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ONCOLOGIA MEDICA
S.ORSOLA-MALPIGHI BOLOGNA

ASCO 2019
Update

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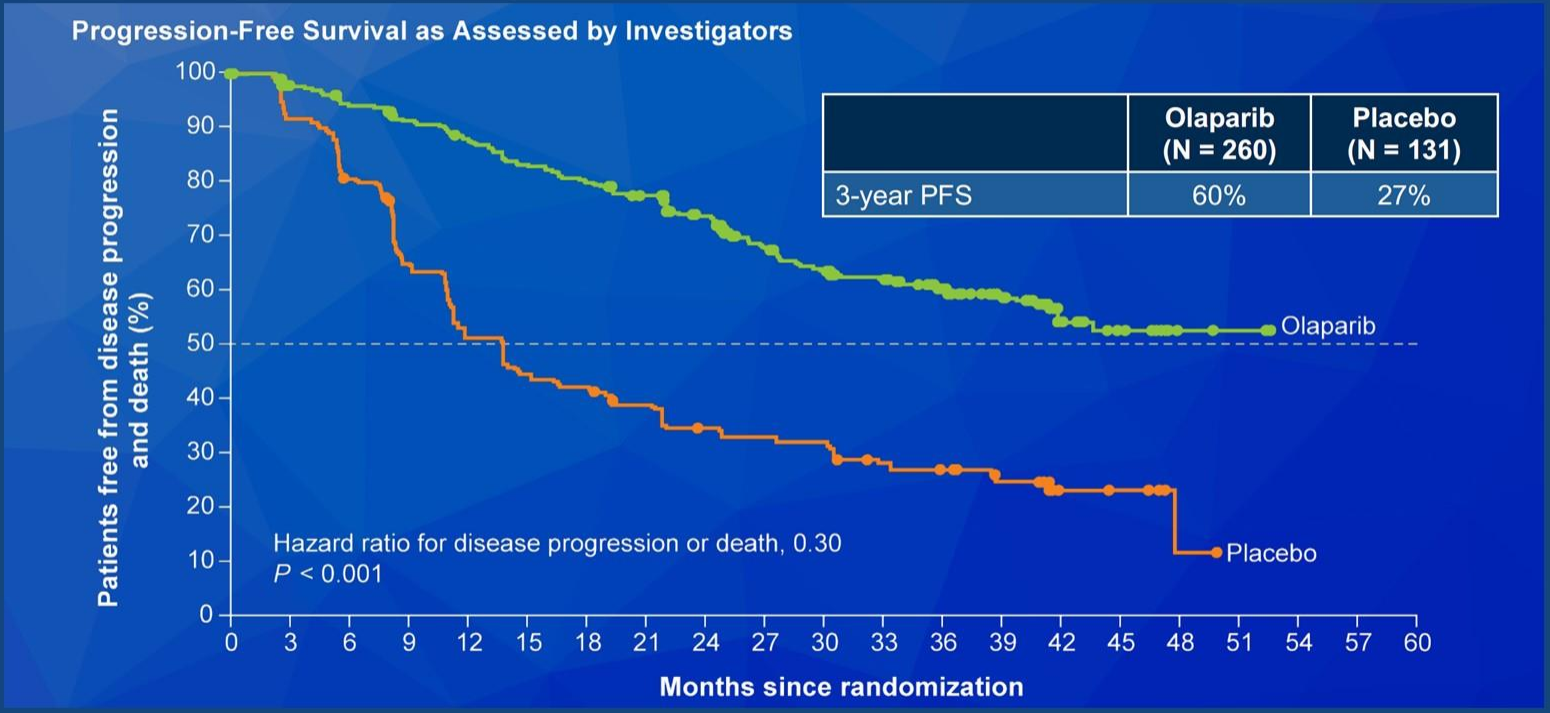
The state of PARP Inhibitors in Ovarian Cancer

Agent	Trial	Volunteer and Study criteria				Efficacy	Toxicity
		ROC	HGS	gBRCA	Maint		
Niraparib	NOVA[1] (n=546)	∫	∫		∫	+++PFS in gBRCA+ and gBRCA-	Nausea, Thrombocytopenia, Fatigue, Anemia
Olaparib	SOLO-2[2] (n=295)	∫	∫	∫	∫	+++PFS	Nausea, Fatigue, Anemia, Emesis
	Phase 2[3] (n=193)	∫	∫	∫		30%ORR 40%SD8w	Fatigue, Nausea, Anemia, Abdominal pain
Rucaparib	ARIEL-3[4]	∫ ≥3 lines	∫		∫	+++PFS in gBRCA+, LOH+, ITT	Nausea, Fatigue, Anemia, Constipation
	Phase 2[5] (n=106)	∫ ≥2 lines	∫	∫ Somatic allowed		54% ORR 9m mDOR	Nausea, Fatigue, Anemia, Abdominal pain

(1) Mirza, et al. NEJM 2016; 375:2154-64; (2) Pujade-Lauraine, et al. Lancet Oncol 2017; 18:1274-84; (3) Ledermann, et al. Lancet Oncol 2014; 15:852-61; (4) Coleman, et al. Lancet 2017; 390:1949-61; (5) Oza, et al. Gynecol Oncol 2017; 147:267-75.

Presented By Don Dizon at 2019 ASCO Annual Meeting

SOLO1: Maintenance PARP after first-line treatment



	Olaparib (N = 260)	Placebo (N = 131)
3-year PFS	60%	27%

Moore, et al. NEJM 2018; 379:2495-505

Olaparib Monotherapy versus Chemotherapy for Germline BRCA-Mutated Platinum-Sensitive Relapsed Ovarian Cancer Patients: Phase III SOLO3 Trial

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ClinicalTrials.gov identifier: NCT02282020
This study was sponsored by AstraZeneca; part of an alliance between AstraZeneca and Merck & Co., Inc., Kenilworth, NJ, USA

Presented By Richard Penson at 2019 ASCO Annual Meeting

Background

- In a randomized Phase II trial (Study 12), olaparib treatment showed antitumor activity and was well tolerated in women with relapsed gBRCA-mutated ovarian cancer who were either partially platinum sensitive (PFI 6–12 months) or platinum resistant[1]
- Based on a pooled analysis of Phase I and II data, olaparib (400 mg bid, capsules) was approved by the FDA for the treatment of patients with gBRCA-mutated advanced ovarian cancer who had received ≥3 prior lines of chemotherapy[2]
- SOLO3 was a confirmatory Phase III study evaluating the efficacy of treatment with olaparib (300 mg bid, tablets) versus physician's choice of non-platinum chemotherapy in women with PSR gBRCA-mutated ovarian cancer who had received ≥2 prior lines of platinum-based chemotherapy

bid, twice daily; FDA, US Food and Drug Administration; gBRCA, germline *BRCA1* or *BRCA2*; PFI, platinum-free interval; PSR, platinum-sensitive relapsed

1. Kaye SB *et al. J Clin Oncol* 2012;30:372–9; 2. Matulonis UA *et al. Ann Oncol* 2016;27:1013–19

Study Design

- Relapsed, high-grade serous or endometrioid ovarian, primary peritoneal, and/or fallopian tube cancer
- Germline BRCAm
- ECOG performance status 0–2
- ≥2 previous lines of platinum-based chemotherapy*
- Platinum sensitive†

Open-label

Study treatment administered until disease progression

Olaparib tablets 300 mg bid (n=178)

2:1 randomization

Stratified by:
- Selected chemotherapy‡
- Number of prior lines of chemotherapy
- Time to progression after previous platinum-based chemotherapy

Non-platinum chemotherapy§ (n=88)
- **PLD (n=47)**
- **Paclitaxel (n=20)**
- **Gemcitabine (n=13)**
- **Topotecan (n=8)**

Primary endpoint

- ORR by BICR (RECIST v1.1)

Secondary endpoints

- PFS
- PFS2
- OS
- TFST
- TSST
- HRQoL
- Safety

*Prior treatment with a PARP inhibitor was not permitted;

†Fully platinum sensitive: progression >12 months after platinum-based chemotherapy; partially platinum sensitive: progression 6–12 months after platinum-based chemotherapy;

‡For each patient, the investigator declared their choice of non-platinum chemotherapy before randomization;

§PLD, 50 mg/m^2 on day 1 q4w; paclitaxel, 80 mg/m^2 on days 1, 8, 15, and 22 q4w; gemcitabine, 1000 mg/m^2 on days 1, 8, and 15 q4w; topotecan, 4 mg/m^2 on days 1, 8, and 15 q4w

BICR, blinded independent central review; BRCAm, *BRCA1* or *BRCA2* mutation; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; PLD, pegylated liposomal doxorubicin; q4w, every 4 weeks; RECIST, response evaluation criteria in solid tumors; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

Patient Disposition

	Olaparib	Chemotherapy
Randomized, n	178	88
Treated, n (%)	178 (100)	76 (86)
BICR-measurable disease at baseline, n (%)	151 (85)	72 (82)
Discontinued study treatment before DCO, n (%)	135 (76)	75 (85)
Objective disease progression	111 (62)	30 (34)
AE	13 (7)	15 (17)
Patient decision	5 (3)	10 (11)
Severe protocol non-compliance	1 (1)	0
Study-specific discontinuation criteria	1 (1)	3 (3)
Other		
Clinical progression	4 (2)	4 (5)
Investigator decision	–	6 (7)
Chemotherapy complete	–	7 (8)
Remained on study treatment at DCO, n (%)	43 (24)	1 (1)

AE, adverse event; DCO, data cut-off

Patient Characteristics

	Olaparib (n=178)	Chemotherapy (n=88)
Primary tumor location, n (%)		
Ovary	160 (90)	74 (84)
Fallopian tube	7 (4)	8 (9)
Primary peritoneal	10 (6)	3 (3)
Other*	1 (1)	3 (3)
gBRCAm by Myriad testing, n (%)		
BRCA1	120 (67)	52 (59)
BRCA2	50 (28)	32 (36)
Negative or missing†	8 (4)	4 (5)
Platinum sensitivity, n (%)		
Progressed ≤6 months after platinum	0	1 (1)
Progressed >6 to ≤12 months after platinum	114 (64)	50 (57)
Progressed >12 months after platinum	64 (36)	37 (42)
Number of previous chemotherapy regimens, n (%)		
2	92 (52)	47 (53)
3	41 (23)	24 (27)
≥4	45 (25)	17 (19)

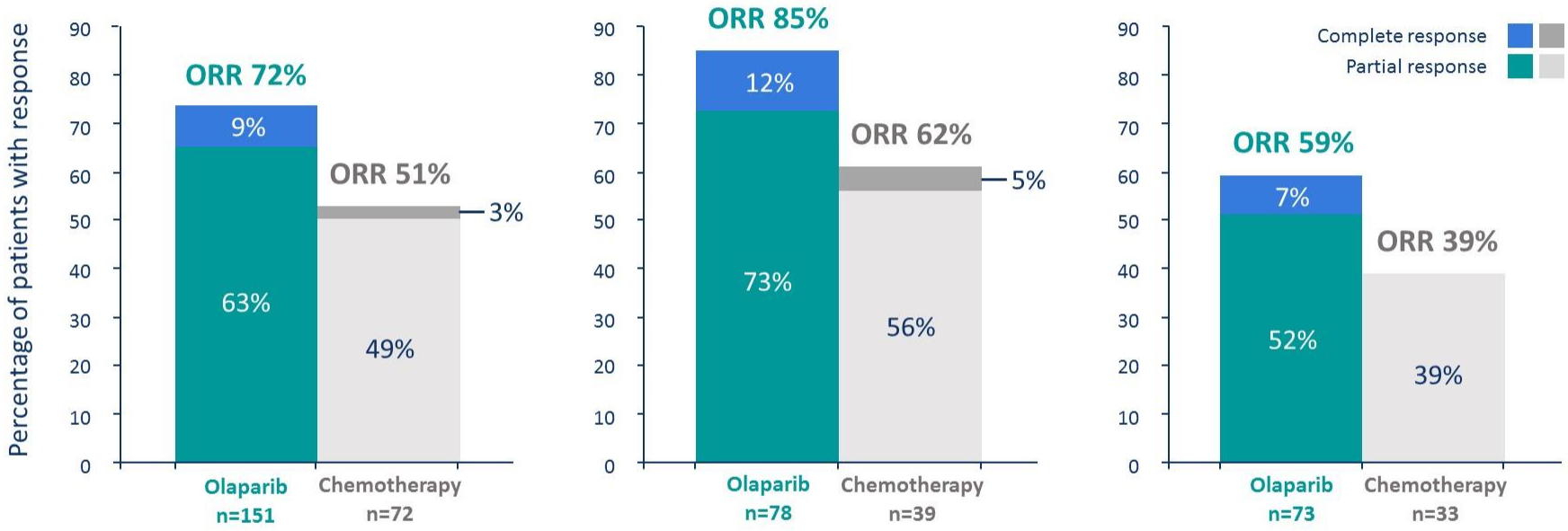
*Other primary tumor locations were "rectal wall" in the olaparib arm, and "uterus", "liver metastasis", and "pleura" in the chemotherapy arm;
†Central Myriad results were either unavailable or negative, but patients had been shown to have a gBRCAm by local testing

Patient Characteristics

	Olaparib (n=178)	Chemotherapy (n=88)
Histology, n (%)		
Serous	157 (88)	80 (91)
Endometrioid	15 (8)	4 (5)
Undifferentiated	3 (2)	3 (3)
Mixed serous/endometrioid	3 (2)	0
Other*	0	1 (1)
ECOG performance status, n (%)		
0	135 (76)	63 (72)
1	42 (24)	25 (28)
2	1 (1)	0
Prespecified study chemotherapy, n (%)		
PLD	90 (51)†	47 (53)
Paclitaxel	37 (21)†	20 (23)
Gemcitabine	36 (20)†	13 (15)
Topotecan	15 (8)†	8 (9)

*The other histology type in the chemotherapy arm was "adenocarcinoma, poorly differentiated";
†For each patient, the investigator declared a choice of non-platinum chemotherapy before randomization. Therefore, the olaparib column shows the chemotherapy option that patients would have received had they been randomized to chemotherapy instead of olaparib

Primary Endpoint: ORR by BICR



All patients*

OR 2.53 (1.40, 4.58) *P*=0.002

Patients with 2 prior lines of chemotherapy*

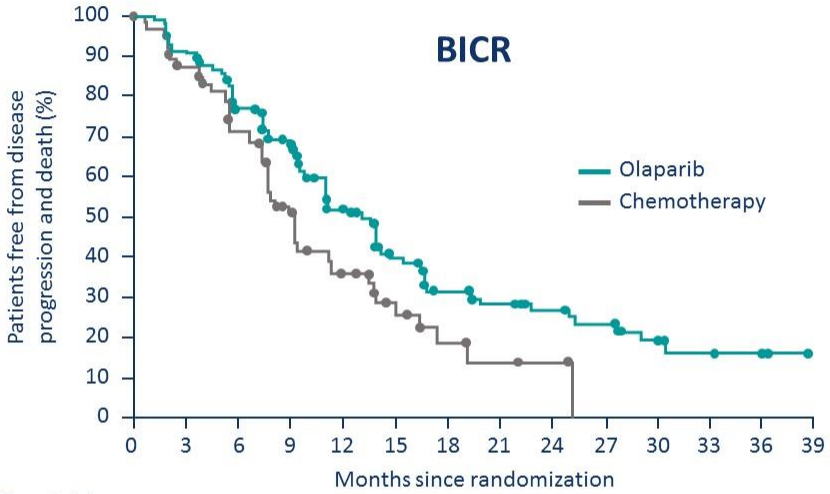
OR 3.44 (1.42, 8.54)

Patients with ≥3 prior lines of chemotherapy*

OR 2.21 (0.96, 5.20)

*Patients with measurable disease at baseline

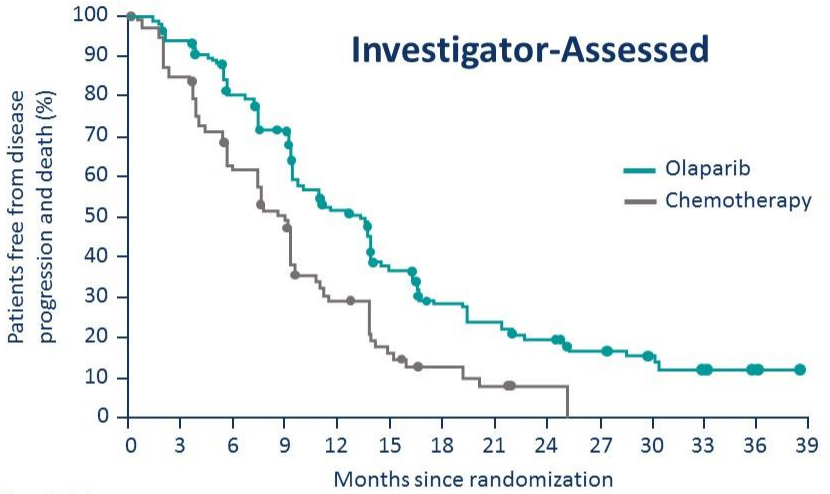
PFS (Intention-To-Treat Population)



No. at risk

Olaparib	178	156	126	108	71	47	30	25	18	14	8	5	2	0
Chemotherapy	88	63	47	31	18	9	5	3	2	0	0	0	0	0

	Olaparib (n=178)	Chemotherapy (n=88)
PFS events, n (%)	110 (62)	49 (56)
Median PFS, months	**13.4**	**9.2**
HR (95% CI), *P* value	**0.62 (0.43, 0.91); *P*=0.013**	



No. at risk

Olaparib	178	155	126	110	72	48	31	26	19	12	8	6	2	0
Chemotherapy	88	62	43	34	18	9	5	3	1	0	0	0	0	0

	Olaparib (n=178)	Chemotherapy (n=88)
PFS events, n (%)	123 (69)	63 (72)
Median PFS, months	**13.2**	**8.5**
HR (95% CI), *P* value	**0.49 (0.35, 0.70); *P*<0.001**	

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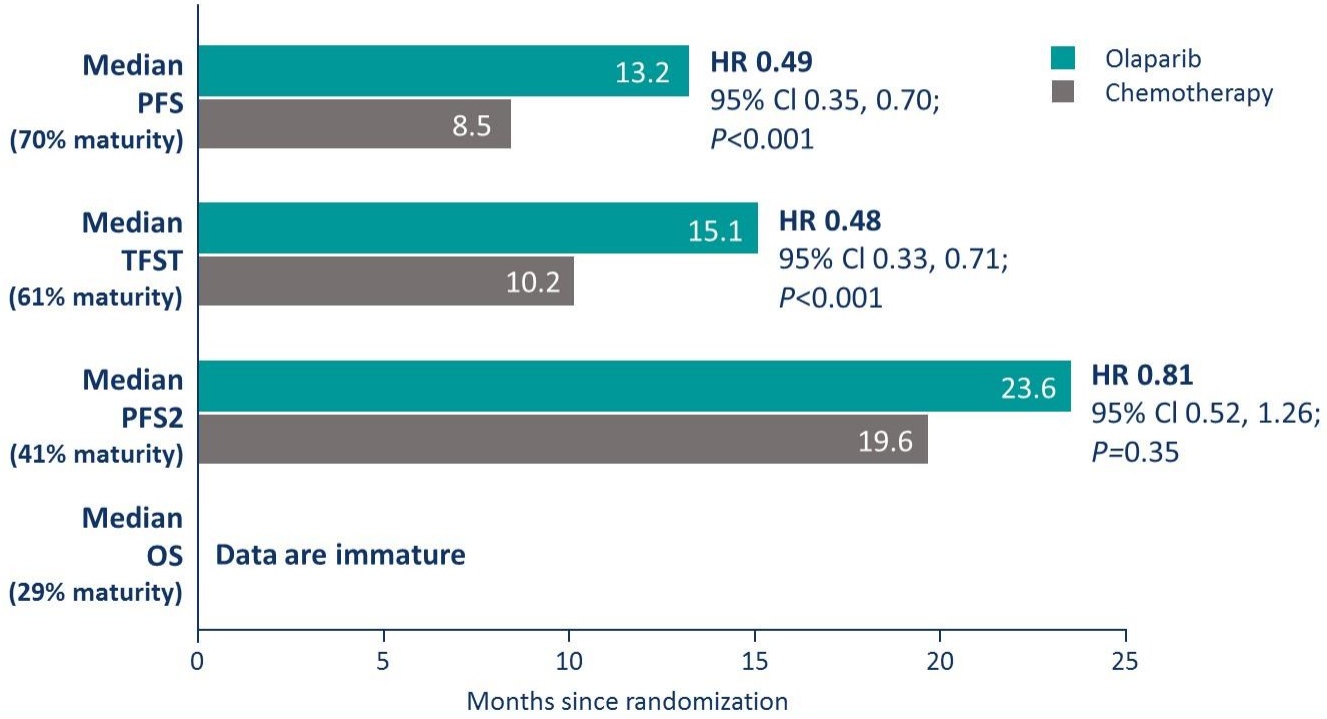
Investigator-Assessed Efficacy Endpoints and Subsequent Therapies



Subsequent Therapies

- 70 patients in the olaparib arm (39%) and 29 in the chemotherapy arm (33%) received platinum as part of their first or second subsequent therapy
- Five patients in the olaparib arm (3%) and 24 in the chemotherapy arm (27%) received a PARP inhibitor as part of their first or second subsequent therapy

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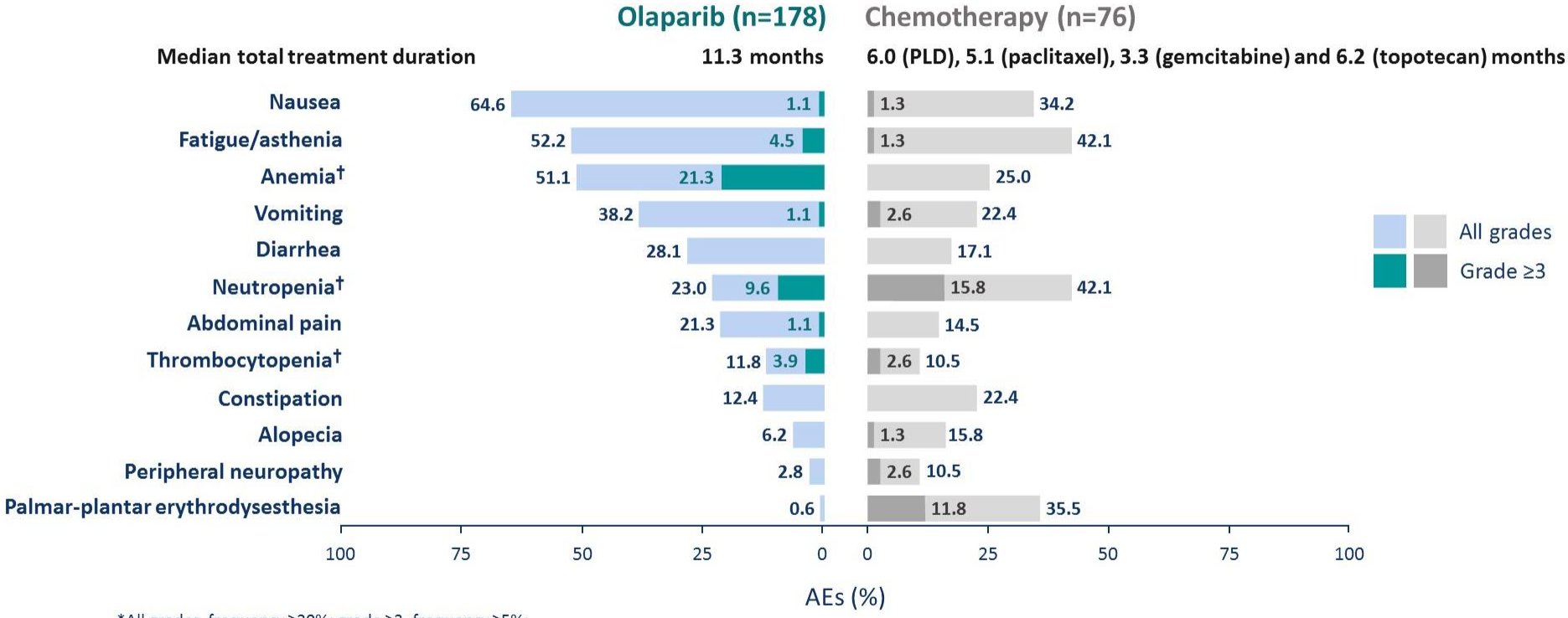
Most common AEs* and selected AEs of interest in either treatment arm



*All grades, frequency ≥20%; grade ≥3, frequency ≥5%;
†Grouped terms

AEs of Special Interest

	Olaparib (n=178)	Chemotherapy (n=76)
MDS/AML, n (%)	4 (2)	3 (4)*
New primary malignancies, n (%)	3 (2)	0

- The three new primary malignancies in the olaparib arm were:
  - Lung cancer (g*BRCA2* mutation)
  - Gastric cancer (g*BRCA1* mutation)
  - Breast cancer (g*BRCA1* mutation)

- No AEs of pneumonitis were reported in the study

*Two patients received PLD as study treatment and one patient received paclitaxel; two of these three patients received a PARP inhibitor as a subsequent treatment
AML, acute myeloid leukemia; MDS, myelodysplastic syndromes

SOLO-3: Things to make you go Hmmmm…

Toxicities: compared to chemotherapy, olaparib associated with:

-- Higher SAE rate (24 vs 18%)

-- Less treatment discontinuation due to an AE (7 vs 20%)

-- MDS/AML in 4 versus 3 patients (BUT 2/3 received PARP later)

-- New cancers in 3 versus 0

Conclusions

- SOLO3 is the first Phase III randomized trial of a PARP inhibitor versus non-platinum-based chemotherapy in women with PSR gBRCA-mutated ovarian cancer
- A statistically significant and clinically relevant improvement in ORR and PFS was observed with olaparib versus non-platinum-based chemotherapy
- The tolerability profiles of olaparib and chemotherapy were consistent with previous data
  - Patients in the chemotherapy arm were more than twice as likely to discontinue study treatment because of an AE
- SOLO3 provides important prospective data on the efficacy of these treatment options for women with heavily pre-treated PSR gBRCA-mutated ovarian cancer

Do you even *need* chemotherapy to treat recurrence?

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Answer: Probably not…..

ASCO 2019	Volunteers	Intervention	Control	Outcome
SOLO-3 #5506	PSOC (n=266)	Olaparib	Chemo	ORR 72 vs 52% OR 2.53 (95%CI 1.40-4.58) PFS 13.4 vs 9.2m HR 0.62 (95%CI 0.43-0.91)

About these volunteers:
- gBRCA+
- ≥2 lines

About the control:
- No platinum

But SOLO 3 not design to answer this question (chemo →olaparib arm missing)

Abstract 5507

CLIO (NCT02822157): Randomized phase II study evaluating efficacy of olaparib monotherapy versus physician's choice chemotherapy in platinum-resistant ovarian cancer (PROC)

Adriaan Vanderstichele[1,2], Els Van Nieuwenhuysen[1,2], Nicole Concin[1,2], Toon Van Gorp[1,2], Patrick Berteloot[1,2], Patrick Neven[1,2], Pieter Busschaert[2], Diether Lambrechts[3,4], Ignace Vergote[1,2]

[1] BGOG & Department of Gynaecology and Obstetrics, University Hospitals Leuven, Leuven, Belgium, EU
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Treatment options for PROC patients

- **4 chemotherapeutic agents** with activity in phase III trials
  Overall response rates (**ORR**) around **15%**
  Median **PFS** of **3-4 months** [1]:
  - paclitaxel
  - pegylated liposomal doxorubicin (PLD)
  - topotecan
  - gemcitabine

- **Single-agent PARP-inhibitor (PARPi) therapy**
  FDA approved in **germline BRCA1/2-mutated relapsed ovarian cancer** (≥3 lines)
  (2 single-arm phase II trials with olaparib[2] and rucaparib[3])

1. Ledermann J et al. Ann Oncol 2013; 2. Kaufman B et al. JCO 2015; 3. Balasubramaniam S et al. Clin Cancer Res 2017

Single-agent PARP-inhibitor treatment in PROC

- Efficacy of single-agent PARPi treatment in **PROC**

PARPi	Biomarker	Patients	Overall response rate
Olaparib [1]	gBRCA mut	mean 4.3 prior lines	**31**% (60/193)
Niraparib [2]	g + sBRCA mut	≥ 3 prior lines	**27**% (10/37)
Rucaparib [3]	g + sBRCA mut	≥ 2 prior lines	**25**% (5/20)
Niraparib [2]	/	≥ 3 prior lines	**6**% (17/289)

- **Limited data in BRCA-wild type PROC** disease (QUADRA)
- **No randomized data** comparing single-agent PARPi with chemotherapy in PROC

1. Kaufman B et al. JCO 2015; 2. Moore K et al. Lancet Oncol 2019; 3. Balasubramaniam S et al. Clin Cancer Res 2017

CLIO Study Design

KU LEUVEN

Randomized open-label study

ENGOT MODEL A

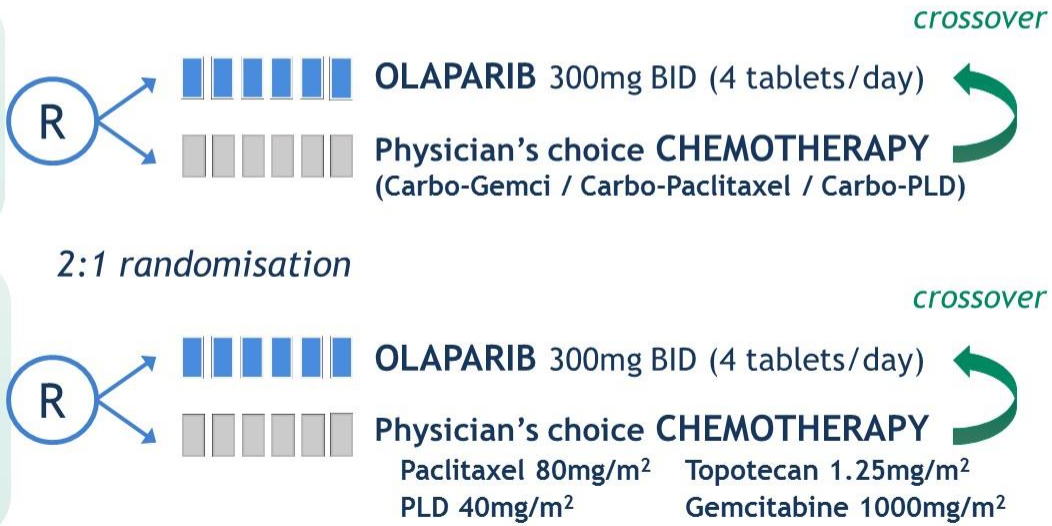
- **RELAPSED OVARIAN CANCER**: at least **1 previous line of chemotherapy**
- HISTOLOGY: High-grade serous, Endometrioid, Clear-Cell, Carcinosarcoma, Undifferentiated
- MEASURABLE DISEASE
- PREVIOUS PARPi ALLOWED

Platinum-sensitive / PSOC (n = 60)

- Relapse ≥ **6 months** after platinum-based chemotherapy
- **Exclusion of patients with known** germline or somatic **BRCA mutation** prior to screening

Platinum-resistant / PROC (n = 100)

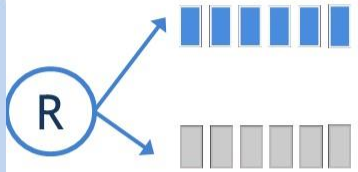
- Relapse < **6 months** after platinum-based chemotherapy), exclusion **primary platinum-refractory disease** (i.e. relapse during or < 28 days after first-line platinum)
- Germline or somatic BRCA mutation allowed



Current analysis

PROC (n = 100)

- Relapse < 6 months after platinum-based chemotherapy)
- Exclusion **primary platinum-refractory disease** (i.e. relapse during or < 28 days after first-line platinum)



2:1 randomisation

OLAPARIB 300mg BID (4 tablets/day)

Physician's choice CHEMOTHERAPY

- Paclitaxel 80mg/m^2 day 1, 8, 15 q3w
- Peg. liposomal doxorubicin 40mg/m^2 q4w
- Topotecan 1.25mg/m^2 d1-5 q3w
- Gemcitabine 1000mg/m^2 d1, 8, 15 q3w

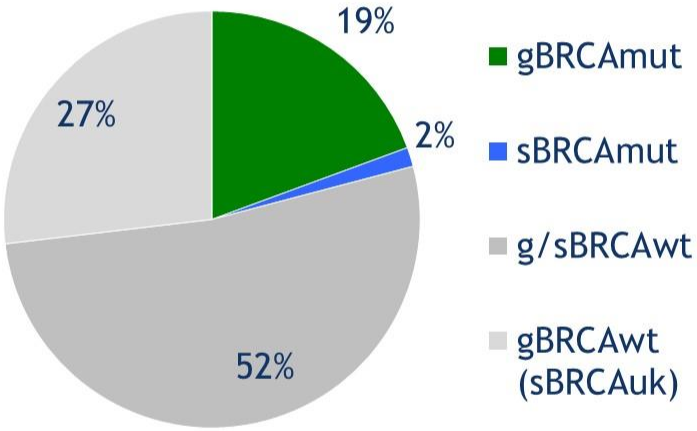
Compare efficacy of single-agent olaparib versus physician's choice chemotherapy in PROC

- Objective response rate (**ORR**)
- Disease-control rate (**DCR**) at 12 weeks
- Duration of response/clinical benefit (**DOR/DCB**)
- Progression-free survival (**PFS**)

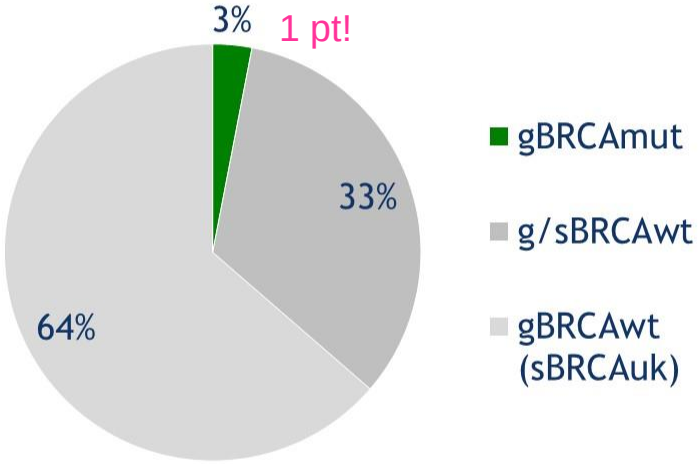
Baseline characteristics (PROC, n=100)

BRCA status

Olaparib (n=67)



Chemotherapy (n=33)

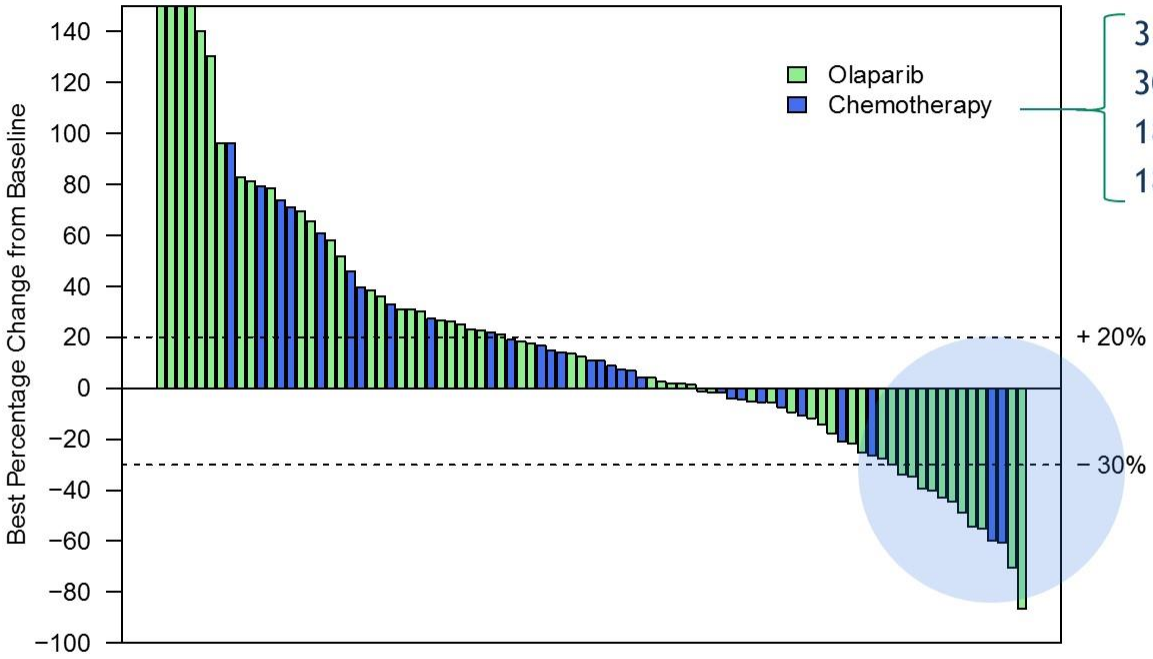


Imbalance in frequency of known BRCA mutations between both groups (p=0.03)

(no stratification performed, incomplete somatic testing mainly in chemo-arm)

sBRCAuk = somatic analysis pending (unknown)

Objective response rate (ORR for PROC, n=100) *



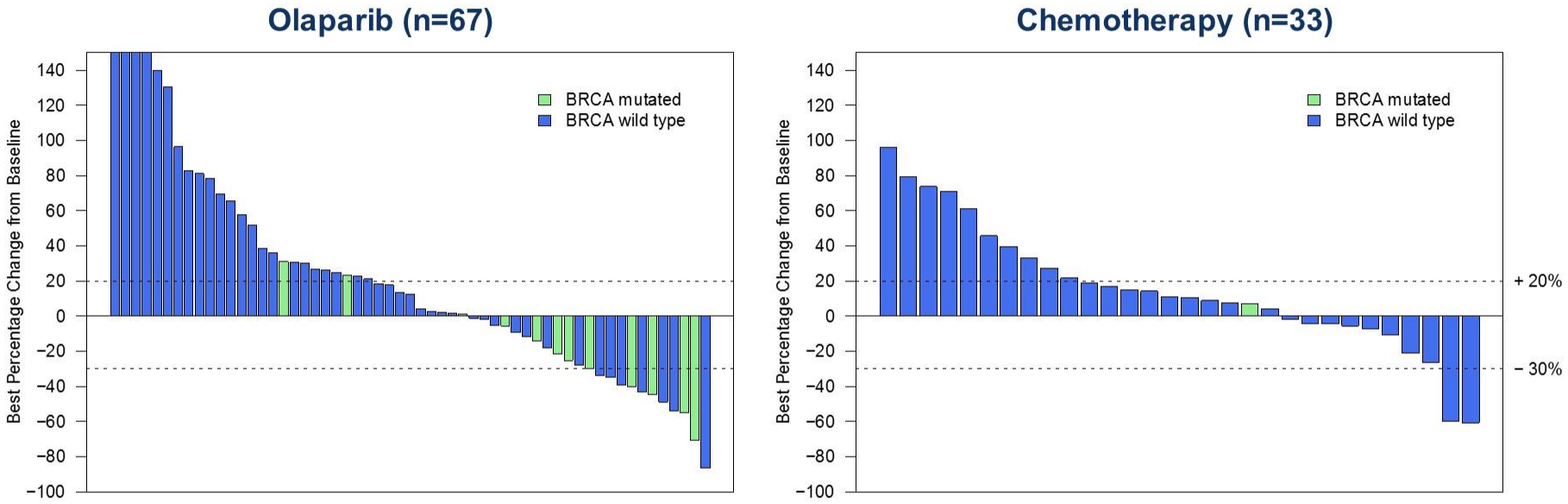
33.3% (**11**/33) Paclitaxel
30.3% (**10**/33) PLD
18.2% (**6**/33) Topotecan
18.2% (**6**/33) Gemcitabine

2 responses under chemotherapy (both <u>taxol weekly</u>)

	OLAPARIB	CHEMOTHERAPY	
All patients	**18** % (12/67)	**6** % (2/33)	p=0.13

* Unconfirmed

ORR according to BRCA status (PROC, n=100)



	OLAPARIB	CHEMOTHERAPY
BRCA mutated	36 % (5/14)	0 % (0/1)
BRCA wild type	13 % (7/53)	6 % (2/32)

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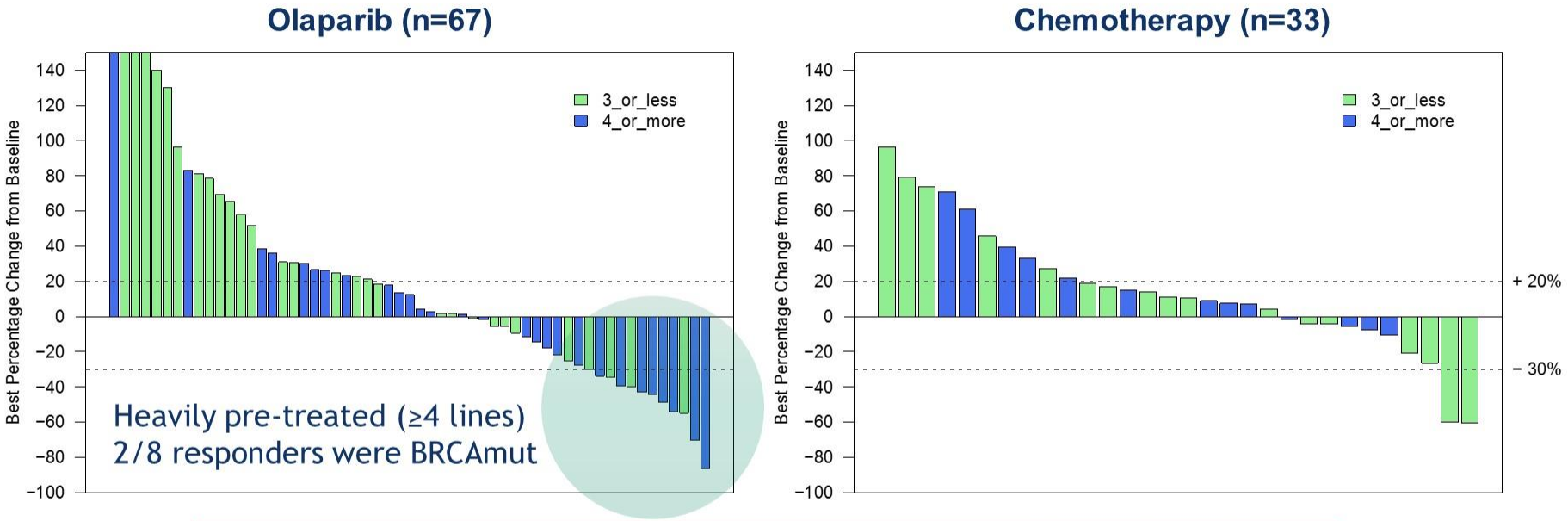
ORR according to prior lines of treatment (PROC, n=100)



	OLAPARIB	CHEMOTHERAPY
3 or less prior lines	13 % (4/32)	11 % (2/19)
4 or more prior lines	23 % (8/35)	0.0 % (0/14)

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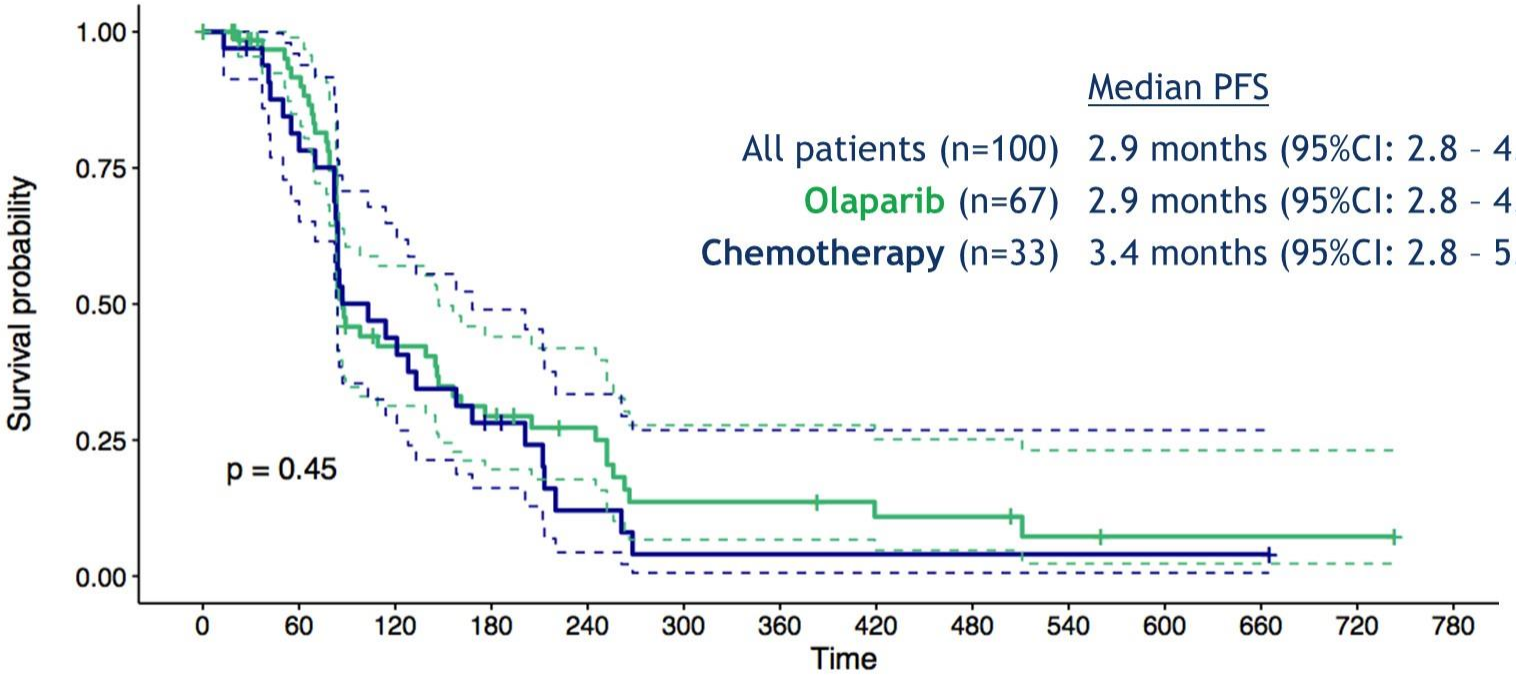
Progression-free survival (PFS)



	Median PFS
All patients (n=100)	2.9 months (95%CI: 2.8 – 4.6)
Olaparib (n=67)	2.9 months (95%CI: 2.8 – 4.8)
Chemotherapy (n=33)	3.4 months (95%CI: 2.8 – 5.5)

No PFS difference between olaparib and standard chemotherapy in PROC

Hazard ratio 1.18 for olaparib (95% CI: 0.75-1.87; p=0.48)

Take home messages

- **Olaparib monotherapy** showed a **favorable objective response rate of 18% in PROC** compared to 6% with standard chemotherapy.
- **BRCA-mutated PROC** patients had a **response rate** of **36%** under olaparib treatment, with a **clinical benefit rate at 12 weeks** of **64%**
- The studied population was **heavily pretreated**, with 49% having received 4 or more prior lines of treatment, 16% of patients received prior PARP inhibitor therapy (including placebo-controlled studies)
- **No new TEAEs** were noted. TEAEs leading to dose discontinuation were rare.

Combination of niraparib and bevacizumab versus niraparib alone as treatment of recurrent platinum-sensitive ovarian cancer: A randomized controlled chemotherapy-free study

ENGOT-OV24/NSGO-AVANOVA2

Mansoor R Mirza[1], E Avall-Lundqvist[2], MJ Birrer[3], R dePont Christensen[4], G-B Nyvang[5], S Malander[6], M Anttila[7], TL Werner[8], B Lund[9], G Lindahl[2], S Hietanen[10], U Peen[11], M Dimoula[12], H Roed[1], A Ør Knudsen[5], L Boufercha[4], S Staff[13], A Krog Vistisen[9], L Bjørge[14], JU Maenpaa[13]

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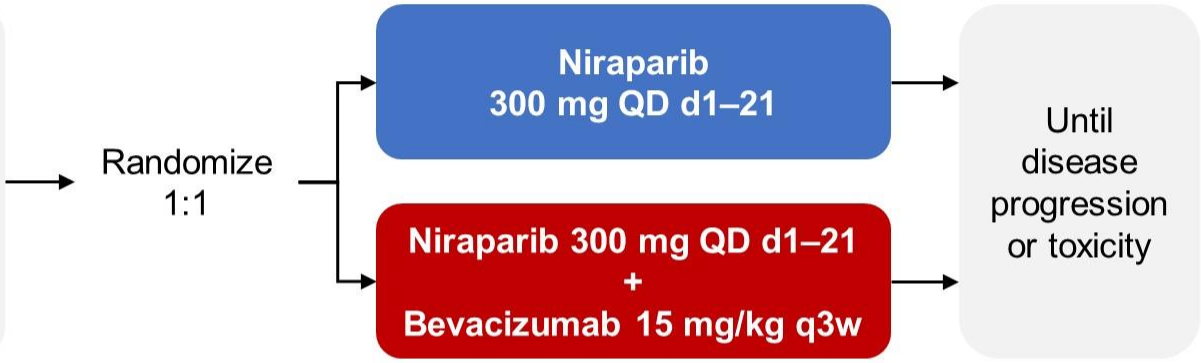
PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Mansoor Raza Mirza

ENGOT-OV24 / NSGO-AVANOVA2 trial design

- High-grade serous/endometrioid PSROC
- Any number of previous lines of therapies
- Measurable/evaluable disease
- Prior bevacizumab permitted



Stratification factors

- HRD status (positive vs negative)
- Chemotherapy-free interval (6–12 vs >12 months)

Primary endpoint: Investigator-assessed PFS in the ITT population

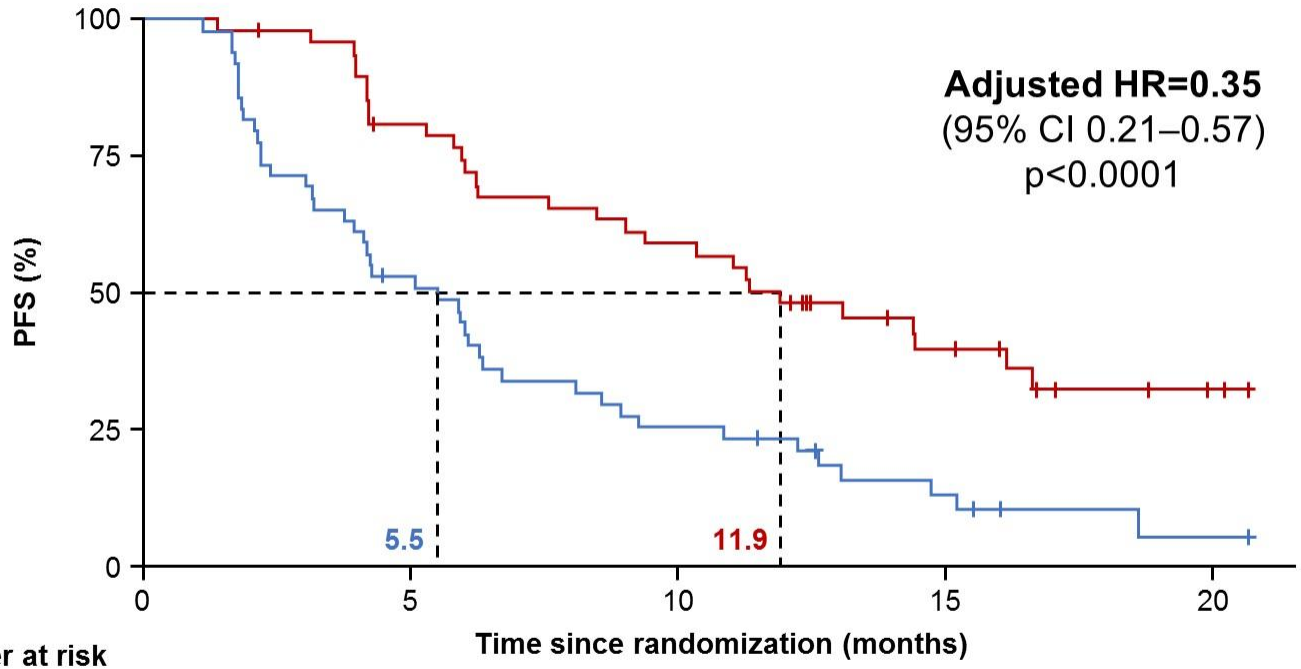
ITT = intention-to-treat; NCT02354131

Baseline patient characteristics (ITT population)

Characteristic, n (%)		Niraparib + bevacizumab (n=48)	Single-agent niraparib (n=49)
Median age, years (range)		66.5 (59–70)	66 (58–70)
Primary tumour site	Ovary Fallopian tube Peritoneum	38 (79%) 5 (10%) 5 (10%)	33 (67%) 9 (18%) 7 (14%)
Chemotherapy-free interval, months	6–12 >12	20 (42%) 28 (58%)	17 (35%) 32 (65%)
HRD status	Positive[a] Negative/unknown	28 (58%) 20 (42%)	30 (61%) 19 (39%)
BRCA mutation	Any Germline Somatic	15 (31%) 6 (13%) 14 (29%)	18 (37%) 9 (18%) 14 (29%)
Pre-existing hypertension		20 (42%)	17 (35%)
Prior bevacizumab		10 (21%)	13 (27%)
Prior lines of therapy	1 2 ≥3	21 (44%) 24 (50%) 3 (6%)	27 (55%) 19 (39%) 3 (6%)

[a]3 patients (1 niraparib + bevacizumab, 2 niraparib) had *BRCA*-mutated tumors but were erroneously considered as HRD negative/unknown for stratification

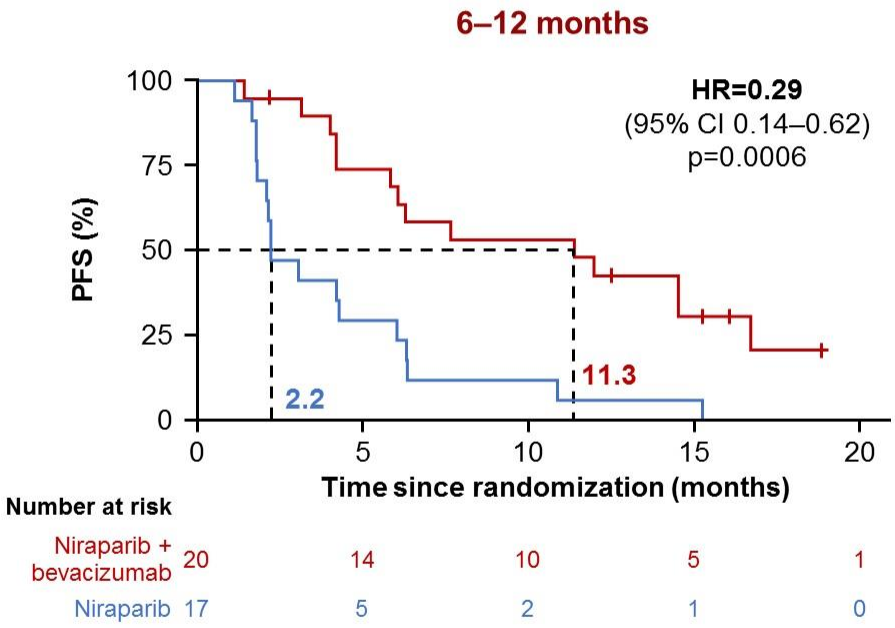
Primary endpoint: PFS in the ITT population

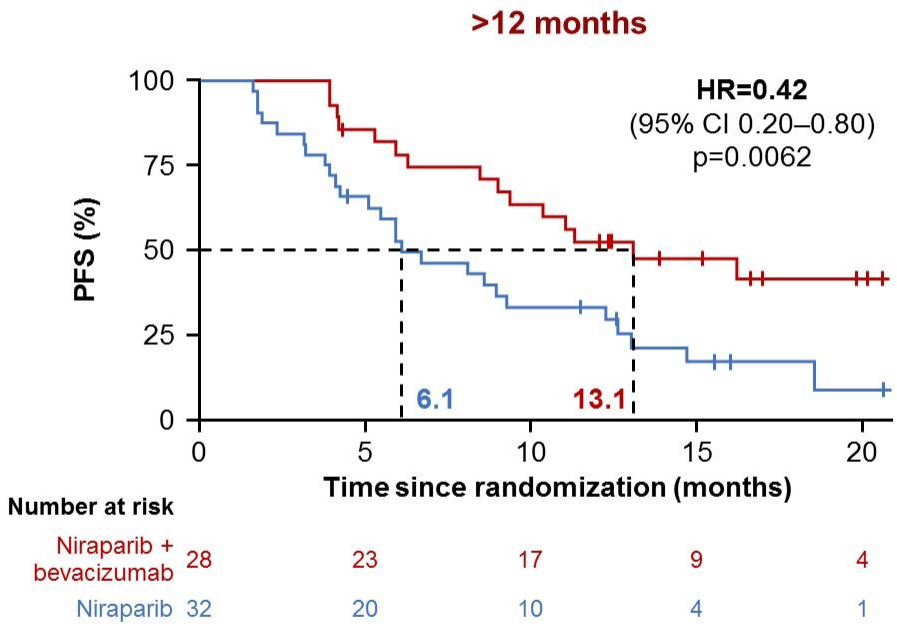


Number at risk					
Niraparib + bevacizumab	48	37	27	14	5
Niraparib	49	25	12	5	1

CI = confidence interval; HR = hazard ratio

PFS by stratification factors: Chemotherapy-free interval





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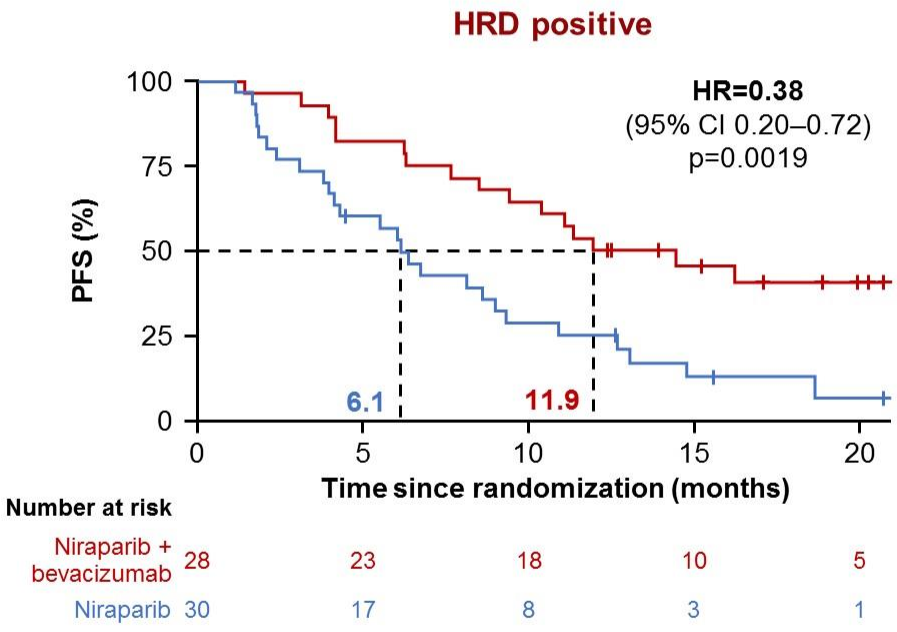
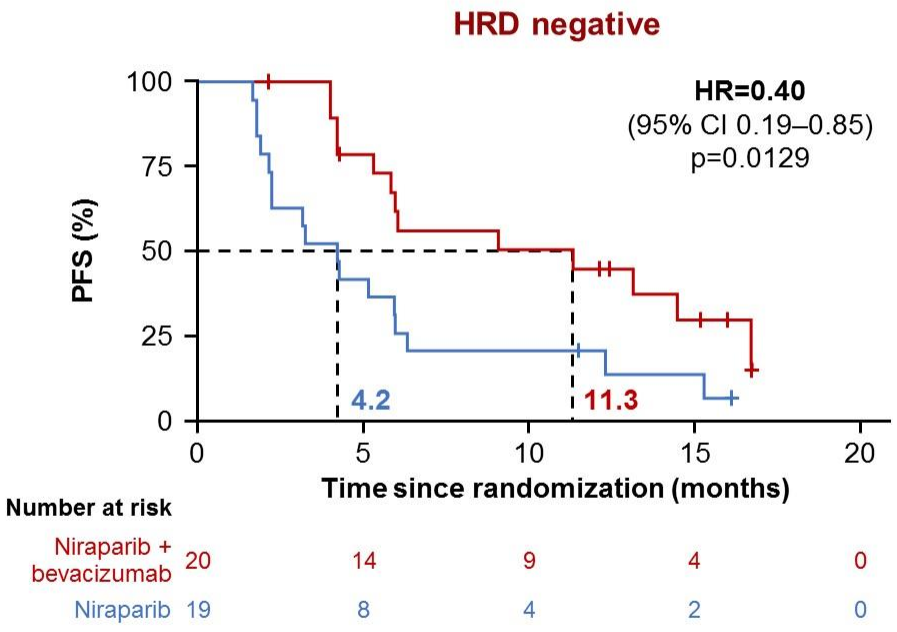
PFS by stratification factors: HRD status





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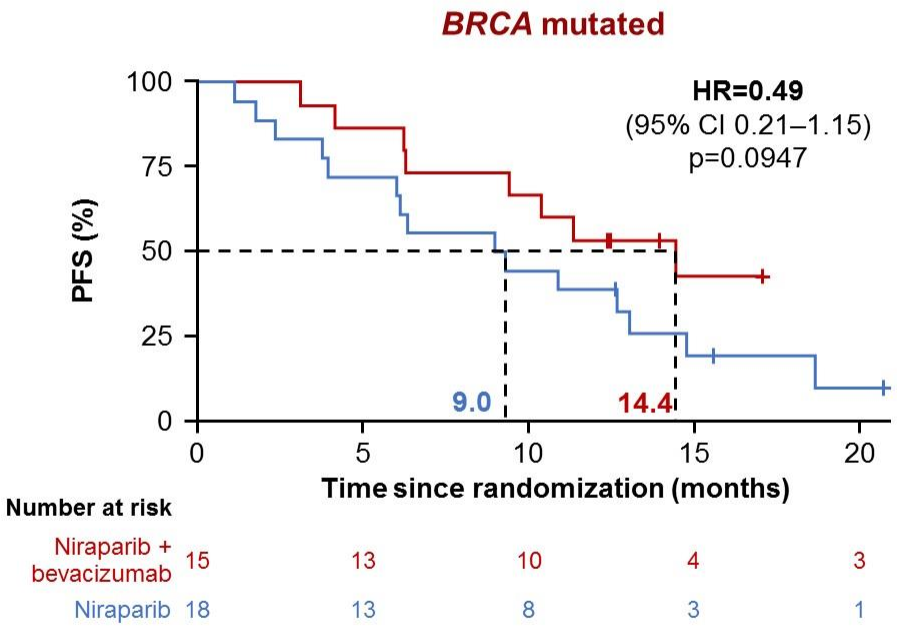
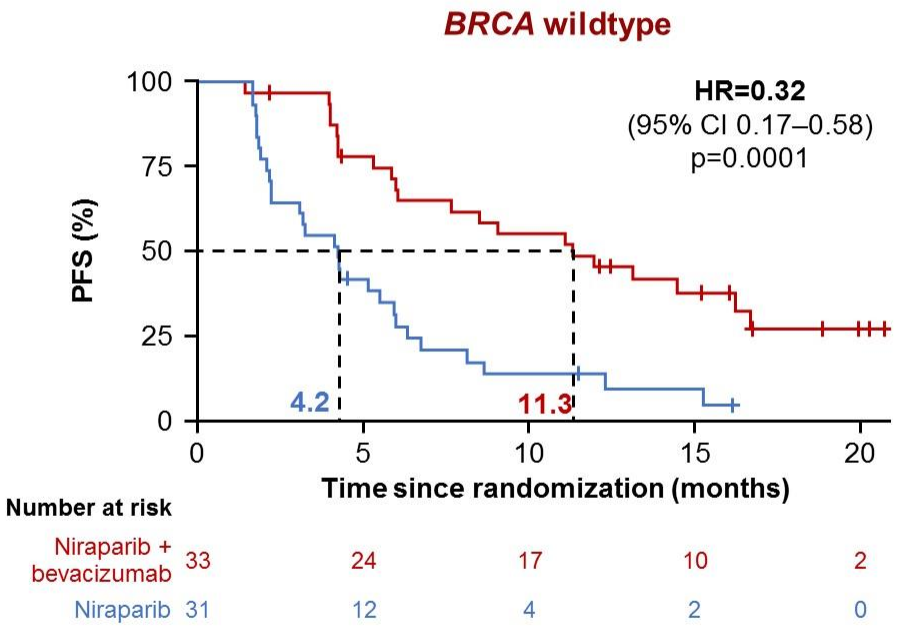
PFS by *BRCA* status





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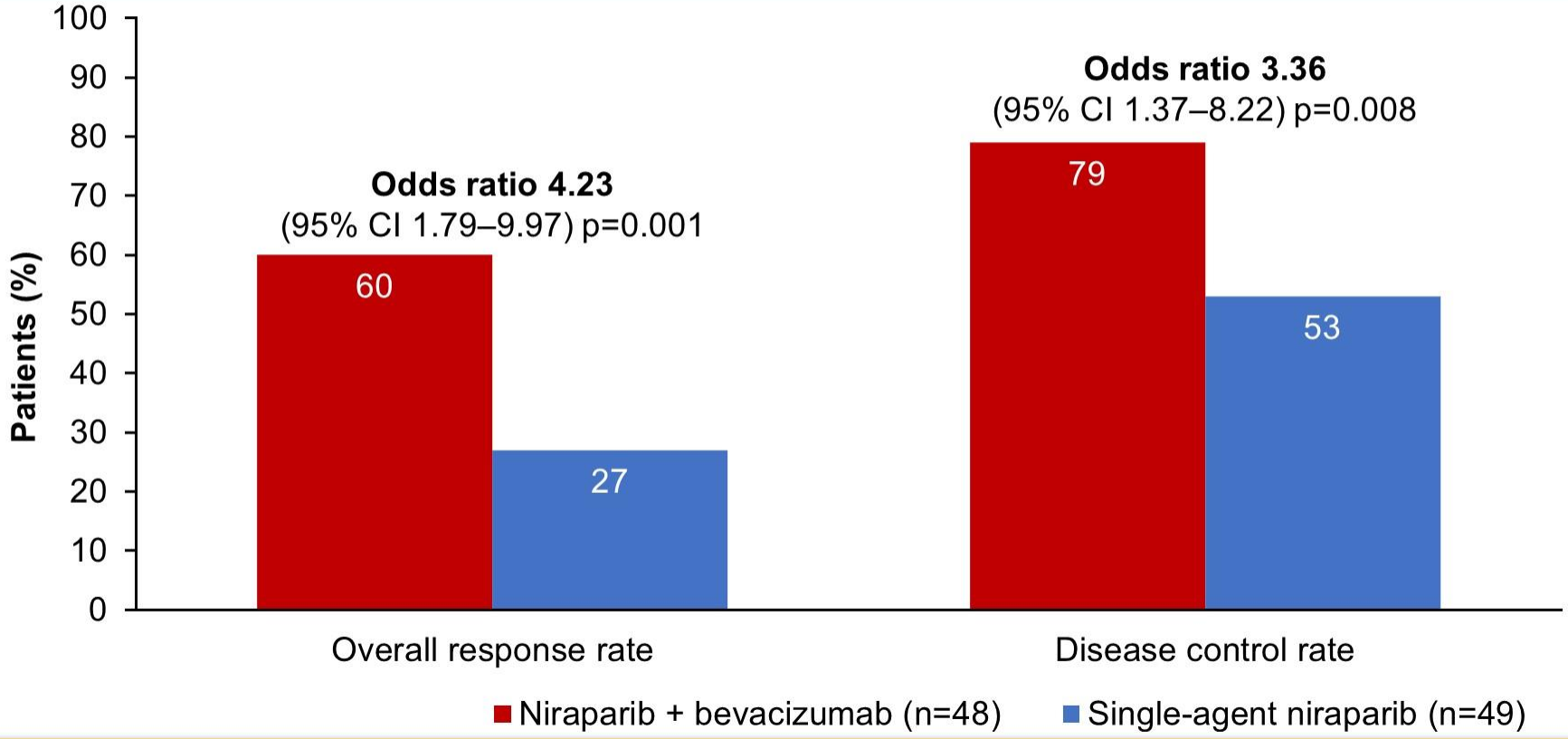
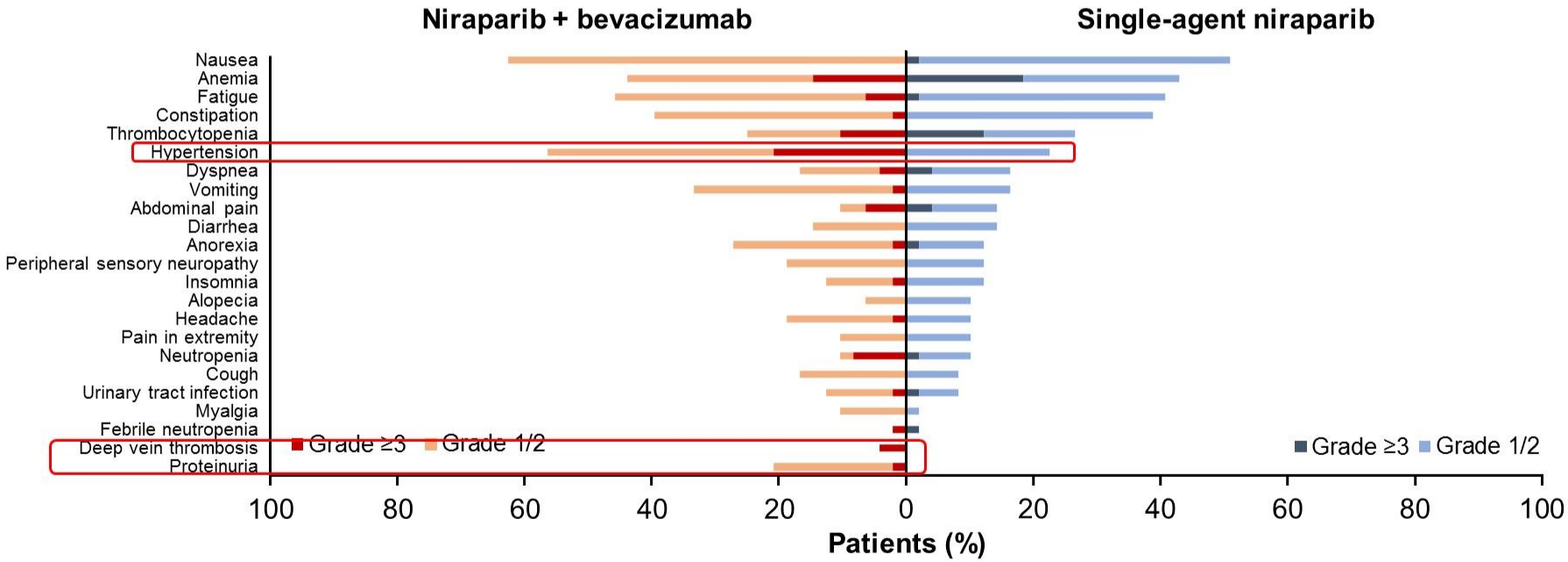
Overall response and disease control rates



Summary of adverse events

Any grade in ≥10% of patients in either arm and/or grade ≥3 in ≥2 patients overall



Additional grade ≥3 adverse events in only 1 patient comprised: gastrointestinal disorder, hypomagnesemia, hyponatremia, ileus, intestinal obstruction, skin pain, pneumonia, respiratory tract infection, and syncope in the niraparib + bevacizumab arm, and ascites, dehydration, pleural effusion, pulmonary embolism, and mucosal inflammation in the niraparib-alone arm

Dose reductions and treatment discontinuations

Number of niraparib dose reductions	Niraparib + bevacizumab (n=48)	Single-agent niraparib (n=49)
None	23 (48%)	21 (43%)
One (300 → 200 mg)	24 (50%)	27 (55%)
Two (300 → 200 → 100 mg)	1 (2%)	1 (2%)

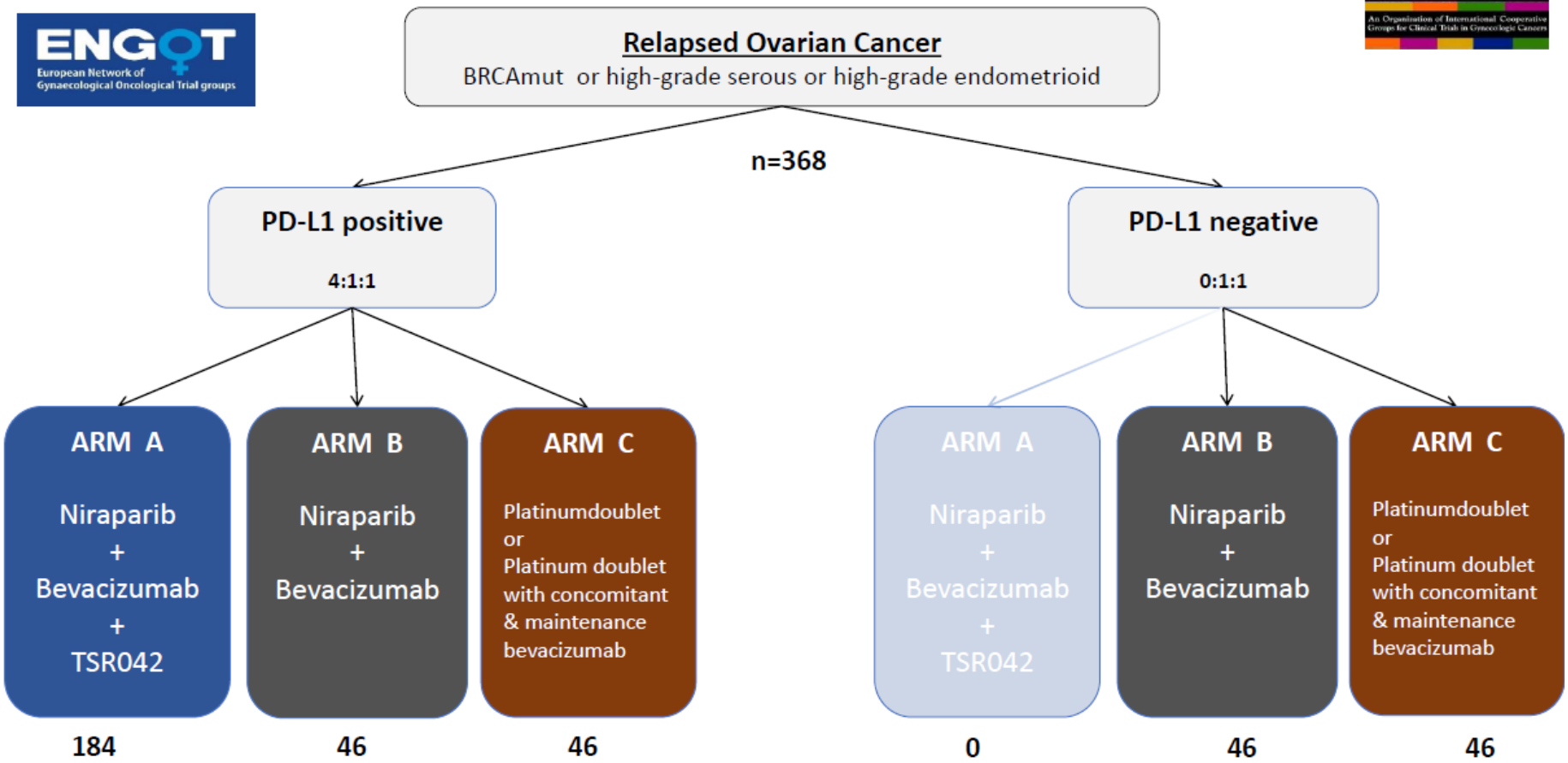
Treatment discontinuations for adverse events	Niraparib + bevacizumab (n=48)	Single-agent niraparib (n=49)
Treatment discontinuation	6 (13%)	5 (10%)

NA = not applicable

Conclusions

- NSGO-AVANOVA2 is the first randomized trial to evaluate a chemotherapy-free combination of two established agents approved for use in recurrent ovarian cancer (niraparib and bevacizumab)
- Compared with niraparib alone, the combination of niraparib + bevacizumab as definitive treatment for ovarian cancer significantly improved PFS, regardless of HRD status or chemotherapy-free interval
- Niraparib + bevacizumab combination therapy was well tolerated; most patients remained on treatment until disease progression
- No detrimental effect on quality of life was observed with combination therapy
- A randomized phase 3 trial (NSGO-AVATAR) is planned to compare this regimen vs standard-of-care therapy in PSROC

ENGOT-OV42 / NSGO-AVATAR



Now we need to figure out---

- For women who are *candidates for PARP inhibition:*
  - In the maintenance setting after primary chemotherapy, should you use it *instead* of bevacizumab, or *with* bevacizumab?
  - In an era following SOLO-1, Can you use a PARP inhibitor *again*?

PARP in 1st line alone or in combination with bevacizumab

Trial	Patients	Maintenance trial	Status
SOLO1 (n= 391)	BRCAm	**Olaparib** vs placebo	Completed, positive
PRIMA (n= 303)	All comers	**Niraparib** vs placebo	On-going
PAOLA (n= 806)	All comers	**Olaparib + bevacizumab** vs placebo + bevacizumab	Accrual completed

EWOC-1: A randomized trial to evaluate the feasibility of three different first-line chemotherapy regimens for vulnerable elderly women with ovarian cancer (OC): A GCIG-ENGOT-GINECO study

C Falandry[1], A-M Savoye[2], L Stefani[3], F Tinquaut[4], D Lorusso[5], J Herrstedt[6], E Bourbouloux[7], A Floquet[8], P-E Brachet[9], A Zannetti[10], M-A Mouret-Reynier[11], R Sverdlin[12], V D'hondt[13], O Guillem[14], O Cojocarasu[15], L Venat-Bouvet[16], F Rousseau[17], A Lortholary[18], E Pujade-Lauraine[19], G Freyer[20]

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EudraCT N° 2013-000266-11
Clinicaltrial NCT02001272

Presented By Claire Falandry at 2019 ASCO Annual Meeting

GINECO has developed a Geriatric Vulnerability Score (GVS) to discriminate vulnerable from fit older patients (1)

GVS items

- Activity of Daily Living (ADL-Katz) score < 6
- Instrumental Activities of Daily Living (IADL-Lawton) score < 25
- Hospital Anxiety and Depression score (HADS) > 14
- Albuminemia < 35g/L
- Lymphocyte count < 1G/L

GVS = Σ scores

GVS ≥ 3 defines vulnerable older patients (> 70 years old)

(1) Falandry et al. Development of a geriatric vulnerability score in elderly patients with advanced ovarian cancer treated with first-line carboplatin: a GINECO prospective trial Annals Oncol 2013

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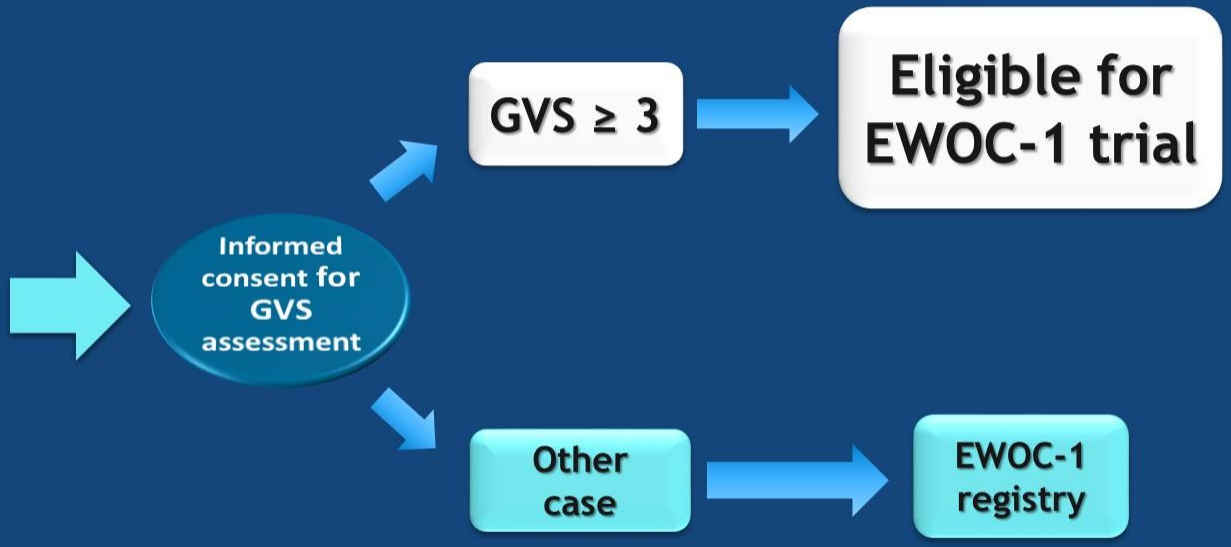
EWOC-1 design

1- Patient selection

Eligibility criteria

- Age > 70yrs
- Histologically or cytologically proven epithelial cancer of the ovary, fallopian tube, and primary peritoneum
- FIGO stage III or IV
- No clinically relevant organ dysfunction
- Life expectancy > 3 months



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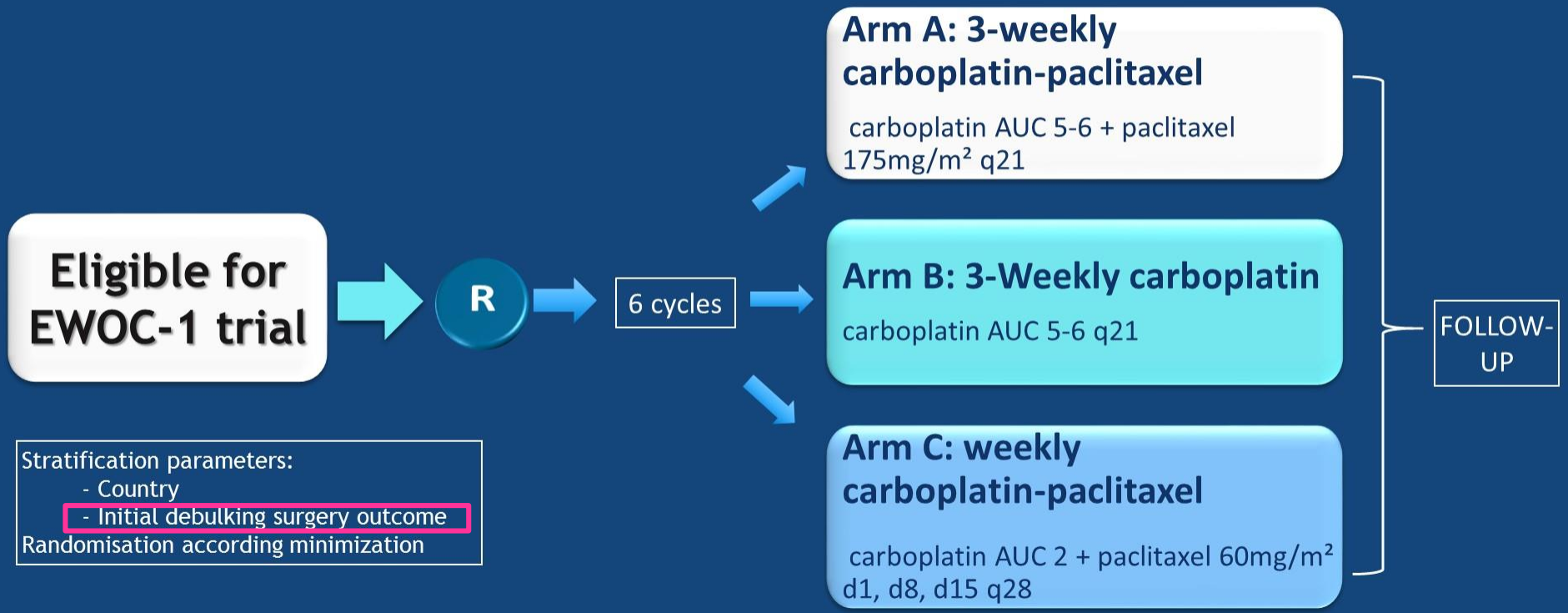
EWOC-1 design

2- Patient randomization



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EWOC-1 endpoints

- **Primary endpoint**

  - To evaluate the feasibility of the 3 different chemotherapy regimens

  Feasibility defined as the completion of 6 courses of chemotherapy without early stopping for disease progression, death or unacceptable toxicity*

- **Secondary endpoints**

  - Safety, Progression-free survival (PFS), Overall survival (OS), Quality of life (QoL), interval debulking and post-operative adjuvant therapy feasibility, geriatric covariates and aging biomarkers

* Unacceptable toxicity: adverse event related to chemotherapy or treatment procedure leading either to early treatment stopping, to an unplanned hospital admission or to death or to a dose delay lasting more than 14 days or more than 2 dose reductions.

EWOC-1 patients' characteristics (1)

Characteristic	Arm A (3wCb-P) N=40	Arm B (3wCb) N=40	Arm C (wCb-P) N=40
Median age, years (range)	79 (71 - 90)	82 (70 - 94)	80 (70 - 90)
GVS global, N (%)			
3	24 (60)	19 (48)	21 (53)
4	14 (35)	14 (35)	15 (37)
5	2 (5)	7 (17)	4(10)
GVS per item, N (%)			
Albuminemia < 35 G/L	32 (80)	33 (82)	34 (85)
ADL score < 6	33 (82)	34 (85)	36 (90)
IADL score < 25	36 (90)	37 (92)	37 (92)
HADS > 14	23 (57)	28 (70)	23 (57)
Lymphocyte count < 1.0 10^9/L	14 (35)	16 (40)	13 (32)
Primary tumour location, N (%)			
Ovary	35 (87)	33 (82)	31 (78)
Fallopian tubes	0 (0)	1 (3)	0 (0)
Primary peritoneal	4 (10)	4 (10)	6 (15)
Unknown	1 (3)	2 (5)	3 (7)

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EWOC-1 patients' characteristics (2)

Characteristic	Arm A (3wCb-P) N=40	Arm B (3wCb) N=40	Arm C (wCb-P) N=40
Histology, N (%)			
serous	24 (60)	24 (60)	28 (70)
others	16 (40)	16 (40)	12 (30)
FIGO stage, N (%)			
III	26 (65)	24 (60)	29 (72)
IV	13 (32)	15 (37)	11 (28)
missing	1 (3)	1 (3)	0 (0)
Debulking surgery, N (%)			
None or macroscopic residue	37 (92)	38 (95)	37 (92)
Complete surgical resection	3 (7)	2 (5)	3 (7)

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EWOC-1 primary endpoint

N = 120	Arm A (3wCb-P) N=40	Arm B (3wCb) N=40	Arm C (wCb-P) N=40
Patients not treated	3	1	1
Completed 6 cycles	**26 (65%)**	**19 (47.5%)**	**24 (60%)**

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EWOC-1 toxicity

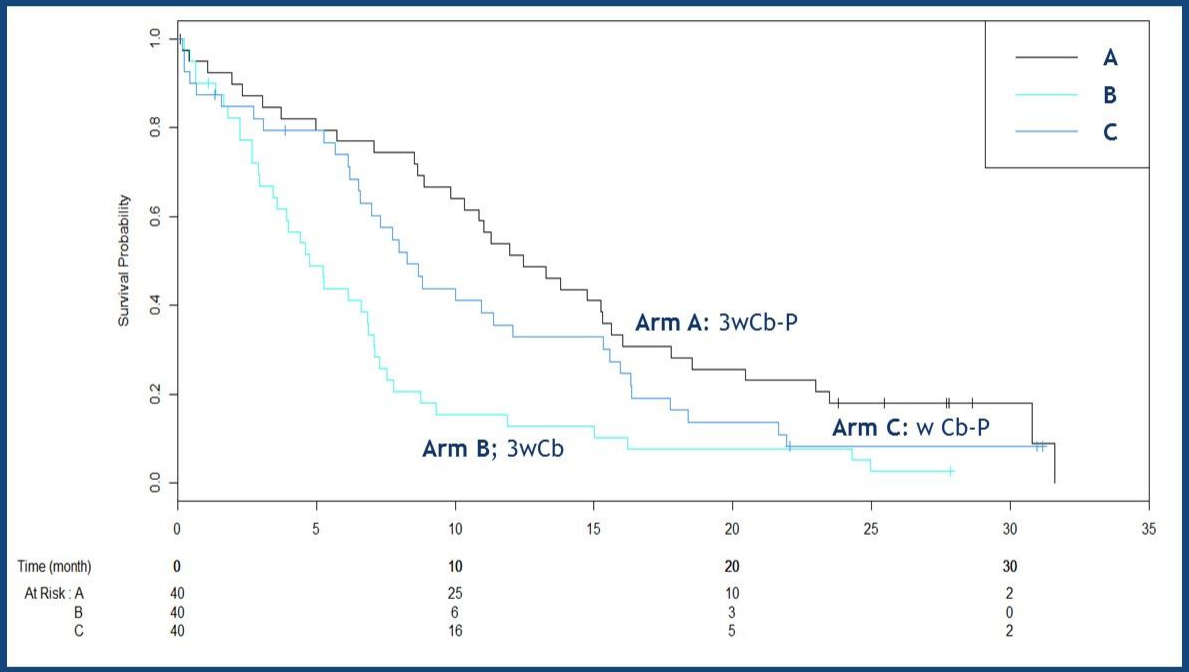
Toxicity	Arm A (3wCb-P)		Arm B (3wCb)		Arm C (wCb-P)	
Haematological toxicity (%)	**Grade≥ 3**					
Anaemia	10		32.5		7,5	
Thrombopenia	5		15		0	
Neutropenia	12.5		20		32.5	
Febrile neutropenia	7.5 (1†)		0		0	
Non-haematological toxicity (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Nausea/vomiting	52.5	5	37.5	2.5	55	0
Constipation	45	0	32.5	0	45	0
Diarrhea	35	7.5	17.5	0	35	2.5
Neuropathy sensory	55	5	7.5	0	32.5	7.5
Total alopecia	32.5	0	2.5	0	15	0
Fatigue	70	10	72.5	7.5	85	10
Pain	42.5	5	47.5	2.5	50	0
General physical health deterioration	2.5	2.5 (1†)	10.0	0	2.5	2.5(1†)
Treatment stopping due to toxicity N (%)	**8 (20)**		**6 (15)**		**9 (22.5)**	

EWOC-1 treatment stopping: other reasons

Reason	Arm A (3wCb-P) N (%)	Arm B (3wCb) N (%)	Arm C (wCb-P) N (%)
Lack of efficacy	3 (7.5)	12 (30)*	2 (5)
Other	0 (0)	2 (5)	2 (5)
Consent withdrawal	0 (0)	0 (0)	2 (5)

* p = 0.003

EWOC-1 Progression-free survival



	Arm A	Arm B	Arm C
Events, N (%)	34 (85)	38 (95)	34 (85)
Median, mos (95% CI)	**12.5** (10.3 - 15.3)	**4.8** (3.6-15.3)	**8.3** (6.6-15.3)
HR (95% CI)	1 (REF)	**2.51** **(1.56,4.04)**	1.41 (0.87,2.28)
P Wald test	-	**< 0.001**	0.162
P Log-Rank	< 0.001		

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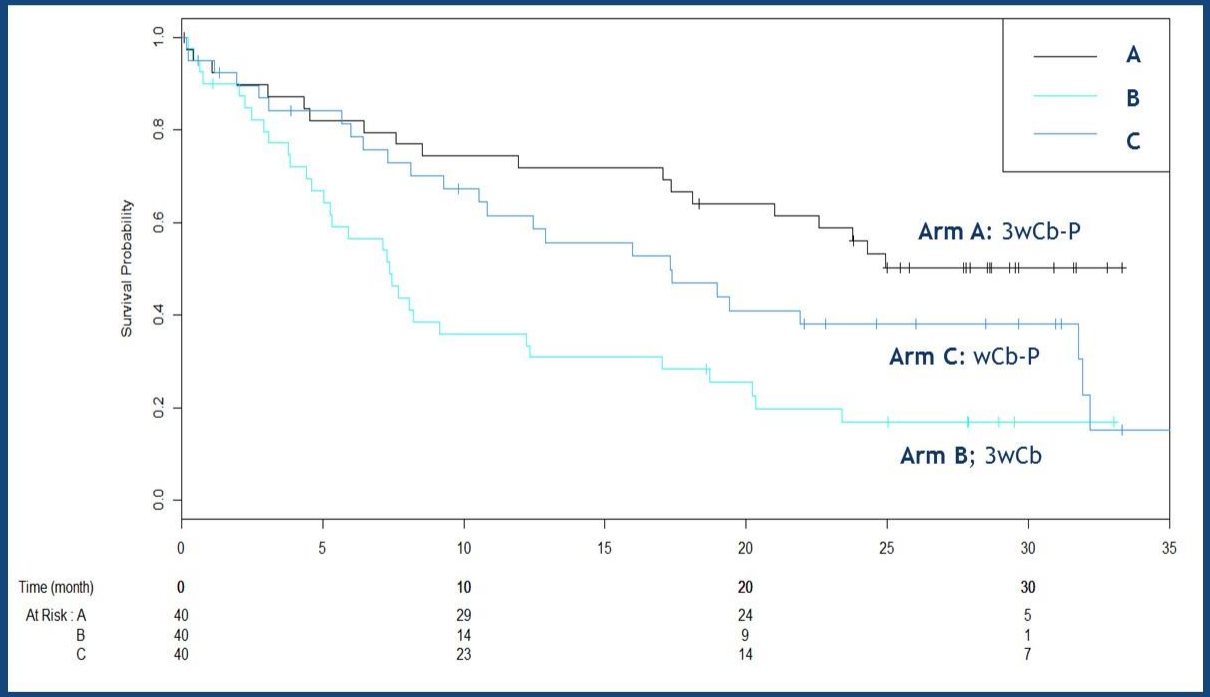
EWOC-1 Overall survival

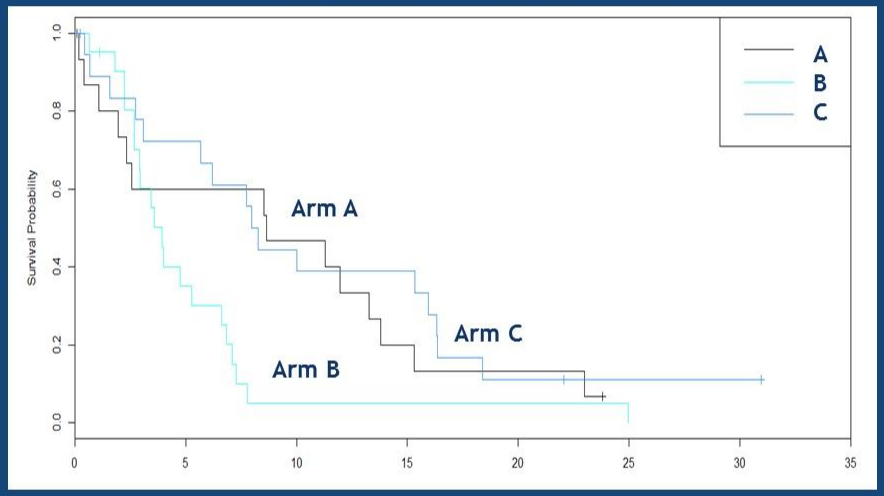


	Arm A	Arm B	Arm C
Events, N (%)	19 (47)	32 (80)	25 (62)
Median, mos (95% CI)	**NR** (21 - 32.2)	**7.4** (5.3 - 32.2)	**17.3** (10.8 - 32.2)
HR (95% CI)	1 (REF)	**2.79** (1.57,4.96)	1.6 (0.88,2.92)
P Wald test	-	**< 0.001**	0.123
P Log-Rank	0.001		

NR: Not reached

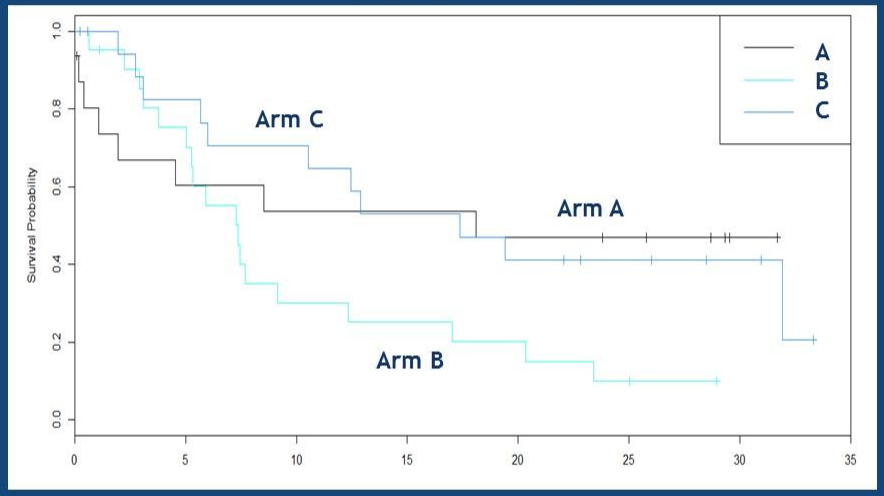
The carboplatin single agent arm is also worse even for the most vulnerable patients (GVS 4 & 5)

Progression-free survival



	Arm A	Arm B	Arm C
Events, N (%)	14 (88)	20 (95)	16 (84)
Median, mos (95% CI)	**8.7** (2.3 - 16.4)	**3.9** (2.9 - 16.4)	**8.1** (5.7 - 16.4)
HR (95% CI)	1 (REF)	**2.34** (1.44,3.8)	1.31 (0.8,2.14)
P wald test	-	< 0,001	0,29
P log-rank		0.002	

Overall survival



	Arm A	Arm B	Arm C
Events, N (%)	8 (50)	18 (86)	11 (58)
Median, mos (95% CI)	**18.1** (3 - NA)	**7.4** (5.3 - NA)	**17.4** (10.5 - NA)
HR (95% CI)	1 (REF)	**2.61** (1.46,4.68)	1.53 (0.83,2.82)
P wald test	-	0,001	0,18
P log-rank		0.003	

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EWOC-1 conclusions

- Compared to 3-weekly and weekly carboplatin-paclitaxel regimens, carboplatin single agent was less active with significant worse survival outcome in vulnerable older pts with GVS $\geq$ 3
- These findings were also observed in the most vulnerable patients (GVS 4 & 5)

Even vulnerable older ovarian cancer patients should be offered a carboplatin-paclitaxel regimen

A randomized phase 3 trial of paclitaxel (P) plus carboplatin (C) versus paclitaxel plus ifosfamide (I) in chemotherapy-naive patients with stage I-IV, persistent or recurrent carcinosarcoma of the uterus or ovary: An NRG Oncology trial.

Matthew A. Powell, Virginia L. Filiaci, Martee L. Hensley, Helen Q Huang, Kathleen N. Moore, Krishnansu S. Tewari, Larry J. Copeland, Angeles Alvarez Secord, David G Mutch, Alessandro Santin, William Richards, David Philip Warshal, Nicola M. Spirtos, Paul Disilverstro, Olga Ioffe, David S. Miller

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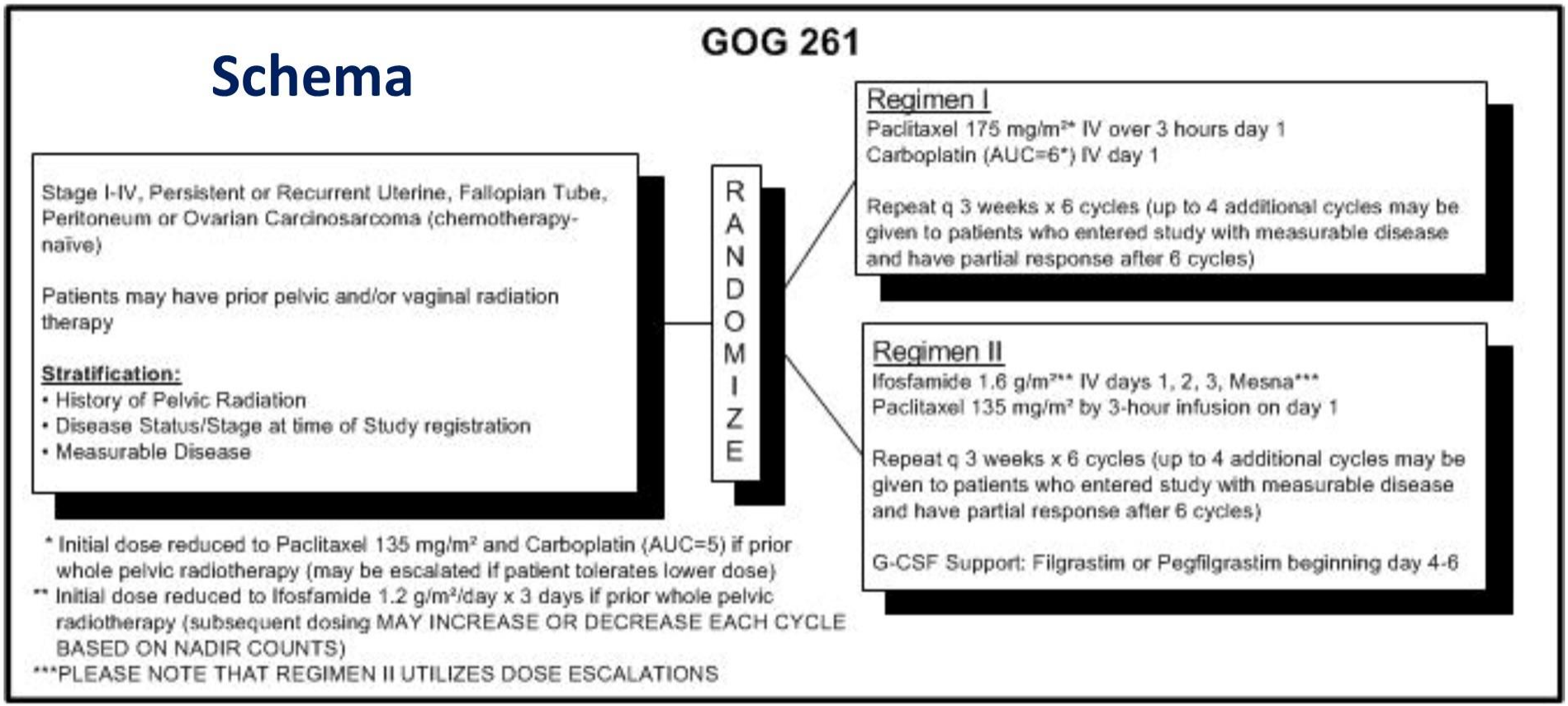
Schema

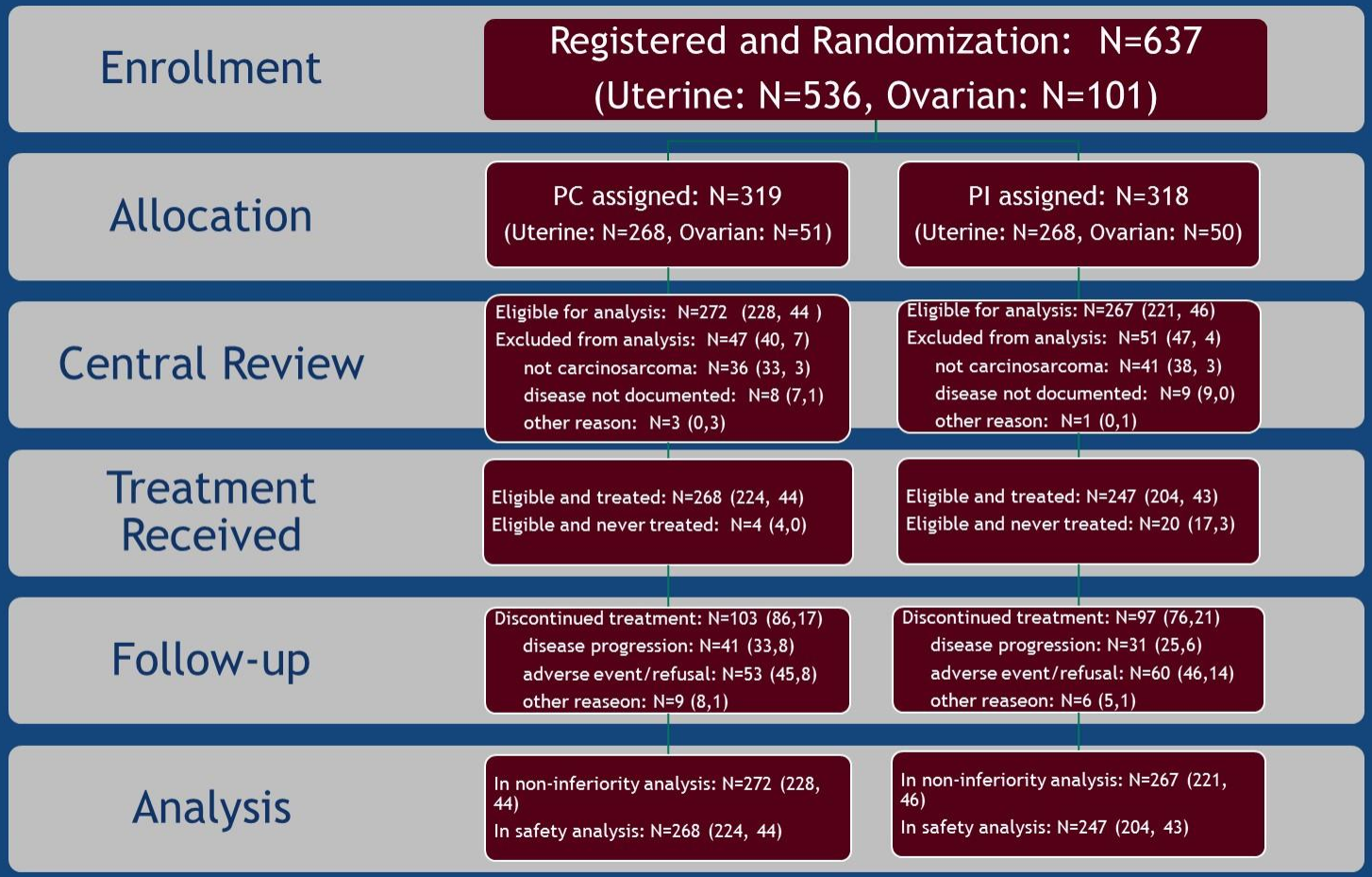


Activated:	08/17/2009
Closed to accrual:	03/24/2014

GOG 0261 Statistical Design: intention-to-treat analysis among eligible patients non-inferiority design

- Primary endpoint: OS
- Secondary endpoints: PFS, AEs, QOL
- Planned sample size: 364
- type I error is limited to 5% for a one-tail stratified log rank test of inferiority (HR=1.2 relative to the ifosfamide and paclitaxel arm) with 80% power.
- Pre-planned interim analysis of survival for efficacy

Consort diagram



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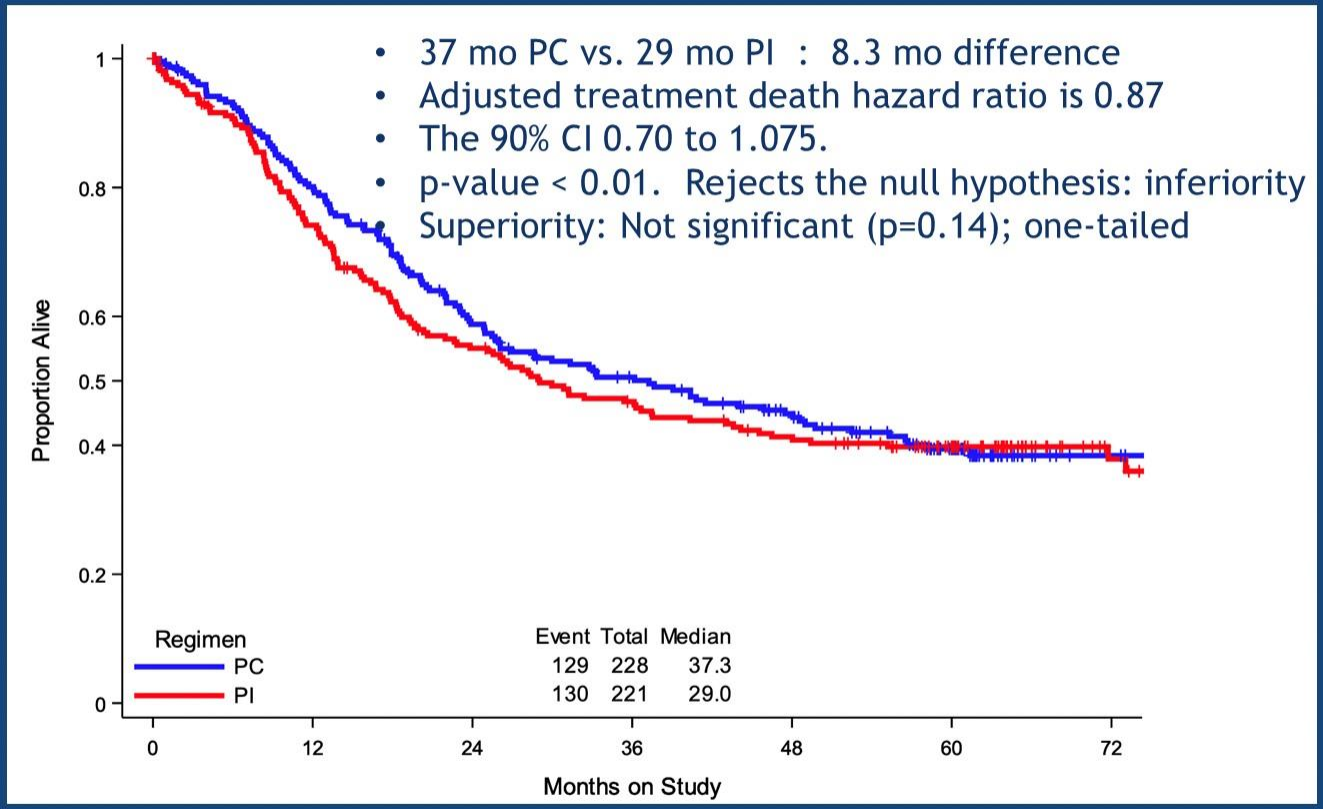
GOG 0261: Patient Characteristics (Uterine) Cohort

Characteristic	Regimen				Total	
	PC		PI			
	N	%	N	%	N	%
Age (median)	65		64			
BMI (median)	30.4		30.7			
Race						
White	150	65.8	133	60.2	283	63.0
Black/African American	66	28.9	72	32.6	138	30.7
Asian	9	3.9	9	4.1	18	4.0
Am Indian/Alaskan Native	2	0.9	1	0.5	3	0.7
Performance Status						
0	149	65.4	119	53.8	268	59.7
1	68	29.8	94	42.5	162	36.1
2	11	4.8	8	3.6	19	4.2
Primary Site						
Uterine Corpus	228	100.0	221	100.0	449	100.0
Disease status (verified)						
Clin/Surg Stage I/II	103	45.2	102	46.2	205	45.7
Stage III/IV	106	46.5	103	46.6	209	46.5
Recurrent/Persistent	19	8.3	16	7.2	35	7.8
Prior RT (verified)						
No	197	86.4	192	86.9	389	86.6
Yes	31	13.6	29	13.1	60	13.4
Measurable Disease (verified)						
No	153	67.1	147	66.5	300	66.8
Yes	75	32.9	74	33.5	149	33.2

	Regimen			
	PC		PI	
	N	%	N	%
Number of cycles				
0 cycles	4	1.8	17	7.7
1-3 cycles	44	19.3	33	14.9
4-6 cycles	160	70.2	159	71.9
7-10 cycles	20	8.8	12	5.4
Total	228	50.8	221	49.2

Protocol Violations	Paclitaxel, Carboplatin		Ifosfamide Paclitaxel	
	N	%	N	%
Minor	38	14.2	55	20.5
Major	21	7.8	32	11.9

GOG 0261: Primary Outcome Uterine Cohort: OS



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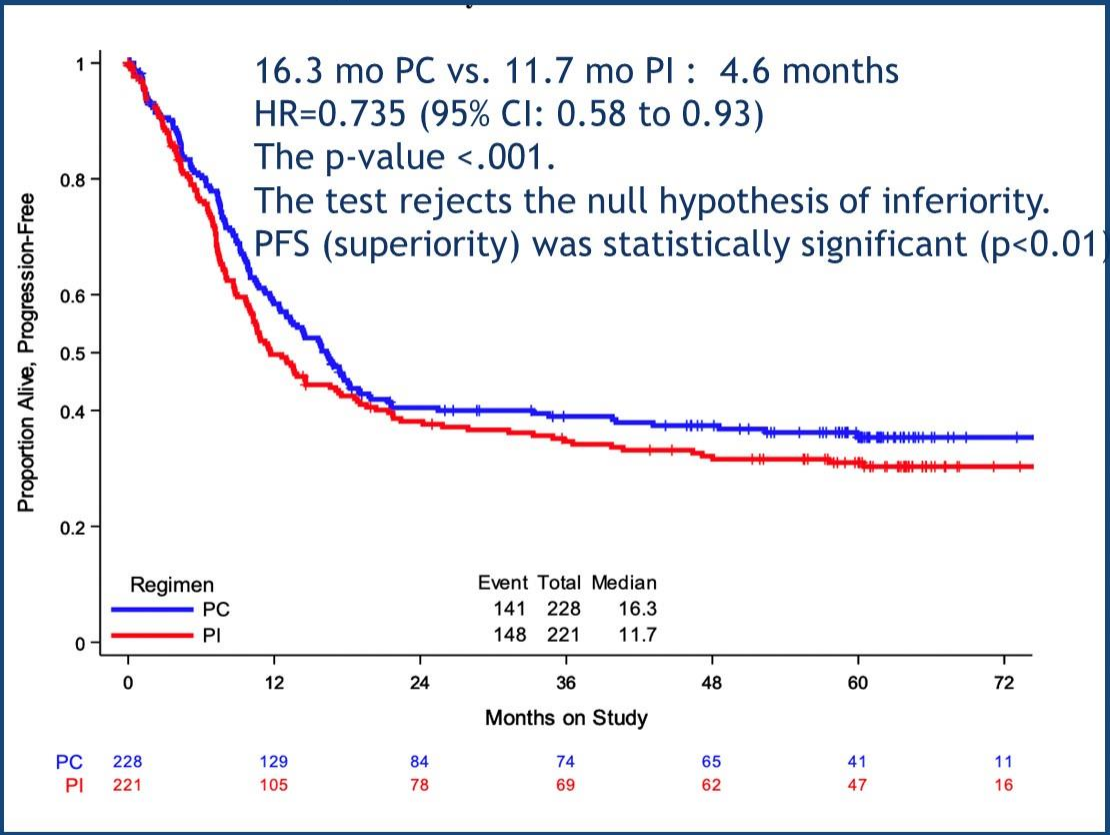
GOG 0261: Secondary Outcomes Uterine Cohort: PFS



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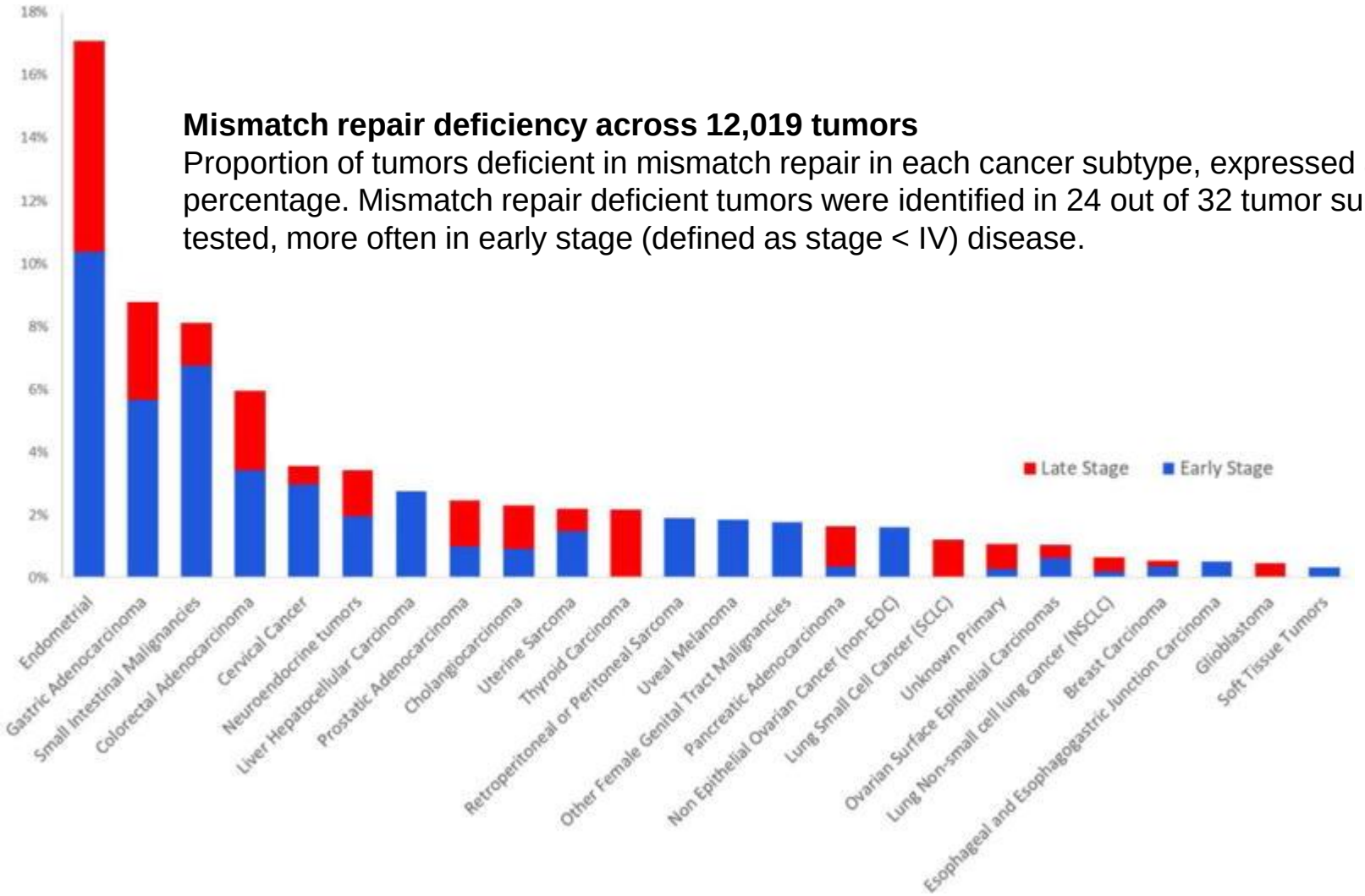
Conclusions

- PC not-inferior to PI with trend towards improved Overall Survival
- Superior PFS for the PC regimen
- Similar predictable toxicity and QOL
- PC regimen likely less expensive (1 day vs 3; limited use of expensive growth factors)

- These results establish a new standard regimen for women with Carcinosarcoma

Cancers deficient in mismatch repair (MMR) contain exceptionally high numbers of somatic mutations



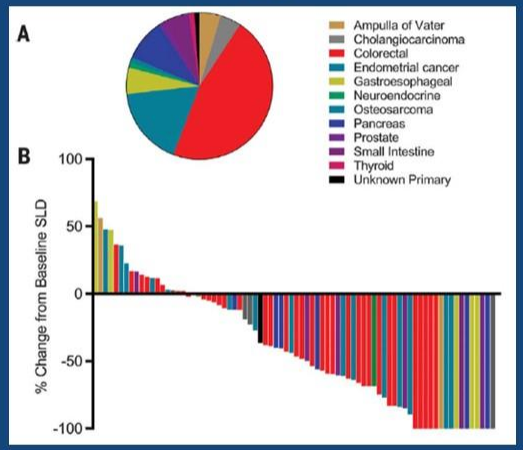
Mismatch repair deficiency across 12,019 tumors

Proportion of tumors deficient in mismatch repair in each cancer subtype, expressed as a percentage. Mismatch repair deficient tumors were identified in 24 out of 32 tumor subtypes tested, more often in early stage (defined as stage < IV) disease.

Dung T. Le et al Science. 2017 Jul 28; 357(6349): 409–413.

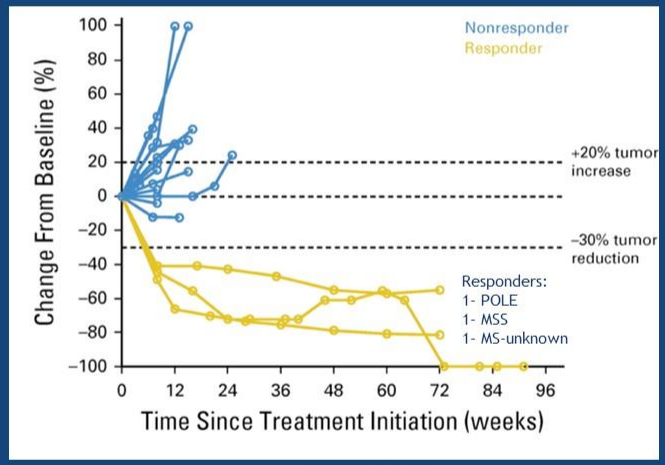
Response to single-agent PD-1 blockade in endometrial cancer

MSI



Endometrial cohort (n=15)
CR: 3 (20%)
PR: 5 (33%)
SD: 3 (20%)

Non-MSI Endometrial (PD-L1)+



ORR 13%

Science. 2017 Jul 28;357(6349):409-413; J Clin Oncol. 2017 Aug 1;35(22):2535-2541.

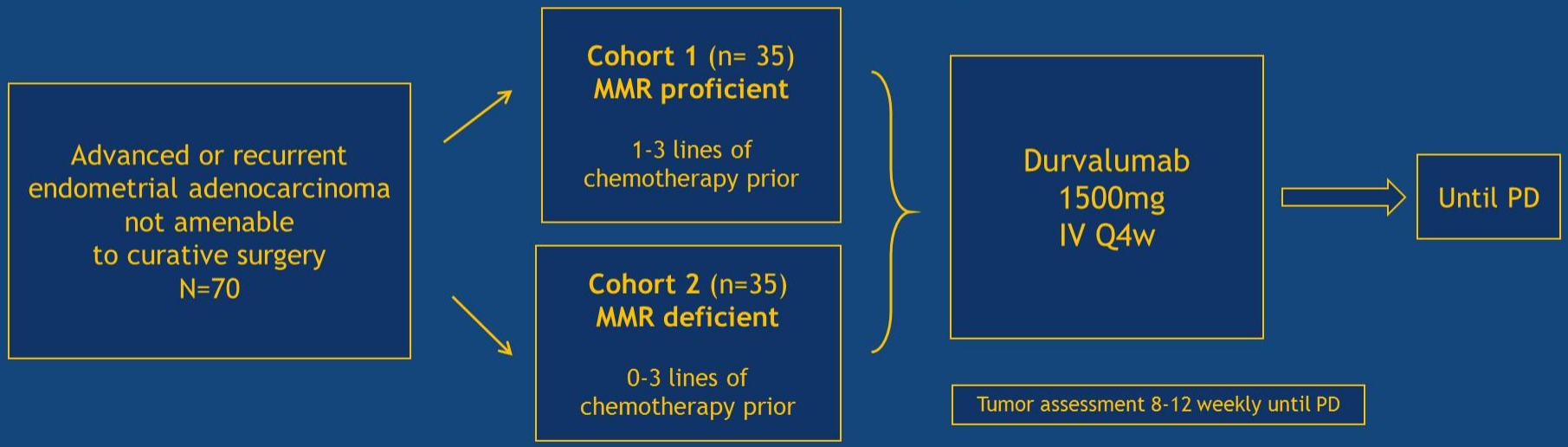
Phase 2 trial of Durvalumab in Advanced Endometrial cancer (PHAEDRA)

Yoland Antill, P-S Kok, E Barnes, K Robledo, M Friedlander, S Baron-Hay, C Shannon, J Coward, P Beale, G Goss, T Meniawy, S Yip, D Smith, A Spurdle, M Parry, J Andrews, M Kelly, MR Stockler and L Mileshkin on behalf of
Australia New Zealand Gynaecological Oncology Group (ANZGOG).

Study Schema

Design: Open-label, multicentre, Phase II, non-comparative trial with 2 cohorts

- MMR proficient (normal MMR protein expression on IHC)
- MMR deficient (loss of expression of at least one MMR protein on IHC)



Aim: To determine the activity and safety of durvalumab in advanced Endometrial Cancer

Primary objective: OTRR (iRECIST)

	dMMR (n =35)	pMMR (n=35)
OTRR	15 (43%)	1 (3%)
DCR	23 (66%)	10 (29%)
CR	5 (14%)	0 (0%)
PR	10 (29%)	1 (3%)
SD	8 (23%)	9 (26%)
Non-evaluable*	0 (0%)	1 (3%)

1 non-evaluable as no RECIST assessment after registration
dMMR- MMR deficient, pMMR- MMR proficient

OTRR: Objective Tumor Response Rate DCR: Disease Control Rate

Numbers of patients with adverse events

All AEs	N =71	
All grade	64	24
Immune-related AEs	Any grade	≥ Grade 3
Hyperthyroidism	8	0
Hypothyroidism	7	0
Hepatitis	1	1
Pneumonitis	2	0
No. of patients who had treatment-related AEs	14 patients	1 patient

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Phase 2, two-group, two-stage study of avelumab in patients (pts) with microsatellite stable (MSS), microsatellite instable (MSI), and polymerase epsilon (*POLE*) mutated recurrent/persistent endometrial cancer (EC) – (NCT02912572)

Panagiotis A. Konstantinopoulos[1], Joyce F. Liu[1], Weixiu Luo[1], Carolyn N. Krasner[1], Jeffrey J. Ishizuka[1], Allison A. Gockley[2], Mary K. Buss[3], Doga C. Gulhan[4], Susana M. Campos[1], Elizabeth Stover[1], Alexi A. Wright[1], Whitfield B. Growdon[5], Jennifer Curtis[1], Ariana Peralta[1], Patrice Basada[1], Roxanne Quinn[1], Kathryn P. Gray[1], Richard T. Penson[5], Stephen A. Cannistra[3], Gini F. Fleming[6], Ursula A. Matulonis[1]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA; [3]Beth Israel Deaconess Medical Center, Boston, MA; [4]Harvard Medical School, Boston, MA; [5]Massachusetts General Hospital, Boston, MA; [6]The University of Chicago Medicine, Chicago, IL

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PRESENTED BY: Panagiotis Konstantinopoulos MD, PhD

Avelumab Confirmed Objective Response and PFS6

RESPONSE	Patients, No	
	MMRD cohort (N=15)	MMRP/non-POLE Cohort (N=16)
Best Overall Response		
CR	1	0
PR	3	1
SD	4	4
PD	4	9
Not evaluable	3	2
ORR, % (95% CI)	26.7 (7.8-55.1)	6.25 (0.16-30.2)
PFS6 Response		
Yes	6	1
No	9	15
PFS6 Response, %	40 (16.3-66.7)	6.25 (0.16-30.2)

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Treatment-Related AEs of any grade in ≥10% of pts OR grade ≥3

Toxicity	Maximum Grade						Total	
	1		2		3			
	N	%	N	%	N	%	N	%
Fatigue	10	32.3	1	3.2	0	0	11	35.5
Nausea	5	16.1	0	0	0	0	5	16.1
Hypothyroidism	1	3.2	2	6.5	1	3.2	4	12.9
Neutrophil count decreased	4	12.9	0	0	0	0	4	12.9
Anemia	1	3.2	0	0	2	6.5	3	9.7
Diarrhea	0	0	1	3.2	2	6.5	3	9.7
Rash acneiform	1	3.2	0	0	1	3.2	2	6.5
Sinus bradycardia	0	0	0	0	1	3.2	1	3.2
Myositis	0	0	0	0	1	3.2	1	3.2

Conclusions

- Checkpoint inhibitors active in dMMR EC
  - Avelumab and durvalumab are active in dMMR EC
- Checkpoint inhibitors as monotherapy show minimal activity in pMMR EC
  - Avelumab and durvalumab monotherapy did not demonstrate activity in pMMR EC
- dMMR status by IHC correlates with response to avelumab and durvalumab
- Routine use of IHC in EC when considering ICB therapy is supported
- Durable responses were observed irrespective of PD-L1 status (avelumab), multiple prior lines of therapy and somatic or germline origin of dMMR
- Biomarkers of response/mechanisms of resistance to ICB in EC need to be optimally defined and validated
- In pMMR EC checkpoint inhibitor combinations and checkpoint inhibitor-targeted therapy combination approaches should be explored