



**FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI**



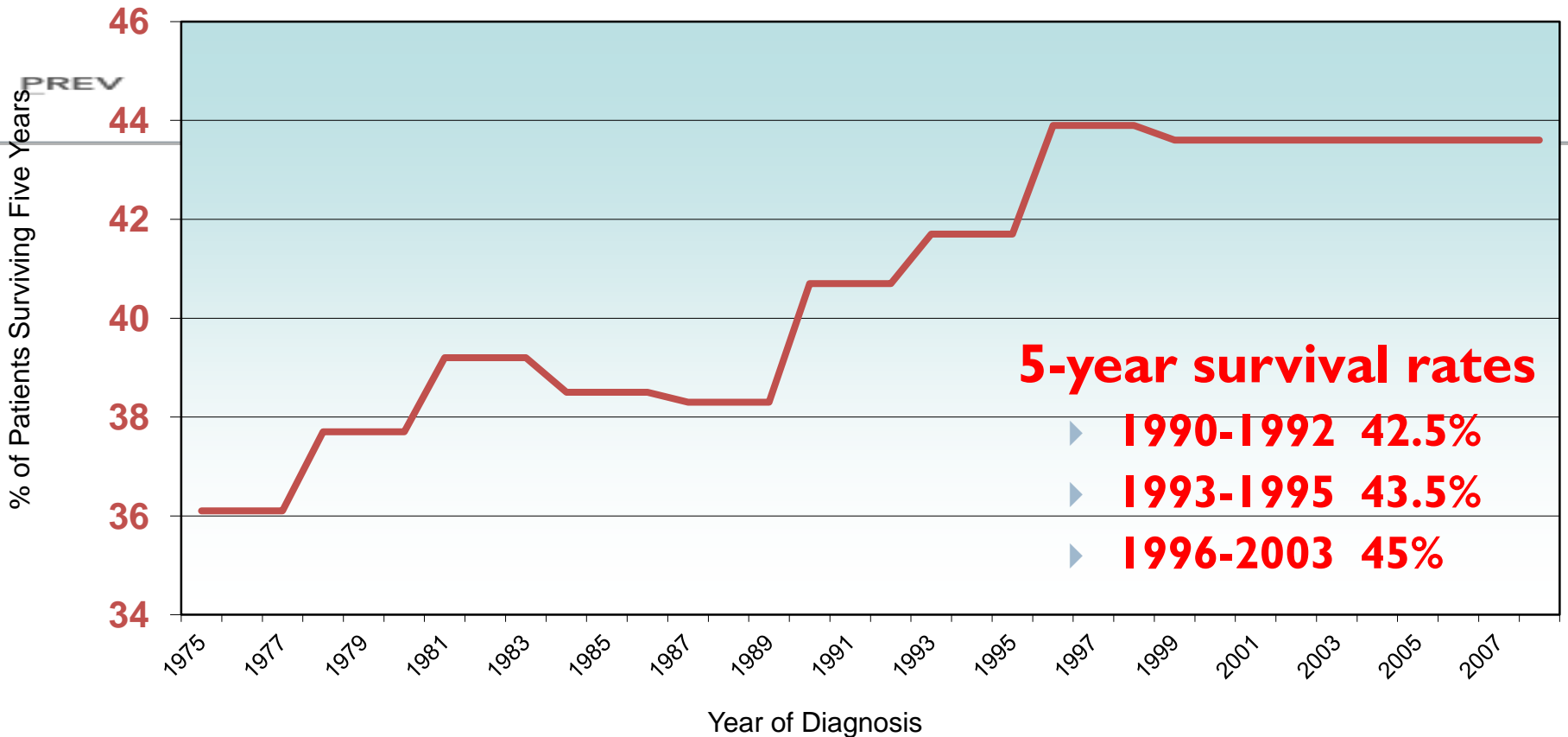
**Oncologia al Femminile 2015
Verona 18/09/2015**



**Domenica Lorusso
Gynecologic Oncologic Unit
National Cancer Institute-Milan**

CARCINOMA OVARICO E BRCA

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%

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

1995

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

2010

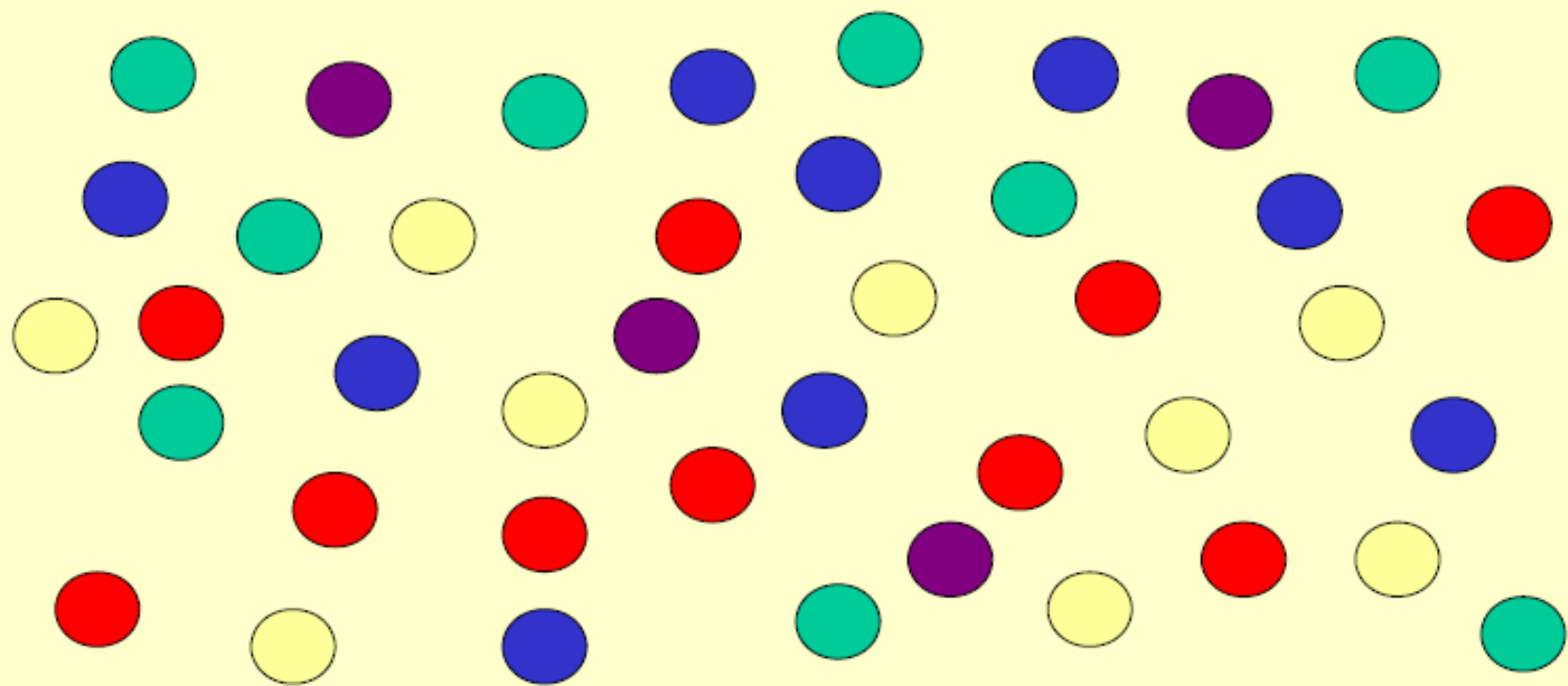
Carbo = carboplatin; cis = cisplatin; CR = complete response; cyclo = cyclophosphamide; gem = gemcitabine; IP = intraperitoneal; IV = intravenous; pac = paclitaxel; PLD = pegylated liposomal doxorubicin; topo = topotecan



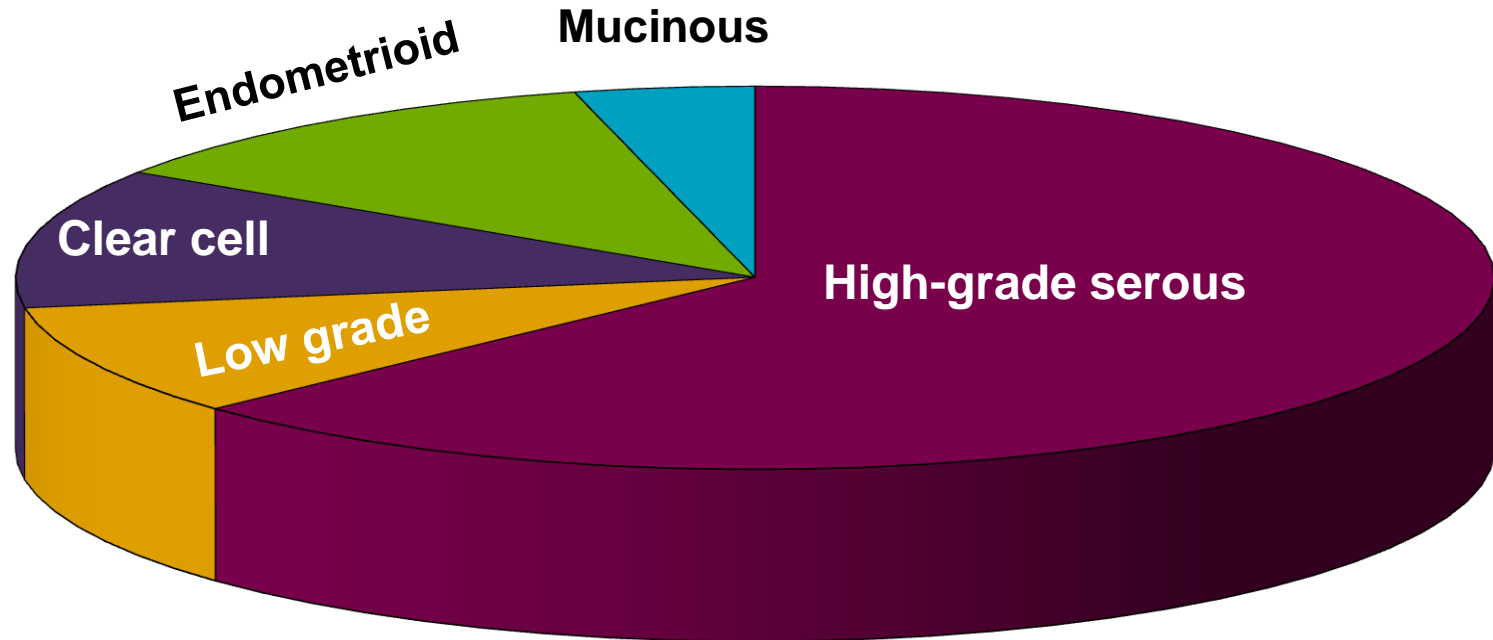
EPITHELIAL OVARIAN TUMORS

A heterogeneous group

Histologic type, Precursor lesions, Genetic alterations ...

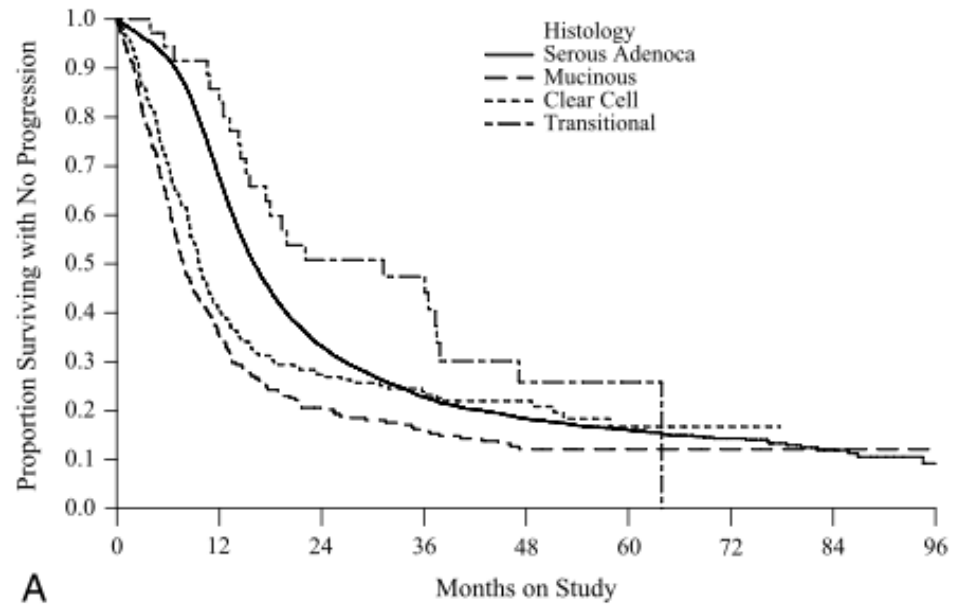
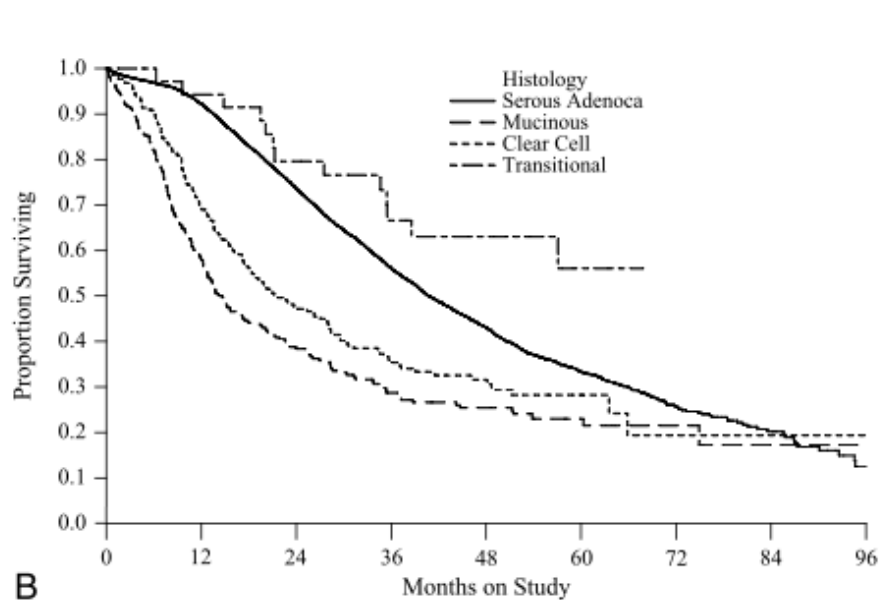


Histopathological subtypes of ovarian cancer



Ovarian cancer not one disease

8704 patients from 7 randomised trials



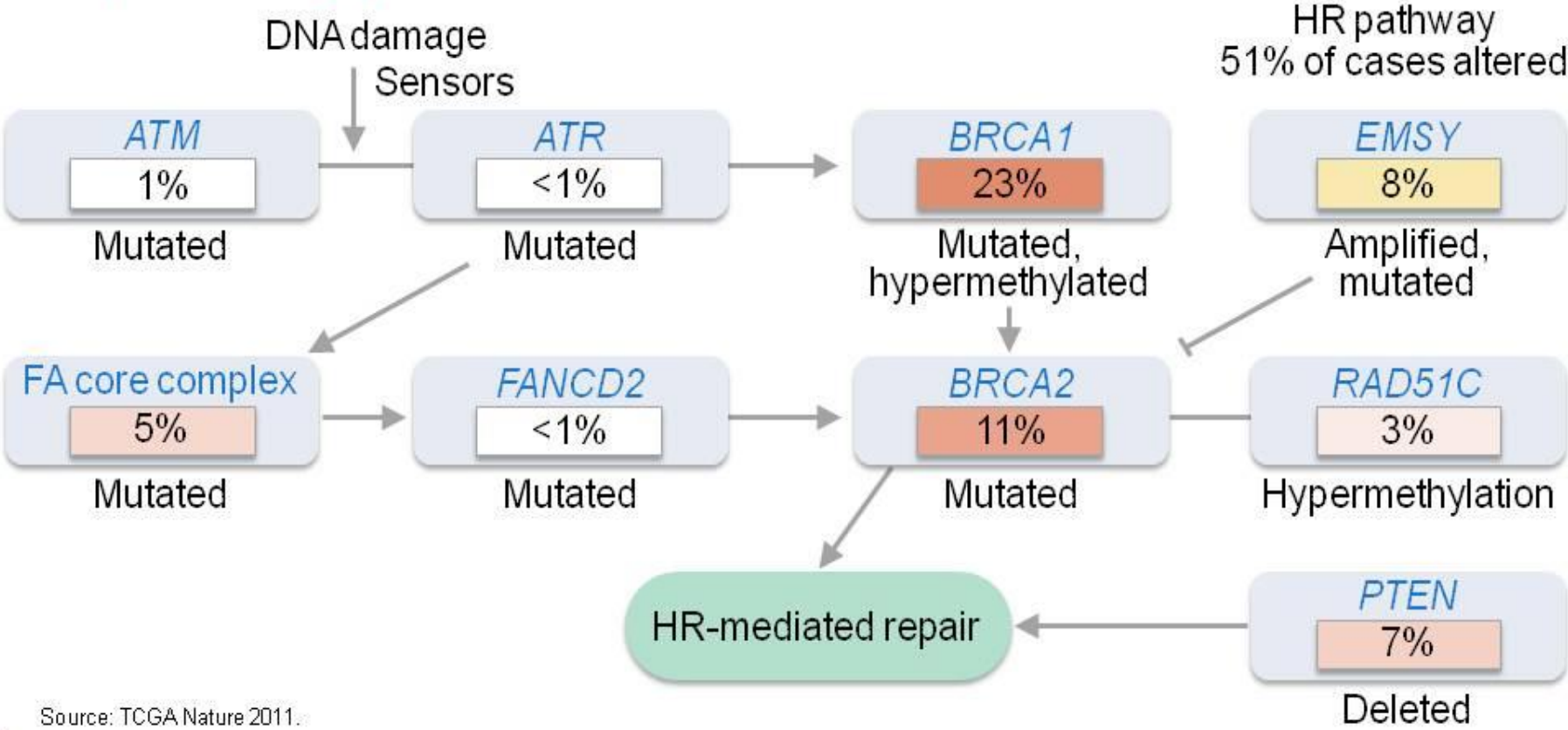
CARCINOMA OVAIO il punto di vista del patologo



→ 5 TIPI ISTOLOGICI

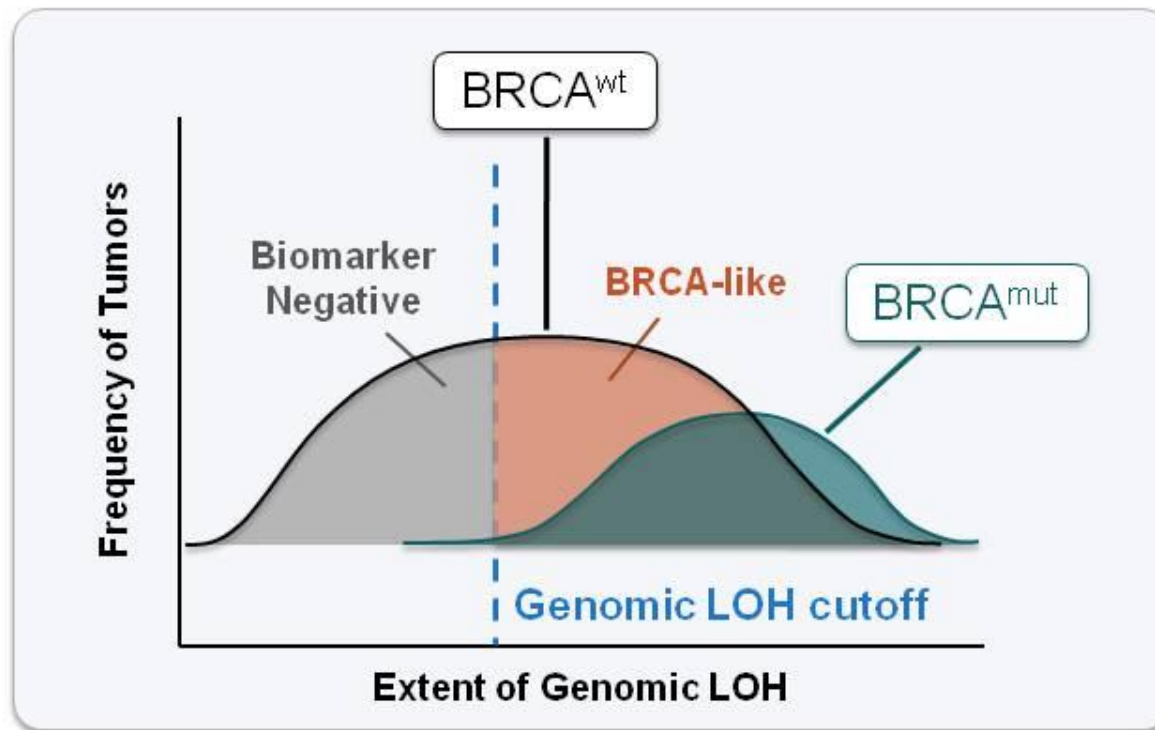
	SIEROSO ALTO GRADO	SIEROSO BASSO GRADO	CELLULE CHIARE	ENDOMETRIOIDE	MUCINOSO
SEDE ORIGINE presunta	Tuba fimbria o metaplasia tubarica in cisti inclusione OSE	Tumore Sieroso Borderline	Endometriosi Adenofibroma Borderline	Endometriosis Adenofibroma Borderline	Adenoma Borderline Teratoma
Rischio Genetico	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-1 β 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?

≈50% of HGOC patients may have alterations in the HR pathway per TCGA



Source: TCGA Nature 2011.

HGOC patients can be classified into three molecular subgroups: BRCA^{mut}, BRCA-like, Biomarker Negative



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

-Alta risposta 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

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

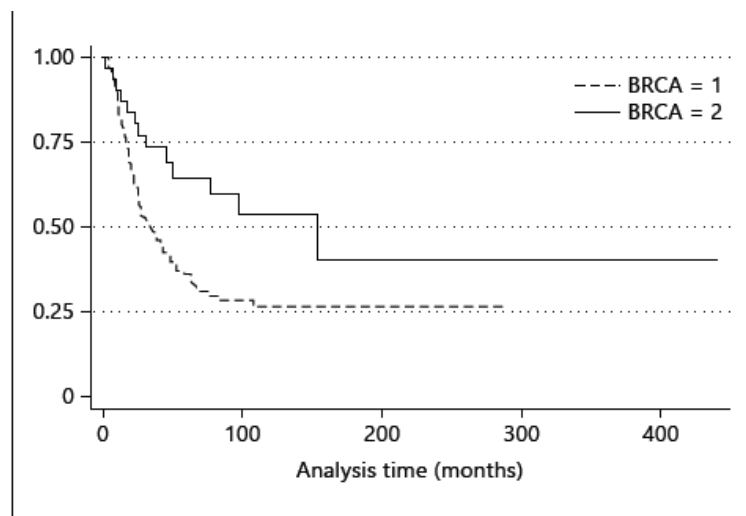


Fig. 1. PFS according to *BRCA* status.

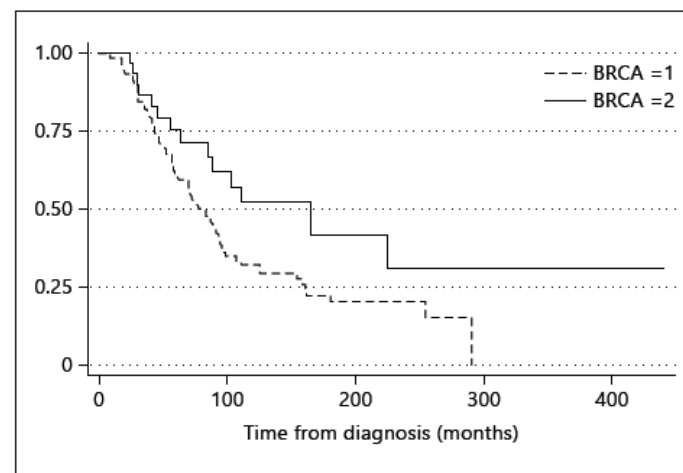
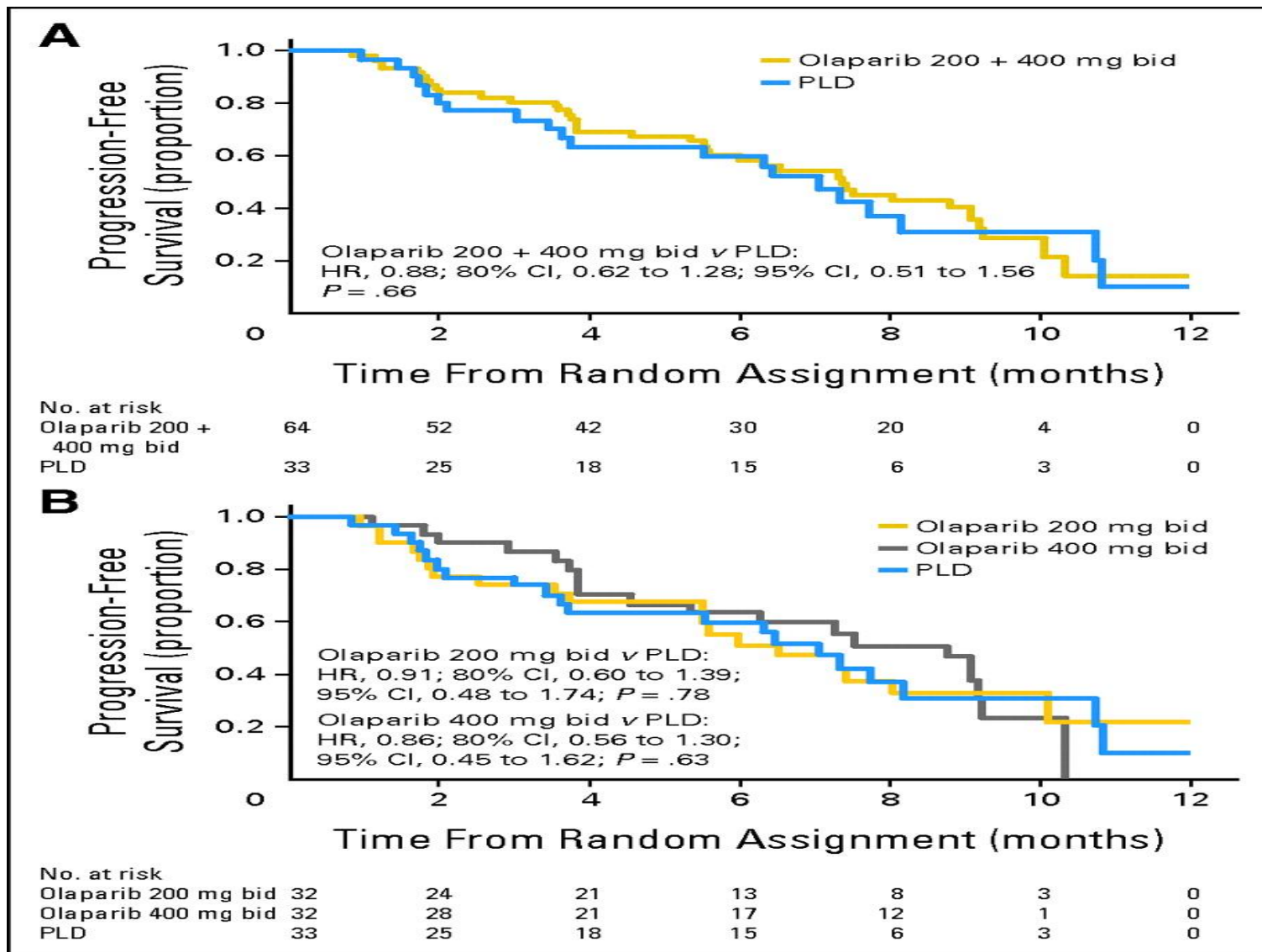


Fig. 2. OS according to *BRCA* status.

Median PFS 27.2 m vs 45.6 m
OS 77.23 m vs 111.47 m
BRCA 1 vs BRCA 2

Phase II, Open-Label, Randomized, Multicenter Study Comparing the Efficacy and Safety of Olaparib, a Poly (ADP-Ribose) Polymerase Inhibitor, and Pegylated Liposomal Doxorubicin in Patients With *BRCA1* or *BRCA2* Mutations and Recurrent Ovarian Cancer



**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

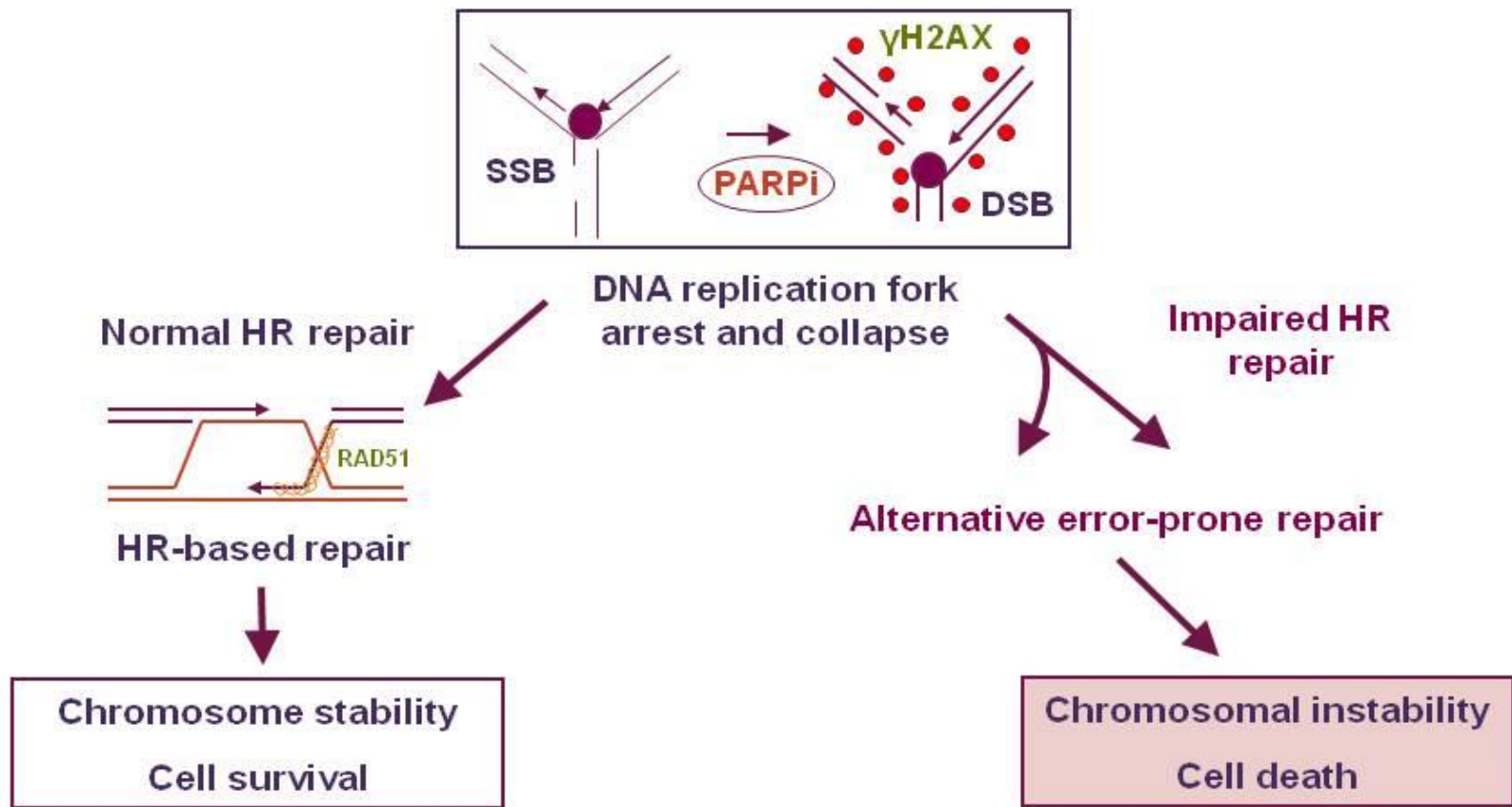
Results

	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

PRESENTED AT: ASCO Annual Meeting '12

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, Charité Gourley, Jacques De Greve, Jan Lubinski, Susan Shanley, Christina Messiou, Roger A. Herr, 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 <i>BRCA</i> mutation expansion studies ¹	Olaparib multicenter Phase II <i>BRCA</i> mutation ovarian cancer study ²	Olaparib multicenter Phase II <i>BRCA</i> +/- study (ovarian cancer patients) ³
Olaparib dose	200 mg bid	400 mg bid	400 mg bid
RECIST CR/PR	28%	33%	<i>BRCA</i> + 41% <i>BRCA</i> - 24%
Disease control rate*	34%	69%	<i>BRCA</i> + 76% <i>BRCA</i> - 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 *BRCA*1/2 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 Matulonis¹³

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**

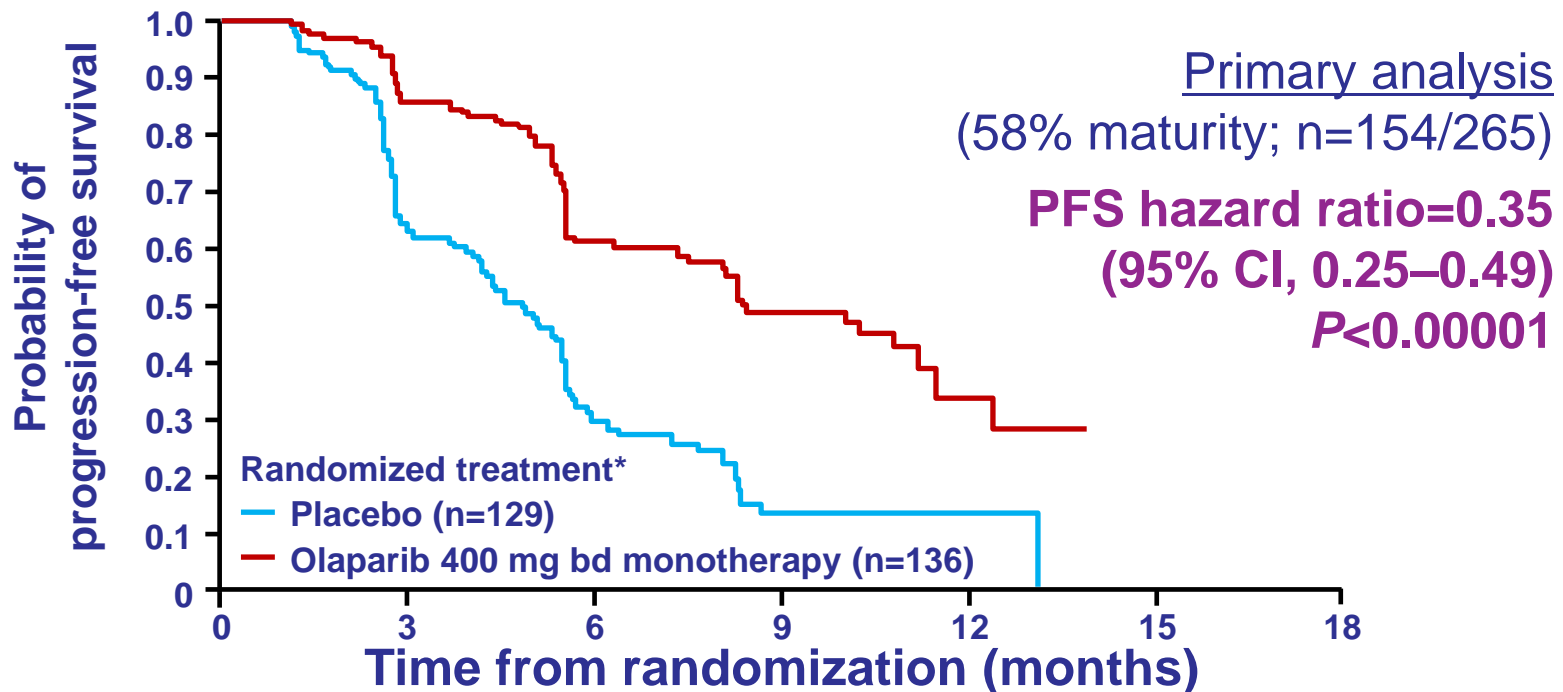
Randomized 1:1

**Placebo
po bid**

**Treatment
until disease
progression**

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

- Patients were randomized after response to platinum-based chemotherapy



*Patients were treated until disease progression

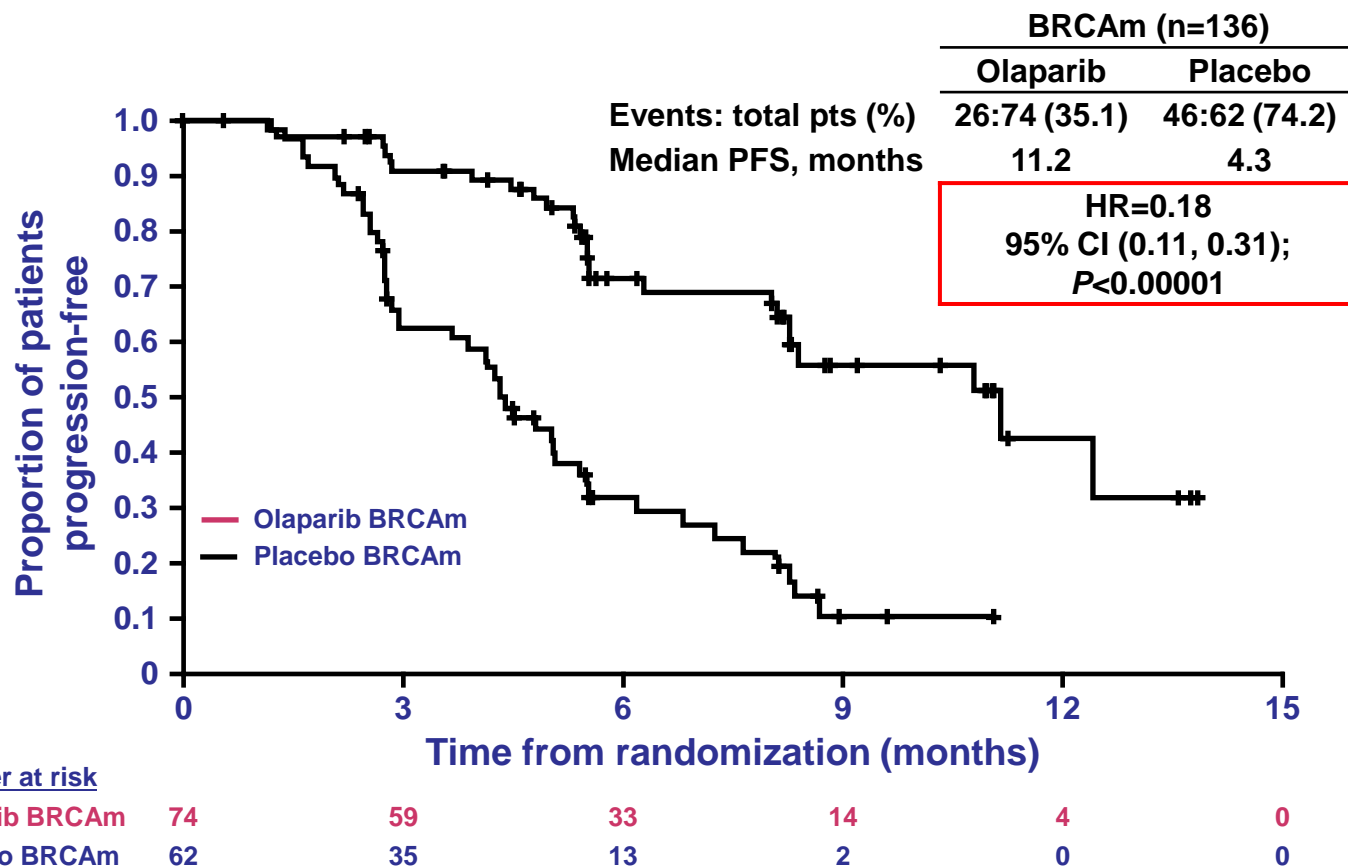
Results: BRCA testing

		tBRCA			TOTAL
		Mutated	Wild type*	Not available	
gBRCA	Mutated	71	3	22	96
	Wild type*	20	79	23	
	Not available	20	16	11	
					265

- 136 (51.3%) patients had a known deleterious BRCAm (BRCAm dataset)
- 118 (44.5%) patients were defined as *BRCA1/2* wild type for this analysis
- 11 (4.2%) patients had neither a tumour nor a germline result available
- The number of patients with a known BRCAm status increased from 97 (36.6%) to **254** (95.8%) out of 265

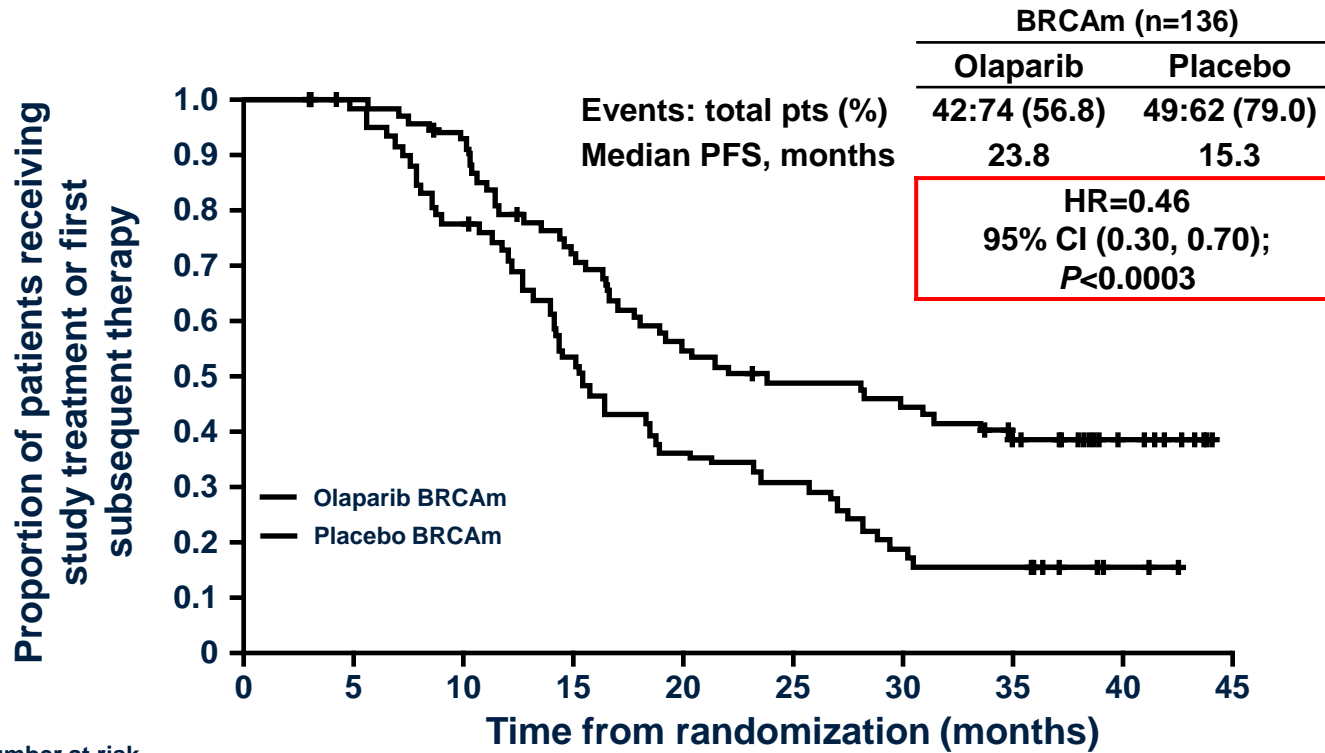
*Wild-type group includes patients with no known BRCAm or a mutation of unknown significance (a non-deleterious mutation)

PFS by BRCAm status



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

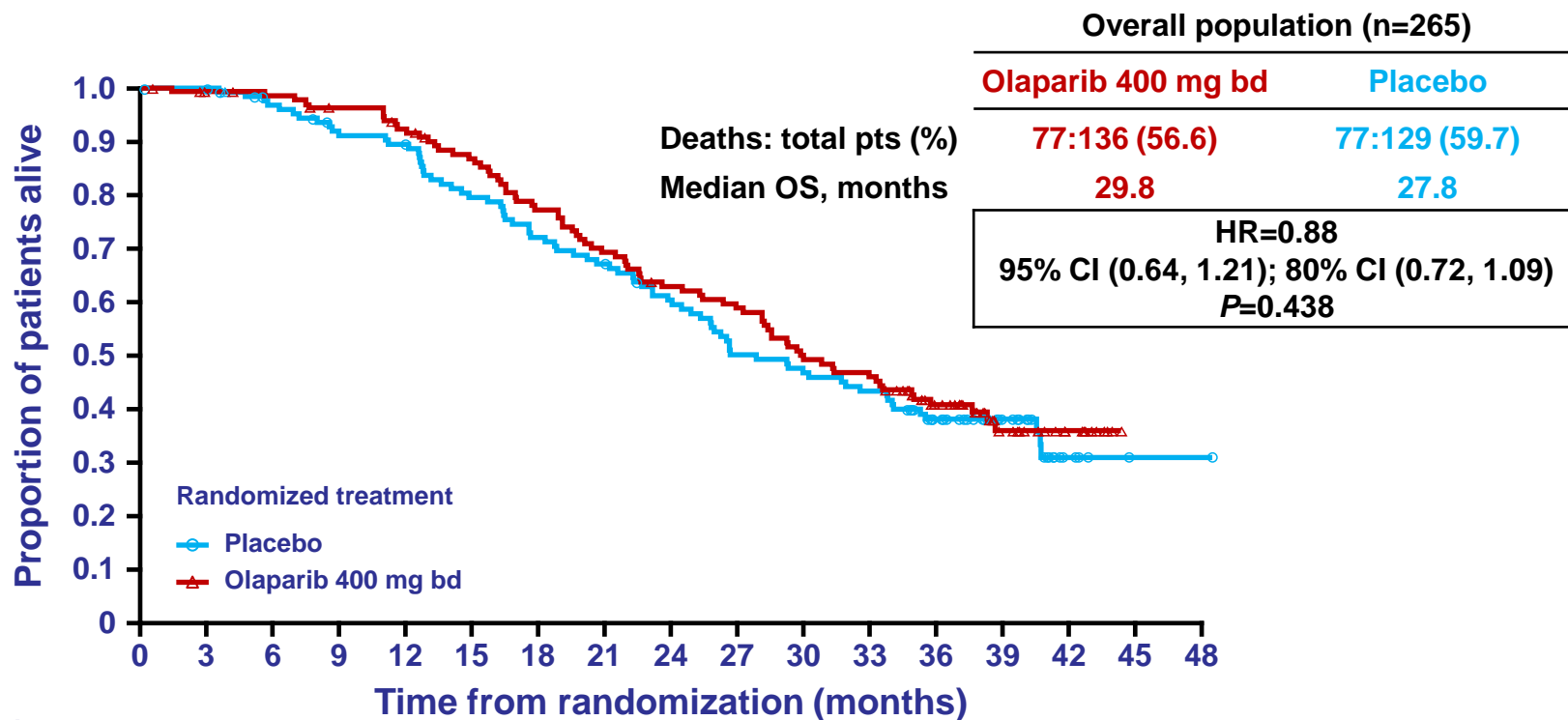
Time to second subsequent therapy (PFS2)



Number at risk

Olaparib BRCaM	74	70	65	50	38	33	30	23	9	0
Placebo BRCaM	62	60	46	31	21	18	11	9	2	0

Study 19 updated overall survival: all patients

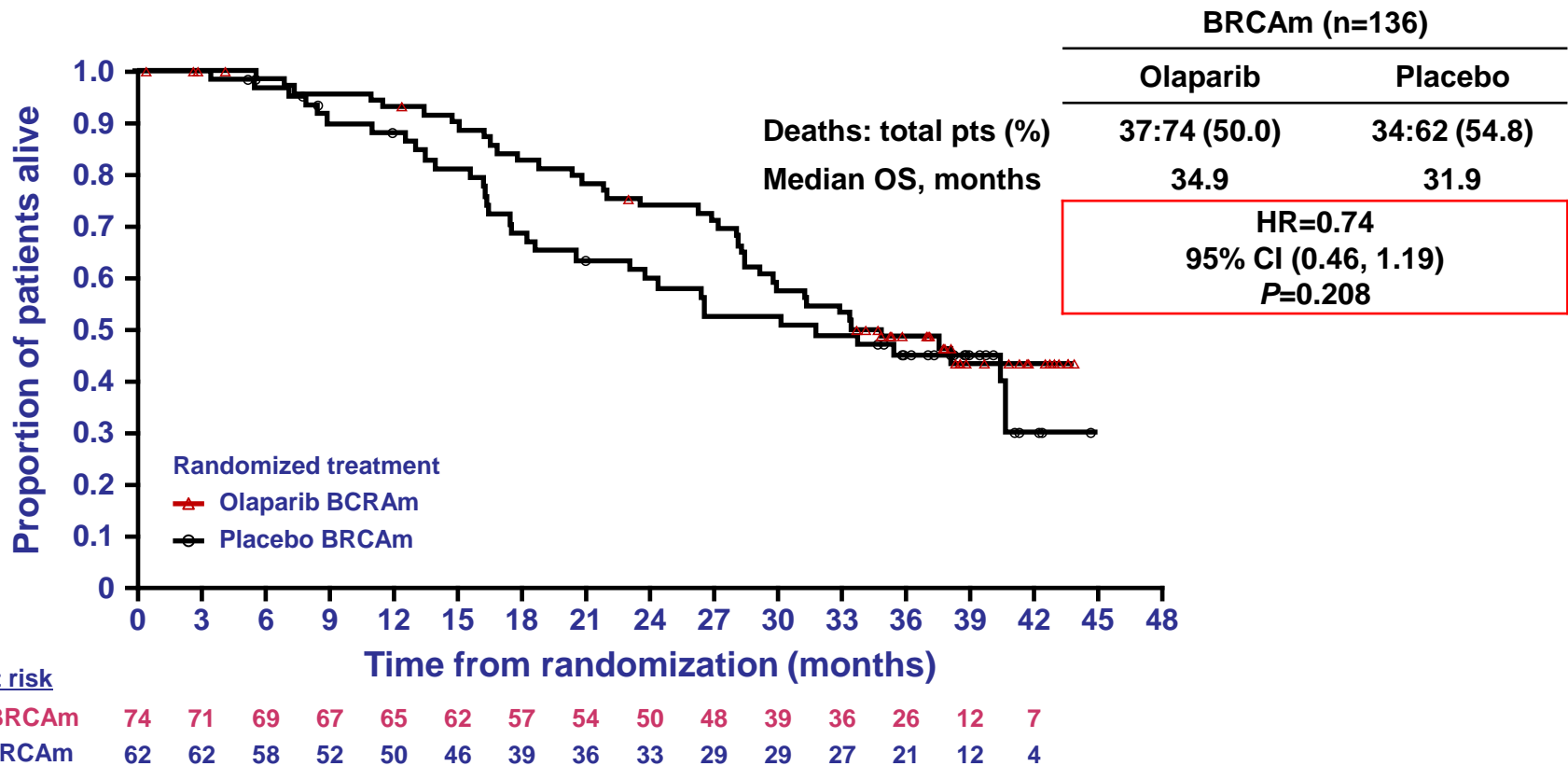


Number at risk

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; $P=0.75$

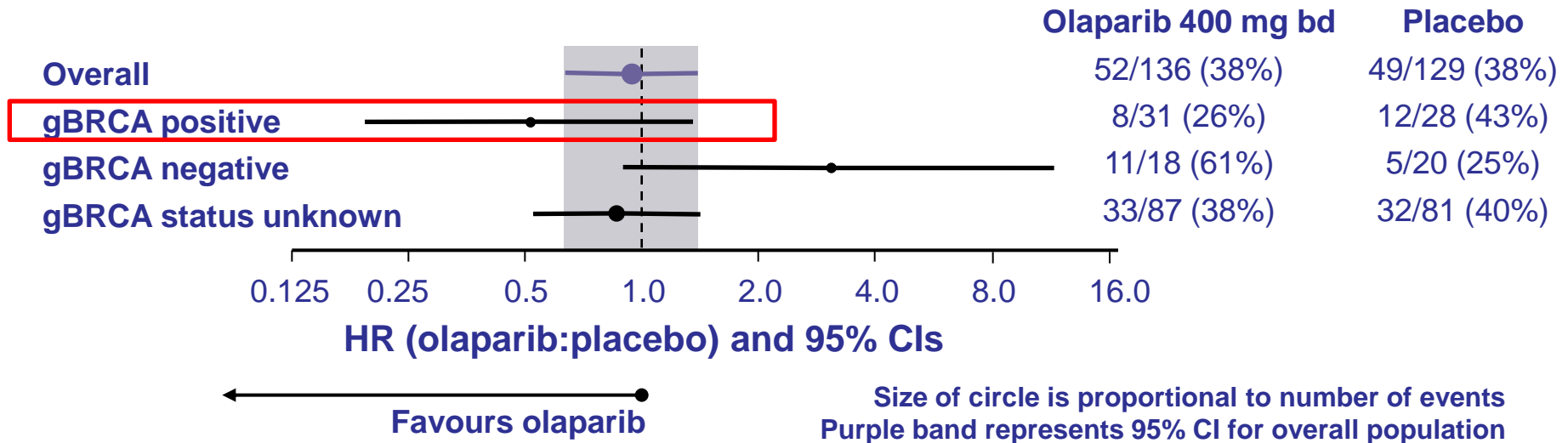
OS in BRCAm patients



- 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

QoL in patients with a BRCAm

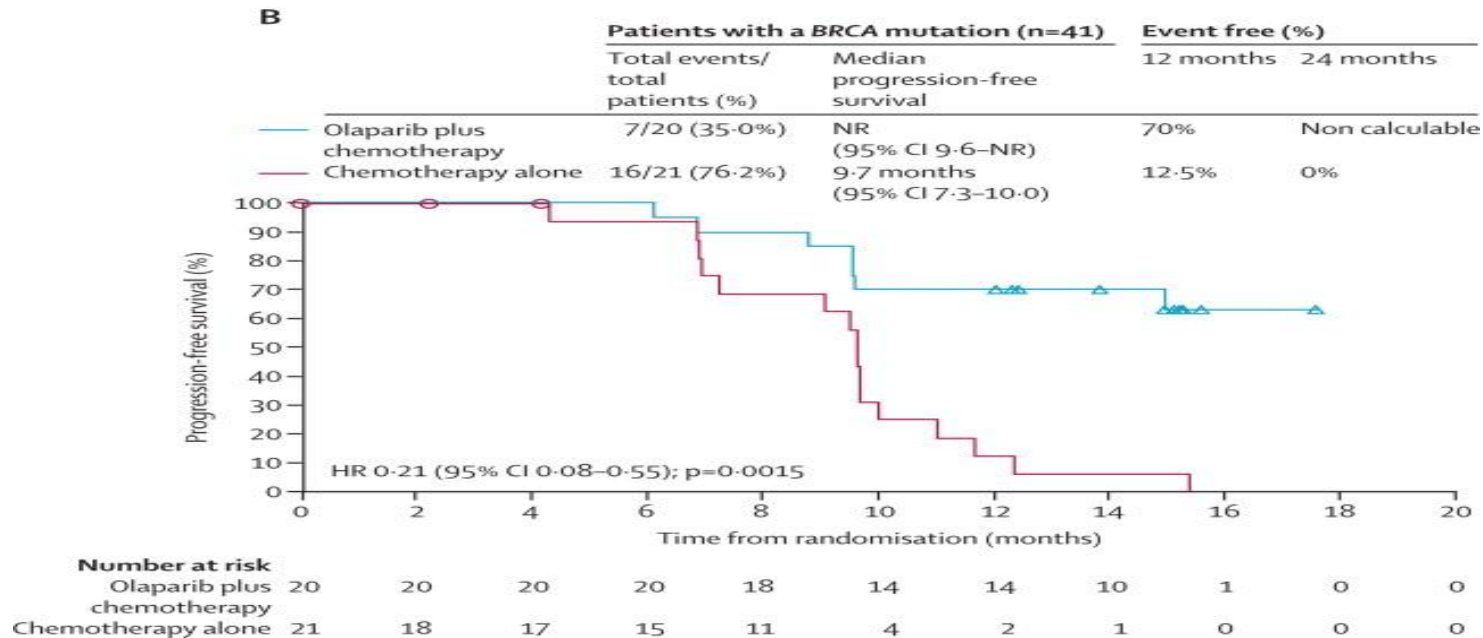
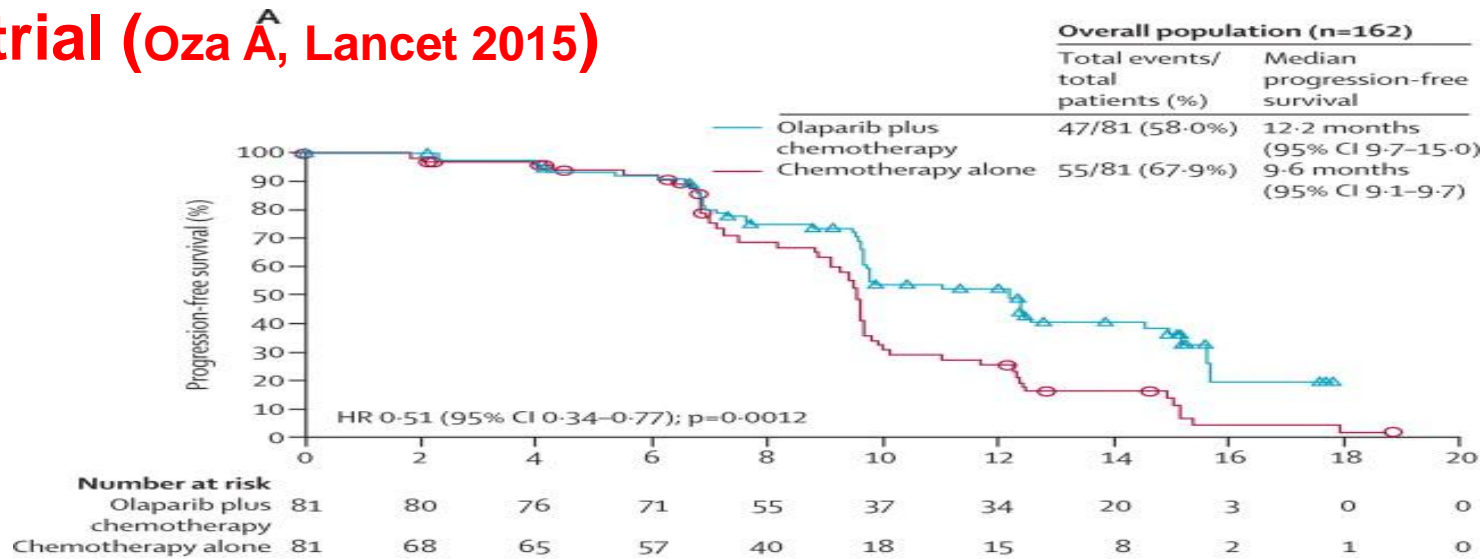
FACT-O domain	Olaparib	Placebo
TOI improved, n (%)	16/64 (25.0)	10/53 (18.9)
	OR, 1.37 95% CI 0.56–3.46, <i>P</i> =0.49	

Odds ratio (OR) >1 favours olaparib

- In patients with a BRCAm:
 - No statistically significant differences were observed in improvement rates or time to worsening of TOI, FOSI and Total FACT-O
 - A numerically higher proportion of patients reported improvements in TOI, FOSI and Total FACT-O following treatment with olaparib vs placebo

TOI, Trial Outcome Index; FACT-O, functional assessment of cancer therapy for ovarian cancer; FOSI, FACT-O Symptom Index

Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial (Oza A, Lancet 2015)



Is Family History a Predictor of a *BRCA* Mutation?

Absence of family history (breast/ovarian)
among *BRCA* mutation carriers

Walsh et al	30%
Alsop et al	44%
Soegaard et al	54%
Malander et al	10%
Jacobi et al	20%
Risch et al	20%

Approximately 30% of *BRCA1/2* mutation carriers
do not have a family history

Raccomandazioni per l'implementazione del test BRCA nei percorsi assistenziali e terapeutici delle pazienti con carcinoma ovarico

A cura del Gruppo di Lavoro AIOM - SIGU - SIBIOC - SIAPEC-IAP

Maria Angela Bella, Ettore Capoluongo, Paola Carrera, Claudio Clemente, Nicoletta Colombo, Laura Cortesi, Gaetano De Rosa, Maurizio Genovani, Stefania Gori, Valentina Guarnieri, Antonio Marchetti, Paola Marchetti, Nicola Normanno, Barbara Pasini, Sandro Pignata, Carmine Pinto, Paolo Radice, Enrico Ricevuto, Antonio Russo, Pierosandro Tagliaferri, Pierfrancesco Tassone, Mauro Truinj, Liliana Varesco

Luglio 2015



Sulla base di queste evidenze, anche se attualmente il test BRCA è formalmente necessario come test predittivo per l'indicazione alla terapia con il PARP-inibitore, è consigliabile considerare l'invio al test BRCA sin dal momento della diagnosi per tutte le pazienti con diagnosi di carcinoma epiteliale ovarico non mucinoso e non borderline, di carcinoma delle tube di Fallopio e di carcinoma peritoneale primitivo, per completare la fase diagnostica molecolare, in previsione di un eventuale utilizzo terapeutico e per favorire l'accesso ad una consulenza genetica oncologica pre-test nell'ambito dei percorsi di prevenzione. La proposta all'esecuzione del

Phase III trials with PARP inhibitors

Recruiting:

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

Results of ARIEL2: A phase 2 trial to prospectively identify ovarian cancer patients likely to respond to rucaparib using tumor genetic analysis

Iain McNeish,¹ Amit Oza,² Robert L. Coleman,³ Clare Scott,⁴ Gottfried Konecny,⁵ Anna Tinker,⁶ David M. O'Malley,⁷ James Brenton,⁸ Rebecca Kristeleit,⁹ Katherine Bell-McGuinn,¹⁰ Ana Oaknin,¹¹ Alexandra Leary,¹² Kevin K. Lin,¹³ Mitch Raponi,¹³ Heidi Giordano,¹³ Sandra Goble,¹³ Lindsey Rolfe,¹³ Roman Yelensky,¹⁴ Andrew Allen,¹³ and Elizabeth Swisher¹⁵

¹Institute of Cancer Sciences, University of Glasgow, ²Princess Margaret Cancer Centre, ³The University of Texas MD Anderson Cancer Center, ⁴Royal Melbourne Hospital, ⁵University of California, ⁶British Columbia Cancer Agency, ⁷The Ohio State University, ⁸Cancer Research UK Cambridge Institute, ⁹University College London, ¹⁰Memorial Sloan-Kettering Cancer Center, ¹¹Vall d'Hebron University Hospital, ¹²Institut Gustave Roussy, ¹³Clovis Oncology Inc., ¹⁴Foundation Medicine Inc., ¹⁵University of Washington School of Medicine

ARIEL2 designed to assess rucaparib efficacy in three prospectively defined molecular subgroups

Key Eligibility (N=180)

- High-grade serous or endometrioid OC
 - Known gBRCA enrollment capped at N=15
- ≥1 prior platinum chemotherapy
- Platinum-sensitive, relapsed, measurable disease
- Tumor tissue (screening biopsy and archival)

gBRCA=germline BRCA.

NGS of tumor tissue allows patients to be classified

600 mg BID rucaparib until disease progression

BRCA^{mut}

BRCA-like

Biomarker Negative

Analysis of HRD Subgroups

Primary endpoint

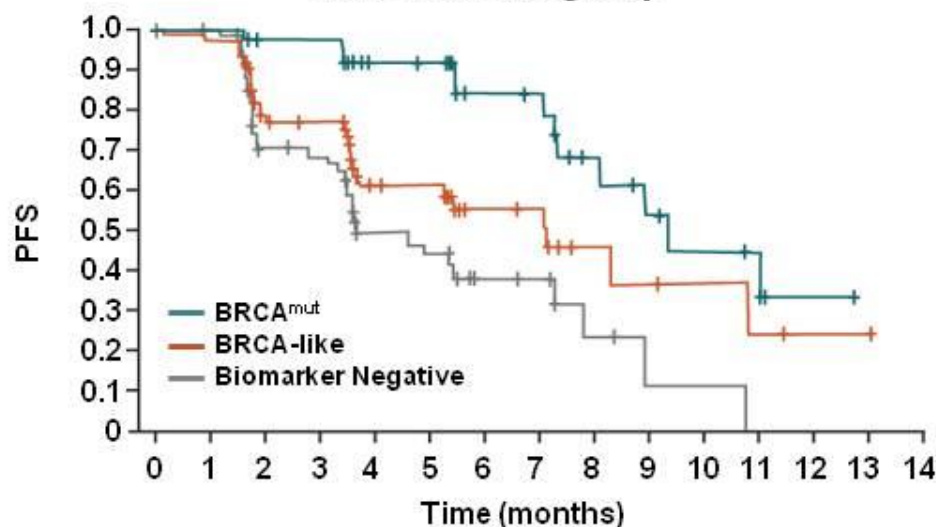
- PFS

Secondary endpoints

- ORR
 - RECIST
 - RECIST + CA-125
- Safety
- PK

Primary efficacy analysis: PFS in BRCA^{mut} and BRCA-like versus Biomarker Negative patients

Progression-free survival by HRD molecular subgroup



Available (endpoint reached)

BRCA ^{mut}	40 (0)	39 (0)	35 (1)	35 (1)	28 (3)	27 (3)	18 (5)	17 (5)	10 (8)	7 (10)	5 (11)	4 (11)	1 (12)	0 (12)	
BRCA-like	81 (0)	72 (2)	48 (15)	45 (16)	24 (24)	23 (24)	13 (26)	12 (26)	5 (28)	4 (29)	3 (29)	2 (30)	1 (30)	1 (30)	0 (30)
Biomarker Negative	69 (0)	62 (0)	37 (17)	35 (18)	18 (27)	16 (29)	8 (31)	7 (31)	3 (33)	1 (34)	1 (34)	0 (35)			

HRD Subgroup	Median PFS, mo (90% CI)
BRCA ^{mut}	9.4 (7.3, Not Reached)
BRCA-like	7.1 (3.7, 10.8)
Biomarker Negative	3.7 (3.5, 5.5)

Subgroup Comparison	Hazard Ratio (90% CI)
BRCA ^{mut} vs Biomarker Negative	0.47 (0.35, 0.64)
BRCA-like vs Biomarker Negative	0.61 (0.41, 0.92)

CI=confidence interval.

In BRCA^{wt} tumors, the BRCA-like subgroup derives enhanced benefit from rucaparib

HRD Subgroup	Median PFS, mo (90% CI)	Overall Response Rate, % (N)	
		RECIST	RECIST + CA-125
BRCA ^{mut}	9.4 (7.3, NR)	69 (27/39)	82 (32/39)
BRCA-like	7.1 (3.7, 10.8)	30 (22/74)	45 (33/74)
Biomarker Negative	3.7 (3.5, 5.5)	13 (8/62)	21 (13/62)

BRCA^{wt} [

NR=not reached.

Rucaparib is generally well tolerated

Adverse Event*	Treatment-Related AEs Reported in $\geq 15\%$ of Patients Number of Patients Total N=204, n (%)	
	Total	Grade 3/4
Nausea	135 (66)	6 (3)
Asthenia/Fatigue	124 (61)	13 (6)
ALT/AST increased**	81 (40)	23 (11)
Dysgeusia	77 (38)	0
Decreased appetite	63 (31)	2 (1)
Vomiting	55 (27)	2 (1)
Anemia/Decreased hemoglobin	54 (27)	33 (16)
Constipation	52 (26)	1 (1)
Diarrhea	38 (19)	3 (2)

*No cases of myelodysplastic syndrome or acute myeloid leukemia reported; **ALT/AST elevations are transient, self-limiting, and not associated with other signs of liver toxicity.

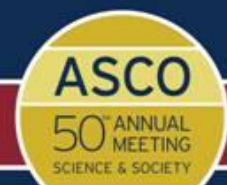
A Randomized Phase 2 Trial Comparing Efficacy of the Combination of the PARP-inhibitor Olaparib and the Anti-angiogenic Cediranib Against Olaparib Alone in Recurrent Platinum-sensitive Ovarian Cancer

Joyce F. Liu¹, William T. Barry¹, Michael Birrer², Jung-Min Lee³, Ronald Buckanovich⁴, Gini Fleming⁵, BJ Rimel⁶, Mary Buss⁷, Sreenivasa Nattam⁸, Jean Hurteau⁹, Weixiu Luo¹, Philippa Quy¹, Lisa Obermayer¹, Christin Whalen¹, Hang Lee², Eric Winer¹, Elise Kohn³, S. Percy Ivy³, Ursula A. Matulonis¹

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



PRESENTED AT THE 2014 ASCO ANNUAL MEETING. PRESENTED DATA IS THE PROPERTY OF THE AUTHOR.



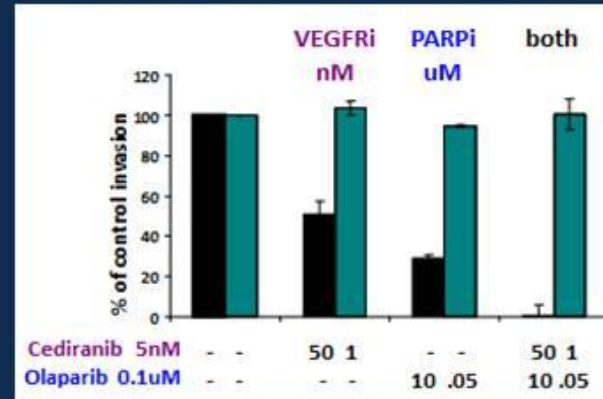
Cediranib and olaparib have synergistic activity *in vitro*

- Pre-clinical data suggesting potential synergy between PARPi and anti-angiogenics
- PARP inhibition or PARP knockout results in decreased *in vivo* angiogenesis¹
- Sensitivity to PARP inhibitors increased in hypoxic cells²

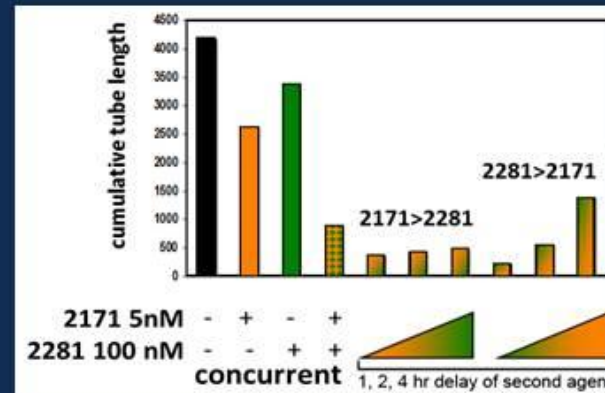
¹Tentori et al., *Eur J Cancer* 2007, 43(14): 2124-33

²Hegan et al., *PNAS* 2010, 107(5): 2201-6

Effect of ced/olap on cell invasion:

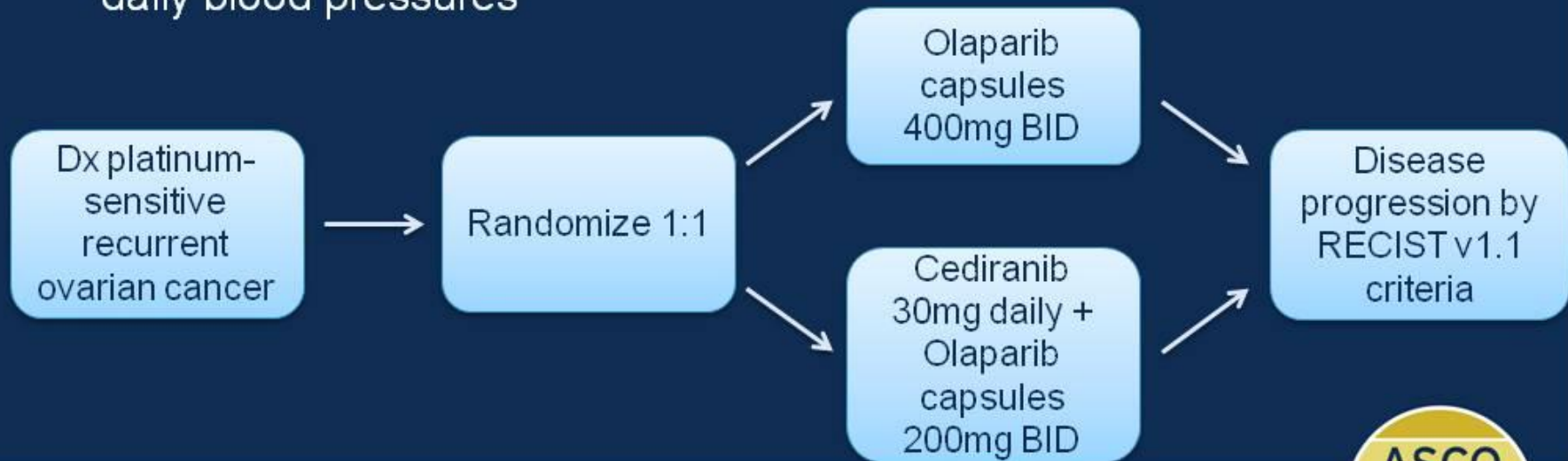


Effect of ced/olap on microvascular cell tube organization:



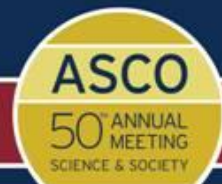
Study Design

- 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



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

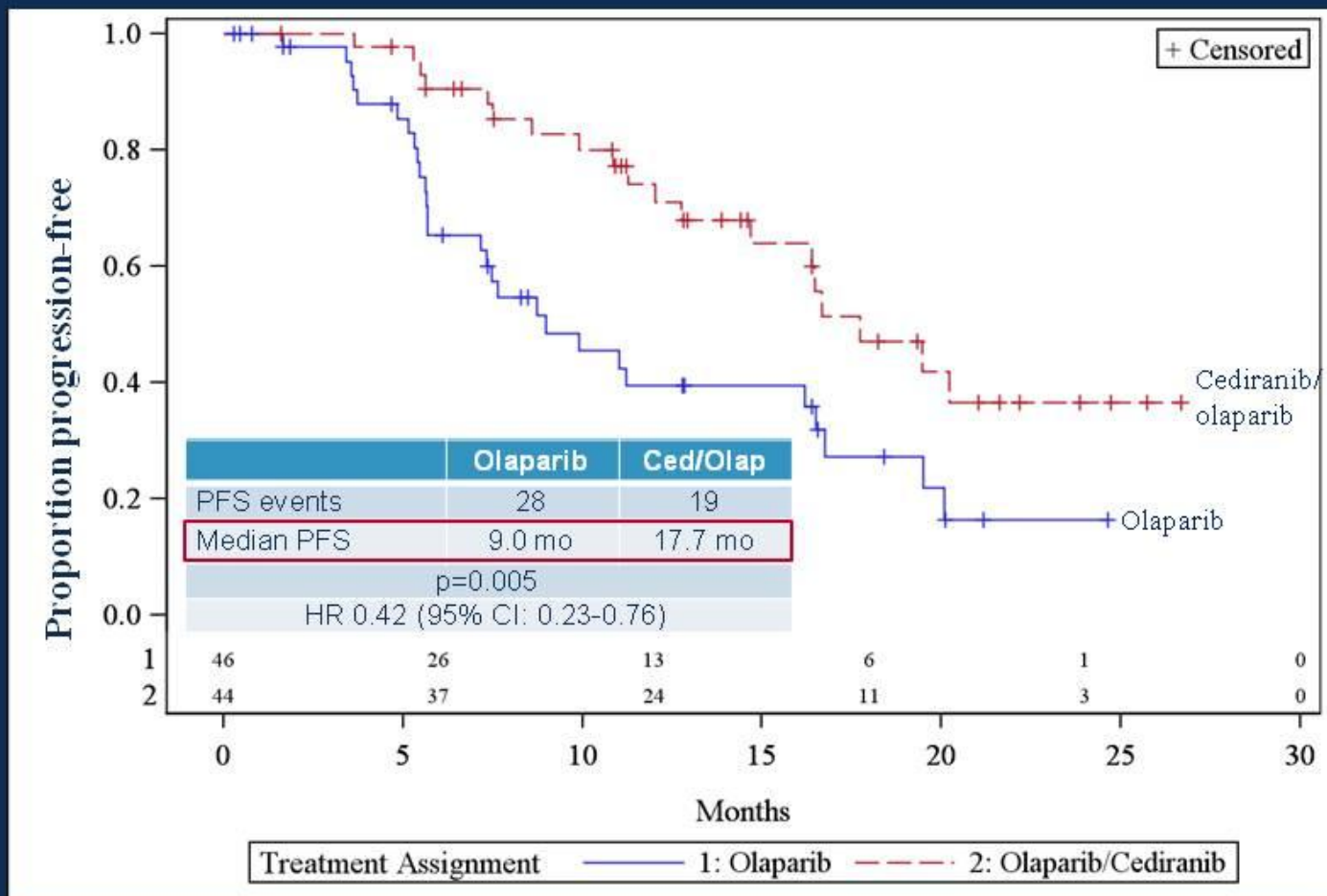
Best overall response

Arm	Treated	CR		PR		SD		PD	
		N	%	N	%	N	%	N	%
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		

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



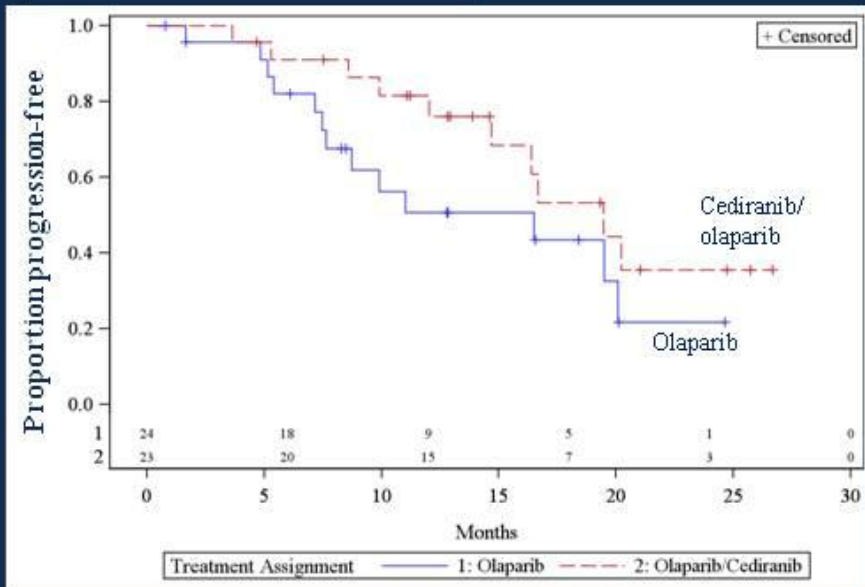
Presented by: Joyce Liu, MD, MPH

PRESENTED AT:

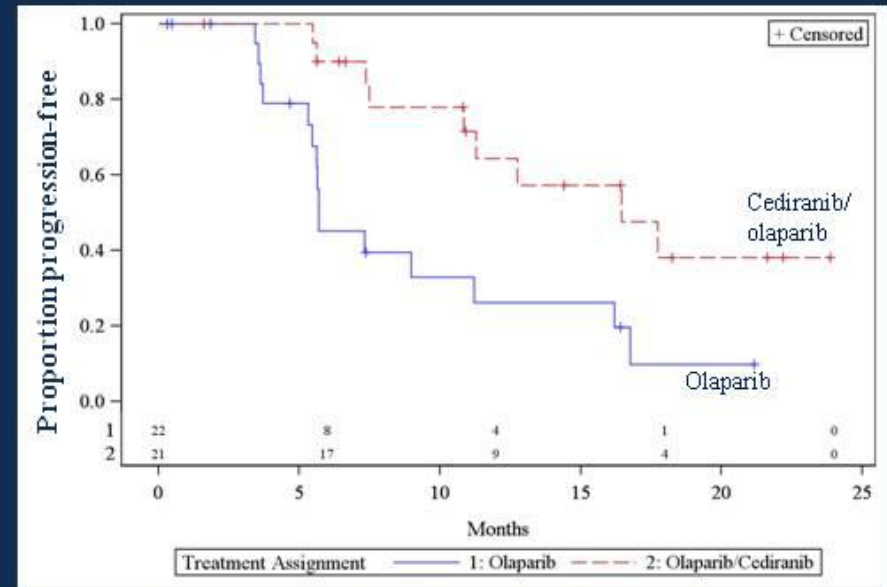


Cediranib/olaparib significantly increased PFS in patients without a BRCA mutation

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:



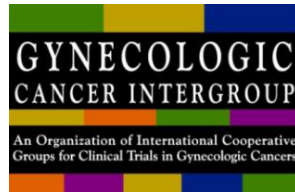
Response to platinum-based chemotherapy in Platinum-sensitive relapsed ovarian cancer

	PFS (med months)	% 1 st 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:





PAOLA1

Platine, Avastin and OLAparib 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.

Recurrent platinum sensitive trial

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 algorithm 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