HIGHLIGHTS IN GYNECOLOGICAL CANCER

DANIELA SAMBATARO
UOC Oncologia Medica
ARNAS GARIBALDI Catania

DISCLOSURES

Tesaro

Astra Zeneca

Teva

Italfarmaco

MSD

Pharmamar

Roche

Principal invastigator: ATHENA, FIRST

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]

OBIETTIVO PRIMARIO:

FATTIBILITA' DI 3 REGIMI CHEMIOTERAPICI

> 70 anni GVS (GERIATRIC VULNERABILITY SCORE –GINECO-) ≥ 3

OBIETTIVI SECONDARI: safety, PFS, OS, QoL, fattibilità interval debulking e terapia adiuvante post chirurgica, geriatric covariates e aging biomarker

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

EWOC-1 design

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

Stratification parameters:
- Country
- Initial debulking surgery outcome

Randomisation according minimization

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

Presented By Claire Falandry at 2019 ASCO Annual Meeting

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%)**

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)

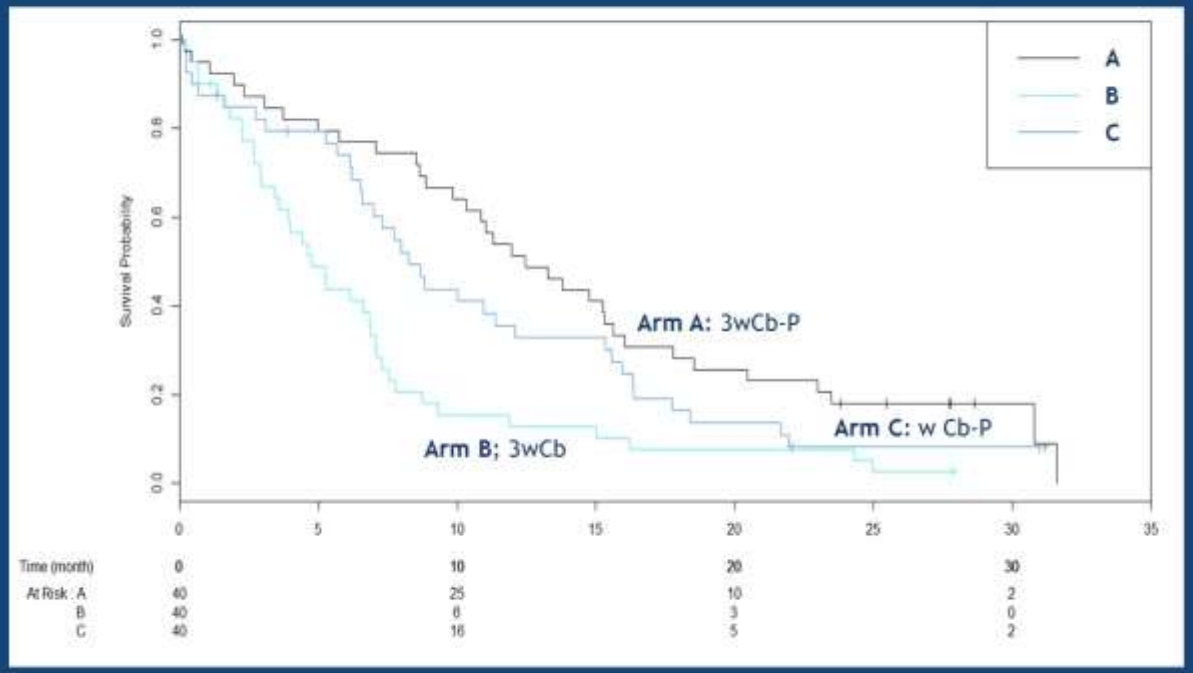
* p = 0.003

EWOC-1 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)**	

Presented By Claire Falandry at 2019 ASCO Annual Meeting

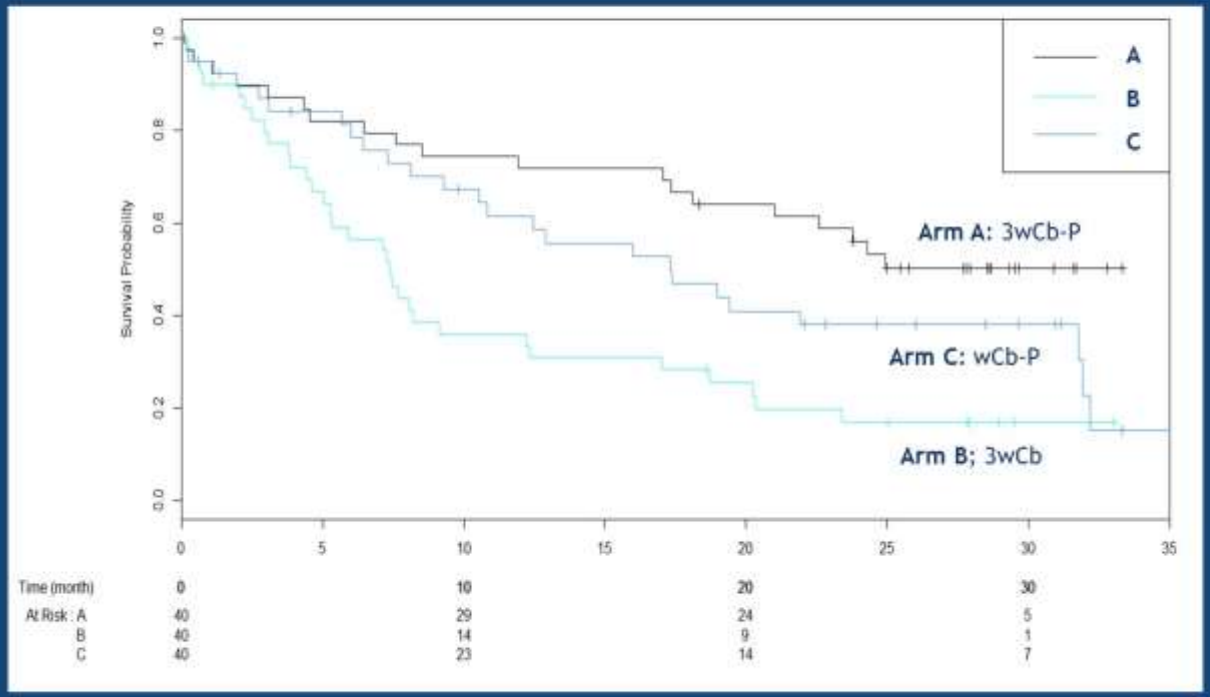
EWOC-1 Progression-free survival



	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	

Presented By Claire Falandry at 2019 ASCO Annual Meeting

EWOC-1 Overall survival



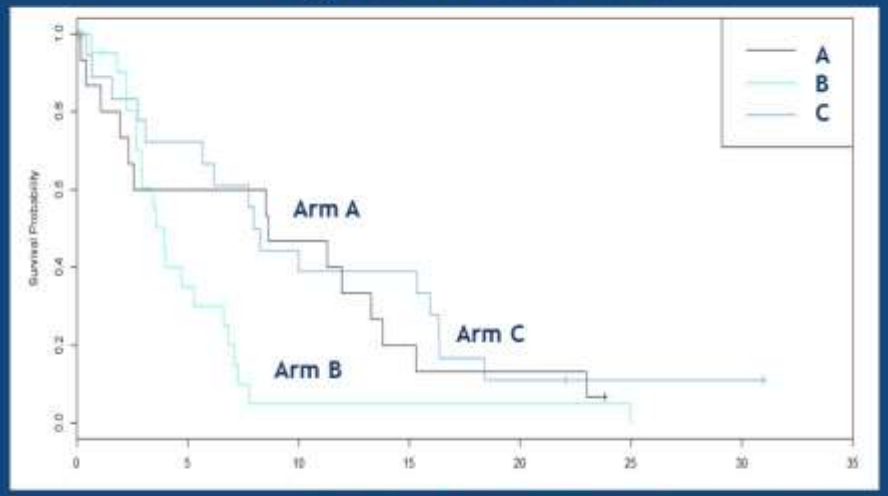
	Arm A	Arm B	Arm C
Events, N (%)	19 (47)	32 (80)	25 (62)
Median, mos (95% CI)	NR (21 - 32.2)	7.4 (5.3 - 32.2)	17.3 (10.8 - 32.2)
HR (95% CI)	1 (REF)	**2.79 (1.57,4.96)**	1.6 (0.88,2.92)
P Wald test	-	**< 0.001**	0.123
P Log-Rank		0.001	

NR: Not reached

Presented By Claire Falandry at 2019 ASCO Annual Meeting

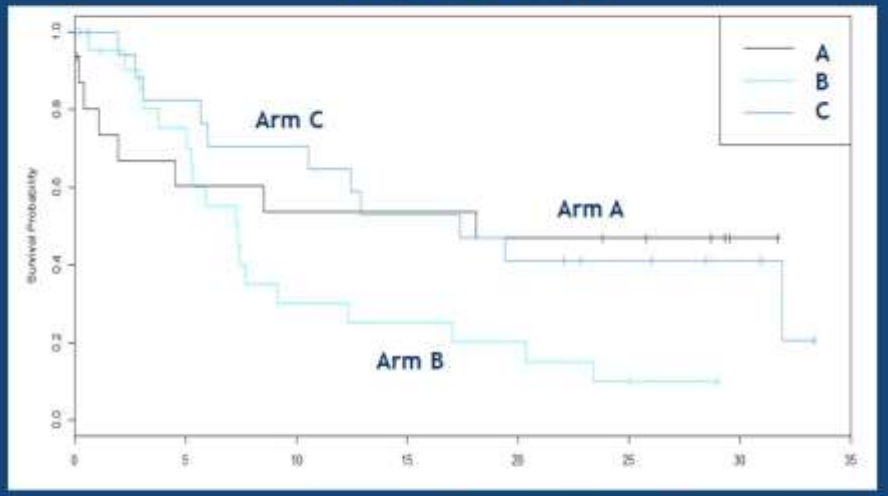
The carboplatin single agent arm is also worse even for the most vulnerable patients (GVS 4 & 5)

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	

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: C FALANDRY

Presented By Claire Falandry at 2019 ASCO Annual Meeting

EWOC-1

ANCHE NELLE PAZIENTI ANZIANE FRAGILI DOVREBBE ESSERE EFFETTUATO UN REGIME CON CARBOPLATINO/PACLITAXEL

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

CARCINOSARCOMA: BACKGROUND

- Rara e aggressiva
- Verosimile origine monoclonale
- Carcinosarcoma ovarico poco studiato

	schema	n	ORR	mPFS (mesi)	mOS (mesi)
GOG 161 Homesley 2007	Ifo vs ifo/paclitaxel	91 vs 88	29% vs 45% p =0.02	3.6 vs5.8 p=0.03	8.4 vs 13.5 p=0.03
GOG 232B Powell 2010	Paclitaxel /carboplatino	46	54%	7.6	14.7

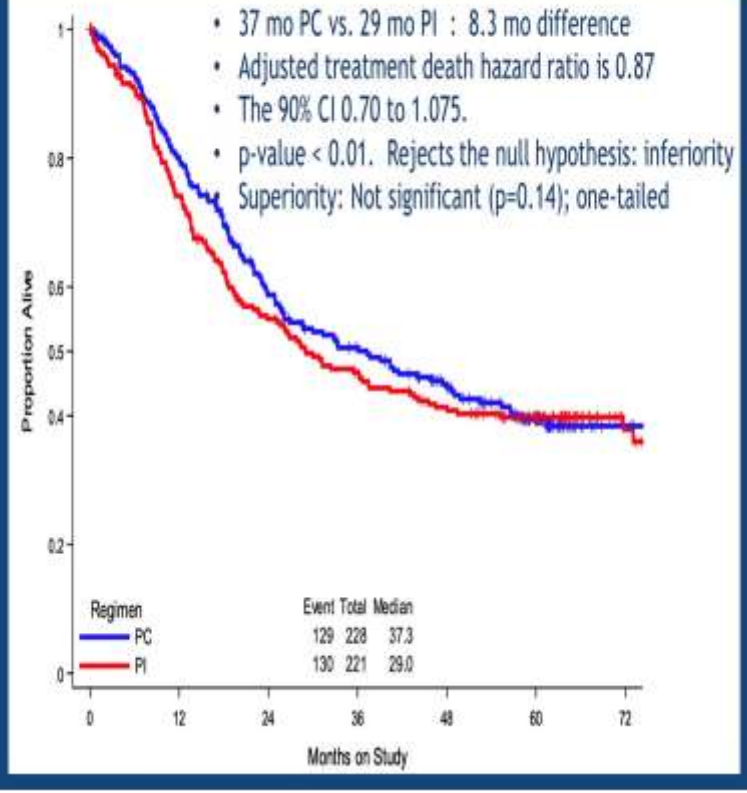
A randomized phase 3 trial of paclitaxel (P) plus carboplatin (C) versus paclitaxel plus ifosfamide (I) in chemotherapy-naive patients with stage I-IV, persistent or recurrent carcinosarcoma of the uterus or ovary: An NRG Oncology trial.

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

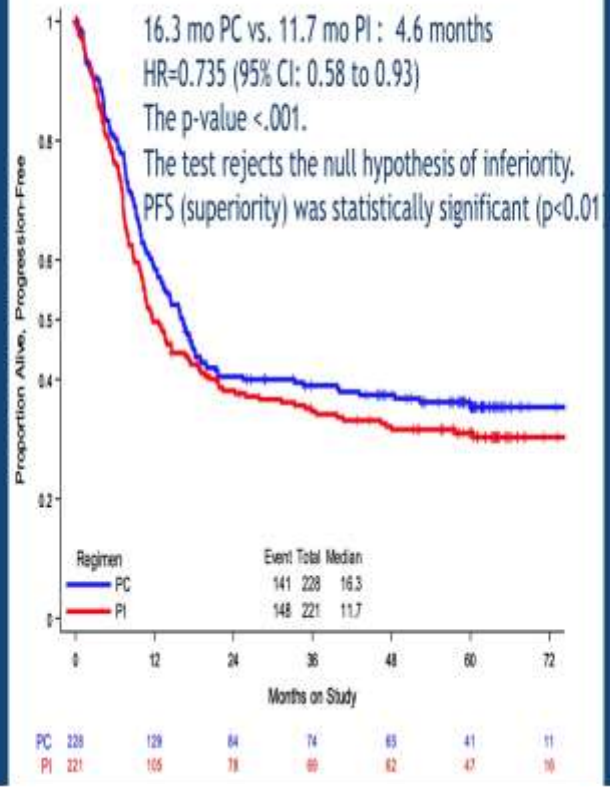
GOG 0261 Statistical Design: intention-to-treat analysis among eligible patients non-inferiority design

- 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

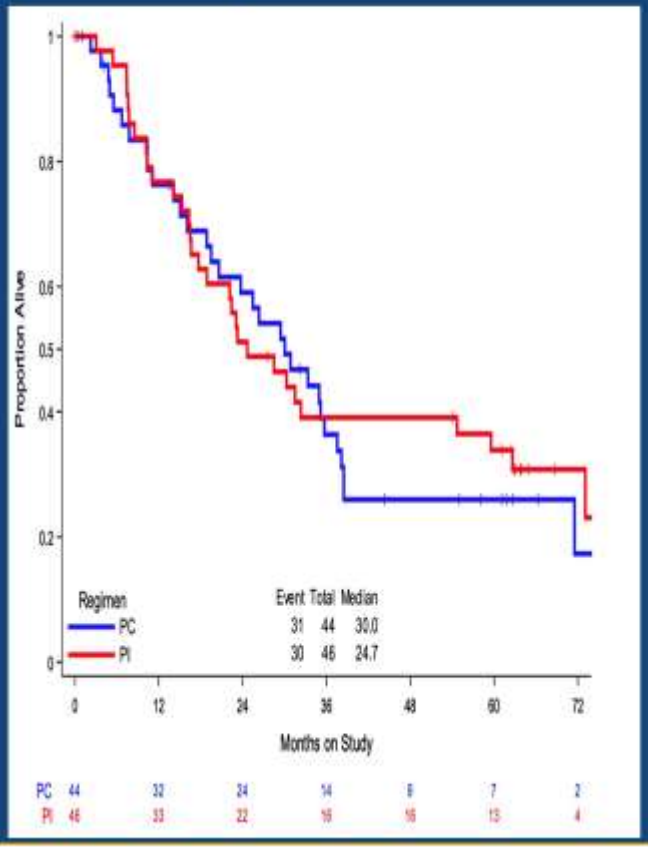
GOG 0261: Primary Outcome Uterine Cohort: OS



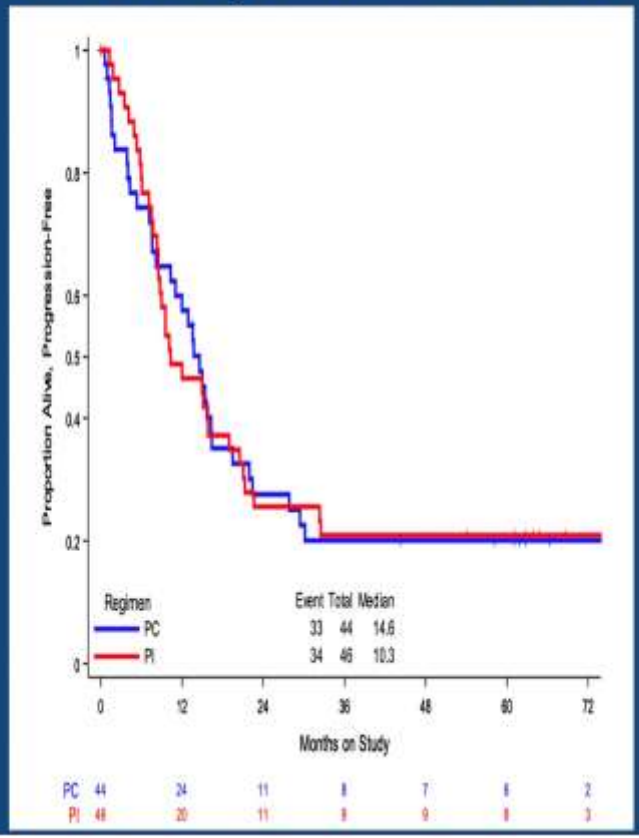
GOG 0261: Secondary Outcomes Uterine Cohort: PFS



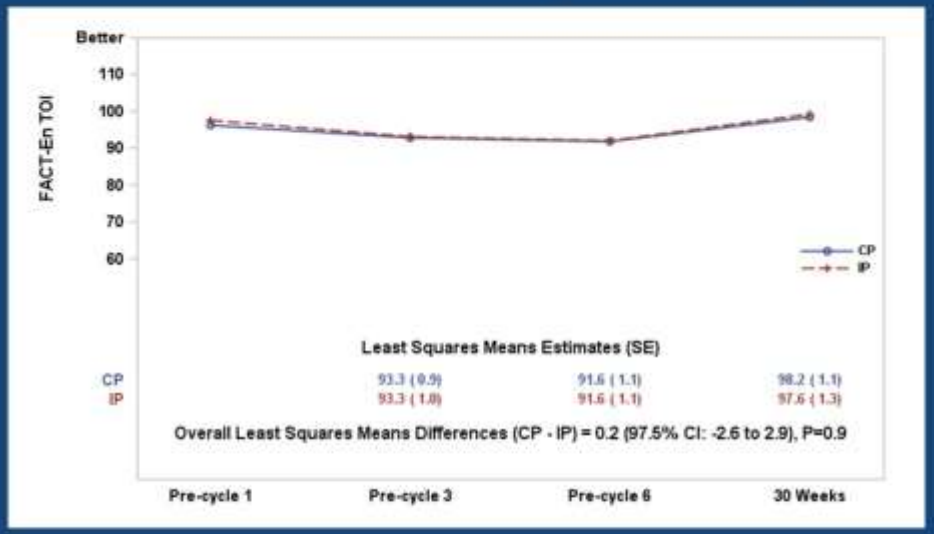
GOG 0261: Primary Outcome Ovarian Cohort: OS

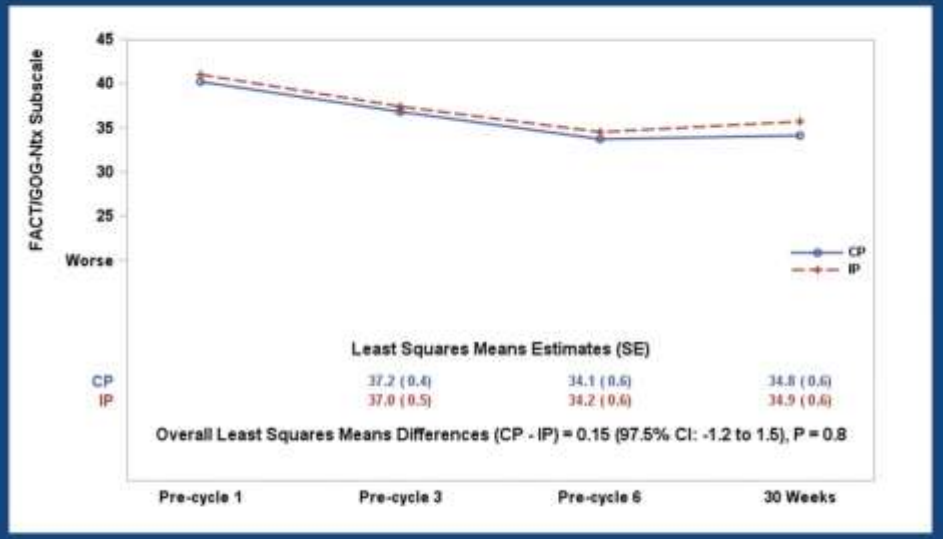


GOG 0261: Secondary Outcomes Ovarian Cohort: PFS



GOG 0261: QOL analysis





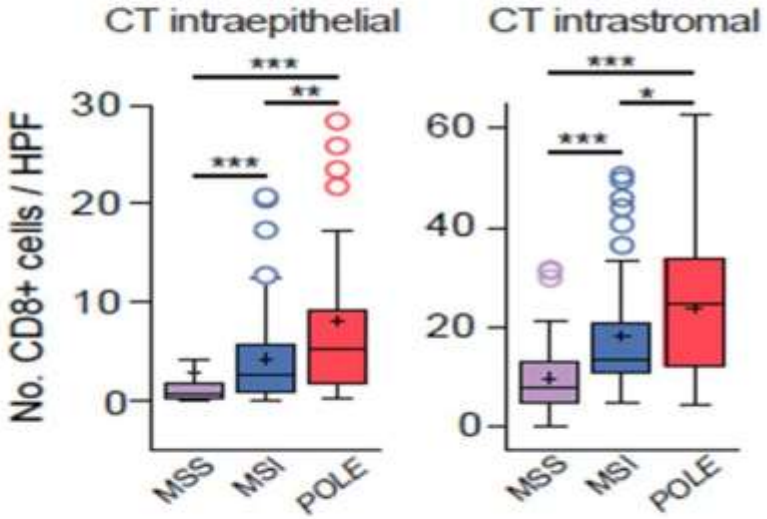
The patient-reported quality of life measured with the FACT-En TOI and the patient-reported neurotoxicity symptoms measured with the FACT/GOG-Ntx subscale were not significantly different.

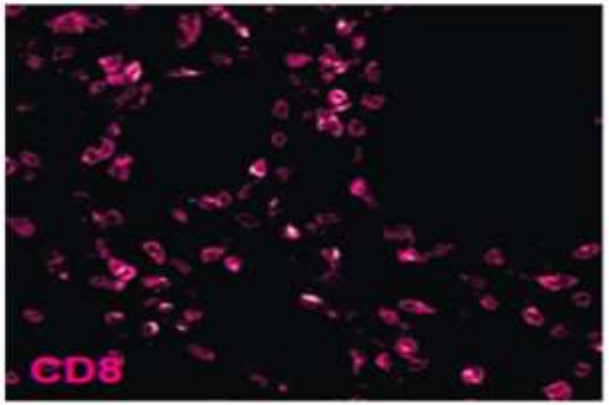
Wenzel, J Clin Oncol 2007

Endometrial Cancer (EC) – Four molecular subtypes

(Integrated genomic, transcriptomic and proteomic characterization)

POLE ultra-mutated *(15x > vs MSI)*	MSI hyper-mutated *(8x > vs MSS)*	Copy number low - endometrioid - *(MSS group)*	Copy number high - serous-like -





CD8 = Cytotoxic T cells (CTL)

Kandoth et al., Nature 2013

Yen, Anal and Gynecol Oncol 2015
Eggink and van Gool et al, Oncoimmunology 2017
Bellone et al, Gynecologic Oncology, 2017

Presented By Kimberly Levinson at 2019 ASCO Annual Meeting

Single Agent IO

	Patient Population	Agent	Results
Single agent IO			
Le et al. (2018)	MMRd tumors (2EC pts included)	Pembrolizumab	ORR 71%
Ott et al. (2017) Keynote 028	24 PD-L1+ pts	Pembrolizumab	ORR 13%
Keynote 158	Multicohort MSI-H (17EC pts included)	Pembrolizumab	ORR 37.7%
Fader et al. (2016)	MMRd tumors recurrent EC	Pembrolizumab	ORR 56% DCR 88.9%
Santin et al. (2016)	2pts (POLE and MSI-H)	Nivolumab	Prolonged response (>7mo) in 2 patients
Hasegawa et al. (2018)	23 Metastatic EC pts	Nivolumab	ORR 23% PFS 3.6mo
Fleming et al. (2017)	15 Metastatic EC pts	Atezolizumab	ORR 13% (1MSI-H) PFS 1.7mo
GARNET	MSI-H recurrent/advanced EC	TSR-042	ORR 52%

Presented By Kimberly Levinson at 2019 ASCO Annual Meeting

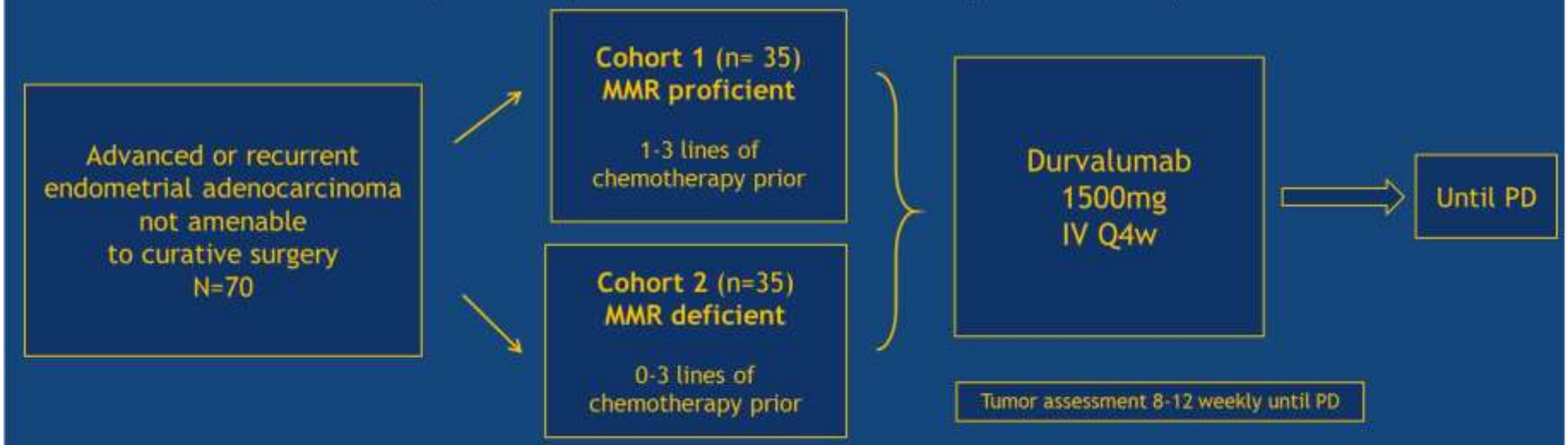
Phase 2 trial of Durvalumab in Advanced Endometrial cancer (PHAEDRA)

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

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%)

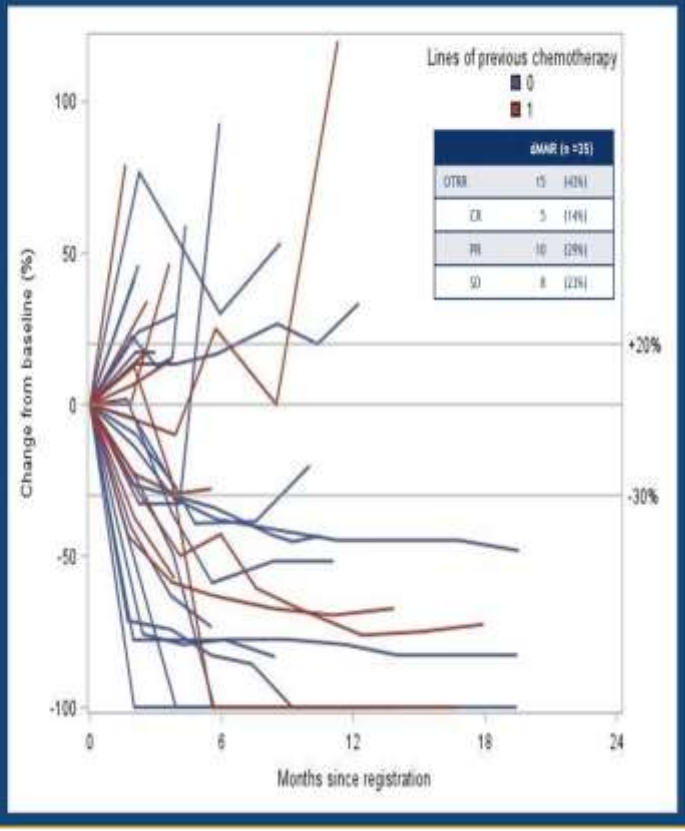
Presented By Yoland Antill at 2019 ASCO Annual Meeting

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

Spider plot: dMMR (n=35)



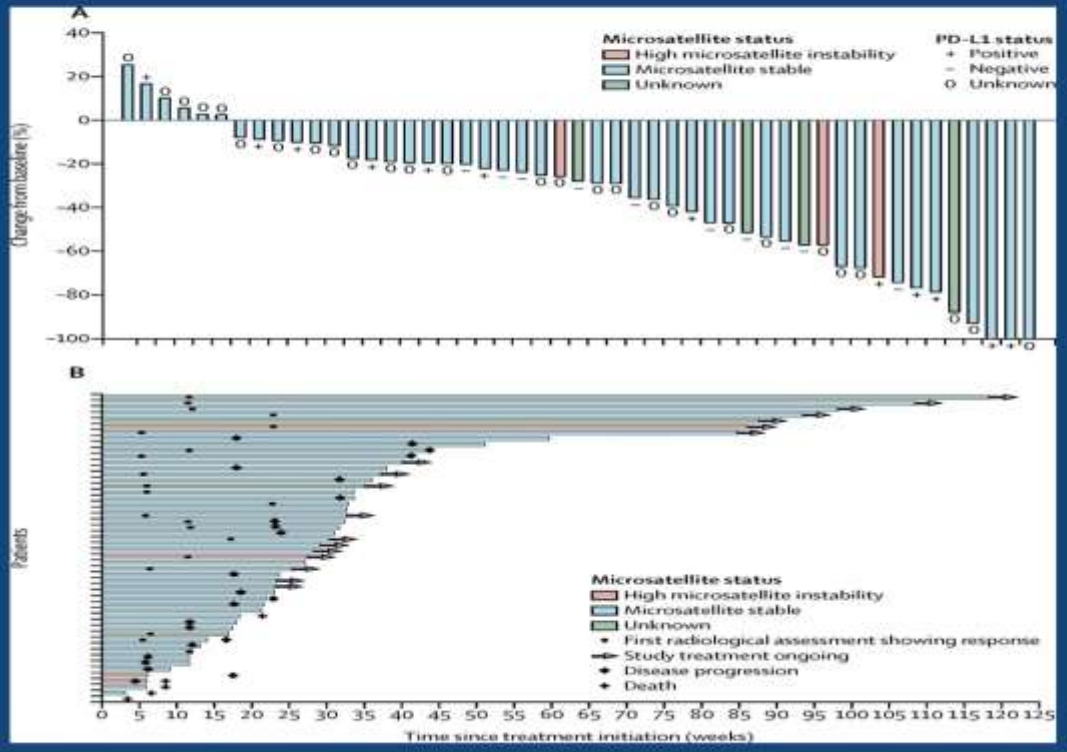
	dMMR (n =35)	pMMR (n=35)*
OTRR	15 (43%)	1 (3%)
DCR at 16 weeks	21 (60%)	7 (20%)
Disease Control Rate	23 (66%)	10 (29%)

CHECKPOINT INHIBITORS CARCINOMA ENDOMETRIO

- ≤20% ORR CARCINOMA ENDOMETRIO AVANZATO IN PROGRESSIONE
- 15-20% MISMATCH REPAIR DEFICIENCY (dMMR)

  IPERMETILAZIONE -MUTAZIONE GERMLINE O SOMATICA
- DURVALUMAB E' ATTIVO dMMR
- dMMR IN IHC CORRELA CON LA RISPOSTA

Study 111/Keynote 146: Lenvatinib plus pembrolizumab in advanced endometrial cancer: interim analysis of a multicentre, open-label, single-arm, phase 2 trial



Combination granted breakthrough designation by FDA in 8/6/2018

Lancet Oncol. 2019 May;20(5):711-718

Presented By Vicky Makker at 2019 ASCO Annual Meeting

Abstract # TPS5607

KEYNOTE-775/E7080-G000-309: Randomized, open-label, phase 3 study to evaluate efficacy and safety of lenvatinib and pembrolizumab vs treatment of physician's choice in patients with advanced EC in patients with advanced EC- NCT03517449

Vicky Makker, Antonio Casado Herraez, Carol Aghajanian, Keiichi Fujiwara, Sandro Pignata, Richard T. Penson, Corina E. Dutcus, Matthew Guo, Lea Dutta, Robert Orlowski, Alan Smith, David S. Miller

Memorial Sloan Kettering Cancer Center, New York, NY; Hospital Universitario San Carlos, Madrid, Spain; Saitama Medical University International Medical Center, Hidaka, Japan; Uro-Gynecological Department, Istituto Nazionale per lo Studio e la Cura dei Tumori, Fondazione "G. Pascale", Naples, Italy; Harvard Medical School, Boston, MA; Eisai Inc., Woodcliff Lake, NJ; Merck & Co, Inc., Kenilworth, NJ; Eisai Ltd., Hatfield, United Kingdom; The University of Texas Southwestern Medical Center, Dallas, TX

Presented By Vicky Makker at 2019 ASCO Annual Meeting

È necessaria la chemioterapia nel trattamento della recidiva del carcinoma ovarico?

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]

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**

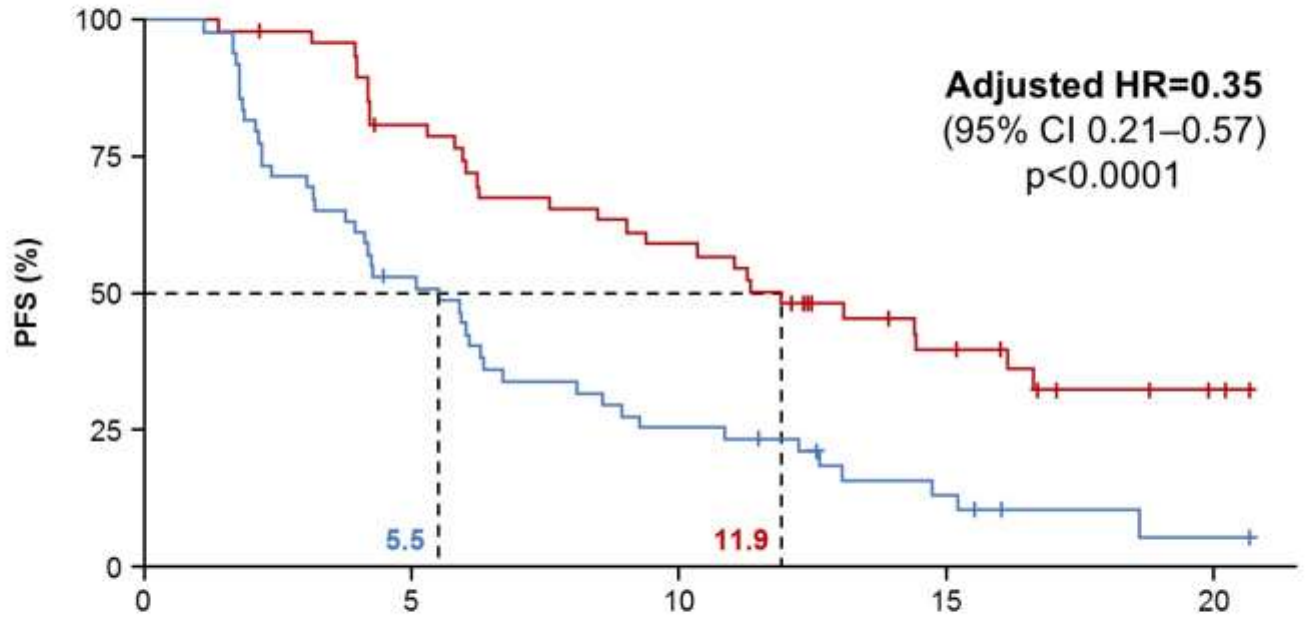
→ Until disease progression or toxicity

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

Primary endpoint: PFS in the ITT population

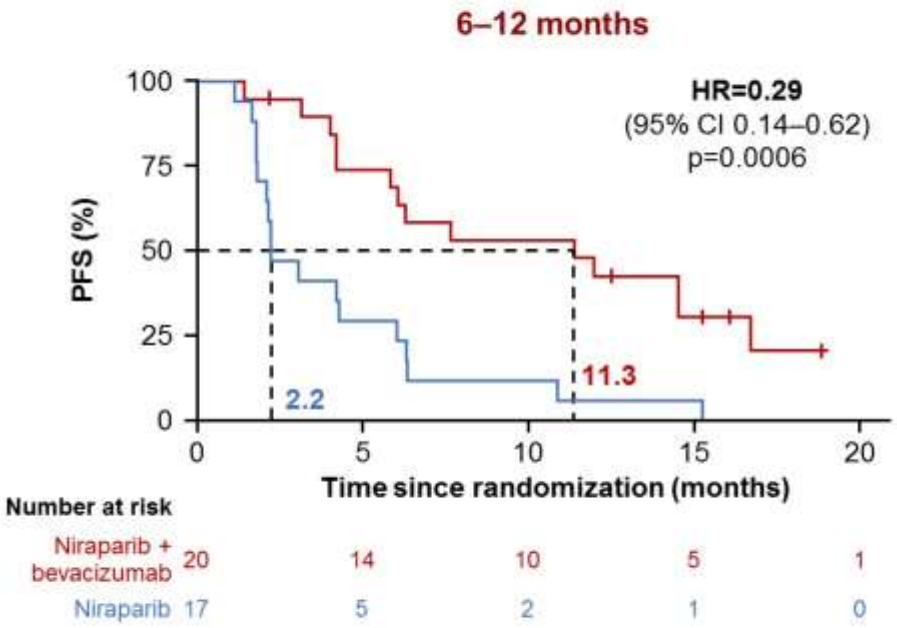


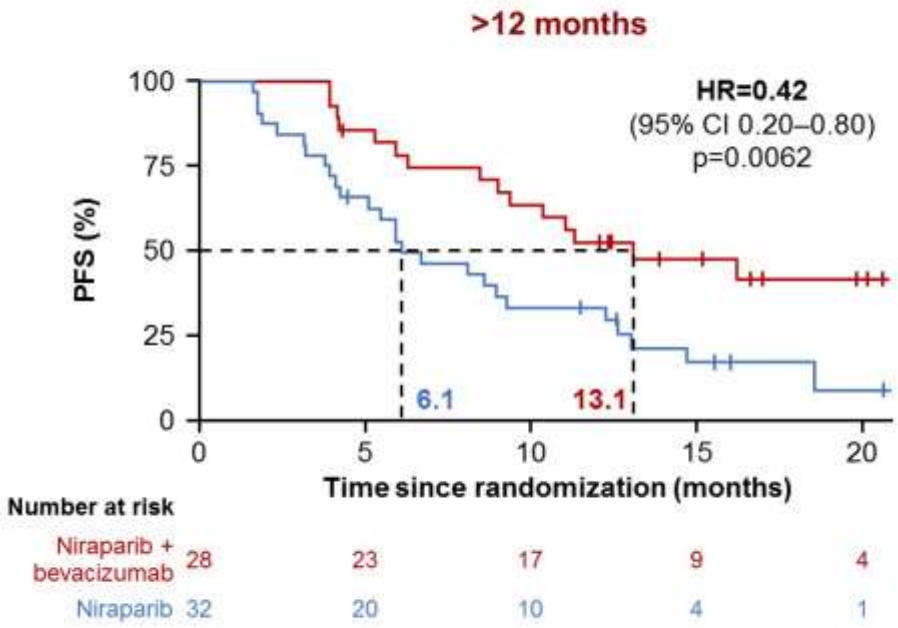
Number at risk					
Niraparib + bevacizumab	48	37	27	14	5
Niraparib	49	25	12	5	1

CI = confidence interval; HR = hazard ratio

Presented By Mansoor Mirza at 2019 ASCO Annual Meeting

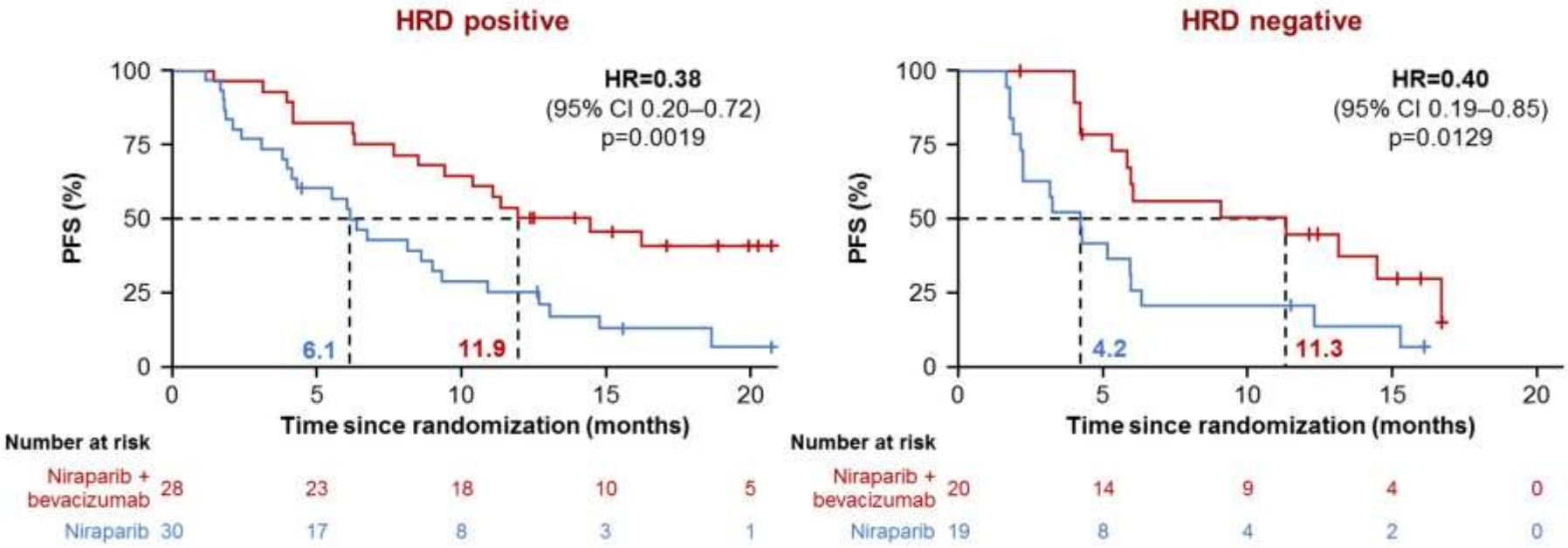
PFS by stratification factors: Chemotherapy-free interval





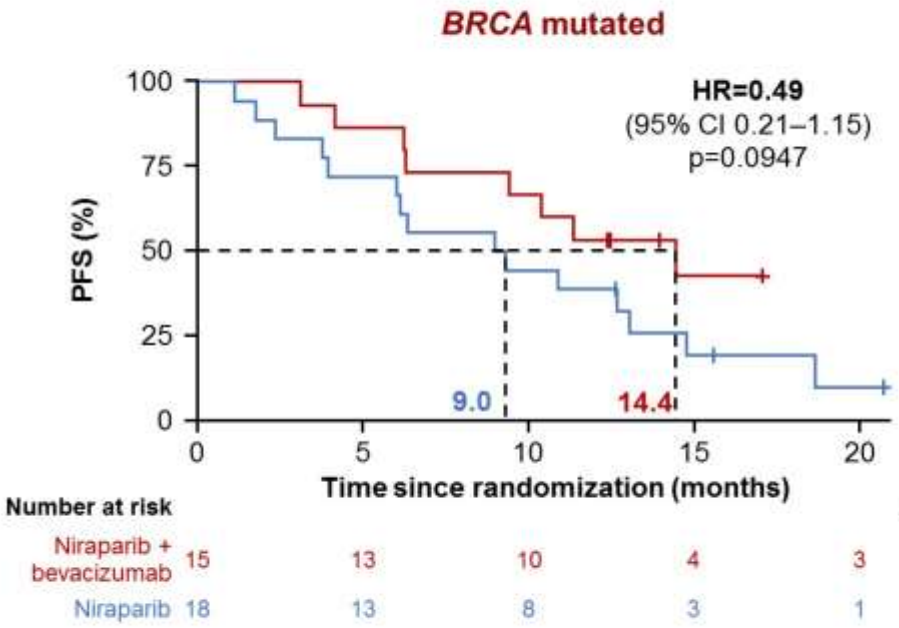
Presented By Mansoor Mirza at 2019 ASCO Annual Meeting

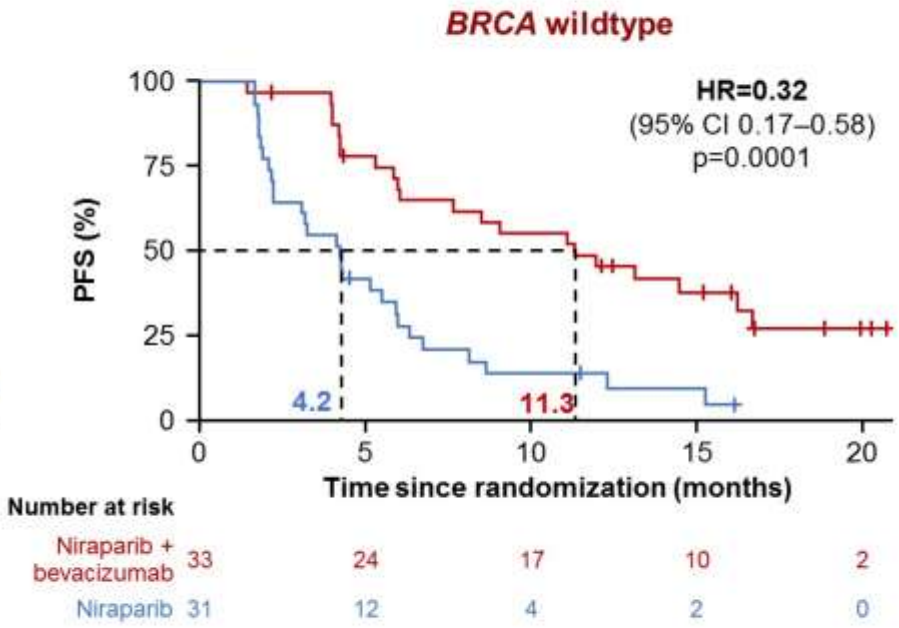
PFS by stratification factors: HRD status



Presented By Mansoor Mirza at 2019 ASCO Annual Meeting

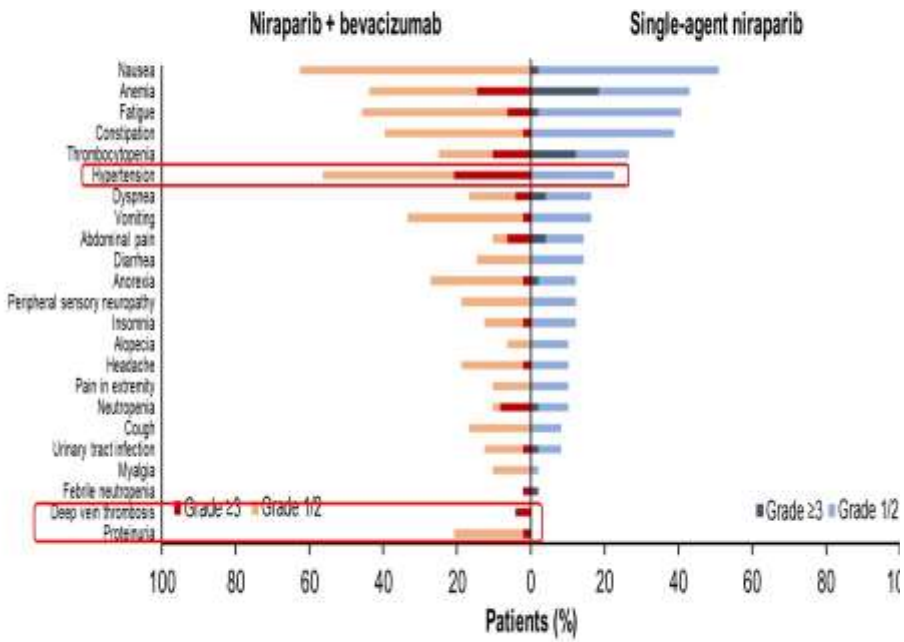
PFS by *BRCA* status





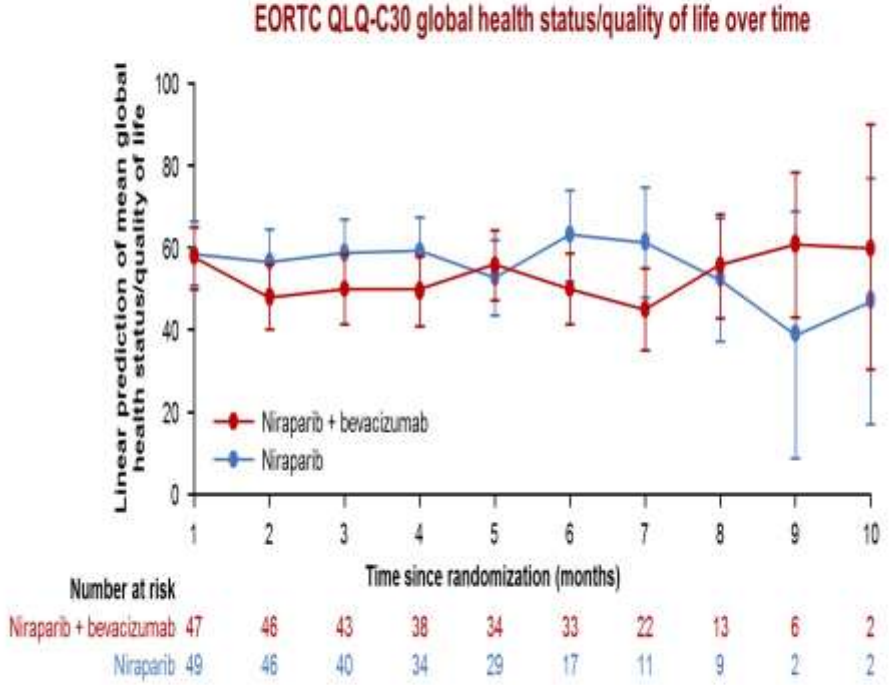
Presented By Mansoor Mirza at 2019 ASCO Annual Meeting

Summary of adverse events



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

Patient-reported outcomes



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

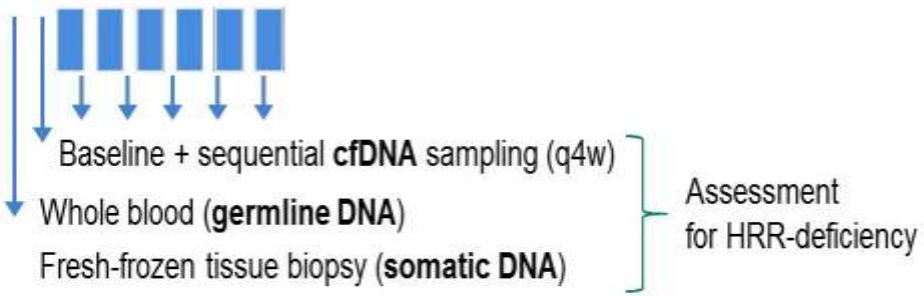
Presented By Mansoor Mirza at 2019 ASCO Annual Meeting

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]

Primary endpoint

- Objective response rate (**OOR**) 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 (**OOR**), **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 (**OOR**), **PFS**, **clinical benefit rate** at 12 weeks and **duration of clinical benefit** for platinum-resistant (**PROC**) cohort treated with olaparib monotherapy versus chemotherapy

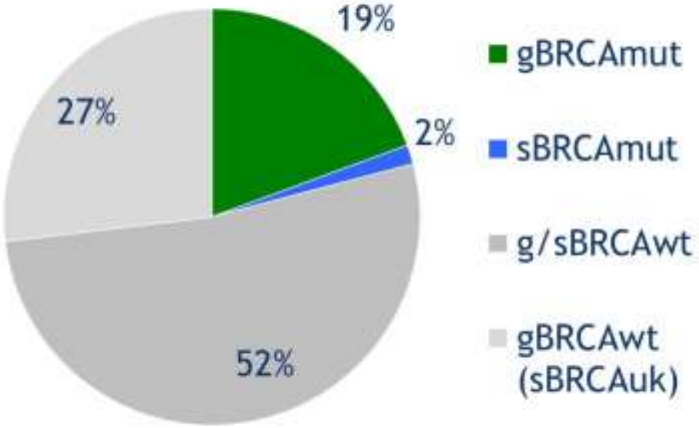
- **Quality of life** analysis of olaparib versus chemotherapy in PROC and PSOC patients

Current report

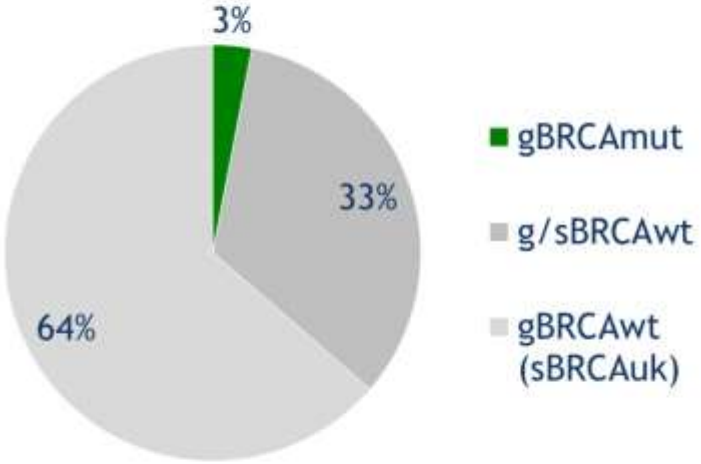
Baseline characteristics (PROC, n=100)

BRCA status

Olaparib (n=67)



Chemotherapy (n=33)

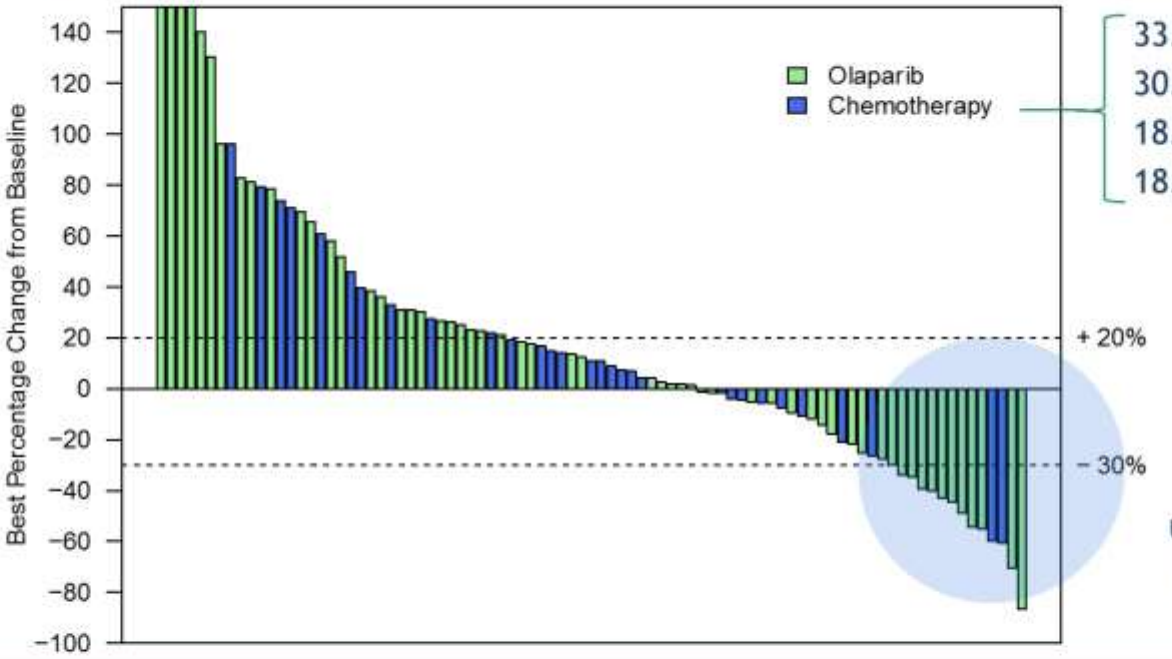


Imbalance in frequency of known BRCA mutations between both groups (p=0.03)

(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 taxol weekly)

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

* Unconfirmed

Presented By Adriaan Vanderstichele at 2019 ASCO Annual Meeting

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)

Clinical benefit rate at 12 weeks

	OLAPARIB	CHEMOTHERAPY
All patients	36 % (24/67) *7 PR, 17 SD*	45 % (15/33) *2 PR, 13 SD*
BRCA mutated	64 % (9/14)	100 % (1/1)
BRCA wild type	28 % (15/53)	44 % (14/32)

Duration of clinical benefit

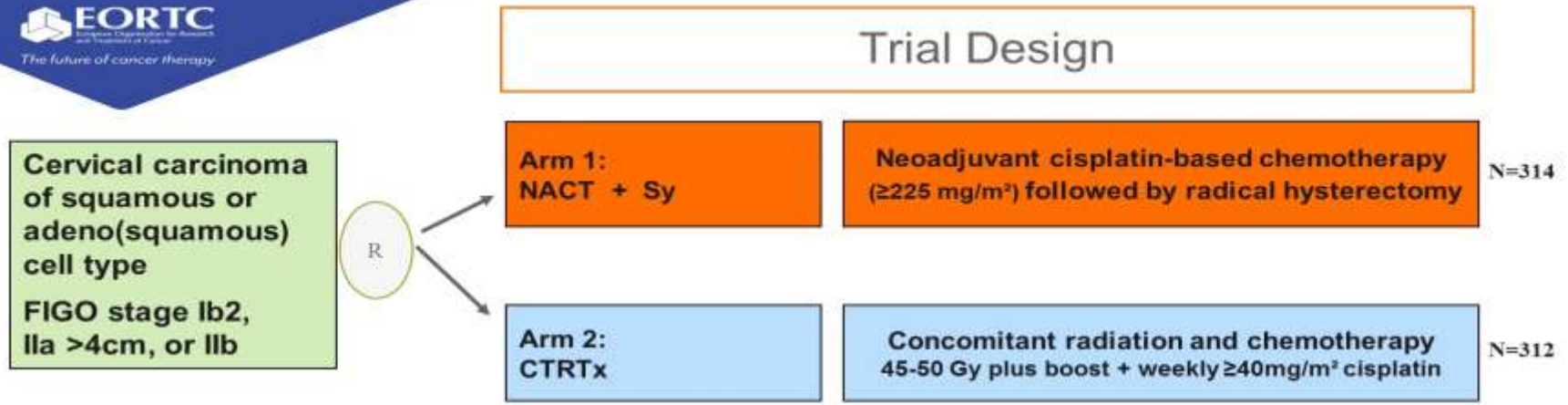
	Median duration of clinical benefit
All patients (n=100)	3.0 months (95%CI: 2.8 - 4.7)
Olaparib (n=67)	3.4 months (95%CI: 1.8 - NA)
Chemotherapy (n=33)	3.0 months (95%CI: 2.8 - 5.7)

Carcinoma della cervice localmente avanzato: chemioterapia seguita da chirurgia o chemio-radioterapia?

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. Kobierski, 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



Endpoints:

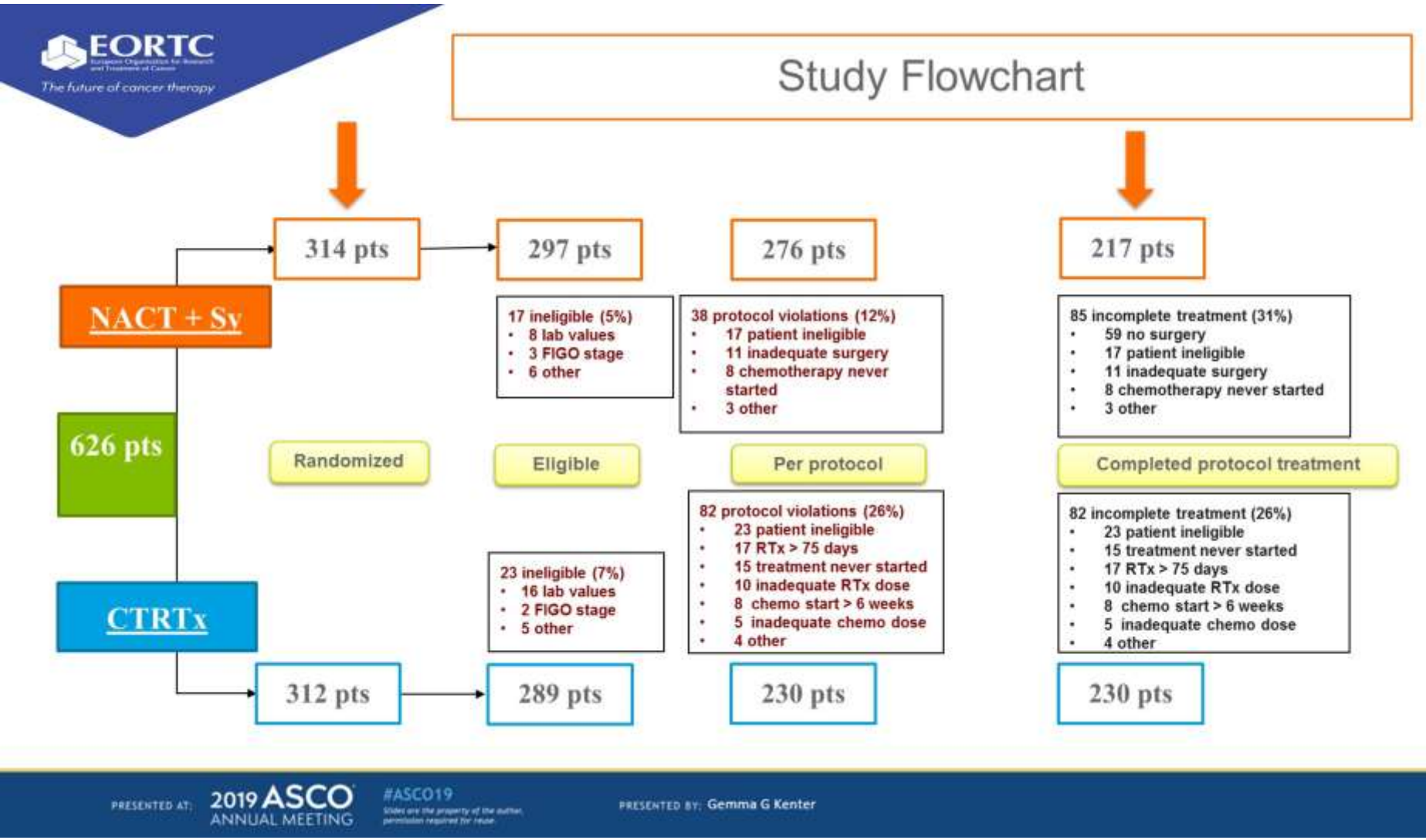
- Primary: overall survival (OS) at 5 years
- Secondary: PFS, toxicity & QoL

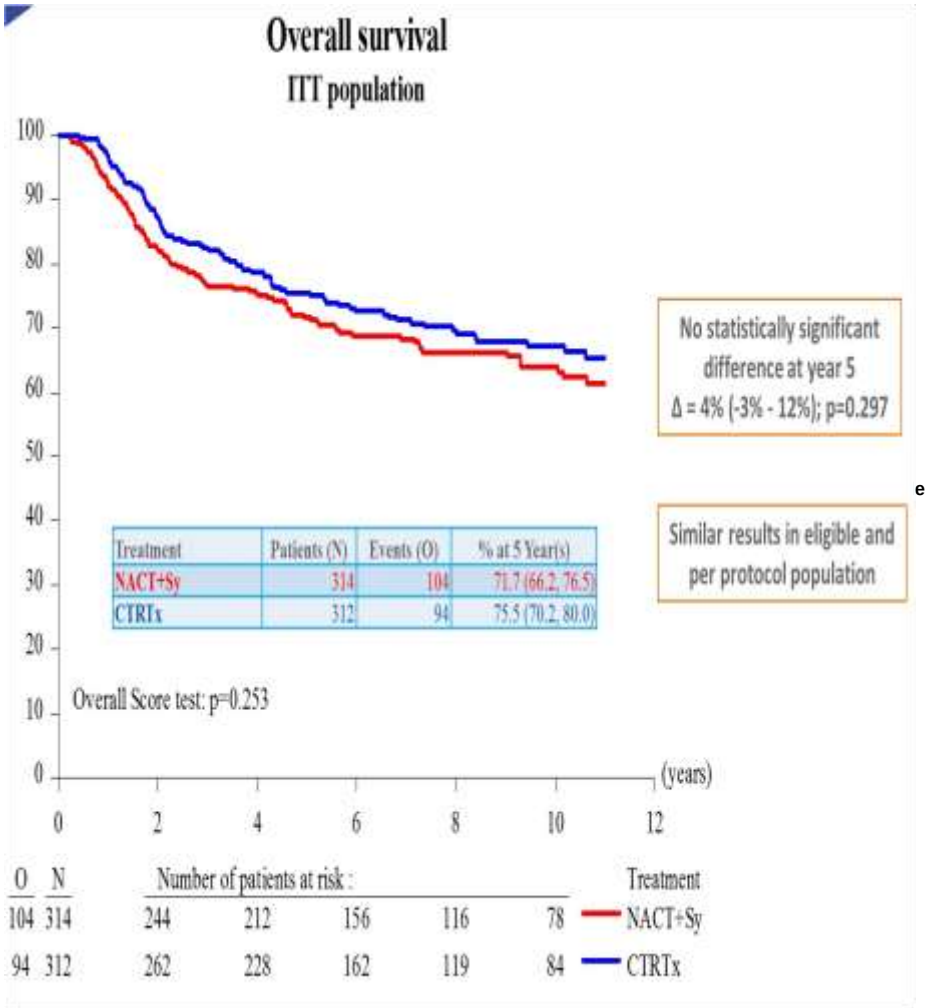
Stratification:

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

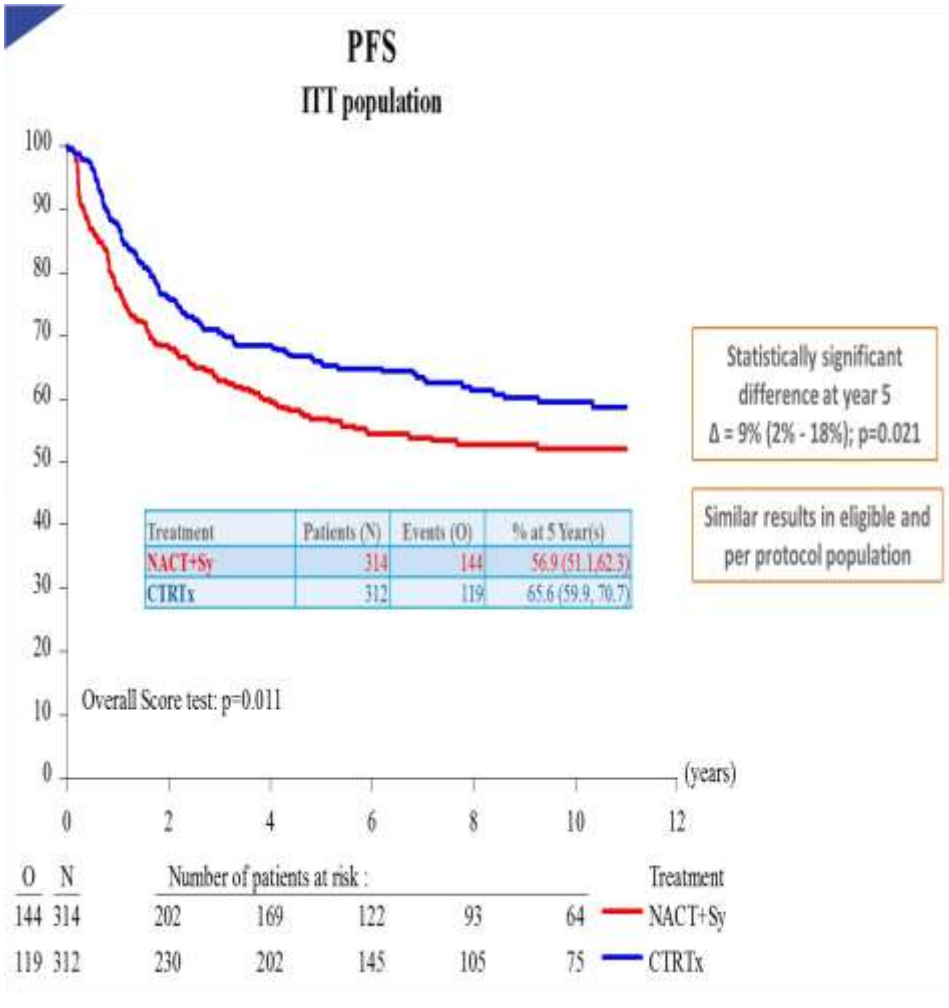
Statistics:
OS at 5 years in the CTRTx arm assumed 67%. To detect a 10% difference with a 2-sided α of 5% and power of 80% a total sample size of 625 patients with 5 years of follow-up is needed.

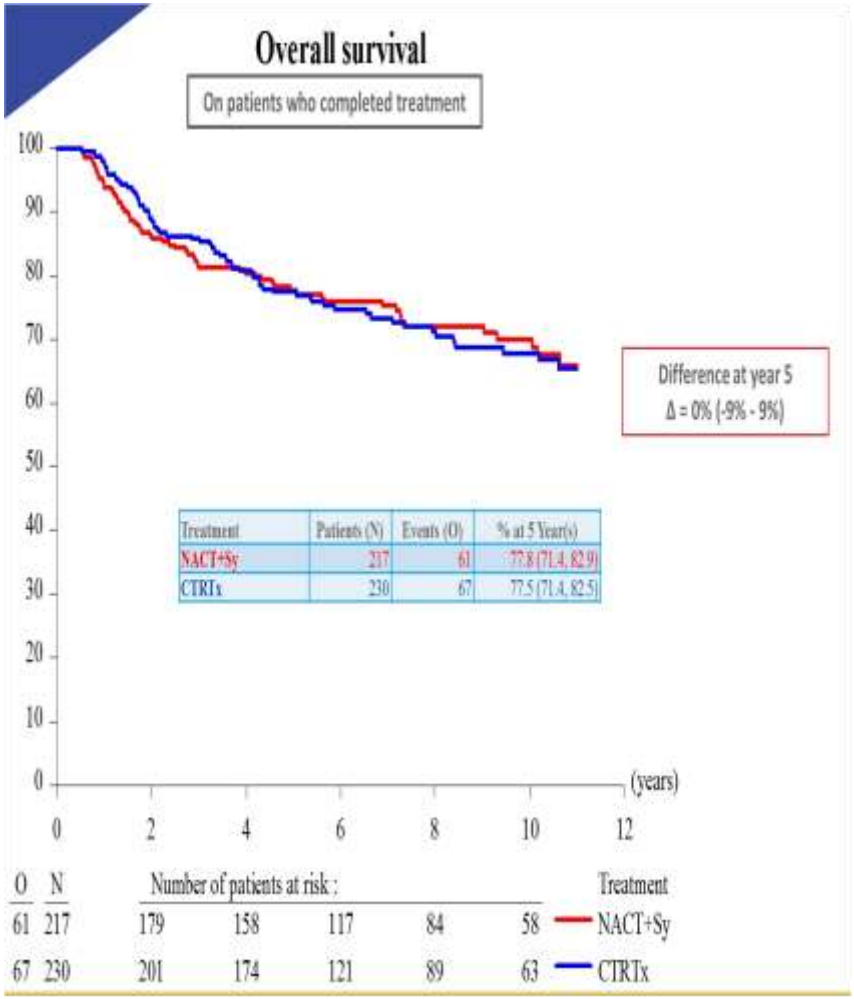
Quality Assurance Program:
A quality assurance project was implemented to check the accuracy of data collection and investigate protocol adherence in the different treatment modalities.

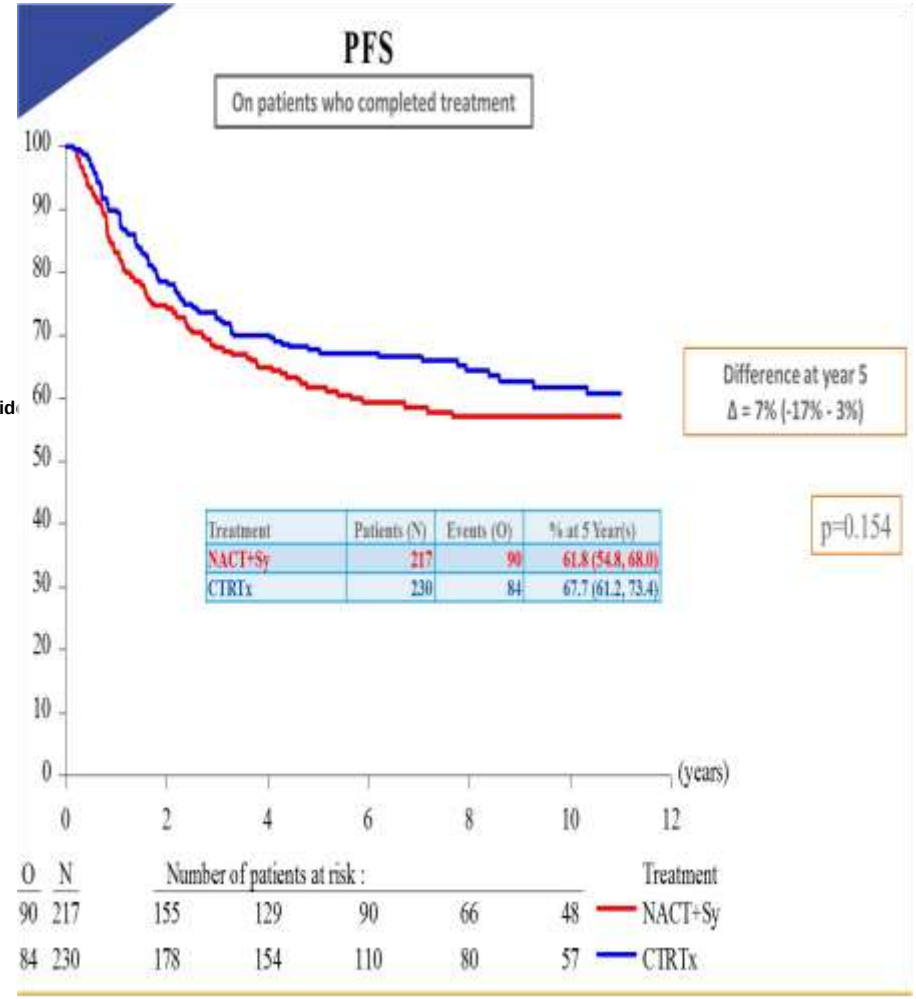

EORTC
The future of cancer therapy
Study Flowchart
314 pts
297 pts
276 pts
217 pts
NACT + Sy
626 pts
CTRTx
17 ineligible (5%)
• 8 lab values
• 3 FIGO stage
• 6 other
38 protocol violations (12%)
• 17 patient ineligible
• 11 inadequate surgery
• 8 chemotherapy never started
• 3 other
85 incomplete treatment (31%)
• 59 no surgery
• 17 patient ineligible
• 11 inadequate surgery
• 8 chemotherapy never started
• 3 other
Randomized
Eligible
Per protocol
Completed protocol treatment
82 protocol violations (26%)
• 23 patient ineligible
• 17 RTx > 75 days
• 15 treatment never started
• 10 inadequate RTx dose
• 8 chemo start > 6 weeks
• 5 inadequate chemo dose
• 4 other
82 incomplete treatment (26%)
• 23 patient ineligible
• 15 treatment never started
• 17 RTx > 75 days
• 10 inadequate RTx dose
• 8 chemo start > 6 weeks
• 5 inadequate chemo dose
• 4 other
23 ineligible (7%)
• 16 lab values
• 2 FIGO stage
• 5 other
312 pts
289 pts
230 pts
230 pts
PRESENTED AT: 2019 ASCO ANNUAL MEETING
#ASCO19
Slides are the property of the author, permission required for reuse
PRESENTED BY: Gemma G Kenter


Overall survival
ITT population
100
90
80
70
60
50
40
30
20
10
0
Treatment | Patients (N) | Events (O) | % at 5 Year(s)
NACT+Sy | 314 | 104 | 71.7 (66.2, 76.5)
CTRTx | 312 | 94 | 75.5 (70.2, 80.0)
Overall Score test: p=0.253
(years)
0 2 4 6 8 10 12
O N
104 314
94 312
Number of patients at risk :
244 212 156 116 78
262 228 162 119 84
Treatment
NACT+Sy
CTRTx
No statistically significant difference at year 5
Δ = 4% (-3% - 12%); p=0.297
Similar results in eligible and per protocol population

e


PFS
ITT population
100
90
80
70
60
50
40
30
20
10
0
Treatment | Patients (N) | Events (O) | % at 5 Year(s)
NACT+Sy | 314 | 144 | 56.9 (51.1,62.3)
CTRTx | 312 | 119 | 65.6 (59.9, 70.7)
Overall Score test: p=0.011
(years)
0 2 4 6 8 10 12
O N
144 314
119 312
Number of patients at risk :
202 169 122 93 64
230 202 145 105 75
Treatment
NACT+Sy
CTRTx
Statistically significant difference at year 5
Δ = 9% (2% - 18%); p=0.021
Similar results in eligible and per protocol population

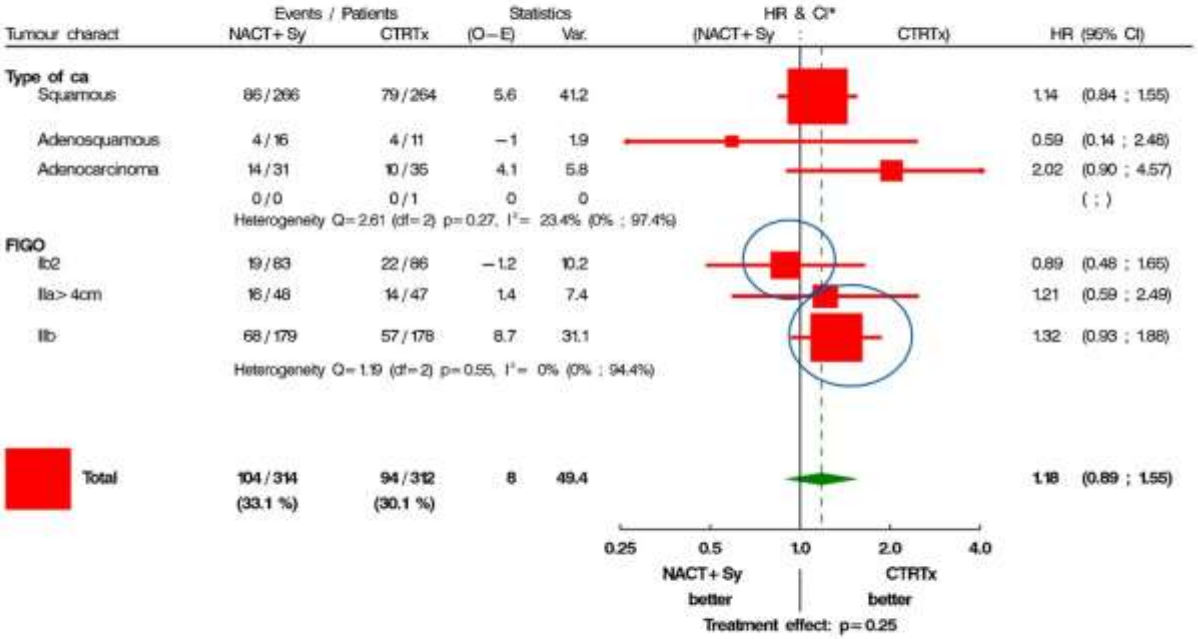

Overall survival
On patients who completed treatment
Difference at year 5
Δ = 0% (-9% - 9%)
Treatment | Patients (N) | Events (O) | % at 5 Year(s)
NACT+Sy | 217 | 61 | 77.8 (71.4, 82.9)
CTRTx | 230 | 67 | 77.5 (71.4, 82.5)
(years)
Number of patients at risk :
O N
61 217 179 158 117 84 58 NACT+Sy
67 230 201 174 121 89 63 CTRTx
Treatment


PFS
On patients who completed treatment
Difference at year 5
Δ = 7% (-17% - 3%)
p=0.154
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)
(years)
Number of patients at risk :
O N
90 217 155 129 90 66 48 NACT+Sy
84 230 178 154 110 80 57 CTRTx
Treatment

EORTC
The future of cancer therapy

Overall Survival

	Pts (N)	Events (O)	OS at 5yr (%)	Δ OS at 5yr (%)
FIGO Ib2				
NACT+Sy	83	19	82%	-6%
CTRTx	86	16	76%	
FIGO IIa>4cm				
NACT+Sy	48	16	69%	+6%
CTRTx	47	14	75%	
FIGO IIb				
NACT+Sy	179	68	68%	+8%
CTRTx	178	57	76%	



*95% CI everywhere

Presented By Gemma Kenter at 2019 ASCO Annual Meeting

WORKING IN PROGRESS: FASE II

ADAVOSERTIB

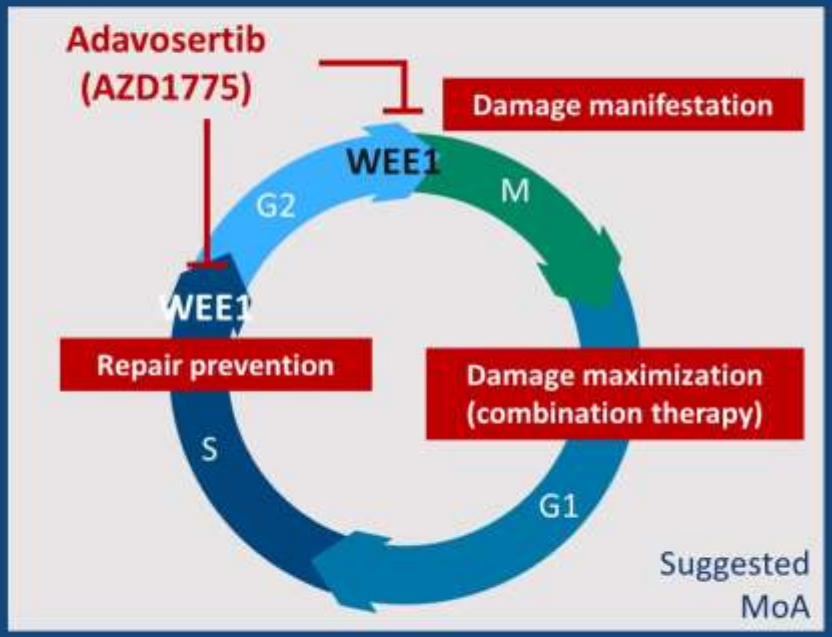
MIRVETUX/BEVACIZUMAB

PEMBROLIZUMAB/CARBOPLATINO BASSE DOSI

LETROZOLO/RIBOCICLIB

OLAPARIB/CEDIRANIB

Adavosertib



- Wee1 inhibitor
- Impairs G2 DNA damage checkpoint
- May lead to apoptosis upon treatment with DNA damaging agents
- Most p53 deficient or mutated cancer lack G1 checkpoint, so those cells rely on G2 checkpoint
- Can lead to mitotic catastrophe
- 4 Arm phase 2 trial, up to 4 prior regimens

Abstract 5513: Adavosertib with chemotherapy in patients with platinum-resistant ovarian cancer: an open-label, four-arm, Phase II study

Kathleen N Moore,[1,2] Setsuko K Chambers,[3] Erika Paige Hamilton,[2,4] Lee-may Chen,[5] Amit M Oza,[6] Sharad A Ghamande,[7] Gottfried E Konecny,[8] Steven C Plaxe ,[9] Daniel Lewis Spitz,[10] Jill JJ Geenen,[11] Tiffany A Troso-Sandoval,[12] Janiel M Cragun,[3] Esteban Rodrigo Imedio,[13] Sanjeev Kumar,[13] Ganesh M Mugundu,[14] Zhongwu Lai,[15] Juliann Chmielecki,[15] Suzanne Fields Jones,[2] David R Spigel,[2,4] Karen A Cadoo[12,16]

Response Rates Platinum Resistant Ovarian Cancer

Study	Agent	N	Response Rate (%)
126-J	Docetaxel	58	22
126-N	Weekly Paclitaxel	48	21
126-Q	Pemetrexed	48	21
126-R	Nab-Paclitaxel	47	23
170-D	Bevacizumab	62	21
AURELIA	Chemo + Bev Chemo Alone	179 181	27.3 11.8
Gordon Ph 3	PLD Topo D1-5	239 235	19.7 17
Study 10 and ARIEL2 subset PROC	Rucaparib	20	25
QUADRA subset BRCAm, PROC	Niraparib	37	27
Current Study	**Carbo + Adavosertib**	**35**	**42.9**

Adverse Events

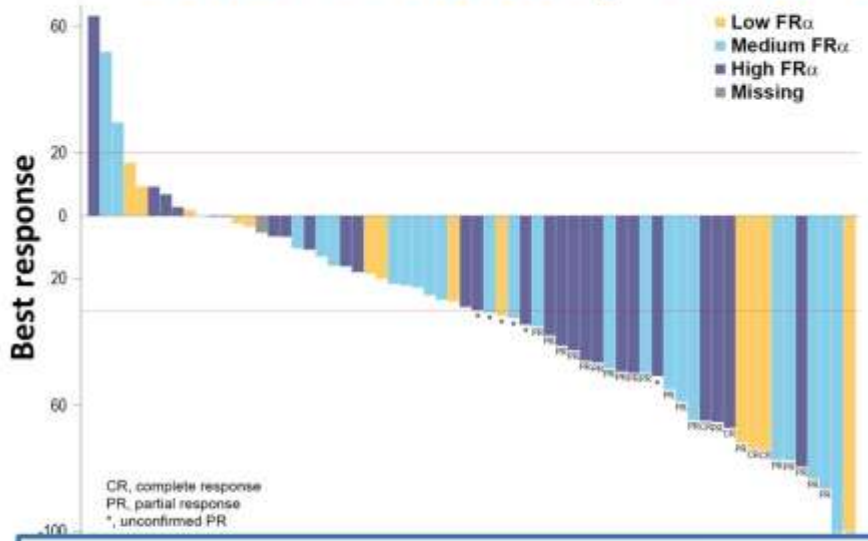
	N=94 (%)
Grade 3 TEAE	38 (40.4)
Grade 4 TEAE	39 (41.5)
Dose Interruptions	60 (63.8)
Dose Reductions	36 (38.3)
Discontinuation	12 (12.8)

1 patient died from neutropenic sepsis (1%)
Most common Gr 3 and 4 TEAEs hematologic toxicity

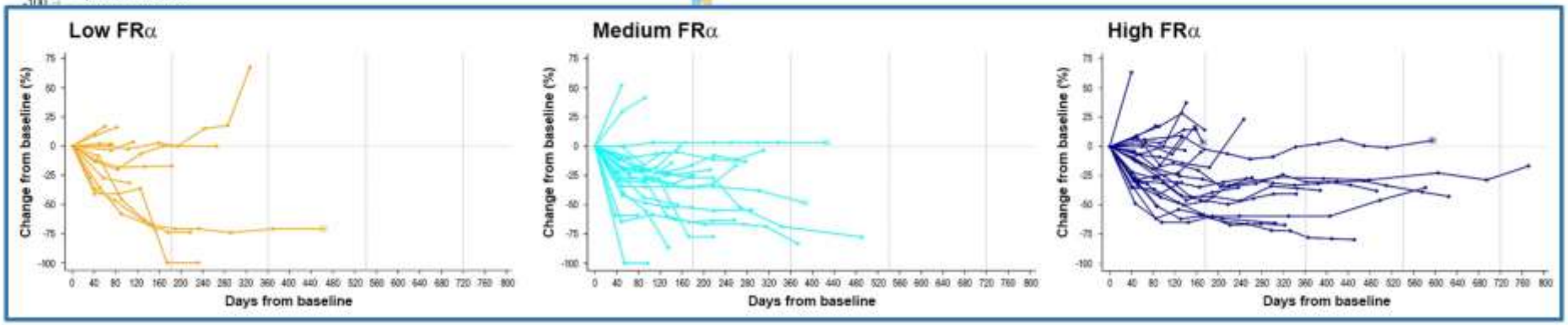
Presented By Joan Walker at 2019 ASCO Annual Meeting

5520 O'Malley et al: Mirvetux/bev in platR EOC

53%/10.4 m



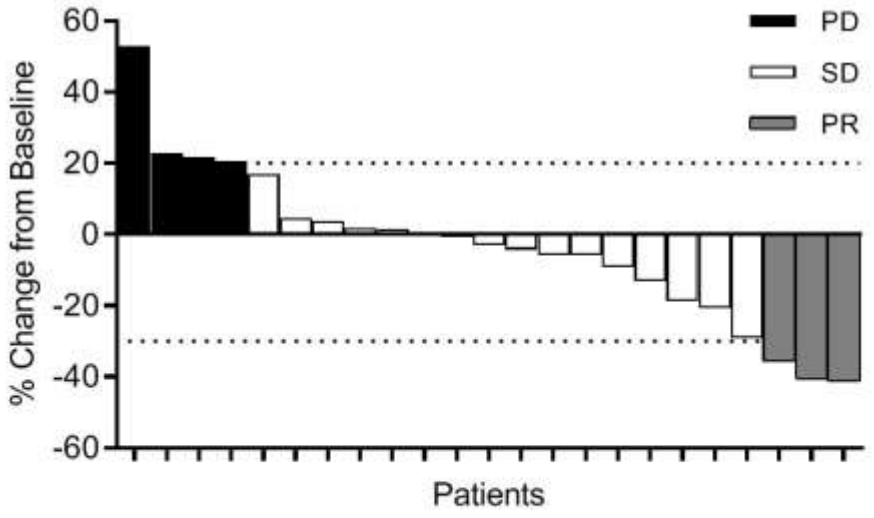
	Total N=66	FRa Expression*			AURELIA-type
Endpoint 95% CI		Low (n = 13)	Medium (n = 24)	High (n = 28)	(n = 16)
ORR confirmed	39% (28, 52)	31% (9, 61)	46% (26, 67)	39% (22, 59)	56% (30, 80)
PFS (mo)	6.9 (4.9, 8.6)	6.0 (2.1, 8.8)	6.9 (4.4, 9.9)	7.1 (4.4, 14.5)	9.9 (4.1, 15.9)

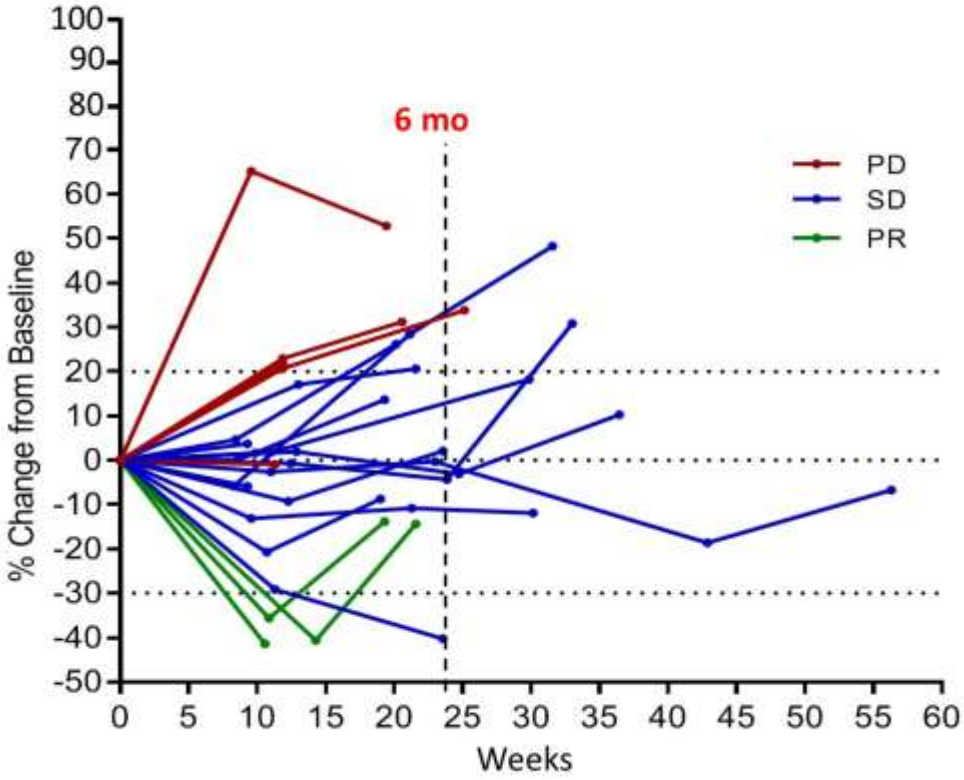


Single Agent CI in EOC

Study/Author	Study Type	Agent	Patient Population	Overall Response Rate (ORR)
Brahmer et al. (2012)	Phase I	PD-L1	Advanced Dx Multiple tumor types	6% (1/16)
Hamanashi et al. (2015)	Phase II	PD-1 Nivolumab	Platinum resistant	15% (3/20)
Disis et al. (2019) JAVELIN	Phase Ib	PD-L1 Avelumab	Recurrent/ refractory	10% (12/125)
Infante et al. (2016)	Phase Ia	PD-L1 Atezolizumab	Recurrent/ Metastatic	22% (2/9)
Keynote 28 Varga et al. (2017)	Phase Ib	Pembrolizumab	PD-L1+ tumors	11.5% (3/26)
Keynote 100 Matulonis et al.(2018)	Phase II	Pembrolizumab	Recurrent	8%

5519 Liao et al: Pembro with low dose carbo in platR EOC





23 PAZIENTI VALUTABILI PER RISPOSTA

PR 13% **SD 65,2%** **PD 21.7%**

Presented By Elise Kohn at 2019 ASCO Annual Meeting

RESULTS OF A PHASE 2 TRIAL OF RIBOCICLIB AND LETROZOLE IN PATIENTS WITH EITHER RELAPSED ESTROGEN RECEPTOR (ER)-POSITIVE OVARIAN CANCERS OR RELAPSED ER-POSITIVE ENDOMETRIAL CANCERS

Gerardo Colón-Otero, S. John Weroha, Valentina Zanfagnin, Nathan R. Foster, Erik J. Asmus, Andrea E. Wahner Hendrickson, Aminah Jatoi, Matthew Stephen Block, Carrie Lynn Langstraat, Gretchen E. Glaser, Tri A. Dinh, Matthew W. Robertson, John K. Camoriano, Kristina Ashley Butler, John A. Copland III

Mayo Clinic College of Medicine, Mayo Clinic Cancer Center
Jacksonville, FL, Rochester, MN and Phoenix, AZ

Patients Characteristics	Cohort A (OV) Ovarian (N=20)	Cohort B (EN) Endometrial (N=20)
Cell Type	High gr serous= 17 (85%) Low gr serous = 3 (15%)	Gr 1-2= 11(55%) Gr 3 = 9 (45%)
Number of previous chemo regimens	0-6 (median 3)	0-6 (median 2)
Platinum resistance	Sensitive= 7 (36.8%) Resistant= 12 (63%)	Sensitive = 8 (44%) Resistant = 10 (55%)

PRIMARY ENDPOINT: PFS12

Patients surviving, progression free, and on study at 12 weeks

- ENDOMETRIAL (B) 11/20 (55%)
  - Progression-free ≥ 23 weeks 9/20 (45%)
- OVARIAN (A) 10/20 (50%)
  - Progression-free ≥ 23 weeks 5/20 (25%)

CLINICALLY SIGNIFICANT BENEFIT (PFS ≥ 23 WEEKS and ON STUDY FOR ≥ 23 weeks)

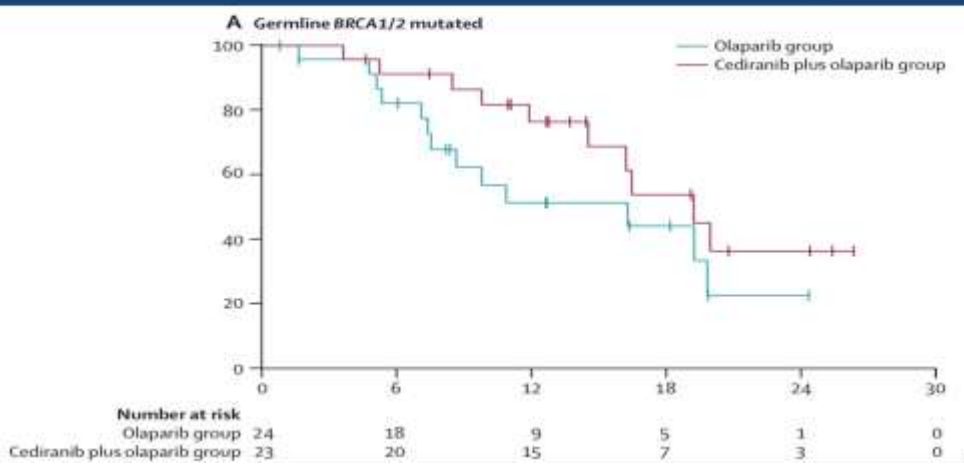
Total patients	14/40 (35%)
Ovarian Group	5/20(25%)
Low-grade serous	3/3 (100%)*
High-grade serous	2/17 (12%)
Endometrial Group	9/20 (45%)
Grade 1-2	7/11 (64%)
Grade 3	2/9 (22%)

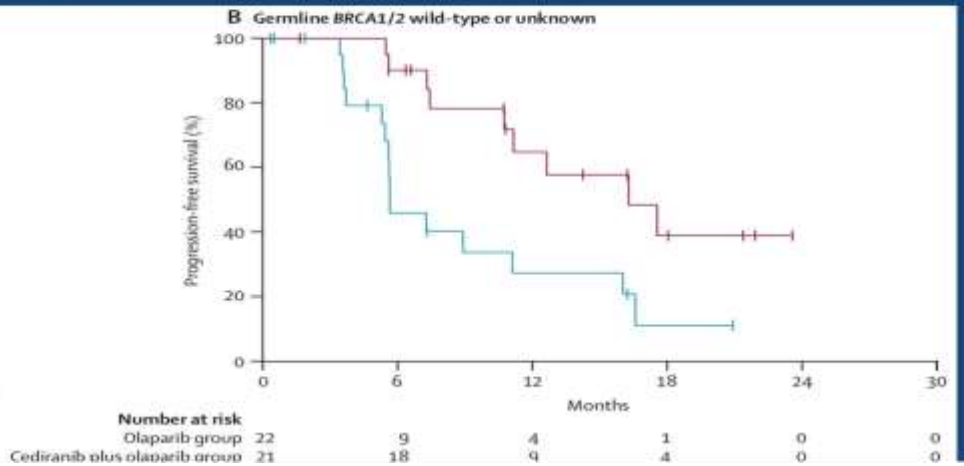
*These patients are still on rx for 28+ months, 24+ months, and 19+ months.

Olaparib/cediranib

Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study

Joyce F Liu, William T Barry, Michael Birrer, Jung-Min Lee, Ronald J Buckanovich, Gini F Fleming, BJ Rimel, Mary K Buss, Sreenivasa Nattam, Jean Hurteau, Weixiu Luo, Philippa Quy, Christin Whalen, Lisa Obermayer, Hang Lee, Eric P Winer, Elise C Kohn, S Percy Ivy, Ursula A Matulonis

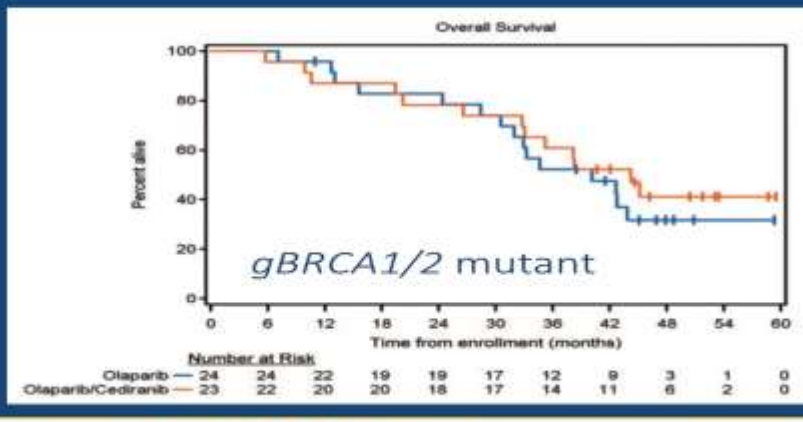


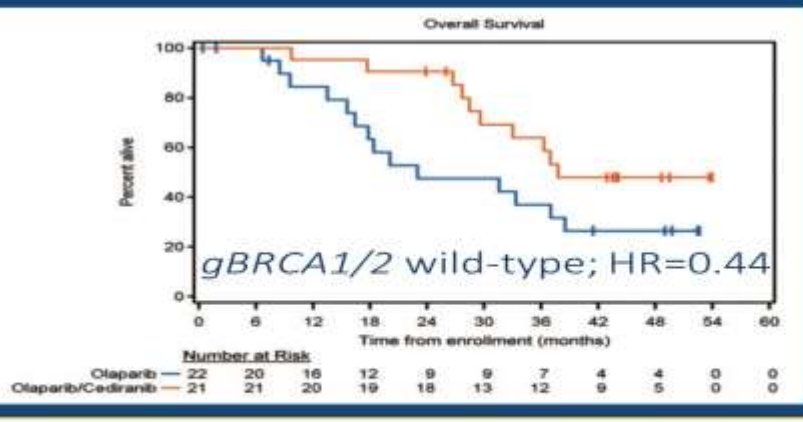


Olaparib/cediranib

Overall survival and updated progression-free survival outcomes in a randomized phase II study of combination cediranib and olaparib versus olaparib in relapsed platinum-sensitive ovarian cancer

J. F. Liu[1*], W. T. Barry[2], M. Birrer[3], J.-M. Lee[4], R. J. Buckanovich[5], G. F. Fleming[6], B. J. Rimel[7], M. K. Buss[8], S. R. Nattam[9], J. Hurteau[10], W. Luo[2], J. Curtis[1], C. Whalen[1], E. C. Kohn[4,11], S. P. Ivy[11] & U. A. Matulonis[1]



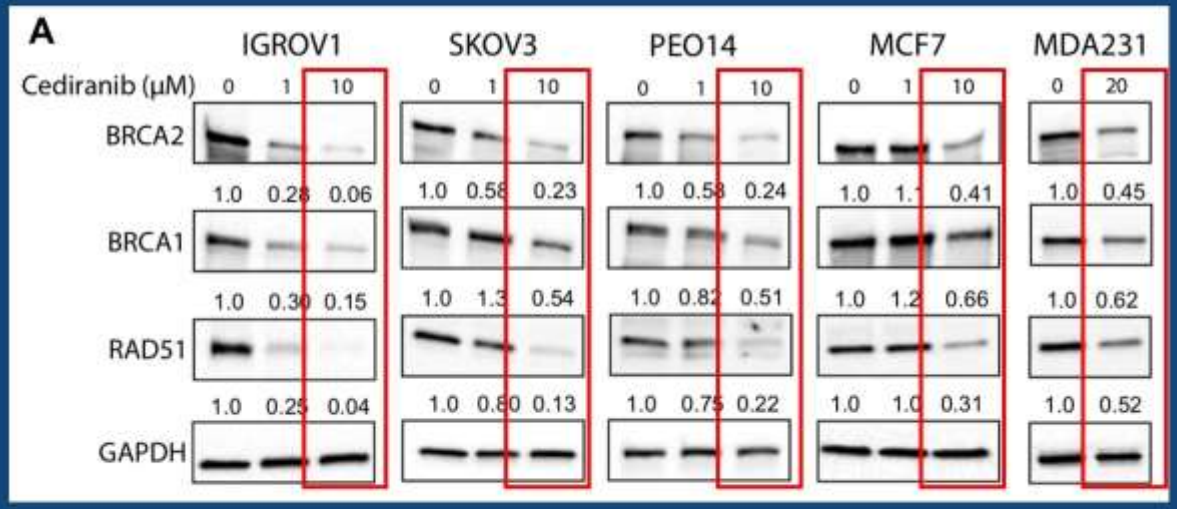


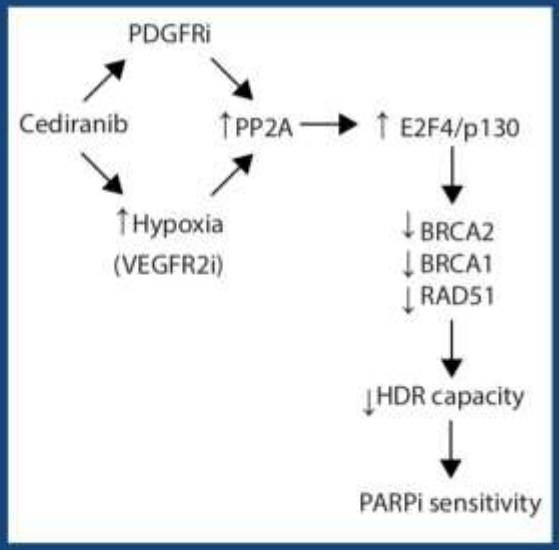
Olaparib/cediranib

CANCER

Cediranib suppresses homology-directed DNA repair through down-regulation of BRCA1/2 and RAD51

Alanna R. Kaplan[1,2], Susan E. Gueble[1,2], Yanfeng Liu[1], Sebastian Oeck[1], Hoon Kim[1], Zhong Yun[1], Peter M. Glazer[1,3]*

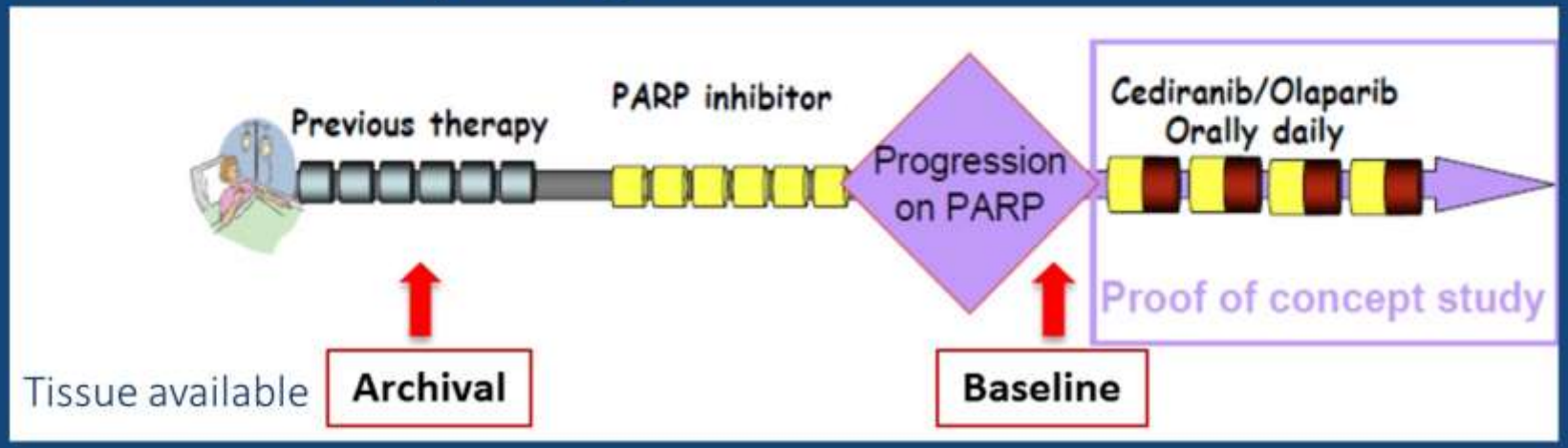




Kaplan et al (2019) Sci. Trans. Med. 11:eaav4508

Presented By Iain McNeish at 2019 ASCO Annual Meeting

EVOLVE - study Design



Platinum SENSITIVE disease N=11

Platinum RESISTANT disease N = 10

EXPLORATORY - Prior PARPi progression, treated with further chemo N = 13

Olaparib tablets 150mg bd
Cediranib 20mg od

21 patients received between 2 - 5 prior lines
13 patients received between 6 - 9 prior lines

Presented By Iain McNeish at 2019 ASCO Annual Meeting

EVOLVE – primary objectives

Best response – per cohort

	SENSITIVE	RESISTANT	EXPLORATORY	OVERALL
PR	0	2	2	4 (12.9%)
SD	9	4	6	19
PD	2	4	2	8

16 weeks PFS – per cohort

- Platinum Sensitive: 54.5% (31.8 -93.6)
- Platinum Resistant: 50% (26.9 – 92.9)
- Exploratory: 36% (15.6 – 82.8)

EVOLVE – putative resistance mechanisms

Mechanisms of Resistance	Archival tumour tissue	Baseline tumour tissue post PARPi
BRCA1/2 reversion	none	4
BRCA1/2 overexpression	none	1
MDR overexpression	none	2
CCNE1 amplification/ overexpression	3	6
Other novel putative mechanisms	0	6

TUMORE OVARICO MALIGNO A CELLULE GERMINALI MOGCT

1-2 % dei tumori ovarici

10-30 anni

Trattamento standard PEB

Abstract 5516: MITO-9 Prospective observational study of non-epithelial ovarian tumors – MOGCT outcomes

Group A	IA dysgerminomas IAG1 immature teratomas	Surveillance	N=12 7 IA dysgerminomas 5 IA G1 immature teratomas
Group B	IB-C1 dysgerminomas IA-IC G2-G3 immature teratomas Stage IA mixed MOGCTs Stage IA yolk sac tumor After CSS	Close surveillance vs Adjuvant chemotherapy	N=24 2/5 (40%) re-staged patients excluded due to positive restaging 15 received surveillance 7 received adjuvant chemotherapy
Group C	All other stage I MOGCTs	Adjuvant chemotherapy	N=5 3 IC yolk sac tumors 2 IC2 mixed MOGCTs (with yolk sac)

Split

5 year-Overall Survival was 100%, while 5 year-disease free survival was 97.5%.
Only one patient in group B with a stage IA G3 immature teratoma treated with adjuvant BEP relapsed as mature teratoma.
None of the patients in the surveillance protocol experienced relapse.

HIGHLIGHTS IN GYNECOLOGICAL CANCER

DANIELA SAMBATARO
UOC Oncologia Medica
ARNAS GARIBALDI Catania