KCE REPORT 285S

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Center

BEVACIZUMAB IN THE TREATMENT OF OVARIAN CANCER

APPENDIX

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KCE REPORT 285S
HEALTH TECHNOLOGY ASSESSMENT

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
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BEVACIZUMAB IN THE TREATMENT OF OVARIAN CANCER

APPENDIX

MATTIAS NEYT, STEPHAN DEVRIESE, CÉCILE CAMBERLIN, JOAN VLAYEN

2017 www.kce.fgov.be

COLOPHON

Title:	Bevacizumab in the treatment of ovarian cancer – Supplement
Authors:	Mattias Neyt (KCE), Stephan Devriese (KCE), Cécile Camberlin (KCE), Joan Vlayen (KCE)
Project coordinator:	Sabine Stordeur (KCE)
Edit summary	Gudrun Briat (KCE), Karin Rondia (KCE), Sabine Stordeur (KCE)
Reviewers:	Raf Mertens (KCE), Caroline Obyn (KCE), Leen Verleye (KCE)
External experts:	Joseph Kerger (Institut Jules Bordet, Bruxelles), Frédéric Kridelka (CHU Liège), Ignace Vergote (UZ Leuven), Peter Vuylsteke (Clinique et Maternité Sainte-Elisabeth Namur)
Stakeholders:	Caroline Lebbe (Landsbond der Christelijke Mutualiteiten – Alliance Nationale des Mutualités Chrétiennes), Ward Rommel (Kom op tegen kanker), Didier Vander Steichel (Fondation contre le cancer), Chris Van Hul (Landsbond van de Onafhankelijke Ziekenfondsen – Union Nationale des Mutualités Libres), Anne Vergison (Union Nationale des Mutualités Socialistes – Nationaal Verbond van Socialistische Mutualiteiten), Anouk Waeytens (RIZIV – INAMI)
External validators:	Keith Cooper (Southampton Health Technology Assessments Centre, Royaume-Uni), Isabelle Ray-Coquard (Université Claude Bernard Lyon, France), Nick Reeds (Beatson Oncology Centre-Gartnavel General Hospital, Royaume-Uni)
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Other reported interests:	Membership of a stakeholder group on which the results of this report could have an impact.: Anne Vergison (Membre de Solidaris – Mutualités Socialistes), Ignace Vergote (KULeuven), Peter Vuylsteke (Investigateur de l'étude AURELIA), Isabelle Ray-Coquard (GINECO group, GCIG, ENGOT) Owner of subscribed capital, options, shares or other financial instruments: Ignace Vergote (KULeuven) Fees or other compensation for writing a publication or participating in its development: Ignace Vergote (KULeuven) Owner of intellectual property rights (patent, product developer, copyrights, trademarks, etc.): Ignace Vergote (KULeuven)

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Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Chris Van Hul (Membre du Groupe de travail « Article 81 »), Ignace Vergote (KULeuven), Anouk Waeytens (expert interne pour la Commission de Remboursement des Médicaments [CRM – INAMI] et membre du Groupe de travail « Article 81 »)

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- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**
- **Finally, this report has been approved by common assent by the Executive Board.**
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1. SEARCH STRATEGIES

1.1. Medical part

Date	24-11-2015
Database	Medline
Search Strategy	1 (ovar$ adj5 neoplas$).tw. (2919) 2 (ovar$ adj5 cancer$).tw. (42374) 3 (ovar$ adj5 carcin$).tw. (17731) 4 (ovar$ adj5 tumo$).tw. (21172) 5 (ovar$ adj5 metasta$).tw. (4110) 6 (ovar$ adj5 malig$).tw. (6782) 7 exp Ovarian Neoplasms/ (69206) 8 or/1-7 (86112) 9 (bevacizumab or avastin).mp. (10409) 10 8 and 9 (454)
Note	

Date	24-11-2015
Database	Embase
Search Strategy	#1 (ovar* NEAR/5 neoplas*):ab,ti OR (ovar* NEAR/5 cancer*):ab,ti OR (ovar* NEAR/5 carcin*):ab,ti OR (ovar* NEAR/5 tumo*):ab,ti OR (ovar* NEAR/5 metasta*):ab,ti OR (ovar* NEAR/5 malig*):ab,ti (91409) #2 'ovary cancer'/exp (83893) #3 #1 OR #2 (118419) #4 'bevacizumab'/exp (37647) #5 avastin:ab,ti (1694) #6 #4 OR #5 (37707) #7 #3 AND #6 (2741) #8 #7 AND ([cochrane review]/lim OR [systematic review]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) (98)
Note	

Date	24-11-2015
Database	Cochrane Library
Search Strategy	#1 (ovar* and (neoplas* or cancer$ or tumo* or carcin* or metasta* or malig*)):ti,ab #2 MeSH descriptor: [Ovarian Neoplasms] 1 tree(s) exploded #3 #1 or #2 #4 (avastin or bevacizumab):ti,ab #5 #3 and #4
Note	CDSR: N=1 CENTRAL: N=73 DARE: N=4 HTA: N=4

1.2. Economic part

In February 2016, the websites of HTA institutes (Table 1) were searched using free text (bevacizumab, avastin, ovarian, peritoneal, fallopian). The combination of these words depended on the number of hits and was determined in a pragmatic way. E.g. if there were no hits with bevacizumab or avastin, the search was stopped. If a limited number of results was found, the references were looked at to identify relevant reports. If the number of hits per website was high from a pragmatic point of view, a combination with ovarian or peritoneal or fallopian was applied.

Table 1 – List of INAHTA member websites searched for HTA reports

Abbreviation	Institute	Country
AETS	Agencia de Evaluación de Tecnologias Sanitarias	Spain
AETSA	Andalusian Agency for Health Technology Assessment	Spain
AGENAS	The Agency for Regional Healthcare	Italy
AHRQ	Agency for Healthcare Research and Quality	USA
AHTA	Adelaide Health Technology Assessment	Australia
AHTAPol	Agency for Health Technology Assessment in Poland	Poland
AQuAS	Agència de Qualitat i Avaluació Sanitàries de Catalunya	Spain
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	Australia
ASSR	Agenzia Sanitaria e Sociale Regionale (Regional Agency for Health and Social Care)	Italy
AVALIA-T	Galician Agency for Health Technology Assessment	Spain
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada
CDE	Center for Drug Evaluation	Taiwan
CEDIT	Comité d'Évaluation et de Diffusion des Innovations Technologiques	France
CEM	Inspection générale de la sécurité sociale (IGSS), Cellule d'expertise médicale	Luxembourg
CENETEC	Centro Nacional de Excelencia Tecnológica en Salud Reforma	Mexico
CONITEC	National Committee for Technology Incorporation	Brazil
CMeRC	Department of Internal Medicine	South Africa
CRD	Centre for Reviews and Dissemination	United Kingdom
DAHTA @DIMDI	German Agency for HTA at the German Institute for Medical Documentation and Information	Germany
DECIT-CGATS	Secretaria de Ciëncia, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia	Brazil
ETESA	Department of Quality and Patient Safety of the Ministry Health of Chile	Chile
FinOHTA	Finnish Office for Health Care Technology Assessment	Finland
G-ba	The German Health Care System and the Federal Joint Committee	Germany
GÖG	Gesundheit Österreich	Austria
HAD-MSP	Health Assessment Division, Ministry of Public Health	Uruguay
HAS	Haute Autorité de Santé	France
HCT-NHSRC	Division of Healthcare Technology, National Health Systems Resource Center	India
HealthPACT	Health Policy Advisory Committee on Technology	Australia
HIQA	Health Information and Quality Authority	Ireland
HIS	Healthcare Improvement Scotland	United Kingdom
HQO	Evidence Development and Standards Branch	Canada
HSAC	Health Services Assessment Collaboration	New Zealand
HTA-HSR/DHTA	HTA & Health Services Research	Denmark
IECS	Institute for Clinical Effectiveness and Health Policy	Argentina
IETS	Instituto de Evaluación Tecnológica en Salud	Colombia
IHE	Institute of Health Economics	Canada

Abbreviation	Institute	Country
INESSS	Institut national d'excellence en santé et en services sociaux	Canada
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE	Belgian Federal Health Care Knowledge Centre	Belgium
LBI of HTA	Ludwig Boltzmann Institut für Health Technology Assessment	Austria
MaHTAS	Health Technology Assessment Section at Ministry of Health of Malaysia	Malaysia
MTU-SFOPH	Medical Technology Unit - Swiss Federal Office of Public Health	Switzerland
NECA	National Evidence-based healthcare Collaboration Agency	Korea
NHC	New Zealand National Health Committee	New Zealand
NHMRC CTC	NHMRC Clinical Trials Centre	Australia
NIHR	National Institute for Health Research	United Kingdom
NOKC	Norwegian Knowledge Centre for Health Services	Norway
OSTEBA	Basque Office for Health Technology Assessment	Spain
RCHD-CS	Ministry of Public Health of the Republic of Kazakhstan, Republican Centre for Health Development, Centre of Standardization, HTA department	Kazakhstan
SBU	Swedish Council on Technology Assessment in Health Care	Sweden
UCEETS	The National Coordination Unit of Health Technology Assessment and Implementation	Argentina
UVT	HTA Unit in A. Gemelli University Hospital	Italy
VASPVT	State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania	Lithuania
ZIN	Zorginstituut Nederland	The Netherlands
ZonMw	The Medical and Health Research Council of The Netherlands	The Netherlands
Selection of ex or non-member websites		
CHE	Centre for Health Economics	United Kingdom
CMT	Center for Medical Technology Assessment	Sweden
EUnetHTA	European Network for HealthTechnology Assessment	Europe
NICE	National Institute for Health and Care Excellence	United Kingdom
PHARMAC	Pharmaceutical Management Agency	New Zealand

The following databases were searched in September 2016: Centre for Reviews and Dissemination (CRD) databases (NHS Economic Evaluation Database (NHS EED) and Health Technology Assessments (HTA)), Medline, and Embase. Table 2 up to Table 6 provide an overview of the applied search strategies.

Table 2 – Search strategy and results for CRD: HTA

Date	**25 September 2016**		
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Ovarian Neoplasms EXPLODE ALL TREES	322
	2	(bevacizumab)	266
	3	(avastin)	48

	4	#2 OR #3	269
	5	* IN HTA	16 565
	6	#1 AND #4	13
	7	#5 AND #6	**3 references**
Note	We also used the "MeSH DESCRIPTOR Bevacizumab EXPLODE ALL TREES" instead of 'bevacizumab' or 'avastin'. The latter approach with free text words was preferred since it identified more potentially relevant references.		

Table 3 – Search strategy and results for CRD: NHS EED

Date	**25 September 2016**		
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Ovarian Neoplasms EXPLODE ALL TREES	322
	2	(bevacizumab)	266
	3	(avastin)	48
	4	#2 OR #3	269
	5	* IN NHSEED	17 613
	6	#1 AND #4	13
	7	#5 AND #6	**6 references**
Note	We also used the "MeSH DESCRIPTOR Bevacizumab EXPLODE ALL TREES" instead of 'bevacizumab' or 'avastin'. The latter approach with free text words was preferred since it identified more potentially relevant references.		

Table 4 – Search strategy and results for Medline (OVID) (part I)

Date	**2 October 2016**		
Date covered	Ovid MEDLINE(R) without Revisions1996 to September Week 3 2016		
Search Strategy	1	economics/	6295
	2	exp "Costs and Cost Analysis"/	139 083
	3	"Value of Life"/ec [Economics]	234
	4	Economics, Dental/	202
	5	exp Economics, Hospital/	12 792
	6	Economics, Medical/	1854
	7	Economics, Nursing/	577
	8	Economics, Pharmaceutical/	2280
	9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	151 644
	10	(econom$ or cost$ or pric$ or pharmacoeconomic$).tw.	426 458
	11	(expenditure$ not energy).tw.	14 846
	12	(value adj1 money).tw.	17
	13	budget$.tw.	13 924
	14	10 or 11 or 12 or 13	440 535
	15	9 or 14	496 823
	16	letter.pt.	591 118
	17	editorial.pt.	307 061
	18	historical article.pt.	149 210
	19	16 or 17 or 18	1 034 647
	20	15 not 19	473 602
	21	Animals/	3 169 772
	22	human/	9 037 446
	23	21 not (21 and 22)	2 041 038
	24	20 not 23	429 892

	25	(metabolic adj cost).ti,ab,sh.	711
	26	((energy or oxygen) adj cost).ti,ab,sh.	1864
	27	24 not (25 or 26)	427 898
	28	(bevacizumab or avastin).mp.	10 843
	29	27 and 28	**429 references**
Note	The above search strategy was also extended by adding the following search terms related to the Patient in the PICO. #30 (ovar$ adj5 neoplas$).tw. 1685 #31 (ovar$ adj5 cancer$).tw. 34230 #32 (ovar$ adj5 carcin$).tw. 11744 #33 (ovar$ adj5 tumo$).tw. 13584 #34 (ovar$ adj5 metasta$).tw. 3064 #35 (ovar$ adj5 malig$).tw. 4425 #36 exp Ovarian Neoplasms/ 44096 #37 30 or 31 or 32 or 33 or 34 or 35 or 36 56722 #38 29 and 37 31 Adding these search terms (#30-€37) was considered to be too strict (only 31 identified references). Going through the title, abstract and keywords of 429 references was judged to be practically acceptable. Therefore, this more sensitive search strategy was selected.		

Table 5 – Search strategy and results for Medline (OVID) (part II)

Date	**2 October 2016**		
Date covered	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present		
Search Strategy	1	cost$.mp.	531 586
	2	economic$.mp.	254 508
	3	budget$.mp.	28 776
	4	expenditure$.mp.	56 772
	5	1 or 2 or 3 or 4	766 578
	6	(bevacizumab or avastin).mp.	13 148
	7	5 and 6	580
	8	(ovar$ adj5 neoplas$).tw.	3227
	9	(ovar$ adj5 cancer$).tw.	48 569
	10	(ovar$ adj5 carcin$).tw.	19 616
	11	(ovar$ adj5 tumo$).tw.	23 711
	12	(ovar$ adj5 metasta$).tw.	4753
	13	(ovar$ adj5 malig$).tw.	7643
	14	8 or 9 or 10 or 11 or 12 or 13	75 980
	15	7 and 14	**43 references**
Note	For our search strategy in the 'In-Process & Other Non-Indexed Citations', it was preferred to add search terms referring to the patient in our search strategy.		

Table 6 – Search strategy and results for EMBASE

Date	**2 October 2016**		
Date covered	All		
Search Strategy	1	socioeconomics'/exp	209 108
	2	cost benefit analysis'/exp	71 294
	3	cost effectiveness analysis'/exp	117 494
	4	cost of illness'/exp	15 945
	5	cost control'/exp	56 509
	6	economic aspect'/exp	1 294 654
	7	financial management'/exp	349 152
	8	health care cost'/exp	236 632
	9	health care financing'/exp	12 068
	10	health economics'/exp	701 828
	11	hospital cost'/exp	30 174
	12	finance'/exp OR 'funding'/exp OR fiscal OR financial	217 369
	13	cost minimization analysis'/exp	2848
	14	cost*:de,cl,ab,ti	795 164
	15	estimate*:de,cl,ab,ti	867 876
	16	variable*:de,cl,ab,ti	815 806
	17	unit:de,cl,ab,ti	502 013
	18	#14' NEAR/1 '#15' OR '#15' NEAR/1 '#14'	102 388
	19	#14' NEAR/1 '#16' OR '#16' NEAR/1 '#14'	252 974
	20	#14' NEAR/1 '#17' OR '#17' NEAR/1 '#14'	50 081
	21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #18 OR #19 OR #20	1 719 993
	22	(ovar* NEAR/5 neoplas*):ab,ti OR (ovar* NEAR/5 cancer*):ab,ti OR (ovar* NEAR/5 carcin*):ab,ti OR (ovar* NEAR/5 tumo*):ab,ti OR (ovar* NEAR/5 metasta*):ab,ti OR (ovar* NEAR/5 malig*):ab,ti	99 928
	23	'ovary cancer'/exp	91 643
	24	#22 OR #23	126 568
	25	'bevacizumab'/exp	41 281
	26	avastin:ab,ti	1805
	27	#25 OR #26	41 348
	28	#24 AND #27	3004
	29	#21 AND #28	**446 references**
Note			

After removal of all duplicates, a total of 858 extra references were identified (Table 7).

Table 7 – Results of search strategy

Database	
CRD HTA	3
CRD NHS EED	6
Medline	429
Medline In-Process & Other	43
Embase	446
Total (incl. duplicates)	**927**
Duplicates	69
Total (excl. duplicates)	**858**

2. SELECTION RESULTS

On November 24, 2015 a search was performed to identify publications regarding the use of bevacizumab in women with ovarian cancer. MEDLINE (including PreMedline), Embase and the Cochrane Library were searched.

634 potential relevant references were identified (Figure 1). After de-duplication and removing references published in an excluded language (other than English, French and Dutch) 504 references remained. Based on title and abstract 452 references were excluded. Of the remaining 52 references, 20 references were included based on full-text evaluation and 32 references were excluded with reason (Table 8).

HTA websites were also searched, and two additional HTA reports were identified.[1, 2]

In total, 12 systematic reviews / HTA reports were included,[1-12] and 10 references concerning 5 different RCTs:

- AURELIA[13, 14]
- GOG-0218[15-17]
- ICON7[18-20]
- OCEANS[21]
- Zhao et al.[22]

Figure 1 – Study flow of selection

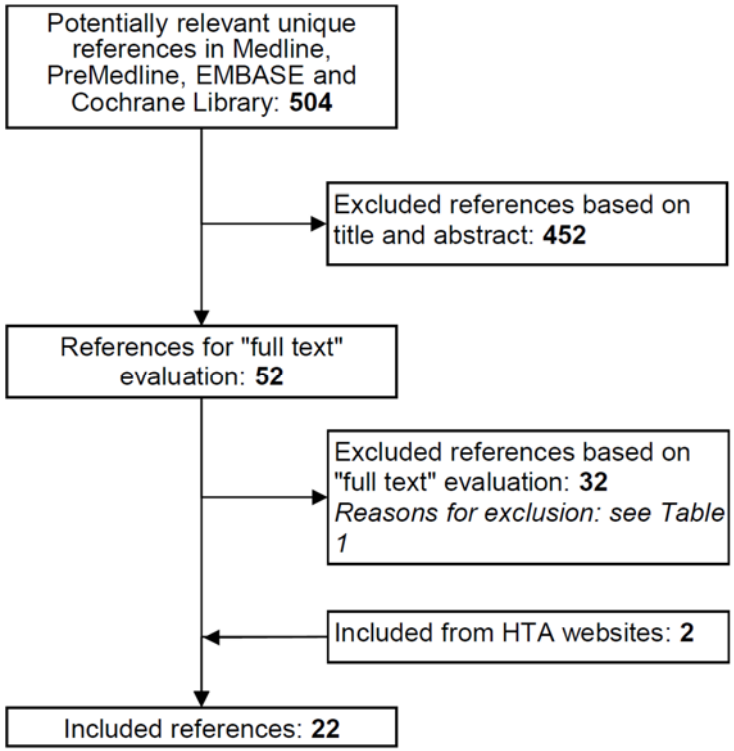


Table 8 – Excluded references

Reference	Reason for exclusion
Bevacizumab (Avastin) for advanced metastatic ovarian cancer (Structured abstract). Health Technology Assessment Database. 2009(4).	No methods described
Abu-Hejleh T, Mezhir JJ, Goodheart MJ, Halfdanarson TR. Incidence and management of gastrointestinal perforation from bevacizumab in advanced cancers. Curr Oncol Rep. 2012;14(4):277-84.	Narrative review
Aghajanian C, Blank S, Goff B, Judson P, Nycum L, Sovak M. Results from a 2nd interim OS analysis in OCEANS: a randomized phase 3 trial of gemcitabine (G), carboplatin (C) and bevacizumab (BV) followed by BV to disease progression in patients with platinum-sensitive recurrent epithelial ovarian (OC), primary peritoneal (PPC), or fallopian tube cancer (FTC. Gynecologic oncology. 2012;125(3):773.	Abstract
Aghajanian C, Blank SV, Goff B, Judson PL, Makhija S, Sharma SK, et al. Efficacy in patient subgroups in OCEANS, a randomized, doubleblinded, placebo-controlled, phase 3 trial of chemotherapy + bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian (OC), Primary Peritoneal (PPC), or Fallopian Tube Cancer (FTC). European journal of cancer. 2011;47:5.	Abstract
Aghajanian C, Blank SV, Goff BA, Judson PL, Nycum LR, Sovak MA, et al. An updated safety analysis of OCEANS, a randomized, double-blind, phase III trial of gemcitabine (G) and carboplatin (C) with bevacizumab (BV) or placebo (PL) followed by BV or PL to disease progression (PD) in patients with platinum-sensitive (Plat-S) recurrent ovarian cancer. Journal of clinical oncology. 2012;30(15 SUPPL. 1).	Abstract
Aghajanian C, Finkler NJ, Rutherford T. OCEANS: a randomized, double-blinded, placebo-controlled phase III trial of chemotherapy with or without bevacizumab (BEV) in patients with platinum-sensitive recurrent epithelial ovarian (EOC), primary peritoneal ((PPC), or fallopian tube cancer (FTC). Clinical journal of oncology: ASCO annual meeting proceedings. 2011;29(suppl):Abstract LBA5007.	Abstract
Burger RA, Brady MF, Bookman MA, Walker JL, Homesley HD, Fowler J. Phase III trial of bevacizumab (BEV) in the primary treatment od advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group Study. Journal of Clinical Oncology. 2010;28(18 Suppl):5.	Abstract
Chan J, Brady M, Penson R, Monk B, Boente M, Walker J, et al. Phase III trial of every-3-weeks paclitaxel vs. Dose dense weekly paclitaxel with carboplatin +/-bevacizumab in epithelial ovarian, peritoneal, fallopian tube cancer: Gog 262 (nct01167712). International journal of gynecological cancer. 2013;23(8 SUPPL. 1):9-10.	Abstract
Dyer M, Richardson J, Robertson J, Adam J. NICE guidance on bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of advanced ovarian cancer. Lancet Oncol. 2013;14(8):689-90.	Comment on NICE guidance
Faruque L.I, Lin M, Battistella M, Wiebe N, Reiman T, Hemmelgarn B, et al. Systematic review of the risk of adverse outcomes associated with vascular endothelial growth factor inhibitors for the treatment of cancer. PLoS ONE. 2014;9(7).	No specific results for ovarian cancer
Garcia K, Ranganathan A, Coleman RL. Addition of bevacizumab to paclitaxel/carboplatin in first-line management of advanced ovarian cancer: Results of the GOG 0218 phase III study. Clinical Ovarian Cancer. 2010;3(2):E1-E5.	Comment
Havrilesky LJ, Abernethy AP. Quality of life in ICON7: need for patients' perspectives. Lancet Oncol. 2013;14(3):183-5.	Comment

Reference	Reason for exclusion
Hayes, Inc. Avastin (bevacizumab) for the treatment of ovarian cancer (Structured abstract). Health Technology Assessment Database. 2008(4).	Not available
Hilpert F, Fabbro M, Jesus RM. Symptoms and adverse effects with chemotherapy +/- bevacizumab for platinum-resistant recurrent ovarian cancer: Analysis of the phase III AURELIA trial. Gynecologic oncology. 2013;130(1):e3.	Abstract
Kristensen G, Perren T, Qian W, Pfisterer J, Ledermann JA, Joly F, et al. Result of interim analysis of overall survival in the GCIG ICON7 phase III randomized trial of bevacizumab in women with newly diagnosed ovarian cancer. Journal of clinical oncology. 2011;29(18 SUPPL. 1).	Abstract
Li J, Li S, Chen R, Yu H, Lu X. The prognostic significance of anti-angiogenesis therapy in ovarian cancer: a meta-analysis. J. Ovarian Res. 2015;8(1).	No quality appraisal
Mazur A, Collinson F, Swart AM, Perren T. ICON7 - a randomised two-arm, multi-centre Gynaecologic Cancer InterGroup trial of adding bevacizumab to standard chemotherapy (carboplatin and paclitaxel) in patients with epithelial ovarian cancer abstract. Proceedings of the Annual Meeting of the British Gynaecological Cancer Society; 2006 Nov 30-dec 1; Manchester, UK. 2006:92.	Conference proceeding
Monk BJ, Huang H, Burger RA, Mannel RL, Homesley HD, Fowler J, et al. Quality of life outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: A gynecologic oncology group study. European journal of cancer. 2011;47:12.	Abstract
Nihr HSC. Bevacizumab (Avastin) for relapsed platinum-resistant ovarian cancer ? second line (Structured abstract). Health Technology Assessment Database. 2013(4).	No methods described
Oza AM, Perren TJ, Swart AM, Schroder W, Pujade-Lauraine E, Havsteen H, et al. ICON7: Final overall survival results in the GCIG phase III randomized trial of bevacizumab in women with newly diagnosed ovarian cancer. European journal of cancer. 2013;49:S4.	Abstract
Pinilla-Dominguez P, Richardson J, Robertson J, Adam J. NICE guidance on bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer. Lancet Oncol. 2013;14(8):691-2.	Comment on NICE guidance
Pujade-Lauraine E, Hilpert F, Weber B. AURELIA: a randomized phase III trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum (PT) resistant recurrent ovarian cancer (OC) abstract. Journal of clinical oncology: ASCO annual meeting proceedings. 2012;30(Suppl):Abstract LBA5002.	Abstract
Pujade-Lauraine E, Oza AM, Perren TJ, Swart AM, Mahner S, Gourley C, et al. ICON7: Final overall survival results in the gcig phase III randomised trial of bevacizumab in newly diagnosed ovarian cancer. International journal of gynecological cancer. 2013;23(8 SUPPL. 1):53-4.	Abstract
Randall LM, Monk BJ. Bevacizumab toxicities and their management in ovarian cancer. Gynecol Oncol. 2010;117(3):497-504.	No quality appraisal
Roncolato F, Ding P, Lord S, Gebski V, Lee C. Risk of treatment-related mortality with bevacizumab treatment in advanced cancers. European journal of cancer. 2013;49:S522.	Abstract

Reference	Reason for exclusion
Rouzier R, Morice P, Floquet A, Selle F, Lambaudie E, Fourchotte V, et al. A randomized, open-label, phase II study assessing the efficacy and the safety of bevacizumab in neoadjuvant therapy in patients with FIGO stage IIIc/IV ovarian, tubal, or peritoneal adenocarcinoma, initially unresectable. Journal of clinical oncology. 2014;32(15 SUPPL. 1).	Abstract
Sorio R, Roemer-Becuwe C, Hilpert F, Reuss A, Garcia Y, Kaern J, et al. Safety and efficacy of single-agent chemotherapy +/- bevacizumab in elderly patients with platinum-resistant recurrent ovarian cancer: Subgroup analysis of Aurelia. International journal of gynecological cancer. 2013;23(8 SUPPL. 1):136-7.	Abstract
Stockler MR, Hilpert F, Friedlander M, King M, Wenzel LB, Lee C, et al. Health-related quality of life (HRQoL) results from the AURELIA trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum-resistant recurrent ovarian cancer (OC). Journal of clinical oncology. 2013;31(15 SUPPL. 1).	Abstract
Wang TS, Lei W, Cui W, Wen P, Guo HF, Ding SG, et al. A meta-analysis of bevacizumab combined with chemotherapy in the treatment of ovarian cancer. Indian Journal of Cancer. 2014;51(3).	No quality appraisal
Witteveen P, Lortholary A, Fehm T, Poveda A, Reuss A, Havsteen H, et al. Final overall survival (OS) results from AURELIA, an open-label randomised phase III trial of chemotherapy (CT) with or without bevacizumab (BEV) for platinum-resistant recurrent ovarian cancer (OC). European journal of cancer. 2013;49:S3-S4.	Abstract
Yu J, Cao XF, Zheng Y, Zhao RC, Yan LQ, Zhao L, et al. Anti-VEGF Therapy with Bevacizumab--limited cardiovascular toxicity. Asian Pac J Cancer Prev. 2014;15(24):10769-72.	No quality appraisal
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(12):e81858.	No quality appraisal

3. QUALITY APPRAISAL

3.1. Quality appraisal tools – medical part

3.1.1. Systematic reviews

AMSTAR criteria were used to assess systematic reviews (Table 9).

Table 9 – AMSTAR checklist

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6. Were the characteristics of the included studies provided?	☐ Yes

In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

3.1.2. Primary studies for therapeutic interventions

To assess risk of bias of randomised controlled trials, we used Cochrane Collaboration's tool (Table 10).

Table 10 – Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

3.2. Quality appraisal results – medical part

Quality appraisal of selected systematic reviews

Table 11 shows the results of the risk of bias assessment for the 12 included systematic reviews / HTA reports, using AMSTAR criteria.
The four reviews that did not report on the quality appraisal of the included studies were excluded from further discussion.

Table 11 – Methodological quality of the included systematic reviews (AMSTAR)

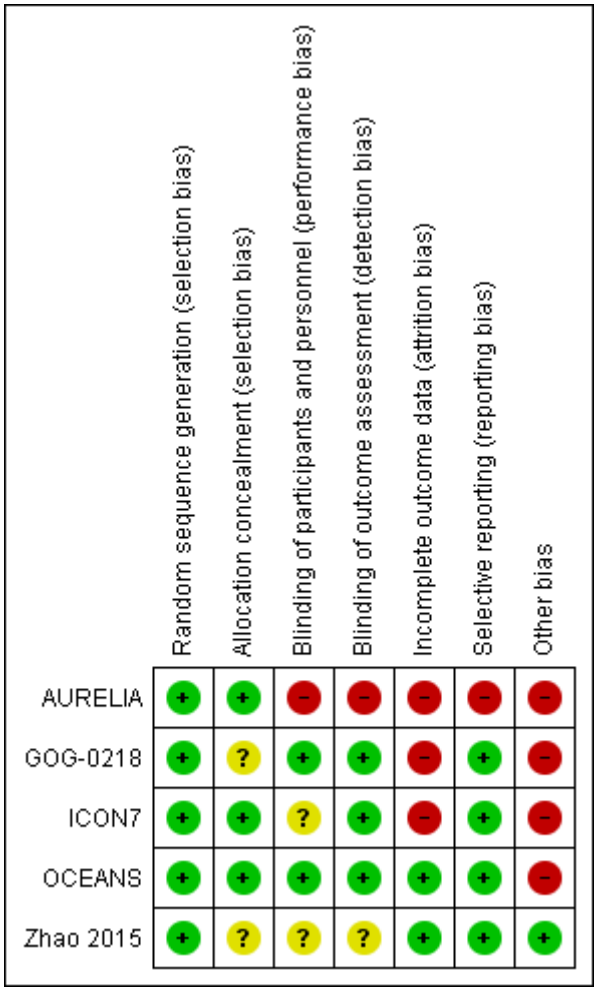
Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Aravantinos 2014	Y	?	Y	N	N	Y	N	N	N	Not applicable	N
Ding 2014	Y	Y	Y	N	N	Y	Y	Y	Y	Not applicable	N
Gaitskell 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Not applicable	N
Huang 2014	Y	?	Y	Y	N	Y	Y	N	Y	Y	N
Li 2015	Y	Y	Y	Y	N	Y	Y	Y	Y	Not applicable	Y
Ludwig Boltzmann Institute 2014	?	?	?	?	N	Y	N	N	Not applicable	Not applicable	Y
Qi 2015	Y	?	Y	N	N	Y	N	N	Y	Y	N
Qi 2014	Y	?	Y	?	N	Y	N	N	Y	Y	N
Ye 2013	Y	?	Y	?	N	Y	Y	Y	Y	Not applicable	N
Zuo 2014	Y	?	Y	N	N	Y	Y	Y	Y	Y	N
NICE TA284 [$]	Y	N	Y	?	Y	Y	Y	Y	Not applicable	Not applicable	N
NICE TA285 [$]	Y	?	Y	Y	Y	Y	Y	Y	Not applicable	Not applicable	N

[$] *Appraisal by NICE of systematic review carried out by manufacturer.*

Quality appraisal of selected RCTs for treatment

Figure 2 shows the results of the risk of bias assessment for the 5 included studies.

Figure 2 – Risk of bias summary of RCTs



3.3. Economic part

3.3.1. Data extraction sheet

Table 12 – Data extraction sheet

	Elements to be extracted from the original economic evaluation
1	Reference (including all authors)
2	Conflict of interest and/or study funding
3	Country
4	Study question
5	Type of analysis (analytic technique) - e.g. cost-effectiveness analysis, cost-utility analysis, …
6	Design - e.g. Markov model, decision tree, …
7	Population
8	Intervention
9	Comparator
10	Time horizon
11	Discount rate for costs and/or effects
12	Perspective
13	Costs: Cost items included; Measurement of resource use; Valuation of resource use; Data sources; Currency and cost year; Other aspects…
14	Outcomes Endpoints taken into account and/or health states; Valuation of health states; Treatment effect and Extrapolation; Utility assessment (Quality of Life); Data sources for outcomes; Other aspects…
15	Uncertainty - Scenario analysis; Sensitivity analysis
16	Assumptions
17	Results Cost-effectiveness and/or cost-utility (base case); Scenario analysis; Sensitivity analysis; Other aspects…
18	Conclusions The conclusion of the authors (which can be discussed in the actual critical appraisal)
19	Remarks- e.g. limitations of the study

3.3.2. The CHEERS checklist

The aim of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement is to provide recommendations, in the form of a checklist, to optimise reporting of health economic evaluations.[23] The 24 items checklist is provided in Table 13.

Table 13 – CHEERS checklist

Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Title of chapter 7
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	No separate abstract is provided for the economic evaluation in this HTA report.
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	1.1 background + part 2: health problems + part 3: description and technical characteristics
		Present the study question and its relevance for health policy or practice decisions.	1.2 Scope and objectives + link to negotiations of reimbursement contract at the end of part 3.
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	7.1.2 Population
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	3.2 Belgian rules for the reimbursement of bevacizumab
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	7.1.1 Perspective of the evaluation
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	7.1.3 Intervention and comparator
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	7.1.5 Time horizon and discount rate
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	7.1.5 Time horizon and discount rate

Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	7.1.4 Analytic technique
Measurement of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	7.1.7 Treatment effect (description of all single-study based estimates) + 5.2.1 Overview of selected studies
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	7.1.8 Quality of life
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	7.1.9 Costs
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	7.1.9 Costs
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	7.1.6 Markov model
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	7.1.10 Sensitivity and scenario analyses This part contains a table with an overview of variables included in scenario analysis + reference to the part in the report were further details are provided.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	7.1.10 Sensitivity and scenario analyses (table with variables and their probability distribution + table with scenario analyses) + 7.1.6 Markov model (half-cycle correction) + 7.1.7 Treatment effect (included trials & description of population + life-time extrapolations)

Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	7.1.10 Sensitivity and scenario analyses (table with variables and their probability distributions) + reference to the relevant parts with further information.
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	7.2.1 Base case results and scenario analyses
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	7.2.1 Base case results and scenario analyses
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	7.2.1 Base case results and scenario analyses
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	7.3 Conclusions + 8 Discussion
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Study performed by KCE (independent federal agency providing advice to our policy makers)
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	
For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist			

4. EVIDENCE TABLES – MEDICAL PART

4.1. Systematic reviews / HTAs

Table 14 – Evidence table of systematic reviews regarding the effect of bevacizumab in ovarian cancer

Ding 2014		
Methods		
• **Design**	Systematic review + meta-analysis	
• **Source of funding and competing interest**	Supported by the Natural Science Foundation of Xinjiang Uygur Autonomous Region (2011211A038) Competing interests not reported	
• **Search date**	Unclear: 2013/2014	
• **Searched databases**	Cochrane Library (2013 No. 4), MEDLINE (1990–2013/2014), EMBASE (1990–2013/2014), Chinese Journal Full-text Database (CNKI, 1979–2013/2014), Chinese Biomedical Literature Database (CBM, 1978–2013/2014), and the VIP Chinese Science and Technology Periodicals Database (VIP, 1989–2013.4); references	
• **Included study designs**	RCTs	
• **Number of included studies**	N=2	
• **Statistical analysis**	Time-related data: hazard ratio using generic inverse variance method Dichotomous data: relative risk or odds ratio	
Patient characteristics		
• **Eligibility criteria**	See below	
• **Exclusion criteria**	Patients were excluded if recurrence occurred beyond second-line chemotherapy failure or bevacizumab (or other anti-angiogenesis inhibitor drugs) had been previously administered. Patients with severe circulatory system disease or with liver and kidney dysfunction were also excluded.	
• **Patient & disease characteristics**	Patients (any race) were aged >18 years, with histologically proven recurrent ovarian cancer on the basis of the GOG criteria, and had not received any treatment after relapse	
Interventions		
• **Intervention group**	Bevacizumab	
• **Control group**	No bevacizumab / placebo	
Results		
• **Progression-free survival**	2 studies, N=781: HR = 0.48 (0.41-0.56)	
• **Overall survival**	1 study, N=480: HR = 1.03 (0.79-1.33)	
• **Adverse events**	Arterial thromboembolic event (any grade)	RR = 1.60 (0.50-5.13)
	Non-CNS bleeding (grade 3+)	RR = 4.76 (1.38-16.37)

Febrile neutropenia (any grade)	RR = 0.95 (0.28-3.26)
Fistula/abscess (any grade)	RR = 1.24 (0.30-5.03)
Hypertension (grade 3+)	RR = 2.30 (1.39-3.83)
Proteinuria (grade 3+)	RR = 1.63 (0.82-3.24)
Venous thromboembolic event (grade 3+)	RR = 1.49 (0.65-3.40)
GI perforation (any grade)	RR = 0.20 (0.01-4.09)
LV systolic dysfunction/CHF (grade 3+)	RR = 0.72 (0.16-3.18)

Limitations and other comments	
• **Limitations**	English and Chinese articles only No list of excluded studies No competing interests of included studies reported Fixed effects model used, even in case of heterogeneity

Gaitskell 2011	
Methods	
• **Design**	Systematic review + meta-analysis
• **Source of funding and competing interest**	No sources of support No competing interests
• **Search date**	October 2010
• **Searched databases**	Cochrane Gynaecological Cancer Review Group's Trial Register, Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, Issue 10), MEDLINE up to October 2010, EMBASE up to October 2010; trial registers; authors
• **Included study designs**	RCTs
• **Number of included studies**	N=2
• **Statistical analysis**	Time-to-event data: hazard ratio using generic inverse variance method Dichotomous data: relative risk
Patient characteristics	
• **Eligibility criteria**	See below
• **Exclusion criteria**	Women with other concurrent malignancies were excluded
• **Patient & disease characteristics**	Adult women with histologically proven ovarian cancer
Interventions (NB: is broader review on angiogenesis inhibitors)	

• **Intervention group**	Bevacizumab	
• **Control group**	No bevacizumab / placebo	
Results		
• **First-line**	Overall survival	HR = 0.87 (0.73-1.03)
	Progression-free survival	HR = 0.75 (0.68-0.83)
	Severe GI events	RR = 2.47 (1.08-5.67)
	Grade 2+ hypertension	RR = 5.13 (1.91-13.82)
	Grade 3+ proteinuria	RR = 2.90 (0.84-10.06)
	Grade 2+ pain	RR = 1.13 (0.97-1.33)
	Severe neutropenia	RR = 1.09 (0.99-1.21)
	Febrile neutropenia	RR = 1.23 (0.76-1.98)
	Venous thromboembolic event	RR = 1.64 (0.76-3.56)
	Arterial thromboembolic event	RR = 1.40 (0.50-3.92)
	Grade 3+ bleeding	RR = 2.90 (1.10-7.62)
	Thrombocytopenia	RR = 1.75 (0.94-3.28)
Limitations and other comments		
• **Limitations**	No competing interests of included trials reported	

Huang 2014	
Methods	
• **Design**	Systematic review + meta-analysis
• **Source of funding and competing interest**	No funding No competing interests
• **Search date**	August 2013
• **Searched databases**	Medline, Embase, CENTRAL; conference abstracts; references
• **Included study designs**	Phase II/III RCTs
• **Number of included studies**	N=3 (ovarian cancer)

• **Statistical analysis**	Mantel-Haenszel method was used to calculate RR and 95%CI
Patient characteristics	
• **Eligibility criteria**	Adverse events reported for both groups separately
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Patients with cancer
Interventions (NB: is broader review on bevacizumab in cancer)	
• **Intervention group**	Bevacizumab
• **Control group**	No bevacizumab / placebo
Results	
• **Fatal adverse events**	RR = 2.35 (1.03-5.33)
Limitations and other comments	
• **Limitations**	Unclear if duplicate study selection No list of excluded studies No conflicts of interest of included studies

Li 2015	
Methods	
• **Design**	Systematic review + meta-analysis
• **Source of funding and competing interest**	Funding not reported Declaration of interests not accessible
• **Search date**	April 2015
• **Searched databases**	MEDLINE (1950 through April 2015), Web of Science (1950 through April 2015), EMBASE (1966 through April 2015), Chinese VIP (1989 through April 2015), CENTRAL; references; conference abstracts; authors; manufacturers
• **Included study designs**	RCTs
• **Number of included studies**	N=4
• **Statistical analysis**	Time-to-event data: HR (fixed-effects) Dichotomous outcomes: OR (fixed effects)
Patient characteristics	
• **Eligibility criteria**	See below

• **Exclusion criteria**	-	
• **Patient & disease characteristics**	Patients with advanced ovarian cancer, first- or second-line	
Interventions		
• **Intervention group**	Bevacizumab	
• **Control group**	No bevacizumab / placebo	
Results		
• **First-line**	Progression-free survival	HR = 0.82 (0.75-0.89)
	Overall survival	HR = 0.86 (0.75-0.99)
	Overall response rate	OR = 2.20 (1.79-2.70)
• **Second-line**	Progression-free survival	HR = 0.48 (0.41-0.57)
	Overall survival	HR = 0.93 (0.78-1.12)
	Overall response rate	OR = 2.91 (2.20-3.84)
• **Adverse events**	Arterial thromboembolic events	OR = 2.33 (1.34-4.03)
	Wound healing disruption grade 3+	OR = 3.60 (1.10-11.83)
	Bleeding grade 3+	OR = 3.51 (1.84-6.69)
	GI perforation	OR = 2.94 (1.45-5.95)
	Proteinuria grade 3+	OR = 5.14 (2.34-11.27)
	Hypertension grade 3+	OR = 16.10 (9.88-26.25)
Limitations and other comments		
• **Limitations**	No list of excluded studies No random effect model in case of heterogeneity	

Ye 2013	
Methods	
• **Design**	Systematic review + meta-analysis
• **Source of funding and competing interest**	Funding not reported No competing interest
• **Search date**	September 2012
• **Searched databases**	PubMed, Web of Science, conference abstracts
• **Included study designs**	RCTs
• **Number of included studies**	N=4

• **Statistical analysis**	Time-to-event data: HR Dichotomous outcomes: OR	
Patient characteristics		
• **Eligibility criteria**	See below	
• **Exclusion criteria**	Case reports, case series, one arm phase I trials, retrospective case-control studies, and phase II non-randomised trials	
• **Patient & disease characteristics**	Adult women with histologically proven ovarian cancer	
Interventions		
• **Intervention group**	Bevacizumab	
• **Control group**	No bevacizumab / placebo	
Results		
• **First-line**	Progression-free survival	HR = 0.83 (0.71-0.95)
	Overall survival	HR = 0.92 (0.80-1.03)
	Overall response rate	OR = 1.90 (1.17-3.06)
• **Second-line**	Progression-free survival	HR = 0.48 (0.41-0.56)
	Overall survival	HR = 1.03 (0.76-1.30)
	Overall response rate	OR = 2.77 (2.00-3.83)
• **Adverse events**	Arterial thromboembolic events	OR = 1.99 (1.21-3.29)
	Venous thromboembolic events	OR = 1.21 (0.93-1.55)
	GI events	OR = 2.74 (1.58-4.76)
	Proteinuria grade 3+	OR = 4.87 (2.62-9.07)
	Hypertension	OR = 4.63 (3.74-5.74)
Limitations and other comments		
• **Limitations**	Unclear if duplicate study selection Search restrictions not reported No list of excluded studies No conflicts of interest of included studies	

Zuo 2014	
Methods	
• **Design**	Systematic review + meta-analysis
• **Source of funding and competing interest**	Supported by the National Natural Science Foundation of China (No81370468) No competing interests
• **Search date**	February 2014
• **Searched databases**	PubMed, Web of Science, conference abstracts; references
• **Included study designs**	RCTs
• **Number of included studies**	N=3
• **Statistical analysis**	RR and CI for cerebrovascular events
Patient characteristics	
• **Eligibility criteria**	Adverse events reported for both groups separately
• **Exclusion criteria**	-
• **Patient & disease characteristics**	Patients with cancer
Interventions (NB: is broader review on bevacizumab in cancer)	
• **Intervention group**	Bevacizumab
• **Control group**	No bevacizumab / placebo
Results	
• **Cerebrovascular events**	RR = 3.42 (0.72-16.35)
Limitations and other comments	
• **Limitations**	Unclear if duplicate study selection English articles only No list of excluded studies No conflicts of interest of included studies

NICE TA284	
Methods	
• **Design**	Technology appraisal by manufacturer
• **Source of funding and competing interest**	Report developed by Roche
• **Search date**	Unclear (appendix of manufacturer's report not accessible)
• **Searched databases**	Unclear (appendix of manufacturer's report not accessible)
• **Included study designs**	RCTs
• **Number of included studies**	N=2
• **Statistical analysis**	Descriptive
Patient characteristics	
• **Eligibility criteria**	Patients with advanced ovarian cancer, first-line treatment
• **Exclusion criteria**	Unclear (appendix of manufacturer's report not accessible)
• **Patient & disease characteristics**	See results of GOG-0218 trial and ICON7 trial
Interventions	
• **Intervention group**	Bevacizumab
• **Control group**	No bevacizumab / placebo
Results	
• **See results of GOG-0218 trial and ICON7 trial**	
Limitations and other comments	
• **Comments**	Appraisal by NICE of systematic review performed by manufacturer Appendix not accessible

NICE TA285	
Methods	
• **Design**	Technology appraisal by manufacturer
• **Source of funding and competing interest**	Report developed by Roche
• **Search date**	Unclear (appendix of manufacturer's report not accessible)
• **Searched databases**	Unclear (appendix of manufacturer's report not accessible)
• **Included study designs**	RCTs
• **Number of included studies**	N=1
• **Statistical analysis**	Descriptive
Patient characteristics	
• **Eligibility criteria**	Patients with recurrent ovarian cancer
• **Exclusion criteria**	Unclear (appendix of manufacturer's report not accessible)
• **Patient & disease characteristics**	See results of OCEANS trial
Interventions	
• **Intervention group**	Bevacizumab
• **Control group**	No bevacizumab / placebo
Results	
• **See results of OCEANS trial**	
Limitations and other comments	
• **Comments**	Appraisal by NICE of systematic review performed by manufacturer Appendix not accessible

4.2. RCTs

Table 15 – Evidence table of intervention studies regarding the effect of bevacizumab in ovarian cancer

AURELIA trial: Pujade-Lauraine 2014, Stockler 2014, Poveda 2015	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Sponsored by F. Hoffmann-La Roche (Basel, Switzerland) Several authors with financial links with Roche
• **Setting**	Multicentre trial, Europe
• **Sample size**	N=361 (randomised)
• **Duration and follow-up**	• Inclusion: Oct 2009 – Apr 2011 • Median follow-up: chemotherapy 13.9m, chemotherapy + bevacizumab 13.0m
• **Statistical analysis**	• Patients were stratified according to selected chemotherapy (PLD vs. paclitaxel vs. topotecan), prior antiangiogenic therapy (yes vs. no), and platinum-free interval (<3 vs. 3 to 6 months from last platinum therapy to subsequent progression) • PFS in the two treatment arms was compared using an unstratified two-sided log-rank test. A post hoc analysis using a stratified two-sided logrank test was also performed. Final OS analysis was performed after deaths in 70% of patients
Patient characteristics	
• **Eligibility criteria**	• Patients with histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal cancer (measurable by RECIST [version 1.0] or assessable by GCIG CA-125 response criteria) that had progressed within 6 months of completing at least four cycles of platinum-based therapy • Age at least 18 years • Eastern Cooperative Oncology Group performance status 2 or less • Adequate liver, renal, and bone marrow function
• **Exclusion criteria**	• Patients who had received > two prior anticancer regimens or who had refractory disease (progression during previous platinum-containing therapy) • Patients with a history of bowel obstruction (including subocclusive disease) related to underlying disease, a history of abdominal fistula, GI perforation, or intra-abdominal abscess, or evidence of rectosigmoid involvement by pelvic examination, bowel involvement on computed tomography, or clinical symptoms of bowel obstruction • Prior radiotherapy to the pelvis or abdomen • Surgery (including open biopsy) within 4 weeks before starting study therapy (within 24 hours for minor surgical procedures) or anticipated need for major surgery during study treatment • Current or recent treatment with another investigational drug within 30 days before first study dose

	• Untreated CNS disease or symptomatic CNS metastasis • History or evidence of thrombotic or hemorrhagic disorders within 6 months before first study treatment • Uncontrolled hypertension or active clinically significant cardiovascular disease • Nonhealing wound, ulcer, or bone fracture
• **Patient & disease characteristics**	<table><tr><th></th><th>Bevacizumab (N=182)</th><th>No bevacizumab (N=179)</th></tr><tr><td>**Median age**</td><td>61y</td><td>62y</td></tr><tr><td>**Origin of cancer: ovary**</td><td>86%</td><td>93%</td></tr><tr><td>**Ascites**</td><td>30%</td><td>33%</td></tr></table>
Interventions	
• **Control group**	Investigators selected single-agent chemotherapy on an individual patient basis from the following options, with appropriate premedication according to local standards: • Paclitaxel 80mg/m² intravenously on days 1, 8, 15, and 22 every 4 weeks; • Pegylated liposomal doxorubicin (PLD) 40 mg/m² IV on day 1 every 4 weeks; • Topotecan 4 mg/m² IV on days 1, 8, and 15 every 4 weeks or 1.25 mg/m2 on days 1 to 5 every 3 weeks
• **Intervention group**	Same chemotherapy + bevacizumab 10 mg/kg every 2 weeks (or 15 mg/kg every 3 weeks in patients receiving topotecan in a schedule repeated every 3 weeks; BEV-CT) Chemotherapy and bevacizumab were continued until disease progression, unacceptable toxicity, or consent withdrawal
Results	
• **Duration of therapy**	• Median: 3 vs. 6 cycles • Range: 1-17 vs. 1-24
• **Progression-free survival**	• HR = 0.48 (0.38-0.60) • Median: 3.4 vs. 6.7m (p<0.001) • Subgroup analysis: o Paclitaxel: HR = 0.46, 95%CI 0.30-0.71 o Pegylated liposomal doxorubicin: HR = 0.57, 95%CI 0.39-0.83 o Topotecan: HR = 0.32, 95%CI 0.21-0.49
• **Overall response rate**	12.6% vs. 30.9% (p<0.001)
• **Overall survival**	• HR = 0.85 (0.66-1.08) • Median: 13.3 vs. 16.6m • Subgroup analysis: o Paclitaxel: HR = 0.65, 95%CI 0.42-1.02 o Pegylated liposomal doxorubicin: HR = 0.91, 95%CI 0.62-1.36

	o Topotecan: HR = 1.09, 95%CI 0.72-1.67
• **Adverse events**	• Fatal events: 5 in each group • Hypertension grade 2+: 1 vs. 7% • Proteinuria: 7 vs. 20% • GI perforation grade 2+: 0 vs. 2% • Fistula/abscess grade 2+: 0 vs. 2% • Bleeding: 1 vs. 1% • Arterial thromboembolic event: 0 vs. 2% • Venous thromboembolic event: 4 vs. 3% • Wound-healing complication: 0% each • RPLS: 0 vs. 1% • Congestive heart failure: 1% each • Cardiac disorders: 0% each
• **Quality of life**	• Baseline questionnaires were available from 89% of patients for QLQ-OV28 and FOSI and 94% of patients for QLQ-C30 • QLQ-OV28, at least 15% improvement: 9.3% vs. 21.9% at week 8/9 (p=0.002), 5.6% vs. 15.5% at week 16/18 (p=0.005) • FOSI, at least 15% improvement: 3.1% vs. 12.2% at week 8/9 (p=0.003), 1.3% vs. 9.0% at week 16/18 (p=0.002) • EORTC QLQ-C30, at least 15% improvement: global health 13.0% vs. 24.4% at week 8/9 (p=0.011) • Subgroup analysis: o Paclitaxel: 13.0% vs. 25.0%, difference = 12.0%, 95%CI -4.9% to 28.9% o Pegylated liposomal doxorubicin: 6.8% vs. 21.1%, difference = 14.3%, 95%CI 0.9% to 27.6% o Topotecan: 8.8% vs. 20.0%, difference = 11.2%, 95%CI -3.2% to 25.7%
Limitations and other comments	
• **Limitations**	Open-label One patient excluded from safety analysis in chemotherapy alone group (N=182); several dropouts for QoL Raw data not reported for QoL

GOG-0218 trial: Burger 2011, Monk 2013		
Methods		
• **Design**	RCT	
• **Source of funding and competing interest**	Supported by the National Cancer Institute and Genentech Several authors with financial links with Genentech	
• **Setting**	Multicentre trial (US, Canada, South Korea, Japan)	
• **Sample size**	N=1873 (randomised)	
• **Duration and follow-up**	• Inclusion: Oct 2005 – Jun 2009 • Median follow-up: 17.4m	
• **Statistical analysis**	• Patients were stratified on the basis of GOG performance-status score and cancer stage and debulking status (stage III cancer and maximal residual lesion diameter ≤1 cm vs. stage III cancer and maximal residual lesion diameter >1 cm vs. stage IV cancer) • Differences in progression-free survival among the three groups were assessed by means of the log-rank test • Relative hazard ratios were estimated with the use of a proportional-hazards model • Differences in FACT-O TOI scores among the three groups were assessed by means of a linear mixed model with adjustment for baseline score and age • Differences among the groups in the severity of adverse events were examined by means of Fisher's exact test	
Patient characteristics		
• **Eligibility criteria**	• Previously untreated, incompletely resectable stage III or any stage IV epithelial ovarian, primary peritoneal, or fallopian-tube cancer histologically confirmed by the Gynecologic Oncology Group (GOG) Pathology Committee after standard abdominal surgery with maximal debulking effort within 12 weeks before study entry • GOG performance status score of 0 (fully active) to 2 (ambulatory and capable of self-care but unable to work; up and about more than 50% of waking hours) • No history of clinically significant vascular events or evidence of intestinal obstruction	
• **Exclusion criteria**	• Patients with stage III disease and no residual lesions greater than 1 cm in maximal diameter were initially excluded, but after a protocol modification they were permitted	
• **Patient & disease characteristics**	**Bevacizumab short (N=625)**	**Bevacizumab long (N=623)** / **No bevacizumab (N=625)**
	Median age	60y / 60y / 60y
	Stage III (1 cm or less)	32.8% / 34.7% / 34.9%
	Stage III (>1 cm)	41.0% / 38.8% / 40.6%
	Stage IV	26.2% / 26.5% / 24.5%
Interventions		

• **Control group**	22 3-week cycles with intravenous infusions on day 1, with the first 6 cycles consisting of standard chemotherapy with carboplatin at an area under the curve of 6 and paclitaxel at a dose of 175 mg per m² of body-surface area; placebo added in cycles 2 through 22
• **Intervention group**	• Bevacizumab-initiation treatment: same chemotherapy with bevacizumab (15 mg per kilogram of body weight) added in cycles 2 through 6 and placebo added in cycles 7 through 22 • Bevacizumab-throughout treatment: same chemotherapy with bevacizumab added in cycles 2 through 22 Treatment was discontinued at the onset of disease progression, unacceptable toxic effects, completion of all 22 cycles, or withdrawal
Results	
• **Progression-free survival**	• Primary analysis: HR = 0.908 (0.795-1.010), p=0.16 for bevacizumab-initiation group; HR = 0.717 (0.625-0.824), p<0.001 for bevacizumab-throughout group • Updated analysis: HR = 0.770 (0.681-0.870) for bevacizumab-throughout group • Median: 10.3 vs. 11.2 vs. 14.1m • Subgroup stage III, macroscopic ≤1 cm: HR = 0.780 (NS) for bevacizumab-initiation group; HR = 0.618 (p<0.05) for bevacizumab-throughout group • Subgroup stage III, macroscopic >1 cm: HR = 0.981 (NS) for bevacizumab-initiation group; HR = 0.763 (p<0.05) for bevacizumab-throughout group • Subgroup stage IV: HR = 0.923 (NS) for bevacizumab-initiation group; HR = 0.698 (p<0.05) for bevacizumab-throughout group
• **Overall survival**	• Primary analysis: HR = 1.036 (0.827-1.297), p=0.76 for bevacizumab-initiation group; HR = 0.915 (0.727-1.152), p=0.45 for bevacizumab-throughout group • Updated analysis: HR = 1.078 (0.919-1.270), p=0.76 for bevacizumab-initiation group; HR = 0.885 (0.750-1.040) for bevacizumab-throughout group • Median: 39.3 vs. 38.7 vs. 39.7m
• **Adverse events**	• Fatal events: 1.0 vs. 1.6 vs. 2.3% • Hypertension grade 2+: 7.2 vs. 16.5 vs. 22.9% • Proteinuria grade 3+: 0.7 vs. 0.7 vs. 1.6% • GI events 2+: 1.2 vs. 2.8 vs. 2.6% • Pain grade 2+: 41.6 vs. 41.5 vs. 47.0% • Neutropenia grade 4+: 57.7 vs. 63.3 vs. 63.3% • Febrile neutropenia: 3.5 vs. 4.9 vs. 4.3% • CNS bleeding: 0 vs. 0 vs. 0.3% • Non-CNS bleeding grade 3+: 0.8 vs. 1.3 vs. 2.1% • Arterial thromboembolic event: 0.8 vs. 0.7 vs. 0.7% • Venous thromboembolic event: 5.8 vs. 5.3 vs. 6.7%

	• Wound disruption: 2.8 vs. 3.6 vs. 3.0% • RPLS: 0 vs. 0.2 vs. 0.2%
• **Quality of life**	• Prior to cycle 4: o FACT-O TOI: 73.8 vs. 71.1 vs. 70.9 o Physical well being: 20.7 vs. 19.7 vs. 19.6 o Functional well being: 17.9 vs. 16.9 vs. 16.7 o Ovarian subscale: 35.3 vs. 34.5 vs. 34.5 • Prior to cycle 7: o FACT-O TOI: 76.0 vs. 74.3 vs. 73.8 o Physical well being: 21.3 vs. 20.6 vs. 20.4 o Functional well being: 18.6 vs. 17.9 vs. 17.7 o Ovarian subscale: 36.2 vs. 35.9 vs. 35.6 • Prior to cycle 13: o FACT-O TOI: 80.6 vs. 80.5 vs. 79.9 o Physical well being: 22.6 vs. 22.8 vs. 22.5 o Functional well being: 20.3 vs. 19.9 vs. 19.7 o Ovarian subscale: 37.8 vs. 37.8 vs. 37.7 • Prior to cycle 21: o FACT-O TOI: 77.6 vs. 79.1 vs. 78.6 o Physical well being: 21.7 vs. 22.3 vs. 21.9 o Functional well being: 19.4 vs. 20.1 vs. 19.6 o Ovarian subscale: 36.7 vs. 37.1 vs. 37.2 • 6 months follow-up: o FACT-O TOI: 75.8 vs. 77.6 vs. 77.8 o Physical well being: 21.5 vs. 21.6 vs. 21.7 o Functional well being: 18.6 vs. 19.8 vs. 19.6 o Ovarian subscale: 36.0 vs. 36.7 vs. 36.7
Limitations and other comments	
• **Limitations**	• The primary end point was initially specified as overall survival but was changed to progression-free survival during the trial • Unclear allocation concealment • Attrition bias for adverse events and quality of life • Industry-sponsored

<table>
<tr><th colspan="2">ICON7 trial: Perren 2011, Stark 2013, Oza 2015</th></tr>
<tr><td colspan="2">Methods</td></tr>
<tr><td>• Design</td><td>RCT</td></tr>
<tr><td>• Source of funding and competing interest</td><td>Supported by MRC, Roche and the National Institute for Health Research, through the UK National Cancer Research Network
Several authors with financial links with Roche</td></tr>
<tr><td>• Setting</td><td>Multicentre trial (Australia, Canada, Denmark, Germany, Spain, Finland, France, UK, Norway, New Zealand, and Sweden)</td></tr>
<tr><td>• Sample size</td><td>N=1528 (randomised)</td></tr>
<tr><td>• Duration and follow-up</td><td>• Inclusion: Dec 2006 – Feb 2009
• Median follow-up: 48.9m (Oza 2015)</td></tr>
<tr><td>• Statistical analysis</td><td>• Stratification according to GCIG group, FIGO stage and residual disease (i.e., FIGO stages I to III and ≤1 cm of residual disease, stages I to III and >1 cm of residual disease, or stage III [inoperable] or IV), and planned interval between surgery and initiation of chemotherapy (≤4 weeks or >4 weeks)
• The primary analysis was carried out with the use of an unstratified log-rank test for the difference in the distribution of progression-free survival between the two groups
• Other planned analyses included a log-rank test that stratified for factors used for randomization (excluding GCIG groups to limit the number of categories being tested); Cox regression analyses that adjusted for baseline covariates to assess the robustness of the result if the proportional-hazards assumption held; flexible parametric survival models to smooth survival curves and estimate survival differences with the use of all survival data collected; and interaction analyses to explore the difference in the relative size of treatment effects in subgroups classified according to baseline characteristics, high risk for progression (i.e., FIGO stage IV disease or FIGO stage III disease and >1.0 cm of residual disease after debulking surgery), and stratification factors</td></tr>
<tr><td colspan="2">Patient characteristics</td></tr>
<tr><td>• Eligibility criteria</td><td>• Women with histologically confirmed, high-risk, early-stage disease (FIGO stage I or IIA and clear-cell or grade 3 tumors) or advanced (FIGO stage IIB to IV) epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (based on local histopathological findings)
• ECOG performance status of 0 to 2
• Adequate coagulation values and bone marrow, liver, and renal function, with no plans for further surgery before disease progression</td></tr>
<tr><td>• Exclusion criteria</td><td>No additional</td></tr>
<tr><td>• Patient & disease characteristics</td><td>
<table>
<tr><th></th><th>Bevacizumab (N=764)</th><th>No bevacizumab (N=764)</th></tr>
<tr><td>Median age</td><td>57y</td><td>57y</td></tr>
<tr><td>Origin of cancer: ovary</td><td>88%</td><td>87%</td></tr>
<tr><td>Stage III</td><td>2%</td><td>2%</td></tr>
<tr><td>Stage IIIA</td><td>3%</td><td>4%</td></tr>
</table>
</td></tr>
</table>

	Stage IIIB	6%	6%
	Stage IIIC	57%	57%
	Stage IV	13%	12%
Interventions			
• **Control group**	Carboplatin (area under the curve 5 or 6) and paclitaxel (175 mg per m² of body-surface area), given every 3 weeks for 6 cycles		
• **Intervention group**	Same chemotherapy + bevacizumab (7.5 mg per kilogram of body weight), given concurrently every 3 weeks for 5 or 6 cycles and continued for 12 additional cycles or until disease progression 470 patients (62%) continued to receive bevacizumab through cycle 18		
Results			
• **Progression-free survival**	• HR = 0.93 (0.83-1.05), p=0.25 • Median: 17.5 vs. 19.9m		
• **Overall response rate**	48% vs. 67% (p<0.001)		
• **Overall survival**	• HR = 0.99 (0.85-1.14) • Median: 58.6 vs. 58.0m		
• **Adverse events**	• Fatal events: 1 vs. 4 • Hypertension grade 2+: 2 vs. 18% • Proteinuria grade 3+: 0.1 vs. 1% • GI perforation grade 3+: 0.4 vs. 1% • Fistula/abscess grade 3+: 1 vs. 1% • Arterial thromboembolic event: 1 vs. 4% • Venous thromboembolic event: 4 vs. 7% • Wound-healing complication: 2% vs. 5% • RPLS: 0 vs. 0% • Congestive heart failure: 0.4% each		
• **Quality of life**	• EORTC QLQ-C30: global quality of life 64.4 vs. 59.2 at 18w (p<0.0001), 76.1 vs. 69.7 at 54w (p<0.0001)		
Limitations and other comments			
• **Limitations**	Unclear blinding of participants Attrition bias for adverse events and quality of life Industry-sponsored		

OCEANS trial: Aghajanian 2012	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Supported by Genentech Several authors with financial links with Genentech
• **Setting**	Multicentre trial
• **Sample size**	N=484 (randomised)
• **Duration and follow-up**	• Inclusion: Apr 2007 – Jan 2010 • Median follow-up: 24m
• **Statistical analysis**	• Kaplan-Meier methodology was applied to estimate the median PFS and DOR for each treatment group • Brookmeyer-Crowley methodology was used to construct 95% CIs for median values • The stratified HR was estimated using a Cox regression model • Stratification factors were time to recurrence since the last platinum therapy (6 to 12 vs. >12 months) and cytoreductive surgery for recurrent disease (yes vs. no) • A two-sided stratified log-rank test was used to compare the two groups • ORRs were compared by the Cochran-Mantel-Haenszel test
Patient characteristics	
• **Eligibility criteria**	• Women with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer • 18+ • Disease progression ≥ 6 months after completion of front-line platinum-based chemotherapy • No prior chemotherapy in the recurrent setting • ECOG performance status of 0 or 1 • Life expectancy of at least 12 weeks • Adequate bone marrow, coagulation, renal, and hepatic function
• **Exclusion criteria**	• Prior treatment with bevacizumab or other VEGFpathway–targeted therapy • Other malignancies within 5 years (unless low risk of recurrence) • History of abdominal fistula, GIP, or intra-abdominal abscess • Clinical signs or symptoms of GI obstruction and/or requirement for parenteral hydration or nutrition • Nonhealing wound, ulcer, or bone fracture • Bleeding diathesis or significant coagulopathy • Known CNS disease (except for treated brain metastases) • Clinically significant cardiovascular disease

	• Major surgical procedure within 28 days of enrollment or anticipated to occur while participating in study
• **Patient & disease characteristics**	**Bevacizumab (N=242)** / **No bevacizumab (N=242)** **Median age** 60y / 61y **Origin of cancer: ovary** 83% / 86%
Interventions	
• **Control group**	Gemcitabine 1000mg/m² on days 1 and 8 + Carboplatin area under the curve 4 mg/mL/min on day 1 (based on the Calvert formula) + placebo Cycles were repeated every 21 days The trial was designed so that patients would receive six cycles of GC but would be allowed to receive up to 10 cycles if continued response was documented
• **Intervention group**	Same chemotherapy + bevacizumab 15 mg/kg intravenously on day 1 of each cycle, before GC Median number of cycles = 12 (range 1-43)
Results	
• **Progression-free survival**	• HR = 0.484 (0.388-0.605), p<0.0001 • Median: 8.4 vs. 12.4m
• **Overall response rate**	57.4% vs. 78.5% (p<0.0001)
• **Overall survival**	• HR = 1.027 (0.792-1.331) • Median: 35.2 vs. 33.3m
• **Adverse events**	• Fatal events: 1 vs. 1 • Hypertension grade 3+: 0.4 vs. 17% • Proteinuria grade 3+: 0.9 vs. 8.5% • GI perforation: 0% each • Fistula/abscess: 0.4 vs. 1.6% • Arterial thromboembolic event: 0.9 vs. 2.8% • Venous thromboembolic event: 2.6 vs. 4% • Wound-healing complication grade 3+: 0 vs. 0.8% • RPLS: 0 vs. 1.2% • LV systolic dysfunction/CHF: 0.9 vs. 1.2%
Limitations and other comments	
• **Limitations**	Industry-sponsored trial

<table>
<tr><th colspan="2">Zhao 2015</th></tr>
<tr><td colspan="2">Methods</td></tr>
<tr><td>• Design</td><td>RCT</td></tr>
<tr><td>• Source of funding and competing interest</td><td>Supported by Clinical and Scientific Research Fundation of PLA General Hospital (2012FC-TSYS-3021), Scientific Research Subject of Clinical Research Department of PLA General Hospital (QN201205) and Beijing Municipal Commission of Science and Technology (2131107002213040)
No competing interests</td></tr>
<tr><td>• Setting</td><td>Single centre, China</td></tr>
<tr><td>• Sample size</td><td>N=58 (randomised)</td></tr>
<tr><td>• Duration and follow-up</td><td>• Inclusion: May 2010 – Nov 2012
• Median follow-up: 24m</td></tr>
<tr><td>• Statistical analysis</td><td>Differences between groups was studied via t test, while Chi-squared test was applied for enumeration data</td></tr>
<tr><td colspan="2">Patient characteristics</td></tr>
<tr><td>• Eligibility criteria</td><td>• Patients with ovarian epithelial cancer
• FIGO stage IIA-IV
• Age 18-75y
• Malignant ascites, ECOG PS score 0–2, expected lifetime more than 3 months, and no major organ dysfunction and with adequate bone marrow, cardiac, hepatic and renal function</td></tr>
<tr><td>• Exclusion criteria</td><td>• Acute or chronic infection
• Receiving other effective therapies at present or prior anti-tumor treatment (including surgery or chemoradiotherapy)
• In pregnancy or women of childbearing age
• Mental disorder including the evidence or suspicion of alcohol or drug abuse or with psychiatric history</td></tr>
<tr><td>• Patient & disease characteristics</td><td>
<table>
<tr><th></th><th>Bevacizumab (N=31)</th><th>No bevacizumab (N=27)</th></tr>
<tr><td>Age <60y</td><td>29%</td><td>30%</td></tr>
<tr><td>Stage IIC-III</td><td>23%</td><td>22%</td></tr>
<tr><td>Stage IV</td><td>77%</td><td>78%</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Interventions</td></tr>
<tr><td>• Control group</td><td>Intraperitoneal cisplatin 40 mg/m² every 2 weeks, in addition to paclitaxel 135 mg/m² and carboplatin AUC 5 every 3 weeks</td></tr>
<tr><td>• Intervention group</td><td>Intraperitoneal cisplatin 40 mg/m² + bevacizumab 300 mg in 20 cc saline every 2 weeks, in addition to paclitaxel 135 mg/m² and carboplatin AUC 5 every 3 weeks</td></tr>
<tr><td colspan="2">Results</td></tr>
</table>

• **Overall response rate (at 6w)**	Complete response: 41% vs. 58% Partial response: 19% vs. 32%
• **Adverse events**	• No grade 3 or 4 adverse effects
• **Performance status**	Karnofsky Performance Status: 94% in the bevacizumab group had an improvement vs. 48% in the control group (p=0.0068)
Limitations and other comments	
• **Limitations**	Unclear allocation concealment Unclear blinding

5. GRADING THE EVIDENCE

5.1. GRADE methodology

For each critical and important outcome, GRADE was used to grade the quality of the supporting evidence. For this report, GRADE for systematic reviews was used. For systematic reviews, quality of evidence refers to

Table 16 and Table 17). For RCTs, quality rating was initially considered to be of high level. The rating was then downgraded if needed based on the judgement of the following quality elements: study limitations, inconsistency, indirectness, imprecision and publication bias. Each quality element considered to have serious or very serious risk of bias was rated down with one's confidence in the estimates of effect. In systematic reviews each outcome is considered separately, in contrast to guidelines, where the evidence is assessed across all outcomes and studies for a particular recommendation.

Following the GRADE methodology, the quality of evidence was classified into four categories: high, moderate, low, and very low (

one or two levels, respectively. The general principles used in this report to downgrade the quality rating are summarized in Table 18. Decisions on downgrading one or two levels were based on the judgement of one assessor. Reasons for (not) downgrading were summarized in the GRADE profiles.

Table 16 – A summary of the GRADE approach to grading the quality of evidence for each outcome

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)
Observational studies	Low			

Source: Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6.

Table 17 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	

Quality level	Definition	Methodological Quality of Supporting Evidence
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

Table 18 – Downgrading the quality rating of evidence using GRADE

Quality element	Reasons for downgrading
Limitations	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of non-validated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down.
Indirectness	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision	Evaluation of the imprecision of results was primarily based on examination of the 95%CI: - For dichotomous outcomes, quality was rated down if the 95%CI around the pooled or best estimate of effect included both 1) no effect and 2) appreciable benefit or appreciable harm. GRADE suggests that the threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%. In general, 95%CI around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. - For continuous outcomes, quality was downgraded when the 95%CI included no effect and the upper or lower confidence limit crossed the minimal important difference (MID), either for benefit of harm (Note: if the MID is not known or the use of different outcomes measures required calculation of an effect size (ES), quality was downgraded if the upper or lower confidence limit crossed an effect size of 0.5 in either direction). Even if 95%CI appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

5.2. GRADE tables

5.2.1. First-line bevacizumab

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab	No bevacizumab	Relative (95% CI)	Absolute		
Progression-free survival												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	1387	1389	HR 0.85 (0.70 to 1.02)	-	⊕OOO VERY LOW	CRITICAL
Overall survival												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	1387	1389	HR 0.94 (0.84 to 1.05)	-	⊕⊕⊕O MODERATE	CRITICAL
Objective response rate (Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision[6]	none	257	263	MD 19.4 higher (10.9 to 27.9 higher)	-	⊕⊕⊕O MODERATE	IMPORTANT
Global Quality of life at 18w												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	1205	1182	SMD 0.21 lower (0.29 to 0.13 lower)	-	⊕⊕⊕O MODERATE	CRITICAL
Global Quality of life at 54-60w												
2	randomised trials	serious[1]	very serious[8]	no serious indirectness	serious[9]	none	929	795	SMD 0.13 lower (0.52 lower to 0.26 higher)	-	⊕OOO VERY LOW	CRITICAL

[1] Both industry-sponsored trials, one with unclear allocation concealment, one with unclear blinding of patients.

[2] I^2 = 80%, overlapping CI, effects in same direction.

[3] CI includes no effect and appreciable benefit.

[4] CI includes no effect, but excludes appreciable harm and benefit.

[5] Industry-sponsored, attrition bias, unclear blinding of patients.

[6] Sample size = 520, CI excludes no effect.

[7] CI excludes no effect.

[8] I^2 = 94%, non-overlapping CI, and effects in opposite direction.

[9] CI includes no effect and appreciable harm.

5.2.2. Second-line bevacizumab

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab	No bevacizumab	Relative (95% CI)	Absolute		
Progression-free survival												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	421	424	HR 0.48 (0.41 to 0.57)	-	⊕⊕⊕O MODERATE	CRITICAL
Overall survival												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	421	424	HR 0.93 (0.77 to 1.12)	-	⊕⊕⊕O MODERATE	CRITICAL
Objective response rate (Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	421	424	MD 19.43 higher (12.72 to 26.14 higher)	-	⊕⊕⊕O MODERATE	IMPORTANT
Quality of life: EORTC QLQ-OV28, abdominal/GI symptom subscale, 8/9 weeks, proportion with ≥15% improvement												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	155	162	Difference 12.7% higher (4.4 to 20.9 higher)	-	⊕OOO VERY LOW	CRITICAL
Quality of life: EORTC QLQ-OV28, abdominal/GI symptom subscale, 16/18 weeks, proportion with ≥15% improvement												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	155	162	Difference 9.9% higher (2.9 to 17.0 higher)	-	⊕OOO VERY LOW	CRITICAL
Quality of life: FOSI, 8/9 weeks, proportion with ≥15% improvement												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	155	162	Difference 9.0% higher (2.9 to 15.2 higher)	-	⊕OOO VERY LOW	CRITICAL
Quality of life: FOSI, 16/18 weeks, proportion with ≥15% improvement												

1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	155	162	Difference 7.7% higher (2.6 to 12.9 higher)	-	⊕OOO VERY LOW	CRITICAL

[1] One open trial, both industry-sponsored trials.
[2] CI includes no effect, but excludes appreciable harm and benefit.
[3] CI excludes no effect; >400 patients.
[4] Industry-sponsored trial, no blinding, attrition bias.
[5] Small sample size (<400).
[6] CI includes no effect and appreciable benefit.

5.2.3. Adverse events

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bevacizumab**	**No bevacizumab**	**Relative (95% CI)**	**Absolute**		
Fatal adverse events												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24/1779 (1.3%)	13/1769 (0.73%)	RR 1.84 (0.94 to 3.60)	6 more per 1000 (from 0 fewer to 19 more)	⊕⊕OO LOW	IMPORTANT
Fistula/abscess any grade												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/992 (1.7%)	11/986 (1.1%)	RR 1.54 (0.73 to 3.29)	6 more per 1000 (from 3 fewer to 26 more)	⊕⊕OO LOW	IMPORTANT
Fistula/abscess grade 2+												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/179 (1.1%)	0/181 (0%)	RR 5.06 (0.24 to 104.57)	-	⊕OOO VERY LOW	IMPORTANT
GI perforation any grade												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/992 (1%)	3/986 (0.3%)	RR 3.37 (0.93 to 12.19)	7 more per 1000 (from 0 fewer to 34 more)	⊕⊕OO LOW	IMPORTANT
GI perforation grade 2+												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab	No bevacizumab	Relative (95% CI)	Absolute		
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/1779 (1.7%)	10/1768 (0.57%)	RR 2.9 (1.44 to 5.82)	11 more per 1000 (from 2 more to 27 more)	⊕⊕⊕O MODERATE	IMPORTANT
Hypertension grade 2+												
3	randomised trials	serious[1]	no serious inconsistency[5]	no serious indirectness	no serious imprecision	none	288/1532 (18.8%)	61/1535 (4%)	RR 5.36 (2.36 to 12.15)	173 more per 1000 (from 54 more to 443 more)	⊕⊕⊕O MODERATE	IMPORTANT
Hypertension grade 3+												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	89/992 (9%)	3/986 (0.3%)	RR 29.15 (9.23 to 92.02)	86 more per 1000 (from 25 more to 277 more)	⊕⊕⊕O MODERATE	IMPORTANT
Proteinuria any grade												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/924 (3.9%)	19/934 (2%)	RR 1.84 (1.07 to 3.18)	17 more per 1000 (from 1 more to 44 more)	⊕⊕⊕O MODERATE	IMPORTANT
Proteinuria grade 3+												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	35/1600 (2.2%)	7/1587 (0.44%)	RR 4.31 (1.74 to 10.68)	15 more per 1000 (from 3 more to 43 more)	⊕⊕⊕O MODERATE	IMPORTANT
Pain grade 2+												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[2]	none	286/608 (47%)	250/601 (41.6%)	RR 1.13 (1 to 1.28)	54 more per 1000 (from 0 more to 116 more)	⊕⊕OO LOW	IMPORTANT
Neutropenia grade 3+												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[2]	none	123/745 (16.5%)	114/753 (15.1%)	RR 1.09 (0.86 to 1.38)	14 more per 1000 (from 21 fewer to 58 more)	⊕⊕OO LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab	No bevacizumab	Relative (95% CI)	Absolute		
Neutropenia grade 4+												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[8]	none	436/855 (51%)	398/834 (47.7%)	RR 1.08 (0.98 to 1.18)	38 more per 1000 (from 10 fewer to 86 more)	⊕⊕⊕O MODERATE	IMPORTANT
Febrile neutropenia												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	51/1600 (3.2%)	40/1587 (2.5%)	RR 1.27 (0.84 to 1.9)	7 more per 1000 (from 4 fewer to 23 more)	⊕⊕OO LOW	IMPORTANT
Thrombocytopenia any grade												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	93/745 (12.5%)	69/753 (9.2%)	RR 1.36 (1.01 to 1.83)	33 more per 1000 (from 1 more to 76 more)	⊕⊕⊕O MODERATE	IMPORTANT
VTE any grade												
3	randomised trials	serious[1]	no serious inconsistency[9]	no serious indirectness	serious[2]	none	96/1532 (6.3%)	74/1535 (4.8%)	RR 1.26 (0.85 to 1.86)	13 more per 1000 (from 7 fewer to 41 more)	⊕⊕OO LOW	IMPORTANT
VTE grade 3+												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/992 (4.2%)	19/986 (1.9%)	RR 2.19 (1.29 to 3.74)	23 more per 1000 (from 6 more to 53 more)	⊕⊕⊕O MODERATE	IMPORTANT
Arterial thromboembolism												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/1779 (2.4%)	18/1768 (1%)	RR 2.15 (1.08 to 4.3)	12 more per 1000 (from 1 more to 34 more)	⊕⊕⊕O MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab	No bevacizumab	Relative (95% CI)	Absolute		
Local thrombosis												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/745 (0.67%)	3/753 (0.4%)	RR 1.68 (0.4 to 7.02)	3 more per 1000 (from 2 fewer to 24 more)	⊕OOO VERY LOW	IMPORTANT
Wound disruption												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[4]	none	18/608 (3%)	17/601 (2.8%)	RR 1.05 (0.54 to 2.01)	1 more per 1000 (from 13 fewer to 29 more)	⊕OOO VERY LOW	IMPORTANT
Wound healing complication any grade												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/924 (4%)	16/934 (1.7%)	RR 2.34 (1.31 to 4.16)	23 more per 1000 (from 5 more to 54 more)	⊕⊕⊕O MODERATE	IMPORTANT
Wound healing complication grade 3+												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/1171 (1%)	3/1167 (0.26%)	RR 3.55 (1.09 to 11.59)	7 more per 1000 (from 0 more to 27 more)	⊕⊕⊕O MODERATE	IMPORTANT
Bleeding any grade												
2	randomised trials	serious[1]	no serious inconsistency[10]	no serious indirectness	no serious imprecision	none	297/924 (32.1%)	89/934 (9.5%)	RR 2.78 (1.13 to 6.85)	170 more per 1000 (from 12 more to 557 more)	⊕⊕⊕O MODERATE	IMPORTANT
CNS bleeding												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/1600 (0.38%)	1/1587 (0.06%)	RR 3.42 (0.72 to 16.35)	2 more per 1000 (from 0 fewer to 10 more)	⊕OOO VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab	No bevacizumab	Relative (95% CI)	Absolute		
Non-CNS bleeding grade 3+												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/855 (3.2%)	7/834 (0.84%)	RR 3.55 (1.46 to 8.61)	21 more per 1000 (from 4 more to 64 more)	⊕⊕⊕O MODERATE	IMPORTANT
Mucocutaneous bleeding any grade												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	276/745 (37%)	55/753 (7.3%)	RR 5.07 (3.87 to 6.65)	297 more per 1000 (from 210 more to 413 more)	⊕⊕⊕O MODERATE	IMPORTANT
LV systolic dysfunction/CHF any grade												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/924 (0.43%)	4/934 (0.43%)	RR 1.01 (0.25 to 4.03)	0 more per 1000 (from 3 fewer to 13 more)	⊕OOO VERY LOW	IMPORTANT
LV systolic dysfunction/CHF grade 3+												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/992 (0.5%)	5/986 (0.51%)	RR 0.98 (0.28 to 3.37)	0 fewer per 1000 (from 4 fewer to 12 more)	⊕OOO VERY LOW	IMPORTANT
Cardiac disorders (excl. CHF) any grade												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[11]	none	0/179 (0%)	0/181 (0%)	No estimate	-	⊕OOO VERY LOW	IMPORTANT
Hyperbilirubinemia												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/745 (0.27%)	0/753 (0%)	RR 5.05 (0.24 to 105.09)	-	⊕OOO VERY LOW	IMPORTANT
Reversible posterior leukoencephalopathy syndrome												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab	No bevacizumab	Relative (95% CI)	Absolute		
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/1779 (0.28%)	0/1768 (0%)	RR 4.22 (0.71 to 24.99)	-	⊕OOO VERY LOW	IMPORTANT

[1] Industry-sponsored trials, incomplete outcome data in most studies.
[2] CI includes no effect and appreciable harm.
[3] Industry-sponsored, no blinding, attrition bias.
[4] CI includes appreciable harm and benefit.
[5] I^2 82%, two studies with non-overlapping, but all studies show strong effect.
[6] Industry-sponsored trial, unclear allocation concealment, attrition bias.
[7] Industry-sponsored trial, unclear blinding of patients, attrition bias.
[8] CI includes no effect, but excludes appreciable harm and benefit.
[9] I^2 32%, but completely overlapping CI.
[10] I^2 33%, overlapping CI.
[11] Very rare event.

6. FOREST PLOTS

6.1. Published trials only

Figure 3 – Progression-free survival: first-line bevacizumab

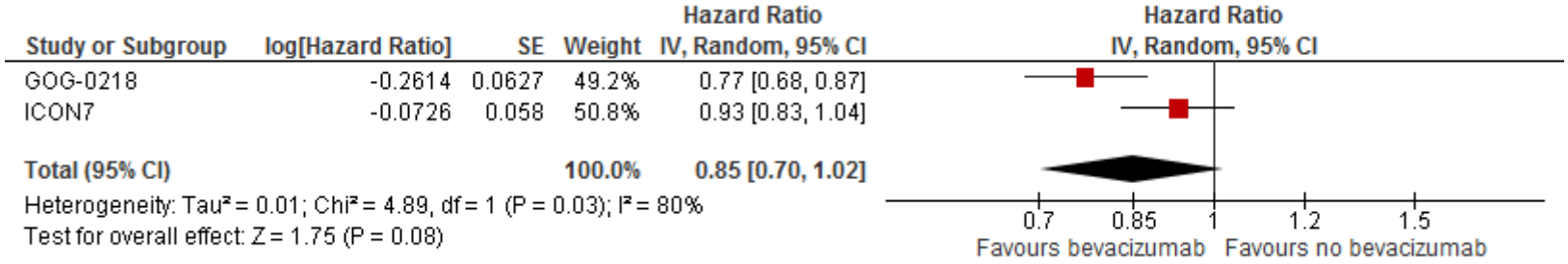


Figure 4 – Overall survival: first-line bevacizumab

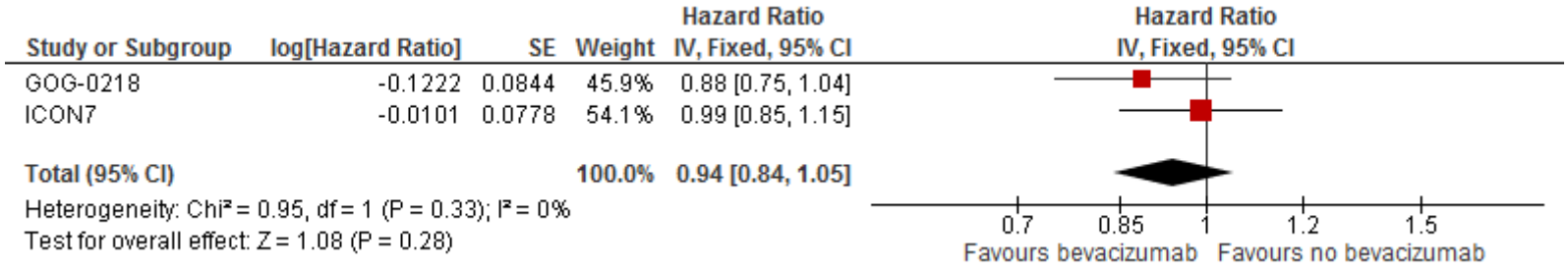


Figure 5 – Global quality of life: first-line bevacizumab

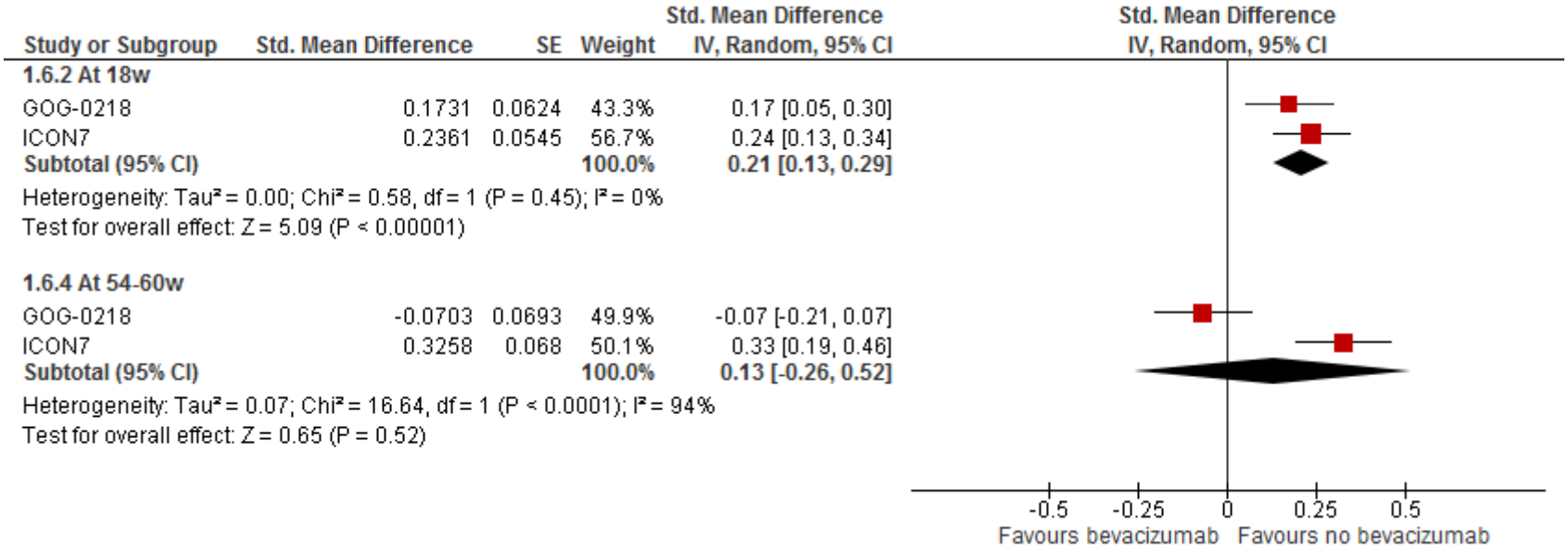


Figure 6 – Progression-free survival: second-line bevacizumab

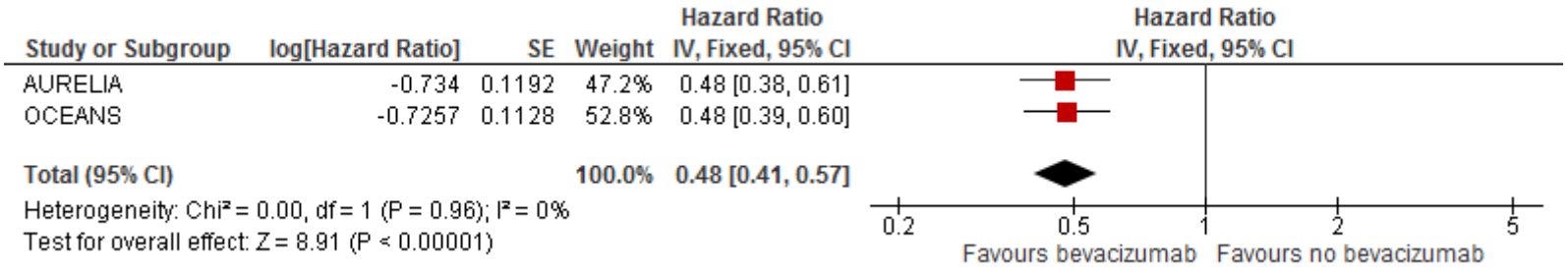


Figure 7 – Overall survival: second-line bevacizumab

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
AURELIA	-0.1625	0.1291	51.3%	0.85 [0.66, 1.09]
OCEANS	0.0266	0.1326	48.7%	1.03 [0.79, 1.33]
Total (95% CI)			**100.0%**	**0.93 [0.77, 1.12]**

Heterogeneity: Tau² = 0.00; Chi² = 1.04, df = 1 (P = 0.31); I² = 4%
Test for overall effect: Z = 0.74 (P = 0.46)

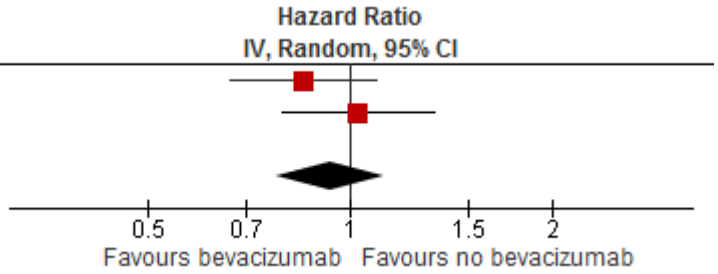


Figure 8 – Objective response rate: second-line bevacizumab

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
AURELIA	-18.3	4.4389	59.5%	-18.30 [-27.00, -9.60]
OCEANS	-21.1	5.378	40.5%	-21.10 [-31.64, -10.56]
Total (95% CI)			**100.0%**	**-19.43 [-26.14, -12.72]**

Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 5.68 (P < 0.00001)

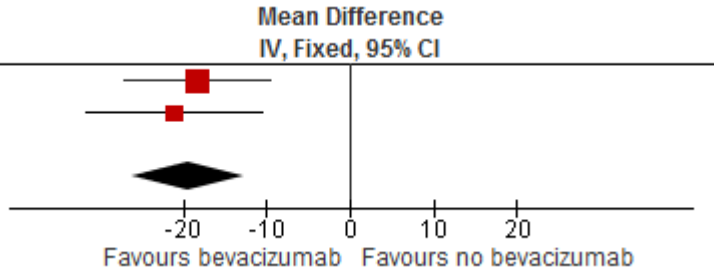


Figure 9 – Fatal adverse events

Study or Subgroup	Bevacizumab Events	Bevacizumab Total	No bevacizumab Events	No bevacizumab Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AURELIA	5	179	5	182	38.1%	1.02 [0.30, 3.45]
GOG-0218	14	608	6	601	46.4%	2.31 [0.89, 5.96]
ICON7	4	745	1	753	7.6%	4.04 [0.45, 36.09]
OCEANS	1	247	1	233	7.9%	0.94 [0.06, 14.99]
Total (95% CI)		**1779**		**1769**	**100.0%**	**1.84 [0.94, 3.60]**
Total events	24		13			

Heterogeneity: Chi² = 1.84, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.78 (P = 0.07)

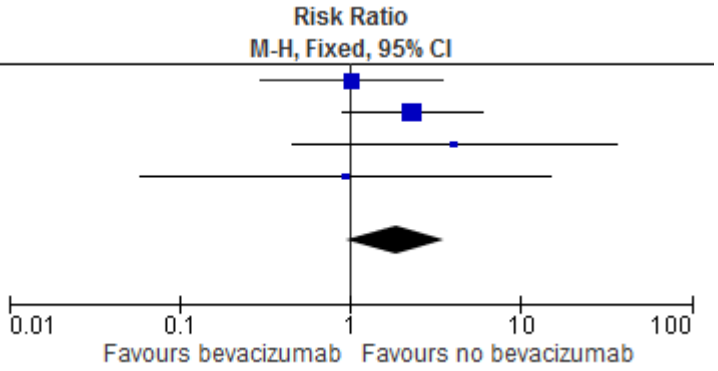


Figure 10 – Fistula/abscess any grade

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ICON7	13	745	10	753	90.6%	1.31 [0.58, 2.98]
OCEANS	4	247	1	233	9.4%	3.77 [0.42, 33.51]
Total (95% CI)		**992**		**986**	**100.0%**	**1.54 [0.73, 3.29]**
Total events	17		11			

Heterogeneity: Chi² = 0.79, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)

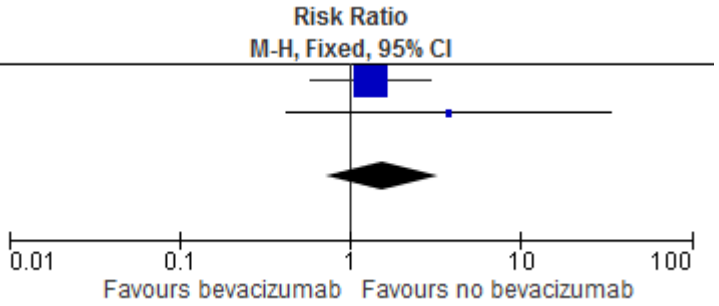


Figure 11 – Gastrointestinal perforation any grade

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ICON7	10	745	3	753	100.0%	3.37 [0.93, 12.19]
OCEANS	0	247	0	233		Not estimable
Total (95% CI)		**992**		**986**	**100.0%**	**3.37 [0.93, 12.19]**
Total events	10		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.85 (P = 0.06)

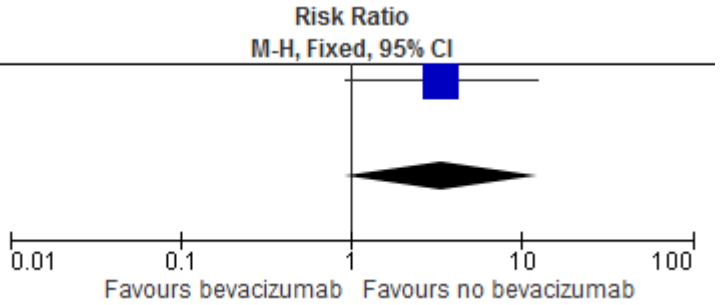


Figure 12 – Gastrointestinal perforation grade 2+

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AURELIA	4	179	0	181	4.7%	9.10 [0.49, 167.79]
GOG-0218	16	608	7	601	66.9%	2.26 [0.94, 5.45]
ICON7	10	745	3	753	28.4%	3.37 [0.93, 12.19]
OCEANS	0	247	0	233		Not estimable
Total (95% CI)		**1779**		**1768**	**100.0%**	**2.90 [1.44, 5.82]**
Total events	30		10			

Heterogeneity: Chi² = 0.95, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.99 (P = 0.003)

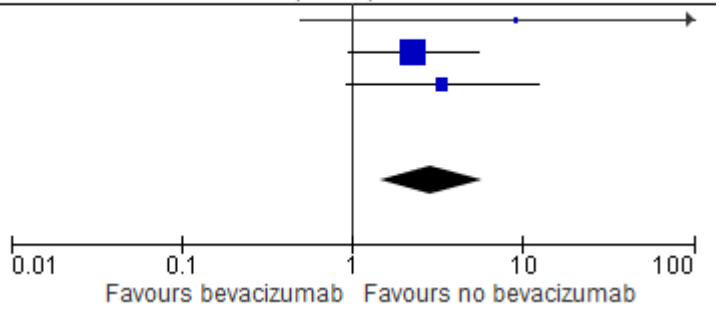


Figure 13 – Hypertension grade 2+

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
AURELIA	13	179	2	181	18.4%	6.57 [1.50, 28.71]
GOG-0218	139	608	43	601	42.7%	3.20 [2.31, 4.41]
ICON7	136	745	16	753	38.9%	8.59 [5.17, 14.28]
Total (95% CI)		**1532**		**1535**	**100.0%**	**5.36 [2.36, 12.15]**
Total events	288		61			

Heterogeneity: Tau² = 0.38; Chi² = 11.12, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 4.02 (P < 0.0001)

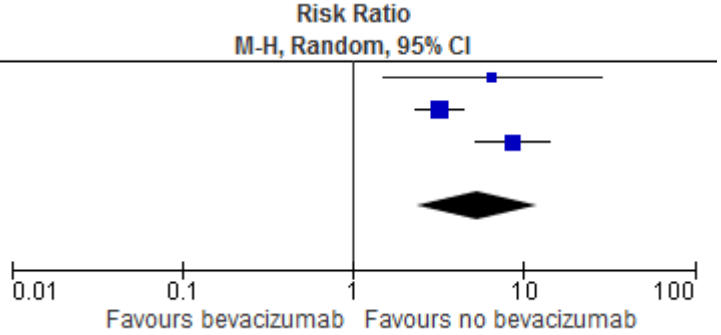


Figure 14 – Hypertension grade 3+

Study or Subgroup	Bevacizumab Events	Bevacizumab Total	No bevacizumab Events	No bevacizumab Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ICON7	46	745	2	753	65.9%	23.25 [5.66, 95.42]
OCEANS	43	247	1	233	34.1%	40.56 [5.63, 292.18]
Total (95% CI)		**992**		**986**	**100.0%**	**29.15 [9.23, 92.02]**
Total events	89		3			

Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 5.75 (P < 0.00001)

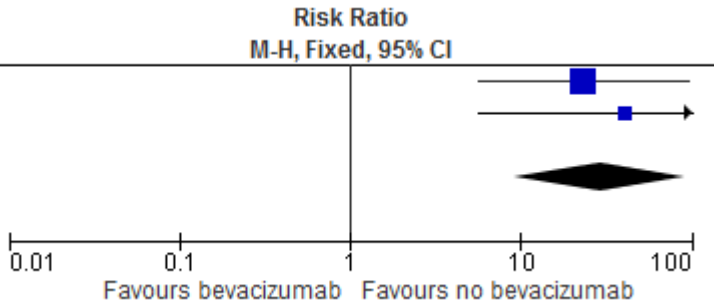


Figure 15 – Proteinuria any grade

Study or Subgroup	Bevacizumab Events	Bevacizumab Total	No bevacizumab Events	No bevacizumab Total	Weight	Risk Ratio M-H, Random, 95% CI
GOG-0218	10	608	4	601	49.6%	2.47 [0.78, 7.84]
ICON7	4	745	1	753	16.1%	4.04 [0.45, 36.09]
OCEANS	21	247	2	233	34.3%	9.90 [2.35, 41.78]
Total (95% CI)		**1600**		**1587**	**100.0%**	**4.31 [1.74, 10.68]**
Total events	35		7			

Heterogeneity: Tau² = 0.09; Chi² = 2.28, df = 2 (P = 0.32); I² = 12%
Test for overall effect: Z = 3.15 (P = 0.002)

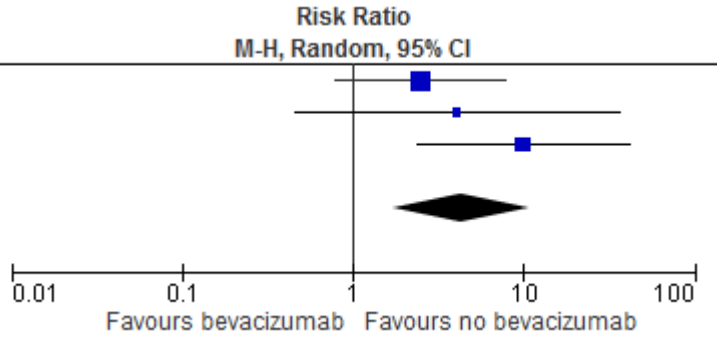


Figure 16 – Neutropenia grade 4+

Study or Subgroup	Bevacizumab Events	Bevacizumab Total	No bevacizumab Events	No bevacizumab Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0218	385	608	347	601	86.9%	1.10 [1.00, 1.20]
OCEANS	51	247	51	233	13.1%	0.94 [0.67, 1.33]
Total (95% CI)		**855**		**834**	**100.0%**	**1.08 [0.98, 1.18]**
Total events	436		398			

Heterogeneity: Chi² = 0.72, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)

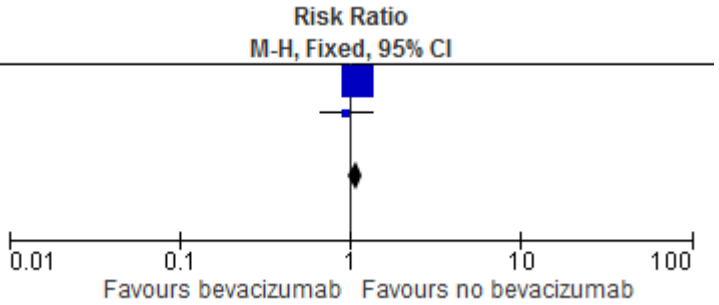


Figure 17 – Febrile neutropenia

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0218	26	608	21	601	52.6%	1.22 [0.70, 2.15]
ICON7	21	745	15	753	37.2%	1.42 [0.74, 2.72]
OCEANS	4	247	4	233	10.3%	0.94 [0.24, 3.73]
Total (95% CI)		**1600**		**1587**	**100.0%**	**1.27 [0.84, 1.90]**
Total events	51		40			

Heterogeneity: Chi² = 0.30, df = 2 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.14 (P = 0.26)

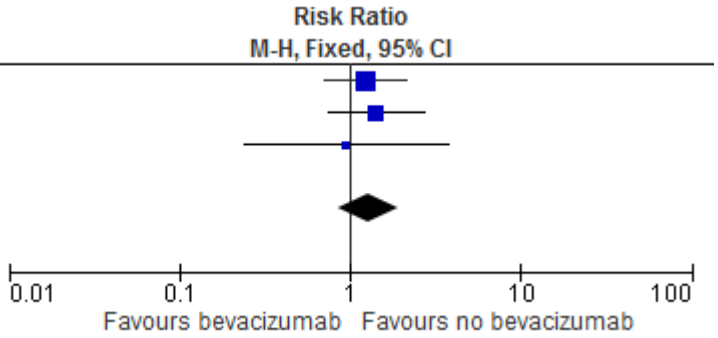


Figure 18 – Venous thromboembolism any grade

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
AURELIA	5	179	8	181	11.2%	0.63 [0.21, 1.89]
GOG-0218	41	608	35	601	44.4%	1.16 [0.75, 1.79]
ICON7	50	745	31	753	44.4%	1.63 [1.05, 2.52]
Total (95% CI)		**1532**		**1535**	**100.0%**	**1.26 [0.85, 1.86]**
Total events	96		74			

Heterogeneity: Tau² = 0.04; Chi² = 2.96, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 1.16 (P = 0.24)

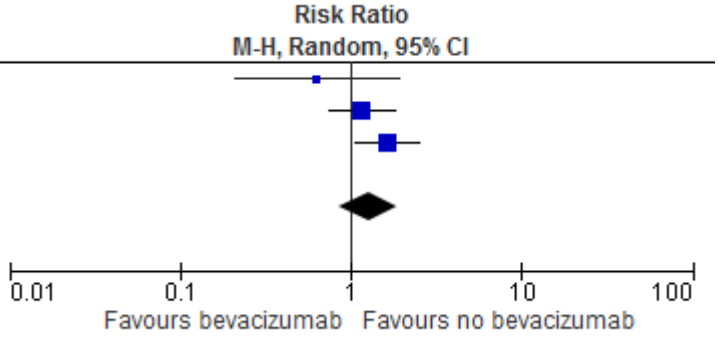


Figure 19 – Venous thromboembolism grade 3+

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ICON7	32	745	13	753	67.7%	2.49 [1.32, 4.70]
OCEANS	10	247	6	233	32.3%	1.57 [0.58, 4.26]
Total (95% CI)		**992**		**986**	**100.0%**	**2.19 [1.29, 3.74]**
Total events	42		19			

Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.88 (P = 0.004)

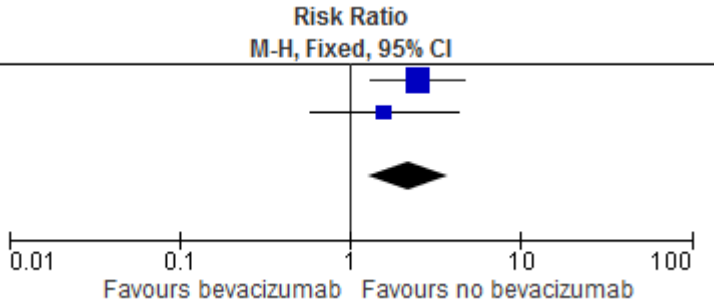


Figure 20 – Arterial thromboembolism any grade

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
AURELIA	4	179	0	181	5.4%	9.10 [0.49, 167.79]
GOG-0218	4	608	5	601	22.7%	0.79 [0.21, 2.93]
ICON7	27	745	11	753	54.9%	2.48 [1.24, 4.96]
OCEANS	7	247	2	233	16.9%	3.30 [0.69, 15.73]
Total (95% CI)		**1779**		**1768**	**100.0%**	**2.15 [1.08, 4.30]**
Total events	42		18			

Heterogeneity: Tau² = 0.10; Chi² = 3.65, df = 3 (P = 0.30); I² = 18%
Test for overall effect: Z = 2.17 (P = 0.03)

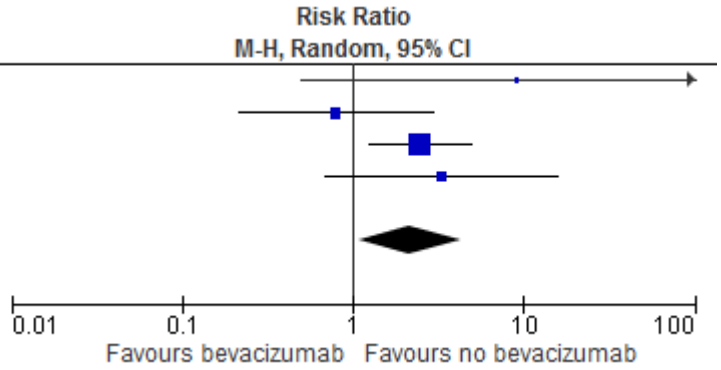


Figure 21 – Wound healing complication any grade

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AURELIA	0	179	0	181		Not estimable
ICON7	37	745	16	753	100.0%	2.34 [1.31, 4.16]
Total (95% CI)		**924**		**934**	**100.0%**	**2.34 [1.31, 4.16]**
Total events	37		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.88 (P = 0.004)

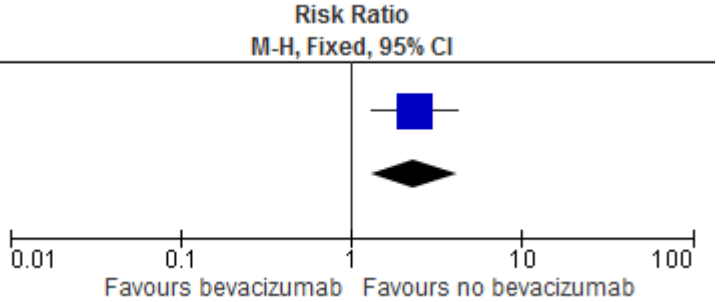


Figure 22 – Wound healing complication grade 3+

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
AURELIA	0	179	0	181		Not estimable
ICON7	10	745	3	753	84.7%	3.37 [0.93, 12.19]
OCEANS	2	247	0	233	15.3%	4.72 [0.23, 97.75]
Total (95% CI)		**1171**		**1167**	**100.0%**	**3.55 [1.09, 11.59]**
Total events	12		3			

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 2.10 (P = 0.04)

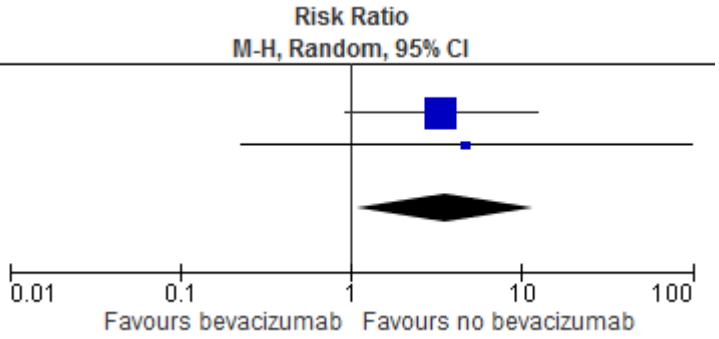


Figure 23 – Bleeding any grade

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
AURELIA	2	179	2	181	17.2%	1.01 [0.14, 7.10]
ICON7	295	745	87	753	82.8%	3.43 [2.76, 4.26]
Total (95% CI)		**924**		**934**	**100.0%**	**2.78 [1.13, 6.85]**
Total events	297		89			

Heterogeneity: Tau² = 0.24; Chi² = 1.49, df = 1 (P = 0.22); I² = 33%
Test for overall effect: Z = 2.22 (P = 0.03)

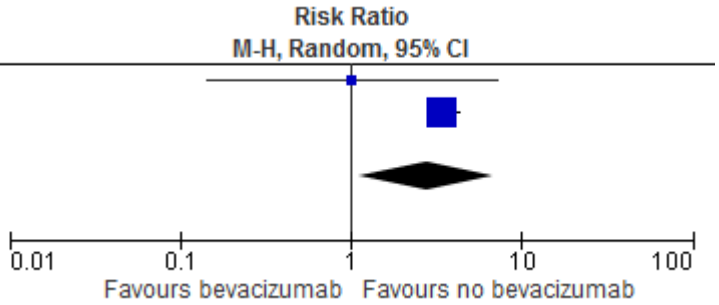


Figure 24 – CNS-bleeding any grade

Study or Subgroup	Bevacizumab Events	Bevacizumab Total	No bevacizumab Events	No bevacizumab Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0218	2	608	0	601	24.8%	4.94 [0.24, 102.73]
ICON7	2	745	0	753	24.5%	5.05 [0.24, 105.09]
OCEANS	2	247	1	233	50.7%	1.89 [0.17, 20.67]
Total (95% CI)		**1600**		**1587**	**100.0%**	**3.42 [0.72, 16.35]**
Total events	6		1			

Heterogeneity: Chi² = 0.36, df = 2 (P = 0.84); I² = 0%
Test for overall effect: Z = 1.54 (P = 0.12)

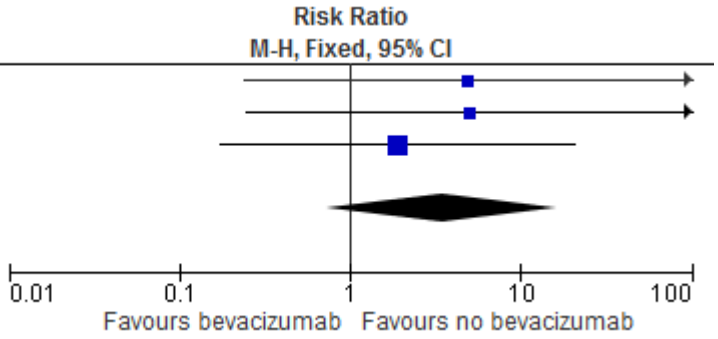


Figure 25 – Non-CNS-bleeding grade 3+

Study or Subgroup	Bevacizumab Events	Bevacizumab Total	No bevacizumab Events	No bevacizumab Total	Weight	Risk Ratio M-H, Random, 95% CI
GOG-0218	13	608	5	601	65.9%	2.57 [0.92, 7.16]
OCEANS	14	247	2	233	34.1%	6.60 [1.52, 28.74]
Total (95% CI)		**855**		**834**	**100.0%**	**3.55 [1.46, 8.61]**
Total events	27		7			

Heterogeneity: Tau² = 0.04; Chi² = 1.09, df = 1 (P = 0.30); I² = 8%
Test for overall effect: Z = 2.80 (P = 0.005)

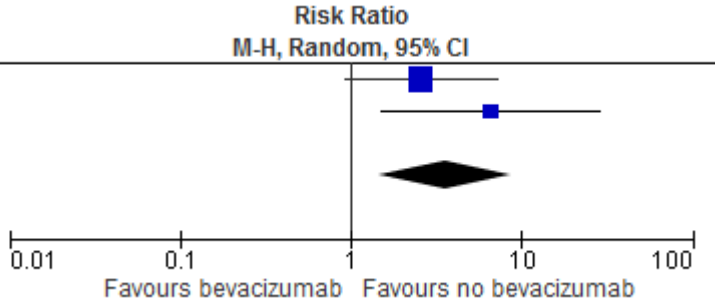


Figure 26 – LV systolic dysfunction/CHF any grade

Study or Subgroup	Bevacizumab Events	Bevacizumab Total	No bevacizumab Events	No bevacizumab Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AURELIA	1	179	1	181	25.0%	1.01 [0.06, 16.04]
ICON7	3	745	3	753	75.0%	1.01 [0.20, 4.99]
Total (95% CI)		**924**		**934**	**100.0%**	**1.01 [0.25, 4.03]**
Total events	4		4			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.99)

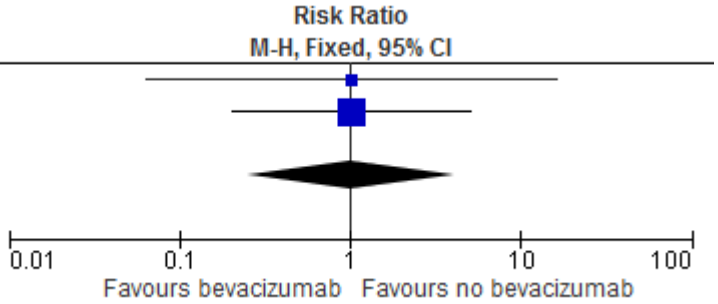


Figure 27 – LV systolic dysfunction/CHF grade 3+

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ICON7	2	745	3	753	59.2%	0.67 [0.11, 4.02]
OCEANS	3	247	2	233	40.8%	1.41 [0.24, 8.39]
Total (95% CI)		**992**		**986**	**100.0%**	**0.98 [0.28, 3.37]**
Total events	5		5			

Heterogeneity: Chi² = 0.33, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)

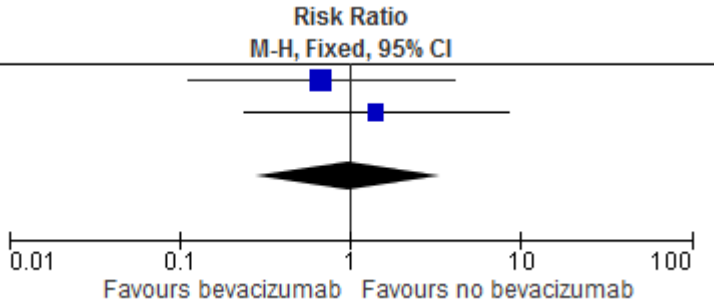
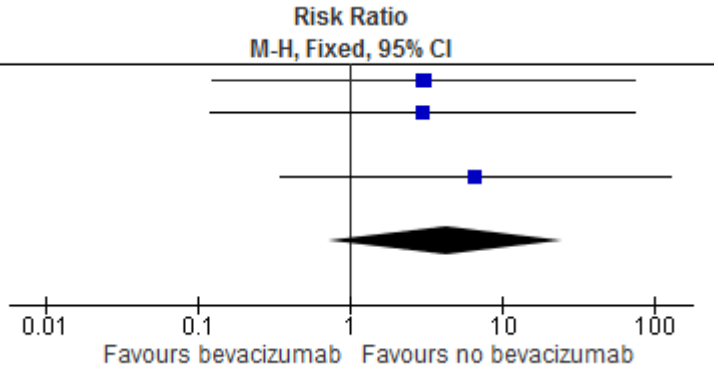


Figure 28 – Reversible posterior leukoencephalopathy syndrome

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AURELIA	1	179	0	181	32.8%	3.03 [0.12, 73.97]
GOG-0218	1	608	0	601	33.2%	2.97 [0.12, 72.65]
ICON7	0	745	0	753		Not estimable
OCEANS	3	247	0	233	34.0%	6.60 [0.34, 127.18]
Total (95% CI)		**1779**		**1768**	**100.0%**	**4.22 [0.71, 24.99]**
Total events	5		0			

Heterogeneity: Chi² = 0.18, df = 2 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.59 (P = 0.11)



6.2. Inclusion of unpublished data

Figure 29 – Progression-free survival: second-line bevacizumab

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
AURELIA	-0.734	0.1192	23.5%	0.48 [0.38, 0.61]
GOG-0213	-0.4943	0.0814	50.3%	0.61 [0.52, 0.72]
OCEANS	-0.7257	0.1128	26.2%	0.48 [0.39, 0.60]
Total (95% CI)			**100.0%**	**0.54 [0.48, 0.61]**

Heterogeneity: Chi² = 4.15, df = 2 (P = 0.13); I² = 52%
Test for overall effect: Z = 10.58 (P < 0.00001)

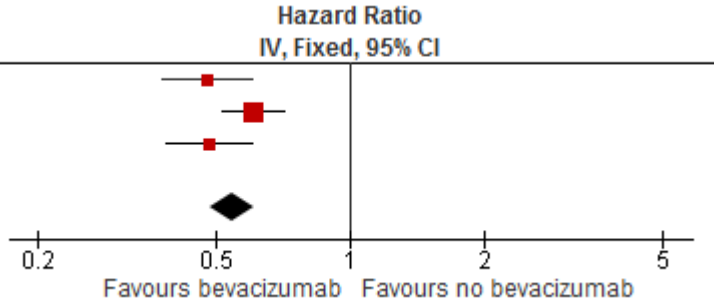


Figure 30 – Overall survival: second-line bevacizumab

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
AURELIA	-0.1625	0.1291	27.4%	0.85 [0.66, 1.09]
GOG-0213	-0.1875	0.0988	46.7%	0.83 [0.68, 1.01]
OCEANS	0.0266	0.1326	25.9%	1.03 [0.79, 1.33]
Total (95% CI)			**100.0%**	**0.88 [0.77, 1.01]**

Heterogeneity: Tau² = 0.00; Chi² = 1.79, df = 2 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.85 (P = 0.06)

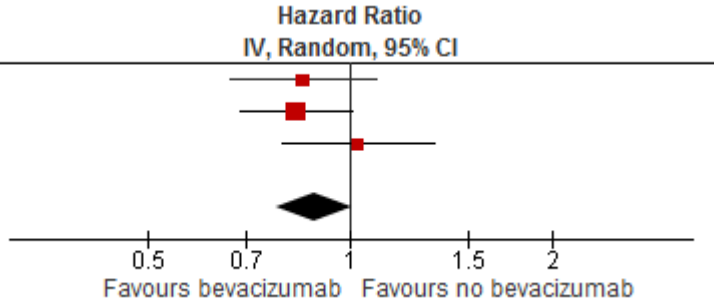


Figure 31 – Fatal adverse events

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AURELIA	5	179	5	182	33.0%	1.02 [0.30, 3.45]
GOG-0213	9	330	2	327	13.4%	4.46 [0.97, 20.48]
GOG-0218	14	608	6	601	40.2%	2.31 [0.89, 5.96]
ICON7	4	745	1	753	6.6%	4.04 [0.45, 36.09]
OCEANS	1	247	1	233	6.8%	0.94 [0.06, 14.99]
Total (95% CI)		**2109**		**2096**	**100.0%**	**2.19 [1.19, 4.02]**
Total events	33		15			

Heterogeneity: Chi² = 3.02, df = 4 (P = 0.55); I² = 0%
Test for overall effect: Z = 2.53 (P = 0.01)

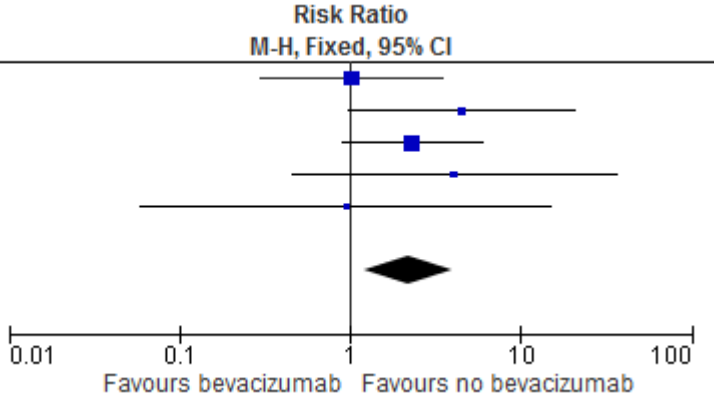


Figure 32 – Gastrointestinal perforation any grade

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0213	49	330	13	327	81.4%	3.73 [2.07, 6.75]
ICON7	10	745	3	753	18.6%	3.37 [0.93, 12.19]
OCEANS	0	247	0	233		Not estimable
Total (95% CI)		**1322**		**1313**	**100.0%**	**3.67 [2.14, 6.28]**
Total events	59		16			

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 4.74 (P < 0.00001)

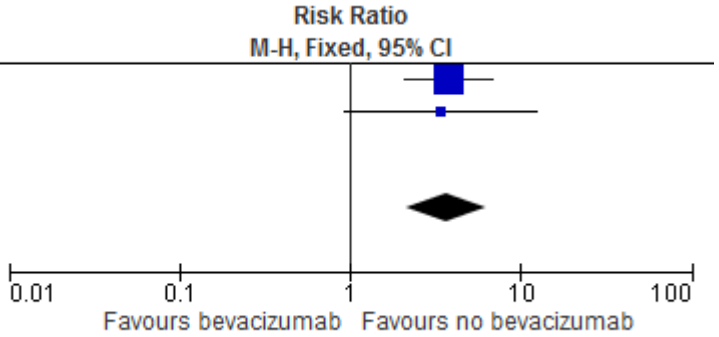


Figure 33 – Gastrointestinal perforation grade 2+

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AURELIA	4	179	0	181	3.7%	9.10 [0.49, 167.79]
GOG-0213	6	330	3	327	22.3%	1.98 [0.50, 7.86]
GOG-0218	16	608	7	601	52.0%	2.26 [0.94, 5.45]
ICON7	10	745	3	753	22.0%	3.37 [0.93, 12.19]
OCEANS	0	247	0	233		Not estimable
Total (95% CI)		**2109**		**2095**	**100.0%**	**2.69 [1.45, 5.01]**
Total events	36		13			

Heterogeneity: Chi² = 1.13, df = 3 (P = 0.77); I² = 0%
Test for overall effect: Z = 3.13 (P = 0.002)

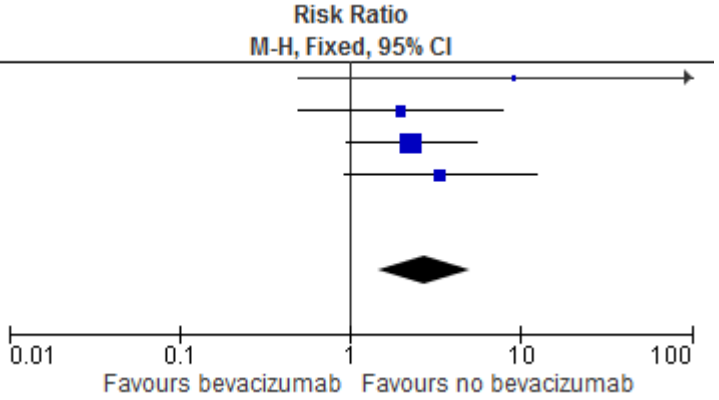


Figure 34 – Hypertension grade 3+

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0213	39	330	2	327	40.0%	19.32 [4.70, 79.36]
ICON7	46	745	2	753	39.6%	23.25 [5.66, 95.42]
OCEANS	43	247	1	233	20.5%	40.56 [5.63, 292.18]
Total (95% CI)		**1322**		**1313**	**100.0%**	**25.22 [10.34, 61.51]**
Total events	128		5			

Heterogeneity: Chi² = 0.37, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 7.10 (P < 0.00001)

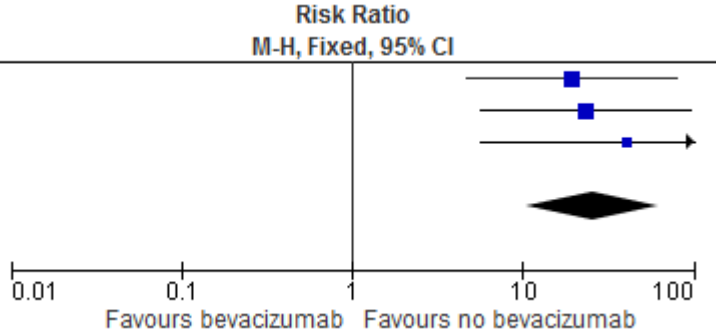


Figure 35 – Proteinuria grade 3+

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
GOG-0213	27	330	0	327	14.6%	54.50 [3.34, 889.76]
GOG-0218	10	608	4	601	35.1%	2.47 [0.78, 7.84]
ICON7	4	745	1	753	20.0%	4.04 [0.45, 36.09]
OCEANS	21	247	2	233	30.3%	9.90 [2.35, 41.78]
Total (95% CI)		**1930**		**1914**	**100.0%**	**6.52 [1.83, 23.23]**
Total events	62		7			

Heterogeneity: Tau² = 0.85; Chi² = 6.35, df = 3 (P = 0.10); I² = 53%
Test for overall effect: Z = 2.89 (P = 0.004)

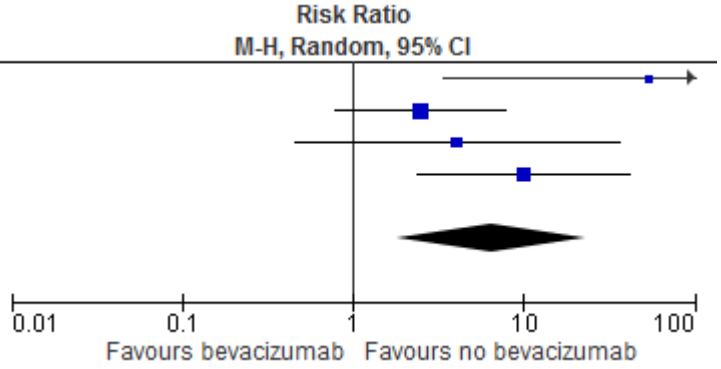


Figure 36 – Neutropenia grade 3+

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0213	276	330	255	327	69.3%	1.07 [1.00, 1.16]
ICON7	123	745	114	753	30.7%	1.09 [0.86, 1.38]
Total (95% CI)		**1075**		**1080**	**100.0%**	**1.08 [0.99, 1.18]**
Total events	399		369			

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.66 (P = 0.10)

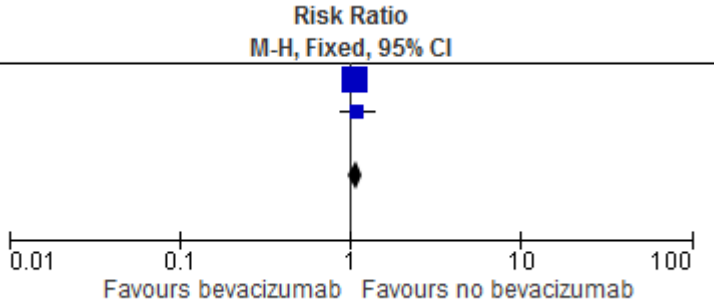


Figure 37 – Febrile neutropenia

Study or Subgroup	Bevacizumab Events	Bevacizumab Total	No bevacizumab Events	No bevacizumab Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0213	20	330	9	327	18.4%	2.20 [1.02, 4.76]
GOG-0218	26	608	21	601	42.9%	1.22 [0.70, 2.15]
ICON7	21	745	15	753	30.3%	1.42 [0.74, 2.72]
OCEANS	4	247	4	233	8.4%	0.94 [0.24, 3.73]
Total (95% CI)		**1930**		**1914**	**100.0%**	**1.44 [1.01, 2.06]**
Total events	71		49			

Heterogeneity: Chi² = 1.85, df = 3 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.99 (P = 0.05)

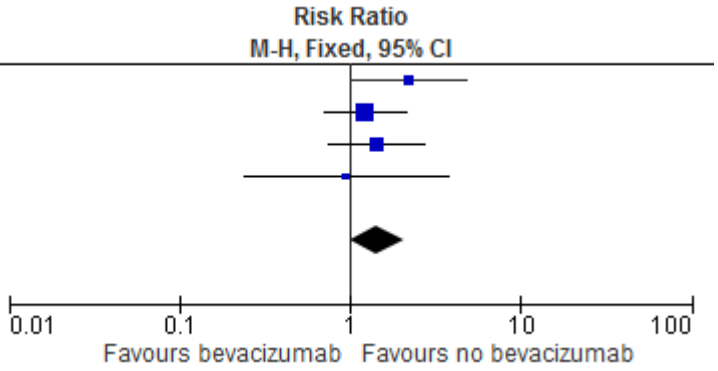


Figure 38 – Venous thromboembolism grade 3+

Study or Subgroup	Bevacizumab Events	Bevacizumab Total	No bevacizumab Events	No bevacizumab Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0213	13	330	4	327	17.4%	3.22 [1.06, 9.77]
ICON7	32	745	13	753	55.9%	2.49 [1.32, 4.70]
OCEANS	10	247	6	233	26.7%	1.57 [0.58, 4.26]
Total (95% CI)		**1322**		**1313**	**100.0%**	**2.37 [1.47, 3.83]**
Total events	55		23			

Heterogeneity: Chi² = 0.97, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 3.52 (P = 0.0004)

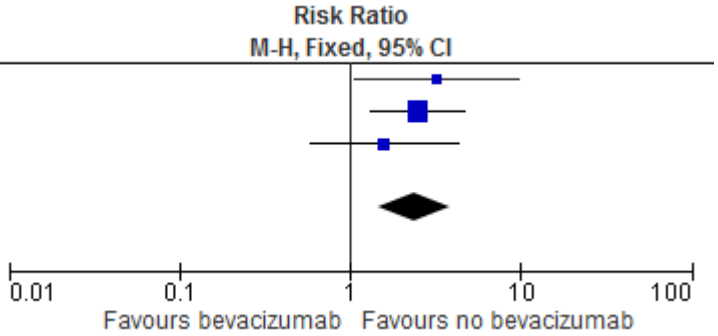


Figure 39 – Arterial thromboembolism any grade

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
AURELIA	4	179	0	181	3.5%	9.10 [0.49, 167.79]
GOG-0213	8	330	2	327	12.4%	3.96 [0.85, 18.52]
GOG-0218	4	608	5	601	17.0%	0.79 [0.21, 2.93]
ICON7	27	745	11	753	54.9%	2.48 [1.24, 4.96]
OCEANS	7	247	2	233	12.1%	3.30 [0.69, 15.73]
Total (95% CI)		**2109**		**2095**	**100.0%**	**2.35 [1.35, 4.07]**
Total events	50		20			

Heterogeneity: Tau² = 0.02; Chi² = 4.16, df = 4 (P = 0.38); I² = 4%
Test for overall effect: Z = 3.03 (P = 0.002)

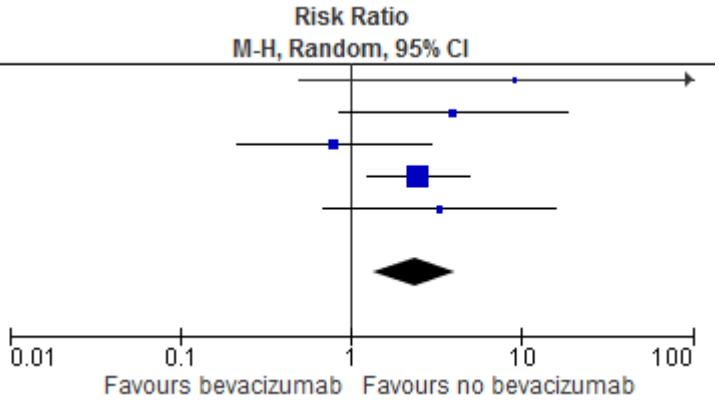


Figure 40 – Wound healing complication grade 3+

Study or Subgroup	Bevacizumab Events	Total	No bevacizumab Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
AURELIA	0	179	0	181		Not estimable
GOG-0213	3	330	0	327	13.8%	6.94 [0.36, 133.76]
ICON7	10	745	3	753	73.0%	3.37 [0.93, 12.19]
OCEANS	2	247	0	233	13.2%	4.72 [0.23, 97.75]
Total (95% CI)		**1501**		**1494**	**100.0%**	**3.89 [1.30, 11.68]**
Total events	15		3			

Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 2 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.42 (P = 0.02)

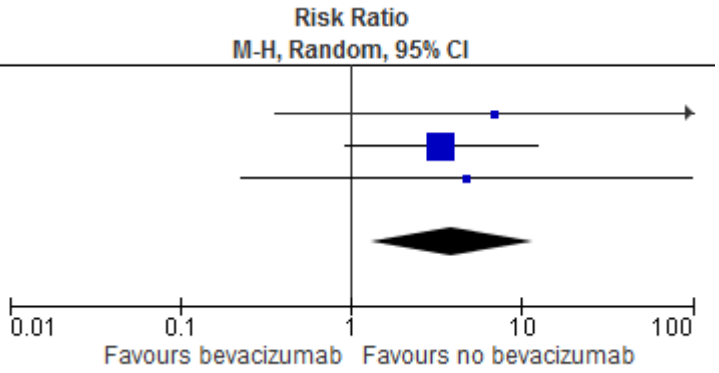


Figure 41 – Non-CNS-bleeding grade 3+

Study or Subgroup	Bevacizumab Events	Bevacizumab Total	No bevacizumab Events	No bevacizumab Total	Weight	Risk Ratio M-H, Random, 95% CI
GOG-0213	6	330	3	327	27.2%	1.98 [0.50, 7.86]
GOG-0218	13	608	5	601	49.0%	2.57 [0.92, 7.16]
OCEANS	14	247	2	233	23.8%	6.60 [1.52, 28.74]
Total (95% CI)		**1185**		**1161**	**100.0%**	**3.00 [1.46, 6.15]**
Total events	33		10			

Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 3.00 (P = 0.003)

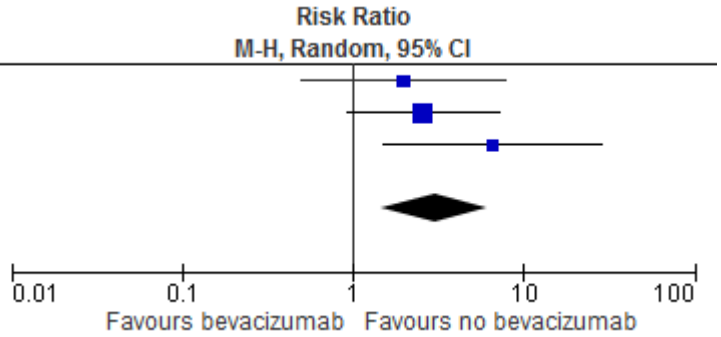
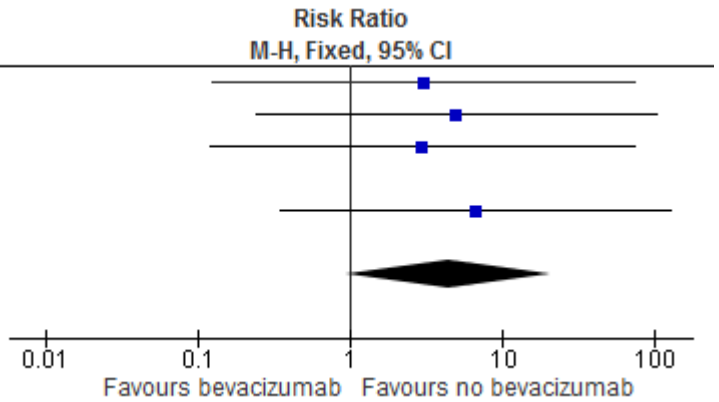


Figure 42 – Reversible posterior leukoencephalopathy syndrome

Study or Subgroup	Bevacizumab Events	Bevacizumab Total	No bevacizumab Events	No bevacizumab Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AURELIA	1	179	0	181	24.7%	3.03 [0.12, 73.97]
GOG-0213	2	330	0	327	24.9%	4.95 [0.24, 102.81]
GOG-0218	1	608	0	601	24.9%	2.97 [0.12, 72.65]
ICON7	0	745	0	753		Not estimable
OCEANS	3	247	0	233	25.5%	6.60 [0.34, 127.18]
Total (95% CI)		**2109**		**2095**	**100.0%**	**4.41 [0.95, 20.41]**
Total events	7		0			

Heterogeneity: Chi² = 0.19, df = 3 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.90 (P = 0.06)



7. COST INFORMATION OF IDENTIFIED ECONOMIC EVALUATIONS

Table 19 – Cost information - NICE TA284, 2012 (UK)

Perspective of the NHS and Personal Social Services (PSS)			
UK pounds sterling (£), 2010-2012*			
Drug cost (per patient, per cycle)			
Bevacizumab			£2,229
Paclitaxel			£21.80
Carboplatin			£18.51
Administration and pharmacy cost (per cycle)			
Carboplatin and paclitaxel (first cycle)			£274.57
Carboplatin and paclitaxel (subsequent cycles)			£94.27
Bevacizumab (first 6 cycles)			£9.20
Bevacizumab (given as monotherapy)			£94.27
Mean treatment duration (GOG 218) (weeks)	PC		PCB + mB
Carboplatin + paclitaxel	16.55		17.66
Bevacizumab			41.93
Mean treatment duration (ICON7) (weeks)	PC		PCB + mB
Carboplatin	15.96		16.35
Paclitaxel	15.66		16.17
Bevacizumab			42.99
Health states and associated costs		Unit cost	Weekly value
PFS - Outpatient visit to consultant oncologist (once every 3 months)		£134	£10.31
Total PFS			*£10.32*
PD - Outpatient visit to consultant oncologist (once per month)		£135	£30.92
PD - CT scan (once every 2 months)		£114	£13.15
Total PD			*£44.07*
List of adverse events and summary of costs (GOG 218)			
(only AEs with a cost per episode are mentioned in this table)		Cost/episode	
Dehydration & Diarrhoea		£940	
Febrile Neutropenia		£5,373	
Haemaglobin decreased		£58	
Hypokalaemia & Hyponatraemia		£940	
Neutrophil count decreased & Neutrophil count decreased (Grade 4)		£738	
Platelet count decreased & Platelet count decreased (Grade 4)		£58	
White blood cell count decreased & White blood cell count decreased (Grade 4)		£738	
List of adverse events and summary of costs (ICON7)			
(only AEs with a cost per episode are mentioned in this table)			
Anaemia		£ 518	
Dyspnoea		£ 236	
Febrile Neutropenia		£ 5,373	
Neutropenia & Neutropenia (Grade 4)		£ 253	
Pulmonary Embolism (Grade 4)		£ 1,362	
Thrombocytopenia		£ 58	
Post-progression treatments	PC		PCB + mB
GOG-0218	not included		not included
ICON7	£3643		£2958
Palliative care costs		£6727	
Model cost outputs by clinical outcome (GOG 218)	PC		PCB + mB
PFS	£5,281		£32,588
PD	£5,593		£5,417
Palliative care	£6,292		£6,248
Total	£17,166		£44,254
Model cost outputs by clinical outcome (ICON7)	PC		PCB + mB
PFS	£1,793		£19,447
PD	£7,917		£8,208
Palliative care	£6,406		£6,190
Total	£16,116		£33,846

**: Resource use in each health state was based on a previous NICE appraisal in ovarian cancer with costs referring to 2010/11. Drug costs (2012) were obtained from the British National Formulary (bevacizumab) or DH Commercial Medicines Unit (paclitaxel and carboplatin).*

Table 20 – Cost information - Cohn et al., 2011 (US)[24]

Third-party payer US dollars, 2009			
Treatment	PC	PCB	PCB + mB
Chemotherapy costs	$440	$6180	+$5740*
Antiemetic medications	$170	$170	+$0*
Infusion of medications	$390	$390	+$200*
Total costs (per cycle)	$1000	$6740	+$5940*
Complications:			
Cost of fatal perforations		$25000	
Cost of nonfatal perforations		$138000	

**: the additional cost of maintenance bevacizumab alone (above the cost of PCB).*

Table 21 – Cost information - Cohn et al., 2015 (US)[25]

Third-party payer US dollars, 2013	PC	PCB	PCB + mB
Treatment cost (per cycle)	$449	$7127	$7127 + $6999
Erythropoietin use, % of all cycles including placebo	6.5%	4.5%	4.2%
Granulocyte colony-stimulating factor use, % of all cycles	5.6%	4.9%	5.5%
Cost growth factors (per cycle)			
Darbepoetin alfa		$1670	
Pegfilgrastim		$2940	
Complications:			
Hypertensive crisis		$5756	
Bowel perforation		$29,375	

Table 22 – Cost information - Mehta et al., 2014 (US)[26]

Mehta et al., 2014 (US)	Societal perspective US dollars, 2013 No transparent details provided for all cost variables.

Table 23 – Cost information - Lesnock et al., 2011 (US)[27]

Perspective of the health care system US dollars, 2009		
Treatment	Estimate	Range
Administration of infusion	$551	$0 – $551
Carboplatin (C), 150 mg	$268.75	$0 – $268.75
Paclitaxel (P), 6 mg/ml, 50 ml	$155.16	$0 – $155.16
Bevacizumab, 25 mg/ml, 16 ml,	$2191.45	$0 – $2191.45
Surveillance		
Office visit	$205	$0 – $205
Lab work	$125	$0 – $125
CA-125	$98	$0 – $98
CT scan	$2841	
Toxicities (costs)		
Bowel perforation	$31,113	$15–60,000
Neuropathy (per episode)	$844	$400–1600

Table 24 – Cost information - Barnett et al., 2013 (US)[28]

Third-party payer perspective		
US dollars, 2011		
Treatment:	estimate	range
Carboplatin/paclitaxel chemotherapy, primary or relapse setting, one cycle:	$508	$250-$1,000
Primary chemotherapy with bevacizumab, one cycle:	$3,266	$1,500-$6,000
Maintenance bevacizumab, one cycle:	$3,064	$1,500-$6,000
Relapse chemotherapy, non-platinum based, one cycle:	$3,923	$2,000-$8,000
Relapse chemotherapy, bevacizumab, one cycle:	$3,064	$1,500-$6,000
Predictive test for bevacizumab responsiveness:	$500	$500-$5,000
Complications:		(median)
Gastrointestinal Perforation	$27,720	($19,874)
Venous Thromboembolism	$10,269	($7,828)
Minor Adverse Event (Hypertension)	$2,081	$1,041-4162

Table 25 – Cost information - Chan et al., 2014 (US)[29]

Health care system perspective	
US dollar, year not mentioned	
Treatment	
PC (6 cycles), cost per cycle:	$535 per cycle
PCB (6 cycles) + mB (12 cycles), cost per cycle:	$3,760 (PCB) and $3,225 (mB)
Complication cost:	$2,000 each occurrence

Table 26 – Cost information - Duong et al., 2016 (Canada)[30]

Third-party payer			
Canadian dollars (CAD), 2014			
	PC		PCB + mB
Drug acquisition costs (CAD per cycle)	CAD153		CAD2653
	PC (cycle 1-6)	PCB + mB (cycle 2-6)	PCB + mB (cycle 7-18)
Administration costs (CAD per cycle)	CAD534	CAD600	CAD104
Supportive care costs (CAD weekly)			
PFS state	CAD8		
Progression state	CAD17		
Adverse event costs (CAD)			
PC	CAD1455		
PCB + mB	CAD1799		

Table 27 – Cost information - Hinde et al., 2016 (UK)[31]

Perspective of the NHS and Personal Social Services.		
UK pounds sterling (£), 2013		
	Mean cost (SE)	
Mean costs per day estimated for the high-risk subgroup:	PC	PCB + mB
Preprogression		
0–1 y	£15.11 (1.67)	£12.98 (2.06)
1–2 y	£3.28 (1.18)	£7.51 (2.37)
2–5 y	£1.25 (1.06)	£5.81 (3.09)
Postprogression	£3.00 (0.56)	£2.40 (0.65)
Trial drugs	£20.19 (0.66)	£72.67 (1.64)

Table 28 – Cost information - Chappell et al., 2016 (US)[32]

Perspective not explicitly mentioned (third-party payer)		
US dollars, 2014		
Treatment	chemo	chemo + B
Model 1:		
Bevacizumab 10 mg/kg (per dose)		$9,338
PLD (per dose)	$3,627	$13,034
Weekly topotecan (per dose)	$701	$10,039
Weekly paclitaxel (per dose)	$387	$9,725
Average cost	$1,572	$10,933
Average number of cycles	3	6
Model 2:		
Topotecan every 3 weeks (per dose)	$654	$7,658
Bevacizumab 15 mg/kg (per dose)		$7,004
Average no. of cycles	3	6
Salvage bevacizumab (occurence)	40%	0%
Salvage bevacizumab (cost per dose, 15 mg/kg)	$6,673.91	
Complications:		
GI fistula	$31,079	
Paracentesis	$112	
Hypertension	$1133	

Table 29 – Cost information - NICE TA285, 2012 (UK)

Perspective of the NHS and Personal Social Services (PSS)			
UK pounds sterling (£), 2010-2012*			
Drug cost (per patient, per cycle)			
Bevacizumab			£2,556
Gemcitabine			£21,53
Carboplatin			£155.43
Administration and pharmacy cost (per cycle)			
Carboplatin and gemcitabine (first cycle)			£274.57
Carboplatin and gemcitabine (subsequent cycles)			£94.27
Gemcitabine (given as monotherapy)			£89.67
Bevacizumab (in combination with chemotherapy)			£4.60
Bevacizumab (given as monotherapy)			£89.67
Mean treatment duration (OCEANS) (weeks)	CG		CGB
Carboplatin	20.50		20.11
Gemcitabine	22.50		22.93
Bevacizumab			50.74
Health states and associated costs		Unit cost	Weekly value
PFS - Outpatient visit to consultant oncologist (once per month)		£134	£30.92
PFS - CT scan (once every 2 months)		£114	£13.15
Total PFS			*£44.07*
PD - Outpatient visit to consultant oncologist (once every 3 months)		£134	£10.31
Total PD			*£10.31*
List of adverse events and summary of costs (OCEANS)			
(only AEs with a cost per episode are mentioned in this table)			
Thrombocytopenia & Thrombocytopenia (grade 4)			£58
Leukopenia & Neutropenia & Neutropenia (grade 4)			£253
Hypertension			£441
Anaemia			£518
Neutrophil count decreased & Neutrophil count decreased (Grade 4) & White blood cell count decreased			£738
Adverse events: total cost used in the model			
Bevacizumab + chemotherapy group			£224
Chemotherapy group			£146
Post-progression treatments (Subsequent lines of chemotherapy, Radiotherapy & Surgical procedures)			
Bevacizumab + chemotherapy group			£1553
Chemotherapy group			£2916
Palliative care costs			£6727

**: year of costing not explicitly mentioned. Unit cost data were retrieved from four major sources referring to the period 2010-2012.*

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