TARGETED AGENTS FOR UTERINE & OVARIAN CANCER

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OBJECTIVES

- 1. Review biomarker testing for Uterine Cancer
- 2. Review targeted agents used for Uterine Cancer
- 3. Review biomarker testing for Ovarian Cancer
- 4. Review targeted agents used for Ovarian Cancer

ENDOMETRIAL CANCER

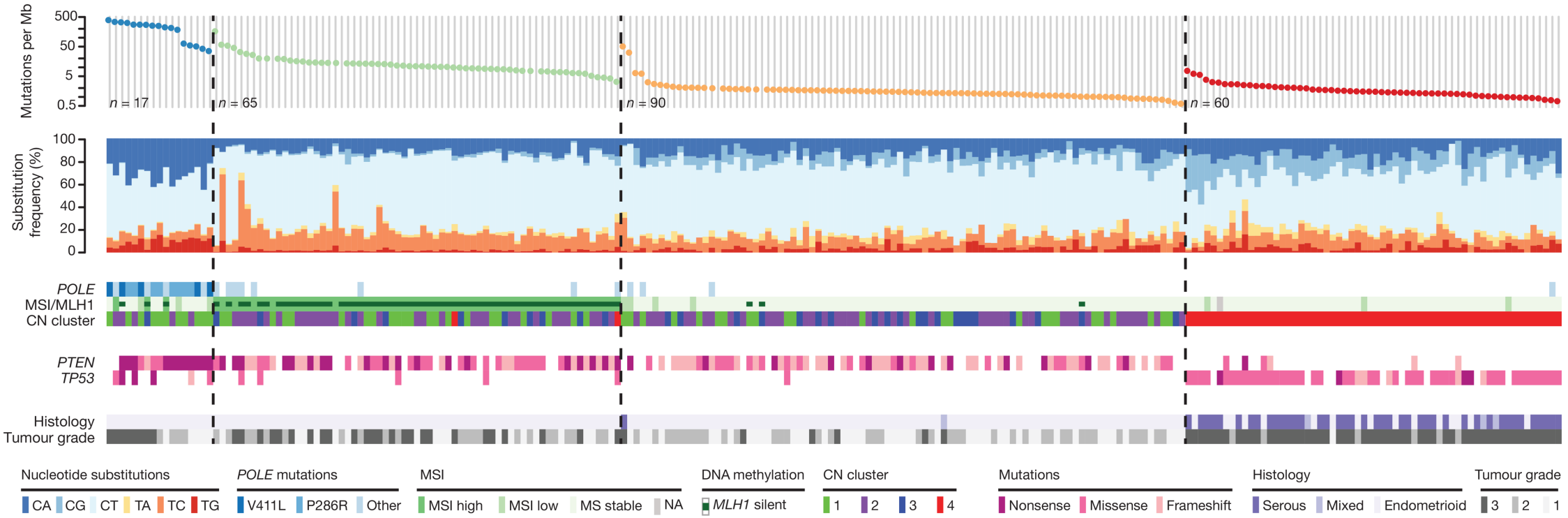
Endometrial Carcinomas Can Be Classified Into 4 Molecular Subgroups

1. *POLE* **(ultramutated)**

2. MSI **(hypermutated)**

3. Copy-number low **(endometrioid)**

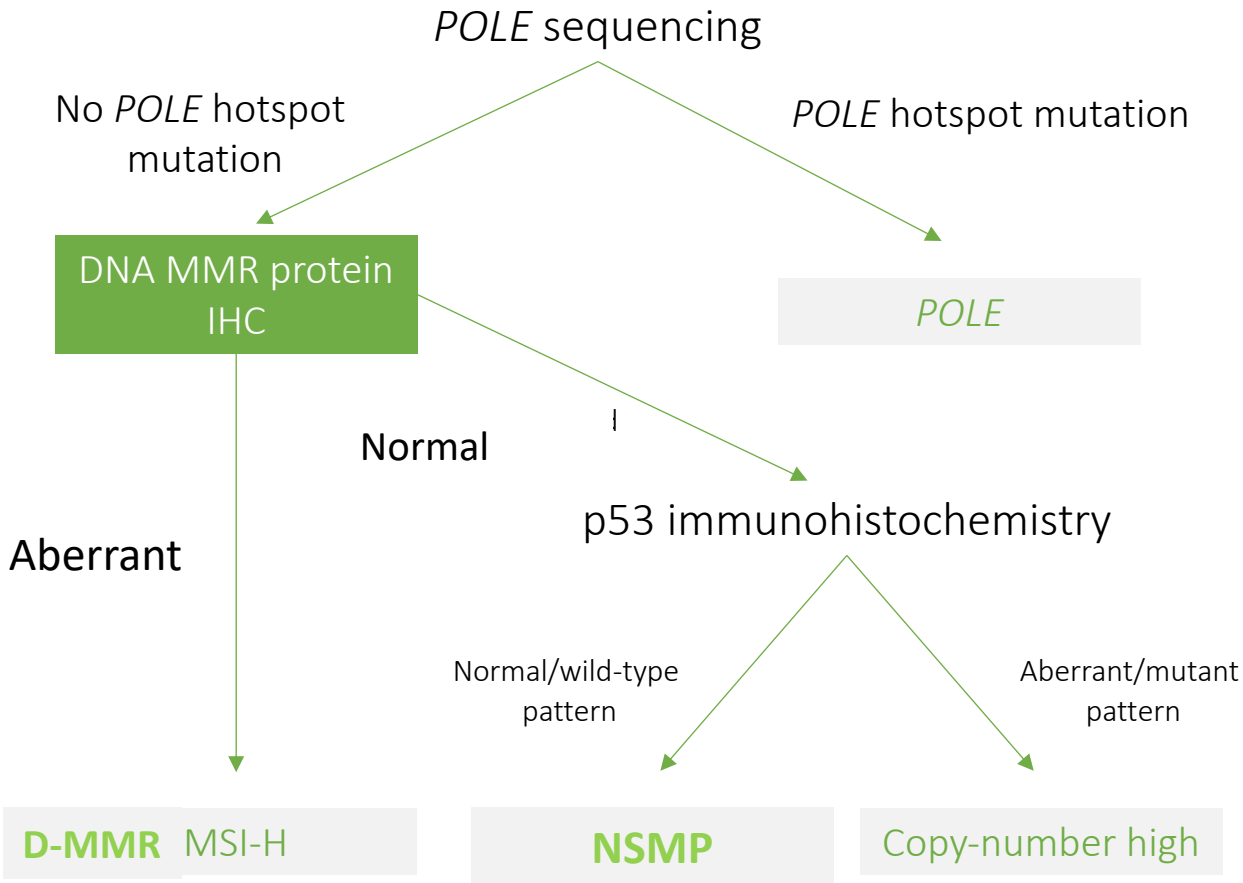
4. Copy-number high **(serous-like)**



The Cancer Genome Atlas Research Network. *Nature*. 2013;497(7447):67-73.

NCCN Guidelines® (V1.2024) Biomarker Testing Recommendations for Endometrial Carcinoma

- 4 clinically significant molecular subgroups identified with different clinical prognoses:
  - *POLE* mutations
  - MSI-H
  - NSMP
  - P53 Aberrant

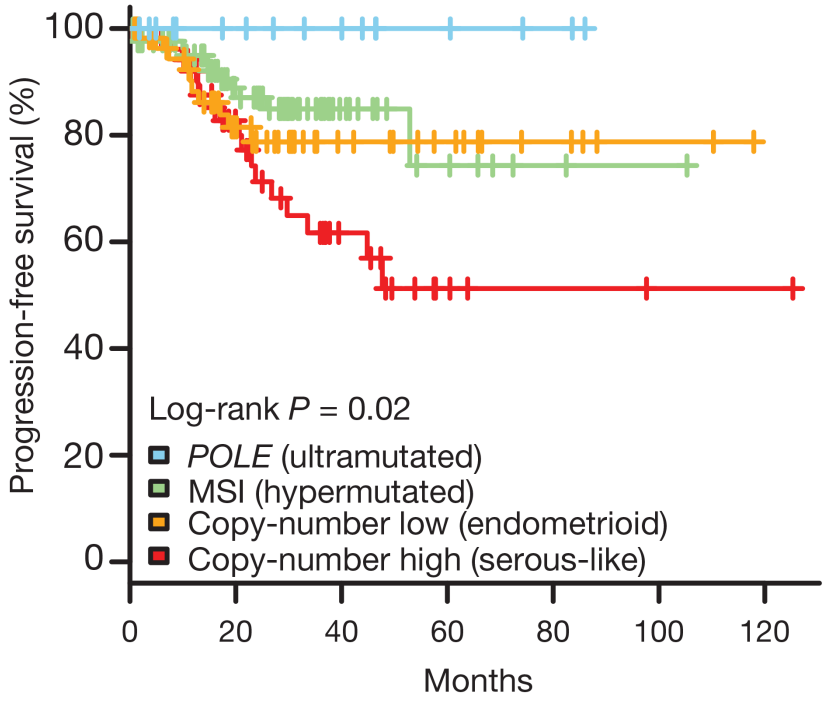


NCCN Guidelines. Version 1.2024-Jan, 2024. Uterine Neoplasms.

Prognostic Value of Molecular Classification in EC

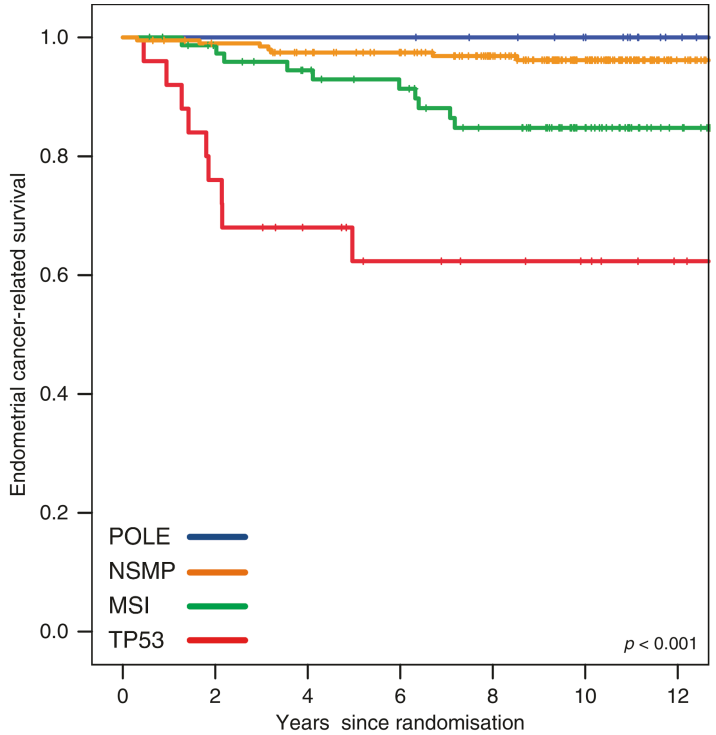
TCGA[1]

PFS (n=373)



PORTEC-2: EBRT vs VBT in High-Risk EC[2]

EC-related survival (n=317)



Number at risk							
POLE	16	16	16	16	14	11	3
NSMP	199	193	184	175	148	98	20
MSI	77	71	64	58	49	31	6
TP53	25	19	14	10	8	6	2

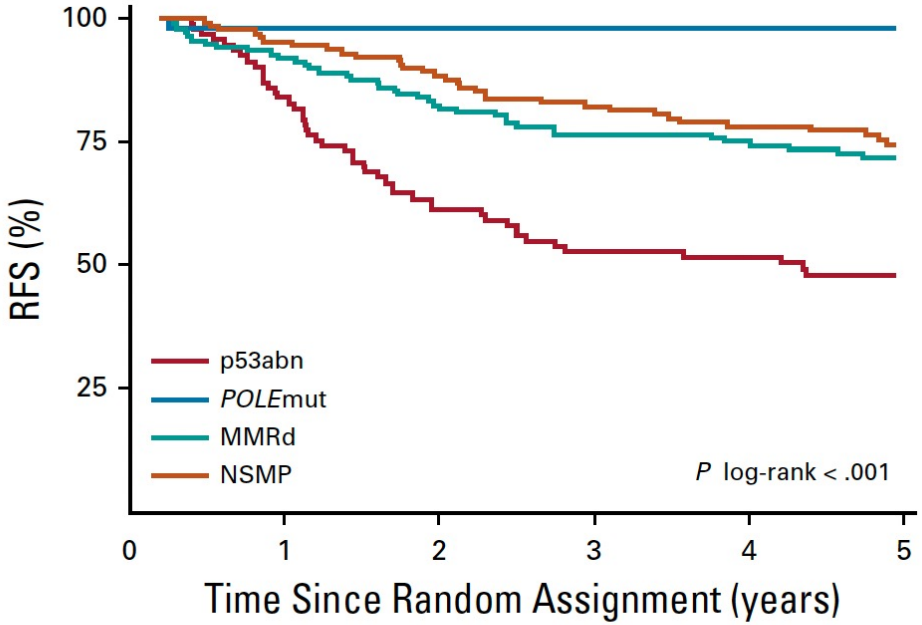
- ***POLE*mut tumors have significantly better survival, whereas *p53*mut (copy-number high) tumors have the poorest outcomes**

1. The Cancer Genome Atlas Research Network. *Nature*. 2013;497(7447):67-73. **2.** Wortman BG, et al. *Br J Cancer.* 2018;119(9):1067-1074.

Prognostic Value of Molecular Classification in EC

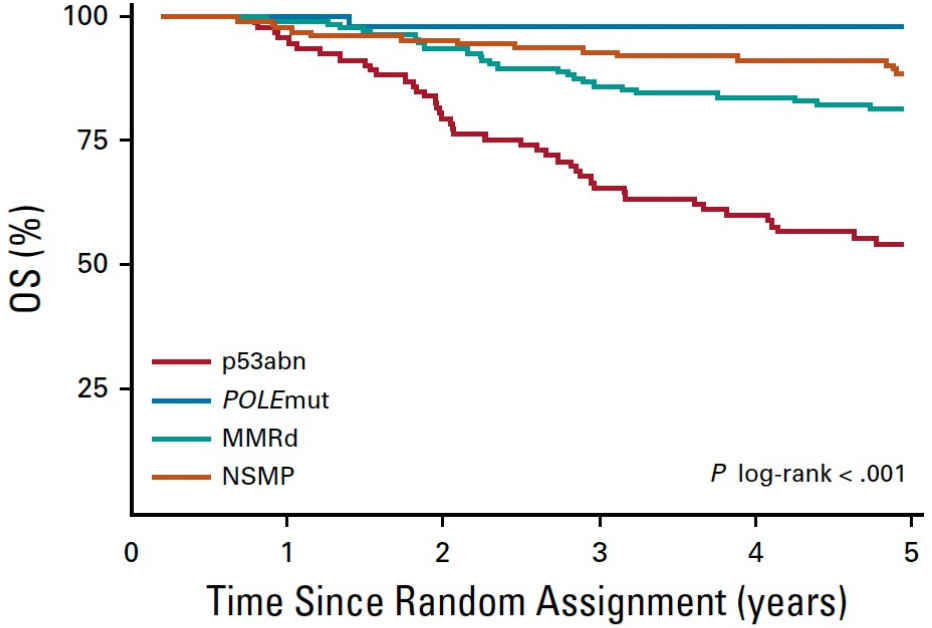
PORTEC-3: CTRT vs RT in High-Risk EC (n=410)

5-year RFS



No. at risk:						
p53abn	93	72	57	49	44	32
*POLE*mut	51	50	50	49	48	37
MMRd	137	124	112	102	96	74
NSMP	129	122	113	105	94	69

5-year OS



No. at risk:						
p53abn	93	87	71	61	52	37
*POLE*mut	51	51	50	49	48	37
MMRd	137	136	128	115	108	85
NSMP	129	125	122	118	110	85

- **Patients with *p53*abn EC had the poorest prognosis**

León-Castillo A, et al. *J Clin Oncol.* 2020;38(29):3388-3397.

Updated FIGO EC Recommendations (2023)

- Data and analyses from the molecular and histological classifications performed and published in the recently developed ESGO/ESTRO/ESP guidelines were used as a template for adding the new subclassifications to the proposed molecular and histological staging system
- Complete molecular classification (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all endometrial carcinomas and as potential influencing factors of adjuvant or systemic treatment decisions
  - If the molecular subtype is known, this is recorded in the FIGO stage by the addition of "m" for molecular classification, and a subscript indicating the specific molecular subtype
  - When molecular classification reveals p53abn or POLEmut status in Stages I and II, this results in upstaging or downstaging of the disease ($IICm_{p53abn}$ or $IAm_{POLEmut}$)

Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage $IAm_{-POLEmut}$	*POLE*mut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage $IICm_{-p53abn}$	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion and regardless of the degree of LVSI or histologic type

Prognosis	Definition
Good prognosis	Pathogenic *POLE* mutation (*POLE*mut)
Intermediate prognosis	Mismatch repair deficiency (dMMR)/microsatellite instability (MSI) dMMR/MSI and no specific molecular profile (NSMP)
Poor prognosis	p53 abnormal (p53abn)

Berek JS, et al. *Int J Gynaecol Obstet.* 2023;162(2):383-394.

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

RECURRENT DISEASE[h,i]

First-Line Therapy for Recurrent Disease[j]	Second-Line or Subsequent Therapy
Preferred • Carboplatin/paclitaxel (category 1 for carcinosarcoma)[k,7] • Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1)[b,c,d,8] • Carboplatin/paclitaxel/dostarlimab-gxly (category 1)[c,d,e,9] • Carboplatin/paclitaxel/trastuzumab[d,g] (for HER2-positive uterine serous carcinoma)[d,10] • Carboplatin/paclitaxel/trastuzumab[d,g] (for HER2-positive carcinosarcoma)[f,10] **Other Recommended Regimens** • Carboplatin/docetaxel[l] • Carboplatin/paclitaxel/bevacizumab[d,m,11,12] **Useful in Certain Circumstances (Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant)** • MMR-proficient (pMMR) tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,13] • TMB-H tumors[n] ▸ Pembrolizumab[c,14] • MSI-H/dMMR tumors[o] ▸ Pembrolizumab[c,15] ▸ Dostarlimab-gxly[c,16]	**Other Recommended Regimens** • Cisplatin/doxorubicin[17] • Cisplatin/doxorubicin/paclitaxel[p,14] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[14] • Albumin-bound paclitaxel[q] • Topotecan • Bevacizumab[m,r,19] • Temsirolimus[20] • Cabozantinib • Docetaxel (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[21] • Cisplatin/ifosfamide (for carcinosarcoma) **Useful in Certain Circumstances (Biomarker-directed therapy)** • pMMR tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,13] • TMB-H tumors[n,12] ▸ Pembrolizumab[c] • MSI-H/dMMR tumors[o] ▸ Pembrolizumab[c,15] ▸ Dostarlimab-gxly[c,16] ▸ Avelumab[c] ▸ Nivolumab[c,22] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[23] • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib

NCCN Guidelines® (V1.2024)

Systemic Therapy for Endometrial Carcinoma

Primary or Adjuvant Treatment	
Preferred Regimens	▪ Carboplatin/paclitaxel ▪ Carboplatin/paclitaxel/pembrolizumab (for stage III-IV tumors, except for carcinosarcoma) (Category 1) ▪ Carboplatin/paclitaxel/dostarlimab-gxly (for stage III-IV tumors) (Category 1) ▪ Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive uterine serous carcinoma) ▪ Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive carcinosarcoma) (Category 2B)

NCCN Guidelines. Version 2.2023-April 28, 2023. Uterine Neoplasms.

NCCN Guidelines® (V1.2024)

Systemic Therapy for Endometrial Carcinoma

Recurrent Disease			
Setting	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances (Biomarker directed: after prior systemic therapy)**
1L Therapy	▪ Carboplatin/paclitaxel ▪ Carboplatin/paclitaxel/pembrolizumab (for stage III-IV tumors, except for carcinosarcoma) (Category 1) ▪ Carboplatin/paclitaxel/dostarlimab-gxly (for stage III-IV tumors) (Category 1) ▪ Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive uterine serous carcinoma) ▪ Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive carcinosarcoma) (Category 2B)	▪ Carboplatin/docetaxel ▪ Carboplatin/paclitaxel/bevacizumab	▪ Lenvatinib/pembrolizumab (Category 1) for MMRp tumors ▪ Pembrolizumab (Category 1) for TMB-H or MSI-H/dMMR tumors ▪ Dostarlimab-gxly for dMMR/MSI-H tumors
2L or Subsequent Line of Therapy		▪ Cisplatin/doxorubicin ▪ Cisplatin/doxorubicin/ paclitaxel ▪ Cisplatin ▪ Carboplatin ▪ Doxorubicin ▪ Liposomal doxorubicin ▪ Paclitaxel ▪ Albumin-bound paclitaxel ▪ Topotecan ▪ Bevacizumab ▪ Temsirolimus ▪ Cabozantinib ▪ Docetaxel (Category 2B) ▪ Ifosfamide (for carcinosarcoma) ▪ Ifosfamide/paclitaxel (for carcinosarcoma) ▪ Cisplatin/ifosfamide (for carcinosarcoma)	▪ Lenvatinib/pembrolizumab (Category 1) for MMRp tumors ▪ Pembrolizumab for TMB-H or MSI-H/dMMR tumors ▪ Dostarlimab-gxly for dMMR/MSI-H tumors ▪ Larotrectinib or entrectinib for NTRK gene fusion–positive tumors (Category 2B) ▪ Avelumab for dMMR/MSI-H tumors ▪ Nivolumab for dMMR/MSI-H tumors ▪ Fam-trastuzumab deruxtecan-nxki for Her2 + (IHC 3+ or 2+)

NCCN Guidelines. Version 2.2023-April 28, 2023. Uterine Neoplasms.

NCCN Guidelines® (V1.2024)

Systemic Therapy for Endometrial Carcinoma

Recurrent, Metastatic, or High-Risk Disease		
	Preferred Regimens	**Other Recommended Regimens**
Hormone therapy	▪ Megestrol acetate/tamoxifen (alternating) ▪ Everolimus/letrozole	▪ Medroxyprogesterone acetate/tamoxifen (alternating) ▪ Progestational agents — Medroxyprogesterone acetate — Megestrol acetate ▪ Aromatase inhibitors ▪ Tamoxifen ▪ Fulvestrant

NCCN Guidelines. Version 1.2024. Uterine Neoplasms.

Approved Combination IO Approaches in Advanced/Recurrent EC: Phase 3 KEYNOTE-775 Study Design and Key Results

KEYNOTE-775

Key Eligibility Criteria

- Advanced, metastatic, or recurrent EC
- Measurable disease by BICR
- 1 prior platinum-based chemotherapy regimen[a]
- ECOG PS 0-1
- Tissue available for MMR testing

1:1

Lenvatinib + Pembrolizumab	Physician's Choice
Lenvatinib 20 mg po qd + Pembrolizumab[b] 200 mg IV q3w	Doxorubicin 60 mg/m^2 IV q3w[c] OR Paclitaxel 80 mg IV mg/m^2 IV q1w (3 weeks on/ 1 week off)

Treat until progression or unacceptable toxicity

Stratification Factors

- MMR status (dMMR vs MMRp)
- MMRp by ECOG PS, geographic region, prior pelvic radiation

Primary Endpoints

- PFS by BICR and OS

Secondary Endpoints

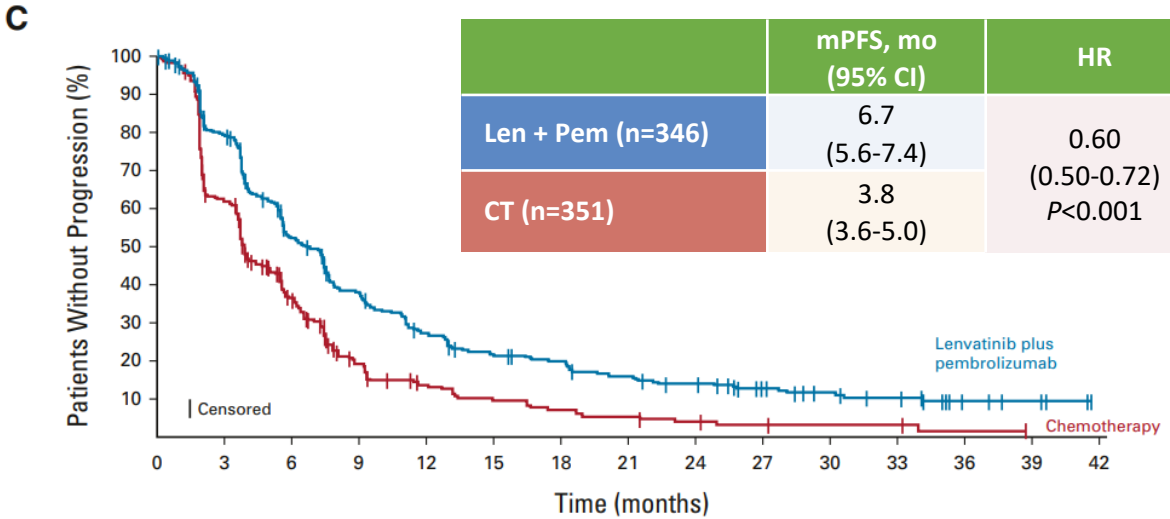
- ORR, HRQoL, PK, safety

Key Exploratory Endpoint

- DOR

mPFS in KEYNOTE-775: MMRp[c]

C



	mPFS, mo (95% CI)	HR
Len + Pem (n=346)	6.7 (5.6-7.4)	0.60 (0.50-0.72) *P*<0.001
CT (n=351)	3.8 (3.6-5.0)	

MMRp population	ORR, % (95% CI)	mDOR, mo (range)	mOS, mo (95% CI)	HR
Len + Pem (n=346)	32.4 (27.5-37.6)	9.3 (1.6+-39.5+)	18.0 (14.2-19.9)	0.70 (0.56-0.83)
CT (n=351)	15.1 (11.5-19.3)	5.7 (0.0+-37.1+)	12.2 (11.0-14.1)	

[a] Patients may have received up to 2 prior platinum-based CT regimens if 1 was given in the neoadjuvant or adjuvant treatment setting.
[b] Maximum of 35 doses. [c] Maximum cumulative dose of 500 mg/m^2. [c]These data were full FDA approval based on mPFS of 6.6 vs 3.8 (HR 0.60) and mOS of 17.4 vs 12.0 (HR 0.68). Makker V, et al. *J Clin Oncol.* 2023;JCO2202152. doi:10.1200/JCO.22.02152.

Approved Single-Agent IO Approaches in Advanced/Recurrent EC: Phase 2 KEYNOTE-158 and Phase 1 GARNET Study Designs

KEYNOTE-158[1,2]

Key Eligibility Criteria
- MSI-H/dMMR advanced EC
- Progression on or intolerance to ≥1 line of standard treatment for unresectable and/or metastatic disease
- Measurable disease per RECIST v1.1
- ECOG PS 0-1
- Provision of a tumor sample for biomarker assessment

Cohort D: EC regardless of MSI status and excluding sarcomas and mesenchymal tumors

Cohort K: any MSI-H/dMMR advanced solid tumor except colorectal

Pembrolizumab
200 mg IV q3w for 35 cycles (2 years) or until disease progression,[a] intolerable toxicity, investigator decision, or patient withdrawal

Primary Endpoint
- ORR per RECIST v1.1 (ICR)

Secondary Endpoints
- DOR and PFS per RECIST v1.1 (ICR)
- OS and safety

GARNET[3,4]

Key Eligibility Criteria
- Advanced or recurrent EC
- Progression on or after platinum doublet therapy
- ≤2 prior lines of treatment for recurrent or advanced disease
- Measurable disease at baseline
- Anti–PD-(L)1 naive

Cohort A1: dMMR /MSI-H EC

Cohort A2: pMMR/MSS EC

Dostarlimab
500 mg IV q3w for 4 cycles, then 1000 mg IV q6w until disease progression

Primary Endpoints
- ORR and DOR (BICR)

Secondary Endpoints
- irORR, irDCR, irDOR (irRECIST)
- DCR (BICR)

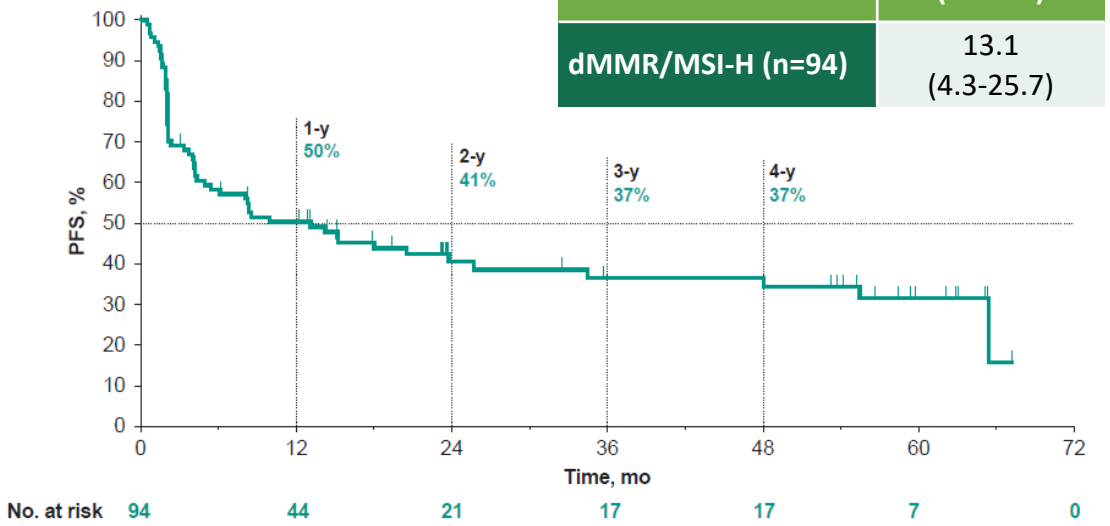
This slide is for illustration only and not for cross-trial comparisons. Side-by-side data should be interpreted with great caution.
[a] Clinically stable patients with radiologic progression could remain on treatment until progression was confirmed on subsequent imaging assessment.

1. O'Malley DM, et al. ESMO 2022. Abstract 546P. **2.** O'Malley DM, et al. *J Clin Oncol.* 2022;40(7):752-761. **3.** Oakin A, et al. *J Immunother Cancer.* 2022;10(1):e003777. **4.** Tinker A, et al. ESMO 2022. Abstract 548P.

Approved Single-Agent IO Approaches in Advanced/Recurrent EC: Phase 2 KEYNOTE-158 and Phase 1 GARNET Key Results

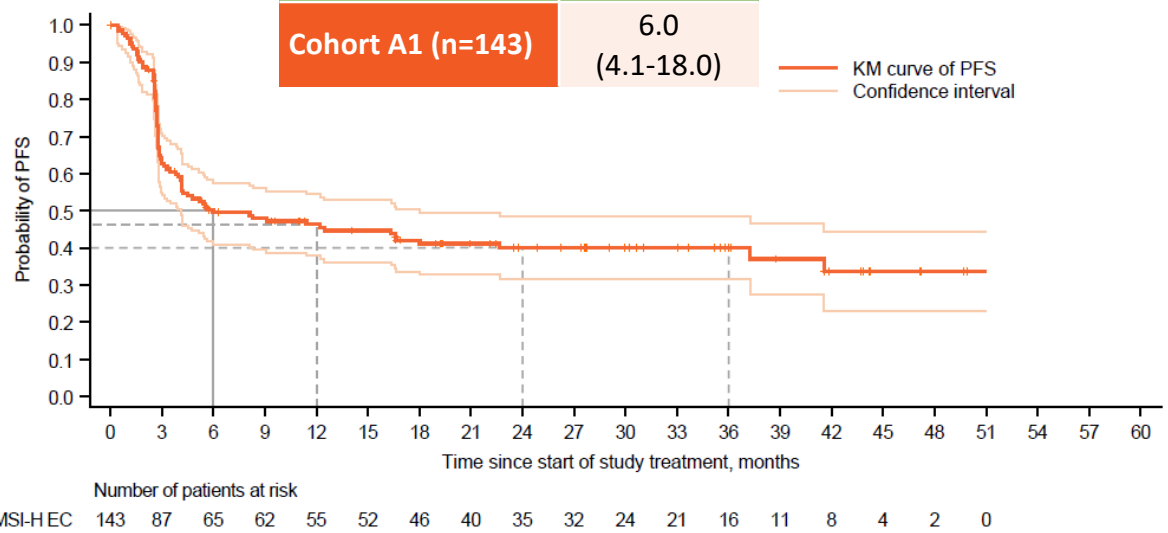
mPFS in KEYNOTE-158: dMMR/MSI-H[1,2,a]

	mPFS, mo (95% CI)
dMMR/MSI-H (n=94)	13.1 (4.3-25.7)



mPFS in GARNET: dMMR/MSI-H[3,4,b]

	mPFS, mo (95% CI)
Cohort A1 (n=143)	6.0 (4.1-18.0)



Prior lines of therapy, no.(%)		ORR, % (95% CI)	mDOR, mo (95% CI)	mOS, mo (95% CI)
1	49 (52)	50%	63.2 (2.9-63.2)	65.4 (29.5-NR)
2	21 (22)			
3	15 (16)			
≥4	9 (10)			

Prior lines of therapy, no.(%)		ORR, % (95% CI)	mDOR, mo (95% CI)	mOS, mo (95% CI)
1	90 (62.9)	45.5 (37.1-54.0)	NR (1.18+ - 47.21+)	NR (27.1-NR)
2	35 (24.5)			
≥3	18 (12.6)			

This slide is for illustration only and not for cross-trial comparisons. Side-by-side data should be interpreted with great caution.

[a] The median follow-up time was 54.5 months. [b] The median follow-up time was 27.6 months.

1. O'Malley DM, et al. ESMO 2022. Abstract 546P. **2.** O'Malley DM, et al. *J Clin Oncol.* 2022;40(7):752-761. **3.** Oakin A, et al. *J Immunother Cancer.* 2022;10(1):e003777. **4.** Tinker A, et al. ESMO 2022. Abstract 548P.

Phase 3 Clinical Trial Data With 1L IO: Study Designs

NRG-GY018[1,2]

Key Eligibility Criteria
- Measurable stage III/IVA or measurable/nonmeasurable stage IVB or recurrent EC
- No prior Chemo except prior adjuvant Chemo if completed ≥12 months before study
- ECOG PS 0-1 or 2

Randomization 1:1

Pembrolizumab 200 mg IV q3w **Paclitaxel** 175 mg/m^2 IV q3w **Carboplatin** AUC 5 IV q3w for 6 cycles	**Pembrolizumab** 400 mg IV q6w for up to 14 additional cycles
Placebo IV q3w **Paclitaxel** 175 mg/m^2 IV q3w **Carboplatin** AUC 5 IV q3w for 6 cycles	**Placebo** IV q6w for up to 14 additional cycles

Stratification Factors
- MMR/MSI status
- ECOG PS (0-1 vs 2)
- Prior adjuvant Chemo

Primary Endpoints
- PFS per RECIST v1.1 by investigator in MMRp and dMMR populations

Secondary Endpoints
- Safety, ORR/DOR, OS (MMRp and dMMR), QOL (MMRp)

GOG-3031/RUBY Part 1[3,4]

Key Eligible Patients
- Histologically/cytologically proven advanced or recurrent EC
- Stage III/IV disease or first recurrent EC with low potential for cure by Rt or Sx alone or in combination
  - Carcinosarcoma, clear cell, serous, or mixed histology permitted
- Naive to systemic therapy or systemic anticancer therapy and recurrence/PD ≥6 months after completing treatment
- ECOG PS 0-1

Randomization 1:1

Dostarlimab IV 500 mg **Carboplatin** AUC 5 mg/mL/min **Paclitaxel** 175 mg/m^2 q3w for 6 cycles	**Dostarlimab IV** 1000 mg q6w up to 3 years
Placebo **Carboplatin** AUC 5 mg/mL/min **Paclitaxel** 175 mg/m^2 q3w for 6 cycles	**Placebo IV** q6w up to 3 years

Stratification Factors
- MMR/MSI status
- Prior pelvic RT
- Disease status

Primary Endpoints
- PFS by INV
- OS

Secondary Endpoints
- PFS by BICR, PFS2, ORR, DOR, DCR , HRQoL/PRO, safety

This slide is for illustration only and not for cross-trial comparisons. Side-by-side data should be interpreted with great caution.

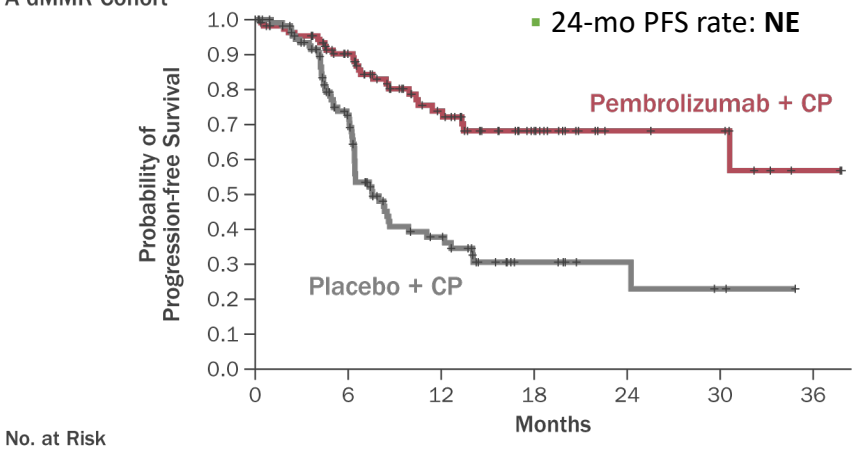
1. Eskander RN, et al. SGO 2023. Abstract 264. **2.** Eskander RN, et al. *N Engl J Med.* 2023. doi:10.1056/NEJMoa2302312
3. Mirza MR, et al. SGO 2023. Abstract 265. **4.** Mirza MR, et al. *N Engl J Med.* 2023. doi: 10.1056/NEJMoa2216334

Most Recent Clinical Trial Data With 1L IO: Key Efficacy

NRG-GY018: PFS in dMMR Population[1,2,a]

	Events, n/N	Median (95% CI), mo	HR stratified; 95% CI
Pembrolizumab + CP	26/112	NR (30.6-NR)	0.30 (0.19-0.48) *P*<0.00001
Placebo + CP	59/113	7.6 (6.4-9.9)	

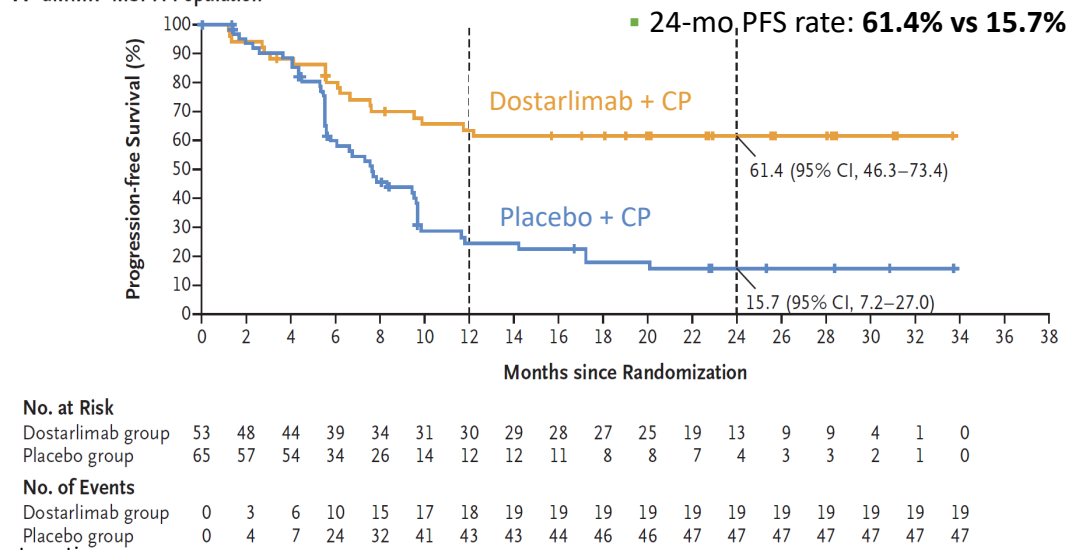
- 12-mo PFS rate: **74% vs 38%**
- 24-mo PFS rate: **NE**



GOG-3031/RUBY Part 1: PFS in dMMR/MSI-H Population[3,4,b]

	Events, n/N	Median (95% CI), mo	HR stratified; 95% CI
Dostarlimab + CP	19/53	NE (11.8-NE)	0.28 (0.16-0.50) *P*<0.001
Placebo + CP	47/65	7.7 (5.6-9.7)	

- 12-mo PFS rate: **63.5% vs 24.4%**
- 24-mo PFS rate: **61.4% vs 15.7%**



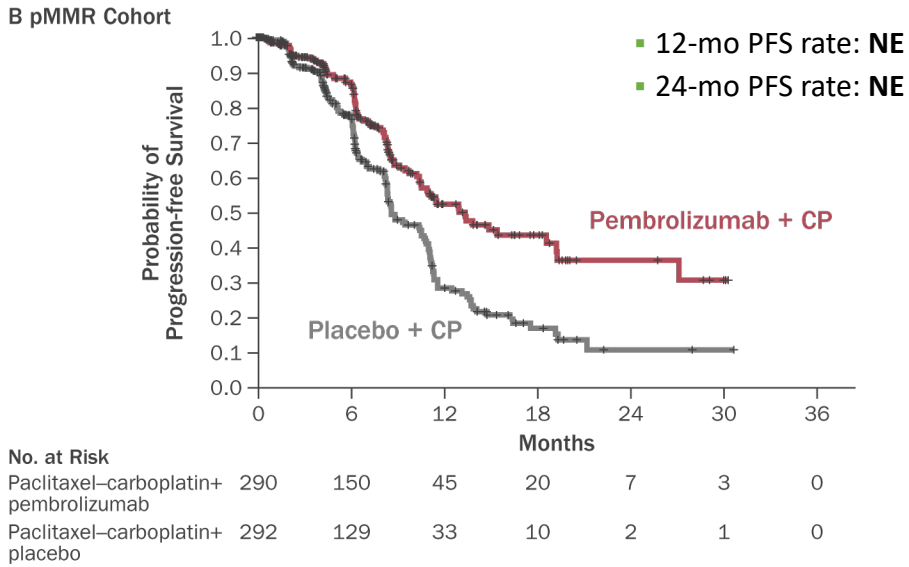
This slide is for illustration only and not for cross-trial comparisons. Side-by-side data should be interpreted with great caution.
[a]Median follow-up time was 12 months. PFS in dMMR population was a primary endpoint of the study [b]Median follow-up time was 24.79 months. PFS in dMMR/MSI-H population was a primary endpoint of the study.

1. Eskander RN, et al. SGO 2023. Abstract 264. **2.** Eskander RN, et al. *N Engl J Med.* 2023. doi:10.1056/NEJMoa2302312
3. Mirza MR, et al. SGO 2023. Abstract 265. **4.** Mirza MR, et al. *N Engl J Med.* 2023. doi: 10.1056/NEJMoa2216334

Most Recent Clinical Trial Data With 1L IO: Key Efficacy (cont'd)

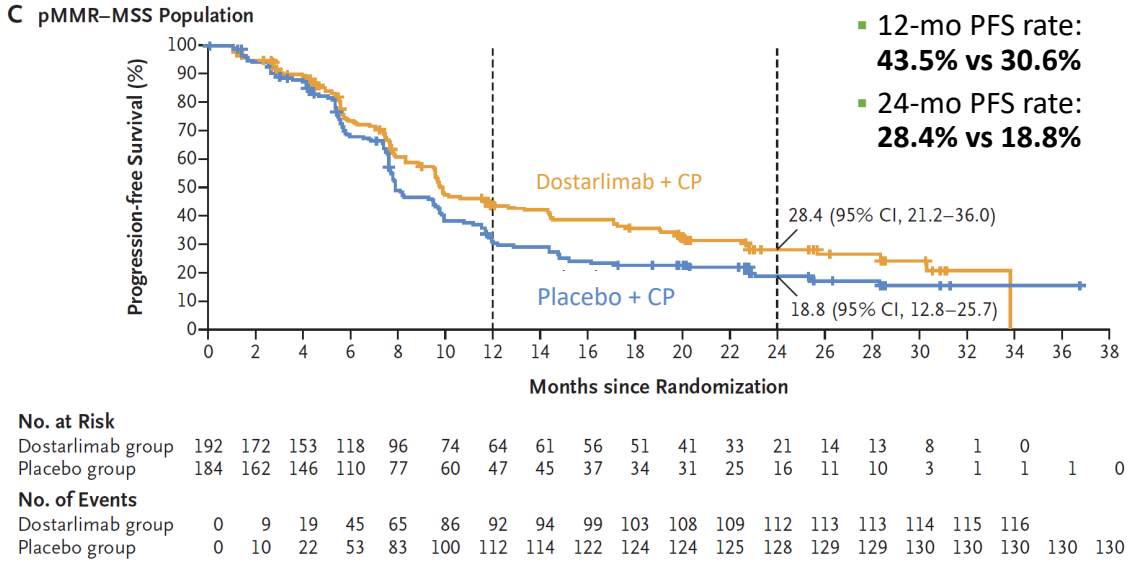
NRG-GY018: PFS in MMRp Population[1,2,a]

	Events, n/N	Median (95% CI), mo	HR stratified; 95% CI
Pembrolizumab + CP	89/290	13.1 (10.5-18.8)	0.54 (0.41-0.71) *P*<0.00001
Placebo + CP	133/292	8.7 (8.4-10.7)	



GOG-3031/RUBY Part 1: PFS in MMRp/MSS Population[3,4,b]

	Events, n/N	Median (95% CI), mo	HR stratified; 95% CI
Dostarlimab + CP	116/192	9.9 (9.0-13.3)	0.76 (0.59-0.98)
Placebo + CP	130/184	7.9 (7.6-9.8)	

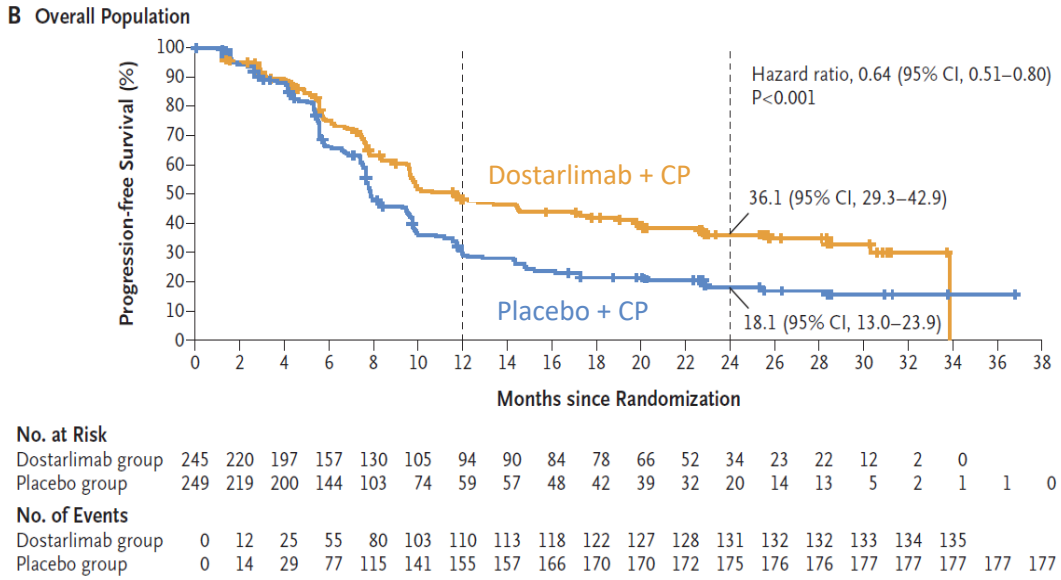


This slide is for illustration only and not for cross-trial comparisons. Side-by-side data should be interpreted with great caution.
[a]Median follow-up time was 7.9 months. PFS in MMRp/MSS population was a primary endpoint of the study. [b]PFS maturity was 65.4%. PFS in MMRp/MSS population was a prespecified subgroup analysis.

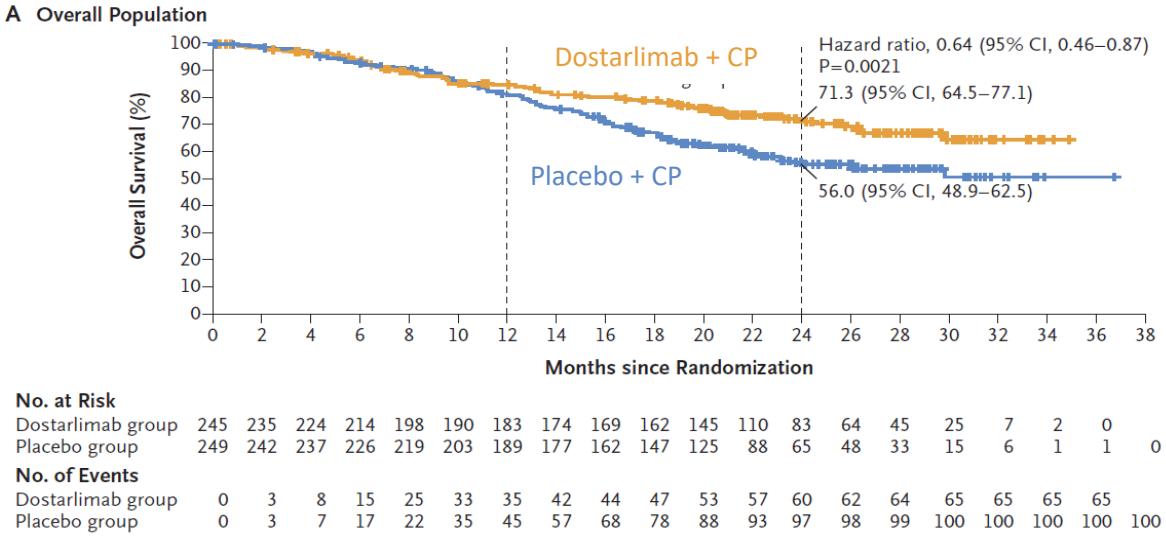
1. Eskander RN, et al. SGO 2023. Abstract 264. **2.** Eskander RN, et al. *N Engl J Med.* 2023. doi:10.1056/NEJMoa2302312
3. Mirza MR, et al. SGO 2023. Abstract 265. **4.** Mirza MR, et al. *N Engl J Med.* 2023. doi: 10.1056/NEJMoa2216334

Most Recent Clinical Trial Data With 1L IO: Key Efficacy (cont'd)

GOG-3031/RUBY Part 1: PFS in ITT Population[1,2,a]



GOG-3031/RUBY Part 1: OS in ITT Population (33% Maturity)[1,2,a]



- Received subsequent immunotherapy: 34.5% of patients on placebo arm; 15.5% of patients on dostarlimab arm

	mPFS (95% CI), mo	HR stratified; 95% CI	PFS rates
Dostarlimab + CP	11.8 (9.6-17.1)	HR=0.64 (0.507-0.800); *P*<0.0001	12-mo: 48.2% 24-mo: 36.1%
Placebo + CP	7.9 (7.6-9.5)		12-mo: 29.0% 24-mo: 18.1%

	mOS (95% CI), mo	HR stratified; 95% CI	OS rates
Dostarlimab + CP	NE (NE-NE)	HR=0.64 (0.46-0.87); *P*=0.0021	12-mo: 84.6% 24-mo: 71.3%
Placebo + CP	NE (23.2-NE)		12-mo: 81.3% 24-mo: 56.0%

This slide is for illustration only and not for cross-trial comparisons. Side-by-side data should be interpreted with great caution.
[a]Median duration of follow-up was 25.38 months. PFS and OS in the ITT populations were primary endpoints. OS *P* value stopping boundary was 0.00177.
1. Mirza MR, et al. SGO 2023. Abstract 265. **2.** Mirza MR, et al. *N Engl J Med.* 2023. doi: 10.1056/NEJMoa2216334

Most Recent Clinical Trial Data With 1L IO: Key Safety

AEs, n (%)	NRG-GY018[1,2,a]				GOG-3031/RUBY Part 1[2,3,b]	
	dMMR (n=215)		MMRp (n=550)			
	Pembro + CT (n=109)	Placebo + CT (n=106)	Pembro + CT (n=276)	Placebo + CT (n=274)	Dostarlimab + CP (n=241)	Placebo + CP (n=246)
Any AE	107 (98.2)	105 (99.1)	258 (93.5)	256 (93.4)	241 (100)	246 (100)
Grade ≥3	69 (63.3)	50 (47.2)	152 (55.1)	124 (45.3)	170 (70.5)	147 (59.8)
Anemia	21 (19.3)	11 (10.4)	38 (13.8)	25 (9.1)	36 (14.9)	40 (16.3)
Neutropenia	13 (11.9)	18 (17.0)	51 (18.5)	22 (12.0)	23 (9.5)	23 (9.3)
AE leading to death	1 (0.9)[c]	2 (1.9)[c]	6 (2.2)[d]	2 (0.7)[d]	5 (2.1)[e]	0 (0)
irAEs						
Hypothyroidism	14 (2.8)	10 (9.4)	37 (13.4)	7 (2.6)	27(11.2)	7 (2.8)

This slide is for illustration only and not for cross-trial comparisons. Side-by-side data should be interpreted with great caution.
[a] Data cutoff date: December 16, 2022. [b] Data cutoff date: September 28, 2022. Median duration of follow-up: 24.79 months. [c] In the dMMR cohort, 3 patients (1.4%) — 1 in the pembrolizumab group and 2 in the placebo group — died from grade 5 adverse events: cardiac arrest, sepsis, and lower gastrointestinal hemorrhage in 1 patient each. [d] In the MMRp cohort, 8 patients (1.5%) — 6 in the pembrolizumab group and 2 in the placebo group — died from grade 5 adverse events: sepsis in 4 patients, cardiac arrest in 2 patients, and small intestinal obstruction and sudden death not otherwise specified in 1 patient each. [e] Five deaths due to adverse events that occurred or worsened during treatment occurred in the dostarlimab group. No deaths occurred in the placebo group. One death that was reported by the investigator as related to the dostarlimab regimen occurred during the first 6 cycles (myelosuppression), one death was related to dostarlimab and occurred during the 90-day safety follow-up (hypovolemic shock), and 3 were judged not to be related to the dostarlimab regimen (opiate overdose, coronavirus disease 2019, and general deterioration of physical health.

1. Eskander RN, et al. SGO 2023. Abstract 264. **2.** Eskander RN, et al. *N Engl J Med.* 2023. doi:10.1056/NEJMoa2302312.

3. Mirza MR, et al. SGO 2023. Abstract 265. **4.** Mirza MR, et al. *N Engl J Med.* 2023. doi: 10.1056/NEJMoa2216334.

OVARIAN CANCERS

High Grade Serous Ovarian Cancer

- Biomarkers (BRCA and BRCA-like, HRD)
- Parp Inhibitors (Olaparib, Niraparib, Rucaparib)
- Checkpoint Inhibitors (Pembrolizumab, Dostarlimab) for MSI-H tumors
- Mirvetuximab-Soravtansin-gynx (Folate Receptor α tumors)
- Hormonal targets (Fulvestrant, Goserelin, Leuprolide, Aromatase inhibitors, Megesterol, Tamoxifen)

Low Grade Serous Ovarian Cancer

- Fulvestrant
- Binimetinib
- Trabetinib

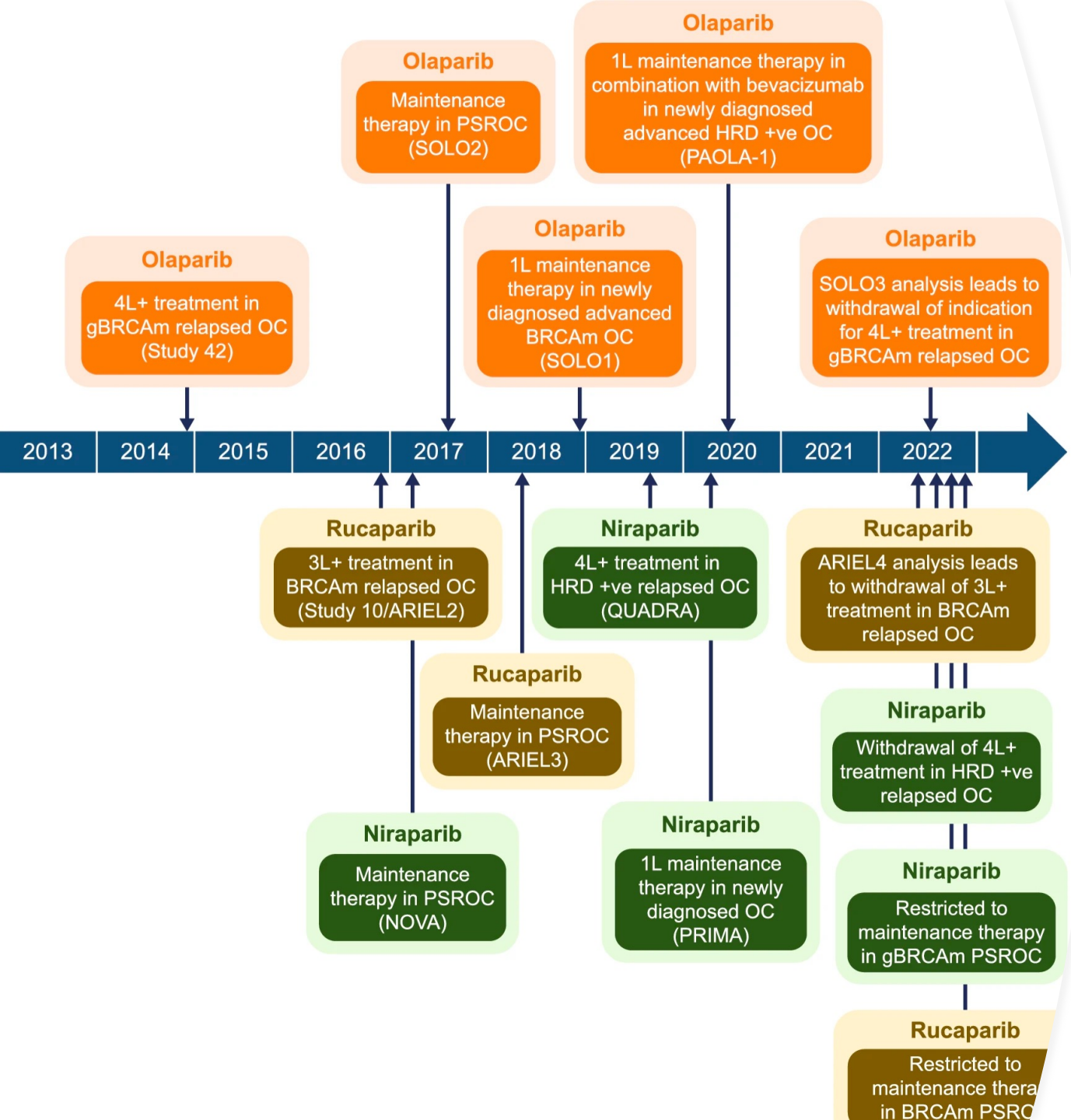
Pan-Tumor Targeted agents in Ovarian NCCN

- Fam-trastuzumab-Deruxtecan (Her2+ on IHC 3+ and 2+)
- Dabrafenib + Trabetinib (BRAF- V600E tumors)
- Selpercatinib (RET fusion)
- Entrectinib and Larotrectinib (NTRK
- Mirvetuximab-Soravtansin-gynx + / - Bevacizumab (Folate Receptor α tumors)

Predictive Biomarkers for Epithelial Ovarian Cancer

Biomarker	Response to	Assigned Level of Evidence	Setting/Comments	References
DNA damage repair				
Germline/somatic *BRCA1/2* mutations	PARPi	I	Maintenance in primary and recurrent setting and monotherapy in recurrent setting	12-19
HRD	PARPi in combination with bevacizumab	I	Frontline maintenance setting	14
Tumor *BRCA1/2* reversion mutations	PARPI in combination with cediranib	II	Post-PARPi progression, associated with nonresponse	20
RAD51C/D mutations	PARPi	II	Monotherapy in recurrent setting	18,21
BRCA1 methylation	PARPi monotherapy		Monotherapy in recurrent setting	22
CCNE1 amplification	Adavosertib plus carboplatin or adavosertib plus carbo/taxol Adavosertib plus gemcitabine Praxaserib	II	Platinum-sensitive recurrent setting Platinum-resistant or refractory setting Recurrrent, BRCA wild-type	23-26
Immunotherapy				
Mismatch repair deficiency	PD-1/PD-L1 inhibitors	I	Positive association with response across cancer types	27
TMB	PD-1/PD-L1 inhibitors	I	Positive association with response across cancer types	28
Oncogenic signaling				
KRAS/NRAS/HRAS mutations (LGSOC)	Binimetinib (MEKi) and binimetinib plus paclitaxel	II	Platinum-resistant setting	29,30

Abbreviations: HRD, homologous recombination deficiency; LGSOC, low grade serous ovarian cancer; PARP, poly (ADP-ribose) polymerase; PARPi, poly (ADP-ribose) polymerase inhibitor; PD-1, programmed death receptor 1; PD-L1, program death receptor ligand-1; TMB, tumor mutational burden.



PARP INHIBITORS FOR OVARIAN CANCER

O'Malley, D.M., Krivak, T.C., Kabil, N. *et al.* PARP Inhibitors in Ovarian Cancer: A Review. *Targ Oncol* **18**, 471–503 (2023). https://doi.org/10.1007/s11523-023-00970-w

NCCN Guidelines Version 1.2024
Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

NCCN Guidelines Index
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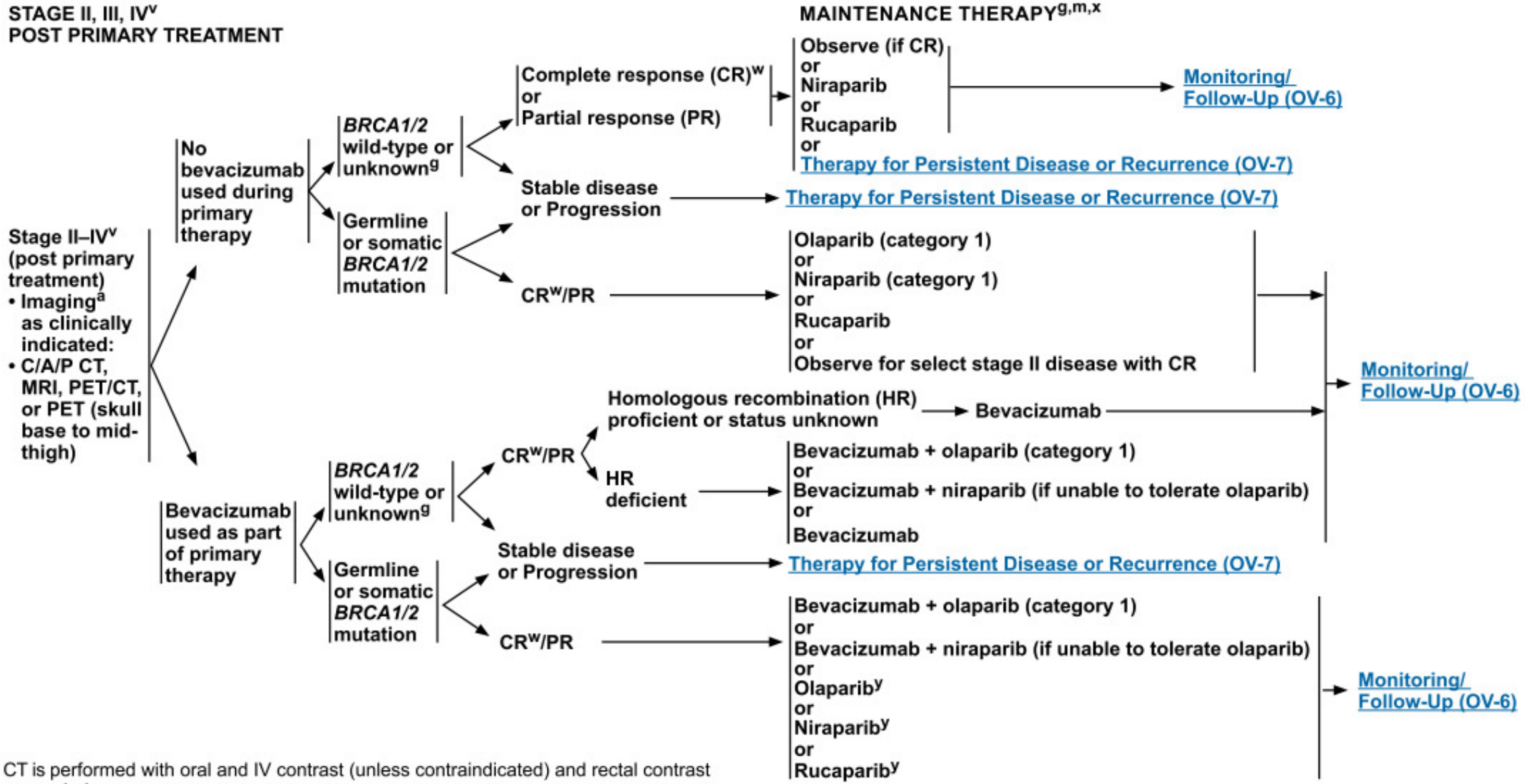
Discussion

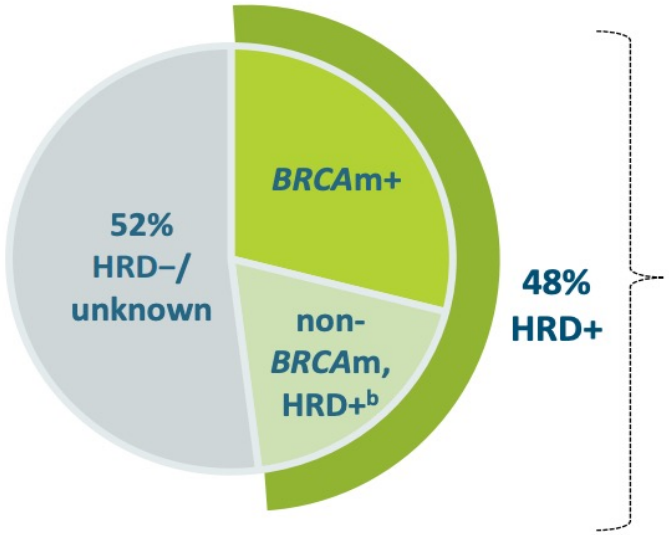


[a] CT is performed with oral and IV contrast (unless contraindicated) and rectal contrast

PAOLA-1 Evaluated the Efficacy and Safety of Olaparib + Bevacizumab vs an Active Comparator (Bevacizumab + Placebo) (cont'd)

HRD Status in the PAOLA-1 Patient Population[1,5]

In PAOLA-1, all trial participants (N=806) were retrospectively evaluated for HRD with Myriad myChoice® CDx.[1,a]



~1 in 2 women with advanced ovarian cancer is HRD positive[2,3,6,7] (including *BRCA*m and genomic instability positive)[1,5]

Key genomic biomarkers of HRD in tumor cells include[5]:

- *BRCA* mutations
- Genomic instability measures include:
  - Loss of heterozygosity (LOH)
  - Telomeric allelic imbalance (TAI)
  - Large-scale state transitions (LSTs)

Gene panels that to not measure genomic instability Are not capturing all HRD status and are not FDA-Approved for diagnostics for this combination.

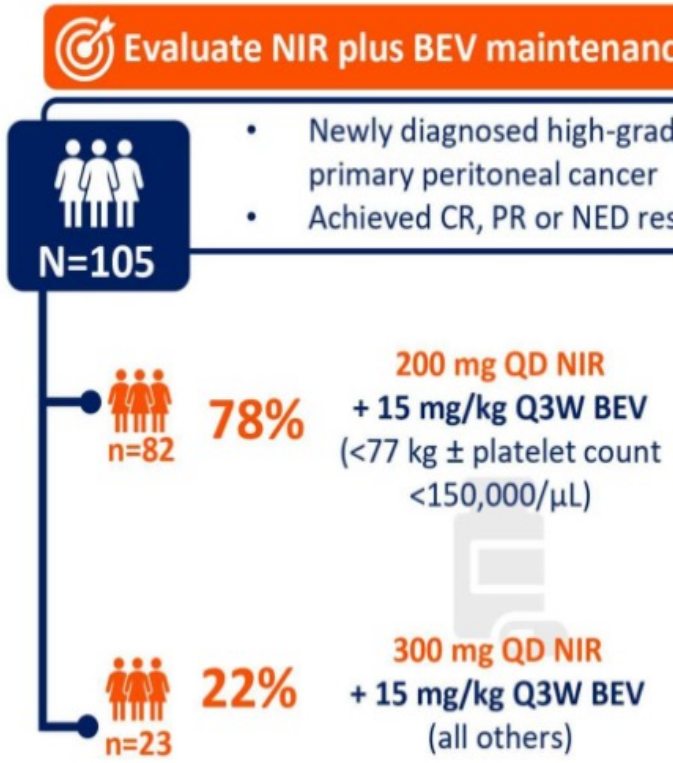
In a prespecified exploratory analysis of HRD-negative and HRD-unknown patients, there was insufficient evidence to suggest differential efficacy between the combination of LYNPARZA + bevacizumab and bevacizumab + placebo.

[a]HRD positive was defined as either a t*BRCA* mutation and/or an HRD score ≥42 by Myriad myChoice® CDx; HRD negative was defined as non–t*BRCA*-mutated and an HRD score <42 by Myriad myChoice® CDx. 4.2% of the test results were missing, 2.1% failed, and 11.3% were inconclusive, yielding approximately 18% of the total PAOLA-1 population with an unknown HRD status.[4,8]

[b]May include markers of genomic instability (eg, LOH, TAI, LST).[5]

OVARIO: Phase II trial of niraparib plus bevacizumab N=105

Hardesty M, et al.



18 mo. PFS:

62% in the overall pop.

76% (95% CI 61–87) in the HRd

47% (95% CI 31–64%) in HRp

56% (95% CI 31–79%) HRnd

28.7 month fFollow up:

PFS 19.6 months in the overall pop.

28.3 mo HRd

14.2 mo. HRp

12.1 mo HRnd

Most common any-grade treatment-related AE:

thrombocytopenia (74/105)

fatigue (60/105)

anemia (55/105

Hardesty, M. Gyn Onc, Volume 166, Issue 2, August 2022, Pages 219-229

PRINCIPLES OF SYSTEMIC THERAPY

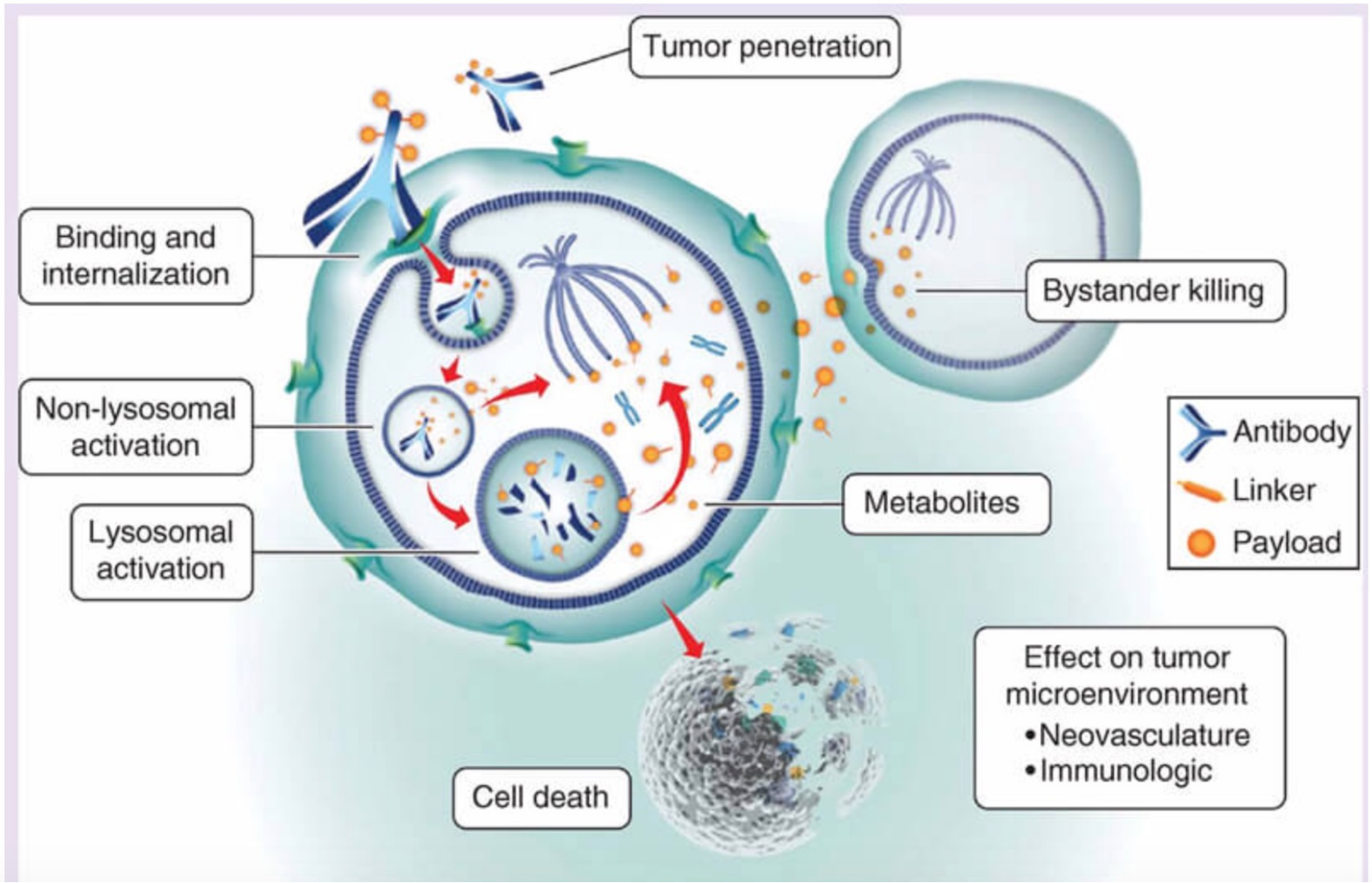
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[p]/Fallopian Tube/Primary Peritoneal Cancer[q]

Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Cytotoxic Therapy Cyclophosphamide (oral)/ bevacizumab[k,39] Docetaxel[40] Etoposide (oral)[41] Gemcitabine[42,43] Liposomal doxorubicin[42,43] Liposomal doxorubicin/ bevacizumab[k,s,44] Paclitaxel (weekly)[g,45] Paclitaxel (weekly)/ bevacizumab[g,k,s,44] Topotecan[46,47] Topotecan/bevacizumab[k,s,44] Targeted Therapy (single agents) Bevacizumab[k,s,21,22] Mirvetuximab soravtansine-gynx (for FRα-expressing tumors)[z,48]	Cytotoxic Therapy[u] Capecitabine Carboplatin[*] Carboplatin/docetaxel[*] Carboplatin/paclitaxel (weekly)[g,*] Carboplatin/gemcitabine[14] ± bevacizumab[k,s,t,15,*] Carboplatin/liposomal doxorubicin[16] ± bevacizumab[k,s,17,*] Carboplatin/paclitaxel[g,18] ± bevacizumab[k,s,t,19,*] Cyclophosphamide Cyclophosphamide (oral)/pembrolizumab/bevacizumab[k,50,51] Doxorubicin Gemcitabine/bevacizumab[k,52] Gemcitabine/cisplatin[20,*] Ifosfamide Irinotecan Ixabepilone/bevacizumab (category 2B)[k,aa,53] Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Sorafenib/topotecan[49] Vinorelbine Targeted Therapy (single agents) Niraparib (category 3)[v,27] Olaparib (category 3)[w,28] Pazopanib (category 2B)[29] Rucaparib (category 3)[x,30] Hormone Therapy Aromatase inhibitors (anastrozole, exemestane, letrozole) Goserelin acetate Leuprolide acetate Megestrol acetate Tamoxifen[j]	Carboplatin/paclitaxel (for age >70)[g,y,*] Carboplatin/paclitaxel, albumin bound (for confirmed taxane hypersensitivity)[*] Immunotherapy Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors)[z,37] Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/ megabase)[z,38] Hormone Therapy Fulvestrant (for low-grade serous carcinoma) Targeted Therapy Dabrafenib + trametinib (for *BRAF* V600E-positive tumors)[z,32] Entrectinib or larotrectinib (for *NTRK* gene fusion-positive tumors)[z] Fam-trastuzumab deruxtecan-nxki (for HER2-positive tumors [IHC 3+ or 2+])[54] Mirvetuximab soravtansine-gynx/bevacizumab (for FRα-expressing tumors)[k,z,55,56] Selpercatinib (for *RET* gene fusion-positive tumors)[z,33] For low-grade serous carcinoma: • Trametinib[34] • Binimetinib (category 2B)[35,36]

* Platinum agents have limited activity when the disease has demonstrated growth through a platinum-based regimen, and platinum rechallenge is generally not

Mirvetuximab an ADC against FR-α for PROC



Mirvetuximab Soravtansine-gynx in FR-aPROC

"…Until this day, no phase 3 study of a novel therapy has ever demonstrated an improvement in overall survival in the platinum-resistant ovarian cancer space."
--Kathleen N. Moore MD

MIRASOL STUDY DESIGN: PHASE 3 REGISTRATION TRIAL FOR MIRVETUXIMAB SORAVTANSINE USING PS2+ SCORING IN FRα HIGH PATIENTS

MIRASOL

Enrollment and Key Eligibility

- 430 patients/330 events for PFS by INV
- Platinum resistant disease (<6 months PFI)
- Prior Bev and PARP allowed
- BRCAmut patients allowed

Statistical Assumptions

- α=0.05 (two-sided), Power = 90%, HR=0.7; control arm mPFS 3.5 mo

Mirvetuximab Soravtansine

6 mg/kg (adjusted ideal body weight) once every 3 weeks

1:1 Randomization

STRATIFICATION FACTORS
IC Chemotherapy Choice (Paclitaxel, PLD, Topotecan)
Prior therapies (1 vs 2 vs 3)

Investigator's Choice Chemotherapy
Paclitaxel, PLD†, or Topotecan

Paclitaxel: *80 mg/m² weekly*
PLD: *40 mg/m² once every 4 weeks*
Topotecan: *4 mg/m² on Days 1, 8, and 15 every 4 weeks; or 1.25 mg/m²*

Primary Endpoint

Progression-free survival by INV
BICR for sensitivity analysis*

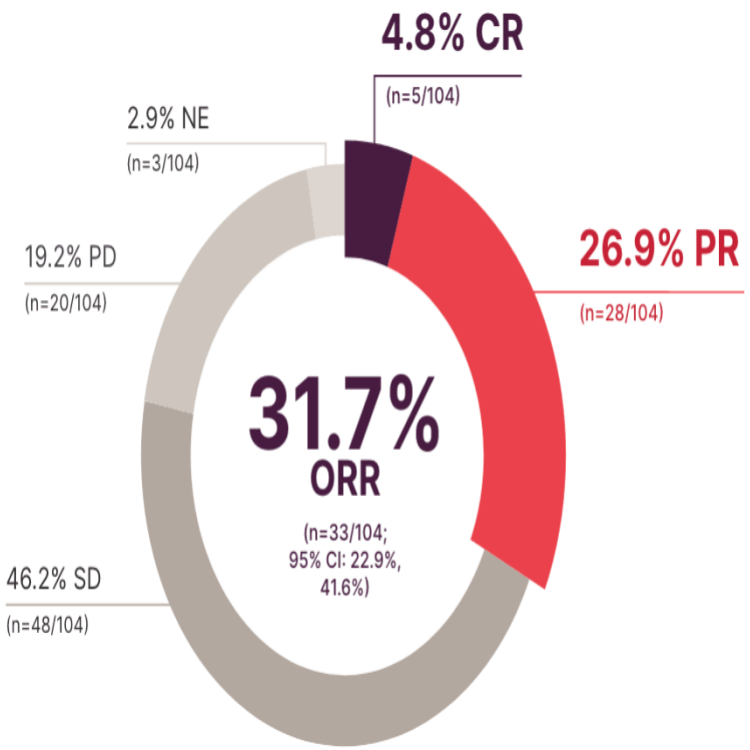
Secondary Endpoints

Overall response rate by INV
Overall survival
Patient reported outcomes

K. Moore et al December 7, 2023 N Engl J Med 2023; 389:2162-2174 DOI: 10.1056/NEJMoa2309169
2023 American Society of Clinical Oncology (ASCO) Annual Meeting (LBA5507).

Mirvetuximab Soravtansine-gynx in FR-α PROC

PHASE 2 **SORAYA** TRIAL (n=104) AND CONFIRMATORY PHASE 3 TRIAL **MIRASOL** (n=453)



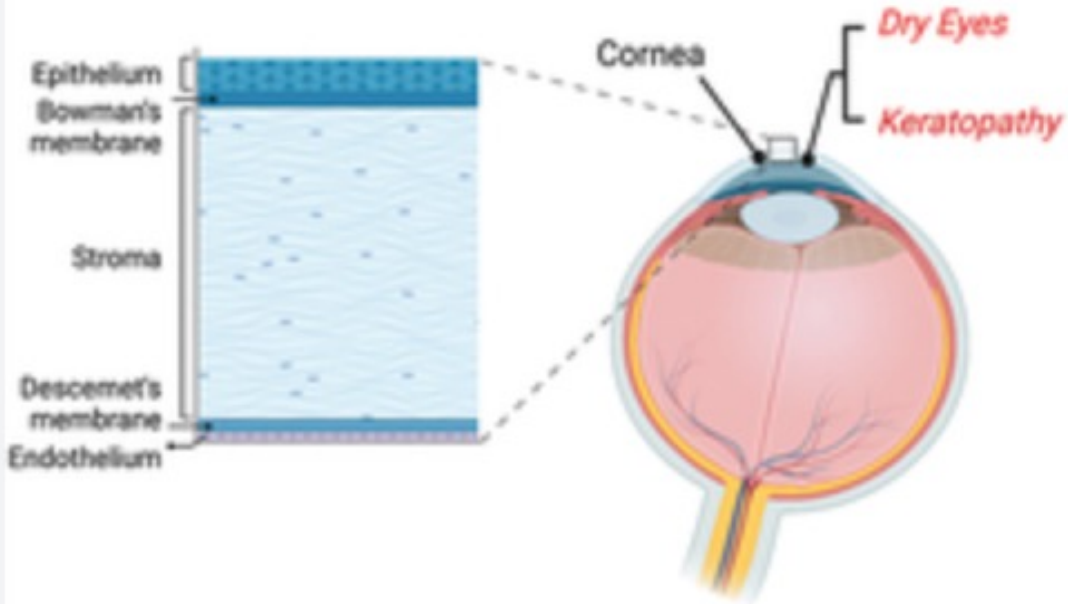
mDOR 6.9 months
(95% CI: 5.6, 9.7)

≥75% of cells with ≥2+ staining intensity

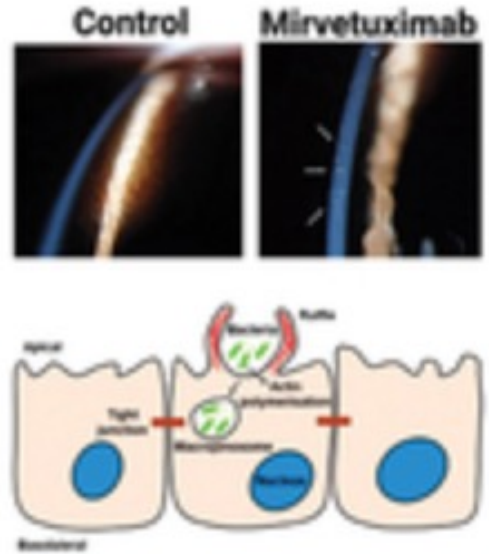
- Improved med PFS (5.62 vs 3.98 mo); [HR]=0.65, med OS(16.46 vs. 12.75 mo); HR=0.67; *P*=.0046) compared with Inv Chc chemo.
- CR in 12 patients (5.3% vs. 0.0%). PFS by BICR was 5.9 vs. 4.3 mo. regardless of prior tx w/ bevacizumab.
- Fewer gr 3 AE's, and disc. Less heme toxicity and alopecia than chemotherapy.
- GI (gr 1 or 2) (29% and 27%) respectively. Ocular toxicity, which included blurred vision (41%), keratopathy (32%), and dry eye (28%) was more common with Mirv

K. Moore et al December 7, 2023 N Engl J Med 2023; 389:2162-2174 DOI: 10.1056/NEJMoa2309169
2023 American Society of Clinical Oncology (ASCO) Annual Meeting (LBA5507).

Pathophysiology of Mirvetuximab-associated Keratopathy



- Development of perilimbal corneal microcysts (top, arrows)
- FRα not expressed in corneal epithelium: *off target toxicity*
- Uptake via macro-pinocytosis may mediate mirvetuximab-associated ocular toxicities (bottom)

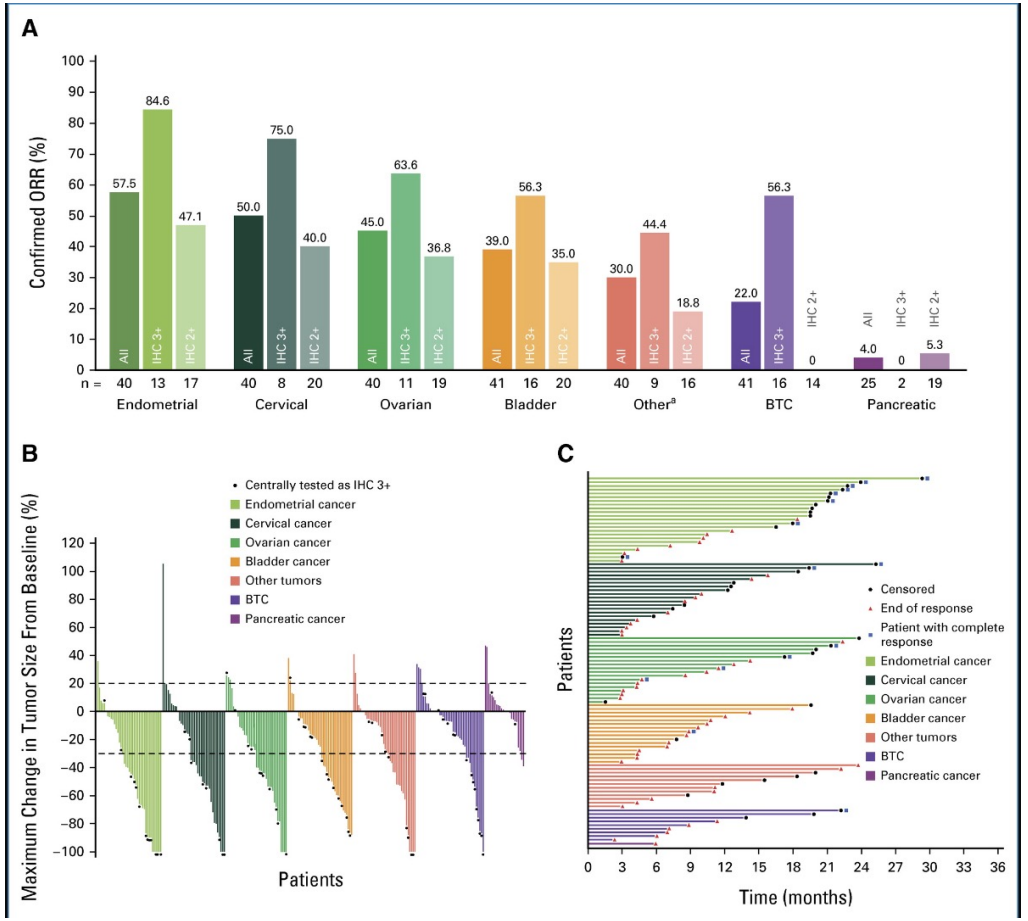


Adapted from Lin et al, Membranes, 2020

Ocular Exams	Risk Modifying Measures	Prophylactic Eye Care
• Baseline ocular exam prior to treatment start including best corrected visual acuity and slit lamp examination • Repeat exams every 2 cycles until cycle 8 • Repeat exams with symptom development	• Avoid use of contact lenses • Use of sunglasses in full sunlight • Minimize exposure to dry eye risk factors: ◦ Medications ◦ Environmental factors ◦ Unnecessary procedures / surgeries	• Daily administration of **preservative-free lubricating** eye drops (Days 1-21) • Administration of **corticosteroid** (e.g. 1% prednisolone) eye drops six times daily on Days 1-5 and four times daily on Days 6-10 throughout treatment

Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial

- ORRs by ICR all patients
  - endometrial 57.5% (95% CI, 40.9 to 73.0)
  - cervical 37.5% (95% CI, 22.7 to 54.2) mOS NR
  - ovarian 42.5% (95% CI, 27.0 to 59.10
- ORR for those with HER2 IHC 3+
  - Endometrial 84.6% [mOS 26]
  - Cervical 75% [mOS NR]
  - Ovarian mOS 20
- Risk of pulmonary AE's (ILD/pneumonitis)



HER2-overexpressing tumors with IHC 3+/2+ (scored using current ASCO/College of American Pathology guidelines for scoring HER2 in gastric cancer

Bernstam, FM J. of Clinic Oncol Volume 42, Number 1

BONUS SLIDES→ CERVIX CANCER

- Tisotumab Vedotin

Tumor-Agnostic Strategy

Tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6) Phase 2 (N = 101)

THE FIRST FDA APPROVED ADC FOR GYN CANCERS

- Monoclonal Antibody binds Tissue Factor expressing cells
- Payload is a small molecule monomethyl auristatin E
- (MMAE) is a microtubule disrupting agent
- When linker is cleaved after endocytosis, the process leads to cell cycle arrest and apotosis of the cell

Median follow-up at the time of analysis was 10·0 months (IQR 6·1–13·0). The confirmed **objective response rate was 24%** (95% CI 16–33), with seven (7%) complete responses and 17 (17%) partial responses. & **72 % DCR**

alopecia (38 [38%] of 101 patients), epistaxis (30 [30%]), nausea (27 [27%]), conjunctivitis (26 [26%]), fatigue (26 [26%]), and dry eye (23 [23%]).

Tumor-Agnostic Strategy

six drugs have received US Food and Drug Administration approval on the following basis:

- pembrolizumab for microsatellite instability high, mismatch repair deficient, or tumor mutational burden high tumors
- dostarlimab for mismatch repair deficient tumors
- larotrectinib or entrectinib for tumors with *NTRK* gene fusions
- dabrafenib plus trametinib for tumors with *BRAF* V600E mutations
- selpercatinib for tumors with *RET* gene fusions