GOG FOUNDATION®
Transforming the standard of care

OVARIAN CANCER – FIRST LINE AND PLATINUM SENSITIVE- THE CURRENT LANDSCAPE

David O'Malley, M.D.
Professor
Division Director, Gynecologic Oncology
Co-Director, Gyn Oncology Phase I Program

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

GOG-P Ovarian Cancer Clinical Trialist

Creating a cancer-free world. One person, one discovery at a time.

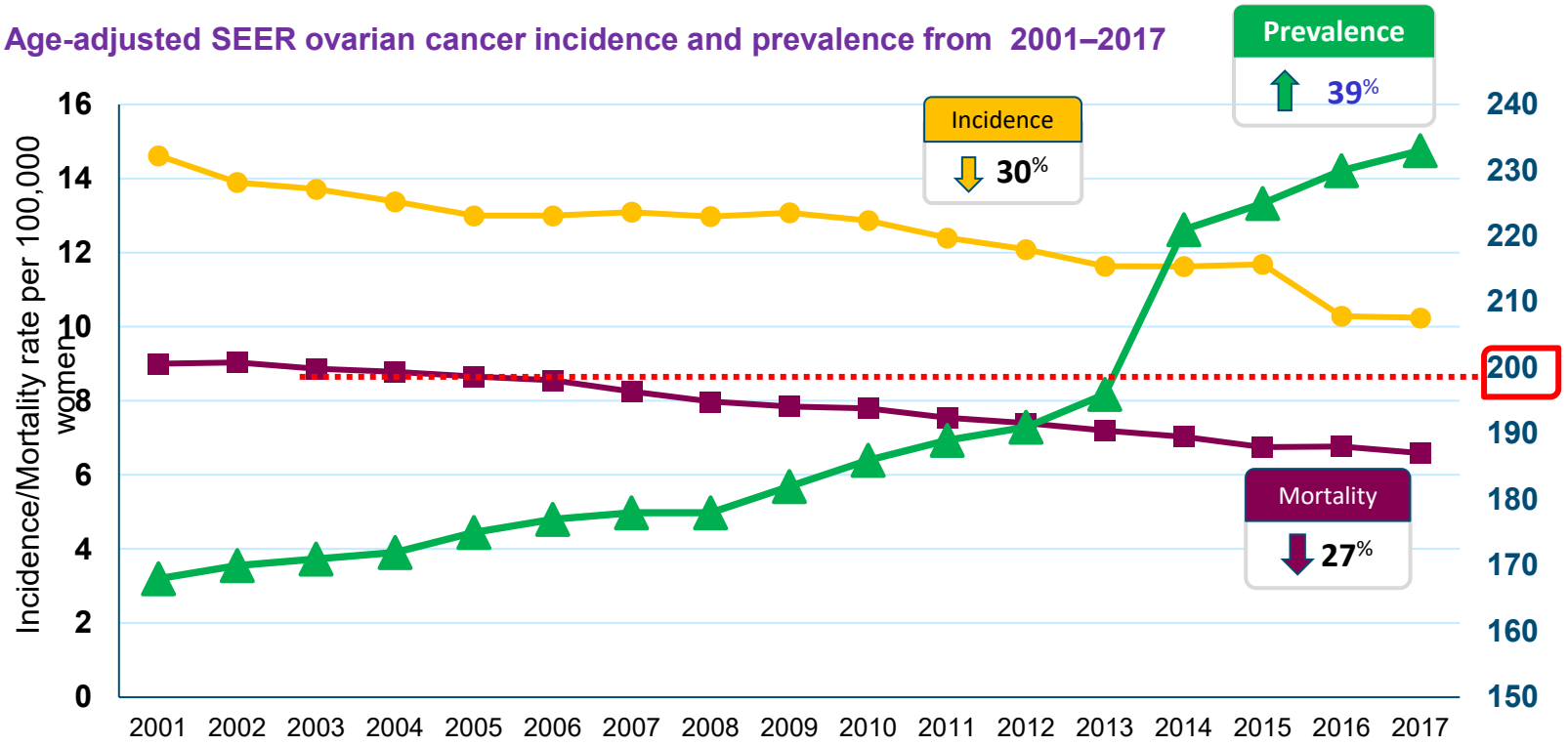



Agenda

GOG Highlight Reel

- Background
- First Line
  - Maintenance
  - PROs
  - Dose Intensity
- Platinum Sensitive
  - PARPi Resistance?
  - Molecular Signature

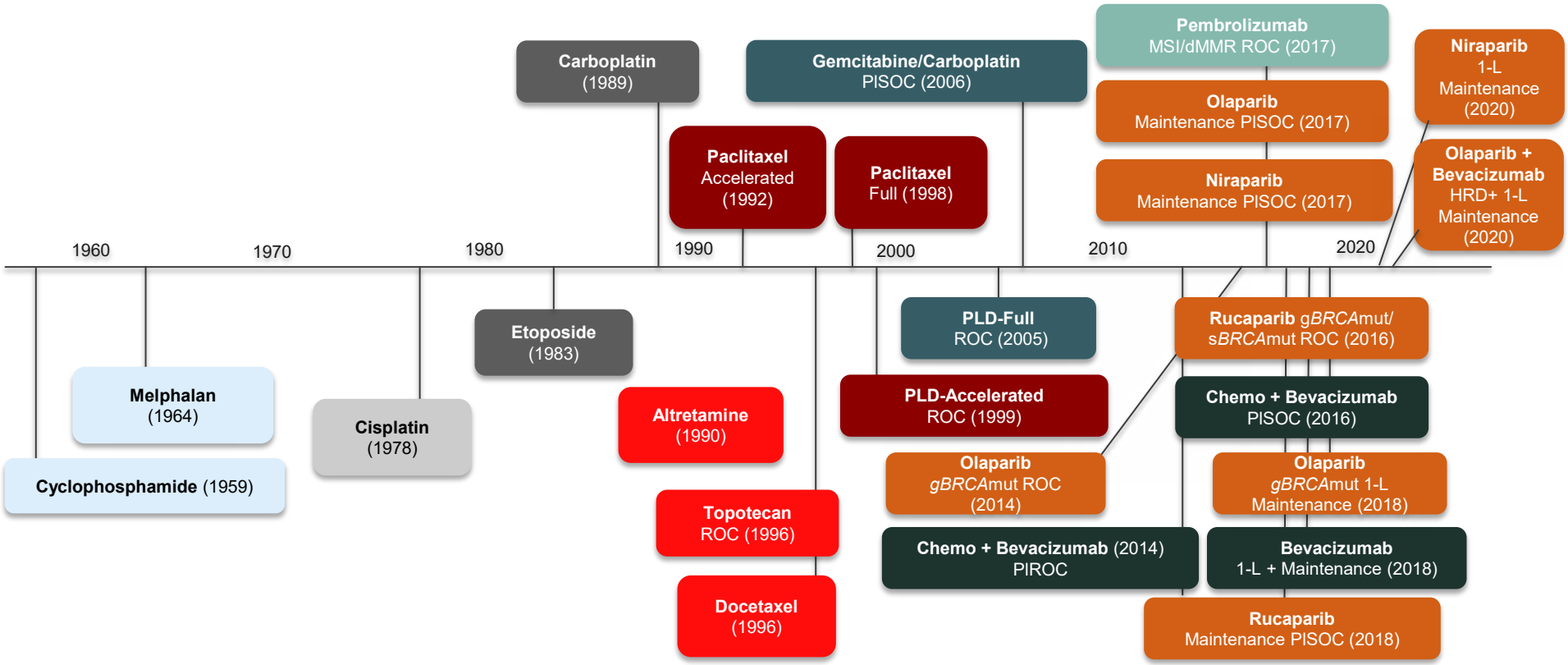
Ovarian Cancer: Clinical Impact



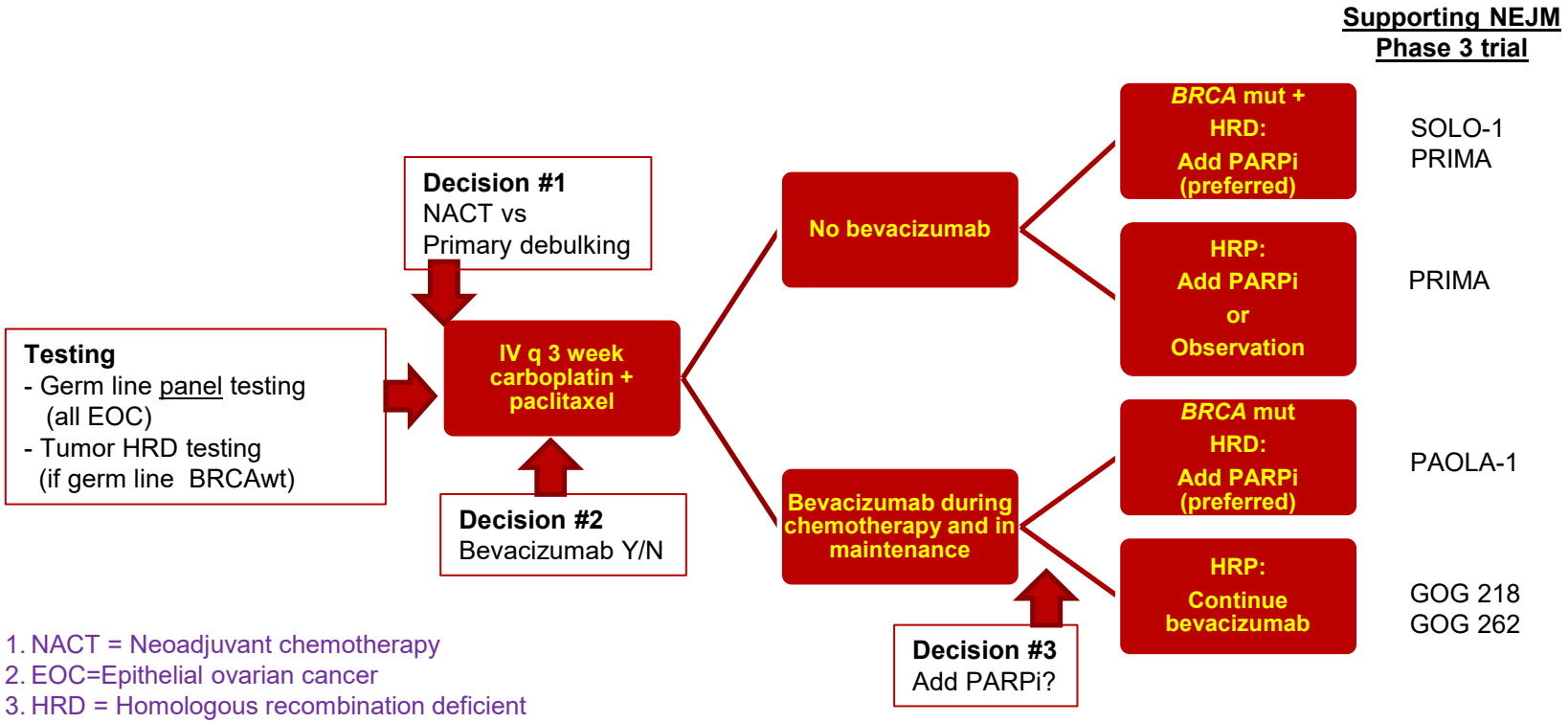
SEER=Surveillance, Epidemiology and End Results.

National Cancer Institute Surveillance, Epidemiology and End Results Program (SEER). SEER Cancer Statistics Review (CSR) 1975-2016 - Ovary. 2016; https://seer.cancer.gov/csr/1975_2016/sections.html. Accessed Apr 14, 2020.

12 (Plus Two Pembrolizumab approvals MSI and TMB) Approvals in the Last 6+ Years



What Is the Standard Systemic Treatment for Newly Diagnosed Advanced EOC 2021?



1. NACT = Neoadjuvant chemotherapy
2. EOC=Epithelial ovarian cancer
3. HRD = Homologous recombination deficient
4. HRP = Homologous recombination proficient
5. PARPi = Poly ADP Ribose inhibitor
6. NEJM = New England Journal of Medicine

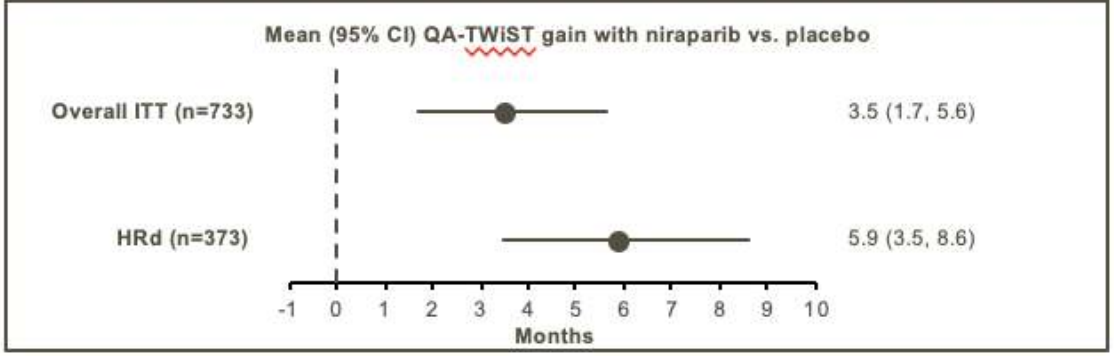
Selecting new upfront regimens for advanced ovarian cancer with biomarker guidance. Chan JK, Liang SY, Kapp DS, Chan JE, Herzog TJ, Coleman RL, Monk BJ, Richardson MT. Gynecol Oncol. 2020 Dec;159(3):604-606.

Quality-Adjusted Time Without Symptoms or Toxicity (QA-TWiST) and Quality-Adjusted Progression-Free Survival (QA-PFS) of First-line Maintenance Niraparib in Patients With Advanced Ovarian Cancer – Results from the PRIMA Trial

Table 2. Mean duration of PFS and QA-PFS per study population at last PFS of the treatment group

Population	Duration, restricted mean (95% CI), months		
	Niraparib	Placebo	Difference
Overall ITT at 27.8 months[a]	n=487	n=246	
PFS	15.5 (14.3, 16.5)	11.9 (10.2, 13.3)	3.6 (1.8, 5.7)
QA-PFS	14.0 (12.6, 15.0)	9.9 (8.6, 11.0)	4.1 (2.2, 5.8)
HRd at 27.8 months[a]	n=247	n=126	
PFS	19.3 (17.6, 20.7)	13.4 (11.0, 15.1)	5.9 (3.5, 8.7)
QA-PFS	17.7 (15.6, 19.1)	11.2 (9.1, 12.6)	6.5 (3.9, 8.9)

Figure 3. QA-TWiST gain for the overall ITT population and HRd population at last PFS of the treatment group



Maria-Pilar Barretina-Ginesta **ESMO 2021**

GOG FOUNDATION® Transforming the standard of care

The James

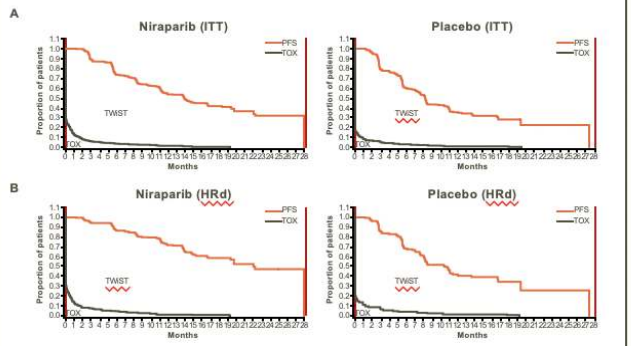
The Ohio State University Wexner Medical Center

Quality-Adjusted Time Without Symptoms or Toxicity (QA-TWiST) and Quality-Adjusted Progression-Free Survival (QA-PFS) of First-line Maintenance Niraparib in Patients With Advanced Ovarian Cancer – Results from the PRIMA Trial

QA-TWiST analyses

- The QA-TWiST analysis for the overall ITT and HRd populations was conducted at the last PFS of patients randomised to niraparib (27.8 months) (**Figure 2**).

Figure 2. Partitioned survival curves for the overall ITT population (A) and the HRd population (B)



Curves show the area under the PFS Kaplan–Meier curves partitioned into two parts: time spent in the TWiST state and time spent in the TOX state. TOX included grade ≥2 AEs of interest (fatigue or asthenia, nausea, vomiting, abdominal pain and abdominal bloating).

- There was a significantly longer restricted mean time spent in the TWiST, but not TOX, state with niraparib compared with placebo (**Table 3**).
- Patients treated with niraparib had significantly greater mean QA-TWiST compared with placebo in the ITT and HRd populations (**Figure 3**).

Table 3. Restricted mean duration of health states for the overall ITT population and HRd population at last PFS of the treatment group

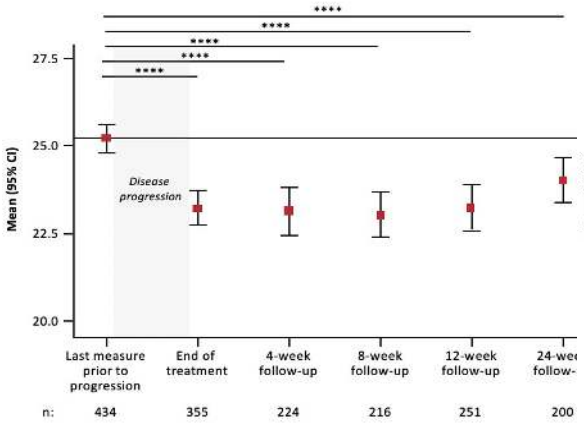
Population	Restricted mean duration (95% CI), months		
	Niraparib	Placebo	Difference
Overall ITT at 27.8 months	n=487	n=246	
TOX[a]	0.7 (0.5, 0.8)	0.4 (0.2, 0.6)	0.2 (−0.1, 0.6)
TWIST	14.8 (13.6, 16.0)	11.5 (9.8, 12.9)	3.3 (1.5, 5.3)
HRd at 27.8 months	n=247	n=126	
TOX[a]	0.7 (0.4, 1.0)	0.6 (0.2, 1.0)	0.1 (−0.4, 0.6)
TWIST	18.6 (16.9, 20.0)	12.8 (10.6, 14.6)	5.8 (3.5, 8.4)

[a]TOX included grade ≥2 AEs of interest (fatigue or asthenia, nausea, vomiting, abdominal pain and abdominal bloating).

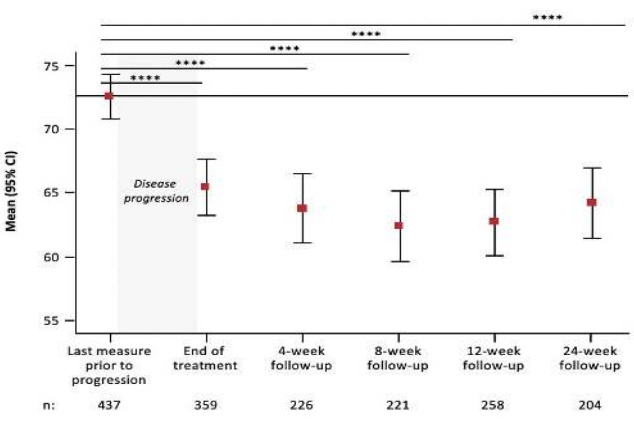
- Maintenance treatment was associated with a significant gain in QA-PFS compared with placebo, indicating a patient-relevant improvement in PFS.
- TWiST demonstrates treated patients remained symptom-free for longer.

Impact of Disease Progression on Health-related Quality of Life of Advanced Ovarian Cancer Patients – Pooled Analysis From the PRIMA Trial

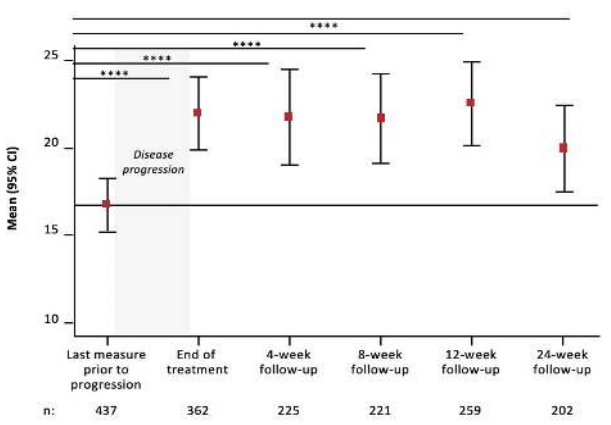
FOSI score



EORTC-QLQ-C30 score



EORTC-QLQ-OV28 abdominal/GI



- There was a **statistically significant decline in HRQoL from pre-progression to EOT** (post-progression) across FOSI, EORTC-C30, EQ-5D VAS and EORTC-OV28 measures
- Preservation of HRQoL is an important therapy goal in the maintenance setting, particularly for asymptomatic patients, and can be **achieved with PFS prolongation**
- HRQoL is **negatively impacted** by disease progression

AGO OVAR BOOST TRIAL

- Histologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer (excluding non-epithelial and borderline tumors)
- FIGO stage IIB–IV (any grade/ histologic subtype)
- Primary debulking surgery ≤8 weeks before treatment start, >4 weeks before first BEV dose
- Adequate coagulation parameters, bone marrow, liver, and renal function
- ECOG PS 0–2
- Standard BEV exclusion criteria

n= 927 Nov 2011 – Aug 2013

R 1:1

BEV 15 mg/kg q3 weeks for 22 cycles (15 months)
Paclitaxel 175 mg/m²
Carboplatin AUC5 q3 weeks

BEV15 (standard arm)

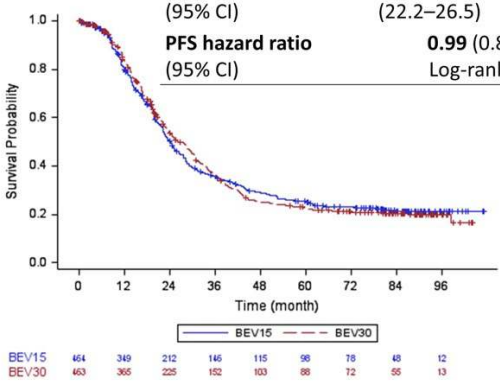
BEV 15 mg/kg q3 weeks for 44 cycles (30 months)
Paclitaxel 175 mg/m²
Carboplatin AUC5 q3 weeks

BEV30 (experimental arm)

Stratification factors
FIGO IIB–IIIC and no residual tumor
versus
FIGO IIB–IIIC with residual tumor *or* FIGO IV

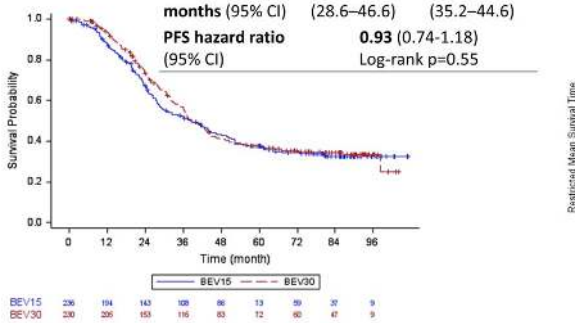
Primary endpoint: PFS

	BEV15 n=464	BEV30 n=463
PFS events, n (%)	333 (72)	340 (73)
Median PFS, months (95% CI)	**24.2** (22.2–26.5)	**26.0** (23.7–29.7)
PFS hazard ratio (95% CI)	**0.99** (0.85–1.15) Log-rank p=0.90	



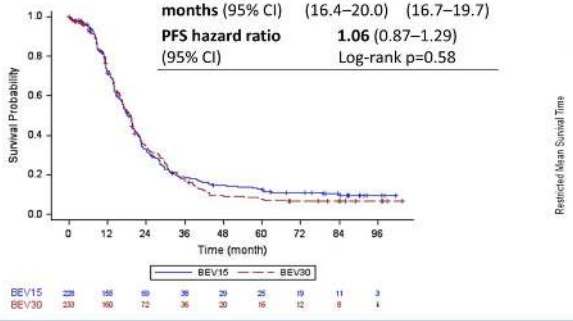
Subgroup analysis of PFS: Stratum FIGO IIB–IIIC and no residual tumor

	BEV15 n=236	BEV30 n=230
PFS events, n (%)	142 (60)	139 (60)
Median PFS, months (95% CI)	**38.4** (28.6–46.6)	**38.8** (35.2–44.6)
PFS hazard ratio (95% CI)	**0.93** (0.74-1.18) Log-rank p=0.55	



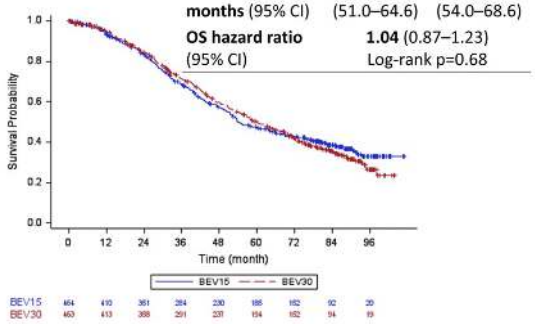
Subgroup analysis of PFS: Stratum FIGO IIB–IIIC with residual tumor *or* FIGO IV

	BEV15 n=228	BEV30 n=233
PFS events, n (%)	191 (83)	201 (86)
Median PFS, months (95% CI)	**19.3** (16.4–20.0)	**18.2** (16.7–19.7)
PFS hazard ratio (95% CI)	**1.06** (0.87–1.29) Log-rank p=0.58	



Overall survival

	BEV15 n=464	BEV30 n=463
OS events, n (%)	257 (55)	275 (59)
Median OS, months (95% CI)	**54.3** (51.0–64.6)	**60.0** (54.0–68.6)
OS hazard ratio (95% CI)	**1.04** (0.87–1.23) Log-rank p=0.68	



J Pfisterer ASCO 2021

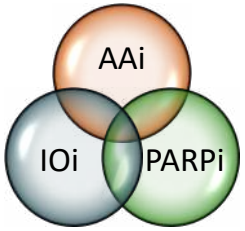
The First-Line Ovarian Cancer Development

First Line Treatment w/ Maintenance	First Line Switch Maintenance
JAVELIN100 (avelumab) - NEG ImaGyn50/GOG-3015 (bevacizumab/atezolizumab) – NEG	ATHENA/GOG-3020 (rucaparib, nivolumab)
FIRST (niraparib/dostarlimab ± bevacizumab)	
GOG-3036/ENGOT-ov43 (olaparib/pembrolizumab ± bevacizumab)	
GOG-3025/ENGOT-ov46 (olaparib/durvalumab ± bevacizumab)	
FLORA-5/GOG-3035 (Oregovomab)	

AAi: Angiogenesis inhibitor

IOi: PD-1/PD-L1 inhibitor

PARPi: PARP inhibitor



GOG Highlight Reel

Platinum Sensitive

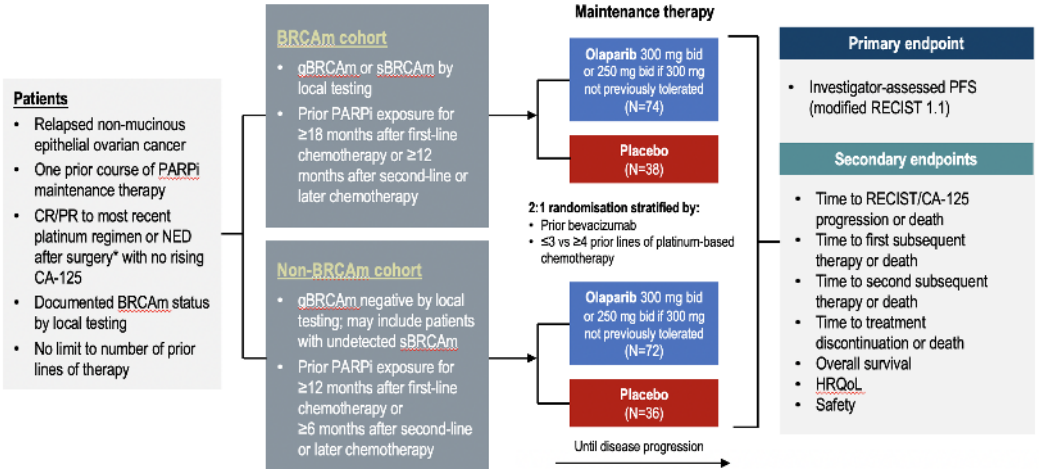
The James

The Ohio State University
Wexner Medical Center

GOG FOUNDATION®
Transforming the standard of care

Maintenance olaparib rechallenge in patients with ovarian carcinoma previously treated with a PARP inhibitor: Phase IIIb OReO/ENGOT Ov-38 trial

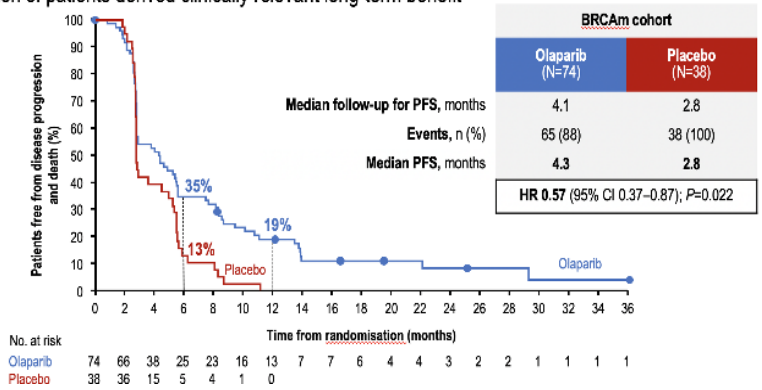
Study design



- Rechallenge with maintenance olaparib following response to platinum-based chemotherapy provided a **statistically significant improvement** in PFS compared with placebo, regardless of BRCAm status
- Being Driven by the tails? Small number of responders?
- Platinum sensitivity a clinical predictor?

A statistically significant PFS benefit was observed with olaparib in the BRCAm cohort

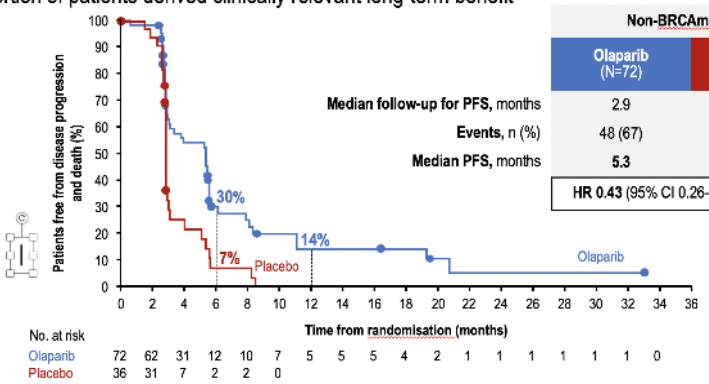
A proportion of patients derived clinically relevant long-term benefit



BRCAm cohort	Olaparib (N=74)	Placebo (N=38)
Median follow-up for PFS, months	4.1	2.8
Events, n (%)	65 (88)	38 (100)
Median PFS, months	4.3	2.8
HR 0.57 (95% CI 0.37–0.87); P=0.022		

A statistically significant PFS benefit was observed with olaparib in the non-BRCAm cohort

A proportion of patients derived clinically relevant long-term benefit



Non-BRCAm cohort	Olaparib (N=72)	Placebo (N=36)
Median follow-up for PFS, months	2.9	2.8
Events, n (%)	48 (67)	30 (83)
Median PFS, months	5.3	2.8
HR 0.43 (95% CI 0.26–0.71); P=0.0023		

GOG FOUNDATION Transforming the standard of care

Eric Pujade-Lauraine ESMO 2021

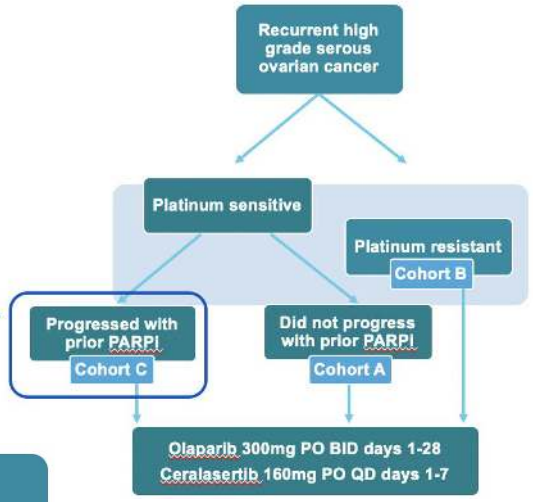
The James

The Ohio State University Wexner Medical Center

Combination of PARP & ATR inhibition (olaparib & ceralasertib) shows clinical activity in acquired PARP inhibitor resistant recurrent ovarian cancer

Aim

- Determine the efficacy and tolerability of the combination of olaparib (PARPi) and ceralasertib (ATRi) in patients who have progressed with prior PARPi (Cohort C)



Platinum sensitive recurrent HGSOC
HR Deficient
Clinical benefit from prior PARPi
No intervening chemotherapy since last PARPi

Olaparib 300mg PO BID days 1-28
Ceralasertib 160mg PO QD days 1-7

Core inclusion criteria

- Platinum sensitive recurrent HGSOC
- Homologous recombination deficiency
  - Germline/somatic BRCA^{MUT}
  - Other HRD mutation
  - HRD positive (≥42 on Myriad My Choice)
- Derived clinical benefit from prior PARPi therapy and then progressed with measurable disease on imaging
- No intervening chemotherapy since PARPi
- Clinical benefit from prior PARPi
  - Maintenance ≥12 months in the front line setting
  - Maintenance ≥6 months in platinum sensitive recurrence
  - Treatment with a decline in CA125 or response on imaging

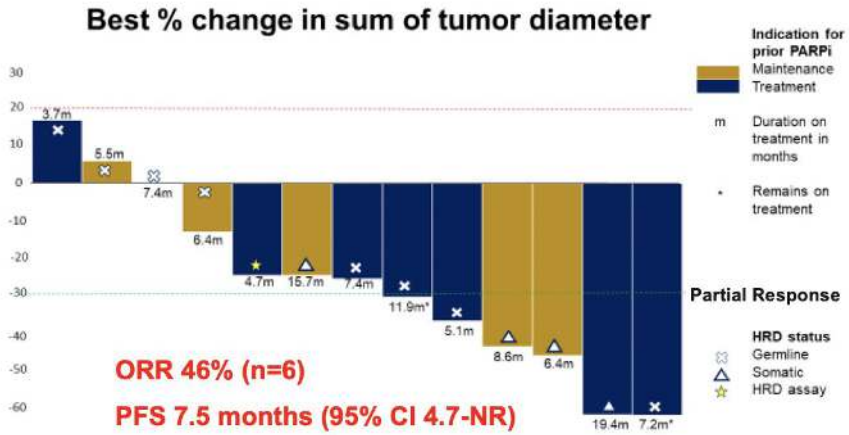
13 subjects

BRCA/HRD

- Germline BRCA^{MUT} 69% (n=9)
- Somatic BRCA^{MUT} 23% (n=3)
- Positive HRD score 8% (n=1)

Prior PARPi

- 1st line maintenance 8% (n=1)
- 2nd line maintenance 38% (n=5
- Treatment 54% (n=7)



Wethington & Simpkins ASCO 2021

GOG FOUNDATION® Transforming the standard of care

The James
The Ohio State University
Wexner Medical Center

Clinical and Molecular Characteristics of ARIEL3 Patients Who Derived Exceptional Benefit From Rucaparib Maintenance Treatment for High-Grade Ovarian Cancer

Table 2. Genetic and Epigenetic Alterations in the Rucaparib Exceptional Benefit and ST Subgroups

Alteration	Exceptional benefit (n=79)	ST subgroup (n=64)	*P* value	Odds ratio (95% CI)
BRCAmut	46 (58.2)	12 (18.8)	**<0.001**	**6.0 (2.8–13.3)**
BRCAwt + *RAD51C/D*	6 (7.6)	0	**0.033**	NA
BRCAwt + other HRR gene	1 (1.3)	5 (7.8)	0.090	0.2 (0.0–1.2)
BRCAwt + LOH-high	18 (22.8)	19 (29.7)	0.443	0.7 (0.3–1.5)
BRCAwt + LOH-low	8 (10.1)	28 (43.8)	**<0.001**	**0.14 (0.1–0.4)**
BRCAwt + high *BRCA1* methylation	6/25 (24.0)	7/47 (14.9)	0.353	1.8 (0.5–6.0)

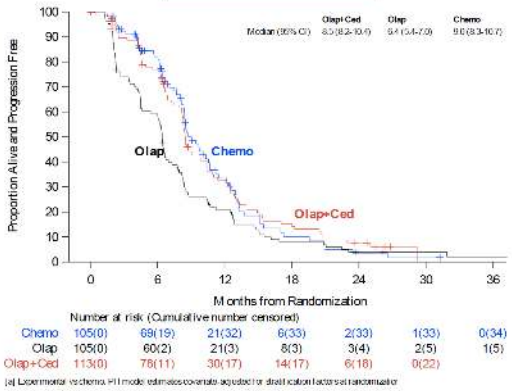
Bold denotes significant result ($P<0.05$). Data are n (%) or n/N (%).
BRCA, *BRCA1* or *BRCA2*; HRR, homologous recombination repair; LOH, loss of heterozygosity; mut, mutated; NA, not applicable; ST, short-term; wt, wild-type.
Data for the placebo arm are available in Supplementary Table 1.

- **In ARIEL3, 21% of patients in the rucaparib-treated arm derived exceptional benefit (progression-free survival ≥2 years) versus only 2% of those in the placebo arm**
- **Exceptional benefit in ARIEL3 was more common in, but not exclusive to, patients with favorable clinical characteristics and known mechanisms of poly(ADP-ribose) polymerase inhibitor sensitivity, including** BRCA1, BRCA2, RAD51C, **and** RAD51D **mutations**

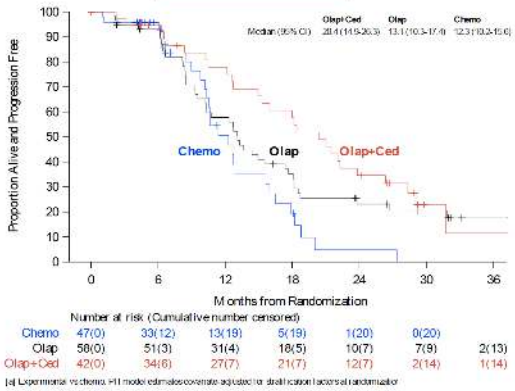
Association of homologous recombination deficiency (HRD) with clinical outcomes in a phase 3 study of olaparib or cediranib and olaparib compared to platinum based chemotherapy in recurrent platinum sensitive ovarian cancer (PSOC): biomarker analyses from NRG GY004

Gene1	Gene2	# Patients	% Patients
ATM	ATM	1	0.68
	BRCA1	1	0.68
	BRCA2	1	0.68
	alone	4	2.72
BARD1	BRCA1	1	0.68
	alone	2	1.36
BRCA1	PALB2	1	0.68
	alone	77	52.38
BRCA2	BRCA2	1	0.68
	NBN	1	0.68
	PALB2	1	0.68
	alone	49	33.33
PALB2	alone	2	1.36
RAD51C	alone	2	1.36
RAD51D	alone	3	2.04
All		**147**	**100**

HRR wild type

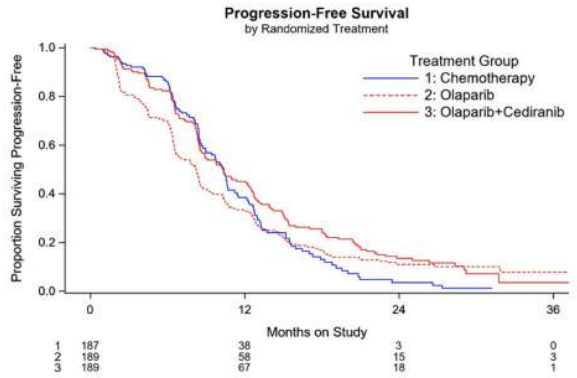


HRR mutant



E Swisher ESMO 2021

- 90% HRD mutations were BRCA
- Both olaparib and cediranib/ olaparib demonstrated activity in patients with HRRmt tumors
- Unclear development plan



J Liu ASCO 2020 The James

Summary

- Five ongoing phase III first line trials
  - 4 completed – at least 1 will likely change the landscape of ovarian cancer
- Maintenance Therapy
  - Keeping cancer away improves Quality of Life
  - BUT Sometimes more isn't better
- What is PARPi resistance? How to overcome?
- Personalized Medicine…..beyond BRCA

GOG FOUNDATION®
Transforming the standard of care

Thank you

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Creating a cancer-free world. One person, one discovery at a time.