Optimal Management of Ovarian cancer- Decisions and options

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SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

Disclosures

Jonathan Ledermann has attended Advisory Boards and given invited lectures for AstraZeneca with remuneration to his institution.

Advisory Boards: Clovis Oncology, Bayer, Oxigene, Merck/MSD,

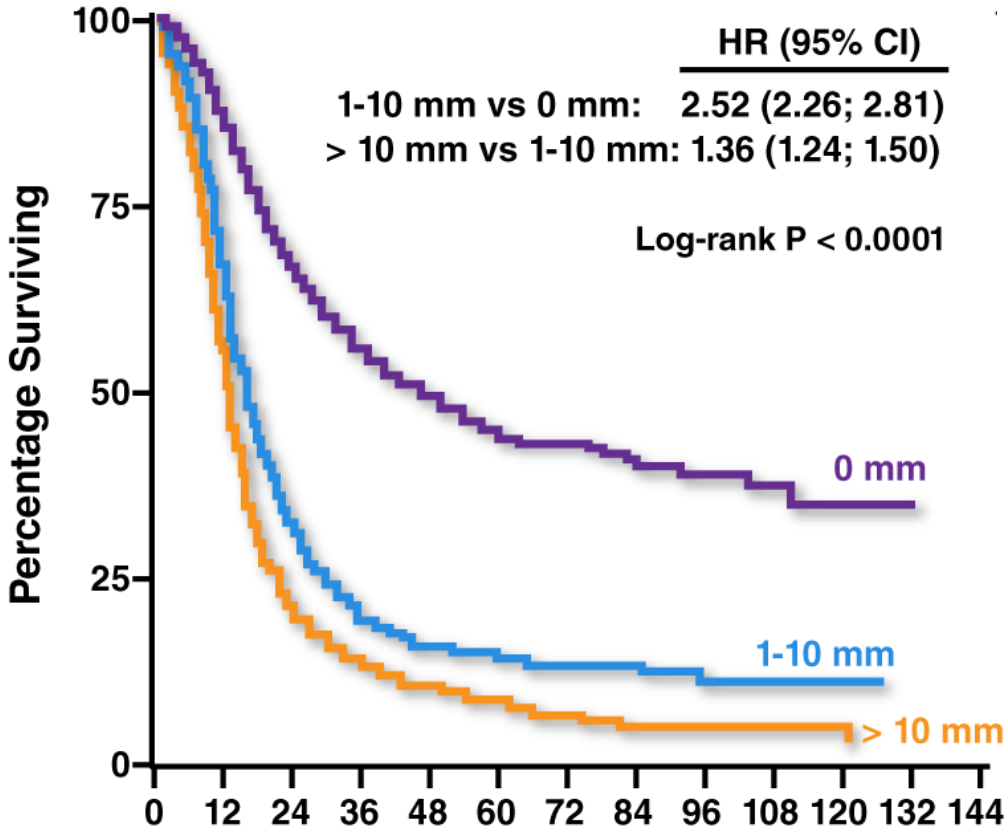
He is the Chief Investigator of Study 19 with olaparib but has not received any financial compensation.

Speaking honoraria Roche

Topics

- Integration of surgery and chemotherapy
- Choices for first line therapy
- Follow-up and re-treatment
- Choices for ‘platinum-sensitive’ recurrence
- BRCA mutation testing - biomarker for treatment
- Challenges for treating ‘platinum-resistant’ disease

Surgery

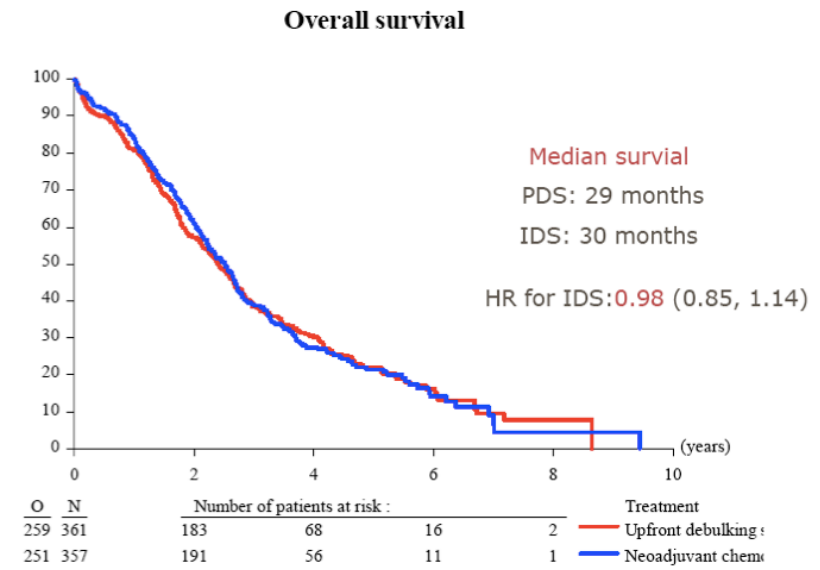


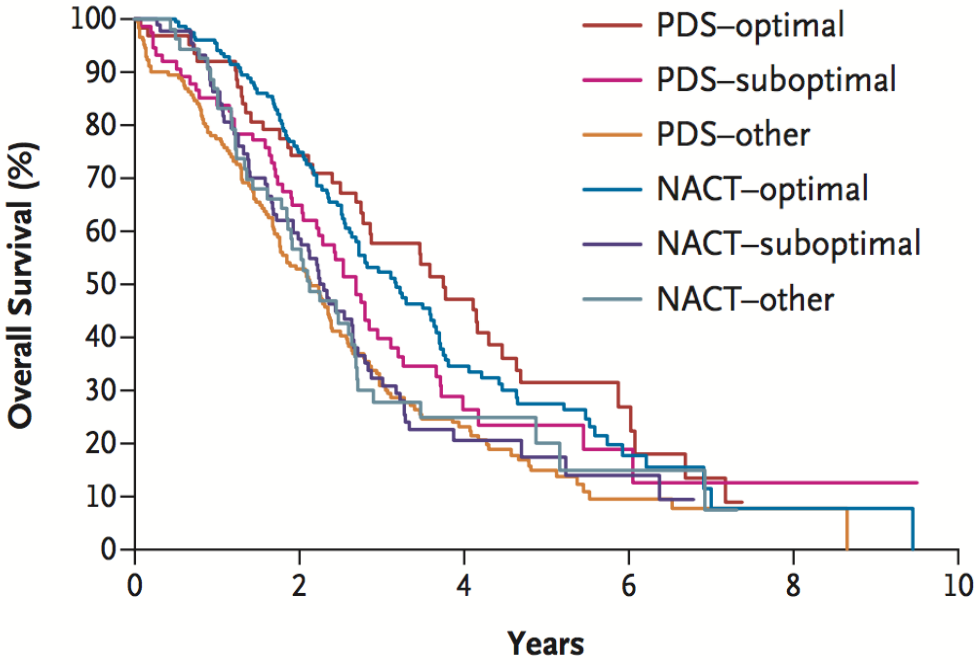
- Complete removal of visible tumour carries prognostic importance
- optimal debulking = no residual disease

No residual disease v < 1 cm
HR 2.20 (95% CI 1.90-2.54)
Cochrane meta-analysis. Elattar et al 2011

du Bois A *et al. Cancer* 2009;115:1234–1244

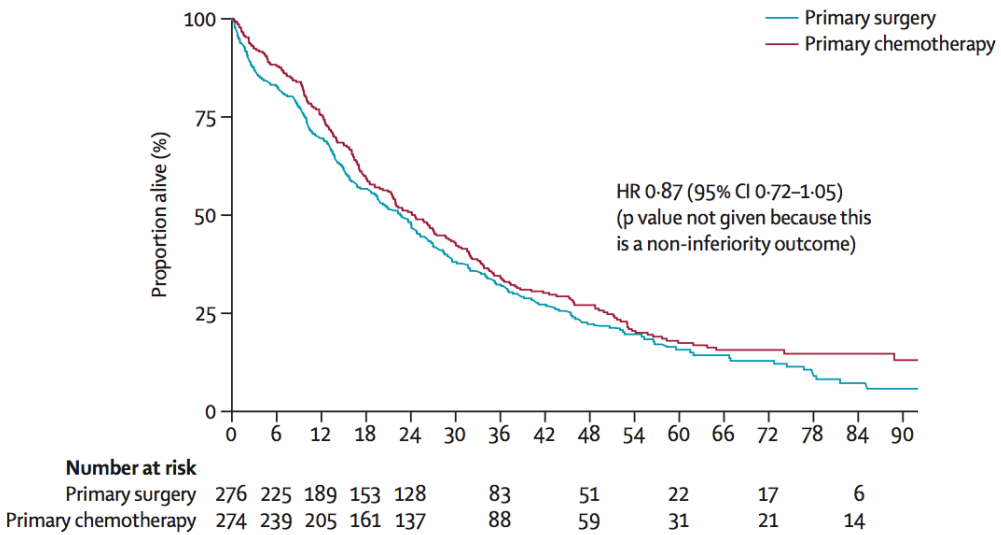
Surgery and ‘neoadjuvant’ (primary) chemotherapy for advanced ovarian cancer





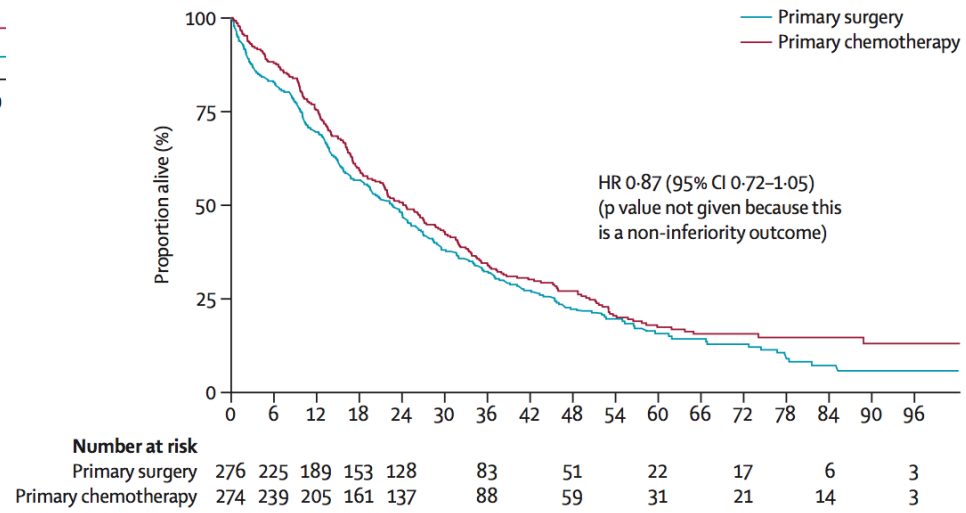
Vergote *et al* 363: 943–53 N Engl J Med 2010

Primary chemotherapy *versus* primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial



N= 550

Kehoe et al Lancet Oncol 2015 386: 249-57

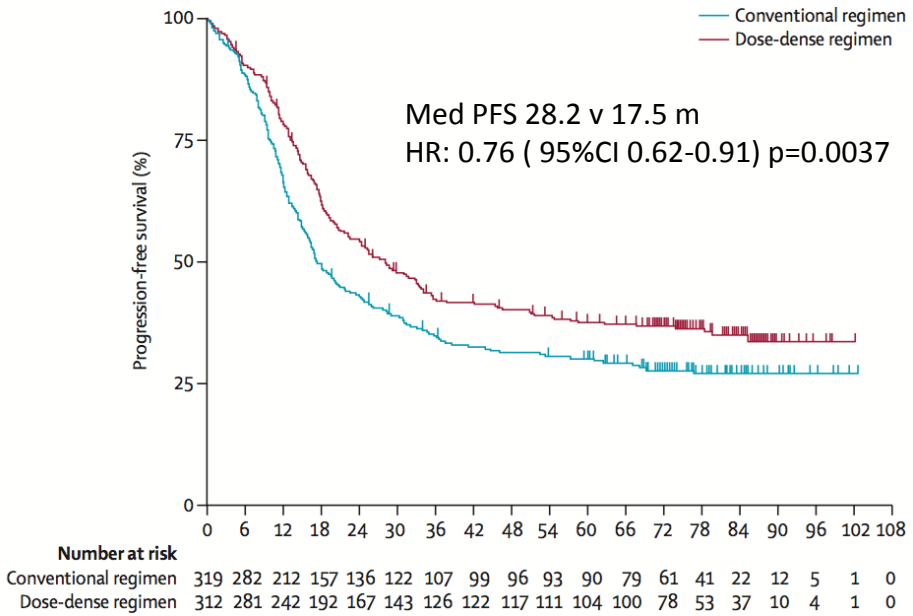


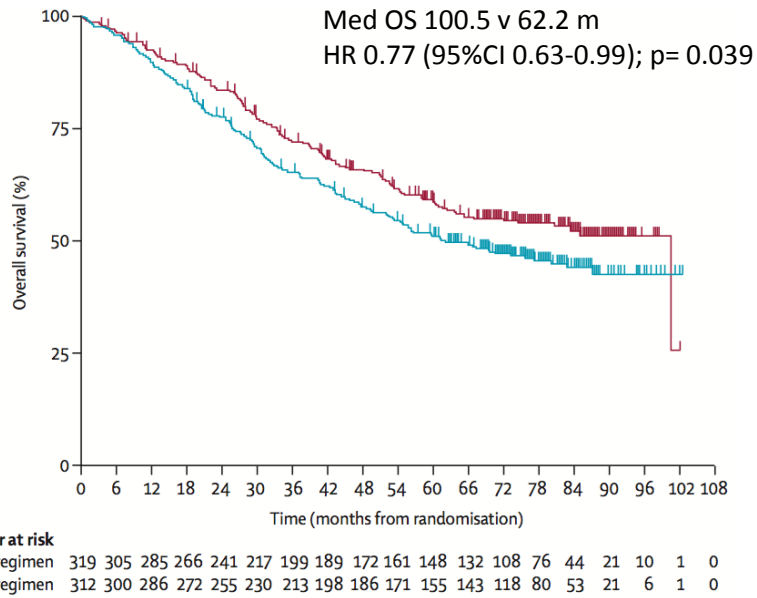
Conclusions

- Surgical debulking has a key role in the management of first line disease- and extent of surgery is prognostic
- For advanced cases- 'borderline operable' neoadjuvant chemotherapy is equivalent to primary surgery
- But PFS and OS results are consistently lower than in trials where primary surgery was performed
- Extrapolation of results to all patients with advanced disease should be made with caution
- Trials of 'radical surgery' – primary or neoadjuvant in specialised surgical centres is being planned

First-line therapy: Is three weekly carboplatin and paclitaxel still the standard of care?

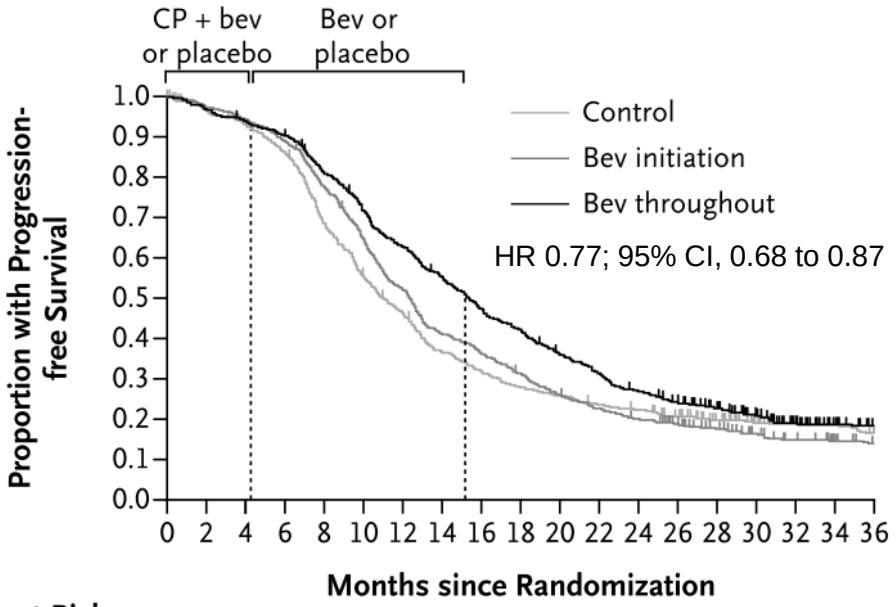
Carboplatin + 3 weekly paclitaxel versus Carboplatin and weekly paclitaxel





Katsumata et al Lancet Oncol 2013 14: 1020-26

Incorporation of bevacizumab into first line therapy



No. at Risk							
Control	625	535	283	169	133	78	49
Bev initiation	625	552	319	190	121	67	40
Bev through-out	623	559	386	256	162	97	56

Burger et al N Engl J Med (2011) 365:2473-83

GOG 218

3-arm trial adding bevacizumab 15 mg/kg to standard carboplatin/paclitaxel continuing for up to 15 months maintenance

PFS Benefit but not OS

Licence by EMA (not FDA)

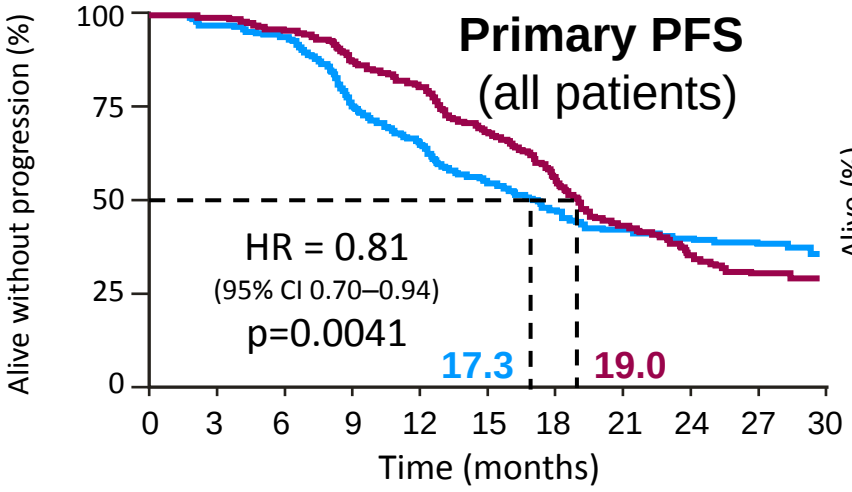
ICON 7

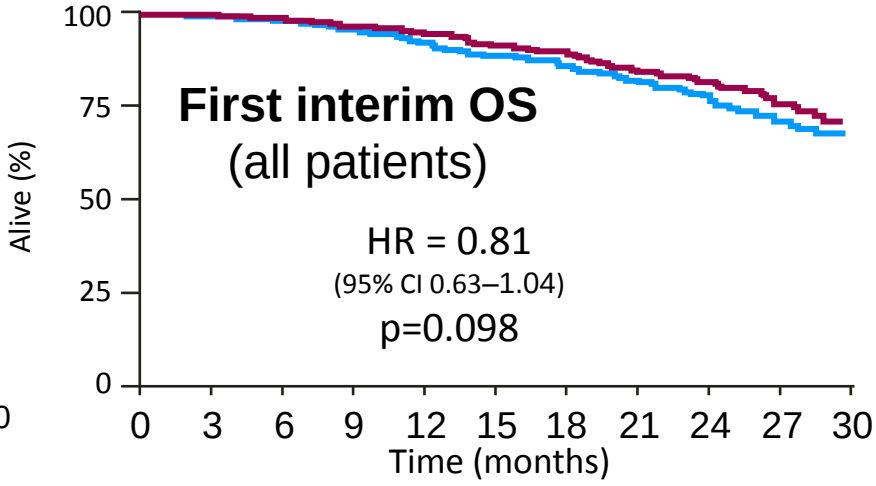
2 arm trial-

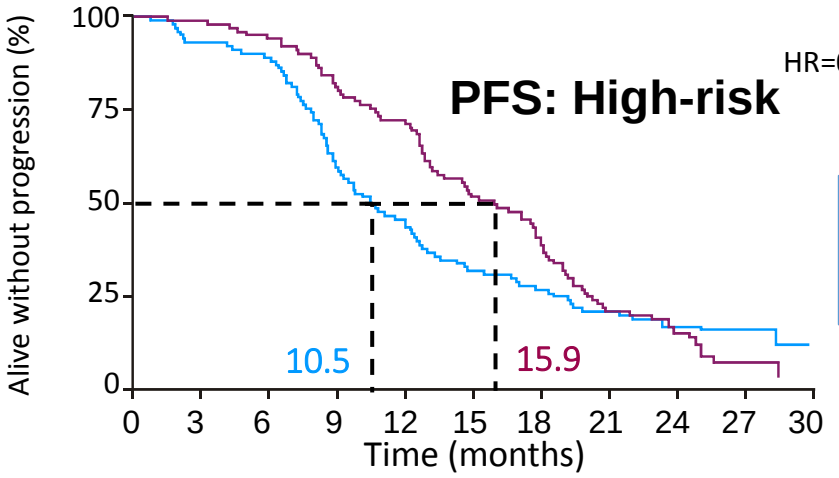
Bevacizumab 7.5 mg/kg 12 month maintenance

PFS outcome similar

ICON 7 Initial results





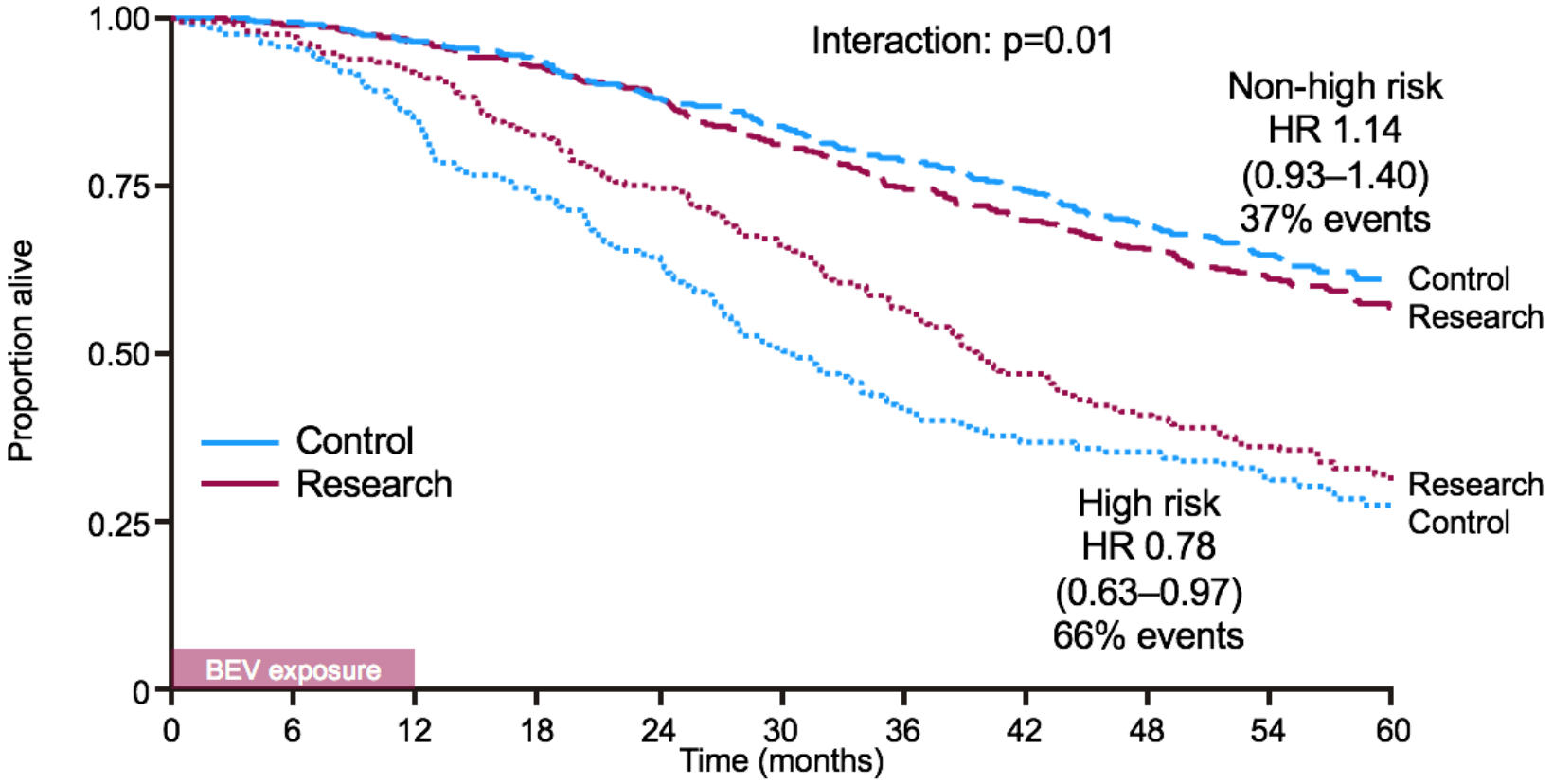


HR=0.73 (0.60–0.93);
P=0.002

Suboptimal stage III > 1 cm residual
Stage IV

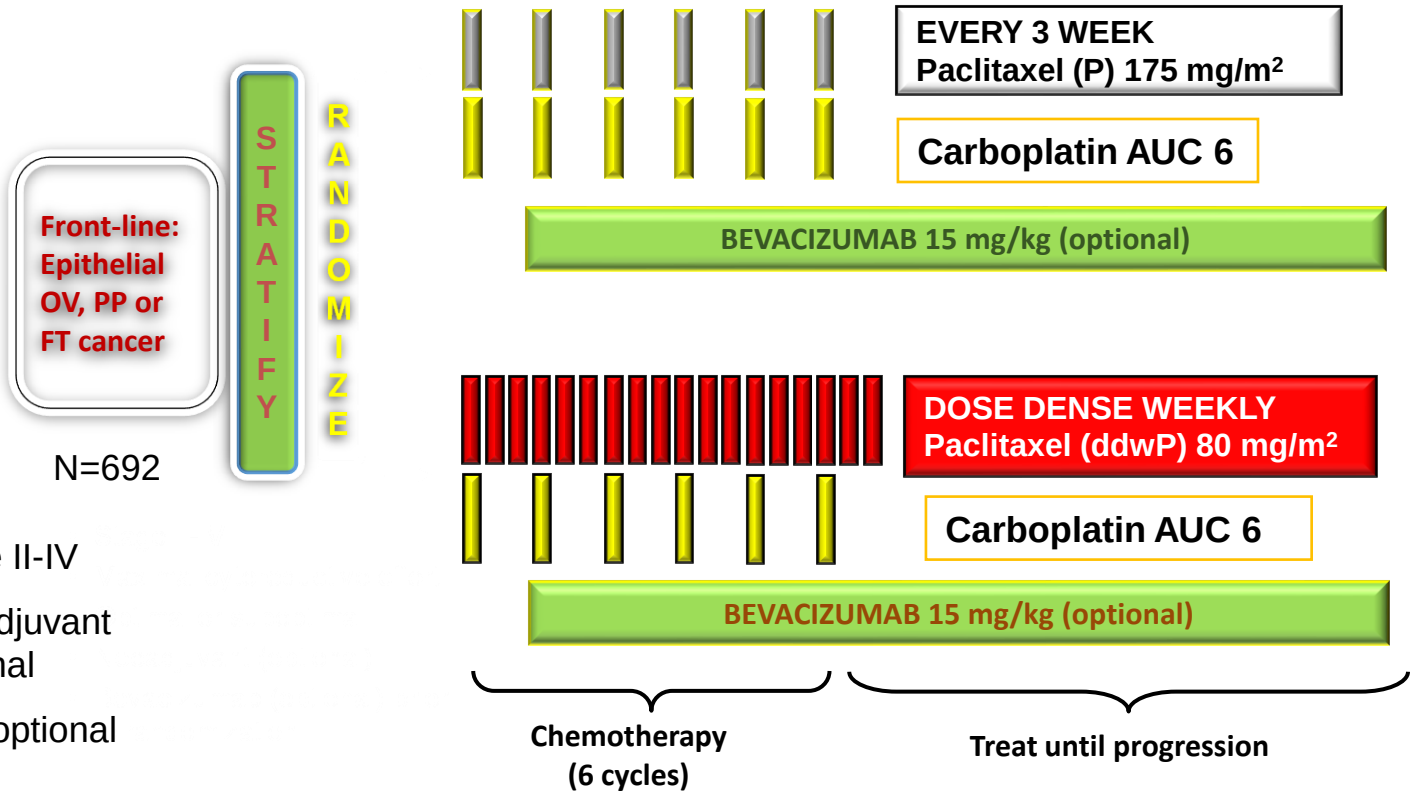
Perren TJ, et al. NEJM 2011

ICON 7 Final Overall Survival by Risk Group



Oza, ECC 2013, Lancet Oncology 2015

Dose-dense chemotherapy and bevacizumab: GOG 262 Schema



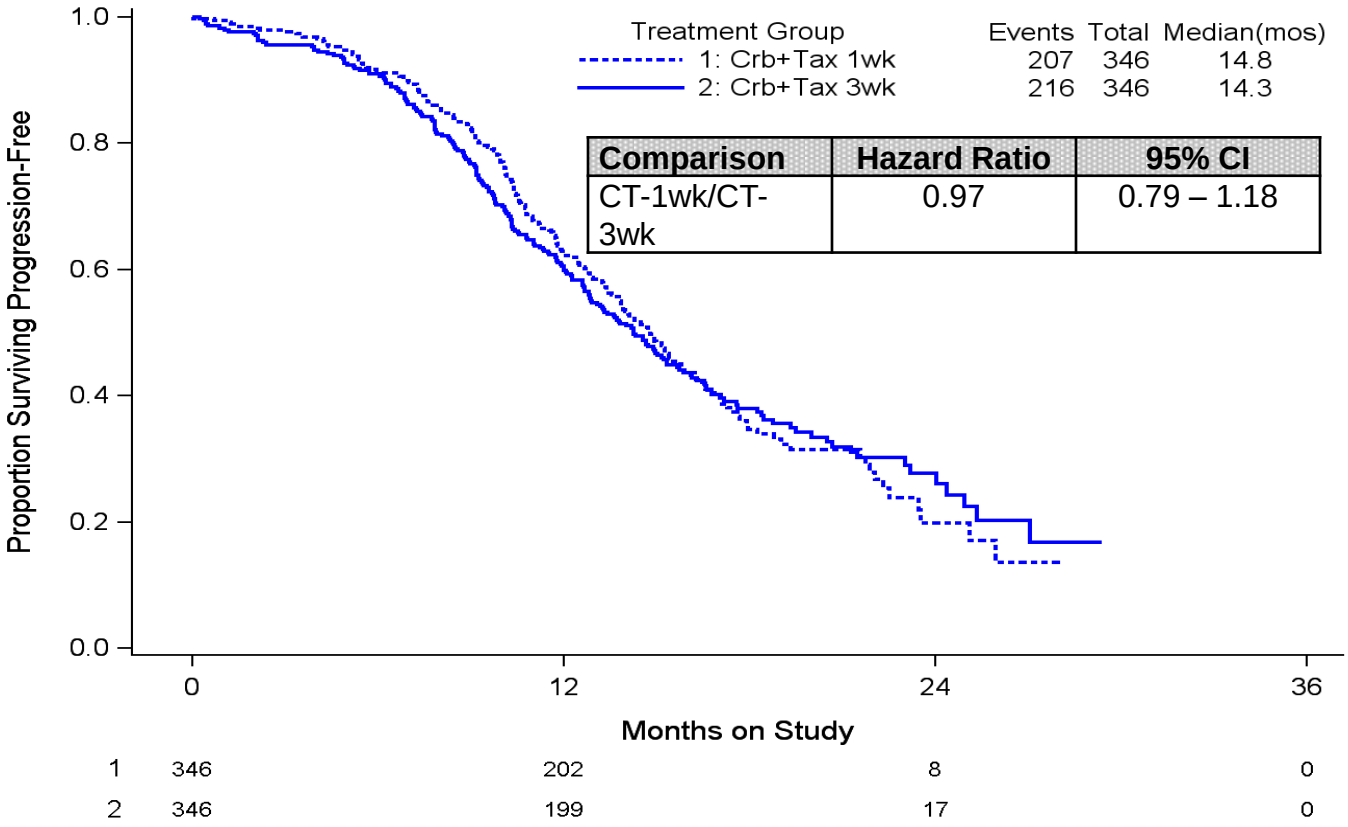
Stage II-IV

Neoadjuvant optional

BEV optional

Chan et al ESGO 2013

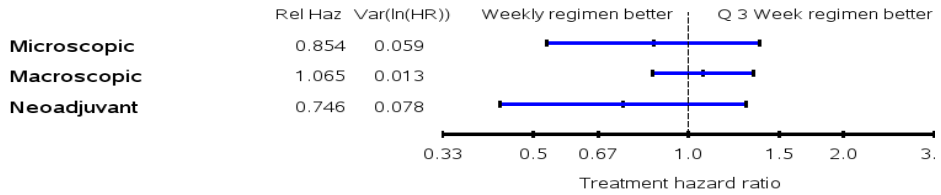
GOG 262: Progression-free survival

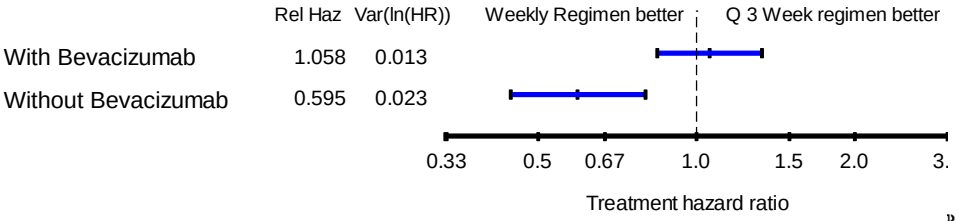


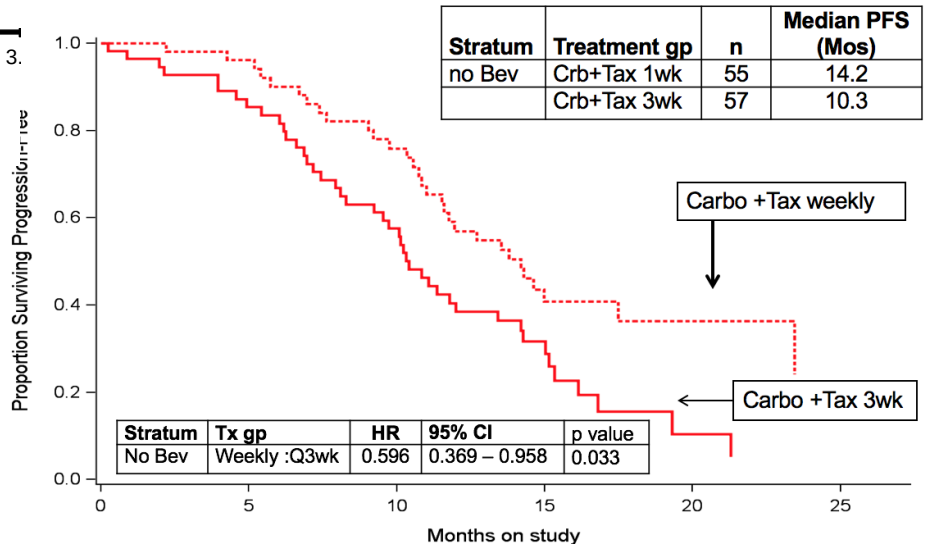
Includes 13 % with neoadjuvant chemotherapy

Chan et al ESGO 2013

GOG 262: subgroup analyses







Chan et al ESGO 2013

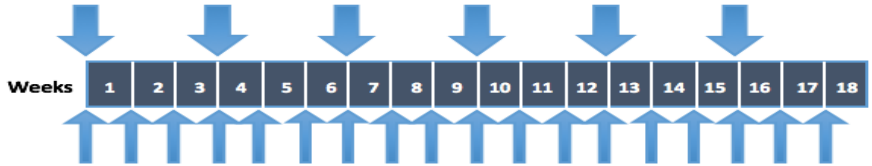
MITO-7 Dose-dense paclitaxel

Random

1:1

Control arm

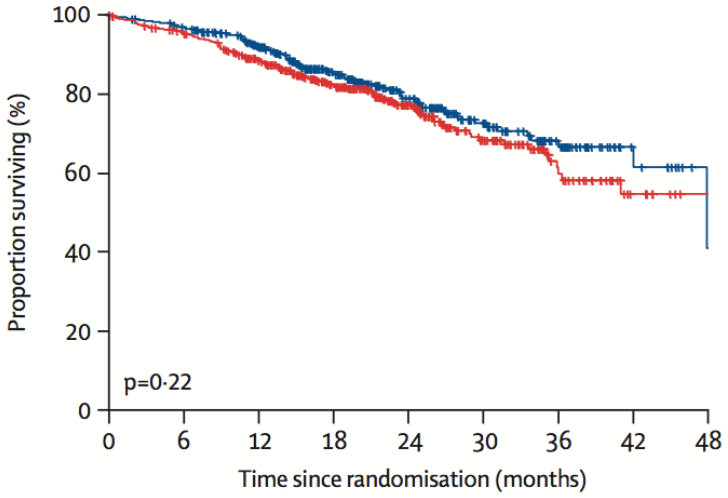
Carboplatin AUC 6, d1 q21
Paclitaxel 175 mg/m², d1 q21
Treatment repeated for 6 cycles



Experimental arm

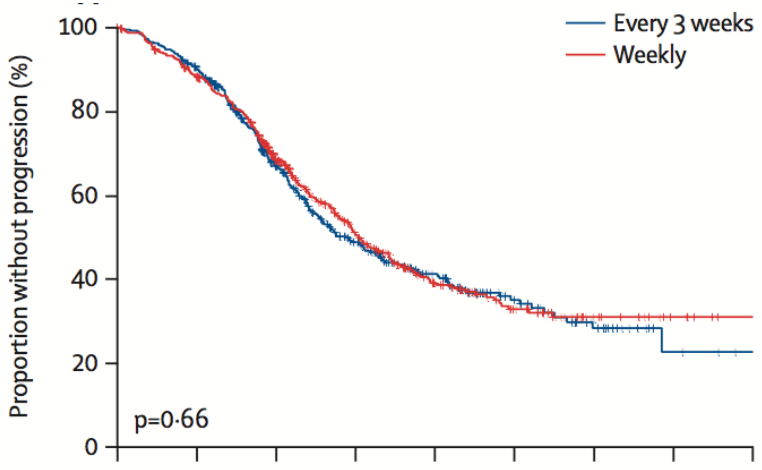
Carboplatin AUC 2, d1, 8, 15 q21
Paclitaxel 60 mg/m², d1, 8, 15 q21
Treatment repeated for 6 cycles

810 patients



Number at risk

Every 3 weeks	404	383	328	231	142	80	43	13	2
Weekly	406	377	323	231	140	80	38	12	4



Number at risk

Every 3 weeks	404	357	240	142	82	39	20	4	1
Weekly	406	352	255	151	80	43	20	9	3

Pignata et al Lancet Oncol 2014

ICON8 trials programme, revised design

ICON8

N=1485

Diagnosis of Stage IC-IV EOC/PPC/FTC

Randomise 1:1:1

- Arm A1 6 cycles
- Arm A2 6 cycles
- Arm A3 6 cycles

Arm 1	Carboplatin AUC 5	q3w
	Paclitaxel 175mg/m^2	q3w
Arm 2	Carboplatin AUC 5	q3w
	Paclitaxel 80mg/m^2	q1w
Arm 3	Carboplatin AUC 2	q1w
	Paclitaxel 80mg/m^2	q1w

ICON8B

N=1170

Diagnosis of Stage III-IV EOC/PPC/FTC with >1cm residual disease after surgery or planned for neoadjuvant chemotherapy

Randomise 1:1:1

- Arm B1 6 cycles
- Arm B2 6 cycles
- Arm B3 6 cycles

Complete 18 cycles Bevacizumab

Arm B1	Carboplatin AUC 5	q3w
	Paclitaxel 175mg/m^2	q3w
	Bevacizumab 7.5mg/kg	q3w
Arm B2	Carboplatin AUC 5	q3w
	Paclitaxel 80mg/m^2	q1w
Arm B3	Carboplatin AUC 5	q3w
	Paclitaxel 80mg/m^2	q1w
	Bevacizumab 7.5mg/kg	q3w

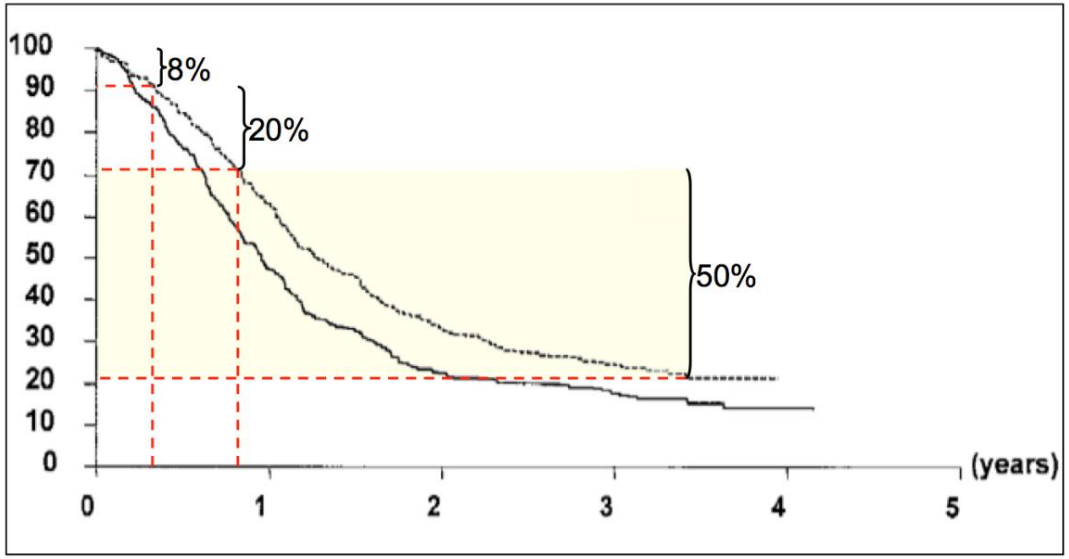
NB. Patients with Stage III & residual disease after surgery or who are planned to receive neoadjuvant chemothererapy OR any patients with stage IV disease are still eligible for ICON8A as well as B so that they may still enter the trial if:

they have contra-indications to or decline bevacizumab
their site does not have access to bev, e.g. in Australia

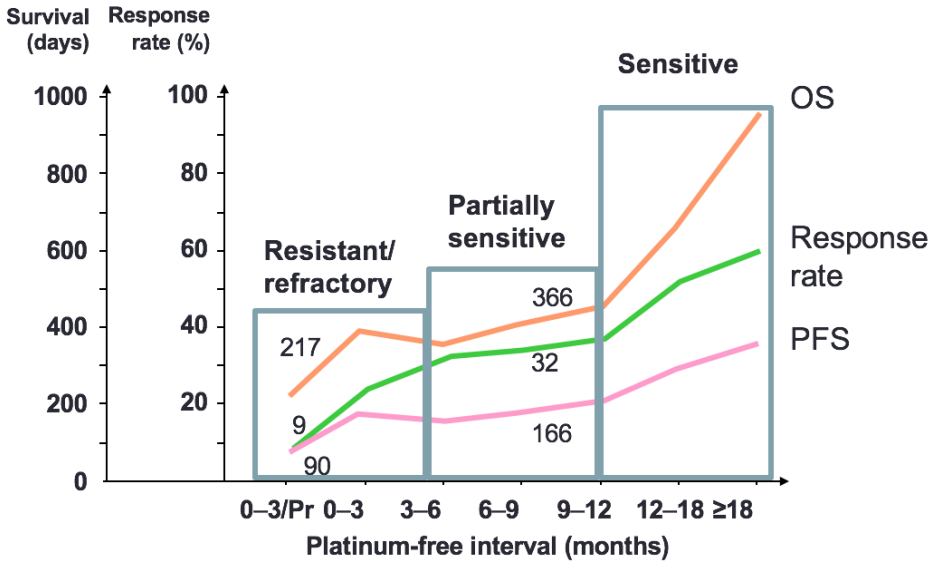
Conclusions for first-line therapy

- Neoadjuvant chemotherapy an acceptable alternative if complete resection of tumour is not possible
  - *Does it replace less good surgery, or is it equivalent only in advanced/inoperable disease?*
- Carboplatin/paclitaxel remains the standard of care
- Addition of bevacizumab an option
  - *Should it be given to all patients with advanced disease or only those in a poor prognostic group?*
- Weekly paclitaxel may be better, or at least as good
  - *Is there an interaction with bevacizumab?*

Recurrent Ovarian Cancer and 'platinum-sensitivity'



Patterns of Relapse:
'Platinum-sensitive' and 'Platinum-resistant' ovarian cancer



Friedlander et al Int J Gyn Cancer 2011

Pujade-Lauraine E, *et al. J Clin Oncol* 2002;21(May 20 Suppl):Abstract 829 and presentation

Does surgical cytoreduction improve survival of patients with 'platinum-sensitive' recurrence?

AGO-OVAR DESKTOP III (Protocol AGO - OVAR OP.4- GCIG study)

Surgery - Randomisation

Platinum-based chemotherapy

+ve AGO score

- ECOG PS = 0
- Complete initial debulking
- <500ml ascites

GOG 213

Surgery - Randomisation

Carboplatin/paclitaxel +/- bevacizumab

Chemotherapy for 'platinum-sensitive' relapse

- **Timing of treatment**
  - OV05/EORTC 55959 showed no survival benefit in offering second-line therapy on the basis of a raised CA125
  - Delay chemotherapy until clinical symptoms/ or significant radiological progression
- **Single agent platinum versus combination therapy?**
  - PFS increased; meta-analysis shows a survival benefit*

Combination of Carboplatin/Paclitaxel (ICON4), Carboplatin/Gemcitabine (OVAR2.5), Carboplatin/PLD (CALYPSO) are all acceptable combination partners

Choice depends on:

- Balance of toxicities
- Timing from first-line therapy

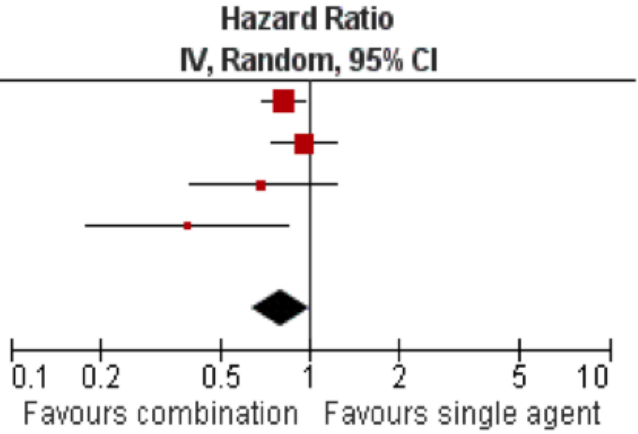
Potential use of drugs for' platinum-resistant' (non-platinum) therapy

* Raja et al Annals Oncol 2014

Meta-analysis of platinum combination therapies

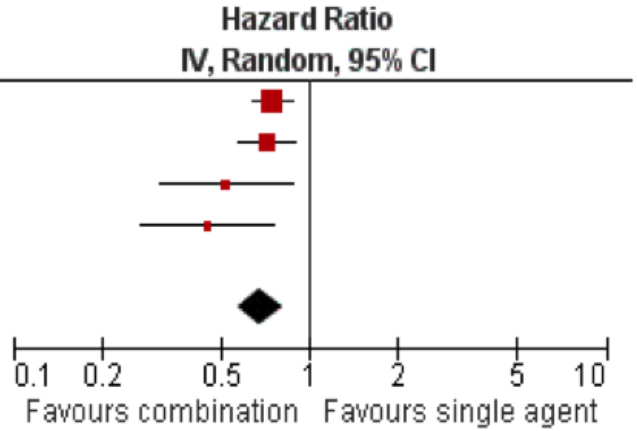
Study	Weight	Hazard Ratio IV, Random, 95% CI
ICON & AGO 2003	44.8%	0.81 [0.69, 0.97]
Pfisterer et al 2006	35.1%	0.96 [0.75, 1.23]
Alberts et al 2007	12.7%	0.69 [0.39, 1.21]
González-Mart. et al 2005	7.5%	0.39 [0.18, 0.84]
Total (95% CI)	**100.0%**	**0.80 [0.64, 1.00]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.44$, df = 3 (P = 0.14); $I^2 = 45\%$
Test for overall effect: Z = 1.96 (P = 0.05)



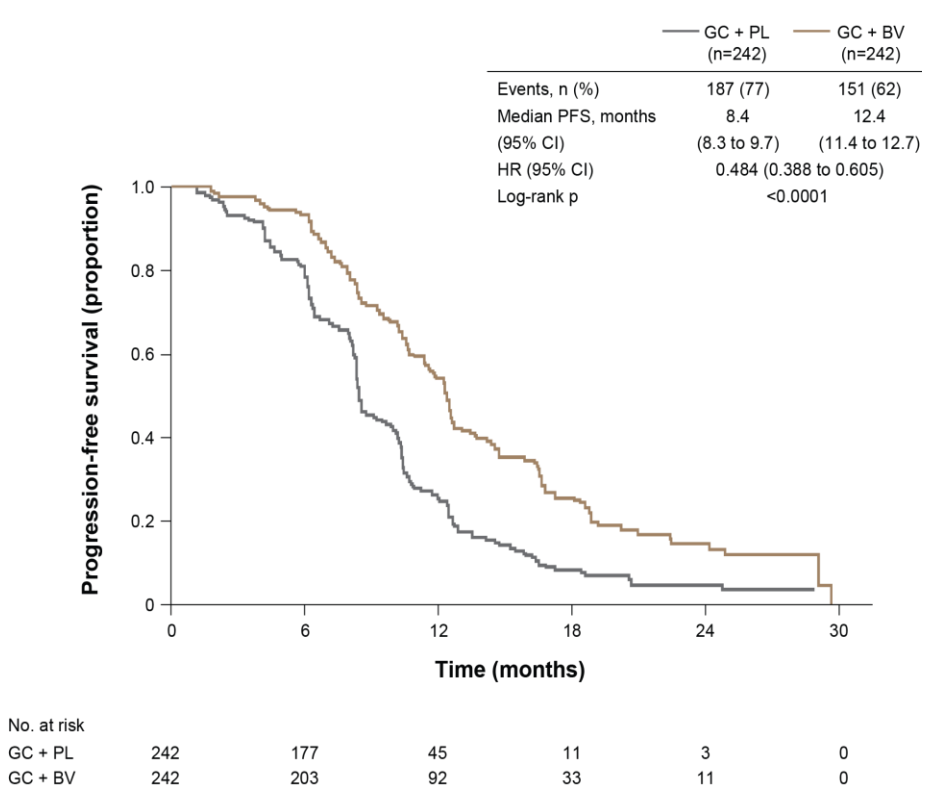
Study	Weight	Hazard Ratio IV, Random, 95% CI
ICON & AGO 2003	46.9%	0.75 [0.65, 0.87]
Pfisterer et al 2006	33.7%	0.72 [0.58, 0.90]
Alberts et al 2007	9.6%	0.52 [0.31, 0.88]
González-Mart. et al 2005	9.8%	0.45 [0.27, 0.76]
Total (95% CI)	**100.0%**	**0.68 [0.57, 0.81]**

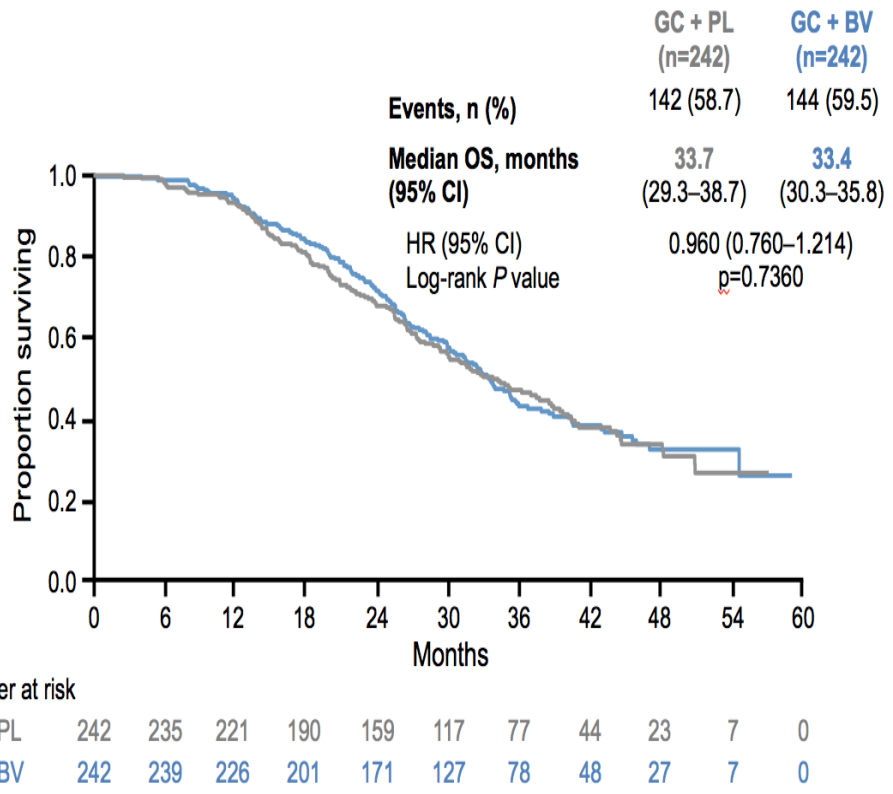
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.70$, df = 3 (P = 0.19); $I^2 = 36\%$
Test for overall effect: Z = 4.30 (P < 0.0001)



Raja et al Ann Oncol 2013

Addition of anti-angiogenic therapy for the treatment of relapsed ovarian cancer- 'platinum sensitive' group





Aghajanian C, et al. *J Clin Oncol.* 2012;30(17):2039-2045

Aghajanian C, et al. *Ann Oncol.* 2014;25(Suppl4): Abstract 967O

Anti-angiogenic agents in 'platinum-sensitive' relapsed ovarian cancer

	Platinum Sensitive			Platinum-resistant (< 6 month PFI) and Partially Platinum-sensitive equally divided
	OCEANS (n= 484)	**GOG213 (n=674)**	**ICON6 N= 456)**	**TRINOVA-1***
	Carboplatin/ gemcitabine ± **bevacizumab**	Carboplatin/ paclitaxel ± **bevacizumab**	Platinum-based ± **cediranib**	Weekly paclitaxel ± **trebananib**
PFS (med. months)	**8.4 v 12.4**	**10.4 v 13.8**	**8.7 v 11.1**	**7.2 v 5.4**
HR	**0.484 (p<0.0001)**	**0.61 (p<0.0001)**	**0.57 (p=0.00001)**	**0.66 (p < 0.0001)**

Pazopanib and Cediranib: Oral VEGF receptor tyrosine kinase inhibitors
Trebananib (AMG386): Peptibody inhibiting angiopoeitin 2

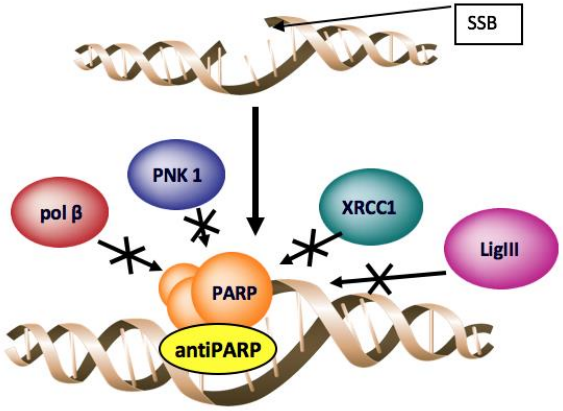
* Non maintenance therapy

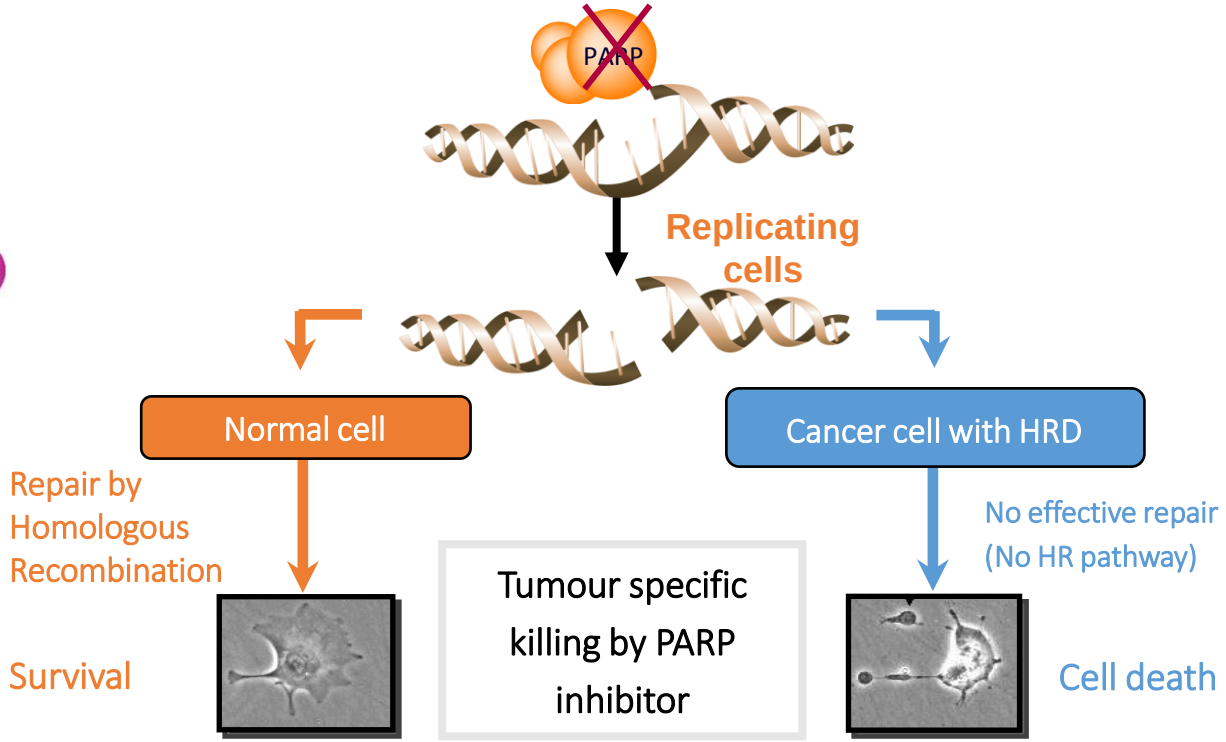
Which to chose and when ?

(OCEANS) Aghajanian et al JCO 2011; (GOG 213) Coleman et al SGO 2015; (ICON6) Ledermann et al ECC (2013); (TRINOVA-1) Monk et al Lancet Oncol 2014; (AURELIA) Pujade-Lauraine et al JCO 2014; (MITO11) Pignata et al Lancet Oncol 2015

PARP Inhibitors and homologous recombination repair of DNA

- PARP is a key regulator of DNA damage repair processes
- Involved in DNA base-excision repair (BER)
- Binds directly to DNA damage
- Produces large branched chains of poly(ADP-ribose)
- Attracts and assists BER repair effectors



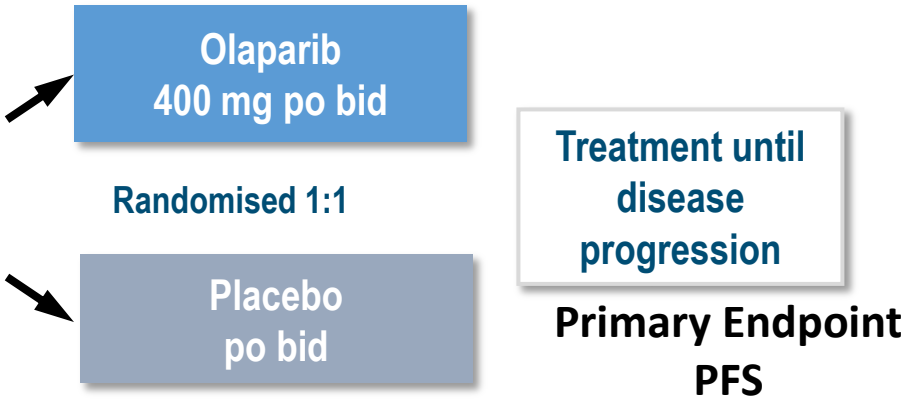


Olaparib maintenance in relapsed ovarian cancer - 'STUDY 19'

- Assess the efficacy of olaparib as a maintenance treatment in patients with platinum-sensitive, high-grade serous ovarian cancer
- Randomised, double-blind, placebo-controlled Phase II trial

Patient eligibility:

- Platinum-sensitive, high-grade serous ovarian cancer
- ≥2 previous platinum regimens
- Last chemotherapy: platinum based with a maintained response
- Stable CA-125 at trial entry
- Randomisation stratification factors:
  - Time to disease progression on penultimate platinum therapy
  - Objective response to last platinum therapy
  - Ethnic descent



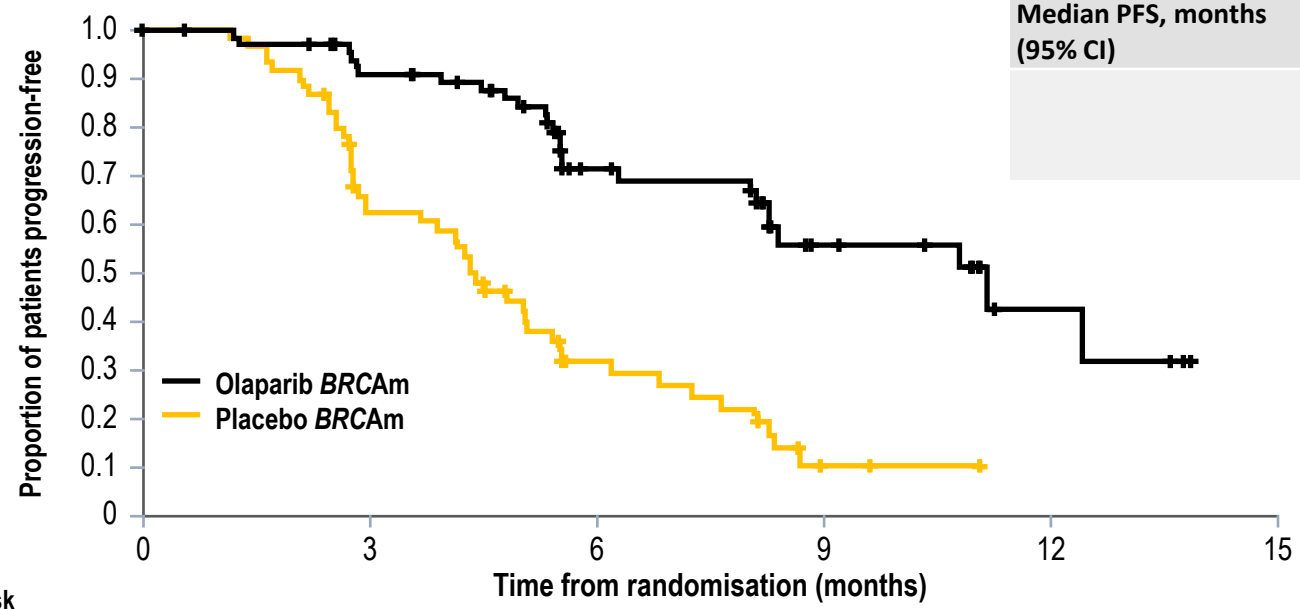
82 sites in 16 countries

ClinicalTrials.gov identifier: NCT00753545
Ledermann J *et al*. *N Engl J Med* 2012;366:1382–1392

265 patients were randomized between September 2008 and February 2010

STUDY 19: Maintenance olaparib in 'platinum-sensitive' BRCA^{mut} high grade serous ovarian cancer

	BRCAm (n=136)	
	Olaparib	Placebo
Events/total patients (%)	26/74 (35%)	46/62 (74%)
Median PFS, months (95% CI)	11.2 (8.3, NC)	4.3 (3.0, 5.4)
	HR=0.18 95% CI: 0.10, 0.31; P<0.0001	



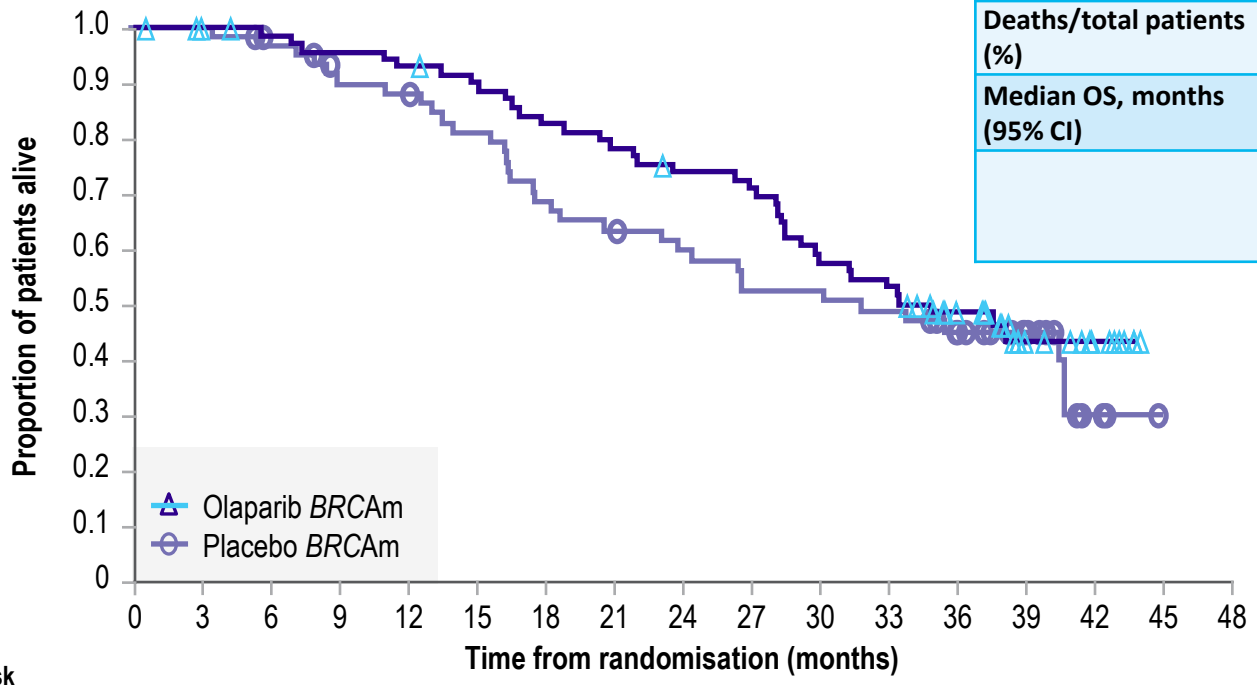
Number at risk						
Olaparib *BRCA*m	74	59	34	15	5	0
Placebo *BRCA*m	62	35	13	2	0	0

NC, not calculable.

Ledermann J et al. Lancet Oncol 2014;15:852–861

Study 19: interim survival in BRCAm population (52% maturity)

	BRCAm (n=136)	
	Olaparib	Placebo
Deaths/total patients (%)	37/74 (50%)	34/62 (55%)
Median OS, months (95% CI)	34.9 (29.2, NC)	31.9 (23.1, 40.7)
	HR=0.73 95% CI: 0.45, 1.17 P=0.19	



Number at risk

Olaparib *BRCA*m	74	71	69	67	65	62	56	53	50	48	39	36	26	12	7	0	0
Placebo *BRCA*m	62	62	58	52	50	46	39	36	33	29	29	27	21	10	4	0	0

Ledermann J et al. Lancet Oncol 2014;15:852–861

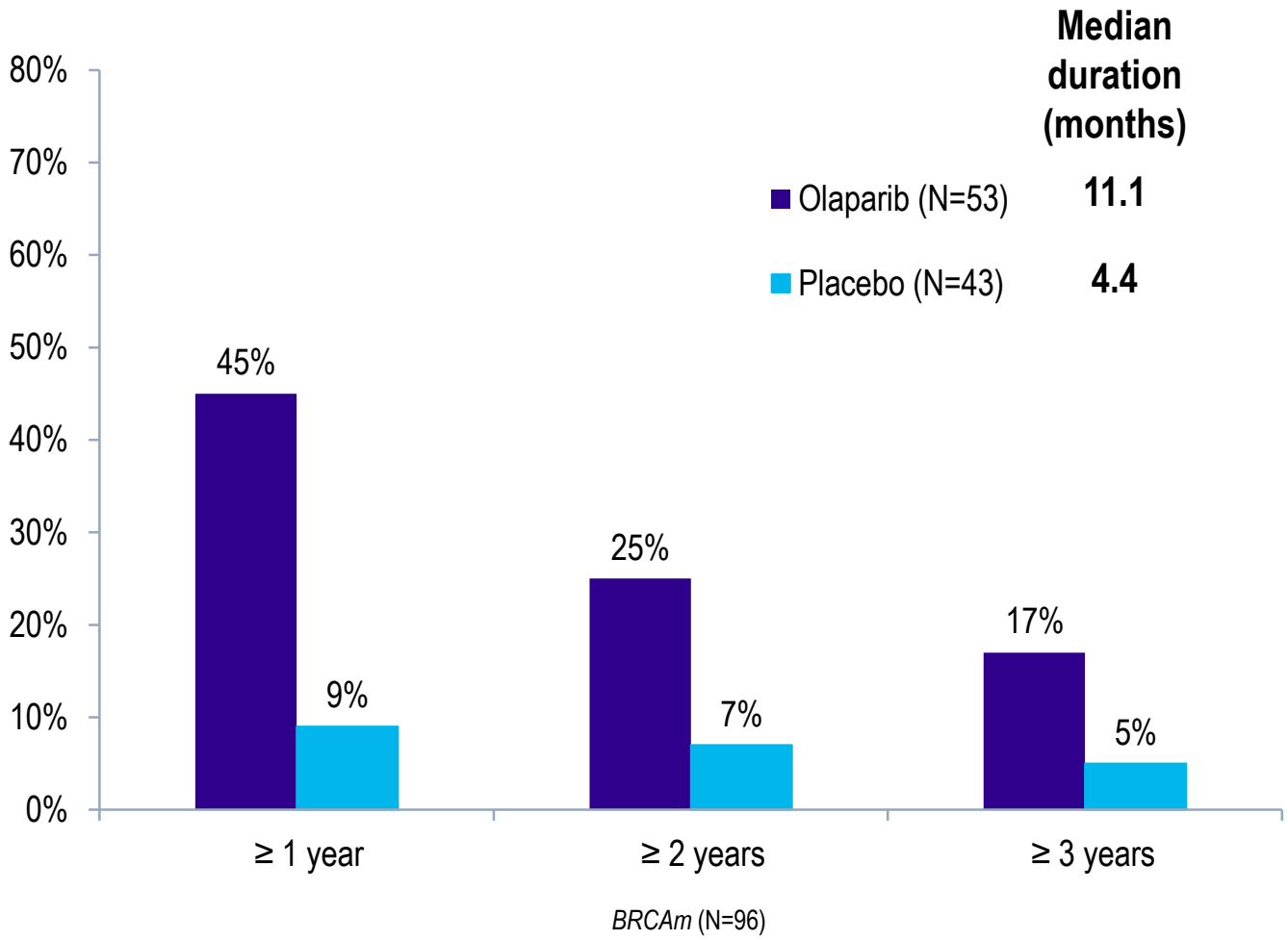
Safety Profile in STUDY 19 (*BRCA*m)

Profile consistent with overall population

	All grades		Grade ≥ 3	
	Olaparib (N=74)	Placebo (N=62)	Olaparib (N=74)	Placebo (N=62)
Nausea	54 (73%)	20 (32%)	* 1 (1%)	0
Fatigue	40 (54%)	23 (37%)	* 5 (7%)	1 (2%)
Vomiting	27 (36%)	5 (8%)	* 2 (3%)	0
Diarrhoea	22 (30%)	12 (19%)	2 (3%)	1 (2%)
Anaemia	19 (26%)	3 (5%)	* 4 (5%)	1 (2%)
Any serious AE	**25 (18.4%)**	**11 (8.6%)**	**16 (21.6%)**	**6 (9.7%)**
AEs leading to dose reductions	34 (25%)	6 (4.7%)	19 (25.7%)	2 (3.2%)
Any AE leading to discontinuation	6 (4.4%)	2 (1.6%)	5 (6.8%)	0

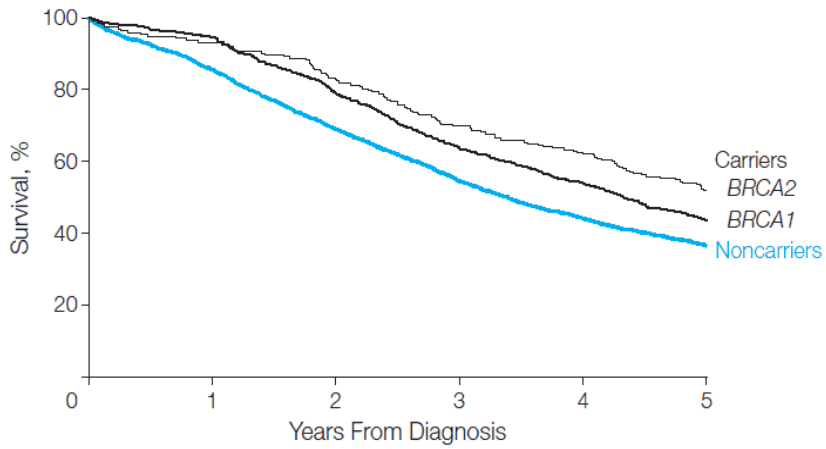
Ledermann J et al. Lancet Oncol 2014;15:852–861

STUDY 19 (*BRCA*m): 25% treated for ≥2 years



Data cut off: 26 November 2012
AstraZeneca data on file

BRCA mutations and HRD – predictive markers for sensitivity to PARP inhibitors- Implications for clinical practice



Noncarriers	1047	1687	1540	1395	1225	1044
BRCA1	327	593	569	490	408	342
BRCA2	117	199	192	179	164	125

Bolton KL, et al. *JAMA* 2012

BRCA-related ovarian cancer

- often responds to multiple rounds of platinum-based therapy
- Survive longer than non-carriers

- Germline BRCA1/2 mutations
  - occur in approx. 1 in 400 women (higher in some ethnic groups eg Ashkenazi Jewish population 1 in 40)
  - approx. 17 % high-grade tumours; 6-8% tumours have somatic BRCA mutations
  - Most commonly in HGSOC- less common in endometrioid or clear cell
  - family history of cancer absent in 30% of BRCA ovarian cancer
  - 25% cases of BRCA ovarian cancer diagnosed over 60 years old
- **Testing for BRCA mutations now needs to be part of routine care of patients with high grade ovarian cancer**

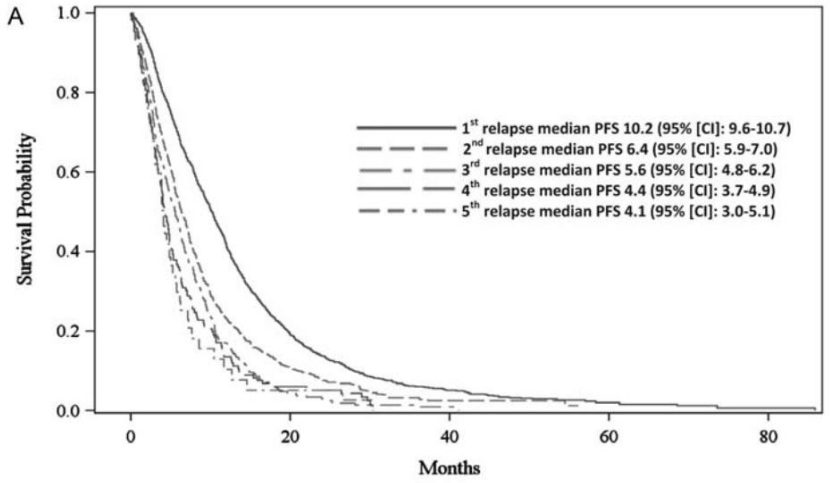
‘Platinum-sensitive’ disease- summary

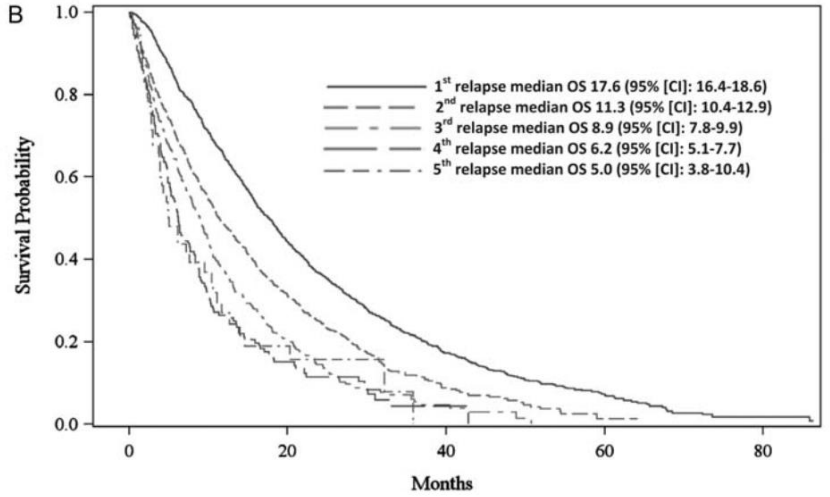
- Role of surgery at relapse remains unproven. Results of trials awaited
- Symptoms, interpretation of imaging and CA125 should guide decisions about re-starting chemotherapy
- Platinum combinations generally recommended
- Choice of platinum partner depends on prior therapy, toxicity profile, patient choice and future treatment plans
- Knowledge of BRCA mutation status prior to starting 2nd line therapy helps to inform choice between PARP inhibitor or bevacizumab

Challenges in multiply pretreated and 'platinum-resistant' ovarian cancer

- **Platinum-resistance covers a wide range of biology**
  - Persistent disease: little or no response to first-line therapy
  - Good partial or complete response and early relapse
  - Previous multiple lines of treatment
- **Clinical Picture variable**
  - Asymptomatic disease
  - Disease likely to cause organ dysfunction
  - Symptomatic progression or relapse
- **Response rate to chemotherapy generally low**
- **Duration of response short (typically median PFS 3-4 months)**
- **Median survival in clinical trials around 12 months**

Response and outcome to several lines of therapy





1620 patients from
3 randomised trials

PFS

24.5% were re-challenged with platinum at 1st and 2nd relapse

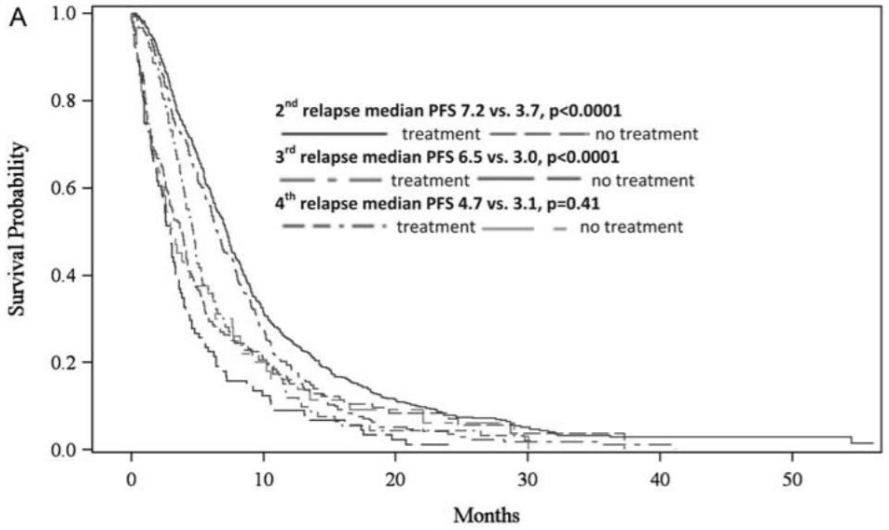
OS

Prognostic factors

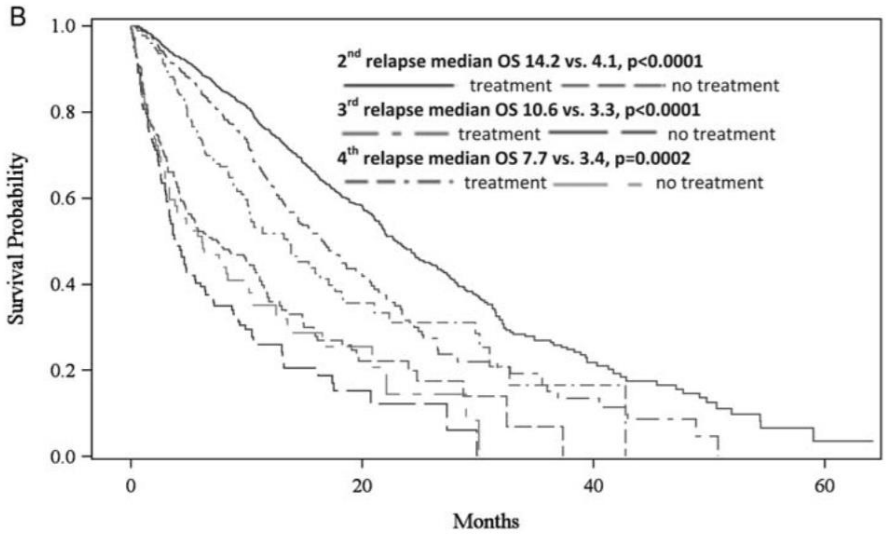
- PFS: **Optimal primary cytoreduction** and **platinum sensitivity**: independent prognostic factors for survival up to 3rd relapse
- OS: **FIGO stage**

Hanker et al Ann Oncol 2012

Value of treatment of multiply relapsed ovarian cancer



PFS



OS

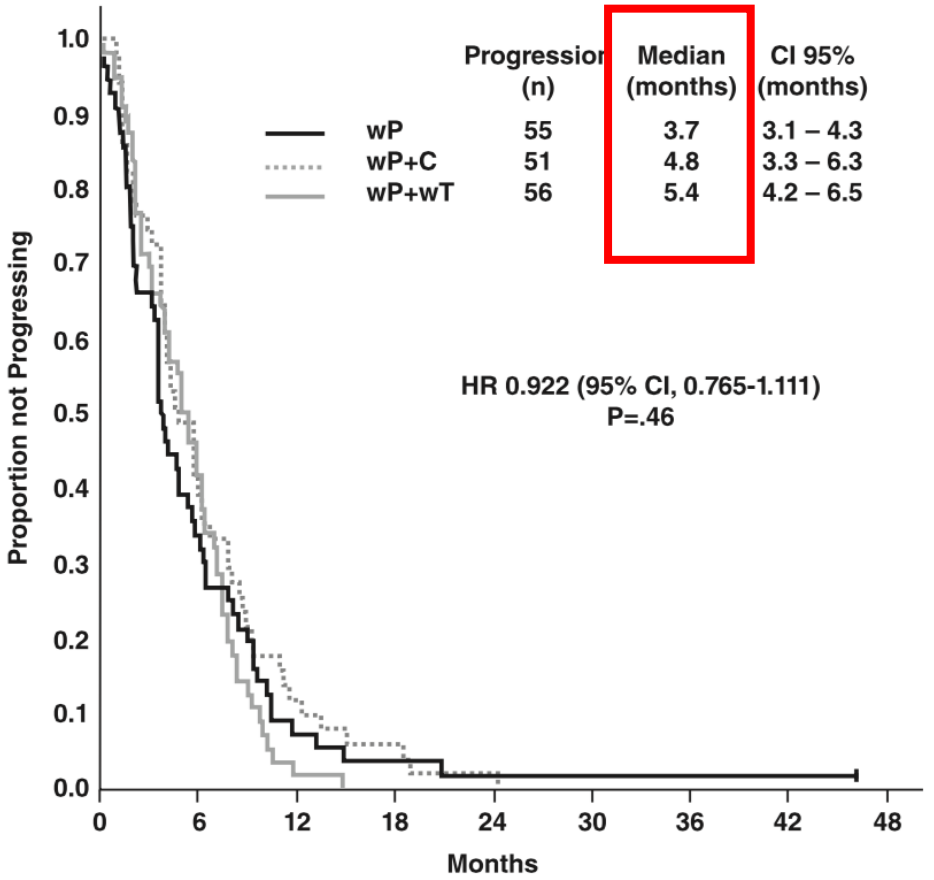
Hanker et al Ann Oncol 2012

Is there value in using platinum in women with 'platinum-resistant' disease?

Regimen	Author	Response Rate
Weekly cisplatin/etoposide	van der Burg et al (2002)	46%
Weekly carboplatin/paclitaxel	van der Burg et al (2013) Markman et al (2006) Sharma et al (2009) Havrilesky et al (2003)	51% 21% 60% 38%
Cisplatin/Gemcitabine	Rose et al (2003)	43%
PLD	Various (6 phase II trials) Green and Rose (2006)	7.7-25%
Weekly paclitaxel	Linch et al (2008) Lortholary et al (2012)	44% 35 %

Randomised phase II trial: of weekly paclitaxel alone, in combination with carboplatin or in combination with topotecan

	wP ($N = 57$)	wP + C ($N = 51$)	wP + wT ($N = 57$)
Overall response rate, *n* (%)	20 (35)	19 (37)	22 (39)
Complete response	3 (5)	7 (14)	6 (10)
Partial response	17 (30)	12 (24)	16 (28)
Stable disease, %	23	29	23
Progression, %	26	26	25
Nonevaluable, %	16	8	14



Lotholary et al Ann Oncol 2012

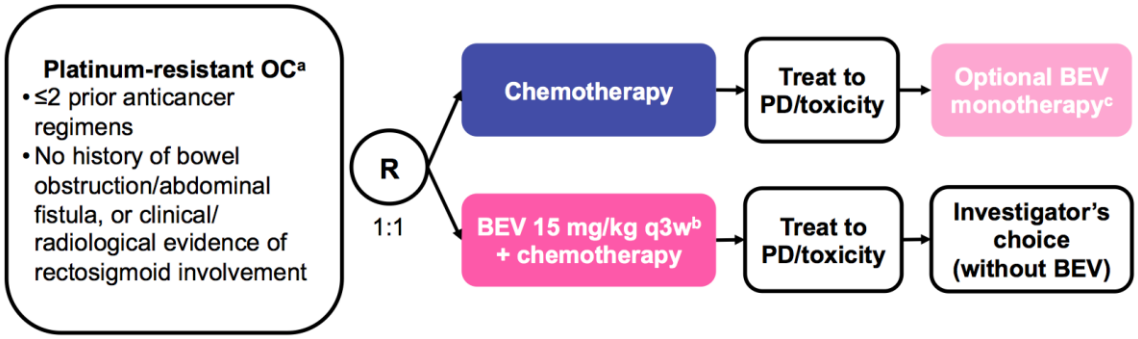
Bevacizumab in 'platinum-resistant' ovarian cancer

Efficacy	GOG-170D[1] (n=62)	AVF2949g[2] (n=44)
Median PFS months	4.7	4.4
6-month PFS rate, %	40.3	27.8
ORR, %	21	16
Median OS, months	16.9	10.7

- 41.9% of patients in GOG-170D had platinum-resistant disease,
- 83.7% of patients in AVF2949g were primarily platinum-resistant

[1]Burger et al. *J Clin Oncol*. 2007; [2]Cannistra et al. *J Clin Oncol.* 2007

AURELIA



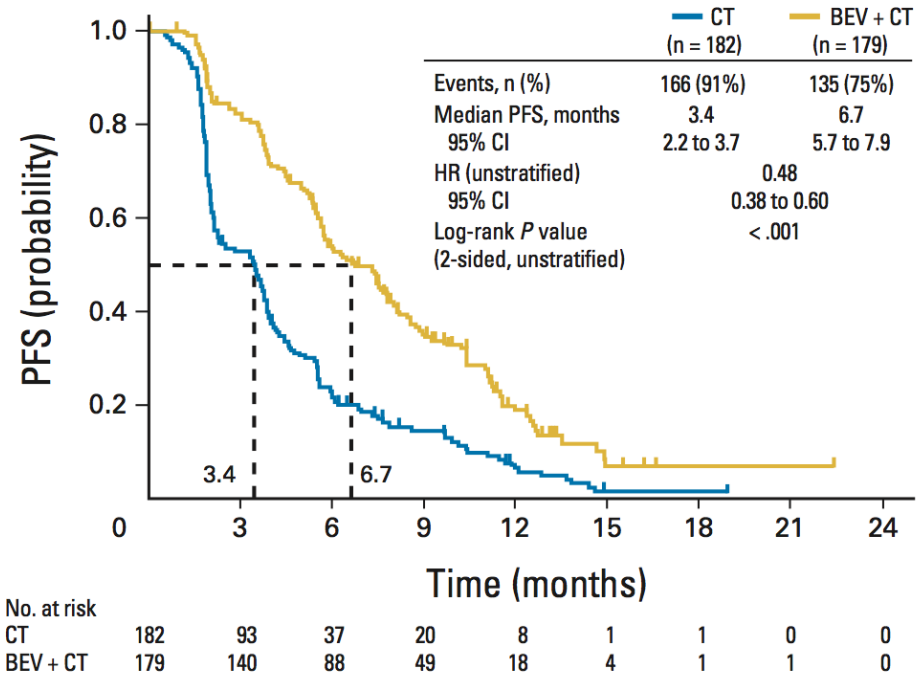
Chemotherapy options (investigator's choice):

- Paclitaxel 80 mg/m^2 days 1, 8, 15, & 22 q4w
- Topotecan 4 mg/m^2 days 1, 8, & 15 q4w (or 1.25 mg/m^2, days 1–5 q3w)
- PLD 40 mg/m^2 day 1 q4w

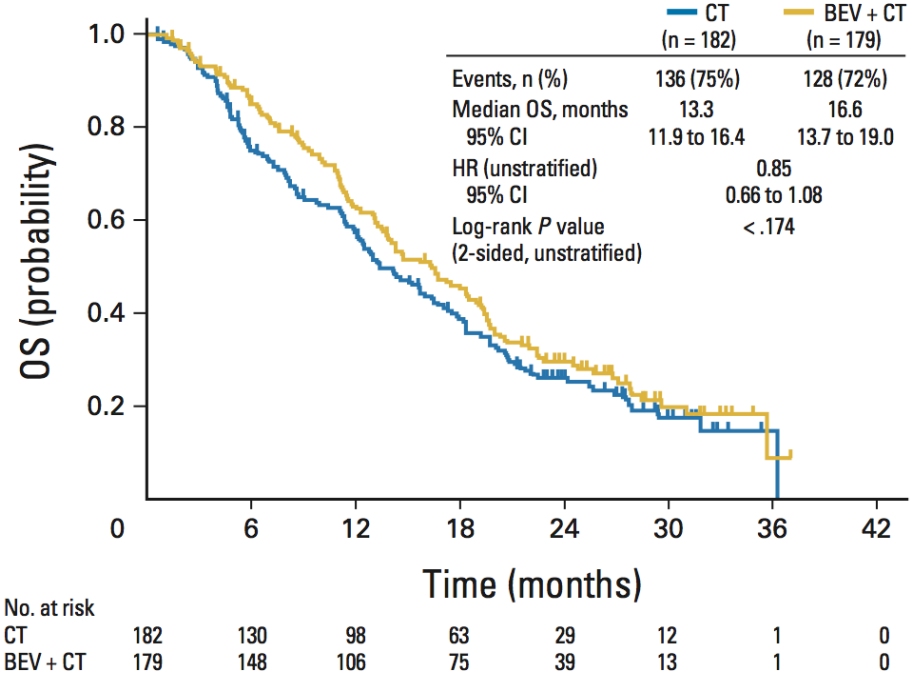
Pujade-Lauraine et al ASCO 2012

AURELIA: bevacizumab in 'platinum-resistant' ovarian cancer (all chemotherapy regimens)

PFS



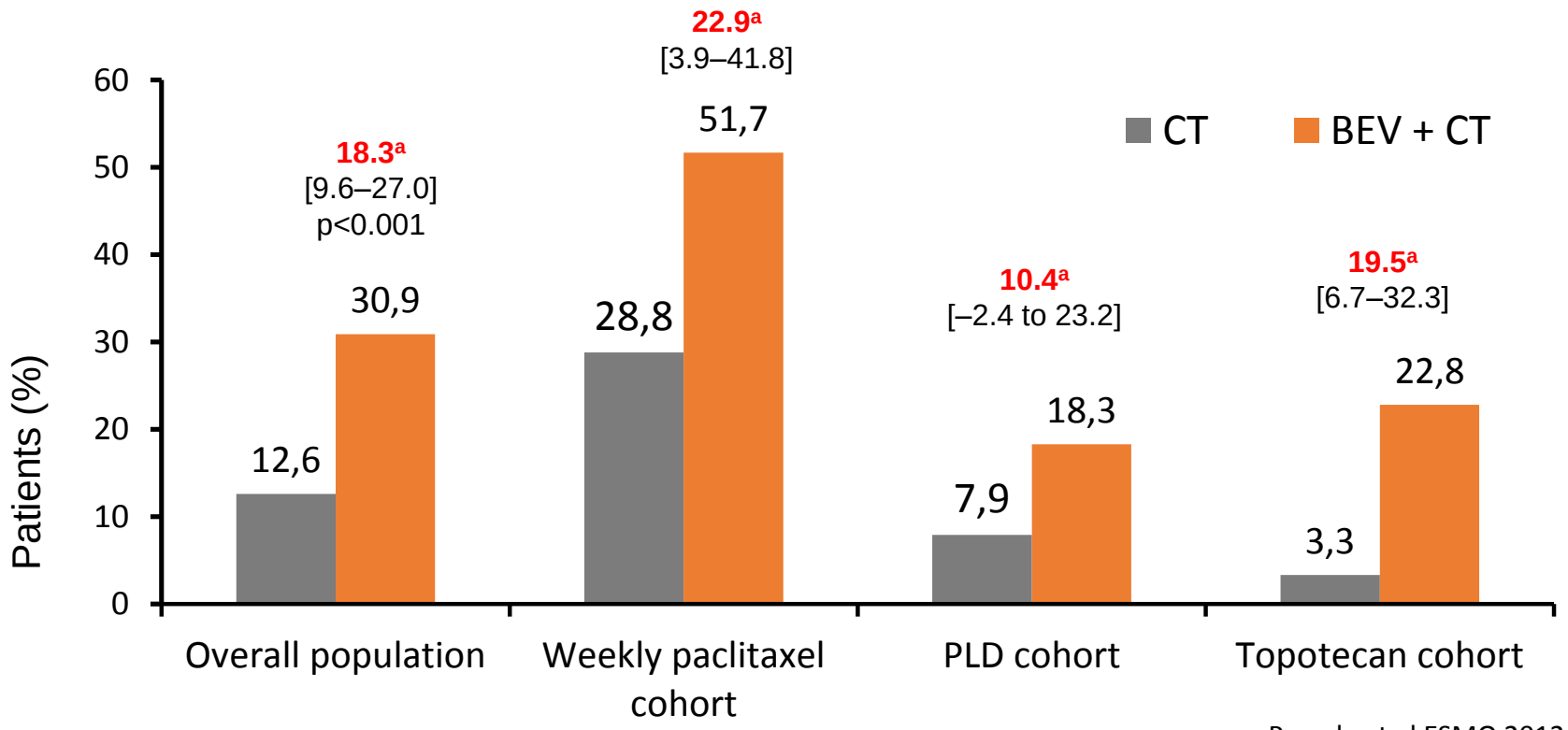
OS



Pujade-Lauraine et al J Clin Oncol 2014

AURELIA Trial : Bevacizumab Added to chemotherapy in 'platinum-resistant' disease

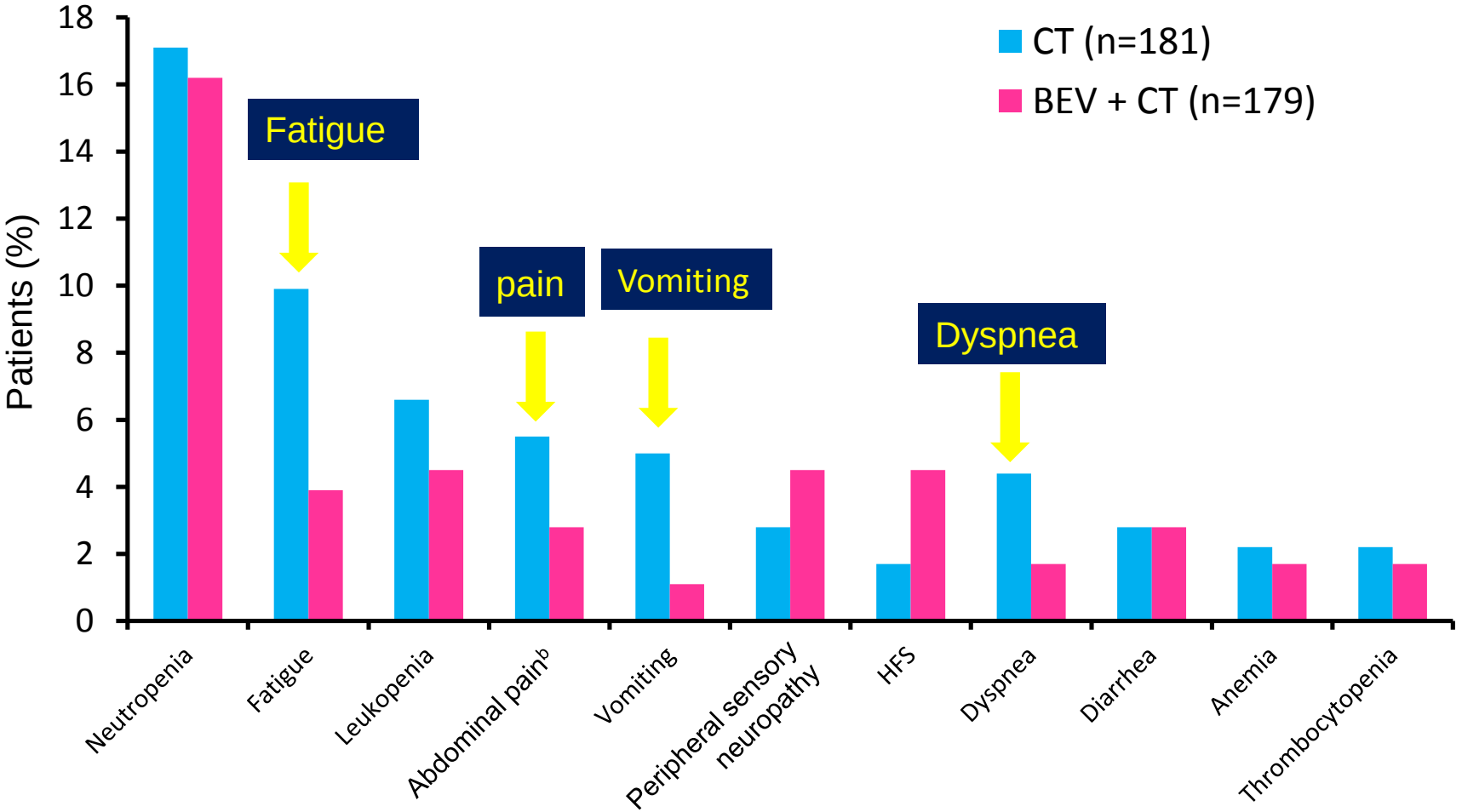
Summary of best overall response rates (RECIST, CA-125 criteria or both)



Poveda et al ESMO 2012

[a]*Difference in overall response rate; 95% CI with Hauck–Anderson continuity correction*

AURELIA Grade ≥3 adverse events (additional to BEV events of interest)



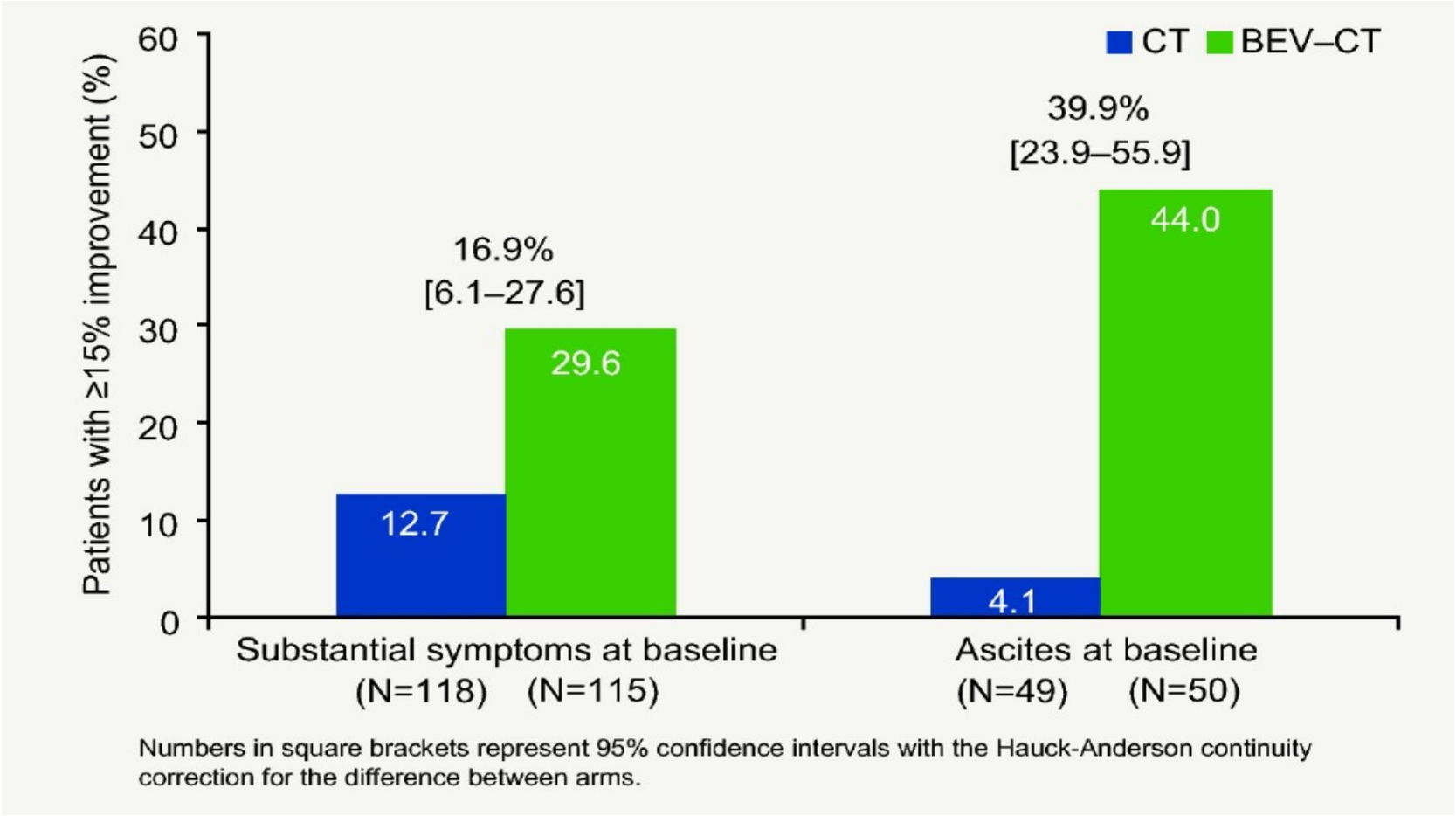
HFS = hand-foot syndrome

[a]Preferred terms. [b]Includes abdominal pain upper

Pujade-lauraine E, ASCO 2012

Aurelia Trial: Health-related QoL

Primary PRO hypothesis (Abdominal/ Gastrointestinal symptoms):
Subgroup analysis week 8/9



Stockler et al ASCO 2013

Conclusions

- Bevacizumab has been shown to add value to chemotherapy in platinum-resistant disease but
  - *Questions about value in > 2nd line therapy, maintenance beyond chemotherapy and effect of previous first-line bevacizumab remain*
- Drug resistance in 'platinum-resistant' disease/multiply pre-treated a major obstacle
- Integration of oncology and palliative care important with emphasis on management of symptoms and QoL