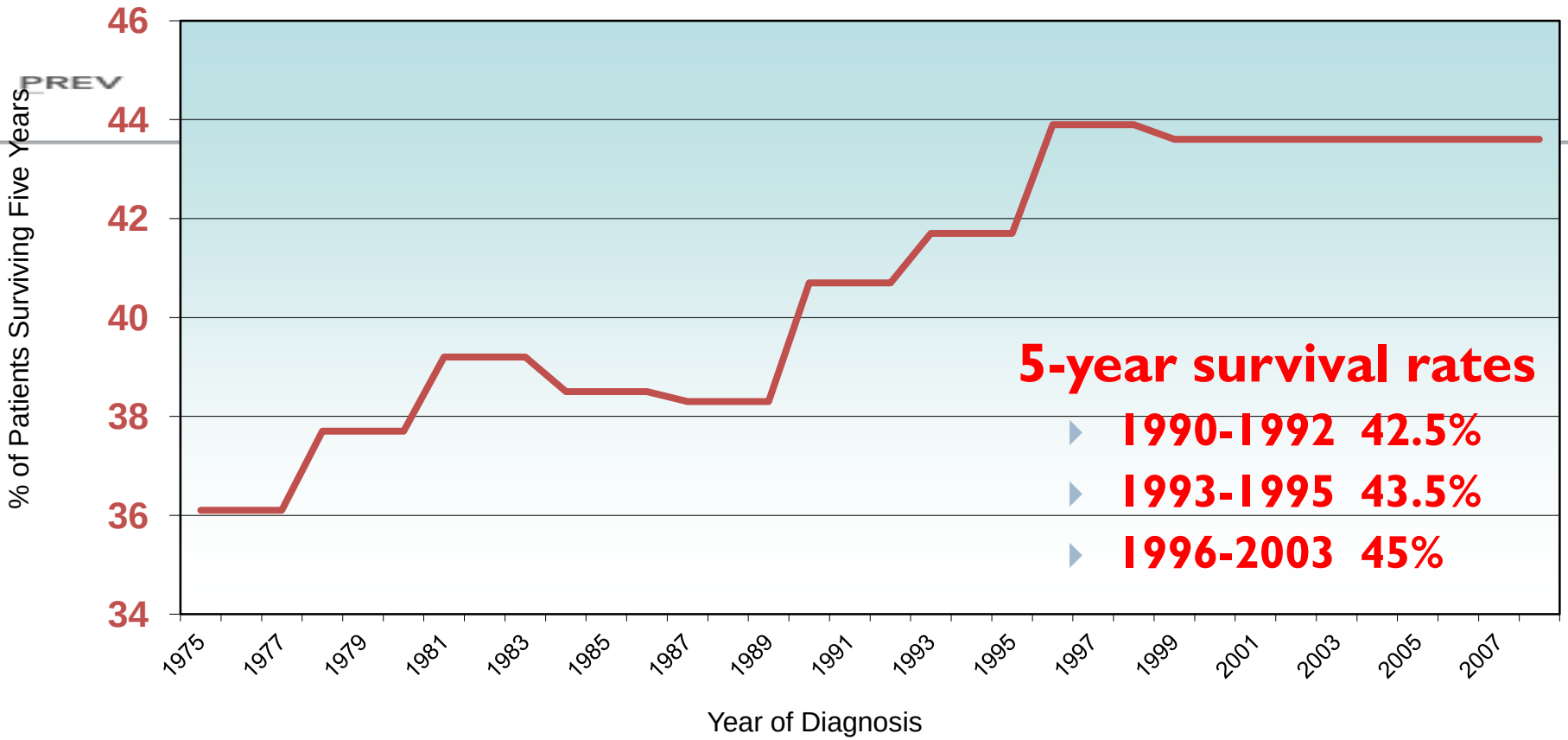
FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

CARCINOMA OVARICO AVANZATO
QUALI NOVITA PER IL 2015'?
Negrar 16 Febbario 2015

Domenica Lorusso
Gynecologic Oncologic Unit
National Cancer Institute-Milan

Gli inibitori di parp nel carcinoma ovarico

Chemotherapy



Ovarian Cancer First-Line: Carboplatin-Paclitaxel Standard

- 70% of patients respond to first line treatment
  - Progression-free survival (PFS): 16-23 months
  - 65% to 70% of patients requiring second-line treatment (within 2 years)
  - Overall survival (OS): 31-65 months
  - 5-year survival 30%

FIGO Annual Report

Carcinoma of the Ovary: 5-yr Survival Rates

Table 11
Carcinoma of the ovary: patients treated in 1996–98. Epithelial ovarian cancer (obviously malignant cases). Five-year survival by stage

Vol.	Year	Cases (*n*)	Ia	Ib	Ic	IIa	IIb	IIc	IIIa	IIIb	IIIc	IV	Overall %
15	1958–62	2320	60.7	(Ib–IIa) 42.0			31.6		(IIIa–IIIc) 6.9			2.6	26.8
16	1963–68	4588	66.7	51.9		49.7	(IIb–IIc) 38.0		(IIIa–IIIc) 8.6			5.0	27.3
17	1969–72	4892	72.0	62.5	57.4	52.2	(IIb–IIc) 37.5		(IIIa–IIIc) 10.8			4.6	30.1
18	1973–75	5268	69.7	63.9	50.3	51.8	(IIb–IIc) 42.2		(IIIa–IIIc) 13.3			4.1	30.5
19	1976–78	6724	72.3	56.1	58.1	47.7	(IIb–IIc) 42.1		(IIIa–IIIc) 13.5			4.5	29.8
20	1979–81	8082	76.6	67.7	59.6	51.1	(IIb–IIc) 43.5		(IIIa–IIIc) 17.4			4.7	30.9
21	1982–86	10912	82.3	74.9	67.7	60.6	(IIb–IIc) 53.8		(IIIa–IIIc) 22.7			8.0	35.0
22	1987–89	2942	83.5	79.3	73.1	64.6	(IIb–IIc) 58.0		(IIIa–IIIc) 22.9			14.3	39.1
23	1990–92	7059	83.5	71.3	79.2	66.6	55.1	57.0	41.1	24.9	23.4	11.1	41.6
24	1993–95	3409	89.9	84.7	80.0	69.9	63.7	66.5	58.5	39.9	28.7	16.8	48.4
25	**1996–98**	**4116**	**89.3**	**64.8**	**78.2**	**79.2**	**64.3**	**68.2**	**49.2**	**40.8**	**28.9**	**13.4**	**46.4**
Total		**60312**											

The challenge of going beyond carboplatin/paclitaxel: key trials worldwide

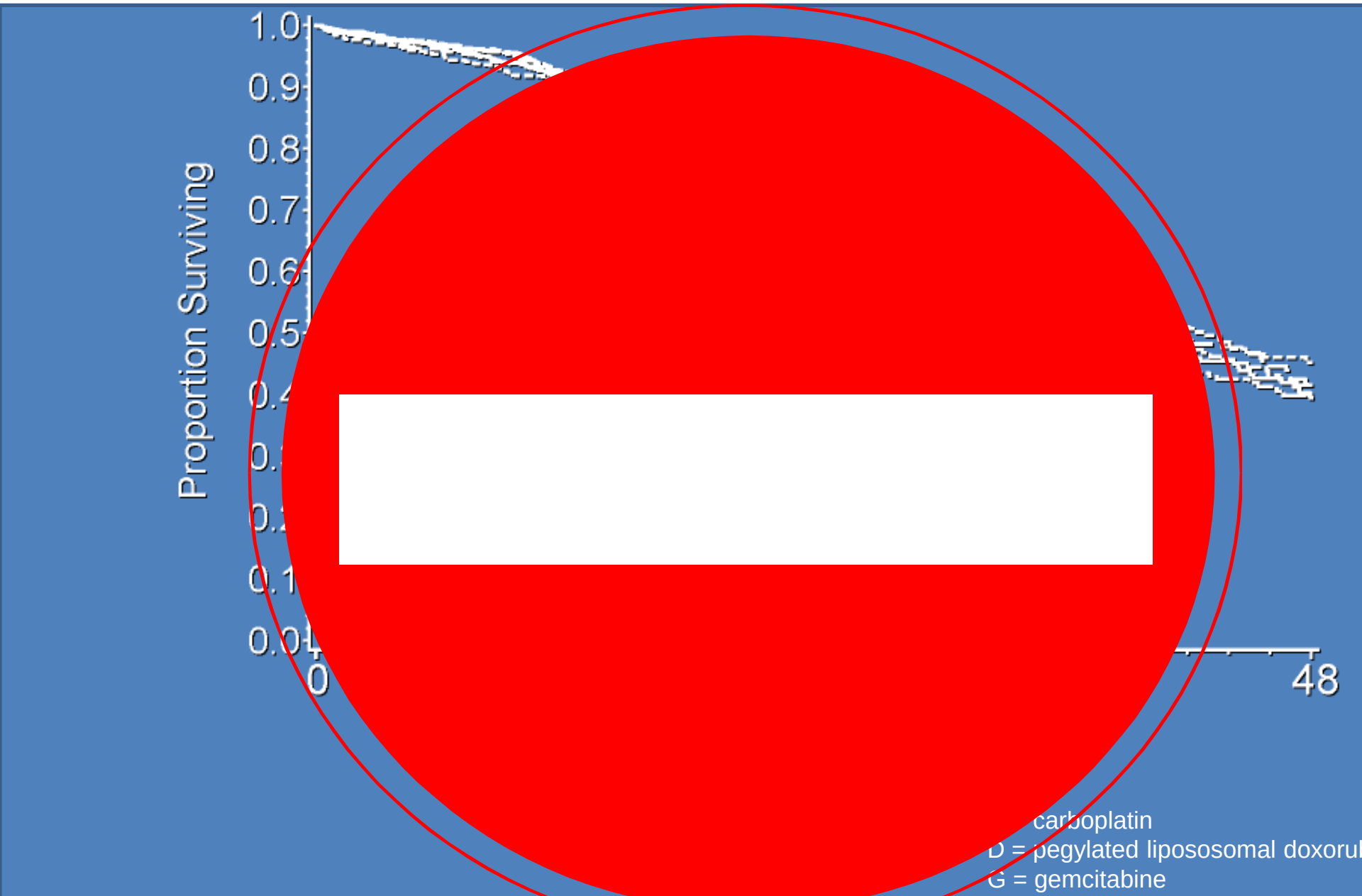
1995

2010

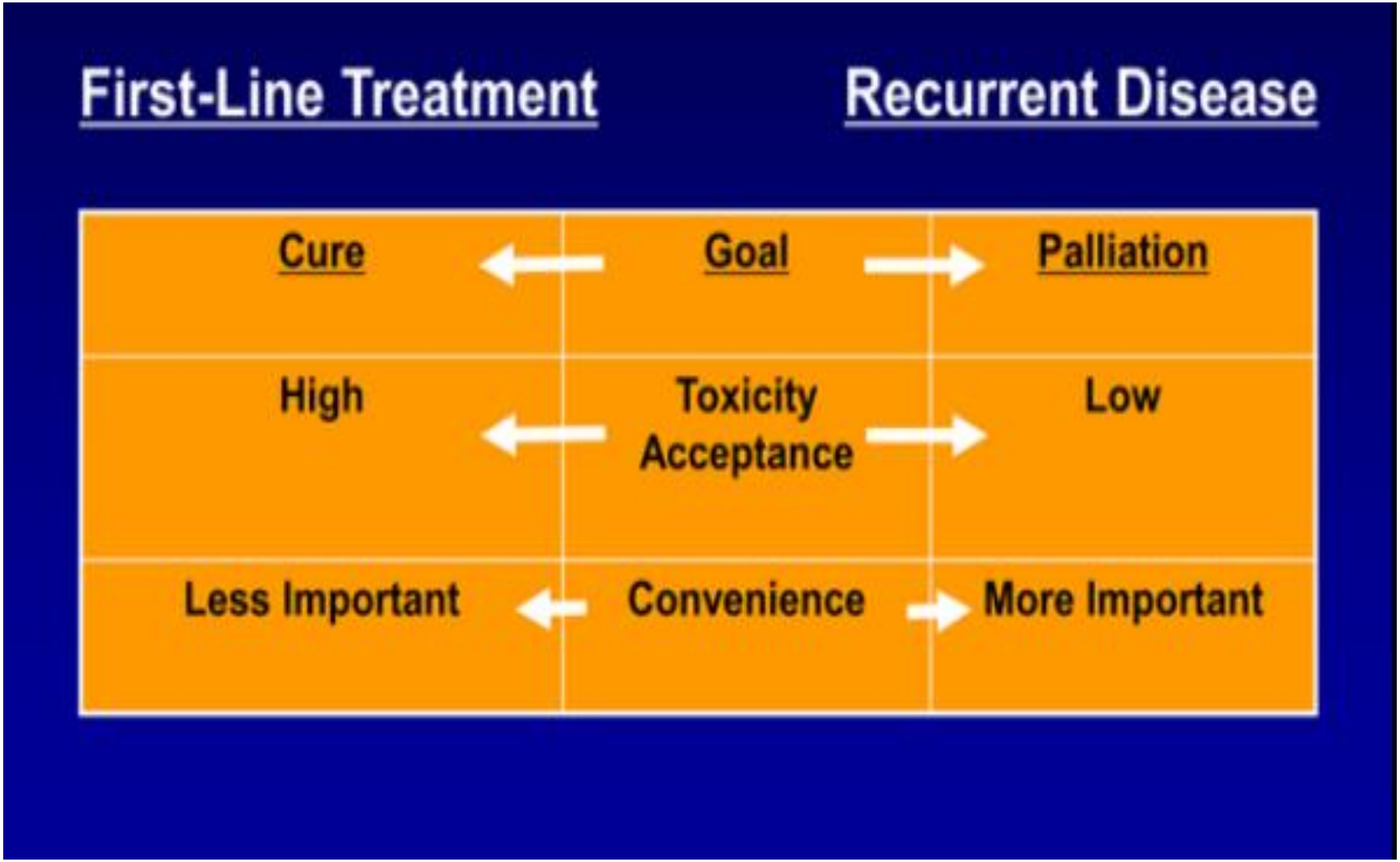
Trial	n	Regimens compared	Outcome
GOG-0162	324	Cis + either 24 h or 96 h pac	Efficacy similar
AGO-GINECO	1,282	Carbo/pac vs carbo/pac/epirubicin	No benefit of a third agent
MITO-1	273	Carbo/pac x6 → topo x4 or surveillance	No PFS benefit with topo maintenance
GOG-0172	**429**	**IV cis/IV pac vs IP cis/IP pac**	**IP has better efficacy/worse toxicity and QoL**
GCIG	887	Carbo/pac vs carbo/pac/epirubicin	No benefit of a third agent
AGO-GINECO	1,308	Carbo/pac → topo x4 or surveillance	No benefit of topo maintenance
GOG-0178	277	Cis/pac → pac x3 vs x12 cycles in patients in CR	PFS improved with pac x12 cycles/no OS difference in a selected patient population
GOG-0182	4,312	Carbo/pac vs carbo/pac/gem (2 regimens) vs carbo/pac/topo vs carbo/pac/PLD	No benefit of a third agent
OV16	819	Carbo/pac x8 vs cis/topo x4 → carbo/pac x4	Efficacy similar; tolerability better with carbo/pac
AGO-OVAR9	1,742	Carbo/pac vs carbo/pac/gem	No benefit of a third agent

Carbo = carboplatin; cis = cisplatin; CR = complete response; cyclo = cyclophosphamide; gem = gemcitabine; IP = intraperitoneal; IV = intravenous; pac = paclitaxel; PLD = pegylated liposomal doxorubicin; topo = topotecan

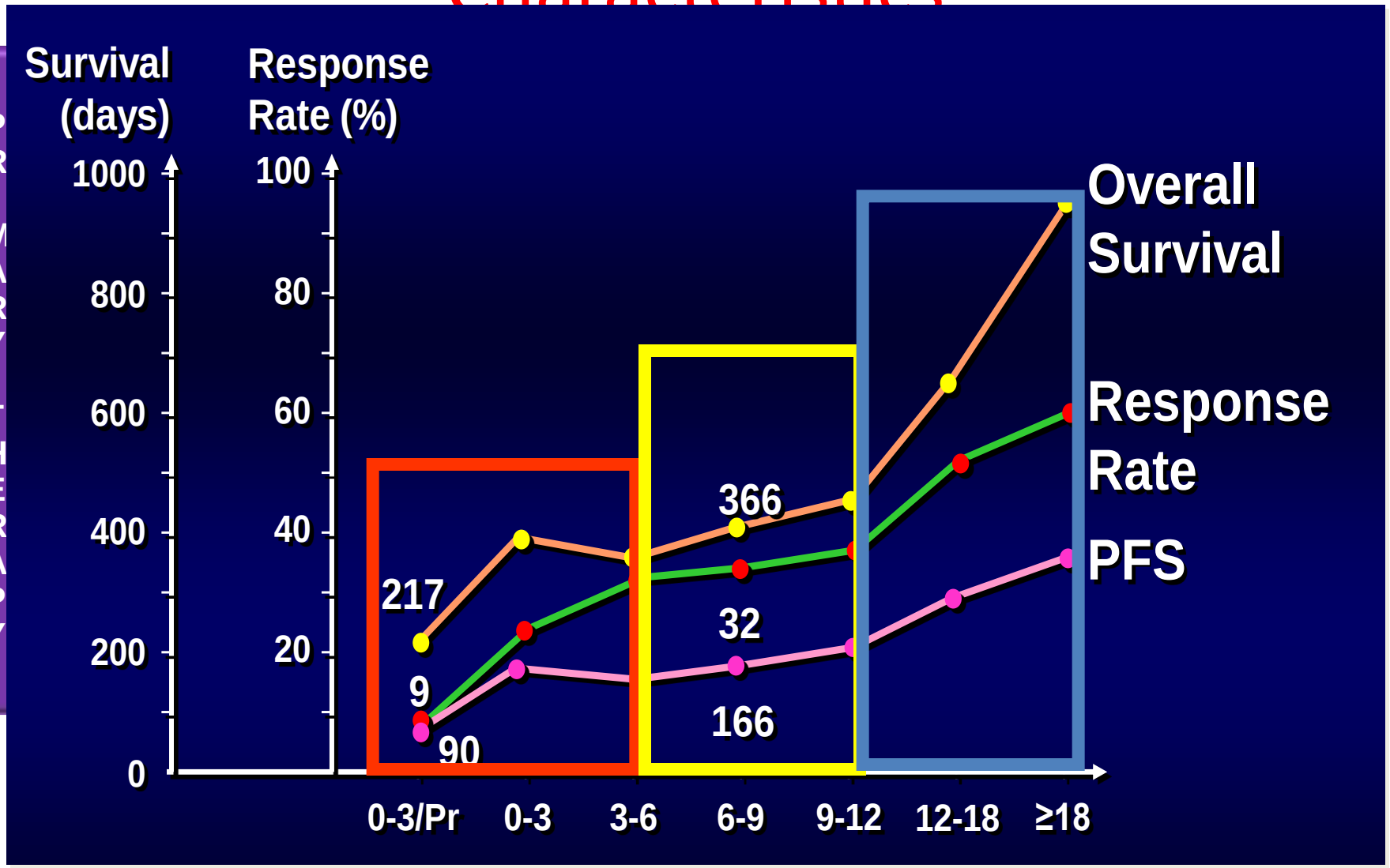
GOG0182-ICON5: Overall Survival



Treatment Considerations



Recurrent Ovarian Cancer: Population Characteristics



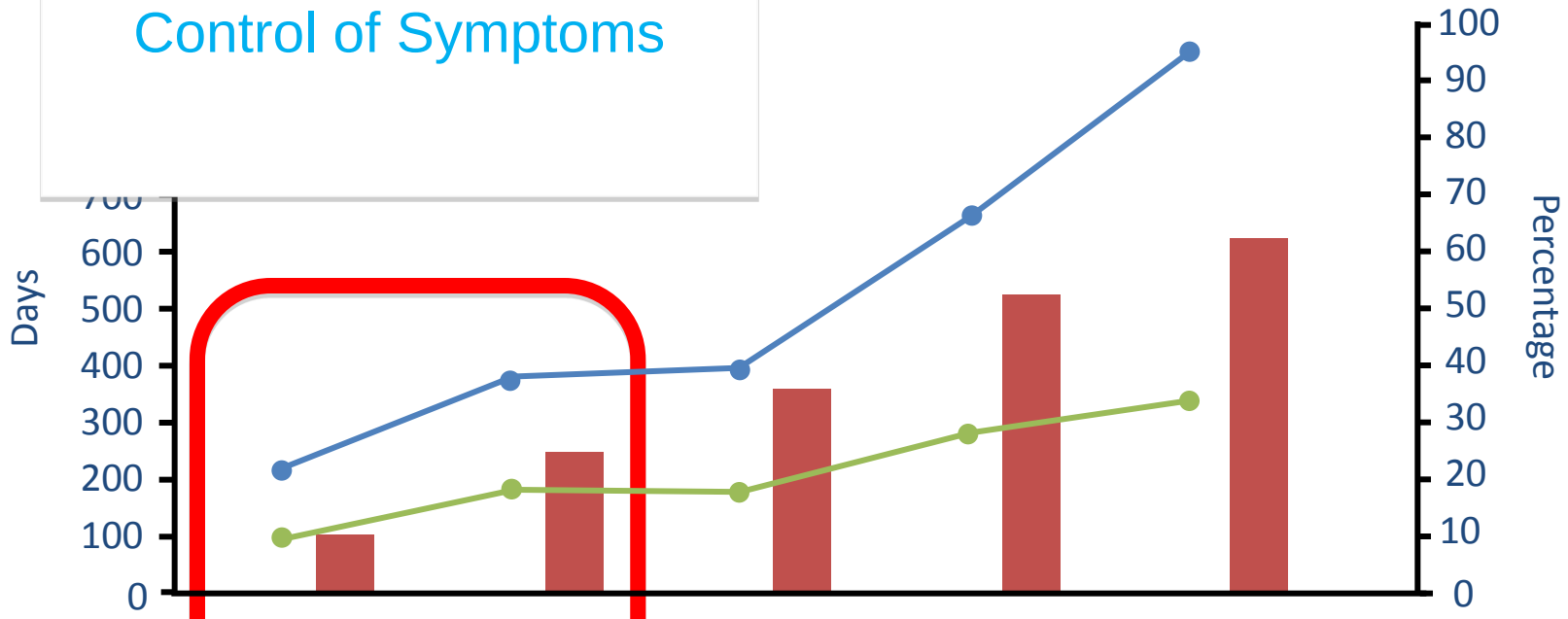
Pisano et al. Ther Clin Risk Manag. 2009;5:421-426; Gadducci et al. Anticancer Res. 2001;21:3525-3533.

Treatment of Recurrent Ovarian Cancer

Early relapse: PFI < 6m
(Platinum-resistant)

QoL

Control of Symptoms



	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.

Active Single-Agents in Recurrent Ovarian Cancer

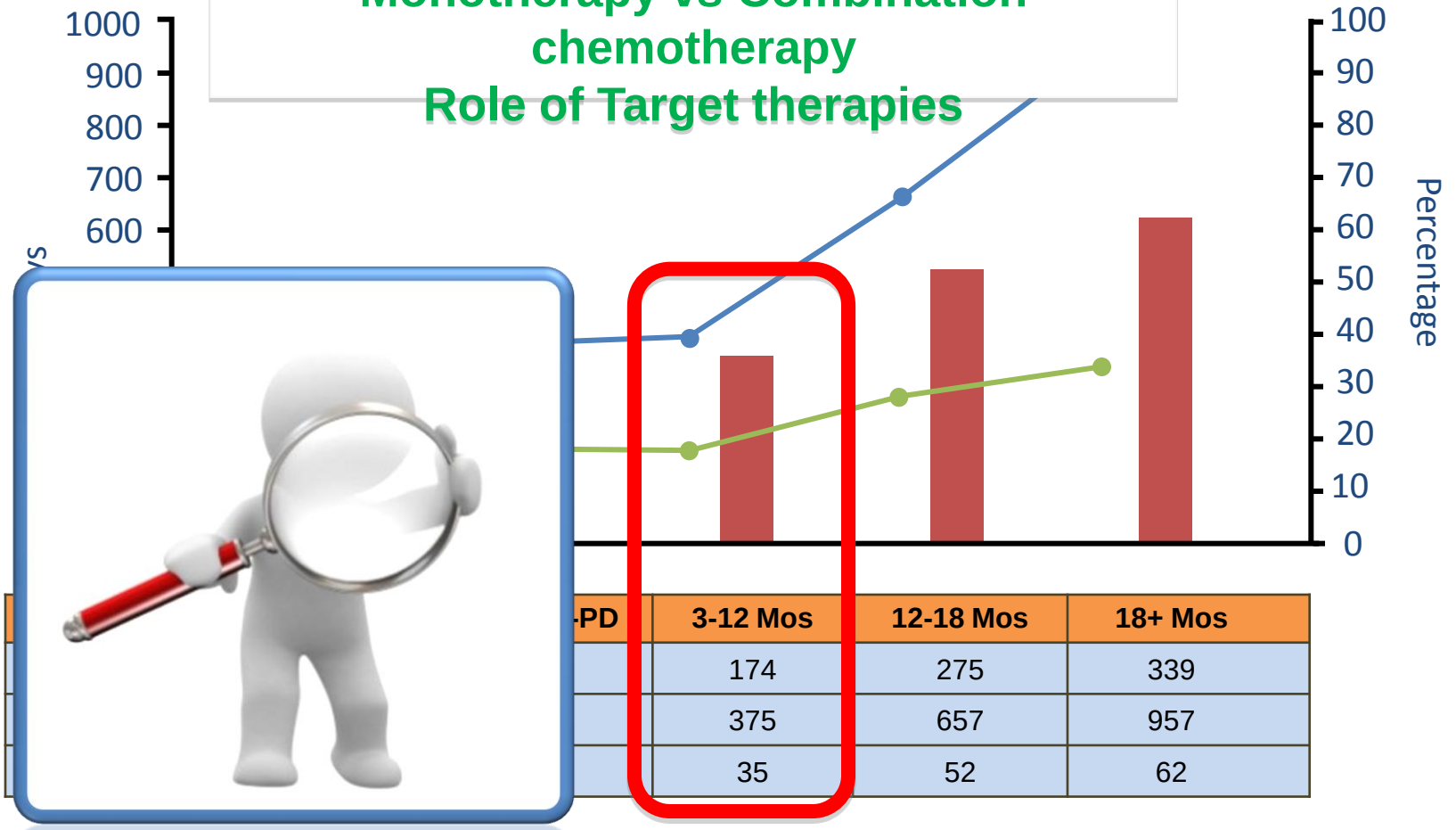
Agent	Response Rates		Patient Tolerance/QoL Issues
	Platinum-Sensitive	Platinum-Resistant	
PLD	28%	7%	HFS, mucositis
Paclitaxel	20-45%	12%	Alopecia, peripheral neuropathy, arthralgias/myalgias
Etoposide	34%	9%	Alopecia, GI toxicity
Gemcitabine	34%	10%	Flu-like constitutional symptoms, hepatic dysfunction, dyspnea
Yondelis	36%	8%	Transaminases elevation, Asthenia, GI toxicity
Vinorelbine	29%	10%	Constipation, nausea, peripheral neuropathy
Topotecan	33%	4%	Asthenia, alopecia, schedule

Armstrong et al. *The Oncologist*. 2002;7:20-28; Herzog. *Clin Cancer Res*. 2004;10:7439-7449.

Treatment of Recurrent Ovarian Cancer

Progression-free interval 6-12m
(Partially Platinum-Sensitive)

Platinum-based vs non-platinum based
Monotherapy vs Combination chemotherapy
Role of Target therapies



-PD	3-12 Mos	12-18 Mos	18+ Mos
	174	275	339
	375	657	957
	35	52	62

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

Recurrent Ovarian Cancer (ROC):

Population Characteristics

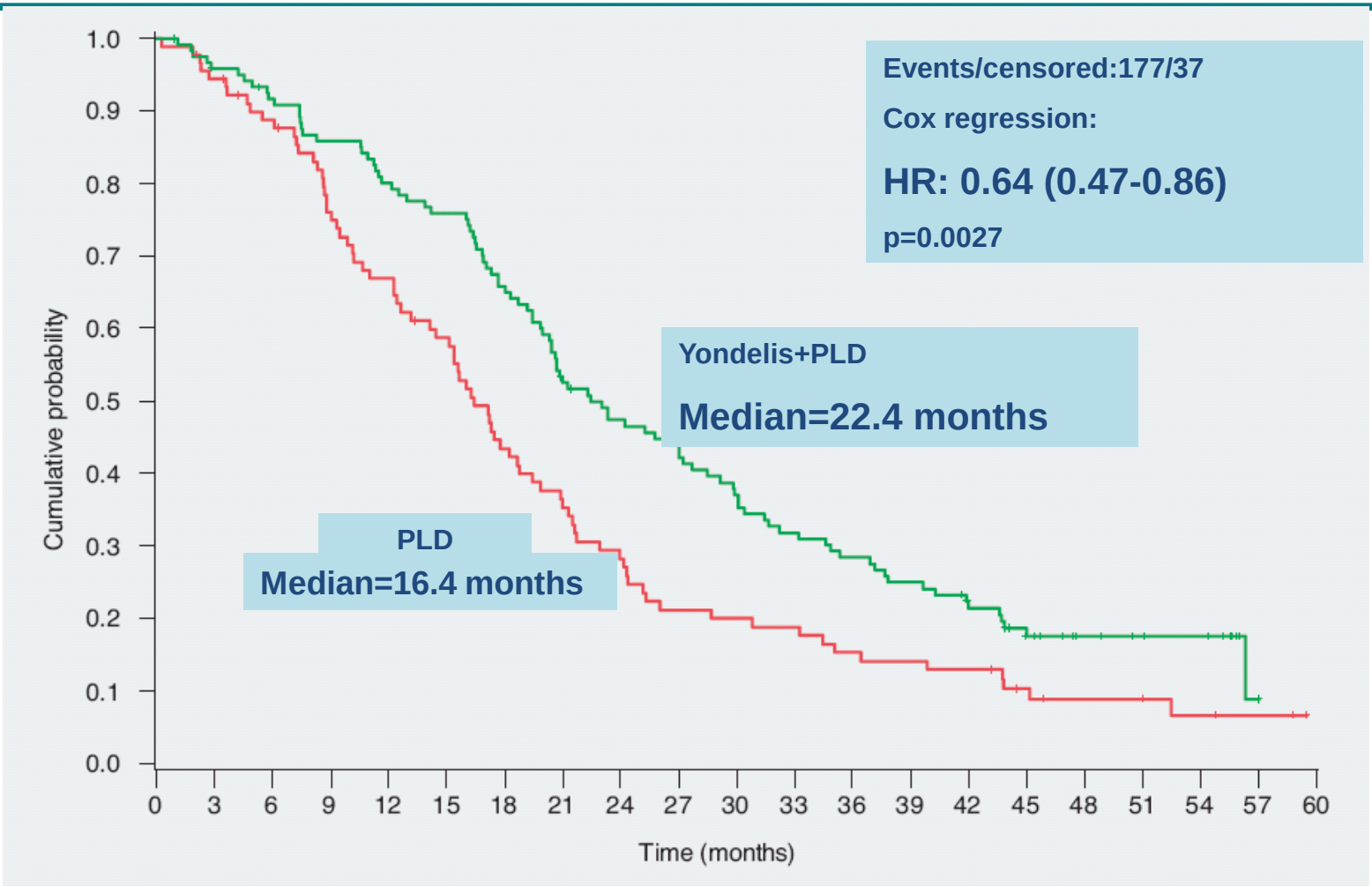
	Response to Platinum	
	Time to Recurrence	Response to Further Platinum
Platinum-sensitive	12 mo	30-60%
Platinum-partially sensitive	6-12 mo	25-30%
Platinum-resistant	< 6 mo	< 10%
Platinum-refractory	No initial response	N/A

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

Armstrong et al. *The Oncologist*. 2002;7:20-28; Herzog. *Clin Cancer Res*. 2004;10:7439-7449.

Role of Yondelis+PLD in PPS Ovarian Cancer: OS data

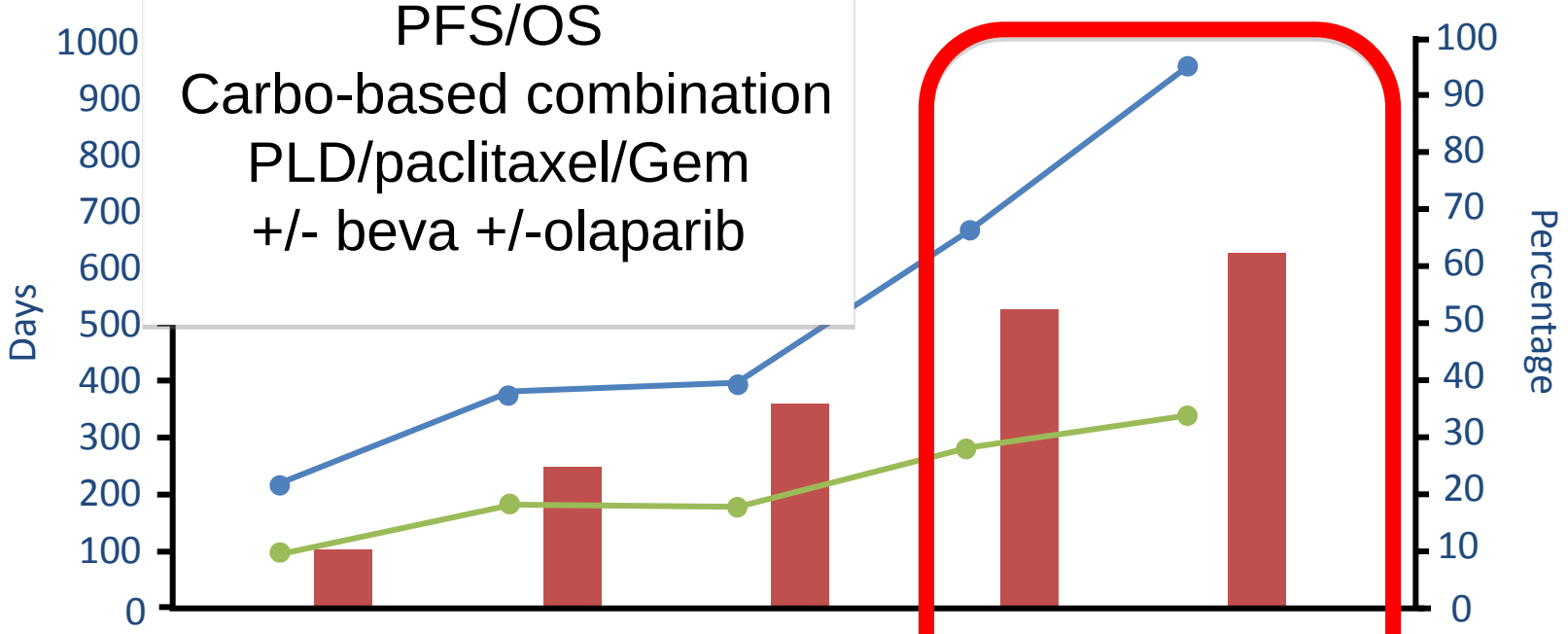


Monk BJ et al. J Clin Oncol. 2011:29(suppl):abstr 5046.
Sehouli J, Gonzalez A. Ann Oncol 2011. Epub 2011 Jul 6. DOI: 10.1093/annonc/mdr321

Treatment of Recurrent Ovarian Cancer

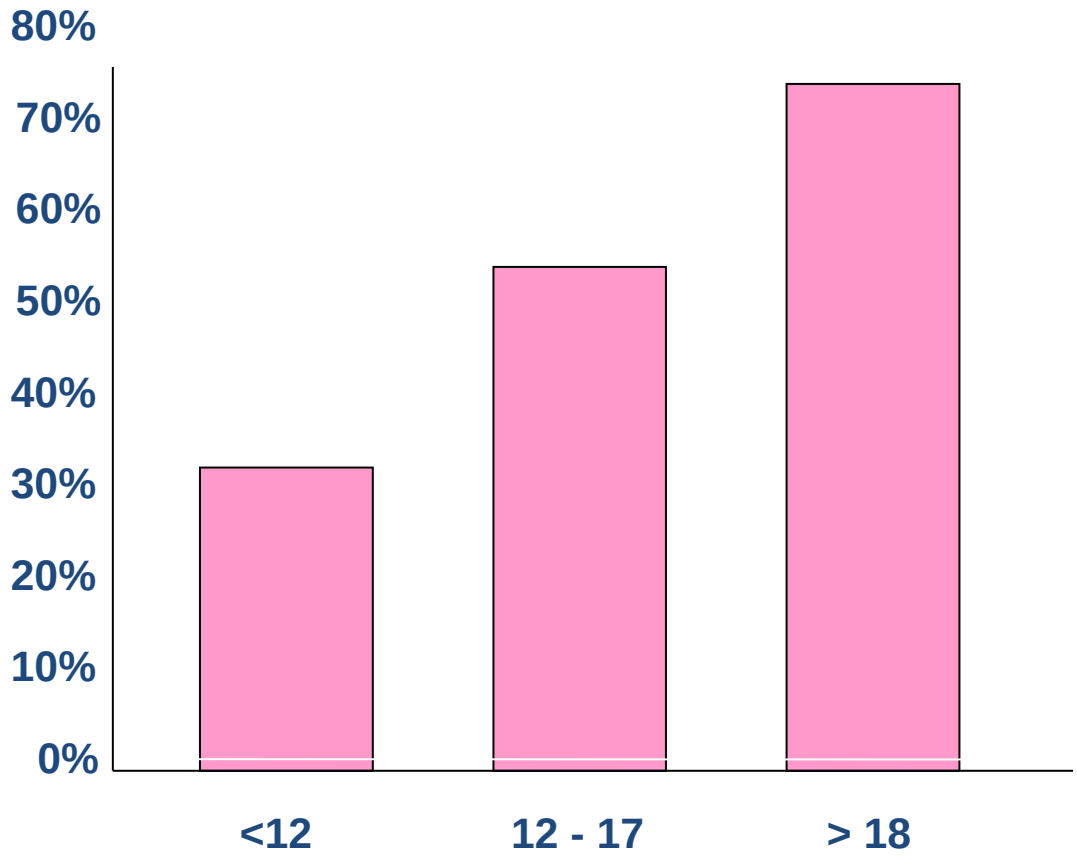
Late relapse: PFI > 12m
(Platinum-Sensitive)

PFS/OS
Carbo-based combination
PLD/paclitaxel/Gem
+/- beva +/-olaparib



	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

Effect of Platinum-Free Interval on Platinum Rechallenge



Markman, J Clin Oncol. 2004

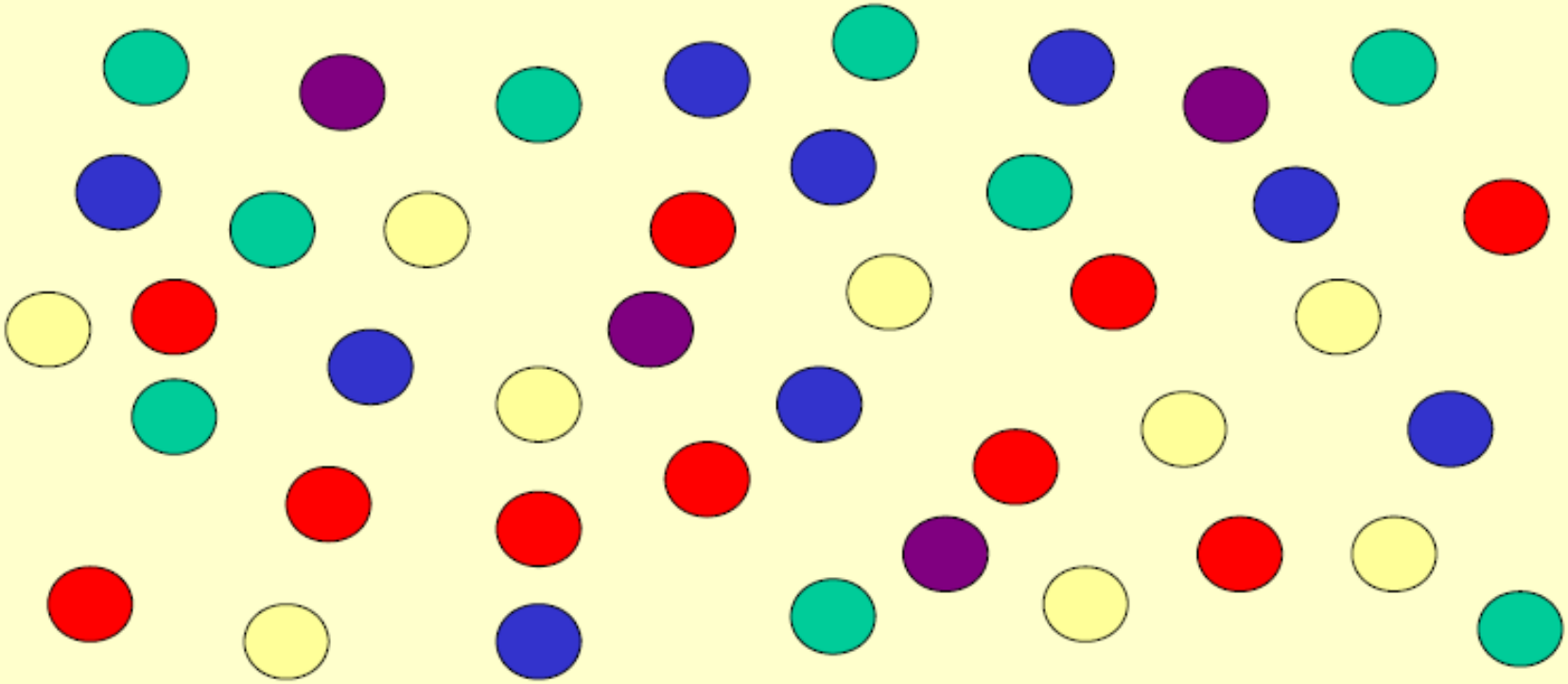
RANDOMIZED PHASE III TRIALS ON PLATINUM-BASED CHEMOTHERAPY IN PARTIALLY PLATINUM SENSITIVE OVARIAN CANCER PATIENTS

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

* on the whole population

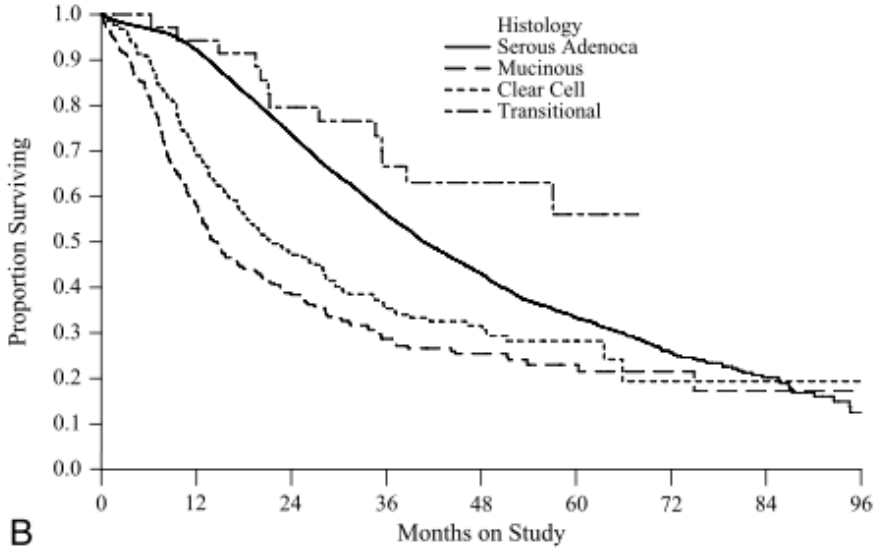
EPITHELIAL OVARIAN TUMORS
A heterogeneous group

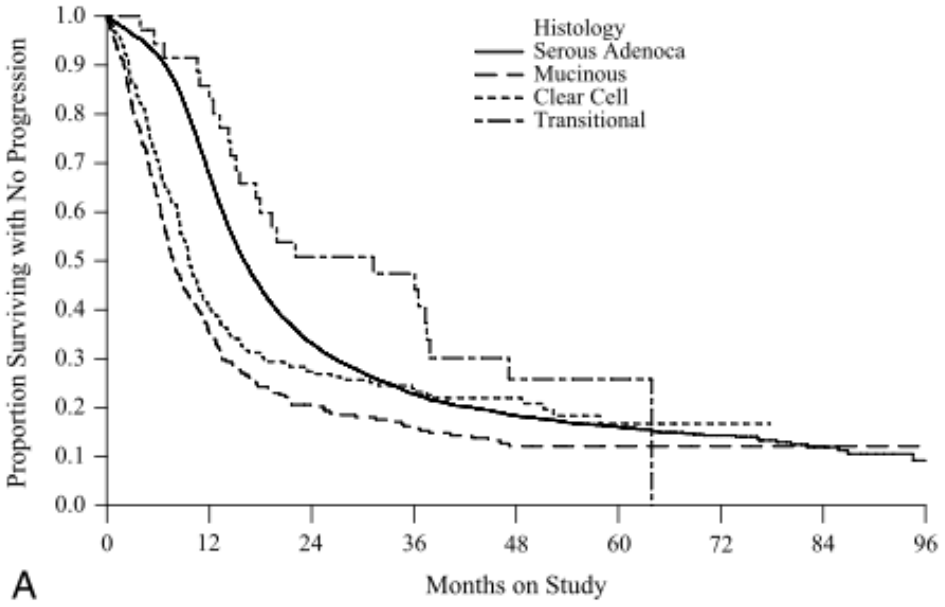
Histologic type, Precursor lesions, Genetic alterations …



Ovarian cancer not one disease

8704 patients from 7 randomised trials

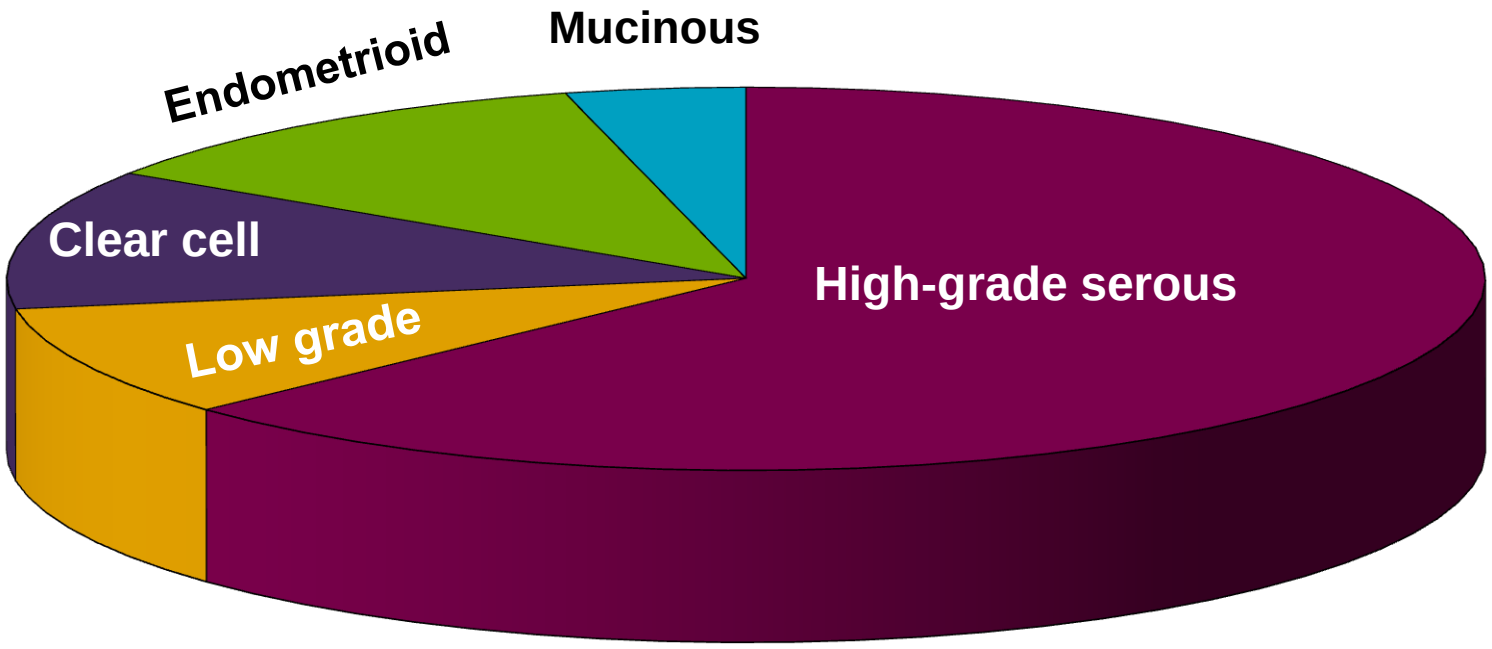




Adenoca: adenocarcinoma

Mackay et al. Int J Gynecol Cancer 2010

Histopathological subtypes of ovarian cancer



Soslow. Int J Gynecol Pathol 2008
McCluggage. Pathology 2011

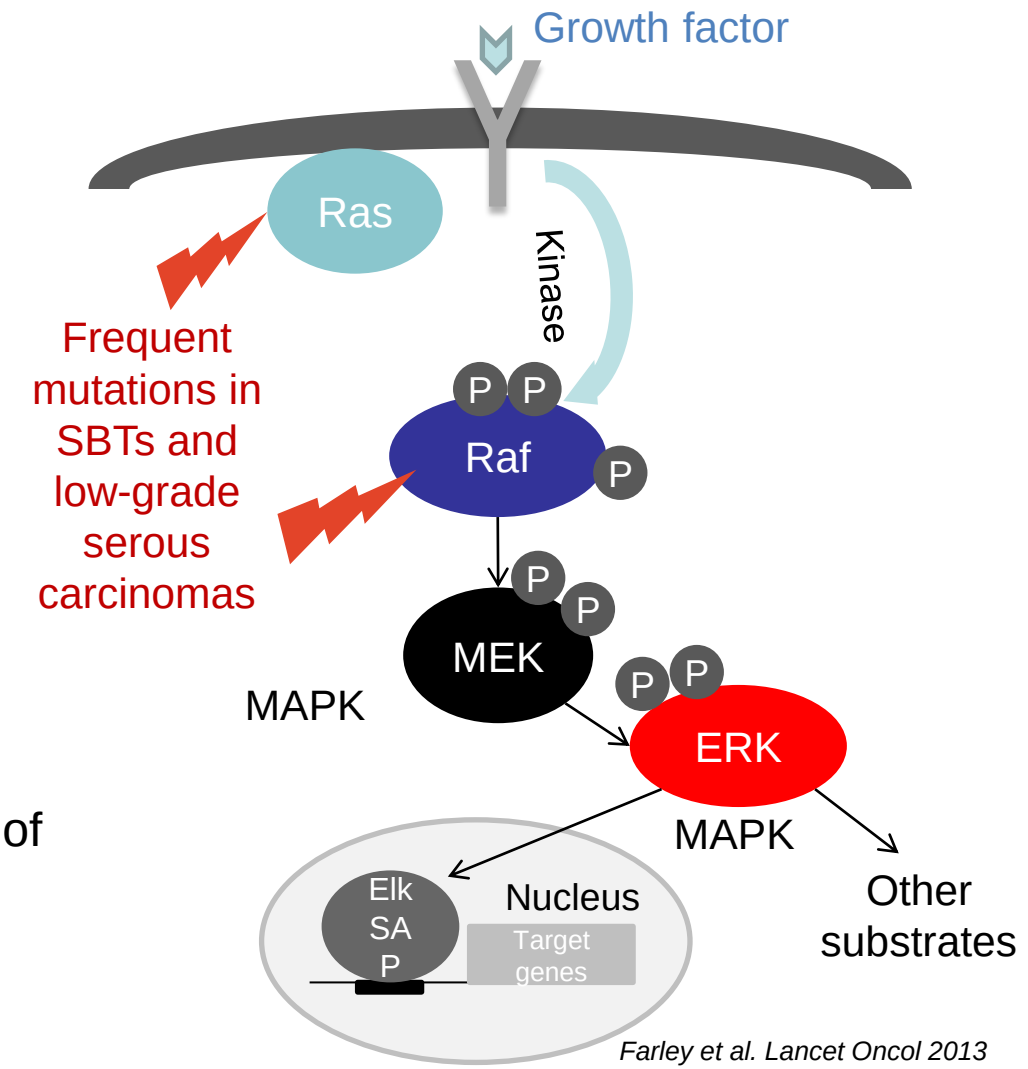
CARCINOMA OVAIO il punto di vista del patologo

5 TIPI ISTOLOGICI

	SIEROSO ALTO GRADO	SIEROSO BASSO GRADO	CELLULE CHIARE	ENDOMETRIOIDE	MUCINOSO
SEDE ORIGINE presunta	**Tuba fimbria o metaplasia tubarica in cisti inclusione OSE**	Tumore Sieroso Borderline	Endometriosi Adenofibroma Borderline	Endometriosis Adenofibroma Borderline	Adenoma Borderline Teratoma
Richio Genetico	**BRCA1/2**	?	?	**HNPCC**	?
Stadio alla diagnosi	Avanzato	Precoce Avanzato	Precoce	Precoce	Precoce
ALTERAZIONI MOLECOLARI	p53 p16 pRb pathway BRAC-HRD	BRAF or K-ras	HNF-1β **IL6/JAK2/STAT3** PI3K MSI ARID1A	PTEN; β-Catenin, K-ras, MSI ARID1A	K-ras HER2
Risposta chemioterapia	**80%**	**26-28%**	**15%**	**?**	**15%**
POTENZIALI TARGTES	**PARPi Angiogenesi**	**BRAF MEK**	**Angiogenesi Come rene?**	**Terap Ormo mTOR**	**Come colon?**

Low-grade serous cancer

- ❑ Younger age: longer survival
- ❑ Resistant to chemotherapy
  - 12–15% RR in the primary setting
  - 2–4% RR in the recurrent setting
- **Selumetinib, trametinib**
  - Potent
  - Selective
  - Orally available
  - Non-ATP competitive inhibitor of the mitogen-activated protein kinase (MAPK), MEK-1/2



SBT: serous borderline tumour

Farley et al. Lancet Oncol 2013
Friday et al. Cancer Res 2008

Phase III Low Grade Serous Ovarian Canc

Patients with Recurrent or Persistent Low-grade Serous Carcinomas of the Ovary, Fallopian Tube or Primary Peritoneum

Must have received prior platinum-containing therapy, but no more than 3 prior chemotherapies; unlimited prior hormonal therapy

N=300

N = 300

Randomization 2:1

Stratification
Platinum-Free Interval:
≤6 months vs. > 6 months
Prior Systemic Tx:
1-2 vs. >2

MEK162 45mg BID

Paclitaxel 80 mg/m² d1,8, 15 q 4 wks, or PLD 40 mg/m² q 4 wks, or Topotecan 1,25 mg/m² d1-5 q 3 wks

Primary endpoint: PFS (Assumed true HR = 0.60, 7 vs 11.67 months)
Key secondary endpoint: OS
Other secondary: ORR, DOR, DCR, Safety, QOL, TR (predictive markers)

FPI planned: May 2013

Sponsor: Array

ENGOT Model: C

NiCCC - Nintedanib in Clear Cell Ovarian Cancer

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

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

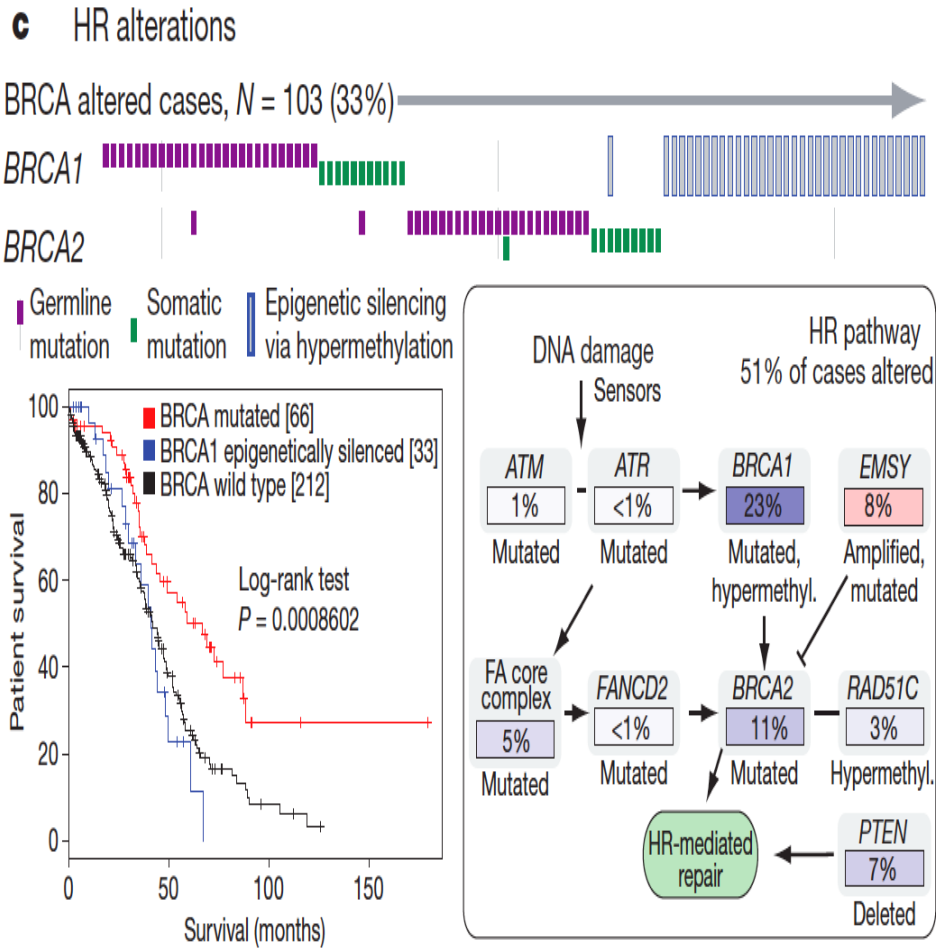
NCRI National Cancer Research Institute

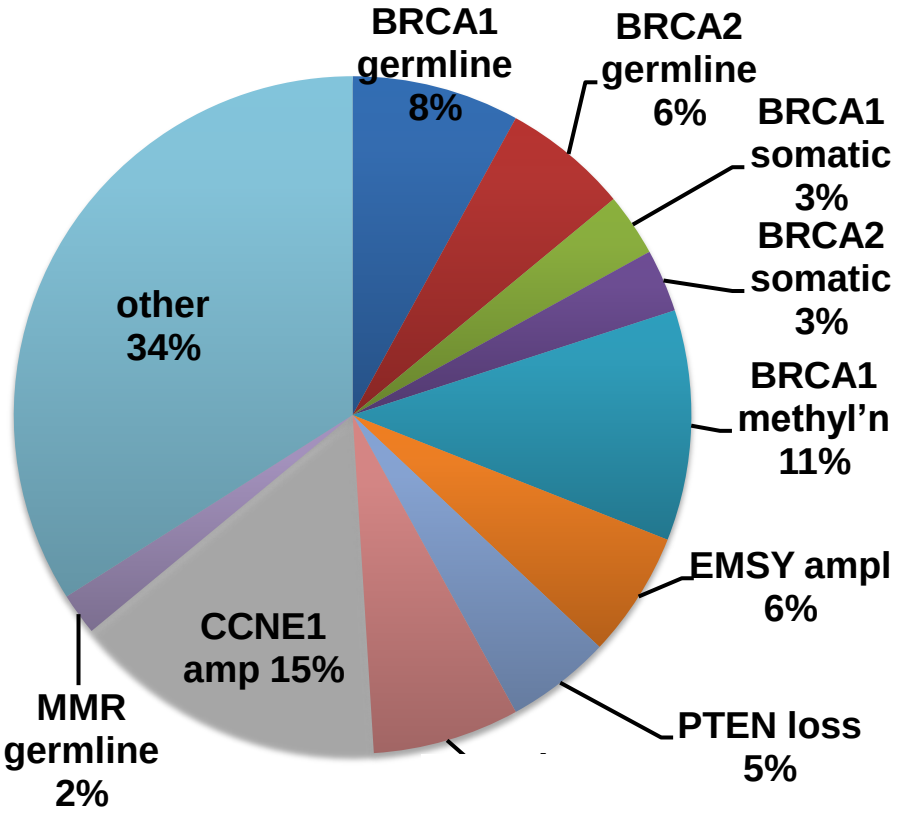
NSGO

EORTC European Organisation for Research and Treatment of Cancer

GINECO ARCAGY

High grade serous Muellerian cancer is a disease of homologous recombination dysfunction





TCGA, *Nature* 2011; Swisher et al, PNAS 2011 in press; Turner, et al NatRevCancer 2004; Weberpals, et al JCO 2008; Tan et al, JCO 2008; Mendes-Pereira et al, EMBO Mol. Med. 2009

Concetto di BRCAness introdotto da Ashworth nel 2004 che identifica cambiamenti fenotipici nei tumori sporadici

TAN et al nel 2008 BRCAness in

-alta risposta al 1° trattamenti a base di platino

-Alto rispota ai trattamenti successivi con platino

-Lunghi periodi di remissione clinica tra un trattamento e il successivo

-Migliorata OS

-Per lo più istotipo sieroso

Queste definizioni possono nascondere delle ambiguità perché non vi è un metodo standardizzato per definire BRCA-ness

Gene Expression Profile of *BRCA*ness That Correlates With Responsiveness to Chemotherapy and With Outcome in Patients With Epithelial Ovarian Cancer

Panagiotis A. Konstantinopoulos, Dimitrios Spentzos, Beth Y. Karlan, Toshiyasu Taniguchi, Elena Fountzilas, Nancy Francoeur, Douglas A. Levine, and Stephen A. Cannistra

See accompanying article on page 3545

60 geni studiati con microerray per definire il profilo BRCAness

70 pts: 35 pts con mutazione e 35 pts senza test ma con ca ovarico sporadico

8/10 avevano profilo BRCAness che correlava con la sensibilita' al platino e ai parp inibitori

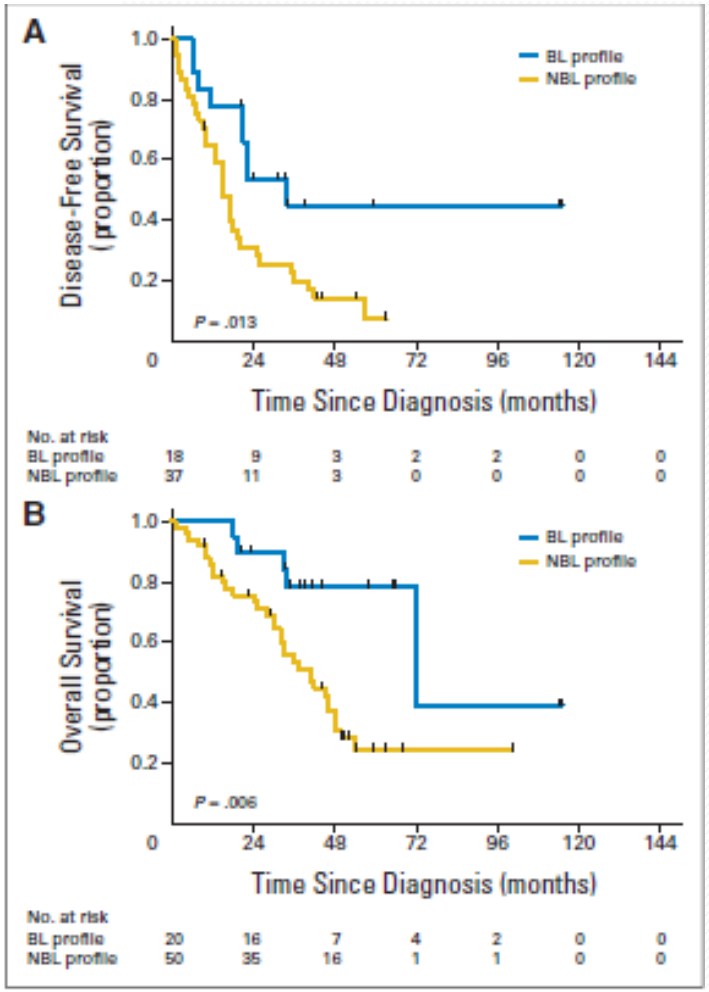


Fig 3. Association of *BRCA*ness profile with disease-free survival (DFS) and overall survival (OS) in the combined patient cohort (N = 70). (A) DFS in the combined patient cohort. The median DFS times for patients with either the *BRCA*-like (BL) or non–*BRCA*-like (NBL) profile were 34 months and 15 months, respectively (log-rank $P = .013$). (B) OS in the combined patient cohort. The median OS times for patients with either the BL or NBL profile were 72 months and 41 months, respectively (log-rank $P = .006$).

References/year	BRCA-Ovarian cancers median survival	Sporadic cancer Median survival
Pharoah et al.1999	20.6 (BRCA1), 16 (BRCA2) months	19.5 months
Aida et al.1998	91.43 months of DF Interval	40.92 months of DF Interval
Boyd et al. 2000	40 months	25 months
Cass et al. 2003	91 months	54 months
Johannsson et al.1998	30% of BRCA1 pts at 5-years	45% control pts at 5-years
Ben David et al. 2002	53.4 months	37.8 months
Zweemwer et al. 2001	40 % 5-years	46% 5-years
Ramus et al. 2001	52 months BRCA1 49 months BRCA2	35 months
Buller et al. 2002	4.5 years	4.6 years
Kringenm et al. 2005	33% BRCA1 5-years	23% 5-years
Pal et al. 2007	27% BRCA1 4 –years 87% BRCA2 4-years	12% 4 years
Chetrit et al. 2008	53.7 months	37.9 months

The Different Impact of *BRCA* Mutations on the Survival of Epithelial Ovarian Cancer Patients: A Retrospective Single-Center Experience

D. Lorusso F. Cirillo M. Mancini G.B. Spatti B. Grijuela A. Ditto F. Raspagliesi

Gynecologic Oncology Unit, Fondazione 'IRCCS' National Cancer Institute, Milan, Italy

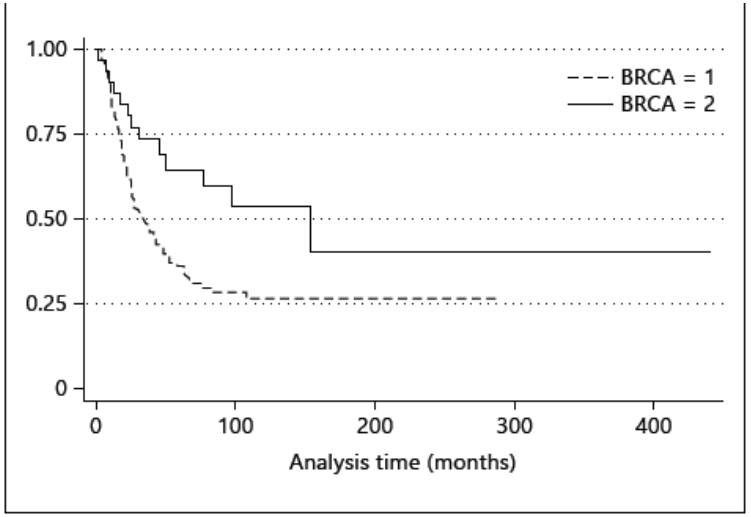


Fig. 1. PFS according to *BRCA* status.

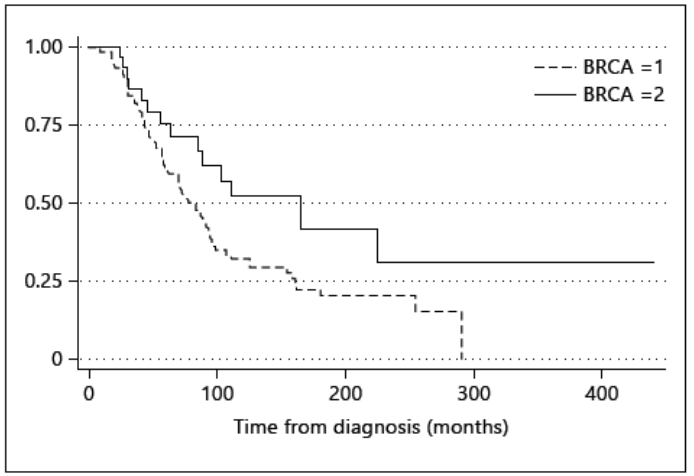


Fig. 2. OS according to *BRCA* status.

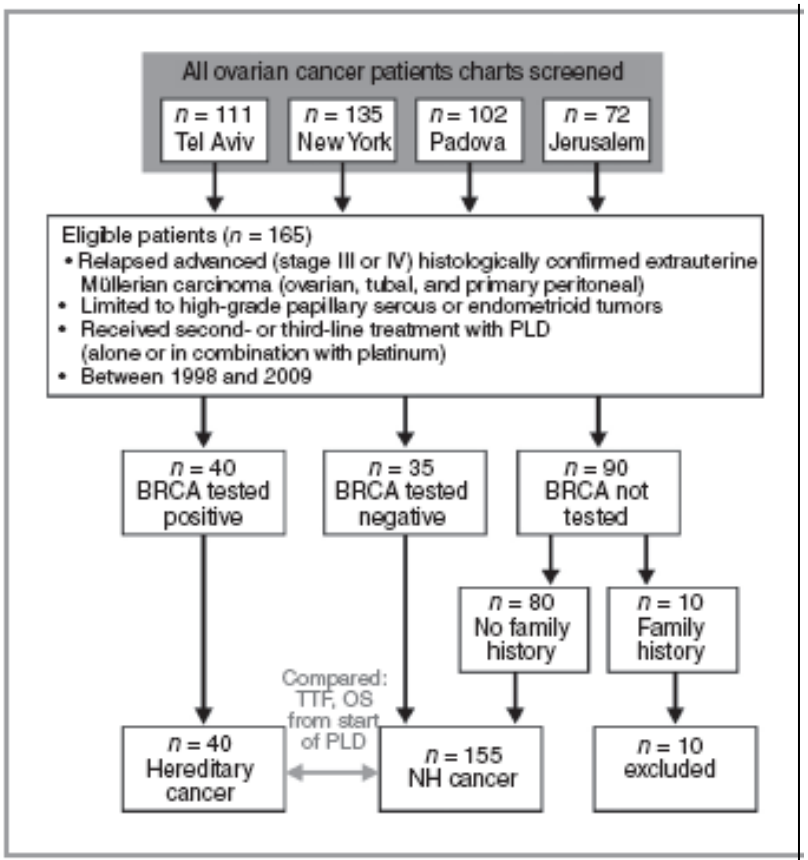
Median PFS 27.2 m vs 45.6 m

OS 77.23 m vs 111.47 m

BRCA 1 vs BRCA 2

BRCA Mutation Status and Determinant of Outcome in Women with Recurrent Epithelial Ovarian Cancer Treated with Pegylated Liposomal Doxorubicin

Tamar Safra[1,3], Lucia Borgato[5], Maria Ornella Nicoletto[5], Linda Rolnitzky[1], Sharon Pelles-Avraham[3], Ravit Geva[3], Martin Edward Donach[1], John Curtin[2], Akiva Novetsky[1], Tal Grenader[4], Wei-Chu V. Lai[2], Alberto Gabizon[4], Leslie Boyd[1], and Franco Muggia[1]



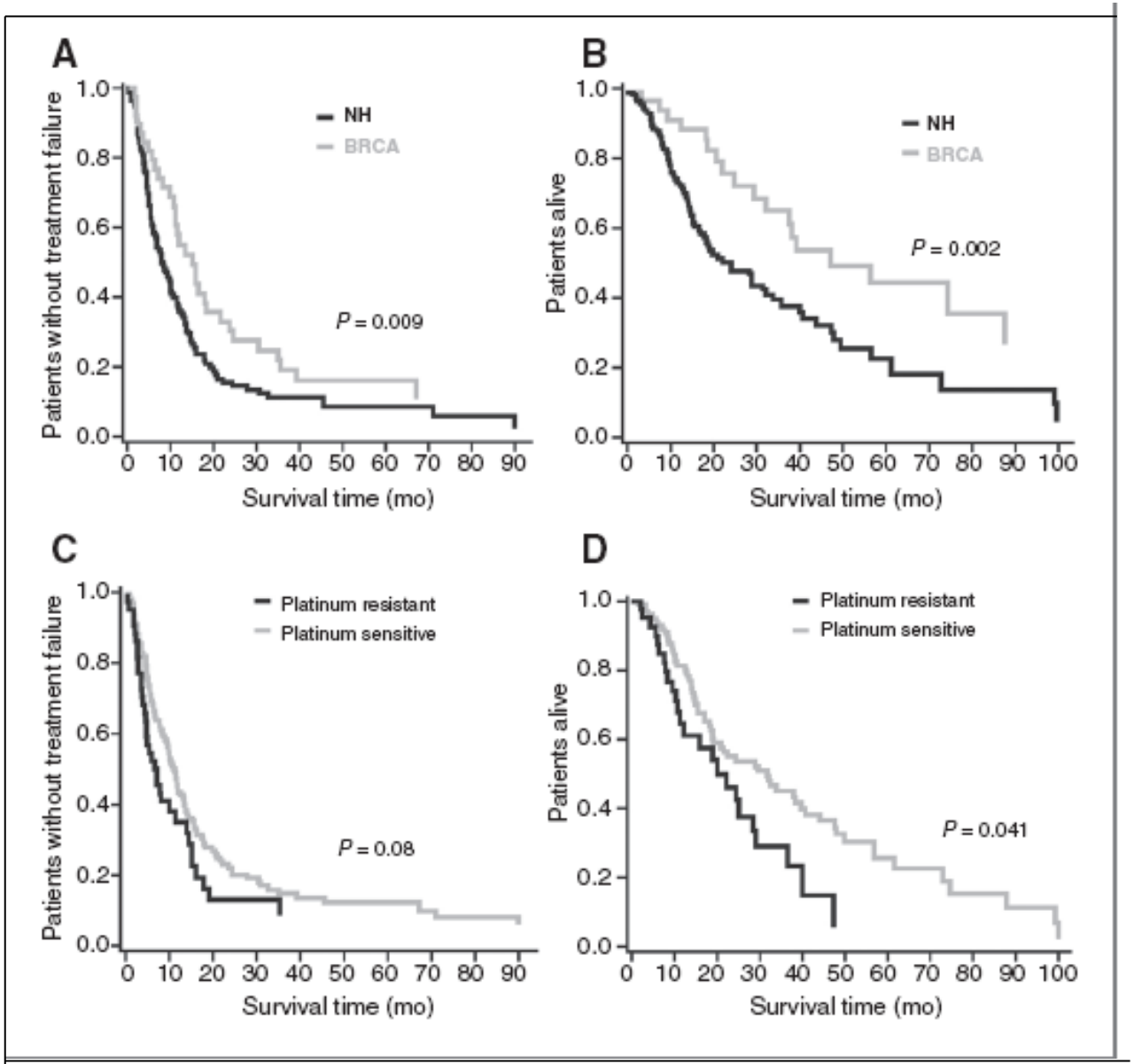


Figure 2. TTF (A) and OS (B) in carriers of the BRCA1/2 mutation versus patients with NH relapsed EOC. TTF (C) and OS (D) in all patients by platinum sensitivity.

Phase II prospective study on trabectedin in BRCA mutated and BRCAness phenotype advanced ovarian cancer patients: the MITO 15 trial

Lorusso D, Ferrandina G, Pignata S, Sorio R, Pietragalla A, Mosconi A, Pisano C, Mangili G, Martinelli F, Masini C, Artioli G, Narducci F, Di Napoli M, Raspagliesi F, Scambia G

Abstract #5530

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Patients and methods

- Advanced ovarian cancer patients
- Documented BRCA mutation or BRCAness
- At least 2 previous response to platinum (P)

Patients stratification	
Moderately P sensitive (MPS)	Highly P sensitive (HPS)
<3 P responses	≥3 P responses

trabectedin 1.3 mg/m^2 q 21 days iv until progression

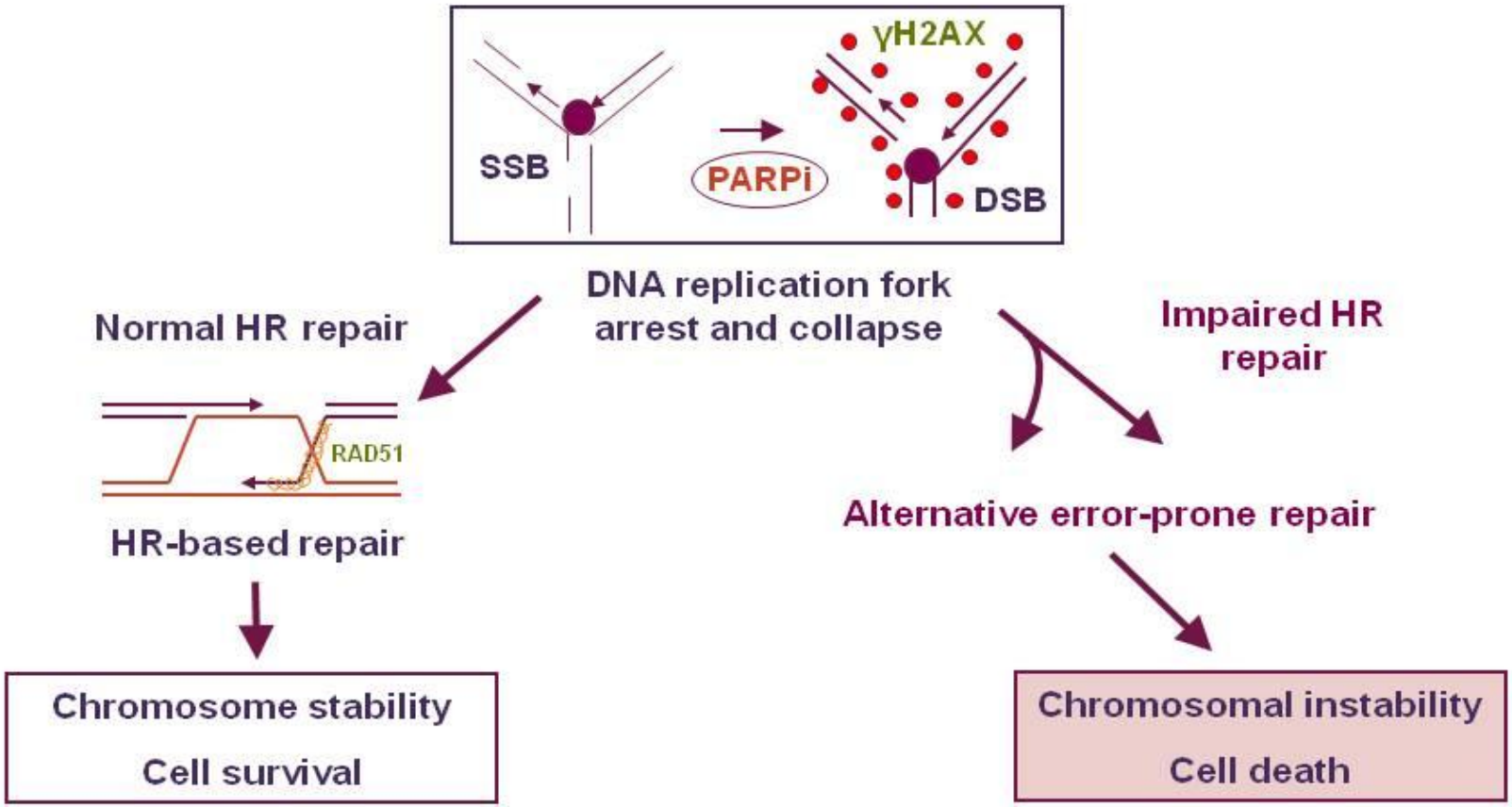
Results

	PR n=46	PS n=42
CR (%)	0	4 (9.5)
PR (%)	15 (32.6)	17 (40.5)
ORR (%)	15 (32.6)	21 (50)
SD (%)	12 (26.1)	10 (23.8)
PD (%)	19 (41.3)	11 (26.2)
PFS (weeks)	11	24
OS (weeks)	40	NR

Toxicities (% per cycle)	
Grade 3-4	Neutropenia 17.3
	Leukopenia 7.7
	Anemia 2.7
	Thrombocytopenia 2.3
Grade 3	Transaminitis 5.2

CR, complete response; PR, partial response; ORR, overall response rate
SD, stable disease; PD, progressive disease; PFS, progression-free survival;
OS, overall survival

PARP inhibition and tumor-selective synthetic lethality



Slide provided with permission by Andrew Tutt

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

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

Poly(ADP)-Ribose Polymerase Inhibition: Frequent Durable Responses in *BRCA* Carrier Ovarian Cancer Correlating With Platinum-Free Interval

Peter C. Fong, Timothy A. Yap, David S. Boss, Craig P. Carden, Marja Mergui-Roelvink, Charlie Gourley, Jacques De Greve, Jan Lubinski, Susan Shanley, Christina Messiou, Roger A'Hern, Andrew Tutt, Alan Ashworth, John Stone, James Carmichael, Jan H.M. Schellens, Johann S. de Bono, and Sam B. Kaye

See accompanying article on page 2505

Olaparib: An orally active PARP inhibitor

	Olaparib Phase I and *BRCA* mutation expansion studies[1]	Olaparib multicenter Phase II *BRCA* mutation ovarian cancer study[2]	Olaparib multicenter Phase II *BRCA+/-* study (ovarian cancer patients)[3]
Olaparib dose	200 mg bid	400 mg bid	400 mg bid
RECIST CR/PR	28%	33%	*BRCA*+41% *BRCA*- 24%
Disease control rate*	34%	69%	*BRCA*+76% *BRCA*- 62%
Median duration of response	7.0 months	9.5 months	NR

*Complete response (CR) + partial response (PR) + stable disease (SD); NR, not reported

Provides clinical evidence of activity in patients with and without *BRCA1/2* mutations

1. Fong PC *et al. J Clin Oncol* 2010;28:2512–2519; 2. Audeh MW *et al. Lancet* 2010;376:245–251; 3. Gelmon KA *et al. J Clin Oncol* 2010;28:abst 3002

Phase II randomized placebo-controlled study of olaparib in patients with platinum-sensitive relapsed serous ovarian cancer

Jonathan Ledermann,[1] P Harter,[2] C Gourley,[3] M Friedlander,[4] I Vergote,[5] G Rustin,[6] C Scott,[7] W Meier,[8] R Shapira Frommer,[9] T Safra,[10] D Matei,[11] E Macpherson,[12] C Watkins,[12] J Carmichael,[12] U Matulonis[13]

Study aim and design

- To assess the efficacy of oral olaparib as a maintenance treatment in patients with platinum-sensitive high-grade serous ovarian cancer
- Randomized, double-blind, placebo-controlled Phase II study
- Multinational study; 82 sites in 16 countries

Patient eligibility:
- Platinum-sensitive high-grade serous ovarian cancer
- >2 previous platinum regimens
- Last chemotherapy: platinum-based with a maintained response
- Stable CA125 at trial entry
- Randomization stratification factors:
  - Time to disease progression on penultimate platinum therapy
  - Objective response to last platinum therapy
  - Ethnic descent

Olaparib 400 mg po bid

Randomized 1:1

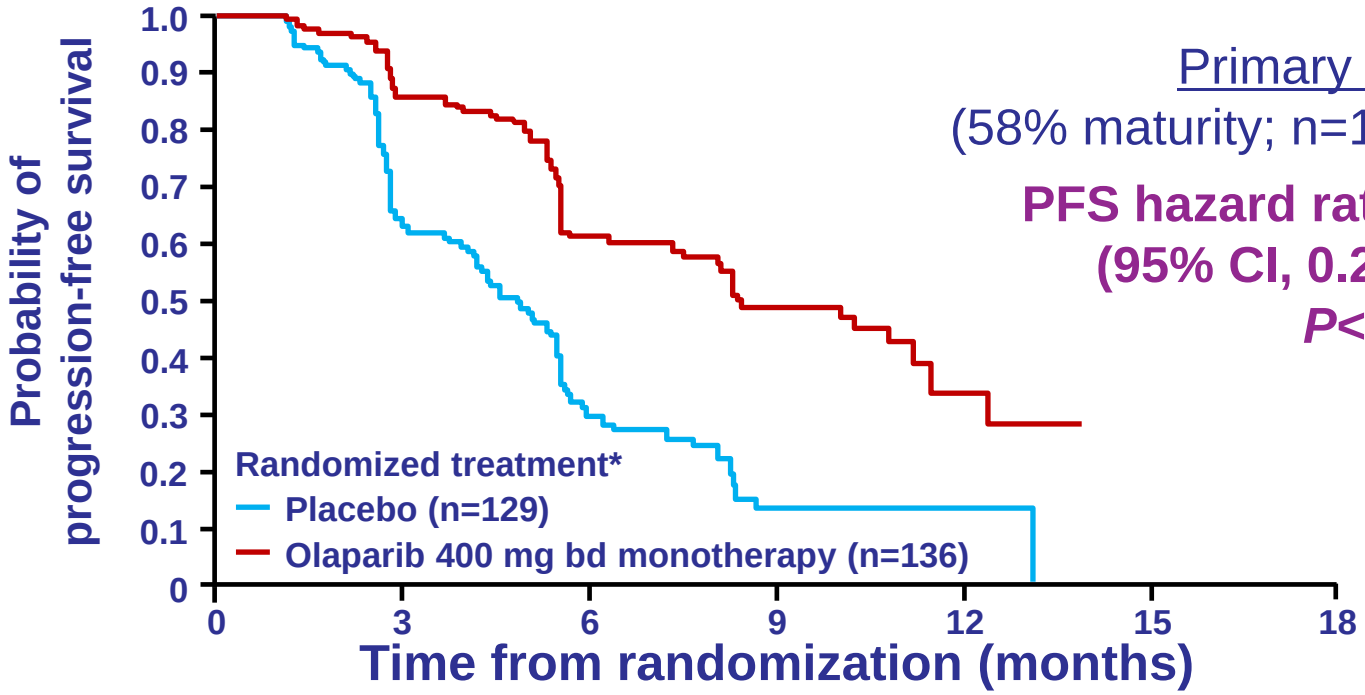
Placebo po bid

Treatment until disease progression

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

Study 19: Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer: 265 patients

- Patients were randomized after response to platinum-based chemotherapy



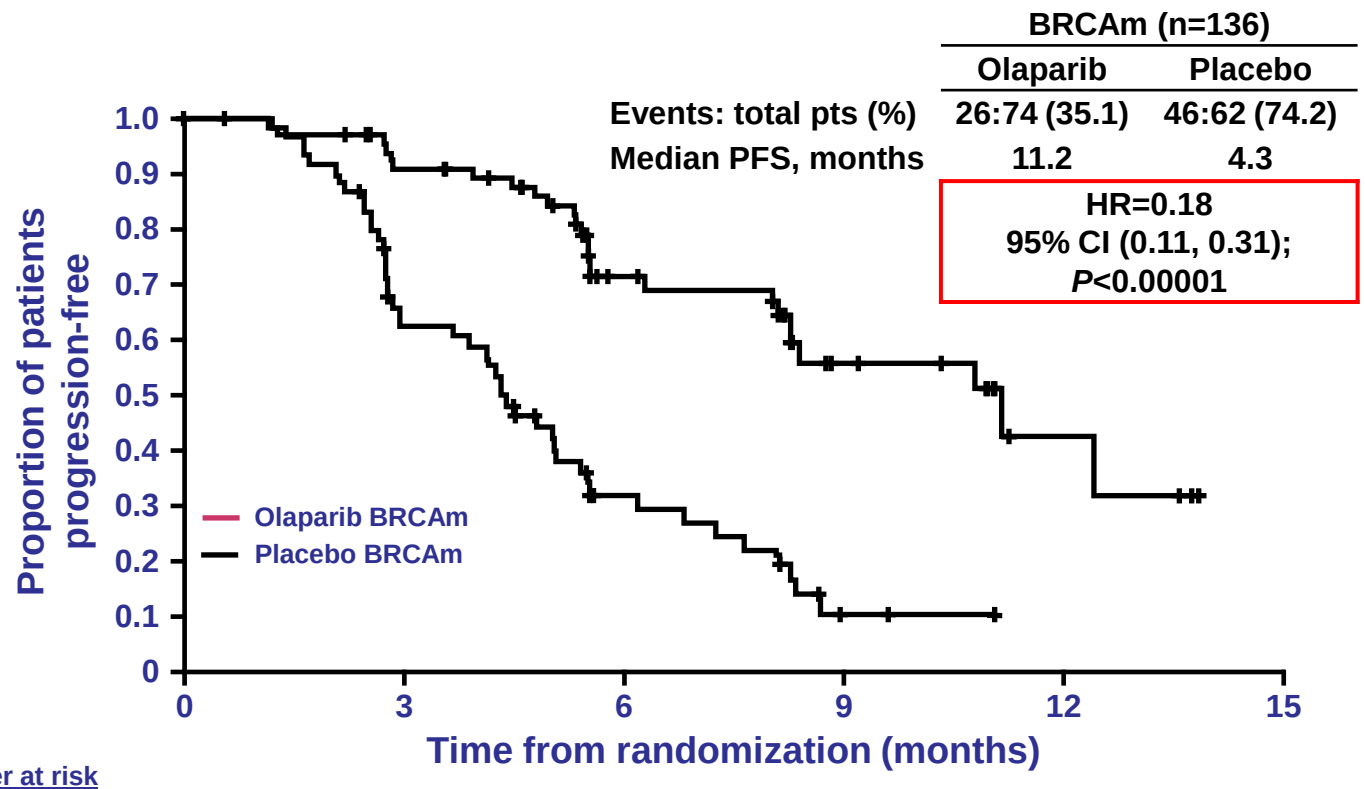
Primary analysis
(58% maturity; n=154/265)

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

*Patients were treated until disease progression

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

PFS by BRCAm status

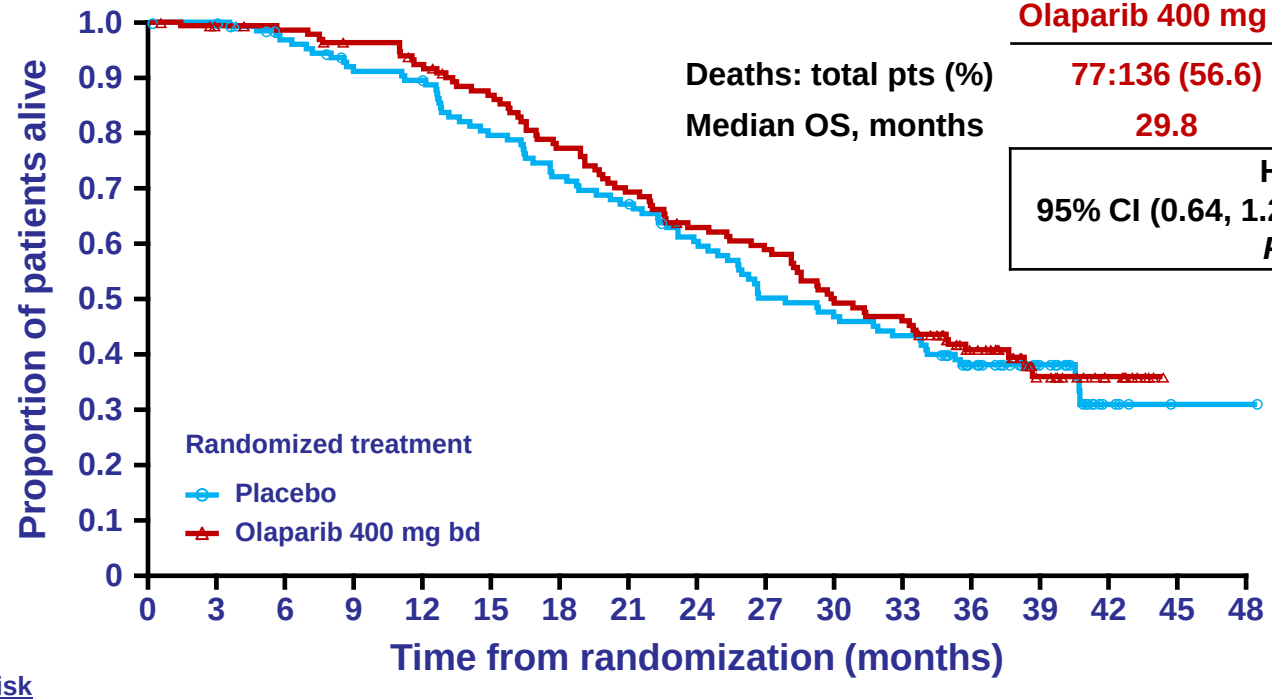


Number at risk

Olaparib BRCAm	74	59	33	14	4	0
Placebo BRCAm	62	35	13	2	0	0

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

Study 19 updated overall survival: all patients



Overall population (n=265)		
	Olaparib 400 mg bd	Placebo
Deaths: total pts (%)	77:136 (56.6)	77:129 (59.7)
Median OS, months	29.8	27.8

HR=0.88
95% CI (0.64, 1.21); 80% CI (0.72, 1.09)
P=0.438

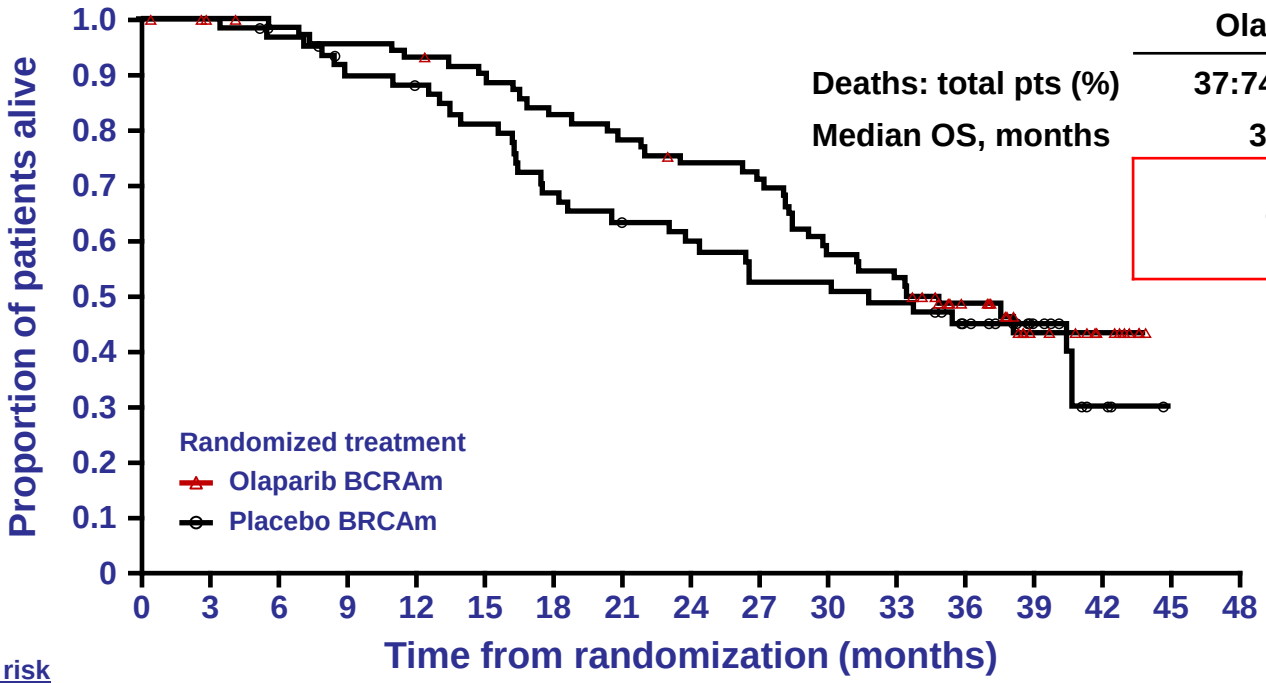
Number at risk

Placebo	129	127	120	111	108	96	87	81	71	59	55	51	37	23	6	1	1
Olaparib 400 mg bd	136	132	129	124	117	109	97	87	78	73	61	57	39	18	9		

- At the interim OS data cut-off (26 Nov 2012), 154/265 (58.1%) patients had died

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

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

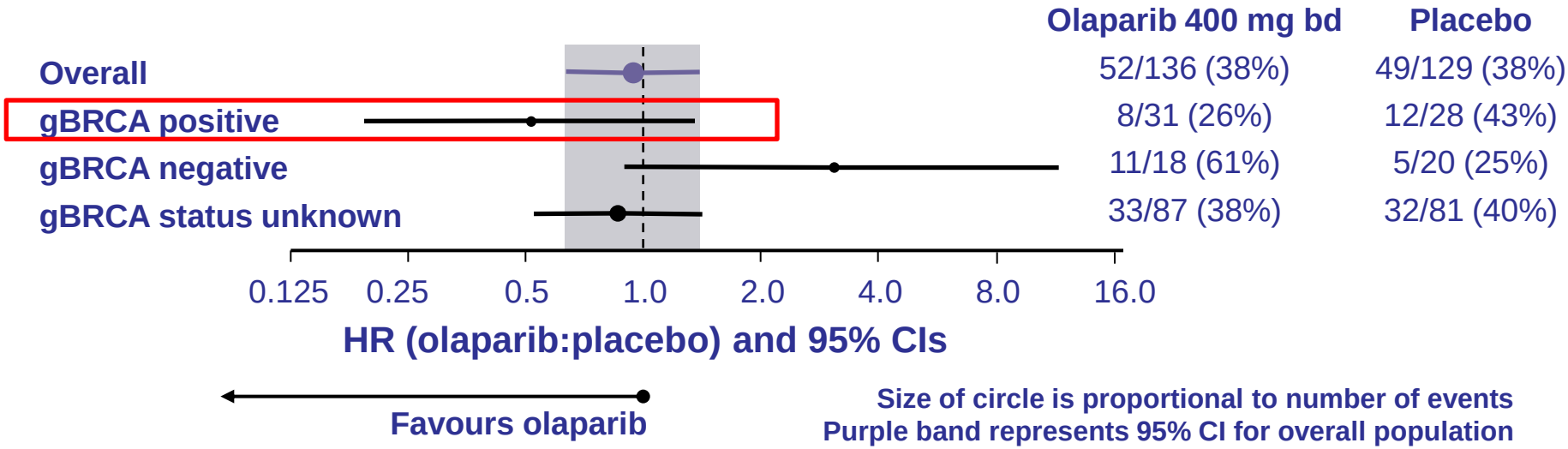
Number at risk

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

Interim overall survival (OS) subgroup analysis* (38% maturity)

- *BRCA1/2* mutation (BRCAm) status was not required for study entry, but was known for 97/265 patients (36.6%)



Hypothesis: olaparib maintenance therapy may lead to a greater PFS and OS benefit vs placebo in patients with a known BRCAm

*Subgroup analysis pre-specified in study protocol

gBRCAm, germline *BRCA1/2* mutation

Presented by: Jonathan Ledermann

Phase III trials with PARP inhibitors

Recruiting:

- SOLO 1 and 2 (olaparib)
  - Randomised maintenance trials in first line and platinum-sensitive recurrent *BRCA*m ovarian cancer
- NOVA (niraparib)
  - Randomised maintenance trial following platinum-based chemotherapy in *BRCA*m and *BRCA*wt high-grade serous cancer
- ARIEL 3 (rucaparib)
  - Randomised maintenance trial following platinum-based chemotherapy in *BRCA*m and *BRCA*wt high-grade serous cancer with companion diagnostic

A Randomized Phase 2 Trial Comparing Efficacy of the Combination of the PARP-inhibitor Olaparib and the Anti-angiogenic Cediranib Against Olaparib Alone in Recurrent Platinum-sensitive Ovarian Cancer

Joyce F. Liu[1], William T. Barry[1], Michael Birrer[2], Jung-Min Lee[3], Ronald Buckanovich[4], Gini Fleming[5], BJ Rimel[6], Mary Buss[7], Sreenivasa Nattam[8], Jean Hurteau[9], Weixiu Luo[1], Philippa Quy[1], Lisa Obermayer[1], Christin Whalen[1], Hang Lee[2], Eric Winer[1], Elise Kohn[3], S. Percy Ivy[3], Ursula A. Matulonis[1]

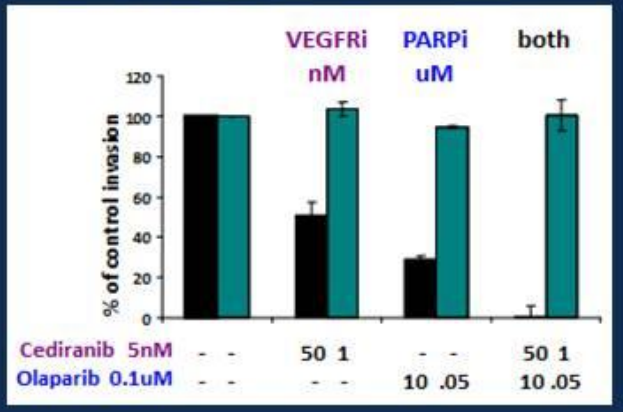
[1]Dana-Farber Cancer Institute, [2]Massachusetts General Hospital, [3]National Cancer Institute, [4]University of Michigan, [5]University of Chicago, [6]Cedars-Sinai Medical Center, [7]Beth Israel Deaconess Medical Center, [8]Fort Wayne Medical Oncology and Hematology, [9]NorthShore Medical Group

Presented By Joyce Liu at 2014 ASCO Annual Meeting

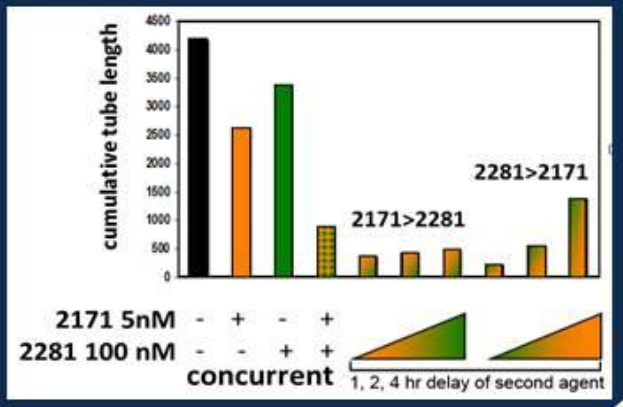
Cediranib and olaparib have synergistic activity *in vitro*

- Pre-clinical data suggesting potential synergy between PARPi and anti-angiogenics
- PARP inhibition or PARP knockout results in decreased *in vivo* angiogenesis[1]
- Sensitivity to PARP inhibitors increased in hypoxic cells[2]

Effect of ced/olap on cell invasion:



Effect of ced/olap on microvascular cell tube organization:



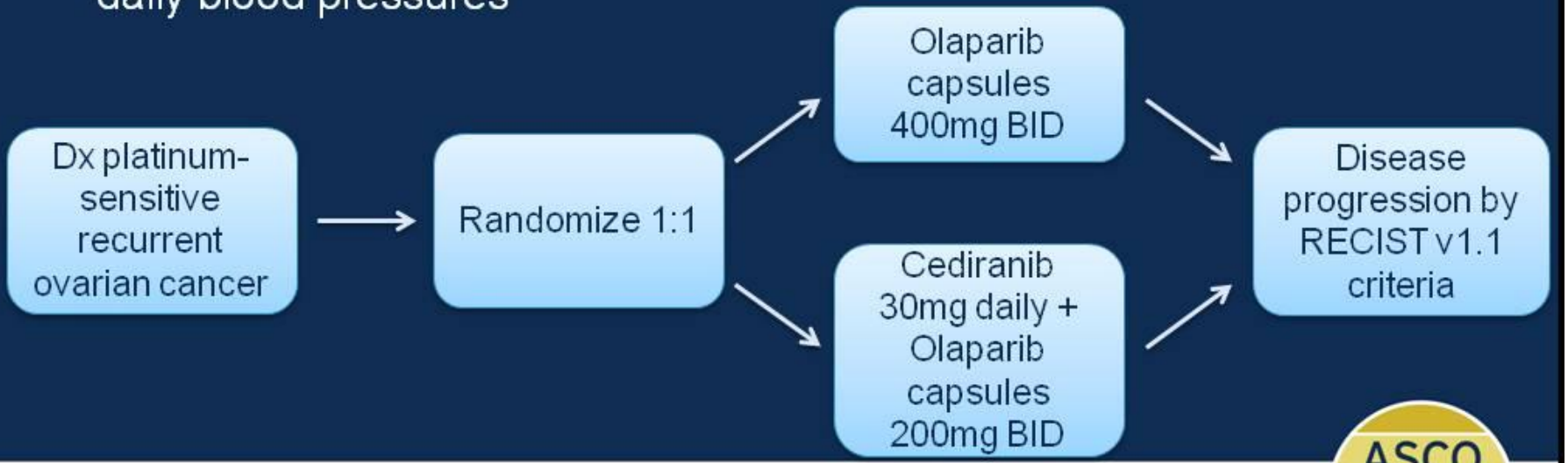
[1]Tentori et al., *Eur J Cancer* 2007, 43(14): 2124-33
[2]Hegan et al., *PNAS* 2010, 107(5): 2201-6

Presented by: Joyce Liu, MD, MPH

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Study Design

- Phase 2 open-label randomized study
- 1:1 randomization to cediranib/olaparib combination or single agent olaparib
- Platinum-sensitive recurrent ovarian, fallopian tube, or primary peritoneal cancer
- Continuation on treatment with CT or MRI imaging every 8 weeks until disease progression by RECIST v1.1 criteria
- Patients randomized to cediranib/olaparib arm required to take twice daily blood pressures



Presented by: Joyce Liu, MD, MPH

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Secondary Outcome: Cediranib/olaparib significantly increased overall response rate (ORR) compared to olaparib alone

Best overall response

Arm	Treated	CR		PR		SD		PD	
	N	N	%	N	%	N	%	N	%
Olap	46	2	4.4	20	43.5	19	41.3	1	2.2
Ced/Olap	44	5	11.4	30	68.2	8	18.2	0	0

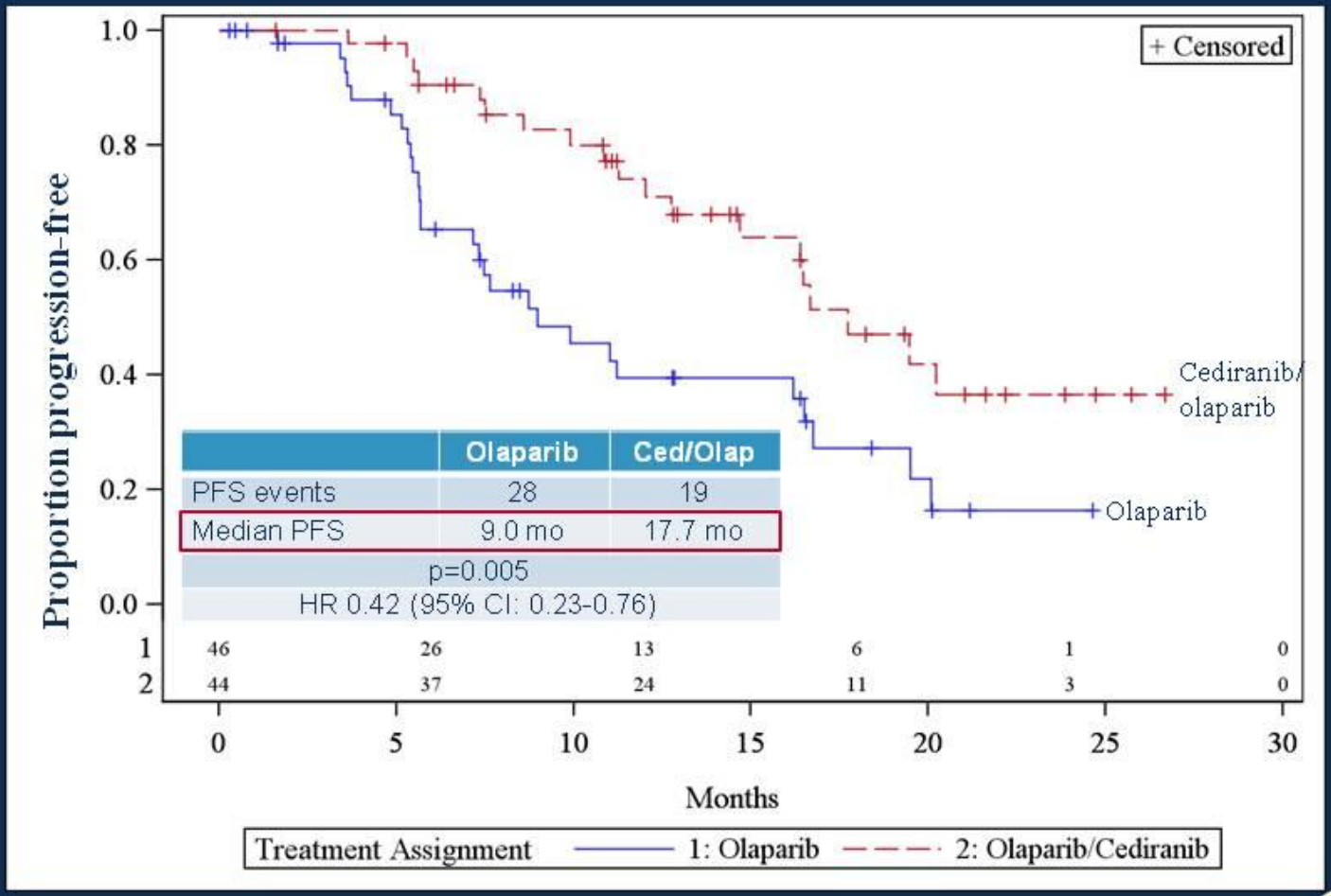
Comparison of overall response rate (ORR)

Arm	ORR	
	N	%
Olaparib alone	22	47.8
Cediranib/Olaparib	35	79.6
	p=0.002	

Presented by: Joyce Liu, MD, MPH

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Primary Outcome: Cediranib/olaparib significantly increased PFS compared to olaparib alone



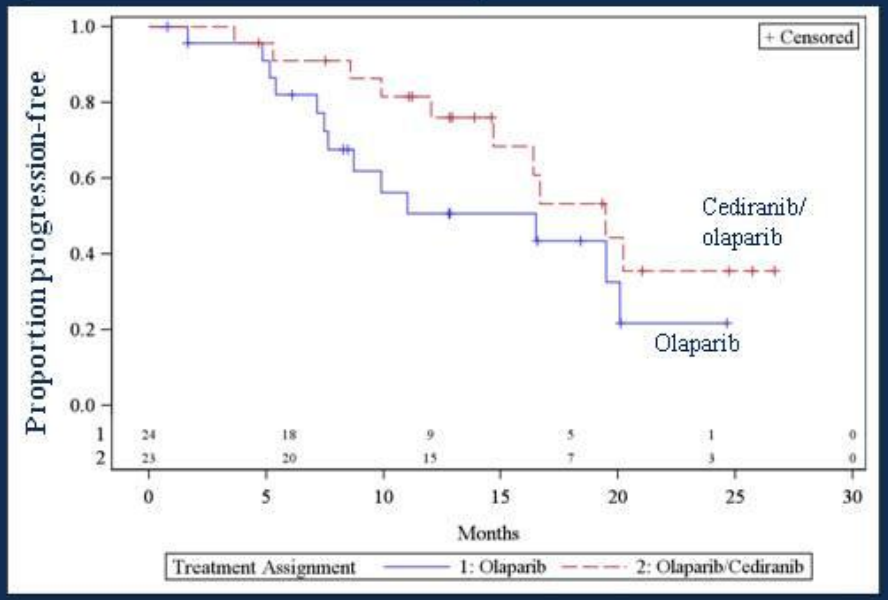
Presented by: Joyce Liu, MD, MPH

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

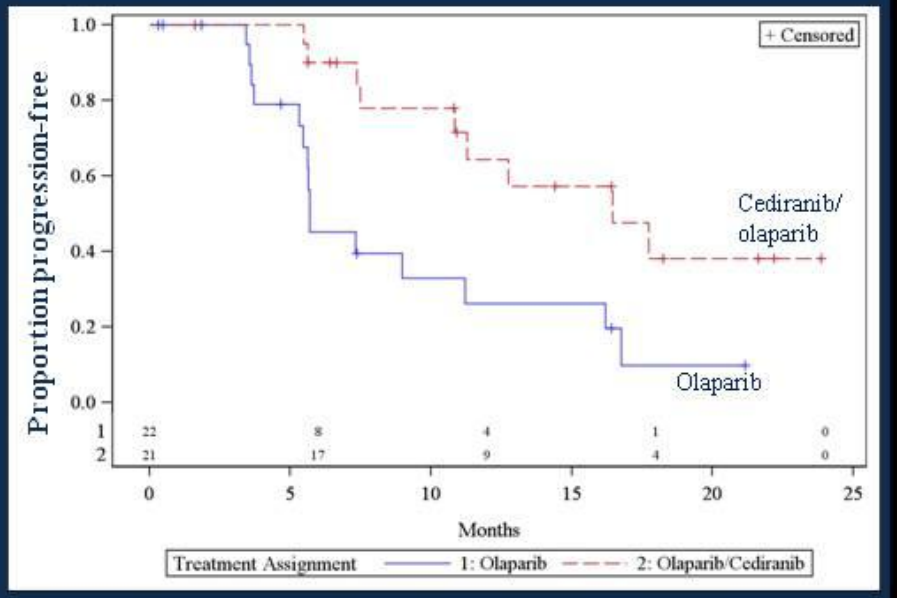
Presented By Joyce Liu at 2014 ASCO Annual Meeting

Cediranib/olaparib significantly increased PFS in patients without a BRCA mutation

BRCA mutation carrier



BRCA non-carrier/unknown



	BRCA Mutation Carrier		BRCA Non-carrier/Unknown	
	Olaparib	Ced/Olap	Olaparib	Ced/Olap
PFS events	13	10	15	9
Median PFS	16.5 mo	19.4 mo	5.7 mo	16.5 mo
	p=0.16		p=0.008	
	HR 0.55 (95% CI: 0.24-1.27)		HR 0.32 (95% CI: 0.14-0.74)	

Presented by: Joyce Liu, MD, MPH

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Treatment-related Adverse Events

Adverse Event	Olaparib alone (N = 46)			Cediranib/Olaparib (N = 44)		
	Maximum Grade			Maximum Grade		
	2	3	4	2	3	4
Non-Hematologic						
Hypertension	-	-	-	15 (34)	17 (39)	1 (2)
Diarrhea	-	-	-	20 (46)	10 (23)	-
Fatigue	7 (15)	5 (11)	-	12 (27)	12 (27)	-
Nausea	12 (26)	-	-	7 (16)	2 (5)	-
Headache	-	-	-	4 (9)	2 (5)	-
Hypothyroidism	1 (2)	-	-	6 (14)	-	-
Hematologic						
Anemia	2 (4)	-	-	1 (2)	-	-
Neutrophil count decreased	4 (9)	-	-	2 (5)	-	-
WBC decreased	3 (7)	-	-	2 (5)	-	-
Platelet decreased	-	-	-	1 (2)	-	-

Presented by: Joyce Liu, MD, MPH

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Joyce Liu at 2014 ASCO Annual Meeting

Response to platinum-based chemotherapy in Platinum-sensitive relapsed ovarian cancer

	PFS (med months)	% 1st relapse	% 6-12 m PFI
OCEANS C/Gem	8.4	100	42
OCEANS + bev	**12.4**	*100*	*41*
CALYPSO C/Pax	9.4	83	36
CALYPSO C/PLD	11.3	83	36
ICON 4 C/Pax	12.0	90	25
OVAR 2.5 C/Gem	8.6	100	40
ICON 6 Plat-based	8.7	100	36
ICON 6 +cediranib	**11.1**	*100*	*30*
OLAPARIB	**9.0**	**37**	**57**
OLAPARIB + CEDIRANIB	**17.7**	**59**	**52**

Presented by: JA Ledermann

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Jonathan Ledermann at 2014 ASCO Annual Meeting

PAOLA1

Platine, **A**vastin and **OLA**parib in 1st line of advanced high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer

Randomized, double-blind, Phase III Trial of olaparib vs. placebo in patients with advanced high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer treated with standard first-line treatment, combining platinum-taxane chemotherapy and bevacizumab concurrent with chemotherapy and in maintenance.

Proposal for Discussion

Randomised Trial of Cediranib and Olaparib Maintenance in Patients with Relapsed Platinum Sensitive Ovarian Cancer

Shibani Nicum and Jonathan Ledermann

For the NCRI Clinical Studies Group

BRCA and Ovarian cancer: conclusions

- Treatment according to histotype is the future!

- Antiangiogenic therapies and PARP inhibitors are changing the treatment algorytm of ovarian cancer

- Up to 50% of high grade serous and endometrioid tumors present a malfunctioning of HR

- In up to 30% of patients without a family history of breast and ovarian cancer BRCA genes are mutated

- Olaparib and Cediranib combination the first non chemotherapy treatment in recurrent platinum sensitive disease and a promising combination