FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Ovarian Cancer Surgery in the PARP inhibitor Era

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Gynecologic Oncology Unit

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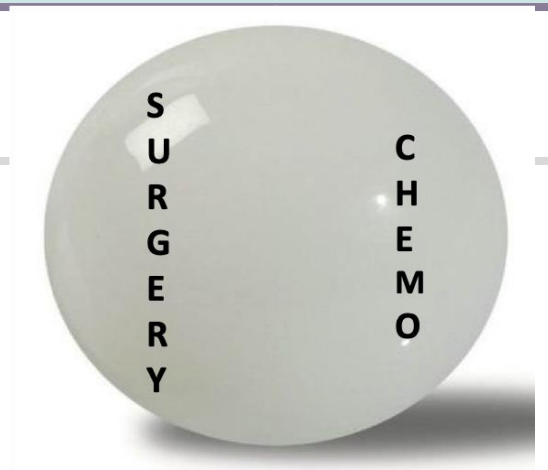
ESMO-ESGO

Recommendation 11.2: complete tumour resection at upfront debulking is the most important prognostic factor for patients with advanced ovarian cancer and is the main goal of surgery.
Level of evidence: IV
Strength of recommendation: A
Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 11.3: when complete surgery with no macroscopic visible disease appears feasible (both spread of disease and general condition of the patient), primary upfront debulking should be offered.
Level of evidence: IV
Strength of recommendation: B
Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

GCIG
Ovarian Cancer
Consensus Conference



NCCN guidelines,

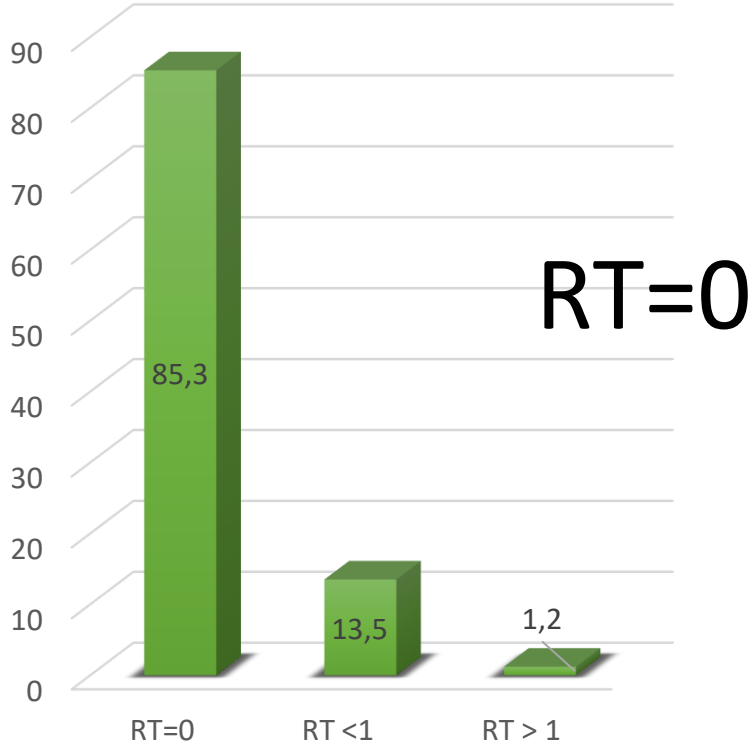
«**PDS is the recommended approach** for advanced-stage disease if the patient is a surgical candidate, optimal cytoreduction appears feasible.....»

Gynecol Oncol. 1998 May;69(2):103-8. doi: 10.1006/gyno.1998.4955.

Complete cytoreductive surgery is feasible and maximizes survival in patients with advanced epithelial ovarian cancer: a prospective study

S M Eisenkop [1], R L Friedman, H J Wang

«….complete cytoreduction of all macroscopic visible disease, since this has been shown to be associated with a significantly increased OS and PFS….»



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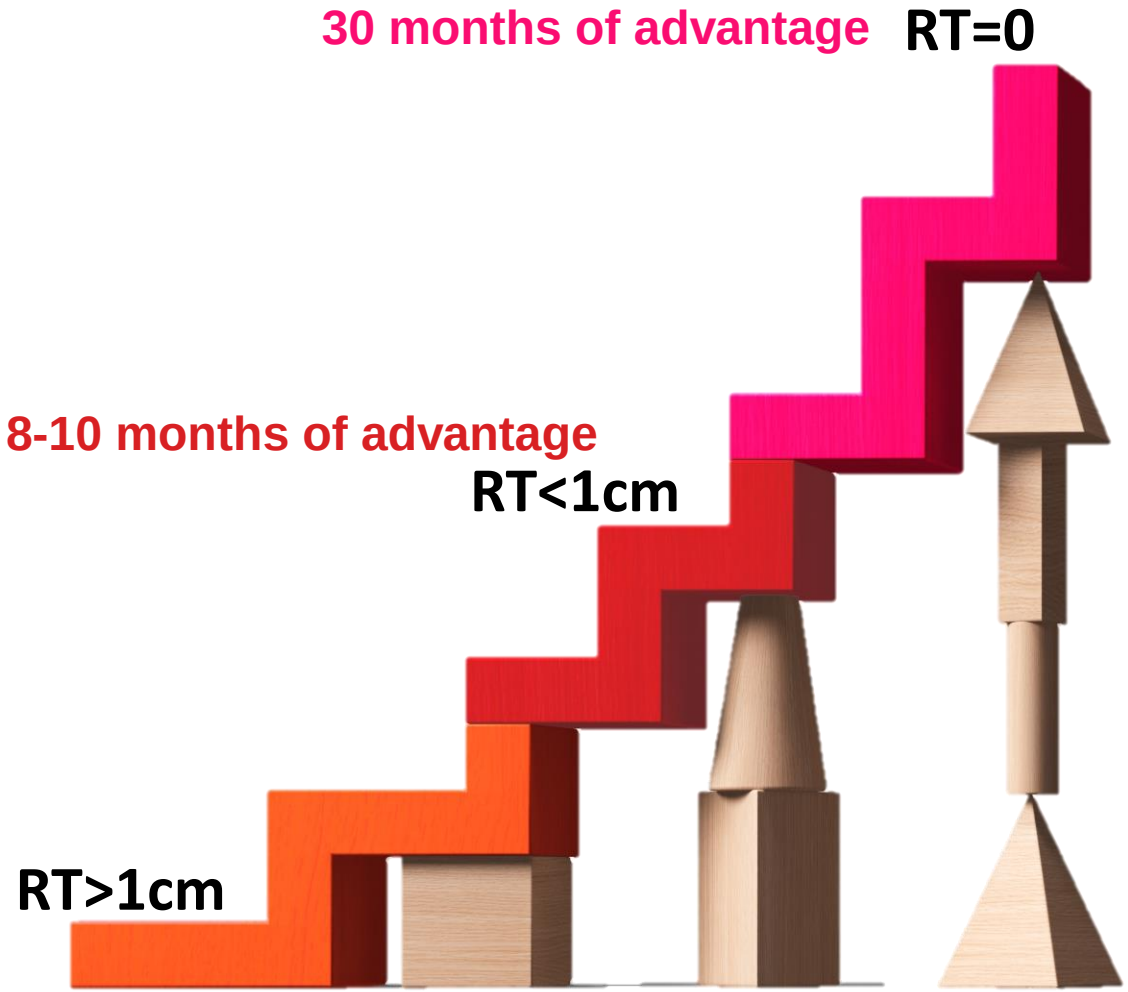
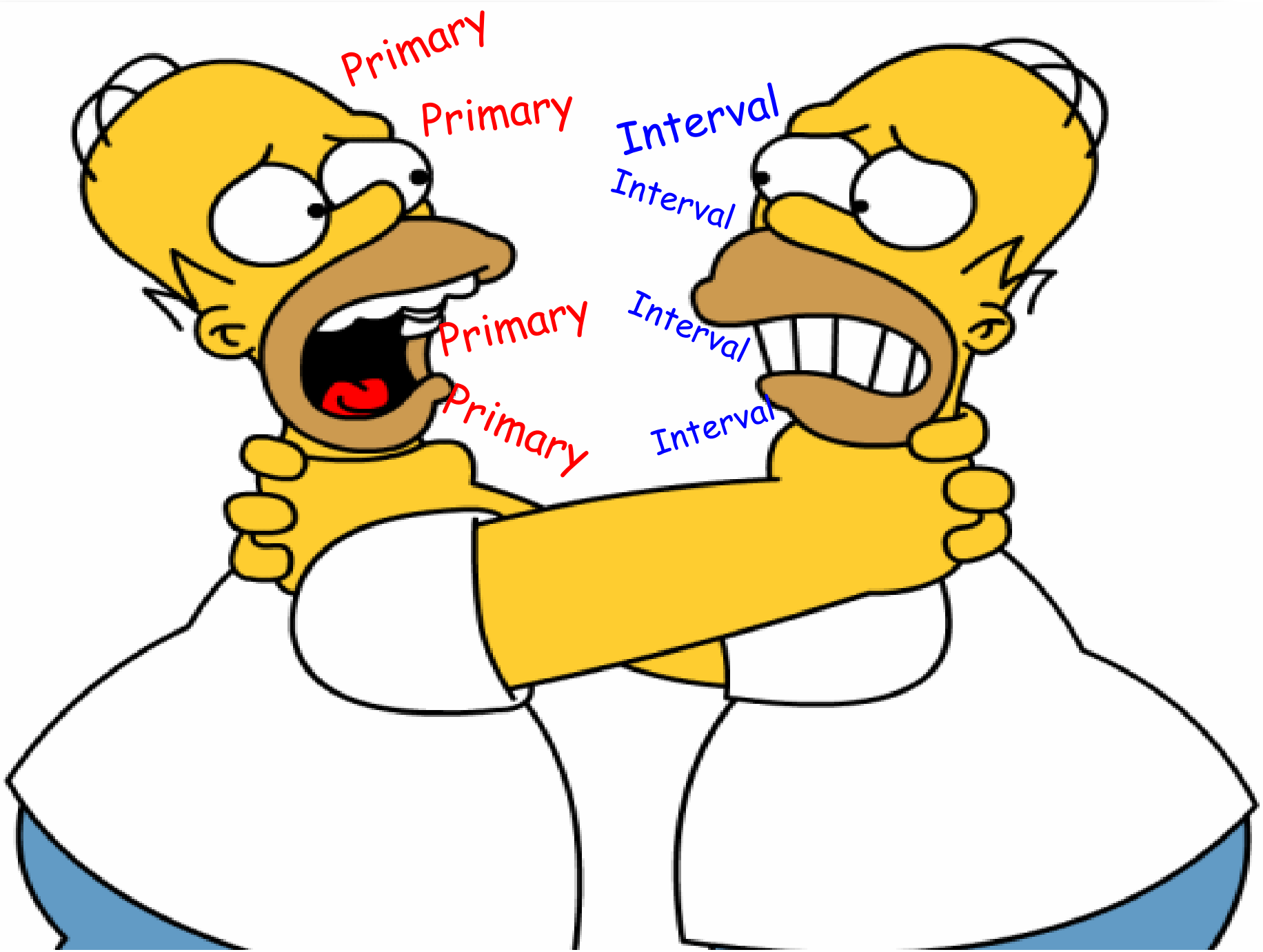




Primar

wed

ch

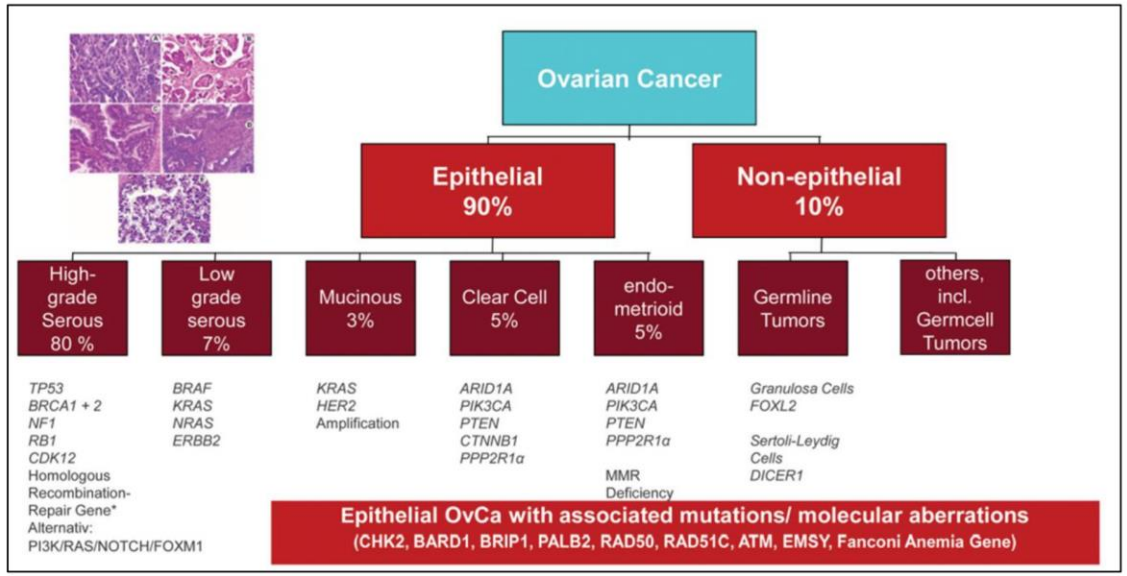
BRCA STATUS and Cytoreductive Surgery

Chemosensitivity

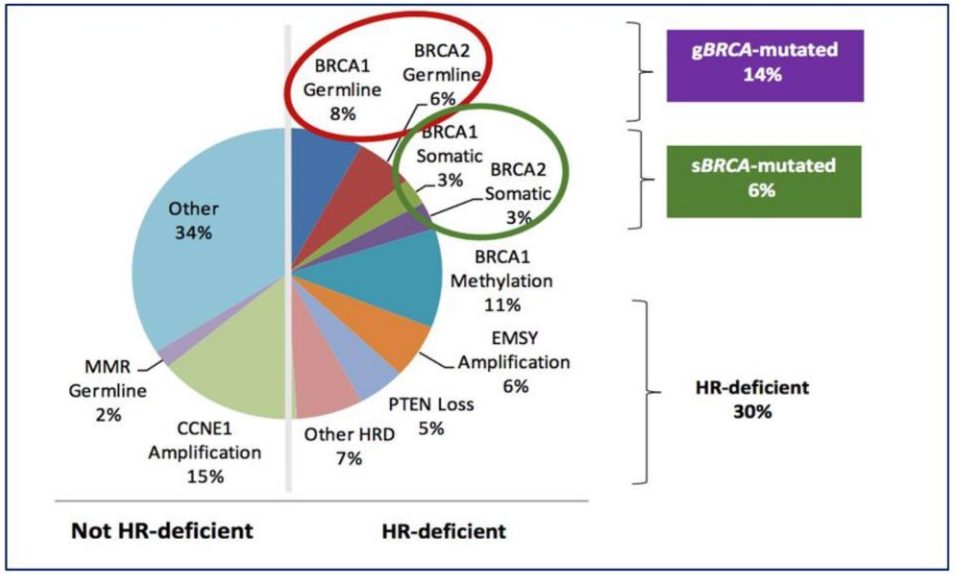
Different expected response rate according to different **histologic subtypes BRCA & HRD status**

Hystologic and Molecolar Predictors to Chemosensitivity

Histotype: Morphological Heterogeneity



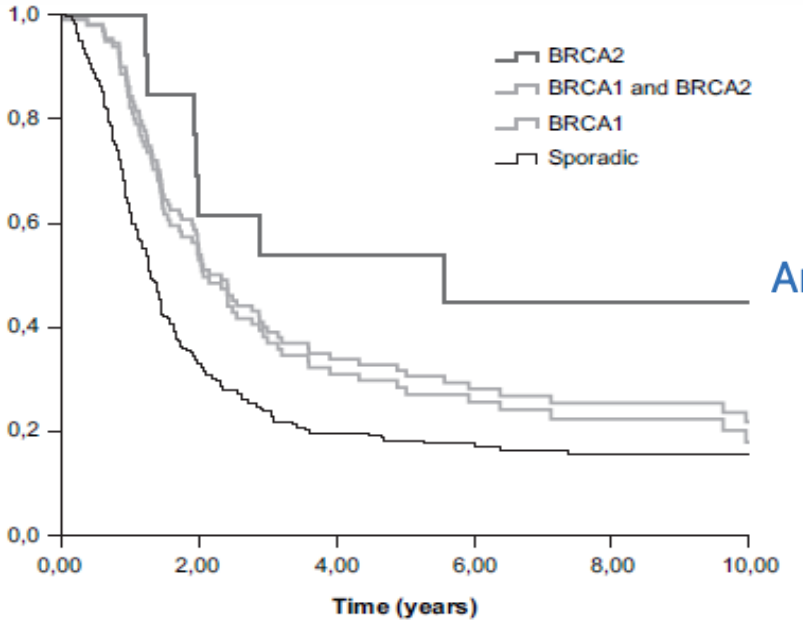
Genomic Factors: BRCA – HRD Status



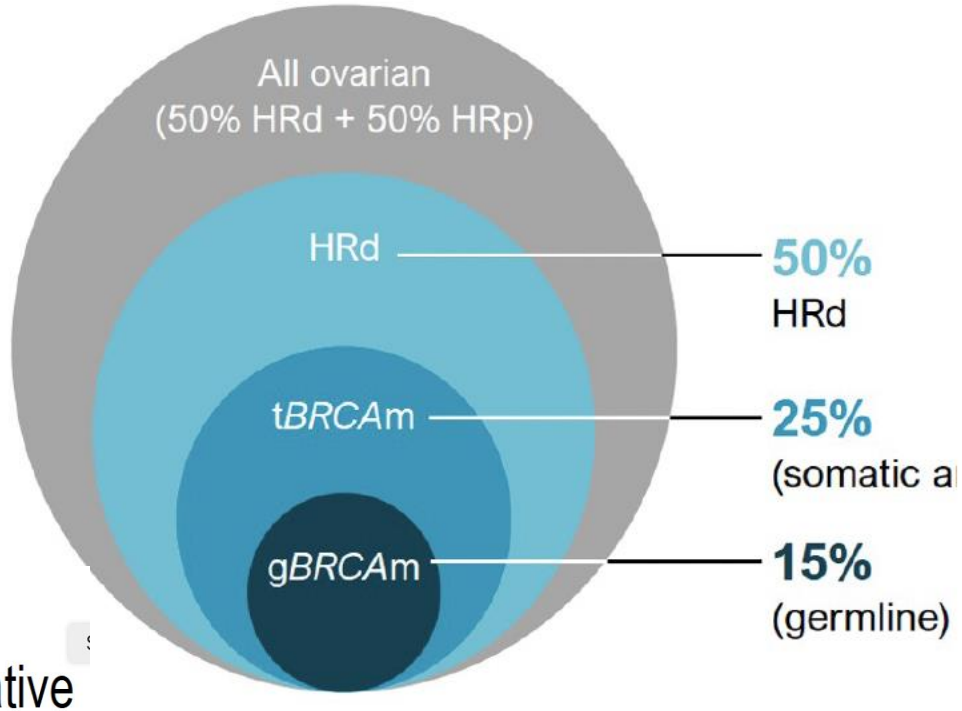
Chemosensitivity and outcome of *BRCA1*- and *BRCA2*-associated ovarian cancer patients after first-line chemotherapy compared with sporadic ovarian cancer patients

P. M. L. H. Vencken[1], M. Kriege[2], D. Hoogwerf[2], S. Beugelink[2], M. E. L. van der Burg[3], M. J. Hooning[2], E. M. Berns[3], A. Jager[2], M. Collée[4], C. W. Burger[1] & C. Seynaeve[2*]

	Response	*BRCA1*			*BRCA2*			Sporadic	
		N	%	*P*	*N*	%	*P*	*N*	%
Platinum with paditaxel	NED/CR	43	94	0.01	4	100	1.00	66	73
	PR/SD	3	6		0	0		14	16
	PD	0	0		0			10	11



Ann Oncol. 2011 Jun;



HG ovarian cancer patients can be divided in two populations with different biological and clinical caracteristics: HRD positive and HRD negative

Among HRD positive, the BRCA mut are those with the best prognosis and the most responsive to Platinum and PARPi

MODERN PATHOLOGY (2014) 27, 1405–1411

Invasion patterns of metastatic high-grade serous carcinoma of ovary or fallopian tube associated with *BRCA* deficiency

Invasion Patterns of Metastatic Extrauterine High-grade Serous Carcinoma With *BRCA* Germline Mutation and Correlation With Clinical Outcomes

Yaser R. Hussein, MD, Jennifer A. Ducie, MD,† Angela G. Arnold, MS,‡ Noah D. Kauff, MD,†‡§ Hebert A. Vargas-Alvarez, MD,§‖ Evis Sala, MD, PhD,‖ Douglas A. Levine, MD,†§ and Robert A. Soslow, MD*§*

Am J Surg Pathol 2016;

DIFFERENT ARCHITECTURE = DIFFERENT PRESENTATION

BRCA wt :

- infiltrative metastasis (papillary or glandular architecture)
- destructive invasion patterns in metastatic sites

BRCA mut :

- Pushing' pattern of metastasis
- Solid, pseudo-Endometrioid, and Transitional-like (SET) features
- **BRCA2>BRCA1 lacked destructive invasion patterns**
- Greater ease of resection
- Higher rate of optimal cytoreduction

High-Grade Serous Ovarian Cancer: Associations between *BRCA* Mutation Status, CT Imaging Phenotypes, and Clinical Outcomes[1]

Radiology

Nougaret 2017

108 cases

Univariate Analysis of the Associations between CT Features and *BRCA* Mutation Status

	Reader 1				Reader 2			
	BRCA				*BRCA*			
CT Feature*	*BRCA* Mutant	Wild Type	Odds Ratio†	*P* Value	*BRCA* Mutant	Wild Type	Odds Ratio†	*P* Value
Ovary								
PD pattern			4.43 (1.79, 10.96)	.001			5.03 (2.03, 12.49)	<.001
Nodular	20	23			18	17		
Infiltrative (reference)	10	51			12	57		
Mesentery								
Mesenteric involvement			0.13 (0.04, 0.40)	<.001			0.10 (0.03, 0.30)	<.001
Present	4	39			4	44		
Absent (reference)	29	36			29	31		
Gastrohepatic ligament			3.00 (1.17, 7.68)	.022			2.83 (1.14, 7.02)	.025
Present	12	12			13	14		
Absent (reference)	21	63			20	61		
Supradiaphragmatic			0.27 (0.10, 0.72)	.009			0.23 (0.08, 0.62)	.004
Present	6	34			6	37		
Absent (reference)	27	41			27	38		

BRCA-mutant

More likely:
nodular peritoneal disease pattern

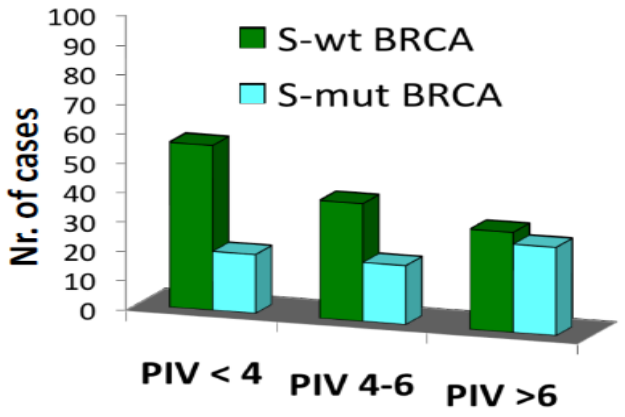
Less likely
infiltrative pattern,

BRCA-wt

…disease in the lesser sac, mesenteric involvement, subdiaphragmatic lymphadenopathy and suprarenal para-aortic lymphadenopathy associated with higher degrees of incomplete resection

BRCA STATUS MAY HELP to identify best therapeutic strategy

2017



273 patients included

p=0.036

GYNECOLOGY

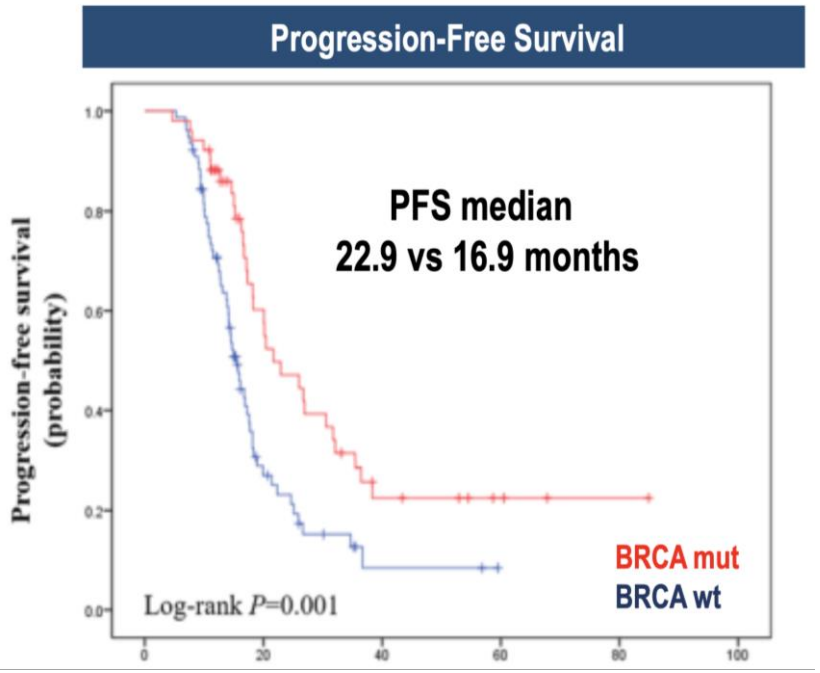
BRCA mutational status, initial disease presentation, and clinical outcome in high-grade serous advanced ovarian cancer: a multicenter study

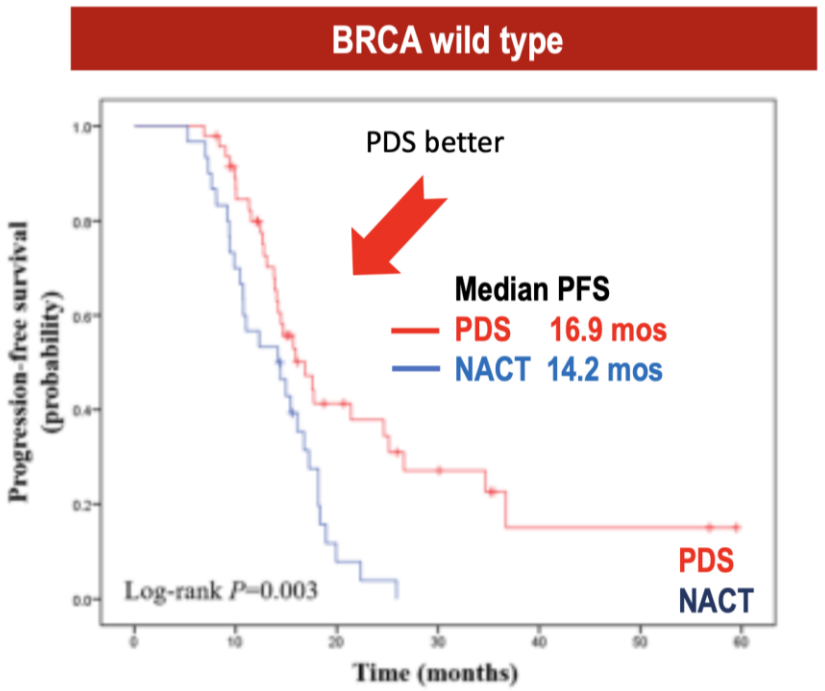
Marco Petrillo, PhD; Claudia Marchetti, PhD; Rossella De Leo, MD; Angela Musella, PhD; Ettore Capoluongo, PhD; Ida Paris, PhD; Pierluigi Benedetti Panici, PhD; Giovanni Scambia, PhD; Anna Fagotti, PhD

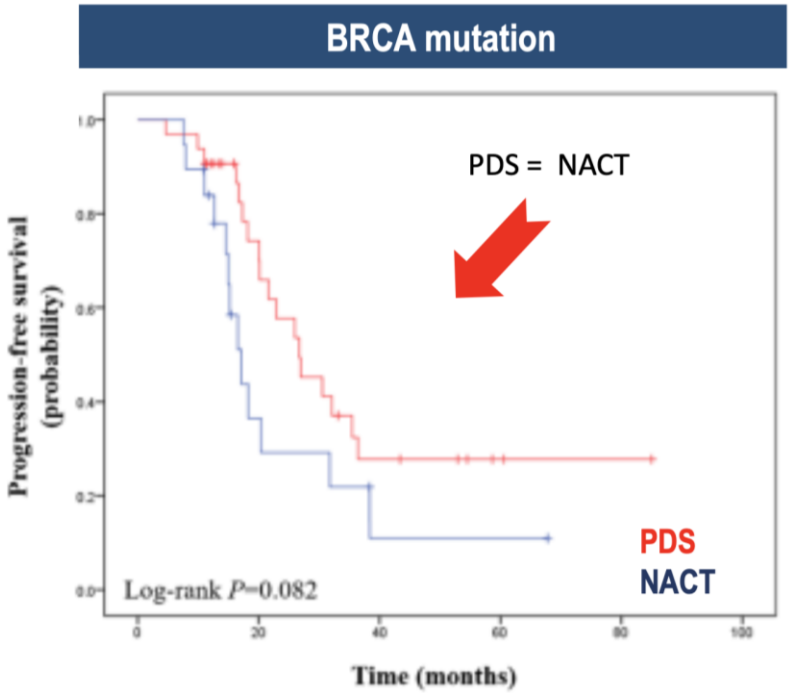
- *PDS 71%; NACT 29%*
- *Complete resection at PDS 88.7%*

- Womens with BRCA1/2 mut : more frequent peritoneal carcinomatosis - higher peritoneal load and bulky nodes compared to BRCAwt
- PDS seems to endure longer PFS in BRCA WT patients comapred to NACH

Effect of BRCA Status on Outcome - Pre PARP-i maintenance era



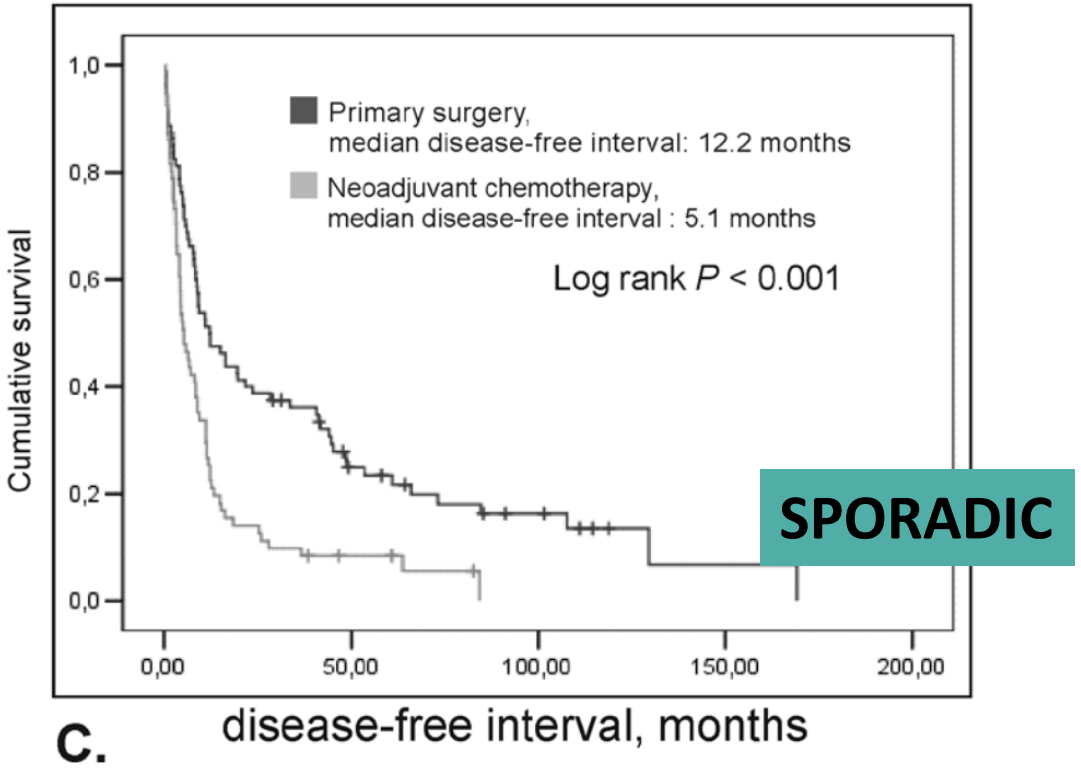




Kim SI, et al. *J Ovarian Research (2019)*

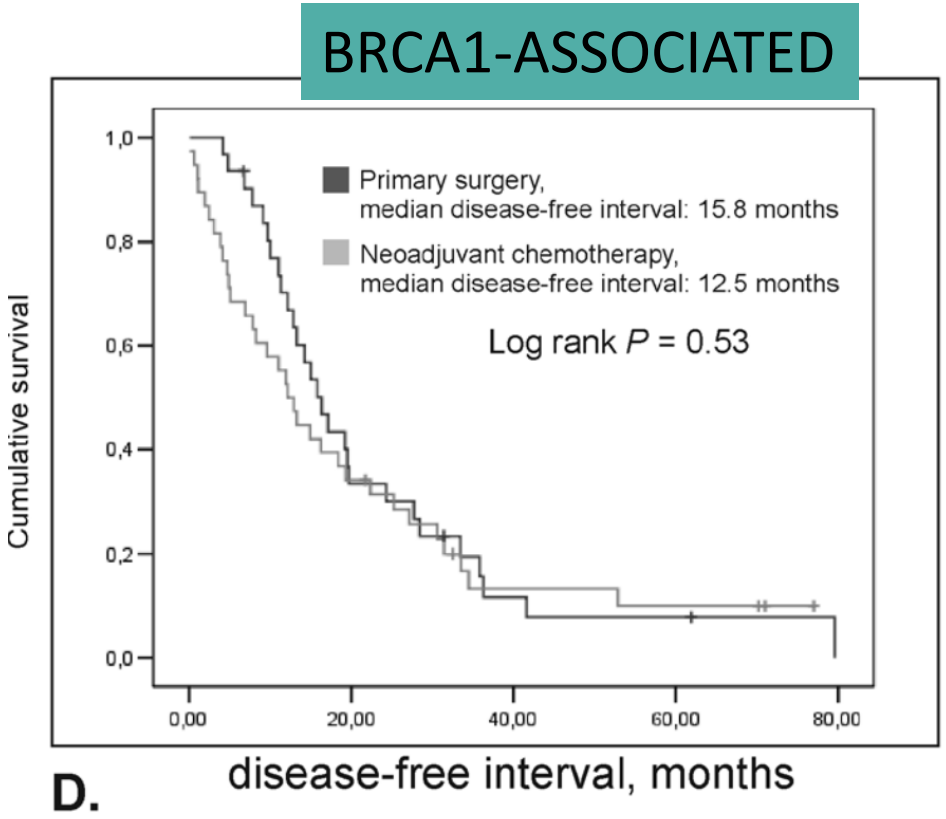
BRCA1-associated and sporadic ovarian carcinomas: outcomes of primary cytoreductive surgery or neoadjuvant chemotherapy

Gorodnova et al, IJGC 2019



SPORADIC

BRCA1-ASSOCIATED

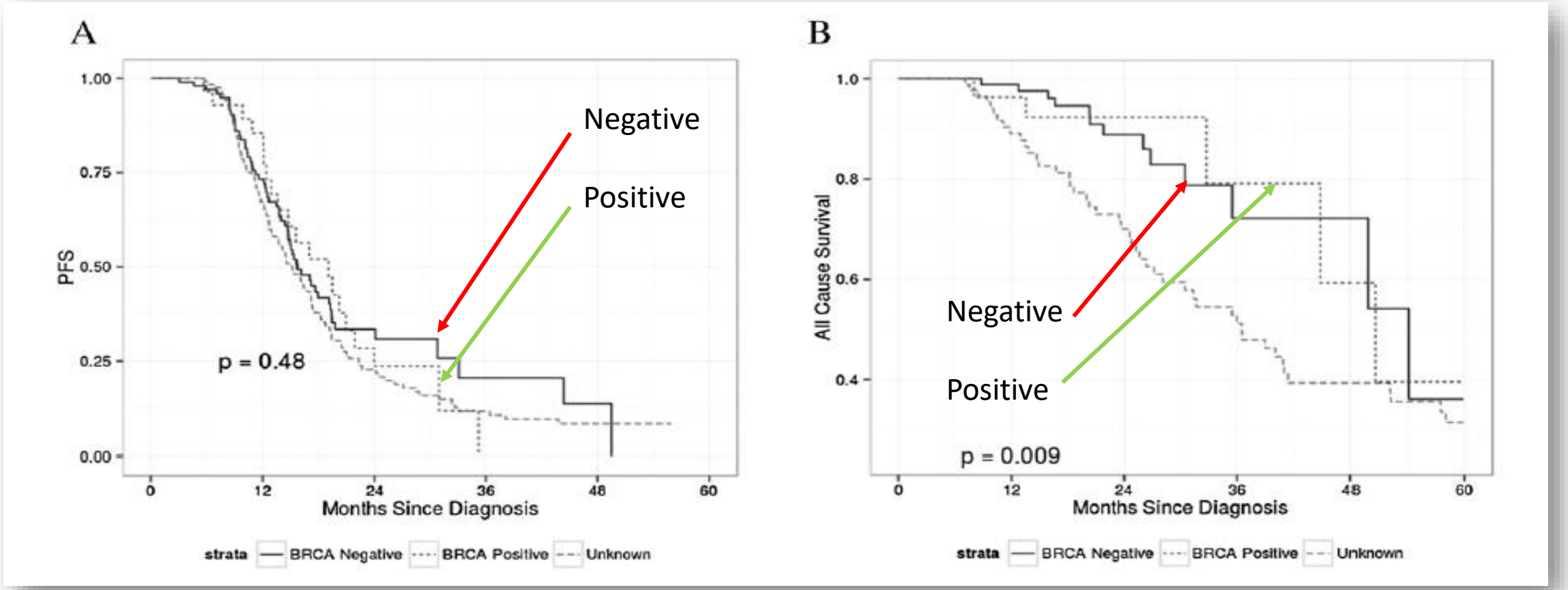


Conclusion: In *BRCA1* mutation carriers, the oncologic outcomes are similar when comparing primary surgery versus neoadjuvant chemotherapy.

Outcome of neoadjuvant chemotherapy in *BRCA*1/2 mutation positive women with advanced-stage Müllerian cancer

Mahdi , Gynecol Oncol 2015

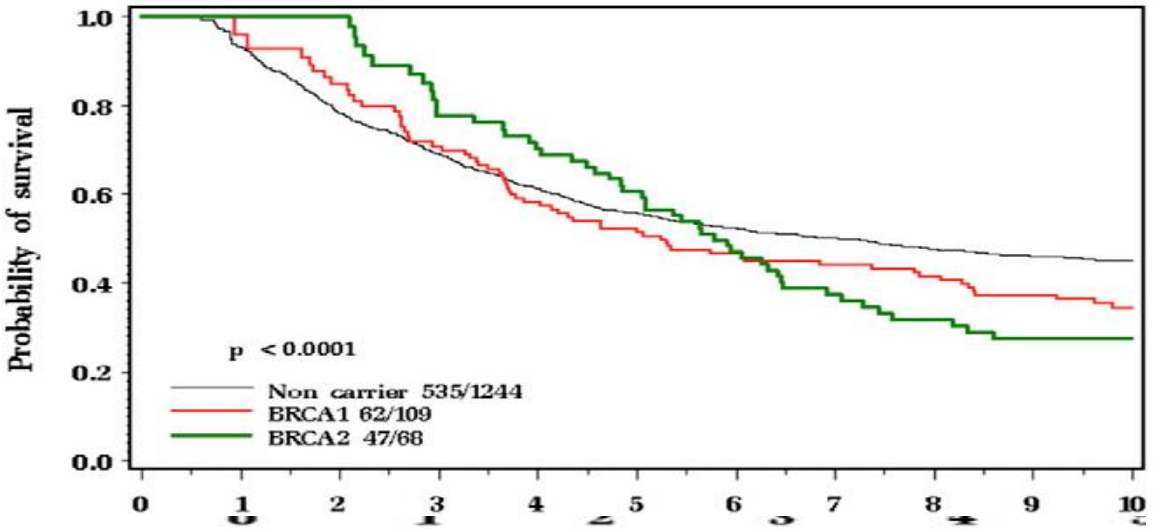
Is NACT actually better in BRCA mutated patients?



Ten-year survival after epithelial ovarian cancer is not associated with *BRCA* mutation status

Gynecologic Oncology 140 (2016)

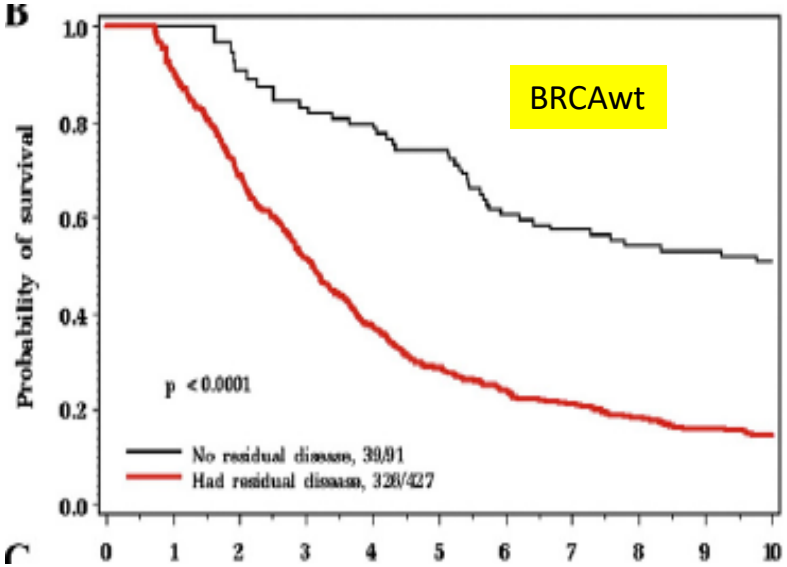
Joanne Kotsopoulos [a,b,*], Barry Rosen [c,d], Isabel Fan [e], Joel Moody [e], John R. McLaughlin [f], Harvey Risch [g], Taymaa May [c,d], Ping Sun [a], Steven A. Narod [a,b]

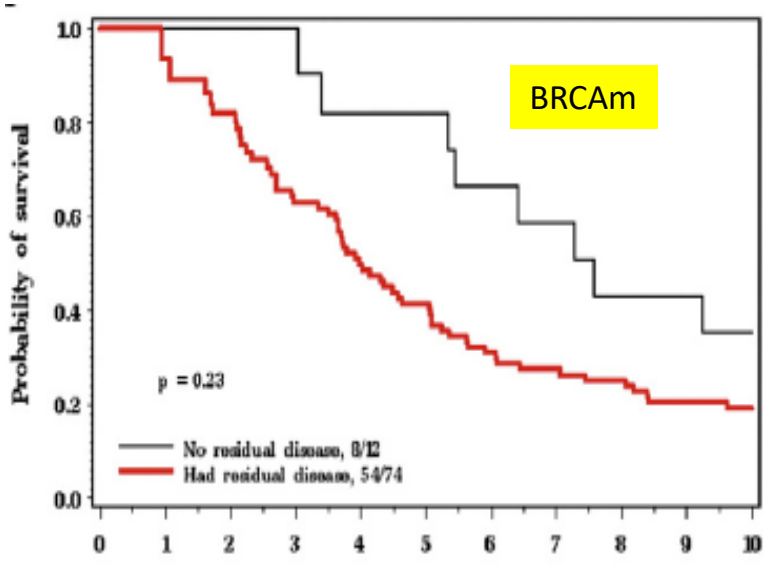


BRCAms have **SHORT-TERM SURVIVAL ADVANTAGE** (higher sensitivity of BRCAm carriers to platinum therapy)

BUT NOT reflected in **LONG-TERM SURVIVAL OUTCOMES**

RT 0= STRONGEST PREDICTOR of long-term survival





Surgery might mitigate BRCA status

Outcomes of primary surgical cytoreduction in patients with *BRCA*-associated high-grade serous ovarian carcinoma

David M. Hyman [a], Kara C. Long [b], Edward J. Tanner [b], Rachel N. Grisham [a], Angela G. Arnold [c], Jasmine Bhatia [c], Mary F. Phillips [a], David R. Spriggs [a], Robert A. Soslow [d], Noah D. Kauff [b,c], Douglas A. Levine [b,*]

Gynecol Oncol 2012

If **multivariate analyis** is performed (for age at diagnosis and location of treatment): **BRCA mutation status no** longer associated with residual tumor volume

- **Only 69 patients** in the BRCA mutated cohort

Surgical outcome Multivariate Analysis (MSKCC and TCGA Patients Combined)*

Variables	No. of Patients	Odds Ratio	95% Confidence Interval	*P*-value
Age (10 years)	361	1.25	1.01 - 1.56	0.05
Cohort				
MSKCC	101	0.47	0.25 - 0.85	0.01
TCGA	260	Ref.		
BRCA				
BRCA (+)	67	0.63	0.31 -1.29	0.21
BRCA (-)	294	Ref.		

Conclusion. *BRCA* mutation status is not associated with the rate of optimal tumor debulking at primary surgery after accounting for differences in patient age. Improved survival of *BRCA* carriers is unlikely the result of better surgical outcomes but instead intrinsic tumor biology.

The correlation between *BRCA* status and surgical cytoreduction in high-grade serous ovarian carcinoma

Soyoun Rachel Kim [a,b], Janet Malcolmson [c,d], Xuan Li [e], Marcus Q. Bernardini [a,b], Liat Hogen [a,b], Taymaa May [a,b,*]

Gynecologic Oncology 162 (2021)

Logistic multivariate regression model to evaluate the correlation between *BRCA* status with complete resectability adjusted for confounding characteristics.

Covariate	OR (95% CI)	p-value
BRCA status		
Negative	Reference	**<0.001**
Positive	5.31 (2.45–11.51)	
Age	1.00 (0.97–1.04)	0.800
Median length of surgery	1.02 (0.86–1.20)	0.830
CA125 at diagnosis	0.99 (0.97–1.00)	**0.046**
FIGO Stage		
3	Reference	0.560
4	1.52 (0.37–6.25)	
Disease score		
Low	Reference	<0.001
Moderate	0.27 (0.09–0.77)	
High	0.02 (9.1e-03-0.07)	
Surgical complexity score		
Low	Reference	0.002
Moderate	5.32 (2.01–14.09)	
High	2.08 (0.55–7.85)	

- **Women with BRCA1/2 mutations: higher rates of primary complete and cytoreduction**
- **BRCA mutation status was inversely associated with residual disease on multivariate**

303 Cases

THE JOURNAL OF
Obstetrics and Gynaecology Research
doi:10.1111/jog.15326 J. Obstet. Gynaecol. Res. Vol. 48, No. 9: 2270–2284, September 2022

Association of BRCA1/2 mutations with prognosis and surgical cytoreduction outcomes in ovarian cancer patients: An updated meta-analysis

Yazhuo Wang, Na Li, Yanan Ren and Jing Zhao
Department of Gynaecology, Hebei General Hospital, Shijiazhuang, China

Sep,2022

BIAS

- Eterogeneous studies
- Different endpoints
- Lack of data

meta-analysis

In conclusion:

- BRCA1/2 mutations were associated with improved OS and PFS
- BRCA2 mutations seemed to have better prognoses
- **No relationship between BRCA status and the surgical resectability rate**

- **BRCA STATUS**
- **MaintenanceTherapy**
- **Cytoreductive Surgery**

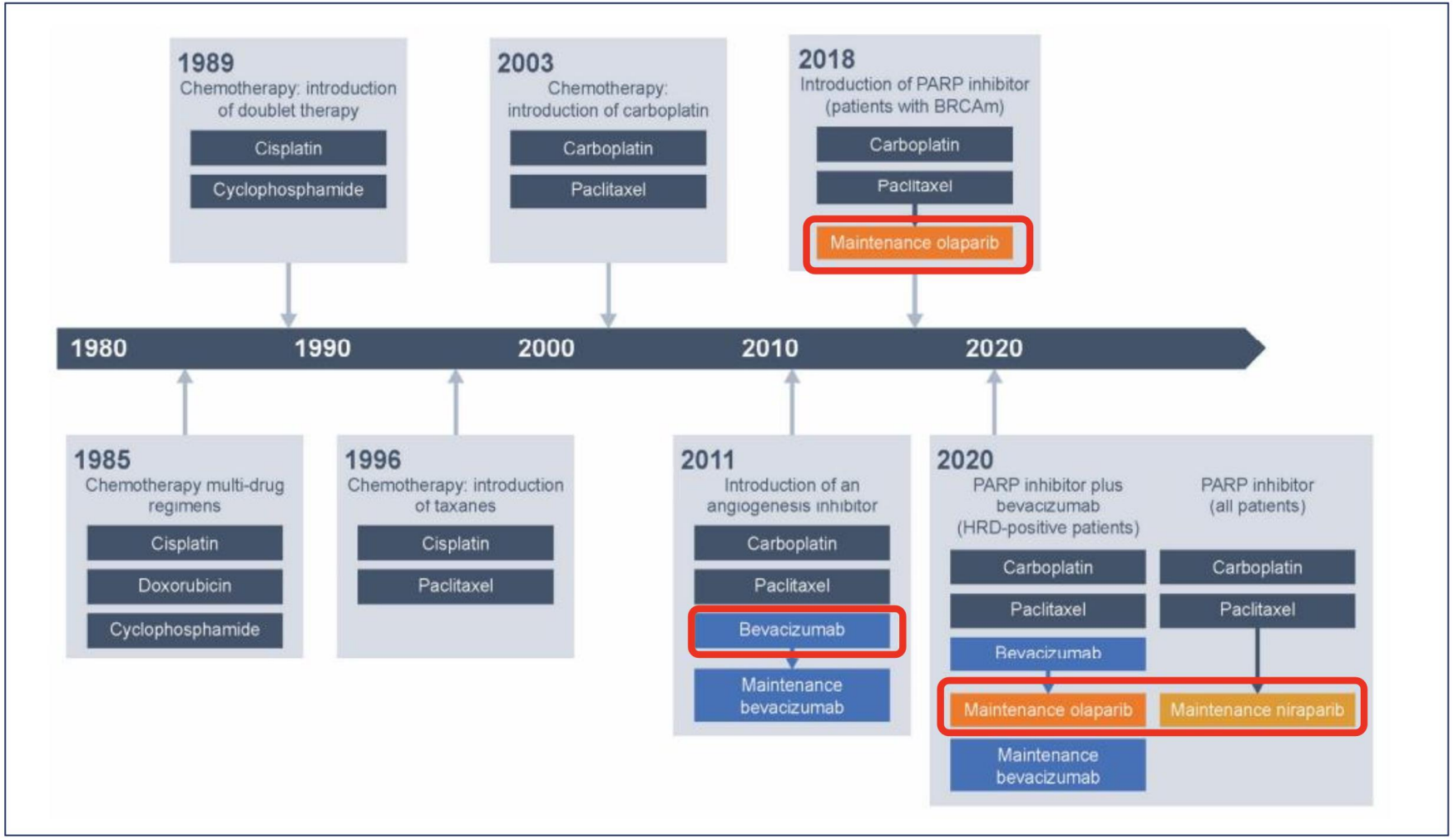
Chemotherapy and Maintenance

CHEMOTHERAPY:
Paclitaxel and Carboplatin
q3w for 6 cycles

+

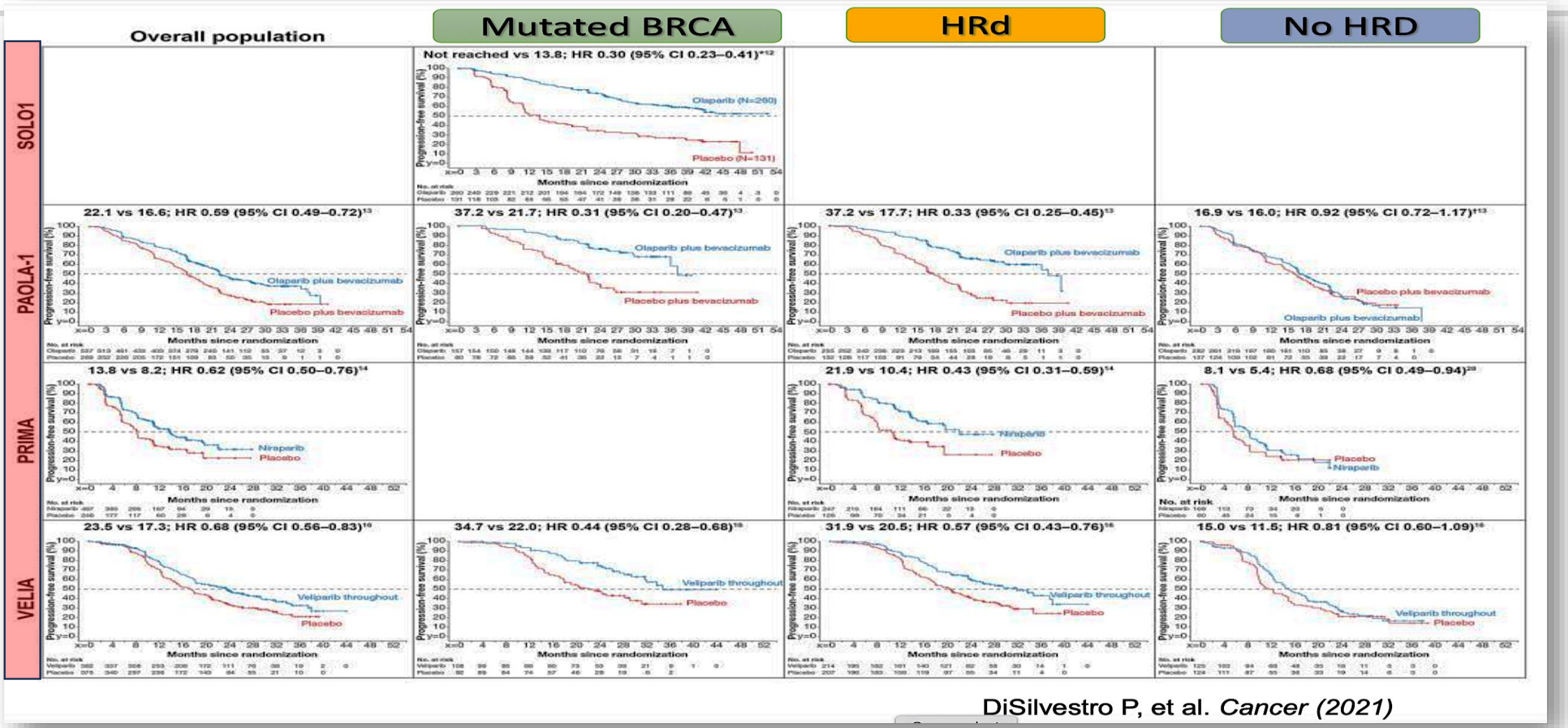
MAINTENANCE:
Targeted Therapies

Development of Standard Treatment



DiSilvestro P, et al. *Cancer (2021)*

PARP-i TIMELINE



DiSilvestro P, et al. *Cancer (2021)*

- All trials on PARPi maintenance in newly diagnosed ovarian cancer are positive for **prolonged PFS**
- **Patients with BRCA mutations** consistently show **the most PFS benefit in these trials**

RT>0 and Maintenance

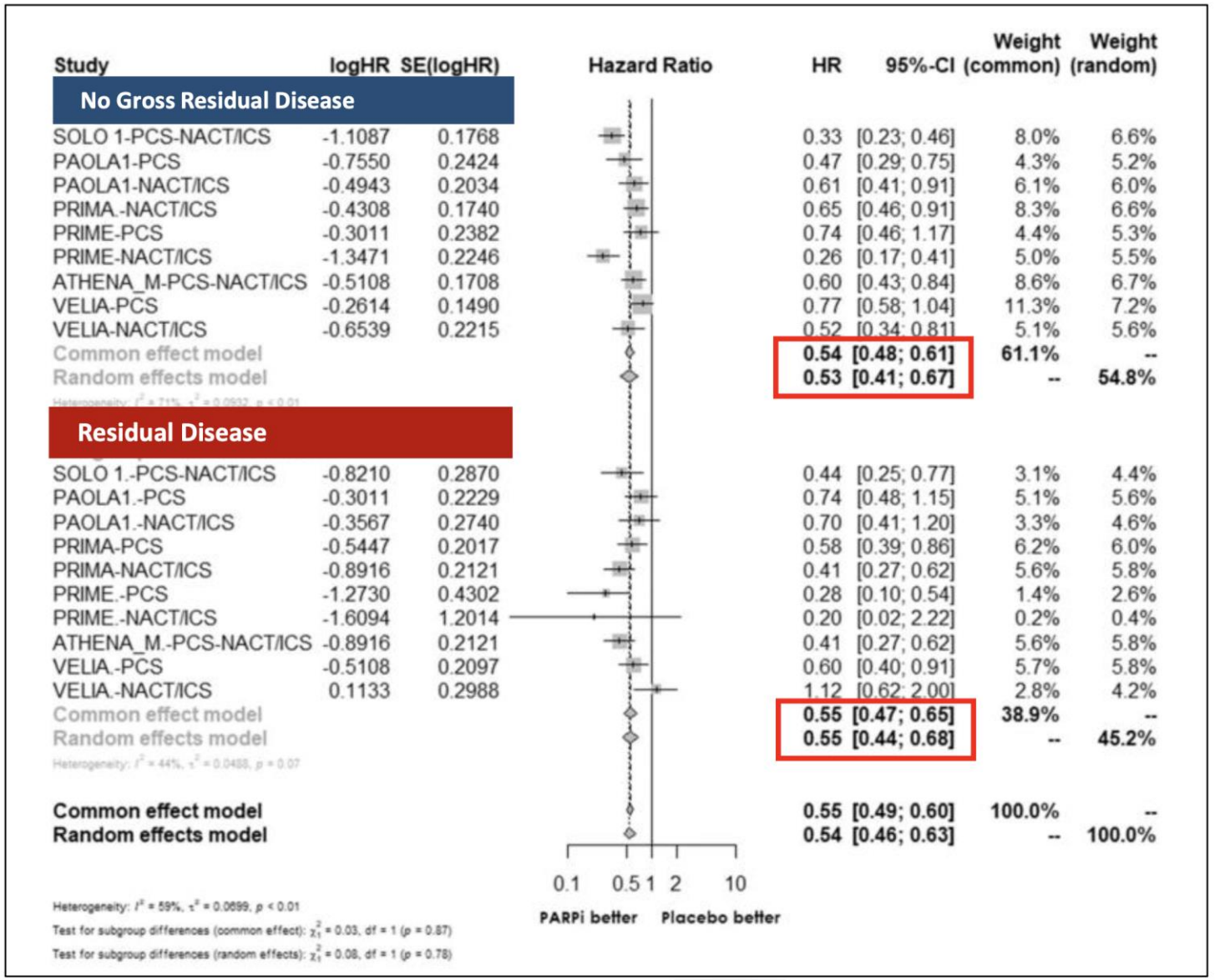
Trial	PARP-i	Placebo
SOLO-1	21%	22%
PAOLA-1	33%	33%
PRIMA	45%	46%
PRIME	24%	19%
ATHENA MONO	25%	26%

30%

Conclusion:
PARP-i: Effettive regardless of RT

DiSilvestro P, et al. *JCO (2020)*
Roy-Coquard I, et al. *NEJM (2019)*
Gonzalez-Martin A, et al. *NEJM (2019)*
Li N, et al. *Presented at SGO (2022)*
Monk BJ, et al. *JCO (2022)*

Forest Plot of the effect of PARP-i Maintenance on PFS according RT

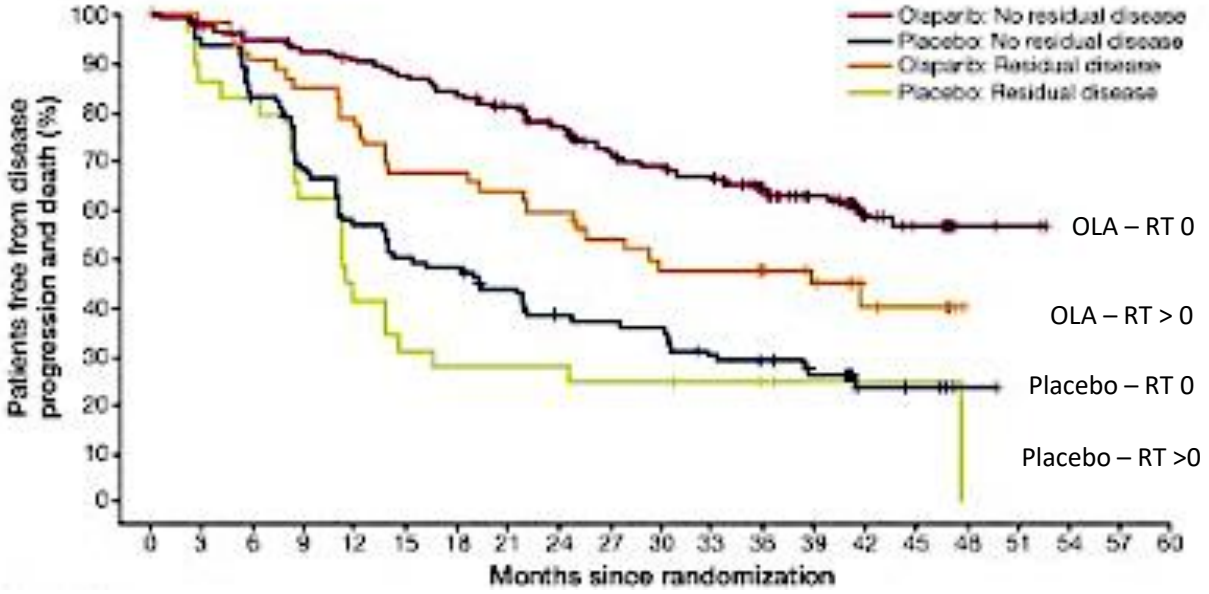


Pts with RT= 0
Better PFS rates

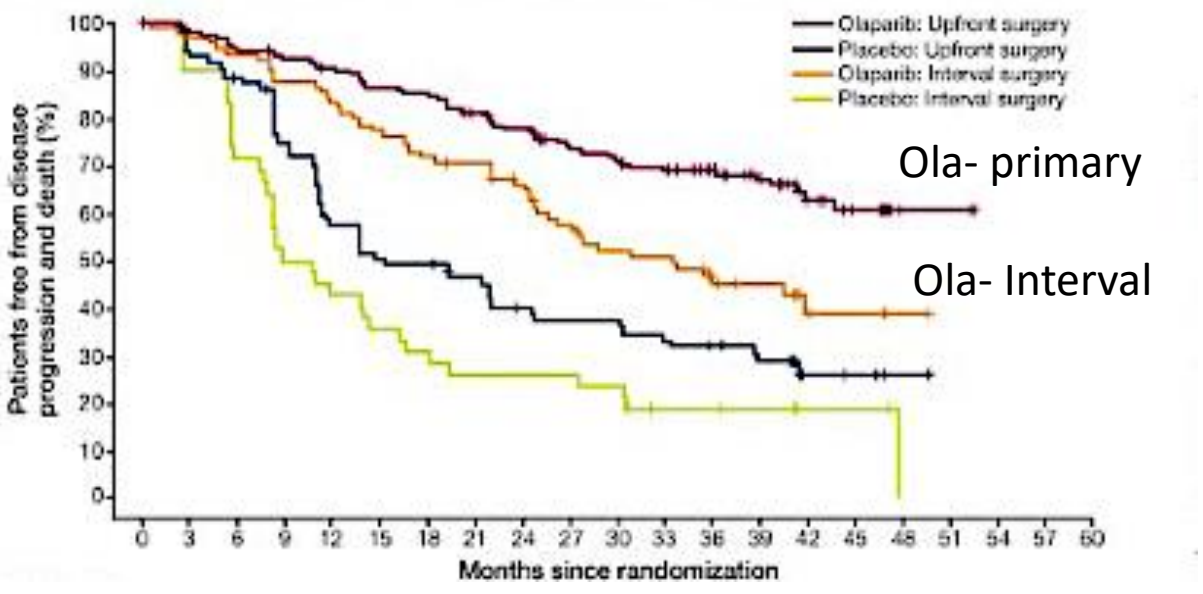
Pts with RT> 0
Lower PFS rates
Equally benefit fom PARP-i

Peters ITA et al. *Eur J Cancer (2023)*

Maintenance olaparib after platinum-based chemotherapy in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation: Efficacy by surgical and tumor status in the Phase III SOLO1 trial



No Residual Disease vs Residual Disease

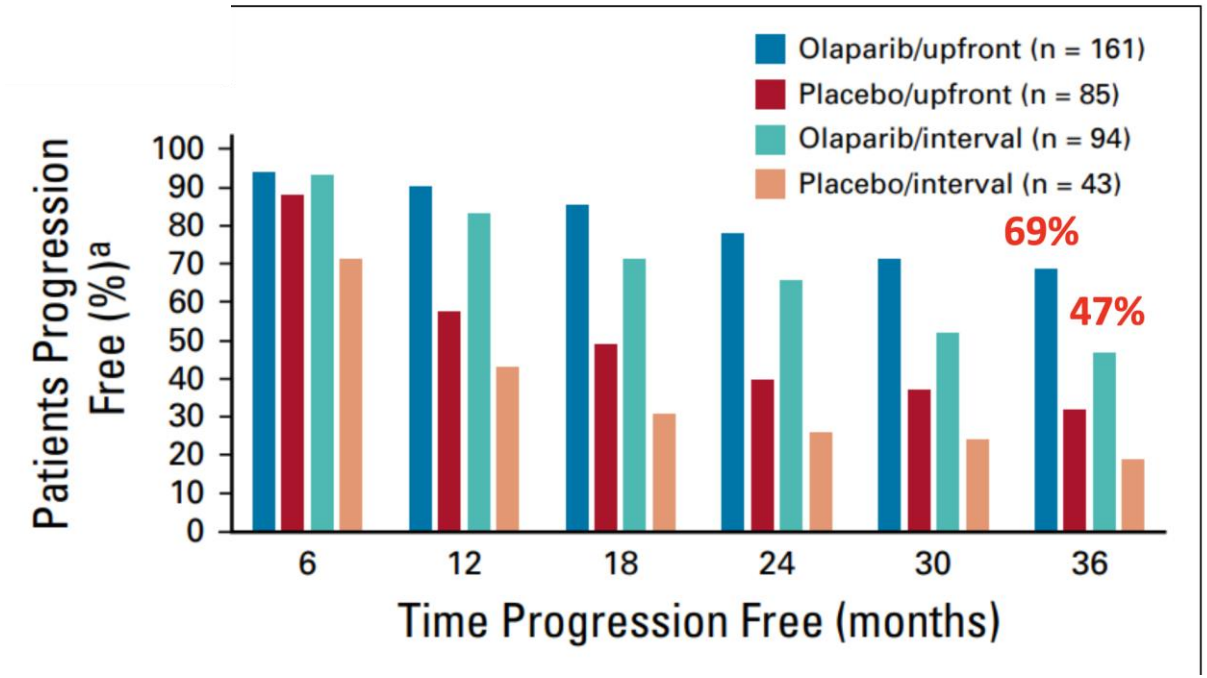


Primary vs Interval

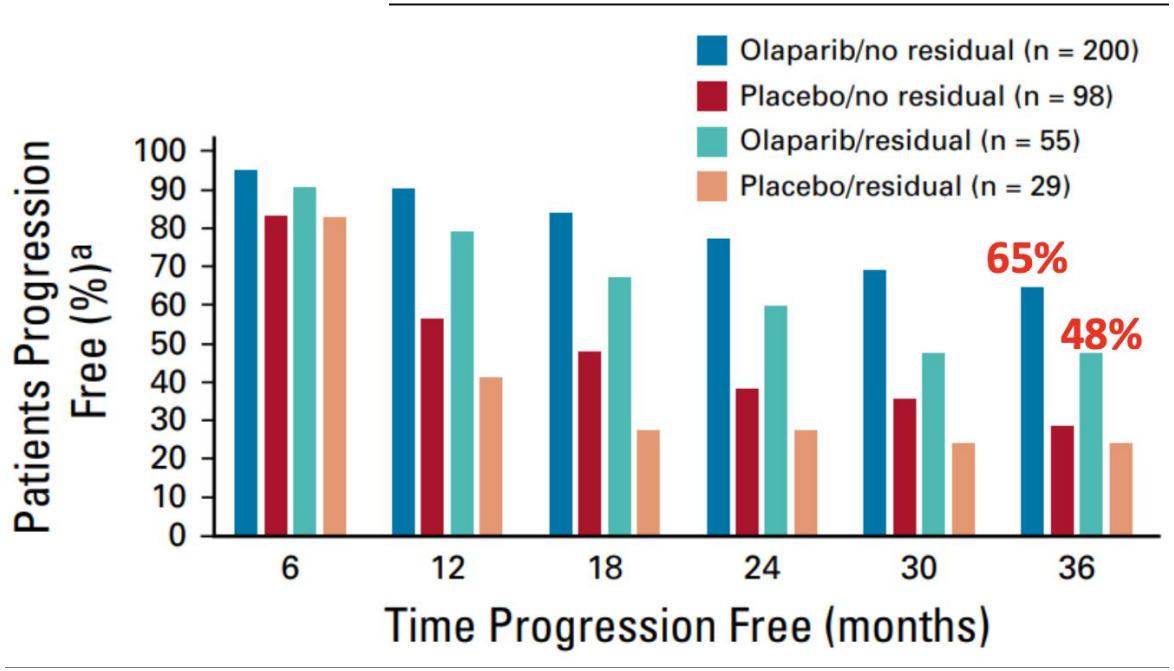
A post-hoc analysis - ASCO 2019:
in BRCA mutated patients the therapeutic efficacy of parp inhibitors (Olaparib) appears to be greater in patients with no residual disease at first surgery

SOLO-1: Subgroup Analysis

Up-Front Surgery vs IDS

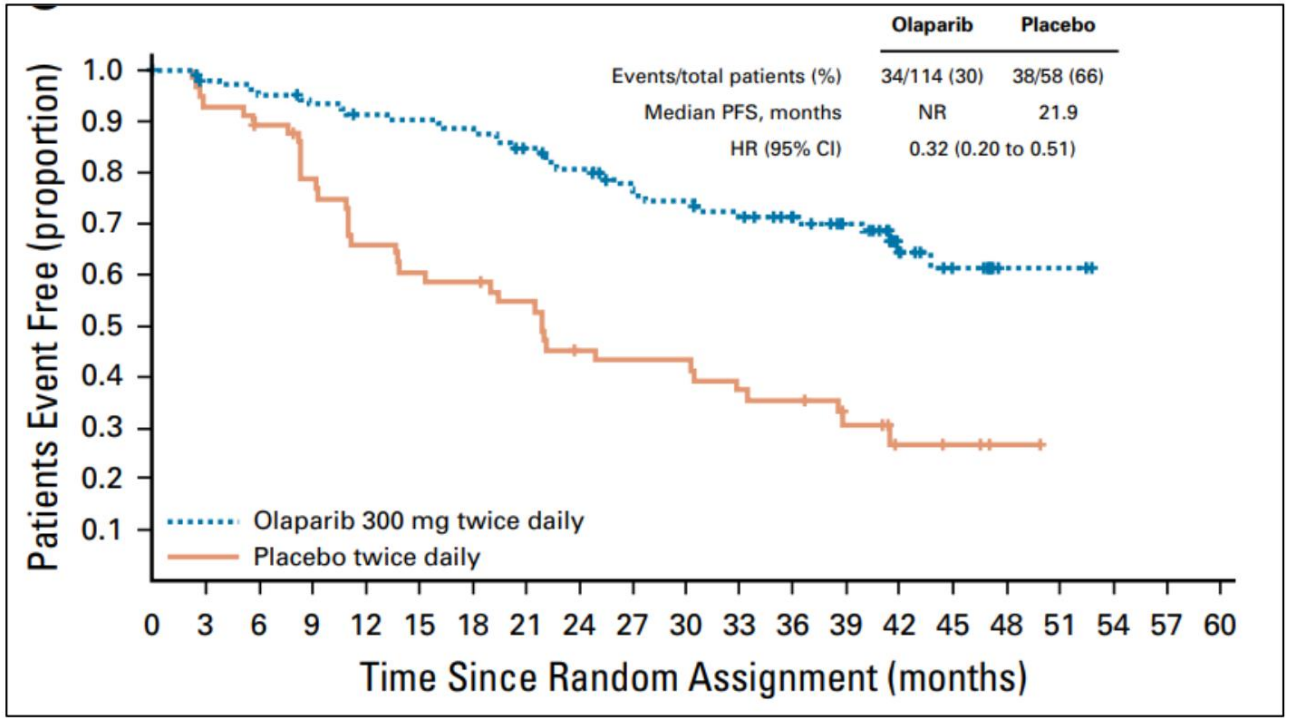


Residual Disease vs NED



SOLO-1: Subgroup Analysis

FIGO Stage III Disease + Up-front Surgery + NED

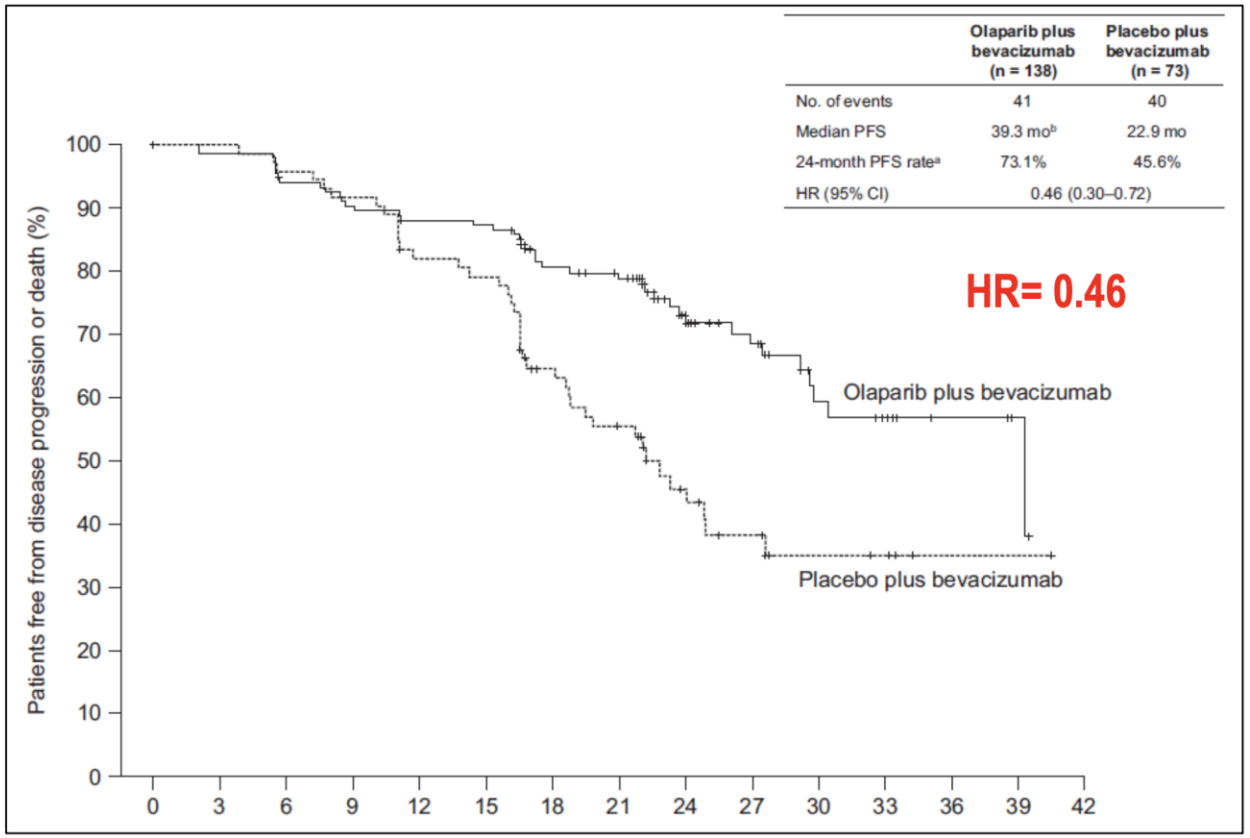


ITT Population (n = 391)	
Olaparib (n = 260)	**Placebo (n = 131)**

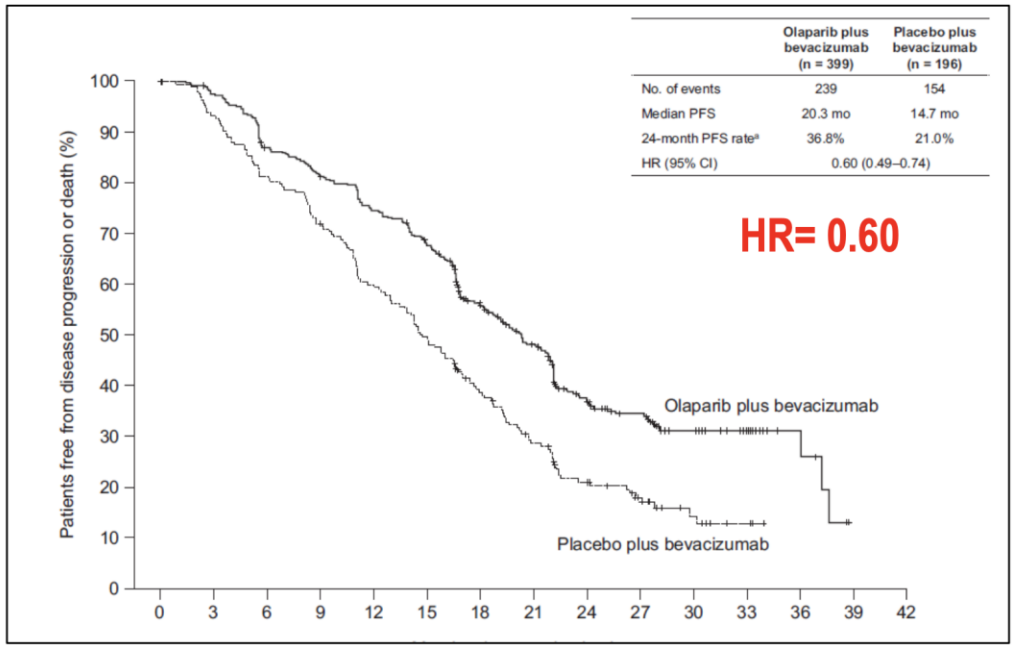
History of cytoreductive surgery, No. (%)		
Upfront surgery	161 (62)	85 (65)
Residual macroscopic disease	37 (23)	22 (26)
No gross residual disease	123 (76)	62 (73)
Unknown	1 (< 1)	1 (1)
Interval cytoreductive surgery	94 (36)	43 (33)
Residual macroscopic disease	18 (19)	7 (16)
No gross residual disease	76 (81)	36 (84)
No surgery before random assignment	4 (1)	3 (2)

PAOLA-1: Outcome According to Clinical Risk

• Lower risk:
Stage III + PDS + NED



• Higher risk
FIGO Stage III + PDS + RT> 0
NACT
FIGO Stage IV



Harter P, et al. *Gynecol Oncol (2022)*

Gynecologic Oncology 166 (2022) 36–43

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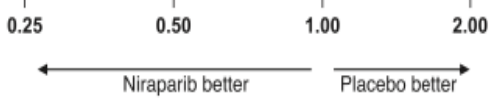
Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Efficacy of niraparib by time of surgery and postoperative residual disease status: A post hoc analysis of patients in the PRIMA/ ENGOT-OV26/GOG-3012 study

Roisin E. O'Cearbhaill [a,*], Jose-Alejandro Pérez-Fidalgo [b], Bradley J. Monk [c], Ignacio Tusquets [d], Colleen McCormick [e,1], Jose Fuentes [f], Richard G. Moore [g], Christof Vulsteke [h], Mark S. Shahin [i], Frédéric Forget [j], William H. Bradley [k], Sakari Hietanen [l], David M. O'Malley [m], Anne Dørum [n], Brian M. Slomovitz [o], Klaus Baumann [p], Frédéric Selle [q], Paula M. Calvert [r], Grazia Artioli [s], Tally Levy [t], Aalok Kumar [u], Izabela A. Malinowska [v], Yong Li [v,2], Divya Gupta [v], Antonio González-Martín [w]

	Niraparib		Placebo		Difference in mPFS, mo	Hazard ratio for PFS (95% CI)
	n/N[a]	mPFS, mo	n/N[a]	mPFS, mo		
Overall population						
All patients	232/487	13.8	155/246	8.2	5.6	0.62 (0.50–0.76)
PDS						
All PDS	77/158	13.7	48/78	8.2	5.5	0.67 (0.47–0.96)
VRD	62/124	11.8	41/59	7.8	4.0	0.58 (0.39–0.86)
NACT/IDS						
All NACT/IDS	145/316	14.2	105/165	8.2	6.0	0.57 (0.44–0.73)
NVRD	82/202	18.2	57/102	10.9	7.3	0.65 (0.46–0.91)
VRD	53/96	11.1	42/53	5.6	5.5	0.41 (0.27–0.62)
Postoperative residual disease status						
All NVRD	92/224	18.2	62/117	11.0	7.2	0.70 (0.50–0.96)
All VRD	115/220	11.2	83/112	5.7	5.5	0.50 (0.38–0.67)



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 19, 2019 VOL. 381 NO. 25

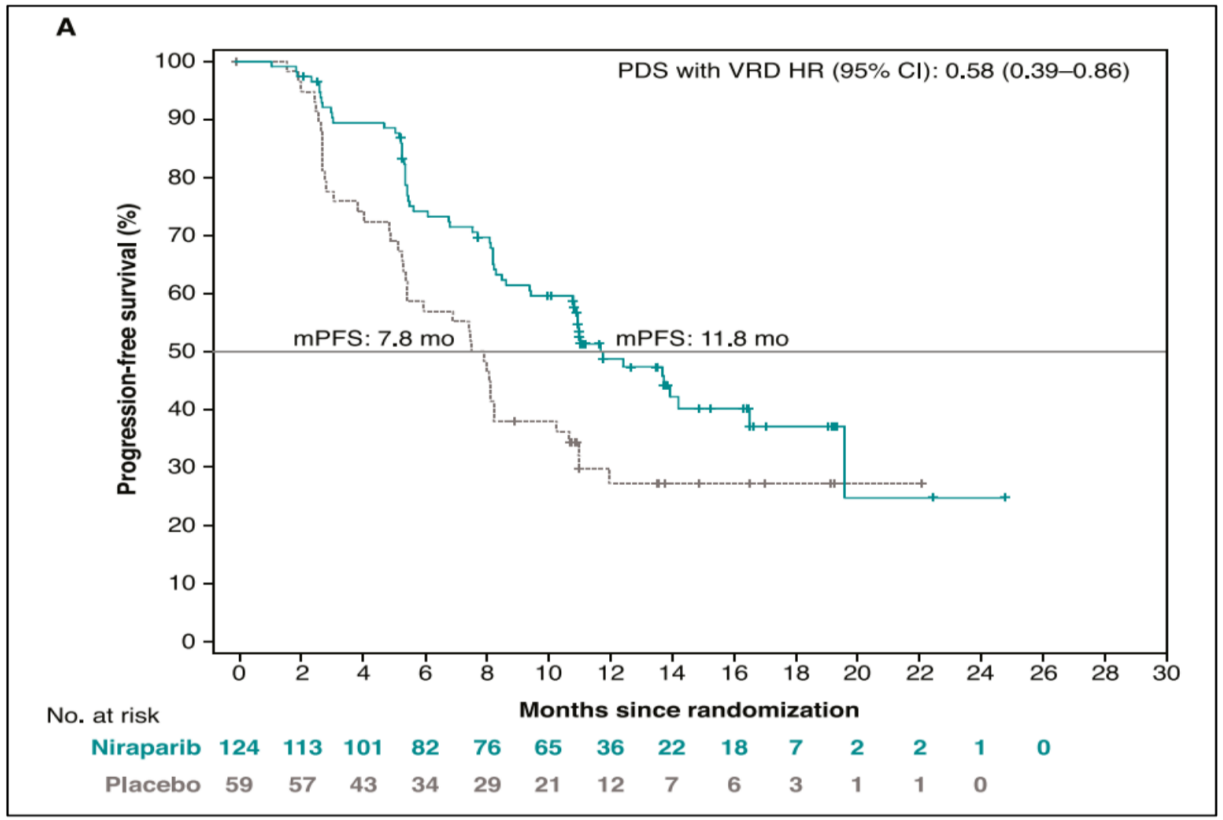
Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

A. González-Martín, B. Pothuri, I. Vergote, R. DePont Christensen, W. Graybill, M.R. Mirza, C. McCormick, D. Lorusso, P. Hoskins, G. Freyer, K. Baumann, K. Jardon, A. Redondo, R.G. Moore, C. Vulsteke, R.E. O'Cearbhaill, B. Lund, F. Backes, P. Barretina-Ginesta, A.F. Haggerty, M.J. Rubio-Pérez, M.S. Shahin, G. Mangili, W.H. Bradley, I. Bruchim, K. Sun, I.A. Malinowska, Y. Li, D. Gupta, and B.J. Monk, for the PRIMA/ENGOT-OV26/GOG-3012 Investigators*

PRIMA study

- Niraparib demonstrated efficacy in both patients with **visible and nonvisibile residual disease at interval cytoreduction**
- Patients who had NACT/IDS and visible tumor load had the highest **reduction in the risk of progression** with niraparib manteinance

PRIMA: Outcome According to Timing of Surgery and RT



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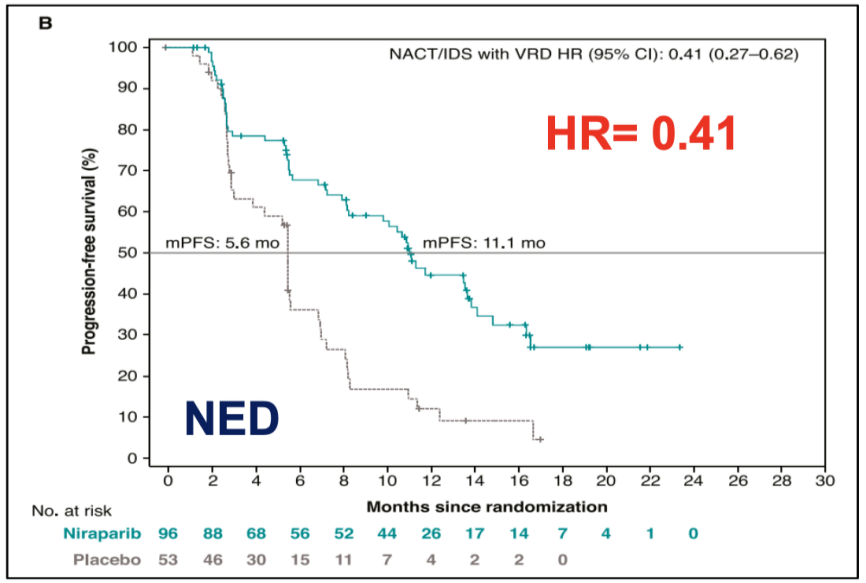
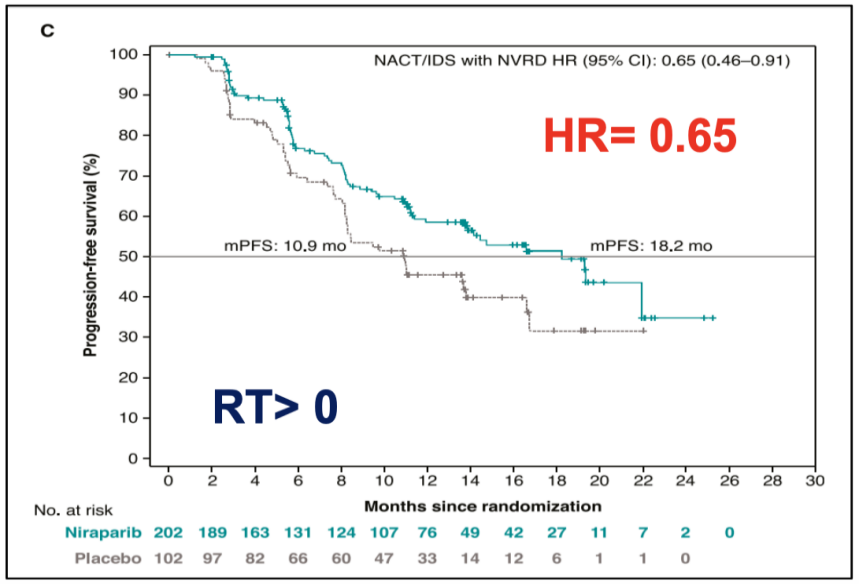


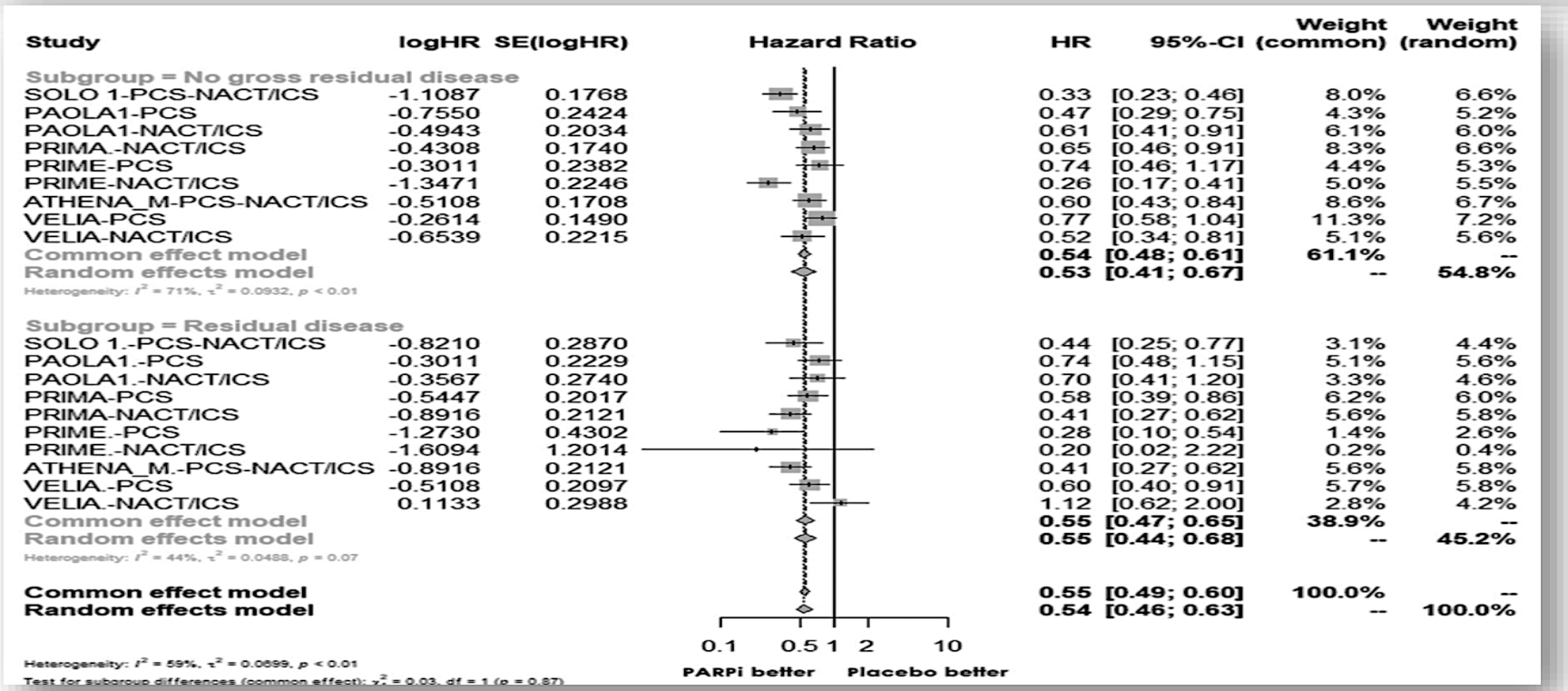


O'Cearbhaill RE, et al. *Gynecol Oncol (2022)*

Cytoreductive surgery for advanced epithelial ovarian cancer in the poly(ADP-ribose) polymerase inhibitors era—Is it time for a new paradigm shift? A systematic review and meta-analysis

Inge T.A. Peters [a,b], Claudia Marchetti [a,b], Antonella De Palma [a,b], Diana Giannarelli [c], Antonella Carcagnì [c], Giovanni Scambia [a,b], Anna Fagotti [a,b,*]

European Journal of Cancer 187 (2023)



- SOLO1
- PAOLA1
- PRIMA
- PRIME
- ATHENA-MONO
- VELIA

Conclusions: Patients with macroscopic residual disease benefit from PARPi at the same extent as cases with complete gross resection. However, patients with complete gross resection who were treated with PARPi show the most favourable PFS rates. Hence, the pursuit of achieving complete cytoreduction remains valid in the PARPi era.

PARP-I and SECONDARY CYTOREDUCTION

RECURRENCES ARE CHANGING OVER TIME with the advent of maintenance therapies

		% P-Part Sens after maintenance	% P-Res after maintenance
ICON 7	BEV+ BEV-	25 20	15 30
SOLO-1	BRCAmut / OLA-	25-30	20
	BRCAmut /OLA+	**10** ⬇	**5** ⬇
PRIMA	All pts / NIRA-	25	40
	All pts / NIRA+	**15** ⬇	**20** ⬇
PAOLA-1	All pts / BEV+	20	15
	All pts / BEV+OLA+	**10** ⬇	**10** ⬇
	*HRD-/ukn /BEV+OLA-	20	15

CYTOREDUCTIVE SURGERY in relapsed ovarian cancer: HOW?

Randomized Controlled Trial > N Engl J Med. 2021 Dec 2;385(23):2123-2131.
doi: 10.1056/NEJMoa2103294.

Randomized Trial of Cytoreductive Surgery for Relapsed Ovarian Cancer

Philipp Harter [1], Jalid Sehouli [1], Ignace Vergote [1], Gwenael Ferron [1], Alexander Reuss [1], Werner Meier [1], Stefano Greggi [1], Berit J Mosgaard [1], Frederic Selle [1], Frédéric Guyon [1], Christophe Pomel [1], Fabrice Lécuru [1], Rongyu Zang [1], Elisabeth Avall-Lundqvist [1], Jae-Weon Kim [1], Jordi Ponce [1], Francesco Raspagliesi [1], Gunnar Kristensen [1], Jean-Marc Classe [1], Peter Hillemanns [1], Pernille Jensen [1], Annette Hasenburg [1], Sadaf Ghaem-Maghami [1], Mansoor R Mirza [1], Bente Lund [1], Alexander Reinthaller [1], Ana Santaballa [1], Adeola Olaitan [1], Felix Hilpert [1], Andreas du Bois [1], DESKTOP III Investigators

Conclusions: In women with recurrent ovarian cancer, cytoreductive surgery followed by chemotherapy resulted in longer overall survival than chemotherapy alone. (Funded by the AGO Study Group and others; DESKTOP III ClinicalTrials.gov number, NCT01166737.).

DESKTOP III

Three trials conflicting data on the value of secondary cytoreduction in PSROC:

1) **GOG0213** trial :SCR did not improve overall survival (OS)

2) **Desktop III** trial the opposite results

3) **SOC-1** study reported an improved PFS in the surgery group, but the OS was immature

Point in common:
first platinum-sensitive recurrence

	GOG 213	DESTKOP III	SOC 1
Country	US, South Korea	Europe	China
N° pts	485	407	357
Accrual	10 y	4 y	7 y
N° Centre	51	87	4
Type of clinical trial	[illegible]	Surgery	[illegible]
Selection Criteria	[illegible]	ECOG0 No A[illegible]e RT=0 [illegible]ary surgery	[illegible]
Median PFI	19.7 m	20 m	16.1 m
Complete Resection	67%	75%	77%
PFS surgery+chemo chemo	2.7 m	4.4 m	5.5 m
OS surgery+chemo chemo	NS	7.5 m	4.2 m
Previous BEVA	11%	-	-
Previous PARPi	-	-	-
Crossover	?	11 %	37%
Maintenance Beva PARPi	84%	23% 5 %	1% 10 %
Stratification for BRCA status	no	no	no

- *Key different point:*

the use of targeted therapy

NO STRATIFICATION FOR BRCA

	GOG-213	SOC-1	DESKTOP-III
SELECTION OF PATIENTS	At Surgeon's Disretion	iMODEL score	AGO score
RATE OF COMPLETE CYTOREDUCTION	67%	77%	75.5%

SCS. Secondary cytoreductive surgery

Clinical Trial > Ann Surg Oncol. 2006 Dec;13(12):1702-10. doi: 10.1245/s10434-006-9058-0.

Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial

Philipp Harter [1], Andreas du Bois, Maik Hahmann, Annette Hasenburg, Alexander Burges, Sibylle Loibl, Martina Gropp, Jens Huober, Daniel Fink, Willibald Schröder, Karsten Muenstedt, Barbara Schmalfeldt, Guenter Emons, Jacobus Pfisterer, Kerstin Wollschlaeger, Hans-Gerd Meerpohl, Georg-Peter Breitbach, Berno Tanner, Jalid Sehouli, Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Committee; AGO Ovarian Cancer Study Group

Affiliations + expand

PMID: 17009163 DOI: 10.1245/s10434-006-9058-0

Combination of

- **PS**
- **Early FIGO stage initially**
- **No residual tumor after first surgery**
- **Absence of ascite**

Predict R0 in 79% of patients

AGO score

Parameter
Eastern Cooperative Oncology Group (ECOG)
Residual disease after primary surgery
Ascites
Localization of recurrence in preoperative diagnostics in pelvis
Residual disease after surgery for recurrence
Platinum-based chemotherapy after surgery for recurrence
Treatment-free interval < 6 months vs. 6–12 months
Treatment-free interval < 6 months vs. > 12 months

SCS. Secondary cytoreductive surgery

TIAN score

Ann Surg Oncol (2012) 19:597–604
DOI 10.1245/s10434-011-1873-2

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

A Risk Model for Secondary Cytoreductive Surgery in Recurrent Ovarian Cancer: An Evidence-Based Proposal for Patient Selection

Wen-Juan Tian, MD[1], Dennis S. Chi, MD[2], Jalid Sehouli, MD, PhD[3], Claes G. Tropé, MD, PhD[4], Rong Jiang, MD[1], Ali Ayhan, MD[5], Gennaro Cormio, MD, PhD[6], Yan Xing, MD, PhD, MSc[7], Georg-Peter Breitbach, MD, PhD[8], Elena Ioana Braicu, MD[3], Catherine A. Rabbitt, MMS[2], Halldis Oksefjell, MD, PhD[4], Christina Fotopoulou, MD, PhD[3], Hans-Gerd Meerpohl, MD, PhD[9], Andreas du Bois, MD, PhD[10], Jonathan S. Berek, MD, MMS[11], Rong-Yu Zang, MD, PhD[1], and Philipp Harter, MD, PhD[10]

- FIGO stage
- Residual disease after PDS
- PFI
- ECOG perfomance status
- CA 125
- Ascites at recurrence

Tian score 0-4.7

→ RISK GROUP → complete cytoreduction in 53.4% of cases

BRCA Mutation Status to Personalize Management of Recurrent Ovarian Cancer: A Multicenter Study

Claudia Marchetti, PhD[1], Rossella De Leo, MD[2], Angela Musella, PhD[1], Marco D'Indinosante, MD[2], Ettore Capoluongo, PhD[3], Angelo Minnucci, PhD[3], Pierluigi Benedetti Panici, PhD[1], Giovanni Scambia, PhD[2], and Anna Fagotti, PhD[2]

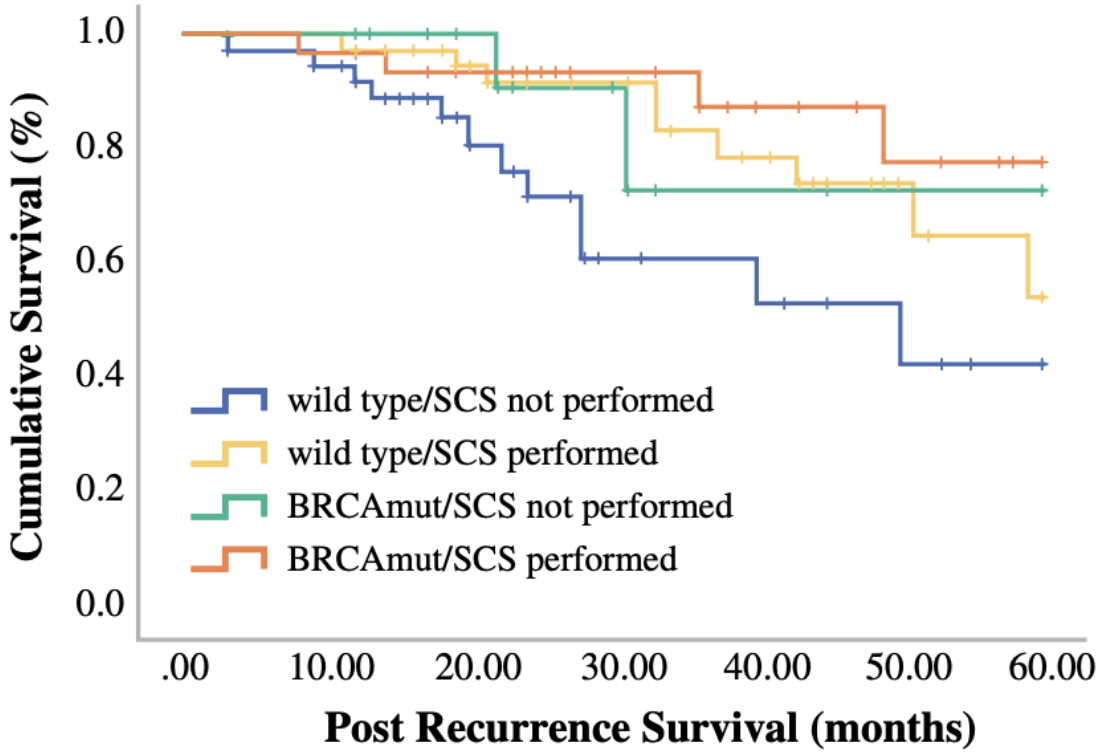
Ann Surg Oncol. 2018

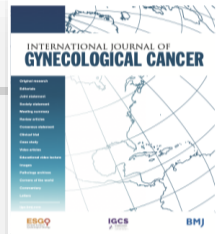
126 cases

«…Our results suggest that:

BRCAm patients
have the best prognosis regardless of SCS

BRCA wt women can improve their PRS after complete secondary cytoreduction…»





Cytoreductive surgery followed by chemotherapy and olaparib maintenance in BRCA 1/2 mutated recurrent ovarian cancer: a retrospective MITO group study

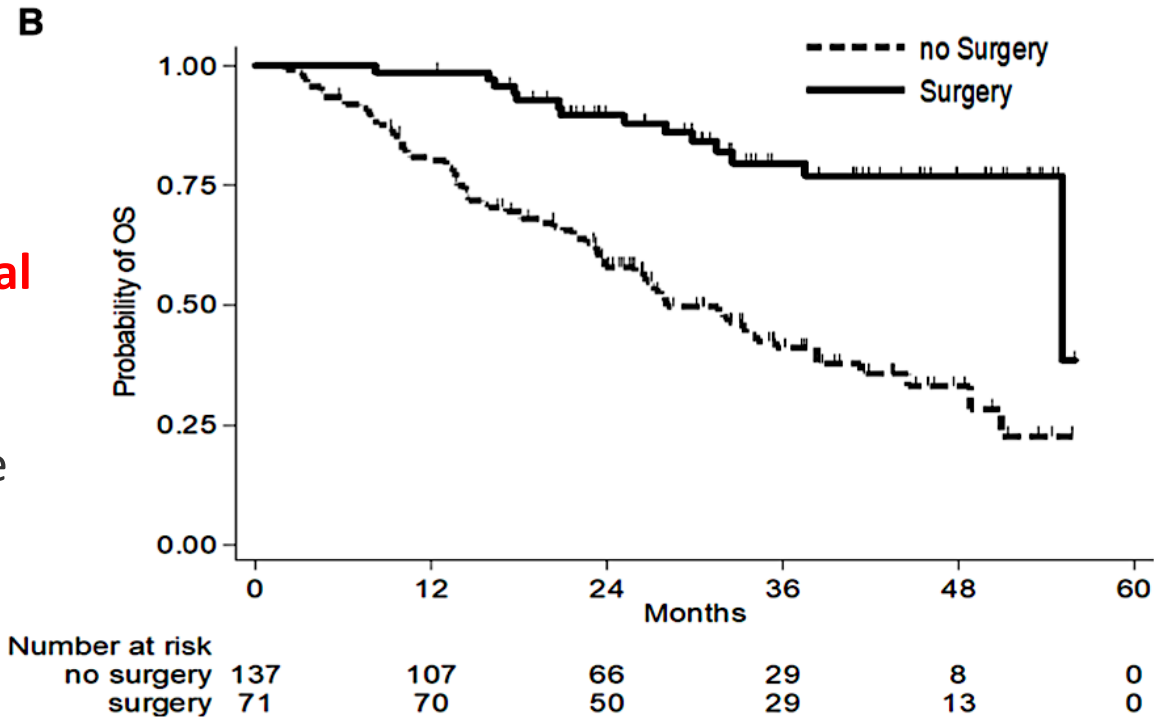
Sabrina Chiara Cecere,[1] Lucia Musacchio,[2,3] Michele Bartoletti ,[4,5] Vanda Salutari,[2] Laura Arenare,[6] Domenica Lorusso,[2,7,8] Graziana Ronzino,[9] Rossella Lauria,[10] Gennaro Cormio,[11] Emanuele Naglieri,[12] Paolo Scollo,[13] Claudia Marchetti,[2] Francesco Raspagliesi,[8] Stefano Greggi,[14] Saverio Cinieri,[15] Alice Bergamini ,[16,17] Michele Orditura,[18] Giorgio Valabrega,[19,20] Giovanni Scambia,[2,7] Fabio Martinelli ,[8] Elisabetta De Matteis,[9] Cinzia Cardalesi,[10] Vera Loizzi,[11] Giorgia Perniola,[3] Claudia Carella,[21] Giuseppa Scandurra,[13] Gaia Giannone,[19,20] Sandro Pignata[1]

2021

BRCA mut patients

Summary

Our data showed that **patients undergoing surgery at the time of epithelial ovarian cancer recurrence before starting platinum therapy and olaparib maintenance had longer overall survival and progression-free survival compared with those receiving only medical therapies**. Although the retrospective nature of the data does not allow for definitive conclusions, we hypothesize that the removal of chemo/PARP inhibitors-resistant cells by surgery may determine better outcomes from maintenance therapy.



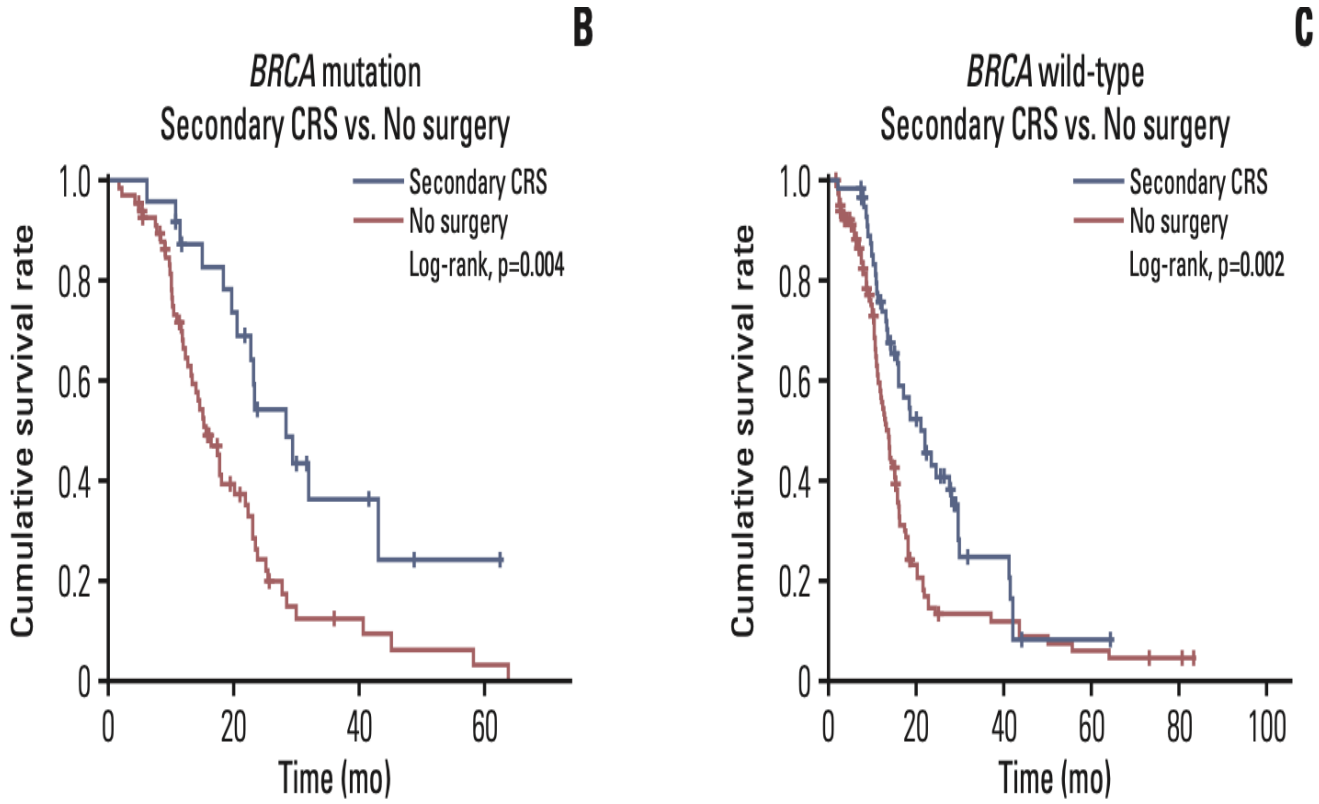
Cancer Res Treat. 2023;55(1):245-257

Effect of *BRCA1/2* Mutational Status on Survival Outcomes According to Secondary Cytoreductive Surgery and Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer: A Real-World Evidence Study

Se Ik Kim[1], Hyunji Lim[1], Hee Seung Kim[1], Hyun Hoon Chung[1], Jae-Weon Kim[1], Noh Hyun Park[1], Yong-Sang Song[1], Maria Lee[1,2]

Single center retrospective study – 262 patients, 91 (34.7%) BRCA1/2m

SCS improved PFS, regardless of BRCA status (p 0.074 e p 0.222)



PATTERNS OF INITIAL OVARIAN CANCER RECURRENCE ON NIRAPARIB MAINTENANCE MONOTHERAPY IN PATIENTS WITH NO BASELINE EVIDENCE OF DISEASE FOLLOWING FIRST LINE CHEMOTHERAPY

PRIMA/ENGOT-ov26/GOG-3012: 314/487 (64,5%) PATIENTS

# of lesions at the time of PD	# of patients (%)
1	62 (44%)
2	46 (33%)
3	24 (17%)
4-5	9 (6%)

- Median follow up: 13.8 mo
- 141/314 (45%) pts had PD
- Average 1.9 (SD 0.9) lesions at PD

RECURRENCE AFTER PARP-I OFTEN APPEARS TO BE OLIGOMETASTATIC

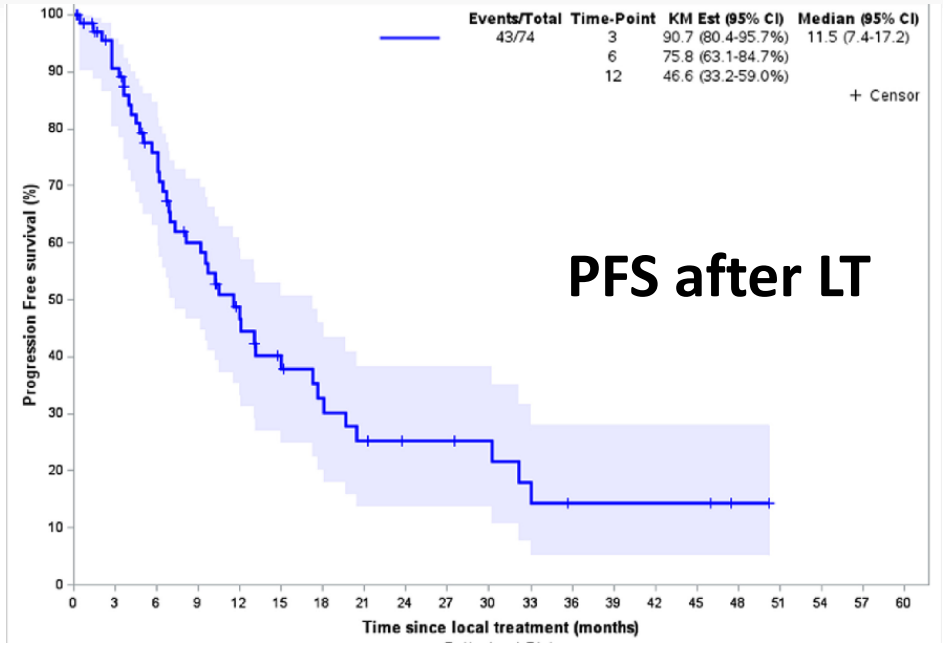
- > 75% of pts with recurrence progressed in 1-2 sites

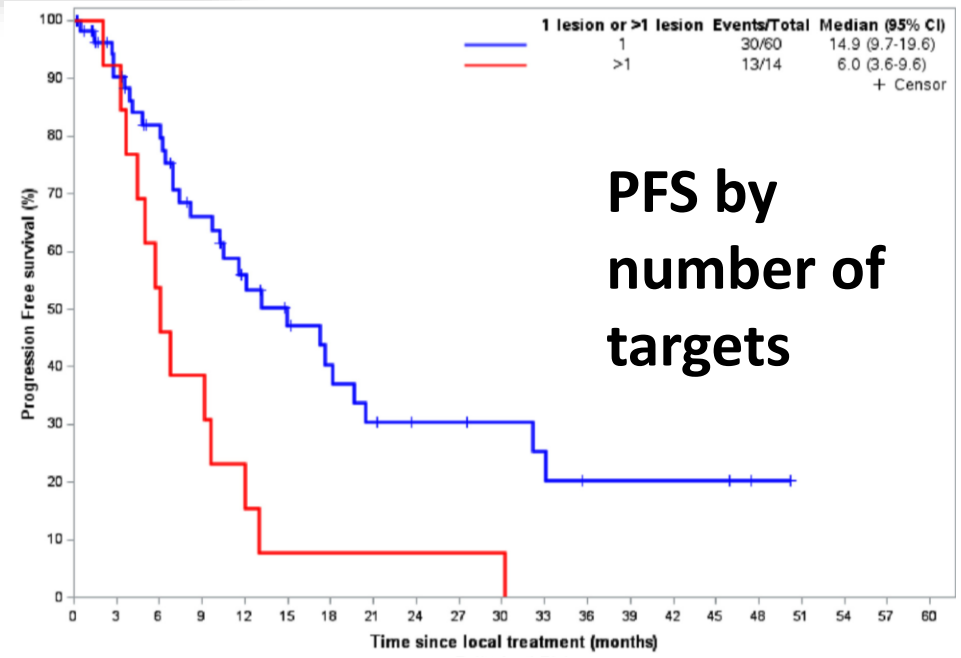
Gynecologic Oncology 173 (2023) 98–105

PARP inhibitors (PARPi) prolongation after local therapy for oligo-metastatic progression in relapsed ovarian cancer patients

Thibault Gauduchon [a], Maria Kfoury [b], Domenica Lorusso [c], Anne Floquet [d], Jole Ventriglia [e], Hélène Salaun [f], Malak Moubarak [g], Romain Rivoirard [h], Laura Polastro [i], Laure Favier [j], Benoit You [k,u], Dominique Berton [l], Thibault de la Motte Rouge [m], Laura Mansi [n], Cyril Abdeddaim [o], Karine Prulhiere [p], Laurence Lancry Lecomte [q], Magali Provansal [r], Cécile Dalban [s], Isabelle Ray-Coquard [a,t,*]

Multicenter retrospective study: 74 patients with oligoprogression





…. the re-introduction of PARPi after local progression treated locally is feasible and reporting a median PFS of 11.5 months can be considered as an interesting option for selected patients.

It should be noted that this strategy might be best in the setting of single site oligometastatic disease but probably less useful in multisite disease.

Concordance between CA-125 and RECIST progression in patients with germline *BRCA*-mutated platinum-sensitive relapsed ovarian cancer treated in the SOLO2 trial with olaparib as maintenance therapy after response to chemotherapy☆

Angelina Tjokrowidjaja [a,b,*], Chee K. Lee [a,b], Michael Friedlander [c], Val Gebski [a], Laurence Gladieff [d], Jonathan Ledermann [e], Richard Penson [f], Amit Oza [g], Jacob Korach [h], Tomasz Huzarski [i], Luis Manso [j], Carmela Pisano [k], Rebecca Asher [a], Sarah J. Lord [a,l], Se Ik Kim [m], Jung-Yun Lee [n], Nicoletta Colombo [o,p], Tjoung-Won Park-Simon [q], Keiichi Fujiwara [r], Gabe Sonke [s], Ignace Vergote [t,u], Jae-Weon Kim [m], Eric Pujade-Lauraine [v,w]

European Journal of Cancer, 2020

Disease status according to S-Ca125	RECIST-defined PD (n=171)	No RECIST-defined PD (n=104)	Total (n=275)
Progressive disease,	77 (96%)	3 (4%)	80
Non-progressive	94 (48%)	101 (52%)	195

FOLLOWING CA125 WITHOUT ROUTINE IMAGING COULD LEAD TO A MISSING RATE OF DIAGNOSIS OF 50%

Multicenter Study > Gynecol Oncol. 2020 Jan;156(1):38-44. doi: 10.1016/j.ygyno.2019.10.023. Epub 2019 Nov 4.

Olaparib as maintenance therapy in patients with BRCA 1-2 mutated recurrent platinum sensitive ovarian cancer: Real world data and post progression outcome

Sabrina Chiara Cecere [1], Gaia Giannone [2], Vanda Salutari [3], Laura Arenare [4], Domenica Lorusso [5], Graziana Ronzino [6], Rossella Lauria [7], Gennaro Cormio [8], Claudia Carella [9], Paolo Scollo [10], Viola Ghizzoni [3], Francesco Raspagliesi [5], Marilena Di Napoli [1], Enrica Mazzoni [11], Claudia Marchetti [12], Alice Bergamini [13], Michele Orditura [14], Giorgio Valabrega [2], Giovanni Scambia [3], Giuseppa Maltese [5], Elisabetta De Matteis [6], Cinzia Cardalesi [7], Vera Loizzi [8], Serena Boccia [12], Emanuele Naglieri [9], Giuseppa Scandurra [10], Sandro Pignata [15]

> Anticancer Drugs. 2021 Nov 1;32(10):1086-1092. doi: 10.1097/CAD.0000000000001219.

PARP inhibitors decrease response to subsequent platinum-based chemotherapy in patients with BRCA mutated ovarian cancer

Peter G Rose [1 2], Meng Yao [3], Laura M Chambers [1 2], Haider Mahdi [1 2], Robert DeBernardo, Roberto Vargas [1 2]

828P **Expected versus observed response to platinum-based chemotherapy after poly (ADP-ribose) polymerase inhibitor treatment for relapsed ovarian cancer**

T. Baert[1], B. Ataseven[1], M. Bommert[1], N. Concin[2], J. Frindte[1], S. Schneider[1], P. Harter[1], A. du Bois[1], F. Heitz[1]

[1]*Gynaecology Oncology Department, Kliniken Essen Mitte Evang. Huyssens-Stiftung, Essen, Germany;* [2]*Department of Gynaecological Oncology, Medical University of Innsbruck, Innsbruck, Austria*

> Cancers (Basel). 2022 Sep 11;14(18):4414. doi: 10.3390/cancers14184414.

Multicenter Real-World Data of Subsequent Chemotherapy after Progression to PARP Inhibitors in a Maintenance Relapse Setting

Margarita Romeo [1], Marta Gil-Martín [2], Lydia Gaba [3], Iris Teruel [1], Álvaro Taus [4], Claudia Fina [5], Maria Masvidal [6], Paola Murata [7], Julen Fernández-Plana [8], Alejandro Martínez [9], Cristina Pérez [10], Yolanda García [11], Valerie Rodriguez [12], Sara Cros [13], Marta Parera [14], Montserrat Zanui [15], Silvia Catot [16], Beatriz Pardo [2], Andrea Plaja [1], Anna Esteve [17], Maria Pilar Barretina-Ginesta [5]

Randomized Controlled Trial > Ann Oncol. 2022 Oct;33(10):1021-1028. doi: 10.1016/j.annonc.2022.06.011. Epub 2022 Jun 27.

Efficacy of subsequent chemotherapy for patients with BRCA1/2-mutated recurrent epithelial ovarian cancer progressing on olaparib versus placebo maintenance: post-hoc analyses of the SOLO2/ENGOT Ov-21 trial

J S Frenel [1], J W Kim [2], N Aryal [3], R Asher [3], D Berton [4], L Vidal [5], P Pautier [6], J A Ledermann [7], R T Penson [8], A M Oza [9], J Korach [10], T Huzarski [11], S Pignata [12], N Colombo [13], T W Park-Simon [14], K Tamura [15], G S Sonke [16], A E Freimund [17], C K Lee [3], E Pujade-Lauraine [18]

Retrospective studies and post-hoc analysis suggested that there is worse response to platinum-based chemotherapy, especially in BRCAm

Acquired resistance to PARP-I overlaps with platinum resistance

Recurrence setting for all studies…can we imply this mechanism for first line too?
PROSPECTIVE STUDIES ARE NEEDED

FUTURE PROSPECTIVE

Clinical trial

Olaparib beyond progression compared with platinum chemotherapy after secondary cytoreductive surgery in patients with recurrent ovarian cancer: phase III randomized, open-label MITO 35b study, a project of the MITO-MANGO groups

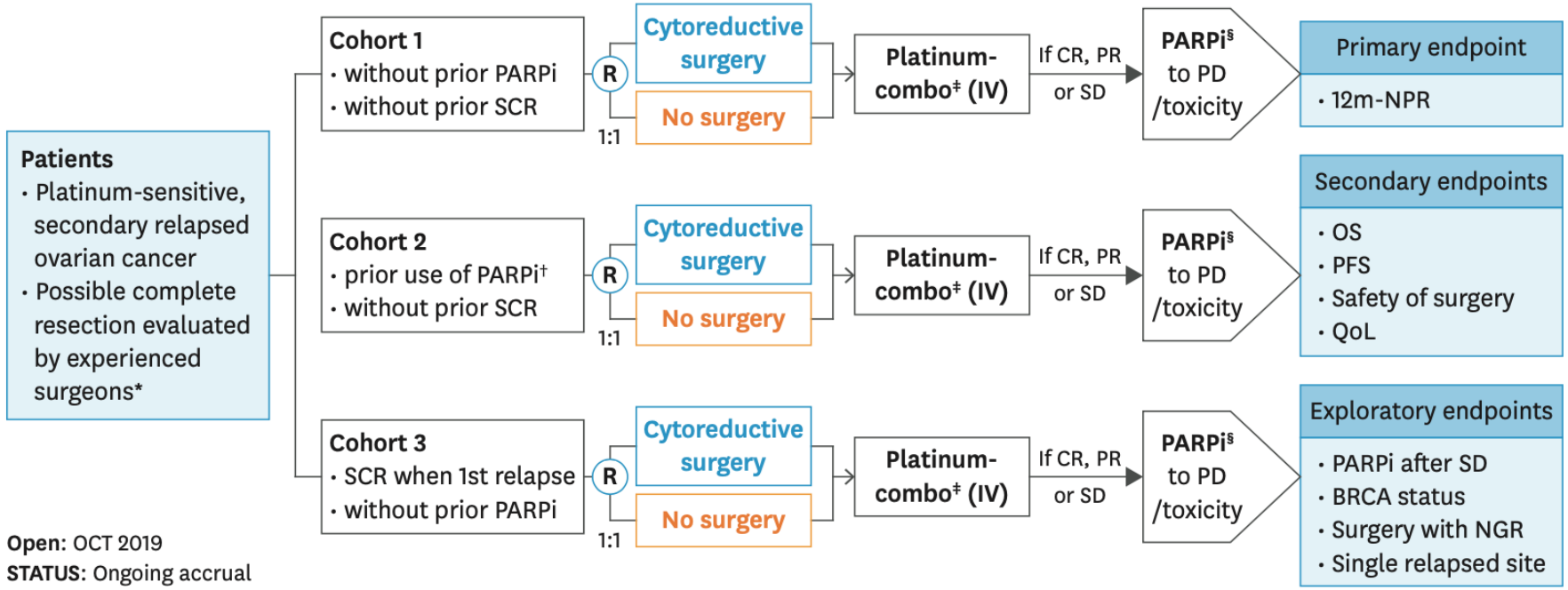
2022

Clorinda Schettino,[1] Lucia Musacchio,[2] Michele Bartoletti ,[3] Paolo Chiodini,[4] Laura Arenare,[1] Gustavo Baldassarre,[5] Daniela Califano,[6] Ettore Capoluongo,[7,8] Maria Paola Costi,[9] Maurizio D'Incalci,[10,11] Sergio Marchini,[11] Delia Mezzanzanica ,[12] Nicola Normanno,[13] Stefania Scala,[6] Stefano Greggi,[14] Francesco Perrone ,[1] Sandro Pignata[15]

Primary Objective To determine the efficacy of olaparib beyond progression compared with standard platinum-based chemotherapy in patients with recurrent ovarian cancer progressed during or after poly (ADP-ribose) polymerase inhibitor maintenance therapy after secondary cytoreductive surgery.

Study Hypothesis Olaparib administered beyond progression is more effective in increasing progression-free survival and progression-free survival 2 compared with second-line platinum-based chemotherapy in patients after secondary cytoreductive surgery.

2022 …ONGOING…



SOC-3 trial, impact of cytoreductive surgery and PARP inhibitor in platinum-sensitive secondary recurrent ovarian cancer: update to the study protocol for a phase II, multicentre, randomised umbrella trial

Tingyan Shi,[1] Libing Xiang,[1] Jianqing Zhu,[2] Jihong Liu,[3] Ping Zhang,[2] Huaying Wang,[4] Yanling Feng,[3] Tao Zhu,[2] Yingli Zhang,[2] Aijun Yu,[2] Wei Jiang,[5] Xipeng Wang,[6] Yaping Zhu,[7] Sufang Wu,[7] Yincheng Teng,[8] Jiejie Zhang,[2] Rong Jiang,[1] Wei Zhang,[9] Huixun Jia,[10] Rongyu Zang [1]

massive cytoreductive surgery followed by platinum-based chemotherapy plus niraparib maintenance therapy

leads to a survival benefit

compared with no-surgery group

in secondary recurrent ovarian cancer with different baseline information, especially confounded by the prior use of PARP inhibitor or prior SCR. >>

TAKE HOME MESSAGES

- Surgery is still essential in first line treatment
- No clear link between cytoreduction feasibility and BRCA status
- Different parp-i seem to show different efficacy in relation to the residual disease and the timing of the surgery
- SCS has still plays a role after PARPi maintenance
- Recurrence is frequently oligometastatic after PARPi and Surgical Local treatment is an effective approach under PARPi recurrence
- The role of CA 125 in follow up of PARPi-patients is still unclear and some recurrences might be missed if only CA125 is monitored;

Gynecologic Oncology Unit

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Thank You