Anti-angiogenic treatments for recurrent ovarian cancer: When, Which, for How long?

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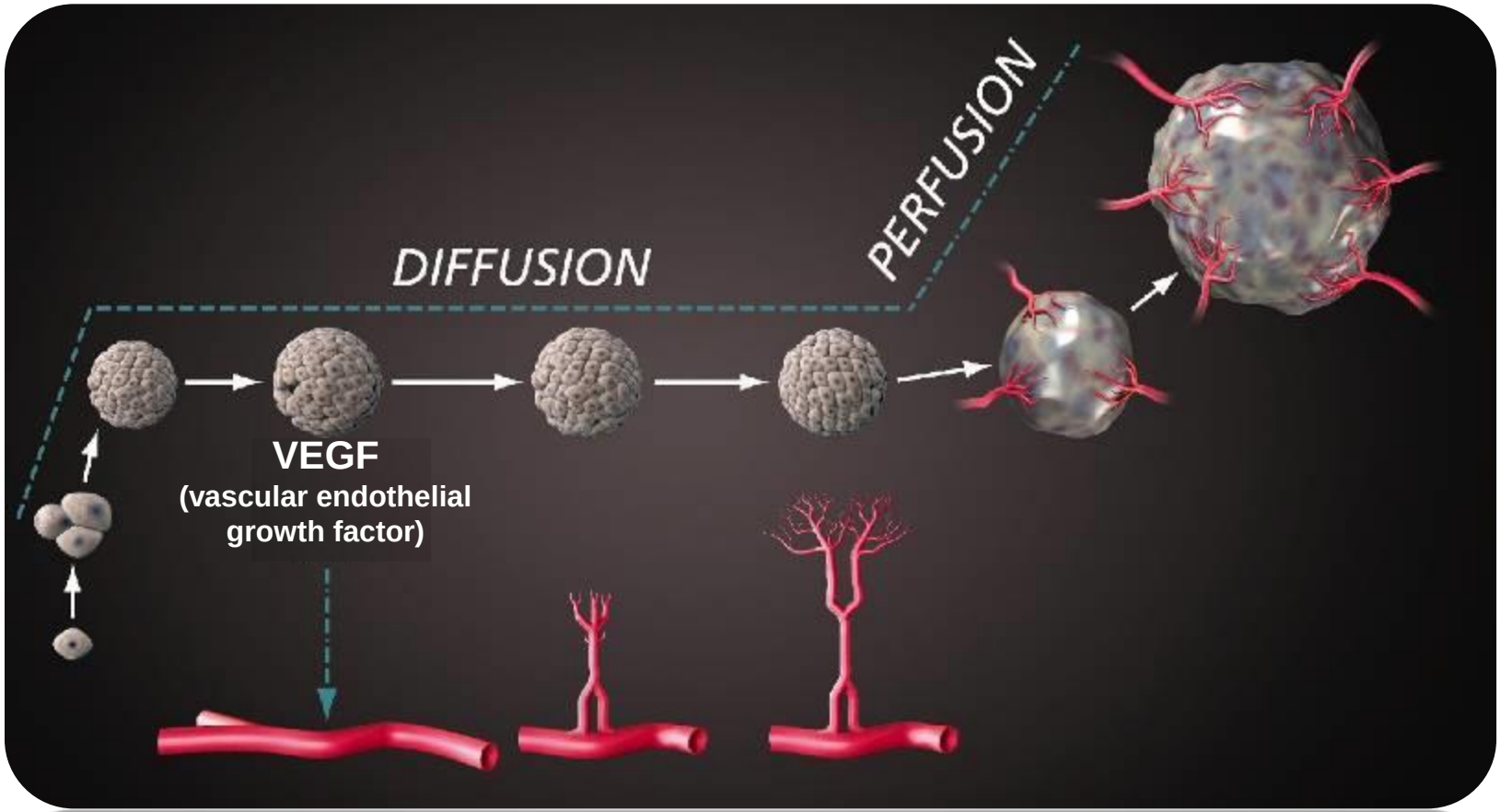
Angiogenesis

Angiogenesis is essential for sustained tumour growth

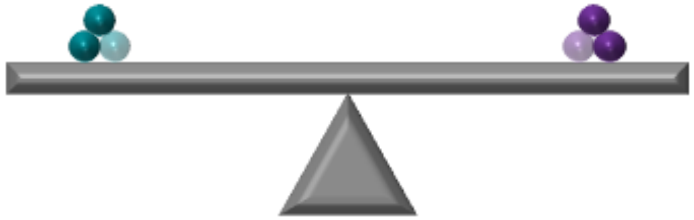


1. Folkman. N EJM 1971; 2. Jain, et al. Nat Rev Neurosci 2007

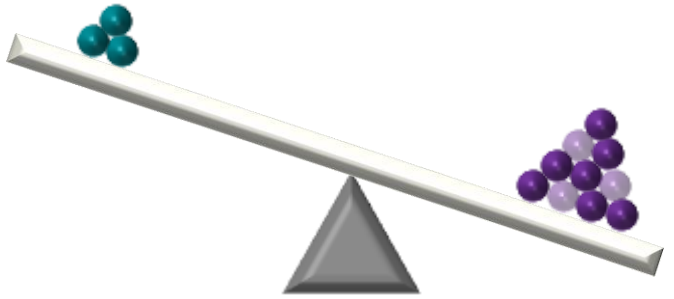
Angiogenesis is triggered by the production of an excess of pro-angiogenic molecules[1]

Anti-angiogenic factors (e.g. thrombospondin-1, angiostatin, IFN-α/β)

Pro-angiogenic factors (e.g. VEGF, bFGF, IL-8)



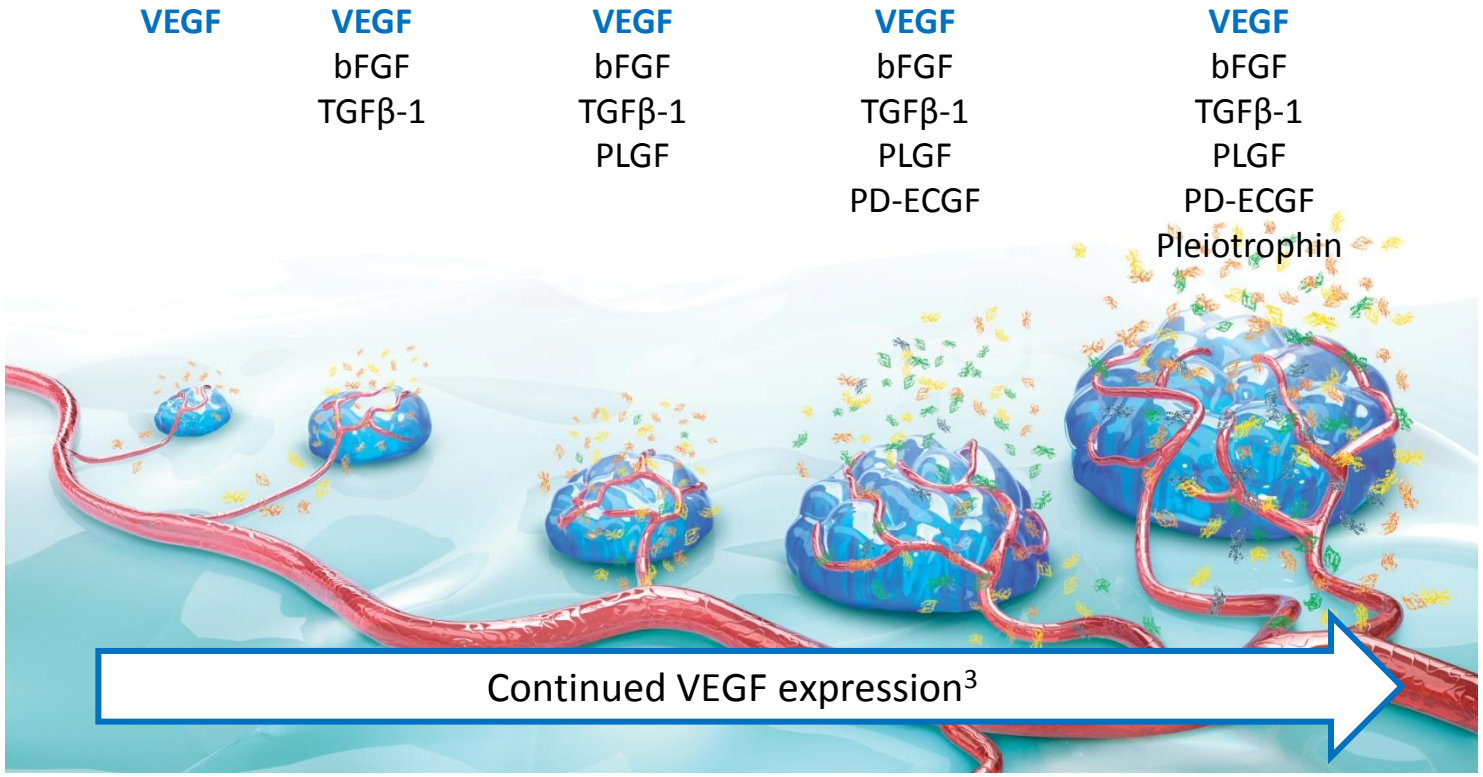
Under normal physiological conditions, the production of pro- and anti-angiogenic molecules is finely balanced



In cancer, angiogenesis is triggered by the production of an excess of pro-angiogenic factors

1. Jain, et al. Nat Rev Neurosci 2007

VEGF is an early and persistent promoter of tumour angiogenesis

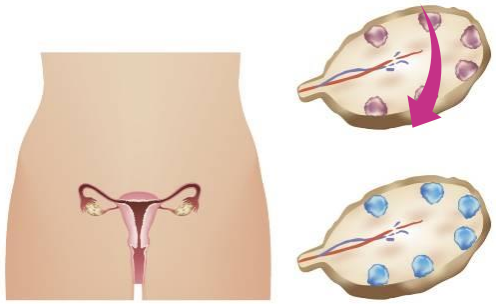


- Tumours continually require VEGF to recruit new vasculature[5]
- VEGF continues to be expressed throughout tumour progression, even as secondary pathways emerge[2,3,6,7]

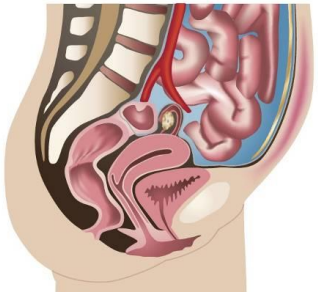
Graphical elaboration from text data.

1. Bergers G, Benjamin LE. Nat Rev Cancer 2003; 3(6): 401-10; 2. Kim KJ, et al. Nature. 1993; 362(6423):841-4; 3. Folkman J. In: DeVita, Hellman, Rosenberg, eds. Cancer: Principles & Practice of Oncology. Vol 2. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005; 4. Ferrara N, et al. Nat Med. 2003; 9(6): 669-76; 5. Inoue M, et al. Cancer Cell 2002; 1(2): 193-202; 6. Mesiano S, et al. Am J Pathol 1998; 153(4): 1249-56; 7. Melnyk O, et al. J Urol 1999; 161(3): 960-3.

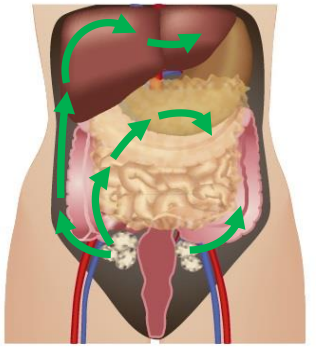
VEGF is highly expressed in ovarian cancer, with multiple effects



Switch from benign to malignant growth pattern.[1]



Accumulation of ascites, by increasing peritoneal blood vessel permeability.[1–5]

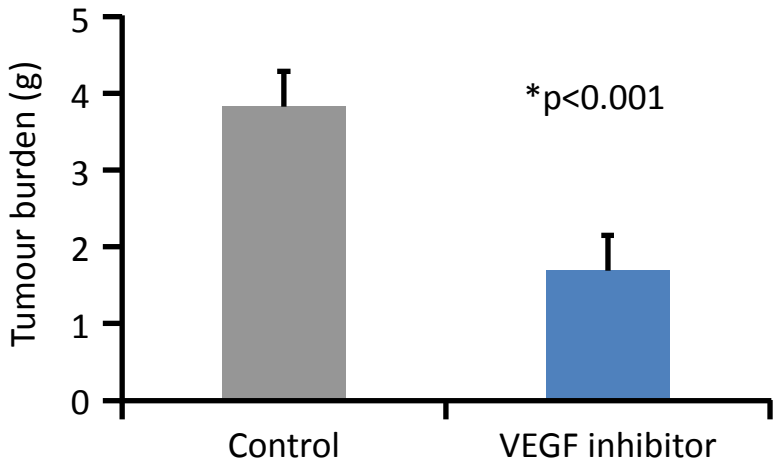


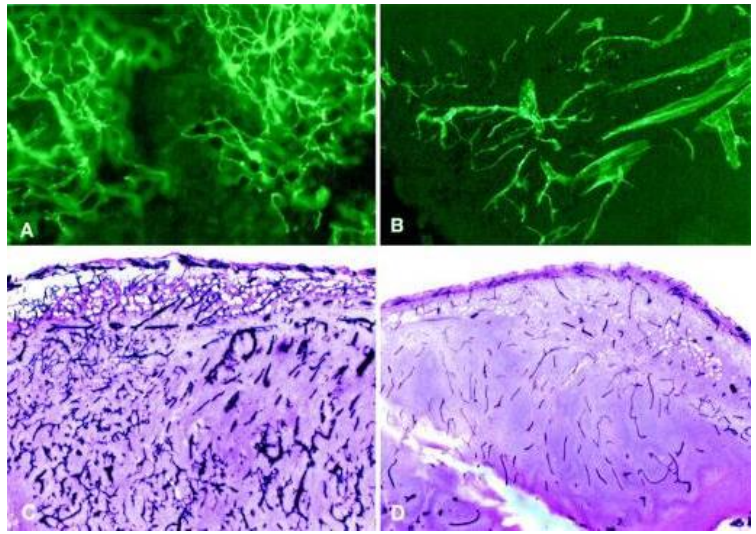
Formation of the metastases typical of ovarian cancer on the peritoneum.[3]

Graphical elaboration from text data.

1. Schumacher JJ, et al. Cancer Res. 2007; 67(8): 3683-90; 2. Ramakrishnan S, et al. Angiogenesis. 2005; 8(2): 169-82; 3. Zhang L et al. Am J Pathol. 2002; 161(6): 2295-309; 4. Trinh XB, et al. Br J Cancer. 2009; 100(6): 971-8; 5. Belotti D, et al. Cancer Res. 2003;63(17): 5224-9.

Angiogenesis (VEGF) in ovarian cancer





Preclinical data

- VEGF inhibitors inhibit tumour growth, abrogate ascites formation and normalise vessels

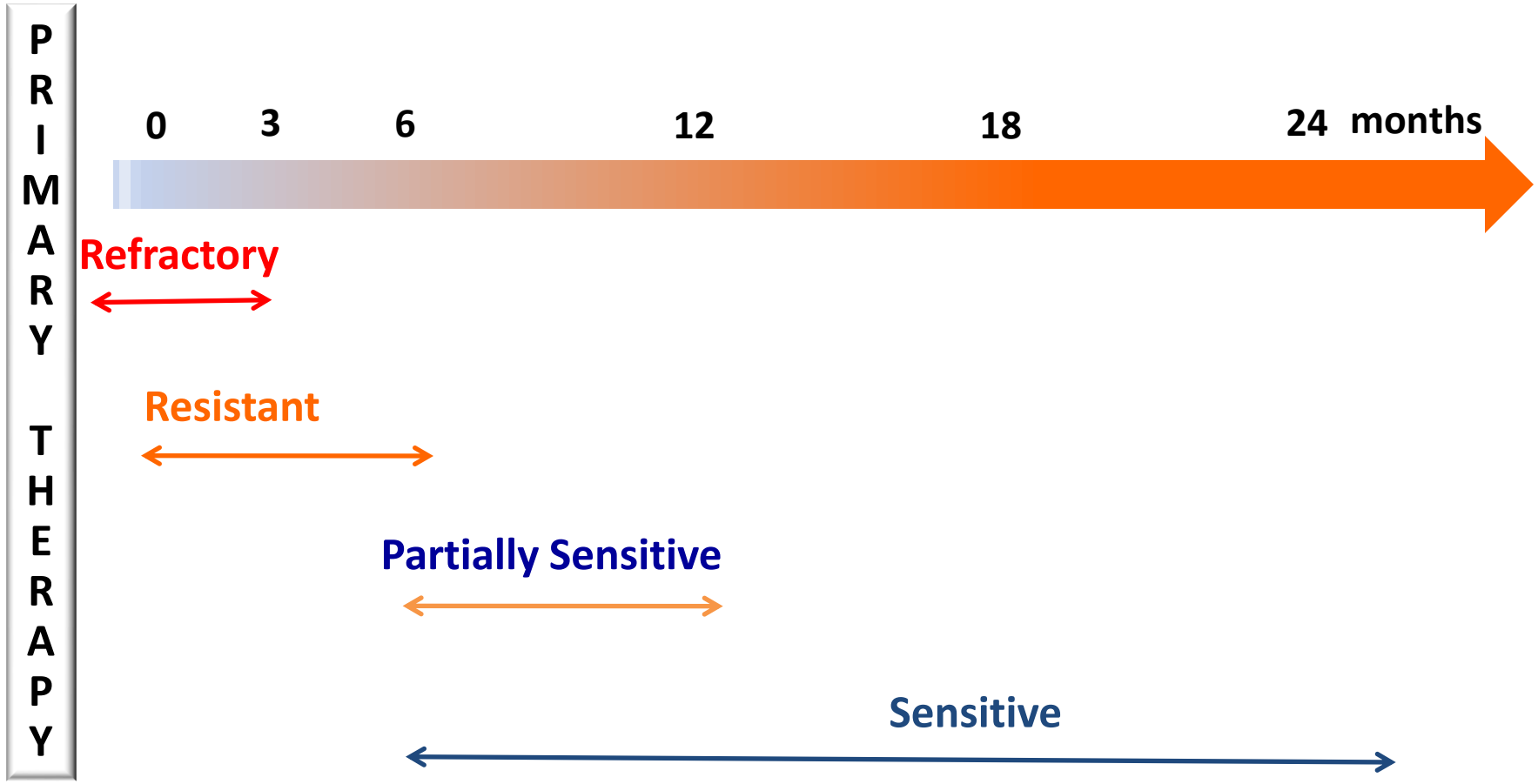
Human data

- VEGF overexpressed and associated with worse outcome
- Associated with ascites and carcinomatosis
- VEGF inhibition is synergistic with chemotherapy

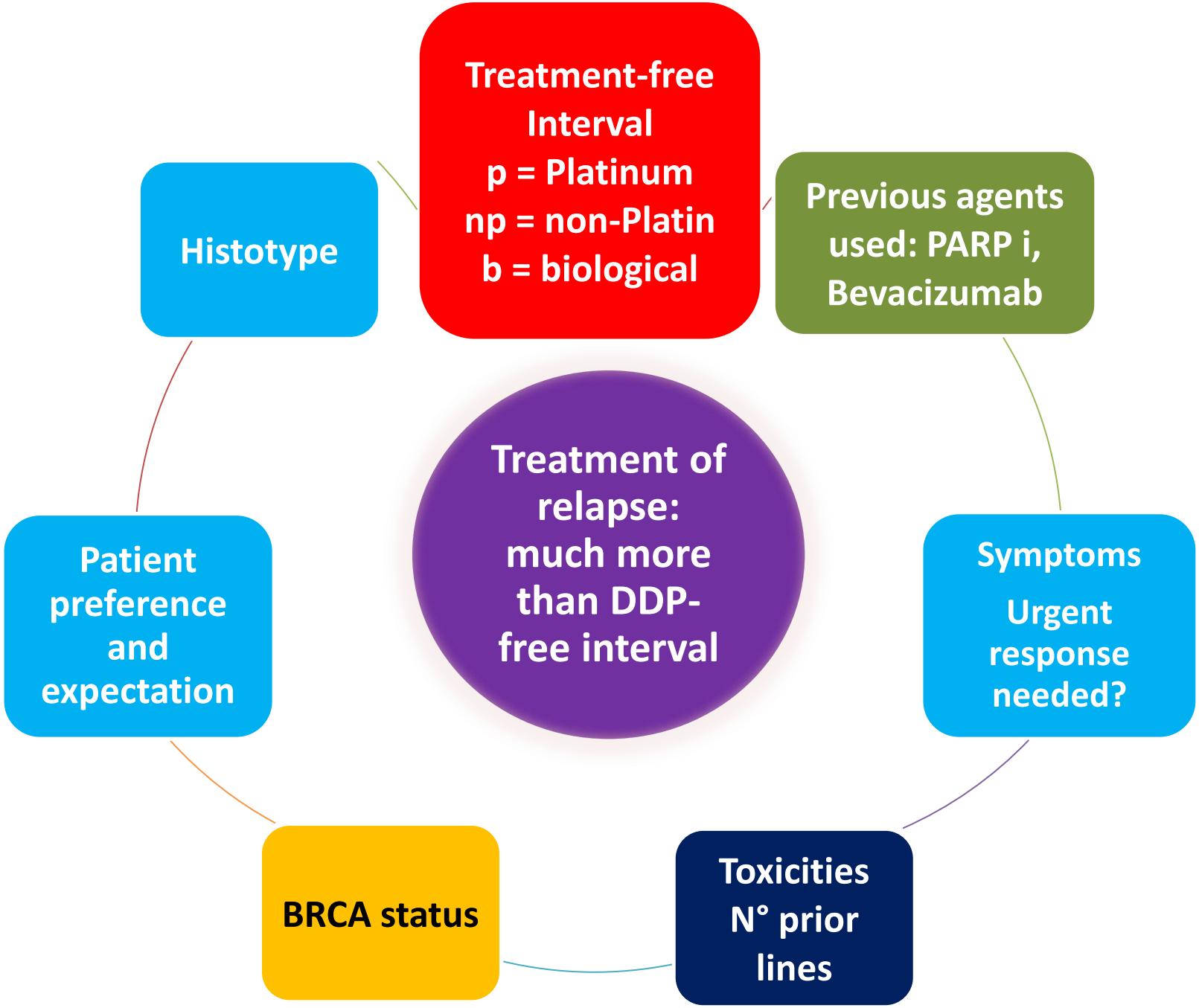
Zhang, et al. Cancer Res 2003; Bozas, et al. Int J Gynecol Cancer 2010
Li, et al. Anticancer Res 2004; Byrne, et al. Clin Cancer Res 2003

Anti-angiogenic treatments for recurrent ovarian cancer: When, Which, for How long?

The “old “ definition of Recurrent Ovarian Cancer



Pisano C, et al. *Ther Clin Risk Manag.* 2009;5(5):421-426. Gadducci A, et al. *Anticancer Res.* 2001;21(5):3525-3533.

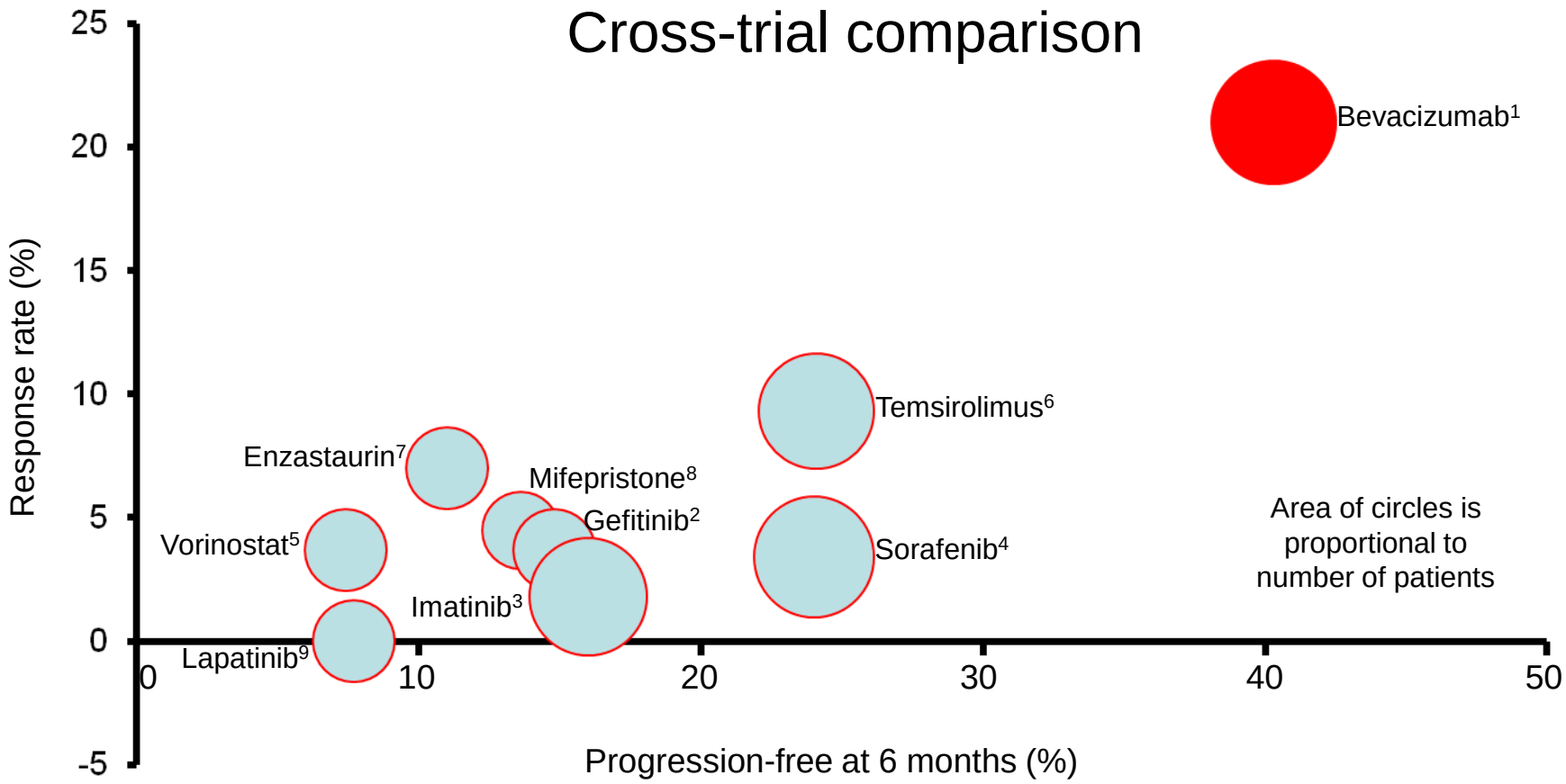

Treatment-free Interval
p = Platinum
np = non-Platin
b = biological
Previous agents used: PARP i, Bevacizumab
Symptoms
Urgent response needed?
Toxicities
N° prior lines
BRCA status
Patient preference and expectation
Histotype
Treatment of relapse: much more than DDP-free interval

Anti-VEGF Therapy

BEVACIZUMAB

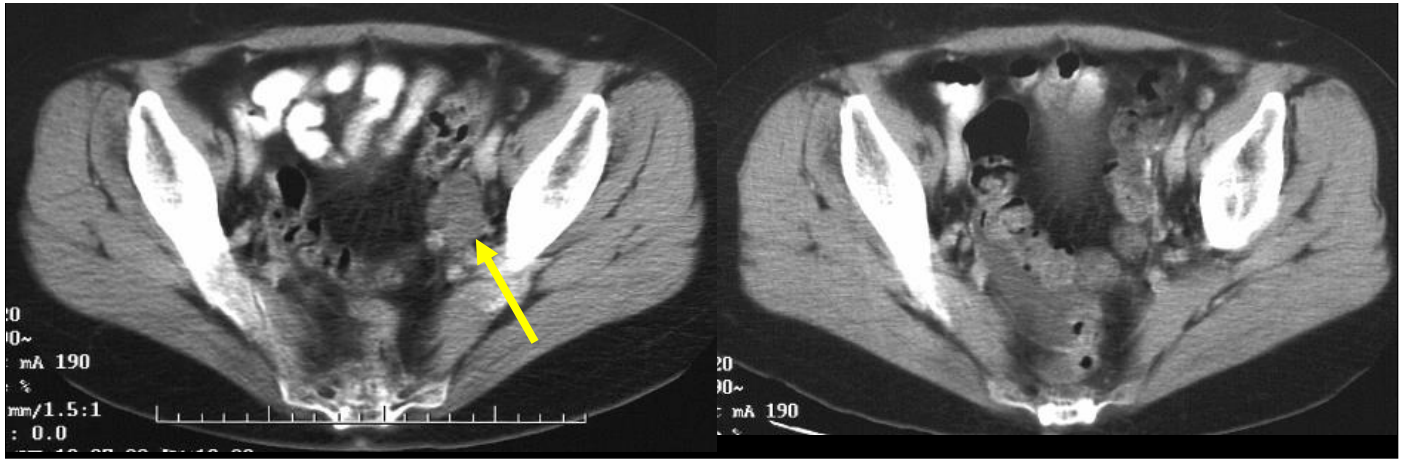
- Humanized monoclonal antibody against VEGFA
- Binds and neutralizes all VEGFA isoforms
- Elimination through the reticulo-endothelial system
- 2-3 weeks half-life after IV infusion

Bevacizumab appears to be active as a single agent in ovarian cancer



- Reproduced with kind permission from Professor Michael Bookman, Arizona Cancer Center, Tucson, AX, USA
- 1. Burger, et al. JCO 2007; 2. Schilder, et al. Clin Cancer Res 2005; 3. Schilder, et al. JCO 2008; 4. Matei, et al. JCO 2011; 5. Modesitt, et al. Gynecol Oncol 2008; 6. Behbakht, et al. Gynecol Oncol 2010; 7. Usha, et al. Gynecol Oncol 2011; 8. Rocereto, et al. Gynecol Oncol 2010; 9. Data from GOG phase II database (2009)

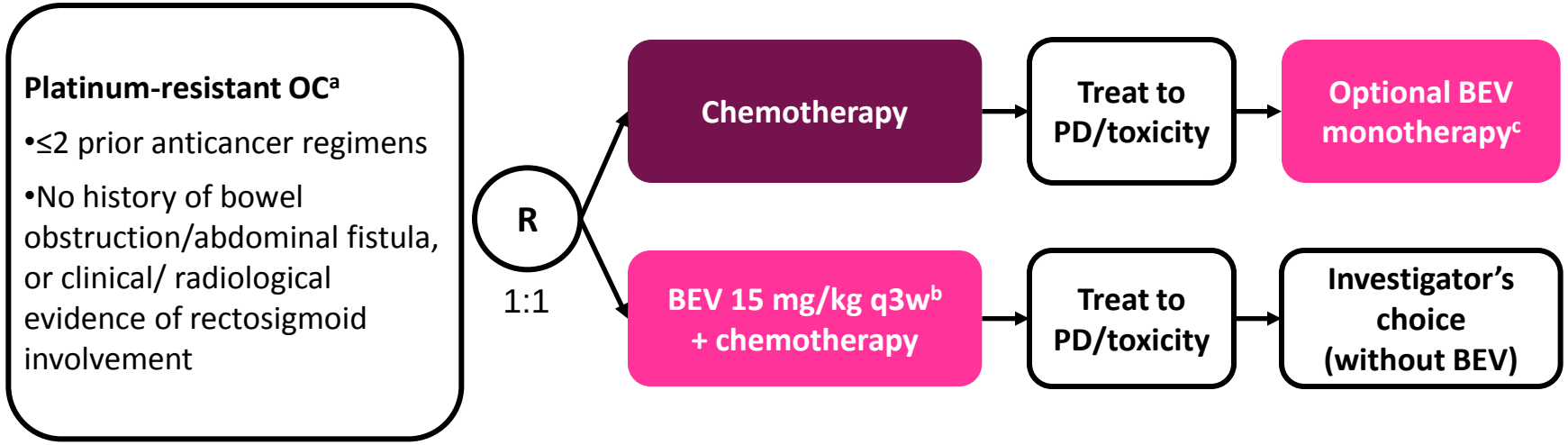
Single-agent bevacizumab in ovarian cancer: more effective than in any other solid tumour except renal



	n	Prior regimens	Platinum sensitive	Platinum resistant	Study therapy	OR (%)	Median PFS (months)	Median OS (months)
Burger 2007[1]	62	≤2	✓	✓	bevacizumab	21	4.7	17
Cannistra 2007[2]	44	2–3		✓	bevacizumab	16	4.4	10.7
Smerdel 2009[3]	38	Median 5	✓	✓	bevacizumab	30	5.9	8.6

1. Burger, et al. JCO 2007; 2. Cannistra, et al. JCO 2007; 3. Smerdel, et al. Gynecol Oncol 2010

AURELIA trial design



Stratification factors:

- **Chemotherapy selected**
- **Prior anti-angiogenic therapy**
- **Treatment-free interval (<3 vs 3–6 months from previous platinum to subsequent PD)**

Chemotherapy options (investigator's choice):

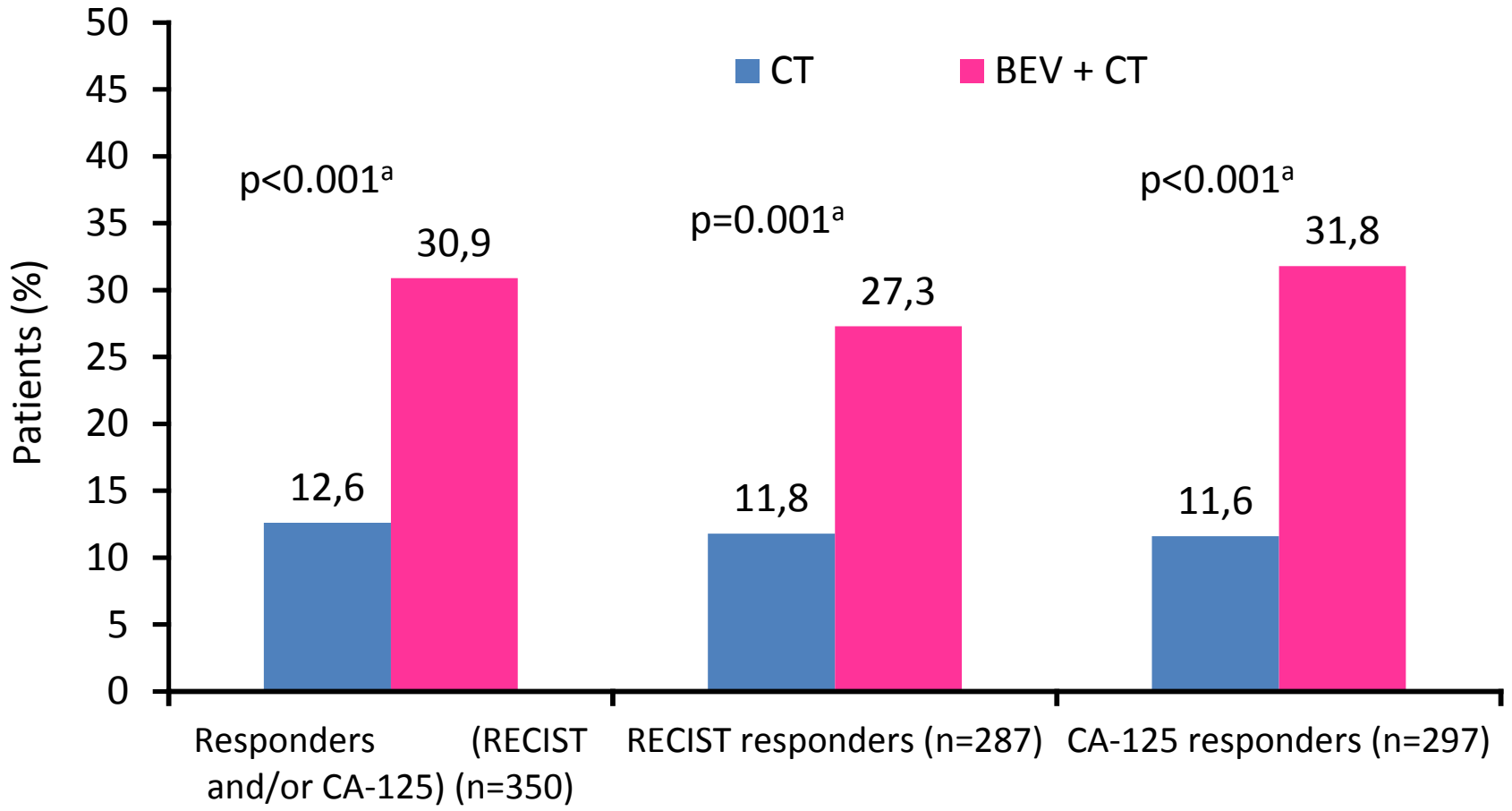
- **Paclitaxel 80 mg/m^2 days 1, 8, 15, & 22 q4w**
- **Topotecan 4 mg/m^2 days 1, 8, & 15 q4w (or 1.25 mg/m^2, days 1–5 q3w)**
- **PLD 40 mg/m^2 day 1 q4w**

PD = progressive disease

[a]Epithelial ovarian, primary peritoneal, or fallopian tube cancer; [b]Or 10 mg/kg q2w; [c]15 mg/kg q3w, permitted on clear evidence of progression

Pujade-Lauraine et al. J Clin Oncol. 2014 Mar 17

Summary of best overall response rates



•[a]*Two-sided chi-square test with Schouten correction*

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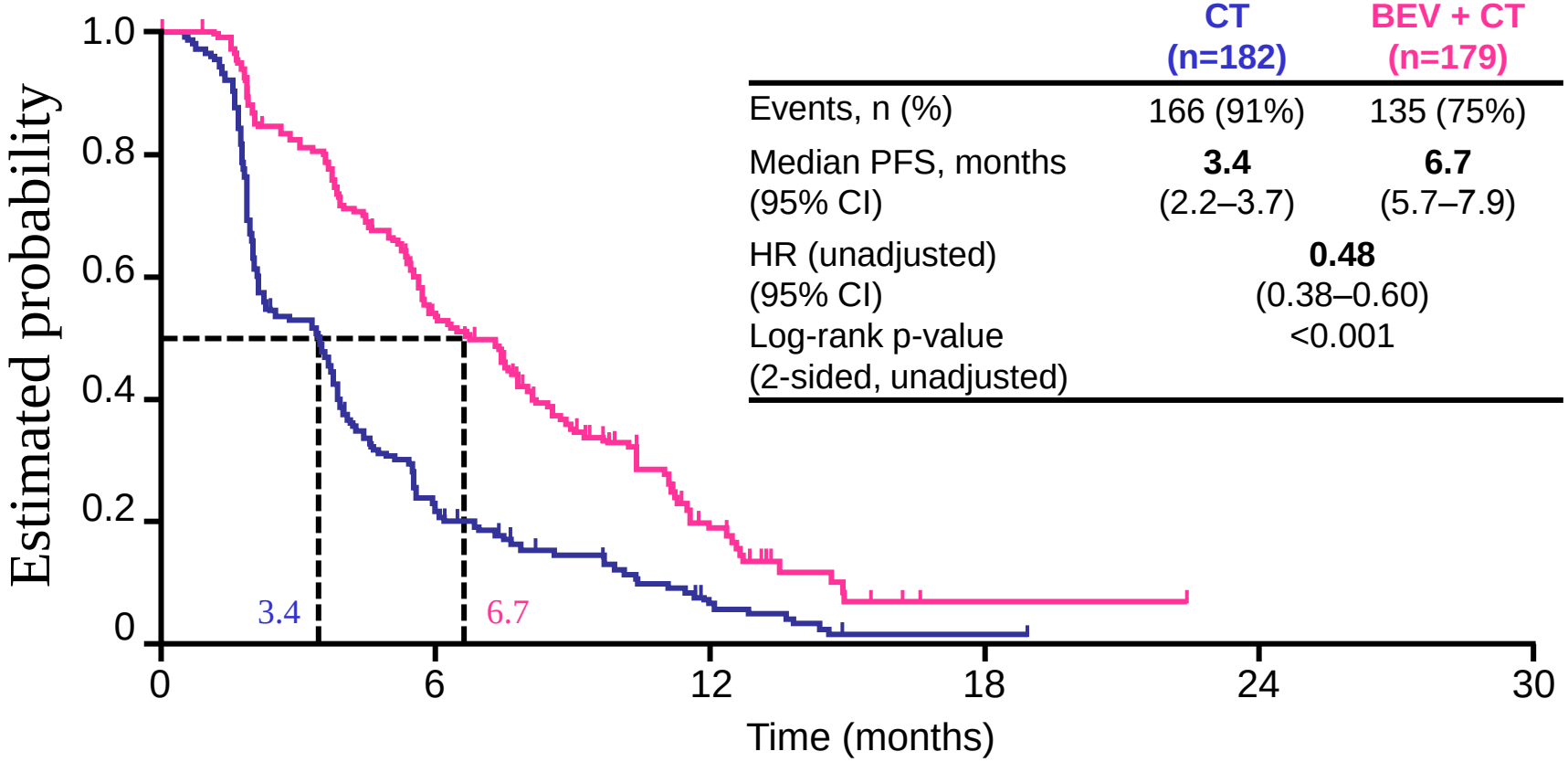
Significant increased Progression-free survival with bevacizumab in platinum resistant recurrent ovarian cancer: Aurelia trial



	CT (n=182)	BEV + CT (n=179)
Events, n (%)	166 (91%)	135 (75%)
Median PFS, months (95% CI)	**3.4** (2.2–3.7)	**6.7** (5.7–7.9)
HR (unadjusted) (95% CI)	**0.48** (0.38–0.60)	
Log-rank p-value (2-sided, unadjusted)	<0.001	

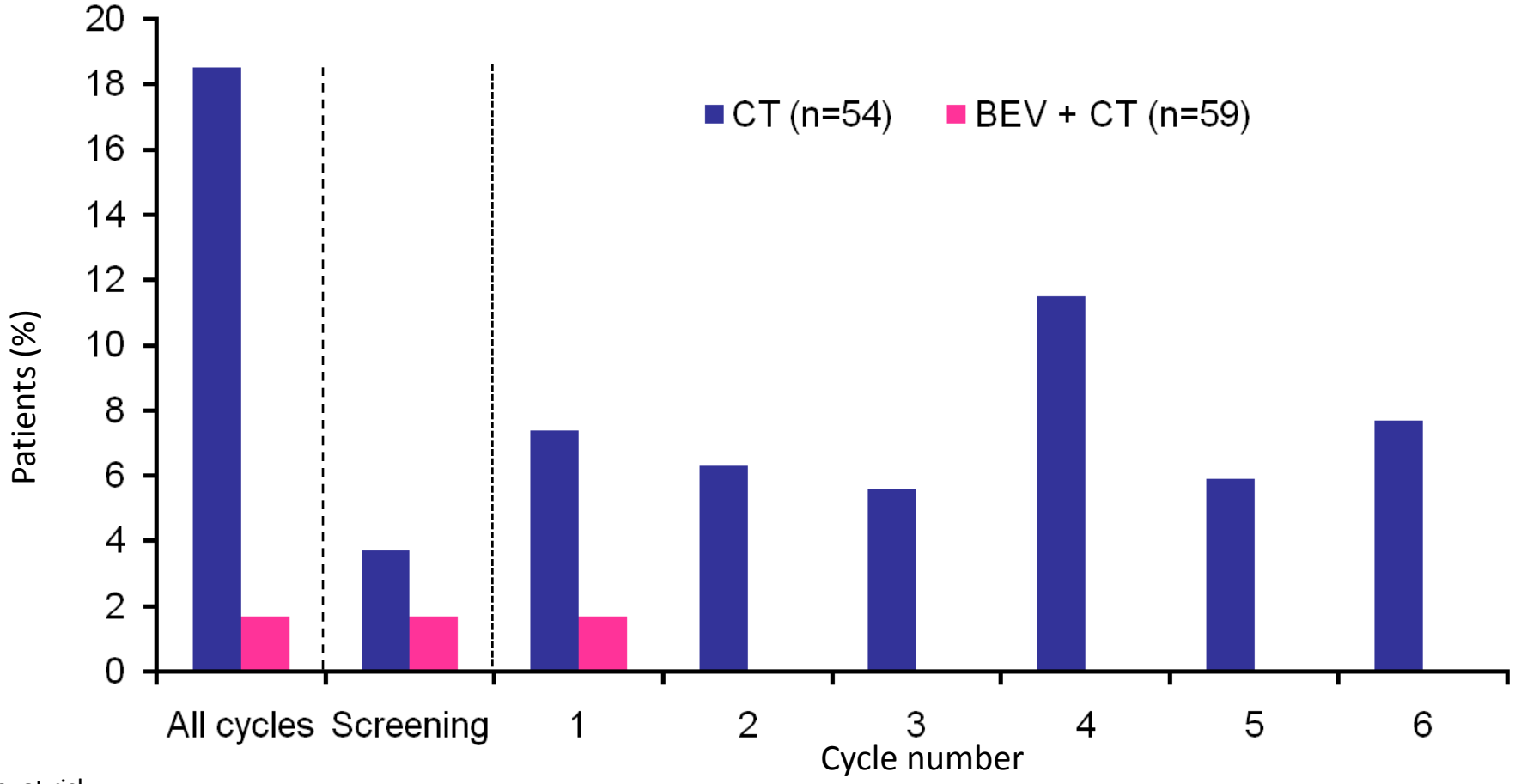
No. at risk:

CT	182	93	37	20	8	1	1	0	0
BEV + CT	179	140	88	49	18	4	1	1	0

Pujade-Lauraine et al. J Clin Oncol. 2014 Mar 17

Median duration of follow-up: 13.9 months (CT arm) vs 13.0 months (BEV + CT arm)

Incidence of paracentesis during study therapy: Subgroup of patients with ascites at baseline



No. at risk:								
CT	54	54	54	48	36	26	17	13
BEV + CT	59	59	59	57	52	44	37	32

Data not shown for cycles with <10 patients in one or both arms

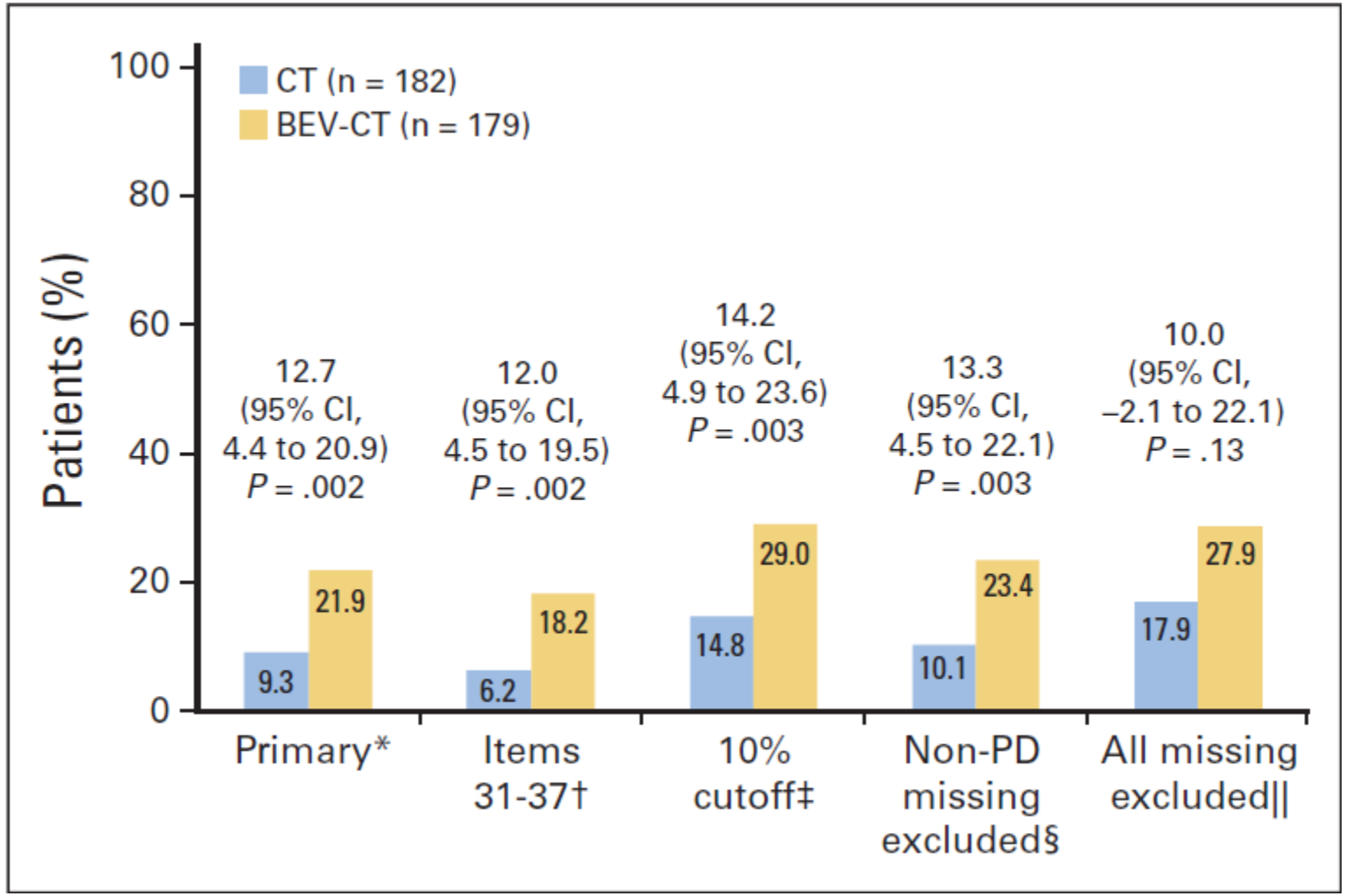
Adverse events of special interest

Grade ≥3 adverse events of special interest, n (%)	CT (n=181)	BEV + CT (n=179)
Hypertension	2 (1.1)	13 (7.3)
Grade ≥2	12 (6.6)	36 (20.1)
Proteinuria	0	3 (1.7)
Grade ≥2	1 (0.6)	19 (10.6)
GI perforation	0	3 (1.7)
Grade ≥2	0	4 (2.2)
Fistula/abscess	0	2 (1.1)
Grade ≥2	0	4 (2.2)
Bleeding	2 (1.1)	2 (1.1)
Thromboembolic event	8 (4.4)	9 (5.0)
Arterial	0	4 (2.2)
Venous	8 (4.4)	5 (2.8)
Wound-healing complication	0	0
RPLS	0	1 (0.6)
CHF	1 (0.6)	1 (0.6)
Cardiac disorders (excluding CHF)	0	0

•*RPLS = reversible posterior leukoencephalopathy syndrome; CHF = congestive heart failure*

Pujade-Lauraine et al. J Clin Oncol. 2014 Mar 17

QOL: primary hypothesis 15% improvement in abdominal/GI symptoms EORTC QLQ-OV28



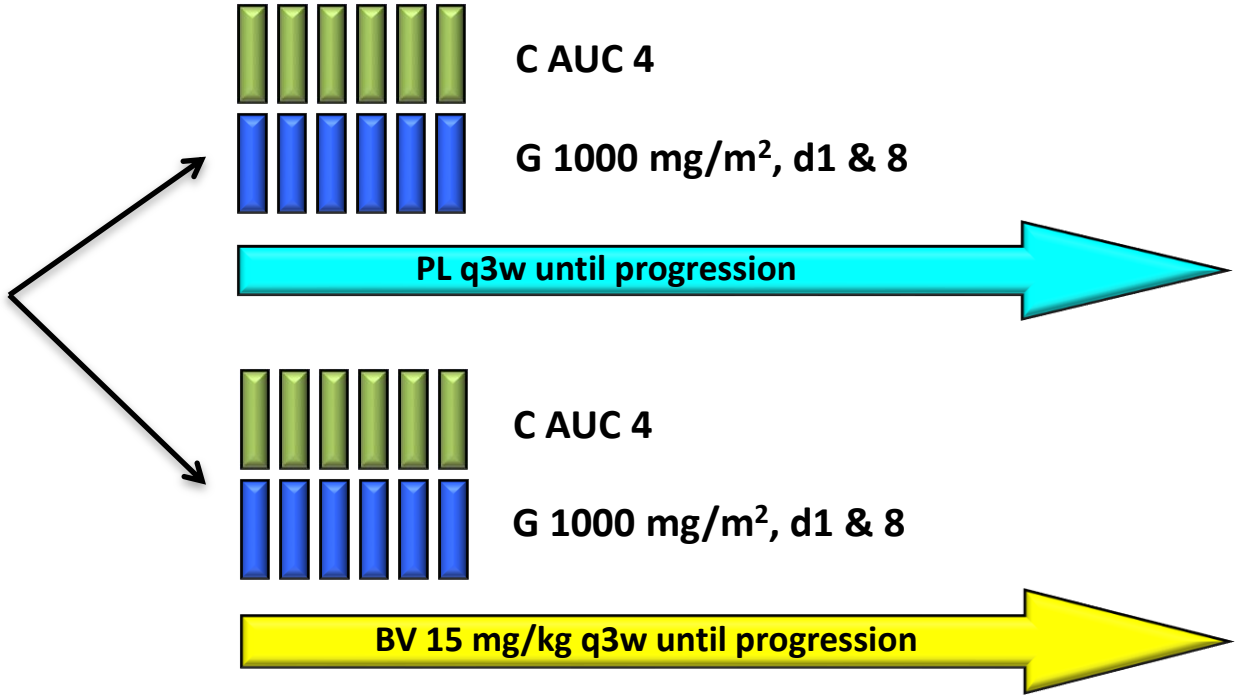
Martin R. Stockler et al. **Published Ahead of Print on March 31, 2014**

OCEANS: Study schema

Platinum-sensitive recurrent OC[a]

- **Measurable disease**
- **ECOG 0/1**
- **No prior chemo for recurrent OC**
- **No prior BV**

(n=484)



CG for 6 (up to 10) cycles

Stratification variables:

- Platinum-free interval (6–12 vs >12 months)
- Cytoreductive surgery for recurrent disease (yes vs no)

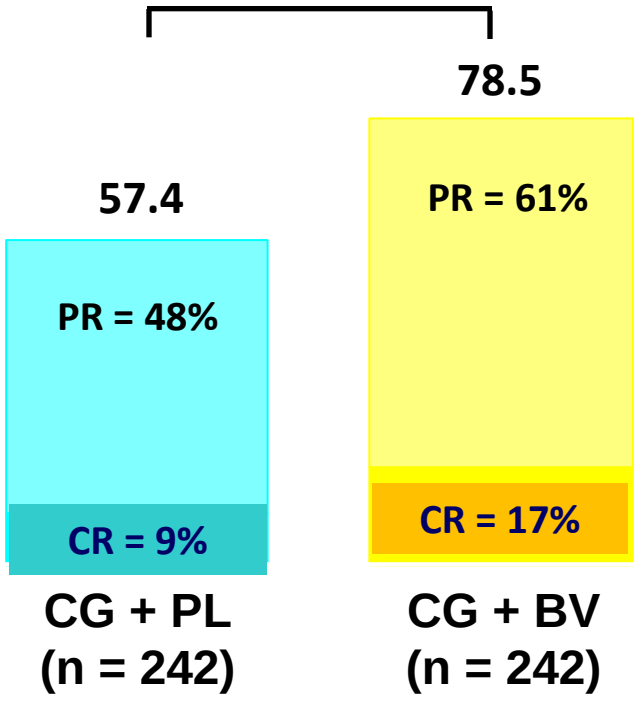
BV = bevacizumab; PL = placebo

[a]Epithelial ovarian, primary peritoneal, or fallopian tube cancer

Aghajanian et al. J Clin Oncol 2012

OCEANS:

Significantly Increased Response Rate With Bevacizumab Compared With Standard Chemotherapy



	CG + PL (n = 139)	CG + BV (n = 190)
ORR, %	57	79
	P<.0001	
Median duration of response (months)	7.4	10.4
HR for duration of response	0.0534	
	P<.0001[a]	

Aghajanian et al. J Clin Oncol 2012

OCEANS:
Adverse Events of Special Interest

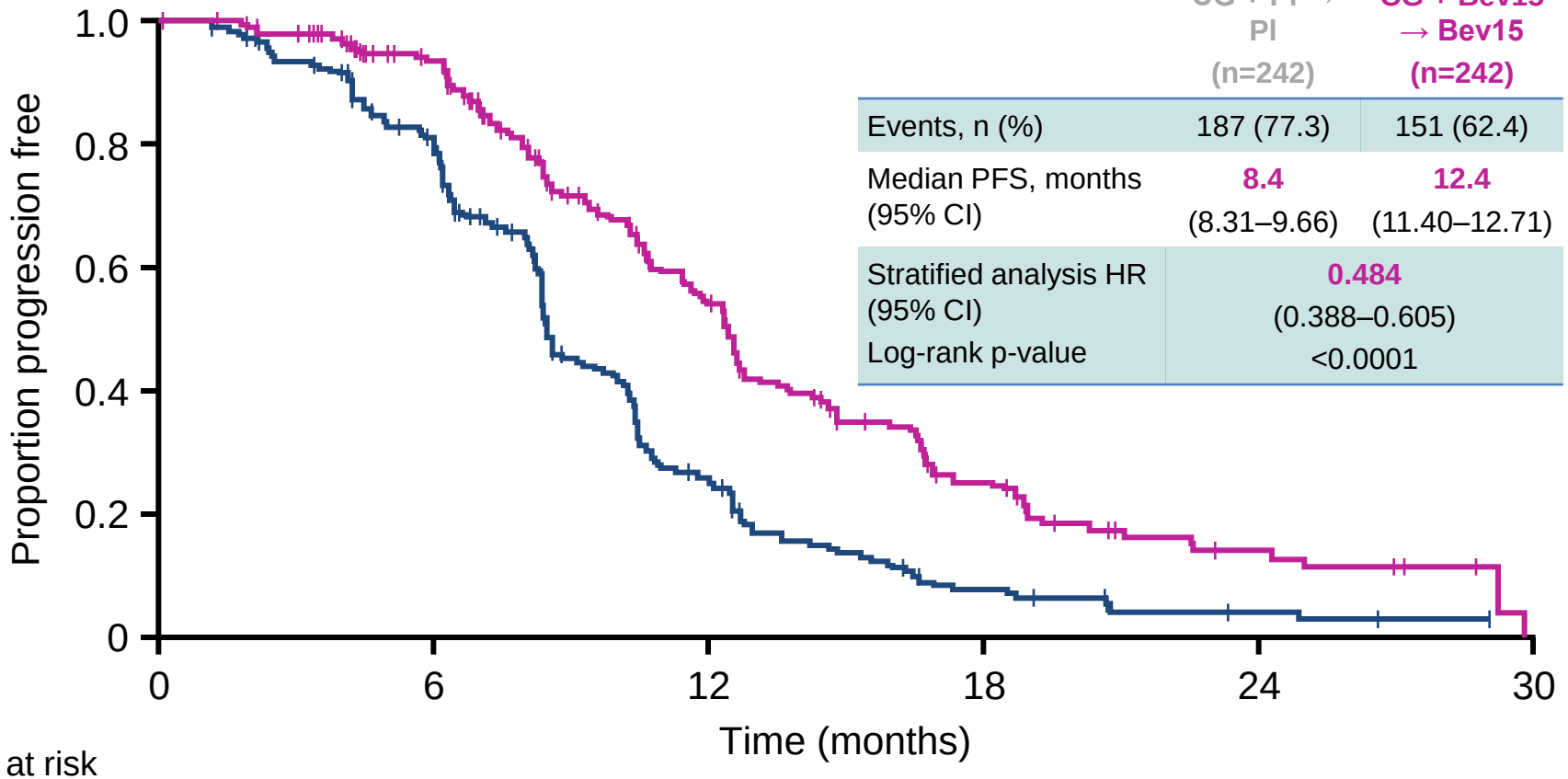
Patients, %	CG + PL (n = 233)	CG + BV (n = 247)
ATE, all grades	1	3
VTE, grade ≥3	3	4
CNS bleeding, all grades	<1	1
Non-CNS bleeding, grades ≥3	1	6
CHF, grades ≥3	1	1
Neutropenia, grade ≥3	56	58
Febrile neutropenia, grade ≥3	2	2
Hypertension, grade ≥3	<1	17
Fistula/abscess, all grades	<1	2
GI perforation, all grades	0	0
Proteinuria, grade ≥3	1	9
RPLS, all grade	0	1
Wound-healing complication, grades ≥3	0	1

ATE, arterial thromboembolic event; CHF, congestive heart failure; GI, gastrointestinal; RPLS, reversible posterior leukoencephalopathy syndrome; VTE, venous thromboembolic event

[a]Two GI perforations occurred 69 days after last BV dose

Aghajanian et al. J Clin Oncol 2012

OCEANS: significantly increased PFS in platinum-sensitive recurrent ovarian cancer



	CG + Pl → Pl (n=242)	CG + Bev15 → Bev15 (n=242)
Events, n (%)	187 (77.3)	151 (62.4)
Median PFS, months (95% CI)	**8.4** (8.31–9.66)	**12.4** (11.40–12.71)
Stratified analysis HR (95% CI)	**0.484** (0.388–0.605)	
Log-rank p-value	<0.0001	

No. at risk						
CG + Av15	242	203	92	33	11	0
CG + Pl	242	177	45	11	3	0

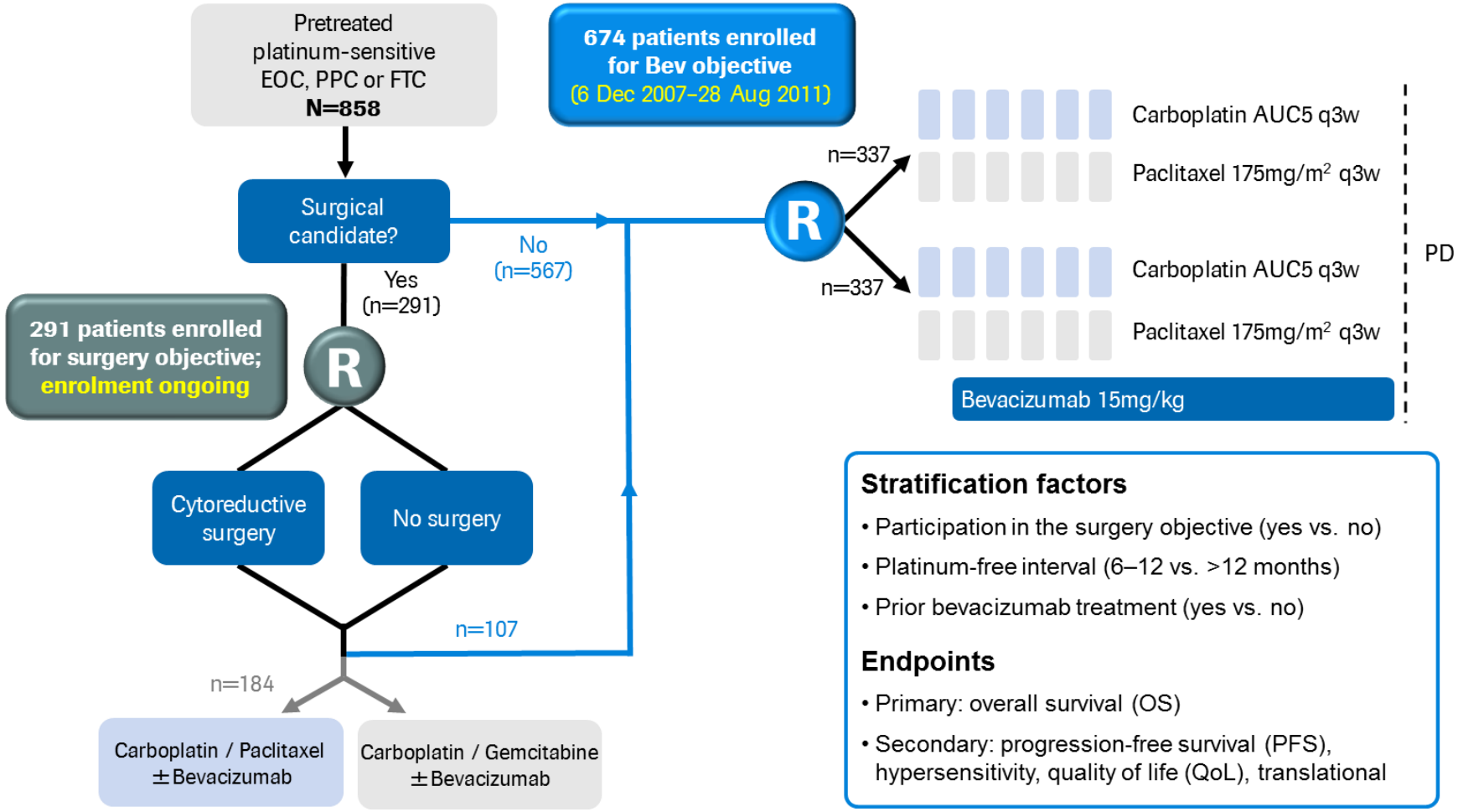
Aghajanian et al. J Clin Oncol 2012

Why no OS benefit?

- Cross over

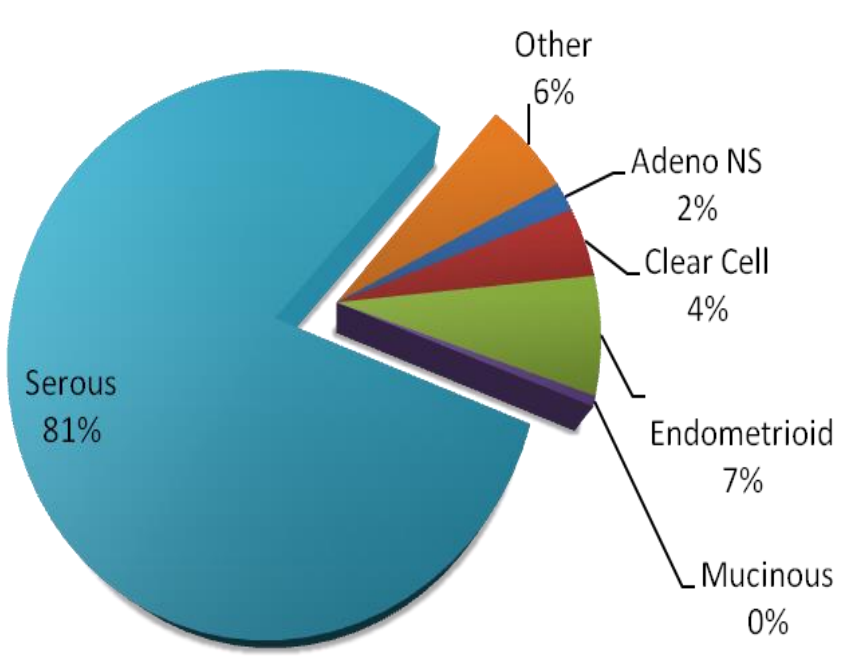
Type of therapy, no. (%)[a]	GC + PL (n=242)	GC + BV (n=242)
Any subsequent anticancer therapy	216 (89.3)	207 (85.5)
Subsequent BV	**85 (39.4)**	**46 (22.2)**
Subsequent chemotherapy[b]	213 (98.6)	203 (98.1)

GOG-0213: trial design

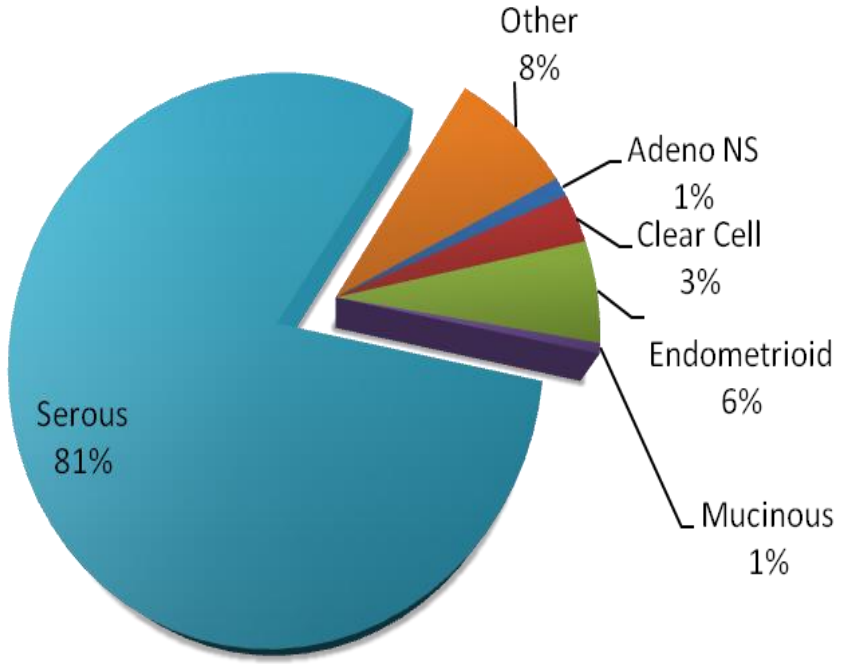


- AUC = area under the curve; EOC = epithelial ovarian cancer; FTC = Fallopian tube cancer; PD = disease progression; PPC = primary peritoneal cancer; q3w = every 3 weeks
- Coleman, et al. SGO 2015 (Abstract 3)

GOG-0213: patient demographics – histology



CT only



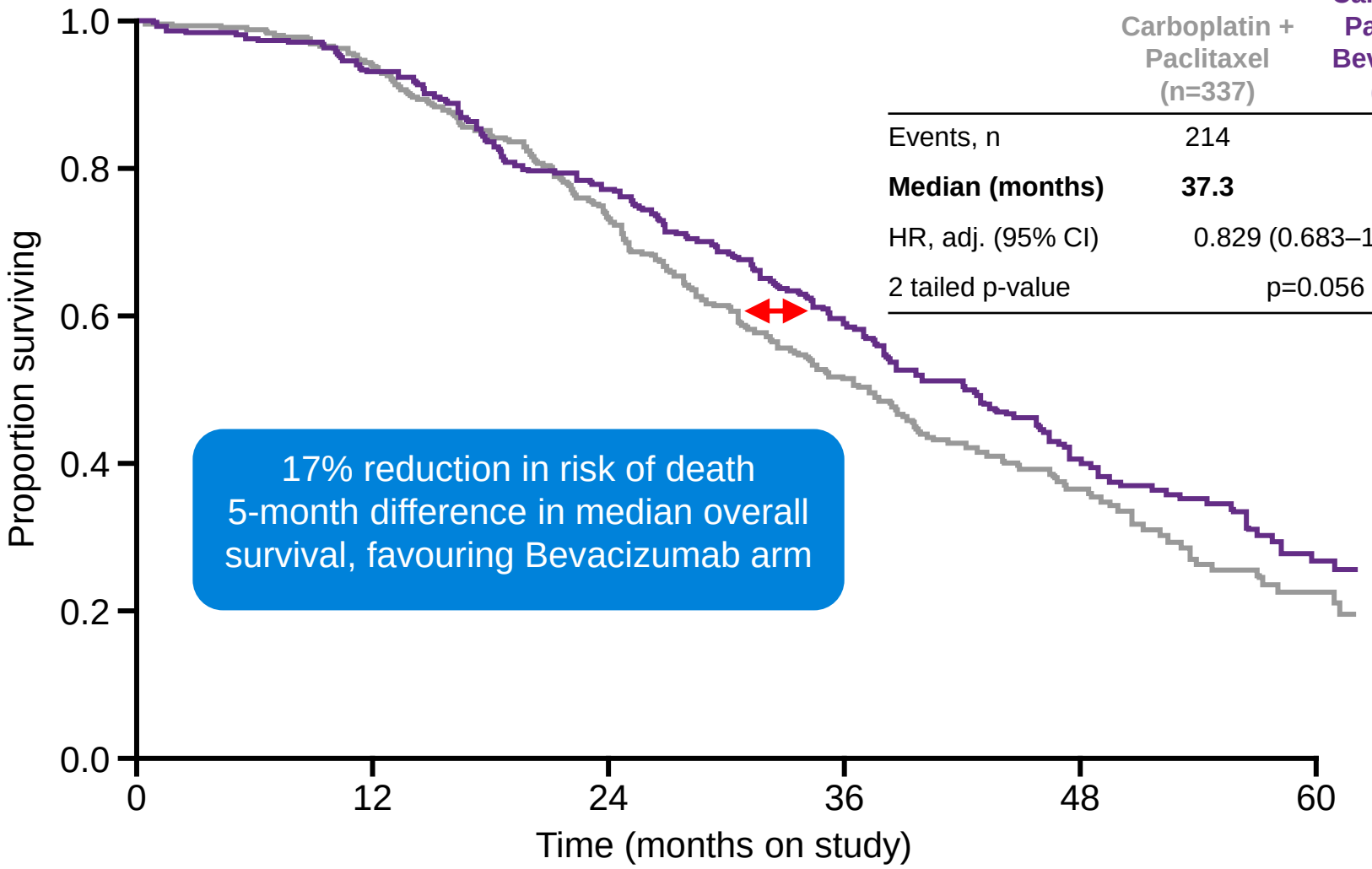
Avastin + CT

- Coleman, et al. SGO 2015 (Abstract 3)

GOG-0213: patient demographics

Patient characteristic, (%)		CT (n=337)	CT + Avastin (n=337)	Total (n=674)
Prior Bevacizumab treatment	Prior Bevacizumab	33 (10)	34 (10)	67 (10)
	No prior Bevacizumab	303 (90)	303 (90)	606 (90)
	Not specified	1 (0.3)	0	1 (0.1)
Randomisation to surgical part of trial	Randomised, no surgery	27 (8)	27 (8)	54 (8)
	Randomised, surgery	27 (8)	26 (8)	53 (8)
	Not randomised	283 (84)	284 (84)	567 (84)
Prior platinum-free interval	6–12 months	105 (31)	105 (31)	210 (31)
	>12 months	232 (69)	232 (69)	464 (69)
Measureable disease	No	50 (15)	63 (19)	113 (17)
	Yes	287 (85)	274 (81)	561 (83)

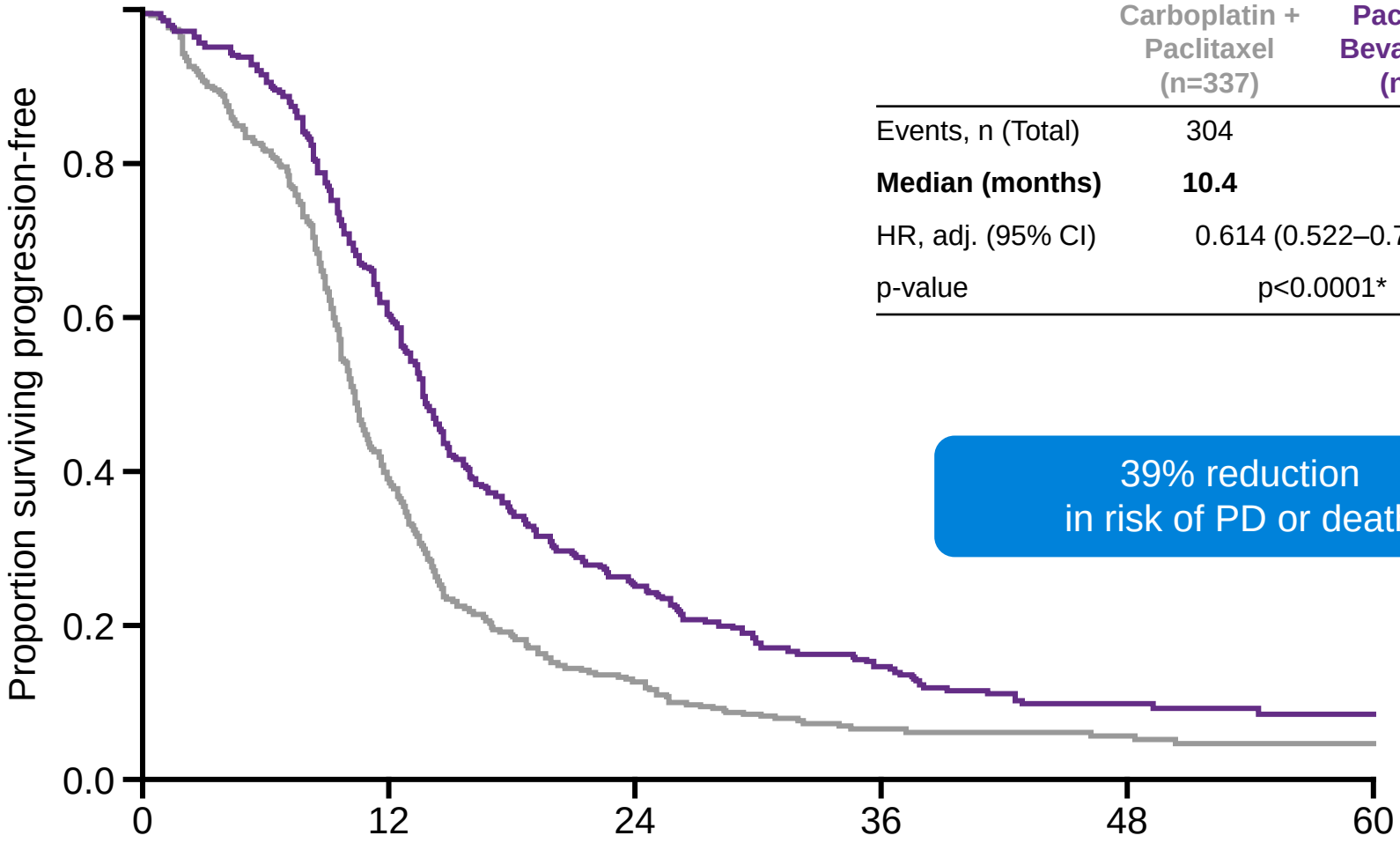
GOG-0213: primary analysis of OS



	Carboplatin + Paclitaxel (n=337)	Carboplatin + Paclitaxel + Bevacizumab (n=337)
Events, n	214	201
Median (months)	**37.3**	**42.2**
HR, adj. (95% CI)	0.829 (0.683–1.005)	
2 tailed p-value	p=0.056	

- Coleman, et al. SGO 2015 (Abstract 3)

GOG-0213: primary analysis of PFS



	Carboplatin + Paclitaxel (n=337)	Carboplatin + Paclitaxel + Bevacizumab (n=337)
Events, n (Total)	304	296
Median (months)	**10.4**	**13.8**
HR, adj. (95% CI)	0.614 (0.522–0.722)	
p-value	p<0.0001*	

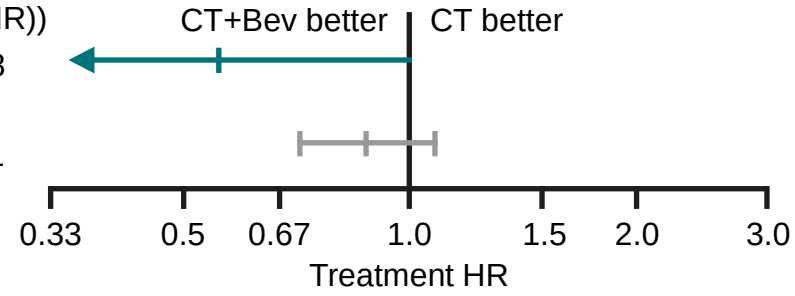
39% reduction
in risk of PD or death

- Coleman, et al. SGO 2015 (Abstract 3)

GOG-0213: primary analysis of OS by stratification factors

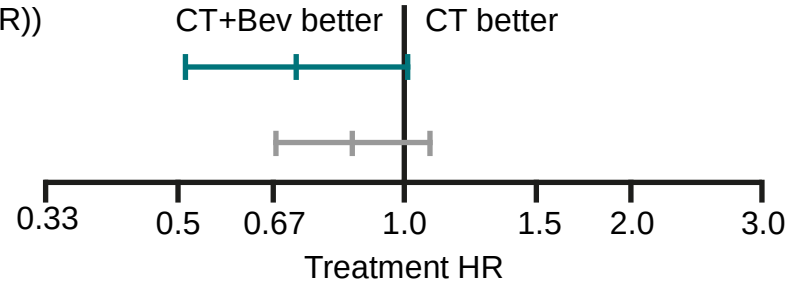
Objective 2

	Rel Haz	Var(ln(HR))
Surgery randomised (N=107; 16%)	0.558	0.088
Surgery not randomised (N=567; 84%)	0.875	0.011



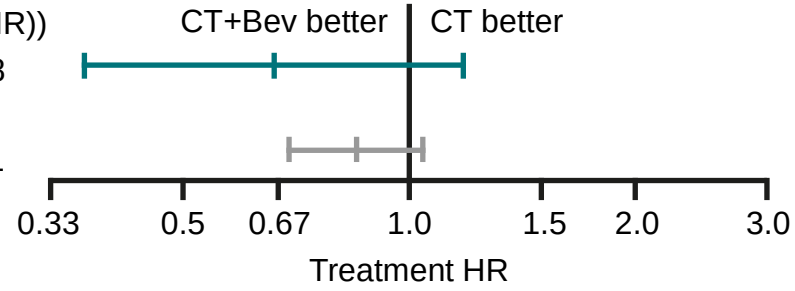
PFI

Platinum-free interval	Rel Haz	Var(ln(HR))
6–12 months (N=181; 27%)	0.719	0.030
>12 months (N=493; 73%)	0.853	0.014



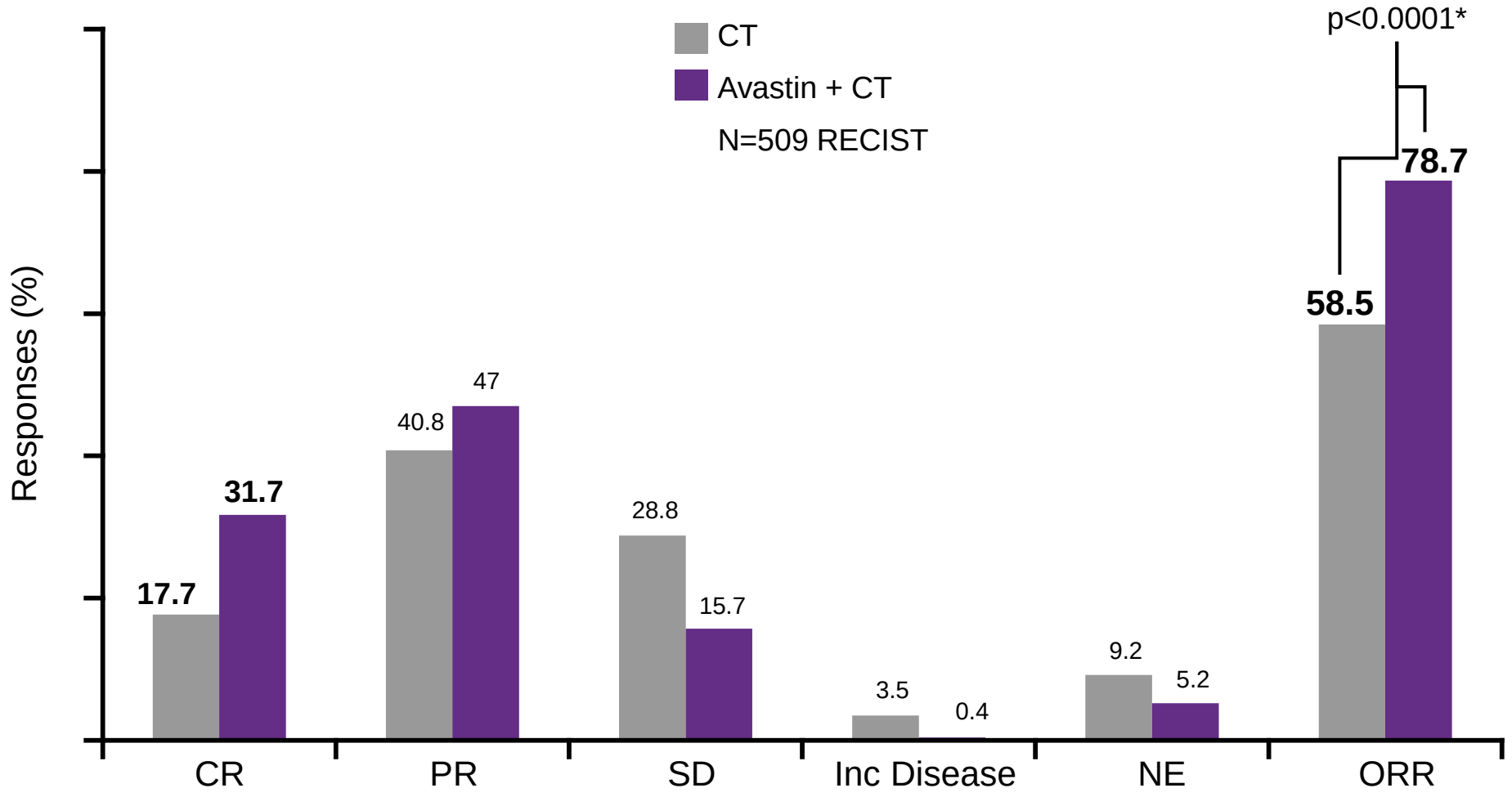
Prior Avastin

	Rel Haz	Var(ln(HR))
Prior Avastin (N=67; 10%)	0.662	0.088
No prior Avastin (N=606; 90%)	0.851	0.011



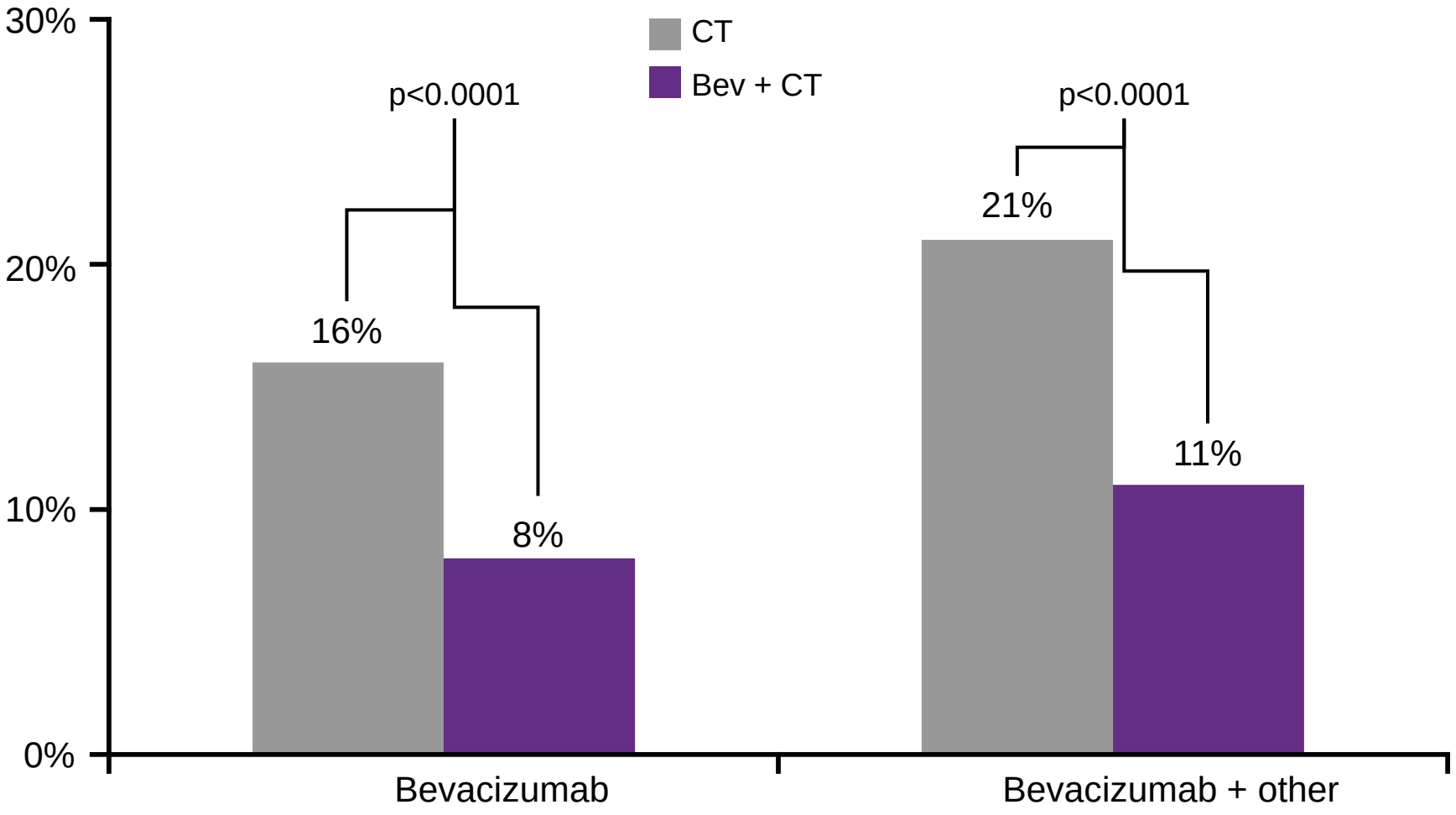
- Coleman, et al. SGO 2015 (Abstract 3)

GOG-0213: overall response rate



- Coleman, et al. SGO 2015 (Abstract 3)

GOG-0213: anti-angiogenic use in immediate next line of therapy



- Coleman, et al. SGO 2015 (Abstract 3)

GOG 213: adverse events of special interest

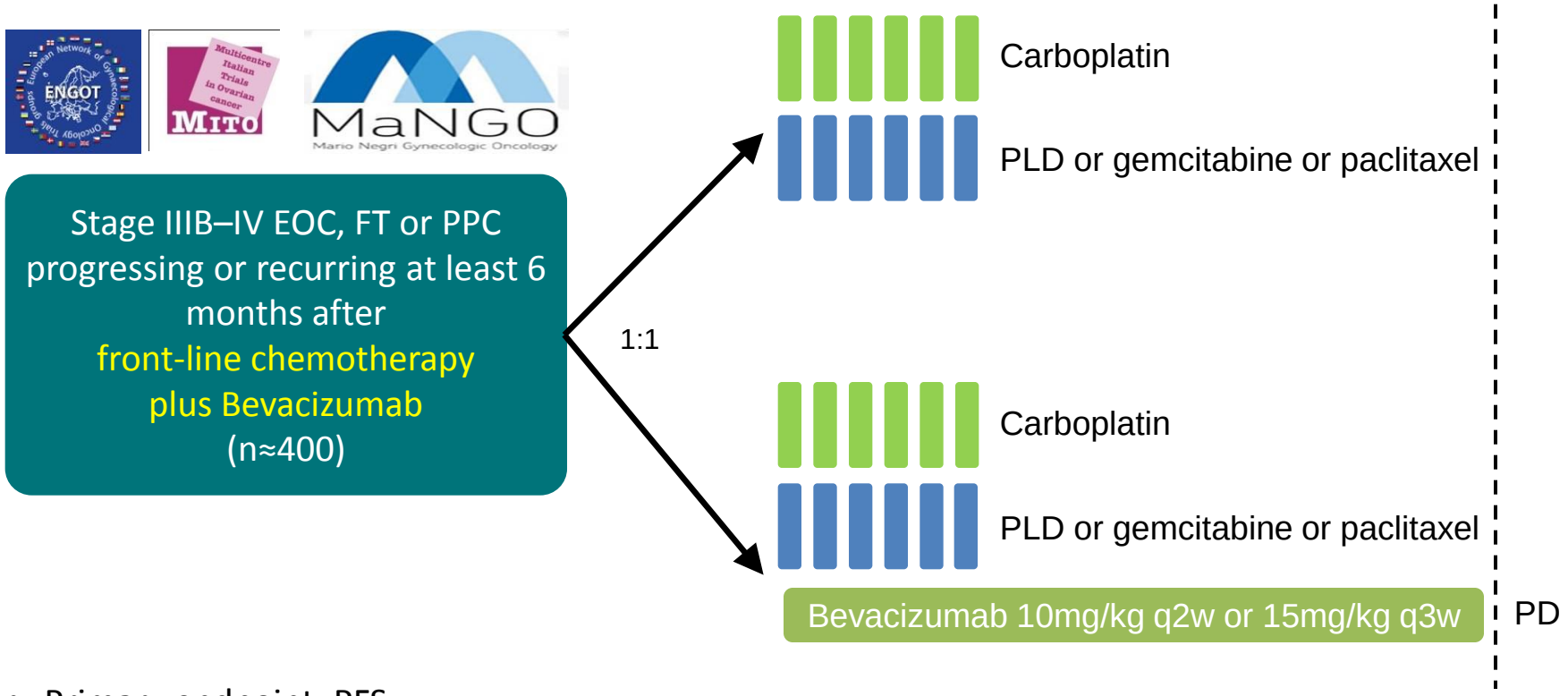
Patients, %	PC (n=327)	PC + Bev (n=330)	P
Thromboembolism, grades ≥3	4 (1%)	13 (4%)	0.05
Arterial thromboembolism, grade ≥3	2 (<1%)	8 (2%)	NS
Non-CNS bleeding, grades ≥3	3 (1%)	6 (2%)	NS
Infection, grades ≥3	19 (6%)	43 (13%)	0.002
Neutropenia, grade ≥3	255 (78%)	276 (84%)	NS
Febrile neutropenia, grade ≥3	9 (3%)	20 (6%)	NS
Hypertension, grade ≥3	2 (<1%)	39 (12%)	<0.001
GI perforation+ fistula +abscess, **all grades**	13 (4%)	49 (15%)	<0.001
GI perforation, fistula/abscess, grade ≥3	3 (1%)	6 (2%)	NS
Proteinuria, grade ≥3	0	27 (8%)	<0.001
Reversible posterior leukoencephalopathy, all grades	0	2 (<1%)	NS
Neuropathy, grades ≥3	12 (4%)	6 (2%)	NS
Joint pain, grades ≥3	15 (5%)	50 (15%)	<0.001
Wound-healing complication, grades ≥3	0	3 (1%)	NS

Efficacy of Bevacizumab in Bevacizumab pre-treated patients in line with effect observed in ITT population

	GOG-213 Bevacizumab pre-treated subgroup (n=69; 10.3%)		
	CP (n=34)	CP + Bev (n=35)	
Median OS, months	32.0	**36.8**	**+4.8 months OS**
HR (95% CI)	0.76 (0.44–1.34)		
Median PFS, months	9.8	**10.7**	**+0.9 months PFS**
HR (95% CI)	0.84 (0.52–1.37)		
ORR	54%	**82%**	**+28% ORR**

Abstr. 5523: GOG-213 Bevacizumab Pre-treated Subgroup

MITO-16/MaNGO OV-2: Bevacizumab plus chemotherapy at progression after front-line Bevacizumab plus chemotherapy

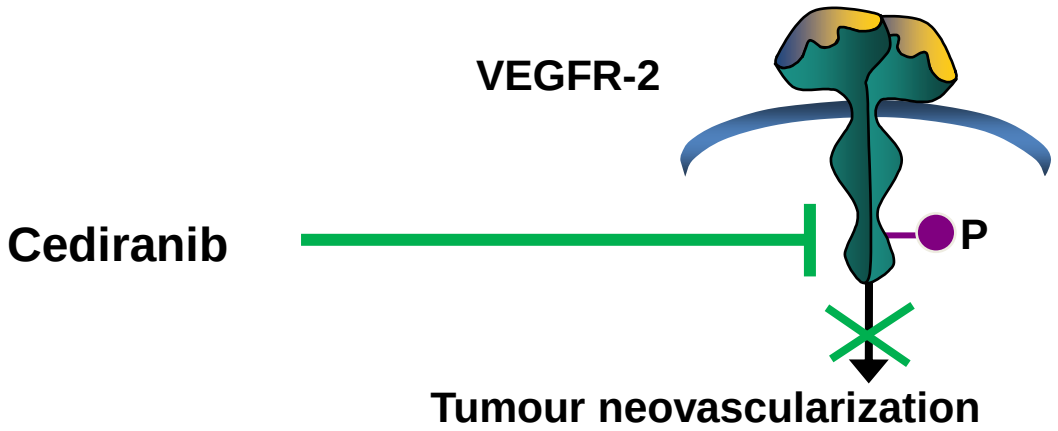


- Primary endpoint: PFS
- Secondary endpoint: OS
- 60 Italian centres involved and involvement of others European groups (ENGOT) (sponsor: INT Napoli)

Anti-angiogenic treatments for recurrent ovarian cancer: When, Which, for How long?

Cediranib (AZD 2171)

Wedge et al Cancer Res 2005



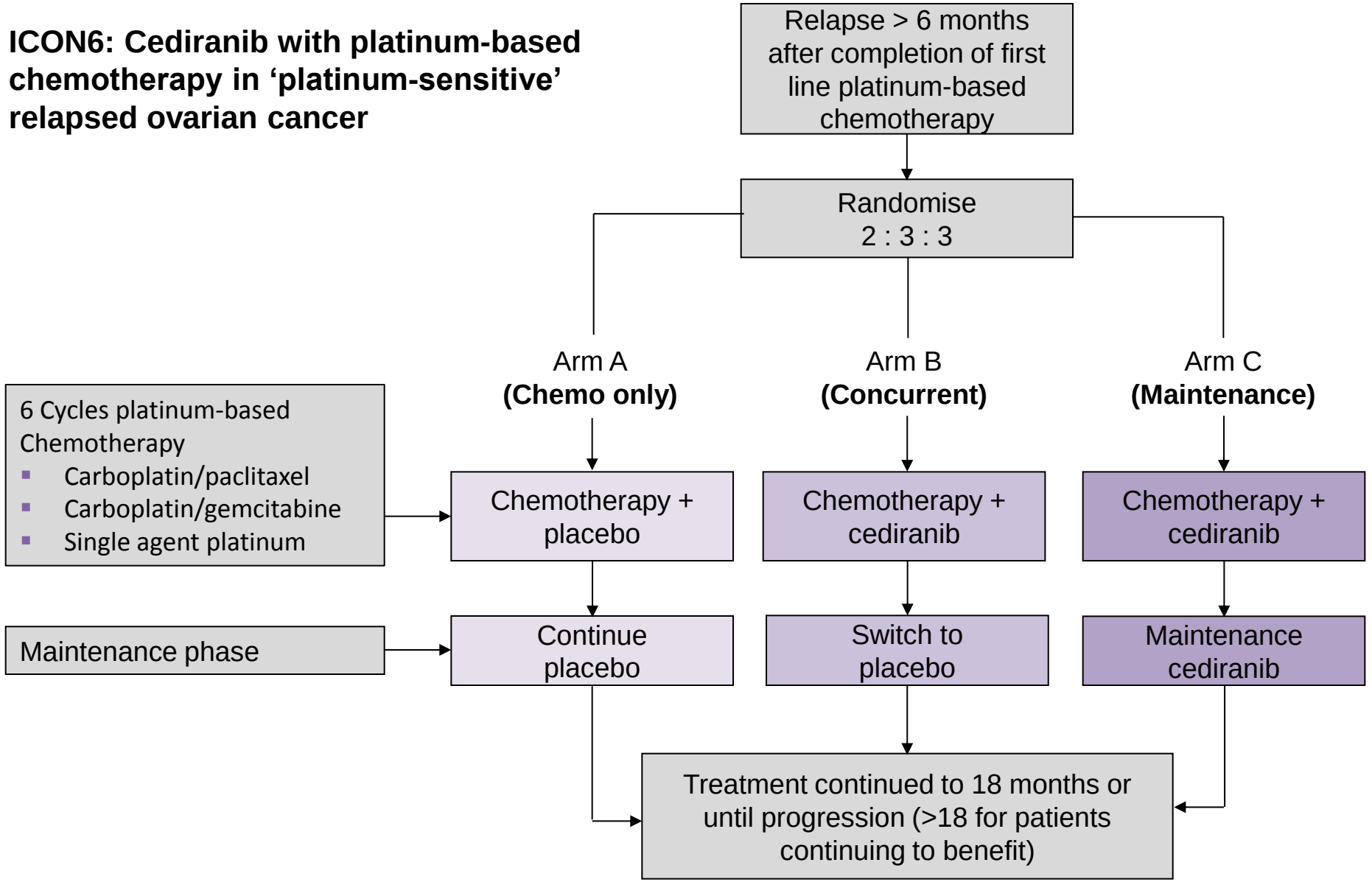
- potent oral inhibitor of vascular endothelial growth factors
- >800–5000 fold selectivity for VEGFR-2
- *in vitro* activity against VEGR-1 and -3
- Inhibits growth of established xenografts – lung, colorectal, prostate, breast and ovary

- Phase II trials showed activity as a single agent in ovarian cancer[1]

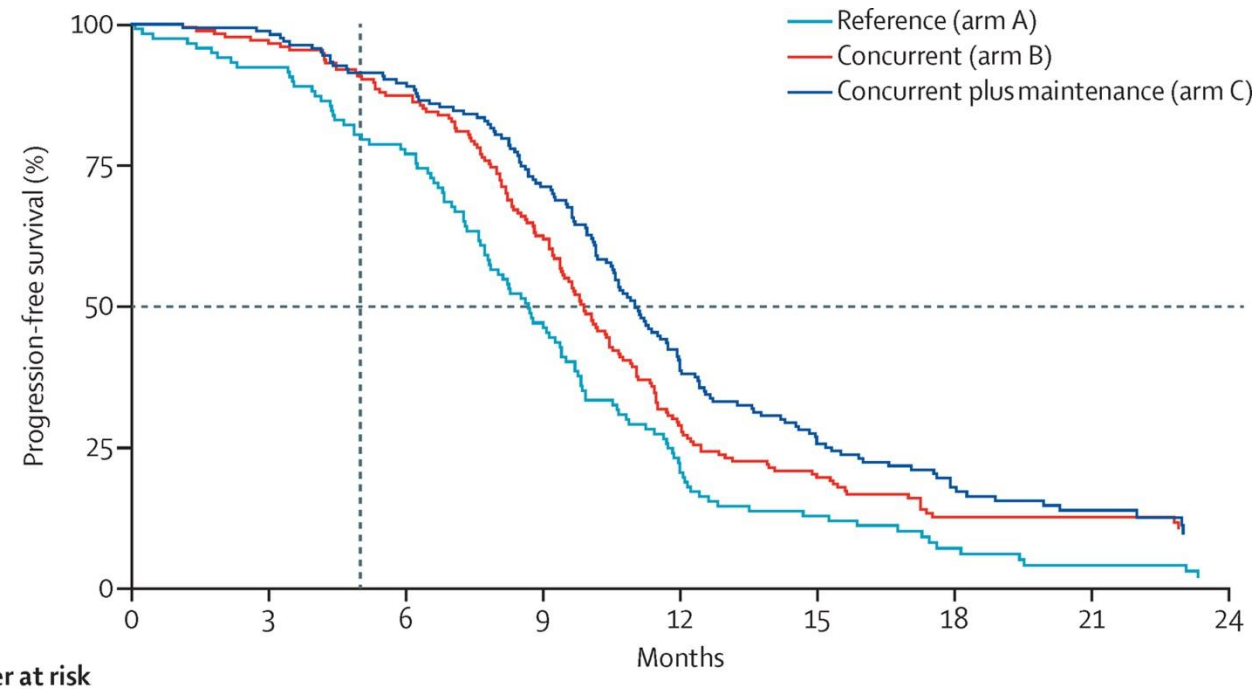
[1] *Matulonis et al 2009; Hirte et al 2010*

Study schema

ICON6: Cediranib with platinum-based chemotherapy in 'platinum-sensitive' relapsed ovarian cancer



Cediranib ICON 6: PFS

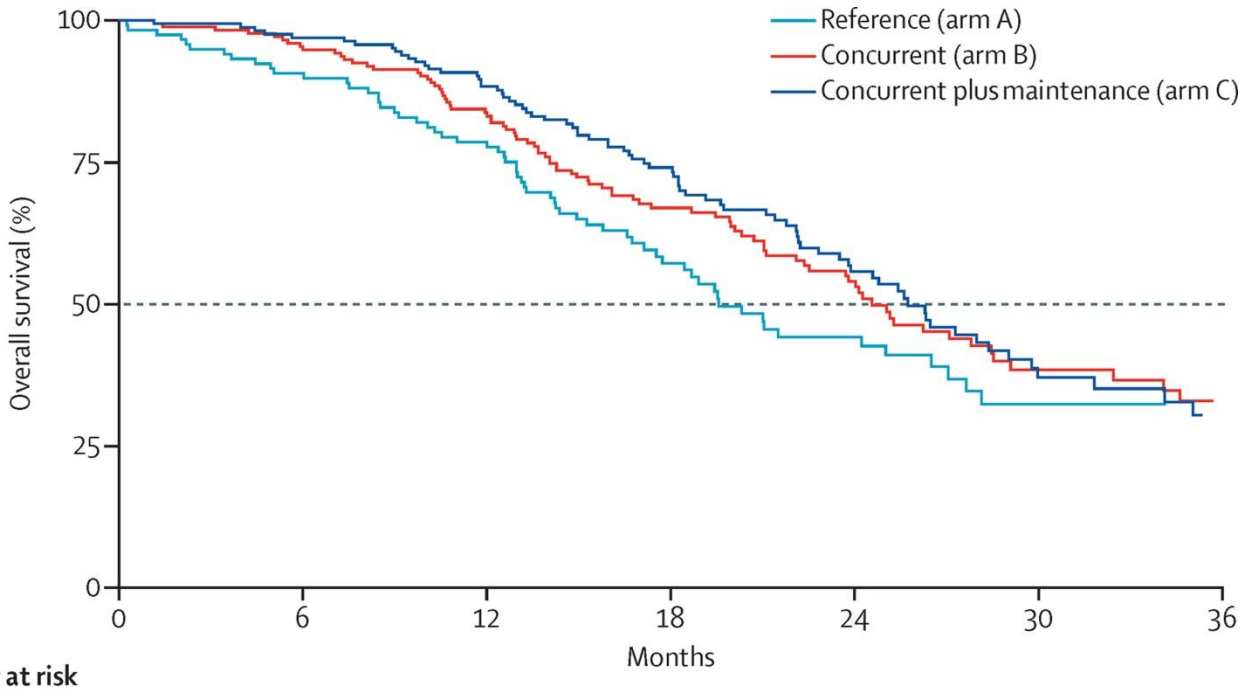


Number at risk (events)									
Arm A	118	(27)	90	(66)	24	(15)	7	(5)	2
Arm B	174	(22)	151	(100)	51	(28)	18	(2)	11
Arm C	164	(17)	146	(83)	63	(32)	22	(8)	7

Median PFS : 11.0 months (95% CI 10.4–11.7) in arm C
8.7 months (7.7–9.4) arm A
hazard ratio 0.56, 0.44–0.72, p<0.0001

Lancet 2016; 387: 1066–74

Cediranib ICON 6: OS



Number at risk (events)							
Arm A	118	(26)	90	(31)	28	(6)	8
Arm B	174	(29)	142	(41)	55	(16)	16
Arm C	164	(19)	141	(41)	51	(17)	12

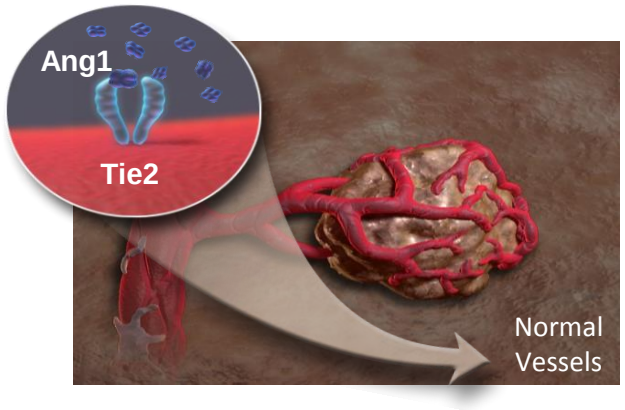
Lancet 2016; 387: 1066–74

Angiopoietin Axis

Ang1 and Ang2 Interact With Tie2 Receptor to Mediate Vascular Remodeling

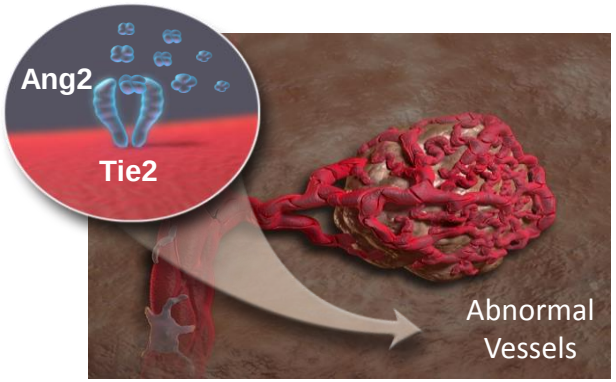
Ang1 stabilizes endothelial junctions and increases pericyte coverage[1,2]

"Vessel quality"



Ang2 promotes endothelial sprouting and increases blood vessel density[1,2,3]

"Vessel quantity"



Ang1 and Ang2 levels are elevated in patients with ovarian carcinoma[4]

1. Augustin HG, et al. *Nat Rev Mol Cell Bio* 2009;10:165–177.
2. Falcon BL, et al. *Am J Pathol* 2009;175:2159–2170.
3. Scharpfenecker M, et al. *J Cell Sci* 2005;118:771–780.
4. Sallinen H, et al. *Int J Gynecol Cancer* 2010;20:498–1505.

Monk et al. Lancet Oncol 2014; 15: 799–808, Gynecol Oncol. 2016 Aug 18

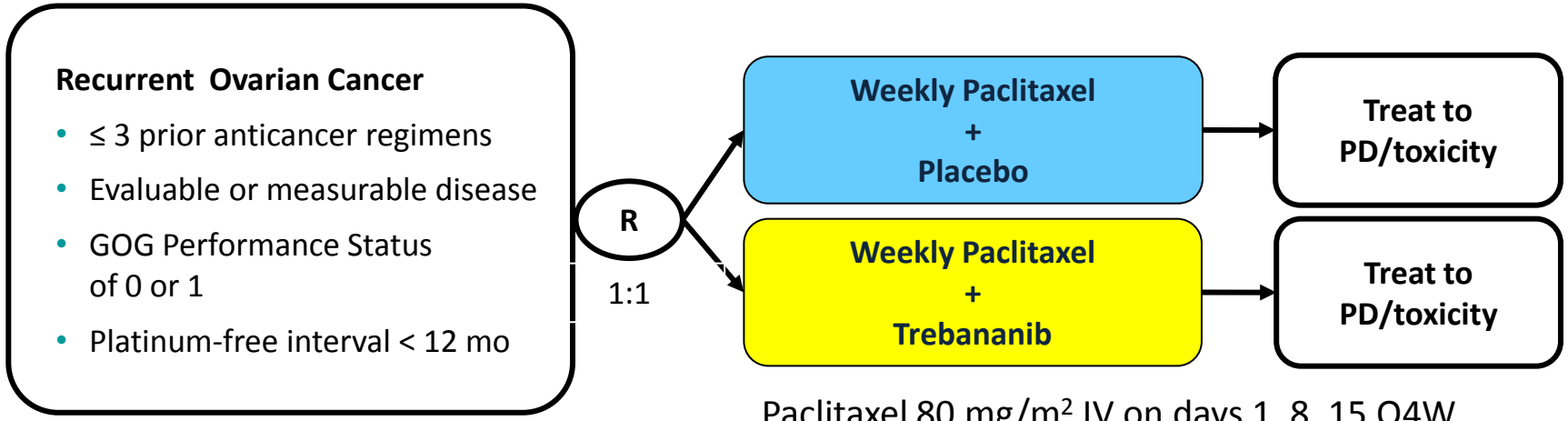
Trebananib (AMG 386)

Peptibody That Binds and Neutralizes Ang1 and Ang2

- Trebananib is an investigational recombinant peptide-Fc fusion protein (“peptibody”)
- In clinical studies trebananib has shown:
  - Single-agent activity in relapsed ovarian cancer
    – Phase 1 study[1]
  - Dose-dependent prolongation of PFS in combination with paclitaxel in recurrent ovarian cancer
    – Randomized phase 2 study[2]

1. Herbst RS, et al. *J Clin Oncol* 2009;27:3557–3565.
2. Karlan BY, et al. *J Clin Oncol* 2012;30:362–371.

TRINOVA-1: Study Design



Paclitaxel 80 mg/m^2 IV on days 1, 8, 15 Q4W

Trebananib 15 mg/kg IV QW

Stratification Factors

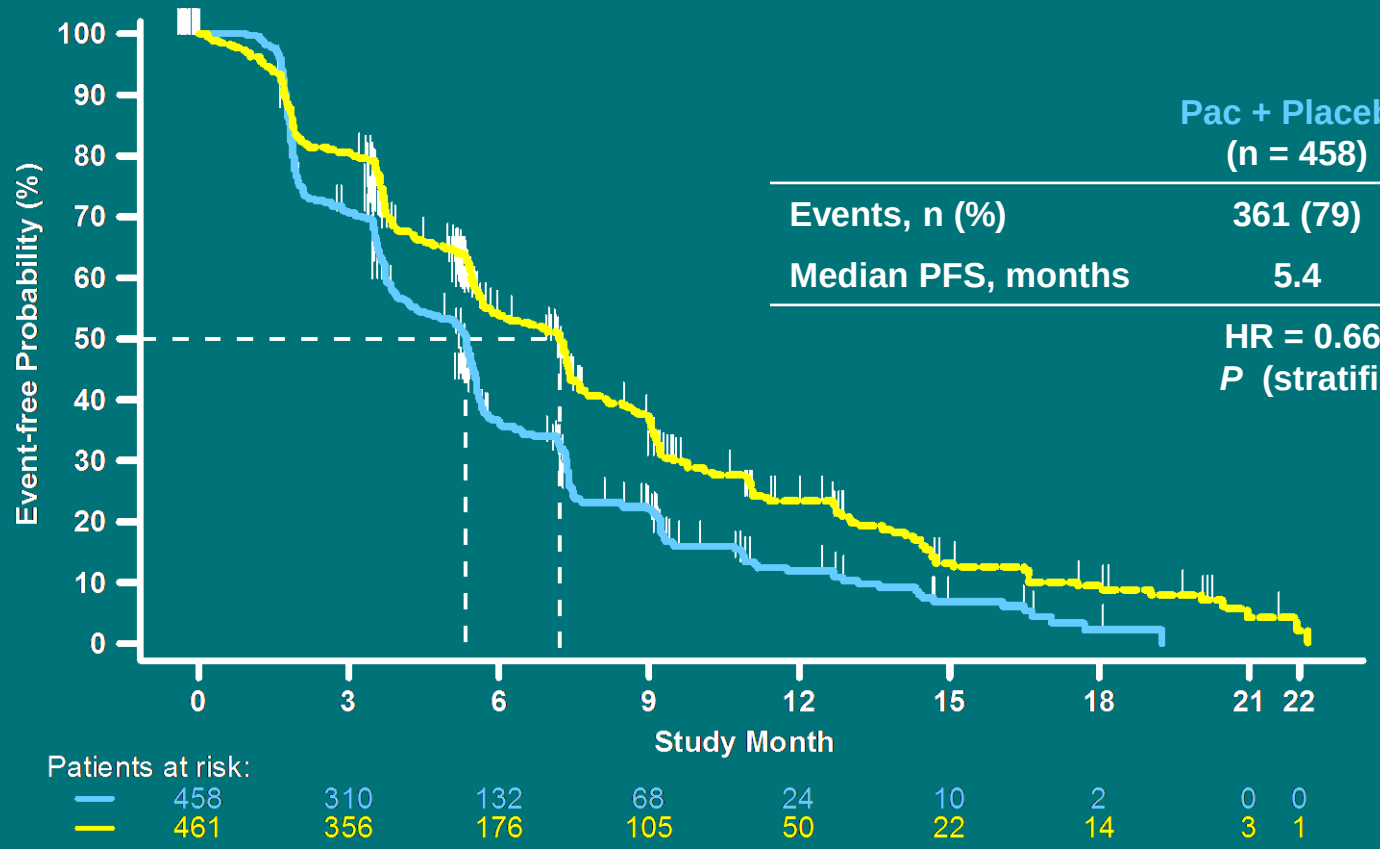
- Platinum-free interval (≤ 6 vs 6 to 12 months)
- Measurable disease (Yes/No)
- Region (North America, Western Europe/Australia, rest of world)

ClinicalTrials.gov Identifier: NCT01204749

EOC = epithelial ovarian cancer, including primary peritoneal or fallopian tube cancer; PD = progressive disease

Monk et al. Lancet Oncol 2014; 15: 799–808, Gynecol Oncol. 2016 Aug 18

PFS Primary Analysis (March 2013*)

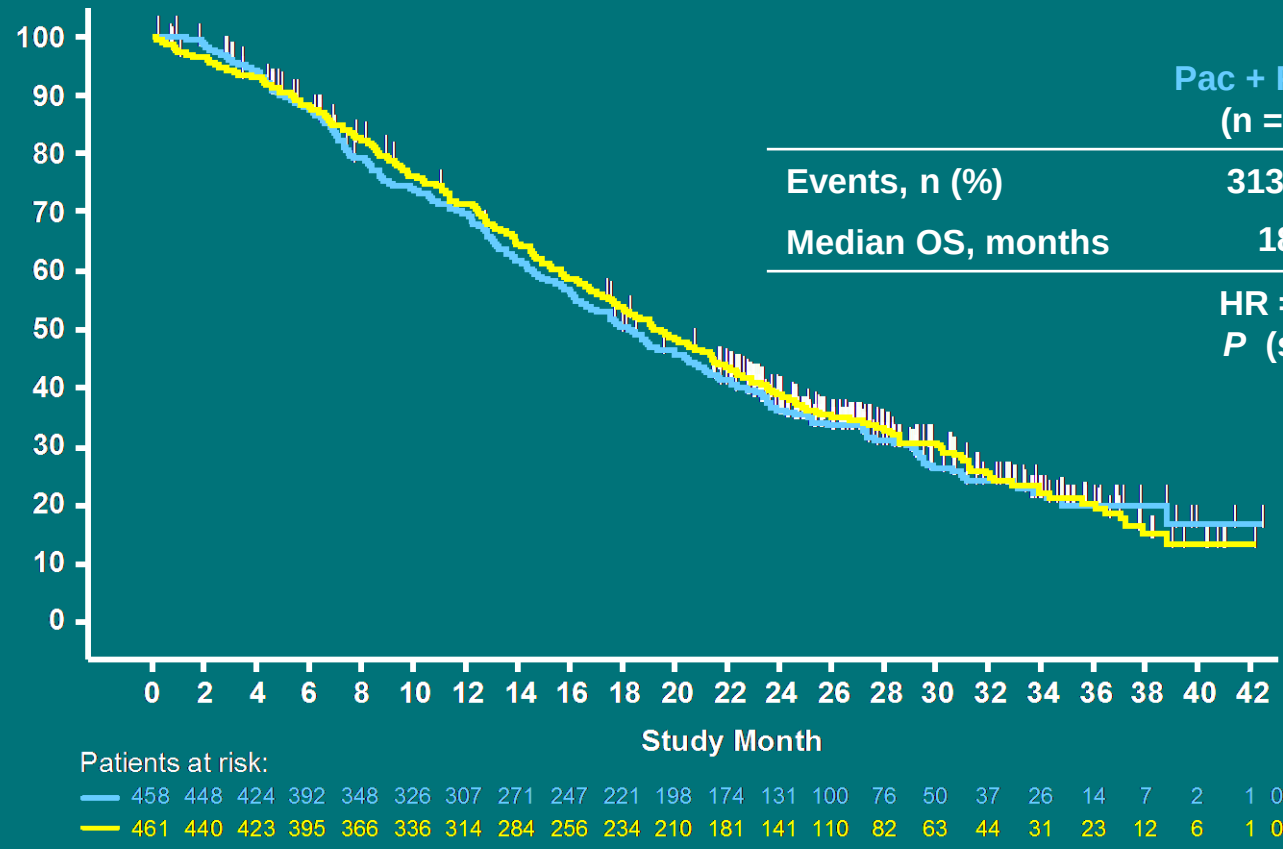


	Pac + Placebo (n = 458)	Pac + Trebananib (n = 461)
Events, n (%)	361 (79)	310 (67)
Median PFS, months	5.4	7.2

HR = 0.66 (95% CI, 0.57–0.77)
P (stratified log-rank) < 0.001

*Monk BJ et al. *Lancet Oncol* 2014;15:799–808.

OS in ITT Population



	Pac + Placebo (n = 458)	Pac + Trebananib (n = 461)
Events, n (%)	313 (68)	315 (68)
Median OS, months	18.3	19.3

HR = 0.95 (95% CI, 0.81–1.11)
P (stratified log-rank) = 0.52

ITT = intent to treat

Monk BJ et al, Abstract # 5503, ASCO 2015, Gynecol Oncol. 2016 Aug 18

Study Design and Stratification

A Phase 3, Randomized, Double-Blind Trial of Pegylated Liposomal Doxorubicin (PLD) Plus AMG 386 or Placebo in Women With Recurrent Partially Platinum Sensitive or Resistant Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer

Recurrent OVC
PFI < 12 m
N = 223

→ PLD 50 mg/m^2 IV Q4W + Trebananib 15 mg/kg IV QW

→ PLD 50 mg/m^2 IV Q4W + Trebananib placebo IV QW

Key Endpoints
- Primary: PFS
- Secondary: OS

Eligibility:
- At least one prior platinum containing therapy
- No more than 3 prior lines of therapy
- ECOG PS 0-1

Stratification Factors
- Region
- Platinum-Free Interval
- Measurable Disease

Protocol allowed PI to stop PLD after 6 cycles while continuing IP

Exclusion :
- Primary platinum refractory therapy
- Platinum-free interval > 12 months from last platinum chemo

ENGOT-ov-6/TRINOVA-2: Results

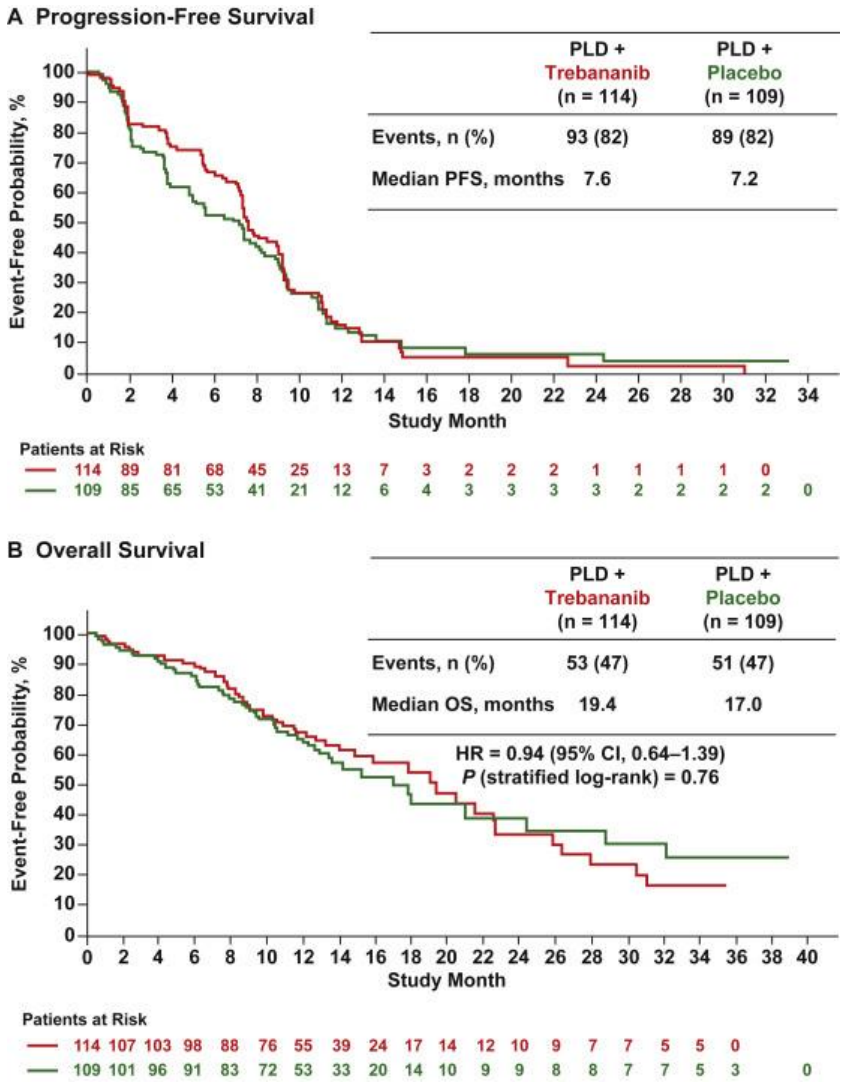


Fig. 2. Kaplan–Meier analysis of (A) PFS and (B) OS. CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; OS = overall survival; PLD = pegylated liposomal doxorubicin.

Christian Marth et al. European Journal of Cancer, Volume 70, 2017, 111–121

http://dx.doi.org/10.1016/j.ejca.2016.09.004

Phase 3 Studies of Angiogenesis Inhibitors in Patients With Recurrent Ovarian Cancer

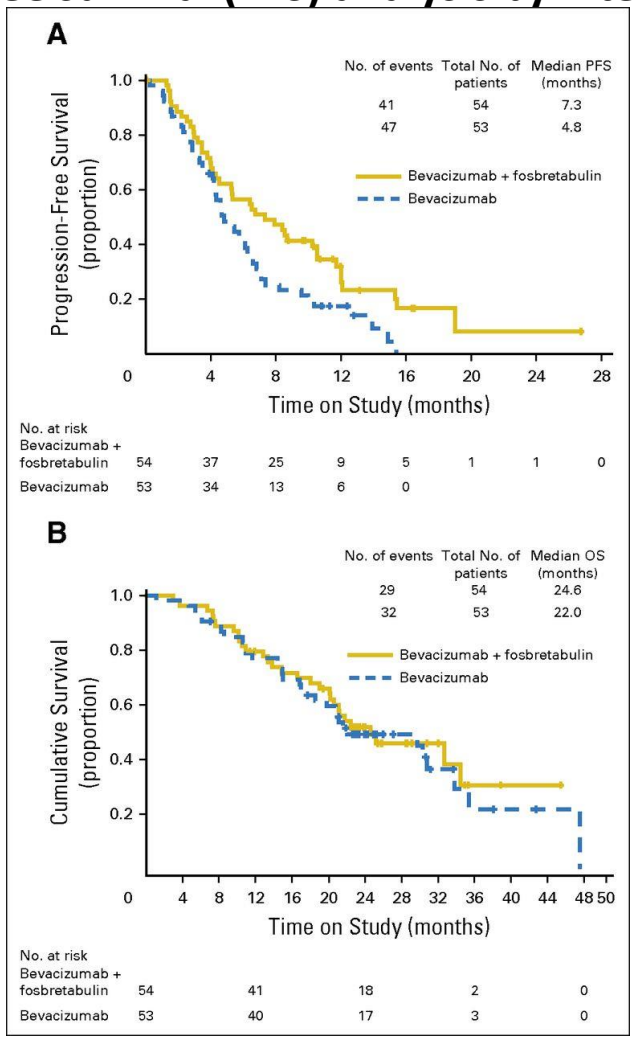
	PFI ≥ 6 months			PFI < 6 months		PFI 0–12 months	PFI 0–12 months
Study	**OCEANS[1]**	**ICON6[2]**	**GOG-213[3]**	**AURELIA[4,5]**	**MITO-11[6]**	**TRINOVA-1[7]**	**TRINOVA-2[8]**
Agent	**Bevacizumab**	**Cediranib**	**Bevacizumab**	**Bevacizumab**	**Pazopanib**	**Trebananib**	**Trebananib**
Difference in PFS, mo†	**4.0**	**2.3**	**3.4**	**3.3**	**2.8**	**2**	**0.4**
PFS HR	**0.48*****	**0.56*****	**0.61*****	**0.48****	**0.42****	**0.70****	**0.92 (NS)**
Difference in OS, mo†	**–1.9**	**2.9**	**4.9**	**3.3**	**5.4**	**1.0**	**2.4**
OS HR	**1.03 (NS)**	**0.77(NS)**	**0.83 (*P*=0.056)**	**0.85 (NS)**	**0.60 (NS)**	**0.95 (NS)**	**0.94 (NS)**

NS, not significant; PFI, platinum-free interval; PFS, progression-free survival; OS=overall survival. **P* < 0.05; ***P* < 0.01; ****P* < 0.0001; †Treatment versus control arm.

1. Aghajanian C, et al. *J Clin Oncol*. 2012;30:2039-2045.
2. Ledermann JA et al. , Lancet 2016; 387: 1066–74
3. Coleman, et al. *Gynecologic Oncol.* 2015;137:3-4.
4. Pujade-Lauraine E, et al. *J Clin Oncol.* 2014;32:1302-1308.
5. Poveda AM, et al. *J Clin Oncol* 2015;63:1408.
6. Pignata S, et al. *Lancet Oncol* 2015;16:561-568.
7. Monk et al. Lancet Oncol 2014; 15: 799–808, Gynecol Oncol. 2016 Aug 18
8. European J Cancer: in press

Phase II Evaluation of Bevacizumab Versus Bevacizumab Plus Fosbretabulin in Recurrent Ovarian, Tubal, or Peritoneal Carcinoma

Progression-free survival (PFS) analysis by intention to treat.



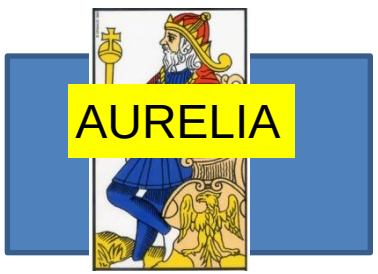
Bradley J. Monk et al. JCO 2016;34:2279-2286

JOURNAL OF CLINICAL ONCOLOGY ASCO

Anti-angiogenic therapy for recurrent ovarian cancer

Which?

Resistant (<6 mos)	Sensitive (6-12 mos)	Sensitive (>12 mos)



bevacizumab

bevacizumab

Not approved

Anti-angiogenic treatments for recurrent ovarian cancer: When, Which, for How long?

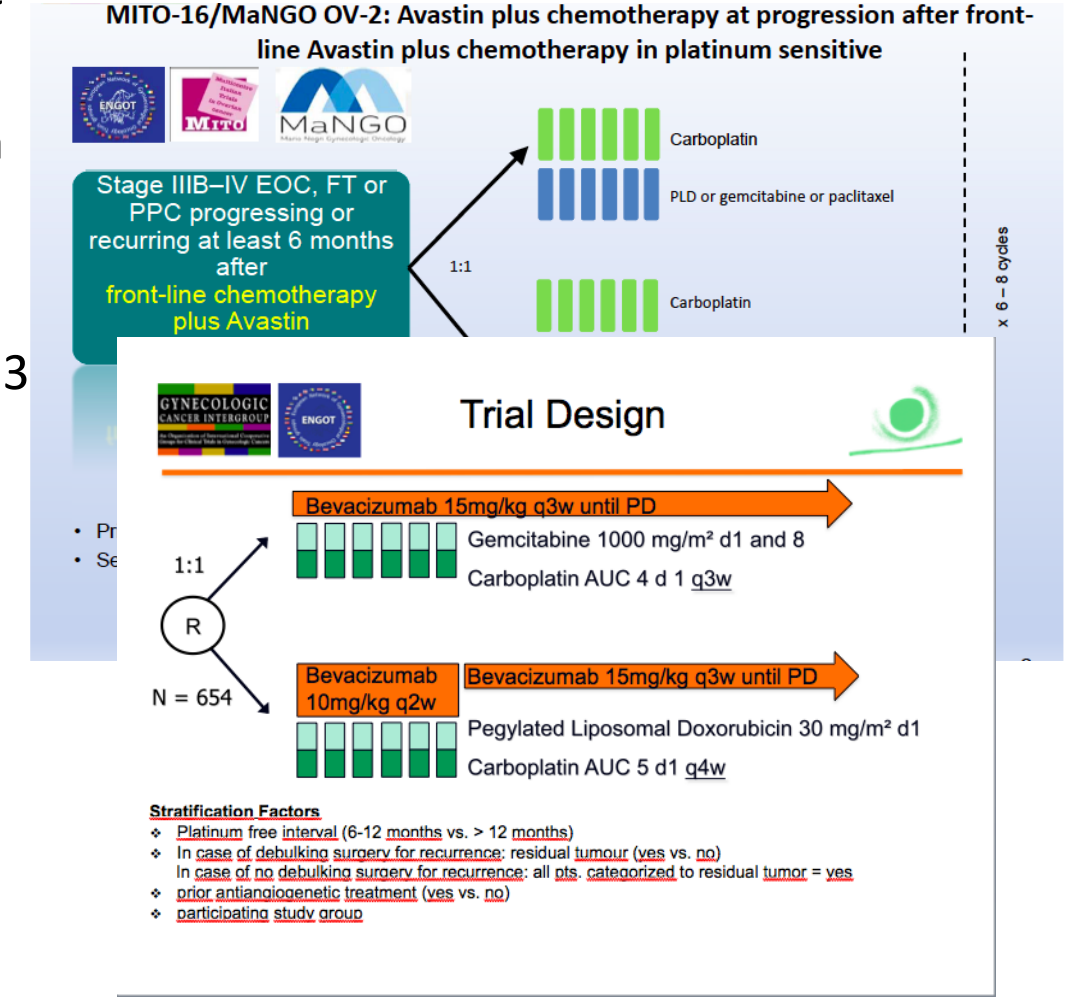
- **Aurelia:** treat until PD/toxicity
- **Oceans:** treat until PD/toxicity
- **GOG213:** treat until PD/toxicity
- **ICON6:** treat until PD/toxicity
- **TRINOVA-1:** treat until PD/toxicity
- **TRINOVA-2:** treat until PD/toxicity

Anti-angiogenic treatments for recurrent ovarian cancer: When ?

Now.

- When you need a rapid response
- To control ascites
- Independently of BRCA mutation
- Independently of PFI
  - < 6 months: AURELIA
  - > 6 months: OCEANS/GOG213
- Only 1 previous line in the platinum-sensitive and 2 in the resistant setting.
- Only with carboplatin and gemcitabine
- No previous use in 1st line
- No medical contraindication

Future



Anti-angiogenic treatments for recurrent ovarian cancer: Which and for how long?

- Bevacizumab is the only approved anti-angiogenic agent both in platinum sensitive and platinum resistant recurrent ovarian cancer
- Treatment should be continued until progression or untolerable toxicity