An Industry Supported Symposium at the IGCS 2025 Annual Global Meeting

The Long Game in Endometrial Cancer: Interpreting PFS, OS, and the Power of Biomarkers

This session is not included in the main event CME/CPD credit

Cape Town, South Africa

Wednesday, November 5, 2025

13:05-14:35 (GMT+2)

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Welcome and Introductions

Ramez N. Eskander, MD

UC San Diego Health, Moores Cancer Center

San Diego, California, USA

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Moderator | Faculty

Ramez N. Eskander, MD

UC San Diego Health
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Robert Coleman, MD

Texas Oncology
Austin, Texas, USA

Bhavana Pothuri, MD

NYU Langone Health,
Perlmutter Cancer Center
New York, New York, USA

Faculty Disclosures

Name	Role in Activity	Disclosures
Ramez N. Eskander, MD	Moderator	• Consultant/Advisory Board: AstraZeneca; Clovis Oncology; Daiichi Sankyo, Inc.; Eisai Inc.; Elevar Therapeutics; GSK; ImmunoGen, Inc.; Mersana Therapeutics; Myriad Genetics, Inc.; Novocure GmbH; Onconova Therapeutics; Nuvectis; PMV Pharmaceuticals; Regeneron; Lilly; AbbVie; Pfizer, . • Other Financial or Material Support for GOG P Associate Clinical Trial Advisor
Robert Coleman, MD	Speaker	• **Consulting/advisory role:** Pharma& Oncology, Genentech/Roche, AstraZeneca/DSI, Genmab/Pfizer, GSK, Toray, Merck, Merck KgA, AbbVie/Immunogen, Corcept, Karyopharm, GOG-Foundation • **Research funding:** AstraZeneca, Pharma&, Karyopharm, Merck, Genentech/Roche, AbbVie/Immunogen
Bhavana Pothuri, MD	Speaker	• **Consultant:** AstraZeneca; Eisai; GlaxoSmithKline; GOG foundation; Merck; Mersana; Seagen Inc.; Sutro • **Grant/Contract:** AstraZeneca; celsion/Immunon; Clovis Oncology, Inc.; Genentec; GlaxoSmithKline; Imab; Immunogen; Incyte Corporation; Karyopharm Therapeutics; Merck; Mersana; Seagen Inc.; Sutro; Toray Industries

Learning Objectives

1. Evaluate and compare recent clinical trial designs and key efficacy outcomes in endometrial cancer, with a focus on how differences in methodology and population selection—particularly in dMMR cohorts—impact therapeutic positioning in a dynamic and evolving treatment landscape.

2. Interpret findings from recent Phase III Trials and implications specific to subgroup analyses of progression-free and overall survival (PFS/OS) in biologically defined populations, including dMMR, MMRp, and explorative subgroups i.e., P53 mutation status, HRD, and IO-sensitive subgroups, to guide personalized treatment strategies.

3. Assess the implications of unplanned subgroup analyses and regulatory approvals, including FDA decisions, on the application of clinical trial data to real-world treatment decisions for patients with dMMR and other molecular subtypes of endometrial cancer (MMR, P53WT, HRD) focusing on how these factors influence treatment options and patient outcomes.

4. Understanding current gaps and unmet needs in the management of endometrial cancer, identifying the differential needs in dMMR, MMRp populations, and explore future outlook in treatments, including ongoing and upcoming clinical trials, novel therapeutic targets and how emerging therapies are addressing limitations in existing treatment paradigms. Strategies to address resistance, improve outcomes and close gaps in care will also be discussed.

5. Apply clinical trial data and biomarker insights to real-world patient cases, using a case-based approach to evaluate treatment strategies for dMMR and other biomarker-defined subgroups in both frontline and recurrent settings. Different guidelines (ESGO, NCCN, published in July)

Agenda

13:05 – 13:10 **Introduction & Welcome**
Ramez N. Eskander, MD, University of California San Diego Health, Moores Cancer Center, San Diego, California, USA

13:10 – 13:30 **Clinical Trial Design & Differentiating Data dMMR Populations**
Robert Coleman, MD, Texas Oncology, Austin, Texas, USA

13:30 – 13:50 **Biology Biomarker-Based Treatment Strategies: Deep Dive into Subgroup Data**
Ramez N. Eskander, MD, University of California San Diego Health, Moores Cancer Center, San Diego, California, USA

13:50 – 14:10 **Case-Based Clinical Decision Making: Applying the Data Impact on Treatment Options and Outcomes**
Bhavana Pothuri, MD, NYU Langone, Perlmutter Cancer Center, New York, New York, USA

14:10 – 14:25 **Future Directions in Endometrial Cancer Treatment**
Ramez N. Eskander, MD, University of California San Diego Health, Moores Cancer Center, San Diego, California, USA

14:25 – 14:35 **Q&A and Discussion**
All Faculty

Clinical Trial Design & Differentiating Data in dMMR Populations

Robert Coleman, MD

Texas Oncology

Austin, Texas, USA

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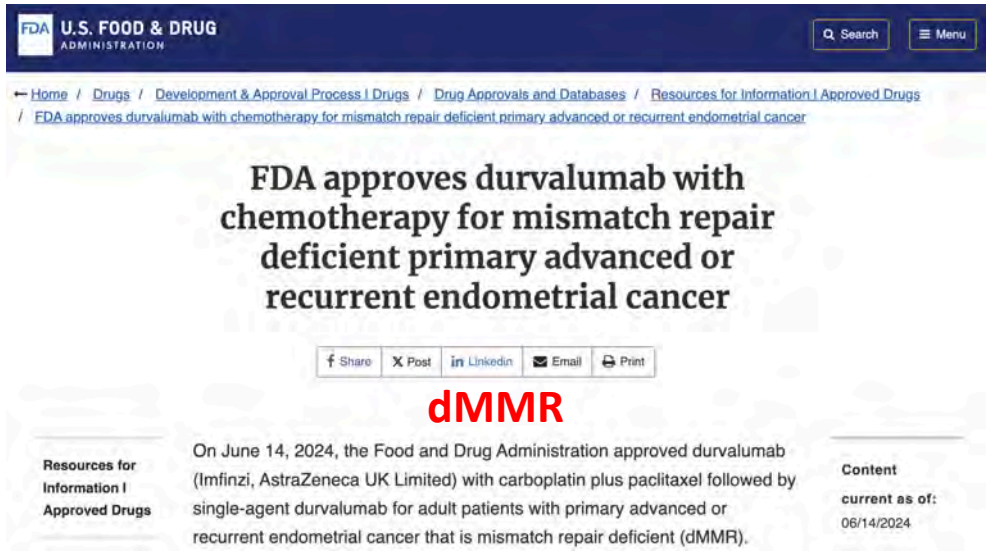
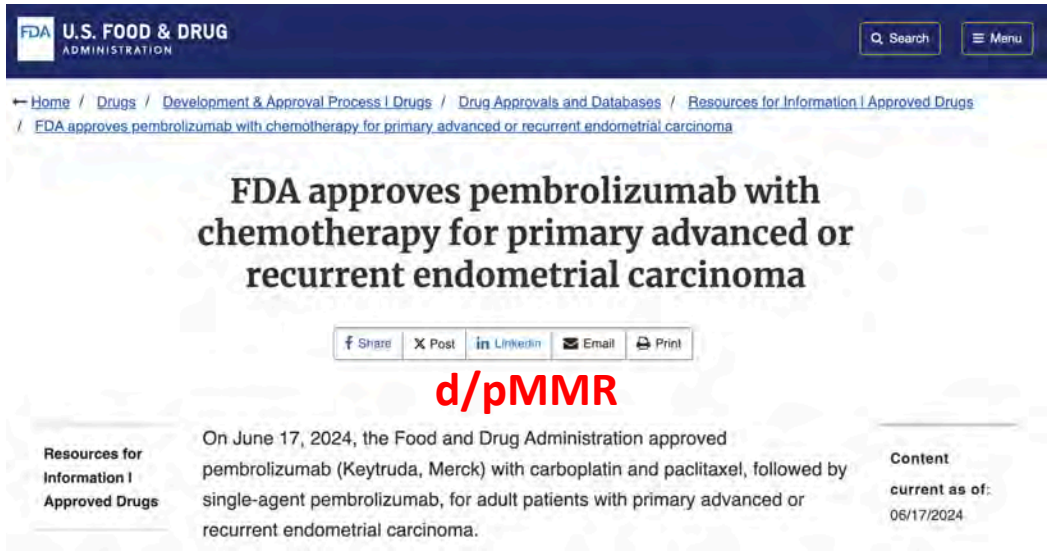
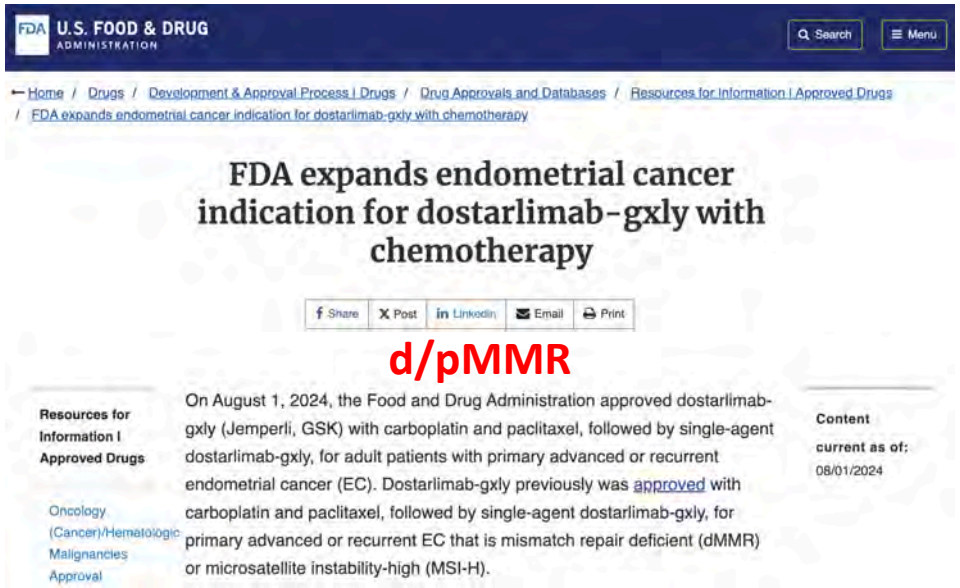
Goal: Successful Regulatory Approval



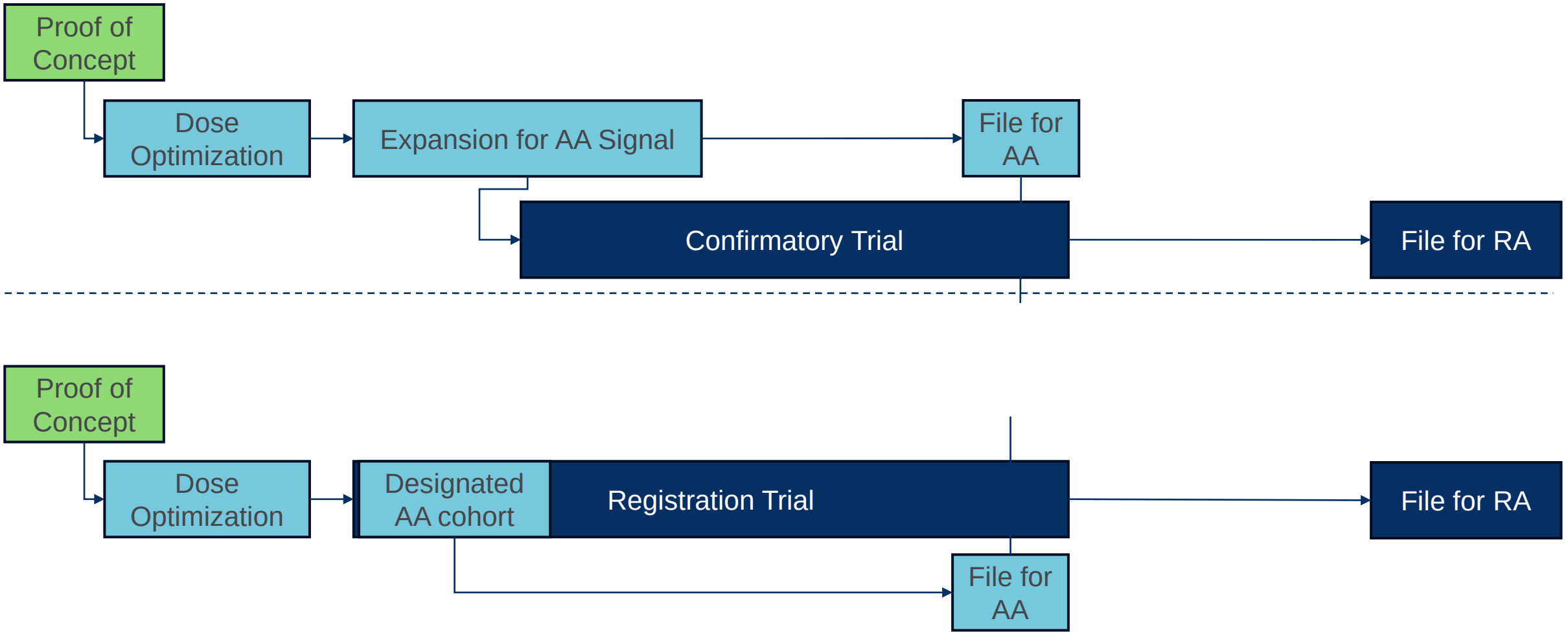




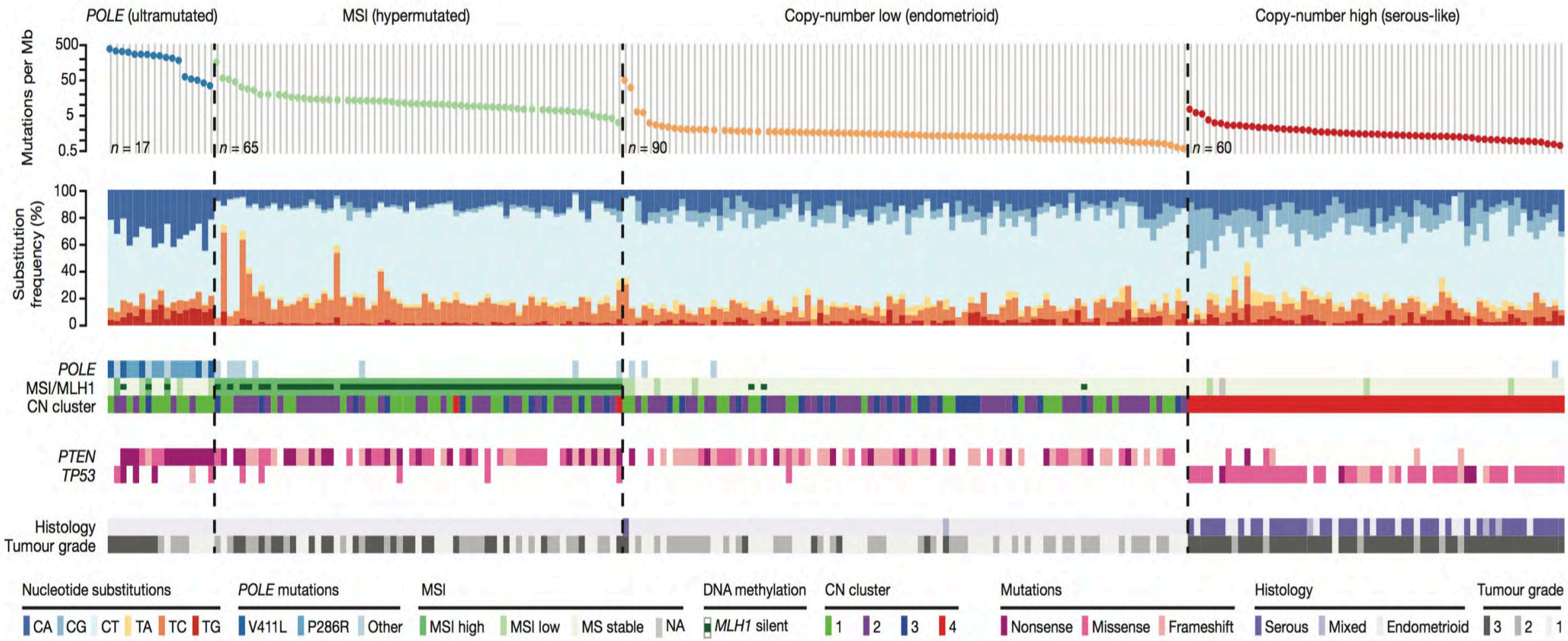
Factors Driving Successful Trial Design: Regulatory Intent

- Homogenous representative population in the clinical target area
- Biomarker enrichment (if possible)
- Appropriate sample size and power for targeted treatment effect
- Randomization with optimized stratification and low-level informative censoring
- Adequate maturity at interim assessments
- Regulatory agency interaction
- “Investigational strategy” (unmet medical need)

Regulatory Playbook: FDA



Molecular Profile of Endometrial Cancer



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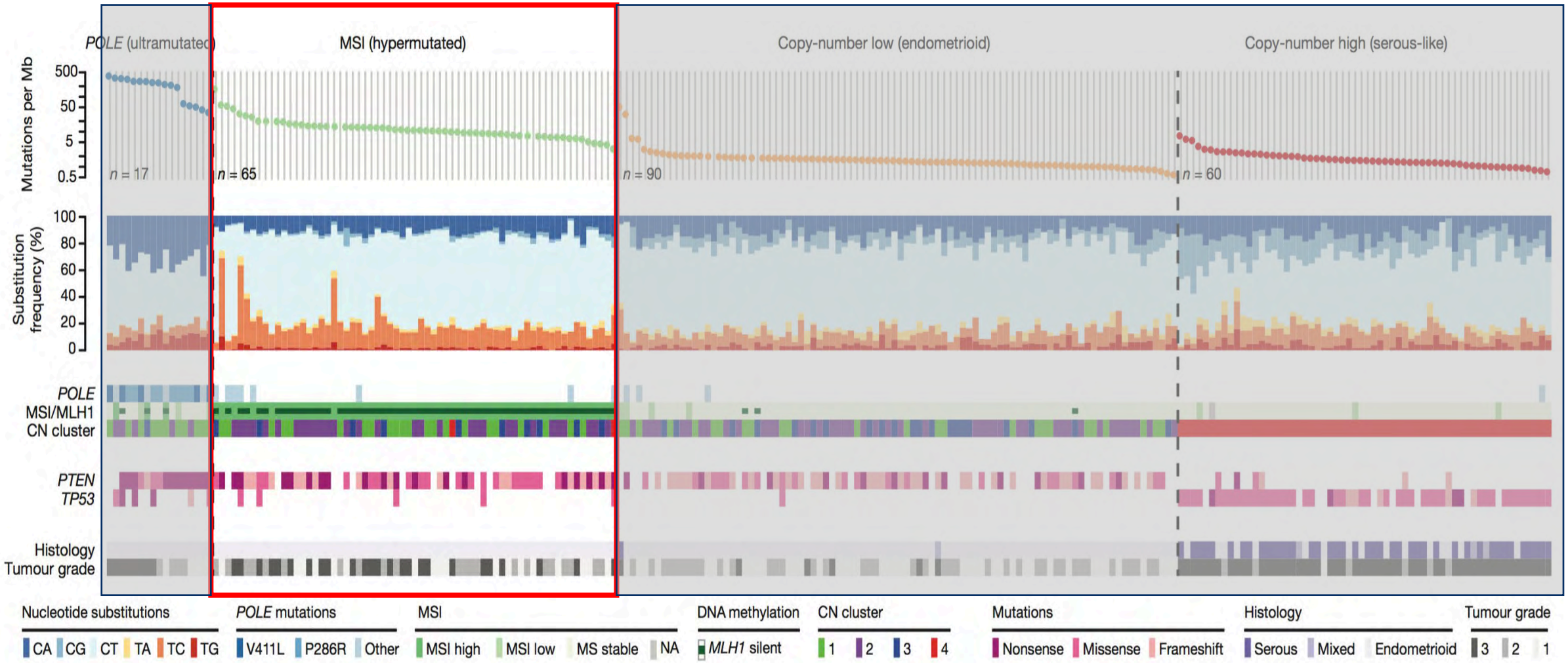
TCGA, Nature 2013

Molecular Profile of Endometrial Cancer



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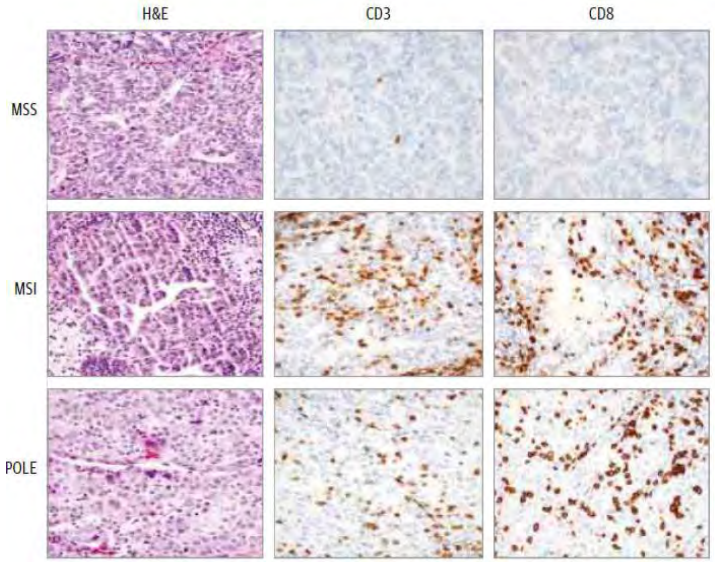
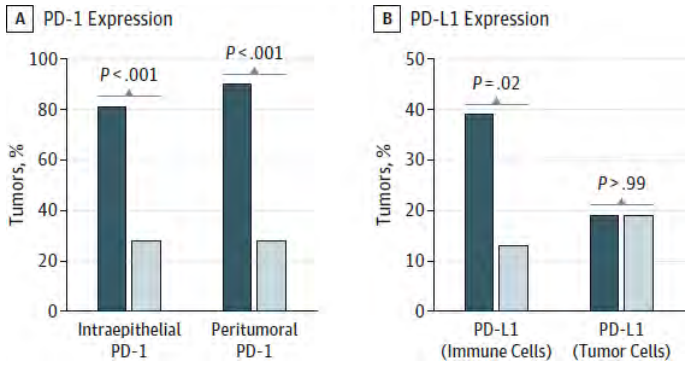
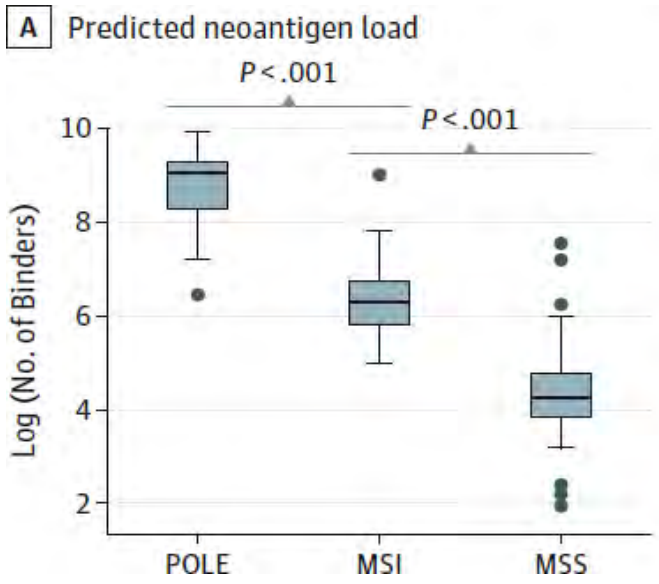
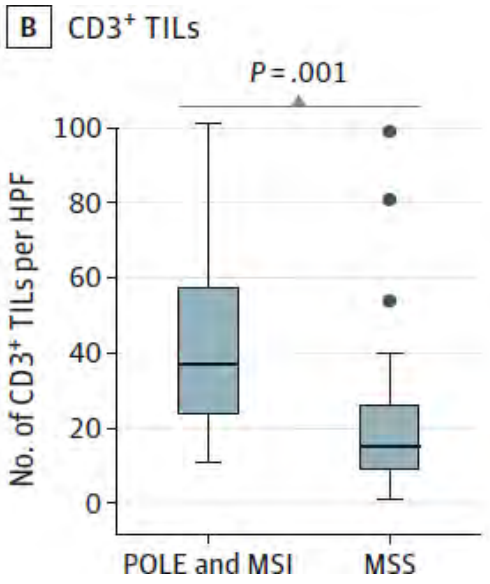
TCGA, Nature 2013

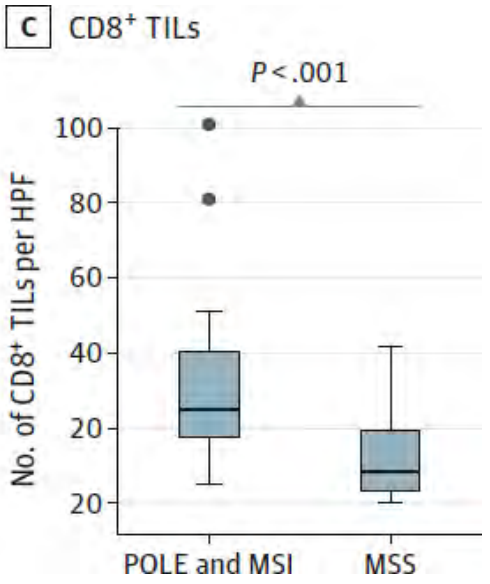
Neoantigen load, TIL, and PD1/PD-L1 Expression in EC











Howitt BE,. JAMA Oncol. 2015 Dec;1(9):1319-23

Single Agent Immune Checkpoint Inhibitor in Recurrent Endometrial Cancer

		MMR-d		MMR-p	
Study	Drug	N	**ORR(%)**	N	ORR(%)
KEYNOTE 158: O'Malley (2019, 22)	Pembrolizumab	79	**48%**	107	11%
GARNET: Oaknin (2022)	Dostarlimab	143	**46%**	156	15%
PHAEDRA: Antill (2019)	Durvalumab	35	**43%**	36	3%
Konstantinopoulos (2019)	Avelumab	15	**27%**	16	6%

O'Malley et al. ESMO 2019. JCO2022; Oaknin, ASCO 2022; Antill ASCO 2019 ; Konstantinopoulos ASCO 2019, Makker NEJM 2022

	RUBY (Mirza NEJM 2023)	GY018 (Eskander NEJM 2023)	ATTEND (Colombo Lancet Oncol 2024)	DUO-E (Arm 2) (Westin JCO 2023)
Advanced/recurrent endometrial carcinoma	Yes	Yes	Yes	Yes
Carcinosarcoma	**Yes (10%)**	No	**Yes (9%)**	**Yes (7%)**
Non-Endometrioid histology	**45%**	20%	**36%**	**41%**
Non-measurable clear cell, serous, mixed histologies	**Yes**	No	**Yes**	**Yes (stage IV)**
ECOG 2	No	1% vs. 4%	Yes, unknown %	No
Time since completion of adjuvant chemotherapy	**≥6 months**	≥12 months	**≥6 months**	≥12 months
Duration of treatment	3 years	2 years	**To Progression**	**To Progression**
Median follow-up	**24.8 months**	12 months MMRd 7.9 months MMRp	**28.3 months**	15.4 months
PFS	**MMRd* 0.28** **ITT* 0.64** MMRp 0.76	**MMRd* 0.30** **MMRp* 0.50**	**MMRd* 0.36** **ITT* 0.74** MMRp 0.92	MMRd 0.42 **ITT* 0.71** MMRp 0.77
OS	**(Maturity:51%) ITT* 0.69 (0.002)** MMRd 0.30 MMRp 0.73	**IF: MMRd 18%** **IF: MMRp 27%** MMRd 0.55 MMRp 0.79	(Maturity:43%) ITT* 0.82 (NS) MMRd 0.41 MMRp 1.00	(Maturity:28%) ITT* 0.77 (NS) MMRd ? MMRp ?

*Primary hierarchical endpoints with formal significance

Successful Trial Design: Eligibility

- **Homogenous representative population in the clinical target area**
- **Biomarker enrichment (if possible)**
- Appropriate sample size and power for targeted treatment effect
- Randomization with optimized stratification and low-level informative censoring
- Adequate maturity at interim assessments
- Regulatory agency interaction
- “Investigational strategy” (unmet medical need)

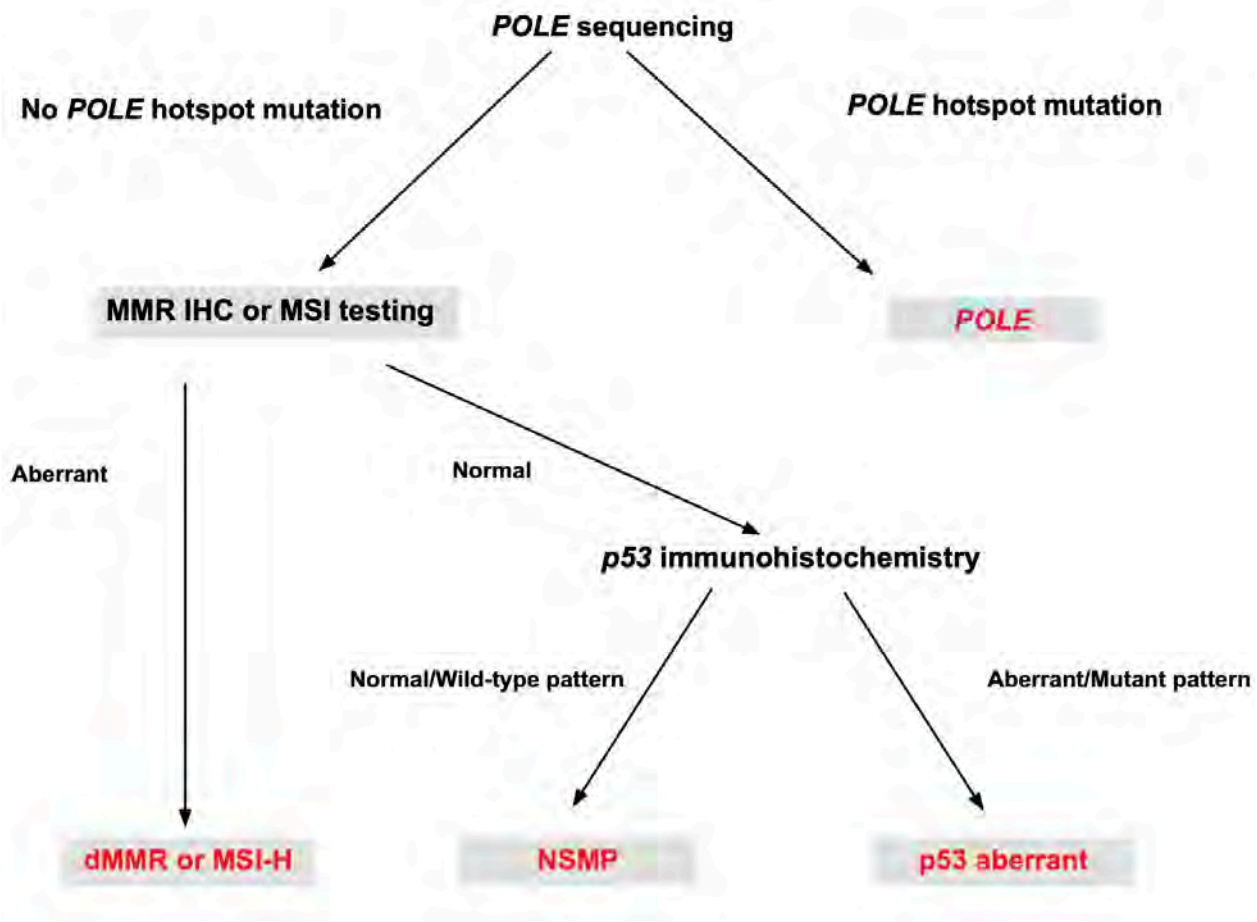
Factors Driving Treatment Decisions

Prognostic

- p53 IHC/TP53-missense – may drive bevacizumab use (post-hoc GOG-86P)
- TP53 wild type may be predictive for SINE and MDM2 targeting therapy

Therapeutic

- HER-2/*neu*
- MSI/MMR
- Tumor mutational burden
  - *POL-e*



Index Case Study

GY018

Placebo
Carboplatin AUC 5
Paclitaxel 175 mg/m²
Q3W for 6 -10 cycles

→ **Placebo IV Q6W**

up to 14 additional cycles

Pembrolizumab 200 mg IV
Carboplatin AUC 5
Paclitaxel 175 mg/m²
Q3W for 6 -10 cycles

→ **Pembrolizumab 400 mg IV Q6W**

up to 14 additional cycles

Both Q3 weeks and same chemo backbone

Both Q6 weeks in maintenance

~2 years

RUBY

Placebo
Carboplatin AUC 5
Paclitaxel 175 mg/m²
Q3W for 6 cycles

→ **Placebo IV Q6W**

up to 26 additional cycles

Dostarlimab IV 500 mg
Carboplatin AUC 5
Paclitaxel 175 mg/m²
Q3W for 6 cycles

→ **Dostarlimab 1000 mg IV Q6W**

up to 26 additional cycles

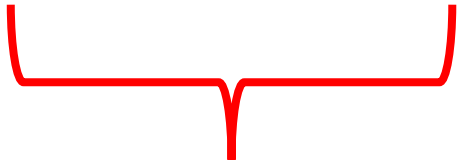
~3 years

Inclusion Criteria

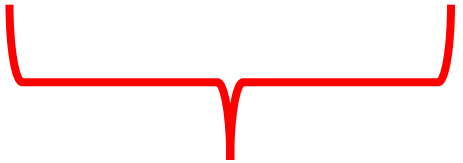
	GY018	RUBY
Measurable stage III/IVA	X	X
Non-measurable stage IVB	X	X
Non-measurable clear cell, carcinosarcoma, serous, mixed, IIIC2-IVA		X
Recurrent EMCA	X	X
Carcinosarcoma		X
PS 0-1	X	X
PS 2	X	
Time since completion of adjuvant chemo	≥12 mo	≥6 mo

Baseline Characteristics

Variable, n (%)	Overall (GY018) (n=816)		Overall (RUBY) (n=494)	
	Pembro + CT (N=407)	Placebo + CT (N=409)	Dostarlimab + CP (N=245)	Placebo + CP (N=249)
dMMR/MSI-H	112 (27.4)	113 (27.6)	53 (21.6)	65 (26.1)
MMRp/MSS	295 (72.5)	296 (72.4)	192 (78.4)	184 (73.9)



dMMR: 28 %



dMMR: 24 %

Successful Trial Design: Stats

- Homogenous representative population in the clinical target area
- Biomarker enrichment (if possible)
- **Randomization with optimized stratification and low-level informative censoring**
- **Appropriate sample size and power for targeted treatment effect**
- Adequate maturity at interim assessments
- Regulatory agency interaction
- “Investigational strategy” (unmet medical need)

Successful Trial Design: Stats

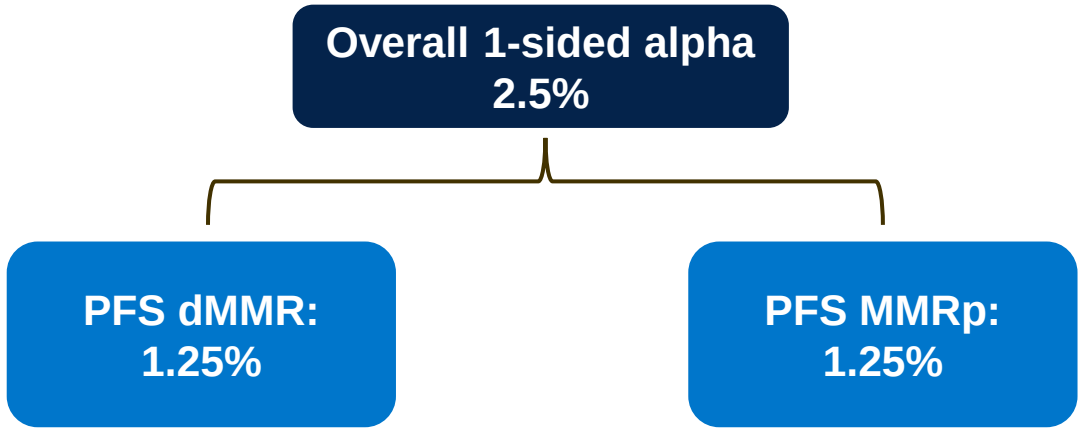
- **Null hypothesis**:
  - **Superiority trial**: there is no difference between intervention and control (historical, contemporary (external), or co-registered)
- **Type I Error**: α **- error (usually set at 0.05 or 1/20)**
  - Probability of incorrectly rejecting the null hypothesis
- **Type II Error**: β **- error (usually set at 0.1 – 0.2 or 1/10 to 1/5)**
  - Probability of incorrectly accepting the null hypothesis
- **Power**: **1-β (usually targeting 80-90%)**
  - Confidence of correctly rejecting null hypothesis

Successful Trial Design: Stratification/Randomization

	GY018	RUBY
MMR status	X	X
ECOG PS (0 or 1 vs 2)	X	
Prior adjuvant chemo (yes vs no)	X	
Prior external pelvic radiotherapy (yes/no)		X
Disease status (recurrent, primary stage III, or primary stage IV		X
1:1 Randomization	X	X

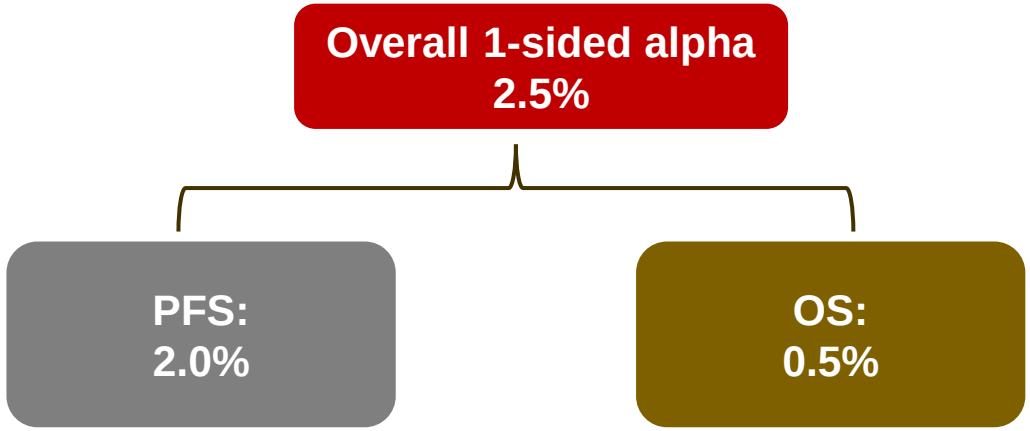
Successful Trial Design: Stats

GY018



- Alpha is split at the beginning for each cohort (MMRp and dMMR)
- PFS of each cohort is only primary endpoint

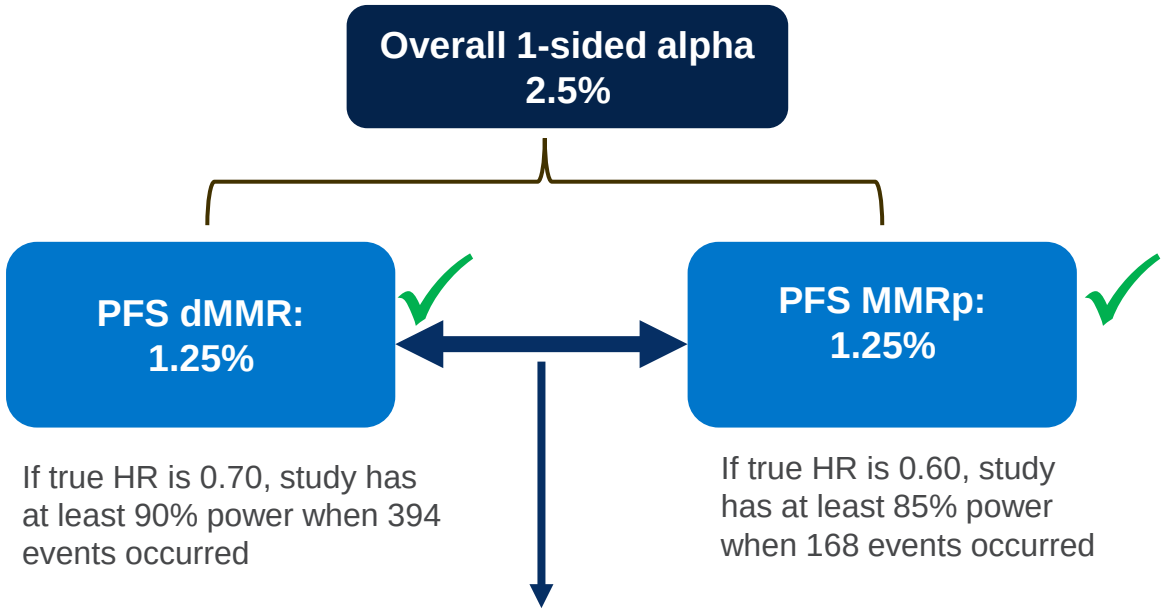
RUBY



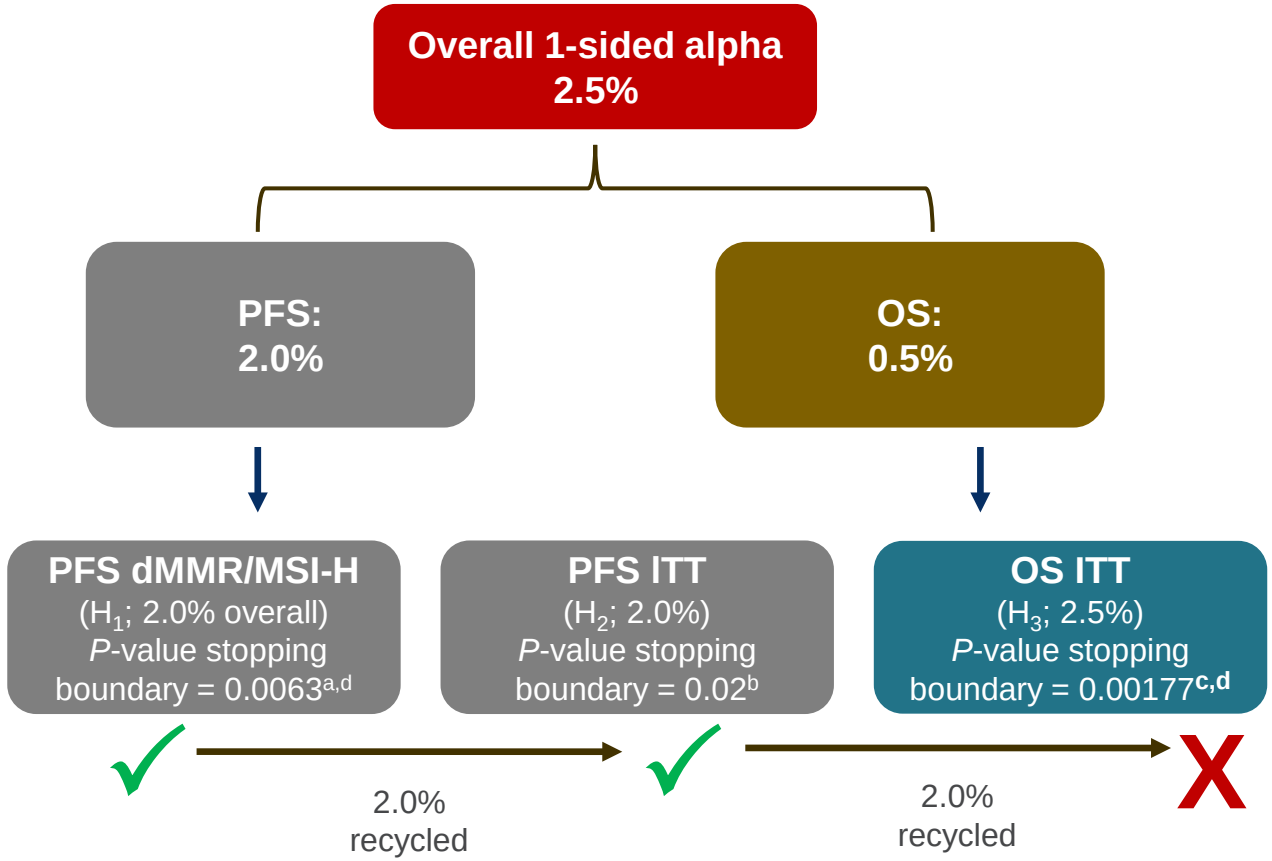
- Hierarchical with sequential testing with individual stopping boundaries
- PFS of dMMR/MSI-H tested first

Successful Trial Design: Stats

GY018



RUBY



Primary Endpoints/Assessments

	GY018	RUBY
PFS per RECIST v1.1 by investigator assessed	x	x
MMRp and dMMR	x	
OS		x
Frequency of imaging	every 9 weeks for the first 9 months, then every 12 weeks thereafter	every 6 weeks until cycle 8, followed by every 9 weeks until week 52, then every 12 weeks thereafter

Successful Trial Design: Outcomes in Unmet Need

- Homogenous representative population in the clinical target area
- Biomarker enrichment (if possible)
- Randomization with optimized stratification and low-level informative censoring
- Appropriate sample size and power for targeted treatment effect
- **Adequate maturity at interim assessments**
- **Regulatory agency interaction**
- **“Investigational strategy” (unmet medical need)**

GY018

Overall 1-sided alpha 2.5%

PFS dMMR: 1.25% ✓

PFS MMRp: 1.25% ✓

If true HR is 0.70, study has at least 90% power when 394 events occurred

If true HR is 0.60, study has at least 85% power when 168 events occurred

If null hypothesis for one population rejected, alpha forwarded to other population

Interim OS futility analysis planned at time of final or significant interim PFS analysis

RUBY

Overall 1-sided alpha 2.5%

PFS: 2.0%

OS: 0.5%

PFS dMMR/MSI-H (H_1; 2.0% overall) *P*-value stopping boundary = 0.0063[a,d] ✓

PFS ITT (H_2; 2.0%) *P*-value stopping boundary = 0.02[b] ✓

OS ITT (H_3; 2.5%) ✓

2.0% recycled

2.0% recycled

Prespecified Subgroups

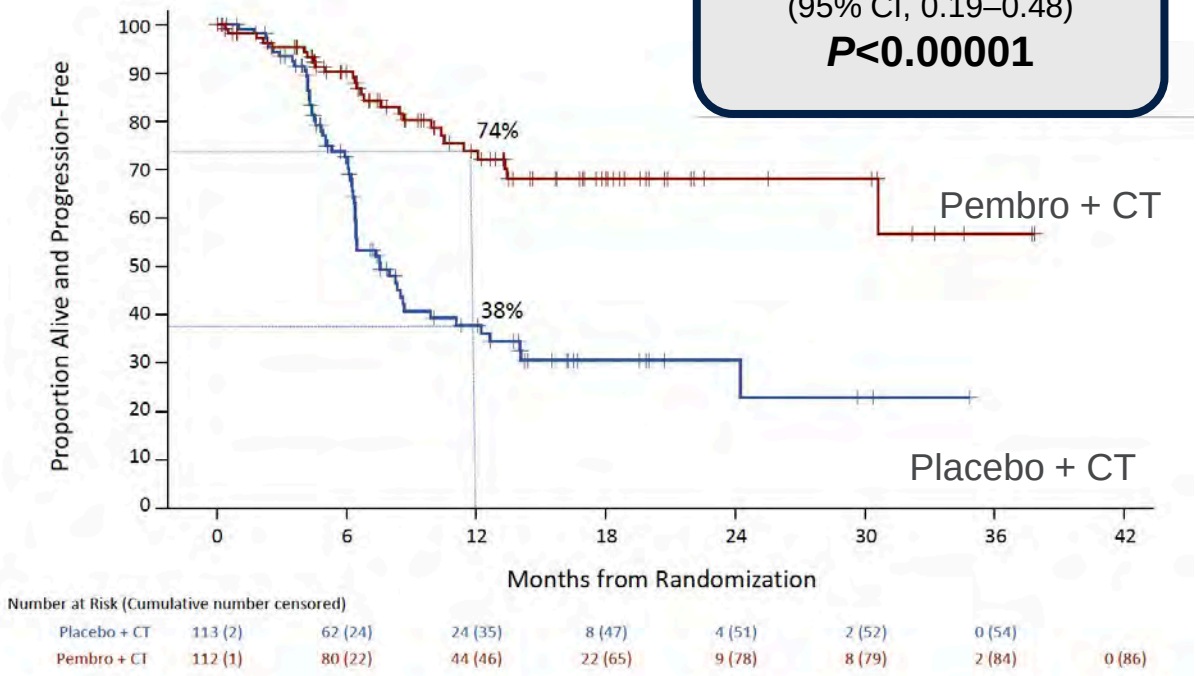
PFS MMRp/MSS

OS dMMR/MSI-H

OS MMRp/MSS

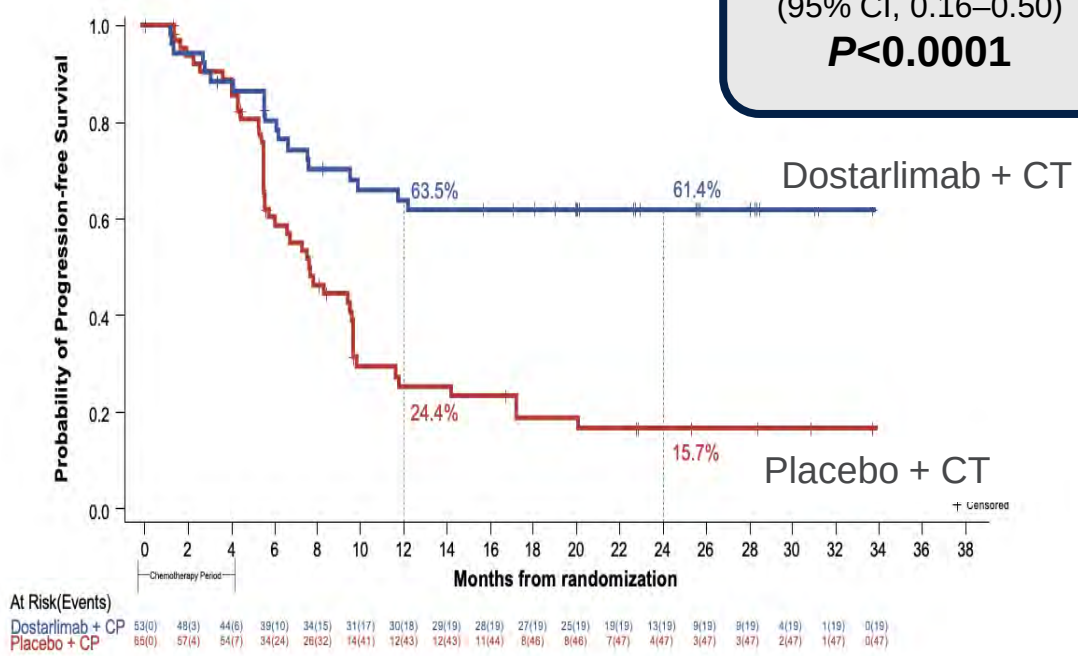
Successful Trial Design: Validation (dMMR/MSI-H)

HR, 0.30
(95% CI, 0.19–0.48)
***P*<0.00001**



	No. with events, %	Median (95% CI), mo
Pembro + CT	23.2	NR (30.6–NR)
Placebo + CT	52.2	7.6 (6.4–9.9)
PFS maturity	37.7	

HR, 0.28
(95% CI, 0.16–0.50)
***P*<0.0001**



	No. with event, %	Median (95%CI), mo
Dostarlimab + CP	35.8	NR (11.8–NR)
Placebo + CP	72.3	7.7 (5.6–9.7)
PFS maturity	55.9	

	RUBY (Mirza NEJM 2023)	GY018 (Eskander NEJM 2023)	ATTEND (Colombo Lancet Oncol 2024)	DUO-E (Arm 2) (Westin JCO 2023)
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Time since completion of adjuvant chemotherapy	≥6 months	≥12 months	≥6 months	≥12 months
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PFS	**dMMR* 0.28** ITT* 0.64 MMRp 0.76	**dMMR* 0.30** MMRp* 0.50	**dMMR* 0.36** ITT* 0.74 MMRp 0.92	dMMR 0.42 ITT* 0.71 MMRp 0.77
OS	(Maturity:51%) ITT* 0.69 (P=0.002) MMRd 0.30 MMRp 0.73	**IF: MMRd 18%** **IF: MMRp 27%** MMRd 0.55 MMRp 0.79	(Maturity:43%) ITT* 0.82 (NS) MMRd 0.41 MMRp 1.00	(Maturity:28%) ITT* 0.77 (NS) MMRd ? MMRp ?

**Primary hierarchical endpoints with formal significance*

Successful Trial Design: Stats

- Null hypothesis:
  - Superiority trial: there is no difference between intervention and control (historical, contemporary (external), or co-registered)
- Type I Error: α - error (usually set at 0.05 or 1/20)
  - Probability of incorrectly rejecting the null hypothesis
- Type II Error: β - error (usually set at 0.1 – 0.2 or 1/10 to 1/5)
  - Probability of incorrectly accepting the null hypothesis
- Power: 1-β (usually targeting 80-90%)
  - Confidence of correctly rejecting null hypothesis
- **Maturity and Informative Fraction**
  - **Maturity** = # of events/# of patients enrolled X 100% (always ≤ 100%)
  - **Informative Fraction** = # of events/# of targeted events (Goal ≥ 80%)

Successful Trial Design: Stats

- **Maturity and Informative Fraction**
  - **Maturity** = # of events/# of patients enrolled X 100% (always ≤ 100%)
  - **Informative Fraction** = # of events/# of targeted events (Goal ≥ 80%)

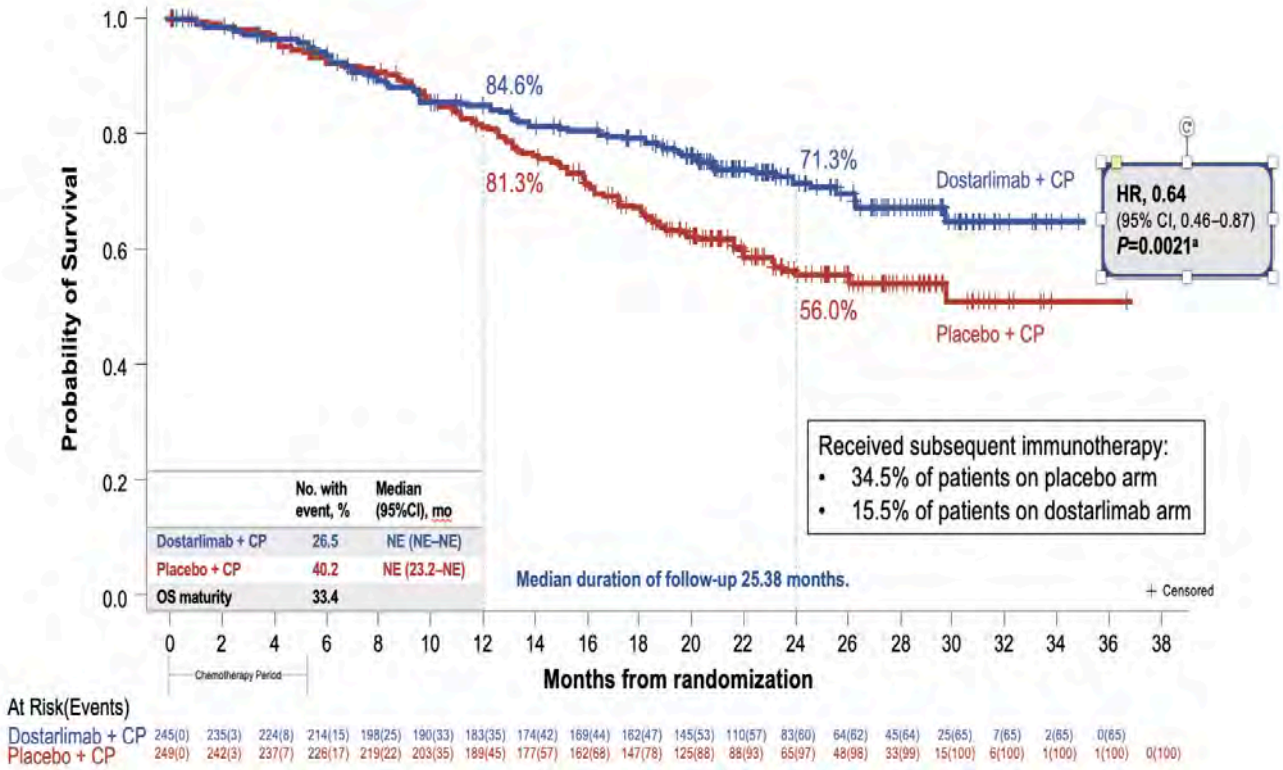
End Point	Population	Analysis[a]	Number of Events (Information Fraction)	P-value Efficacy Stopping Boundary[b]	Cumulative One-Sided Alpha Spent
OS	All comers	IA1	165 (51.4%)	0.0017702	0.0017702
		IA2	~221 (~68.8%)	0.0063549	0.0069065
		IA3	~273 (~85.0%)	0.0128988	0.0150791
		FA	321	0.0200982	0.025

[a]IA1 was already conducted when 165 deaths were observed (planned number of deaths at IA1 was ~170). IA2, IA3 and FA are the future OS analyses planned. Number of events listed for IA2, IA3 and FA in this table were planned and the actual number of events may change.
[b]Stopping boundaries provided in the table were calculated based on the information fraction listed in column "Number of Events (Information Fraction)" and the Lan-DeMets (O'Brien-Fleming) alpha spending function.[2]

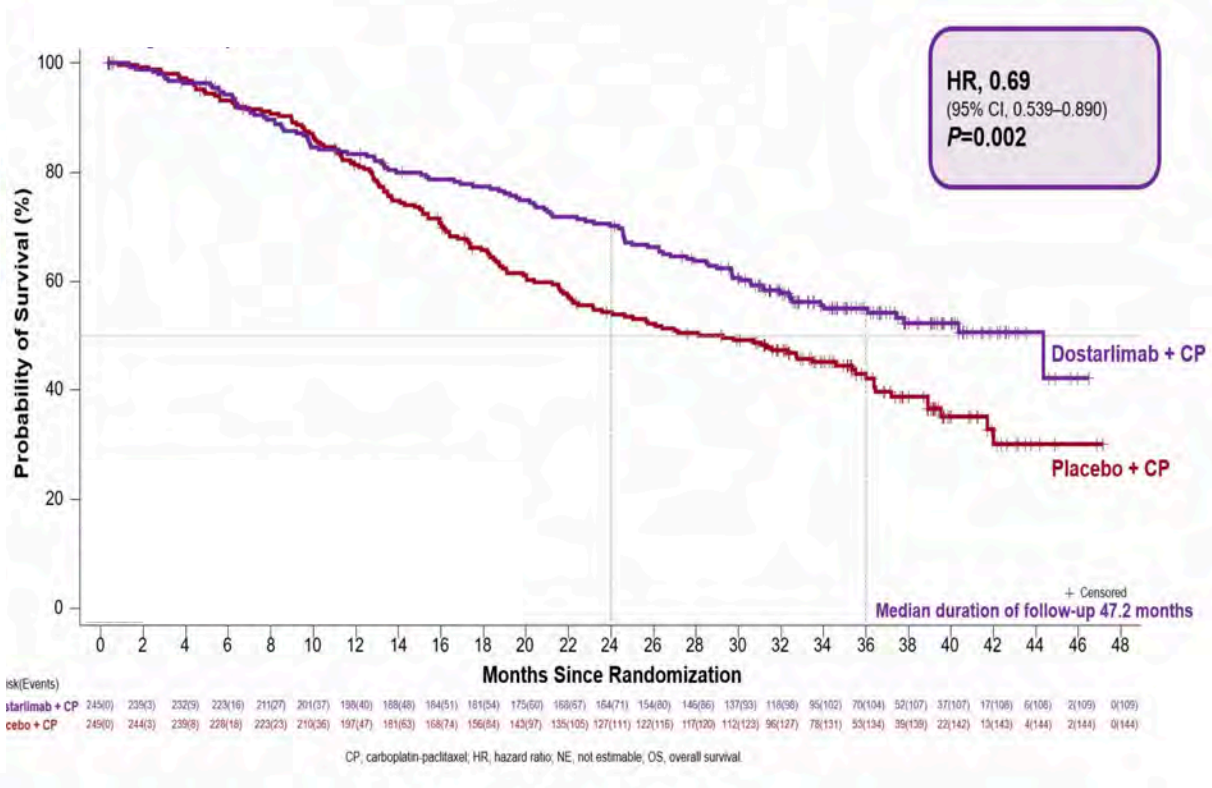
Overall Survival: RUBY

ITT Population was Analytical
P-values valid

Interim Analysis 1



Interim Analysis 2

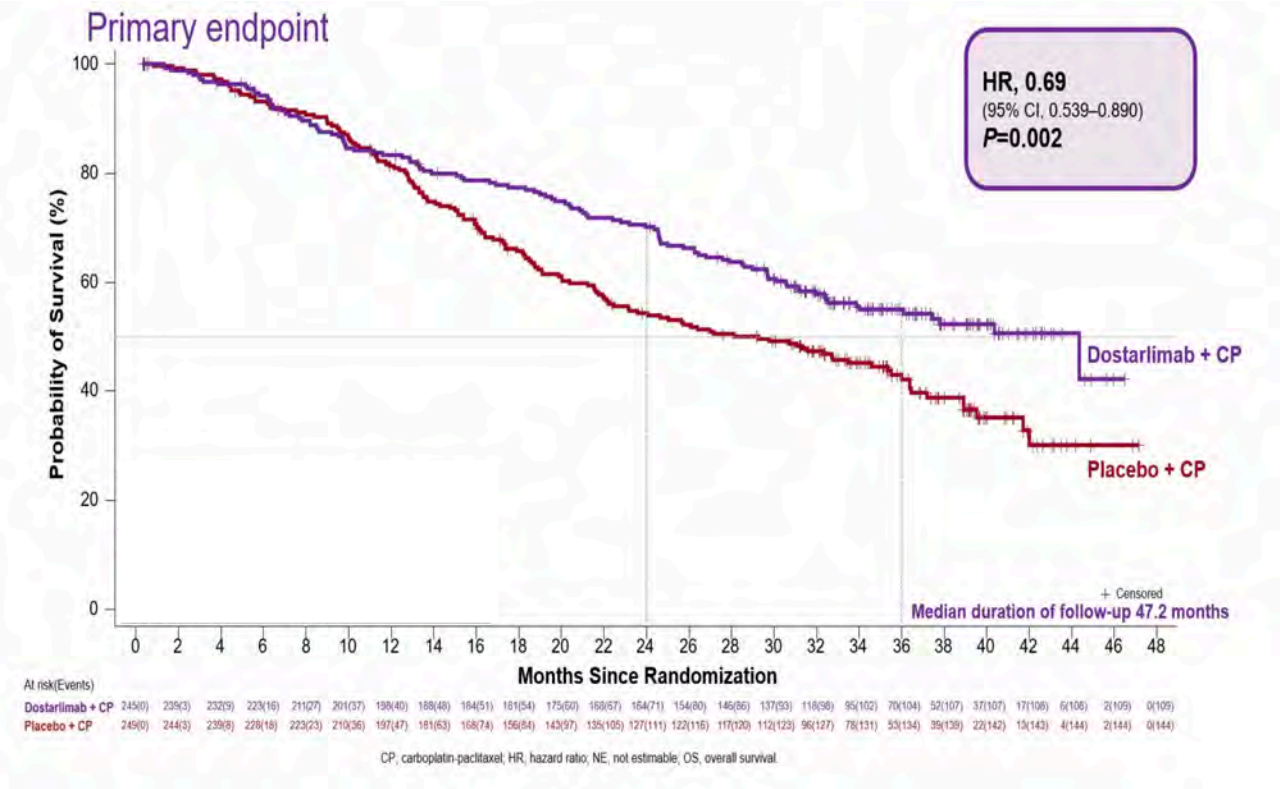


Target 321 OS “Events”; 163 events @ data lock
Maturity: 163/494 = 33%;
Informative Fraction: 163/321 = 51.2% - **P-value did not cross the pre-specified threshold (≤0.00177)**

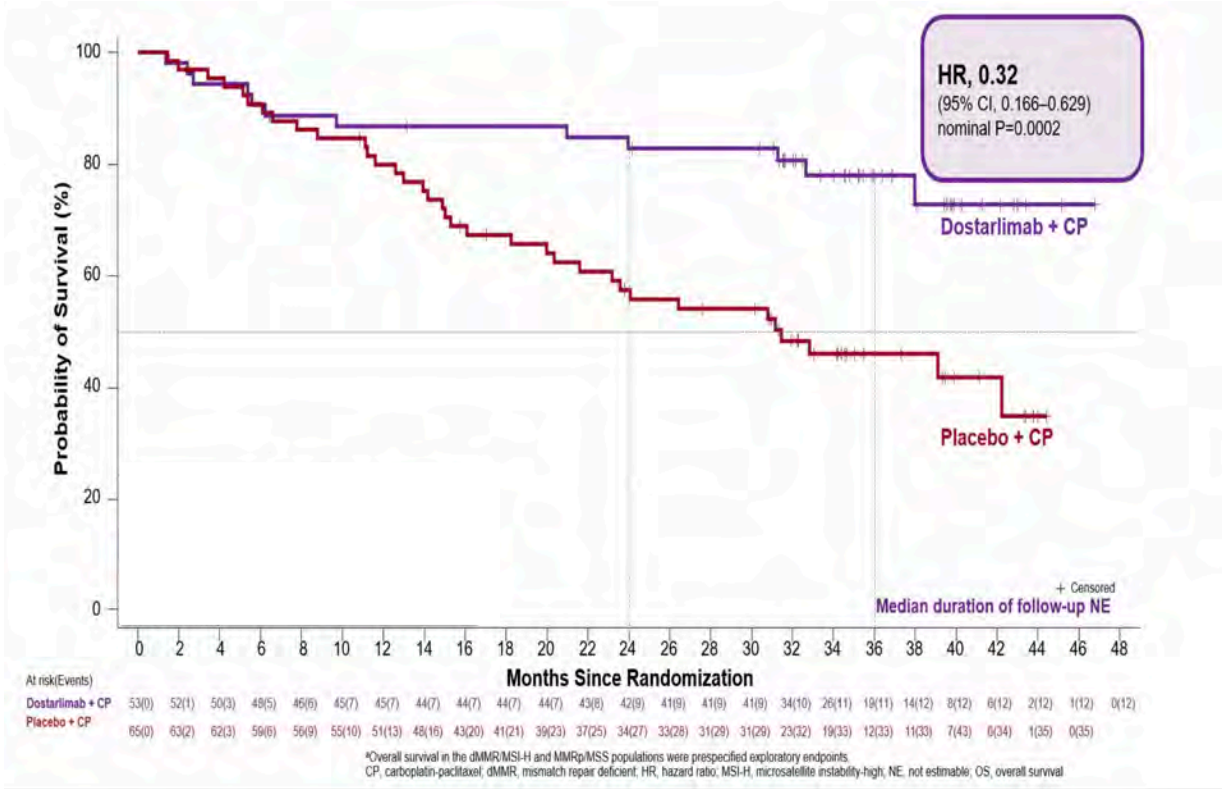
Target 321 OS “Events”; 163 events @ data lock
Maturity: 253/494 = 51.2%;
Informative Fraction: 253/321 = 79% - **P-value crossed the pre-specified threshold (≤0.006)**

Overall Survival: RUBY

ITT Population was Analytical
P-value valid



dMMR Population was Not Analytical
P-value NOT valid

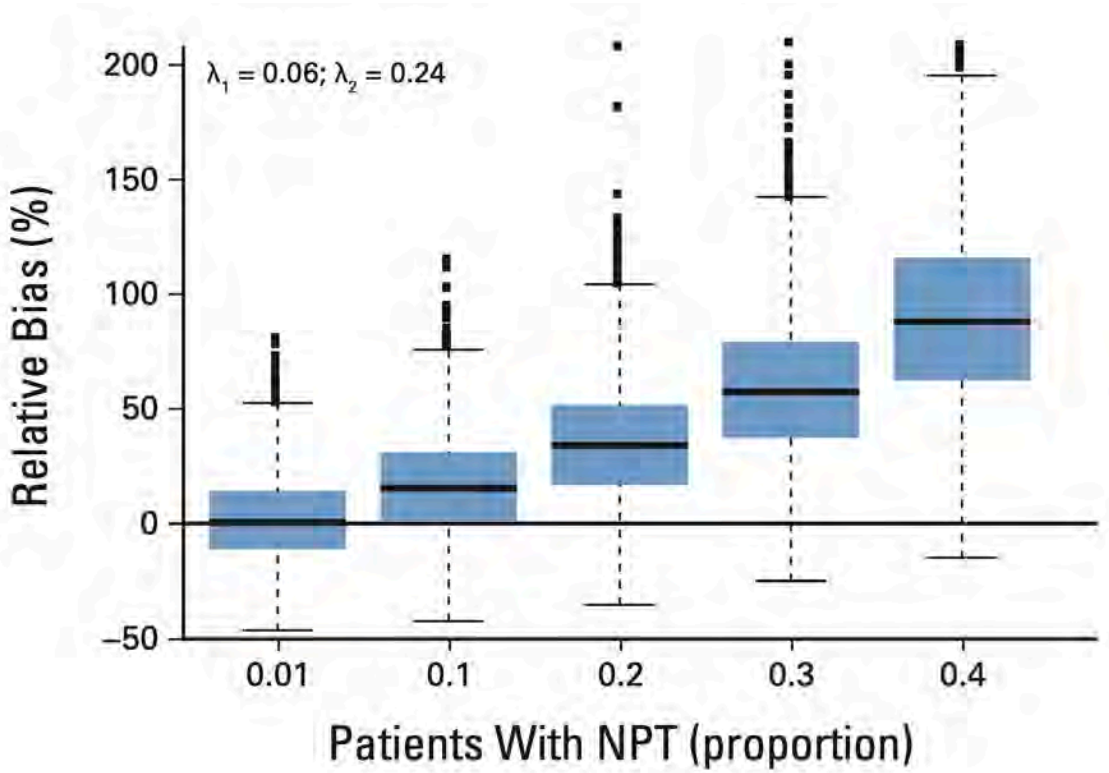


Successful Trial Design: Low Informative Censoring

- Very difficult to ascertain from the presented/published data but risk would be expected to be highest in dMMR cohort
  - Availability of pembrolizumab and dostarlimab single agent use before progression in dMMR likely low due to availability to global sites

- RUBY: unexplained censoring was <10.5%

- GY-018: unclear especially since trial was unblinded after PFS read



Campigotto, J Clin Oncol 2014

Chemo + IO: dMMR Population

- Nice story rooted in strong biological rationale
- Trial designs (mostly) appropriate for population (unmet need)
- Statistical plan (mostly) appropriate to patient-level inference on PFS and OS
- Low rate of bias
- Confirmed findings

Biomarker-Based Treatment Strategies: Deep Dive into Subgroup Data

Ramez N. Eskander, MD

UC San Diego Health, Moores Cancer Center

San Diego, California, USA

GOG FOUNDATION® *Transforming the standard of care*

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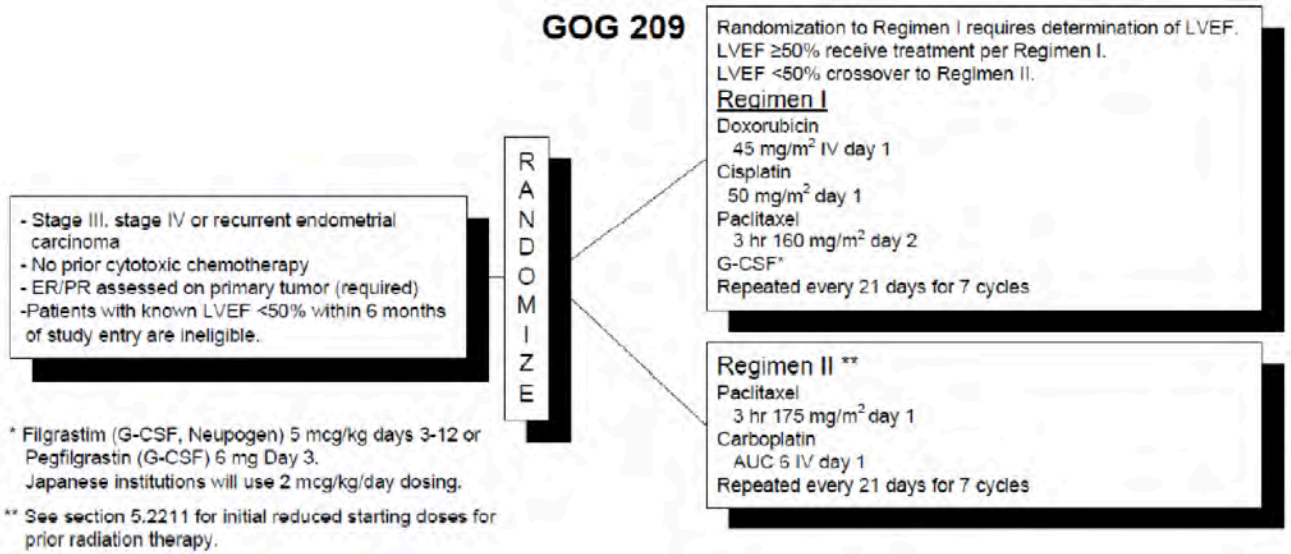
Treatment of advanced stage/recurrent Endometrial Cancer

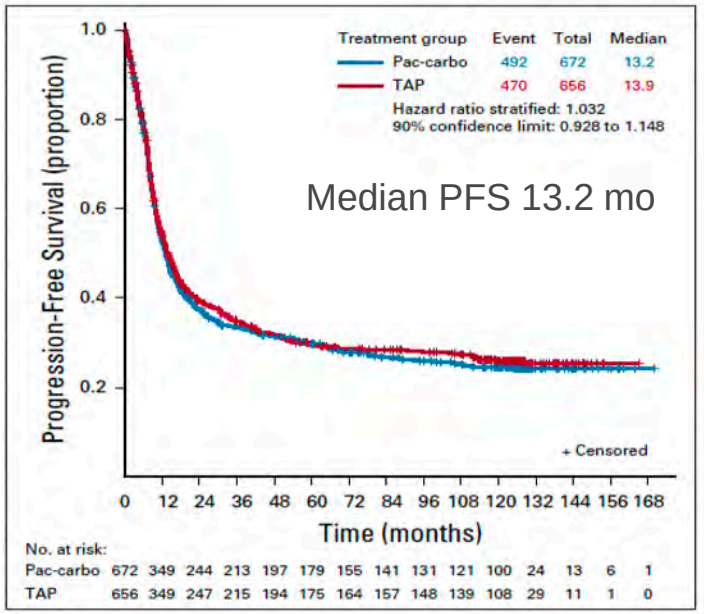
	RT agent vs. Doublet	Single agent vs. Doublet		Doublet vs. Doublet	Doublet vs. Triplet	TAP vs. TC
	GOG 122 Randall et al. JCO ’06	**EORTC55872** Van Wijk Ann Onc ’03	**GOG 107** Thigpen JCO ’04	**GOG 163** Fleming. Ann Onc ’04	**GOG 177** Fleming JCO ’03	**GOG 209** Miller SGO ´12
Population (Stage)	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

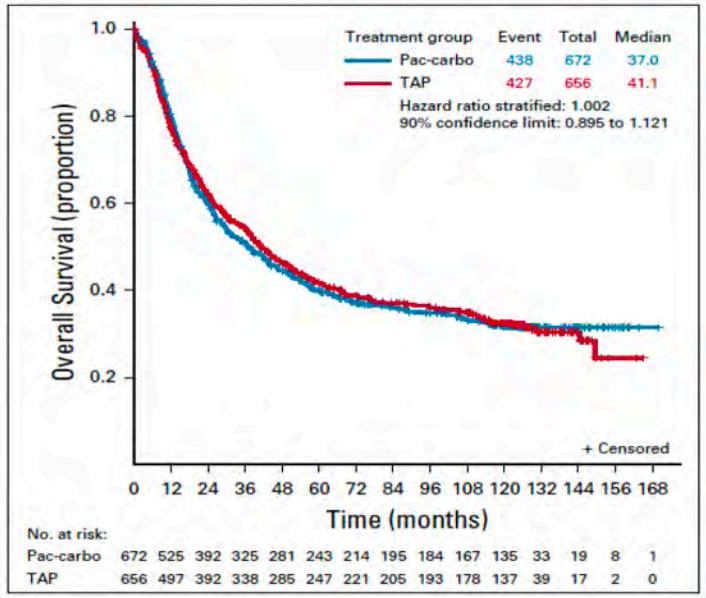
Established carboplatin and paclitaxel as the chemotherapy backbone for patients with advanced stage or recurrent disease



Progression Free Survival



Overall Survival



Key eligibility criteria

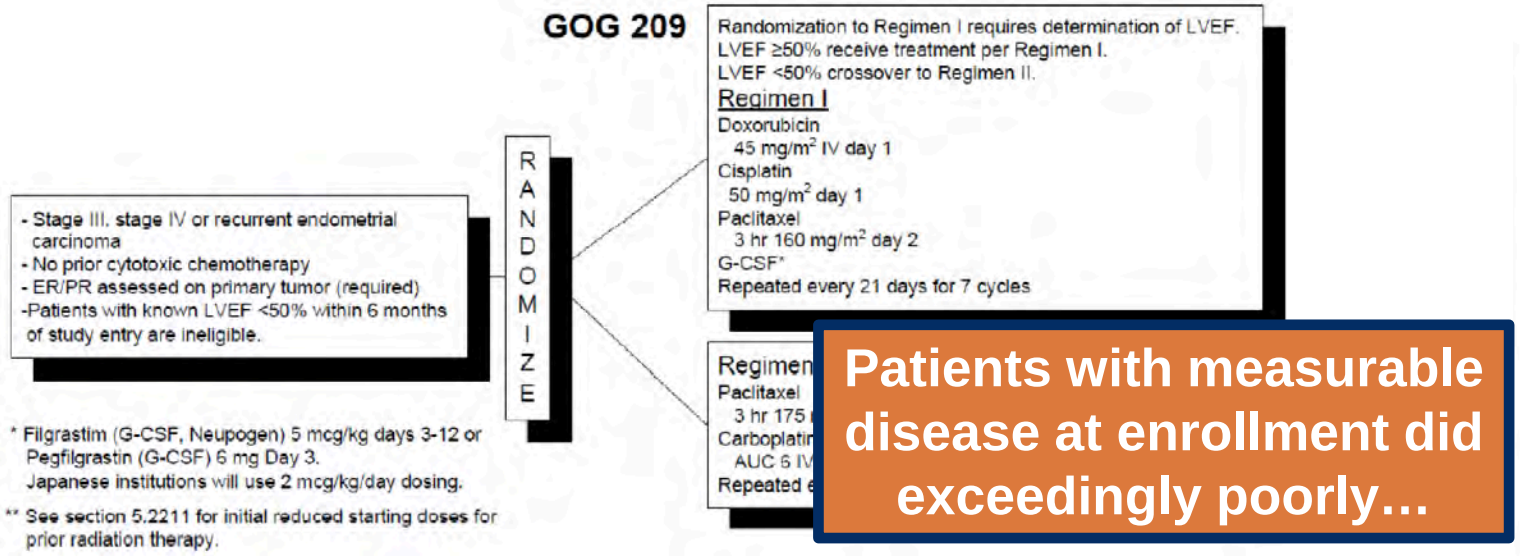
- **Stage III, Stage IV or recurrent endometrial carcinoma. No mandate for measurable disease**
- **NO prior cytotoxic chemotherapy**, including chemotherapy used for radiation sensitization
- GOG PS 0,1 or 2

GOG FOUNDATION® Transforming the standard of care GOG PARTNERS

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

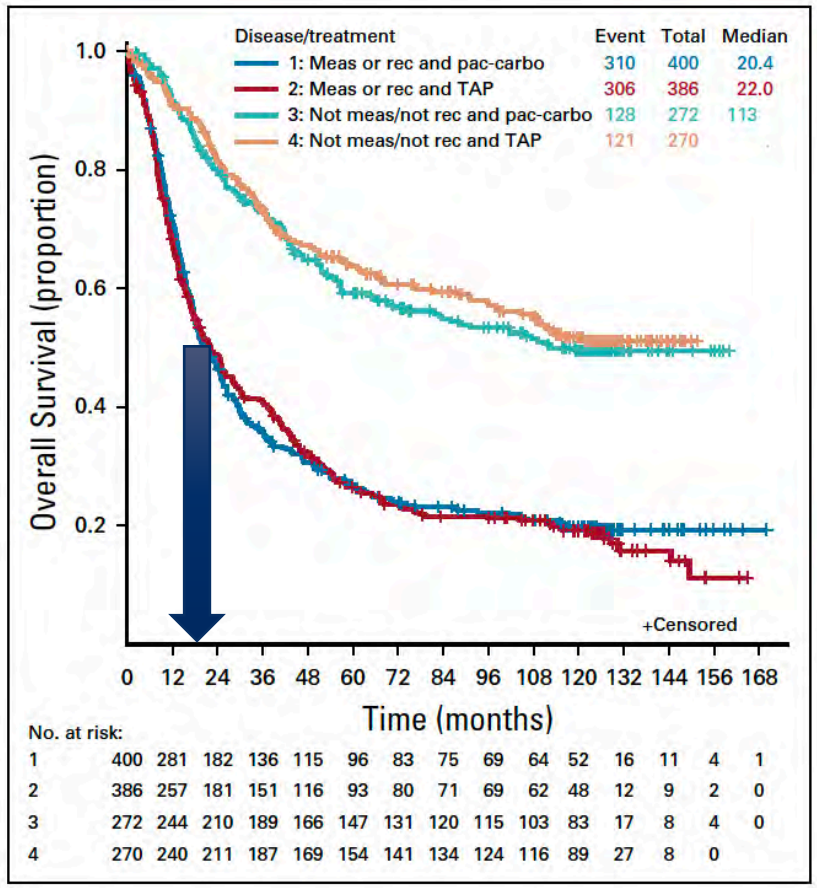
GOG 209

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



Patients with measurable disease at enrollment did exceedingly poorly…

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

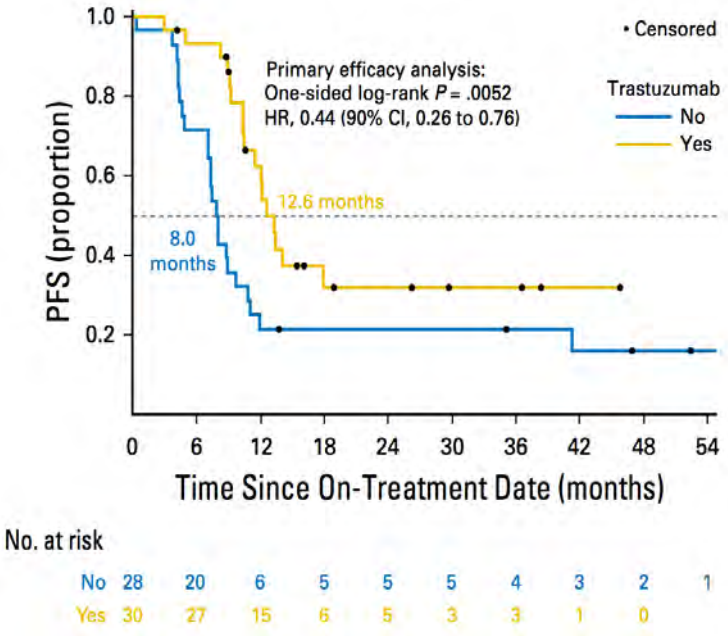
GOG FOUNDATION® Transforming the standard of care GOG PARTNERS

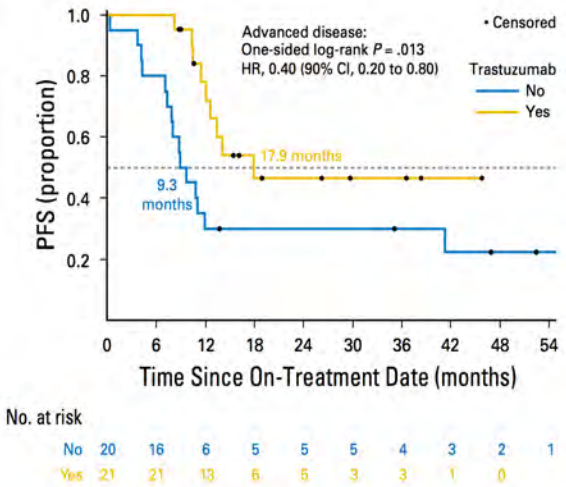
Miller DS, et al. J Clin Oncol. 2020 Nov 20;38(33):3841-3850.

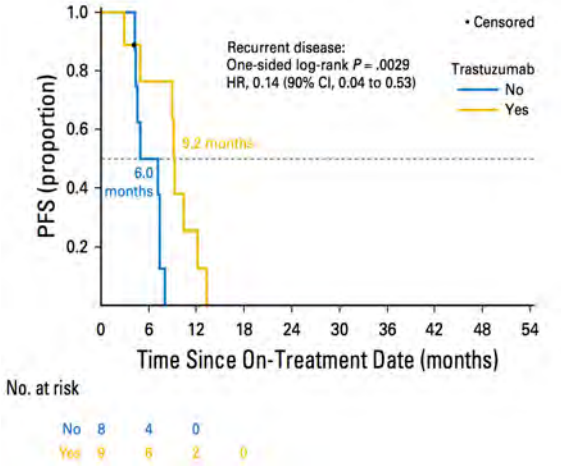
Incorporation of anti-HER-2 treatment: Trastuzumab with Chemotherapy

Key eligibility criteria

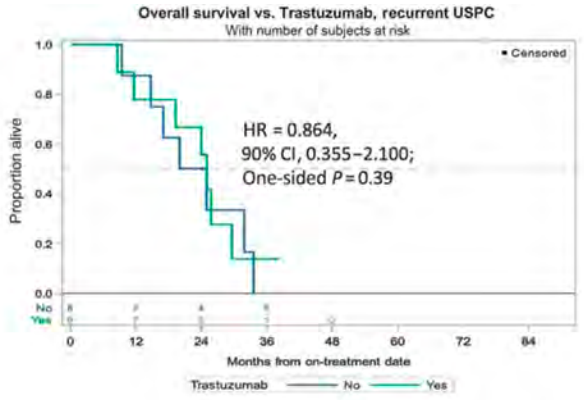
- Primary stage III or IV or recurrent HER2/neu-positive USC: IHC score 3+, or 2+ with + FISH
- ECOG 0-2
- ≤3 prior lines of therapy
- “platinum sensitive” recurrence (6 mo)







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).



Nickles-Fader J Clin Oncol 2018

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

Response to single agent IO in **recurrent 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

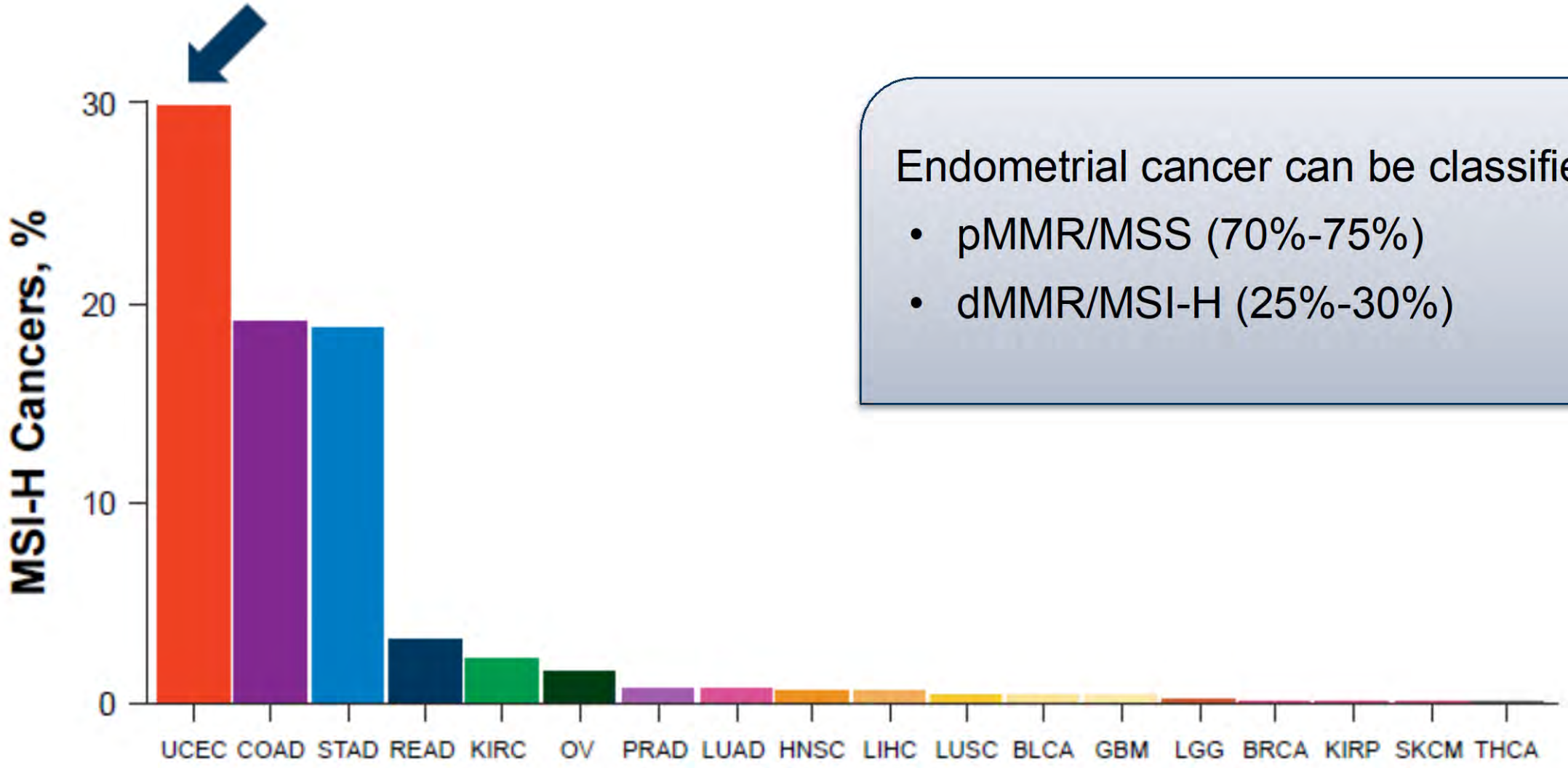
Single Agent IO in “non-biomarker” Selected Endometrial Cancer Populations

Response to single agent IO in recurrent pMMR or MSS endometrial cancer

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

Frequency of dMMR in Endometrial Cancer



Endometrial cancer can be classified as

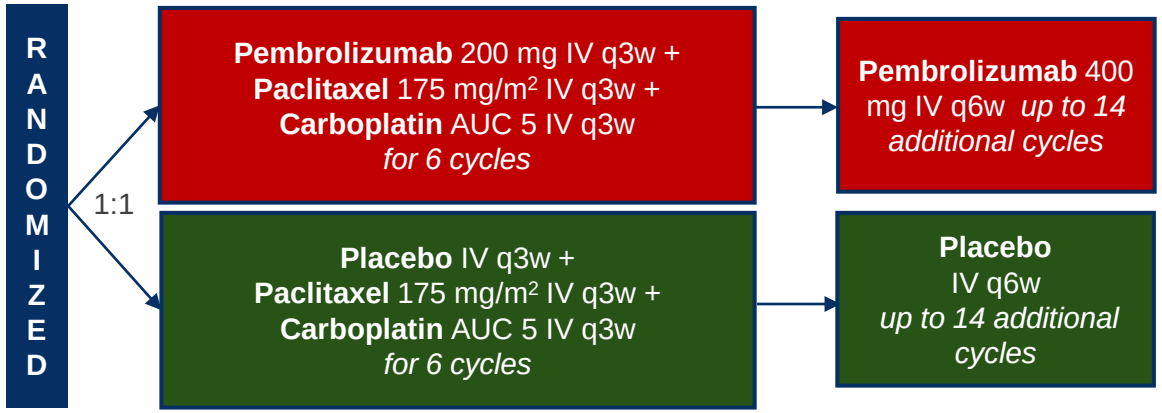
- pMMR/MSS (70%-75%)
- dMMR/MSI-H (25%-30%)

[a] *UCEC (n = 437); COAD (n = 294); STAD (n = 278); READ (n = 96); KIRC (n = 279); OV (n = 63); PRAD (n = 463); LUAD (n = 480); HNSC (n = 506); LIHC (n = 338); LUSC, (n = 443); BLCA (n = 253); GBM (n = 262); LGG (n = 513); BRCA (n = 266); KIRP (n = 207); SKCM (n = 268); THCA (n = 484).*

1. Hause RJ et al. Nat Med. 2016;22:1342-1350.

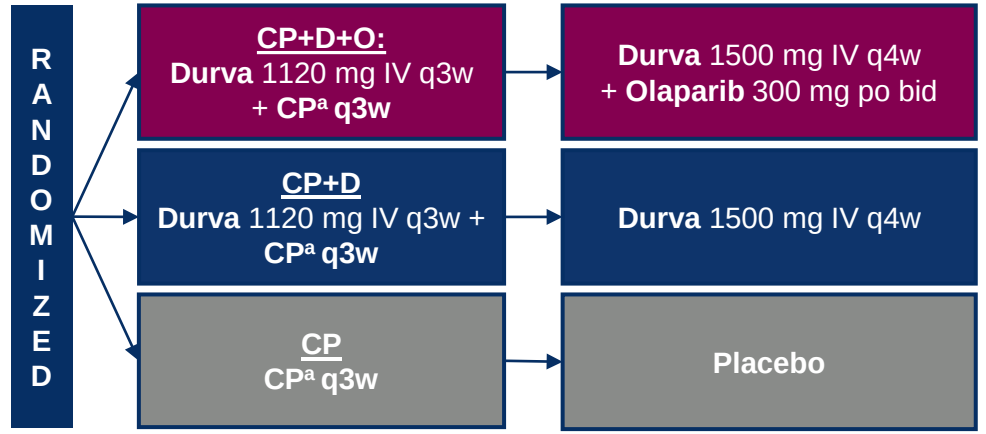
Transformative Clinical Trials in the Advanced Stage/Recurrent EC

NRG GY018



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

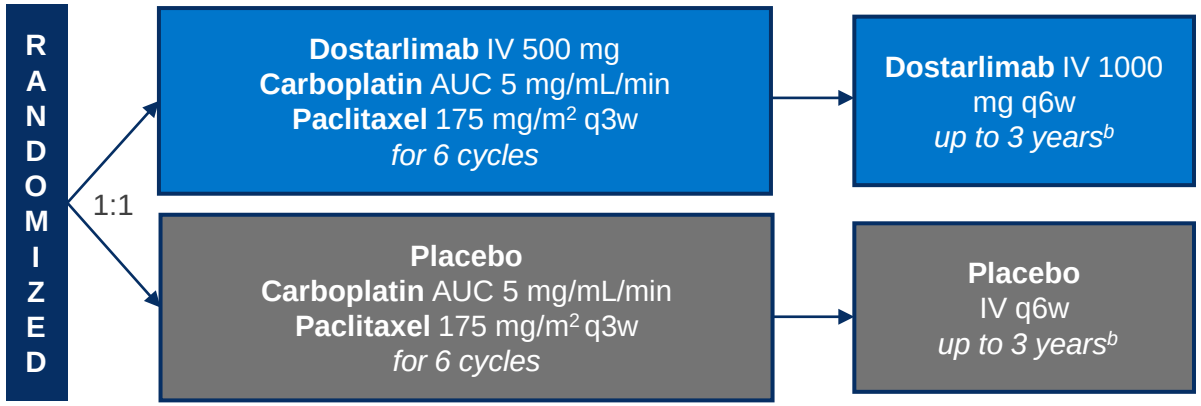
DUO-E/GOG 3041



Stratified by MMR status, Disease status, Region of world

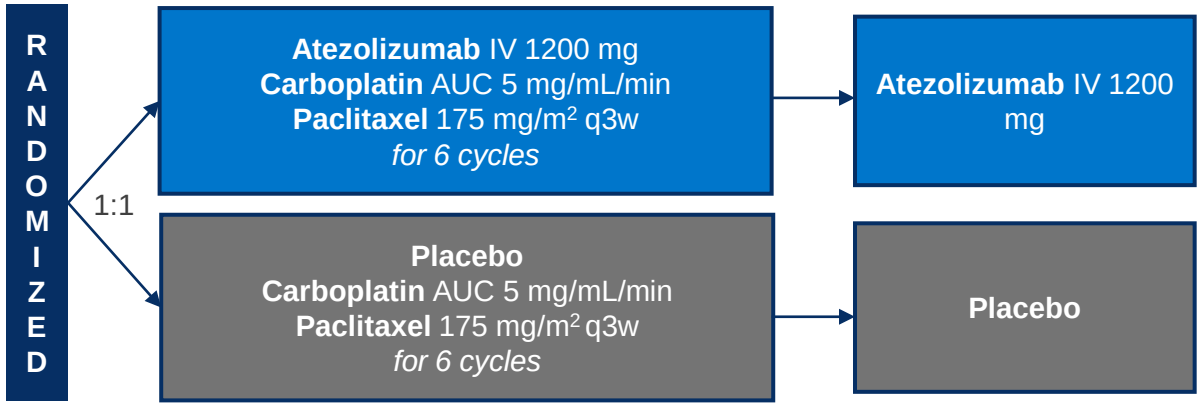
Patients without PD went on to maintenance

GOG 3031/RUBY



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

AtTEnd



Stratified by MMR status, Disease status, Region of world, histology

GOG FOUNDATION Transforming the standard of care GOG PARTNERS

Eskander R, et al. SGO 2023. Abstract 264. N Eng J Med March 2023; Mirza MR, et al. SGO 2023. Abstract 265. N Eng J Med March 2023; Westin, S et al. ESMO 2023 and J Clin Oncol Jan 2024; Colombo et al. ESMO 2023

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

M.R. Mirza, D.M. Chase, B.M. Slomovitz, R. dePont Christensen, Z. Novák, D. Black, L. Gilbert, S. Sharma, G. Valabrega, L.M. Landrum, L.C. Hanker, A. Stuckey, I. Boere, M.A. Gold, A. Auranen, B. Pothuri, D. Cibula, C. McCourt, F. Raspagliesi, M.S. Shahin, S.E. Gill, B.J. Monk, J. Buscema, T.J. Herzog, L.J. Copeland, M. Tian, Z. He, S. Stevens, E. Zografos, R.L. Coleman, and M.A. Powell, for the RUBY Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D., Richard G. Moore, M.D., Joanie M. Hope, M.D., Fernanda B. Musa, M.D., Robert Mannel, M.D., Mark S. Shahin, M.D., Guilherme H. Cantuaria, M.D., Eugenia Girda, M.D., Cara Mathews, M.D., Juraj Kavecansky, M.D., Charles A. Leath III, M.D., M.S.P.H., Lilian T. Gien, M.D., Emily M. Hinchcliff, M.D., M.P.H., Shashikant B. Lele, M.D., Lisa M. Landrum, M.D., Floor Backes, M.D., Roisin E. O'Cearbhaill, M.D., Tareq Al Baghdadi, M.D., Emily K. Hill, M.D., Premal H. Thaker, M.D., Veena S. John, M.D., Stephen Welch, M.D., Amanda N. Fader, M.D., Matthew A. Powell, M.D., and Carol Aghajanian, M.D.

ASCO Journal of Clinical Oncology®

Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial

Shannon N. Westin, MD, MPH[1]; Kathleen Moore, MD[2]; Hye Sook Chon, MD[3]; Jung-Yun Lee, MD[4]; Jessica Thomes Pepin, MD[5]; Michael Sundborg, MD[6]; Ayelet Shai, MD, PhD[7]; Joseph de la Garza, MD[8]; Shin Nishio, MD[9]; Michael A. Gold, MD[10]; Ke Wang, MD[11]; Kristi McIntyre, MD[12]; Todd D. Tillmanns, MD[13]; Stephanie V. Blank, MD[14]; Ji-Hong Liu, MD[15]; Michael McCollum, MD[16]; Fernando Contreras Mejia, MD[17]; Tadaaki Nishikawa, MD[18]; Kathryn Pennington, MD[19]; Zoltan Novak, MD, PhD[20]; Andreia Cristina De Melo, MD[21]; Jalid Sehouli, MD[22]; Dagmara Klasa-Mazurkiewicz, MD[23]; Christos Papadimitriou, MD[24]; Marta Gil-Martin, MD[25]; Birute Brasiuniene, MD, PhD[26]; Conor Donnelly, PhD[27]; Paula Michelle del Rosario, MD[28]; Xiaochun Liu, MD, PhD[29]; and Els Van Nieuwenhuysen, MD[30]; on behalf of the DUO-E Investigators

DOI https://doi.org/10.1200/JCO.23.02132

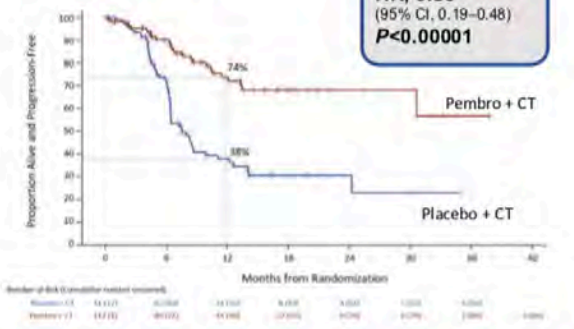
Atezolizumab and chemotherapy for advanced or recurrent endometrial cancer (AtTEnd): a randomised, double-blind, placebo-controlled, phase 3 trial

*Nicoletta Colombo, Elena Biagioli, Kenichi Harano, Francesca Galli, Emma Hudson, Yoland Antill, Chel Hun Choi, Manuela Rabaglio, Frederic Marmé, Christian Marth, Gabriella Parma, Lorena Fariñas-Madrid, Shin Nishio, Karen Allan, Yeh Chen Lee, Elisa Piovano, Beatriz Pardo, Satoshi Nakagawa, John McQueen, Claudio Zamagni, Luis Manso, Kazuhiro Takehara, Giulia Tasca, Annamaria Ferrero, Germana Tognon, Andrea Alberto Lissoni, Mariacristina Petrella, Maria Elena Laudani, Eliana Rulli, Sara Uggeri, M Pilar Barretina Ginesta, and AtTEnd study group**

Lancet Oncol 2024; 25: 1135–46

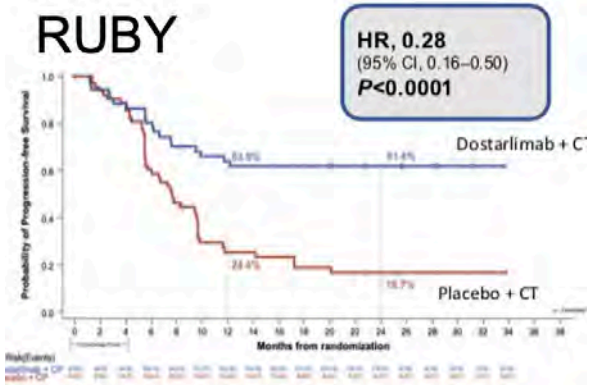
Benefit of IO + Chemo in the dMMR EC population

GY018



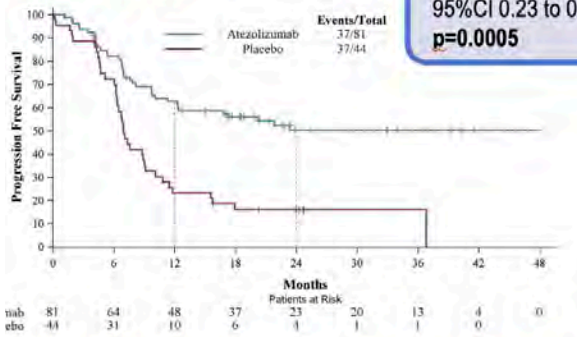
	No with events%	Median
Pembro + CT	23.2	NR (30.6-NR)
Placebo + CT	52.2	7.6 (6.4-9.9)

RUBY



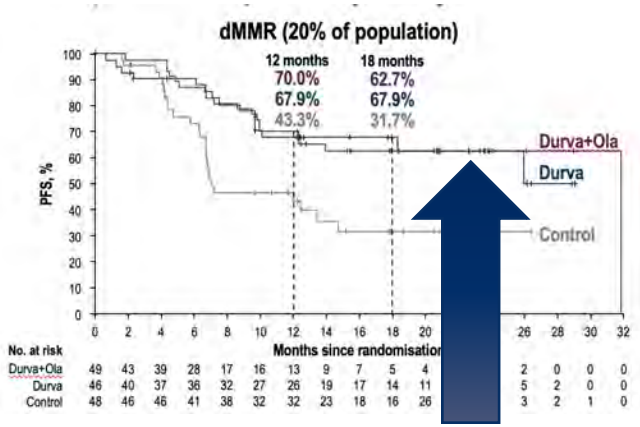
	No with events%	Median
Dorsta + CT	35.8	NR (11.8-NR)
Placebo + CT	72.3	7.7 (5.6-9.7)

AtTEnd



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

DUO-E



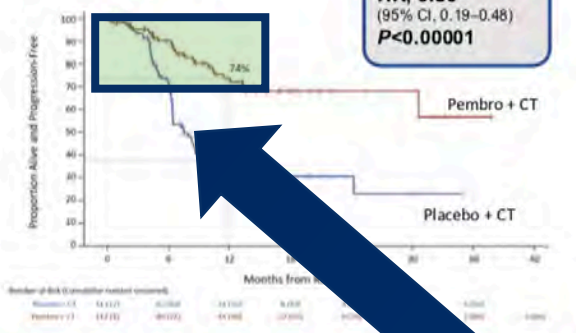
CT		
Placebo + CT	51	7.0 (6.7-14.8)

There is no role for PARPi in the dMMR population

Slide courtesy of Dr. David Tan ESMO 2023 - Revised

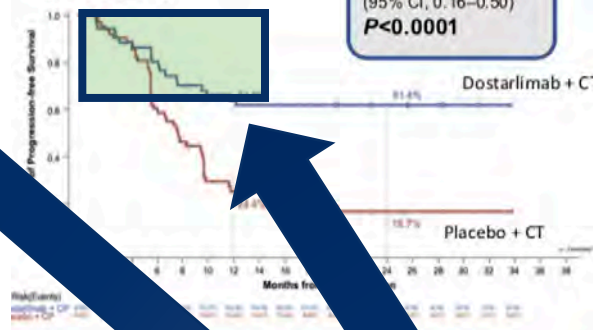
Benefit of IO + Chemo in the dMMR EC population

GY018



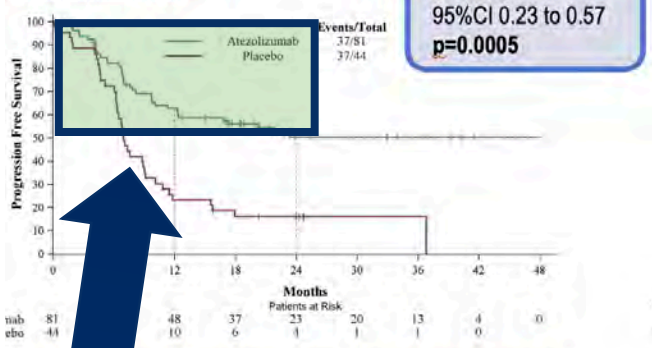
	No with events%	Me
Pembro + CT	23.2	NR (30.6-NR)
Placebo + CT	52.2	7.6 (6.4-9.9)

RUBY



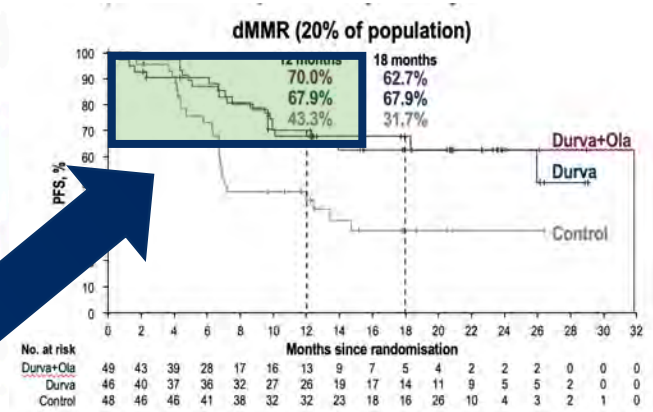
	h	dian
Dorsta + CT	35.8	(1 R)
Placebo + CT	72.3	7.7 (

AtTEnd



	No with events%	Median
zo + T	45.7	NR (12.3-NR)
cebo + CT	84.1	6.9 (6.2

DUO-E



	No with events %	Median
Durva + CT	32.6	NR (NR-NR)
Durva + O + CT	37.5	31.8 (12.4-NR)
Placebo +	51	7.0 (6.7-14.8)

Who are these 25-30% of dMMR patients who progress on immune checkpoint inhibition?

- I suspect dMMR but TMB low

Benefit of IO + Chemo in the dMMR EC population

Immune Checkpoint Inhibition + CT is the new standard of care in advanced stage or recurrent dMMR EC…

July 31, 2023

FDA approves dostarlimab-gxly with chemotherapy for endometrial cancer

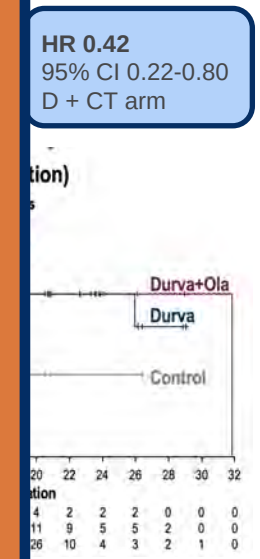
June 14, 2024

FDA approves durvalumab with chemotherapy for mismatch repair deficient primary advanced or recurrent endometrial cancer

approved test, or microsatellite instability-high (MSI-H).

June 17, 2024

FDA approves pembrolizumab with chemotherapy for primary advanced or recurrent endometrial carcinoma



events %	Median
	NR (NR-NR)
	31.8 (12.4-NR)
	7.0 (6.7-14.8)

Slide courtesy of Dr. David Tan ESMO 2023 - Revised

What about IO in early stage completely resected dMMR: (ENGOT-EN11/GOG-3053/KEYNOTE-B21)

Key Eligibility Criteria

- Newly diagnosed EC or carcinosarcoma
- Curative surgery with no residual disease
- At high risk for recurrence:
  - FIGO (2009) surgical stage I/II, non-endometrioid with myometrial invasion
  - FIGO (2009) surgical stage I/II of any histology with known aberrant p53 expression or *TP53* mutation with myometrial invasion
  - FIGO (2009) surgical stage III/IVA of any histology
- No prior radiation or systemic therapy (including neoadjuvant) for EC

Stratification Factors

- **MMR status (pMMR vs dMMR)**, and within pMMR stratum:
  - Planned radiation (chemo-EBRT vs EBRT vs no EBRT)
  - Histology (endometrioid vs non-endometrioid)
  - FIGO (2009) surgical stage (I/II vs III/IVA)

R 1:1
N=1095

	Stage 1	Stage 2
	Carboplatin (AUC 5 or 6) + paclitaxel 175 mg/m^2 (Q3W, 4 or 6 cycles)[a]	± radiotherapy ± cisplatin[b]
	Pembrolizumab 200 mg Q3W (6 cycles)	Pembrolizumab 400 mg Q6W (6 cycles)
	Carboplatin (AUC 5 or 6) + paclitaxel 175 mg/m^2 (Q3W, 4 or 6 cycles)[a]	± radiotherapy ± cisplatin[b]
	Placebo Q3W (6 cycles)	Placebo Q6W (6 cycles)

Dual primary endpoints

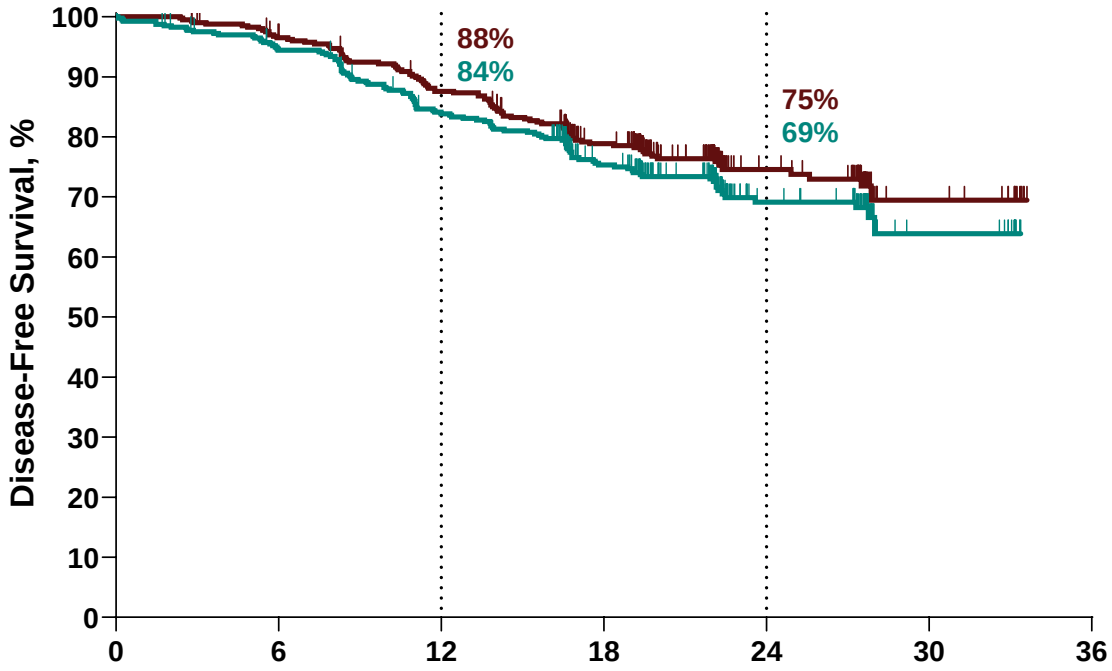
- DFS as assessed radiographically by the investigator or by histopathologic confirmation
- OS

Van Gorp et al. ESMO 2024

What about IO in early stage completely resected dMMR: (ENGOT-EN11/GOG-3053/KEYNOTE-B21)

pMMR Subgroup

	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembro + CT	111 (27)	NR (NR–NR)	1.20 (0.91–1.57)
Placebo + CT	96 (23)	NR (NR–NR)	

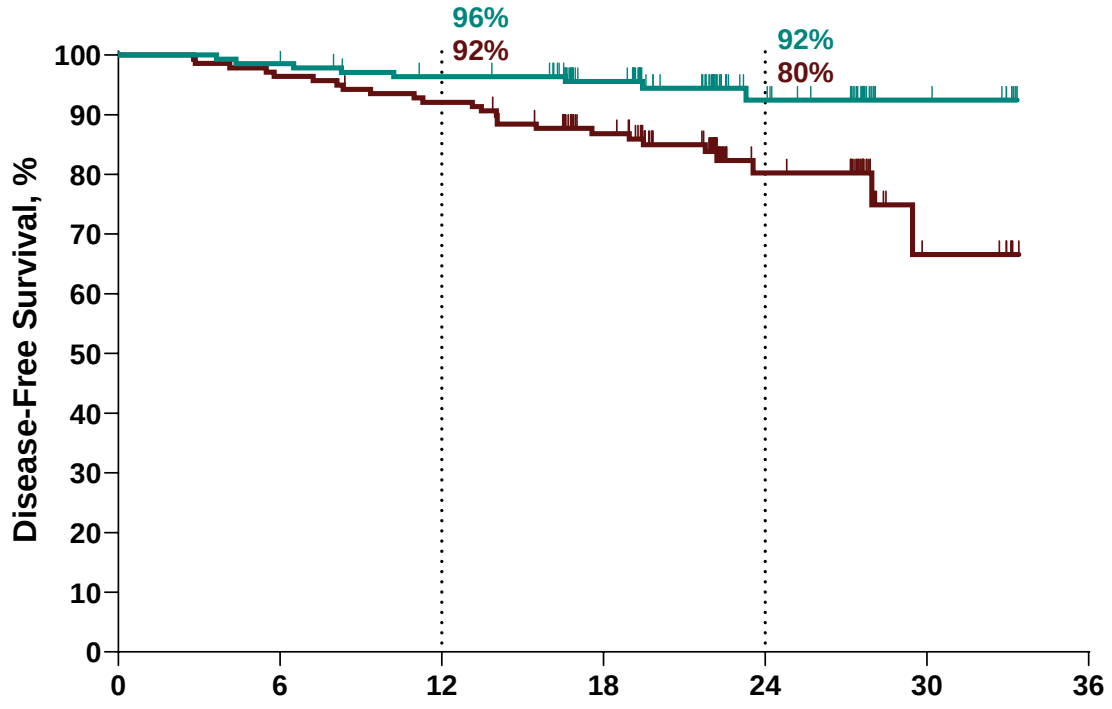


No. at risk

Pembro + CT	404	369	323	244	88	17	0
Placebo + CT	410	381	343	259	94	16	0

dMMR Subgroup

	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembro + CT	8 (6)	NR (NR–NR)	0.31 (0.14–0.69)
Placebo + CT	25 (18)	NR (29.5–NR)	



No. at risk

	141	136	129	103	46	10	0
	140	134	127	99	38	7	0

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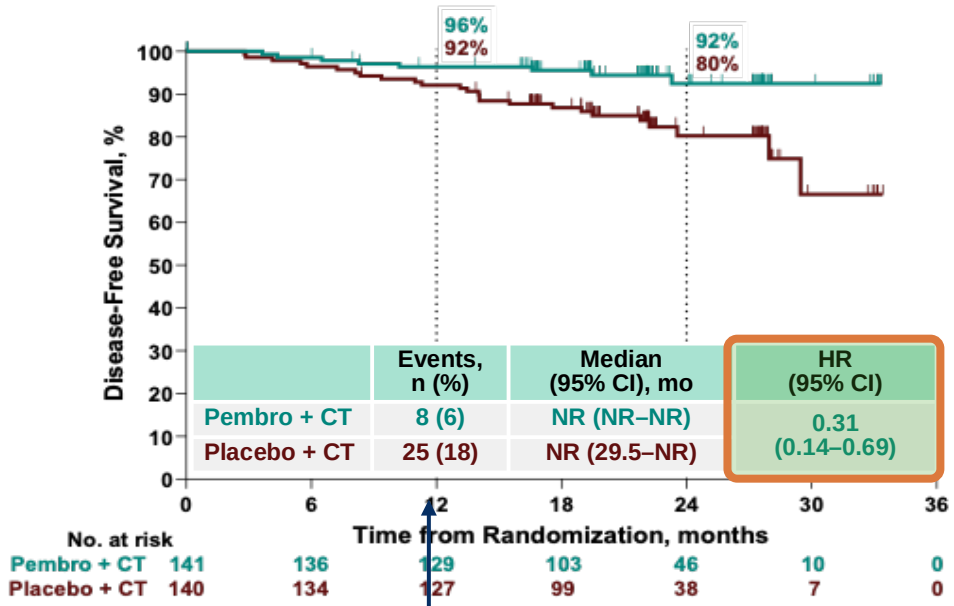
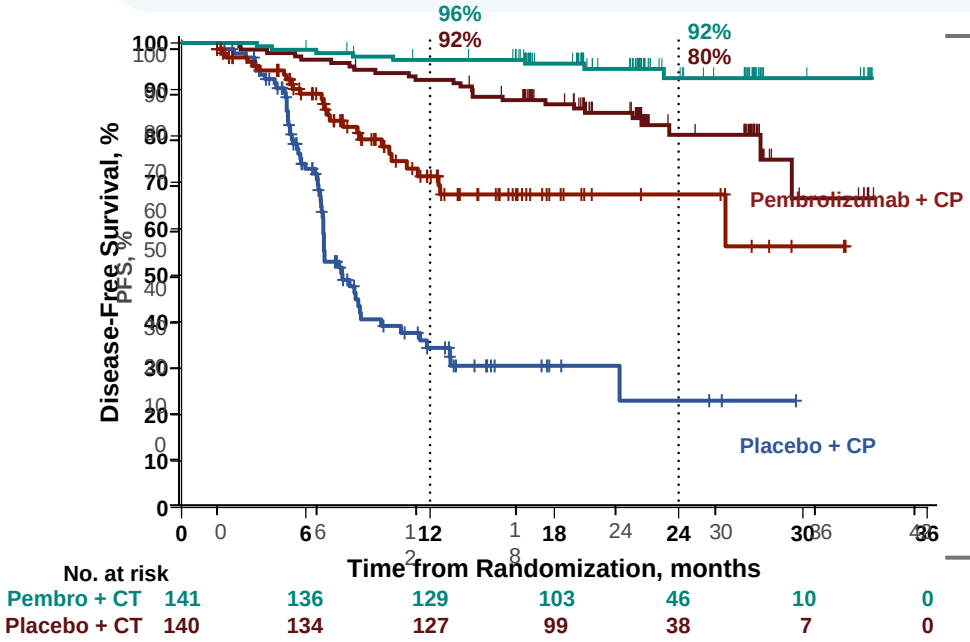
KEYNOTE-B21: Phase 3 Study of Pembro or Placebo in Combination With Adjuvant CT With or Without RT in Newly Diagnosed, High-risk EC



Only 8 recurrences in the pembrolizumab arm…

Although not a primary hypothesis-tested analysis, the **HR of 0.31 in dMMR EC is provocative** and argues for use of pembrolizumab in combination with chemotherapy in adjuvant setting for advanced stage dMMR patients

Perhaps analogous to expansion of PARPi in stage 2 EOC BRCAmut population

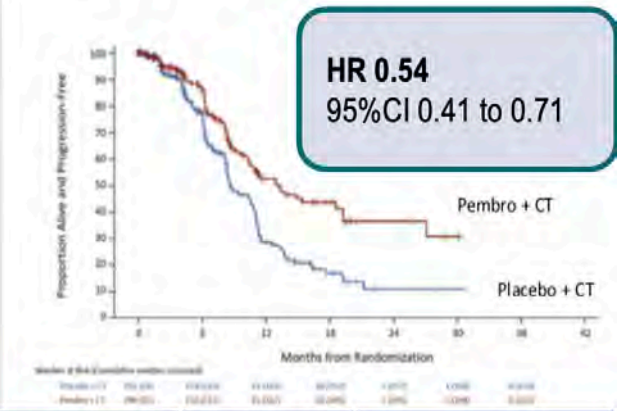


Based on the morphology of these curves, no indication to "hold" ICI until recurrence…

Van Gorp T et al. Annals Oncol. 2024;35(Suppl 2):S1221 (Presentation).

Benefit of IO + Chemo in the pMMR EC population

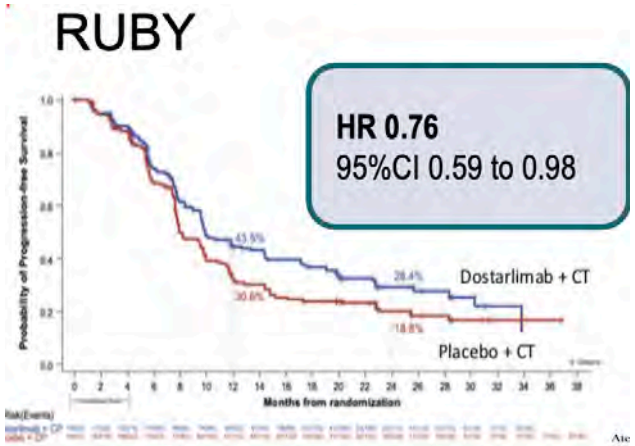
GY018



	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%	

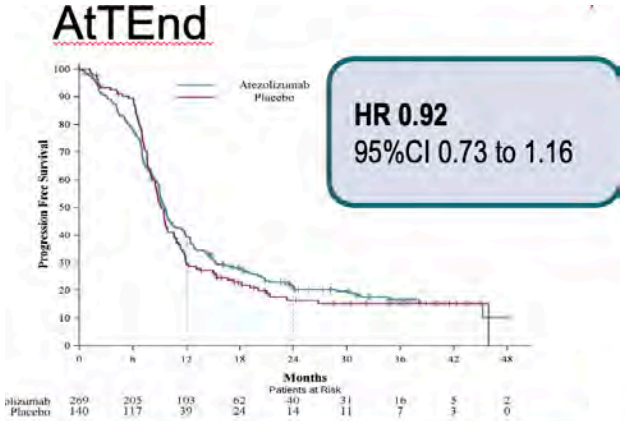
Only trial with prespecified alpha allocated analysis in pMMR EC cohort as primary endpoint

RUBY



	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%	

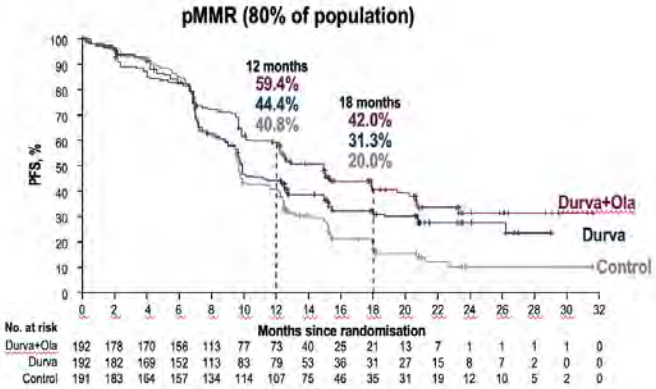
AtTEnd



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

DUO-E

HR 0.57
95% CI 0.44-0.73
D + O + CT arm



	No with events %	Median
Durva + CT	64.6	9.9 (9.4-12.5)
Durva + O + CT	56.5	15 (12.4-18)
Placebo + CT	77.1	9.7 (9.2-10.1)

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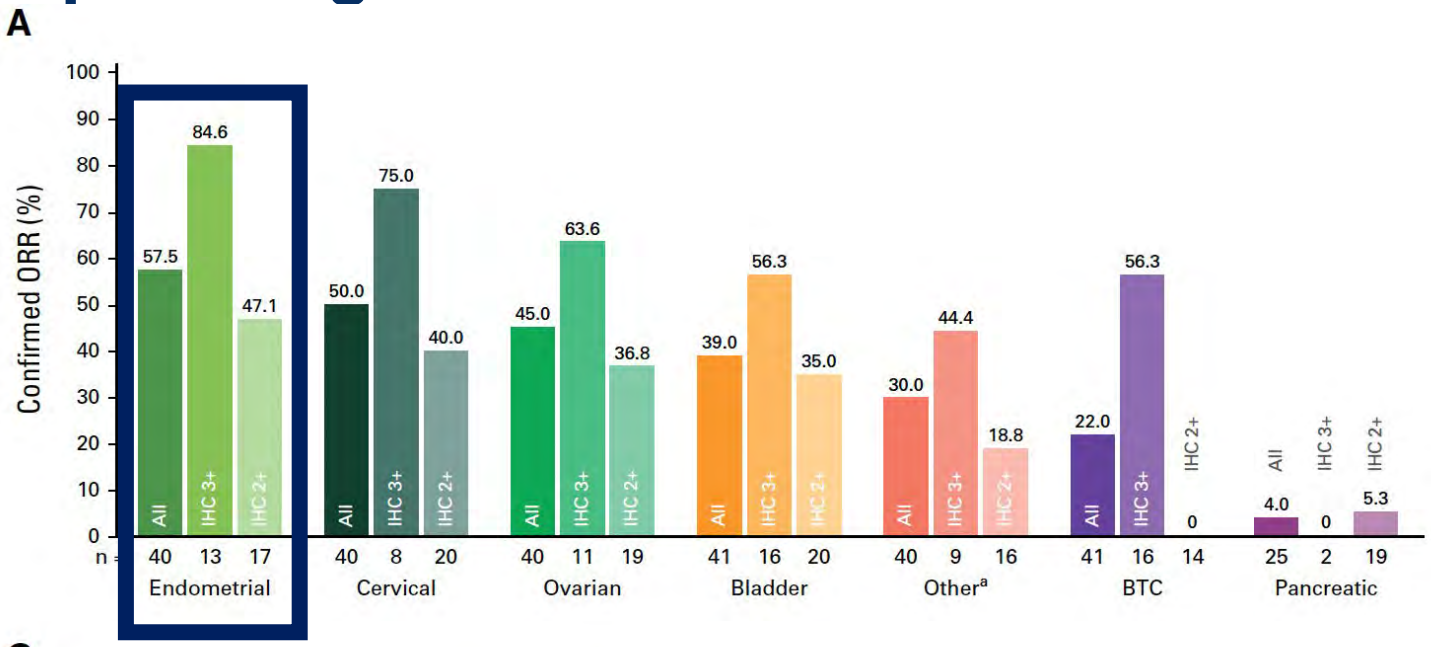
Why the discrepancy between trials in pMMR…?

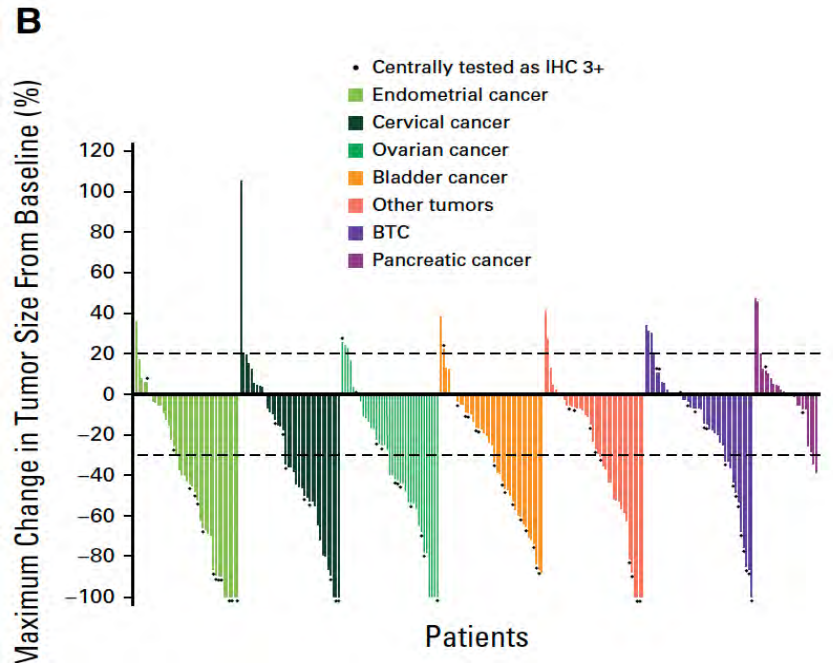
- Statistical design…should the pMMR cohort have been independently powered in all trials (primary endpoint)?
- Carcinosarcoma excluded from GY018, but included in RUBY, AtTEnd and DUO-E (~10%)…
- Racial/ethnic composition (Asian 20% in AtTEnd)…
- Interval from prior adjuvant therapy (12 vs 6 months)…
- Anti PD-1 vs anti PD-L1…

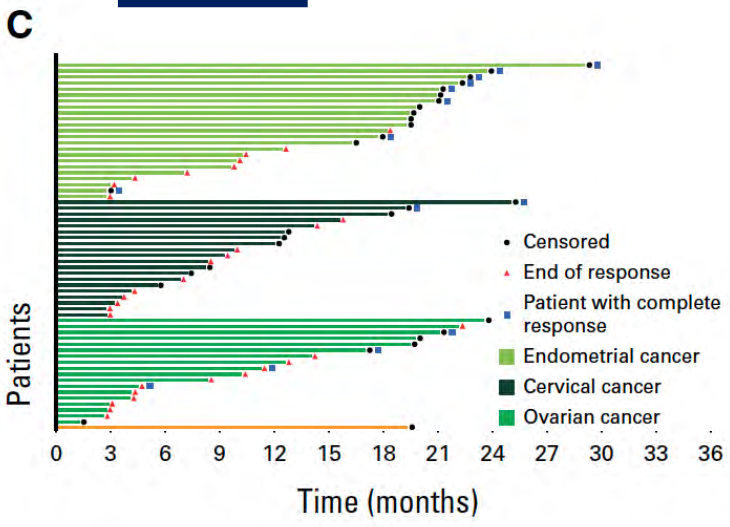
June 17, 2024 **FDA approves pembrolizumab with chemotherapy for primary advanced or recurrent endometrial carcinoma**

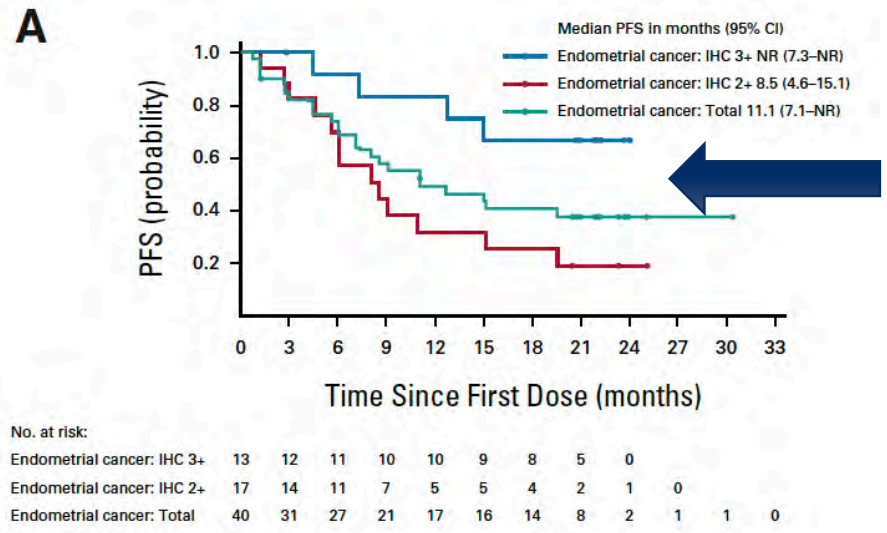
August 1, 2024 **FDA expands endometrial cancer indication for dostarlimab-gxly with chemotherapy**

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





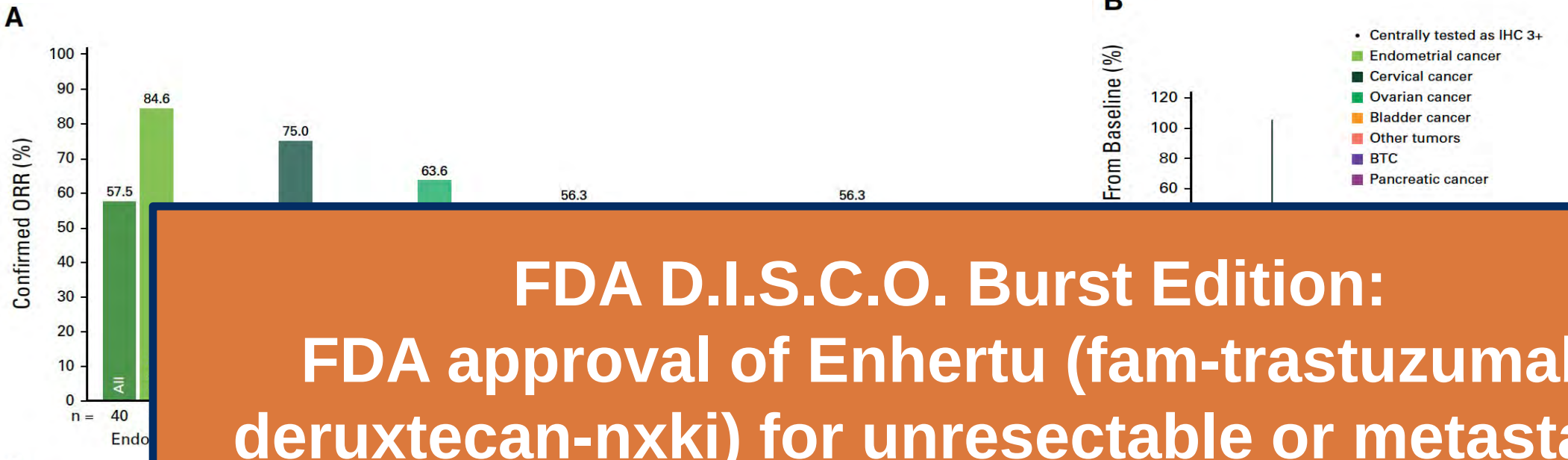




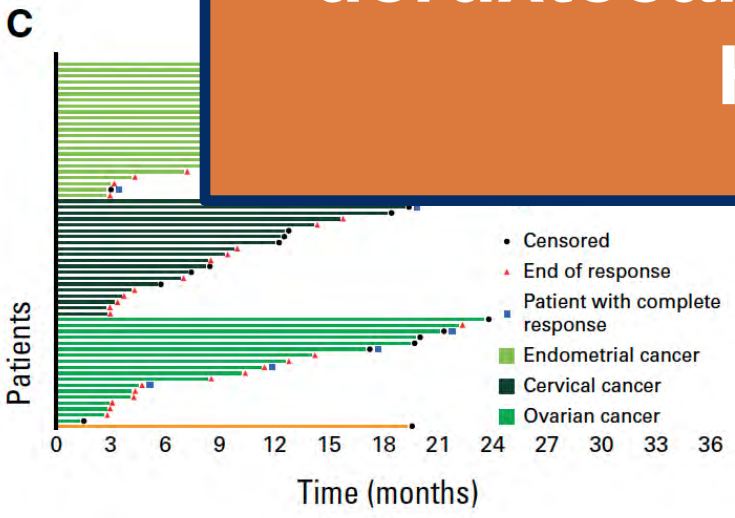
Appears to be driven by the HER2 IHC 3+

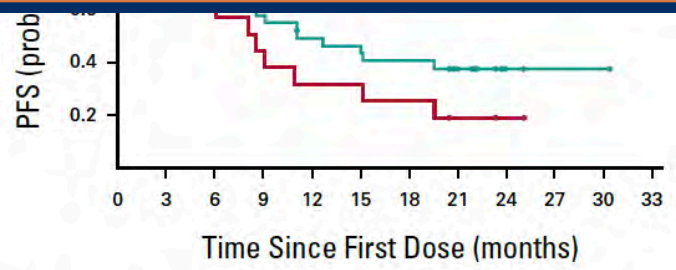
Meric-Burnstam et al. J Clin Oncol 2024

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



FDA D.I.S.C.O. Burst Edition:
FDA approval of Enhertu (fam-trastuzumab deruxtecan-nxki) for unresectable or metastatic HER2-positive solid tumors





No. at risk:

Endometrial cancer: IHC 3+	13	12	11	10	10	9	8	5	0			
Endometrial cancer: IHC 2+	17	14	11	7	5	5	4	2	1	0		
Endometrial cancer: Total	40	31	27	21	17	16	14	8	2	1	1	0

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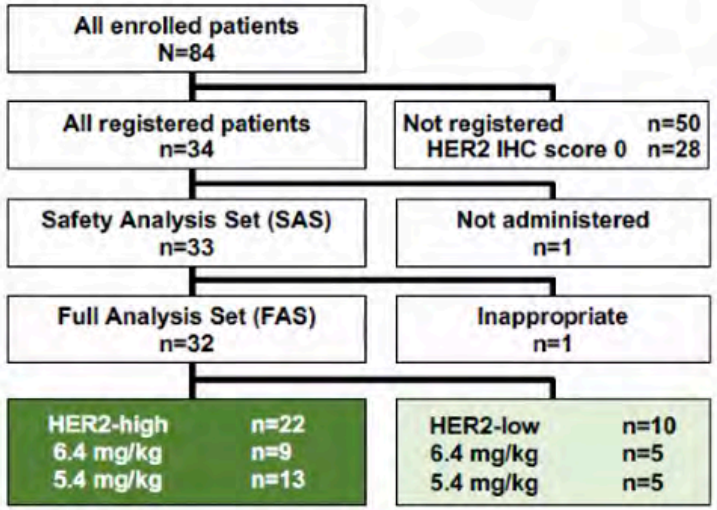
Meric-Burnstam et al. J Clin Oncol 2024

Trastuzumab deruxtecan for the treatment of UCS

Patient Flow Diagram

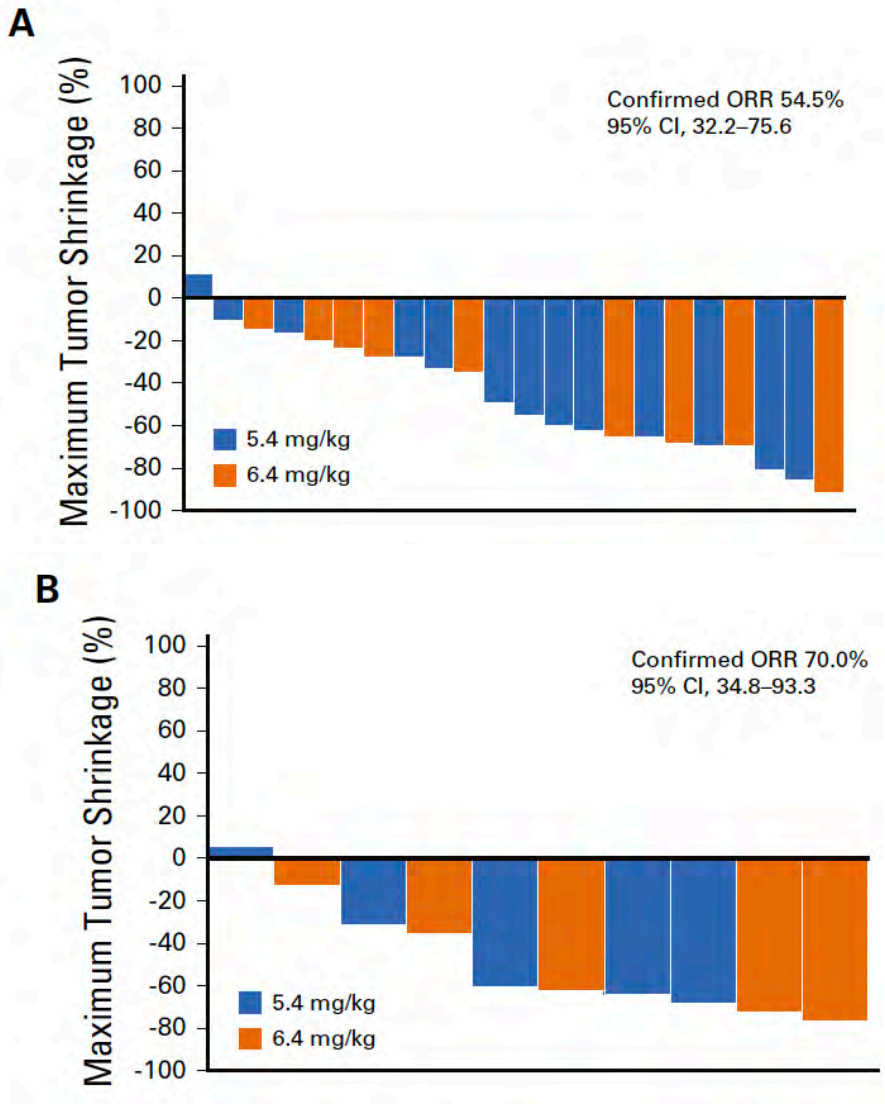
- Patients were enrolled from February 2018 to June 2020 at 7 institutions in Japan
- Data cut-off was done in December 2020
- Twenty-eight patients (33.3%) were excluded from registration due to HER2 IHC score 0
- One patient did not receive T-DXd due to progression of UCS
- One patient was excluded 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)



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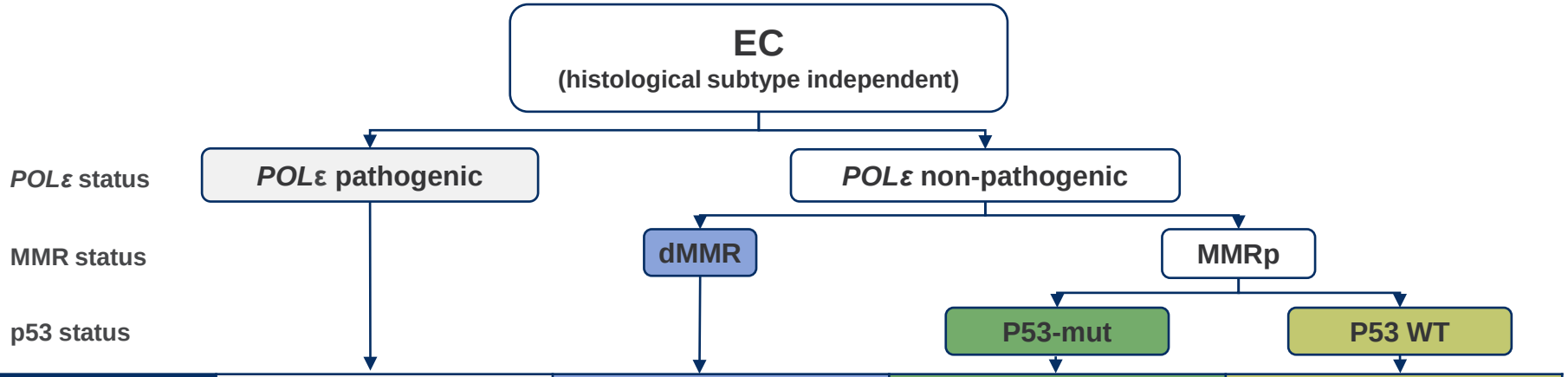
Nishikawa et al. J Clin Oncol 2023

Are There Biomarkers Beyond dMMR and HER2?

GOG-3031/RUBY: Molecular Classification Algorithm

In RUBY Part 1, **molecular classification was performed for all participants with WES** results – 400 of 494 patients (80%)



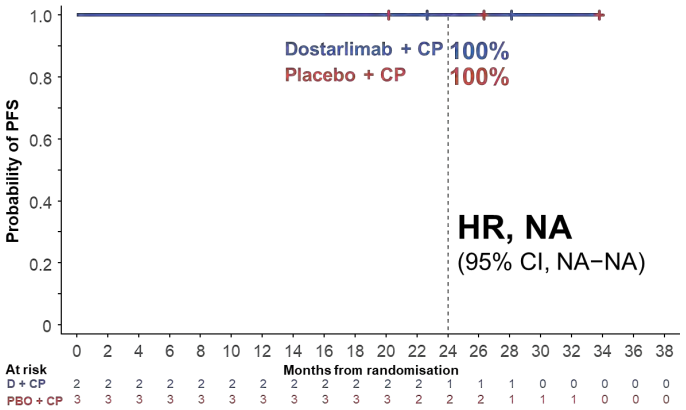
Integrated diagnosis	POLεmut (EDM)	dMMR (or MSI-H)	TP53 aberrant	NSMP
Prevalence in RUBY, % (n/N)	**1.25%** (5/400)	**22.75%** (91/400)	**22%** (88/400)	**54%** (216/400)
Diagnostic test	WES	Results of local (IHC, NGS, PCR) or central test (IHC) provided for RUBY at randomization	WES	

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.

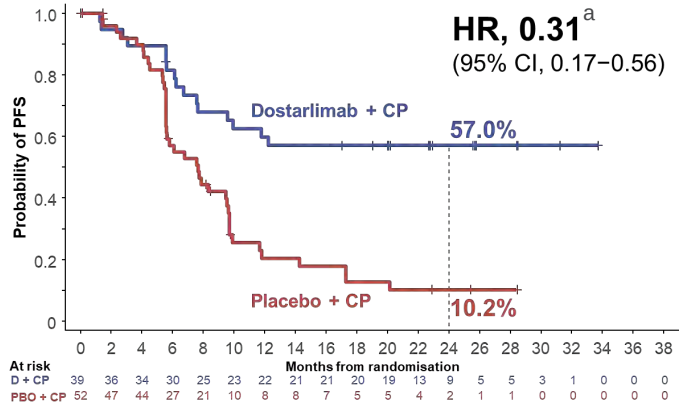
Mirza MR, et al. ESMO 2023.

GOG-3031/RUBY: PFS according to molecular subgroup

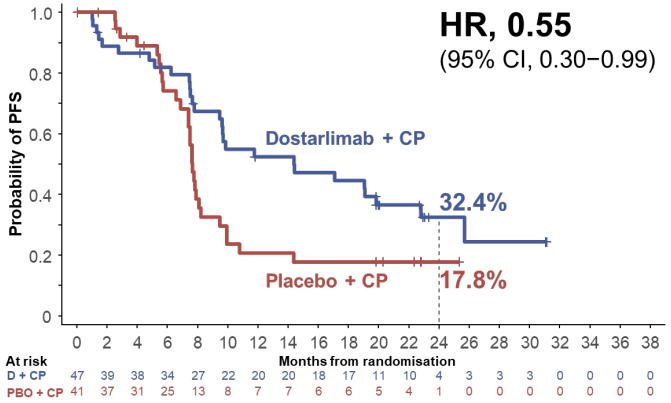
POLε mut



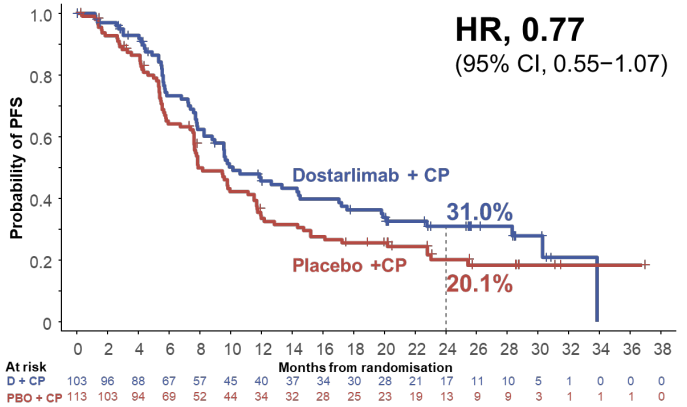
dMMR/MSI-H



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.

GOG-3031/RUBY: PFS according to molecular subgroup

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

POLε mut

TP53 mut

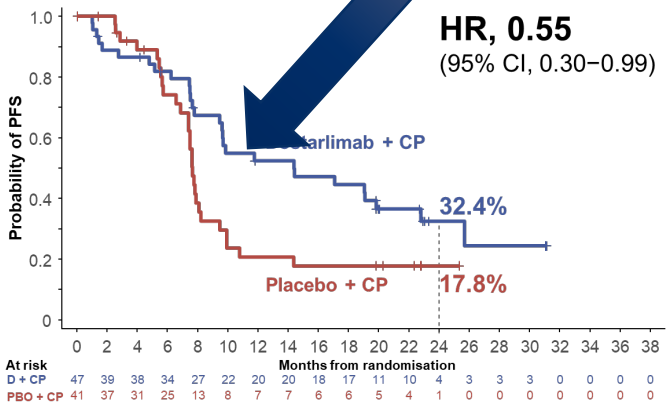
dMMR/MSI-H

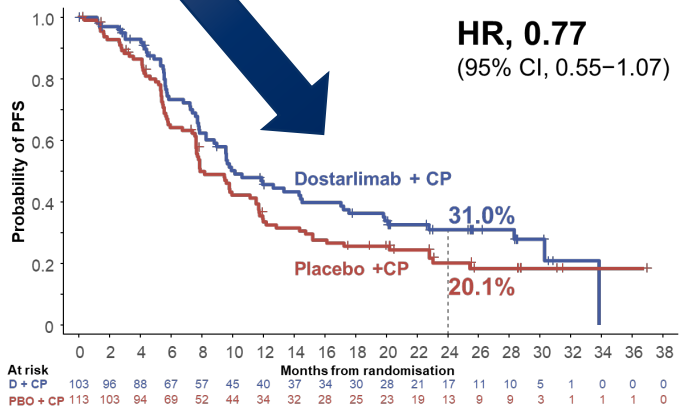
NSMP

More questions…

Which patients are contained in each of these cohorts?

This remains principally exploratory in nature…and must be confirmed in a prospective trial





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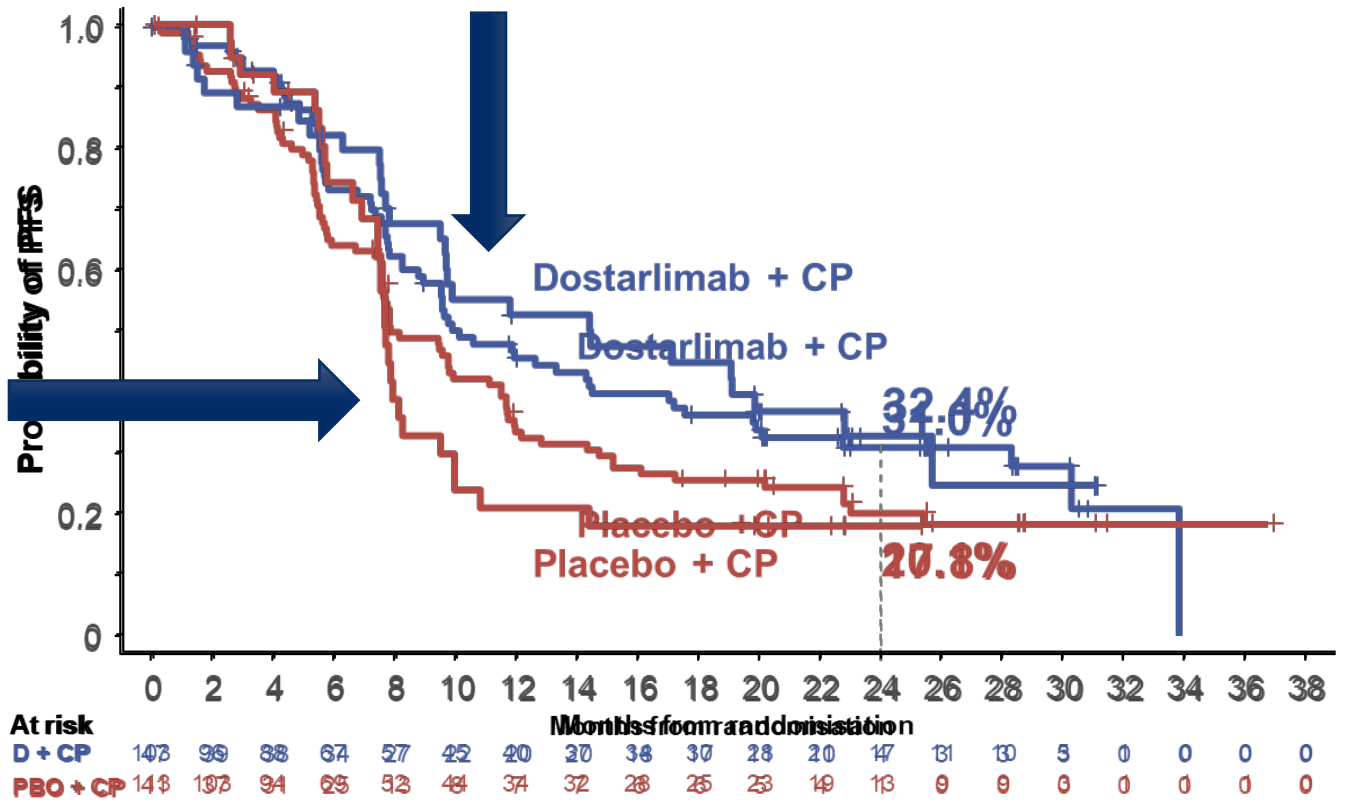
Mirza MR, et al. ESMO 2023.

GOG-3031/RUBY: PFS according to molecular subgroup

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

TP53 mut



NSMP

Mirza MR, et al. ESMO 2023.

GOG-3041/DUO-E:
pMMR Biomarker Exploratory Subgroup Analysis

In the pMMR subpopulation (n=575), biomarker status was known in:

575 patients (100%)	for histology at diagnosis
562 patients (98%)	for PD-L1* status
494 patients (86%)	for *POLE*m and *TP53*m†,‡ status
494 patients (86%)	for HRRm†,§ status
494 patients (86%)	for BRCAm† status

Biomarker-known population:
486 patients
(85% of pMMR subpopulation)
had known status for all
biomarkers of interest

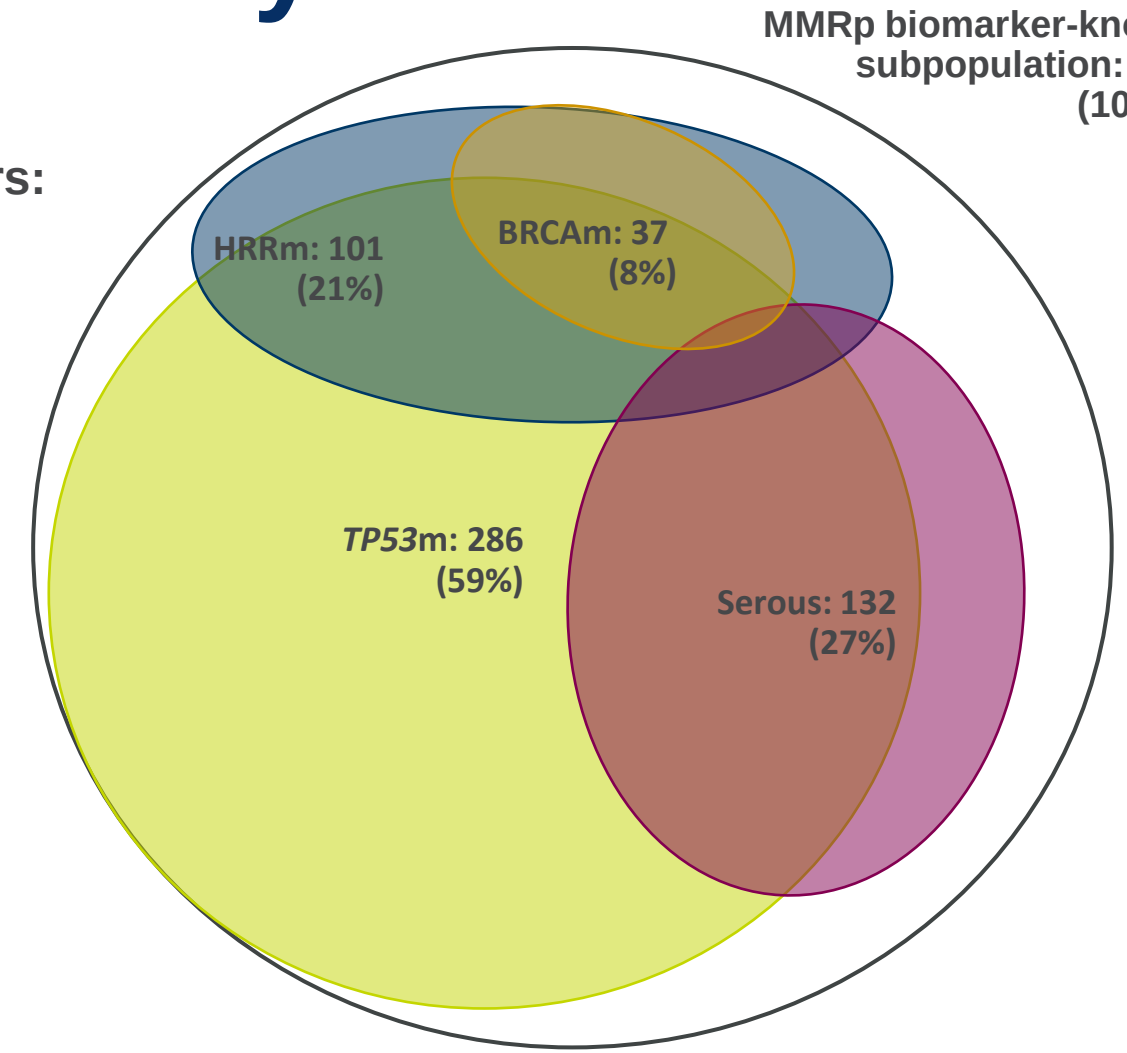
Westin S, et al. IGCS 2024

GOG-3041/DUO-E: pMMR Biomarker Exploratory Subgroup Analysis

The pMMR biomarker-known (n=486) subpopulation was heterogeneous, with a large overlap of biomarkers:

- **84%** of patients were positive for one or more biomarkers
- **PD-L1 positive and *TP53*m were the most prevalent biomarkers**

	PD-L1 positive	*TP53*m	HRRm	BRCAm	*POLE*m	Serous
PD-L1 positive	67%	44%	16%	6%	2%	20%
*TP53*m	44%	59%	14%	6%	2%	24%
HRRm	16%	14%	21%	8%	2%	6%
BRCAm	6%	6%	8%	8%	1%	3%
*POLE*m	2%	2%	2%	1%	2%	0%
Serous	20%	24%	6%	3%	0%	27%



Westin S, et al. IGCS 2024

TP53mut Prevalence in 1L Advanced Stage/Recurrent EC Clinical Trials

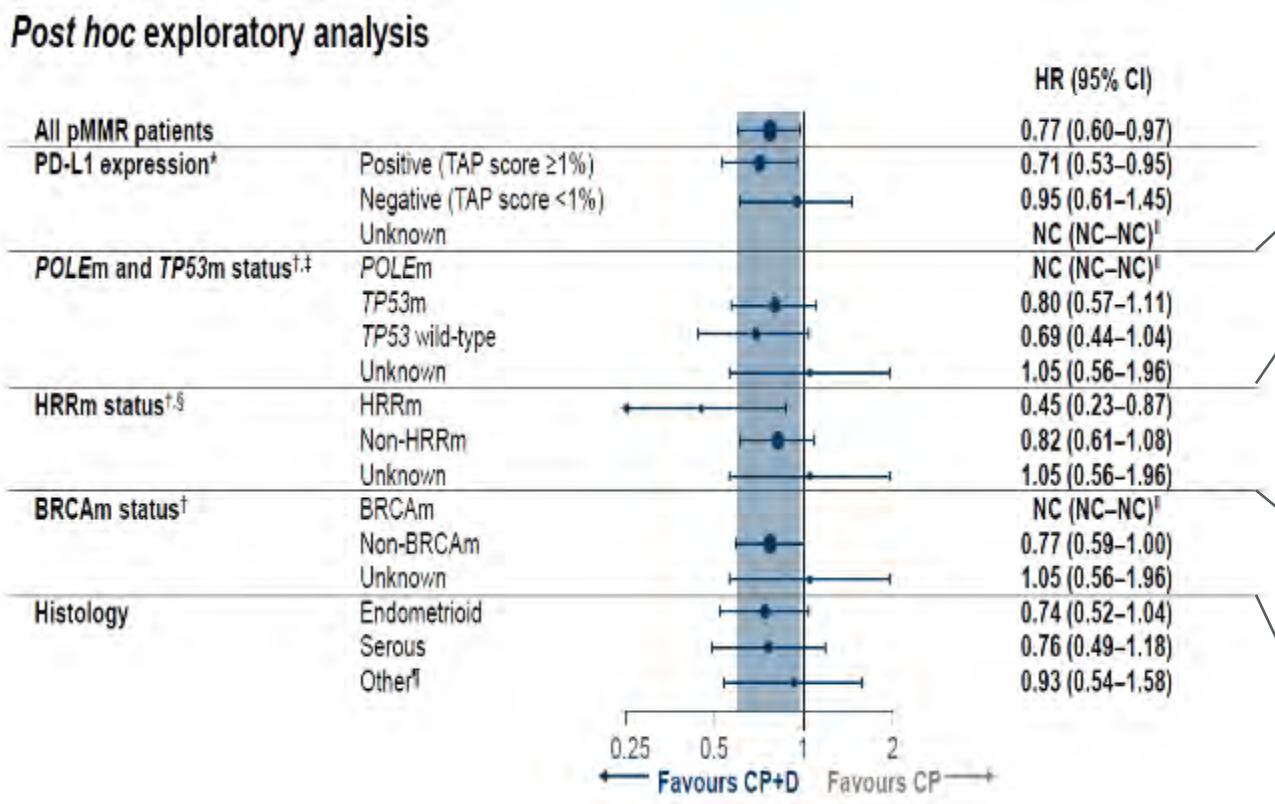
	DUO-E[1] CT-durva+/-ola	RUBY-1[2] CT-dostar	RUBY-2[3] CT-dostar-nira	UTOLA[4] CT-ola maintenance therapy	MITO-END-3[5] CT-avelumab
BM evaluable population (n)	494 (out of MMRp)	400 (out of ITT)	175 (ITT)	125 MMRp	109 (out of ITT)
BM samples	Aggregate tissue/ctDNA	Tissue	Tissue	Tissue	Tissue
P53 Dx test methodology	NGS F1 CDx assay F1 Liquid CDx	WES	ND but probably WES	NGS (127 gene panel) and IHC	NGS F1 CDx 150
Non-dMMR P53m prevalence	59%	28%	28%	60%	64%
Notes on testing		Non-dMMR/MSI-H *OR* POLE			Non-MSI-H population

BM, biomarker; CDx, companion diagnostic; CT, chemotherapy; ctDNA, circulating tumor DNA; Dx, diagnostic; EC, endometrial cancer; F1, FoundationOne; IHC, immunohistochemistry; ITT, intention-to-treat; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; ND, not disclosed; NGS, next-generation sequencing; nira, niraparib; ola, olaparib; P53, tumor protein p53; P53m, mutant tumor protein p53; POLE, polymerase epsilon; WES, whole exome sequencing.

1. Westin S, et al. Presented at: International Gynecologic Cancer Society (IGCS) Annual Global Meeting; 16-18 October 2024; Dublin, Ireland; 2. Mizra MR, et al. Presented at European Society of Medical Oncology (ESMO) Annual Meeting; 20-24 October 2023; Madrid, Spain;

3. Mizra MR, et al. Presented at: Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer; March 16-18, 2024; San Diego, CA, USA; 4. Joly F, et al. Int J Gynecol Cancer. 2022;32(Suppl 2):A118-A119 [ESGO 2022 Abstract 2022-RA-922-ESGO]; 5. Pignata S, et al. Ann Oncol. 2024;35(7):667-676. doi: 10.1016/j.annonc.2024.04.007.

GOG-3041/DUO-E pMMR cohort: PFS by Biomarker Subgroup (CP + Durvalumab versus CP + placebo)



		CP	CP+D
	HR (95% CI)	n/N	
*TP53*m	**0.80 (0.57–1.11)**	73/90	69/101
TP53 wild-type	**0.69 (0.44–1.04)**	54/71	36/60

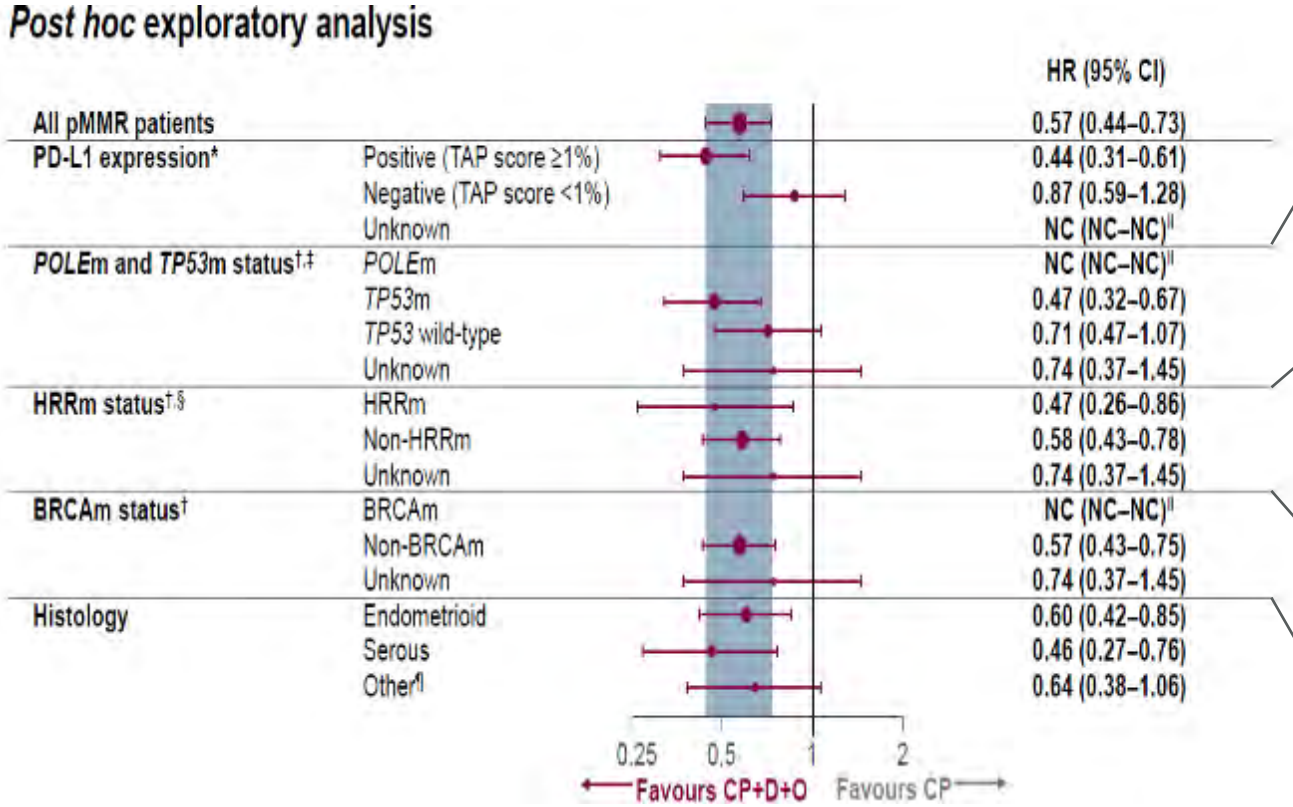
_TP53_ wt associated with improved response…

		CP arm	CP+D arm
BRCAm	Events, n/N (%)	11/13 (84.6)	4/10 (40.0)
	Median, months (95% CI)†	9.9 (4.2–12.5)	15.0 (8.7–NR)
	HR (95% CI) vs CP‡		NC
Non-BRCAm	Events, n/N (%)	116/149 (77.9)	101/156 (64.7)
	Median, months (95% CI)†	9.7 (8.8–12.0)	9.9 (9.5–12.6)
	HR (95% CI) vs CP‡		0.77 (0.59–1.00)

BRCAmut associated with improved response…

1. Westin SN et al. Int J Gynecol Cancer. 2024;34(3):A4-A5 (Presentation).
2. Van Nieuwenhuysen E, et al. J Clin Oncol 2024;42(16_suppl):abstract #5595 (Poster 466).

GOG-3041/DUO-E pMMR cohort: PFS by Biomarker Subgroup (CP + Durvalumab + Olaparib versus CP + placebo)



	HR (95% CI)	CP n/N	CP+D+O n/N
*TP53*m	**0.47 (0.32–0.67)**	73/90	52/89
TP53 wild-type	**0.71 (0.47–1.07)**	54/71	41/72

***TP53mut* associated with improved response…**

		CP arm	CP+D arm	CP+D+O arm
BRCAm	Events, n/N (%)	11/13 (84.6)	4/10 (40.0)	7/14 (50.0)
	Median, months (95% CI)[†]	9.9 (4.2–12.5)	15.0 (8.7–NR)	15.2 (5.3–NR)
	HR (95% CI) vs CP[‡]		NC	NC
Non-BRCAm	Events, n/N (%)	116/149 (77.9)	101/156 (64.7)	87/152 (57.2)
	Median, months (95% CI)[†]	9.7 (8.8–12.0)	9.9 (9.5–12.6)	15.0 (12.4–19.4)
	HR (95% CI) vs CP[‡]		0.77 (0.59–1.00)	0.57 (0.43–0.75)

Non-*BRCAmut* associated with improved response…

1. Westin SN et al. Int J Gynecol Cancer. 2024;34(3):A4-A5 (Presentation).
2. Van Nieuwenhuysen E, et al. J Clin Oncol 2024;42(16_suppl):abstract #5595 (Poster 466).

DUO-E IGCS MMRp Subpopulation Analyses – TP53 Status

(Post-hoc Exploratory Analyses)

	59% TP53mut 24% of TP53mut were serous histology	22% TP53mut 38% of TP53mut were serous adenocarcinoma	46% TP53mut 26% of TP53mut were serous papillary
PFS HR (95% CI)	**DUO-E MMRp CP + durva vs CP**	**RUBY1 ITT CP + dostar vs CP**	**MITO END-3 CP + avelumab vs CP**
*TP53*m	0.80 (0.57–1.11)	0.55 (0.30–0.99)	1.71 (0.89–3.28)
TP53wt/NSMP	0.69 (0.44–1.04)	0.77 (0.55–1.07)	0.47 (0.23–0.97)
Unknown	1.05 (0.56–1.96)	NR	NR

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1. Westin SN et al. Int J Gynecol Cancer. 2024;34(3):A4-A5 (Presentation); 2. Mirza MR, et al. Annals Oncol. 2023;34(suppl_2):2507 (Presentation); 3. Pignata S, et al. Ann Oncol. 2024;35(7):667–76.

DUO-E IGCS MMRp Subpopulation Analyses – PD-L1 Status

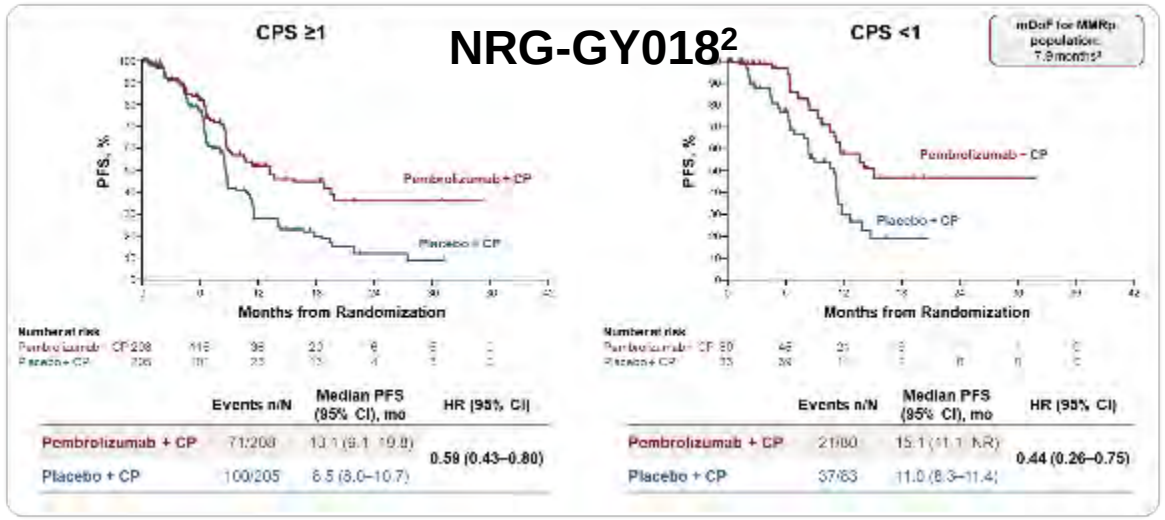
(Post-hoc Exploratory Analyses)

- 494/575 (MMRp) had POLEm and TP53m information available (~14% missing data)
- 562/575 (MMRp) had PD-L1 status known (2% missing data)
- HRRm based on identified mutation in 14 predefined genes (~14% missing data)
- No data available for patients enrolled in China?

Discordant findings for PD-L1 status across trials[1]

DUO-E (durva + CP) in MMRp[1]

NRG-GY018[2]



RUBY Part 2[3]

Eskander et al. IGCS 2024 (distillation)

Limitations of Exploratory Data and Potential for Utilizing Other Biomarkers for Classification of EC

Significance of Utilizing Other Biomarkers in EC

Biomarkers With Demonstrated Predictive Response	
TMB-H	Robust data indicative of ICI utilization in TMB-H dMMR patients across multiple clinical trials
MMR	Robust data indicative of ICI utilization in TMB-H dMMR patients across multiple clinical trials
HER2	**Relevance of HER2** biomarker is evolving in EC (threshold; breast versus gastric…)

Biomarkers With Limited Evidence	
HRD	Limited data on assay, cut-off, and validation criteria impact how HRD is visualized in EC
ER/PR	Limited data informing use and cut-off for ER / PR expression in profiling EC
PD-L1	Limited value given lack of validation and discordant results across trials
TP53	Limited value given lack of validation and discordant results across trials

Limited data on novel biomarkers challenges the interpretation and validation of utilizing biomarkers as predictive or prognostic in EC population

More work needs to be done!

dMMR, deficient mismatch repair; EC, endometrial cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HRD, homologous recombination deficiency; MMR, mismatch repair; MMRp, mismatch repair proficient; PD-L1, programmed death-ligand 1; PR, progesterone receptor; TMB-H, tumor mutational burden-high

Interpreting Exploratory Hypothesis-Generating Data

In the words of the economist Ronald Coase:

"If you torture the data enough, it will confess to anything."

Beware of "HARKENING":

- Hypothesizing after the study results are known… prone to multiplicity, driving us towards false discovery
- If 10 comparisons of the primary endpoint are done across different subgroups, there is at least a 40% chance of having a "positive" finding

Biostatistics Primer

What a Clinician Ought to Know: Subgroup Analyses

Helen Barraclough, MSc, and Ramaswamy Govindan, MD†‡*

Grimes, D.R. BJC reports 2024

Case-Based Clinical Decision Making: Applying the Data Impact on Treatment Options and Outcomes

Bhavana Pothuri, MD

NYU Langone Health, Perlmutter Cancer Center

New York, New York, USA

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Case Studies:
Audience Engagement

Please scan the QR Code below to participate in the audience questions

Case 1: patient with dMMR tumor recurrence

- 48 yo with family hx of colon ca, breast, and bladder ca presents with irregular vaginal bleeding
- Endometrial biopsy: endometrioid em ca, loss of MSH6 on IHC, HER2 1+
- Surgery Robotic hysterectomy/Bilateral Salpingoophorectomy, SLN bx- 1 R pelvic LN with micrometastes - stage IIIC1 dx 12/2021
- Genetics confirms Lynch Syndrome with MSH6 mutation, cascade testing of family members
- Pt undergoes chemotherapy with paclitaxel/carboplatin X 6 cycles
- 18 mos after completion of chemotherapy patient presents with persistent cough
- CT scan: multiple pulmonary nodules
- Bx confirms recurrent endometrioid endometrial cancer

Case 1: patient with dMMR tumor recurrence

Treatment options:

1. paclitaxel/carboplatin
2. Paclitaxel/carboplatin/dostarlimab or paclitaxel/carboplatin/pembrolizumab
3. Dostarlimab or pembrolizumab
4. Doxorubicin or weekly paclitaxel
5. Lenvatinib + pembrolizumab

Case 1: patient with dMMR tumor recurrence

- Patient undergoes paclitaxel/carboplatin/checkpoint inhibitor, followed by maintenance checkpoint inhibitor X 2 yrs

Pivotal Phase III Trials of Immunotherapy in Advanced Endometrial Cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

M.R. Mirza, D.M. Chase, B.M. Slomovitz, R. dePont Christensen, Z. Novák, D. Black, L. Gilbert, S. Sharma, G. Valabrega, L.M. Landrum, L.C. Hanker, A. Stuckey, I. Boere, M.A. Gold, A. Auranen, B. Pothuri, D. Cibula, C. McCourt, F. Raspagliesi, M.S. Shahin, S.E. Gill, B.J. Monk, J. Buscema, T.J. Herzog, L.J. Copeland, M. Tian, Z. He, S. Stevens, E. Zografos, R.L. Coleman, and M.A. Powell, for the RUBY Investigators*

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D., Richard G. Moore, M.D., Joanie M. Hope, M.D., Fernanda B. Musa, M.D., Robert Mannel, M.D., Mark S. Shahin, M.D., Guilherme H. Cantuaria, M.D., Eugenia Girda, M.D., Cara Mathews, M.D., Juraj Kavecansky, M.D., Charles A. Leath III, M.D., M.S.P.H., Lilian T. Gien, M.D., Emily M. Hinchcliff, M.D., M.P.H., Shashikant B. Lele, M.D., Lisa M. Landrum, M.D., Floor Backes, M.D., Roisin E. O'Cearbhaill, M.D., Tareq Al Baghdadi, M.D., Emily K. Hill, M.D., Premal H. Thaker, M.D., Veena S. John, M.D., Stephen Welch, M.D., Amanda N. Fader, M.D., Matthew A. Powell, M.D., and Carol Aghajanian, M.D.

ASCO Journal of Clinical Oncology®

Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial

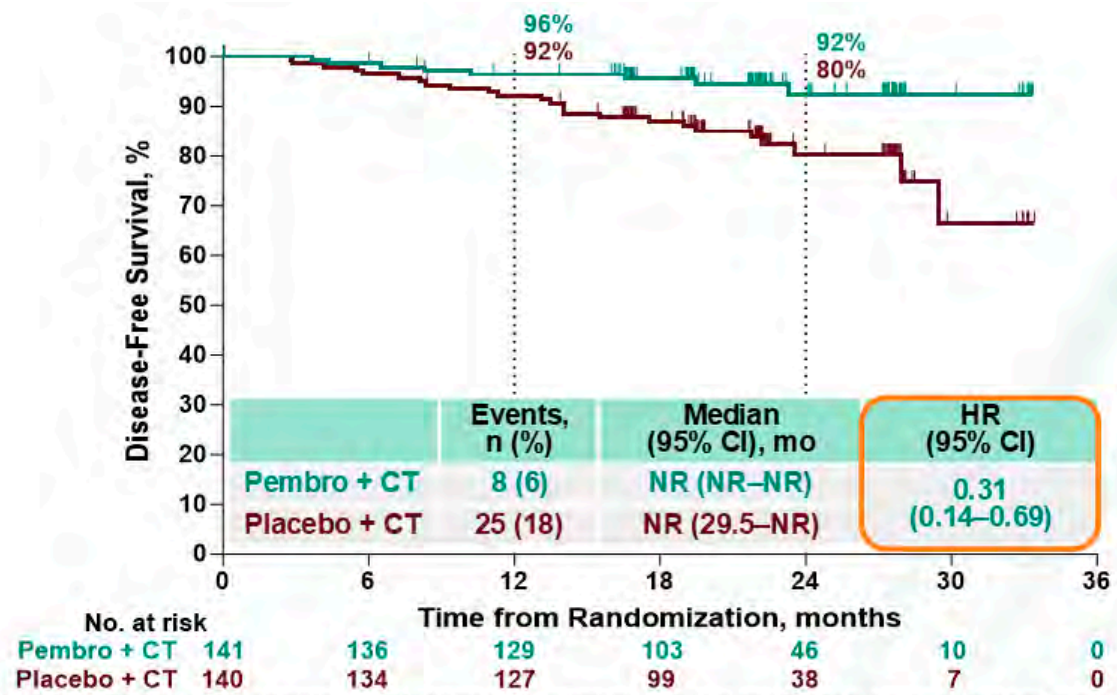
Shannon N. Westin, MD, MPH[1]; Kathleen Moore, MD[2]; Hye Sook Chon, MD[3]; Jung-Yun Lee, MD[4]; Jessica Thomes Pepin, MD[5]; Michael Sundborg, MD[6]; Ayelet Shai, MD, PhD[7]; Joseph de la Garza, MD[8]; Shin Nishio, MD[9]; Michael A. Gold, MD[10]; Ke Wang, MD[11]; Kristi McIntyre, MD[12]; Todd D. Tillmanns, MD[13]; Stephanie V. Blank, MD[14]; Ji-Hong Liu, MD[15]; Michael McCollum, MD[16]; Fernando Contreras Mejia, MD[17]; Tadaaki Nishikawa, MD[18]; Kathryn Pennington, MD[19]; Zoltan Novak, MD, PhD[20]; Andreia Cristina De Melo, MD[21]; Jalid Sehouli, MD[22]; Dagmara Klasa-Mazurkiewicz, MD[23]; Christos Papadimitriou, MD[24]; Marta Gil-Martin, MD[25]; Birute Brasiuniene, MD, PhD[26]; Conor Donnelly, PhD[27]; Paula Michelle del Rosario, MD[28]; Xiaochun Liu, MD, PhD[29]; and Els Van Nieuwenhuysen, MD[30]; on behalf of the DUO-E Investigators

DOI https://doi.org/10.1200/JCO.23.02132

Atezolizumab and chemotherapy for advanced or recurrent endometrial cancer (AtTEnd): a randomised, double-blind, placebo-controlled, phase 3 trial

*Nicoletta Colombo, Elena Biagioli, Kenichi Harano, Francesca Galli, Emma Hudson, Yoland Antill, Chel Hun Choi, Manuela Rabaglio, Frederic Marmé, Christian Marth, Gabriella Parma, Lorena Fariñas-Madrid, Shin Nishio, Karen Allan, Yeh Chen Lee, Elisa Piovano, Beatriz Pardo, Satoshi Nakagawa, John McQueen, Claudio Zamagni, Luis Manso, Kazuhiro Takehara, Giulia Tasca, Annamaria Ferrero, Germana Tognon, Andrea Alberto Lissoni, Mariacristina Petrella, Maria Elena Laudani, Eliana Rulli, Sara Uggeri, M Pilar Barretina Ginesta, and AtTEnd study group**

ENGOT-EN11/GOG-3053/KEYNOTE-B21: dMMR



[a]DFS was defined as the time from randomization to local or distant recurrence of EC (assessed radiographically by the investigator or by histopathologic confirmation) or death from any cause. Data cutoff date: March 4, 2024.

Slomovitz, et al IGCS 2024
Slomovitz et al JCO, 2025

Case 1:
patient with dMMR tumor recurrence

What if same patient recurs with pulmonary nodules within 6 mos completion of primary chemotherapy?

Case 1: patient with dMMR tumor recurrence

Treatment options:

1. paclitaxel/carboplatin
2. Paclitaxel/carboplatin + ICI followed by ICI maintenance
3. Dostarlimab or pembrolizumab
4. Doxorubicin or weekly paclitaxel
5. Lenvatanib + pembrolizumab

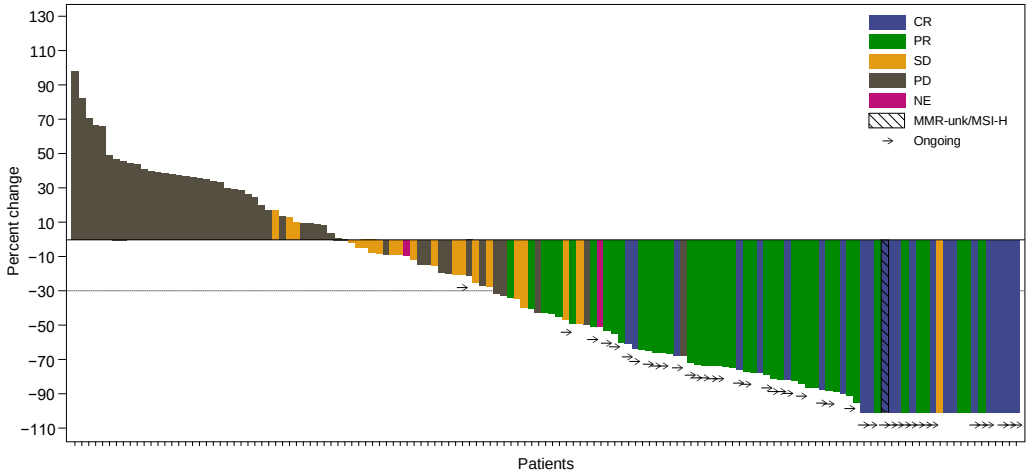
Case 1: patient with dMMR tumor recurrence

Patient received single agent dostarlimab with complete resolution of disease at 6 months

Dostarlimab (Garnet A1): Anti-tumor Activity in dMMR/MSI-H

	dMMR/MSI-H EC N=143	MMRp/MSS EC N=156
Median follow-up time, months	27.6	33.0
ORR, % (95% CI; n/N) Complete response, n (%) Partial response, n (%) Stable disease, n (%) Progressive disease, n (%) Not evaluable, n (%)	**45.5%** (37.1–54.0; 65/143) 23 (16.1%) 42 (29.4%) 21 (14.7%) 51 (35.7%) 6 (4.2%)	**15.4%** (10.1–22.0; 24/156) 4 (2.6%) 20 (12.8%) 29 (18.6%) 88 (56.4%) 15 (9.6%)
Median time from cycle 1 day 1 to best overall response, mo Complete response Partial response	 2.79 2.69	 2.81 2.79
Disease control rate, % (95% CI; n/N)	60.1% (51.6–68.2; 86/143)	34.0% (26.6–42.0; 53/156)
Response ongoing, n (%)	54 (83.1%)	9 (37.5%)
Median duration of response (range), months	**NR** (1.18+ to 47.21+)	**19.4** (2.8 to 47.18+)
Probability of maintaining response, % 6 months 12 months 24 months	 96.8 93.3 83.7	 82.6 60.3 44.2

dMMR/MSI-H EC



FDA Approval April 2021

Dostarlimab was granted accelerated approval for adult patients with dMMR-recurrent or advanced endometrial cancer**; FDA Regular Approval Feb 9, 2023**

EMA Approval

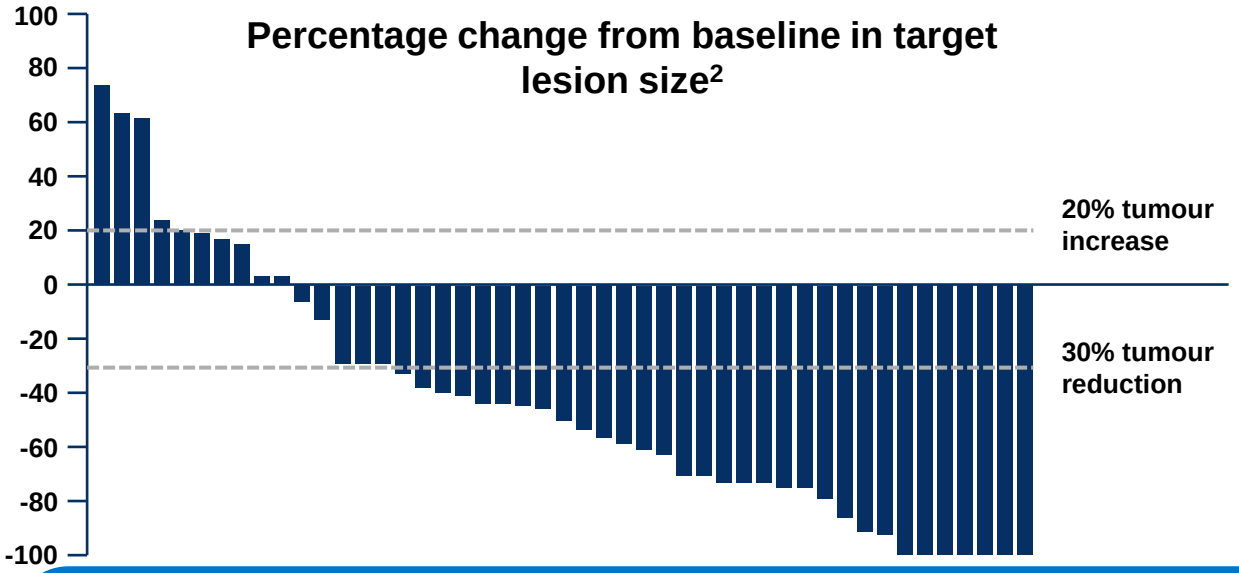
Approved for adult patients with dMMR recurrent or advanced endometrial cancers

Oaknin, J Immunother Cancer. 2022

Pembrolizumab (KEYNOTE-158): Antitumor Activity in Patients With MSI-H/dMMR Advanced EC

Confirmed Objective Response per RECIST v1.1 by BIRC[1]	MSI-H/dMMR EC, N=79[a] (Cohorts D + K)
ORR, % (95% CI)	48 (37-60)[a]
Best objective response, n (%)	
Complete response	11(14)
Partial response	27 (34)
Stable disease	14 (18)
Progressive disease	23 (29)
Not evaluable	1 (1)
Not assessed[b]	3 (4)
Time to response, median (range), mo	2.3 (1.3-10.6)

- Median DOR not reached: at 36 months, 68% of patients were
- still in response
- Median PFS: 13.1 months
- Median OS: Not reached



FDA Approval May 2017

First FDA approval based on a biomarker regardless of tumor type

Regular approval March 2022, Endometrial ca, MSI-H/dMMR progression following prior systemic therapy

Also, **EMA approval**

[a]Patients who received ≥1 dose of pembrolizumab and had been enrolled ≥26 weeks before data cutoff. [b]Patients with baseline assessment evaluated by the central radiology assessment but no postbaseline assessment on the data cutoff date including missing, discontinuing, or death before the postbaseline scan.

Data cut off data: October 5, 2020.

dMMR, mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability-high; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

1. O'Malley D, et al. Ann Oncol. 2021;32(suppl_5):S725-S772.. 2. Mirza M. Presented at The 22nd European Congress on Gynaecological Oncology. October 23–25. Prague, Czech Republic.

Case 1: patient with dMMR tumor recurrence

How long do you continue checkpoint inhibitor?

1. 2 years
2. Until progression
3. Until CR
4. 1 year
5. 3 years

Case 2:
Patient with P53wt/MMRp EC

- 80 yo Ashkenazi Jewish hx of PMB starting Oct. 2020 went to ER
- CT: 10/5/20 distended endometrial cavity, inguinal and left pelvic side wall adenopathy
- Em bx: 10/7/20: Endometrium, biopsy: Endometrial adenocarcinoma, endometrioid type FIGO grade 2 (architectural grade 1, nuclear grade 2-3); p53 Wt, MMR IHC intact, MSS
- Planned for EUA, palliative hysterectomy and excision of inguinal LN

Case 2:
Patient with P53wt/MMRp EC

- s/p DIAGNOSTIC LAPAROSCOPY, LYSIS OF ADHESIONS, DILATION AND CURETTAGE, LEFT INGUINAL MASS EXCISION on 10/20/20
- **Operative findings:** Adhesions of multiple loops of small bowel and omentum to anterior abdominal wall, anterior surface of the uterus adherent to bladder and anterior abdominal wall and covered with extensive tumor plaques, rectum densely adherent to posterior uterine surface, normal appearing bilateral ovaries/fallopian tubes
- **PATH: A. Endometrium, Endometrial Curetting:**
  - Endometrial adenocarcinoma, endometrioid type, FIGO grade 3 (Architectural grade 2, Nuclear grade 3)
- **B. Lymph node, Left Groin Node, dissection:**
  - Metastatic poorly differentiated carcinoma, with focal squamous differentiation
- **FM:** 1/19/21 MSS, TMB 6 muts/Mb, ARID1A S539*, CTNNB1 S37F, KEAP1 R380S, KRAS G12R, PIK3CA H1047R, PTEN R130G, PTEN splice site 801+1G>A
- Stage IVB em ca- endometrioid Gr 3, HER2 1+

Case 2:
Patient with P53wt/MMRp EC, Stage IVB, Gr 3 endometrioid em ca

Next steps:

1. Paclitaxel/carboplatin followed by Selinexor maintenance
2. Paclitaxel/carboplatin
3. Paclitaxel/carboplatin/pembrolizumab or Paclitaxel/carboplatin/ dostarlimab, followed by maintenance pembrolizumab or dostarliamb
4. Paclitaxel/carboplatin trastuzumab

Case 2:
Patient with P53wt/MMRp EC, Stage IVB, Gr 3 endometrioid em ca

- Started Ruby Trial – paclitaxel/carboplatin/dostarlimab on 11/2020
- Completed 3 yrs dostarlimab 11/2023
- CT 11/2023: notes residual dz in uterus, CtDNA low positive (0.08)
- Pt advised hysterectomy, but declined as concerned re health and ability to tolerate surgery despite excellent PS
- Repeat PET/CT 3/2024: Essentially stable metabolic activity and size of the endometrial adenocarcinoma. 2. There is no PET/CT evidence of regional metabolically active metastatic disease
- CTDNA: 3/11/24 0.16 (previous 0.08)
- Pt agreed to surgery – EUA, Robotic Hysterectomy, Extensive LOA
- Intra-op Findings: Uterus with dense adhesions to sigmoid colon and bladder. B/L adnexa normal appearing . The upper abdomen was free of disease. Nice response to treatment.

Case 2:
Patient with P53wt/MMRp EC, Stage IVB, Gr 3 endometrioid em ca

PATH 4/2/24:

Corpus

- Endometrioid carcinoma, myometrial invasion: 0.6 cm out of 1.0 cm (60%), no lymphovascular space invasion, lower uterine segment: involved by carcinoma
  Adnexa: B/L negative
- Pelvic adhesions: negative

Cervix

- Endometrioid carcinoma, invading cervical stroma, Depth of invasion: 0.4 cm out of 0.9 cm
- Margins: 0.5 cm from the deep/radial margin and 0.6 cm from the vaginal resection margin

- P53wt IHC, MMR IHC intact, HER2 1+
- CT DNA post-op May 1, 2024= 0.00

Case 2: Patient with P53wt/MMRp EC, Stage IVB, Gr 3 endometrioid em ca

Next step:

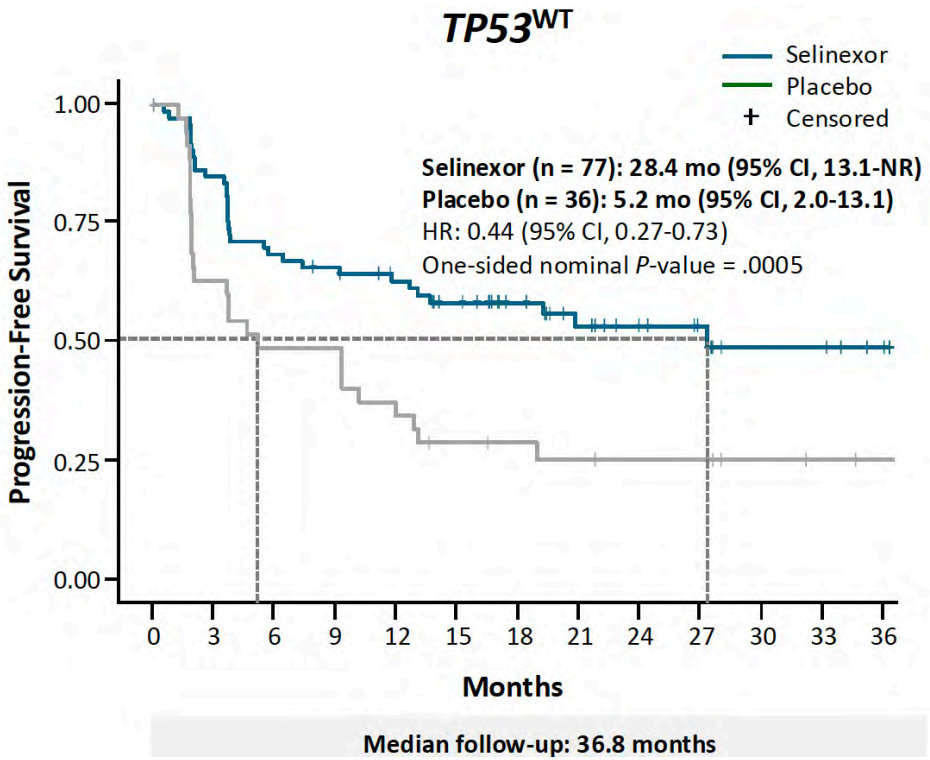
1. doxorubicin or paclitaxel
2. Pelvic XRT/Vaginal brachytherapy
3. Pelvic XRT/vag brachytherapy plus chemotherapy
4. Paclitaxel/carboplatin/pembrolizumab or paclitaxel/carboplatin /dostarlimab
5. Paclitaxel/carboplatin
6. Lenvatinib/pembrolizumab
7. Paclitaxel/carboplatin followed by Selinexor
8. No further treatment

Case 2:
Patient with P53wt/MMRp EC, Stage IVB, Gr 3 endometrioid em ca

- Pt counseled re chemotherapy options, pt declined
- Discussed Pelvic RT vs vaginal brachytherapy by Rad Onc and received vag brachytherapy – completed 6/2024
- Pt continues NED at last F/U 9/2025

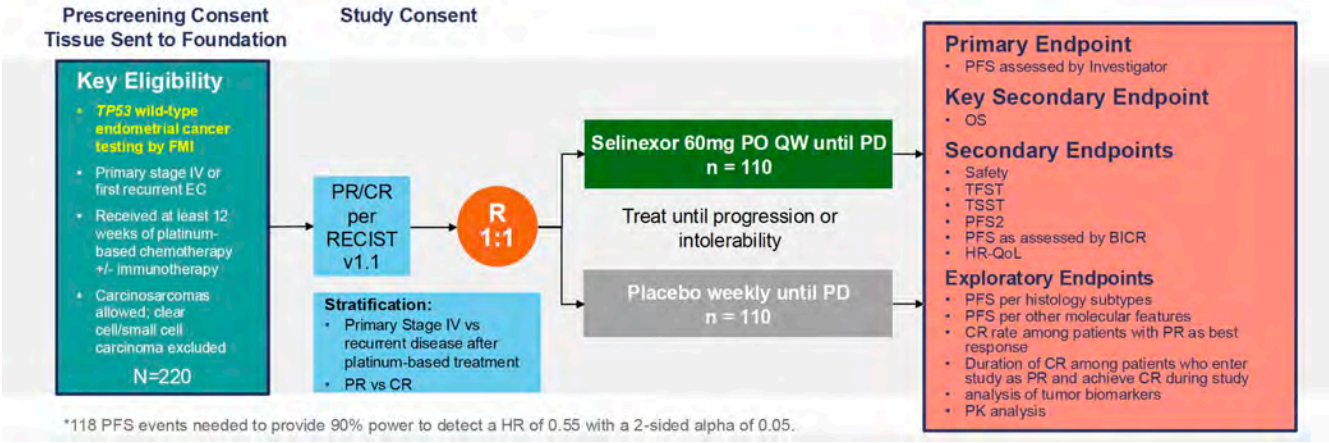
P53wt/MMRp EC, Stage IVB, Gr 3 endometrioid

SIENDO ENGOT-EN5/GOG-3055



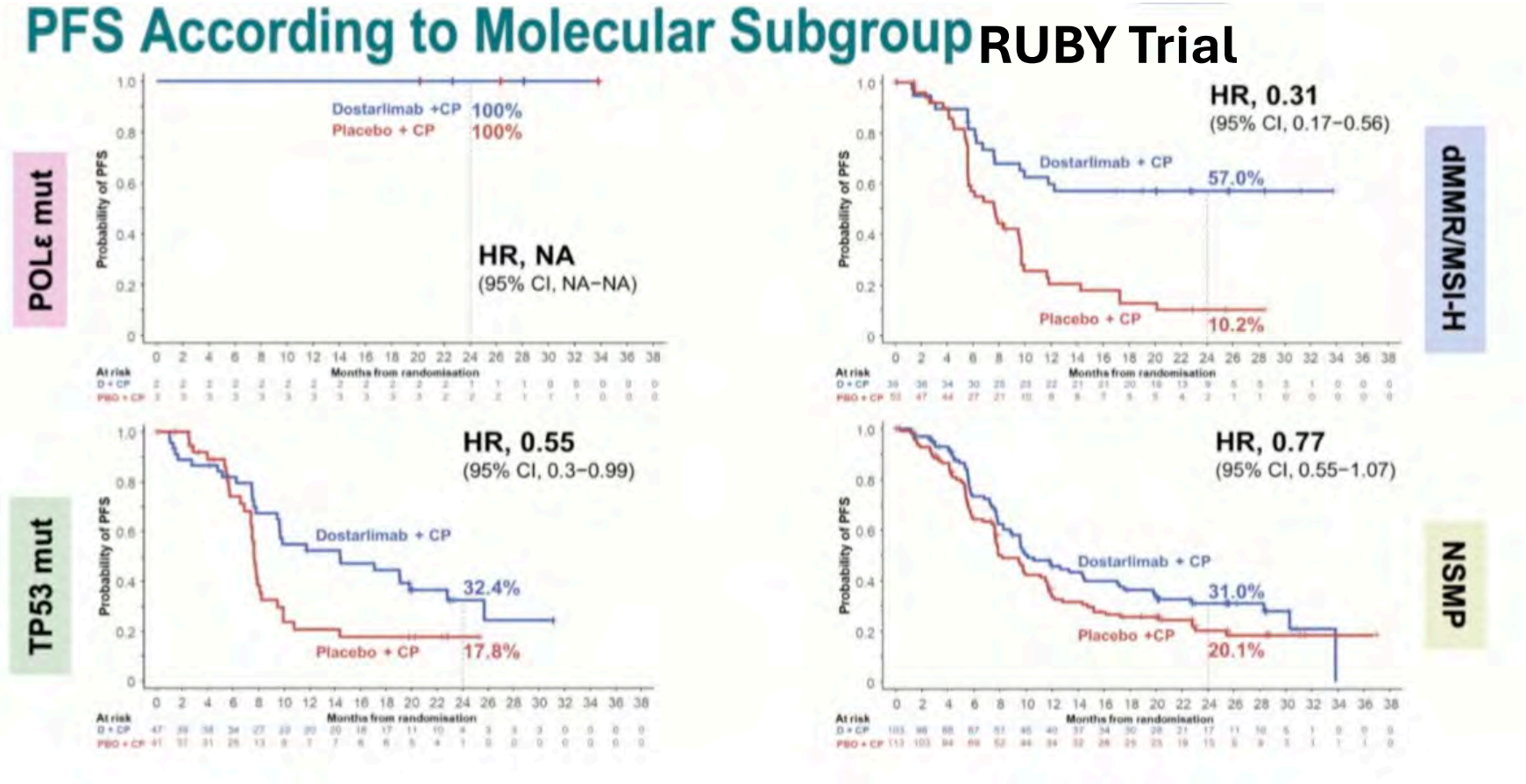
XPORT-EC-042/GOG 3083

A Phase 3 of Selinexor in Maintenance Therapy After Systemic Therapy for Patients With TP53 Wild-type, Advanced, or Recurrent EC



Vergote, et al, JCO 2023

Caution re utilizing post-hoc subgroup data



Mirza, ESMO 2023

Case 2: Patient with P53wt/MMRp EC, Stage IVB, Gr 3 endometrioid

If relapses, next option:

1. Doxorubicin or paclitaxel
2. Clinical trial with TROP2 or FR alpha ADC
3. Best Supportive Care

2 Randomized Phase 3 trials of TROP2 ADC in recurrent Endometrial Cancer

Phase 3 ENGOT-en23/GOG-3095/MK-2870-005[1]
N=710

Key Eligibility Criteria

- Histologically confirmed endometrial carcinoma or carcinosarcoma
- Radiographically evaluable disease, either measurable or nonmeasurable per RECIST v1.1 (by BICR)
- Must have received prior platinum-based chemo and anti–PD-1/anti–PD-L1 therapy, either separately or in combination
- Has not received >3 prior lines of therapy

R

MK-2870 4 mg/kg IV on day 1 of each 14-day cycle

Doxorubicin 60 mg/m² IV on day 1 of each 21-day cycle
or
Paclitaxel 80 mg/m² IV on days 1, 8, and 15 of each 28-day cycle

- **Primary endpoints**: PFS, OS
- **Secondary endpoints**: ORR, DOR, safety, HRQOL

NCT06132958

GOG Global PI: Pothuri
Mentored PI:Lightfoot

Phase 3 GOG-3104/ENGOT-en26
N=520

Key Eligibility Criteria

- Histologically confirmed endometrial carcinoma or carcinosarcoma
- Radiographically evaluable disease, either measurable or nonmeasurable per RECIST v1.1 (by BICR)
- Must have received prior platinum-based chemo and anti–PD-1/anti–PD-L1 therapy, either separately or in combination
- Has not received >3 prior lines of therapy

R

Sacituzumab govitecan 10mg/kg D1, D8

Doxorubicin 60 mg/m² IV on day 1 of each 21-day cycle
or
Paclitaxel 80 mg/m² IV on days 1, 8, and 15 of each 28-day cycle

- **Primary endpoints**: PFS, OS
- **Secondary endpoints**: ORR, DOR, safety, HRQOL

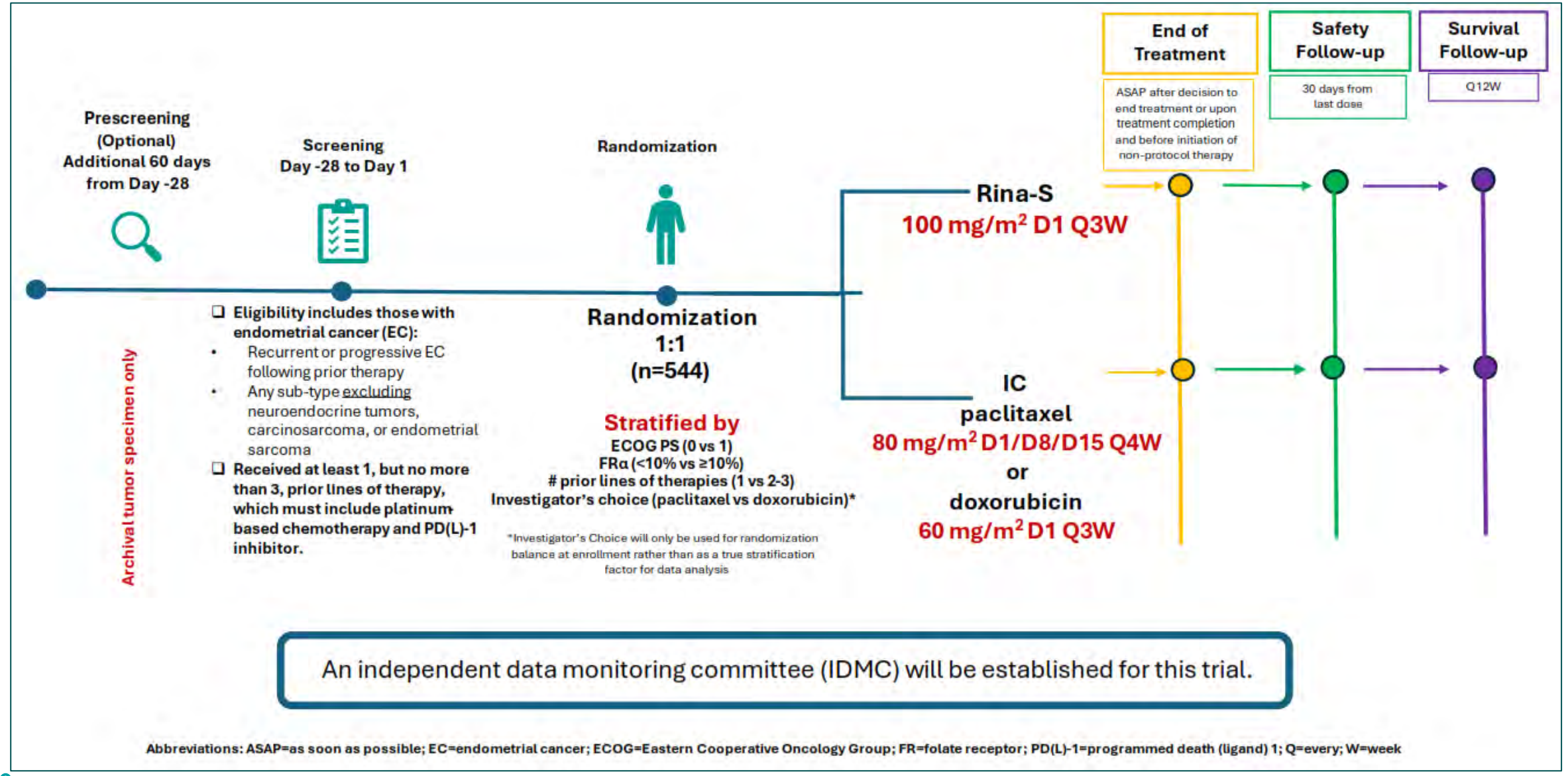
NCT06486441

GOG Global PI: Eskander
Mentored PI:Corr

1. NCT06132958 via ClinicalTrials.gov. Accessed April 29, 2024.; 2. NCT05382268 via ClinicalTrials.gov. Accessed Sept 1, 2024 .

RAINFOL-03 Study Design

Global, Open-label, Randomized Phase 3



An independent data monitoring committee (IDMC) will be established for this trial.

Abbreviations: ASAP=as soon as possible; EC=endometrial cancer; ECOG=Eastern Cooperative Oncology Group; FR=folate receptor; PD(L)-1=programmed death (ligand) 1; Q=every; W=week

Case 3:
Patient with P53abnormal /MMRp EC

- 76 yo hx DM, Htn, Hashimotos dz, PMB X 5 wks
- Em bx 5/11/23: Endometrial carcinoma, consistent with high grade serous carcinoma, p53 aberrant IHC, MMR IHC intact, HER2 3+
- CT scan 5/18/23: Heterogenous uterus compatible with known neoplasm, no evidence of adenopathy or distant metastatic disease
- FH: daughter ovary cancer, brother- bladder ca
- s/p Robotic hysterectomy/BSO/ SLN bx
- PATH: Uterus 99% myometrial invasion, LVSI+, LUS involved by carcinoma, serosa not involved, B/L ovary nl, Right and left external iliac sentinel LN + metastatic serous carcinoma- stage 3C1
- NYU genome pact: PIK3CA c.1633G>A p.Glu545Lys, TP53 c.844C>T p.Arg282Trp, FBXW7 c.1436 G>A p.Arg479Gln

Case 3:
Patient with P53abnormal /MMRp EC, HER2+

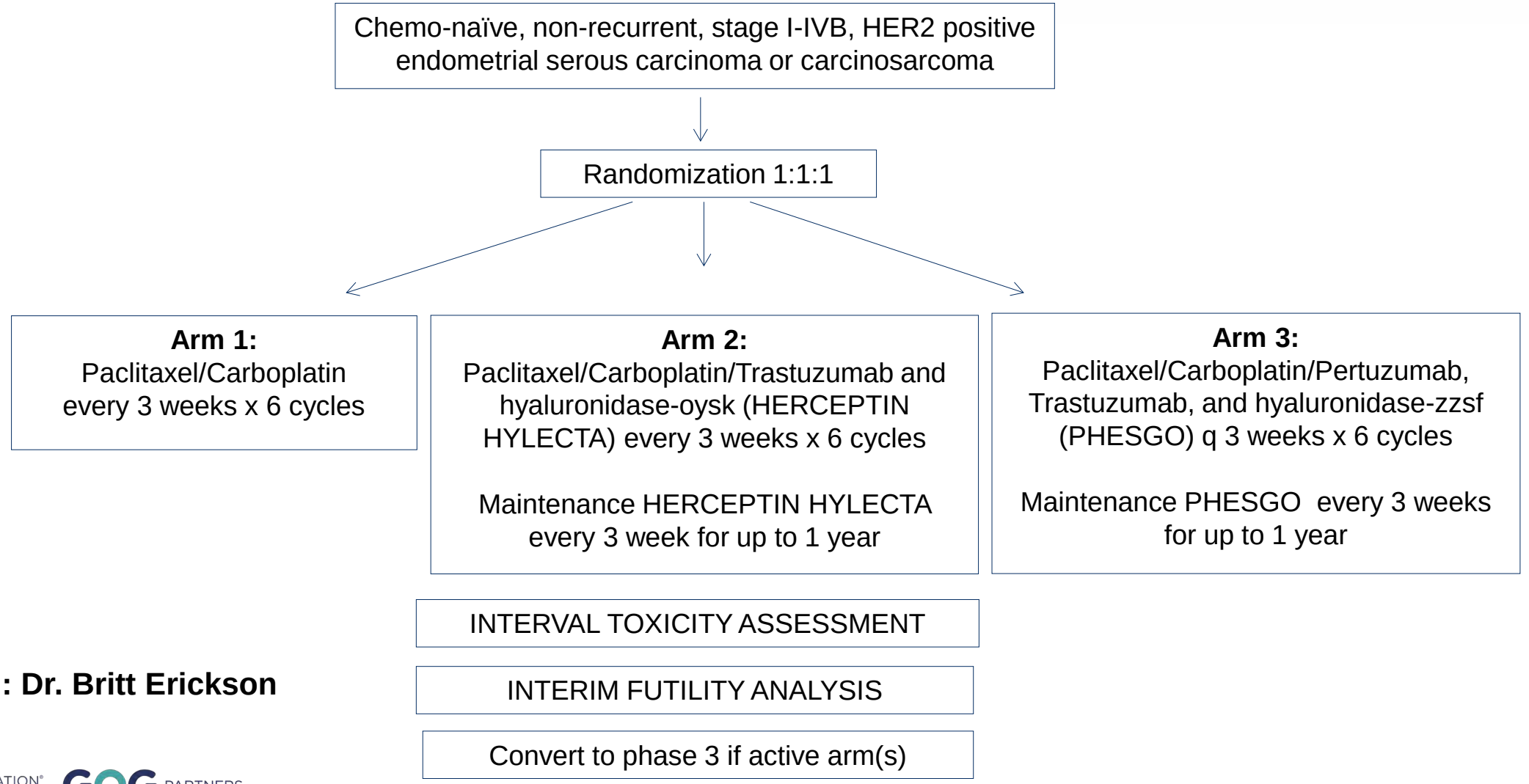
Treatment:

1. paclitaxel/carboplatin
2. paclitaxel/carboplatin/trastuzumab
3. trastuzumab deruxtecan
4. no further treatment

Case 3:
Patient with P53abnormal /MMRp EC, HER2+

- Patient participated in clinical trial –GY-026 and was randomized to carboplatin/paclitaxel/trastuzumab arm
- Continued on trastuzumab maintenance until POD in 10/2024

NRG- GY026 Study Schema- Study Ongoing



PI: Dr. Britt Erickson

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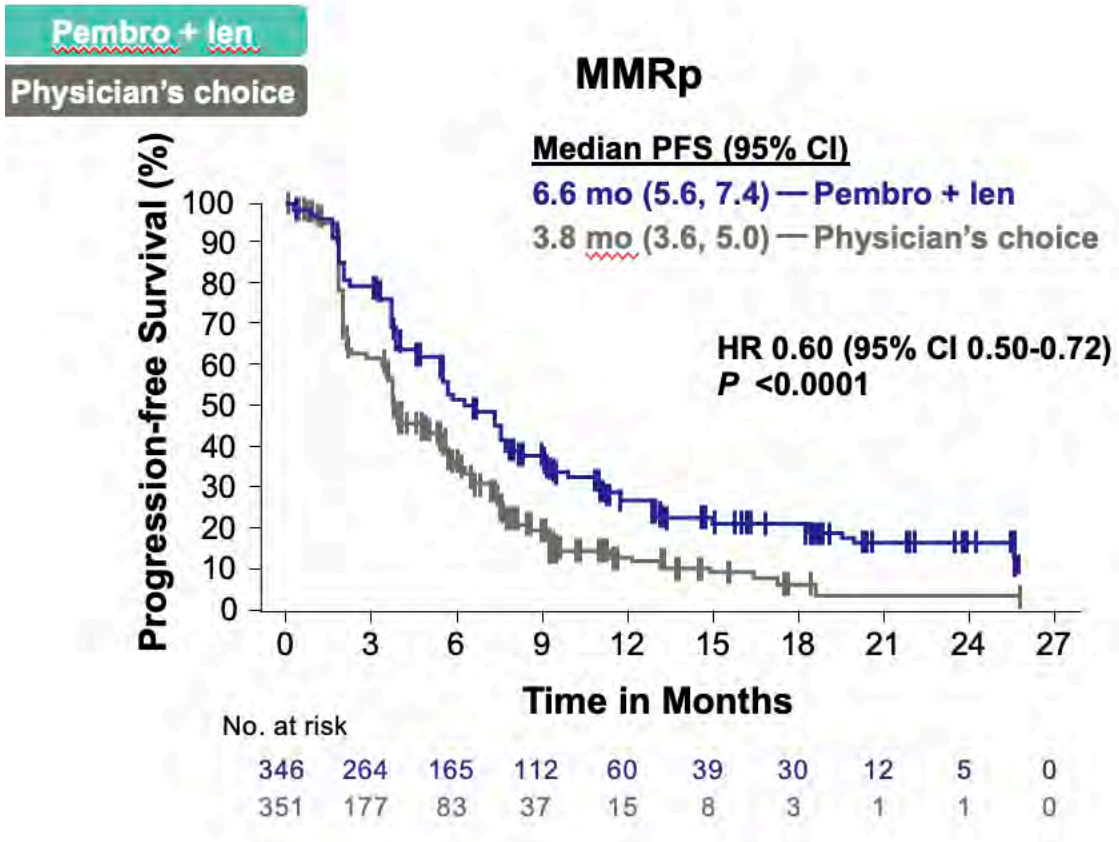
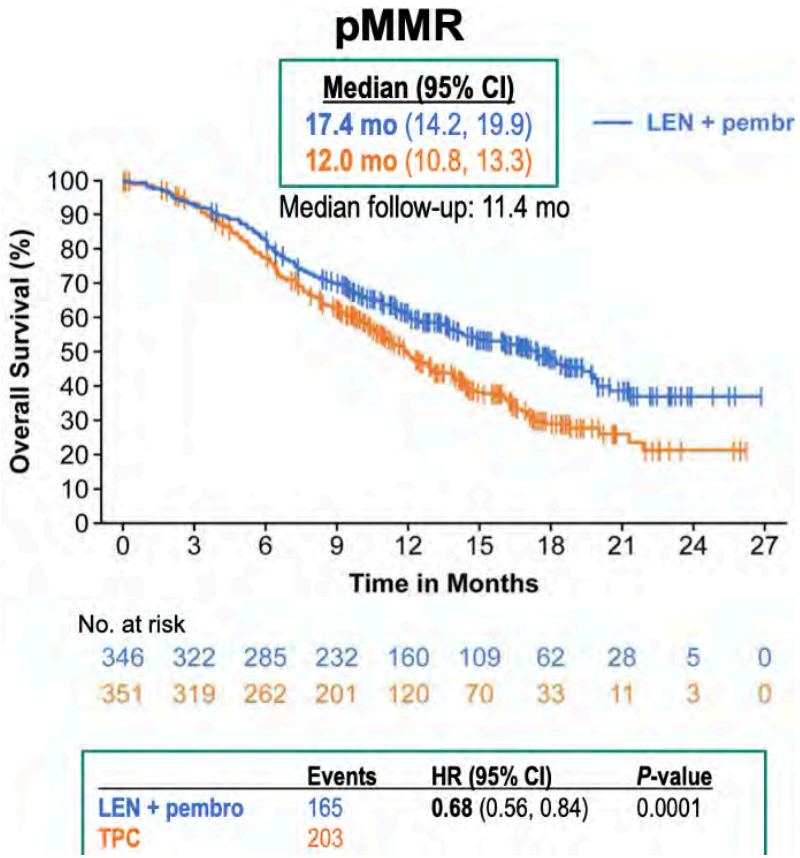
Case 3:
Patient with P53abnormal /MMRp EC, HER2+ POD on Chemotherapy/trastuzumab

Treatment options:

1. Lenvatinib/pembrolizumab
2. Doxorubicn or weekly paclitaxel
3. Trastuzumab deruxtecan
4. Paclitaxel/carboplatin + ICI followed by maintenance ICI

Pembrolizumab + Lenvatinib (KEYNOTE-775): Clinically Meaningful Improvement Over Physician's Choice Therapy in MMRp Patients[1]





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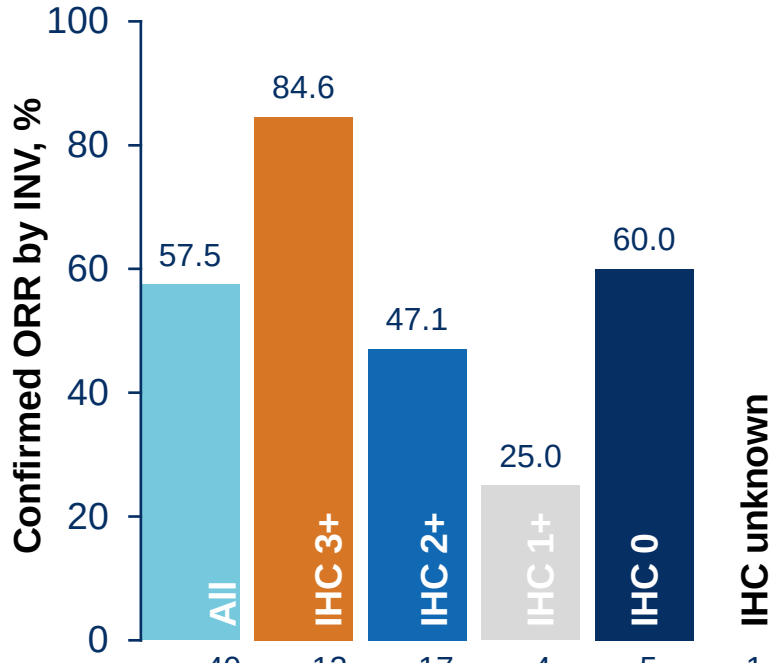
1. Makker V, et al N Engl J Med. 2022 Feb 2. Colombo N, et al. Ann Oncol. 2021;32(suppl_5):S725-S772

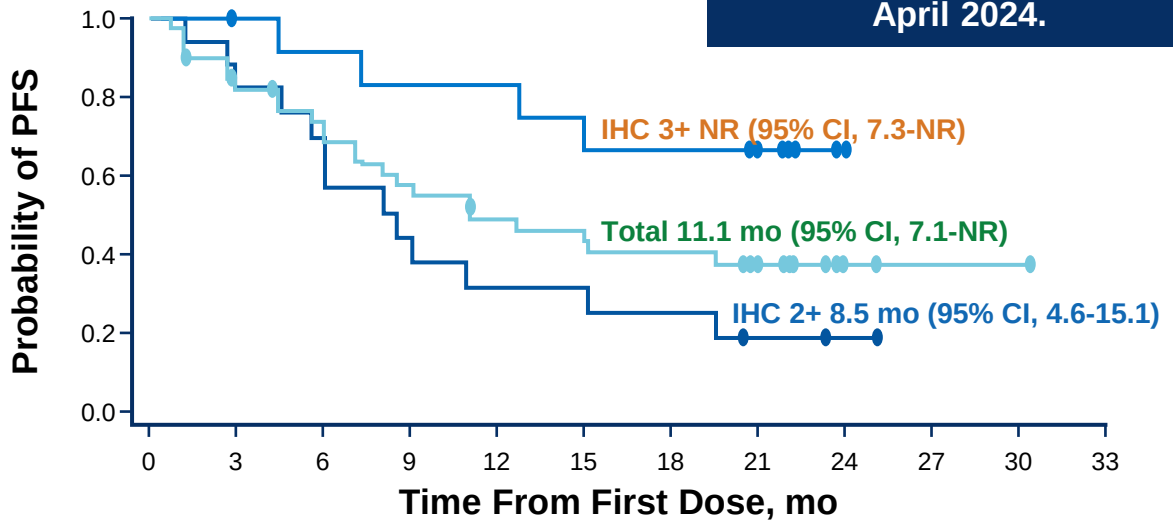
T-DXd: Efficacy by HER2 Status[1-3]

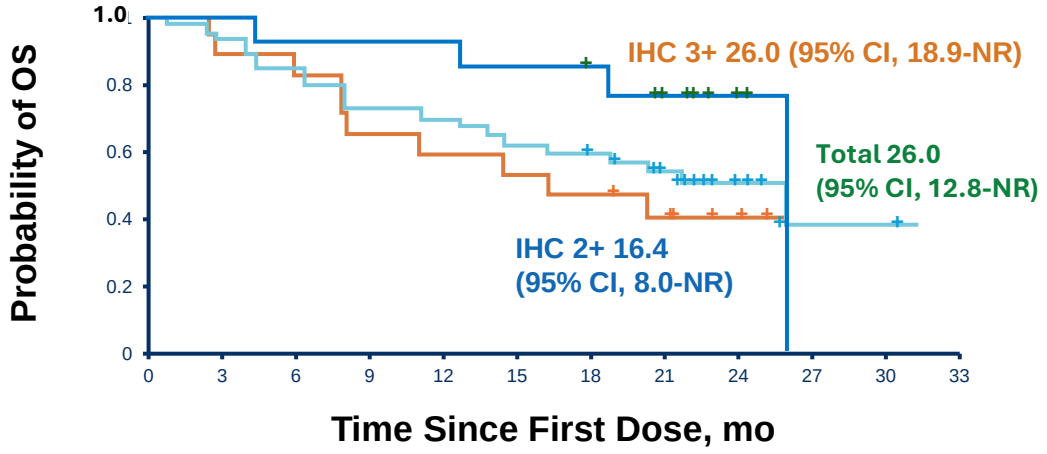
FDA granted accelerated approval to trastuzumab deruxtecan for unresectable or metastatic 3+HER2-positive solid tumors in April 2024.

Endometrial cancer



	All	IHC 3+	IHC 2+	IHC 1+	IHC 0	IHC unknown
Total n in subgroup	40	13	17	4	5	1
n of responders	23	11	8	1	3	0
Median DOR, months[c]	NR	NR	18.2	NR	9.9	-
95% CI[d]	9.9, NE	9.6, NE	3.0, NE	-	2.8, NE	-





[a] HER2 status by central testing. [b] Similar ORR and DOR results were reported by retrospective independent central review. [c] Median DOR reported for patients with a confirmed an objective response only. [d] CI not shown where n = 1 responder.

1. Lee J et al. Int J Gynecol Cancer. 2023;33:A6-A7. 2. Meric-Bernstam F et al. ESMO 2023. Abstract LBA34. 3. Meric-Bernstam F et al. J Clin Oncol. 2024;42:47-58.

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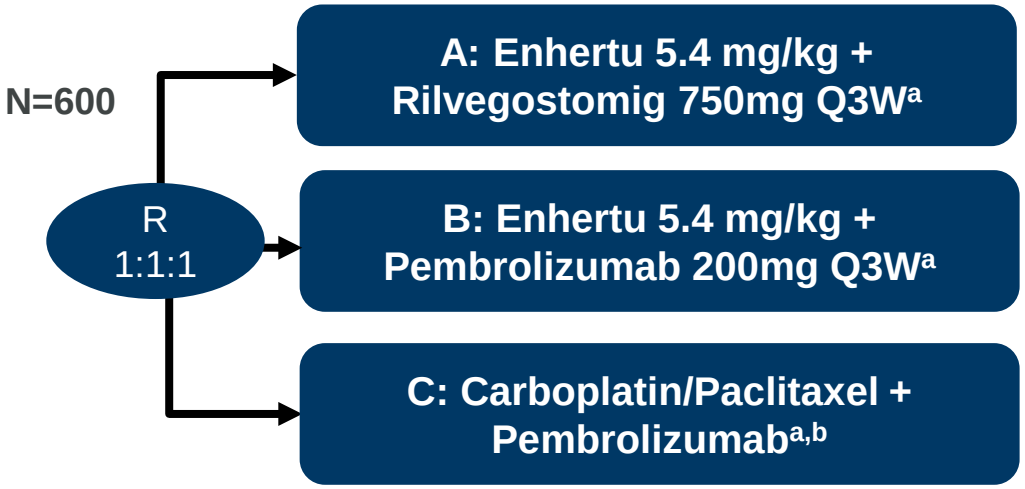
DESTINY-Endometrial01/ GOG-3098/ ENGOT-EN24: A Phase III Study of Trastuzumab Deruxtecan Plus Rilvegostomig or Pembrolizumab as First-Line Treatment of HER2-Expressing (IHC 3+/2+), Mismatch Repair Proficient (pMMR) Endometrial Cancer

Patient Population

- HER2 expressing (IHC 3+/2+) EC by central test
- pMMR EC by central test
- Stage III, Stage IV, or recurrent, histologically-confirmed endometrial cancer
- Stage III must have measurable disease
- Any histological subtype except for sarcomas
- May have received 1 prior line of adjuvant/ neoadjuvant chemotherapy (chemotherapy and/ or chemoradiation) if recurrence ≥ 6 months after last dose of chemo
- No prior exposure to ADCs or ICIs
- ECOG PS 0 or 1

IHC 3+25%; IHC 2+ 75% (capped)



Stratification factors:
- HER2 IHC 3+ vs 2+
- PD-L1 TAP ≥1% vs TAP <1%
- Asia vs Non-Asia

Endpoints

Primary:
- PFS (BICR) in ITT

Secondary:
- OS (key secondary endpoint)
- PFS (Investigator)
- ORR
- PFS2
- HRQoL

[a] Treatment will continue until objective disease progression according to RECIST v1.1 as assessed by the Investigator and confirmed by BICR or until other discontinuation criteria is met, whichever occurs first.
[b] Carboplatin AUC5, paclitaxel 175 mg/m2, and pembrolizumab 200 mg IV once Q3W x 6 cycles*, followed by maintenance with pembrolizumab 400 mg IV Q6W. Treatment with pembrolizumab will continue for up to 20 total cycles (approximately 24 months, accounting for combination and maintenance phases) or until other discontinuation criteria is met, whichever occurs first.
* At the discretion of the treating Investigator, participants may continue to receive carboplatin, paclitaxel and pembrolizumab Q3W for up to 10 cycles.

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ENGOT European Network of Gynaecological Oncological Trial groups

NSGO-CTU Nordic Society of Gynaecological Oncology - Clinical Trial Unit

TroFuse-033: Ph3, Randomized, Open-label, 1L sac-TMT Maintenance in TROP2 all-comer pMMR Endometrial Cancer

Participants:
- Primary advanced/recurrent endometrial carcinoma
- pMMR
- No prior systemic therapy OR recurred after adjuvant (no PFI required)
- No prior anti-PD-1/PD-L1
- Radiologically apparent disease (measurable Stage III or measurable/non-measurable Stage IV)
- Available tissue to test for TROP2 / MMR / p53
- ECOG 0 to 1

Induction

N ~ 1123

6 cycles[1]

Carboplatin
Paclitaxel
Pembrolizumab
q3w

Without PD

Eligibility for Randomization:
- Without PD as determined by INV
- Completed 6 cycles of Induction
- AEs resolved to ≤ Grade 1
- ECOG 0 to 1
- Valid TROP2 result from central lab

Maintenance

Randomize 1:1
N ~ 842

sac-TMT 4 mg/kg q2w + Pembrolizumab q6w

Pembrolizumab q6w

Treatment duration:
Treat until intolerable toxicities / PD or up to ~1.5 years (14 administrations of Pembrolizumab / 42 administrations of sac-TMT).[2]

PD

Subsequent Treatment[3]:

sac-TMT +/- Pembrolizumab

Dual Primary Endpoints
(using a TROP2 enrichment strategy)

- PFS (BICR)
- OS

[1] If pt. needs more time to recover after 6 cycles of Carboplatin/ Paclitaxel/ Pembrolizumab, two additional cycles of pembrolizumab (cycle 7 + 8) may be administered after sponsor consultation; [2] Pts. with confirmed CR by BICR (following Induction or Maintenance) may discontinue sac-TMT after 6 months of sac-TMT after sponsor consultation; [3]Patients with PD on Induction Treatment will be randomized to sac-TMT vs. sac-TMT + pembrolizumab if eligible per safety criteria outlined in IC/EC

Case 3:
Patient with P53abnormal /MMRp EC, HER2+ POD on Chemotherapy/trastuzumab

- Pt started on TDXd in 10/24 and continues on tx with PR
- Pt has lenvatinib/pembrolizumab option with POD

Q&A and Discussion

All Faculty

Ramez Eskander, MD

Robert Coleman, MD

Bhavana Pothuri, MD

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Thank You

View this symposium as part of the IGCS on-demand program following the meeting

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