ESMO 2022 GYN Review

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October 2022

ESMO 2022
Top-line advances

	PARPi?	IO	Other targeted Tx
Ovarian Cancer	👍👍👍	👎...	👍
Cervical Cancer	👎	👍👍	?
Endometrial Cancer	?	👍👍	👍

PARIS 2022 ESMO congress

Clare L Scott

Ovary/FT Cancer

BRCA mutations open the door to biomarker directed therapy of ovarian cancer

A decade of maintenance therapy in advanced ovarian cancer

Jonathan A Ledermann

1. Ledermann J, et al. N Engl J Med. 2012;366(15):1382–92. 2.Ledermann et al Lancet Oncol 2014 15: 852-61 3. Mirza MR, et al. N Engl J Med 2016;375:2154-64; 4. Pujade-Lauraine E, et al. Lancet Oncol 2017;18:1274–84; 5. Coleman R, et al. Lancet 2017;390:1949–61; 6. Moore K, et al. N Engl J Med 2018;379:2495–505; 7. González-Martín A, et al. N Engl J Med. 2019;381:2391–402; 8. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416–28.

PARPis have changed the management of front-line Advanced OC

	SOLO-1[1]	PAOLA-1[2]	PRIMA[3]	PRIME[4]	ATHENA-MONO[5]
PARPi	Olaparib	Olaparib	Niraparib	Niraparib	Rucaparib
Bevacizumab	No	Yes	No	No	No
Population	BRCAmut	All comers	All comers	All comers (Chinese)	All comers
HRD test	NA				
BRCAmut HR (CI-95%)	0.33 (0.25–0.43)	0.31* (0.20–0.47)	0.40* (0.27–0.62)	0.40* (0.23-0.68)	0.31* (0.20–0.47)
BRCAwt/HRD+ HR (CI-95%)	-	0.43* (0.28-0.66)	0.50* (0.31-0.83)	0.58* (0.36-0.93)	0.58* (0.33-1.01)
BRCAwt/HRD- HR (CI-95%)	-	0.92* (0.72-1.17)	0.68* (0.49-0.94)	0.41* (0.25-0.65)	0.65* (0.45-0.95)

*exploratory

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

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

SOLO1 Study design and updated PFS analysis

- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- BRCAm
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical complete† or partial response after platinum-based chemotherapy

Olaparib 300 mg bid (N=260)

2:1 randomization

Stratified by response to platinum-based chemotherapy

Placebo (N=131)

For up to 2 years or until disease progression‡

Primary endpoint

- PFS (investigator-assessed)

Secondary endpoints included:

- OS
- TFST
- TSST
- Safety

Primary PFS analysis[1] (DCO 17 May 2018)

	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
3-year PFS rate, %	60.4	26.9
HR 0.30 (95% CI 0.23–0.41)		
P<0.001		

Updated PFS analysis[2] (DCO 5 March 2020)

	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	118 (45.4)	100 (76.3)
Median PFS, months	56.0	13.8
5-year PFS rate, %	48.3	20.5
HR 0.33 (95% CI 0.25–0.43)		

*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease. †Including patients with no evidence of disease; ‡Patients with evidence of disease at 2 years could continue to receive study treatment if, in the investigator's opinion, this was in the patient's best interest

bid, twice daily; CI, confidence interval; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NR, not reached; PFS, progression-free survival; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

1. Moore K *et al. N Engl J Med* 2018;379:2495–505; 2. Banerjee S *et al. Lancet Oncol* 2021;22:1721–31

SOLO1 Statistical analysis

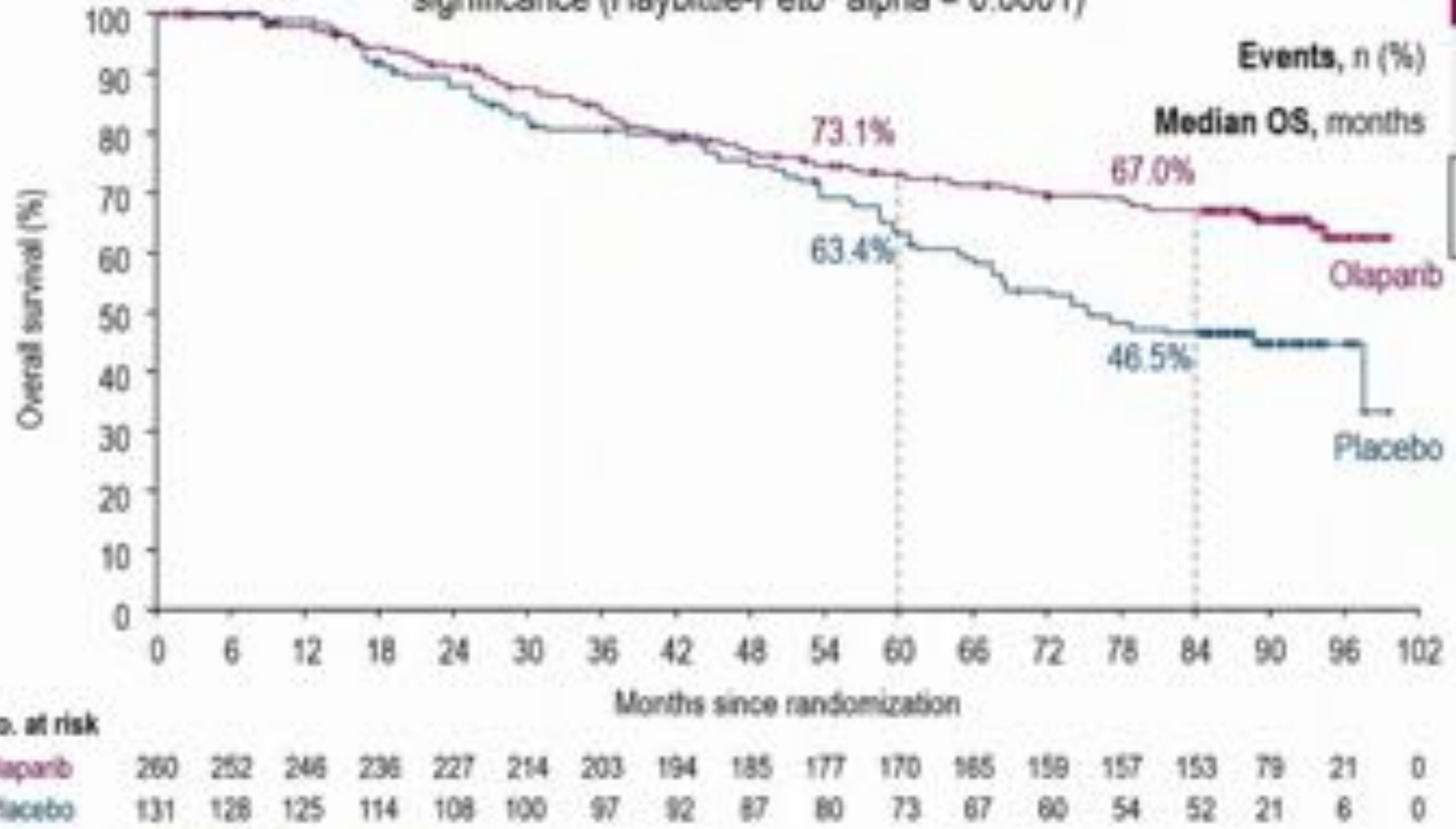
- Prespecified descriptive OS analysis conducted 7 years after the last patient was randomized:
  - OS unadjusted for subsequent PARP inhibitor therapy
- Two-sided *P* value of <0.0001 required to declare statistical significance (Haybittle-Peto[1] alpha = 0.0001)
- Prespecified final OS analysis currently planned to be conducted at approximately 60% data maturity

1. Haybittle JL. *Br J Radiol* 1971;44:793–7

SOLO1 7 Year Overall Survival Analysis

Maintenance olaparib provided a clinically meaningful OS benefit

- Two-sided *P* value of <0.0001 required to declare statistical significance (Haybittle-Peto[1] alpha = 0.0001)



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	**NR**	**75.2**

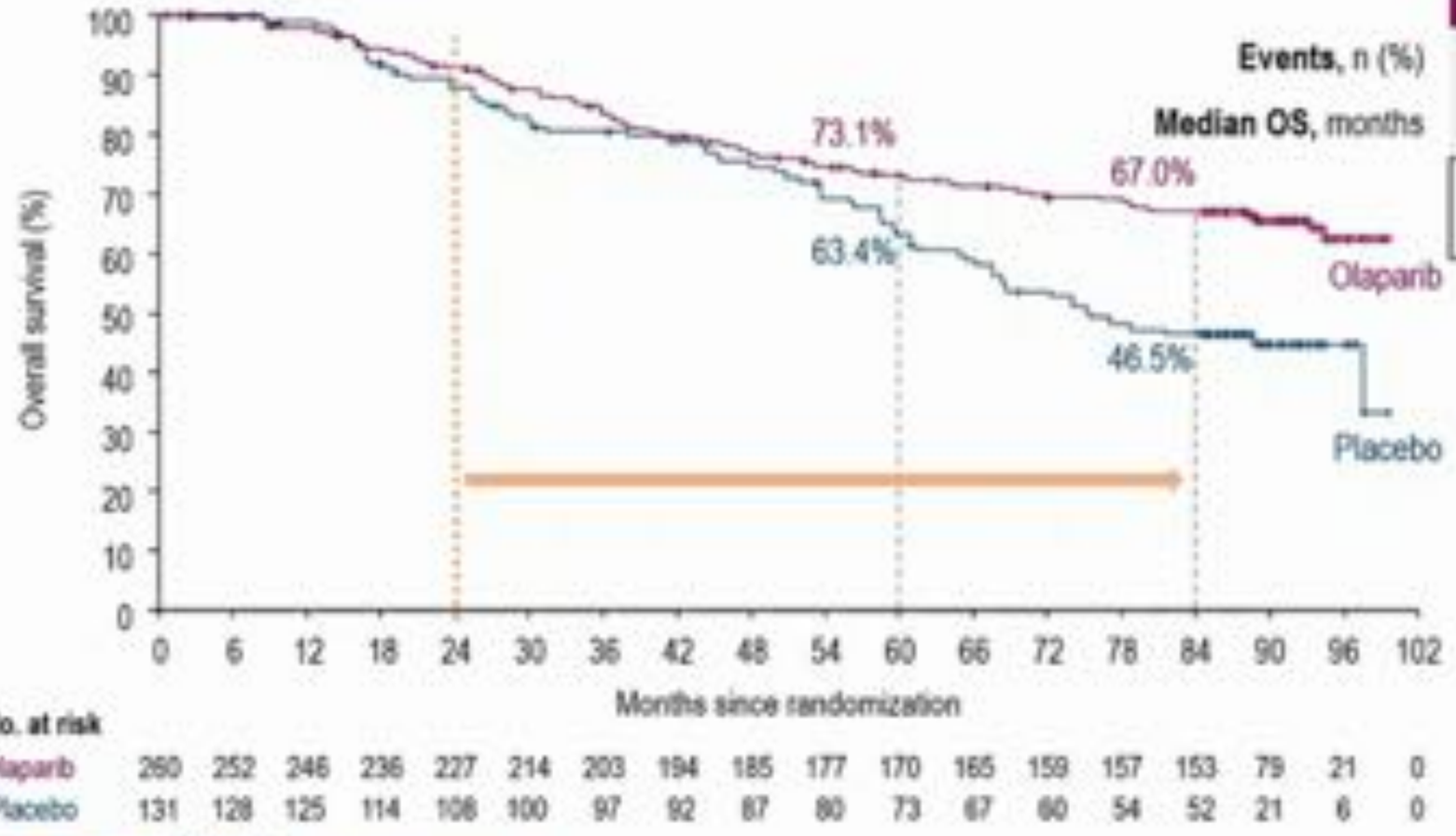
HR 0.55 (95% CI 0.40–0.76); *P*=0.0004*

No. at risk																		
Olaparib	260	252	246	236	227	214	203	194	185	177	170	165	159	157	153	79	21	0
Placebo	131	128	125	114	108	100	97	92	87	80	73	67	60	54	52	21	6	0

*P<0.0001 required to declare statistical significance

SOLO1 7 Year Overall Survival Analysis

Maintenance olaparib provided a clinically meaningful OS benefit



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	**NR**	**75.2**

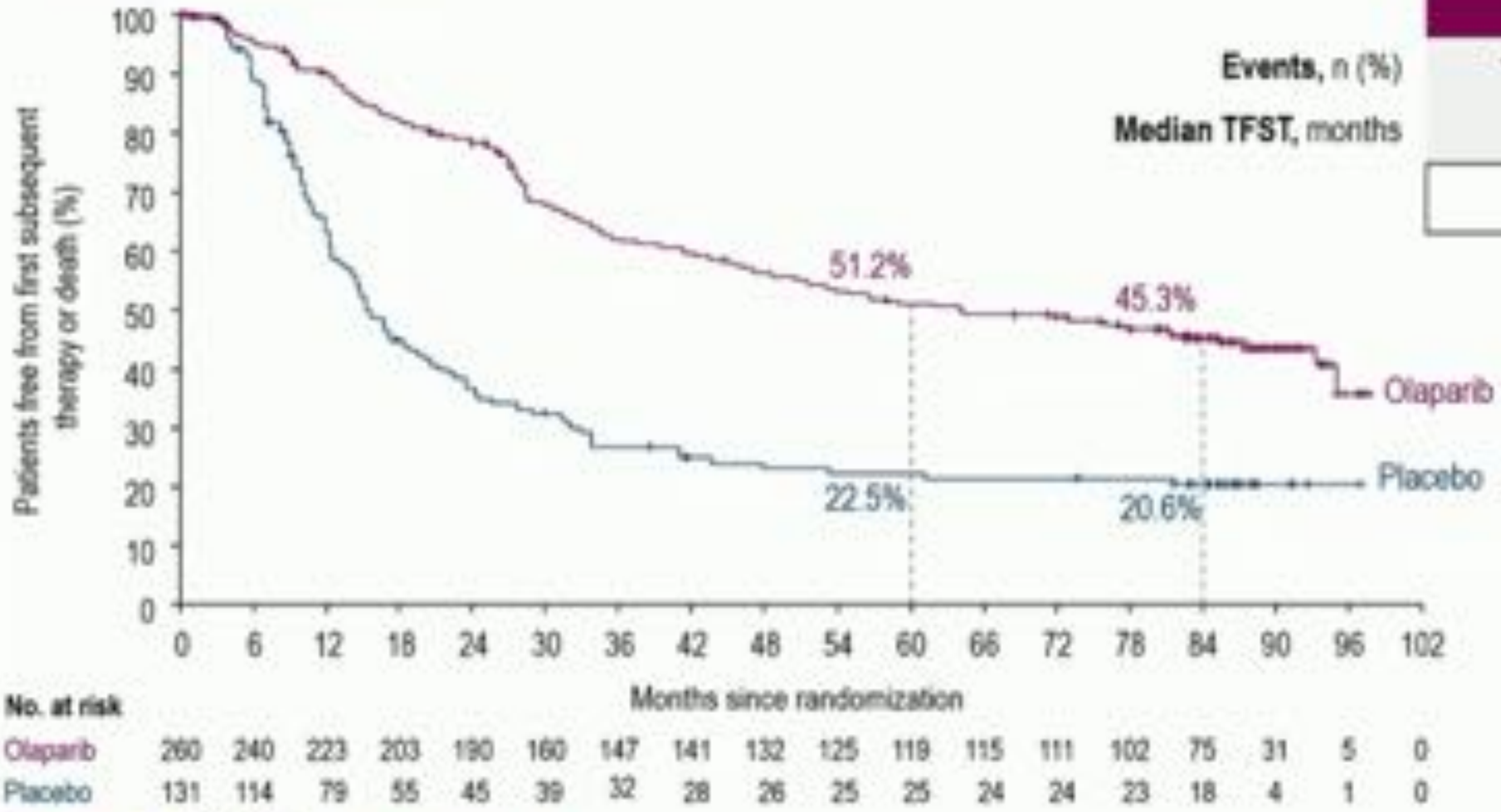
HR 0.55 (95% CI 0.40–0.76); *P*=0.0004*

44.3% of patients in the placebo group received subsequent PARP inhibitor therapy, compared with 14.6% of patients in the olaparib group

*P<0.0001 required to declare statistical significance

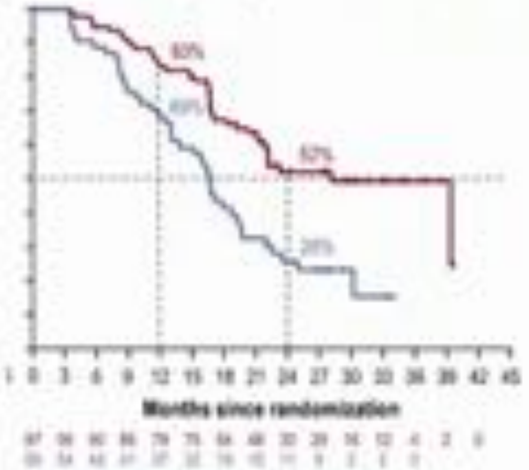
SOLO1 TFST substantially delayed by maintenance Olaparib TSST similar

	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)		

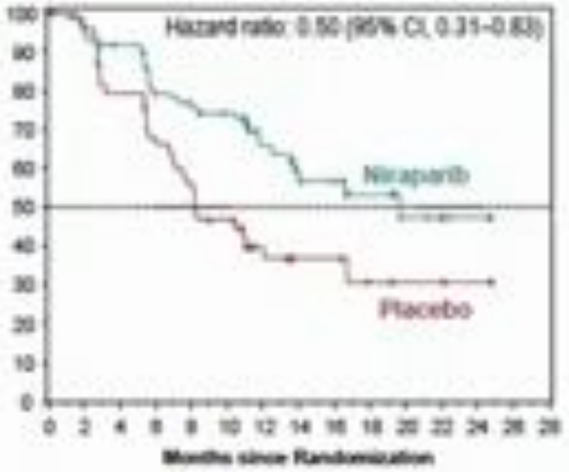


1st Line PARPi HRD/LOH positive (excluding *BRCA*-mutated) PFS

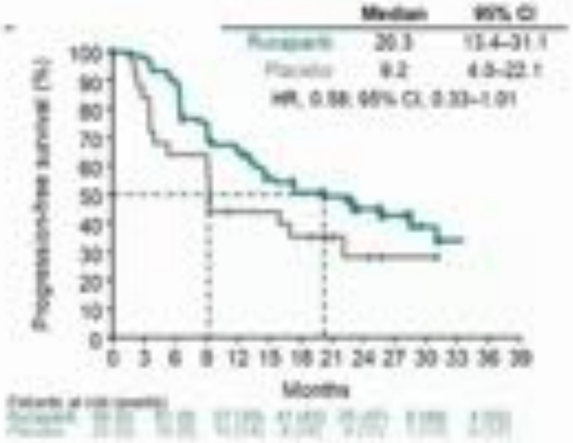
PAOLA1: Ray-Coquard et al ESMO 2019



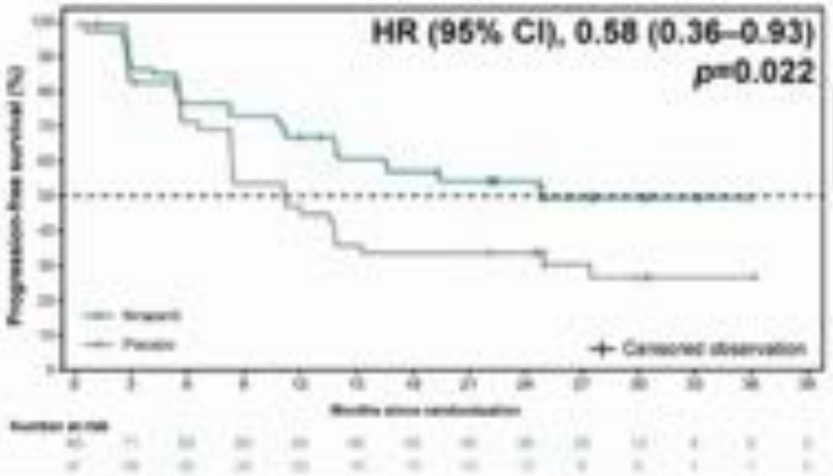
PRIMA: Gonzalez et al ESMO 2019



ATHENA MONO, Monk et al ASCO 2022



PRIME: Li et al, SGO 2022



	Niraparib (N=85)	Placebo (N=47)
mPFS (95% CI), months	24.8 (14.0–NE)	11.1 (8.3–13.8)

David SP Tan

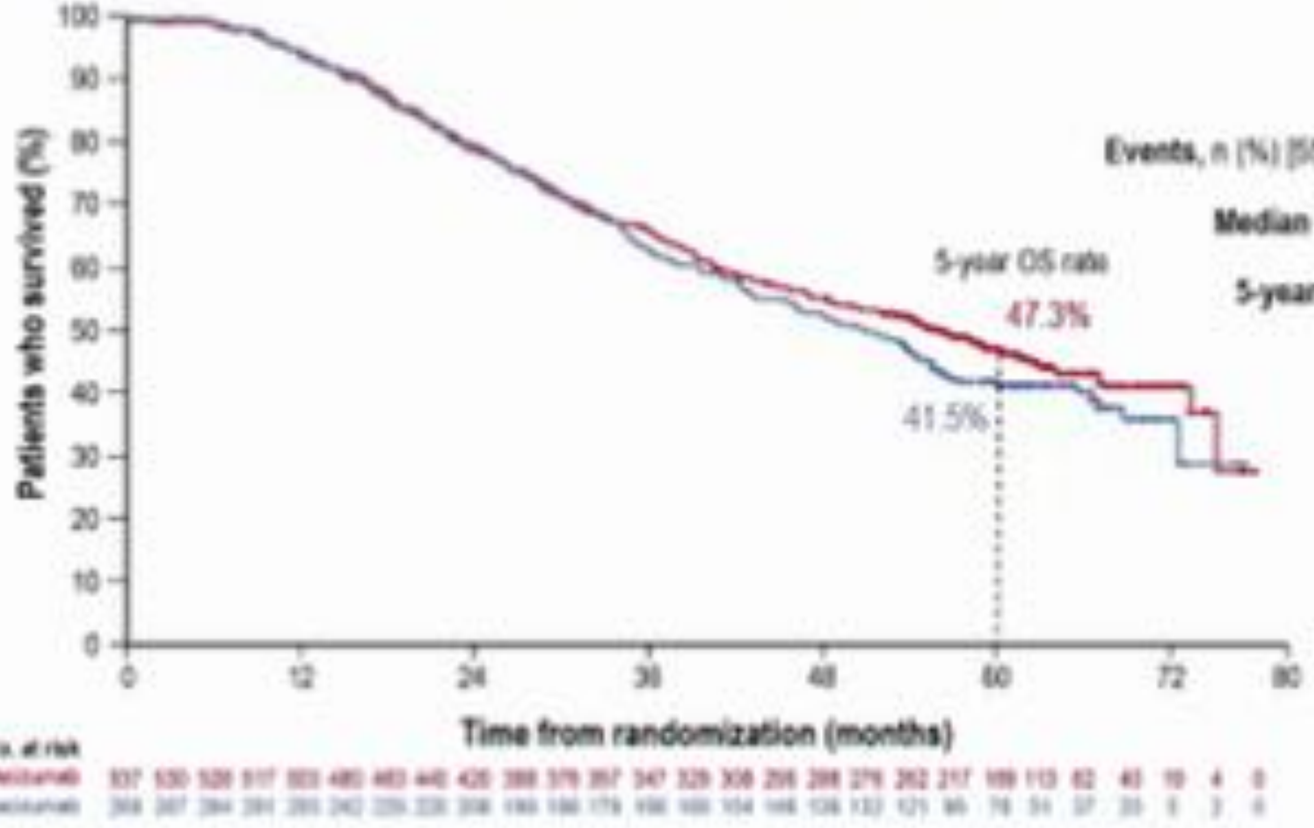
HRD assays do not reliably exclude PARPi benefit

Setting	Platinum-sensitive, newly-diagnosed, advanced OC					Platinum-sensitive, relapsed OC			
Study	PRIMA[1] Niraparib vs placebo PFS (BICR)	PRIME (Zai Lab)[2,3] Niraparib vs placebo PFS (BICR)	ATHENA-MONO[4] Rucaparib vs placebo PFS (IA)	PAOLA-1[5] Olaparib + bev vs bev alone PFS (IA)	VELIA[6,7] CT + velparib > velparib vs CT + placebo > placebo PFS (IA)	NOVA[8] Niraparib vs placebo PFS (BICR)	ARIEL3[9] Rucaparib vs placebo PFS (IA)	Study 19[10] Olaparib vs placebo PFS (IA)	OReO[11] Olaparib vs placebo PFS (IA), post-PARPi
Hazard ratio (95% CI) for PARPi vs placebo									
*BRCA*wt/ HRd	0.50	0.58*	0.58†	0.43	0.74	0.38	0.44	0.48	0.52
HRp	0.68	0.41‡	0.65§	1.00	0.81	0.58	0.58	0.60	0.49
Test type and HRnd/failure rate									
Test/ cutoff	≥42	test** N/A	≥16				≥16		Myriad MyChoice ≥42
HRnd/ Test failure, % (n/N)[11]	15 (111/733)	N/A	12 (66/538)[11]	18% (142/802)	11% (87/757)	15% (54/350)	9% (49/564)	N/A	20% (22/108)

So 1st line PARPi for all advanced ovarian cancers??

David SP Tan

PAOLA-1 OS analysis: ITT population



	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [65% maturity]	288 (53.6)	158 (58.7)
Median OS, months	**56.5**	**51.6**
5-year OS rate, %	**47.3**	**41.5**

HR 0.92 (95% CI 0.76–1.12); **P=0.4118**

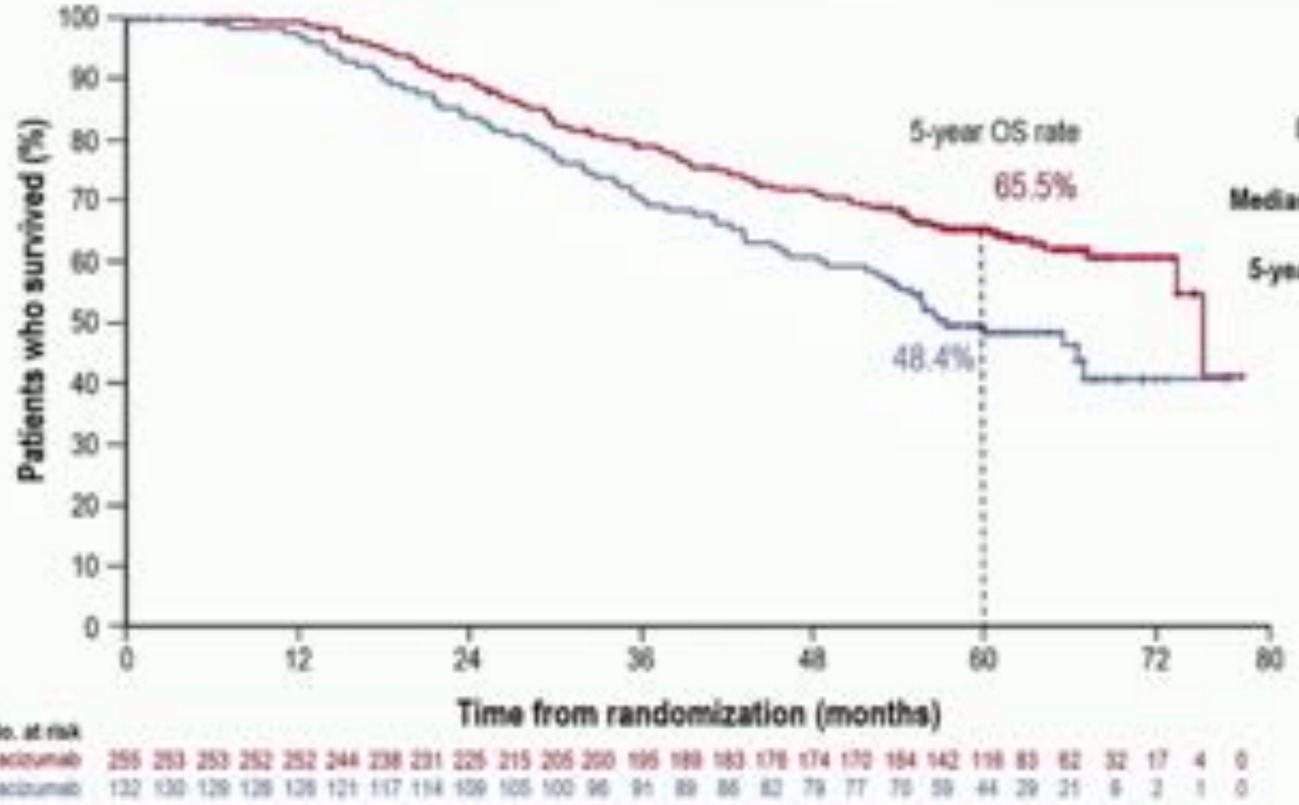
Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **19.6%** (105/537)
Placebo + bevacizumab: **45.7%** (123/269)

Median time from first cycle of chemotherapy to randomization = 6 months

No. at risk																									
Olaparib + bevacizumab	537	530	528	517	503	480	463	445	425	388	376	357	347	329	308	295	288	276	262	217	169	113	62	43	19	4	0
Placebo + bevacizumab	269	267	264	261	255	242	229	228	208	190	186	179	166	160	154	148	136	132	121	95	76	54	37	33	8	3	0

PARP, poly(ADP-ribose) polymerase

OS was prolonged in the HRD-positive subgroup



	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	93 (36.5)	69 (52.3)
Median OS, months	**75.2** (unstable)*	**57.3**
5-year OS rate, %	**65.5**	**48.4**

HR 0.62 (95% CI 0.45–0.85)

38% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone

Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **17.3%** (44/255)
Placebo + bevacizumab: **50.8%** (67/132)

No. at risk																									
Olaparib + bevacizumab	255	253	253	252	252	244	238	231	225	215	205	200	195	189	183	176	174	170	164	142	116	83	62	32	17	4	0
Placebo + bevacizumab	132	130	129	126	126	121	117	114	109	105	100	96	91	89	86	82	79	77	70	59	44	29	21	6	2	1	0

*Median unstable; <50% data maturity
HRD positive defined as a tBRCAm and/or genomic instability score of ≥42 on the Myriad myChoice HRD Plus assay

PAOLA-1 OS subgroup analysis by BRCAm and HRD status

5Y OS	O/B vs Pl/B		
BRCAm	73 VS 54 %	**HR 0.60** (95% CI 0.39–0.93) N=157/80	
HRD pos	54 vs 48 %	**HR 0.62** (95% CI 0.45–0.85) N=255/132	**51% X-over**
HRD POS BRCA WT	55 VS 44 %	**HR 0.71** (95% **CI 0.45–1.13**) N=**97/55**	
ITT ALL COMERS	47 vs 41 %	**HR 0.92** (95% **CI 0.76–1.12**) N=537/269	**46% X-over**
***P*=0.412**			

5 YR PFS (updated)

HRD pos 46 vs 19% **HR 0.41** (95% CI 0.32–0.54)

Long-term side effects of PARP inhibitors - no change

SOLO1

	Primary PFS analysis (DCO 17 May 2018)		7-year descriptive OS analysis (DCO 7 March 2022)	
	Olaparib (N=260)	Placebo (N=130)	Olaparib (N=260)	Placebo (N=130)
MDS/AML*	3 (1.2)	0	4 (1.5)	1 (0.8)
New primary malignancies*	5 (1.9)	3 (2.3)	14 (5.4)†	8 (6.2)‡
Pneumonitis/ILD	5 (1.9)	0	5 (1.9)	0

PAOLA1

Jonathan A Ledermann

	Primary PFS analysis (DCO 22 March 2019)		Final OS analysis (DCO 22 March 2022)	
	Olaparib + bev (N=535)	Placebo + bev (N=267)	Olaparib + bev (N=535)	Placebo + bev (N=267)
MDS/AML/AA, n (%)	6 (1.1)	1 (0.4)	9 (1.7%)	6 (2.2%)
New primary malignancies,* n (%)	7 (1.3)	3 (1.1)	22 (4.1%)	8 (3.0%)
Pneumonitis/ILD/bronchiolitis†	6 (1.1)	0 (0)	7 (1.3%)	2 (0.7%)

2022 ASCO® ANNUAL MEETING

GOG FOUNDATION®

ENGOT European Network of Gynaecological Oncological Trial groups

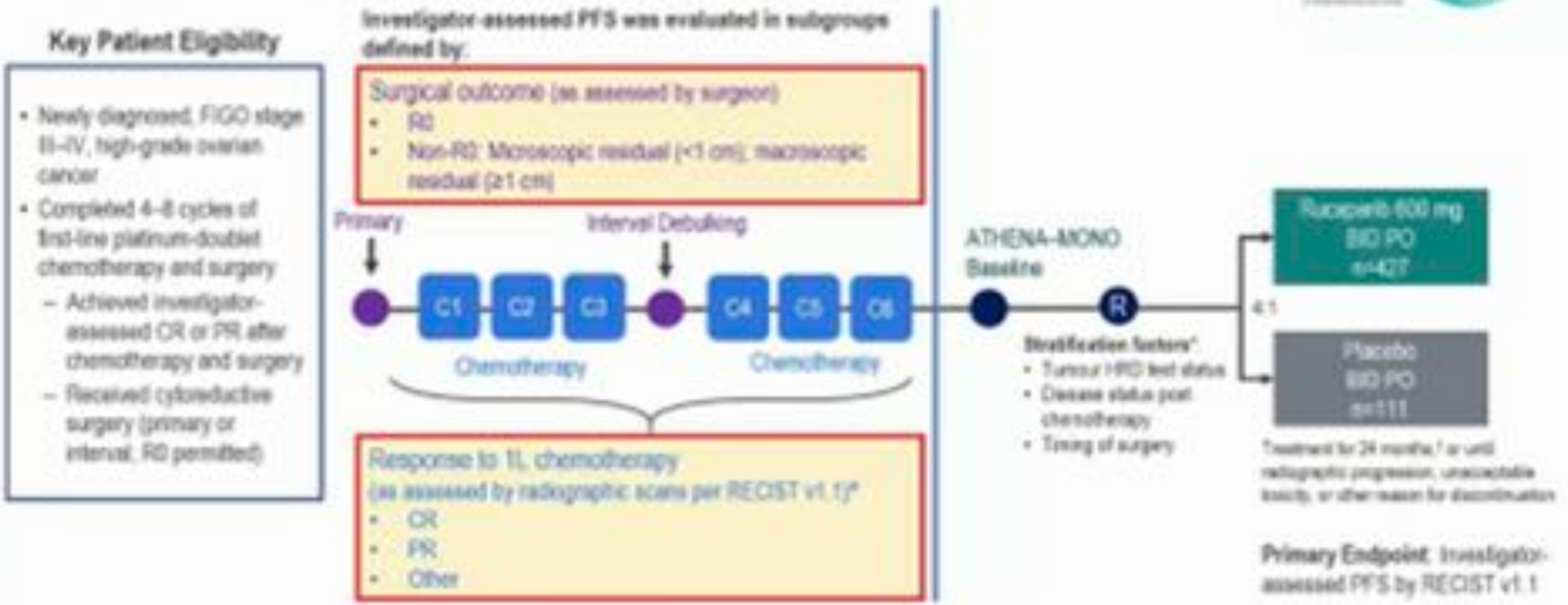
NRG Oncology-Japan

ATHENA–MONO (GOG-3020/ENGOT-ov45): A Randomized, Double-blind, Phase 3 Trial Evaluating Rucaparib Monotherapy Vs Placebo As Maintenance Treatment Following Response To First-line Platinum-based Chemotherapy In Ovarian Cancer

Bradley J. Monk,[1] Christine Parkinson,[2] Myong Cheol Lim,[3] David M. O'Malley,[4] Ana Oaknin,[5] Michelle K. Wilson,[6] Robert L. Coleman,[7] Domenica Lorusso,[8] Amit Oza,[9] Sharad Ghamande,[10] Athina Christopoulou,[11] Emily Prendergast,[12] Fuat Demirkiran,[13] Ramey D. Littell,[14] Anita Chudecka-Głaz,[15] Mark A. Morgan,[16] Sandra Goble,[17] Stephanie Hume,[17] Keiichi Fujiwara,[18] Rebecca S. Kristeleit[19]

[1]GOG Foundation, HonorHealth Research Institute, University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, AZ, USA; [2]Addenbrooke's Hospital, Cambridge, UK; [3]National Cancer Center Korea, Goyang-si, Gyeonggi-do, Republic of Korea; [4]The Ohio State University, James Cancer Center, Columbus, OH, USA; [5]Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [6]Auckland City Hospital, Auckland, New Zealand; [7]US Oncology Research, The Woodlands, TX, USA; [8]MITO and Fondazione Universitario A. Policlinico Gemelli IRCCS and Catholic University of Sacred Heart, Rome, Italy; [9]Princess Margaret Hospital Cancer Centre, Toronto, Ontario, Canada; [10]Augusta University, Augusta, GA, USA; [11]St. Andrews General Hospital, Patras, Greece; [12]Minnesota Oncology and Metro-Minnesota Community Oncology Research Consortium, Minneapolis, MN, USA; [13]Istanbul University, Cerrahpaşa, Istanbul, Turkey; [14]Kaiser Permanente Northern California Gynecologic Cancer Program, San Francisco, CA, USA; [15]Pomeranian Medical University, Szczecin, Poland; [16]University of Pennsylvania Health System, Philadelphia, PA, USA; [17]Clovis Oncology, Inc., Boulder, CO, USA; [18]Saitama Medical University International Medical Center, Hidaka, Saitama, Japan; [19]Guy's and St Thomas' NHS Foundation Trust, London, UK

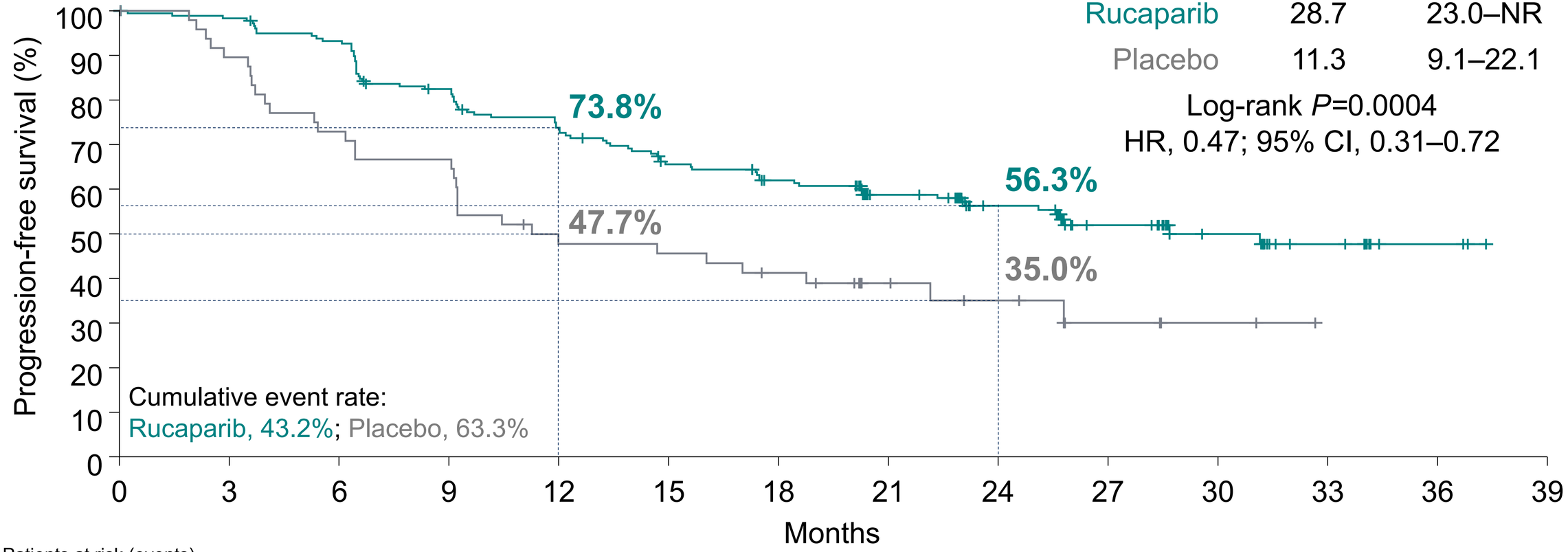
ATHENA–MONO Study Design



Primary Endpoint – Investigator-Assessed PFS: HRD Population

	Median	95% CI
Rucaparib	28.7	23.0–NR
Placebo	11.3	9.1–22.1

Log-rank *P*=0.0004
HR, 0.47; 95% CI, 0.31–0.72



Patients at risk (events)

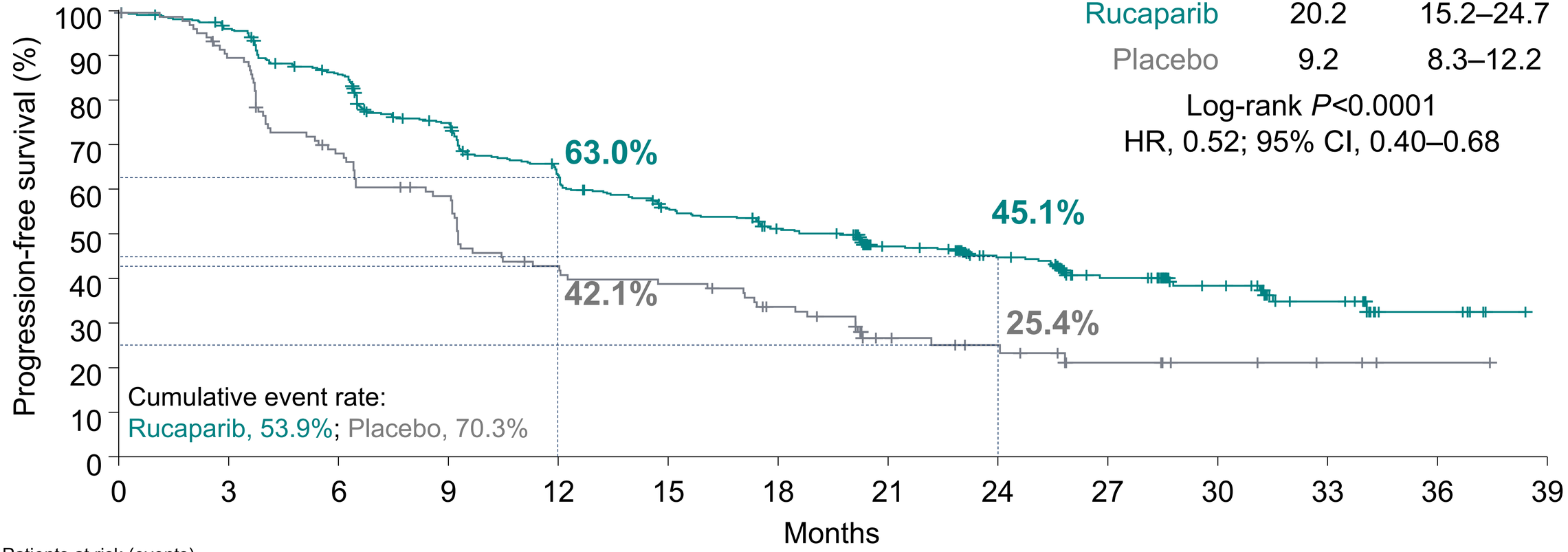
Rucaparib	185(0)	175(3)	165(12)	143(31)	127(46)	110(60)	100(66)	82(71)	59(74)	36(78)	22(79)	12(80)	3(80)	0(80)
Placebo	49(0)	43(5)	35(13)	32(16)	22(25)	21(26)	18(28)	11(29)	8(30)	4(31)	2(31)	0(31)		

Data cut off date: March 23, 2022.
HR, hazard ratio; HRD, homologous recombination deficiency; NR, not reached; PFS, progression-free survival.

Primary Endpoint – Investigator-Assessed PFS: ITT Population

	Median	95% CI
Rucaparib	20.2	15.2–24.7
Placebo	9.2	8.3–12.2

Log-rank $P<0.0001$
HR, 0.52; 95% CI, 0.40–0.68



Patients at risk (events)

Rucaparib	427 (0)	398 (15)	351 (57)	298 (101)	245 (149)	213 (176)	190 (193)	151 (207)	114 (214)	67 (224)	42 (226)	23 (229)	7 (230)	0 (230)
Placebo	111 (0)	97 (11)	72 (34)	60 (44)	42 (61)	39 (64)	31 (69)	18 (75)	14 (76)	8 (78)	5 (78)	3 (78)	1 (78)	0 (78)

Data cutoff date: March 23, 2022.
HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

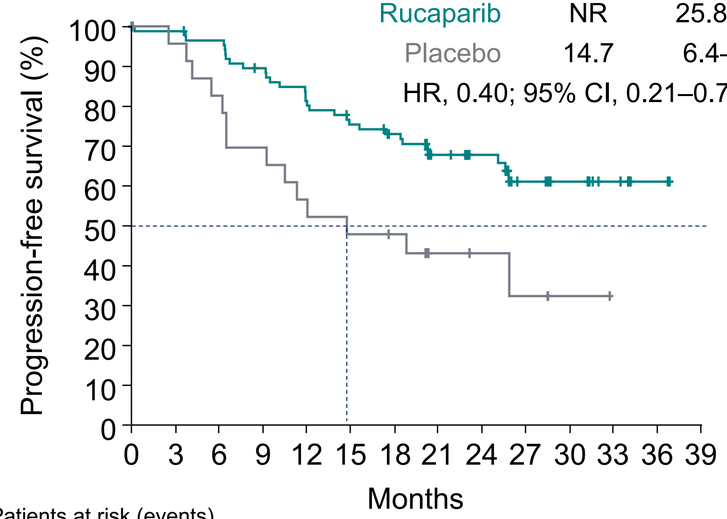
Investigator-Assessed PFS: Exploratory Subgroups

HRD positive

BRCA^{mut}

	Median	95% CI
Rucaparib	NR	25.8–NR
Placebo	14.7	6.4–NR

HR, 0.40; 95% CI, 0.21–0.75

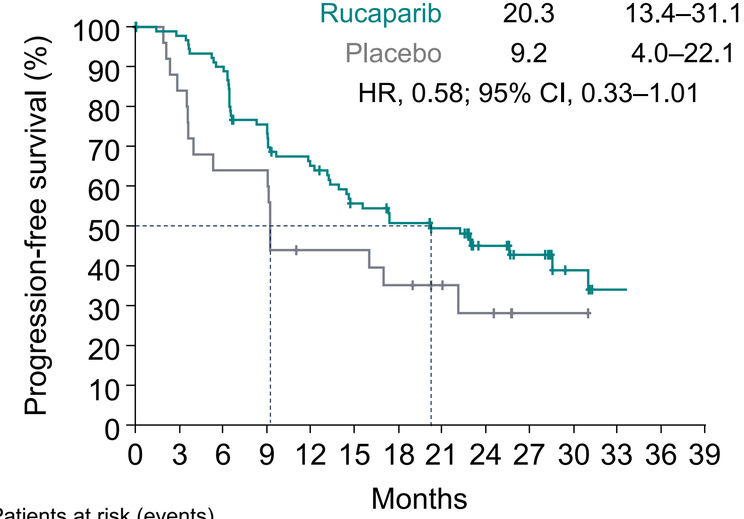


Patients at risk (events)							
Rucaparib	91 (0)	84 (3)	70 (16)	59 (23)	34 (27)	14 (30)	2 (30)
Placebo	24 (0)	19 (4)	12 (11)	10 (12)	4 (13)	1 (14)	0 (14)

BRCA^{wt}/LOH^{high}

	Median	95% CI
Rucaparib	20.3	13.4–31.1
Placebo	9.2	4.0–22.1

HR, 0.58; 95% CI, 0.33–1.01



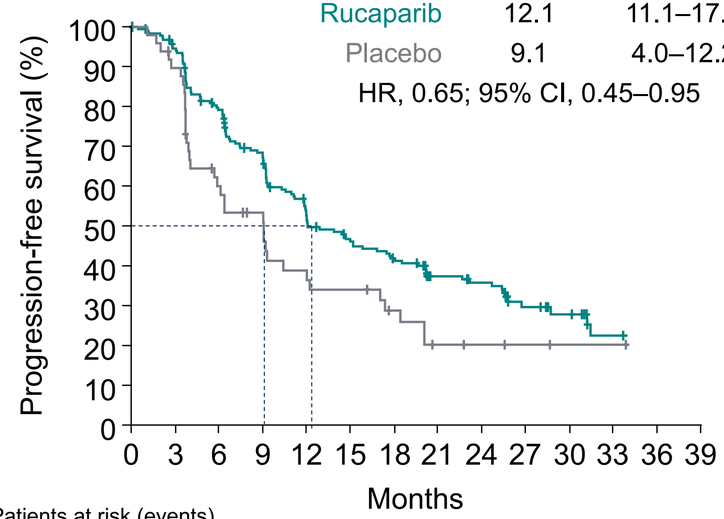
Patients at risk (events)							
Rucaparib	94 (0)	81 (9)	57 (30)	41 (43)	25 (47)	8 (49)	4 (50)
Placebo	25 (0)	16 (9)	10 (14)	8 (16)	4 (17)	1 (17)	0 (17)

HRD negative

BRCA^{wt}/LOH^{low}

	Median	95% CI
Rucaparib	12.1	11.1–17.7
Placebo	9.1	4.0–12.2

HR, 0.65; 95% CI, 0.45–0.95



Patients at risk (events)							
Rucaparib	189 (0)	142 (38)	89 (84)	68 (102)	42 (111)	15 (118)	8 (120)
Placebo	49 (0)	27 (19)	16 (28)	10 (32)	5 (35)	3 (35)	3 (35)

- Rucaparib demonstrated treatment benefit vs placebo regardless of BRCA mutation and HRD status

Data cutoff date: March 23, 2022.

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.

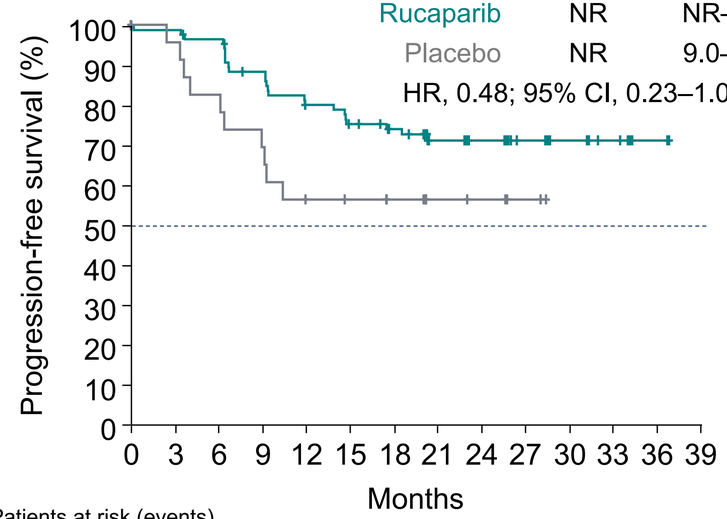
BICR-Assessed PFS: Exploratory Subgroups

HRD positive

BRCA^{mut}

	Median	95% CI
Rucaparib	NR	NR–NR
Placebo	NR	9.0–NR

HR, 0.48; 95% CI, 0.23–1.00

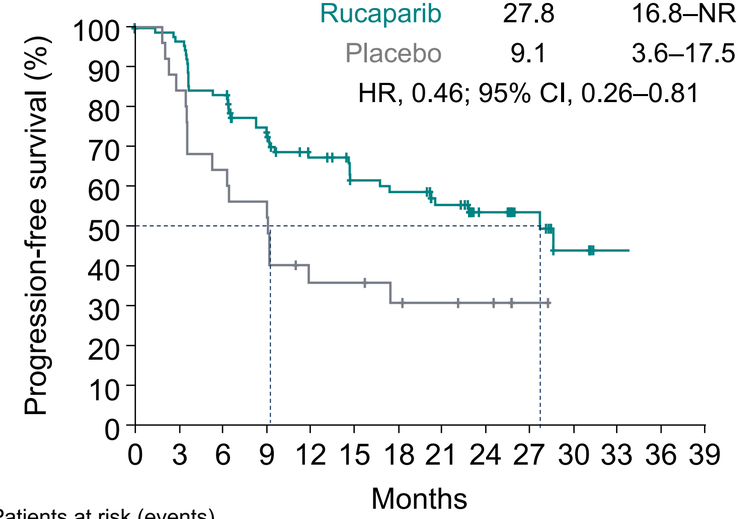


Patients at risk (events)							
Rucaparib	91 (0)	84 (3)	67 (17)	57 (22)	31 (24)	13 (24)	2 (24)
Placebo	24 (0)	19 (4)	12 (10)	9 (10)	4 (10)	0 (10)	

BRCA^{wt}/LOH^{high}

	Median	95% CI
Rucaparib	27.8	16.8–NR
Placebo	9.1	3.6–17.5

HR, 0.46; 95% CI, 0.26–0.81



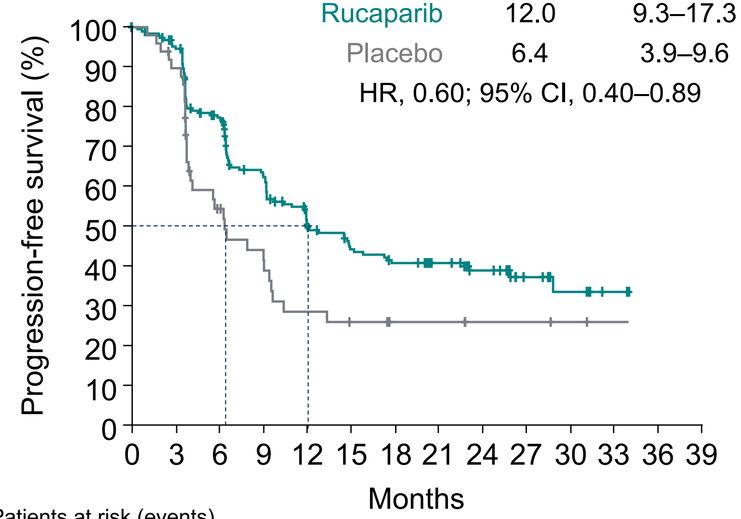
Patients at risk (events)							
Rucaparib	94 (0)	74 (15)	50 (28)	40 (34)	20 (37)	7 (39)	3 (39)
Placebo	25 (0)	16 (9)	8 (16)	6 (17)	4 (17)	0 (17)	

HRD negative

BRCA^{wt}/LOH^{low}

	Median	95% CI
Rucaparib	12.0	9.3–17.3
Placebo	6.4	3.9–9.6

HR, 0.60; 95% CI, 0.40–0.89



Patients at risk (events)							
Rucaparib	189 (0)	133 (41)	76 (85)	58 (99)	37 (101)	9 (103)	4 (103)
Placebo	49 (0)	22 (21)	11 (31)	6 (32)	4 (32)	3 (32)	2 (32)

- 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

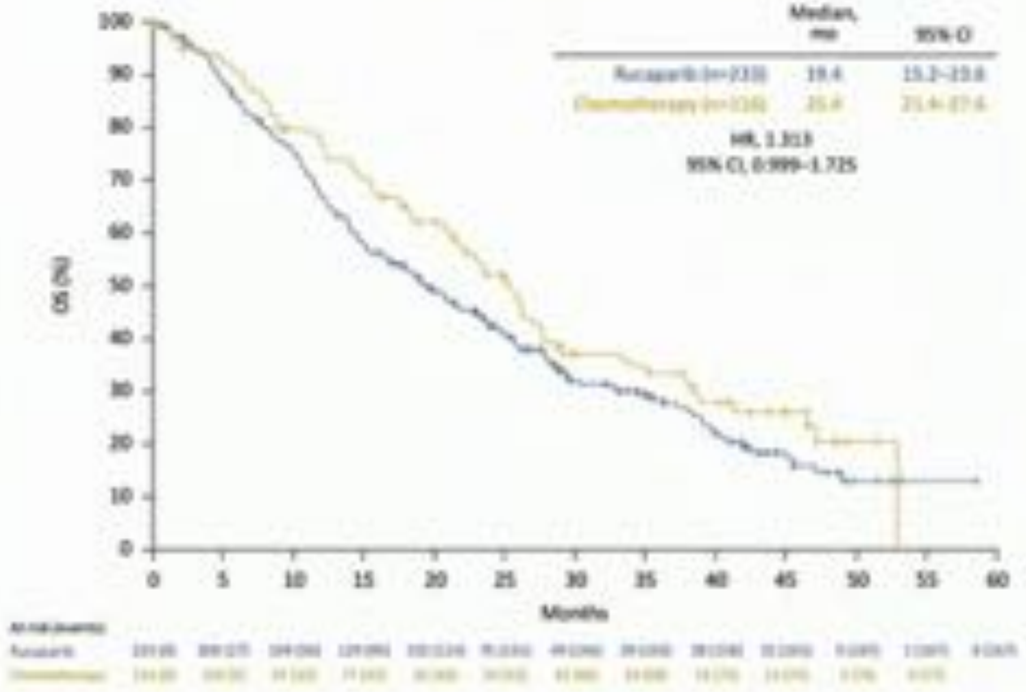
ARIEL 4: Later line treatment with PARPi Rucaparib in *BRCA*^{mut} recurrent ovarian cancer

Schema and Overall Survival in the ITT population

Deleterious germline/somatic *BRCA*^{mut}

Prespecified secondary endpoint:

OS in the ITT population



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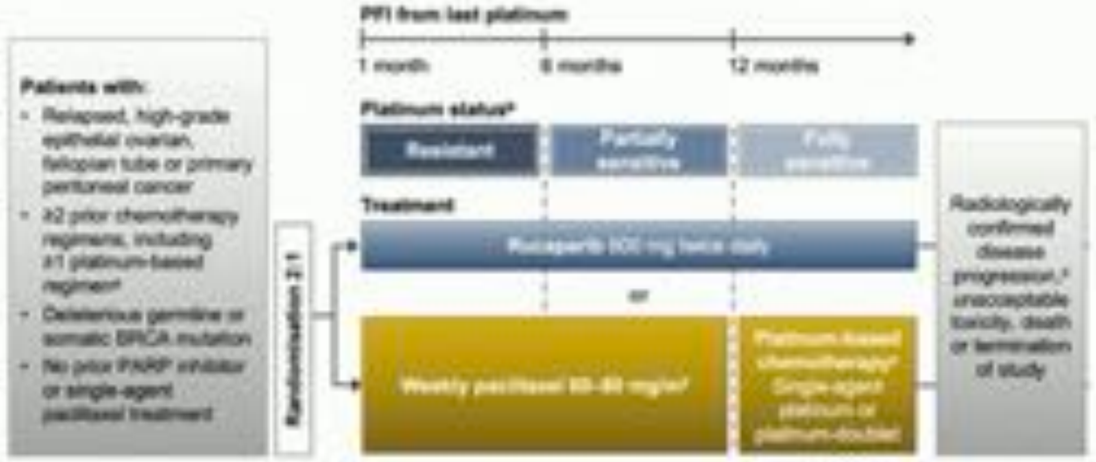
Amit M. Oza

ARIEL 4: Later line treatment with PARPi Rucaparib in *BRCA*^{mut} recurrent ovarian cancer

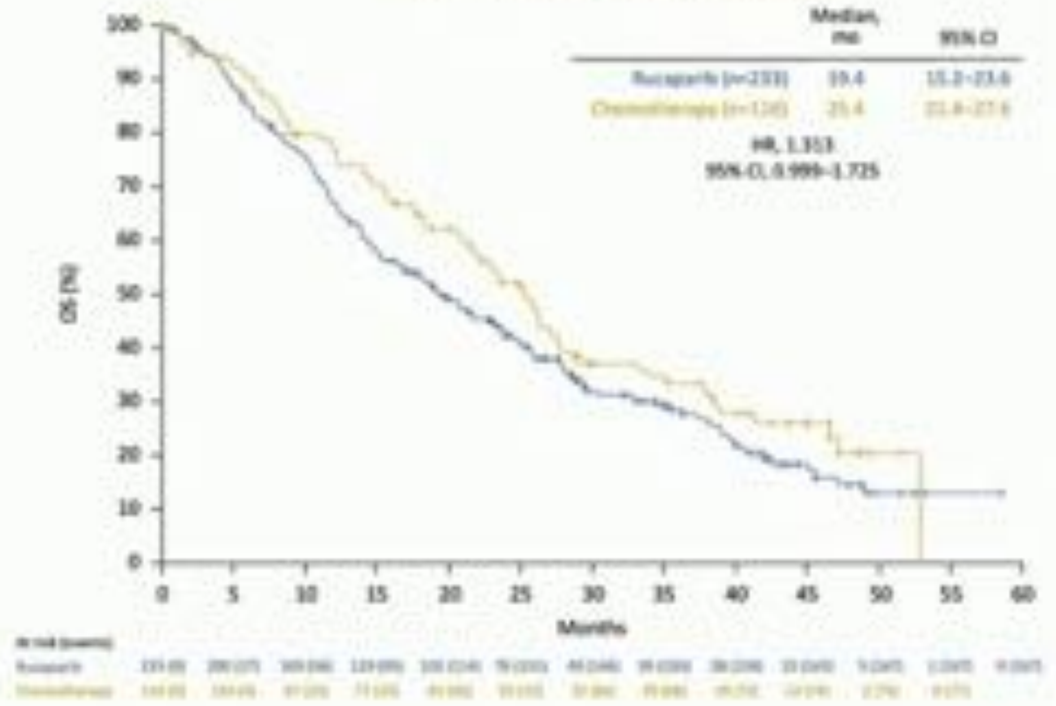
Schema and Overall Survival in the ITT population

Deleterious germline/somatic *BRCA*^{mut}



Prespecified secondary endpoint:

OS in the ITT population



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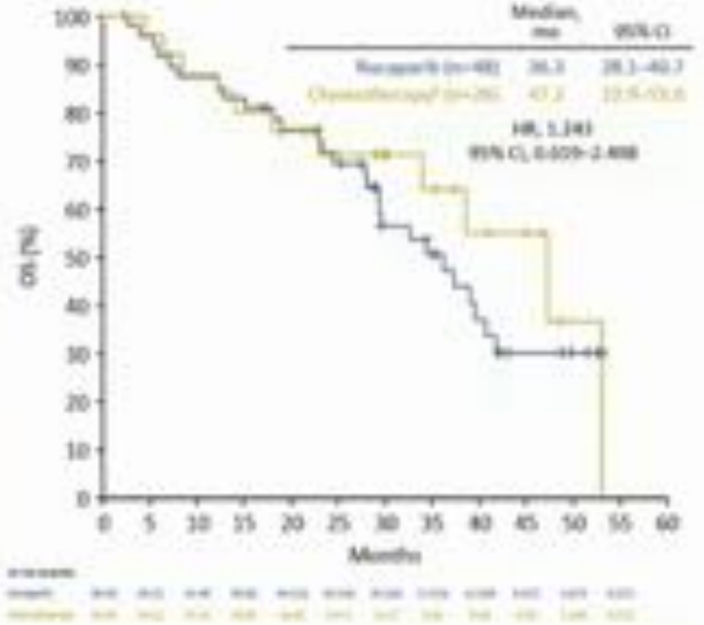
ARIEL 4: Platinum Sensitive sub-group OS

'Platinum Sensitive' Group



N=17 pts from 3 yrs on Rucaparib
N= 9 pts from 3 yrs on Chemo

	Rucaparib (n=48)	Chemotherapy (n=26)
Median time since diagnosis, mo (range)	59 (25–185)	62 (24–140)
Median number of prior platinum-based therapies, n (range)	2 (1–6)	2 (1–4)
≥1 Prior nonplatinum regimens immediately before randomisation, n (%)	6 (12.5)	3 (11.5)

	Rucaparib (n=48)	Chemotherapy (n=26)	
Median duration of randomised treatment, mo (range)[a]	13.7 (0–53)	3.4 (1–6)	
Subsequent anticancer treatment reported, n (%)	26 (54.2)	22 (84.6)	
Type of first subsequent treatment, n (%)			
Crossover rucaparib	NA	14 (63.6)	82%
Other PARPi	1 (3.8)	4 (18.2)	
Platinum-based chemotherapy	20 (76.9)	2 (9.1)	
Nonplatinum-based chemotherapy	5 (19.2)	1 (4.5)	
Other[a]	0	1 (4.5)	
Median duration of crossover rucaparib, mo (range)	NA	9.9 (1–37)	
<6 months, n (%)	NA	2 (14.3)	
≥6 months, n (%)		12 (85.7)	86%

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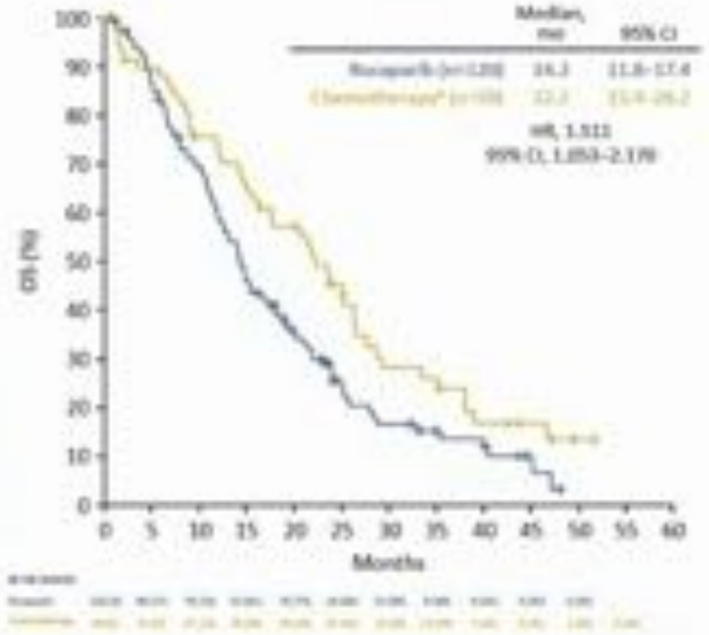
ARIEL 4: Platinum Resistant sub-group OS

'Platinum Resistant' Group



	Rucaparib (n=120)	Chemotherapy (n=59)
Median time since diagnosis, mo (range)	36 (13–146)	35 (14–119)
Median number of prior platinum-based therapies, n (range)	2 (1–6)	2 (1–5)
≥3	38 (31.7)	22 (37.3)
≥1 Prior nonplatinum regimens immediately before randomisation, n (%)	25 (20.8)	12 (20.3)

	Rucaparib (n=120)	Chemotherapy (n=59)	
Median duration of randomised treatment, mo (range)[a]	5.6 (0–44)	4.4 (0–25)	
Subsequent anticancer treatment n (%)	69 (57.5)	45 (76.3)	
Type of first subsequent treatment, n (%)			
Crossover rucaparib	NA	41 (91.1)	91%
Other PARPi	1 (1.4)	0	
Platinum-based chemotherapy	29 (42.0)	1 (2.2)	
Nonplatinum-based chemotherapy	36 (52.2)	2 (4.4)	
Other[b]	3 (4.3)	1 (2.2)	
Median duration of crossover rucaparib, mo (range)	NA	9.4 (2–39)	
<6 months, n (%)	NA	14 (34.1)	
≥6 months, n (%)		27 (65.9)	66%

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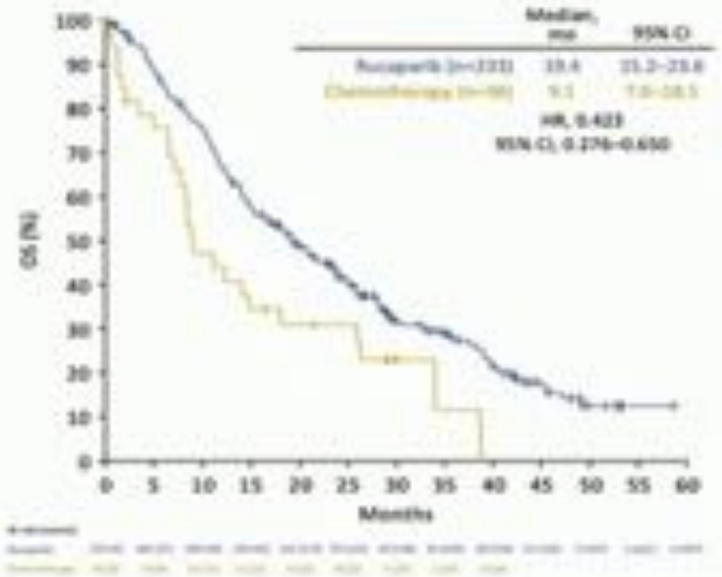
ARIEL4 – Cross-Over and post progression therapy

Excluding Patients Who Crossed Over From Chemotherapy to Rucaparib



Trial	Crossover	HR (95%CI)
Study 19 (incl *BRCA*wt)	12%	0.73 (0.55-0.95)
SOLO2 (gBRCA)	38%	0.74 (0.54-1.00)
NOVA (gBRCA)	46% (31% missing)	0.93 (0.63-1.36)
ARIEL4 (gBRCA)	89%	1.31 (0.99-1.725)

Clovis Oncology with permission

PFS benefit for rucaparib did not result in OS benefit – WHY?

PARP inhibitor monotherapy with rucaparib (ARIEL4) in recurrent *BRCA*^{mut} ovarian cancer

Why is the chemotherapy group doing better?

- Crossover to later PARPi
- Long post-progression survival - need many more patients to overcome crossover

Is it clinically relevant in a secondary analysis - and are the subgroup analyses meaningful

- small n – but very different outcomes for PSR vs PROC (PROC outweighs PSR effect)

Are the benefits of *'maintenance therapy'* different from *'monotherapy'*?

- ? Need prior chemotherapy (DNA damage?) – to maximise effect of PARPi

Cell cycle is key for targeting DDR in ovarian cancer

Due to almost ubiquitous loss of P53, frequent loss of RB1 and amplification of CCNE1 in 14% (which all act at G1/S checkpoint) ovarian cancer cells are highly dependent on S phase and G2-M checkpoints

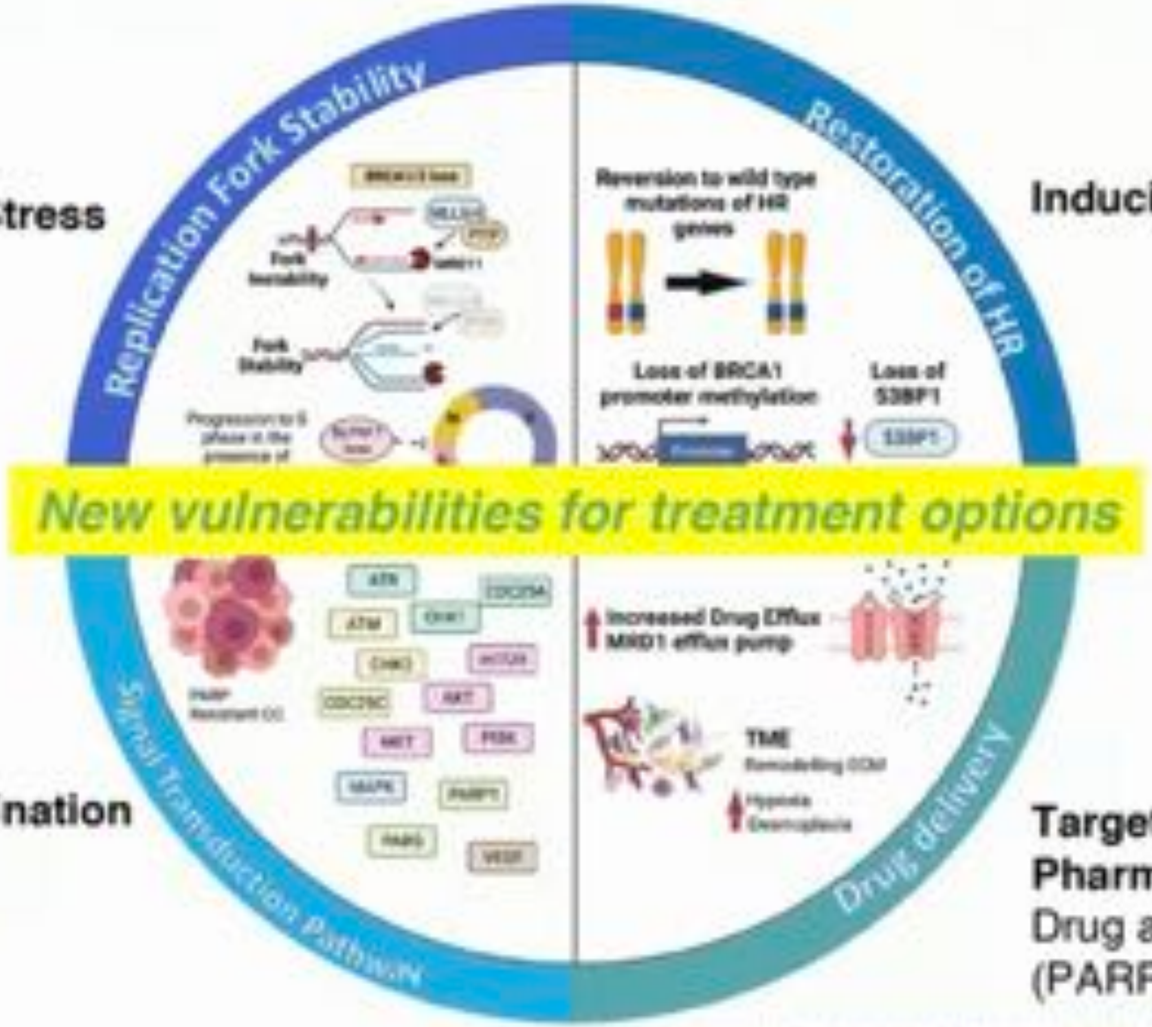
Showing it works outside of HRD (e.g. in CCNE1 amplified tumours) would be important

Also evidence that some mechanisms of PARPi resistance rely on cell cycle so targeting DDR could overcome these

Charlie Gourley

Rationales for overcoming PARPi resistance

Targeting Replication Stress
Others DDR Agents



Inducing HRD

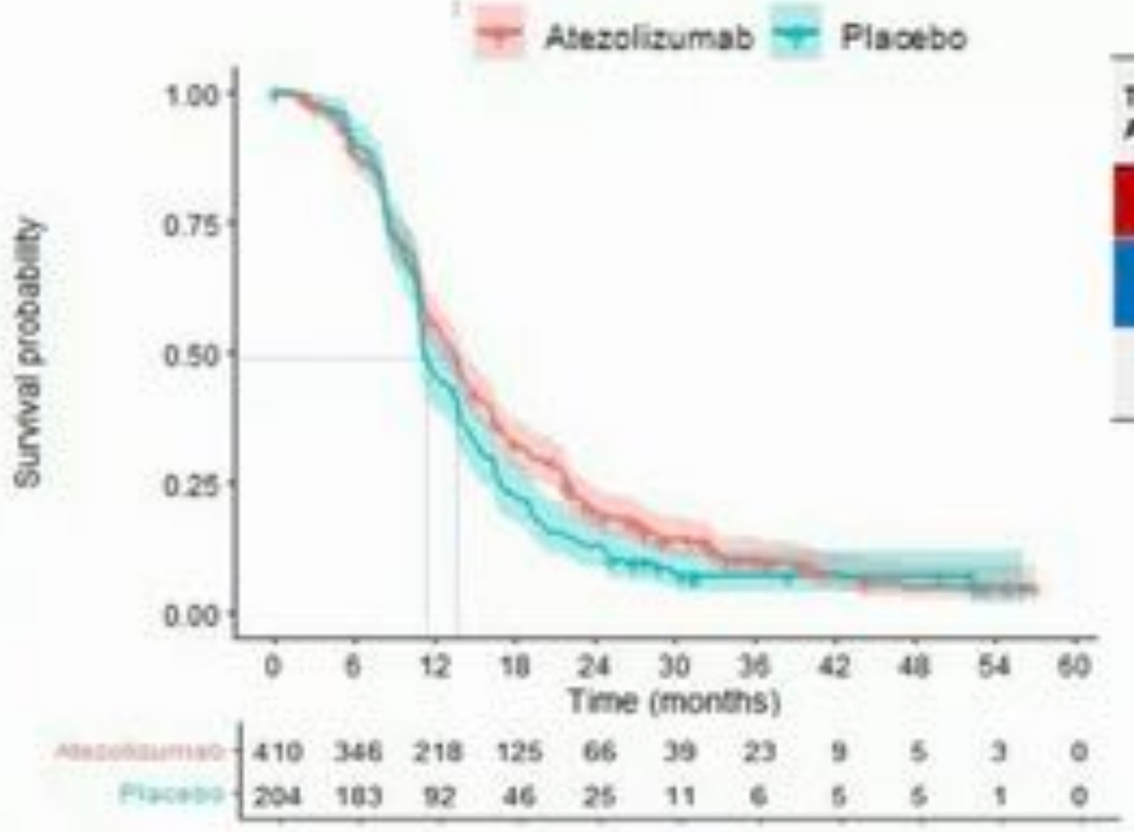
New vulnerabilities for treatment options

Different pathways Combination
Cross talk network

Targeting Microenvironment Pharmaco
Drug avoiding efflux pump MDR1 (PARP new generation) / ADC

Veneziani et al, Submitted to TAMO

ATALANTE Progression-free survival (ITT)



Treatment Arm	N	Event N (%)	PFS at 6m % (95% CI)	PFS at 12m % (95% CI)	PFS at 18m % (95% CI)	Median PFS (95% CI)
Atezo	410	348 (85)	88 (85-91)	56 (51-61)	32 (28-37)	**13.5 mos** (12.2-14.2)
Placebo	204	187 (92)	91 (87-95)	46 (39-53)	23 (18-30)	**11.3 mos** (11.0-13.5)
		Hazard ratio= 0.83 [0.69-0.99]				**P=.041**

median follow-up : 36.6 months

The ATALANTE trial did not meet its primary objective:
PFS1 in the ITT population
PD-L1 data similar

MEDIOLA BRCA WT ESMO 2022

Sequential cohorts

Patient population

- Confirmed non-gBRCAm PSR OC
- 1–2 prior lines of PBC
- PARP inhibitor naive
- IO agent naive

Sequential enrolment*

Triplet

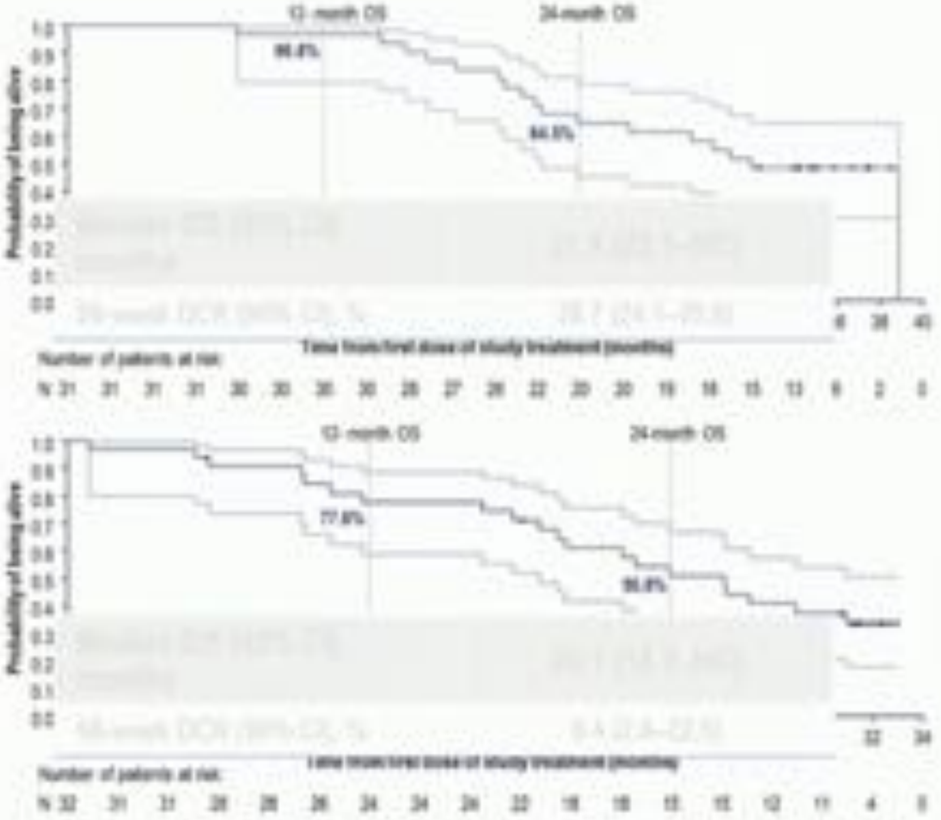
- Olaparib 300 mg po bid
- Durvalumab 1.5 g IV q4w
- Bevacizumab 10 mg/kg IV q2w

Doublet

- Olaparib 300 mg po bid
- Durvalumab 1.5 g IV q4w

Secondary endpoints include:

- OS
- DCR at 56 weeks†



Trials with PARPi + CPI +/- Bevacizumab in AOC

	FRONT LINE				RECURRENT
	ENGOT Ov43	ENGOT Ov44 FIRST	ENGOT Ov45 ATHENA	ENGOT Ov46 DUO-O	ENGOT OV41 ANITA
Arm 1	CP +/- Bev Placebo-Placebo	CP +/- Bev **Niraparib**-Placebo	**Rucaparib** Placebo	CP + Bev Placebo-Placebo	Carbo-doublet-**Niraparib**-Placebo
Arm 2	CP +/- Bev **Pembro**-Placebo	CP +/- Bev **Niraparib-TSR042**	Placebo **Nivolumab**	CP + Bev **Durva**-Placebo	Carbo-doublet-**Niraparib-Atezolizumab**
Arm 3	CP +/- Bev **Pembro-Olaparib**		**Rucaparib Nivolumab**	CP + Bev **Durva-Olaparib**	
Arm 4			Placebo Placebo		

CPI: Check point inhibitors; CP: Carboplatin-Paclitaxel

2022 ASCO® ANNUAL MEETING

Mirvetuximab Soravtansine in Patients with Platinum-Resistant Ovarian Cancer with High Folate Receptor Alpha (FRα) Expression: Characterization of Anti-Tumor Activity in the SORAYA Study

Ursula A. Matulonis[1], Ana Oaknin[2], Sandro Pignata[3], Hannelore Denys[4], Nicoletta Colombo[5], Toon Van Gorp[6], Jason Konner[7], Margarita Romeo[8], Philipp Harter[9], Conleth Murphy[10], Jiuzhou Wang[11], Brooke Esteves[11], Michael Method[11], Robert L. Coleman[12], Domenica Lorusso[13]

1. Dana-Farber Cancer Institute, Boston, MA, USA. **2.** Institute of Oncology, Hospital Quirónsalud Barcelona, Barcelona, Spain. **3.** National Cancer Institute, Naples, Italy. **4.** Ghent University Hospital - UZ Gent, Gent, Belgium. **5.** European Institute of Oncology, Milan, Italy. **6.** UZ Leuven, Leuven,Belgium. **7.** Memorial-Sloan Kettering Cancer Center, Middletown, NJ, USA. **8.** Catalan Institute of Oncology, Badalona, Spain. **9.** Kliniken Essen-Mitte, Essen, Germany. **10.** Bon Secours Hospital, Cork, Ireland. **11.** ImmunoGen Inc, Waltham, MA, USA. **12.** US Oncology Research, The Woodlands, TX, USA. **13.** Gynaecology Oncology Unit, Fondazione IRCCS, National Cancer Institute, Milan, Italy.

Table 3. Response-Related Efficacy End Points

End Point	Investigator Assessed (N=135)	BICR Assessed (N=96)
Response rates[a]		
ORR, n (%)[b]	**34 (12.4)**	**29 (30.2)**
95% CI[c]	[21.6-42.2]	[21.3-40.4]
Best overall response, n (%)		
Complete response	**5 (4.5)**	**6 (6.3)**
Partial response	29 (27.6)	23 (24.0)
Stable disease[d]	48 (46.7)	54 (56.3)
Progressive disease	20 (19.0)	9 (9.4)
Not evaluable	3 (2.9)	4 (4.2)
Duration of response / time to response[e]		
mDOR[f], months	**6.9**	**NR**
95% CI[c]	[5.6, 9.7]	[5.0, NR]
Median time to response, months (range)	**1.5** (1.0-5.6)	**1.4** (1.0-5.4)

CR, complete response; NR, not reached; PD, progressive disease; PR, partial response.
Data cutoff: April 29, 2022.
[a]Based on RECIST v1.1. [b]ORR is defined as the proportion of patients with a confirmed CR or PR. Patients without at least 1 postbaseline RECIST assessment were treated as not evaluable. [c]Clopper-Pearson exact CI. [d]Minimum duration of 35 days from date of first dose of M6Fc. [e]Kaplan-Meier estimate. DOR was defined as time from the date of first response (CR or PR) to the date of PD or death from any cause, whichever occurred first. DOR was only defined for patients with a confirmed best overall response (BOR) of CR or PR only.

Conclusions

- MIRV is the first biomarker-directed agent demonstrating antitumor activity in patients with FRα-high PROC
- Tumor reduction occurred in 71% of patients, and DCR (CR, PR, SD ≥ 12 weeks) was 51%
- Patients with BRCA mutations, both with and without prior PARPi, demonstrated robust antitumor activity
- In responders, depth and duration of response did not appear to be affected by dose reductions
- Preliminary mOS was 13.8 months
- Safety and tolerability of MIRV in SORAYA are consistent with that observed in previous studies
- Adverse events were primarily low-grade gastrointestinal and ocular events that generally resolved with supportive care or, if needed, dose modifications
- The discontinuation rate due to TRAEs was 9%
- In SORAYA, MIRV demonstrated a favorable benefit-risk profile in patients with FRα-high PROC

Cervical Cancer

Sentex Trial - SLN

SLN from 647 patients processed by a staging protocol

Standard assessment ≈ frozen section

Only 26% MIC found by standard assessment

	FROZEN SECTION	ULTRASTAGING			TOTAL % of all patients
		1st level	2nd - 4th level	≥ 5th level	
MAC	36 (83.7%)	6 (14.0%)	1 (2.3%)	0 (0%)	43 (6.6%)
MIC	10 (25.6%)	14 (35.9%)	8 (20.5%)	6 (15.4%)	39 (6.0%)
ITC	2 (9.1%)	6 (27.3%)	10 (45.4%)	4 (18.2%)	22 (3.4%)
pN1 (MAC + MIC)	46 (56.1%)	20 (24.4%)	9 (11.0%)	6 (7.3%)	82 (12.7%)

ITC: isolated tumour cells; MAC: macrometastases; MIC: micrometastases

44% pN1 cases found by ultrastaging

93% pN1 cases detected by 4-levels ultrastaging

David Cibula

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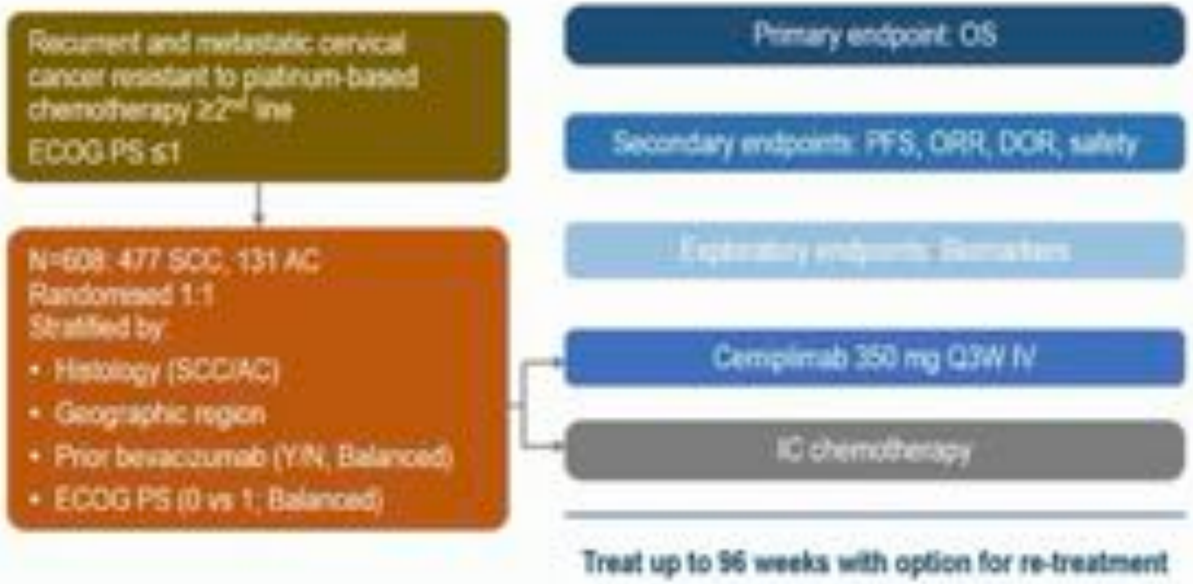
EMPOWER Background and design



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Survival with Cemiplimab in Recurrent Cervical Cancer

K.S. Tewari, B.J. Monk, I. Vergote, A. Miller, A.C. de Melo, H.-S. Kim, Y.M. Kim, A. Lisyanskaya, V. Samouëlian, D. Lorusso, F. Damian, C.-L. Chang, E.A. Gotovkin, S. Takahashi, D. Ramona, J. Pikiel, B. Markowiak-Matejczyk, E.M. Guerra Alia, N. Colombo, Y. Makarova, D. Rischin, S. Lheureux, K. Hasegawa, K. Fujiwara, J. Li, S. Jamil, V. Jankovic, C.-I Chen, F. Seebach, D.M. Weinreich, G.D. Yancopoulos, I. Lowy, M. Mathias, M.G. Fury, and A. Oaknin, for the Investigators for GOG Protocol 3016 and ENGOT Protocol En-Cd9*

ABSTRACT

BACKGROUND

Patients with recurrent cervical cancer have a poor prognosis. Cemiplimab, the fully human programmed cell death 1 (PD-1)–blocking antibody approved to treat lung and skin cancers, has been shown to have preliminary clinical activity in this population.

NEJM 2022; 386:544-55

EMPOWER characteristics

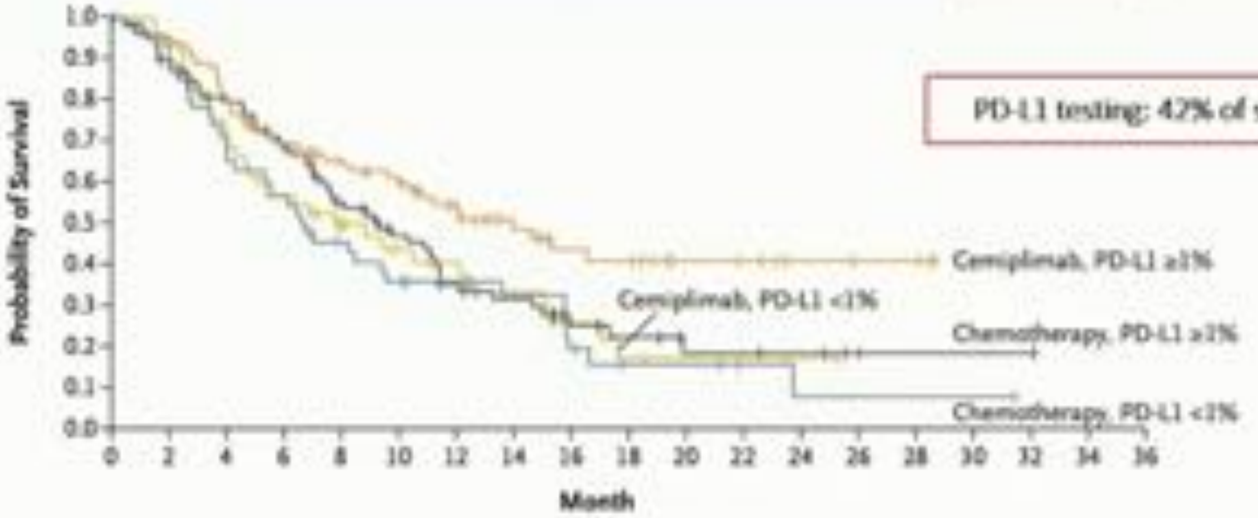
- In NEJM publication 254/608 (42%) had PD-L1 testing (64% "positive")
- PD-L1 status - SP263 monoclonal antibody
- Tumor cell percent ≥1% considered positive
- Only samples stained with in 6 months were analyzed

Updated Analysis:

- **60% of participants had PD-L1 data**
- **Overall PD-L1 positivity is 64%**

n (%)	Cemiplimab (n=304)	Chemotherapy (n=304)	Total (N=608)
Extent of disease			
Metastatic	284 (93.4)	290 (95.4)	574 (94.4)
Recurrent/persistent	20 (6.6)	14 (4.6)	34 (5.6)
Prior bevacizumab use			
Yes	149 (49.0)	147 (48.4)	296 (48.7)
No	155 (51.0)	157 (51.6)	312 (51.3)
Number of prior lines of therapy for recurrent or metastatic disease			
1	177 (58.2)	169 (55.6)	346 (56.9)
>1	124 (40.8)	135 (44.4)	259 (42.6)
Frequency of PD-L1 expression per tumour cell			
PD-L1 ≥1%	**116**	**121**	**237**
PD-L1 <1%	**66**	**68**	**134**

Cemiplimab monotherapy significantly improved OS vs chemotherapy regardless of PD-L1 status (NEJM publication)



No. at Risk																			
Cemiplimab, PD-L1 ≥1%	82	78	65	55	45	39	30	22	16	15	10	9	4	3	3	0	0	0	0
Cemiplimab, PD-L1 <1%	44	41	30	25	18	13	11	9	6	4	3	3	1	0	0	0	0	0	0
Chemotherapy, PD-L1 ≥1%	80	69	58	50	36	28	20	16	10	8	5	5	4	2	1	1	1	0	0
Chemotherapy, PD-L1 <1%	48	40	30	26	19	15	12	10	6	4	4	2	1	1	1	1	0	0	0

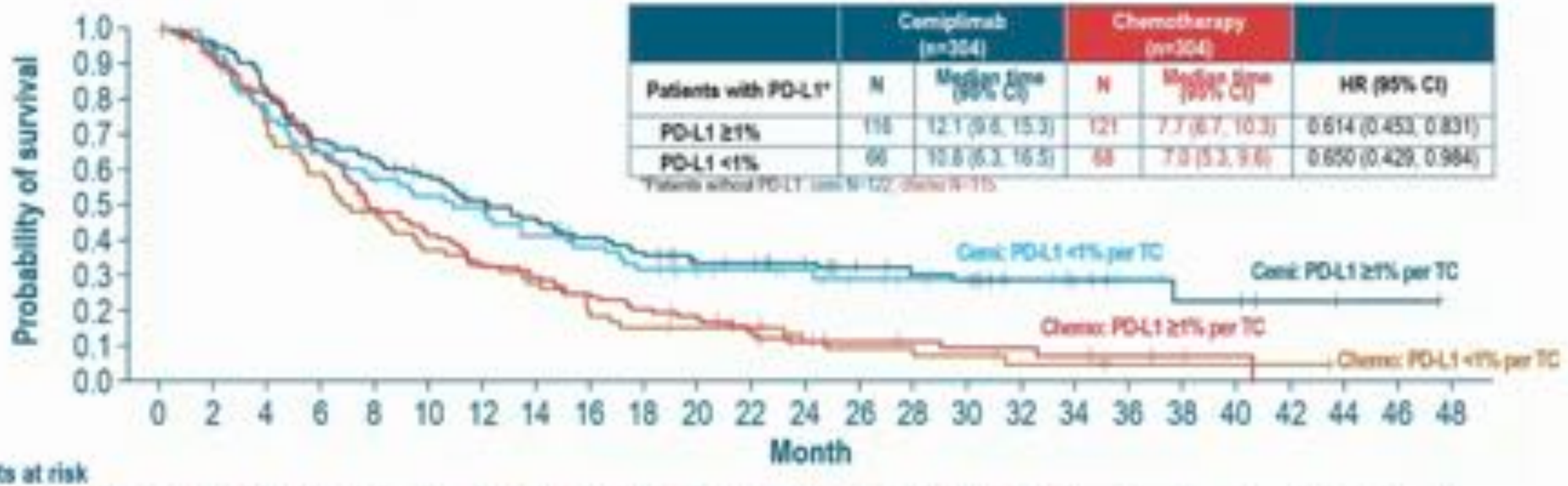
Figure 3. Overall Survival According to PD-L1 Expression Status in the Overall Trial Population.

Kaplan–Meier estimates of overall survival according to PD-L1 expression status are shown. Patients with PD-L1 expression (measured as the tumor cell expression score [the percentage of tumor cells expressing PD-L1]) of 1% or greater generally had enhancement of the overall survival benefit. Patients with PD-L1 expression of less than 1% generally had an overall survival benefit as good as or slightly better than that of patients who received chemotherapy. Tick marks indicate censored data.

Cemiplimab monotherapy significantly improved OS vs chemotherapy regardless of PD-L1 status

	Cemiplimab (n=304)		Chemotherapy (n=304)		
Patients with PD-L1*	N	Median time (95% CI)	N	Median time (95% CI)	HR (95% CI)
PD-L1 ≥1%	116	12.1 (9.6, 15.3)	121	7.7 (6.7, 10.3)	0.614 (0.453, 0.831)
PD-L1 <1%	66	10.8 (6.3, 16.5)	68	7.0 (5.3, 9.6)	0.650 (0.429, 0.984)

*Patients without PD-L1 data: N=122; data N=115



Patients at risk

Cemi: PD-L1 ≥1% per TC	116	110	93	77	71	63	55	48	41	36	30	29	25	20	17	16	10	9	5	4	4	2	1	1	0
Cemi: PD-L1 <1% per TC	66	61	49	43	36	33	30	26	24	20	16	14	12	9	7	5	5	3	1	0	0	0	0	0	0
Chemo: PD-L1 ≥1% per TC	121	107	92	73	54	46	37	33	27	23	19	13	9	7	6	5	5	4	3	2	1	0	0	0	0
Chemo: PD-L1 <1% per TC	68	60	46	39	30	24	21	18	12	10	9	9	6	5	4	4	2	2	1	1	1	1	0	0	0

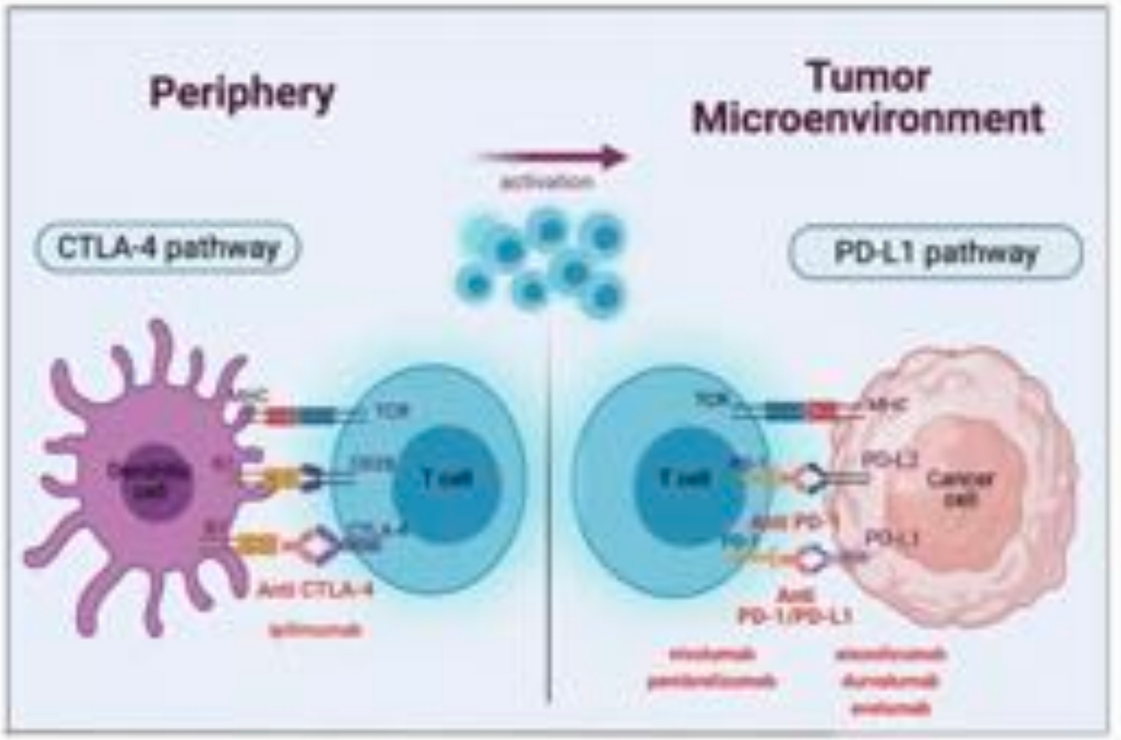
Kaplan–Meier curves of overall survival in the full analysis set; **Data cutoff date: 4 Jan 2022**

Cemi, cemiplimab; Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death-ligand 1; TC, tumour cell; PD-L1 expression was detected with the SP263 monoclonal antibody (Ventana; Tewari et al., NEJM, 2022)

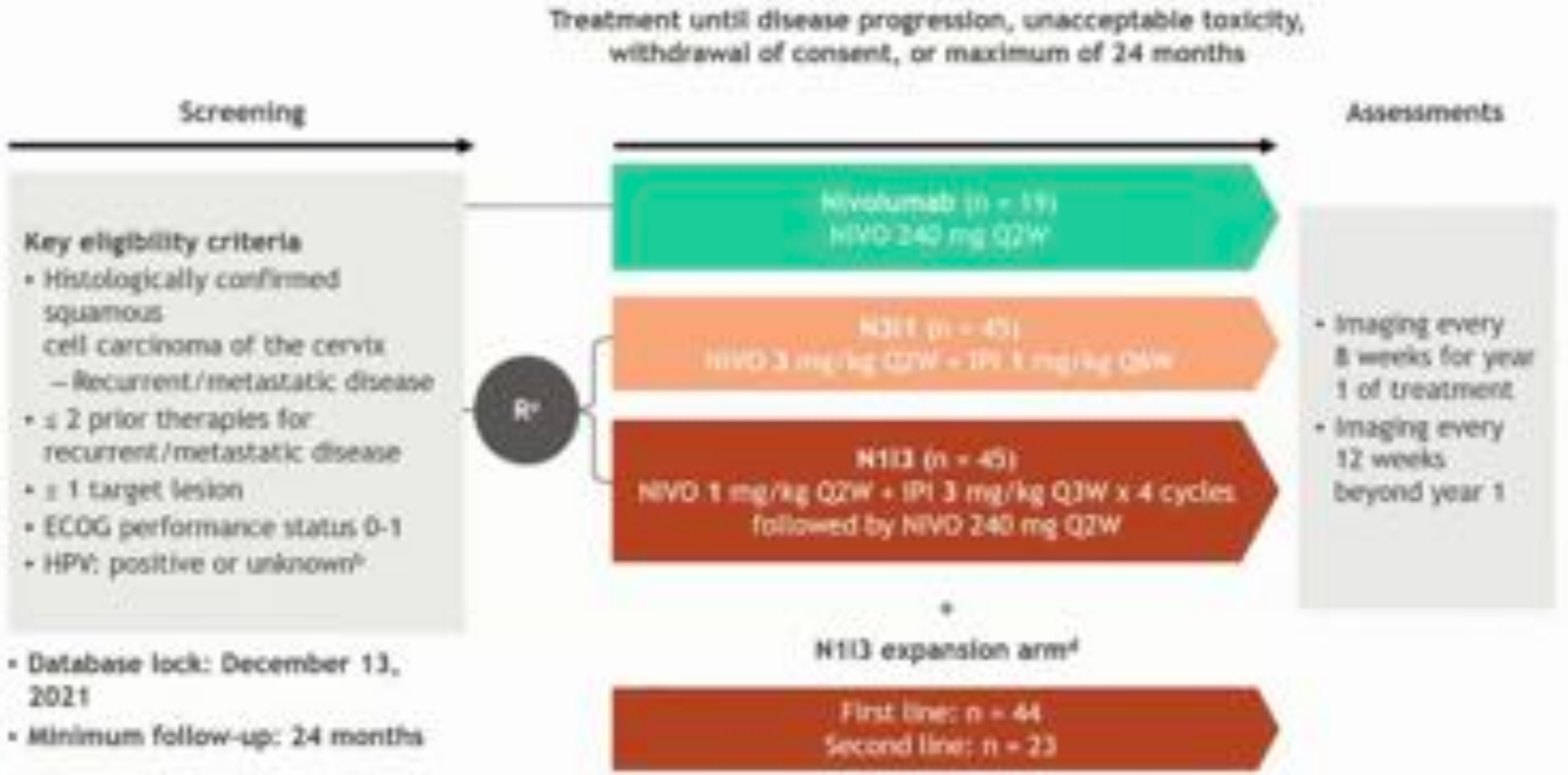
Ana Oaknin

Combining PD-1/L1i and CTLA-4i – increase in efficacy?

- PD-1/L1 and CTLA-4: Immune checkpoints involved with education and activation of the immune surveillance
- Pharmacological inhibition has led to increased activity (and toxicity) over single agents in many solid tumor



Checkmate 358: Ipi Nivo in Cervical Cancer



Primary endpoint:
- Investigator-assessed ORR

Secondary endpoints:
- DOR
- Investigator assessed PFS
- OS

For all treatment arms, an ORR of ≥ 10% will be considered of clinical interest, and an ORR of ≥ 25% will be considered of strong clinical interest

Ana Oaknin

Checkmate 358 Investigator-assessed objective response rate

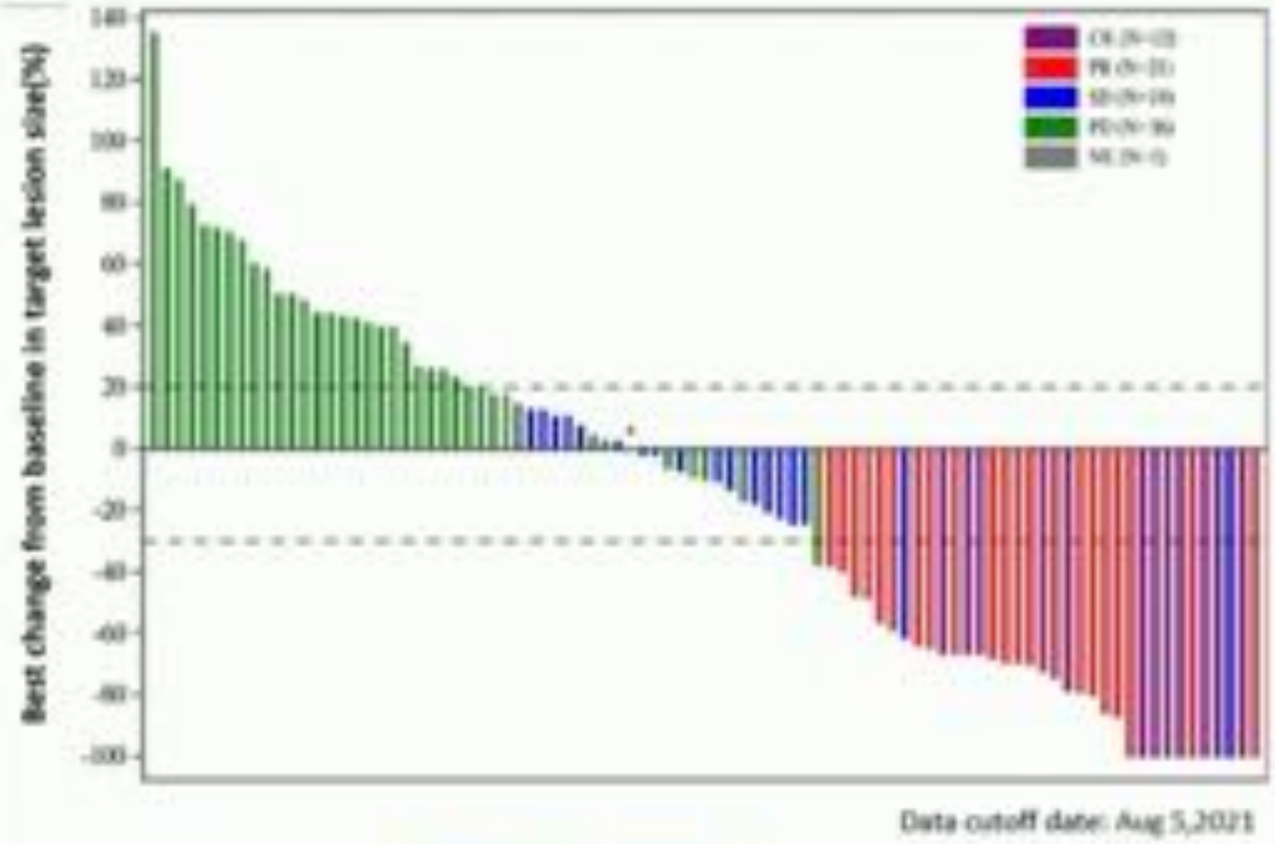
	NIVO	N3I1 (randomized)			N1I3 Pooled (randomized + expansion)		
	All (n = 19)	All (n = 45)	1L (n = 18)	≥ 2L (n = 27)	All (n = 112)	1L (n = 69)	≥ 2L (n = 43)
ORR, % (95% CI)	26 (9-51)	31 (18-47)	39 (17-64)	26 (11-46)	38 (29-48)	41 (29-53)	35 (21-51)
PD-L1* ≥ 1%, responders/evaluable (%)	3/11 (27)	9/25 (36)	4/12 (33)	5/13 (38)	19/53 (36)	13/33 (39)	6/20 (30)
PD-L1* < 1%, responders/evaluable (%)	1/7 (14)	3/15 (20)	2/3 (67)	1/12 (8)	11/36 (31)	6/19 (32)	5/17 (29)
Median DOR, months (95% CI)	NR (35.3-NR)	24.4 (8.7-NR)	34.6 (6.6-NR)	21.1 (7.5-NR)	34.1 (11.5-NR)	25.6 (9.2-NR)	NR (5.2-NR)

- As expected, more responses were noted in the first- vs second-or-later-line setting
- N1I3 showed a higher response rate than N3I1 in both first- and second-or-later-line setting
- **Durable responses were observed regardless of tumor PD-L1 status across all treatment arms**
  - **There are fewer responses seen in patients with PD-L1 < 1% treated with nivolumab monotherapy compared with patients with PD-L1 < 1% treated with nivolumab and ipilimumab**
  - **Therapy was tolerable, no new safety signals, toxicity higher in N1I3 compared with N3I1**

*PD-L1 expression by tumor proportion score; TP263 assay.

Ana Oaknin

Cadonilimab AK104 : Activity in Cervical Ca
Bi-specific antibody



Response	FAS-IRRC [1] (N = 100)
ORR(CR+PR),n(%) (95%CI)	33(33.0) (23.9, 43.1)
CR,n (%)	12 (12.0)
PR,n (%)	21 (21.0)
SD,n (%)	19 (19.0)
DCR(CR+PR+SD),n(%) (95%CI)	52(52.0) (41.8, 62.1)
mTTR,mos (range)	1.84 (1.68, 6.74)
Median DoR,mos (range)	NR[2] (0.95+, 16.43+)[3]

1. IRRC: Independent radiological review committee
2. NR=Not Reached
3. +Represents deletion (no disease progression or death)

Phase 3 underway

Robert L Coleman

Endometrial Cancer

2022 ASCO® ANNUAL MEETING

Dostarlimab in Advanced/Recurrent Mismatch Repair Deficient/Microsatellite Instability–High or Proficient/Stable Endometrial Cancer: the GARNET study

Ana Oaknin,[1] Bhavana Pothuri,[2] Lucy Gilbert,[3] Renaud Sabatier,[4] Sharad Ghamande,[5] Adriano Gravina,[6] Emiliano Calvo,[7] Susana Banerjee,[8] Rowan E. Miller,[9] Joanna Pikiel,[10] Mansoor R. Mirza,[11] Tao Duan,[12] Sybil Zildjian,[13] Eleftherios Zografos,[14] Jennifer Veneris,[13] Anna V. Tinker[15]

[1]Gynaecologic Cancer Programme, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [2]Gynecologic Oncology Group (GOG) and Department of Obstetrics/Gynecology, Laura & Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; [3]Division of Gynecologic Oncology, McGill University Health Centre, Montreal, Quebec, Canada; [4]Department of Medical Oncology, Institut Paoli Calmettes, Aix-Marseille University, Marseille, France; [5]Department of Obstetrics & Gynecology, Georgia Cancer Center, Augusta University, Augusta, GA, USA; [6]Clinical Trial Unit, Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy; [7]START Madrid–CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; [8]Gynaecology Unit, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK; [9]University College London, St. Bartholomew's Hospitals London, London, UK; [10]Department of Chemotherapy, Regional Center of Oncology, Gdansk, Poland; [11]Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Denmark, Nordic Society of Gynaecologic Oncology–Clinical Trial Unit, Copenhagen, Denmark; [12]GlaxoSmithKline, Pennington, NJ, USA; [13]GlaxoSmithKline, Waltham, MA, USA; [14]GlaxoSmithKline, London, UK; [15]Department of Medicine, British Columbia Cancer, Vancouver Centre, University of British Columbia, Vancouver, British Columbia, Canada

Methods

- GARNET is a phase 1, multicenter, open-label, single-arm study of dostarlimab monotherapy in patients with advanced or recurrent solid tumors
- Patients were enrolled to cohort A1 (dMMR/MSI-H) or cohort A2 (MMRp/MSS) based on MMR IHC assessment
- Patients received 500 mg IV dostarlimab every 3 weeks for 4 cycles, followed by 1000 mg IV every 6 weeks until disease progression, discontinuation, or withdrawal
- Primary endpoints were evaluation of antitumor activity (in terms of ORR and DOR by BICR per RECIST v1.1), safety, and tolerability

BICR, blinded independent central review; dMMR, mismatch repair deficient; DOR, duration of response; EC, endometrial cancer; IHC, immunohistochemistry; IV, intravenous; MMR, mismatch repair; MMRp, mismatch repair proficient; MSI, microsatellite instability; MSI-H, microsatellite instability–high; MSS, microsatellite stable; NSCLC, non–small cell lung cancer; ORR, objective response rate; PD, progressive disease; PROC, platinum-resistant ovarian cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Demographics and Baseline Characteristics

Characteristic, n (%)	dMMR/MSI-H EC N=143	MMRp/MSS EC N=156
Age, median (range), years	65.0 (39–85)	66.0 (30–86)
FIGO disease stage at diagnosis[a]		
Stage I or II	62 (43.4)	57 (36.5)
Stage III or IV	81 (56.6)	98 (62.8)
Histology		
Grade 1 or 2 endometrioid carcinoma	92 (64.3)	36 (23.1)
Serous	7 (4.9)	63 (40.4)
Grade 3 endometrioid	21 (14.7)	14 (9.0)
Clear cell	1 (0.7)	11 (7.1)
Squamous	1 (0.7)	3 (1.9)
Undifferentiated	4 (2.8)	3 (1.9)
Carcinosarcoma	0	2 (1.3)
Mixed carcinoma	7 (4.9)	11 (7.1)
Unspecified	4 (2.8)	9 (5.8)
Other[b]	4 (2.8)	4 (2.6)
Unknown	2 (1.4)	0

Characteristic, n (%)	dMMR/MSI-H EC N=143	MMRp/MSS EC N=156
Prior anticancer treatment	143 (100)	156 (100)
Prior lines of therapy, n (%)[c]		
1	90 (62.9)	72 (46.2)
2	35 (24.5)	67 (42.9)
≥3	18 (12.6)	17 (10.9)
Patients with only adjuvant or neoadjuvant therapy	49 (34.3)	42 (26.9)
Neoadjuvant setting only	3 (2.1)	3 (1.9)
Adjuvant setting only	44 (30.8)	39 (25.0)
Only adjuvant and neoadjuvant	2 (1.4)	0
Prior radiation, n (%)	101 (70.6)	95 (60.9)

[a]One patient with MMRp EC had disease status/stage unknown. [b]Other includes dedifferentiated, endometrial adenocarcinoma, endometrial adenocarcinoma NOS, endometrial neuroendocrine carcinoma, high grade uterine carcinoma, and undiffereciated clear cell carcinoma. [c]Includes lines of therapy in the adjuvant setting.
dMMR, mismatch repair deficient; EC, endometrial cancer; FIGO, International Federation of Gynecology and Obstetrics; MMRp, mismatch repair proficient; MSI-H, microsatellite instability–high; MSS, microsatellite stable.

Primary Endpoint Analysis

	dMMR/MSI-H EC N=143	MMRp/MSS EC N=156
Median follow-up time, months	**27.6**	**33.0**
ORR, % (95% CI; n/N) Complete response, n (%) Partial response, n (%) Stable disease, n (%) Progressive disease, n (%) Not evaluable, n (%)	**45.5%** (37.1–54.0; 65/143) **23** (16.1) **42** (29.4) 21 (14.7) 51 (35.7) 6 (4.2)	**15.4%** (10.1–22.0; 24/156) **4** (2.6) **20** (12.8) 29 (18.6) 88 (56.4) 15 (9.6)
Median time from cycle 1 day 1 to best overall response, mo Complete response Partial response	 2.79 2.69	 2.81 2.79
Disease control rate, % (95% CI; n/N)	**60.1%** (51.6–68.2; 86/143)	**34.0%** (26.6–42.0; 53/156)
Response ongoing, n (%)	54 (83.1)	9 (37.5)
Median duration of response (range), months	**NR** (1.18+ to 47.21+)	**19.4** (2.8 to 47.18+)
Probability of maintaining response, % 6 months 12 months 24 months	 96.8 93.3 83.7	 82.6 60.3 44.2

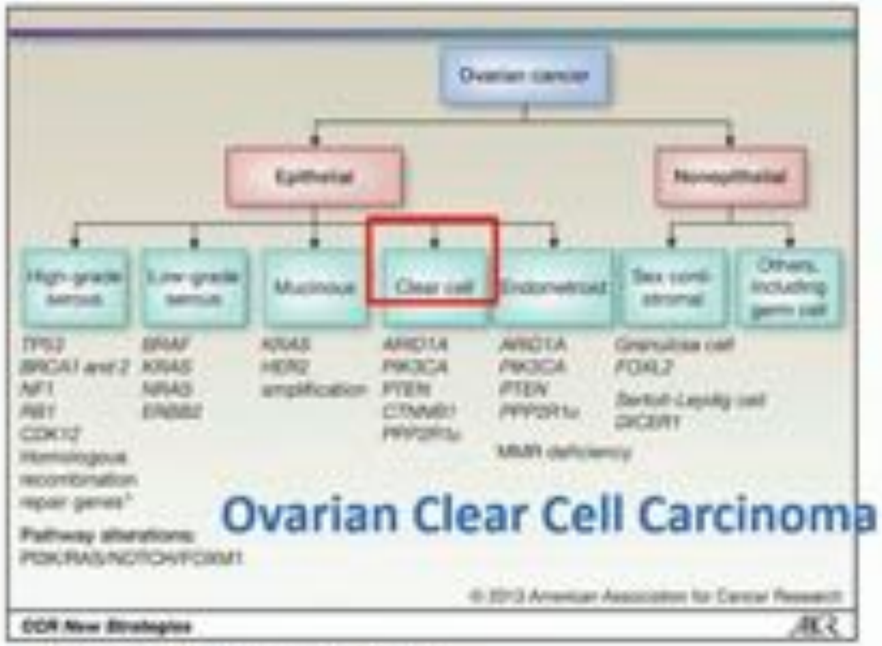
dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; MSI-H, microsatellite instability–high; MSS, microsatellite stable; NR, not reached; ORR, objective response rate.

Maintenance Selinexor Improves PFS in advanced or Recurrent Endometrial Cancer: SIENDO/GOG3055/ENGOTEN5

- Stage IV or recurrent endometrial ca (EM, serous, undifferentiated & Carcinosarcoma)
- All patients received at least 12 weeks of taxane and carboplatin and had PR/CR
- Selinexor 80 mg po weekly v placebo (selectively inhibiting XPO1, reactivating tumor suppressing proteins, and inducing tumor cell apoptosis)
- Primary end point: Investigator assessed PFS
- Median PFS: 5.7 mo Selinexor v 3.8 mo placebo
  - Endometrioid 9.2 mo Selinexor v 3.8 mo placebo
  - Serous 3.8 mo Selinexor v 3.7 mo placebo
  - Wild type p53 13.7 mo Selinexor v 3.7 mo placebo
- TEAE: Nausea 84%, Vomiting 52%, Constipation 37%, Thrombocytopenia 37%

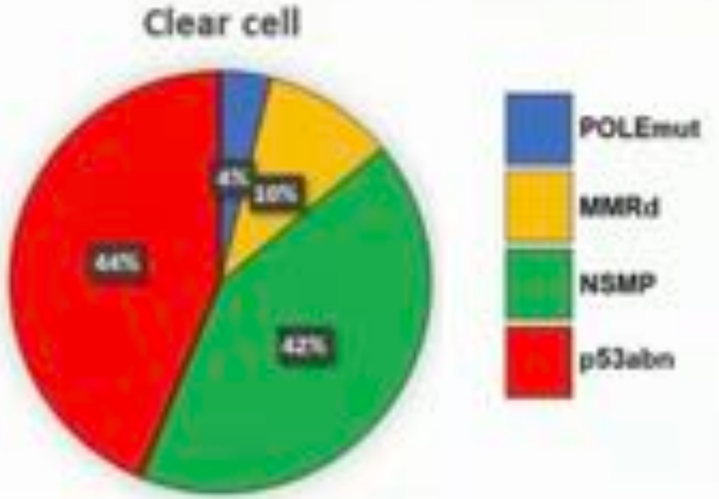
PRESENTED BY:
Ignace Vergote, MD PhD

Gynae Clear Cell Carcinoma – Rare and underserved



Ovarian Clear Cell Carcinoma

Endometrial Clear Cell Carcinoma



- OCCC is rare (1-12%)
- higher prevalence in East Asia (up to 25%)
- Median OS 25 mo

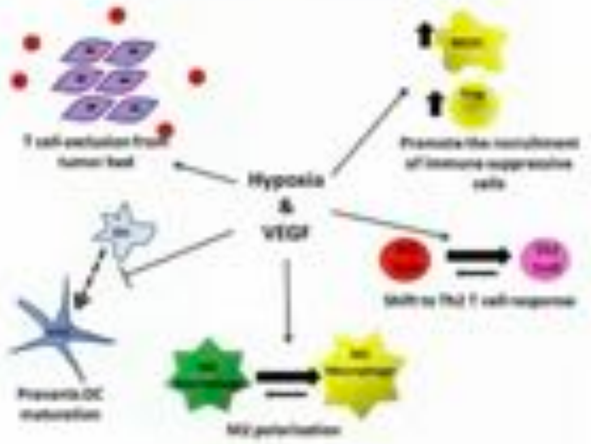
NEED TO IMPROVE TREATMENT STRATEGIES

- Banerjee et al. Clin Can Res 2013;1:19(5):961-8.; Chan JK et al. Gynecol Oncol 2008;109:370–6; Pearce CLet al. Lancet Oncol. 2012;13(4):385–94; Hermens M, et al.. Am J Obstet Gynecol 2020;223:107.e1–107.e11;. Takano M, et al.. Int J Gynecol Cancer 2008;18:937–42.; Irodi A, et al. BJOG 2020;65:Crotzer, D et al Cy, Gynecol. Oncol. 105 (2007) 404–408.

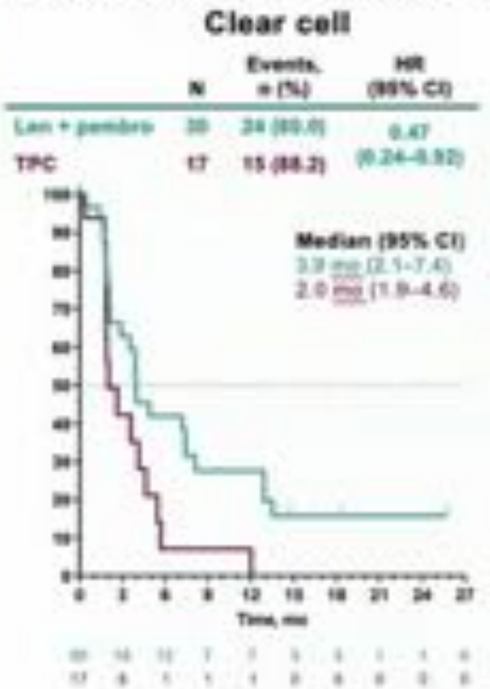
IO+Antiangiogenic Therapy:
Advanced Endometrial Clear Cell Carcinoma

Lenvatinib plus pembrolizumab vs physician's choice chemotherapy (Study 309/KEYNOTE-775)

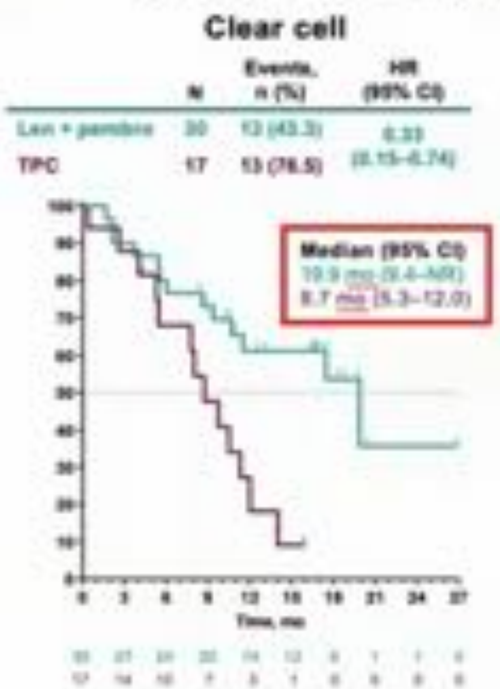
- Post-hoc analyses: Lenvatinib + Pembrolizumab improved PFS and OS including clear cell histology



Progression-free Survival

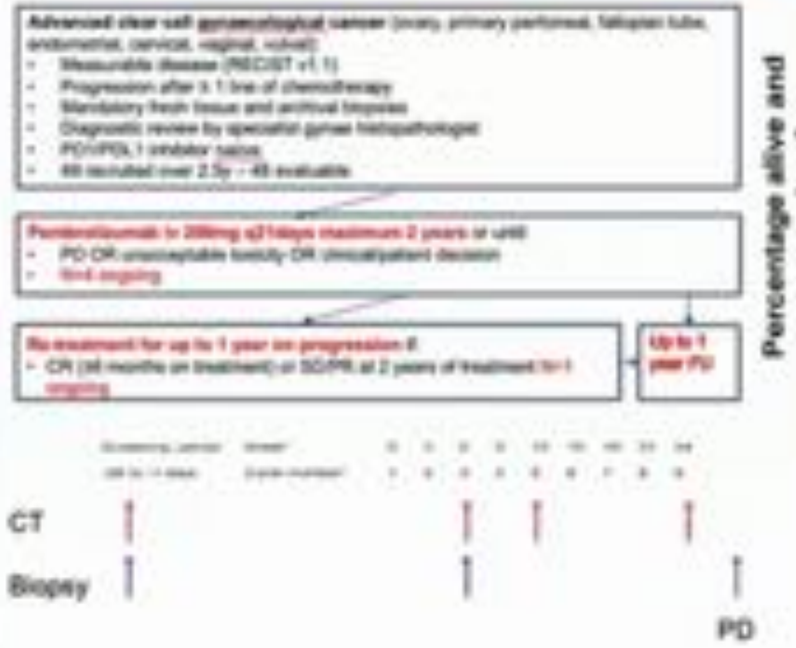


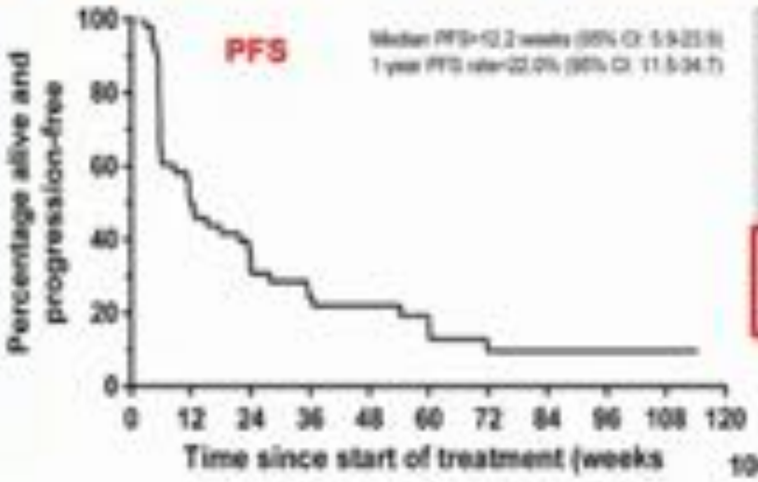
Overall Survival



- Colombo et al ESMO 2021 Annals of Oncology (2021) 32 (suppl_5): S725-S772. 10.1016/annonc/annonc703

PEACOCC Results: Pembrolizumab in CCC (~Ov and endom)





PFS at 12 weeks 43.8%
Median PFS 12.2 weeks
Response rate 25% (12/48)
Duration of response (DOR) 48.1 wk

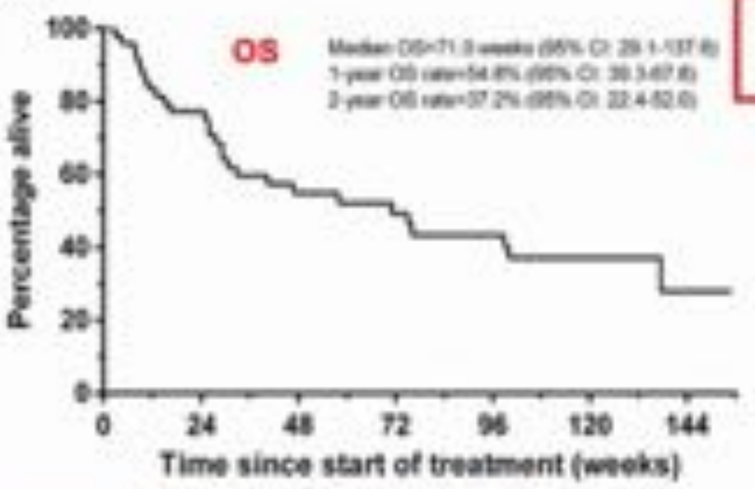
1 year DOR 47.7%

Median OS 71 weeks

(Median follow-up 2.1 years)

85.4% (n=41)Ovarian
12.5% (n=6) Endometrial
2.1% (n=1) Cervical

39.6% prior antiangiogenic
All PD1/-L1 inhibitor naive

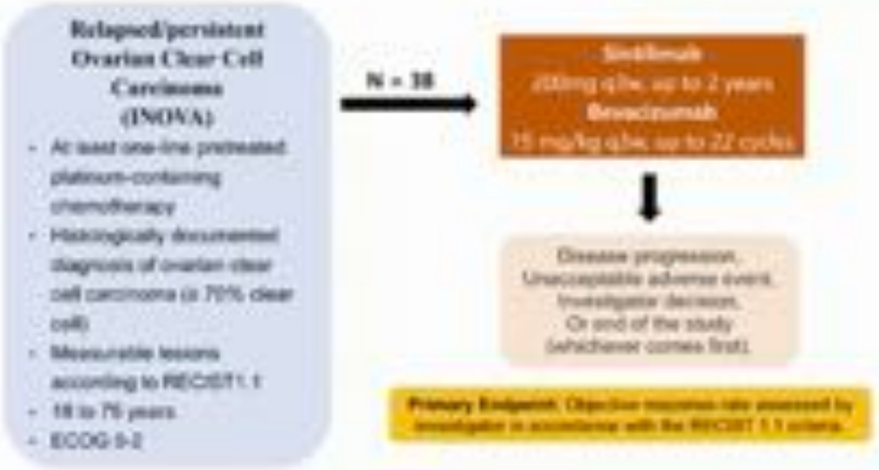


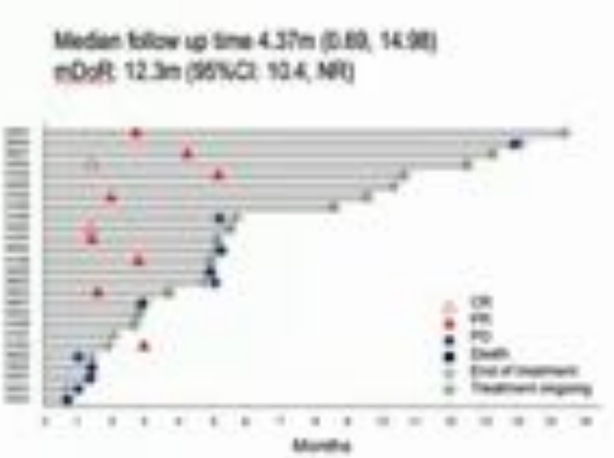
18 mo

No new safety signals: 16.7% grade 3 TRAE; 6.3% discontinuation due to TRAE

- Kristeleit et al ESMO 2022

PD-1i+Antiangiogenic Therapy: INOVA preliminary results





Trial ongoing: Results of 26 patients enrolled out of planned 38 (median follow-up 4.37 months)

ORR 38.5% (10/26)

Median DOR 12.3 months

23.1% (6/26) prior bevacizumab

76.9% platinum-resistant

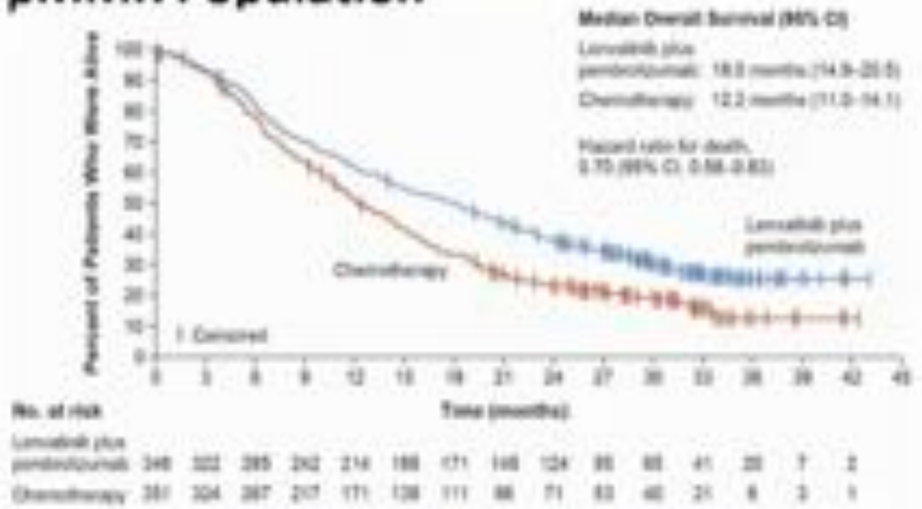
Safety profile acceptable and no new signals

- Liu et al ESMO 2022
- Li R, ... JMU Open 2022;12:e058132

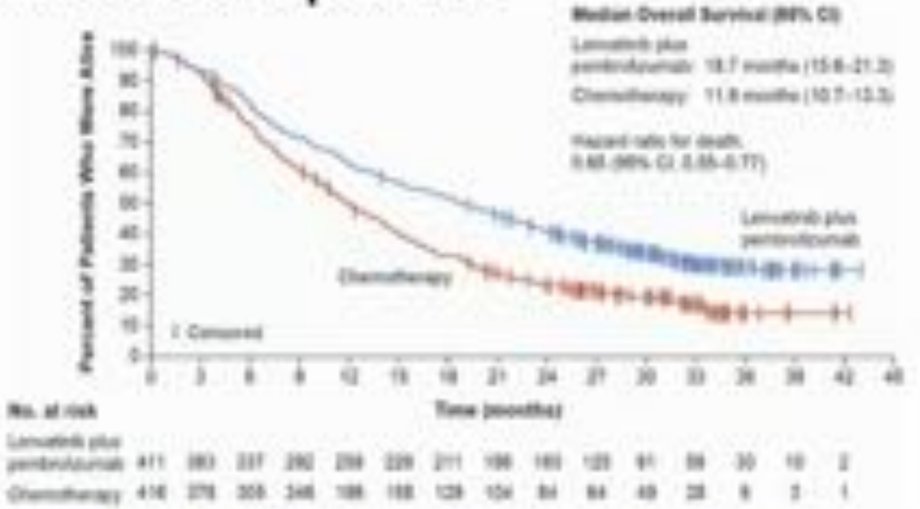
Study 309/KEYNOTE-775 - Updated efficacy and safety of lenvatinib plus pembrolizumab versus treatment of physician's choice in patients with advanced endometrial cancer:

Continued OS benefit with follow-up extended by over 16 months

pMMR Population



All-Comer Population

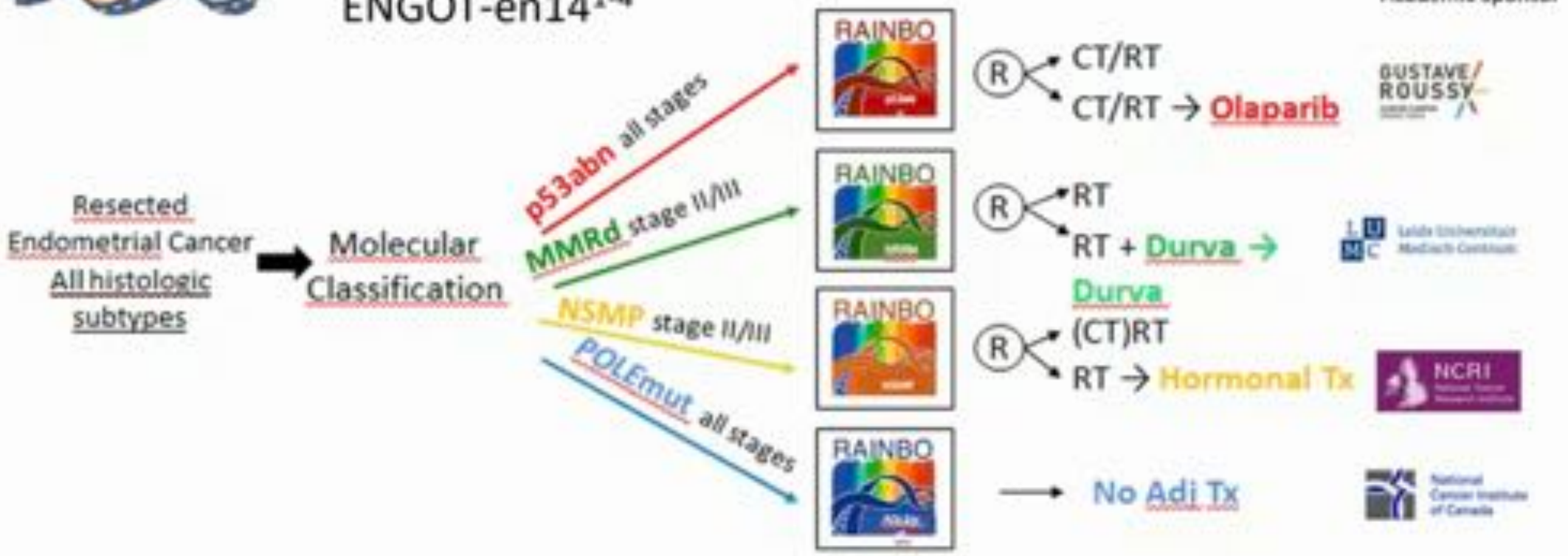


- OS favored lenvatinib plus pembrolizumab despite some pts in the chemotherapy arm receiving subsequent lenvatinib plus pembrolizumab.
- In the chemotherapy arm, 10.0% of pts in the pMMR population and 8.7% of pts in the all-comer population received subsequent lenvatinib plus pembrolizumab.
  - After excluding these pts, the pMMR OS HR was 0.64 (95% CI, 0.54, 0.76);
  - the all-comer OS HR was 0.60 (95% CI, 0.51, 0.71).

RAINBO: Refining Adjuvant treatment IN endometrial cancer Based On molecular profile

ENGOT-en14[1-4]

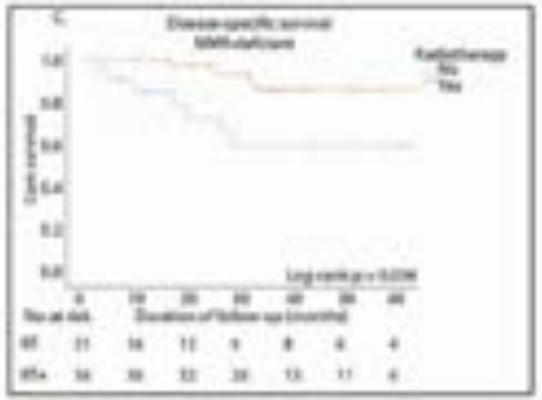
Academic Sponsor



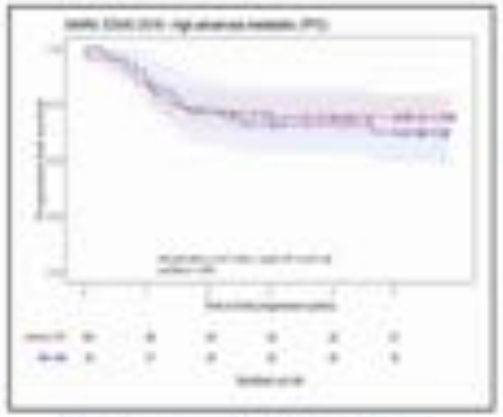
RAINBO platform program of personalized, **molecular based, adjuvant** treatment of pts with high risk EC to **↑ cure and ↓ toxic** treatment in defined subsets.

MMRd: what do we know about treatment of 'high risk' disease?

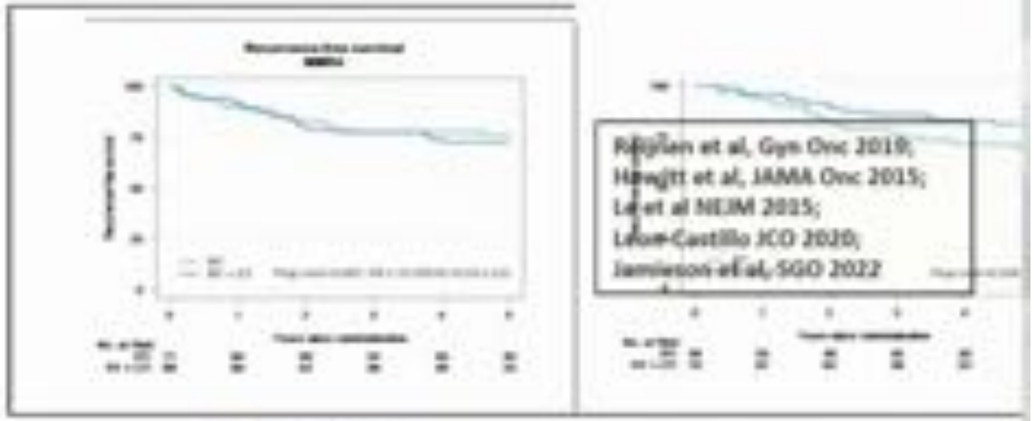
- Staging impactful– increase risk LN mets in MMRd→direct adjuvant Rx
  - ? more likely LNM with MLH1 meth vs germline? Different outcomes, response?
- Importance of **radiation**
- Opportunities for **immune checkpoint blockade** –for advanced or rec dz
- No apparent benefit of chemotherapy? (toxicity w/o benefit?)



Retrospective, multicenter



Jamieson/SGO 2022



PORTEC 3

Jessica McAlpine, 2022

Management of MMRd patients with single agent IO?

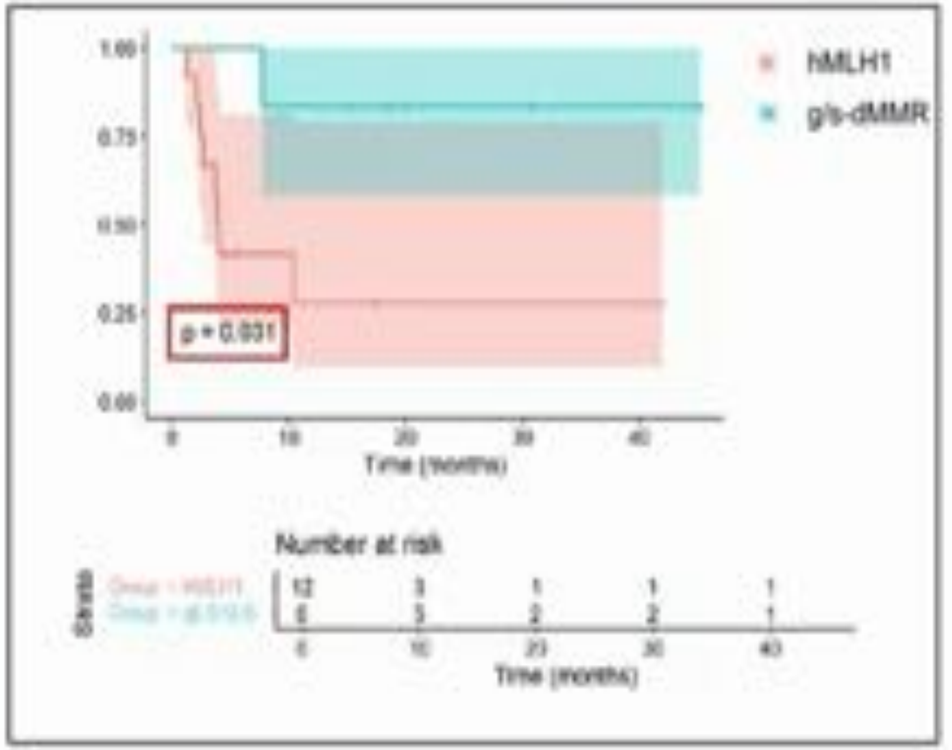
Is IO single agent an adequate treatment for MMRd?

Single agent/single arm in phase II versus combination in a randomized Phase III?

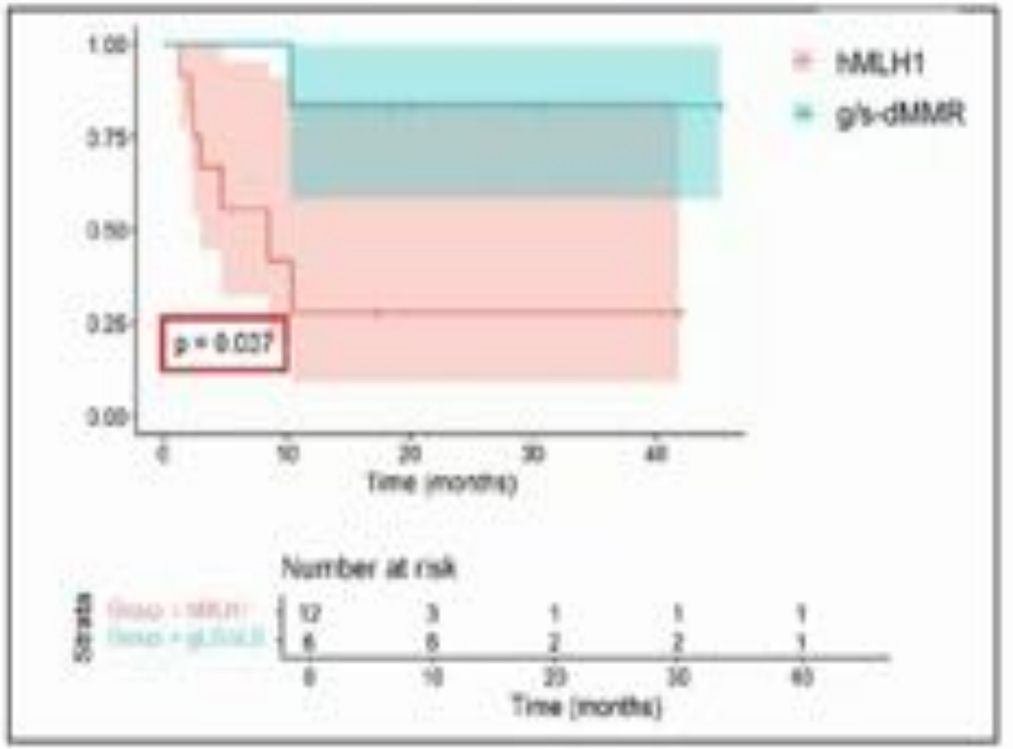
SGO 2022

MLH1 promoter hypermethylation predicts poor outcomes with pembrolizumab in recurrent endometrial cancer

Recurrence-free survival



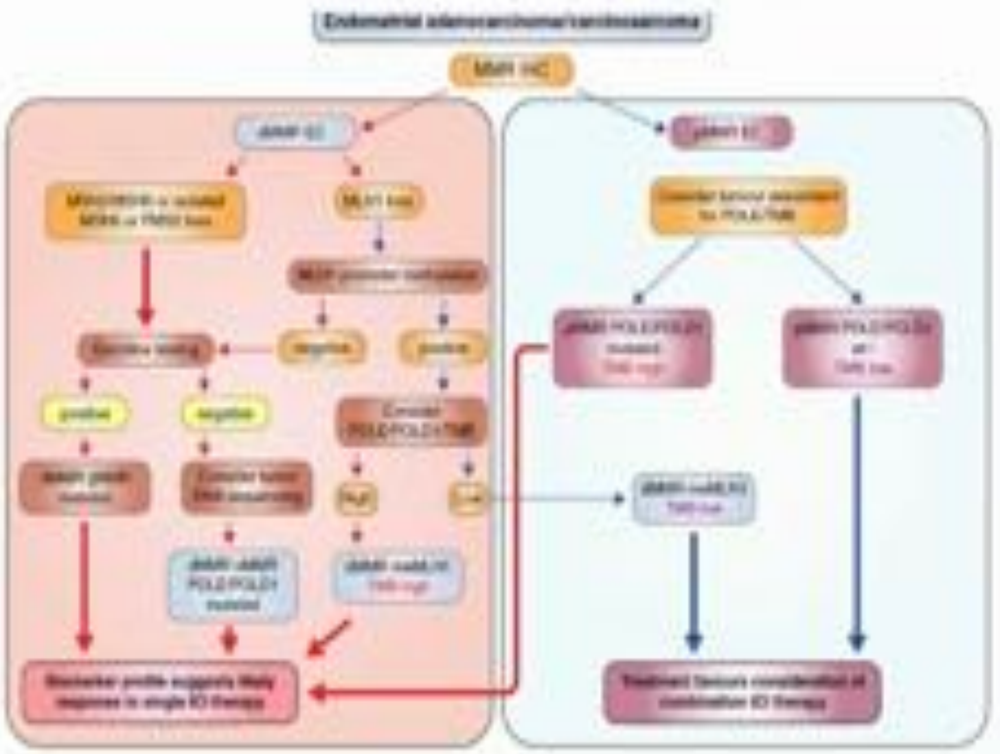
Overall survival



PARIS 2022 ESMO congress

Mismatch repair and clinical response to immune checkpoint inhibitors in endometrial cancer

Yoland Antill, BMed, MD[1,2]; Daniel D. Buchanan, BSc, PhD[3,4,5]; and Clare L. Scott, MBBS, PhD[1,2,6]



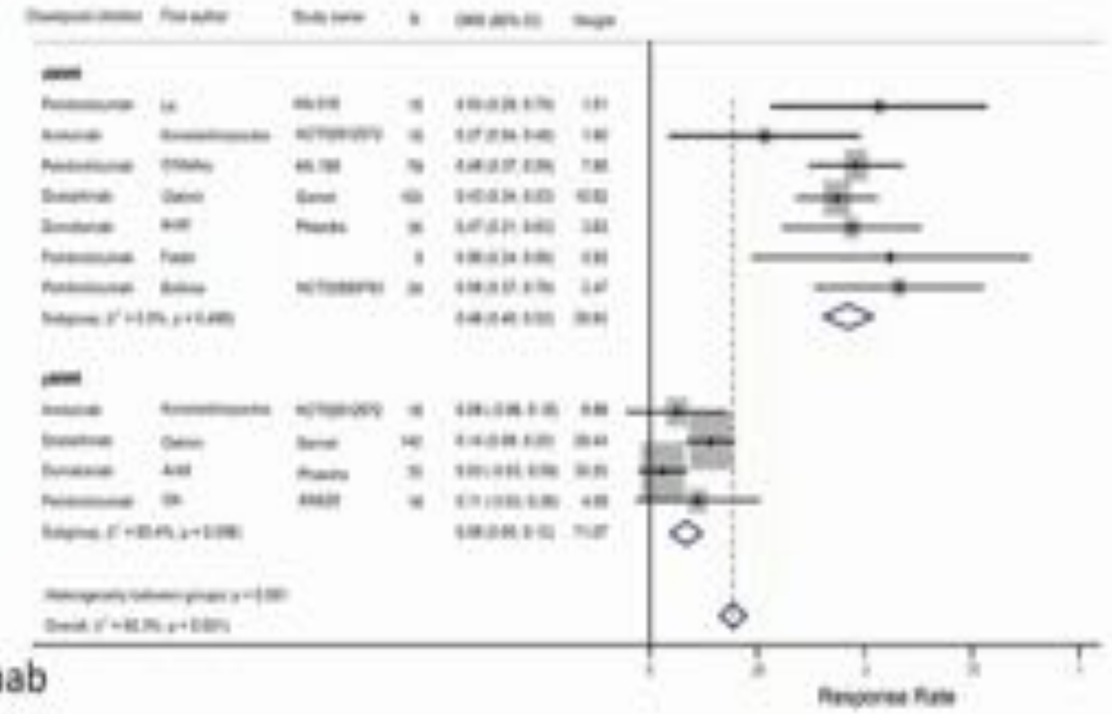
DOI: 10.1002/cncr.34024, Published online Dec 7, 2021

Based on Bellone S et al. A phase 2 evaluation of pembrolizumab for recurrent Lynch-like versus sporadic endometrial cancers with microsatellite instability. Cancer. 2021;127. doi:10.1002/cncr.34025

The Impact of Single-agent PD-1- or PD-L1-Inhibition on advanced endometrial cancers: Meta-analysis

Peey-Sei Kok, Yoland C. Antill, Clare L. Scott*
Chee Khoon Lee*

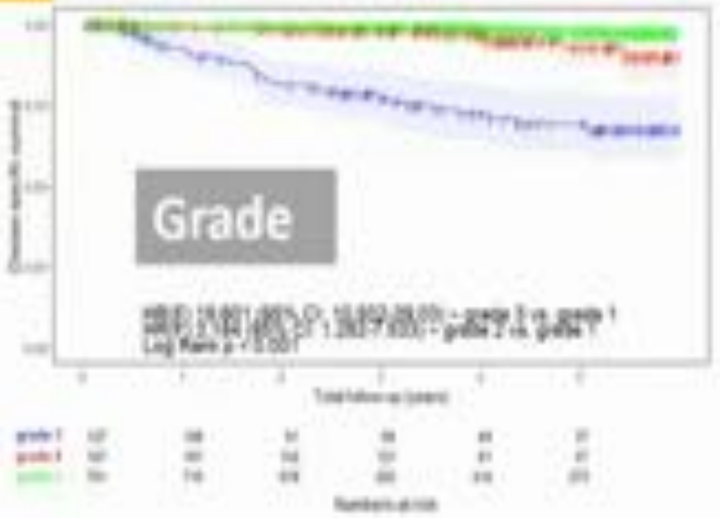
In Press ESMO Open



NSMP– Unlike *POLE*mut ECs, multiple 'adverse' clinicopathologic and molecular parameters are prognostic….

- E.g., Grade, stage, LVI, nodal status, ER, PR, L1CAM, *PIK3CA*…all associated with clinical outcomes on univariate analyses

NSMP



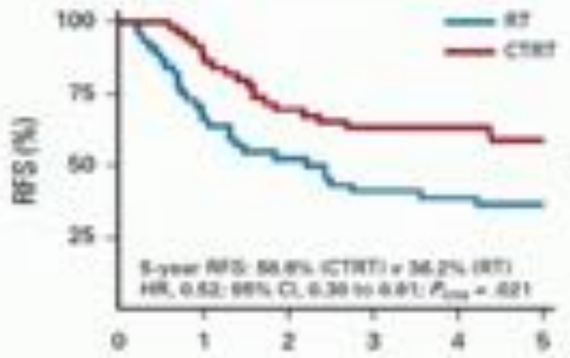
Jessica McAlpine, 2022

Jamieson, Havila, …McAlpine, under review
Momeni-Boroujeni, Mod Path 2022
Embargoed– do not share

Is there a rationale for PARP inhibition in p53Abn EC?

p53abn EC have features of homologous recombination deficiency…. Like high grade OC

TP53 EC are platinum sensitive…



De Boer Lancet Onc 2018; Leon-Castillo JCO 2020, TCGA Nature 2011

Is there a rationale for PARP inhibition in p53Abn EC?

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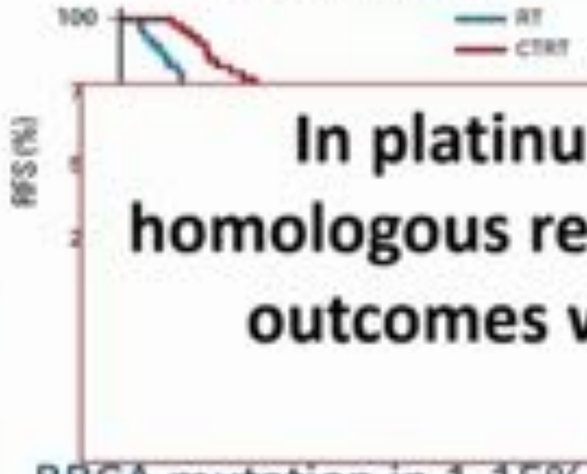
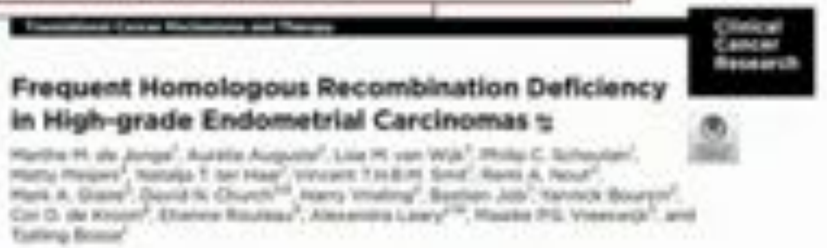
TP53 EC are platinum sensitive…



Same high genomic instability as high grade serous OC

In platinum sensitive p53Abn EC with frequent homologous recombination deficiency, could we improve outcomes with PARPi maintenance after adjuvant chemotherapy?

BRCA mutation in 1-15% EC depending on cohort (Pothuri B. BRCA1/2 somatic mutations in patients with advanced or recurrent endometrial cancer. SGO 2020)

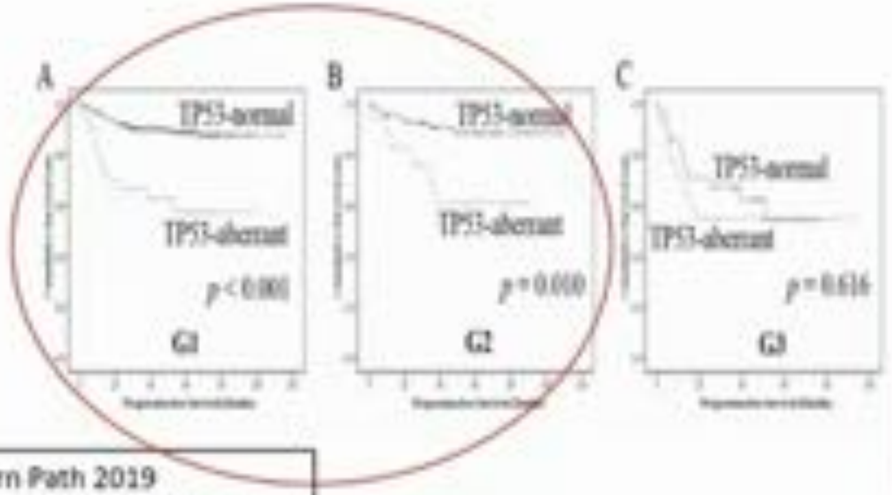

Clinical Cancer Research

Frequent Homologous Recombination Deficiency in High-grade Endometrial Carcinomas

Hanne M. de Jonge, Aurelie Augustin, Lisa M. van Wijk, Philip C. Schouten, Matty Meijers, Natalja T. ter Haar, Vincent T.H.B.M. Smit, Rene A. Nout, Mark A. Glaire, David N. Church, Harry Vreeling, Bastian Jobs, Yannick Bourron, Cor D. de Kroon, Etienne Rouleau, Alexandra Leary, Maaike P.G. Vreeswijk, and Tjalling Bosse

De Boer Lancet Onc 2018; Leon-Castillo JCO 2020, TCGA Nature 2011

What about p53abn low grade EC? E.g 'missed' high risk cases



Yano et al, Modern Path 2019
Jamieson et al, IGCS abstracts 2022

p53abn grade 1 and 2 endometrioid ECs:

- Older women
- Lower BMI
- More had advanced stage disease
  - i.e behave more like serous ca
- Worse survival outcomes compared to p53wt ECs

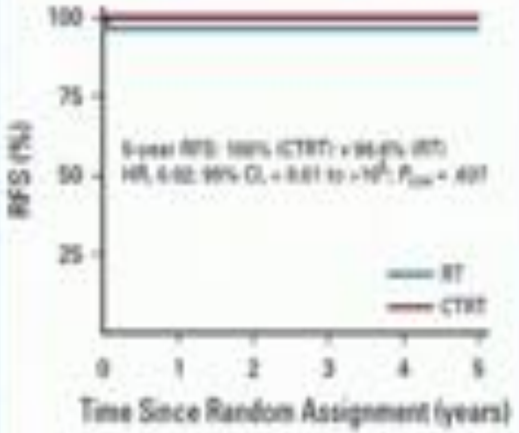
Expert pathology review of PORTEC 1,2 series confirmed presence of low grade endometrioid p53abn ECs; not just glandular variants of serous ca, and these patients had markedly worse outcomes (IGCS abstract, 2022)

Don't forget to check for HER2 (IHC or NGS) in p53 mu EC – search out HER2 targeted therapies
NCI trial beginning Q4 2022 Erikson B PI chemo vs Trastuzumab vs Trastuzumab Pertuzumab

Jessica McAlpine, 2022

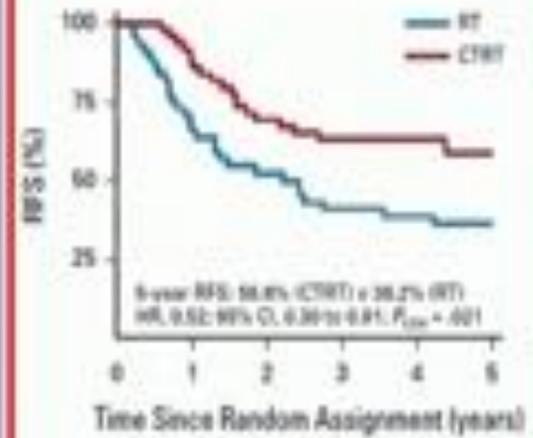
Can molecular subtypes personalise adjuvant medical therapy further in Endometrial Cancer?

*POLE*mut



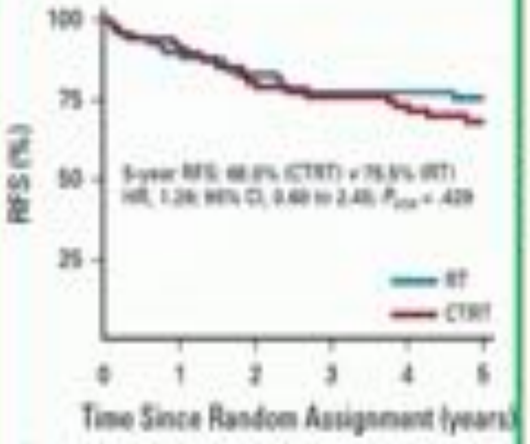
De-escalate

p53abn



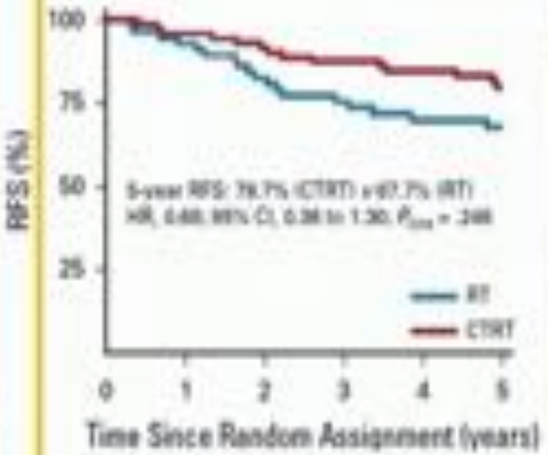
Need to do better:
PARPi
Or anti-HER2

MMRd



Adj immunotherapy?

NSMP



adj
Hormonal therapy?

Alexandra LEARY


PARIS 2022 ESMO congress
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