Uterine Cancer, the Knowns and Unknowns – A Heated Discussion on Pivotal Changing Data

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Transforming the standard of care™

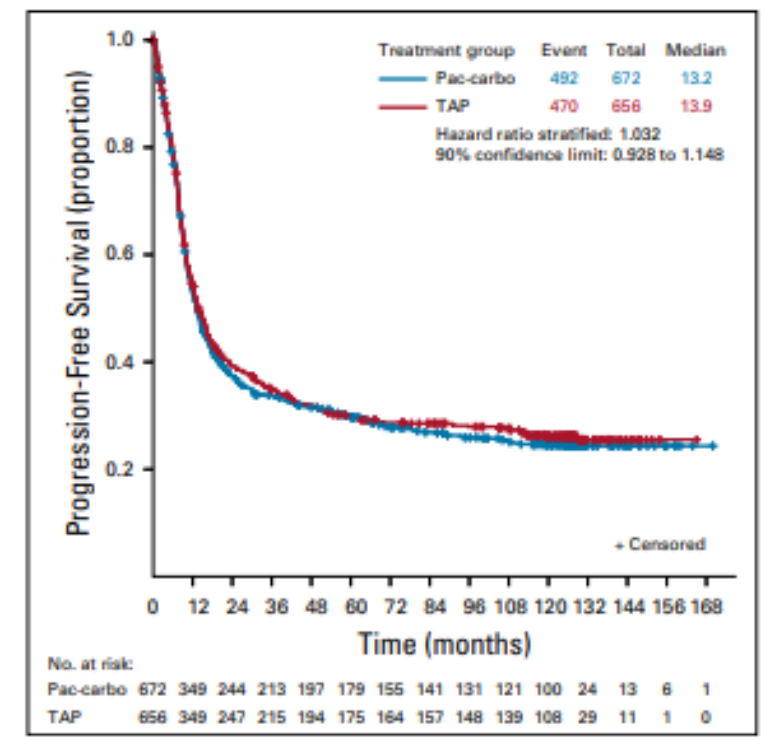
GOG Highlight Reel

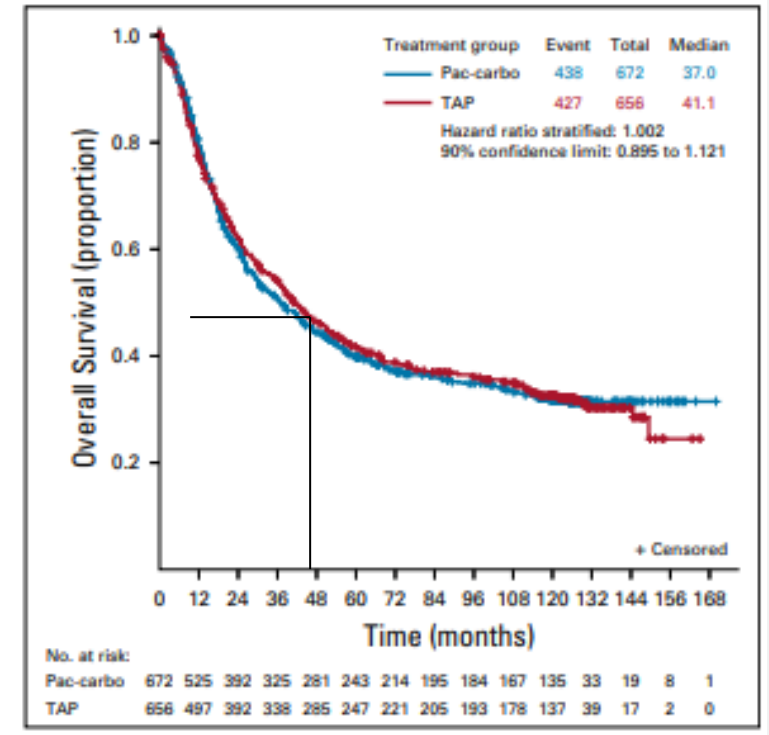
Advanced/Recurrent Endometrial Cancer

2000's: Chemotherapy has been standard of care

2010: Carboplatin and paclitaxel became the preferred regimen (GOG209)

PFS ~13 months, OS ~20 months, Response Rate 52% rates



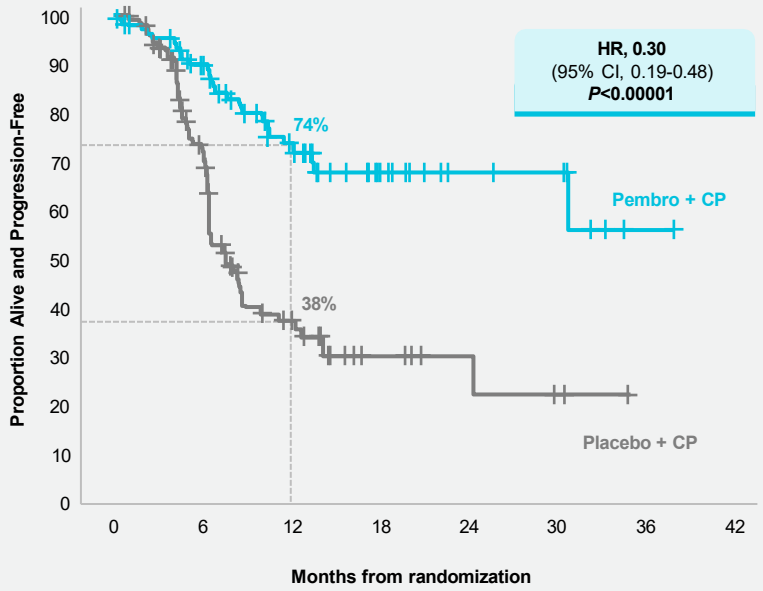


Miller DS, et al. J Clin Oncol. 2020 Nov 20;38(33):3841-3850.

Miller DS J Clin Oncol 2020.

PFS benefit of IO + chemo in dMMR

GY018

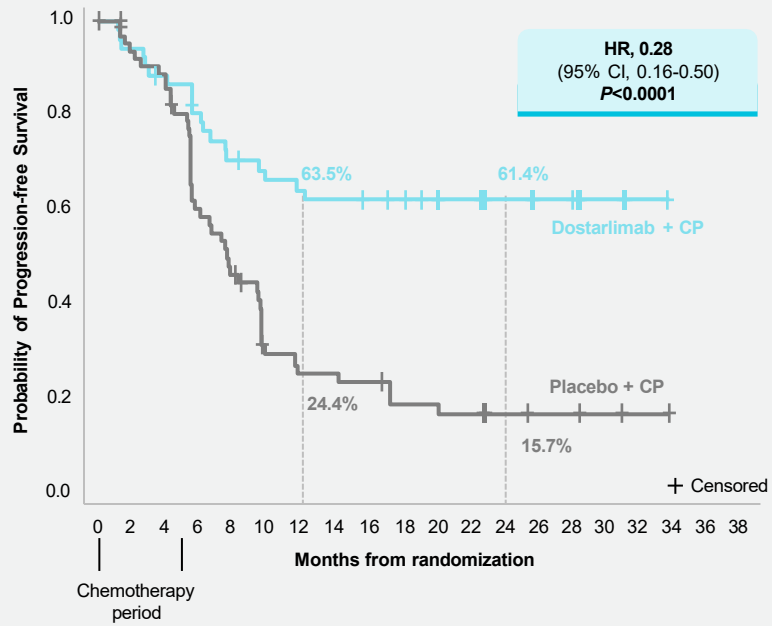


Number at Risk (Cumulative number censored)

PBO + CP	113 (2)	62 (24)	24 (35)	8 (47)	4 (51)	2 (52)	(54)	0
P + CP	112 (1)	80 (22)	44 (46)	22 (65)	9 (78)	8 (79)	2 (64)	0 (<____>)

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

RUBY

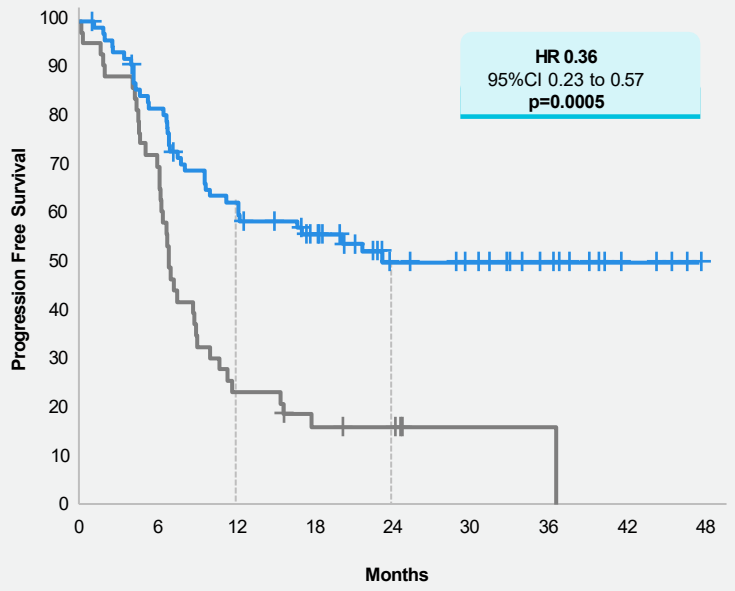


At risk (events)

D + CP	53 (0)	48 (3)	44 (6)	39 (10)	34 (15)	31 (17)	30 (18)	29 (19)	28 (19)	27 (19)	25 (19)	19 (19)	13 (19)	9 (19)	9 (19)	4 (19)	1 (19)	0	
PBO + CP	65 (0)	57 (4)	54 (7)	34 (24)	26 (32)	14 (41)	12 (43)	12 (43)	11 (44)	8 (46)	8 (46)	7 (47)	4 (47)	3 (47)	3 (47)	2 (47)	1 (47)	0	

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

AtTEnd

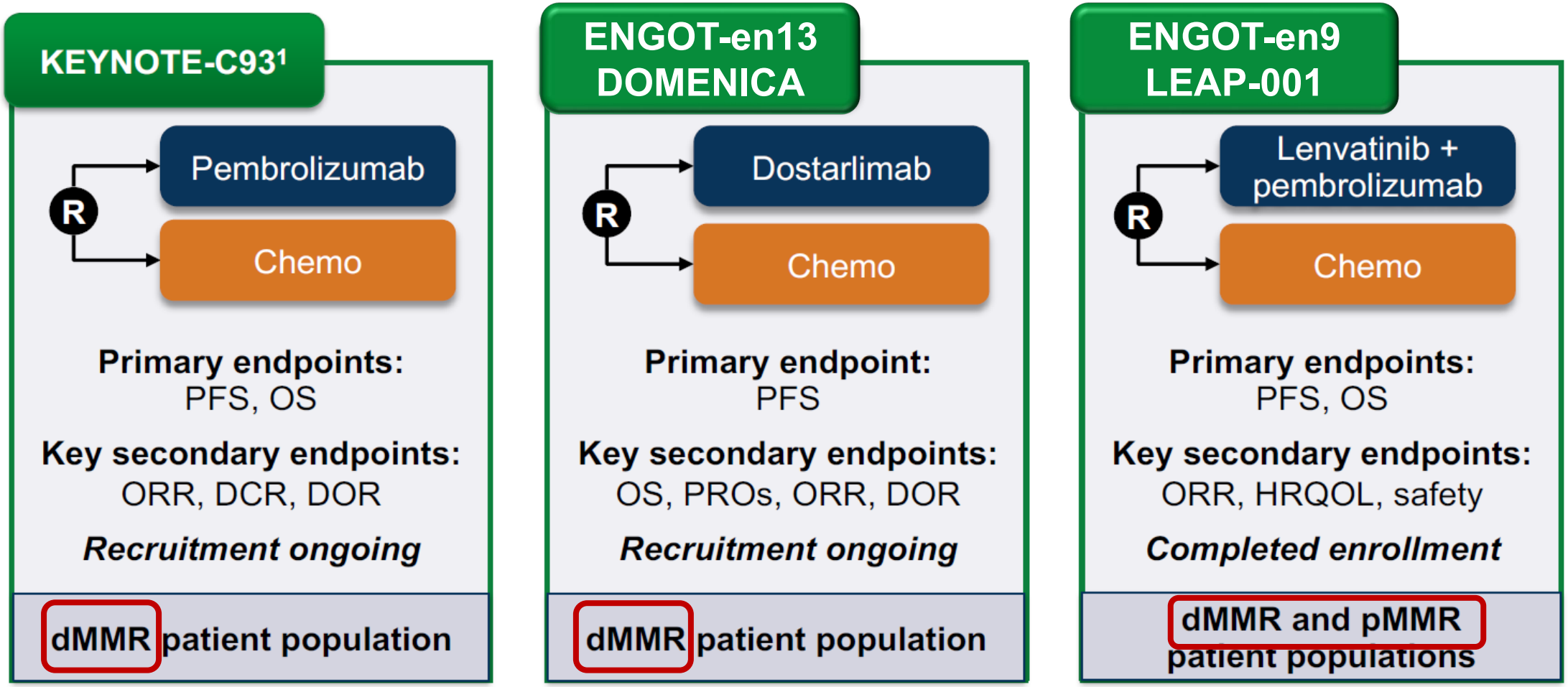


Patients at Risk

Atezolizumab	81	64	48	37	23	20	13	4	0
Placebo	44	31	10	6	4	1	1	0	

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

First-line Chemotherapy-free Regimens in the dMMR population??



PFS in pMMR

Primary Endpoint: Prespecified

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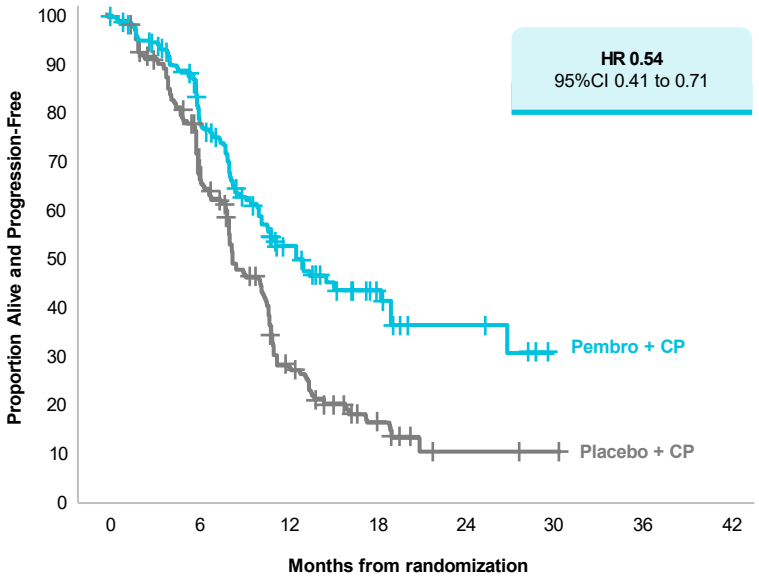


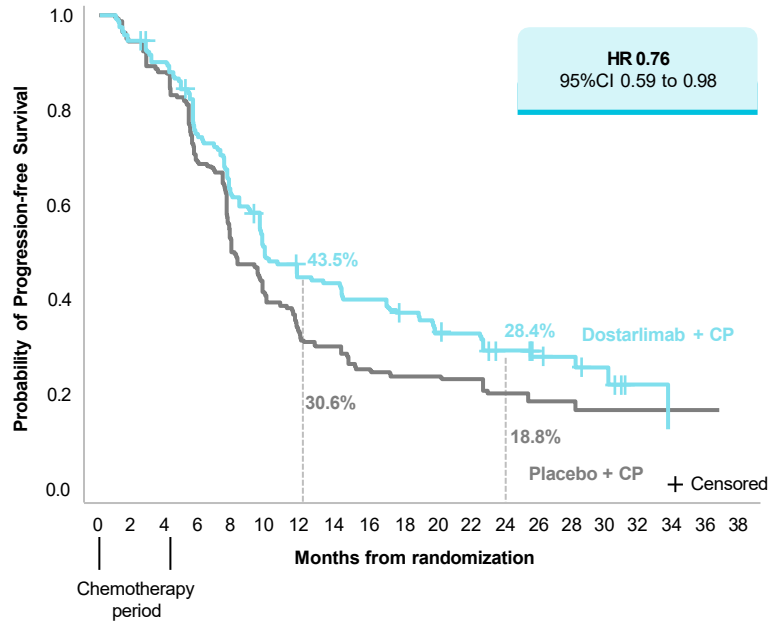
Number at Risk (Cumulative number censored)

PBO + CP	292	129 (115)	33 (141)	10 (152)	2 (<____>)	1 (<____>)	0 (<____>)
P + CP	290 (15)	150 (112)	45 (167)	20 (185)	7 (195)	1 (<____>)	0 (<____>)

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

Secondary Analysis: Not prespecified

RUBY

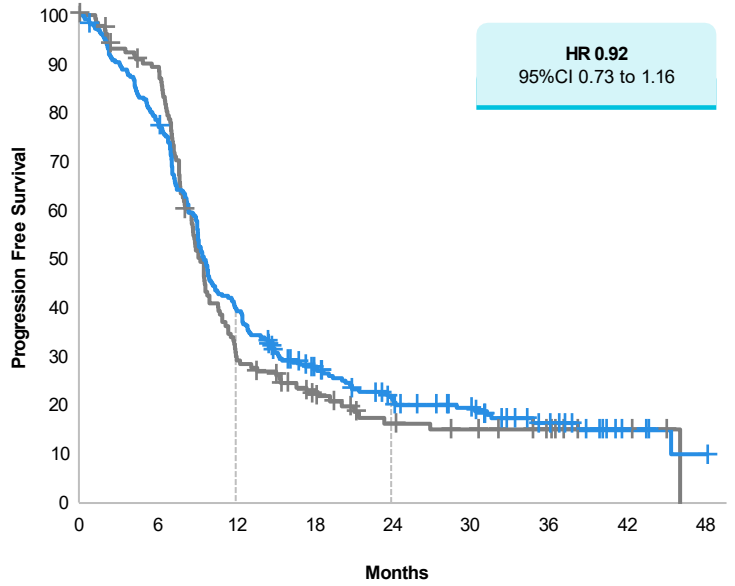


At risk (events)

D + CP	<_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_>																								
PBO + CP	<_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_><_>																								

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

AtTEnd



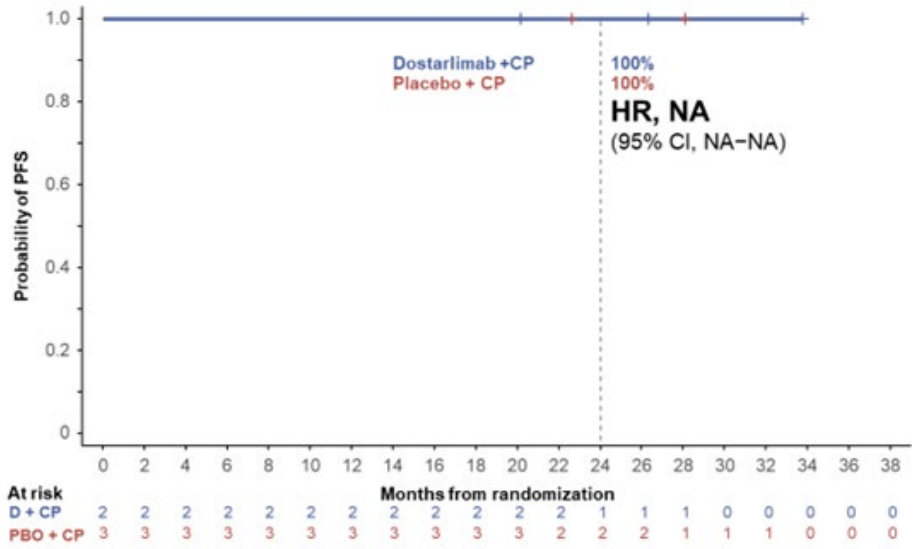
Patients at Risk

Atezolizumab	269	205	103	62	40	31	16	5	2
Placebo	140	117	39	24	14	11	7	3	0

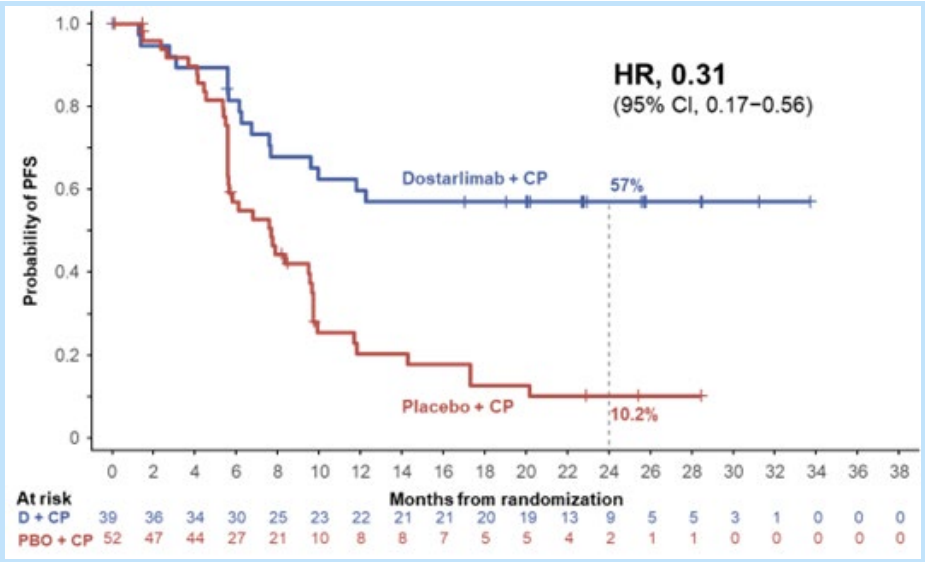
	No with events%	Median
Atezo + CT	78	9.5 (9.0-10.4)
Placebo + CT	77	9.2 (8.5-9.9)
Maturity	78%	

PFS According to Molecular Subgroup

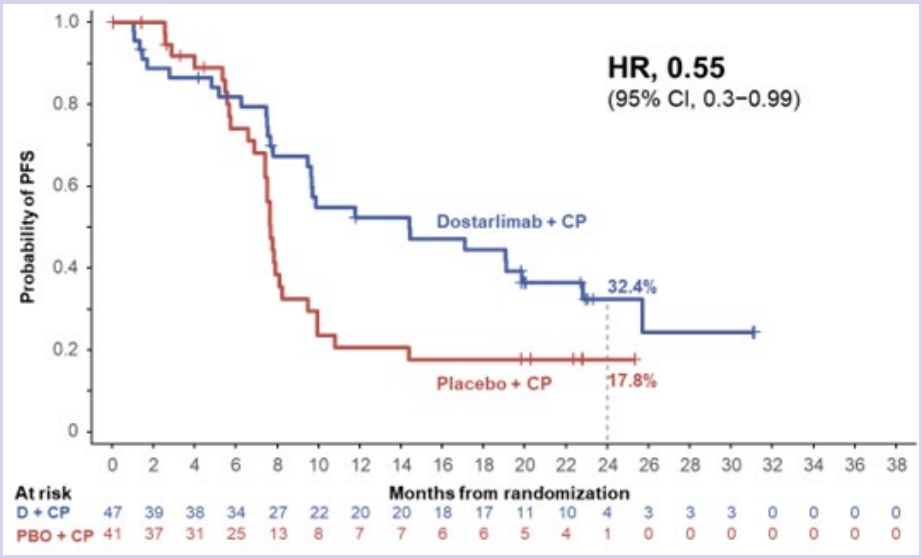
POLε mut



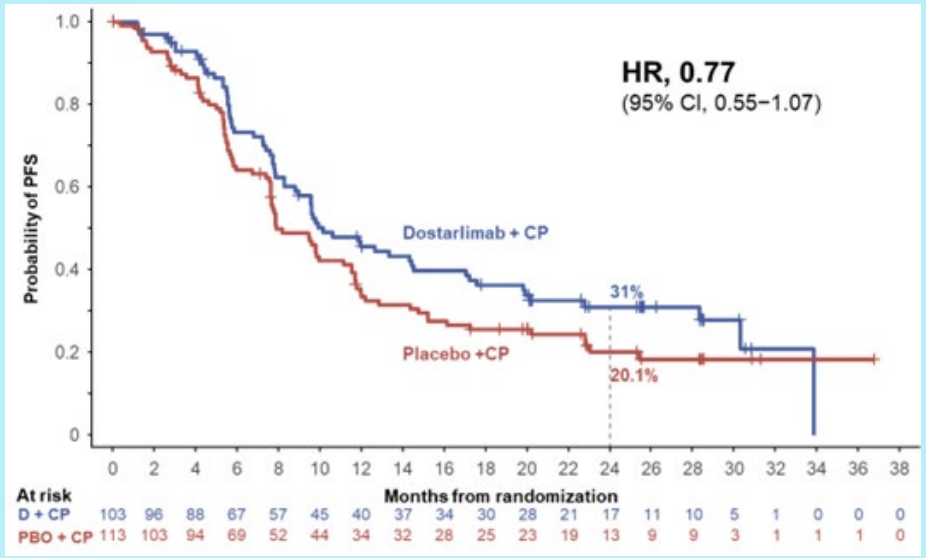
dMMR/MSI-H



TP53 mut



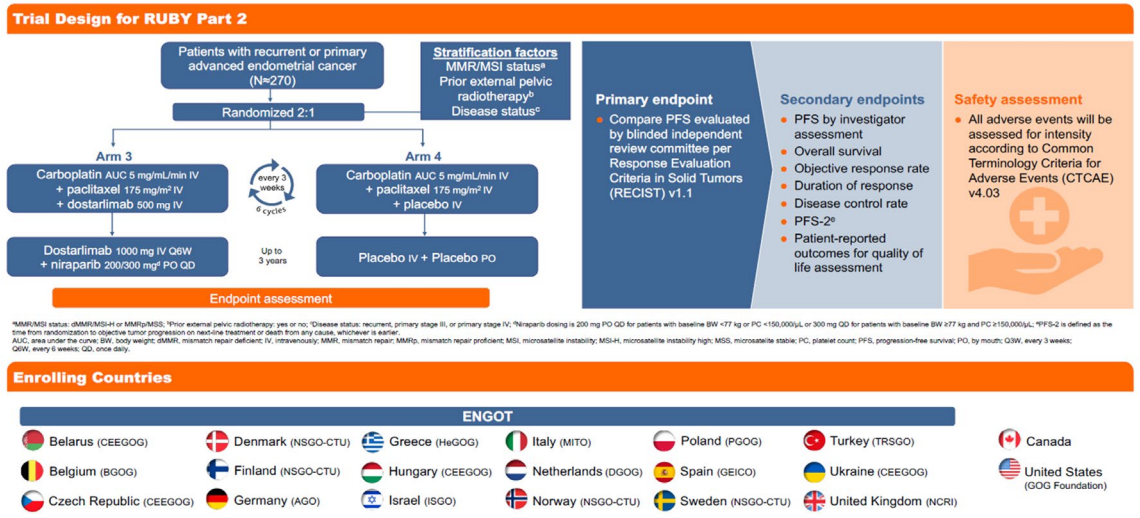
NSMP



PARPis plus ICIs in advanced Endometrial Cancer
Ongoing phase III randomized trials

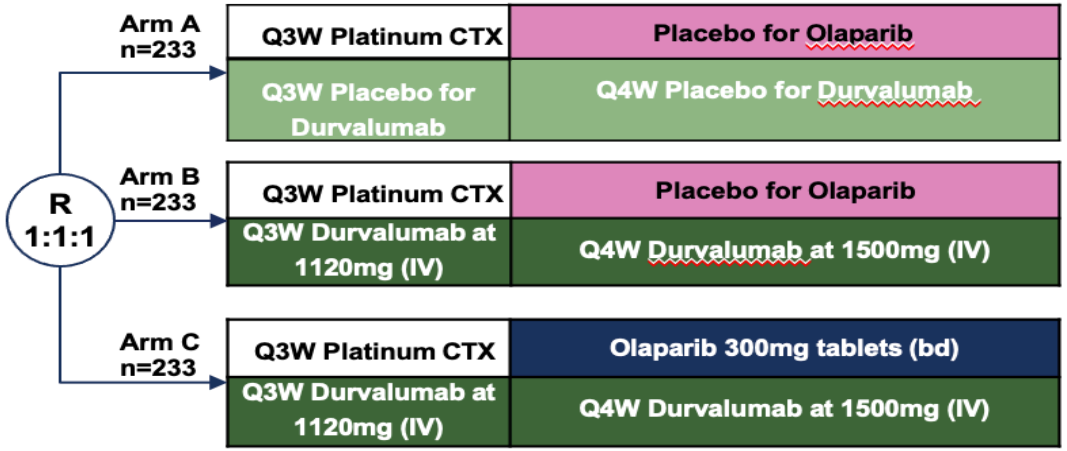
RUBY trial Part 2

Multicenter Phase 3 study that will evaluate the efficacy and safety of DOSTARLIMAB + carboplatin-paclitaxel followed by DOSTARLIMAB + NIRAPARIB



DUO-E trial

Multicenter Phase 3 study that will evaluate the efficacy and safety of DURVALUMAB + carboplatin-paclitaxel followed by DURVALUMAB + OLAPARIB or DURVALUMAB or OLAPARIB



clinicaltrials.gov:01244789; clinicaltrials.gov:05173987.

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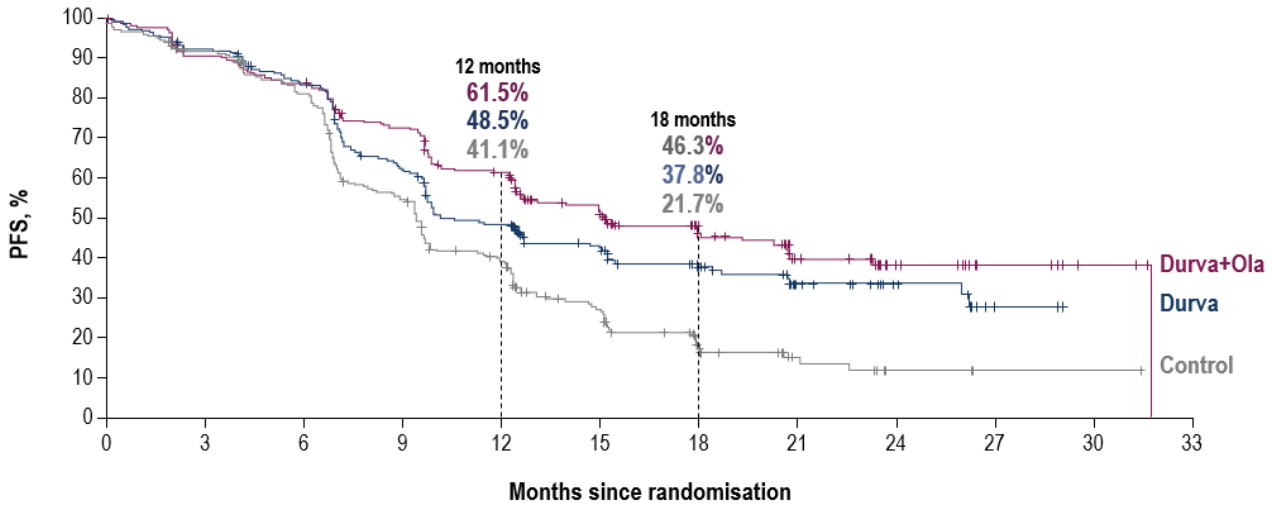
DUO-E: PFS

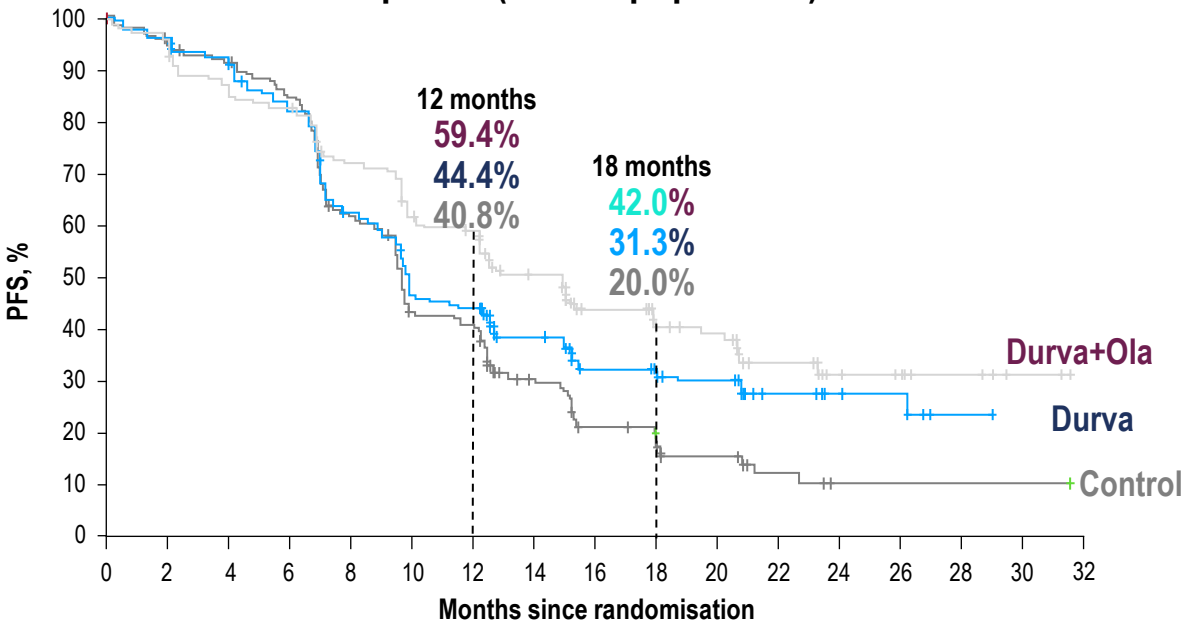
PFS: ITT (primary endpoint)



	Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS (95% CI),* months	9.6 (9.0–9.9)	10.2 (9.7–14.7)	15.1 (12.6–20.7)
HR (95% CI) vs Control†		**0.71** (0.57–0.89); *P*=0.003	**0.55** (0.43–0.69); *P*<0.0001
HR (95% CI) vs Durva†			0.78 (0.61–0.99)

Overall data maturity 61.0%

PFS: pMMR (80% of population)

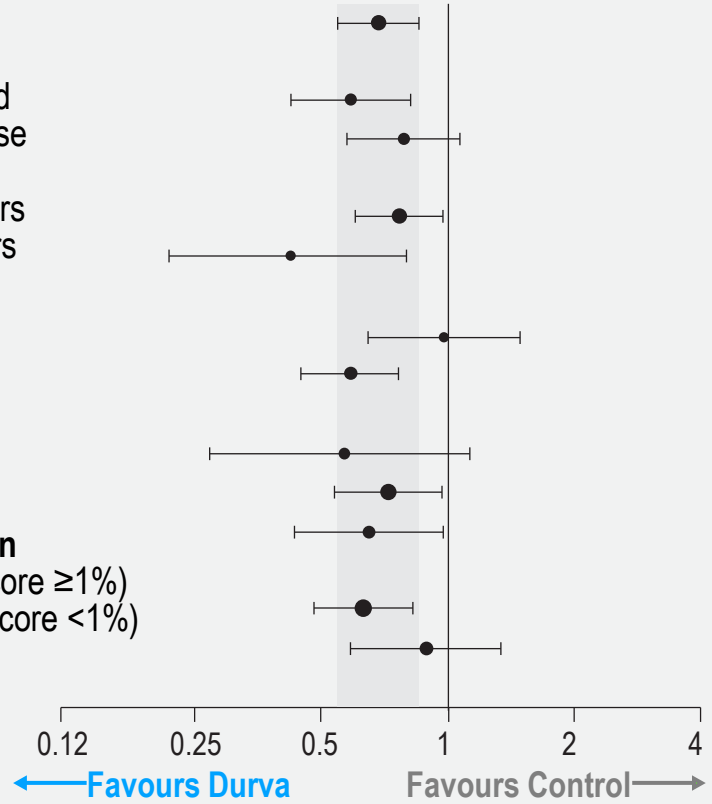


	Control (N=192)	Durva (N=192)	Durva+Ola (N=191)
Events, n (%)	148 (77.1)	124 (64.6)	108 (56.5)
Median PFS (95% CI),* months	9.7 (9.2–10.1)	9.9 (9.4–12.5)	15.0 (12.4–18.0)
HR (95% CI) vs Control†		**0.77 (0.60–0.97)**	**0.57 (0.44–0.73)**
HR (95% CI) vs Durva†			**0.76 (0.59–0.99)**

Westin S. ESMOA 2023.

Subgroup analysis of PFS: Durva vs Control

By stratification factors and biomarker status



	HR (95% CI)	Durva n/N (%)	Control n/N (%)
All patients	0.68 (0.55–0.86)	139/238 (58.4)	173/241 (71.8)
Disease status			
Newly diagnosed	0.59 (0.42–0.82)	67/113 (59.3)	81/115 (70.4)
Recurrent disease	0.79 (0.58–1.07)	72/125 (57.6)	92/126 (73.0)
MMR status			
Proficient tumours	0.77 (0.60–0.97)	124/192 (64.6)	148/192 (77.1)
Deficient tumours	0.42 (0.22–0.80)	15/46 (32.6)	25/49 (51.0)
Region			
Asia	0.98 (0.65–1.49)	44/68 (64.7)	45/68 (66.2)
Non-Asia	0.59 (0.45–0.76)	95/170 (55.9)	128/173 (74.0)
HRRm status			
HRRm	0.57 (0.27–1.13)	12/26 (46.2)	23/32 (71.9)
Non-HRRm	0.72 (0.54–0.97)	85/138 (61.6)	96/132 (72.7)
Unknown	0.65 (0.43–0.97)	42/74 (56.8)	54/77 (70.1)
PD-L1 expression			
Positive (TAP score ≥1%)	0.63 (0.48–0.83)	97/170 (57.1)	114/163 (69.9)
Negative (TAP score <1%)	0.89 (0.59–1.34)	38/61 (62.3)	57/75 (76.0)
Unknown	NC (NC–NC)	4/7 (57.1)	2/3 (66.7)

Stratification factors (disease status, MMR status, and geographic region) are per the randomisation code. PD-L1 status in baseline tumour tissue was determined centrally using Ventana PD-L1 SP263 immunohistochemistry assay. Expression was assessed using a TAP score, calculated based on the proportion of the tumour area populated by tumour cells or immune cells with membranous PD-L1 staining. HRRm status was assessed in baseline tumour tissue using the Foundation One CDx NGS assay and includes a mutation in any of these genes: *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D,* or *RAD54L*. HRRm status unknown includes patients recruited in China where HRR testing was not performed and patients with samples that were unavailable for testing.

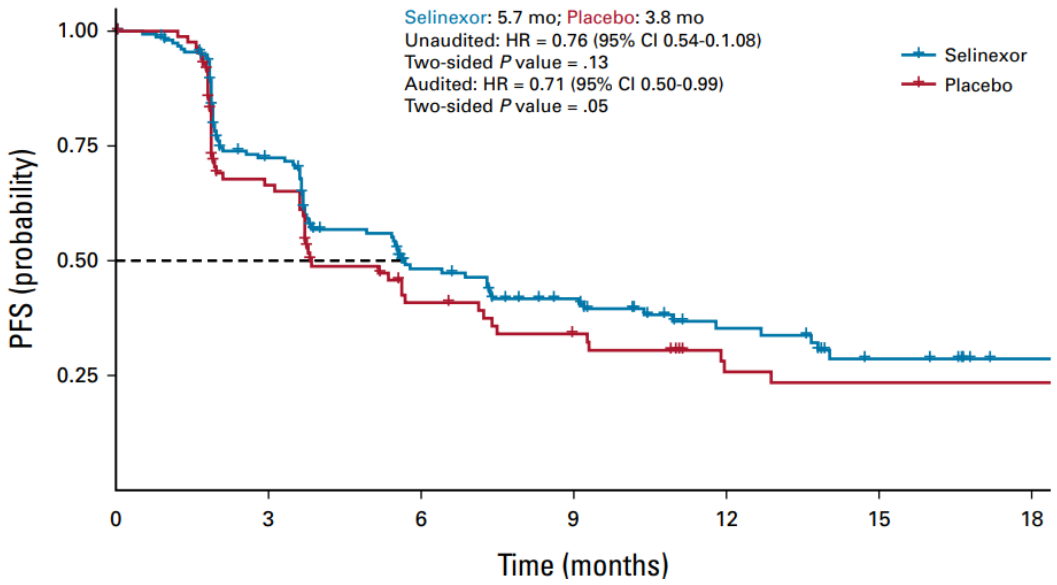
MAINTENANCE THERAPY

Cancer cells export tumor suppressor proteins (p53) from the nucleus

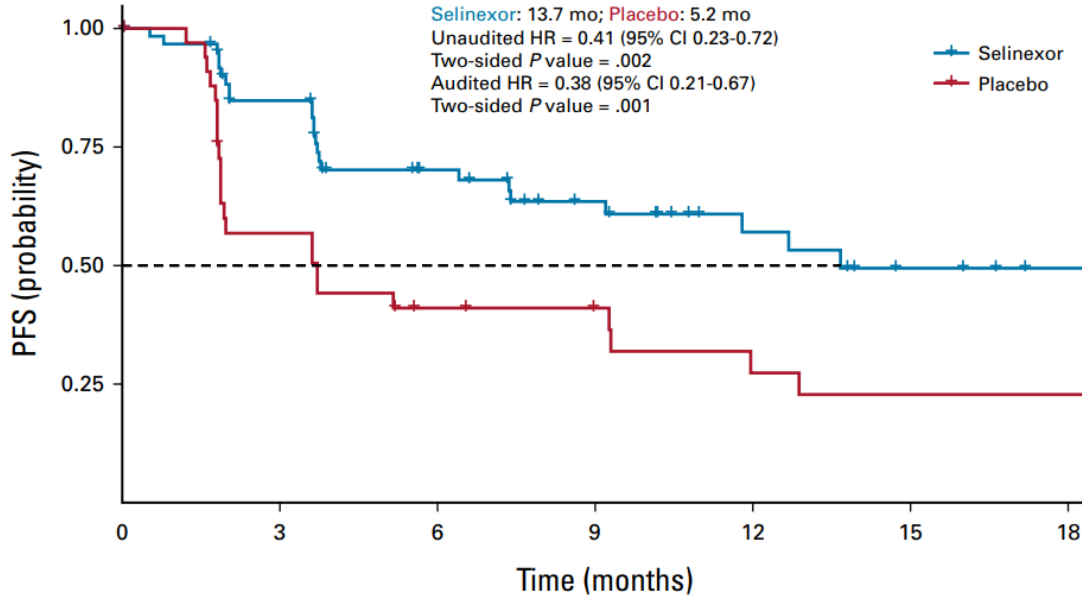
Restoring function of p53 mediated apoptosis

- Selinexor XPO1 inhibitor
- Navtemadlin: MDM2 inhibitor

PFS ITT

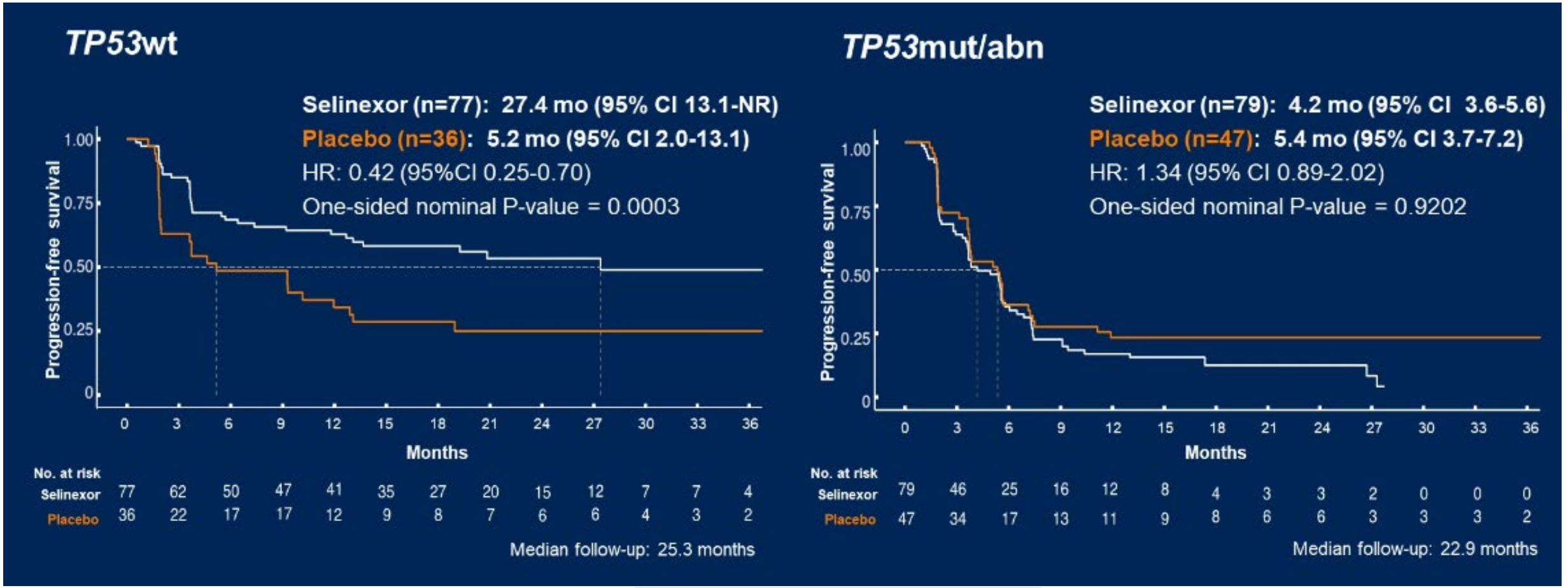


PFS Pre-specified subgroup: P53wt



Vergote I. J Clin Oncol 2023.

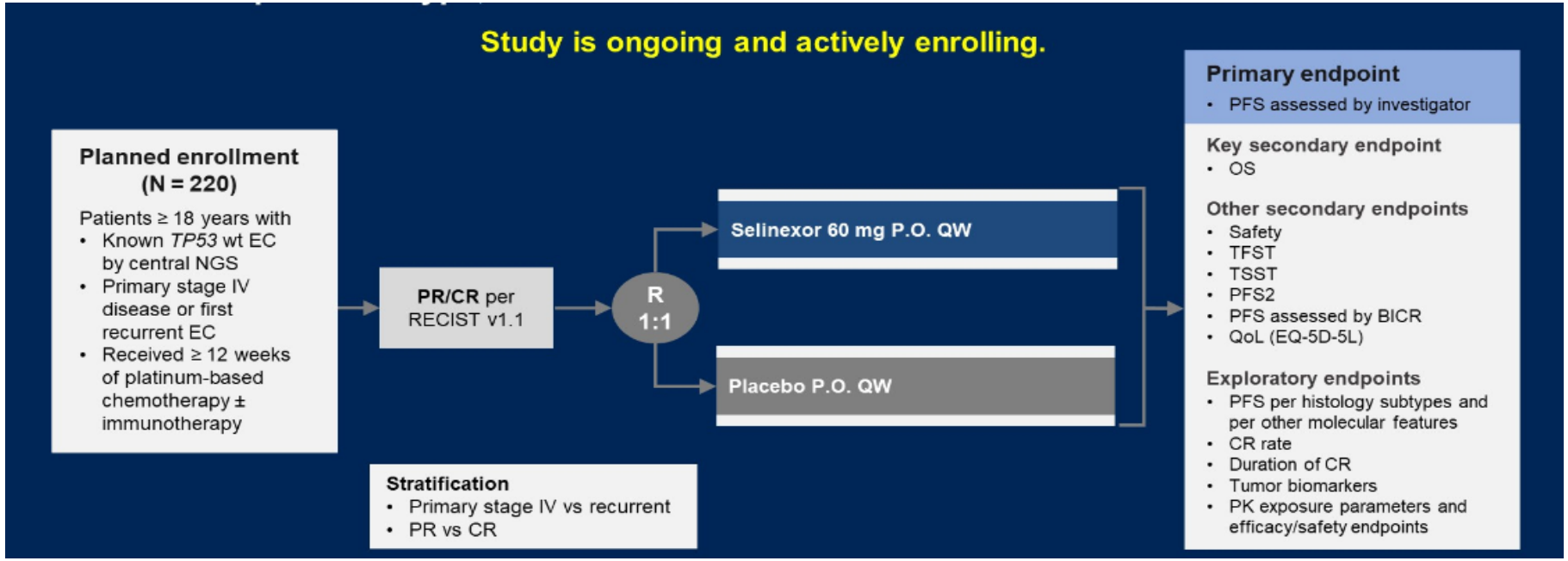
SIENDO: Long-term PFS, *TP53*



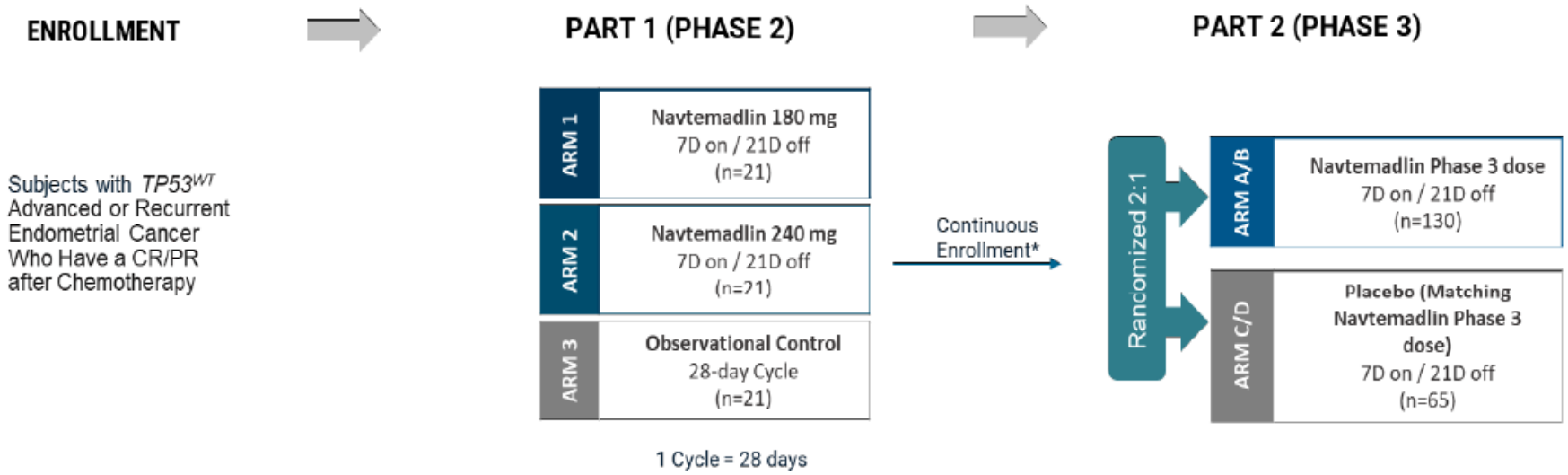
Pre-specified subgroups

Ongoing Trials

ENGOT-EN20/GOG-3083
XPORT-EC-42



KRT-232-118/GOG-3089



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

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

Study & Drug	Patient Population	Outcome
Keynote 158: Pembrolizumab (N=49)	Advanced stage or metastatic dMMR endometrial cancer	ORR: 57.1%
PHAEDRA trial: Durvalumab (N=35 dMMR)	Advanced stage or metastatic endometrial cancer	ORR in dMMR: 43%
GARNET study: Dostarlimab (N=70)	Previously treated, recurrent advanced stage endometrial cancer	ORR in dMMR: 45%
Ph II Avelumab study (N= 15 dMMR)	Advanced stage or metastatic endometrial cancer	ORR: 26.7%

Marabelle A, et al. J Clin Oncol, 2019
Antill PSK et al. J Clin Oncol 2019
Oaknin A et al. SGO virtual meeting 2020
Konstantinopoulos PA et al. J Clin Oncol 2019

Single Agent IO in "non-biomarker" Selected Endometrial Cancer Populations

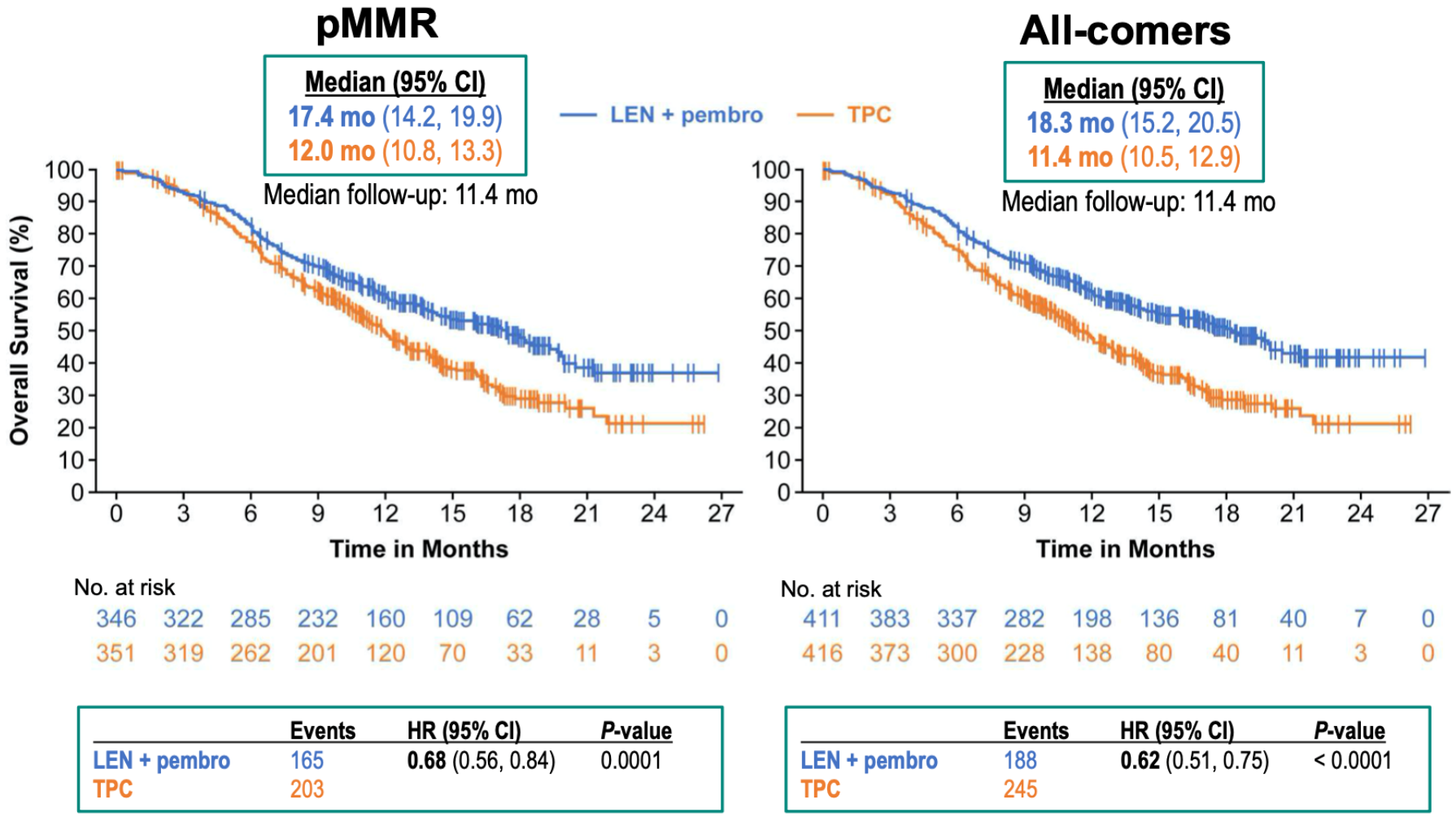
Response to single agent IO in pMMR or MSI-stable endometrial cancer has been modest

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

** = updated data in the pMMR cohort has not been presented

Ott PA et al. J Clin Oncol 2017
Antill PSK et al. J Clin Oncol 2019
Oaknin A et al. Gynecol Oncol 2019
Konstantinopoulos PA et al. J Clin Oncol 2019

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



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

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

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

Checkpoint Combinations in Endometrial Cancer

Study	**Publication/Presentation**	Treatment	Number of Patients	Median PFS (months)	HR	Median OS (months)	Log-rank p	ORR	DOR (months)
Randomized Phase 2 Trial Cabozantinib /Nivolumab vs Nivolumab [1]	JITC 2022	Cabozantinib + Nivolumab Nivolumab	36 18	5.3 (90% CI 3.5-9.2) 1.9 (90% CI 1.6-3.4)	0.59 (90% CI 0.35, 0.98) P= 0.09	13.0 months (90%CI 10.2 to 18.4) 7.9 months (90%CI 6.1 to not estimable)	0.09	25.0 % 16.7 %	6 4
Prior IO cohort [1]:		Cabozantinib + Nivolumab	20					25.0%	
Activate Ph 1/2: etigilimab (anti-TIGIT) with nivolumab (anti-PD1) in recurrent/advanced solid tumors [2]	ESMO 2023	Nivolumab + etigilimab	40 solid tumor 10 em ca	-	-	-	-	25% 30%	-

[1]Lheureux S, Matei DE, Konstantinopoulos PA, *et al. Journal for ImmunoTherapy of Cancer* 2022;**10:**e004233.
[2]M. Mckean, E.E. Dumbrava, O. Hamid, et al ESMO 2023

GOG-3038/POD1UM-204

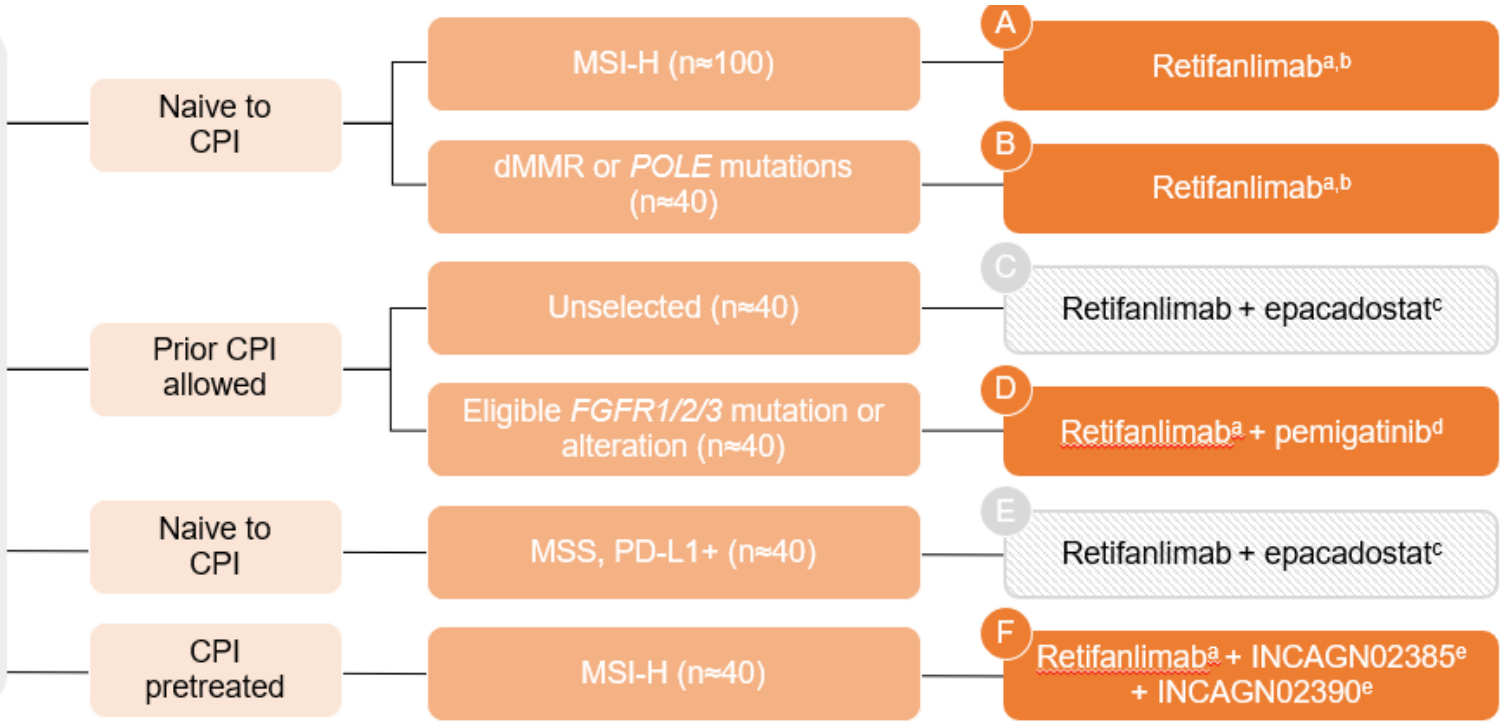
An Umbrella Study of INCMGA00012 Alone and in Combination With Other Therapies in Participants With Advanced or Metastatic Endometrial Cancer Who Have Progressed on or After Platinum-Based Chemotherapy (PI: Brian Slomovitz, MD)

PLEASE ENROLL

Select eligibility criteria

- Histologically confirmed advanced or metastatic endometrial cancer
- Disease progression on or after treatment with ≥1 platinum-containing regimen
- At least 1 measurable tumor lesion per RECIST v1.1
- Willing to provide tumor tissue sample
- ECOG PS of 0 to 1

Target N≈300



Primary endpoint: ORR, per RECIST v1.1 and determined by ICR (group A)[1,2]
Secondary objectives: DoR, DCR, PFS, OS (groups A-B); ORR (groups B-F); safety (all groups)[1,2]

a Patients eligible to receive retifanlimab monotherapy will first be considered for group A until fully enrolled, unless they do not meet MSI-H criteria. Retifanlimab administered iv on day 1 of each 28-day cycle for up to 26 cycles, if patients continue to derive benefit and do not meet any study treatment discontinuation criteria. b Patients in group A or group B who experience disease progression on retifanlimab monotherapy may be eligible for further treatment with one of the combination regimens in groups D or F. c Closed enrollment groups. d Pemigatinib (FGFR1/2/3 inhibitor) administered orally qd. e INCAGN02385 and INCAGN02390 administered iv q2w.
dMMR, deficient mismatch repair; ICR; independent central review; MSI-H, microsatellite instability-high; MSS, microsatellite stable; POLE, DNA polymerase epsilon.
1. Slomovitz BM, et al. IGCS 2022. Poster 1455. 2. ClinicalTrials.gov. Accessed May 2023. https://clinicaltrials.gov/ct2/show/NCT04463771

NCT04463771

Wee-1 Inhibitors in Endometrial Cancer

Trial Name	Phase	Publication/Presentation	Number of patients	Median Duration of Response	Overall Response Rate	Median Progression-Free Survival
A phase II study of the WEE1 inhibitor adavosertib in recurrent uterine serous carcinoma	II	ASCO 2022	72	9.0 months	29.4%	-
ADAGIO: A phase IIb international study of the Wee1 inhibitor adavosertib in women with recurrent or persistent uterine serous carcinoma	IIb	JCO 2023	167	-	24.2%	5.3 months
ZN-c3 Phase 1 Monotherapy Expansion Cohort in Patients with Advanced/Recurrent Uterine Serous Carcinoma	I	AACR 2022	43	-	27.3%	9.9 months

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[1]Lheureux S, Matei DE, Konstantinopoulos PA, *et al. Journal for ImmunoTherapy of Cancer* 2022;**10:**e004233.
[2]M. Mckean, E.E. Dumbrava, O. Hamid, et al ESMO 2023

GOG Highlight Reel

TETON / GOG-3065 / ZN-c3-004 (version 3)

Evaluating Azenosertib in Uterine Serous Carcinoma

Key Eligibility: Recurrent or persistent USC; ≥1 prior platinum-based chemotherapy regimen; Prior HER-2 directed therapy for known HER2+; Prior anti-PD(L)1[i]; Measurable disease per RECIST; ECOG PS 0-1

All Comers Enrollment

Cohort 1 (N=30)[ii]
Azenosertib 400 mg QD 5:2

All Comers Enrollment

Cohort 2 (N=60)[ii]
Azenosertib 400 mg QD 5:2

Endpoints (ICR)

ORR
DOR

ClinicalTrials.gov NCT04814108

[i] Except for sites outside the US where aPD1 is not available, or for subjects ineligible for aPD(L)1
[ii] Response-evaluable subjects
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; RECIST, response evaluation criteria in solid tumors; ORR, objective response rate; DOR, Duration of Response

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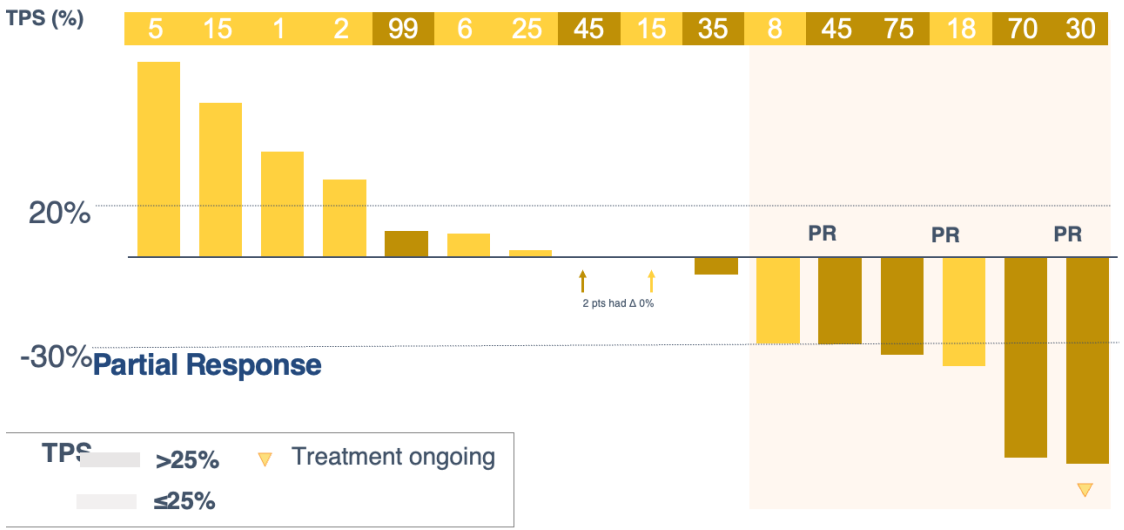
GOG Highlight Reel

ADC's in Endometrial Cancer

Luveltamab Tazevibulin (STRO-OO2): Early Evidence Of Anti-tumor Activity in FolRα Expressing EC: Phase 1 Dose expansion

Maximum Reduction in Target Lesions*



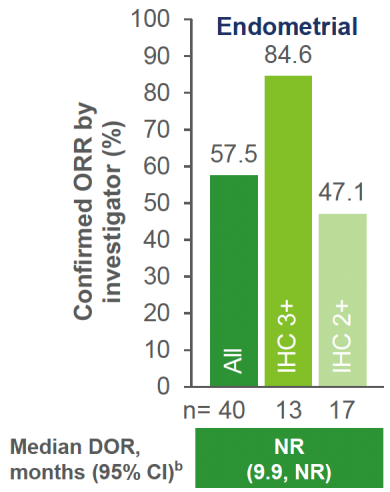
Anti-tumor Activity*

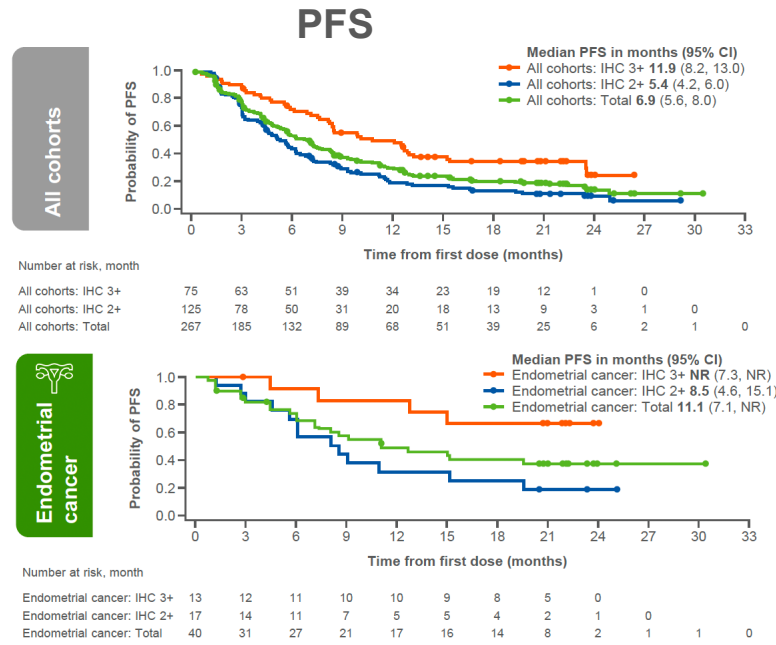
n (%)	Overall FolRα ≥1% (n=16)	FolRα ≤25% (n=9)	FolRα >25% (N=7)
PR	3 (19)	1 (11)	2 (29)
SD†	8 (50)	4 (44)	4 (57)
PD	5 (31)	4 (44)	1 (14)
DCR	11 (69)	5 (56)	6 (86)

†3 unconfirmed PRs

Pothuri B, Naumann W, Martin L, et al ESMO 2023

Trastuzumab Deruxtecan: Td-XD Efficacy by HER2 Expression





NCCN Guidelines1.2024 9/20/23

Useful in Certain Circumstances (Biomarker-directed therapy)

- pMMR tumors
  - Lenvatinib/pembrolizumab (category 1)[c,]
- TMB-H tumors[n,12]
  - Pembrolizumab[c]
- MSI-H/dMMR tumors[o]
  - Pembrolizumab[c,15]
  - Dostarlimab-gxly[c,16]
  - Avelumab[c]
  - Nivolumab[c,22]

HER2-positive tumors (IHC 3+ or 2+)
- Fam-trastuzumab deruxtecan-nxki[23]

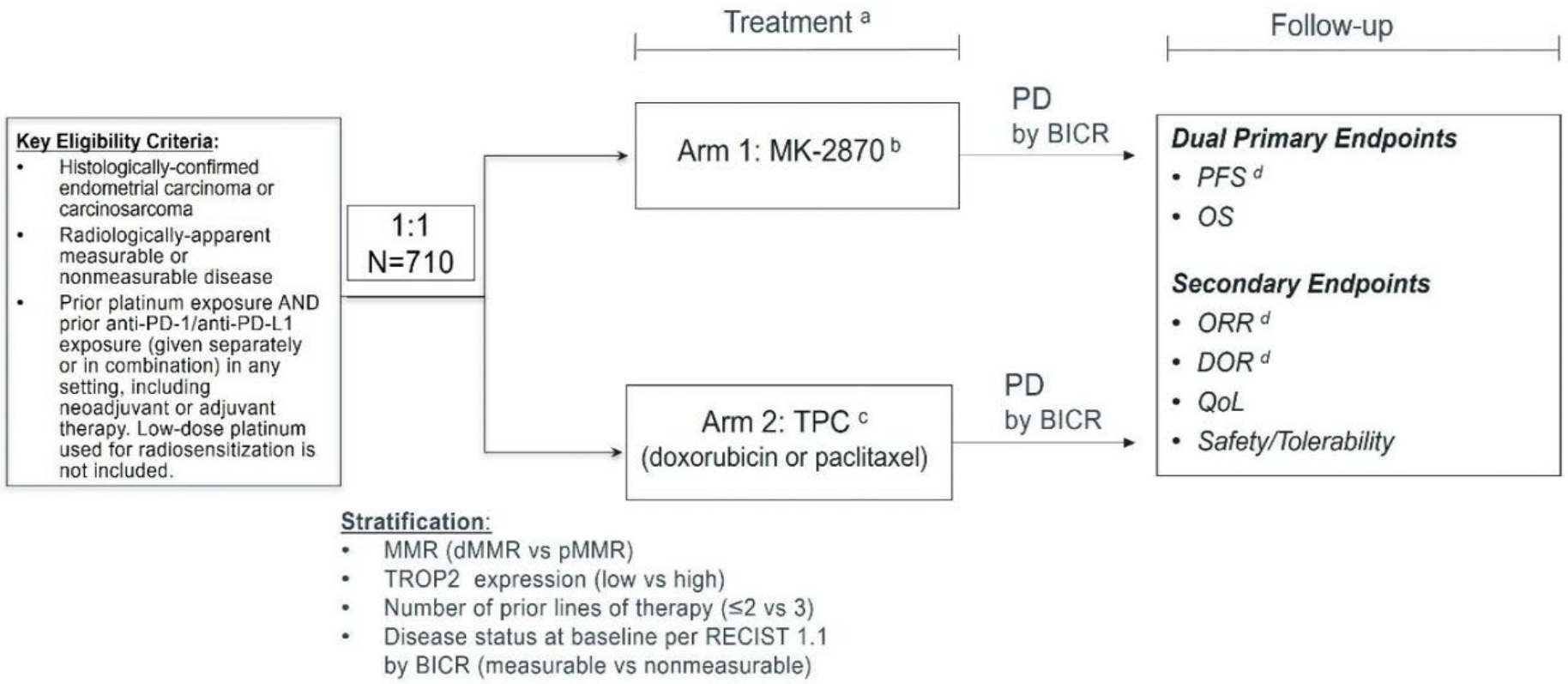
- *NTRK* gene fusion-positive tumors
  - Larotrectinib
  - Entrectinib

F. Meric-Bernstam, V. Makker, A. Oaknin, et al ESMO 2023

GOG-3095/MK-2870 in Post Platinum and Post Immunotherapy Endometrial Cancer

ClinicalTrials.gov ID NCT06132958

Figure 1 Study Design



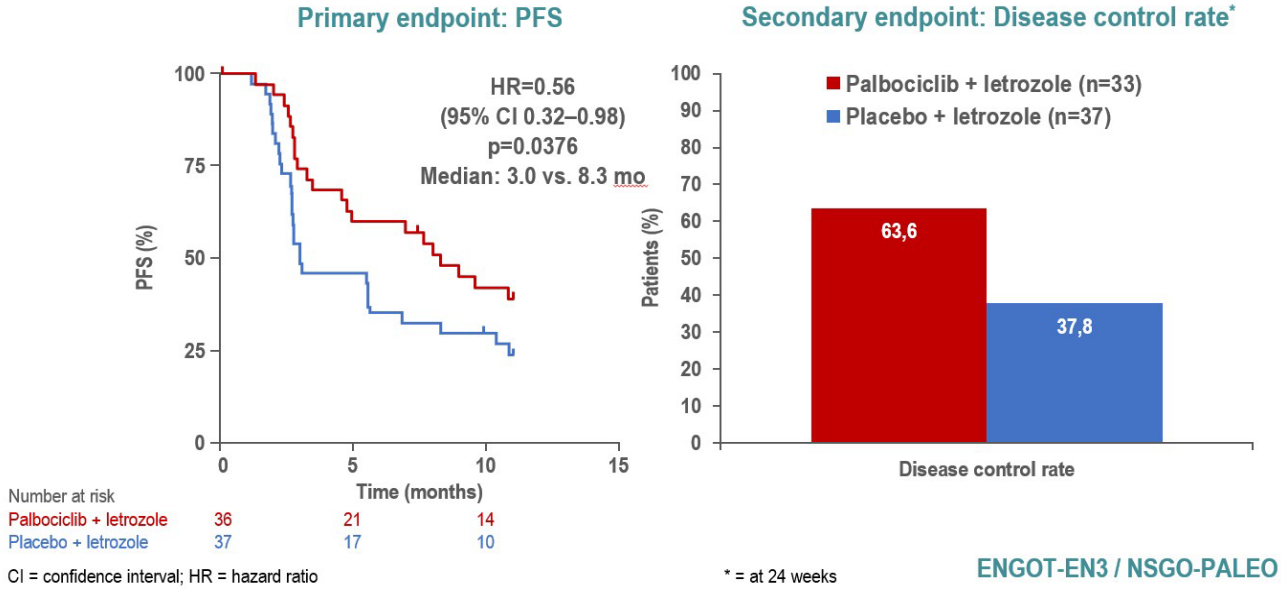
Hormonal Therapy

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

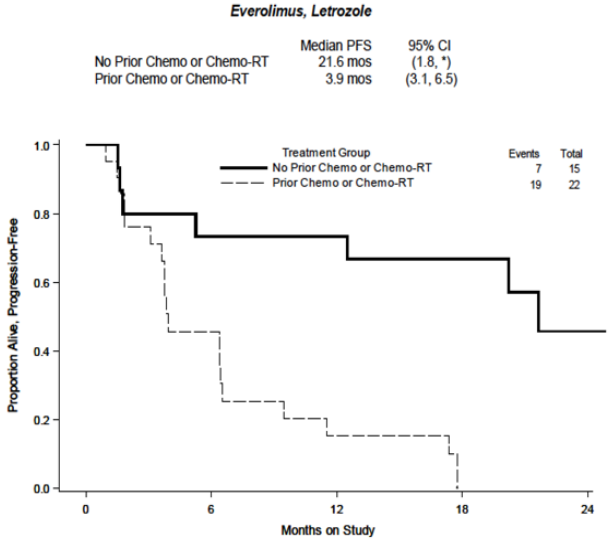
Option for 1st line or ≥2nd line:

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

ENGOT-EN3/NSGO-PALEO



GOG 3007



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

MacKay HJ, 2020 ASCO Educational Book; Ethier et al Gynecologic Oncology 2017; Meenakshi Singh et al. Gynecologic Oncology 2007; Mirza et al. ESMO 2020 ; Slomovitz et al, Gyn Oncol 2022

Summary

- dMMR tumors have unprecedented responses to CPI and should be the standard of care
- pMMR tumors do have improved outcomes with CPI; however, better treatment options remain an unmet need and should be further explored (PARP, non-IO, etc)
- The role of IO after IO needs to be investigated as limited efficacy data to date
- Non-IO treatment options are needed to provide better treatment options; enrollment into clinical trials is crucial