An Industry Supported Symposium at the 2025 SGO Winter Meeting

Shredding New Paths:

Integrating Targeted Therapies in Ovarian and Endometrial Cancer, Clinical Runs and Future Slopes

Thursday, January 30, 2025
8:15pm – 9:30pm PST

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Welcome and Introductions

Thomas Herzog, MD
University of Cincinnati
Cincinnati, Ohio

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Our Expert Panel

Thomas Herzog, MD
University of Cincinnati
Cincinnati, Ohio

Angeles Alvarez Secord, MD
Duke University
Durham, North Carolina

Jubilee Brown, MD
Atrium Health Wake Forest University
Charlotte, North Carolina

Matthew Powell, MD
Washington University
St. Louis, Missouri

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Faculty Disclosures

Name	Role in Activity	Disclosures
Thomas Herzog, MD	**Moderator**	**Scientific Advisory Boards:** AstraZeneca; Caris; Clovis Oncology; Eisai; Epsilogen; Genentech; J&J; Merck; Mersana; Novocure; Seattle Genetics
Angeles Alvarez Secord, MD	Speaker	**Advisory Board:** AbbVie **Uncomp Advisory Board:** Aravive; Gilead; Oncoquest/Canaria Bio; VBL **Research funds to institution:** AstraZeneca; AbbVie; Aravive; Clovis Oncology; Eisai; Ellipses Pharma; Roche/Genentech; GSK; I-MAB Biopharma; Immunogen; Karyopharm; Merck; Mersana; Seagen; VBL Therapeutics; Zentalis **Steering Committee:** Aravive; Oncoquest/Canaria Bio; VBL
Jubilee Brown, MD	Speaker	**Consultant:** Eisai; Genentech; GSK; Tesaro; Verastem **Steering Committee:** Genentech
Matthew Powell, MD	Speaker	**Consultant:** AstraZeneca; Clovis Oncology; Eisai; Genentech USA; GSK; Immunogen; Merck; Seattle Genetics

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Shredding New Paths

Pre-Test

SCAN ME

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Agenda

Topic	Presenter
Welcome and Introduction *5 minutes, 8:15-8:20pm PST*	**Thomas Herzog, MD** University of Cincinnati
Controlled Risk: **Navigating the Ski Slopes of Endometrial Cancer** *15 minutes + 5-minute Q&A Interactive Discussion, 8:20-8:40pm PST*	**Matthew Powell, MD** Washington University
Mogul-Level Efficacy & Black Diamond Implications of PARPi: **Emerging Data and Integration into Clinical Practice** *15 minutes + 5-minute Q&A Interactive Discussion, 8:40:-9:00pm PST*	**Angeles Alvarez Secord, MD** Duke University
Navigating New Mountains: **Fresh Tracks on ADCs in Endometrial and Ovarian Cancers, Up and Coming Innovations on the Vista** *15 minutes with Integrated Discussion, 9:00-9:15pm PST*	**Jubilee Brown, MD** Atrium Health Wake Forest University
Wrap Up and Key Takeaways With Panel *15 minutes, 9:15-9:30pm PST*	**Thomas Herzog, MD** University of Cincinnati

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Controlled Risk: Navigating the Ski Slopes of Endometrial Cancer

Matthew Powell, MD
Washington University
St. Louis, Missouri

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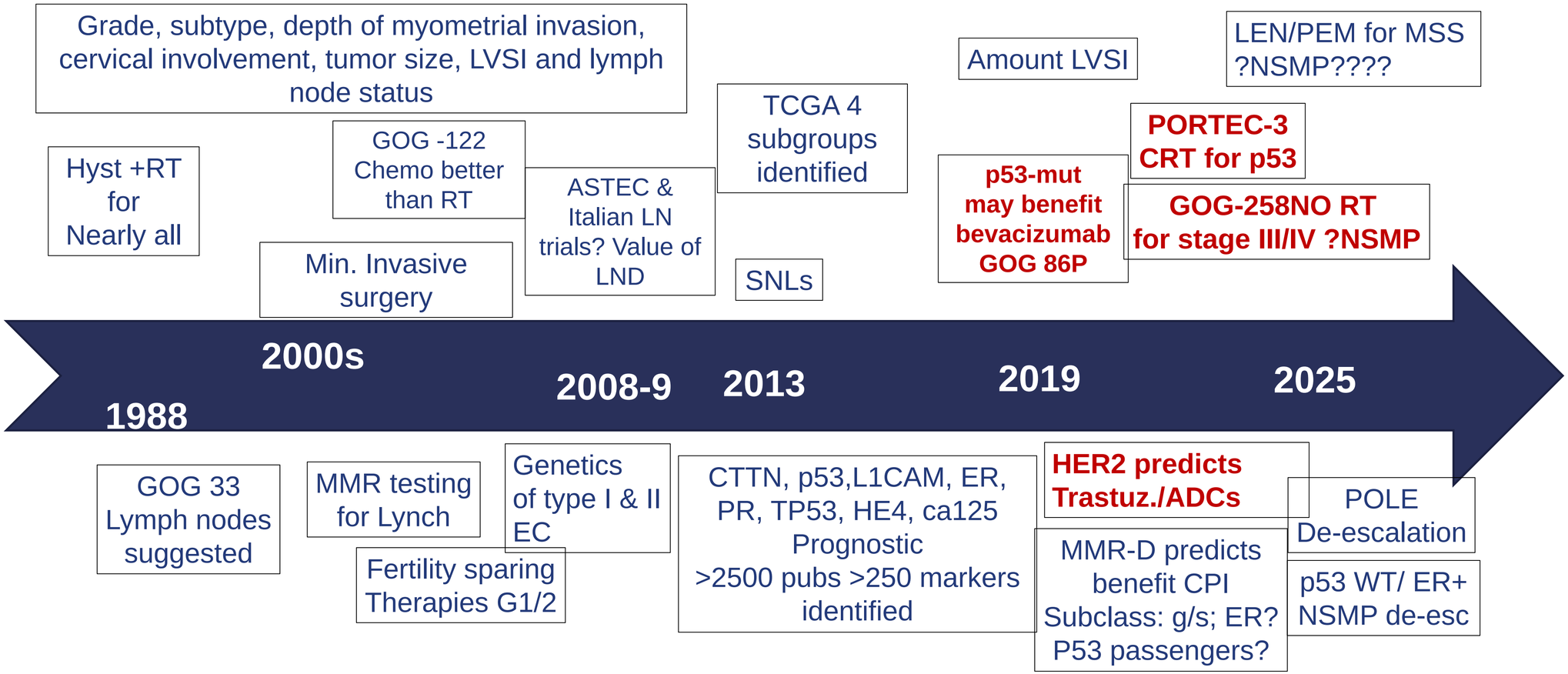
History of Management of Endometrial Cancer:
Journey from Prognostic to Predictive Markers

GOG 99/249/PORTEC 1/2 ”High Intermediate RISK”: why was AGE in the model: gave us a crude estimate of TP53 & dMMR



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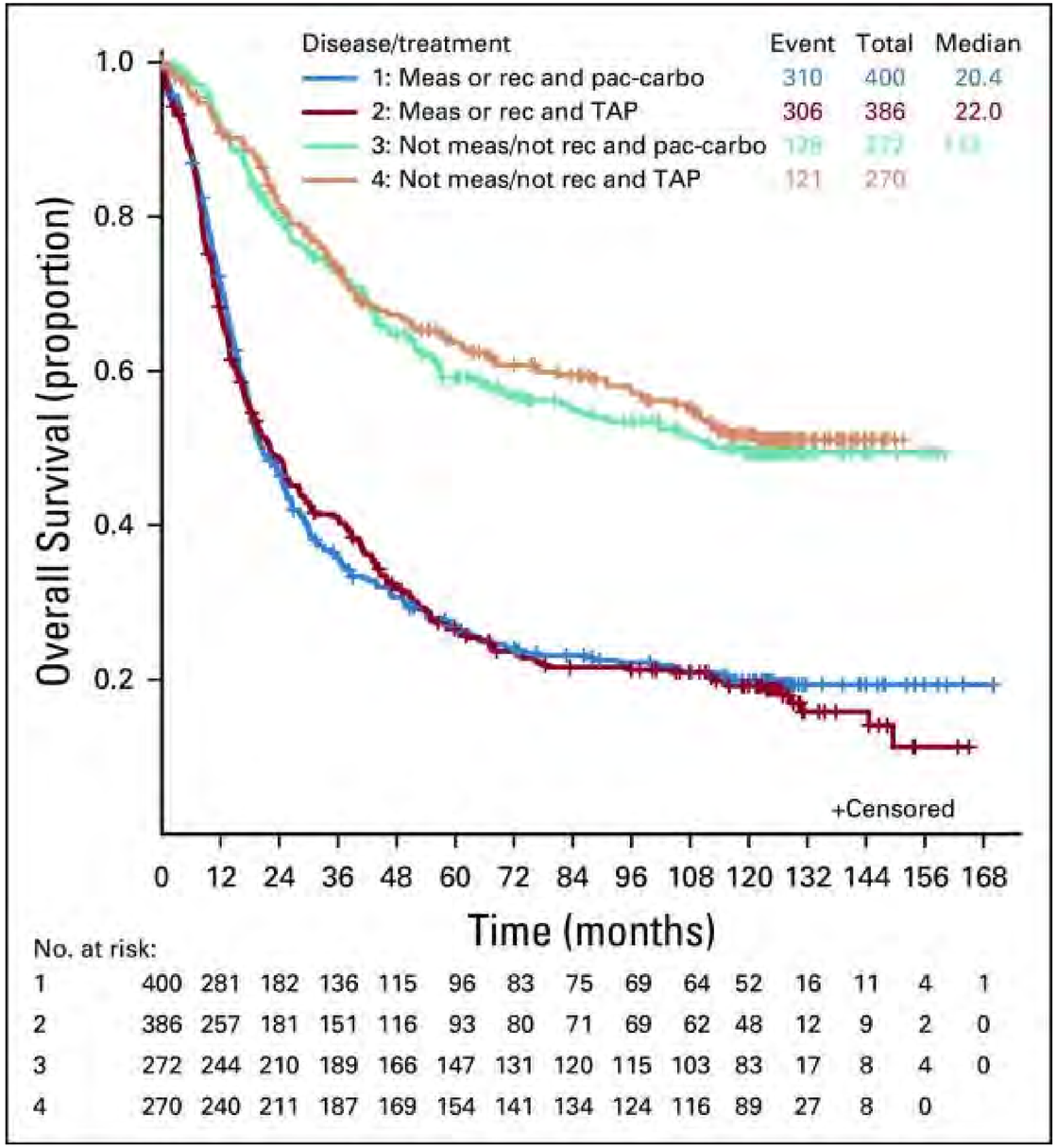
GOG-0209

- Initially accrued only measurable advanced or recurrent EC in 2003
- In 2006 expanded to include non-measurable stage III-IV recurrent EC → accrual rapidly increased
- All chemo naïve
- Measurable/Recurrent patients do very poorly with PC/TAP



Miller DS, et al. *J Clin Oncol*. 2020,Nov;38(33):3841-3850. doi:10.1200/JCO.20.01076.

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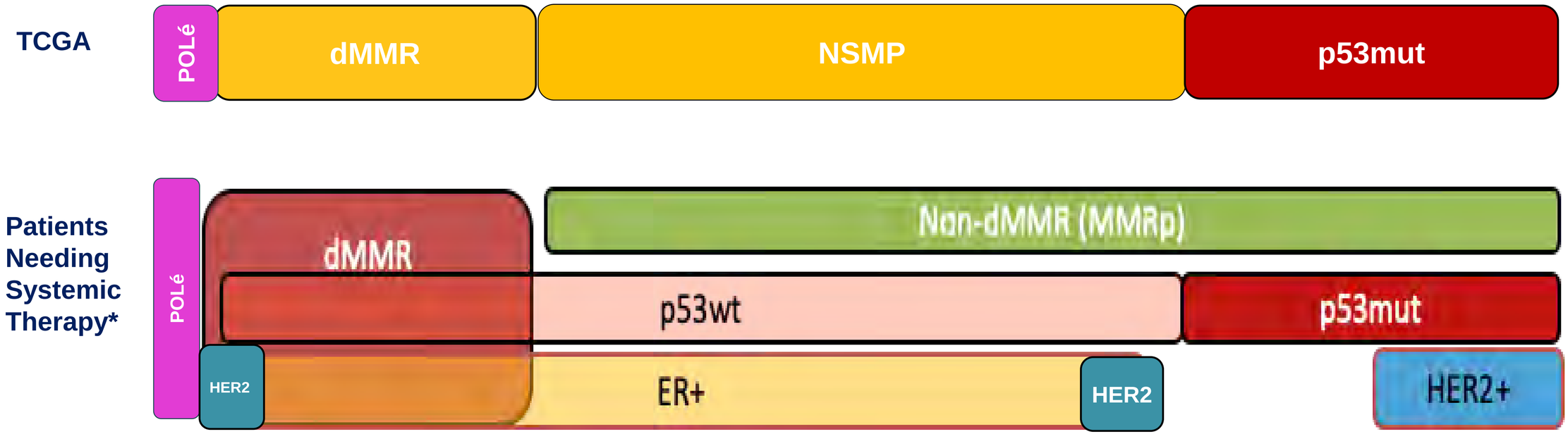
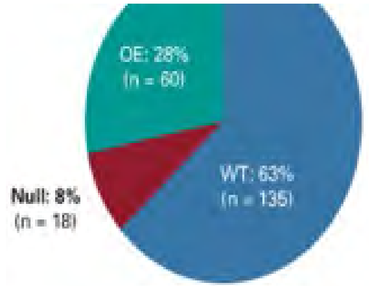
Molecular Profile of Endometrial Cancers

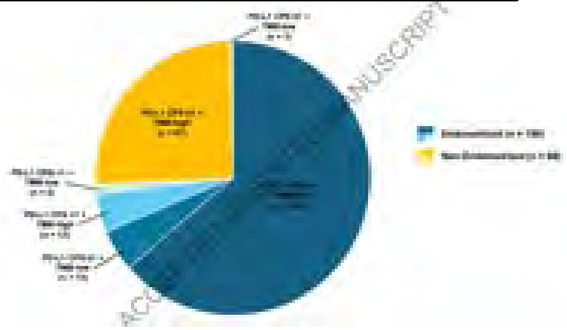


A large portion of what we see in practice:
IIIC1/2 NON-measurable pMMR patients
- Few included in Ruby, -018, DUO-E
- Most of what we see included in B21 trial



TP53: 85-92% concordance
IHC vs sequencing: 70% GOF vs 30% null

25% of dMMR
NON-Endometrioid
47% withTP53 abn IHC



TP53 GOF:P151S, Y163C, R175H, L194R, Y220C, R248Q, R248W, R273C, R273H, R273L, and R282W

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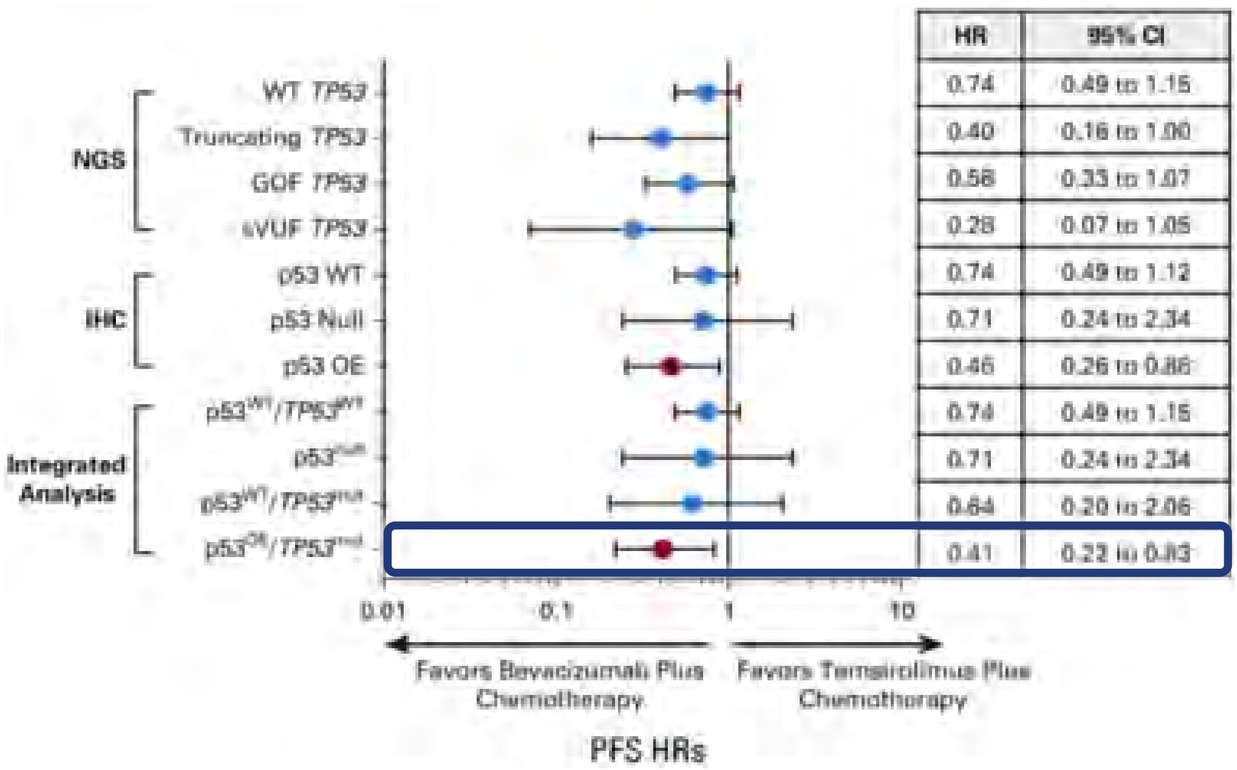
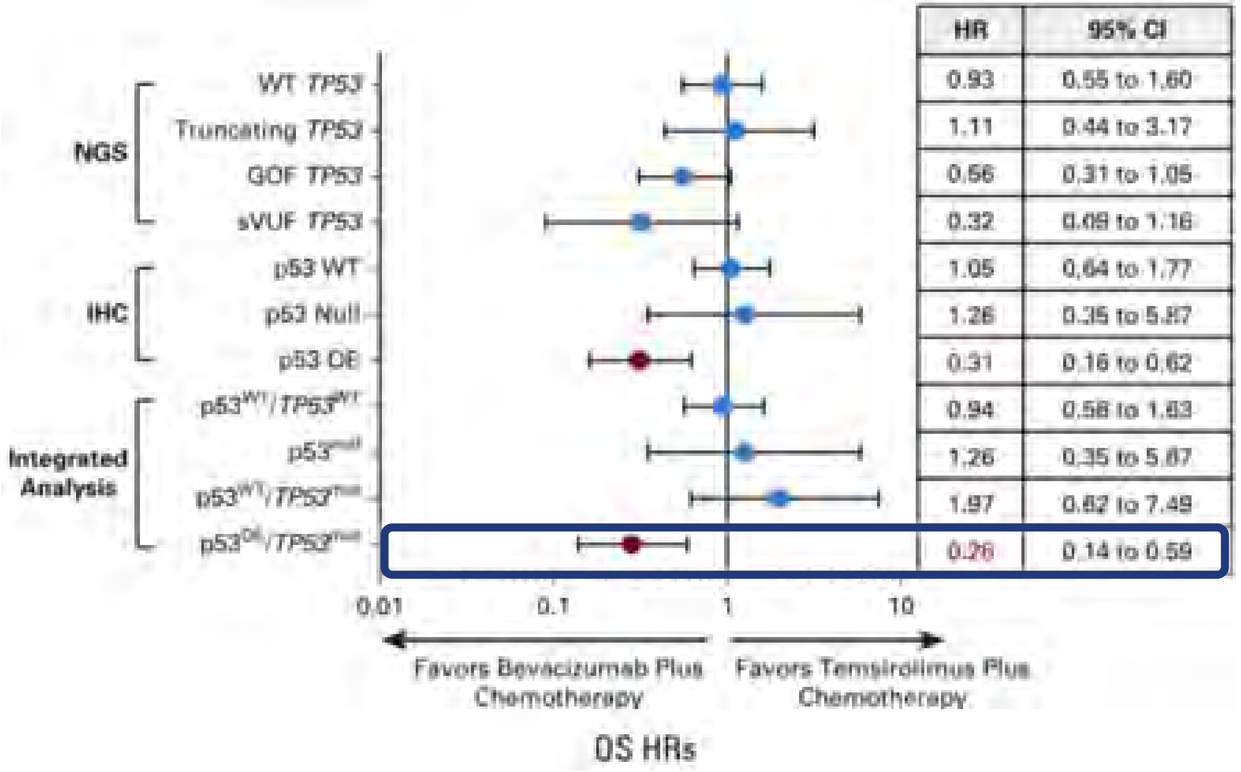
Support for PROMIS+ (ER, HER2, TP53mut characterization)

GOF p53 Matter Most

TP53 Sequencing and p53 IHC Predict Outcomes When Bevacizumab is Added to 1L Chemotherapy in EC:
An NRG Oncology/Gynecologic Oncology Group Study





Thiel KW, et al. *J Clin Onc.* 2022;40(28):3289-3300. doi:10.1200/JCO.21.02506.

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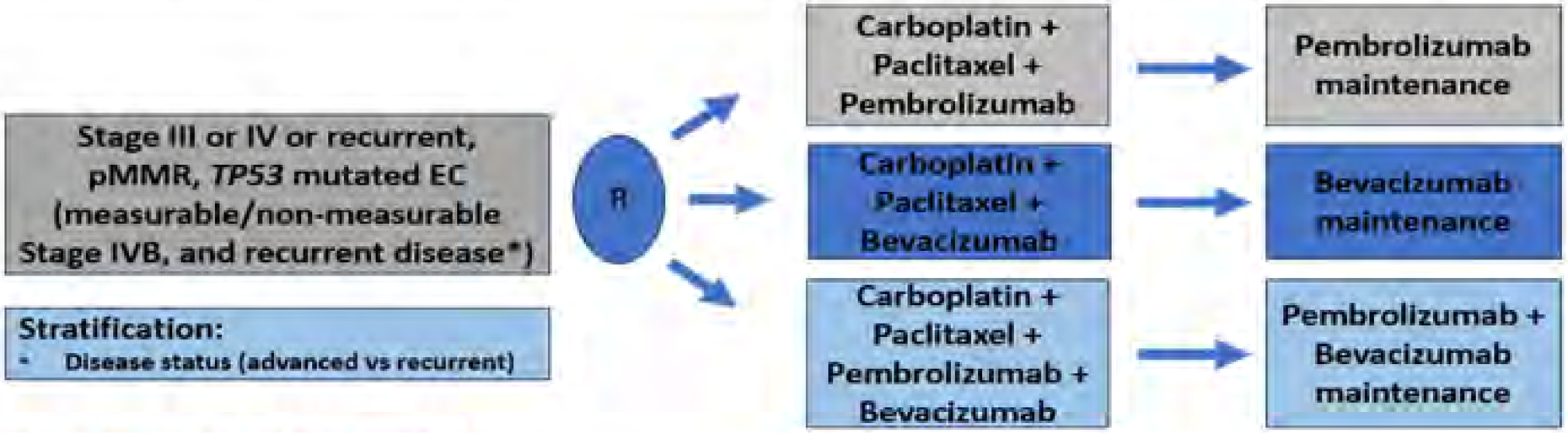
GY035 (UC2323): Prelim trial design building on results of GY018 & 86P in *TP53* mutated Endometrial cancer patients: approved by GCSC

Randomized Phase II/III Study of Carboplatin + Paclitaxel + Pembrolizumab vs. Carboplatin + Paclitaxel + Bevacizumab vs. Carboplatin + Paclitaxel + Pembrolizumab + Bevacizumab in Patients with Advanced or Recurrent, pMMR and *TP53* mutated Endometrial Cancer



*Primary Phase II endpoint: PFS by RECIST V1.1

*Primary Phase III endpoint: OS

Treatment Plan:

Arm 1: IV carboplatin AUC 5 + IV paclitaxel 175 mg/m^2 + IV pembrolizumab 200 mg on day 1 every 3 weeks x 6-10 cycles followed by 14 additional cycles of pembrolizumab 400 mg IV maintenance every 6 weeks.

Arm 2: IV carboplatin AUC 5 + IV paclitaxel 175 mg/m^2 + bevacizumab 15 mg/kg on day 1 every 3 weeks x 6-10 cycles followed by 28 additional cycles of bevacizumab 15 mg/kg maintenance every 3 weeks.

Arm 3: IV carboplatin AUC 5 + IV paclitaxel 175 mg/m^2 + IV pembrolizumab 200 mg + bevacizumab 15 mg/kg on day 1 every 3 weeks x 6-10 cycles followed by 14 additional cycles of pembrolizumab 400 mg IV maintenance every 6 weeks and 28 additional cycles of bevacizumab 15 mg/kg IV maintenance every 3 weeks.

*Patients with recurrent disease who have received prior adjuvant therapy must have a platinum-free interval of >/=12 months.

Is this similar To PC ->LEN/ Pembro?

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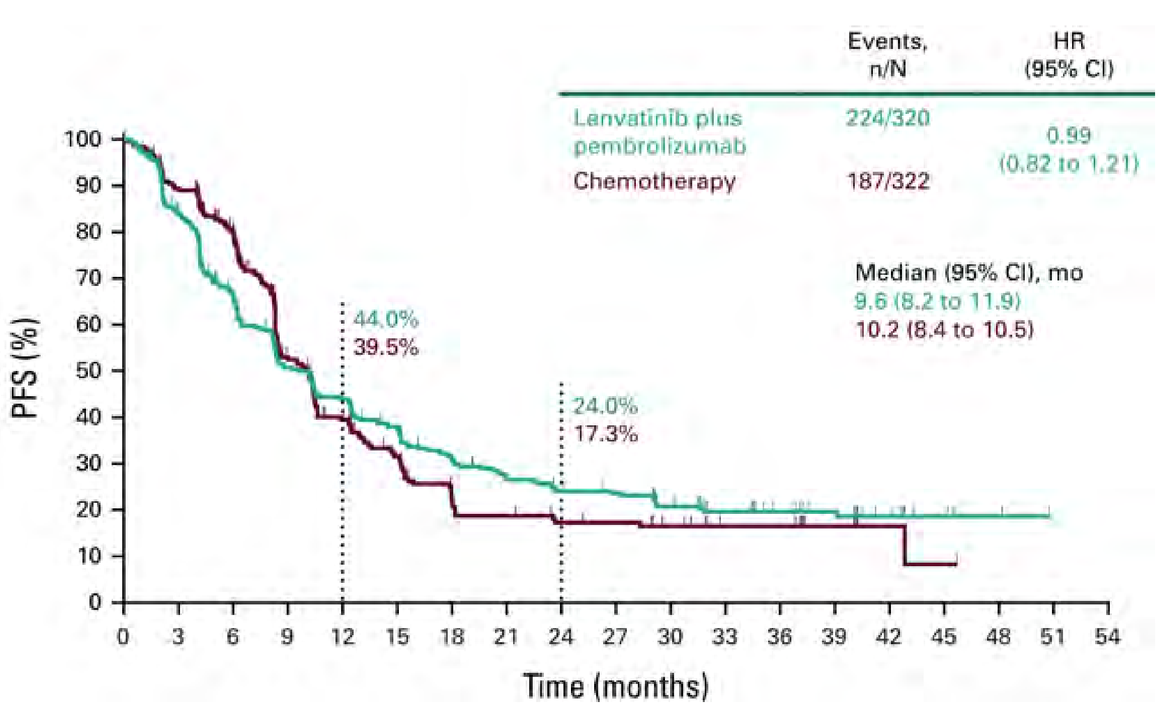
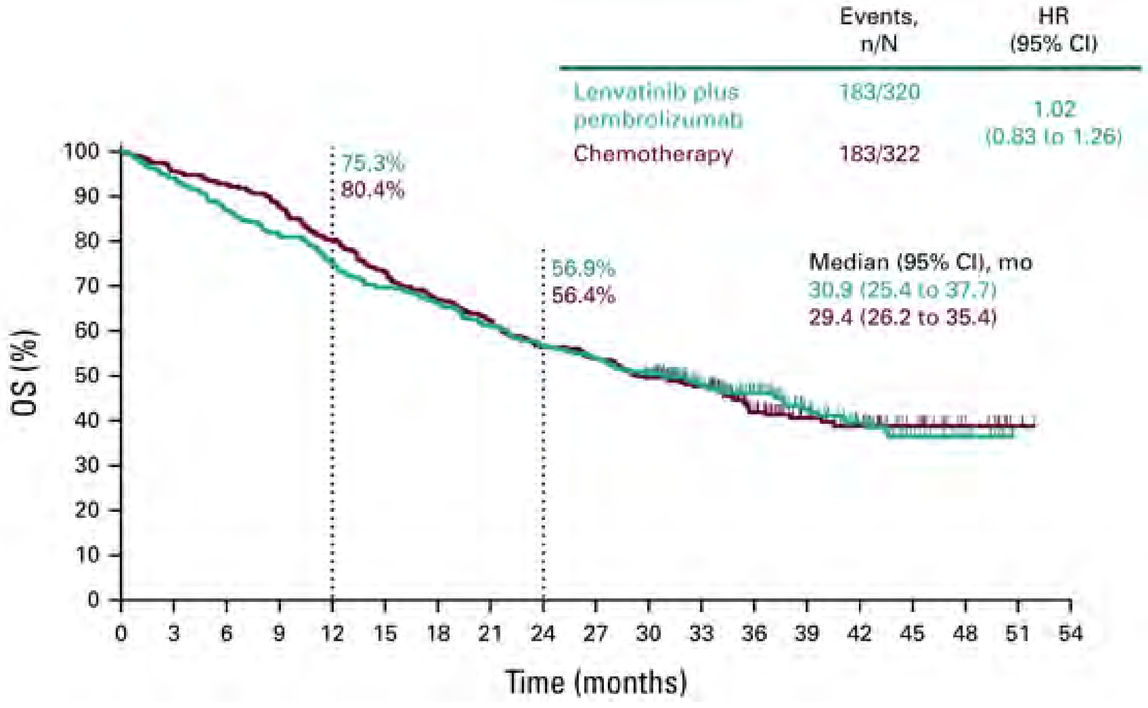
LEAP-001: Lenvatinib + Pembrolizumab vs Chemotherapy Mostly 1L therapy: *pMMR population*

LEAP-001 did not meet its dual primary endpoints of PFS and OS, in both ITT and MMRp/MSS populations





Marth C, et al. *J Clin Oncol.* 2024;0. doi:10.1200/JCO-24-0132

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Paradigm-Shifting Data in EC Management

Name	EN6-RUBY Part 1[1]	EN7 AtTEnd[2]	NRG-GY018[3]	B21[4]	EN6-RUBY Part 2[5]	DUO-E[6]	EN9 LEAP-001[7]	EN15/C93[8]	EN13[9] DOMENICA
Lead Group Study Chair(s)	NSGO-CTU Mirza/Powell	MaNGO Colombo	NRG Eskander/ Powell	BGOG Van Gorp	NSGO-CTU Mirza/Powell	GOG-P Westin	AGO-A Marth	GOG-P Slomovitz	GINECO Joly
Investigational Agent	Dosta + Chemor	Atezo + Chemo	Pembro + Chemo	Pembro + Chemo	Dosta + Nira + Chemo	Durva + Ola + Chemo	Pembro + Lenva	Pembro	Dosta
N	494	551	816	990	291	718	842	350	260
Concomitant	+	+	+	+	+	+	Pembro + Lenva vs. Chemo	Pembro vs. Chemo	Dosta vs. Chemo
Maintenance	+	+	+	+	+	+			
Readout	NEJM 2023	ESMO 2023	NEJM 2023	Negative *AnnOnc*	SGO 2024	JCO 2023	“negative” ESGO 2024	?	?

1. Mirza MR, et al. *NEJM.* 2023;388(23):2145-2158; 2. Colombo N, et al. *Ann Oncol.* 2023;34(Suppl 2):S1254-S1335 [ESMO abstract LBA40]; 3. Eskander RN, et al. *NEJM.* 2023;388(23):2159-2170;
4. ClinicalTrials.gov. NCT04634877. Available at: https://clinicaltrials.gov/study/NCT04634877; 5. Mirza MR, et al. Presented at: Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer; 16-18 March 2024; San Diego, CA, USA [oral presentation]; 6. Westin SN, et al. *J Clin Oncol.* 2024;42(3):283-299; 7. Marth C, et al. *Int J Gynecol Cancer.* 2024;34(Suppl 1):A570-A571 [ESGO abstract 88];
8. Slomovitz BM, et al. *J Clin Oncol.* 2022;40(Suppl 16):TPS5623; 9. Joly F, et al. *J Clin Oncol.* 2023;41(Suppl 16):TPS5630.

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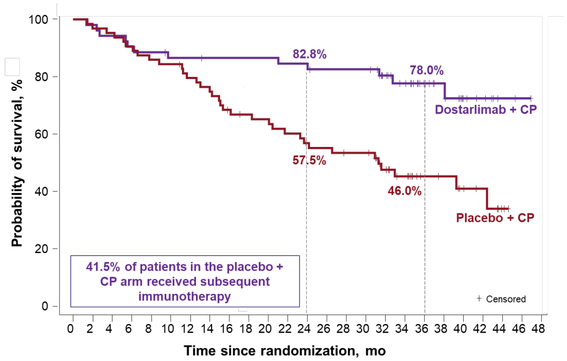
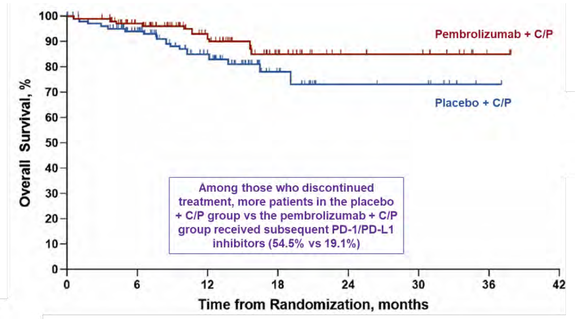
dMMR EC: Substantial and Unprecedented PFS and OS Benefit of ICI + Chemotherapy

EN6-RUBY Part 1[1–3]



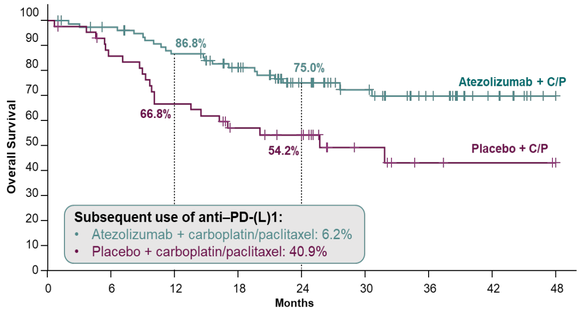
OS Data	Events, %	Median (95% CI), mo
Dostarlimab + C/P	22.6	NE (NE-NE)
Placebo + C/P	53.8	31.4 (20.3-NE)
OS data maturity	39.8%	
Median follow-up, mo	36.6	

NRG-GY018[4–5]



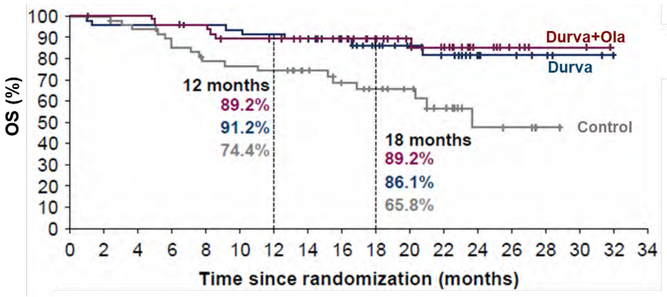
OS Data	Events, %	Median (95% CI), mo
Pembrolizumab + C/P	9.1	NR (NR-NR)
Placebo + C/P	15.1	NR (NR-NR)
OS data maturity	18%	
Median follow-up, mo	13.3-13.7	

EN7-AtTEnd[6]



OS Data	Events, %	Median (95% CI), mo
Atezolizumab + C/P	24.7	NE (NE-NE)
Placebo + C/P	47.7	25.7 (13.5-NE)
OS data maturity	--	
Median follow-up, mo	--	

DUO-E[7,8]



OS Data	Events, %	Median (95% CI), mo
Durvalumab + C/P	15.2	NR (NR-NR)
Placebo + C/P	36.7	23.7 (16.9-NR)
OS data maturity	21.7%	
Median follow-up, mo	--	

PFS	**HR 0.28** (95% CI, 0.16-0.50); P<0.001	**HR 0.30** (95% CI, 0.19-0.48); P<0.001	**HR 0.36** (95% CI, 0.23-0.57); P=0.0005	**HR 0.42** (95% CI, 0.22-0.80); Durva + C/P arm
OS	**HR 0.32** (95% CI, 0.17-0.63); Nominal P=0.0002	**HR 0.55** (95% CI, 0.25-1.19)	**HR 0.41** (95% CI, 0.22-0.76)	**HR 0.34** (95% CI, 0.13-0.79) Durva + C/P arm

1. Mirza MR, et al. *N Engl J Med.* 2023;388:2145-2158.; 2. Mirza MR, et al. *Ann Oncol.* 2023;34:500-501.; 3. Eskander RN, et al. *N Engl J Med.* 2023;388:2159-2170.; 4. Eskander RN, et al. Presented at: Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer; March 25-28 2023; Tampa, FL, USA.; 5. Arend RC, et al. Presented at: SGO 2023.; 6. Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; [Presentation #LBA40].; 7. Westin SN, et al. *J Clin Oncol.* 2023; doi: 10.1200/JCO.23.02132.; 8. Powell MA, et al. Presented at: SGO; March 16-18 2024; San Diego, CA, USA. [Presentation #LBA1].; 9. Eskander RN, et al. Presented at: SGO 2024. [Presentation #LBA2].; 10. Colombo N et al. Presented at: ESMO. October 20-24, 2023; Madrid, Spain; Presentation [#LBA40].; 11. Baurain JF, et al. Presented at: SGO 2024. [Scientific Plenary V].

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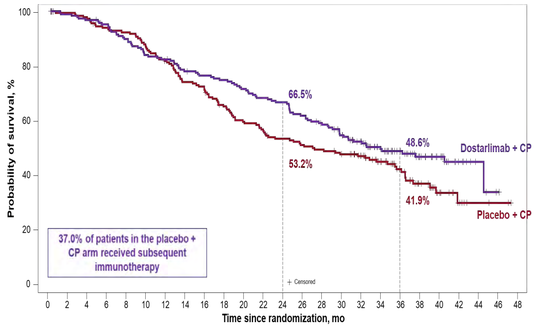
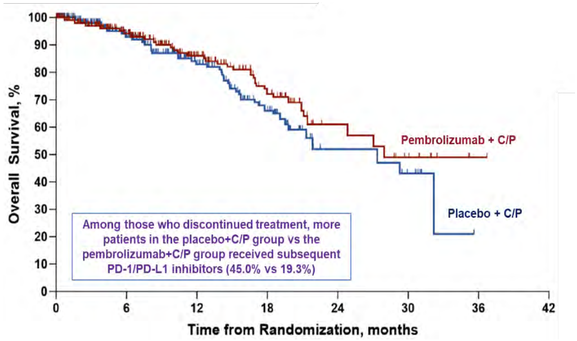
MMRp EC: Clinically Meaningful PFS and OS Benefit of ICI + Chemotherapy

EN6-RUBY Part 1[1–3]



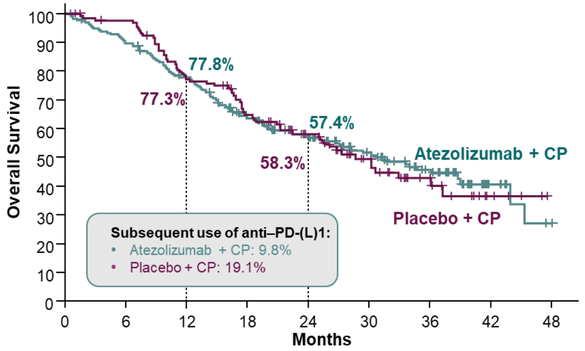
OS Data	Events, %	Median (95% CI), mo
Dostarlimab + C/P	50.5	34.0 (28.6-NE)
Placebo + C/P	59.2	27.0 (21.5-35.6)
OS data maturity	54.8%	
Median follow-up, mo	37.5	

NRG-GY018[4–5]



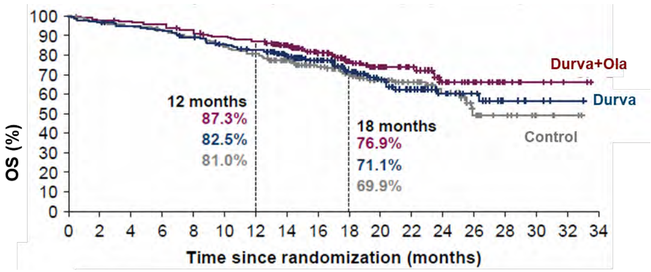
OS Data	Events, %	Median (95% CI), mo
Pembrolizumab + C/P	15.3	28.0 (21.4-NR)
Placebo + C/P	18.3	27.4 (19.5-NR)
OS data maturity	27.2%	
Median follow-up, mo	8.4-8.8	

EN7-AtTEnd[6]



OS Data	Events, %	Median (95% CI), mo
Atezolizumab + C/P	47.2	31.5 (25.0-38.9)
Placebo + C/P	46.4	28.6 (22.4-37.2)
OS data maturity	--	
Median follow-up, mo	--	

DUO-E[7,8]



OS Data	Events, %	Median (95% CI), mo
Durvalumab + C/P	30.2	NR (NR-NR)
Placebo + C/P	33.3	25.9 (25.1-NR)
OS data maturity	29.2%	
Median follow-up, mo	--	

PFS	**HR 0.76** (95% CI, 0.59-0.98);	**HR 0.54** (95% CI, 0.41-0.71); P<0.001	**HR 0.92** (95% CI, 0.73-1.16);	**HR 0.77** (95% CI, 0.60-0.97); Durva + C/P arm
OS	**HR 0.79** (95% CI, 0.60-1.04); Nominal p=0.0493	**HR 0.79** (95% CI, 0.53-1.17) Nominal p=0.1157	**HR 1.00** (95% CI, 0.74-1.35)	**HR 0.91** (95% CI, 0.64-1.30) Durva + C/P arm

1. Mirza MR, et al. *N Engl J Med.* 2023;388:2145-2158.; 2. Mirza MR, et al. *Ann Oncol.* 2023;34:500-501.; 3. Eskander RN, et al. *N Engl J Med.* 2023;388:2159-2170.; 4. Eskander RN, et al. Presented at: Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer; March 25-28 2023; Tampa, FL, USA.; 5. Arend RC, et al. Presented at: SGO 2023.; 6. Colombo N et al. Presented at: European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; [Presentation #LBA40].; 7. Westin SN, et al. *J Clin Oncol.* 2023; doi: 10.1200/JCO.23.02132.; 8. Powell MA, et al. Presented at: SGO; March 16-18 2024; San Diego, CA, USA. [Presentation #LBA1].; 9. Eskander RN, et al. Presented at: SGO 2024. [Presentation #LBA2].; 10. Colombo N et al. Presented at: ESMO. October 20-24, 2023; Madrid, Spain; Presentation [#LBA40].; 11. Baurain JF, et al. Presented at: SGO 2024. [Scientific Plenary V].

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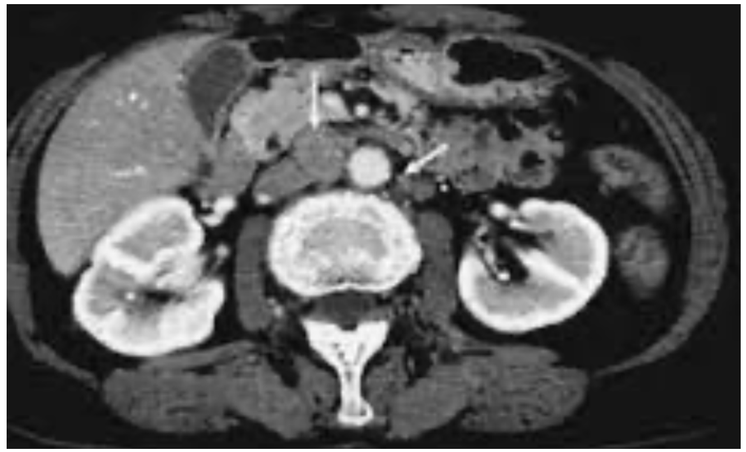
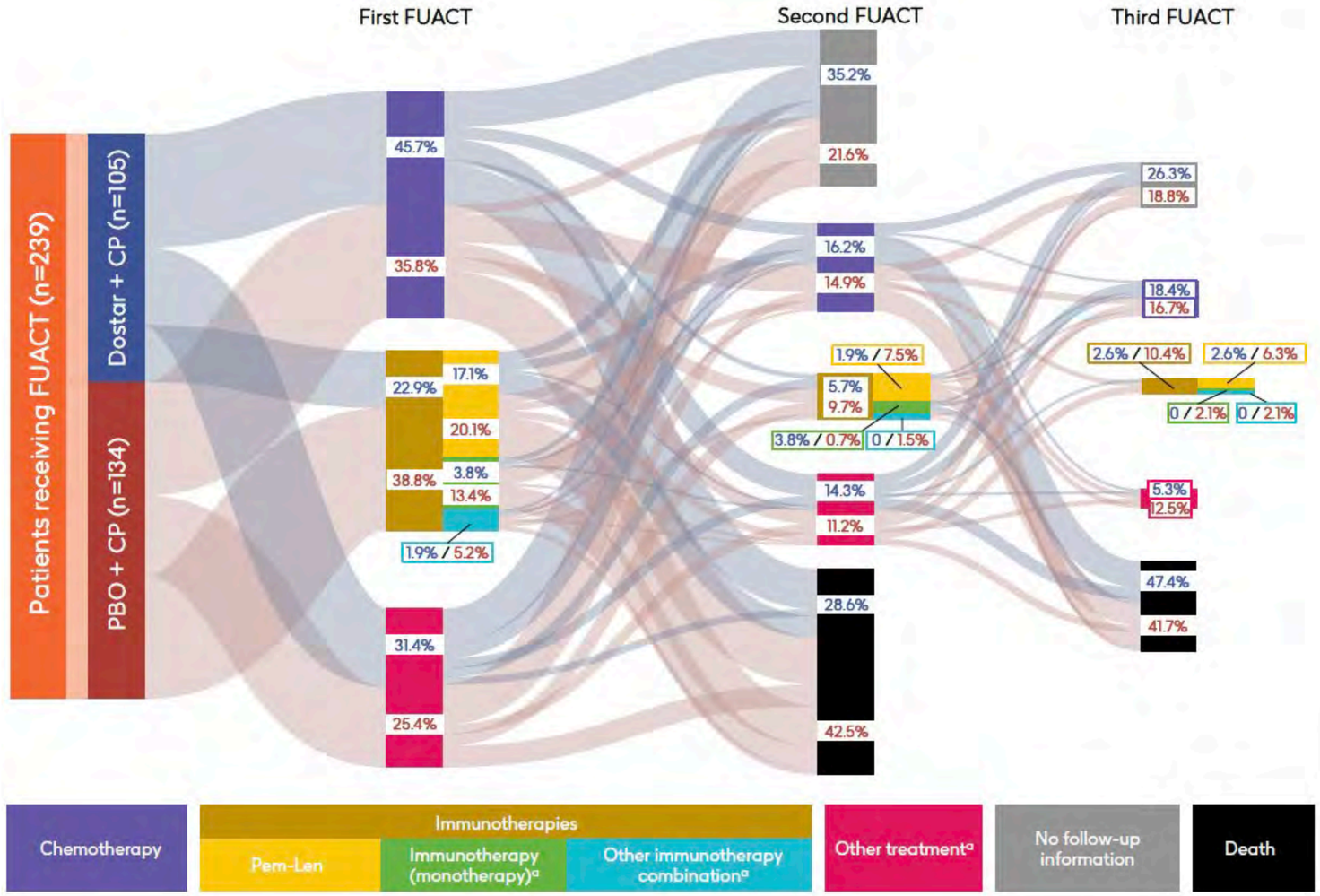
54-year-old with Stage IIIC2 G3 (measurable; pMMR)

- 54-year-old with Stage IIIC2 (para-aortic node positive), grade 3 endometrial cancer (pMMR). No additional biomarkers identified with HER2 IHC 0 status. No medical co-morbidities. She declines participation in a clinical trial
- Surgery followed by CT scan shows measurable disease in para-aortic lymph nodes with indeterminate pulmonary nodules on CT after surgery

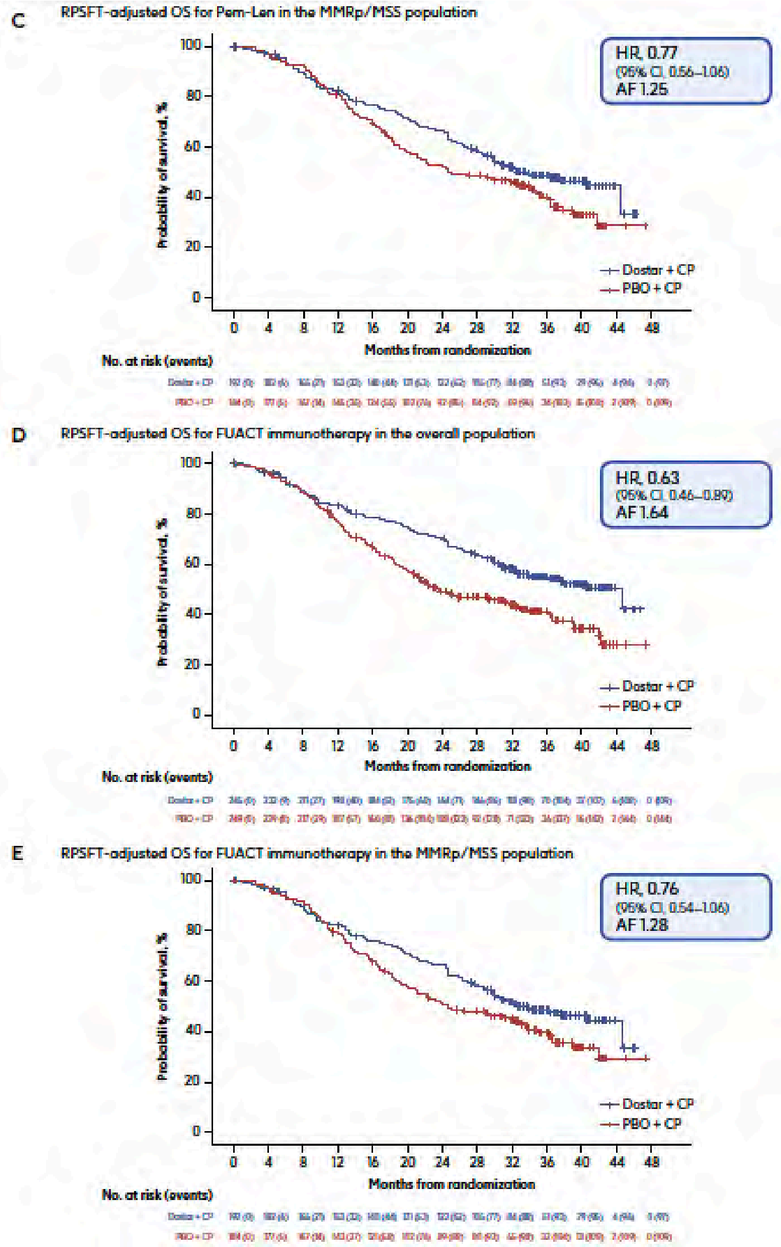


- **Recommendations?**
  - Does TP53 mutation status matter?
  - Role for PARP inhibitor?
- **Case modifications:**
  - What if dMMR?
  - What if pMMR with HER2- 2+ FISH+?
  - What if pathology is carcinosarcoma (pMMR, HER2 negative by IHC ?
  - What if age 75 years old? Expected differences in outcome?
  - What if IIIC1 non-measurable (B-21 eligible)?

ICI Upfront or After Relapse?



CP, carboplatin-paclitaxel; Dostar, dostarlimab; FUACT, follow-up anticancer therapy; PBO, placebo.



Mirza MR, et al. Presented at: European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain [731P].

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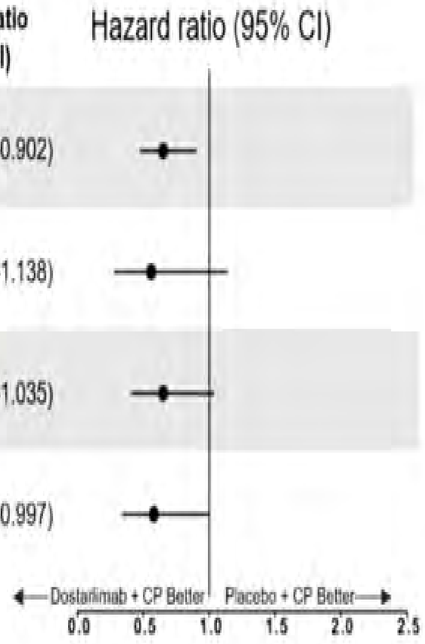
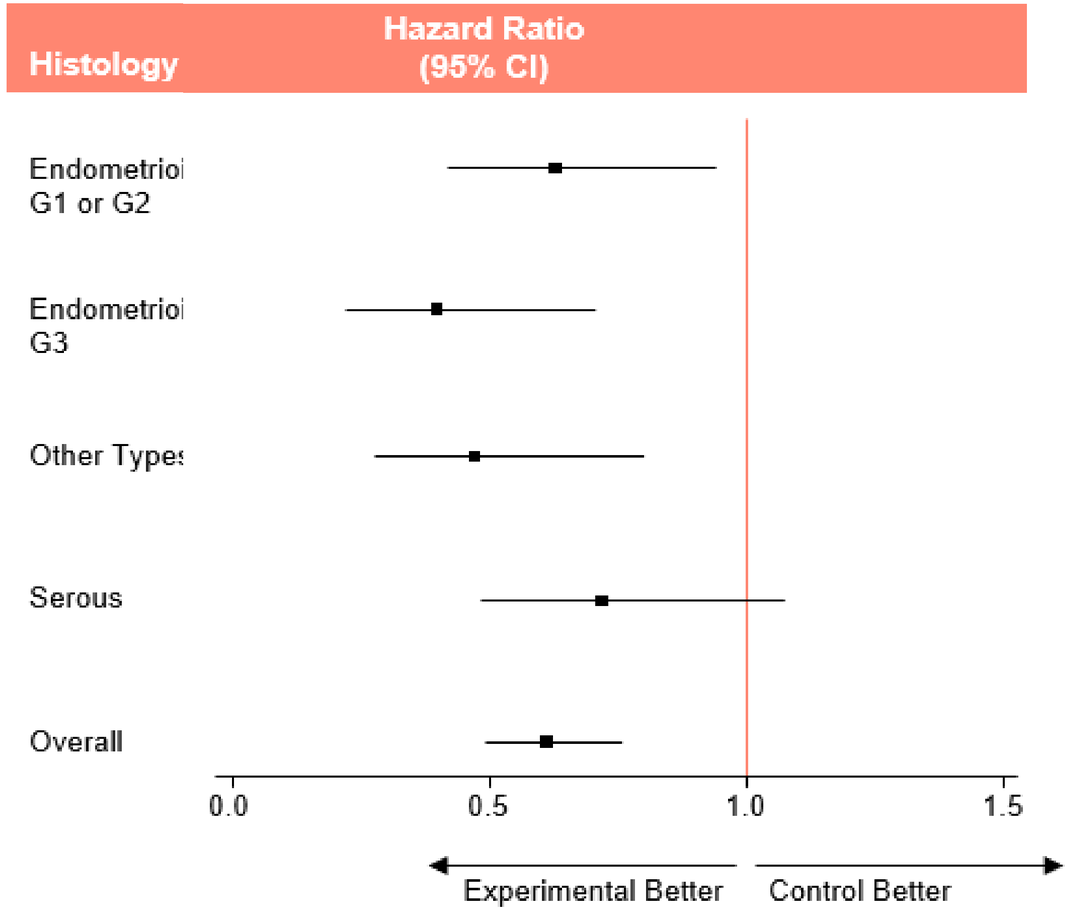
RUBY: Histology and Hazard Ratios[1]

PFS According to Histological Subgroups (ITT)[a]

Histology	Dostarlimab + CP (no. of events/no. of patients)	Placebo + CP (no. of events/no. of patients)	Hazard ratio (95% CI)
Endometrioid carcinoma	64/130	89/136	0.65 (0.473–0.902)
Carcinosarcoma[b]	14/24	18/22	0.56 (0.278–1.138)
Serous adenocarcinoma	36/55	35/48	0.65 (0.403–1.035)
Other	21/36	35/43	0.58 (0.335–0.997)



GY018: PFS by Histology in pMMR Population[2]



Ramez N. Eskander
Data Cut off Date, August 18, 2023

1. Mirza MR, et al. Presented at: European Society for Medical Oncology (ESMO) Annual Meeting; 20-24 October 2023; Madrid, Spain.;
2. Eskander RN, et al. Presented at: European Society for Medical Oncology (ESMO) Annual Meeting; 20-24 October 2023; Madrid, Spain.

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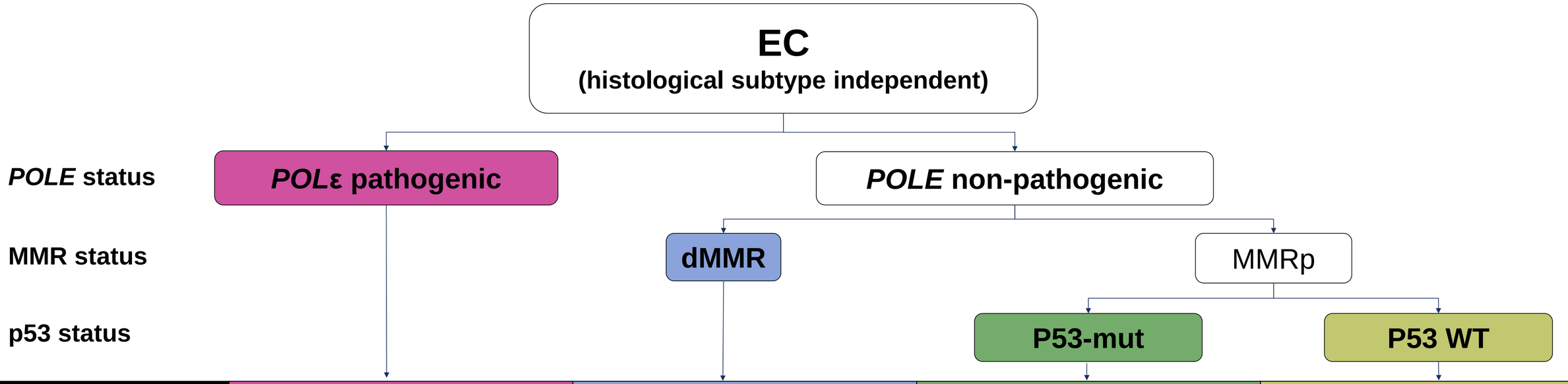
Most Recent Clinical Trial Data with 1L IO: RUBY

RUBY Molecular Classification Algorithm

In RUBY Part 1, molecular classification was performed for all participants with WES results – 400 of 494 patients



Integrated diagnosis	POLεmut (EDM)	dMMR (or MSI-H)	TP53 aberrant	NSMP
Prevalence in RUBY (n/N)	**1.25%** (5/400)	**22.75%** (91/400)	**22%** (88/400)	**54%** (216/400)
Diagnostic test	WES	Results of local (IHC, NGS, PCR) or central test (IHC) provided for RUBY at randomization	WES	

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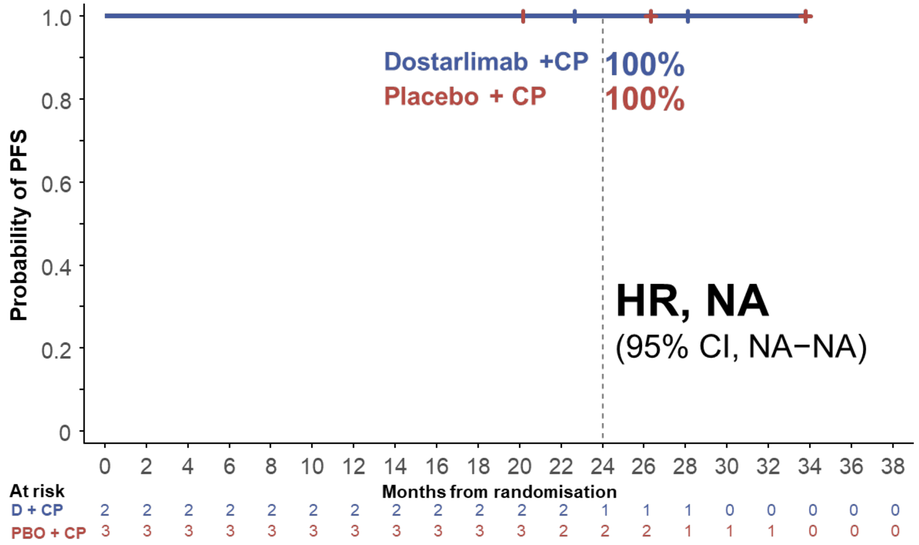
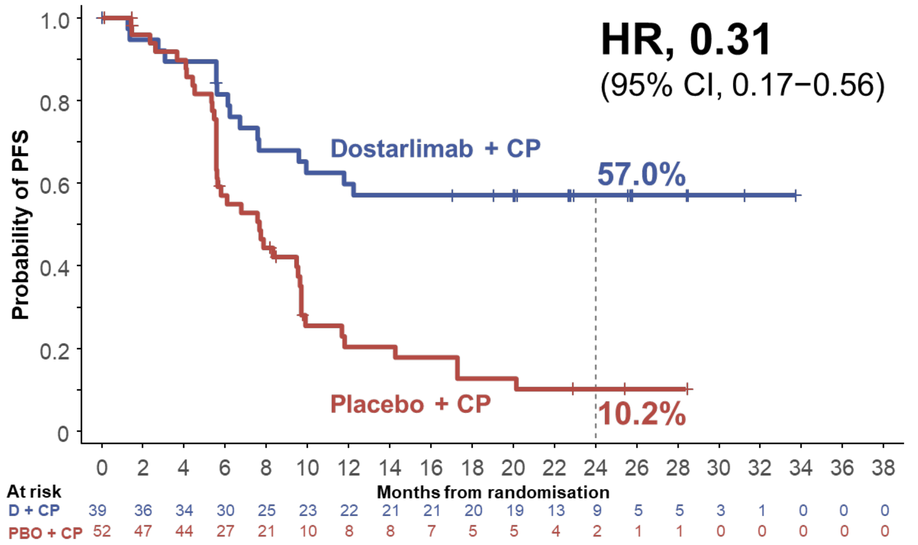
Mirza MR, et al. Presented at: European Society for Medical Oncology (ESMO) Annual Meeting; 20-24 October 2023; Madrid, Spain.

Most Recent Clinical Trial Data with 1L IO: *RUBY PFS According to Molecular Subgroup*

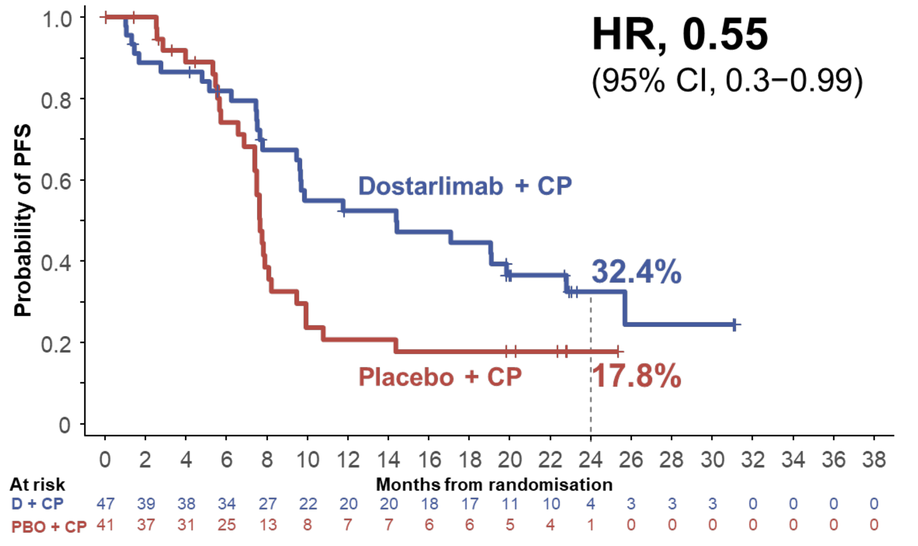
POLε mut



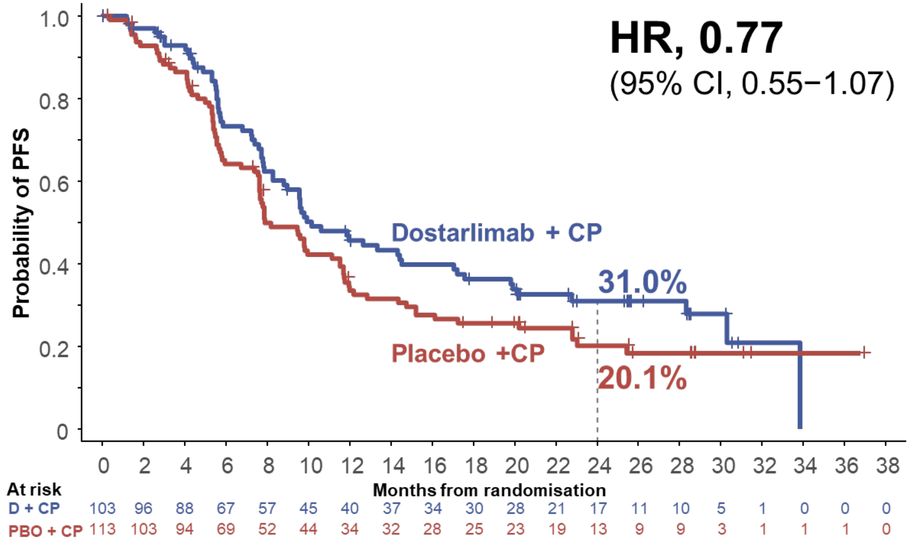
dMMR/MSI-H



TP53 mut



NSMP



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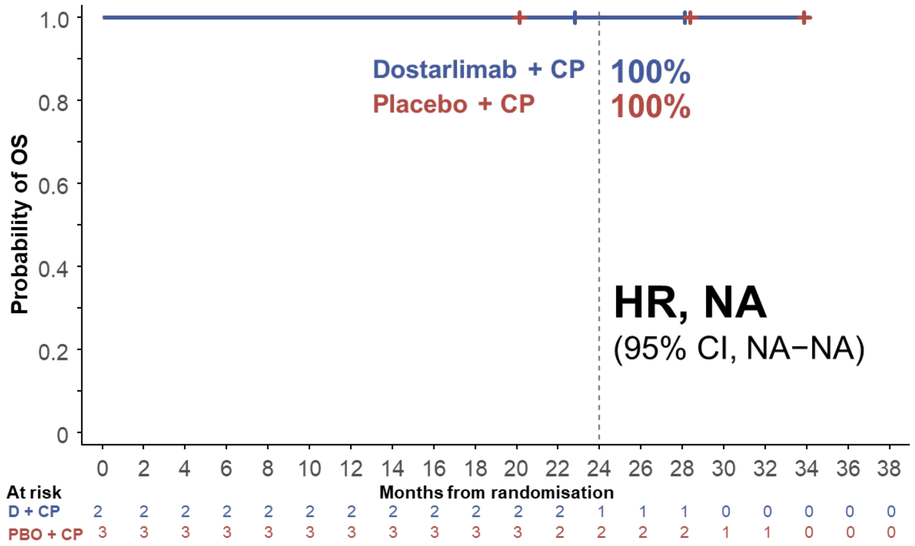
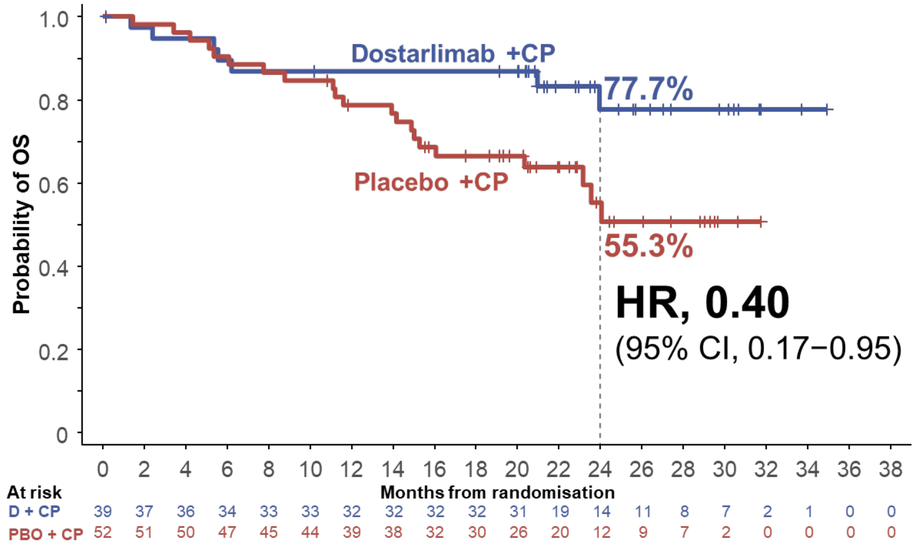
Mirza MR, et al. Presented at: European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain.

Most Recent Clinical Trial Data with 1L IO: *RUBY OS According to Molecular Subgroup*

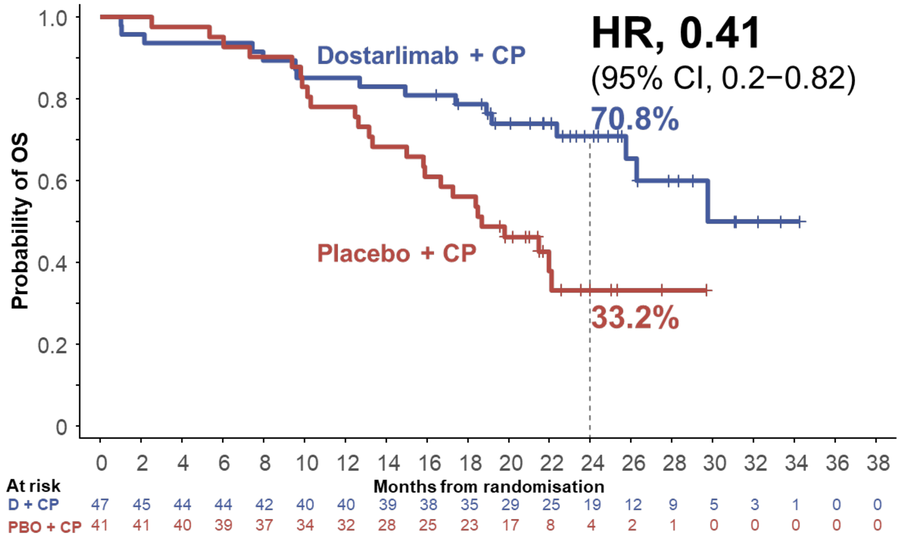
POLε mut



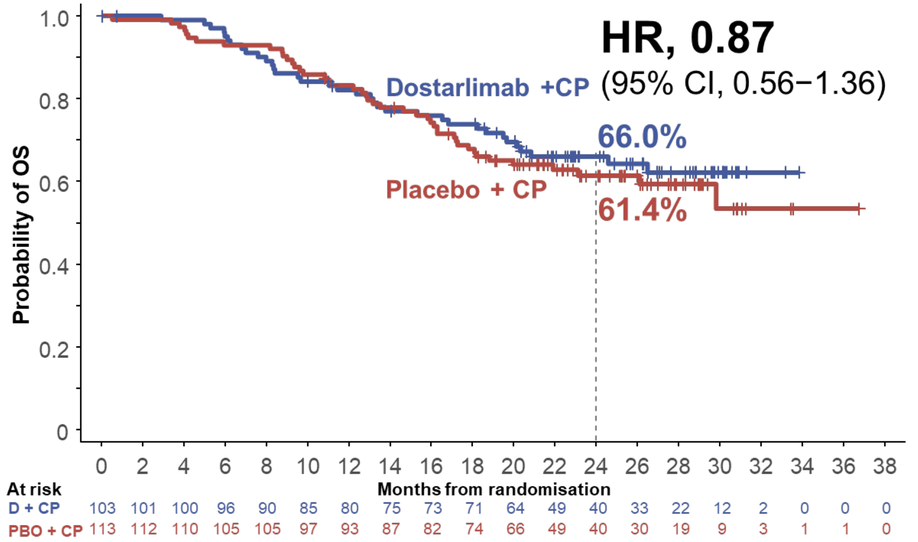
dMMR/MSI-H



TP53 mut



NSMP



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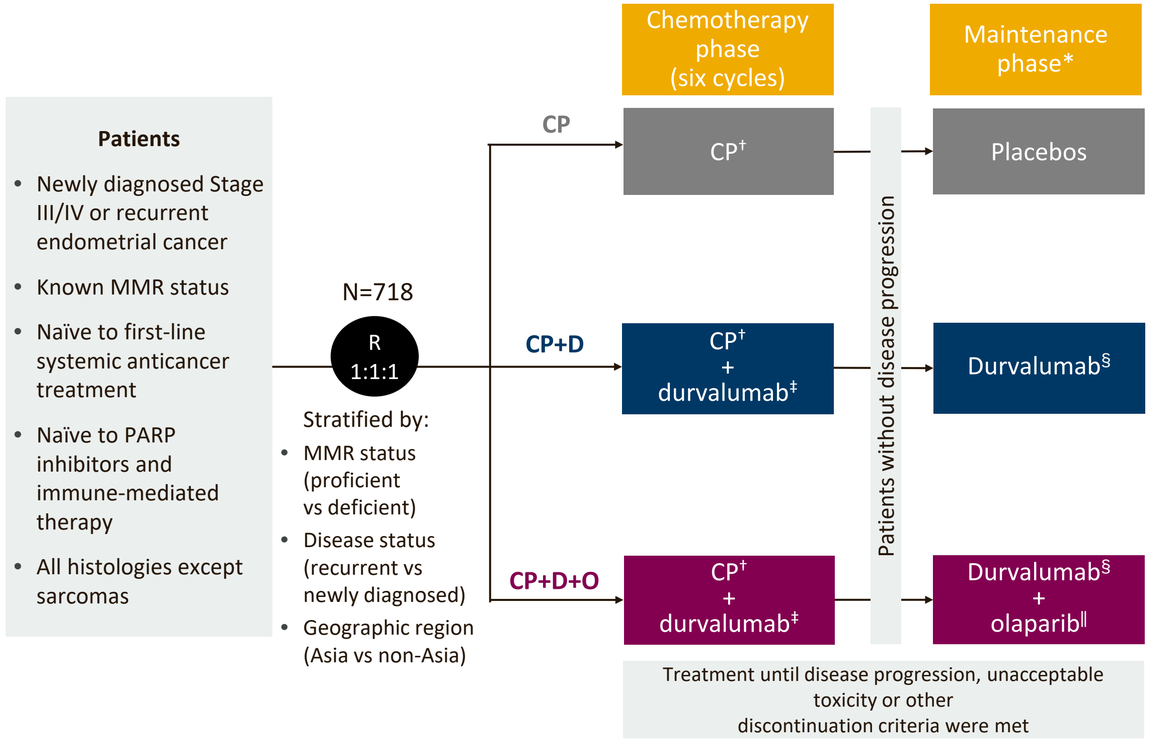
Mirza MR, et al. Presented at: European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain.

DUO-E Met its Dual Primary Endpoints

Randomized, placebo-controlled, double-blind study



Endpoints

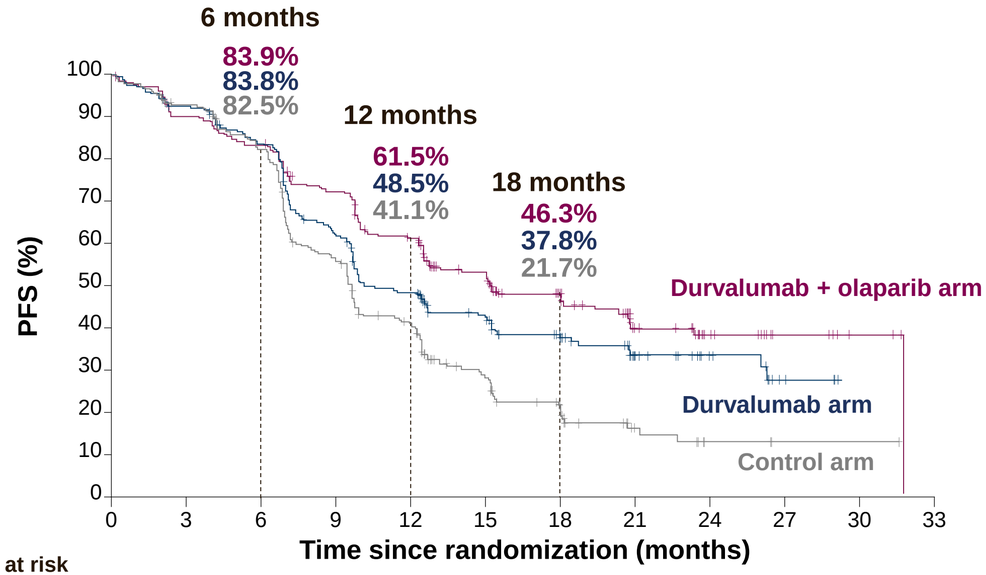
Primary (ITT): PFS (RECIST per investigator) in CP+D versus CP and CP+D+O versus CP

Secondary (ITT): OS (key secondary) and safety

Prespecified exploratory analyses: Subpopulation analyses of PFS by MMR status

Post hoc exploratory analyses: PFS by molecular subgroup in the pMMR subpopulation

ITT population: PFS – primary endpoints[1]



No. at risk												
Durvalumab + olaparib arm	239	214	198	169	139	95	51	30	16	7	3	0
Durvalumab arm	238	211	188	138	105	69	45	26	13	5	0	0
Control arm	241	213	184	125	86	45	26	10	3	1	1	0

	Control arm (N=241)	Durvalumab arm (N=238)	Durvalumab + olaparib arm (N=239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS (95% CI), months	**9.6** (9.0–9.9)	**10.2** (9.7–14.7)	**15.1** (12.6–20.7)
HR (95% CI) versus CP		**0.71** (0.57–0.89); ***P*=0.003**	**0.55** (0.43–0.69); ***P*<0.0001**

MMR status was evaluated using the Ventana MMR RxDx panel. *Maintenance therapy started 3–9 weeks after the last chemotherapy infusion; †Six cycles of carboplatin at an AUC of 5 or 6 mg/mL/min q3w and paclitaxel 175 mg/m^2 q3w; ‡Durvalumab 1120 mg IV q3w; §Durvalumab 1500 mg IV q4w; ‖Olaparib 300 mg tablets bid.

Westin SN, et al. *J Clin Oncol* 2024;42:283–99. doi/full/10.1200/JCO.23.02132.

GOG FOUNDATION®

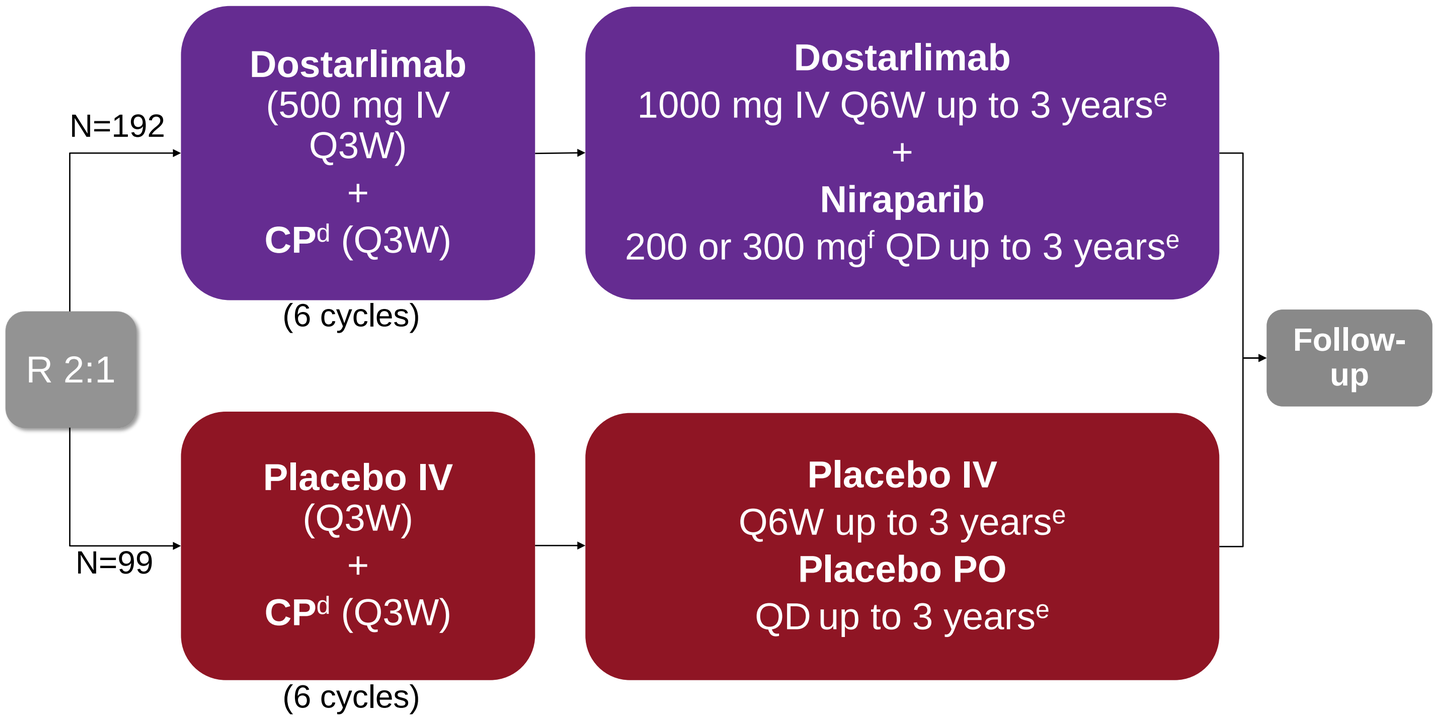
ENGOT-EN6-NSGO/GOG-3031/RUBY Part 2

Eligible patients

- Stage III/IV disease or first recurrent EC[a]
  - All histologies except sarcomas[b]
- Naive to systemic anticancer therapy or had a recurrence or PD ≥6 months after completing systemic anticancer therapy
- Naive to PARP inhibitor therapy

Stratification

- MMR/MSI status[c]
  - 25% dMMR/MSI-H
  - 75% MMRp/MSS
- Prior external pelvic radiotherapy
- Disease status



Primary endpoint

- PFS by INV per RECIST v1.1
  - Overall
  - MMRp/MSS

Secondary endpoints

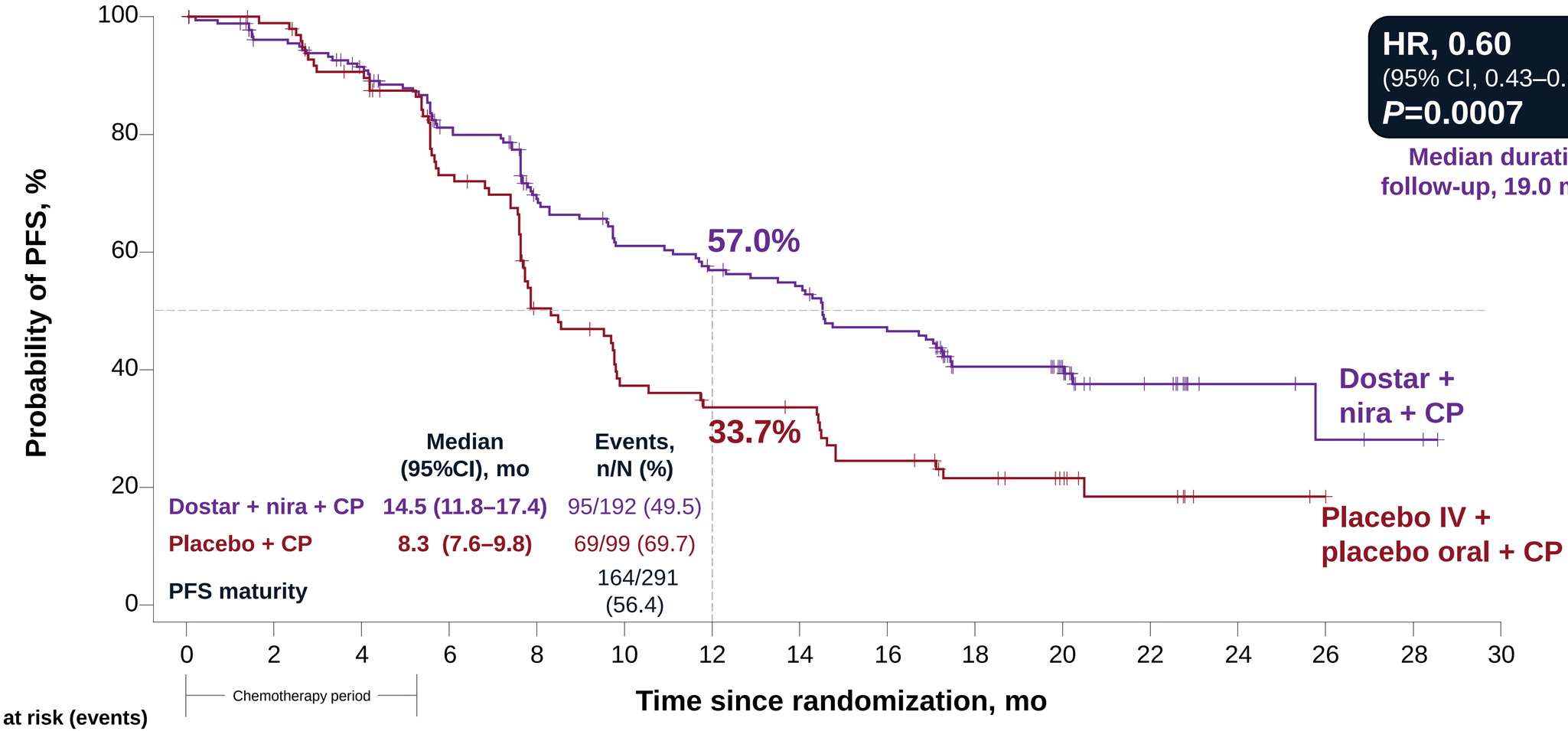
- OS
- PFS by BICR
- ORR
- DOR
- DCR (BOR of CR, PR, or SD)
- PFS2
- HRQOL/PRO
- PK
- Safety

On-study imaging assessments were performed Q6W (±7 days) from the randomization date until week 25 (cycle 8), followed by Q9W (±7 days) until week 52. Subsequent tumor imaging was performed every 12 weeks (±7 days) until radiographic PD was documented by investigator assessment per RECIST v1.1 followed by 1 additional imaging 4–6 weeks later, or subsequent anticancer therapy was started, whichever occurred first. Thereafter, scans were performed per standard of care.
[a]Histologically/cytologically proven advanced or recurrent EC; stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination. [b]Carcinosarcoma, clear cell, serous, or mixed histology permitted (mixed histology containing ≥10% carcinosarcoma, clear cell, or serous histology). [c]Patients were randomized based on either local or central MMR/MSI testing results. Central testing was used with local results were not available. For local determination of MMR/MSI status, IHC, next-generation sequencing, and polymerase chain reaction assays were accepted. For central determination of MMR/MSI status IHC per Ventana MMR RxDx panel was used. [d]Carboplatin AUC 5 mg/mL/min and paclitaxel 175 mg/m^2. [e]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the sponsor and the investigator. [f]Dose of 300 mg in patients with body weight ≥77 kg and platelet count ≥150,000/µL and 200 mg in patients with body weight <77 kg or platelet count <150,000/µL or both. AUC, area under the plasma or serum concentration-time curve; BICR, blinded independent central review; BOR, best overall response; CP, carboplatin-paclitaxel; CR, complete response; DCR, disease control rate; dMMR, MMR deficient; DOR, duration of response; EC, endometrial cancer; HRQOL, health-related quality of life; IHC, immunohistochemistry; INV, investigator assessment; MMR, mismatch repair; MMRp, MMR proficient; MSI, microsatellite instability; MSI-H, MSI high; MSS, microsatellite stable; ORR, objective response rate; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetic; PO, by mouth; PR, partial response; PRO, patient-reported outcome; Q3W, every 3 weeks; Q6W, every 6 weeks; Q9W, every 9 weeks; QD, once daily; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

1. Mirza M, et al. Presented at SGO 2024, San Diego, USA; 2. Westin SH, et al. Presented at ESMO 2023, Madrid, Spain

Statistically Significant PFS Benefit in Overall Population

Primary Endpoint



No. at risk (events)															
Dostarlimab + niraparib +CP	192(0)	169(7)	155(15)	131(32)	104(51)	91(63)	84(69)	79(73)	68(84)	43(92)	37(92)	16(94)	6(94)	3(95)	2(95)	0(95)
Placebo IV + placebo oral + CP	99(0)	96(1)	86(9)	66(25)	43(45)	31(56)	27(59)	26(59)	19(66)	14(68)	10(68)	6(69)	2(69)	1(69)	0(69)	

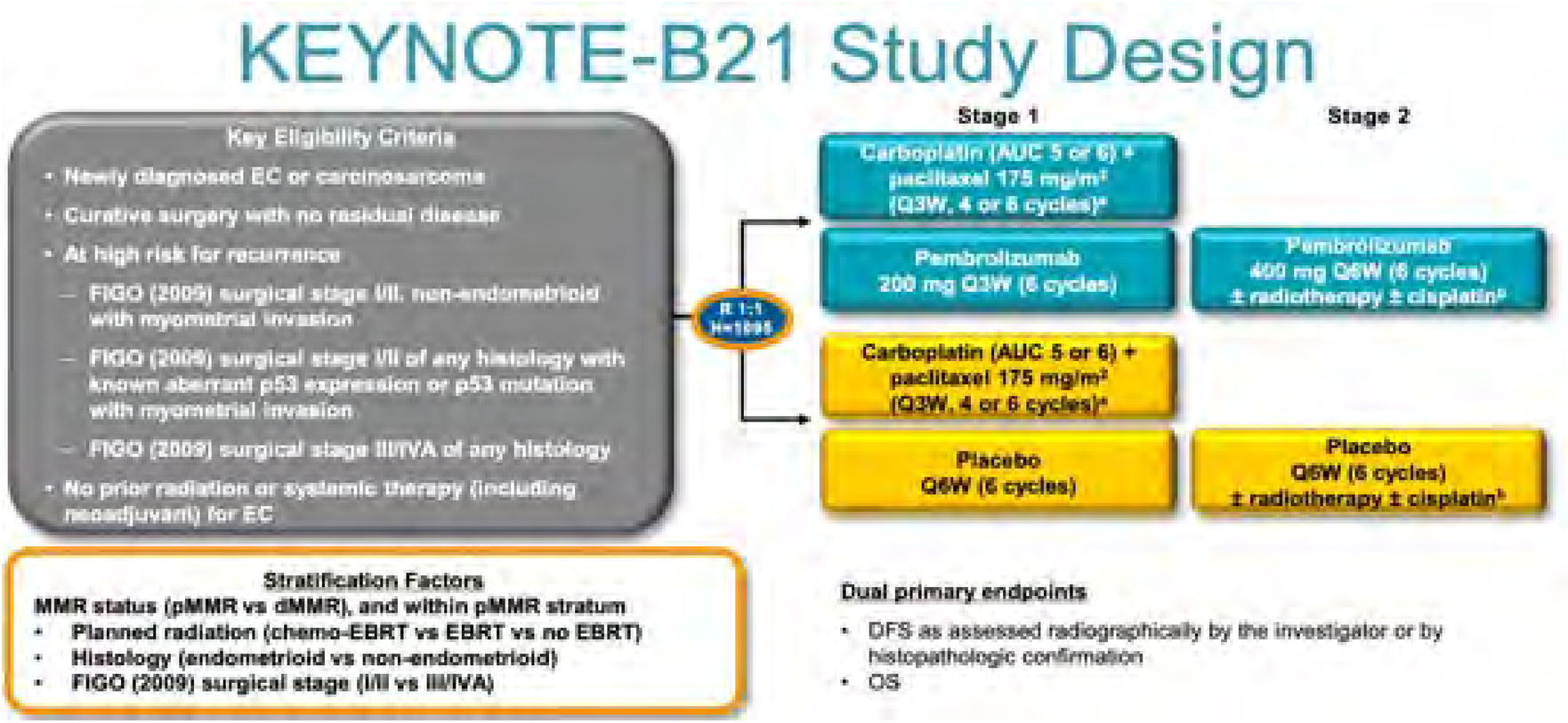
[a]Median expected duration of follow-up.
CP, carboplatin-paclitaxel; dostar, dostarlimab; HR, hazard ratio; nira, niraparib; PFS, progression-free survival.

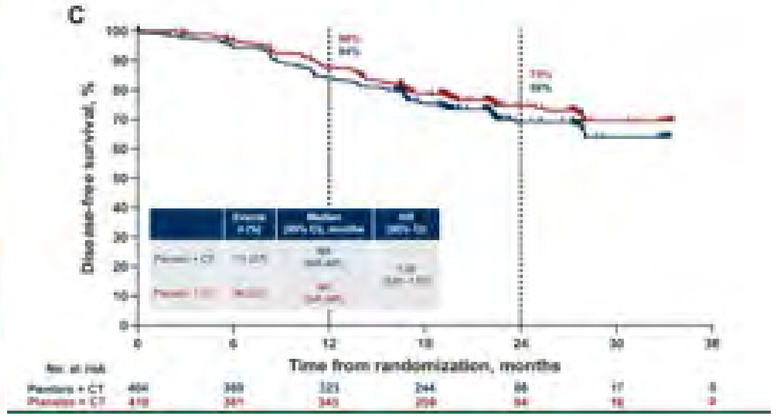
1. Mirza M, et al. Presented at SGO 2024, San Diego, USA; 2. Westin SH, et al. Presented at ESMO 2023, Madrid, Spain

Role of PARPi in Endometrial Cancer…

Audience??

B21-03 / ENGOT-en11/ GOG-3053: n=814 pMMR patients





Participants in this trial represent the vast majority of patients we see requiring systemic therapy.
?For pMMR we need measurable tumor to get an immune response.
More neoadjuvant approaches likely necessary.

Van Gorp T, et al. *Ann Oncol.* 2024;35(Suppl2):S1221.

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Stage II Non-Measurable

RUBY

- Primary advanced stage IIIC1 disease with carcinosarcoma, clear-cell, serous, or mixed histologic characteristics, regardless of the presence of disease that could be evaluated or measured
- Primary advanced stage IIIC2 or stage IV disease, regardless of the presence of disease that could be evaluated or measured
- Primary stage III: 92/494
  - pMMR: 68
  - dMMR: 24
- No measurable disease: 63/494
  - pMMR: 52
  - dMMR: 11

Keynote-b21

- Primary stage I/II, non-endometrioid with myometrial invasion
- Primary stage I/II of any histology with known aberrant p53 expression or p53 mutation with myometrial invasion
- Primary surgical stage III/IVA of any histology
- Primary stage III: ITT/overall: 714/1095
  - pMMR: 504
  - dMMR: 210
- Total population non-measurable: 1095
  - pMMR: 814
  - dMMR: 281

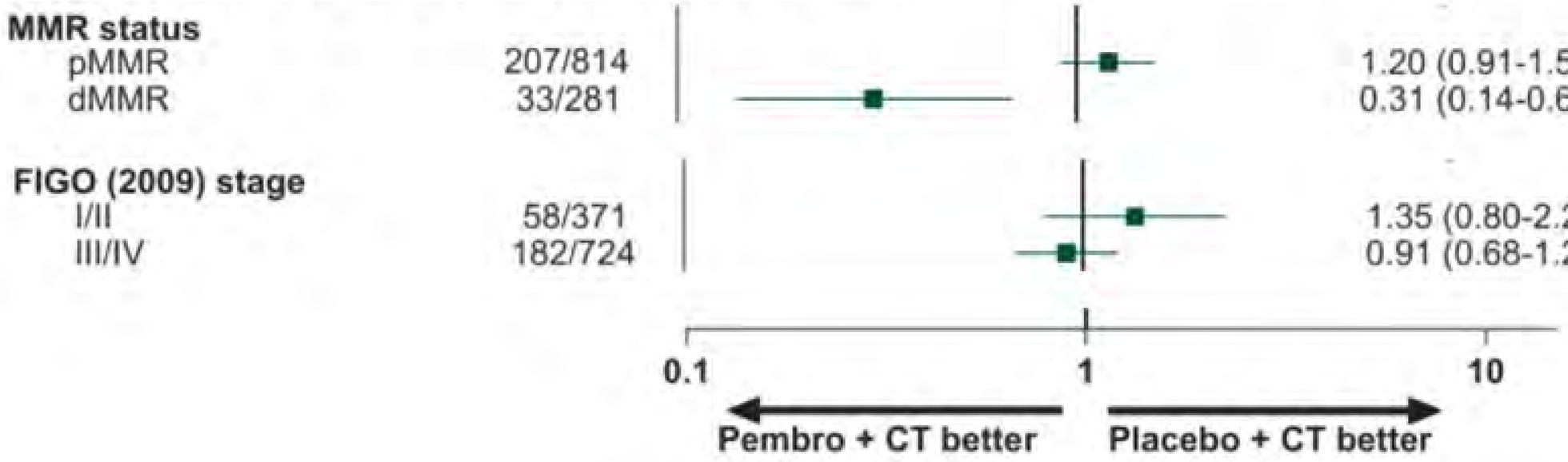
Mirza MR, et al. *N Engl J Med.* 2023;388(23):2145-2158.; Van Gorp T, et al. *Ann Oncol.* 2024;35(Suppl2):S1221.

Stage III Non-Measurable

RUBY: Overall population

Disease status			
Recurrent	68/117	89/119	0.56 (0.408–0.775)
Primary stage III	21/45	21/47	1.03 (0.563–1.891)
Primary stage IV	46/83	67/83	0.57 (0.392–0.836)
No disease at baseline	12/33	12/30	1.16 (0.520–2.590)

Keynote-b21: Overall/ITT population



Mirza MR, et al. *N Engl J Med.* 2023;388(23):2145-2158.; Van Gorp T, et al. *Ann Oncol.* 2024;35(Suppl2):S1221.; Van Gorp T, et al. *Ann Oncol.* 2024;35(11):968-980.

IO Therapy for Non-Measurable Endometrial Cancer…

Audience??

Paradigm-Shifting Data in EC Management

Name	EN6-RUBY Part 1[1]	EN7 AtTEnd[2]	NRG-GY018[3]	B21[4]	EN6-RUBY Part 2[5]	DUO-E[6]	EN9 LEAP-001[6]	EN15/C93[7]	EN13[8] DOMENICA
Lead Group Study Chair(s)	NSGO-CTU Mirza/Powell	MaNGO Colombo	NRG Eskander/ Powell	BGOG Van Gorp	NSGO-CTU Mirza/Powell	GOG-P Westin	AGO-A Marth	GOG-P Slomovitz	GINECO Joly
Investigational Agent	Dostar + Chemo	Atezo + Chemo	Pembro + Chemo	Pembro + Chemo	Dosta + Nira + Chemo	Durva + Ola + Chemo	Pembro + Lenva	Pembro	Dosta
N	494	551	816	990	291	718	842	350	260
Concomitant	+	+	+	+	+	+	Pembro + Lenva vs. Chemo	Pembro vs. Chemo	Dosta vs. Chemo
Maintenance	+	+	+	+	+	+			
Readout	NEJM 2023	ESMO 2023	NEJM 2023	Negative *AnnOnc*	SGO 2024	JCO 2023	“Negative”E SGO 2024	?	?
☺*	Statistically significant PFS dMMR & ITT, OS ITT	Statistically significant PFS dMMR and ITT	Statistically significant PFS dMMR and MMRp	?	Statistically significant PFS, ITT, and PFS MMRp	Statistically significant PFS ITT for Durva and Durva + Ola		?	?
☹*	Not powered for MMRp	OS immature	Not powered for OS	?	Chemo + ICI arm is missing. OS immature	Not powered for ICI+chemo +/- PARPi. Not powered for MMRp or dMMR	Negative for PFS & OS for MMRp & ITT	Chemo + ICI arm is missing	Chemo + ICI arm is missing

1. Mirza MR, et al. *NEJM.* 2023;388(23):2145-2158; 2. Colombo N, et al. *Ann Oncol.* 2023;34(Suppl 2):S1254-S1335 [ESMO abstract LBA40]; 3. Eskander RN, et al. *NEJM.* 2023;388(23):2159-2170;
4. ClinicalTrials.gov. NCT04634877. Available at: https://clinicaltrials.gov/study/NCT04634877; 5. Mirza MR, et al. Presented at: Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer; 16-18 March 2024; San Diego, CA, USA [oral presentation]; 6. Westin SN, et al. *J Clin Oncol.* 2024;42(3):283-299; 7. Marth C, et al. *Int J Gynecol Cancer.* 2024;34(Suppl 1):A570-A571 [ESGO abstract 88];
8. Slomovitz BM, et al. *J Clin Oncol.* 2022;40(Suppl 16):TPS5623; 9. Joly F, et al. *J Clin Oncol.* 2023;41(Suppl 16):TPS5630.

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How Should We Treat Endometrial Cancer

1L Therapy	2L Therapy
CPI +/- Chemo	• MSS/MSI - HER2+ (≥1+ HER2 ADCs) - ER+ (endocrine therapies) - CPI/IO combinations - ADCs other than HER2
Endocrine Therapy/ SINE Maint (CPI-Naïve)	• MSI - Dostarlimab - Pembrolizumab • MSS - Lenvatinib/pembrolizumab
Chemo + Trastuzumab/Pertuzumab	• Most are MSS - Lenvatinib/pembro would be SOC - HER2 ADCs

This will be uncommon

How would you sequence?

SINE = selective inhibitor of nuclear export; HER = human epidermal growth factor receptor; ADC = antibody-drug conjugate; ER = estrogen receptor

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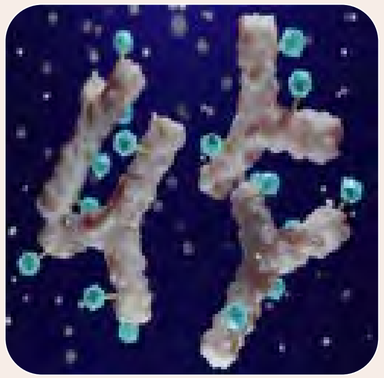
Additional Biomarkers Currently Being Evaluated in EC

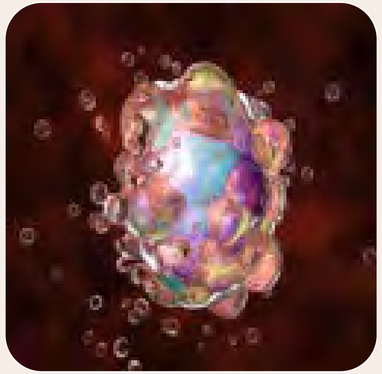
Targeting HER2



Trastuzumab deruxtecan[1]

Trastuzumab ± C/P[2]

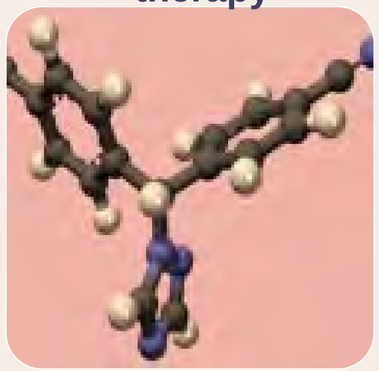
Kickstarting apoptosis



Selinexor[3,4]

Navtemadlin[5]

Revisiting endocrine therapy



Letrozole + abemaciclib[6]

Letrozole + palbociclib[7]

FR-α inhibition

Mirvetuximab soravtansine + gemcitabine[8]

Farletuzumab ecteribulin[9,10]

Inhibiting TROP-2

Sacituzumab govitecan[11]

MK-2870[12]

1. Meric-Bernstam F, et al. *J Clin Oncol.* 2023;41(suppl_17):LBA3000.; 2. Fader AN, et al. *Clin Cancer Res.* 2020;26:3928-3935.; 3. Makker V, et al. *J Clin Oncol.* 2022;40:5511-5511.; 4. Vergote IB, et al. *J Clin Oncol.* 2023;41(16_suppl):TPS5627-TPS5627.; 5. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT05797831. Accessed August 23, 2023. 6. Konstantinopoulos PA, et al. *J Clin Oncol.* 2022;41:599-608.; 7. Mirza MR, et al. *Ann Oncol.* 2020;31(s4):S1160.; 8. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT02996825. Accessed August 23, 2023.;
9. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03386942. Accessed August 23, 2023.; 10. Shimizu T, et al. *Clin Cancer Res.* 2021;27:3906-3915.;
11. Santin A, et al. *J Clin Oncol.* 2023;41(suppl_16):abst 5599.; 12. Gynecologic Cancer Intergroup. https://gcigtrials.org/content/mk-2870-005-engot-en23. Accessed September 28, 2023.

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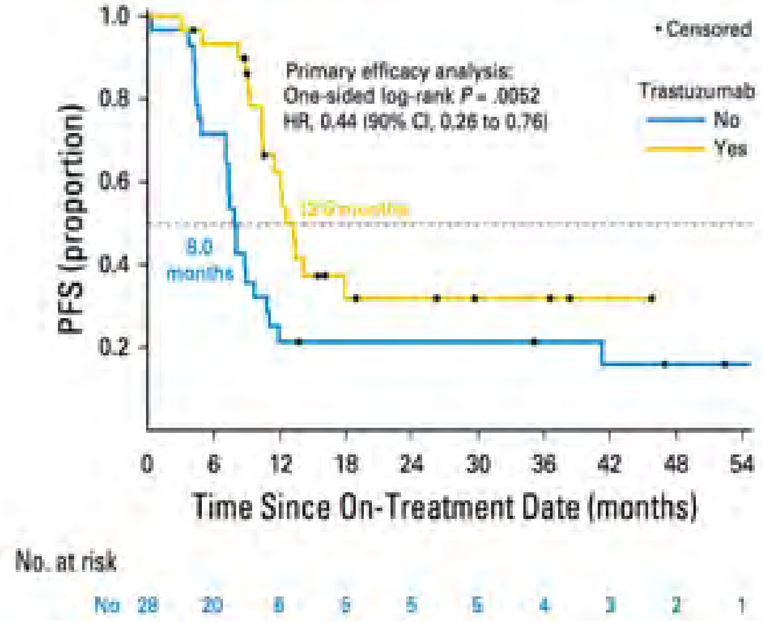
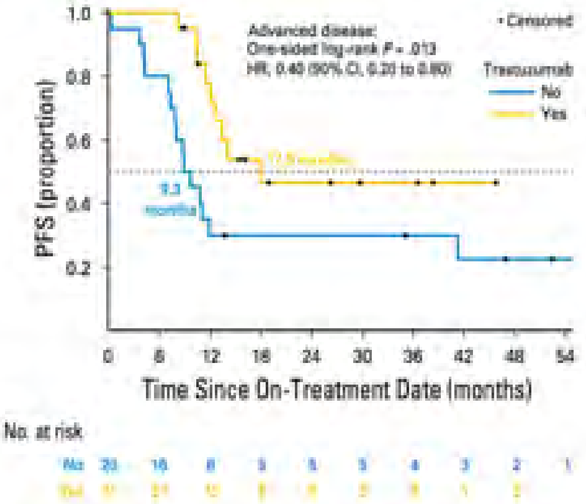
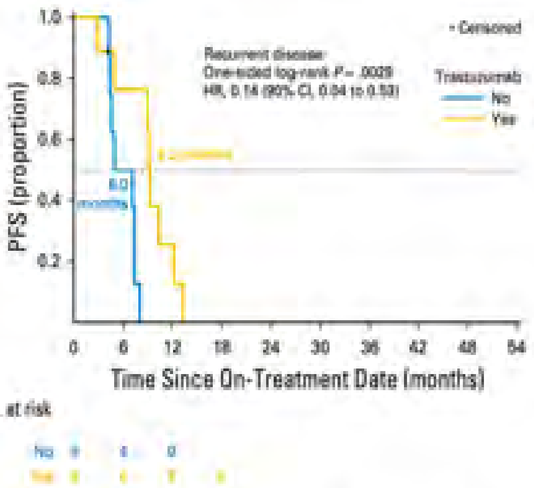
HER2 Directed Therapy

Key eligibility criteria

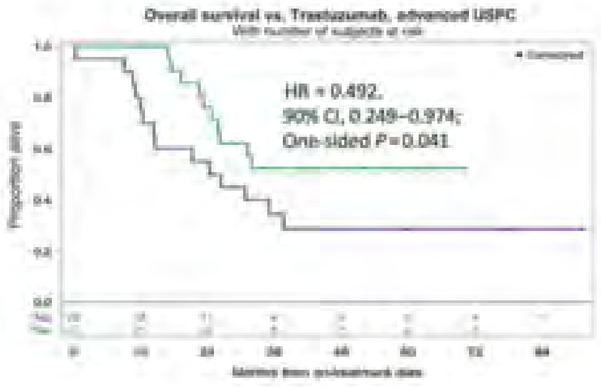
- Primary stage III or IV or recurrent HER2/neu-positive USC: IHC score 3+, or 2+ with + FISH
- ECOG 0-2
- ≤3 prior lines of therapy
- “platinum sensitive” recurrence (6 mo)

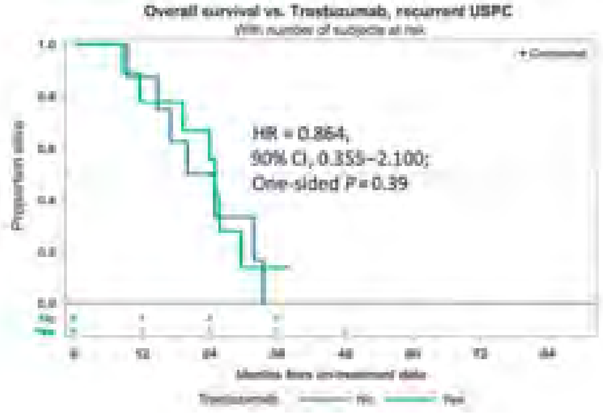






OS benefit particularly striking in stage III–IV patients, OS median of 25.4 months (control) versus NR (p = 0.041, HR = 0.49, 90% CI 0.25–0.97).





Fader AN, et al. *Clin Cancer Res.* 2020;26:3928-3935

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NRG GY-026

PI: Britt Erickson
Co-PI: Amanda Fader
Intl Co-PI: Clare Scott
TransIx PI: Alessandro Santin

Newly Diagnosed, Stage I-IVB, HER2 positive uterine serous or carcinosarcoma

Randomize 1:1:1

Arm 1:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles (may continue to 10 cycles if measurable disease and SD or PR)

Arm 2:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles + trastuzumab 8 mg/kg IV loading dose f/b 6 mg/kg IV q 21 days

Maintenance trastuzumab 6mg/kg IV every 21 days x 1 year (or progression/ prohibitive toxicity)

Safety Lead-In (n=45)

Arm 3:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles + fixed dose trastuzumab 600 mg/ pertuzumab 600 mg SQ (with initial 1200 mg SQ pertuzumab loading dose w 1st cycle)

Maintenance fixed dose trastuzumab 600 mg/ pertuzumab 600 mg SQ q 21 days for 1 year (or until disease progression or prohibitive toxicity)

Strata:
- **Stage (I-II vs III-IV)**
- **Measurable vs. non-measurable dz**
- **Histology (serous vs carcinosarcoma)**

NCT05256225

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Re-Visiting Hormonal Therapy: Pts Now Larger

	ORR	CBR	PFS (months)	OS (months)	DOR (months)	Reference
Progesterone single agent	25%	46%	7.6	8.9	8.9	Lentz, Thigpen
Progesterone/ tamoxifen	19-33%	69%	2.7-4	8.6-17	31	Pandya, Fiorica, Whitney, Slomovitz
SERM/SERD	10%	34%	1.9-2.3	8.8-18.9	1.9	Thigpen, Covens, Emons
Aromatase inhibitor	9-17%	17-44%	1-3.9	6-10.9	6.7	Rose, Heudel, Lindemann
Aromatase and mTOR inhibitor	22-32%	40-78%	3-6	14-31	30	Slomovitz, Heudel
Aromatase and CDK4/6 inhibitor	10-30%	64-73%	5.4-9.7	15.7-21.6	7.4	Colon-Otero, Konstantinopoulos, Mirza

Adjuvant Therapy for EC

RAINBO: Phase II/III Trials Investigating Adjuvant Therapy in Endometrial Cancer Based on Molecular Features

Patient Population (N≈1615)

- Hysterectomy and bilateral salpingo-oophorectomy ± lymphadenectomy or sentinel node biopsy, without residual disease after surgery
- Endometrioid, serous, clear cell, un/dedifferentiated, mixed, and carcinosarcoma cell types
- Full molecular classification performed according to the WHO 2020 diagnostic algorithm
- Expected start of adjuvant treatment (if applicable) within 10 weeks after surgery
- No distant metastases as determined by presurgical or postsurgical imaging (CT scan of chest, abdomen, and pelvis or whole-body PET-CT scan)

p53abn stage IA (MI+) to III (n~554)	p53abn RED	1:1	Adjuvant CRT Adjuvant CRT followed by olaparib[a]
dMMR stage IB/II (LVSI+)/III (n~316)	dMMR GREEN	1:1	Adjuvant EBRT Adjuvant EBRT+ durvalumab[b]
NSMP ER+ stage II (LVSI+)/III (n~600)	NSMP ORANGE	1:1	Adjuvant CRT Adjuvant EBRT followed by progestogens
*POLE*mut stage I-III (n~120)	*POLE*mut BLUE		No adjuvant Adjuvant EBRT or vaginal brachytherapy[c]

Primary Endpoints

- 3-year RFS (p53abn-RED, dMMR-GREEN, and NSMP-ORANGE trials)
- 3-year pelvic RFS (*POLE*mut-BLUE trial)

Secondary Endpoints

- 5-year RFS (overall, pelvic)
- 3- and 5-year vaginal RFS
- 3- and 5-year survival (overall and EC-specific)
- Safety and HRQoL

[a]Olaparib and progestogens ≤ 2 years after adjuvant RT. [b]Durvalumab for 1 year total (during and after adjuvant RT). [c]The *POLE*mut-BLUE trial will recruit 120 patients with select stage I–II *POLE*mut endometrial cancer in the main "lower risk" study cohort.

WHO = World Health Organization; CT = computed tomography; PET-CT = positron emission tomography-CT; LVSI = lymphovascular space invasion; MI = microsatellite instability; HRQoL = health-related quality of life.

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated July 13, 2023. Accessed April 10, 2024.
https://clinicaltrials.gov/study/NCT05255653. RAINBO Research Consortium. *Int J Gynecol Cancer*. 2022;33(1):109-117.

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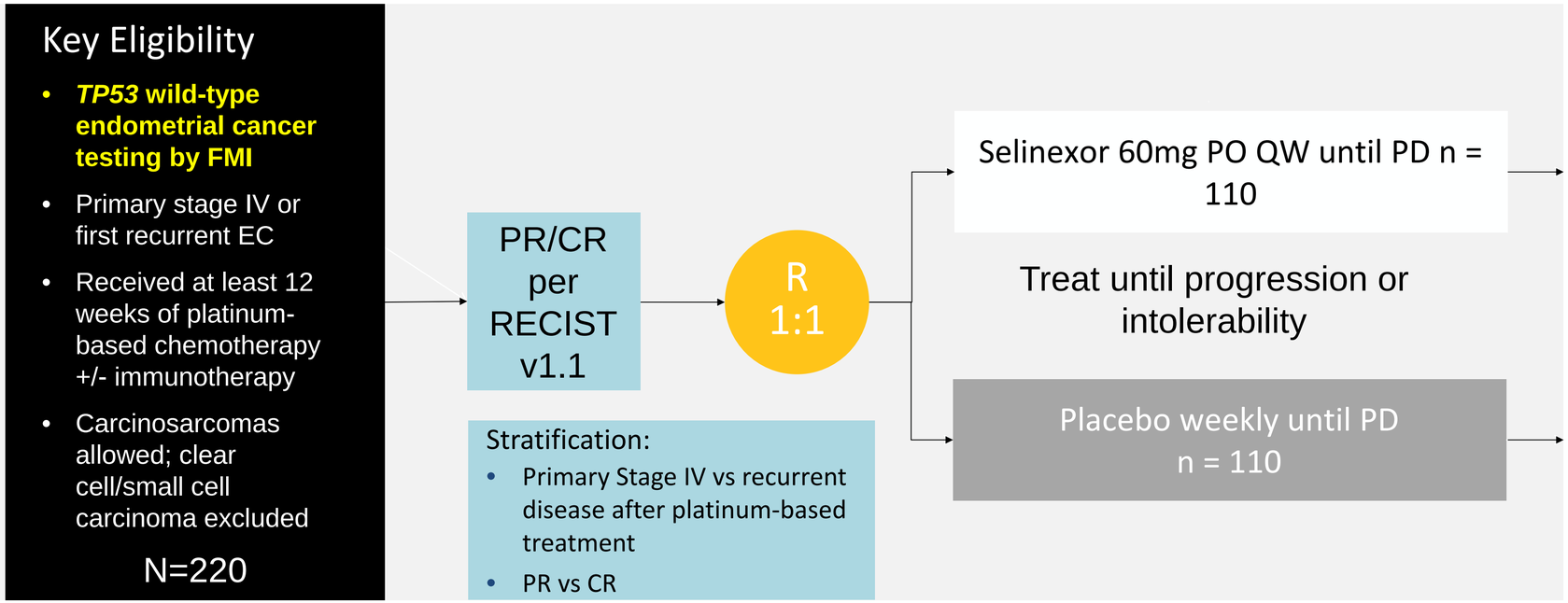
XPORT-EC-042 (NCT05611931): A Phase 3, Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial of Selinexor in Maintenance Therapy After Systemic Therapy for Patients with *TP53* Wild-type, Advanced, or Recurrent EC

Prescreening Consent Tissue sent to Foundation

Study Consent



Primary Endpoint

- PFS assessed by Investigator

Key Secondary Endpoint

- OS

Secondary Endpoints

- Safety
- TFST
- TSST
- PFS2
- PFS as assessed by BICR
- HR-QoL

Exploratory Endpoints

- PFS per histology subtypes
- PFS per other molecular features
- CR rate among patients with PR as best response
- Duration of CR among patients who enter study as PR and achieve CR during study
- analysis of tumor biomarkers
- PK analysis

*118 PFS events needed to provide 90% power to detect a HR of 0.55 with a 2-sided alpha of 0.05

EC, endometrial cancer; FMI, Foundation Medicine; BICR, blinded independent central review; CR, complete response; DCR, disease control rate; EC, endometrial cancer; HR-QoL, health-related quality of life; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PFS2, time from randomization until the second progression event; PD, progressive disease; PK, pharmacokinetics; PR, partial response; R, randomized; RECIST, Response Evaluation Criterial in Solid Tumors; TFST, time to first subsequent treatment; TSST, time to second subsequent treatment; QW, every week.

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Advancing Hormone Therapy

PI3K Inhibitors + SERD

GOG 3069: Phase 2 Study of Alpelisib and Fulvestrant for PIK3CA Mutated, Estrogen Receptor Positive Endometrioid Endometrial Cancer

Screening/Registration

↓

TREATMENT
Alpelisib 300mg orally daily
+
Fulvestrant 500mg IM Day 1 and Day 15 of Cycle 1, then Day 1 each 28-day cycle

↓

Disease evaluations every 8 weeks for the first 3 evaluations then every 12 weeks until PD

Primary Outcome: ORR
Secondary outcomes: safety/toxicity, PFS, OS, DoR

NCT05154487

AKT Inhibitor + Progestin

NRG GY028: RPh2 of MPA +/- Ipatasertib

NRG-GY028
A Phase IB and Randomized Phase II Trial of Medroxyprogesterone Acetate With or Without Ipatasertib in Recurrent or Metastatic Endometrioid Endometrial Cancer (PI: Michaela Onstad-Grinsfelder, Co-PI: Shannon Westin)

Open to accrual: 1/13/2023
Accrual: 0/18

Planned Accrual:
- **Phase Ib = 6-18**
- **Phase II = 78**

Primary endpoint:
- **Phase Ib: Safety**
- **Phase II: PFS**

NCT05538897

P13K=phosphoinositide 3-kinase; AKT=AKR (mouse) transforming; SERD=selective estrogen receptor degrader.

Gaillard S, et al. *J Clin Oncol.* 2024;42(16 suppl):5639.; NRG Oncology [www.nrgoncology.org], https://www.nrgoncology.org/Clinical-Trials/Protocol/nrg-gy028?filter=nrg-gy028.

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Strategies for EC Post-IO? IO Combinations

PD-1/CTLA4

NRG GY025
RPH2 of Nivolumab and Ipilimumab vs Nivolumab in MMRd Recurrent EC

Recurrent MMR deficient Endometrial Carcinoma with Measurable or Non-measurable (detectable) Disease

STRATIFICATION
- **Prior Radiation**
- **Prior anti-PD1/PD-L1 therapy**
- **Measurable disease (yes/no)**

RANDOMIZATION*
R 2:1

Arm 1
Nivolumab Q3W and
Low-Dose Ipilimumab Q6W (every other cycle x 4) and then nivolumab alone Q4W until disease progression, unacceptable toxicities or CR*
See Section 5.1
*patients with CR will receive maintenance therapy for up to 12 additional months after radiologic evidence of complete response.

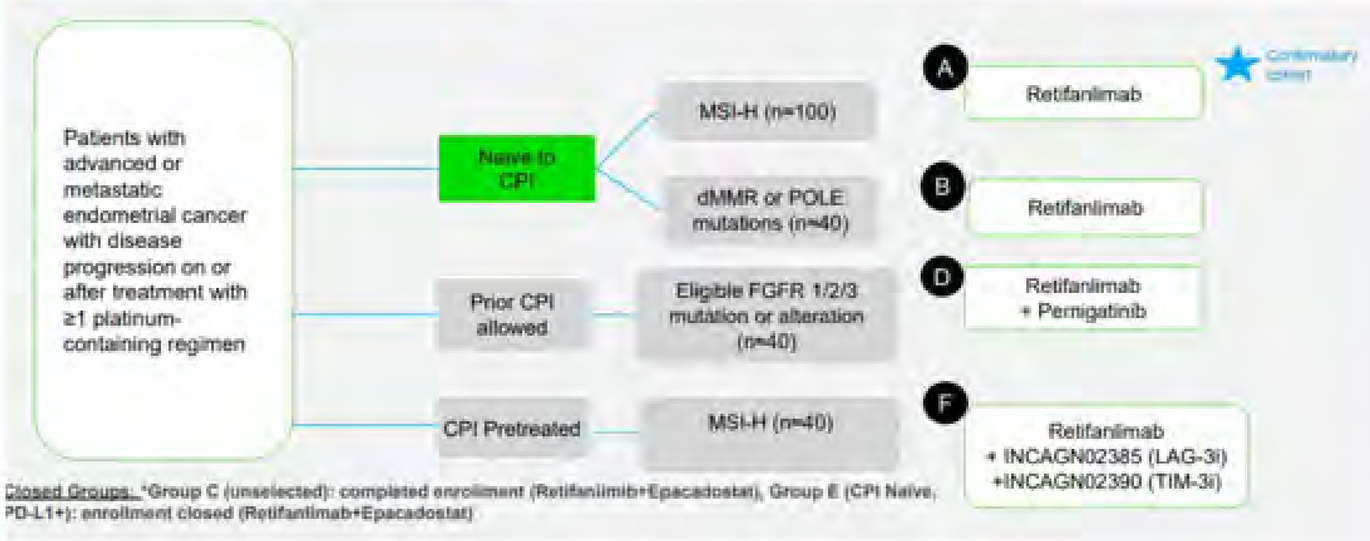
Arm 2
Nivolumab Q3W x 8 cycles then Q4W until disease progression, unacceptable toxicities or CR*
See Section 5.1
*patients with CR will receive maintenance therapy for up to 12 additional months after radiologic evidence of complete response.

*Randomization is 2:1 (Arm 1 vs Arm 2). Twice as many patients will be randomized to Arm 1.

NCT05112601

PD-1 + LAG3

PODIUM 204/GOG 3038
Novel CPI Combinations



Closed Groups: *Group C (unselected): completed enrollment (Retifanlimib+Epacadostat), Group E (CPI Naive, PD-L1+): enrollment closed (Retifantimab+Epacadostat)

NCT04463771

FGFR=fibroblast growth factor receptor.

NRG Oncology [www.nrgoncology.org], https://www.nrgoncology.org/Clinical-Trials/Protocol/nrg-gy025?filter=nrg-gy025.; Slomovitz BM, et al. Presented at: Society for Immunotherapy of Cancer (SITC) 35th Anniversary Annual Meeting; 9-14 November 2020; Virtual. [Poster 348].

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Key Takeaways

- Molecular profiling of this disease has completely transformed our therapeutic approach
- Which stage IIIC patients are really just like stage 3 borderline tumor of the ovary?
- **ICI + C/P is the new standard of care for patients with advanced/recurrent EC**
- Sorting out: Asian patients, BMI, Asians from western countries, molecular subgroups

- **However,** this is just the beginning of an unprecedented improvement in the outcomes of our patients. We need to understand:
  - Which are the dMMR patients that do not benefit from ICI + chemotherapy?
  - Can we replace chemotherapy in dMMR patients in view of ICI-only treatment? And in which patients?
  - How to treat patients who experience relapse post-chemotherapy + immunotherapy?
  - How do we further validate the prognostic value of molecular subgroups for identifying those patients who will benefit the most?
  - What are the predictive biomarkers to understand which patients benefit most from PARPi addition to ICI in MMRp EC?

Audience Q & A

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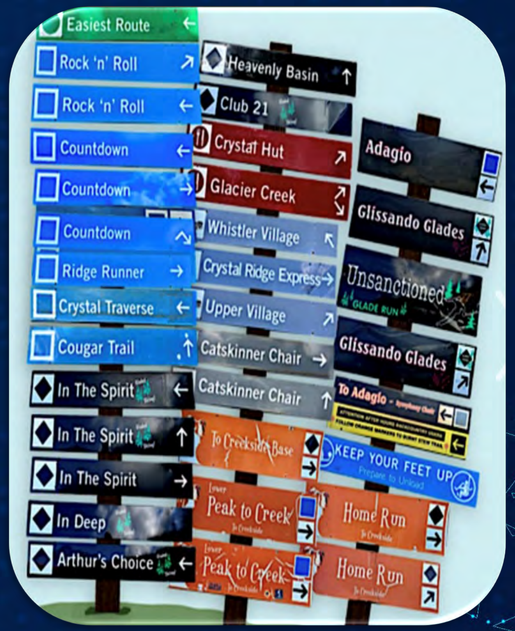
Mogul-Level Efficacy & Black Diamond Implications of PARPi: Emerging Data and Integration into Clinical Practice



Angeles Alvarez Secord, MD, MHSc

Duke University

Durham, North Carolina

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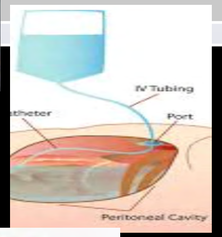
Epithelial Ovarian Cancer Landscape

2003

1990s – The Taxane Era

- Taxane platinum chemotherapy improves survival outcomes; becomes standard of care

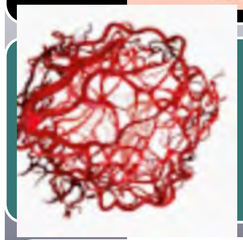
2006



2000s – IP Therapy

- Intraperitoneal therapy becomes standard of care; limited due to toxicity and administration challenges

2011



2011 – Antiangiogenic therapy

- Bevacizumab improved PFS versus chemotherapy alone; selective use

2018

2014-Beyond – The Era of PARP inhibitors and personalized therapy

- 2014 approved for patients with BRCA mutations
- 2018 front-line therapy for patients
- ADC and targeted directed therapies

Olaparib	**SOLO-1 NCT01844986**	**Niraparib**	**PRIMA NCT02655016**	**Olaparib + Bevacizumab**	**PAOLA-1 NCT02477644**	**Rucaparib**	**ATHENA-mono NCT03522246**

McGuire WP, et al. *N Engl J Med.*1996;334(1):1-6.; Armstrong DK, et al. *N Engl J Med.* 2006;354(1):34-43.; du Bois A, et al. *J Natl Cancer Inst.* 2003;95(17):1320-1329.; Burger RA, et al. *N Engl J Med.* 2011;365(26):2473-2483.; Perren TJ, et al. *N Engl J Med.* 2011;365(26):2484-2496.; Moore K, et al. *N Engl J Med.* 2018;379(26):2495-2505.; González-Martin A, et al. *N Engl J Med.* 2019;381(25):2391-2402. doi:10.1056/NEJMoa1910962.; Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428. doi:10.1056/NEJMoa1911361.; Monk BJ, et al. *J Clin Oncol.* 2022;40(28):3197-3208. doi:10.1200/JCO.22.01003.

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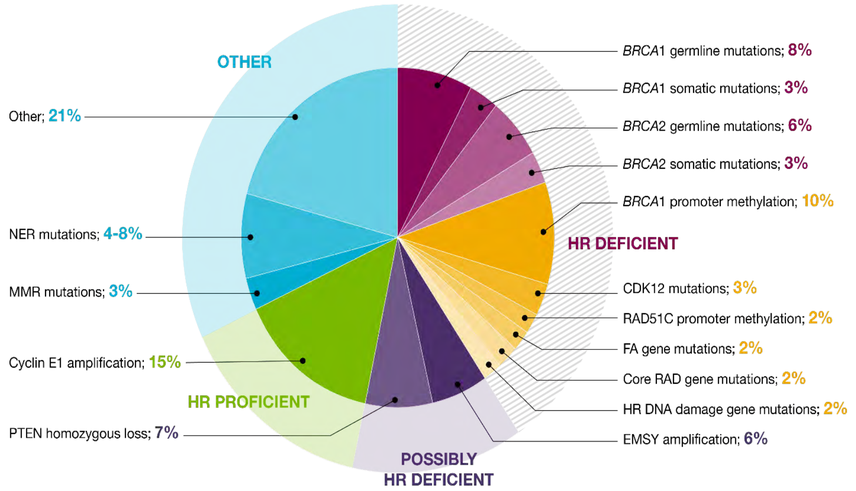
Ovarian Cancer Case: *BRCAm/HRD+*

63-y.o. woman with newly diagnosed high-grade serous ovarian cancer s/p neoadjuvant chemotherapy, robotic interval debulking with BSO, omentectomy, argon beam diaphragm, and liver resection, 6 cycles of chemotherapy with bevacizumab. CA125 normal. CT scan negative.

What do you need to know first?

Management options:

- ❑ **Observation**
- ❑ **Bevacizumab maintenance**
- ❑ **Bevacizumab and olaparib maintenance**
- ❑ **PARP inhibitor maintenance**



Approximately 50% high grade epithelial ovarian cancers have homologous recombination deficiency and mutation in DNA repair gene pathway

Konstantinopoulos PA, et al. *Cancer Discov*. 2015;5(11):1137-1154. doi:10.1158/2159-8290.CD-15-0714.

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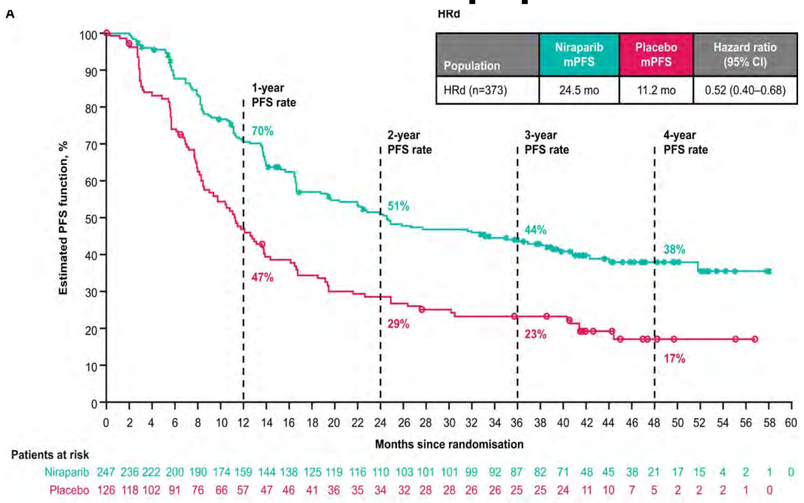
PRIMA

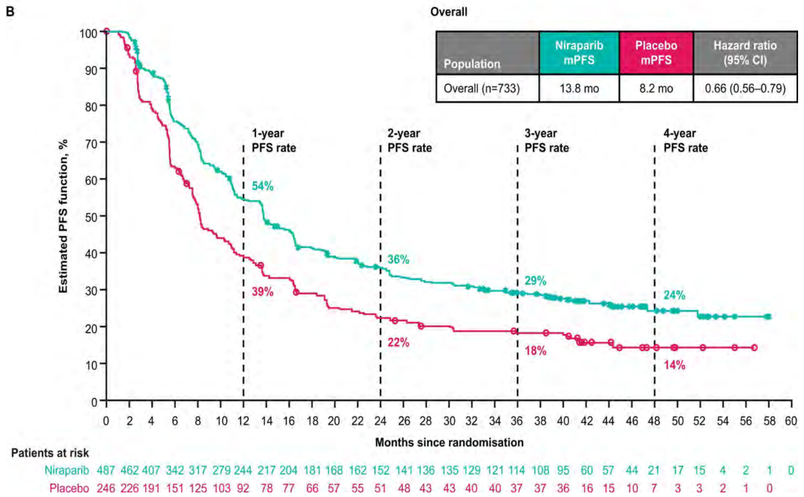
The NEW ENGLAND JOURNAL of MEDICINE

Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

PFS in the HRD+ population



PFS in the Overall population

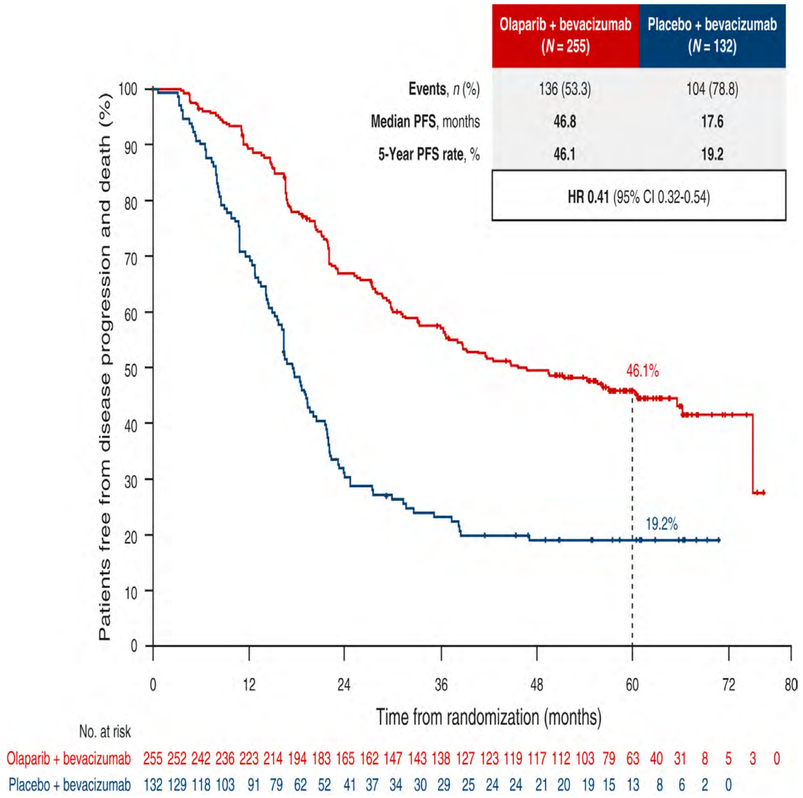


PAOLA-1

The NEW ENGLAND JOURNAL of MEDICINE

Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer

PFS in the HRD+ population

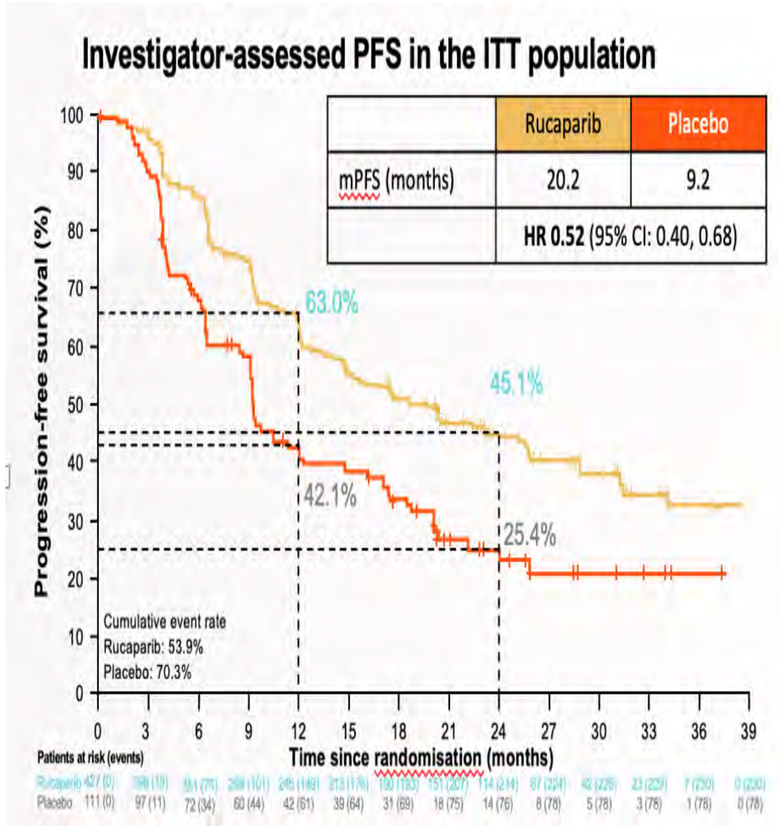


ATHENA

Journal of Clinical Oncology

A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45)

Investigator-assessed PFS in the ITT population



González-Martin A, et al. *N Engl J Med.* 2019;381(25):2391-2402. doi:10.1056/NEJMoa1910962; González-Martin A, et al. *Eur J Cancer.* 2023;181:24-36. doi:10.1016/j.ejca.2023.04.024.; Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428. doi:10.1056/NEJMoa1911361.; Monk BJ, et al. *J Clin Oncol.* 2022;40(28):3197-3208. doi:10.1200/JCO.22.01003.

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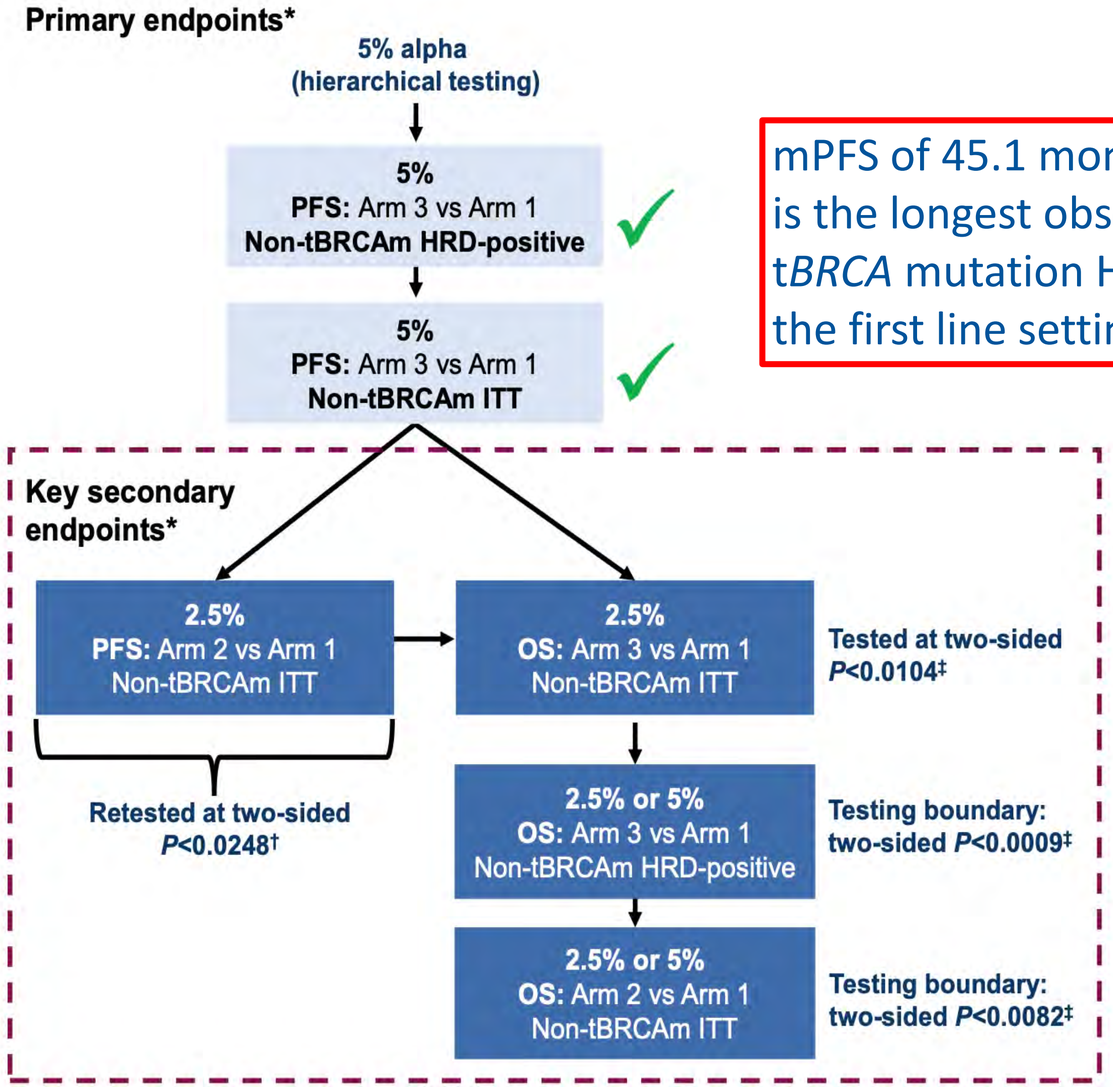
GOG-3025 DUO-O: Chemotherapy and Bevacizumab +/- Durvalumab +/- Olaparib

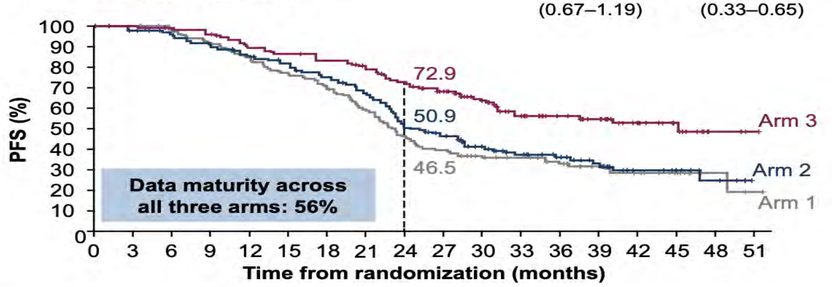


mPFS of 45.1 months in B+D+O arm is the longest observed for non-t*BRCA* mutation HRD+ patients in the first line setting

Final PFS

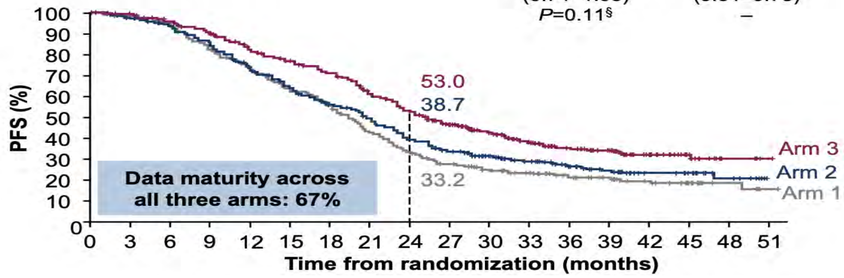
Non-tBRCAm HRD-positive

	Arm 1 PC + B N=143	Arm 2 PC + B + D N=148	Arm 3 PC + B + D + O N=140
Median follow-up,* months	38.4	33.1	34.6
Events, n (%)	94 (66)	89 (60)	57 (41)
mPFS,† months	23.3	25.1	45.1
HR (95% CI) vs Arm 1‡		0.89 (0.67–1.19)	0.46 (0.33–0.65)



Non-tBRCAm ITT

	Arm 1 PC + B N=378	Arm 2 PC + B + D N=374	Arm 3 PC + B + D + O N=378
Median follow-up,* months	34.5	33.1	32.0
Events, n (%)	283 (75)	257 (69)	221 (58)
mPFS,† months	19.3	20.6	25.1
HR (95% CI) vs Arm 1‡		0.87 (0.74–1.03) P=0.11§	0.61 (0.51–0.73) –



Harter P, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; 2-6 June 2023; Chicago, IL USA.;
Harter P, et al. Presented at: Society of Gynecologic Oncology's (SGO) Annual Meeting on Women's Cancer; 18-21 March 2022; Phoenix, AZ USA.

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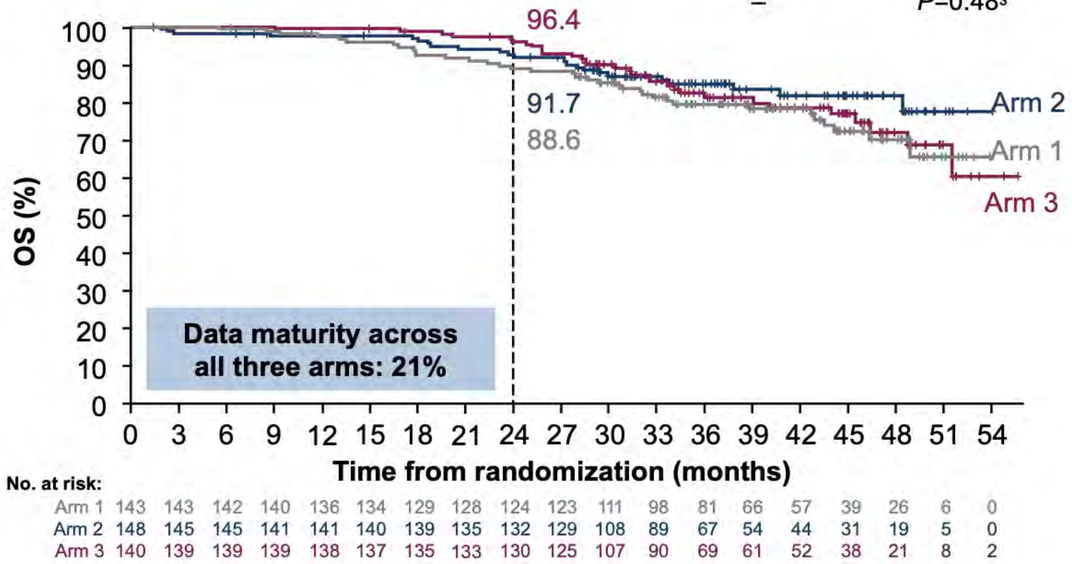
GOG-3025 DUO-O: Chemotherapy and Bevacizumab +/- Durvalumab +/- Olaparib *cont.*

Interim OS

Non-tBRCAm HRD-positive

	Arm 1 PC + B N=143	Arm 2 PC + B + D N=148	Arm 3 PC + B + D + O N=140
Median follow-up,* months	40.7	36.5	38.0
Events, n (%)	35 (24)	24 (16)	30 (21)
mOS,† months	NR	NR	NR
HR (95% CI) vs Arm 1‡		**0.69** (0.41–1.15) –	**0.84** (0.51–1.37) *P*=0.48§

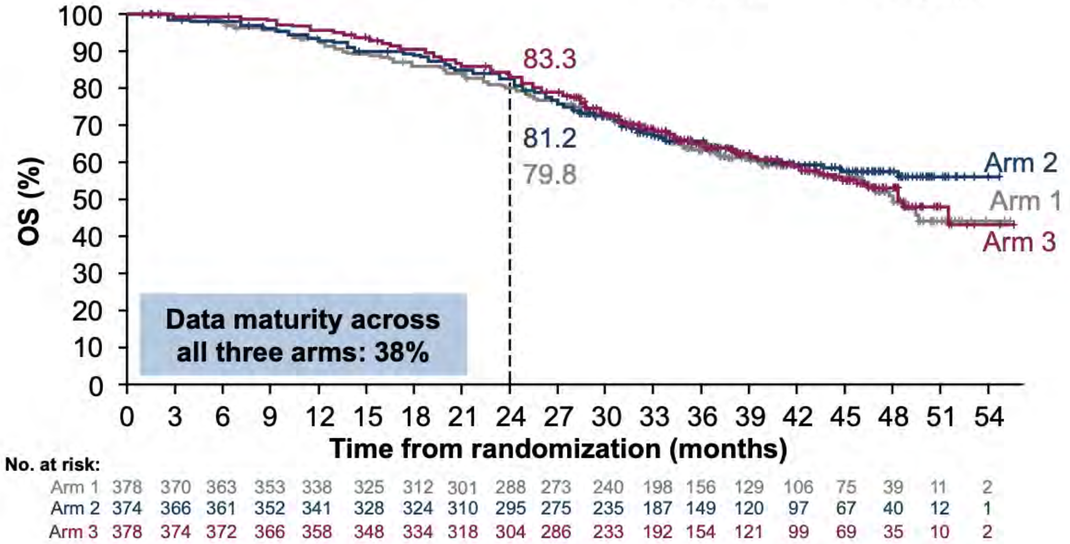


No. at risk:

Arm 1	143	143	142	140	136	134	129	128	124	123	111	98	81	66	57	39	26	6	0
Arm 2	148	145	145	141	141	140	139	135	132	129	108	89	67	54	44	31	19	5	0
Arm 3	140	139	139	139	138	137	135	133	130	125	107	90	69	61	52	38	21	8	2

Non-tBRCAm ITT

	Arm 1 PC + B N=378	Arm 2 PC + B + D N=374	Arm 3 PC + B + D + O N=378
Median follow-up,* months	38.7	37.8	37.6
Events, n (%)	150 (40)	137 (37)	145 (38)
mOS,† months	48.0	NR	48.5
HR (95% CI) vs Arm 1‡		**0.92** (0.73–1.16) *P*=0.48§	**0.95** (0.76–1.20) *P*=0.68§



No. at risk:

Arm 1	378	370	363	353	338	325	312	301	288	273	240	198	156	129	106	75	39	11	2
Arm 2	374	366	361	352	341	328	324	310	295	275	235	187	149	120	97	67	40	12	1
Arm 3	378	374	372	366	358	348	334	318	304	286	233	192	154	121	99	69	35	10	2

Harter P, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; 2-6 June 2023; Chicago, IL USA.;
Harter P, et al. Presented at: Society of Gynecologic Oncology's (SGO) Annual Meeting on Women's Cancer; 18-21 March 2022; Phoenix, AZ USA.

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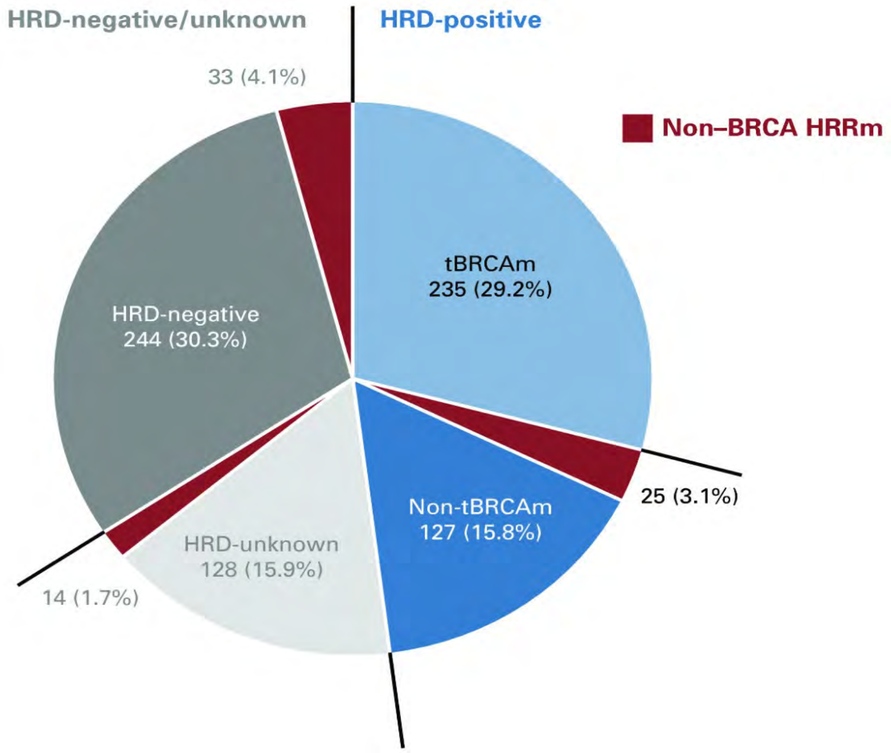
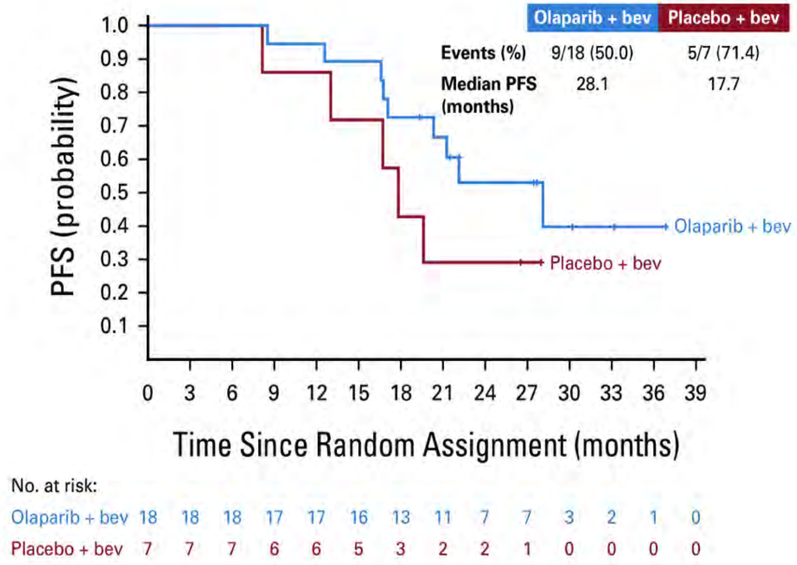
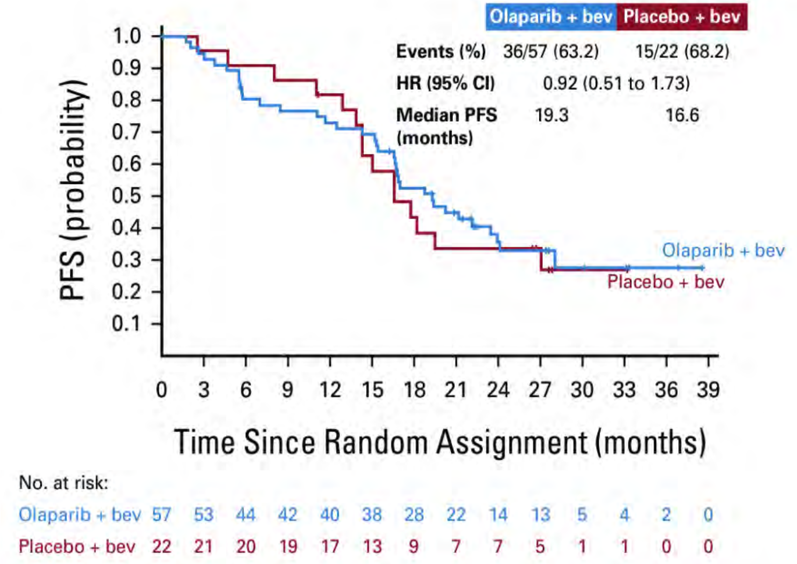
HRRm Gene Panel and HRD Genomic Instability Tests Are Not Interchangeable



HRD



HRR



Pujade-Lauraine E, et al. *JCO Precis Oncol*. 2023;7:e2200258. doi:10.1200/PO.22.00258.

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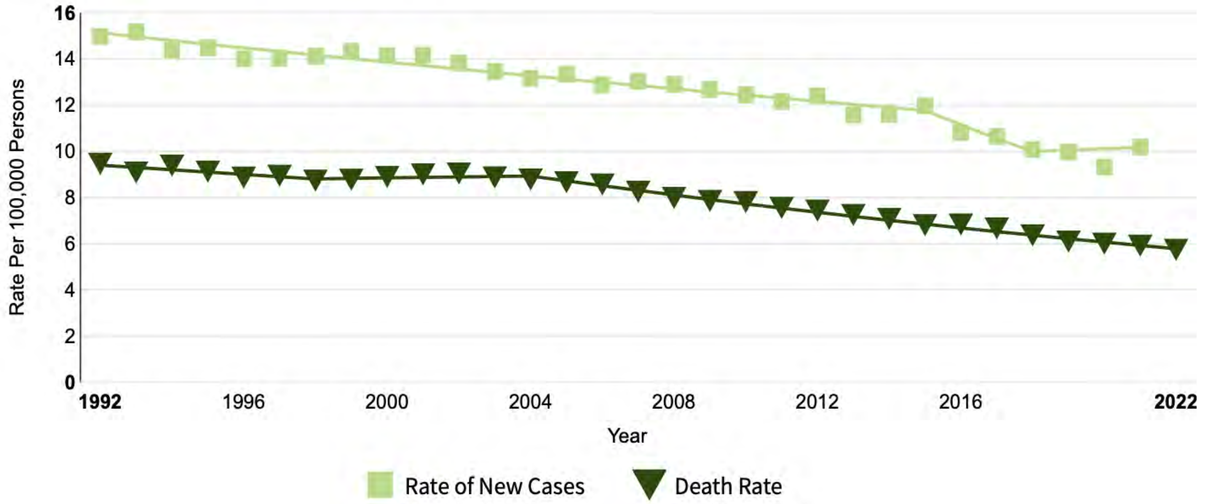
Ovarian Cancer Survival Improving

Estimated New Cases in 2024	19,680
% of All New Cancer Cases	1.0%

Estimated Deaths in 2024	12,740
% of All Cancer Deaths	2.1%

5-Year Relative Survival
50.9%
2014–2020



National Cancer Institute (NCI). SEER Data & Software. Accessed from: Seer.cancer.gov. Access date: 06-01-2024.

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Ovarian Cancer Case: *BRCAm/HRD+*

64-y.o. woman with BRCAm/HRD+ high-grade serous ovarian cancer s/p neoadjuvant chemotherapy, debulking, PARPi maintenance for 5.5 months with rising CA125 and CT scan with pulmonary effusion, carcinomatosis, and hepatic metastatic disease.

Treatment options:

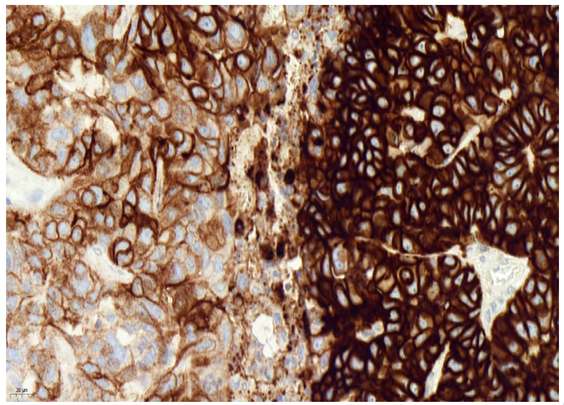
- ❑ **Mirvetuximab**
- ❑ **Paclitaxel with bevacizumab**
- ❑ **Trastuzumab deruxtecan**
- ❑ **Clinical trial**

What do you need to know first?

FRα Scoring

Determined by staining intensity and percentage of tumor cells staining at 0, 1+, 2+, or 3+

PS2+ Scoring Positive: ≥ 50% tumor cells with ≥ 2+ FRα membrane staining.



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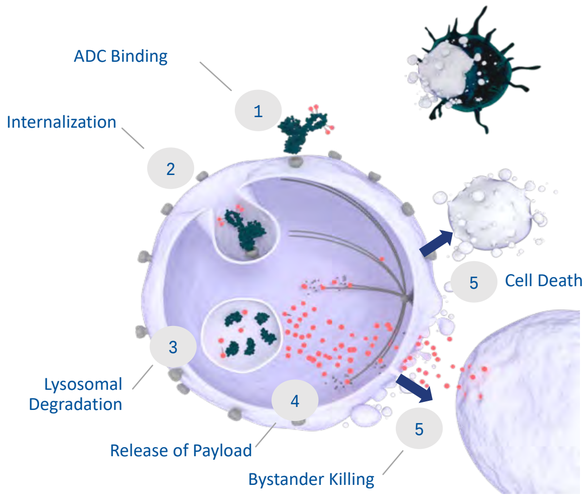
Mirvetuximab soravtansine (Elahere), the first FRα-targeted ADC approved for treatment of PROC



MIRV is an ADC comprising an FRα-binding antibody, cleavable linker, and a maytansinoid DM4 payload

SORAYA (NCT04296890) was a global, single-arm pivotal study evaluating mirvetuximab soravtansine in adult patients with FRα-positive platinum-resistant epithelial ovarian, primary peritoneal, or fallopian tube cancer

Key Eligibility Criteria

- Platinum-resistant ovarian cancer
- Prior bevacizumab required, prior PARPi allowed
- 1–3 prior lines of therapy
- Patients with *BRCA* mutations allowed
- FRα-positive (≥75% of cells staining positive with ≥2+ staining intensity)

Mirvetuximab soravtansine (N=106)[2]

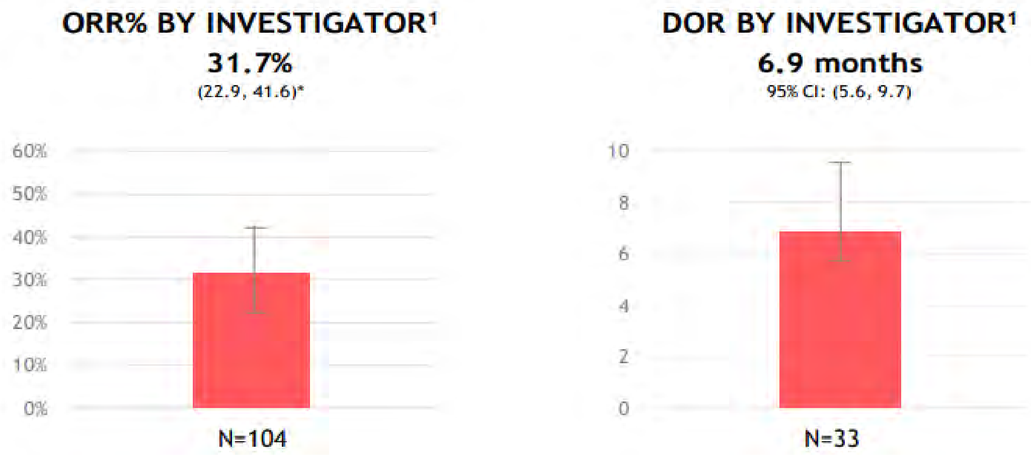
6.0 mg/kg adjusted ideal body weight (AIBW) q3w

Primary endpoint

- ORR per Investigator

Secondary endpoints

- DOR, PFS, OS, CA-125 response by GCIG criteria, safety



FDA grants accelerated approval to mirvetuximab soravtansine-gynx for FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or peritoneal cancer

Moore KN, et al. *Cancer*. 2017;123(20):3456-3464. doi:10.1002/cncr.30812.; Matulonis UA, et al. *J Clin Oncol*. 2023;41(15):2831-2842. doi:10.1200/JCO.23.00123

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MIRASOL Phase III Trial: Platinum Resistant Ovarian Cancer

An open-label, phase 3 randomized trial of MIRV vs investigator's choice chemotherapy in patients with FRα-high platinum-resistant ovarian cancer

Patient Population
(N=453)

Enrollment and Key Eligibility

Platinum-resistant disease
(PFI ≤6 mo)

FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells

High-grade serous histology

1⁰ platinum-refractory disease excluded (primary PFI <3 mo)

1-3 prior lines of therapy

Prior BEV and PARPi allowed

Patients with BRCA mutations allowed

1:1 Randomization

Treatment Regimen-Experimental

MIRV
(6 mg/kg AIBW Q3W)

Treatment Regimen-Control

Investigator's Choice Chemotherapy
(Paclitaxel, PLD, or Topotecan)

Stratification Factors

IC chemo: paclitaxel, PLD, or topotecan
Prior lines of therapy: 1 vs 2 vs 3

Primary Endpoint

PFS by INV
(BICR sensitivity analysis)

Key Secondary Endpoints

1) ORR by INV
2) OS
3) Primary PRO analysis[a]

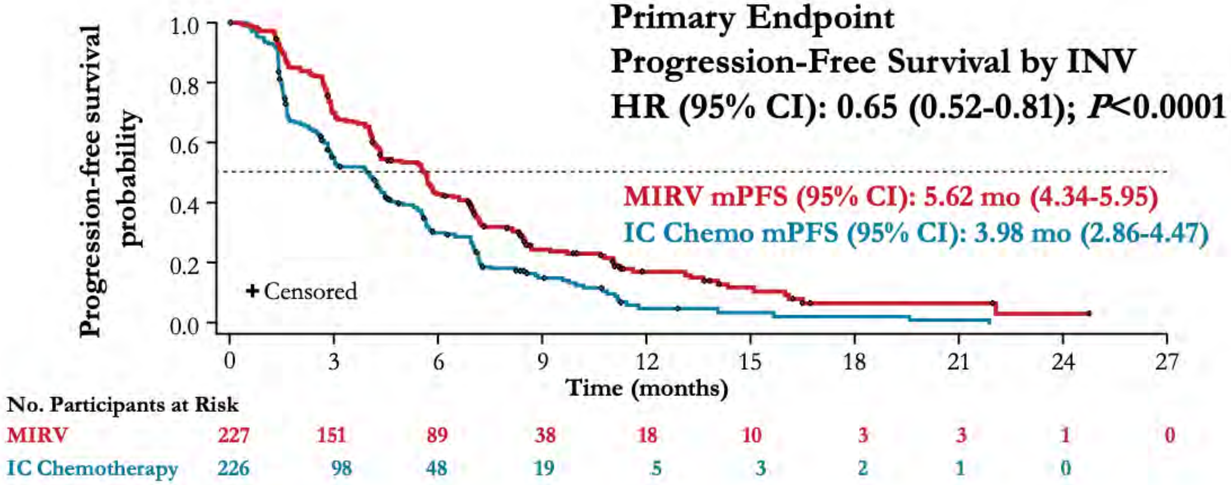
Secondary Endpoints

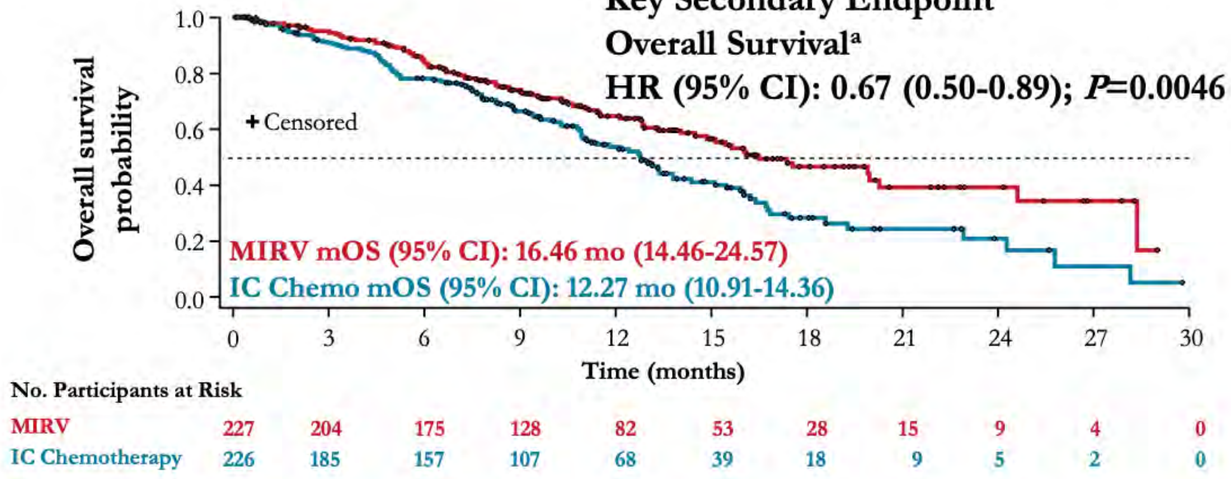
Safety and tolerability
DOR
CA-125 response[b]
PFS2

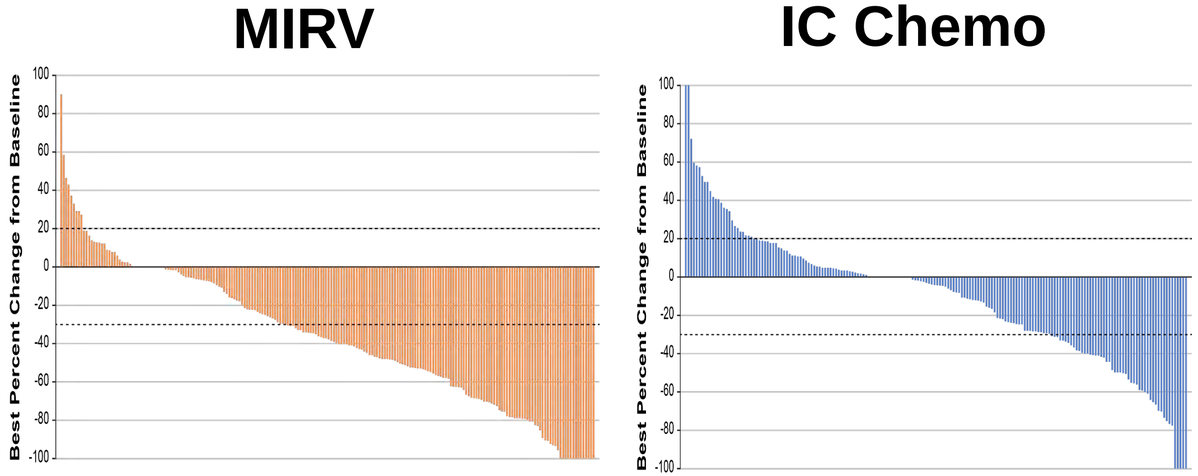
- The primary PRO assessment in MIRASOL (a prespecified key secondary endpoint) evaluated improvements in OV28 Abdominal/GI subscale score from baseline at Week 8/9, with a **conservative improvement threshold** of 15-point[a] decrease
- Anchor-based analyses were performed to further evaluate meaningful change thresholds in abdominal/GI symptoms
- All PROs were assessed at screening and on day 1 of every treatment cycle
  - Upon discontinuation and end of treatment, PRO assessment visit took place within 7 days

Moore KN, et al. *New Engl J Med.* 2023;389:2162-2174. doi:10.1056/NEJMoa2309169.;
Konecny GE, et al. Presented at: Society of Gynecologic Oncology's (SGO) Annual Meeting on Women's Cancer; 18-21 March 2022; Phoenix, AZ USA.

MIRASOL Phase III Trial: PROC *cont.*







Key Secondary Endpoint: Objective Response Rate by INV

	MIRV (n=227)	IC Chemotherapy (n=226)
ORR by INV, (%)[b] n (95% CI)	42.3% 96 (35.8-49.0)	15.9% 36 (11.4-21.4)
ORR Difference (95% CI), 26.4% (18.4-34.4)		
Odds Ratio (95% CI), 3.81 (2.44-5.94)		
P<0.0001		

Moore KN, et al. *New Engl J Med.* 2023;389:2162-2174. doi:10.1056/NEJMoa2309169.;
Konecny GE, et al. Presented at: Society of Gynecologic Oncology's (SGO) Annual Meeting on Women's Cancer; 18-21 March 2022; Phoenix, AZ USA.

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Ovarian Cancer Case: *BRCAm/HRD+*

65-y.o. woman with BRCAm/HRD+ high-grade serous ovarian cancer s/p neoadjuvant chemotherapy, debulking, PARPi maintenance for 18 months with rising CA125 and CT scan with pulmonary effusion, carcinomatosis, and hepatic metastatic disease.

Treatment options:

FRα Scoring = 90%

- ❑ **Carboplatin doublet**
- ❑ **Carboplatin doublet with bevacizumab**
- ❑ **Mirvetuximab**
- ❑ **Surgical debulking with HIPEC**

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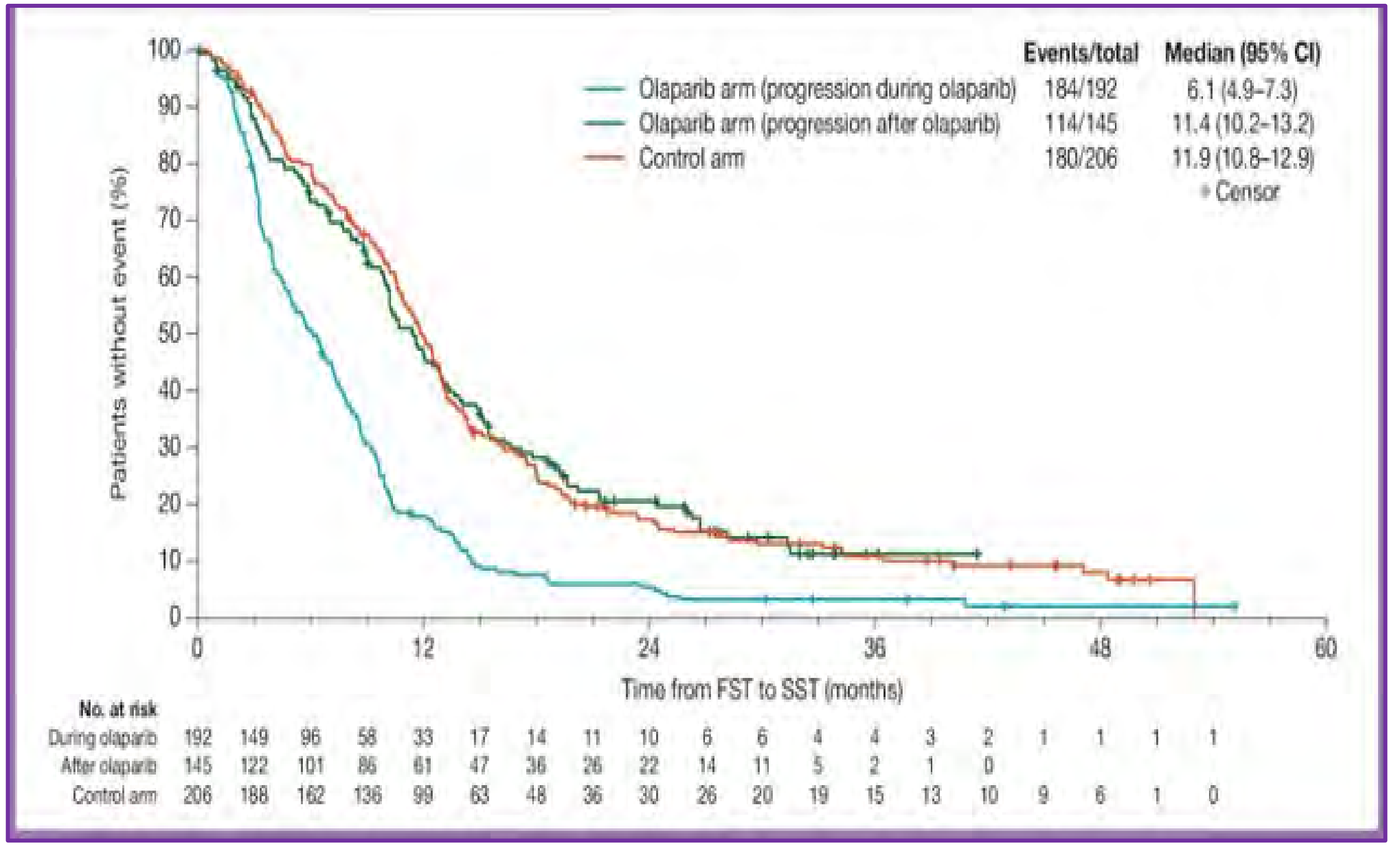
Progression after PARP inhibitor maintenance therapy in patients with platinum-sensitive disease



Time from first subsequent therapy to second subsequent therapy in patients who received any chemotherapy

Harter P. *J Clin Oncol.* 2023;41(17_suppl):LBA5506. doi:10.1200/JCO.2023.41.17_suppl.LBA5506.

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Prospective PSOC Randomized Trials

Trial Name	*BRCA* mut Status	Prior Lines of Therapy	Prior PARPi Bev*	Treatment Arms	ORR (%)	mPFS, Months (95%CI)
OCEANS (n=484)	--	1	No	Carbo/Gem Carbo/Gem + B	57.4% 78.5%	8.4 (8.3-9.7) 12.4 (11.4-12.7)
GOG-0213 (n=674)	--	1	No 10%	Carbo Doublet Carbo Doublet + B	59% 78%	10.4 (9.7-11.0) 13.8 (13.0-14.7)
AGO OVAR 2.21 (n=682)	--	1	No 47.5%	Carbo/Gem + B Carbo/PLD + B	-- --	11.6 (11.0-12.7) 13.3 (11.7-14.2)
NRG-GY004 (n=565)	23.7%	1 – 65.7% 2 – 26.6% ≥3 – 7.7%	No 8.5%	Carbo Doublet Olaparib-Cediranib	71.3% 69.4%	10.3 (8.7-11.2) 10.4 (8.5-12.5)
ATALANTE (n=614)	11.7%	1 – 73.9% 2 – 26.1%	18.6% 50.5%	Carbo Doublet + B Carbo Doublet + B + Atezo	66% 62%	11.3 (11.0-13.5) 13.5 (12.2-14.2)
ANITA (n=417)	14%	1 – 86% 2 – 14%	11% 54%	Carbo Doublet + Niraparib Carbo Doublet + N + Atezo	43% 45%	10.1 (9.2-11.2) 11.2 (10.1-12.1)

*** Anti-VEGF or bevacizumab**

Aghajanian C, et al. *J Clin Oncol.* 2012;30(17):2039-2045.; Coleman RL, et a. *Lancet Oncol.* 2017;18(10):1378-1391. doi:10.1016/S0140-6736(17)32440-6.; Pfisterer J, et al. *Lancet Oncol.* 2020;21(5:)699-709. doi:10.1016/S1470-2045(20)30142-X.; Liu JF, et al. *J Clin Oncol.* 2022; 40(24):2436-2446. doi:10.1200/JCO.22.01003.; Kurtz JE, et al. *J Clin Oncol.* 2023; 41(16):2004-2015. doi:10.1200/JCO.23.00123. González-Martin A, et al. *J Clin Oncol.* 2024;42(6):e76. doi:10.1200/JCO.2024.42.6.e76.

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Retrospective Series: Efficacy Post PARPi

Disease Setting	*BRCA* Mutation Present	Prior Lines of Therapy	Prior Bev	Sample Size (N)	ORR	mPFS, Months (Plat therapy)
POST-HOC ANALYSES OF PHASE III TRIALS						
Post-Hoc SOLO2	100%	2 – 52.6% ≥ 3 – 47.4%;	18%	78		7.0
Post-Hoc PAOLA-1	--	--	100%	157	--	7.3 (5.7-8.4)
REAL WORLD (RW) ANALYSES AND RETROSPECTIVE SERIES						
RW Analysis Cecere et al.	100%	--	≥ 41.5%	66	13.6%	--
RW Analysis Romeo et al.	*BRCA*m - 47.3% BRCAwt- 52.7%	2 – 59.3% > 2 – 40.7%;	--	35 39	40% 43%	3.5 (2.5-8.6) 7.5 (6.5-10.1)
Ang et al.	100%	1 – 15% 2 – 34% ≥ 3 – 50%;	--	**89** 67 48 (Plat)	36% 40%	5.5
Park et al.	100%	≥ 2 – 100%;	10.5%	33	20.4%	8.9

Frenel JS, et al. *Ann Oncol.* 2022; 33(10):1021-1028. doi:10.1016/j.annonc.2022.06.011.; Harter P. *J Clin Oncol.* 2023;41(17_suppl):LBA5506. doi:10.1200/JCO.2023.41.17_suppl.LBA5506.; Cecere SC, et al. *Gynecol Oncol.* 2020; 159(1):21-27. doi:10.1016/j.ygyno.2020.07.001.; Romeo MA, et al. *Cancers.* 2022;14(18):4414. doi:10.3390/cancers14184414.; Park J, et al. *Gynecol Oncol.* 2022;33(6):e71. doi:10.3802/jgo.2022.33.e71.; Ang JE, et al. *Clin Cancer Res.* 2013; 19(19):5485-5493. doi:10.1158/1078-0432.CCR-13-1262.

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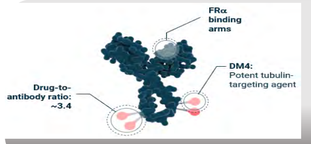
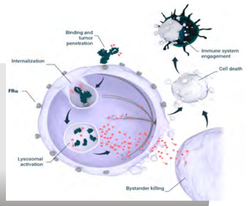
PICCOLO (NCT05041257) – Study Design



A single-arm, open-label, phase 2 trial of MIRV in patients **with ≥3L platinum**-sensitive ovarian cancer with FRα-high expression



PICCOLO Patient Population (N=**79**)

Enrollment and Key Eligibility

- Platinum-sensitive disease (defined as radiographic progression >6 months from last dose of most recent platinum therapy)
- FRα detected by IHC with PS2+ intensity **among ≥75% of viable tumor** cells[a]
- At least 2 prior platinum-containing regimens[b]
- Prior PARPi required if *BRCA*+
- Prior BEV not required
- Appropriate for single-agent therapy

Treatment Regimen

MIRV
(6 mg/kg AIBW Q3W)

Primary Endpoint

ORR by INV

Key Secondary Endpoint

DOR by INV

Other Secondary Endpoints

- Safety and tolerability
- CA-**125 response** (GCIG criteria)
- PFS
- OS
- Sensitivity analyses[c]

MIRV is comprised of an FRα-binding antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent

Ab O, et al. *Mol Cancer Ther.* 2015; 14(7):1605-1613. doi:10.1158/1535-7163.MCT-14-1095.; Moore KN, et al. *Cancer*. 2017;123(20):3456-3464. doi:10.1002/cncr.30812.;
Alvarez Secord A, et al. Presented at: European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain.

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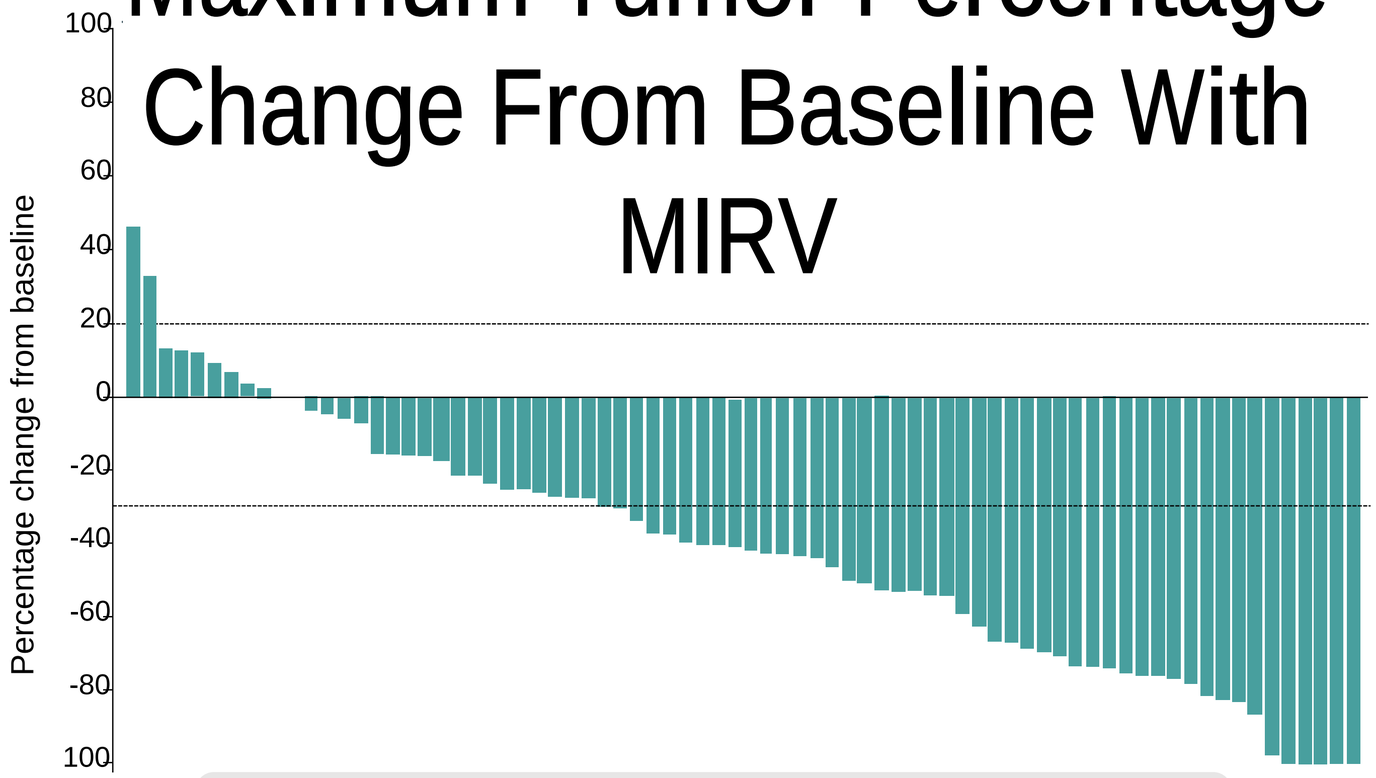
Investigator-Assessed Efficacy Measures

Maximum Tumor Percentage Change From Baseline With MIRV



Median time to response was 1.58 months
Median number of treatment cycles was 9 (range, 1 to 27)

Primary Endpoint	N=79
ORR, n (%) 95% CI	41 (51.9) 40.4-63.3
Best overall response, n (%)	
CR	6 (7.6)
PR	35 (44.3)
SD	29 (36.7)
PD	7 (8.9)
Not evaluable	2 (2.5)

Secondary Endpoints	
Median DOR[a]	n=41
Months (95% CI)	8.25 (5.55-10.78)
Median PFS	N=79
Months (95% CI)	6.93 (5.85-9.59)
CA-**125** response[b]	n=47
n (%)	35 (74.5)
95% CI	59.7-86.1

Data cutoff: January 17, 2024. [a]**Calculated among participants who had a complete or partial response.** [b]Analysis performed on the CA-**125**–evaluable **population. CA-125, cancer antigen 125; CI, confidence interval; CR, complete response; DOR, duration of response; MIRV,** mirvetuximab soravtansine-gynx; **ORR, objective response rate; PFS, progression-free survival; PD, progressive disease; PR, partial response; SD, stable disease.**

Alvarez Secord A, et al. Presented at: European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain.

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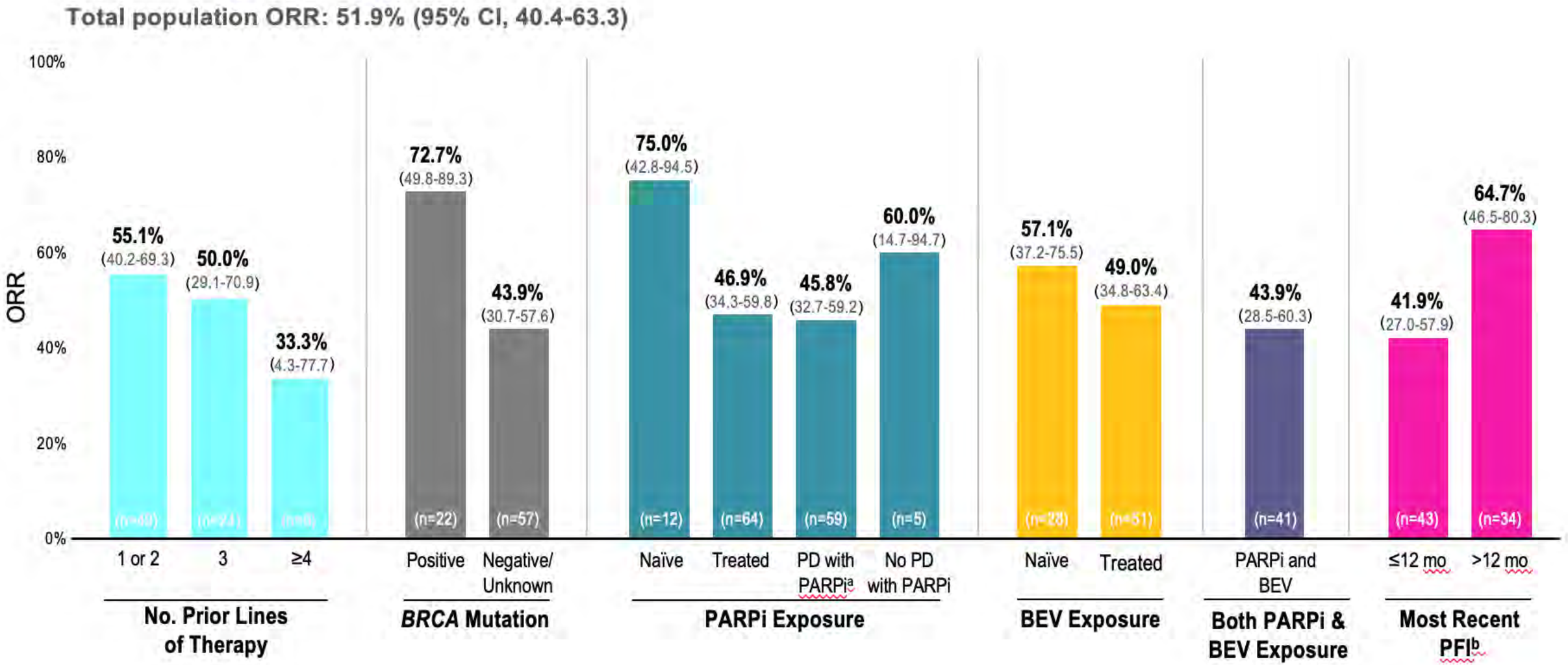
ORR by Subgroups



Dat

discontinuation of a PARPi, the participant was defined as having progressive disease on prior PARPi and was included in this ca**tegory.** [b]Platinum-free interval is defined as time from last dose of the latest line platinum therapy to the date of disease progression and/or relapse following that line of therapy (time rounded to whole number). **BEV, bevacizumab; *BRCA*, Breast Cancer gene; CI, confidence interval; PARPi,** poly (adenosine diphosphate [ADP]-**ribose) polymerase inhibitor; PD, progressive disease; PFI, platinum-free interval; ORR, objective response rate.**

Alvarez Secord A, et al. Presented at: European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain.

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WHAT WOULD YOU DO???

Ovarian Cancer Case: *BRCAm/HRD+*

65-y.o. woman with BRCAm/HRD+ high-grade serous ovarian cancer s/p neoadjuvant chemotherapy, debulking, PARPi maintenance for 18 months with rising CA125 and CT scan with pulmonary effusion, carcinomatosis, and hepatic metastatic disease.

FRα Scoring = 90%

Treatment options:

- ❑ **Carboplatin doublet**
- ❑ **Carboplatin doublet with bevacizumab**
- ❑ **Mirvetuximab**
- ❑ **Surgical debulking with HIPEC**

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Audience Q & A

GOG FOUNDATION®
Transforming the standard of care

Navigating New Mountains: Fresh Tracks on ADCs in Endometrial and Ovarian Cancers, Up and Coming Innovations on the Vista

Jubilee Brown, MD

Atrium Health Wake Forest University

Charlotte, North Carolina

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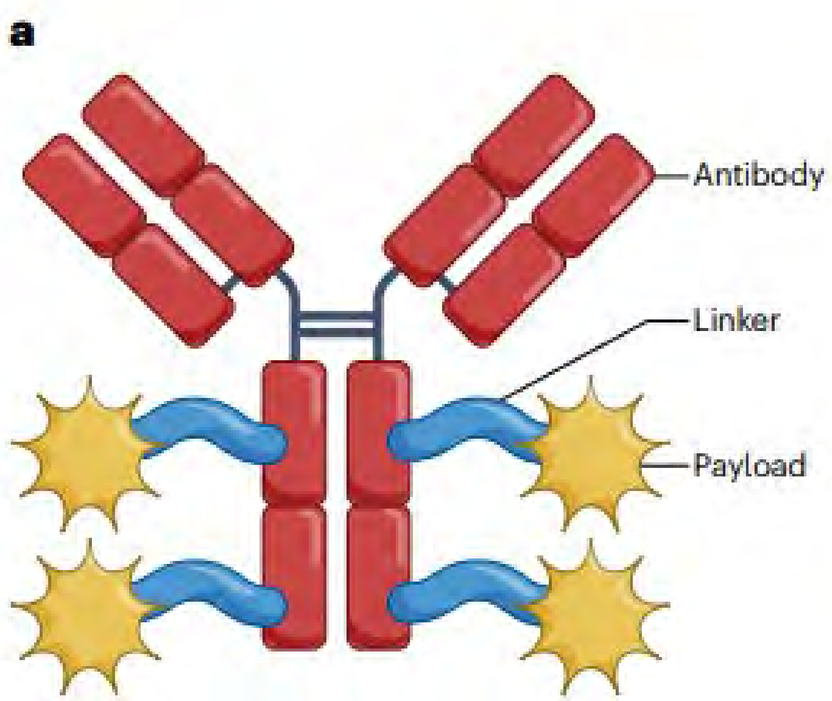
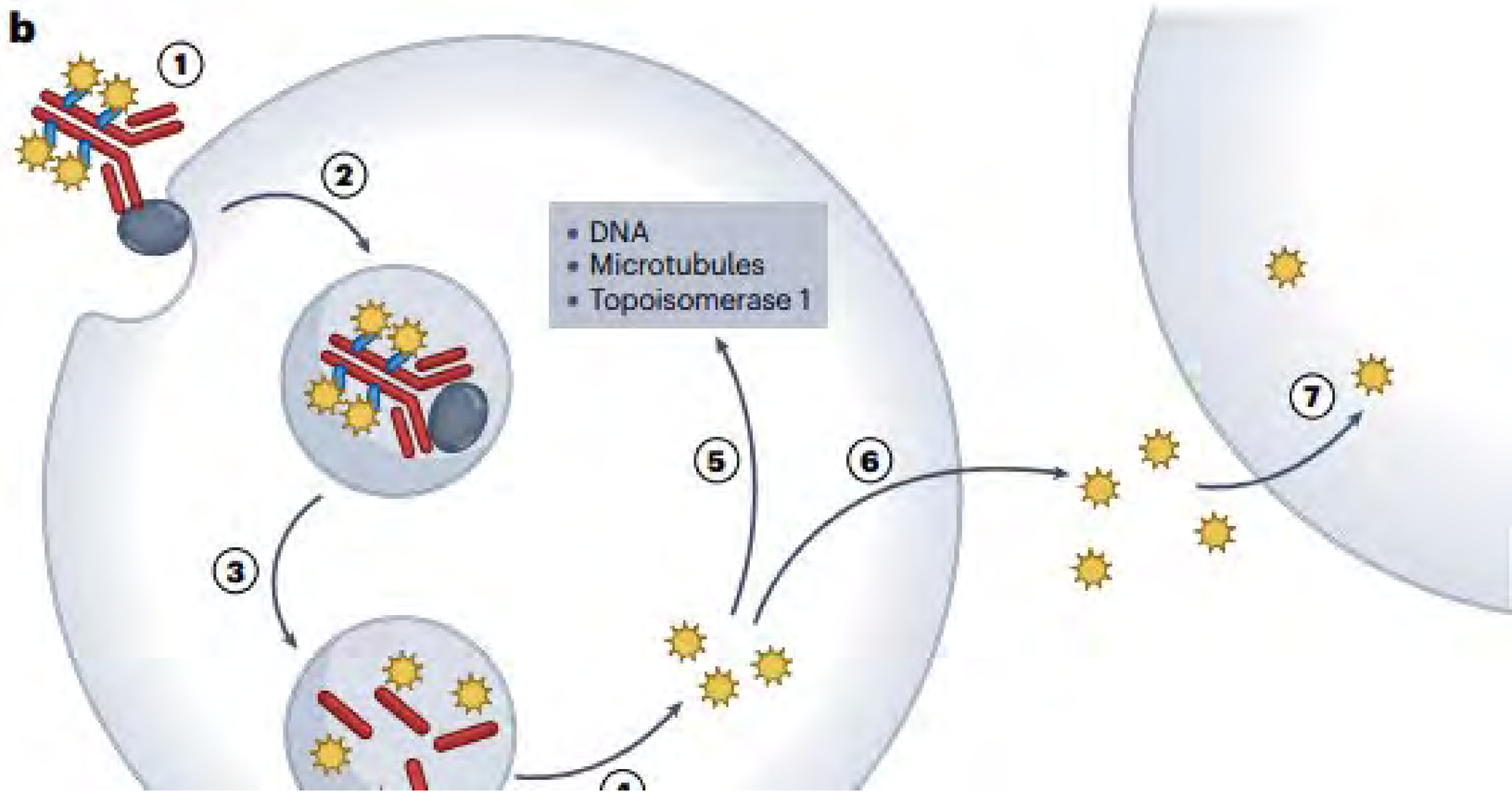
Transforming the standard of care

Targeted Cancer Treatment That Combines an Antibody with a Drug: *Antibody Drug Conjugate (ADC)*





Dumontet C, et al. *Nat Rev Drug Discov.* 2023;22:641-661.

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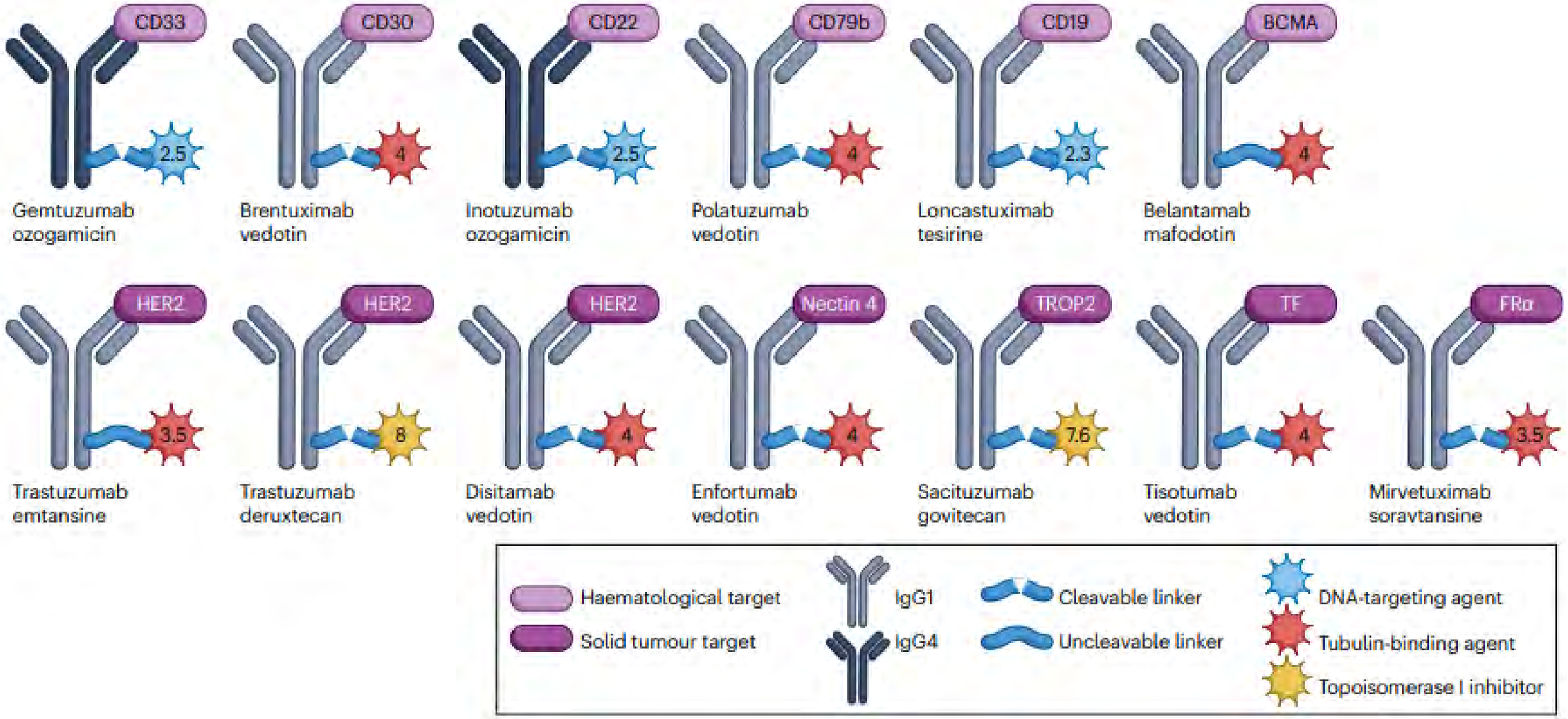
ADC: Ab, Linker, Payload, DAR



Dumontet C, et al. *Nat Rev Drug Discov.* 2023;22:641-661.

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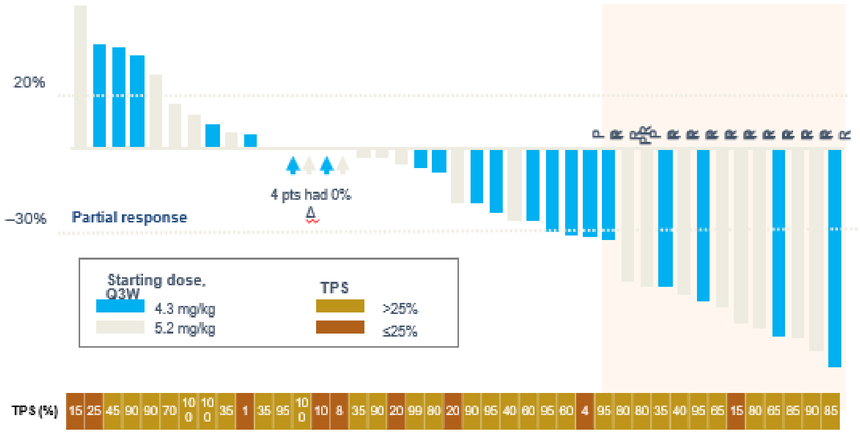
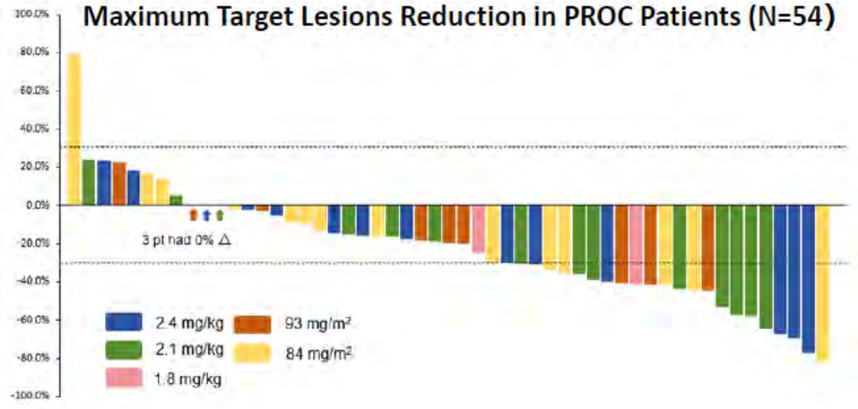
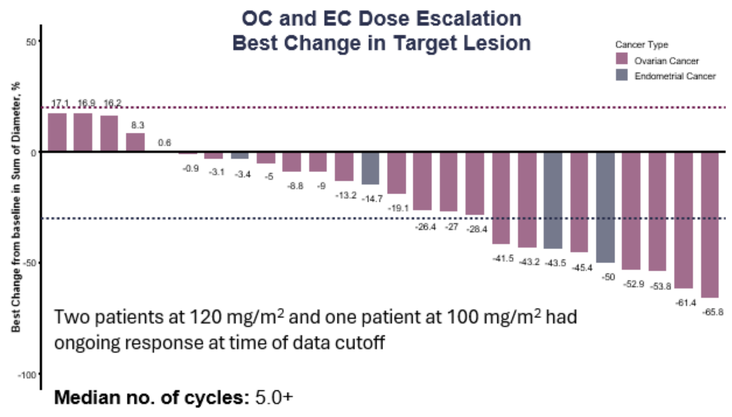
Targeting FRα in Ovarian Cancer: What is Next?

	Luveltamab Tazevibulin **NCT03748186**	BAT-8006 **NCT05378737**	Rinatabart sesutecan **NCT05579366**
Payload	SC-209 – Hemiasterelin derivative cytotoxic	Exatecan	Exatecan
ORR	43.8% FRα >25% by TPS (5.2mg/kg) 31.2% (4.3mg/kg)	37% All FRα 39%> 50% FRα 46.7% > 75% FRα	50% (n=18 at 120mg/m2)
mPFS	FRα > 25% 6.1 (95% CI 4.1- 7.2)	7.47 (4.27- NR)	NR
mOS	NR	NR	NR







Oaknin A, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; 31 May-4 June 2024; Chicago, IL USA.; Jia F, et al. Presented at: ASCO 2024.; Lee E, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain.; Shapira-Frommer R, et al. Presented at: ESMO 2024. [Abstract 754P].

@DrKatyMoore

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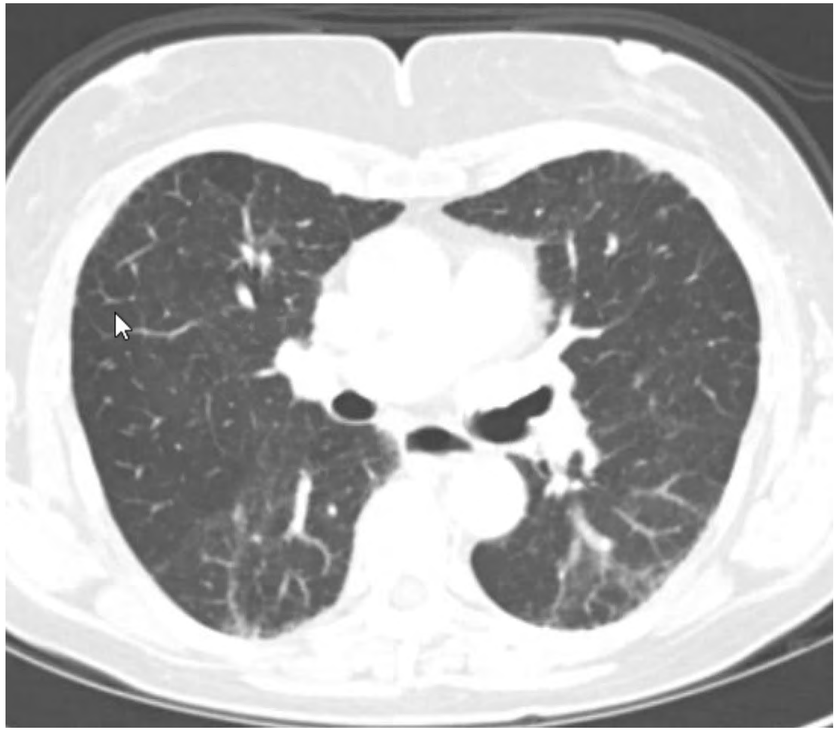
Target	Name	Payload	Payload	DAR	Linker	Development stage
HER2	Trastuzumab deruxtecan	Topo1i	deruxtecan	8	Cleavable	Phase II – FDA acc appr
	DB-1303 (BNT323)	Topo1i	P1003	8	Cleavable	Phase I/IIA – FDA BTD
	Trastuzumab duocarmazine	DNA alkylating	duocarmazine	2.8	Cleavable	Phase II
	Disitamab vedotin (RC48)	Anti-microtubule	MMAE	4	Cleavable	Phase II
FRα	Mirvetuximab soravtansine	Anti-microtubule	DM4	3.5	Cleavable	Phase II
	Luveltamab tazevibulin (STRO-002)	Anti-microtubule	SC209	4	Cleavable	Phase I/IIA
	Rinatabart sesutecan (Rina-S, PRO1184)	Topo1i	exatecan	8	Cleavable	Phase I/II
	IMGN151	Anti-microtubule	DM21	3.5	Cleavable	Phase I
TROP2	Sacituzumab govitecan (IMMU-132)	Topo1i	SN38	7.6	Cleavable	Phase II
	Sacituzumab tirumotecan (MK-2870)	Topo1i	tirumotecan	7.4	Cleavable	Phase III
	Datopotamab deruxtecan (DS-1062)	Topo1i	deruxtecan	4	Cleavable	Phase II
	LCB84	Anti-microtubule	MMAE	4	Cleavable	Phase I/II
B7-H4	SGN-B7H4V	Anti-microtubule	MMAE	4	Cleavable	Phase I
	HS-20089	Topo1i	undisclosed	6	Cleavable	Phase II
	XMT-1660	Anti-microtubule	MMAF	6	Cleavable	Phase I
	AZD8205	Topo1i	AZ14170133	8	Cleavable	Phase I/IIA
B7-H3	Ifinatamab veruxtecan (DS-7300a)	Topo1i	deruxtecan	4	Cleavable	Phase I
TF	Tisotumab vedotin	Anti-microtubule	MMAE	4	Cleavable	Phase II
	XB002	Anti-microtubule	MMAE	3.3	Cleavable	Phase I
AXL	Enapotamab vedotin	Anti-microtubule	MMAE	4	Cleavable	Phase I/II
Claudin6	TORL-1–23	Anti-microtubule	MMAE	?	Cleavable	Phase I

Slide courtesy of Toon van Gorp, MD

Case Study

- 73 y.o. Female with Stage IIIC2 uterine serous carcinoma
- pMMR, HER2+, *TP*53m
- Surgery 12/23 -> paclitaxel, carboplatin, and trastuzumab x 6
- Progressed 6/24: 2.5 cm R Ext iliac LN & bony metastasis to T8
    - Paclitaxel, carboplatin, dostarlimab
    - Doxorubicin
    - TDXd (trastuzumab deruxtecan)
    - Radiation
    - Megestrol acetate



DESTINY – PanTumor02 (HER2+)

T-DXd for HER2-expressing solid tumors

A Phase 2, open-label, multicenter study (NCT04482309)

Key eligibility criteria

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)*
  - Cervical cohort was expanded to include five IHC 1+ patients†
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd 5.4 mg/kg Q3W

n≈40 per cohort‡

Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR, DCR, PFS, OS
- Safety

Exploratory analyses

- Subgroup analyses by HER2 status§
- Subgroup analyses by biomarkers§

Primary analysis DCO

- June 8, 2023

Meric-Bernstam F, et al. *J Clin Oncol.* 2024;42(1):47-58. doi: 10.1200/JCO.23.02005.

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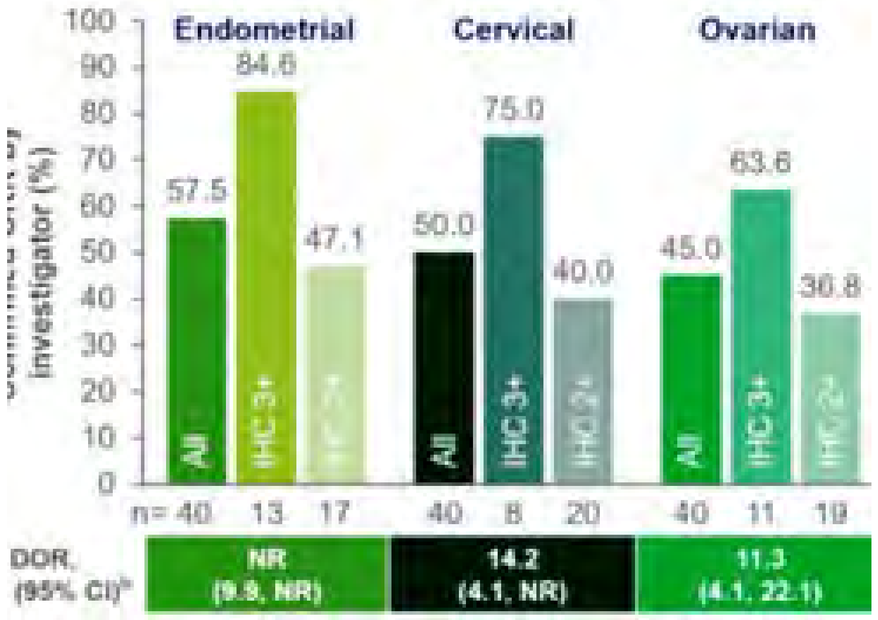
DESTINY – PanTumor02 (HER2+) *cont.*

Characteristic	Endometrial (N=40)	Cervical (N=40)	Ovarian (N=40)
Her2-IHC 3+ IHC 2+	16 (40%) 24 (60%)	10 (25%) 25 (63%)	15 (38%) 25 (63%)
Prior HER2 therapy	9 (23%) 5 (13%)	1 (3%) 1 (3%)	2 (5%) 2 (5%)

- 84% response rate if IHC3+
- Even in heavily pretreated patients
- Durable, deep responses



Meric-Bernstam F, et al. *J Clin Oncol.* 2024;42(1):47-58. doi: 10.1200/JCO.23.02005.

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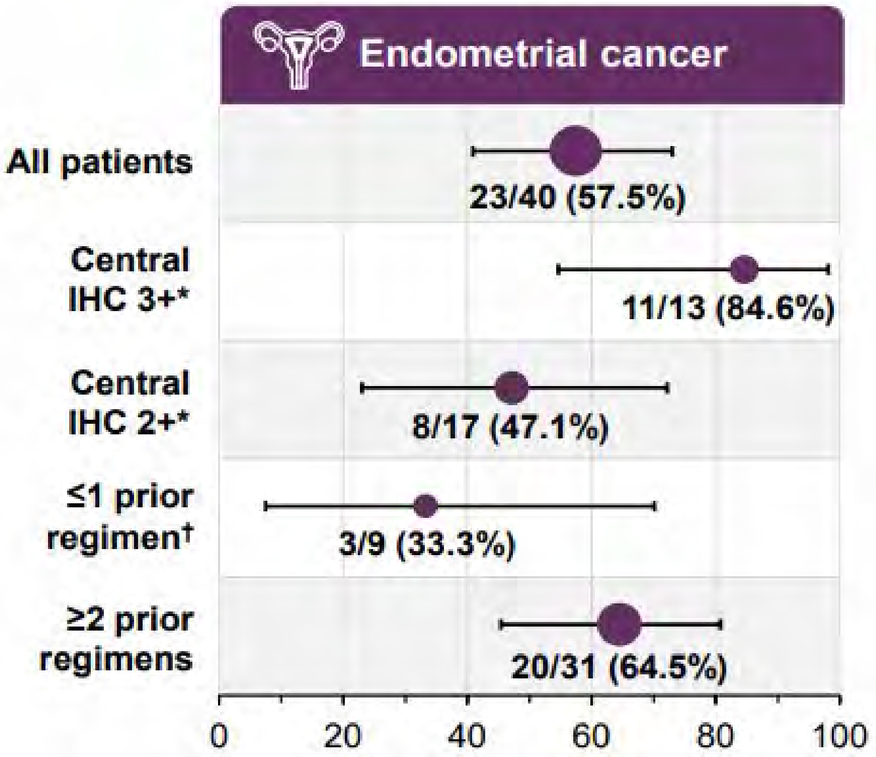
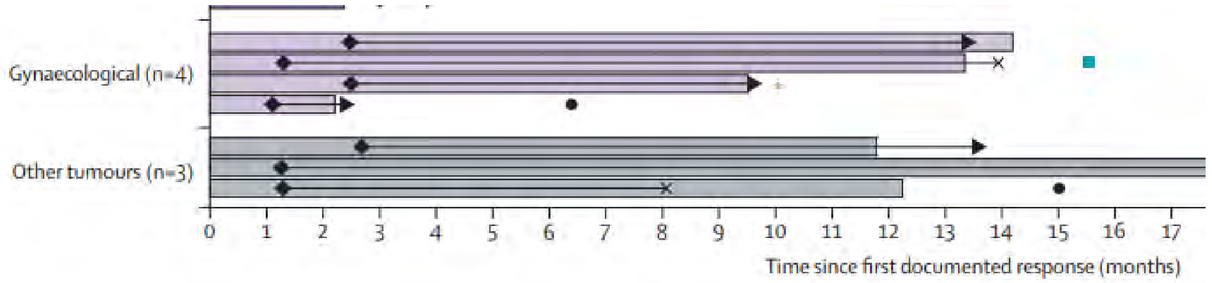
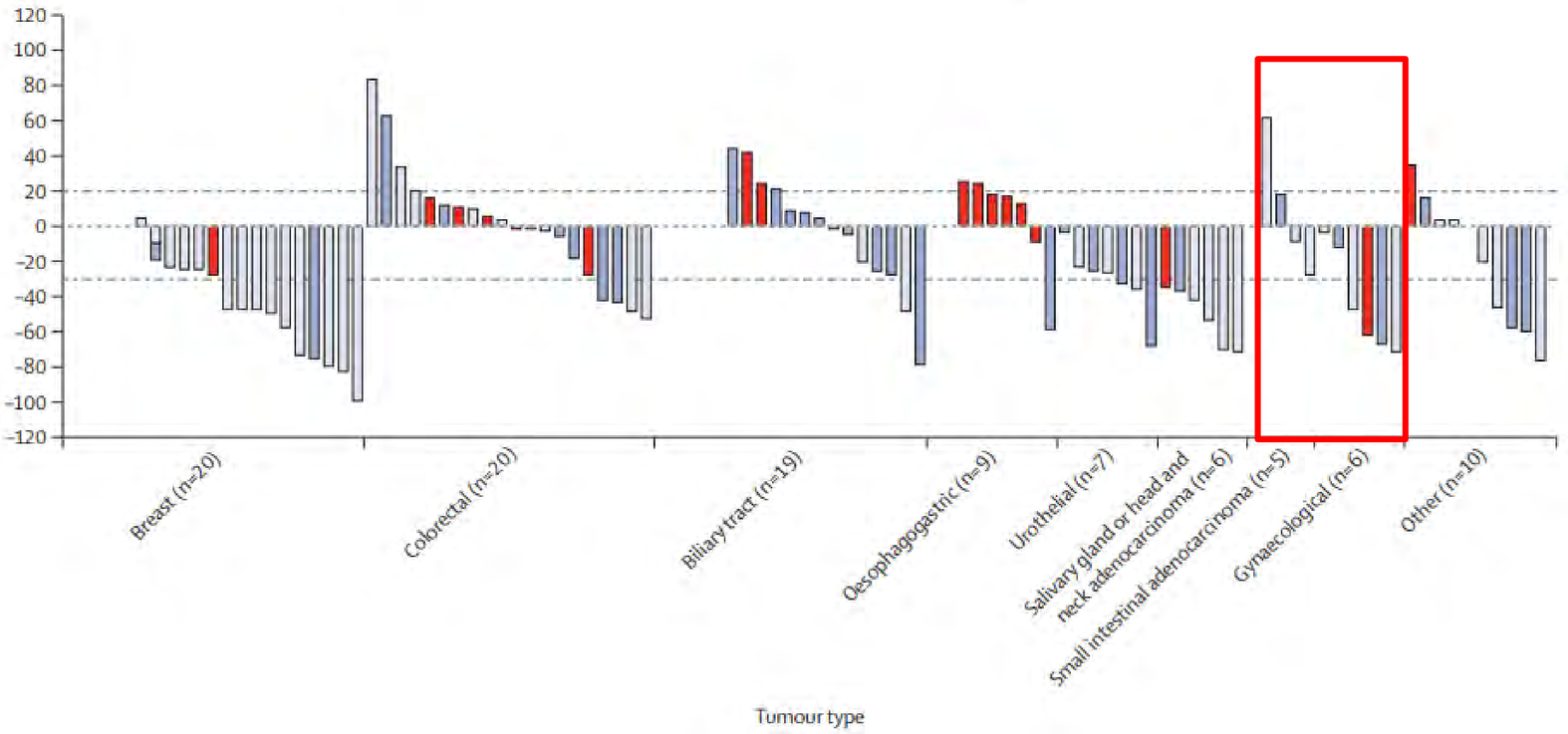
DESTINY – PanTumor02 (HER2+): ORR







Meric-Bernstam F, et al. *J Clin Oncol.* 2024;42(1):47-58. doi: 10.1200/JCO.23.02005.

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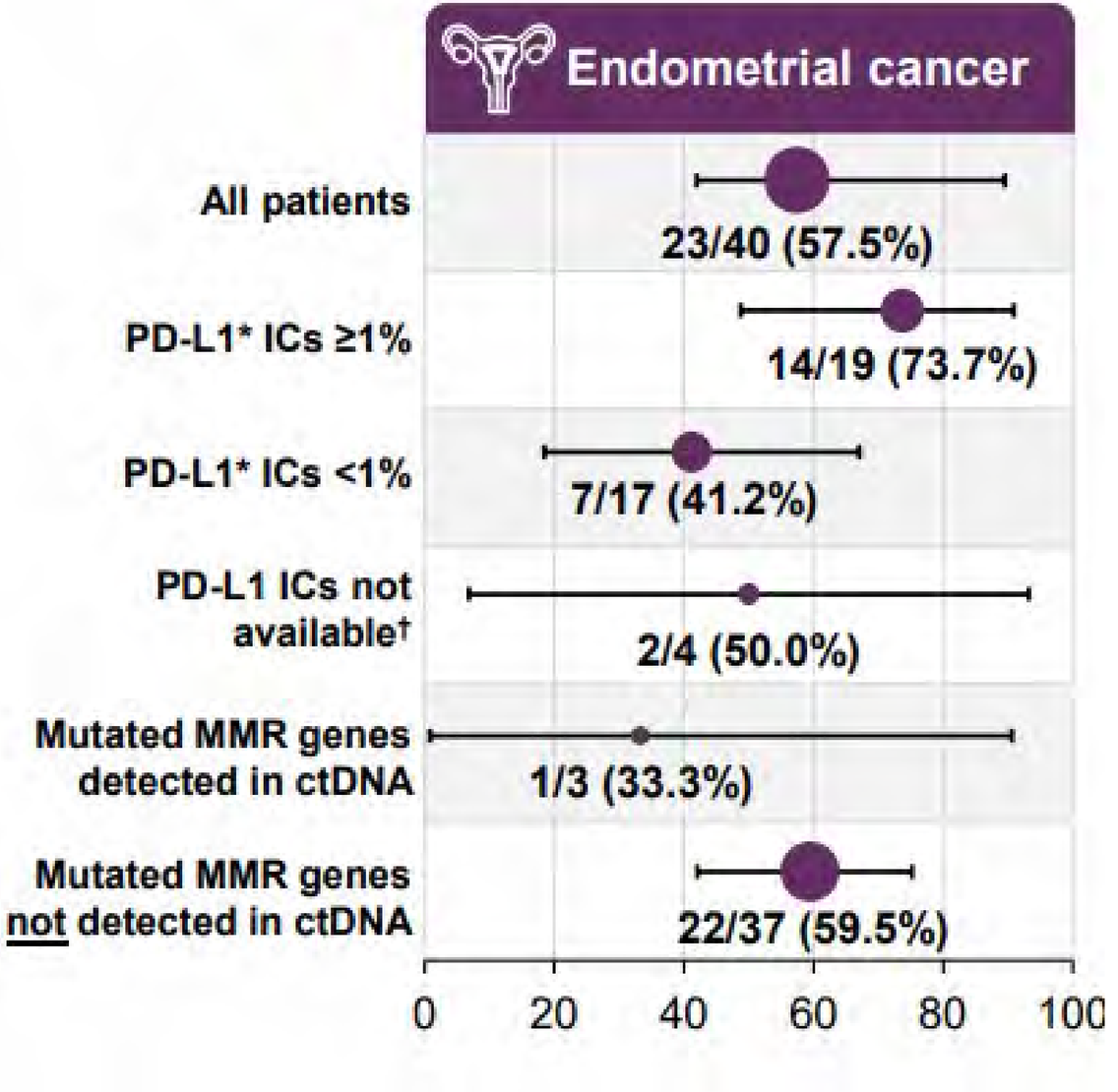
DESTINY – PanTumor02 (HER2+): ORR

- Regardless of PD-L1 or MMR status



Meric-Bernstam F, et al. *J Clin Oncol.* 2024;42(1):47-58. doi: 10.1200/JCO.23.02005.

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Case Study

- 68 y.o. Female with Stage IIIC high grade serous Fallopian tube CA
- History of DCIS, negative genetic testing but HRD
- NACT paclitaxel/carboplatin x 3 cycles, R-zero laparoscopic TRS, 3 more cycles
- Niraparib x 7m, progressed; gem/carbo with stable disease and progression; PLD + bev x 15 cycles with partial response then progression (peritoneal carcinomatosis)
- What next?

Case Study

- 68 y.o. Female with Stage IIIC high grade serous Fallopian tube CA
- History of DCIS, negative genetic testing but HRD+
- NACT paclitaxel/carboplatin x 3 cycles, R-zero laparoscopic TRS, 3 more cycles
- Niraparib x 7m, progressed; gem/carbo with stable disease and progression; PLD + bev x 15 cycles with partial response then progression (peritoneal carcinomatosis)
- What next? FRa testing 3+
  - Paclitaxel + carboplatin
  - Topotecan
  - Mirvetuximab
  - Mirvetuximab + bevacizumab
  - Bevacizumab

Story of Mirvetuximab (MIRV)

FORWARD-1: Initial Randomized Phase III trial of MIRV vs IC

- Did NOT meet primary endpoint for PFS in PROC (10x scoring)

SORAYA: Single arm Phase 2 trial of mirvetuximab vs chemo in PROC

- Used 75% with PS2+ scoring (biomarker selected population)
- Supported accelerated approval by FDA

MIRASOL: Phase III confirmatory trial of MIRV + IC in PROC

- Used 75% with PS2+ scoring (biomarker selected population)
- Showed improvement in PFS and OS
- Lead to FDA approval for MIRV in PROC

Moore KN, et al. *Annals Oncol.* 2021;32(6):757-765. doi:10.1016j.annonc.2021.02.017.; Matulonis UA, et al. *J Clin Oncol.* 2023;41(13):2436-2445. doi:10.1200/JCO.22.01900.;
Moore KN, et al. *NEJM.* 2023;389:2162-2174. doi:10.1056/NEJMoa2309169.

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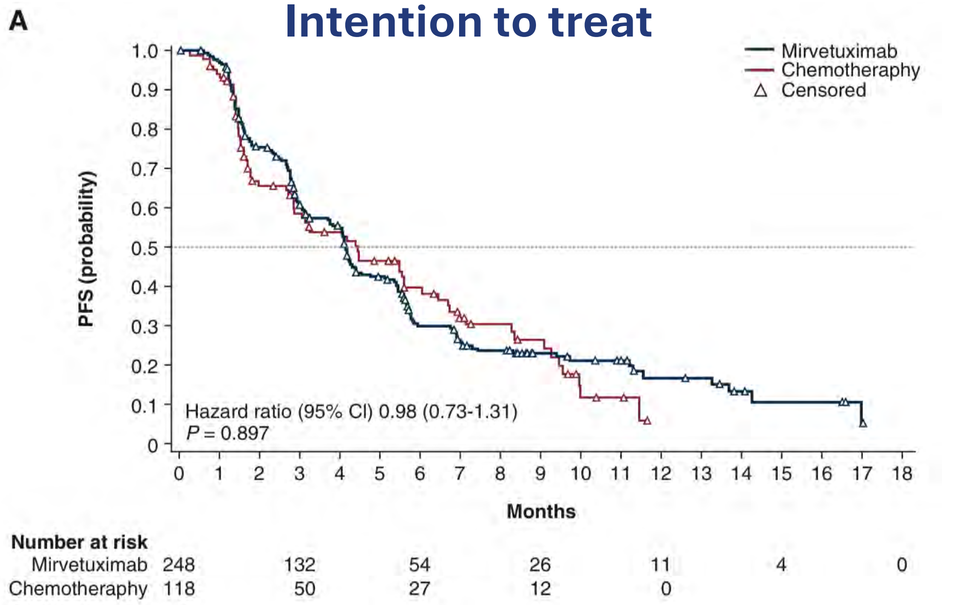
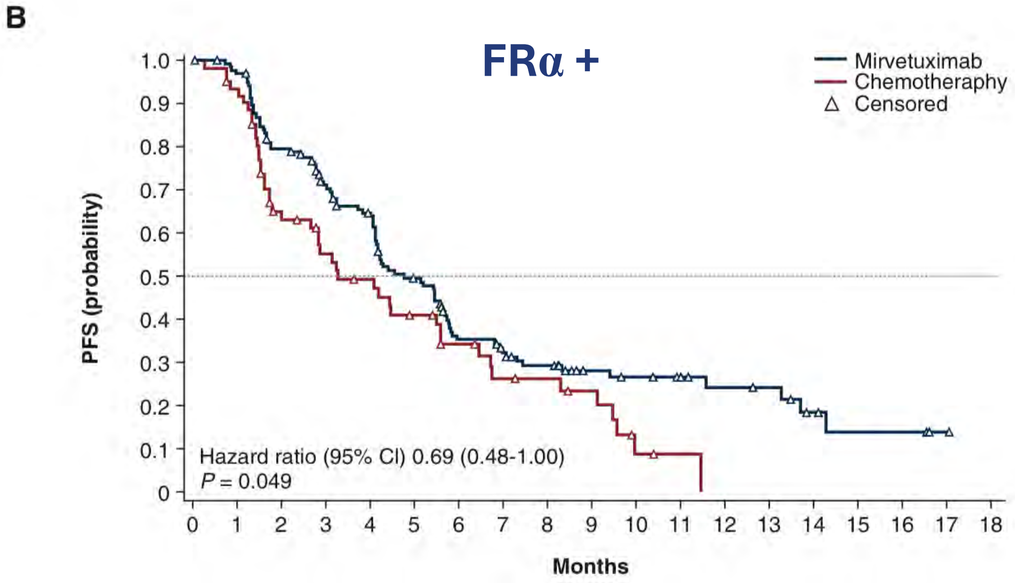
FORWARD-1 Trial

- Mirvetuximab
- Randomized open-label Phase 3
- MIRV vs Investigator's Choice chemo
- Platinum Resistant Ovarian Cancer
- Did NOT meet primary endpoint (PFS)
- Why? Used 10x scoring instead of intensity+propensity: diluted effect of MIRV
- Prompted additional trial…





Moore KN, et al. *Annals Oncol.* 2021;32(6):757-765. doi:10.1016j.annonc.2021.02.017.

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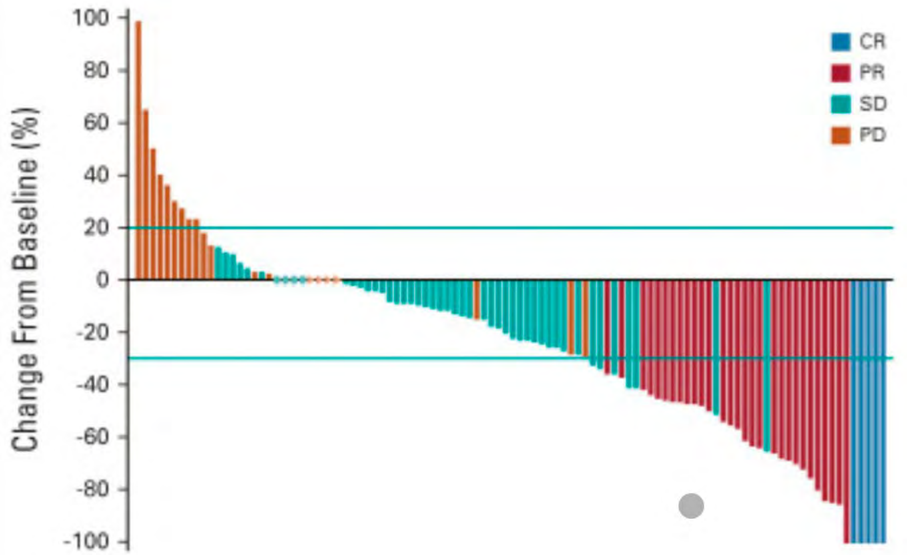
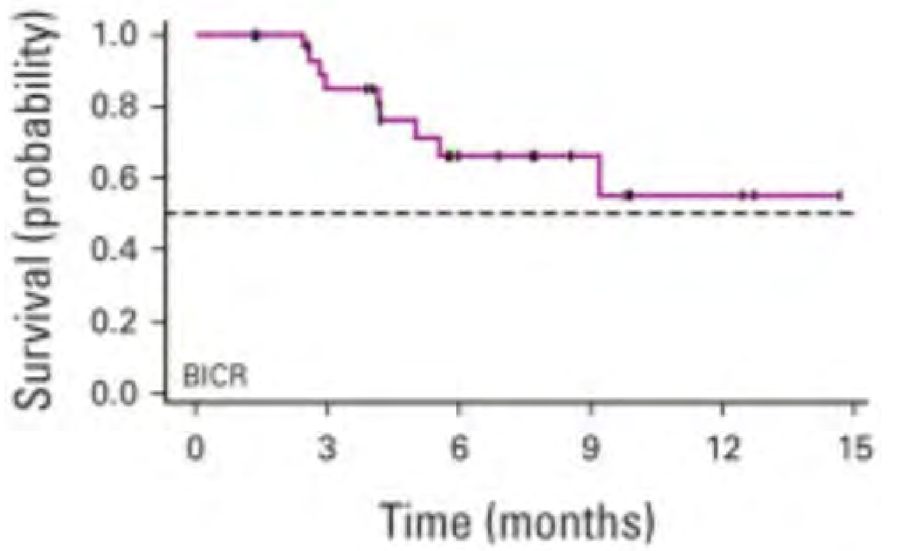
Soraya

- Mirvetuximab vs IC
- Single arm Phase 2 study
- Platinum resistant OC (h/o bev)
- N=106
- Used 75% with PS2+
  - Biomarker selected population
- ORR = 32.4%
  - 30% in patients with 3 priors
- Favorable tolerability and safety
- Supported accelerated approval





Matulonis UA, et al. *J Clin Oncol.* 2023;41(13):2436-2445. doi:10.1200/JCO.22.01900.

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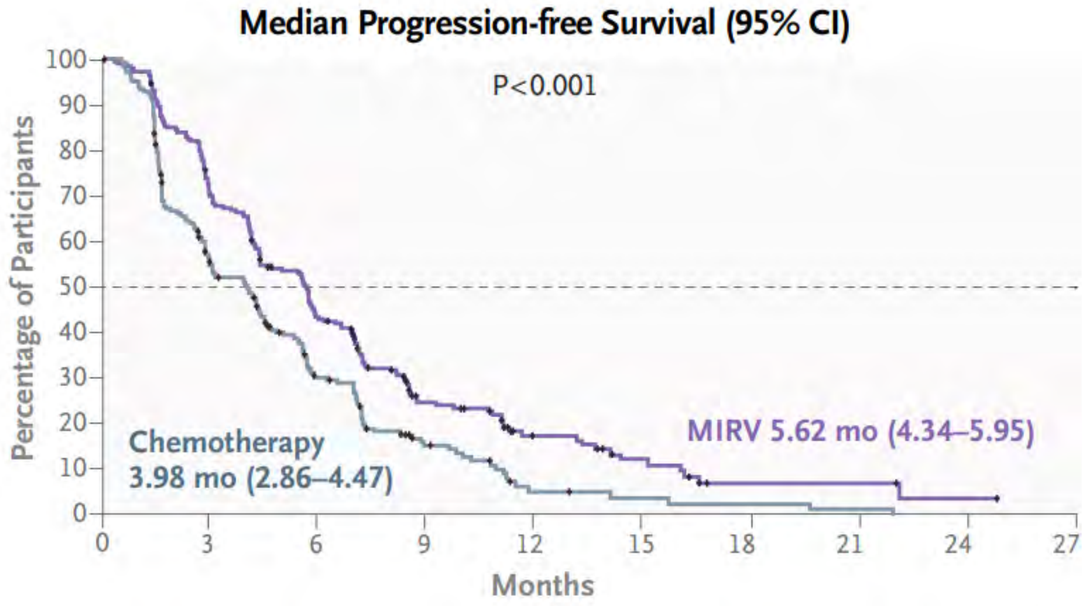
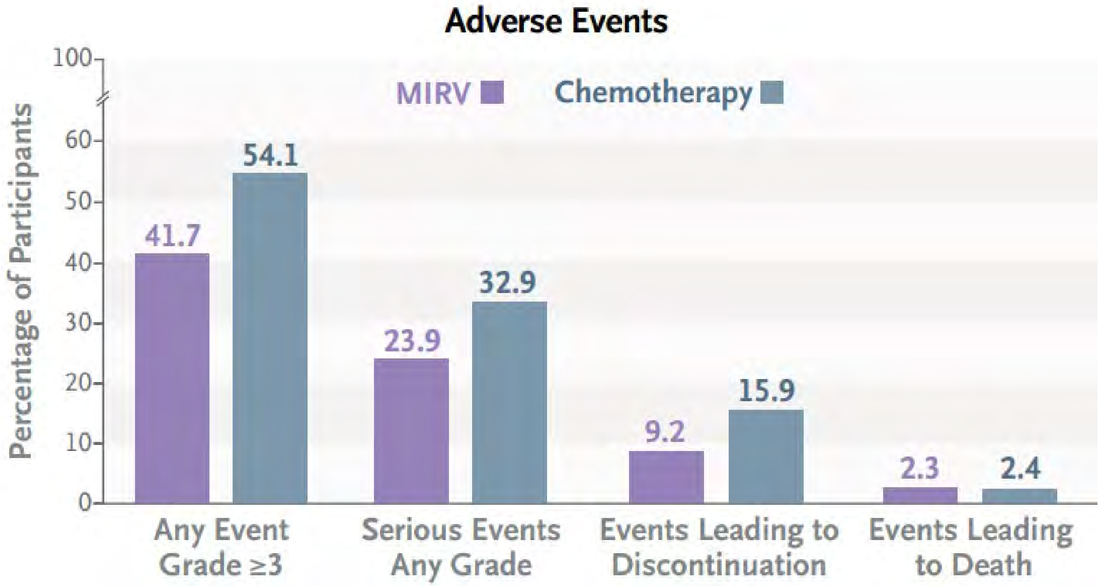
MIRASOL

- Mirvetuximab vs IC
- Phase III confirmatory trial
- Platinum resistant OC
- N = 453
- Used >75% cell with PS 2/3+ FRa
  - Biomarker selected population
- ORR: 42 vs 15% (OR 3.8)
- OS: 16.5 vs 12.8m (HR 0.67)
- Fewer G3/4 AEs: 41.7% vs 54.1%
- FDA approval for MIRV in PROC





Moore KN, et al. *New Engl J Med.* 2023;389:2162-2174. doi:10.1056/NEJMoa2309169.

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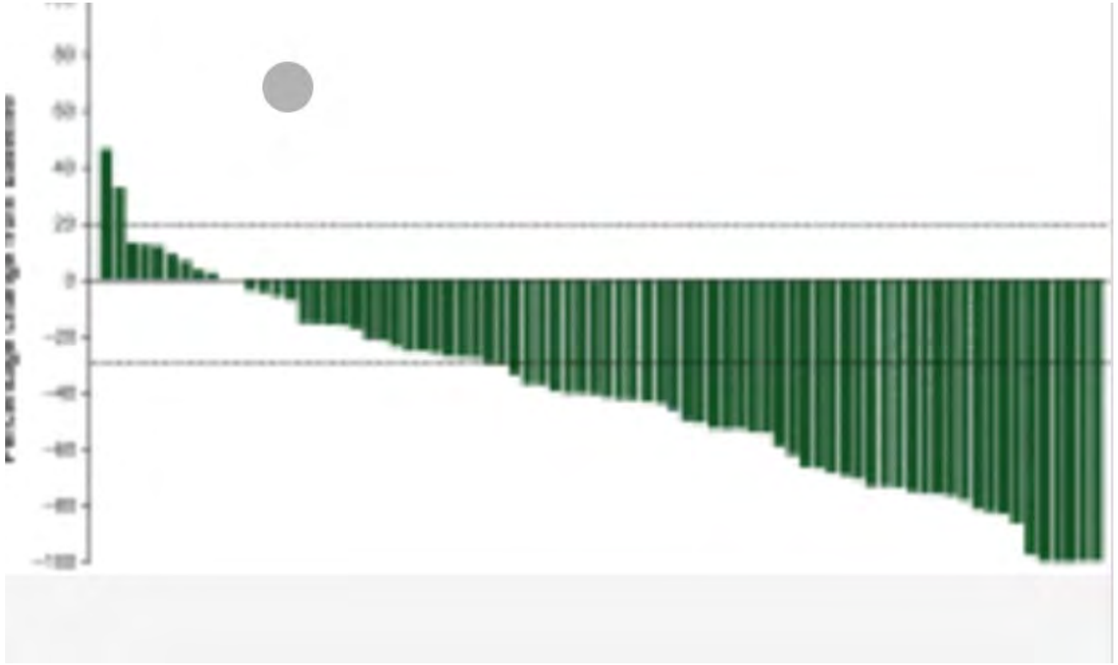
PICCOLO

- Phase II global open-label, single arm
- Mirvetuximab single agent
- Platinum sensitive OC (2 plat prior)
- N = 79
- Used >75% cell with PS 2/3+ FRa
  - Biomarker selected population
- ORR: 51.9%
- Median DOR: 8.3 m, mPFS 8.9 m
- OS not mature at ESMO2024



Secord AA, et al. *Ann Oncol.* 2024;35(1):45-56. doi:10.1016/j.annonc.2023.10.012.

Story of Mirvetuximab (MIRV) + Bevacizumab (bev)

FORWARD-II: Phase Ib/II study of MIRV + bev /carbo/PLD

- Mixed population with range of FRa status and bev exposure

GLORIOSA: Randomized Phase 3 trial of MIRV + bev vs. Bev

- Maintenance in PSOC
- Enrolling

Gilbert L, et al. *Gynecol Oncol.* 2023;170:241-247. doi:10.1016/j.ygyno.2023.04.024.; O'Malley D, et al. *Future Oncol.* 2024;20(32):2423-2436. doi:10.1080/14796694.2024.2372241.

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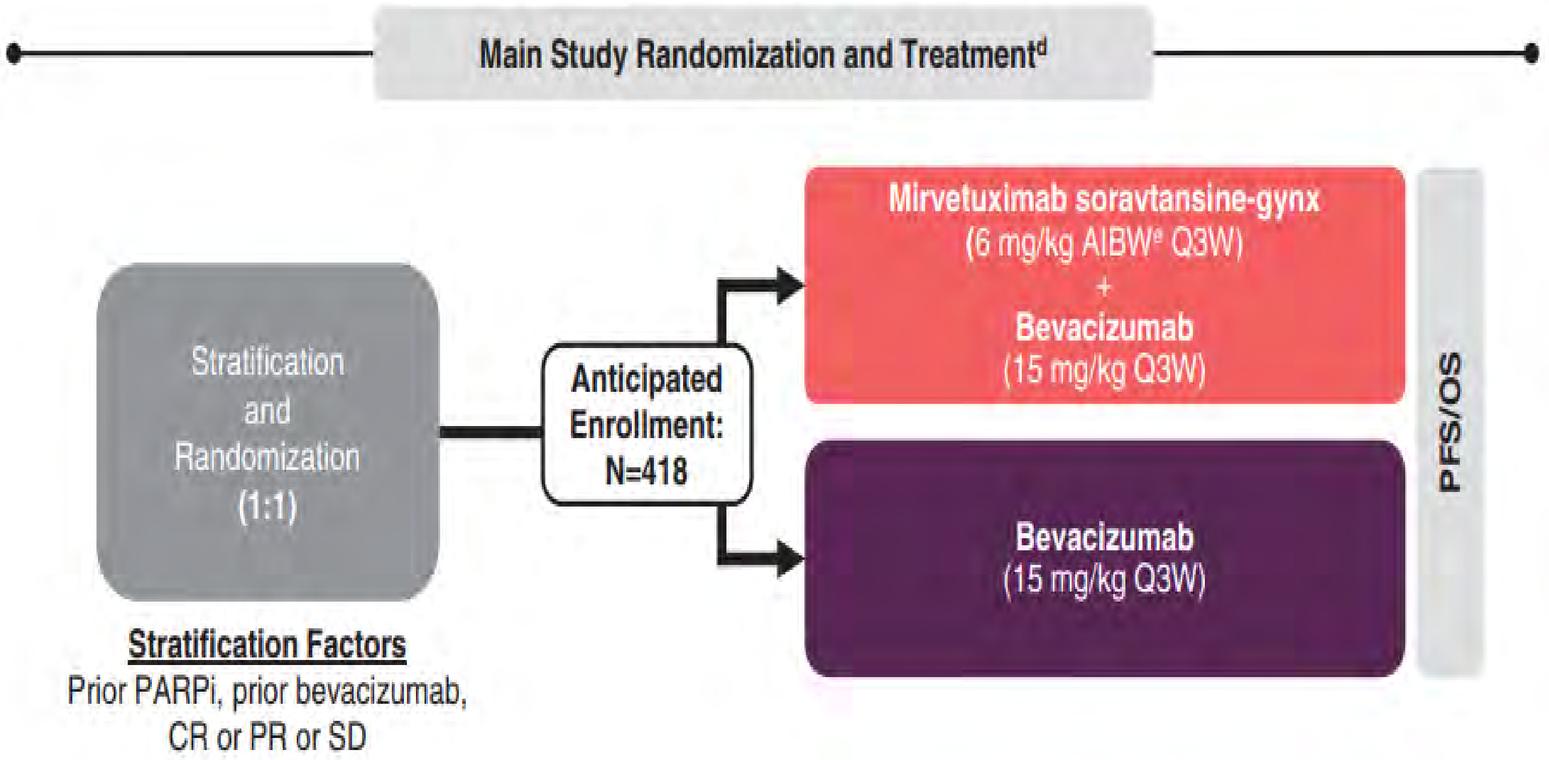
GLORIOSA



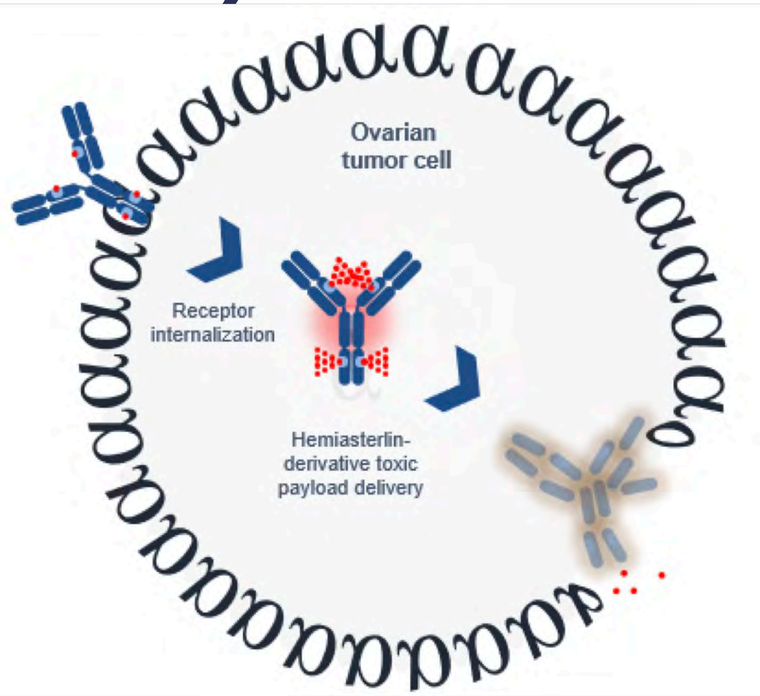
Eligibility

- **Randomized, open-label Phase III trial**
- **MIRV + bev vs Bev as maintenance in FRa high PSOC**
- **Disease must not have progressed after 2L platinum, doublet + bev**
- **Must have had 4-8 prior platinum doublet cycles with bev**
- **Primary endpoint: PFS**
- **Secondary endpoint: OS**

O'Malley D, et al. *Future Oncol.* 2024;20(32):2423-2436. doi:10.1080/14796694.2024.2372241.

Luveltamab (STRO-002-GM1)

Phase 1 dose escalation study with an initial dose ranging expansion cohort in advanced progressive/recurrent epithelial ovarian cancer



- Relapsed and/or progressive disease
- Platinum resistant
  1-3 prior regimens or platinum-sensitive
  2-3 prior lines
- All FolRα levels
- Fresh or archival tissue required
- At least 1 target lesion

1:1

Luveltamab
4.3 mg/kg Q3W
N=23

Luveltamab
5.2 mg/kg Q3W
N=21

- Primary endpoint: ORR by RECIST v1.1
- Secondary endpoints: Safety, PK, PFS, DOR, 12-month OS rate

NCT03748186. Accessed from: www.clinicaltrials.gov/ct2/show/NCT03748186.; Oaknin A, et al. *J Clin Oncol.* 2023;41(suppl 16). doi:10.1200/JCO.2023.41.16_suppl.550.

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Luveltamab (STRO-002-GM1) *cont.*

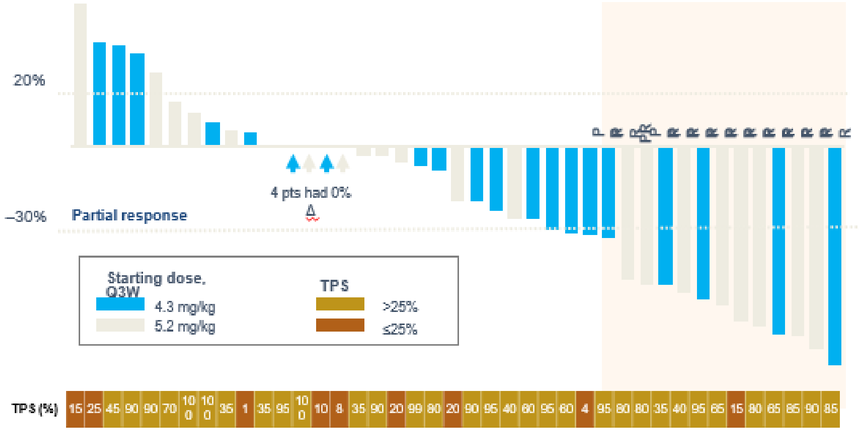
- PROC after 1-3 lines or PSOC after 2-3 lines
- Luveltamab 4.3 or 5.2 mg/kg IV q21d until progression
- FRα not required (analyzed post-study)
- N=44 patients
- Activity seen at both doses
- ORR 31-44%
- Best activity TPS>25%
- Informs Phase 2-3 trial
- Minimal ocular toxicity;
  - Grade 1-2, 23% dry eye

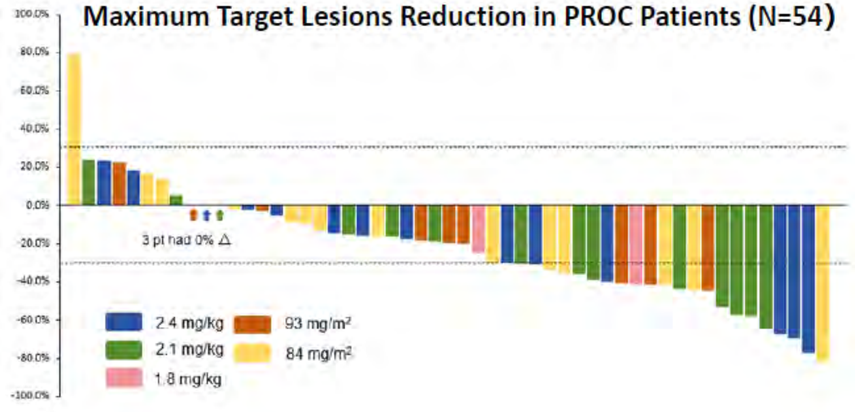
Population	Endpoint	All	4.3 mg/kg	5.2 mg/kg
RECIST Evaluable		N=32 pts	N=16 pts	N=16 pts
	ORR (95% CI)	37.5% (21.1, 56.3)	31.3% (11.0, 58.7)	43.8% (19.8, 70.1)
	mDOR (95% CI)	5.5m (2.5, 11.0)	13m (4.5, NE)	5.4m (2.4, 6.1)
Enrolled		N=35 pts	N=19 pts	N=16 pts
	mPFS (95% CI)	6.1m (4.1, 7.0)	6.1m (4.0, 8.3)	6.6m (2.9, 7.6)

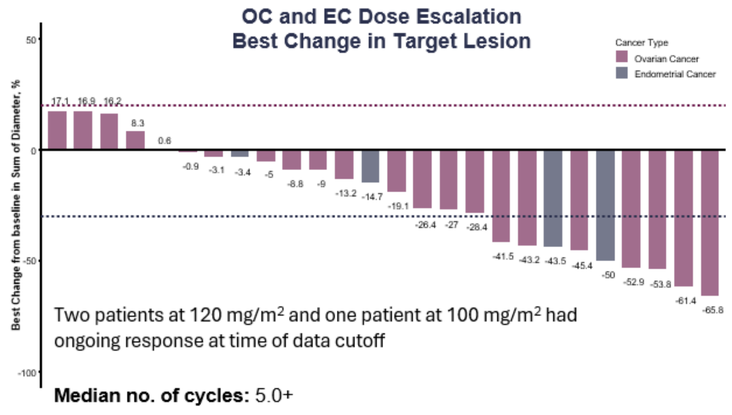
Oaknin A, et al. *J Clin Oncol.* 2023;41(suppl 16). doi:10.1200/JCO.2023.41.16_suppl.550.

Targeting FRα in Ovarian Cancer: What is Next?

	Luveltamab Tazevibulin NCT03748186	BAT-8006 NCT05378737	Rinatabart sesutecan NCT05579366
Payload	SC-209 – Hemiasterelin derivative cytotoxic	Exatecan	Exatecan
ORR	43.8% FRα >25% by TPS (5.2mg/kg) 31.2% (4.3mg/kg)	37% All FRα 39%> 50% FRα 46.7% > 75% FRα	50% (n=18 at 120mg/m2)
mPFS	FRα > 25% 6.1 (95% CI 4.1- 7.2)	7.47 (4.27- NR)	NR
mOS	NR	NR	NR







Oaknin A, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; 31 May-4 June 2024; Chicago, IL USA.; Jia F, et al. Presented at: ASCO 2024.; Lee E, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain.; Shapira-Frommer R, et al. Presented at: ESMO 2024. [Abstract 754P].

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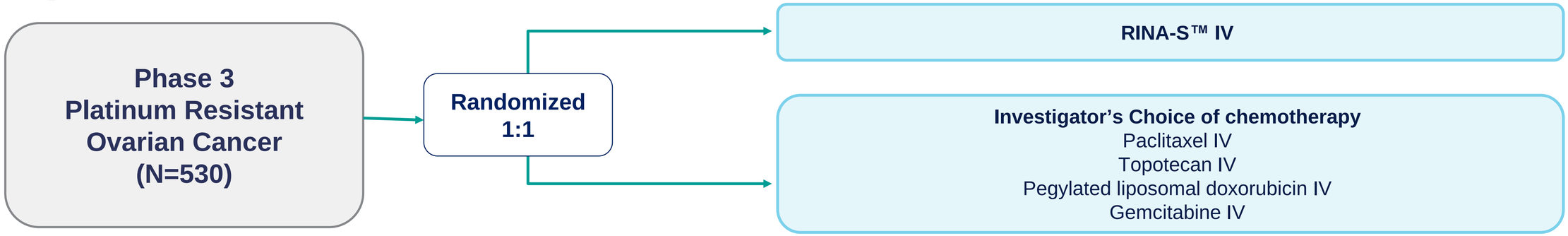
Efficacy of Rina-S Compared to Treatment of Investigator's Choice in Participants with PROC: ENGOT-OV86/GOG-3107/RAINFOL-OV2



Evaluation of Study Objectives*

Primary Outcome Measure

- **Progression-Free Survival**

Secondary Outcome Measures

- **Overall Survival**
- **Objective Response Rate**
- **Duration of Response**
- **CA-125 response by GCIG criteria**
- **Adverse Events**
- **GHS/QoI (EORTC-QLQ-C30)**

Key Inclusion Criteria*

- Histologically or cytologically confirmed high grade serous or endometrioid epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer
- Prior treatment with the following:
  - Platinum-based therapy
  - Bevacizumab (unless contraindicated)
  - PARP inhibitor (if known BRCA mutation)
  - Mirvetuximab (if positive FRα expression and available in the region)
- Platinum-resistant disease
- No prior ADC therapy containing a topoisomerase 1 inhibitor
- No known active central nervous system metastases or carcinomatous meningitis

NCT06619236. Accessed from: https://clinicaltrials.gov/study/NCT06619236.

NCT06619236

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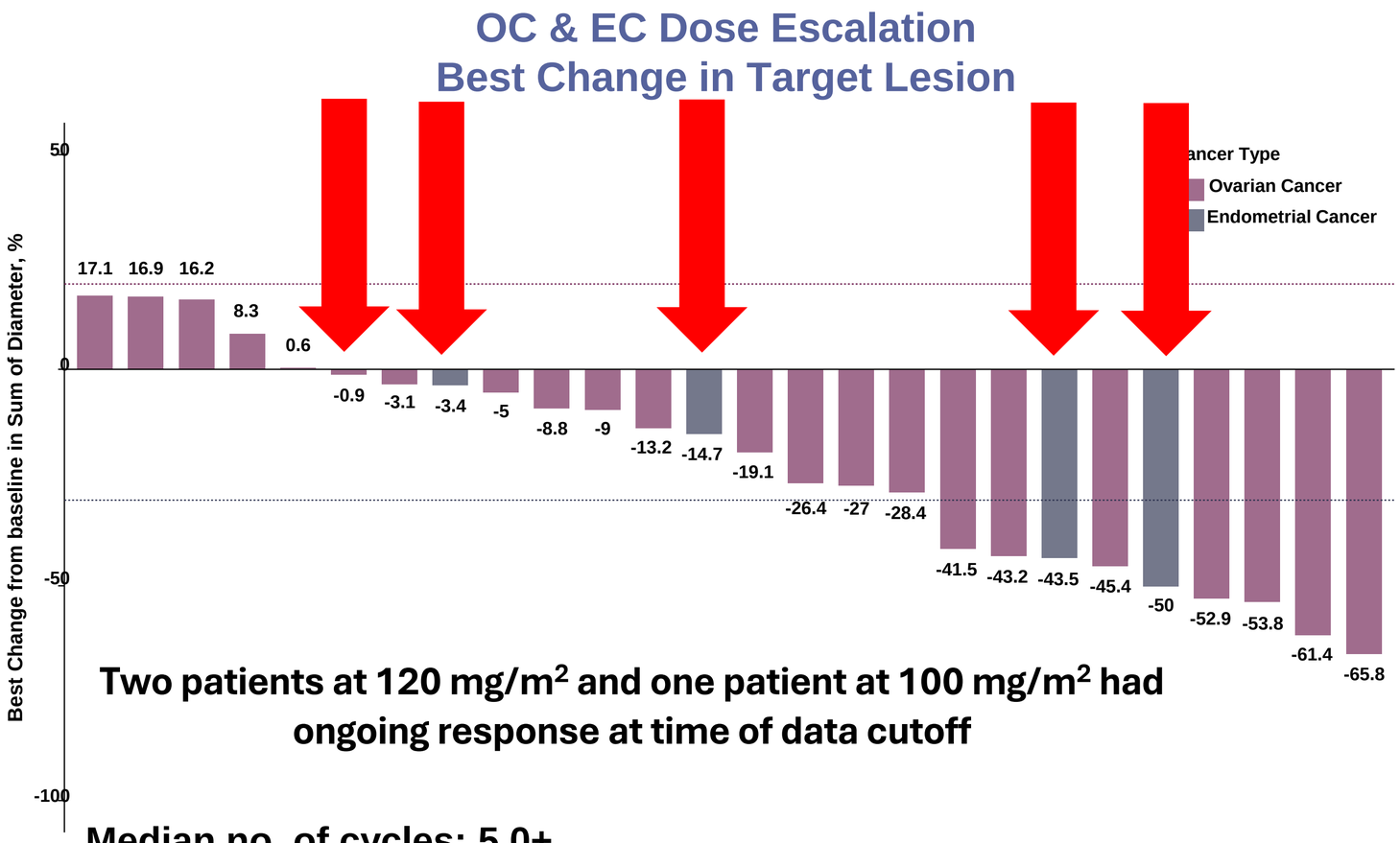
Rinatabart Sesutecan Antitumor Activity | OC, EC – Dose Escalation

Rina-S showed encouraging antitumor activity in heavily pretreated patients with OC and EC

Part A: OC and EC Dose Escalation	
Rina-S (100 mg/m^2 and 120 mg/m^2) n = 26[a]	
Confirmed ORR,[b] % (95% CI)	30.8 (14.3-51.8)
Best overall response,[b] n (%)	
PR	8 (30.8)
SD	15 (57.7)
PD	3 (11.5)
DCR, % (95% CI)	88.5 (69.8-97.6)
Median DOR, weeks (95% CI)	35.3 (20.14-NE)



Two patients at 120 mg/m^2 and one patient at 100 mg/m^2 had ongoing response at time of data cutoff

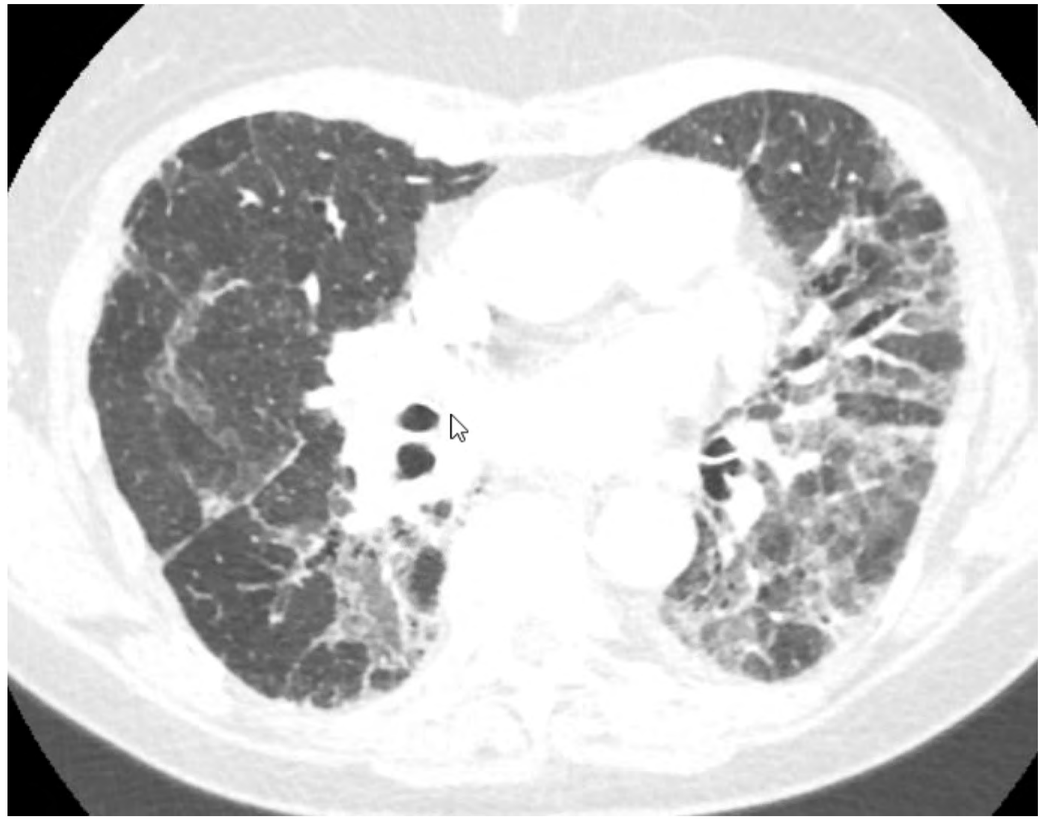
Median no. of cycles: 5.0+

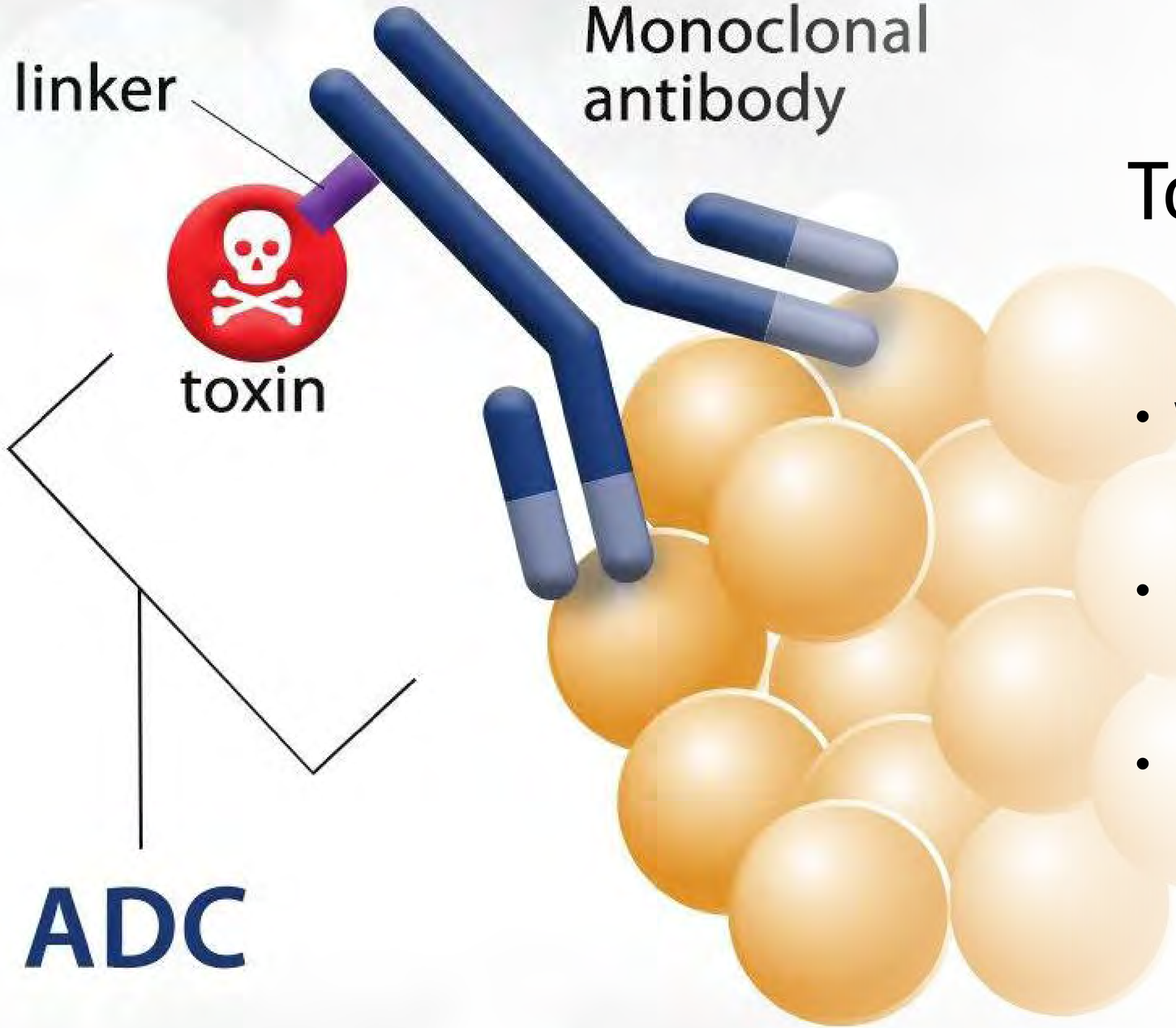
[a]Response-evaluable population. The response evaluable population set includes all treated patients who had a baseline and at least 1 evaluable postbaseline tumor assessment, or who had documented progression of disease at any time after the first dose of Rina-S. Response assessment per RECIST v1.1. [b]Based on investigator assessment. [c]For all patients who received Rina-S 100 mg/m^2 or 120 mg/m^2. [d]For patients with OC and EC who received Rina-S 100 mg/m^2 or 120 mg/m^2. CI confidence interval; DCO, data cutoff; DCR, disease control rate; DOR, duration of response; EC, endometrial cancer; OC, ovarian cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; Rina-S, rinatabart sesutecan; SD, stable disease.

Lee EK, et al. Presented at: Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain.

Case Study

- She receives 3 cycles of TDXd
- Complete response
- And: dyspnea, cough
- Sees pulmonologist – CT, needs O2
  - Continue TDXd
  - Treat with 10 days doxycycline
  - Stop TDXd and give steroids
  - Stop TDXd and give steroids and hospitalize
  - Immediate intubation





Toxicity: Why?

- Wrong target
  - Payload delivered to non-cancerous cell
- Unstable linkers
  - Cleavable linkers with premature release
- Immune responses
  - Secondary damage

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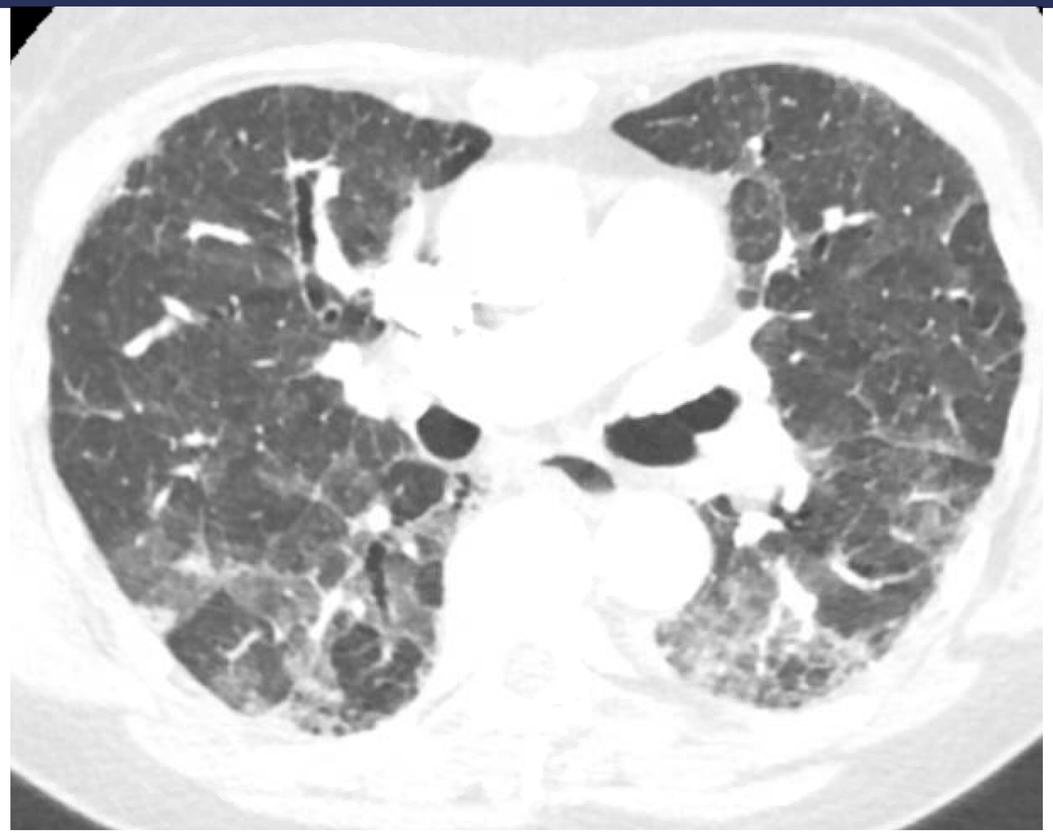
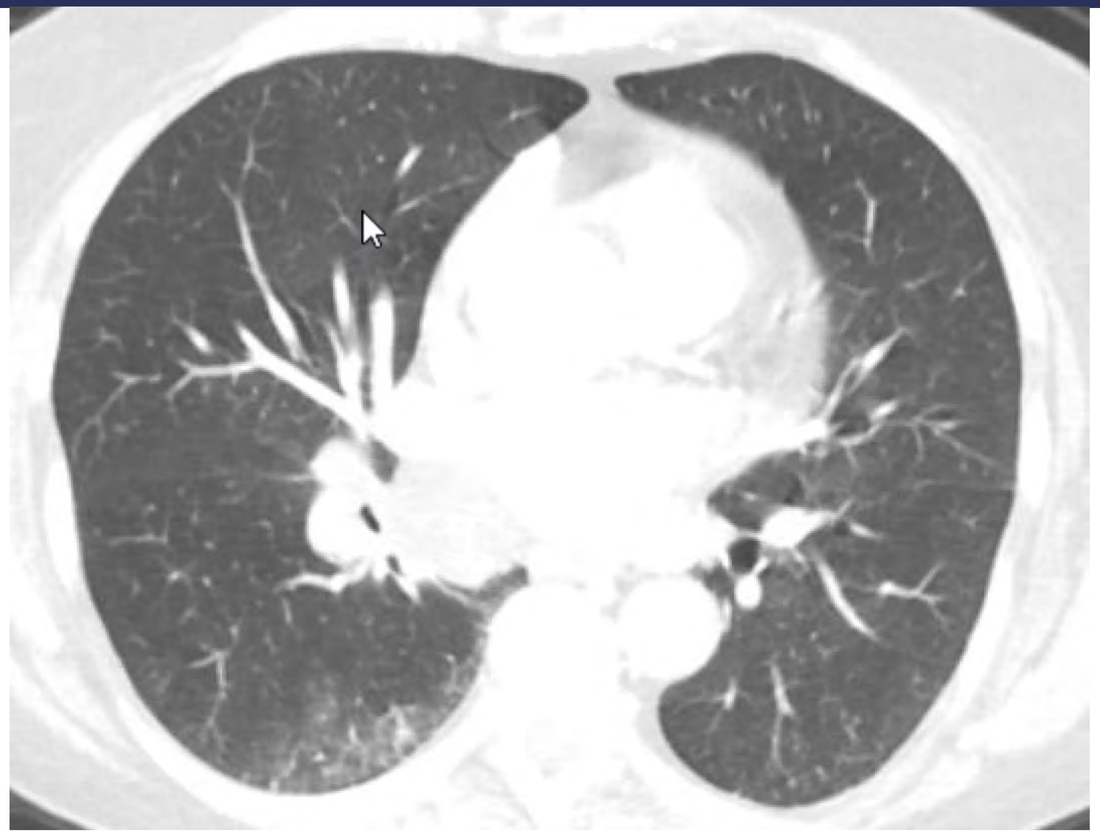
Toxicity Management

Table 1. Recommended Ocular Mitigation Strategies

Ocular Exam	Eye Drops		
Tisotumab Vedotin Baseline + prior to each cycle **Mirvetuximab** Baseline + every other cycle for 1st 8 cycles **Cold Packs** **ONLY Tisotumab Vedotin** Cover eyes with cold packs × 60 mins - start before infusion & use until 20 mins after infusion	**Lubricating** (preservative-free) **Tisotumab Vedotin** OU: Daily + PRN + for 30 days after last cycle **Mirvetuximab** OU: ≥ QID	**Corticosteroid** (Dexamethasone 0.1% or equivalent) **Tisotumab Vedotin** 1 drop OU TID 1st drop - 10min before infusion (days 1-3) **Mirvetuximab** 1 drop OU 6x/day (days 1-4) 1 drop OU QID (days 5-8)	**Vasoconstrictor** (Brimonidine 0.2%) **Tisotumab Vedotin** 3 drops OU right before infusion **Mirvetuximab** Not recommended **Contact Lenses** **Tisotumab Vedotin &** Mirvetuximab **AVOID USE**
	Eye drops products should be separated by 10-15 minutes (Ex. Lubricating drops *wait 10-15 minutes* then administer next product)		

Offerdahl T. *Cancer Therapy Advisor.* 2023. Accessed at: https://www.cancertherapyadvisor.com/features/antibody-drug-conjugates-pose-risk-of-ocular-adverse-effects/.





ILD: Lung Toxicity

CTCAE – Pneumonitis

G1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated

G2: Symptomatic, medical intervention indicated; limiting instrumental ADL

G3: Severe symptoms; limiting self care ADL; oxygen indicated

G4: Life-threatening respiratory compromise; urgent intervention indicated (tracheotomy or intubation)

G5: Death

U.S. Department of Health and Human Services. 2017(Nov). Accessed at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.

ILD: *Lung Toxicity*

- Multidisciplinary team: oncology, pulmonary, radiology, pharmacy

- High index of suspicion

- Grade by CTCAE

Grade 1:
- STOP ADC, monitor
- Prednisone >0.5 mg/kg/d
- Repeat chest CT in 2w

Improvement?
- 4 week taper
- Can restart at same dose if baseline reached in <4w
- Can restart at dose reduction if baseline >4w
- NO improvement – see G2

Grade 2:
- STOP ADC, monitor
- Prednisone 1 mg/kg/d
- Repeat chest CT in 1w

Improvement in 1 week?
- Steroids until G0
- Minimum of 4w taper
- Possible restart with dose reduction
- NO improvement – see G3/4

Grade 3/4:
- **<u>STOP ADC PERMANENTLY</u>**
- Monitor, consider admitting
- Prednisolone 500-1000mg/dx3d, then IV prednisone >0.5 mg/kg/d
- Infection prevention

Improvement in 1 week?
- Steroids until G0
- Minimum of 4w taper
- **NO MORE ADC**
- **NO improvement: ICU**

Xu, C, et al. *Cancer.* 2023;129(4):789-798.

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ILD: *Management*

Assess up front

- H/O lung disease, smoker, elderly, frail
- Baseline CT and frequent monitoring

Monitor

- **STOP ADC if suspected**; may be radiologic change or symptoms (dyspnea, cough, fever)

Confirm

- High resolution CT, pulmonology consult, cultures, CBC, pulse ox, PFTs, ABG
- Follow until resolution

Manage

- **STOP <u>upon suspicion</u>**
- G 1-2: Stop until fully resolved
- G 3-4: Stop permanently

Follow-up

- CT q3-4m, pulmonary rehab, NO similar drugs

Xu, C, et al. *Cancer.* 2023;129(4):789-798.

GI Toxicity Mitigation Strategies for ADCs

- **Dose optimization**: Adjusting the dose, frequency, or duration of treatment
- **Response-guided dose adjustments**: Adapting the dose based on the patient's initial response
- **Supportive treatment**: Reducing the severity of toxicity with additional treatment
- **Treatment delays or discontinuation**: Stopping or delaying treatment in some cases
- **Co-dosing with antibody backbones**: Administering ADCs with antibody backbones to reduce toxicity
- **Complete blood count (CBC) assessment**: Evaluating blood counts before and during treatment to identify and manage hematological toxicities

Wrap Up & Key Takeaways with Panel & Audience

GOG FOUNDATION®
Transforming the standard of care

EC Case Studies:

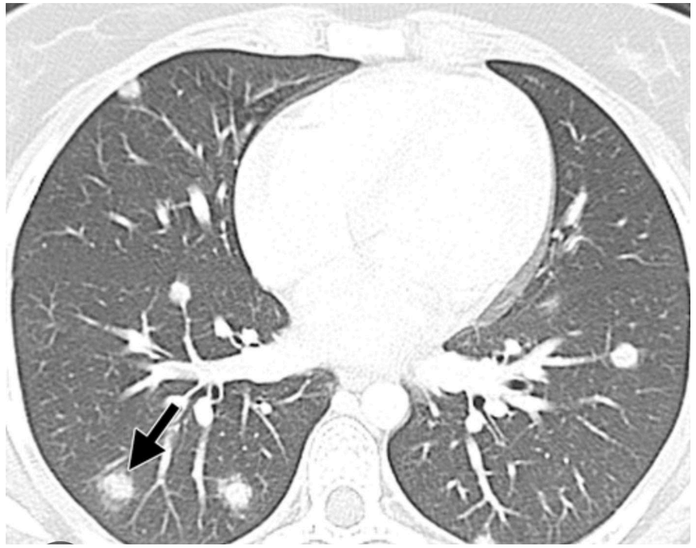
An Interactive Discussion

GOG FOUNDATION®
Transforming the standard of care

59-year-old with Recurrent Stage IB High-Grade Serous EC (pMMR)

- 59-year-old with Stage IB high-grade serous endometrial cancer (pMMR), TP53 Mutated
- Surgery followed by carboplatin and paclitaxel x 6 cycles completed 9 months ago
- Presents with persistent cough. CT scans demonstrates multiple pulmonary nodules and carcinomatosis in abdomen
- Biopsy confirms recurrent EC, with HER2 IHC 0 status. She declines participation in a clinical trial

- **Recommendations?**
  - Role for PARPi
- **Case Modifications:**
  - What if recurred at 14 months?
  - What if HER2 IHC 3+?
  - What if carcinosarcoma?
  - What if recurrent stage IB pMMR, P53 WT, ER-strong positive--> role for hormone therapy?



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2025 SGO Winter Meeting
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