



OVARIALKARZINOM UND ANDERE GENITALMALIGNOME

Edgar Petru

Univ. Frauenklinik Graz

Ovarialkarzinom

Ovarialkarzinom PARP-Inhibition

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

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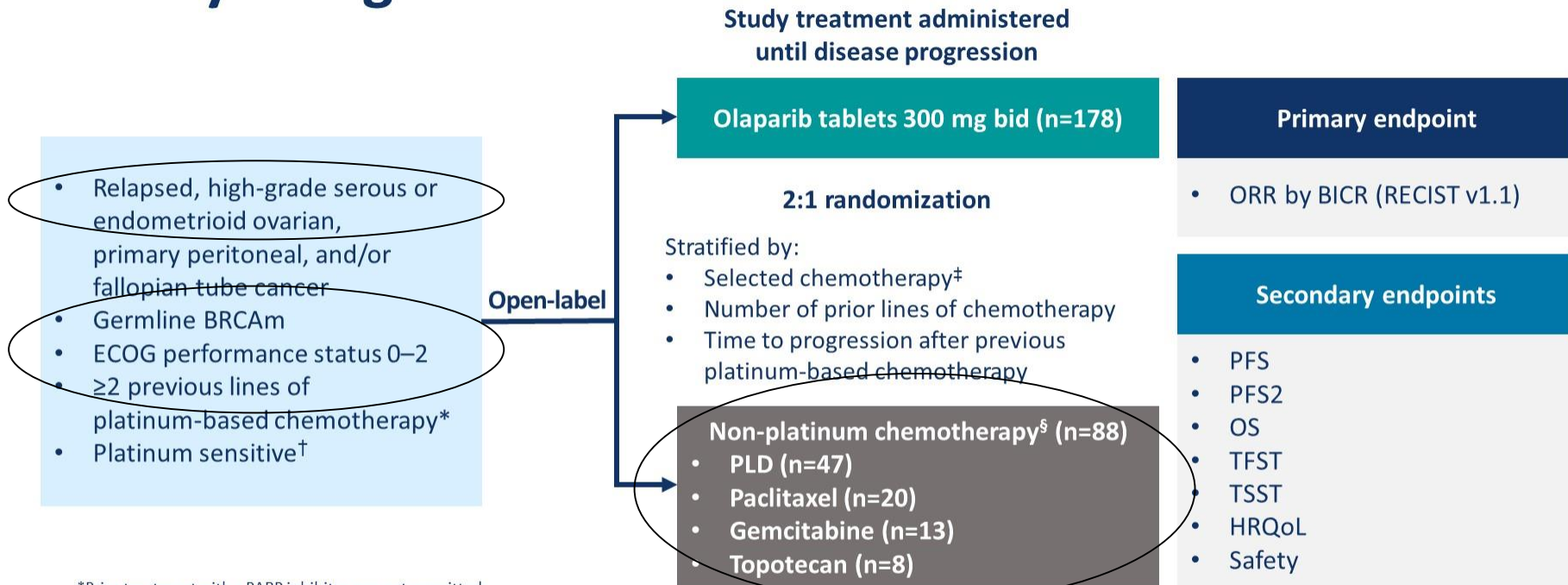
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Study Design



*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/m² on day 1 q4w; paclitaxel, 80 mg/m² on days 1, 8, 15, and 22 q4w; gemcitabine, 1000 mg/m² on days 1, 8, and 15 q4w; topotecan, 4 mg/m² 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 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

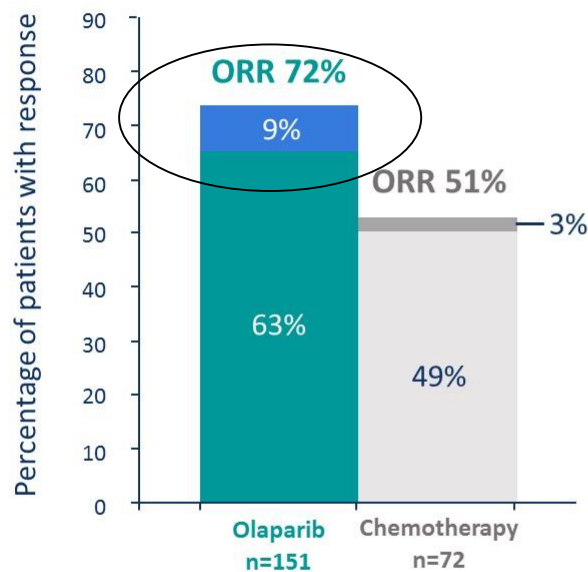
Patient Characteristics

	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”;

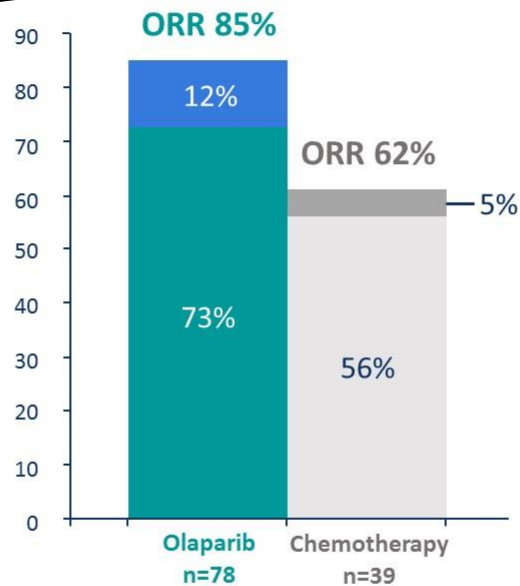
[†]For each patient, the investigator declared a choice of non-platinum chemotherapy before randomization. Therefore, the olaparib column shows the chemotherapy option that patients would have received had they been randomized to chemotherapy instead of olaparib

Primary Endpoint: ORR by BICR

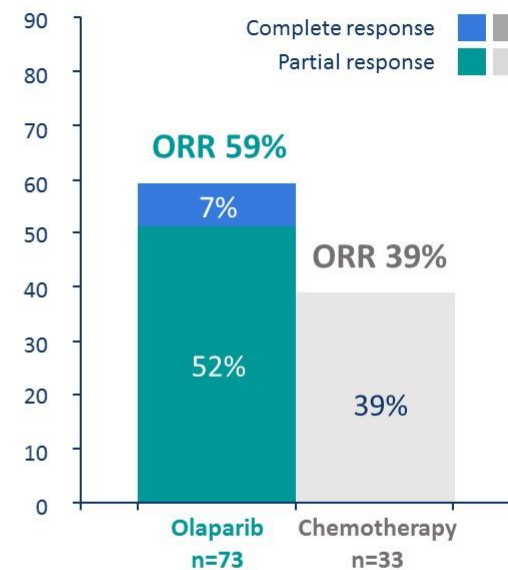


All patients*
OR 2.53 (1.40, 4.58) $P=0.002$

*Patients with measurable disease at baseline

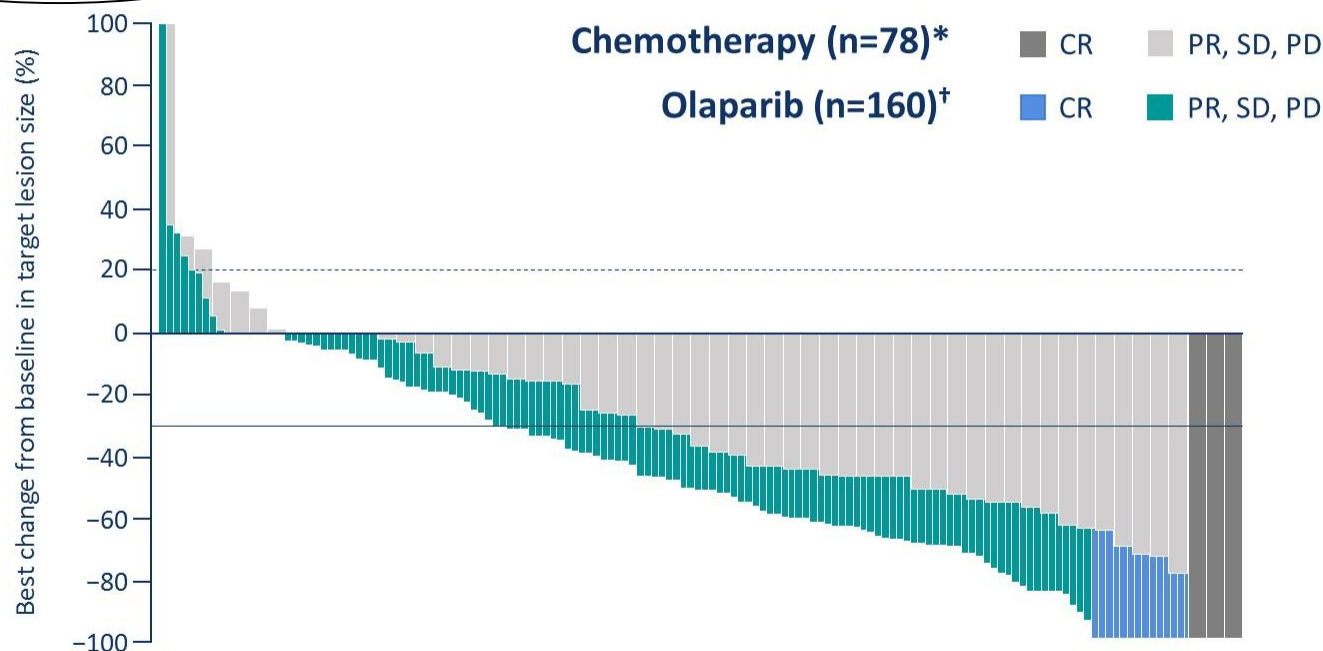


**Patients with
2 prior lines of chemotherapy***
OR 3.44 (1.42, 8.54)



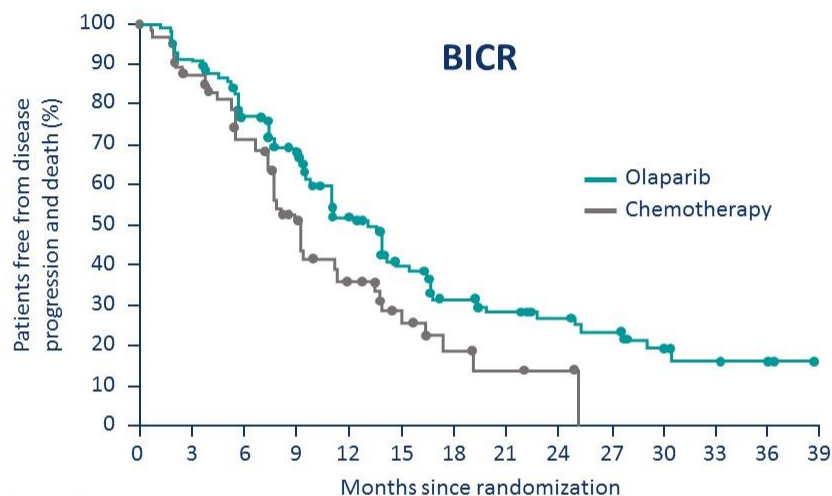
**Patients with
≥3 prior lines of chemotherapy***
OR 2.21 (0.96, 5.20)

Investigator-Assessed Best Response for Target Lesions by Patient



*19 patients were not evaluable for investigator-assessed best response; †11 patients were not evaluable for investigator-assessed best response

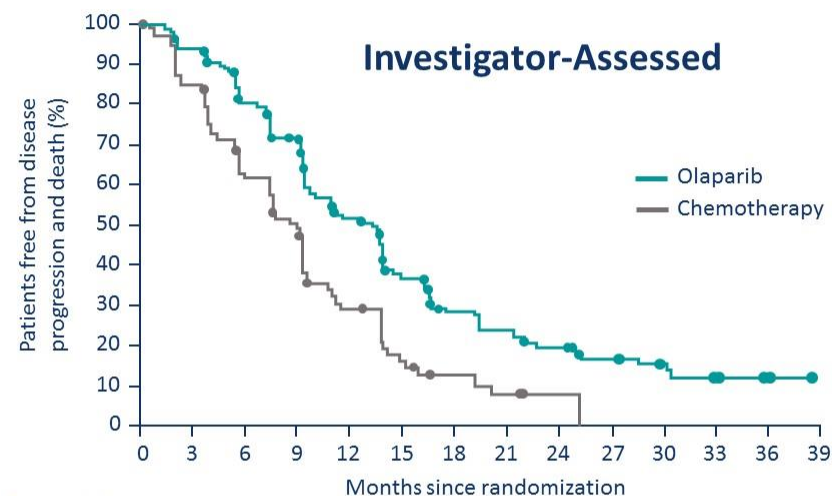
PFS (Intention-To-Treat Population)



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), <i>P</i> value	0.62 (0.43, 0.91); <i>P</i> =0.013	

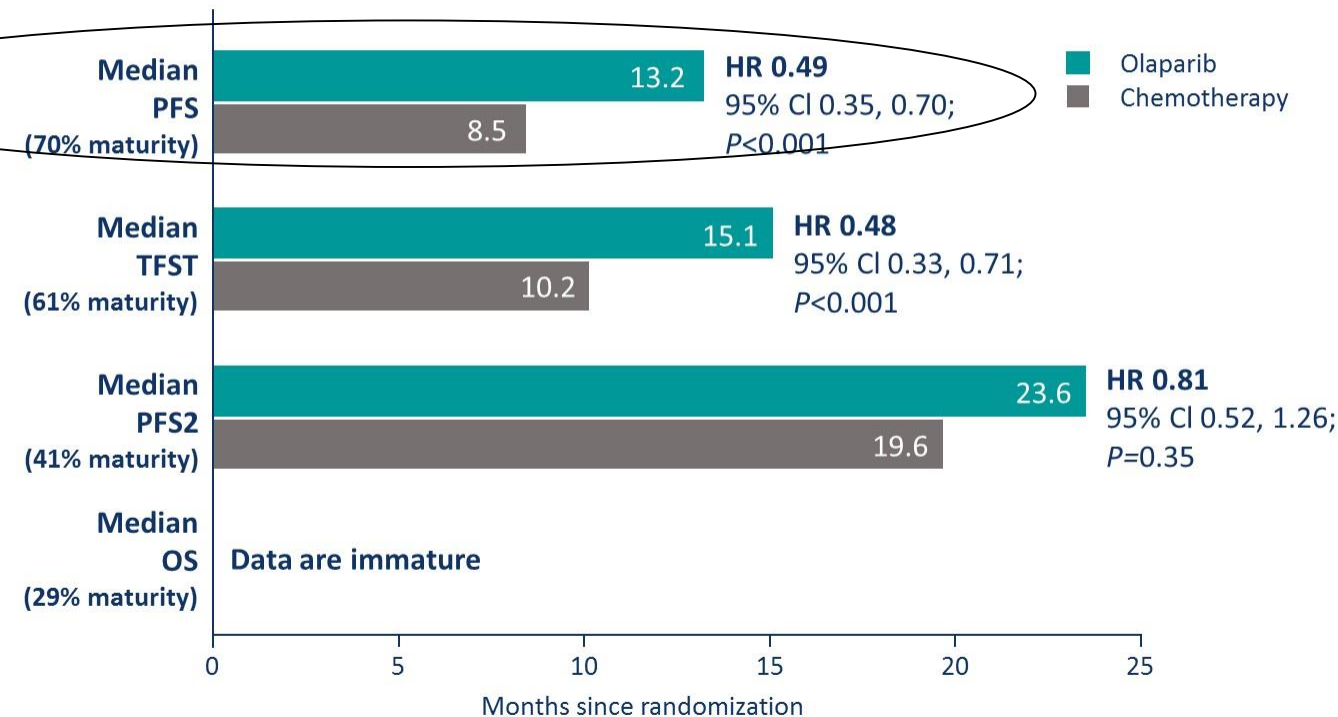


No. at risk

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), <i>P</i> value	0.49 (0.35, 0.70); <i>P</i> <0.001	

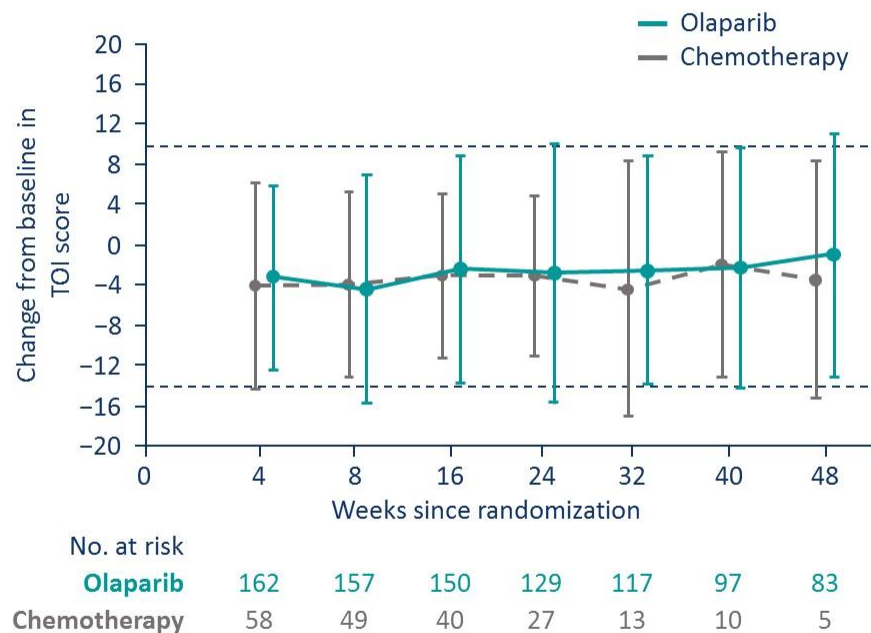
Investigator-Assessed Efficacy Endpoints and Subsequent Therapies



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

HRQoL: FACT-O TOI Score



	Olaparib (n=167)	Chemotherapy (n=62)
Least squares mean change in TOI	-2.3	-4.8
Difference (95% CI), P value	2.5 (-0.5, 5.5) P=0.108	

- Higher scores represent better HRQoL. A clinically meaningful difference in FACT-O TOI score is defined as ± 10 points
- **There was no clinically or statistically significant difference in HRQoL between the olaparib and chemotherapy arms**

FACT-O, Functional Assessment of Cancer Therapy– Ovarian; TOI, Trial Outcome Index

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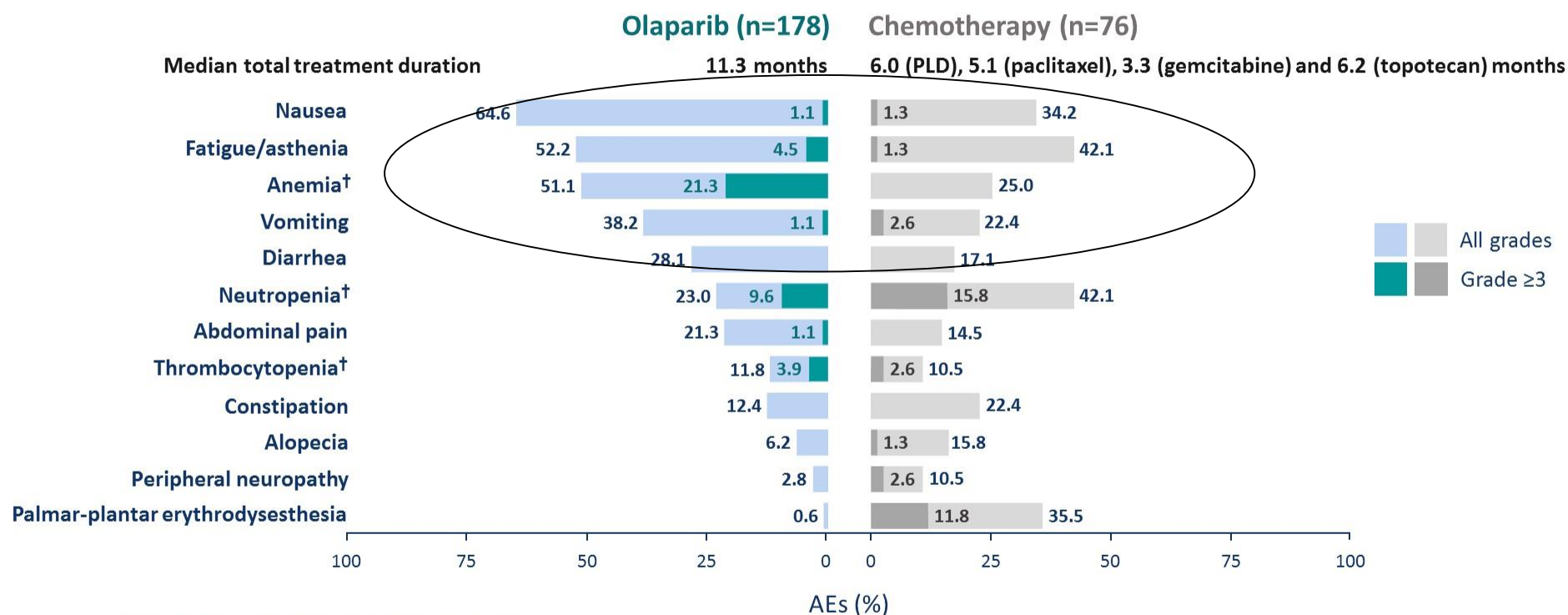
Safety Overview

	Olaparib (n=178)	Chemotherapy (n=76)
All-grade AEs, n (%)	174 (98)	73 (96)
Grade ≥3 AEs, n (%)	89 (50)	36 (47)
Serious AEs, n (%)*	42 (24)	14 (18)
AEs leading to dose interruption, n (%)	85 (48)	32 (42)
AEs leading to dose reduction, n (%)	48 (27)	25 (33)
AEs leading to treatment discontinuation, n (%)†	13 (7)	15 (20)
Median total treatment duration (range), months		
Olaparib	11.3 (0.1–39.5)	–
PLD	–	6.0 (0.9–15.4)
Paclitaxel	–	5.1 (1.8–18.2)
Gemcitabine	–	3.3 (0.7–14.3)
Topotecan	–	6.2 (2.3–9.7)

*Most common serious AE in the olaparib arm was anemia (3%) and in the chemotherapy arm was vomiting (4%);

†Most common AEs leading to treatment discontinuation in the olaparib arm were vomiting, anemia, and thrombocytopenia (all 1%), and in the chemotherapy arm were PPE (9%), mucosal inflammation, peripheral neuropathy, and neutropenia (all 3%)
PPE, palmar-plantar erythrodysesthesia

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



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

†Grouped terms

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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 (gBRCA2 mutation)
 - Gastric cancer (gBRCA1 mutation)
 - Breast cancer (gBRCA1 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

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

CLIO (NCT02822157):

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

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⁴ Center for Cancer Biology, VIB, Leuven, Belgium, EU

Treatment options for PROOC 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 olaparib² and rucaparib³)

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

CLIO Study Design

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

R



OLAPARIB 300mg BID (4 tablets/day)



Physician's choice CHEMOTHERAPY
(Carbo-Gemci / Carbo-Paclitaxel / Carbo-PLD)

crossover



2:1 randomisation

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

R



OLAPARIB 300mg BID (4 tablets/day)



Physician's choice CHEMOTHERAPY

Paclitaxel 80mg/m²

PLD 40mg/m²

Topotecan 1.25mg/m²

Gemcitabine 1000mg/m²

crossover

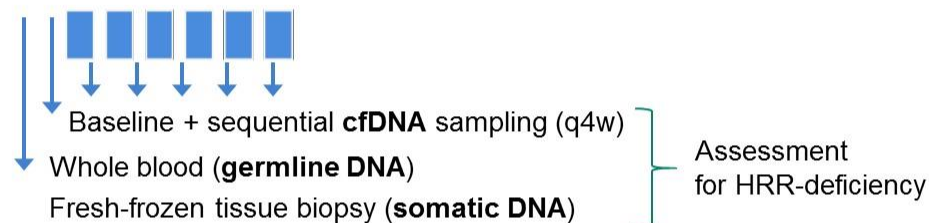


CLIO study endpoints

ctDNA guiding olaparib treatment in ovarian cancer

Primary endpoint

- Objective response rate (**OOOR**) in **all** patients on olaparib monotherapy based on HRR-deficiency: **HRR-deficient versus HRR-proficient cases** (HRD status determined in ctDNA / tissue DNA)

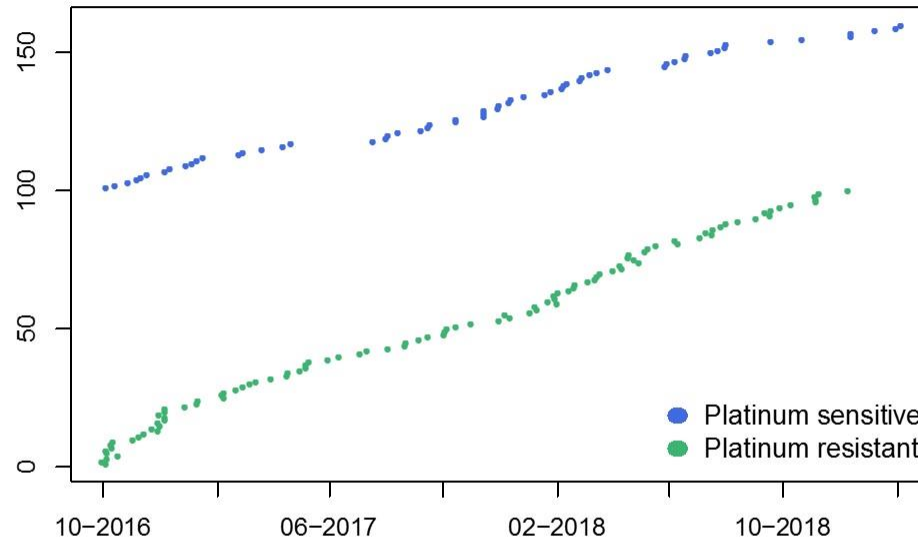


Secondary endpoint

- Objective response rate (**OOOR**), **PFS**, **clinical benefit rate** at 12 weeks and **duration of clinical benefit** for platinum-sensitive (**PSOC**) cohort treated with olaparib monotherapy versus chemotherapy
- Objective response rate (**OOOR**), **PFS**, **clinical benefit rate** at 12 weeks and **duration of clinical benefit** for platinum-resistant (**PROC**) cohort treated with olaparib monotherapy versus chemotherapy
- Quality of life** analysis of olaparib versus chemotherapy in PROC and PSOC patients

Current report

Study recruitment



Single-center study, University Hospitals Leuven (Belgium, EU)
160 patients were recruited between Oct-2016 and Feb-2019 (29 months)
(100 **PROC** / 60 **PSOC**)

Median follow-up time for PROC patients 16.5 months (95%CI: 13.5 - NA)

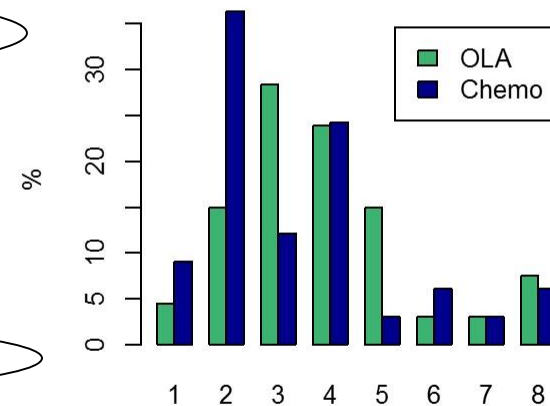
Demographics (PROC, n = 100)

	OLAPARIB	CHEMOTHERAPY	*
Number of patients	67	33	
Median age at randomization	60 (IQR: 55-68, Range: 38-82)	63 (IQR: 60-68, Range: 47-78)	
18 - 69 years	53 (79%)	25 (76%)	
>=70 years	14 (21%)	8 (24%)	
WHO score 0	34 (51%)	18 (55%)	
1	33 (49%)	15 (45%)	
Histology High-grade serous	60 (90%)	30 (91%)	
Clear-cell	6 (9%)	3 (9%)	
Endometrioid	1 (1%)	0 (0%)	

Baseline characteristics (PROC, n = 100)

Prior treatment

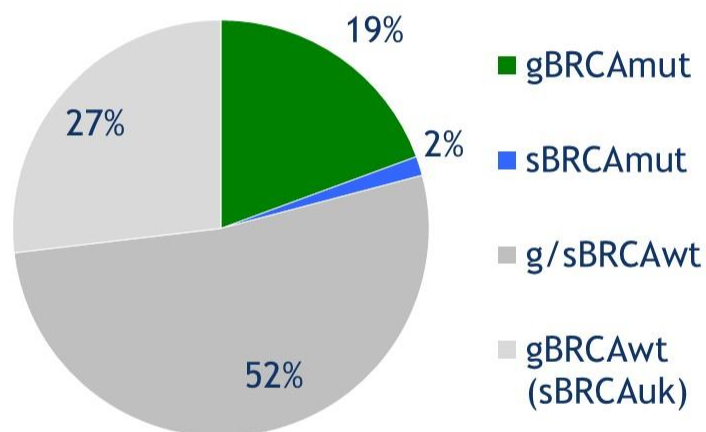
	OLAPARIB	CHEMOTHERAPY *
Number of patients	67	33
Median years since diagnosis	3.7 (95%CI: 2.8 - 5.0)	3.2 (95%CI: 2.2 - 3.9)
Median prior lines	4 (IQR: 3-5, Range: 1-8)	3 (IQR: 2-4, Range: 1-8)
1	3 (5%)	3 (9%)
2	10 (15%)	12 (36%)
3	19 (28%)	4 (12%)
4 or more	35 (52%)	14 (42%)
Prior bevacizumab	36 (54%)	14 (42%)
Prior PARPi	5 (8%)	2 (6%)
Prior PARPi (incl. placebo-controlled trials)	10 (15%)	6 (18%)



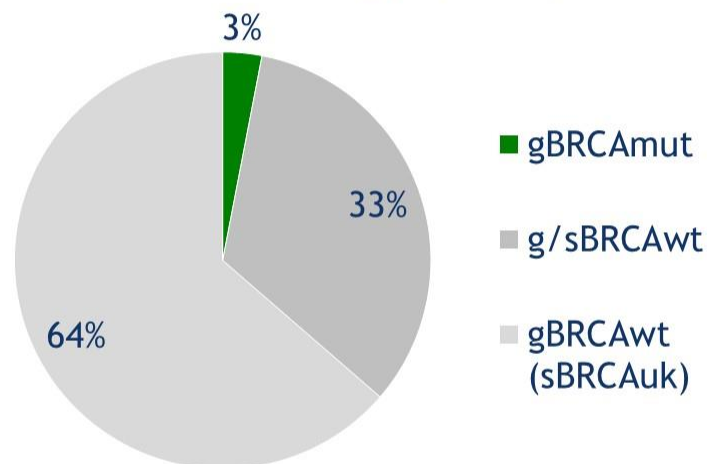
Baseline characteristics (PROC, n=100)

BRCA status

Olaparib (n=67)

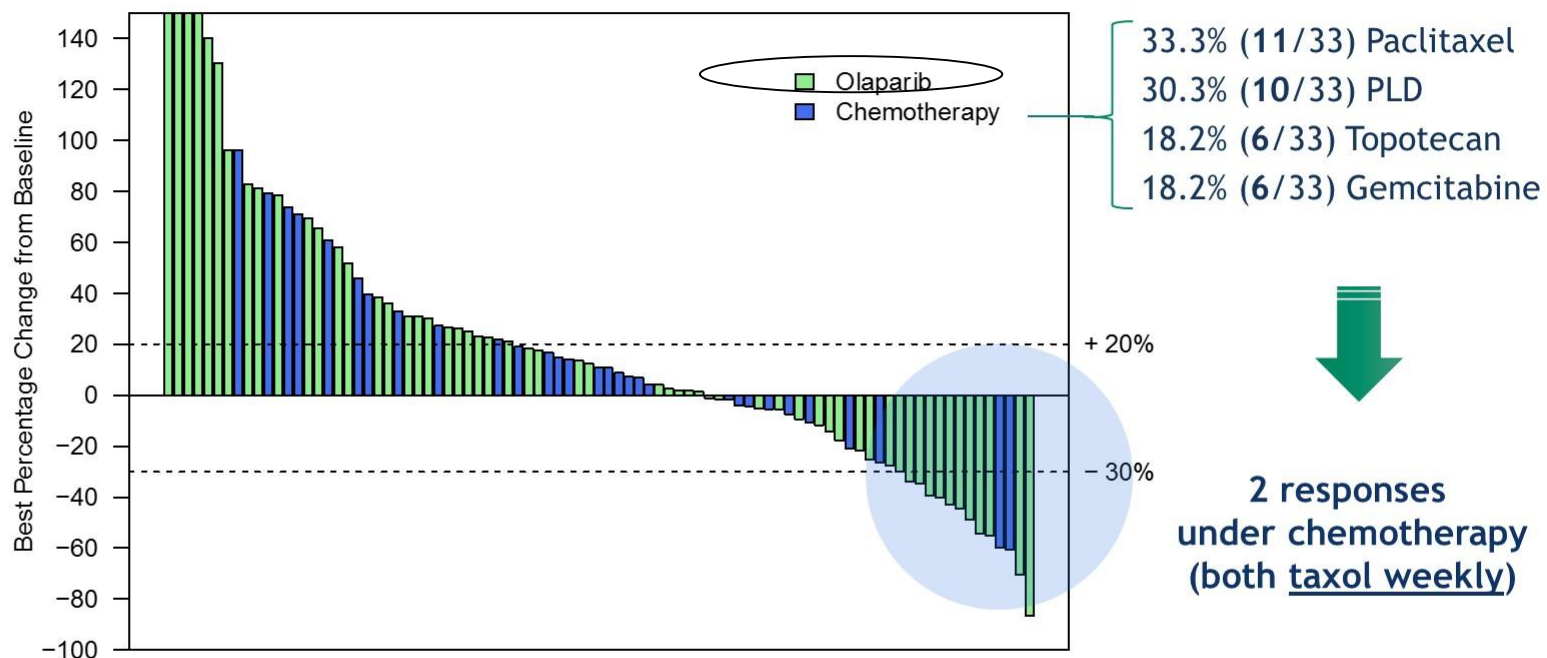


Chemotherapy (n=33)



Imbalance in frequency of known BRCA mutations between both groups ($p=0.03$)
(no stratification performed, incomplete somatic testing mainly in chemo-arm)

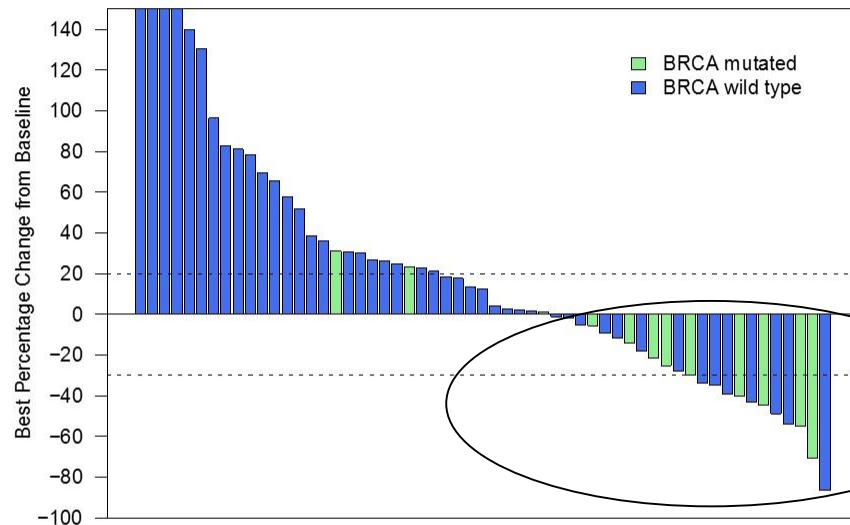
Objective response rate (ORR for PROC, n=100) *



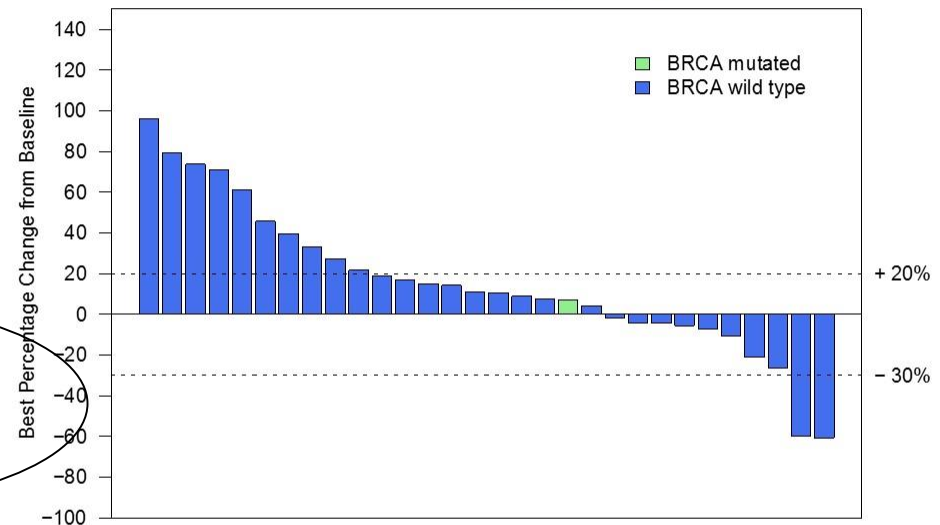
	OLAPARIB	CHEMOTHERAPY	
All patients	18 % (12/67)	6 % (2/33)	p=0.13

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

Olaparib (n=67)



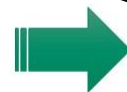
Chemotherapy (n=33)



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

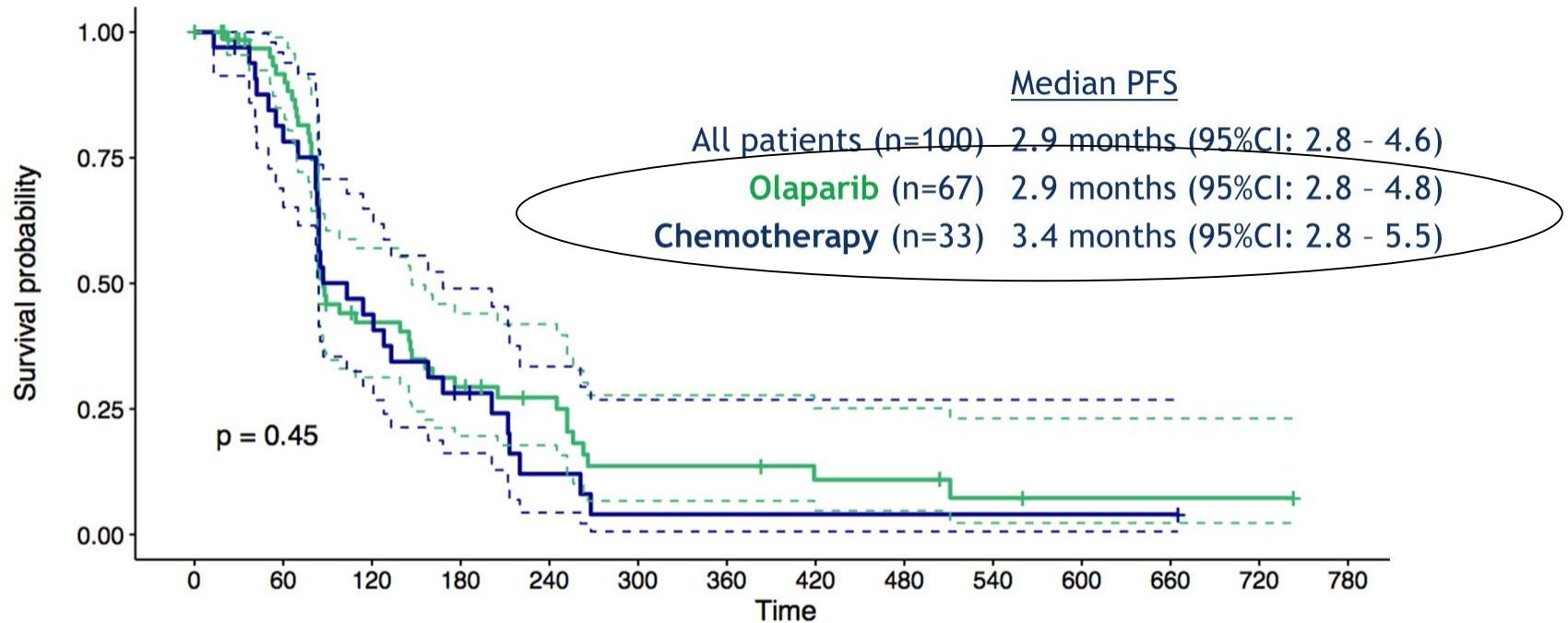
ORR in RAD51C/D and BRIP1-mutated cases

- All patients underwent germline HBOC gene panel screening (“Hereditary breast/ovarian cancer”: BRCA1, BRCA2, RAD51C, RAD51D, BRIP1)
- In olaparib-arm: 17 out of 67 patients (25.4%) with germline HBOC mutation
 - 10 BRCA1
 - 3 BRCA2
 - 2 BRIP1 (c.2111T>G and c.2400C>G)
 - 1 RAD51C (c.966-2A>C)
 - 1 RAD51D (c.803G>A)



No responses were observed in 4 PROC patients with germline BRIP1, RAD51C/D mutations

Progression-free survival (PFS)



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)

Treatment emergent adverse events (TEAEs)

MedDRA System Preferred Term	Olaparib (n=67)	Chemotherapy (n=33)
Any CTCAE Grade ≥ 3 TEAE (>5%)	n (%)	n (%)
Anaemia	24 (36)	6 (18)
Neutrophil count decreased	2 (3)	10 (30)
Platelet count decreased	3 (5)	3 (9)
Vomiting	5 (7)	0 (0)
Malaise	4 (6)	1 (3)
TEAE (any grade) leading to dose reduction	14 (21)	5 (15)
TEAE (any grade) leading to dose discontinuation	5 (7)	1 (3)

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-AVANOA2

Mansoor R Mirza¹, E Avall-Lundqvist², MJ Birrer³, R dePont Christensen⁴, G-B Nyvang⁵, S Malander⁶, M Anttila⁷, TL Werner⁸, B Lund⁹, G Lindahl², S Hietanen¹⁰, U Peen¹¹, M Dimoula¹², H Roed¹, A Ør Knudsen⁵, L Boufercha⁴, S Staff¹³, A Krog Vistisen⁹, L Bjørge¹⁴, JU Maenpaa¹³

¹Nordic Society of Gynecological Oncology (NSGO) & Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; ²NSGO & Linköping University Hospital, Linköping, Sweden; ³The University of Alabama at Birmingham, Birmingham, AL, USA; ⁴NSGO Clinical Trials Unit & University of Southern Denmark, Odense, Denmark; ⁵NSGO & Odense University Hospital, Odense, Denmark; ⁶NSGO & Lund University Hospital, Lund, Sweden; ⁷NSGO & Kuopio University Hospital, Kuopio, Finland; ⁸University of Utah, Salt Lake City, UT, USA; ⁹NSGO & Aalborg University Hospital, Aalborg, Denmark; ¹⁰NSGO & Turku University Hospital, Turku, Finland; ¹¹NSGO & University Hospital of Herlev, Rungsted, Denmark; ¹²NSGO & Sahlgrenska University Hospital, Göteborg, Sweden; ¹³NSGO & Tampere University Hospital, Tampere, Finland; ¹⁴NSGO & Haukeland University Hospital, Bergen, Norway

ENGOT-OV24 / NSGO-AVANOVA2 trial design

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

Randomize
1:1

**Niraparib
300 mg QD d1–21**

**Niraparib 300 mg QD d1–21
+
Bevacizumab 15 mg/kg q3w**

Until
disease
progression
or toxicity

Stratification factors

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

Primary endpoint: Investigator-assessed PFS in the ITT population

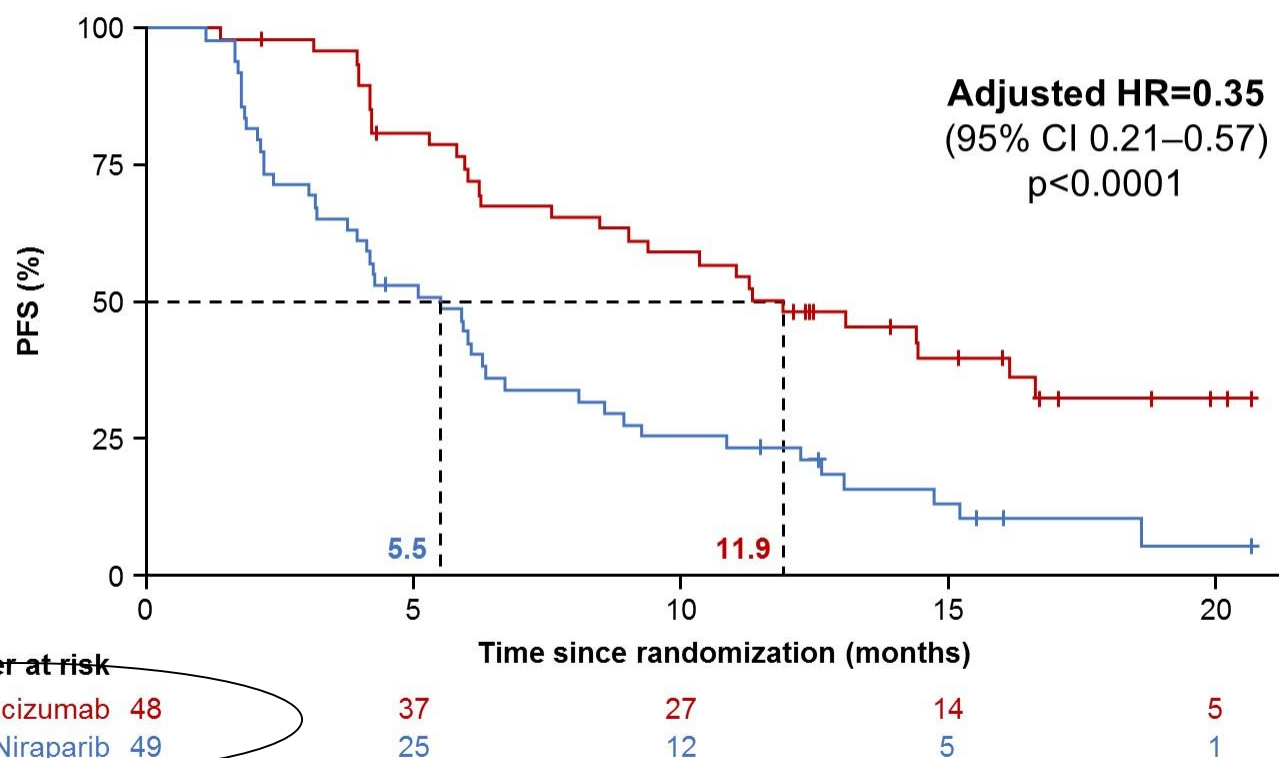
ITT = intention-to-treat; NCT02354131

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	38 (79%)	33 (67%)
	Fallopian tube	5 (10%)	9 (18%)
	Peritoneum	5 (10%)	7 (14%)
Chemotherapy-free interval, months	6–12	20 (42%)	17 (35%)
	>12	28 (58%)	32 (65%)
HRD status	Positive ^a	28 (58%)	30 (61%)
	Negative/unknown	20 (42%)	19 (39%)
BRCA mutation	Any	15 (31%)	18 (37%)
	Germline	6 (13%)	9 (18%)
	Somatic	14 (29%)	14 (29%)
Pre-existing hypertension		20 (42%)	17 (35%)
Prior bevacizumab		10 (21%)	13 (27%)
Prior lines of therapy	1	21 (44%)	27 (55%)
	2	24 (50%)	19 (39%)
	≥3	3 (6%)	3 (6%)

^a3 patients (1 niraparib + bevacizumab, 2 niraparib) had BRCA-mutated tumors but were erroneously considered as HRD negative/unknown for stratification

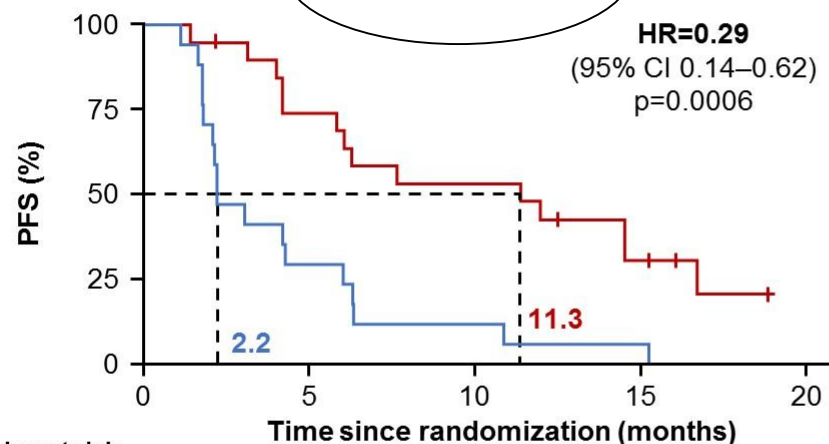
Primary endpoint: PFS in the ITT population



CI = confidence interval; HR = hazard ratio

PFS by stratification factors: Chemotherapy-free interval

6–12 months

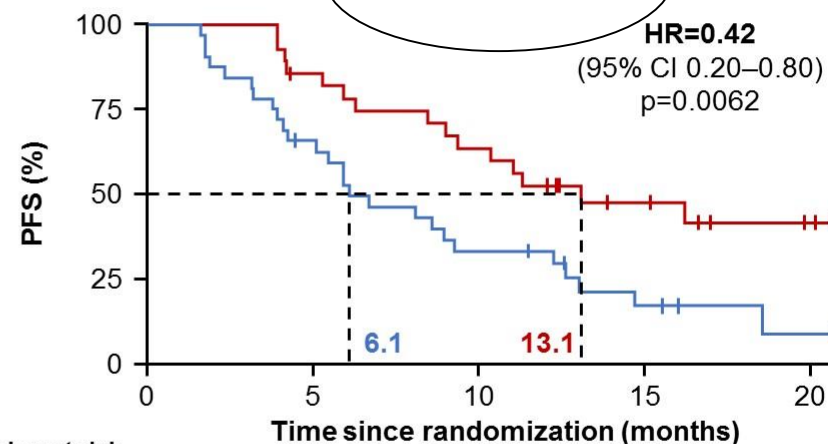


Number at risk

Niraparib +
bevacizumab 20
Niraparib 17

14 10 5 1
5 2 1 0

>12 months



Number at risk

Niraparib +
bevacizumab 28
Niraparib 32

23 17 9 4
20 10 4 1

PRESENTED AT:

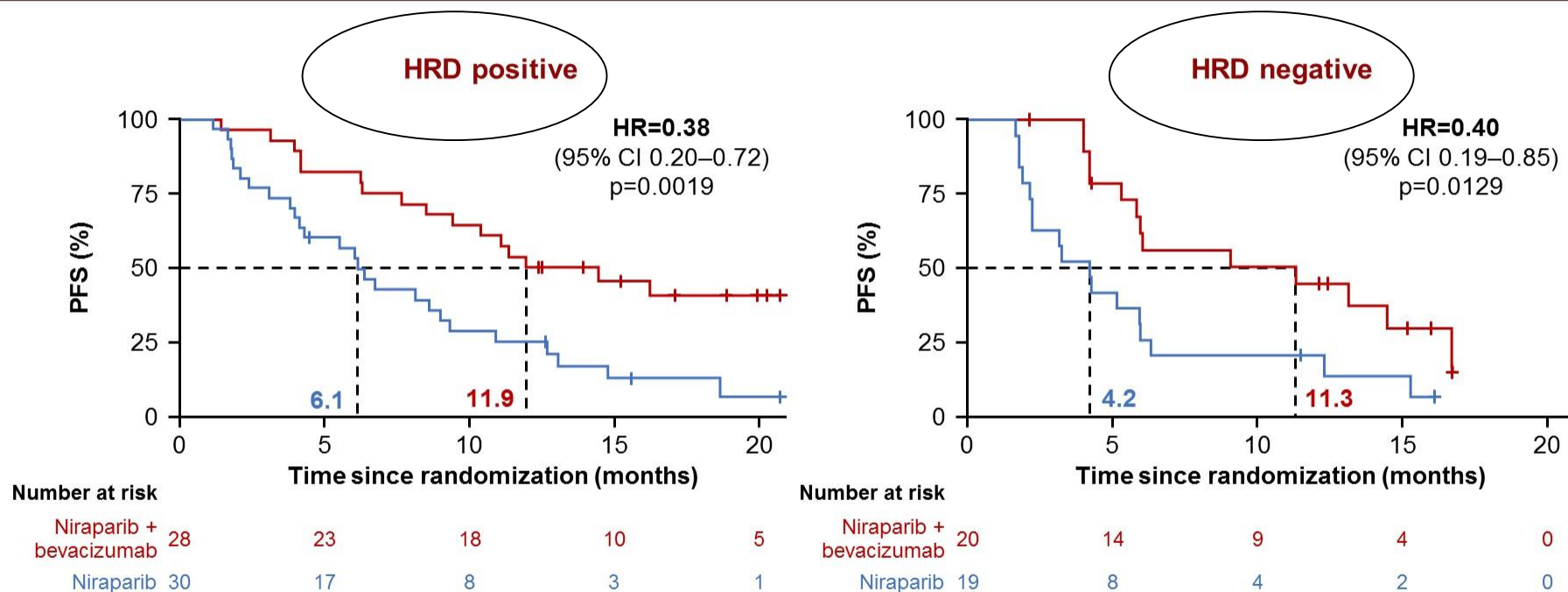
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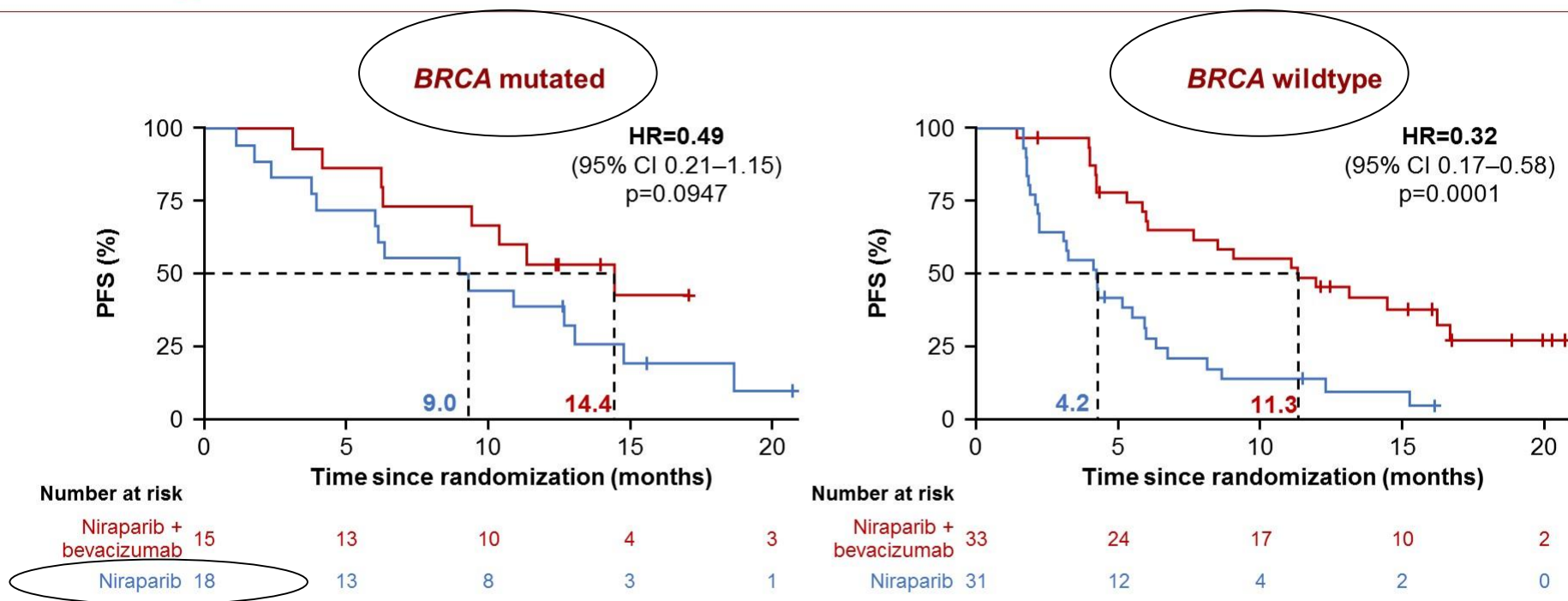
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PRESENTED BY: Mansoor Raza Mirza

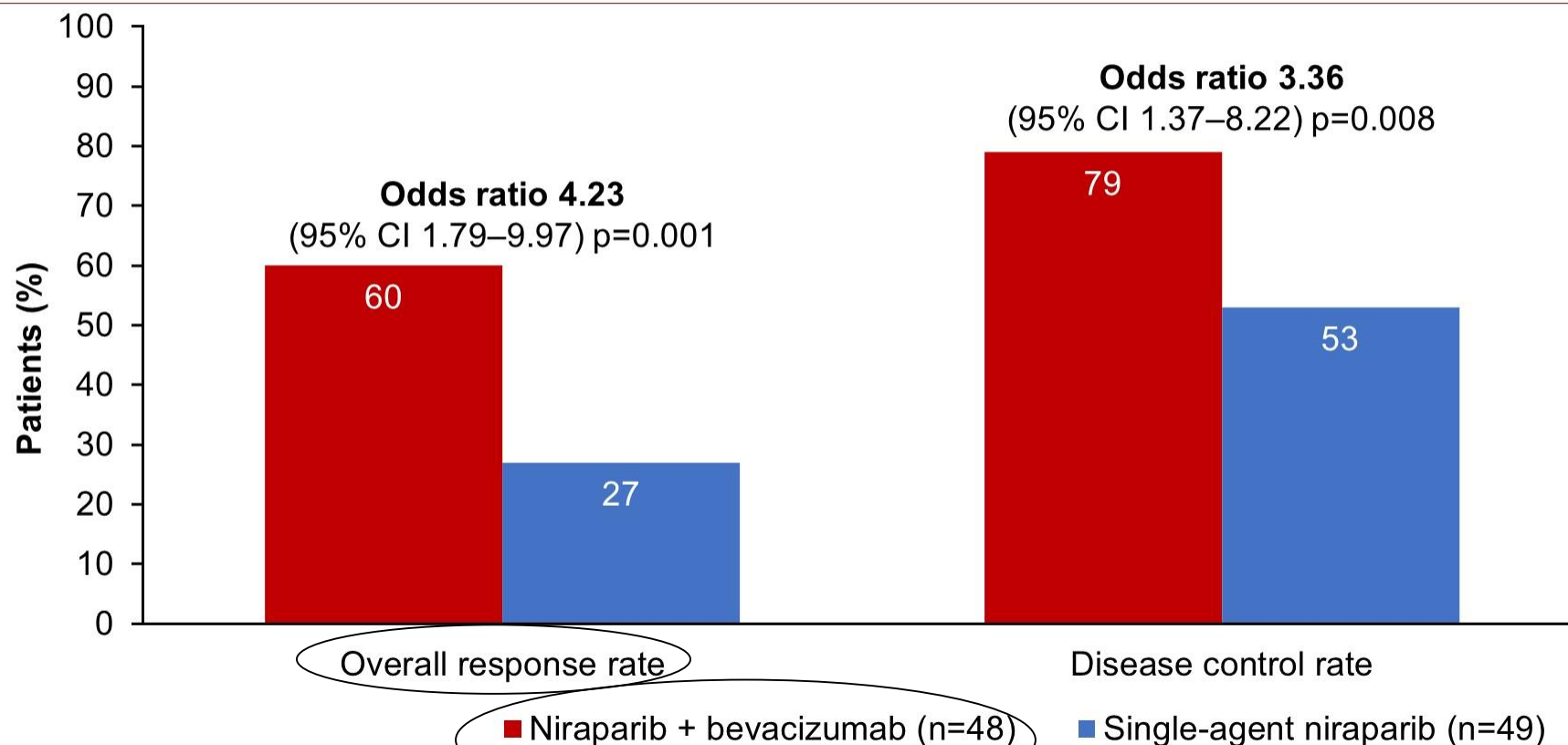
PFS by stratification factors: HRD status



PFS by *BRCA* status



Overall response and disease control rates

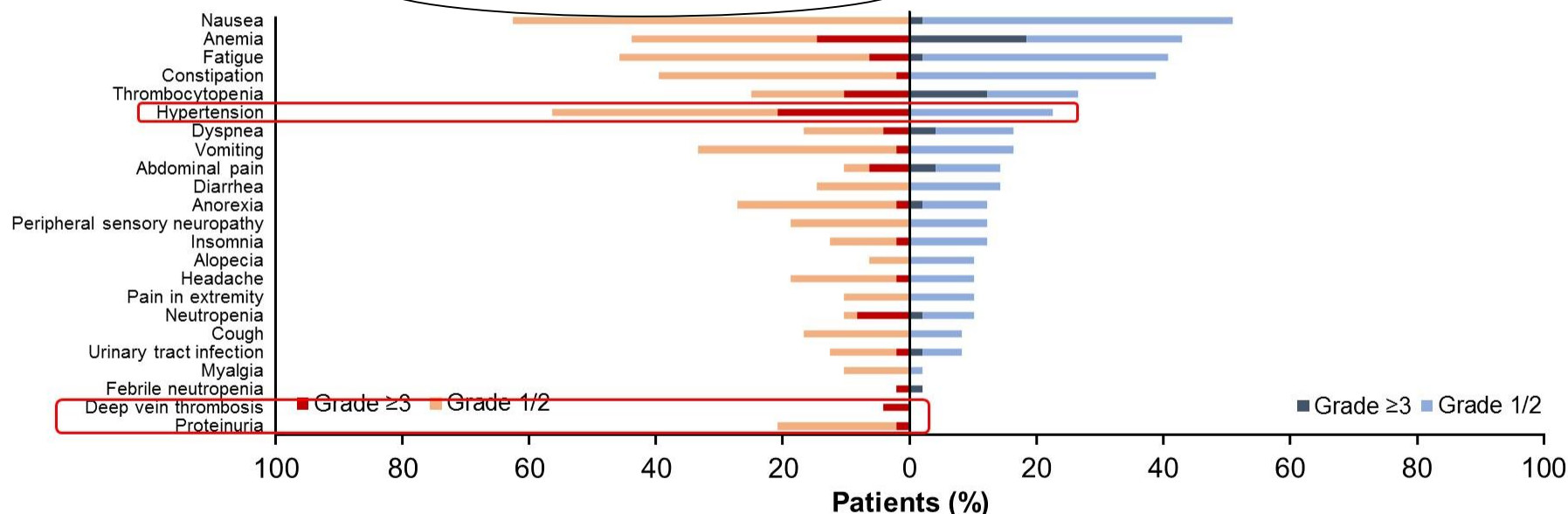


Summary of adverse events

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

Niraparib + bevacizumab

Single-agent niraparib



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

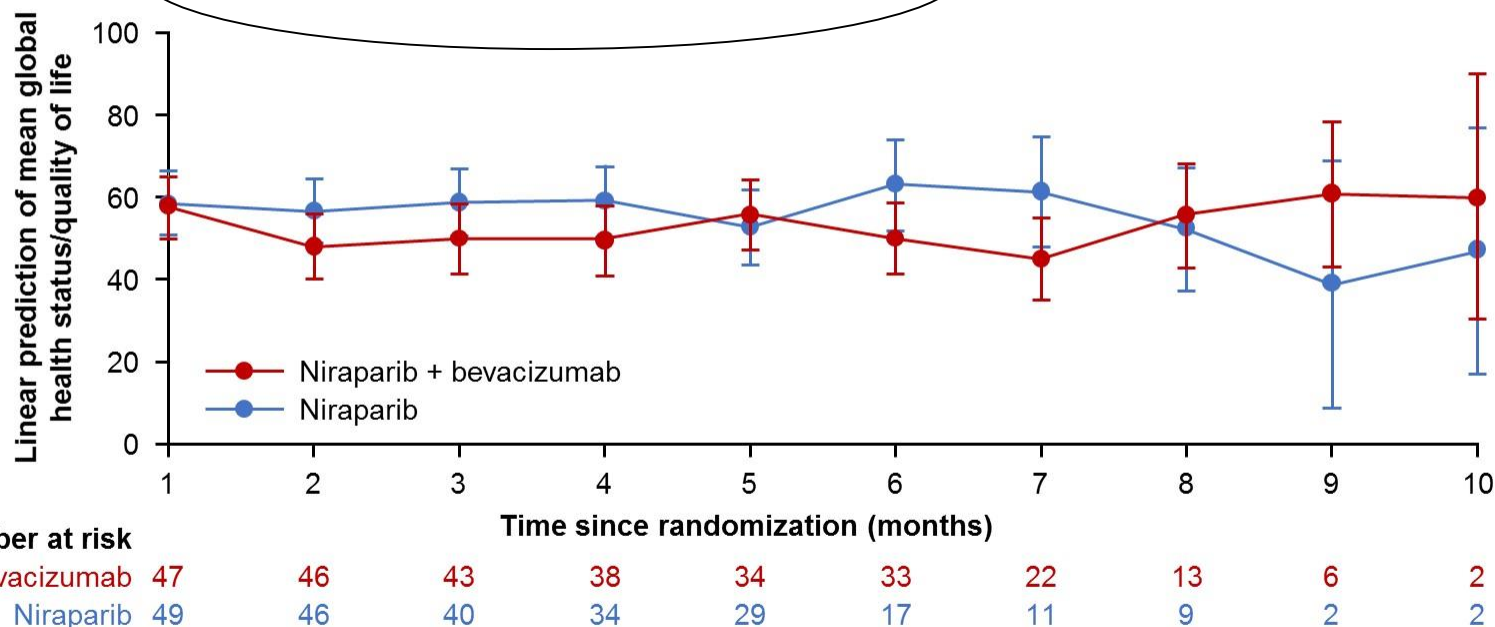
Number of niraparib dose reductions	Niraparib + bevacizumab (n=48)	Single-agent niraparib (n=49)
None	23 (48%)	21 (43%)
One (300 → 200 mg)	24 (50%)	27 (55%)
Two (300 → 200 → 100 mg)	1 (2%)	1 (2%)

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

NA = not applicable

Patient-reported outcomes

EORTC QLQ-C30 global health status/quality of life over time



EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Module

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

Ovarialkarzinom Elderly: Carboplatin \pm Paclitaxel

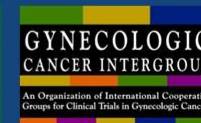


EWOC-1: A randomized trial to evaluate the feasibility of three different first-line chemotherapy regimens for vulnerable elderly women with ovarian cancer (OC): A GCIG-ENGOT-GINECO study

C Falandry¹, A-M Savoye², L Stefani³, F Tinquaut⁴, D Lorusso⁵, J Herrstedt⁶, E Bourbouloux⁷, A Floquet⁸, P-E Brachet⁹, A Zannetti¹⁰, M-A Mouret-Reynier¹¹, R Sverdlin¹², V D'hondt¹³, O Guillem¹⁴, O Cojocarasu¹⁵, L Venat-Bouvet¹⁶, F Rousseau¹⁷, A Lortholary¹⁸, E Pujade-Lauraine¹⁹, G Freyer²⁰

¹GINECO-Centre Hospitalier Lyon Sud, Pierre-Benite, France; ²GINECO-Institut Jean Godinot, Reims, France; ³GINECO-Centre Hospitalier Annecy Genevois, Pringy, France; ⁴GINECO Statistician - Institut de Cancérologie de la Loire, St. Priest En Jarez, France; ⁵MITO and Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy; ⁶Nordic Society of Gynecologic Oncology (NSGO) and Odense University Hospital, Odense, Denmark; ⁷GINECO-ICO René Gauducheau, Saint Herblain, France; ⁸GINECO and Institut Bergonié, Bordeaux, France; ⁹GINECO-Centre François Baclesse, Caen, France; ¹⁰GINECO-Centre Hospitalier de Cholet, Cholet, France; ¹¹GINECO-Centre Jean Perrin, Clermont-Ferrand, France; ¹²GINECO-Groupe Hospitalier Paris Saint Joseph, Paris, France; ¹³GINECO-Institut du Cancer de Montpellier, Montpellier, France; ¹⁴GINECO-Centre Hospital de Gap, Gap, France; ¹⁵GINECO-Centre Hospitalier du Mans, Le Mans, France; ¹⁶GINECO-Centre Hospitalier Universitaire Dupuytren, Limoges, France; ¹⁷GINECO-Institut Paoli Calmettes, Marseille, France; ¹⁸GINECO and Hôpital Privé du Confluent, Nantes, France; ¹⁹GINECO, Paris, France; ²⁰GINECO & Centre Hospitalier Lyon-Sud, Lyon, France

EudraCT N° 2013-000266-11
Clinicaltrial NCT02001272



PRESENTED AT: **2019 ASCO**
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PRESENTED BY: C FALANDRY

1

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

$$\text{GVS} = \sum \text{scores}$$

GVS \geq 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

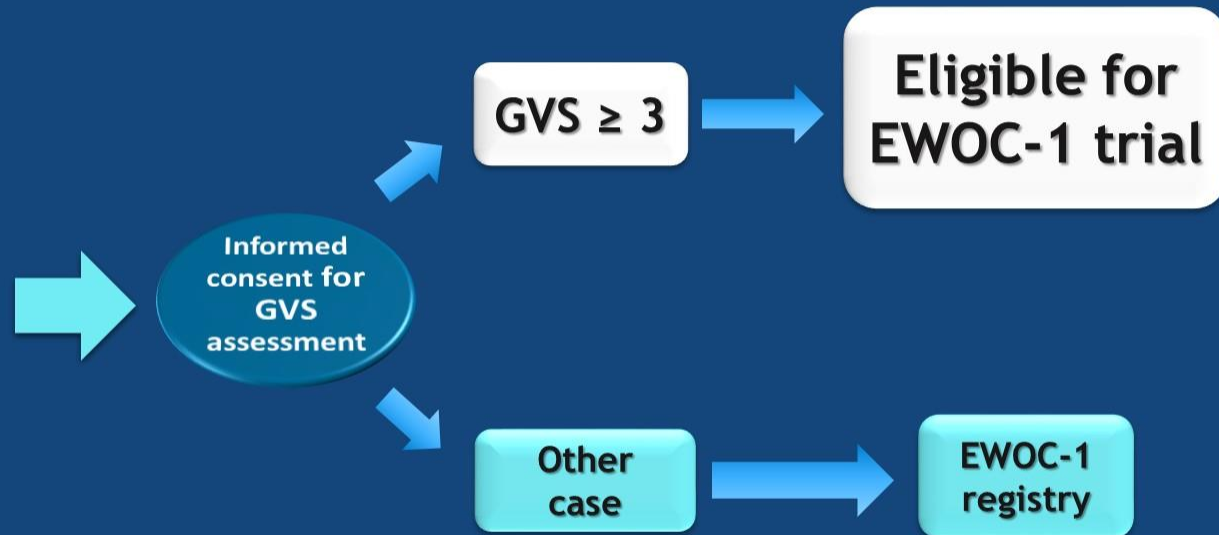
EWOC-1 design

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



EWOC-1 design

2- Patient randomization



**Eligible for
EWOC-1 trial**



6 cycles



**Arm A: 3-weekly
carboplatin-paclitaxel**

carboplatin AUC 5-6 + paclitaxel
175mg/m² q21

Arm B: 3-Weekly carboplatin

carboplatin AUC 5-6 q21

**Arm C: weekly
carboplatin-paclitaxel**

carboplatin AUC 2 + paclitaxel 60mg/m²
d1, d8, d15 q28

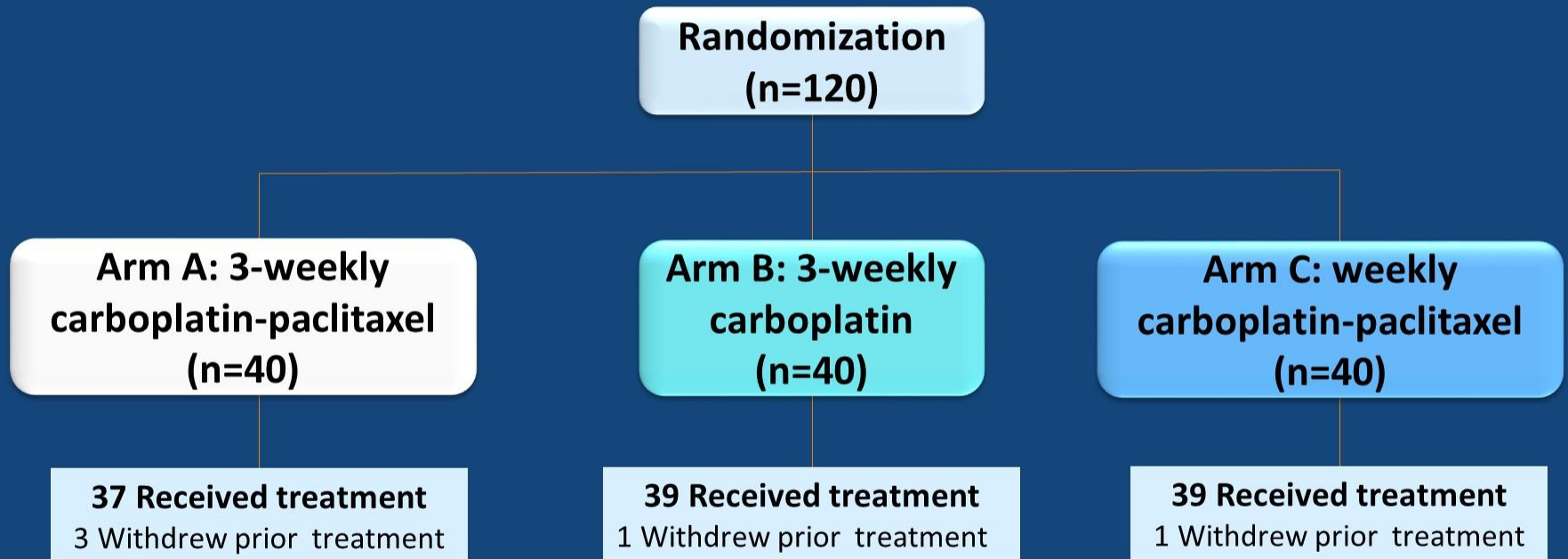
**FOLLOW-
UP**

Stratification parameters:

- Country
- Initial debulking surgery outcome

Randomisation according minimization

EWOC-1 CONSORT diagram



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)

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)

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%)

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)	

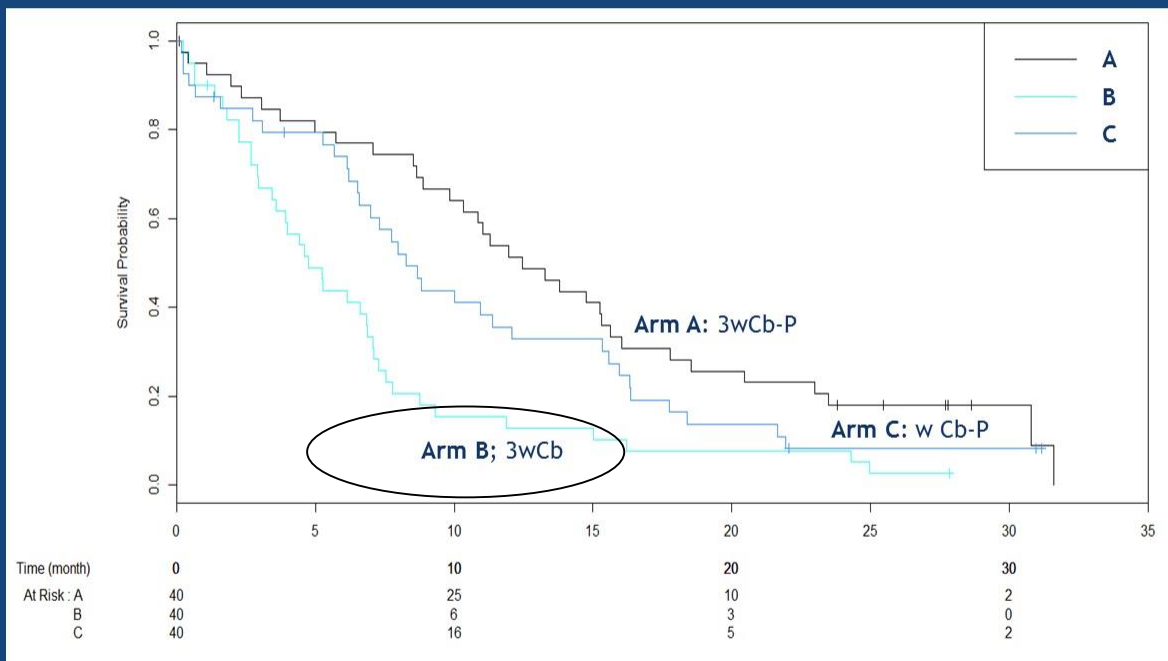
EWOC-1 treatment stopping: other reasons



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)

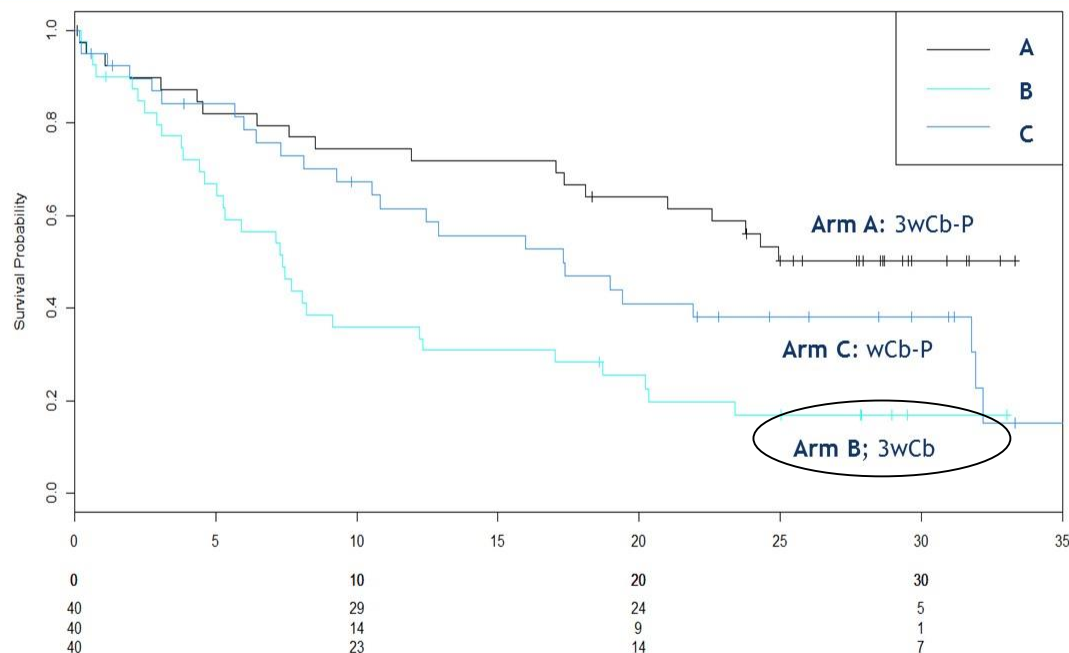
* p = 0.003

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		

EWOC-1 Overall survival

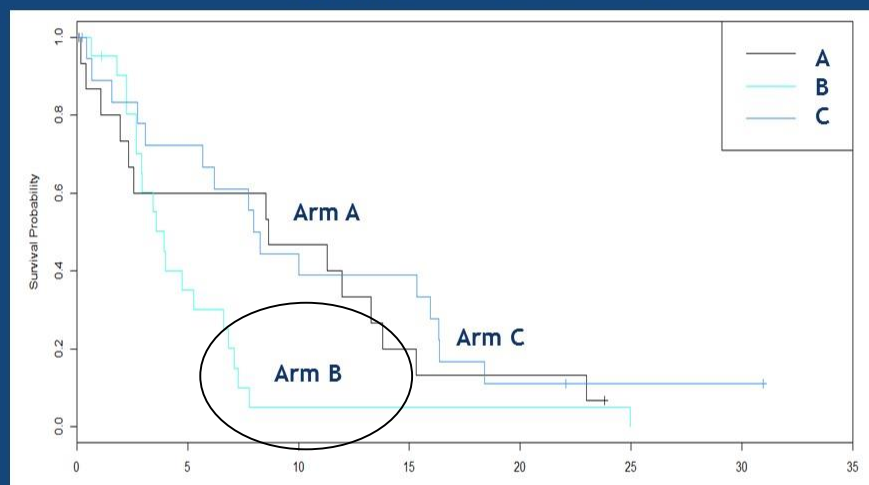


	Arm A	Arm B	Arm C
Events, N (%)	19 (47)	32 (80)	25 (62)
Median, mos (95% CI)	NR (21 - 32.2)	7.4 (5.3 - 32.2)	17.3 (10.8 - 32.2)
HR (95% CI)	1 (REF)	2.79 (1.57, 4.96)	1.6 (0.88, 2.92)
P Wald test	-	< 0.001	0.123
P Log-Rank	0.001		

NR: Not reached

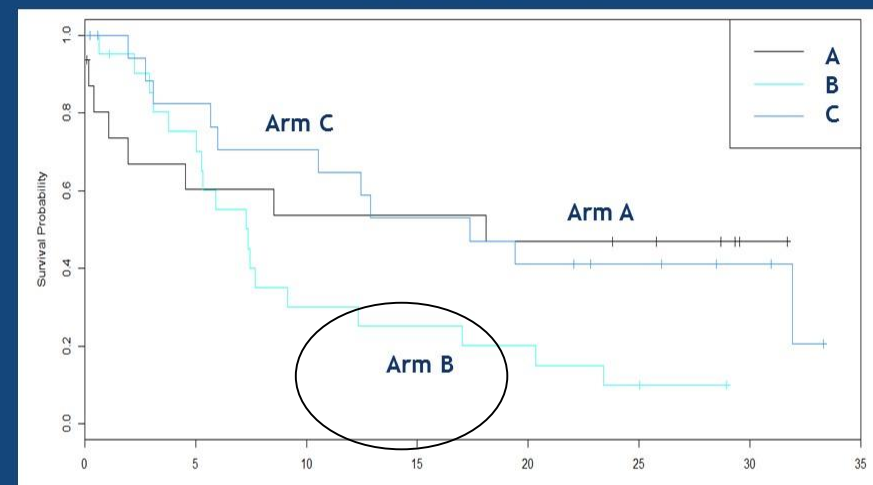
The carboplatin single agent arm is also worse even for the most vulnerable patients (GVS 4 & 5)

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		

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 ≥ 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

Zervixkarzinom

Zervixkarzinom

**Neoadjuvante Chemotherapie versus
definitive Radiochemotherapie**

Results from neoadjuvant chemotherapy followed by surgery
compared to chemoradiation for stage Ib2-IIb cervical cancer
EORTC GCG 55994

G. Kenter, S. Greggi, I. Vergote, D. Katsaros, F J. Kobiński, L.
Massuger, H. van Doorn, F. Landoni, J. van der Velden, E. Van Dorst,
N. Reed, N. Colombo, C. Coens, I. van Luijk, P. Ottevanger, A. Casado
Herráez

Trial Design

**Cervical carcinoma
of squamous or
adeno(squamous)
cell type**

**FIGO stage Ib2,
IIa >4cm, or IIb**

R

**Arm 1:
NACT + Sy**

**Neoadjuvant cisplatin-based chemotherapy
(≥ 225 mg/m²) followed by radical hysterectomy**

N=314

**Arm 2:
CTRTx**

**Concomitant radiation and chemotherapy
45-50 Gy plus boost + weekly ≥ 40 mg/m² cisplatin**

N=312

+
N=626

Endpoints:

- Primary: overall survival (OS) at 5 years
- Secondary: PFS, toxicity & QoL

Stratification:

- Age (<50 vs >50), Cell type, FIGO stage (1994), and Institution

Statistics:

OS at 5 years in the CTRTx arm assumed 67%. To detect a 10% difference with a 2-sided α of 5% and power of 80% a total sample size of 625 patients with 5 years of follow-up is needed.

Quality Assurance Program:

A quality assurance project was implemented to check the accuracy of data collection and investigate protocol adherence in the different treatment modalities.

Treatment period: CTC grade 3/4

N (%)	Treatment		Total (N=591)
	NACT+Sy (N=299)	CTRTx (N=292)	
	122 (40.8%)	66 (22.6%)	188 (31.8%)
Gastrointestinal	34 (11.4)	20 (6.8)	54 (9.1)
Blood/Bone Marrow	36 (12.0)	15 (5.1)	51 (8.6)
Infection	25 (8.4)	8 (2.7)	33 (5.6)
Cardiovascular	10 (3.3)	11 (3.8)	21 (3.6)
Renal/genitourinary	16 (5.4)	4 (1.4)	20 (3.4)
Hemorrhage	15 (5.0)	2 (0.7)	17 (2.9)
Constitutional	7 (2.3)	8 (2.7)	15 (2.5)
Dermatology	14 (4.7)	1 (0.3)	15 (2.5)
Metabolic	8 (2.7)	5 (1.7)	13 (2.2)
Neurology	9 (3.0)	2 (0.7)	11 (1.9)
Pain	3 (1.0)	7 (2.4)	10 (1.7)

Follow-up period: Chassagne score gr 3/4

N (%)	Treatment		Total (N=583)
	NACT+Sy (N=293)	CTRTx (N=290)	
	44 (15.0%)	60 (20.7%)	104 (17.8%)
Small bowel	5 (1.7)	21 (7.2)	26 (4.5)
Bladder and urethra	13 (4.4)	11 (3.8)	24 (4.1)
Ureter	12 (4.1)	11 (3.8)	23 (3.9)
Uterus-vagina-vulva	6 (2.0)	14 (4.8)	20 (3.4)
Colon (non sigmoid)	5 (1.7)	8 (2.8)	13 (2.2)
Pelvic soft tissues	6 (2.0)	5 (1.7)	11 (1.9)
Rectum	4 (1.4)	5 (1.7)	9 (1.5)
Sigmoid colon	1 (0.3)	5 (1.7)	6 (1.0)
Bone	4 (1.4)	2 (0.7)	6 (1.0)
Peripheral nerves	3 (1.0)	3 (1.0)	6 (1.0)
Hemopoietic tissue	2 (0.7)	2 (0.7)	4 (0.7)
Non specific abdominal	1 (0.3)	1 (0.3)	2 (0.3)
Vesicular	1 (0.3)	1 (0.3)	2 (0.3)
Stomach and duodenum	0 (0.0)	1 (0.3)	1 (0.2)
Cutaneous	0 (0.0)	1 (0.3)	1 (0.2)

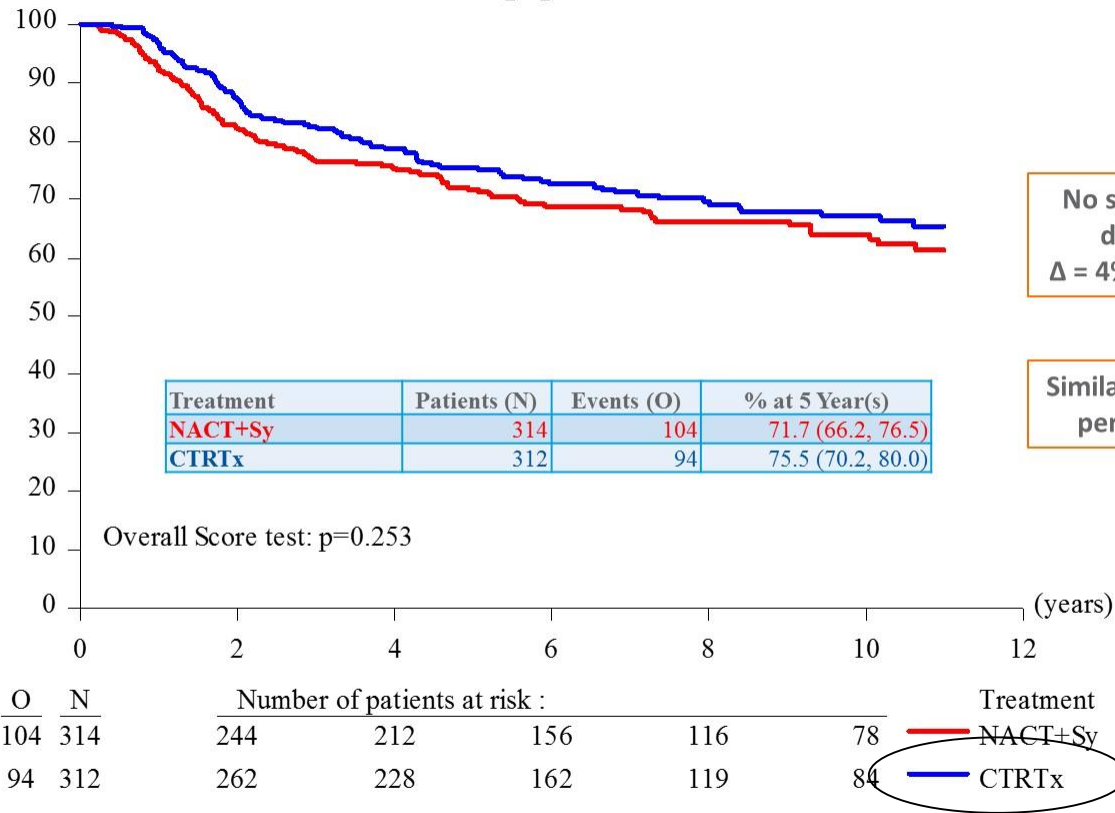
Two patients in CTRTx arm died due to complications:

- Chronic small bowel obstruction + malabsorption eventually death
- Infection following surgery for rectal stricture.

Adjuvant treatment after normal protocol completion: 27% and 8%

	NACT+Sy –arm (222)		CTRTx-arm (257)	
	N	%	N	%
No adjuvant treatment	160	73	237	92
Radiotherapy	32	14		
Surgery			10	4
Combination	28	13	10	4

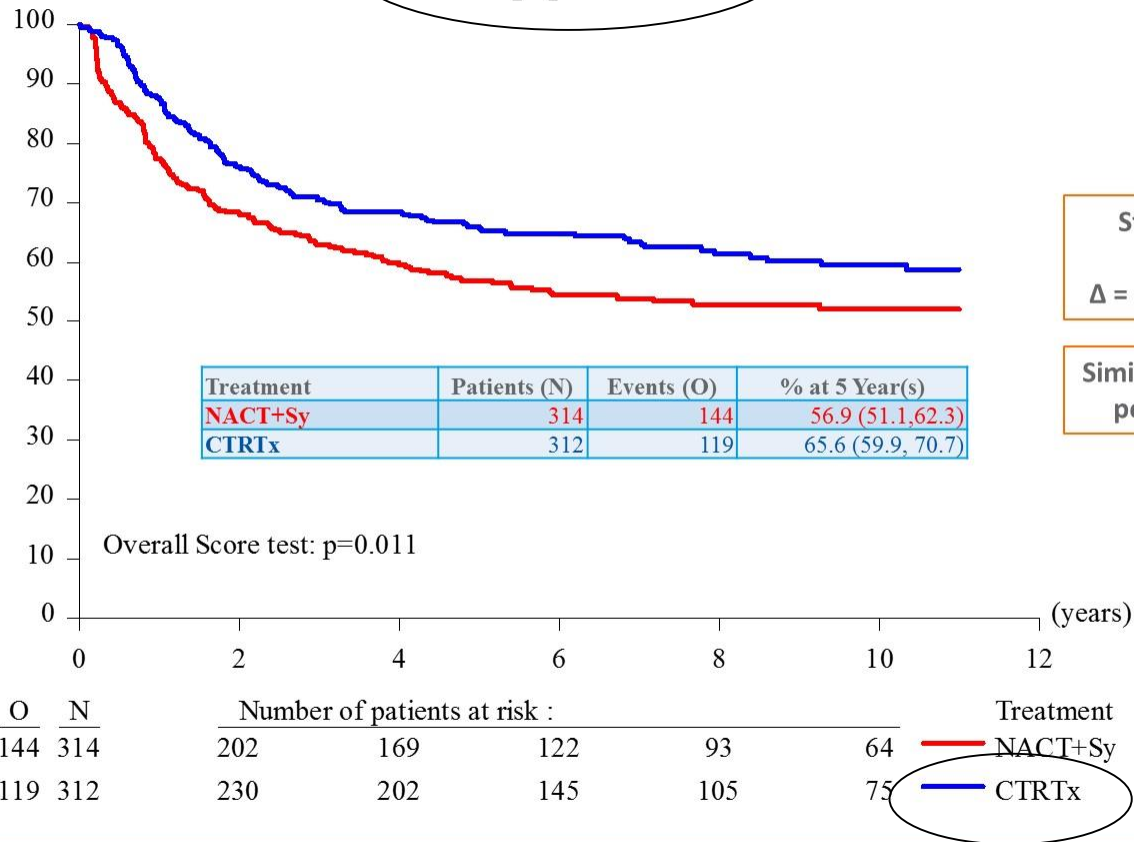
Overall survival ITT population



No statistically significant
difference at year 5
 $\Delta = 4\%$ (-3% - 12%); $p=0.297$

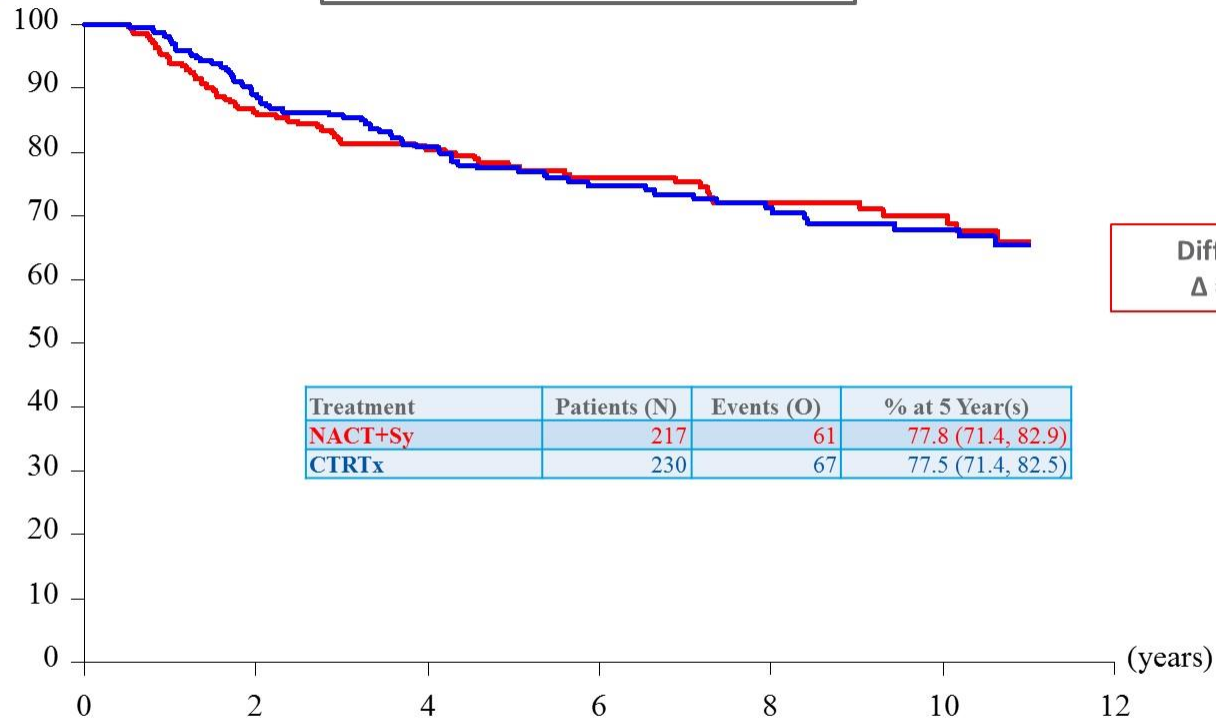
Similar results in eligible and
per protocol population

PFS
ITT population



Overall survival

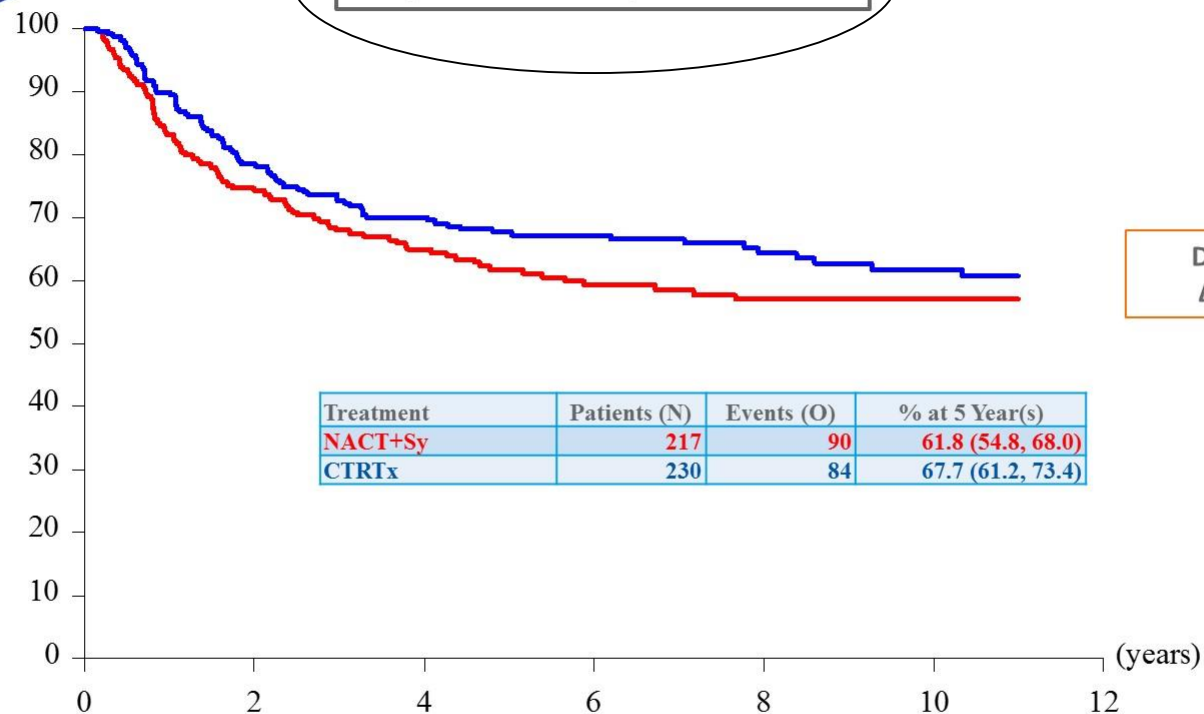
On patients who completed treatment



O	N	Number of patients at risk :						Treatment
61	217	179	158	117	84	58		NACT+Sy
67	230	201	174	121	89	63		CTRTx

PFS

On patients who completed treatment



Treatment	Patients (N)	Events (O)	% at 5 Year(s)
NACT+Sy	217	90	61.8 (54.8, 68.0)
CTRTx	230	84	67.7 (61.2, 73.4)

O	N	Number of patients at risk :					Treatment
90	217	155	129	90	66	48	NACT+Sy
84	230	178	154	110	80	57	CTRTx

Summary and conclusions

- RCT in 626 patients with cervical cancer stage Ib2-IIb
- Median FU 8 years 198/626=32% death and 263 = 42% events
- OS 72% in NACT+Sy arm and 76% in CTRTx arm (*difference not stat sign*)
- PFS 57% in NACT+Sy arm and 66% in CTRTx arm (*difference stat sign*)
- Difference in PFS disappears for patients completing total treatment
- Trend for better results in NACT+Sy arm for stage Ib2
- Trend for better results for CTRTx arm 2 for stage IIb, BMI<25 and age> 50 yr
- Trend for better results in NACT+ Sy arm for combination chemo
- Short term gr 3 and 4 toxicity higher in NACT+Sy arm (41 vs 22 %)
- Long term toxicity higher in CTRTx arm (15 vs 21%)

Endometriumkarzinom



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 Mileschkin on behalf of Australia New Zealand Gynaecological Oncology Group (ANZGOG).

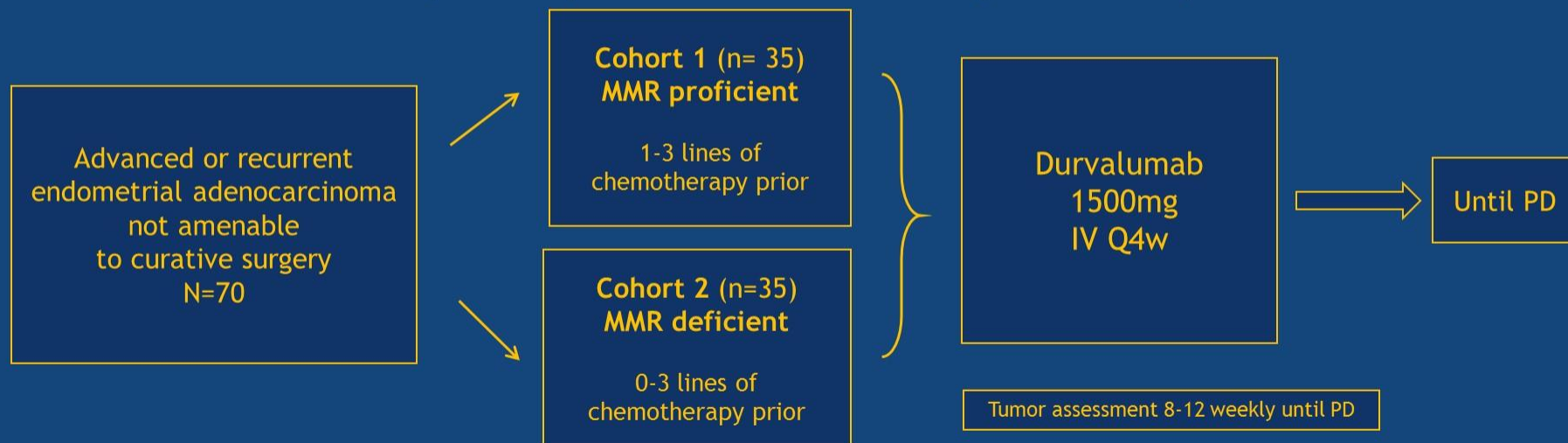
Rationale

- Endometrial cancer (EC) is a common gynaecological cancer with risk factors including:
 - Conditions associated with hyper-estrogenism, hyper-insulinaemia and hereditary syndromes
- Advanced EC (AEC) progressing after ≥ 1 lines of chemotherapy
 - Area of unmet need
 - Objective tumour response rates $\leq 20\%$
- 15-20% of ECs are associated with mismatch repair deficiency (dMMR) due to:
 - Acquired hypermethylation
 - Germline mutation
 - Somatic mutation

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

Key inclusion criteria

- Advanced or recurrent endometrial adenocarcinoma, not amenable to curative therapy
 - Known MMR status tumor tissue by IHC
 - **MMR proficient: 1-3 lines of chemotherapy prior allowed**
 - **MMR deficient: 0-3 lines of chemotherapy prior allowed**
- Tumour tissue (FFPE) available for PD-L1 testing with a repeat core biopsy if the only available tumour tissue sample was obtained before previous chemotherapy or > 1 year previously
- Measurable disease by RECIST v1.1
- ECOG performance status of 0-2
- Adequate organ functions
- No contraindication to immunotherapy

Baseline characteristics

Characteristic	N =71	
	MMR deficient (n=35)	MMR proficient(n=36)
Median age (range)	66 (36-76)	69 (37-81)
ECOG		
0	18 (51%)	17 (47%)
1	14 (40%)	19 (53%)
2	3 (9%)	-
Grade at diagnosis		
1	9 (26%)	6 (17%)
2	16 (47%)	4 (11%)
3	9 (26%)	26 (72%)
Pathology		
Endometrioid	33 (94%)	21 (58%)
Serous	-	11 (31%)
Others	2 (6%)	4 (11%)
Prior surgery	31 (89%)	32 (89%)
Prior radiotherapy	26 (74%)	21 (58%)

Baseline characteristics

Characteristic	N =71	
	MMR deficient (n=35)	MMR proficient(n=36)
Median age (range)	66 (36-76)	69 (37-81)
ECOG		
0	18 (51%)	17 (47%)
1	14 (40%)	19 (53%)
2	3 (9%)	-
Grade at diagnosis		
1	9 (26%)	6 (17%)
2	16 (47%)	4 (11%)
3	9 (26%)	26 (72%)
Pathology		
Endometrioid	33 (94%)	21 (58%)
Serous	-	11 (31%)
Others	2 (6%)	4 (11%)
Prior surgery	31 (89%)	32 (89%)
Prior radiotherapy	26 (74%)	21 (58%)

Baseline characteristics

Characteristic	N =71	
	MMR deficient (n=35)	MMR proficient(n=36)
Median age (range)	66 (36-76)	69 (37-81)
ECOG		
0	18 (51%)	17 (47%)
1	14 (40%)	19 (53%)
2	3 (9%)	-
Grade at diagnosis		
1	9 (26%)	6 (17%)
2	16 (47%)	4 (11%)
3	9 (26%)	26 (72%)
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Prior radiotherapy	26 (74%)	21 (58%)

Baseline characteristics- Previous therapy

Characteristic	N =71	
	MMR deficient (n=35)	MMR proficient (n=36)
Previous chemotherapy		
Platinum doublets	18 (51%)	34 (94%)
Platinum monotherapy	3 (9%)	5 (14%)
Taxane monotherapy	- -	3 (8%)
Doxorubicin/ liposomal doxorubicin	1 (3%)	4 (11%)
Other cytotoxic chemotherapy	1 (3%)	2 (6%)
Previous hormonal therapy	2 (6%)	5 (14%)
Previous bevacizumab	- -	2 (6%)
Hormone status		
ER+	26 (93%)	19 (66%)
PR+	21 (84%)	14 (58%)
Lines of prior systemic treatment for advanced disease*		
0	21 (60%)	3 (8%)
1	13 (37%)	23 (64%)
≥2	1 (3%)	10 (27%)

* Excluding hormone, bevacizumab, adjuvant and neo-adjuvant chemotherapy received ≥12 months prior to registration

Baseline characteristics- Previous therapy

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* Excluding hormone, bevacizumab, adjuvant and neo-adjuvant chemotherapy received ≥12 months prior to registration

Results: MMR status

MMR IHC result	N
Proficient	36
Deficient	35
MLH1 and PMS2 loss	27 (77%)
MSH2 and MSH6 loss	4 (11%)
Isolated PMS2 loss	1 (3%)
Isolated MSH6 loss	2 (6%)
PMS2 and MSH6 loss	1 (3%)
Total	71

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

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

Take home messages

- As a single agent, anti-PDL1 immunotherapy with durvalumab appears:
 - active in dMMR: RR 43% overall, 52% 1st line, 31% 2nd line
 - minimally active in pMMR: RR 3%
- Few immune-related adverse events
- These results warrant further exploration of immune therapy in the setting of advanced endometrial cancer.

Zusammenfassung:

OVAR

PARP-Inhibition Option auch anstelle Chemotherapie

PARP + Angiogeneinhibitor chemotherapiefreie Option

Elderly: Carboplatin-Paclitaxel effektiver als Carbo Mono

ZERVIX

Neoadjuvante Chemotherapie beim IB2 + IIB Ca unterlegen
einer definitiven RT-CT

ENDOMETRIUM

PDL1-Inhibition hoffnungsvolle Signale