Anti-Angiogenics in Ovarian Cancer: *Where are we now?*

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Outline

- The biological basis of clinical research of VEGF/R inhibition in OVCA
- Randomized clinical studies since GOG-0218
- Interpretation of Findings:
  - Biological effects and clinical benefits
- Questions and Controversies
  - Endpoints
  - Selection biomarkers for angiogenesis inhibitors

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Vascular Endothelial Growth Factor (VEGF) and Receptor (VEGFR):

Rational Targets in Ovarian Cancer

- VEGF expression in OVCA:
  - Promotes ascites and effusions
  - Is an independent predictor of patient prognosis
- Preclinical Studies of VEGF(R) inhibition:
  - Decreases ascites formation in murine OVCA
  - Is active in human ovarian xenografts
- Phase II clinical trials in recurrent OVCA:
  - Response rates seen with several angiogenesis inhibitors including bevacizumab (21% in GOG 172)

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Byrne AT, Clin Can Res 2003; Luo JC, Cancer Res 1998, Shen GH, Br J Cancer 2000; Wedge SR, Clin Can Res 2005, Burger RA J Clin Oncol 2007

GOG 0218:
First Reported Randomized Trial of Bevacizumab in Ovarian Cancer

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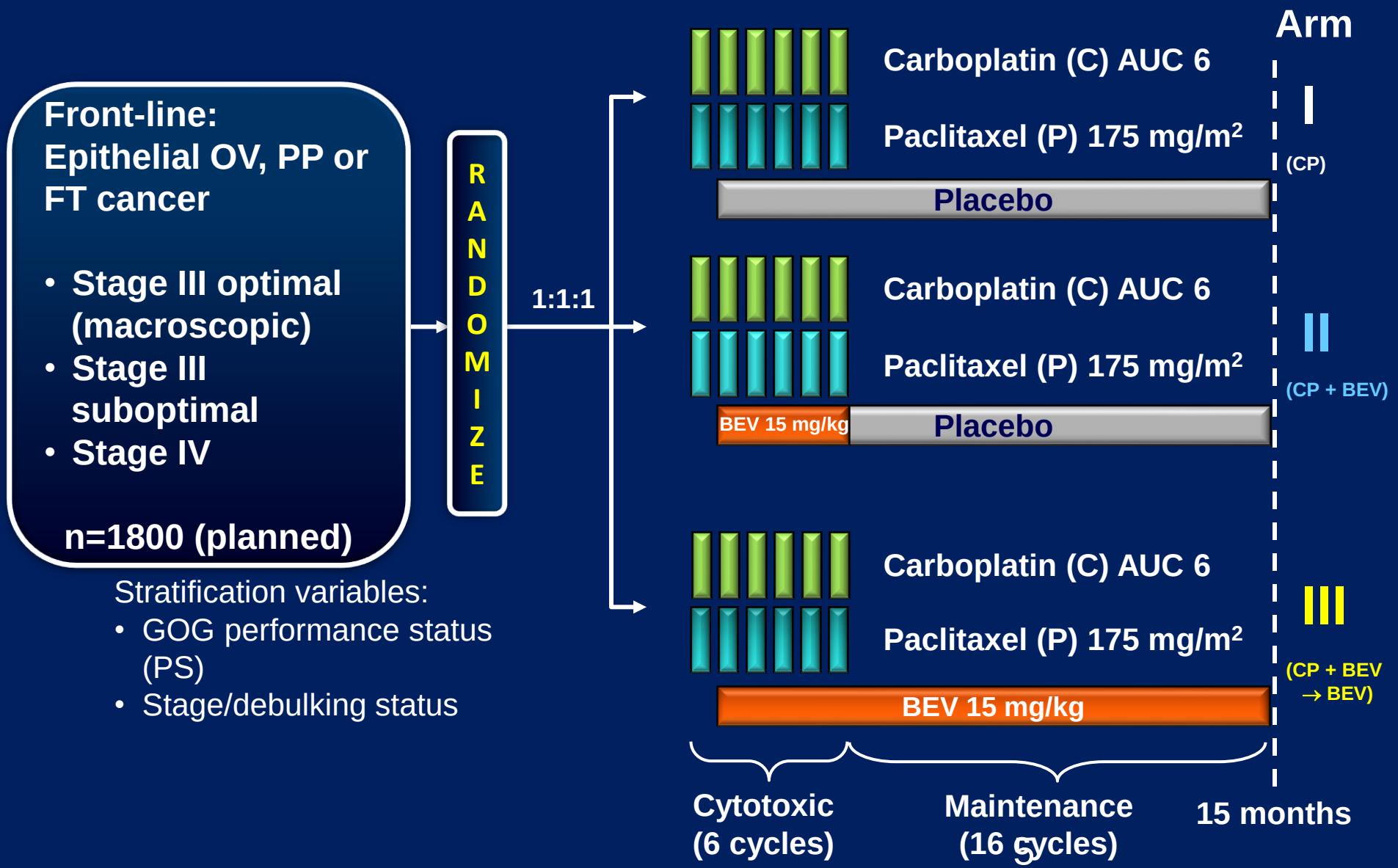
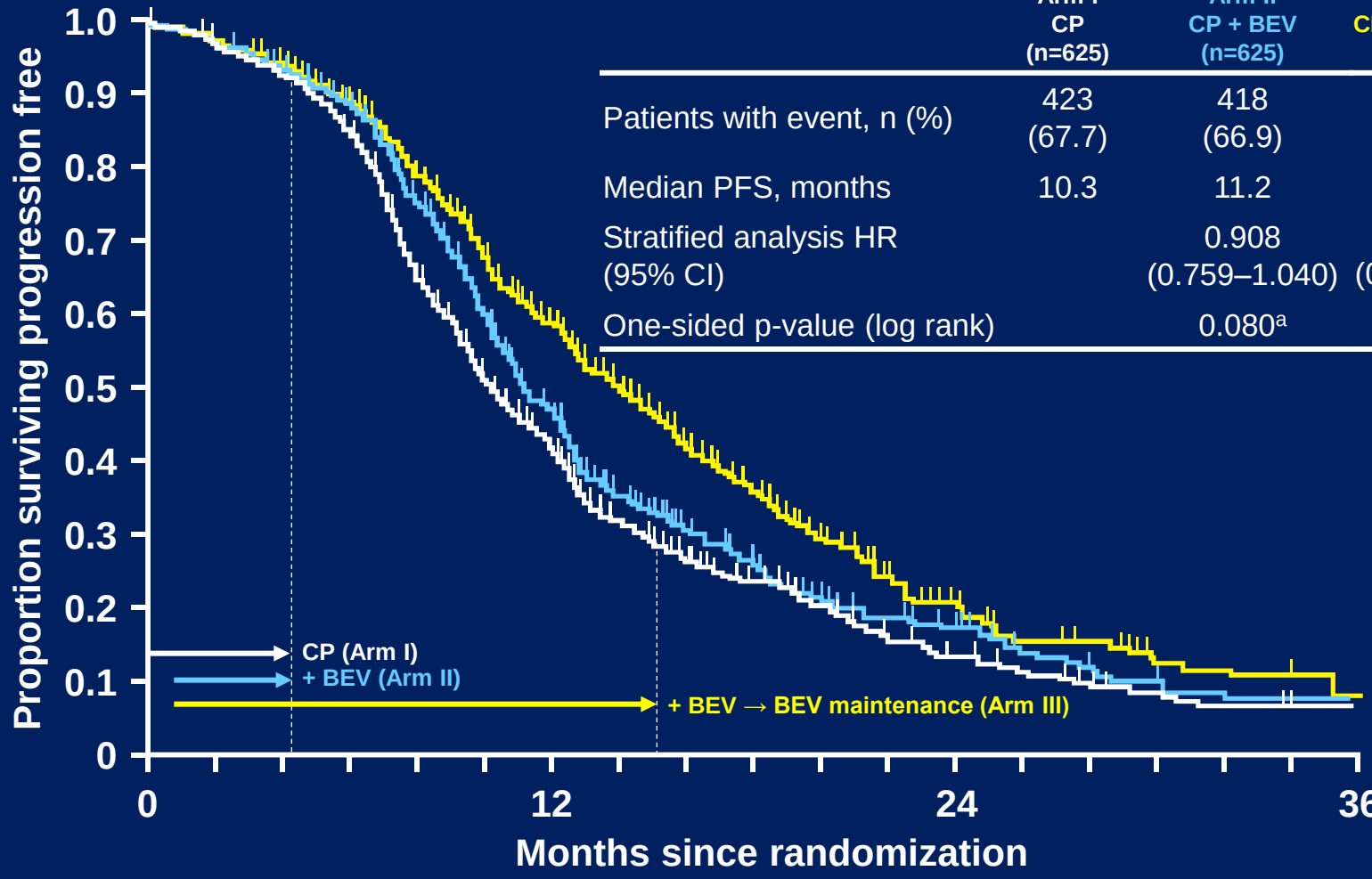
GOG-0218: Schema



Stratification variables:
- GOG performance status (PS)
- Stage/debulking status

GOG-0218: Investigator-Assessed PFS

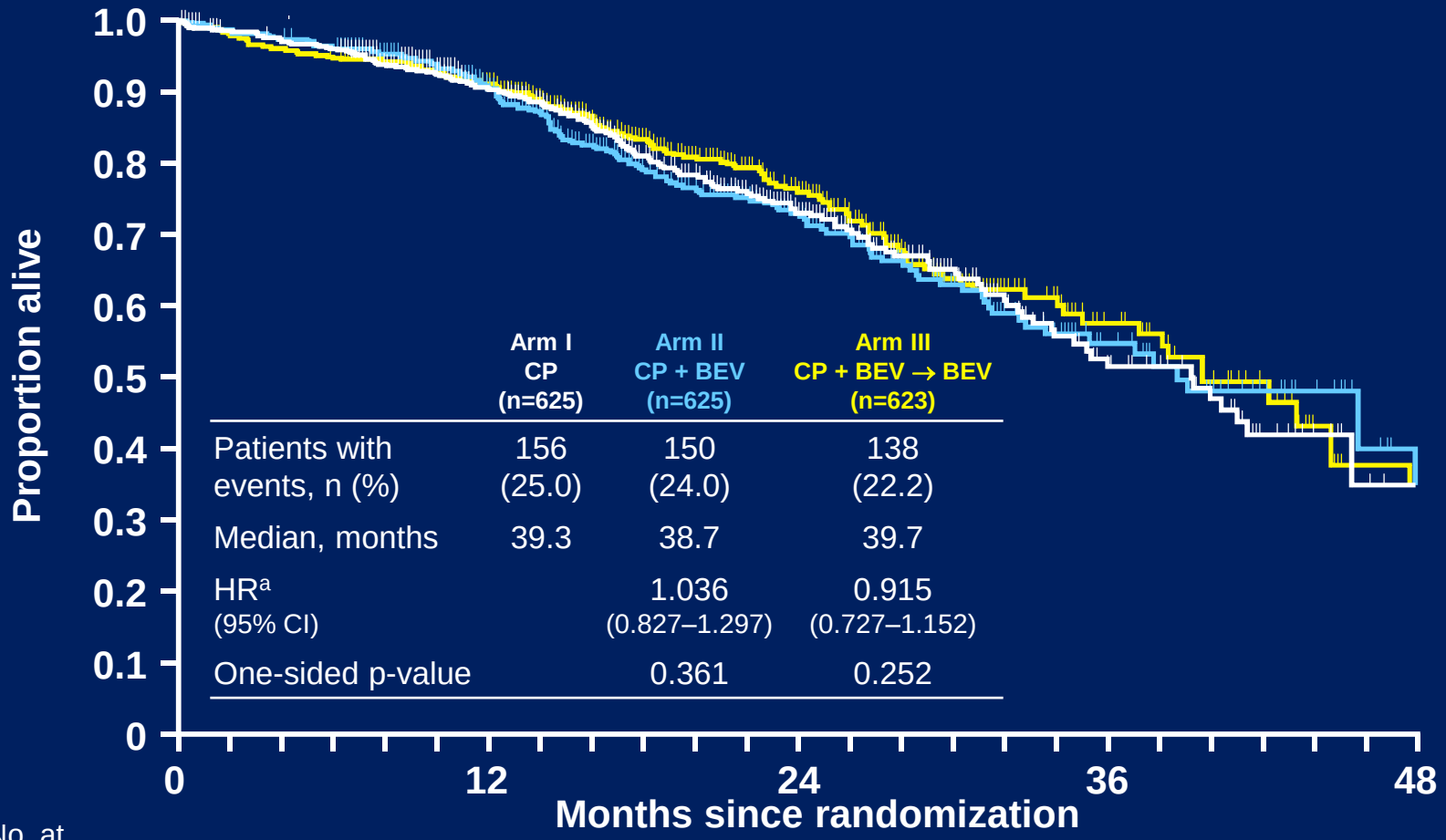


	Arm I CP (n=625)	Arm II CP + BEV (n=625)	Arm III CP + BEV → BEV (n=623)
Patients with event, n (%)	423 (67.7)	418 (66.9)	360 (57.8)
Median PFS, months	10.3	11.2	14.1
Stratified analysis HR (95% CI)		0.908 (0.759–1.040)	0.717 (0.625–0.824)
One-sided p-value (log rank)		0.080[a]	<0.0001[a]

[a]p-value boundary = 0.0116

GOG-0218: Overall Survival Analysis

23.7% of Patients had died



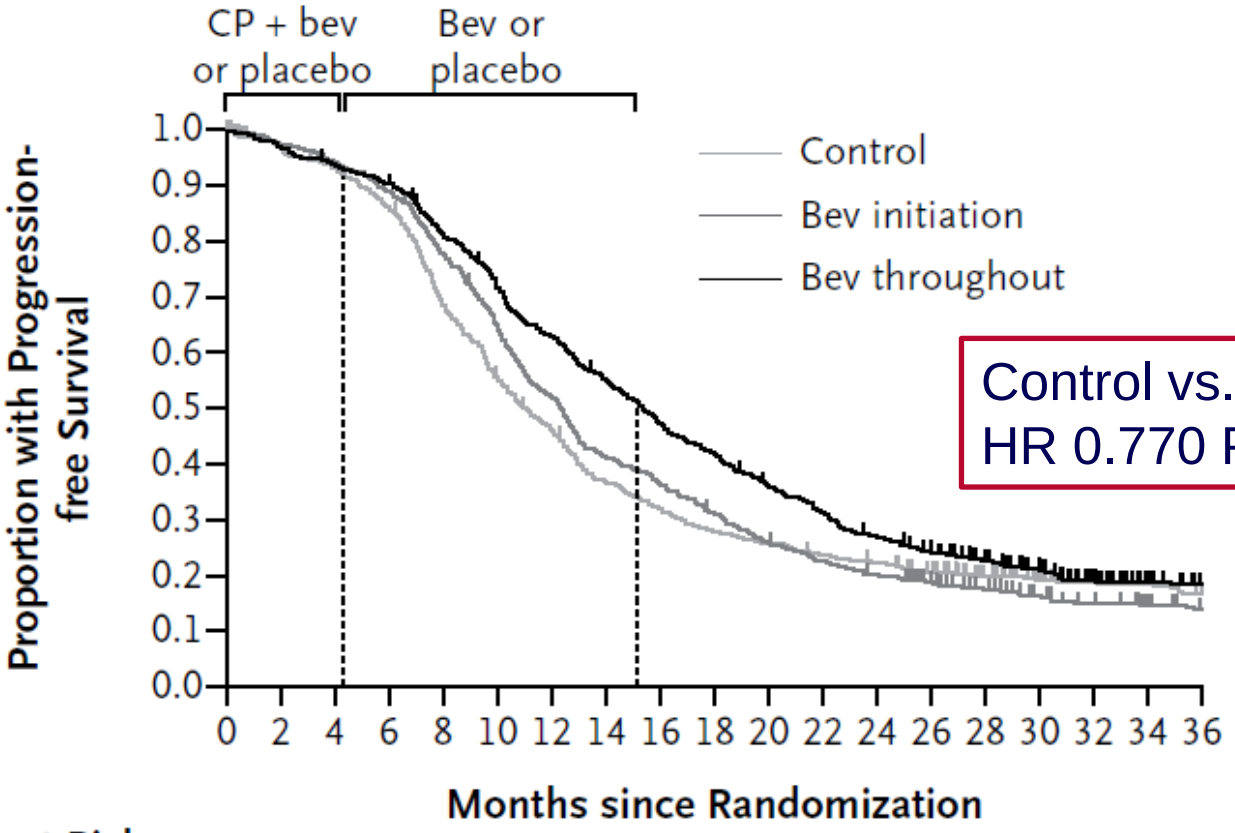
	Arm I CP (n=625)	Arm II CP + BEV (n=625)	Arm III CP + BEV → BEV (n=623)
Patients with events, n (%)	156 (25.0)	150 (24.0)	138 (22.2)
Median, months	39.3	38.7	39.7
HR[a] (95% CI)		1.036 (0.827–1.297)	0.915 (0.727–1.152)
One-sided p-value		0.361	0.252

No. at risk				
	625/625/623	442/432/437	173/162/171	46/39/40

[a]Stratified analysis

GOG-0218 - Progression Free Survival

(analysis as of August 26, 2011)
(N = 1873 patients)



Control vs. Bev throughout:
HR 0.770 PFS gain ~ 4 months

No. at Risk

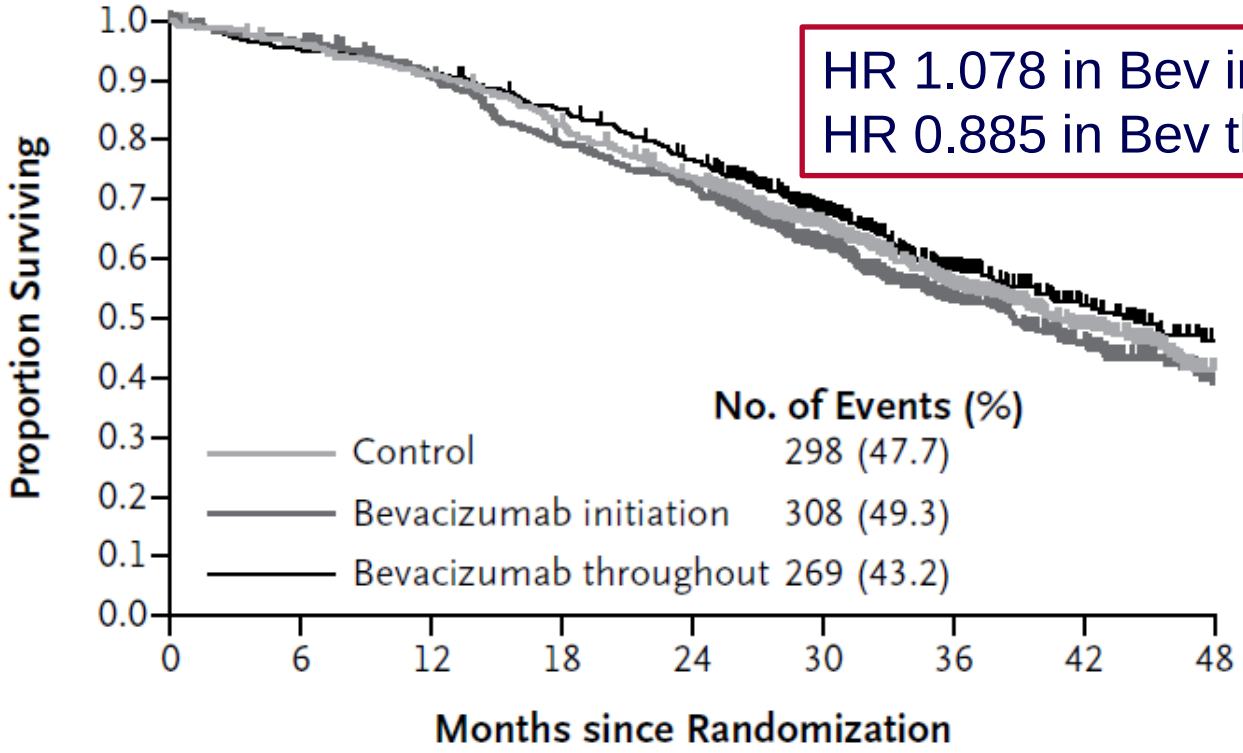
Control	625	535	283	169	133	78	49
Bev initiation	625	552	319	190	121	67	40
Bev through-out	623	559	386	256	162	97	56

Burger et al, N Engl J Med, 2011

GOG-0218 - Overall Survival

(analysis as of August 26, 2011)

47% of patients have died



HR 1.078 in Bev initiation - NS
HR 0.885 in Bev throughout - NS

No. at Risk									
Control	625	595	558	506	446	322	200	116	56
Bevacizumab initiation	625	598	557	486	440	304	191	108	54
Bevacizumab throughout	623	587	561	519	463	321	201	114	62

Six additional Phase III Trials Evaluating Addition of an Angiogenesis Inhibitor in Epithelial OVCA

Agent	Trial ID	N	Line of therapy	Chemo	Primary Efficacy Endpoint	Status
Bevaci-zumab	GOG0218	1873	First	TC	PFS	Published
	ICON7	1528	First	TC	PFS and OS	Published
	OCEANS	484	Recurrent – *P sens*	GC	PFS	Published
	AURELIA	361	Recurrent – P res	T or Topo or Lipodox	PFS	Presented (ESMO 2012)
BIBF	AGO-OVAR 12	1300	First	TC	PFS	Closed
Cediranib	ICON6 (GCIG study)	2000	Recurrent – *P sens*	TC	PFS and OS	Closed
Pazopanib	AGO-OVAR 16	900	First (*maintenance only*)	TC (Bev allowed)	PFS	Active

Results of Reported Randomized Trials

All are Bevacizumab Studies

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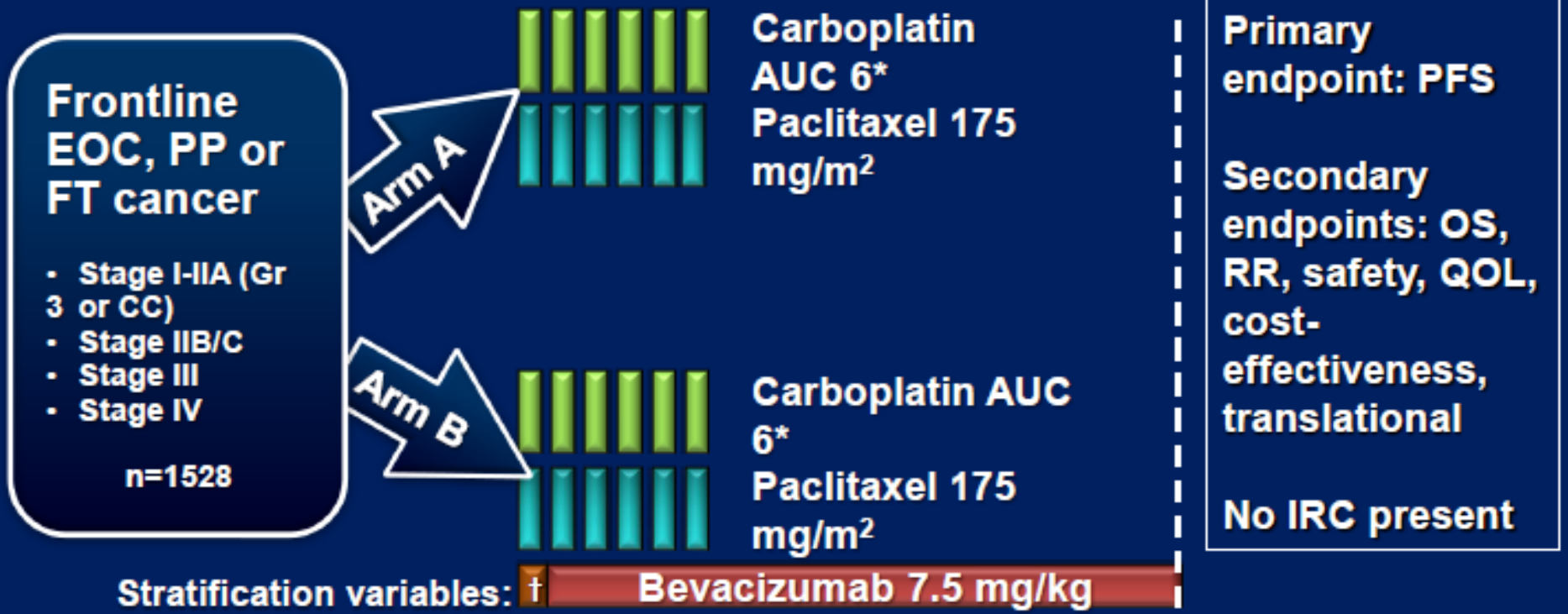
ICON7: Study Design

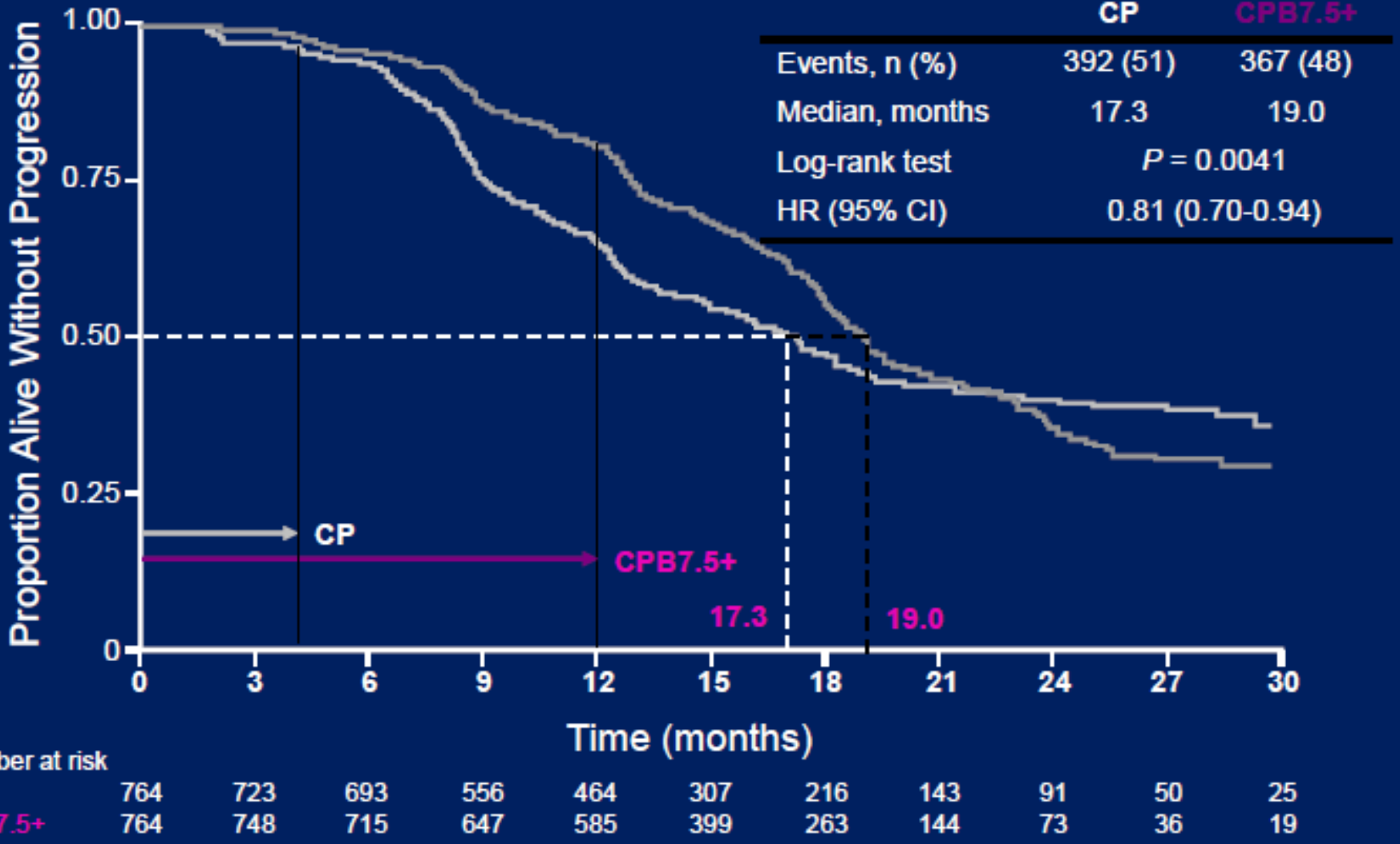


Stratification variables:
- Stage / surgery
- Time since surgery
- GCIG group

*Might vary based on GCIG group.
†Omit cycle 1 bevacizumab if < 4 weeks from surgery.

ICON7 PFS Benefit: Academic Analysis

ESMO 2010



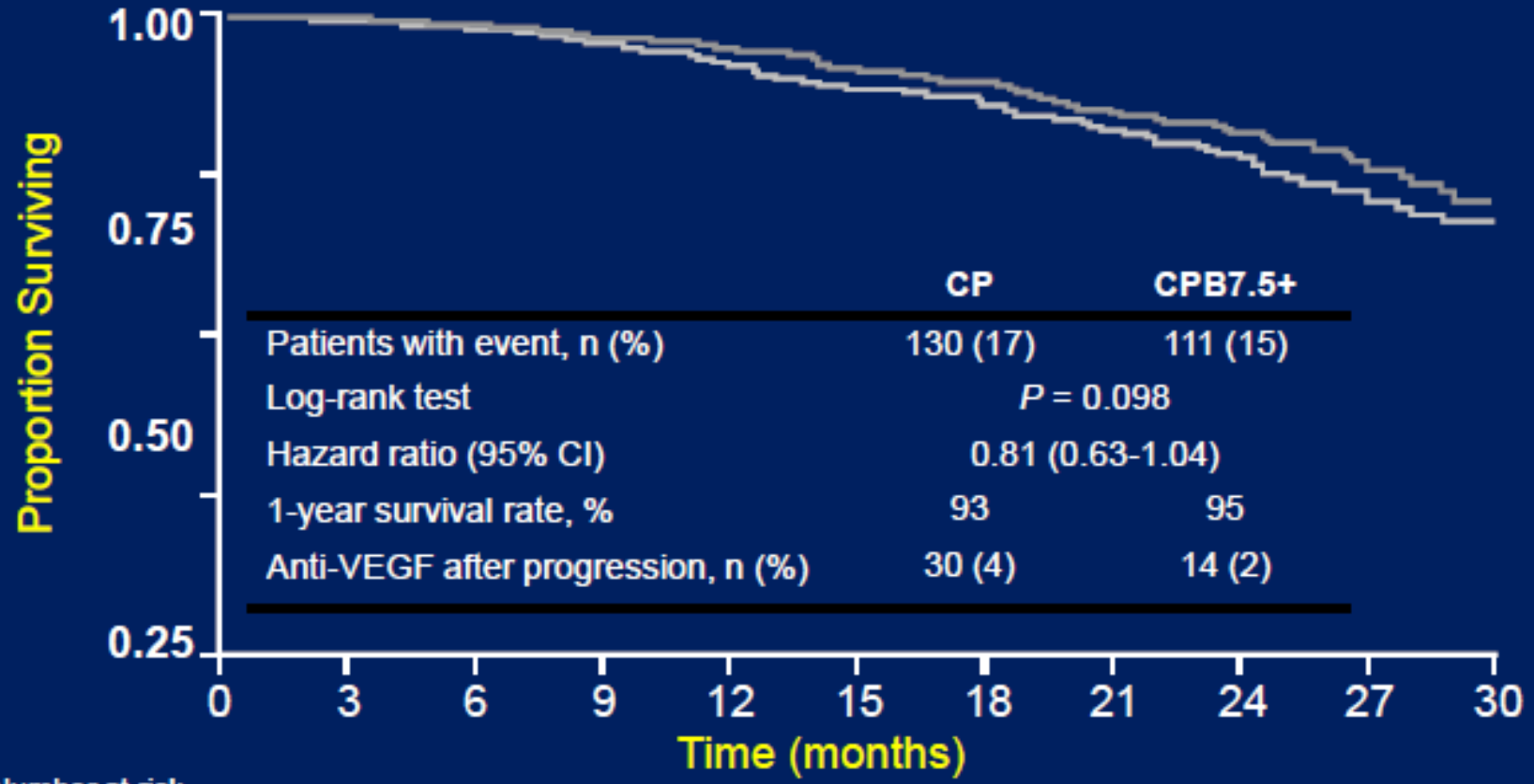
	CP	CPB7.5+
Events, n (%)	392 (51)	367 (48)
Median, months	17.3	19.0
Log-rank test	*P* = 0.0041	
HR (95% CI)	0.81 (0.70-0.94)	

Number at risk											
CP	764	723	693	556	464	307	216	143	91	50	25
CPB7.5+	764	748	715	647	585	399	263	144	73	36	19

Perren T, et al. *Annals Oncol*. 2010;21(suppl 8). Abstract LBA4.

ICON7: Preliminary Analysis of Overall Survival*

ESMO 2010



	CP	CPB7.5+
Patients with event, n (%)	130 (17)	111 (15)
Log-rank test	*P* = 0.098	
Hazard ratio (95% CI)	0.81 (0.63-1.04)	
1-year survival rate, %	93	95
Anti-VEGF after progression, n (%)	30 (4)	14 (2)

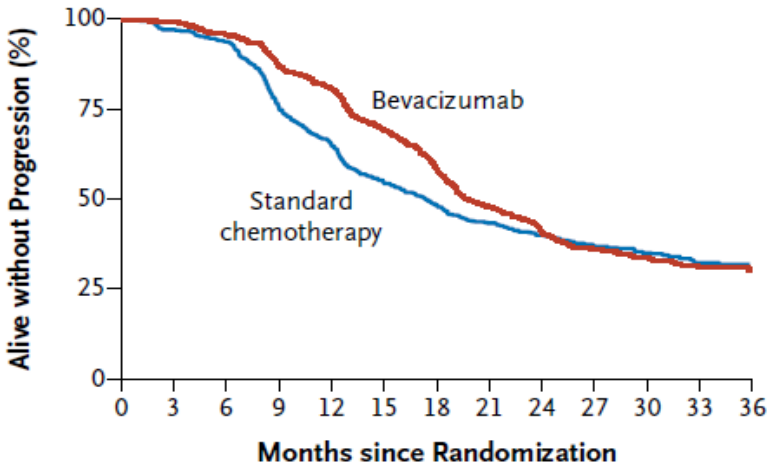
Number at risk

	0	3	6	9	12	15	18	21	24	27	30
CP	764	741	724	701	652	486	368	252	159	83	33
CPB7.5+	764	753	737	716	678	525	404	259	162	89	40

*Based on immature OS data (241 of 715 required events, 16% of all patients) as required by regulatory authorities (approved by IDMC and TSC).

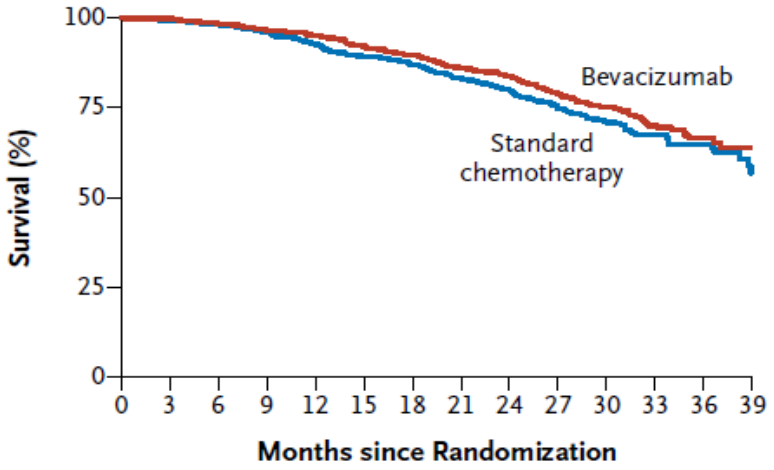
Perren T, et al. *Annals Oncol.* 2010;21(suppl 8). Abstract LBA4.

A Updated Data, Progression-free Survival



No. at Risk							
Standard chemo-therapy	764	693	474	350	221	114	39
Bevacizumab	764	716	599	430	229	107	27

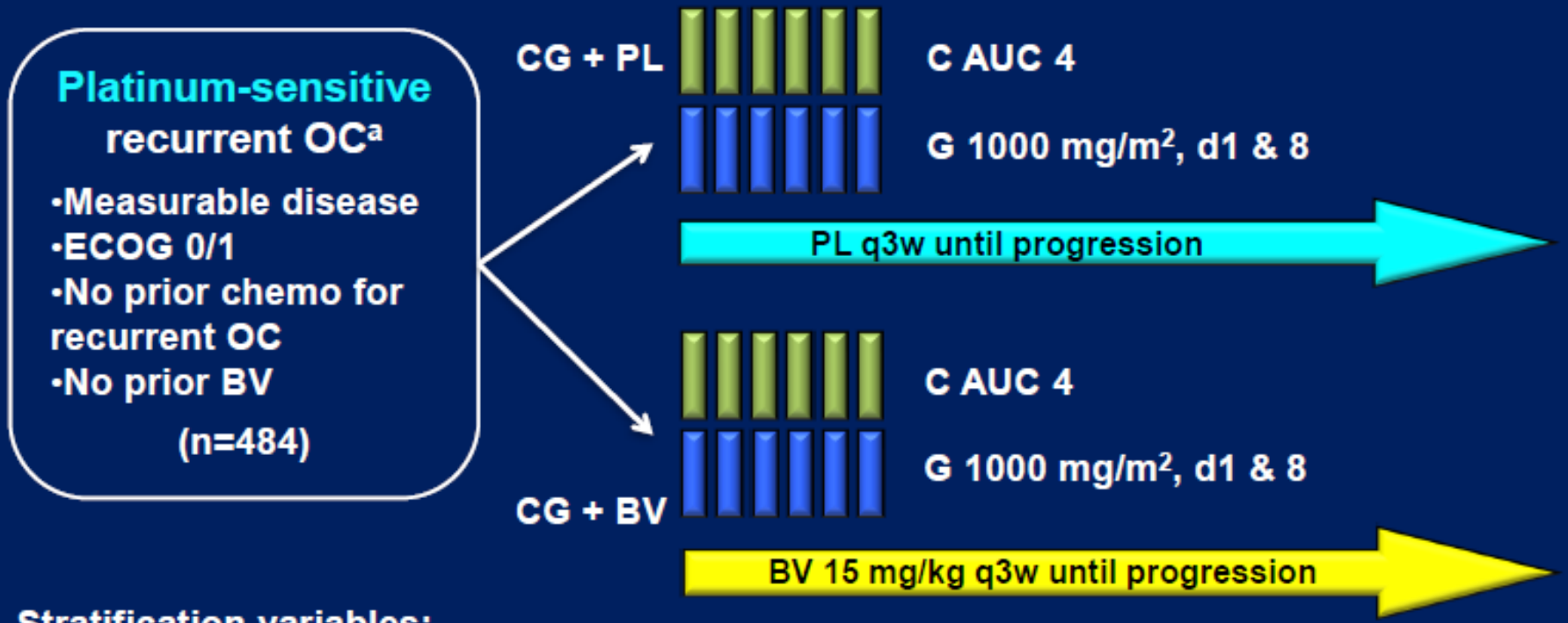
C Updated Data, Overall Survival



No. at Risk														
Standard chemo-therapy	764	741	724	703	672	646	623	542	421	304	212	132	71	26
Bevacizumab	764	753	737	717	702	680	657	592	459	329	228	129	69	19

Updated ICON 7 PFS and OS Perren T et al, NEJM 2011

OCEANS: Study schema



Stratification variables:

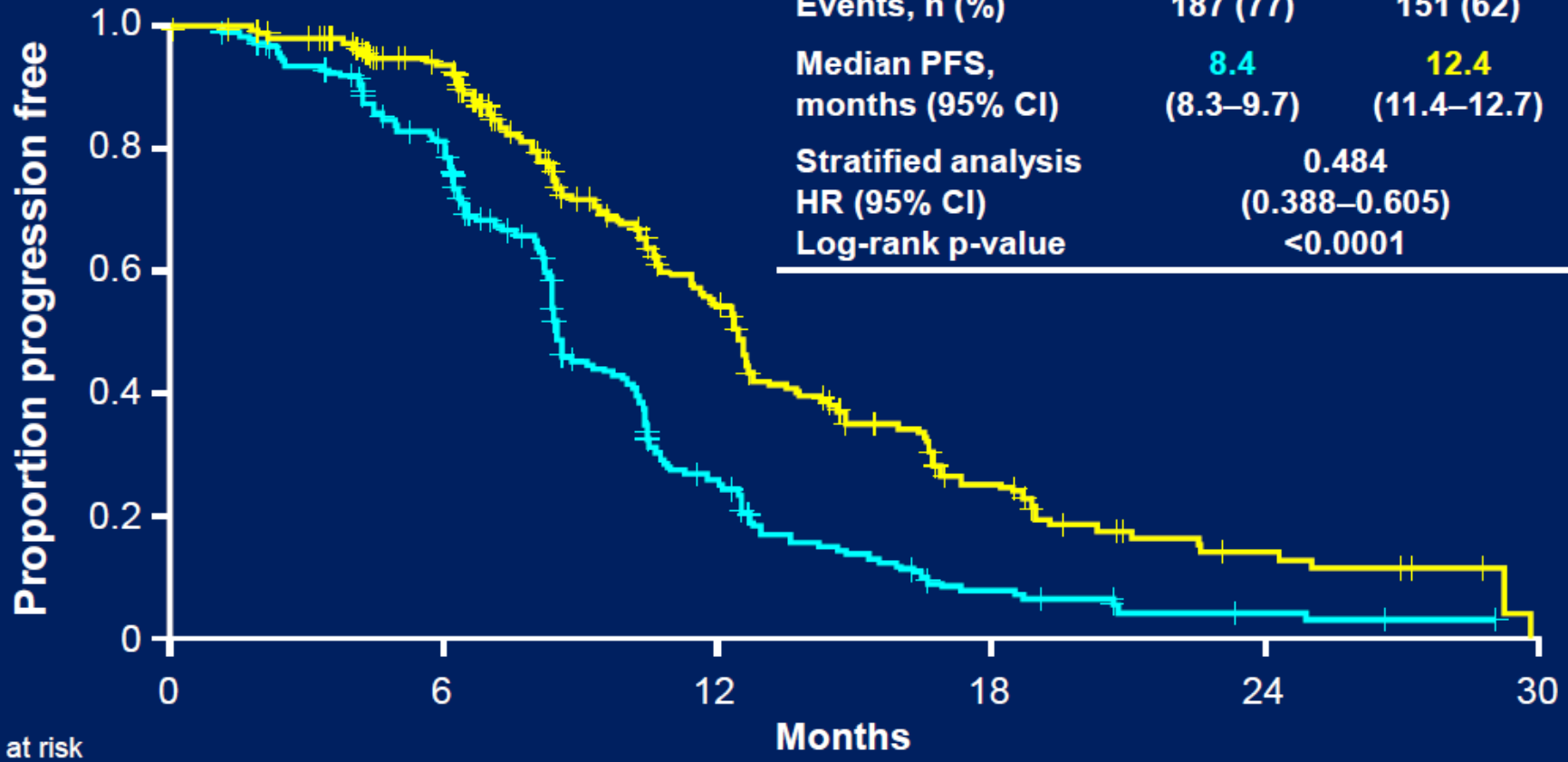
- Platinum-free interval (6–12 vs >12 months)
- Cytoreductive surgery for recurrent disease (yes vs no)

BV = bevacizumab; PL = placebo

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

OCEANS: Primary analysis of PFS

	CG + PL (n=242)	CG + BV (n=242)
Events, n (%)	187 (77)	151 (62)
Median PFS, months (95% CI)	8.4 (8.3–9.7)	12.4 (11.4–12.7)
Stratified analysis HR (95% CI)	0.484 (0.388–0.605)	
Log-rank p-value	<0.0001	



Aghajanian et al. J Clin Oncol 2011;29 (suppl; abstr LBA5007)

OCEANS – Overall Survival Data

- Still not mature – and results not stable
- 31% of GC pts have received Bev post PD
- 15% of GC-Bev pts have received Bev post PD

	First Interim OS Analysis (29% died)		Second Interim OS Analysis (48.6% died)	
	GC	**GC Bev**	**GC**	**GC Bev**
Median (mo)	29.9	35.5	35.2	33.3
HR 95% CI	**0.751** 0.537-1.052		**1.027** 0.792 – 1.331	

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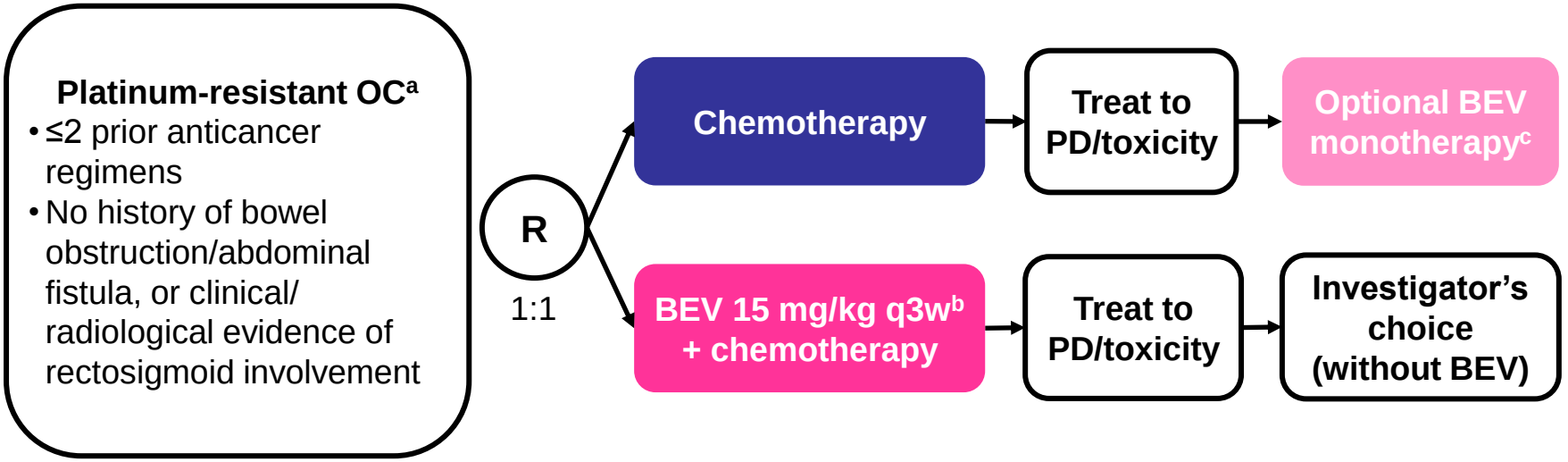
AURELIA trial design



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; PLD = pegylated liposomal doxorubicin
[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

Poveda A, et al, ESMO 2012

Statistical design

Primary objective: To compare PFS with CT alone vs BEV + CT according to RECIST v1.0

Secondary objectives: To compare

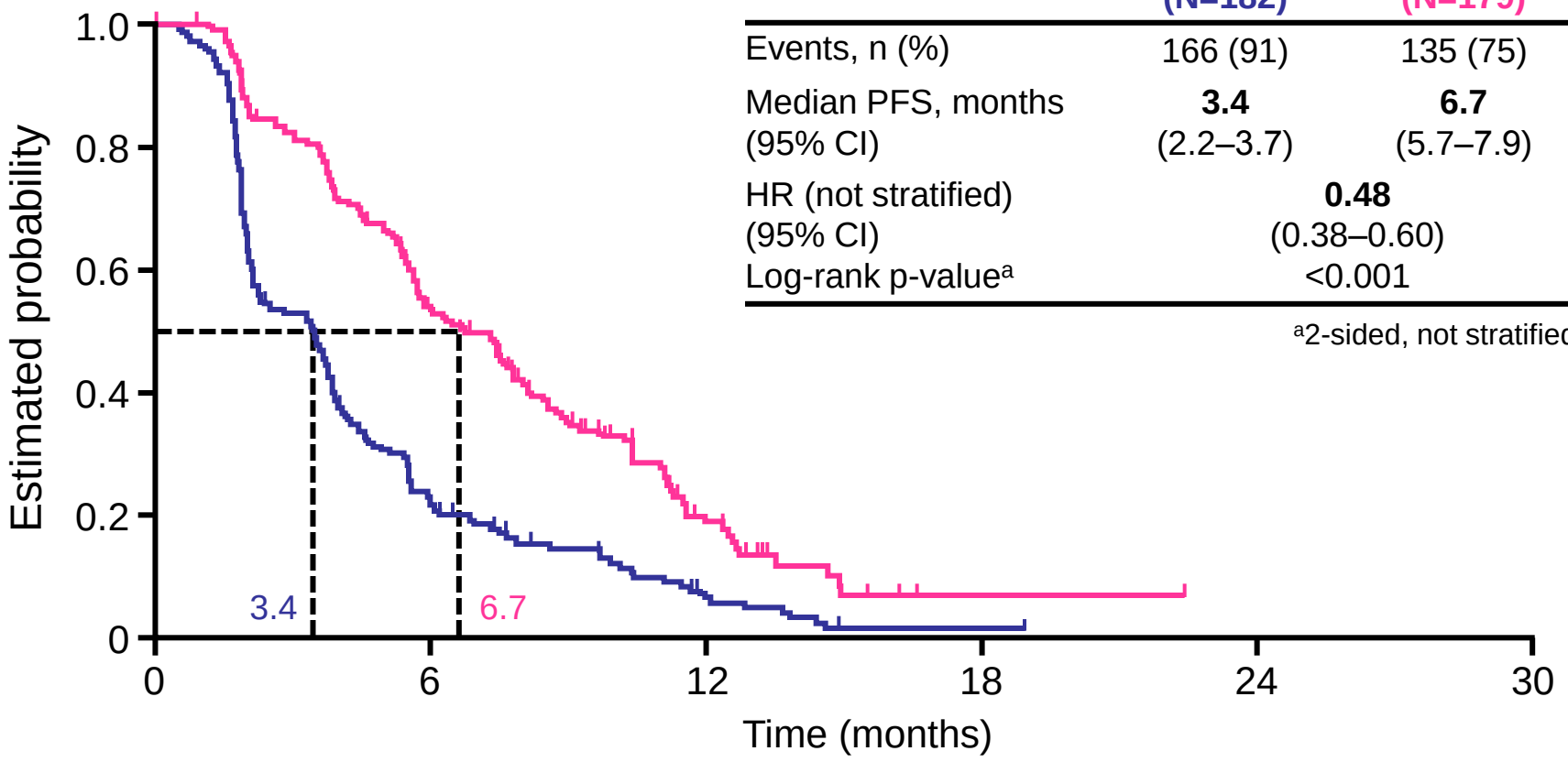
- Objective response rate (ORR) according to RECIST v1.0 and/or GCIG CA-125 criteria
- Overall survival
- Quality of life
- Safety and tolerability

Exploratory objectives: Including evaluation of safety and efficacy according to CT cohort (investigator's choice)

CT **choice** was a stratification factor but patients were not randomised between the CT cohorts

RECIST = Response Evaluation Criteria in Solid Tumours

Progression-free survival: Overall population



	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 (not stratified) (95% CI)	**0.48** (0.38–0.60)	
Log-rank p-value[a]	<0.001	

[a]2-sided, not stratified

No. at risk:

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

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

Summary of Randomized Trials – *All are Bevacizumab Studies*

- Clear **biological** effect of bevacizumab in OVCA
- Survival data not mature in any trial – preliminary data suggest lesser effect than on PFS.
- Toxicity greater in bevacizumab arms and cost of treatment is considerable (data not shown)
- ***QUESTIONS:***
  - ***Should bevacizumab be used in OVCA treatment?***
  - ***If so, in what line of therapy?***
  - ***And in which patients?***

NS = not significant; TE = too early, NR = not reported

Issues in Interpreting Benefit of PFS

- Progression definitions are arbitrary (RECIST, GCIG criteria) –
  - created to categorize observed changes in tumour size
  - not based on a degree of change known to be associated with specific clinical implication – i.e. definition created first - clinical meaning assigned post hoc
- Nevertheless, use of Progression Free Survival in advanced disease trials has migrated from secondary to primary endpoint.
- What are implications?

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Arguments for Use of PFS to Change Practice

1. Longer PFS may signal ***better disease symptom control***
2. Longer PFS may be a ***indicate improved overall survival***
3. In circumstance of no evidence of disease, longer PFS (RFS) may provide patient with ***time free of disease and symptoms***
4. Longer PFS may be all that can be measured if second/third line ***obscures survival benefit***

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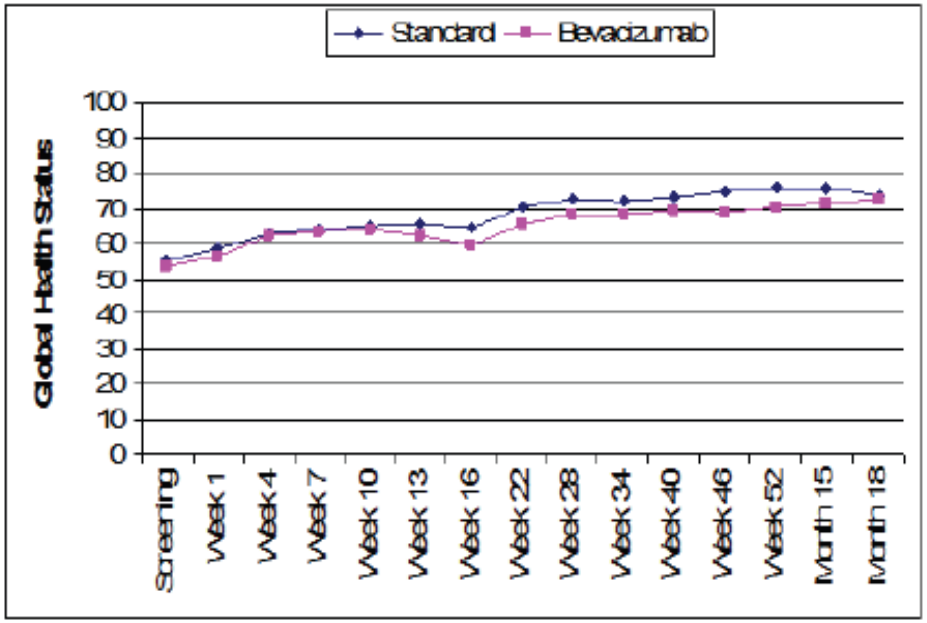
1. Symptom Control – What do first line data show?

- Data reported to date have not shown QoL differences.
  - GOG- 0218: FACT-O TOI in post-chemo period no differences.
  - ICON7·

Figure 3S. Global health status score over time (a higher score indicates better Quality of Life)



SYMPTOM data, particularly at time when PFS curves diverging will be important

Perren T et al, NEJM 2011, Suppl Appendix Fig 3S

1. Symptom Control – what do recurrent disease data show?

- Arguably much more important in recurrent disease where symptom improvement or delay in symptom progression highly relevant.
  - OCEANS study – QoL / symptom benefit not endpoints according to clinicaltrials.gov listing
  - AURELIA study – QoL secondary endpoint. Not reported yet.
    - This trial most likely of all to show ***disease-related*** symptom benefit based on PFS findings.

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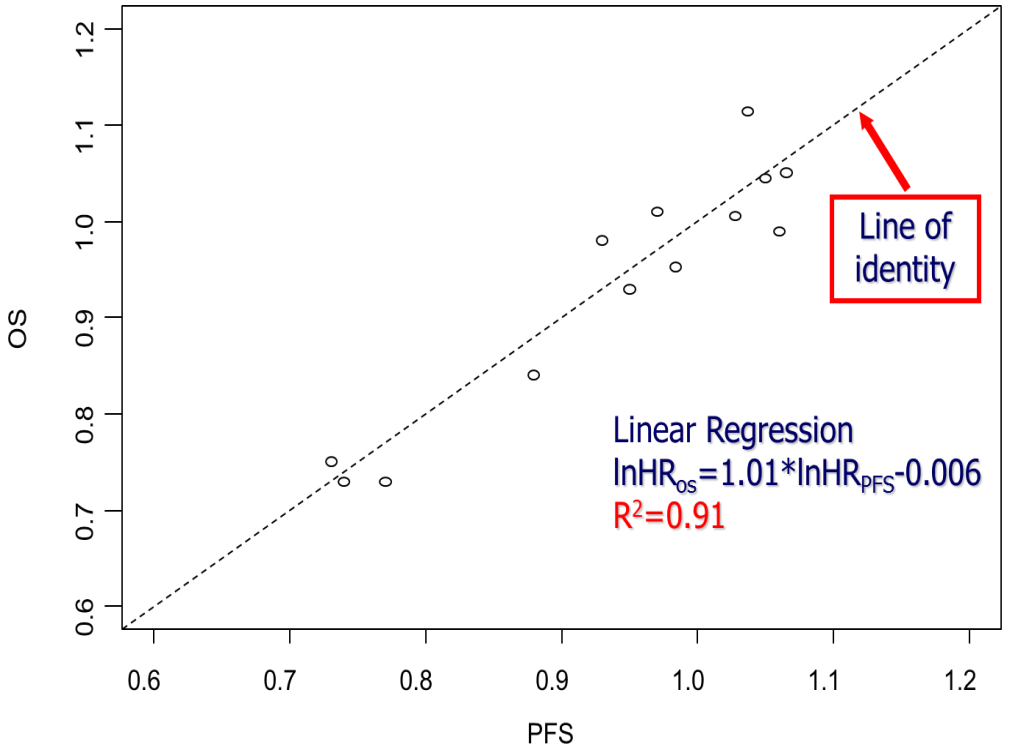
2. *Longer PFS may → Improved OS*

- PFS has been reliable in predicting OS gains in 1st line OVCA trials – in chemo era.
- Data not mature in OVCA bevacizumab trials - survival most likely to be positive in AURELIA where gain in PFS is near end of disease trajectory – **these data needed.**



HR PFS vs. OS in First-Line OVCA trials of chemotherapy

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4. PFS has to be used – because OS impact obscured by second/third line treatment

- Somewhat tautological argument that could potentially lead to adoption of ineffective therapies.
- This argument implies **absolute gains** from post progression treatment has to be ***greater in the standard arm than the treated arm*** (provided trial is powered to detect same absolute gain in OS as was seen in PFS)

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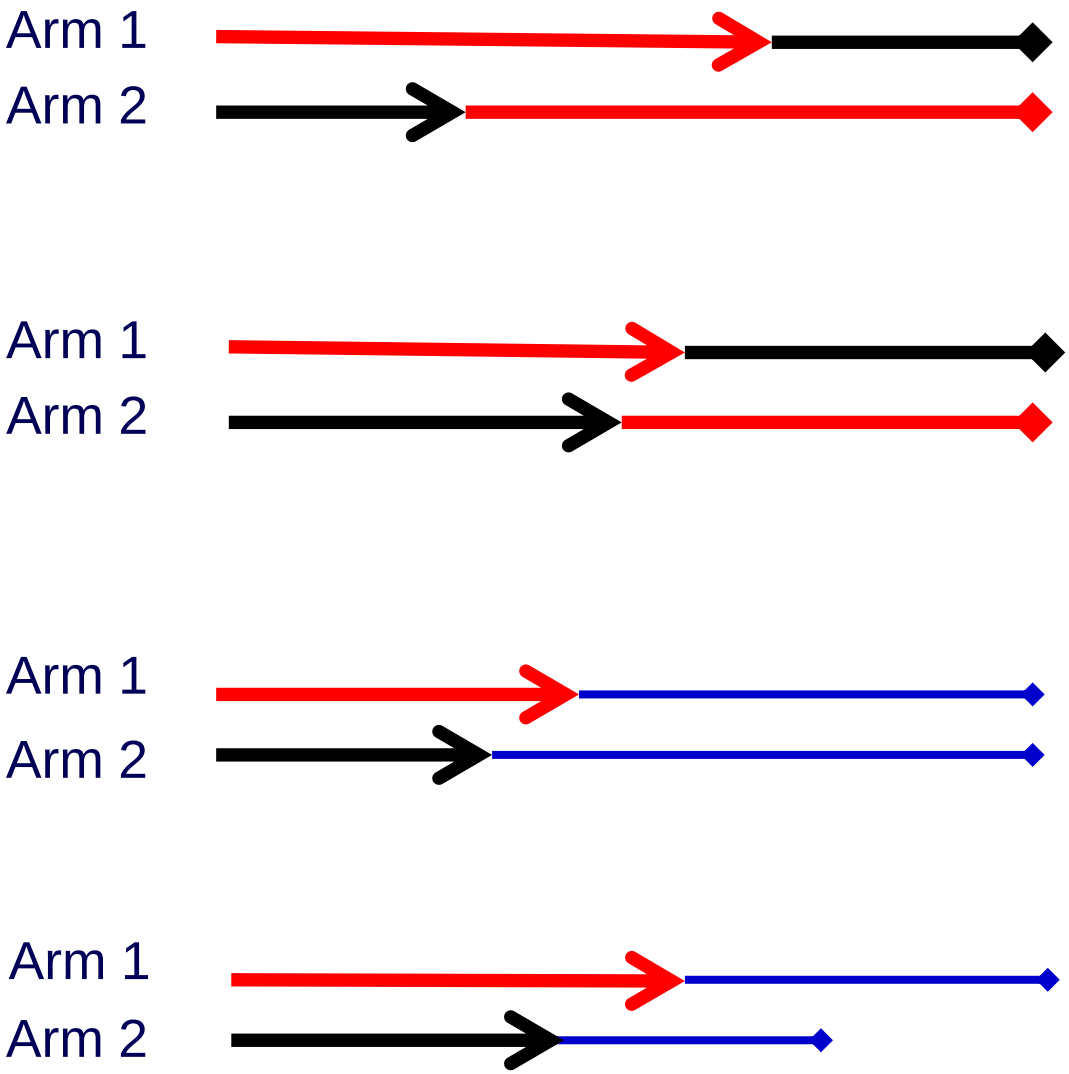

PFS large effect, OS NS

Cross over design or experimental treatment widely available.

PFS Arm 1 >> Arm 2

PFS Arm 2 >> Arm 1 after crossover

New treatment possibly has impact on OS

PFS modest effect, OS NS

Cross over design or experimental treatment widely available.

PFS Arm 1 > Arm 2

PFS similar after crossover

PFS effect too small, or false +, or disease more aggressive post Arm1 treatment.

New treatment of dubious value

PFS modest effect, OS NS

"active" 2nd line Rx, no or < 50% crossover

PFS Arm 1 >Arm 2

PFS effect too small, or false +, or disease more aggressive post Arm1 treatment.

New treatment of dubious value

PFS modest effect, OS Superior

"active" 2nd line Rx, no or < 50% crossover

PFS Arm 1 >Arm 2

PFS effect translates into OS benefit

New treatment has impact on OS

Booth, Eisenhauer J Clin Oncol 2012

Biomarkers for Selection of Patients for Anti- Angiogenesis Treatments

- Knowing which patients do not / do benefit could aid greatly in debate - sparing toxicity and cost from those who will not being helped
- IDEAL biomarker:
  - Easily measurable, validated
  - Measurable PRIOR to treatment to select “who to treat”
  - Clearly delineates subgroup with NO benefit versus those with SOME benefit (KRAS in CRC good example)
  - This is ONLY possible to determine from randomized trial data where differential impact of treatment can be evaluated within biomarker defined subsets.

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Biomarkers for Selection of Patients for Anti- Angiogenesis Treatments

- What are the options?
  - Clinical features of disease
  - Biological measures of tumour
  - Biological measures of patients

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Clinical Features – Tumor burden?

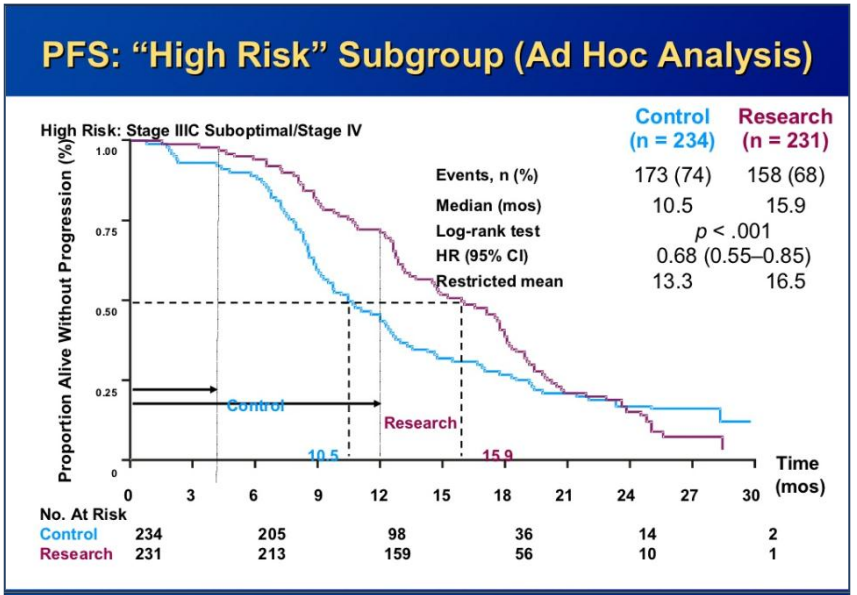
- Decreasing PFS, worse prognosis patients
- Greater relative effect of bevacizumab (lower HR)
- *Increasing anti-angiogenesis effect??*

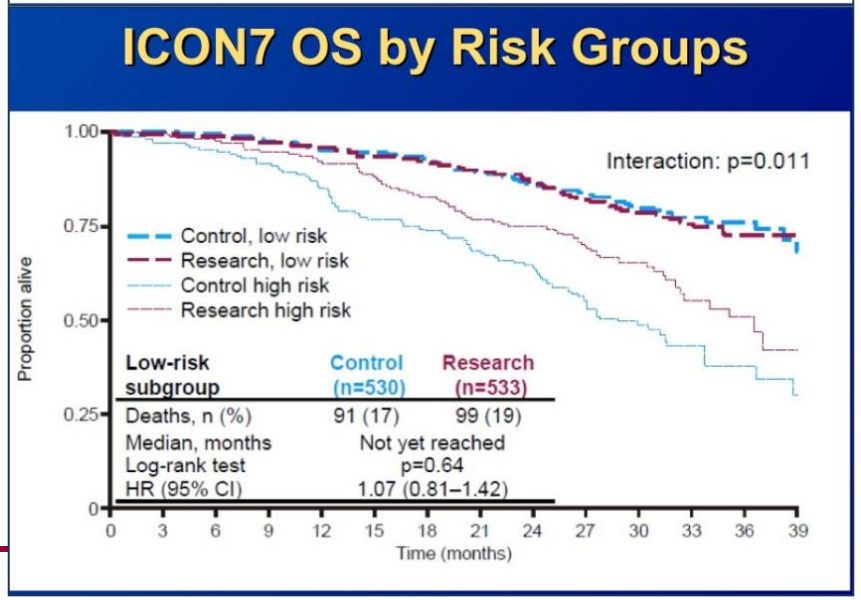
Trial ID	N	Line of	Chemo	Med PFS	PFS HR	OS HR	Ref
IC				17.3 19.0	**.81**	NS (TE) (sub – group?)	Perren NEJM 2011
G				10.3 11.2 14.1	.908 **.717**	NS (TE)	Burger NEJM 2011
O				8.4 12.4	**.48**	NS (TE)	Aghajanian JCO 2012
A		*< 6 mo*	Tax/ Topo / LDc ev	3.4 6.7	**.48**	NR	Pujade-Luaraine ASCO 2012

NS = not significant; TE = too early, NR = not reported

High Tumor Burden as Predictive Factor?

- ICON 7 subgroup analysis suggests greater relative impact of bevacizumab in high risk patients (subopt. Stage IIIC, IV)
- HR for PFS 0.68 in high risk (in contrast to <u>overall</u> HR 0.81 – low risk HR not given)
- <u>Preliminary/subgroup</u> analysis of OS in same direction (**caution** in interpretation – only about 33% patients have died)





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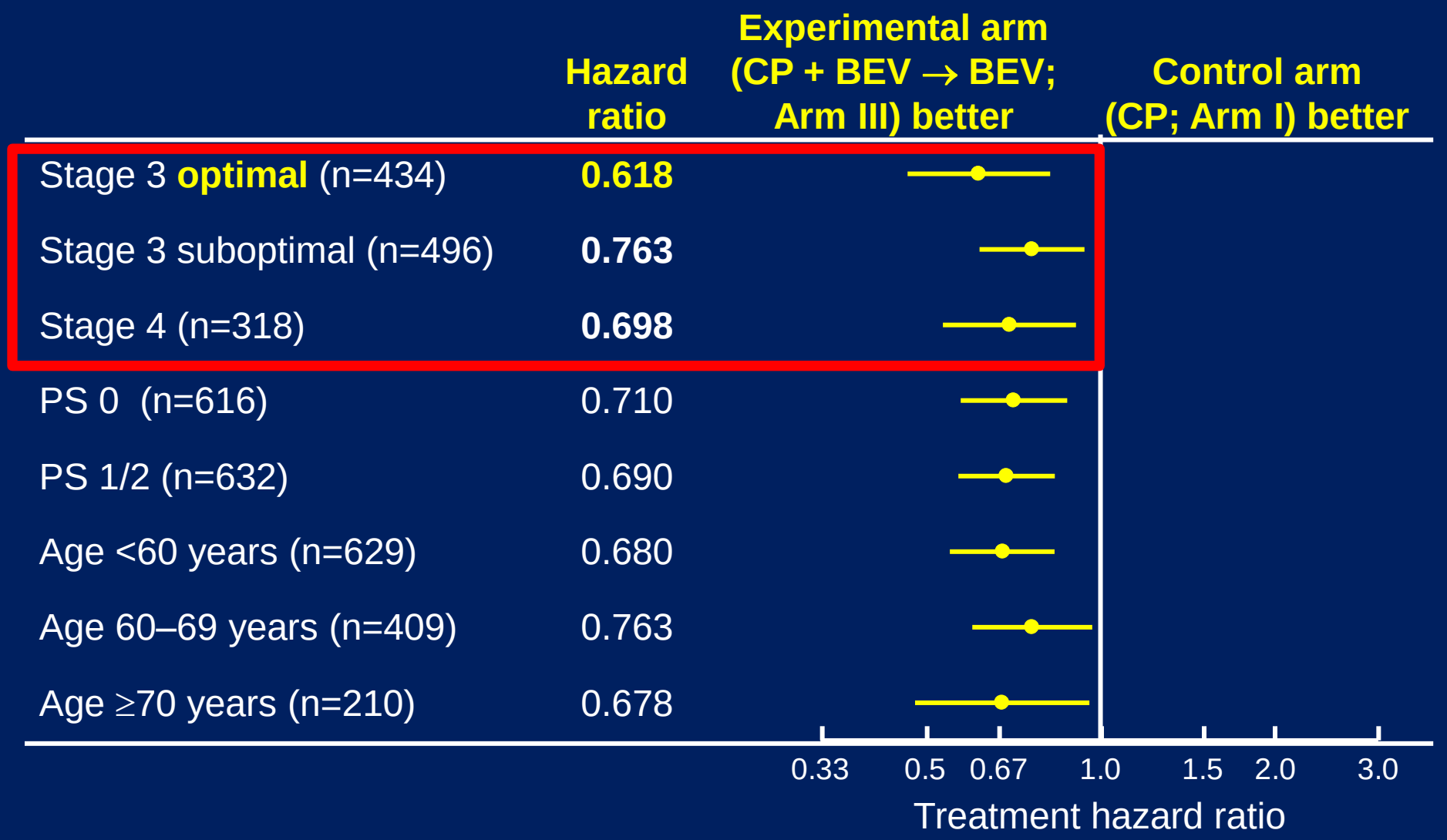
GOG-0218: Optimal/Suboptimal data show different trend – **optimal** cases had lower HR



Nevertheless…

- If AURELIA study shows a survival gain, there would be an argument in favour of defining recurrent/resistant OVCA patients as the group who should received bevacizumab.

- Rationale would be: why give the drug early to everyone when it can be given later only to the subset who recur – and who truly benefit?

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Biological Selection Markers:
Applies not only to Ovarian Cancer!

- Search for biomarkers for anti-angiogenic treatment has been long and challenging – generally studies have been *exploratory* in *non-randomized* cohorts
- Examples of potential candidate markers:
  - Malignant tissue:
    - Microvessel density, VEGF-A, VEGFR
  - Patient:
    - Plasma VEGF, circulating endothelial cells, genetic polymorphisms in VEGF, or VEGFR

Findings variable, inconclusive

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Host VEGFR Variants?

VEGF pathway genetic variants as biomarkers of treatment outcome with bevacizumab: an analysis of data from the AViTA and AVOREN randomised trials

Diether Lambrechts, Bart Claes*, Paul Delmar, Joke Reumers, Massimiliano Mazzone, Betül T Yesilyurt, Roland Devlieger, Chris Verslype, Sabine Tejpar, Hans Wildiers, Sanne de Haas, Peter Carmeliet, Stefan J Scherer, Eric Van Cutsem*

- VEGF Receptor 1 allelic variant identified that showed ***significant genotype by treatment interaction*** in **pancreatic cancer** trial of gemcitabin/erlotinib +/- bevacizumab (p=0.01)

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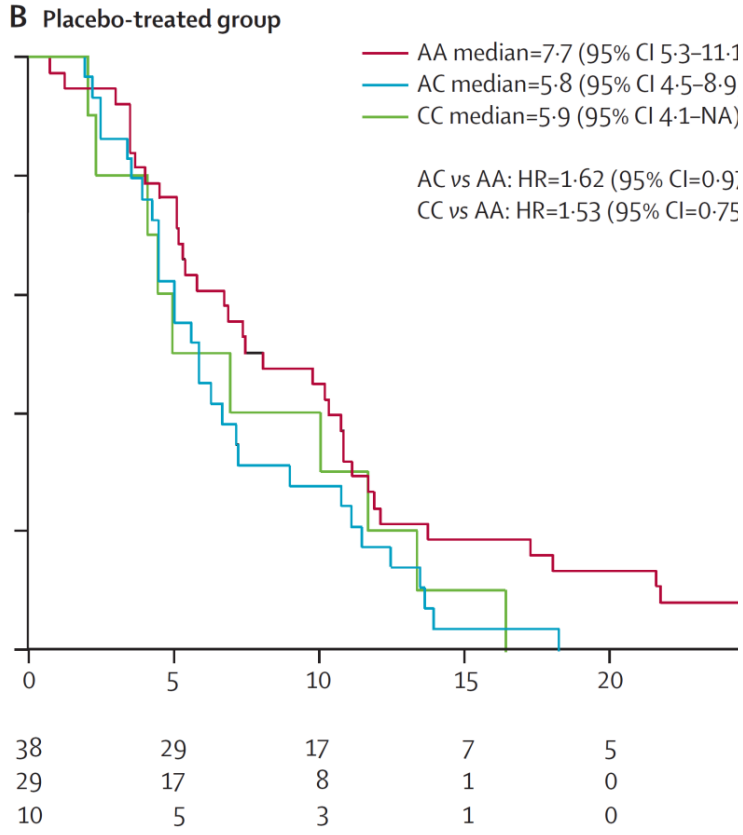
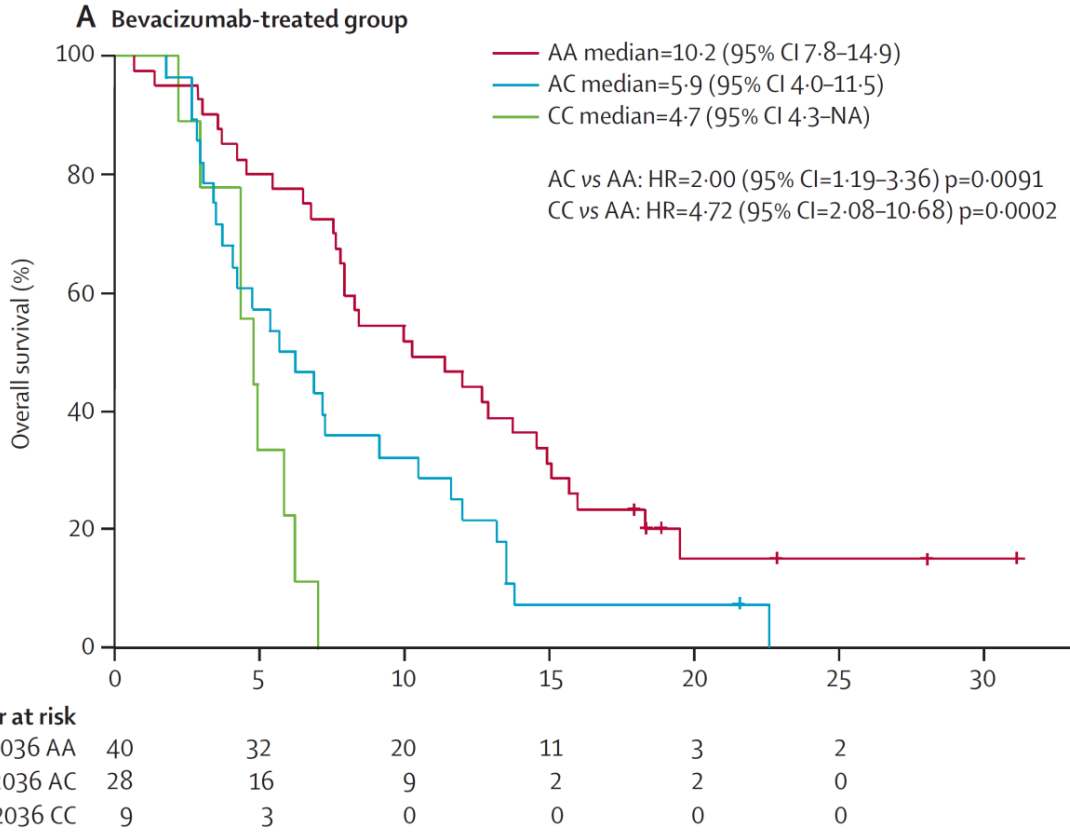
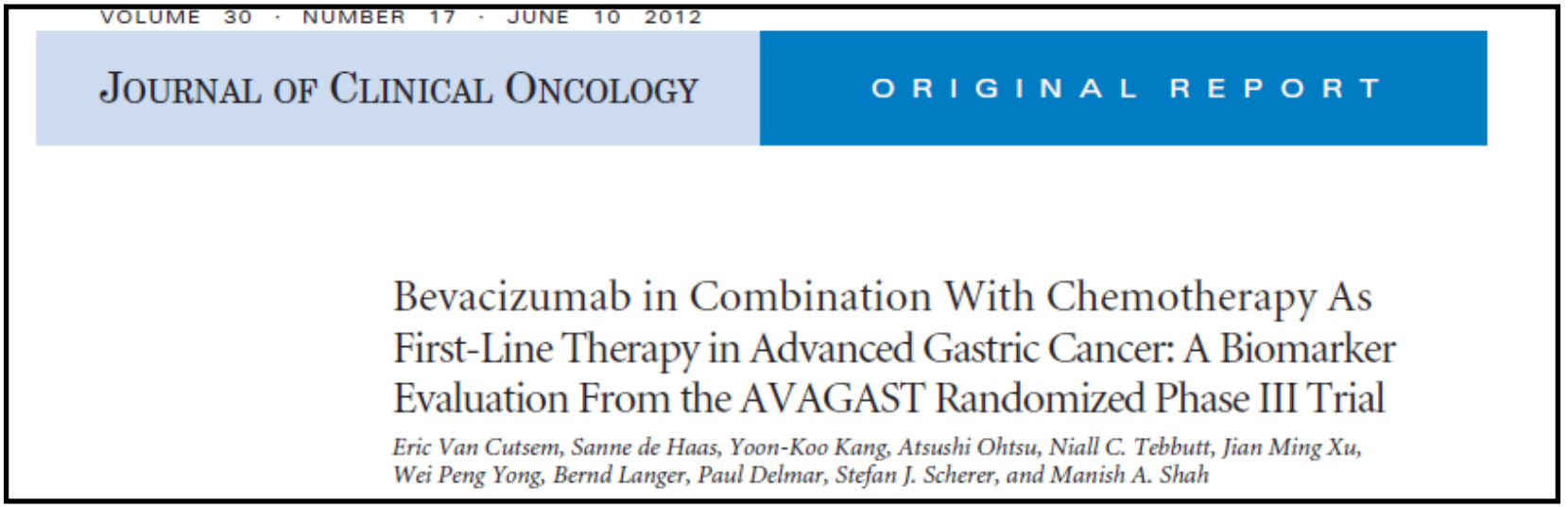
Survival by Genotype in Bevaciumab and Placebo Treated Patients.





Plasma VEGFA?



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ORIGINAL REPORT

Bevacizumab in Combination With Chemotherapy As First-Line Therapy in Advanced Gastric Cancer: A Biomarker Evaluation From the AVAGAST Randomized Phase III Trial

Eric Van Cutsem, Sanne de Haas, Yoon-Koo Kang, Atsushi Ohtsu, Niall C. Tebbutt, Jian Ming Xu, Wei Peng Yong, Bernd Langer, Paul Delmar, Stefan J. Scherer, and Manish A. Shah

- In a trial of chemotherapy +/- bevacizumab, in **gastric cancer**, ***trend*** to greater impact of bevacizumab in patients with higher baseline plasma VEGFA (test for interaction 0.07)

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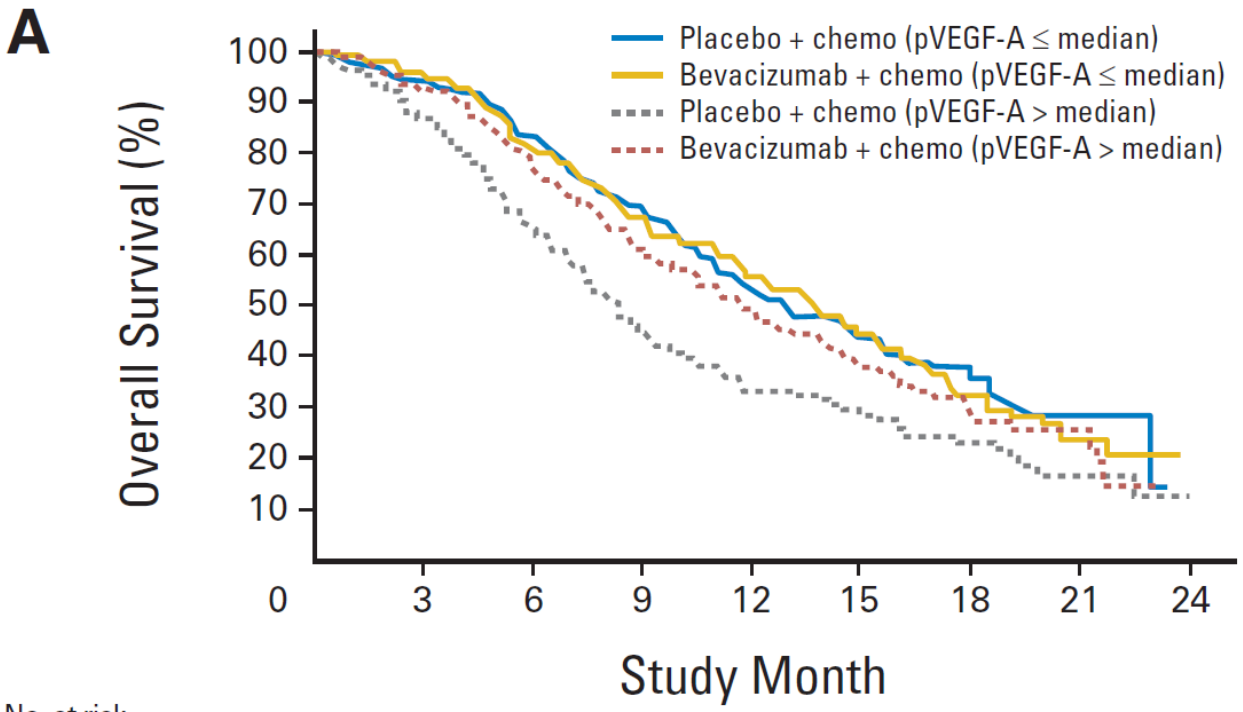
Survival impact of Bevacizumab Stratified by > or ≤ median pVEGF-A



No. at risk									
Placebo + chemo (≤ median)	173	161	139	112	83	57	33	9	0
Placebo + chemo (> median)	184	158	115	80	56	37	21	6	0
Bevacizumab + chemo (≤ median)	184	174	144	119	94	57	31	9	0
Bevacizumab + chemo (> median)	171	156	130	101	79	44	18	10	0

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Biomarkers for Ovarian Cancer?

- VEGF-A levels, genetic pathway variants of VEGF/R are exciting potential markers to evaluate in the 4 RCTs of bevacizumab in OVCA – work is ongoing
- Unclear, even if validated predictive biomarker for bevacizumab can be found in one trial, if it will apply to:
  - All cancers
  - All stages of the cancer in which it appears to be useful
  - All angiogenesis inhibitors
- But these studies raise possibility that there is hope that selection biomarkers can be found.

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Summary – Angiogenesis Inhibitors in Ovarian Cancer

- Great progress in completion of phase III trials of angiogenesis inhibitors in OVCA over past 2-3 years.
- Clear phase III evidence of biological effect (PFS) of bevacizumab. Trials of other agents not yet reported
- Overall survival data not mature
- Will PFS gains will translate into symptom benefit or OS gains? In which patients? – ***highest priority questions.***
- **Also critical**: use data and biological samples from these trials to test selection biomarker hypotheses – esp. those found promising in other cancers.

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Thank You

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To you for your attention

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