Updates in the Frontline Treatment of Advanced Ovarian Cancer

Decision making and biomarker guidance

David Barrington, MD

Gynecologic Oncology

Ochsner Health System

Disclosures

- None

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Ovarian Cancer at a glance

1st

Most lethal gynaecological cancer in women in the United States[1,2]

4th

Most common female cancer after breast, cervical, and corpus uteri[3,*]

8th

Most common cause of cancer-related mortality in women worldwide[3,*]

3.4%

Of an estimated **8.6 million new cases of cancer** in women worldwide[3,*]

5–11 /100,000

Incidence rate is **higher in high income vs. middle/low income countries**[4]

10x

Higher prevalence than incidence in the United states[5]

*Based on GLOBOCAN 2018 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer, with a focus on geographic variability across 20 world regions.[3] 1. CDC Ovarian Cancer Epidemiology in the US. 2017, https://www.cdc.gov/cancer/ovarian/statistics/index.htm (Accessed: Auf 2020); 2. Chan JK, et al. Clin Exp Metastasis 2018;35:521–33; 3. Bray F, et al. CA Cancer J Clin 2018;68:394–424; 4. WCRF: Worldwide data, https://www.wcrf.org/dietandcancer/ovarian-cancer (Accessed: Feb 2020); 5. https://seer.cancer.gov/statfacts/html/ovary.html (Accessed: Aug 2020).

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Ovarian Cancer Treatment: The Changing Paradigm.

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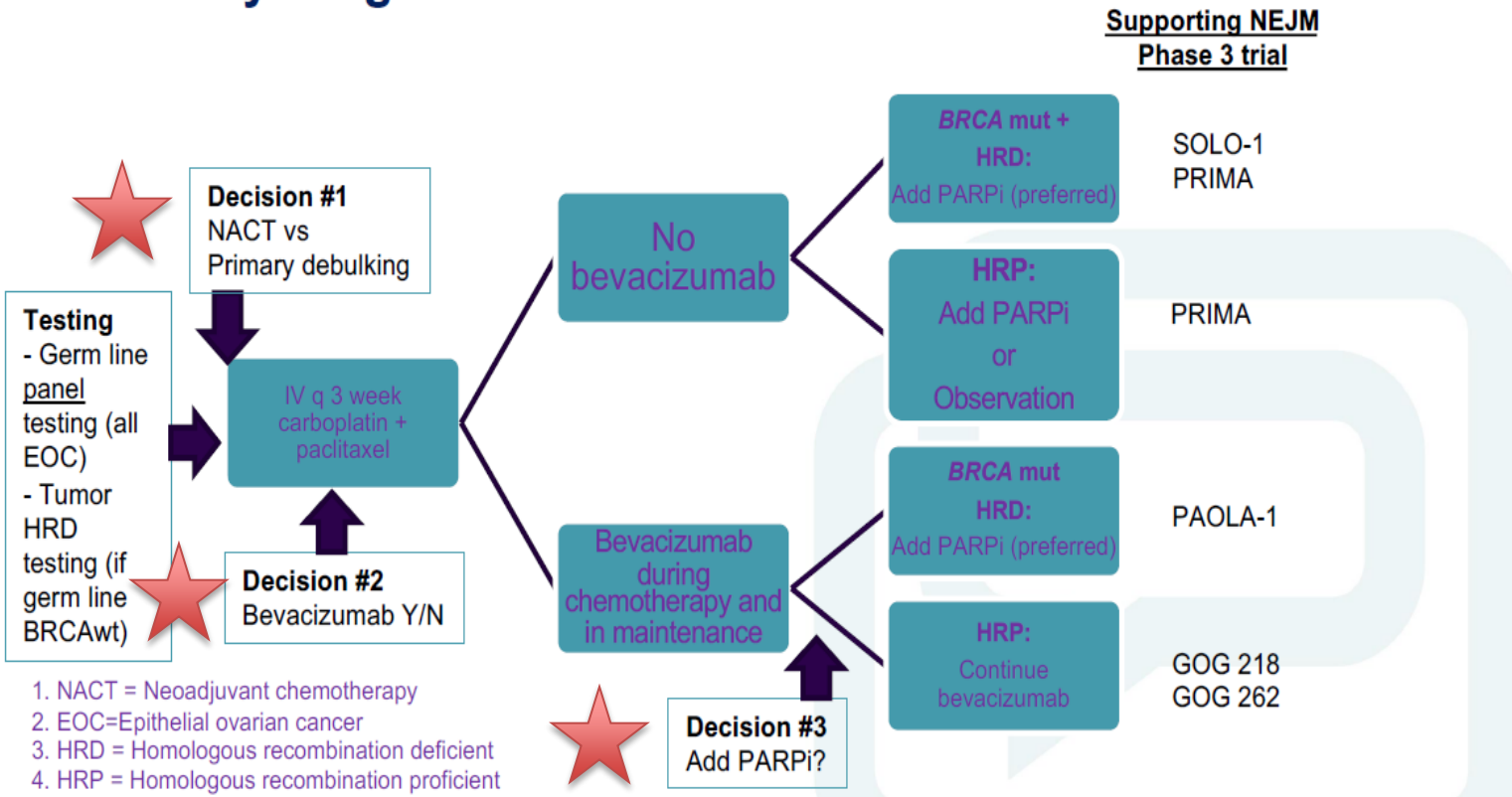
What Is the Standard Systemic Treatment for Newly Diagnosed Advanced EOC 2020?



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.

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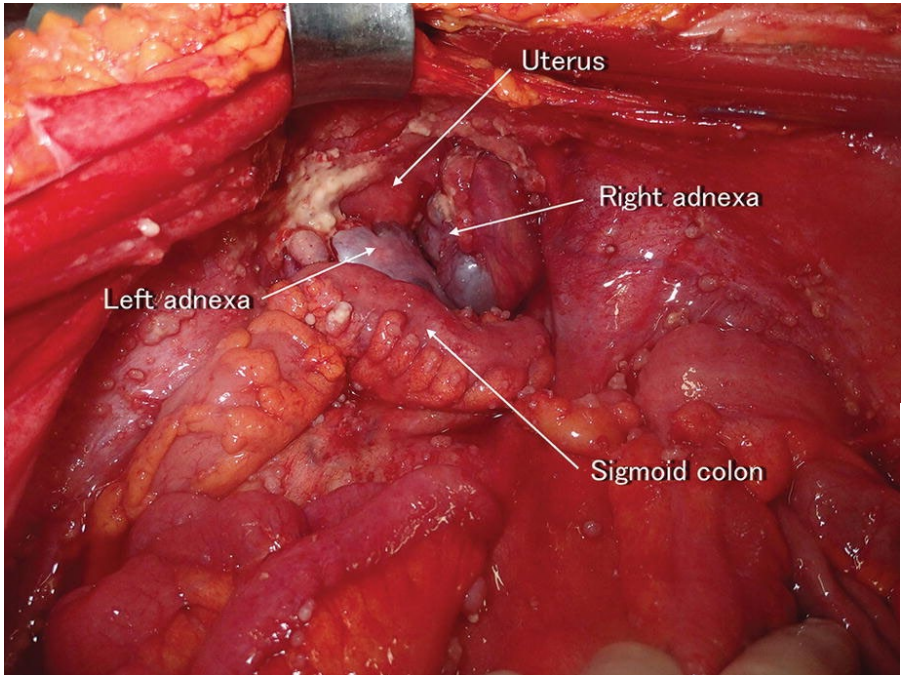
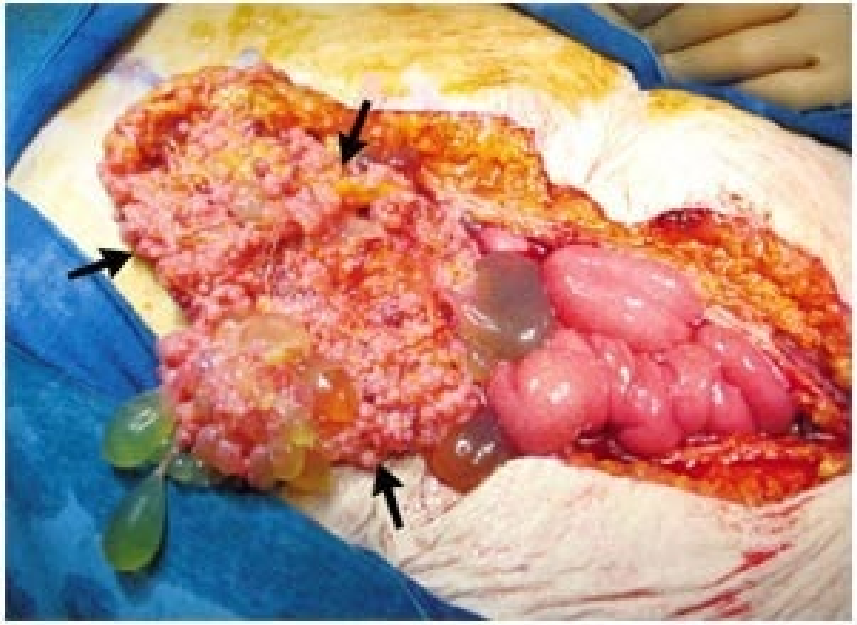
Decision #1: Upfront surgery or NACT





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Surgical Options

- Primary Debulking Surgery (PDS)
- Neoadjuvant Chemotherapy (NACT)

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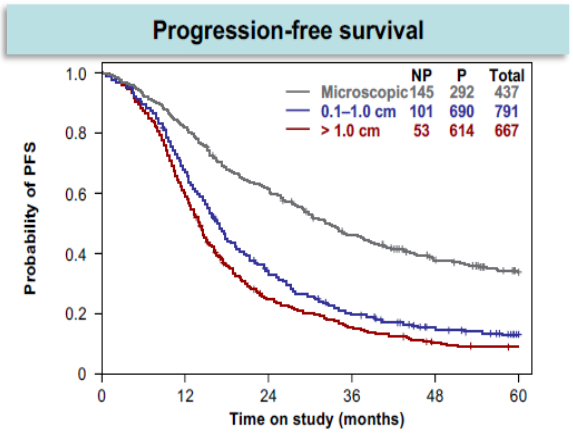
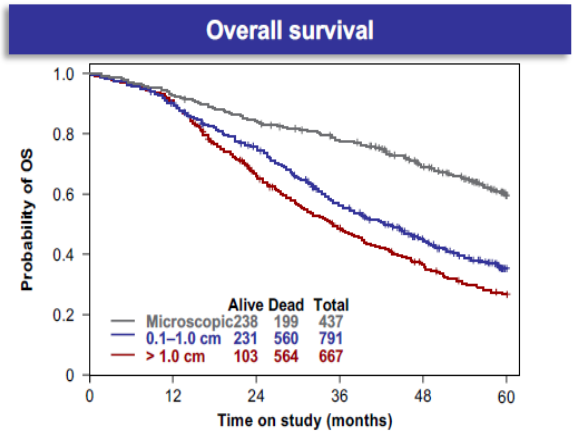
Residual disease volume

As a predictor in newly diagnosed stage III ovarian cancer





NP, no progression; P, progression; OS, overall survival; PFS, progression-free survival.

Winter WE, et al. J Clin Oncol 2007;25:3621–7. Reprinted with permission. © (2007) American Society of Clinical Oncology (TBC).

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Upfront surgery or NACT

- NACT versus Primary Surgery
  - EORTC 55971 (2010)
  - CHORUS trial (2015)
  - SCORPION (2016, 2020)
  - JCOG 0602 (2016, 2020)
- What did we learn?
  - NACT non-inferior to PDS for OS and PFS (55971 & CHORUS)
  - 55971 / CHORUS suggest PDS better for less extensive disease, NACT for extensive disease
  - NACT non-inferiority not confirmed by JCOG 0602
  - SCORPION - NACT not superior to PDS for PFS or OS in high disease burden
  - NACT had lower morbidity & mortality across trials
  - Median survivals , operative times, optimal cytoreduction low across trials

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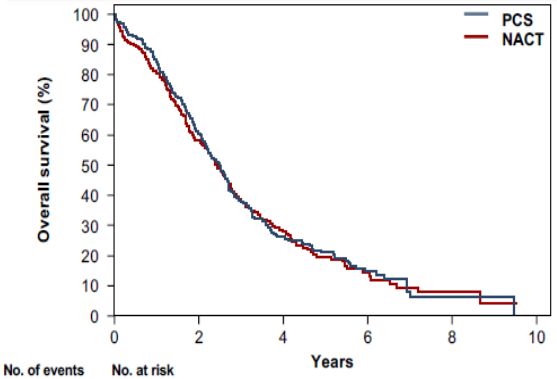
Vergote et al. N Engl J Med 2010;363(10);943
Kehoe et al. Lancet 2015;386:249-57
Vergote et al. Lancet Oncol 2018;19:1680-7
Onda et al. Eur J Cancer 2020;130:114
Fagotti et al. Int J Gynecol Cancer 2020;30:1657-1664

Neoadjuvant chemotherapy

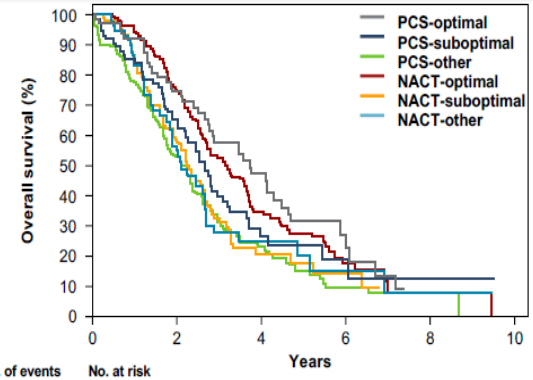
Is non-inferior to primary cytoreductive surgery

OS by treatment group



No. of events	No. at risk					
PCS	253	336	189	62	14	2
NACT	245	334	195	46	13	2

OS by treatment group and residual tumour



No. of events	No. at risk					
PCS–optimal	42	62	46	22	6	0
PCS–suboptimal	52	74	46	11	3	1
PCS–other	136	169	86	29	5	1
NACT–optimal	100	152	110	30	8	2
NACT–suboptimal	67	87	49	9	3	0
NACT–other	41	53	29	6	2	0

NACT, neoadjuvant chemotherapy; OS, overall survival; PCS, primary cytoreductive surgery.

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Heated intraperitoneal chemotherapy at time of IDS

- Cytotoxicity from **synergy** of local intraperitoneal chemotherapy administration and hyperthermia
- **Heat** known to **increase cytotoxicity** of platinum through increased **DNA adduct formation**
- Intraperitoneal administration
  - High concentration of cytotoxic drug to tumor
  - Reduced systemic absorption and toxicity
  - High peritoneal to plasma ratio promotes extended exposure → increased locoregional therapeutic effect

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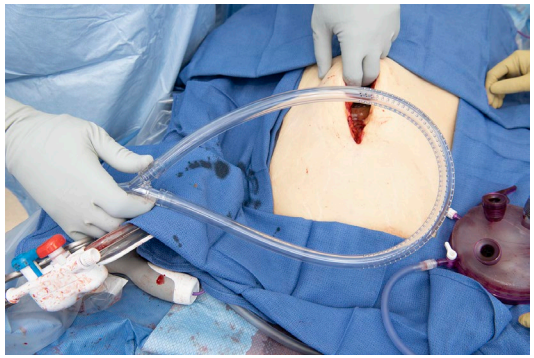
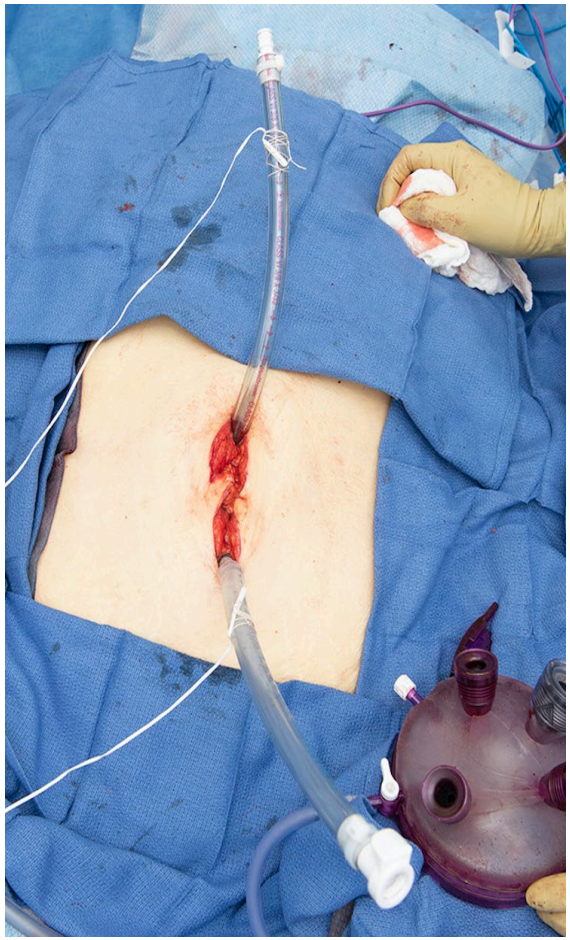
Steps

- Completion of CRS
- Placement of catheters
- Temporary closure of abdomen
- 90 min infusion of chemotherapy heated to 41-43℃





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Van Driel, OVHIPEC, NEJM, 2018

- Multicenter, P3 trial of 245 women with at least stable disease after 3 cycles of Carboplatin AUC 5/6 + Paclitaxel 175mg/m2 to undergo:
  - IDS + HIPEC with Cisplatin 100mg/m2: 122
  - IDS alone: 123
  - 3 additional cycles of Carboplatin/Paclitaxel given post-op
- Primary Objective: PFS
- Secondary Objectives: OS, toxicity, QOL
- Power: 245 patients, for 80% power to detect 50% longer PFS

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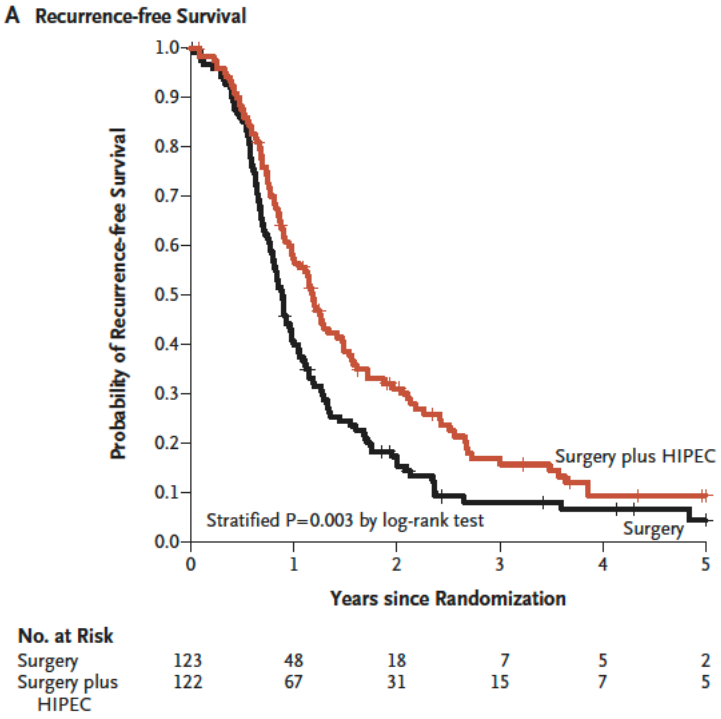
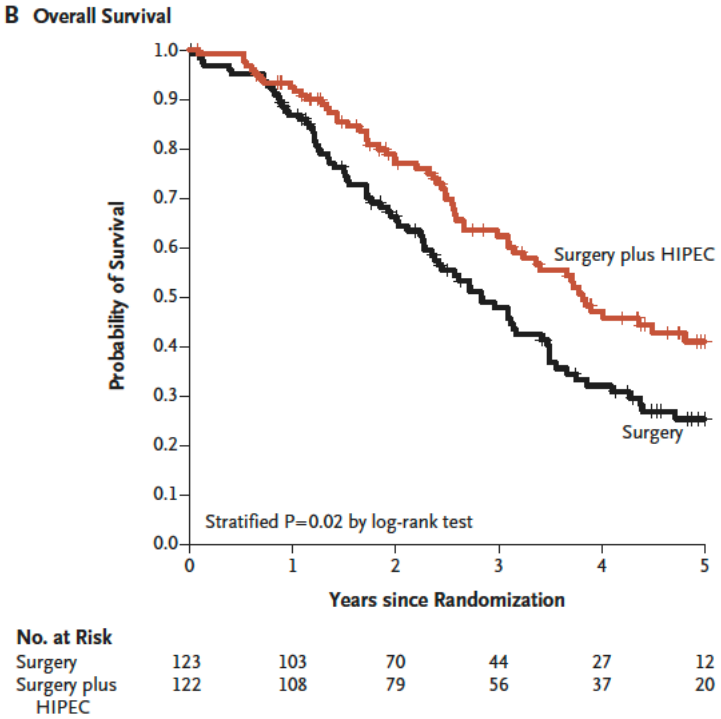
Van Driel, OVHIPEC, NEJM, 2018





Improved PFS - 14.2 vs. 10.7 months; HR 0.66, 95% CI 0.50, 0.67, p=0.003

Improved OS – 45.7 vs. 33.9 months; HR 0.67, 95% CI 0.48, 0.94, p=0.02

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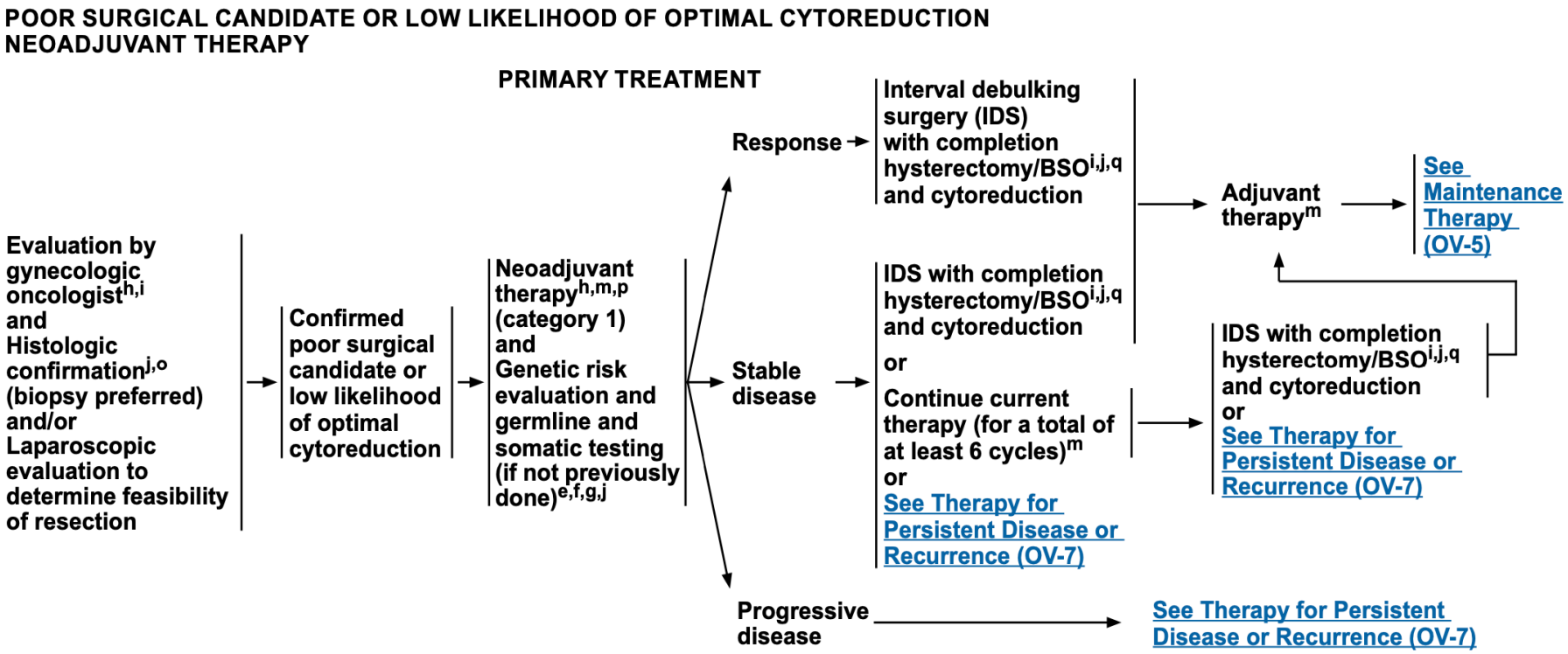
NCCN Guidelines for HIPEC



[q] Hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin (100 mg/m^2) can be considered at the time of IDS for stage III disease.

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Upcoming Trials

Table 1
Ongoing Phase III randomized clinical trials evaluating HIPEC in ovarian cancer.

NCT number	Study Acronym	Study Title	Phase	Indication	Study description	HIPEC Drug	n	Primary outcome	Country	Study duration	Status
NCT03842982	CHIPPI	Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Ovarian Cancer	III	Primary EOC	Arm 1: 1'CRS or IDS with HIPEC Arm 2: 1'CRS or IDS without HIPEC	Cisplatin 100 mg/m^2 x 90 min	432	DFS	France	4/2019–6/2024	Recruiting
NCT02681432	HIPEC-OVA	Hyperthermic Intraperitoneal Chemotherapy With Paclitaxel in Advanced Ovarian Cancer	III	Primary EOC	HIPEC-arm: 1'CRS with HIPEC No HIPEC-arm: 1'CRS without HIPEC	Paclitaxel 175 mg/m^2 x 60 min.	60	OS	Spain	1/2012–12/2019	Recruiting
NCT03772028	OVHIPEC-2	Primary Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy (HIPEC)	III	Primary EOC	Arm 1: 1' CRS with HIPEC Arm 2: 1'CRS without HIPEC	Cisplatin 100 mg/m^2 x 90 min	538	OS	Netherlands	11/2019–4/2025	Recruiting
NCT03373058	HIPEC-04	Efficacy of HIPEC in the Treatment of Advanced-Stage Epithelial Ovarian Cancer After Cytoreductive Surgery	III	Primary EOC	Arm 1: 1'CRS followed by successive postop HIPEC before and after 48 h Arms 2: 1'CRS without HIPEC	Docetaxel 75 mg/m^2, Cisplatin 75 mg/m^2, x 90 min	310	DFS	China	7/2021–7/2023	Recruiting
NCT03180177	HIPEC-03	Efficacy of HIPEC as NACT and Postoperative Chemotherapy in the Treatment of Advanced-Stage Epithelial Ovarian Cancer	III	Primary EOC	Arm 1: NACT followed by IDS followed by successive postop HIPEC 24 h, 48 h after IDS Arm 2: NACT followed by IDS without HIPEC	Paclitaxel 175 mg/m^2 (24h post-op) Cisplatin 75 mg/m^2 (48h postop), x 90 min	263	DFS PR/SD rate	China	3/2018–7/2022	Recruiting
NCT03220932	HIPOVA-01	Cytoreductive Surgery and HIPEC in First or Secondary Platinum-resistant Recurrent Ovarian Epithelial Cancer	III	Recurrent (platinum-refractory)	Arm 1: Carbo/Taxol/Bev x3 followed by IDS with HIPEC followed by Carbo/Taxol/Bev x3 Arm 2: Carbo/taxol/bev without CRS/HIPEC	Cisplatin 70 mg/m^2 x 60 min	132	PFS	France	9/2019–9/2022	Not yet recruiting
NCT01376752	CHIPOR	Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in Relapse Ovarian Cancer Treatment	III	Recurrent (platinum-sensitive)	Arm 1: Platinum-based NACT x 6 cycles, followed by 2'CRS with HIPEC Arm2: Platinum-based NACT x 6 cycles, followed by 2'CRS without	Cisplatin 75 mg/m^2 x 60 min	404	OS	Belgium/France	4/2011–4/2025	Recruiting

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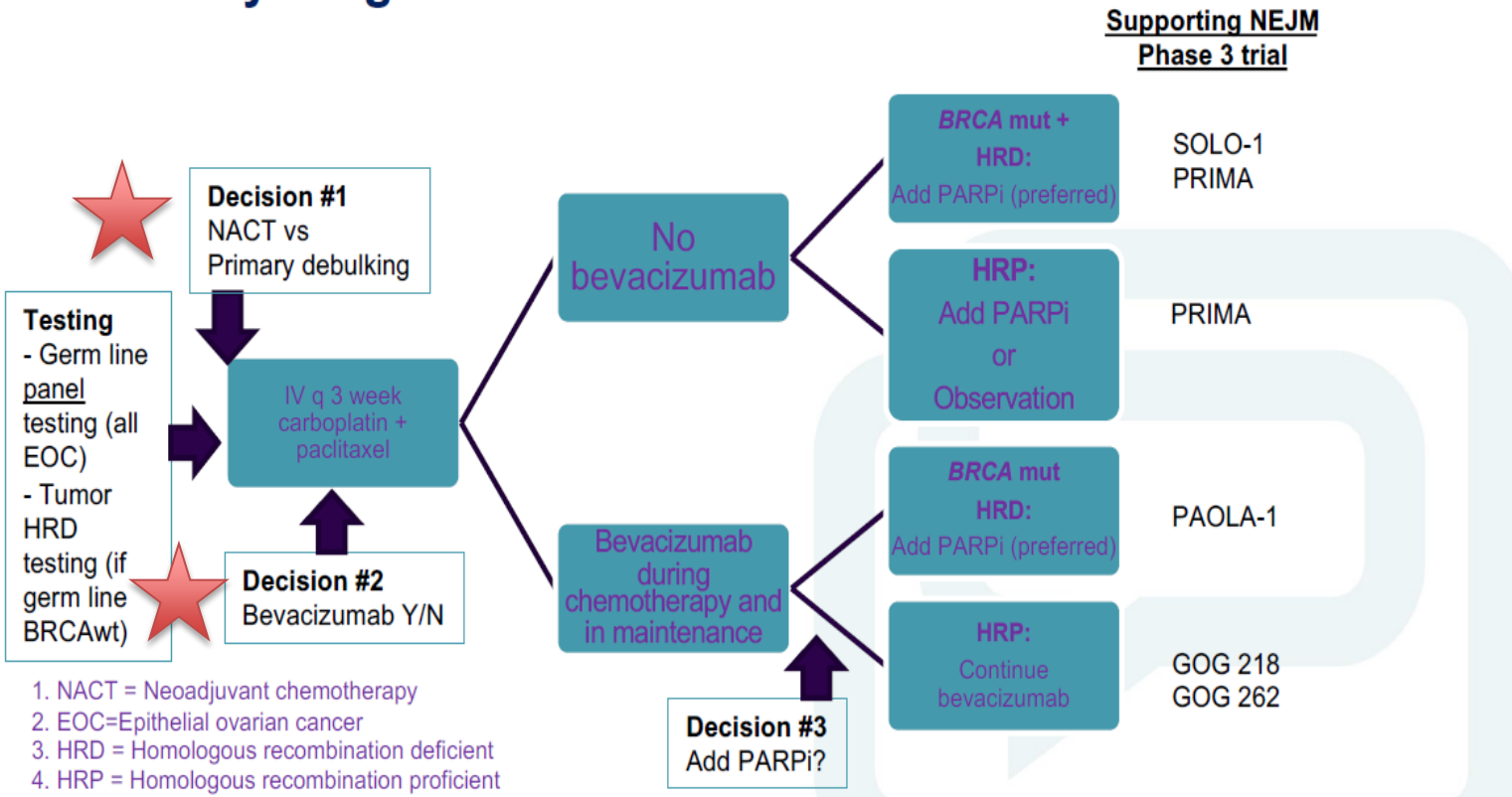

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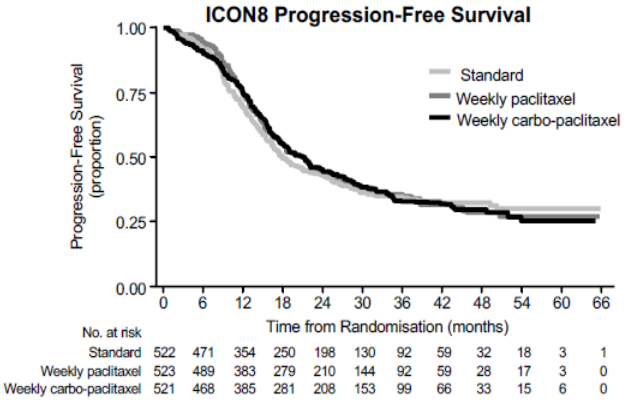
Decision #2: Addition of bevacizumab to primary systemic chemotherapy

First-Line Chemotherapy [Historical] Standard of Care: Every 3 week IV Carboplatin and Paclitaxel



	Standard (n=522)	Weekly paclitaxel (n=523)	Weekly carbo-paclitaxel (n=521)
Progressions	330 (63%)	335 (64%)	338 (65%)
Median PFS, mo	17.9	20.6	21.1
Log rank (vs standard)		*P*=0.45	*P*=0.56
HR vs Standard (97.5% CI)		0.92 (0.77–1.09)	0.94 (0.79–1.12)
Restricted means	24.4 months	24.9 months	25.3 months

Weekly dose-dense chemotherapy can be delivered successfully as first-line epithelial ovarian cancer treatment without substantial toxicity increase; it does not significantly improve PFS compared to standard 3-weekly chemotherapy

CI=confidence interval; HR=hazard ratio; PFS=progression-free survival.
Clamp AR et al. Presented at: ESMO Annual Meeting; 2017.

Lancet. 2019 Dec 7;394(10214):2084-2095.

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- Bevacizumab
  - GOG 218
    - PFS 14.1 v 10.3 in favor of bev throughout (18 v 12 when CA125 data censored) *(HR 0.717; 95% CI, 0.625-0.824; P < .001)*
    - OS 43.4 v 41.1 (not significant)
    - Stage IV OS 42.8 v 32.6 (significant; exploratory subgroup analysis)
    - **no OS benefit in exploratory analysis classifying patients as ICON7 high-risk subgroup**
  - ICON-7
    - PFS 22.4 v 24.1 in favor of bev throughout *(P = 0.04)*
    - OS 45.5 v 44.6 (not significant)
    - Stage IV, suboptimal stage III OS 39.3 v 34.5 (significant; exploratory)

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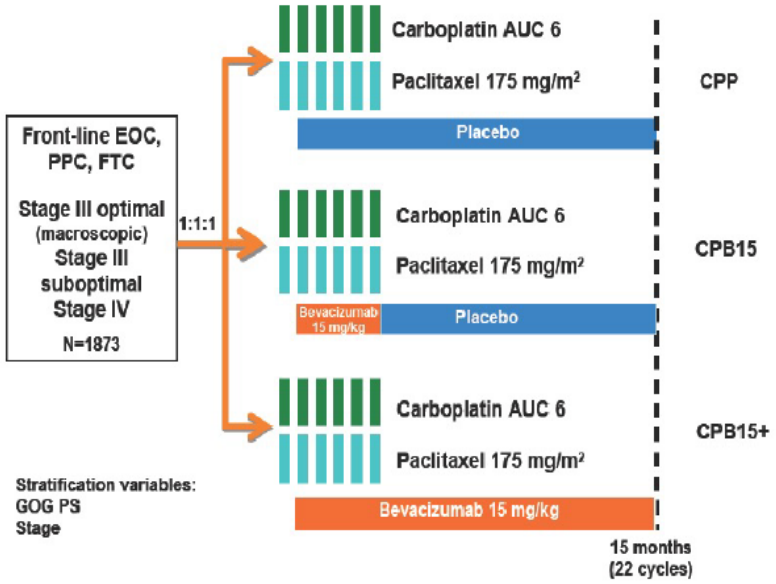
Burger et al. N Engl J Med. 365(26) (2011) 2473-2483
Tewari et al. J Clin Oncol. 37(26) (2019) 2317-2328
Perren et al. N Engl J Med. 365(26) (2011)2484-96
Oza et al. Lancet Oncol. 16(8) (2015) 928-936

Phase III GOG-218 Study of Adjuvant Chemotherapy + Bevacizumab: Design

GOG-218[2] (NCT00262847) was a double-blinded, randomized, controlled phase 3 trial that included 1,873 women with stage III-IV disease, all of whom received CT.[b] Participants randomized to: CT + placebo (PBO, cycles 2–22; control), CT + bev (bev, 15 mg/kg cycles 2–6), followed by PBO (cycles 7–22, bev-initiation), or CT + bev (15 mg/kg cycles 2–22, bev-throughout)



Primary endpoint: PFS

Baseline characteristics:

- 40% suboptimally resected stage III
- 26% stage IV

N Engl J Med. 2011 Dec 29;365(26):2473-83.
J Clin Oncol. 2019 Sep 10;37(26):2317-2328.

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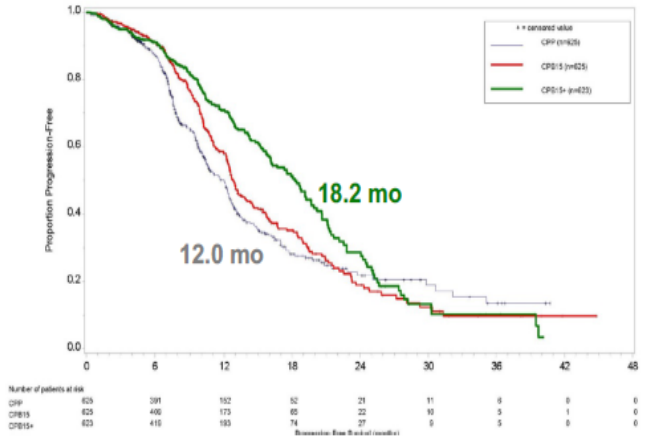
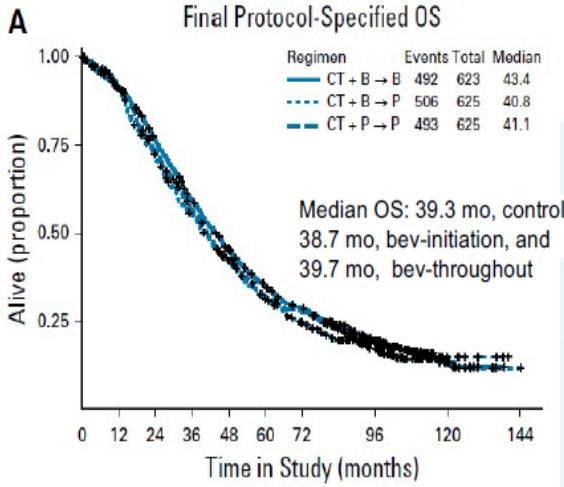
Phase 3 GOG-218 Study of Adjuvant Chemotherapy + Bevacizumab: Efficacy Outcomes

PFS (Primary Endpoint)

	Bev Throughout (CPB15+)	Bev Initiation (CPB15)	Control (CPP)
mPFS (mo)	18.2	12.8	12.0
HR (95% CI) P-value	0.62 (0.52, 0.75) < 0.0001	0.83 (0.70, 0.98) NS	



Final OS (103 month follow up)



No survival differences observed with addition of bevacizumab compared with CT alone

N Engl J Med. 2011 Dec 29;365(26):2473-83.
J Clin Oncol. 2019 Sep 10;37(26):2317-2328.

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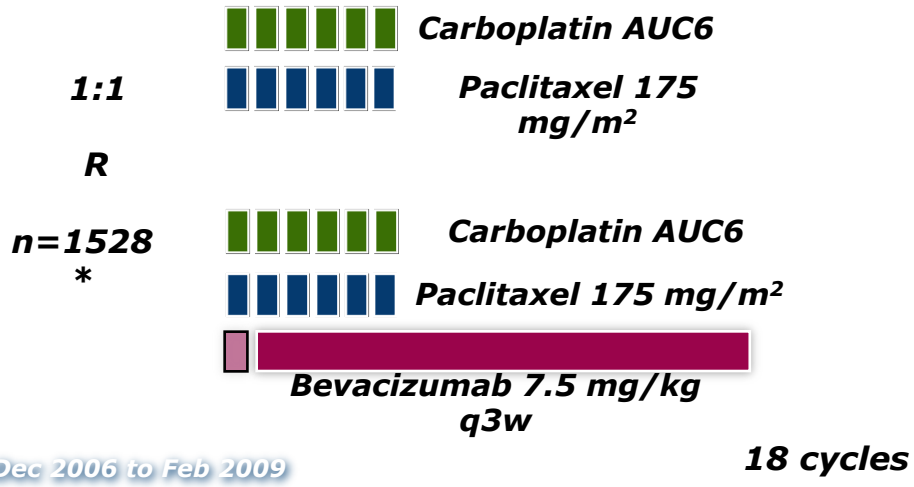
ICON7:Study Design

Academic-led, industry-supported trial to investigate use of bevacizumab and to support licensing



Stratification variables
Stage and extent of debulking: I–III debulked ≤1cm vs I–III debulked >1 cm vs IV and inoperable III
Timing of intended treatment start: ≤ vs > 4 weeks after surgery
GCIG group

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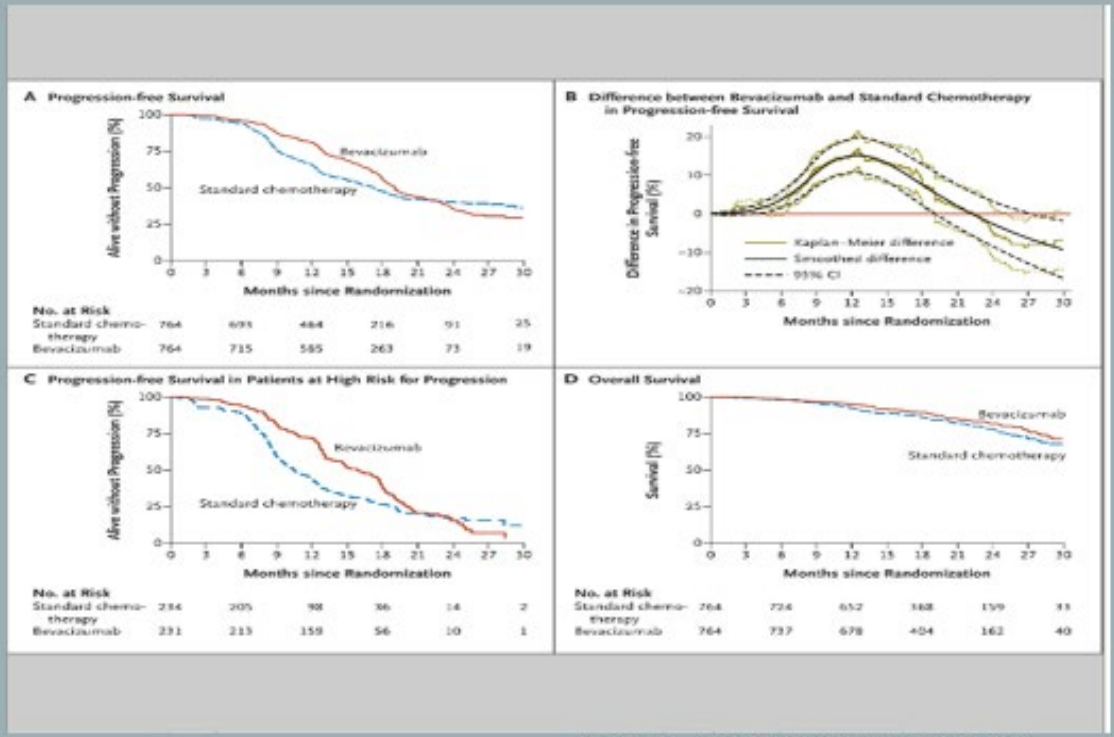
ICON 7 PFS/OS

- 17.3m vs 19m (bev) (p=0.004)
- no diff 44m vs 45m



Perren TJ, *et al. NEJM*; 365(26):2484-96, 2011

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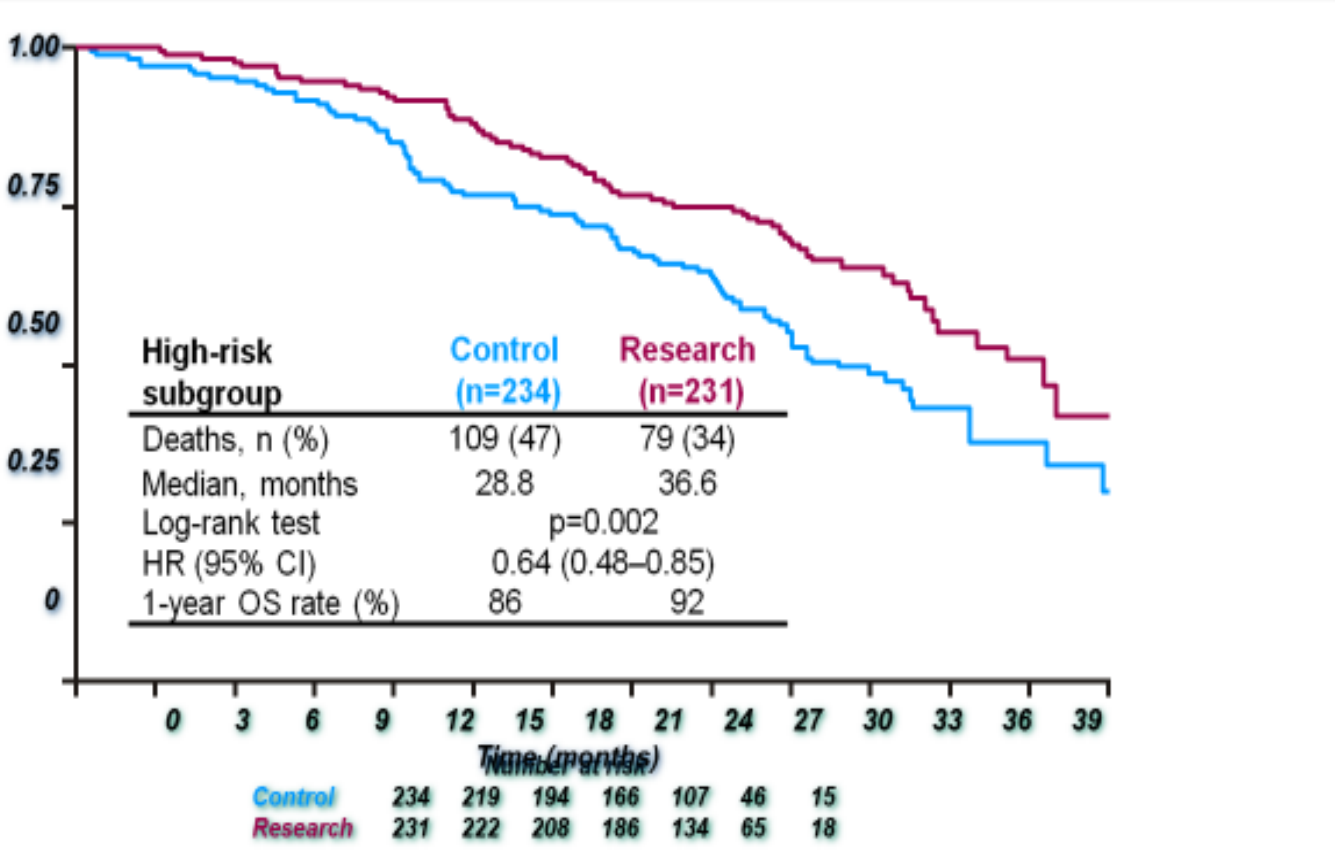
ICON7: High-Risk OS



- overall benefit of bev modest. addition of Bev in up front ovary CA adds 2mo to PFS, no difference in OS (18 total cycles [12mo] rather than 22 in 218)
- bev has greatest benefit in high risk pts (stage 4, inoperable or suboptimal stage 3)—these pts comprised 1/3 of study population—improved PFS & OS
-no diff w bev in outcomes w clear cell, LGSC, or low stage high grade tumors

Kristensen G, et al. ASCO 2011

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Primary Systemic Therapies

- Paclitaxel / carboplatin q 3weeks
- Paclitaxel / carboplatin/bevacizumab + maintenance bevacizumab

→ *NCCN "Preferred"*

- Paclitaxel weekly / carboplatin weekly
- Docetaxel / carboplatin
- Carboplatin / liposomal doxorubicin
- Paclitaxel weekly / carboplatin q3weeks

→ *NCCN "other recommended"*

- IP/IV paclitaxel / cisplatin

→ *NCCN "useful in certain circumstances"*

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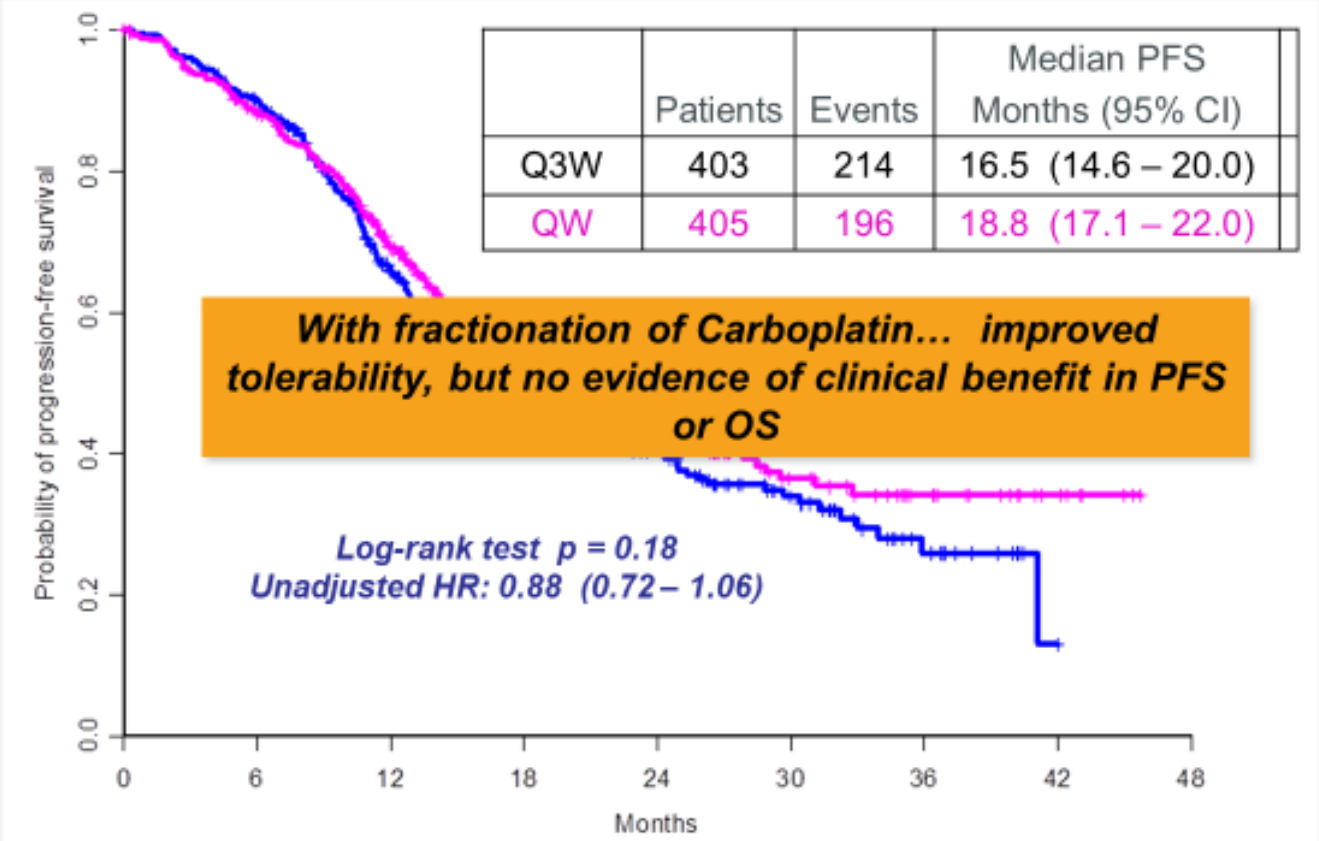
MITO 7: Weekly Therapy

Differences from JGOG study:
- q3wk regimen in JGOG G3-4 neutropenia 88%, thrombocytopenia 38%, and anemia 44% vs 50%, 7%, and 8%
- (? polymorphisms in genes that metabolize drugs lead to diff toxic effects in Asians compared to Europeans)--25% lower dose qwk tax than JGOG (60mg/m2 vs 80mg/m2)



	Patients	Events	Median PFS Months (95% CI)
Q3W	403	214	16.5 (14.6 – 20.0)
QW	405	196	18.8 (17.1 – 22.0)

With fractionation of Carboplatin… improved tolerability, but no evidence of clinical benefit in PFS or OS

Pignata S, for MITO, ASCO 2013

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From: **Efficacy and Safety of First-line Single-Agent Carboplatin vs Carboplatin Plus Paclitaxel for Vulnerable Older Adult Women With Ovarian Cancer: A GINECO/GCIG Randomized Clinical Trial**

JAMA Oncol. 2021;7(6):853-861. doi:10.1001/jamaoncol.2021.0696

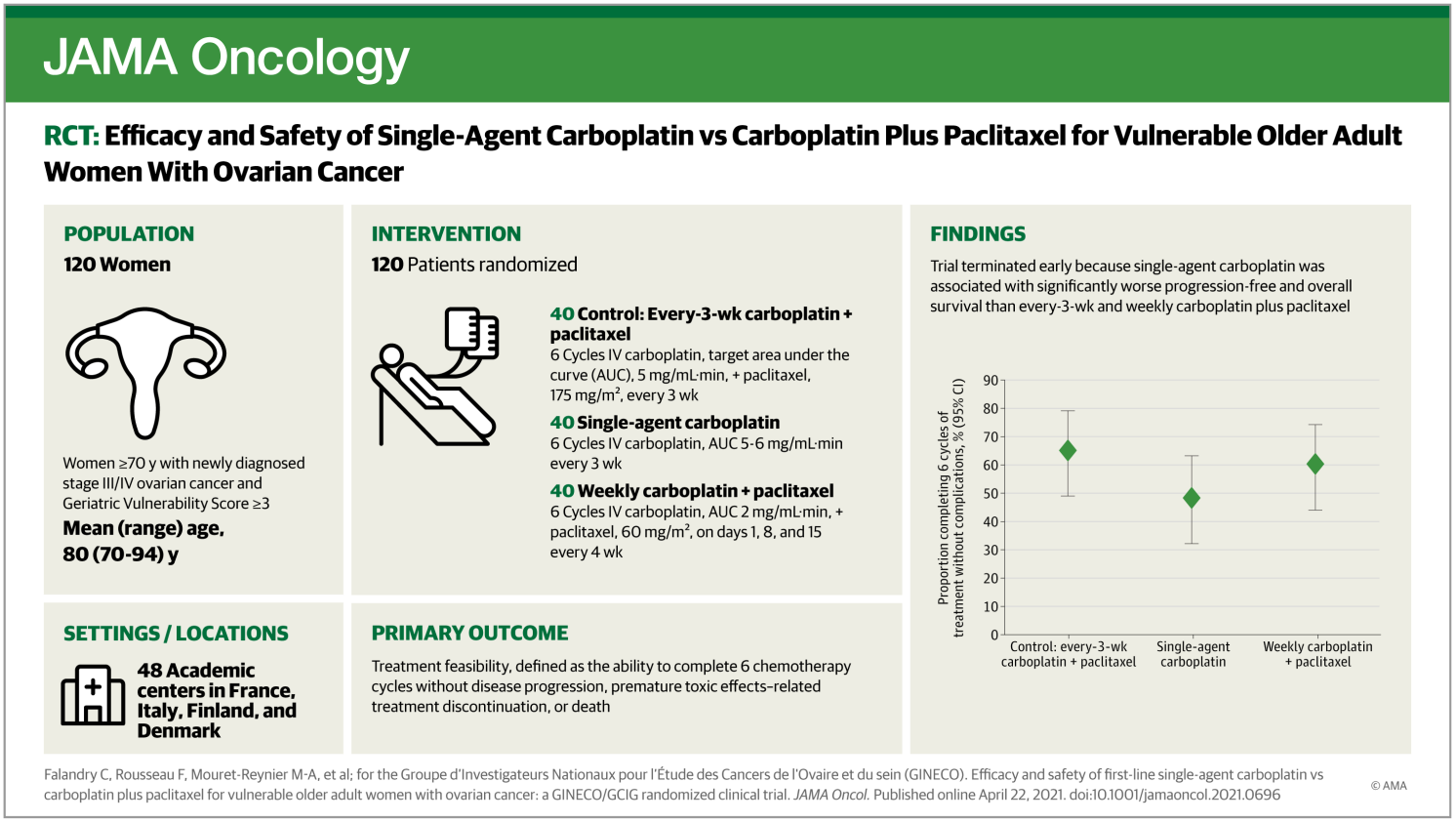

Figure Legend:

Efficacy and Safety of Single-Agent Carboplatin vs Carboplatin Plus Paclitaxel for Vulnerable Older Adult Women With Ovarian Cancer

From: **Efficacy and Safety of First-line Single-Agent Carboplatin vs Carboplatin Plus Paclitaxel for Vulnerable Older Adult Women With Ovarian Cancer: A GINECO/GCIG Randomized Clinical Trial**

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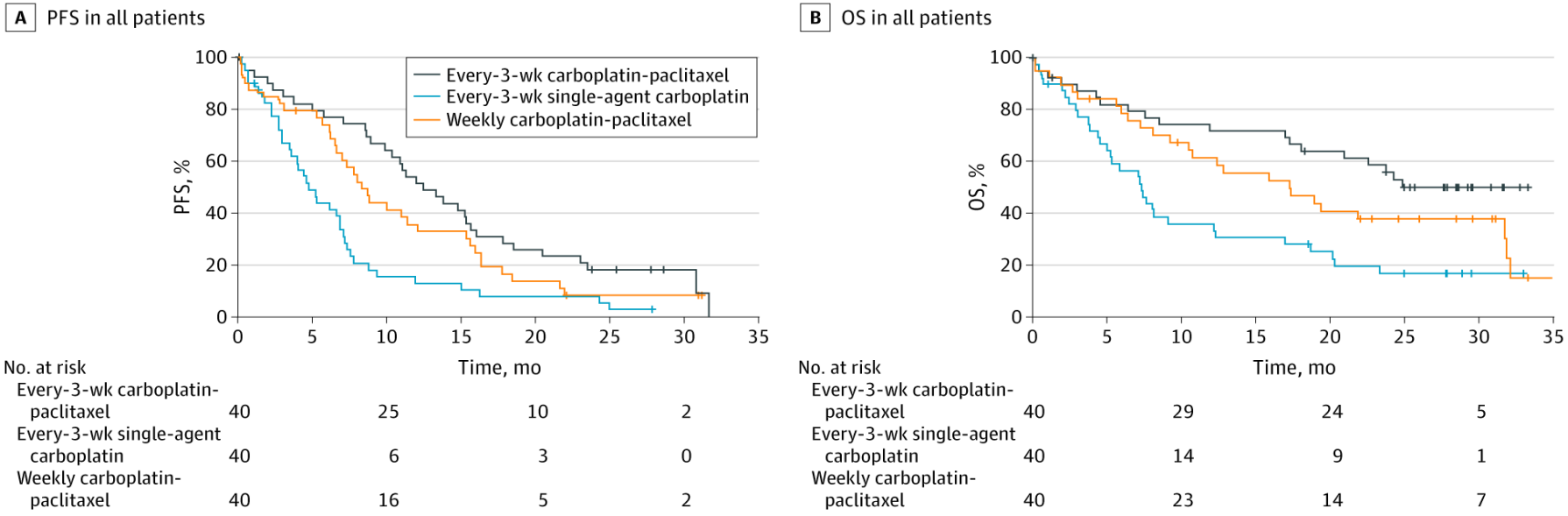

Figure Legend:

Progression-Free Survival (PFS) and Overall Survival (OS) in All Patients and Those With Geriatric Vulnerability Score (GVS) 4-5

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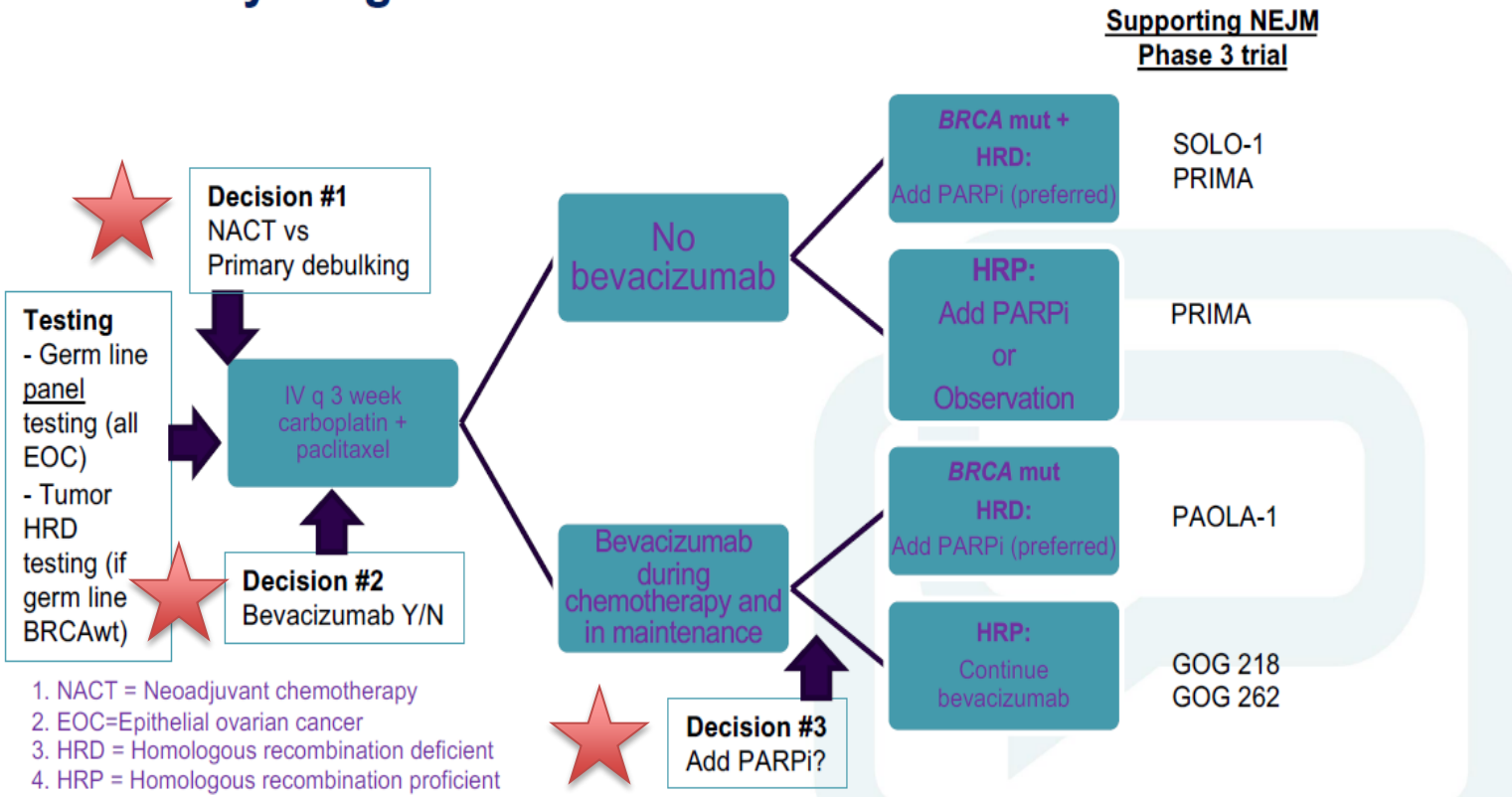

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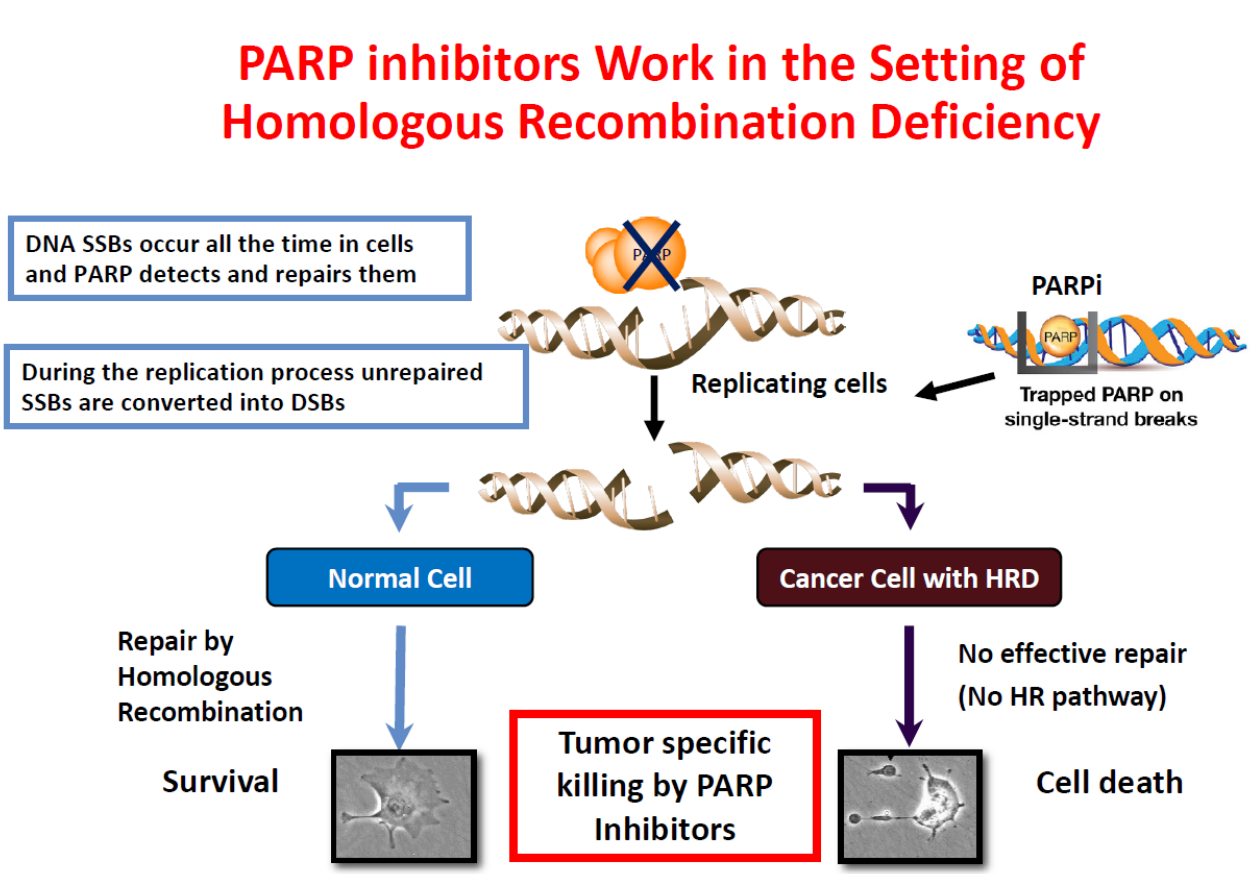
Decision #3: Maintenance PARP inhibitor (alone or in combination with bevacizumab)

#2

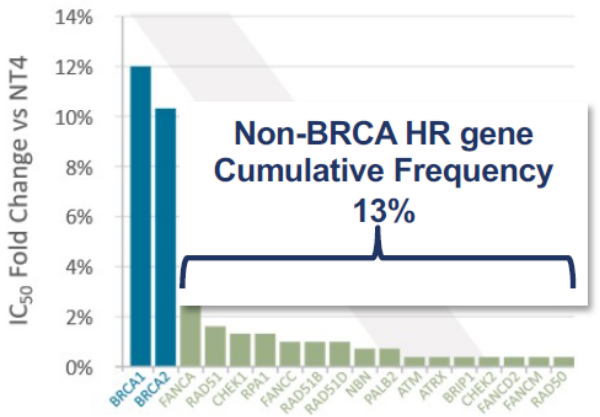


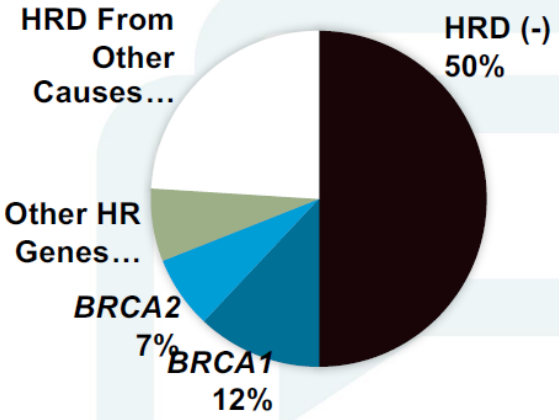
Ochsner Health System

Contribution of non-*BRCA* Mutations to HRD in Ovarian Cancer

Mutation frequency in 28 HR genes analyzed (~250 women)

- Low frequency of mutations found in 16 genes
- No mutations found in 12 genes





https://myriad.com/products-services/precision-medicine/mychoice-cdx/

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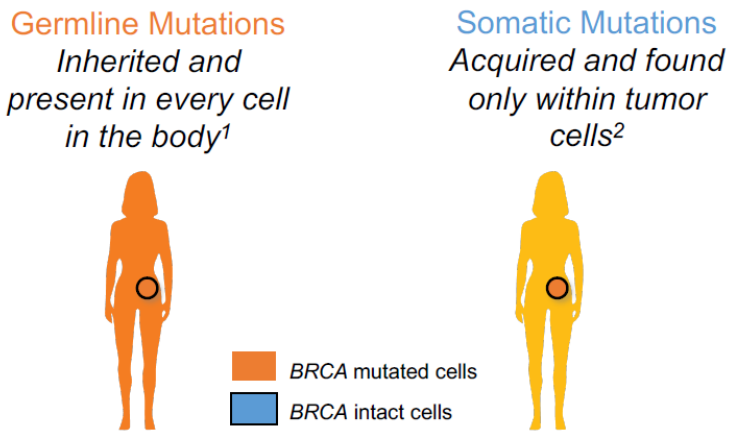
BRCA1/2 Mutations Can Be Germline or Somatic



- **Blood- or saliva-based diagnostics that do not test tumor DNA cannot detect somatic *BRCA* mutations**
- ***BRCA* testing of the tumor, including archival tumor tissue, can detect both germline and somatic *BRCA* mutations**

1. Petrucelli et al. *BRCA2* Hereditary Breast and Ovarian Cancer. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. Seattle (WA): University of Washington, Seattle; 1993-2016 [cited 01 Aug 2016]. [about p 56]. Accessed from: http://www.ncbi.nlm.nih.gov/books/NBK1247/
2. Moschetta et al. Ann Oncol. 2016;27(8):1449-55.

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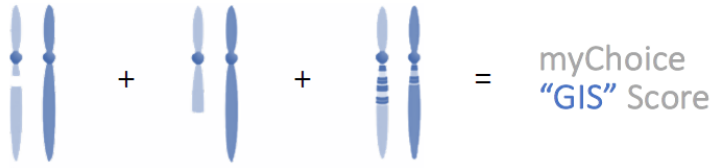
Direct HRD/LOH Assays[a]

myChoice

(CDx olaparib, niraparib, veliparib)



Loss of Heterozygosity (LOH)

Telomeric Allelic Imbalance (TAI)

Large-Scale State Transitions (LST)

Homologous recombination status is determined by Genomic Instability Score:

- **HR-deficient tumors:** tissue GIS ≥42 ***or*** a *BRCA* mutation
- **HR-proficient tumors:** tissue GIS <42
- HR not determined

FoundationOne LOH

(CDx rucaparib)

Loss of Heterozygosity (LOH)

Indirect HRD/LOH

Deleterious alteration in HRD genes

- Germline or somatic (eg, *BRCA*mut by definition is HRD)

[a] Test have not been compared head to head. Paired with development of respective drugs.

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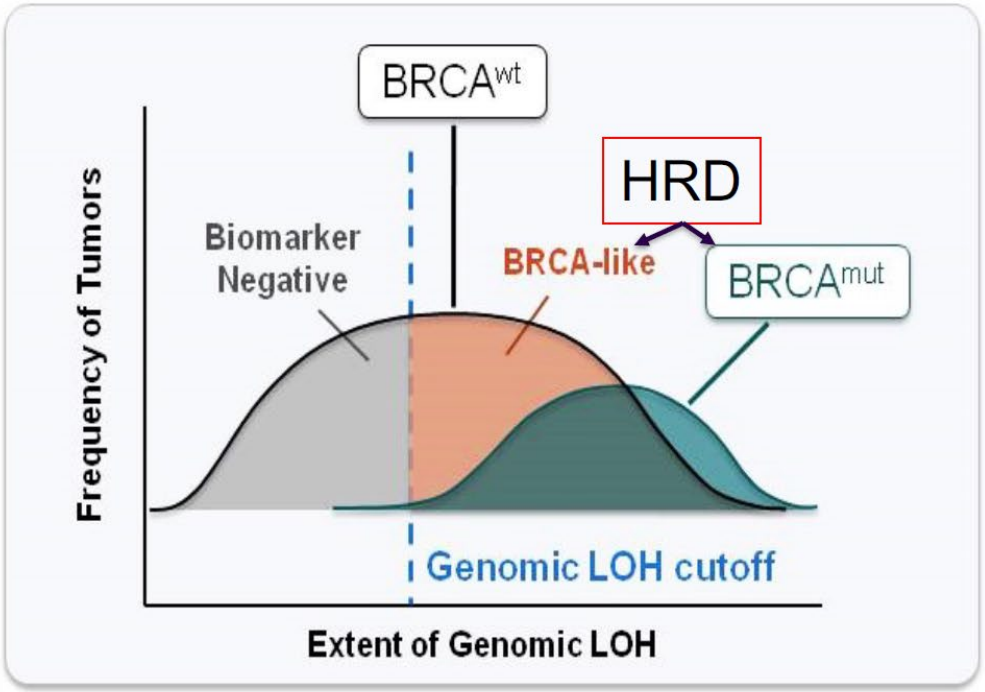
HGOC Patients Can Be Classified Into Three Molecular Subgroups: BRCAmut, BRCA-Like, Biomarker Negative

#3



Modified From Iain McNeish, et al. J Clin Oncol. 2015;33(Suppl): Abstract 5508.

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PARP Inhibitor Approvals: Beyond Molecular Subgroups

	Olaparib[1]	Rucaparib[2]	Niraparib[3]
MOA	PARP-1, PARP-2, and PARP-3 inhibitor	PARP-1, PARP-2, and PARP-3 inhibitor	PARP-1 and PARP-2 inhibitor
Treatment indication	≥3 lines of chemotherapy with deleterious or suspected g*BRCA*m OC	≥2 lines of chemotherapy with deleterious g/s*BRCA*m EOC, FTC, PPC	≥3 lines of chemo with HRD+ OC/FTC/PPC • Deleterious or suspected *BRCA*m, or • Genomic instability and progression >6 mo after response to last platinum-based chemo
Maintenance indication	2L maintenance for recurrent EOC, FTC, PPC 1L maintenance for high-risk, advanced, *BRCA*m, high-grade EOC, FTC, PPC 1L maintenance + bevacizumab for HRD+	2L maintenance for recurrent EOC, FTC, PPC	2L maintenance for recurrent EOC, FTC, PPC 1L maintenance regardless of *BRCA*m status
Recommended dose	300 mg PO twice daily	600 mg PO twice daily	300 mg PO once daily (Individualized based on weight and platelet count in first line)
Approval dates	December 2014, August 2017, December 2018, and May 2020	December 2016 and April 2018	March 2017, October 2019, and April 2020

1. Lynparza (olaparib) Prescribing Information. https://www.azpicentral.com/lynparza_tb/lynparza_tb.pdf.
2. Rubraca (rucaparib) Prescribing Information. https://clovisoncology.com/media/1094/rubraca-prescribing-info.pdf.
3. Zejula (niraparib) Prescribing Information. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Zejula/pdf/ZEJULA-PI-PIL.PDF

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Upfront Maintenance Regimens

- Bevacizumab with chemo and continued maintenance
  - FDA Approved June 2018
  - GOG 218: PFS benefit of 6.2 months over placebo
- Olaparib maintenance
  - FDA Approved December 2018
  - SOLO-1: PFS benefit of 34 months over placebo
- Niraparib maintenance
  - FDA Approved April 2020
  - PRIMA: PFS benefit of 5.6 months (11.5 in HRD) over placebo
- Olaparib + Bevacizumab maintenance
  - FDA Approved May 2020
  - PAOLA-1: PFS benefit of 5.5 months (19.5 in HRD) over Bev + Placebo

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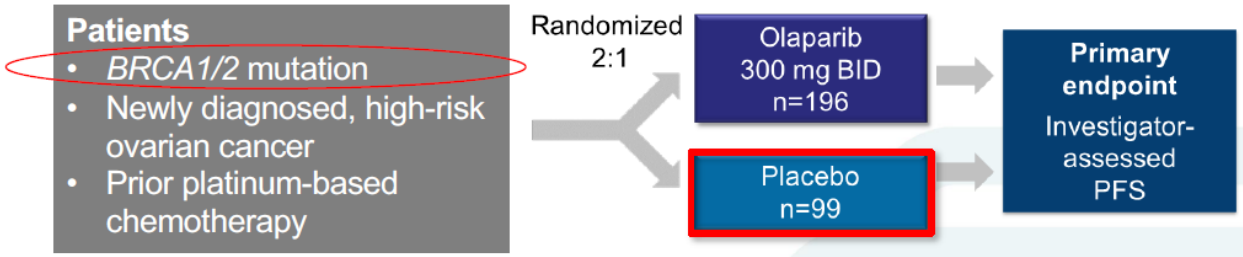
Phase III SOLO1: Olaparib Maintenance After First-Line Chemotherapy



- **Secondary endpoints:** second PFS, OS, time to first subsequent therapy or death, time to second subsequent therapy or death, HRQOL

- 391 patients randomized
- Most patients NED, good PS, and CA-125 WNL

Mutations
- n = 391, g*BRCA1/2*
- n = 1, *BRCA* VUS
- n = 2, somatic *BRCA*

N Engl J Med. 2018 Dec 27;379(26):2495-2505.

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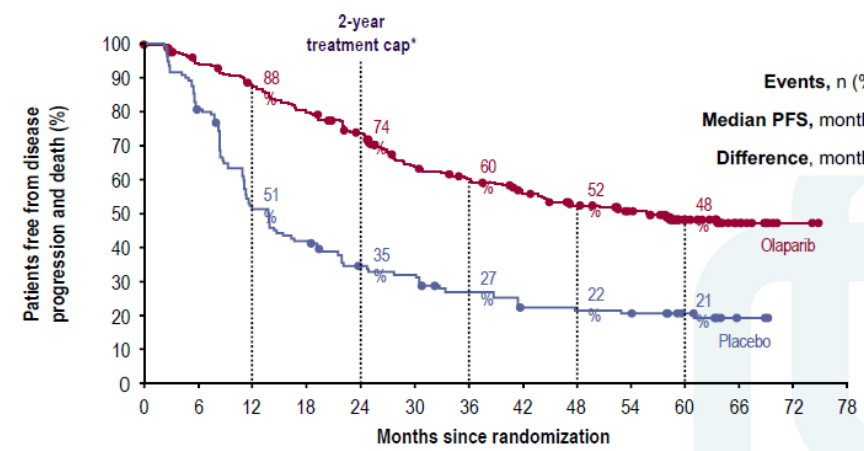
Phase 3 SOLO1: PFS at 5 Years of Follow-Up



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	118 (45)	100 (76)
Median PFS, months	**56.0**	**13.8**
Difference, months	42.2	
HR 0.33 (95% CI 0.25–0.43)		

Median treatment duration:
Olaparib, 24.6 months
Placebo†, 13.9 months

*13 patients, all in the olaparib arm, continued study treatment past 2 years; †n=130 (safety analysis set)
Investigator-assessed by modified RECIST v1.1. DCO: 5 March 2020

Median follow-up for PFS: olaparib, 4.8 y; placebo, 5.0 years.

2020 Virtual ESMO Congress. September 14, 2020. Abstract 811MO.

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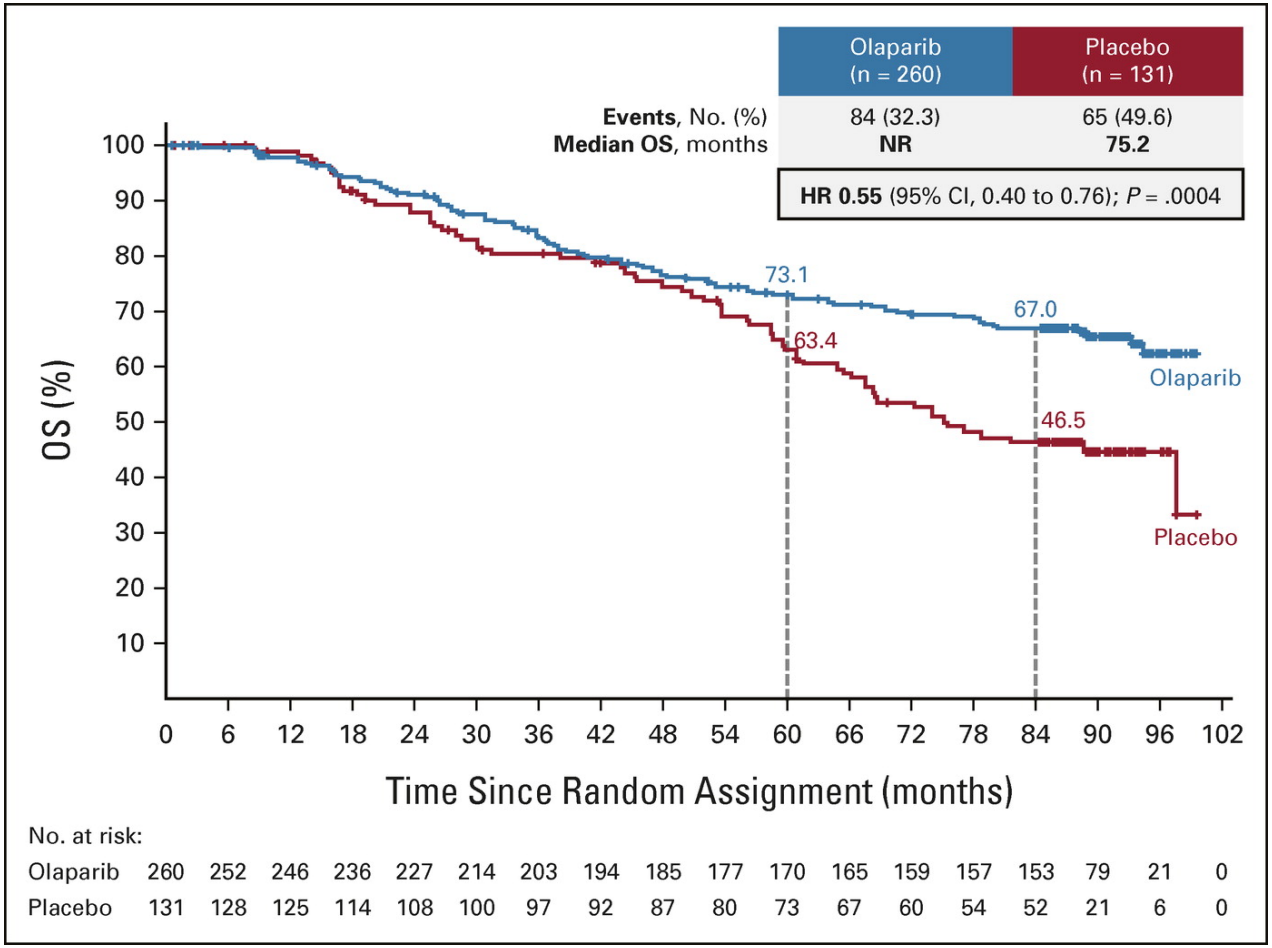
SOLO 1 OS Update at 7 years



40% crossover to PARPi in later lines of therapy for the placebo group

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Upfront Maintenance Regimens

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- Olaparib maintenance
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  - SOLO-1: PFS benefit of 34 months over placebo
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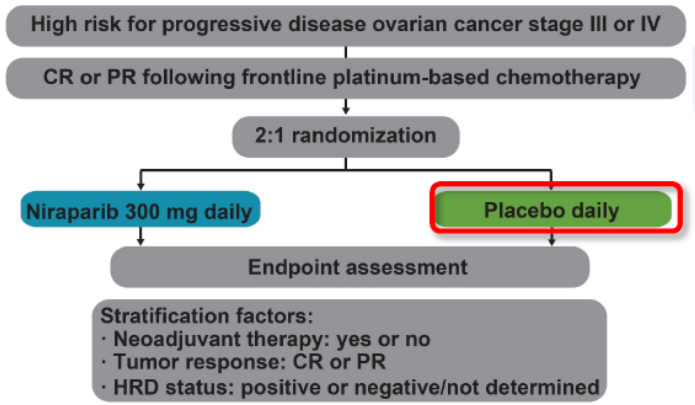
PRIMA/ENGOT-OV26/GOG-3012: Niraparib vs Placebo in High-risk First-line Ovarian Cancer Patients of any *BRCA* Status

- Double-blind, randomized, placebo-controlled phase III study
- Tested "weights and plates" starting dose reduction to 200 mg for patients <77kg or baseline platelet count <150K
- Assessed homologous recombination deficiency (HRD, including *BRCA*mut) vs. HR proficiency (HRD-) using Myriad myChoice® HRD test (Myriad Genetics, Salt Lake City, UT, USA)



Primary endpoint: PFS by BICR

N Engl J Med. 2019 Dec 19;381(25):2391-2402.

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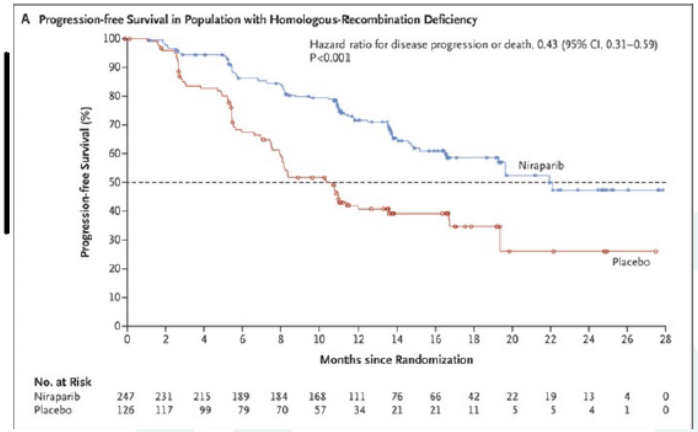
Phase III PRIMA/ENGOT-OV26/GOG-3012: PFS by Subgroup

HRD

mPFS: 21.9 mo vs 10.4 mo (Δ 11.5 mo)

HR: 0.43 (95% CI, 0.31-0.59), *P* <.001



PFS	HRD, *BRCA*m		HRD, *BRCA*wt		HRP	
	N (n=152)	PBO (n = 71)	N (n = 95)	PBO (n = 55)	N (n = 169)	PBO (n = 80)
Median	**22.1**	**10.09**	**19.6**	**8.2**	**8.1**	**5.4**
HR (95% CI)	0.40 (0.27–0.62)		0.50 (0.31–0.83)		0.68 (0.49–0.94)	
P -value	<0.001		0.006		0.020	

N Engl J Med. 2019 Dec 19;381(25):2391-2402.

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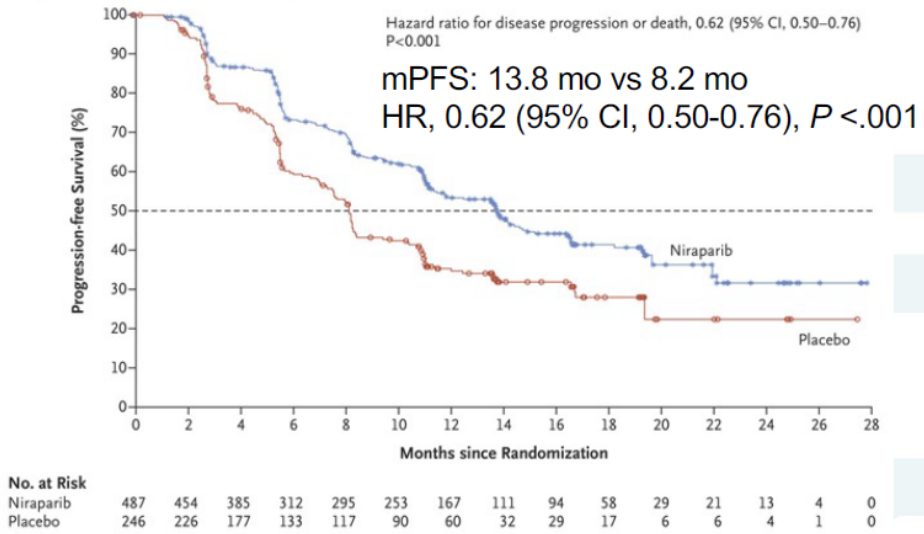
Phase III PRIMA/ENGOT-OV26/GOG-3012: PFS Primary Endpoint (Overall Population)



OS at 24-mo interim analysis: 84%, niraparib and 77%, placebo (HR, 0.70; 95% CI, 0.44-1.11)

N Engl J Med. 2019 Dec 19;381(25):2391-2402.

- PFS of HRD group 21.9 v 10.4 months
  - 57% reduction in risk of progression or death
- PFS in Overall population 13.8 v 8.2 months
  - 38% reduction in risk of progression or death

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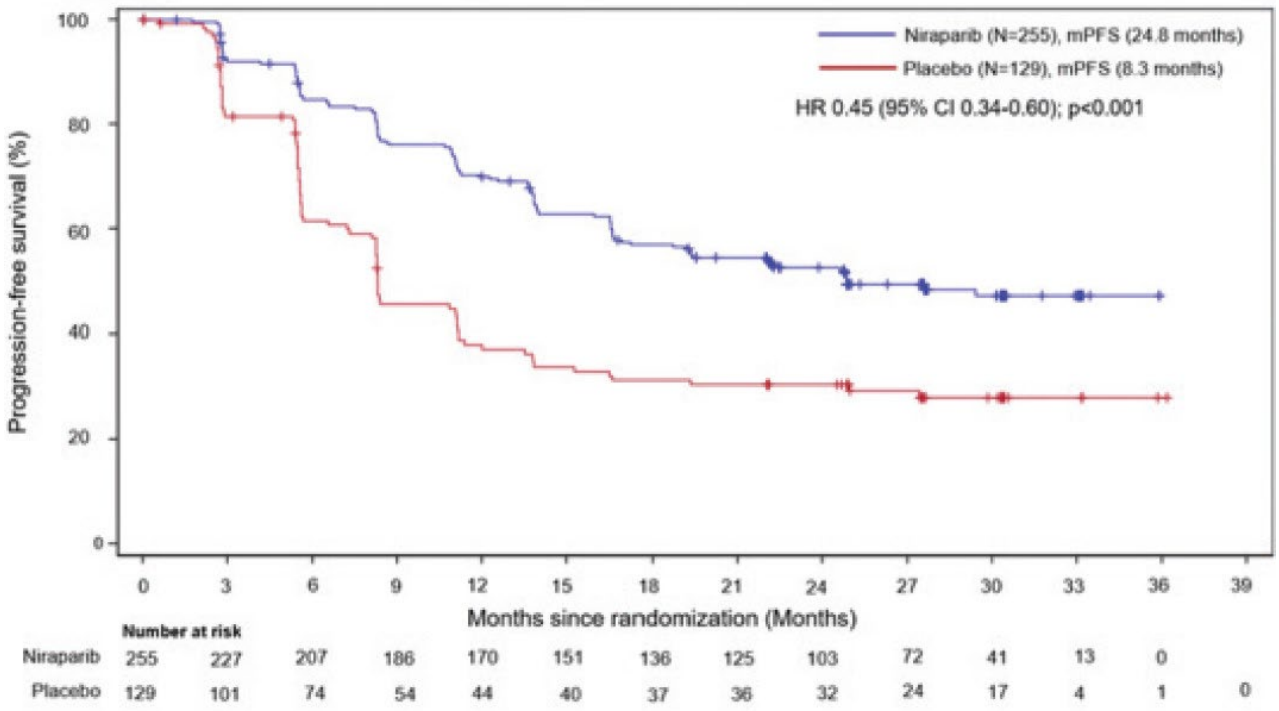
PRIME Study

Figure 1. Progression-free survival assessed by blinded independent central review in the intent-to-treat population



Censored data are indicated by plus signs. CI, confidence interval; HR, hazard ratio; mPFS: median progression-free survival

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Li 2022 SGO

Upfront Maintenance Regimens

- Bevacizumab with chemo and continued maintenance
  - FDA Approved June 2018
  - GOG 218: PFS benefit of 6.2 months over placebo
- Olaparib maintenance
  - FDA Approved December 2018
  - SOLO-1: PFS benefit of 34 months over placebo
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  - FDA Approved May 2020
  - PAOLA-1: PFS benefit of 5.5 months (19.5 in HRD) over Bev + Placebo

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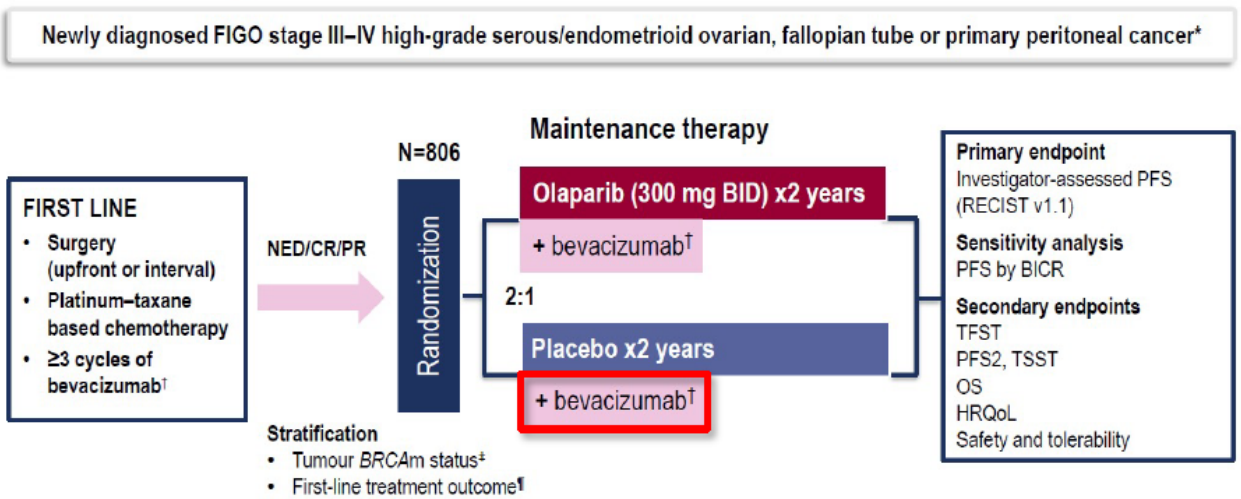
Phase III PAOLA-1: Platinum + Bev With Olaparib + Bev 1L Maintenance

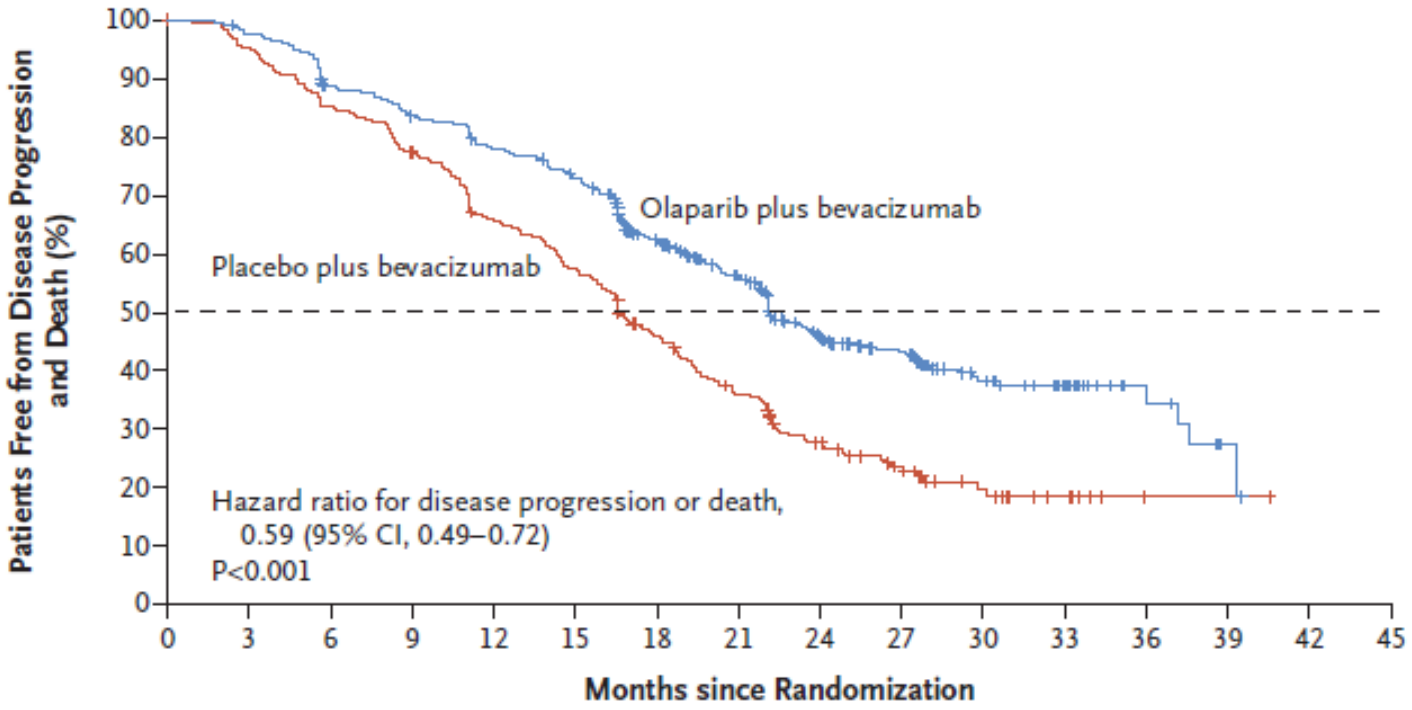
Study design



*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation
†Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy; ‡By central labs; ¶According to timing of surgery and NED/CR/PR
BICR, blinded independent central review; HRQoL, health-related quality of life; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria in Solid Tumours; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

N Engl J Med. 2019 Dec 19;381(25):2416-2428.

PAOLA-1



- PFS: 22.1 (Olap + Bev) v 16.6 months (Bev only)
  - 41% reduction in risk of progression or death
- PFS in HRD 37.2 v 17.7 months
  - 67% reduction in risk of progression or death
- PFS in HRP 16.6 v 16.2 months (NS)

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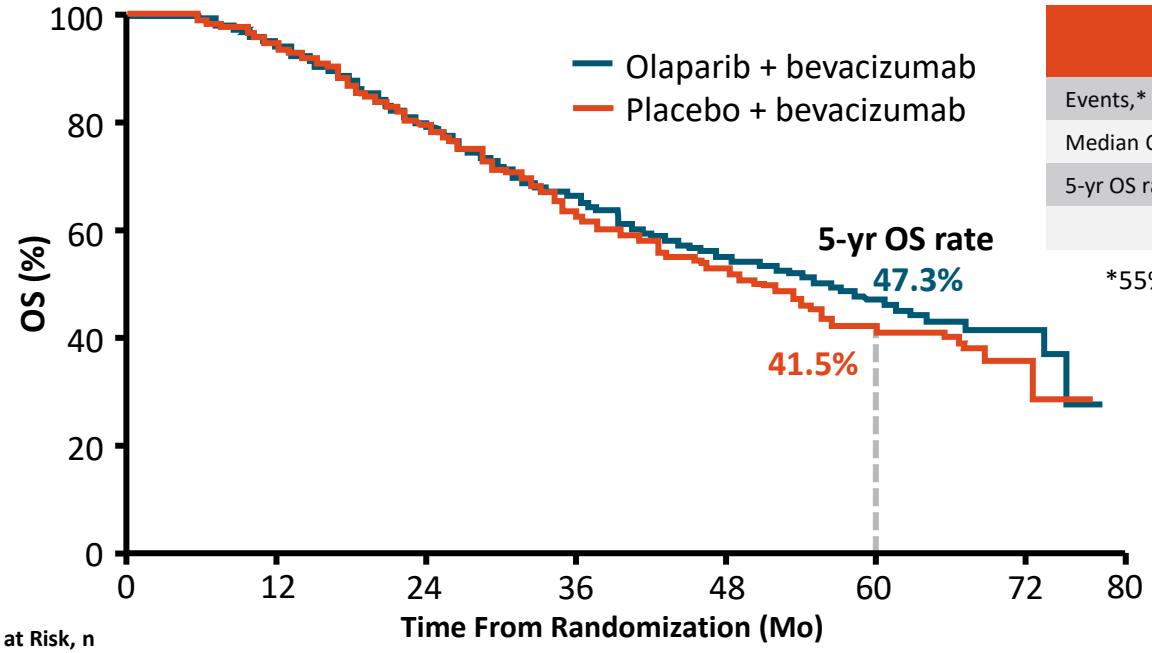
PAOLA-1: OS (ITT Population)



Patients at Risk, n

Olaparib + bevacizumab	537	530	528	517	503	480	463	440	420	398	376	357	347	329	308	295	286	276	262	217	169	113	82	40	19	4	0
Placebo + bevacizumab	269	267	264	261	250	242	229	220	208	199	188	179	166	160	154	146	139	132	121	96	76	51	37	20	5	2	0

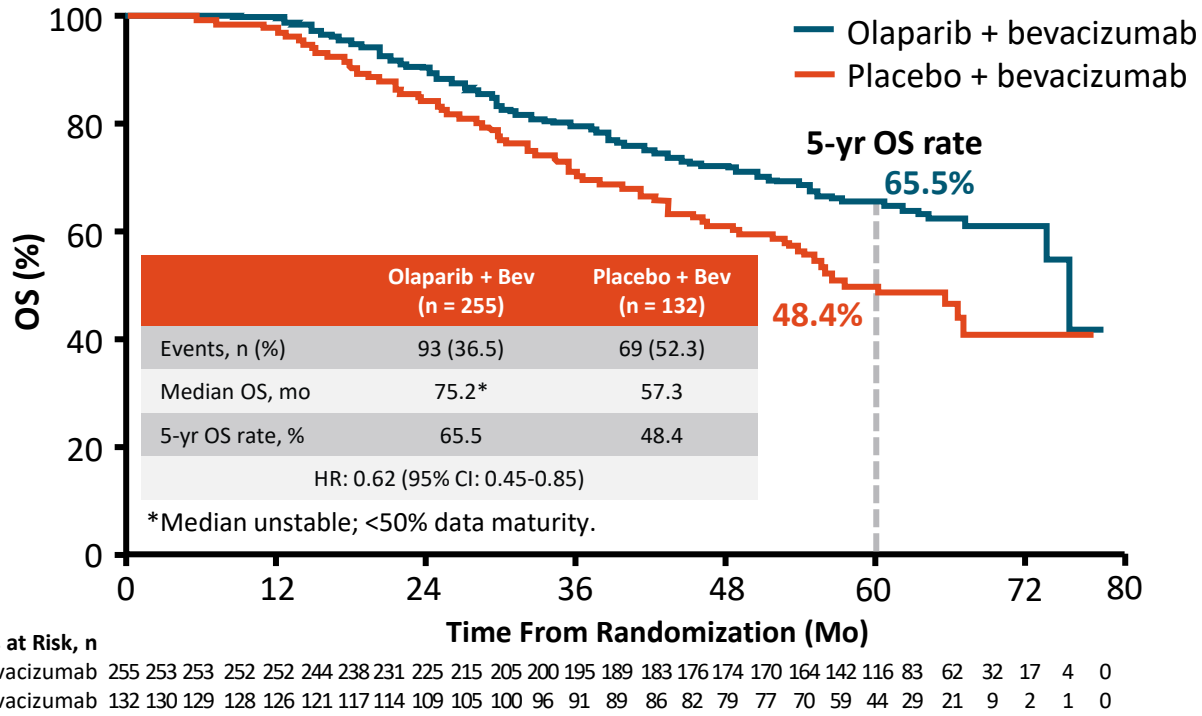
	Olaparib + Bev (n = 537)	Placebo + Bev (n = 269)
Events,* n (%)	288 (53.6)	158 (58.7)
Median OS, mo	56.5	51.6
5-yr OS rate, %	47.3	41.5
HR: 0.92 (95% CI: 0.76-1.12; *P* = .4118)		

*55% maturity.

- 19.7% and 45.7% of patients in olaparib + Bev and placebo + Bev arms, respectively, received PARP inhibitor during any subsequent treatment
- Median time from first cycle of chemotherapy to randomization: 6 mo

Ray-Coquard. ESMO 2022. Abstr LBA29. Reproduced with permission.

PAOLA-1: OS in HRD-Positive Subgroup



	Olaparib + Bev (n = 255)	Placebo + Bev (n = 132)
Events, n (%)	93 (36.5)	69 (52.3)
Median OS, mo	75.2*	57.3
5-yr OS rate, %	65.5	48.4
HR: 0.62 (95% CI: 0.45-0.85)		

*Median unstable; <50% data maturity.

Patients at Risk, n

Olaparib + bevacizumab	255	253	253	252	252	244	238	231	225	215	205	200	195	189	183	176	174	170	164	142	116	83	62	32	17	4	0
Placebo + bevacizumab	132	130	129	128	126	121	117	114	109	105	100	96	91	89	86	82	79	77	70	59	44	29	21	9	2	1	0

- 17.3% and 50.8% of patients in olaparib + Bev and placebo + Bev arms, respectively, received PARP inhibitor during any subsequent treatment

Ray-Coquard. ESMO 2022. Abstr LBA29. Reproduced with permission.

PARP Toxicities

Toxicity	Description	PARPi
GI	Nausea, constipation, vomiting and diarrhea LFTs	All PARPi LFTS: Rucaparib
Renal	Increase in creatinine: inhibits MATE inhibitors	Rucaparib
Fatigue	Universal for all PARPi	ALL PARPi
Respiratory	Dyspnea/cough/pneumonitis	ALL PARPi
Cardiac	Hypertension/tachycardia	Niraparib
Skin	Photosensitivity	Rucaparib
Muscle	Arthralgia/back pain	ALL PARPi

GI, gastrointestinal; LFT, liver function tests.

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Niraparib

If weight: <77 kg or
baseline platelets: <150,000/µL

200
mg/day

First dose reduction:
100 mg/day

Second dose reduction:
discontinue

If weight: ≥77 kg and
baseline platelets: ≥150,000/µL

300
mg/day

First dose reduction:
200 mg/day

Second dose reduction:
100 mg/day

Third dose reduction:
discontinue

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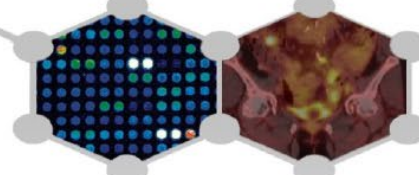

NRG ONCOLOGY

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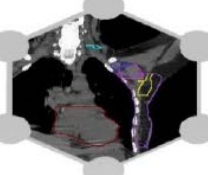

Risk of AML and MDS:

Trial	AML/MDS events in PARPi arm, n/N (%)	AML/MDS events in placebo arm, n/N (%)	Comparator Arm
SOLO1	3/260 (1.2%)	0/130 (0%)	Placebo
PRIMA	1/484 (<1%)	0/244 (0%)	Placebo
PAOLA-1	6/535 (1%)	1/267 (<1%)	Bevacizumab
Study 19	2/136 (1.5%)	1/129 (0.8%)	Placebo
SOLO2	4/195 (2.1%)	4/99 (4%)	Placebo
NOVA	1/367 (0.3%)	2/179 (1.1%)	Placebo
ARIEL3	3/375 (1%)	0/189 (0%)	Placebo

1. Moore K et al. N. Engl. J. Med (2018) ;379:2495-505/supplemental a.; 2. Moore K et al. N. Engl. J. Med. (2018) ;379:2495-505. [supplementary appendix]; 3. Gourley, C. et al. J Clin Oncol 35 (poster related to suppl; abstr 5533) (2017); 4. Pujade-Lauraine E, et al. Lancet Oncol 2017:18(9)1274–1284; 5. Mirza et al. NEJM (2016); 375(22):2154-2164 6. Coleman RE et al. Lancet (2017) 390(10106): 1949-1961

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Updated ASCO rapid PARPi guidelines

Recurrent Ovarian Cancer: Second-Line or Greater Maintenance and Treatment

Recommendation 3.0. PARPi monotherapy maintenance (second-line or more) may be offered to patients with EOC who have not already received a PARPi and who have responded to platinum-based therapy regardless of *BRCA* mutation status; treatment is continued until progression of disease or toxicity despite dose reductions and best supportive care. Options include olaparib 300 mg every 12 hours, rucaparib 600 mg every 12 hours or niraparib 200-300 mg once daily. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.) Maintenance treatment with niraparib for patients without germline or somatic *BRCA* mutation should weigh potential PFS benefit against possible OS decrement. (Type: Evidence-based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Moderate.)

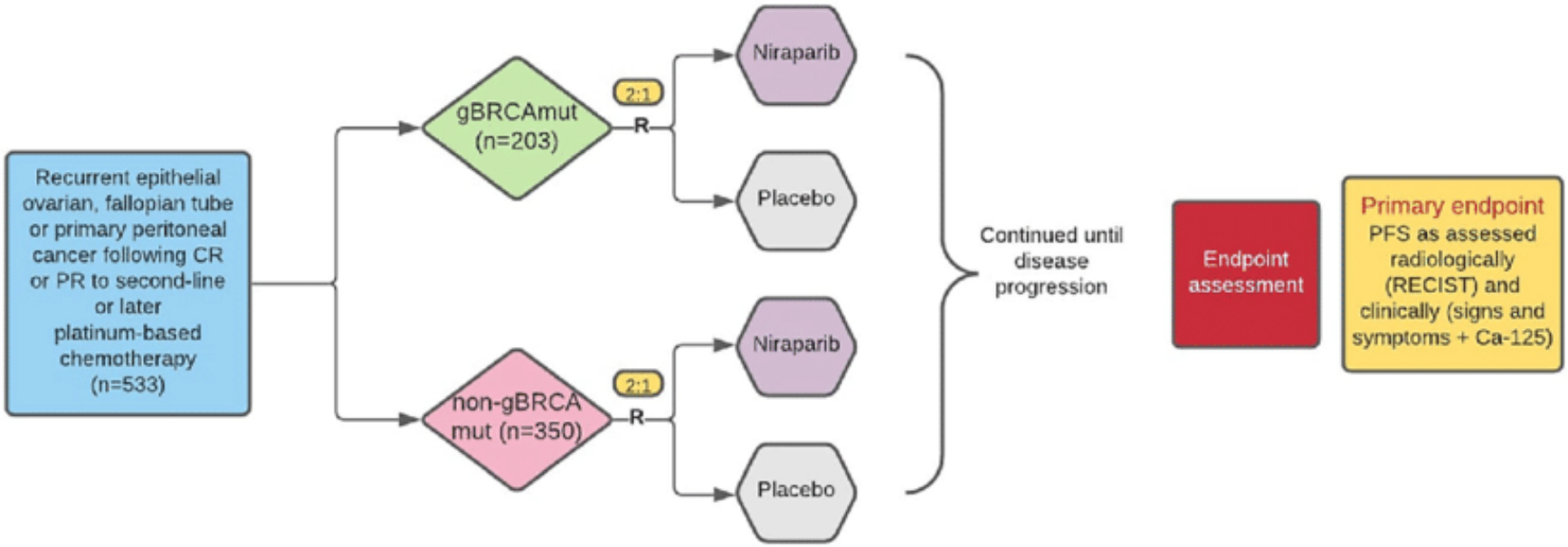
Recommendations 3.1/3.2. PARPi monotherapy should not be routinely offered to patients for the treatment of recurrent platinum sensitive EOC. (Type: Evidence-based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate.) *Evidence on PARPi use in this setting is evolving and data are continuing to emerge. Any decision to proceed with PARPi treatment in select populations* (BRCA *mutation, No prior PARPi use, Platinum Sensitive, Advanced Lines of Treatment) should be based on individualized patient and provider assessment of risks, benefits, and preferences.*

Recommendation 3.3. PARPi monotherapy is not recommended for treatment for patients with either *BRCA* wild-type or platinum-resistant recurrent EOC. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.)

Ochsner™ Health System

NOVA: Study Design

Phase III trial of niraparib maintenance therapy in platinum sensitive, recurrent advanced ovarian cancer



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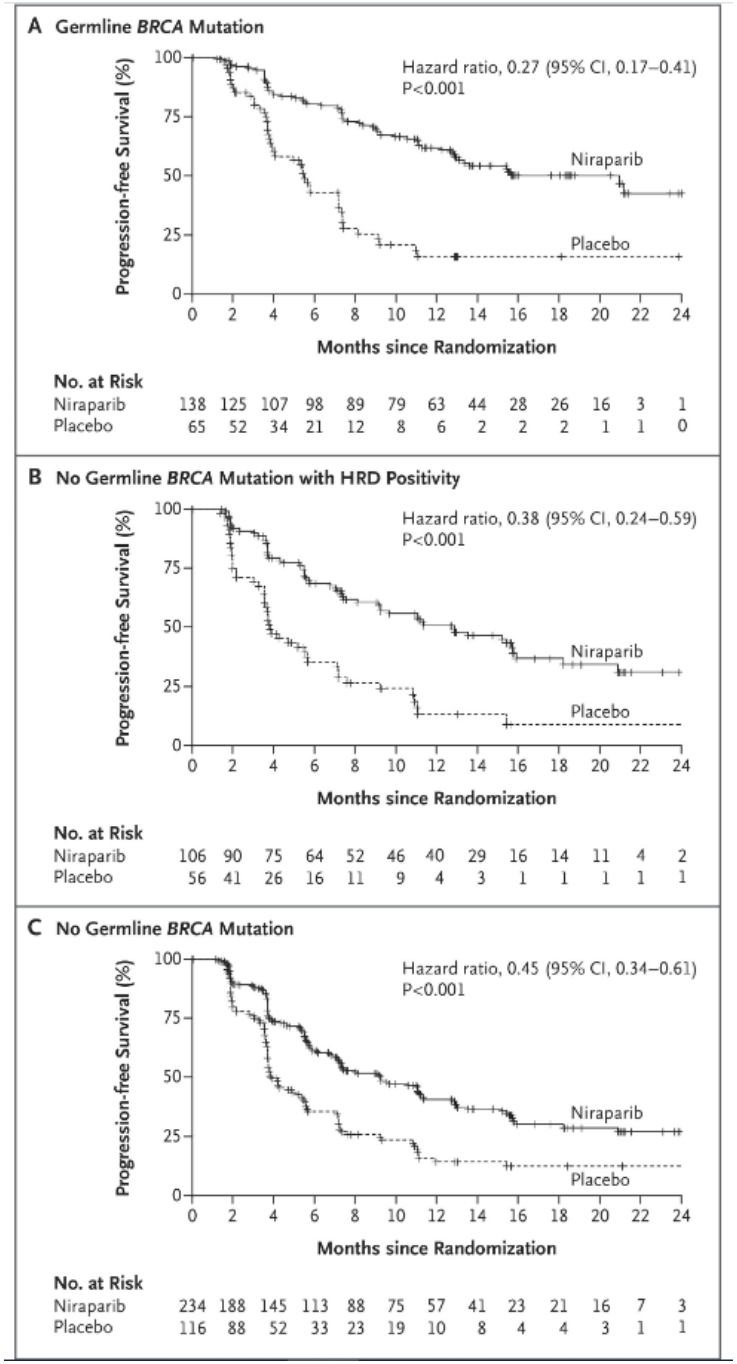
NOVA- PFS



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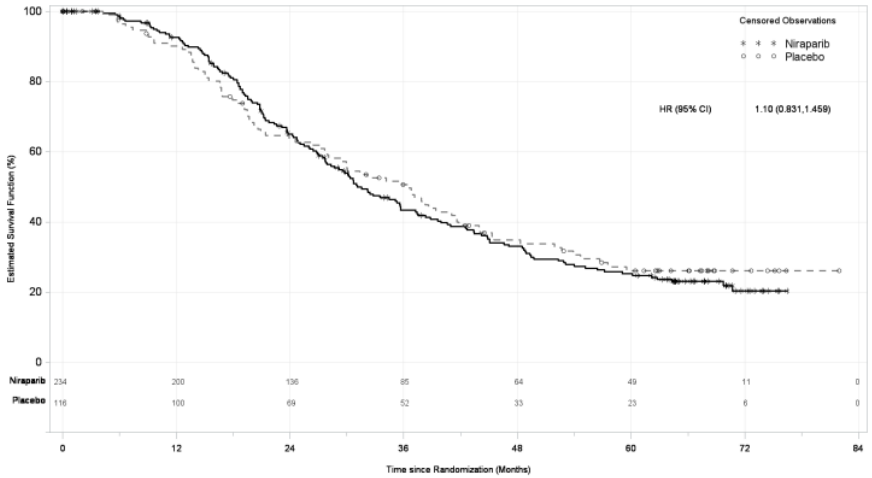
Mirza 2016 NEJM

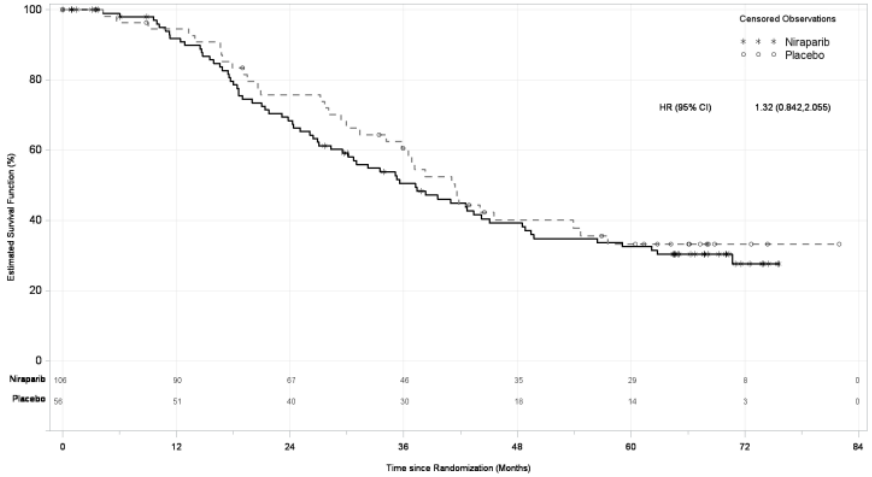
NOVA - OS

Figure 1: OS Kaplan Meier curve for the non-g*BRCA*mut cohort



Non-g*BRCA*mut
HR: 1.10

Figure 2: OS Kaplan Meier curve for the non-g*BRCA*mut HRD positive subgroup



Non-g*BRCA*mut HRD
HR: 1.32

Ochsner Health System

Unpublished data
released by GSK 2022

Updated ASCO rapid PARPi guidelines

Recurrent Ovarian Cancer: Second-Line or Greater Maintenance and Treatment

Recommendation 3.0. PARPi monotherapy maintenance (second-line or more) may be offered to patients with EOC who have not already received a PARPi and who have responded to platinum-based therapy regardless of *BRCA* mutation status; treatment is continued until progression of disease or toxicity despite dose reductions and best supportive care. Options include olaparib 300 mg every 12 hours, rucaparib 600 mg every 12 hours or niraparib 200-300 mg once daily. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.) Maintenance treatment with niraparib for patients without germline or somatic *BRCA* mutation should weigh potential PFS benefit against possible OS decrement. (Type: Evidence-based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Moderate.)

Recommendations 3.1/3.2. PARPi monotherapy should not be routinely offered to patients for the treatment of recurrent platinum sensitive EOC. (Type: Evidence-based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate.) *Evidence on PARPi use in this setting is evolving and data are continuing to emerge. Any decision to proceed with PARPi treatment in select populations* (BRCA *mutation, No prior PARPi use, Platinum Sensitive, Advanced Lines of Treatment) should be based on individualized patient and provider assessment of risks, benefits, and preferences.*

Recommendation 3.3. PARPi monotherapy is not recommended for treatment for patients with either *BRCA* wild-type or platinum-resistant recurrent EOC. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.)

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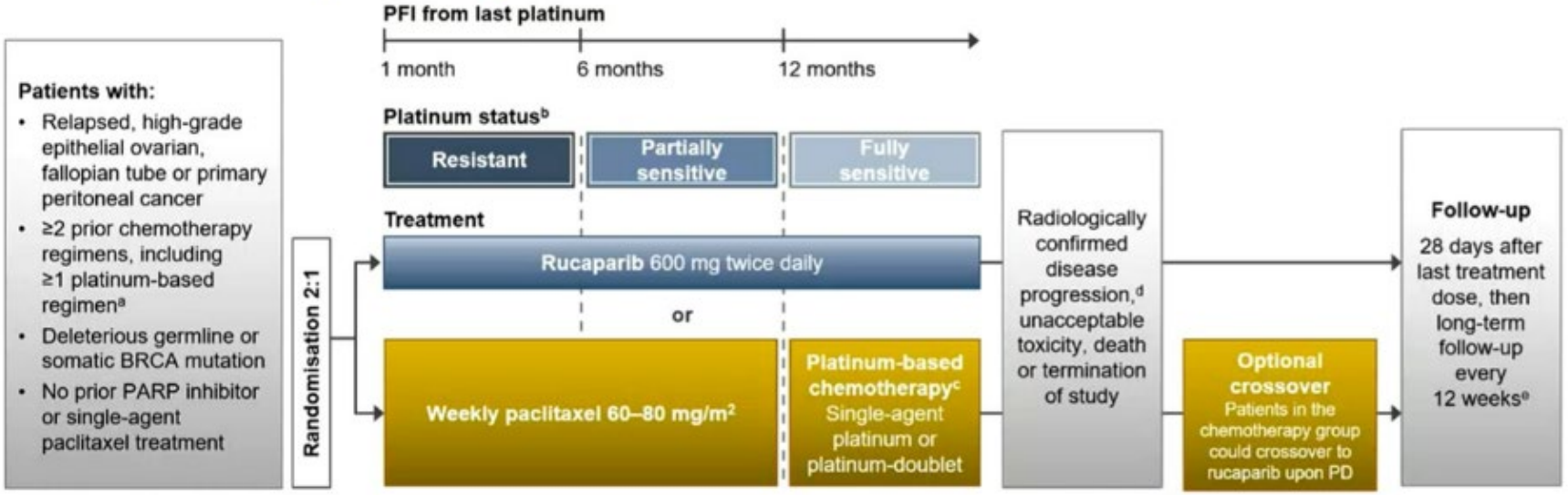
ARIEL4 Study Design



- Efficacy endpoints
  - Prespecified secondary endpoint: OS in the ITT population
  - Exploratory endpoints: OS in platinum-status subgroups; PFS2 in the ITT population and in platinum-status subgroups

[a]With treatment-free interval ≥6 months following first chemotherapy received. [b]Randomisation stratification factor. [c]At investigator's discretion. [d]Per RECIST. [e]Patients who discontinued for reasons other than PD were followed every 8 weeks. BRCA, *BRCA1* or *BRCA2*; ITT, intent-to-treat; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PFI, progression-free interval; PFS, progression-free survival; PFS2, PFS from randomisation to progression on the subsequent line of therapy; RECIST, Response Evaluation Criteria in Solid Tumors, version 1.1.

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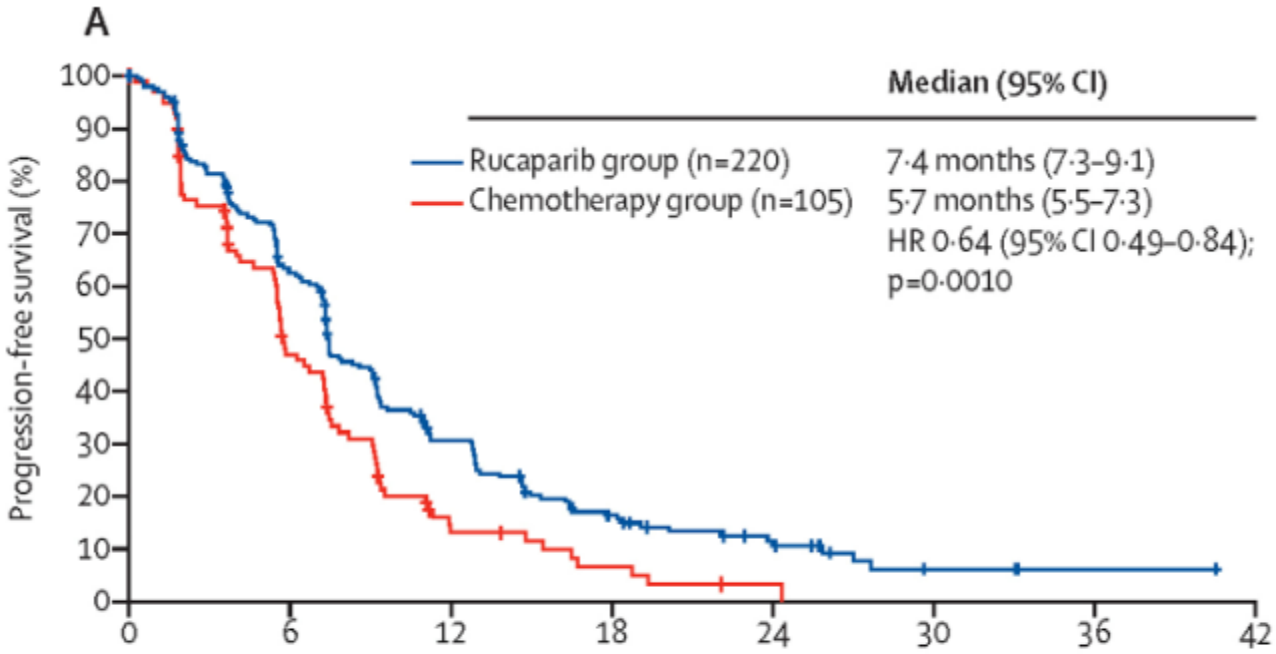
ARIEL 4 PFS



Number at risk (number censored)								
Rucaparib group	220 (0)	121 (24)	53 (33)	23 (39)	11 (44)	3 (49)	1 (51)	0 (52)
Chemotherapy group	105 (0)	42 (13)	9 (18)	4 (19)	1 (20)	0 (20)	..	..

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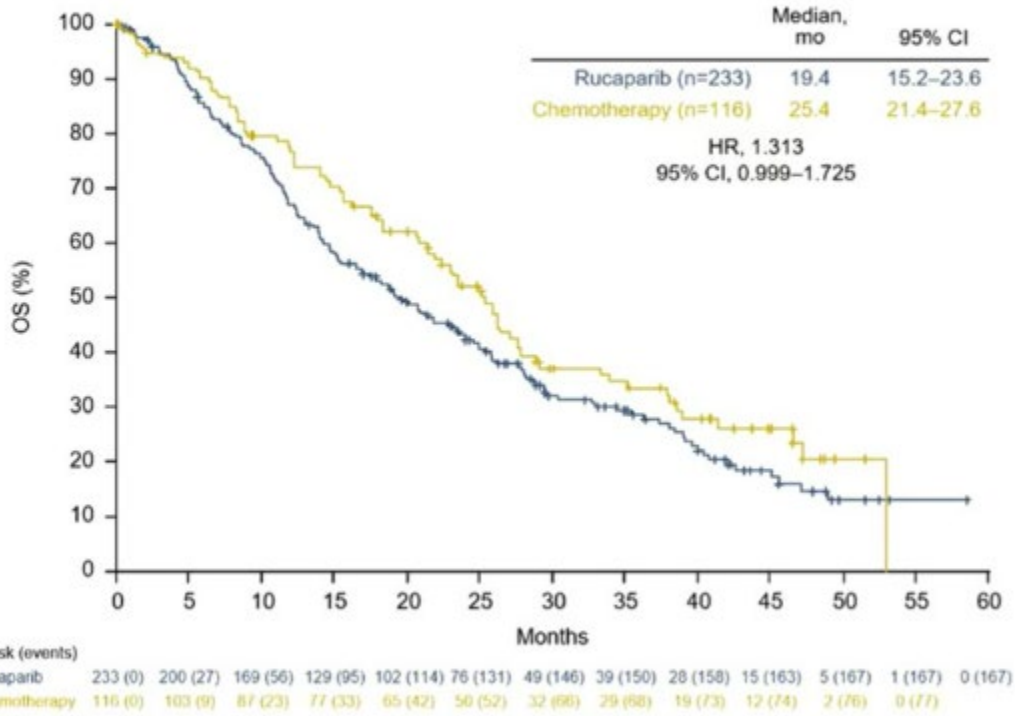
ARIEL 4 OS

OS: ITT Population



Data cutoff: 10 April 2022. HRs estimated with a Cox proportional hazards model.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months; OS, overall survival.

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Other Select Clinical Trials:
New Agents for Advanced OC in the Frontline Setting

Trial	Patients	Study Treatment	Key Endpoints	Results, mo/Status
VELIA[a]	N = 1140	Veliparib + CTX in 1L/maintenance vs PBO	mPFS	*BRCA*m: 34.7 vs 22.0 HRD/*BRCA*+: 31.9 vs 20.5
ATHENA[b]	*N = 1000	Maintenance rucaparib/nivolumab vs PBO	Investigator-assessed PFS	Ongoing
JAVELIN OVARIAN 100[c]	N = 998	Carbo/pac or carbo/pac + maintenance avel or avel + carbo/pac, maintenance avel	mPFS ORR	NE vs 16.8 vs 18.1 30.4% vs 30.4% vs 36.0%
ENGOT-OV44/FIRST[d]	N = 912	Dorstarlimab + niraparib + SOC vs SOC	PFS	Ongoing

*Target enrollment.

a. Coleman RL, et al. *N Engl J Med*. 2019;381:2403-2415; b. Westin SN, et al. AACR 2019. Abstract CT158; c. Ledermann JA, et al. SGO 2020. Abstract 23; d. Hardy-Bessard A-C, et al. *J Clin Oncol*. 2019;37:TPS5600.

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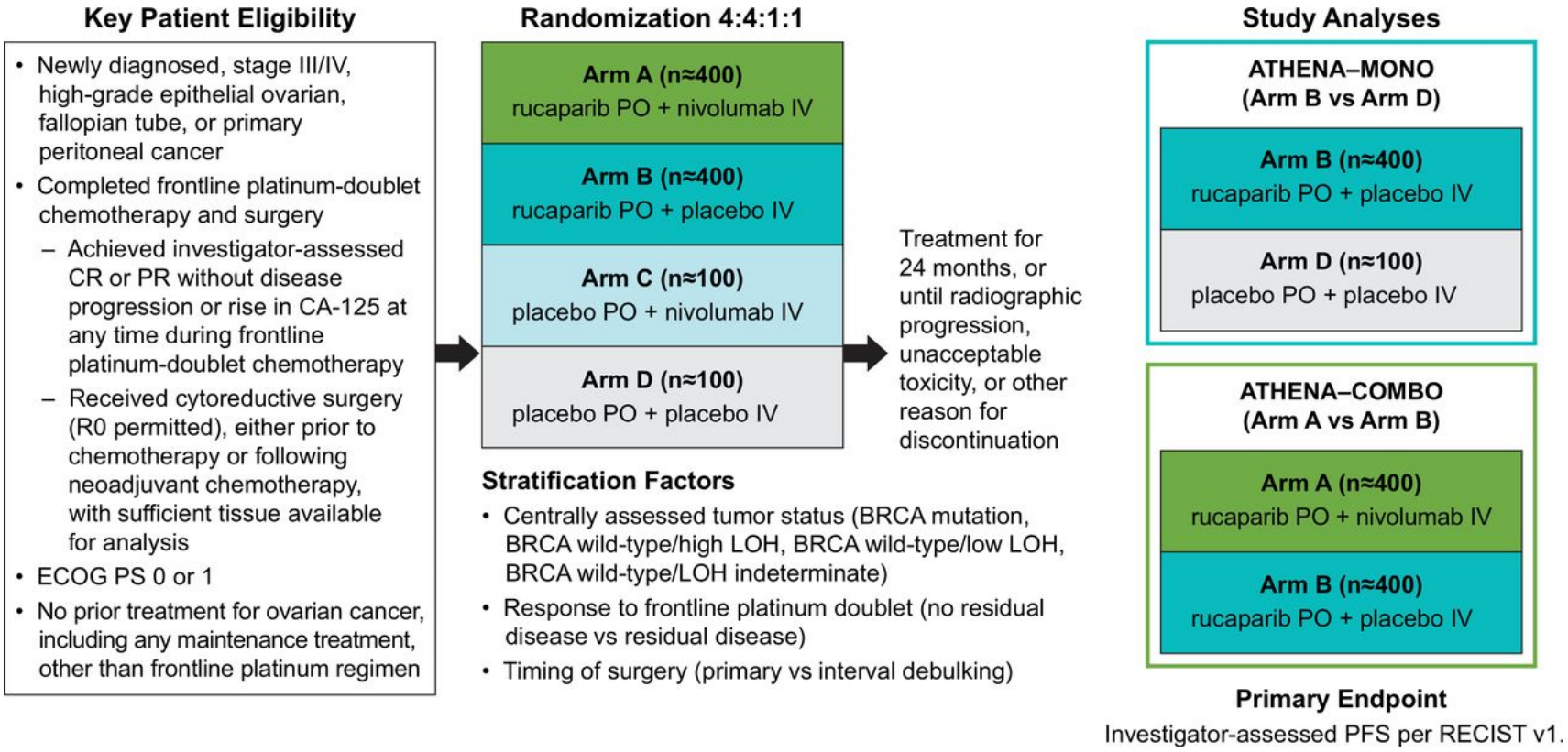
ATHENA Study schema



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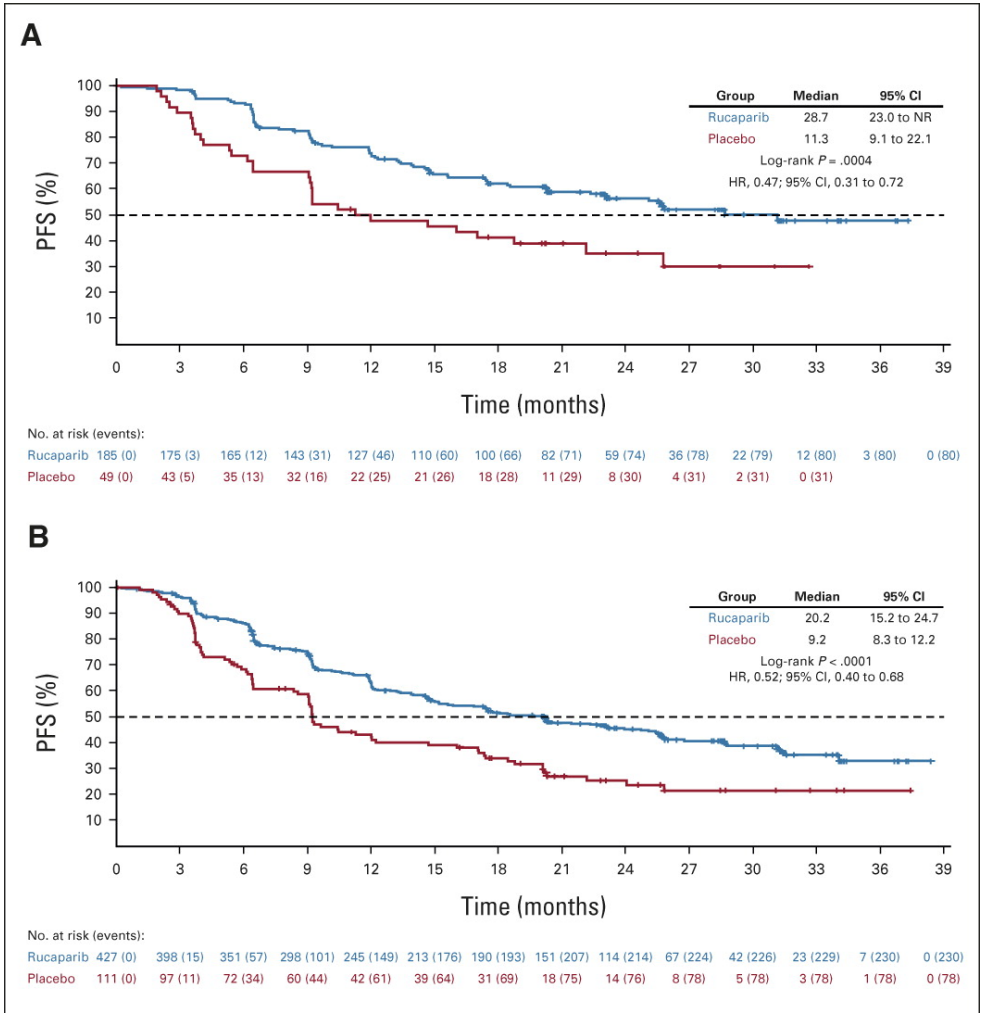
ATHENA – MONO PFS



HRD
-mPFS 28.7 vs 11.3 m
-HR 0.47

ITT
-mPFS 20.2 vs 9.2 m
-HR 0.52

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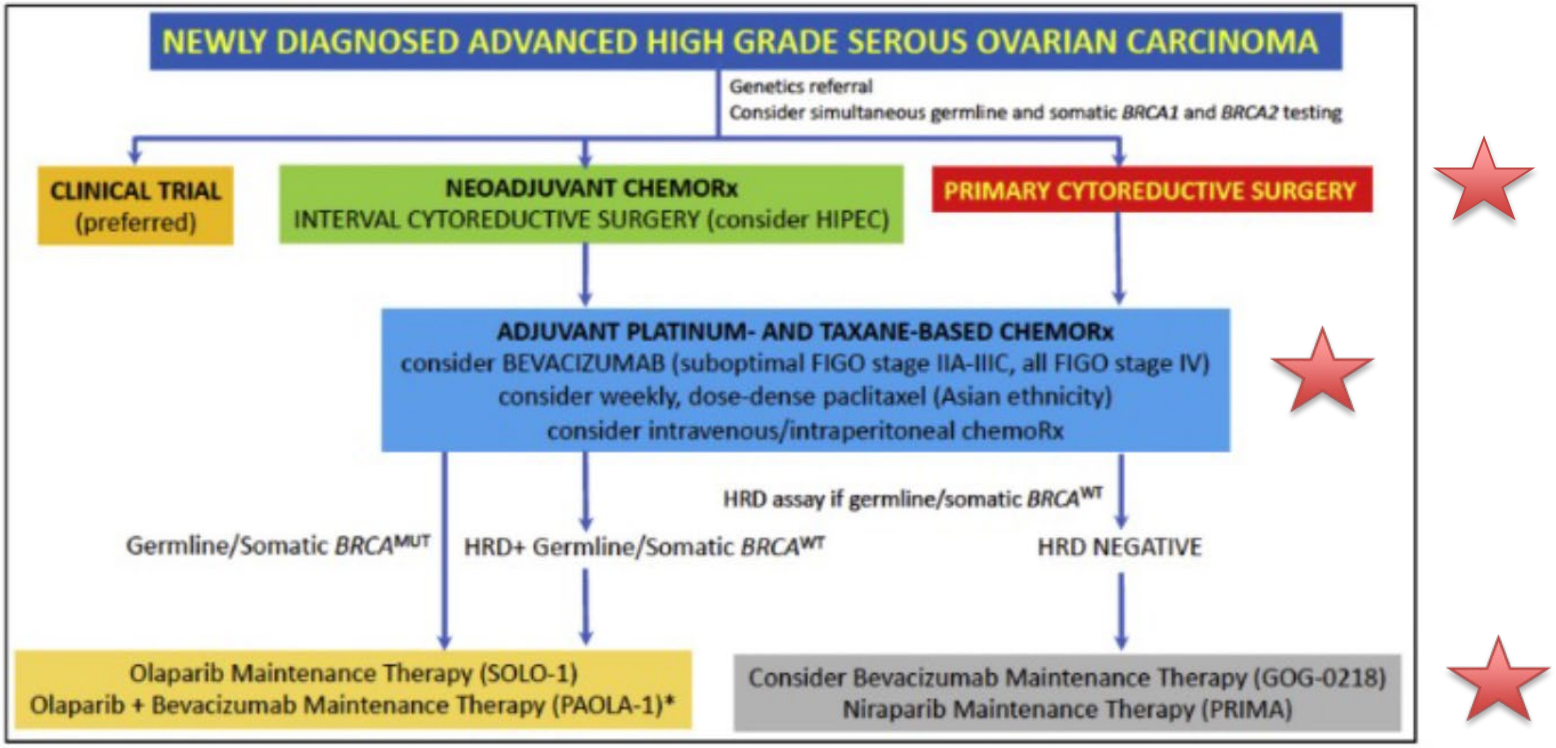
Suggested Algorithms:



Haunschild and Tewari. Gynecol Oncol 2021; 160: 333

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Thank you

Questions?

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