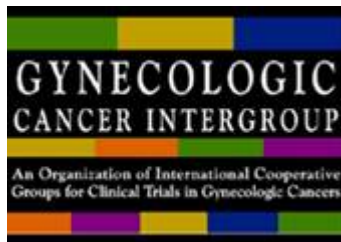

ICON7: A phase III Gynaecologic Cancer InterGroup (GCI G) trial of adding bevacizumab to standard chemotherapy in women with newly diagnosed epithelial ovarian, primary peritoneal or fallopian tube cancer

Tim Perren, Ann Marie Swart, Jacobus Pfisterer,
Jonathan Ledermann, Alain Lortholary, Gunnar Kristensen,
Mark Carey, Philip Beale, Andres Cervantes, Amit Oza
on behalf of GCI G ICON7 collaborators
(MRC/NCRI, AGO-OVAR, GINECO, NSGO, ANZGOG, GEICO, NCIC-CTG)



ICON7
Bevacizumab in Ovarian Cancer

-
- Dr Perren has attended Roche advisory boards to discuss the development of bevacizumab in ovarian cancer
 - Consultancy fees not accepted
 - Travel and accommodation accepted
 - Roche provided bevacizumab and grants for the study

- **The women who participated in the trial and their families**
- **Participating GCI G groups**
AGO, ANZGOG, GEICO, GINECO, MRC/NCRI, NSGO, NCIC
- **The 263 clinical sites and their staff**
- **Trial Management Group**
T Perren, A Oza, AM Swart, W Qian, C Griffin, M Parmar, L Farrelly, E Hainsworth, C Kwakye, N Thompson, C Irl, G Jayson, D Stark, M Sculpher, J Pfisterer, G Elser, A Kruger, P Beale, J Martyn, K Gillies, A Cervantes, F Nepote; E Pujade Lauraine, F Marmion, B Votan, M Carey, M Bacon, R Meyer, G Kristensen, G Andersen
- **MRC Clinical Trials Unit Coordination**
E Hainsworth, C Kwakye, L Farrelly, AM Swart, W Qian, C Griffin
- **Trial Physicians**
F al-Terkait, S Sim, F Collinson

- Ovarian cancer (OC) treatment remains a challenge
 - Fourth most common cause of cancer-related death in women, 200 000 cases and 125 000 deaths/year worldwide
- Despite a good response to surgery and platinum-based chemotherapy, >50% of women will eventually die from their disease
- Angiogenesis plays a central role in progression of OC¹
 - Pharmacological inhibitors of VEGF (eg bevacizumab) may improve outcomes
 - Single-agent activity of bevacizumab in recurrent OC^{2,3}
 - Activity of bevacizumab in metastatic colorectal, lung, renal, breast and brain cancers⁴

1. Burger et al. *J Clin Oncol* 2007; 25: 2902–8

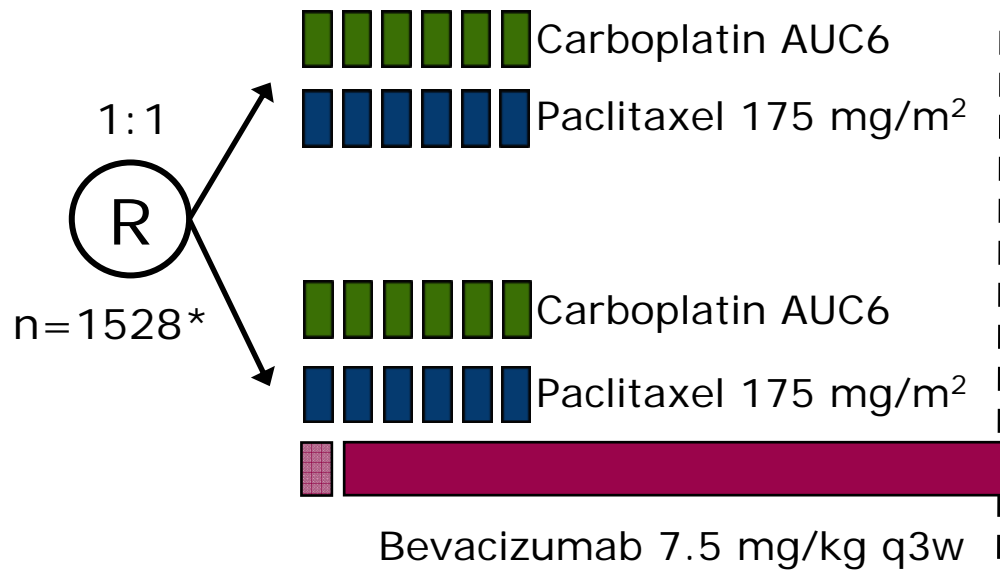
2. Burger et al. *J Clin Oncol* 2007; 25: 5165–71

3. Cannistra et al. *J Clin Oncol* 2007; 25: 5180–6

4. Eskens & Sleijfer. *Eur J Cancer* 2008; 44: 2350–6

- Histologically confirmed epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer
- Prior surgical debulking with the aim of maximal surgical cytoreduction undertaken AND no planned further surgical debulking before disease progression
- FIGO stage
 - I–IIA if high risk: Grade 3 or clear cell histology (10%)
 - IIB–IV: All grades and histological subtypes
 - Patients with inoperable stage III/IV disease eligible after biopsy only if no further surgery planned
- ECOG performance status 0–2

Academic-led, industry-supported trial to investigate use of bevacizumab and to support licensing



Stratification variables:

- **Stage & extent of debulking:**
I–III debulked ≤1cm vs
I–III debulked >1 cm vs
IV and inoperable stage III
- **Timing of intended treatment start**
≤4 vs >4 weeks after surgery
- **GCIG group**

*Dec 2006 to Feb 2009

18 cycles

	Year 1	Years 2–3	Years 4–5
CT	Baseline; after cycles 3 & 6; at 9 & 12 months	Every 6 months	As indicated
CA-125/clinical assessment	Every chemotherapy cycle; every 6 weeks during maintenance phase	Every 3 months	Every 6 months

- **Primary endpoint:** Progression-free survival (PFS)
 - Disease progression defined by RECIST guidelines on radiological, clinical or symptomatic progression
 - CA-125 elevation **alone** not defined as disease progression
 - 1520 patients randomised over 2 years (684 events) → 5% significance level, 90% power to detect:
 - PFS hazard ratio (HR) of 0.78
 - Increase of median PFS from 18 to 23 months
- **Secondary endpoints:** Overall survival (due 2012), response rate, toxicity
- **Substudies:** Quality of life, health economics, translational research

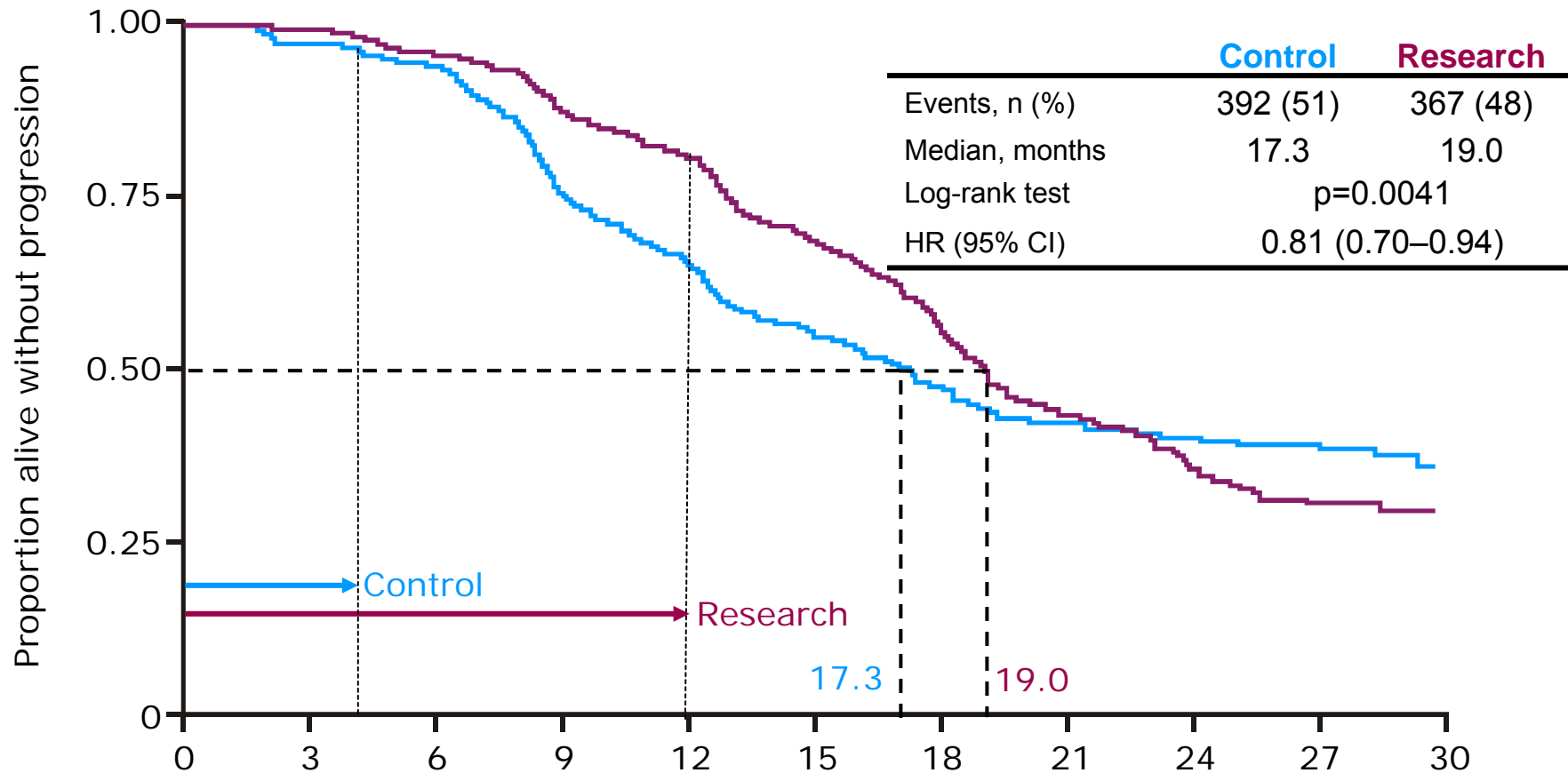
Characteristic	Control (n=764)	Research (n=764)
Median age (range)	57 (18–81)	57 (24–82)
ECOG PS, n (%)		
0	358 (47)	334 (45)
1	354 (47)	366 (49)
2	43 (6)	45 (6)
Origin of cancer, n (%)		
Ovary (epithelial)	667 (87)	673 (88)
Fallopian tube	29 (4)	27 (4)
Primary peritoneal	56 (7)	50 (6)
Multiple sites	12 (2)	14 (2)
Histology		
Serous	529 (69)	525 (69)
Clear cell	60 (8)	67 (9)
Endometrioid	57 (7)	60 (8)
Mucinous	15 (2)	19 (2)
Mixed/other	103 (13)	93 (12)
Grade, n (%)		
1	56 (7)	41 (5)
2	142 (19)	175 (23)
3	556 (74)	538 (71)
Unknown	10	10

Characteristic, n (%)	Control (n=764)	Research (n=764)
FIGO stage, n (%)		
I/IIA	75 (10)	67 (9)
IIB–IIIB	160 (21)	155 (20)
IIIC/IV	529 (69)	542 (71)
Debulking surgery/residuum		
Optimal surgery (≤ 1 cm)	552 (74)	559 (74)
Suboptimal surgery (> 1 cm)	195 (26)	192 (26)
No surgery	17 (2)	13 (2)
FIGO stage and residuum*		
Stage I–III (≤ 1 cm)	508 (66)	518 (68)
Stage I–III (> 1 cm)	150 (20)	140 (18)
Stage III (inoperable)/IV	106 (14)	106 (14)
Intent to start chemotherapy*		
≤ 4 weeks from surgery	328 (43)	326 (43)
> 4 weeks from surgery	436 (57)	438 (57)

*Stratification variable

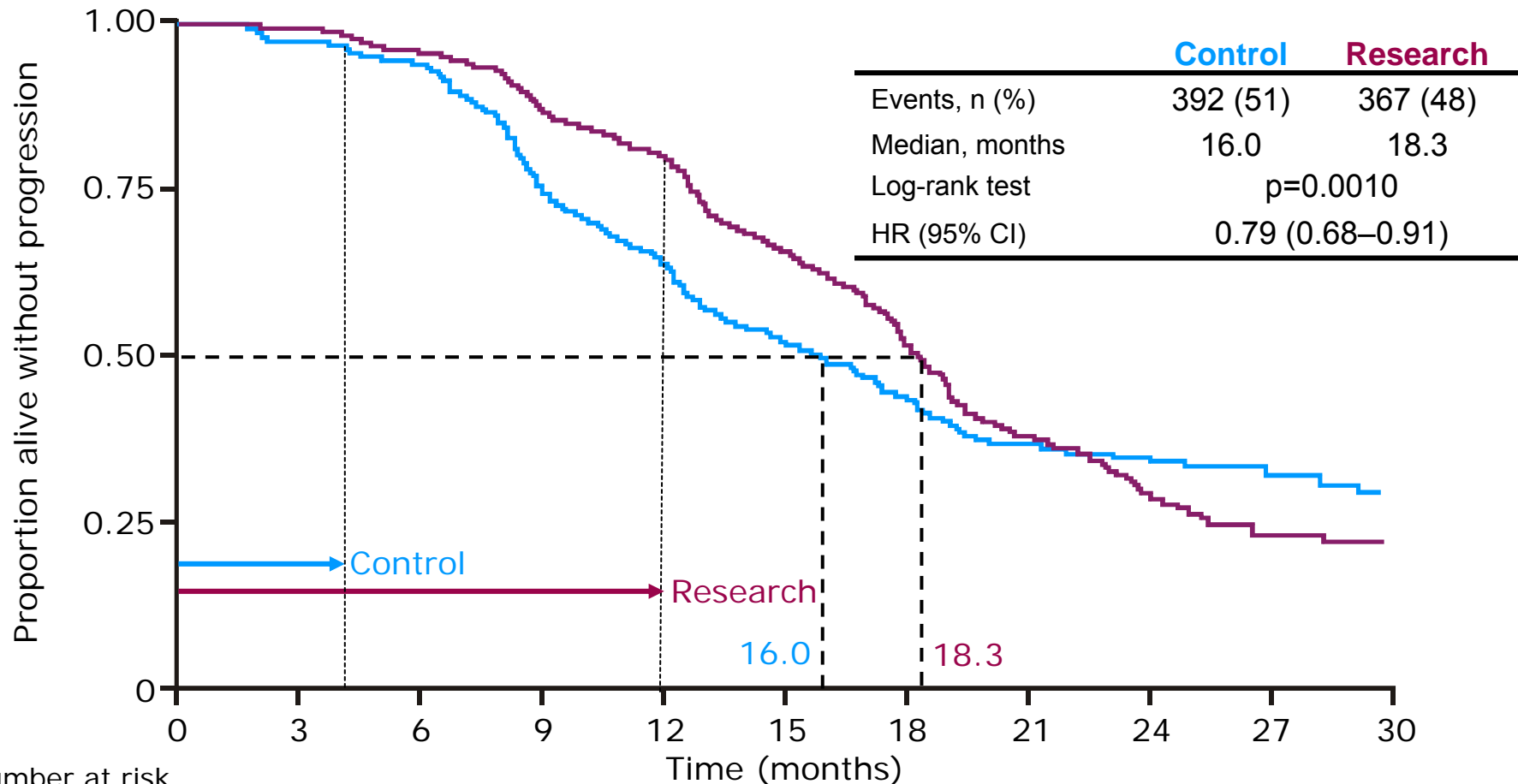
- Median follow-up: 19.4 months
 - 2 patients still on treatment
 - 759 progressions or deaths
 - 241 deaths (16%; 715 required)
- PFS censoring
 - Academic: Later of date of CT scan or last clinical follow-up
 - Regulatory: Date of last CT scan

Academic analysis



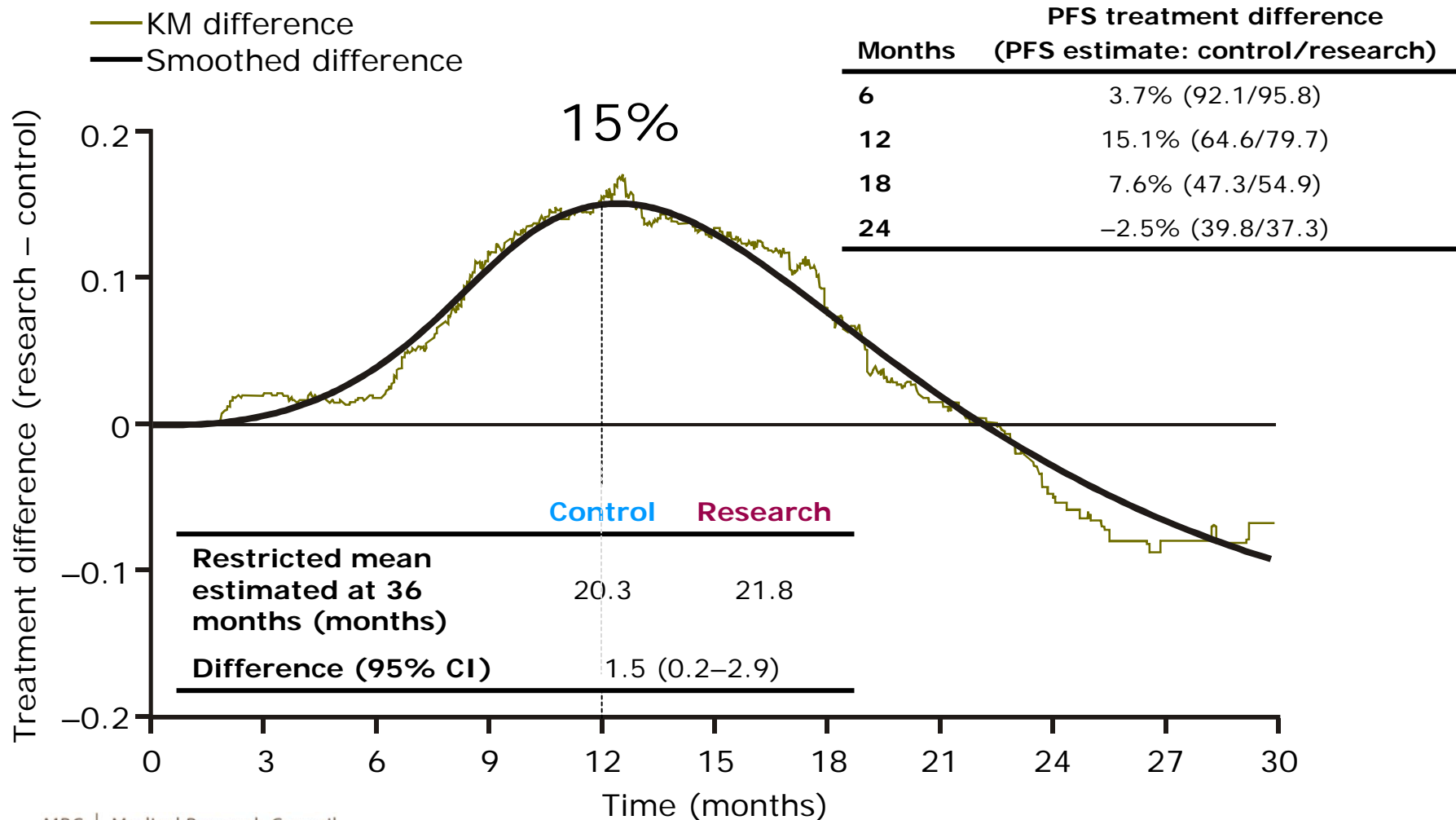
	0	3	6	9	12	15	18	21	24	27	30
Number at risk											
Control	764	723	693	556	464	307	216	143	91	50	25
Research	764	748	715	647	585	399	263	144	73	36	19

Regulatory analysis

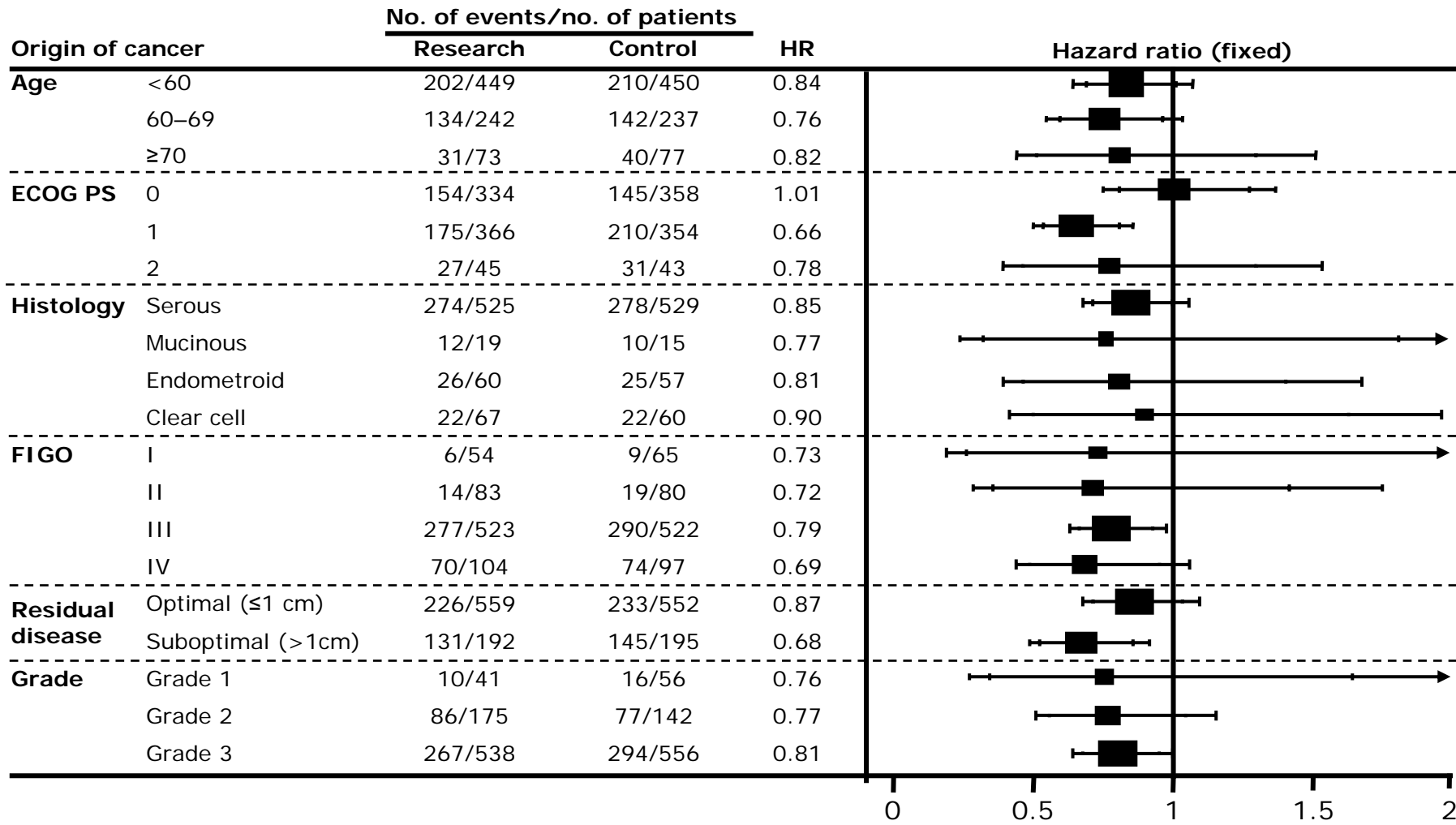


	0	3	6	9	12	15	18	21	24	27	30
Number at risk											
Control	764	715	676	529	419	247	175	91	65	26	16
Research	764	733	696	617	546	330	232	100	62	19	11

Absolute difference in PFS



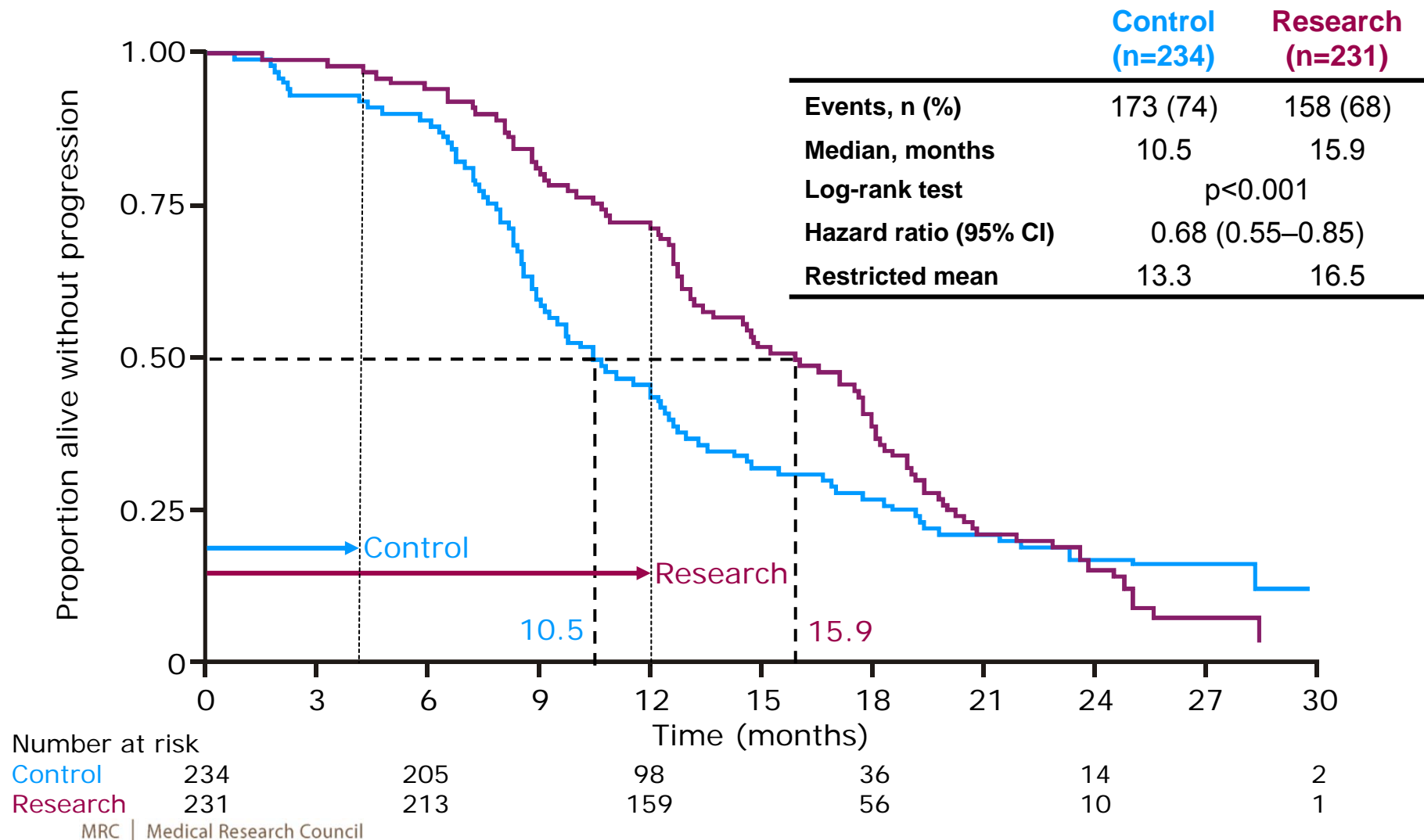
Subgroup analysis of PFS

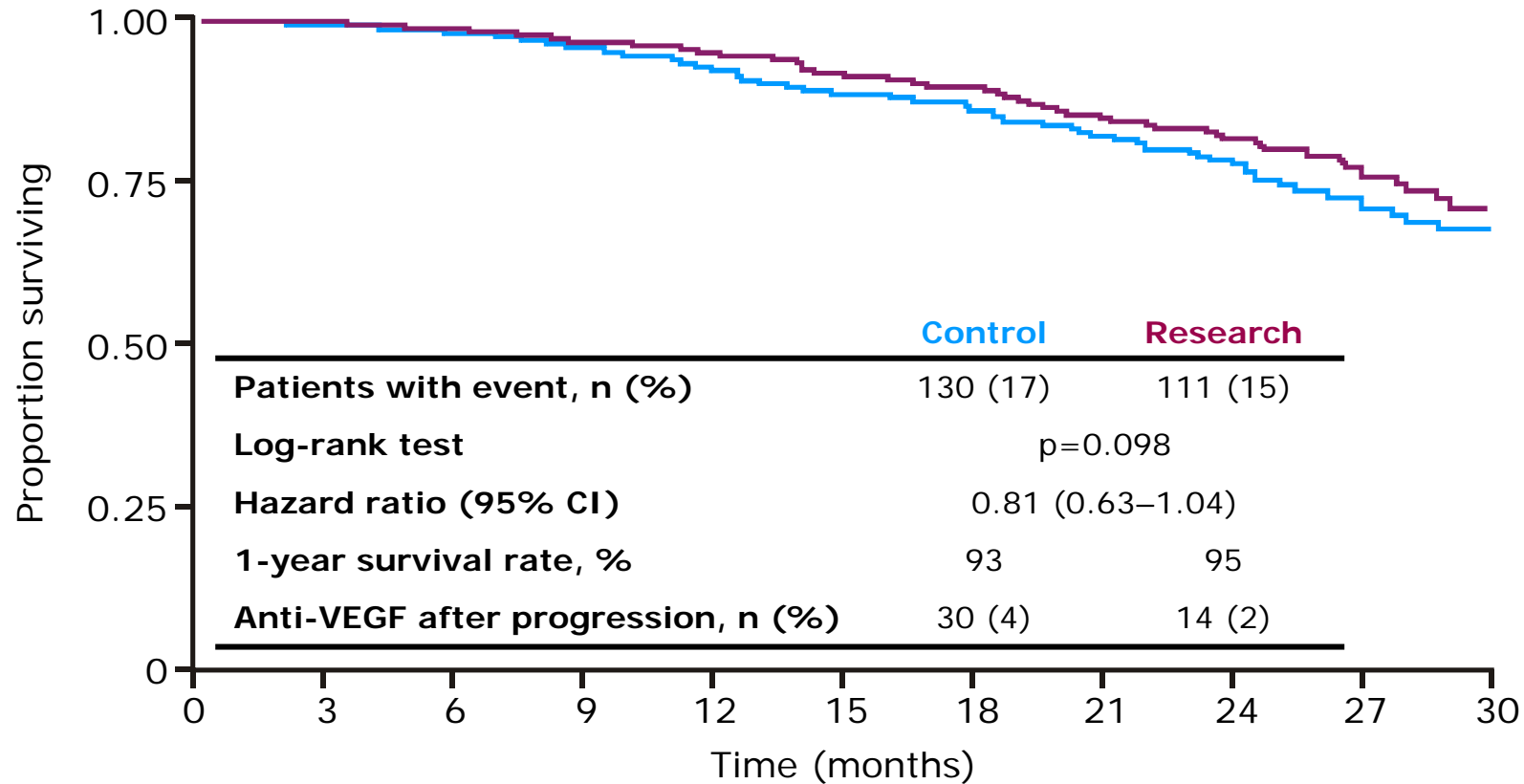


Age: Trend p=0.69, interaction p=0.83; ECOG: Trend p=0.027, interaction p=0.022
 Histology: Interaction test p=0.085; FIGO: Trend p=0.71, interaction p=0.91
 Residual disease: Trend p=0.10; Grade: Trend p=0.76, interaction p=0.95

Research better Control better

PFS: FIGO stage III suboptimal and FIGO stage IV with debulking



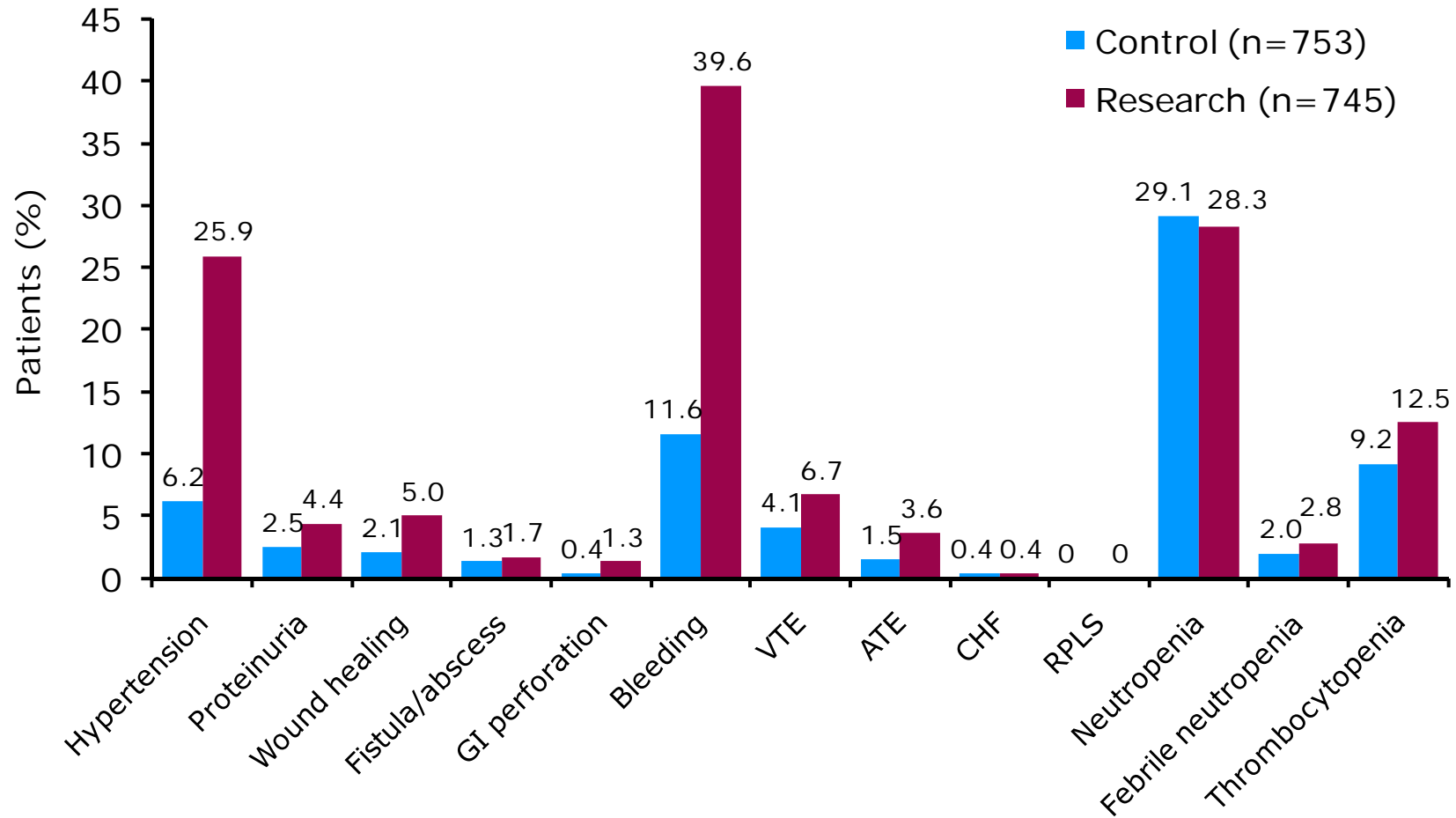


Number at risk

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

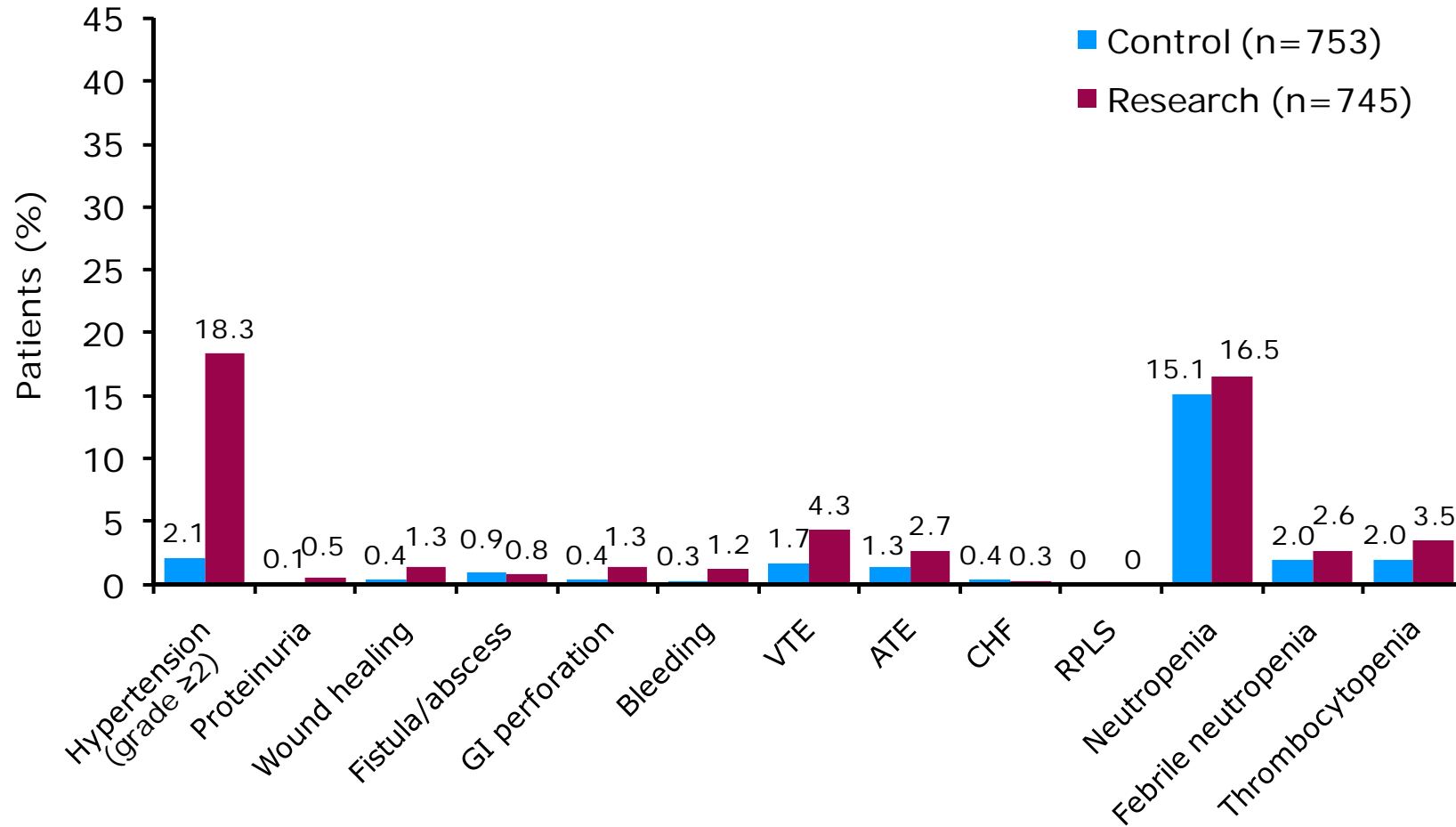
Based on immature OS data (241 of 715 required events, 16% of all patients) as required by regulatory authorities (approved by IDMC and TSC)

Selected adverse events (all grades)



ATE = arterial thromboembolism; CHF = congestive heart failure; RPLS = reversible posterior leucoencephalopathy syndrome; VTE = venous thromboembolism

Selected grade ≥ 3 adverse events



ATE = arterial thromboembolism; CHF = congestive heart failure; RPLS = reversible posterior leucoencephalopathy syndrome; VTE = venous thromboembolism

- The addition of concurrent and maintenance bevacizumab (7.5 mg/kg for 12 months) to standard chemotherapy statistically significantly improved PFS
- Due to non-proportional hazards, benefit is complicated to describe:
 - 15% improvement in PFS at 12 months
 - 1.7 month improvement in median PFS
 - 1.5 month overall improvement in PFS (restricted mean)
 - Treatment effect is numerically greater in advanced-stage patients
- Second positive phase III trial of bevacizumab in ovarian cancer
- Treatment was well tolerated with no new safety concerns
- Longer term PFS, mature OS and translational research results are anticipated in 2012
- Results of ICON7 will influence treatment decisions and design of future clinical trials