ICON7
Bevacizumab in Ovarian Cancer

MRC Clinical Trials Unit

ICON7: Final overall survival results in the GCIG phase III randomized trial of bevacizumab in women with newly diagnosed ovarian cancer

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on behalf of the ICON7 investigators
(MRC/NCRI, AGO-OVAR, GINECO, NSGO, ANZGOG, GEICO, NCIC-CTG)

GYNECOLOGIC CANCER INTERGROUP

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Disclosures

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- AM Oza: Clinical trial funding (ROSiA); travel reimbursement for advisory boards (Roche)
- TJ Perren: Honoraria for advisory boards and lectures; travel and congress funding (Roche)
- E Pujade-Lauraine: Honoraria (Roche)
- AM Swart, A Cervantes, AC Embleton, M Parmar: None

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Acknowledgements

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- **Participating GCIG groups**
  AGO, ANZGOG, GEICO, GINECO, MRC/NCRI, NSGO, NCIC CTG
- **The 263 clinical sites and their staff**
- **Trial Management Group**
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- **Trial Physicians**
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Schema

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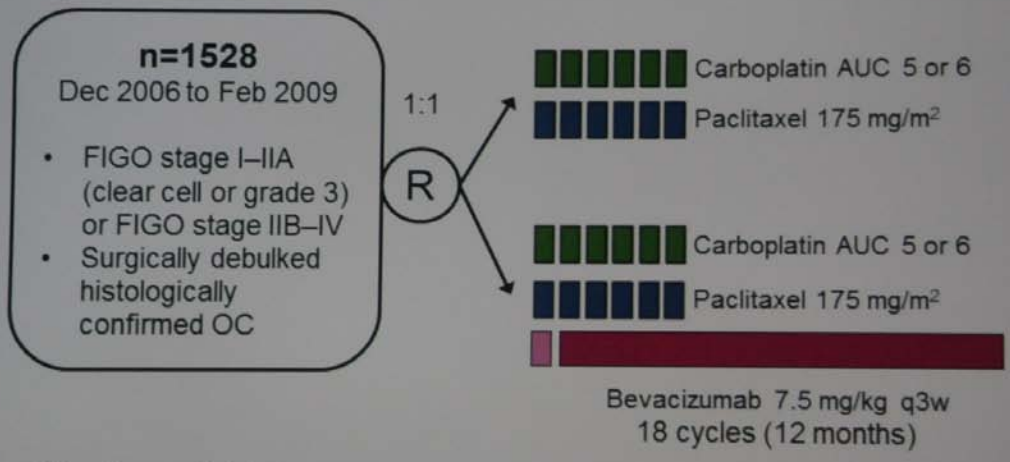

Stratification variables:

- **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**

OC = epithelial ovarian, primary peritoneal or fallopian tube cancer

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Overview of analyses

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ICON7 was powered for both PFS and OS, designed to detect:

- PFS HR = 0.78 (684 events; 90% power)
- OS HR = 0.81 (715 events; 80% power)

	Median follow-up, months	PFS events	OS events (% of required events)
Mature PFS analysis (cut-off Feb 28, 2010; ESMO 2010)	19	759	241 (34%)
Updated interim OS analysis requested by regulatory authorities (cut-off Nov 30, 2010; ASCO 2011)	28	934	378 (53%)
Final OS analysis	49	1080	714 (100%)

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Primary analysis (2010)

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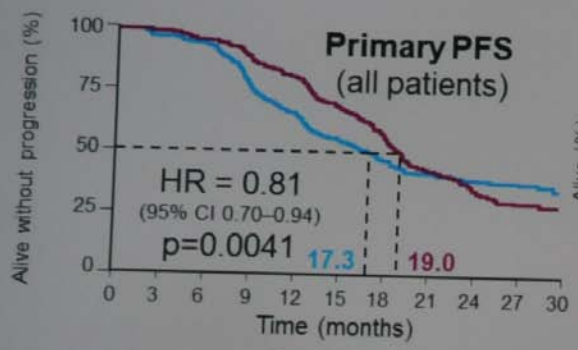

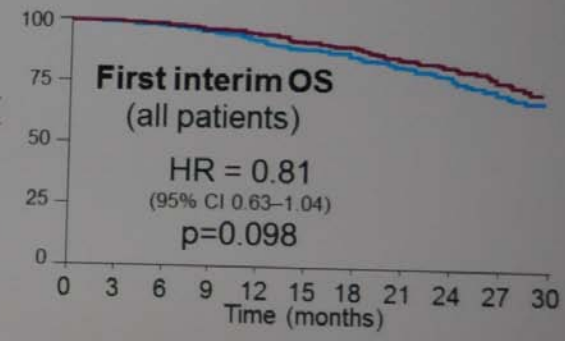

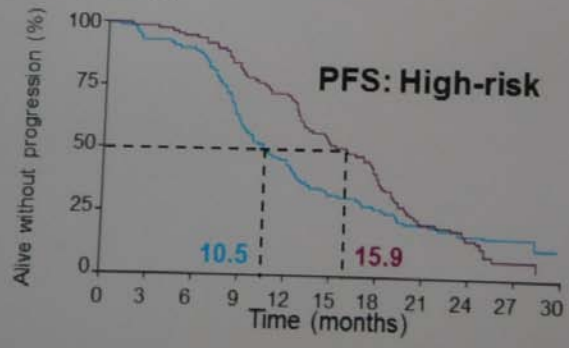

Perren T.J. et al. NEJM 2011

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Baseline characteristics

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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)	548 (72)	555 (73)
0 cm	353 (46)	340 (45)
>0, ≤1 cm	175 (23)	194 (25)
Unknown	20 (3)	21 (3)
Suboptimal surgery (>1 cm)	199 (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

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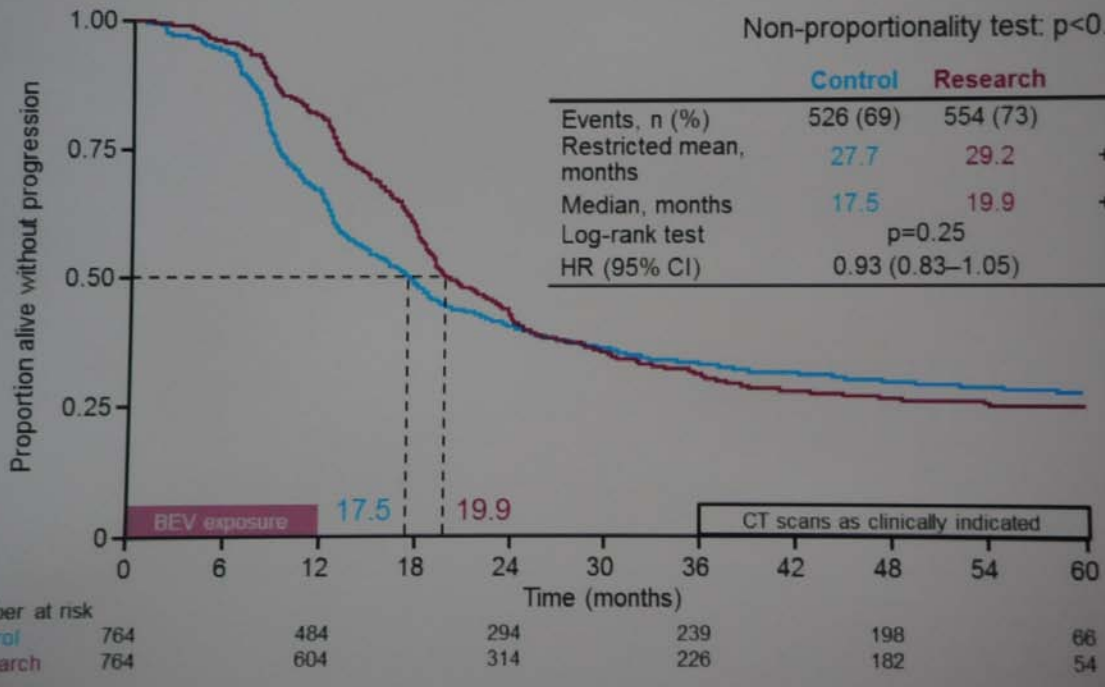

Number at risk

Control	764	484	294	239	198	66
Research	764	604	314	226	182	54

ICON7 Final OS (n=1528)

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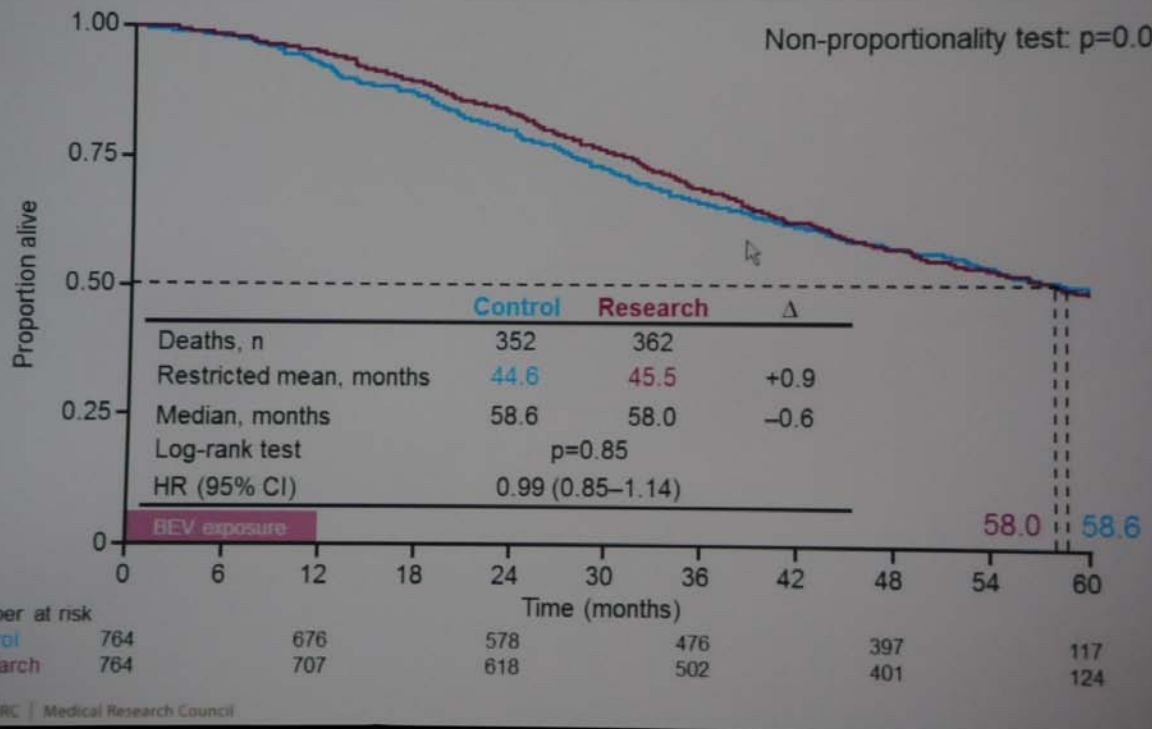

Number at risk

Control	764	676	578	476	397	117
Research	764	707	618	502	401	124

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Absolute difference in PFS & OS (n=1528)

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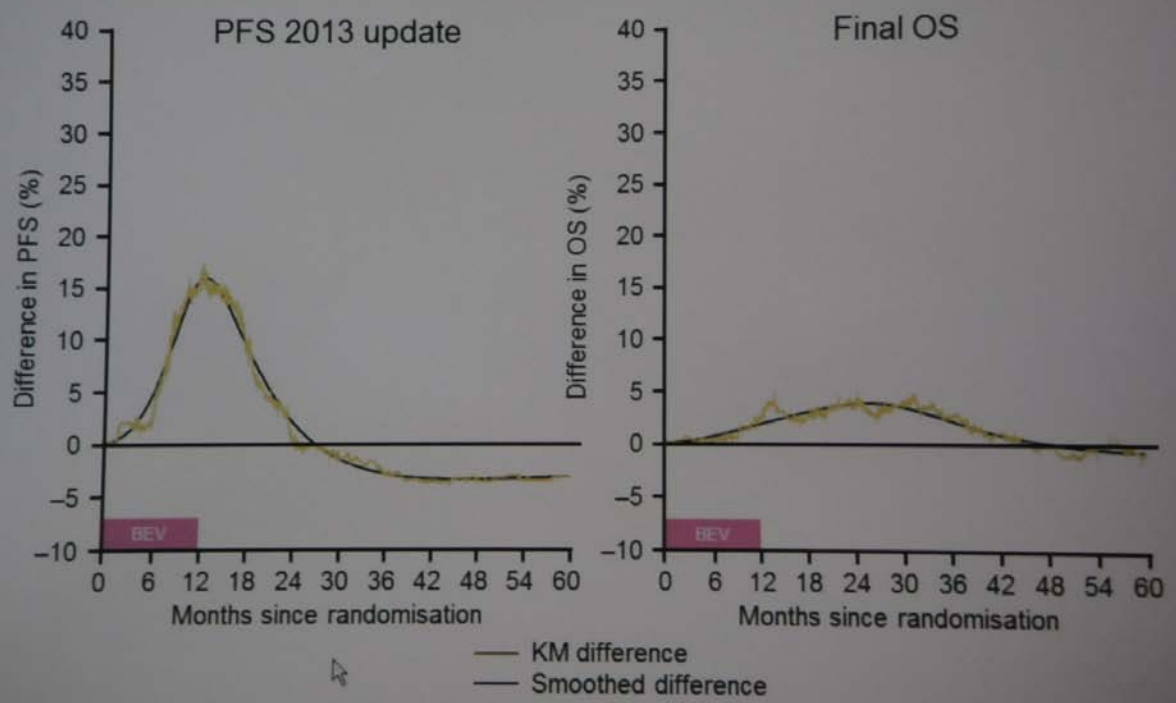

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Definition of high-risk subgroup

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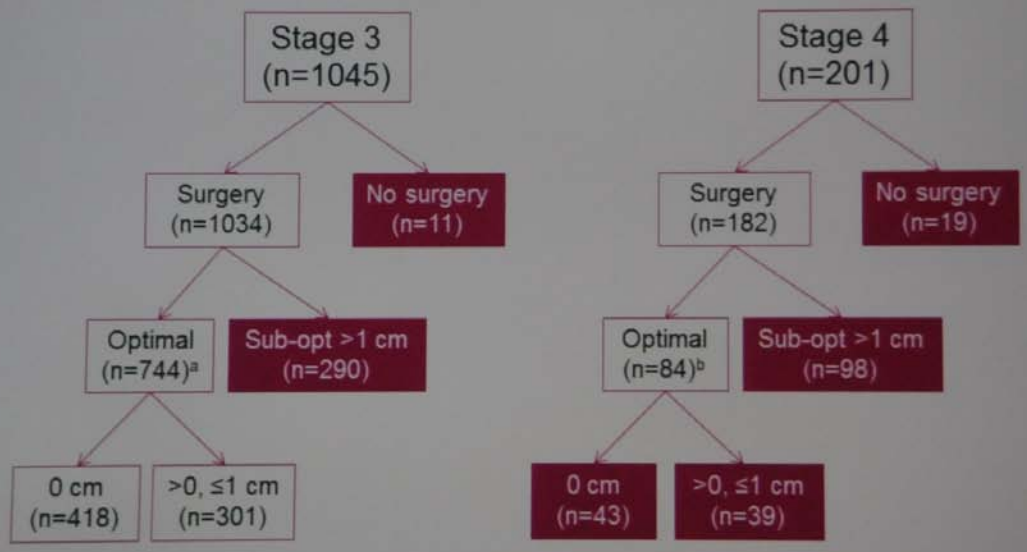

Modified ICON7 high-risk group (n=502)

Original ICON7 high-risk group (n=472)

[a]Optimal unknown residual size (n=25)
[b]Optimal unknown residual size (n=2)

PFS (2013 update): High-risk (n=502)

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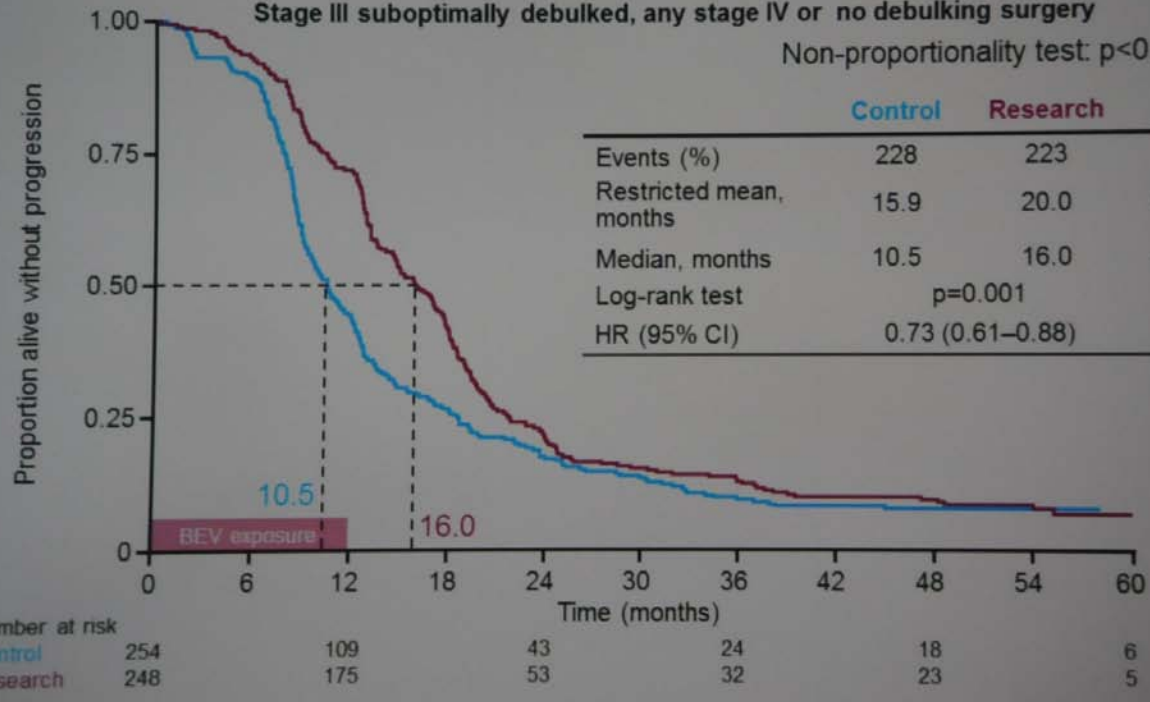
Stage III suboptimally debulked, any stage IV or no debulking surgery

Non-proportionality test: p<0.0001

	Control	Research	Δ
Events (%)	228	223	
Restricted mean, months	15.9	20.0	+4.1
Median, months	10.5	16.0	+5.5
Log-rank test	p=0.001		
HR (95% CI)	0.73 (0.61–0.88)		



Number at risk						
Control	254	109	43	24	18	6
Research	248	175	53	32	23	5

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Final OS: High-risk (n=502)

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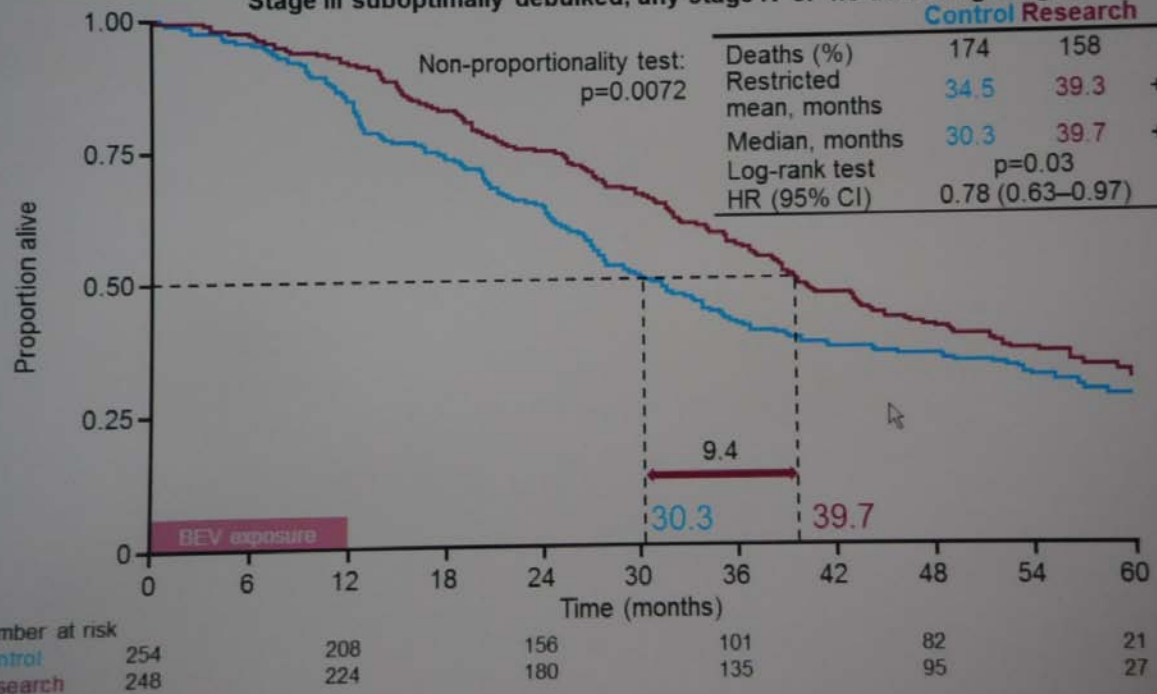
Stage III suboptimally debulked, any stage IV or no debulking surgery



	Control	Research	Δ
Deaths (%)	174	158	
Restricted mean, months	34.5	39.3	+4.8
Median, months	30.3	39.7	+9.4
Log-rank test	p=0.03		
HR (95% CI)	0.78 (0.63–0.97)		

Number at risk						
Control	254	208	156	101	82	21
Research	248	224	180	135	95	27

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Final OS by risk groups

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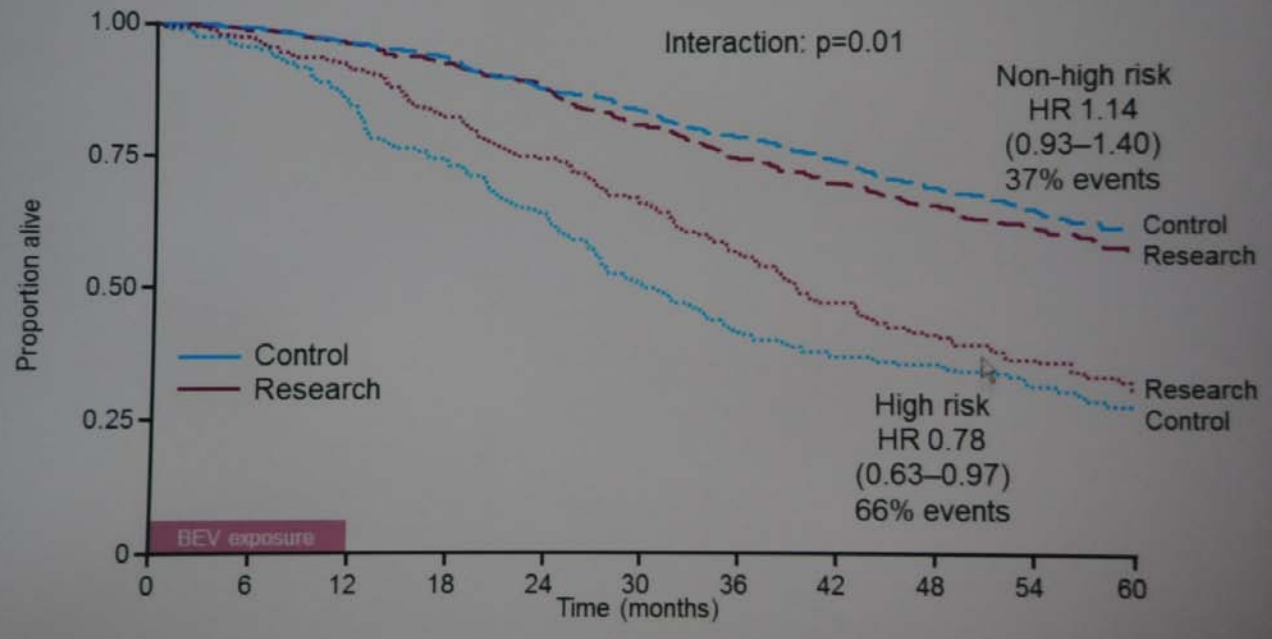

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Absolute difference in PFS & OS: High-risk subgroup

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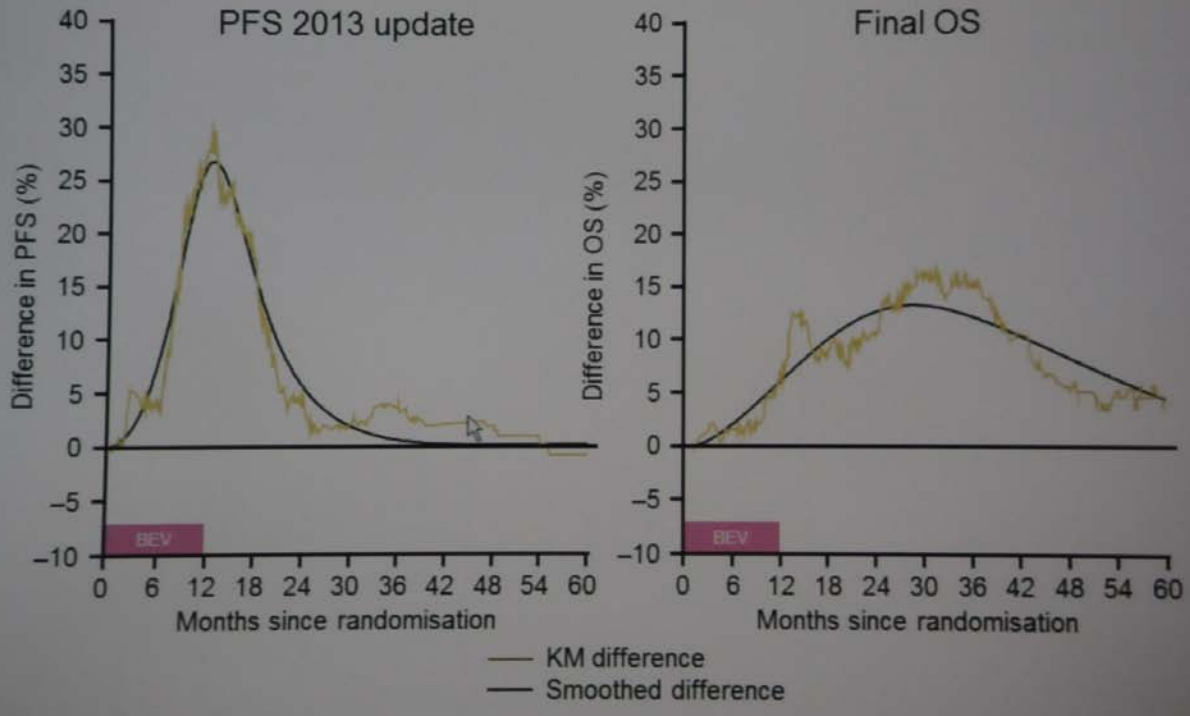

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Final OS

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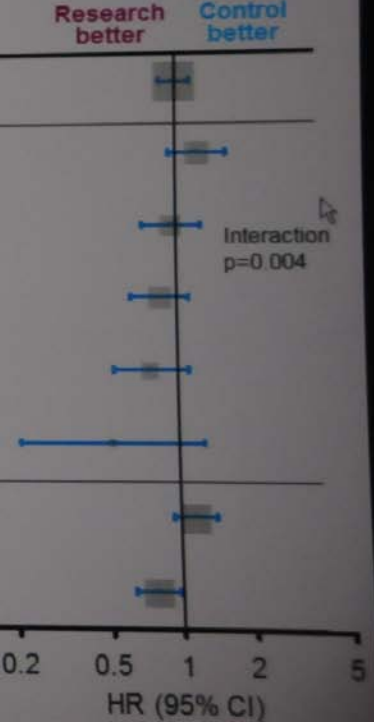
Subgroup	Restricted mean OS Control	Restricted mean OS Research	Median OS, months Control	Median OS, months Research	HR (95% CI)	n
All patients	44.6	45.5	58.6	58.0	0.99 (0.85–1.14)	1528
Stage I, II, III (0 cm)	52.6	51.9	NR	NR	1.23 (0.93–1.62)	725
Stage III >0, ≤1 cm	42.6	41.9	45.7	44.2	0.95 (0.71–1.26)	301
Stage III >1 cm	36.1	40.2	32.1	39.7	0.84 (0.63–1.11)	290
Stage IV	33.4	38.4	29.4	39.6	0.76 (0.53–1.10)	182
Non operated	24.9	35.5	20.8	40.4	0.52 (0.21–1.27)	30
Non-high-risk	49.7	48.4	NR	67.2	1.14 (0.93–1.40)	1026
High-risk	34.5	39.3	30.3	39.7	0.78 (0.63–0.97)	502



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Conclusions

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Final OS analyses for ICON7 show:

- In the entire population:
  - OS curves are non-proportional → restricted mean is the appropriate statistic for the difference (0.9 months)
  - No evidence of a difference in OS (log-rank p=0.85)
  - Any OS difference is not clinically meaningful
- In the high-risk subgroup (suboptimally debulked stage III, stage IV and non-operated patients):
  - Significant OS improvement with bevacizumab 7.5 mg/kg (log-rank p=0.03, non-proportionality test p=0.007)
  - 4.8 months' improvement by restricted means
  - 9.4 months' median difference with HR 0.78 (95% CI 0.63–0.97)
  - OS difference in high-risk subgroup is clinically meaningful

Conclusion

ecco

- Practice changing pivotal trials – bevacizumab is an active drug in advanced bulky ovarian cancer
- Bevacizumab with weekly paclitaxel should be considered a new paradigm in platinum resistant ovarian cancer
  - Most favourable clinical benefit/cost ratio
- First line bevacizumab and 3-weekly chemotherapy should be considered a standard of care in high risk ovarian cancer
  - Prioritise most high risk: eg inoperable, stage 4, ?miliary residual disease and those least likely to tolerate in subsequent line