PARSGO

The Pan-Arabian Research Society of Gynecological Oncology

GYNECOLOGIC CANCER INTERGROUP

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

Current concepts of maintenance therapy in recurrent ovarian cancer

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Disclosure

Funded Research: EU, FWF, Astra Zeneca, Roche

Honoraria/Expenses: Roche, Novartis, Amgen, MSD, Pharmamar, Astra Zeneca, Tesaro

Consulting/Advisory Board: Roche, Novartis, Amgen, MSD, Astra Zeneca, Pfizer, Pharmamar, Cerulean, Vertex, Tesaro

NCI Dictionary of Cancer Terms

Maintenance Therapy:

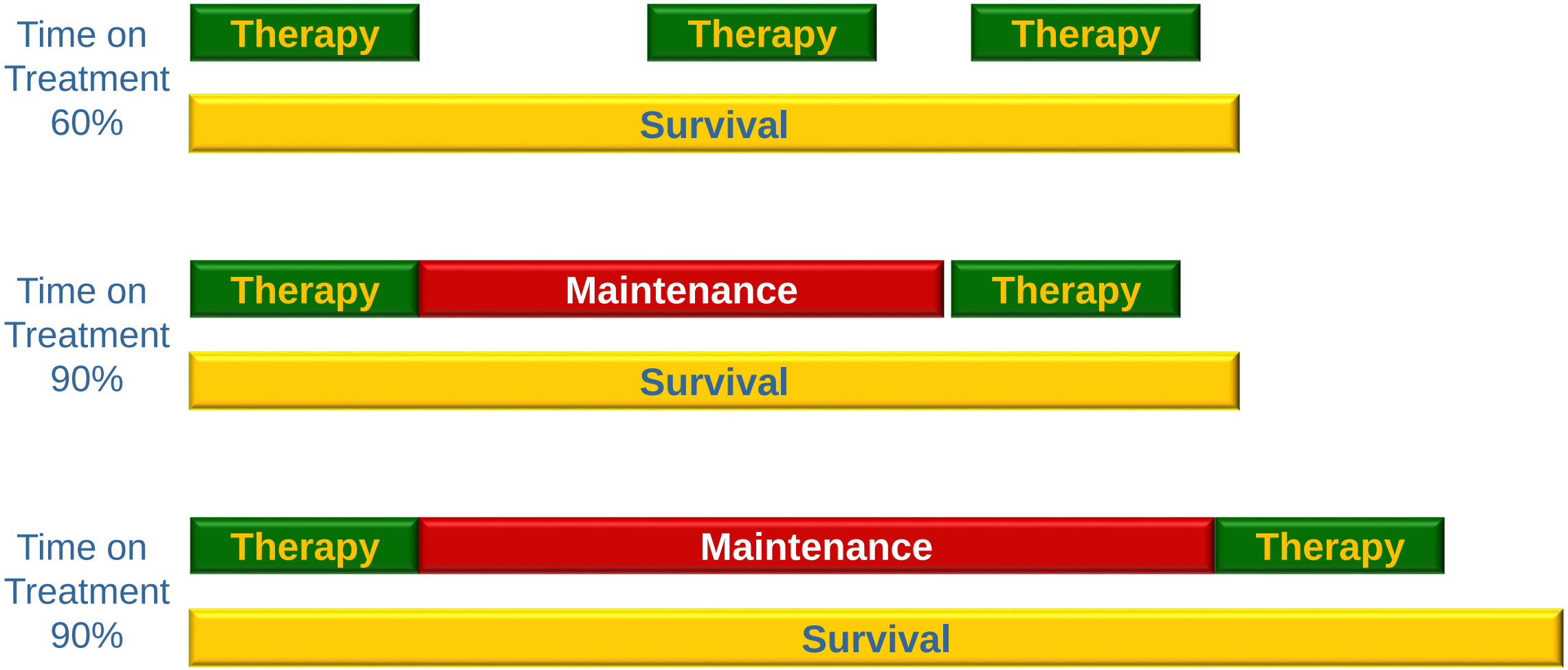
Treatment that is given to help…

- keep cancer from coming back…
- after it has disappeared following the initial therapy.
- It may include treatment with drugs, vaccines, or antibodies that kill cancer cells, and it may be given for a long time.

What is the aim of Maintenance Therapy?

1. Increasing Cure Rate ✓
2. Increasing Overall Survival ✓
3. Prolongation of Progression-free Survival ?
4. Improving the Quality of Life ?

Maintenance Therapy



Control Arm in Recurrent Ovarian Cancer

The choice of control arms for the subgroup of patients who can receive platinum must be supported by evidence and it must integrate available predictors and prior exposure, which may limit selection for further lines. This currently includes three potential control arms:

- Platinum combination
- Platinum combination with a licensed anti-angiogenic agent
- Platinum combination followed by a licensed PARP inhibitor

5. OCCC of the GCIG: recurrent disease. Wilson MK et al., Annals of Oncology 28: 727, 2017

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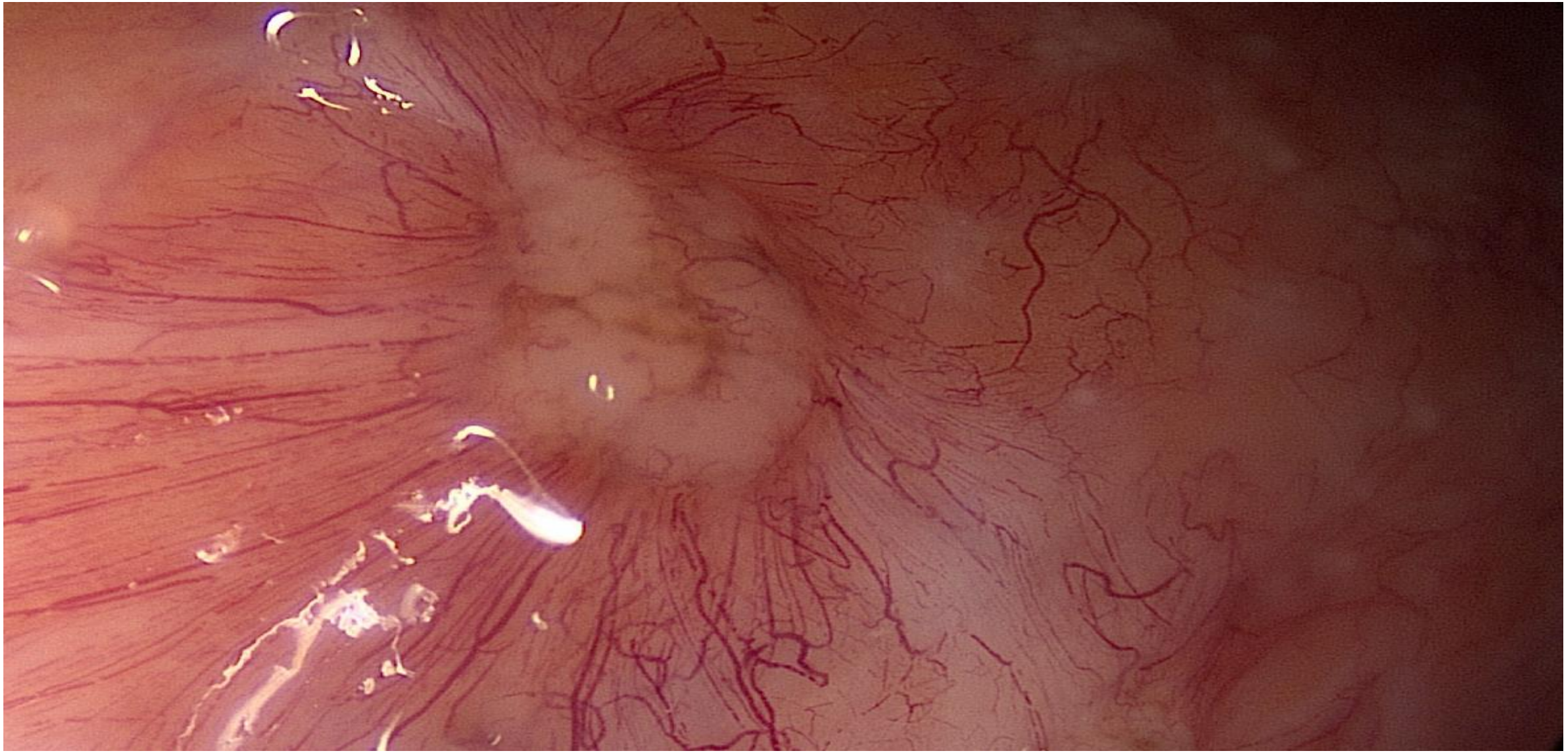
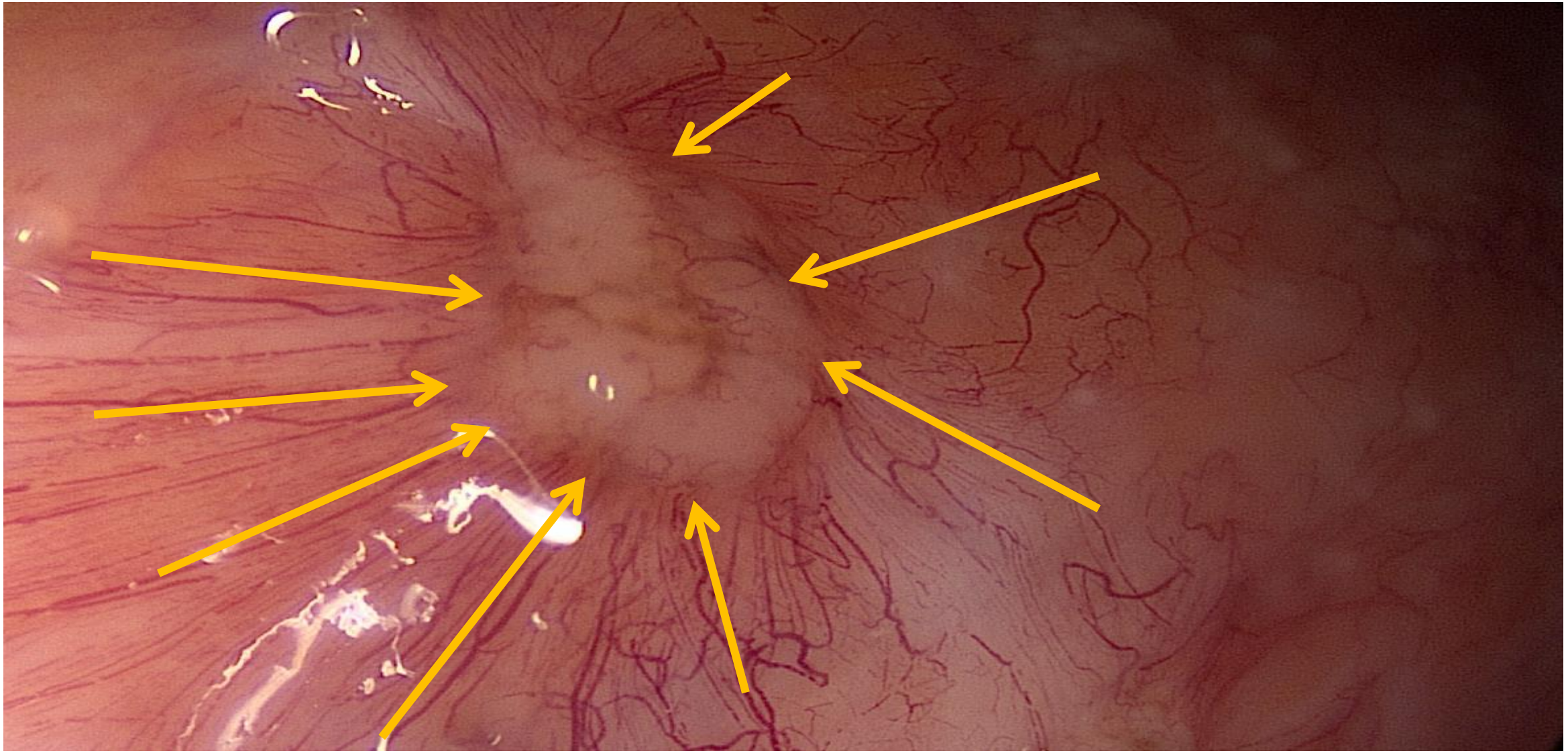
Ovarian Cancer Maintenance Therapy

1. Angiogenesis Inhibitors
2. PARP-Inhibitors
3. Immunotherapy

Ovarian Cancer: Peritoneal Carcinomatosis



Ovarian Cancer: Peritoneal Carcinomatosis



Phase 3 Studies of Angiogenesis Inhibitors in Patients With Recurrent Ovarian Cancer

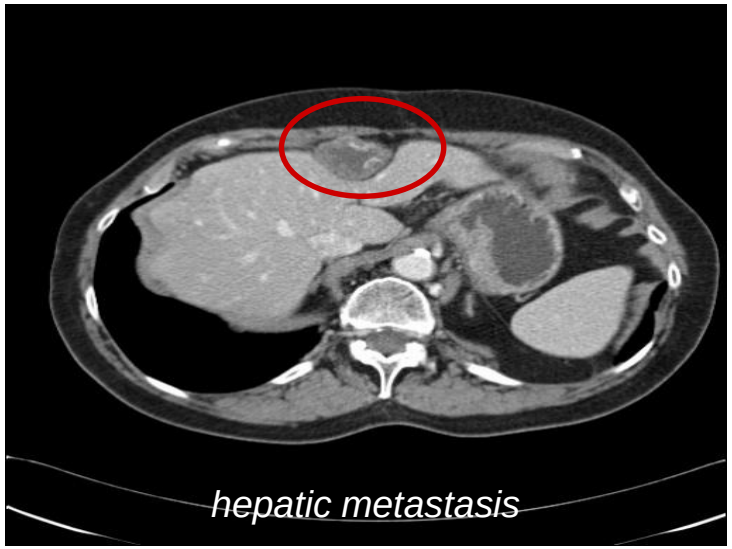
	PFI ≥ 6 months			PFI < 6 months		PFI 0–12 months	
Study	**OCEANS[1]**	**ICON6[2]**	**GOG-213[3]**	**AURELIA[4,5]**	**MITO-11[6]**	**TRINOVA-1[7,8]**	**ENGOT-OV6[9]**
Agent	**Bevacizumab**	**Cediranib**	**Bevacizumab**	**Bevacizumab**	**Pazopanib**	**Trebananib**	**Trebananib**
Difference in PFS, mo†	**4.0**	**3.2**	**3.4**	**3.3**	**2.9**	**1.8**	**0.4**
PFS HR	**0.48*****	**0.56*****	**0.61*****	**0.48****	**0.42****	**0.66*****	**0.92 (NS)**
Difference in OS, mo†	**–1.9**	**2.3**	**4.9**	**3.3**	**5.4**	**1.0**	**2.4**
OS HR	**1.03 (NS)**	**0.85 (NS)**	**0.83 (*P*=0.056)**	**0.85 (NS)**	**0.60 (NS)**	**0.95 (NS)**	**0.96 (NS)**

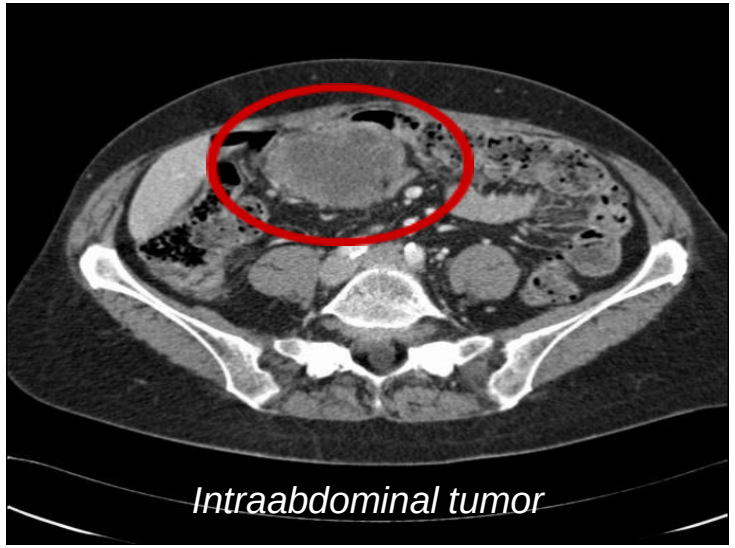
HR, hazard ratio; NS, not significant; PFI, platinum-free interval; PFS, progression-free survival; OS=overall survival. **P* < 0.05; ***P* < 0.01; ****P* < 0.0001; †Treatment versus control arm.

1. Aghajanian C, et al. *J Clin Oncol*. 2012;30:2039-2045.
2. Ledermann JA, et al. *Journal of Clinical Oncology 2017 35: 5506*.
3. Coleman, et al. *Gynecologic Oncol.* 2015;137:3-4.
4. Pujade-Lauraine E, et al. *J Clin Oncol.* 2014;32:1302.
5. Poveda AM, et al. *J Clin Oncol* 2015;63:1408.
6. Pignata S, et al. *Lancet Oncol* 2015;16:561-568.
7. Monk BJ, et al. *Lancet Oncol.* 2014;15:799-808.
8. Monk BJ, et al. *J Clin Oncol.* 2015; 33(15 S):5503.
9. Marth C et al., Eur J Cancer 2017;70:111-121

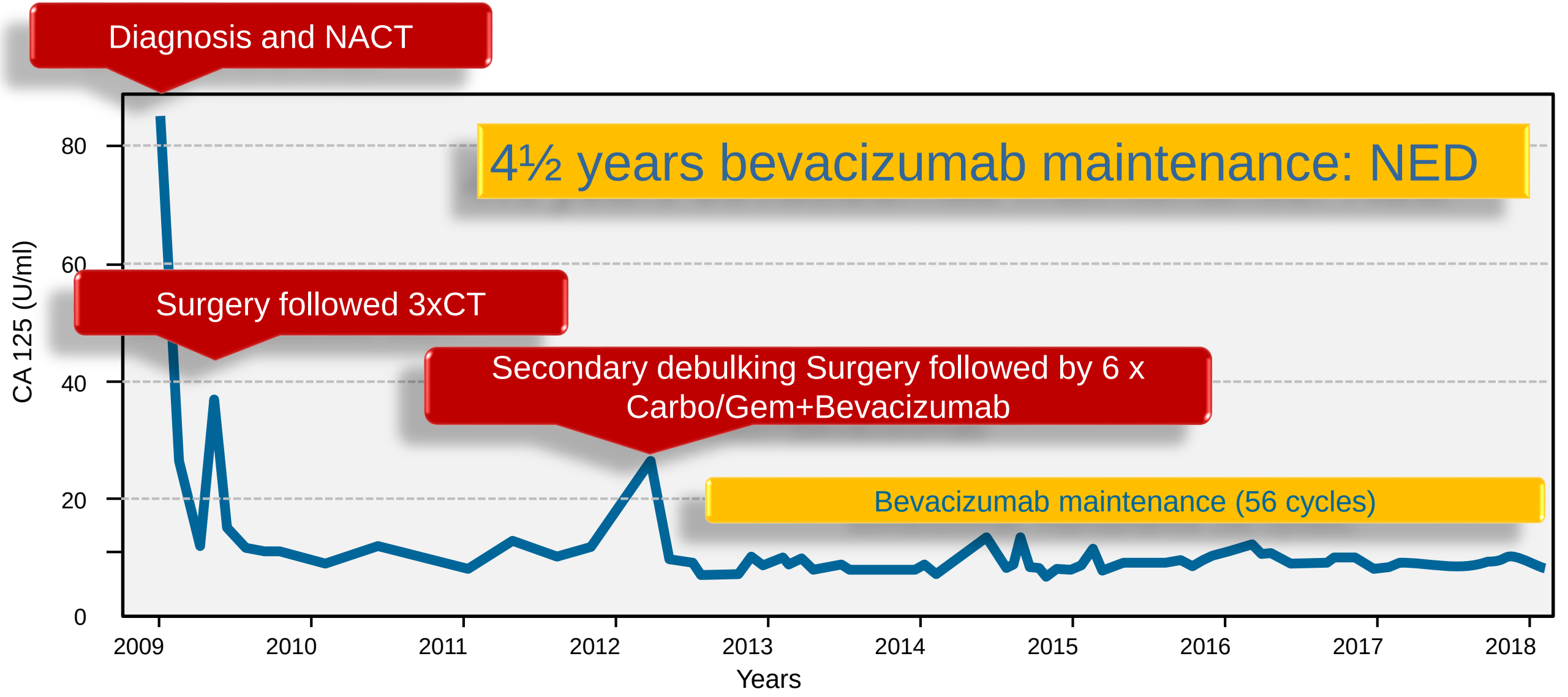
Case Report

- 08/2009
- 69 years
- Laparoscopy with biopsy: HGSOC
- 3 cycles Neo-Adjuvant Chemotherapy
- Complete Debulking
- 3 cycles Carboplatin/paclitaxel
- 05/2012
- Progression
- No gBRCA mutation
- Secondary debulking: No residual tumor
- 6 cycles Carboplatin/Gemcitabine plus Bevacizumab: NED
- Single agent Bevacizumab maintenance

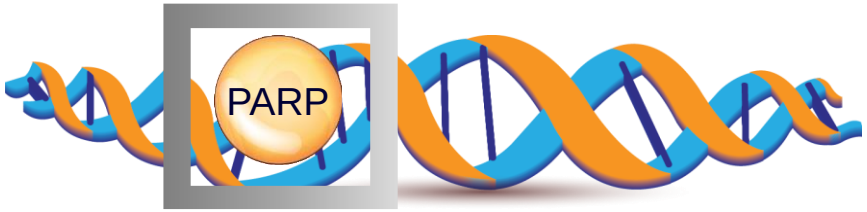




Case Report


Diagnosis and NACT
4½ years bevacizumab maintenance: NED
Surgery followed 3xCT
Secondary debulking Surgery followed by 6 x Carbo/Gem+Bevacizumab
Bevacizumab maintenance (56 cycles)
CA 125 (U/ml)
0
20
40
60
80
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Years

Mechanisms of Action of PARP-Inhibitors



Trapped PARP on single-strand breaks

Increase in double-strand breaks in replicating cells

Double-strand breaks

HRD

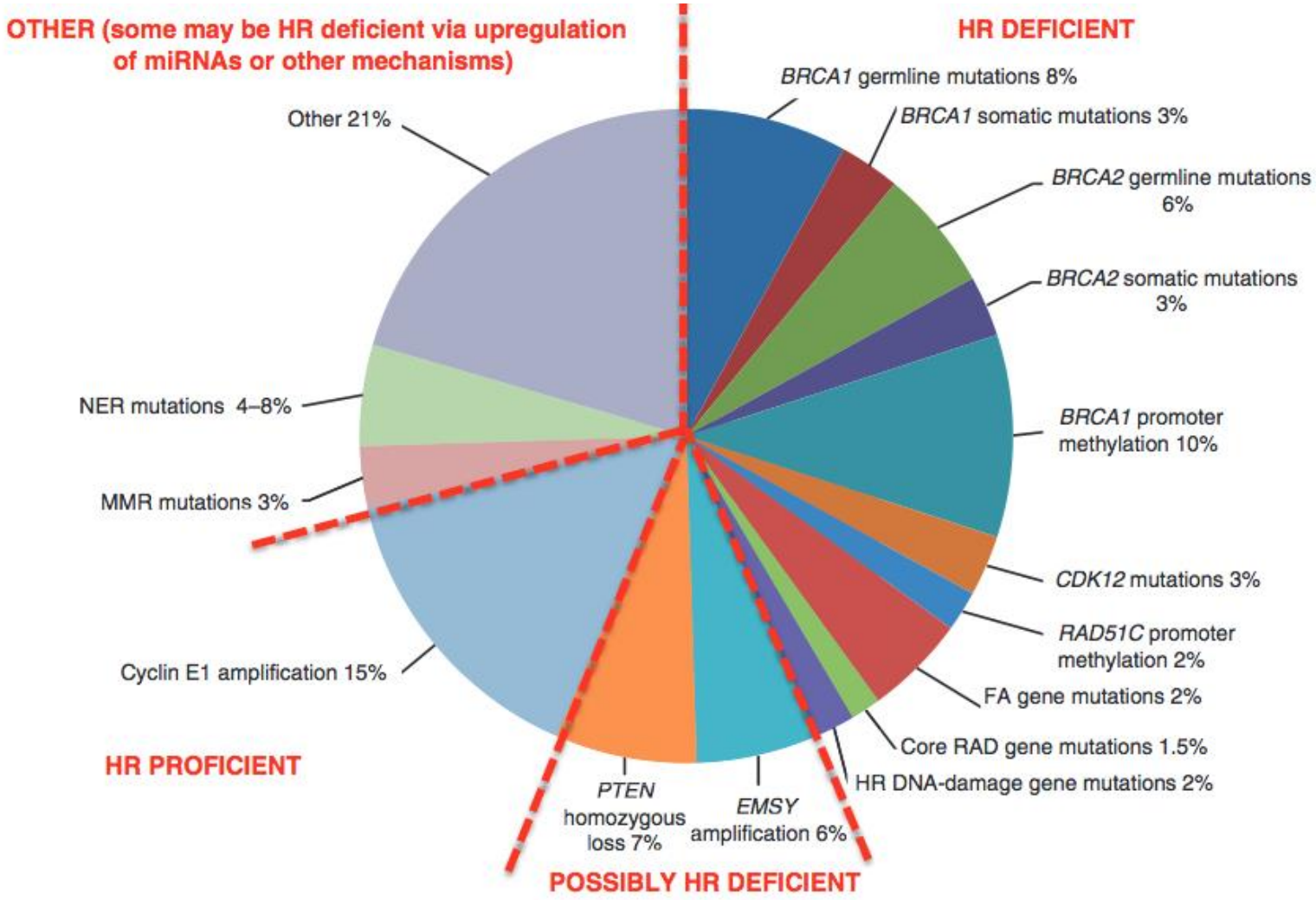
e.g. BRCA Mutation

Normal cell

Repair by homologous recombination

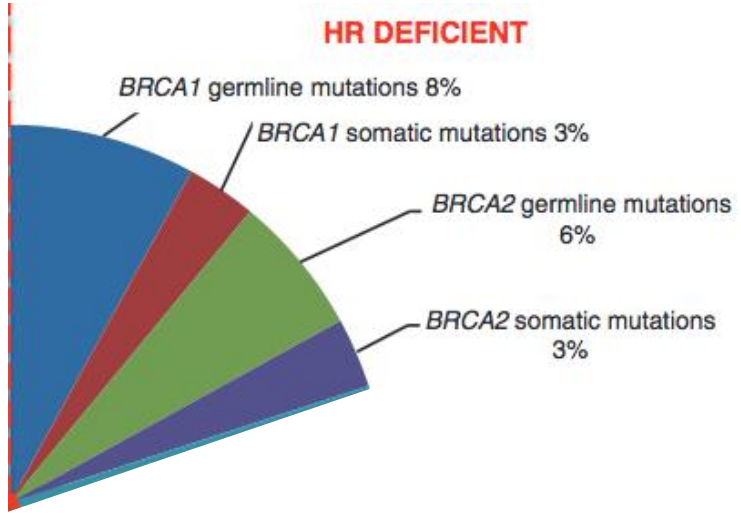
Murai J, et al. *Cancer Res.* 2012;72(21):5588-5599. Pommier Y, et al. *Sci Transl Med.* 2016;8(362):362ps17.

Using genomic biomarkers for HRD detection?



Konstantinopoulos, Nature 2011

Using genomic biomarkers for HRD detection?



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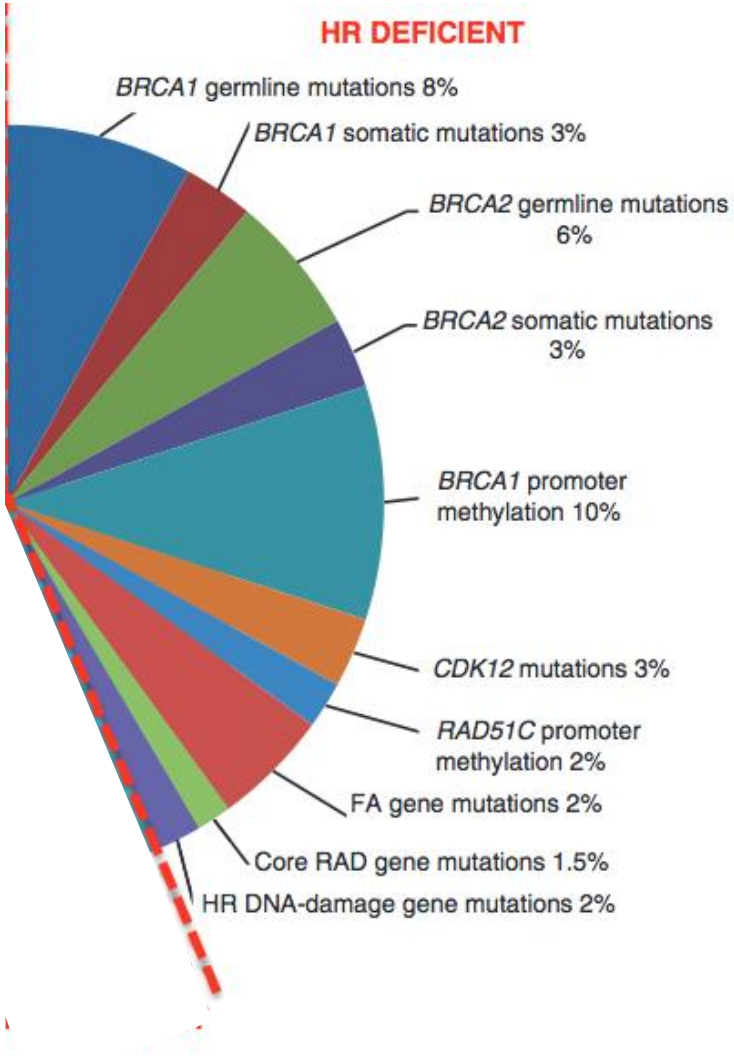

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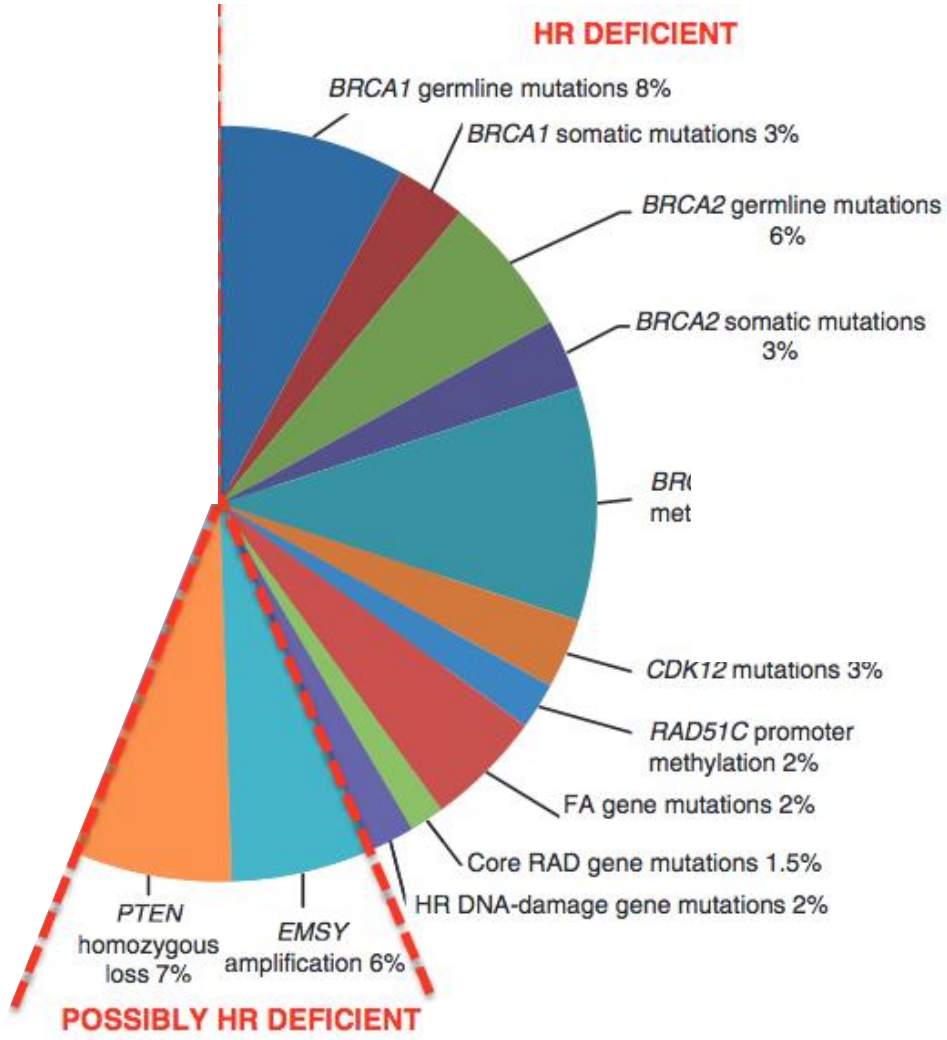

Konstantinopoulos, Nature 2011

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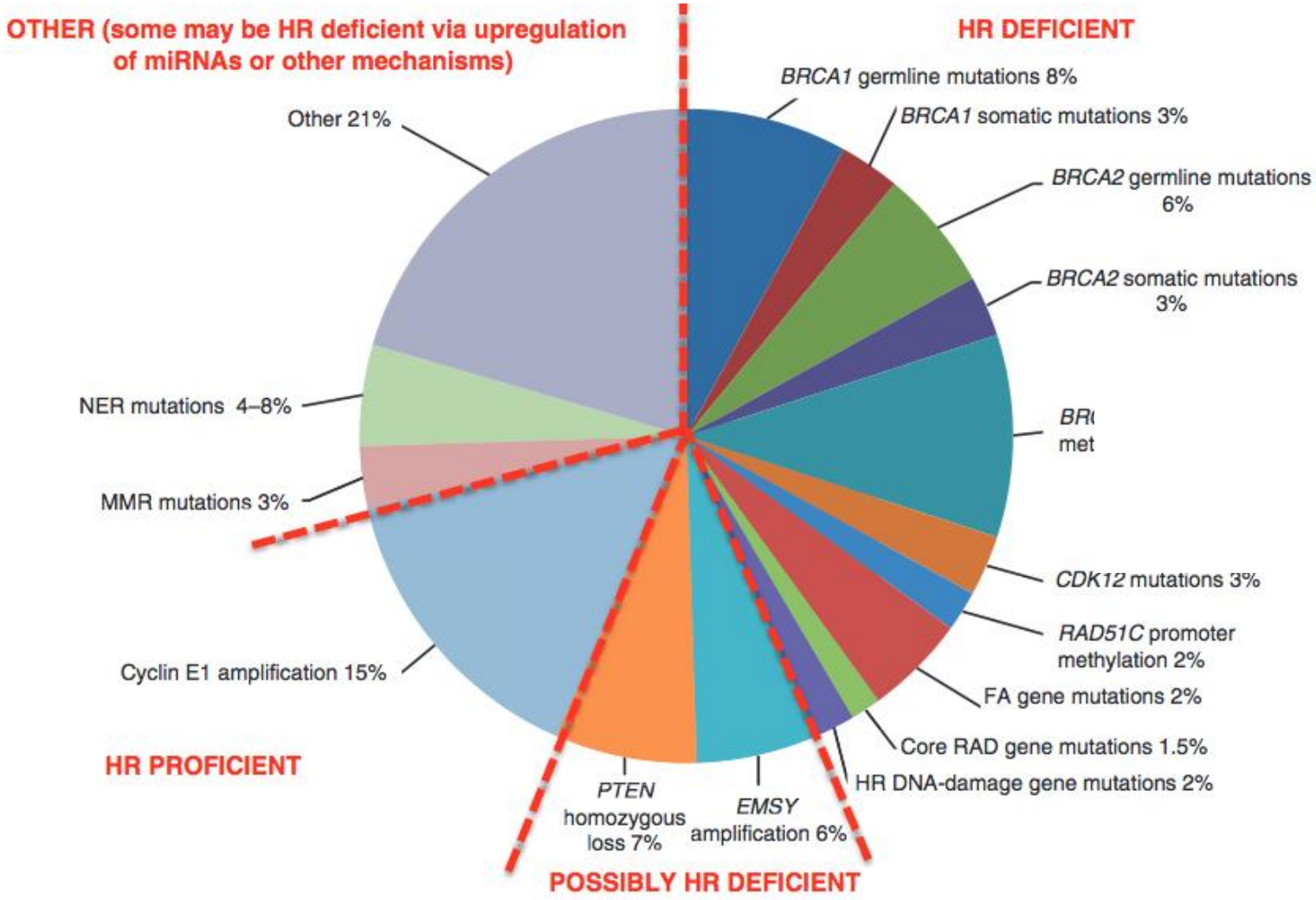

Konstantinopoulos, Nature 2011

Phase 3 Studies of PARP Inhibitors in Patients With Recurrent Ovarian Cancer

	TESARO NOVA	solo2 BRCAm Ovarian Cancer	ARIEL 3
Relapsed ovarian cancer			
HGSOC			
BRCA mutation			
HRD-test	myriad		FOUNDATION MEDICINE
BRCA wild type			
>2 lines platinum			
CR or PR to last platinum therapy			

1. Mirza MR et al., NEJM 2016
2. Pujade-lauraine E. et al., SGO 2017
3. Coleman RL, et al. Lancet. 2017

Phase 3 Studies of PARP Inhibitors in Patients With Recurrent Ovarian Cancer

	Maintenance after Response to Platinum					
Study	**ENGOT-OV16/NOVA[1]**		**SOLO2[2]**	**ARIEL3[3]**		
Agent	**Niraparib**		**Olaparib**	**Rucaparib**		
Inclusion	**gBRCA**	**No gBRCA**	**gBRCA**	**ITT**	**HRD+**	**g/sBRCA**
Difference PFS, months	**15.5**	**5.4**	**14.6**	**5.4**	**8.2**	**11.2**
PFS HR	**0.27*** **	**0.45 *** **	**0.30*** **	**0.36*** **	**0.32*** **	**0.23*** **

HR, hazard ratio; NS, not significant; PFI, platinum-free interval; PFS, progression-free survival; OS=overall survival. *$P < 0.05$; **$P < 0.01$; ***$P < 0.0001$; †Treatment versus control arm.

1. Mirza MR et al., NEJM 2016
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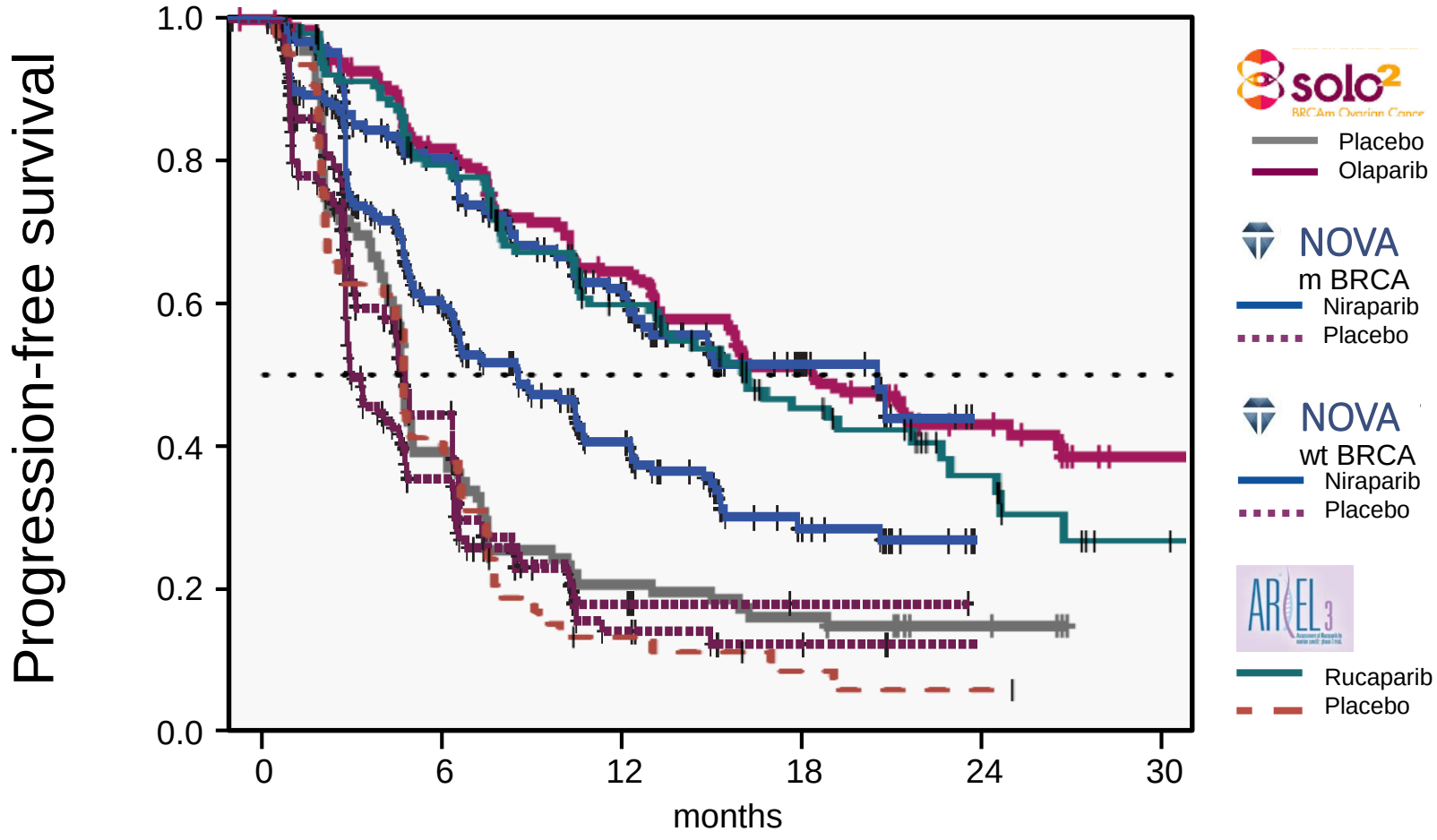
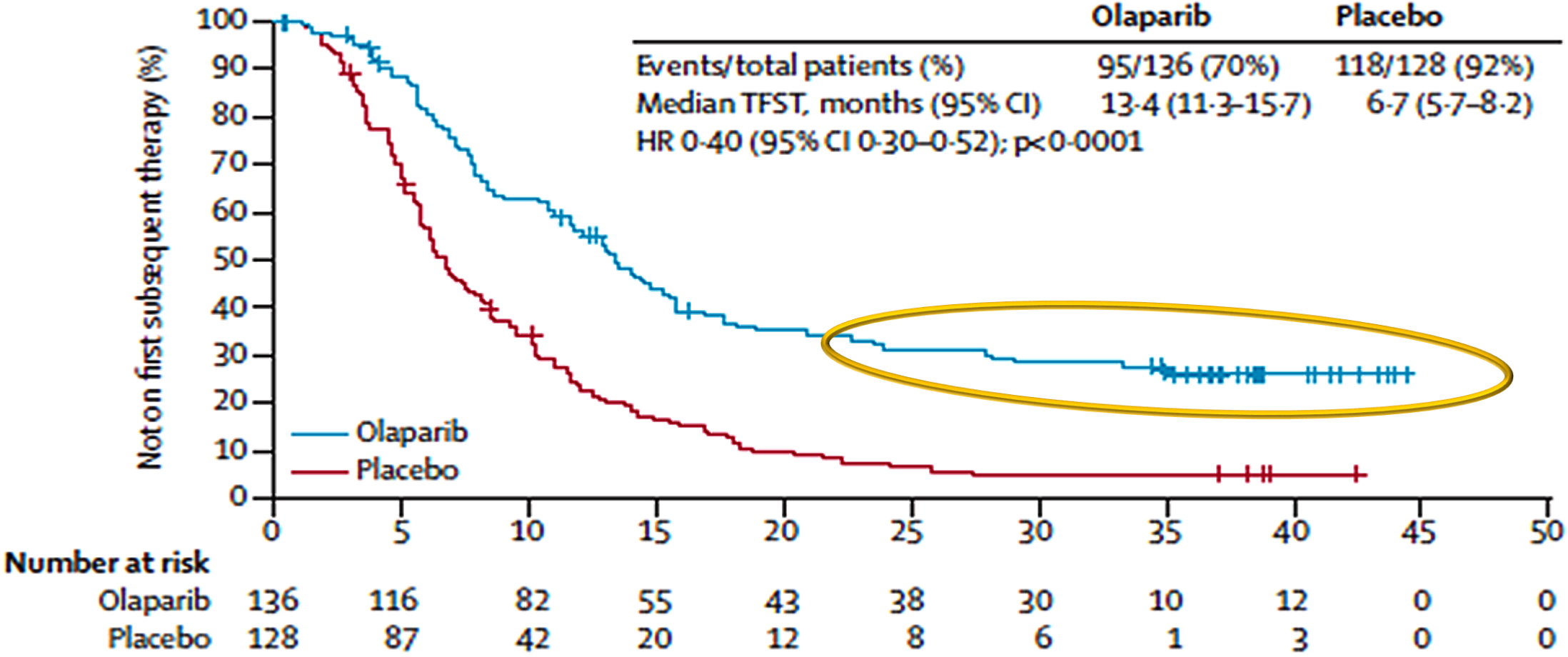


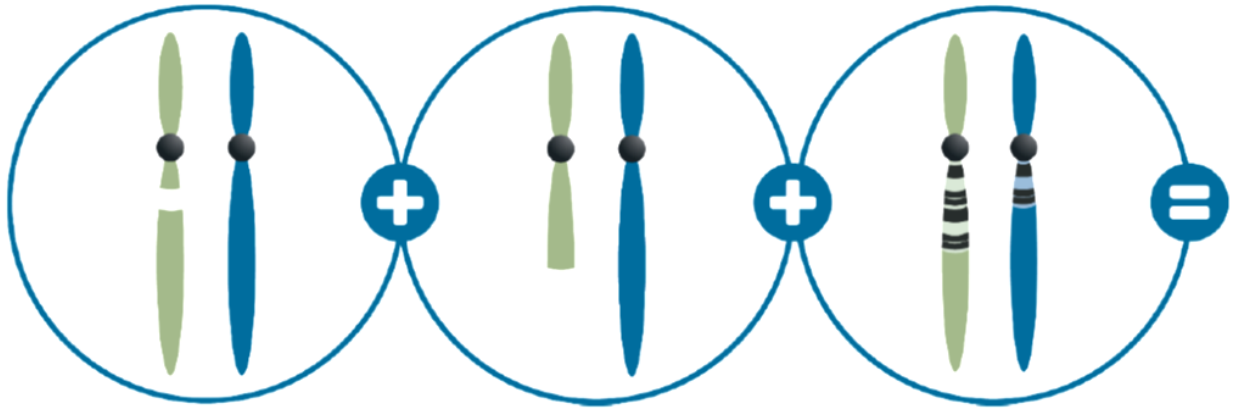
Olaparib maintenance therapy in patients with platinum sensitive relapsed serous ovarian cancer: Study 19

Time to first subsequent therapy or death in all patients (n=264)



Ledermann et al, Lancet Oncol 2014

HRD Test



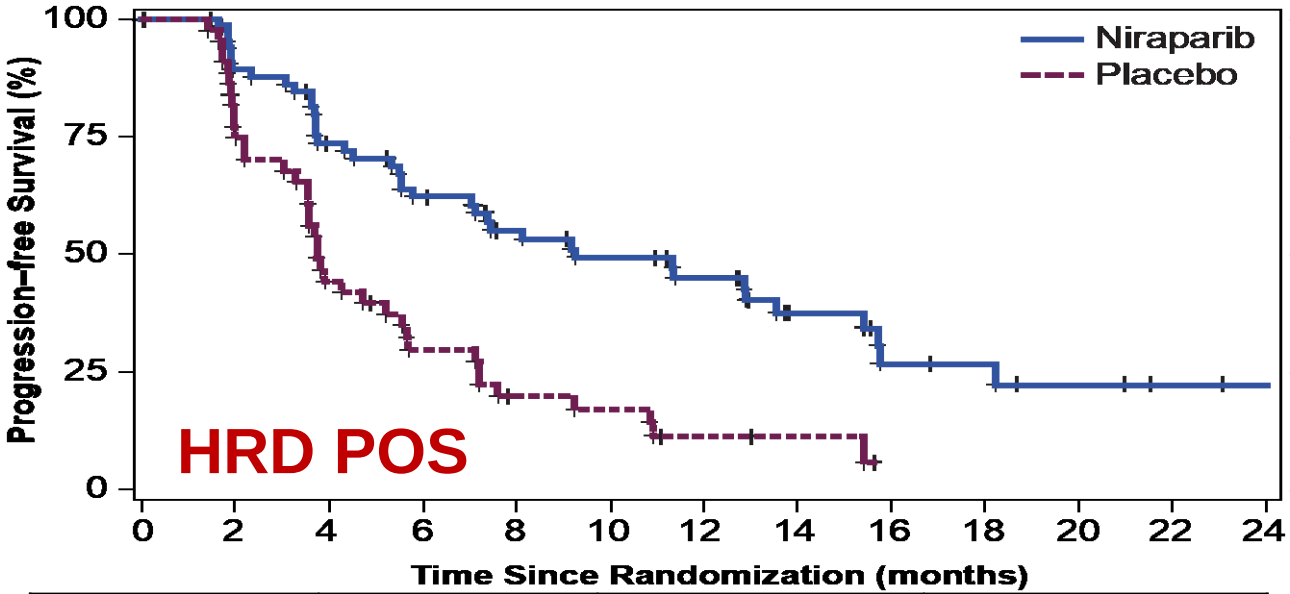
Loss of Heterozygosity (LOH)

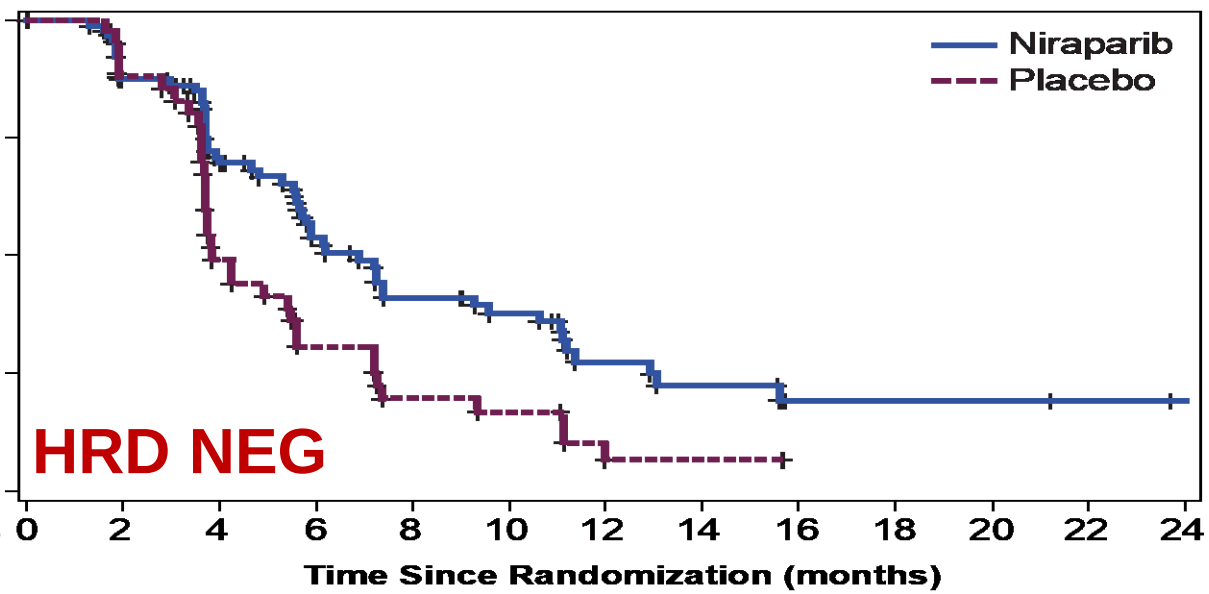
Telomeric Allelic Imbalance (TAI)

Large-Scale State Transitions (LST)

Myriad‘s myChoice HRD Test

Niraparib maintenance in PSOC: PFS in no gBRCA





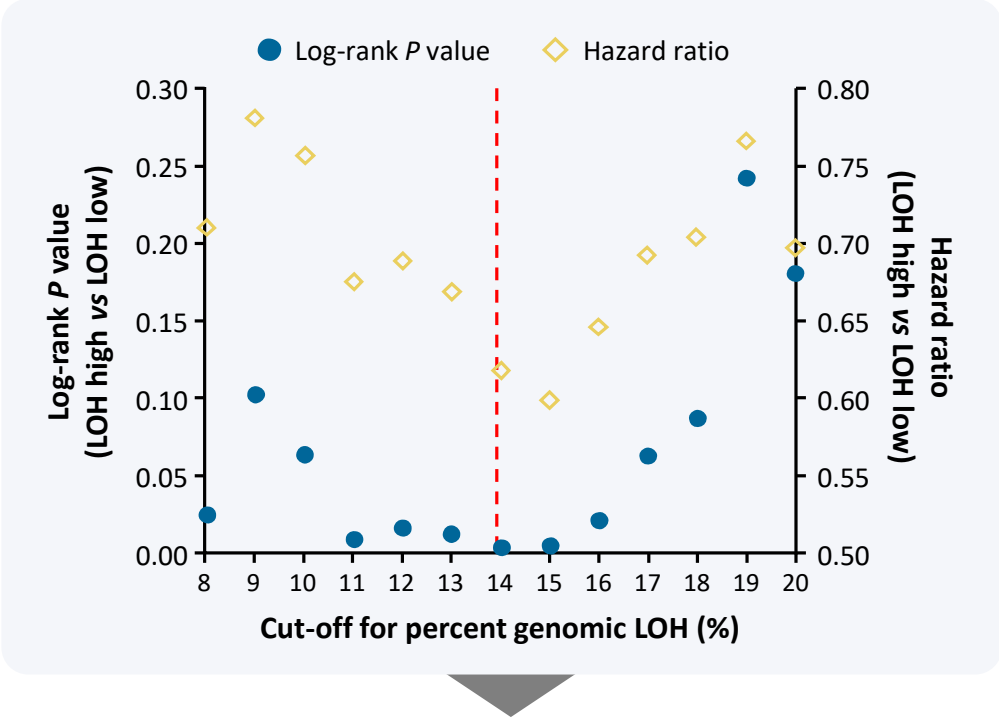
Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=71)	**9.3** (5.8, 15.4)	**0.38** (0.231, 0.628) p=0.0001	45%	**27%**
Placebo (N=44)	**3.7** (3.3, 5.6)		11%	6%

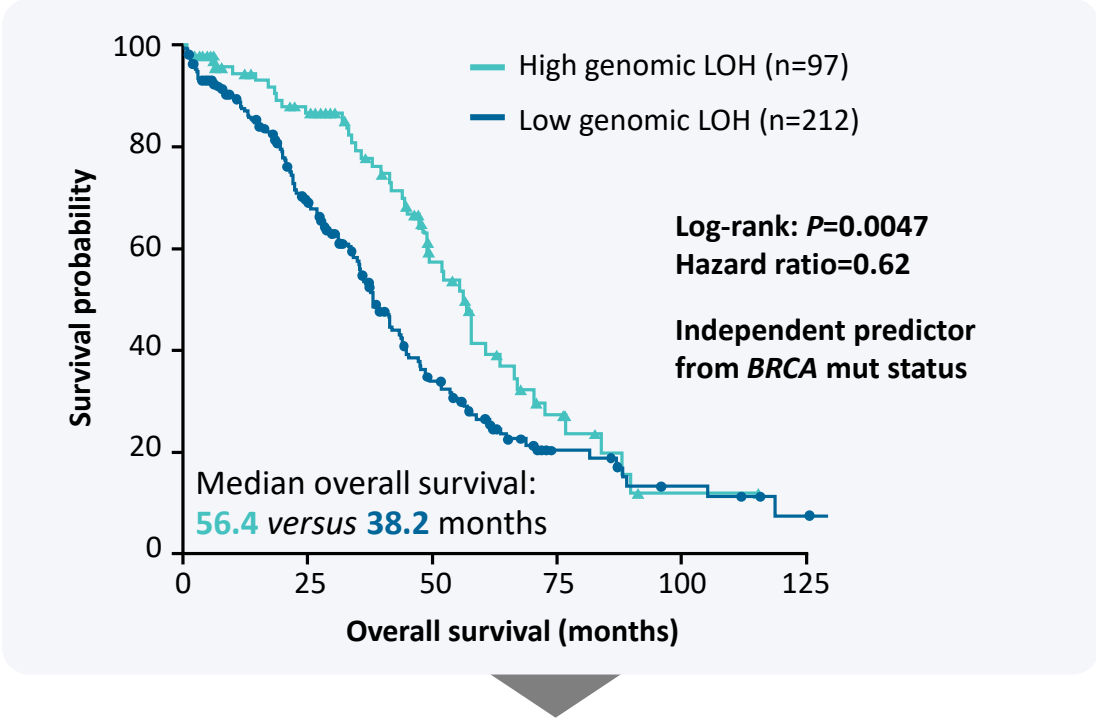
Treatment	**PFS Median (95% CI) (Months)**	**Hazard Ratio (95% CI) p-value**	**% of Patients without Progression or Death**	
			12 mo	**18 mo**
Niraparib (N=92)	**6.9** (5.6, 9.6)	**0.58** (0.361, 0.922) p=0.0226	27%	**19%**
Placebo (N=42)	**3.8** (3.7, 5.6)		7%	7%

Mirza et al., NEJM 2016

Initial Genomic LOH Cut-Off Derived from Public Data and Prospectively Tested in ARIEL2

TCGA and AOCS overall survival data used to develop LOH cut-off to identify HGOC patient tumours with *BRCA*-like signature





Prospective testing of prespecified cut-off in ARIEL2

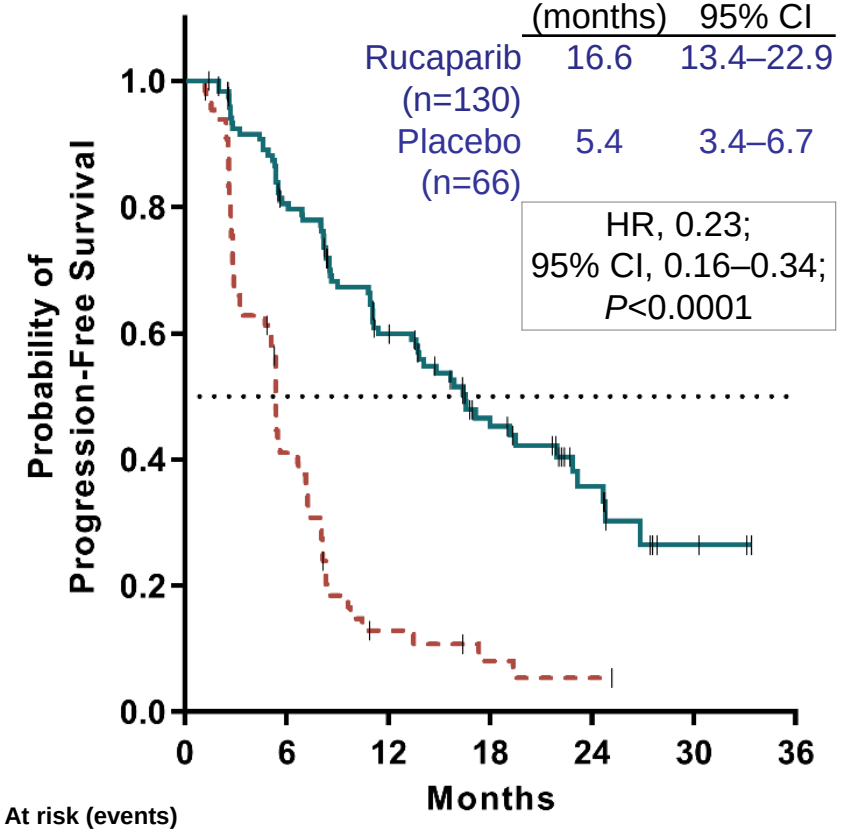
Swisher EM, et al. *Lancet Oncol.* 2017;18(1):75-87.

ARIEL3: Investigator-Assessed Progression-Free Survival

BRCA mutant

	Median (months)	95% CI
Rucaparib (n=130)	16.6	13.4–22.9
Placebo (n=66)	5.4	3.4–6.7

HR, 0.23;
95% CI, 0.16–0.34;
P<0.0001



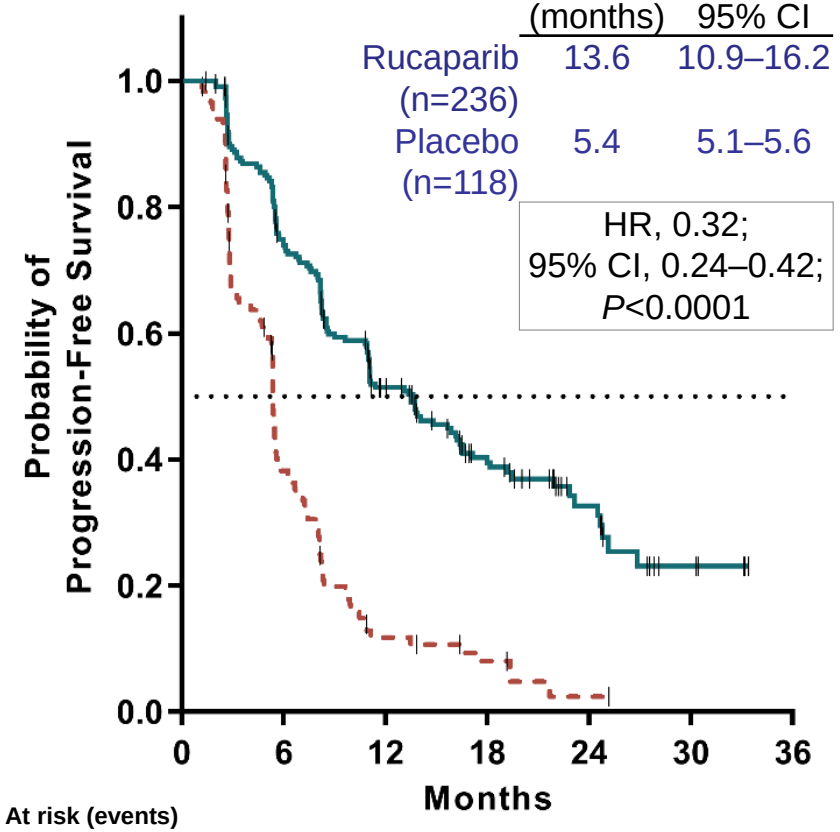
At risk (events)							
Rucaparib	130 (0)	93 (23)	63 (46)	35 (58)	15 (64)	3 (67)	0 (67)
Placebo	66 (0)	24 (37)	6 (53)	3 (55)	1 (56)	0 (56)	

Rucaparib, 48% censored Placebo, 15% censored

HRD

	Median (months)	95% CI
Rucaparib (n=236)	13.6	10.9–16.2
Placebo (n=118)	5.4	5.1–5.6

HR, 0.32;
95% CI, 0.24–0.42;
P<0.0001



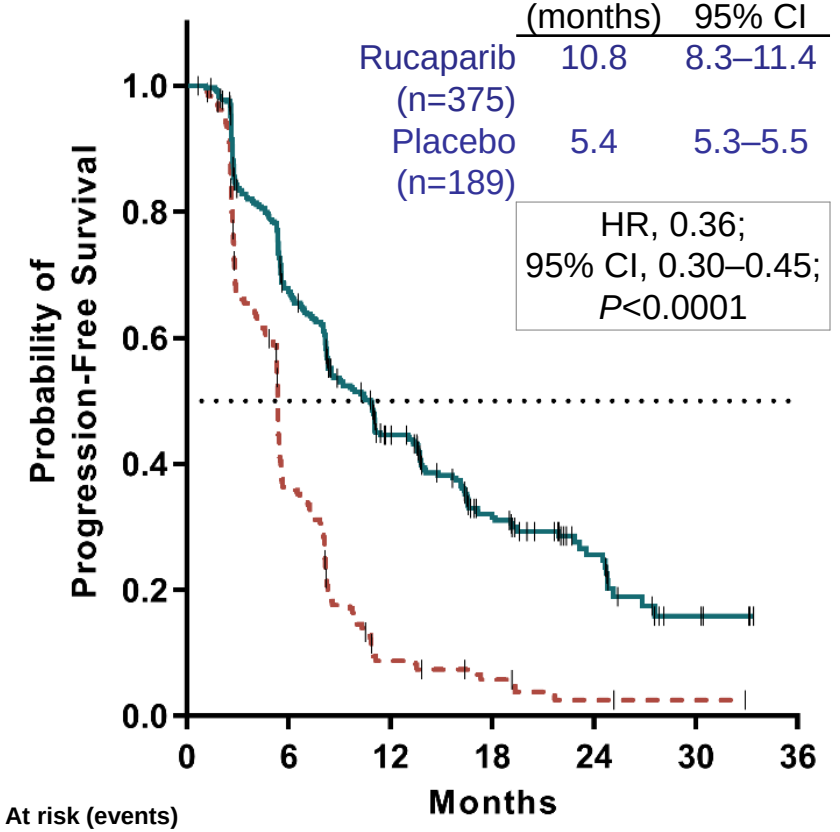
At risk (events)							
Rucaparib	236 (0)	161 (55)	96 (104)	54 (122)	21 (129)	5 (134)	0 (134)
Placebo	118 (0)	40 (68)	11 (95)	6 (98)	1 (101)	0 (101)	

Rucaparib, 43% censored Placebo, 14% censored

ITT

	Median (months)	95% CI
Rucaparib (n=375)	10.8	8.3–11.4
Placebo (n=189)	5.4	5.3–5.5

HR, 0.36;
95% CI, 0.30–0.45;
P<0.0001



At risk (events)							
Rucaparib	375 (0)	228 (111)	128 (186)	65 (217)	26 (226)	5 (234)	0 (234)
Placebo	189 (0)	63 (114)	13 (160)	7 (164)	2 (167)	1 (167)	0 (167)

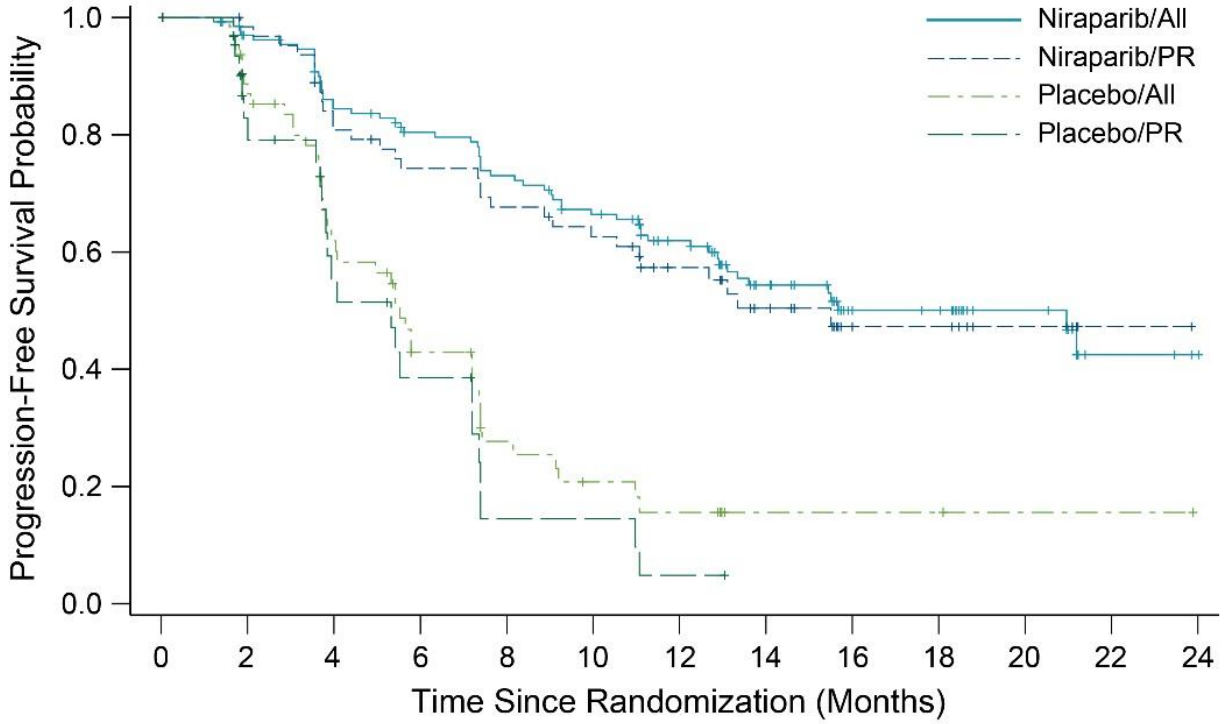
Rucaparib, 38% censored Placebo, 12% censored

Visit cutoff date: 15 April 2017.

Ledermann JA, et al. *Ann Oncol.* 2017;28(Suppl 5):Abstract LBA40_PR; Coleman RL, et al. *Lancet*. 2017;390(10106):1949-1961.

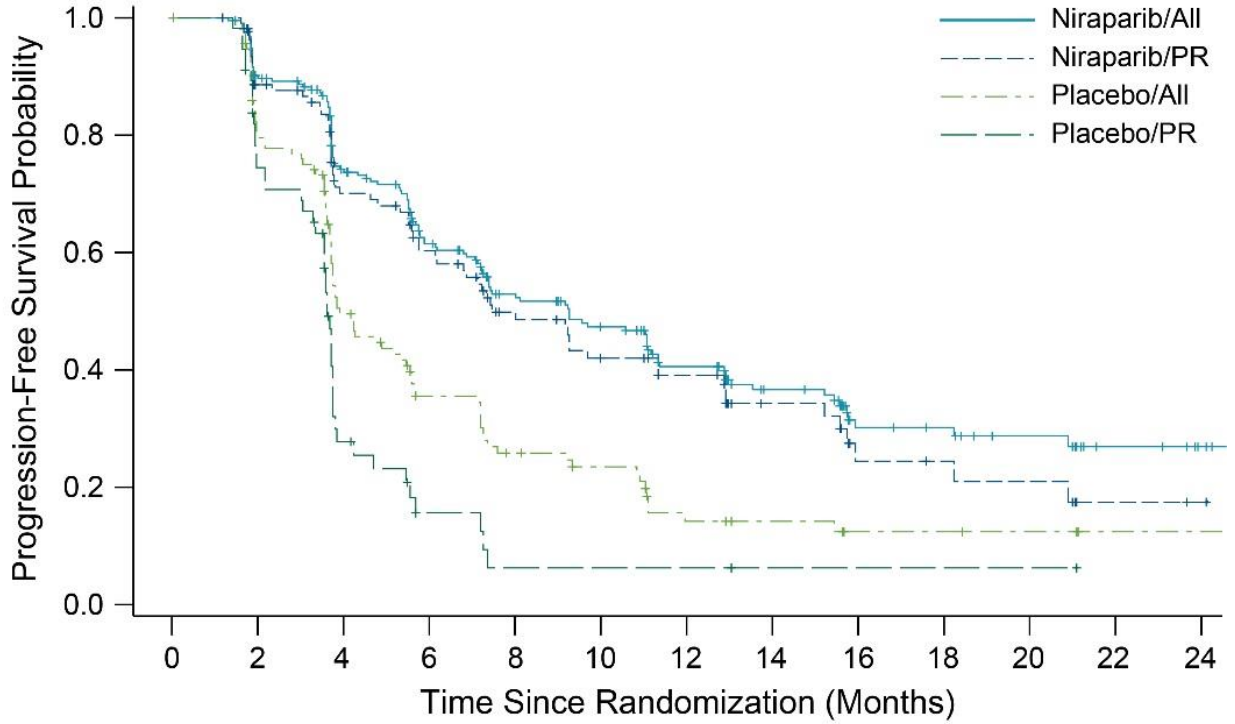
PFS for Patients with a PR to the Last Platinum-Based Chemotherapy

g*BRCA*mut Cohort



Niraparib/All	138	125	107	98	89	79	63	44	28	26	16	3	1
Niraparib/PR	67	62	50	45	41	37	27	19	10	9	5	1	0
Placebo/All	65	52	34	21	12	8	6	2	2	2	1	1	0
Placebo/PR	32	22	14	9	3	3	1	0					

Non-g*BRCA*mut Cohort



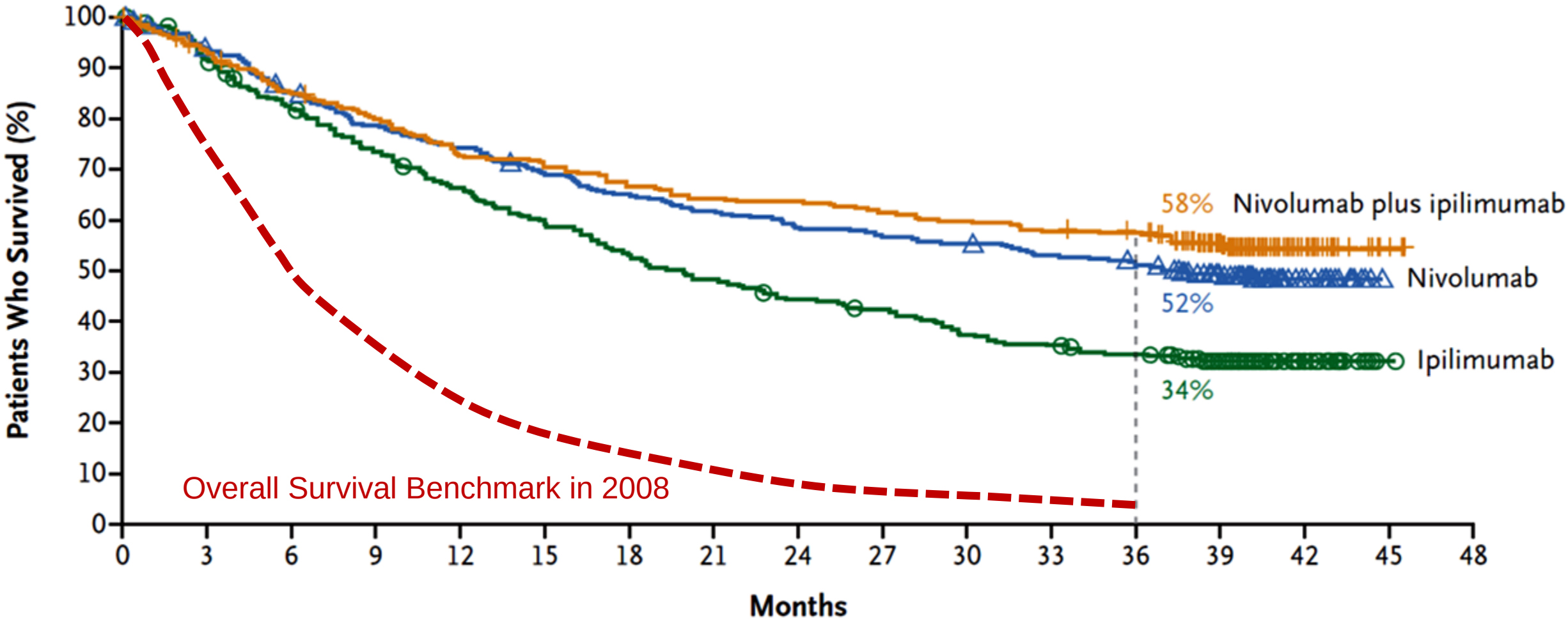
Niraparib/All	234	188	145	113	88	75	57	41	23	21	16	7	3
Niraparib/PR	117	90	66	54	39	31	26	16	8	7	6	2	1
Placebo/All	116	88	52	33	23	19	10	8	4	4	3	1	1
Placebo/PR	56	40	13	5	2	2	2	1	1	1	1	0	

Mansoor R. Mirza et al., ASCO 2017

Patterns of Toxicity of PARP Inhibitors

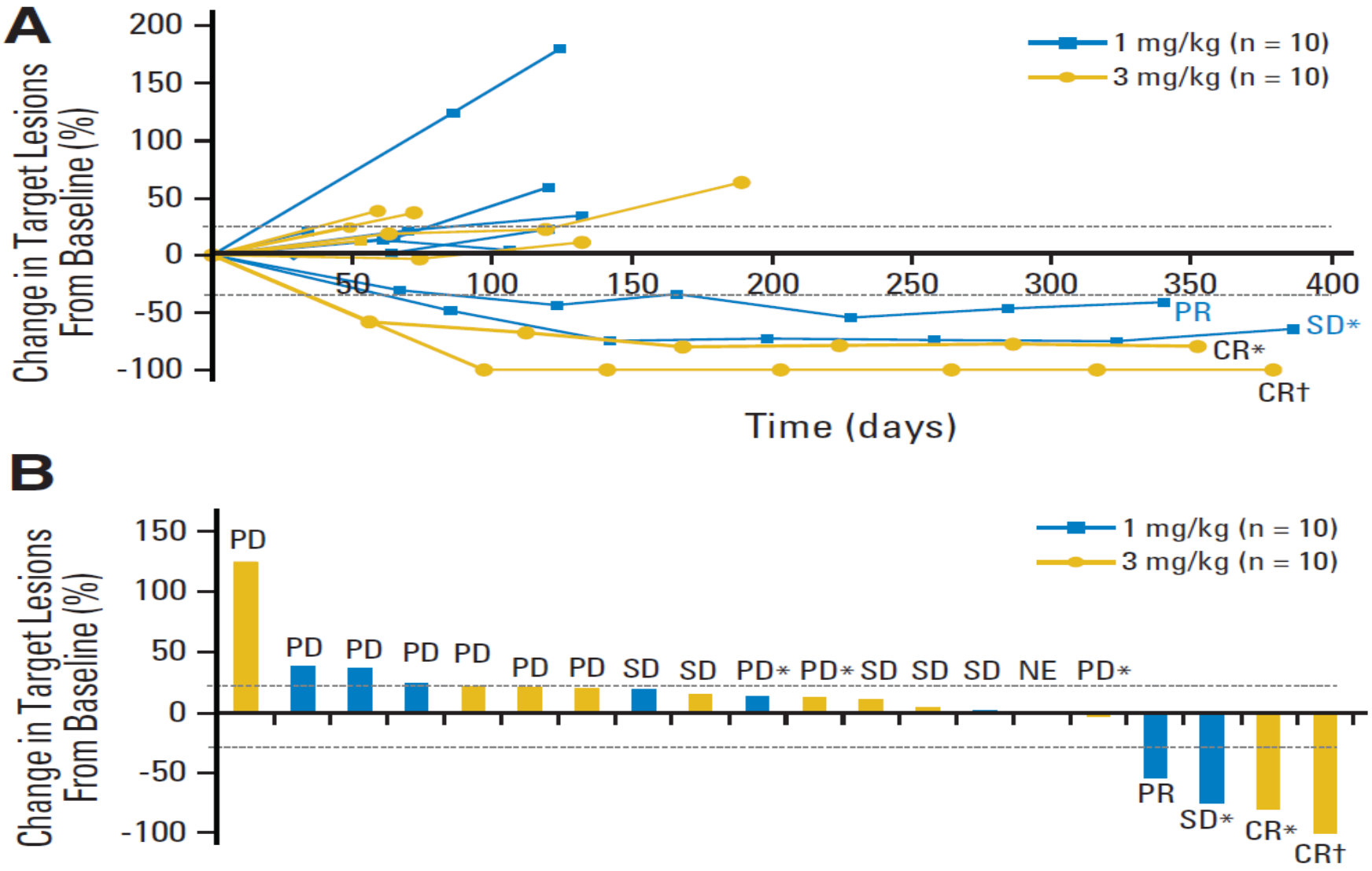
	OLAPARIB	NIRAPARIB	RUCAPARIB
Fatigue	+++	++	+++
Nausea/Vomiting	+++	+++	+++
Anaemia	+++	+++	+++
Neutropenia	+	++	+
Thrombocytopenia	++	+++	++
Diarrhoea	++	+	+
Headache	++	+	+
Insomnia	+	-	-
Dysguesia	++	-	++
Raised ALT/AST	-	-	++
Photosensitive rash	-	-	+
Hypertension	-	++	-

Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma



JeddD. Wolchok, et al. NEJM September 2017, Edward L. Korn, et al., J Clin Oncol 26:527-534 2008

Safety and Antitumor Activity of Anti–PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer



Best overall responses in all patients in two cohorts with anti–programmed death 1 (PD-1) antibody.

Hamanishi et al, JCO 2015

Single agent therapy with immune checkpoint inhibitors in ovarian cancer

	Nivolumab[1]	Pembrolizumab (KEYNOTE-28)[2]	Avelumab[3]	Atezolizumab[4]
	Anti-PD1	**Anti-PD1**	**Anti-PD-L1**	**Anti-PD-L1**
Patients	20	26	124	12
Prior Therapy	≥4 (55%)	≥3 (65%)	≥3 (58%)	>6 (58%)
PDL-1 +	80% [IHC]	100% [IHC]	77% [eval in 60%]	83%
ORR	15%	11.5%	9.7%	25%
Duration	4 (20%) > 24 wks	7 (30%) > 24 wks	16.1% @24 wks	mPFS ~12 wks

1. Hamanishi J et al. *J Clin Oncol*. 2015;33(34):4015-4022.
2. Varga A et al. ASCO 2015. Abstract 5510.
3. Disis ML et al. ASCO 2016. Abstract 5533.
4. Infante J et al. ESMO 2016. Abstract 871P.

Single agent therapy with immune checkpoint inhibitors in ovarian cancer

	Nivolumab[1]	Pembrolizumab (KEYNOTE-28)[2]	Avelumab[3]	Atezolizumab[4]
	Anti-PD1	Anti-PD1	Anti-PD-L1	Anti-PD-L1
Patients	20	26	124	12
Prior Therapy	≥4 (55%)	≥3 (65%)	≥3 (58%)	>6 (58%)
PDL-1 +	80% [IHC]	100% [IHC]	77% [eval in 60%]	83%
ORR	15%	11.5%	9.7%	25%
Duration	4 (20%) > 24 wks	7 (30%) > 24 wks	16.1% @24 wks	mPFS ~12 wks

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2. Varga A et al. ASCO 2015. Abstract 5510.
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How to incorporate new treatment modalities?

ENGOT
European Network of Gynaecological Oncological Trial groups

PAOLA-1
Platine, Avastin and OLAparib in 1st line

GINECO

FIGO
IIIB-IV
HG-SOC
or
HG-Endo
O,P,F Cancer

PR/CR
NED

Randomize

2:1

Arm A
Olaparib
300 mg bd x 2 years

n=408

Arm B
Placebo
bd x 2 years

n=204

n=612

PFS 1

PFS 2, OS

First-line Surgery
+ Chemotherapy
(Dose-dens, IP, NACT allowed)

Bevacizumab (15mg/kg/3wk) ≥ 3 cycles combined with chemo +
Maintenance in both arms (15 months total)

PFS: 2018

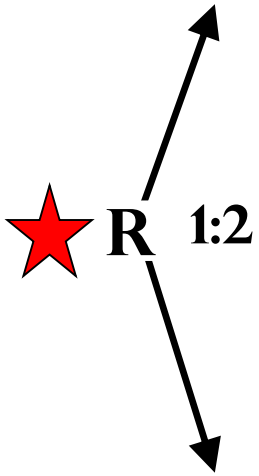
AGO AUSTRIA · BGOG · GEICO · GOTIC · MaNGO · MITO · NSGO · Frauenheilkunde Innsbruck

ATALANTE trial design

ENGOT
European Network of Gynaecological Oncological Trial groups

Recurrent Platinum-sensitive N=351

- Non-mucinous histology
- TFIp >6 months
- One or 2 prior lines of Cx
- Measurable disease
- ECOG ≤1



Carboplatin-based chemotherapy

BEV +Placebo → PD

Carboplatin-based chemotherapy

BEV+Atezolizumab → PD

Stratification factors:

PFI, PD-L1 expression, Chemotherapy cohort

Chemotherapy-based schedule options (investigator's choice)

- Carboplatin AUC5 + paclitaxel 175mg/m² + BEV 15mg/kg + placebo/atezolizumab 1200mg, I.V., d1, q3w
- *Carboplatin AUC4, d1 + gemcitabine 1000 mg/m², d1&8 + BEV 15mg/kg d1 + placebo/atezolizumab 1200mg, I.V., d1, q3w
- *Carboplatin AUC5 d1 + PLD 30mg/m² d1+ BEV 10mg/kg d1&15 + placebo/atezolizumab 800mg, I.V., d1&15, q4w

Maintenance (for all regimens): BEV 15mg/kg + placebo/atezolizumab 1200mg, I.V., d1, q3w

★=Biopsy; **PFI**: platinum-free interval; **BEV**: bevacizumab; **PLD**: pegylated liposomal doxorubicin; *no systematic steroid as premedication

Recurrent Ovarian Cancer Maintenance Therapy

1 Angiogenesis Inhibitors ✓

2 PARP-Inhibitors ✓

- mBRCA Tumors and response to platinum-containig therapy: First choice
- wtBRCA tumors and response to platinum-containing therapy: Option to consider

3 Immunotherapy ?


Small steps,
made over time,
move mountains
india cmarth

شكرا لكم على اهتمامكم