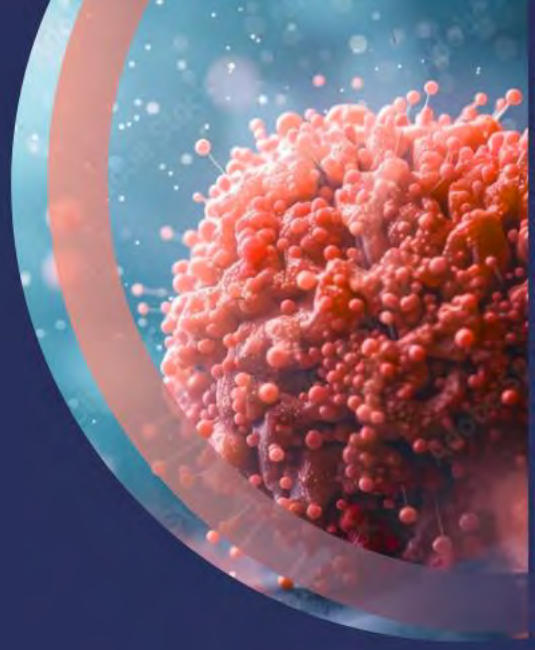
An Industry Supported Symposium at the IGCS 2024 Annual Global Meeting

Truth or Perception: Demystifying Emergent Data in the Competitive Endometrial Cancer Landscape



Dublin, Ireland

Friday, October 18, 2024

12:45 - 14:15 IST/GMT+1

GOG FOUNDATION® Transforming the standard of care

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

Welcome & Introductions

All Faculty

GOG FOUNDATION® Transforming the standard of care GOG PARTNERS

Moderators | Faculty

Thomas Herzog, MD
University of Cincinnati
Cincinnati, Ohio, USA

Matthew Powell, MD
Washington University
St. Louis, Missouri, USA

Robert Coleman, MD
Texas Oncology
The Woodlands, Texas, USA

Mansoor Mirza, MD, PhD
Rigshopitalet –
CopenhagenUniversity
HospitalKøbenhavn, Denmark

Isabelle Ray-Coquard, MD, PhD
Centre Leon Berard
Lyon, France

Faculty Disclosures

Name	Role in Activity	Disclosures
Thomas Herzog, MD	Moderator	• **Scientific Advisory Boards:** Astra Zeneca; Caris; Clovis; Eisai; Epsilogen; Genentech; GSK; J&J; Merck; Mersana; Novocure; Seattle Genetics
Matthew Powell, MD	Moderator	• **Consultant:** AstraZeneca; Clovis Oncology, Inc.; EISAI INC.; Genentech USA, Inc.; GlaxoSmithKline, LLC.; Merck; Seattle Genetics
Robert Coleman, MD	Speaker	• **Consulting/advisory role:** Clovis Oncology, Genentech/Roche, Esperance, NCCN, AstraZeneca/MedImmune, Genmab, GamaMabs Pharma, Tesaro, OncoMed, Sotio, Oncolytics, AbbVie • **Travel/accommodations/expenses**: Merck, AstraZeneca/MedImmune, Array Biopharma, Clovis, Roche/Genentech, Research to Practice, GOG, Sotio, Vaniam Group • **Research funding:** AstraZeneca/MedImmune, Esperance, OncoMed, Array, Clovis, Johnson & Johnson, Merck, Roche/Genentech, Abbott/AbbVie
Mansoor Mirza, MD, PhD	Speaker	• **Consulting Fees**: AstraZeneca, Merck, Clovis, GSK • **Support for Attending Meetings and/or travel:** AstraZeneca • **Participation on Data Safety Monitoring Board/Advisory Board:** Merck BioNTech, GSK, AstraZeneca • **Leadership/Fiduciary Role in Other Board, Society, Committee, or Advoacy Group paid/unpaid:** Karyopharm Therapeutics Inc. • **Stock/Stock Options:** Karyopharm Therapeutics Inc.
Isabelle Ray-Coquard, MD, PhD	Speaker	• **Honoraria (personal):** Adaptimmune, Agenus, Amgen, AstraZeneca, BMS, Clovis, Daiichi Sankyo, Deciphera, Eisai, EQRx, GSK, MacroGenics, Merck Serono, Mersana, Novartis, Onxeo, Roche, Sutro Biopharma • **Honoraria (institution):** MSD (translational research)Funding (institution): BMSPrincipal investigator: PAOLA-1 (unrecompensed)President: GINECO (unrecompensed)

Learning Objectives

1. Analyze and interpret emerging data from key endometrial cancer studies, including RUBY Parts I&II, GY018, ATTEND, DUO-E, B21 and other relevant trials, to gain a comprehensive understanding of treatment outcomes and therapeutic trends in the field.

2. Evaluate the design complexities of clinical trials in endometrial cancer research, critically assessing study methodologies and identifying potential sources of confusion or bias that may impact data interpretation and clinical decision-making.

3. Examine the significance of emerging biomarkers in endometrial cancer management, including their role in patient selection (e.g. immune checkpoint inhibitors (ICI), PARP inhibitor (PARPi) therapy) and their potential impact on treatment efficacy, sequencing and patient outcomes.

4. Engage in interactive discussions and question-and-answer sessions to clarify misconceptions and deepen understanding of key concepts, fostering a collaborative learning environment that encourages active participation and knowledge exchange among participants.

Agenda

12:45 - 12:55: **Welcome and Introductions**
All Faculty

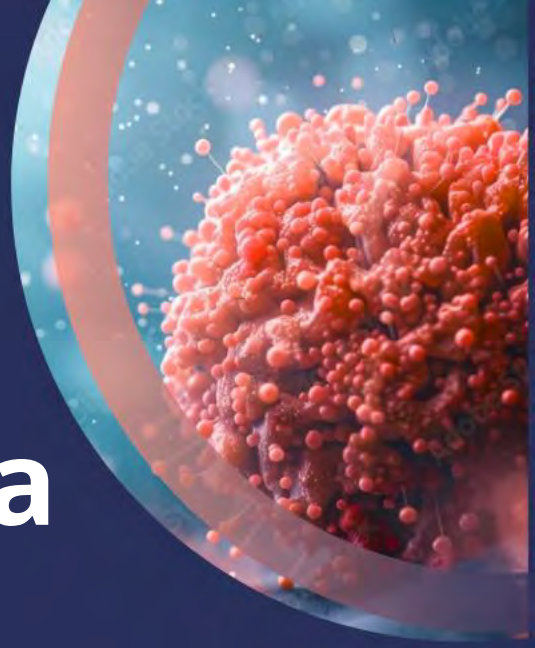
12:55 – 13:15: **Deciphering Endometrial Cancer Studies, Analyzing Emerging Data and Therapeutic Trends**
Mansoor Mirza, MD, PhD, Rigshopitalet – Copenhagen, University Hospital, København, Denmark

13:15 - 13:35: **BioMarkers in Focus: Exploring ICI, PARPi, and others Role in the treatment of Endometrial Cancer**
Isabelle Ray-Coquard, MD, PhD, Centre Leon Berard, Lyon, France

13:35 - 13:55: **Unraveling Endometrial Data Complexities: Confusion on Data and clarity for NCCN Guidelines**
Robert Coleman, MD, Texas Oncology, Vaniam Group, The Woodlands, Texas, USA

13:55 – 14:15: **Interactive Dialogue: Clarifying Misconceptions and Enhancing Understanding Sequencing for Endometrial Cancer Treatments**
All Faculty

Deciphering Endometrial Cancer Studies, Analyzing Emerging Data and Therapeutic Trends



Mansoor Raza Mirza, MD

Rigshopitalet – Copenhagen University Hospital
København, Denmark

Background:
Cochrane meta-analysis of 8 clinical trials (n = 3628)

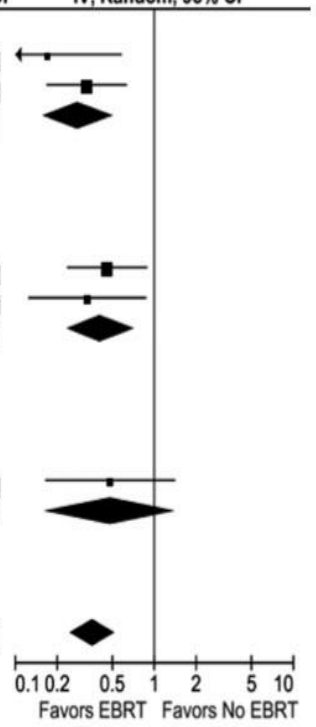
Overall Survival

Study or Subgroup	log[Hazard Ratio]	SE	EBRT Total	No EBRT Total	Weight	Hazard Ratio IV, Random, 95% CI
EBRT vs no additional treatment						
GOG 99 (1)	0.04	0.38	128	132	8.4%	1.04 [0.49, 2.19]
PORTEC-1	0.2	0.2	354	360	30.4%	1.22 [0.83, 1.81]
Subtotal (95% CI)			**482**	**492**	**38.8%**	**1.18 [0.83, 1.67]**
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (*P* = .71); I² = 0%						
Test for overall effect: Z = 0.93 (*P* = .35)						
EBRT vs no additional treatment (VBT balanced across groups)						
ASTEC/EN.5	0.15	0.218	358	335	25.6%	1.16 [0.76, 1.78]
Sorbe 2011 (2)	-0.14	0.23	264	263	23.0%	0.87 [0.55, 1.36]
Subtotal (95% CI)			**622**	**598**	**48.6%**	**1.01 [0.74, 1.38]**
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 1 (*P* = .36); I² = 0%						
Test for overall effect: Z = 0.08 (*P* = .94)						
EBRT vs VBT						
PORTEC-2 (3)	-0.14	0.31	183	183	12.6%	0.87 [0.47, 1.60]
Subtotal (95% CI)			**183**	**183**	**12.6%**	**0.87 [0.47, 1.60]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (*P* = .65)						
Total (95% CI)			**1287**	**1273**	**100.0%**	**1.05 [0.85, 1.31]**
Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 4 (*P* = .77); I² = 0%						
Test for overall effect: Z = 0.48 (*P* = .63)						
Test for subgroup differences: Chi² = 0.85, df = 2 (*P* = .65), I² = 0%						

(1) Defined by investigators as low-intermediate risk (LIR)
(2) All women received VBT. This trial expressed HRs in terms of VBT; we have expressed the HR in terms of EBRT.
(3) True high-intermediate risk after pathology review (N=366). HR expressed in terms of EBRT.

Locoregional Control

Study or Subgroup	log[Hazard Ratio]	SE	EBRT Total	No EBRT Total	Weight	Hazard Ratio IV, Random, 95% CI
EBRT vs no additional treatment						
GOG 99	-1.77	0.63	190	202	9.3%	0.17 [0.05, 0.59]
PORTEC-1	-1.12	0.34	354	360	31.9%	0.33 [0.17, 0.64]
Subtotal (95% CI)			**544**	**562**	**41.2%**	**0.28 [0.16, 0.51]**
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 1 (*P* = .36); I² = 0%						
Test for overall effect: Z = 4.23 (*P* < .0001)						
EBRT vs no additional treatment (VBT balanced across groups)						
ASTEC/EN.5 (1)	-0.78	0.34	452	453	31.9%	0.46 [0.24, 0.89]
Sorbe 2011 (2)	-1.11	0.5	264	263	14.7%	0.33 [0.12, 0.88]
Subtotal (95% CI)			**716**	**716**	**46.6%**	**0.41 [0.24, 0.72]**
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (*P* = .59); I² = 0%						
Test for overall effect: Z = 3.15 (*P* = .002)						
EBRT vs VBT						
PORTEC-2 (3)	-0.73	0.55	214	213	12.2%	0.48 [0.16, 1.42]
Subtotal (95% CI)			**214**	**213**	**12.2%**	**0.48 [0.16, 1.42]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.33 (*P* = .18)						
Total (95% CI)			**1474**	**1491**	**100.0%**	**0.36 [0.25, 0.52]**
Heterogeneity: Tau² = 0.00; Chi² = 2.31, df = 4 (*P* = .68); I² = 0%						
Test for overall effect: Z = 5.33 (*P* <.00001)						
Test for subgroup differences: Chi² = 1.19, df = 2 (*P* = .55), I² = 0%						



(1) 54% in EBRT group and 52% in the No EBRT group received VBT
(2) All women received VBT. This trial expressed HRs in terms of VBT; we have expressed the HR in terms of EBRT.
(3) This trial expressed HR's in terms of VBT (VBT vs EBRT); we have expressed the HR in terms of EBRT.

Kong A, et al. *J Natl Cancer Inst.* 2012;104(21):1625-1634.

Background: GOG0209: PFS & OS

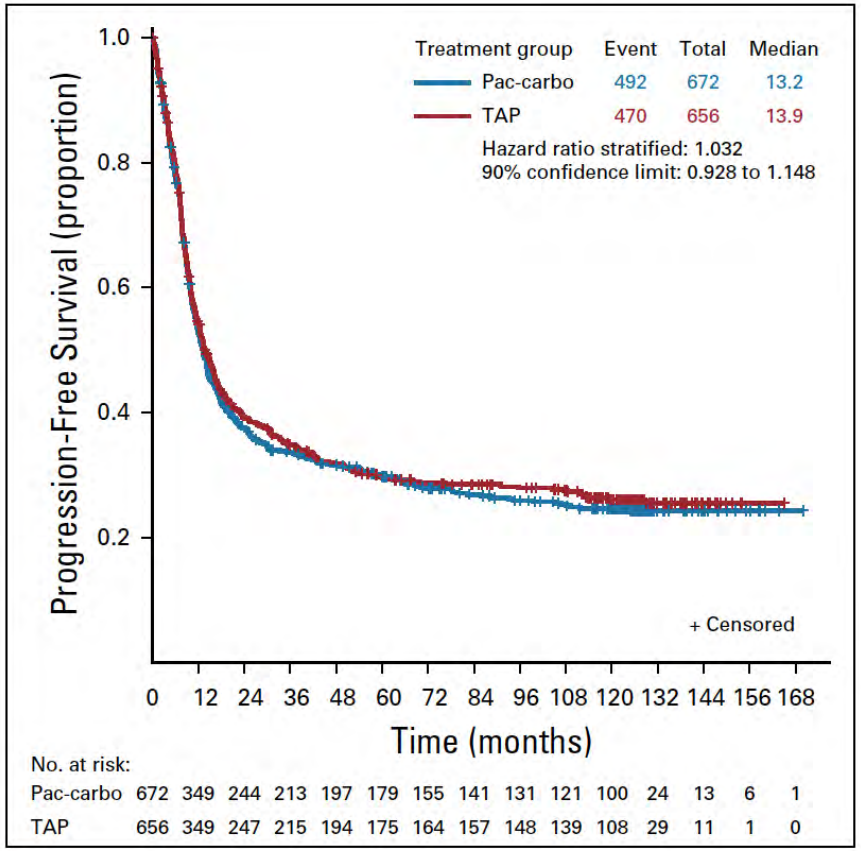


FIG 2. Updated progression-free survival time distribution by randomized treatment group. Carbo, carboplatin; pac, paclitaxel; TAP, paclitaxel-doxorubicin-cisplatin.

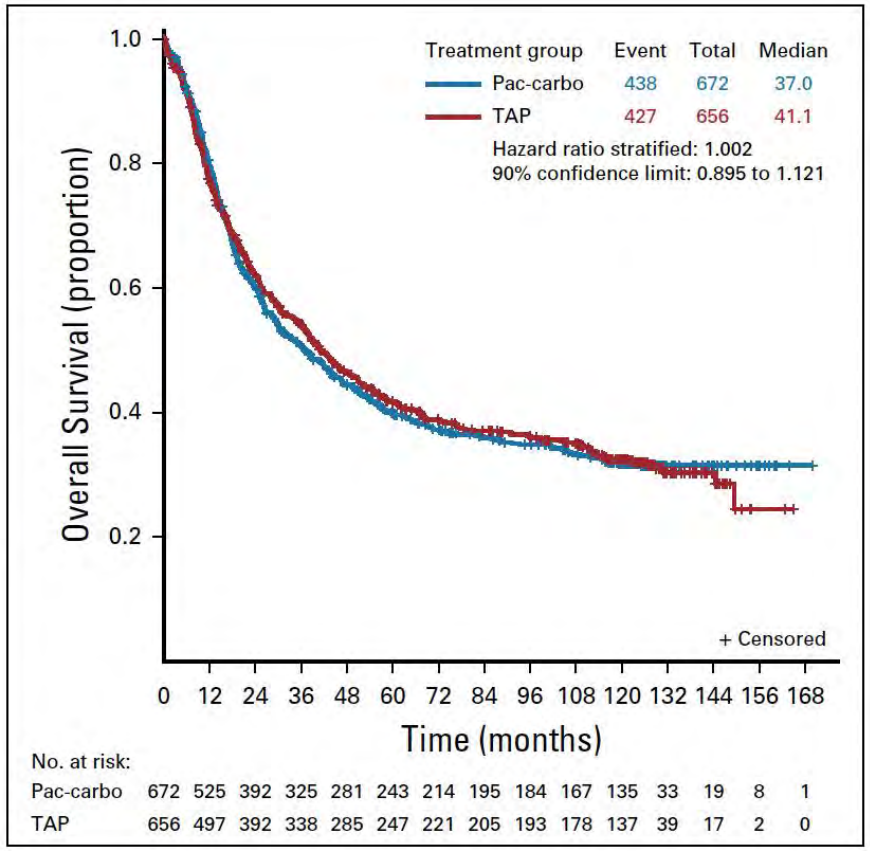
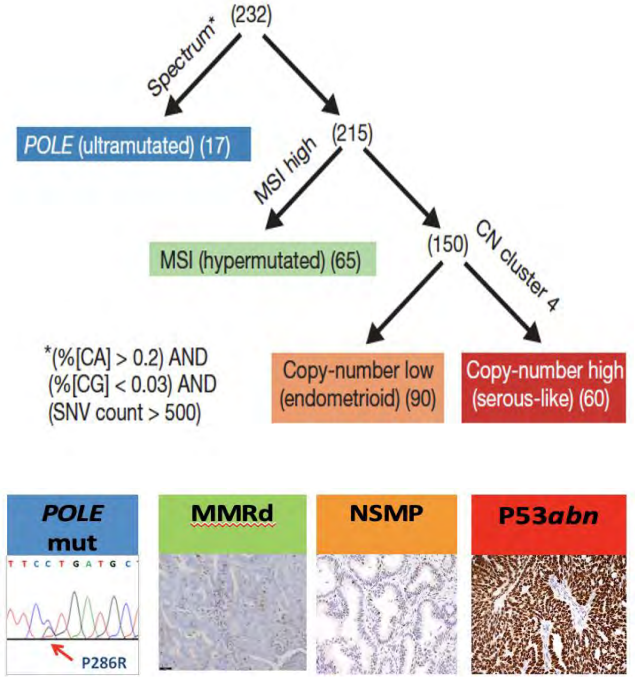
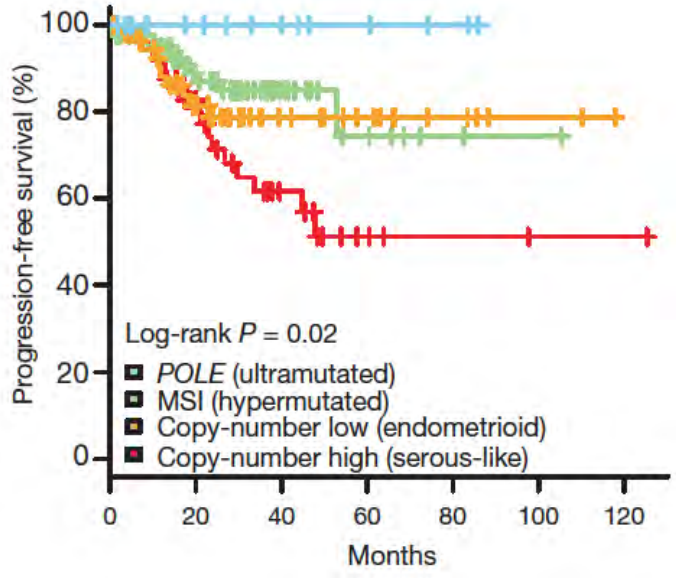


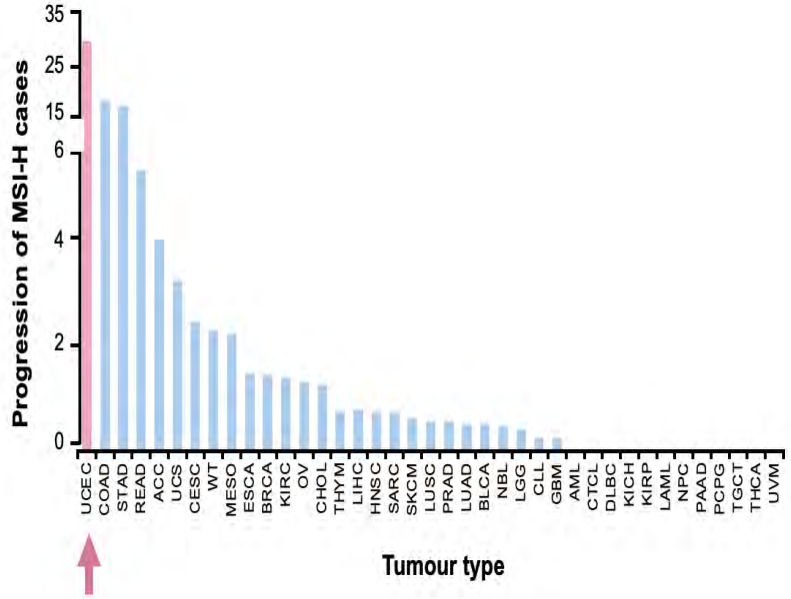
FIG 3. Updated overall survival time distribution by randomized treatment group. Carbo, carboplatin; pac, paclitaxel; TAP, paclitaxel-doxorubicin-cisplatin.

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

Background:
What the Cancer Genome Atlas (TCGA) has taught us







- Immunohistochemistry for p53 and mismatch repair proteins
- DNA sequencing for POLE exonuclease domain mutations

The Cancer Genome Atlas Research Network. *Nature*. 2013; 497: 67–73; Talhouk A, et al. *Cancer*. 2017; 123: 802–813; Luchini C, et al. *Ann Oncol*. 2019; 30:1232–1243; Bonneville R, et al. *JCO Precis Oncol*. 2017;1:PO.17.00073; Kandoth C, et al, *Nature*. 2013;502(7471):333-339; Stelloo E, et al. *Clin Cancer Research*. 2016;22(16):4215-4224.

Rationale of Combining Immune Checkpoint Inhibitor and PARP Inhibitor with Chemotherapy

Immune-Checkpoint Inhibitors:

- Durable activity in both dMMR/MSI-H and MMRp/MSS previously treated EC1
- dMMR/MSI-H EC is associated with:
  - High TMB/TILs2
  - Higher response rate to anti–PD-11

Chemotherapy

- Enhances immunogenic cell-death3,4
- Reduces immunosuppression in TME3,4
- Broad clinical activity when combined with anti–PD-1 in several cancers5–8

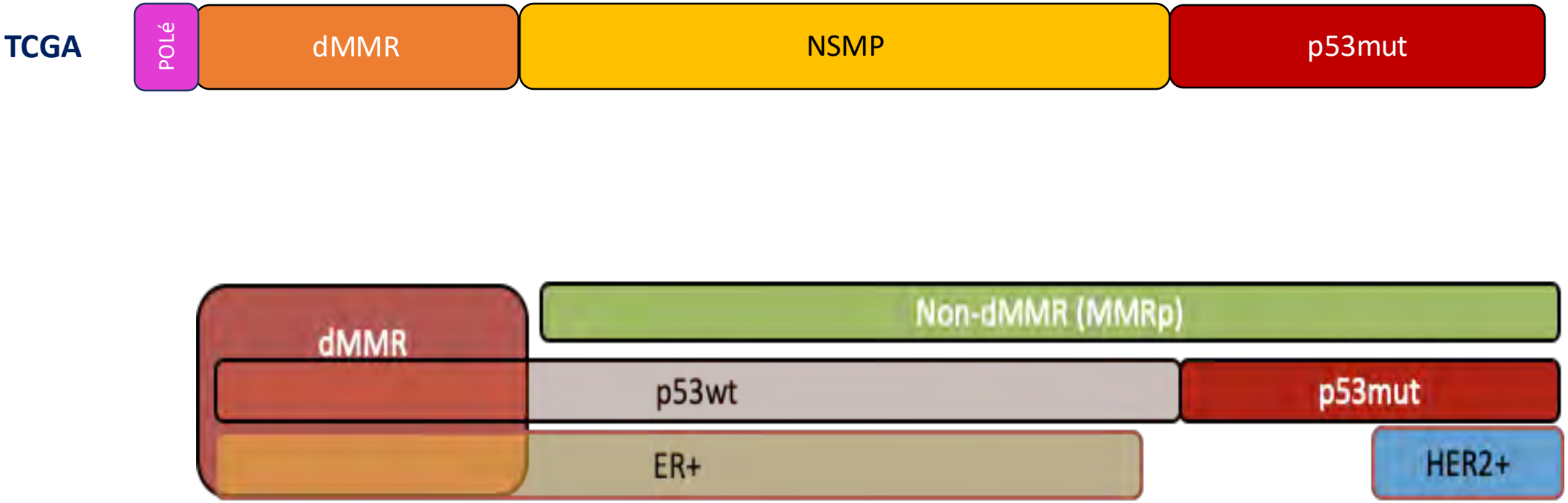
Addition of PARP Inhibitor

- Adding a PARPi to immune checkpoint inhibitor may further improve outcomes, including in patients with MMRp/MSS disease, a population with high unmet need9–12

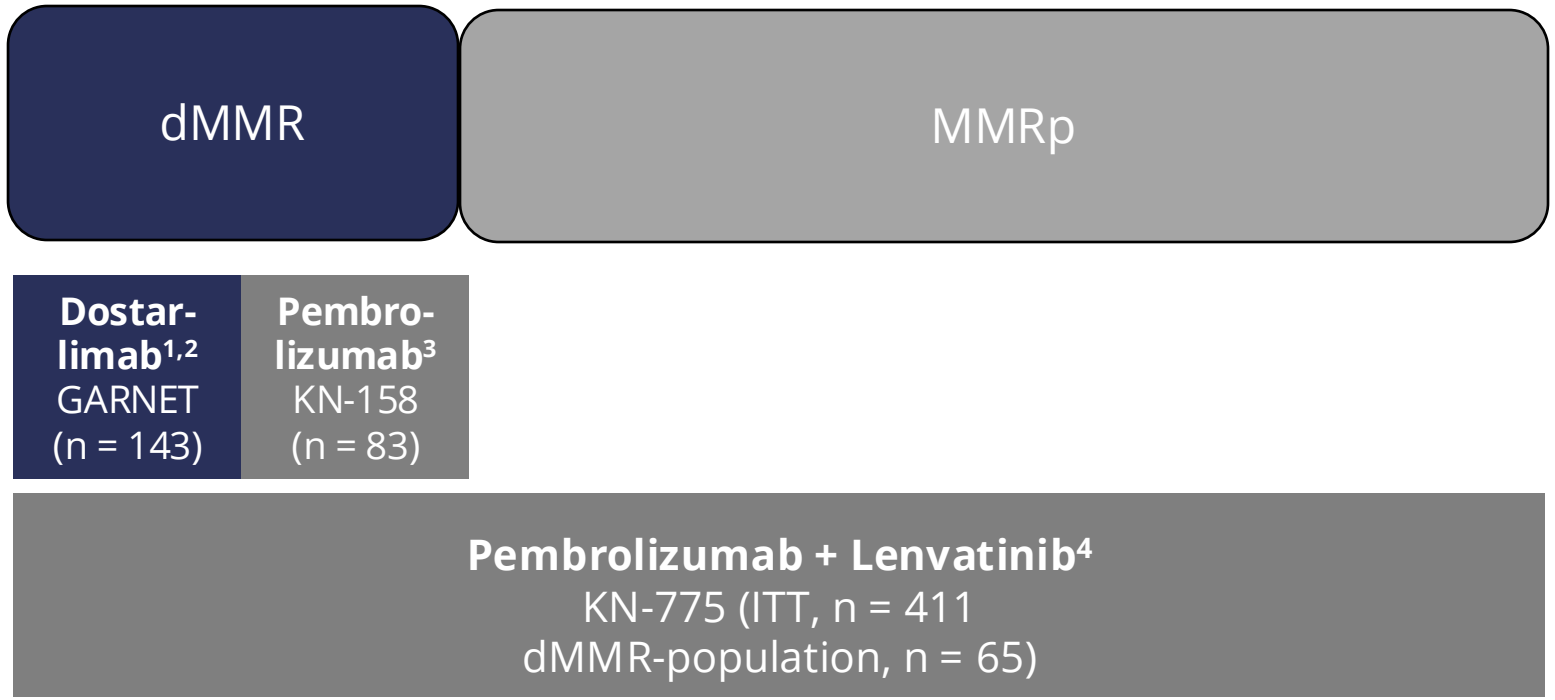
dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; PD-1, programmed death protein-1; TIL, tumor infiltrating lymphocytes; TMB, tumor mutational burden; TME, tumor microenvironment. CP, carboplatin-paclitaxel; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitor;

1. Oaknin A, Gilbert L, Tinker AV, et al. *J Immunother Cancer*. 2022;10:e003777; 2. Song Y, et al. *Onco Targets Ther.* 2021;14:4485-4497; 3. Emens LA, Middleton G. *Cancer Immunol.* 2015;3(5):436-443; 4. Hato SV, et al. *Clin Cancer Res.* 2014;20:2831-2837; 5. Gandhi L, et al. *N Engl J Med.* 2018;378:2078-92; 6. Paz-Ares L, et al. *N Engl J Med*. 2018;379:2040-51; 7. Janjigian YY, et al. *Lancet.* 2021;398:27-40; 8. Burtness B, et al. *Lancet.* 2019;394:1915-1928; 9. McGranahan N, et al. *Science.* 2016;351(6280):1463–1469; 10. Jiao S, et al. *Clin Cancer Res.* 2017;23(14):3711–3720; 11. Bang Y-J, et al. *J Clin Oncol*. 2019;37(suppl 4):140; 12. Westin SN, et al. *J Clin Oncol*. 2024;42(3):283–299.

Molecular profile of endometrial cancers



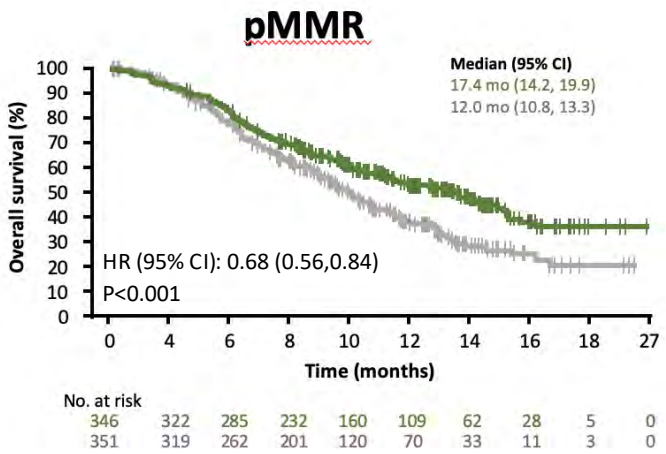
Currently Approved IO-treatment Options for Advanced/Recurrent EC After Pt-Failure

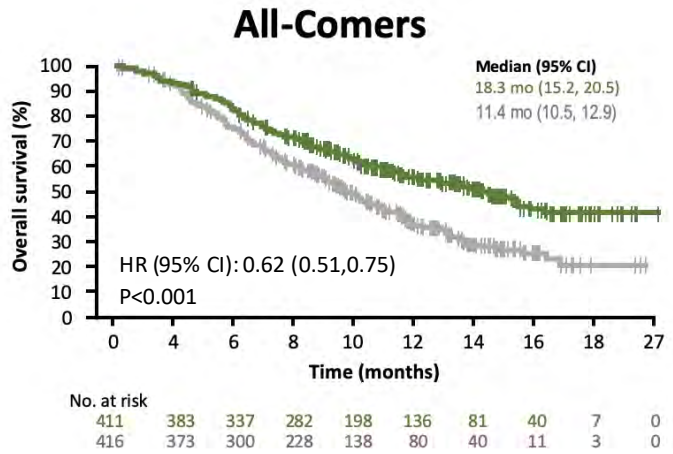


1. Oaknin A, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting, 3-7 June 2022; Chicago, Illinois, USA. 2. Dostarlimab Fachinformation. Stand Dezember 2022. 3. Fachinformation Pembrolizumab, Stand März 2023. 4. Fachinformation Lenvatinib, Stand März 2023.

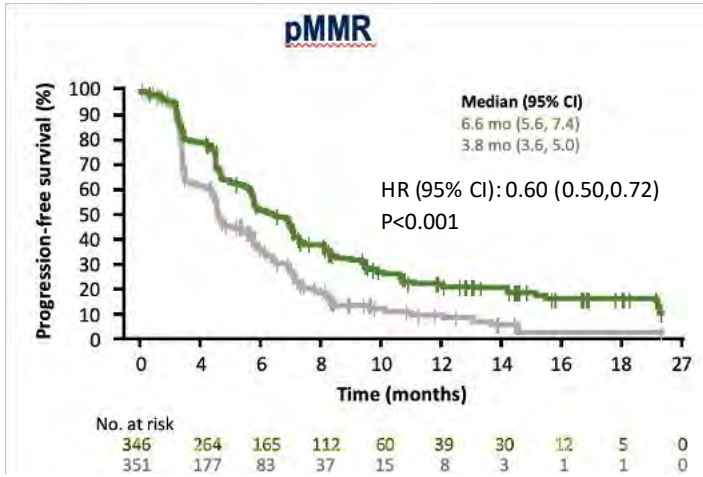
KEYNOTE-775: Primary Endpoints

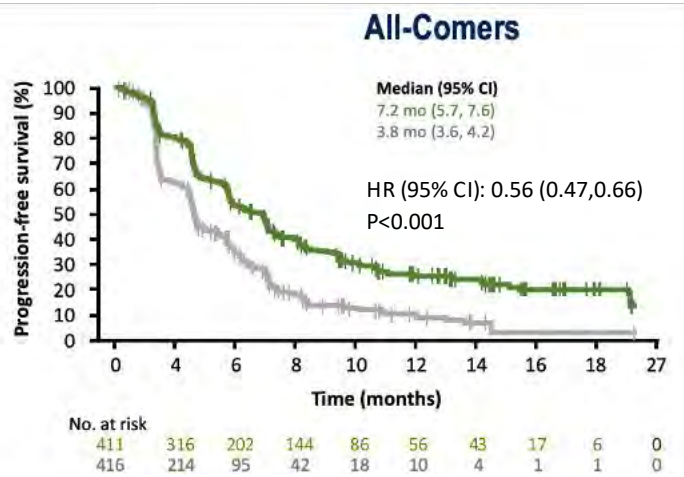
OS in pMMR and All-Comers





PFS in pMMR and All-Comers





Key:
- Lenvatinib+ Pembrolizumab
- Chemotherapy

Makker V, et al. *N Engl J Med.* 2022; 386: 437–448.

Paradigm-Shifting Data in EC Management

Name	EN6 RUBY Part 1[1]	EN7 ATTEND[2]	NRG-GY018[3]	EN11[4]
Lead group Study chair	NSGO-CTU Mirza	MaNGO Colombo	NRG Eskander	BGOG Van Gorp
Investigational agent	Dosta + Chemo	Atezo + Chemo	Pembro + Chemo	Pembro + Chemo
N	494	551	816	990
Concomitant	+	+	+	+
Maintenance	+	+	+	
Readout	**NEJM 2023**	**ESMO 2023**	**NEJM 2023**	**Negative**

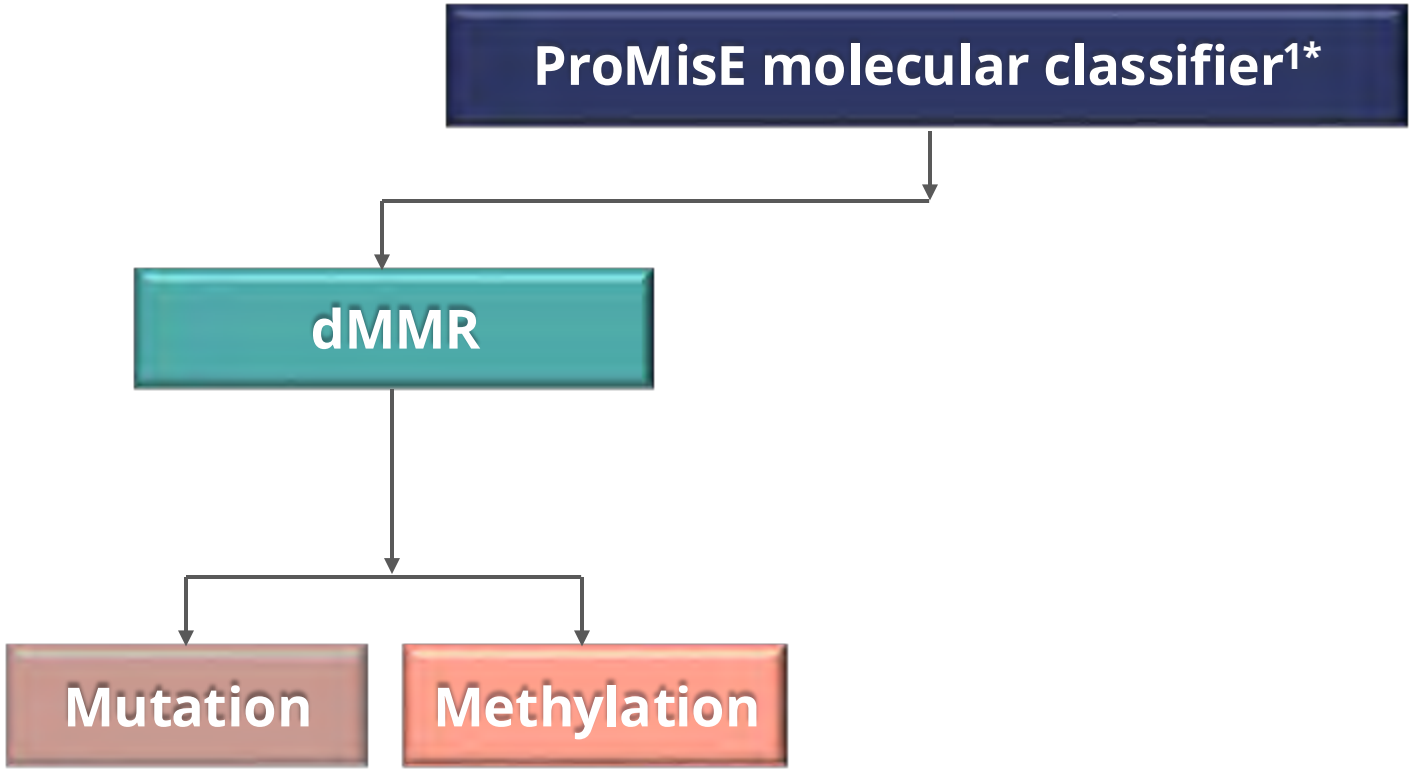
Paradigm-Shifting Data in EC Management

Name	EN6 RUBY Part 1[1]	EN7 ATTEND[2]	NRG-GY018[3]	EN11[4]	EN6 RUBY Part 2[5]	DUO-E[6]
Lead group Study chair	NSGO-CTU Mirza	MaNGO Colombo	NRG Eskander	BGOG Van Gorp	NSGO-CTU Mirza	GOG-P Westin
Investigational agent	Dosta + Chemo	Atezo + Chemo	Pembro + Chemo	Pembro + Chemo	Dosta + Nira + Chemo	Durva + Ola + Chemo
N	494	551	816	990	291	718
Concomitant	+	+	+	+	+	+
Maintenance	+	+	+		+	+
Readout	**NEJM 2023**	**ESMO 2023**	**NEJM 2023**	**Negative**	**SGO 2024**	**JCO 2023**

Paradigm-Shifting Data in EC Management

Name	EN6 RUBY Part 1[1]	EN7 ATTEND[2]	NRG-GY018[3]	EN11[4]	EN6 RUBY Part 2[5]	DUO-E[6]	EN9 LEAP-001[7]	EN15[8]	EN13[9] DOMENICA
Lead group Study chair	NSGO-CTU Mirza	MaNGO Colombo	NRG Eskander	BGOG Van Gorp	NSGO-CTU Mirza	GOG-P Westin	AGO-A Marth	GOG-P Slomovitz	GINECO Joly
Investigational agent	Dosta + Chemo	Atezo + Chemo	Pembro + Chemo	Pembro + Chemo	Dosta + Nira + Chemo	Durva + Ola + Chemo	Pembro + Lenva	Pembro	Dosta
N	494	551	816	990	291	718	842	350	260
Concomitant	+	+	+	+	+	+	Pembro + Lenva vs. Chemo	Pembro vs. Chemo	Dosta vs. Chemo
Maintenance	+	+	+		+	+			
Readout	**NEJM 2023**	**ESMO 2023**	**NEJM 2023**	**Negative**	**SGO 2024**	**JCO 2023**	**ESGO 2024**	?	?

Patient Characteristics in First-Line EC trials



dMMR = mismatch repair deficient; EC = endometrial cancer; HRneg = homologous recombinant deficient negative; HRpos = homologous recombinant deficient positive; MMRp = mismatch repair proficient; MSS = microsatellite stable; NSMP = non-specific molecular profile

Kommoss S, et al. *Ann Oncol*. 2018;29(5):1180–1188.

How to Treat dMMR Population ?

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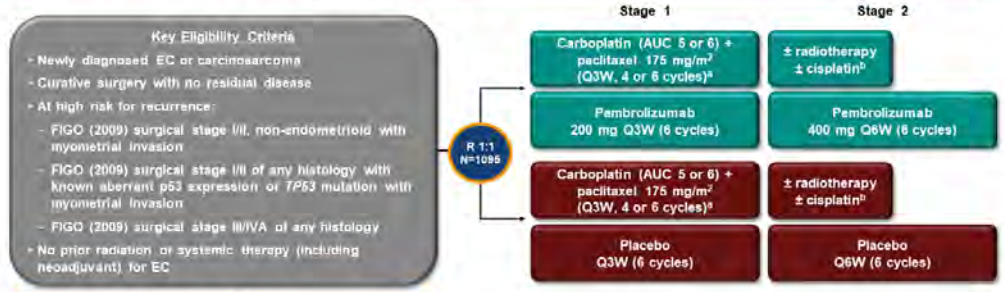
ENGOT-EN11/GOG-3053/KEYNOTE-B21 Study Design



[a]Chemotherapy was administered for 4 cycles in patients planned to receive chemoradiotherapy and 6 cycles for all other patients, including those planned for radiotherapy without radiosensitizing cisplatin. [b]Radiotherapy was optional at the discretion of the investigator, and cisplatin may have been given with EBRT as radiosensitizer; radiotherapy was started within 6 weeks after completion of carboplatin and paclitaxel (radiation may have been initiated during Stage 1 or Stage 2 depending on the number of cycles of chemotherapy that were administered).

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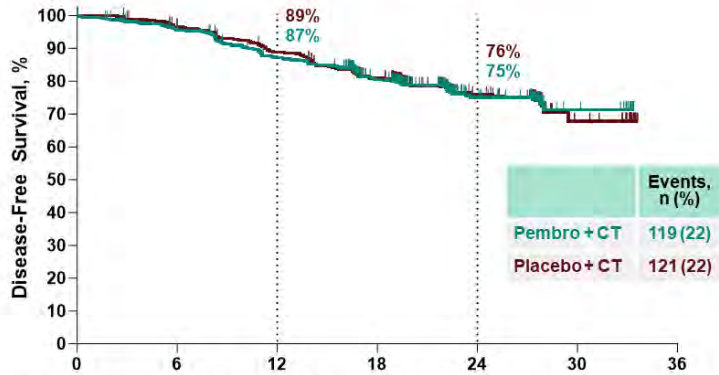
DFS[a] Similar Between Treatment Groups: ITT Population (Primary Endpoint)



	Events, n (%)	Median (95% CI), mo	HR (95% CI)	*P* value
Pembro + CT	119 (22)	NR (NR–NR)	1.02 (0.79–1.32)	0.570
Placebo + CT	121 (22)	NR (NR–NR)		

No. at risk							
Pembro + CT	545	505	452	347	134	27	0
Placebo + CT	550	515	470	358	132	23	0

[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.

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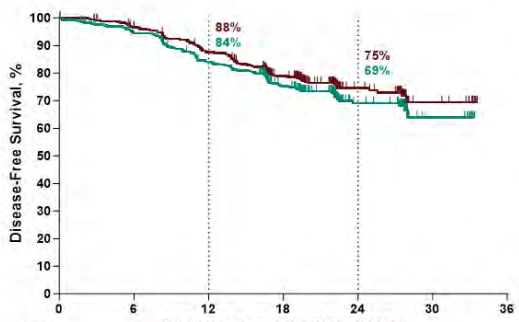
Pembrolizumab Plus Chemotherapy Improved DFS[a] in dMMR Subgroup

pMMR Subgroup

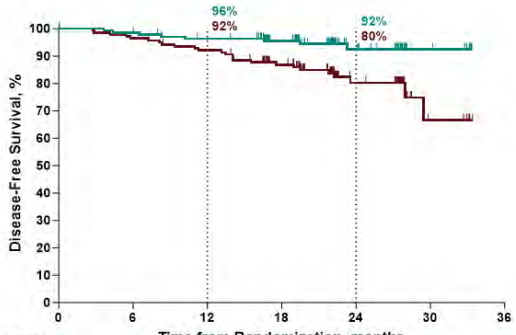
	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembro + CT	111 (27)	NR (NR–NR)	1.20 (0.91–1.57)
Placebo + CT	96 (23)	NR (NR–NR)	



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)	

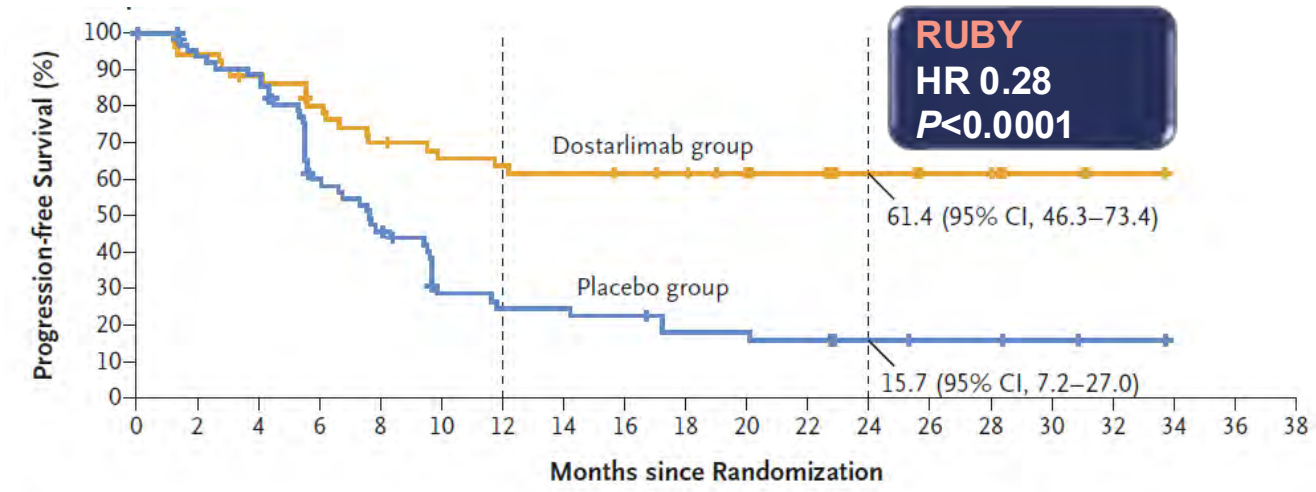


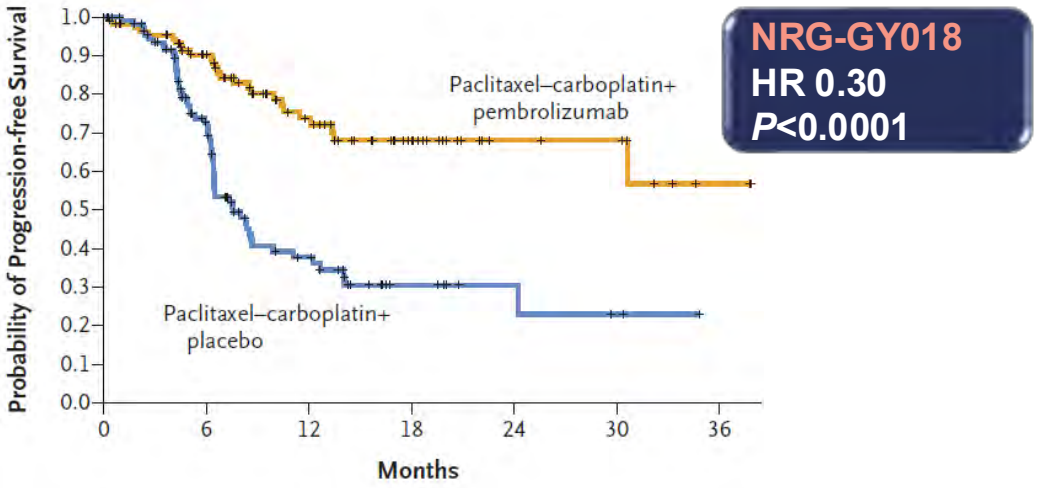
No. at risk							
Pembro + CT	141	136	129	103	46	10	0
Placebo + CT	140	134	127	99	38	7	0

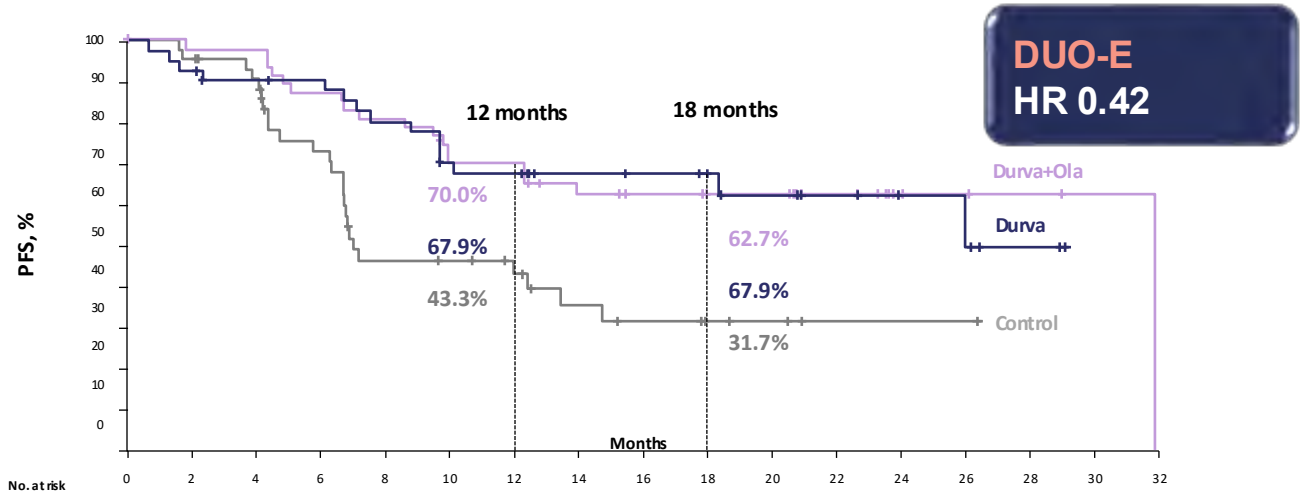
[a]DFS was defined as the time from randomization to local or distant recurrence of EC (assessed radiographically by the investigator or by histopathologic confirmation) or death from any cause.
Data cutoff date: March 4, 2024.

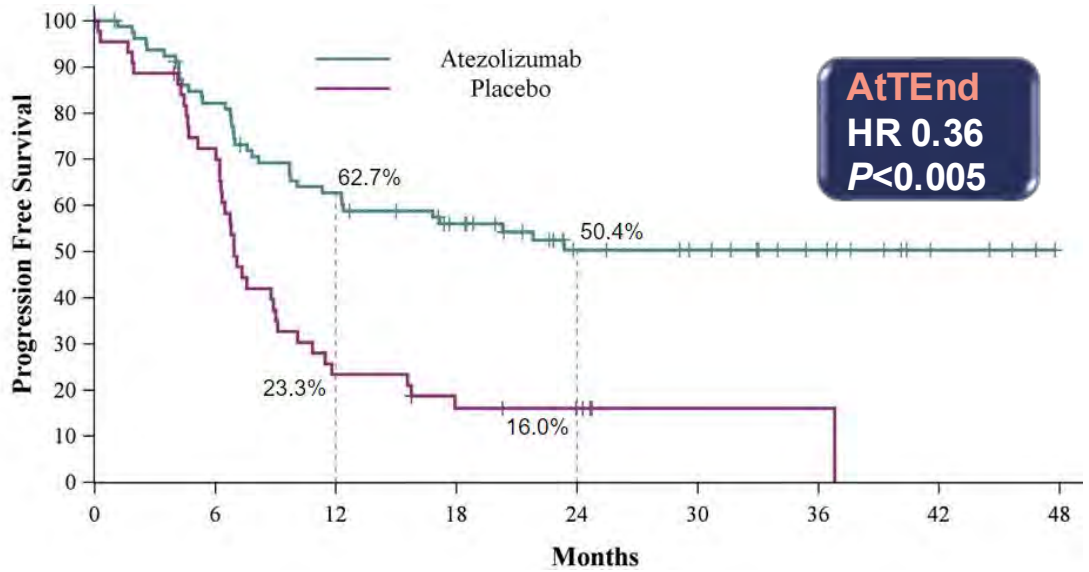
NSGO-CTU Rigshospitalet ENGOT ESGO

ICI in Endometrial Cancer: PFS in dMMR Tumors







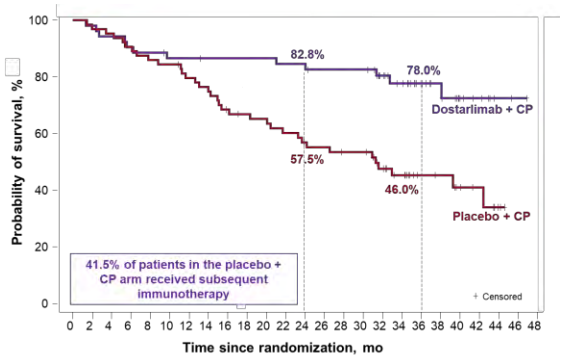


1. Mirza MR, et al. *N Engl J Med.* 2023;388(23):2145-2158. doi:10.1056/nejmoa2216334; 2. Eskander RN, et al. *N Engl J Med.* 2023;388(23):2159-2170. doi:10.1056/NEJMoa2302312; 3. Westin SN, et al. *J Clin Oncol.* 2024;42(3):283-299. doi: 10.1200/JCO.23.02132; 4. Colombo N, et al. *Lancet Oncol.* 2024,Sep;25(9):1135-1146. doi: 10.1016/S1470-2045(24)00334-6.

dMMR EC

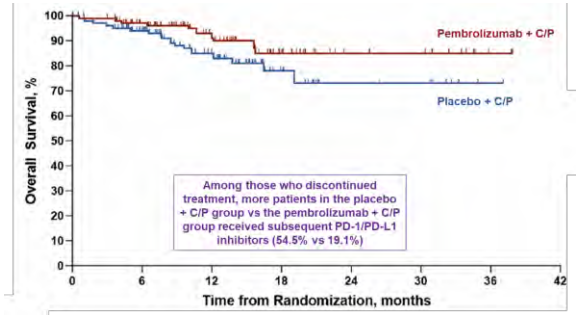
Substantial and unprecedented PFS and OS benefit of ICI + chemotherapy

EN6-RUBY Part 1[1-3]



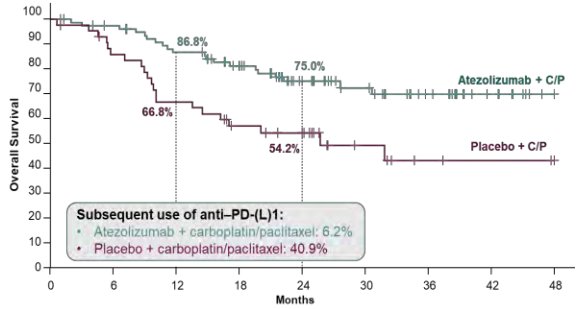
OS Data	Events, %	Median (95% CI), mo
Dostarlimab + C/P	22.6	NE (NE-NE)
Placebo + C/P	53.8	31.4 (20.3-NE)
OS data maturity	39.8%	
Median follow-up, mo	36.6	

NRG-GY018[4-5]



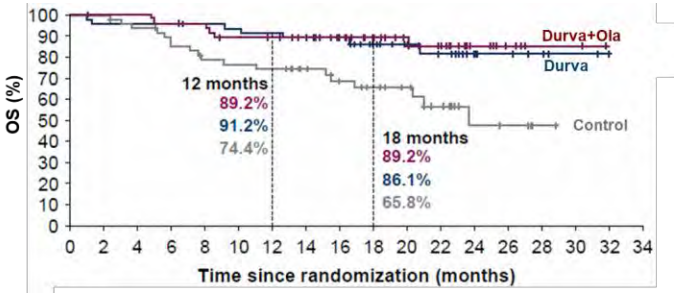
OS Data	Events, %	Median (95% CI), mo
Pembrolizumab + C/P	9.1	NR (NR-NR)
Placebo + C/P	15.1	NR (NR-NR)
OS data maturity	18%	
Median follow-up, mo	13.3-13.7	

EN7-AtTEnd[6]



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

DUO-E[7,8]



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

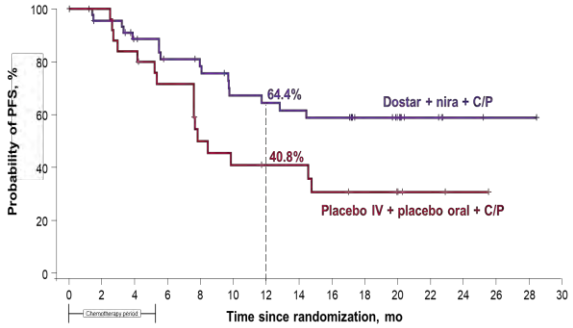
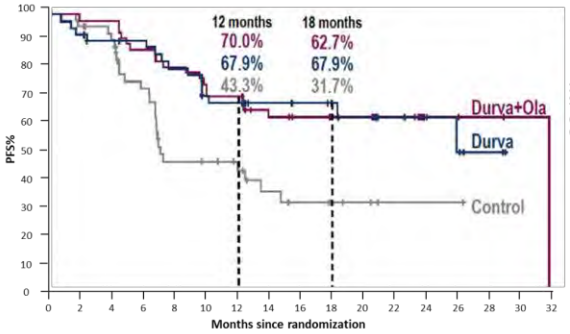
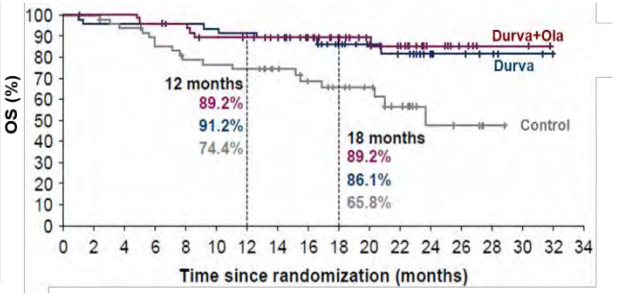
PFS	**HR 0.28** (95% CI, 0.16-0.50); P<0.001	**HR 0.30** (95% CI, 0.19-0.48); P<0.001	**HR 0.36** (95% CI, 0.23-0.57); P=0.0005	**HR 0.42** (95% CI, 0.22-0.80); Durva + C/P arm
OS	**HR 0.32** (95% CI, 0.17-0.63); Nominal P=0.0002	**HR 0.55** (95% CI, 0.25-1.19)	**HR 0.41** (95% CI, 0.22-0.76)	**HR 0.34**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

dMMR = mismatch repair deficient; MSI-H = microsatellite instability-high; PFS = progression free survival; OS = overall survival.

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

No Additional Benefit of PARPi in dMMR EC

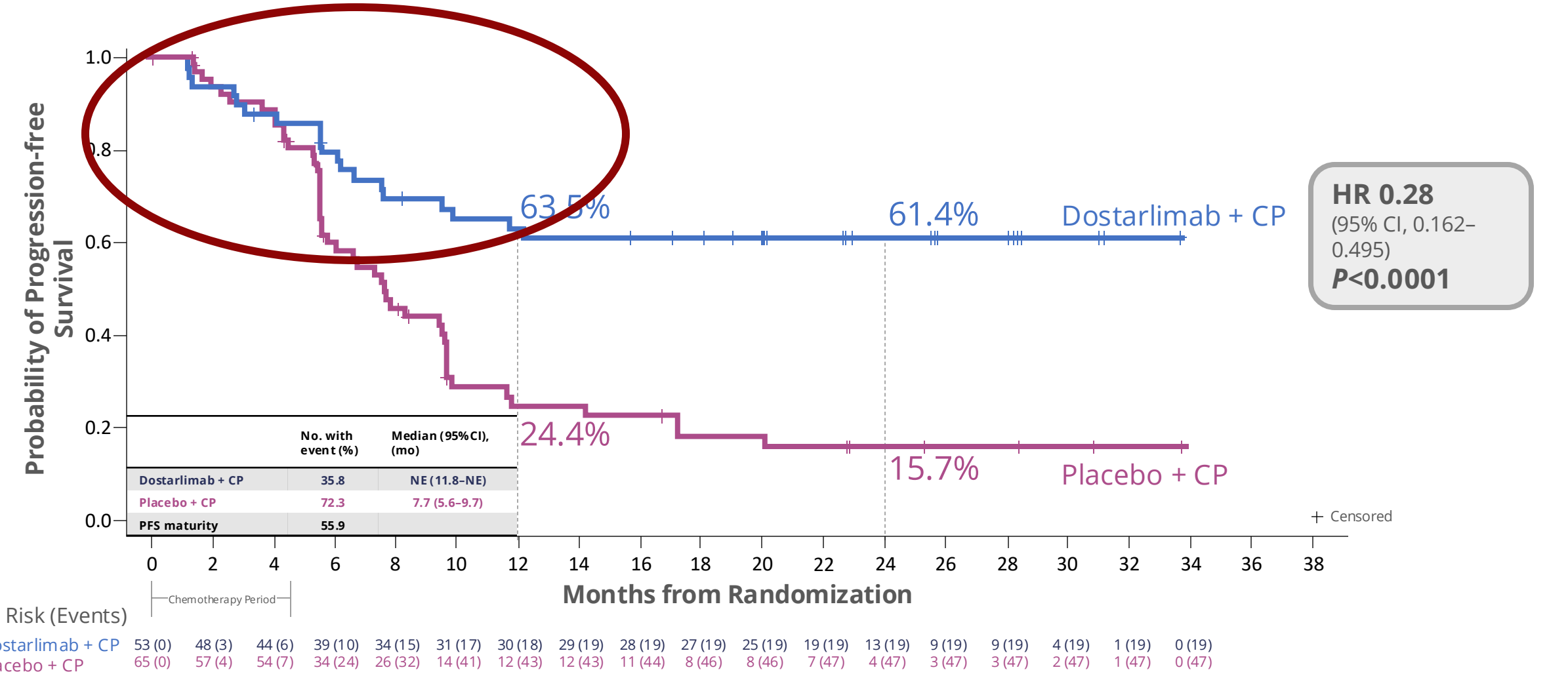
The effect is predominantly driven by anti-PD-(L)1

EN6-RUBY Part 2[1]		DUO-E[2,3]	
PFS	**OS**	**PFS**	**OS**
	Not mature*		
HR 0.48 (95% CI, 0.27-0.96); *Nominal P*<0.0174 Dostar+Nira+C/P arm	**HR 0.28** (95% CI, 0.16-0.50); *P*<0.001 Dostar+C/P arm	Not mature	**HR 0.33** (95% CI, 0.17-0.63); *Nominal P*=0.0002 Dostar+C/P arm
HR 0.41 (95% CI, 0.21-0.75); Durva+Ola+C/P arm	**HR 0.42** (95% CI, 0.22-0.80) Durva+C/P arm	**HR 0.28** (95% CI, 0.10-0.68); *Durva+Ola+C/P arm*	**HR 0.34** (95% CI, 0.13-0.79); *Durva+C/P arm*

dMMR = mismatch repair deficient; MSI-H = microsatellite instability-high; OS = overall survival.

1. Mirza MR, et al. Presented at: Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer 2024. Presentation #LBA2.; 2. Westin SN, et al. J Clin Oncol. 2023; DOI: 10.1200/JCO.23.02132; 3. Baurain JF, et al. Presented at: SGO Annual Meeting on Women's Cancer 2024. Scientific Plenary V.

Why Do 1/3 Patients Progress Within First 12 Months ?



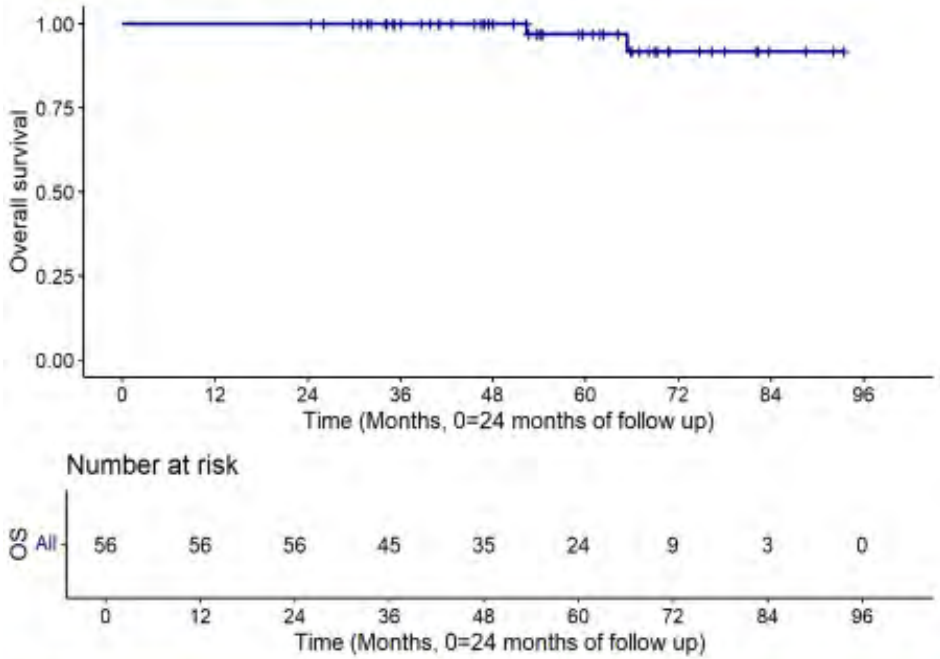
[a]*Median duration of follow-up 24.79 months.*
CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; PFS, progression-free survival.

What Should be the Duration of ICI?

PFS in dMMR Tumors

Figure 3. sOS in the overall cohort of MMRd r/mEC pts with Extended Clinical Benefit (ECB form ICIs

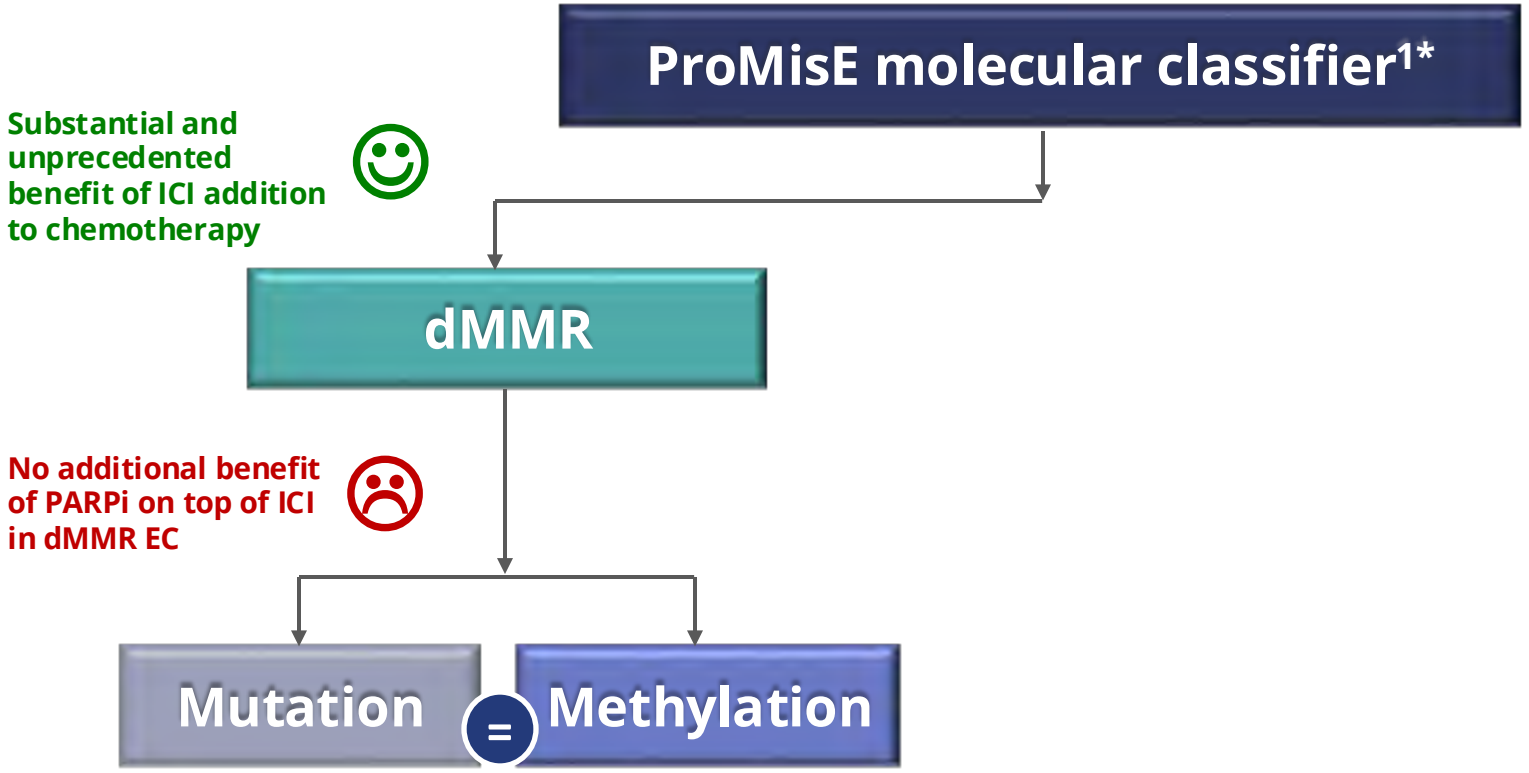
Timepoint	12 m	24 m	36 m
sOS rate (%) (95%CI; %)	100 (100 - 100)	100 (100 - 100)	100 (100 - 100)



Among pts with MMRd r/m EC with ECB from ICIs, long-term OS rates are notably high

Grau Bejar JF, et al. Presented at: European Society for Medical Oncology (ESMO) Annual Meeting; September 13-17; Barcelona, Spain; 736P.

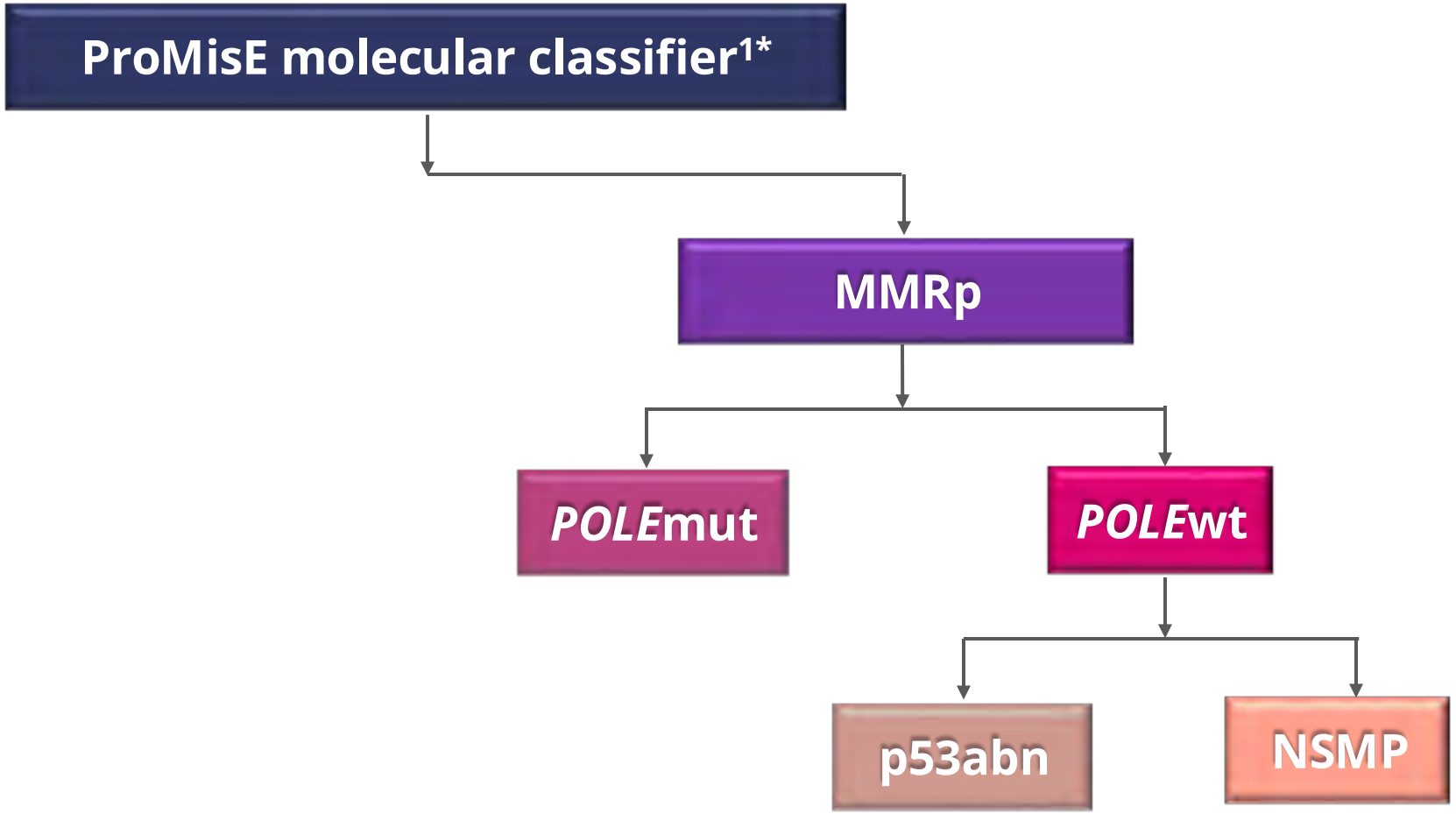
Patient Characteristics in First-Line EC Trials



dMMR = mismatch repair deficient; EC = endometrial cancer; HRneg = homologous recombinant deficient negative; HRpos = homologous recombinant deficient positive; MMRp = mismatch repair proficient; MSS = microsatellite stable; NSMP = non-specific molecular profile

1. Mirza MR, et al. *N Engl J Med*. 2023;388:2145-2158; 2. Mirza MR, et al. *Ann Oncol.* 2023;34:500-501; 3. Eskander RN, et al. *N Engl J Med*. 2023;388:2159-2170. 4. Eskander RN, et al. Presented at: SGO; March 25-28 2023; Tampa, FL, USA. 5. Arend RC, et al. Presented at: SGO; March 25-28, 2023; Tampa, FL, USA.; 6. Colombo N, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40; 7. Westin SN, et al. *J Clin Oncol*. 2023; doi: 10.1200/JCO.23.02132.

Patient Characteristics in First-Line EC Trials



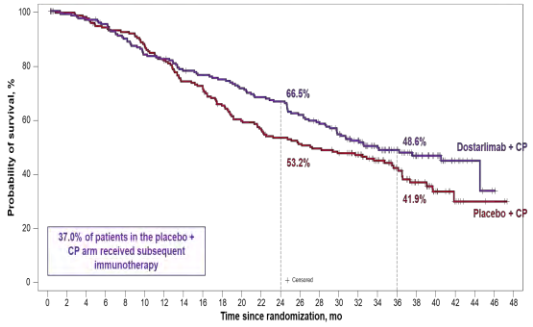
dMMR = mismatch repair deficient; EC = endometrial cancer; HRneg = homologous recombinant deficient negative; HRpos = homologous recombinant deficient positive; MMRp = mismatch repair proficient; MSS = microsatellite stable; NSMP = non-specific molecular profile

Kommoss S, et al. *Ann Oncol.* 2018;29(5):1180–1188.

MMRp EC

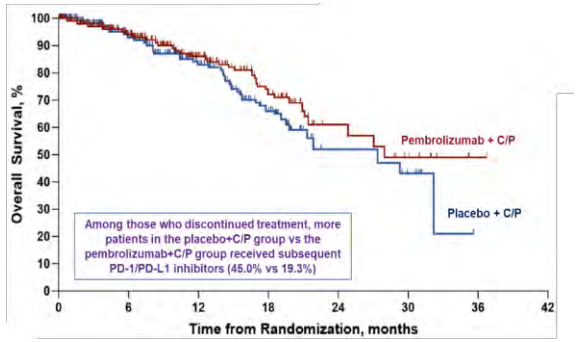
Clinically meaningful PFS and OS benefit of ICI + chemotherapy

EN6-RUBY Part 1[1-3]



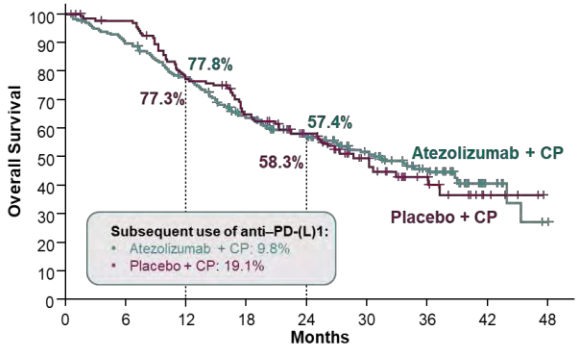
OS Data	Events, %	Median (95% CI), mo
Dostarlimab + C/P	50.5	34.0 (28.6-NE)
Placebo + C/P	59.2	27.0 (21.5-35.6)
OS data maturity	54.8%	
Median follow-up, mo	37.5	

NRG-GY018[4-5]



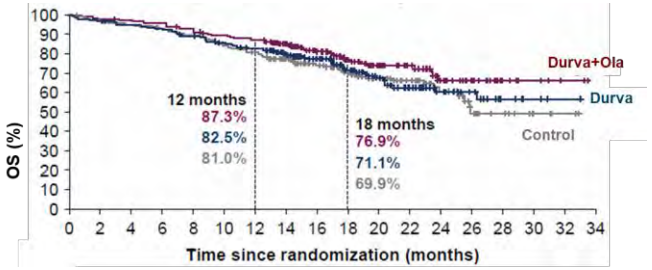
OS Data	Events, %	Median (95% CI), mo
Pembrolizumab + C/P	15.3	28.0 (21.4-NR)
Placebo + C/P	18.3	27.4 (19.5-NR)
OS data maturity	27.2%	
Median follow-up, mo	8.4-8.8	

EN7-AtTEnd[6]



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

DUO-E[7,8]



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

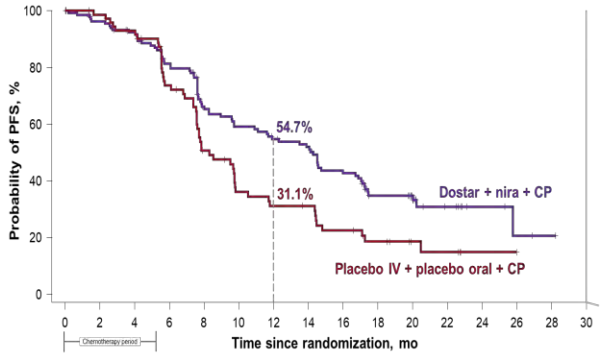
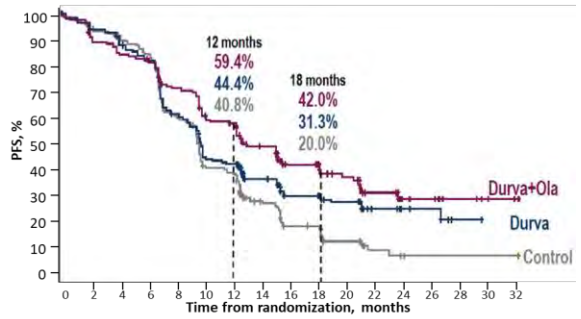
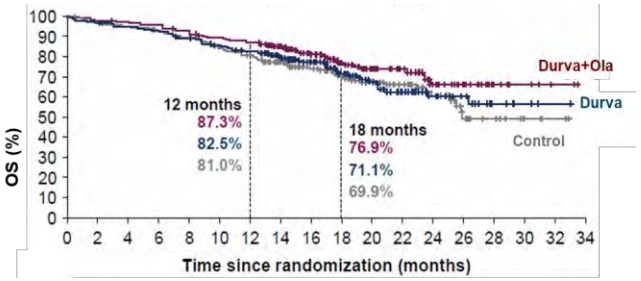
PFS	**HR 0.76** (95% CI, 0.59-0.98);	**HR 0.54** (95% CI, 0.41-0.71); P<0.001	**HR 0.92** (95% CI, 0.73-1.16);	**HR 0.77** (95% CI, 0.60-0.97); Durva + C/P arm
OS	**HR 0.79** (95% CI, 0.60-1.04); Nominal p=0.0493	**HR 0.79** (95% CI, 0.53-1.17) Nominal p=0.1157	**HR 1.00** (95% CI, 0.74-1.35)	**HR 0.91**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

MSS = microsatellite stable; pMMR = mismatch repair proficient; OS = overall survival.

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

Potential Benefit of PARPi In Addition to ICI + chemotherapy in MMRp EC

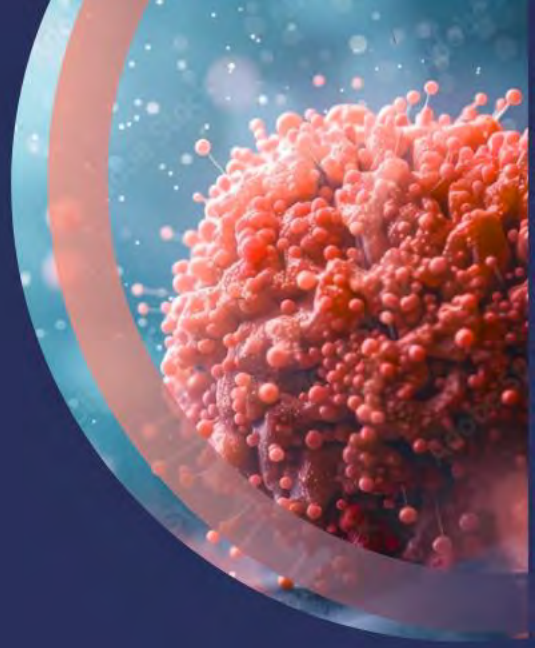
More analysis needed to identify which subgroup derives the most benefit

EN6-RUBY Part 2[1]		DUO-E[2,3]	
PFS	**OS**	**PFS**	**OS**
	Not mature*		
HR 0.63 (95% CI, 0.44-0.91); P=0.0060 Dostar+Nira+C/P arm	**HR 0.76** (95% CI, 0.59-0.98); Dostar+C/P arm	Not mature	**HR 0.79** (95% CI, 0.60-1.04); Nominal P=0.0493 Doster+C/P arm
HR 0.57 (95% CI, 0.44-0.73); Durva+Ola+C/P arm	**HR 0.77** (95% CI, 0.60-0.97) Durva+C/P arm	**HR 0.69** (95% CI, 0.47-1.00); Durva+Ola+C/P arm	**HR 0.91** (95% CI, 0.64-1.30); Durva+C/P arm

MSS = microsatellite stable; pMMR = mismatch repair proficient; OS = overall survival.

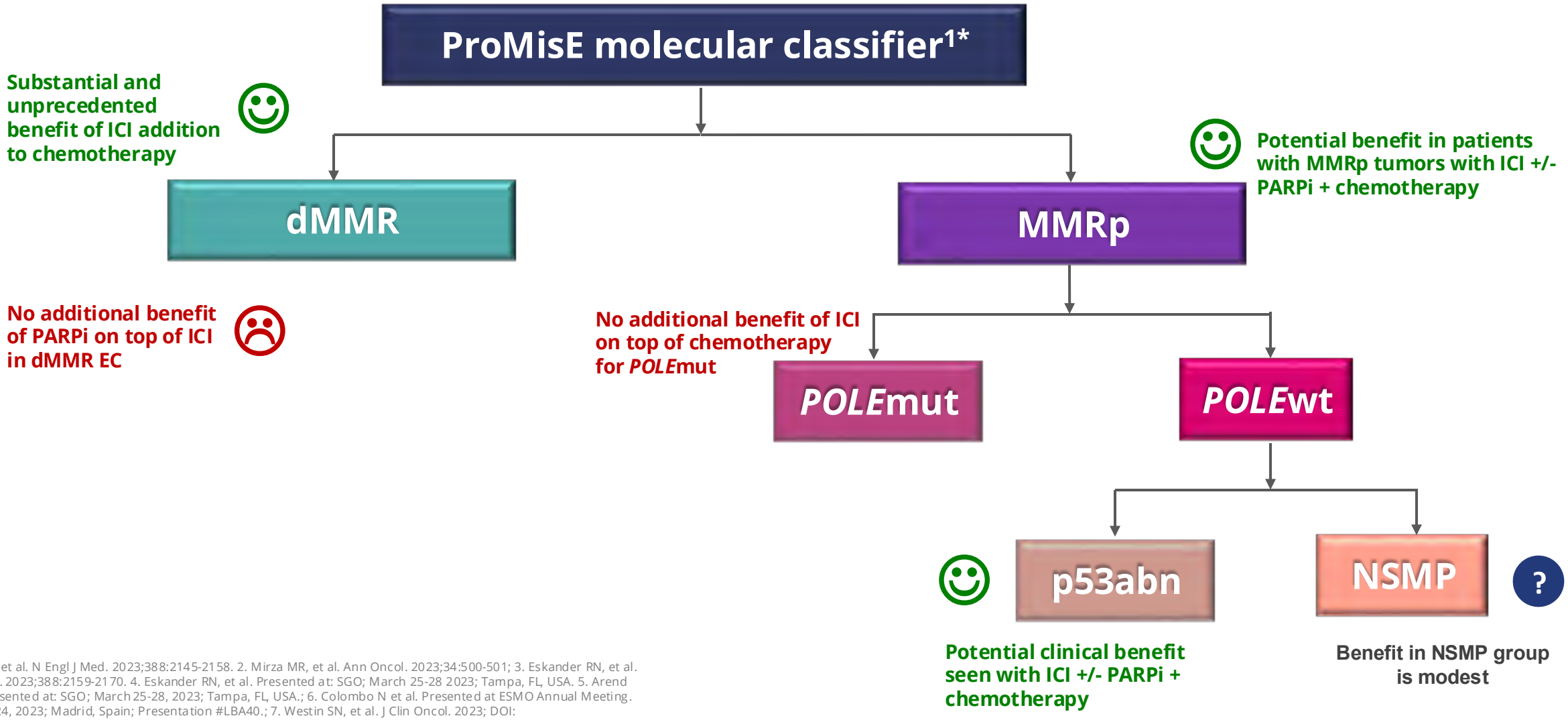
1. Mirza MR, et al. *N Engl J Med.* 2023;388:2145-2158. 2. Mirza MR, et al. *Ann Oncol.* 2023;34:500-501; 3. Eskander RN, et al. *N Engl J Med.* 2023;388:2159-2170. 4. Eskander RN, et al. Presented at: SGO; March 25-28 2023; Tampa, FL, USA. 5. Arend RC, et al. Presented at: SGO; March 25-28, 2023; Tampa,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

Which MMRp EC Patients May Benefit From ICI + Chemotherapy (±) PARPi?



EC, endometrial cancer; ICI, immune checkpoint inhibitor; MMRp, mismatch repair proficient; PARPi, Poly (ADP-ribose) polymerase inhibitor.

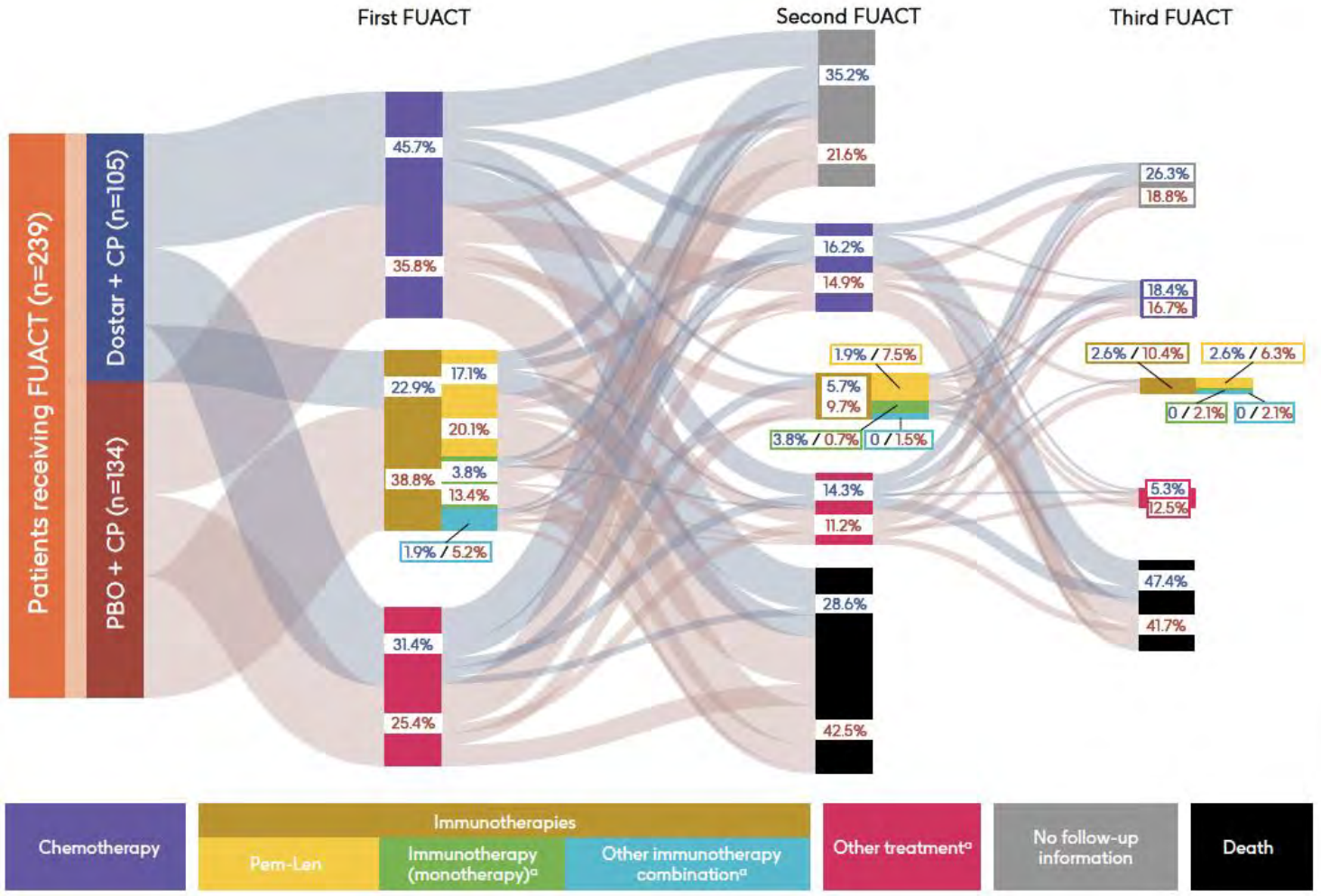
Patient Characteristics in First-Line EC Trials

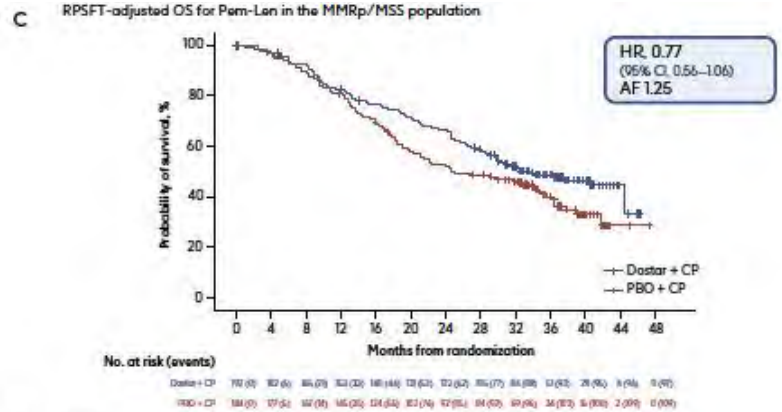


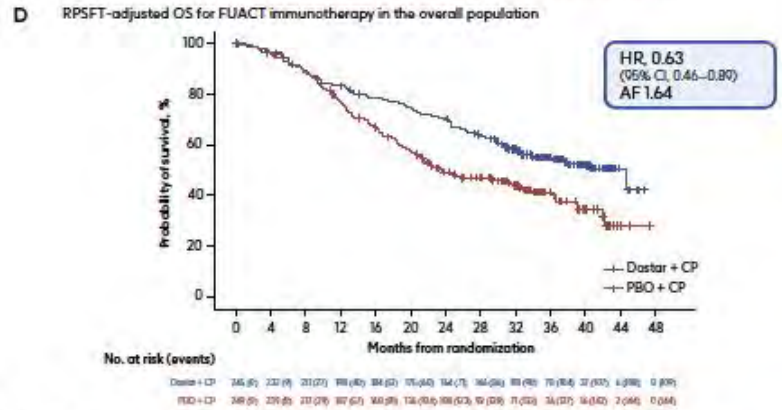
1. Mirza MR, et al. N Engl J Med. 2023;388:2145-2158. 2. Mirza MR, et al. Ann Oncol. 2023;34:500-501; 3. Eskander RN, et al. N Engl J Med. 2023;388:2159-2170. 4. Eskander RN, et al. Presented at: SGO; March 25-28 2023; Tampa, FL, USA. 5. Arend RC, et al. Presented at: SGO; March 25-28, 2023; Tampa, FL, USA.; 6. Colombo N et al. Presented at ESMO Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.; 7. Westin SN, et al. J Clin Oncol. 2023; DOI: 10.1200/JCO.23.02132.; 6. Powell MA, et al. Presented at the SGO Annual Meeting 2024. Presentation #LBA1; 7. Eskander RN, et al. Presented at the SGO Annual Meeting 2024. Presentation #LBA2; 8. Baurain JF, et al. Presented at the SGO Annual Meeting 2024. Scientific Plenary V; 9. Mirza MR, et al. Presented at the SGO Annual Meeting 2024. Presentation #LBA2

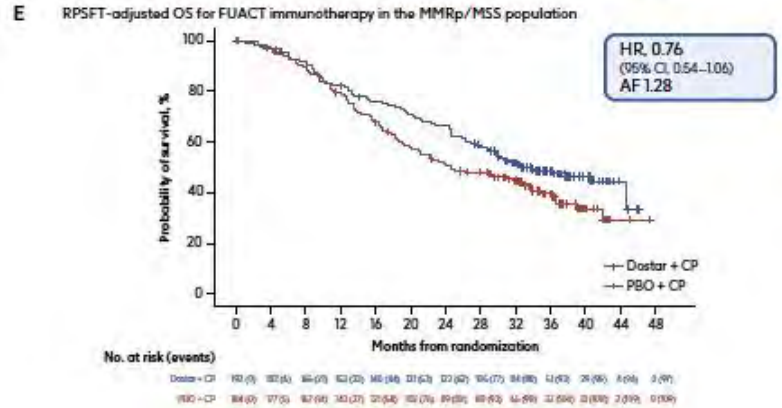
ICI Upfront or After Relapse?

FUACT in the MMRp/MSS populations









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

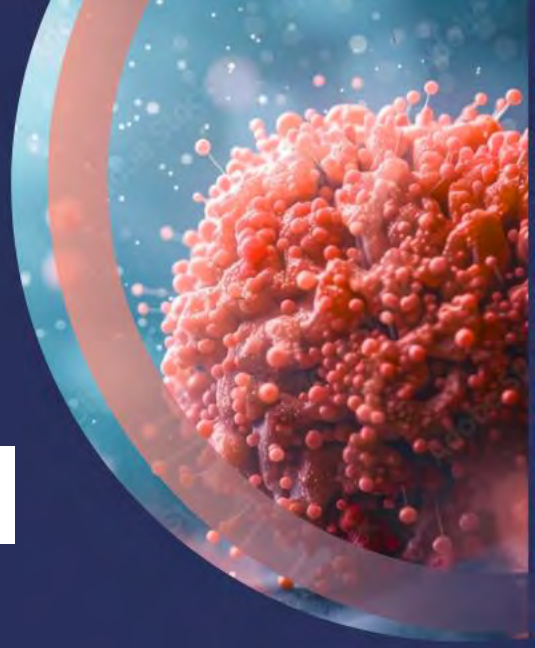
Mirza MR et al. ESMO 2024; 731P,

Safety
Example: DUO-E

AEs, n (%)	Overall (chemotherapy + maintenance phase)			Maintenance phase only		
	Control (N=236)	Durva (N=235)	Durva+Ola (N=238)	Control (N=169)	Durva (N=183)	Durva+Ola (N=192)
Any AEs	236 (100.0)	232 (98.7)	237 (99.6)	143 (84.6)	158 (86.3)	184 (95.8)
Grade ≥3 AEs	133 (56.4)	129 (54.9)	160 (67.2)	28 (16.6)	30 (16.4)	79 (41.1)
Serious AEs	73 (30.9)	73 (31.1)	85 (35.7)	19 (11.2)	22 (12.0)	42 (21.9)
AEs with outcome of death	8 (3.4)	4 (1.7)	5 (2.1)	2 (1.2)	0	3 (1.6)
AEs of special interest to olaparib						
MDS/AML*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New primary malignancies*	3 (1.3)	1 (0.4)[§]	2 (0.8)	2 (1.2)	1 (0.5)[§]	1 (0.5)
Pneumonitis[†]	1 (0.4)	4 (1.7)	12 (5.0)	0	3 (1.6)	8 (4.2)
Any immune-mediated AEs[‡]	16 (6.8)	66 (28.1)	56 (23.5)	6 (3.6)	27 (14.8)	27 (14.1)
AEs leading to discontinuation of study treatment	44 (18.6)	49 (20.9)	58 (24.4)	7 (4.1)	11 (6.0)	27 (14.1)
AEs leading to discontinuation of carboplatin/paclitaxel	32 (13.6)	31 (13.2)	31 (13.0)	–	–	–
AEs leading to discontinuation of durvalumab/placebo	19 (8.1)	26 (11.1)	22 (9.2)	4 (2.4)	9 (4.9)	16 (8.3)
AEs leading to discontinuation of olaparib/placebo	5 (2.1)	11 (4.7)	21 (8.8)	5 (3.0)	10 (5.5)	21 (10.9)
AEs leading to dose interruption/delay of study treatment[‖]	118 (50.0)	128 (54.5)	164 (68.9)	37 (21.9)	52 (28.4)	113 (58.9)
AEs leading to dose reduction of olaparib/placebo	5 (2.1)	14 (6.0)	65 (27.3)	4 (2.4)	13 (7.1)	63 (32.8)

Includes AEs with onset or worsening on or after the date of first dose of durvalumab/placebo or olaparib/placebo (overall) or first dose of olaparib/placebo (maintenance phase) until initiation of the first subsequent anticancer therapy following last dose of study treatment or until the end of the safety follow-up period, whichever occurs first. AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). *MDS/AML and new primary malignancies include AEs from first dose of investigational product (durvalumab/olaparib/placebo) until the end of the study (includes cases reported beyond the safety follow-up period); [†]Grouped term: includes pneumonitis, bronchiolitis, and interstitial lung disease; [‡]As assessed by the investigator, and programmatically derived from individual causality assessments for combination studies. Missing responses are counted as related; [§]Excludes one event of basal cell carcinoma; [‖]For durvalumab/placebo, this includes dose interruption during infusion as well as doses that were skipped or delayed. AE, adverse event; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome.

Westin SN, et al. *J Clin Oncol*. 2023; DOI: 10.1200/JCO.23.02132



Can We Replace Conventional Chemotherapy with ICI Alone or ICI + VEGFi?

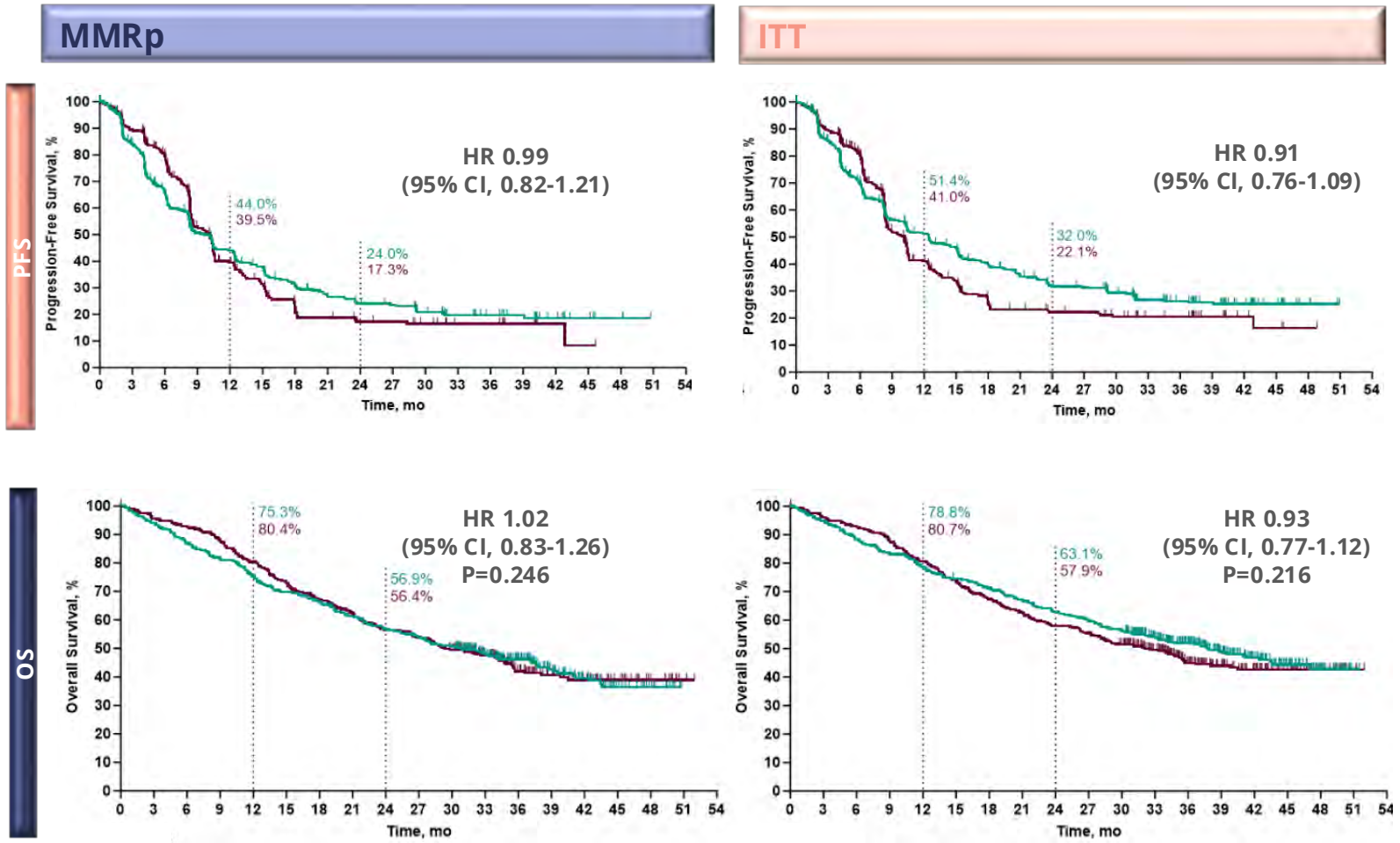
ICI, immune checkpoint inhibitor; VEGFi, vascular endothelial growth factor inhibitor.

Paradigm-Shifting Data in EC Management

Name	EN6 RUBY Part 1[1]	EN7 ATTEND[2]	NRG-GY018[3]	EN11[4]	EN6 RUBY Part 2[5]	DUO-E[6]	EN9 LEAP-001[7]	EN15[8]	EN13[9] DOMENICA
Lead group Study chair	NSGO-CTU Mirza	MaNGO Colombo	NRG Eskander	BGOG Van Gorp	NSGO-CTU Mirza	GOG-P Westin	AGO-A Marth	GOG-P Slomowitz	GINECO Joly
Investigational agent	Dosta + Chemo	Atezo + Chemo	Pembro + Chemo	Pembro + Chemo	Dosta + Nira + Chemo	Durva + Ola + Chemo	Pembro + Lenva	Pembro	Dosta
N	494	551	816	990	291	718	842	350	260
Concomitant	+	+	+	+	+	+	Pembro + Lenva vs. Chemo	Pembro vs. Chemo	Dosta vs. Chemo
Maintenance	+	+	+		+	+			
Readout	**NEJM 2023**	**ESMO 2023**	**NEJM 2023**	**Negative**	**SGO 2024**	**JCO 2023**	**ESGO 2024**	?	?
☺*	**Statistically significant PFS dMMR[1] & ITT[1], OS ITT[10]**	**Statistically significant PFS dMMR and ITT[2]**	**Statistically significant PFS dMMR and MMRp[11]**	?	**Statistically significant PFS ITT and PFS MMRp[5]**	**Statistically significant PFS ITT for Durva and Durva + Ola[12]**		?	?
☹*	**Not powered for MMRp**	**OS immature**	**Not powered for OS**	?	**Chemo + ICI arm is missing OS immature**	**Not powered for ICI+chemo +/- PARPi Not powered for MMRp or dMMR**	**Negative for both PFS & OS for MMRp & ITT**	**Chemo + ICI arm is missing**	**Chemo + ICI arm is missing**

LEAP-001: Lenvatinib + Pembrolizumab vs Chemotherapy

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



Other Chemotherapy-Free ICI Trials in Primary Advanced/Recurrent EC

	DOMENICA | ENGOT-EN13[1]	KEYNOTE-C93 | ENGOT-EN15[2,3]	LEAP-001 | ENGOT-EN9[4–6]
Investigational agent	Dostarlimab	Pembrolizumab	Pembrolizumab + Lenvatinib
Patient population	dMMR	dMMR	MMRp
Study status	Recruitment ongoing	Recruitment complete	Results announced
Lead group **Study chair**	GINECO Joly	MITO[7] Slomovitz	AGO-A[8] Marth
Treatment	• Dostarlimab • Carboplatin-paclitaxel	• Pembrolizumab • Carboplatin-paclitaxel	• Pembrolizumab + Lenvatinib • Carboplatin-paclitaxel
N	260	280	842
Primary endpoint	PFS (BICR)	PFS (BICR)/ OS	PFS (BICR)/ OS

Key Takeaways

- Molecular profiling of this disease has completely transformed our therapeutic approach
- **ICI + C/P is the new standard of care for patients with advanced/recurrent endometrial cancer**
- **However,** this is just the beginning of an unprecedented improvement in the outcome of our patients. We need to understand:
  - Which are the dMMR patients that do not benefit from ICI + chemotherapy?
  - Can we replace chemotherapy in dMMR patients in view of ICI-only treatment? And in which patients?
  - How to treat patients who experience relapse post-chemotherapy + immunotherapy?
  - How do we further validate the prognostic value of molecular subgroups for identifying those patients who will benefit the most?
  - What are the predictive biomarkers to understand which patients benefit most from PARPi addition to ICI in MMRp EC?

BioMarkers in Focus: Exploring ICI, PARPi, and Others Role in the Treatment of Endometrial Cancer

Isabelle Ray-Coquard, MD, PhD

Centre Leon Berard
Lyon, France

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Predictive Biomarkers in EC

Established

- **dMMR/MSI-H** for the use of anti-PD(L)1[1,2,3]
- **HER2** for the use of anti-HER2 therapies[8-10]

Exploratory

- **HRR/HRD status** for the use of PARPi[4,5]
- **P53 status** for the use of IO or PARPi[6]
- **PDL1 status** for IO or IO + PARPi[5]
- **TMB status** for the use of IO[7]
- **ER/PR status** for response to endocrine therapies[11]

Investigational Actionable Targets

- **TROP2**[10]
- **Folate Receptor a**[10]
- **MDM2**
- **B7H4**

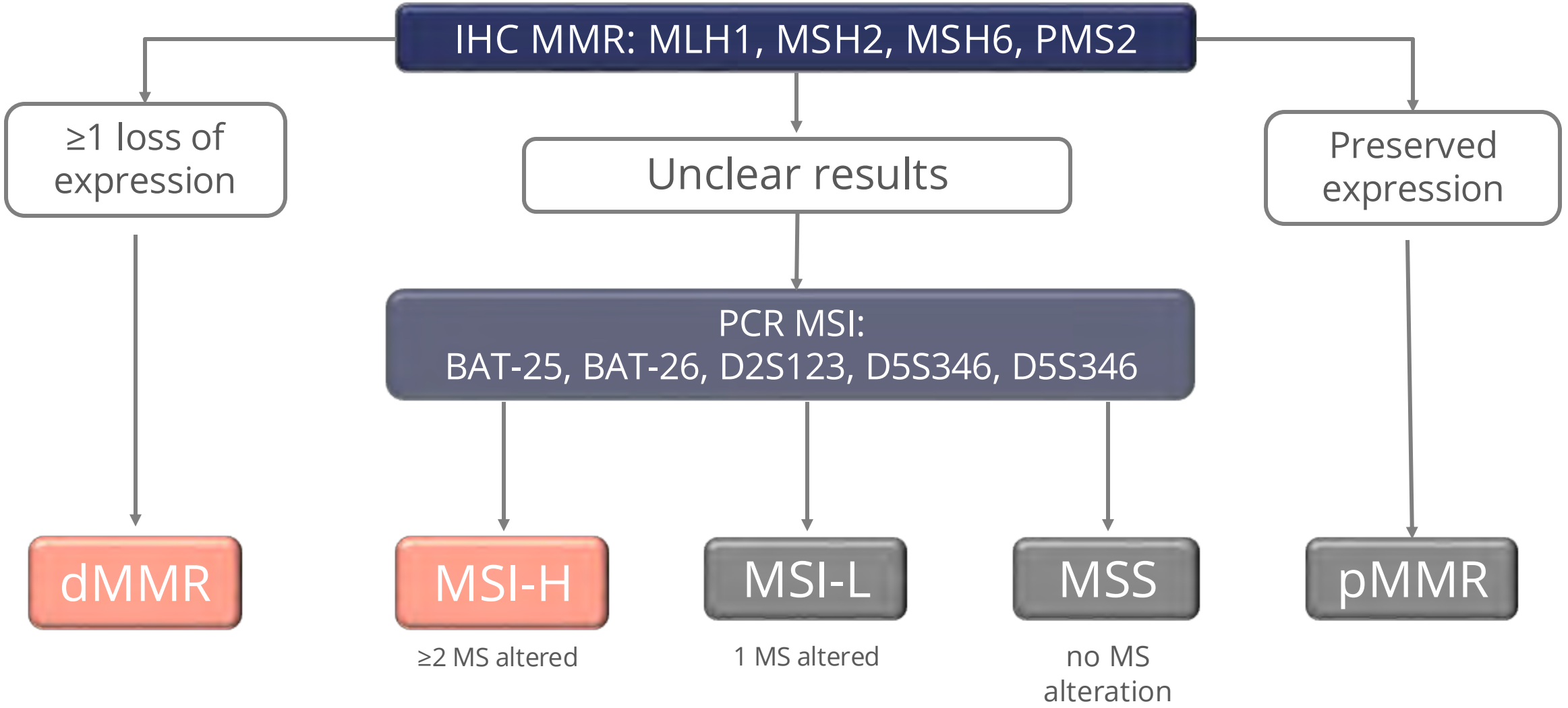
Mismatch Repair Deficiency/High Microsatellite Instability (dMMR/MSI-H) Status

Methods (CAP1, ASCO2): IHC, PCR, NGS

- For patients with EC being considered for ICI therapy, pathologists should use MMR-IHC over MSI by PCR or NGS for the detection of DNA mismatch repair defects
- TMB should not be used as a surrogate of dMMR

1. Bartley et al. Arch Pathol Lab Med 2022; 146:1194-210; 2. Vikas et al. J Clin Oncol 2022;41:1943-8

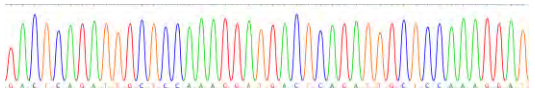
dMMR/MSI-H Testing for EC



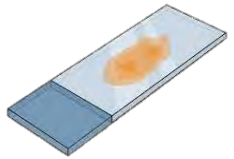
Noh et al. Cancer Res Treat 2022;54:1200-8

MSI vs dMMR in EC

- **subclonal loss of MMR protein expression (n=18)**
- **MSS or MSI-low cases with dMMR (n= 20)**
- **MSI-low or MSI-high with pMMR (n=3)**

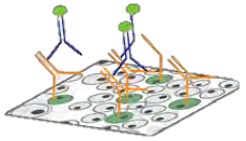


MSI
pentaplex panel

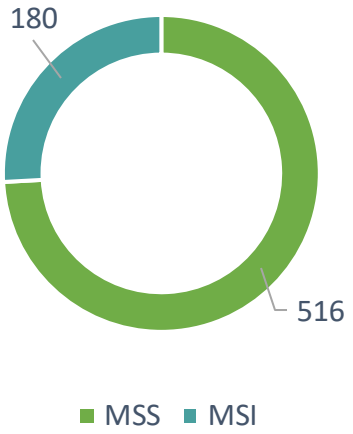


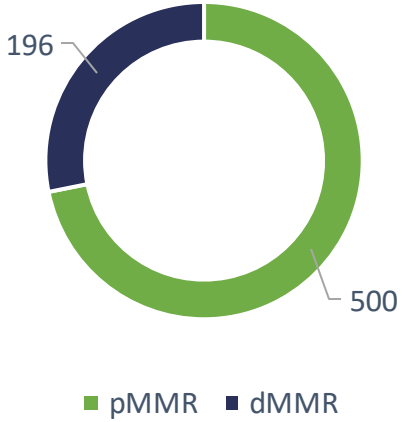
696

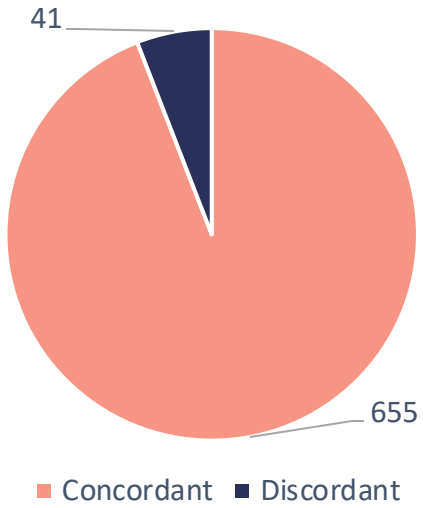
ENDOMETRIAL CARCINOMAS (from PORTEC-1 and PORTEC-2 trials)



MMR protein expression
MLH1, PMS2, MSH2, and MSH6







6% Discordance

- Most of these cases could be explained by M**LH1 promoter hypermethylation**
- 5/7 cases with solitary loss of PMS2 or MSH6 protein expression carried somatic gene variants
- 2 MSI-high cases with retained MMR protein expression carried a POLE-EDM variant
- Clonal heterogeneity in MMR expression to variable epitope expression or variable MLH1 methylation/second-hit mutation. Or variable tumor differentiation (e.g., mucinous or poorly differentiated)

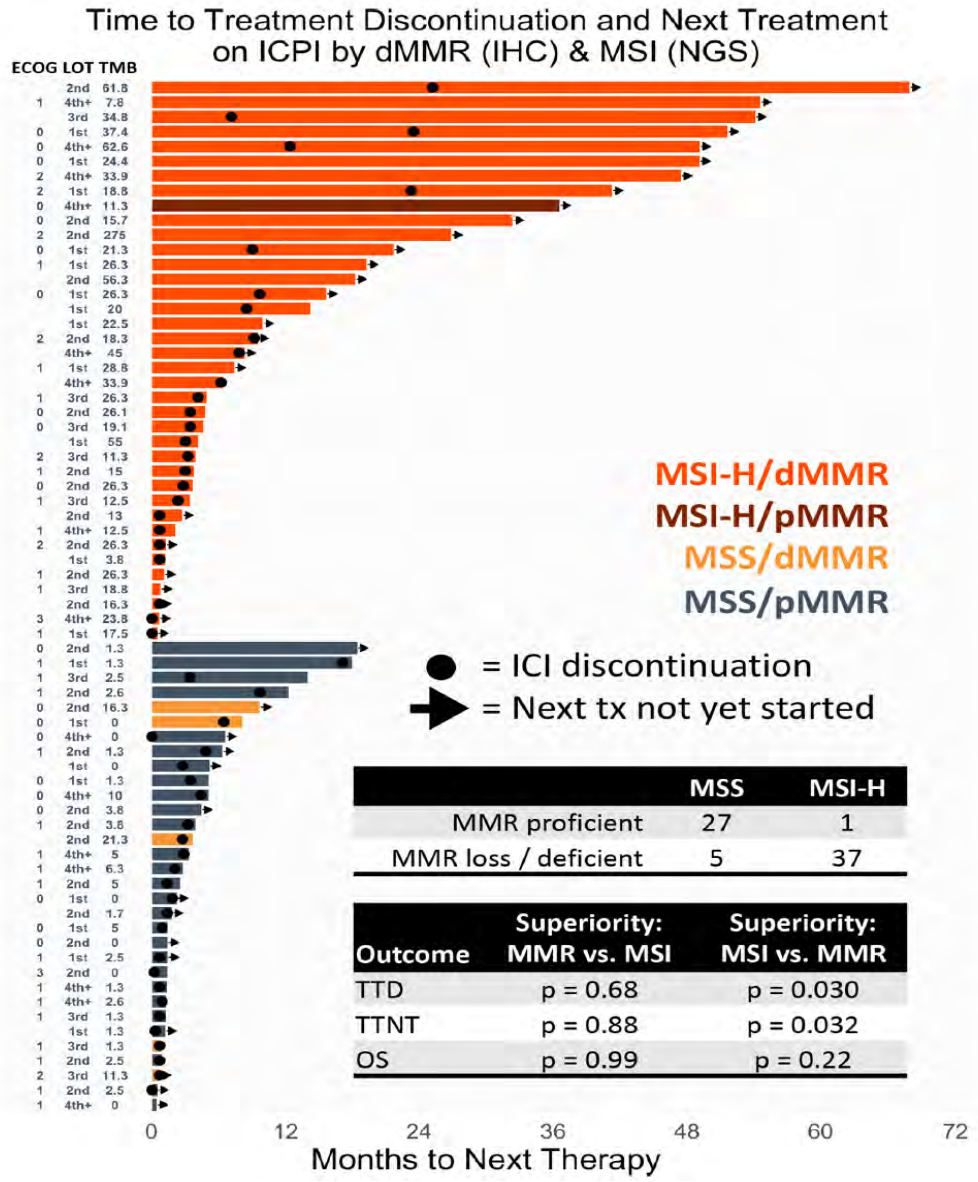
Stelloo E., Ann Oncol. 2017

Mismatch repair deficiency, next-generation sequencing-based microsatellite instability, and tumor mutational burden as predictive biomarkers for immune checkpoint inhibitor effectiveness in frontline treatment of advanced stage endometrial cancer

Breana L Hill,[1] Ryon P Graf,[2] Kunal Shah,[3] Natalie Danziger,[4] Douglas I Lin,[4] Julia Quintanilha,[5] Gerald Li,[5] James Haberberger,[6] Jeffrey S Ross,[4] Alessandro D Santin,[7] Brian Slomovitz,[8] Julia A Elvin,[4] Ramez N Eskander[1]

Int J Gynecol Cancer 2023;**33**:504–513

Conclusion Immune checkpoint inhibitors may have improved efficacy over chemotherapy in frontline treatment for advanced endometrial cancer defined by MSI-high using next-generation sequencing as a nominally better predictor of outcomes than dMMR with immunohistochemistry. This provides the biologic rationale of active phase III trials.



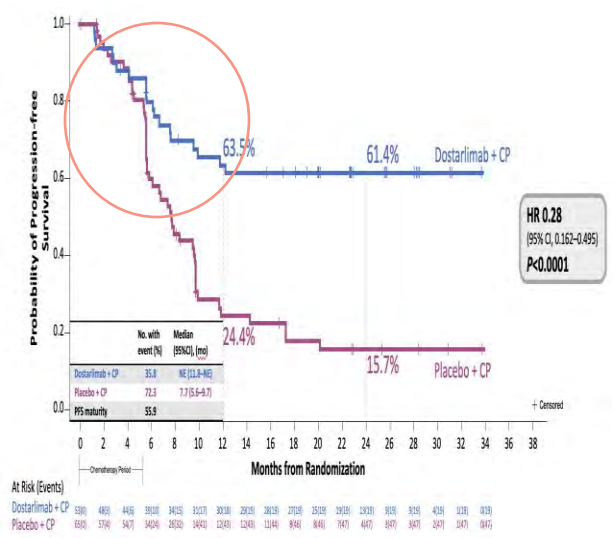
	MSS	MSI-H
MMR proficient	27	1
MMR loss / deficient	5	37

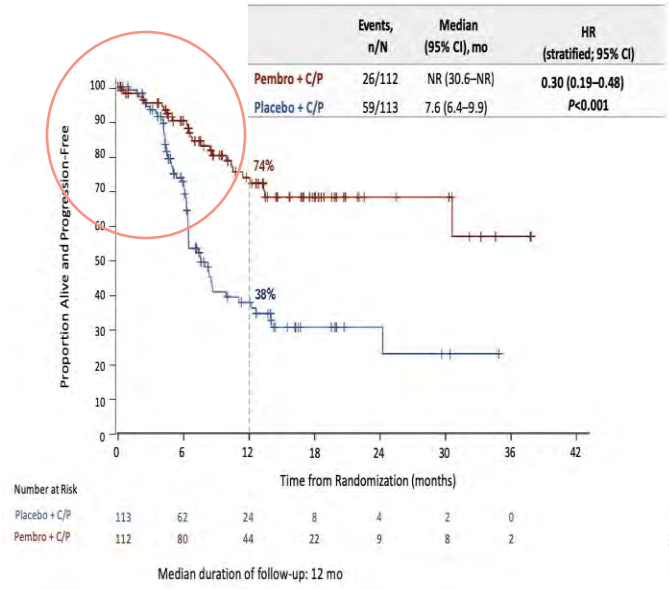
Outcome	Superiority: MMR vs. MSI	Superiority: MSI vs. MMR
TTD	p = 0.68	p = 0.030
TTNT	p = 0.88	p = 0.032
OS	p = 0.99	p = 0.22

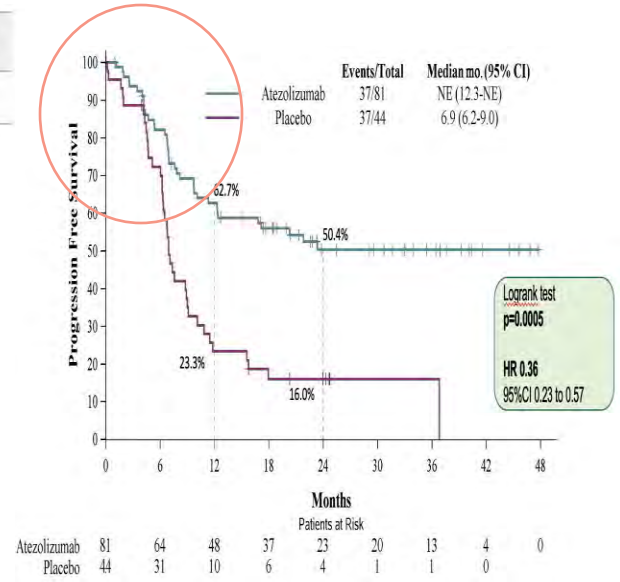
dMMR/MSI-H* tests are good to predict efficacy IO for all?

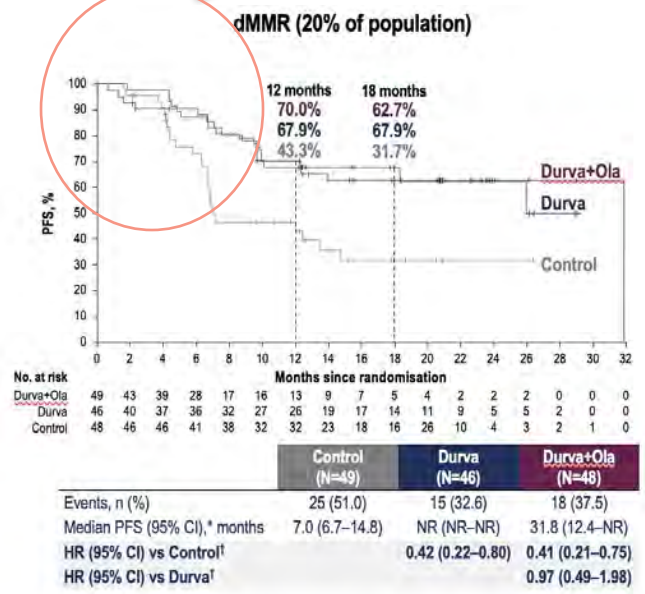
TRIAL	ICI	HR PFS
RUBY-Part 1	Dostarlimab	0.28 (95% CI 0.16-0.49)
NRG-GY018	Pembrolizumab	0.30 (95% CI 0.19-0.48)
AtTEnd	Atezolizumab	0.36 (95% CI 0.23-0.57)
DUO-E – Arm 2	Durvalumab	0.42 (95% CI 0.22-0.80)

Are misdiagnosed MSI-H?
Subclonal dMMR?
Particular molecular subgroups?









	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)

Mirza MR. et al N Engl J Med. 2023 Jun 8;388(23):2145-2158. Eskander RN et al; N Engl J Med. 2023 Jun 8;388(23):2159-2170
Nicoletta Colombo et al. Presented at ESMO Meeting , Madrid 2023 ; Westin SN et al J Clin Oncol. 2023 Oct 21:JCO2302132

Impact on Immune Therapy Benefice?

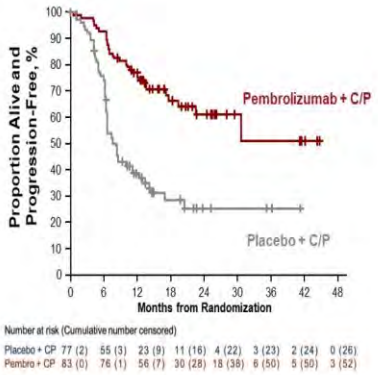
No difference seen in patients with MMRD EC based on mechanism of MMR loss

NRG-GY018: PFS by methylation status in the dMMR population

Methylation

Pembro + C/P vs Placebo + C/P

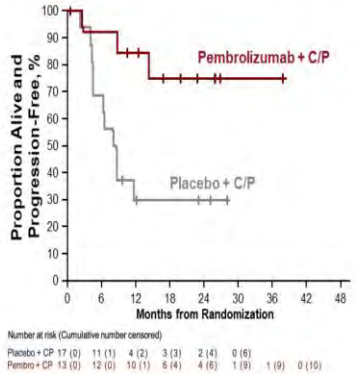
	Events n/N	Median (95% CI), mo	HR (95% CI)
Placebo + C/P	51/77	7.5 (6.4–11.3)	0.307 (0.19–0.49) *Nominal* P* <0.0001
Pembro + C/P	28/83	NR (22.3–NR)	



No methylation

Pembro + C/P vs Placebo + C/P

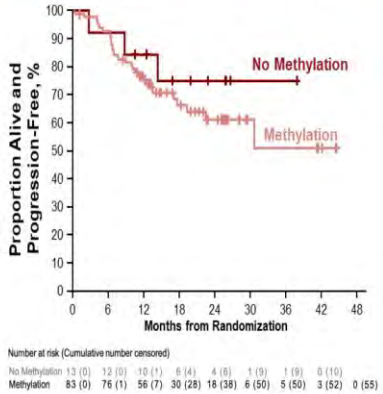
	Events n/N	Median (95% CI), mo	HR (95% CI)
Placebo + C/P	11/77	8.3 (4.4–NR)	0.263 (0.07–0.99) Nominal* P =0.0172
Pembro + C/P	3/13	NR (14.2–NR)	



Methylation status

Pembro + C/P arm

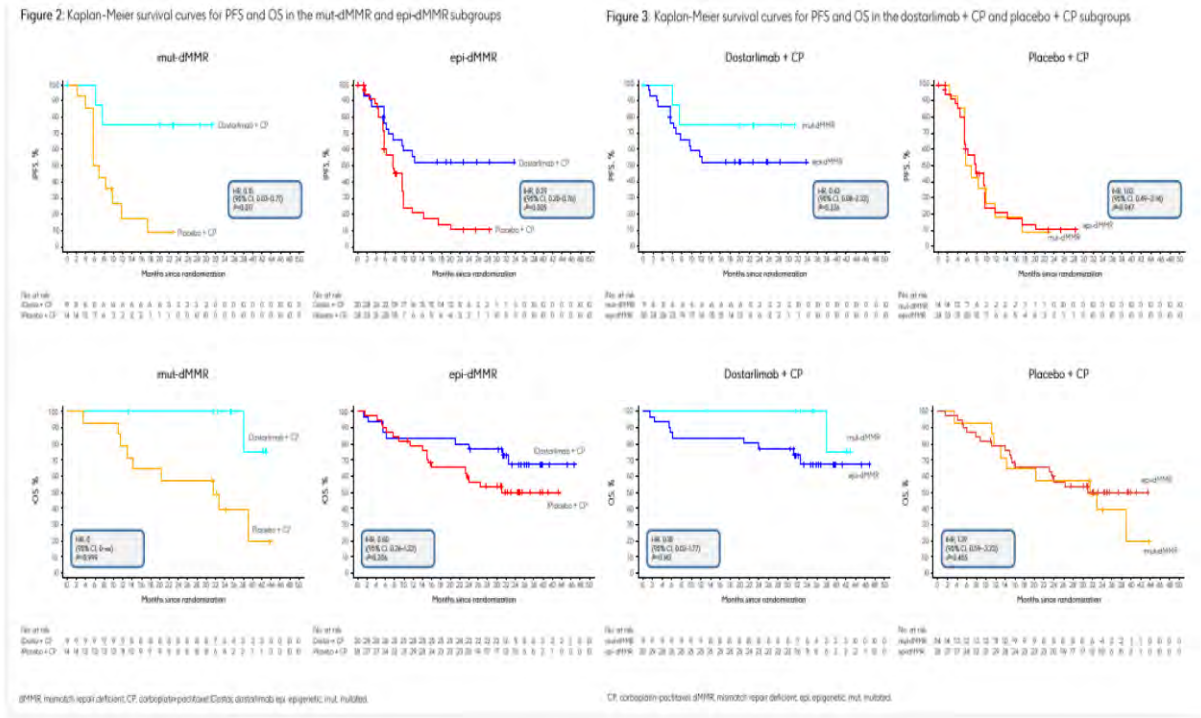
	Events n/N	Median (95% CI), mo
No Methylation	3/13	NR (14.2–NR)
Methylation	28/83	NR (22.3–NR)



CP = carboplatin/paclitaxel; dMMR = mismatch repair deficient; MMR = mismatch repair; PFS = progression-free survival; OS = overall survival.
Data cut off date, August 18, 2023.

1. Eskander RN, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20–24, 2023; Madrid, Spain; Presentation #LBA43.

RUBY Trial: PFS & OS by methylation status in the dMMR population

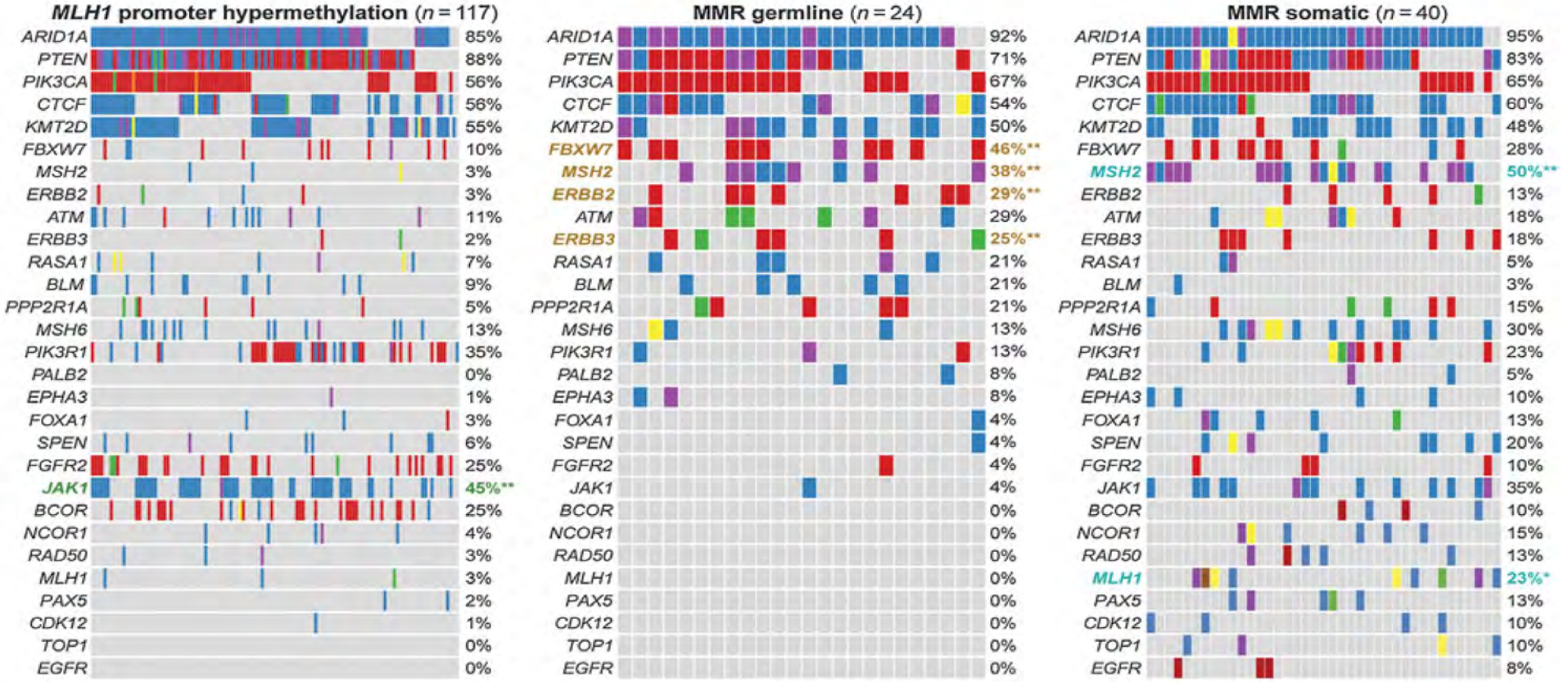


1. Mirza MR, et al. Presented at American Society of Clinical Oncology (ASCO) Annual Meeting. May 31– June 4 2024; Chicago, USA

Is It So Sure?

Microsatellite Instability–High Endometrial Cancers with *MLH1* Promoter Hypermethylation Have Distinct Molecular and Clinical Profiles

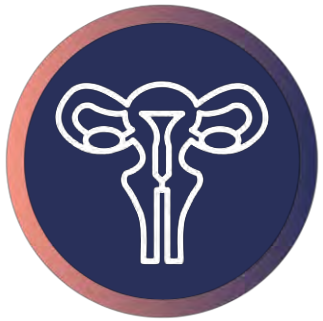
Beryl L. Manning-Geist[1], Ying L. Liu[2,3,4], Kelly A. Devereaux[5], Arnaud Da Cruz Paula[1], Qin C. Zhou[6], Weining Ma[7], Pier Selenica[5], Ozge Ceyhan-Birsoy[5], Lea A. Moukarzel[1], Timothy Hoang[5], Sushmita Gordhandas[1], Maria M. Rubinstein[2,4], Claire F. Friedman[2,4], Carol Aghajanian[2,4], Nadeem R. Abu-Rustum[1,8], Zsofia K. Stadler[2,3,4], Jorge S. Reis-Filho[5], Alexia Iasonos[6], Dmitriy Zamarin[2,4], Lora H. Ellenson[5], Yulia Lakhman[7], Diana L. Mandelker[5], and Britta Weigelt[5]



Median TMB was significantly lower among endometrial cancers with *MLH1*ph (**32 mt/Mb**, range 13–302 mt/Mb) compared with germline (**44 mt/Mb**, range 1–74 mt/MB) and somatic MMR mutations (**48 mt/Mb**, range 25–89 mt/Mb; $P < 0.001$

HER2 IHC Prevalence in EC

Endometrial



ICH 3+
6-17%[2,3]

ICH 2+
13-39%[2,3]

ICH 1+
17%[2,3]

~16%

Uterine Carcinosarcoma

Table 5. Performance of two endometrial cancer-specific HER2 testing algorithms

	HER2 IHC on all cases with DISH performed on cases scored	
	IHC-2+/-3+	IHC-2+
Sensitivity	100%	100%
Specificity	100%	97%
Accuracy	100%	97%
Positive predictive value	100%	90%
Negative predictive value	100%	100%

1. Vermij L et al., Histopathology, 79, 533–543 (2021)
2. Halle MK, et al. Br J Cancer. 2018;118:378–387;
3. Vermij L, et al.Cancers.2021;13:44;

HER2 Amplification Seems to be Restricted to the p53 Abnormal Subtype

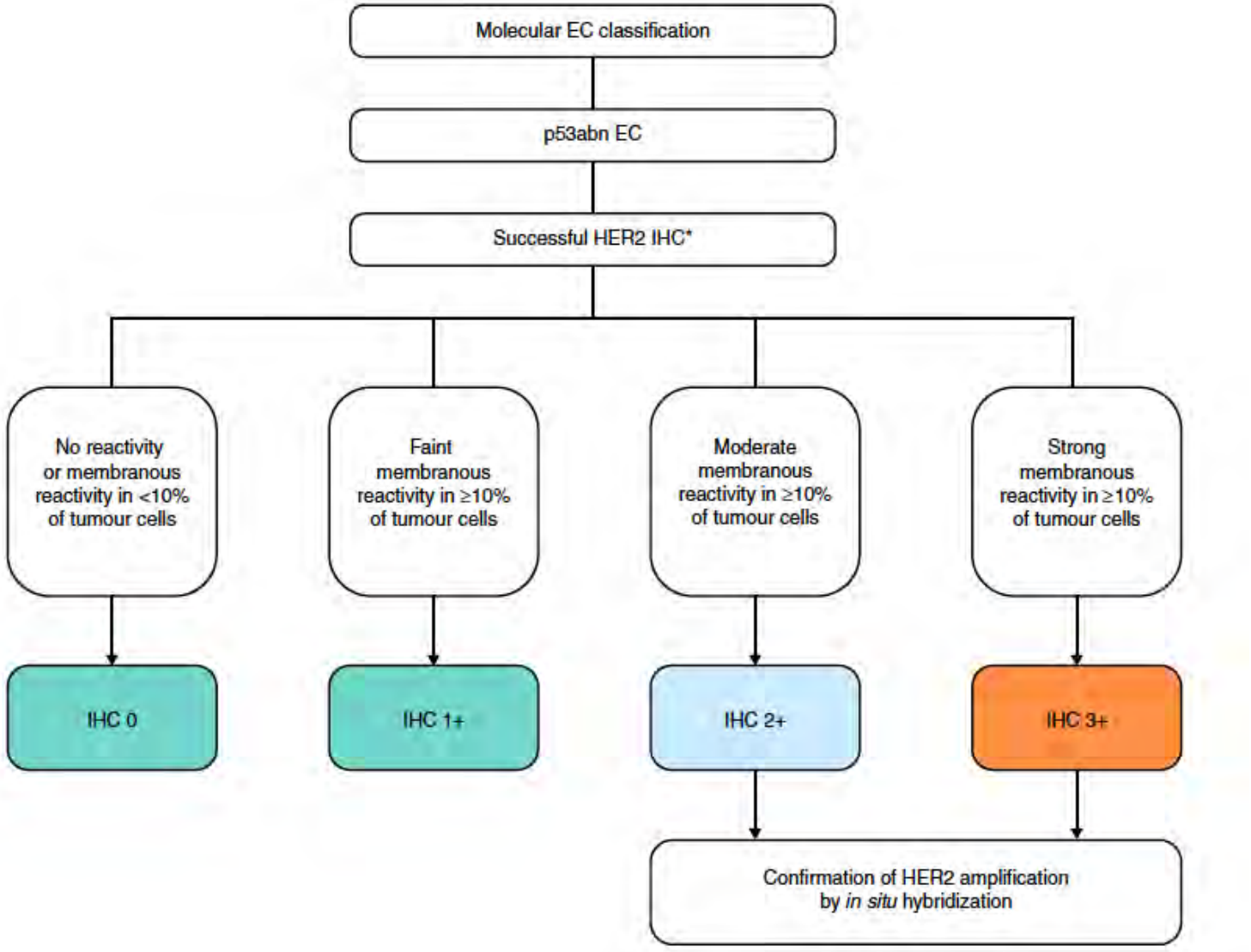
Table 2. Association between the HER2 status and molecular EC classification.

Cohort	Molecular Subgroup					
	Total *n* = 405	*POLE*mut *n* = 52 (12.8%)	MMRd *n* = 135 (33.3%)	NSMP *n* = 126 (31.1%)	P53 *n* = 92 (22.7%)	*p*-Value
PORTEC-3						<0.0001
HER2-negative	381 (94.1)	52 (100.0)	135 (100.0)	125 (99.2)	69 (75.0)	
HER2-positive	24 (5.9)	0 (0.0)	0 (0.0)	1 (0.8)	23 (25.0)	
	Total *n* = 506	*POLE*mut *n* = 49 (9.7%)	MSI *n* = 148 (29.2%)	CN-low *n* = 146 (28.9%)	CN-high *n* = 163 (32.3%)	*p*-Value
UCEC TCGA PanCancer						<0.0001
Non-*ERBB2*-amplified	481 (95.1)	49 (100.0)	148 (100.0)	146 (100.0)	138 (84.7)	
ERBB2-amplified	25 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	25 (15.3)	

Abbreviations: *POLE*mut, *POLE*-(ultra-)mutated; MMRd, mismatch repair-deficient; NSMP, no specific molecular profile; p53abn, p53-abnormal; TCGA, the Cancer Genome Atlas; UCEC, uterine corpus endometrial carcinoma; MSI, microsatellite-unstable; CN-low, copy number-low; CN-high, copy number-high.

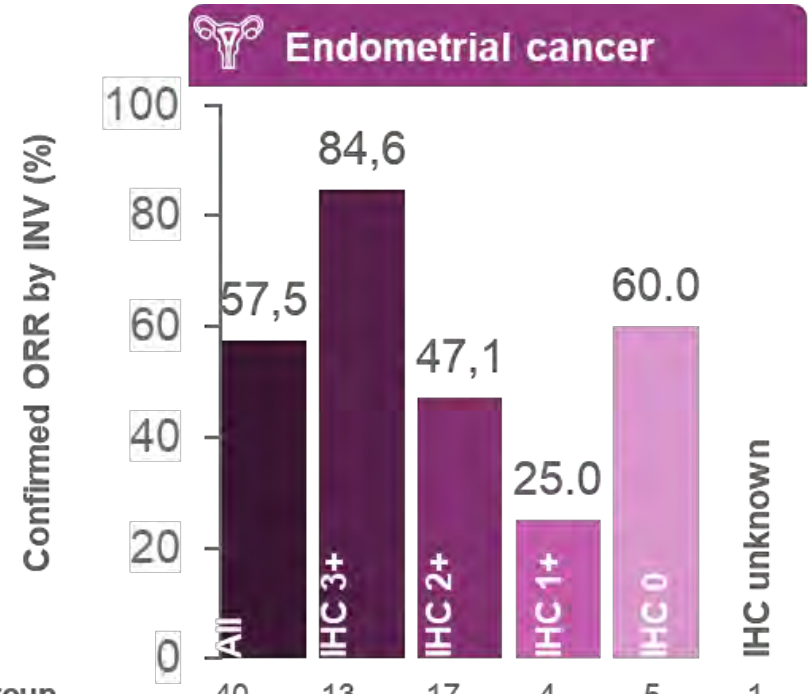
Vermij L, Cancers 2021, 13, 44

Proposed Endometrial Cancer-Specific HER2 Testing Algorithm for HER2 Status Assignment in p53-Abnormal Endometrial Cancer



Rottman et al. Modern Pathology 2020

DESTINY PAN TUMOR: ENDOMETRIAL COHORT ORR and DOR (INV)*



	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†	NR	NR	18.2	NR	9.9	-
95% CI‡	9.9, NE	9.6, NE	3.0, NE	-	2.8, NE	-

Funda Meric-Bernstam et al J Clin Oncol 2024 Jan 1;42(1):47-58. doi: 10.1200/JCO.23.02005. Epub 2023 Oct 23

HER2 amplification was evaluated centrally using Ventana dual ISH on archival tissue and detected in baseline plasma ctDNA using Guardant Health OMNI assay. Unknown tissue HER2amp and plasma HER2amp results have not been included. *Focal amplification only.
amp, amplification; ctDNA, circulating tumor DNA; ERBB2, erb-b2 receptor tyrosine kinase 2; HER2, human epidermal growth factor receptor 2; INV, investigator; ISH, in situ hybridization; ORR, objective response rate

Limitations?
Exploratory Biomarker Analyses of HER2 Expression

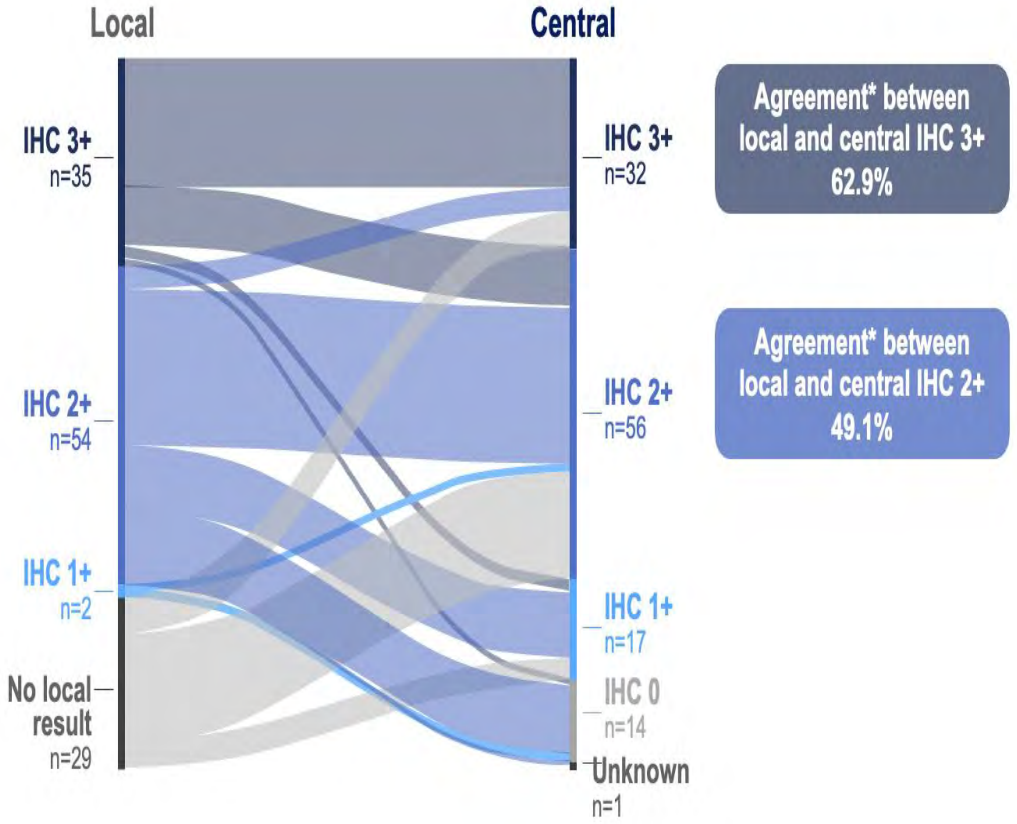
All patients cohort

Agreement between local and central IHC results

		Central HER2 HercepTest™					
		IHC 3+	IHC 2+	IHC 1+	IHC 0	IHC unknown†	Total
Local HER2 IHC	IHC 1+	0	1	0	1	0	2
	IHC 2+	6	55 (54%)	17	23	6	107
	IHC 3+	51 (59%)	26	4	6	6	93
Centrally enrolled		18	44	3	0	0	65
	Total	75	126	24	30	12	267

		Central HER2 HercepTest™					
		IHC 3+	IHC 2+	IHC 1+	IHC 0	IHC unknown†	Total
Local HER2 HercepTest™	IHC 1+	0	0	0	1	0	1
	IHC 2+	0	7 (70%)	2	1	1	11
	IHC 3+	8 (73%)	2	1	0	1	12
	Total	8	9	3	2	2	24

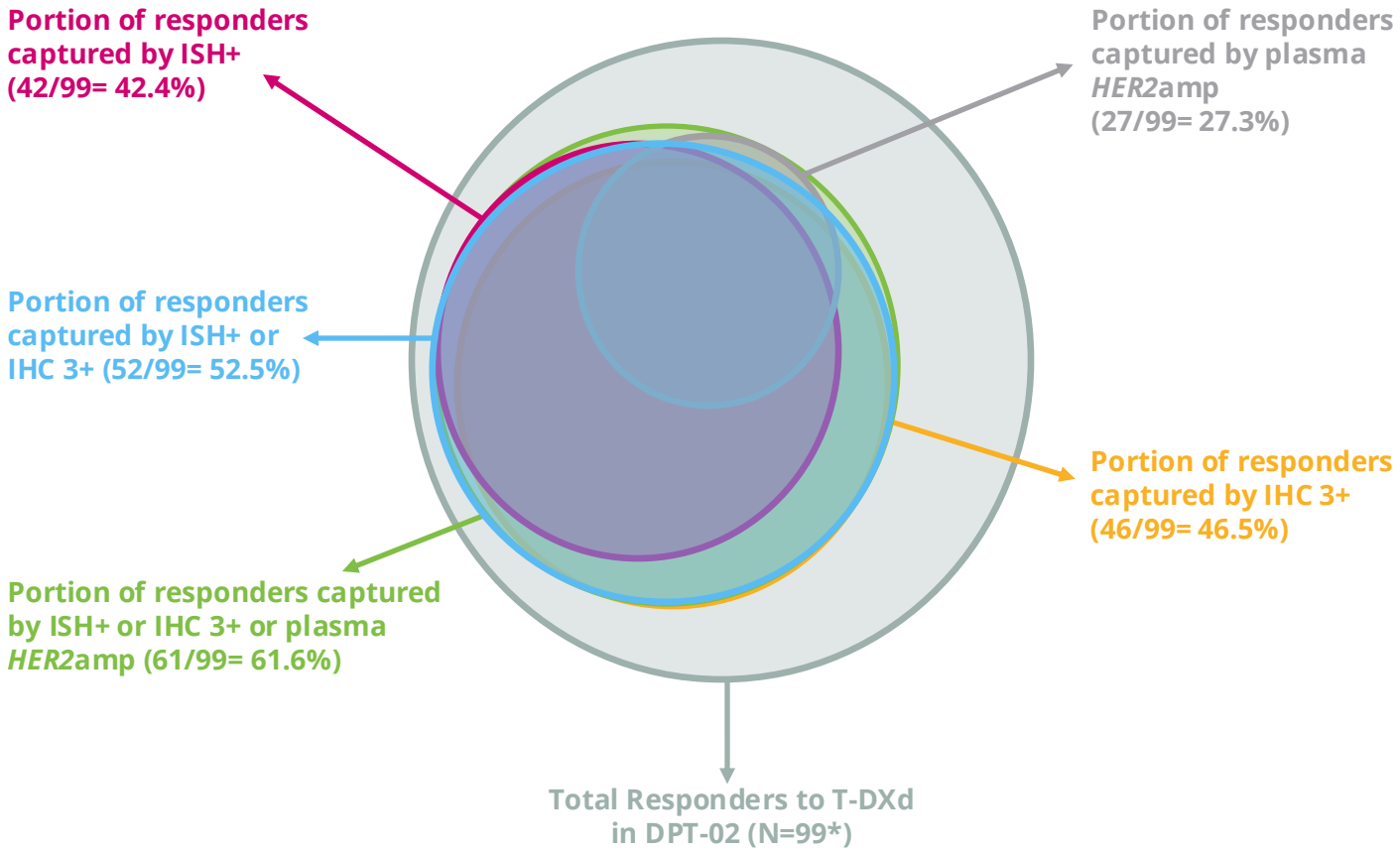
Gyn cohort



Presented by Makker V. et al. SGO 2024; Presented by Jung-Yun Lee et al at IGCS 2023

*Agreement was defined as the percentage of samples classified with the same IHC score by both local and central testing; agreement was calculated excluding central IHC unknown samples

Tissue samples or Blood Samples? Responders Captured by IHC 3+ or ISH+ or Plasma HER2 Amplification



Integration of IHC 3+ or ISH+ or plasma *HER2* amplification captures the majority of responders

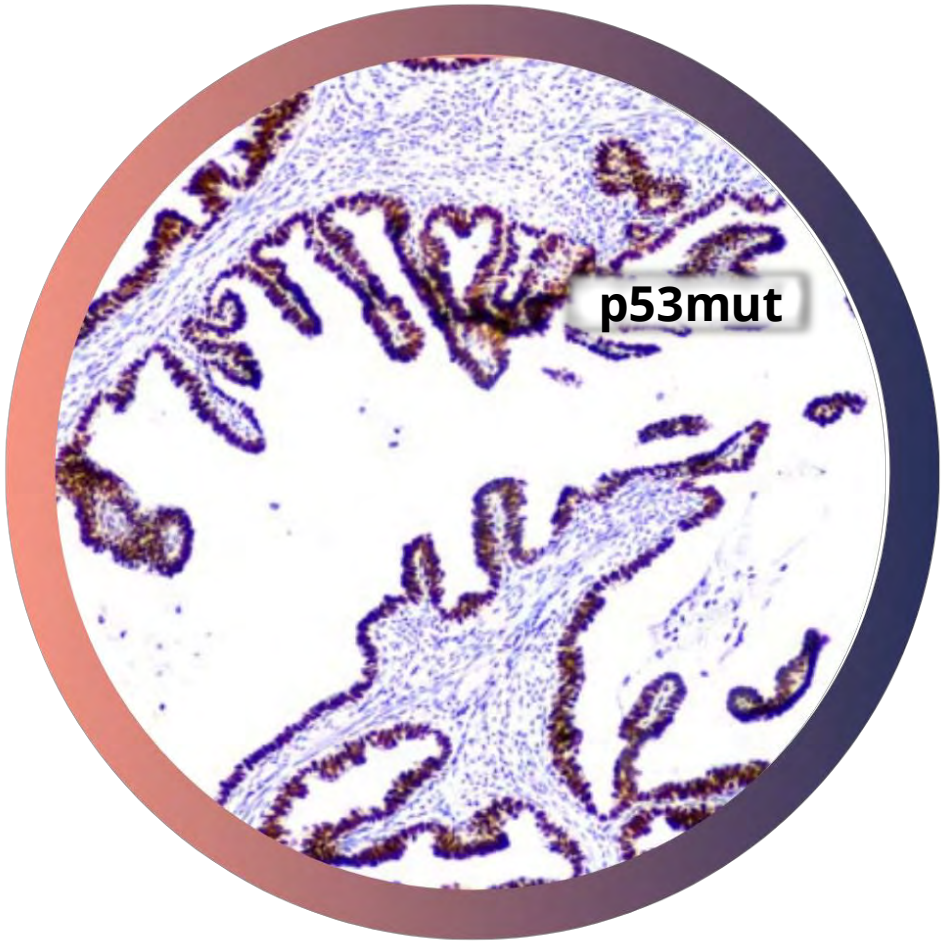
Presented by Makker V. et al. SGO 2024

HER 2 Evaluation: Some Considerations

- HER2 overexpression/ amplification strongly correlates with p53 abnormal molecular subtype
- Serous carcinoma and carcinosarcoma frequently affected but also other histological types with abnormal p53
- The moderate concordance rate may be attributed to the age of the tissue blocks, tumor heterogeneity, inter-pathologist variability, lack of a standardized test for HER2 in indications other than BC and GC, variation in HER2 antibodies, and different HER2 scoring algorithms between local and central testing
- ctDNA testing may help identify patients with HER2 amplification but is not yet a substitute for tissue-based HER2 IHC and ISH testing
- **The low rate of false positives indicated that the ctDNA assay was specific, but the sensitivity was poor**
- **These data support the need for a validated clinical diagnostic test and algorithm to score HER2 across tumor types in addition to GC**

TP53 and p53mut

- Molecular classification[1,2]
- Prognostic[1,3,4]
- Associated with higher frequency of HRD-positive (79% *vs.* 23%) (UTOLA trial)[5]
- Possible benefit of PARPi (UTOLA trial)[5]
- Benefits of external beam radiotherapy in early stage (PORTEC-1, PORTEC-2)[6]

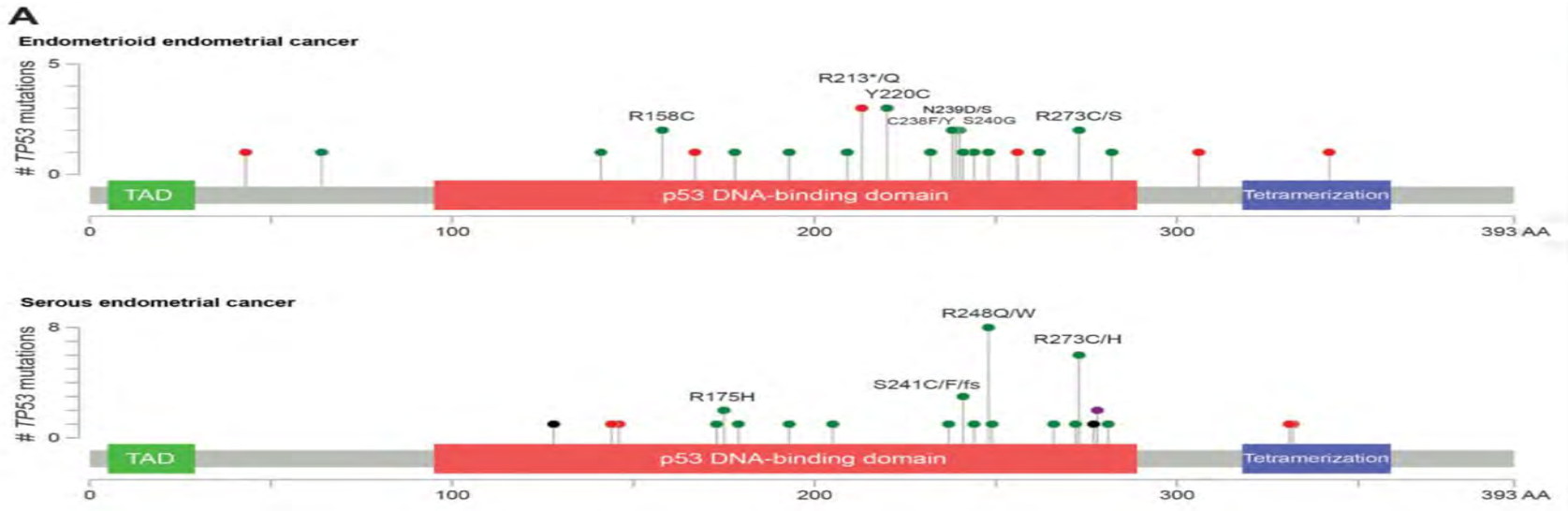


1- TCGA. Nature 2013;497(7747):67-73; 2- Kommoss et al. Ann Oncol 2018;29:1180-8; 3-Concin et al. Virchows Arch 2021;478:153-90; 4- Oaknin et al. Ann Oncol 2022;33:860-77; 5, Joly et al Ann Oncol 2023; 6-Horeweg et al. JCO 2023;41:4369-80

TP53 Mutations in EC

Accuracy of p53 IHC[1]	
Overall concordance	155/168 (92.3%)
Concordance excluding dMMR and POLE	117/123 (95.1%)
Discordances	Null staining pattern without mutation
Sub-clonal mutant p53 IHC	9/177 (5.1%) (4/9: dMMR or POLE)
Inter-laboratory reproducibility	Excellent
IHC and NGS concordance	100%, but: • Different patterns of staining (nuclear, null, cytoplasmatic) • Different types and positions of TP53 mutations

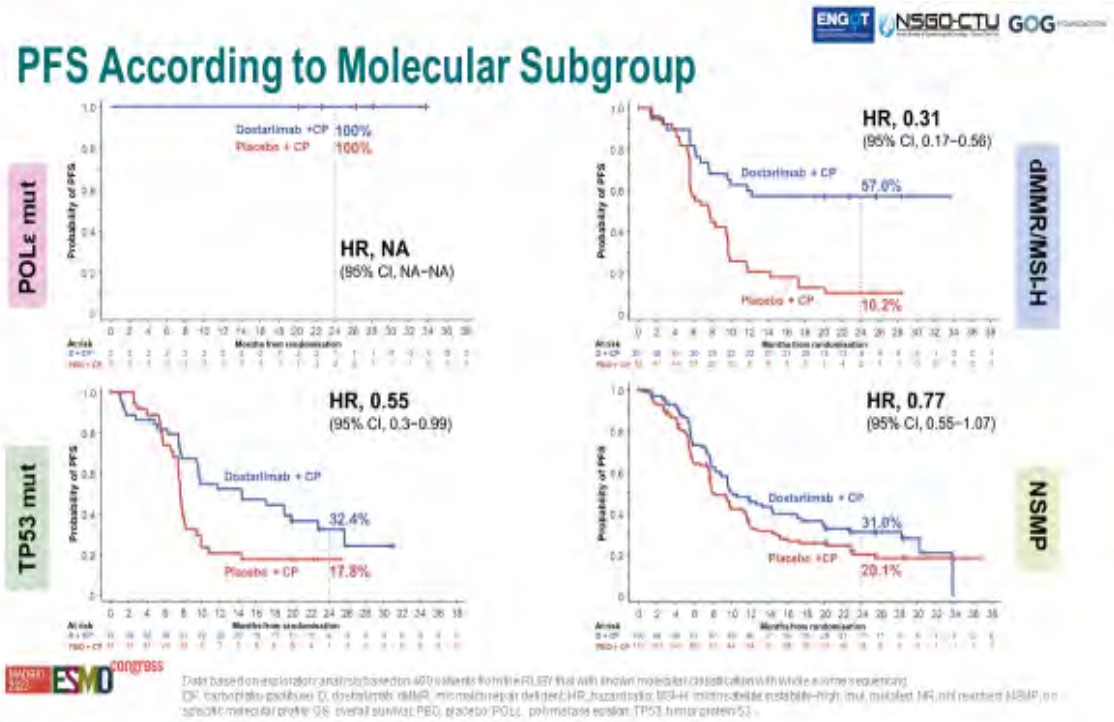
1-Singh et al. J Pathol 2020;250:336-45; 2- Matsumoto et al. Int J Gynecol Pathol 2023;42:567-75; 3-



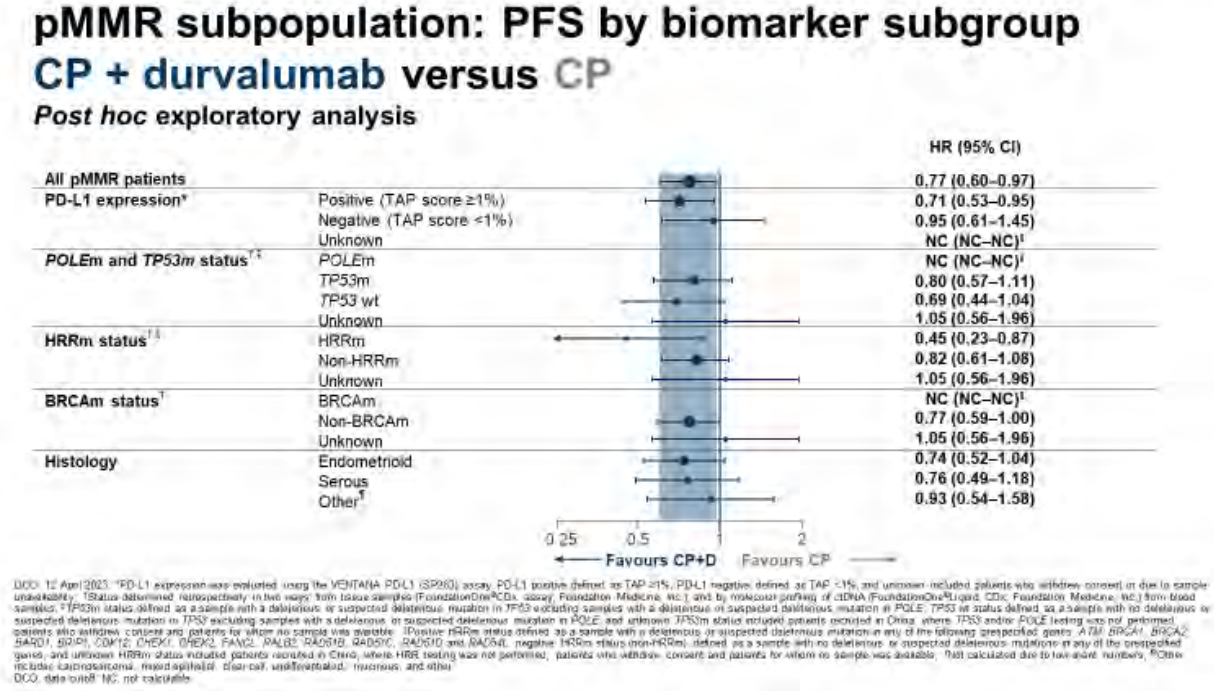
- Missense mutations
- Truncating mutations
- In-frame indels

- Different IHC patterns
- Not all mutations are IHC-detectable
- Not all are pathogenic
- Differences according to histological subtypes

P53 Status Predicts IO Activity?

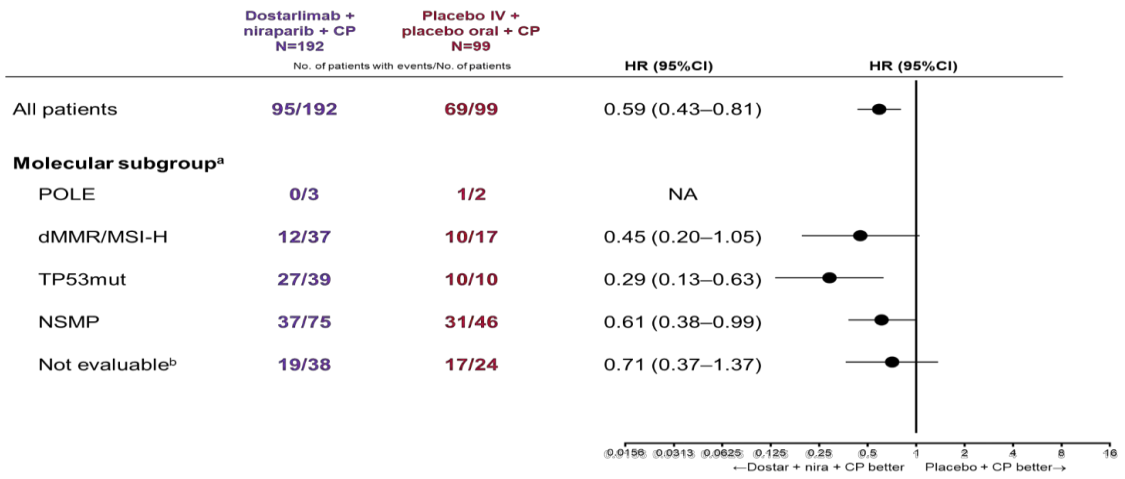


M Mirza, ESMO 2023



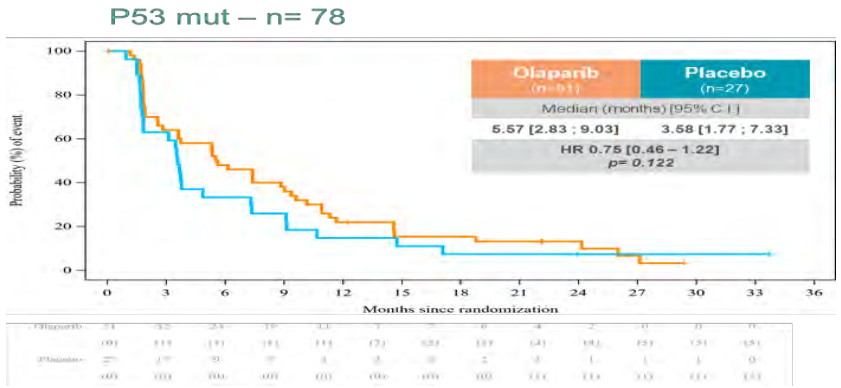
S Westin, IGSC 2024

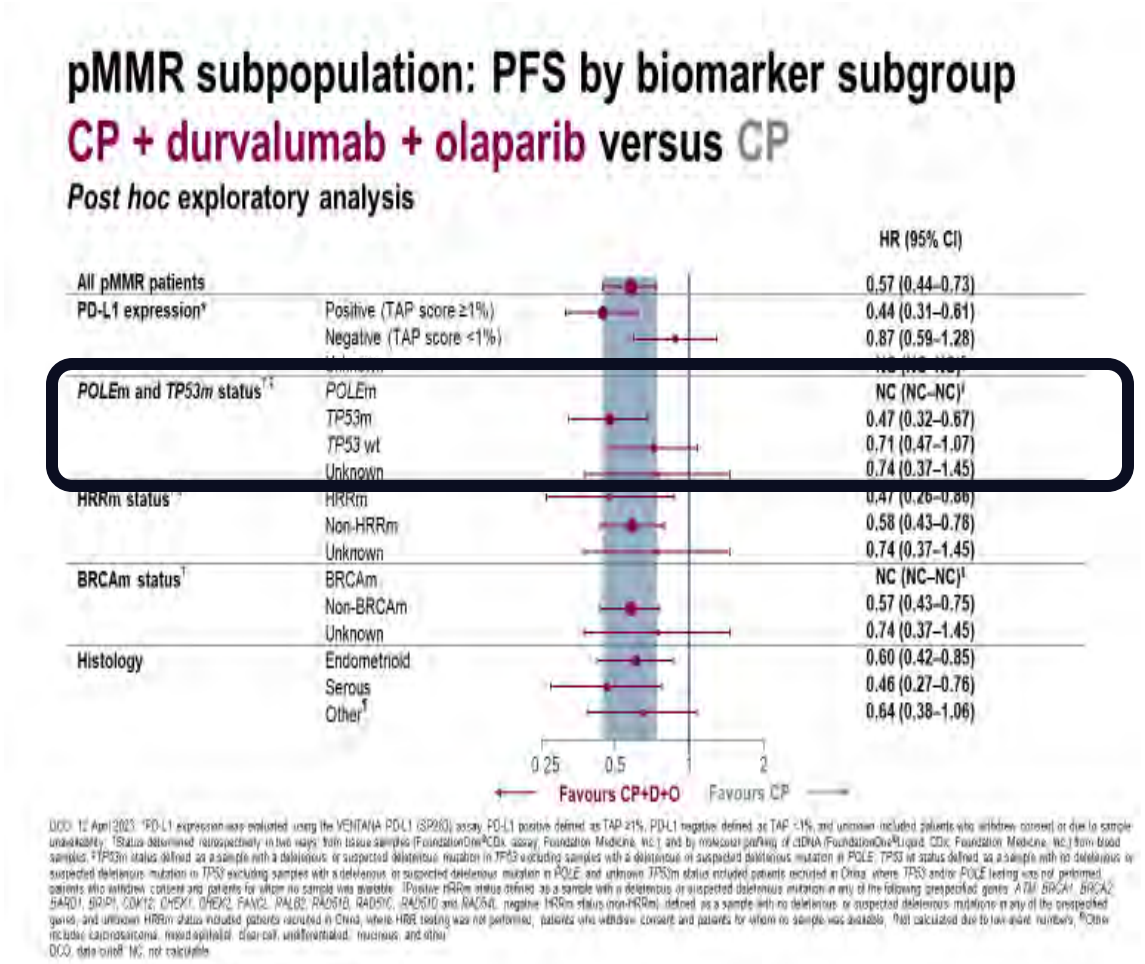
P53 Status Predicts PARPi Activity?



RUBY Part 2, M Mirza et al SGO 2024

UTOLA trial F Joly et al ESMO 2023





S Westin, IGSC 2024

HRRm in Endometrial Cancer

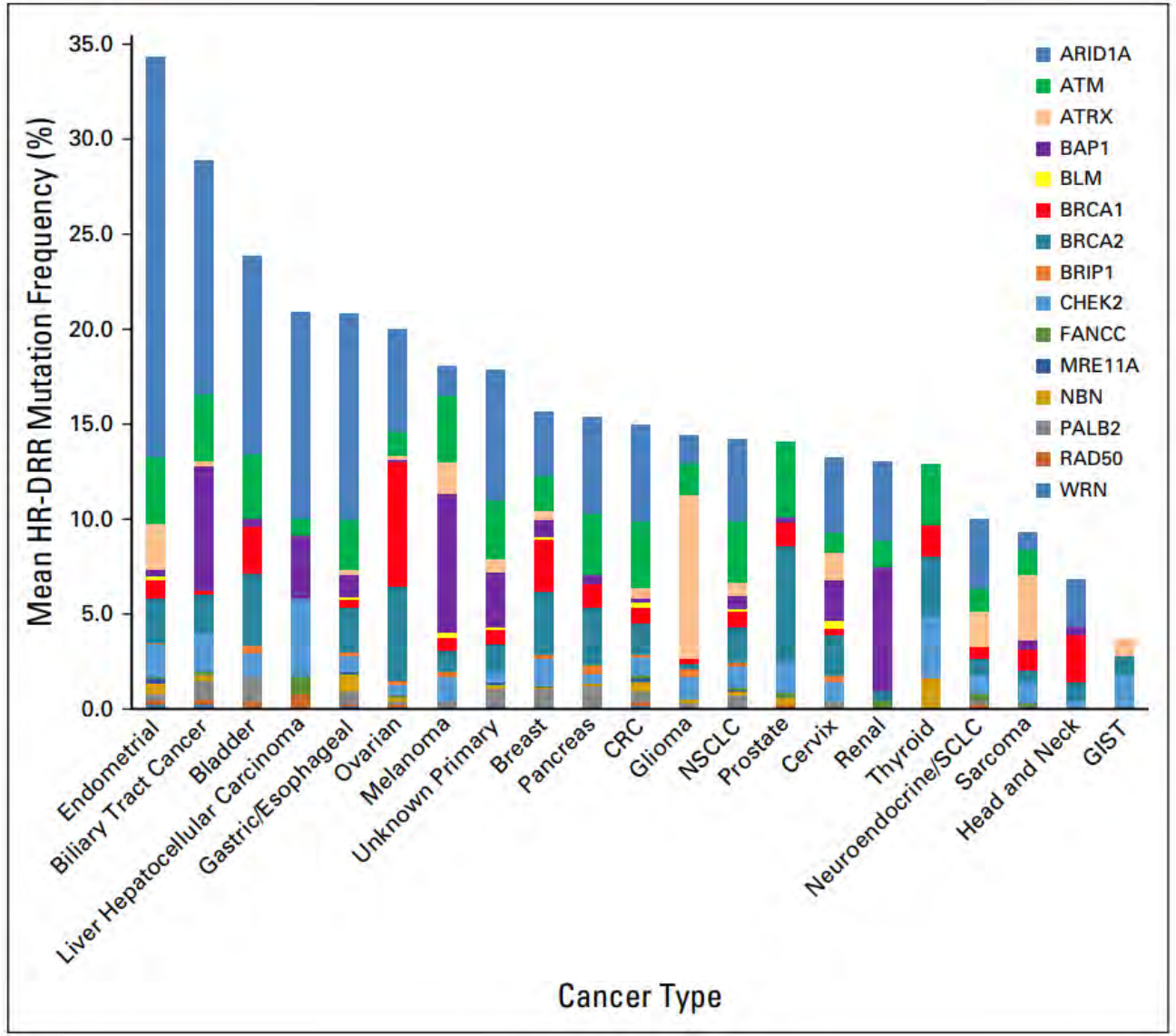
n=52,426 solid tumors

HR-DRR genes: ARID1A, ATM, ATRX, BAP1, BARD1, BLM, BRCA1/2, BRIP1, CHEK1/2, FANCA/C/D2/E/F/G/L, MRE11A, NBN, PALB2, RAD50, RAD51, RAD51B, or WRN

HR-DRR mutations: 17.4%

Endometrial: 34.4%

Ovarian: 20.0%

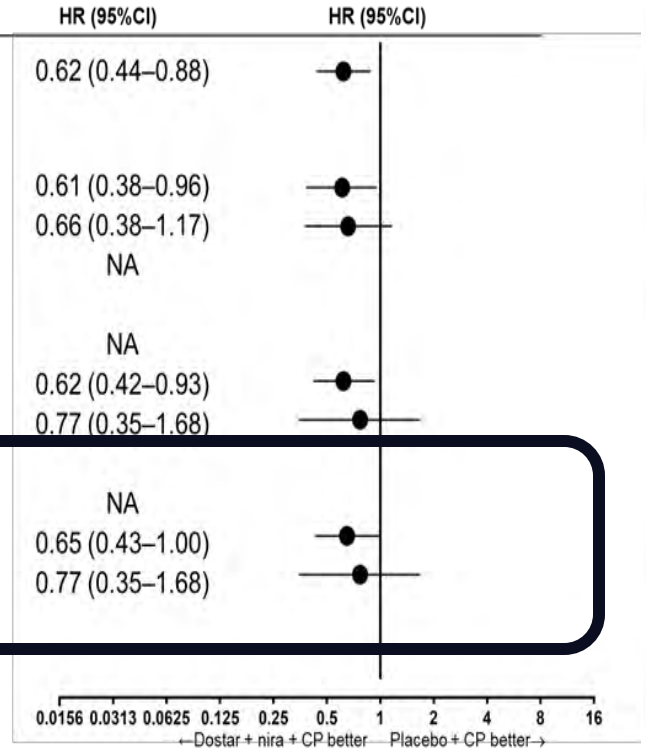


Heeke, JCO Precision Oncology 2018

HRR Predicts PARPi Activity?

MMRp/MSS population

	Dostarlimab + Niraparib + CP N=142	Placebo IV + Placebo oral + CP N=74	HR (95%CI)
	No. of patients with events/No. of patients		HR (95%CI)
All patients	79/142	53/74	0.62 (0.44–0.88)
PD-L1 Status[a]			
PD-L1+	46/88	31/44	0.61 (0.38–0.96)
PD-L1-	32/53	20/26	0.66 (0.38–1.17)
Not evaluable[b]	1/1	2/4	NA
BRCA mutation status			
Positive	1/4	2/3	NA
Negative	63/113	40/55	0.62 (0.42–0.93)
Not evaluable[b]	15/25	11/16	0.77 (0.35–1.68)
HRR mutation status[c]			
Positive	3/10	8/11	NA
Negative	61/107	34/47	0.65 (0.43–1.00)
Not evaluable[b]	15/25	11/16	0.77 (0.35–1.68)

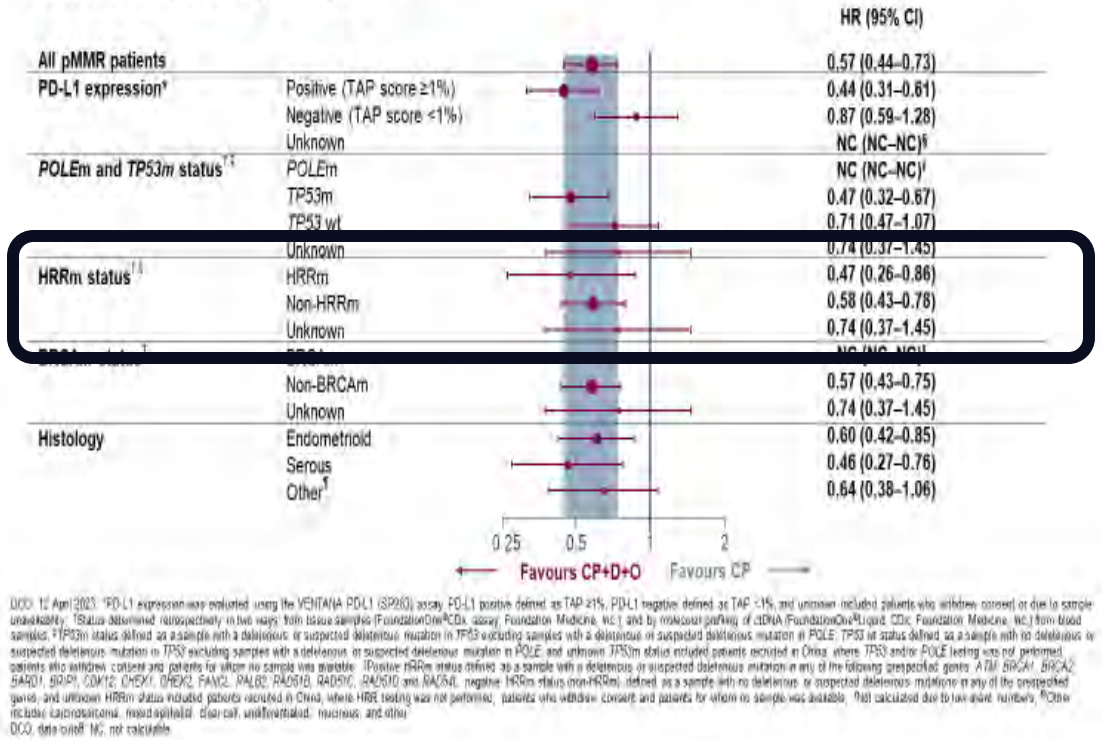


RUBY Part 2, M Mirza et al SGO 2024

pMMR subpopulation: PFS by biomarker subgroup

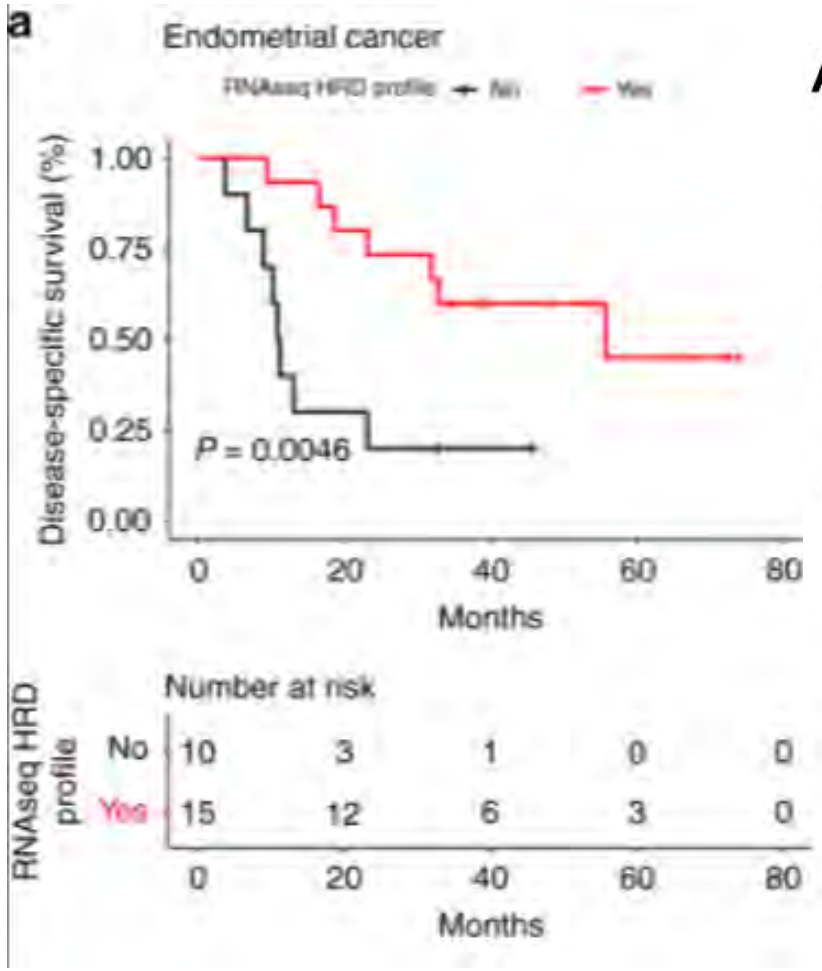
CP + durvalumab + olaparib versus CP

Post hoc exploratory analysis

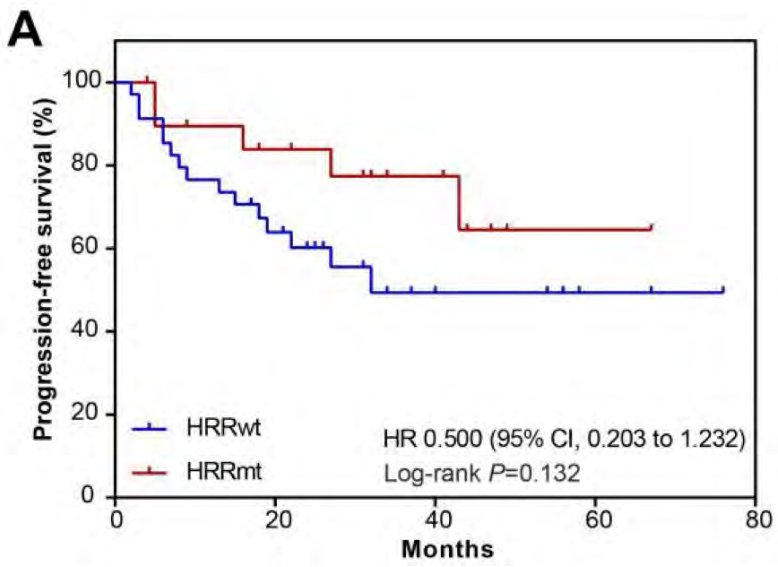


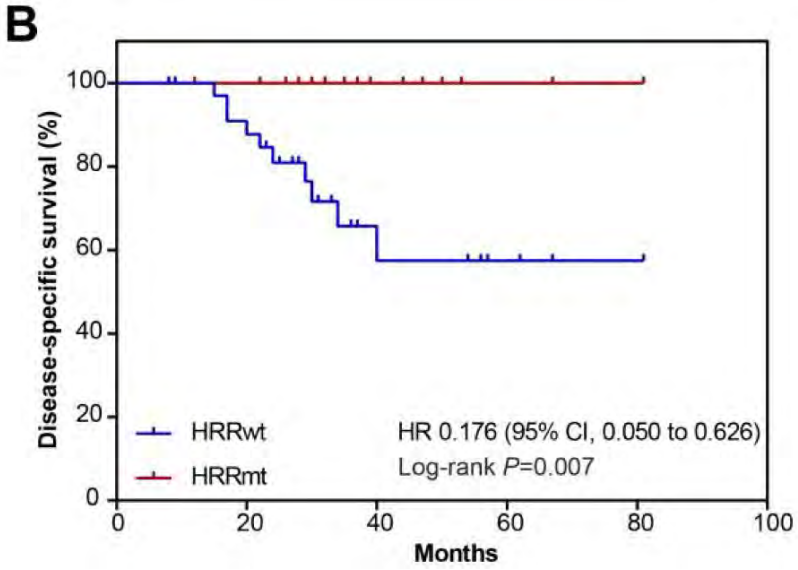
S Westin, IGSC 2024

HRD May Have Prognostic Implications in EC



Uterine serous Carcinoma

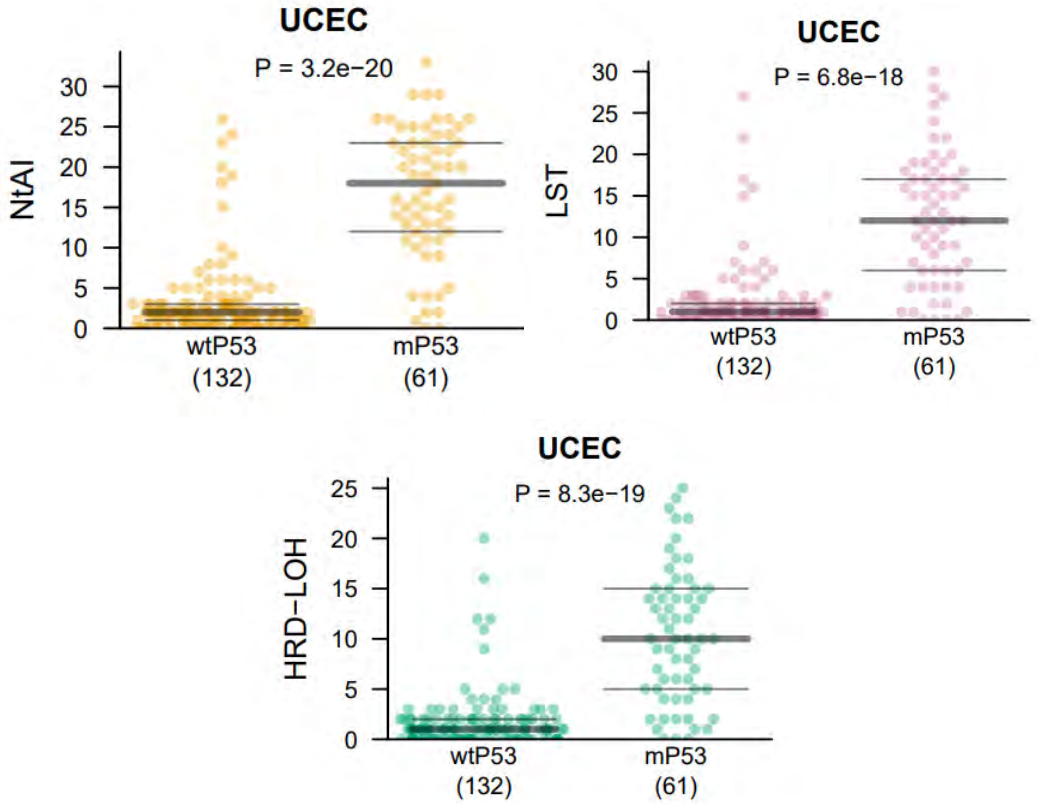


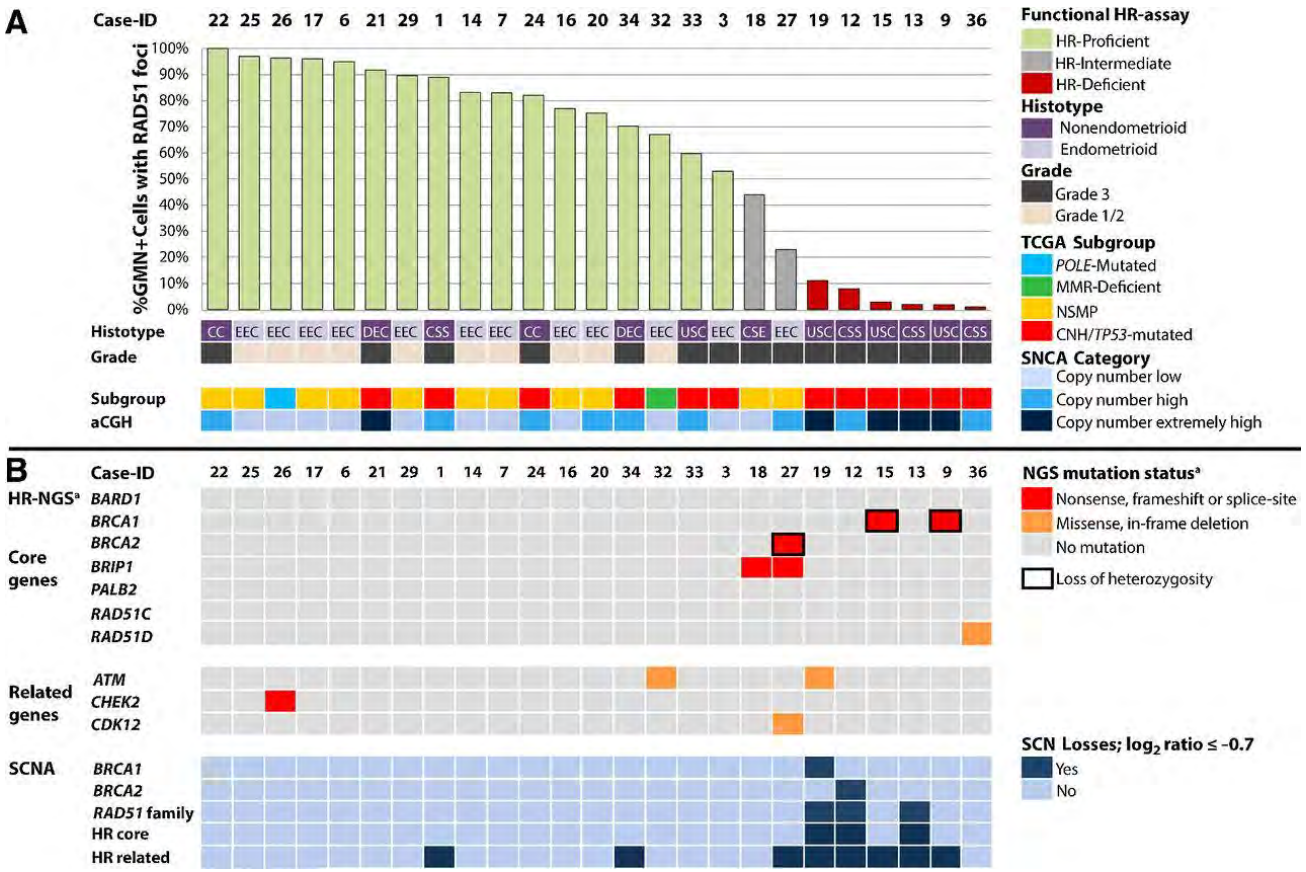


Due to the potential improved outcomes for patients with an HRD phenotype with chemotherapy, interpretation of exploratory HRR outputs from current EC trials is challenging

1. Beinse G, et al. BMJ 2022;127:1123–32. 2. Dong L, et al. Cells 2022;11:3563.

HRD in Endometrial Cancer





HRD is more common in:

- Serous EC
- TP53 mutated
- BRCA 1/2 and BRIP mutations

Marquard, Biomarker Research 2015

De Jonge, CCR 2019

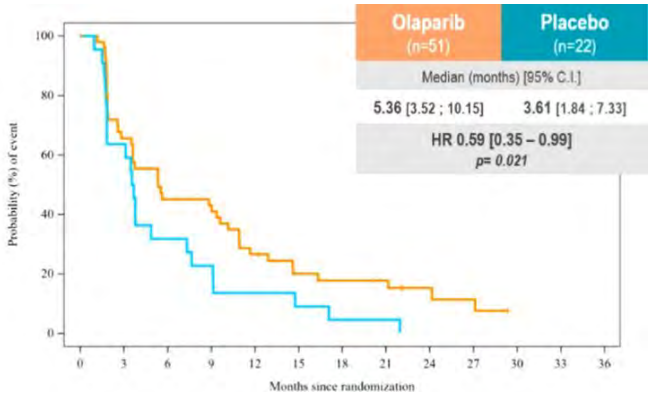
HRD Test to Predict PARPi Activity in EC?

There is emerging for the utility of these tests in this tumor type

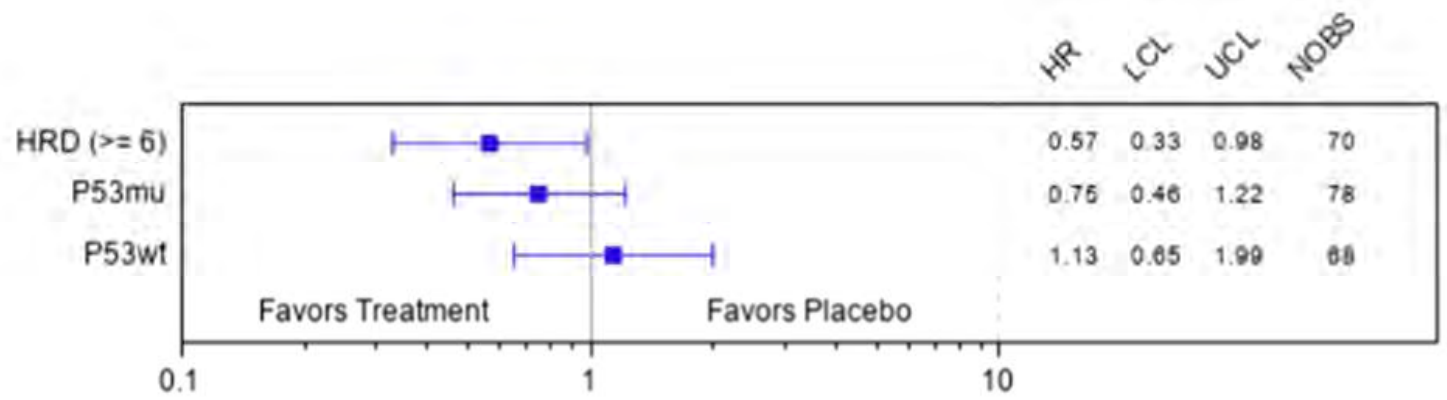
UTOLA trial: Genomic Instability Scar (GIScar)[1,2]

- 127-gene panel, including BRCA variants and genomic instability
- Number of large genomic events (LGE) + structural instability + allelic imbalance

UTOLA: Exploratory subgroup analysis
PFS in HRD (LGE ≥6) (n=73)



UTOLA: PFS by subgroups[2]



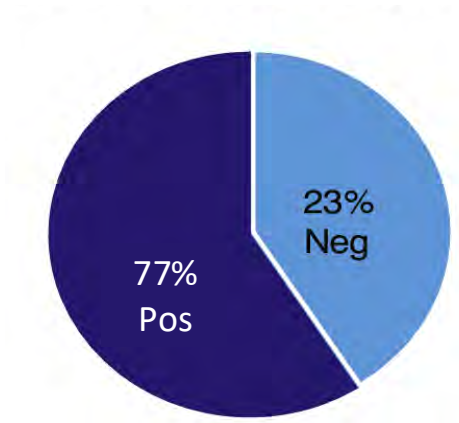
No HRD test has been validated in EC

1-Leman et al. Clin Cancer Res 2023;29:4419-29; 2- Joly Lobbedez et al. Ann Oncol 2023;34(Suppl 2):S1283-4;

Prevalence of PD-L1 Expression in Endometrial Cancer[1,2]

PD-L1 Expression Meta-analyses[1]	
Prevalence	5.3-76.5%
High risk (MI>50%, LVSI+, N+)	40% (vs 20%)
TPP ≥1% cut-off	45.1%
TPS ≥5% cut-off	22.8%

PD-L1 Status in Primary Tumors[2]



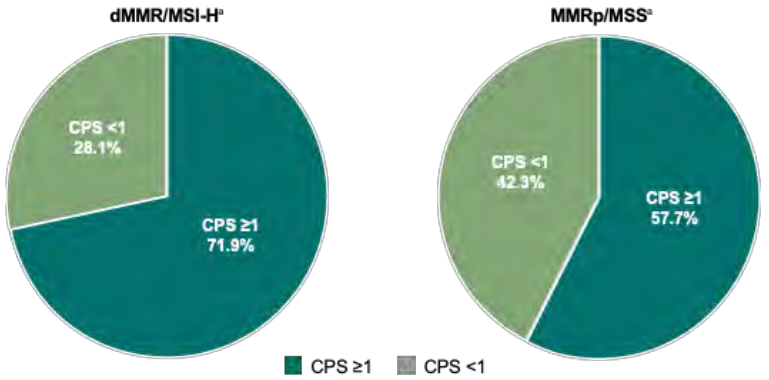
Higher stage of disease is associated increased prevalence of PD-L1

Clinicopathological features	No. of studies	OR (95%CI)	*p*	Effects model	Heterogeneity	
					I^2	(%) P
Histological type (Endometrioid vs. Non-endometrioid)	5	1.01 (0.25–4.06)	0.987	REM	84.5	<0.001
Differentiation (Poor vs. Moderate/well)	5	2.82 (1.96–4.06)	< 0.001	FEM	0	0.983
Stage (III-IV vs. I-II)	6	1.71 (1.12–2.60)	0.013	FEM	40.3	0.137
LVSI (Yes vs. No)	7	1.46 (0.80–2.65)	0.218	REM	65.4	0.008

LVSI, lymphovascular space invasion; OR, odds ratio.

1. Hanlin Fu (2023) Critical Rev Heamacol. 2. Engerud H, et al. Gynecol Oncol. 2020;157:260–7.

GARNET Post-Hoc Analysis: PD-L1 Data ORR by Molecular Subtype



Molecular classification[a]	ORR, n/N % (95% CI)	
	dMMR/MSI-H EC Patients	MMRp/MSS EC Patients
Overall	45.5 (37.1–54.0; 65/143)	15.4 (10.1–22.0; 24/156)
CPS (PD-L1 expression)		
≥1 pooled cohorts	**40.8%** (32.7–49.4)	
≥1 by cohort	**54.9%** (43.5–65.9)	**21.7%** (12.1–34.2)
<1 pooled cohorts	**17.1%** (9.4–27.5)	
<1 by cohort	**31.3%** (16.1–50.0)	**6.8%** (1.4–18.7)

PD-L1 CPS scores demonstrated a modest ability to predict response however:

- dMMR/MSI-H status was better able to delineate response from non-response
- High response rates were seen in both PDL1 <1 and >1 in the dMMR/MSI-H cohort
- The predictive value appeared strongest in the MMRp/MSS cohort, but confidence intervals were overlapping
- This analysis was post-hoc and exploratory

[a]*Patients with missing data for a subgroup were not included in calculations.*

CI = confidence interval; CPS = combined positive score; dMMR = mismatch repair deficient; EC = endometrial cancer; MMR = mismatch repair; MMRp = mismatch repair proficient; MSI-H = microsatellite instability high; MSS = microsatellite stable; mut = mutated; ORR = objective response rate; PD-L1 = programmed death ligand 1; TMB-H = high tumor mutational burden; TMB-L = low tumor mutational burden.
Oaknin et al. Clin Cancer Res. 2023;CCR-22-3915.

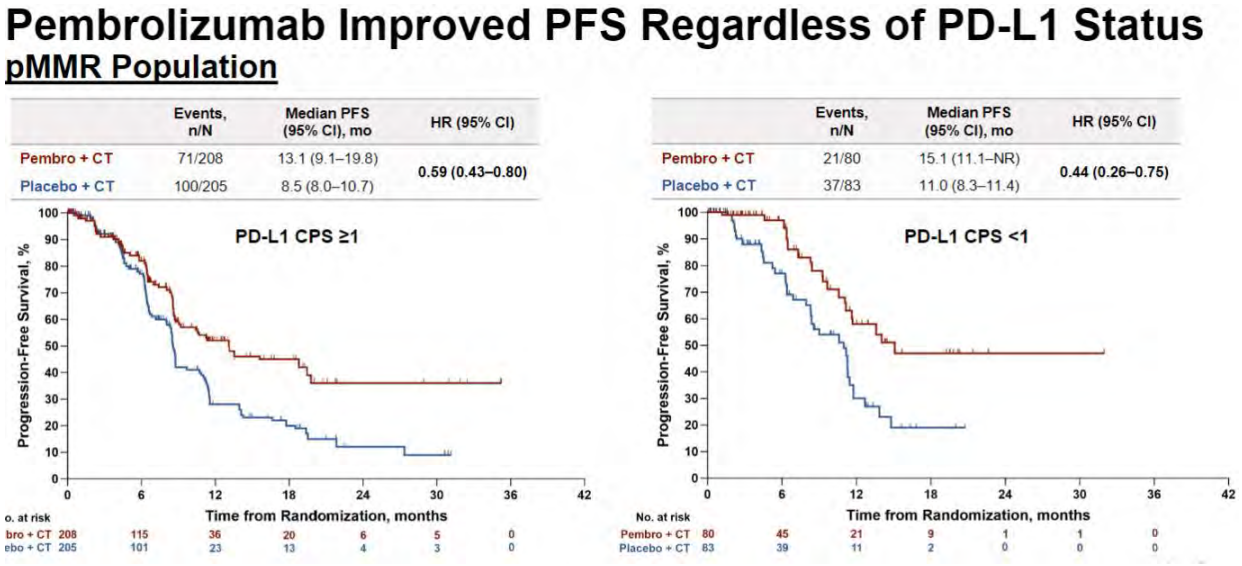
NRG-GY018
Focus on PD-L1

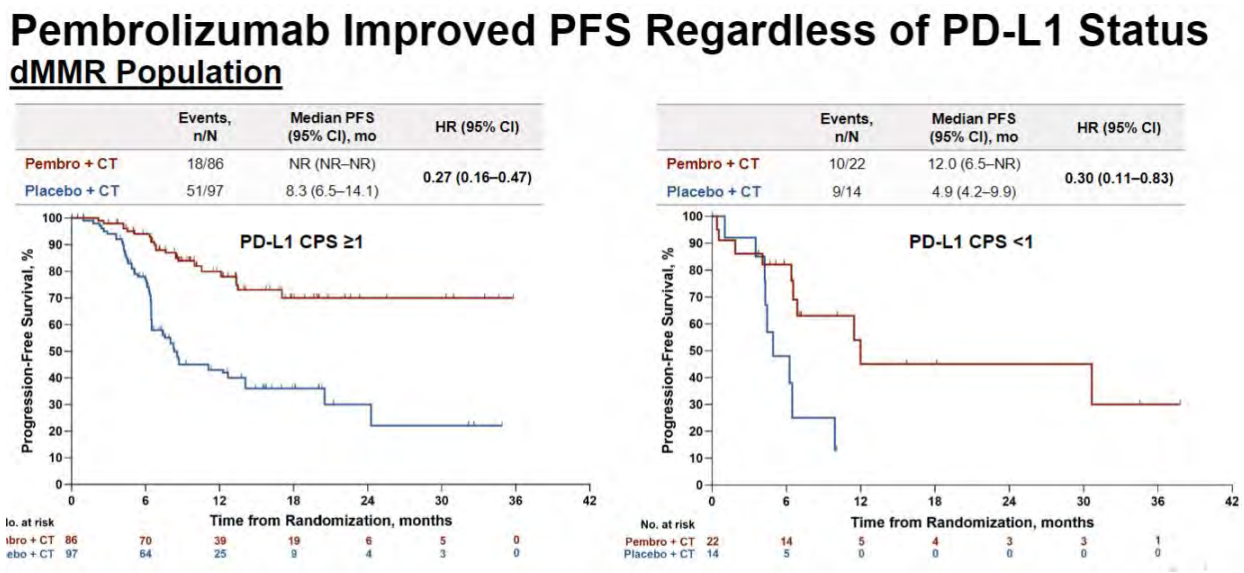
SGO 2024:

PFS by PD-L1 status

Analyse in pMMR & dMMR per PD-L1 status:

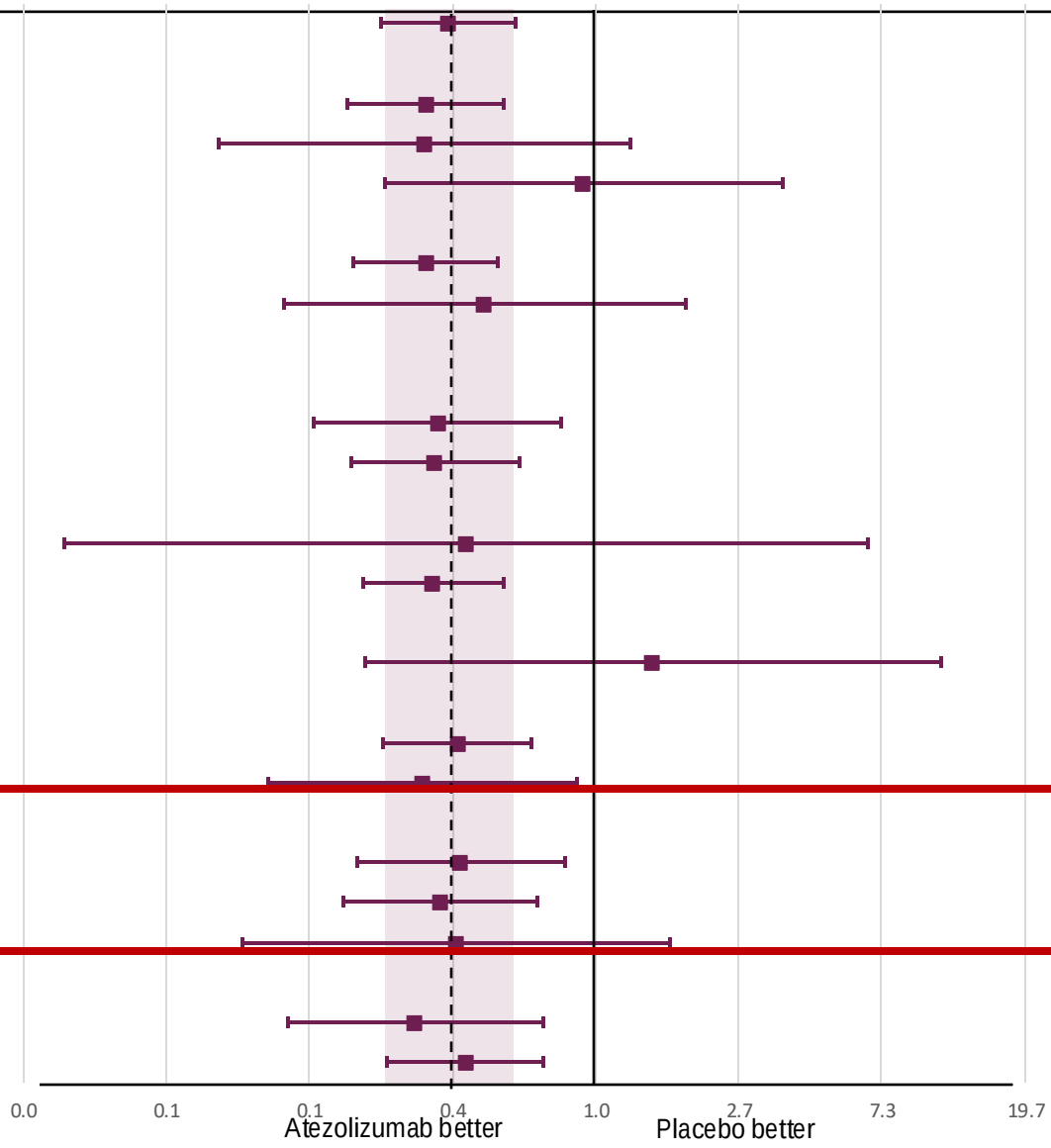
- In pMMR pts (months):
  - PFS in PD-L1+: 13.1 (CT+pembro) vs 8.5 (CT); HR=0.59
  - PFS in PD-L1-: 15.1 (CT+pembro) vs 11.0 (CT); HR=0.44
- In dMMR pts (months):
  - PFS in PD-L1+: NR (CT+pembro) vs 8.3 (CT); HR=0.27
  - PFS in PD-L1-: 12.0 (CT+pembro) vs 4.9 (CT); HR=0.30





AtTEnd Trial: Subgroup Analysis of PFS in dMMR

Subgroup	Placebo no. events/no. pts	Atezolizumab no. events/no. pts	HR (95% CI)
Overall	37/44 (84%)	37/81 (46%)	0.36 (0.23-0.57)
Geographic region			
Europe	28/31 (90%)	27/61 (44%)	0.31 (0.18-0.53)
Asia	6/9 (67%)	3/11 (27%)	0.31 (0.07-1.28)
Australia/New Zealand	3/4 (75%)	7/9 (78%)	0.92 (0.23-3.66)
Race			
Caucasian	31/33 (94%)	34/70 (49%)	0.31 (0.19-0.51)
Asian	6/11 (55%)	3/11 (27%)	0.46 (0.11-1.88)
Status of disease			
Newly diagnosed-Stage III	0/1 (0%)	4/6 (67%)	NE
Newly diagnosed-Stage IV	13/15 (87%)	10/23 (43%)	0.33 (0.14-0.79)
Recurrent	24/28 (86%)	23/52 (44%)	0.33 (0.18-0.59)
Histological type			
Carcinosarcoma	1/1 (100%)	1/3 (33%)	0.41 (0.03-6.62)
Endometrioid	33/38 (87%)	34/74 (46%)	0.32 (0.20-0.53)
Papillary serous	-	-	NE
Other	3/5 (60%)	2/4 (50%)	1.49 (0.20-11.00)
Pre-treated with chemotherapy			
No	28/33 (85%)	31/67 (46%)	0.38 (0.23-0.64)
Yes	9/11 (82%)	6/14 (43%)	0.30 (0.10-0.89)
PD-L1 (IC) expression			
Positive	14/17 (82%)	17/38 (45%)	0.39 (0.19-0.81)
Negative	18/22 (82%)	17/37 (46%)	0.34 (0.17-0.67)
Not evaluable	5/5 (100%)	3/6 (50%)	0.38 (0.09-1.67)
ARID1A expression			
Intact	10/12 (83%)	11/27 (41%)	0.29 (0.12-0.70)
Loss	27/32 (84%)	26/54 (48%)	0.41 (0.23-0.70)



Nicoletta Colombo et al. Presented at ESMO Meeting , Madrid 2023; Colombo N. et al; The Lancet Oncology, Volume 25, Issue 9, 1135 - 1146

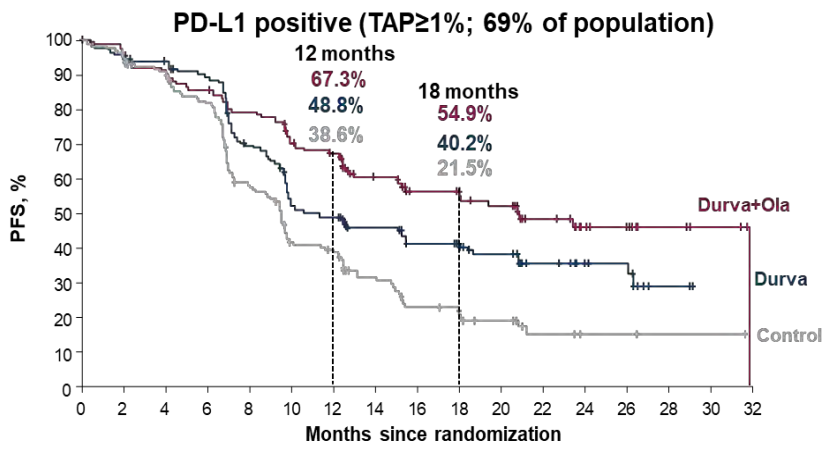
PFS: progression free survival. dMMR: mismatch repair deficient. PD-L1: programmed death ligand-1. IC: tumor infiltrating immune cells. AT-rich interactive domain-containing protein 1A. 95%CI: confidence interval at 95%. PTS: patients.

Exploratory Analysis of Durvalumab With or Without Olaparib as Maintenance Therapy After First-Line Treatment of Advanced and Recurrent EC (DUO-E)

PD-L1 expression: Ventana SP263 IHC assay (Roche Diagnostics); TAP score, cutoff ≥1%

PD-L1-positive: PFS benefit for durvalumab and durvalumab + olaparib

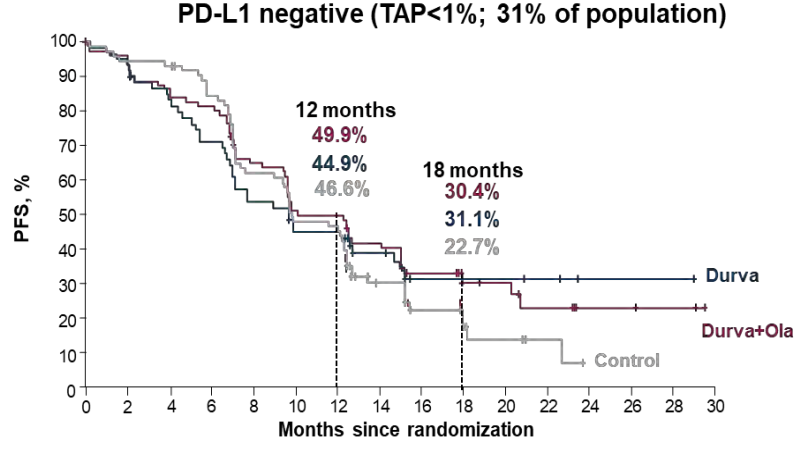
Prespecified exploratory subgroup analysis by PD-L1 status[1,2]



No. at risk

Durva+Ola	150	144	135	126	116	101	95	66	45	40	37	23	13	10	5	3	0
Durva	170	158	152	142	109	80	75	53	43	38	33	21	12	11	3	0	0
Control	163	149	139	122	85	58	53	33	22	17	13	7	3	3	1	1	0

	Control (N=163)	Durva (N=170)	Durva+Ola (N=150)
Events, n (%)	114 (69.9)	97 (57.1)	68 (45.3)
Median PFS (95% CI),[a] months	9.5	11.3	20.8
HR (95% CI) vs Control[b]		**0.63 (0.48–0.83)**	**0.42 (0.31–0.57)**
HR (95% CI) vs Durva[b]			**0.67 (0.49–0.91)**



No. at risk

Durva+Ola	82	78	69	66	51	40	39	28	18	10	9	6	3	3	2	0	
Durva	61	57	48	41	31	25	25	16	9	6	4	3	1	1	1	0	
Control	75	69	68	60	44	34	33	16	10	9	4	2	0	0	0	0	

	Control (N=75)	Durva (N=61)	Durva+Ola (N=82)
Events, n (%)	57 (76.0)	38 (62.3)	55 (67.1)
Median PFS (95% CI),[a] months	9.9	9.7	10.1
HR (95% CI) vs Control[b]		**0.89 (0.59–1.34)**	**0.80 (0.55–1.16)**
HR (95% CI) vs Durva[b]			**0.93 (0.61–1.41)**

Exploratory subgroup analysis. PD-L1 expression evaluated using Ventana SP263. Prevalence shown is based on patients with known PD-L1 status. Rates were estimated by the KM method. [a]CI for median PFS was derived based on the Brookmeyer–Crowley method; [b]The HR and CI were estimated from an unstratified Cox proportional hazards model. CI = confidence interval; Durva = durvalumab; HR = hazard ratio; KM = Kaplan-Meier; Ola = olaparib; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; TAP = tumor area positivity.

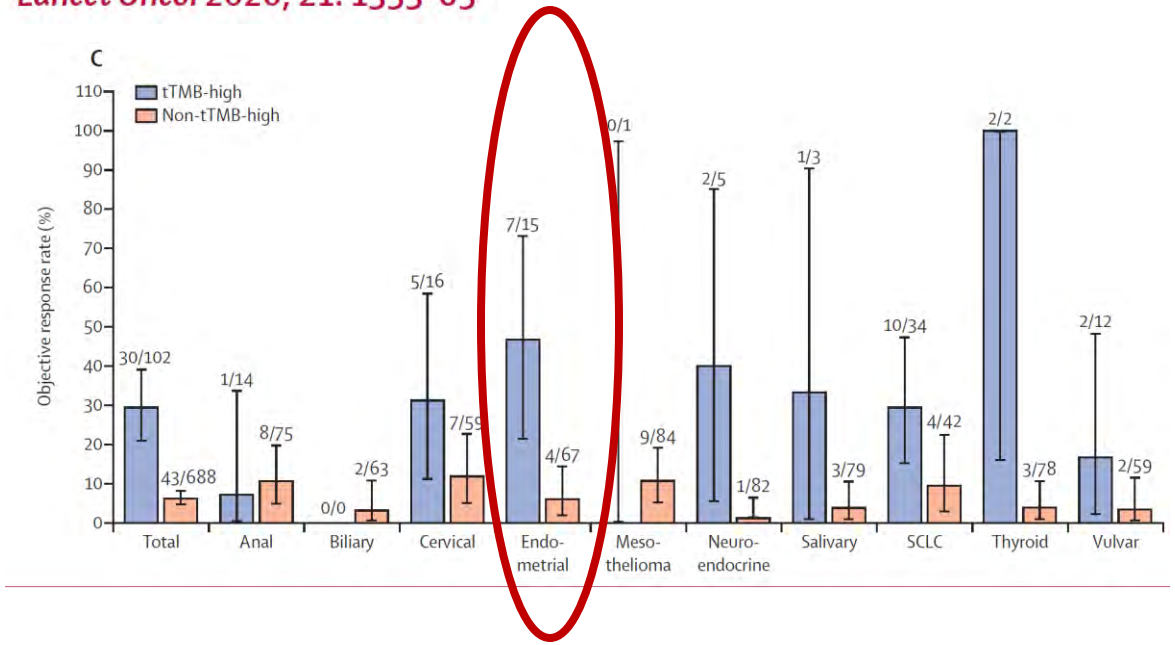
1. Westin SH, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA41. 2. Westin SN, et al. J Clin Oncol. 2023. DOI:10.1200/JCO.23.02132.

Can TMB bring more interest?

Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study

Aurélien Marabelle, Marwan Fakih, Juanita Lopez, Manisha Shah, Ronnie Shapira-Frommer, Kazuhiko Nakagawa, Hyun Cheol Chung, Hedy L Kindler, Jose A Lopez-Martin, Wilson H Miller Jr, Antoine Italiano, Steven Kao, Sarina A Piha-Paul, Jean-Pierre Delord, Robert R McWilliams, David A Fabrizio, Deepti Aurora-Garg, Lei Xu, Fan Jin, Kevin Norwood, Yung-Jue Bang

Lancet Oncol 2020; 21: 1353–65



IMPERFECT OVERLAP BETWEEN MSI AND TMB IN EC

Cancer Medicine

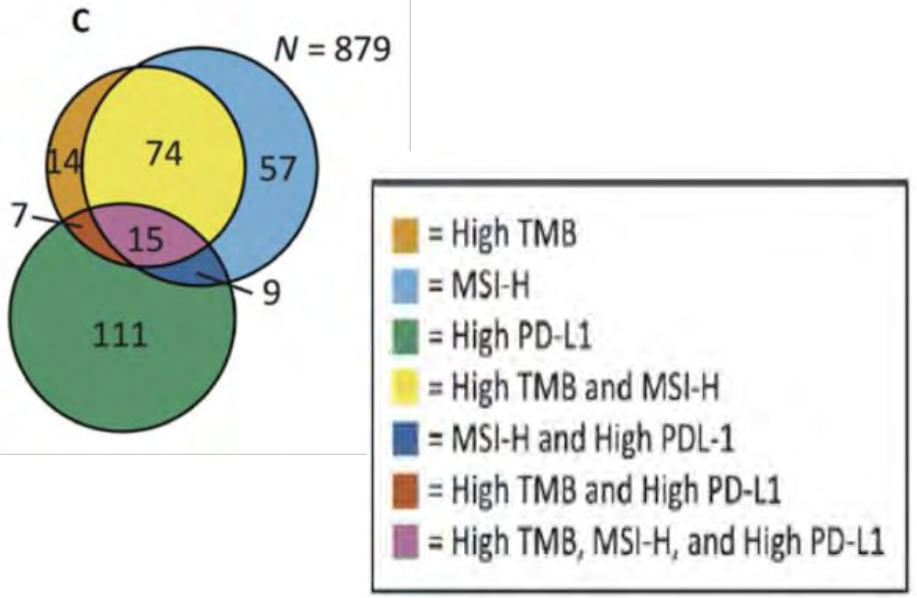
Open Access

ORIGINAL RESEARCH

Microsatellite instability status determined by next-generation sequencing and compared with PD-L1 and tumor mutational burden in 11,348 patients

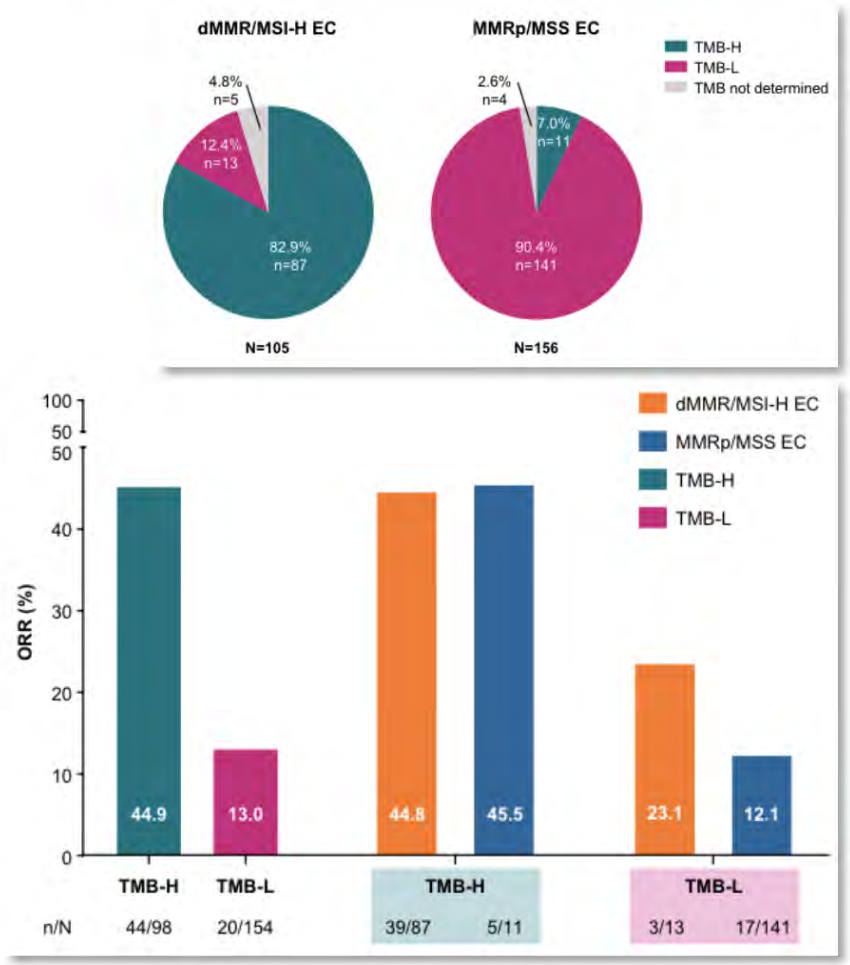
Ari Vanderwalde[1], David Spetzler[2], Nianqing Xiao[2], Zoran Gatalica[2] & John Marshall[2,3]

[1]The University of Tennessee Health Science Center and West Cancer Center, Memphis, Tennessee
[2]Caris Life Sciences, Phoenix, Arizona
[3]Lombardi Cancer Center, Georgetown University Hospital, Washington, District of Columbia



TMB-H as Biomarker ?

Analysis in the GARNET trial:



Oaknin A. et al. Presented at ESMO 2021 Congress

The association of tumor mutational burden, microsatellite stability, and mismatch repair deficiency in an endometrial cancer patient cohort (194)

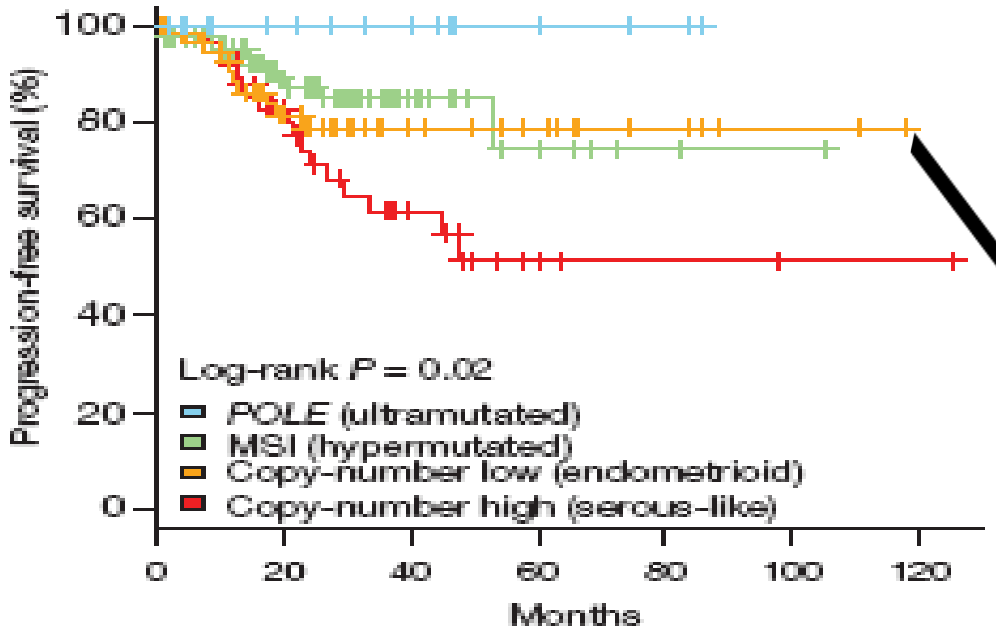
Sarah Lee, MD, MBA[1], Olivia Lara, MD, MS[2], Hannah Karpel, MS[1], Bhavana Pothuri, MD, MS[1]

[1]NYU Grossman School of Medicine, New York, NY, United States, [2]NYU Langone Health, New York, NY, United States

	161 patients
High TMB + MSI/MMRD	25 pts (15.5 %)
High TMB + MSS/MMRP	6 pts (3.7 %)
Low TMB + MSI/MMRD	5 pts (3.1 %)
Low TMB + MSS/MMRP	125 pts (77.6 %)

Abstracts / Gynecologic Oncology 166/S1 (2022) S3–S291

Endometrial Carcinoma, NSMP
Are there some biomarkers of interest?



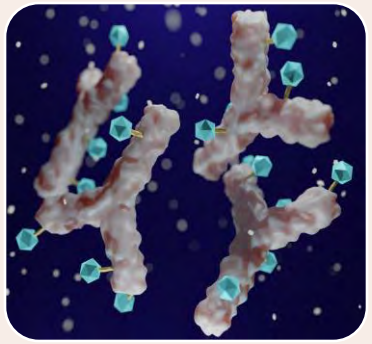
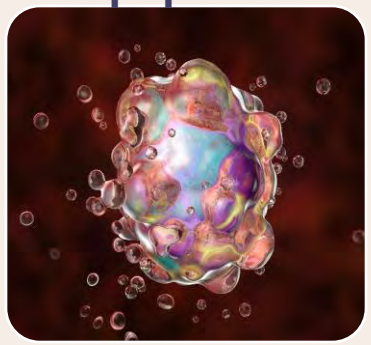
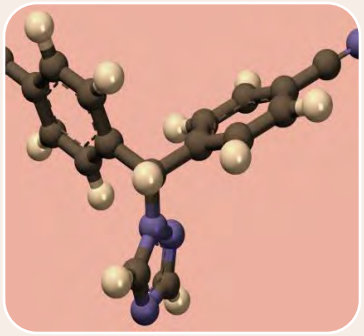
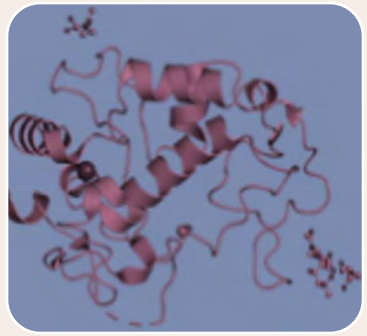
Potential markers to stratify patients in the LCN-NSMP group:

Estrogen receptor status
L1CAM
CTNNB1 (beta-catenin) mutations

Histologic grade

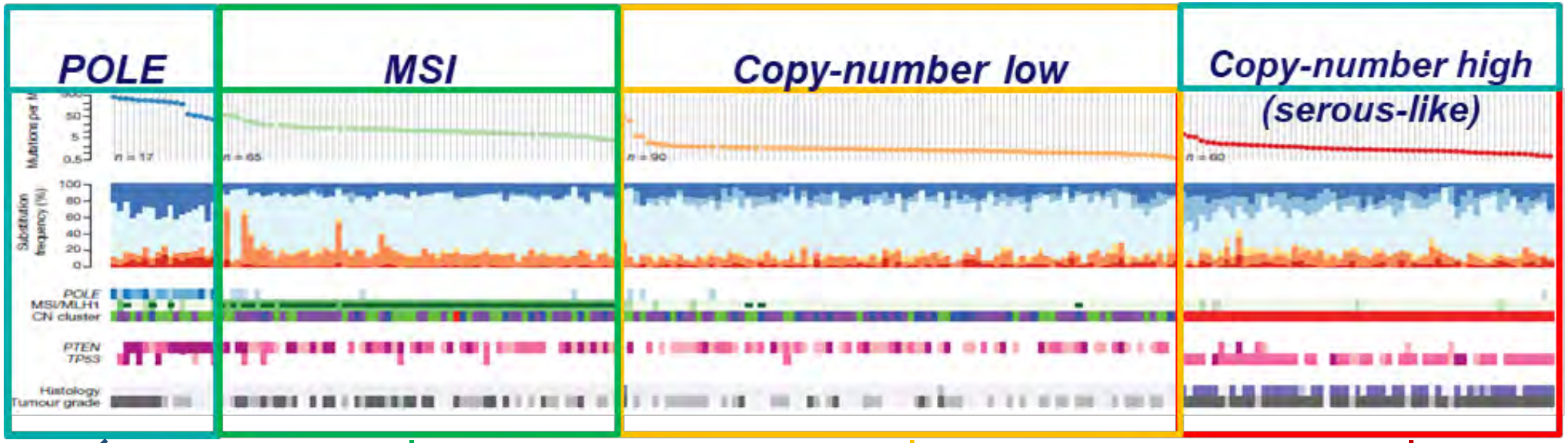
Histologic type (ex: Mesonephric-like carcinomas)

Additional Biomarkers Currently Being Evaluated in EC

Targeting HER2	Kickstarting apoptosis	Revisiting endocrine therapy	FR-α inhibition	Inhibiting TROP-2
				
Trastuzumab deruxtecan[1] Trastuzumab ± C/P[2]	Selinexor[3,4] Navtemadlin[5]	Letrozole + abemaciclib[6] Letrozole + palbociclib[7]	Mirvetuximab soravtansine + gemcitabine[8] Farletuzumab ecteribulin[9,10]	Sacituzumab govitecan[11] MK-2870[12]

FR-α = folate receptor alpha; HER2 = human epidermal growth factor 2; TROP-2 = Trophoblast cell surface antigen 2.

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



- <10%
- Ultra-mutated
- PTEN 94%
- KRAS 53%
- PIK3CA 71%
- PIK3R1 65%
- ARID1A 76%
- FBXW7 82%
- ARID5B 47%

- 25-30%
- Hypermutated
- PTEN 88%
- KRAS 35%
- PIK3CA 71%
- RPL22 33%
- PI3KCA 54%
- PIK3R1 40 %
- ARID1A 37%
- FGFR2 13%

- 30-40%
- MSS
- Low copy number
- PTEN 77%
- CTNNB1 52%
- PI3KCA 53%
- PI3KR1 33%
- ARID1A 42%
- FGFR2 20%

- 25-30%
- MSS
- High copy number
- TP53 92%
- PPP2R1A 22%
- PI3KCA 47%
- Chromosomal Instability
- Activation of MYC, ERBB2, CCNE1, FGFR3…

Biomarkers in EC

1. Validated biomarkers have well defined predictive and/or prognostic value MSI, P53, POLE, HER2

2. Exploratory biomarkers need validation in EC

3. EC has several biomarkers in different validation process
   - MMRd/MIS endometrial cancers are heterogeneous regarding mechanisms of mismatch repair, secondary alterations, microenvironmental features, and clonal/subclonal status.
     → This heterogeneity may have an impact in the response to immunotherapy
   - It is not clear if p53 abnormal tumors may respond more to immunotherapy than wtP53
   - HRR/HRD needs more work to conclude
   - HER2 should be integrated in the EC panel at least in the relapse setting

4. All work is not done!

BioMarkers in Focus: Exploring ICI, PARPi, and Others Role in the Treatment of Endometrial Cancer

Robert Coleman, MD

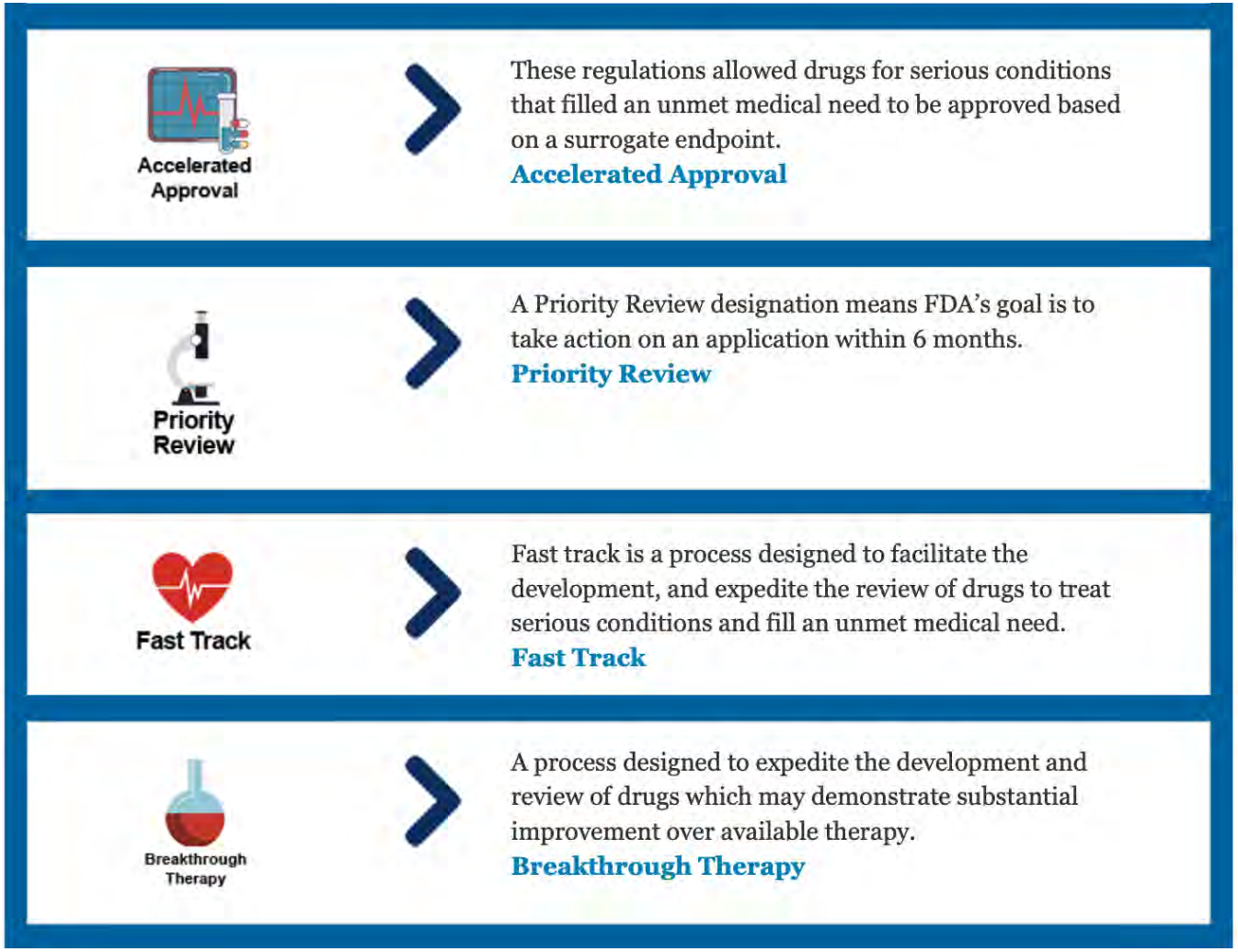
Texas Oncology
The Woodlands, Texas, USA

GOG FOUNDATION® Transforming the standard of care GOG PARTNERS

Outline

- Brief review of the FDA regulatory programs
- Discuss how these programs impact clinical trial strategy and design
- Review recent studies outcomes and hypotheses raised by subgroup associations
- Relate outcomes from trial and guideline listing

Key Programs In Accelerating Drug Development



Established 1992

Established 1992

Established 1997

Established 2012

FDA Guidance for Accelerated Approval (May 2024)

Guidance for Industry

Expedited Programs for Serious Conditions – Drugs and Biologics

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

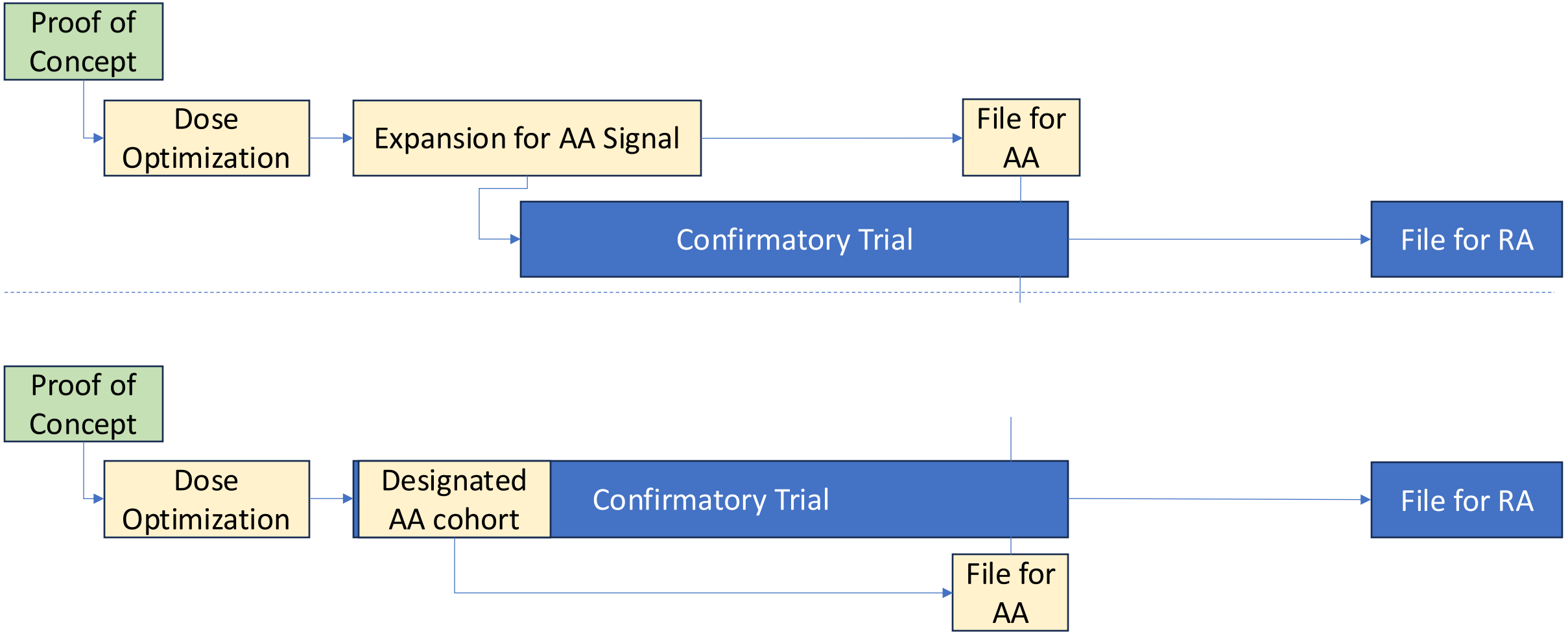
and/or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., WO71, Room 3128
Silver Spring, MD 20993
Phone: 800-835-4709 or 240-402-7800
ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2014
Procedural

Regulatory Playbook: FDA



FDA Accelerated Approval (1992)

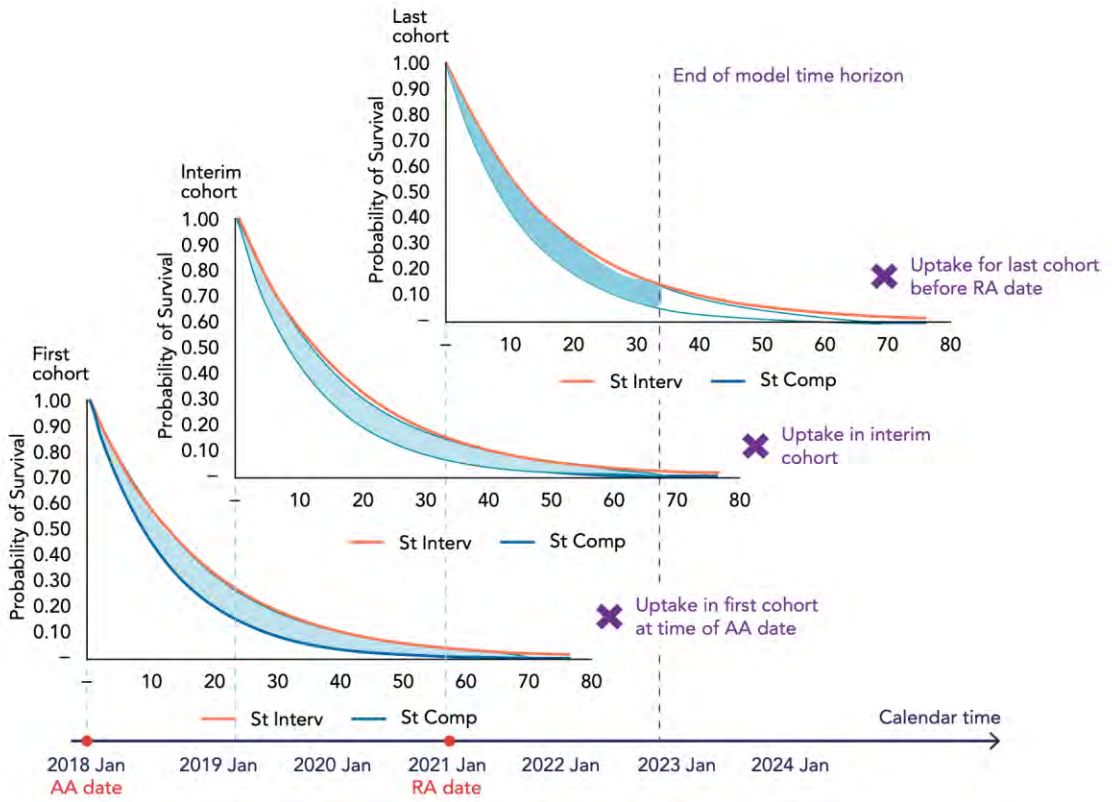
- Initially launched to foster rapid development of HIV medications (first: zalcitabine)
- Rapidly pivoted to oncology: 84% of AA applications are oncology
- Tenets:
  - Serious or life-threatening diseases
  - Provides a benefit over existing therapies (N.B. Agents with AA are not "existing" until regular approval
  - A surrogate biomarker reasonably likely to predict **clinical benefit**
  - Subject to the requirement to verify benefit
  - Post-marketing trials would usually be underway
  - Applicant should carry out studies with due diligence

FDA Accelerated Approval: Nuances

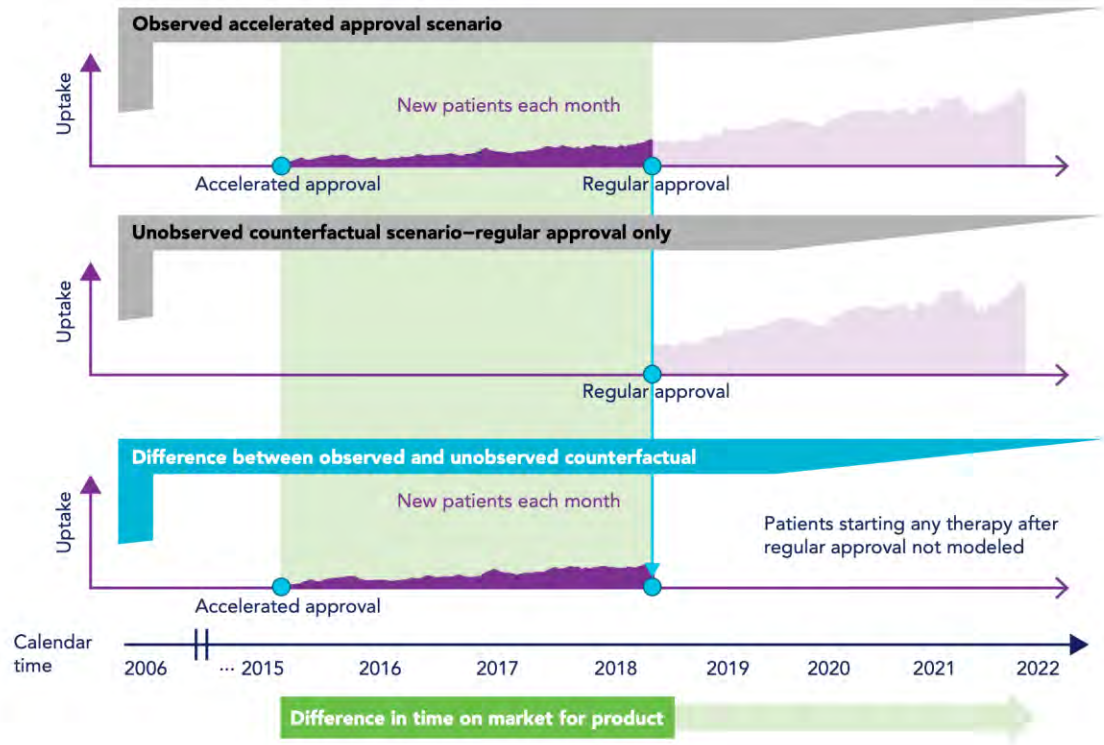
- Surrogate of clinical benefit is the primary focus
  - Single agent studies: ORR; combination studies: PFS
    - ORR: Investigator or BICR assessed; PFS: BICR and placebo-controlled (preferred)
    - Duration of response (DOR) required (target: 2 assessment cycles) with minimum follow-up of 6 months from last response
    - Number of complete responses (CR) considered
- Sample size of 100 homogeneous evaluable, well-defined, "US-like" subjects
- Safety database of 200-300 subjects
  - Tolerability is an important review issue
- Confirmatory study in same tumor type "significantly enrolled" at time of accelerated approval

Impact of Accelerated Approval Program

Potential Population Survival Benefit



Market Access Benefit



Benedict, J Natl Compr Canc Netw 2024;22(6):382–389

GUIDANCE DOCUMENT

Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Draft Guidance for Industry; Availability

JANUARY 2023

Download the Draft Guidance Document | Read the Federal Register Notice

Draft

Not for implementation. Contains non-binding recommendations.

Docket Number: FDA-2022-D-2827

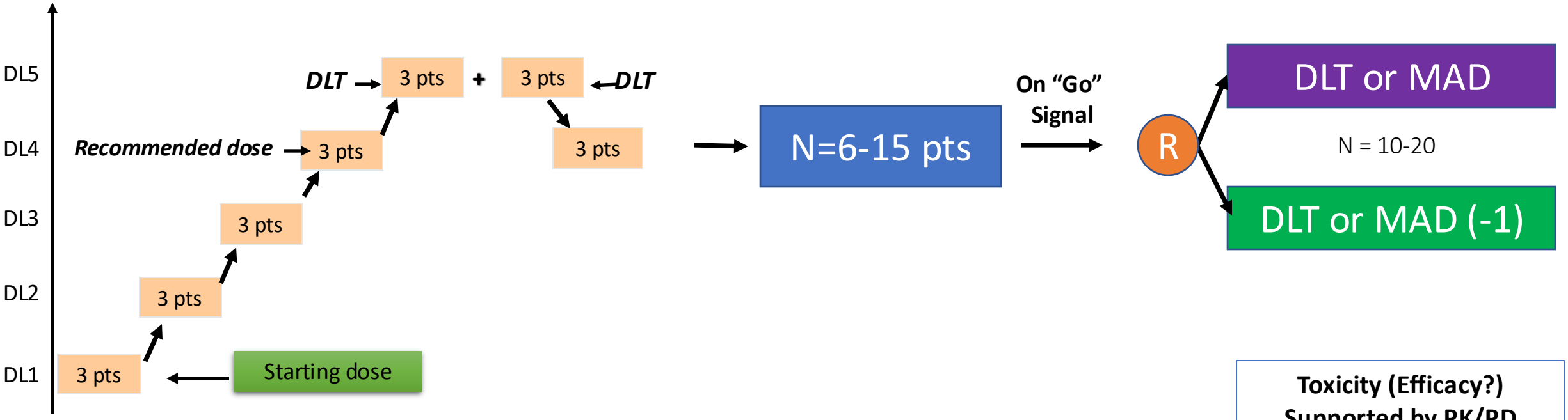
Issued by: Oncology Center of Excellence
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research

Strategy for Dose Optimization: Example

Some Form of Dose-Escalation

Some Form of Dose-Expansion

Some Form of Dose-Evaluation



Toxicity (Efficacy?) Supported by PK/PD Dose-Response characteristics

Considering FDA Approval: Endometrial Cancer

Setting	Available Therapy (ORR)	Contemporary Clinical Trials
First Line* (adv/recurrent) *might become separate catergories	45-55% Might be similar to PSOC, not amenable to AA	Multiple GOG-0209, GY-018, GOG-3041, GOG-3053, GOG-3064, GOG-3055 (maintenance)
≥ Second Line dMMR/MSI	45-55%	KN-158, GARNET
≥ Second Line pMMR/MSS	30%	KN-775
≥ Second Line IO failure	10-15% (Unknown ADC impact)	Multiple

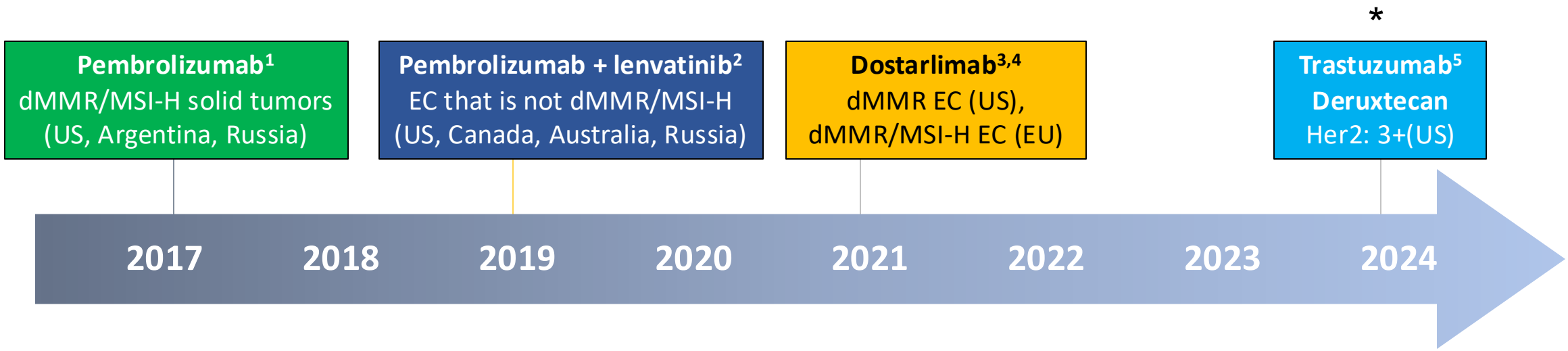
Courtesy of Monk BJ

Immune Checkpoint Inhibitor Efficacy in EC 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%
KEYNOTE 775 Makker (2022)	Pembrolizumab + Lenvatinib	65	42%	346	32%

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

Accelerated Approvals in Advanced/Recurrent or High-risk EC



*AA in Breast (August 2022) and endometrial (May 2024) under pan-tumor approval
Confirmatory trial in endometrial cancer currently not publicly disclosed

1. US FDA. Press Release. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-cancer-treatment-any-solid-tumor-specific-genetic-feature. Published: May 23, 2017. Accessed: May 14, 2021.
2. US FDA. Press Release. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/simultaneous-review-decisions-pembrolizumab-plus-lenvatinib-australia-canada-and-us. Published: September 17, 2019. Accessed: May 14, 2021.
3. US FDA. Press Release. Available at: FDA Approves Immunotherapy for Endometrial Cancer with Specific Biomarker | FDA. Published: April 22, 2021. Accessed: June 7, 2021.
4. EMA: Jemperli. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/jemperli. Accessed June 7, 2021
5. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2.

Accelerated Approval of T-DxD in Recurrent Endometrial Cancer

U.S. FOOD & DRUG ADMINISTRATION

Home / Drugs / Development & Approval Process | Drugs / Drug Approvals and Databases / Resources for Information | Approved Drugs / FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors

FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors

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Resources for Information | Approved Drugs

- Oncology (Cancer)/Hematologic Malignancies Approval Notifications
- Ongoing | Cancer Accelerated Approvals
- Verified Clinical Benefit | Cancer Accelerated Approvals
- Withdrawn | Cancer Accelerated Approvals

On April 5, 2024, the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo, Inc.) for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

Full prescribing information for Enhertu will be posted here.

Efficacy was evaluated in 192 adult patients with previously treated unresectable or metastatic HER2-positive (IHC 3+) solid tumors who were enrolled in one of three multicenter trials: DESTINY-PanTumor02 (NCT04482309), DESTINY-Lung01 (NCT03505710), and DESTINY-CRC02 (NCT04744831). All three trials excluded patients with a history of interstitial lung disease (ILD)/pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening and clinically significant cardiac disease. Patients were also excluded for active brain metastases or ECOG performance status >1. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity.

Content current as of:
04/05/2024

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2

Current Treatment of Advanced/Recurrent or High-risk EC

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Endometrial Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

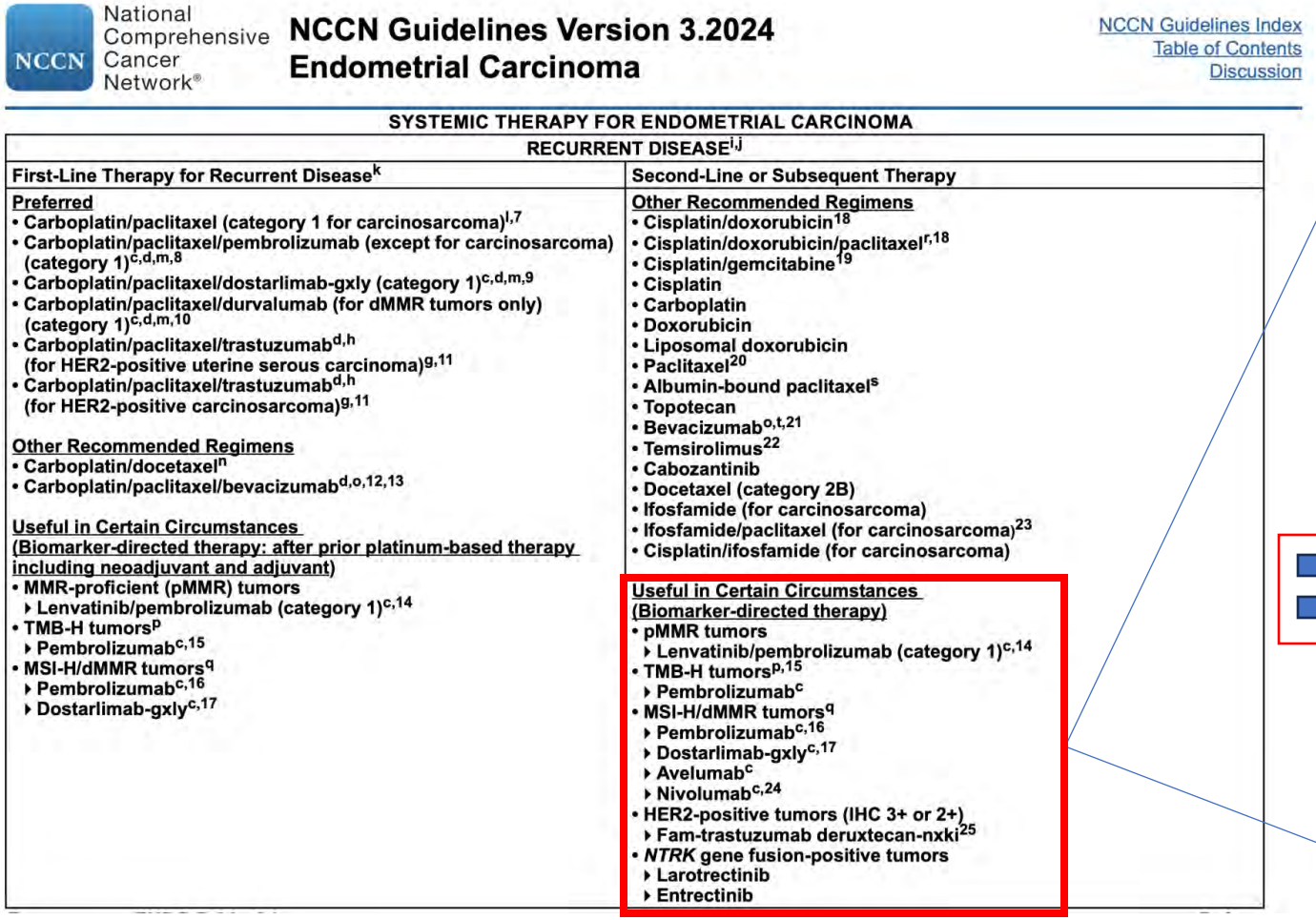
SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

RECURRENT DISEASE[i,j]

First-Line Therapy for Recurrent Disease[k]	Second-Line or Subsequent Therapy
Preferred • Carboplatin/paclitaxel (category 1 for carcinosarcoma)[l,7] • Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1)[c,d,m,8] • Carboplatin/paclitaxel/dostarlimab-gxly (category 1)[c,d,m,9] • Carboplatin/paclitaxel/durvalumab (for dMMR tumors only) (category 1)[c,d,m,10] • Carboplatin/paclitaxel/trastuzumab[d,h] (for HER2-positive uterine serous carcinoma)[g,11] • Carboplatin/paclitaxel/trastuzumab[d,h] (for HER2-positive carcinosarcoma)[g,11] **Other Recommended Regimens** • Carboplatin/docetaxel[n] • Carboplatin/paclitaxel/bevacizumab[d,o,12,13] **Useful in Certain Circumstances (Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant)** • MMR-proficient (pMMR) tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,14] • TMB-H tumors[p] ▸ Pembrolizumab[c,15] • MSI-H/dMMR tumors[q] ▸ Pembrolizumab[c,16] ▸ Dostarlimab-gxly[c,17]	**Other Recommended Regimens** • Cisplatin/doxorubicin[18] • Cisplatin/doxorubicin/paclitaxel[r,18] • Cisplatin/gemcitabine[19] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[20] • Albumin-bound paclitaxel[s] • Topotecan • Bevacizumab[o,t,21] • Temsirolimus[22] • Cabozantinib • Docetaxel (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[23] • Cisplatin/ifosfamide (for carcinosarcoma) **Useful in Certain Circumstances (Biomarker-directed therapy)** • pMMR tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,14] • TMB-H tumors[p,15] ▸ Pembrolizumab[c] • MSI-H/dMMR tumors[q] ▸ Pembrolizumab[c,16] ▸ Dostarlimab-gxly[c,17] ▸ Avelumab[c] ▸ Nivolumab[c,24] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[25] • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib

https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1473

Current Treatment of Advanced/Recurrent or High-risk EC



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Endometrial Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

RECURRENT DISEASE[i,j]

First-Line Therapy for Recurrent Disease[k]	Second-Line or Subsequent Therapy
Preferred • Carboplatin/paclitaxel (category 1 for carcinosarcoma)[l,7] • Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1)[c,d,m,8] • Carboplatin/paclitaxel/dostarlimab-gxly (category 1)[c,d,m,9] • Carboplatin/paclitaxel/durvalumab (for dMMR tumors only) (category 1)[c,d,m,10] • Carboplatin/paclitaxel/trastuzumab[d,h] (for HER2-positive uterine serous carcinoma)[g,11] • Carboplatin/paclitaxel/trastuzumab[d,h] (for HER2-positive carcinosarcoma)[g,11] **Other Recommended Regimens** • Carboplatin/docetaxel[n] • Carboplatin/paclitaxel/bevacizumab[d,o,12,13] **Useful in Certain Circumstances (Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant)** • MMR-proficient (pMMR) tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,14] • TMB-H tumors[p] ▸ Pembrolizumab[c,15] • MSI-H/dMMR tumors[q] ▸ Pembrolizumab[c,16] ▸ Dostarlimab-gxly[c,17]	**Other Recommended Regimens** • Cisplatin/doxorubicin[18] • Cisplatin/doxorubicin/paclitaxel[r,18] • Cisplatin/gemcitabine[19] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[20] • Albumin-bound paclitaxel[s] • Topotecan • Bevacizumab[o,t,21] • Temsirolimus[22] • Cabozantinib • Docetaxel (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[23] • Cisplatin/ifosfamide (for carcinosarcoma) **Useful in Certain Circumstances (Biomarker-directed therapy)** • pMMR tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,14] • TMB-H tumors[p,15] ▸ Pembrolizumab[c] • MSI-H/dMMR tumors[q] ▸ Pembrolizumab[c,16] ▸ Dostarlimab-gxly[c,17] ▸ Avelumab[c] ▸ Nivolumab[c,24] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[25] • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib

Useful in Certain Circumstances (Biomarker-directed therapy)

- **pMMR tumors**
  - ▸ **Lenvatinib/pembrolizumab (category 1)[c,14]**
- **TMB-H tumors[p,15]**
  - ▸ **Pembrolizumab[c]**
- **MSI-H/dMMR tumors[q]**
  - ▸ **Pembrolizumab[c,16]**
  - ▸ **Dostarlimab-gxly[c,17]**
  - ▸ **Avelumab[c]**
  - ▸ **Nivolumab[c,24]**
- **HER2-positive tumors (IHC 3+ or 2+)**
  - ▸ **Fam-trastuzumab deruxtecan-nxki[25]**
- ***NTRK* gene fusion-positive tumors**
  - ▸ **Larotrectinib**
  - ▸ **Entrectinib**

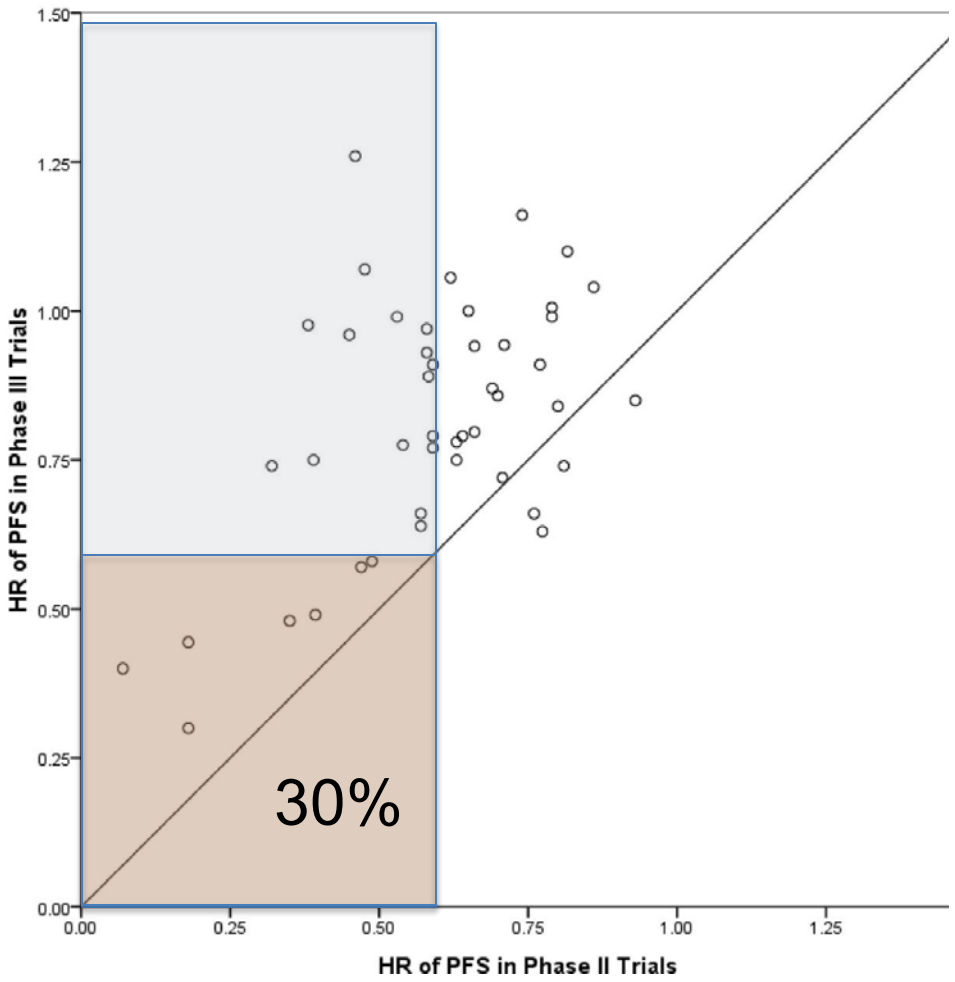
https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1473

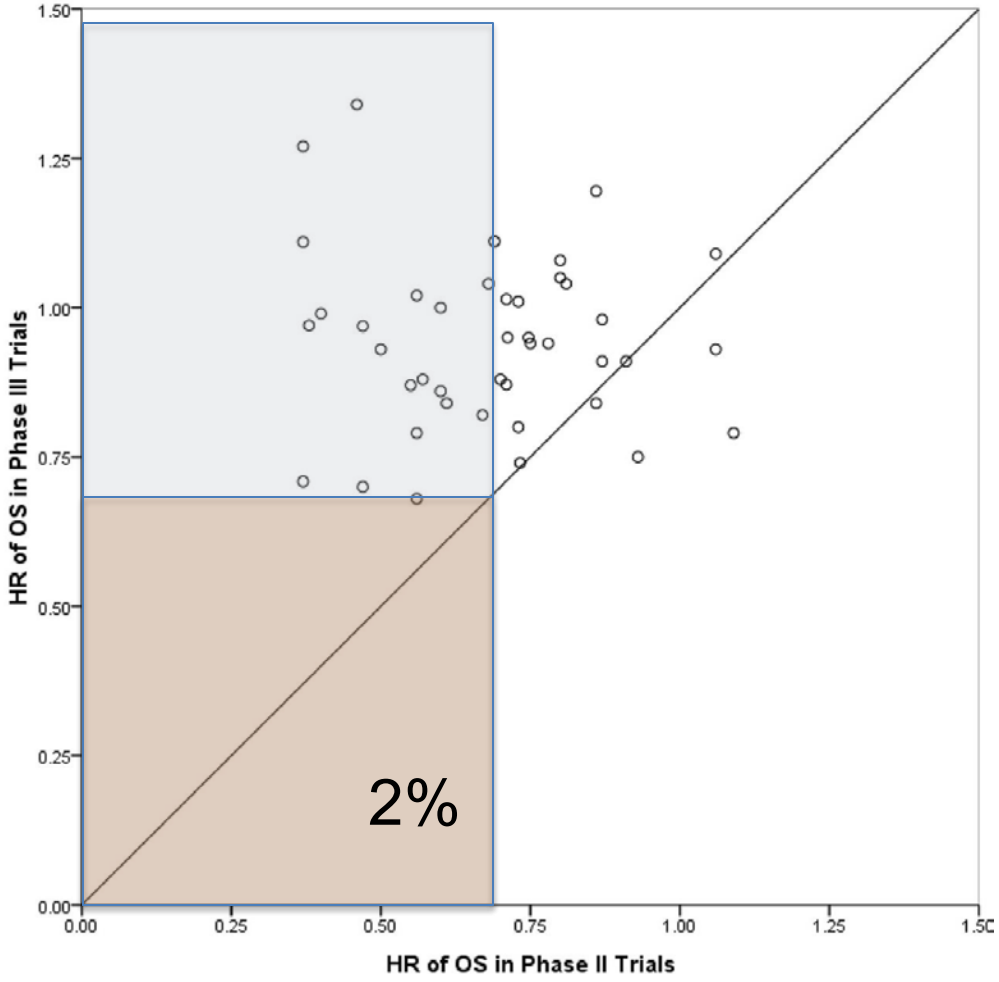
Confirmatory Immunotherapy Trials in EC

Name	EN6-RUBY[1]	NRG-GY-018[2]	DUO-E[3]	KN-775[4]
Investigational agent	Dostarlimab	Pembrolizumab	Durvalumab + Olaparib	Pembrolizumab + Lenvatinib
N	740	816	699	875
Concomitant	+	+	+	Pembro + Lenvatinib vs. Chemotherapy
Maintenance	+	+	+	
dMMR/MSI evaluation	+	+	+	+
EU	+	+	+	+
US	+	+	+	+

1. Mirza N Engl J Med 338:2145-2158 (2023)
2. Eskander, N Engl J Med 338:2159-2170 (2023)
3. Westin, J Clin Oncol 42:283-299 (2024)
4. Makker, N Engl J Med 386:437-448

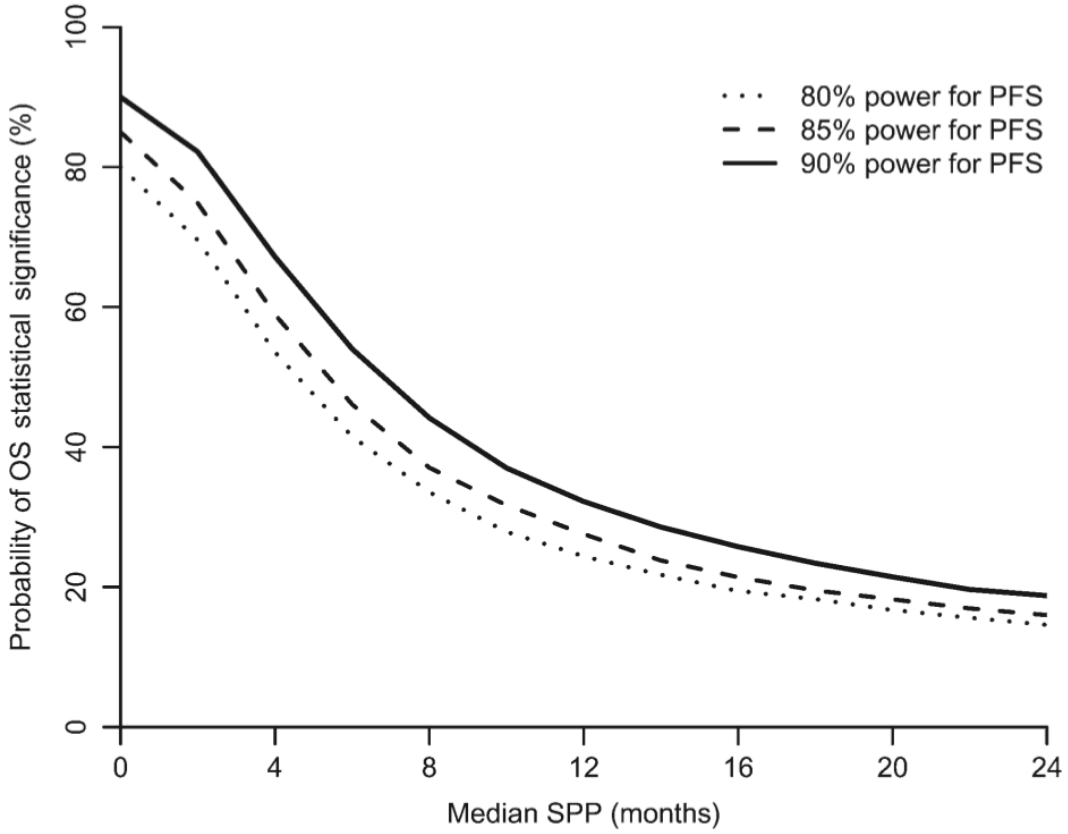
Successful Registration Trials are Hard!

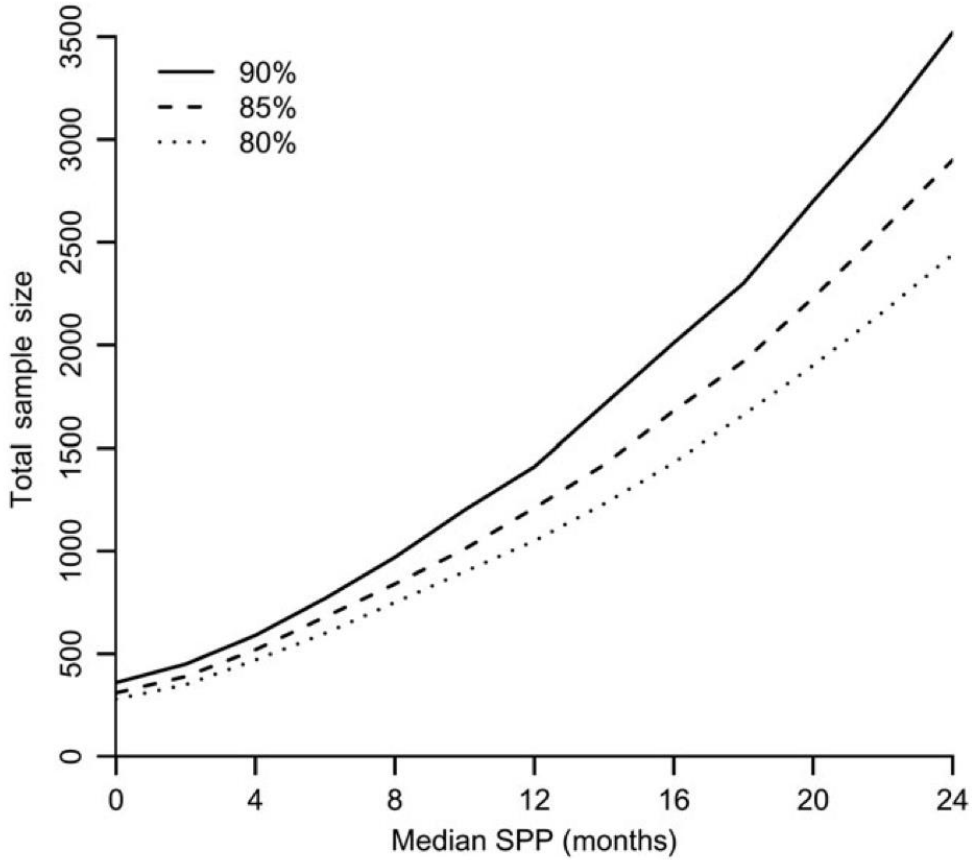




Liang, Eur J Cancer 2019 121, 19-28

PFS as a Surrogate of OS

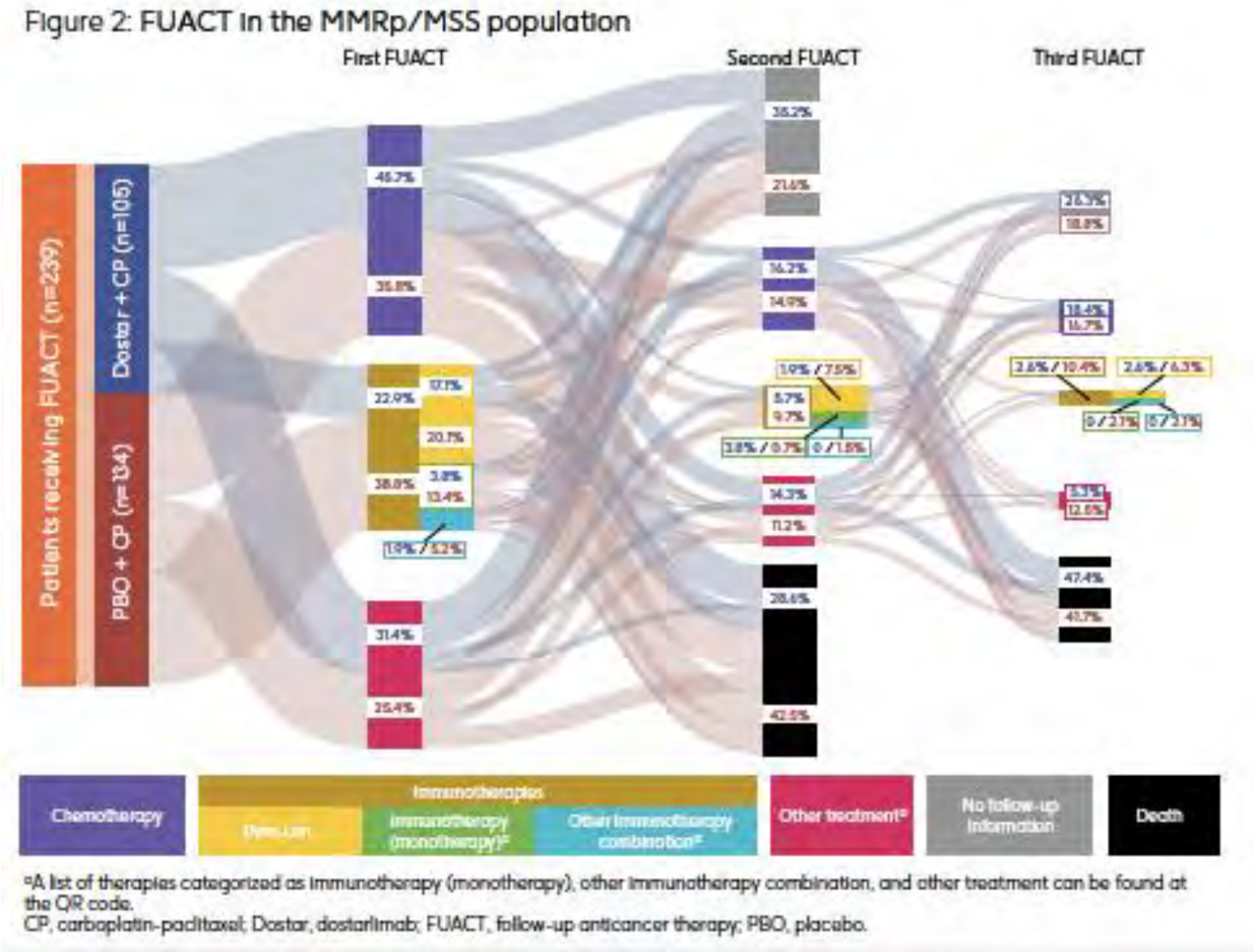




Assumption PFS gain 6 to 9 mos, HR: 0.66

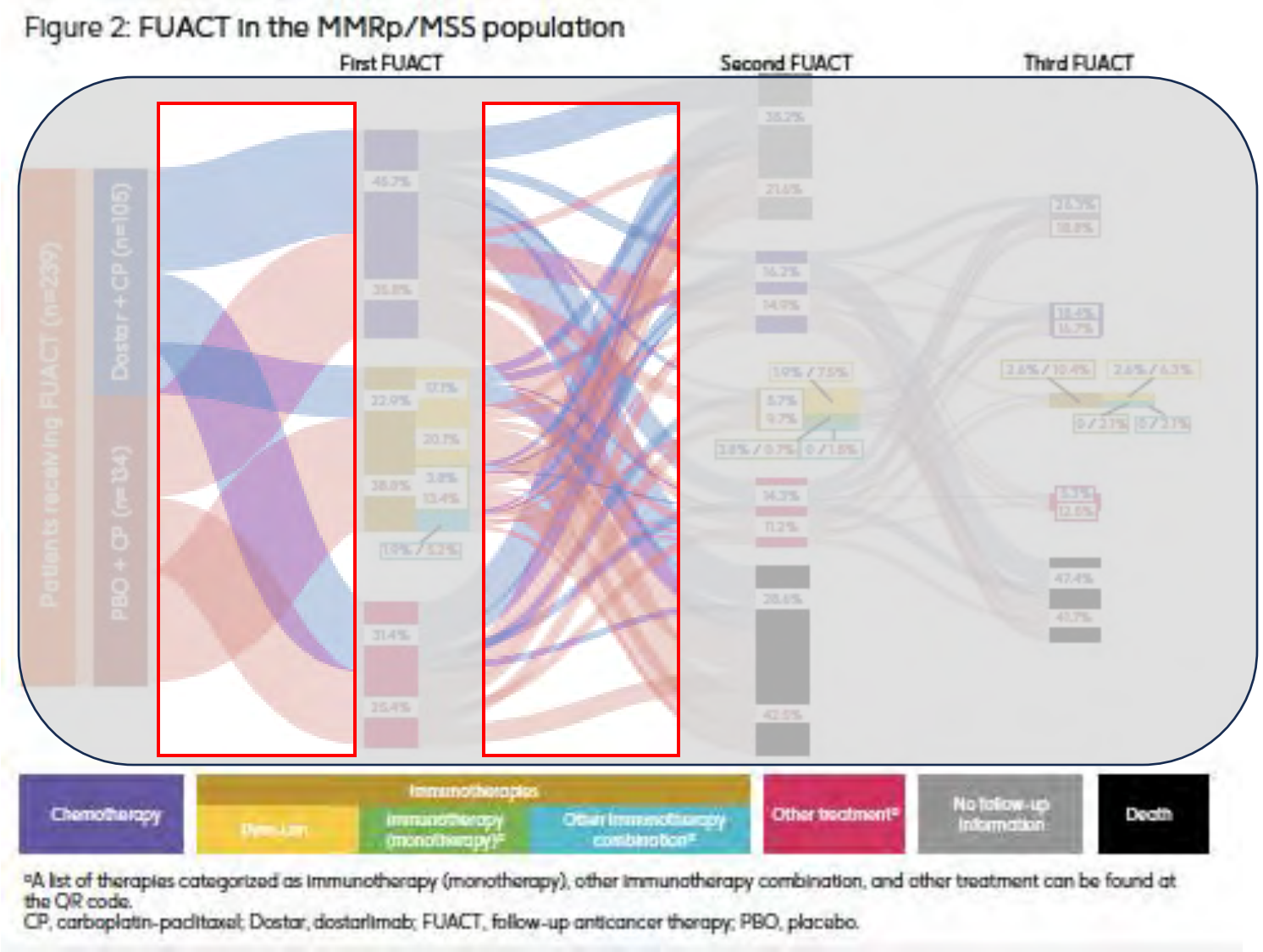
Broglio & Berry, J Natl Cancer Inst (2009) 101:1642-1649

Impact of Post-Progression Therapy: RUBY Example



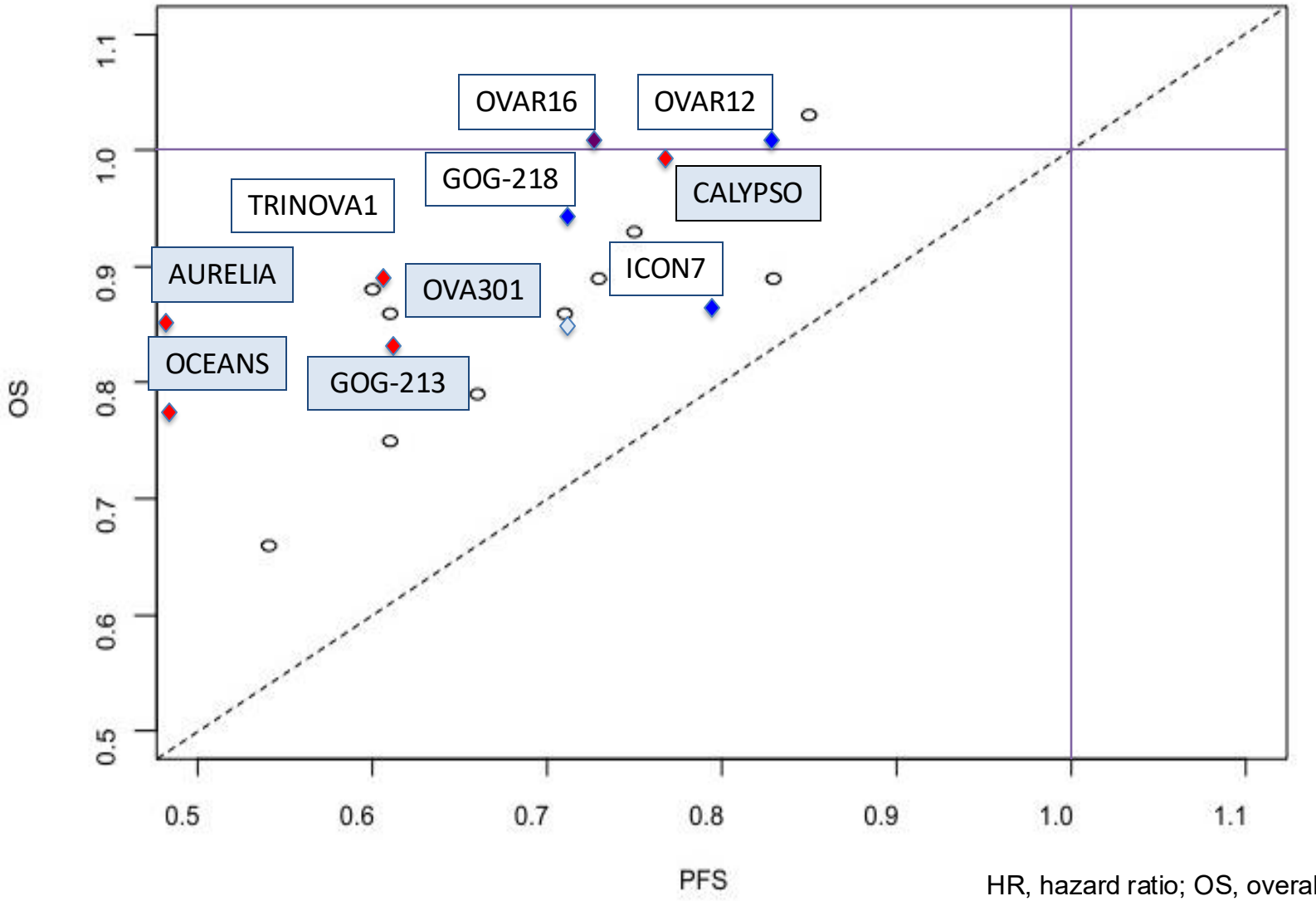
Mirza MR et al. ESMO 2024; 731P,

Impact of Post-Progression Therapy: RUBY Example



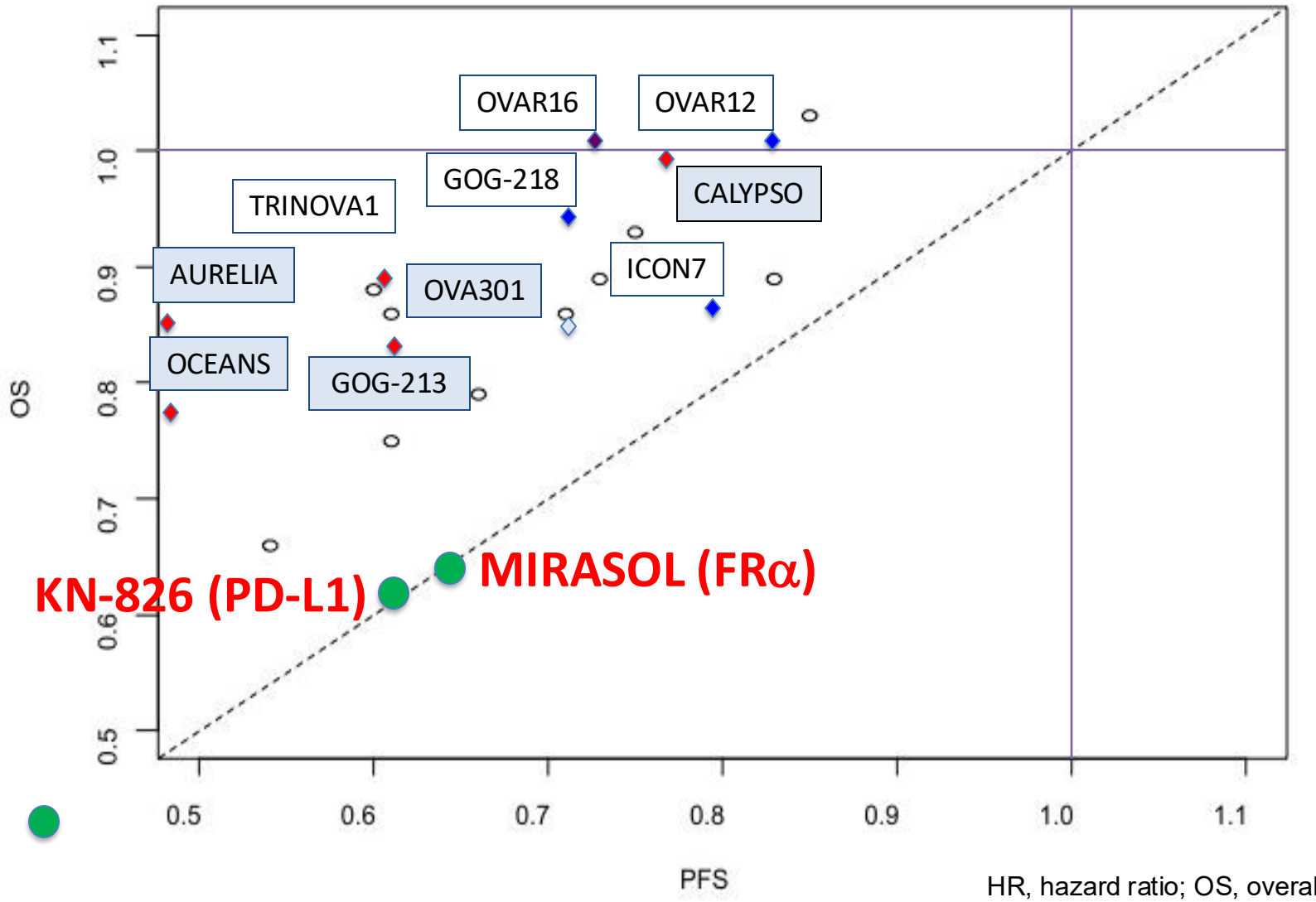
Mirza MR et al. ESMO 2024; 731P,

Value of a Predictive Biomarker



HR, hazard ratio; OS, overall survival; PFS, progression free survival; Courtesy of E. Eisenhauer ASCO 2010

Value of a Predictive Biomarker



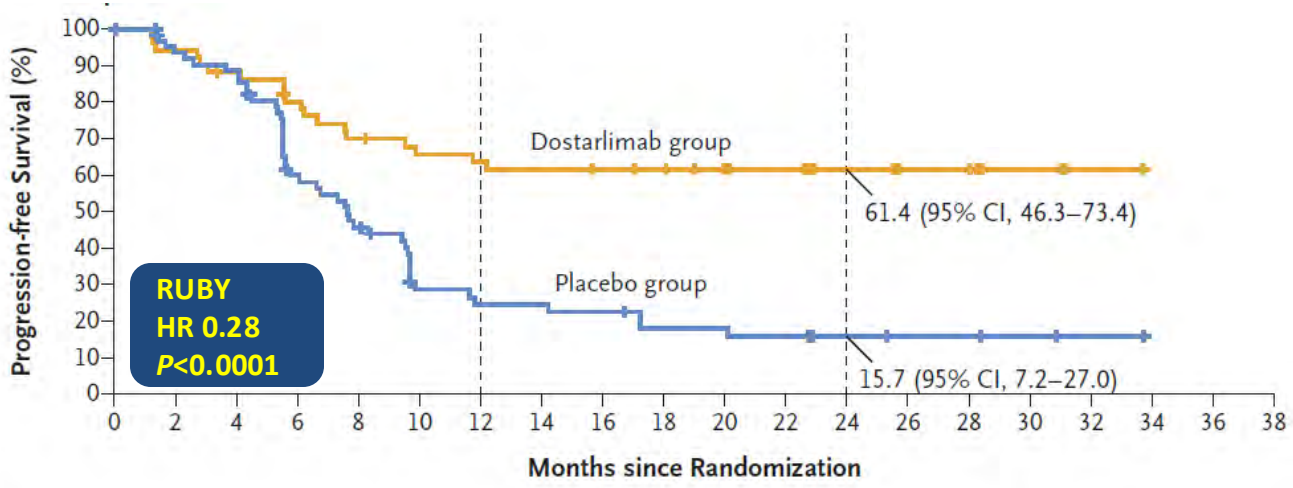
KN-826 (PD-L1)

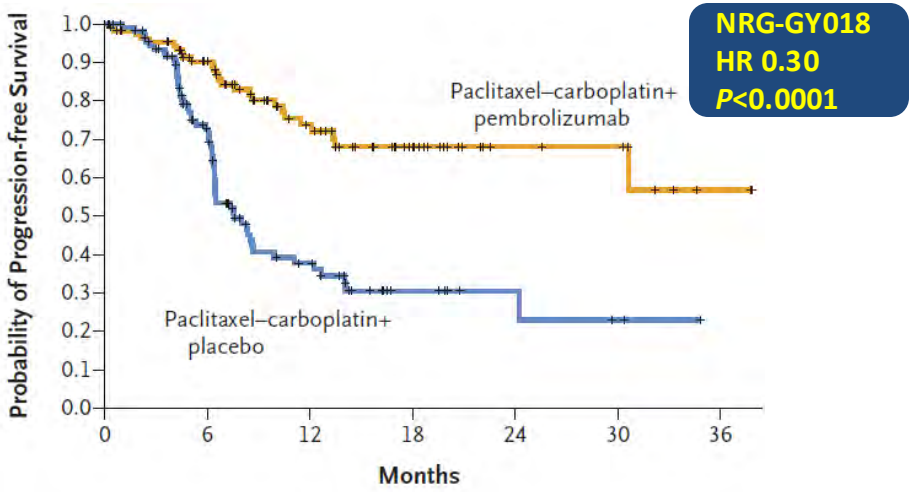
MIRASOL (FRα)

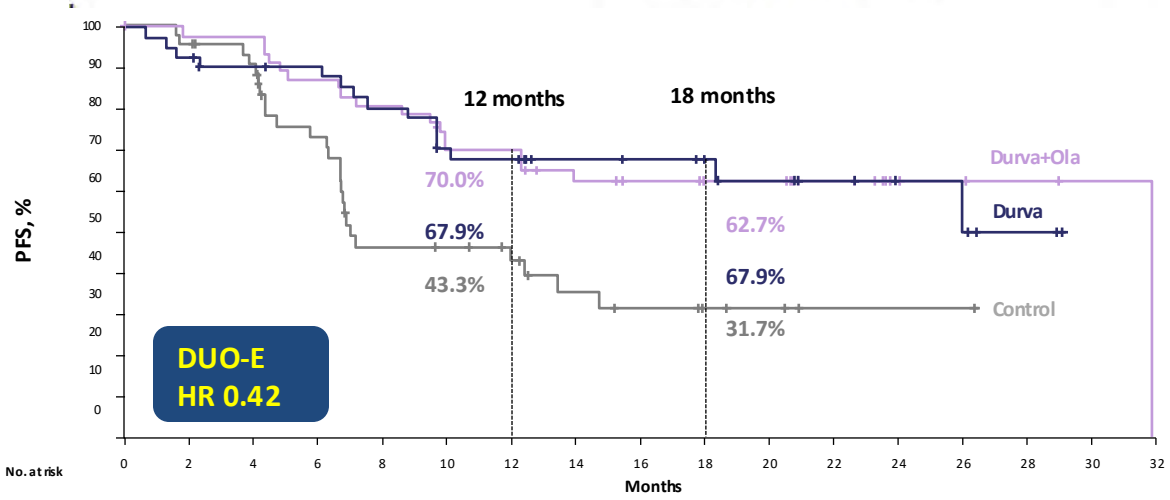
RUBY (MSI)

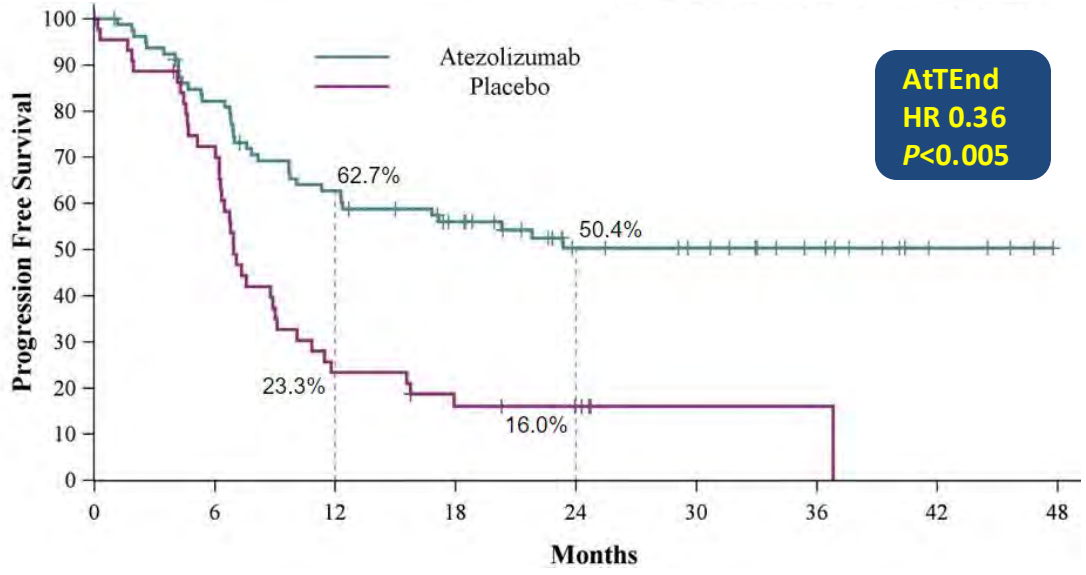
HR, hazard ratio; OS, overall survival; PFS, progression free survival; Courtesy of E. Eisenhauer ASCO 2010

Impact of Strong Biomarker Treatment Effect





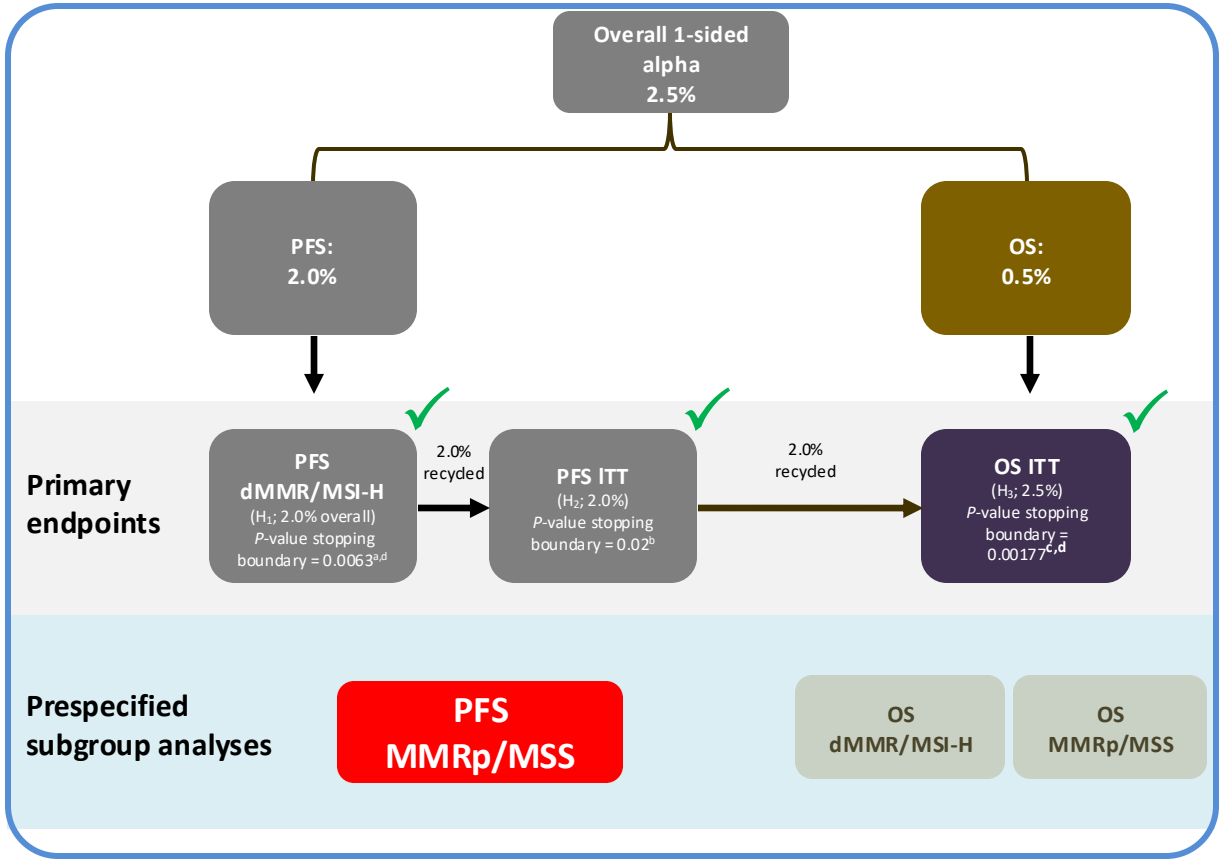




Mansoor R. Mirza et al. NEJM August 2023,
Ramez N. Eskander et al. NEJM August 2023,
Westin SN, et al. J Clin Oncol 2024,
Nicoletta Colombo et al., Lancet Oncol 2024

Subgroup Situation

RUBY



GY018

General

- Analysis populations
  - Efficacy: Intent to treat[a]
  - Safety: All treated patients
- pMMR and dMMR populations evaluated separately and independently
- Power calculations for PFS (primary endpoint)
  - **pMMR population**
    - **If true HR is 0.70, study has at least 90% power when 394 events occurred**
  - dMMR population
    - If true HR is 0.60, study has at least 85% power when 168 events occurred
- **Null hypothesis was tested at α = 0.0125 using a stratified log-rank test**

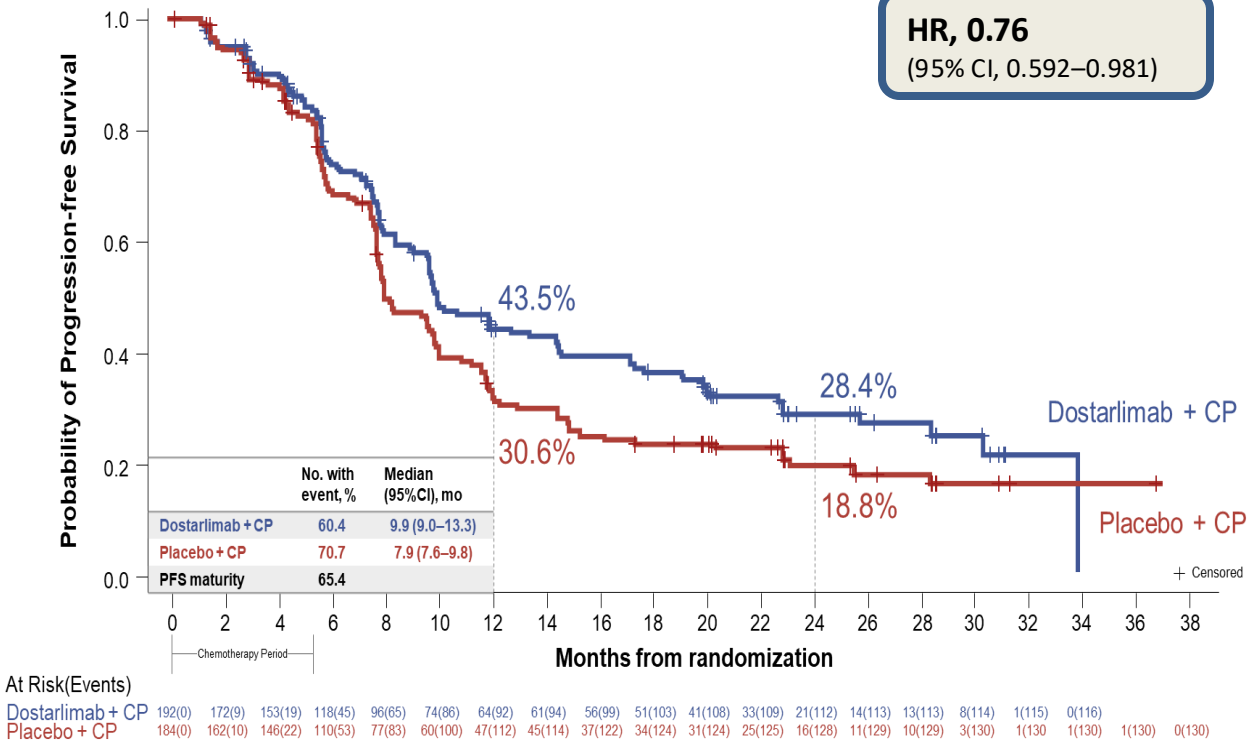
Mirza N Engl J Med 338:2145-2158 (2023)
Eskander, N Engl J Med 338:2159-2170 (2023)

Subgroup Situation

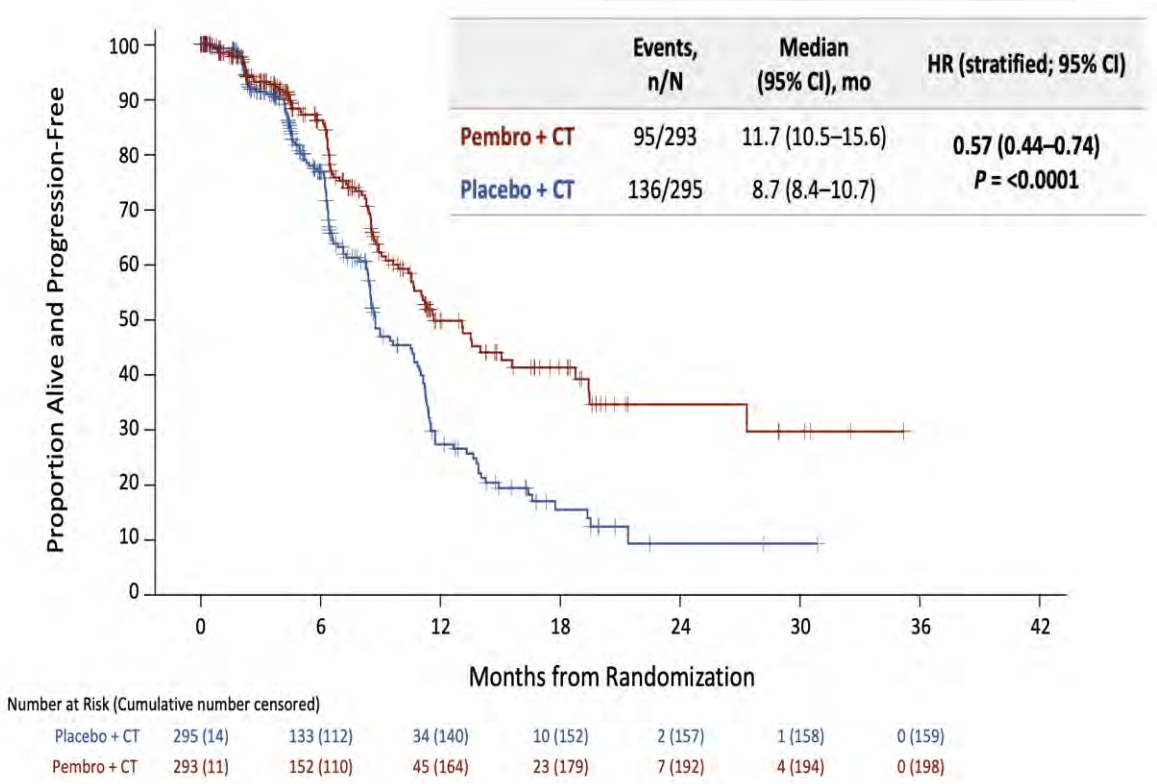
RUBY - Inferred

MMRp - PFS

HR, 0.76
(95% CI, 0.592–0.981)



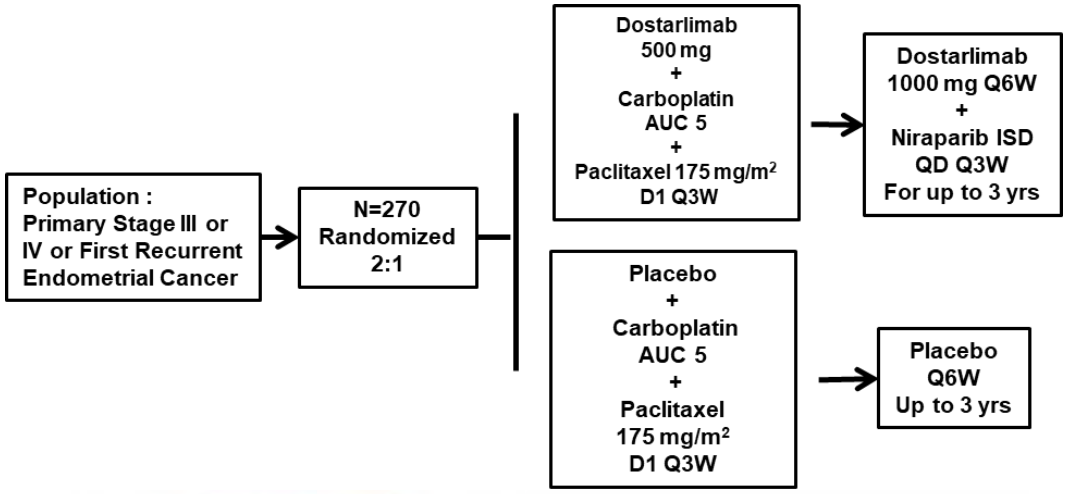
GY018 - Analytical

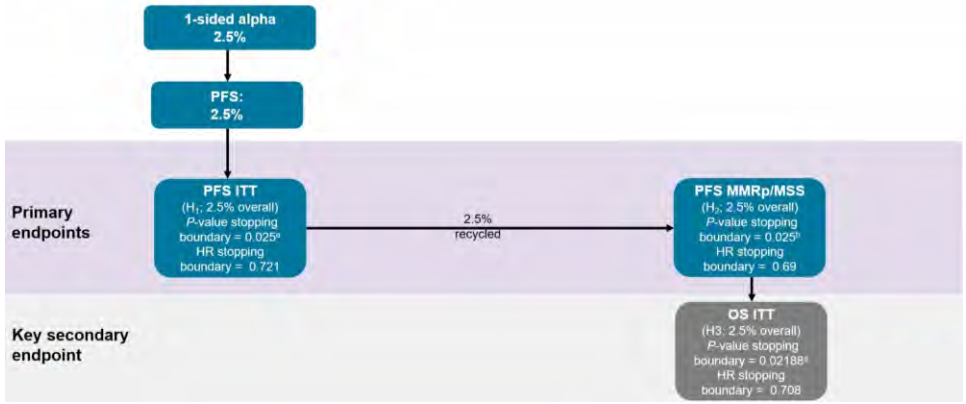


Mirza N Engl J Med 338:2145-2158 (2023)
Eskander, N Engl J Med 338:2159-2170 (2023)

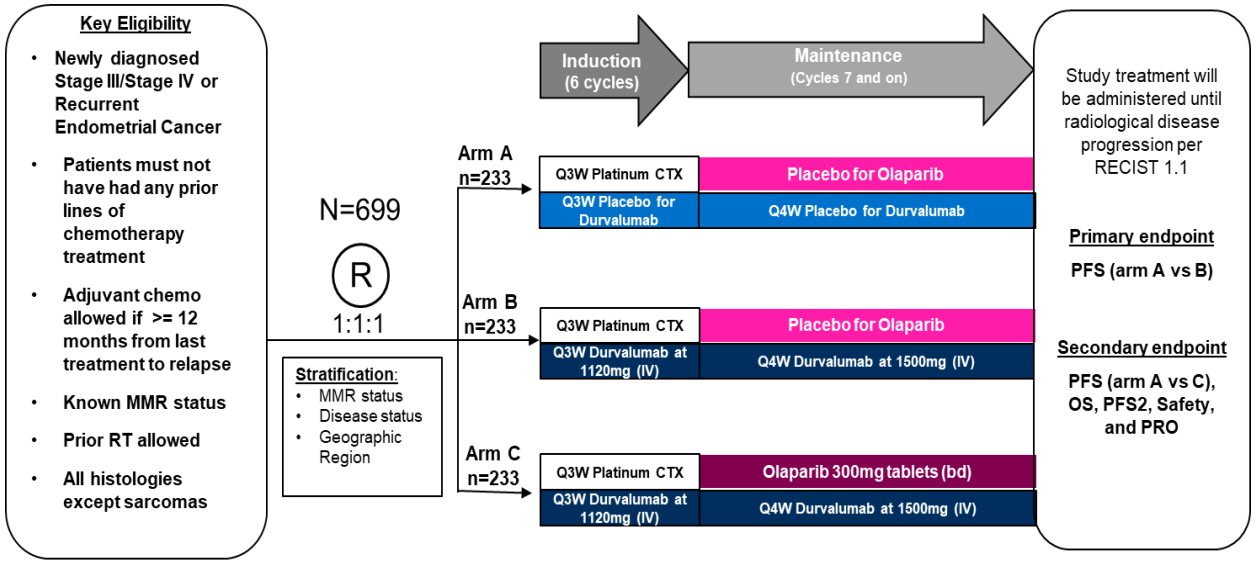
Contribution of Components…PARPi

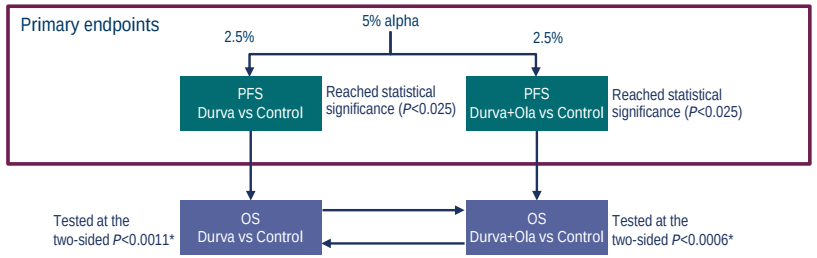
GOG 3031 Ruby Part 2: NCT03981796





GOG 3041: DUO-E NCT04269200





Event-driven analysis

The planned sample size was ~699 patients. The primary PFS/first interim OS analysis was planned after:

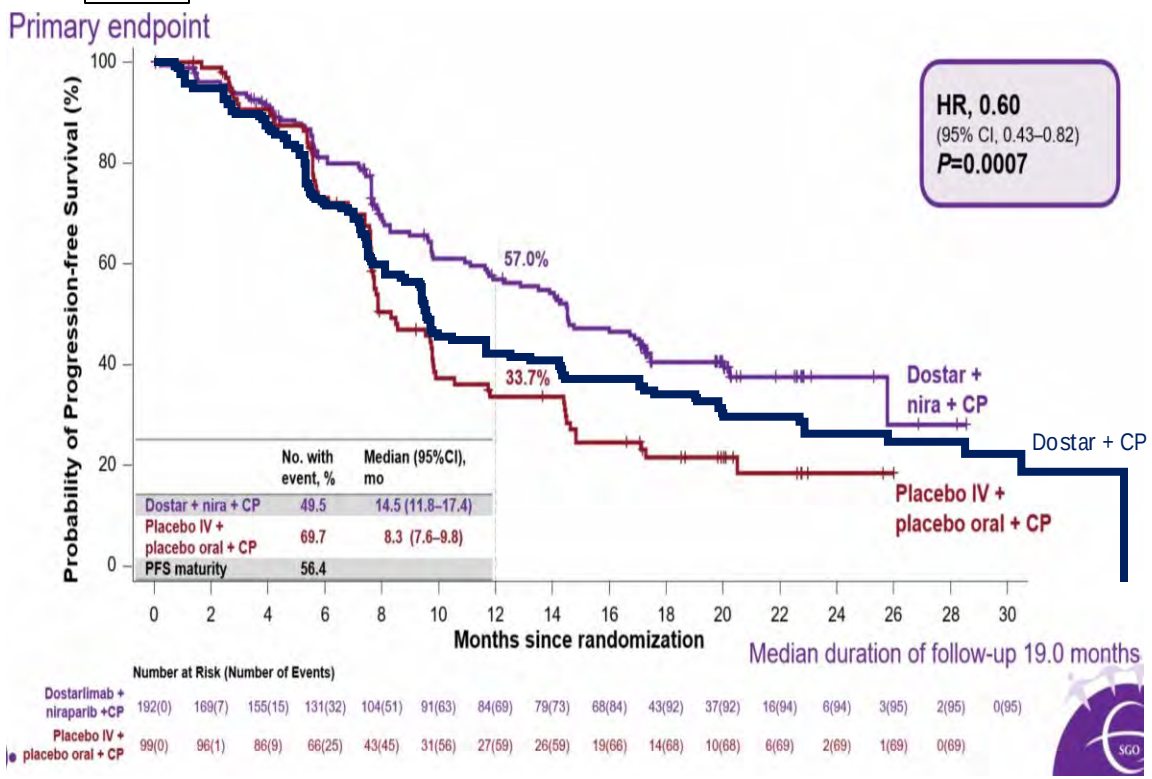
- ~ 299 PFS events (64% maturity) for the Durva vs Control comparison and
- ~ 281 PFS events (60% maturity) for the Durva+Ola vs Control comparison

Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.
Westin SN, et al. J Clin Oncol. 2023; DOI: 10.1200/JCO.23.02132

Contribution of Components…PARPi

GOG 3031 Ruby Part 2: NCT03981796

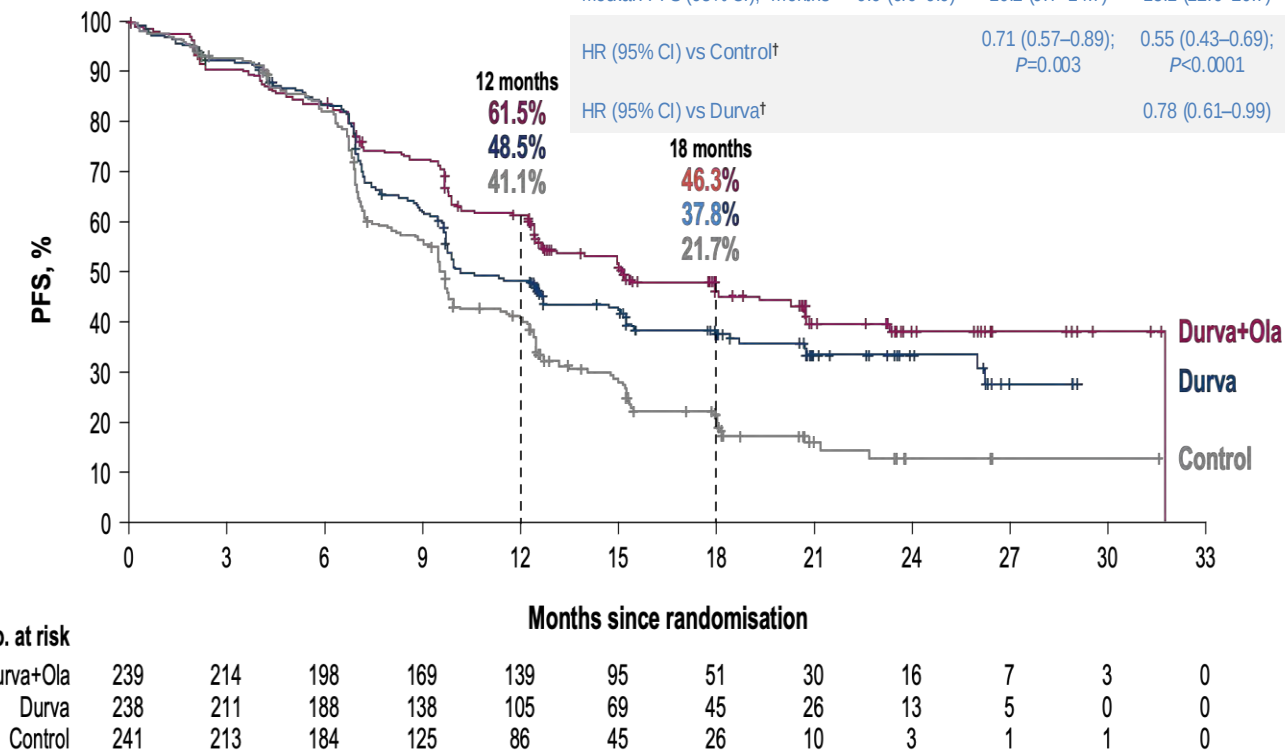
ITT



GOG 3041: DUO-E NCT04269200

ITT

	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)



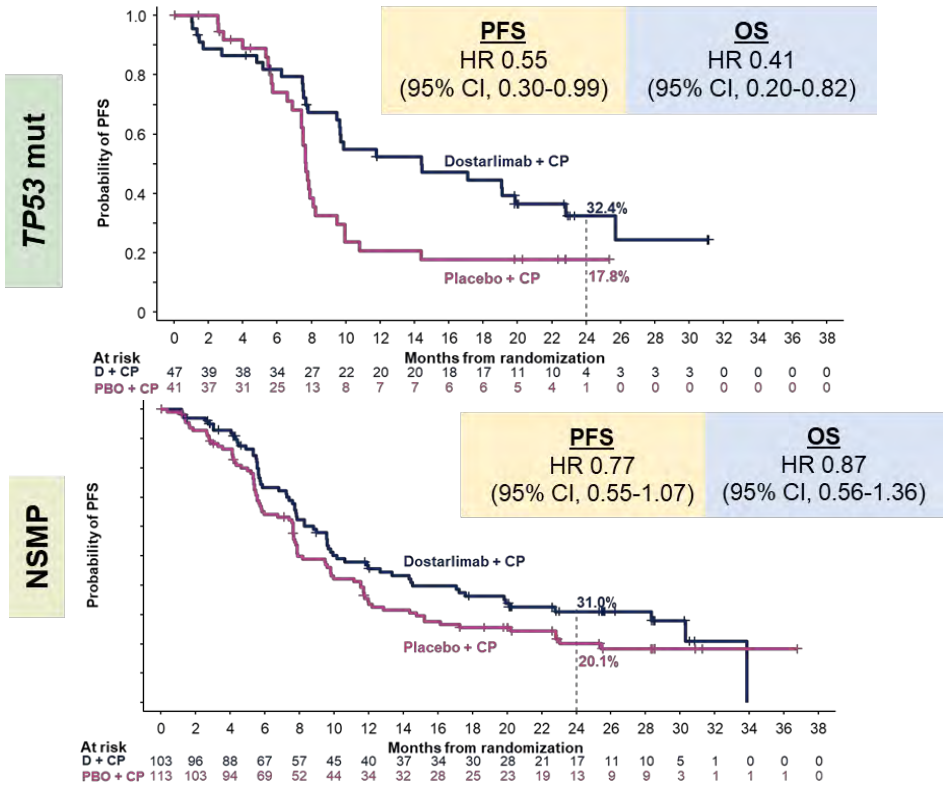
*Caution: Don’t do this at home!!!

Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.
Westin SN, et al. J Clin Oncol. 2023; DOI: 10.1200/JCO.23.02132

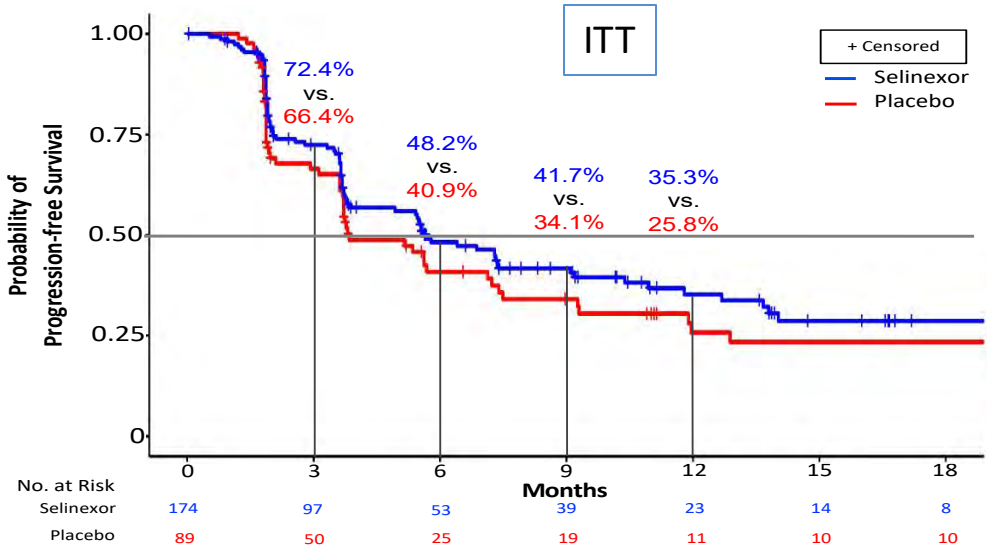
Subgroup Hypothesis Testing: TP53 or NSMP and IO

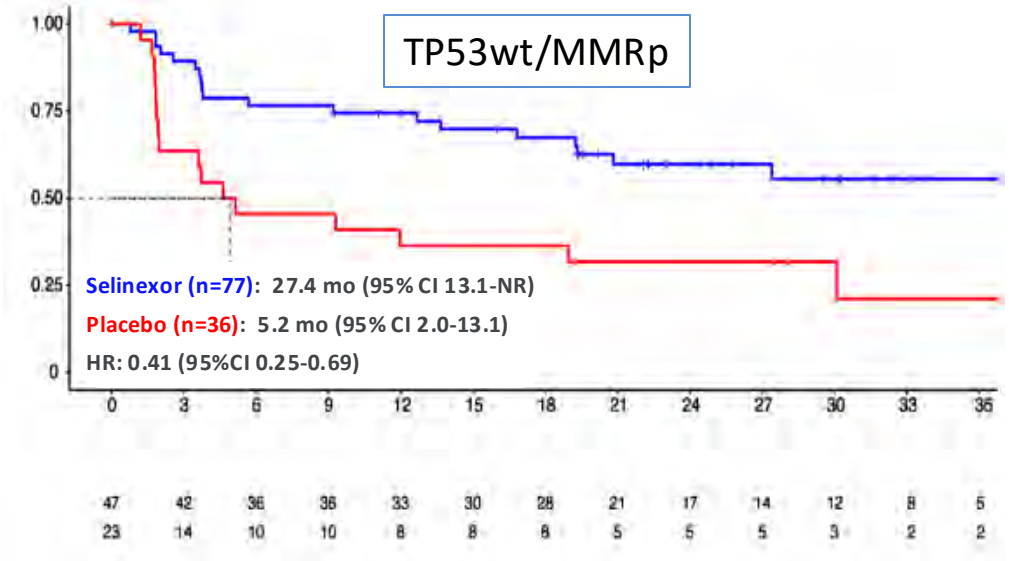
RUBY Part 1[1,2]

Molecular subgroup analysis based on 400/494 patients with known molecular classification per WES



SIENDO[3]



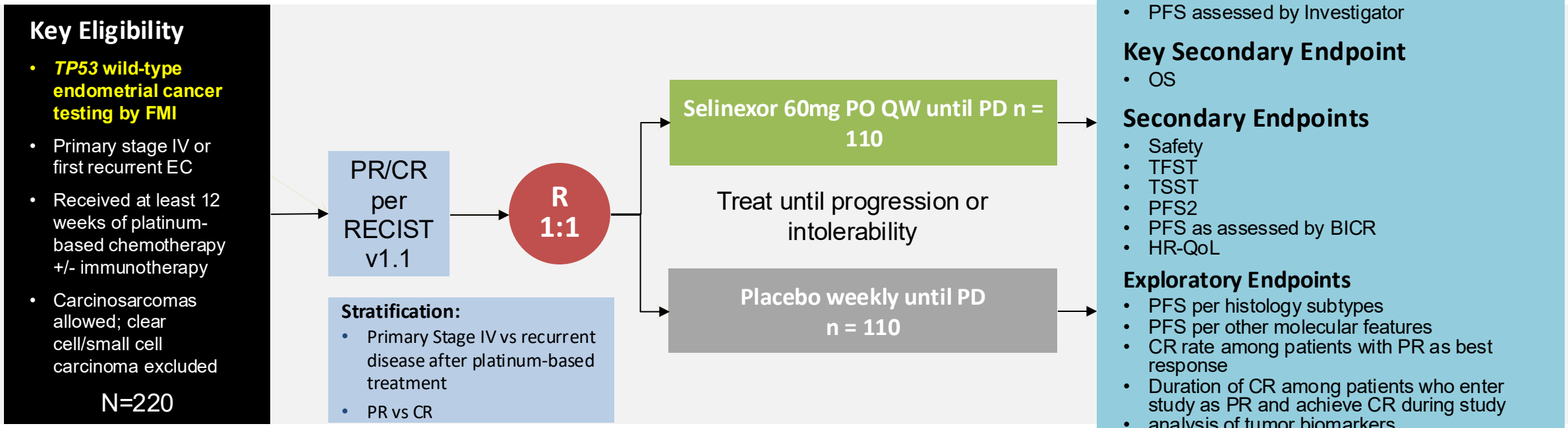


1. Adapted from Mirza MR, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #740MO;
2. Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2.
3. Sehouli, et al. Presented at ESGO 2024, Barcelona.

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

Prescreening Consent Tissue sent to Foundation

Study Consent

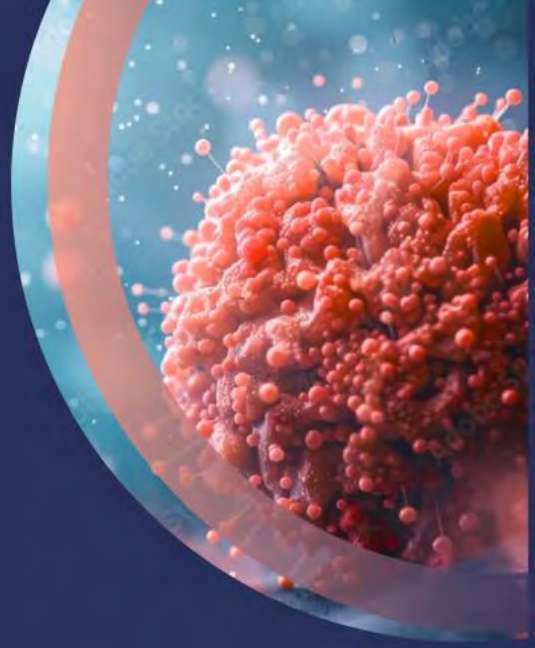


*118 PFS events needed to provide 90% power to detect a HR of 0.55 with a 2-sided alpha of 0.05.

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

Summary

- FDA regulatory programs have significantly impacted therapeutic opportunities for patients
- Regulatory guidance has had a profound impact on trial design and endpoints albeit imperfect
- Analytical strategies are challenged by dose-optimization, biomarker impact, survival endpoints, subgroup over interpretation
- Guidelines generally follow regulatory approval, but some are more lenient



Interactive Dialogue: Clarifying Misconceptions and Enhancing Understanding Sequencing for Endometrial Cancer Treatments

All Faculty

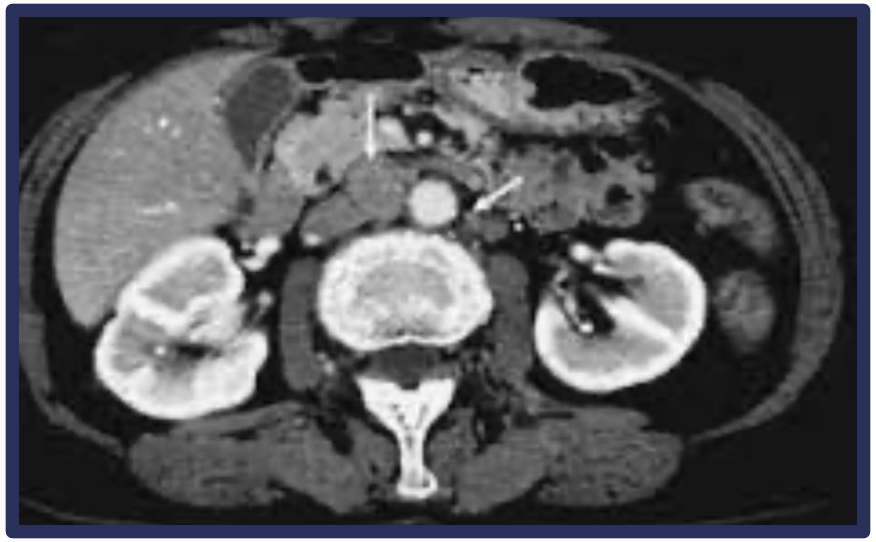
GOG FOUNDATION® Transforming the standard of care GOG PARTNERS

Case Study 1

- 54-year-old with Stage IIIC2 (para-aortic node positive), grade 3 endometrial cancer (pMMR). No additional biomarkers were identified with HER2 IHC 0 status. No medical co-morbidities . She declines participation in a clinical trial.

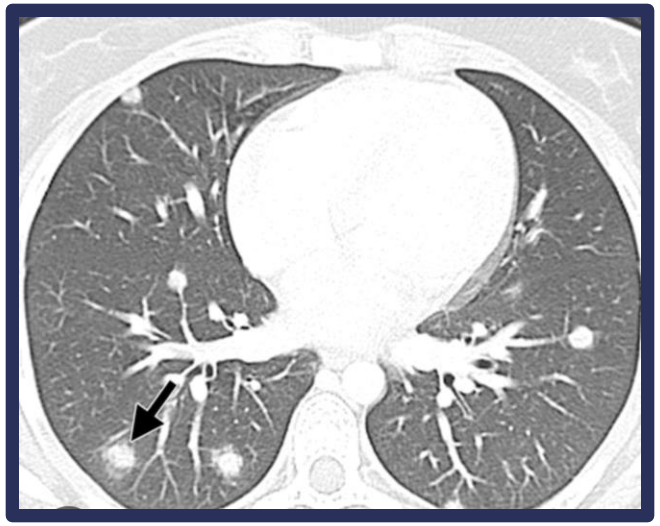
- Surgery followed by CT scan shows measurable disease in the para-aortic lymph nodes with indeterminate pulmonary nodules on CT after surgery.

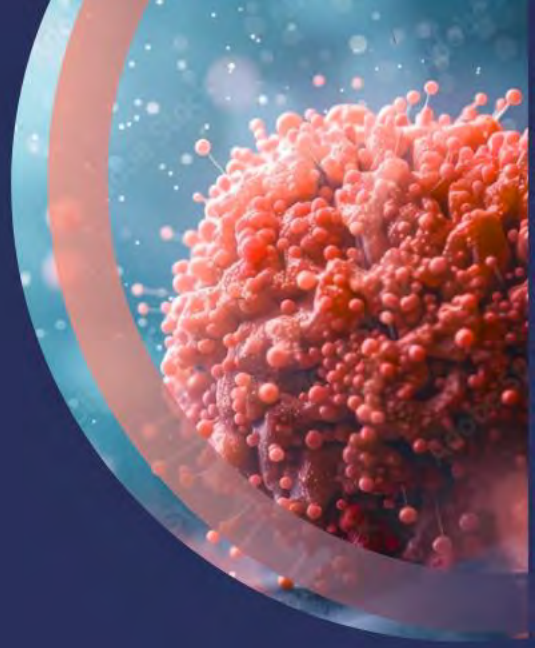
- Recommendations?



Case Study 2

- 59-year-old with Stage IB high-grade serous endometrial cancer (pMMR). No additional biomarkers were identified.
- Surgery followed by carboplatin and paclitaxel x 6 cycles completed 9 months ago.
- She presents with a persistent cough and CT scans demonstrates multiple pulmonary nodules and carcinomatosis in abdomen.
- Biopsy confirms recurrent endometrial cancer, with HER2 IHC 0 status. She declines participation in a clinical trial.





Thank You

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

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