foro debate oncología

Zaragoza 26-29 septiembre 2023

Hospital Universitario 12 de Octubre

Estado del arte y alternativas futuras en…

Cáncer de ovario

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Disclosures

- Employment: Hosp. Univ. 12 de Octubre
- Consultant or Advisory Role: Lilly, Tesaro, Astra-Zeneca, Roche, Novartis, Pfizer, Celgene,
- Research Funding: Tesaro
- Speaking: Lilly, Roche, Astra-Zeneca, Novartis, Pfizer

TOPICS

- Introduction.
- First-line maintenance in advanced ovarian cancer (AOC).
- AOC relapse.
- Platinum resistant.

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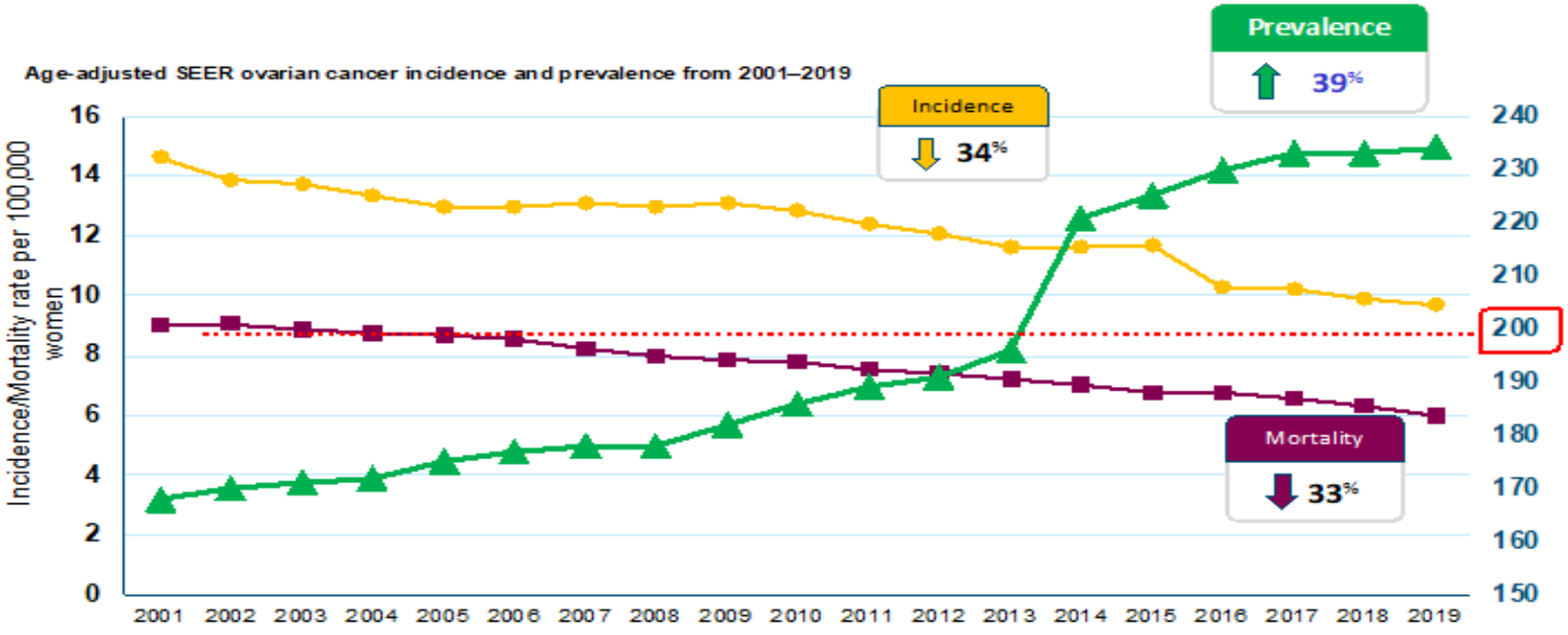
RECENT OVARIAN CANCER EPIDEMIOLOGY

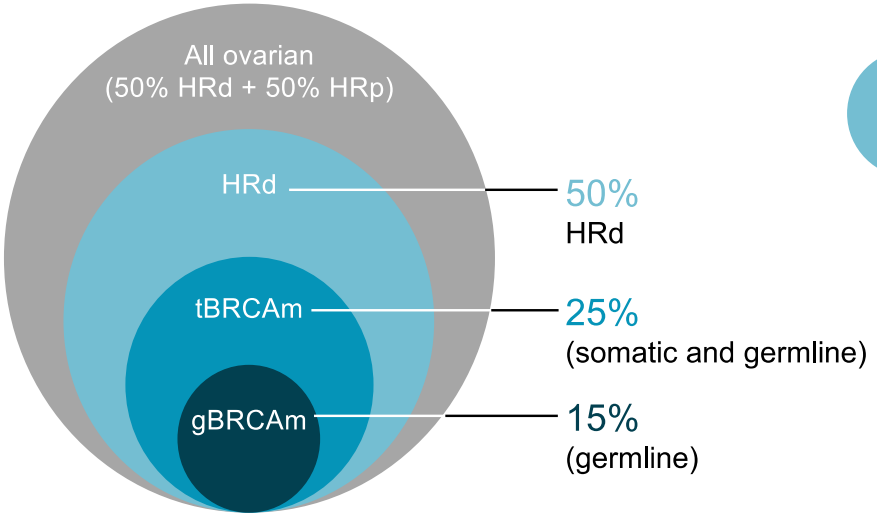
Ovarian Cancer: Clinical Impact



https://seer.cancer.gov/statisticsnetwork/explorer/application.html?site=61&data_type=9&graph_type=2&compareBy=rate_type&chk_rate_type_1=1&chk_rate_type_2=2&chk_rate_type_3=3&hdn_sex=3&race=1&age_range=1&hdn_stage=101&advopt_precision=1&advopt_show_ci=on&hdn_view=0&advopt_display=2

Biomarkers play an important role in diagnosing and defining patient populations in ovarian cancer

Half of high-grade serous OC exhibits a high degree of genomic instability due to deficiencies in homologous recombination



50% are HRd including *BRCA*m, *BRCA*1/2 and RAD51 promoter methylation, BRIP1, and other genes involved in homologous recombination[1,2]

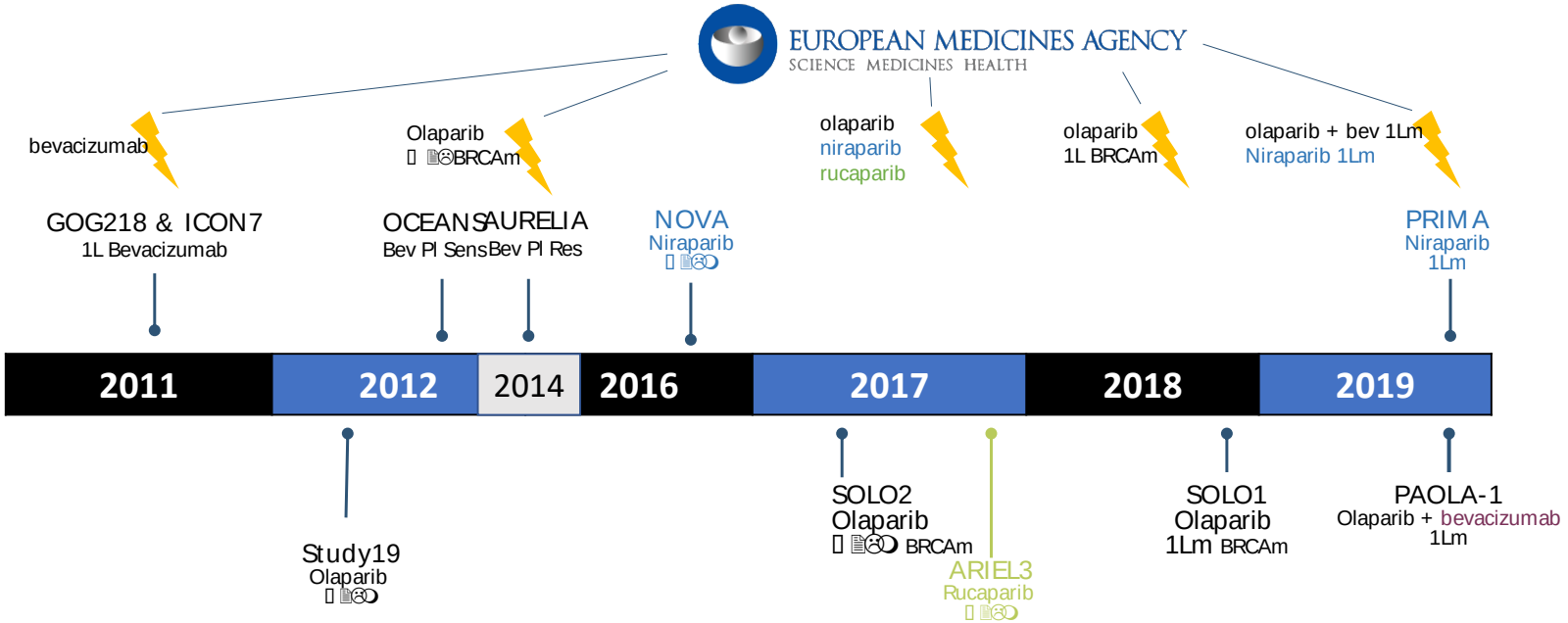
25% are t*BRCA*m at diagnosis[1,2]

15% are g*BRCA*m at diagnosis[1,2]

BRCA, breast cancer gene; BRIP1, *BRCA*1-interacting protein; g*BRCAm*, germline *BRCA* mutant; HRd, homologous recombination deficient; HRp, homologous recombination proficient; OC, ovarian cancer; t*BRCA*m, tumour *BRCA* mutant.

1. Abkevich V, et al. Br J Cancer 2012;107:1776–82; 2. The Cancer Genome Atlas Research Network. Nature 2011;474:609–15.

Maintenance therapy in advanced ovarian cancer



Bevacizumab	PARPi in relapse	PARPi in firstline
Perren T…Mirza MR, et al. NEJM 2011	Ledermann J, et al. NEJM 2012	Moore K, et al. NEJM 2018
Burger R, et al. NEJM 2011	Mirza MR, et al. NEJM 2016	Gonzales-Martin A…Mirza MR, et al. NEJM 2019
	Pujade-Lauraine E, et al. Lancet Oncol 2017	Ray-Coquard I, et al NEJM 2019
	Coleman RL, et al. Lancet 2017	

TOPICS

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PARPi 1L maintenance therapy options in advanced ovarian cancer

United States and Europe

Niraparib [1,2]	Olaparib [3,4]	Olaparib [3,4] PLUS Bev
All biomarker subgroups	*BRCA*m	*BRCA*m and/or HRd

1. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf
2. https://www.ema.europa.eu/en/medicines/human/EPAR/zejula
3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208558s001lbl.pdf
4. https://www.ema.europa.eu/en/medicines/human/EPAR/lynparza

Magnitude of benefit with PARPi is related to biomarker
Even patients with HRp (HRD-) benefit from PARPi

	SOLO-1[1]	PRIMA[2]	PAOLA-1[3]	ATHENA-MONO[4]	PRIME[5]
PARPi	Olaparib	Niraparib	Olaparib + Bev	Rucaparib	Niraparib
Control	Placebo	Placebo	Bevacizumab	Placebo	Placebo
Population	BRCAmut	All comers	All comers	All comers	All comers (Chinese)
HRD test	NA	MyChoice	MyChoice	Foundation-One	BGI
BRCAmut	0.33 (0.25–0.43)	0.40* (0.27–0.62)	0.31* (0.20–0.47)	0.31* (0.20–0.47)	0.40* (0.23-0.68)
BRCAwt/HRD+	-	0.50* (0.31-0.83)	0.43* (0.28-0.66)	0.58* (0.33-1.01)	0.58* (0.36-0.93)
BRCAwt/HRD-	-	0.68* (0.49-0.94)	0.92* (0.72-1.17)	0.65* (0.45-0.95)	0.41* (0.25-0.65)

+++
++
+

*exploratory

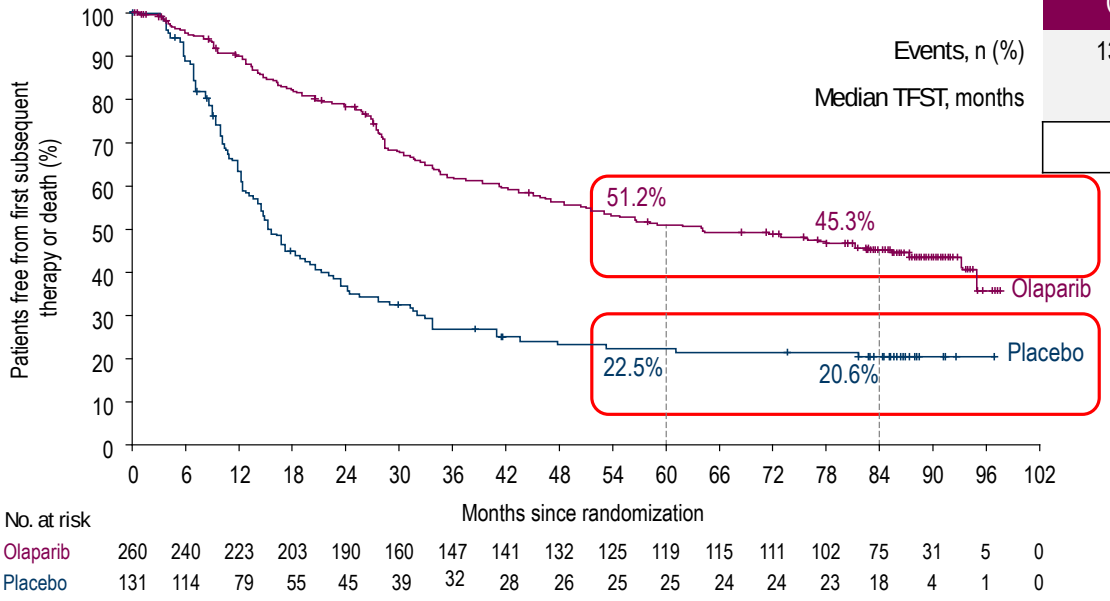
The aim of the table is not the cross-trial comparison

1. Moore. NEJM 2018; 2. Gonzalez-Martin. NEJM 20193; 3. Ray-Coquard. NEJM 2019;
4. Monk. J Clin Oncol 2022; 5. Li.SGO 2022

Rationale for PARP inhibitors in ovarian cancer

SOLO1 updated Time to First Subsequent Therapy

Surrogate for updated PFS



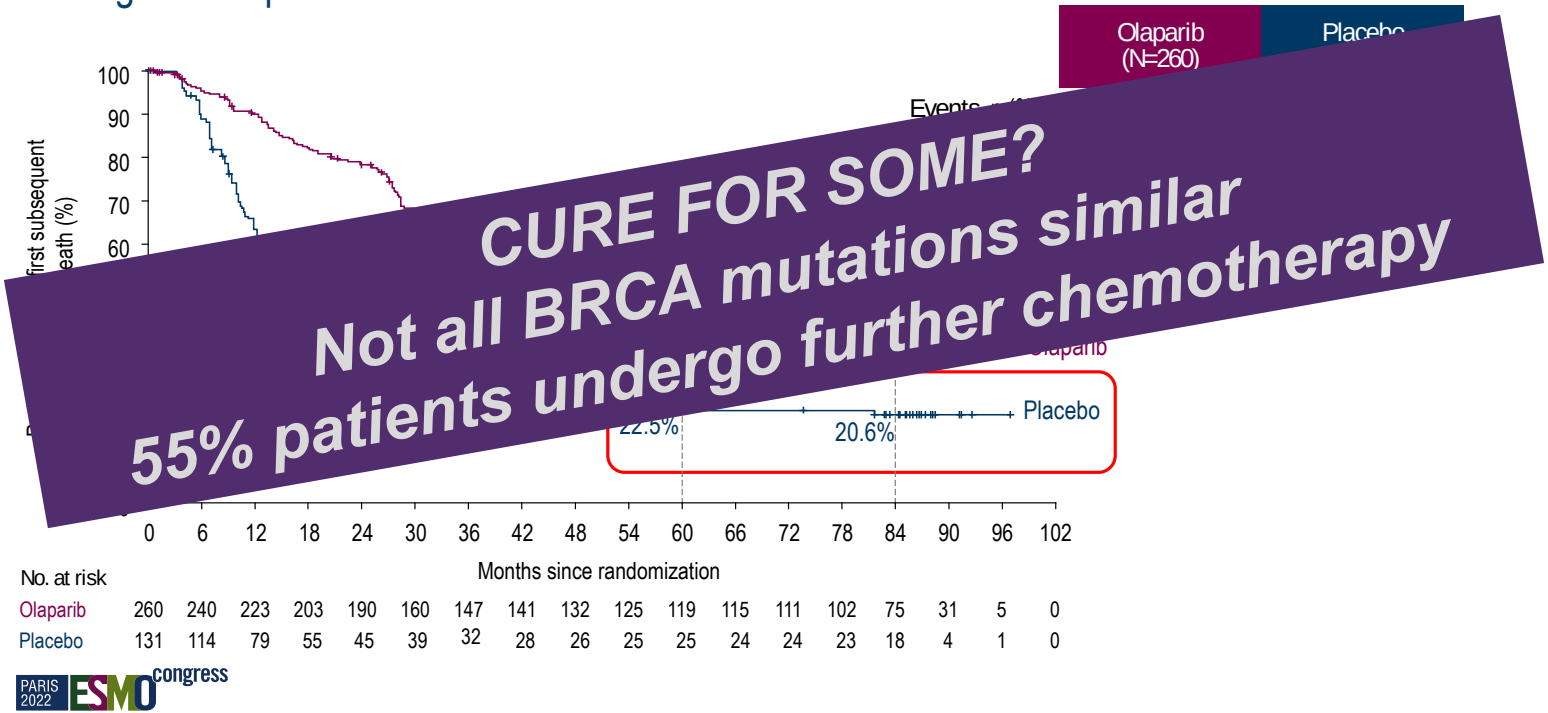
	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	135 (51.9)	98 (74.8)
Median TFST, months	64.0	15.1
HR 0.37 (95% CI 0.28–0.48)		

PARIS 2022 ESMO congress

Rationale for PARP inhibitors in ovarian cancer

SOLO1 updated Time to First Subsequent Therapy

Surrogate for updated PFS



CURE FOR SOME?
Not all BRCA mutations similar
55% patients undergo further chemotherapy

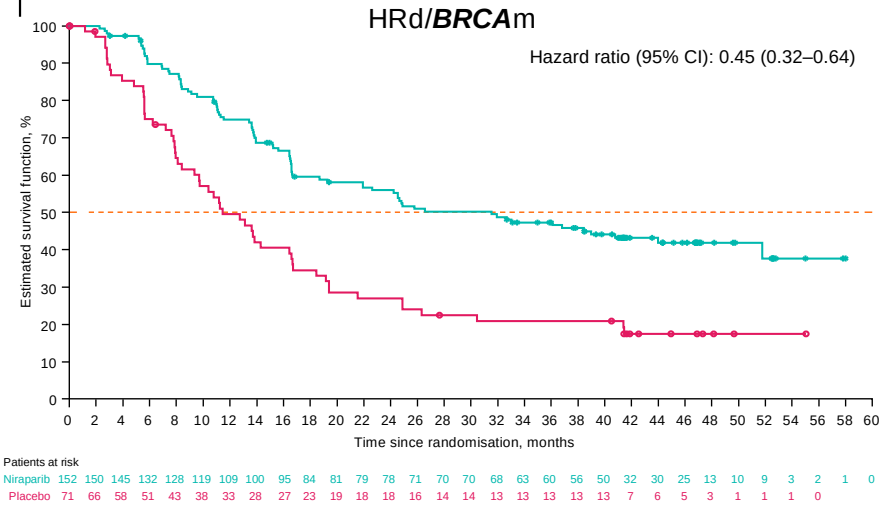
PARIS 2022 ESMO congress

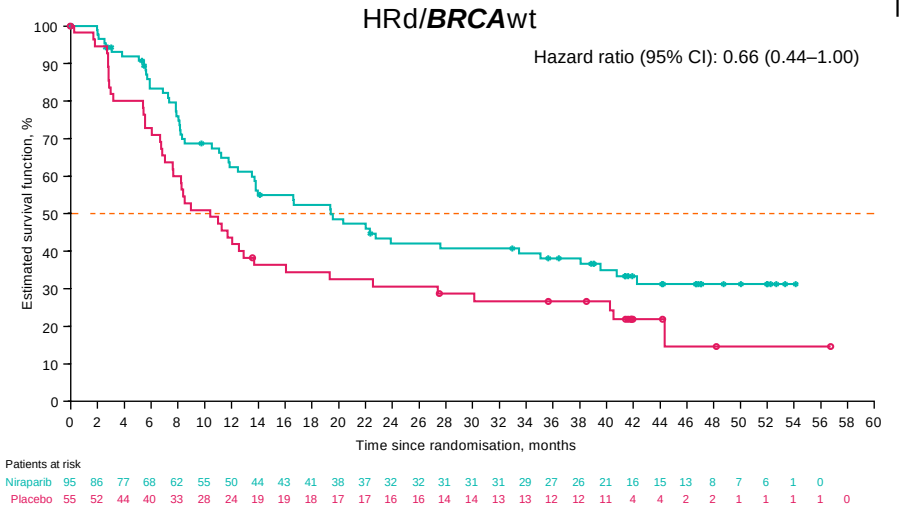
Rationale for PARP inhibitors in ovarian cancer

PRIMA LT updated analysis: Sustained and durable PFS benefit in patients with newly diagnosed advanced OC at the highest risk of early relapse

BRCAwt/HRD

HRd





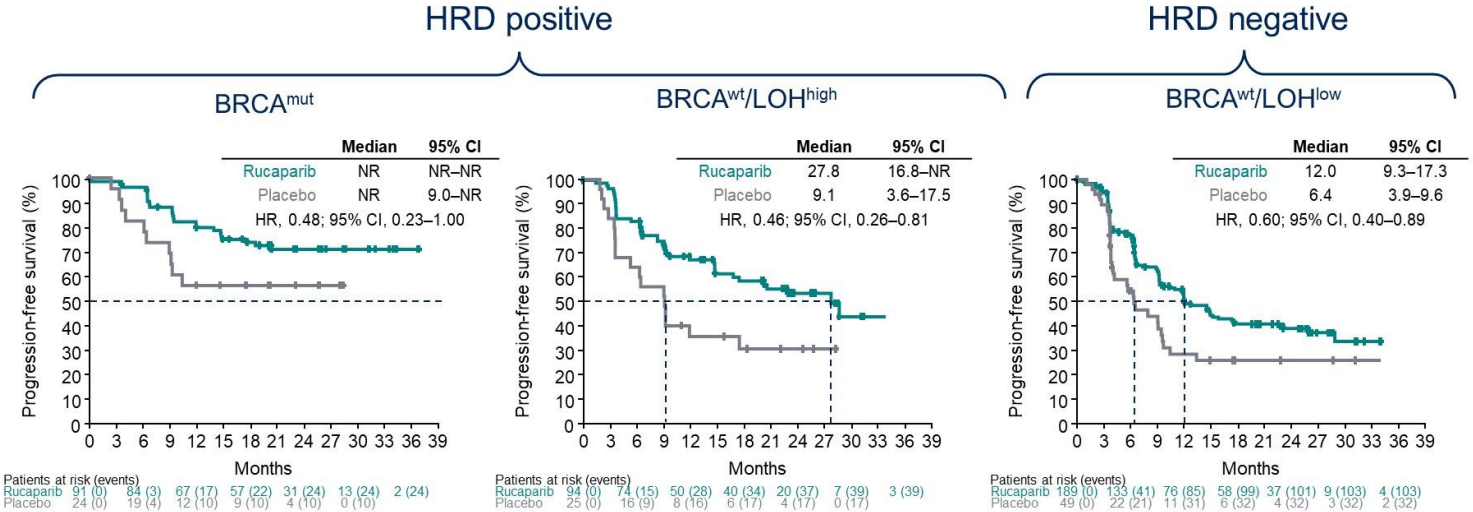
*BRCA*m, *BRCA* mutated; *BRCA*wt, *BRCA* wild-type; HRd, homologous recombination–deficient; HRp, homologous recombination–proficient.

CI, confidence interval; HRd, homologous recombination deficient; ITT, intent-to-treat; mPFS, median progression-free survival; OC, ovarian cancer; PFS, progression-free survival.

1. González-Martín A, et al. Presented at ESMO 2022 (Poster #530), 9–13 Sep, Paris, France.

Rationale for PARP inhibitors in ovarian cancer

BICR-Assessed PFS: Exploratory Subgroups



- Data were similar with BICR-assessed PFS for HRD subgroups

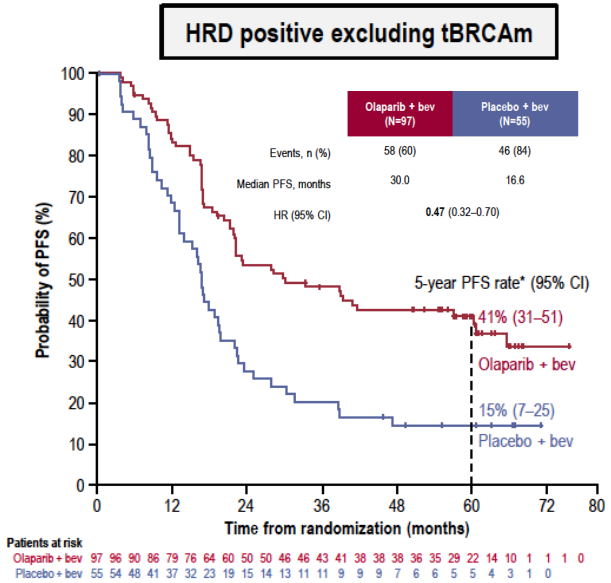
Data cutoff date: March 23, 2022.

BICR, blinded independent central radiology review; BRCA, *BRCA1* or *BRCA2*; HR, hazard ratio; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; mut, mutant; NR, not reached; PFS, progression-free survival; wt, wild type

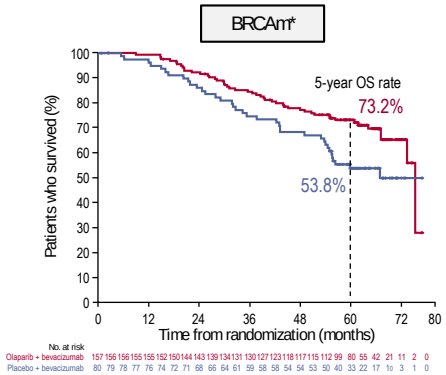
PRESENTED BY:
Bradley J. Monk, MD, FACS, FACOG (LBA5500)

Rationale for PARP inhibitors in ovarian cancer

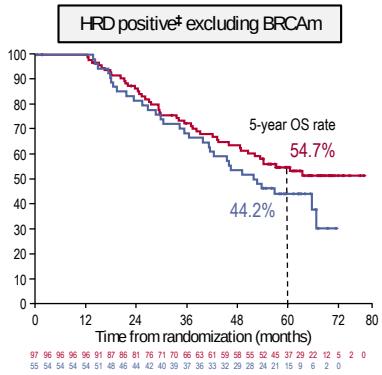
5y PFS HRD positive excluding t*BRCA*m



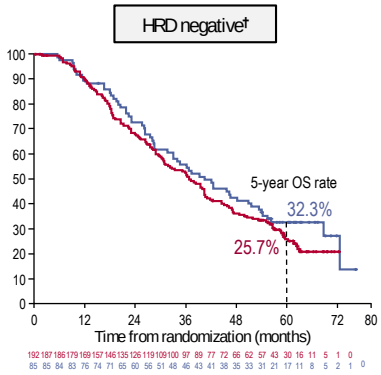
OS subgroup analysis by BRCAm and HRD status



	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)†	66.9
5-year OS rate, %	73.2	53.8
PARPi as subsequent treatment, n (%)	38 (24.2)	44 (55.0)
HR 0.60 (95% CI 0.39–0.93)		



	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
	44 (45.4)	32 (58.2)
	NR	52.0
	54.7	44.2
	9 (9.3)	23 (41.8)
HR 0.71 (95% CI 0.45–1.13)		



	Olaparib + bevacizumab (N=192)	Placebo + bevacizumab (N=85)
	140 (72.9)	58 (68.2)
	36.8	40.4
	25.7	32.3
	46 (24.0)	34 (40.0)
HR 1.19 (95% CI 0.88–1.63)		

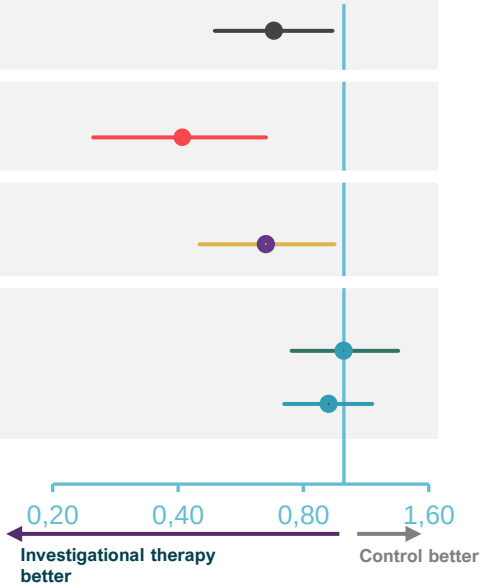
*By central labs; †Unstable median; <50% data maturity; ‡By Myriad myChoice HRD Plus. NR, not reported.

Ray-Coquard I, et al. N Engl J Med 2019;381:2416-28

Rationale for PARP inhibitors in ovarian cancer

HRD

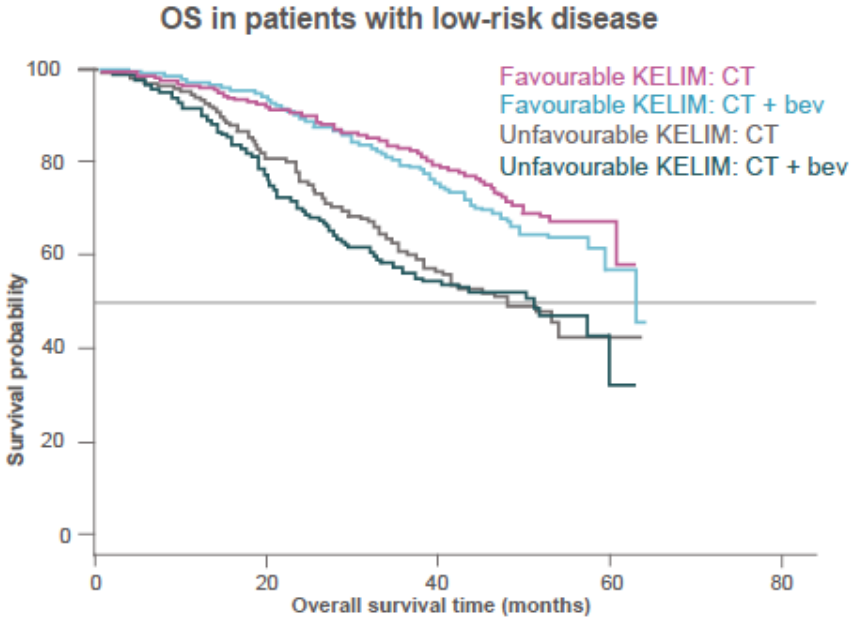
Population	mPFS treatment vs control, months	Hazard ratio (95% CI)
PRIMA[1,2] (niraparib vs placebo)		
HRp (n=249)	8.1 vs 5.4	0.68 (0.49-0.94)
PRIME[3]*(niraparib vs placebo)		
HRp/unknown (n=127)	14.0 vs 5.5	0.41 (0.25-0.65)
ATHENA[4] (rucaparib vs placebo)		
HRp (*BRCA*wt/LOH^{low}) (n=139)	12.0 vs 6.4	0.60 (0.40-0.89)
PAOLA-1[5] (olaparib + bev vs placebo + bev)		
HRp (n=277)	16.6 vs 16.2	1.00 (0.75-1.35)
HRp/unknown (n=419)	Not reported	0.92 (0.72-1.17)

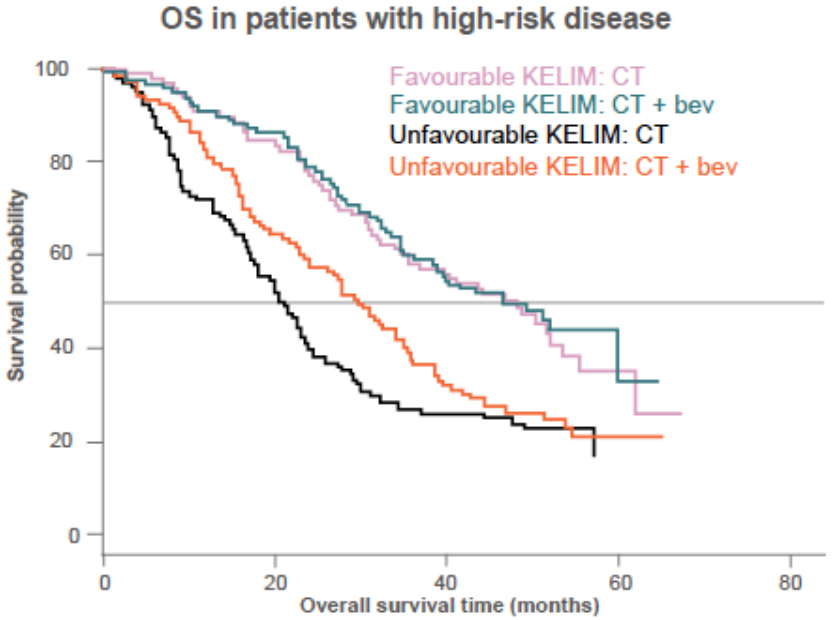


- **Subgroup analysis of PRIMA, PRIME and ATHENA-MONO suggest benefit for monotherapy PARPi maintenance in HRp patients**

*PRIME was sponsored by Zai Lab (Shanghai) Co., Ltd. PRIME homologous recombination subgroup data should be interpreted with caution as a different HRD test (BGI HRD test) was applied compared with all other studies using the Myriad myChoice CDx (PRIMA, PAOLA-1). Bev, bevacizumab; *BRCA*wt, breast cancer gene wild-type; CI, confidence interval; HRD, homologous recombination deficiency; HRp, homologous recombination proficient; LOH, loss of heterozygosity; mPFS, median progression-free survival; PARPi, poly(ADP-ribose)polymerase inhibitor. 1. González-Martín A, et al. N Engl J Med 2019;381:2391–402; 2. Braicu EI, et al. presented at ESGO SoA 2020 (Abstract), 14–16 Dec (virtual); 3. Li N, et al. presented at SGO 2022 (Abstract); 18–21 Mar; Phoenix, Arizona; 4. Moore KJ, et al. J Clin Oncol. https://doi.org/10.1200/JCO.22.01003; 5. Ray-Coquard I, et al. N Engl J Med 2019;381:2416–28.

KELIM & bevacizumab benefit in ICON-7



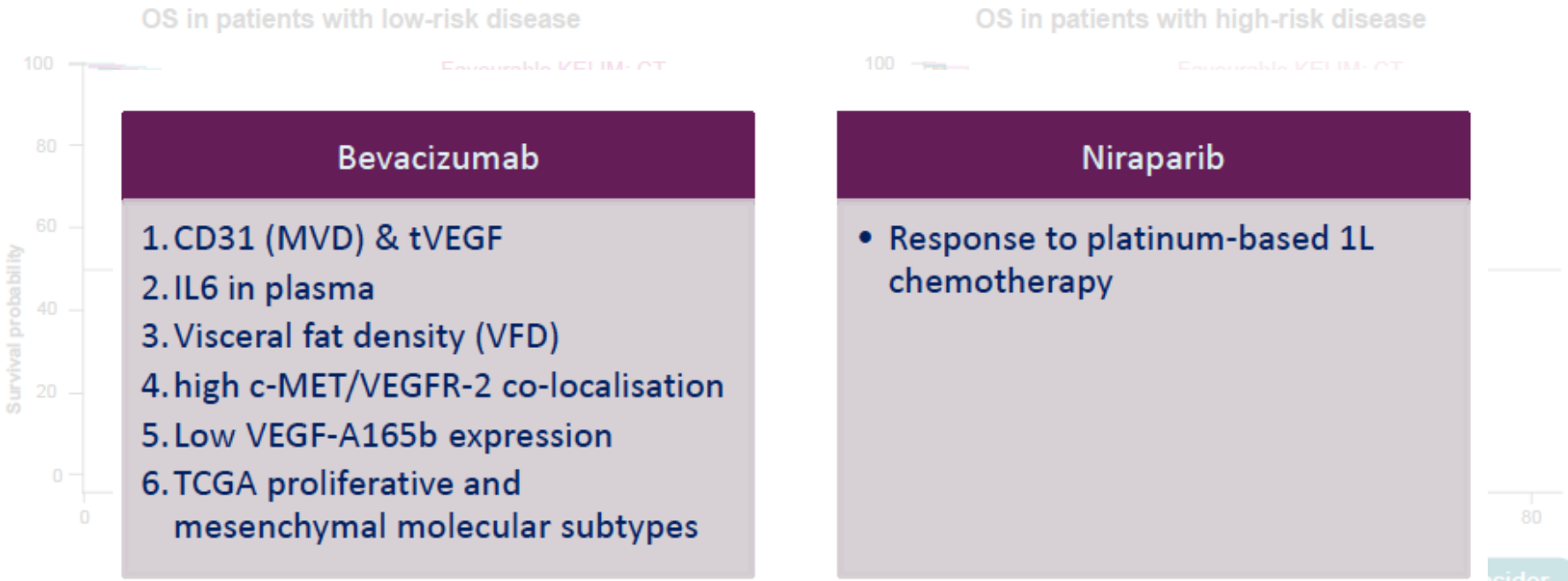


Unfavorable KELIM	<1.0
Favorable KELIM	≥1.0

Chemosensitivity, as assessed by KELIM, may be a complementary covariate to consider for decision-making about bevacizumab prescription. Approximately 47% of high-risk patients may not derive survival benefit from the addition of bevacizumab, however, the remaining 53% patients with poorly chemo-sensitive diseases may achieve the maximum survival gain of approximately 9 months.

Colomban O et al. JNCI Cancer Spectr. 2020;4(3):pkaa026. doi:10.1093/jncics/pkaa026

KELIM & bevacizumab benefit in ICON-7



Bevacizumab

1. CD31 (MVD) & tVEGF
2. IL6 in plasma
3. Visceral fat density (VFD)
4. high c-MET/VEGFR-2 co-localisation
5. Low VEGF-A165b expression
6. TCGA proliferative and mesenchymal molecular subtypes

Niraparib

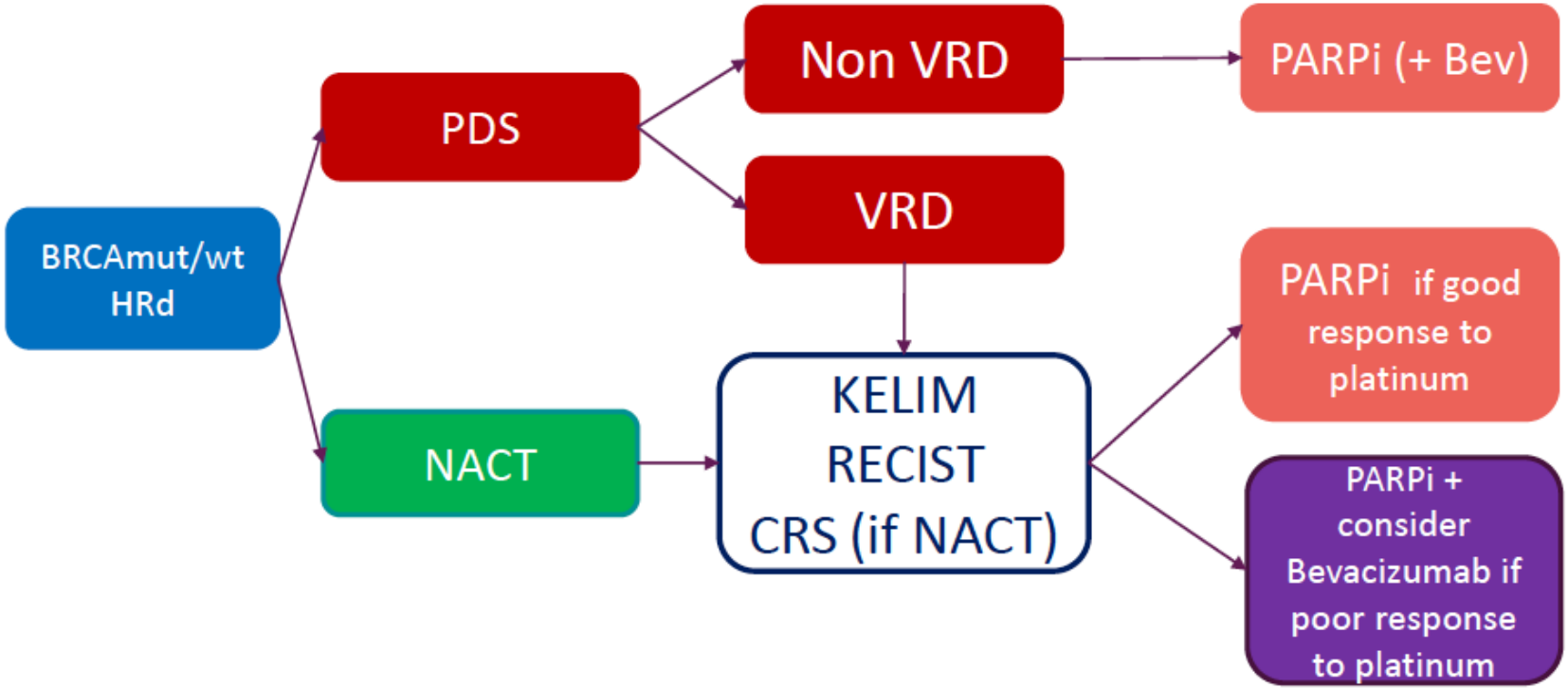
- Response to platinum-based 1L chemotherapy

Unfavorable KELIM	<1.0
Favorable KELIM	

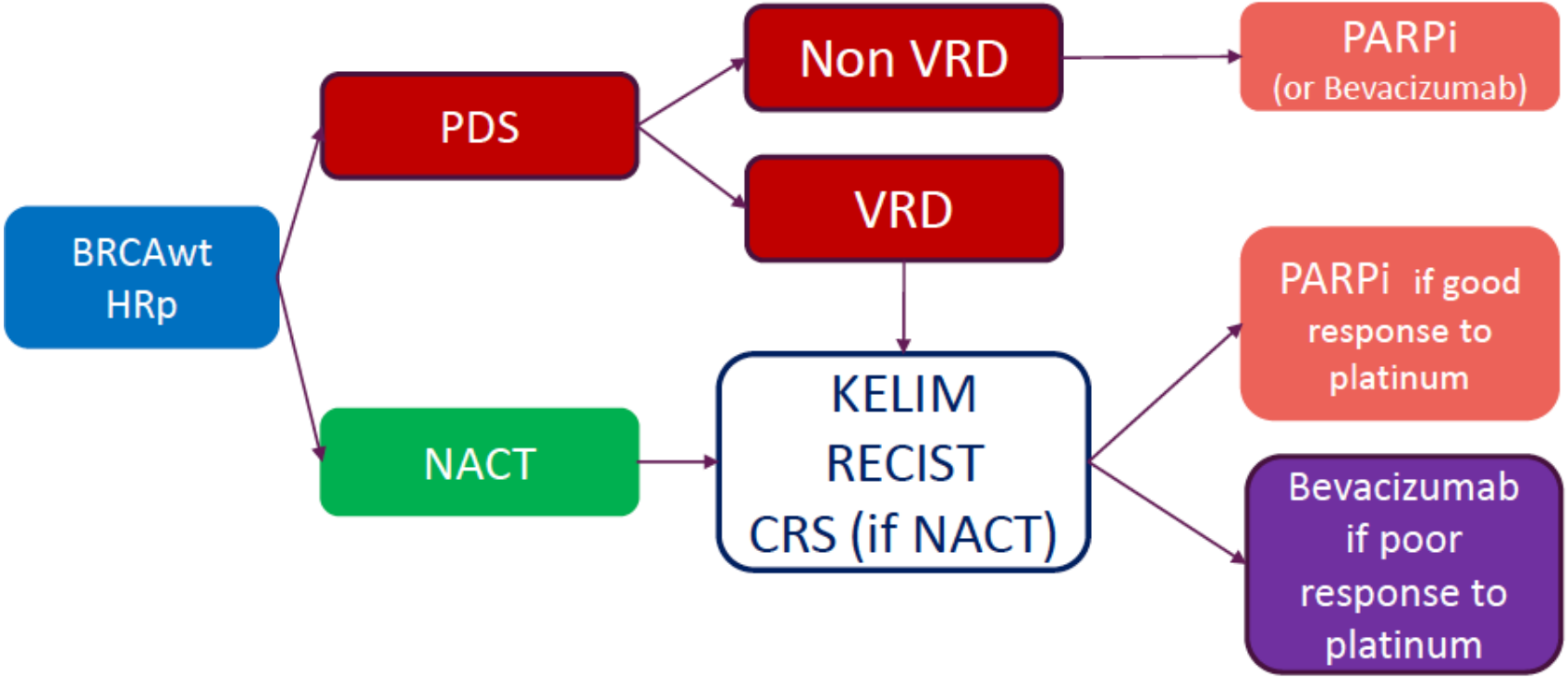
for decision-making about bevacizumab prescription. Approximately 47% of high-risk patients may not derive survival benefit from the addition of bevacizumab, however, the

1.BaisC et al. J NatlCancerInst. 2017 Nov 1;109(11):djx066. doi: 10.1093/jnci/djx066 (GOG-218)
2.AlvarezSecordet al. ClinCancerRes. 2020 Mar 15;26(6):1288-1296. doi: 10.1158/1078-0432.CCR-19-0226. (GOG-218)
3.Buechelet al. GynecolOncol. 2021 May;161(2):382-388. doi: 10.1016/j.ygyno.2021.02.032. (GOG-218)
4.Morgan R et al. BMC Med. 2022 Feb 11;20(1):59. doi: 10.1186/s12916-022-02270-y. (ICON-7)
5.Wimbergeret al. Clin Cancer Res. 2022 Aug 24:CCR-22-1326. doi: 10.1158/1078-0432.CCR-22-1326. (ICON-7)
6.Kommos et al. Clin Cancer Res. 2017 Jul 15;23(14):3794-3801. doi: 10.1158/1078-0432.CCR-16-2196 (ICON-7)

How to chose maintenance for patients in first-line if HR-deficient ?



How to chose maintenance for patients in first-line if BRCAwt/HRproficient ?



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- AOC relapse.
- Platinum resistant.

Improvement In PFS may not result in an improved OS

Some updated information in maintenance platinum sensitive recurrence……

All Resources

SUMMARY: REVISIONS TO FDA APPROVALS FOR PARP INHIBITORS IN THE MANAGEMENT OF OVARIAN CANCER

FEDERAL REGULATIONS, REPORT, STATEMENTS, CANCER CARE, OVARIAN CANCER

Dec 9, 2022

Below is a brief summary of the newly ***withdrawn FDA approvals*** *for PARP inhibitors in the management of epithelial ovarian cancer.*

Withdrawn Indications for Maintenance Therapy

- **2nd or greater line** *maintenance* following response to platinum-based chemotherapy for recurrent platinum-sensitive ovarian cancer
  - Niraparib
    - *Non*-germline *BRCA* [4,7] *no longer FDA approved* in this setting

***Anticipated Withdrawal* of Indication for Maintenance Therapy**

- **2nd or greater line** *maintenance* following response to platinum-based chemotherapy for recurrent platinum-sensitive ovarian cancer **
  - Rucaparib
    - *Non-BRCA*[8] *will no longer be FDA approved* in this setting

Withdrawn Indications for Single-agent Treatment

- Olaparib [3,6], rucaparib [2,5] and niraparib [9,10] *no longer FDA approved* in this setting

https://www.sgo.org/resources/revisions-to-fda-approvals-for-parp-inhibitors/

OVERALL SURVIVAL IN RANDOMIZED TRIALS WITH PARP INHIBITION IN RECURRENCE

Subgroups of patients without BRCA mutation

		NOVA[1]		ARIEL-3[2]		NORA[3]	
		Niraparib	Placebo	Rucaparib	Placebo	Niaraparib	Placebo
gBRCAwt HRDpos	N	106	56	106	52	-	-
	mOS (mos)	35.6	41.4	36.8	44.7	-	-
	HR 95% CI	**1.29 (0.85-1.95)**		**1.28 (0.84-1.94)**		-	
gBRCAwt HRDneg	N	92	42	107	54	-	-
	mOS (mos)	27.9	27.9	28.6	32.6	-	-
	HR 95% CI	**0.93 (0.61, 1.41)**		**1.15 (0.78-1.68)**		-	
gBRCAwt HRD unknown	N	36	18	33.9	26.7	-	-
	mOS (mos)	29.8	20.2	28.6	32.6	-	-
	HR 95% CI	**0.62(0.29, 1.36)**		**0.67 (0.30-1.48)**		-	

1. DHCP Letter GSK November 2022; 2. Coleman et al. ESGO 2022; 3. Mirza et al. ESMO Virtual Plenary 2022

PROGRESSION-FREE SURVIVAL WITH PARP INHIBITORS RANDOMISED TRIALS IN RECURRENT OVARIAN CANCER

			HR	Med PFS months Control	Med PFS months PARPi
Study 19	Olaparib	All	**0.35**	4.8	8.4
SOLO2*	Olaparib	*BRCAm*	**0.30**	5.5	19.1
NOVA	Niraparib	gBRCAm	**0.27**	5.5	21.0
		non-gBRCAm	**0.45**	3.9	9.3
ARIEL3	Rucaparib	ITT (all)	**0.36**	5.4	10.8
ARIEL 4	Rucaparib	*BRCAm (all)*	**0.64**	5.7	7.4
SOLO3	Olaparib	*BRCAm*	**0.62**	9.2	13.4

Primary endpoint PFS was met in all trials in recurrent ovarian cancer – significantly positive results

Ledermann et al, NEJM 2012; Pujade-Laurainеet al Lancet Oncol 2017 ; Mirza et al NEJM 2016; Coleman et al, Lancet 2017; Kristeleitet al; lancet Oncol 2022; Penson et al J Clin Oncol 2020

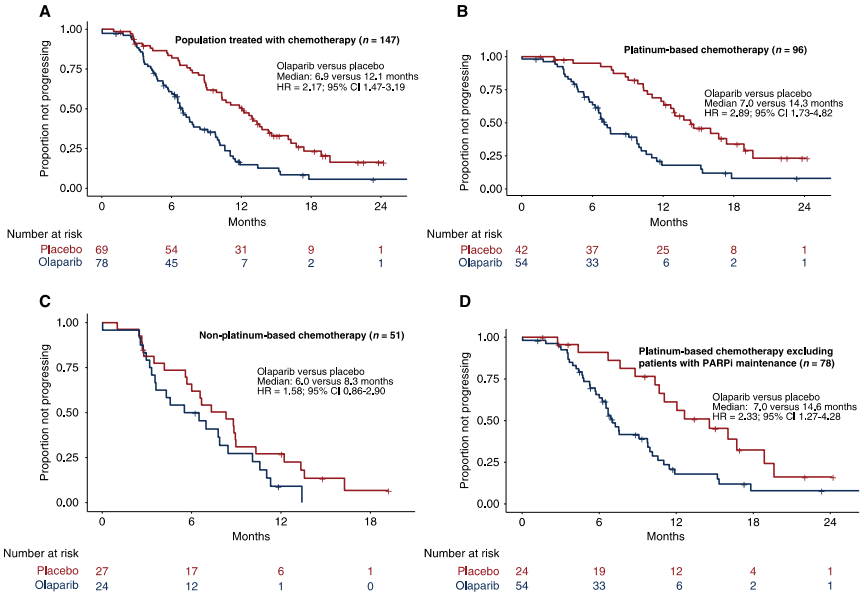
POTENTIAL EXPLANATIONS

1. Statistical analysis
2. Subsequent therapy and crossover
3. Safety issues
4. Induction of cross-resistance

Cross-resistance

EDITORIAL

Life after SOLO-2: is olaparib really inducing platinum resistance in BRCA-mutated (BRCAm), PARP inhibitor (PARPi)-resistant, recurrent ovarian cancer?



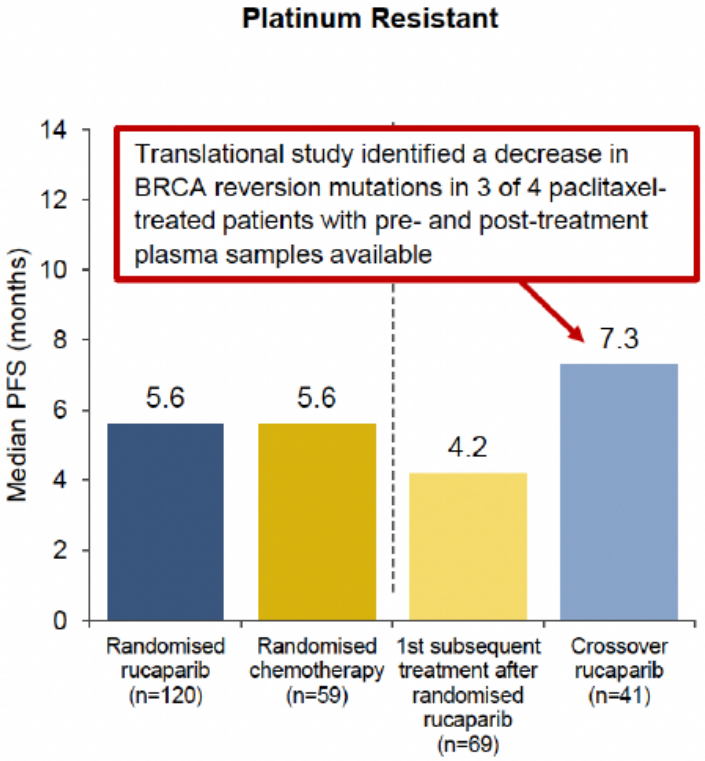
Frenel et al. Ann Oncol 2022

Highly selected, imbalanced, poorer prognosis subset of the SOLO-2 olaparib-treated population has been analysed that may not be representative of the whole population with respect to subsequent platinum response.

R. S. Kristeleit & K. N. Moore https://doi.org/10.1016/j.annonc.2022

Cross-resistance

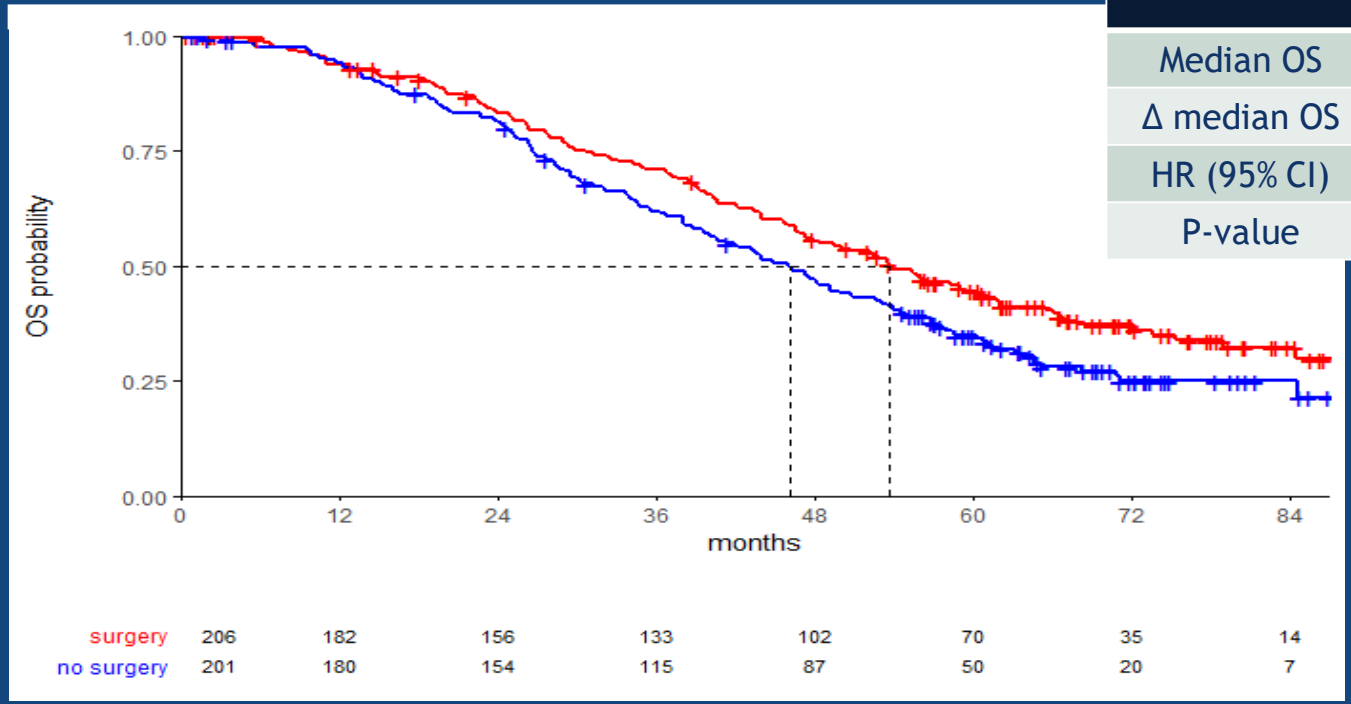
EXPLORATORY ANALYSIS IN ARIEL-4



Sequence of non-platinum chemotherapy may matter

AGO DESKTOP III: Outcome 1 (OS, ITT population)

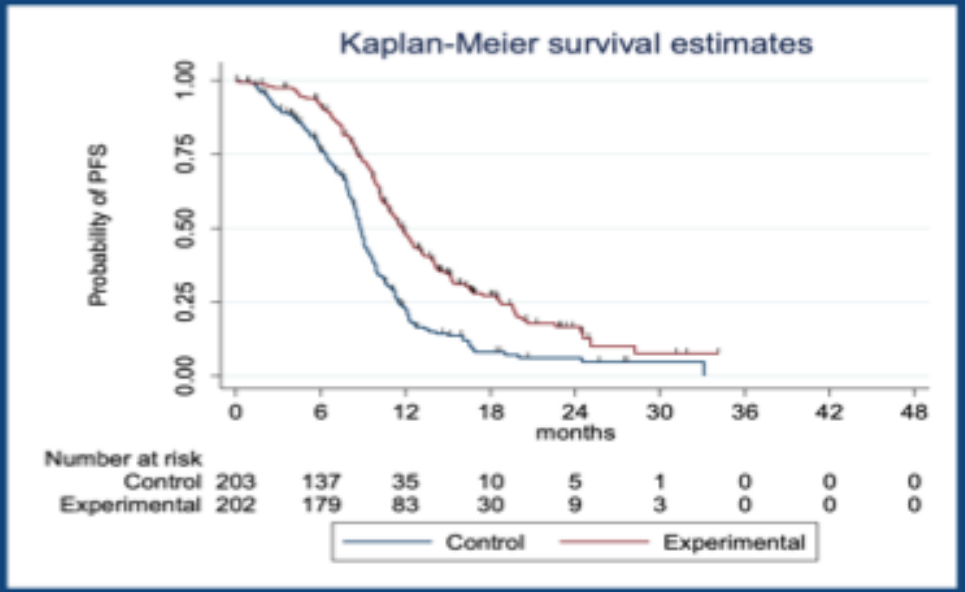
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)



	surgery	no surgery
Median OS	53.7 mos	46.0 mos
Δ median OS	7.7 mos	
HR (95% CI)	0.75 (0.58 - 0.96)	
P-value	0.02	

Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line. The randomized phase 3 trial MITO16B - MaNGO OV2B - ENGOT OV17

PFS Investigator assessed (primary end-point)



	Standard	Experimental	Log Rank P
# events	161	143	
Median PFS	8.8 mos	11.8 mos	<0.001
HR* (95%CI)	0.51 (0.41-0.65)		

*adjusted by:
age, PS, centre size, bevacizumab at relapse, chemo backbone, residual disease at initial surgery

Sandro Pignata

TOPICS

- Introduction.
- First-line maintenance in advanced ovarian cancer (AOC).
- AOC relapse.
- Platinum resistant.

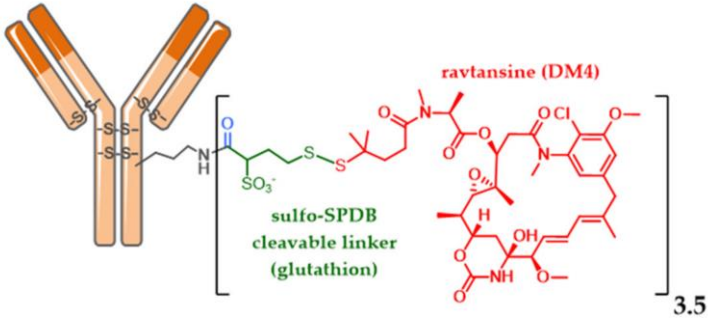
- Our current situation and reference for new agents…

Therapy	ORR	PFS	OS
Paclitaxel 80 mg/m2 d1,8,15,22 q4w +/- Bevacizumab	30.2% vs 53.3% (Δ 23.1%)	3.9 months vs 10.4 months (HR 0.46)	13.2 months vs 22.4 months (HR 0.65)
PLD 40 mg/m2 q4w +/- Bevacizumab	7.8% vs 13.7% (Δ 5.9%)	3.5 months vs 5.4 months (HR 0.57)	14.1 months vs 13.7 months (HR 0.91)
Topotecan 4 mg/m2 d1,8,15 q4w or 1.25 mg/m2 d1-5 q3w +/- Bevacizumab	0.0% vs 17.0% (Δ 17.0%)	2.1 months vs 5.8 months (HR 0.32)	13.3 months vs 13.8 months (HR 1.09)
Gemcitabine 1000 mg/m2 d1,8 q3w or d1,8,15 q4w	10-29%	3.6-4.7 months	10-12.7 months

Pujade-Lauraine E. J Clin Oncol 2014; 32:1302-8. Poveda AM. J Clin Oncol 2015; 33:3836-8. Mutch DG. J Clin Oncol 2007; 25:2811-8. Ferrandina G. J Clin Oncol 2008; 26:890-6

Antibody drug conjugates (ADCs)

Target	Expression	Examples
FRα	67-100%	**Mirvetuximab** STRO-02 MORAB-B-202
Mesothelin	55-100%	**Anetumab**
HER-2	2-66%	Trastuzumab-Dx TDM1
MUC16/CA125	70-90%	DMUC5754A DMUC4064A
TROP2	82-92%	Sacituzumab govitecan
NaPi2b	80-93%	**Upifitamab rilsodotin** Lifastuzumab Vedotin
TF	23-100%	Tisotumab Vedotin
CDH6	70%	Praluzatamab ravtansine



anti-Folate R1 **mirvetuximab soravtansine**

Birrer et al. JNCI 2019

Antibody drug conjugates (ADCs)

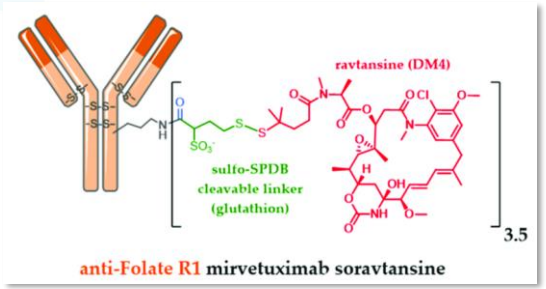
How to treat platinum-resistant patients?

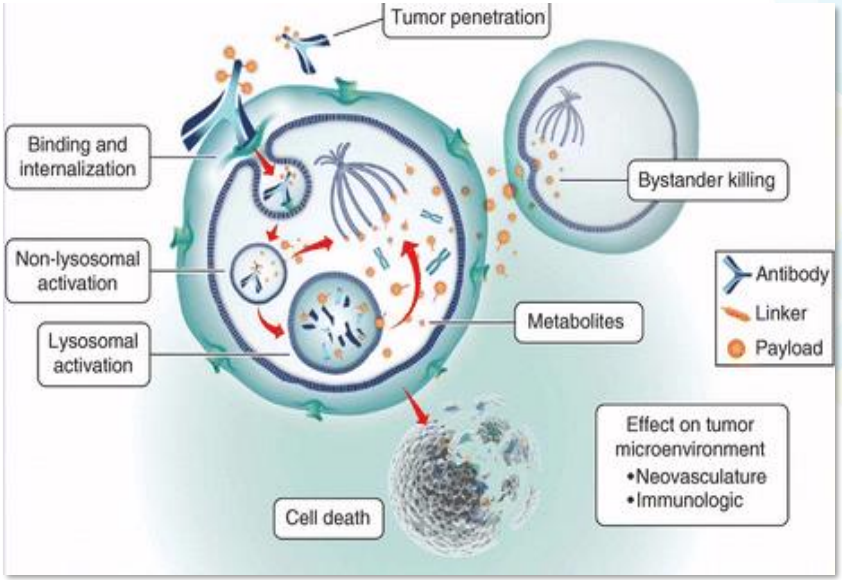
NEW AGENTS KNOCKING ON THE DOOR

- *MIRVETUXIMAB SORAVTANSINE*

  - Folate receptor-α (FRα) is a cell surface protein overexpressed in 70-100% of EOC

  - MS is an antibody–drug conjugate that targets FRα to deliver the microtubule-disrupting agent DM4 directly to the tumor





Moore KN, et al. Ann Oncol 2021; 32: 757-765

Antibody drug conjugates (ADCs)

2023 ASCO ANNUAL MEETING

Phase III MIRASOL (GOG 3045/ENGOT-ov55) Study: Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancers with High Folate Receptor-Alpha (FRα) Expression

Kathleen N. Moore[1], Antoine Angelergues[2], Gottfried E. Konecny[3], Susana Banerjee[4], Sandro Pignata[5], Nicoletta Colombo[6], John Moroney[7], Casey Cosgrove[8], Jung-Yun Lee[9], Andrzej Roszak[10], Shani Breuer[11], Jacqueline Tromp[12], Diana Bello Roufai[13], Lucy Gilbert[14], Rowan Miller[15], Tashanna Myers[16], Yuemei Wang[17], Anna Berkenblit[17], Domenica Lorusso[18], Toon Van Gorp[19]

[1]Stephenson Cancer Center University of Oklahoma College of Medicine, Oklahoma City, OK, USA; [2]Groupe Hospitalier Diaconesses Croix Saint Simon, Paris, France; [3]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [4]The Royal Marsden NHS Foundation Trust - Royal Marsden Hospital, London, UK; [5]Istituto Nazionale Tumori- G. Pascale, Naples, Italy; [6]European Institute of Oncology IRCCS, Milan, Italy and University of Milan-Bicocca, Milan, Italy; [7]The University of Chicago, Chicago, IL, USA; [8]The Ohio State University, Columbus, OH, USA; [9]Severance Hospital, Seoul, South Korea; [10]Wielkopolskie Centrum Onkologii, Poznan, Poland; [11]Hadassah Ein Kerem – Sharett, Jerusalem, Israel; [12]Amsterdam UMC, Amsterdam, The Netherlands; [13]Hopital Rene Huguenin, Institut Curie, Saint-Cloud, France; [14]McGill University Health Centre, Montreal, Canada; [15]University College London Hospital, London, UK; [16]Baystate Medical Center, Springfield, MA, USA; [17] ImmunoGen, Inc., Waltham, MA, USA; [18]Fondazione Policlinico Universitario A. Gemelli, IRCCS and Catholic University of Sacred Heart, Rome, Italy; [19]University Hospital Leuven Leuven Cancer Institute, Leuven, Belgium

ENGOT European Network of Gynaecological Oncological Trial groups

GOG FOUNDATION® Transforming the standard of care™

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Antibody drug conjugates (ADCs)

MIRASOL (NCT04209855) – Study Design[1,2]

An open-label, phase 3 randomized trial of MIRV vs investigator's choice chemotherapy in patients with FRα-high platinum-resistant ovarian cancer

Patient Population
(N=453)

Enrollment and Key Eligibility
Platinum-resistant disease (PFI ≤6 mo)
FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells
High-grade serous histology
1º platinum-refractory disease excluded (primary PFI <3 mo)
1-3 prior lines of therapy
Prior BEV and PARPi allowed
Patients with BRCA mutations allowed

1:1 Randomization

Treatment Regimen-Experimental
MIRV
(6 mg/kg AIBW Q3W)

Treatment Regimen-Control
Investigator's Choice Chemotherapy
(Paclitaxel, PLD, or Topotecan)

Stratification Factors
IC chemo: paclitaxel, PLD, or topotecan
Prior lines of therapy: 1 vs 2 vs 3

Primary Endpoint
PFS by INV
(BICR sensitivity analysis)

Key Secondary Endpoints
1) ORR by INV
2) OS
3) PROs[a]

Secondary Endpoints
Safety and tolerability
DOR
CA-125 response[b]
PFS2

AIBW, adjusted ideal body weight; BEV, bevacizumab; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; chemo, chemotherapy; DOR, duration of response; FRα, folate receptor alpha; IC, investigator's choice; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PFS2, time from randomization until second disease progression; PLD, pegylated liposomal doxorubicin; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks.
[a]PROs will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (OV28) study instrument.
[b]Gynecological Cancer InterGroup (GCIG) criteria.

1. ClinicalTrials.gov identifier: NCT04209855. Updated June 16, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04209855
2. Moore K, et al. Presented at: 2020 American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual. Abstract TPS6103.

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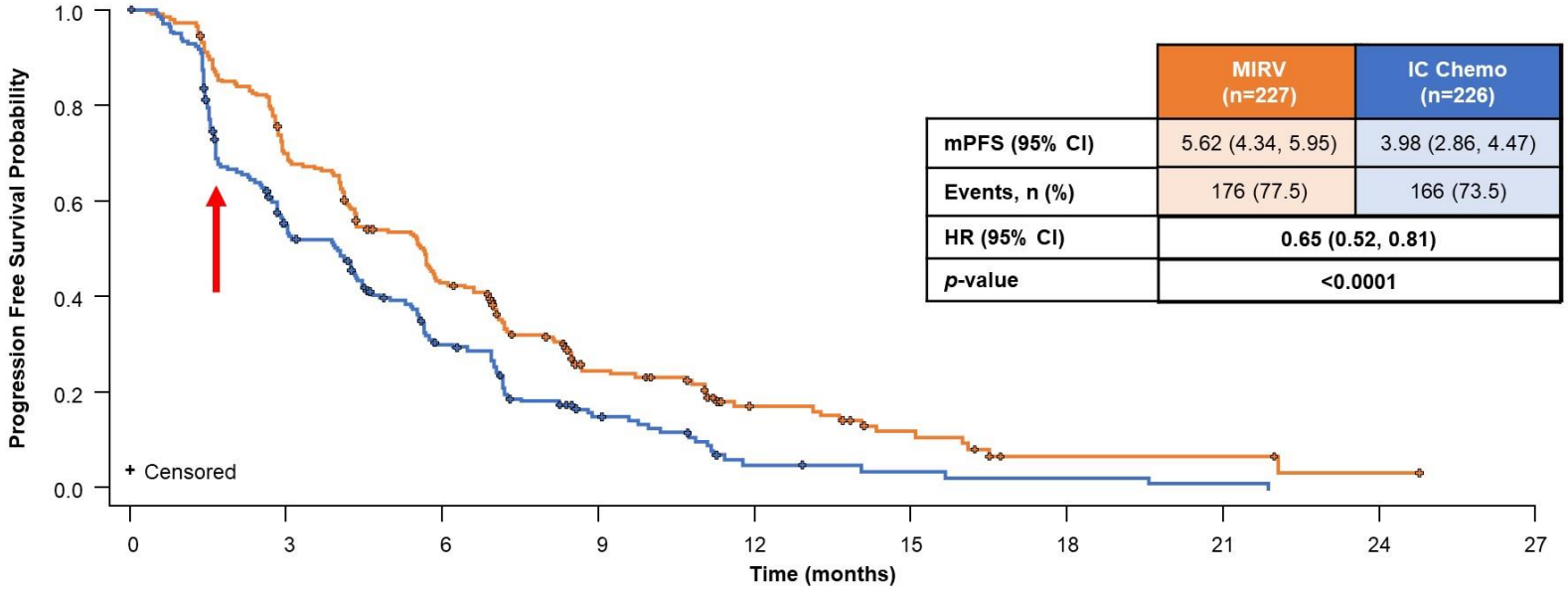
Antibody drug conjugates (ADCs)

Primary Endpoint: Progression-Free Survival by Investigator



	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Events, n (%)	176 (77.5)	166 (73.5)
HR (95% CI)	0.65 (0.52, 0.81)	
p-value	<0.0001	

No. Participants at Risk

MIRV	227	151	89	38	18	10	3	3	1	0
IC Chemo	226	98	48	19	5	3	2	1	0	

Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mPFS, median progression-free survival; CI, confidence interval; HR, hazard ratio.

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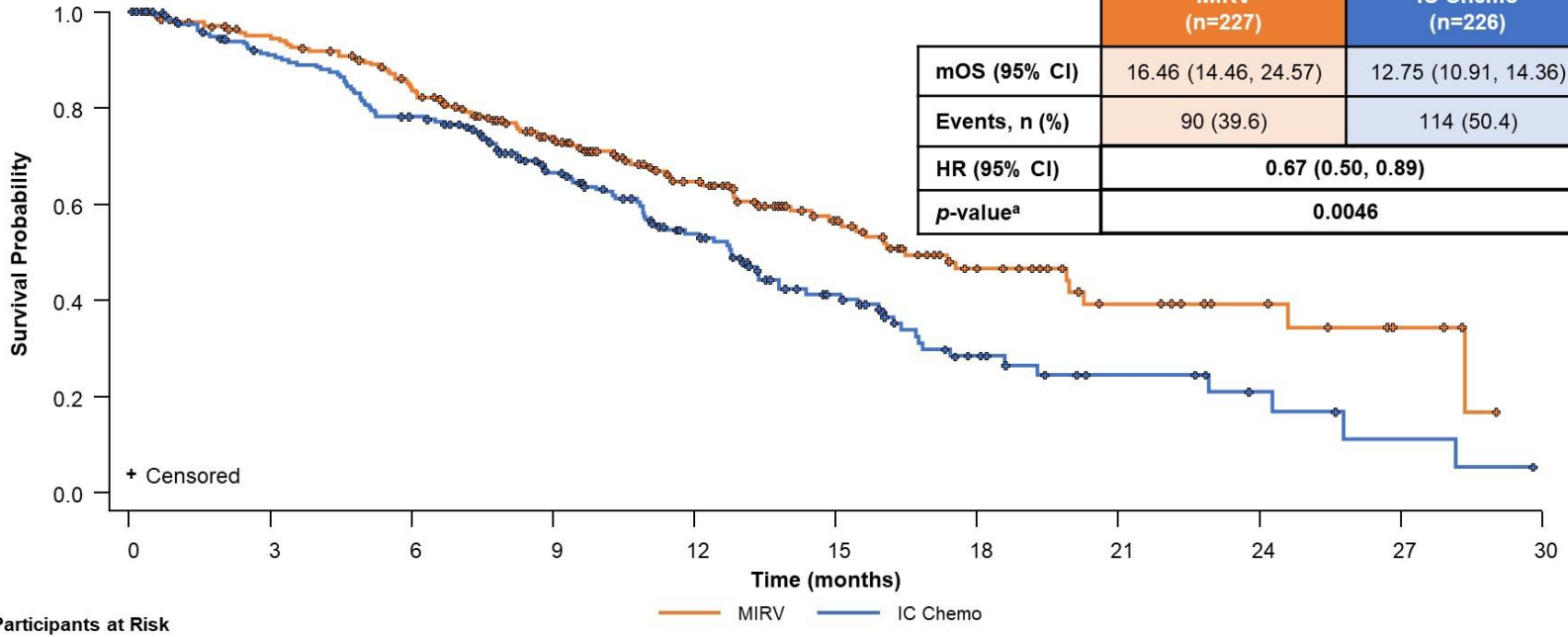
Antibody drug conjugates (ADCs)

Overall Survival



	MIRV (n=227)	IC Chemo (n=226)
mOS (95% CI)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
Events, n (%)	90 (39.6)	114 (50.4)
HR (95% CI)	0.67 (0.50, 0.89)	
p-value[a]	0.0046	

No. Participants at Risk

MIRV	227	204	175	128	82	53	28	15	9	4	0
IC Chemo	226	185	157	107	68	39	18	9	5	2	0

Data cutoff: March 6, 2023; median follow-up time: 13.11 months
MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mOS, median overall survival; CI, confidence interval; HR, hazard ratio.
[a]Overall survival is statistically significant based on pre-specified boundary p-value at interim analysis = 0.01313

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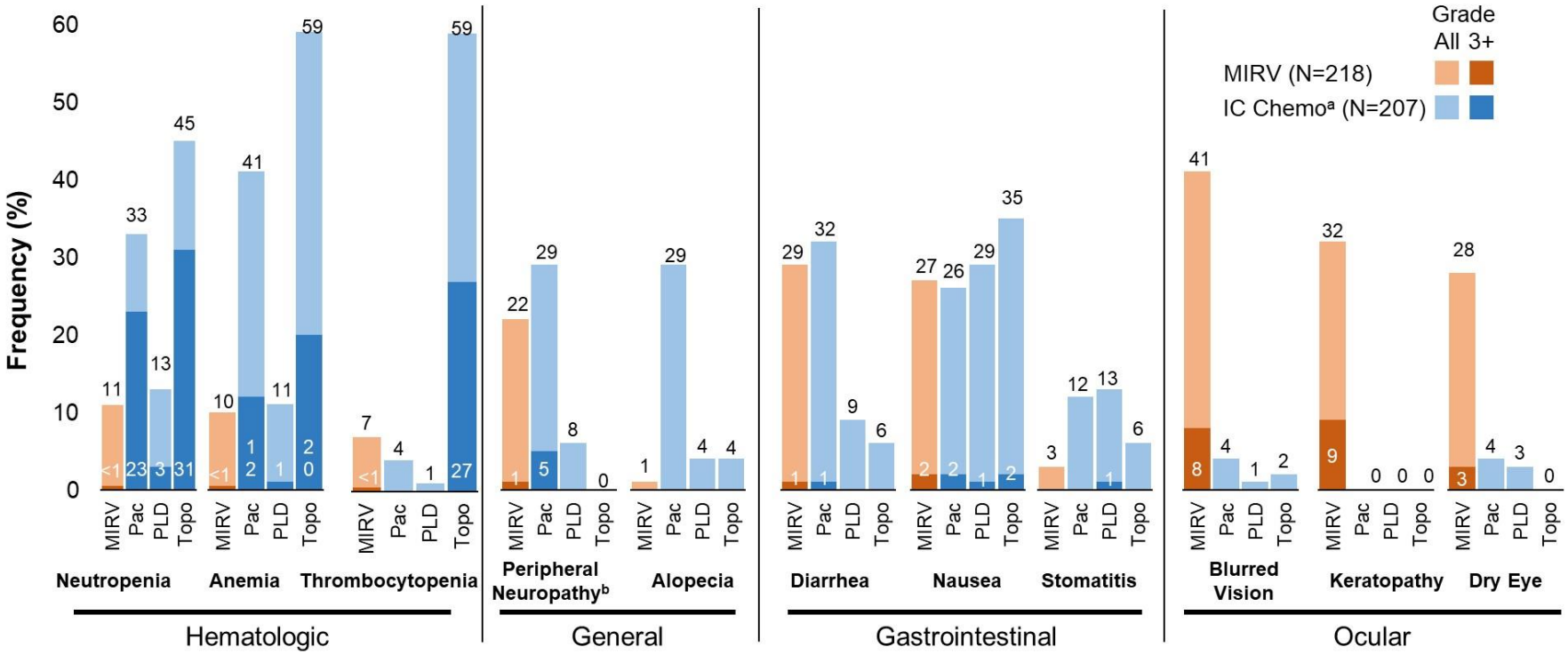
Antibody drug conjugates (ADCs)

Differentiated Safety Profile: Treatment-Emergent Adverse Events



Data cutoff: March 6, 2023
MIRV, mirvetuximab soravtansine; IC Chemo: investigator's choice chemotherapy; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; Topo, topotecan.
[a]Pac n=82 (39%), PLD n=76 (37%), Topo n=49 (24%). [b]Grade 2+ peripheral neuropathy events were observed in 12% and 16% of patients that received MIRV or paclitaxel, respectively.

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Antibody drug conjugates (ADCs)

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FRα	67-100%	**Mirvetuximab** STRO-02 MORAB-B-202
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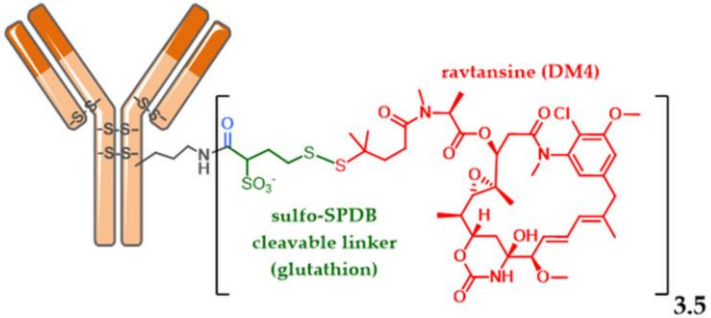

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[illegible]OP2	82-92%	Sacituzumab govitecan
[illegible]	80-93%	**Upifitamab rilsodotin** Lifastuzumab Vedotin
[illegible]	23-100%	Tisotumab Vedotin
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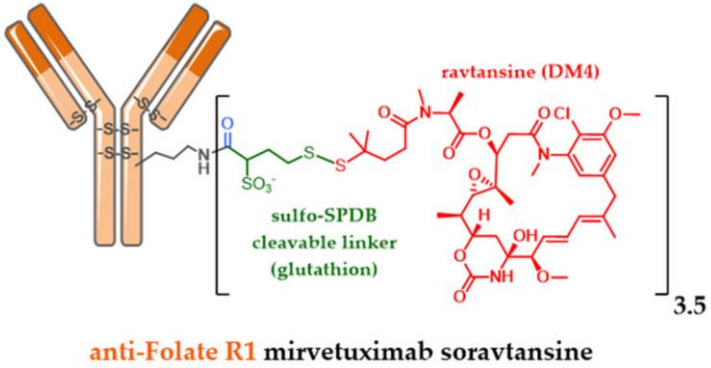
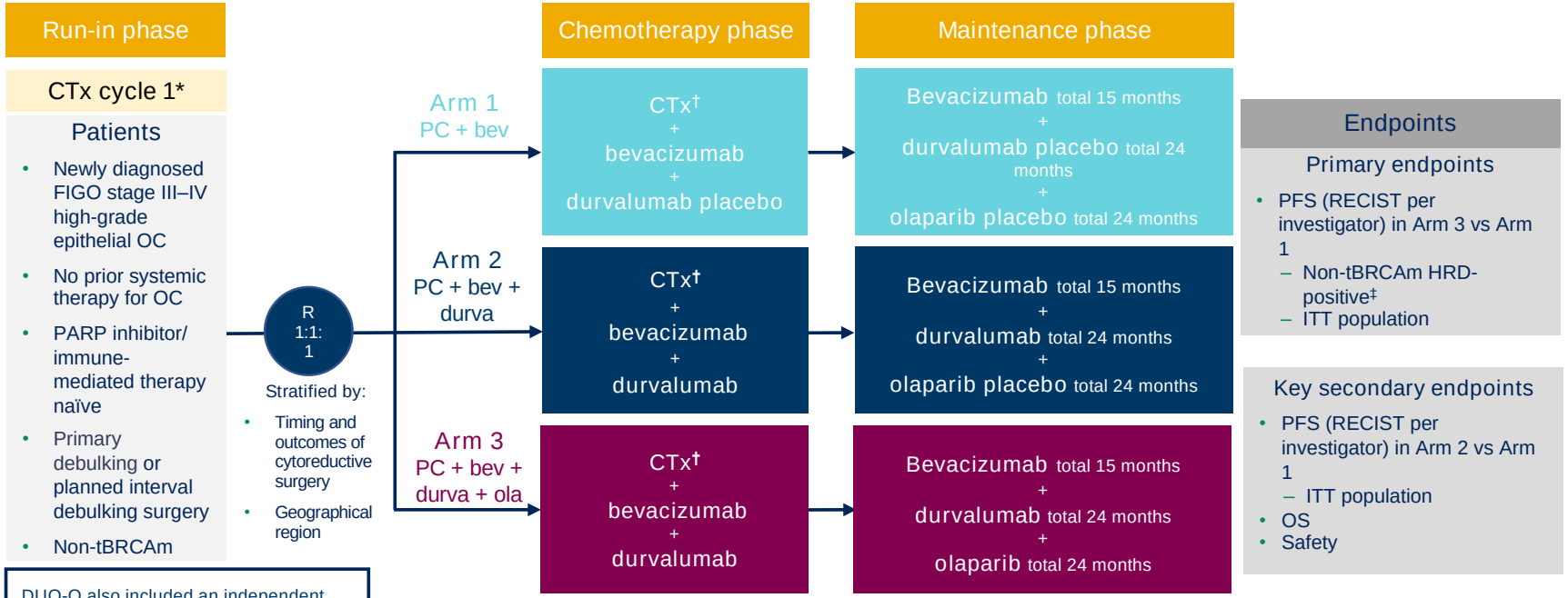


anti-Folate R1 **mirvetuximab soravtansine**

Birrer et al. JNCI 2019

IMMUNOTHERAPY

DUO-O study design



Endpoints

Primary endpoints

- PFS (RECIST per investigator) in Arm 3 vs Arm 1
  - Non-tBRCAm HRD-positive‡
  - ITT population

Key secondary endpoints

- PFS (RECIST per investigator) in Arm 2 vs Arm 1
  - ITT population
- OS
- Safety

DUO-O also included an independent, single-arm, open-label tBRCAm cohort – results are not presented

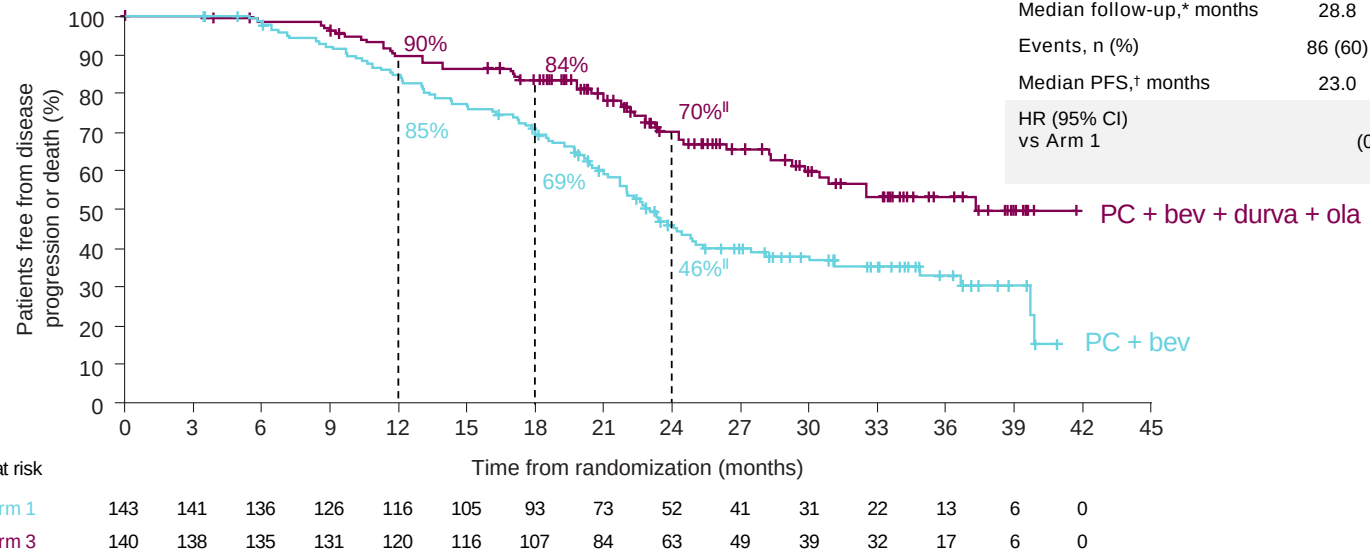
Treatment continued until disease progression, study treatment was complete or other discontinuation criteria were met

Dosing and schedule: bevacizumab (15 mg/kg IV q3w); durvalumab (1120 mg IV q3w); olaparib (300 mg po bid); chemotherapy: paclitaxel 175 mg/m^2 IV q3w and carboplatin at AUC5 or AUC6 IV q3w. PFS interim analysis DCO: December 5, 2022.
*With or without bevacizumab according to local practice; †Cycles 2–6; ‡Genomic instability score ≥42 assessed prospectively by Myriad MyChoice CDx assay.
AUC, area under the curve; bev, bevacizumab; bid, twice daily; CTx, chemotherapy; DCO, data cutoff; durva, durvalumab; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intent-to-treat; IV, intravenous; ola, olaparib; OS, overall survival; PC, paclitaxel/carboplatin; po, by mouth; q3w, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria for Solid Tumors.

PFS: Non-tBRCAm HRD-positive population

Arm 3 vs Arm 1

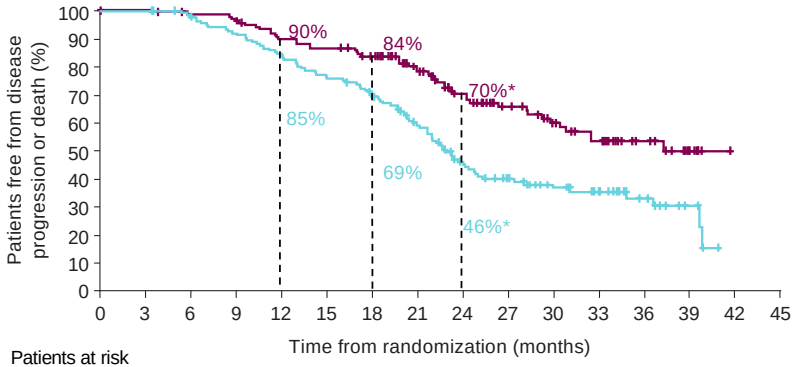
	Arm 1 PC + bev N=143	Arm 3 PC + bev + durva + ola N=140
Median follow-up,* months	28.8	25.6
Events, n (%)	86 (60)	49 (35)
Median PFS,† months	23.0	37.3‡
HR (95% CI) vs Arm 1	0.49 (0.34–0.69)§ *P*<0.0001	



*In censored patients; †Medians and rates were estimated by KM method; ‡Median PFS in Arm 3 unstable; §HR and CI were estimated from a stratified Cox proportional hazards model. *P* value from a stratified log rank text. Model stratified by timing and outcome of cytoreductive surgery; ‖24-month PFS rates unstable.
CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier.

Subgroup analysis of PFS by HRD status

Non-tBRCAm HRD-positive

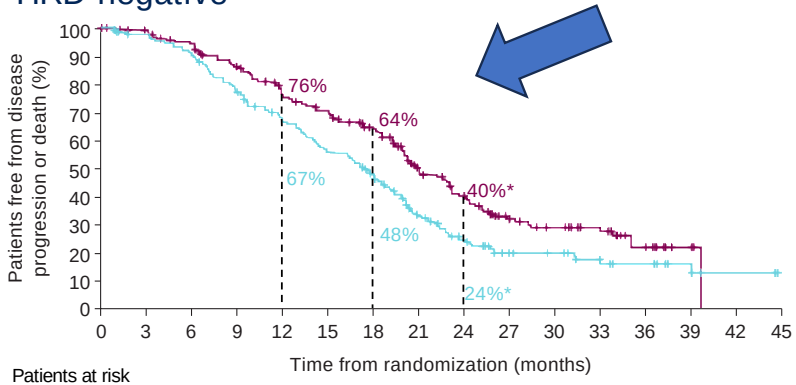


Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

	Arm 1 PC + bev N=143	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	49 (35)
Median PFS, months†	23.0	37.3‡
HR (95% CI) vs Arm 1		0.51 (0.36–0.72)§

HRD-negative



Patients at risk

Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0	

	Arm 1 PC + bev N=216	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	127 (60)
Median PFS, months†	17.4	20.9
HR (95% CI) vs Arm 1		0.68 (0.54–0.86)§

*24-month PFS rates unstable; †Medians and rates were estimated by KM method; ‡Median PFS in HRD-positive subgroup Arm 3 and Arm 2 unstable; §HR and CI were estimated from an unstratified Cox proportional hazards model.

PARPi now in First line: What's next?

- Targeting glucocorticoid receptor
- Targeting Cell Cycle Regulation and DNA Repair
- Improved drug delivery system : ADC
- Targeting PARPi resistance
- Enhancing PARPi activity (inducing HRD)
- New Generation PARPi
- Targeting the tumor microenvironment
    - Fusion proteins
    - Novel immunotherapy approaches

Take home messages

- **PARP inhibitors are a major addition to our treatment armamentarium.**
- **Our best selective biomarkers remain platinum-sensitivity and DDR genotypes.**
- **There may be a curative benefit for a subset of patients. Further data maturation is required.**
- **PostPARPi progression directions are needed.**
- **MIRV a new standard of care or patients with FRα-positive PROC.**