

ICON7

Bevacizumab in Ovarian Cancer

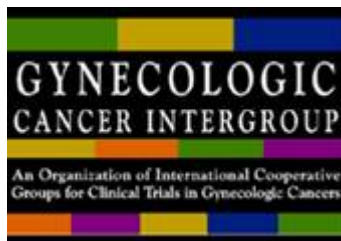
MRC

Clinical
Trials
Unit

Quality of life in the ICON7 GCIG phase III randomised clinical trial

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on behalf of the ICON7 QoL subgroup and the GCIG ICON7 collaborators (MRC/NCRI, AGO-OVAR, GINECO, NSGO, ANZGOG, GEICO, NCIC-CTG)



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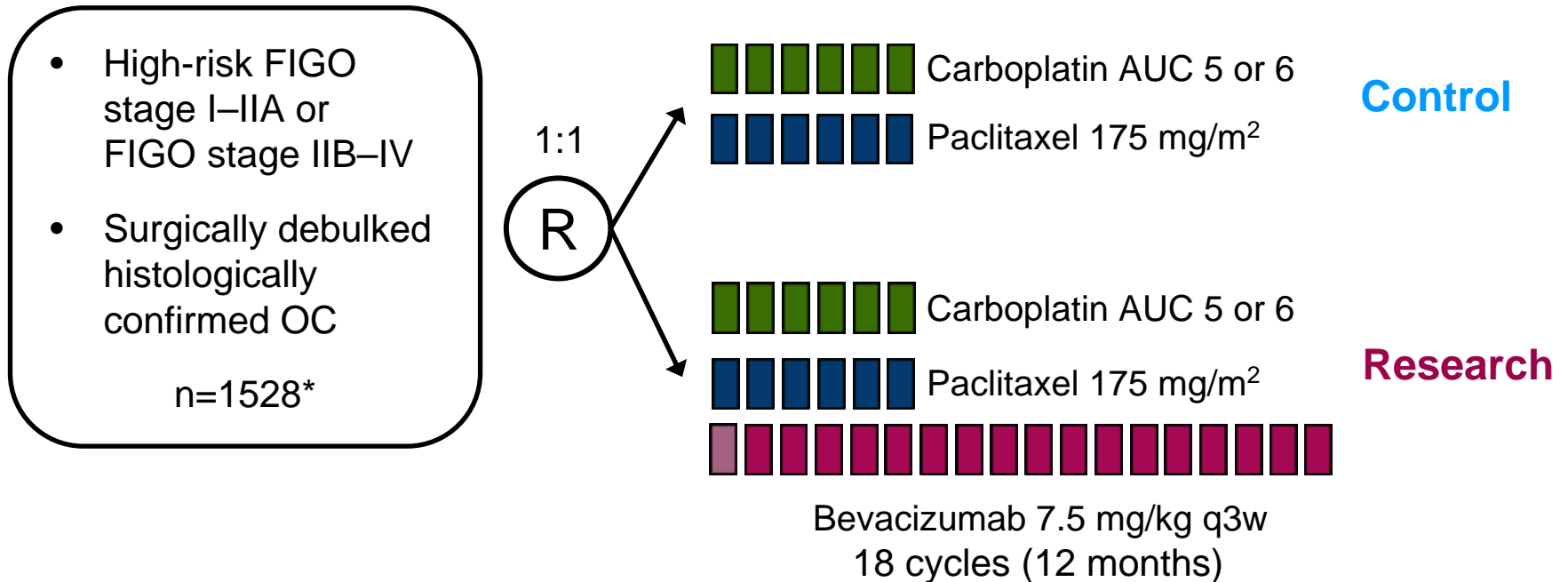


Declaration of conflicts of interest



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- Dr Stark has no conflicts of interest to declare
 - Roche provided bevacizumab and grants for the study

Academic-led, industry-supported Gynaecologic Cancer InterGroup (GCIC) phase III trial to investigate use of bevacizumab and to support licensing



*Dec 2006 to Feb 2009

OC = epithelial ovarian, primary peritoneal or fallopian tube cancer

PFS benefit demonstrated

- ESMO 2010: Primary PFS analysis¹
 - Improved PFS with **concurrent and continued bevacizumab** vs **control**
 - Trend for improvement in OS (data immature)
- ASCO 2011: Interim OS analysis (53% of required events)²
 - Continued improvement in PFS
 - Continued trend for improved OS in the whole population
 - In the subgroup at high risk of recurrence
 - 1-year OS **92%** vs **86%** (p=0.002)

- Instrument: EORTC QLQ-OV28 subscale, with QLQ-C30^{1,2}
 - Validated patient self-report measure
 - Includes key symptoms and impact upon family and social activities³
 - Multiple validated translations across GCIG
- Objectives
 - Primary: Compare week 54 global QoL scale between treatment arms
 - Secondary: Address 3 specific hypotheses
 - Exploratory: Evaluate other subscales

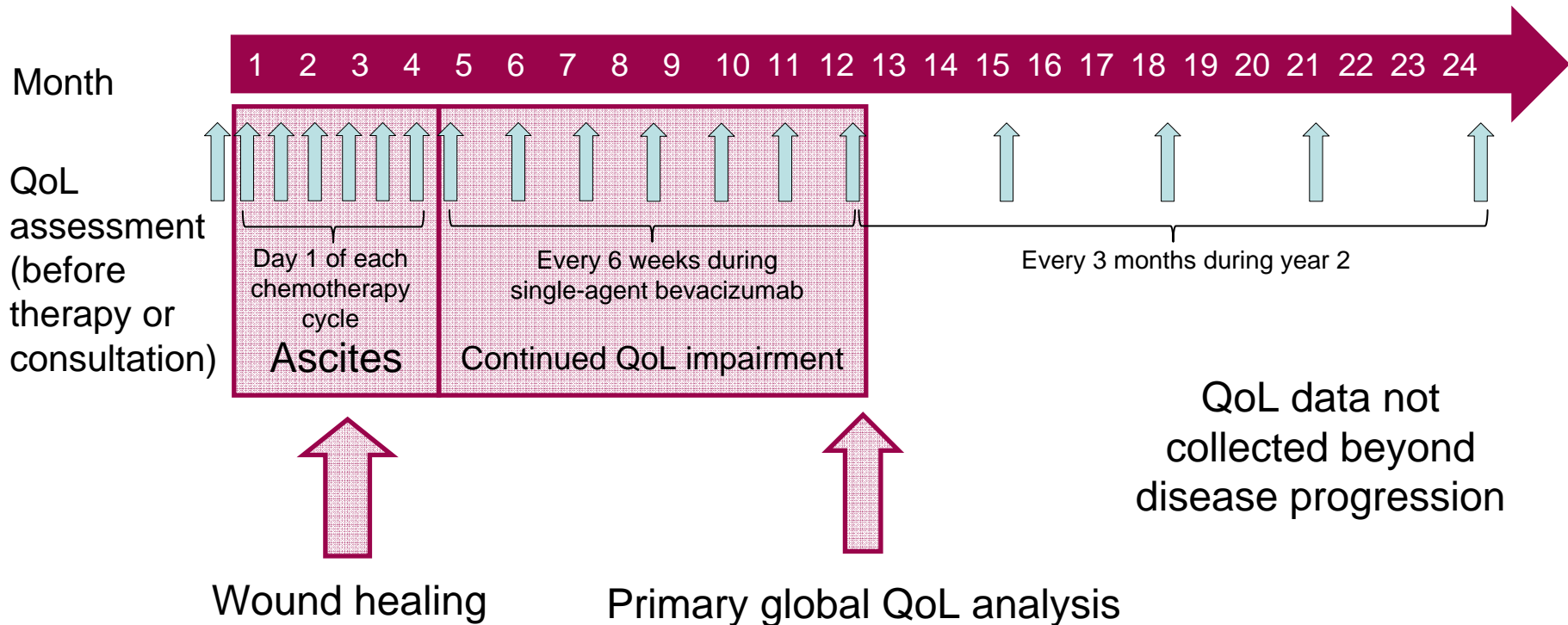
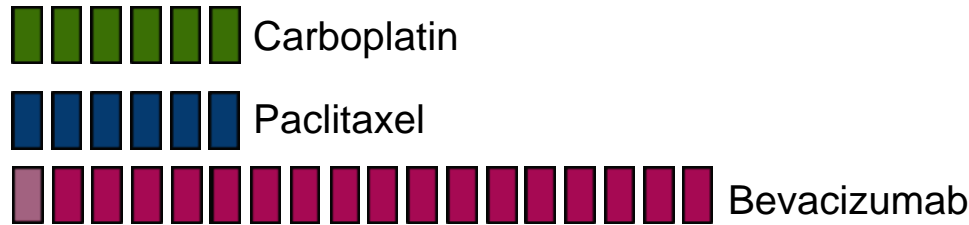
EORTC = European Organisation for Research and Treatment of Cancer;
QLQ = quality of life questionnaire; QoL = quality of life

1. Cull et al. Eur J Cancer 2001; 2. Greimel et al. Eur J Cancer 2003; 3. Lockett Ann Oncol 2011

Specific hypotheses tested

Phase (analysis variable)	Hypothesis	Scale (instrument)
Early (AUC weeks 1–18)	Bevacizumab reduces time to resolution of ascites	Abdominal/GI subscale (QLQ-OV28)
Mid (mean score, day 1 cycle 4)	Bevacizumab slows wound healing and increases scar symptoms	Pain, physical function, social function (QLQ-C30); body image (QLQ-OV28)
Late (change in score, week 18 to week 54)	Continued single-agent bevacizumab prolongs QoL impairment	Social function, fatigue (QLQ-C30)

QoL assessed at key time points



Clinical significance^{1,2}

Instrument	Change (points)	Significance
EORTC	0–4	Trivial
QLQ-C30	4–10	Small
global QoL	10–15	Moderate
	Effect size	
QLQ-OV28	0.3	Small to moderate

Statistical significance

- $p < 0.05$ for primary global QoL and a priori hypotheses
- $p < 0.01$ for exploratory analyses

Outcome	Control (n=764)	Research (n=764)
Data available at baseline and week 54, n (%)	333 (44)	444 (58)
Mean global QoL (SD)		
Baseline	58.6 (20.64)	55.1 (20.84)
Week 54	76.1 (18.17)	69.7 (19.08)

Small QoL difference between arms

Outcome	Control (n=764)	Research (n=764)
Data available at baseline and week 54, n (%)	333 (44)	444 (58)
Mean global QoL (SD)		
Baseline	58.6 (20.64)	55.1 (20.84)
Week 54	76.1 (18.17)	69.7 (19.08)
Difference between arms		6.4
		p<0.0001^a
		Small effect size
		Favours control¹

^aAdjusted for baseline

- No evidence of interaction between high-/low-risk groups (p=0.89)

- 23% missing data by design*
 - Why?
 - Difficult to collect comprehensively
 - Difficult to interpret without detailed clinical data
 - High emotional and practical patient burden after disease progression
 - But 3-year data (in all patients still alive)

- Due to patient preference or centre omission (27%)
 - Detailed reasons prospectively collected

	% Forms received/No. of pts alive without progression	
	Control	Research
Baseline/cycle1	89	92
After chemotherapy	84	93
End of maintenance	86	89
Month 18	86	83

Three methods for imputation of missing week 54 data

- 1) Worst QoL in study if missing data due to progressive disease
- 2) Best QoL in study for all missing data
- 3) Worst QoL in study for all missing data

Method	Control (n=764)		Research (n=764)		Difference	
	n	Mean (SD)	n	Mean (SD)	Size	p-value
1	594	43 (40.2)	596	52 (34.6)	9	0.001
2	764	90 (16.9)	764	82 (20.8)	8	<0.001
3	764	33 (39.6)	764	41 (37.4)	8	0.001

A priori hypotheses not supported

		Mean score		Difference	p-value
		Control	Research		
Early	GI symptoms	76.4	74.7	1.7	0.43
Mid	Scar symptoms				
	Pain	22.0	22.7	0.7	0.64
	Physical functioning	80.5	78.8	1.7	0.60
	Social functioning	70.6	70.2	0.4	0.17
	Body image	36.2	35.4	0.8	0.62
Late	Social functioning	13.7	11.9	1.8	0.30
	Fatigue	-15.8	-14.9	0.9	0.58

Scale (QLQ-C30)	Mean score at week 54		Difference	p-value ^a	Effect size ¹
	Control	Research			
Role functioning	84.5	75.6	8.9	<0.001	Small
Cognitive functioning	84.9	81.4	3.5	0.033	Small
Emotional functioning	77.5	75.4	2.1	0.002	Trivial
Nausea and vomiting	2.6	3.7	1.1	0.120	Trivial
Dyspnoea	11.8	14.8	3.0	0.104	Trivial
Appetite loss	4.2	7.6	3.4	0.004	Trivial
Finance	12.8	18.9	6.1	0.007	Small
Diarrhoea	5.0	7.3	2.3	0.037	Trivial
Sleep	24.4	28.6	4.2	0.078	Small
Constipation	13.0	15.8	2.8	0.143	Trivial

^aPrespecified boundary for statistical significance p<0.01

Ovarian-specific subscale	Mean score		Difference	p-value	Effect size and interpretation ¹	
	Control	Research				
Attitude to disease and treatment	27.6	33.3	5.7	0.003	0.22	<small
Peripheral neuropathy	6.3	9.3	3.0	0.05	0.16	
Hormonal	13.0	17.3	4.3	0.004	0.23	<small
Rash	12.4	18.0	5.6	0.001	0.25	<small

- Perhaps unsurprisingly, women receiving bevacizumab had a statistically significant but clinically small detriment in global QoL at week 54
- None of our a priori hypotheses was supported
- Women receiving bevacizumab had statistically significant but clinically small detriments in role function and finance scales
- Sensitivity analyses indicate caution in interpretation
 - Data were missing, due in part to our study design
- Future work:
 - Analyses modeling missing data¹
 - Further QoL analyses alongside OS analyses (anticipated 2013)
 - QoL in all women alive at 3 years

- **The women who participated in the trial and their families**
- **Participating GCIg groups:** AGO-OVAR, ANZGOG, GEICO, GINECO, MRC/NCRI, NSGO, NCIC-CTG
- **The 263 clinical sites and their staff**
- **Trial Management Group:** T Perren, A Oza, AM Swart, W Qian, M Parmar, L Farrelly, 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 Anderson
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