Treatment for relapsing patients

Educational session
Ovarian Cancer

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Disclosure slide

- Honoraria from Roche, AZ, Pharmamar, GSK

- Epidemiology of the recurrence
- The role of surgery
- When starting therapy
- The dogma of platinum free interval
  - Resistant
  - Partially sensitive
  - Sensitive
- New drugs.. Toward a personalized therapy

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Ovarian Cancer

- First cause of death among gynecological malignancies
- 75% of patients respond to first line platinum-based chemotherapy
- 70% of them experience recurrences within 24 months

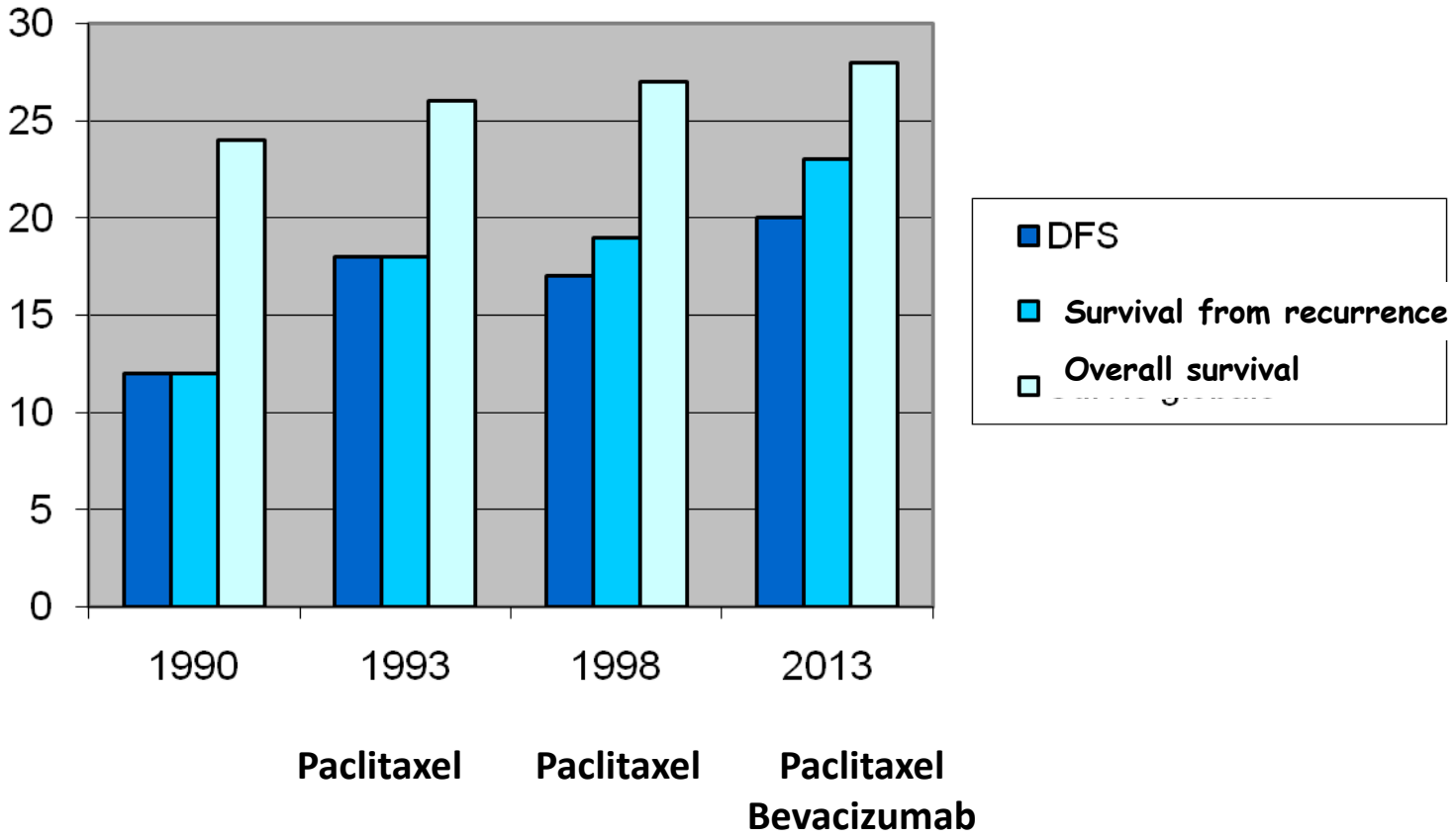
Risk of recurrence depends on stage

Recurrence

Initial disease	Frequency (%)	Recurrence (%)
Stage I-II, favorable	10	10
Stage I-II, unfavorable	15	20
Stage III, residual < 2 cm.	30	60-70
Stage III-IV, residual	45	80-85
Overall	100*	62

AJR Am J Roentgenol 1979;133:221

The 5-years OS increase in ovarian cancer is mainly due to a better treatment of recurrent disease



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C1:What is the role of cytoreductive surgery for recurrent ovarian cancer ?

- Surgery may be appropriate in selected patients.

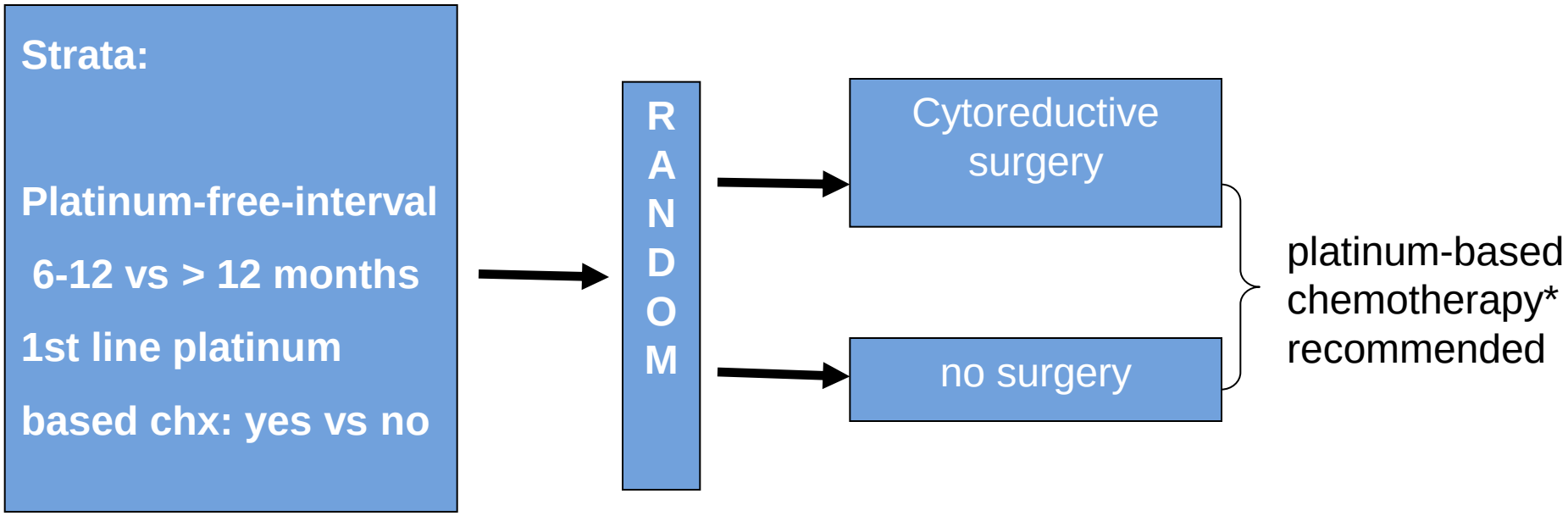
- As yet there is no level I evidence which demonstrates a survival advantage associated with surgical cytoreduction for women with recurrent ovarian cancer

- Randomised phase III trials evaluating the role of surgery in recurrent ovarian cancer are a priority.

- Cytoreductive surgery for women with recurrent ovarian cancer may be beneficial if it results in optimal cytoreduction (No residual disease)

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

A randomized trial evaluating cytoreductive surgery
in patients with platinum-sensitive recurrent ovarian cancer



* Recommended platinum-based chemotherapy regimens:
- carboplatin/paclitaxel
- carboplatin/gemcitabine
- carboplatin/pegliposomal doxorubicin
-or other platinum combinations in prospective trials

- Epidemiology of the recurrence
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When start therapy for recurrence?

- Ca 125 increase (> 100U/ml)
- Radiological relapse
- Clinical relapse

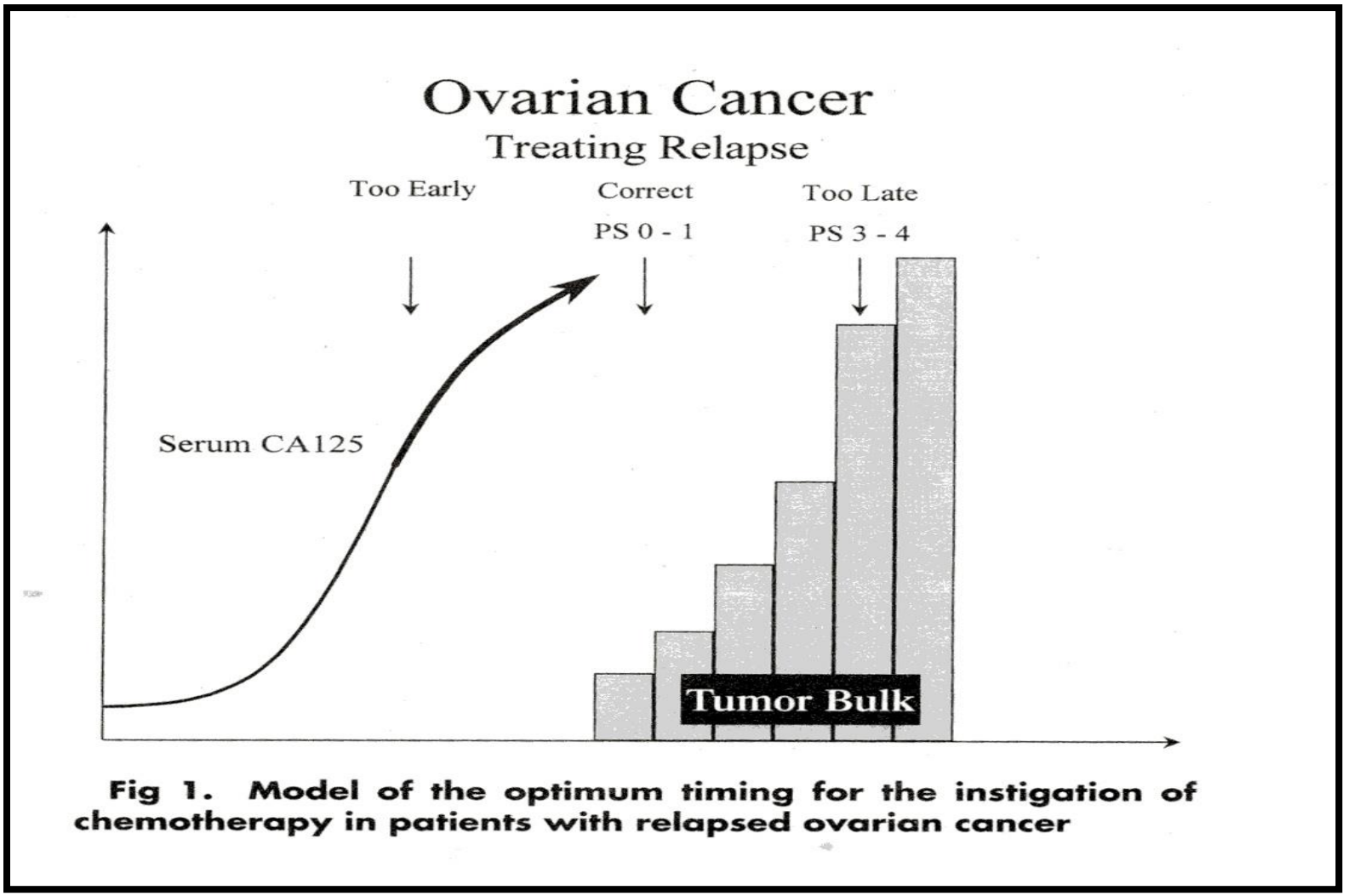
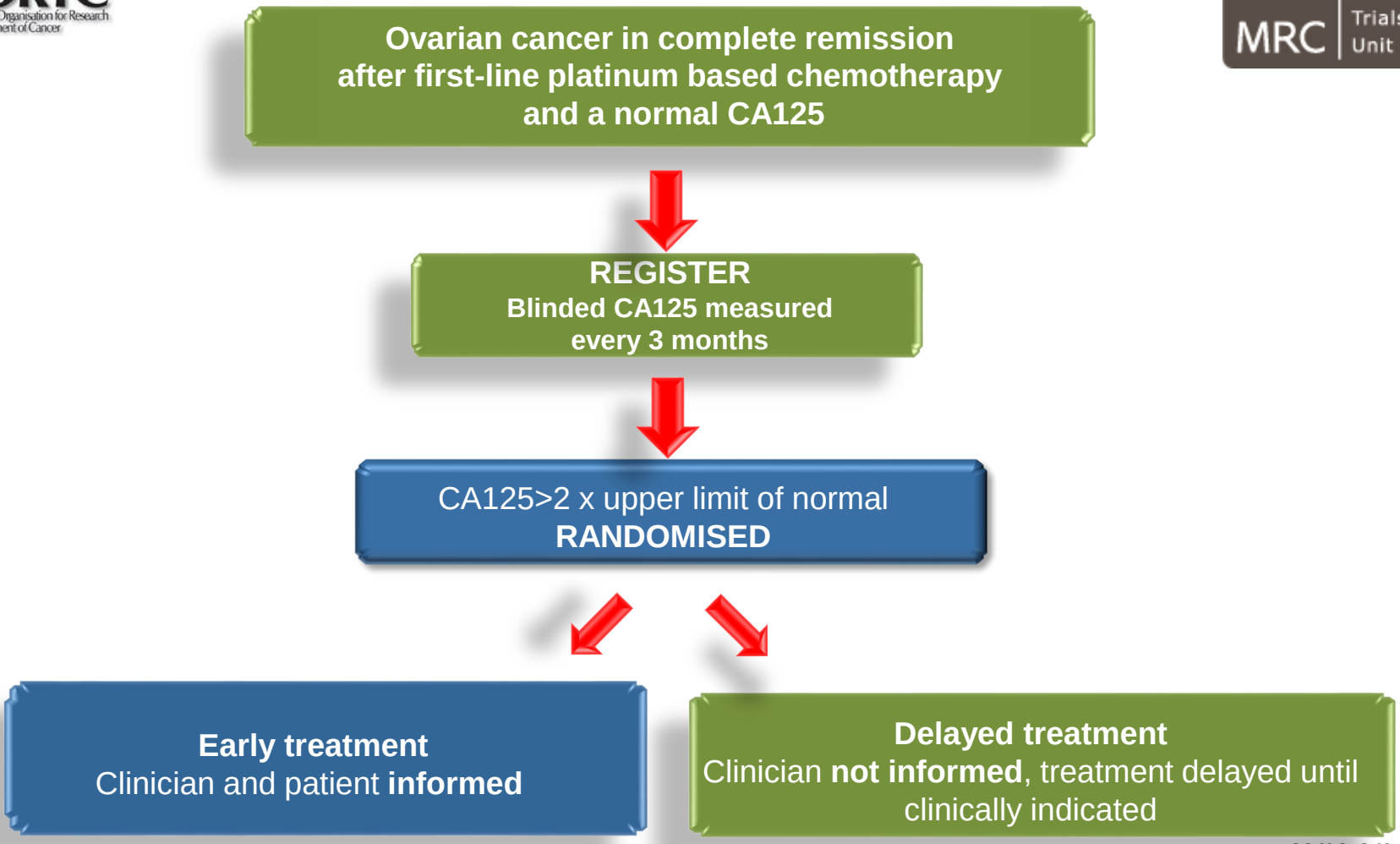


Fig 1. Model of the optimum timing for the instigation of chemotherapy in patients with relapsed ovarian cancer

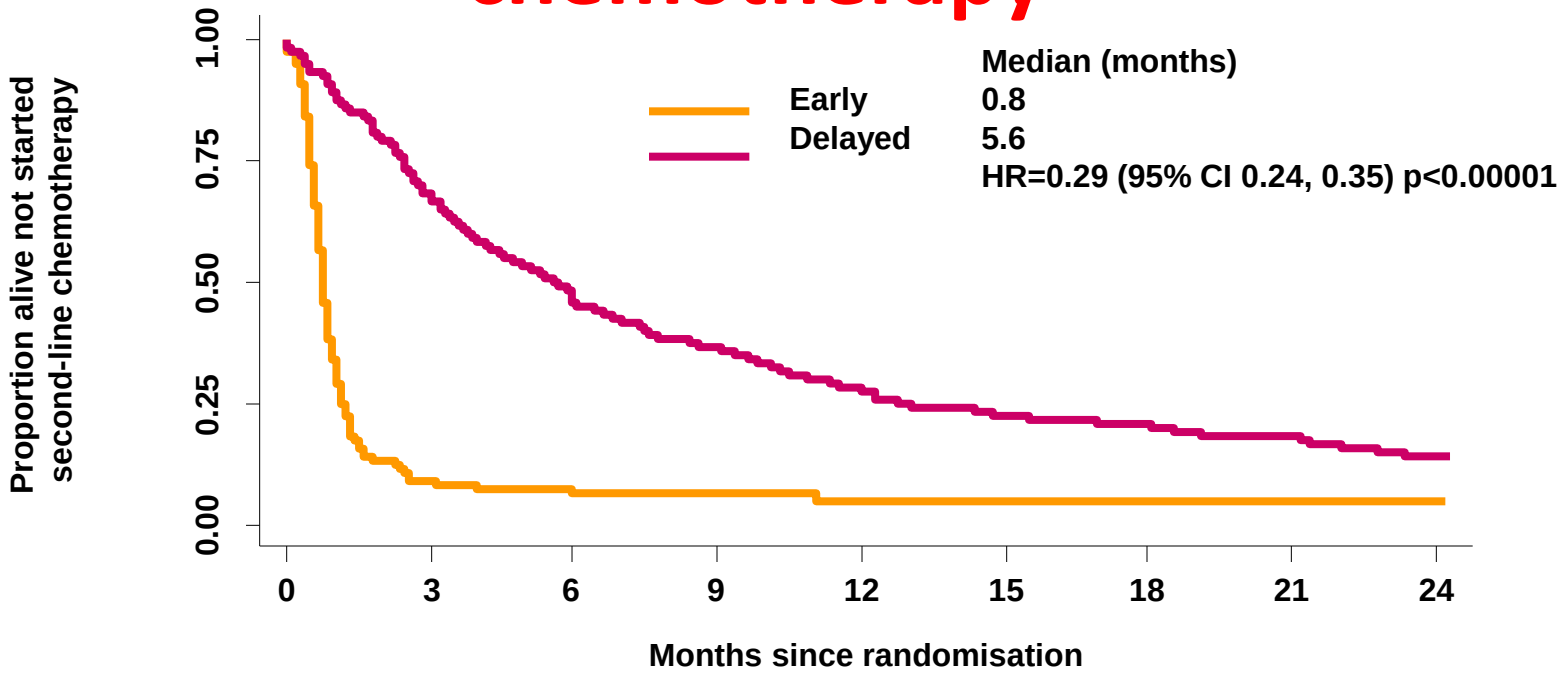
EORTC Trial Design

EORTC European Organisation for Research and Treatment of Cancer

MRC Clinical Trials Unit



Time from randomisation to second-line chemotherapy



Number at risk										
	Early	265	23	16	14	11	11	10	10	9
	Delayed	264	177	116	91	69	56	49	42	33

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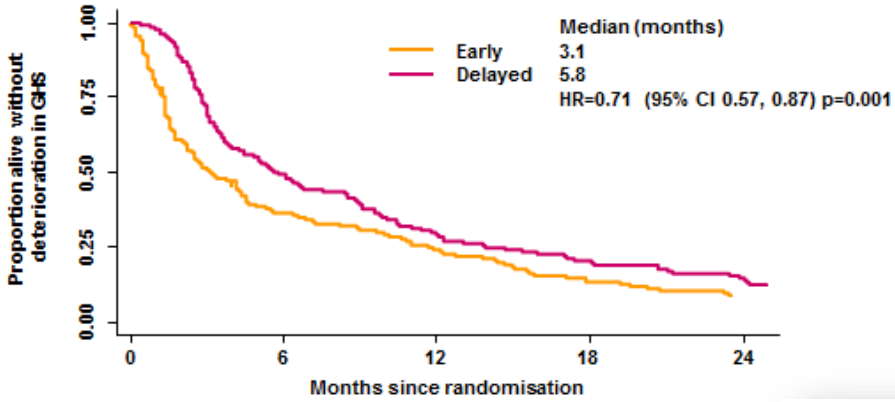
EORTC European Organisation for Research and Treatment of Cancer

MRC Clinical Trials Unit

Time from randomisation to first deterioration in Global Health Score (or death)

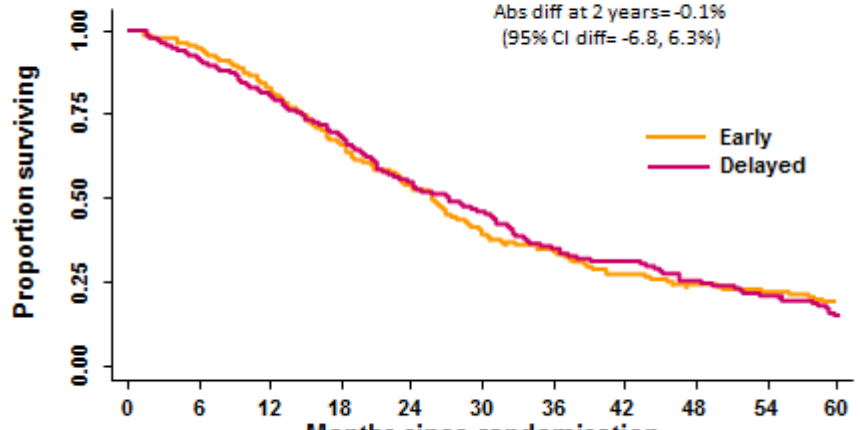


Number at risk

Early	190	68	44	23	12
Delayed	194	93	55	38	25

Overall Survival

HR=1.00 (95%CI 0.82-1.22) p=0.98



Number at risk

Early	265	247	211	165	131	94	72	51	38	31	22
Delayed	264	236	203	167	129	103	69	53	38	31	19

- Epidemiology of the recurrence
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C2: How to define distinct patient populations in need of specific therapeutic approaches?

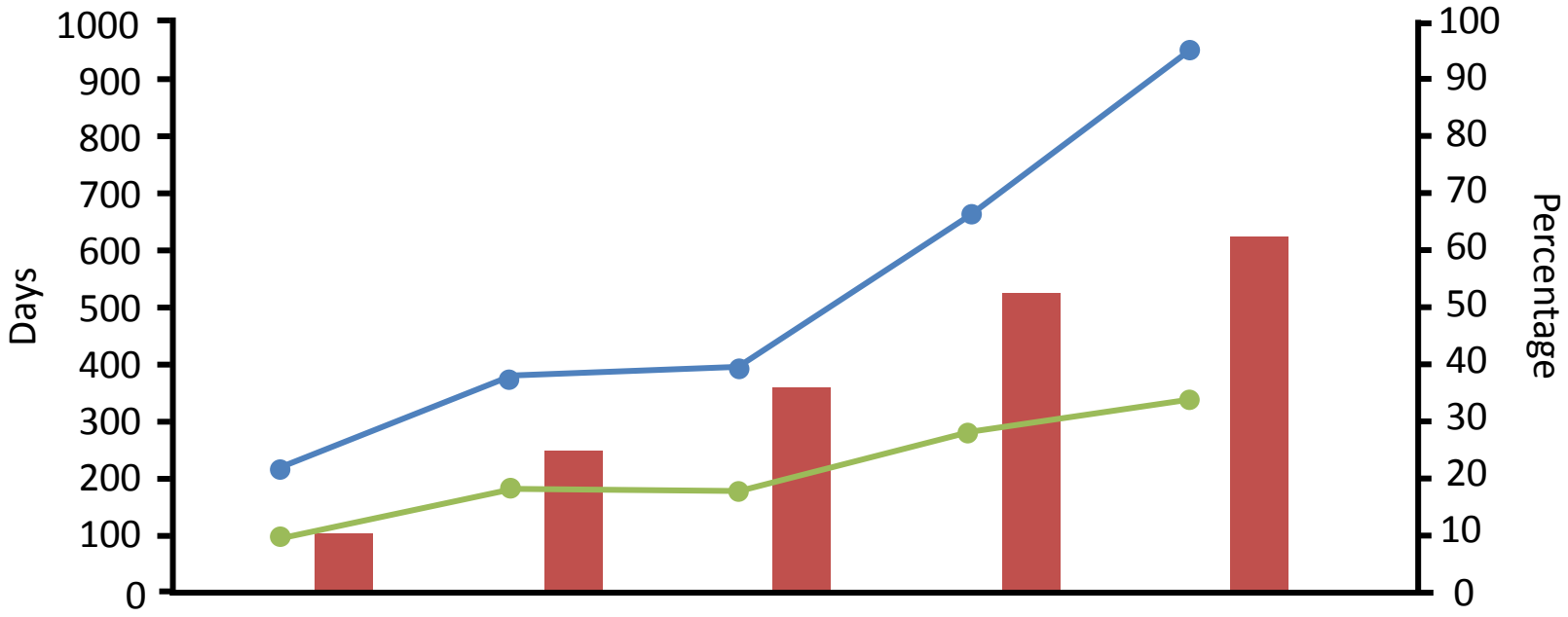
- Distinct Patient Populations for clinical trial enrollment may be considered by interval from Last Platinum Therapy
- PFI is defined from the last day of platinum until PD

- The following subgroups should be considered:
- Progression while receiving last line of platinum therapy or within 4 weeks of last platinum dose
- Progression-free interval since last line of platinum of < 6 months
- Progression-free interval since last line of platinum of 6-12 months
- Progression-free interval since last line of platinum of > 12months*

*For this group a platinum based combination should be the control arm in randomized clinical trials.

Friedlander et al. Int J Gynecol Cancer 2011; 21: 771-775

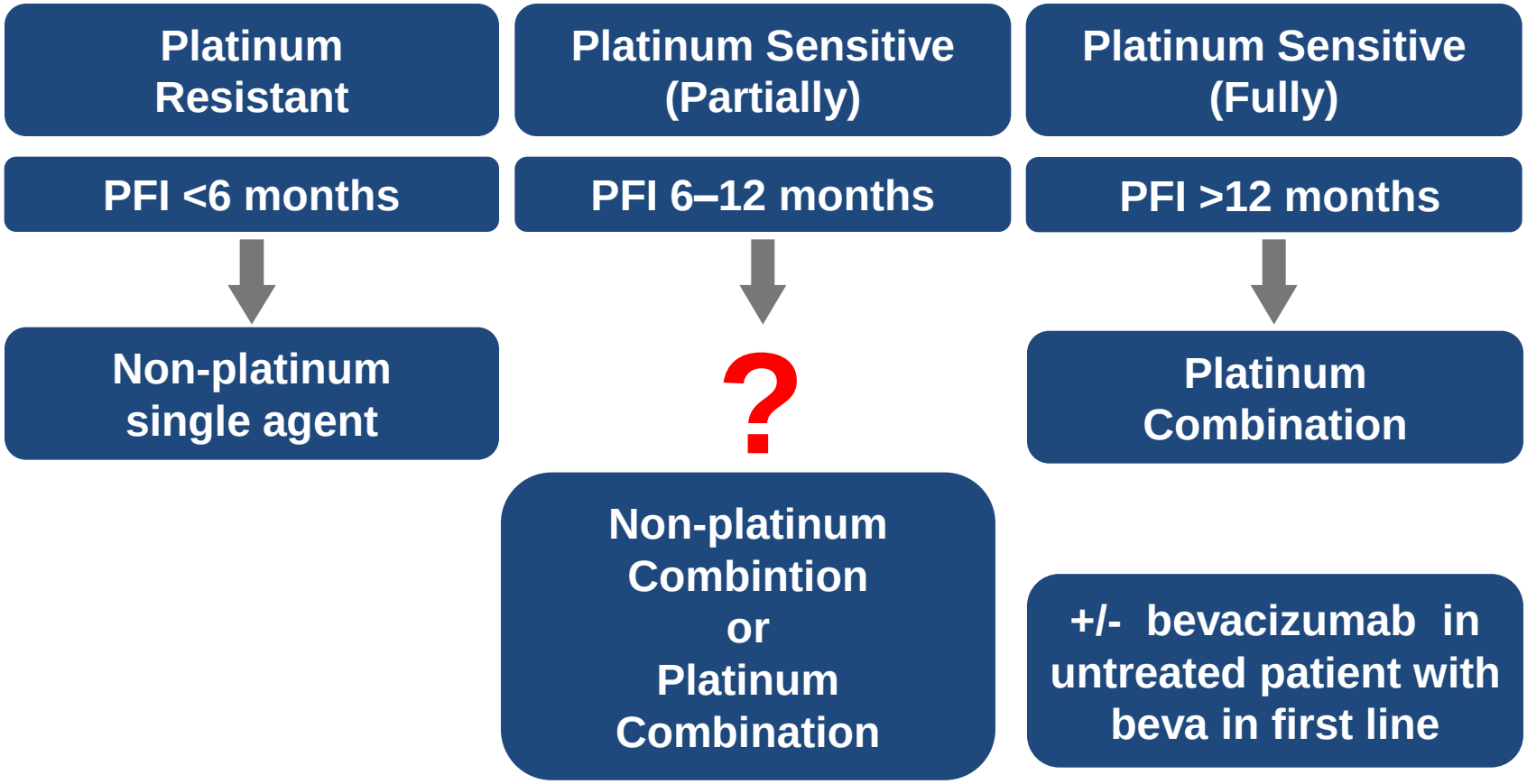
Treatment of Recurrent Ovarian Cancer



	0-3 Prog	0-3 Non-PD	3-12 Mos	12-18 Mos	18+ Mos
PFS, days	90	176	174	275	339
OS, days	217	375	375	657	957
Response, %	9	24	35	52	62

Pujade-Lauraine E, et al. ASCO 2002. Abstract 829.

Ovarian Cancer Treatment Proposed Algorithm: Chemotherapy at Relapse



Platinum resistant disease

Active Single-Agents in Recurrent Ovarian Cancer

Agent	Response Rates		Patient Tolerance/QoL Issues
	Platinum-Sensitive	Platinum-Resistant	
PLD	28%	12-16%	HFS, mucositis
Paclitaxel	20-45%	7-17%	Alopecia, peripheral neuropathy, arthralgias/myalgias
Etoposide	34%	27%	Alopecia, GI toxicity
Gemcitabine	34%	13-19%	Flu-like constitutional symptoms, hepatic dysfunction, dyspnea
Yondelis	36%	7-16%	Transaminases elevation, Asthenia, GI toxicity
Vinorelbine	29%	15-19%	Constipation, nausea, peripheral neuropathy
Topotecan	33%	12-19%	Asthenia, alopecia, schedule

Randomized phase III trials of chemotherapy single agents in platinum refractory/resistant ovarian cancer

Author	N pts	Drugs	RR (%)	PFS (median)	OS (median)
O' Byrne 2002	213	PLD vs TAX	19* 23	16 w 20 w	37w 54w
ten Bokkel Huinit 2004	226	TAX vs TPT x 5 d	6.7 13.3	14.7* w 18.9 w	53* w 63 w
Gordon 2004	574	TPT X 5d vs PLD	6.5 12.3	13.6 w 9.1 w	41.3 w 35.6 w
Mutch 2006	195	PLD vs GEM	8.3 6.1	3.1 m 3.6 m	13.5 m 12.7 m
Ferrandina 2008	153	PLD vs GEM	16* 29	16 w* 20 w	56 w* 51 w
Vergote 2009	461	CAN vs PLD or TPT	4.3 10.9	2.3 m§ 4.3 m	8.5 m§ 13.5 m
Meier 2009	114	TPT Treosulafan	- -	4.2 2.1	11.3 7.4
Colombo 2012	829	EPO 906 vs PLD	15.5 7.9	3.7 m 3.7 m	13.2 m 12.7 m

* On the whole population; § $p<0.01$

Single agent PLD, weekly paclitaxel, gemcitabine, topotecan considered options in resistant recurrences

- Chemo combination are not better than single agent
- Previous toxicity important for the selection of therapy
- Discussion with the patient because of the palliative intent

Single agent activity of bevacizumab

Tumor Type	Dose	ORR (PR+CR)
Ovarian Cancer	15mg/kg q3wk	16-21%
Renal Cell	10mg/kg q2wk	10%
Met Breast Cancer	3-20mg/kg q2wk	7%
NHL	10mg/kg q2wk	5%
CRC	10mg/kg q2wk	3%
HRPC	10mg/kg q2wk	0%

Bevacizumab: AURELIA trial

Platinum-resistant OC[a]

- ≤2 prior anticancer regimens
- No history of bowel obstruction/abdominal fistula, or clinical/ radiological evidence of rectosigmoid involvement

R

1:1

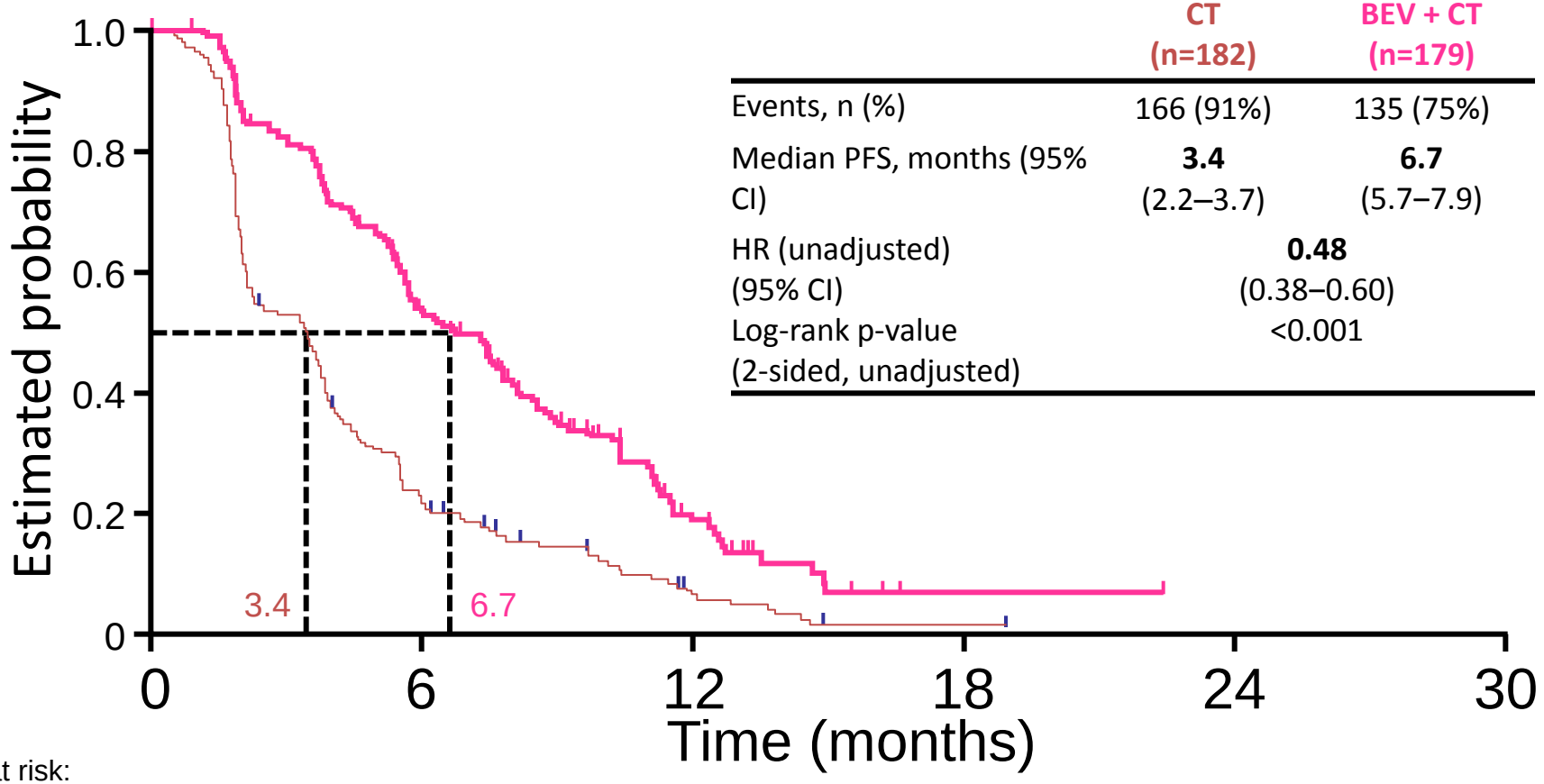
- Chemotherapy → Treat to PD/toxicity → Optional BEV monotherapy[c]
- BEV 15 mg/kg q3w[b] + chemotherapy → Treat to PD/toxicity → Investigator's choice (without BEV)

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

- *PD = progressive disease*
- *[a]Epithelial ovarian, primary peritoneal, or fallopian tube cancer; [b]Or 10 mg/kg q2w;*
- *[c]15 mg/kg q3w, permitted on clear evidence of progression*

Progression-free survival



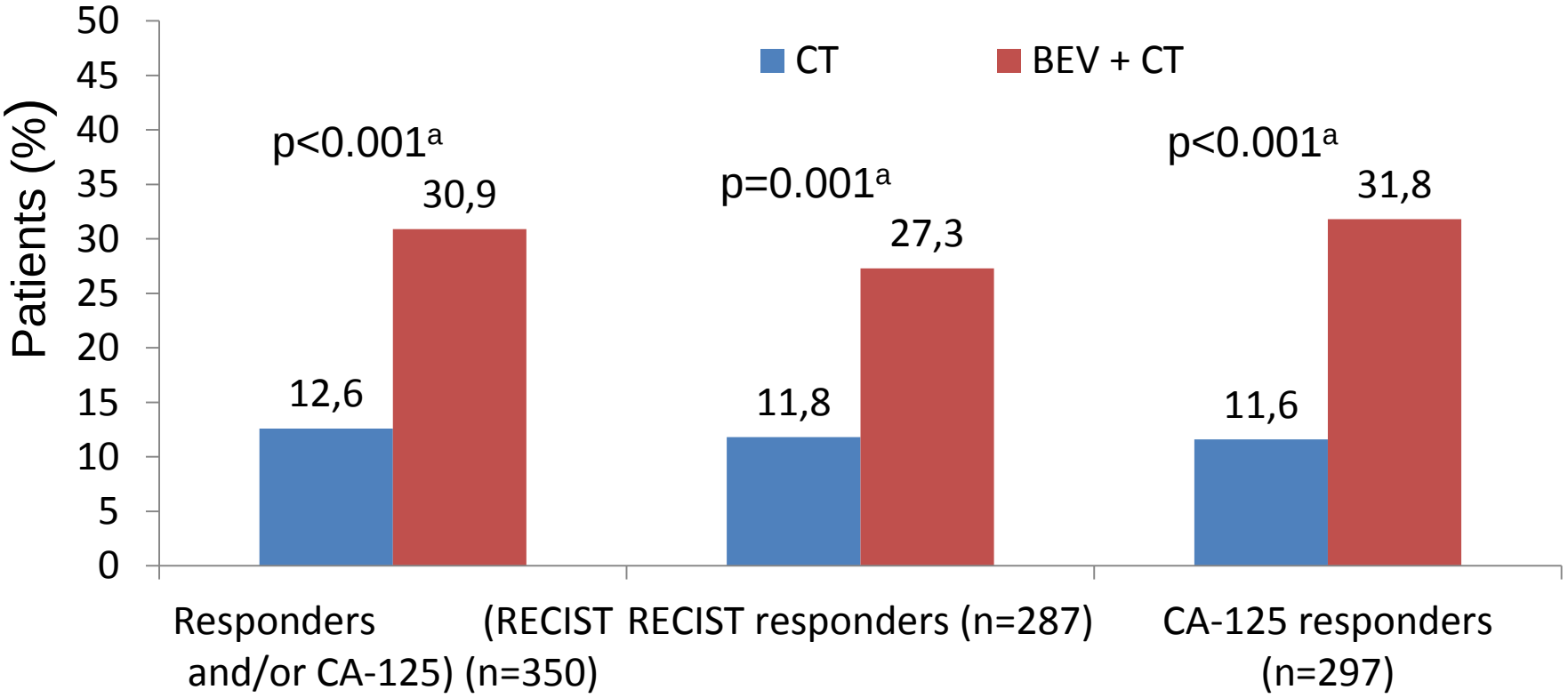
	CT (n=182)	BEV + CT (n=179)
Events, n (%)	166 (91%)	135 (75%)
Median PFS, months (95% CI)	**3.4** (2.2–3.7)	**6.7** (5.7–7.9)
HR (unadjusted) (95% CI)	**0.48** (0.38–0.60)	
Log-rank p-value (2-sided, unadjusted)	<0.001	

No. at risk:

CT	182	93	37	20	8	1	1	0	0
BEV + CT	179	140	88	49	18	4	1	1	0

Median duration of follow-up: 13.9 months (CT arm) vs 13.0 months (BEV + CT arm)

Summary of best overall response rates



[a] *Two-sided chi-square test with Schouten correction*

AURELIA TRIAL: QoL

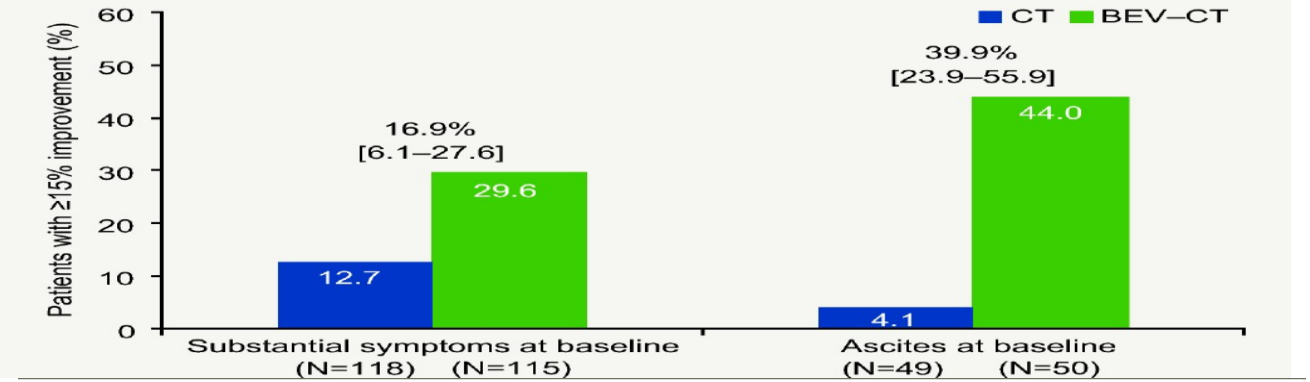
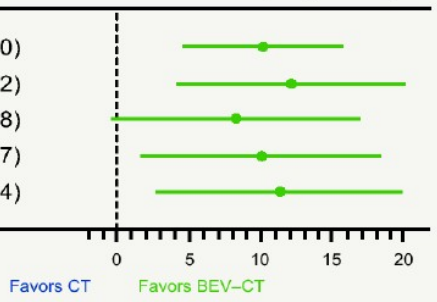
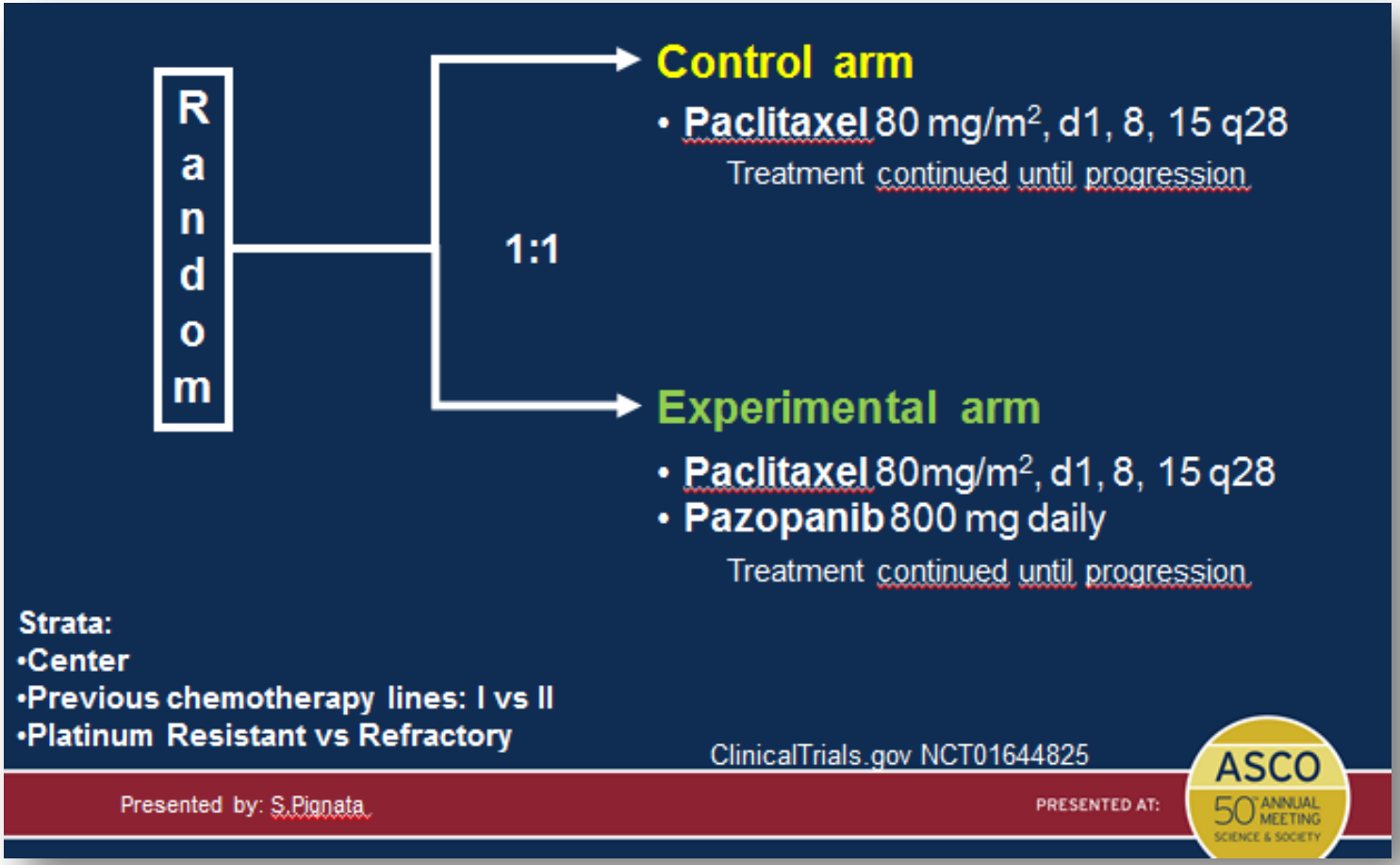


Figure 7. Secondary PRO hypothesis (QLQ-C30): Patients with improvement from baseline, week 8/9

Subscale	Patients achieving a ≥15% improvement from baseline, n/N (%) CT (N=182)	BEV–CT (N=179)
Physical functional	3/170 (1.8)	20/167 (12.0)
Role functional	17/170 (10.0)	37/167 (22.2)
Emotional functional	26/168 (15.5)	39/164 (23.8)
Social functional	21/167 (12.6)	37/163 (22.7)
Global health status/QoL score	22/169 (13.0)	40/164 (24.4)

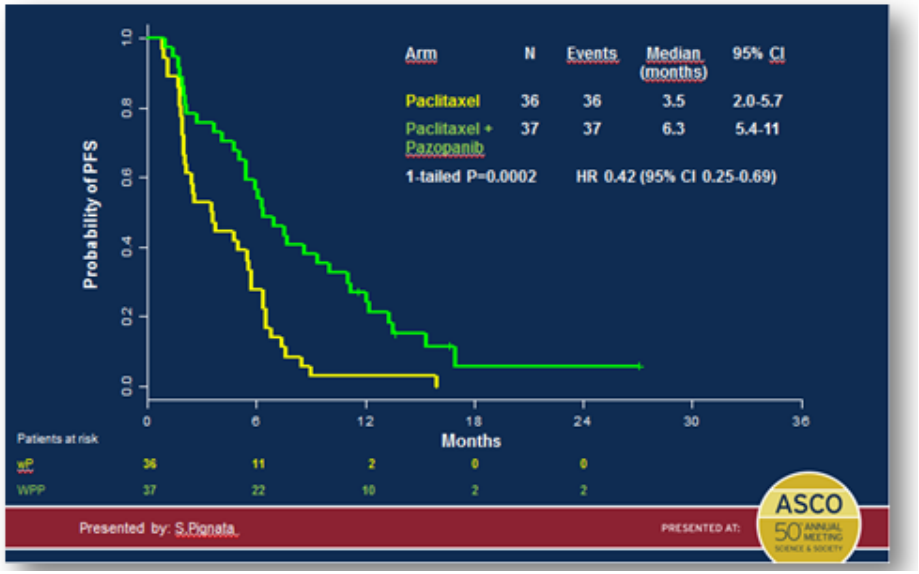


Pazopanib: MITO 11 trial

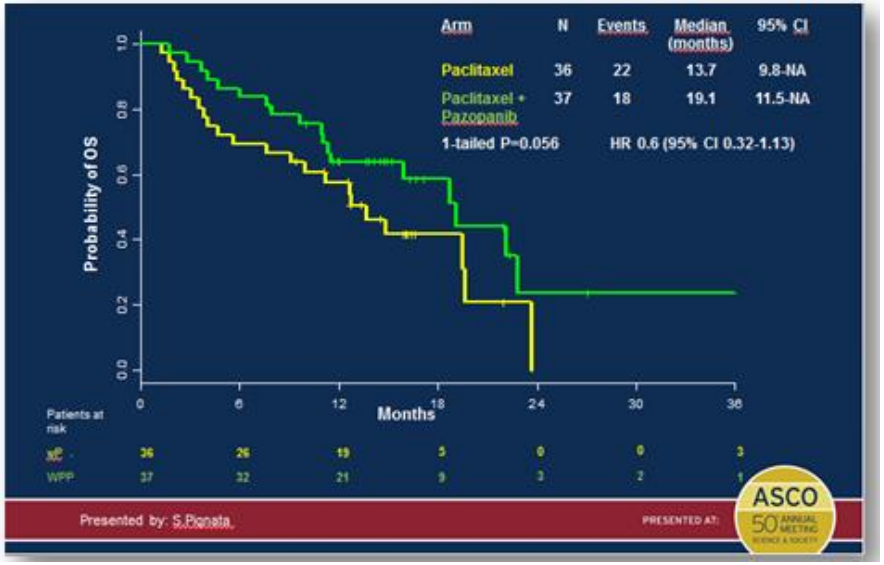


MITO 11 trial

Progression-free survival



Overall survival



Platinum resistant: Summary

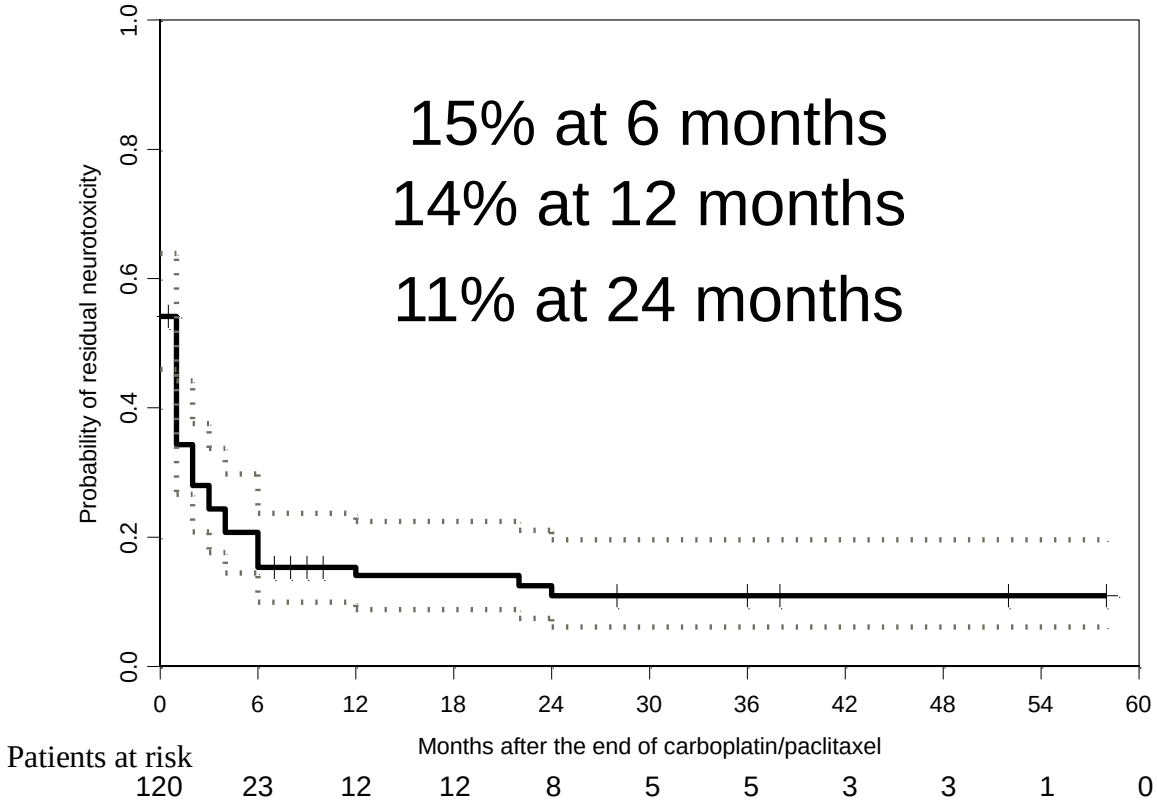
- Palliation intent
- Single agent chemotherapy +/-bevacizumab
- Targeting angiogenesis is effective (AURELIA), but..... No data in patients previously treated with bevacizumab

Platinum sensitive disease

Randomized phase III Trials on Platinum-based chemotherapy in Platinum Sensitive Patients

Author	Treatment	PFS HR	OS HR	Toxicities
Parmar 2003	CBDA vs CBDA+TAX	0.76*	0.82*	Neurotocity Alopecia Allergic reactions
Pfisterer 2006	CBDA vs CBDA+GEM	0.69	1.0	Myelotoxicity Allergic Reactions
Gladieff 2012	CBDA+TAX vs CBDA+PLD	0.73	1.01	Myelotoxicity

MITO 4 study: Duration of neurotoxicity after the end of chemotherapy



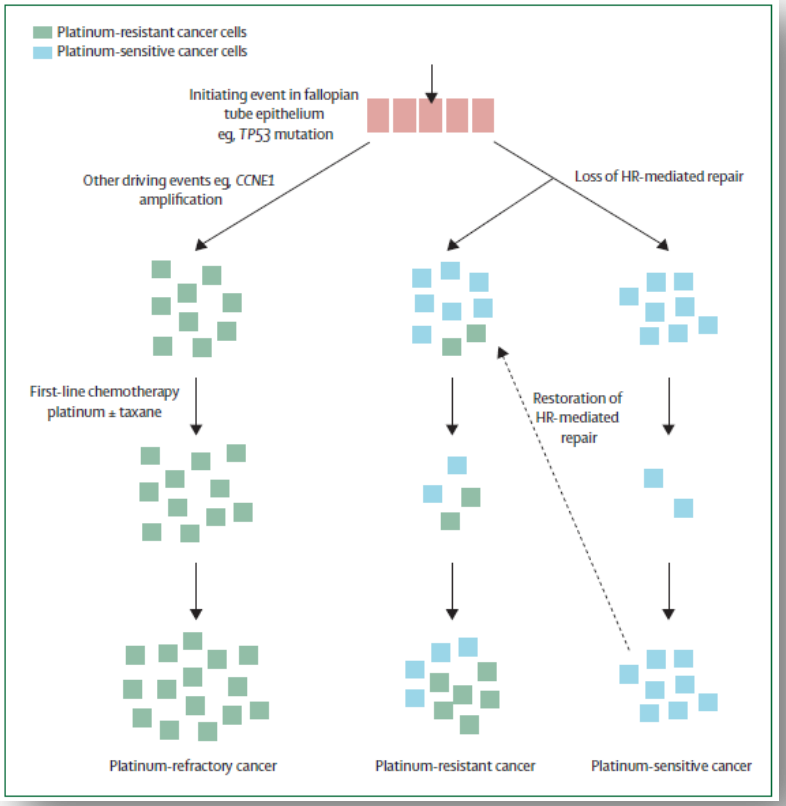
Pignata S. BMC Cancer 2006

The dilemma of the partially sensitive patients with 6-12 months PFI

"prolonging the platinum-free interval with a non-platinum agent in relapsed ovarian cancer can increase the likelihood of response to platinum reinduction at the next relapse".

Bookman. The Oncologist 1999

Selection of sub-populations sensitive to cisplatin

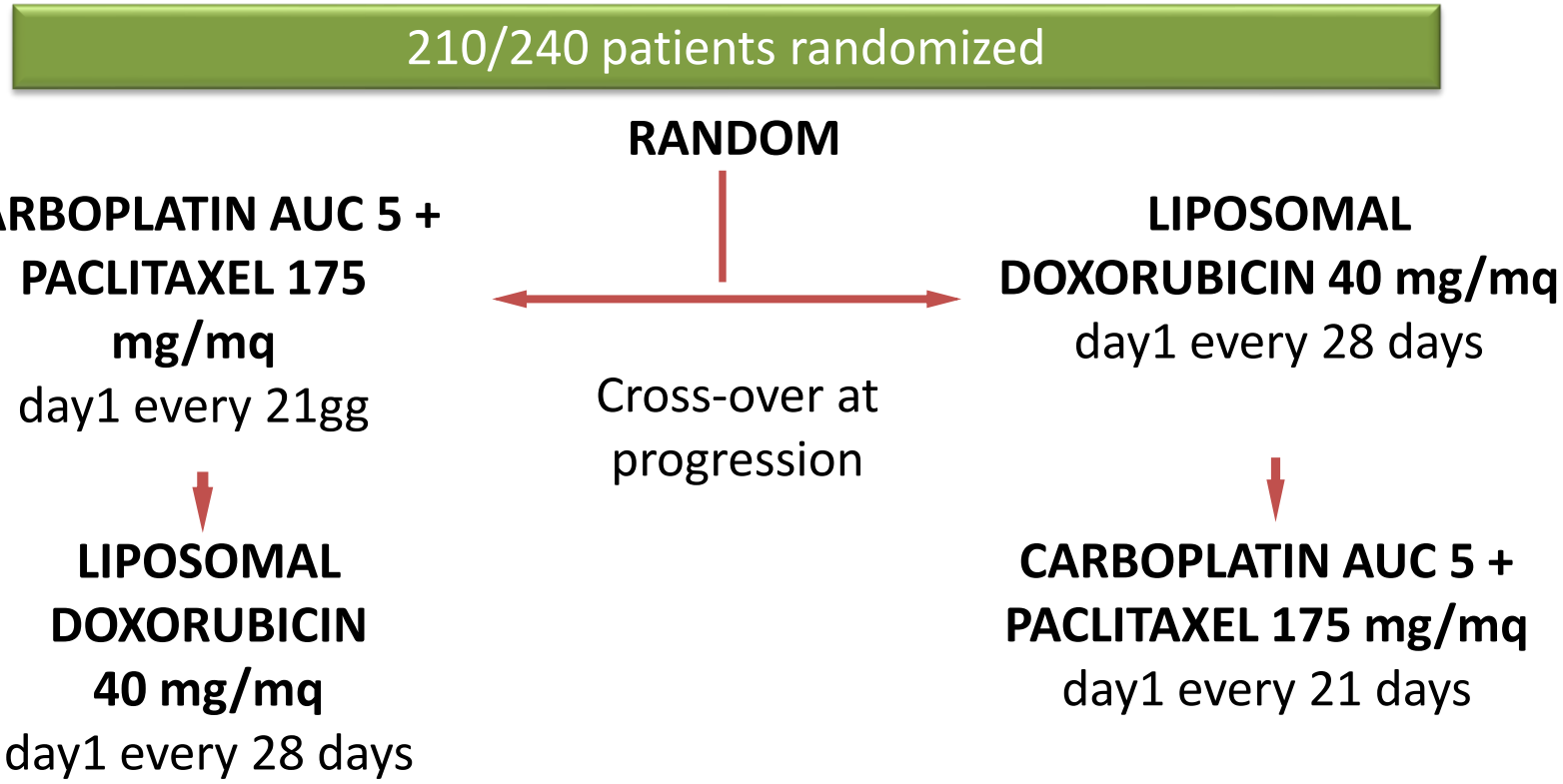


- **Genetic instability or**
- **Cancer cell dormancy**
- **Stem cells**
- **Progressive prevalence of resistant cells**

S.Cooke Lancet Oncology 2011

MITO-8: trial design

- Primary end point: OS
- Patients with 6-12 months of platinum free interval



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INOVATYON

Relapsed ovarian cancer

with platinum-free interval (PFI) of 6-12 months

↓

Randomization

(strata: ECOG, Measurable disease, PFI)

↓

PLD 30 mg/m2 1 hour i.v. + Carboplatin AUC 5 q4weeks

Up to 6 cycles or progression

↓

3rd line chemotherapy: at investigator discretion

↓

PLD 30 mg/m2 1 hour i.v. + Trabectedin 1.1 mg/m2 q3weeks

Up to 6 cycles or progression

↓

3rd line chemotherapy: platinum rechallenge

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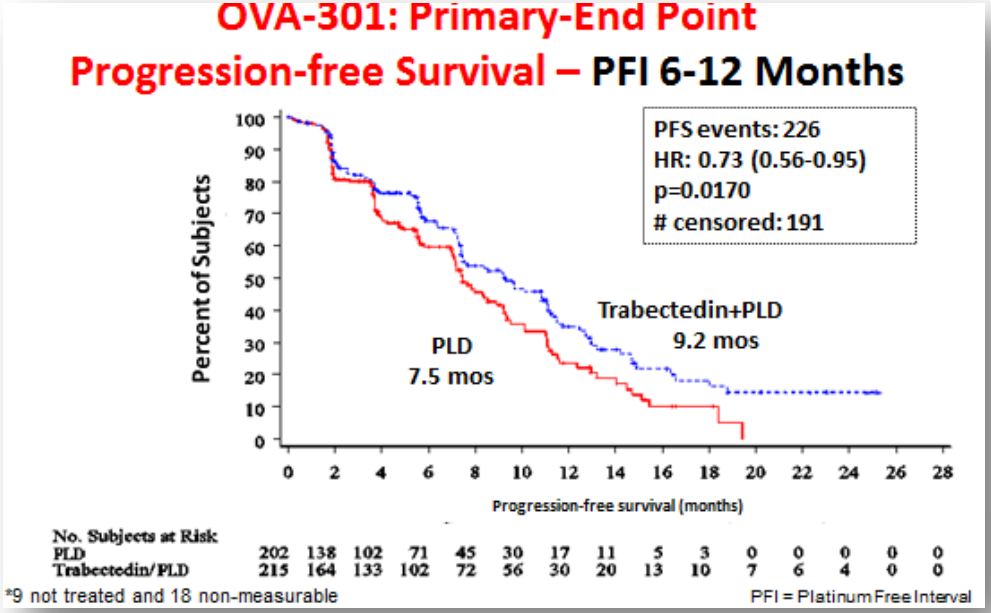
TRABECTEDINE OVA-301

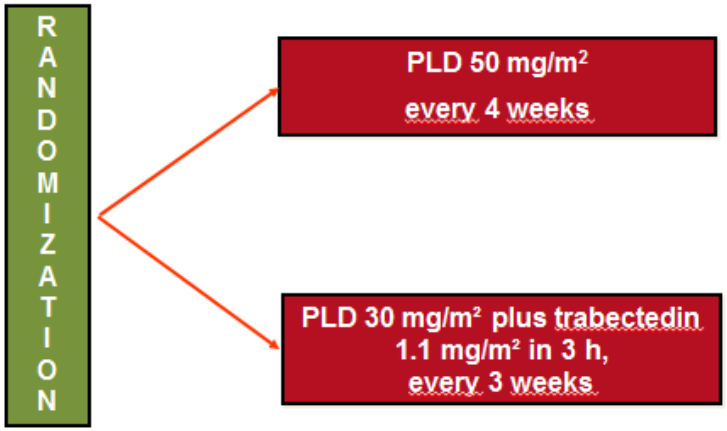
OVA-301: Primary-End Point
Progression-free Survival – PFI 6-12 Months



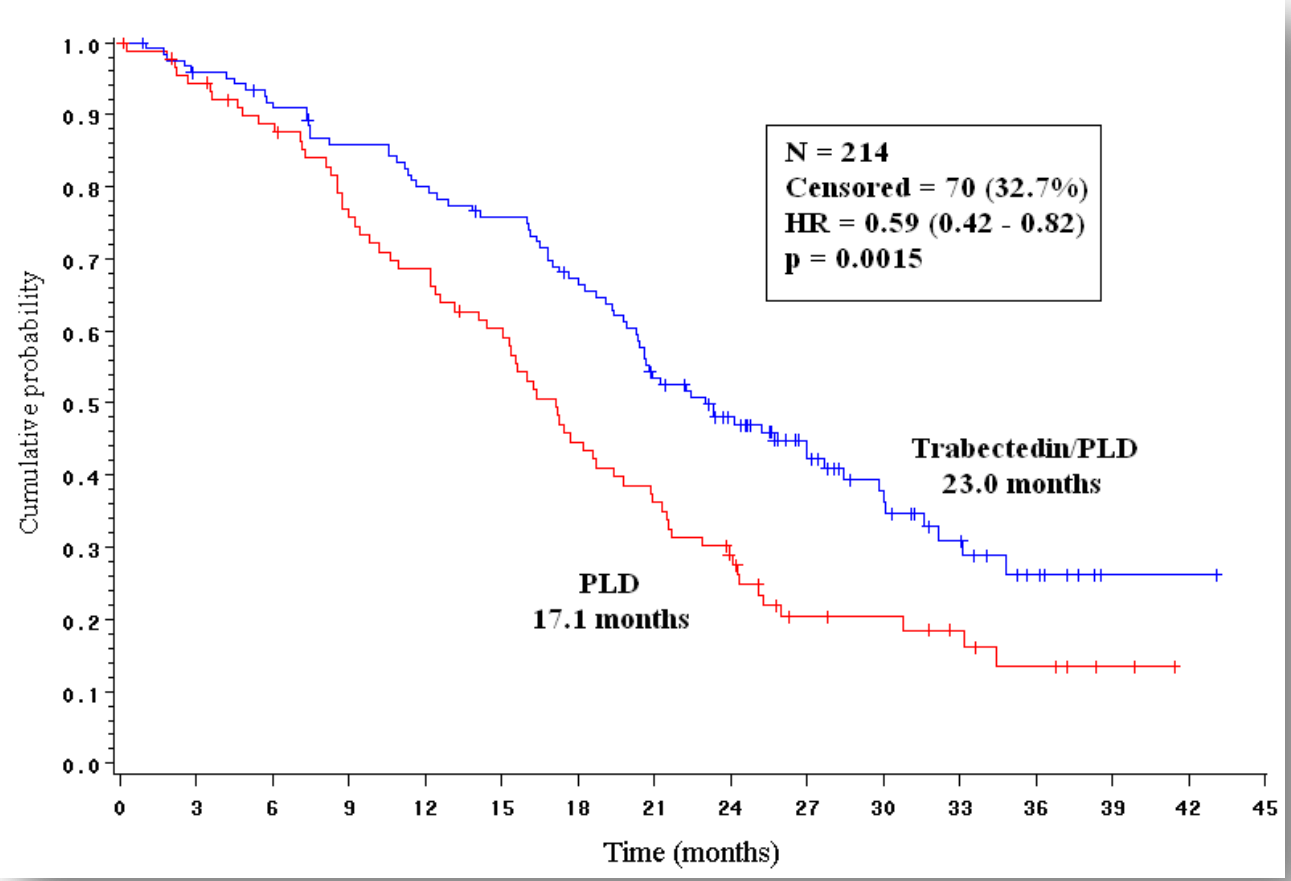
*9 not treated and 18 non-measurable

PFI = Platinum Free Interval

TRABECTEDINE OVA-301: Study design

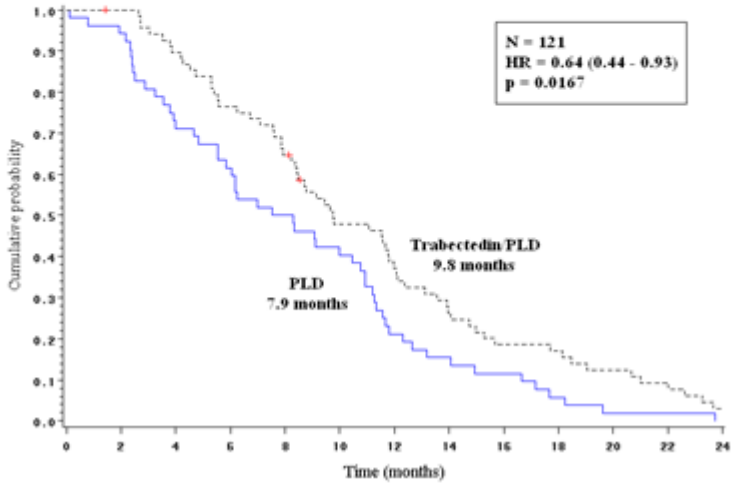


OS in partially platinum-sensitive population

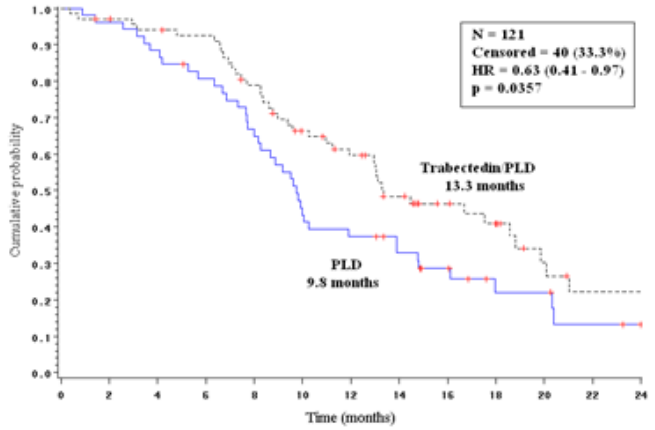


Poveda A et al. Annals of Oncology 2010; doi:10.1093/annonc/mdq352

Time to the following platinum from randomization to first administration of subsequent platinum (any further lines)



Survival from first administration of subsequent platinum (any further lines)

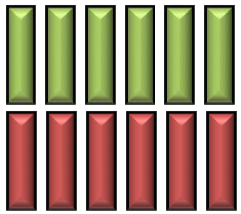


Bevacizumab OCEANS trial

- Platinum-sensitive recurrent OC
- Measurable disease
- ECOG 0/1
- No prior chemo for recurrent OC
- No prior BV

(n=484)

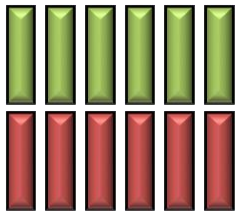
CG + PL



CBDCA AUC 4
GEM 1,000 mg/m²
d1, 8

PL q3w until progression

CG + BV



CBDCA AUC 4
GEM 1,000 mg/m²
d1, 8

BV 15 mg/kg q3w until progression

CG for 6 (up to 10) cycles

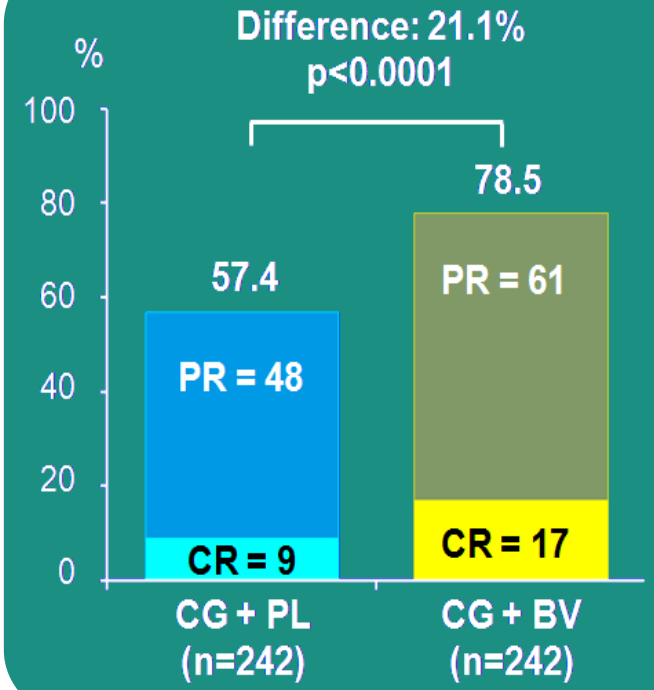
Stratification variables:

- platinum-free interval (6-12 vs >12 months)
- cytoreductive surgery for recurrent disease (yes vs no)

BV: bevacizumab; PL: placebo
Epithelial ovarian, primary peritoneal, or fallopian tube cancer

Response rate is improved by bevacizumab

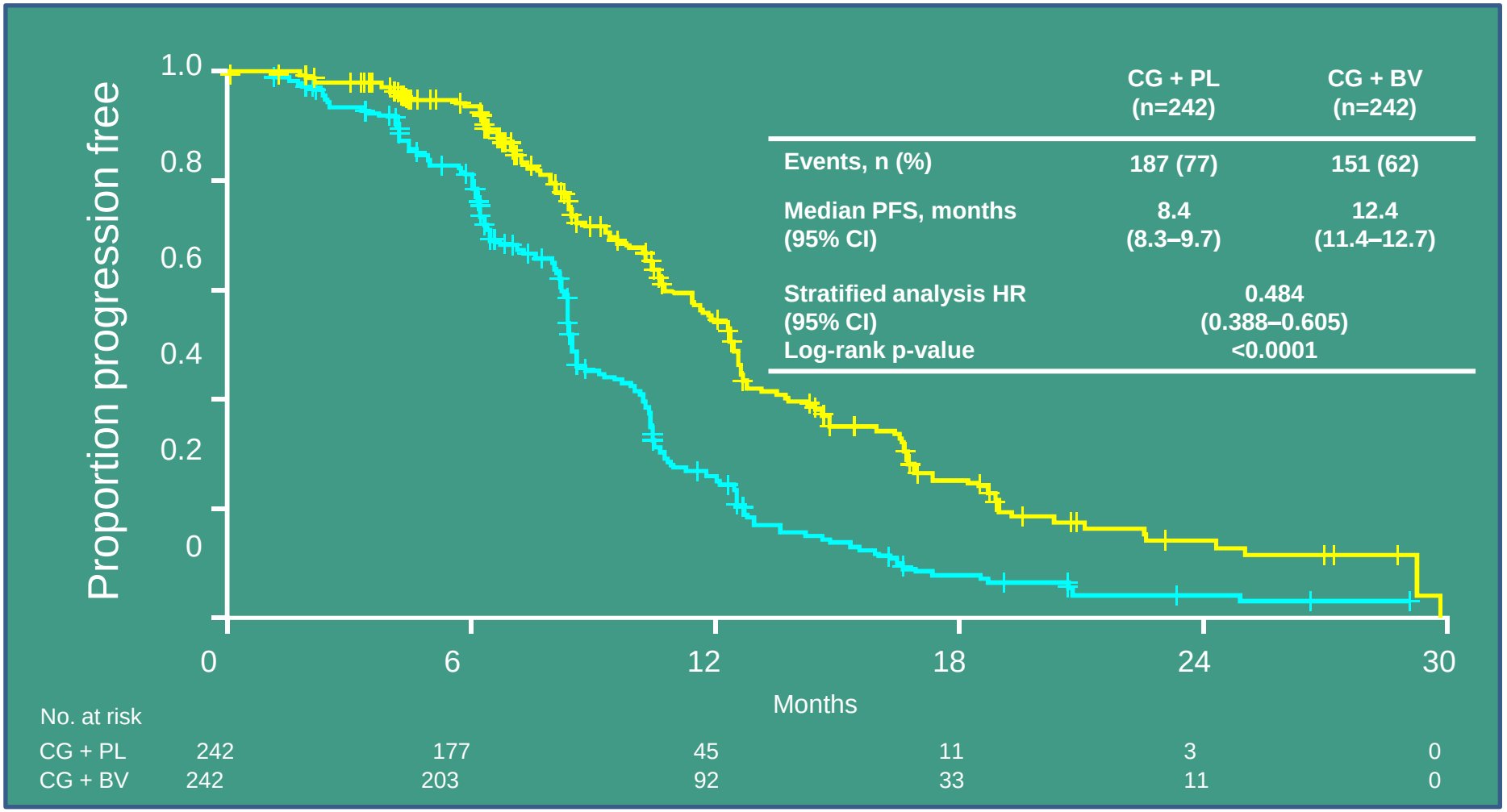
OCEANS: Objective response



Duration of response	CG + PL (n=139)	CG + BV (n=190)
Median, months	7.4	10.4
HR (95% CI)	0.534 (0.408–0.698)	
	p<0.0001[a]	

[a]Compared for descriptive purposes only

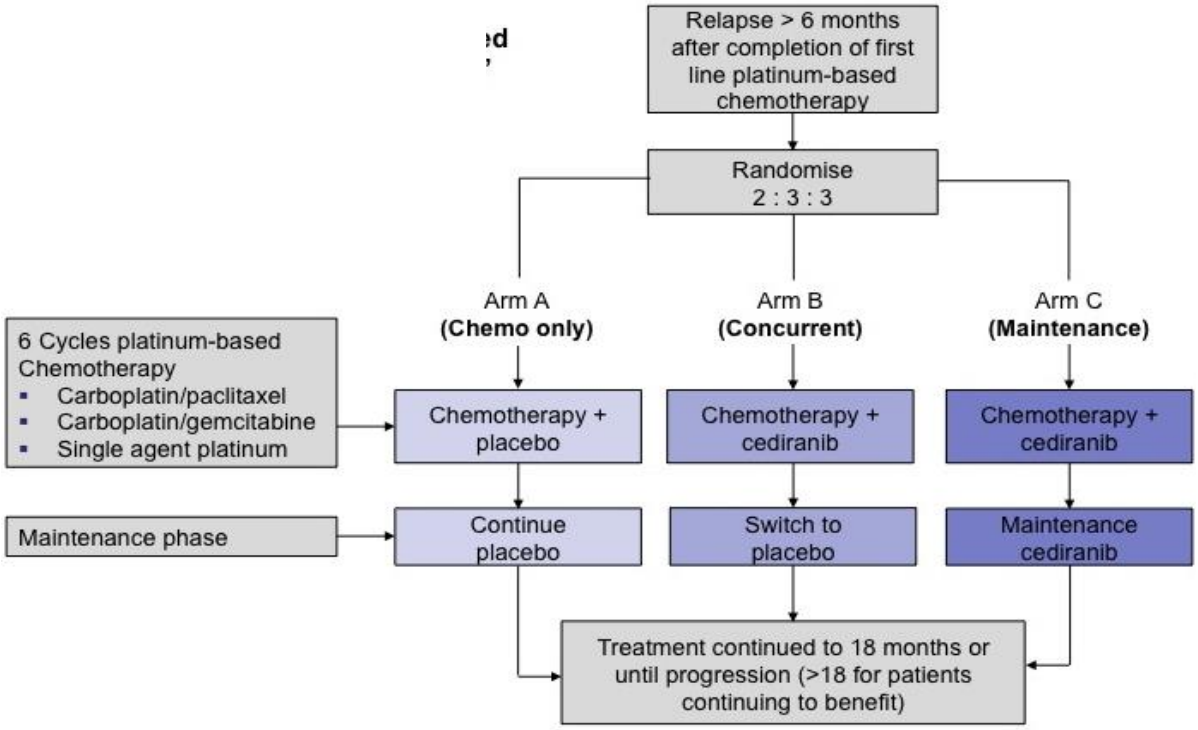
OCEANS: Primary analysis of PFS



	CG + PL (n=242)	CG + BV (n=242)
Events, n (%)	187 (77)	151 (62)
Median PFS, months (95% CI)	8.4 (8.3–9.7)	12.4 (11.4–12.7)
Stratified analysis HR (95% CI)	0.484 (0.388–0.605)	
Log-rank p-value	<0.0001	

ICON 6 trial

- Cediranib with platinum-based chemotherapy in "platinum-sensitive" relapsed ovarian cancer



Courtesy of Ledermann JA *et al*. Eur J Cancer 2013;49(Suppl 3):LBA10

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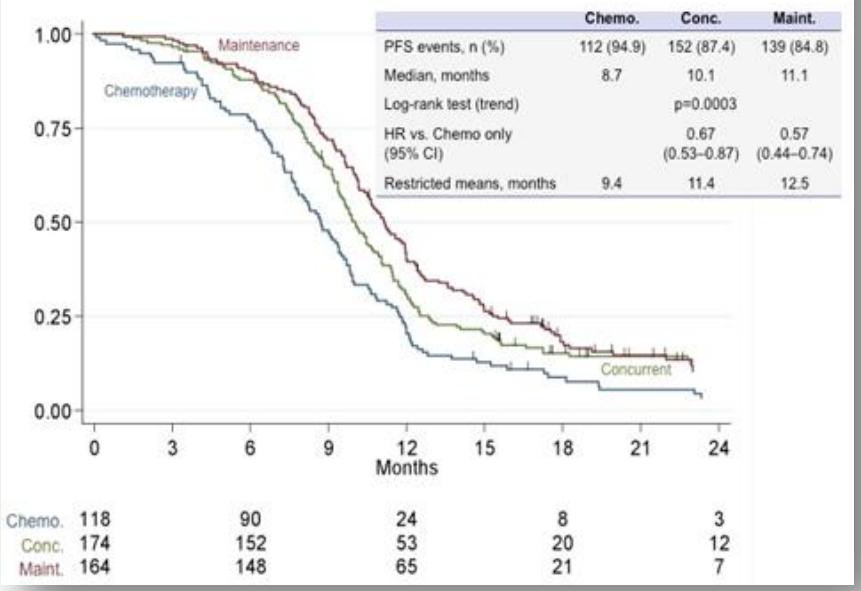
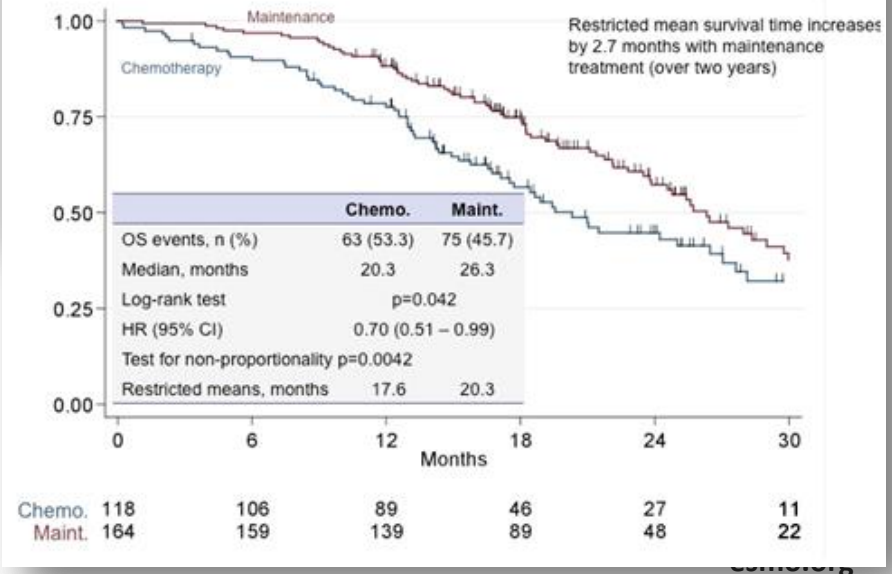
ICON 6 trial

Progression-free survival



	Chemo.	Conc.	Maint.
PFS events, n (%)	112 (94.9)	152 (87.4)	139 (84.8)
Median, months	8.7	10.1	11.1
Log-rank test (trend)		p=0.0003	
HR vs. Chemo only (95% CI)		0.67 (0.53–0.87)	0.57 (0.44–0.74)
Restricted means, months	9.4	11.4	12.5

Overall survival



	Chemo.	Maint.
OS events, n (%)	63 (53.3)	75 (45.7)
Median, months	20.3	26.3
Log-rank test	p=0.042	
HR (95% CI)	0.70 (0.51 – 0.99)	
Test for non-proportionality	p=0.0042	
Restricted means, months	17.6	20.3

Courtesy of Ledermann JA *et al*. Eur J Cancer 2013;49(Suppl 3):LBA10

In which setting it is better to give bevacizumab in ovarian cancer?

- Bevacizumab improves PFS when added to first line carboplatin-paclitaxel (GOG 218, ICON7)
- Bevacizumab improves PFS when added to carboplatin-gemcitabine in platinum sensitive recerrences (OCEAN)
- Bevacizumab improve PFS when added to chemo in platinum resistant (AURELIA)
- Ipothesis that treatment in multiple lines of therapy improves the outcome (never proved prospectively)
- Positive results for colon cancer

MADRID 2014 ESMO congress

MITO-16/MaNGO OV-2: Avastin plus chemotherapy at progression after front-line Avastin plus chemotherapy in platinum sensitive

Stage IIIB–IV EOC, FT or PPC progressing or recurring at least 6 months after front-line chemotherapy plus Avastin (n≈400)

1:1

- Carboplatin
- PLD or gemcitabine or paclitaxel

- Carboplatin
- PLD or gemcitabine or paclitaxel

Avastin15mg/kg q3w

x 6 – 8 cycles

until PD

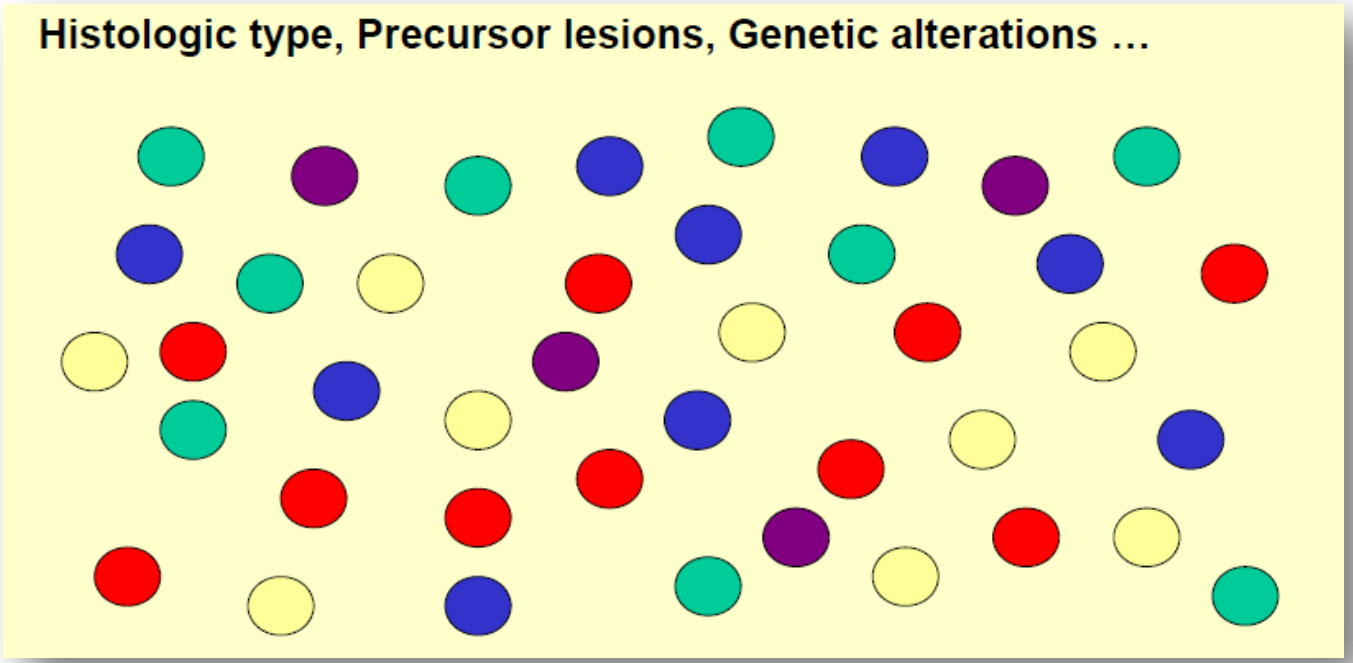
- Principal investigators: Sandro Pignata, Nicoletta Colombo
- Primary endpoint: **PFS**
- Secondary endpoint: **OS**
- 60 Italian centres involved and involvement of others European groups (ENGOT – Italy, Germany, France, Greece, Switzerland) (sponsor: INT Napoli)

Phase III study

- Epidemiology of the recurrence
- The role of surgery
- When starting therapy
- The dogma of platinum free interval
  - Resistant
  - Partially sensitive
  - Sensitive
- New drugs.. Toward a personalized therapy

Toward a personalized therapy

- Low grade serous
- Clear cells
- High grade BRCA +



MADRID 2014 ESMO congress

Nintedanib in Clear Cell Ovarian Cancer

A Randomised Phase II Study of Nintedanib versus Chemotherapy in Recurrent Clear Cell Carcinoma of the Ovary

Primary Endpoint: PFS

Secondary Endpoints: OS, Toxicity, RR, QoL, Q-Twist

90 pts with progressive or relapsed CCC of ovary within 6 months of previous platinum.

→ RANDOMISE

Chemotherapy

Ovary:

- PLDH (40mg/m^2 day 1q28)
- Weekly Paclitaxel (80mg/m^2 day 1, 8, 15 q28)
- Weekly Topotecan iv (4mg/m^2 day 1, 8, 15 q28)

Nintedanib 200mg bd until progression

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

CANCER RESEARCH UK

scottish gynaecological cancer trials group

NCRI National Cancer Research Institute

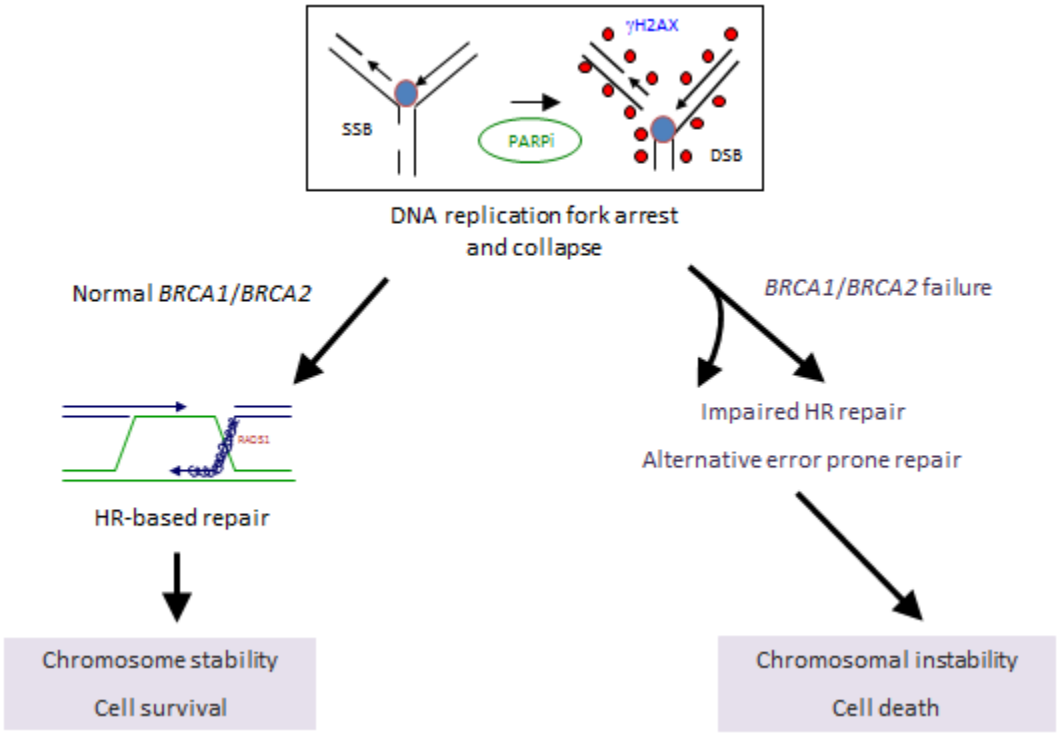
NSGO

EORTC European Organisation for Research and Treatment of Cancer

GINECO ARCAGY

PARP INHIBITORS IN HIGH GRADE OVARIAN CANCER BRCA +

PARP inhibition and tumour-selective synthetic lethality



HR, homologous recombination; SSB, single-strand break; DSB, double-strand break

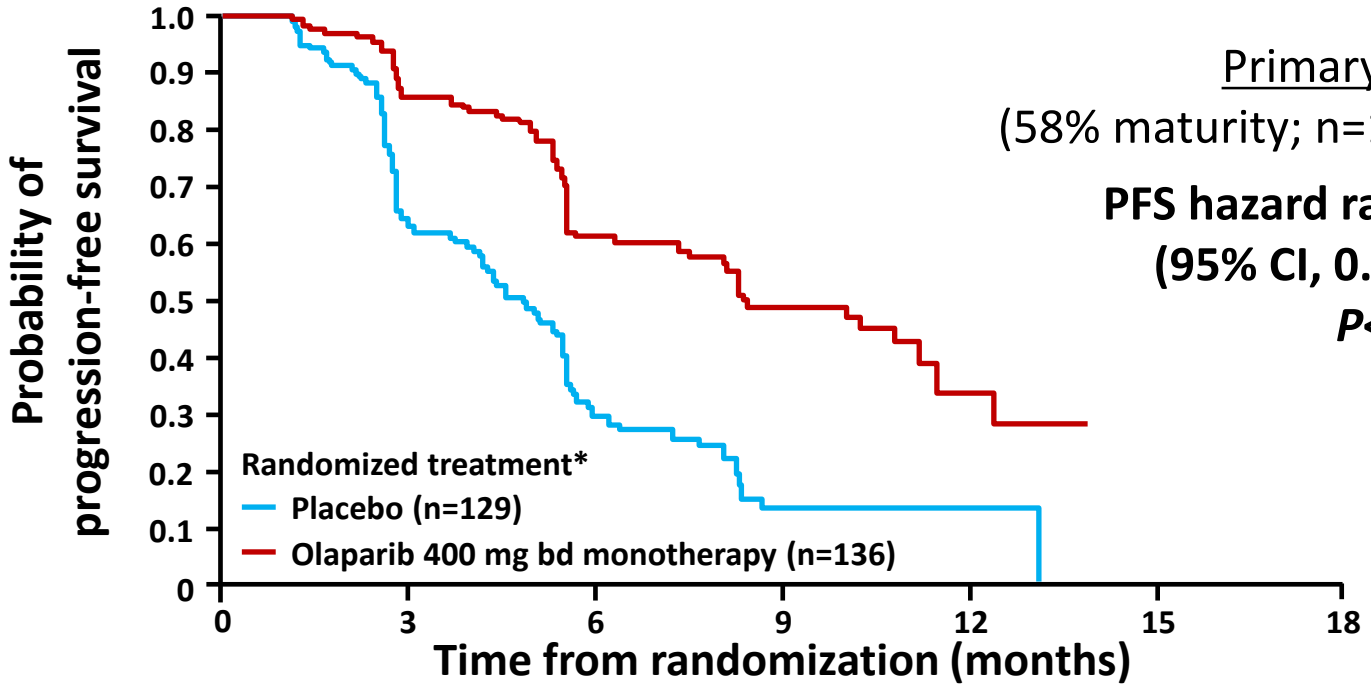
Farmer H *et al. Nature* 2005;**434**:917–921; Bryant HE *et al. Nature* 2005;**434**:913–917

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Study 19: Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer

- Patients were randomized after response to platinum-based chemotherapy



Primary analysis
(58% maturity; n=154/265)

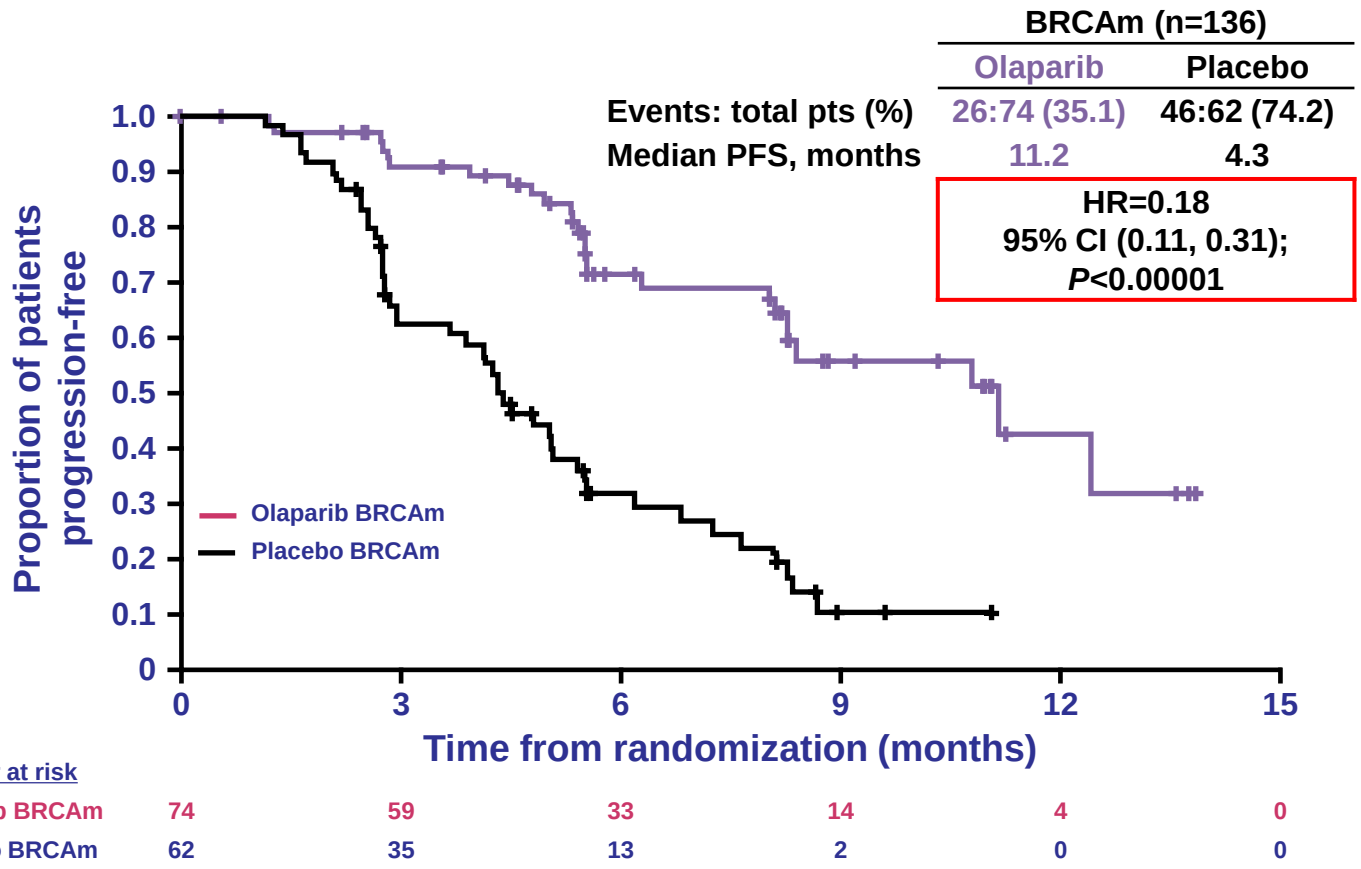
PFS hazard ratio=0.35
(95% CI, 0.25–0.49)
***P*<0.00001**

- Interim OS analysis (38% maturity): HR=0.94; 95% CI, 0.63–1.39; *P*=0.75

*Patients were treated until disease progression

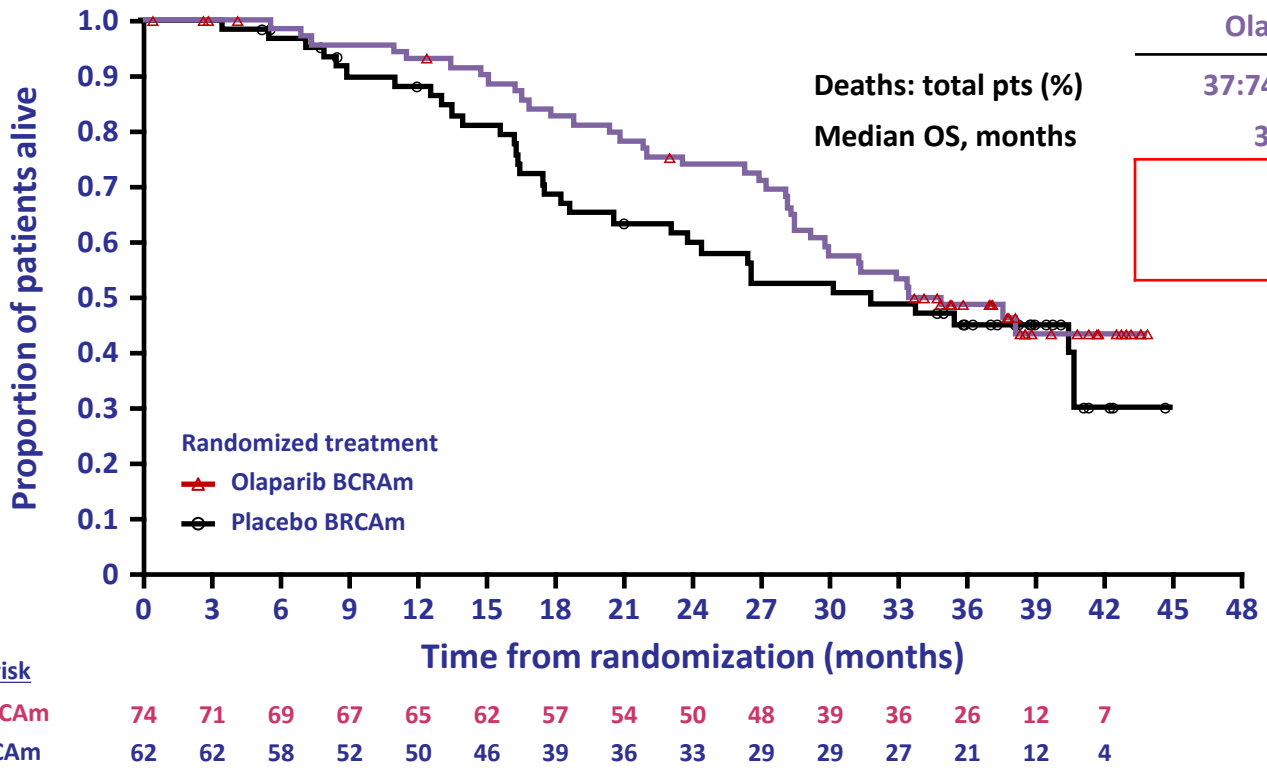
Ledermann J *et al*. *N Engl J Med* 2012;366:1382–1392

PFS by BRCAm status



- 82% reduction in risk of disease progression or death with olaparib

OS in BRCAm patients



BRCAm (n=136)	
Olaparib	Placebo
Deaths: total pts (%) 37:74 (50.0)	34:62 (54.8)
Median OS, months 34.9	31.9

HR=0.74
95% CI (0.46, 1.19)
P=0.208

Number at risk

Olaparib BRCAm	74	71	69	67	65	62	57	54	50	48	39	36	26	12	7
Placebo BRCAm	62	62	58	52	50	46	39	36	33	29	29	27	21	12	4

- OS in BRCAwt patients: HR=0.98; 95% CI, 0.62–1.55; *P*=0.946
  - Median OS: olaparib, 24.5 months; placebo, 26.2 months
- 14/62 (22.6%) placebo patients switched to a PARP inhibitor

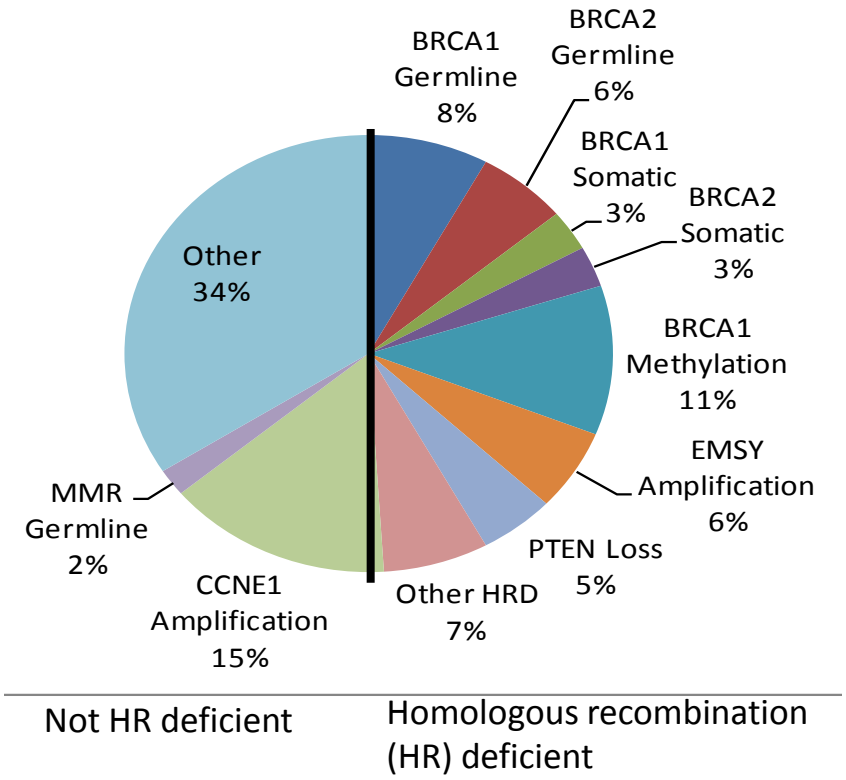
SOLO
BRCAm Ovarian Cancer

First line

Second line

Potential of PARP inhibitors in sporadic ovarian cancer

The Cancer Genome Atlas, Molecular profiling of serous ovarian cancer, D. Levine 2011

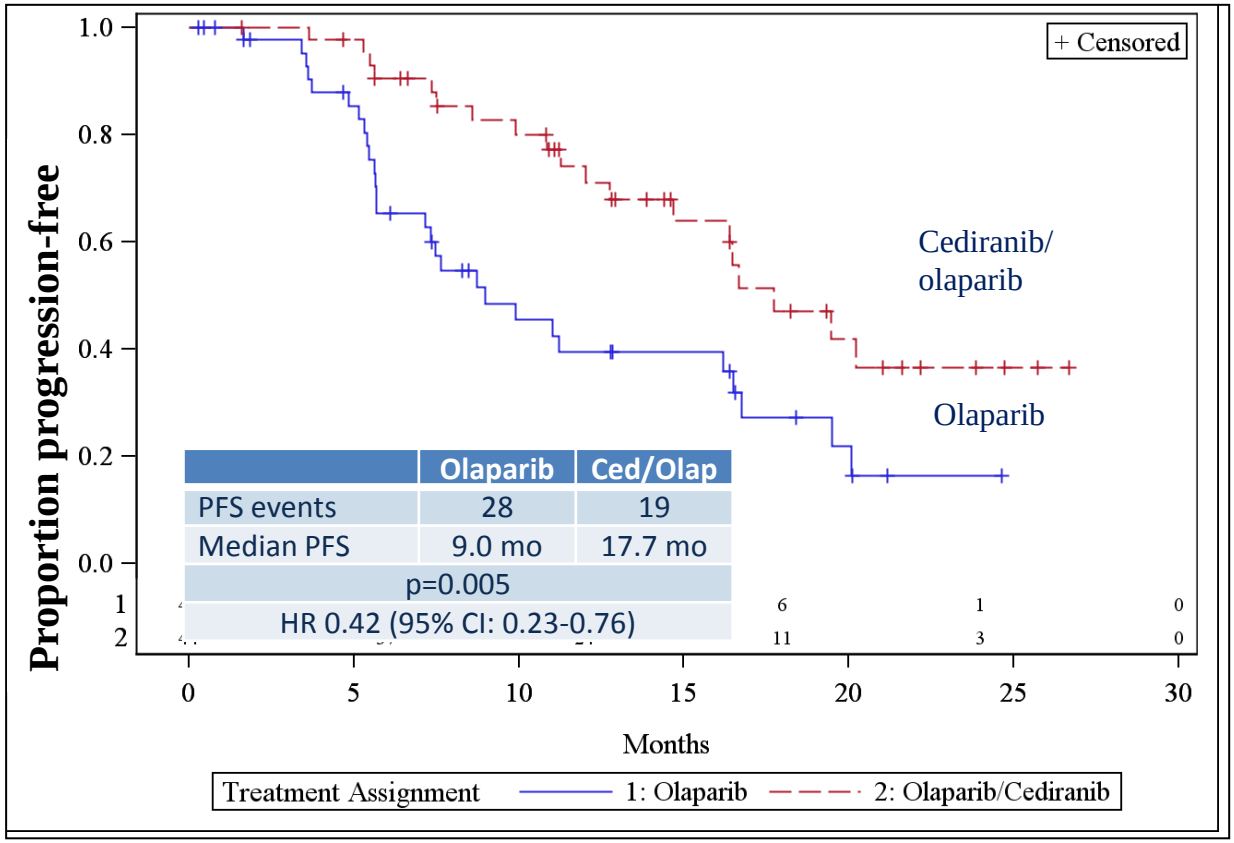


- approximately 50% of patients with high grade serous ovarian cancer predicted to be candidates for PARPi therapy

Further development for PARP inhibition in ovarian cancer

- Patients with somatic mutations or epigenetic silencing
- Combination wih antiangiogenetic drugs

Cediranib/olaparib significantly increased PFS compared to olaparib alone



Joyce Liu, et al. ASCO 2014

General conclusions

- Surgery can be considered in selected patients
- Chemo given according to platinum-free interaval and previous toxicity
- Chemotherapy can probably chronicize the disease although poorly effective in resistant disease
- Bevacizumab first drug added to chemotherapy based on positive phase III trials
- PARPi most promising drugs
- Moving vs an histology driven therapy