Overall survival results of ICON6: a trial of chemotherapy and cediranib in relapsed ovarian cancer

Ledermann JA, Embleton AC, Perren T, Jayson GC, Rustin GJS, Kaye SB, Hirte HW, Oza AM, Vaughan MM, Friedlander M, Gonzalez-Martin A, Clark E, Popoola BO, Farrelly L, Swart AM, Cook A, Kaplan RS, Parmar MKB

on behalf of the ICON6 Collaborators

(NCRI, NCIC-CTG, ANZGOG, GEICO)

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

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The ICON6 trial team would like to thank:

- Patients and their families
- Investigators – 45 UK sites, 10 Canada, 5 Australia, 2 Spain
- Collaborating GCIG Groups – NCIC-CTG, ANZGOG, GEICO
- ICON6 TMG members and staff at the MRC Clinical Trials Unit at UCL – J. Ledermann, G. Rustin, F. Raja, R. Kaplan, AM. Swart, L. Farrelly, L. Clark, A. Embleton, A. Cook, S. Townsend, R. Meyer, H. Hirte, C. Davidson, M. Vaughan, J. Martyn, K. Carlton, A. González Martín, F. Nepote, G. Jayson, D. Stark, D. Fry, S. Mannix, E. Burnett, M. Tomiczek, J. Petrie, C. Jones, W. Qian, C. Griffin
- ICON6 IDMC and TSC members – R. Coleman, W. Sauerbrei, R. Buckstein, U. Menon J. Whelan, R. Rudd, D. Fink, P. Johnson
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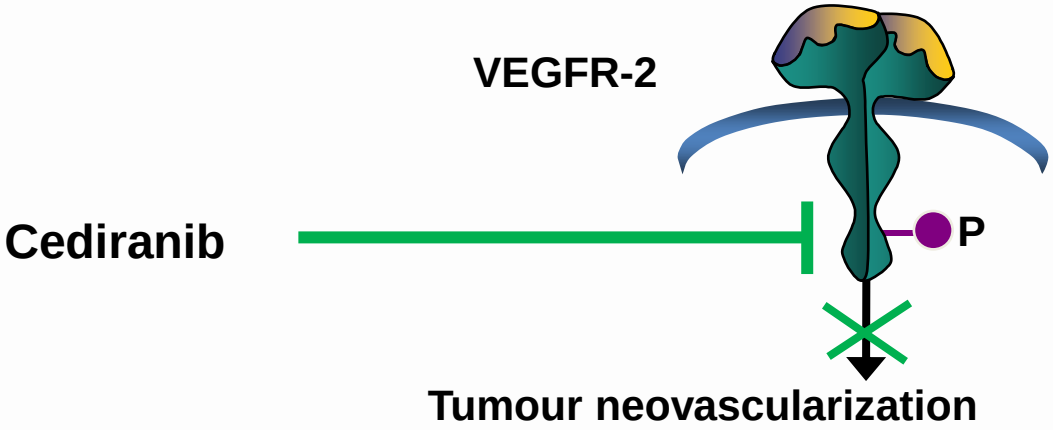
Cediranib (AZD 2171)



Wedge et al Cancer Res 2005

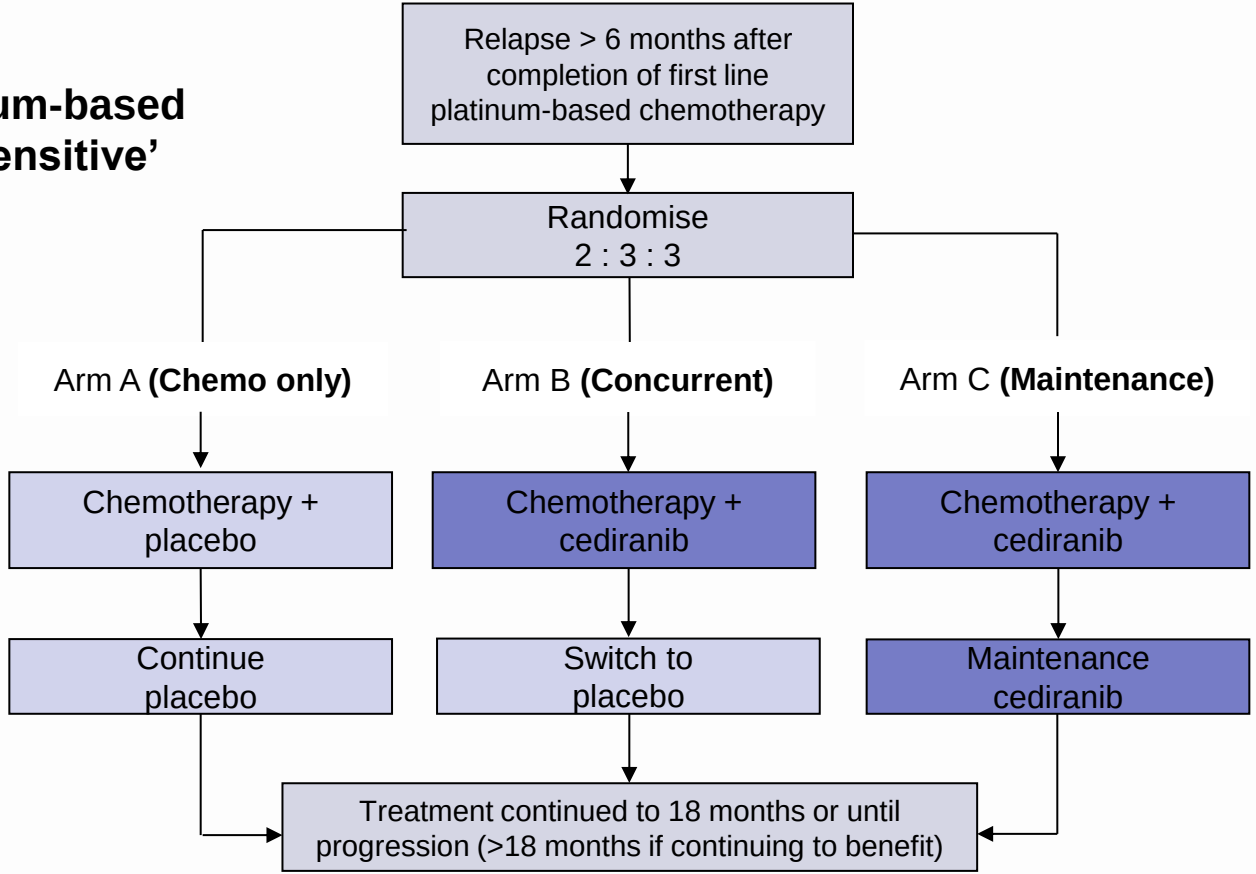
- potent oral inhibitor of vascular endothelial growth factors
- >800–5000 fold selectivity for VEGFR-2
- *in vitro* activity against VEGFR-1 and -3
- Inhibits growth of established xenografts – lung, colorectal, prostate, breast and ovary

- Phase II trials showed activity as a single agent in ovarian cancer[1]

[1] *Matulonis et al 2009; Hirte et al 2010*

Study schema

ICON6: Cediranib with platinum-based chemotherapy in 'platinum-sensitive' relapsed ovarian cancer



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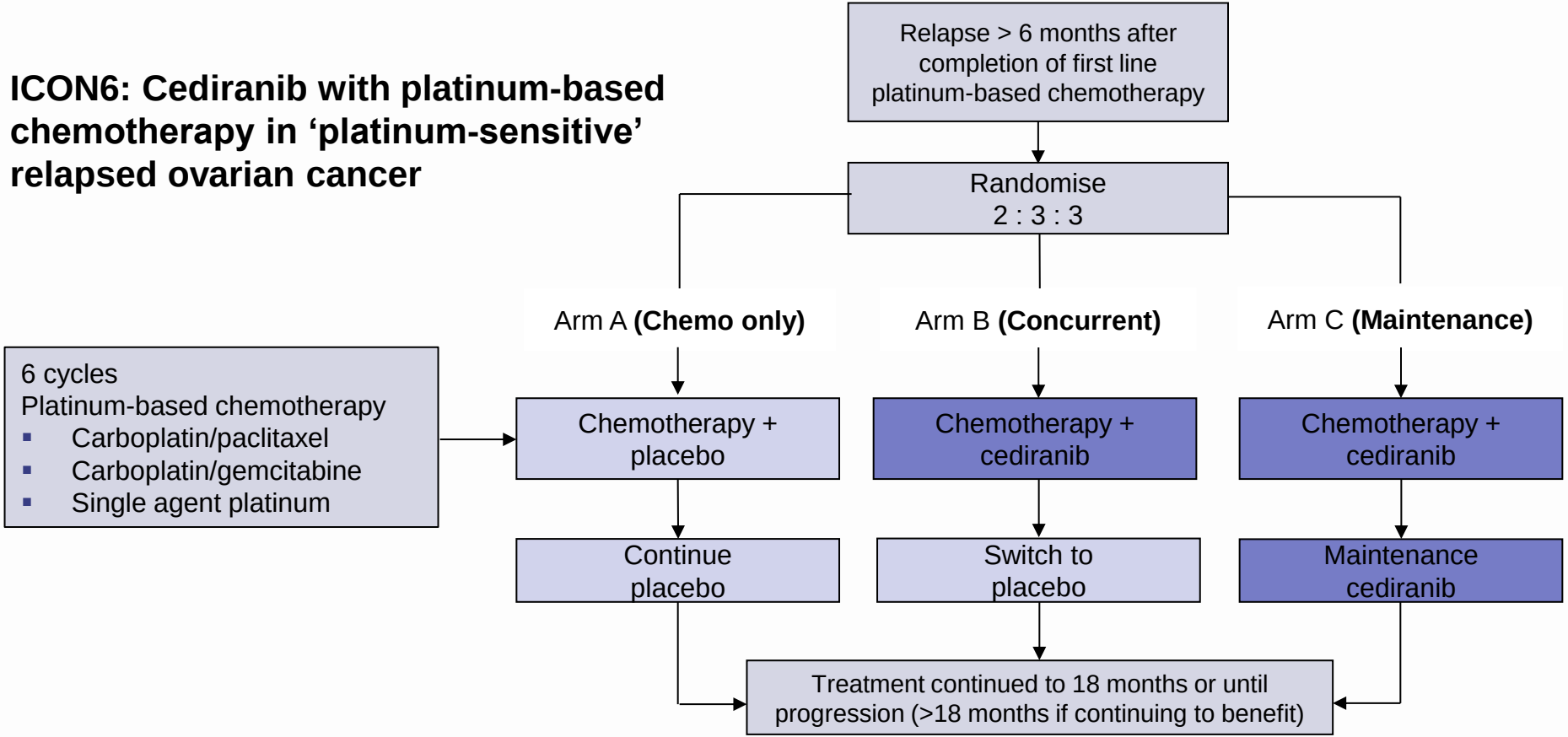

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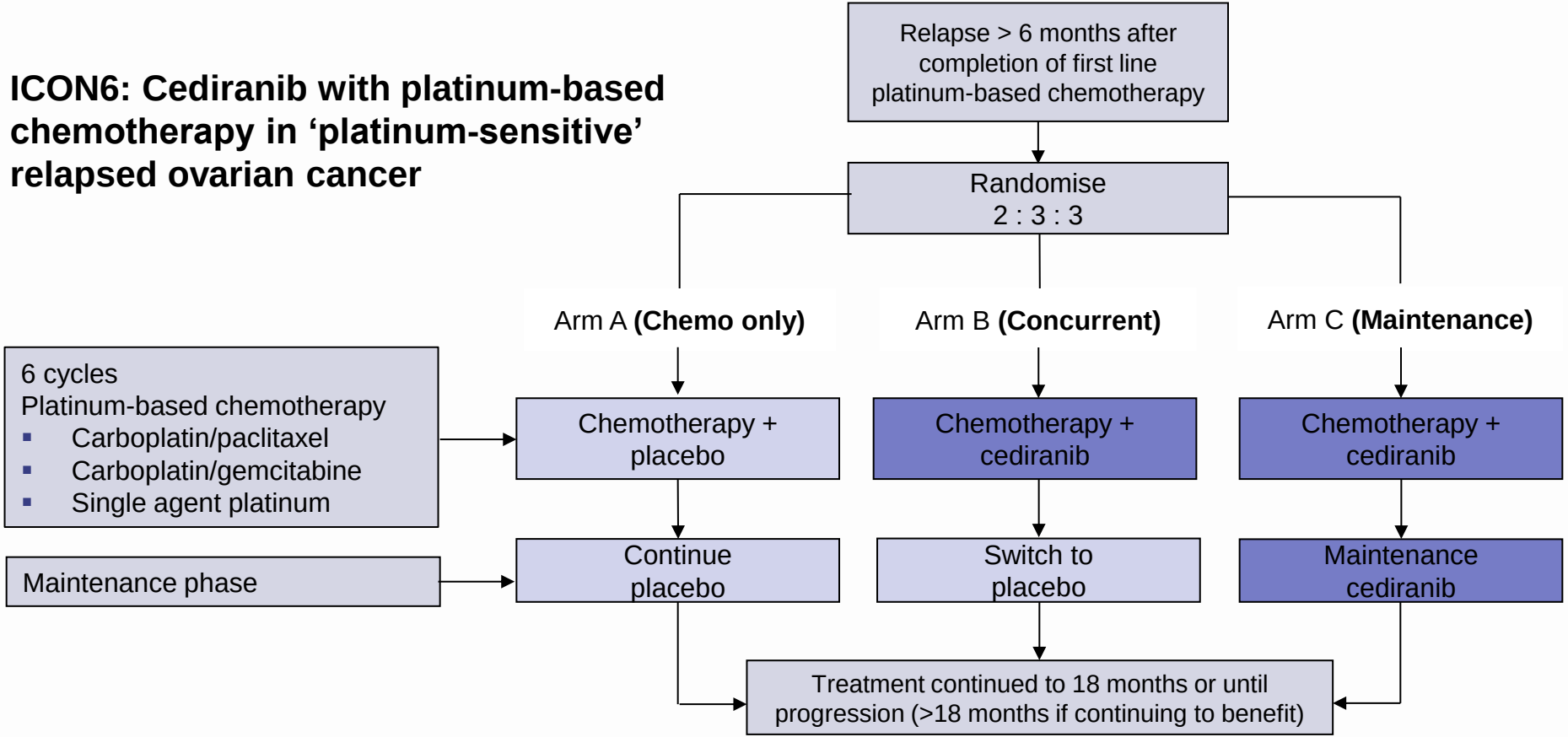


Entry criteria

- Epithelial ovarian, fallopian tube or serous primary peritoneal cancer relapsing >6 months after first-line chemotherapy
- CT or MRI proven relapsed disease (measurable or non-measurable) with a clinical need for chemotherapy, not just a raised CA125
- Performance status 0 or 1 and able to receive platinum-based chemotherapy
- No contraindications to oral cediranib (uncontrolled hypertension; arterial thrombosis/haemorrhage; recent surgery)
- Previous maintenance treatment biological therapy (e.g. bevacizumab) permitted but not chemotherapy maintenance

Stages and outcomes

	Original design			
Safety stage		Safety*	33 pts	
Activity stage	Primary	PFS/OS	600 pts	A vs. B+C
Efficacy stage	Primary	OS	2000 pts	A vs. B
				A vs. C
				B vs. C

*Cediranib reduced from 30 to 20 mg daily after safety stage

Stages and outcomes

	Original design				Revised design			
Safety stage		Safety*	33 pts			Safety*	33 pts	
Activity stage	Primary	PFS/OS	600 pts	A vs. B+C				
Efficacy stage	Primary	OS	2000 pts	A vs. B	Primary	PFS	440 pts	A vs. C
				A vs. C	Secondary	OS		
				B vs. C		Toxicity		

*Cediranib reduced from 30 to 20 mg daily after safety stage

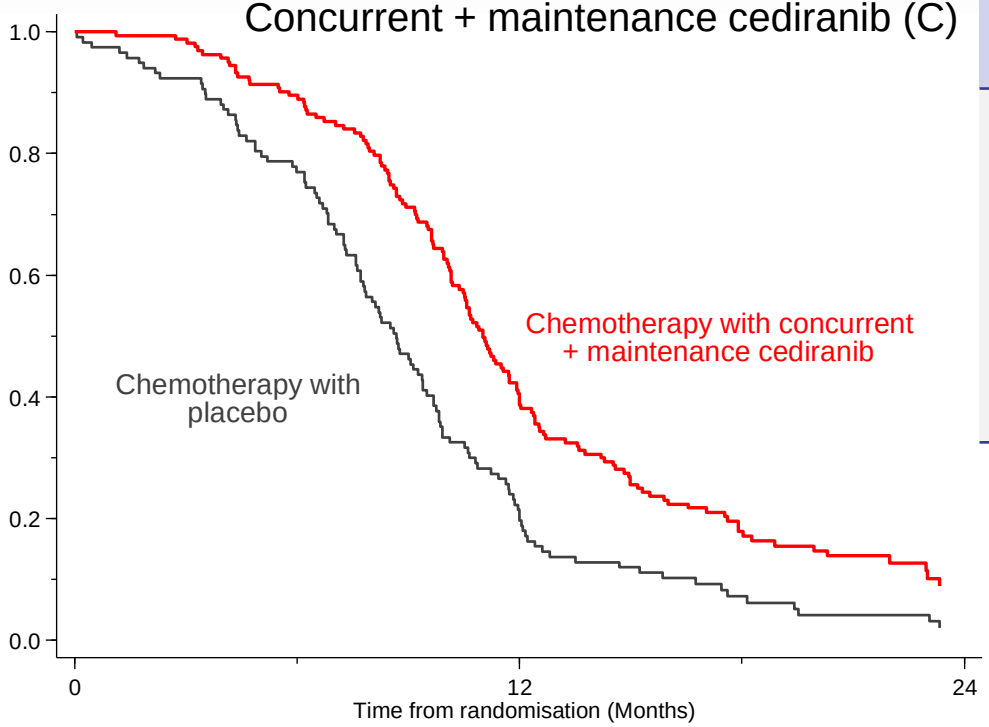
- Revised design in October 2011 as AstraZeneca discontinued cediranib development after disappointing outcomes in pivotal trials of other cancer types
- The prospective analysis plan was modified – with no outcome analysis done
  - Primary outcome altered to **PFS**
  - HR of 0.65 between Arm A and Arm C (5% significance level and at least 80% power)
  - Requirement: 440 patients (20mg dose) [456 recruited]

Baseline characteristics *(2013)*

	Chemotherapy + placebo (A) n=118		***Chemotherapy + concurrent cediranib (B)*** *n=174*		**Concurrent + maintenance cediranib (C)** n=164	
Randomisation ratio	**2**		***3***		**3**	
Age						
Median (range)	62	(37-77)	*62*	*(30-85)*	62	(32-86)
ECOG status						
0	69	(**59%**)	*109*	(***63%***)	95	(**58%**)
1	47	(**41%**)	*64*	(***37%***)	68	(**42%**)
Time since last chemotherapy						
6—12 months	43	(**36%**)	*59*	(***34%***)	50	(**30%**)
>12 months	75	(**64%**)	*115*	(***66%***)	114	(**70%**)
Previous paclitaxel						
Yes	103	(**87%**)	*154*	(***89%***)	148	(**90%**)
VEGF/EGFR						
Bevacizumab	6	(**5%**)	*9*	(***5%***)	9	(**5%**)
Erlotinib	0	-	*1*	(***1%***)	0	-

Progression-Free Survival *(2013)*

Chemotherapy + placebo (A) *versus*
Concurrent + maintenance cediranib (C)



Arm A	118	(27)	90	(67)	23	(14)	7	(5)	2
Arm B	164	(17)	146	(83)	63	(32)	22	(9)	7

	Placebo (A)	Cediranib (C)
PFS events, n (%)	112 (94.9)	139 (84.8)
Median, months	8.7	11.1
Log-rank test	*p*=0.00001	
HR (95% CI)	0.57 (0.45—0.74)	

European Cancer Congress Plenary (2013)
The Lancet 387, 1066–1074 (2016)

Trial drug discontinuation *(2013)*

	Arm A Chemotherapy with placebo	Arm C Concurrent + maintenance cediranib
Overall	**115**	**158**
Discontinued due to		
Toxicity	12%	39%
Progression/death	78%	44%
Other	4%	9%
Chemotherapy phase	**115**	**158**
Discontinued due to		
Toxicity	7%	27%
Progression/death	14%	4%
Other	3%	8%
Maintenance phase	**85**	**95**
Discontinued due to		
Toxicity	5%	20%
Progression/death	87%	67%
Other	2%	4%

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Diarrhoea
Hypertension
Hypothyroidism
Voice Changes

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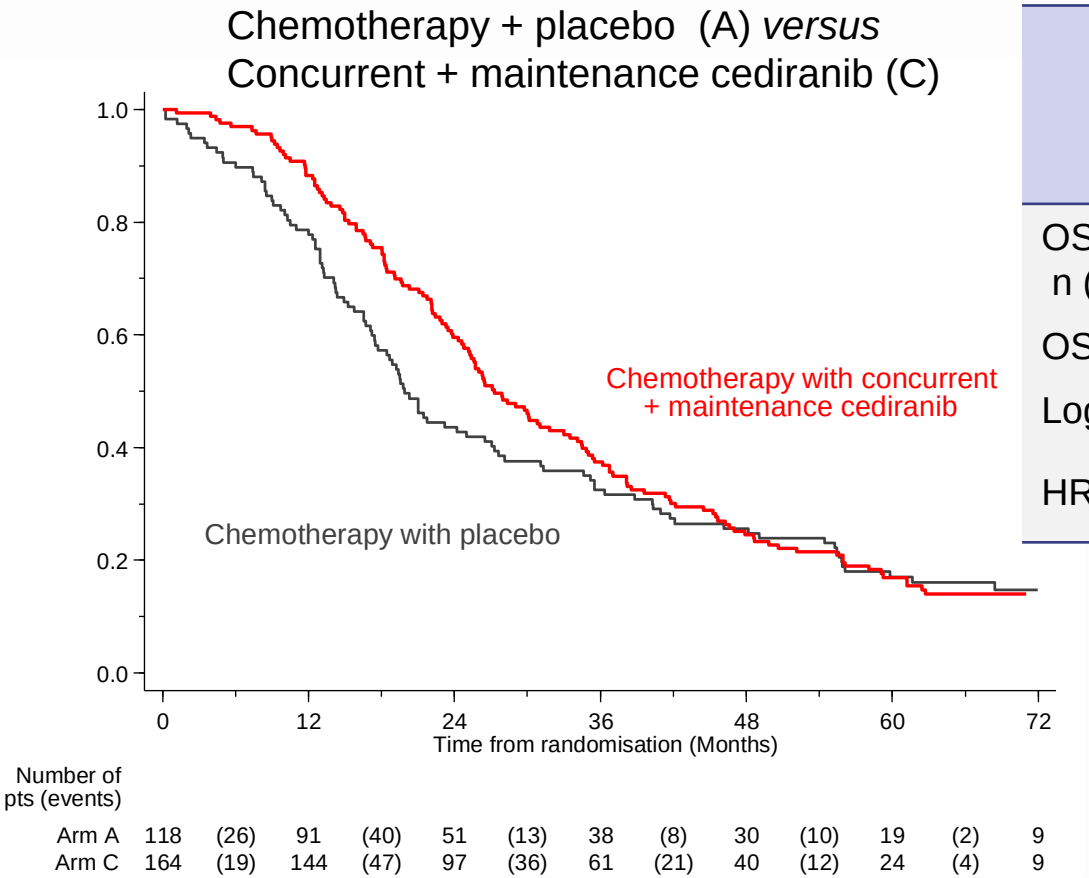
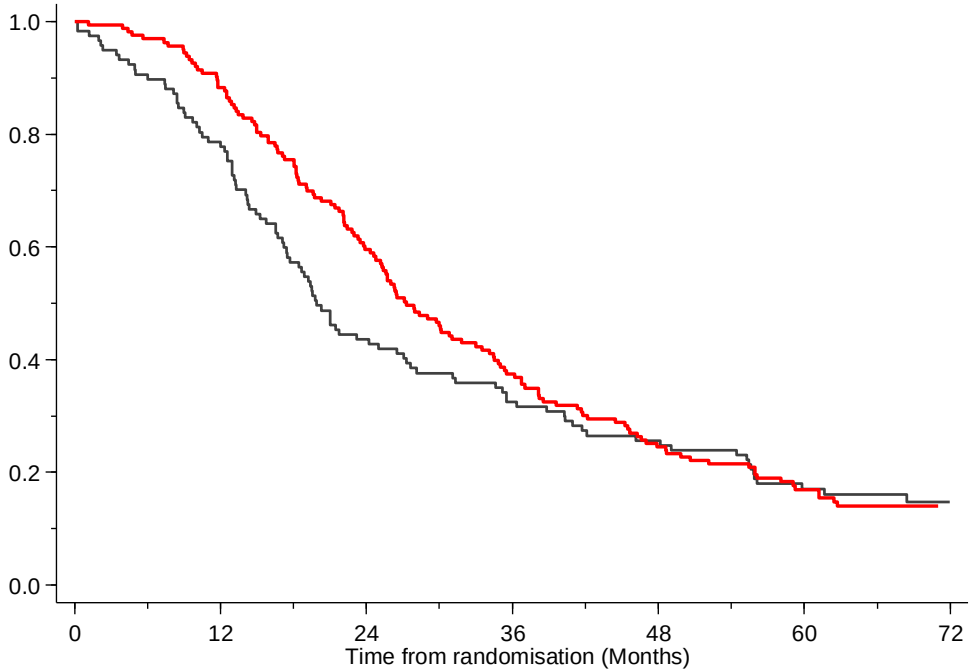
OS results *(2017)*



	Chemo + Placebo (A)	Concurrent + maintenance cediranib (C)
OS events, n (%)	102/118 (86)	140/16 (85)
OS median, mths	19.9	27.3
Log-rank test	*p*= 0.21	
HR (95% CI)	0.85 (95% CI: 0.66-1.10)	

OS results *(2017)*



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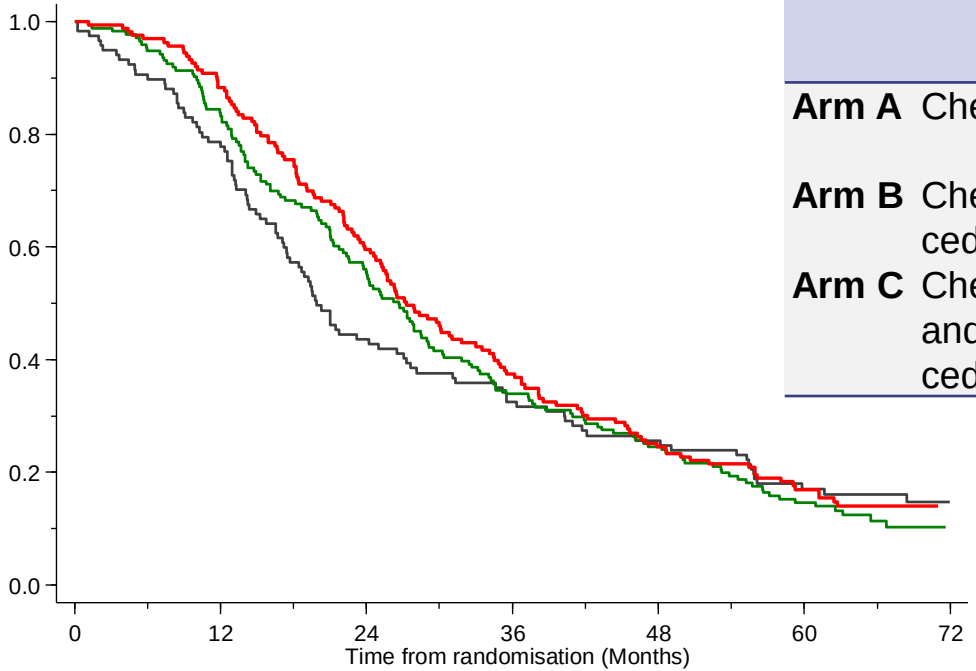

		Events (%)		Median survival (mths)
Arm A	Chemo + placebo	102/118	86%	19.9
Arm B	Chemo + concurrent cediranib	152/174	88%	26.6
Arm C	Chemo + concurrent and maintenance cediranib	140/164	85%	27.3

Updated OS results *(2017)*

- Pre-specified in analysis to assess the proportionality of the hazard ratio of survival curves – the underlying assumption behind common survival analysis techniques
- If the Grambsch-Thernau test was significant a Restricted Mean Survival Time would be used to describe the size of the treatment effect

	Chemo + Placebo (A)	**Concurrent + maintenance cediranib (C)**
Cox HR (95% CI)	0.85 (0.66-1.10)	
OS median (months)	19.9 (17.4-26.5)	27.3 (24.8- 33.0)

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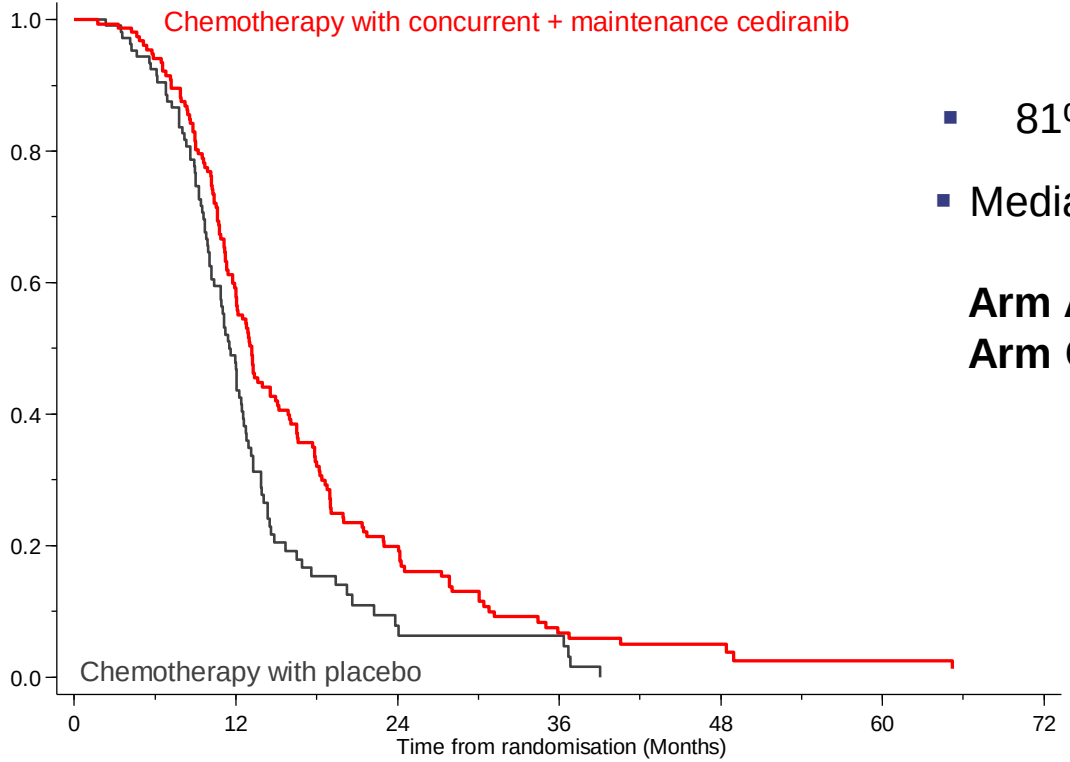
	Chemo + Placebo (A)	**Concurrent + maintenance cediranib (C)**
Cox HR (95% CI)	0.85 (0.66-1.10)	
OS median (months)	19.9 (17.4-26.5)	27.3 (24.8- 33.0)
Test for non-proportionality	*P=0.0029*	
Restricted mean survival time (months)	29.4	34.2
RMST difference (months) over 6 years (95% CI)	4.8 (-0.1-9.8)	

Post-progression treatment *(2017)*

Chemotherapy + placebo (A) *versus* Concurrent + maintenance cediranib (C)



- 81% patients had a 3rd line of treatment
- Median time to next line of treatment (95% CI):

Arm A: 10.7 months (10.4—12.4)
Arm C: 13.2 months (12.0—14.9)

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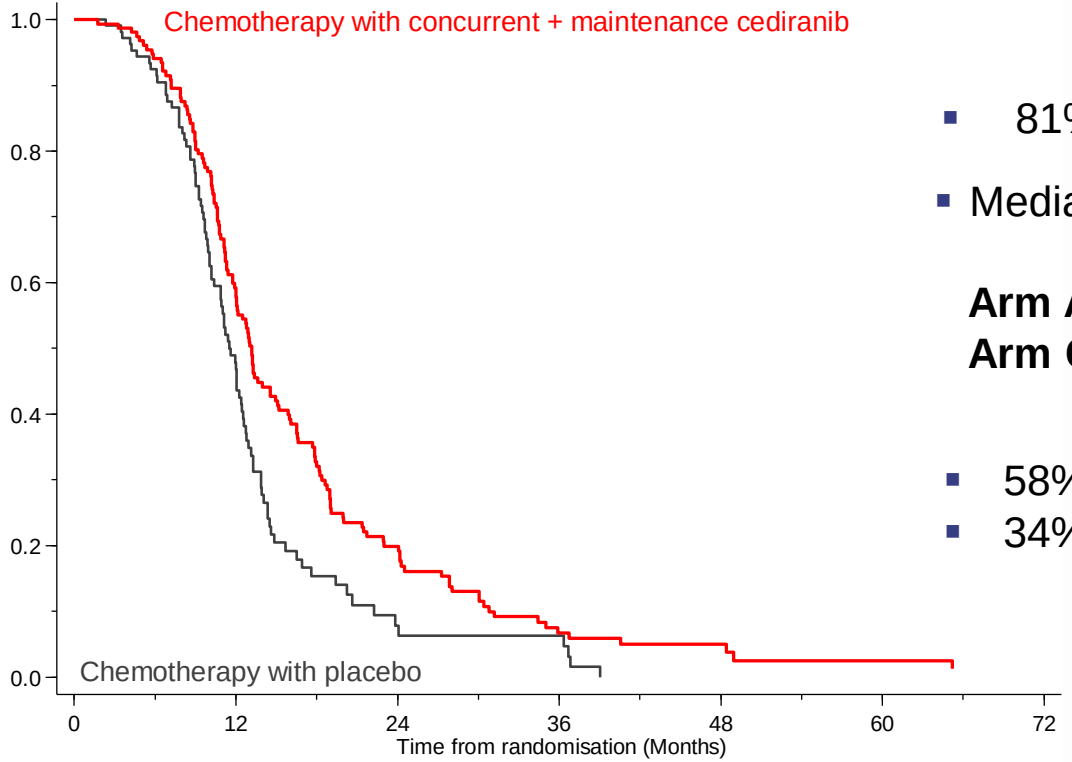

- 81% patients had a 3rd line of treatment
- Median time to next line of treatment (95% CI):

Arm A: 10.7 months (10.4—12.4)
Arm C: 13.2 months (12.0—14.9)

- 58% patients had a 4th line of treatment
- 34% patients had 5 or more lines in total

Overall Survival analyses

	Primary *(Apr 2013)*	Interim *(Nov 2014)*	OS *(Jan 2017)*
Purpose	*The Lancet* publication ▪ PFS primary ▪ OS secondary	*EMA* requested Not published	Long-term OS analysis

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Deaths	52%	73%	86%

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Purpose	*The Lancet* publication ▪ PFS primary ▪ OS secondary	*EMA* requested Not published	Long-term OS analysis
Deaths	52%	73%	86%
HR (CI)	0.77 (0.55—1.07)	0.84 (0.63—1.11)	0.85 (0.66—1.10)

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Median survival	Arm A 21.0 months Arm C 26.3 months	19.9 months 27.9 months	19.9 months 27.3 months

Time from histological diagnosis to death:
8 month increase in median survival: 43.3 months to 51.3 months with maintenance cediranib

Conclusions

- Clear evidence that cediranib extends PFS and the consistent trend in favour of OS benefit suggests a promising future for cediranib
- Recognised that a revised design of ICON6 was unavoidably underpowered for survival
- Median difference in overall survival at final analysis 7.4 months
- A benefit is seen with chemotherapy and during maintenance, where toxicity is less. The maintenance strategy with cediranib is being explored further in ICON9
    - addition of cediranib to olaparib maintenance following platinum-based therapy for first platinum-sensitive relapse in BRCA mutated and BRCAwt high grade ovarian cancers