FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

2016 inc Research Clinical Research Site Award RECIPIENT

XVIII Congresso di
Oncologia Trevigliese
Treviglio 28/09/2017

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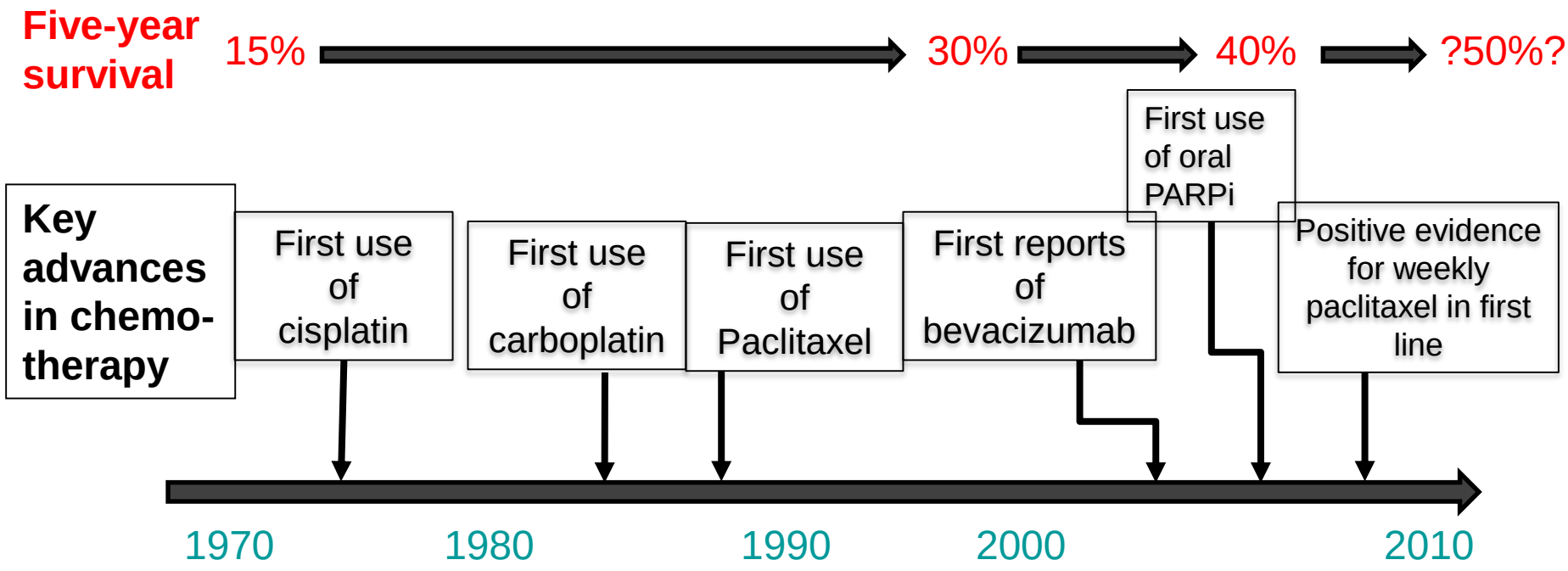
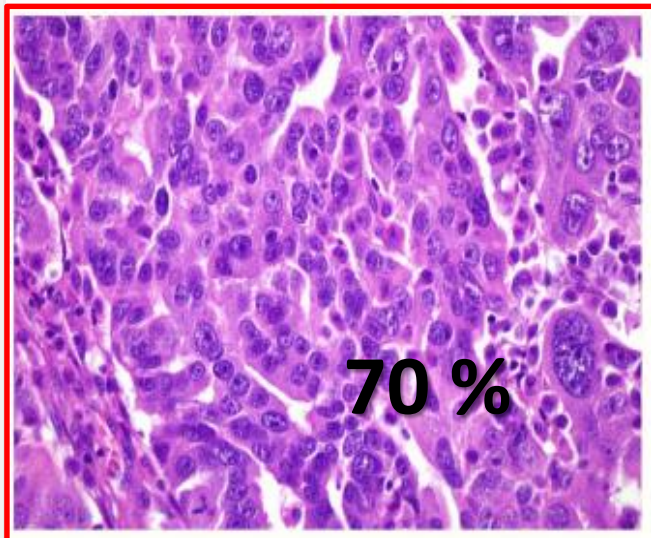
Gynecologic Oncologic Unit
National Cancer Institute-Milan

UN INCIDENTE DI PERCORSO:
I TUMORI GINECOLOGICI

Progress in the Management of Ovarian Cancer: Evolution Over 40 Years

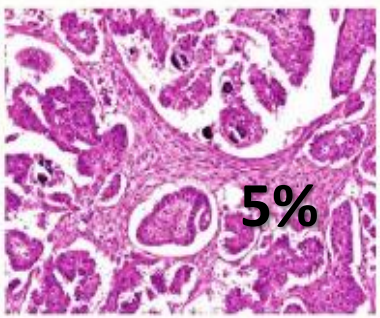


Ovarian cancer is not a single disease

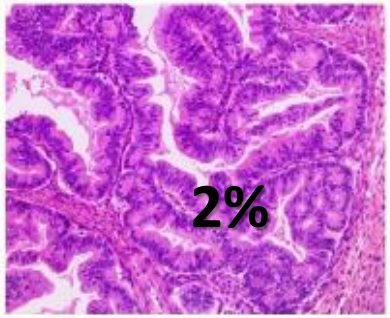


High-grade serous ovarian cancer

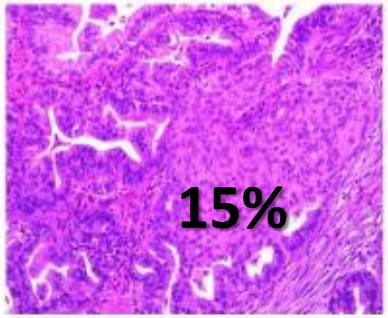
- *TP53*: encodes a protein that regulates the cell cycle
- *BRCA1* and *BRCA2*: encode proteins that are involved in genome protection



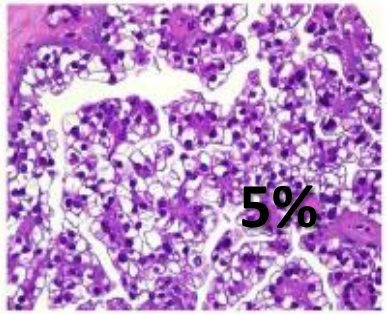
Low-grade serous
BRAF; KRAS



Mucinous carcinoma
KRAS



Endometrioid carcinoma
PTEN (low grade); *TP53*; *BRCA1/2*



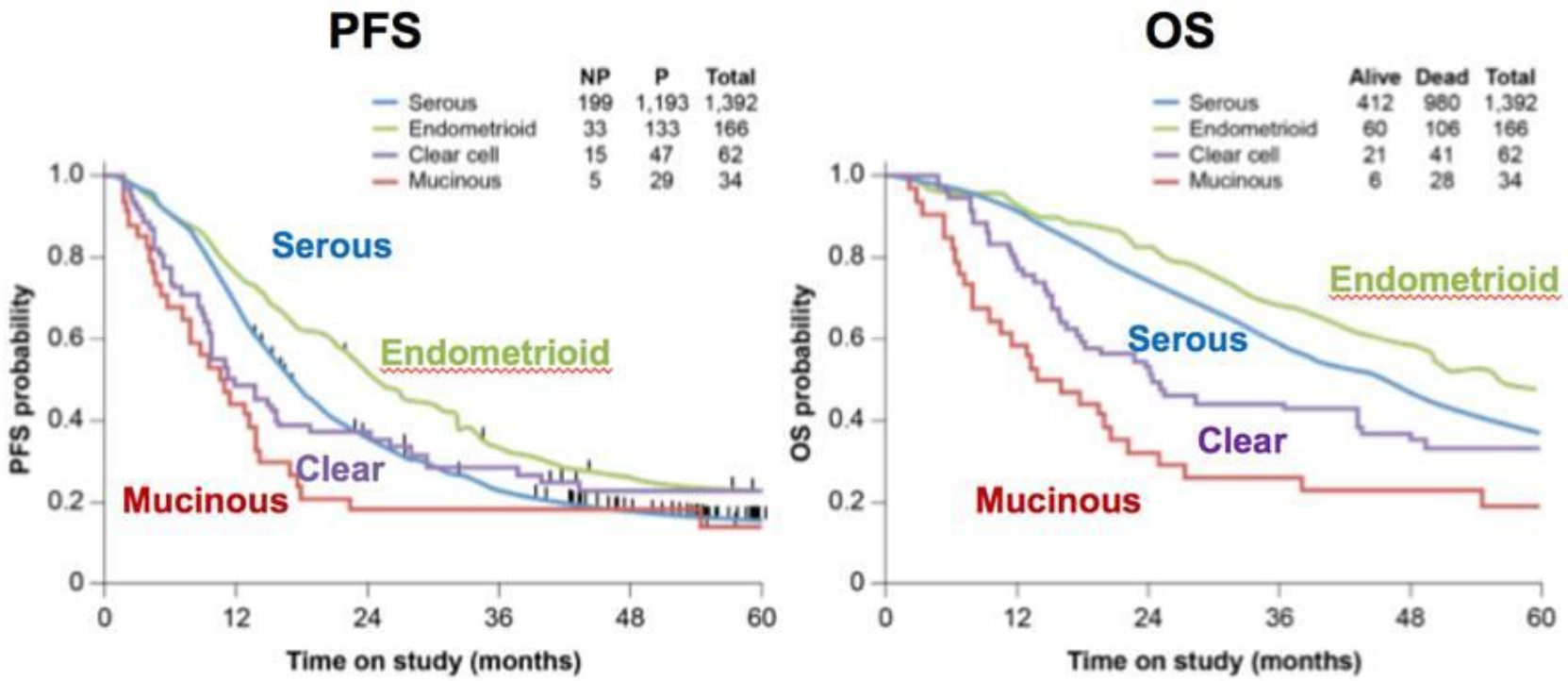
Clear cell carcinoma
PTEN; *PIK3CA*; *ARID1A*

Other subtypes

Romero I et al. Endocrinology 2012; 153: 1593-1602

Ovarian Cancer - not one disease
Outcome depends on histiotype

(GOG Trials #111, 114, 132, 152, 158, 172)



Winter WE III, et al. J Clin Oncol 2007;25:3621–7.


GCIG 5th Ovarian Cancer Consensus Conference
- International Consensus for Designing Better Clinical Trials -
November 7-9, 2015
The Jikei University School of Medicine, Tokyo, JAPAN

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

B1. What defines the clinical subgroups that should be used for comparator studies?

1. After initial diagnosis of advanced disease patients should be assessed for primary debulking surgery by a qualified gynecologic oncology surgeon or primary chemotherapy forming 2 separate major clinical subgroups

2. Primary surgery where the goal is macroscopic complete resection.

   - Patients with complete resection of macroscopic disease have a better prognosis. The extent of residual disease must be clearly documented by the surgeon.

3. After primary chemotherapy 2 clinical subgroups emerge, those who are candidates for interval debulking surgery and those who are not suitable for surgery

   - After interval debulking surgery 2 clinical subgroups groups emerge, no macroscopic residual, macroscopic residual disease. The extent of residual disease must be clearly documented by the surgeon.

4. Patients receiving neoadjuvant chemotherapy should be considered for novel combination therapy trials, particularly window of opportunity studies

GYNECOLOGIC CANCER INTERGROUP

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

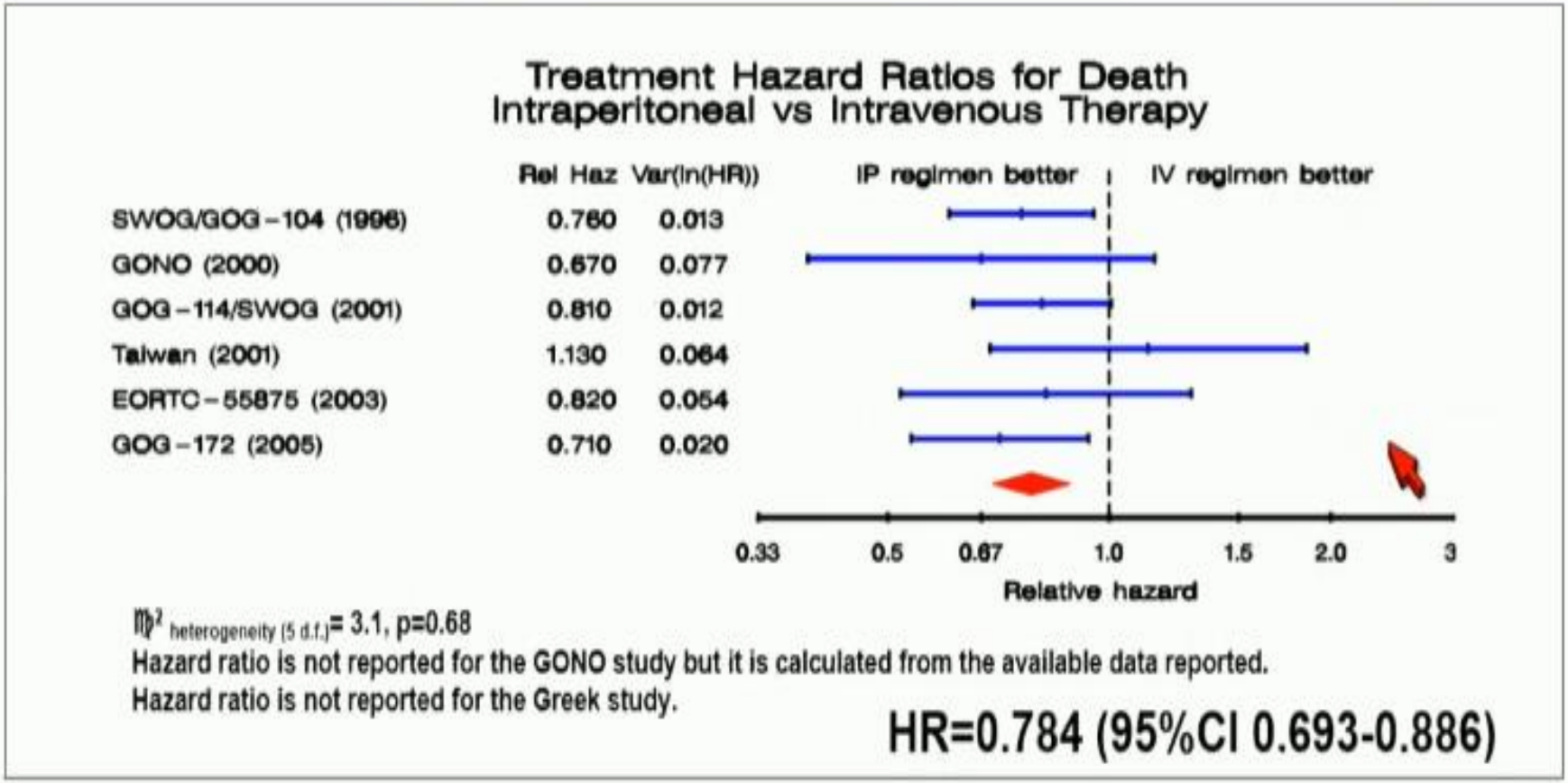
B2. What different control arms could be considered for trials of first-line therapy?

1. Intravenous 3-weekly carboplatin and paclitaxel remain the standard chemotherapy drugs for first-line therapy in advanced stage ovarian cancer
2. Acceptable additions or variations in dose, schedule, and route of delivery should be supported by at least one clinical trial demonstrating non-inferiority or superiority to a taxane/platinum. So far the following alternatives have been identified

   - Weekly intravenous paclitaxel with 3-weekly intravenous carboplatin.
   - Platinum/taxane and bevacizumab.
   - Intraperitoneal therapy after primary surgery with less than 1 cm residual disease. Both platinum and paclitaxel should be included using a validated schedule.

3. If more than one of the above regimens are included in the control arm of the same study then they should be stratified for.
4. Trials are needed to define the control arm for elderly and frail patients, defined on the basis of comprehensive geriatric assessment.
5. If chemotherapy is to be used in early stage disease platinum based chemotherapy should be the control arm.

A Meta-analysis of the Reported Studies on IP Chemotherapy



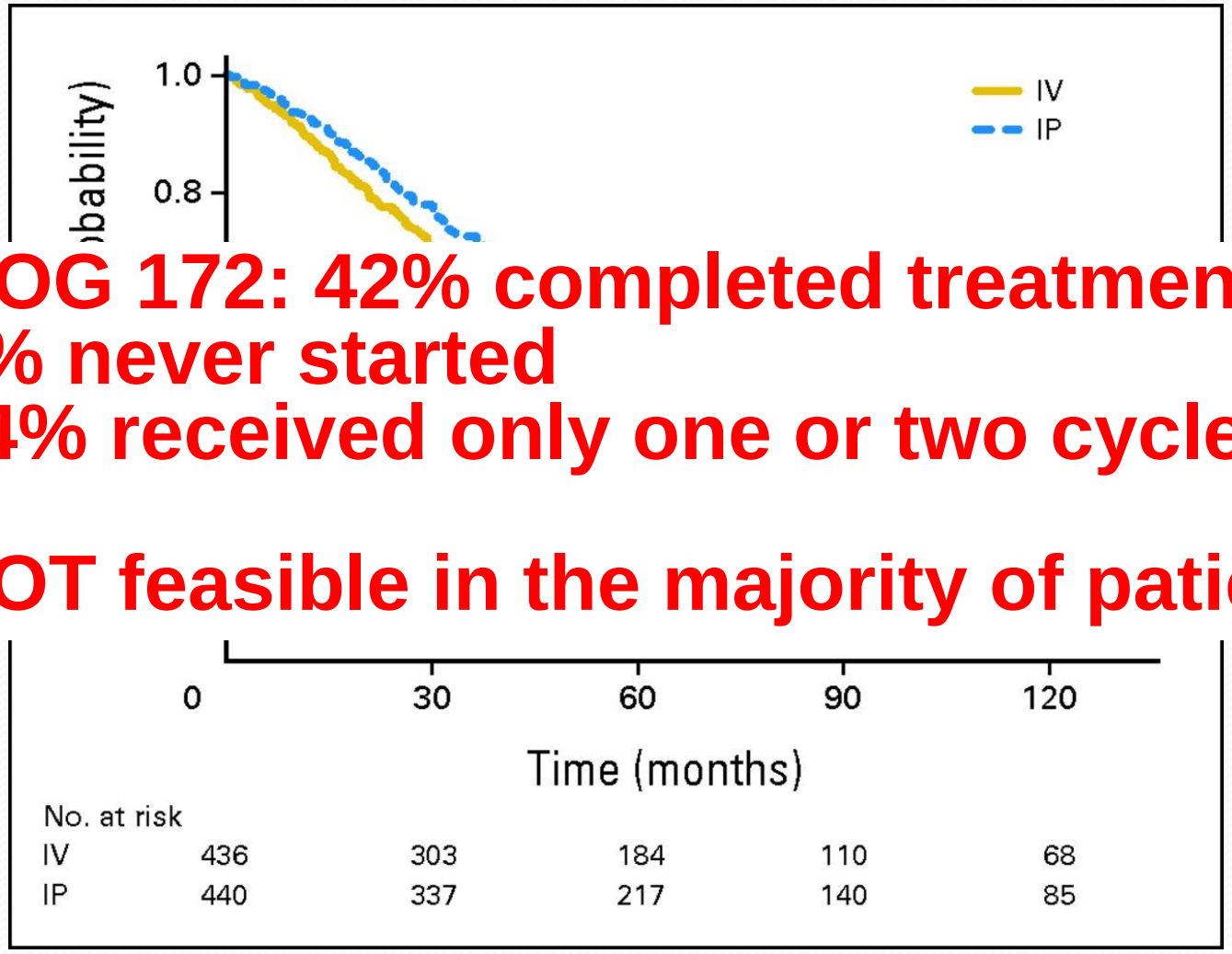
χ^2 heterogeneity (5 d.f.)= 3.1, p=0.68

Hazard ratio is not reported for the GONO study but it is calculated from the available data reported.

Hazard ratio is not reported for the Greek study.

HR=0.784 (95%CI 0.693-0.886)

Long-term overall survival of patients treated with intravenous (IV) versus intraperitoneal (IP) chemotherapy (P = .04).

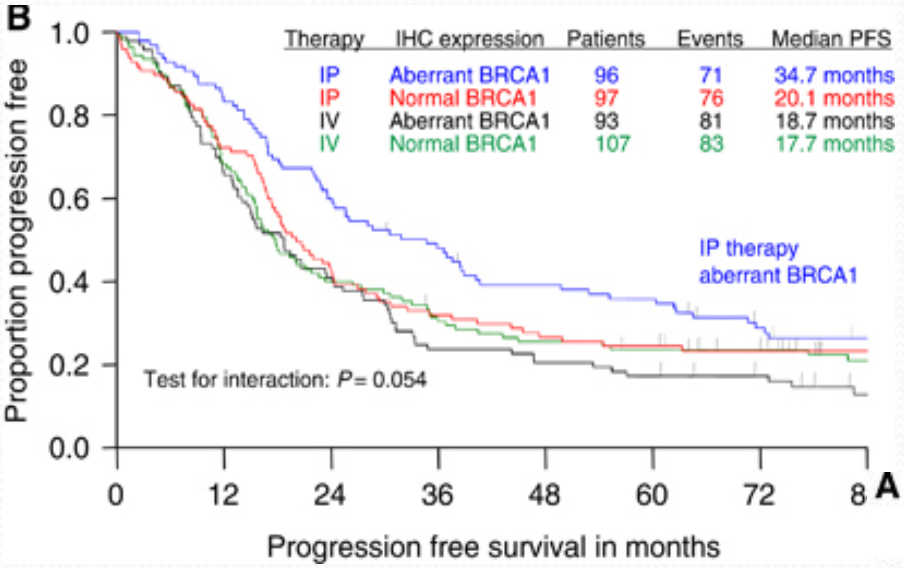


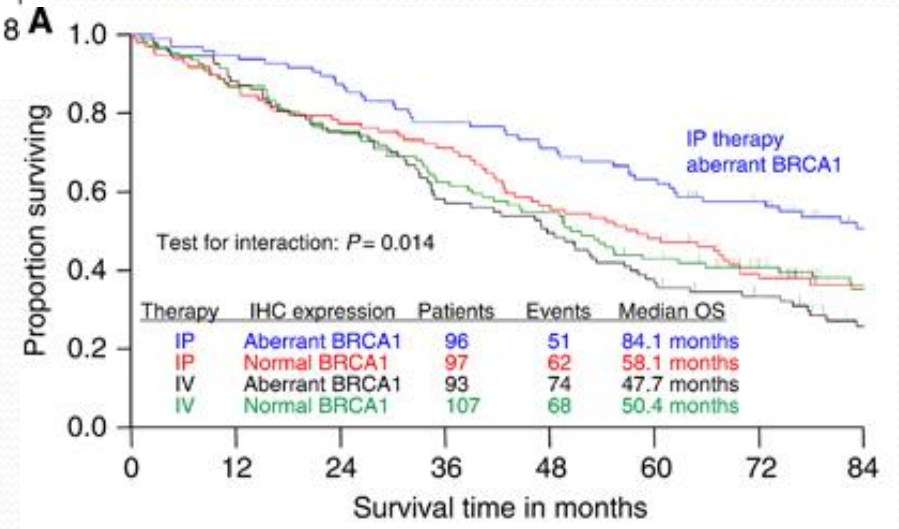
GOG 172: 42% completed treatment
8% never started
34% received only one or two cycles

NOT feasible in the majority of patients

Devansu Tewari et al. JCO doi:10.1200/JCO.2014.55.9898

BRCA1 expression and improved survival in ovarian cancer patients treated with intraperitoneal cisplatin and paclitaxel: a Gynecologic Oncology Group Study





Lesnock et al. British Journal of Cancer (2013) **108**, 1231–1237

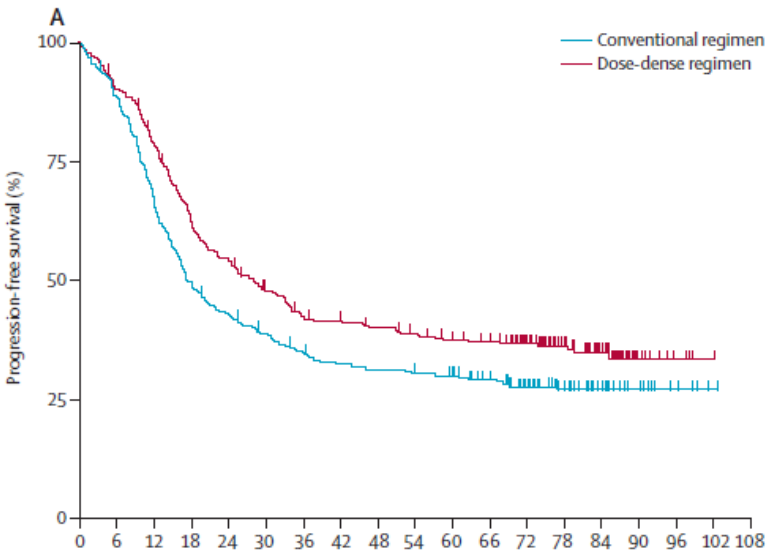
IP Chemotherapy

- Reasonable to conclude IP "strategy" may be appropriately considered one potential approach in the evolving management of OC in a variety of settings (e.g., after interval surgery following primary chemotherapy; combined with weekly paclitaxel in suboptimal residual disease) rather than either a *mandated* or a *discarded* concept

First line Dose dense in ovarian cancer

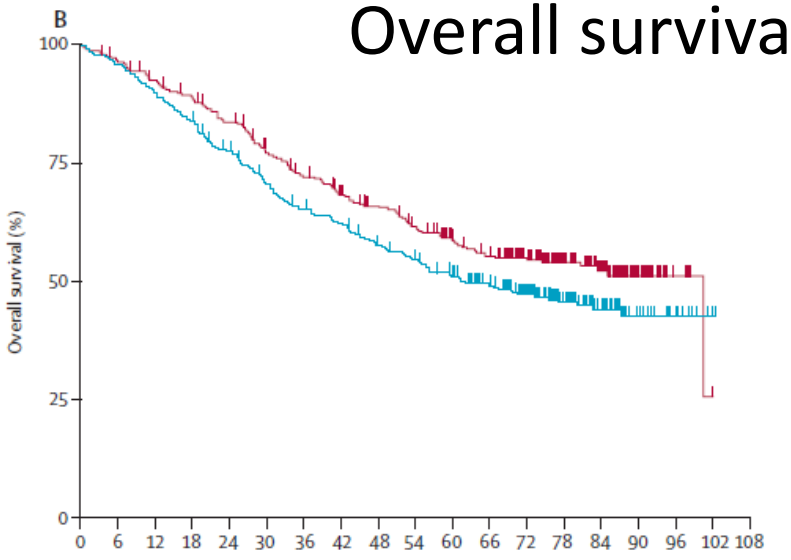
JGOG-3016

PFS



Median PFS
28.2 months vs 17.5 months
(HR 0.76, 95% CI 0.62–0.91; p=0.0037).

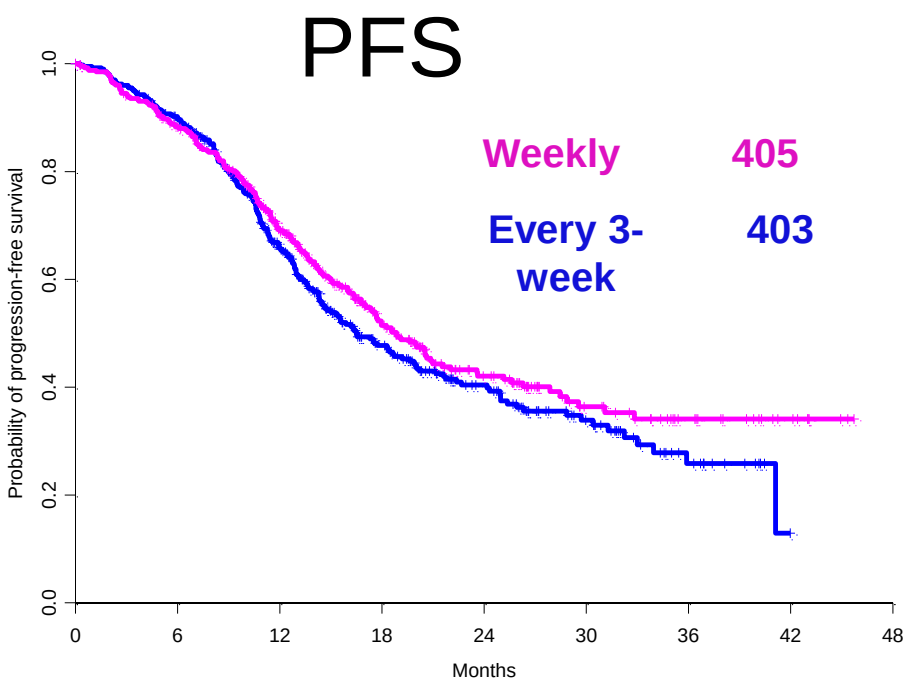
Overall survival

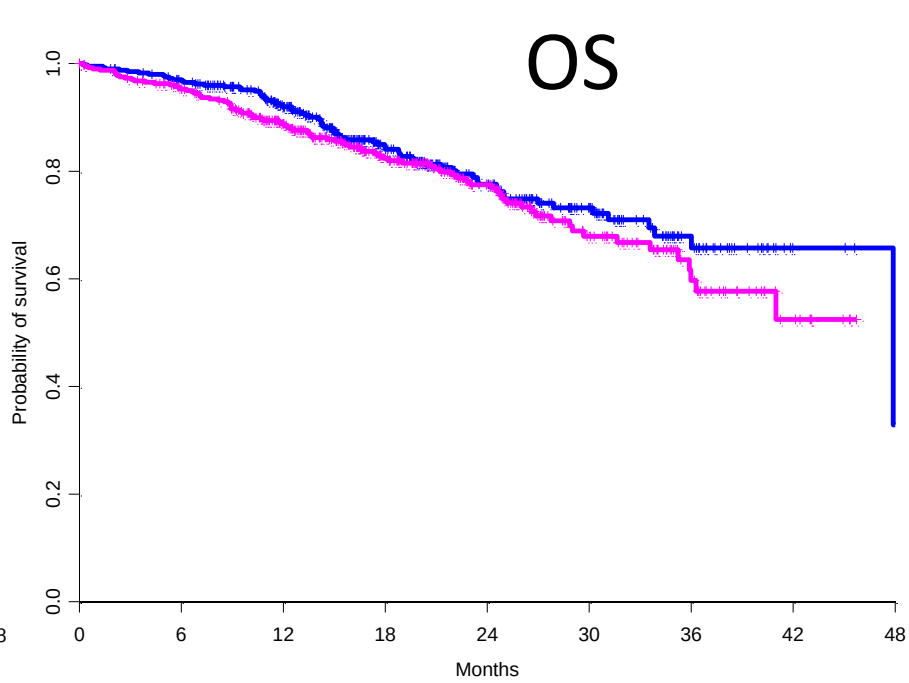


Median overall survival was
100.5 vs 62.2 months
(HR 0.79, 95% CI 0.63–0.99; p=0.039).

*Noriyuki Katsumata et al .**Lancet Oncol 2013; 14: 1020–26***

First line Dose dense in ovarian cancer
MITO 7





Median PFS 18.8 vs 16.5
Log-rank test p = 0.18
Unadjusted HR: 0.88 (0.72 – 1.06)

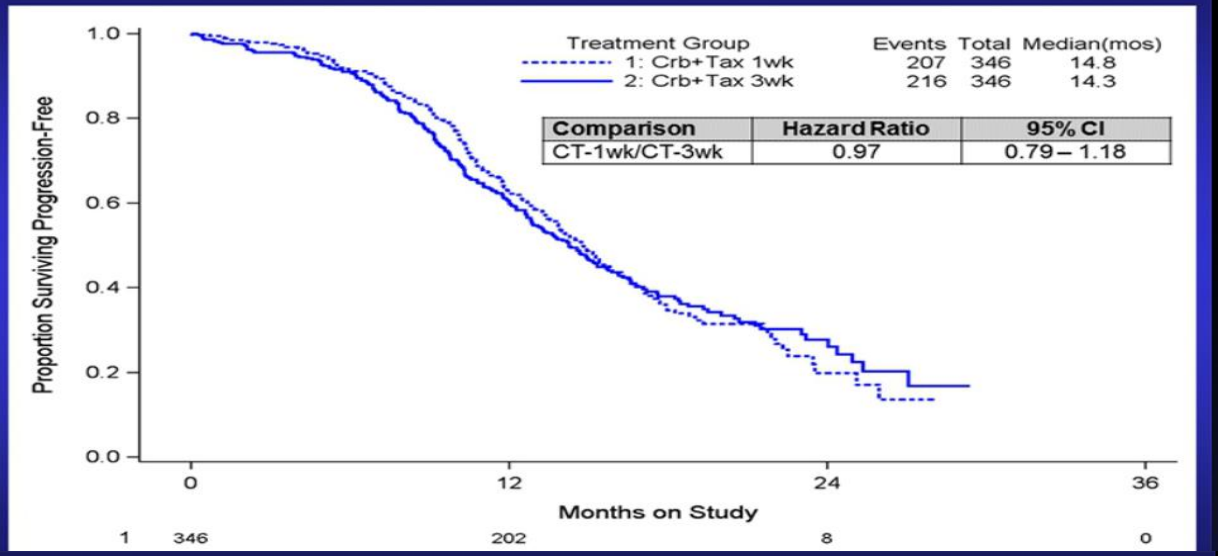
Median OS n.a. vs 47.9
Log-rank test p = 0.24
Unadjusted HR: 1.20 (0.88 – 1.63)

Presented by: S.Pignata

Pignata et al. Lancet Oncol. 2014 Apr;15(4):396-405

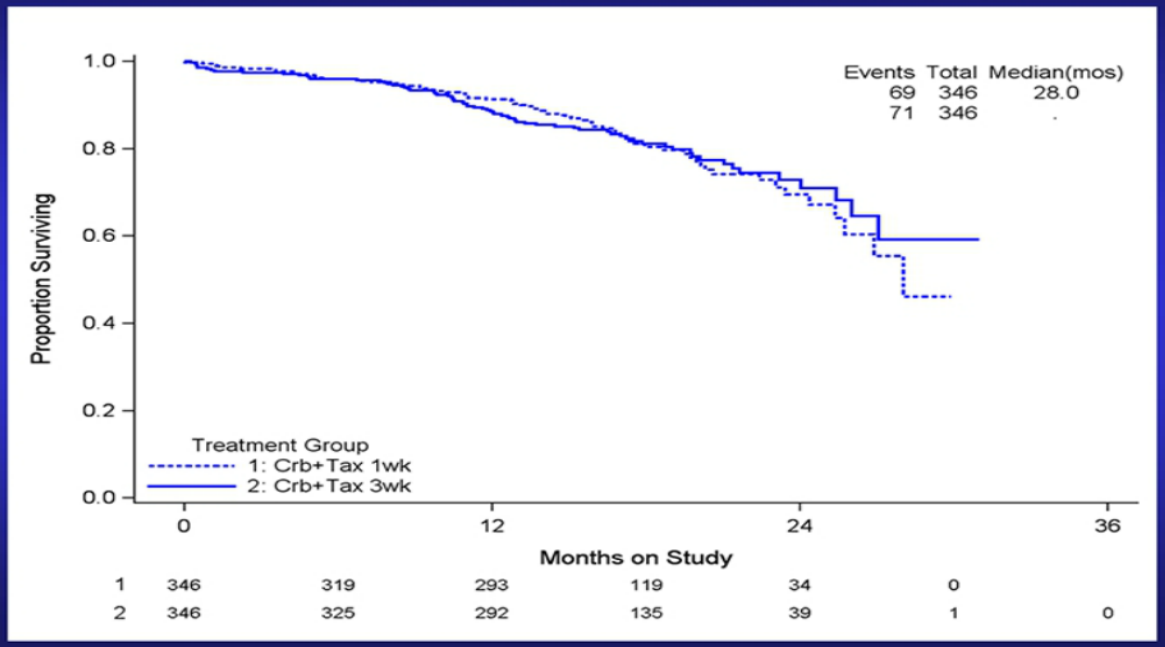
Upfront ovarian cancer treatment - modifying dose regimen

GOG 262: Progression-Free Survival by Randomized Treatment (n=692)



Upfront ovarian cancer treatment - modifying dose regimen

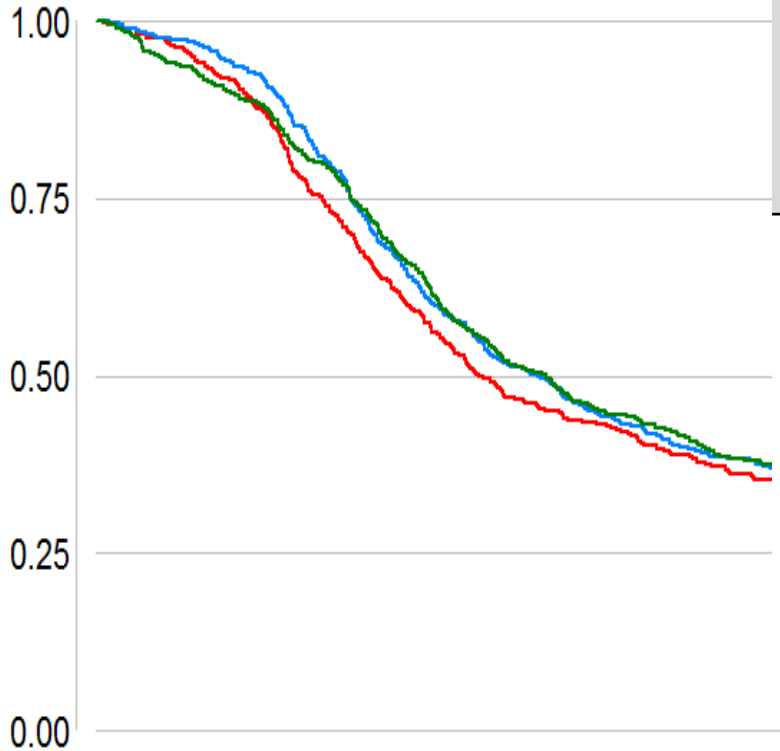
GOG 262: Overall Survival by Randomized Treatment (n=692)



Presented by: John K. Chan, MD ESGO 2013

GOG 262

ICON8 PROGRESSION FREE SURVIVAL (PFS)



Total Patients	Arm 1 Standard N=522	Arm 2 Weekly paclitaxel N=523	Arm 3 Weekly carbo-paclitaxel N=521
Progressions	330 (63%)	335 (64%)	338 (65%)
Median PFS	17.9 months	20.6 months	21.1 months
Log rank (vs Arm1)		p=0.45	p=0.56
HR vs Arm 1 (97.5% CI)		0.92 (0.77, 1.09)	0.94 (0.79, 1.12)
Restricted means	24.4 months	24.9 months	25.3 months

0 6 12 18 24 30 36 42 48 54 60 66

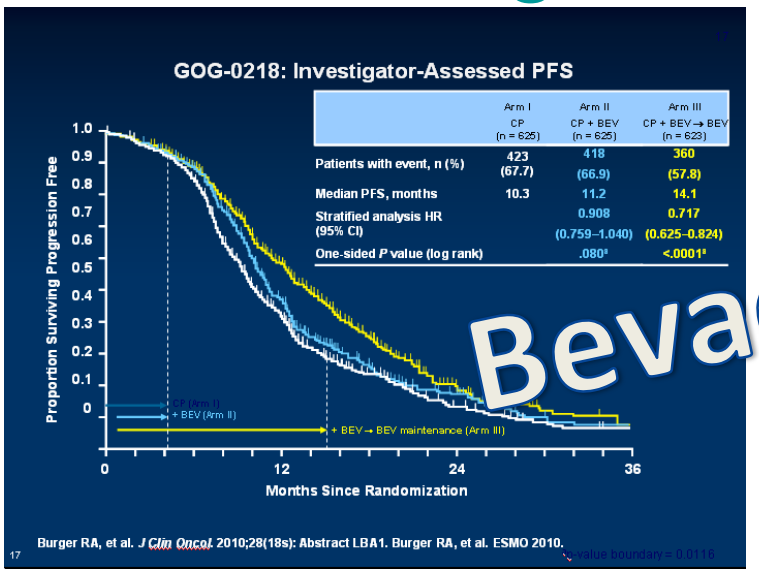
Months from randomisation

At risk:

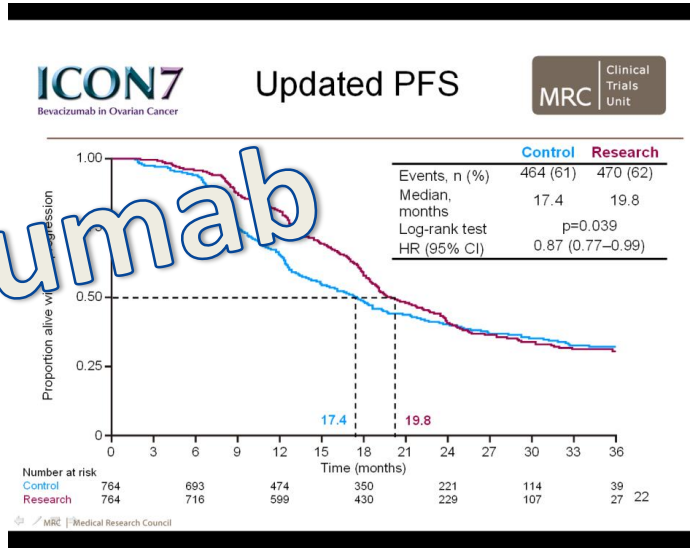
Standard	522	471	354	250	198	130	92	59	32	18	3	1
Weekly paclitaxel	523	489	383	279	210	144	92	59	28	17	3	0
Weekly carbo-paclitaxel	521	468	385	281	208	153	99	66	33	15	6	0

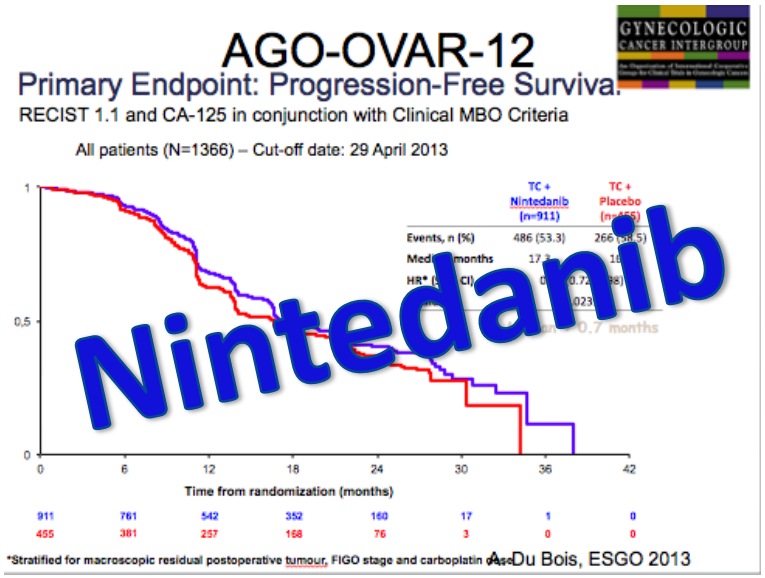
Standard Weekly paclitaxel Weekly carbo-paclitaxel

Four positive trials with antiangiogenic agents in front line

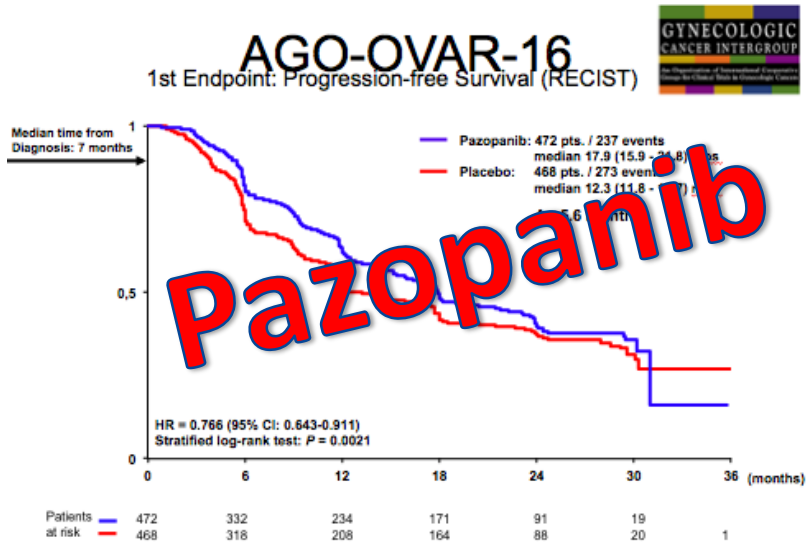


Bevacizumab



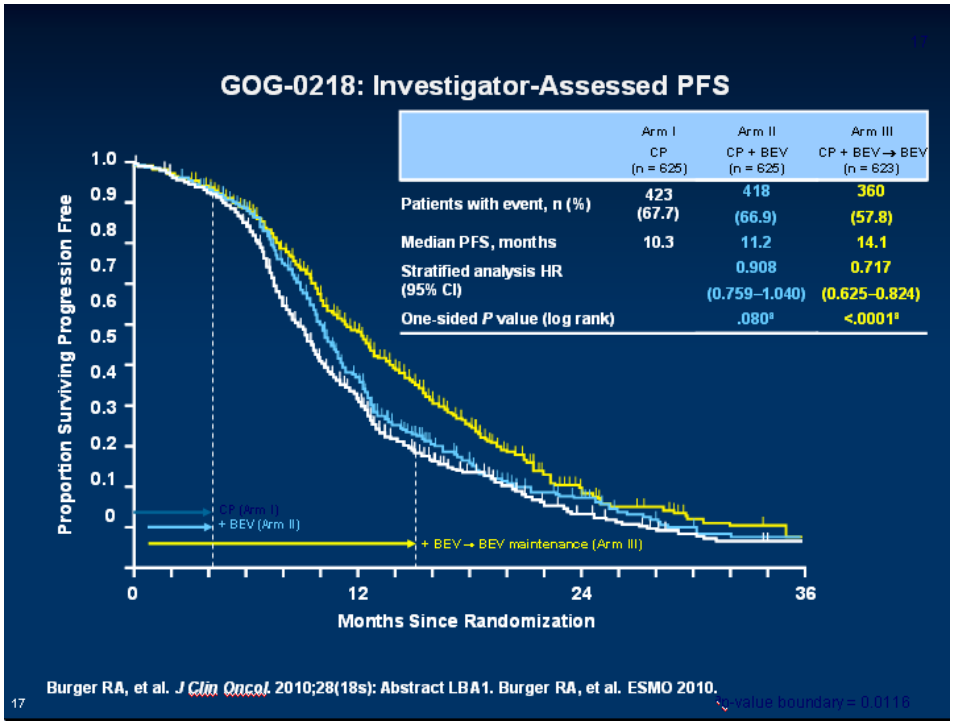


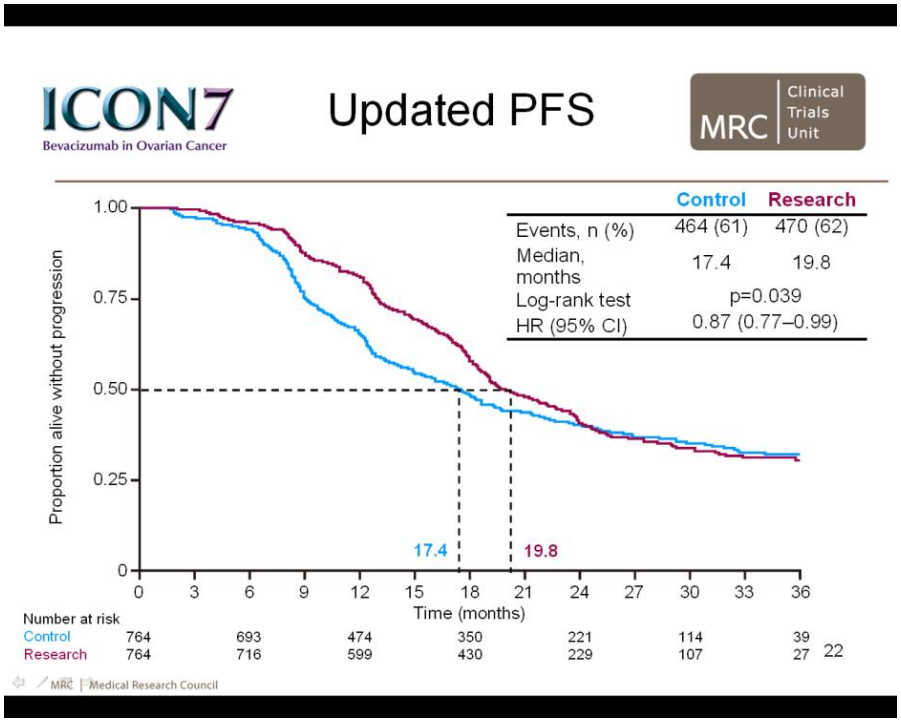
Nintedanib



Pazopanib

Two positive trials with bevacizumab in front line





Overall Survival

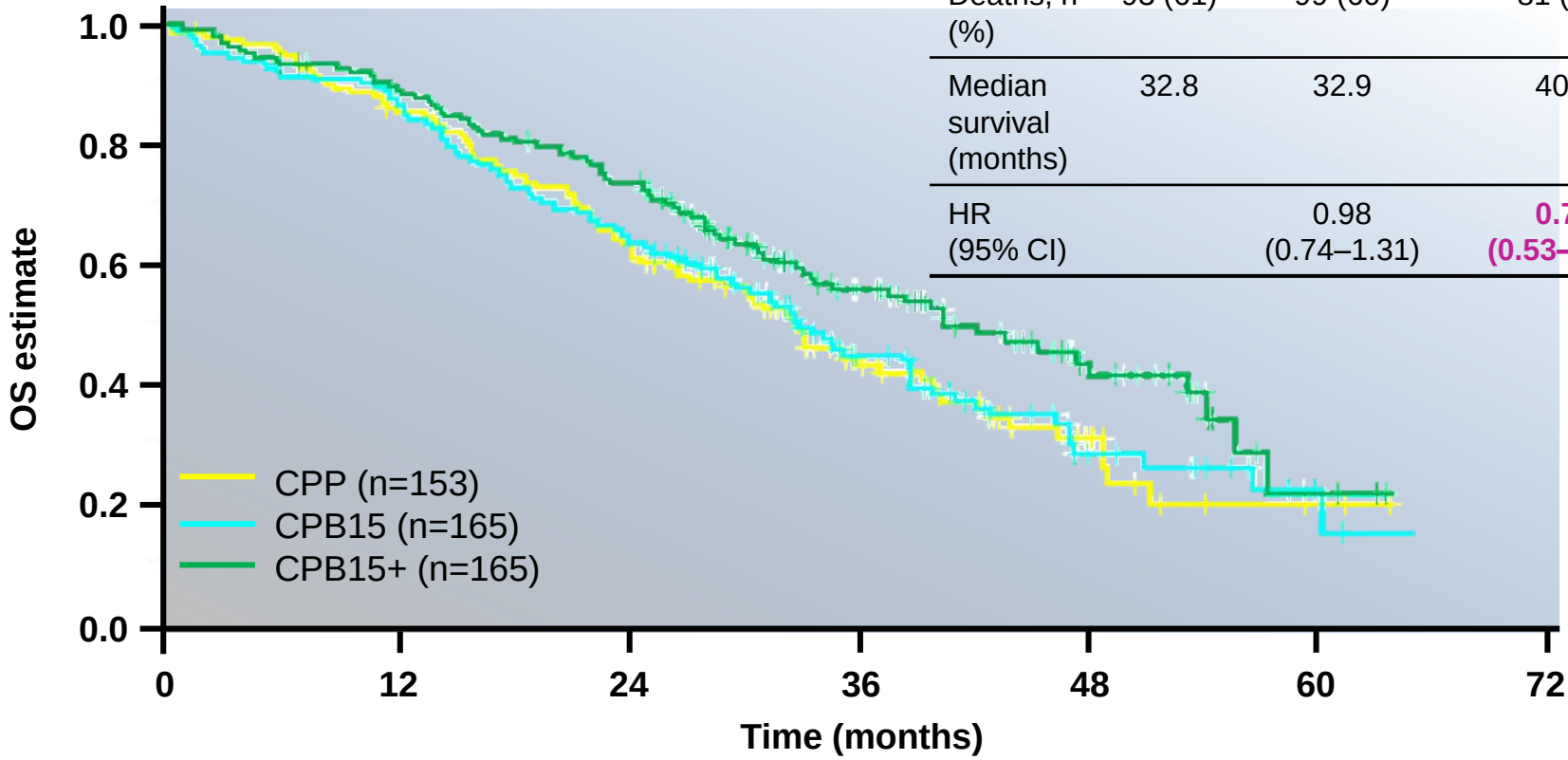
	Arm I CP (n = 625)	Arm II CP + Bev (n = 625)	Arm III CP + Bev → Bev (n = 623)
Deaths	156 (25.0%)	150 (24.0%)	138 (22.2%)
1-Year Survival	90.6%	90.4%	91.3%

Events were observed in ~ 24% of patients at the time of database lock.

Burger RA et al. *Proc ASCO* 2010;Abstract LBA1.

OS benefit is suggested with chemotherapy + Avastin and continued single-agent Avastin in stage IV disease

	CPP	CPB	CPB15
Deaths, n (%)	93 (61)	99 (60)	81 (49)
Median survival (months)	32.8	32.9	40.6
HR (95% CI)		0.98 (0.74–1.31)	**0.72 (0.53–0.97)**



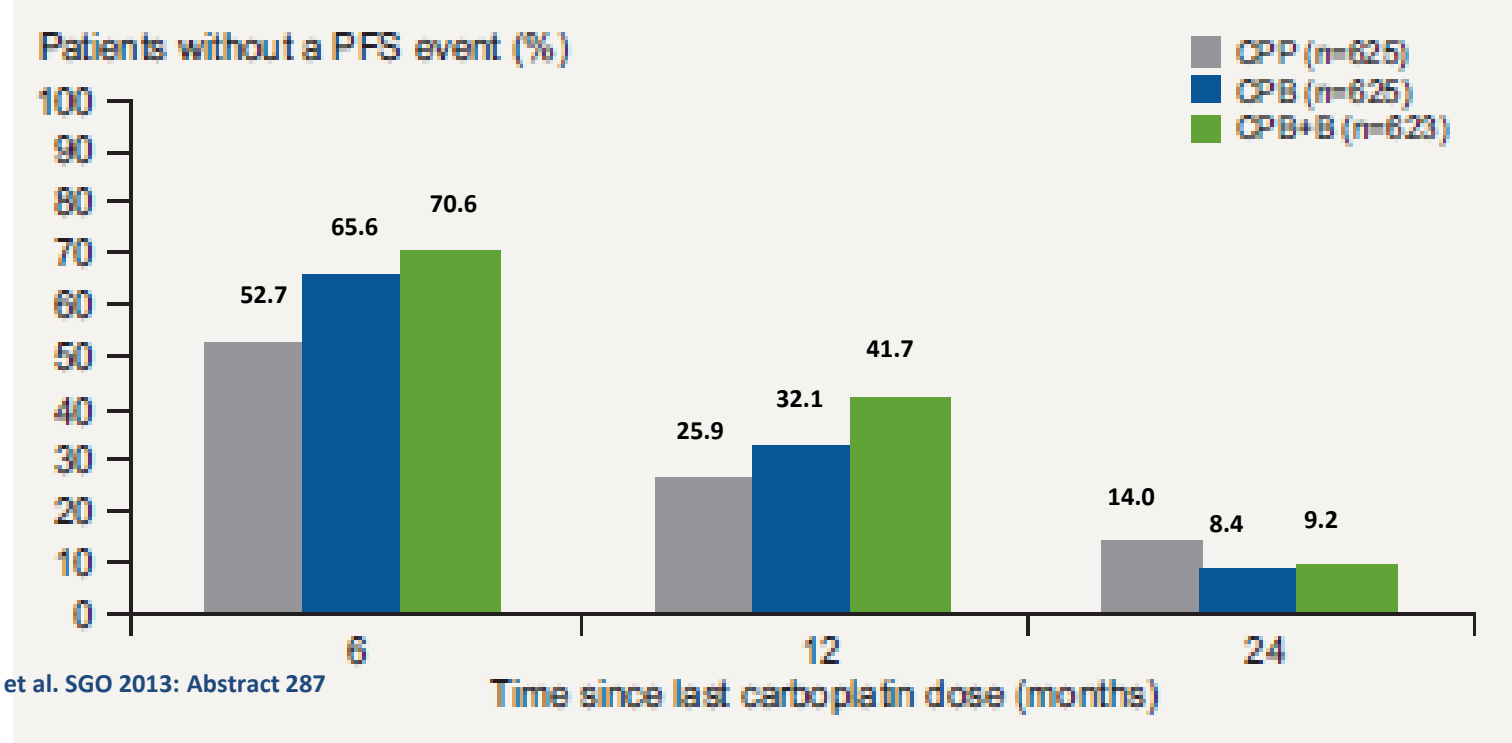
CPP	153	144	129	113	95	72	42	28	15	5	3	0	0
CPB	165	149	142	117	104	73	44	30	15	10	3	1	0
CPB15	165	154	144	130	117	83	57	37	21	10	3	0	0

Randall, et al. SGO 2013: Abstract 80

Chemotherapy + Avastin with continued single-agent Avastin improves progression-free interval

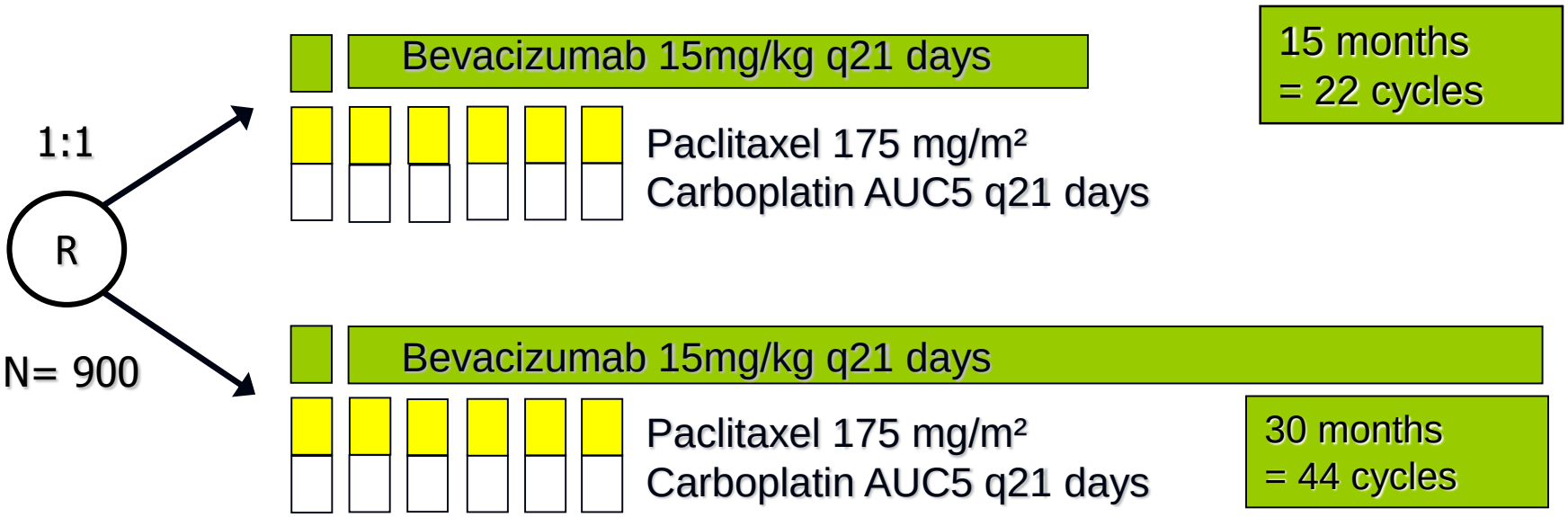
– The proportion of patients progression-free 6 and 12 months after last dose of carboplatin is increased with Avastin-based therapy (70.6 vs 52.7) at 6 months and (41.7 vs 25.9) at 12 months

GOG analysis



Randall, et al. SGO 2013: Abstract 287

ENGOT Ov-15 Trial
AGO-OVAR 17
Study Design



Strata

- macroscopic residual tumor (yes vs no)
- FIGO Stage (IIB-IIIC vs IV)
- Study Group

Primary endpoint:

- PFS (non inferiority -> superiority)

Main question: treatment duration Bev

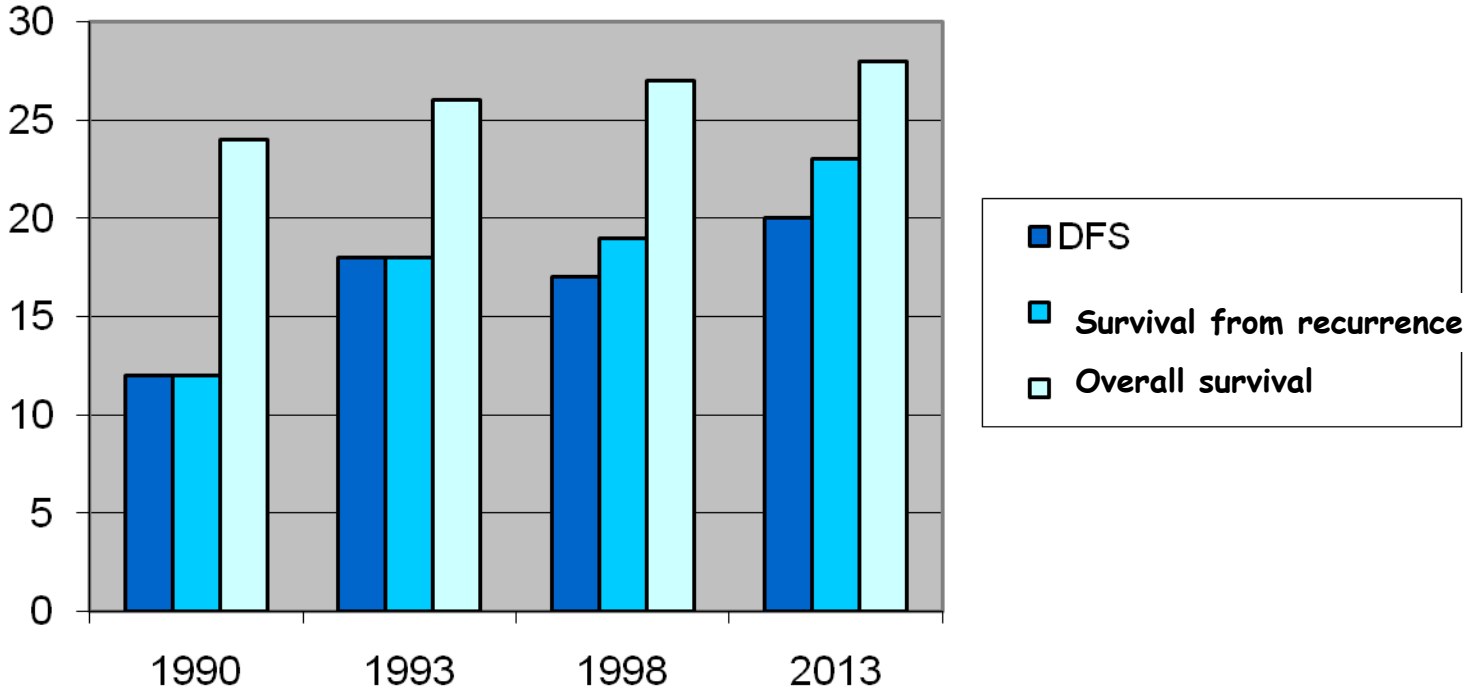
TREATMENT OF RECURRENT DISEASE:

-First cause of death among gynecological malignancies

-75% of patients responde to first line platinum-based chemotherapy

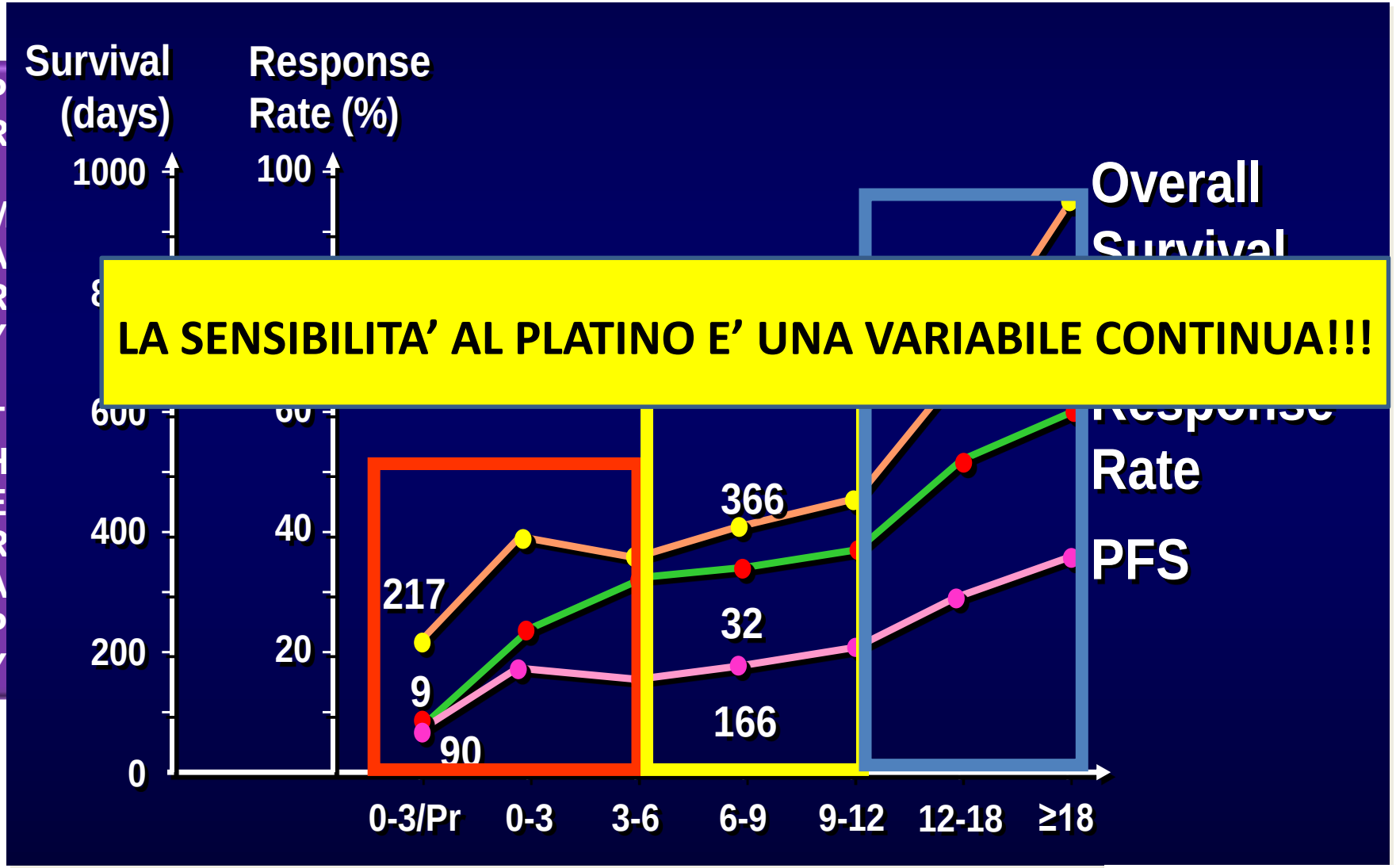
- 70% of them experience recurrences within 24 months

The overall survival increase in ovarian cancer is mainly due to the treatment of recurrent disease



Cisplatin	Cisplatin Paclitaxel	Carboplatin Paclitaxel	Platinum Paclitaxel Bevacizumab

Recurrent Ovarian Cancer: Population Characteristics



Pisano et al. Ther Clin Risk Manag. 2009;5:421-426; Gadducci et al. Anticancer Res. 2001;21:3525-35

What is the impact of cytoreductive surgery on the time to recurrence?

Population	Study	Treatment	PFS
Optimal Stage 3	GOG 114	IV Carb & Pac, IP Cis	28 mos
	GOG 172	**IV Pac, IP Cis & Pac**	**24 mos**
	GOG 158	**IV Pac & Carb**	**21 mos**
	GOG 114	IV Pac & Cis	22 mos
	GOG 158	IV Pac & Cis	19 mos
	GOG 172	IV Pac & Cis	18 mos
Suboptimal 3 & 4	GOG 111	IV Pac & Cis	18 mos
	GOG 162	**IV Pac Cis**	**12 mos**
	GOG 152	**IV Pac Cis**	**11 mos**
All Stage 3 & 4	GOG 182	IV Pac/Carbo x 8	16 mos

GYNECOLOGIC CANCER INTERGROUP
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D2. What are the control arms for clinical trials in recurrent ovarian cancer?

1. In patients where platinum is not an option a control arm can include a non-platinum drug as a single agent or in combination.
2. The choice of control arms for the subgroup who can receive platinum must be supported by evidence and integrate available predictors and prior exposure which may limit selection for further lines. This currently includes 3 potential control arms:
    1. Platinum combination
    2. Platinum combination with a licensed anti-angiogenic agent
    3. Platinum combination followed by a licensed PARP inhibitor
3. There is a subgroup (e.g. medically compromised and/or elderly patients) where less toxic therapy or best supportive care may be the most appropriate control arm.
4. There is no proven effective therapy for patients who have asymptomatic CA125 relapse.

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

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

Hypersensitivity, incidence and development

- Incidence seems to be correlated with increased number of cycles of carboplatin administered occurring in less than 1% of the patients during primary treatment but in **8–44%** of patients during 2nd or 3rd line.[1-2]
- The risk of hypersensitivity reactions rises with a longer platinum-free interval.[3]
- Particular caution is advised in patients receiving:[4]
  - eighth course of carboplatin
  - **second platinum dose after reintroduction in second-line chemotherapy.**

1. Sliesoraitis S, Chikhale PJ. Int J Gynecol Cancer. 2005;15:13-8; 2. Gaducci et al. Int J Gynecol Cancer. 2008;18(4):615-20; 3. O´Cearbhaill R, et al. Gynecol Oncol. 2011;116(3):326-31; 4. Markman M, et al. J Clin Oncol.1999;17(4):1141-5

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.

Clinical Activity of the Poly(ADP-Ribose) Polymerase (PARP) Inhibitor Rucaparib in Patients with High-Grade Ovarian Carcinoma and a *BRCA* Mutation: Analysis of Pooled Data from Study 10 (Parts 1, 2a, and 3) and ARIEL2 (Parts 1 and 2)

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[1]University College London, Cancer Institute, London, UK; [2]Sheba Medical Center, Ramat Gan, Israel; [3]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]GINECO, Centre Léon Bérard and University Claude Bernard, Lyon, France; [5]University of Pennsylvania, Philadelphia, PA, USA; [6]British Columbia Cancer Agency, Vancouver, BC, Canada; [7]Gynecological Oncology, Massachusetts General Hospital, Department of Medicine, Harvard Medical School, Boston, MA, USA; [8]Division of Medical Oncology, London Regional Cancer Program, London, ON, Canada; [9]Clinical Area of Gynecologic Oncology, Valencian Institute of Oncology, Valencia, Spain; [10]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [11]University of California Los Angeles, Los Angeles, CA, USA; [12]Clovis Oncology, Inc., Boulder, CO, USA; [13]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

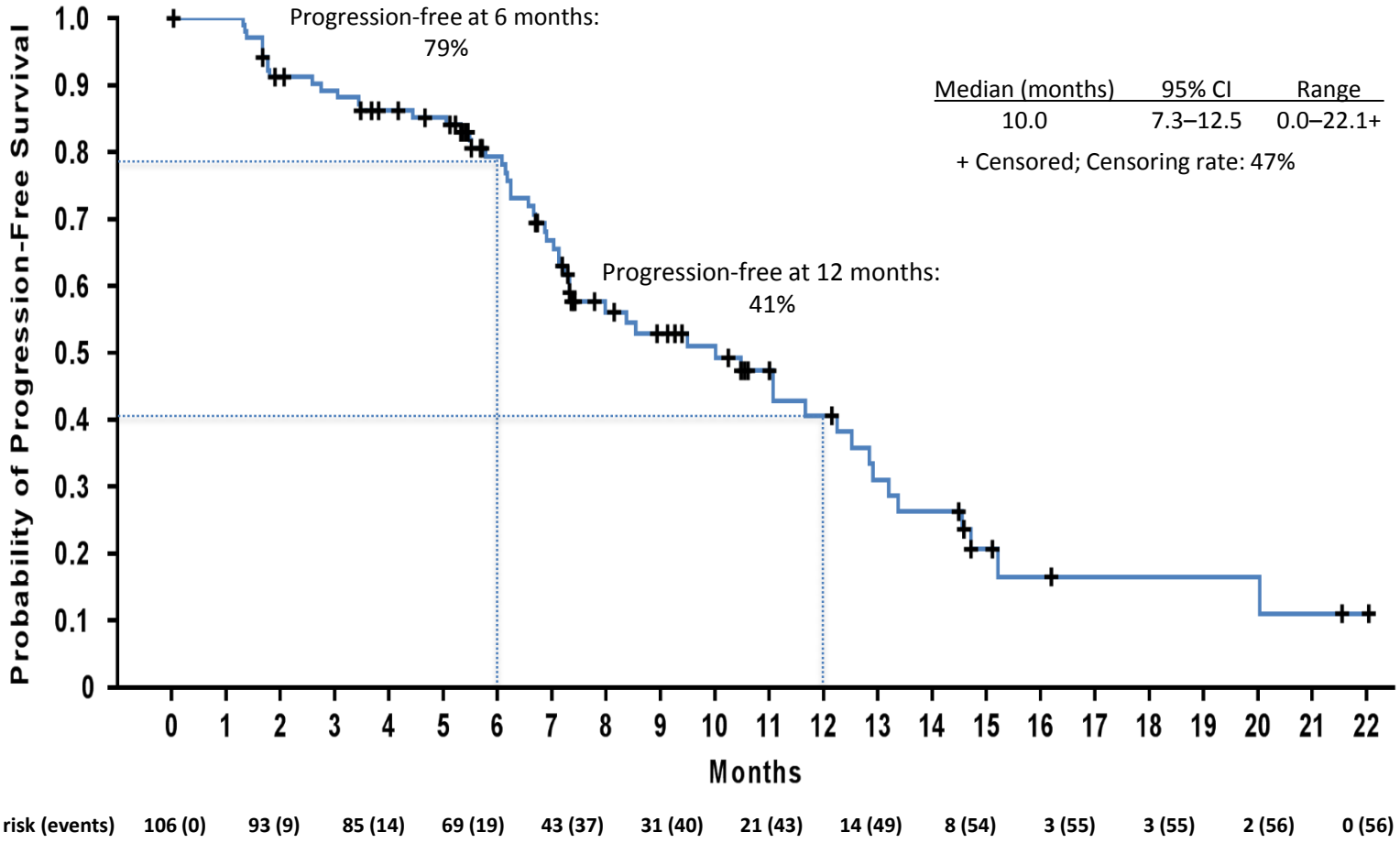
Investigator-Assessed ORR in the Efficacy Population

Parameter	Study 10 n=42	ARIEL2 n=64	Efficacy population n=106
	n (%) [95% CI]		
Investigator-assessed RECIST ORR (confirmed CR+PR)	**25 (59.5) [43.3–74.4]**	**32 (50.0) [37.2–62.8]**	**57 (53.8) [43.8–63.5]**
CR	4 (9.5)	5 (7.8)	9 (8.5)
PR	21 (50.0)	27 (42.2)	48 (45.3)
SD	12 (28.6)	24 (37.5)	36 (34.0)
PD	2 (4.8)	7 (10.9)	9 (8.5)
NE	3 (7.1)	1 (1.6)	4 (3.8)
Investigator-assessed RECIST/GCIG CA-125 ORR			**75 (70.8) [61.1–79.2]**

Data cutoff dates: 30 Nov 2015 (Study 10); 29 Feb 2016 (ARIEL2).

CI, confidence interval; CR, complete response; GCIG, Gynecologic Cancer InterGroup; NE, not evaluable; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors.

Progression-Free Survival in the Efficacy Population

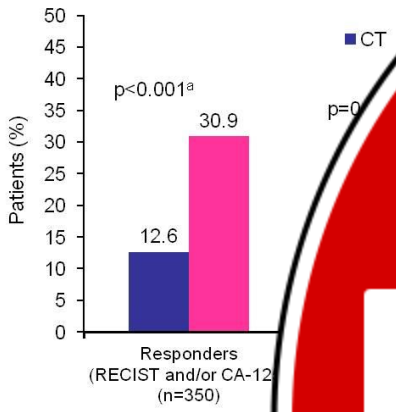


- 32 patients had not progressed as of the cutoff dates

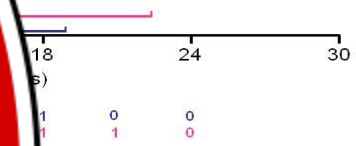
Data cutoff dates: 30 Nov 2015 (Study 10); 29 Feb 2016 (ARIEL2).

STUDIO AURELIA

Summary of best overall response rat… survival



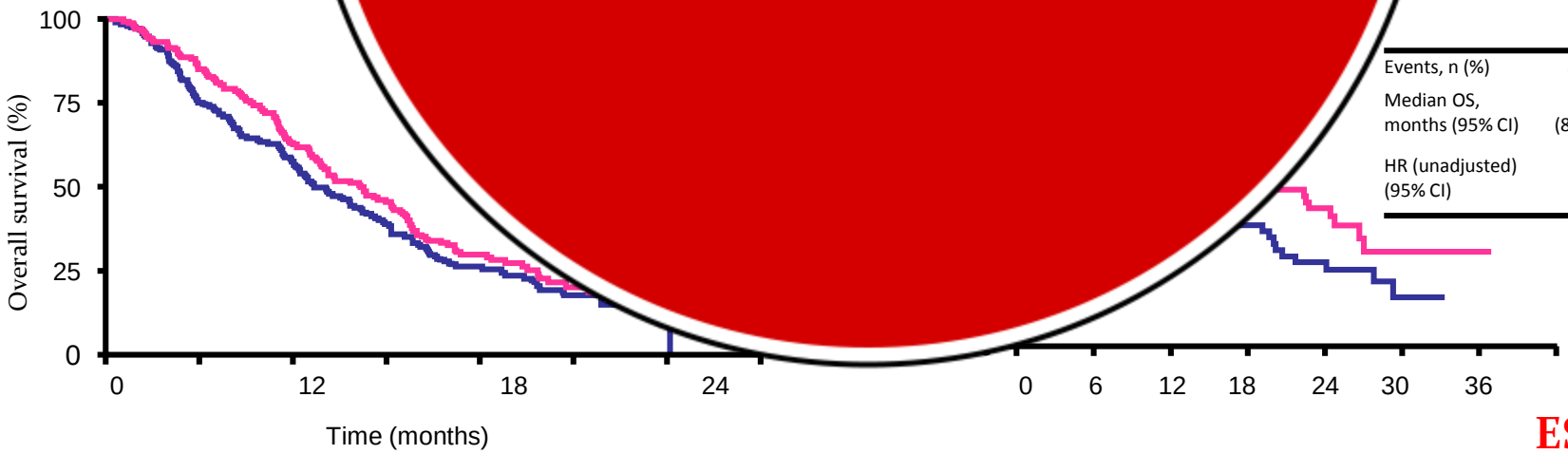
	CT (n=182)	BEV + CT (n=179)
Events, n (%)	166 (91%)	135 (75%)
…edian PFS, months	3.4	6.7
…% CI)	(2.2–3.7)	(5.7–7.9)
…unadjusted)	0.48	
…CI)	(0.38–0.60)	
…nk p-value	<0.001	
…, unadjusted)		



ASCO Annual '12 Meeting

ASCO 2012

Sopravvivenza … ale: w paclitaxel



	CT (N=55)	BEV + CT (N=60)
Events, n (%)	41 (75)	36 (60)
Median OS, months (95% CI)	13.2 (8.2–19.7)	22.4 (16.7–26.7)
HR (unadjusted) (95% CI)	0.65 (0.42–1.02)	

ESMO 2013

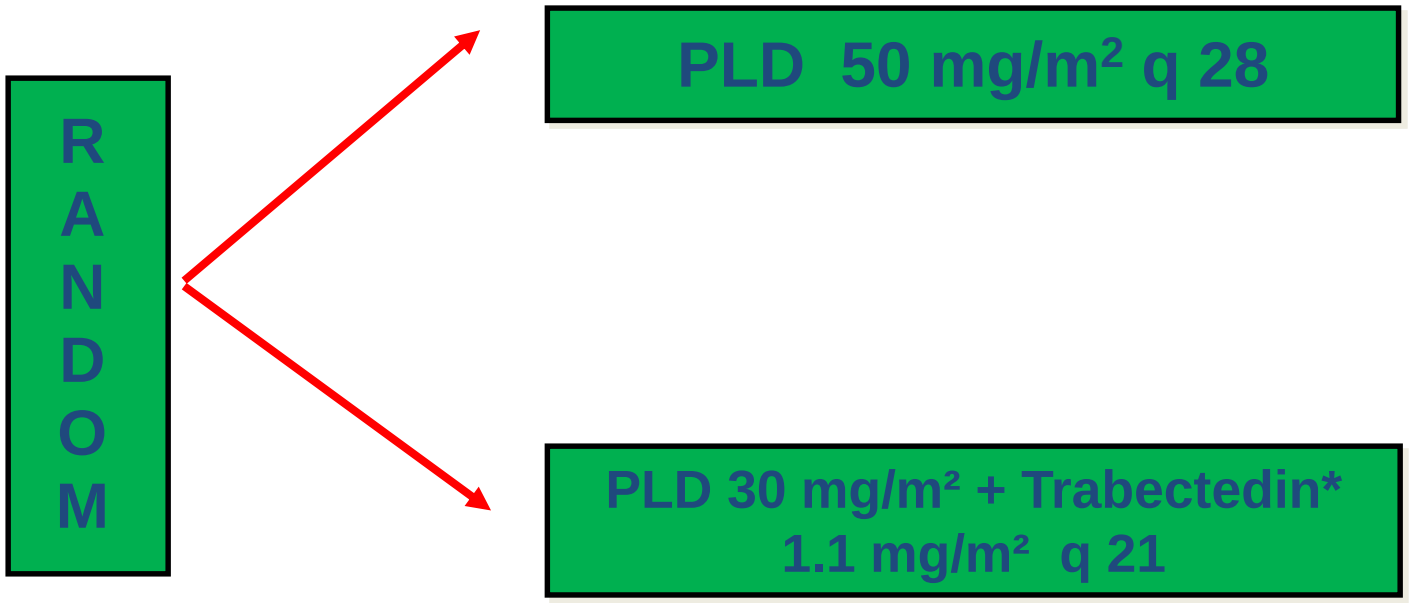
Trabectedin Plus Pegylated Liposomal Doxorubicin in Recurrent Ovarian Cancer

Bradley J. Monk, Thomas J. Herzog, Stanley B. Kaye, Carolyn N. Krasner, Jan B. Vermorken, Franco M. Muggia, Eric Pujade-Lauraine, Alla S. Lisyanskaya, Anatoly N. Makhson, Janusz Rolski, Vera A. Gorbounova, Prafull Ghatage, Mariusz Bidzinski, Keng Shen, Hextan Yuen-Sheung Ngan, Ignace B. Vergote, Joo-Hyun Nam, Youn Choi Park, Claudia A. Lebedinsky, and Andrés M. Poveda

VOLUME 28 · NUMBER 19 · JULY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

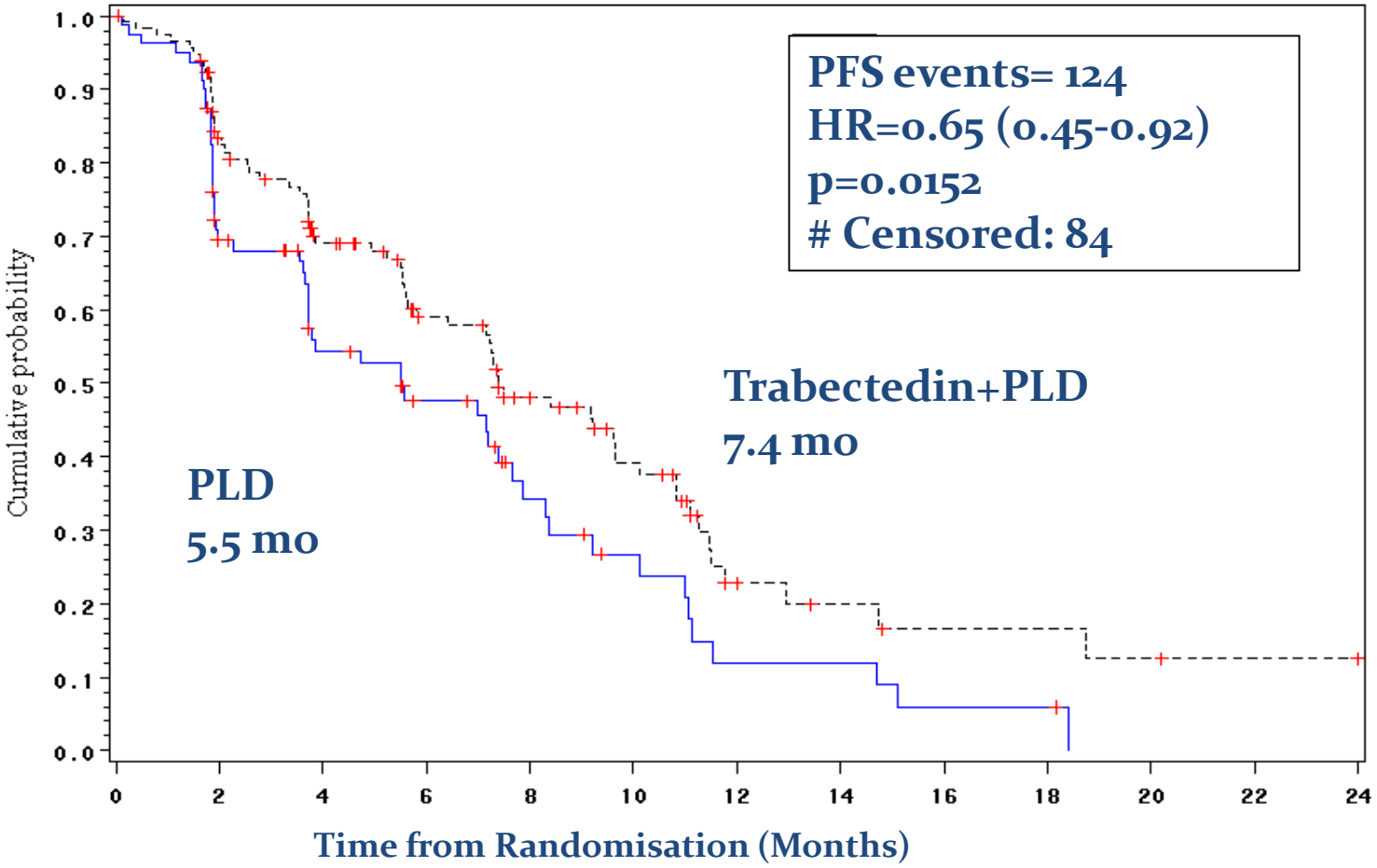
ORIGINAL REPORT



672 patients

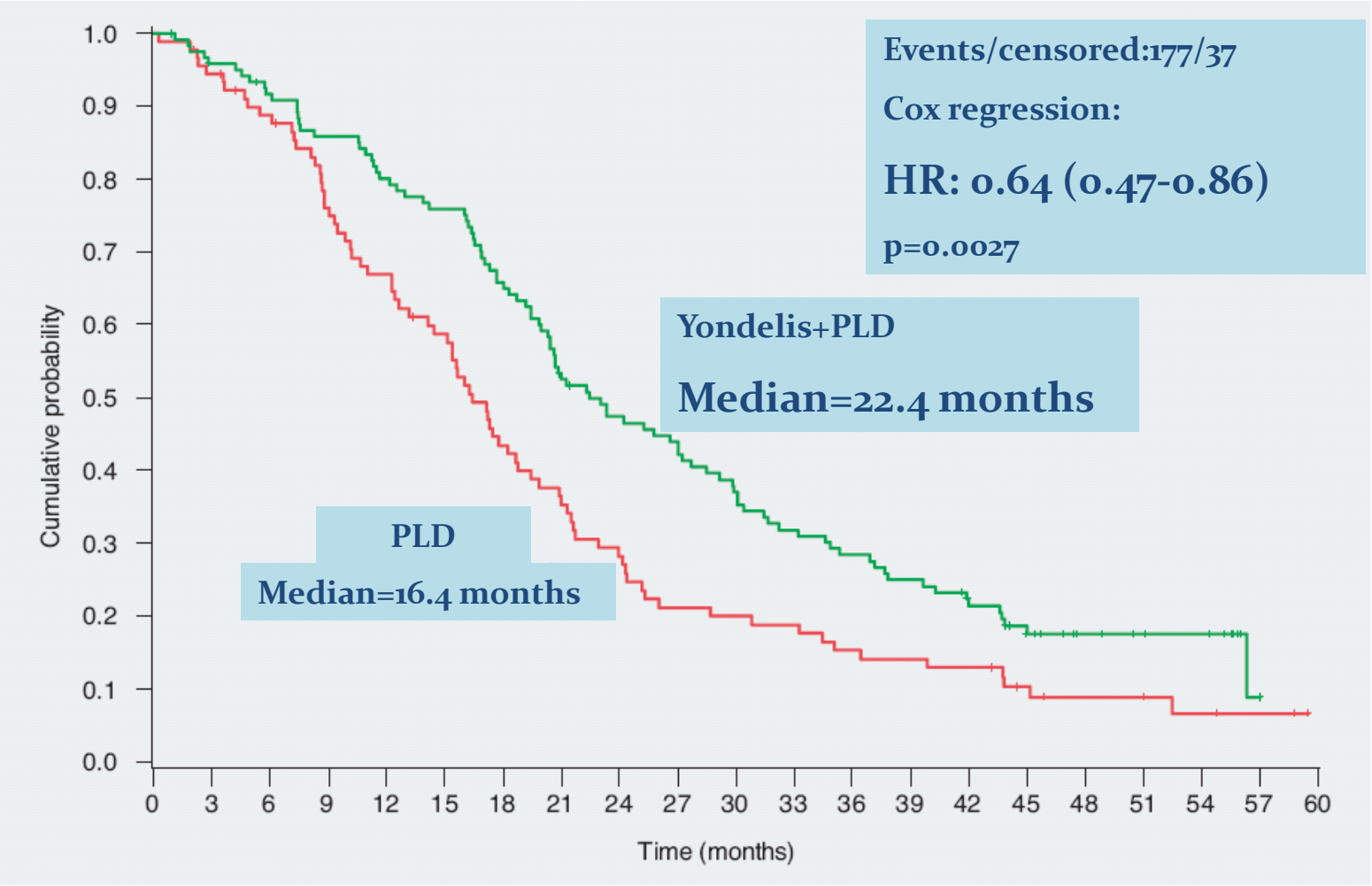
	PLD		PLD+ET743	
Platinum-free interval, months*				
< 6	117	35	115	35
6 to < 12	91	28	123	37
≥ 12	122	37	95	29

Trabectedin-PLD PFS – Intermediate Sensitivity (PFI 6-12 mo)



PFI = Platinum Free Interval

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

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

D2. What are the control arms for clinical trials in recurrent ovarian cancer?

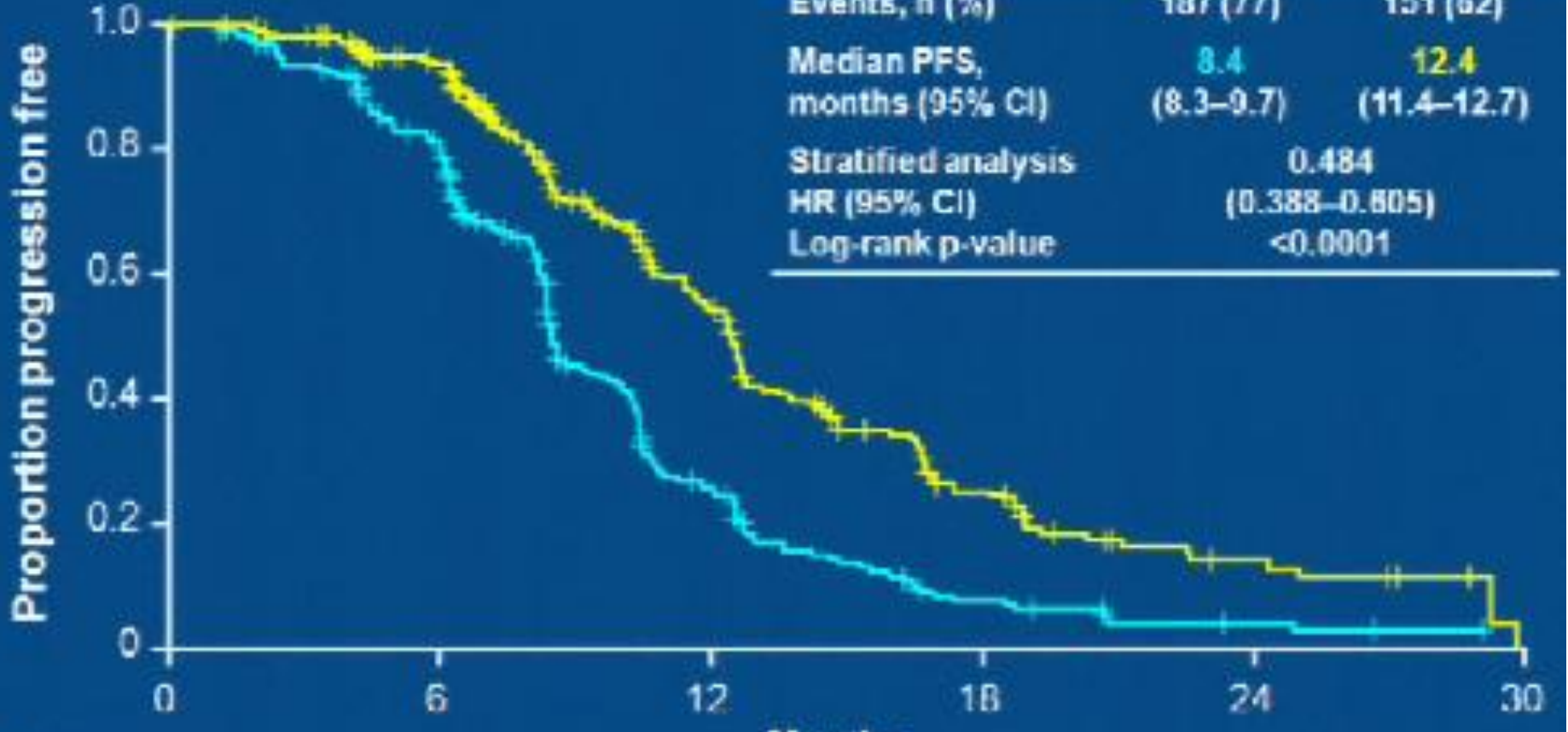
1. In patients where platinum is not an option a control arm can include a non-platinum drug as a single agent or in combination.
2. The choice of control arms for the subgroup who can receive platinum must be supported by evidence and integrate available predictors and prior exposure which may limit selection for further lines. This currently includes 3 potential control arms:
    1. Platinum combination
    2. Platinum combination with a licensed anti-angiogenic agent
    3. Platinum combination followed by a licensed PARP inhibitor
3. There is a subgroup (e.g. medically compromised and/or elderly patients) where less toxic therapy or best supportive care may be the most appropriate control arm.
4. There is no proven effective therapy for patients who have asymptomatic CA125 relapse.

STUDI RANDOMIZZATI DI FASE III SULLE COMBINAZIONI A BASE DI PLATINO NELLA RECIDIVA PLATINO SENSIBILE DI CARCINOMA DELL'OVAIO

Autore	Trattamento	PFS HR	OS HR	Tossicita'
Parmar 2003	CBDA vs CBDA+TAX	0.76	0.82	Neurotossicita Alopecia Reazioni allergiche
Pfisterer 2006	CBDA vs CBDA+GEM	0.72	0.96	Mielotossicita Reazioni allergiche
Pujade 2010	CBDA+TAX vs CBDA+PLD	0.82	0.99	Piastrinopenia PPE

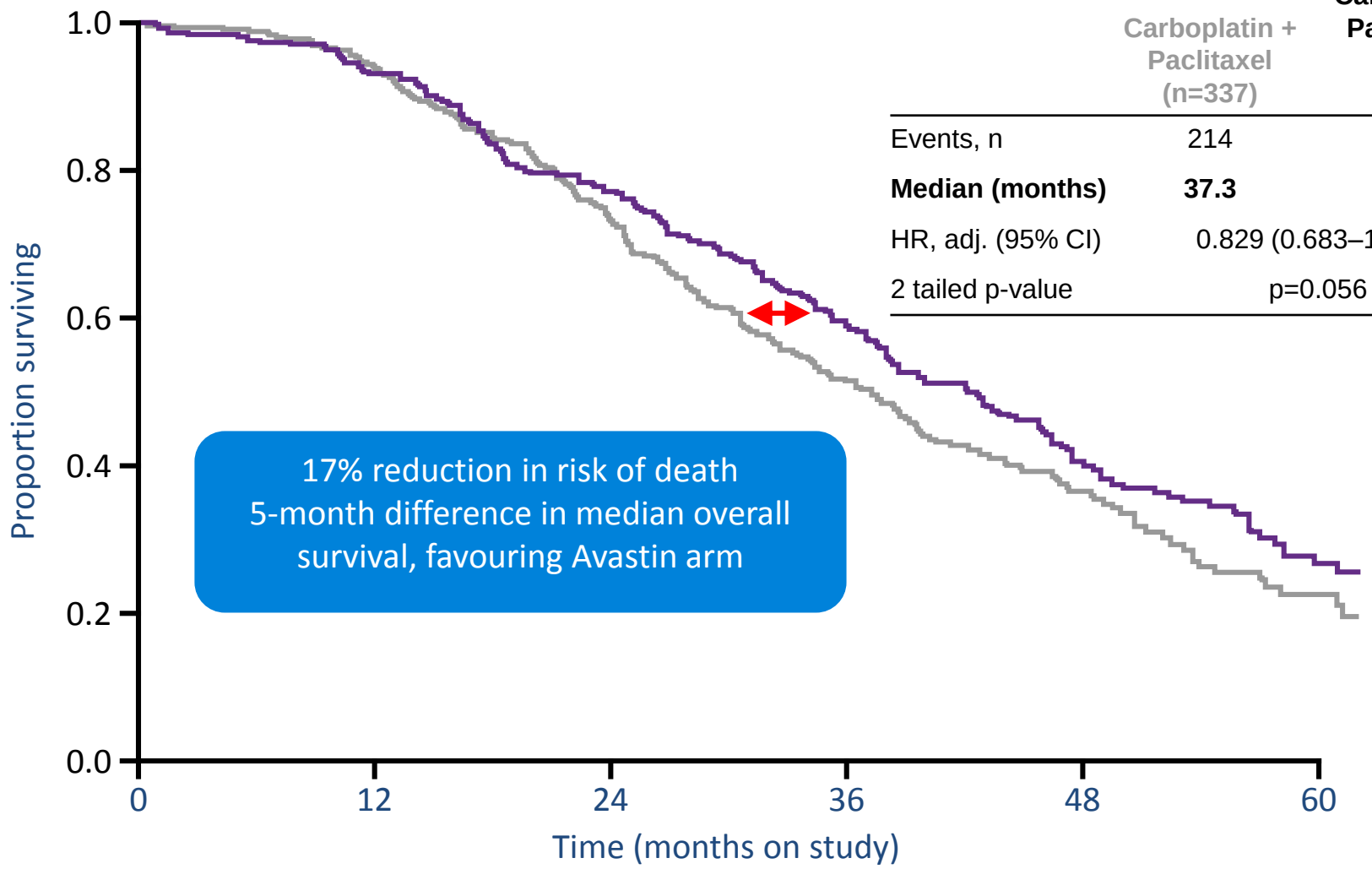
OCEANS: Primary analysis of PFS

	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	



No. at risk						
CG + PL	242	177	45	11	3	0
CG + BV	242	203	92	33	11	0

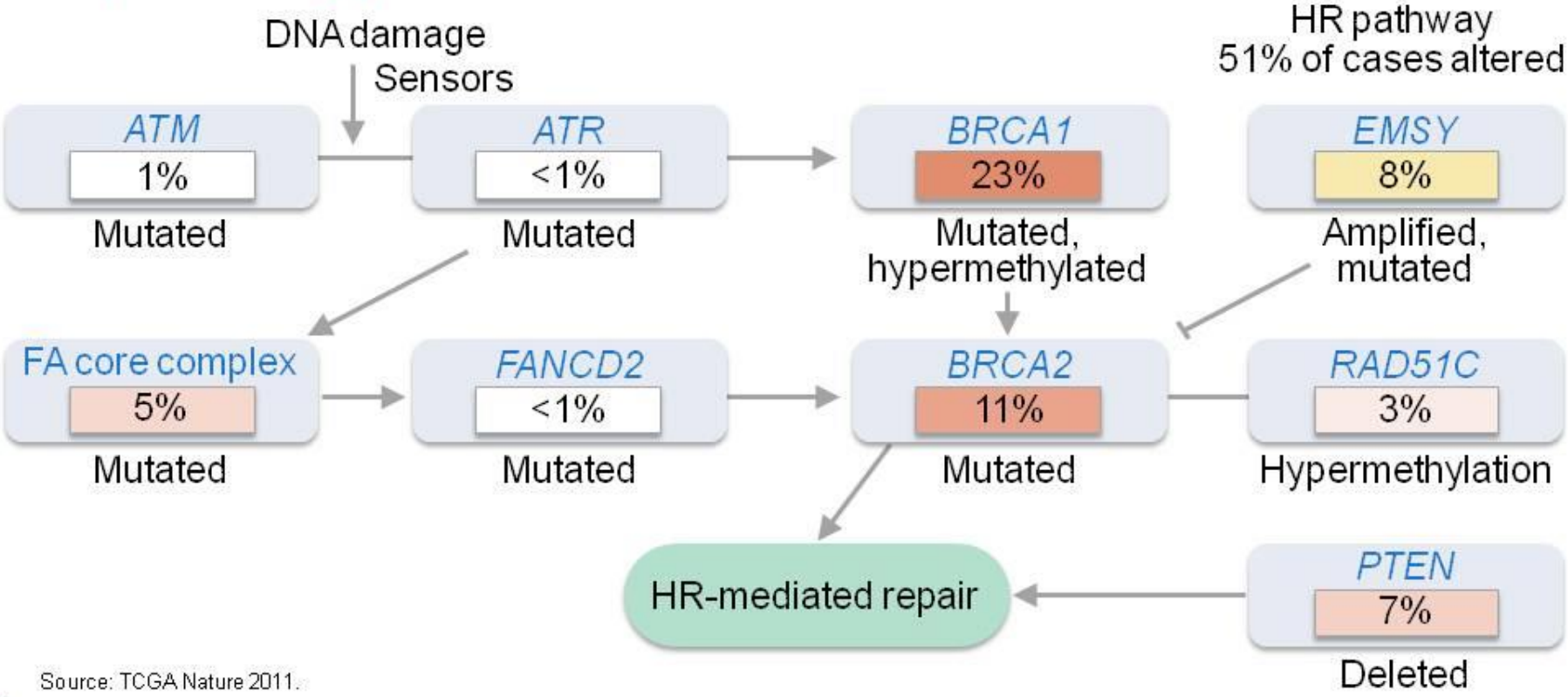
GOG-0213: primary analysis of OS



	Carboplatin + Paclitaxel (n=337)	Carboplatin + Paclitaxel + Avastin (n=337)
Events, n	214	201
Median (months)	**37.3**	**42.2**
HR, adj. (95% CI)	0.829 (0.683–1.005)	
2 tailed p-value	p=0.056	

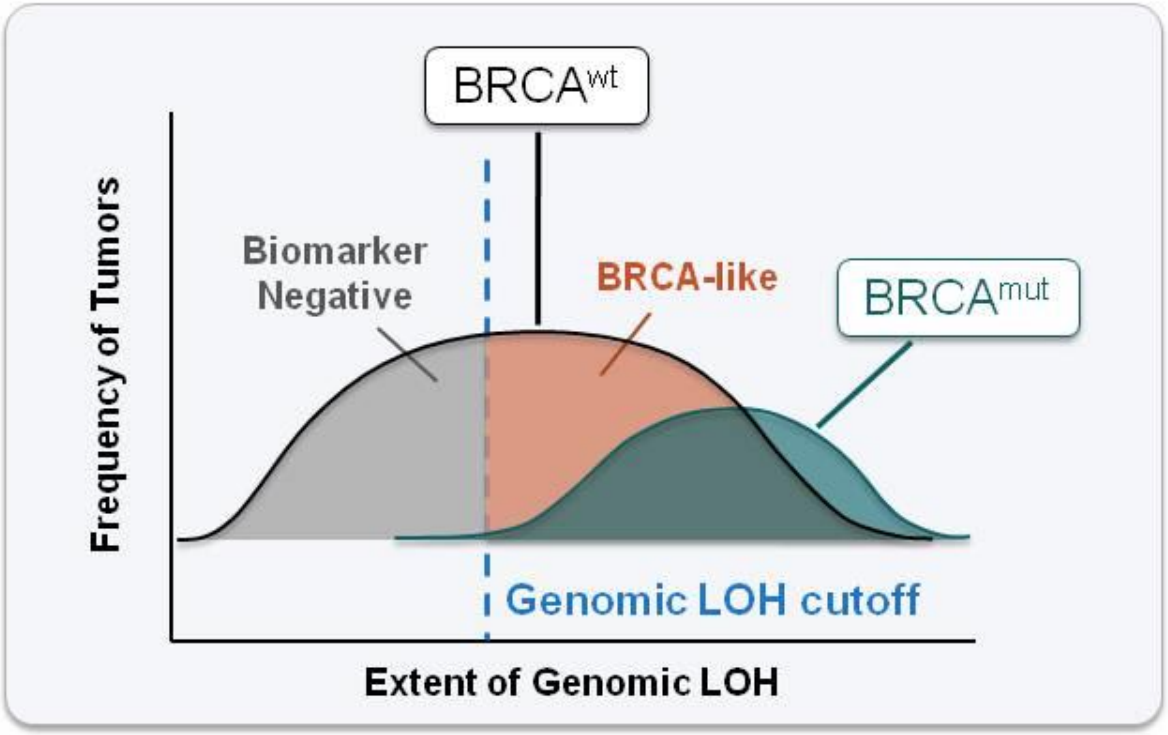
- Coleman, et al. SGO 2015 (Abstract 3)

≈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



PARP Inhibitors: A Recap

PARP inhibitors approved for use in patients with ovarian cancer

PARP inhibitor	Authority	Indication
Olaparib	EMA Dec 2014	**Monotherapy for the maintenance treatment** of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy[1] Olaparib is not approved in Europe as a monotherapy in the treatment setting
	US FDA Dec 2014	**Monotherapy** in patients with deleterious or suspected deleterious germline *BRCA*-mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy[2]
	Aug 2017	**Maintenance treatment** of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy[2]
Niraparib	EMA Sept 2017	**Maintenance treatment** of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy[3]
	US FDA Mar 2017	**Maintenance treatment** of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy[3]
Rucaparib	EMA	Not approved for use in Europe
	US FDA Dec 2016	**Monotherapy** for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic; as detected by an FDA-approved companion diagnostic for rucaparib) associated advanced ovarian cancer who have been treated with two or more chemotherapies[4]

PARP inhibitors in clinical development

Platinum combination followed by iPARP

Olaparib study design and patient selection

Study-19 aim and design

265 patients

- **Platinum-sensitive high-grade serous ovarian cancer**
- ≥2 previous platinum regimens
- Last chemotherapy was platinum-based to which they had a maintained PR or CR prior to enrolment
- Stable CA-125

Olaparib 400 mg po bid

Randomized 1:1

Placebo po bid

Primary end point : PFS

Ledermann J, et al. N Engl J Med 2012;366:1382–92

SOLO-2 aim and design

295 patients

- *Germilne BRCA1/2* mutation
- Platinum-sensitive relapsed ovarian cancer
- At least 2 prior lines of platinum therapy
- CR or PR to most recent platinum therapy

Randomized 2:1

Olaparib 300 mg bid n=196

Placebo n=99

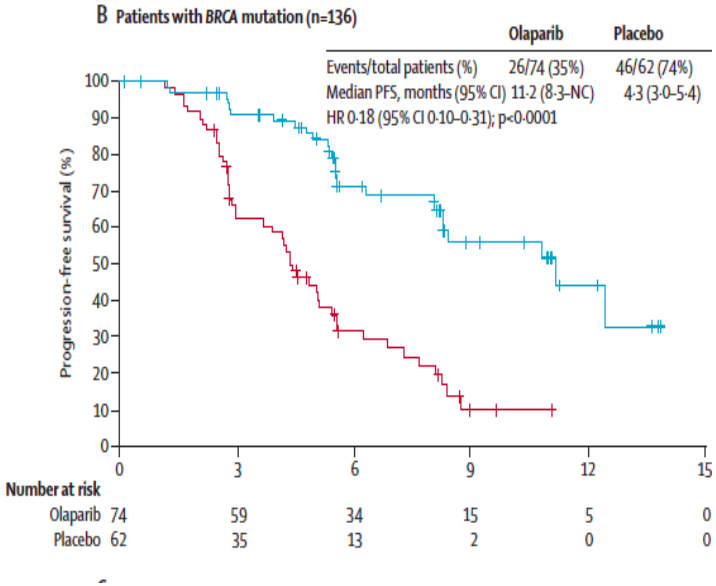
Primary endpoint: Investigator-assessed PFS

Pujade-Laurine et al. SGO 2017

Platinum combination followed by iPARP

Olaparib data on primary endpoint: BRCA mutated patients

Study-19 PFS

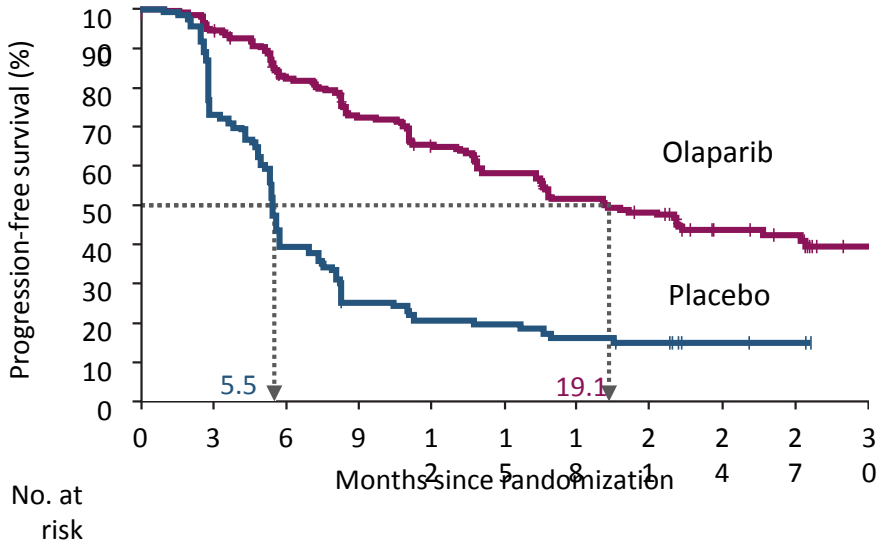


11.2 vs 4.3 months

HR 0.18 (95% CI: 0.10-0.31)

Ledermann et al. Lancet Oncol. 2014;15(8):852–861

SOLO-2 PFS



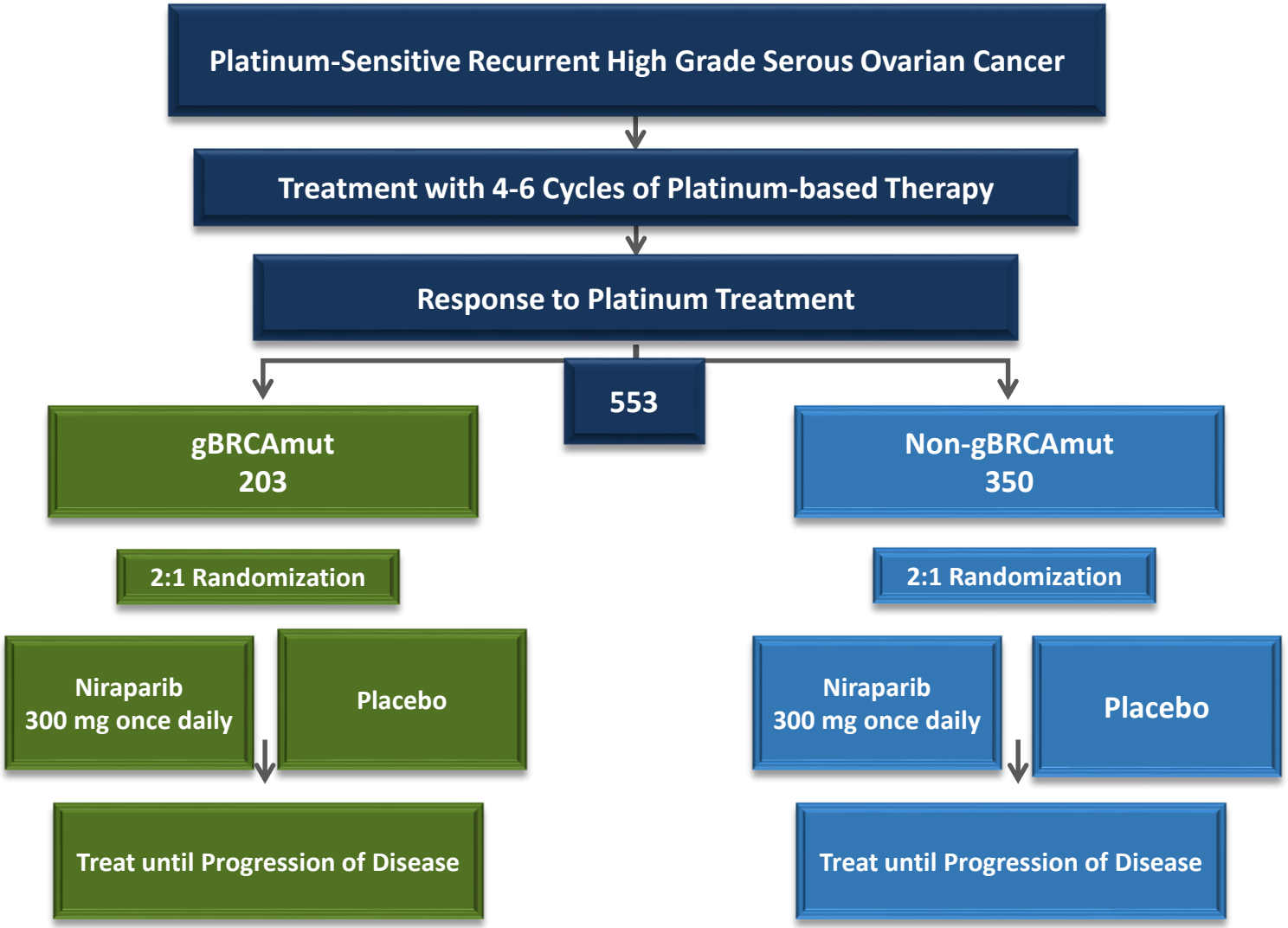
19.1 VS 5.5 months

HR 0.3 (95% CI: 0.22-0.41)

Pujade-Laurine et al. SGO 2017

Platinum combination followed by iPARP

Niraparib: ENGOT ov16-NOVA study design



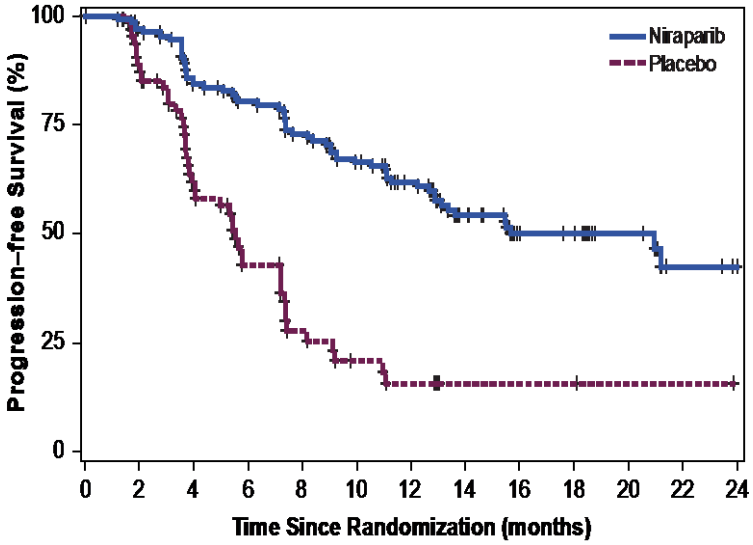
Mirza MR et al. N Engl J Med 2016

Platinum combination followed by iPARP

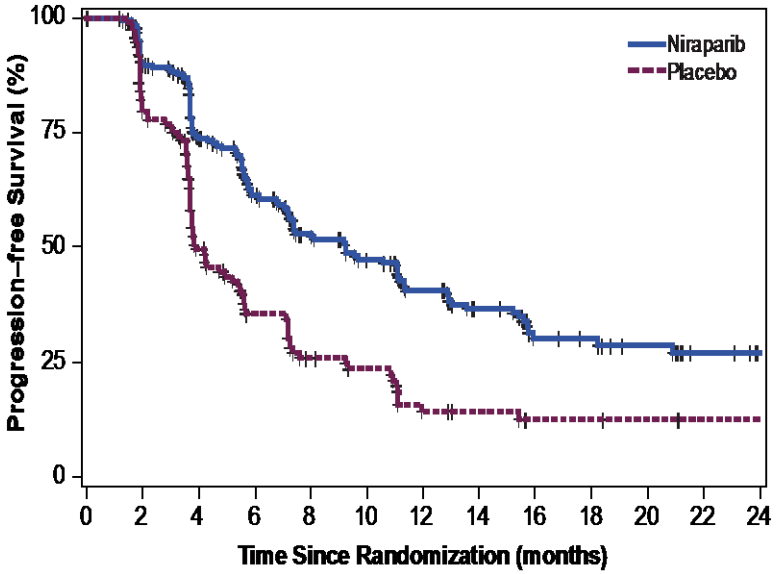
Niraparib: ENGOT ov16-NOVA primary end-point

MADRID 2017 ESMO congress

PFS: gBRCAmut



PFS: non-gBRCAmut



Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value
Niraparib (N=138)	**21.0** (12.9, NR)	**0.27** (0.173, 0.410)
Placeb		p<0.000

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value
Niraparib (N=234)	**9.3** (7.2, 11.2)	**0.45** (0.338, 0.607)
Placeb		

Mirza MR et al. N Engl J Med 2016

Platinum combination followed by iPARP

Niraparib: ENGOT ov16-NOVA exploratory analyses

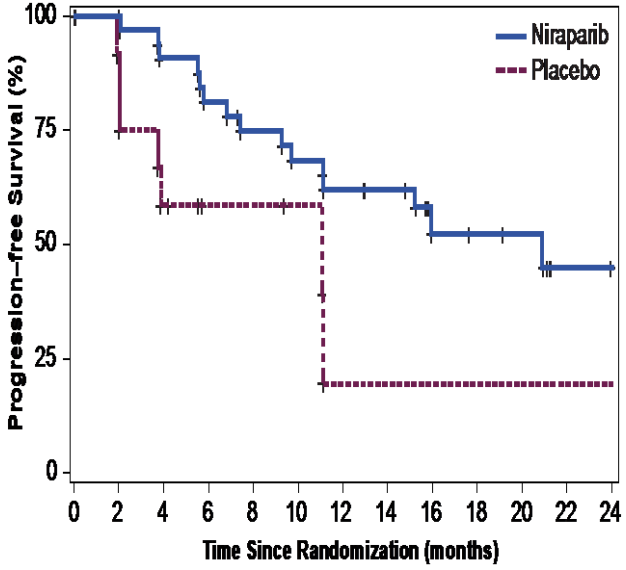
MADRID 2017 ESMO congress

HRD-positive

HRD-negative

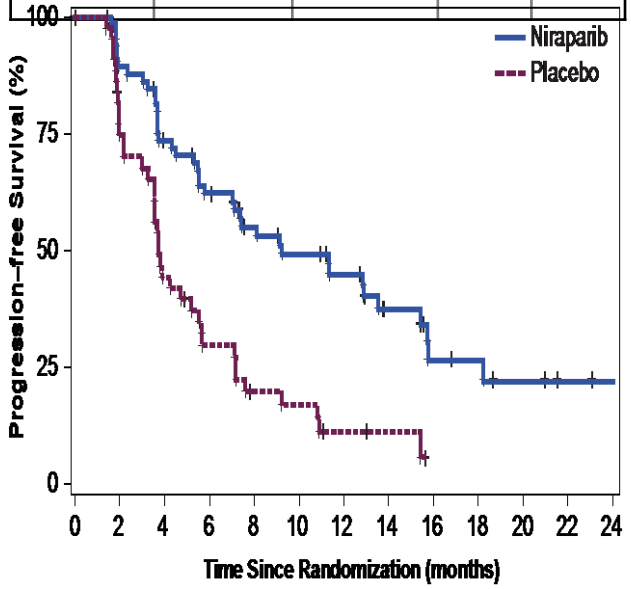
sBRCAmut

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=35)	**20.9** (9.7, NR)	**0.27** (0.081, 0.903) p=0.0248	62%	**52%**
Placebo (N=12)	**11.0** (2.0, NR)		19%	19%

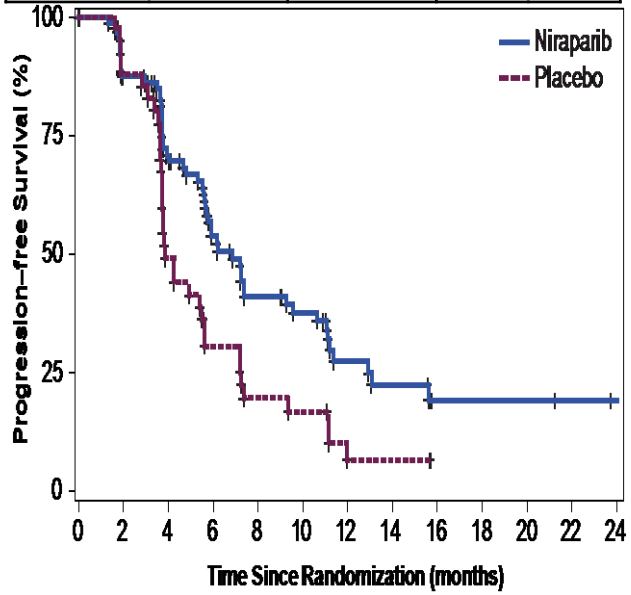


BRCAwt

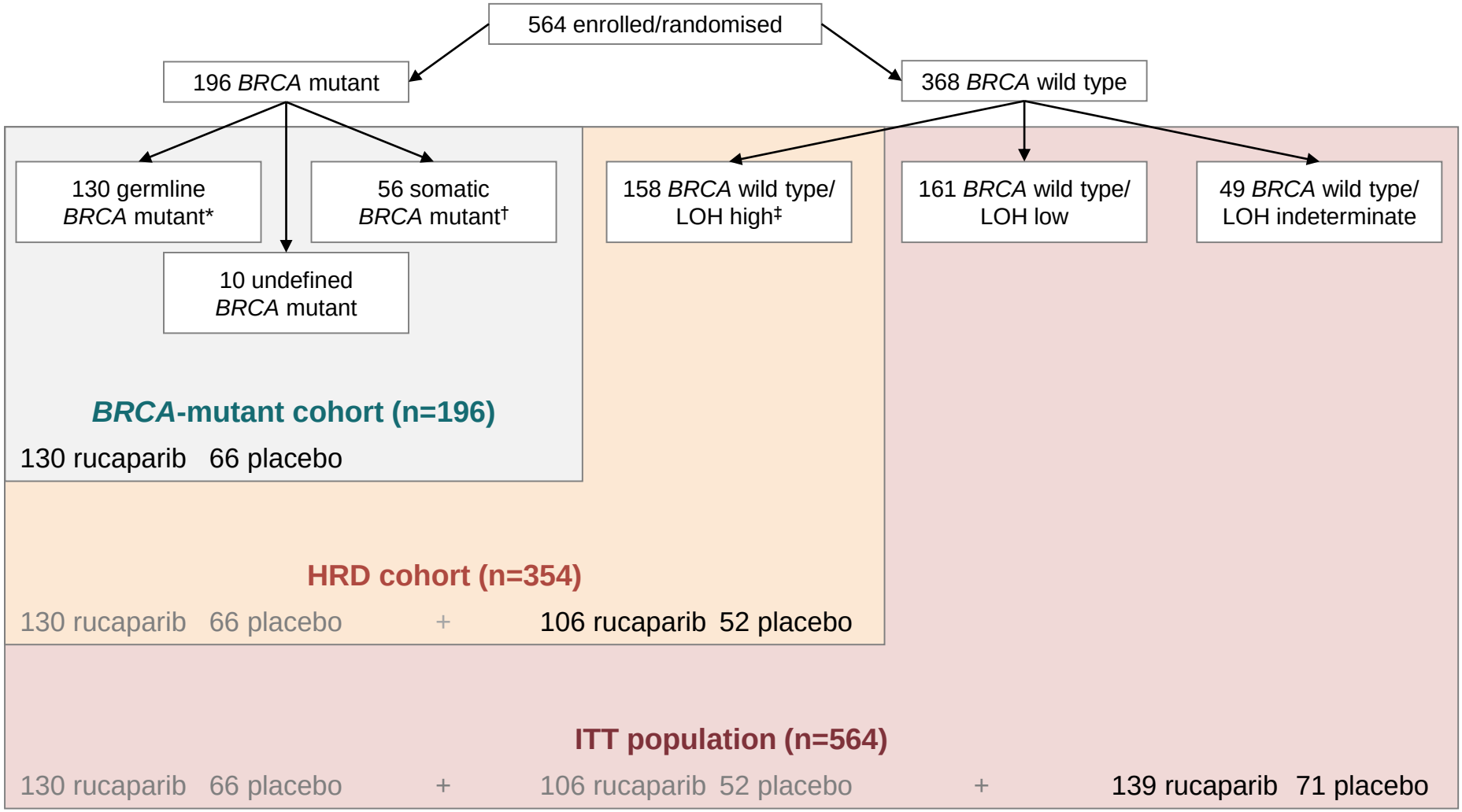
Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=71)	**9.3** (5.8, 15.4)	**0.38** (0.231, 0.628) p=0.0001	45%	**27%**
Placebo (N=44)	**3.7** (3.3, 5.6)		11%	6%



Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=92)	**6.9** (5.6, 9.6)	**0.58** (0.361, 0.922) p=0.0226	27%	**19 %**
Placebo (N=42)	**3.8** (3.7, 5.6)		7%	7%

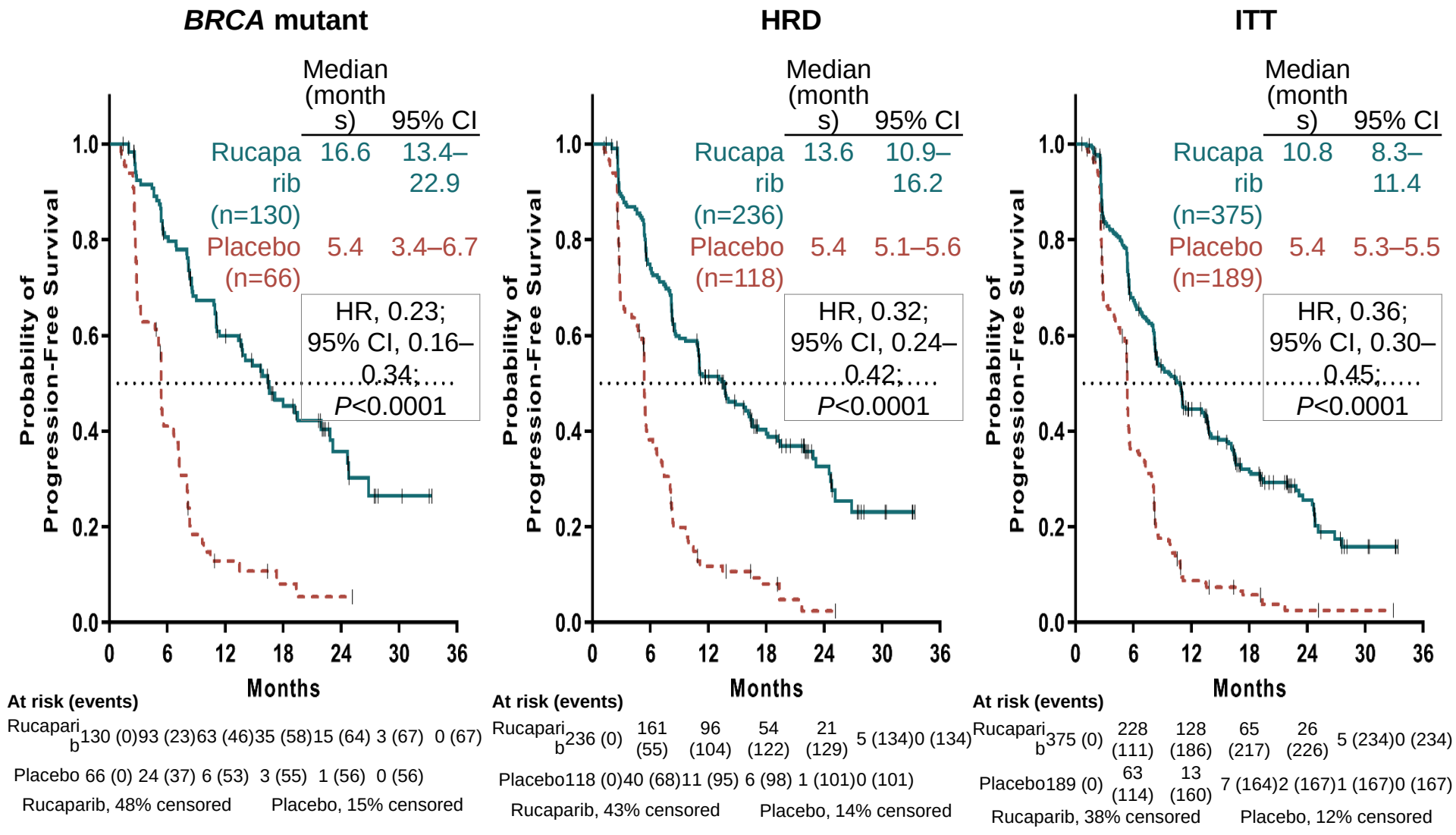


ARIEL3: Diagram of Analysis Cohorts



*No more than 150 patients with a known deleterious germline *BRCA* mutation were to be enrolled to ensure enough patients with carcinomas associated with a somatic *BRCA* mutation or wild-type *BRCA* were enrolled to determine statistical significance between rucaparib and placebo in the HRD cohort and the ITT population. †Deleterious *BRCA* mutation detected by next-generation sequencing of tumour tissue but not by central germline blood test. ‡For LOH high, a cutoff of ≥16% genomic LOH was prespecified for ARIEL3.

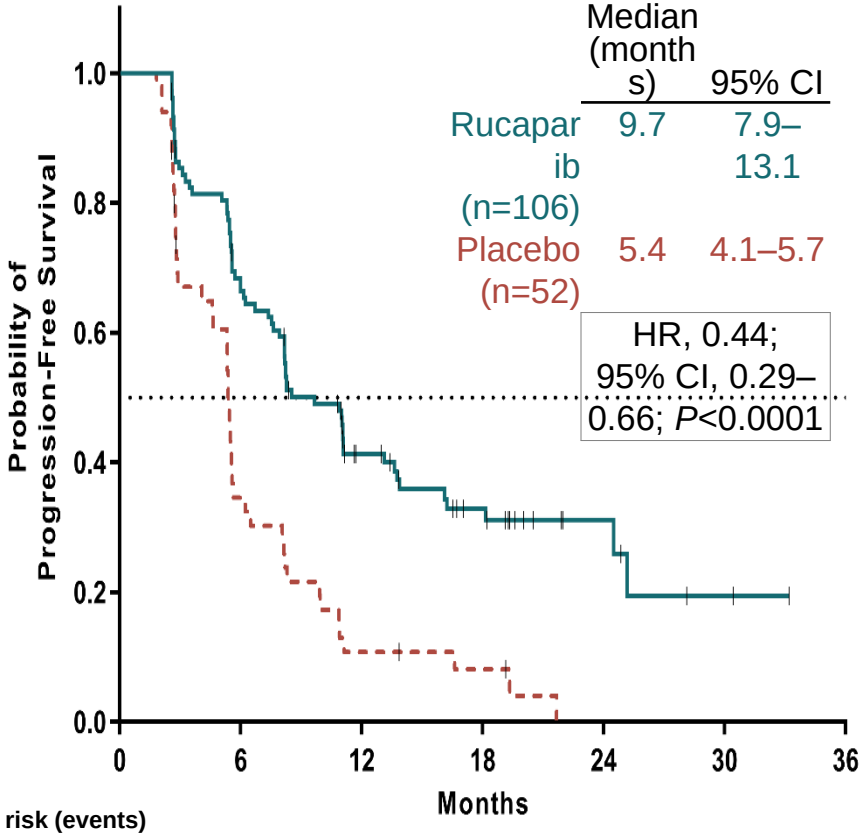
ARIEL3: Investigator-Assessed Progression-Free Survival



Visit cutoff date: 15 April 2017.

ARIEL3: Investigator-Assessed Progression-Free Survival: Patients with *BRCA* Wild-Type OC (Exploratoy Analysis)

LOH high



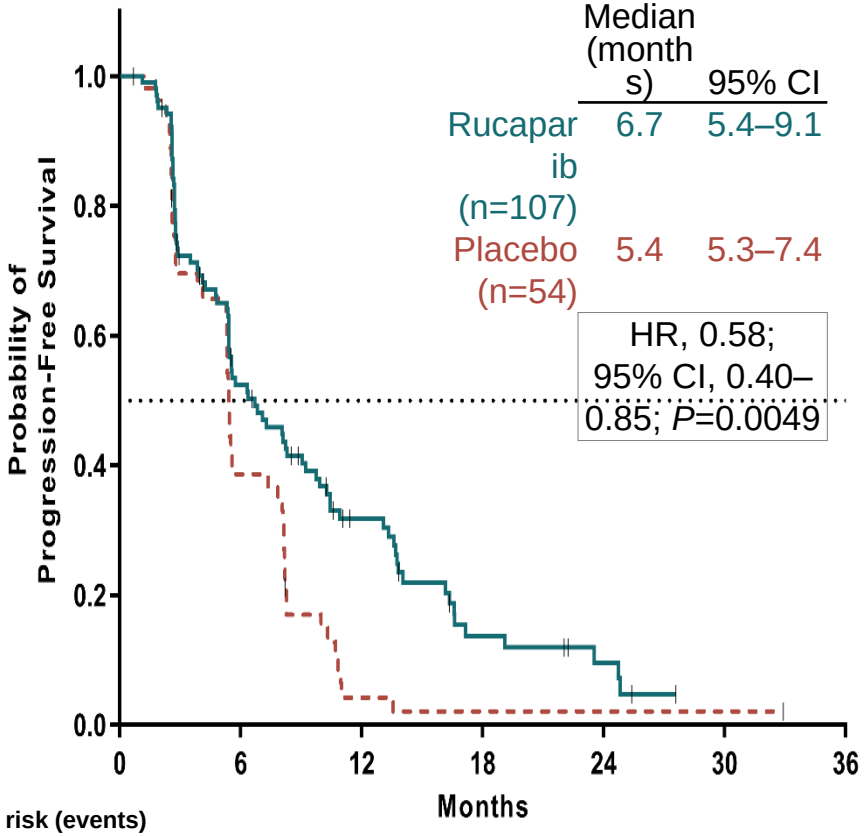
At risk (events)

Rucaparib	106 (0)	68 (32)	33 (58)	19 (64)	6 (65)	2 (67)	0 (67)
Placebo	52 (0)	16 (31)	5 (42)	3 (43)	0 (45)		

Rucaparib, 37% censored

Placebo, 13% censored

LOH low



At risk (events)

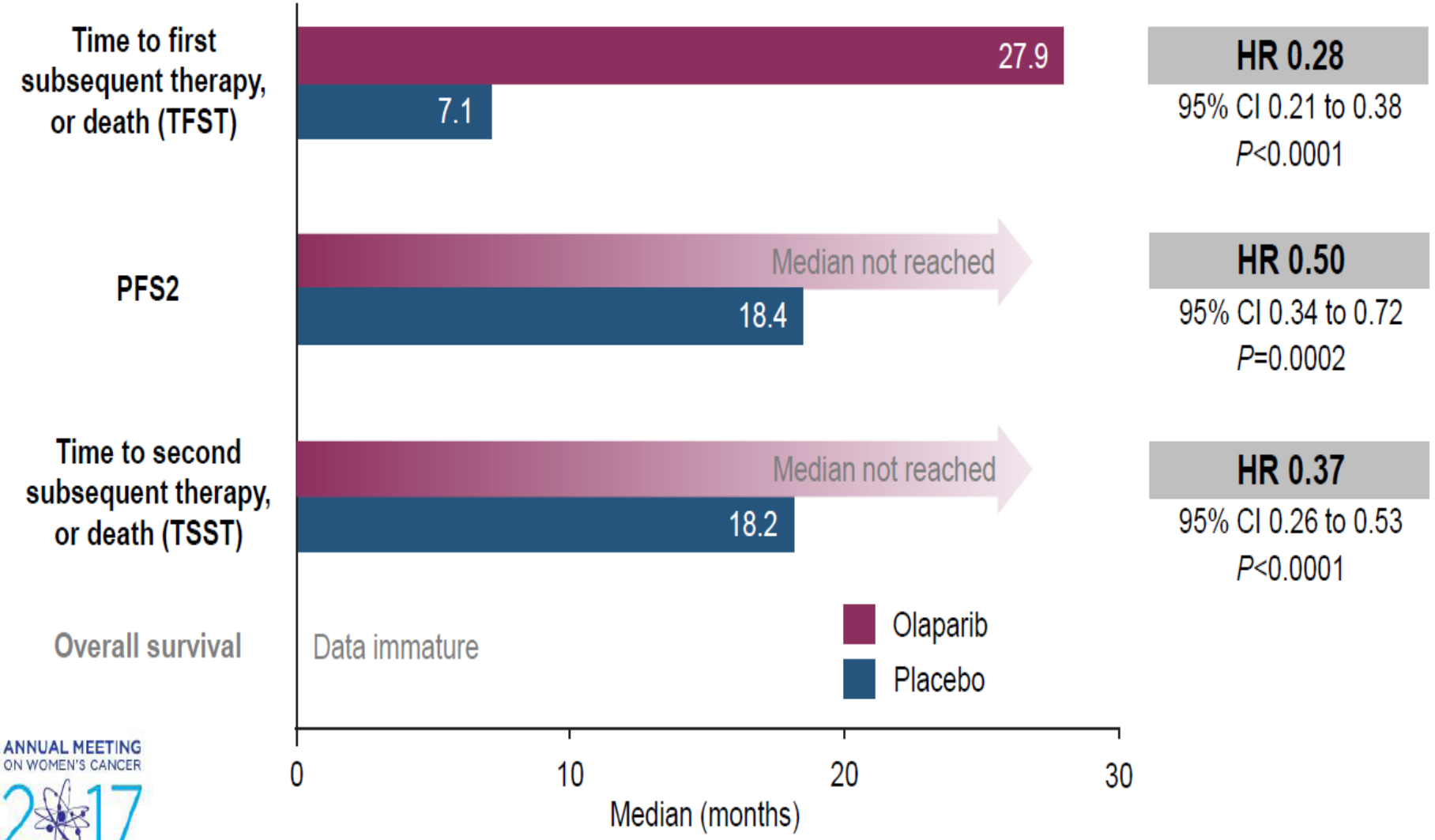
Rucaparib	107 (0)	49 (47)	23 (65)	8 (77)	4 (79)	0 (81)	
Placebo	54 (0)	20 (32)	2 (49)	1 (50)	1 (50)	1 (50)	0 (50)

Rucaparib, 24% censored

Placebo, 7% censored

Visit cutoff date: 15 April 2017.

Secondary efficacy endpoints



Tolerance (CTCAE grade 3/4)

	Olaparib (SOLO2) (n=195)	Niraparib (NOVA) (n=367)	Rucaparib (ARIEL 3) (n=561)
Dose reductions due to AEs, (%)	25	**66.5**	54.6
Treatment discontinuation due to AEs, (%)	10.8	**14.7**	13.4
Hematologic toxicity (Gr 3/4)			
- Anemia	19.5	**25**	18.8
- Neutropenia	5	**20**	6.7
- Thrombocytopenia	0	**34**	5.1
Hypertension	NR	**8**	NR
ASAT/ALAT	2	NR	**10.5**

GYNECOLOGIC CANCER INTERGROUP

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

A1-3. What are the most important factors to be evaluated prior to initial therapy?

Biomarkers

1. Germline mutation testing to include BRCA1/2 is recommended for all patients enrolled on clinical trials
   - Stratification (if possible) should be performed and knowledge of mutation status should be incorporated into primary endpoint analysis
   - Somatic mutation analysis for BRCA 1/2 is recommended
2. Predictive biomarkers for targeted agents to be included as companion diagnostics

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 Genuardi, Stefania Gori, Valentina Guarneri, Antonio Marchetti, Paolo Marchetti, Nicola Normanno, Barbara Pasini, Sandro Pignata, Carmine Pinto, Paolo Radice, Enrico Ricevuto, Antonio Russo, Pierosandro Tagliaferri, Pierfrancesco Tassone, Mauro Truini, 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

ENGOT-OV16/NOVA trial presented by Mansoor R Mirza

TREATMENT ALGORYTMS IN OVARIAN CANCER

- Treatment according to histotype is the future!

- Antiangiogenic agents and parp inhibitors are changing the natual history of ovarian cancer disease.

- The best treatment algorytm is the one which allows patients to receive all the available and effective treatment options.

- Immunotherapy the raising star for the future!!!!