BEVASITSUMABI MUNASARJASYÖVÄN ENSILINJAN HOITOON?

Prof. Johanna Mäenpää
TaY ja TAYS, naistentaudit ja synnytykset

18.11.2011

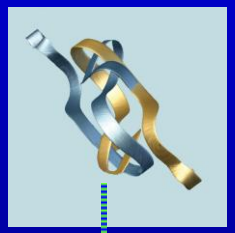
JM 11

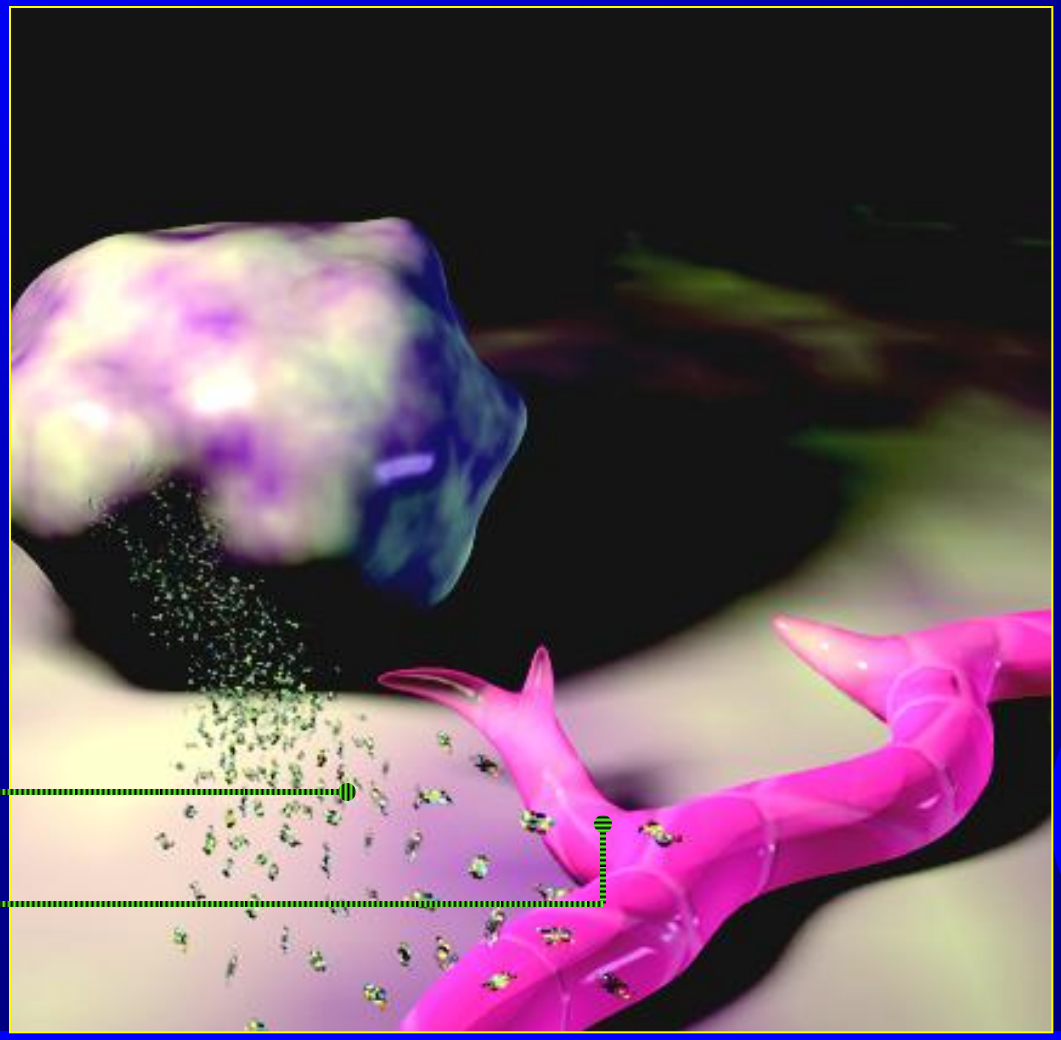
SIDONNAISUUDET

- Jossain vaiheessa yhteistyötä käytännössä kaikkien gynekologiseen tai rintasyöpään liittyviä lääkkeitä valmistavien yritysten kanssa

The angiogenic switch triggers growth of new vessels

VEGF

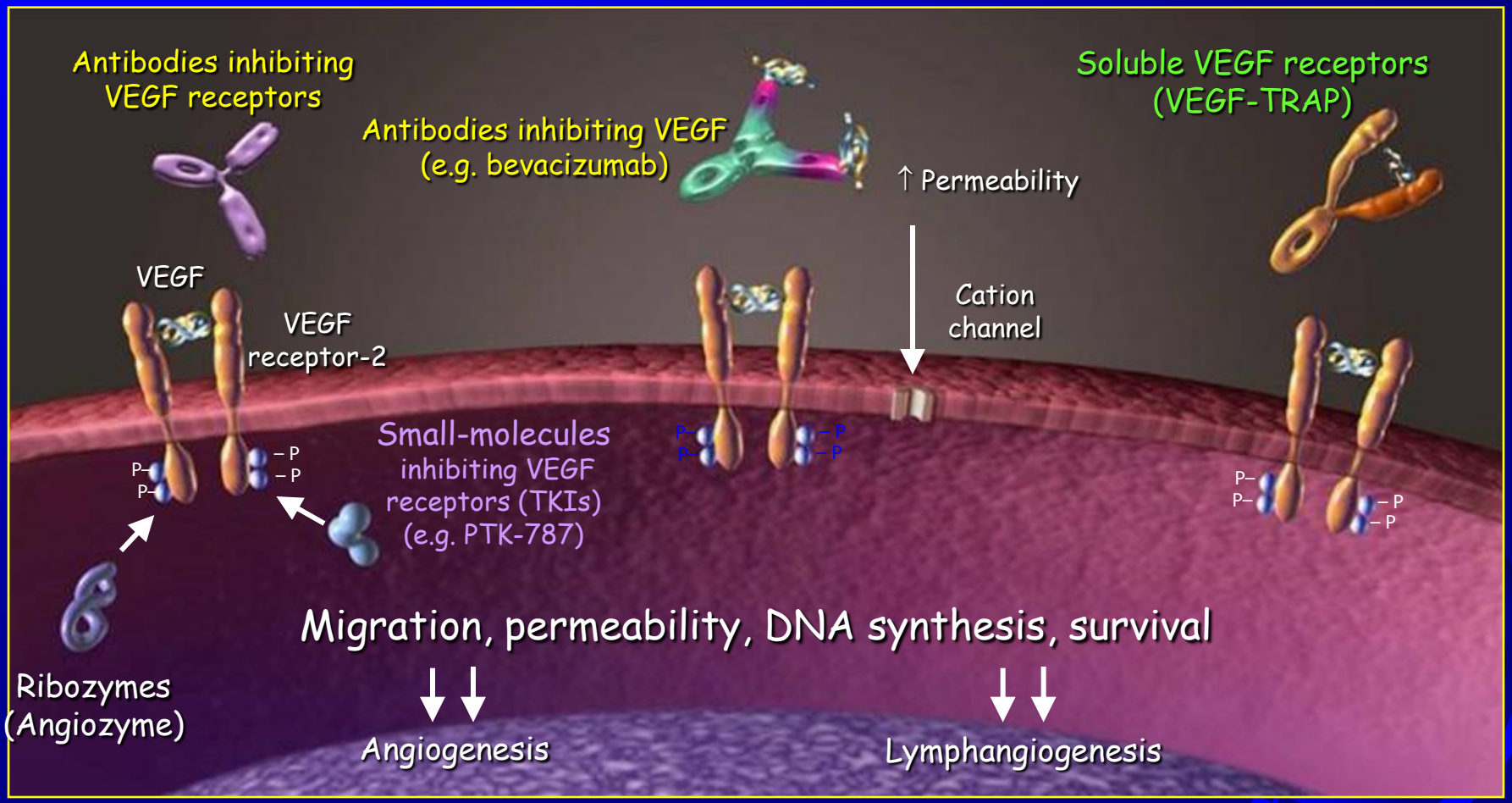




Angiogenesis

Laakkonen 2007

Agents targeting the VEGF pathway



Laakkonen 2007

BEVASITSUMABIN SIVUVAIKUTUKSET

- Hypertensio
- Proteinuria
- Haavaongelmat
- Veritulpat
- Suoliperforaatiot
- Keuhkoverivuodot (keuhkosyöpä)

VEGF JA MUNASARJASYÖPÄ

- Keskeinen merkitys terveelle ovariolle
- (Seröösi) munasarjasyöpä ilmentää runsaasti VEGF:iä
- Munasarjasyövälle tyypillinen ascites liittyy VEGF:n yliekspressioon (kapillaarien permeabiliteetti lisääntyy)

Trial	Rx	Total	Sens.	Res.	CR+ PR	SD	PD	Unk.
Burger 07	Bevacizumab 15 mg/kg q3wk	61	36	25	13 (21%)	31	16	1
Cannistra 07	Bevacizmab 15 mg/kg q3wk	44	-	44	7 (16%)	27	5	5
Chura 07	Bev 10 mg/kg Q2wk + CTX 50 mg/d	15	11	4	8 (53%)	3	4	-
Garcia 08	Bev 10 mg/kg Q2wk + CTX 50 mg/d	70	42	28	17 (24%)	44	9	-
All		190	89 (47%)	101 (53%)	45 (24%)	105 (55%)	34 (18%)	6 (3%)

JM08

BEVASITSUMABI EPITELIAALISEN MUNASARJASYÖVÄN ENSILINJAN HOIDOSSA

Phase III Trial of Bevacizumab in the Primary Treatment of Advanced Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer: A Gynecologic Oncology Group (GOG) Study

R.A. Burger,1 M.F. Brady,2 M.A. Bookman,3 J.L. Walker,4 H.D. Homesley,5 J. Fowler,6 B.J. Monk,7 B.E. Greer,8 M. Boente,9 S.X. Liang10

1Fox Chase Cancer Center, Philadelphia, PA; 2Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY; 3University of Arizona Cancer Center, Tucson, AZ; 4University of Oklahoma Health Sciences Center, Oklahoma City, OK; 5Brody School of Medicine, Greenville, NC; 6James Cancer Hospital at the Ohio State University, Hilliard, OH; 7University of California, Irvine Medical Center, Orange, CA; 8Seattle Cancer Care Alliance, Seattle, WA; 9Minnesota Oncology and Hematology, Minneapolis, MN; 10State University of New York at Stony Brook, Stony Brook, NY, USA

J Clin Oncol 2010;28 (suppl):18s (abstract LBA1)

JM2011

GOG-0218: Schema

Front-line: Epithelial OV, PP or FT cancer

- Stage III optimal (macroscopic)
- Stage III suboptimal
- Stage IV

n=1800 (planned)

RANDOMIZE

1:1:1

Arm

I (CP)

Carboplatin (C) AUC 6

Paclitaxel (P) 175 mg/m^2

Placebo

II (CP + BEV)

Carboplatin (C) AUC 6

Paclitaxel (P) 175 mg/m^2

BEV 15 mg/kg

Placebo

III (CP + BEV → BEV)

Carboplatin (C) AUC 6

Paclitaxel (P) 175 mg/m^2

BEV 15 mg/kg

Cytotoxic (6 cycles)

Maintenance (16 cycles)

15 months

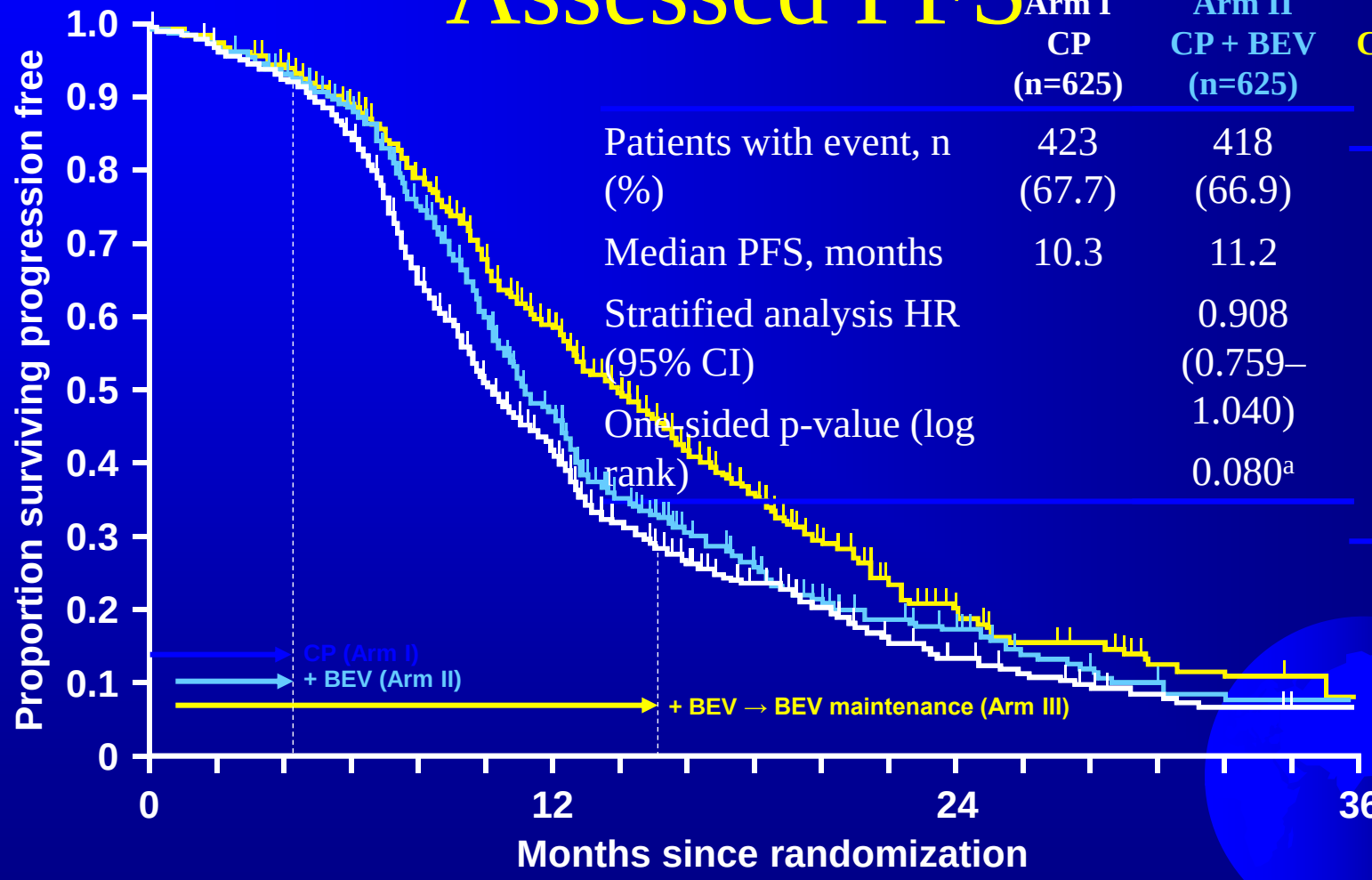
Stratification variables:

- GOG performance status (PS)
- Stage/debulking status

GOG-0218: Baseline Characteristics

Characteristic, n (%)	Arm I CP (n=625)	Arm II CP + BEV (n=625)	Arm III CP + BEV → BEV (n=623)
Stage/residual size			
III optimal (macroscopic)	218 (35)	205 (33)	216 (35)
III suboptimal	254 (41)	256 (41)	242 (39)
IV	153 (25)	164 (26)	165 (27)
Histology			
Serous	543 (87)	523 (84)	525 (84)
Endometrioid	20 (3)	15 (2)	25 (4)
Clear cell	11 (2)	23 (4)	18 (3)
Mucinous	8 (1)	5 (<1)	8 (1)
Tumor grade			
3[a]	412 (66)	435 (70)	430 (69)
2	94 (15)	77 (12)	92 (15)
1	33 (5)	28 (4)	16 (3)
Not specified/pending	86 (14)	85 (14)	85 (14)

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: PFS DATA

	CP n=625	**CP+B** n=625	**CP+B→B** n=623
Pts. with event n (%)	423 (67.7)	418 (66.9)	360 (57.8)
Median PFS (mo)	***10.3***	***11.2***	***14.1***
Stratified anal. HR (95%CI)		0.908 (0.579-1.040)	0.717* (0.625-0.824)

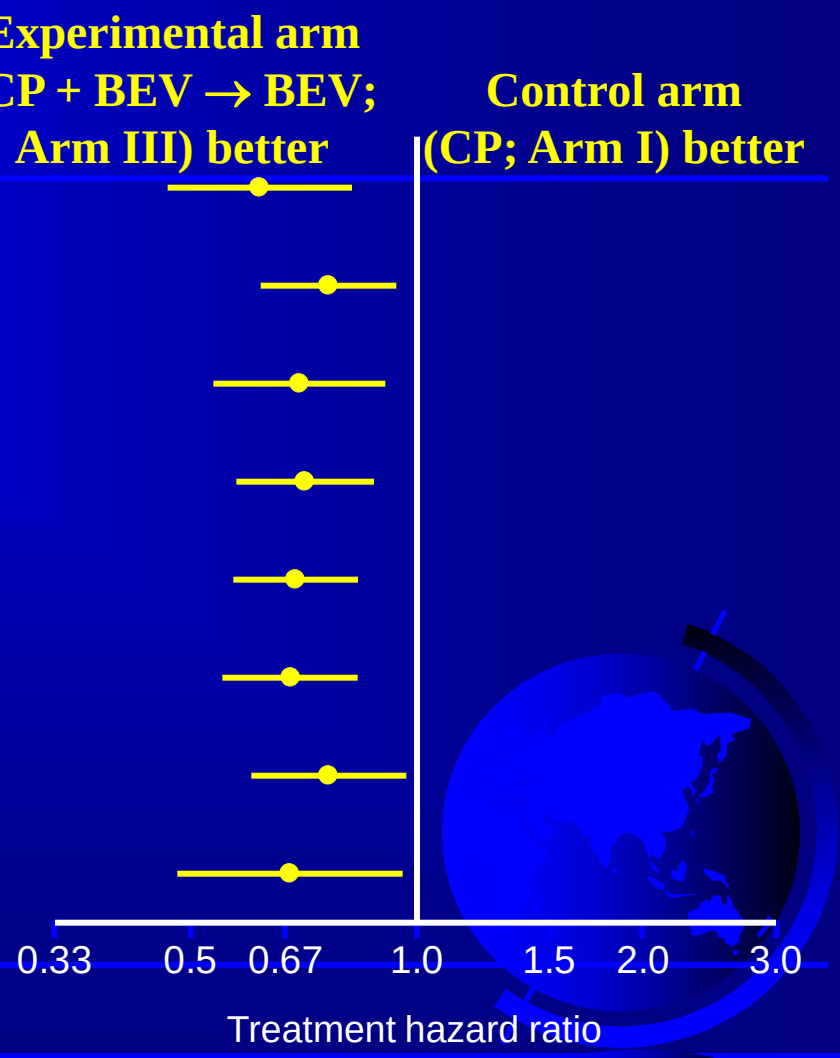
***p<0.0001**

JM11

GOG-0218: Subgroup Analyses of PFS

CP + BEV → BEV (Arm III) vs CP (Arm I)

	Hazard ratio
Stage 3 optimal (n=434)	0.618
Stage 3 suboptimal (n=496)	0.763
Stage 4 (n=318)	0.698
PS 0 (n=616)	0.710
PS 1/2 (n=632)	0.690
Age <60 years (n=629)	0.680
Age 60–69 years (n=409)	0.763
Age ≥70 years (n=210)	0.678



GOG-0218: selected adverse events

	CP	CP+B	CP+B→B
GI ≥ Gr.2 (%)*	1.2	2.8 n.s.	2.6 n.s.
Hyper-tension ≥2	7.2	16.5**	22.9**
Proteinuria ≥3	0.7	0.7 n.s.	1.6 n.s.

***perforation/fistula/ necrosis/leak**

****p<0.05**

JM11

ICON7: a phase III Gynecologic Cancer InterGroup (GCIG) trial of adding bevacizumab to standard chemotherapy in women with newly diagnosed epithelial ovarian, primary peritoneal or fallopian tube cancer

GCIG ICON7 collaborators

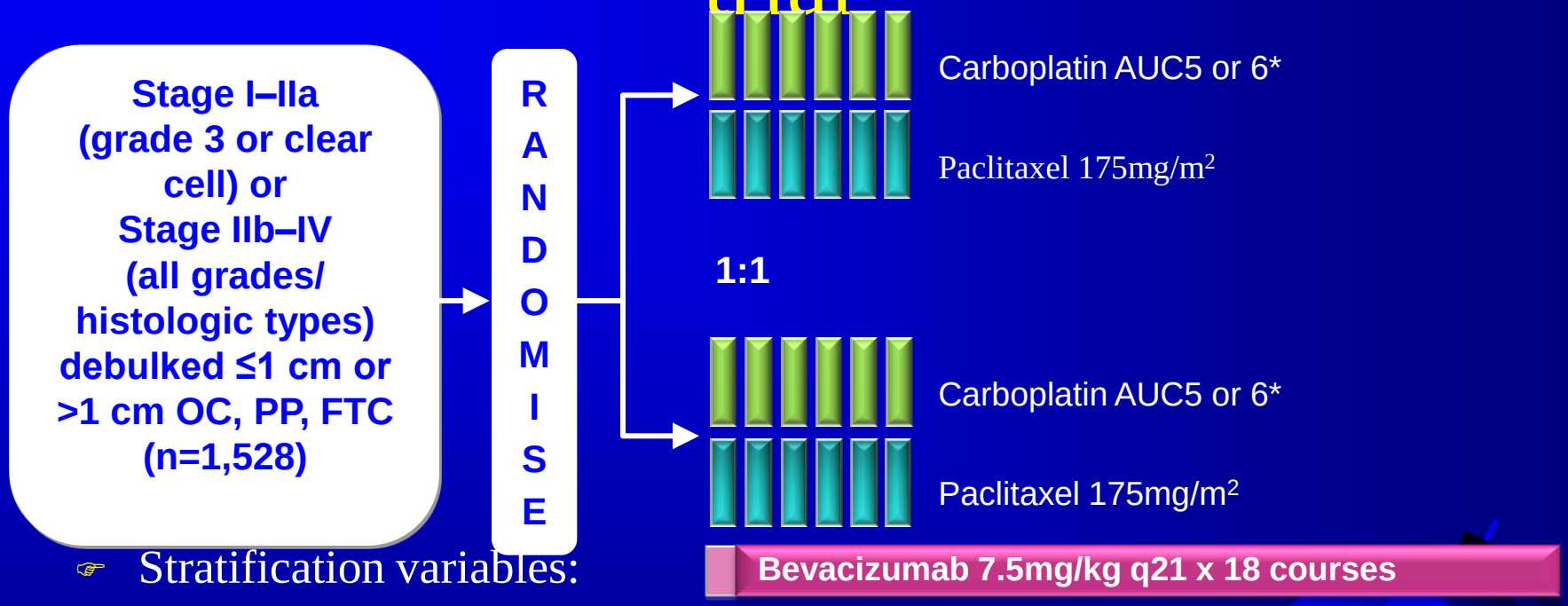
(MRC/NCRI = leading group, AGO-OVAR, GINECO, NSGO, ANZGOG, GEICO, NCIC-CTG)

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

ICON7
Bevacizumab in Ovarian Cancer

duBois 2010

ICON7 (AGO OVAR 11): a randomised, open-label, phase III trial

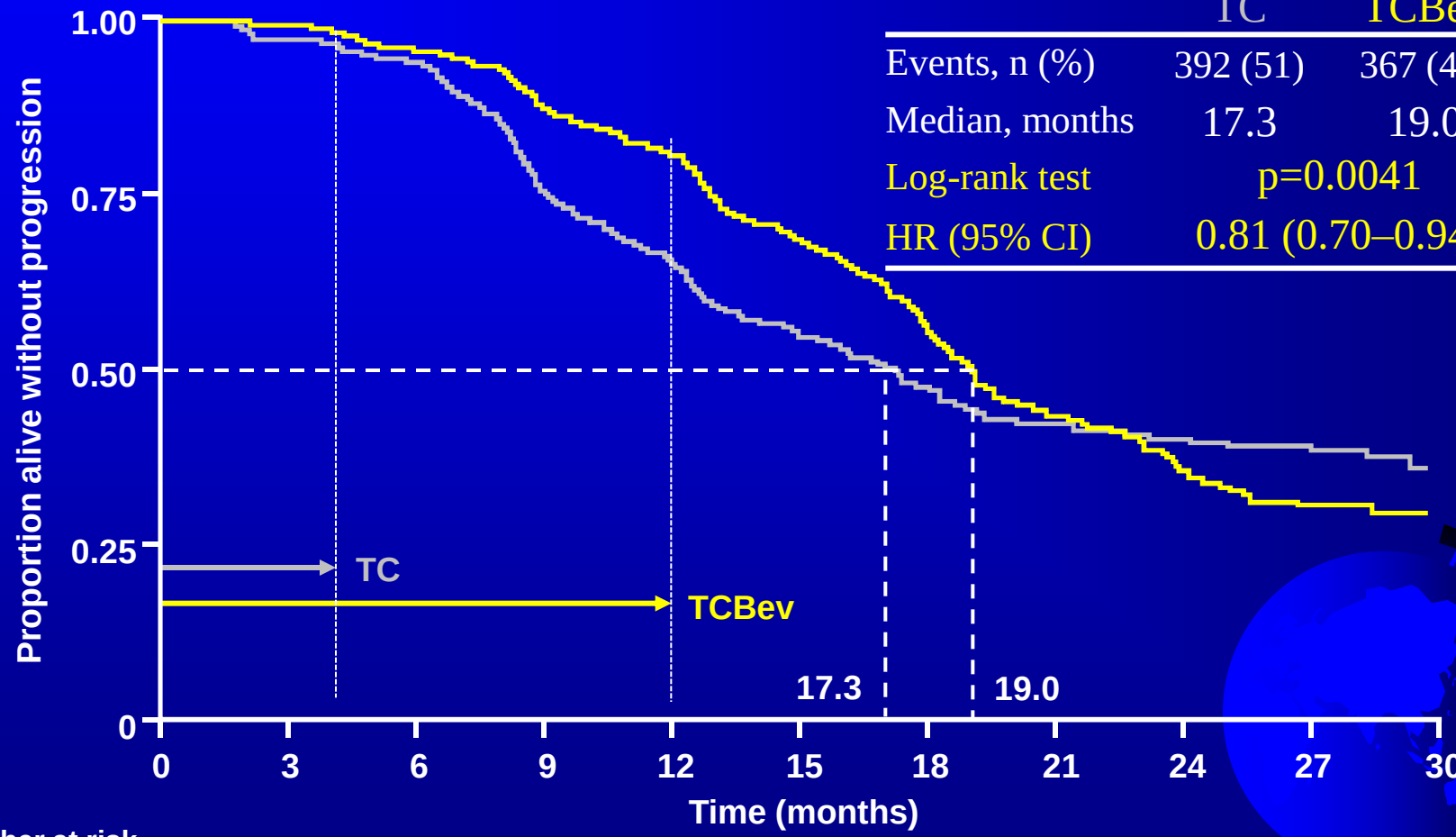


- Stratification variables:
- Stage and extent of debulking: I–III debulked ≤1cm vs stage I–III debulked >1cm vs stage IV and inoperable stage III
- Timing of intended treatment start: ≤ vs > 4 weeks after surgery
- GCIG group (*also choice of AUC dose 5 [AGO, NSGO, GINECO] or 6)

duBois 2010

PFS: academic analysis duBois 2010

	TC	TCBev
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)	

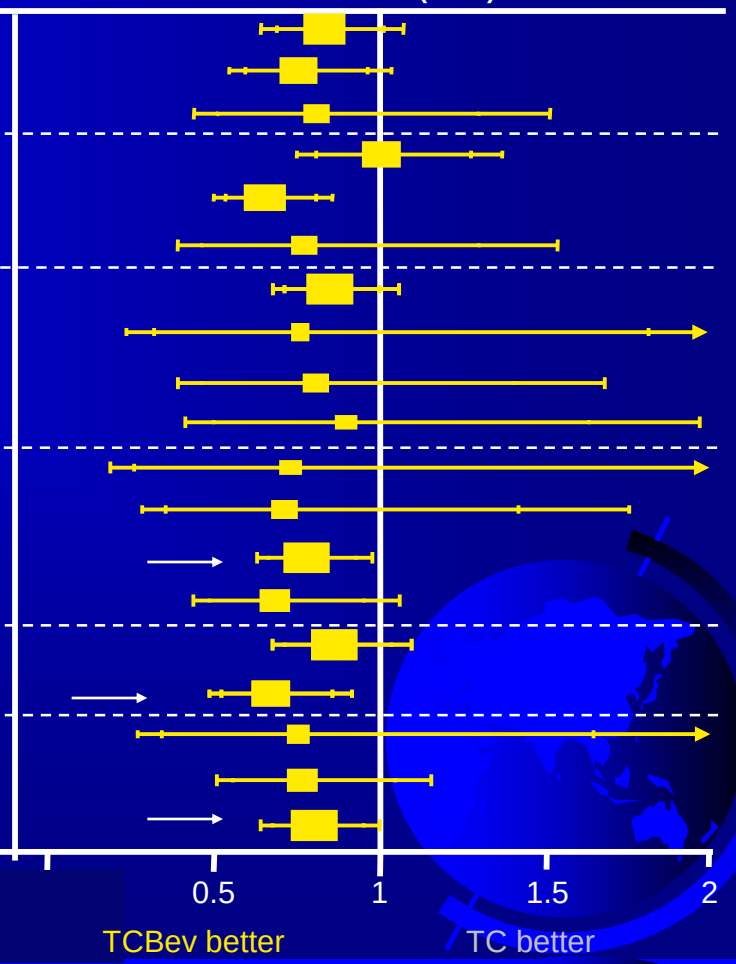


Number at risk

TC	764	723	693	556	464	307	216	143	91	50	25
TCBev	764	748	715	647	585	399	263	144	73	36	19

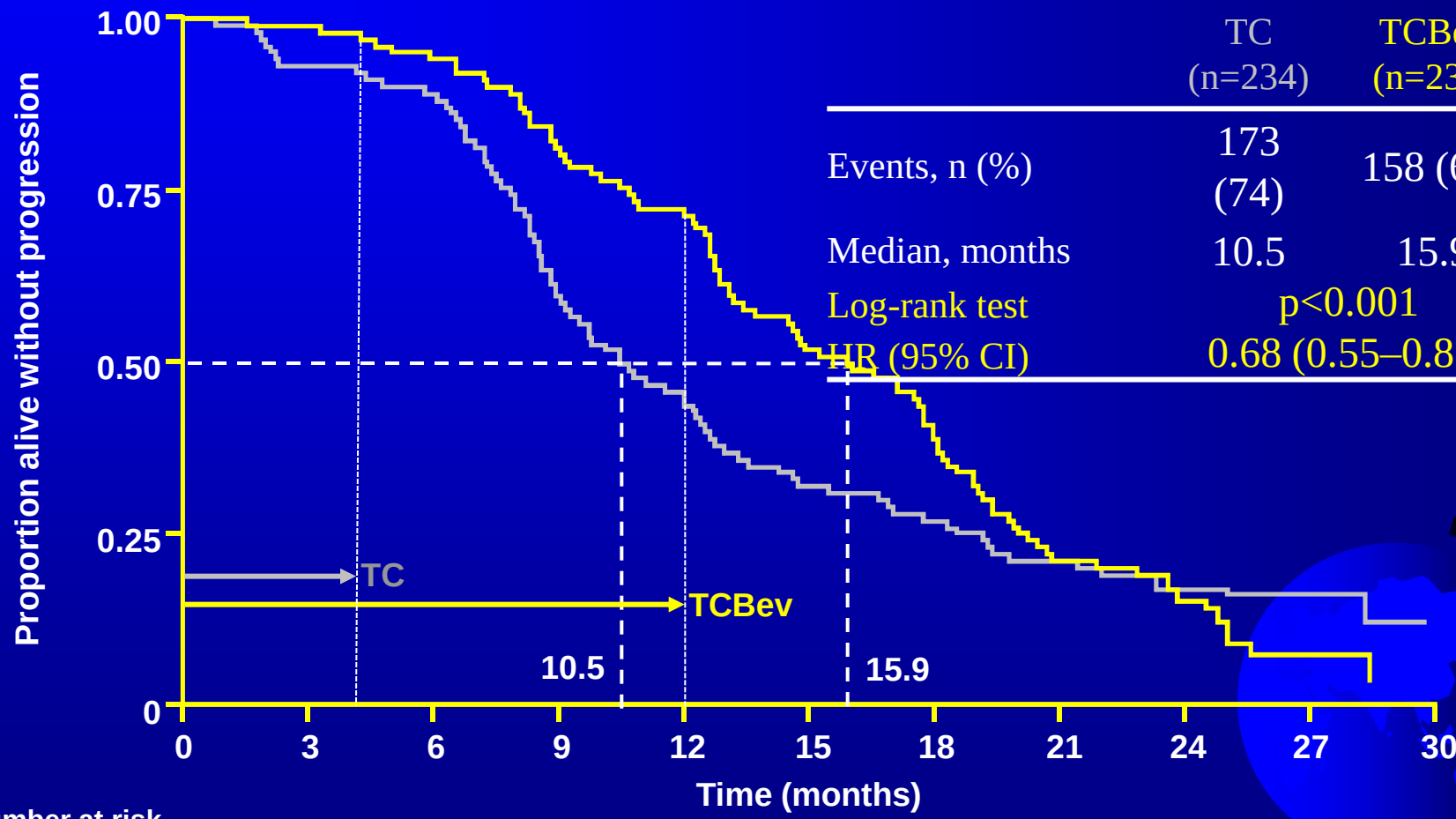
ICON7: Subgroup analysis of PFS duBois 2010/JM 2011

Origin of cancer		No. of events/no. of patients Research	Control	HR
Age	<60	202/449	210/450	0.84
	60–69	134/242	142/237	0.76
	≥70	31/73	40/77	0.82
ECOG PS	0	154/334	145/358	1.01
	1	175/366	210/354	0.66
	2	27/45	31/43	0.78
Histology	Serous	274/525	278/529	0.85
	Mucinous	12/19	10/15	0.77
	Endometroid	26/60	25/57	0.81
	Clear cell	22/67	22/60	0.90
FIGO	I	6/54	9/65	0.73
	II	14/83	19/80	0.72
	III	277/523	290/522	0.79
	IV	70/104	74/97	0.69
Residual disease	Optimal (≤1 cm)	226/559	233/552	0.87
	Suboptimal (>1cm)	131/192	145/195	0.68
Grade	Grade 1	10/41	16/56	0.76
	Grade 2	86/175	77/142	0.77
	Grade 3	267/538	294/556	0.81



Age: Trend p=0.69, interaction p=0.83; ECOG: Trend p=0.027, interaction p=0.022
Histology: Interaction test p=0.085; FIGO: Trend p=0.71, interaction p=0.91
Residual disease: Trend p=0.10; Grade: Trend p=0.76, interaction p=0.95

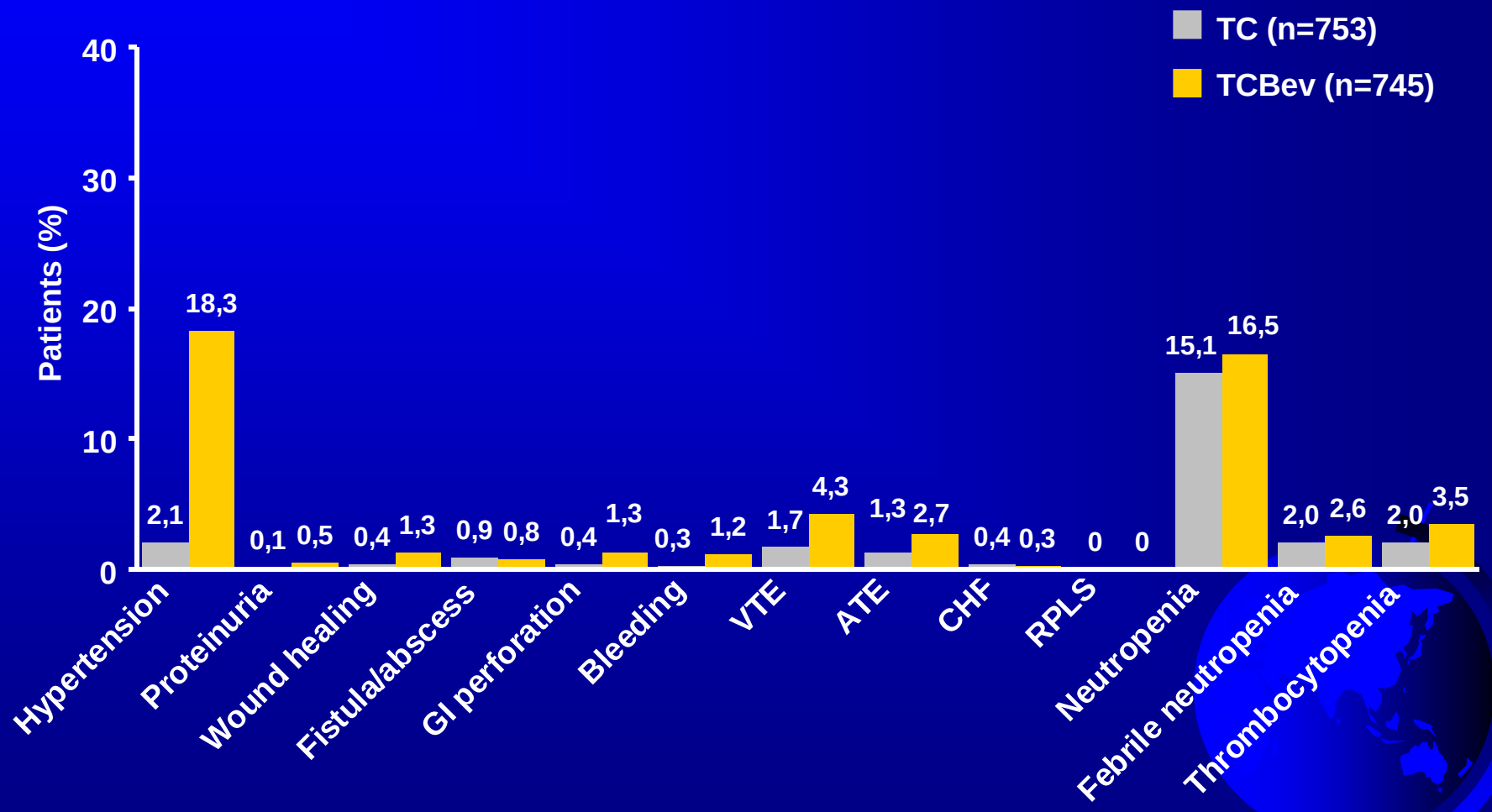
Exploratory analysis of PFS in a subgroup similar to GOG study: operated FIGO III and residuals >1cm and FIGO IV duBois 2010



	TC (n=234)	TCBev (n=231)
Events, n (%)	173 (74)	158 (68)
Median, months	10.5	15.9
Log-rank test	p<0.001	
HR (95% CI)	0.68 (0.55–0.85)	

Number at risk						
TC	234	205	98	36	14	2
TCBev	231	213	159	56	10	1

Safety profile: selected grade ≥3 events duBois 2010



‘Comparing’ GOG-0218 and ICON7: design

Trial	ICON7	GOG-0218
Design	☞ Open-label ☞ 2 arms ☞ Bevacizumab for 12 months ☞ Bevacizumab 2.5mg/kg/week	☞ Double-blind, placebo-controlled ☞ 3 arms ☞ Bevacizumab for 15 months ☞ Bevacizumab 5mg/kg/week
Primary endpoint	☞ PFS (RECIST) ☞ CA-125 only not allowed ☞ No IRC	☞ PFS (RECIST + CA-125) ☞ Regulatory-required PFS (censored for CA-125 and non-protocol therapy) ☞ Exploratory: IRC-assessed PFS
Patient population	Early and advanced stages Including patients w/o residual tumour	Advanced stage Only patients with macro residuals

Burger, et al. ASCO 2010

‘Comparing’ GOG-0218 to ICON7: cross-trial comparison of efficacy

	GOG-0218 (Arm I vs III)	ICON7
Results of primary analysis		
n	1,248	1,528
PFS (HR)	0.72	0.81
Median PFS, months	10.3 vs 14.1	17.3 vs 19.0
PFS Δ , months	3.8	1.7
p value	<0.0001	0.0041
Results based on RECIST only (regulatory analysis*)		
n	1,248	1,528
PFS (HR)	0.65	0.79
Median PFS, months	12.0 vs 18.0	16.0 vs 18.3
PFS Δ , months	6	2.3
p value	<0.0001	0.001
Subgroup of advanced disease only (operated FIGO IV/IIIC 1cm+ residuals)		
N		465
PFS (HR)		0.68
Median PFS, months		10.5 vs 15.9
PFS Δ , months		5.4
p value		<0.001

***Censoring CA 125**

Burger, et al. ASCO 2010

ICON7: A phase III Gynaecologic Cancer InterGroup (GCIG) trial of adding bevacizumab to standard chemotherapy in women with newly diagnosed epithelial ovarian, primary peritoneal, or fallopian tube cancer

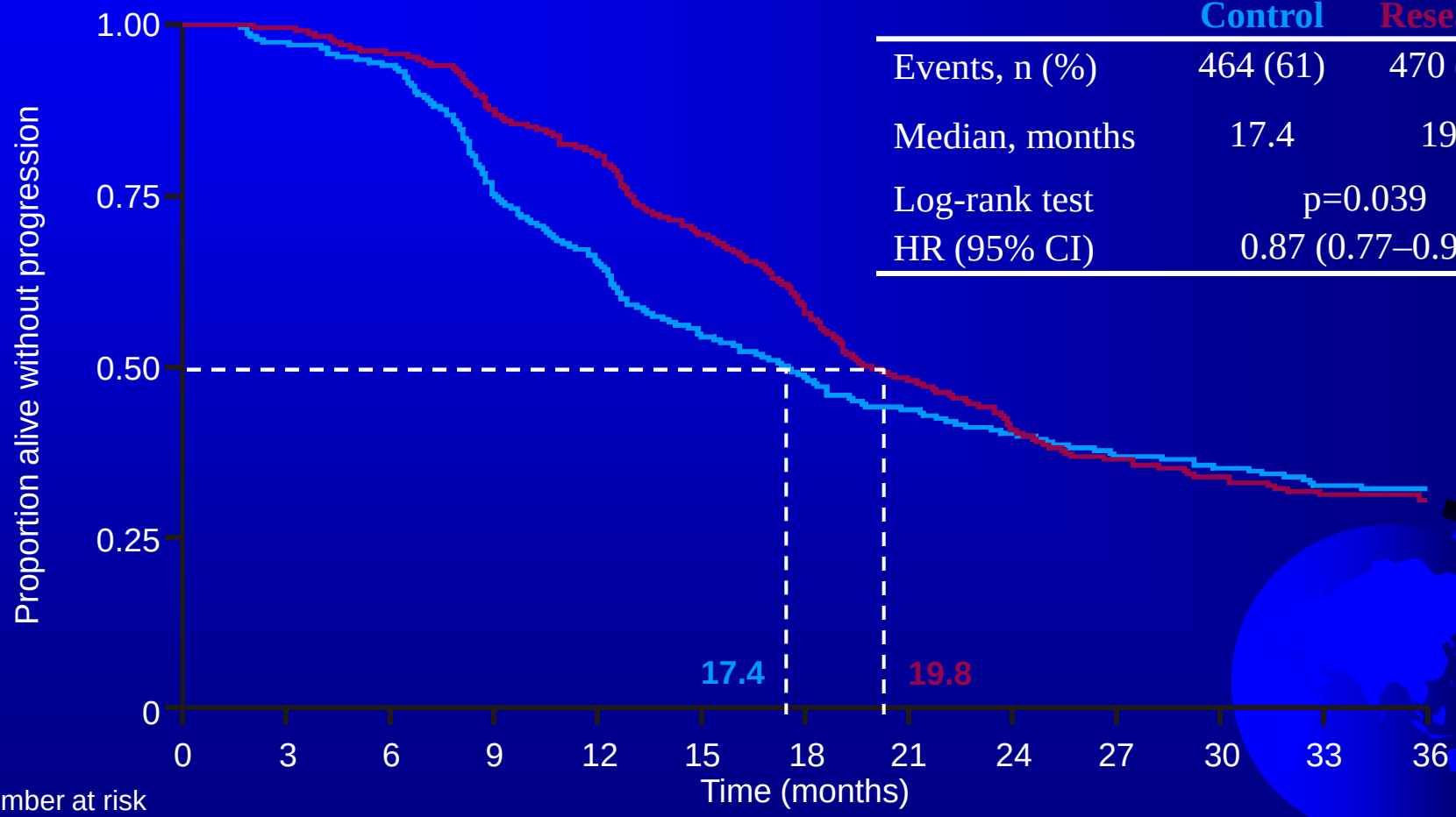
Interim analysis on overall survival

Gunnar Kristensen, Tim Perren, Wendi Qian, Jacobus Pfisterer, Jonathan Ledermann, Françoise Joly, Mark Carey, Philip Beale, Andreas Cervantes, Amit Oza
on behalf of the GCIG ICON7 collaborators
(MRC/NCRI, AGO-OVAR, GINECO, NSGO, ANZGOG, GEICO, NCIC-CTG)

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

ASCO
American Society of Clinical Oncology
Making a world of difference in cancer care

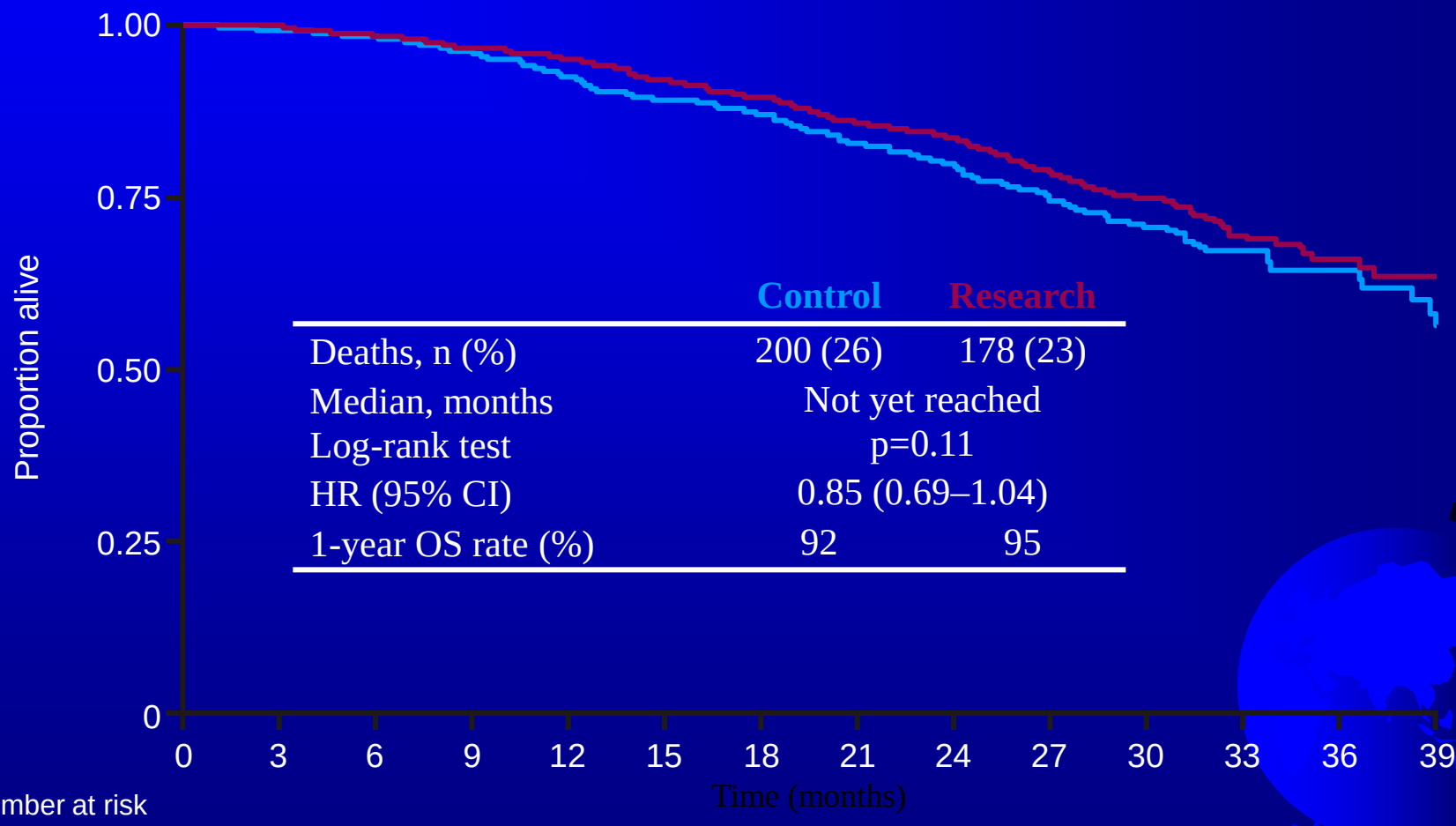
Updated PFS



	Control	Research
Events, n (%)	464 (61)	470 (62)
Median, months	17.4	19.8
Log-rank test	p=0.039	
HR (95% CI)	0.87 (0.77–0.99)	

Number at risk							
Control	764	693	474	350	221	114	39
Research	764	716	599	430	229	107	27

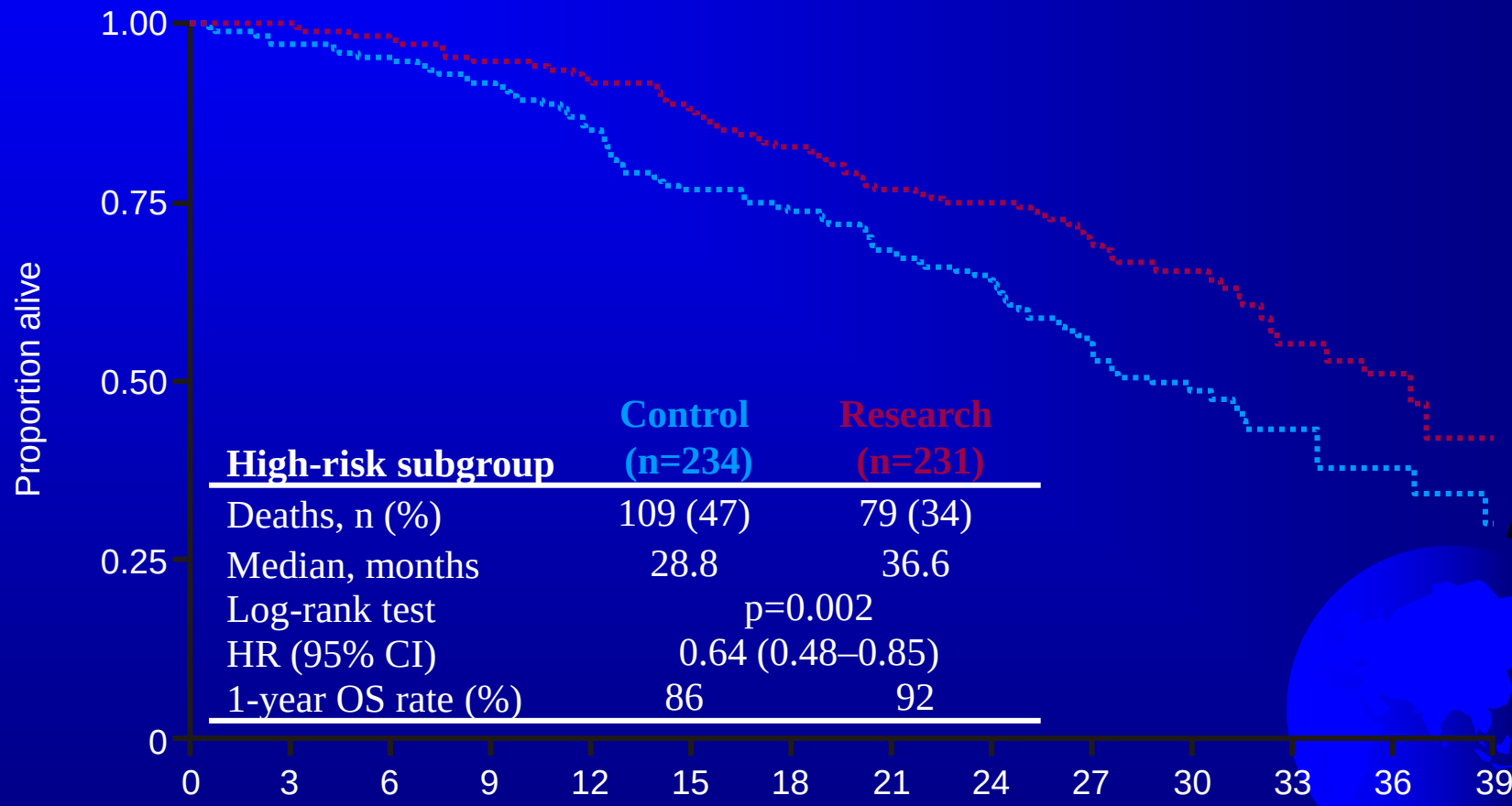
Interim OS analysis
(regulatory request)



	Control	Research
Deaths, n (%)	200 (26)	178 (23)
Median, months	Not yet reached	
Log-rank test	p=0.11	
HR (95% CI)	0.85 (0.69–1.04)	
1-year OS rate (%)	92	95

Number at risk														
Control	764	741	724	703	672	646	623	542	421	304	212	132	71	26
Research	764	753	737	717	702	680	657	592	459	329	228	129	69	19

OS: High-risk subgroup



High-risk subgroup	Control (n=234)	Research (n=231)
Deaths, n (%)	109 (47)	79 (34)
Median, months	28.8	36.6
Log-rank test	p=0.002	
HR (95% CI)	0.64 (0.48–0.85)	
1-year OS rate (%)	86	92

Number at risk							
Control	234	219	194	166	107	46	15
Research	231	222	208	186	134	65	18

KENELLE BEVASITSUMABI (AVASTIN®) MUNASARJASYÖVÄN ENSILINJAN HOIDOSSA?

JM2011

ONGELMAT

- Onko muutaman kuukauden TAUDITTOMAN elinajan ero KLIINISESTI merkitsevä?
- Tuleeko KOKONAISelinaikaeroa?
- Banaaniefektin merkitys?
- Pitäisikö jatkaa taudin etenemiseen asti?
- Mikä on oikea annos? 7,5 vai 15 mg/kg?
- ONKO MEILLÄ VARAA?
- KUKA HYÖTYY?

Surrogate markers of angiogenesis and anti-angiogenic drug activity

- ✓ Optimal therapeutic dose vs. maximal tolerated dose
- ✓ Circulating endothelial cells (CECs) CD13+/VEGFR-2+/CD45-
- ✓ Circulating endothelial progenitor cells (CEPs) CD13+/VEGFR-2+/CD45-/CD117+

Laakkonen 2007

MUITA MAHDOLLISIA VASTEEN ENNUSTAJIA

- Verenpaineen nousu
- Proteinuria
- Seerumin VEGF-pitoisuuden lasku

THE TIMING OF NORMALIZATION OF CA125 LEVELS DURING PRIMARY CHEMOTHERAPY IS PREDICTIVE OF SURVIVAL IN PATIENTS WITH EPITHELIAL OVARIAN CANCER

Rocconi RP et al.

Gynecol Oncol 2009;114:242-5

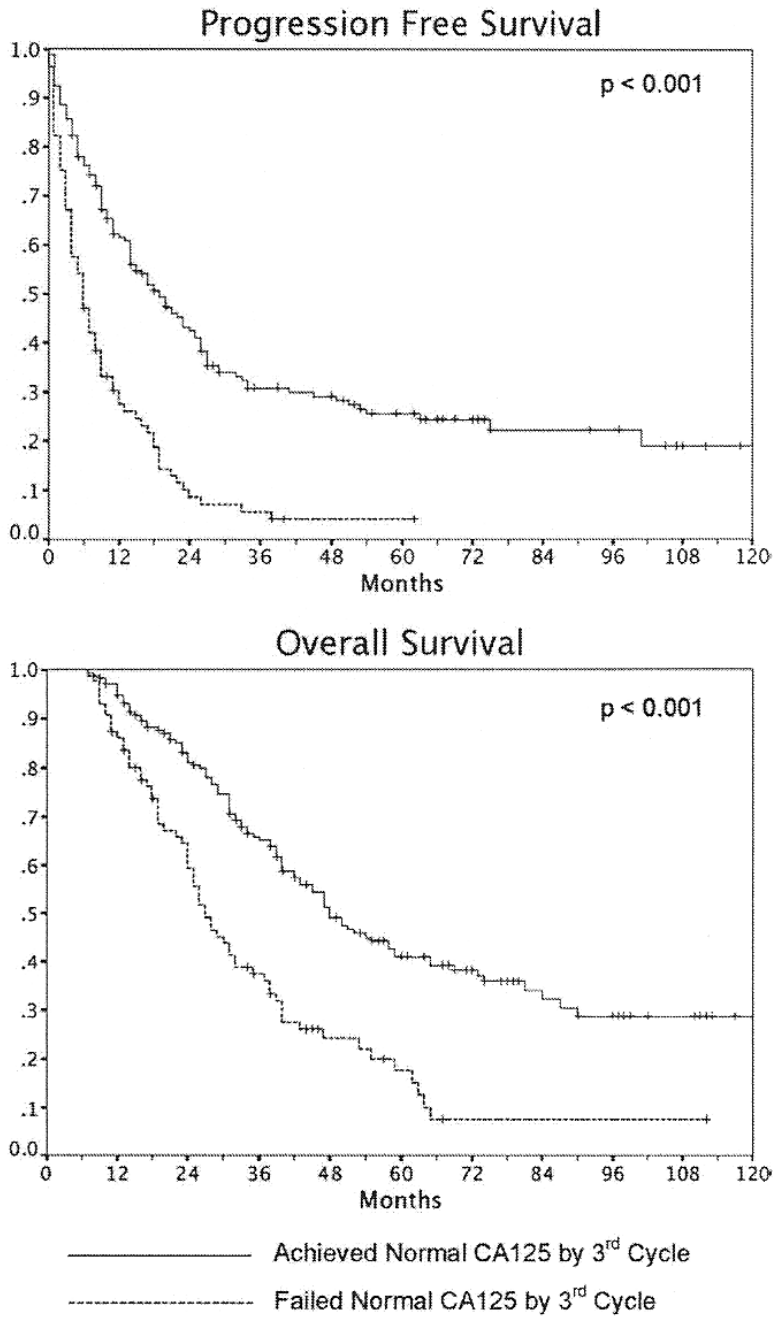


Fig. 1. Progression free survival.

JM09

JOHTOPÄÄTÖKSENI:
Bevasitsumabi munasarjasyövän ensilinjan hoidossa

- Bevasitsumabilla on tehoa (tason B näyttö)
- Bevasitsumabia EI kannata antaa kaikille
- Ehdotan, että bevasitsumabia VOI harkita, JOS

1. suboptimaalinen leikkaus,
2. ei suunnitella intervallisytoreduktiota
3. eikä CA-125 ole (lähes) normalisoitunut 3. hoitosykliin mennessä?

KIITOS!