Management of Advanced Stage & Recurrent Endometrial Cancer: Working Towards a New Standard of Care

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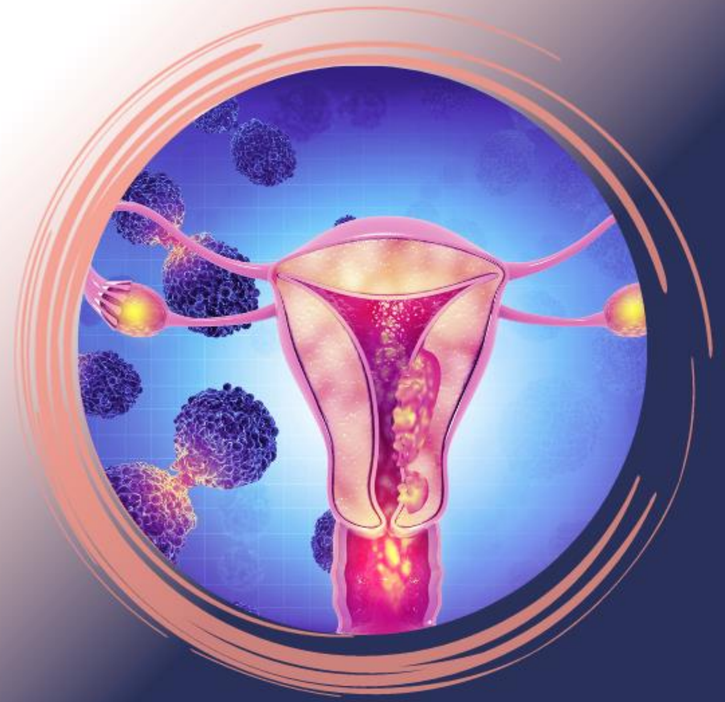

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Endometrial Cancer 2023

- ***Only gynecologic cancer with rising incidence and mortality***
- Corrected for hysterectomy rates, uterine cancer is the **2nd most common cancer amongst women**

66,200 new cases* | **13,030 deaths***

~80% of these will be early stage and low grade with excellent prognosis

~20% will have high grade or advanced stage disease

Population of interest

Increasing Incidence

Increasing Mortality

Is anticipated to surpass ovarian cancer mortality in the coming years

Siegel et al. Cancer Statistics 2023
Cancer Facts & Figures 2023. American Cancer Society. Available at https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf. Accessed January 31, 2023.

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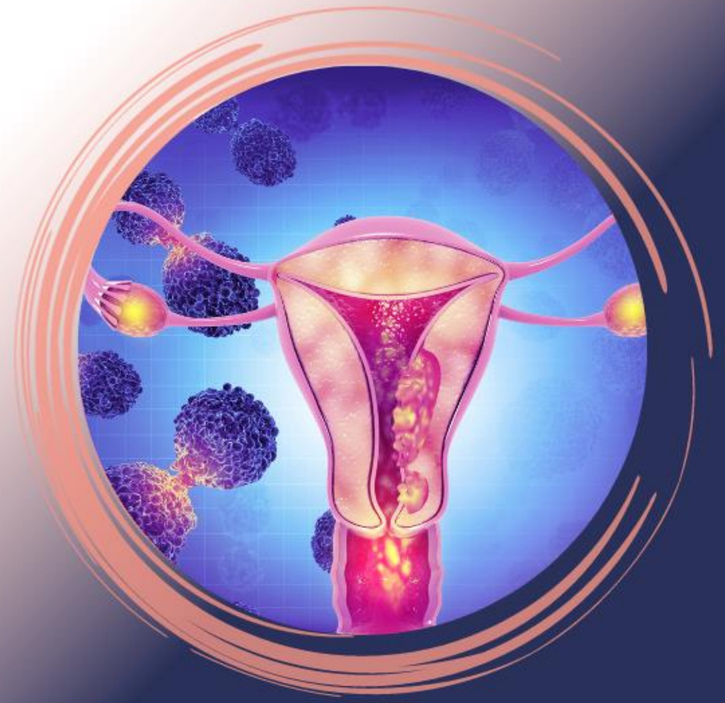
Adjuvant Therapy and 1L Treatment



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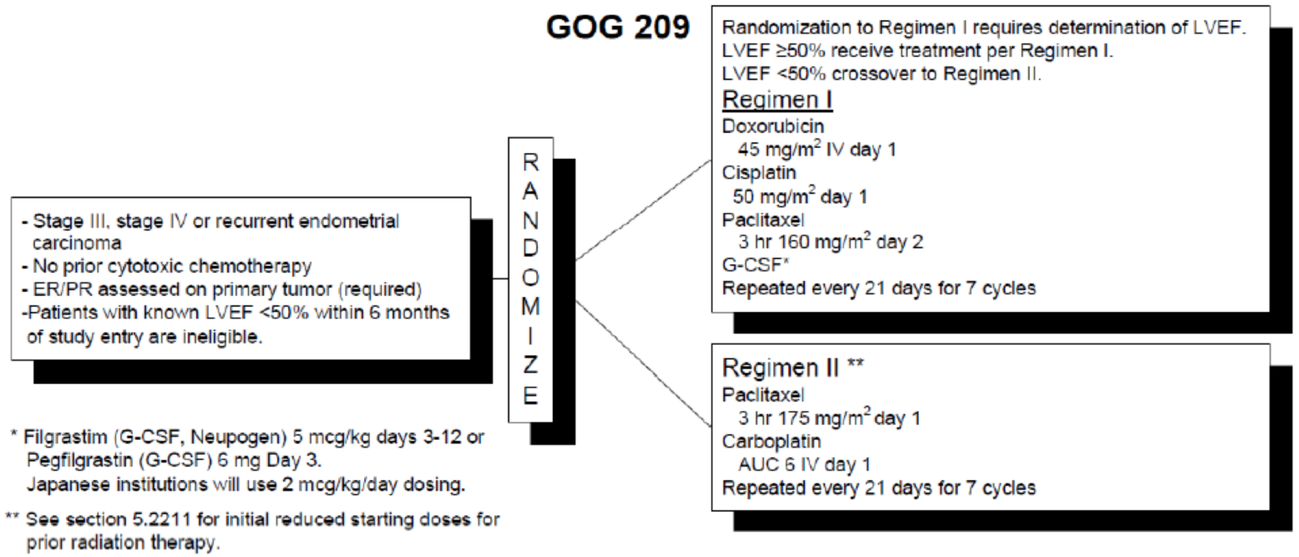
Treatment of advanced stage/recurrent Endometrial Cancer

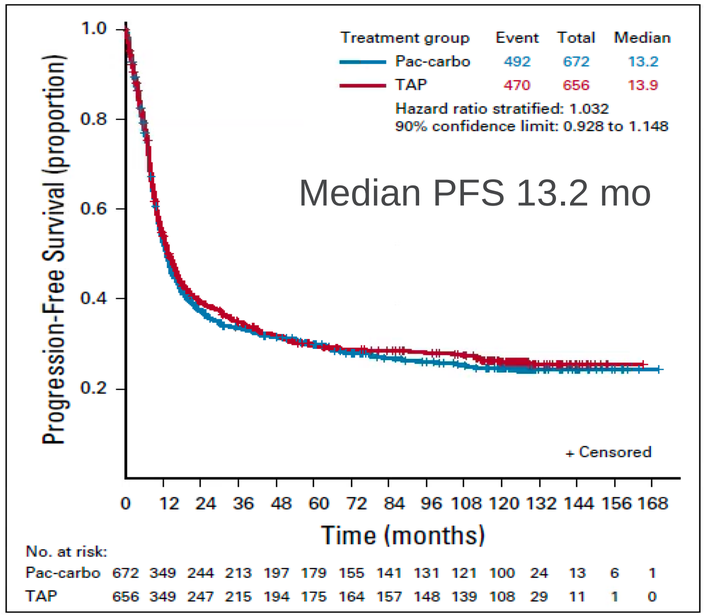
	RT agent vs. Doublet	Single agent vs. Doublet		Doublet vs. Doublet	Doublet vs. Triplet	TAP vs. TC
	GOG 122 Randall et al. JCO ’06	**EORTC55872** Van Wijk Ann Onc ’03	**GOG 107** Thigpen JCO ’04	**GOG 163** Fleming. Ann Onc ’04	**GOG 177** Fleming JCO ’03	**GOG 209** Miller SGO ´12
Population (Stage)	III-IV	Stage 3-4 & Relapsed	Stage 3-4 & Relapsed	Stage 3-4 & Relapsed	Stage 3-4 & Relapsed	Stage 3-4
n	396	177	299	317	273	
Regimen	WART vs Dox-Cis	Dox vs. Dox-Cis	Dox (A) vs. Dox-Cis (AC)	Dox-Cisplat vs. Dox-Paclitax	Dox-Cisplat vs. Dox-Cisplat-Tax	Carbo-Tax vs. Dox-Cisplat-Tax
PFS	Signif HR 0.71	NS	Signif HR 0.73	NS	Signif P < 0.01	NS
OS	Signif HR 0.68	NS	NS	NS	Signif P < 0.037	NS

GOG 209

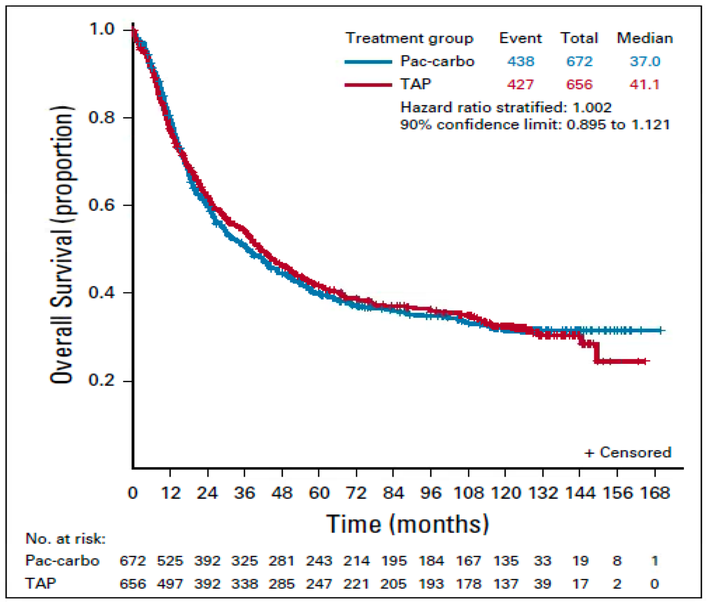
- **Established carboplatin and paclitaxel as the chemotherapy backbone for patients with advanced stage or recurrent disease**



Progression Free Survival



Overall Survival

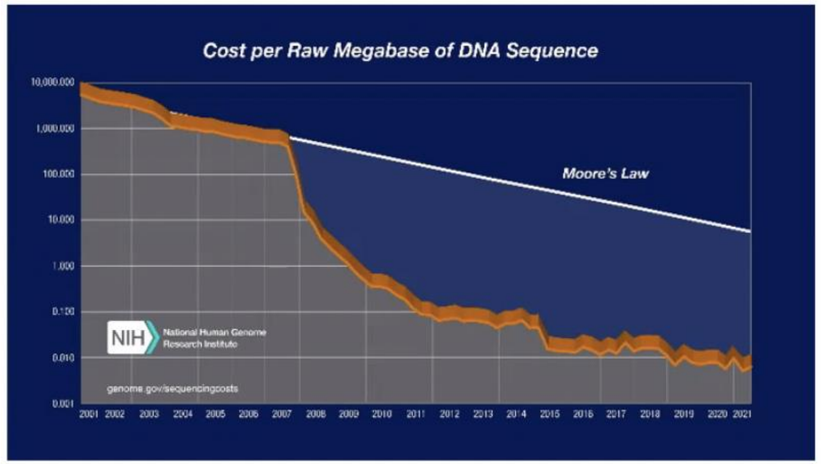


Key eligibility criteria

- **Stage III, Stage IV or recurrent endometrial carcinoma. No mandate for measurable disease**
- **NO prior cytotoxic chemotherapy**, including chemotherapy used for radiation sensitization
- GOG PS 0,1 or 2

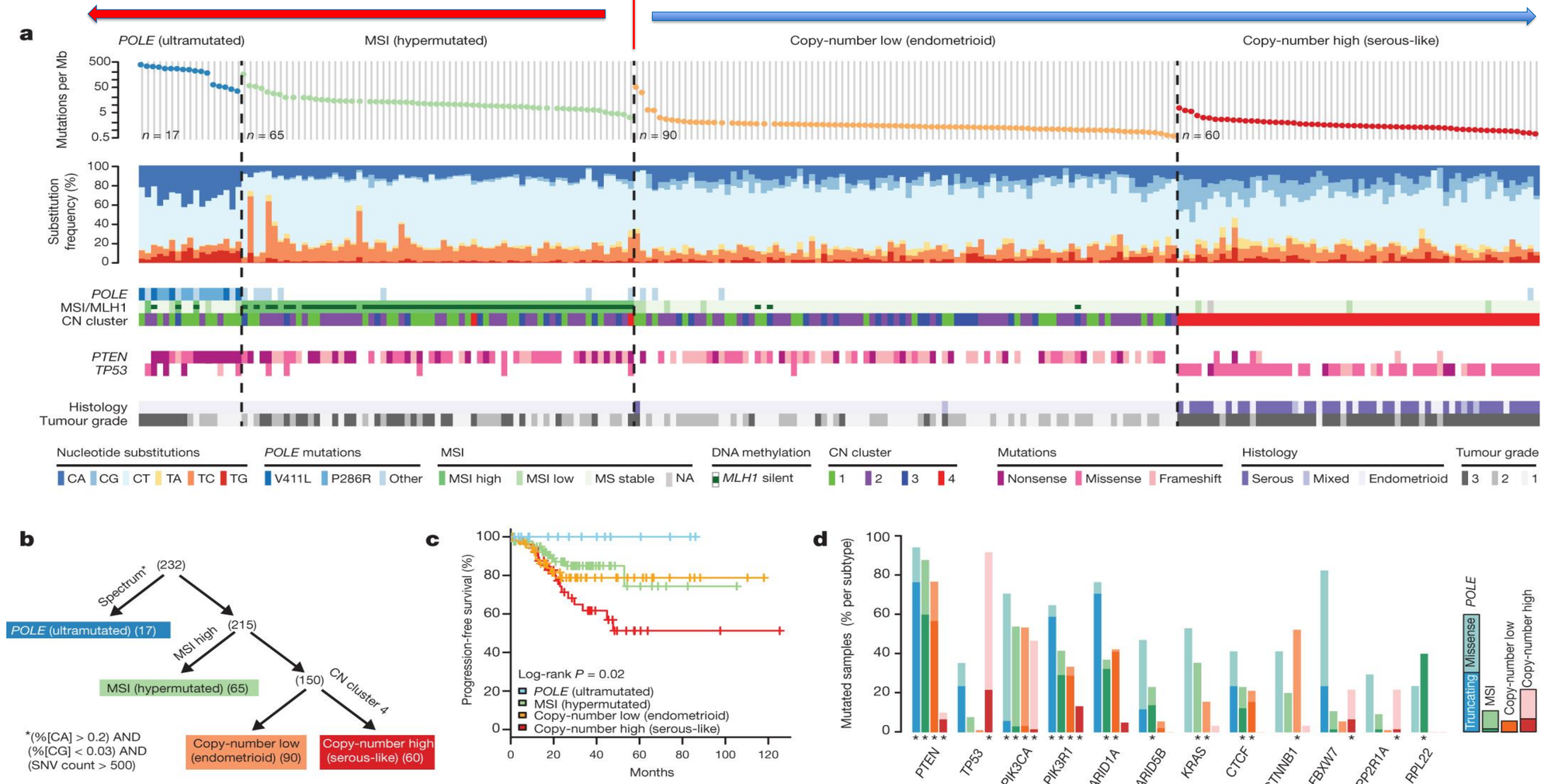
Miller DS, et al. J Clin Oncol. 2020 Nov 20;38(33):3841-3850.

Moving from the Light Microscope to the Molecular Microscope



Disease Homogeneity to Molecular Granularity

Immunologically Responsive | Immunologically Non-Responsive



G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

Endometrial Cancer: Molecular Subtypes

***POLE* ultramutated**	• Ultra-high somatic mutation frequency; MSS; frequent mutations in the exonuclease domain of *POLE*; high ASNS and CCNB1 expression • Represents ~4% of endometrioid tumors* • Best prognosis	Clear IO Efficacy
MSI hypermutated	• High mutation rate and few copy number alterations; high rate of *MLH1* promoter methylation; high phospho-AKT; low PTEN expression; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations • Represents ~39% of endometrioid tumors*†	Clear IO Efficacy
Copy-number low‡	• High frequency of mutations in *CTNNB1*, *KRAS*, *SOX17*; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations; elevated levels of progesterone receptor and RAD50 expression • Represents ~49% of endometrioid tumors*	? Role for IO Hormonal Txt ? Novel targets
Copy-number high‡	• Greatest transcriptional activity; frequent *TP53* mutations; decreased levels of phospho-AKT; mutually exclusive *PIK3CA*, *PIK3R1,* and *PTEN* mutations • Represents ~9% of endometrioid tumors* • Worst prognosis	? Role for IO ? Anti-Her2 ? Other ADCs ? VEGF targets

G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

“Biomarker” Guided Therapy in Endometrial Cancer

- **MMR deficient & MSI-H population**
  - Harbor hundreds to thousands of somatic mutations that encode potential neoantigens and are thus immunogenic
- **Phase II Keynote 158 Study** (27 independent tumor types)
  - **Endometrial (n=49)**, gastric (n=24), cholangiocarcinoma and pancreatic cancer most common
  - In the entire cohort: ORR 34.3%, (95% CI, 28.3% to 40.8%). Median PFS 4.1 months (95% CI, 2.4 to 4.9 months) and median OS 23.5 months (95% CI, 13.5 months to not reached).

TABLE 3. Antitumor Activity for Tumor Types With Greatest Enrollment

Tumor Type	No.	CR, No.	PR, No.	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Median DOR, Months (range)
Endometrial	49	8	20	57.1 (42.2 to 71.2)	25.7 (4.9 to NR)	NR (27.2 to NR)	NR (2.9 to 27.0+)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)	NR (6.3 to 28.4+)
Cholangiocarcinoma	22	2	7	40.9 (20.7 to 63.6)	4.2 (2.1 to NR)	24.3 (6.5 to NR)	NR (4.1+ to 24.9+)
Pancreatic	22	1	3	18.2 (5.2 to 40.3)	2.1 (1.9 to 3.4)	4.0 (2.1 to 9.8)	13.4 (8.1 to 16.0+)
Small intestine	19	3	5	42.1 (20.3 to 66.5)	9.2 (2.3 to NR)	NR (10.6 to NR)	NR (4.3+ to 31.3+)
Ovarian	15	3	2	33.3 (11.8 to 61.6)	2.3 (1.9 to 6.2)	NR (3.8 to NR)	NR (4.2 to 20.7+)
Brain	13	0	0	0.0 (0.0 to 24.7)	1.1 (0.7 to 2.1)	5.6 (1.5 to 16.2)	–

Marabelle A, et al. J Clin Oncol, 2019

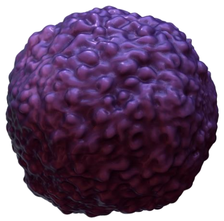
Single Agent IO in “biomarker” Selected Endometrial Cancer Populations (dMMR)

- **Response to single agent IO in dMMR or MSI-high endometrial**

Study & Drug	Patient Population	Outcome
Keynote 158: Pembrolizumab (N=90)	Advanced stage or metastatic dMMR endometrial cancer	ORR: 48%
PHAEDRA trial: Durvalumab (N=35 dMMR)	Advanced stage or metastatic endometrial cancer	ORR in dMMR: 43%
GARNET study: Dostarlimab (N=129)	Previously treated, recurrent advanced stage endometrial cancer	ORR in dMMR: 43.5%
Ph II Avelumab study (N= 15 dMMR)	Advanced stage or metastatic endometrial cancer	ORR: 26.7%

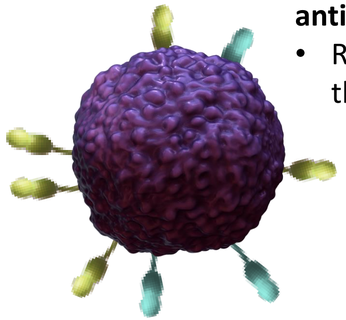
O’Malley D, et al. J Clin Oncol, 2022
Antill PSK et al. J Clin Oncol 2019
Oaknin A et al. Journal for ImmunoTherapy of Cancer 2022
Konstantinopoulos PA et al. J Clin Oncol 2019

Rational for Combinatorial Approach with Chemotherapy + IO



Tumor cell death

- Immunogenic cell death
- Reduction of tumor cells producing immunosuppressive mediators



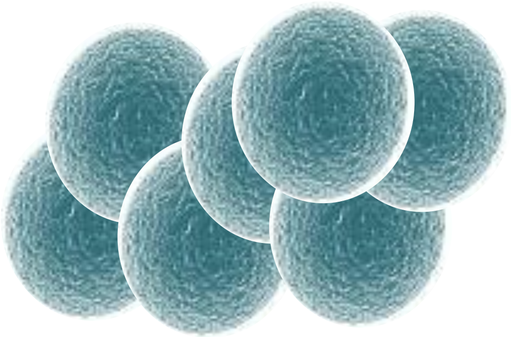
Increased expression of tumor antigens

- Recognized and targeted by the immune system

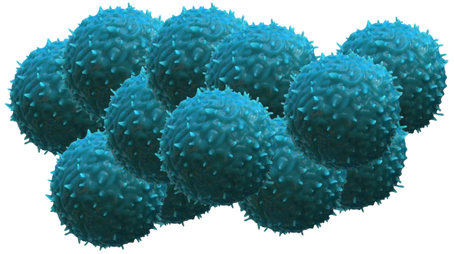
Anti-PD(L)1

Chemo

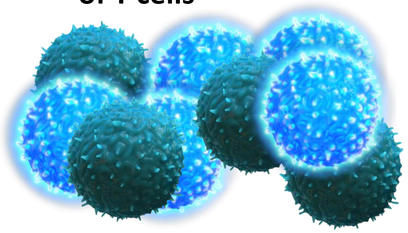
MDSC depletion



Treg depletion



Homeostatic proliferation of T cells

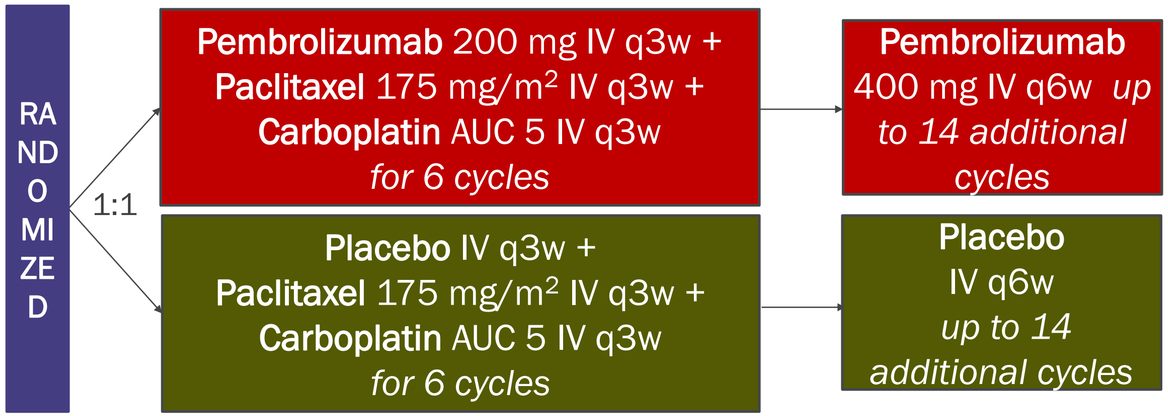


1. Hato SV et al. *Clin Cancer Res.* 2014. 2. Chen Y et al. *Am J Cancer Res*. 2021. 3. Pfannenstiel T et al. *Cell Immunol*. 2010.
4. Sevko A et al. *J Immunol*. 2013.

NRG GY018: Phase 3 Trial of Pembrolizumab + Chemo for Measurable Stage 3 or 4a, Stage 4b, or Recurrent EC – Study Design and Patients

Key Eligibility Criteria

- Measurable stage III/IVA or measurable/nonmeasurable stage IVB or recurrent EC
- MMR IHC testing
- ECOG PS 0-2
- No prior Chemo except adjuvant Chemo if completed ≥12 mo before study



Stratified by MMR status (pMMR vs dMMR), ECOG status, and prior adjuvant Chemo

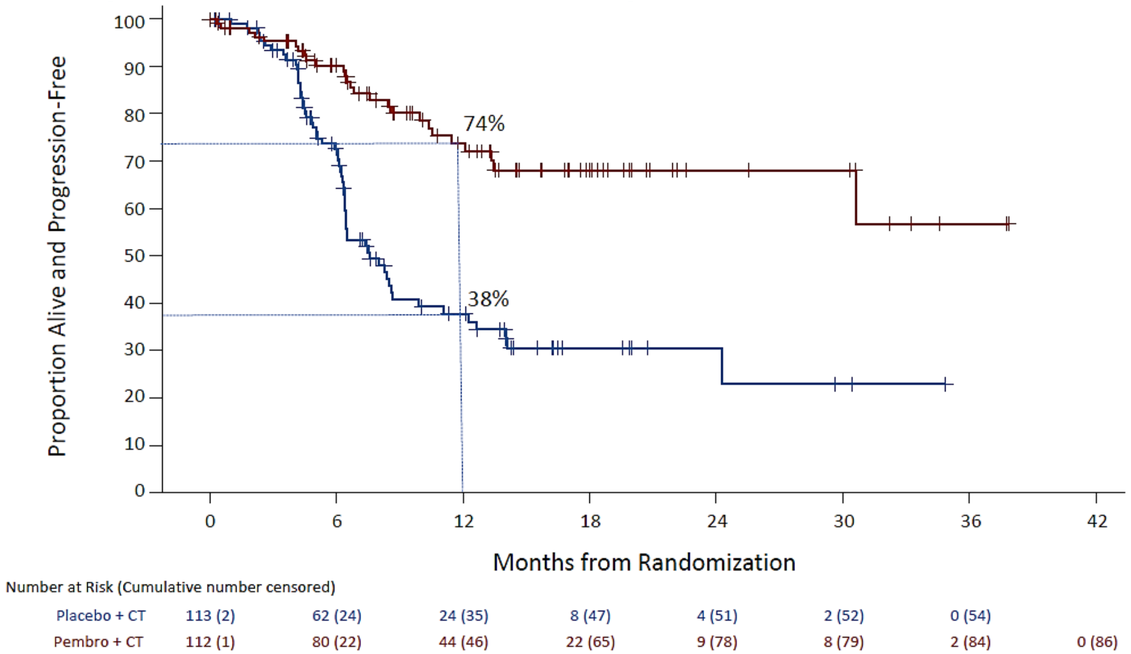
Primary endpoints: PFS per RECIST v1.1 by INV in pMMR and dMMR cohorts
Secondary endpoints: Safety, ORR/DOR, OS, PRO/QoL, concordance of MMR testing results

Patient Characteristics, n (%)		dMMR (n=225)		pMMR (n=588)	
		Pembro + CT (n=112)	Placebo + CT (n=113)	Pembro + CT (n=293)	Placebo + CT (n=295)
Median age (range), years		67 (38-81)	66 (37-85)	66 (31-93)	65 (29-90)
ECOG PS	0	72 (64.3)	73 (64.6)	196 (66.9)	198 (67.1)
	1	39 (34.8)	35 (31.0)	88 (30.0)	88 (29.8)
	2	1 (0.9)	5 (4.4)	9 (3.1)	9 (3.1)
Histology					
Clear cell		1 (0.9)	0	17 (5.8)	20 (6.8)
Endometrioid, G1		21 (18.8)	35 (31.0)	54 (18.4)	46 (15.6)
Endometrioid, G2		52 (46.4)	41 (36.3)	51 (17.4)	58 (19.7)
Endometrioid, G3		15 (13.4)	16 (14.2)	53 (18.1)	42 (14.2)
Serous		4 (3.6)	1 (0.9)	78 (26.6)	72 (24.4)
No prior chemotherapy		107 (95.5)	105 (92.9)	221 (75.4)	218 (73.9)

Data cutoff: December 16, 2022 for dMMR; December 6, 2022 for pMMR.
Eskander R, et al. SGO 2023. Abstract 264.

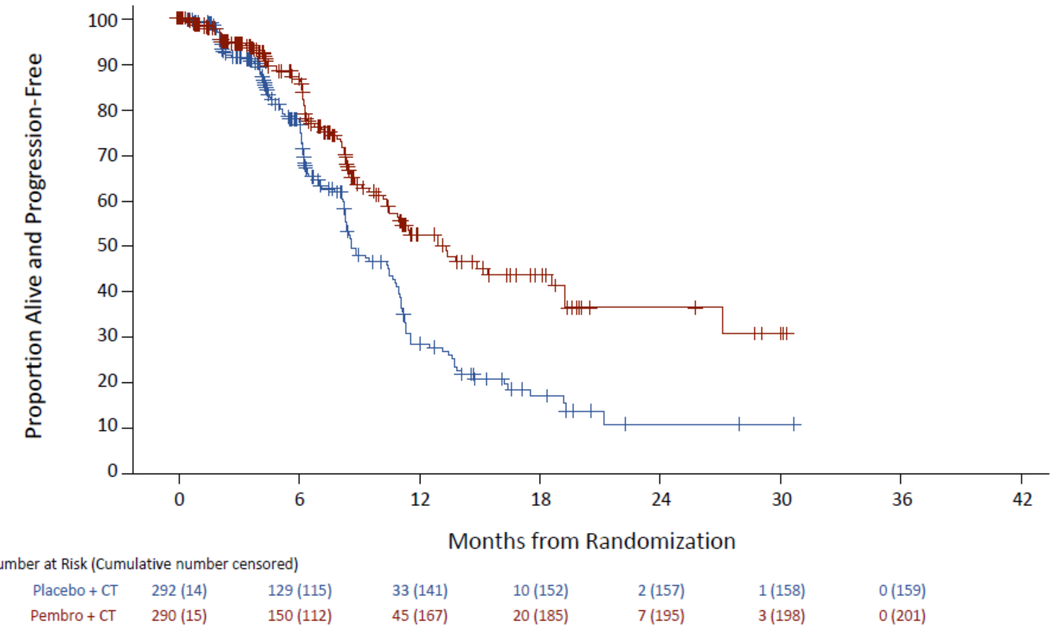
NRG GY018: Phase 3 Trial of Pembrolizumab + Chemo for Measurable Stage 3 or 4a, Stage 4b, or Recurrent EC – PFS

PFS per RECIST v1.1 in dMMR Population



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

PFS per RECIST v1.1 in pMMR Population

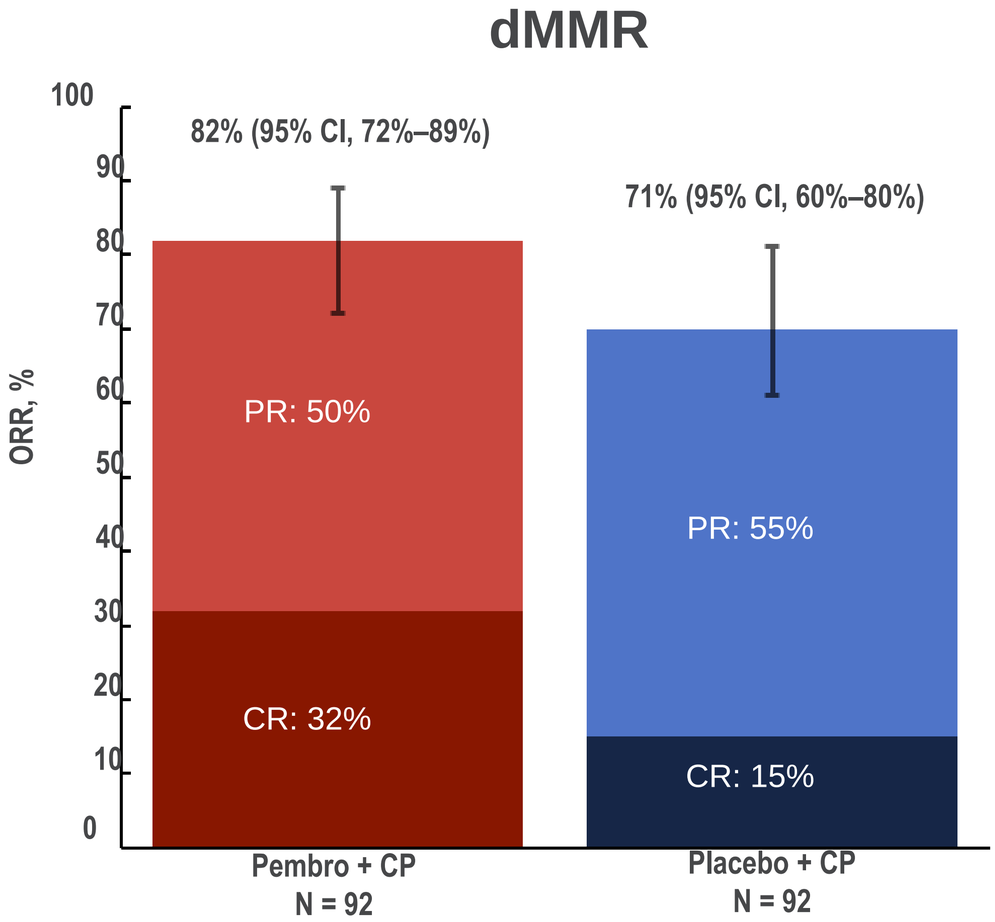


	Events, n/N	Median (95% CI), mo	HR (stratified; 95% CI)
Pembro + CT	89/290	13.1 (10.5-18.8)	**0.54 (0.41-0.71)** ***P*<0.00001**
Placebo + CT	133/292	8.7 (8.4-10.7)	

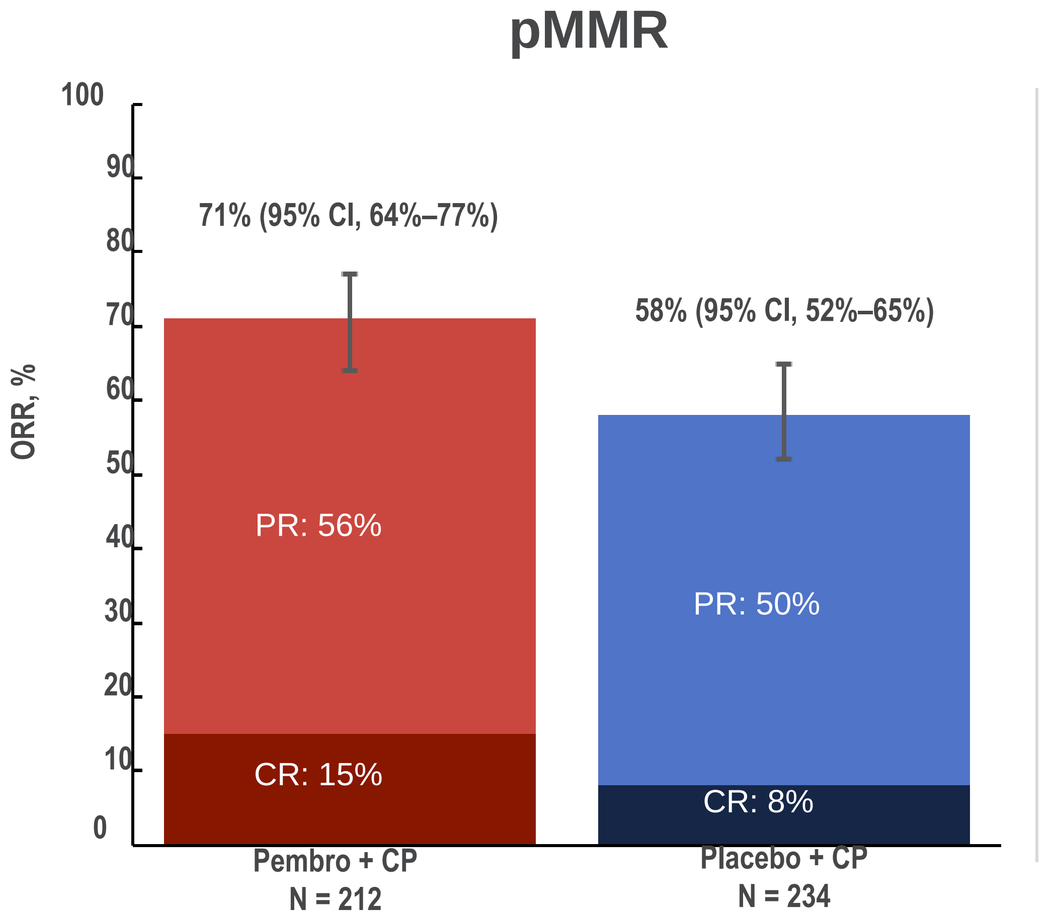
- Median follow-up: 12 months for dMMR, 7.9 months for pMMR

Data cutoff: December 16, 2022 for dMMR; December 6, 2022 for pMMR.
Eskander R, et al. N Eng J Med. March 2023

NRG GY018: ORR in dMMR and pMMR populations



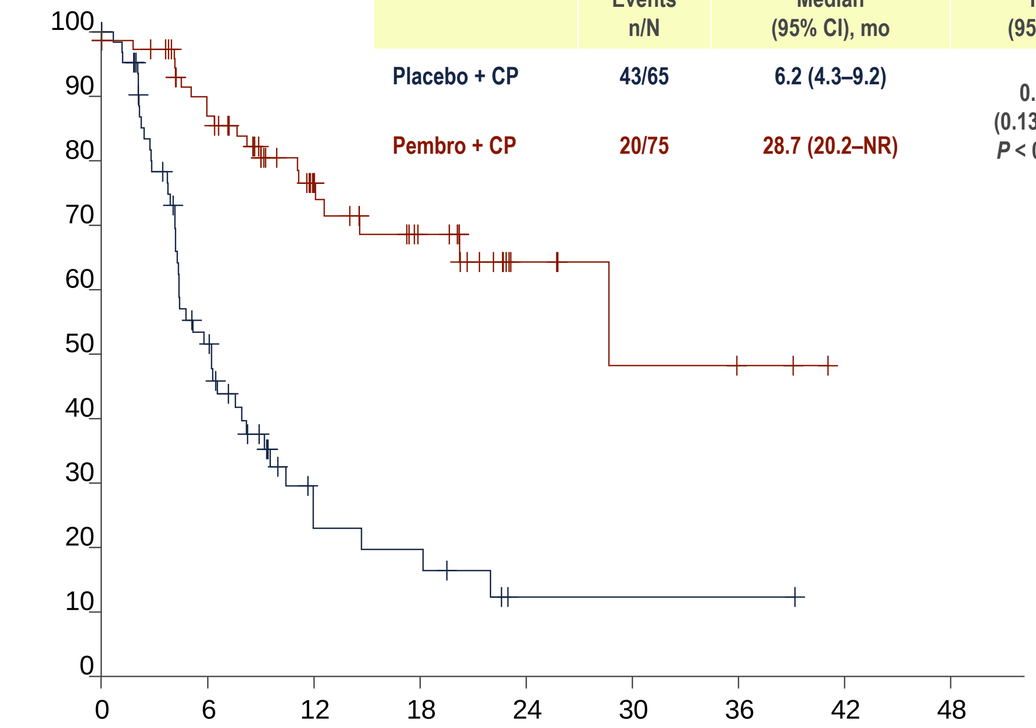
Odds ratio for response with Pembro + CP: 1.83 (95% CI, 0.92–3.66)



Odds ratio for response with Pembro + CP: 1.74 (95% CI, 1.18–2.58)

NRG GY018: Duration of Response by MMR status (Patients with CR or PR)

dMMR

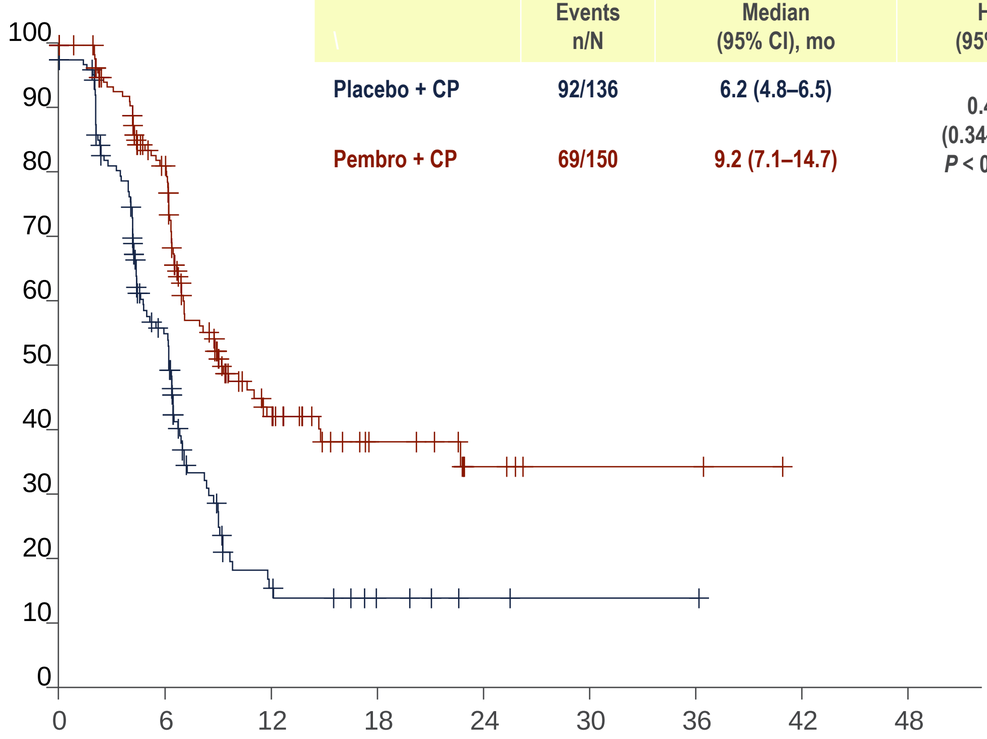


	Events n/N	Median (95% CI), mo	HR (95% CI)
Placebo + CP	43/65	6.2 (4.3–9.2)	0.218 (0.13–0.37) *P* < 0.0001
Pembro + CP	20/75	28.7 (20.2–NR)	

Number at risk (Cumulative number censored)

Placebo + CP	65 (2)	28 (9)	7 (18)	6 (18)	1 (21)	1 (21)	1 (21)	0 (22)
Pembro + CP	75 (2)	58 (8)	31 (29)	20 (37)	6 (50)	3 (52)	2 (53)	0 (55)

pMMR



	Events n/N	Median (95% CI), mo	HR (95% CI)
Placebo + CP	92/136	6.2 (4.8–6.5)	0.467 (0.34–0.64) *P* < 0.0001
Pembro + CP	69/150	9.2 (7.1–14.7)	

Number at risk (Cumulative number censored)

Placebo + CP	136 (5)	59 (21)	11 (34)	5 (39)	2 (42)	1 (43)	1 (43)	0 (44)
Pembro + CP	150 (6)	98 (26)	30 (54)	13 (69)	5 (76)	2 (79)	2 (79)	0 (81)

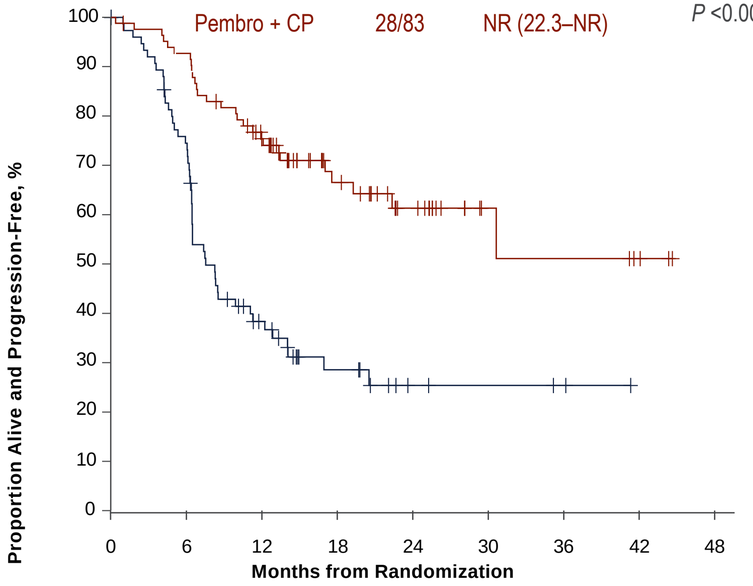
Data cutoff: Aug 18, 2023

Eskander R, et al. ESMO 2023

NRG GY018: PFS by MMR methylation status in the dMMR EC cohort

Methylation
Pembro + CP vs Placebo + CP

	Events n/N	Median (95% CI), mo	HR (95% CI)
Placebo + CP	51/77	7.5 (6.4–11.3)	
Pembro + CP	28/83	NR (22.3–NR)	0.307 (0.19–0.49) *P* <0.0001

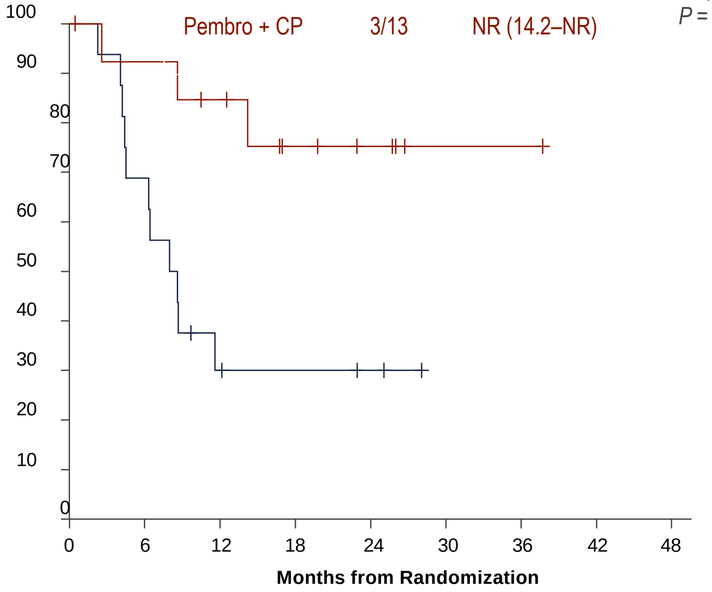


Number at risk (Cumulative number censored)

Placebo + CP	77 (2)	55 (3)	23 (9)	11 (16)	4 (22)	3 (23)	2 (24)	0 (26)	
Pembro + CP	83 (0)	76 (1)	56 (7)	30 (28)	18 (38)	6 (50)	5 (50)	3 (52)	0 (55)

No Methylation
Pembro + CP vs Placebo + CP

	Events n/N	Median (95% CI), mo	HR (95% CI)
Placebo + CP	11/17	8.3 (4.4–NR)	
Pembro + CP	3/13	NR (14.2–NR)	0.263 (0.07–0.99) *P* = 0.0172

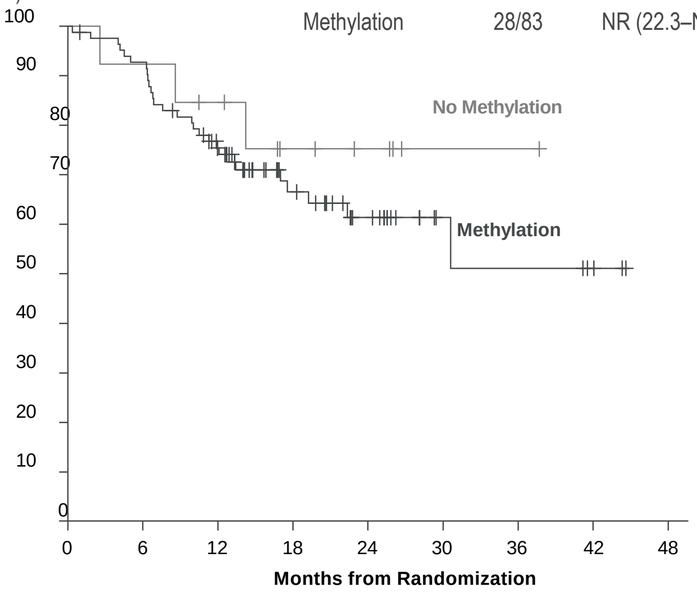


Number at risk (Cumulative number censored)

Placebo + CP	17 (0)	11 (1)	4 (2)	3 (3)	2 (4)	0 (6)			
Pembro + CP	13 (0)	12 (0)	10 (1)	6 (4)	4 (6)	1 (9)	1 (9)	0 (10)	

Methylation Status
Pembro + CP Arm

	Events n/N	Median (95% CI), mo
No Methylation	3/13	NR (14.2–NR)
Methylation	28/83	NR (22.3–NR)



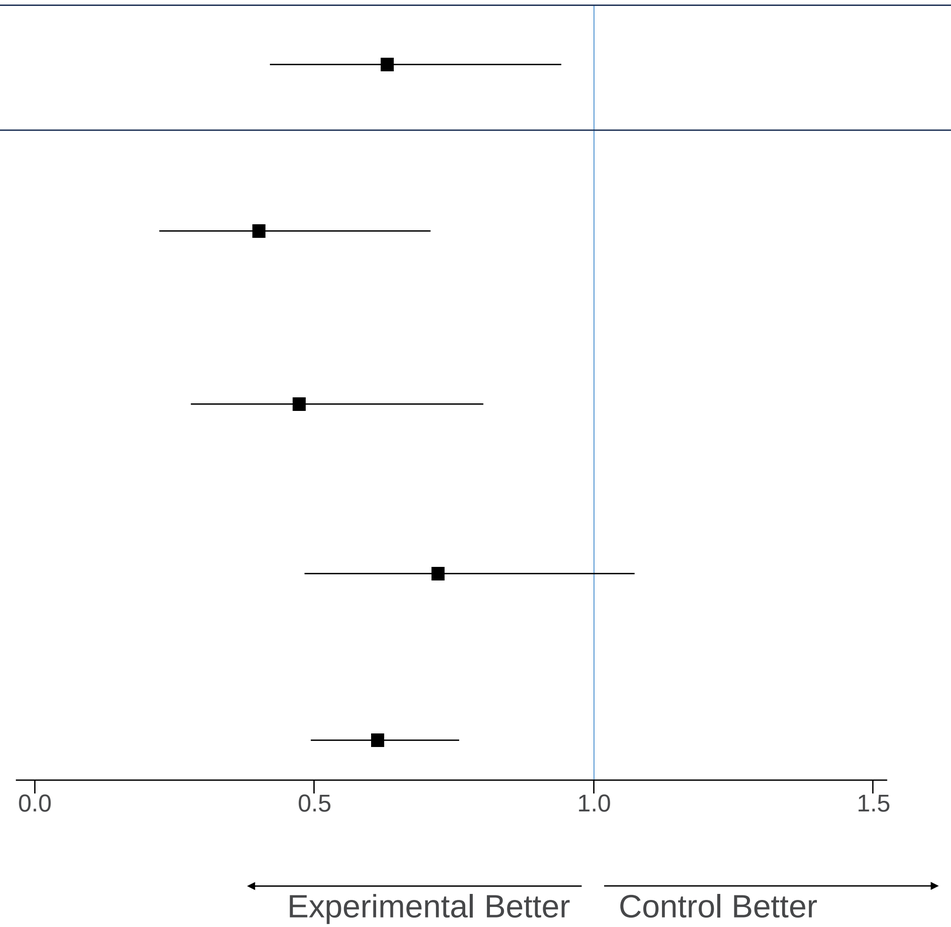
Number at risk (Cumulative number censored)

No Methylation	13 (0)	12 (0)	10 (1)	6 (4)	4 (6)	1 (9)	1 (9)	0 (10)	
Methylation	83 (0)	76 (1)	56 (7)	30 (28)	18 (38)	6 (50)	5 (50)	3 (52)	0 (55)

Data cutoff: Aug 18, 2023
Eskander R, et al. ESMO 2023

NRG GY018: PFS by histology in the pMMR population

Histology	No. of Patients	Hazard Ratio (95% CI)
Endometrioid, G1 or G2	207	
Endometrioid, G3	96	
Other Types	128	
Serous	155	
Overall	586	

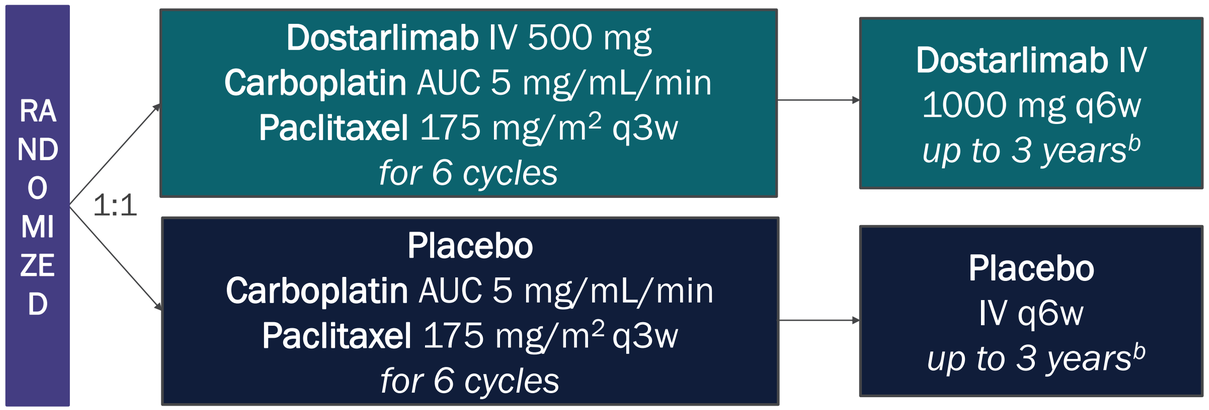


Data cutoff: Aug 18, 2023
Eskander R, et al. ESMO 2023

GOG-3031/RUBY: Phase 3 Trial of Dostarlimab + Chemo for Primary Advanced/Recurrent EC – Study Design and Patients

Key Eligibility Criteria

- Histologically/cytologically proven stage III/IV or first recurrent EC
- Carcinosarcoma, clear cell, serous, or mixed histology permitted[a]
- ECOG PS 0-1
- Naive to systemic therapy or systemic anticancer therapy and had a recurrence or PD ≥6 months after completing treatment



Stratified by MMR/MSI status,[c] prior external pelvic radiotherapy, and disease status

Primary endpoints: PFS by INV, OS
Secondary endpoints: PFS by BICR, PFS2, ORR, DOR, DCR, HRQOL/PRO, safety

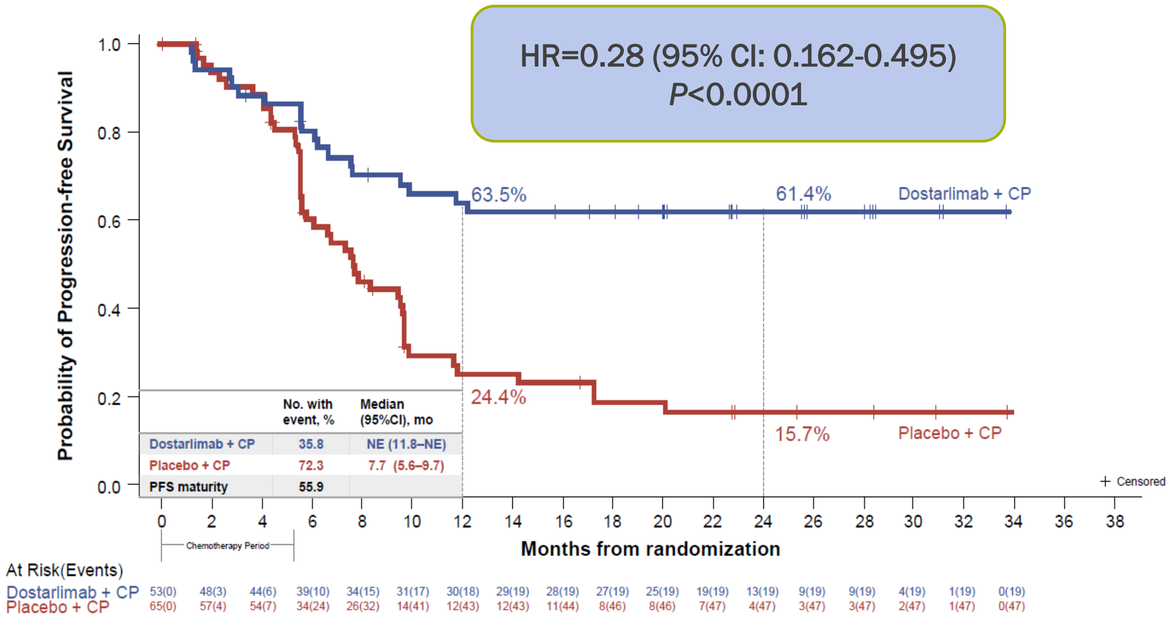
Patient Characteristics, n(%)		dMMR/MSI-H		Overall	
		Dostarlimab + CP (n=53)	Placebo + CP (n=65)	Dostarlimab + CP (n=245)	Placebo + CP (n=249)
Median age (range), years		61 (45-81)	66 (39-85)	64 (41-81)	65 (28-85)
ECOG PS	0	28 (53.8)	39 (60.0)	145 (60.2)	160 (65.0)
	1	24 (46.2)	26 (40.0)	96 (39.8)	86 (35.0)
Histology					
Clear cell		0	0	8 (3.3)	9 (3.6)
Carcinosarcoma		4 (7.5)	1 (1.5)	25 (10.2)	19 (7.6)
Endometrioid		44 (83.0)	56 (86.2)	134 (54.7)	136 (54.6)
Prior systemic therapy		7 (13.2)	10 (15.4)	48 (19.6)	52 (20.9)
Carboplatin/ paclitaxel		4 (7.5)	6 (9.2)	36 (14.7)	39 (15.7)
Measurable disease at baseline		49 (92.5)	58 (89.2)	212 (86.5)	219 (88.0)

- [a] Mixed histology containing at least 10% carcinosarcoma, clear cell, or serous histology. [b] Treatment ends after 3 years. [c] Patients were randomized based on either local or central MMR/MSI testing results. For local determination of MMR/MSI status, IHC, NGS, and PCR assays were accepted. For central determination of MMR/MSI status IHC per Ventana MMR RxDx Panel was used. Central testing was used when local results were not available.

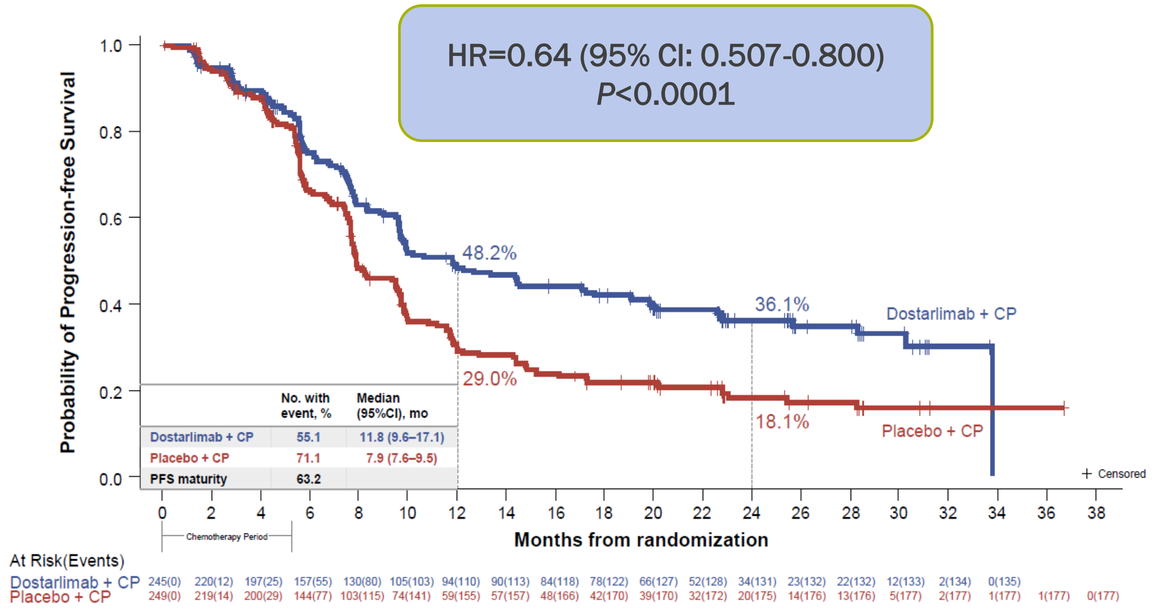
- Mirza MR, et al. SGO 2023. Abstract 265.

GOG-3031/RUBY: Phase 3 Trial of Dostarlimab + Chemo for Primary Advanced/Recurrent EC – PFS

PFS in dMMR/MSI-H Population



PFS in Overall Population

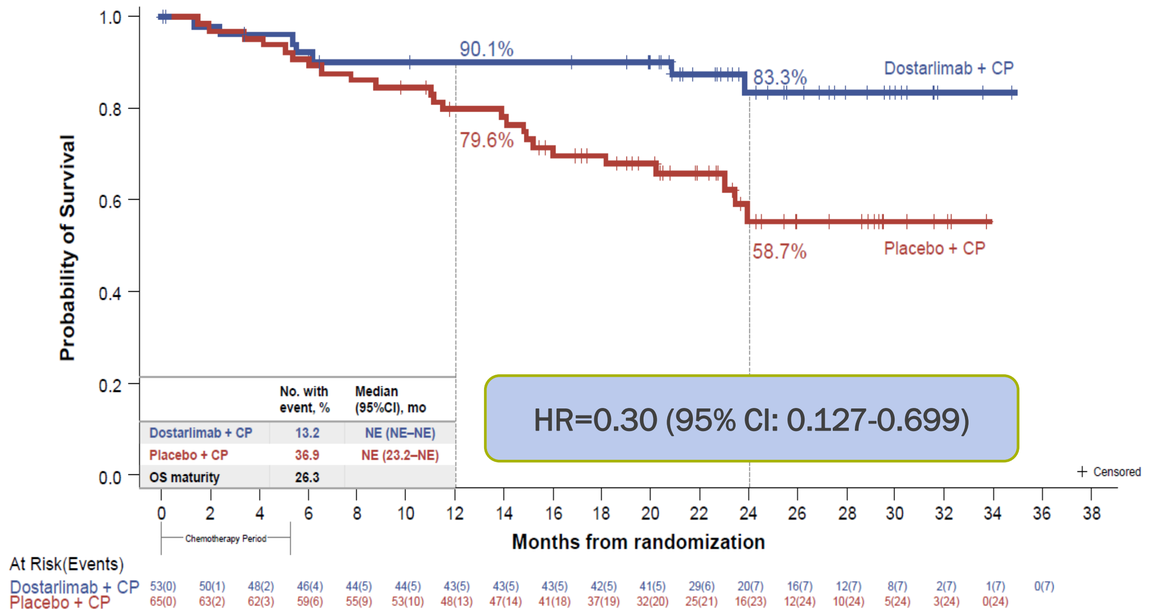


- Median duration of follow-up in the dMMR/MSI-H population was 24.79 months
- Median duration of follow-up in the overall population was 25.38 months

Data cutoff: September 28, 2022.
Mirza MR, et al. SGO 2023. Abstract 265.

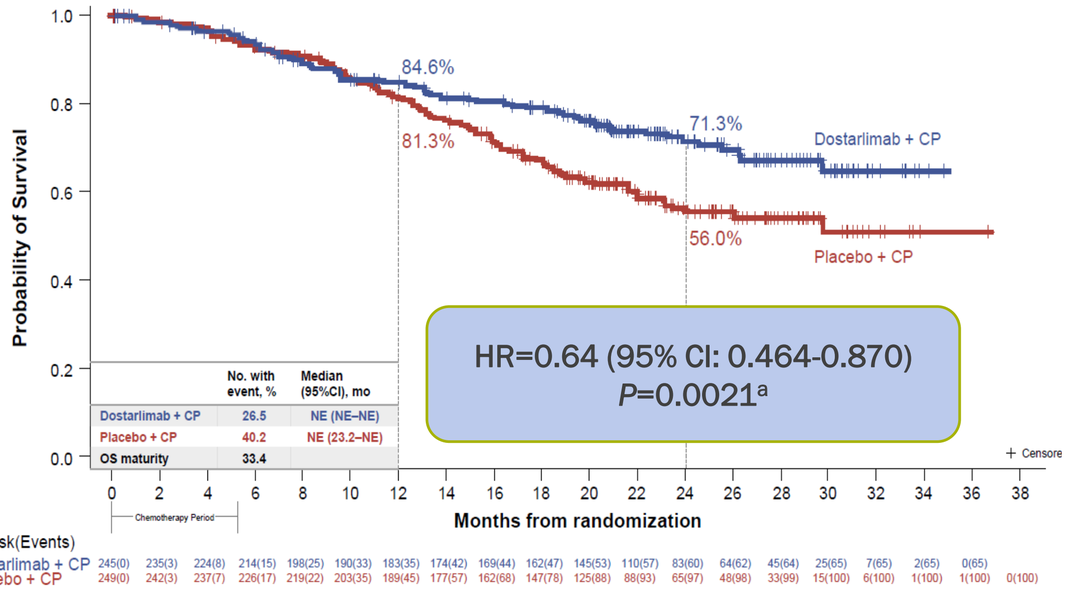
GOG-3031/RUBY: Phase 3 Trial of Dostarlimab + Chemo for Primary Advanced/Recurrent EC – OS

OS in dMMR/MSI-H Population



Received subsequent immunotherapy:
- 38.5% of patients on placebo arm
- 15.1% of patients on dostarlimab arm

OS in Overall Population (33% Maturity)

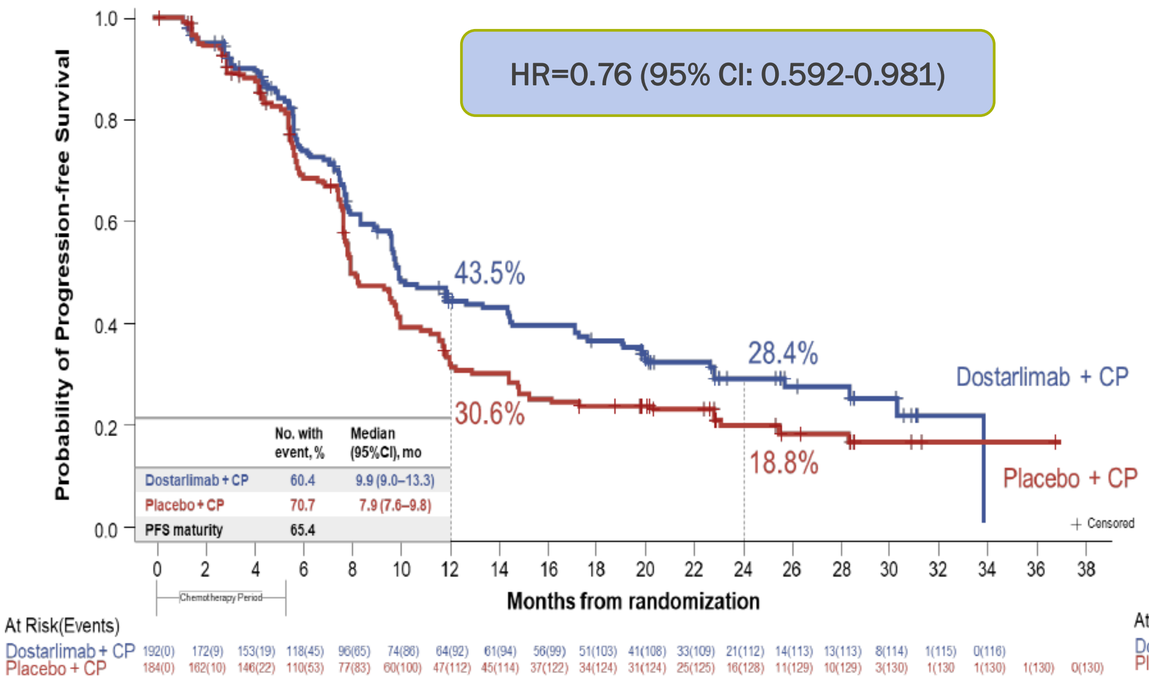


Received subsequent immunotherapy:
- 34.5% of patients on placebo arm
- 15.5% of patients on dostarlimab arm

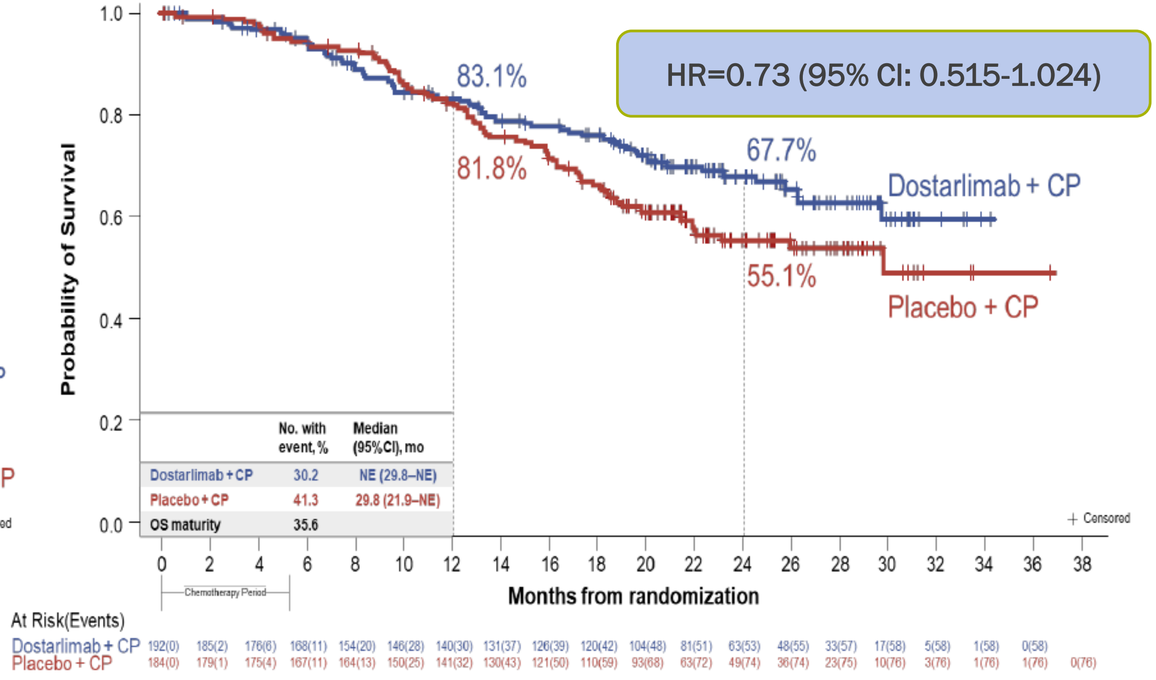
Data cutoff: September 28, 2022. Median duration of follow-up in overall population was 25.38 months.
[a] $P \leq 0.00177$ required to declare statistical significance at first interim analysis.
Mirza MR, et al. SGO 2023. Abstract 265.

GOG-3031/RUBY: Phase 3 Trial of Dostarlimab + Chemo for Primary Advanced/Recurrent EC – Efficacy in pMMR/MSS Population

PFS in pMMR/MSS Population



OS in pMMR/MSS Population



Received subsequent immunotherapy:

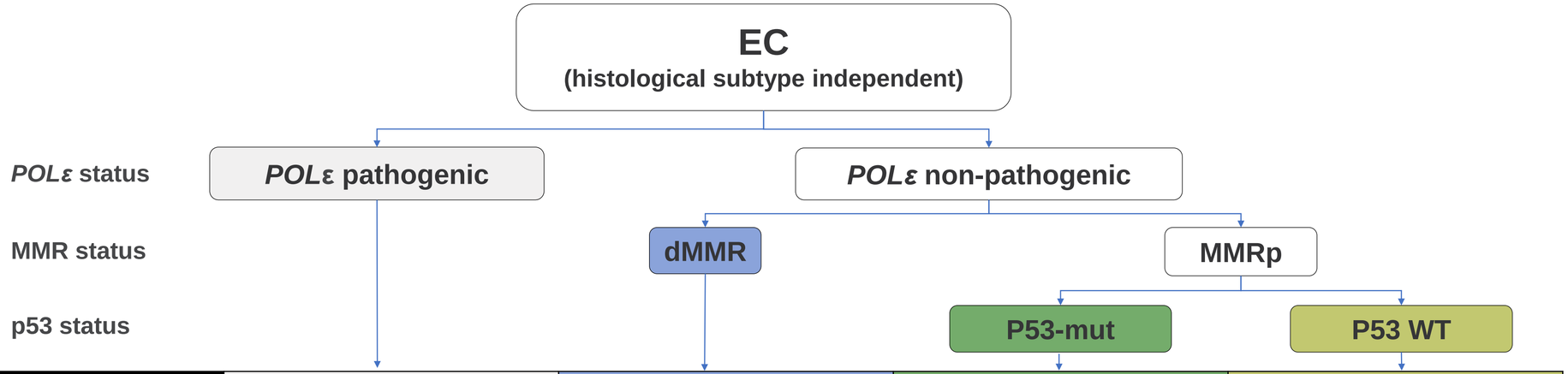
- 33.2% of patients on placebo arm
- 15.6% of patients on dostarlimab arm

Data cutoff: September 28, 2022.

Mirza MR, et al. SGO 2023. Abstract 265.

GOG-3031/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	

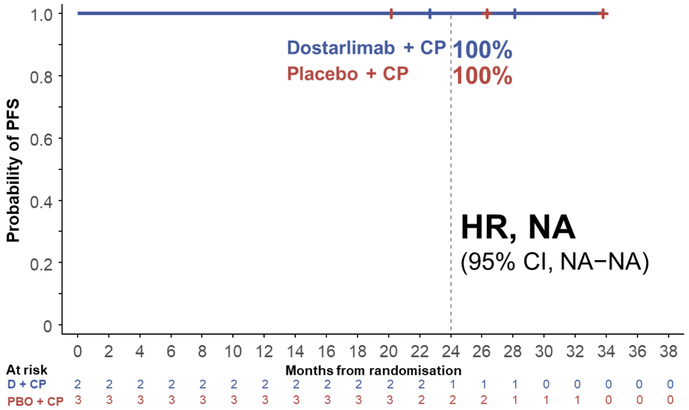
Efficacy per molecular classification was an exploratory analysis.
dMMR, mismatch repair deficient; EC, endometrial cancer; EDM, exonuclease domain; IHC, immunohistochemistry; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; mut, mutated; NGS, next generation sequencing; NSMP, no specific molecular profile; PCR, polymerase chain reaction; POLε, polymerase epsilon; TP53, tumor protein 53; WES, whole exome DNA sequencing; WT, wild type.

Mirza MR, et al. ESMO 2023.

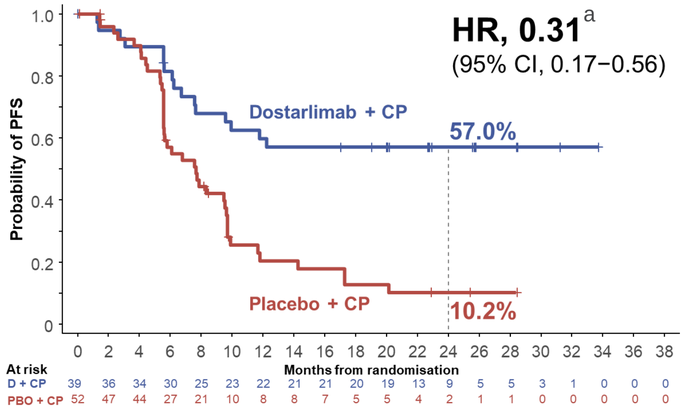
GOG-3031/RUBY: PFS according to molecular subgroup

Based on 400/494 patients with known molecular classification per whole exome sequencing

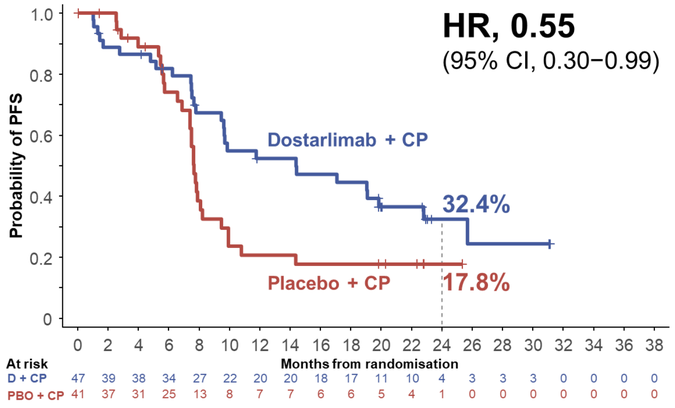
POLε mut



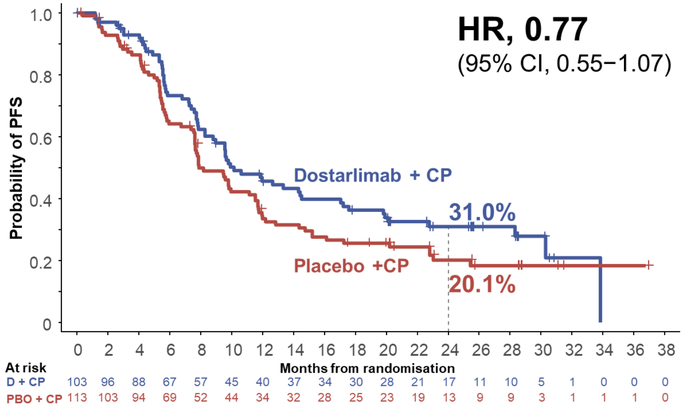
dMMR/MSI-H



TP53 mut



NSMP

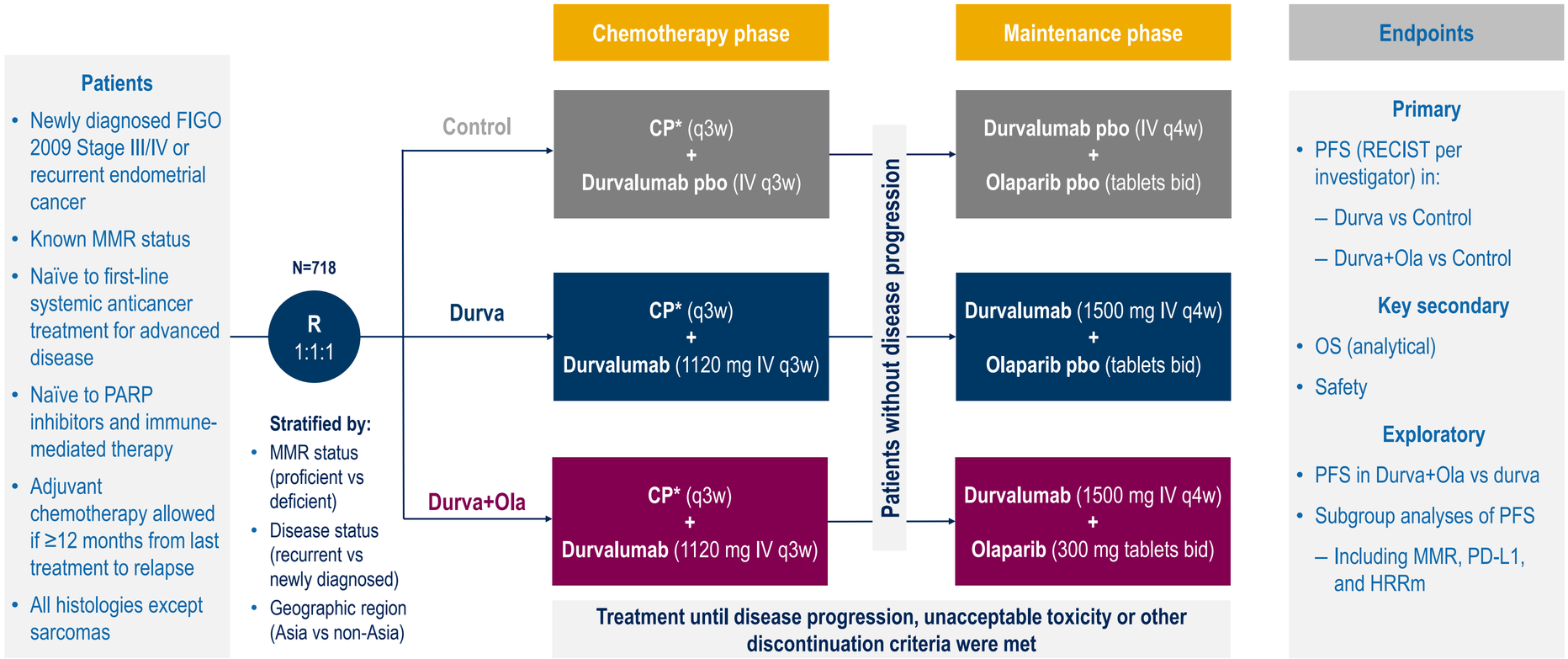


[a]Primary endpoint of PFS in dMMR/MSI-H patients (n=118) showed HR, 0.28; *P*<0.0001

CP, carboplatin-paclitaxel; D, dostarlimab; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability–high; mut, mutated; NA, not applicable; NSMP, no specific molecular profile; PBO, placebo; PFS, progression-free survival; POLε , polymerase epsilon; TP53, tumor protein 53.

Mirza MR, et al. ESMO 2023.

DUO-E/GOG-3041/ENGOT-en10



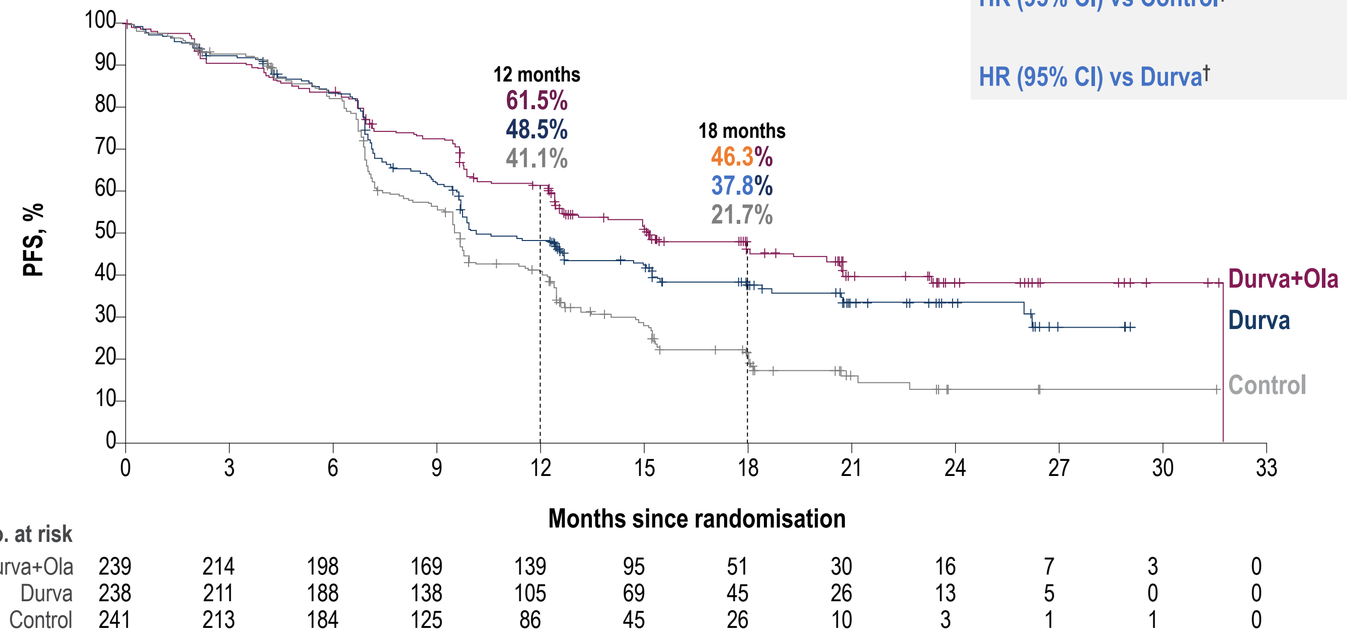
*Six cycles of carboplatin at an area under the concentration–time curve of 5 or 6 mg per mL/min and paclitaxel 175 mg/m^2.
bid, twice daily; CP, carboplatin/paclitaxel; durva, durvalumab; FIGO, International Federation of Gynaecology and Obstetrics; HRRm, homologous recombination repair mutation; IV, intravenously; ola, olaparib; pbo, placebo; q3(4)w, every 3(4) weeks; R, randomisation; RECIST, Response Evaluation Criteria for Solid Tumours.

Westin, S et al. ESMO 2023.

DUO-E: PFS in the ITT population

	Control (N=241)	Durva (N=238)	Durva+Ola (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) vs Control†		**0.71** (0.57–0.89); *P*=0.003	**0.55** (0.43–0.69); *P*<0.0001
HR (95% CI) vs Durva†			0.78 (0.61–0.99)

Overall data maturity 61.0%

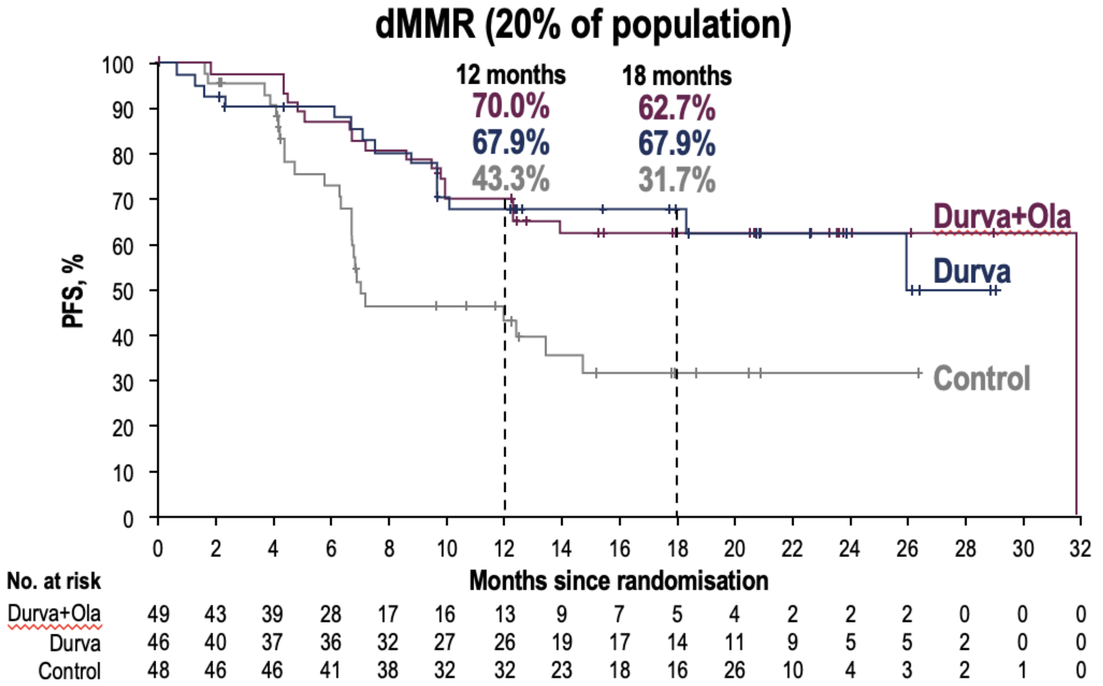


No. at risk												
Durva+Ola	239	214	198	169	139	95	51	30	16	7	3	0
Durva	238	211	188	138	105	69	45	26	13	5	0	0
Control	241	213	184	125	86	45	26	10	3	1	1	0

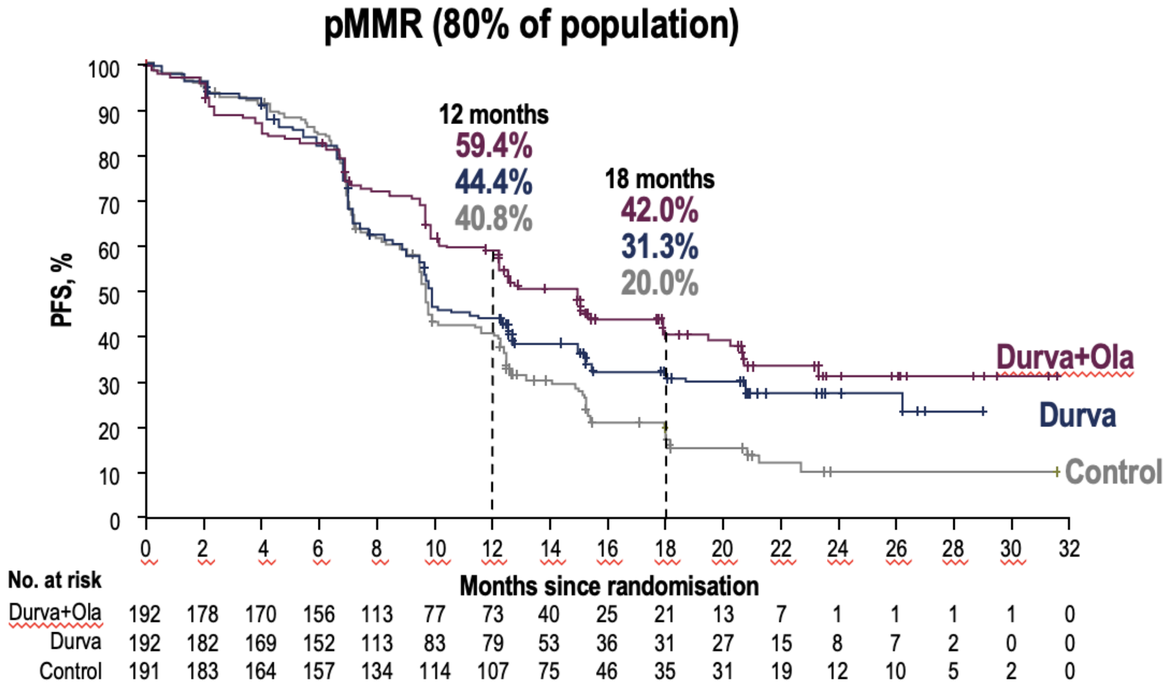
The median (range) duration of follow-up for PFS was 12.6 (0.0–31.6), 15.4 (0.0–29.1), and 15.4 (0.0–31.7) months in censored patients for the Control, Durva, and Durva+Ola arms, respectively. PFS rates were estimated by the KM method. *CI for median PFS is derived based on the Brookmeyer–Crowley method; †The primary PFS analysis for each comparison was performed separately. The HR and CI were estimated from a Cox proportional hazards model stratified by MMR and disease status. The CI was calculated using a profile likelihood approach. The *P* value was calculated using a log-rank test stratified by MMR and disease status. ITT, intent-to-treat; KM, Kaplan–Meier.

Westin, S et al. ESMO 2023.

DUO-E: Subgroup analysis of PFS by MMR status



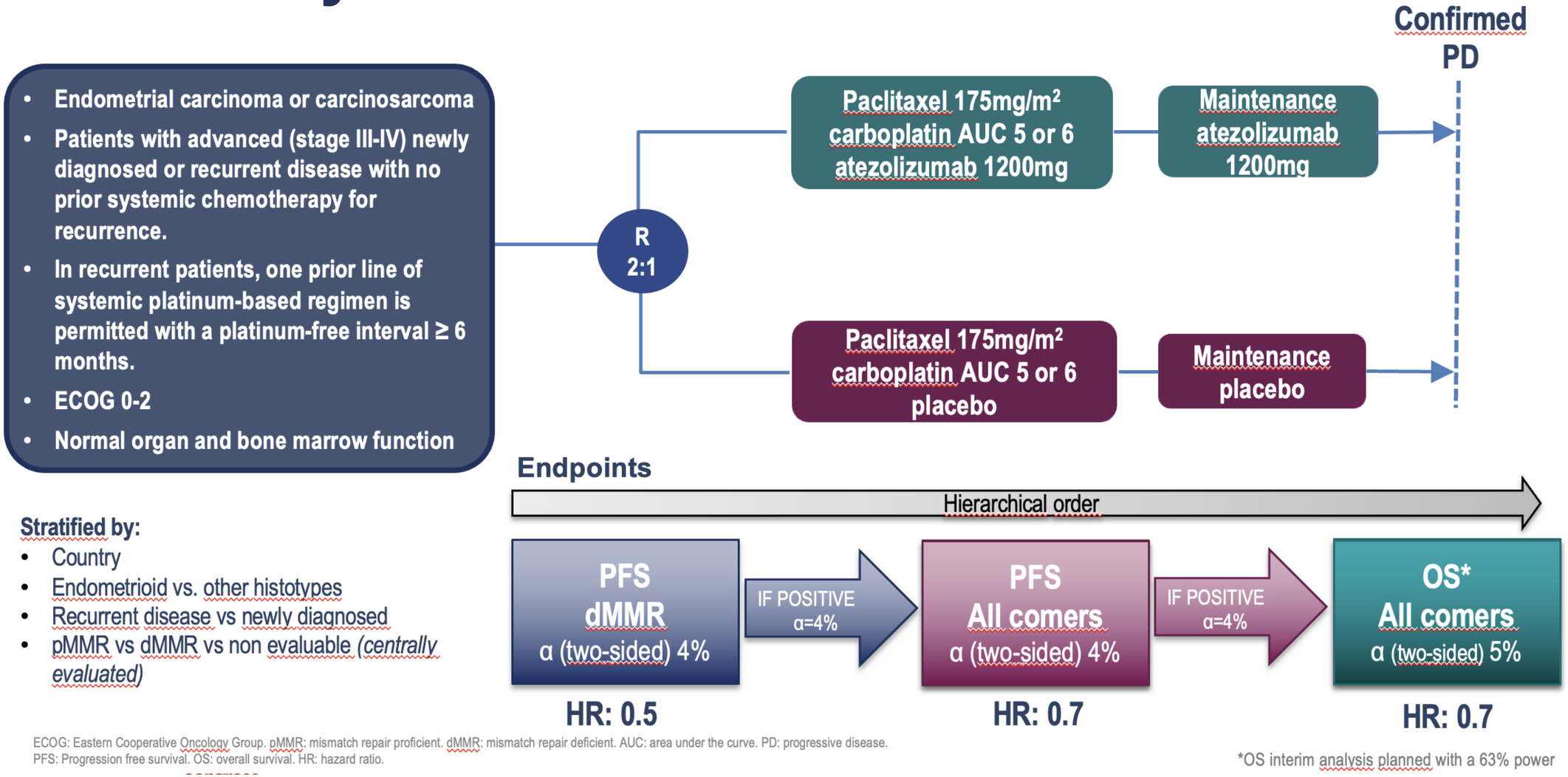
	Control (N=49)	Durva (N=46)	Durva+Ola (N=48)
Events, n (%)	25 (51.0)	15 (32.6)	18 (37.5)
Median PFS (95% CI),* months	7.0 (6.7–14.8)	NR (NR–NR)	31.8 (12.4–NR)
HR (95% CI) vs Control†		**0.42 (0.22–0.80)**	**0.41 (0.21–0.75)**
HR (95% CI) vs Durva†			**0.97 (0.49–1.98)**



	Control (N=192)	Durva (N=192)	Durva+Ola (N=191)
Events, n (%)	148 (77.1)	124 (64.6)	108 (56.5)
Median PFS (95% CI),* months	9.7 (9.2–10.1)	9.9 (9.4–12.5)	15.0 (12.4–18.0)
HR (95% CI) vs Control†		**0.77 (0.60–0.97)**	**0.57 (0.44–0.73)**
HR (95% CI) vs Durva†			**0.76 (0.59–0.99)**

Westin, S et al. ESMO 2023.

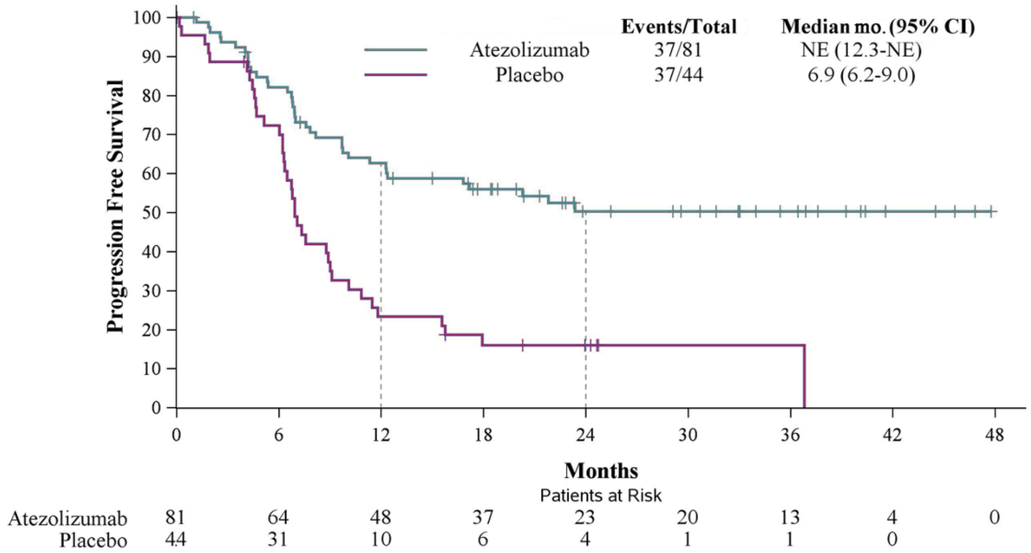
AtTEnd Study Schema



Colombo N et al. ESMO 2023.

AtTEnd: dMMR EC cohort PFS and OS

PFS dMMR



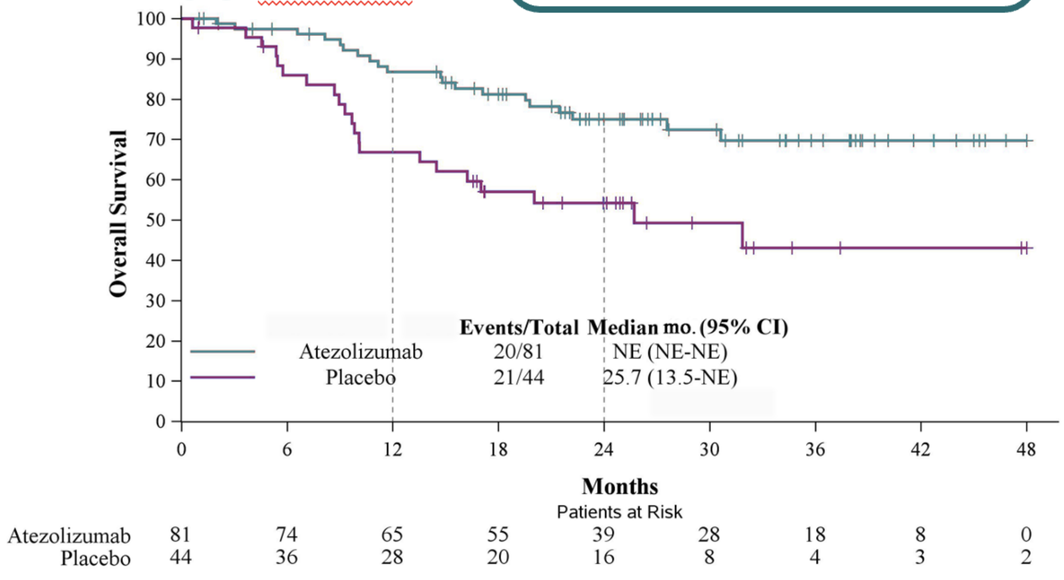
Logrank test **p=0.0005**

HR 0.36 95%CI 0.23 to 0.57

Subsequent immunotherapy

Atezolizumab arm	*6.2%*
Placebo arm	*40.9%*

OS dMMR

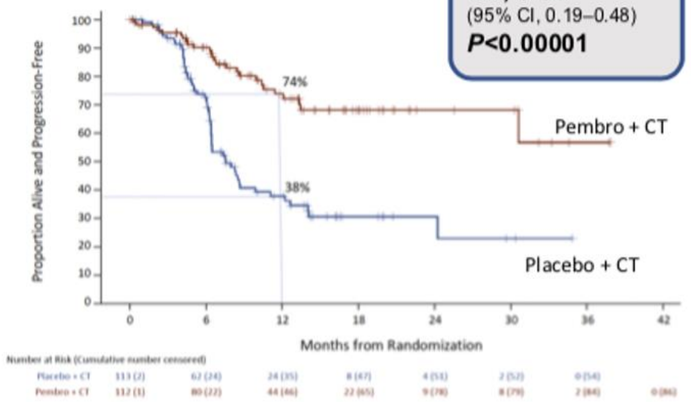


HR 0.41
95%CI 0.22 to 0.76

Colombo N et al. ESMO 2023.

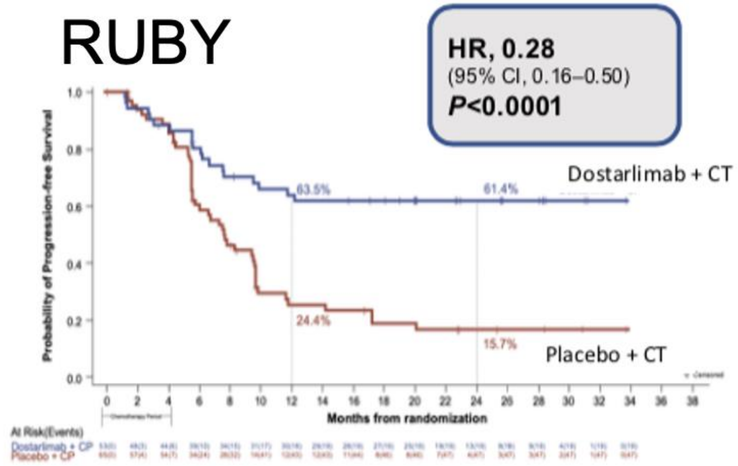
Benefit of IO + Chemo in the dMMR EC population

GY018



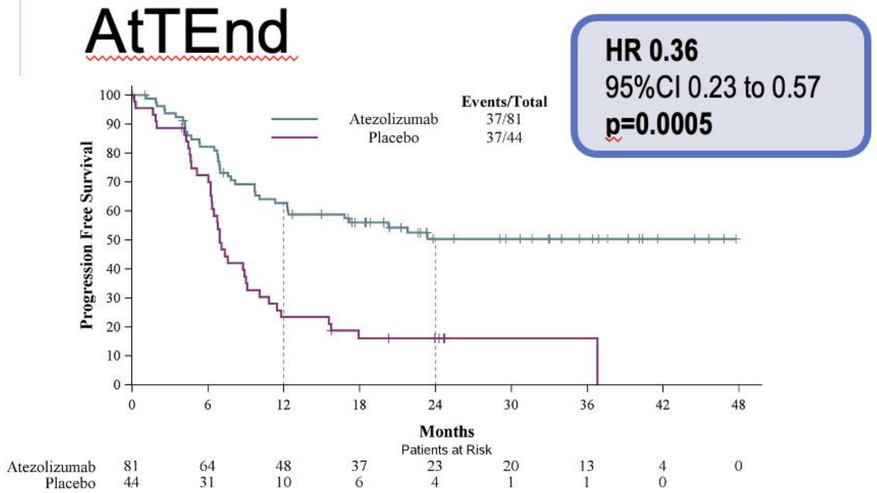
	No with events%	Median
Pembro + CT	23.2	NR (30.6-NR)
Placebo + CT	52.2	7.6 (6.4-9.9)

RUBY



	No with events%	Median
Dorsta + CT	35.8	NR (11.8-NR)
Placebo + CT	72.3	7.7 (5.6-9.7)

AtTEnd



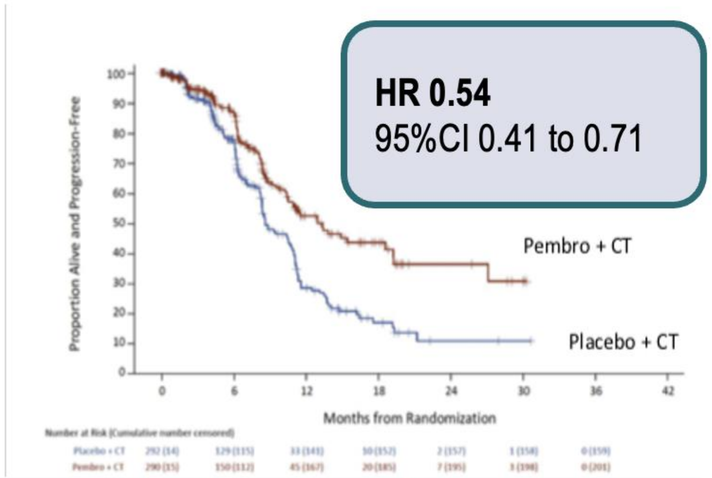
	No with events%	Median
Atezo + CT	45.7	NR (12.3-NR)
Placebo + CT	84.1	6.9 (6.2-9.0)

Slide courtesy of Dr. David Tan; ESMO 2023.

Benefit of IO + Chemo in the pMMR EC population

Primary Endpoint: Prespecified

GY018

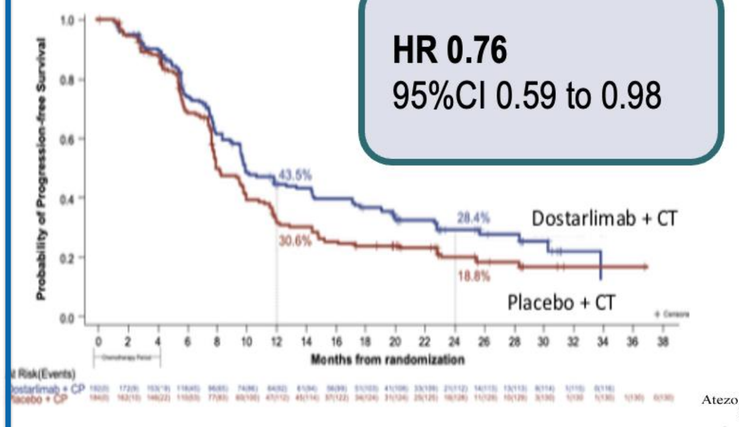


HR 0.54
95%CI 0.41 to 0.71

	No with events%	Median
Pembro + CT	30.6	13.1 (10.5-18.8)
Placebo + CT	45.5	8.7 (8.4-10.7)
Maturity	38.1%	

Secondary Analysis: Not prespecified

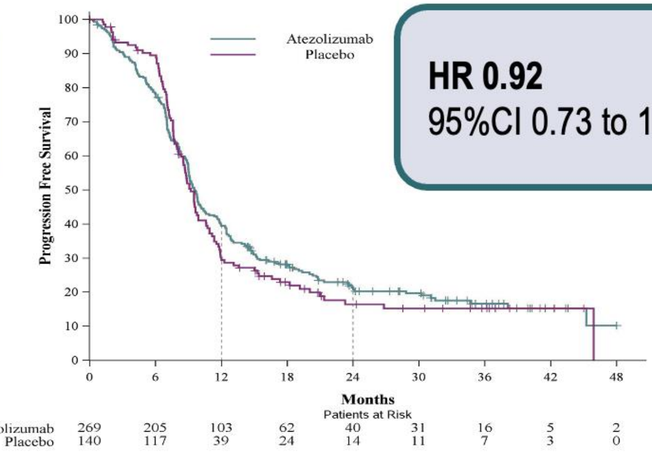
RUBY



HR 0.76
95%CI 0.59 to 0.98

	No with events%	Median
Dorsta + CT	60.4	9.9 (9.0-13.3)
Placebo + CT	70.7	7.9 (7.6-9.8)
Maturity	65.4%	

AtTEnd



HR 0.92
95%CI 0.73 to 1.16

	No with events%	Median
Atezo + CT	78	9.5 (9.0-10.4)
Placebo + CT	77	9.2 (8.5-9.9)
Maturity	78%	

Slide courtesy of Dr. David Tan; ESMO 2023.

Benefit of IO + Chemo in the pMMR EC population

Primary Endpoint: Prespecified

Secondary Analysis: Not prespecified

Why the discrepancy between trials…?

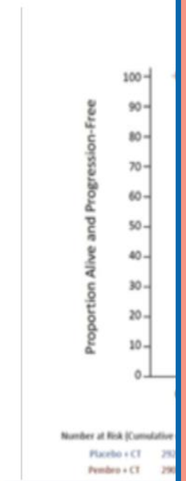
GY018 only study powered to examine the pMMR cohort independently?

Carcinosarcoma excluded from GY018, but included in RUBY, and AtTEnd (~10%)?

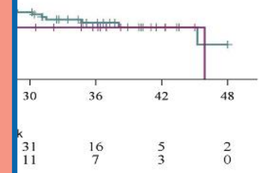
Racial/ethnic composition (Asian 20% in AtTEnd)?

Prior adjuvant therapy (12 vs 6 months)?

Anti PD-1 vs anti PD-L1?



HR 0.92
95%CI 0.73 to 1.16



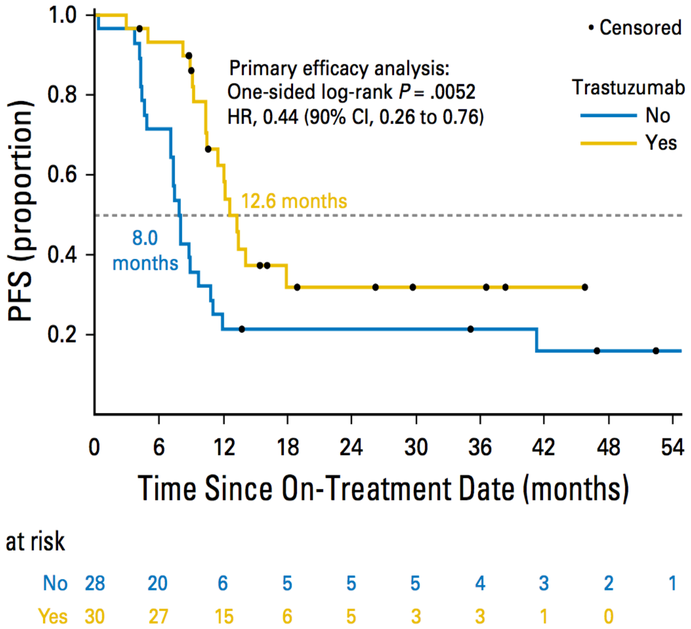
	Median
Pembro + CT	9.5 (9.0-10.4)
Placebo + CT	9.2 (8.5-9.9)
Maturity	78%

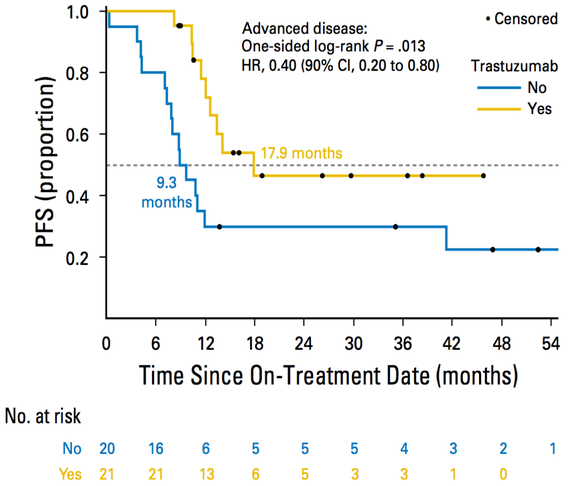
Slide courtesy of Dr. David Tan; ESMO 2023.

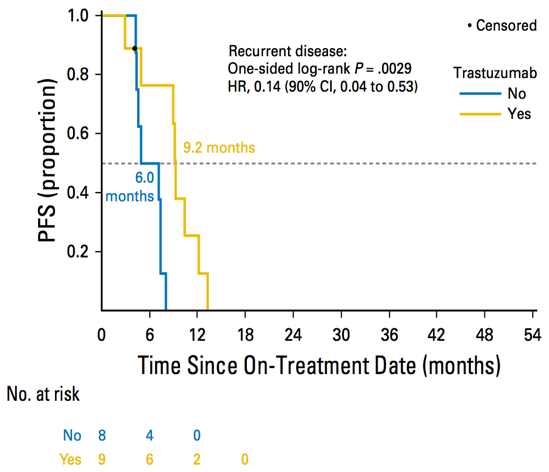
Incorporation of anti-HER-2 treatment: Trastuzumab with Chemotherapy

Key eligibility criteria

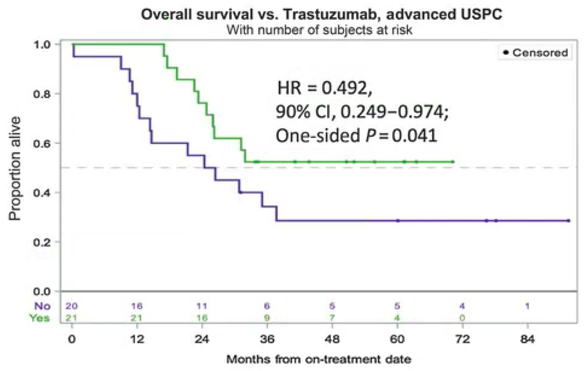
- Primary stage III or IV or recurrent HER2/neu-positive USC: IHC score 3+, or 2+ with + FISH
- ECOG 0-2
- ≤3 prior lines of therapy
- “platinum sensitive” recurrence (6 mo)

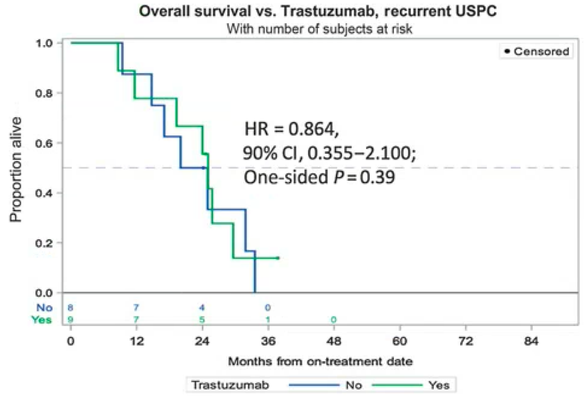






<u>OS benefit particularly striking in stage III–IV patients, OS median of 25.4 months (control) versus NR (p = 0.041, HR = 0.49, 90% CI 0.25–0.97).</u>





Nickles-Fader J Clin Oncol 2018

NRG-GY026 Study Schema

NCT05256225

Chemo-naïve, non-recurrent, stage I-IVB, HER2 positive endometrial serous carcinoma or carcinosarcoma

Stratification
- Stage I-II v. III-IV
- Histology (serous vs carcinosarcoma)
- Plan for vaginal brachytherapy (yes vs no)

Randomization 1:1:1

Arm 1:
Paclitaxel/Carboplatin every 3 weeks x 6 cycles

Arm 2:
Paclitaxel/Carboplatin/Trastuzumab and hyaluronidase-oysk (HERCEPTIN HYLECTA) every 3 weeks x 6 cycles

Maintenance HERCEPTIN HYLECTA every 3 week for up to 1 year

Arm 3:
Paclitaxel/Carboplatin/Pertuzumab, Trastuzumab, and hyaluronidase-zzsf (PHESGO) q 3 weeks x 6 cycles

Maintenance PHESGO every 3 weeks for up to 1 year

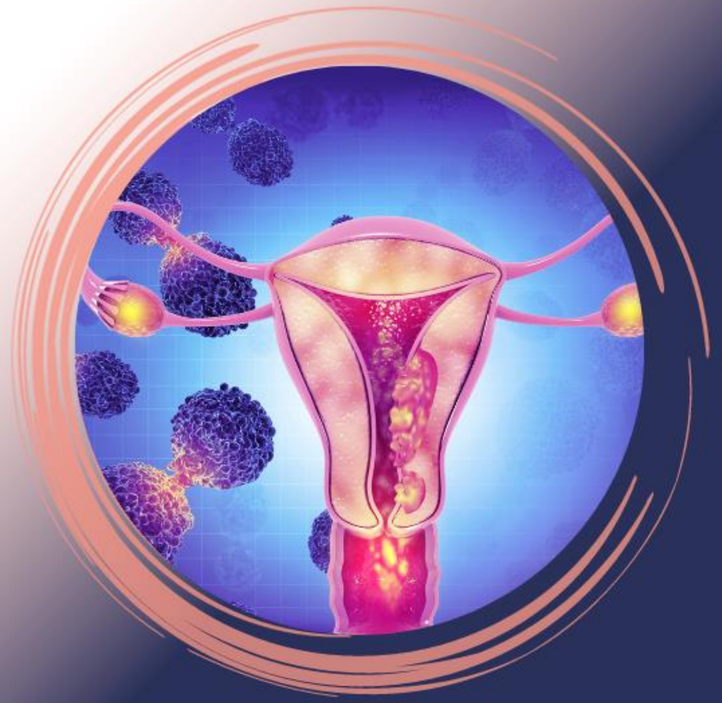
INTERVAL TOXICITY ASSESSMENT

INTERIM FUTILITY ANALYSIS

Convert to phase 3 if active arm(s)

Courtesy of Dr. B. Erickson

Systemic Therapy for Recurrent Disease



Eisai has sponsored this initiative with IGCS and had no input into or influence over the content.

Limited Efficacy with Chemotherapy in Previously Treated Patients

- Phase 2/3 studies involving a combined total of **1887 patients**

Type of Study and Number of EC Patients	Treatment	ORR	Durability of Response
Phase 2 N=42[1]	PLD	9.5%	Median # courses, 2.5; **OS: 8.2 months**
Phase 2 N=22[2]	Topotecan	9.0%	Median # courses, 4
Phase 2 N=44[3]	Paclitaxel	27.3%	DOR: 4.2 months; **OS:10.3 months**
Phase 2 N=52[4]	Oxaliplatin	13.5%	DOR: 10.9+ months
Phase 2 N=26[5]	Docetaxel	7.7%	PFS: 2.0 months; **OS: 6.4 months**
Phase 2 N=50[6]	Ixabepilone	12%	PFS: 2.9 months; **OS: 8.7+ months**
Group I N=586 for patients who received 2L in Phase 3 GOG trials Group II N=275 patients 2L chemo trials Phase 2[7]	Various		**OS: <11months**
Phase 2 (N=23)[8]	Gemcitabine	4.0%	PFS: 1.7 months
Phase 2 (N=28)[9]	Everolimus	0%	Median duration of SD: 4.5 months
Phase 2 (N=25 for patients previously treated with chemotherapy)[10]	Temsirolimus	4.0%	PFS: 3.25 months
Phase 2 (N=52)[11]	Bevacizumab	13.5%	PFS: 4.17 months; **OS: 10.55 months**
Phase 2 (N=45)[12]	Ridaforolimus	11%	6-month PFS: 18%
Phase 2 (N=35)[13]	Everolimus and letrozole	31.4%	PFS: 3.0 months; **OS: 14 months**
Phase 3 RCT (N=496)[14]	Ixabepilone vs paclitaxel or doxorubicin	15.2% vs 15.7%	Ixabepilone: PFS:3.4 months; **OS:10.9 months** Paclitaxel or Doxorubicin: PFS:4.0 months; **OS, 12.3 months**
Phase 2 trial (N=82)[15]	Anastrozole	7%	PFS 3.2 months

2L, second-line; DOR, duration of response; EC, endometrial cancer, GOG, Gynecologic Oncology Group; ORR, objective response rate; OS, overall survival, PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; RCT, randomized controlled trial; SD. stable disease.

1. Muggia FM et al. *J Clin Oncol* 2002;20:2360-2364. 2. Miller DS et al. *Gynecol Oncol* 2002;87:247-251. 3. Lincoln S et al. *Gynecol Oncol* 2003;88:277-281. 4. Fracasso PM et al. *Gynecol Oncol* 2006;103:523-526. 5. Garcia AA et al. *Gynecol Oncol* 2008;111:22-26. 6. Dizon DS et al. *J Clin Oncol* 2009;27:3104-3108. 7. Moore KN et al. *Cancer* 2010;116:5407-5414. 8. Tait DL et al. *Gynecol Oncol* 2011;121:118-121. 9. Slomovitz BM et al. *Cancer* 2010;116:5415-5419. 10. Oza AM et al. *J Clin Oncol* 2011;29:3278-3285. 11. Aghajanian C et al. *J Clin Oncol* 2011;29:2259-2265. 12. Colombo N et al. *Br J Cancer* 2013;108:1021-1026. 13. Slomovitz BM et al. *J Clin Oncol* 2015;33:930-936. 14. McMeekin S et al. *Gynecol Oncol* 2015;138:18-23. 15. Mileshkin L et al. *Gynecol Oncol* 2019;154:29-37.

Single Agent IO in “non-biomarker” Selected Endometrial Cancer Populations

- Response to single agent IO in pMMR or MSI-stable endometrial cancer has been modest

Study & Drug	Patient Population	Outcome
Keynote 28: Pembrolizumab (N=24)	Advanced stage or metastatic PD-L1 + endometrial cancer	ORR: 13%
PHAEDRA trial: Durvalumab (N=36 pMMR)	Advanced stage or metastatic endometrial cancer	ORR in pMMR: 3%
GARNET study: Dostarlimab (N=94)	Previously treated, recurrent advanced stage endometrial cancer	ORR in pMMR: 13.9%
Ph II Avelumab study (N= 16 pMMR)	Advanced stage or metastatic endometrial cancer	ORR: 6.25%

Ott PA et al. J Clin Oncol 2017
Antill PSK et al. J Clin Oncol 2019
Oaknin A et al. Gynecol Oncol 2019
Konstantinopoulos PA et al. J Clin Oncol 2019
Pothuri et al. SGO Annual Meeting 2021

Combinatorial IO approach: Lenvatinib + Pembrolizumab Keynote 775 (NCT03517449)

- **Advanced, recurrent or metastatic endometrial**
- **Progressive disease 1-2 prior platinum regimens**
- **Measurable disease per RECIST 1.1**
- **Available archival tumor tissue**
- **Performance status of 0 to1**
- **Adequate organ function**

R

1:1

Pembrolizumab 200 mg IV q 3 weeks plus lenvatinib 20 mg PO once daily (QD) during each 21-day cycle for up to 35 cycles.

EITHER: <u>Doxorubicin</u> 60 mg/m2 IV q 3 weeks (max cumulative dose of 500 mg/m2) OR <u>Paclitaxel</u> 80 mg/m2 administered by IV on a 28-day cycle: 3 weeks receiving paclitaxel once a week and 1 week not receiving paclitaxel.

Stratification:

1. MMR status (pMMR or dMMR)
2. ECOG performance status (0 or 1)
3. Geographic region
4. Prior history of pelvic radiation (yes or no)

Primary endpoints:

1) Progression-free Survival (PFS) by RECIST 1.1 by BICR
2) Overall Survival (OS).

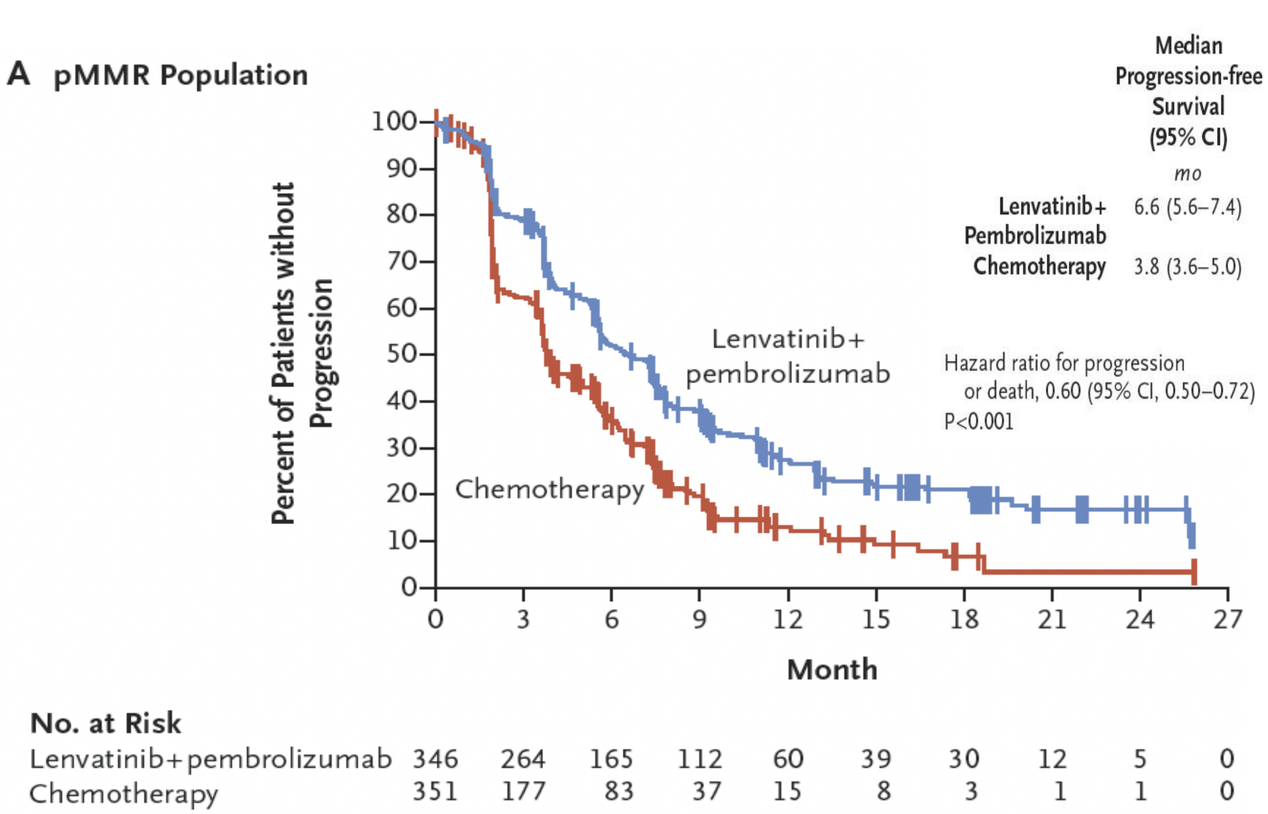
Secondary endpoints:

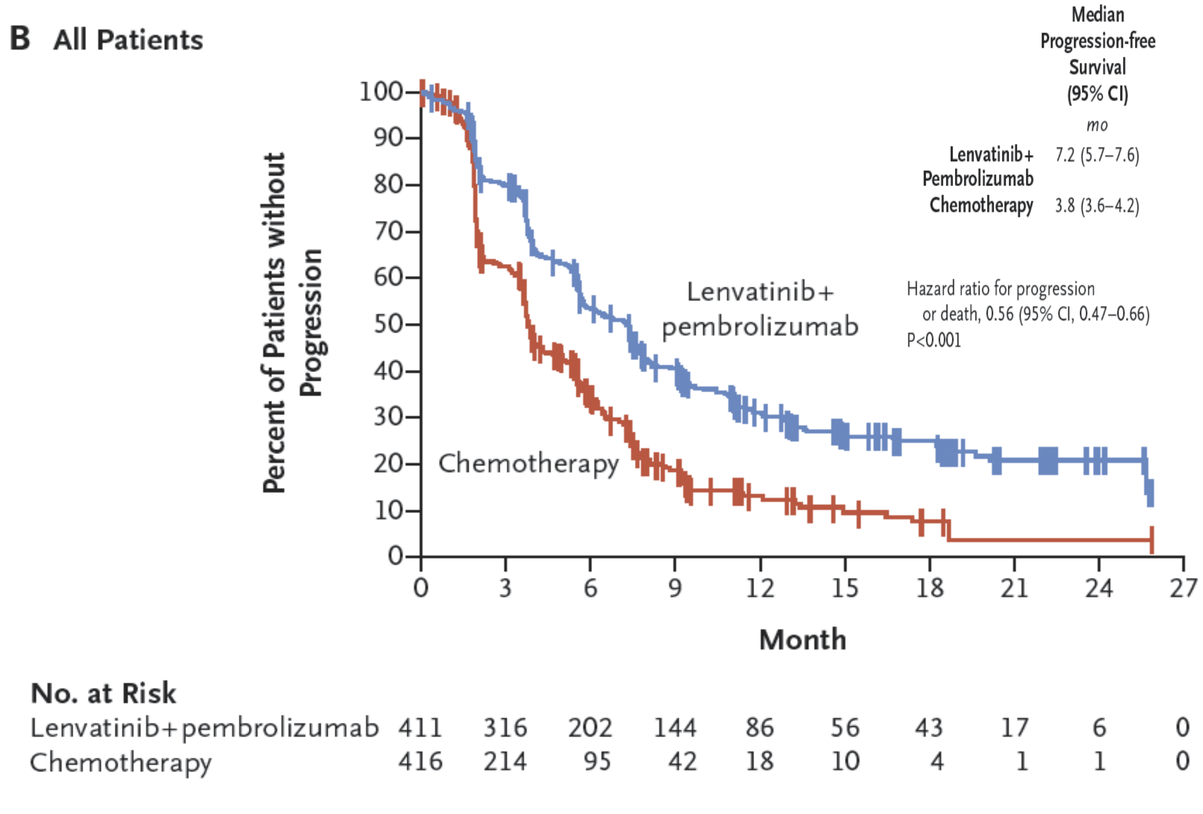
1) ORR, DOR, TTF, AEs, PK, PROs

Makker et al. N Eng J Med. 2022

Combinatorial IO approach: Lenvatinib + Pembrolizumab Keynote 775 (NCT03517449)

Progression Free Survival

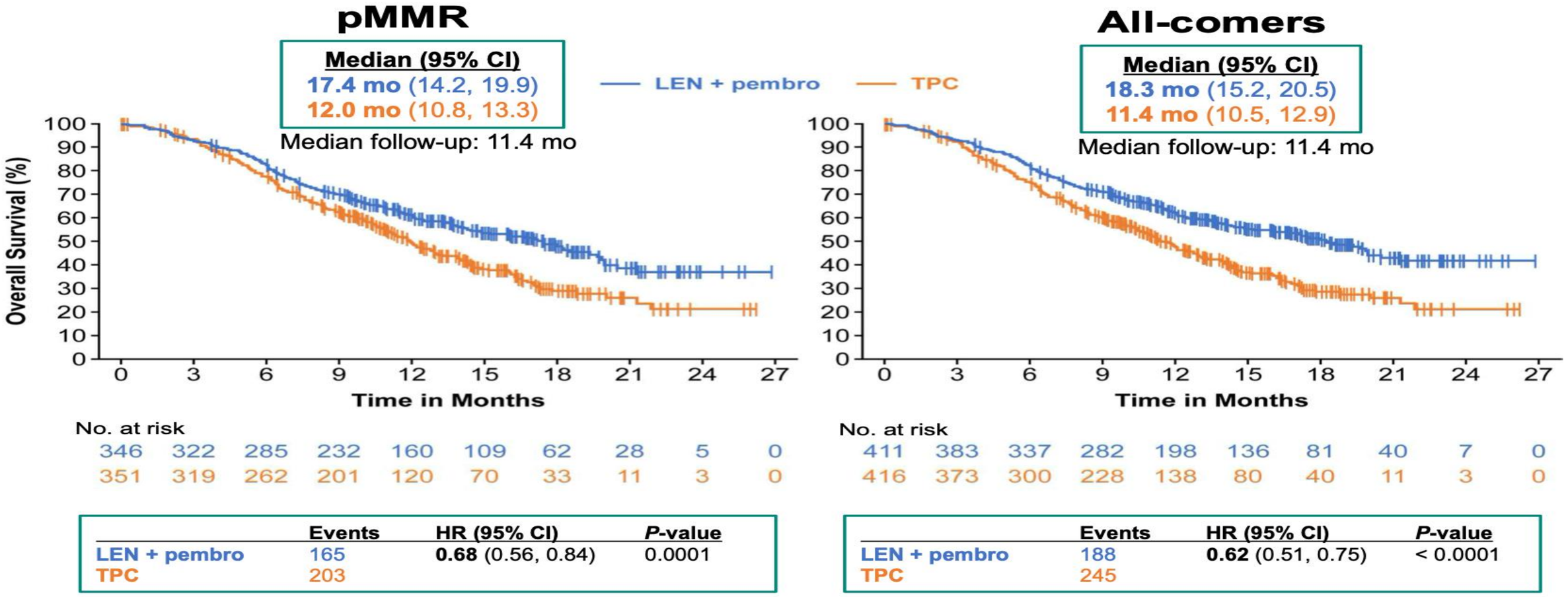




Makker et al. N Eng J Med. 2022

Combinatorial IO approach: Lenvatinib + Pembrolizumab Keynote 775 (NCT03517449)

Overall Survival



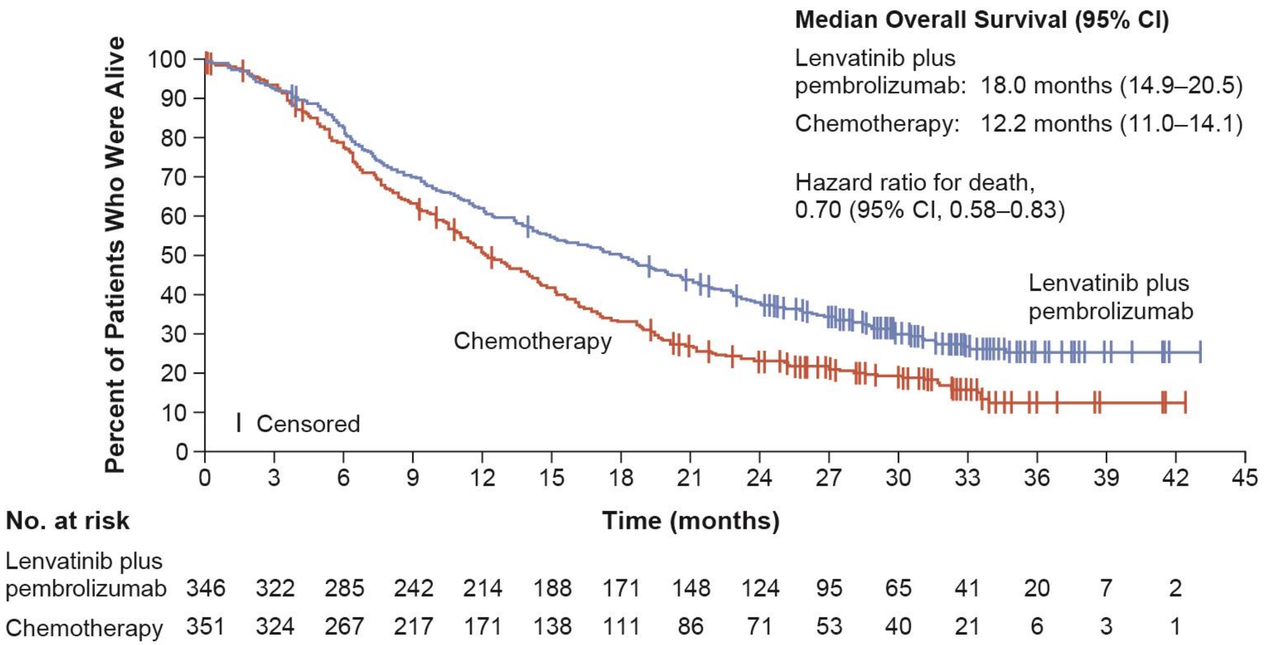
	Events	HR (95% CI)	*P*-value
LEN + pembro	165	**0.68** (0.56, 0.84)	0.0001
TPC	203		

	Events	HR (95% CI)	*P*-value
LEN + pembro	188	**0.62** (0.51, 0.75)	< 0.0001
TPC	245		

Makker et al. N Eng J Med. 2022

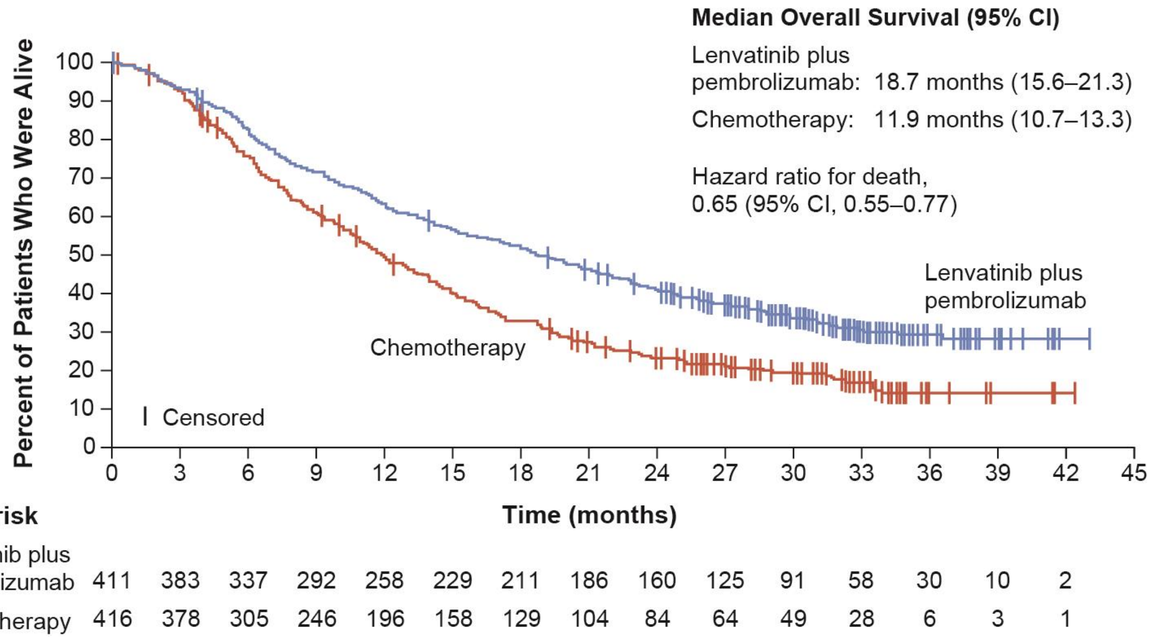
Continued OS benefit of lenvatinib plus pembrolizumab vs chemotherapy with follow-up extended by over 16 months

pMMR Population



No. at risk															
Lenvatinib plus pembrolizumab	346	322	285	242	214	188	171	148	124	95	65	41	20	7	2
Chemotherapy	351	324	267	217	171	138	111	86	71	53	40	21	6	3	1

All-Comer Population



No. at risk															
Lenvatinib plus pembrolizumab	411	383	337	292	258	229	211	186	160	125	91	58	30	10	2
Chemotherapy	416	378	305	246	196	158	129	104	84	64	49	28	6	3	1

- OS favors lenvatinib plus pembrolizumab despite some pts in the chemotherapy arm receiving subsequent lenvatinib plus pembrolizumab. **(In the chemotherapy arm, 10.0% of pts in the pMMR population and 8.7% of pts in the all-comer population).**
  - After excluding these pts, the **pMMR OS HR was 0.64 (95% CI, 0.54, 0.76); the all-comer OS HR was 0.60 (95% CI, 0.51, 0.71).**

Makker et al. J Clin Oncol. 2023

Evolution of Molecularly Directed Therapy in Endometrial Cancer

TP53

- Predictor of response to anti angiogenic therapy…
- **GOG-86P:**
  PFS HR 0.48 vs 0.87 in mutant TP53 vs. TP53wt
- Inhibition of nuclear export of wild type TP53
  - **Selinexor median PFS in TP53wt of 13.7 mo vs 3.7 months with placebo (HR 0.71)**

Anti-HER2

- Evolution of anti-HER2 treatments…
- **DESTINY-Pan Tumor02**:
  ORR 57.5%; Median DOR: NR
- **Nishikawa et al. 2023: ORR** 54.5% & 70%
- **NRG GY026…**

DNA Damage Repair

- Potential opportunity in the mutant TP53 population
- **ADAGIO:** Adavosertib single agent Medial prior LOT = 3
  BICR ORR 26%
  Median PFS 2.8mo
- **PARPi (UTOLA) – Joly F et al. ESMO 2023**
- **DUO-E- Westin et al. ESMO 2023**

Hormonal Therapies

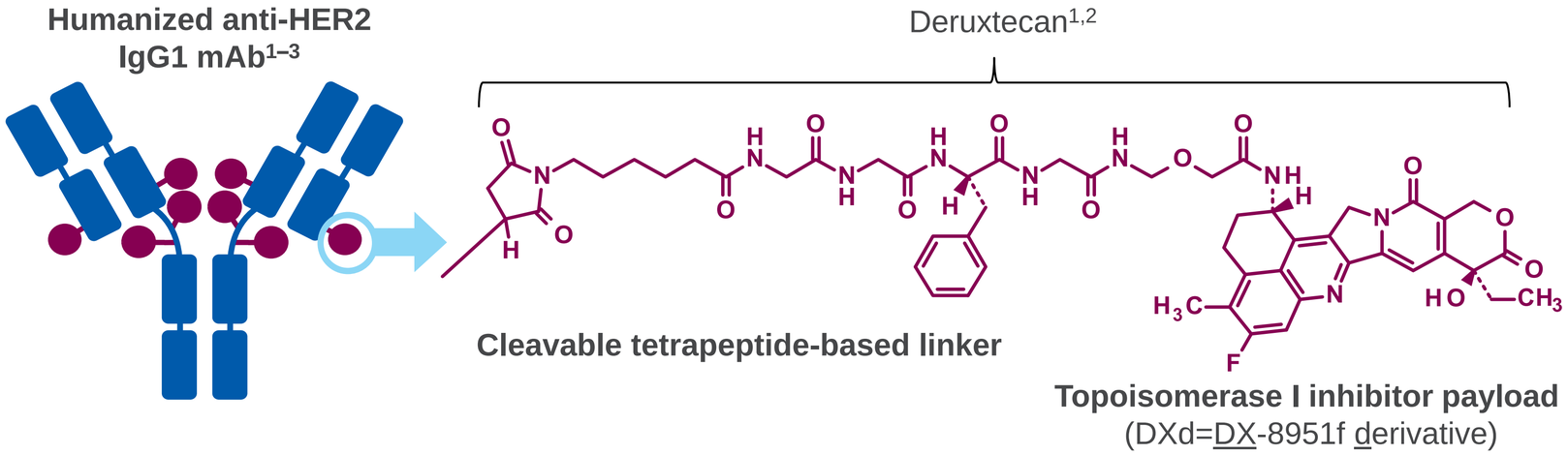
- Possible role in the copy number low TP53wt population
- **PALEO Study:** Letrozole vs Palbocilcib + letrozole
  HR 0.56
  Median PFS 8.3 vs 3 mo
- **Letrozole + Abemaciclib: ORR 30%**

- Aghajanian et al. J Clin Oncol. 2011; Leslie K. et al. Gyncol Oncol 2021; Nickles-Fader J Clin Oncol 2018; Nickles-Fader Clin Cancer Research 2020; Nishikawa et al. J Clin Oncol. 2023; Liu JF, et al. SGO 2023. Abstract 219; Mirza et al. ESMO 2020; P Konstantinopoulos et al. J Clin Oncol 2022; Funda Meric-Bernstam, MD et al. ASCO 2023. Vergote et al. J Clin Oncol 2023

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 interim results

T-DXd is an ADC with three components:

1. A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
2. A topoisomerase I inhibitor payload, an exatecan derivative
3. A tetrapeptide-based cleavable linker



[a]The clinical relevance of these features is under investigation.

ADC, antibody–drug conjugate; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; mAb, monoclonal antibody; T-DXd, trastuzumab deruxtecan.

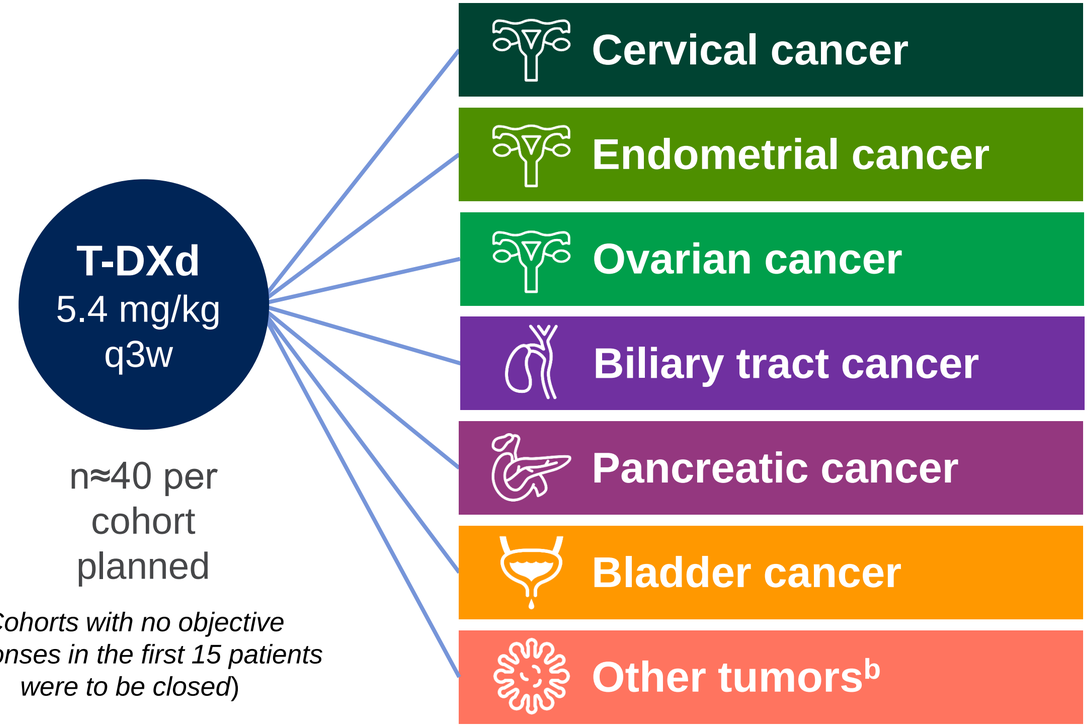
1. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173–185. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097–5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126–142. 4. Okamoto H, et al. *Xenobiotica*. 2020;50(10):1242–1250. 5. Nagai Y, et al. *Xenobiotica*. 2019;49(9):1086–1096.

Eisai has sponsored this initiative with IGCS and had no input into or influence over the content.

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 interim results

An open-label, multicenter study (NCT04482309)

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



n≈40 per cohort planned

(*Cohorts with no objective responses in the first 15 patients were to be closed*)

Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

- Nov 16, 2022

Funda Meric-Bernstam, MD et al. ASCO 2023

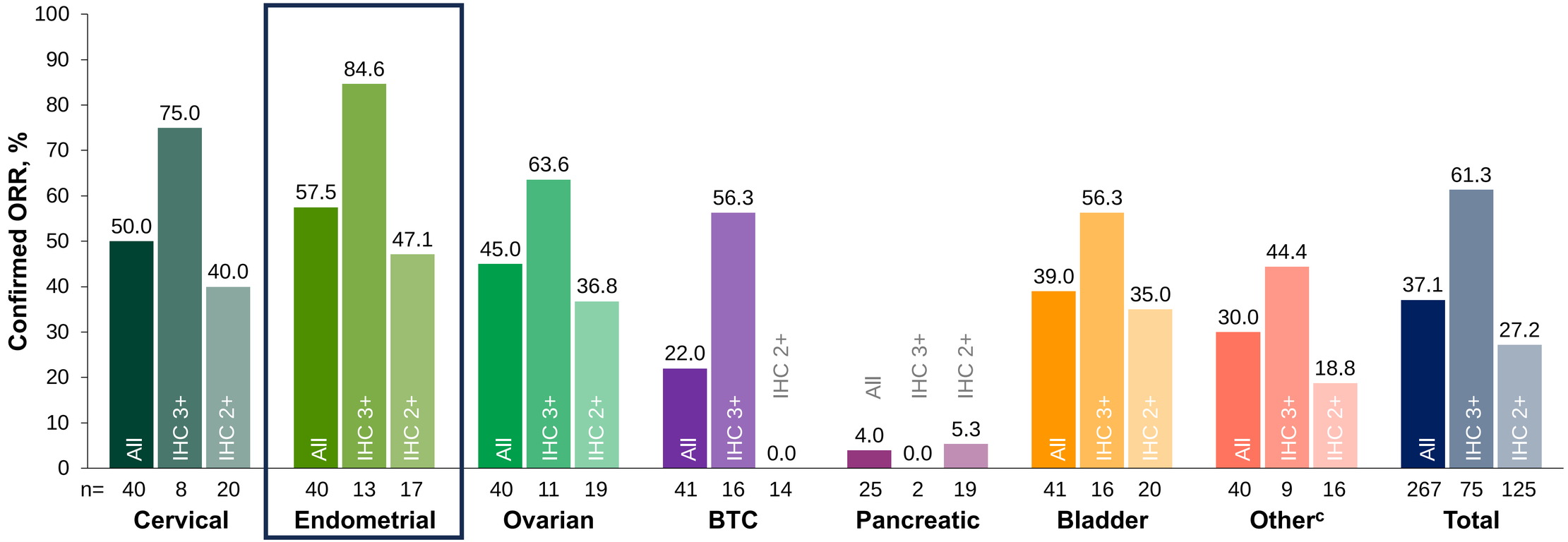
[A] Patients were eligible for either test. All patients were centrally confirmed. [b]Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer.
[c]Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.
2L, second-line; ASCO, American Society of Clinical Oncology; DCR, disease control rate; CAP, College of American Pathologists; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2;
IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.
1. Hofmann M, et al. *Histopathology 2008*;52(7):797–805.

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 interim results

		Cervical (n=40)	Endometrial (n=40)	Ovarian (n=40)	BTC (n=41)	Pancreatic (n=25)	Bladder (n=41)	Other (n=40)	All patients (N=267)
Investigator assessment									
ORR, n (%)		**20 (50.0)**	**23 (57.5)**	**18 (45.0)**	**9 (22.0)**	**1 (4.0)**	**16 (39.0)**	**12 (30.0)**	**99 (37.1)**
Best overall response, n (%)	Complete response	2 (5.0)	7 (17.5)	4 (10.0)	1 (2.4)	0	1 (2.4)	0	15 (5.6)
	Partial response	18 (45.0)	16 (40.0)	14 (35.0)	8 (19.5)	1 (4.0)	15 (36.6)	12 (30.0)	84 (31.5)
	Stable disease	12 (30.0)	13 (32.5)	14 (35.0)	25 (61.0)	17 (68.0)	18 (43.9)	24 (60.0)	123 (46.1)
	PD	7 (17.5)	4 (10.0)	7 (17.5)	7 (17.1)	7 (28.0)	7 (17.1)	3 (7.5)	42 (15.7)
	Not evaluable	1 (2.5)	0	1 (2.5)	0	0	0	1 (2.5)	3 (1.1)
DCR[a] at 12 weeks, n (%)		27 (67.5)	32 (80.0)	28 (70.0)	27 (65.9)	9 (36.0)	29 (70.7)	30 (75.0)	182 (68.2)
Median DOR, months (95% CI)		9.8 (4.2–NE)	NR (9.9–NE)	11.3 (4.1–NE)	8.6 (2.1–NE)	NR	8.7 (4.3–11.8)	NR (4.1–NE)	11.8 (9.8–NE)
Independent central review: ORR, n (%)		16 (40.0)	21 (52.5)	17 (42.5)	11 (26.8)	3 (12.0)	17 (41.5)	13 (32.5)	98 (36.7)

Funda Meric-Bernstam, MD et al.
ASCO 2023

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 interim results

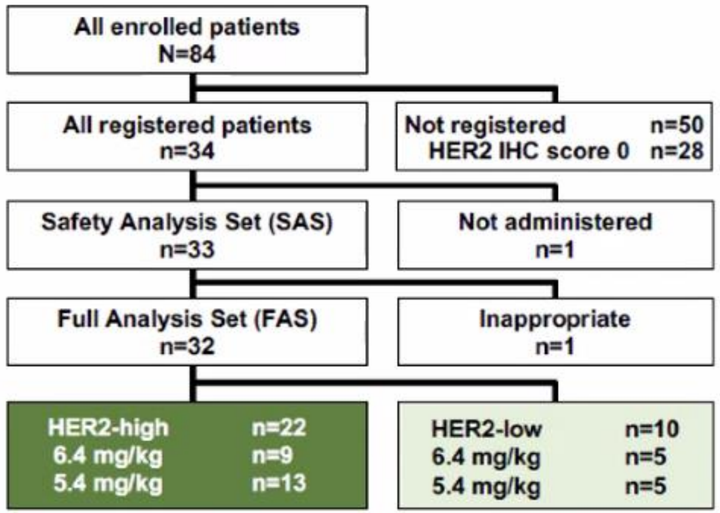


	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Trastuzumab deruxtecan for the treatment of UCS

Patient Flow Diagram

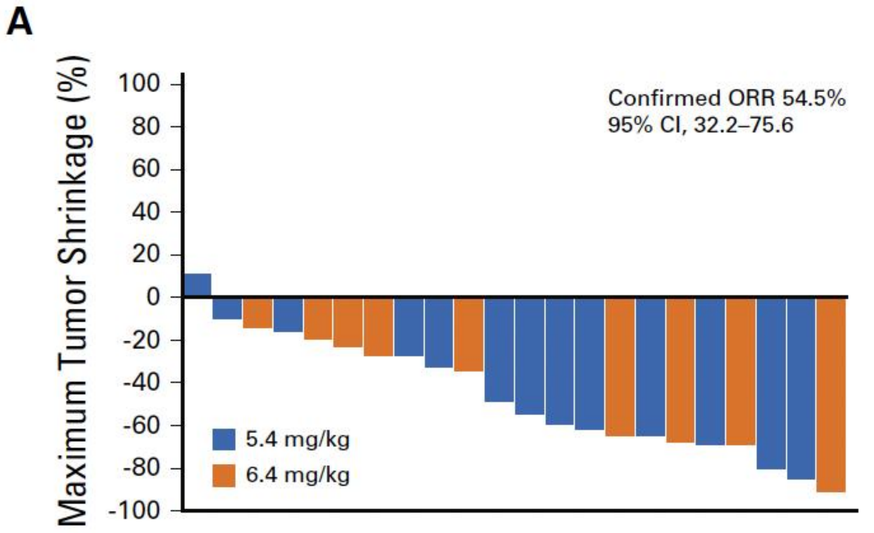
- Patients were enrolled from February 2018 to June 2020 at 7 institutions in Japan
- Data cut-off was done in December 2020
- Twenty-eight patients (33.3%) were excluded from registration due to HER2 IHC score 0
- One patient did not receive T-DXd due to progression of UCS
- One patient was excluded from FAS due to central review with no measurable target lesion

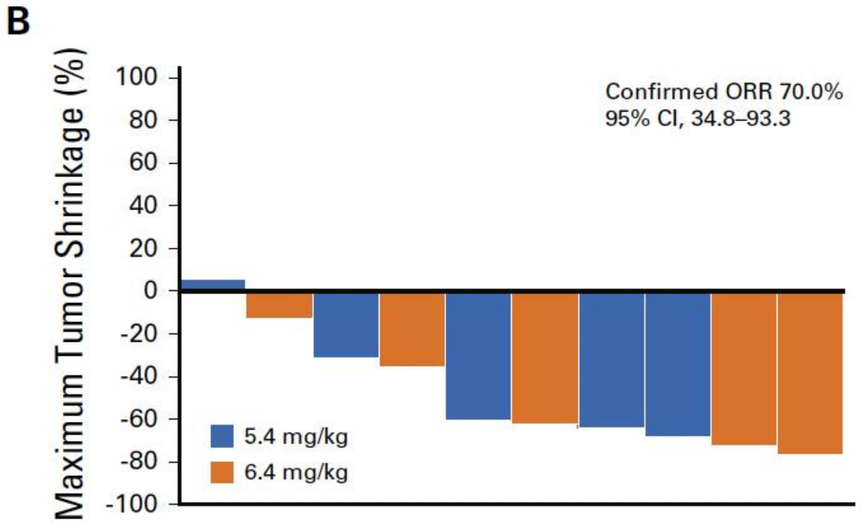


Patient Characteristics

HER2 IHC score (N=84)
0: 28 (33%), 1: 24 (29%)
2: 22 (26%), 3: 10 (12%)

		All (n=34)	(%)	FAS (n=32)	(%)
Age (years)		45- 81	65.5 (median)	45-81	64.5 (median)
PS (ECOG)	0	25	(73.5)	24	(75)
	1	9	(26.5)	8	(25)
HER2 (IHC)	1	11	(32.4)	10	(31.3)
	2	16	(47.1)	15	(46.9)
	3	7	(20.6)	7	(21.9)
HER2 (FISH)	Negative	26	(76.5)	24	(75)
	Positive	8	(23.5)	8	(25)
Prior regimens	1			17	(53.1)
	2			9	(28.1)
	≥ 3			6	(18.8)

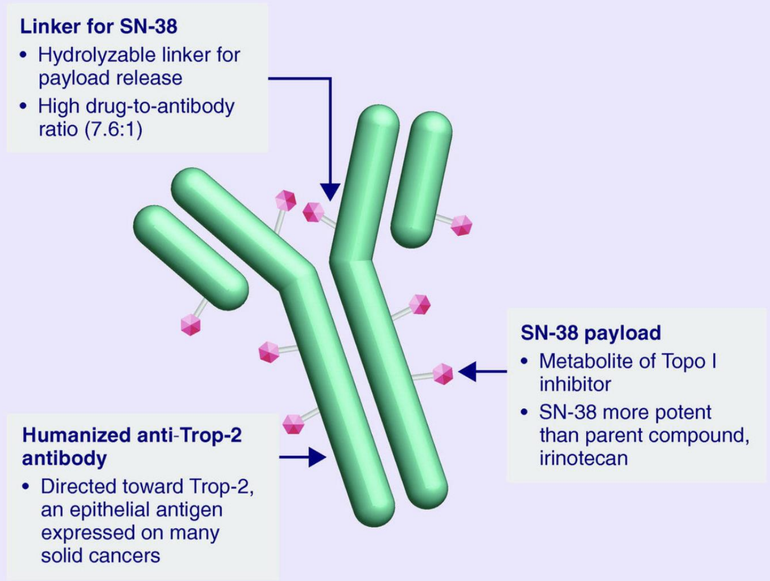




Nishikawa et al. J Clin Oncol 2023

Sacituzumab govitecan (SG) in patients (pts) with previously treated metastatic endometrial cancer (mEC): results from a phase I/II study.

ORR 33% in mEC



Sacituzumab govitecan ADC: anti–Trop-2 antibody linked to drug SN-38. Future Medicine. 2020 Mar. doi:10.2217/fon-2020-0163

Table 1. Demographics and clinical characteristics	SG (n = 21)
Median age at study entry, y (range)	63 (47-77)
Race, n (%)	
White	15 (71.4)
Black or African-American	0
Asian	2 (9.5)
Other	4 (19.0)
Histological/cytological diagnosis, n (%)	
Serous	10 (47.6)
Endometrioid	6 (28.6)
Carcinosarcoma	3 (14.3)
Other	2 (9.5)
Number of prior anticancer regimen, n (%)	
1-3	11 (52.4)
> 3	10 (47.6)
Median prior anticancer regimens, n (range)	3 (1-6)
Median follow up duration, m (IQR)	17 (7.6-35.2)

Table 2. Overall response rate and durable disease control	SG (n = 21) n (%)
Best overall response	
Confirmed complete response (CR)	1 (4.8)
Confirmed partial response (PR)	6 (28.5)
Stable disease	11 (47.6)
Progressive disease	3 (14.3)
Objective response rate (confirmed CR + PR)	7 (33.3)
Durable disease control (confirmed CR + PR + SD ≥ 6 months)	7 (35.0)*

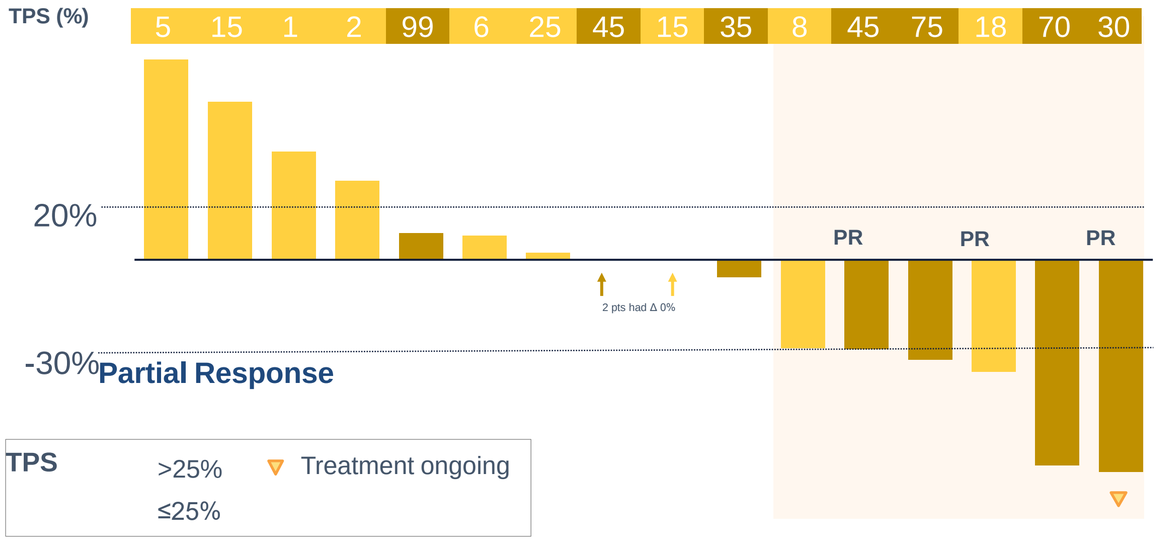
*Out of 20 patients evaluable for durable disease control

Table 3. Most Common Treatment-Related Adverse Events	Grade ≥ 3 (≥ 10% of patients)
Neutropenia	9 (43%)
Fatigue	4 (19%)
Anemia	3 (14%)
Diarrhea	3 (14%)
Febrile neutropenia	2 (10%)

Santin A et al ASCO Abstract 5599. DOI: 10.1200/JCO.2023.41.16_suppl.5599

ADCs Emerging as Highly Active Therapeutics in EC- Folate Receptor α- STRO-002-GM1: Phase 1 Dose Expansion cohort of luveltamab tazevibulin in EC-NCT03748186

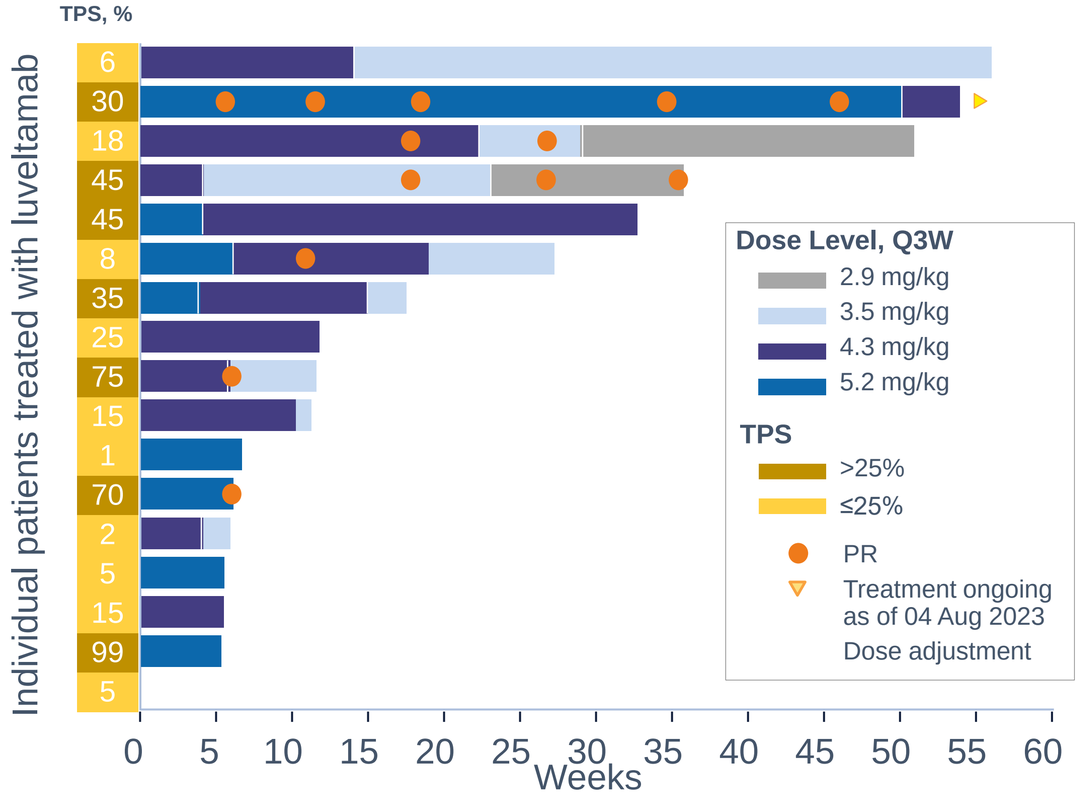
Maximum Reduction in Target Lesions*



Anti-tumor Activity*

n (%)	Overall FolRα ≥1% (n=16)	FolRα ≤25% (n=9)	FolRα >25% (N=7)
PR	3 (19)	1 (11)	2 (29)
SD†	8 (50)	4 (44)	4 (57)
PD	5 (31)	4 (44)	1 (14)
DCR	11 (69)	5 (56)	6 (86)

Treatment Duration and Dose Modifications



- Median exposure (range): 12 (3–53) weeks
- 5 of 17 (29%) patients received ≥5 cycles
- Median follow-up: 10.1 months

†3 unconfirmed PRs

Data cutoff: 04 August 2023. *n=16 response evaluable patients. DCR, disease control rate; EC, endometrial cancer; PR, partial response;

Q3W, every 3 weeks; TPS, tumor proportion score.

Pothuri B. et al. ESMO 2023

Hormonal Therapy In Endometrial Cancer

Hormonal treatment of advanced/recurrent endometrial cancer

Study	*N*	Treatment	RR	PFS	OS	DOR
GOG 153 [2]	56	MA 80 mg b.i.d. X 3 weeks alternating with T 20 mg b.i.d. p.o. X 3 weeks	27% (21.4 CR, 5.4 PR) [Cl 17–38%]	2.7 mos	14.0 mos	28 mos
GOG 121 [8]	58	Phase II—High dose MA 800 mg/day	24%	2.5 mos	7.6 mos	8.9 mos
GOG 81 [9]	145	MPA high dose: 1000 mg/day p.o. vs	High: 15%	2.5 mos	7.0 mos	NR
	154	MPA low dose: 200 mg/day p.o.	Low: 25%	3.2 mos	11.1 mos	
GOG 119 [3]	58	Daily T (20 mg b.i.d.) with MPA (100 mg p.o. b.i.d.) Intermittent weekly	33% [Cl 21–46%] (10.3% CR, 23.4% PR)	3.0 mos	12.8 mos	NR
GOG B1F [10]	68	T 20 mg b.i.d.	10% [Cl 5.7–17.9%]	1.9 mos [1.7–3.2]	8.8 mos [7.0–10.1]	NR

MA, Megestrol acetate; MPA, medroxy progesterone acetate; T, Tamoxifen; Cl, confidence interval (95%); RR, response rate; PFS, progression free survival (median); OS, overall survival (median); DOR, duration of response (median); NR, not reported.

Progestins and endometrial cancer: hormone response by tumor grade

Study	Response—Grade 1	Response—Grade 2	Response—Grade 3
GOG 153 [2]	33%	24%	22%
GOG 119 [3]	NR	NR	NR
GOG 81 [9]	37%	23%	9%
GOG 121 [8]	37% combined		8%
GOG 81F [10]	23%	14%	3%

GOG 153: No prior hormonal or chemotherapy

GOG 119: No prior hormonal or chemotherapy

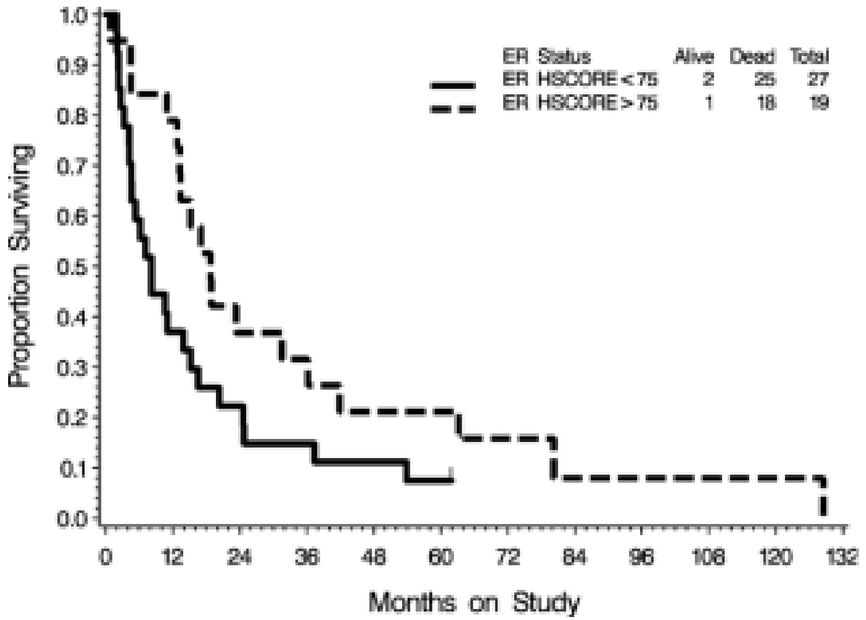
Hormonal Therapy

Agent	RR
Megestrol Acetate	24%
Tamoxifen	10%-53%
MA alternating w/ tamoxifen	27 - 33%
Anastrazole	9%
Letrozole	9%
Leuprolide	~10%

Option for 1st line or ≥2nd line:

- 1st line ORR = 21.6%
- 2nd line ORR = 18.5%
- Median PFS = 2.8mths
- Median OS = 10.2 months
- ↑ORR ER+ (26.5%)/ PgR+ (35.5%) disease
- ↓ORR in ER− (9.2%) or PgR− (12.1%) tumors.
- ↓ORR older age and high grade.

GOG 119 OS



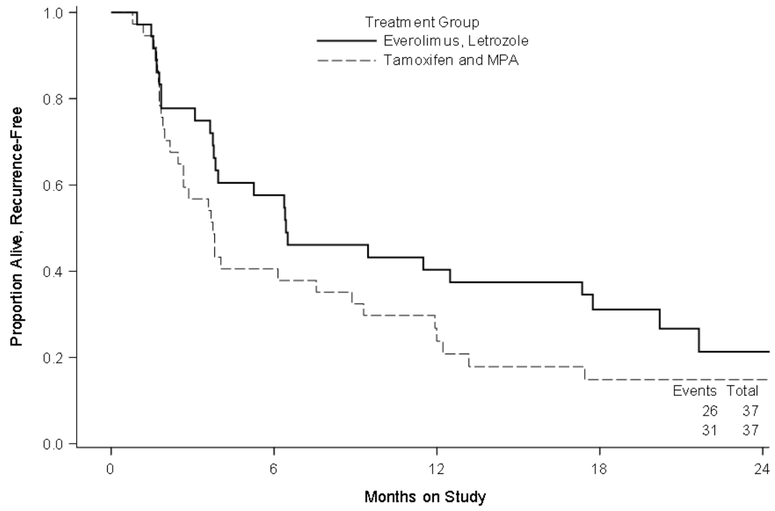
Slide courtesy of Dr. David Tan; ESMO 2023.

MacKay HJ, 2020 ASCO Educational Book; Ethier et al Gynecologic Oncology 2017; Meenakshi Singh et al. Gynecologic Oncology 2007

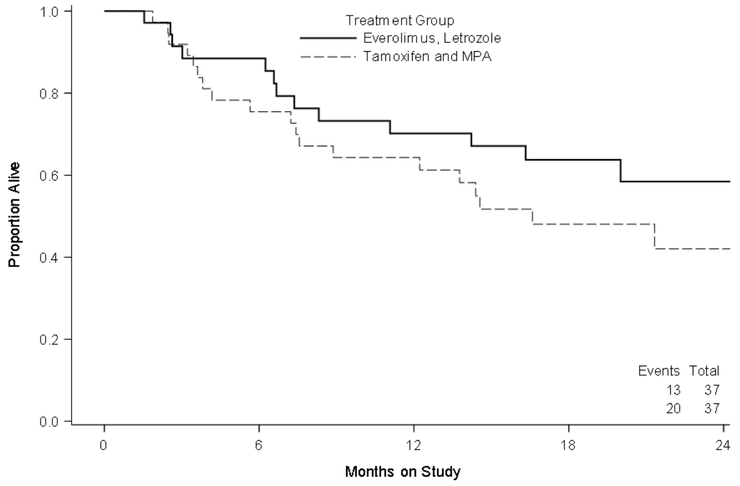
GOG 3007: Everolimus/Letrozole vs. Tamoxifen/Megestrol Acetate

Regimen	N	Objective Response - ITT	Objective Response – No prior chemo	CBR	PFS	OS
Everolimus/ Letrozole	37	24%	53%	78%	6.3 months	Not reached
MA/ Tamoxifen	36	22%	43%	69%	3.8 months	16.6 months

PFS by Regimen



Overall Survival by Regimen



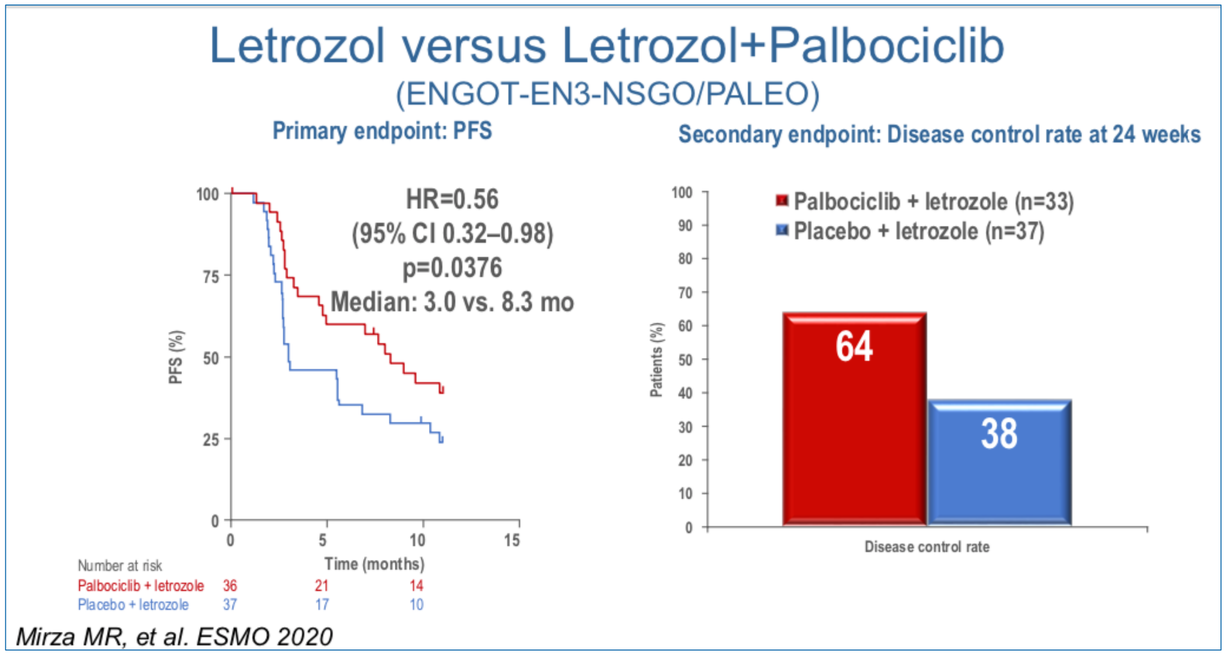
Greater benefit in chemo-naïve patients

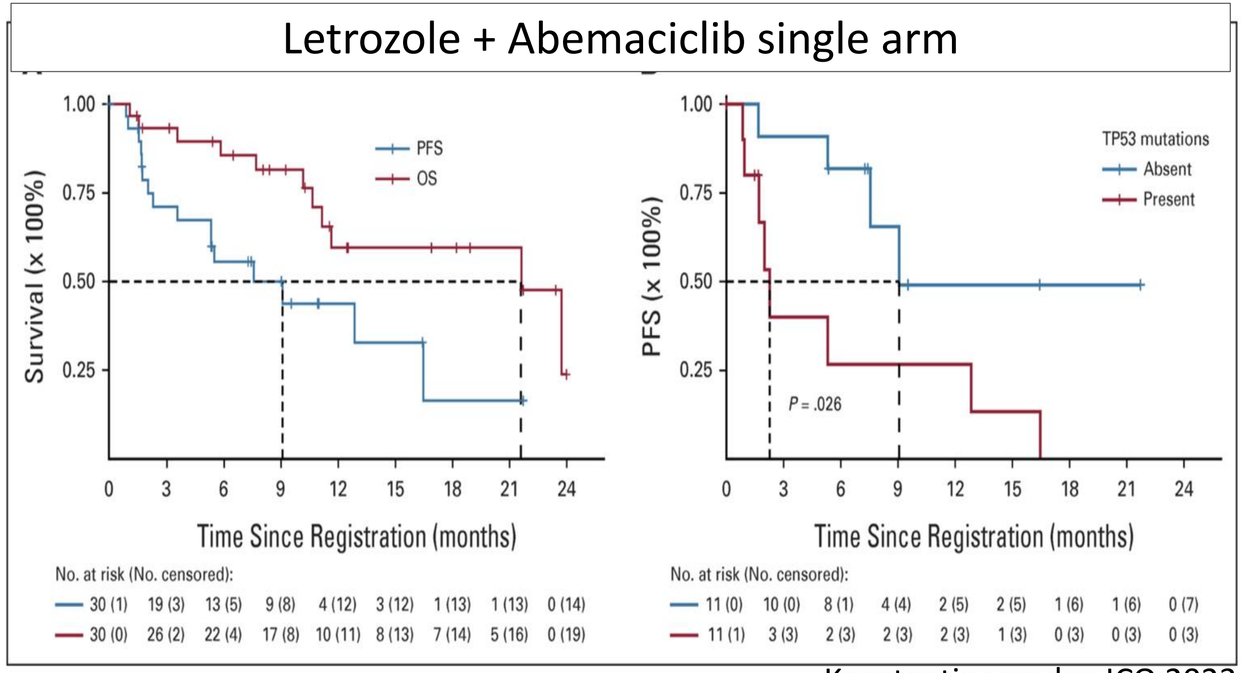
	Prior-chemo PFS (mths)	Chemo-naïve PFS (mths)
Letrozole/ everolimus	4	28
MA/ tamoxifen	3	5

Slomovitz BM, et al. SGO 2018, Abstract #1. Slomovitz Gyn Onc 2022

Aromatase inhibtors + CDK4/6 inhibitors in EC

- **AI + CDK4/6i; median PFS 8-9 months**





Konstantinopoulos JCO 2023

PALEO trial

- **N= 77, Stage 4 or relapsed ER-positive EC**
- **PFS = 8.3 vs 3 mths (p=0.0376)**
- **DCR = 63.6% vs 37.8%**

- **N= 30 (28 endometrioid EC)**
- **ORR 30%, all endometrioid**
- **Median PFS = 9.1 months**
- **Predictors of response: (*CTNNB1/KRAS/CDKN2A* mut)**
- **Predictors no response(*TP53mut*)**

Slide courtesy of Dr. David Tan; ESMO 2023.