 179 9 6 6 1649 780 37 179 9 8 6 337 37 179 9 8 6 332	Control Total 455 625 725 254 879 242 242 242 242 242 242 374 05 55 55 155 1606 1606 1606 182 242 374 18 18 18 18 18 18 18 18 18 18 18 18 18	Weight 31.2% 33.1% 565 565 578 5.1% 5.2% 5.1% 100.0% 13.7% 14.6% 5.2% 5.1% 10.0% 12.2% 5.1% 10.0%	Hazard Ratio (), Random, 95%, C/ 0.84 (0.72, 0.98) 0.72 (0.63, 0.82) 0.93 (0.83, 1.05) 0.83 (0.71, 0.97) 0.72 (0.63, 0.82) 0.73 (0.61, 0.88) 0.72 (0.65, 0.81) 0.72 (0.65, 0.81) 0.64 (0.52, 0.72) Not estimate 0.76 (0.49, 1.16) 0.75 (0.46, 1.17) 0.75 (0.46, 1.17) 0.56 (0.43, 0.83) 0.56 (0.52, 0.72) 0.56 (0.54, 0.72) 0.56 (0.54, 0.72) 0.56 (0.48, 0.64) 0.42 (0.38, 0.60) 0.44 (0.38, 0.60) 0.44 (0.38, 0.60) 0.44 (0.38, 0.64) 0.42 (0.38, 0.64) 0.42 (0.38, 0.64) 0.43 (0.38, 0.64)	100 D.1 1 10 100 Faxours [experimental] Faxours [control] Hazard Ratio M. Randem, 95% Cl
(B) Study or Subgroup 1.2.1 first line treatment Bois 2019(NCT01015118); Burger 2011(OCG-0218) Oraz 2015 (ICON 7) Subtotal (BSK C) Hearographic, Tau' = 0.01; Ch' = 8.07, df = 2 (P = C) Test for overall effect Z = 2.55 (P = 0.02) 1.2.2 first line treatment(High-lisk of progression Burger 2011(OCG-0218) Caz 2015 (ICON 7) Subtotal (BSK C) Hearographic, Tau' = 0.00; Ch' = 0.03, df = 1 (P = C) Test for overall effect Z = 5.76 (P = 0.00001) 1.2.3 Recurrent ovarian cancer Aplagianna 2015(OCG-0213) Colleb 2012(NCT00478817) Nonk 2016 (NCT010478817) Subtotal (BSK C) Hearographic, Tau' = 0.01; Ch' = 1.319, df = 8 (P = Test for overall 2016(ACTELIA) Scholla 2016(NCT01047881) Subtotal (BSK C) Hearographic, Tau' = 0.01; Ch' = 3.19, df = 8 (P = Test for overall 2016(NCT01052144) Scholla 2016(NCT01052144) Scholla 2016(NCT01047881) Subtotal (BSK C) Hearographic, Tau' = 0.01; Ch' = 2.91, df = 2 (P = C) Test for overall 2016(NCT01052144) Scholla 2016(NCT01052144) Sc	log[Hazard Ratio] -0.1744 -0.3318 -0.080 -0.080 -0.3318 -0.3111 1.86); IP = 0% -0.7246 -0.4879 0 -0.2739 -0.2739 -0.2739 -0.2739 -0.5151 0.11); IP = 0%	0.0705 0.0835 0.0835 0.0835 0.0835 0.0827 0.2242 0.0827 0.2242 0.0827 0.2242 0.0827 0.2242 0.0827 0.2250 0.1578 0.1578	Experimental Total 911 623 764 2298 623 248 871 0 533 164 9 1649 242 374 461 377 374 1649 242 374 374 1649 780 780 302	Control Total 455 625 75 75 55 55 55 55 55 55 55 168 86 1606 1606 1606 1606 1606 1606 16	Weight 31.2% 33.1% 35.6% 100.0% 63.8% 36.2% 100.0% 13.7% 5.1% 5.2% 5.2% 5.2% 5.2% 10.0% 30.7% 4.1% 13.2% 5.2% 5.2% 5.2% 5.2% 5.2% 10.0% 10.0% 12.2% 5.2%	Hazard Ratio (V. Random. 95% Cf 0.84 (0.72, 0.88) 0.72 (0.63, 0.82) 0.93 (0.83, 1.05) 0.83 (0.71, 0.97] 0.72 (0.63, 0.82) 0.73 (0.61, 0.88) 0.72 (0.63, 0.82) 0.73 (0.61, 0.88) 0.72 (0.65, 0.81) 0.64 (0.52, 0.72) Not estimate 0.76 (0.46, 1.64) 0.76 (0.46, 1.64) 0.48 (0.38, 0.60) 0.66 (0.52, 0.72) 0.56 (0.48, 0.64) 0.56 (0.48, 0.64) 0.48 (0.38, 0.60) 0.66 (0.48, 0.64) 0.48 (0.38, 0.60) 0.65 (0.48, 0.64) 0.48 (0.38, 0.60) 0.65 (0.48, 0.64) 0.48 (0.38, 0.60) 0.65 (0.42, 0.60)	0.01 0.1 1 00 100 Faxours [experimental] Faxours [control] Hazard Ratio Hazard Ratio Hazard Ratio
(B) Study or Subgroup 1.2.1 first line tearment Bois 2019(NCT01015118); Burg 2011(SOG 60218) Burg 2015 (ICON 7) Subtotal (BSK C) Heterogramity: Taa' = 0.01: Chi' = 0.07, df = 2 (P = 0 Test for overall effect: Z = 2.35 (P = 0.02) 1.2.2 first line tearment(High-risk of progression Burge 2011(GOG-0218) Coz 2015 (BOG-0218) Subtotal (BSK C) Heterogramity: Taa' = 0.01: Chi' = 0.03, df = 1 (P = 0 Test for overall effect: Z = 5.76 (P < 0.00001) 1.2.3 Recurrent overain cancer Aphaginana 2012(NCT00478817)MK0 386 at 10mg/kg Karian 2012(NCT00478817)MK0 386 at 20mg/kg Ladermana 2016(NCT00427841) Subtotal (BSK C) Heterogramity: Taa''= 0.01: Chi' = 1.319, df = 8 (P = Test for overall effect: Z = 9.73 (P < 0.00001) 1.2.4 Platfum-sensitive recurrent ovarian cancer Aphaginana 2015(NCT016247841) Subtotal (BSK C) Heterogramity: Taa''= 0.01: Chi' = 1.319, df = 8 (P = Test for overall effect: Z = 9.73 (P < 0.00001) 1.2.4 Platfum-sensitive recurrent ovarian cancer Aphaginana 2016(NCT01624781) Subtotal (BSK C) Heterogramity: Taa''= 0.01: Chi' = 1.319, df = 2 (P = 0 Test for overall effect: Z = 9.73 (P < 0.00001) 1.2.4 Platfum-sensitive recurrent ovarian cancer Aphaginana 2016(NCT01624781) Subtotal (BSK C) Heterogramity: Taa''= 0.01: Chi' = 2.31, df = 2 (P = 0 Test for overall effect: Z = 9.77 (P < 0.00001) 1.2.5 Platinum-resistant recurrent ovarian cancer Pignals 2015(NCT01634825) Pigde-Lauring 2016(NCT01637181) Subtotal (BSK C) Heterogramity: Taa''= 0.01: Chi' = 1.80, df = 2 (P = 0 Test for overall effect: Z = 7.07 (P < 0.00001) 1.2.5 Platinum-resistant recurrent ovarian cancer Pignals 2015(NCT01634825) Pigde-Lauring 2016(NCT0163781) Subtotal (BSK C) Heterogramity: Taa''= 0.01: Chi' = 1.80, df = 2 (P = 0 Test for overall effect: Z = 7.07 (P < 0.00001) 1.2.5 Platinum-resistant recurrent ovarian cancer Pignals 2015(NCT0163781) Subtotal (BSK C) Heterogramity: Taa''= 0.00: Chi' = 1.80, df = 2 (P = 0 Test for overall effect: Z = 7.07 (P < 0.00001) 1.2.5 Platinum-resistant recurrent ov	log[Hazard Ratio] 0.1744 0.2318 0.02318 0.0318 0.3318 0.3318 0.3111 0.3318 0.3111 0.4729 0.4729 0.4729 0.4729 0.4729 0.4729 0.4729 0.5151 0.11½ P = 39% 0.4912 0.4912 0.4912 0.4912 0.4912 0.5151 0.11½ P = 31% 0.7382 0.5151 0.11½ P = 0%	0.0786 0.0705 0.08 0.0705 0.0935 0.0935 0.1133 0.0270 0.2273 0.1256 0.1678 0.1099 0.083 0.1256 0.083 0.1256	Experimental Total 911 623 764 2298 623 248 871 242 374 374 374 375 353 353 53 353 164 461 464 164 9 779 737 779 769 86 302	Control Total 455 5764 1844 879 242 374 879 242 374 458 860 1606 122 242 374 118 860 242 242 374 118 182 860 304	Weight 31.2% 32.1% 35.6% 100.0% 63.8% 36.2% 100.0% 13.7% 5.2% 5.2% 12.2% 12.2% 12.2% 12.2% 12.2% 12.2% 100.0% 12.0% 59.4% 28.8% 100.0%	Hazard Ratio (V. Random. 95% Cf 0.84 (0.72, 0.68) 0.72 (0.63, 0.63) 0.93 (0.63, 1.05) 0.93 (0.63, 1.05) 0.93 (0.63, 1.05) 0.72 (0.63, 0.62) 0.73 (0.61, 0.68) 0.72 (0.65, 0.81) 0.74 (0.52, 0.72) 0.61 (0.52, 0.72) 0.61 (0.52, 0.72) 0.62 (0.54, 1.72) 0.63 (0.54, 1.72) 0.64 (0.52, 0.72) 0.64 (0.52, 0.72) 0.64 (0.52, 0.72) 0.65 (0.52, 0.65] 0.44 (0.38, 0.60) 0.65 (0.52, 0.64] 0.42 (0.25, 0.68] 0.42 (0.25, 0.68] 0.42 (0.25, 0.68]	0.01 0.1 1 00 100 Faxours [experimental] Favours [control] Hazard Ratio I. IV. Randem. 95% Cl
(B) Study or Subgroup 1.2.1 first line treatment Boiz 2016(NCT01015118) Burger 2011(GCS-2018) Coz 2015 (CCM 7) Subtool (8%5 C) 1.2.2 first line treatment(High-risk of progression Burger 2011(GCS-2018) Coz 2015 (CCM 7) Subtool (8%5 C) Heterogeneity: Tau ² = 0.01; Chi ² = 0.07, df = 2 (P = C) Test for overall effect: Z = 2.35 (P = 0.02) 1.2.2 first line treatment(High-risk of progression Burger 2011(GCS-QC18) Subtool (9%5 C) Heterogeneity: Tau ² = 0.01; Chi ² = 0.03, df = 1 (P = C) Test for overall effect: Z = 5.76 (P < 0.0001) 1.2.3 Recurrent ovarian cancer Applagina 2012(OCEANS) Codema 2015(OCG C0213) Codelbe 2012(NCT00478817),MO 386 at 10mg/kg Karian 2012(NCT00478817),MO 386 at 30mg/kg Lederman 2016(NCT0042749) Pignale 2016(NCT01204749) Pignale 2016(NCT01204749) Pignale 2016(NCT01204749) Pignale 2016(NCT01204749) Pignale 2016(NCT01204749) Pignale 2016(NCT01204749) Heterogeneity: Tau ² = 0.37; C+ 2.00,df = 0 (P = C) Test for overall effect: Z = 9.73 (P < 0.0001) 1.2.4 Platinum-essistant recurrent ovarian cancer Applagna 2015(NCT01204749) Heterogeneity: Tau ² = 0.51; Chi ² = 2.31, df = 2 (P = C) Test for overall effect: Z = 8.07 (P < 0.0001) 1.2.4 Platinum-essistant recurrent ovarian cancer Applagna 2016(NCT01204749) Subtool (9%5 C) Heterogeneity: Tau ² = 0.07; C+L = 1.80, df = 2 (P = C) Test for overall effect: Z = 8.07 (P < 0.0001) 1.2.5 Platinum-essistant recurrent ovarian cancer Pignale 2016(NCT01204749) Subtool (9%5 C) Heterogeneity: Tau ² = 0.07; C+L = 1.80, df = 2 (P = C) Test for overall effect: Z = 7.17 (P < 0.0001) 1.2.5 Platinum-essistant recurrent ovariant cancer Pignale 2016(NCT0105491) Subtool (9%5 C) Heterogeneity: Tau ² = 0.07; C+L = 1.80, df = 2 (P = C) Test for overall effect: Z = 7.17 (P < 0.0002) 1.2.5 Platinum-essistant recurrent ovariant cancer Pignale 2016(NCT0105491) Subtool (9%5 C) Heterogeneity: Tau ² = 0.07; C+L = 1.80, df = 2 (P = C) Test for overall effect: Z = 7.17 (P < 0.0002) 1.2.5 Platinum essistant recurrent ovar	log[Hazard Ratio] -0.1744 -0.2316 -0.0691 -0.0691 -0.3316 -0.3111 -0	0.0786 0.0705 0.08 0.0705 0.0935 0.0935 0.0935 0.2242 0.2273 0.2242 0.2273 0.2242 0.2273 0.2259 0.1165 0.16578 0.0838 0.116578	Experimental Total 9111 623 764 2298 623 248 871 0 53 54 53 54 53 54 53 54 54 54 54 54 54 54 54 54 54 54 54 54	Control Total 455 625 764 1844 879 242 242 242 242 374 0 5 55 55 55 55 55 55 188 879 242 242 242 2374 188 86 304 304 468 304	Weight 31.2% 33.1% 40.0% 5.36.5% 100.0% 5.1% 5.1% 13.7% 19.5% 5.1% 13.3% 4.1% 13.3% 4.1% 13.3% 4.1% 13.3% 100.0% 13.7% 10.0% 13.7% 10.0% 5.1% 10.0% 5.1% 10.0% 5.1% 10.0% 5.1% 10.0% 5.1% 10.0% 5.1% 10.0% 5.1% 10.0% 5.1% 10.0% 5.1% 10.0% 5.1% 5.1% 10.0% 5.1% 5.1% 10.0% 5.1% 5.2% 5.1% 10.0% 5.1% 5.2% 5.1% 10.0% 5.1% 5.2% 5.5% 5.2% 5.5	Hazard Ratio (V. Random, 95% Cf. 0.84 (0.72, 0.98) 0.72 (0.63, 0.82) 0.73 (0.63, 0.82) 0.73 (0.61, 0.82) 0.73 (0.61, 0.82) 0.72 (0.63, 0.82) 0.73 (0.61, 0.89) 0.72 (0.65, 0.81) 0.48 (0.39, 0.60) 0.61 (0.52, 0.72) Not estimate 0.76 (0.49, 1.18) 0.76 (0.43, 0.60) 0.68 (0.33, 0.60) 0.68 (0.33, 0.60) 0.68 (0.34, 0.72) 0.56 (0.44, 0.72) 0.56 (0.44, 0.72) 0.56 (0.43, 0.63) 0.60 (0.43, 0.63)	100 D.1 1 10 100 Favours [experimental] Favours [control] Haard Ratio IV. Random, 95% Cl.
(B) Study or Subgroup 1.2.1 first line treatment Bois 2016(NC1015116) Burger 2011(GCG-0218) Coa 2015 (CC017) Subtoal (BS% C0) Heterogeneity: Tau' = 0.01; Ch ² = 8.07, df = 2 (P = C) Test for overal effect Z = 2.35 (P = 0.02) 1.2.2 first line treatment(High-risk of progression Burger 2011(GCG-0218) Coa 2015 (Con 7) Subtoal (BS% C0) Heterogeneity: Tau' = 0.00; Ch ² = 0.03, df = 1 (P = C) Test for overal effect Z = 5.76 (P = 0.00001) 1.2.3 Recurrent ovarian cancer Aphalman 2013(OCGAV8)) Codema 2012(OCGAV8) Paisto-Laursine 2016(AURELIA) Externation 2012(OCT01642817) Monk 2016 (NCT0184422) Paisto-Laursine 2016(AURELIA) Externation 2012(OCCT01642817) Subtoal (BS% C0) Heterogeneity: Tau' = 0.01; Ch ² = 1.3.19, df = 6 (P = Test for overal effect Z = 0.71 (P = 0.00001) 1.2.4 Platinum-sensitive recurrent ovarian cancer Aphalprina 2012(OCCEANS) Codema 2012(OCCT01642817) Subtoal (BS% C0) Heterogeneity: Tau' = 0.01; Ch ² = 1.3.19, df = 6 (P = Test for overal effect Z = 0.71 (P = 0.00001) 1.2.5 Platinum-sensitive recurrent ovarian cancer Aphalprina 2012(OCCEANS) Codema 2012(OCCEANS) Codema 2012(OCCEANS) Subtoal (BS% C0) Heterogeneity: Tau' = 0.01; Ch ² = 2.91, df = 2 (P = C) Test for overal effect Z = 0.71 (P = 0.00001) 1.2.5 Platinum-sensitive recurrent ovarian cancer Aphalprina 2012(OCCEANS) Codema 2012(OCCEANS) Codema 2012(OCCEANS) Subtoal (BS% C0) Heterogeneity: Tau' = 0.01; Ch ² = 1.80, df = 2 (P = C) Test for overal effect Z = 1.71 (P = 0.00001) 1.2.5 Platinum-sensitive recurrent ovarian cancer Aphalprina 2012(OCCEANS) Subtoal (BS% C0) Heterogeneity: Tau' = 0.01; Ch ² = 1.80, df = 2 (P = C) Test for overal effect Z = 7.71 (P = 0.00001) 1.2.5 Platinum-resistant recurrent Dubis A 2014(CT00826817) Hetorog 2015(VCT0164282) Plate-1.2016(VCT082818) Subtoal (BS% C0) Heterogeneity: Tau' = 0.00; Ch ² = 1.80, df = 2 (P = C) Test for overal effect Z = 7.71 (P = 0.00001)	Log[Hazard Ratio] -0.1744 -0.2316 -0.0681 -0.0816 -0.3316 -0.3111 -0.3111 -0.7246 -0.4879 0.2399 -0.2885 -0.5747 -0.7392 -0.5747 -0.7392 -0.5747 -0.7392 -0.5747 -0.7392 -0.4974 -0.7392 -0.4974 -0.7392 -0.4974 -0.7392 -0.4974 -0.7392 -0.4974 -0.7392 -0.5787 -0.7392 -0.5787 -0.7392 -0.5191 -0.7515 -0.5787 -0.7315 -0.5787 -0.7392 -0.5191 -0.7515 -0.5787 -0.5787 -0.7515 -0.5787 -0	0.0795 0.0705 0.08 0.0705 0.0935 0.0935 0.0935 0.0935 0.0935 0.2242 0.2273 0.2242 0.2273 0.2242 0.0765 0.0259 0.1657 0.1678 0.1099 0.0259 0.1165 0.1678	Experimental Total 911 623 764 2298 623 774 871 242 374 871 0 53 53 53 53 53 53 53 53 53 54 54 242 374 461 37 45 37 45 37 45 37 45 37 66 302 37 42 242 374 45 37 43 44 37 43 44 37 43 44 37 43 44 37 44 10 37 44 37 4 3 37 4 3 37 4 3 37 4 3 37 4 3 37 4 3 37 4 3 37 4 3 37 4 3 37 4 3 37 4 3 37 4 3 4 3	Control Total 456 625 254 879 242 242 242 242 242 242 374 0 55 55 55 55 1606 1802 242 374 18606 1802 242 374 18606 304 36 1823 304 304 304 304 304 304 304 304 304 30	Weight 31.2% 33.1% 40.0% 43.8% 5.5% 5.1% 5.5% 5.1% 13.7% 13.7% 13.7% 13.8% 5.2% 5.1% 13.8% 2.2% 19.7% 4.1% 13.8% 13.2% 13.2% 13.8% 5.2% 5.1% 13.6% 5.2% 5.1% 13.2% 13.2% 13.6% 5.2% 5.1% 13.6% 5.2% 5.1% 13.6% 5.2% 5.1% 13.6% 5.2% 5.1% 13.6% 5.2% 5.1% 13.6% 5.2%	Hazard Ratio (V. Random. 95% Cf 0.84 (0.72, 0.98) 0.72 (0.63, 0.82) 0.93 (0.83, 0.62) 0.73 (0.61, 0.87) 0.72 (0.63, 0.82) 0.73 (0.61, 0.88) 0.72 (0.65, 0.81) 0.72 (0.65, 0.81) 0.72 (0.65, 0.81) 0.72 (0.64, 0.91) 0.76 (0.49, 1.18) 0.76 (0.49, 1.18) 0.76 (0.49, 1.19) 0.76 (0.49, 1.19) 0.76 (0.49, 1.19) 0.76 (0.49, 1.19) 0.76 (0.49, 1.19) 0.48 (0.39, 0.60) 0.48 (0.39, 0.60) 0.66 (0.52, 0.72) 0.56 (0.43, 0.83) 0.56 (0.52, 0.72) 0.56 (0.43, 0.83) 0.56 (0.54, 0.72) 0.56 (0.44, 0.38) 0.60 (0.43, 0.83) 0.56 (0.44, 0.38) 0.50 (0.42, 0.68) 0.42 (0.25, 0.68) 0.44 (0.39, 0.60) 0.45 (0.41, 0.82) 0.78 (0.64, 0.91) 1.08 (0.72, 1.63) 0.58 (0.44, 1.102)	100 D.1 1 10 100 Favours [control] Favours [control]
(B) <u>Study or Subgroup</u> 1.2. first line treatment Bois 2016(NC-01015116) Burger 2011(GCG-0218) Coa 2015 (CON 7) Subtool (BS% C0) Heterogeneity: Tau' = 0.01; Ch ² = 8.07, df = 2 (P = C Test for overal effect: Z = 2.35 (P = 0.02) 1.2.2 first line treatment(High-risk of progression Burger 2011(GCG-0218) Coa 2015 (Con 7) high risk Subtool (BS% C0) Heterogeneity: Tau' = 0.00; Ch ² = 0.03, df = 1 (P = C Test for overal effect: Z = 5.76 (P = 0.00001) 1.2.3 Recurrent ovarian cancer Aphajama 2012(OCEANS) Coloman 2012(OCEANS) Coloman 2012(OCEANS) Coloman 2012(OCEANS) Coloman 2012(OCTO0479817)AMG 386 at 10mg/kg Karian 0012(NCT00479817)AMG 386 at 10mg/kg Karian 0012(NCT00479817) Subtool (BS% C0) Heterogeneity: Tau' = 0.01; Ch ² = 1.3.19; df = 6 (P = Test for overal effect: Z = 8.07 (P = 0.00001) 1.2.4 Platinum-sensitive recurrent ovarian cancer Aphajama 2013(COCEANS) Coleman 2015(CGC-0213) Lederman 2015(CGC-0213) Lederman 2015(CCT0184282) PlateL-Laursina 2016(ALRELIA) Subtool (BS% C0) Heterogeneity: Tau' = 0.01; Ch ² = 2.91; df = 2 (P = C Test for overal effect: Z = 8.07 (P = 0.00001) 1.2.5 Platinum-resistant recurrent ovarian cancer Pignala 2015 (NCT0184282) PlateL-Laursina 2016(ALRELIA) Subtool (BS% C0) Heterogeneity: Tau' = 0.01; Ch ² = 1.80; df = 2 (P = C Test for overal effect: Z = 7.71 (P = 0.00001) 1.2.6 Pure maintenance treatment Dubick A 2014(RCT00862887) Hercog 2013(NCT0074778) Subtool (BS% C0) Heterogeneity: Tau' = 0.02; Ch ² = 3.16; df = 2 (P = C Test for overal effect: Z = 7.71 (P = 0.00001) 1.2.6 Pure maintenance treatment Dubick A 2014(RCT00862887) Hercog 2013(NCT07674782) Subtool (BS% C0) Hercog 2013(NCT07	Log[Hazard Ratio] -0.1744 -0.2316 -0.020 -0.75% -0.3316 -0.3111 1.86); I° = 0% -0.7246 -0.4879 00.7246 -0.4879 00.7279 -0.5747 -0.7392 -0.5747 -0.7392 -0.5747 -0.7392 -0.4912 -0.4912 -0.4912 -0.4912 -0.4912 -0.5787 -0.7262 -0.4912 -0.5787 -0.7392 -0.5151 1.41); I° = 0% -0.2703 0.4399 -0.2703 0.4399 -0.2703 0.4399 -0.2703 -0.4399 -0.2703 -0.4399 -0.2703 -0.4399 -0.2703 -0.4399 -0.2703 -0.4399 -0.2703 -0.4399 -0.2703 -0.4399 -0.2703 -0.4399 -0.2703 -0.4399 -0.2703 -0.4399 -0.2703 -0.4399 -0.2703 -0.5717 -0.578	0.0795 0.0705 0.0835 0.0835 0.0827 0.2242 0.2273 0.2242 0.2735 0.1678 0.1678 0.1256 0.1678 0.1678 0.259 0.1165 0.1678	Experimental Total 911 623 764 2298 623 764 871 242 374 374 374 461 377 179 86 1649 242 374 472 374 374 374 374 374 374 374 374 374 374	Control Total 455 625 754 879 242 242 242 242 242 242 242 242 242 374 879 0 55 55 1606 1606 186 86 186 86 186 86 186 87 9 304 468 304 812 812 812 812 812 812 812 812 812 812	Weight 31.2% 33.1% 56.5% 100.0% 5.365% 5.1% 5.5% 5.1% 13.7% 5.1% 5.2% 5.1% 13.3% 5.2% 5.1% 13.3% 5.2% 5.1% 13.2% 5.2% 5.1% 13.3% 5.2% 5.1% 10.0% 5.3% 5.2% 5.3% 5.2% 5.3% 5.2% 5.3% 5.2% 5.3% 5.2% 5.3% 5.2% 5.3% 5.2% 5.3% 5.2% 5.3% 5.2% 5.3% 5.2% 5.3% 5.2% 5.3% 5.2% 5.3% 5.2	Hazard Ratio (), Random, 95%, C(), Random, 95%, C(), 20, 40, 40, 40, 40, 40, 40, 40, 40, 40, 4	100 D.1 1 10 100 Favours [control] Favours [control]

0.01 0.1 1 10 100 Favours [experimental] Favours [control]

FIGURE 3. Forest plots: A, OS and B, PFS.



FIGURE 4. Forest plots: A, OS and B, PFS.

treatment option for recurrent ovarian cancer. Among them, bevacizumab, a kind of antiangiogenics by binding VEGF, has demonstrated a significant clinical benefit from several trials, and on the basis of these trials, bevacizumab was approved for first-line and second-line treatment of patients with both platinum-sensitive and platinum-resistant ovarian cancer.²⁶ However, its activity in patients whose disease relapses after first-line bevacizumab-containing therapy is still unknown. Hence, further studies addressing this issue need to be performed.

Maintenance therapy has been one proposed strategy to improve outcomes, and incorporation of angiogenesis inhibitors had also been of interest. Recently, a number of clinical trials took combined strategies, using angiogenesis inhibitors in the maintenance setting. In the present study, we mainly analyzed the maintenance antiangiogenics monotherapy in the trials, which recruited patients who responded to previous chemotherapy (ie, a Partial Response or Complete Response according to the RECIST criteria in patients with measurable disease). In the trial,²⁵ BIBF 1120 was not given to treat recurrent disease but to prolong the progression-free interval. It was evaluated after the completion of chemotherapy for relapsed ovarian cancer. The other 2 trials^{28,29} were designed to compare pazopanib or sorafenib to placebo as maintenance treatment after first-line therapy with systemic chemotherapy, and pazopanib showed a significant better PFS in the maintenance setting. However, pooled analysis of the 3 studies suggested no significant improvement in either PFS or OS. The lack of statistical significance may be because of lack of statistical power. In addition, more patients in the experience arm required dose modifications and discontinued treatment because of severe AEs, such as severe liver-related toxicity, severe gastrointestinal events, resulting in reduced dose of the planned dose. As a group, both short-term and longer-term adverse effects, the negative impact on quality of life associated with frequent visits to a physician or clinic and the cost may resulting in no significantly clinical benefit. Hence, further study should be performed to select patients who can really benefit from longterm maintenance treatment, particularly those who are at high risk of progression.

Adverse events were more common in the angiogenesis inhibitors-containing arm compared with the control arm, several significantly so (severe gastrointestinal events, severe hypertension, severe proteinuria, arterial thromboembolism, and complication of wound healing). It is necessary to monitor and manage these adverse events during the antiangiogenics therapy to minimize the risks. If severe adverse events such as gastrointestinal events can be controlled, antiangiogenics can be used safely.

This updated meta-analysis included 15 RCTs with 8721 patients, whereas the previous publication contained 12 RCTs with 7775 patients. One additional trial, NCT00327444,¹⁵ to our knowledge, was the first phase 2 study to show the effectiveness of VEGF blockade (aflibercept) in the reduction of malignant ascites for advanced chemoresistant ovarian cancer and recurrent symptomatic malignant ascites. The other 2 additional trials had final results published in abstract form from conference proceedings. Moreover, the most recent meta-analysis divided 12 trials into 3 groups: the bevacizumb group, the VEGFRIs group, the trebananib group. Improvement on PFS was seen in all groups and only the trebananib group demonstrated a significant prolongation on OS. However, to assess the role of clinical setting to use angiogenesis inhibitors in the treatment benefit, we divided 15 trials into 3 groups: first-line setting, the recurrent setting, and pure maintenance setting. Our results indicated that combination treatment with angiogenesis inhibitors and chemotherapy improved PFS and OS in the recurrent setting and high-risk progression subgroup, with no statistically significant improvement in OS for newly diagnosed ovarian cancer. We detected no significant improvement for either PFS or OS in pure maintenance setting.

A limitation of this analysis is clinical heterogeneity across the studies, including the different chemotherapy regimens, the tumor stages, and the length of follow-up. Secondly, there are 2 trials, the data of which have thus far been published only as conference abstracts, and they must be judged as being at high risk of bias until further details are known. Thirdly, although most of the included studies were published in highimpact journals, there were study features that carry potential risk of bias such as pharmaceutical industry funding and openlabel design. Fourthly, there are differences in angiogenesis inhibitors (which include VEGF blockade, VEGF-R tyrosine kinase inhibitors, angiopoietin inhibitor) that might dictate an optimal choice for combination with chemotherapy or other biological agents. Finally, issues such as the optimize duration and timing of treatment, the potential tumor or host biologic factors to identify, which patients will benefit most (and perhaps more importantly, those who are not likely to respond), have not been established.

CONCLUSIONS

Together, although there are significant differences of increased risks of adverse events with antiangiogenics therapy, findings from our meta-analysis are relatively promising. Our findings clearly lend support to the use of angiogenesis inhibitors in combination with chemotherapy in the clinical management of patients with newly diagnosed (especially for high-risk patients) or recurrent ovarian cancer. However, no statistically significant clinical benefit was identified in the pure maintenance settings.

REFERENCES

- 1. Holmes D. Ovarian cancer: beyond resistance. *Nature*. 2015;527:S217. doi:10.1038/527S217a.
- Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2017;18:75–87.
- Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med.* 2011;365:2473–2483.
- 4. Jayson GC, Kohn EC, Kitchener HC, et al. Ovarian cancer. *Lancet.* 2014;384:1376–1388.
- Gonzalez-Martin A, Bover I, Del Campo JM, et al. SEOM guideline in ovarian cancer 2014. *Clin Transl Oncol.* 2014;16:1067–1071.
- Katsumata N, Yasuda M, Isonishi S, et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. *Lancet Oncol.* 2013;14:1020–1026.
- 7. Pujade-Lauraine E. How to approach patients in relapse. *Ann Oncol.* 2012;23(suppl 10):x128–x131.
- 8. Kaimal R, Aljumaily R, Tressel SL, et al. Selective blockade of matrix metalloprotease-14 with a monoclonal antibody abrogates invasion, angiogenesis, and tumor growth in ovarian cancer. *Cancer Res.* 2013;73:2457–2467.
- 9. Eldridge L, Moldobaeva A, Zhong Q, et al. Bronchial artery angiogenesis drives lung tumor growth. *Cancer Res.* 2016;76:5962–5969.
- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646–674.
- Frumovitz M, Sood AK. Vascular endothelial growth factor (VEGF) pathway as a therapeutic target in gynecologic malignancies. *Gynecol Oncol.* 2007;104:768–778.
- Hall M, Gourley C, McNeish I, et al. Targeted anti-vascular therapies for ovarian cancer: current evidence. *Br J Cancer*. 2013;108:250–258.
- Eskander RN, Tewari KS. Incorporation of anti-angiogenesis therapy in the management of advanced ovarian carcinoma-mechanistics, review of phase III randomized clinical trials, and regulatory implications. *Gynecol Oncol.* 2014;132:496–505.
- Li X, Zhu S, Hong C, et al. Angiogenesis inhibitors for patients with ovarian cancer: a meta-analysis of 12 randomized controlled trials. *Curr Med Res Opin.* 2016;32:555–562.
- Gotlieb WH, Amant F, Advani S, et al. Intravenous aflibercept for treatment of recurrent symptomatic malignant ascites in patients with advanced ovarian cancer: a phase 2, randomised, double-blind, placebo-controlled study. *Lancet Oncol.* 2012;13:154–162.

- 16. Coleman RL, Brady MF, Herzog TJ, et al. A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinumsensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 0213). *Gynecol Oncol.* 2015;137:3–4.
- Sehouli J, Hilpert F, Mahner S, et al. Topotecan (T) ± sorafenib (S) in platinumresistant ovarian cancer (PROC): a doubleblind placebocontrolled randomized NOGGO-AGO intergroup Trial-TRIAS. J Clin Oncol. 2016;34.
- Karlan BY, Oza AM, Richardson GE, et al. Randomized, double-blind, placebo-controlled phase II study of AMG 386 combined with weekly paclitaxel in patients with recurrent ovarian cancer. *J Clin Oncol.* 2012;30:362–371.
- 19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21:1539–1558.
- 20. Eng C, Kramer CK, Zinman B, et al. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet*. 2014;384:2228–2234.
- 21. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol.* 2012;30:2039–2045.
- 22. Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol.* 2015;16:928–936.
- 23. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol.* 2014;32:1302–1308.
- 24. du Bois A, Kristensen G, Ray-Coquard I, et al. Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol.* 2016;17:78–89.
- 25. Ledermann JA, Hackshaw A, Kaye S, et al. Randomized phase II placebo-controlled trial of maintenance therapy using the oral triple angiokinase inhibitor BIBF 1120 after chemotherapy for relapsed ovarian cancer. *J Clin Oncol.* 2011;29:3798–3804.
- 26. Monk BJ, Poveda A, Vergote I, et al. Final results of a phase 3 study of trebananib plus weekly paclitaxel in recurrent ovarian cancer (TRINOVA-1): long-term survival, impact of ascites, and progression-free survival-2. *Gynecol Oncol.* 2016;143:27–34.
- Pignata S, Lorusso D, Scambia G, et al. Pazopanib plus weekly paclitaxel versus weekly paclitaxel alone for platinum-resistant or platinum-refractory advanced ovarian cancer (MITO 11): a randomised, open-label, phase 2 trial. *Lancet Oncol.* 2015;16:561–568.
- du Bois A, Floquet A, Kim JW, et al. Incorporation of pazopanib in maintenance therapy of ovarian cancer. *J Clin Oncol.* 2014;32:3374–3382.
- 29. Herzog TJ, Scambia G, Kim BG, et al. A randomized phase II trial of maintenance therapy with Sorafenib in front-line ovarian carcinoma. *Gynecol Oncol.* 2013;130:25–30.
- Ledermann JA, Embleton AC, Raja F, et al. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;387:1066–1074.