# Efficacy and toxicity of bevacizumab in recurrent ovarian disease: an update meta-analysis on phase III trials

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## ABSTRACT

Background: To analyze the efficacy and toxicity of bevacizumab on survival outcomes in recurrent ovarian cancer.

Results: Bevacizumab was associated with significant improvement of PFS and OS compared with standard treatment with HRs of 0.53 (95% CI 0.44 – 0.63; p < 0.00001) and 0.87 (95% CI, 0.77 to 0.99; p = 0.03), respectively.

Bevacizumab increased the incidence of G3/G4 hypertension (RR 19.01, 95% CI 7.77 – 46.55; p < 0.00001), proteinuria (RR 17.31, 95% CI 5.42 – 55.25; p < 0.00001), arterial thromboembolic events (ATE) (RR 4.99, 95% CI 1.29 – 19.27; p = 0.02) and bleeding (RR 3.14, 95% CI 1.35 – 7.32; p = 0.008).

Materials and Methods: Three randomized phase III trials representing 1502 patients were identified.

Pooled hazard ratio (HR), odd ratio (OR), risk ratio (RR) with 95% confidence interval (CI) were calculated using fixed or random effects model.

Conclusions: Adding bevacizumab to standard chemotherapy improved ORR, PFS and OS, and it had a higher, but manageable, incidence of toxicities graded 3 to 4.

# **INTRODUCTION**

The vast majority of patients with primary epithelial ovarian cancer (OC) will experience a recurrence of their disease despite aggressive primary cytoreduction surgery and adjuvant cytotoxic chemotherapy.

Randomized phase III trials of bevacizumab in postoperative patients with primary OC have shown an improvement in progression free survival (PFS) without an appreciable significantly longer overall survival (OS) [1–2]. This benefit of bevacizumab incorporation into standard chemotherapy was also confirmed in recurrent disease after adjuvant platinum-based chemotherapy [3–4]. But neither of the two largest trials of bevacizumab in addition to standard chemotherapy in recurrent disease showed evidence of OS improvement over chemotherapy alone. Recently randomized GOG 213 trial has been presented and results have demonstrated improved PFS rates, as well as positive trend in OS, with HR 0.829 (95% CI 0.683 to 1.005, p = 0.056) [5]. However the survival benefit must be weighed in light of the acute toxicity. Thus we performed an update meta-analysis to include all randomized bevacizumab trials to test whether bevacizumab regimen in recurrent OC could be superior to standard chemotherapy, in term of efficacy and toxicity.

## RESULTS

#### **Description of patients**

The selection of trials is depicted in the flow chart (Figure 1). Briefly, 158 articles were identified, of which 132 were excluded because they did not fulfill inclusion criteria. Twenty-six clinical trials were potentially eligible but 23 were excluded because they were not randomized phase III clinical trials. In total, 3 randomized phase III trials that evaluated bevacizumab plus chemotherapy versus chemotherapy alone for the treatment of recurrent OC were selected [3–5]. In the OCEANS trial no prior chemotherapy in the recurrent setting was allowed, whereas in the AURELIA trial and in the GOG 213 trial a total of 26 patients (7%) and 67 patients (10%), received prior antiangiogenic therapy, respectively.

## Overall survival and progression free survival

The OS analysis was based on 3 trials, 1502 patients. The HR for OS was 0.87 (95% CI, 0.77 to 0.99; p = 0.03). There was no evidence of significant statistical heterogeneity with an  $I^2$  value of 0% ( $\chi^2$  test for heterogeneity, p = 0.61). If we considered the only platinum-sensitive population, the HR became 0.88 (95% CI, 0.76 – 1.02; p = 0.09). The forest plot of OS is shown on Figure 2.

The benefit of bevacizumab on PFS was significant (HR 0.53, 95% CI 0.44 – 0.63; p < 0.00001;  $\chi^2$  test for heterogeneity, p = 0.11;  $I^2 = 55\%$ ; Figure 3).

## **Objective response rate**

Bevacizumab has a significantly better ORR, with OR of 2.74 (95% CI 2.17 – 3.47; p < 0.00001;  $\chi^2$  test for heterogeneity, p = 0.90;  $I^2 = 0$ %). Details are shown in Figure 4.

## Toxicity

Among the 8 analyzed toxicities, only grade 3 to 4 hypertension (RR 19.01, 95% CI 7.77 – 46.55; p < 0.00001), proteinuria (RR 17.31, 95% CI 5.42 – 55.25; p < 0.00001), ATE (RR 4.99, 95% CI 1.29 – 19.27; p = 0.02) and bleeding (RR 3.14, 95% CI 1.35 – 7.32; p = 0.008) were significantly different between the two groups, with heterogeneity among trials. Data on the ATE were not available for OCEANS trial [3], thus ATE toxicity was calculated without those patients.

Details of RR of toxicities associated with bevacizumab plus chemotherapy versus chemotherapy alone are shown in Figure 5.

## DISCUSSION

This meta-analysis provides an high level of evidence regarding the beneficial effect of bevacizumab in recurrent OC. The addiction of bevacizumab to standard chemotherapy confers a survival benefit, both progressionfree and overall, which is consistent also in platinumsensitive patients.

Actually, the VEGF-neutralizing monoclonal antibody bevacizumab has shown activity in OC treatment, on both first-line and recurrent setting and it has been the first anti-angiogenesis agent to be approved for treatment of OC in the front-line setting [1–2]. In the recurrent setting, two large randomized clinical trials have



Figure 1: Flow-chart of meta-analysis.

demonstrated the benefit of the addition of bevacizumab to a second-line regimen in both platinum sensitive [3] and platinum resistant [4] settings. No OS benefit was found, in both trials. More recently the GOG 213 trial [5], found that paclitaxel, carboplatin, and bevacizumab extended OS in patients with platinum-sensitive recurrent OC, but narrowly missed that statistical upper limit of significance. The combination was also associated with a significant improvement in PFS as well as ORR.

This meta-analysis consists of OC patients with recurrent disease included in randomized trials of bevacizumab combined with chemotherapy. In the light of the most recent evidences and with the update of each trial, it adds significant evidences compared with previous published meta-analysis [6–7].

Our analysis showed that the combination of bevacizumab with standard treatment of recurrent OC is beneficial in prolonging PFS (HR 0.53, 95% CI 0.44 - 0.63) and assuring an increased response rate (OR 2.74, 95% CI 2.17 - 3.47). Unfortunately, we did not analyze data concerning QoL as they were lacking or not homogeneous. Active treatment is generally undertaken with the goals of providing improved quantity and/or quality of patient survival. It has been demonstrated a strong association between PFS, cancerrelated symptoms, and QoL among patients with cancer [8]. Nonetheless, it should be underlined that in both the AURELIA trials and in the GOG 213 trial a quality-of-life assessment showed no deterioration of life quality in patients randomized to bevacizumab. Notably,



#### Figure 2: Forest plot for overall survival.

			Hazard Ratio	Hazaro	l Ratio	
Study or Subgroup	log[Hazard Ratio] SE	Weight	IV, Random, 95% CI	IV, Rando	m, 95% CI	
Aghajanian 2012 (OCEANS)	-0.734 0.1059	32.0%	0.48 [0.39, 0.59]	+		
Coleman 2015 (GOG 213)	-0.4943 0.0814	39.6%	0.61 [0.52, 0.72]	<b>•</b>		
Pujade-Lauraine 2014 (AURELIA)	-0.734 0.1192	28.4%	0.48 [0.38, 0.61]	+		
Total (95% CI)		100.0%	0.53 [0.44, 0.63]	•		
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = Test for overall effect: Z = 7.33 (P	= 4.46, df = 2 (P = 0.11); l <sup>2</sup> = < 0.00001)	: 55%		0.01 0.1 Favor CT with Bevacizumab	1 10 Favor CT alone	100

#### Figure 3: Forest plot for progression free survival.

	CT alone		CT with Bevacizumab			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Aghajanian 2012 (OCEANS)	190	242	139	242	34.6%	2.71 [1.82, 4.03]	
Coleman 2015 (GOG 213)	260	330	191	327	47.1%	2.64 [1.88, 3.73]	<del>_</del>
Pujade-Lauraine 2014 (AURELIA)	55	179	23	182	18.3%	3.07 [1.79, 5.26]	
Total (95% CI)		751		751	100.0%	2.74 [2.17, 3.47]	•
Total events	505		353				
Heterogeneity. $Chi^2 = 0.21$ , df = 2	(P = 0.9)	0); l <sup>2</sup> =	0%				
Test for overall effect: $Z = 8.44$ (P	< 0.0000	01)					Favor CT alone Favor CT with Bevacizumab

#### Figure 4: Forest plot for objective response rate.

Sindy or Subgroup Events Total Verifie Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% C		CT alo	ne CT	with Bevaci	zumab		Risk Ratio	Risk Ratio
5.1.3 Nettopenia 5.1.3 Netto	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
$ \begin{array}{c} \text{Applaphan 2012 (OCLNS)} & 1 \\ \text{Applaphan 2012 (OCLNS)} & 1 \\ \text{State cents} & 30 \\ \text{Field events} & 30$	5.1.1 Neutropenia		242					
$ \begin{array}{c} \text{Lotentar 100 } \text{Lot 1201 } Lot $	Aghajanian 2012 (OCEANS)	2	242	0	242	0.2%	5.00 [0.24, 103.61]	
Subscient (95x C) $(-1)^{-1}$ (2 (2 (2 (2 (2 (2 (2 (2 (2 (2 (2 (2 (2	Pulade-Lauraine 2014 (AURELIA)	29	179	31	182	9.4%	0.95 [0.60, 1.51]	
Table events $307 = 226$ Test for overall effect: $2 = 1.53 \ (r = 0.6)$ Test for overall effect: $2 = 1.53 \ (r = 0.6)$ Adaptation 2012 (COCLANS) $0$ $242$ $0$ Action 2013 <b>5.13</b> $272$ $0.56$ $1.05 \ (r, 5.86)$ <b>7.12</b> $0.256$ $7.12 \ (0.37, 7.36)$ Heterogenety: $Ch^2 = 0.46 \ (r = 0.46)$ <b>7.13</b> $731$ $222$ $0.56$ $1.05 \ (r, 7.36)$ Heterogenety: $Ch^2 = 0.46 \ (r = 0.46)$ <b>7.14</b> $242$ $0.256$ $7.12 \ (0.37, 7.36)$ Heterogenety: $Ch^2 = 0.51 \ (r = 0.46)$ <b>7.15</b> $731$ $1.256$ $1.050 \ (r, 7.36)$ <b>7.15</b> $1.256$ $1.050 \ (r, 7.36)$ <b>7.16</b> $1.050 \ (r, 7.36)$ Heterogenety: $Ch^2 = 0.460 \ (r = 0.10)$ <b>7.16</b> $1.050 \ (r, 7.36)$ <b>7.17</b> $1.256 \ (r, 7.36)$ <b>7.18</b> $1.256 \ (r, 7.36)$ <b>7.19</b> $1.256 \ (r, 7.36)$ <b>7.10</b> $1.256 \ (r, 7.36)$ <b>7.10</b> $1.256 \ (r, 7.36)$ <b>7.10</b> $1.256 \ (r, 7.36)$ <b>7.11</b> $1.256 \ (r, 7.36)$	Subtotal (95% CI)		751	51	751	88.3%	1.07 [0.98, 1.16]	•
$\begin{aligned} \text{Heterogenety:} (Lh^2 = 1.26, d = 2.9 = 0.53) (t^2 = 0.65) \\ \text{S12 Cattorinestinal} \\ \text{Oderman 2015 (GCC 213)} & 0.242 & 0.242 & 0.25 & 7.12 & 0.13 & 6.23 \\ \text{Oderman 2015 (GCC 213)} & 0.242 & 0.25 & 7.12 & 0.13 & 6.23 \\ \text{Subbal (95N C)} & 2 & 7.12 & 0.13 & 6.23 & 7.21 & 0.13 & 6.23 \\ \text{Subbal (95N C)} & 2 & 7.12 & 0.13 & 6.23 & 7.21 & 0.13 & 6.23 & 7.21 & 0.13 & 6.23 \\ \text{Cattorinestinal} & 2 & 0.34 & 1.00 & (5.97 & 309 & 76) \\ \text{Aplanan 2015 (GCC 1M)} & 0.1 & d = 1.9 & 0.45 & t^2 = 0.05 \\ \text{Aplanan 2015 (GCC 1M)} & 0.1 & d = 1.9 & 0.45 & t^2 = 0.05 \\ \text{Aplanan 2015 (GCC 1M)} & 0.21 & t^2 & 2.25 \\ \text{Aplanan 2015 (GCC 1M)} & 1.2 & 0.27 & t^2 = 2.85 \\ \text{Tat for overall effect 2 = 1.60 & 0^2 = 0.27 & t^2 = 2.85 \\ \text{Tat for overall effect 2 = 0.45 & t^2 = 0.200011 \\ \text{S1.4 Proteinmus} \\ \text{Aplanan 2015 (GCC 1M)} & 1.2 & 1.24 & 2.242 & 0.66 & 10.50 & 1.249 & 4.239 \\ \text{Aplanan 2015 (GCC 1M)} & 1.2 & 1.24 & 2.2 & 2.242 & 0.66 & 10.50 & 1.249 & 4.239 \\ \text{Aplanan 2015 (GCC 1M)} & 1.2 & 1.24 & 2.2 & 2.242 & 0.66 & 10.50 & 1.249 & 4.239 \\ \text{Aplanan 2015 (GCC 1M)} & 1.2 & 1.24 & 2.2 & 2.242 & 0.66 & 1.0.50 & 1.249 & 4.239 \\ \text{Aplanan 2015 (GCC 1M)} & 1.2 & 1.24 & 2.2 & 2.242 & 0.66 & 1.0.50 & 1.249 & 4.239 \\ \text{Aplanan 2015 (GCC 1M)} & 1.24 & 2.2 & 2.242 & 0.66 & 1.0.50 & 1.249 & 4.239 \\ \text{Aplanan 2015 (GCC 1M)} & 1.24 & 2.27 & 0.268 & 1.46 & 1.1.631 & 1.47 \\ \text{Aplanan 2015 (GCC 1M)} & 1.24 & 2.2 & 2.24 & 0.66 & 1.0.50 & 1.249 & 1.26 & 1.0.61 \\ \text{Aplanan 2015 (GCC 1M)} & 1.24 & 0.229 & 1.28 & 1.27 & 0.68 & 1.3.96 & 1.8.1 & 1.26 & 1.0.47 \\ \text{Aplanan 2015 (GCC 1M)} & 1.24 & 0.229 & 1.28 & 1.27 & 0.28 & 1.26 & 0.1.6 & 1.0.47 \\ \text{Aplanan 2015 (GCC 1M)} & 1.24 & 0.228 & 1.22 & 0.28 & 1.3.9 & 0.38 & 1.0.8 & 1.22 & 0.28 \\ \text{Aplanan 2015 (GCC 1M)} & 1.24 & 0.228 & 1.22 & 0.28 & 1.3.9 & 0.38 & 1.0.8 & 1.22 & 0.28 \\ \text{Aplanan 2015 (GCC 1M)} & 1.24 & 0.228 & 1.22 & 0.28 & 1.3.9 & 0.38 & 0.37 & 1.22 & 0.28 & 1.3.9 & 0.38 & 0.37 & 1.22 & 0.28 & 1.3.9 & 0.38 & 0.3.7 & 1.22 & 0.28 & 1.3.9 & 0.38 & 0.3.7 & 1.22 & 0.28 & 1.3.9 & 0.38 $	Total events	307		286				
Tes for overall effect: $2 - 1.33 (p = 0.13)$ 21.2 Cattroineresimal Anjanan 2012 (OCLANS) 0 2 422 0 242 005 1.08 [0.50, 7.86] Pajde-Lauraine 2014 (AURLIA) 3 173 0 3122 0.255 7.12 [0.37, 136, 73] Total events 9 5 Total events 9 5 1.31 Stypertension Anjanan 2012 (OCLANS) 43 242 1 2 242 0.355 43.00 [5.97, 139, 76] Coleman 2015 (OCC 2113 1 3 130 2 2 127 0.056 1.031, 12, 75, 70, 73, 86] Pajde-Lauraine 2014 (AURLIA) 13 173 2 182 0.056 6.561 1.51, 28, 87] Pajde-Lauraine 2014 (AURLIA) 13 173 2 182 0.056 6.561 1.51, 28, 87] Heterogenety: Chi = 2.65, df = 2.0 = 0.27p; F = 2.85 Total events 95 5 2 1.056 1.057, 146, 57] Total events 95 7 751 0.751 0.257, 136, 79] Subtaid (95K CO 7) 751 751 0.258, 167 (0.62, 4.51] Coleman 2015 (COCLANS) 10 242 C 0.257; F 1 0.058 1.67 (0.62, 4.51) 1.52, 83, 71] Total events 1 7 Total events 2 0 Heterogenety: Chi = 2.45, df = 2.0 = 0.450; F = 0.68 Total events 2 0 Heterogenety: Chi = 2.45, df = 2.0 = 0.450; F = 0.68 Total events 2 0 Total events	Heterogeneity: Chi <sup>2</sup> = 1.26, df = 2	2 (P = 0.53	$(1); 1^2 = 0\%$					
$ \begin{array}{c} \textbf{S.12-Cartexinestical} \\ Coleman 2015 (COCLANS) & 0 & 242 & Net estimable \\ Coleman 2015 (COCLANS) & 1373 & 751 & 128 (0.50, 7.86) \\ Subcal (95K C) & 751 & 751 & 751 & 128 \\ Coleman 2015 (COCLANS) & 0 & 44, 92 = 0.6 \\ Test for overall effect: 2 = 1.60 (P = 0.11) \\ \hline \textbf{S.13 bypertension} \\ Aphalamin 2012 (COCLANS) & 43 & 242 & 242 & 0.35 & 43.00 (5.97, 109, 7.6) \\ Coleman 2015 (COCLANS) & 43 & 242 & 242 & 0.35 & 43.00 (5.97, 109, 7.6) \\ Coleman 2015 (COCLANS) & 43 & 242 & 242 & 0.35 & 43.00 (5.97, 109, 7.6) \\ Tabler expensity. Ch2 = 2.63, df = 2 = 0.271, l2 = 2.65 \\ Test for overall effect: 2 = 4.50 (P = 0.271, l2 = 2.65 \\ Test for overall effect: 2 = 4.50 (P = 0.271, l2 = 2.65 \\ Test for overall effect: 2 = 4.50 (P = 0.20001) \\ \hline \textbf{S.1.5 Venous thromboembolic events} \\ Aphalamin 2012 (COCLANS) & 12 & 124 & 2 \\ Aphalamin 2012 (COCLANS) & 12 & 124 & 2 \\ Coleman 2015 (COC 211) & 12 & 212 & 22 \\ Test for overall effect: 2 = 4.52 (P = 0.00001) \\ \hline \textbf{S.1.5 Venous thromboembolic events} \\ Aphalamin 2012 (COCLANS) & 12 & 242 & 2.242 & 0.66 & 10.50 [2.49, 44.29] \\ Coleman 2015 (COC 211) & 12 & 320 & 2 \\ Test for overall effect: 2 = 4.52 (P = 0.0001) \\ \hline \textbf{S.1.5 Venous thromboembolic events} \\ Aphalamin 2012 (COCLANS) & 12 & 242 & 2.242 & 0.66 & 1.65 (0.54, 51.15, 52.51) \\ Test for overall effect: 2 = -0.52 (P = 0.28) (P = 0.6) \\ \hline \textbf{S.1.6 Arctal thromboembolic events} \\ Aphalamin 2012 (COCLANS) & 12 & 242 & 2.242 & 0.66 & 5.16, 5.240 \\ \hline \textbf{Test for overall effect: 2 = -0.52 (P = 0.020) \\ \hline \textbf{S.1.6 Arctal thromboembolic events} \\ Aphalamin 2012 (COCLANS) & 14 & 242 & 2 \\ Coleman 2015 (COC 211) & 8 & 330 & 2 \\ Coleman 2015 (COC 211) & 8 & 330 & 2 \\ Coleman 2015 (COC 211) & 8 & 330 & 2 \\ Coleman 2015 (COC 11) & 14 & 242 & 2 \\ Coleman 2015 (COC 211) & 14 & 242 & 2 \\ Coleman 2015 (COC 211) & 14 & 242 & 2 \\ Coleman 2015 (COC 211) & 14 & 242 & 2 \\ Coleman 2015 (COC 211) & 14 & 242 & 2 \\ Coleman 2015 (COC 211) & 14 & 242 & 2 \\ Coleman 2015 (COC 211) & 14 & 242 & 2 \\ Coleman 2015 (COC 211) & 14 & 242 & 2 \\ Coc$	Test for overall effect: Z = 1.53 (P	= 0.13)						
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$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c}$	Achaianian 2012 (OCEANS)	0	242	0	242		Not estimable	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Coleman 2015 (GOG 213)	6	330	3	327	0.9%	1.98 [0.50, 7.86]	
Subcla (95% C) 751 751 751 751 751 751 751 751 751 751	Pujade-Lauraine 2014 (AURELIA)	3	179	ő	182	0.2%	7.12 [0.37, 136.79]	
Total events 9 3 Test for overall effect 2 = 0.61 of 1 = 10 = 0.48; t <sup>2</sup> = 0.55 Test for overall effect 2 = 0.51 of 1 = 10 = 0.48; t <sup>2</sup> = 0.55 Test for overall effect 2 = 0.51 of 1 = 10 = 0.48; t <sup>2</sup> = 0.55 Total events 9 5 Total events 9 5 Total events 9 5 Total events 9 7 Total events 9 7	Subtotal (95% CI)		751		751	1.1%	2.71 [0.80, 9.15]	
$\begin{aligned} \text{Heterogeneity: } Ch4 = 0.61, df = 1.04 = 0.41; f4 = 0.65 \\ \text{rest for overall effect: 2 = 1.60 (ff = 0.11); \\ \begin{array}{r} \textbf{3.13 Propertension} \\ \text{Aphylamica 2015 (GOC 213)} & 39 & 330 & 2 \\ \text{Subtal (295K C0} & 751 \\ Subtal (295$	Total events	9		3				
Test for overall effect $2 = 0.36 = 0.113$ Aphaginan 2012 (OCLMS) 43 242 1 242 0,35 41,0 (5,97, 100,76) Coloman 2015 (OCC 213) 39 330 2 327 0,66 1,9.27 (4,70, 79,36) Pujdet-Luaraine 2014 AURELIAL 13 179 2 182 0,66 6,61 [1,51, 28,87] Subtrat (95% CO 751 751 1,55 19,01 [7,77, 46,55] Total events 95 Subtrat (95% CO 751 751 751 0,09, 17,37, 165,79] Pujdet-Luaraine 2014 AURELIAL 3 179 0 182 0,26 7,12 (0,37, 136,79] Pujdet-Luaraine 2014 AURELIAL 3 179 0 182 0,26 7,12 (0,37, 136,79] Subtrat (95% CO 751 751 751 0,09, 17,31 [5,42, 55,25] Total events 51 Reterogeneity: Ch <sup>+</sup> = 1.46, $d = 2 = 0.48$ ; $t^+ 0.05$ Test for overall effect $2 = 4.32 0 \notin 0.0000110$ S1.5 Venous thromboembolic events Aphaginan 2012 (OCLMS) 0 242 0 242 0,06 (0,21, 1,91] Subtrat (95% CO 751 751 751 751 751 751 751 751 751 751	Heterogeneity: Chi <sup>2</sup> = 0.61, df = 1	1 (P = 0.44	$(1); 1^2 = 0\%$					
	Test for overall effect: Z = 1.60 (P	= 0.11						
$ \begin{array}{c} \mbox{application} 2012 (OCCANS) & 43 & 242 & 1 & 242 & 0.38 & 41.00 (5.97, 100.76) \\ \mbox{columa 2015 (COC 213) & 39 & 330 & 2 & 327 & 0.68 & 19.23 (42.07, 93.6) \\ \mbox{Pidet-Lauraine 2014 AURELAN 13 & 179 & 2 & 182 & 0.66 & 6.61 [1.51, 2.8.87] \\ \mbox{Pidet-duaraine 2014 AURELAN 13 & 179 & 2 & 182 & 0.66 & 6.61 [1.51, 2.8.87] \\ \mbox{Total events } 95 & 5 & 5 \\ \mbox{Tats for overall effect. 2 = 6.45 & 0^{\circ} < 0.0000110 \\ \mbox{Pidet-duaraine 2014 AURELAN 3 & 179 & 0 & 182 & 0.28 & 7.12 (0.37, 136.79] \\ \mbox{Pidet-duaraine 2014 AURELAN 3 & 179 & 0 & 182 & 0.28 & 7.12 (0.37, 136.79] \\ \mbox{Pidet-duaraine 2014 AURELAN 3 & 179 & 0 & 182 & 0.28 & 7.12 (0.37, 136.79] \\ \mbox{Pidet-duaraine 2014 AURELAN 5 & 15 & 0 \\ \mbox{Test for overall effect. 2 = 4.82 & 0^{\circ} & 0.0000110 \\ \mbox{Subtat (95% CD & 751 & 751 & 0.58 \\ \mbox{Test for overall effect. 2 = 0.458, 1^{\circ} & 0.28 & 1.48 \\ \mbox{Test for overall effect. 2 = 0.69 & 0^{\circ} & 0.291; 1^{\circ} & 188 \\ \mbox{Subtat (95% CD & 751 & 751 & 0.58 & 4.99 & 1.26 [0.65, 2.40] \\ \mbox{Test for overall effect. 2 = 0.69 & 0^{\circ} & 0.291; 1^{\circ} & 188 \\ \mbox{Subtat (95% CD & 751 & 751 & 0.58 & 4.99 [1.29, 19.27] \\ \mbox{Test for overall effect. 2 = 0.69 & 0^{\circ} & 0.291; 1^{\circ} & 188 \\ \mbox{Test for overall effect. 2 = 0.69 & 0^{\circ} & 0.291; 1^{\circ} & 188 \\ \mbox{Test for overall effect. 2 = 0.302; 1^{\circ} & 0.58 \\ \mbox{Test for overall effect. 2 = 0.303 & 12 & 22 \\ \mbox{Test for overall effect. 2 = 0.303 & 0^{\circ} & 0.291 \\ \mbox{Test for overall effect. 2 = 0.303 & 0^{\circ} & 0.291 \\ \mbox{Test for overall effect. 2 = 0.303 & 0^{\circ} & 0.291 \\ \mbox{Test for overall effect. 2 = 0.303 & 0^{\circ} & 0.291 \\ \mbox{Test for overall effect. 2 = 0.303 & 0^{\circ} & 0.291 \\ \mbox{Test for overall effect. 2 = 0.303 & 0^{\circ} & 0.291 \\ \mbox{Test for overall effect. 2 = 0.303 & 0^{\circ} & 0.291 \\ \mbox{Test for overall effect. 2 = 0.303 & 0^{\circ} & 0.291 \\ \mbox{Test for overall effect. 2 = 0.303 & 0^{\circ} & 0.291 \\ \mbox{Test for overall effect. 2 = 0.303 & 0^{\circ} & 0.291 \\ Test for overall effec$	5.1.3 Hypertension							
$ \begin{array}{c} \text{Coleman 2015} (\text{COC 213}) & 19 & 330 & 2 & 127 & 0.066 & 19.32 (2.470, 79.36) \\ \text{Subtal (955 CO)} & 751 & 751 & 128 & 0.666 & 661 (1.51, 2.88.87) \\ \text{Total events} & 95 & \\ \text{Heterogeneity: Ch' = 2.63, df = 2 (P = 0.27); h' = 2.466 \\ \text{Test for overall effect: 2 = -6.5 (P < 0.00001)} \\ \hline \textbf{S1.4 Proteinuria} & \\ \text{Aphalama 2017} (\text{OCDANS}) & 21 & 242 & 242 \\ \text{Aphalama 2017} (\text{OCDANS}) & 21 & 242 & 242 \\ \text{Subtal (955 CO)} & 751 & 751 & 273 & 0.98 & 1233 (5.42, 55.25) \\ \text{Test for overall effect: 2 = -4.82 (P < 0.00001)} \\ \hline \textbf{S1.5 Venous thromboerhoolic events} & \\ \text{Aphalama 2017} (\text{OCCDANS}) & 10 & 242 & 6 & 242 & 1.88 & 1.67 (0.62, 4.51] \\ \text{Ocleman 2015} (\text{COC 213}) & 5 & 330 & 2 & 327 & 0.668 & 2.48 (0.48, 12.76 Pi) \\ \text{Subtal (955 CO)} & 10 & 242 & 6 & 242 & 1.88 & 1.67 (0.62, 4.51] \\ \text{Test for overall effect: 2 = -4.82 (P < 0.00001)} \\ \hline \textbf{S1.5 Venous thromboerhoolic events} & \\ \text{Aphalama 2017} (\text{OCCDANS}) & 0 & 242 & 6 & 242 & 1.88 & 1.67 (0.62, 4.51] \\ \text{Test for overall effect: 2 = -0.69 (P = 0.49)} \\ \hline \textbf{Test for overall effect: 2 = 0.69 (P = 0.49)} \\ \hline \textbf{Test for overall effect: 2 = 0.69 (P = 0.29); t' = 18X \\ \hline \textbf{Test for overall effect: 2 = -2.39 (P = 0.29); t' = 18X \\ \hline \textbf{Test for overall effect: 2 = -2.39 (P = 0.29); t' = 0.05 \\ \hline \textbf{Test for overall effect: 2 = -2.39 (P = 0.29); t' = 0.05 \\ \hline \textbf{Test for overall effect: 2 = -2.39 (P = 0.29); t' = 0.05 \\ \hline \textbf{Test for overall effect: 2 = -2.66 (P = 0.008) \\ \hline \textbf{S1.5 Would NEELINA & 179 & 0.05 \\ \hline \textbf{Test for overall effect: 2 = -2.66 (P = 0.008) \\ \hline \textbf{S1.6 Would NEELINA & 2 & 22 \\ \hline \textbf{Test for overall effect: 2 = -2.66 (P = 0.08) \\ \hline \textbf{S1.6 Would NEELINA & 2 & 22 \\ \hline \textbf{Test for overall effect: 2 = -1.66 (P = 0.10) \\ \hline \textbf{Test for overall effect: 2 = -1.66 (P = 0.10) \\ \hline \textbf{Tat levents} & 5 \\ \hline \textbf{Test for overall effect: 2 = -1.66 (P = 0.10) \\ \hline \textbf{Tat levents} & 5 \\ \hline \textbf{Test for overall effect: 2 = -1.66 (P = 0.10) \\ \hline \textbf{Tat levents} & 5 \\ \hline \textbf{Test for overall effect: 2 = -1.66 (P = 0.10) \\ \hline \textbf{Tat levents} & 5 \\ \hline Test for overall$	Aghajanian 2012 (OCEANS)	43	242	1	242	0.3%	43.00 [5.97, 309.76]	
$\begin{array}{c} Pijdet-Lauraine 2014 (AURELIA) 13 179 2 751 5$	Coleman 2015 (GOG 213)	39	330	2	327	0.6%	19.32 [4.70, 79.36]	
Subtol (95% C0) 751 751 751 1.5% 19.01 [7.77, 46.55] Heterogeneity: $Ch^2 = 2.63, df = 2(P = 0.27); h^2 = 24\%$ Test for overall effect: $2 = 4.65 (P < 0.0001)$ S.1.4 Proteinuria Aphalama. 2012 (OCLANS) 21 242 2 Aphalama. 2012 (OCLANS) 21 242 2 Subtol (95% C0) 751 751 751 0.9% 17.31 [5.42, 55.25] Total events 5 Subtol (95% C0) 751 751 0.9% 17.31 [5.42, 55.25] Total events 5 Subtol (95% C0) 751 751 0.9% 17.31 [5.42, 55.25] Total events 1 Total events 1 S.1.5 Venous thromboembolic events Aphalama. 2012 (OCLANS) 0 242 6 Coleman 2015 (OCC 213) 751 0.2% 0.2% 54.50 [3.4, 88.7.6] Publed-Lauraine 2014 (AURELIA) 5 1.73 8 Subtol (95% C0) 751 16 Total events 2014 (AURELIA) 5 1.73 8 Subtol (95% C0) 751 16 Total events 2014 (AURELIA) 5 1.73 8 Subtol (95% C0) 751 16 Total events 2014 (AURELIA) 4 1.79 182 0.2% 9.15 [0.50, 16.8, 72] Publed-Lauraine 2014 (AURELIA) 4 1.79 0 182 0.2% 9.15 [0.50, 16.8, 72] Publed-Lauraine 2014 (AURELIA) 4 1.79 0 182 0.2% 9.15 [0.50, 16.8, 72] Publed-Lauraine 2014 (AURELIA) 4 1.79 0 182 0.2% 9.15 [0.50, 16.8, 72] Publed-Lauraine 2014 (AURELIA) 4 1.79 0 182 0.2% 9.15 [0.50, 16.8, 72] Publed-Lauraine 2014 (AURELIA) 4 1.79 0 182 0.2% 9.15 [0.50, 16.8, 72] Publed-Lauraine 2014 (AURELIA) 4 1.79 0 182 0.2% 9.15 [0.50, 16.8, 72] Publed-Lauraine 2014 (AURELIA) 2 1.79 27 Total events 12 2 Publed-Lauraine 2014 (AURELIA) 2 1.79 27 Total events 12 7 Total events 227 7 Total events 9 S1.8 Wood Healing Aphalamia 2012 (OCCANS) 2 2.42 0 2.2% 5.00 [0.24, 10.3.61] Coleman 2015 (OCCANS) 2 2.42 0 2.2% 5.00 [0.24, 10.3.61] Coleman 2015 (OCCANS) 2 2.42 0 2.2% 5.00 [0.24, 10.3.61] Coleman 2015 (OCCANS) 2 2.42 0 2.2% 5.00 [0.24, 10.3.61] Coleman 2015 (OCCANS) 2 2.42 0 2.2% 5.00 [0.24, 10.3.61] Coleman 2015 (OCCANS) 2 2.42 0 2.2% 5.00 [0.24, 10.3.61] Coleman 2015 (OCCANS) 2 2.42 0 2.2% 5.00 [0.24, 10.3.61] Coleman 2015 (OCCANS) 2 2.42 0 2.2% 5.00 [0.24, 10.3.61] Coleman 2015 (OCCAN	Pujade-Lauraine 2014 (AURELIA)	13	179	2	182	0.6%	6.61 [1.51, 28.87]	
Total events 95 5 Heterogeneity: Ch <sup>2</sup> = 2.63, df = 2 ( $P = 0.27$ ); h <sup>2</sup> = 24% Test for overall effect: 2 = -6.45 ( $P < 0.00001$ ) <b>5.1.4 Proteinuria</b> Aphajania 2012 (OCENX5) 21 242 2 Coleman 2013 (GO 211) 27 333 0 12 0.25 5.45 (013,4, 885,76] Polymeria elevities 0.14 (AURELIA) 3 129 0 12 0.25 5.45 (013,4, 885,76] Polymeria elevities 0.14 (AURELIA) 3 129 0 12 0.25 5.45 (013,4, 885,76] Polymeria elevities 0.14 (AURELIA) 3 129 0 12 0.25 5.45 (013,4, 885,76] Polymeria elevities 0.14 (AURELIA) 5 129 0 Total events 2014 (AURELIA) 5 179 8 12 2.45 (0.66, 2.46] (0.48, 12.68] Polydet-Lauraine 2014 (AURELIA) 5 179 8 12 2.45 (0.66, 2.46] (0.48, 12.68] Polydet-Lauraine 2014 (AURELIA) 5 179 8 12 2.45 (0.66, 2.46] (0.48, 12.68] Polydet-Lauraine 2014 (AURELIA) 5 179 8 12 2.45 (0.66, 2.46] (0.48, 12.68] Polydet-Lauraine 2014 (AURELIA) 5 179 8 12 2.45 (0.66, 2.40] Total events 2 Aphajania 2012 (OCENX5) 12 242 0 Shoto (1955 CO) 751 751 0.85 4.99 [1.29, 150.27] Subtool (1955 CO) 751 751 0.85 4.99 [1.29, 150.27] Subtool (1955 CO) 751 751 0.28 4.99 [1.29, 150.27] Total events 2 Shoto (1955 CO) 751 751 0.28 4.99 [1.29, 150.27] Total events 2 Shoto (1955 CO) 751 751 0.28 4.99 [1.29, 150.27] Total events 2 Shoto (1955 CO) 751 751 0.28 5.00 [1.61, 30.47] Coleman 2015 (OCC 213) A 22 242 0.66 7.00 [1.61, 30.47] Total events 2 S1.5 More relating Aphajania 2012 (OCCNS) 14 242 2 Co (24 0.26 5.00 [0.24, 10.36, 1] Aphajania 2012 (OCCNS) 2 242 7 Total events 2 S1.5 More relating Aphajania 2012 (OCCCNS) 2 242 7 Total events 5 0 Total events	Subtotal (95% CI)		751		751	1.5%	19.01 [7.77, 46.55]	-
$ \begin{array}{c} \text{Meterogeneity: } (Lh^* = 2.83, df = 2 \ (P = 0.27), f = 2.45 \\ \text{rest for overall effect: Z = 6.45 \ (P < 0.00001) \\ \hline \textbf{S1.4 Proteinuria} \\ Aphajinia 2012 (OCLANS) & 21 & 242 & 2 \\ Coloman 2015 (OCCANS) & 21 & 242 & 2 \\ Coloman 2015 (OCCANS) & 11 & 27 & 310 & 0 \\ Pujde-Lauraine 2014 (AURELIA) & 179 & 0 & 182 \\ Ocleman 2015 (OCCANS) & 10 & 242 & 0 \\ Pujde-Lauraine 2014 (AURELIA) & 5 & 175 & 2 \\ Pujde-Lauraine 2014 (AURELIA) & 5 & 175 & 2 \\ Pujde-Lauraine 2014 (AURELIA) & 5 & 175 & 2 \\ Pujde-Lauraine 2014 (AURELIA) & 5 & 175 & 2 \\ Pujde-Lauraine 2014 (AURELIA) & 5 & 175 & 2 \\ Pujde-Lauraine 2014 (AURELIA) & 5 & 175 & 2 \\ Pujde-Lauraine 2014 (AURELIA) & 5 & 175 & 2 \\ Pujde-Lauraine 2014 (AURELIA) & 5 & 175 & 2 \\ Pujde-Lauraine 2014 (AURELIA) & 5 & 12 & 2 \\ Peterogenenity: (Lh^+ = 2.45, df = 2 \ (P = 0.29); \ f = 1.85 \\ Test for overall effect: Z = 0.69 \ (P = 0.49) \\ \hline \textbf{S1.5 Prost SC D } & 751 & 751 & 0.58 & 4.99 \ [1.29, 192.7] \\ Total events & 20 & 16 \\ Heterogenenity: (Lh^+ = 2.45, df = 2 \ (P = 0.29); \ f = 1.85 \\ Test for overall effect: Z = 2.33 \ (P = 0.02); \ f = 1.85 \\ Test for overall effect: Z = 2.33 \ (P = 0.02); \ f = 0.58 \\ \hline \textbf{S1.5 Prost SC D } & 751 & 751 & 0.58 & 4.99 \ [1.29, 192.7] \\ Total events & 12 & 2 \\ Heterogenenity: (Lh^+ = 2.45, df = 2 \ (P = 0.02); \ f = 0.58 \\ \hline \textbf{S1.5 Prost SC D } & 751 & 751 & 0.58 & 4.99 \ [1.29, 192.7] \\ \hline \textbf{Subtoal (95% CD } & 751 & 751 & 0.58 & 4.99 \ [1.29, 192.7] \\ \hline \textbf{Subtoal (95% CD } & 751 & 751 & 0.58 & 4.99 \ [1.29, 192.7] \\ \hline \textbf{Subtoal (95% CD } & 751 & 751 & 0.38 & 5.97 \ [0.72, 4.94.5] \\ \hline \textbf{Subtoal (95% CD } & 751 & 751 & 0.38 & 5.97 \ [0.72, 4.94.5] \\ \hline \textbf{Subtoal (95% CD } & 751 & 751 & 0.38 & 5.97 \ [0.72, 4.94.5] \\ \hline Caloma Pointy: Ch' = 0.02, \ (H = 0.08); \ F = 0.5 \\ \hline \textbf{Retroponety: Ch' = 0.02, \ (H = 0.08); \ F = 0.5 \\ \hline \textbf{Retroponety: Ch' = 0.02, \ (H = 0.08); \ F = 0.5 \\ \hline \textbf{Retroponety: Ch' = 0.02, \ (H = 0.08); \ F = 0.5 \\ \hline \textbf{Retroponety: Ch' = 0.02, \ (H = 0.08); \ F = 0.5 \\ \hline \textbf{Retroponety: Ch' = 0.02, \ (H = 0.08); \ F = 0.$	Total events	95		5				
$ \begin{array}{c} 1 \text{ sty tor overall effect: 2 = 0.45 (p < 0.0001) \\ \hline \textbf{S1.4 Proteinuria} \\ Aphjaniar 2012 (OCCANS) & 21 & 242 & 2 \\ Coleman 2015 (GOC 211) & 27 & 330 & 0 \\ pijde - Lauraine 2014 (AURELIA) & 3 & 179 & 0 \\ pijde - Lauraine 2014 (AURELIA) & 3 & 179 & 0 \\ 1 \text{ sty tor overall effect: 2 = 4.82 (p < 0.048), t2 = 0.83 \\ \text{ rest for overall effect: 2 = 4.82 (p < 0.048), t2 = 0.83 \\ \text{ rest for overall effect: 2 = 4.82 (p < 0.048), t2 = 0.83 \\ \text{ rest for overall effect: 2 = 4.82 (p < 0.020), t2 = 1.88 \\ \text{ rest for overall effect: 2 = 4.82 (p < 0.020), t2 = 1.88 \\ \text{ rest for overall effect: 2 = 4.82 (p < 0.020), t2 = 1.88 \\ \text{ rest for overall effect: 2 = 4.82 (p < 0.020), t2 = 1.88 \\ \text{ rest for overall effect: 2 = 4.82 (p < 0.020), t2 = 1.88 \\ \text{ rest for overall effect: 2 = 4.82 (p < 0.020), t2 = 1.88 \\ \text{ rest for overall effect: 2 = 0.69 (p = 0.02), t2 = 1.88 \\ \text{ rest for overall effect: 2 = 2.33 (p = 0.02); t2 = 0.8 \\ \text{ rest for overall effect: 2 = 2.33 (p = 0.02); t2 = 0.8 \\ \text{ rest for overall effect: 2 = 2.33 (p = 0.02); t2 = 0.8 \\ \text{ rest for overall effect: 2 = 2.66 (p = 0.028) \\ \text{ subtoal (95% CO) } \\ \text{ rest for overall effect: 2 = 2.66 (p = 0.028) \\ \text{ subtoal (95% CO) } \\ \text{ rest for overall effect: 2 = 2.66 (p = 0.028) \\ \text{ subtoal (95% CO) } \\ \text{ rest for overall effect: 2 = 2.66 (p = 0.028) \\ \text{ subtoal (95% CO) } \\ \text{ rest for overall effect: 2 = 2.66 (p = 0.028) \\ \text{ subtoal (95% CO) } \\  rest for overall effect: 2 = 1.66 (p = 0.10) \\ \text{ rest for overall effect: 2 = 1.66 (p = 0.10) \\ \text{ rest for overall effect: 2 = 1.66 (p = 0.10) \\ \text{ rest for overall effect: 2 = 1.66 (p = 0.10) \\ \text{ rest for overall effect: 2 = 1.66 (p = 0.10) \\ \text{ rest for overall effect: 2 = 1.66 (p = 0.10) \\ \text{ rest for overall effect: 2 = 1.66 (p = 0.10) \\ \text{ rest for overall effect: 2 = 1.66 (p = 0.10) \\ \text{ rest for overall effect: 2 = 1.66 (p = 0.10) \\ \text{ rest for overall effect: 2 = 1.66 (p = 0.10) \\ \text{ rest for overall effect: 2 = 1.66 (p = 0.10) \\ \text{ rest for overall effect: 2 = 1$	Heterogeneity: Chi <sup>e</sup> = 2.63, df = 2	Z (P = 0.27)	7); I <sup>c</sup> = 249	5				
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Test for overall effect: Z = 6.45 (P	< 0.0000	1)					
	5.1.4 Proteinuria							
$ \begin{array}{c} \text{Coleman 2015 (GOC 213)} & 27 & 330 & 0 & 327 & 0.28 & 54.50 (3.34, 889.76] \\ \text{Subtal (95% CD)} & 751 & 0 & 751 & 0.98 & 17.31 [5.42, 55.25] \\ \text{Subtal (95% CD)} & 751 & 0.98 & 17.31 [5.42, 55.25] \\ \text{Test for overall effect: 2 = 4.82 (P = 0.48); P^2 = 0.68 & 2.88 (A.8, 12.68] \\ \text{Pijde-Lauraine 2014 AURELIA} & 5 & 179 & 5 & 751 & 0.98 & 1.57 [0.62, 4.51] \\ \text{Coleman 2015 (GOC 213)} & 5 & 330 & 2 & 327 & 0.68 & 2.48 (A.8, 12.68] \\ \text{Pijde-Lauraine 2014 AURELIA} & 5 & 179 & 5 & 751 & 4.98 & 1.26 [0.66, 2.40] \\ \text{Test for overall effect: 2 = 0.69 (P = 0.48); P^2 = 0.48 P^2 = 0.29; P^2 = 188 & 1.67 [0.65, 168, 12.68] \\ \text{Pijde-Lauraine 2014 AURELIA} & 5 & 179 & 5 & 751 & 751 & 4.98 & 1.26 [0.66, 2.40] \\ \text{Test for overall effect: 2 = 0.69 (P = 0.48); P^2 = 0.48 P^2 = 0.29; P^2 = 188 & 1.67 (0.65, 168, 72] \\ \text{Subbrail (95% CD)} & 751 & 751 & 4.98 & 1.26 [0.66, 2.40] \\ \text{Total events} & 20 & 4.48 (P = 0.62); P^2 = 0.88 & 4.59 (1.68, 72) \\ \text{Subbrail (95% CD)} & 751 & 751 & 0.88 & 4.59 (1.28, 18.27] \\ \text{Total events} & 20 & 4.40 \\ \text{Coleman 2015 (GOC 213)} & 8 & 330 & 2 & 327 & 0.66 & 3.06 (0.52, 158, 72] \\ \text{Subbrail (95% CD)} & 751 & 2.5 & df = 1 (P = 0.62); P^2 = 0.8 \\ \text{Test for overall effect: 2 = 2.33 (P = 0.02)} \\ \text{S1.F Betrogeneity: Ch2 = 0.25, df = 1 (P = 0.62); P^2 = 0.8 \\ \text{Test for overall effect: 2 = 2.33 (P = 0.02)} \\ \text{Total events} & 22 \\ \text{Aphjanian 2012 (OCEANS)} & 14 & 242 & 2 & 242 & 0.66 & 7.00 [1.61, 3.0.47] \\ \text{Subbrail (95% CD)} & 751 & 751 & 278 & 278 & 0.58 (1.03, 0.14, 7.14] \\ \text{Subbrail (95% CD)} & 751 & 751 & 224 & 5.00 [0.24, 10.3.61] \\ \text{Coleman 2015 (GOC 213)} & 3 & 330 & 0 & 327 & 0.28 & 5.09 [0.24, 10.3.61] \\ \text{Coleman 2015 (GOC 213)} & 3 & 330 & 0 & 327 & 0.28 & 5.09 [0.24, 10.3.61] \\ \text{Coleman 2015 (GOC 213)} & 3 & 330 & 0 & 327 & 0.28 & 6.94 [0.36, 13.3.76] \\ \text{Pijde-Lauraine 2014 AURELIA} & 177 & 182 & 0.38 & 5.97 [0.72, 49.45] \\ \text{Total events} & 5 & 0 \\ Feterogeneity: Ch2 = 0.02, df = 1 (P = 0.88), P^2 = 0.88 \\ \text{Test for overall effect: 2 = 1$	Aghajanian 2012 (OCEANS)	21	242	2	242	0.6%	10.50 [2.49, 44,29]	
$\begin{array}{c} \text{Pijde-Lauraine 2014 (AURELIA)} & 3 & 179 & 0 & 182 & 0.2\% & 7.12 [0.37, 136, 79] \\ \hline \text{Total events} & 5 & 1 & 2 \\ \text{theterogeneity} & (n^2 + 1.6, 6, 2 + 0^2 - 0.46, 16, 1^2 + 0\%) \\ \text{Test for overall effect: } Z = 4.82 (P < 0.00001) \\ \hline \text{S1.5 Venous thromboembolic events} \\ \text{Aphjanka 2012 (OCEANS)} & 10 & 242 & 6 & 242 & 1.8\% & 1.67 [0.62, 4.51] \\ \text{Oleman 2015 (GOC 213)} & 5 & 330 & 2 & 327 & 0.6\% & 2.48 [0.46, 12.68] \\ \text{Total events} & 20 & 1/6 \\ \text{Heterogeneity} & \text{Chi } = 2.45, df = 2 (P = 0.29); 1^2 = 1.8\% \\ \text{Test for overall effect: } Z = 0.69 (P = 0.49) \\ \hline \text{S1.5 Arterial thromboembolic events} \\ \text{Aphjanka 2012 (OCEANS)} & 0 & 242 & 0 \\ \text{Aphjanka 2012 (OCEANS)} & 0 & 242 & 0 \\ \text{Aphjanka 2012 (OCEANS)} & 0 & 242 & 0 \\ \text{Aphjanka 2012 (OCEANS)} & 0 & 242 & 0 \\ \text{S1.6 Arterial thromboembolic events} \\ \text{Aphjanka 2012 (OCEANS)} & 0 & 242 & 0 \\ \text{Aphjanka 2012 (OCEANS)} & 0 & 242 & 0 \\ \text{S1.7 Electing} \\ \text{Aphjanka 2012 (OCEANS)} & 14 & 242 & 2 & 242 \\ \text{Meterogeneity: Chi' = 0.25, df = 1 (P = 0.62); 1^2 = 0\% \\ \text{Total events} & 12 & 2 \\ \text{Heterogeneity: Chi' = 0.25, df = 1 (P = 0.62); 1^2 = 0\% \\ \text{Total events} & 22 \\ \text{Note estimable} \\ \text{Aphjanka 2012 (OCEANS)} & 14 & 242 & 2 & 242 \\ \text{Meterogeneity: Chi' = 0.25, df = 2 (P = 0.024); 1^2 = 10\% \\ \text{Total events} & 22 \\ \text{Note events} & 244 \\ \text{Aphjanka 2012 (OCEANS)} & 14 & 242 & 2 & 242 \\ \text{Olema 2015 (GOC 213)} & 3 & 327 & 0.2\% & 1.08 [0.51, 7.86] \\ \text{Pijde-Lauraine 2014 AURELIA} & 2 & 179 & 2 & 182 \\ \text{Olema 2015 (GOC 213)} & 3 & 330 & 0 & 327 & 0.2\% & 5.00 [0.24, 103.61] \\ \text{Olema 2015 (GOC 213)} & 3 & 330 & 0 & 327 & 0.2\% & 5.00 [0.24, 103.61] \\ \text{Olema 2015 (GOC 213)} & 3 & 330 & 0 & 327 & 0.2\% & 5.00 [0.24, 103.61] \\ \text{Olema 2015 (GOC 213)} & 3 & 330 & 0 & 327 & 0.2\% & 5.00 [0.24, 103.61] \\ \text{Olema 2015 (GOC 213)} & 3 & 330 & 0 & 327 & 0.2\% & 5.00 [0.24, 103.61] \\ \text{Olema 2015 (GOC 213)} & 3 & 330 & 0 & 327 & 0.2\% & 5.07 [0.72, 49.45] \\ \text{Total events} & 5 & 0 \\ Heterogeneity: Chi' = 0.02, df = 1 (P = 0.38); 1^2 = 0\% \\ \text{Test for $	Coleman 2015 (GOG 213)	27	330	õ	327	0.2%	54.50 [3.34, 889.76]	
Subtal (95% C) 751 751 751 0.9% 17.31 [5.42, 55.25] Heterogeneity: Ch <sup>2</sup> = 1.45, df = 2 ( $P = 0.48$ ); $l^2 = 0.65$ Test for overall effect: 2 = 4.82 ( $P < 0.00001$ ) 51.5 Venous thromboembolic events Aphajania 7012 (OCEANS) 10 242 6 2.327 0.66 2.48 (1.64, 1.2.68) Pujade-Lauraine 2014 (AURELIA) 5 179 8 182 2.4% 0.64 (0.24, 1.9.1] Subtal (95% C) 751 751 4.9% 1.26 [0.66, 2.40] Total events 2 0 16 Heterogeneity: Ch <sup>2</sup> = 2.45, df = 2 ( $P = 0.29$ ); $l^2 = 18\%$ Test for overall effect: 2 = 0.69 ( $P = 0.49$ ) 51.6 Arterial thromboembolic events Aphajania 7012 (OCEANS) 0 242 0 242 Not estimable Coleman 2015 (GOC 213) 8 330 2 337 0.6% 3.96 [0.85, 1.85.2] Pujade-Lauraine 2014 (AURELIA) 4 179 0 182 0.2% 9.15 (0.50, 168.52] Subtal (95% C) 751 751 0.8% 4.99 [1.29, 19.27] Total events 12 2 Heterogeneity: Ch <sup>2</sup> = 0.25, df = 1 $P = 0.62$ ; $l^2 = 0.05$ 51.7 Blecting Aphajania 7012 (OCEANS) 14 242 2 242 0.6% 7.00 [1.61, 30.47] Coleman 2015 (GOC 213) 6 310 3 327 0.9% 1.98 (1.50, 7.86] Pujade-Lauraine 2014 (AURELIA) 4 179 0 182 0.6% 1.02 [0.14, 7.14] Subtal (95% C) 751 751 751 2751 751 2.2% 3.14 [1.35, 7.32] Total events 12 2 7 Heterogeneity: Ch <sup>2</sup> = 2.56 ( $P = 0.208$ ) 51.7 Blecting Aphajania 7012 (OCEANS) 2 242 0 242 0.2% 5.00 [0.24, 103.61] Coleman 2015 (GOC 213) 3 30 0 327 0.2% 6.94 [0.36, 133.76] Not estimable Subtal (95% C) 751 751 751 0.3% 5.97 [0.72, 4.945] Heterogeneity: Ch <sup>2</sup> = 0.00, df = 1 ( $P = 0.38$ ); $l^2 = 0.05$ Test for overall effect: $Z = 1.66 (P = 0.10)$ Total events 5 0 Heterogeneity: Ch <sup>2</sup> = 0.00, df = 1 ( $P = 0.08$ ); $l^2 = 0.05$ Total events Test for overall effect: $Z = 1.66 (P = 0.10)$ Total events 120 0.00, df = 1 ( $P = 0.38$ ); $l^2 = 0.65$ Test for overall effect: $Z = 1.66 (P = 0.10)$	Pujade-Lauraine 2014 (AURELIA)	3	179	0	182	0.2%	7.12 [0.37, 136.79]	
Total events 51 2 Heterogeneity: $Ch^2 = 1.46, (df = 2/P = 0.48); t^2 = 0%$ Test for overall effect: $Z = 4.82$ ( $P < 0.00001$ ) 5.1.5 Venous thromboembolic events Aphapaina 2012 (OCEANS) 10 242 6 Coleman 2015 (GOC 213) 5 330 2 Subtoal (95% CD 751 751 4.9% 1.26 [0.66, 2.40] Total events 20 16 Coleman 2015 (GOC 213) 6 330 2 Subtoal (95% CD 751 751 751 0.5% 4.99 [1.29, 1.921] Subtoal (95% CD 751 751 751 751 0.5% 4.99 [1.29, 1.921] Subtoal (95% CD 751 751 751 751 751 0.5% 4.99 [1.29, 1.921] Total events 20 16 Heterogeneity: $Ch^2 = 0.25, df = 1/P = 0.62; t^2 = 0.05$ Heterogeneity: $Ch^2 = 0.25, df = 1/P = 0.62; t^2 = 0.05$ Total events 20 4(AURELIA) 4 179 0 182 0.2% 9.15 [0.50, 1.65, 7.18, 5.21] Pujade-Lauraine 2014 (AURELIA) 4 179 0 182 0.2% 9.15 [0.50, 7.86] Pujade-Lauraine 2014 (AURELIA) 4 179 0 0.62; t <sup>2</sup> = 0.05 Test for overall effect: $Z = 2.33 (P = 0.062); t^2 = 0.05$ Test for overall effect: $Z = 2.33 (P = 0.062); t^2 = 0.05$ Test for overall effect: $Z = 2.66 (P = 0.008)$ 5.1.7 Block of $T = 0.25, df = 1/P = 0.62; t^2 = 30\%$ Test for overall effect: $Z = 2.66 (P = 0.008)$ 5.1.8 Wound Healing Aphajania 2012 (OCEANS) 2 242 0 242 0.2% 5.00 [0.24, 103.61] Coleman 2015 (GOC 213) 3 330 0 327 0.2% 6.94 [0.36, 13.76] Pujade-Lauraine 2014 (AURELIA) 0 179 0 182 No restimable Subtoal (95% CD 751 751 0.3% 5.97 [0.72, 49.45] Total events 5 0 Heterogeneity: $Ch^2 = 0.02, df = 1 (P = 0.88); t^2 = 0.05$ Total events 5 0 Heterogeneity: $Ch^2 = 0.02, df = 1 (P = 0.88); t^2 = 0.5$ Heterogeneity: $Ch^2 = 0.02, df = 1 (P = 0.88); t^2 = 0.5$ Total events 5 0 Heterogeneity: $Ch^2 = 0.02, df = 1 (P = 0.88); t^2 = 0.5$ Total events 5 0 Heterogeneity: $Ch^2 = 0.02, df = 1 (P = 0.88); t^2 = 0.5$ Total events 5 0 Heterogeneity: $Ch^2 = 0.02, df = 1 (P = 0.88); t^2 = 0.5$ Total events 5 0 Heterogeneity: $Ch^2 = 0.02, df = 1 (P = 0.88); t^2 = 0.5$ Total events 5 0 Heterogeneity: $Ch^2 = 0.02, df = 1 (P = 0.88); t^2 = 0.5$ Total events 5 0 Heterogeneity: $Ch^2 = 0.02, df = 1 (P = 0.88); t^2 =$	Subtotal (95% CI)		751		751	0.9%	17.31 [5.42, 55.25]	
$ \begin{array}{c} \text{Meterogeneity: Ch' = 1.46, df = 2 (P = 0.48); l' = 0\% \\ \text{Test for overall effect: Z = 4.26 (Q = 2.00001) \\ \hline \textbf{S1.5 Venous thromboembolic events} \\ \text{Aphajnian 2012 (OCEANS) 10 242 6 2327 0.6% 2.48 [0.48, 12.68] \\ \text{Pujade-Lauraine 2014 (AURELIA) 5 179 8 182 2.4% 0.64 [0.21, 1.91] \\ \text{Total events 2 0 16 \\ \text{Meterogeneity: Ch' = 2.45, df = 2 (P = 0.39); l' = 18\% \\ \text{Test for overall effect: Z = 0.69 (P = 0.49) \\ \hline \textbf{S1.5 Arterial thromboembolic events} \\ Aphajnian 2012 (OCEANS) 0 242 0 242 \\ \text{Obteroal (95% CD) 751 751 751 751 751 751 751 751 751 751$	Total events	51		2				
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Heterogeneity: $Chi^{\circ} = 1.46$ , $df = 2$	2 (P = 0.48)	$(3); 1^{c} = 0\%$					
<b>5.1.5 Venous thromboembolic events</b> Aghajanian 2012 (OCEANS) 10 242 6 242 1.8% 1.67 [0.62, 4.51] Pujade-Lauraine 2014 (AURELIA) 5 179 8 182 2.4% 0.64 [0.21, 1.91] Pujade-Lauraine 2014 (AURELIA) 5 179 8 182 2.4% 0.64 [0.21, 1.91] Total events 20 16 Heterogeneity: Ch <sup>2</sup> = 2.45, df = 2 ( $P = 0.29$ ); l <sup>2</sup> = 18% Test for overall effect: Z = 0.69 ( $P = 0.49$ ) <b>5.1.6 Arterial thromboembolic events</b> Aghajanian 2012 (OCEANS) 0 242 0 242 Not estimable Coleman 2015 (GOC 213) 8 330 2 327 0.6% 3.96 [0.85, 18, 52] Pujade-Lauraine 2014 (AURELIA) 4 179 0 182 0.2% 9.15 [0.50, 168, 72] Total events 12 Coleman 2015 (GOC 213) 6 330 3 327 0.9% 1.98 [0.50, 7.66] Pujade-Lauraine 2014 (AURELIA) 2 179 2 182 0.6% 1.002 [0.14, 7.14] Subtotal (95% CO) 751 751 2.2% 3.14 [1.35, 7.32] Total events 22 7 Heterogeneity: Ch <sup>2</sup> = 2.45, df = 2 ( $P = 0.24$ ); l <sup>2</sup> = 30% Test for overall effect: Z = 2.66 ( $P = 0.008$ ) <b>5.1.8 Wound Healing</b> Aghajanian 2012 (GOCANS) 2 242 0 242 0.2% 5.00 [0.24, 103.61] Coleman 2015 (GOC 213) 3 330 0 327 0.2% 6.94 [0.36, 133.76] Pujade-Lauraine 2014 (AURELIA) 0 179 0 182 Coleman 2015 (GOC 213) 3 330 0 327 0.2% 6.94 [0.36, 133.76] Pujade-Lauraine 2014 (AURELIA) 0 179 0 182 Coleman 2015 (GOC 213) 3 330 0 327 0.2% 5.97 [0.72, 49.45] Coleman 2015 (GOC 213) 3 330 0 327 0.2% 5.97 [0.72, 49.45] Coleman 2015 (GOC 213) 751 0.3% 5.97 [0.72	Test for overall effect: Z = 4.82 (P	< 0.0000	1)					
Aghajanian 2012 (OCEANS) 10 242 6 242 1.8% 1.67 (0.62, 4.51) Coleman 2015 (GOC 213) 5 330 2 327 0.6% 2.48 [0.48, 12.68] Pujade-Lauraine 2014 (AURELIA) 5 173 8 182 2.4% 0.64 (0.21, 1.91) Subtoal (95% C) 751 751 4.9% 1.26 [0.66, 2.40] Total events Aghajanian 2012 (OCEANS) 0 242 0 16 Heterogeneity: Chi <sup>2</sup> = 2.45, df = 2 (P = 0.29); l <sup>2</sup> = 18% Test for overall effect: 2 = 0.69 (P = 0.49) <b>5.1.6 Arterial thromboembolic events</b> Aghajanian 2012 (OCEANS) 0 242 0 242 Not estimable Coleman 2015 (GOC 213) 8 330 2 327 0.6% 3.96 [0.85, 1.852] Pujade-Lauraine 2014 (AURELIA) 4 179 0 182 0.2% 9.15 [0.30, 168, 72] Subtoal (95% C) 751 751 0.8% 4.99 [1.29, 19.27] Total events <b>5.1.7 Biceding</b> Aghajanian 2012 (OCEANS) 14 242 2 242 0.6% 7.00 [1.61, 30.47] Coleman 2015 (GOC 213) 6 330 3 227 0.9% 1.98 [0.50, 7.86] Pujade-Lauraine 2014 (AURELIA) 2 179 2 182 0.6% 1.02 [0.14, 7, 14] <b>5.1.7 Biceding</b> Aghajanian 2012 (OCEANS) 14 242 7 Poster for overall effect: 2 = 2.86, df = 2 (P = 0.24); l <sup>2</sup> = 30% Test for overall effect: 2 = 2.66 (P = 0.008) <b>5.1.8 Wound Healing</b> Aghajanian 2012 (OCEANS) 2 242 0 242 0.2% 5.00 [0.24, 103.61] Coleman 2015 (GOC 213) 3 330 0 327 0.2% 6.94 [0.36, 133.76] Pujade-Lauraine 2014 (AURELIA) 179 0 182 Not estimable Coleman 2015 (OCEANS) 2 242 0 242 0.2% 5.00 [0.24, 103.61] <b>5.1.8 Wound Healing</b> Aghajanian 2012 (OCEANS) 2 242 0 242 0.2% 5.97 [0.72, 49.45] <b>5.1.8 Wound Healing</b> Aghajanian 2012 (OCEANS) 2 242 0 242 0.2% 5.97 [0.72, 49.45] <b>5.1.8 Wound Healing</b> Aghajanian 2014 (AURELIA) 179 0 182 Not estimable Subtoal (95% C) 751 751 0.3% 5.97 [0.72, 49.45] <b>5.1.8 Wound Healing</b> Aghajanian 2014 (AURELIA) 0 179 0 182 Not estimable Total events <b>5.1.8 Wound Healing</b> Aghajanian (1.16) (1.90 100 CT alore CT with Bezacizumab	5.1.5 Venous thromboembolic e	vents						
Coleman 2015 (COC 213) 5 330 2 327 0.6% 2-48 [0.48, 12.68] Phylade-Lauraine 2014 (AURELIA) 5 179 8 182 2.4% 0.64 [0.21, 1.91] Subtotal (95% CD) 751 751 4.9% 1.26 [0.66, 2.40] Total events 20 16 Heterogeneity: Chi <sup>2</sup> = 2.45, df = 2 (P = 0.29); l <sup>2</sup> = 18% Test for overall effect: Z = 0.69 (P = 0.49) 5.1.6 Arterial thromboembolic events Aphajania 2012 (OCEANS) 0 242 0 242 Not estimable Coleman 2015 (COC 213) 8 330 2 327 0.6% 3.96 [0.85, 18.52] Subtotal (95% CD) 751 751 0.8% 4.99 [1.29, 19.27] Total events 12 2 Heterogeneity: Chi <sup>2</sup> = 0.25, df = 1 (P = 0.62); l <sup>2</sup> = 0% Test for overall effect: Z = 2.33 (P = 0.02) 5.1.7 Bleeding Aphajania 2012 (OCEANS) 14 242 2 242 0.6% 7.00 [1.61, 30.47] Coleman 2015 (COC 213) 6 330 3 227 0.9% 1.98 [0.50, 7.86] Phylade-Lauraine 2014 (AURELIA) 2 179 2 182 0.6% Total events 22 7 Heterogeneity: Chi <sup>2</sup> = 2.86, df = 2 (P = 0.24); l <sup>2</sup> = 30% Test for overall effect: Z = 2.66 (P = 0.04); 5.1.8 Would Heding Aphajanian 2012 (OCEANS) 2 242 0 242 0.2% 5.00 [0.24, 103.61] Coleman 2015 (COC 213) 3 330 0 327 0.2% 6.94 (0.64 stimable Not estimable Not estimable Not estimable Subtotal (95% CD) 751 751 0.3% 5.97 [0.72, 49.45] Output - Unit 2014 (AURELIA) 0 179 0 182 Subtotal (95% CD) 751 751 0.3% 5.97 [0.72, 49.45] Output - Unit 2014 (AURELIA) 0 179 0 182 Subtotal (95% CD) 751 751 0.3% 5.97 [0.72, 49.45] Output - Unit 2014 (AURELIA) 0 179 0 182 Subtotal (95% CD) 751 751 0.3% 5.97 [0.72, 49.45] Output - Unit 2014 (AURELIA) 0 179 0 182 Subtotal (95% CD) 751 751 0.3% 5.97 [0.72, 49.45] Output - Unit 2014 (AURELIA) 0 179 0 182 Subtotal (95% CD) 751 751 0.3% 5.97 [0.72, 49.45] Output - Unit 2014 (AURELIA) 0 100 CT alore CT with Bezacizumable Output - Unit 2014 (AURELIA) 0 100 CT alore CT with Bezacizumable	Aghajanian 2012 (OCEANS)	10	242	6	242	1.8%	1.67 [0.62, 4.51]	
Pujade-Lauralne 2014 (AURELIA) 5 179 8 182 2.4% $0.64 [0.21, 1.91]$ Total events 20 16 Heterogeneity: Ch <sup>2</sup> = 2.45, df = 2 ( $P = 0.29$ ); l <sup>2</sup> = 18X Test for overall effect: 2 = 0.69 ( $P = 0.49$ ) <b>5.1.6 Arterial thromboembolic events</b> Aghajanian 2012 (OCEANS) 0 242 0 242 Not estimable Coleman 2012 (OCEANS) 0 242 0 242 Not estimable Coleman 2012 (OCEANS) 0 242 0 242 Not estimable Subtotal (95% CD) 751 751 0.8% 4.99 [1.29, 19.27] Total events 12 2 2 Heterogeneity: Ch <sup>2</sup> = 0.25, df = 1 ( $P = 0.62$ ); l <sup>2</sup> = 0.% Test for overall effect: 2 = 2.33 ( $P = 0.02$ ) <b>5.1.7 Bieeding</b> Aghajanian 2012 (OCEANS) 14 242 2 242 0.6% 7.00 [1.61, 30.47] Coleman 2012 (OCEANS) 14 242 2 242 0.6% 1.02 (0.14, 7.14] Subtotal (95% CD) 751 751 751 2751 2.2% 3.14 [1.35, 7.32] Total events 22 7 Heterogeneity: Ch <sup>2</sup> = 2.86, df = 2 ( $P = 0.24$ ); l <sup>2</sup> = 30X Test for overall effect: 2 = 2.66 ( $P = 0.0.08$ ) <b>5.1.8 Wound Healing</b> Aghajanian 2012 (OCEANS) 2 242 0 242 0.2% 5.00 [0.24, 103.61] Coleman 2012 (OCEANS) 2 242 0 242 0.2% 6.94 (0.36, 13.76] Coleman 2012 (OCEANS) 2 242 0 242 0.2% 6.94 (0.36, 13.76] Coleman 2012 (OCEANS) 2 242 0 242 0.2% 6.94 (0.36, 13.76] Pujade-Lauraine 2014 (AURELIA) 0 179 0 182 Not estimable Subtotal (95% CD) 751 751 0.3% 5.97 [0.72, 49.45] Total events 5 0 Heterogeneity: Ch <sup>2</sup> = 0.02, df = 1 ( $P = 0.88$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 ( $P = 0.10$ )	Coleman 2015 (GOG 213)	5	330	2	327	0.6%	2.48 [0.48, 12.68]	
Subtotal (95% CI) 751 751 751 751 4.9% 1.26 [0.66, 2.40] Total events 20 16 Heterogeneity: Ch <sup>2</sup> = 2.45, df = 2 ( $P = 0.29$ ); l <sup>2</sup> = 18% Test for overall effect: Z = 0.69 ( $P = 0.29$ ); l <sup>2</sup> = 18% Test for overall effect: Z = 0.69 ( $P = 0.29$ ); l <sup>2</sup> = 18% Total events 20 242 0 242 Not estimable Coleman 2015 (GOC 213) 8 330 2 327 0.6% 3.96 [0.55, 18.52] Total events 12 2 Heterogeneity: Ch <sup>2</sup> = 0.25, df = 1 ( $P = 0.62$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 2.66 ( $P = 0.08$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 2.66 ( $P = 0.08$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 ( $P = 0.88$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 ( $P = 0.88$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 ( $P = 0.88$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 ( $P = 0.88$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 ( $P = 0.88$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 ( $P = 0.88$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 ( $P = 0.88$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 ( $P = 0.88$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 ( $P = 0.88$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 ( $P = 0.88$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 ( $P = 0.10$ )	Pujade-Lauraine 2014 (AURELIA)	5	179	8	182	2.4%	0.64 [0.21, 1.91]	
Total events 20 16 Heterogeneity: Ch <sup>2</sup> = 2.45, df = 2 ( $P = 0.29$ ); l <sup>2</sup> = 1.8% Test for overall effect: Z = 0.69 ( $P = 0.49$ ) <b>5.1.6 Arterial thromboembolic events</b> Aghajanian 2012 (OCEANS) 0 242 0 242 Not estimable Coleman 2015 (GOC 213) 8 330 2 327 0.6% 3.96 [0.85, 18.52] Pujdet-Lauraine 2014 (AURELIA) 4 179 0 182 0.2% 9.15 [0.50, 168.72] Total events 12 7 Total events 12 7 <b>5.1.7 Biceding</b> Aghajanian 2012 (OCEANS) 14 242 2 242 0.6% 7.00 [1.61, 30.47] Coleman 2015 (GOC 213) 6 330 3 227 0.9% 1.98 [0.50, 7.66] Pujdet-Lauraine 2014 (AURELIA) 2 179 2 182 0.6% 7.00 [1.61, 30.47] Coleman 2015 (GOC 213) 6 330 3 227 0.9% 1.98 [0.50, 7.66] Pujdet-Lauraine 2014 (AURELIA) 2 179 2 182 0.6% 7.00 [1.61, 30.47] Total events 22 7 Total events 22 7 Heterogeneity: Ch <sup>2</sup> = 2.86, df = 2 ( $P = 0.24$ ); l <sup>2</sup> = 30% Test for overall effect: Z = 2.66 ( $P = 0.008$ ) <b>5.1.8 Wound Healing</b> Aghajanian 2012 (OCEAN5) 2 242 0 242 0.2% 5.00 [0.24, 103.61] Coleman 2015 (GOC 213) 3 330 0 327 0.2% 6.94 [0.36, 133.76] Pujdet-Lauraine 2014 (AURELIA) 0 179 0 182 Not estimable Subtotal (95% CD) 751 751 0.3% 5.97 [0.72, 49.45] Total events 5 7 Heterogeneity: Ch <sup>2</sup> = 0.02, df = 1 ( $P = 0.88$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 ( $P = 0.10$ ) Total events 5 7 Heterogeneity: Ch <sup>2</sup> = 0.02, df = 1 ( $P = 0.88$ ); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 ( $P = 0.10$ )	Subtotal (95% CI)		751		751	4.9%	1.26 [0.66, 2.40]	+
$\begin{array}{c} \text{Netrogeneity: Ch^{2} = 2.65 (p^{2} = 0.29) \\ \text{St. 56 Arterial thromboembolic events} \\ \text{Aphajanian 2012 (OCEANS) 0 242 0 242 Not estimable} \\ \text{Coleman 2015 (GOC 213) 8 330 2 327 0.6\% 3.96 [0.85, 18.52]} \\ \text{Pujade-Lauraine 2014 (AURELIA) 4 179 0 182 0.2\% 9.15 [0.50, 168.72]} \\ \text{Subtoral (95% CI) 751 751 0.8\% 4.99 [1.29, 19.27]} \\ \text{Total events 1 2 2 } \\ \text{Heterogeneity: Ch^{2} = 0.25, df = 1 (P = 0.62); l^{2} = 0\% \\ \text{Test for overall effect: Z = 2.33 (P = 0.02)} \\ \text{S.1.7 Bleeding } \\ Aphajanian 2012 (OCEANS) 14 242 2 242 0.6\% 7.00 [1.61, 30.47] \\ \text{Coleman 2015 (GOC 213) 6 330 3 227 0.9\% 1.98 [0.50, 7.66] \\ \text{Pujade-Lauraine 2014 (AURELIA) 2 179 2 182 0.6\% 1.02 [0.14, 7.14] \\ \text{Subtoral (95% CI) 751 751 751 22\% 3.14 [1.35, 7.32] 751 2.2\% 3.15 [1.3, 1.3, 7.6] 751 0.3\% 5.397 [0.72, 49.45] 751 0.3\% 5.397 [0.72, 49.45] 751 0.3\% 5.397 [0.72, 49.45] 751 0.3\% 5.397 [0.72, 49.45] 751 0.3\% 5.397 [0.72, 49.45] 751 0.3\% 751 0.3\% 5.397 [0.72, 49.45] 751 0.3\% 5.397 [0.72, 49.45] 751 0.3\% 751 0.3\% 5.397 [0.72, 49.45] 751 0.3\% 751 0.3\% 5.397 [0.72, 49.45] 751 0.3\% 751 0.3\% 5.397 [0.72, 49.45] 751 0.3\% 751 0.3\% 751 0.3\% 751 0.3\% 751 0.3\% 751 0.3\% 751 0.3\% 751 0.3\% 751 0.3\% 751 0.3\% 751 0.3\% 751 0.3\% 751 0.3\% 751 0.3\% 751 0.3\% 751 0.3\% 751 0.$	Total events	20	1 17 - 1 89	16				
S.1.6 Arterial thromboembolic events Aphajanian 2012 (OCEANS) 0 242 0 242 Not estimable Coleman 2015 (GOC 213) 8 330 2 327 0.6% 3.96 [0.85, 18, 52] Pujade-Lauraine 2014 (AURELIA) 4 179 0 182 0.2% 9.15 [0.50, 168, 72] Subtotal (95% C) 751 0.2% 4.99 [1.29, 19.27] Total events 1 2 2 Coleman 2012 (OCEANS) 14 242 2 242 0.6% 7.00 [1.61, 30.47] Coleman 2015 (GOC 213) 6 330 3 227 0.9% 1.98 [0.50, 7.86] Pujade-Lauraine 2014 (AURELIA) 2 179 2 182 0.6% 1.02 [0.14, 7, 14] Subtotal (95% C) 751 751 2.2% 3.14 [1.35, 7.32] Total events 2 2 7 Heterogeneity: $Ch^2 = 2.86$ , $df = 2 (P = 0.24)$ ; $l^2 = 30\%$ Test for overall effect: Z = 2.66 (P = 0.008) S.1.8 Wound Healing Aphajanian 2012 (OCEANS) 2 242 0 242 0.2% 5.00 [0.24, 103.61] Coleman 2015 (GOC 213) 3 330 0 327 0.2% 6.94 [0.36, 133.76] Pujade-Lauraine 2014 (AURELIA) 0 179 0 182 Not estimable Subtotal (95% C) 751 751 0.3% 5.97 [0.72, 49.45] Total events 5 5 0 Heterogeneity: $Ch^2 = 0.02$ , $df = 1 (P = 0.38)$ ; $l^2 = 0\%$ Test for overall effect: Z = 1.66 (P = 0.10) Total events 5 5 0 Heterogeneity: $Ch^2 = 0.02$ , $df = 1 (P = 0.38)$ ; $l^2 = 0\%$ Test for overall effect: Z = 1.66 (P = 0.10) (T alore CT with Bevacizumab	Test for overall effect: $Z = 0.69$ (P	r = 0.49	7,1 = 187	•				
5.1.6 Arterial thromboembolic events   Aghajanian 2012 (OCEANS) 0 242 Not estimable   Coleman 2015 (GOC 213) 8 330 2 327 0.6% 3.96 [0.85, 18.52]   Pujade-Lauraine 2014 (AURELIA) 4 179 0 182 0.2% 9.15 [0.50, 168.72]   Total events 12 2   Heterogeneity: Chi <sup>2</sup> = 0.25, df = 1 (P = 0.62); l <sup>2</sup> = 0.6 751 0.8% 4.99 [1.29, 19.27]   Soltotal (95% CI) 751 751 0.8% 4.99 [1.29, 19.27]   Soltotal (95% CI) 751 751 0.8% 1.98 [0.50, 7.86]   Pujade-Lauraine 2014 (AURELIA) 2 179 2 182 0.6% 1.02 [0.14, 7.14]   Subtotal (95% CI) 751 751 2.2% 3.14 [1.35, 7.32] 1.08 [0.30, 7.86]   Pujade-Lauraine 2014 (AURELIA) 2 7 182 0.6% 1.02 [0.14, 7.14] 1.09 [0.14, 7.14]   Subtotal (95% CI) 751 751 0.2% 5.00 [0.24, 103.61] 1.04 [0.36, 133.76]   Pujade-Lauraine 2014 (AURELIA) 0 179 0 182 Not estimable		- 0.157						
Aghajanian 2012 (OCEANS) 0 242 0 242 Not estimable Coleman 2015 (GOG 213) 8 330 2 327 0.6% 3.96 [0.85, 18.52] Pujade-Lauraine 2014 (AURELIA) 4 179 0 182 0.2% 9.15 [0.50, 168, 72] Subtotal (95% CI) 751 751 0.8% 4.99 [1.29, 19.27] Total events 12 Heterogeneity: Chi <sup>2</sup> = 0.25, df = 1 ( $P = 0.62$ ); $I^2 = 0.6$ Test for overall effect: Z = 2.33 ( $P = 0.02$ ) S.1.7 Bleeding Aghajanian 2012 (OCEANS) 14 242 2 242 0.6% 7.00 [1.61, 30.47] Coleman 2015 (GOC 213) 6 330 3 227 0.9% 1.98 [0.50, 7.86] Pujade-Lauraine 2014 (AURELIA) 2 179 2 182 0.6% 1.02 [0.14, 7.14] Total events 22 7 Heterogeneity: Chi <sup>2</sup> = 2.86, df = 2 ( $P = 0.24$ ); $I^2 = 30\%$ Test for overall effect: Z = 2.66 ( $P = 0.008$ ) S.1.8 Wound Healing Aghajanian 2012 (OCEANS) 2 242 0 242 0.2% 5.00 [0.24, 103.61] Coleman 2015 (GOC 213) 3 330 0 327 0.2% 6.94 [0.36, 133.76] Pujade-Lauraine 2014 (AURELIA) 0 179 0 182 Note estimable Subtotal (95% CI) 751 751 0.3% 5.97 [0.72, 49.45] Total events 5 0 Heterogeneity: Chi <sup>2</sup> = 0.02, df = 1 ( $P = 0.88$ ); $I^2 = 0\%$ Test for overall effect: Z = 1.66 ( $P = 0.10$ ) Test for overall effect: Z = 1.66 ( $P = 0.10$ )	5.1.6 Arterial thromboembolic e	vents						
Coleman 2015 (GOG 213) 8 330 2 327 0.6% 3.96 [0.85, 18.52] Puidet-Lauraine 2014 (AURELIA) 4 179 0 182 0.2% 9.15 [0.50, 168.72] Subtotal (95% CI) 751 751 0.8% 4.99 [1.29, 19.27] Total events 12 2 2 SL7 Bleeding Aghajanian 2012 (OCEANS) 14 242 2 242 0.6% 7.00 [1.61, 30.47] Coleman 2015 (GOG 213) 6 330 3 327 0.9% 1.98 [0.50, 7.86] Puidet-Lauraine 2014 (AURELIA) 2 179 2 182 0.6% 1.02 [0.14, 7.14] Subtotal (95% CI) 751 751 2.2% 3.14 [1.35, 7.32] Total events 2 2.266 (P = 0.008) SL8 Wound Healing Aghajanian 2012 (OCEANS) 2 242 0 244 0.2% 5.00 [0.24, 103.61] Coleman 2015 (GOG 213) 3 330 0 327 0.2% 6.94 [0.36, 133.76] Puidet-Lauraine 2014 (AURELIA) 0 179 0 182 Not estimable Subtotal (95% CI) 751 751 0.3% 5.97 [0.72, 49.45] Total events 5 0 Heterogeneity: Chi <sup>2</sup> = 0.02, df = 1 (P = 0.88); 1 <sup>2</sup> = 0% Test for overall effect: Z = 1.66 (P = 0.10)	Aghajanian 2012 (OCEANS)	0	242	0	242		Not estimable	
Pujade-Lauraine 2014 (AURELIA) 4 179 0 182 0.25 9.15 [0.30, 188.72] Total events 12 2 Heterogeneity: Chi <sup>2</sup> = 0.25, df = 1 (P = 0.62); l <sup>2</sup> = 0% Test for overall effect: Z = 2.33 (P = 0.02) <b>5.1.7 Bieeding</b> Aghajanian 2012 (OCEANS) 14 242 2 242 0.6% 7.00 [1.61, 30.47] Coleman 2015 (GCC 213) 6 330 3 327 0.9% 1.98 [0.50, 7.86] Pujade-Lauraine 2014 (AURELIA) 2 179 2 182 0.6% 1.02 [0.14, 7.14] Subtotal (95% CI) 751 751 2.2% 3.14 [1.35, 7.32] Total events 22 7 Heterogeneity: Chi <sup>2</sup> = 2.86, df = 2 (P = 0.24); l <sup>2</sup> = 30% Test for overall effect: Z = 2.66 (P = 0.008) <b>5.1.8 Wound Healing</b> Aghajanian 2012 (OCEANS) 2 242 0 242 0.2% 5.00 [0.24, 103.61] Coleman 2015 (GCG 213) 3 330 0 327 0.2% 6.94 [0.36, 133.76] Pujade-Lauraine 2014 (AURELIA) 0 179 0 182 Not estimable Subtotal (95% CI) 751 751 0.3% 5.97 [0.72, 49.45] Total events 5 0 Heterogeneity: Chi <sup>2</sup> = 0.02, df = 1 (P = 0.88); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 (P = 0.10) CT alore CT with Bevacizumab	Coleman 2015 (GOG 213)	8	330	2	327	0.6%	3.96 [0.85, 18.52]	
Subtraining (Strein) F31	Pujade-Lauraine 2014 (AURELIA) Subtotal (95% CI)	4	179	0	182	0.2%	9.15 [0.50, 168.72]	
$\begin{array}{c} \text{Notified of the constraints} \\ \text{Test for overall effect: } \mathbb{Z} = 2.33 \ (P = 0.25), \ df = 1 \ (P = 0.62); \ l^2 = 0\% \\ \text{Test for overall effect: } \mathbb{Z} = 2.33 \ (P = 0.02) \\ \hline \textbf{S.1.7 Bleeding} \\ \text{Aghajanian 2012 (OCEANS)} & 14 & 242 & 2 \\ \text{Aghajanian 2015 (GOC 213)} & 6 & 330 & 3 \\ \text{Pujade-Lauraine 2014 (AURELIA)} & 2 & 179 & 2 \\ \text{Pujade-Lauraine 2014 (AURELIA)} & 2 & 179 & 2 \\ \text{Test for overall effect: } \mathbb{Z} = 2.66 \ (P = 0.008) \\ \hline \textbf{S.1.8 Wound Healing} \\ \text{Aghajanian 2012 (OCEANS)} & 2 & 242 & 0 \\ \text{Coleman 2015 (GOC 213)} & 3 & 330 & 0 \\ \text{Subtoal (95% CI)} & 2 & 242 & 0 \\ \text{Subtoal (95% CI)} & 2 & 242 & 0 \\ \text{Subtoal (95% CI)} & 751 & 751 \\ \text{Total events} & 5 & 0 \\ \text{Heterogeneity: Chi^2 = 0.02, \ df = 1 \ (P = 0.88), \ l^2 = 0\% \\ \text{Test for overall effect: } \mathbb{Z} = 1.66 \ (P = 0.10) \\ \hline \end{array} $	Total events	12	/ 31	2	/ 31	0.075	4.55 [1.25, 1527]	
Test for overall effect: Z = 2.33 (P = 0.02) <b>5.1.7 Bleeding</b> Aghajanian 2012 (OCEANS) 14 242 2 242 0.6% 7.00 [1.61, 30.47] Coleman 2015 (GOG 213) 6 330 3 327 0.9% 1.98 [0.50, 7.86] Pujade-Lauraine 2014 (AURELIA) 2 179 2 182 0.6% 1.02 [0.14, 7.14] Subtotal (95% CI) 751 751 2.2% 3.14 [1.35, 7.32] Total events 22 7 Heterogeneity: Chi <sup>2</sup> = 2.86, df = 2 (P = 0.24); l <sup>2</sup> = 30% Test for overall effect: Z = 2.66 (P = 0.008) <b>5.1.8 Wound Healing</b> Aghajanian 2012 (OCEANS) 2 242 0 242 0.2% 5.00 [0.24, 103.61] Coleman 2015 (GOG 213) 3 330 0 327 0.2% 6.94 [0.36, 133.76] Pujade-Lauraine 2014 (AURELIA) 0 179 0 182 Not estimable Subtotal (95% CI) 751 751 0.3% 5.97 [0.72, 49.45] Total events 5 0 Heterogeneity: Chi <sup>2</sup> = 0.02, df = 1 (P = 0.88); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 (P = 0.10) CT alone CT with Bevacizumab	Heterogeneity: Chi <sup>2</sup> = 0.25, df = 3	1 (P = 0.62	$1^2 = 0\%$					
S.1.7 Bleeding   Aghajanian 2012 (OCEANS) 14 242 2 242 0.6% 7.00 [1.61, 30.47]   Coleman 2015 (GOG 213) 6 330 3 327 0.9% 1.98 [0.50, 7.86]   Pujade-Lauraine 2014 (AURELIA) 2 179 2 182 0.6% 1.02 [0.14, 7.14]   Subtoal (95% CI) 751 751 751 2.2% 3.14 [1.35, 7.32]   Total events 22 7   Heterogeneity: Chi <sup>2</sup> = 2.86, df = 2 (P = 0.24); l <sup>2</sup> = 30% 751 0.2% 5.00 [0.24, 103.61]   Coleman 2015 (GOG 213) 3 330 0 327 0.2% 5.00 [0.24, 103.61]   Coleman 2015 (GOG 213) 3 330 0 327 0.2% 5.00 [0.24, 103.61]   Coleman 2015 (GOG 213) 3 330 0 327 0.2% 5.97 [0.72, 49.45]   Subtotal (95% CI) 751 751 0.3% 5.97 [0.72, 49.45] 10   Total events 5 0 0 1 10 10   Vest for overall effect: Z = 1.66 (P = 0.10) 10 10 10 10	Test for overall effect: Z = 2.33 (P	= 0.02)						
S.1.7 Biecoling   Aghajanian 2012 (OCEANS) 14 242 2 242 0.6% 7.00 [1.61, 30.47]   Coleman 2015 (GCC 213) 6 330 3 327 0.9% 1.98 [0.50, 7.86]   Pujade-Lauraine 2014 (AURELIA) 2 179 2 182 0.6% 1.02 [0.14, 7.14]   Subtotal (95% CI) 751 751 2.2% 3.14 [1.35, 7.32]   Total events 22 7   Heterogeneity: Chi <sup>2</sup> = 2.86, df = 2 (P = 0.24); l <sup>2</sup> = 30% 7   Test for overall effect: Z = 2.66 (P = 0.008) 330 0 327 0.2% 5.00 [0.24, 103.61]   Subtotal (95% CI) 751 0.3% 5.97 [0.72, 49.45] 0.3% 5.97 [0.72, 49.45]   Pujade-Lauraine 2014 (AURELIA) 0 179 0 182 Not estimable   Subtotal (95% CI) 751 0.3% 5.97 [0.72, 49.45] 0.1 10 100   Coleman 2015 (GCC 213) 3 330 0 327 0.2% 5.97 [0.72, 49.45] 0.3% 5.97 [0.72, 49.45] 0.3%   Total events 5 0 0.1 1.0 <t< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>								
Aghajanian 2012 (OCLANS) 14 242 2 242 0.6% 7.00 [1.61, 30.47] Coleman 2015 (GOG 213) 6 330 3 327 0.9% 1.98 [0.50, 7.86] Pujade-Lauraine 2014 (AURELIA) 2 179 2 182 0.6% 1.02 [0.14, 7.14] Subtotal (95% CI) 751 751 2.2% 3.14 [1.35, 7.32] Total events 22 7 Heterogeneity: Chi <sup>2</sup> = 2.86, df = 2 (P = 0.24); l <sup>2</sup> = 30% Test for overall effect: Z = 2.66 (P = 0.008) S.1.8 Wound Healing Aghajanian 2012 (OCEANS) 2 242 0 242 0.2% 5.00 [0.24, 103.61] Coleman 2015 (GOC 213) 3 330 0 327 0.2% 6.94 [0.36, 133.76] Pujade-Lauraine 2014 (AURELIA) 0 179 0 182 Not estimable Subtotal (95% CI) 751 751 0.3% 5.97 [0.72, 49.45] Total events 5 0 Heterogeneity: Chi <sup>2</sup> = 0.02, df = 1 (P = 0.88); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 (P = 0.10) CT alone CT with Bevacizumab	5.1.7 Bleeding		2.02	~				
Comman 2013 (COC 213) 6 330 5 327 0.5% 1.98 [0.50, 7.86]   Pujade-Lauraine 2014 (AURELLA) 2 179 2 182 0.6% 1.02 [0.14, 7.14]   Subtotal (95% CI) 751 751 751 2.2% 3.14 [1.35, 7.32]   Total events 22 7   Heterogeneity: Chi <sup>2</sup> = 2.86, df = 2 (P = 0.24); l <sup>2</sup> = 30% 7   S.1.8 Wound Healing 4	Aghajanian 2012 (OCEANS)	14	242	2	242	0.6%	7.00 [1.61, 30.47]	
Total events 2 751 751 751 2.2% 3.14 [1.35, 7.32]   Total events 22 7   Heterogeneity: Chi <sup>2</sup> = 2.86, df = 2 (P = 0.24); l <sup>2</sup> = 30% 7   Test for overall effect: Z = 2.66 (P = 0.008) 7 7   S.1.8 Wound Healing 22 242 0.2% 5.00 [0.24, 103.61]   Coleman 2015 (GOG 213) 3 330 0 327 0.2% 6.94 [0.36, 133.76]   Pujade-Lauraine 2014 (AURELIA) 0 179 0 182 Not estimable   Subtotal (95% CI) 751 751 0.3% 5.97 [0.72, 49.45] 0.11   Total events 5 0 0 0.11 100 100   Heterogeneity: Chi <sup>2</sup> = 0.02, df = 1 (P = 0.88); l <sup>2</sup> = 0% 0 0.1 100 0.1 100   CT alone CT with Bevacizumab 0 0.1 100 100 0.1 100 100	Coleman 2015 (GOG 213) Pulade-Lauraine 2014 (AURELIA)	6	179	3	327	0.9%	1.98 [0.50, 7.86]	
Total events 22 7   Heterogeneity: Chi <sup>2</sup> = 2.86, df = 2 (P = 0.24); l <sup>2</sup> = 30% 7   Test for overall effect: Z = 2.66 (P = 0.008) 7   S.1.8 Wound Healing Aghajanian 2012 (OCEANS) 2 242 0 242 0.2% 5.00 [0.24, 103.61]   Coleman 2015 (GOG 213) 3 330 0 327 0.2% 6.94 [0.36, 133.76]   Pujade-Lauraine 2014 (AURELIA) 0 179 0 182 Not estimable   Subtotal (95% Cl) 751 751 0.3% 5.97 [0.72, 49.45] 10   Total events 5 0 0 10 100 100   Heterogeneity: Chi <sup>2</sup> = 0.02, df = 1 (P = 0.88); l <sup>2</sup> = 0% 751 0.3% 5.97 [0.72, 49.45] 10   Test for overall effect: Z = 1.66 (P = 0.10) 0.1 1 10 100	Subtotal (95% CI)	2	751	2	751	2.2%	3.14 [1.35, 7.32]	-
Heterogeneity: Chi <sup>2</sup> = 2.86, df = 2 (P = 0.24); l <sup>2</sup> = 30% Test for overall effect: Z = 2.66 (P = 0.008) <b>5.1.8 Wound Healing</b> Aghajanian 2012 (OCEANS) 2 242 0 242 0.2% 5.00 [0.24, 103.61] Coleman 2015 (GOG 213) 3 330 0 327 0.2% 6.94 [0.36, 133.76] Pujade-Lauraine 2014 (AURELIA) 0 179 0 182 Not estimable <b>Subtotal (95% CI)</b> 751 751 0.3% 5.97 [0.72, 49.45] Total events 5 0 Heterogeneity: Chi <sup>2</sup> = 0.02, df = 1 (P = 0.88); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 (P = 0.10)	Total events	22		7				
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Subtotal (95% Cl) 751 751 0.3% 5.97 [0.72, 49.45] Total events 5 0 Heterogeneity: Chi <sup>2</sup> = 0.02, df = 1 (P = 0.88); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 (P = 0.10)	Puiade-Lauraine 2014 (AURFLIA)	0	179	0	182	0.2%	Not estimable	
Total events 5 0 Heterogeneity: Chi <sup>2</sup> = 0.02, df = 1 (P = 0.88); l <sup>2</sup> = 0% Test for overall effect: Z = 1.66 (P = 0.10)	Subtotal (95% CI)		751		751	0.3%	5.97 [0.72, 49.45]	
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Test for overall effect: Z = 1.66 (P = 0.10)	Heterogeneity: Chi <sup>2</sup> = 0.02, df = 3	1 (P = 0.88)	$3); I^2 = 0\%$					
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CT alone CT with Bevacizumab								
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# Figure 5: Forest plot for toxicity.

platinum-resistant OC patients form the AURELIA trial receiving bevacizumab plus chemotherapy showed a response rate of more than 30%, and significant prolongation of PFS but also a 15% improvement in abdominal and gastrointestinal symptoms, significantly greater than in the chemotherapy group (21.9% versus 9.3%, 95% CI: 4.4 - 20.9, p = 0.002) [9]. Therefore it might be speculate that the adjunct of bevacizumab has not any detrimental effect in terms of QoL; conversely, it might have a positive effect in those with the greatest symptomatology, as the platinum resistant group of patients.

In terms of toxicity, we have analyzed G3/G4 toxicities as we focused on those toxicities that might have been disadvantageous in terms of outcomes and QoL. Overall, there were more side effects in the group that used bevacizumab-containing regimen but all remained within expected parameters and also toxicities were all manageable. Interestingly, should be noticed that toxicity data from the GOG 213, which included approximately 10% of women who had previously received bevacizumab, are in agreement with those previously published, with an higher occurrence of G3/G4 thromboembolisms, hypertension and proteinuria compared with standard arm. As there is an increase in toxicity, attention should be given to patients that have an increased risk of bleeding, recent or current use of aspirin or oral and/or parenteral anticoagulants. Hypertension and proteinuria are usually controllable events and do not require permanent discontinuation of bevacizumab.

Finally, we also presented data about OS, which were not mature when previous meta-analysis have been published. The addition of bevacizumab was associated with a small but significant improvement in OS (HR:0.87; 95% CI 0.77 - 0.99). When considering only platinum sensitive patients, the analysis points again to a benefit of chemotherapy plus bevacizuamb, although in a different extent (HR 0.88, 95% CI, 0.76 - 1.02).

Remarkably, it should be pointed out that AURELIA and OCEANS trials were designed and powered to evaluate PFS and not OS as primary end-point; conversely, GOG 213 trial had OS as primary end-point and narrowly missed the significance (p = 0.056). Nonetheless, when it was designed in 2007 the superiority of adding the angiogenesis inhibitor was not still proven and therefore investigators used two-tailed statistical analysis. But currently, as bevacizuamb's knowledge has increased, it is more common to use a one-tailed test, which would have allowed the significance to be reached. Moreover, the estimated median OS of control arm was fixed to 22 months and this underestimation might have contribute to the trial to miss the statistical cut-off.

This trend was found also when considering only sensitive disease but without clear significance, suggesting that further prospective studies are needed to investigate if OS could be improved through bevacizumab plus standard chemotherapy in some selected population. Furthermore, even if no definitive evaluation of the usefulness of bevacizumab beyond chemotherapy can be made within the current meta-analysis, should be underlined that in all 3 studies, differently from randomized studies in the first-line setting in which no global OS benefit was found [1–2], bevacizumab was administered as monotherapy until disease progression or unacceptable toxicity in those patients who did not progress during the protocol of the six cycles of combination. This might be of interest in the debate concerning the length of administration of this compound, which is the object of several trials (BOOST trial, NCT01462890; MITO16/ MANGO2b trial; NCT01802749) currently ongoing in the first line setting.

Our analysis was limited by its use of summary data rather than data from the individual patients from each trial. Individual patient data are needed to better account for the control arm, to standardize the analysis to perform an intent-to-treat analysis, to draw survival curves, to perform a more complete analysis of the variation of treatment effects according to patient. It was originally intended that this summary level analysis would be followed by an analysis of individual patient data from the eligible trials but, ultimately, this has not been possible.

Further trials are needed, which should also consider the QoL as well as the cost of bevacizumab plus chemotherapy combination in the recurrent setting; moreover the next challenge is to identify those biomarkers that might allow to better define the subgroup population who may benefit at most of this compound.

# **MATERIALS AND METHODS**

# Data collection and trials selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed to perform the meta-analysis. It includes randomized clinical trials, written in English, without any restrictions on publication date. The last search was done on July 2015. Literature electronic databases (Pubmed, Medline and Scopus) were searched for "recurrent", "ovarian cancer" and "bevacizumab" in the title. Trials that compared bevacizumab plus chemotherapy administration to standard chemotherapy alone in women with recurrent OC were eligible. To reduce publication bias, data from all clinical randomized trials, both published and unpublished, were included using literature electronic databases searching (Pubmed, Medline and Scopus) and hand searching (meeting proceedings of Society of Gynecologic Oncology, European Society of Medical Oncology and American Society of Clinical Oncology). Reference lists of previously published reviews and metaanalyses were explored. Review articles, case reports, commentaries and letters were not included.

Two independent investigators (CM and FDF) selected the identified studies based on the title and abstract. If the study's topic could not be ascertained from its title or abstract, the full-text version would be retrieved for evaluation. Disagreement was resolved by discussion or consensus or with a third party (LM).

Trials were eligible if patients had a proven OC recurrence. In the closer evaluation of potentially eligible articles, when two articles appeared to report results with overlapping data, only the data representing the most recent publication date were included in the meta-analysis. From all including studies were extracted: first author's last name, publication year, the study name, sample size of cases and controls, regimen used, data on PFS, OS, objective response rate (ORR) and acute toxicities  $\geq$  G3. Update information on survival and date of last follow-up were requested.

## **End-points**

End-points were the PFS, defined as the time from random assignment to progression disease or death, the OS, defined as the time from randomization to death, the objective response rate (ORR) and toxicity. The hazard ratios (HR) and 95% confidence interval (CI) for PFS and OS were derived from each study; whereas for ORR and toxicities were derived the odd ratios (OR) and risk ratios (RR), respectively.

The toxicities analyzed were graded > 2 and were gastrointestinal (GI), hypertension, proteinuria, venous thromboembolic events (VTE), arterial thromboembolic events (ATE), bleeding, would healing and neutropenia. If the grade  $\geq$  3 adverse events were not directly provided in the text, they were estimated resulting from data in the appropriate Figure/Table.

# Statistical analysis

Statistical analysis of pooled ORR, PFS, OS and toxicities were performed using Review manager 5.0 software (http://www.cochrane.org). The pooled HR, OR and RR were calculated using a fixed or random effect models, depending on heterogeneity. Forest plot were used for graphical representation of each study and pooled analysis.

The size of every box represents the weight that the corresponding study exerts in the meta- analysis; CI of each study are displayed as horizontal line through the box. The pooled HR, OR and RR are symbolized by a solid diamond at the bottom of the forest plot and the width of the square represents the 95% CI of HR.

HR, OR, RR and 95% CI for each study were extracted or calculated based on the published studies according to the methods described by Tierney in 2007 [10]. A significant two-way *p*-value for comparison was defined as p < 0.05. The size of the square represents the weight

that the corresponding study exerts in the meta-analysis. Statistical heterogeneity between studies was examined using both the Cochrane Q statistic (significant at p < 0.1) and the P value (significant heterogeneity if > 50%) [11]. Publication bias was examined using analyses described by Egger and Begg [12–13].

# CONCLUSION

This meta-analysis of randomized studies indicates that integrate bevacizumab in the standard treatment for patients with recurrent OC prolongs PFS and OS, without unexpected toxicity patterns.

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None.

# **CONFLICTS OF INTEREST**

The authors have declared no conflicts of interest.

# REFERENCES

- Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, Carey MS, Beale P, Cervantes A, Kurzeder C, du Bois A, Sehouli J, Kimmig R, et al. ICON7 Investigators. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011; 365:2484–96.
- Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, Mannel RS, Homesley HD, Fowler J, Greer BE, Boente M, Birrer MJ, Liang SX. Gynecologic Oncology Group. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011; 365:2473–83.
- Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, Sovak MA, Yi J, Nycum LR. 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; 30:2039–45.
- 4. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, Sorio R, Vergote I, Witteveen P, Bamias A, Pereira D, Wimberger P, Oaknin A, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol. 2014; 32:1302–8.
- Coleman RL, et al. GOG213. Presented at: Society of Gynecologic Oncology 2015 Annual Meeting on Women's Cancer; March 28–31, 2015; Chicago, Illinois. Abstract 3.
- Zhou M, Yu P, Qu X, Liu Y, Zhang J. Phase III trials of standard chemotherapy with or without bevacizumab for ovarian cancer: a meta-analysis. PLoS One. 2013; 8:e81858.

- 7. Ye Q, Chen HL. Bevacizumab in the treatment of ovarian cancer: a meta-analysis from four phase III randomized controlled trials. Arch Gynecol Obstet. 2013; 288:655–66.
- Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? J Clin Oncol. 2012; 30:1030–3.
- Stockler MR, Hilpert F, Friedlander M, King MT, Wenzel L, Lee CK, Joly F, de Gregorio N, Arranz JA, Mirza MR, Sorio R, Freudensprung U, Sneller V, et al. Patient-reported outcome results from the open-label phase III AURELIA trial evaluating bevacizumab-containing therapy for platinum-resistant ovarian cancer. J Clin Oncol. 2014; 32:1309–16.
- Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007; 8:16.
- Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327:557–560.
- Egger M, Davey SG, Schneider M, Minder C. Bias in metaanalysis detected by a simple, graphical test. BJM. 1997; 315:629–634.
- Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50:1008–1101.