Immunotherapy For Uterine Cancer

New Standards For Upfront Treatment For Advanced Or Recurrent Disease

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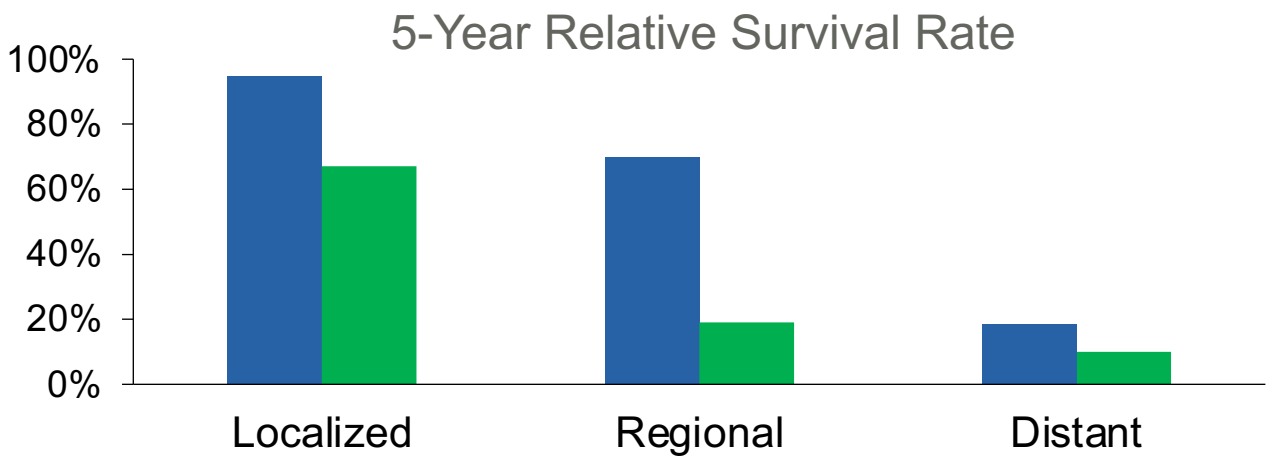
Objectives

- Provide an endometrial cancer overview
- Review trials of immunotherapy in frontline treatment of EC
- Discuss ongoing trials
- Brief review of immunotherapy in recurrent setting

Overview of Endometrial Cancer

- Estimated 66,200 new cases (3.4% of all cancers)
  - ~70% are diagnosed in early stages
  - ~1/3 are diagnosed with high grade or advanced disease
- Estimated 13,030 deaths



5-year relative survival rate

Cases by stage at diagnosis

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Siegel et al, 2023.

Biomarkers in Endometrial Cancer

Immunologically responsive

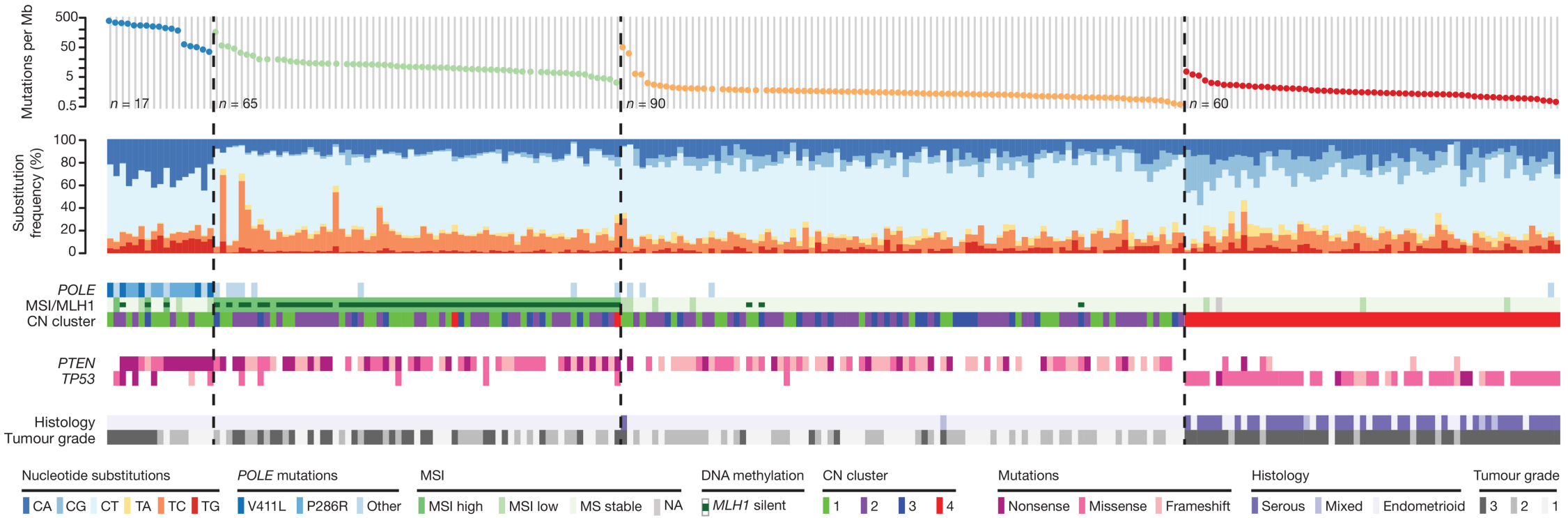
Immunologically non-responsive

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

2. MSI **(hypermutated)**

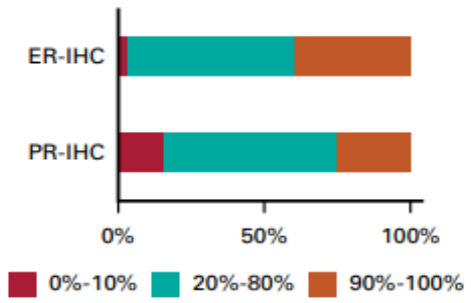
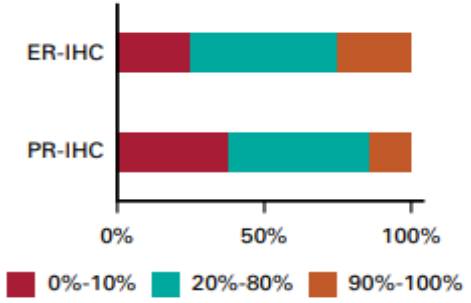
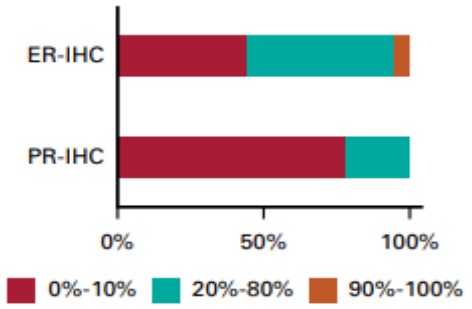
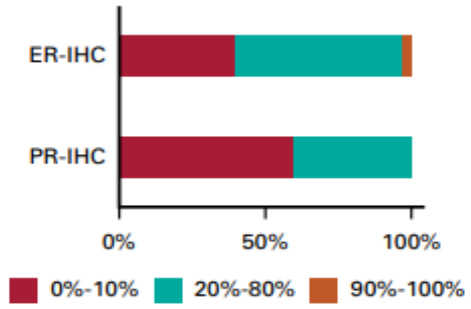
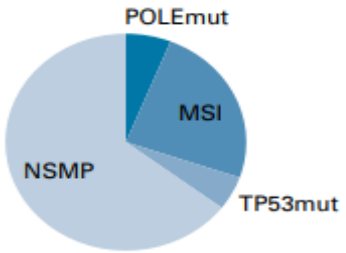
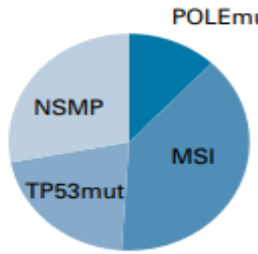
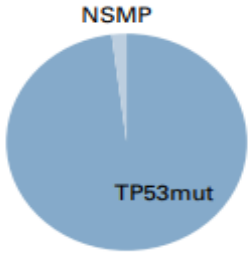
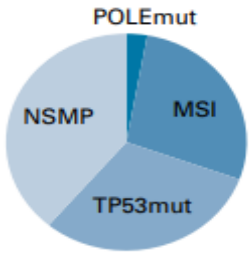
3. Copy-number low **(endometrioid)**

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



MSI, microsatellite instability. Levine et al, 2013.

Relation Between Different Classifications

Bokhman's classification	Type 1	Type 2		
Grade	Grade 1-2	Grade 3		
Histology	Endometrioid	Endometrioid	Serous	Clear cell
ER/PR-IHC expression[a]				
Molecular subgroup[b]				

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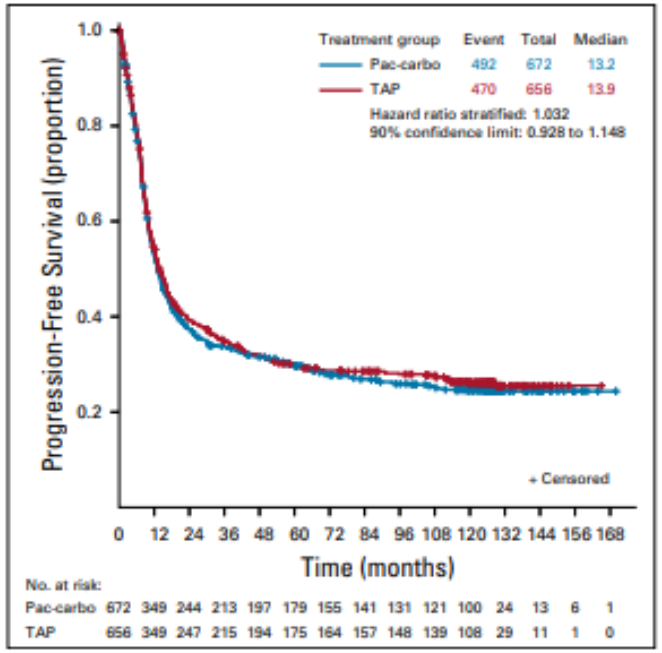
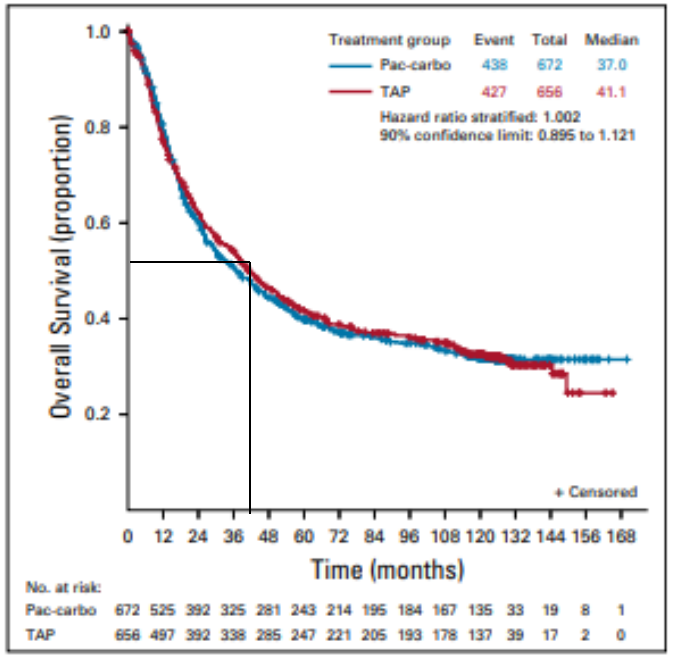
Pijnenborg JMA. JCO. 2023

Advanced Endometrial Cancer

- 2000's: Chemotherapy has been standard of care
- 2010: Carboplatin and paclitaxel became the preferred regimen





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Miller DS J Clin Oncol 2020.

Endometrial Cancer Recurrence Risk

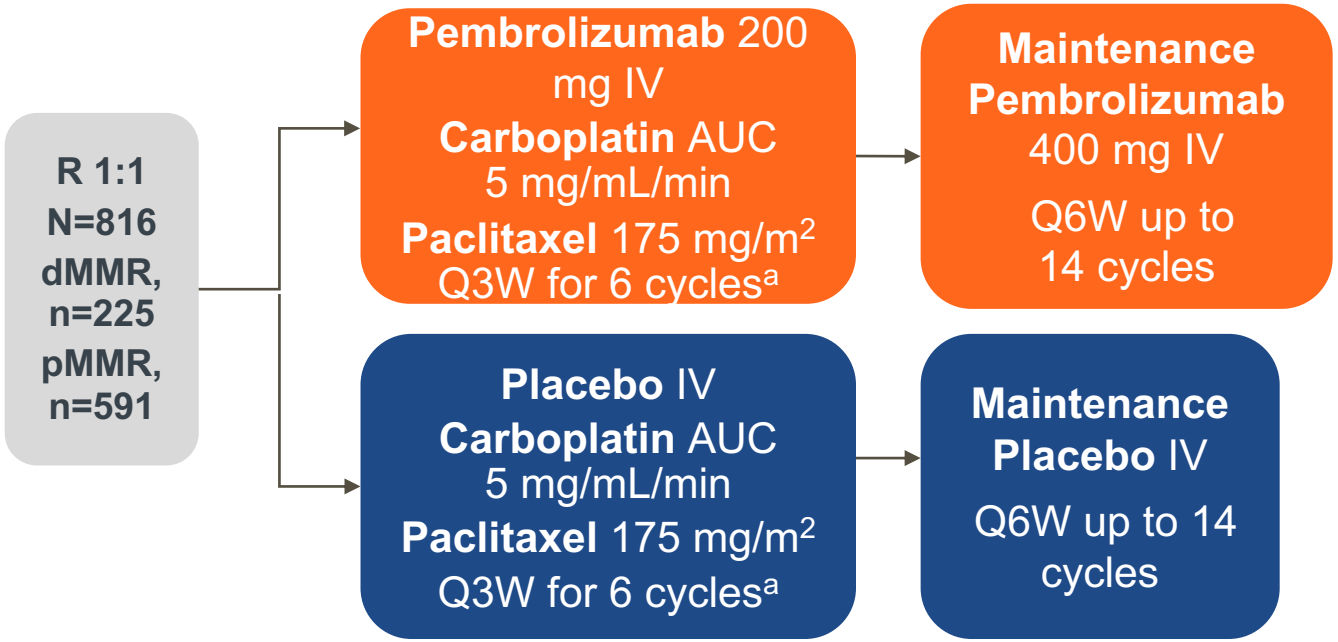
- 80% will recur within first two years

Study (control arm) Carboplatin and Paclitaxel	Median PFS (months)
GY-018	8.7m
RUBY	7.9m
GOG 209	13m
MITO END-2	10.5m
FANDANGO	7.2m
SIENDO	5.2m

GY018 (KEYNOTE 868): Study Schema

Eligible patients

- Histologically confirmed recurrent or advanced (stage III, IVA, or IVB) EC
- ECOG PS of 0-2
- Results of institutional MMR IHC testing
- Submission of tumor specimens for centralized MMR IHC testing
- No prior chemotherapy treatment for EC
- Prior adjuvant chemotherapy allowed if completed ≥12 months before enrollment



Primary end point: PFS (IA)

Secondary end points: AEs, ORR, DOR, OS, QOL, concordance between institutional MMR IHC and centralized MMR IHC

Stratification

- MMR status
- ECOG PS (0, 1 or 2)
- Prior chemotherapy (yes/no)

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Eskander RN. N Engl J Med. 2023.

GY018: Patient Characteristics

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

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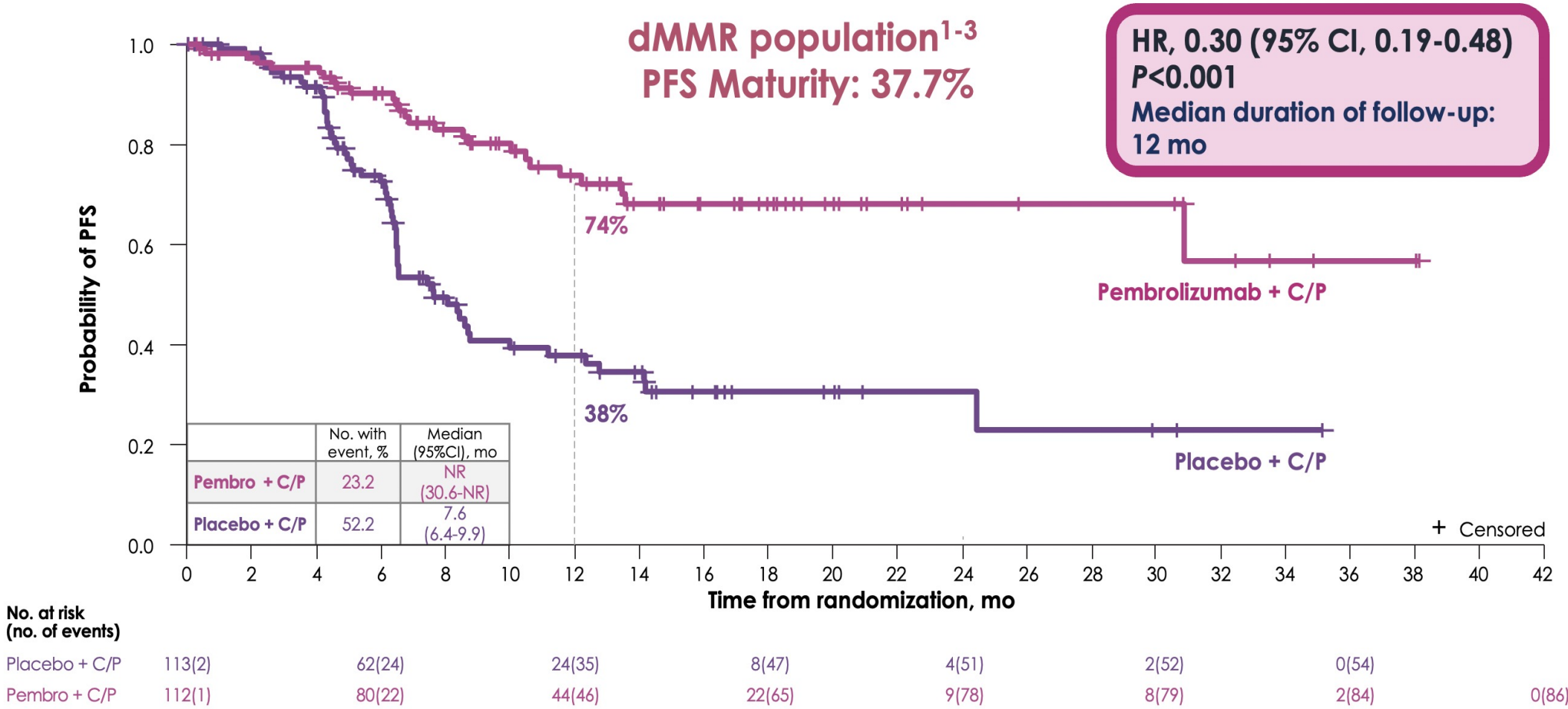
GY018 PFS dMMR



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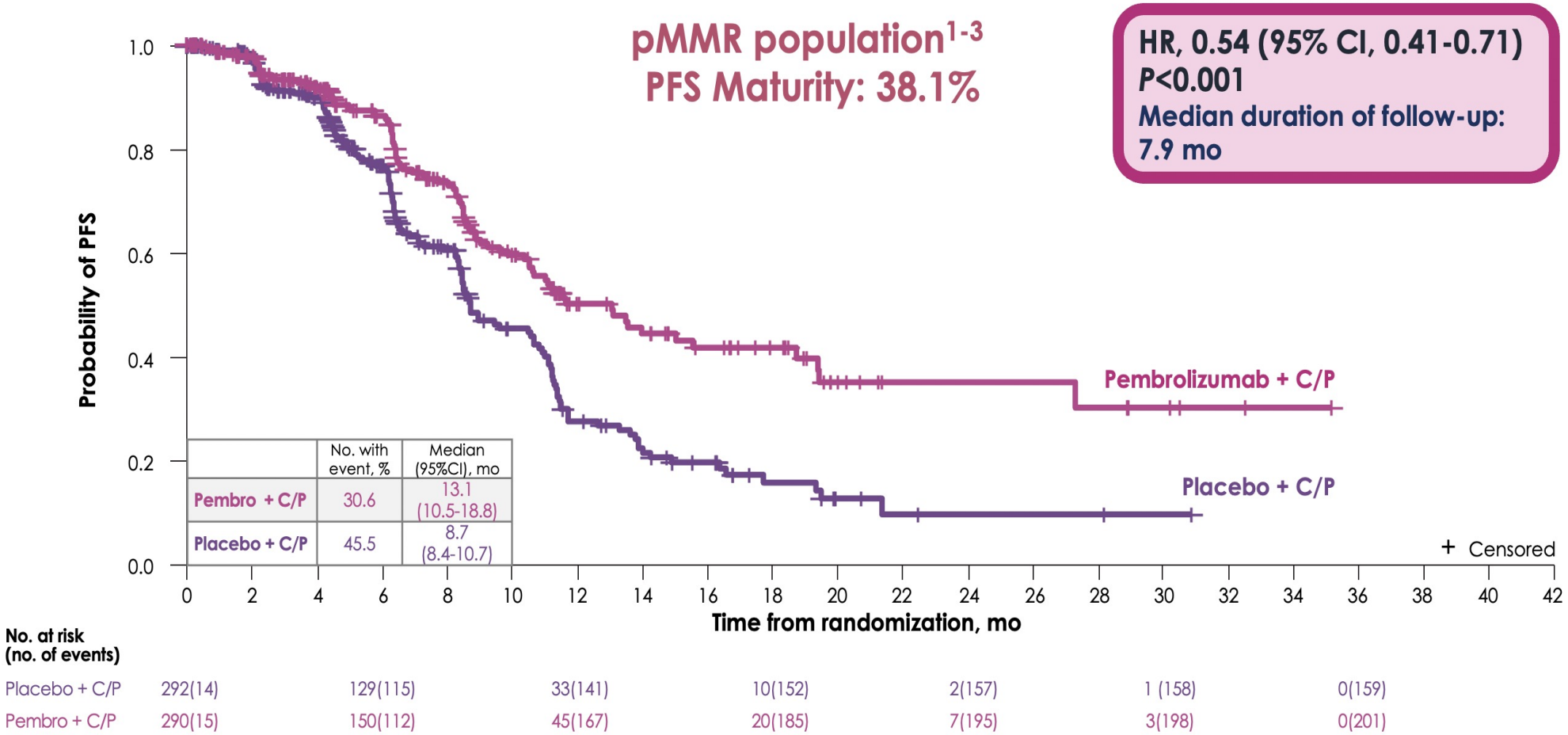
GY018: PFS pMMR



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GY018: Adverse Events

Adverse Events	dMMR Population		MMRp Population	
	Pembrolizumab + CP (n=109)	**Placebo + CP** (n=106)	**Pembrolizumab + CP** (n=276)	**Placebo + CP** (n=274)
Any AE (all cause), n (%)	107 (98.2)	105 (99.1)	258 (93.5)	256 (93.4)
Grade 3-5	69 (63.3)	50 (47.2)	152 (55.1)	124 (45.3)
Event leading to death	1 (0.9)[a]	2 (1.9)[a]	6 (2.2)[b]	2 (0.7)[b]
AEs of interest, n (%)[c]				
Any[d]	42 (38.5)	28 (26.4)	92 (33.3)	54 (19.7)
Grade 3-5	9 (8.3)	6 (5.7)	10 (3.6)	7 (2.6)

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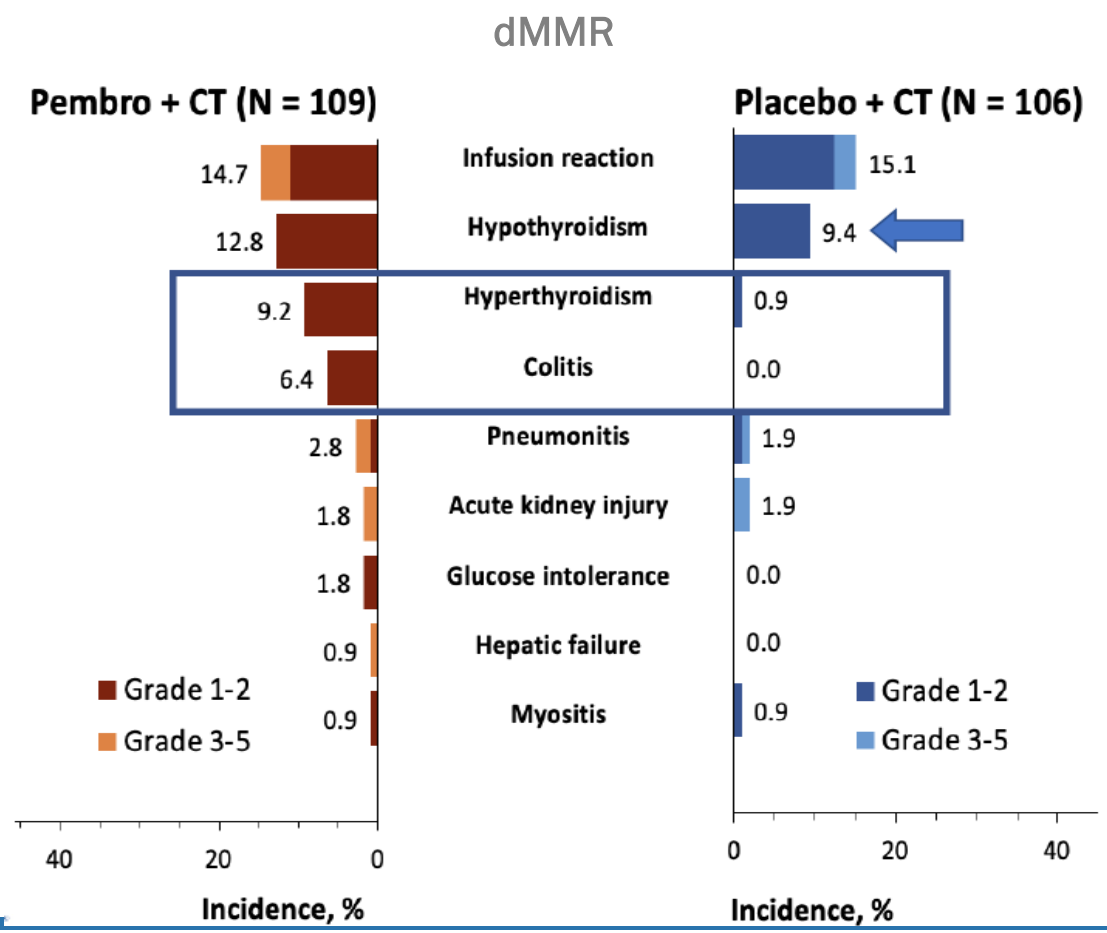
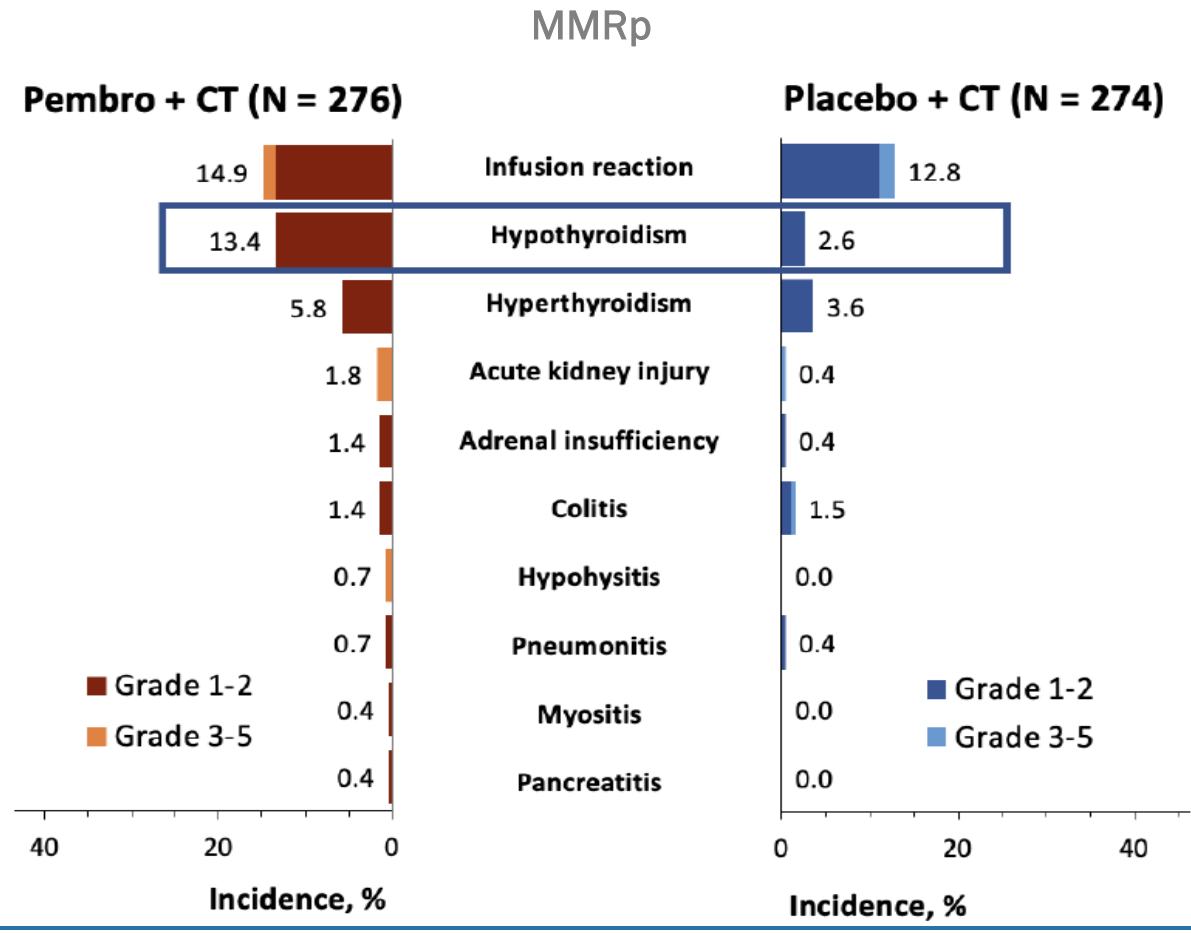
GY018: Adverse Events





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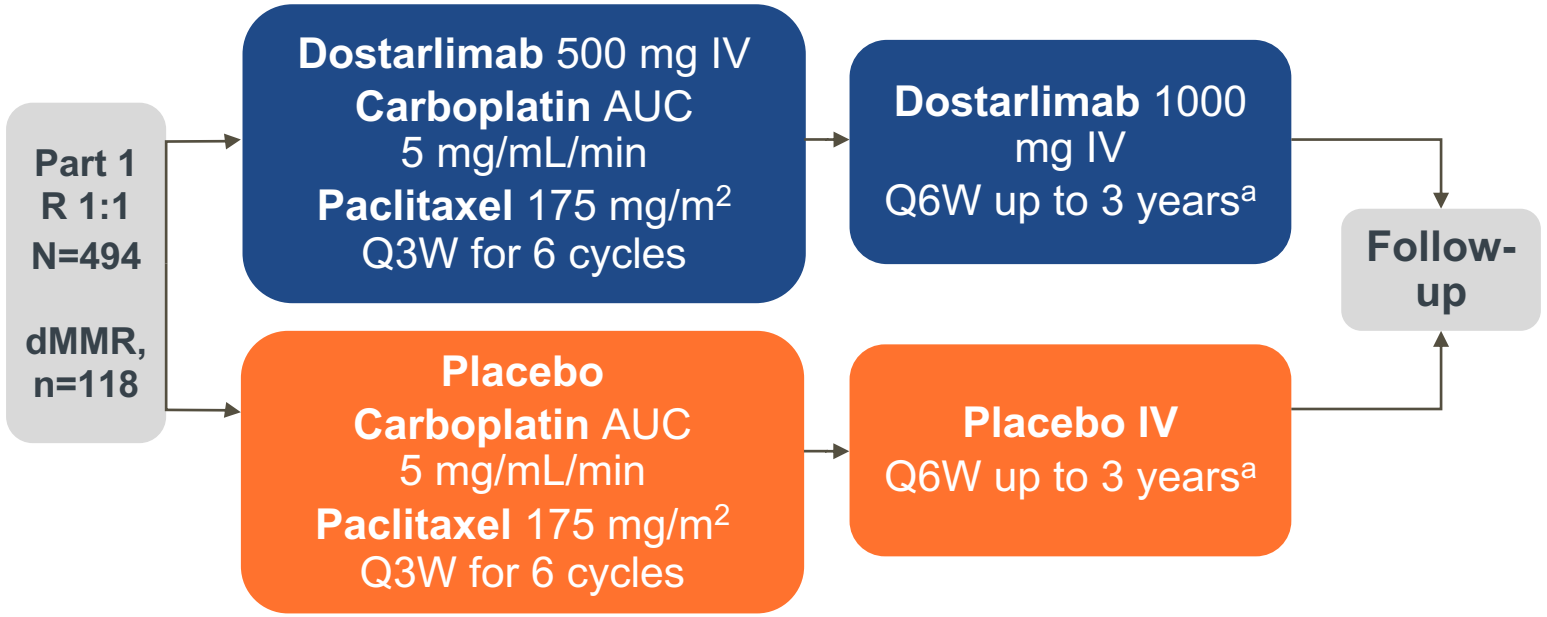
RUBY: ENGOT-en6/GOG 3031

Eligible patients

- Histologically or cytologically proven EC with recurrent or advanced disease
- Stage III or IV disease or first recurrence of EC with low potential for cure by use of radiation therapy or surgery alone or in combination
  - Carcinosarcoma, clear cell, serous, or mixed histology
- Naive to systemic therapy or systemic anticancer therapy and recurrence or PD ≥6 months after completing treatment
- ECOG PS 0 or 1
- Adequate organ function



Primary end points: PFS (IA), OS

Secondary end points: PFS (BICR), PFS2, ORR/DOR/DCR, QOL, PK and immunogenicity, safety

Stratification

- MMR/MSI status
- Prior radiotherapy
- Disease status

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RUBY: Patient Characteristics

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

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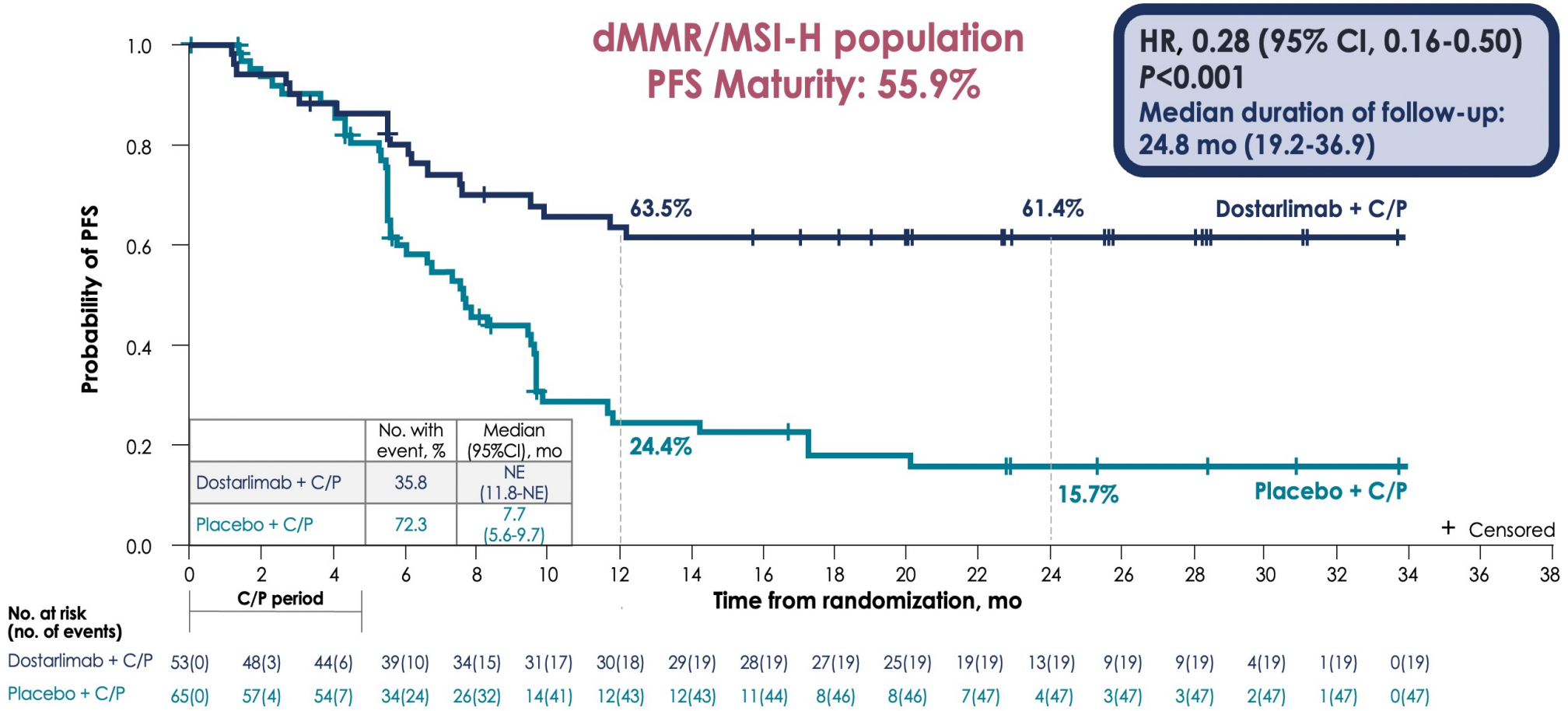
RUBY: PFS dMMR



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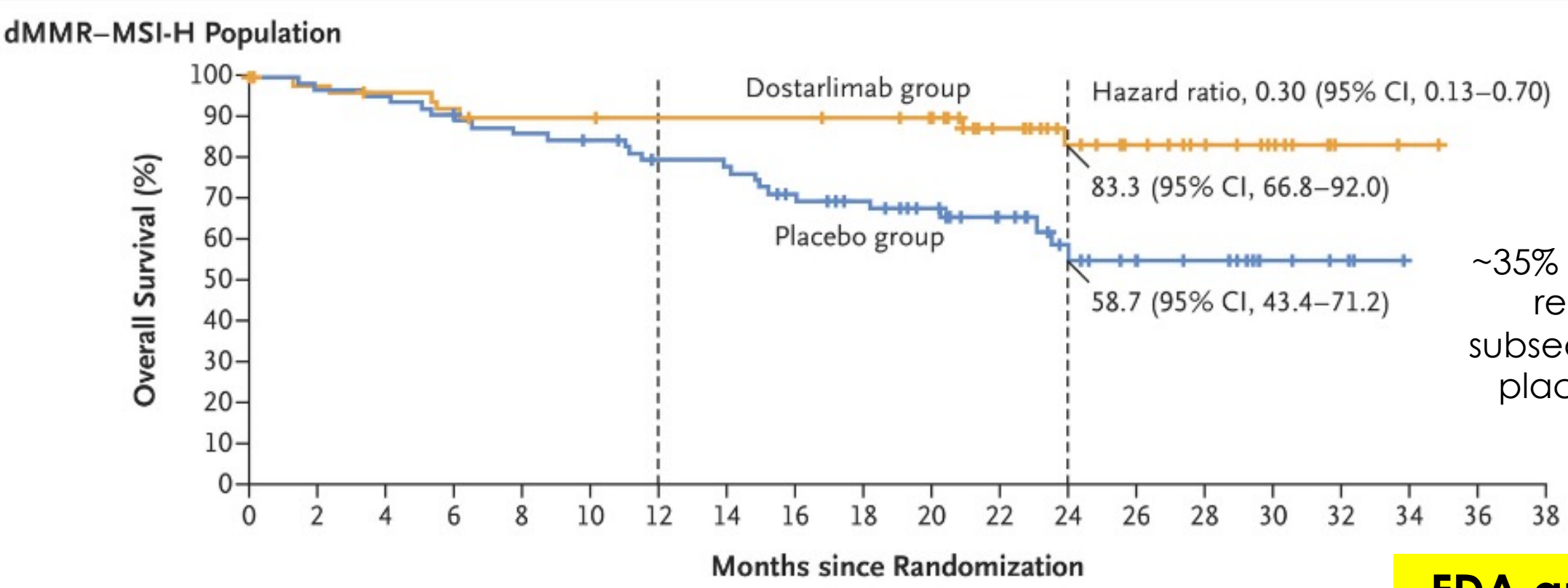
RUBY Trial: OS dMMR



~35% of patients received subsequent IO in placebo arm

FDA approval in dMMR population on 7/31/2023

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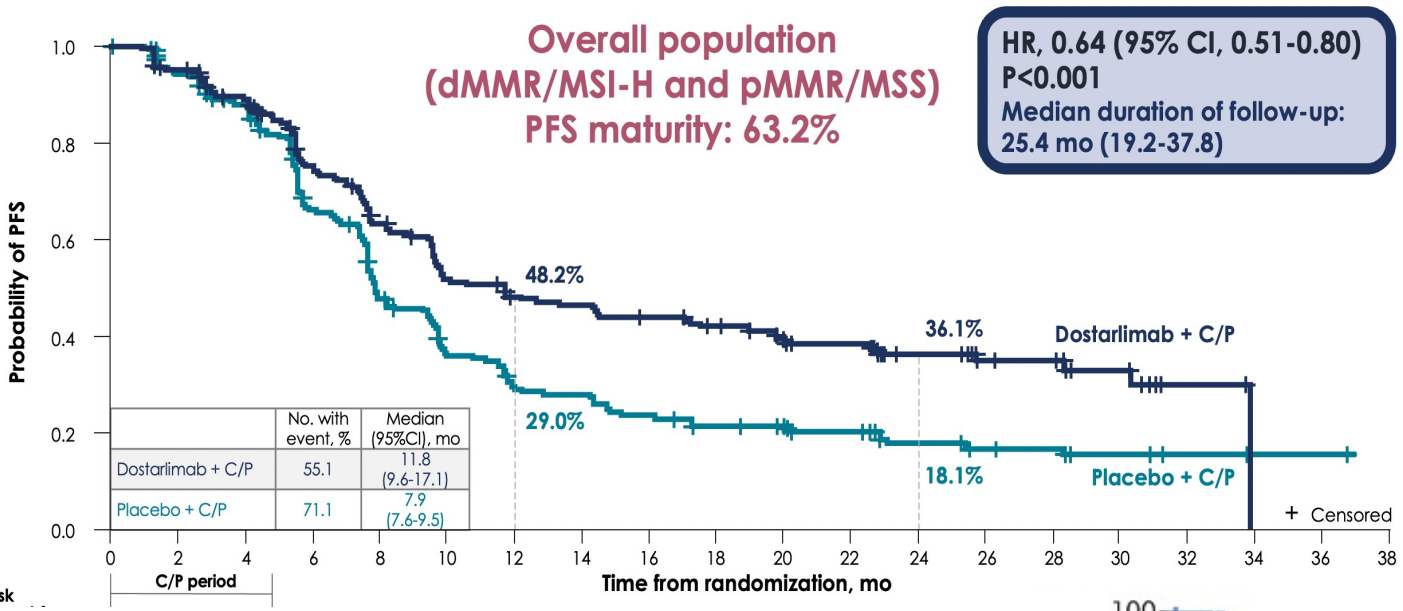
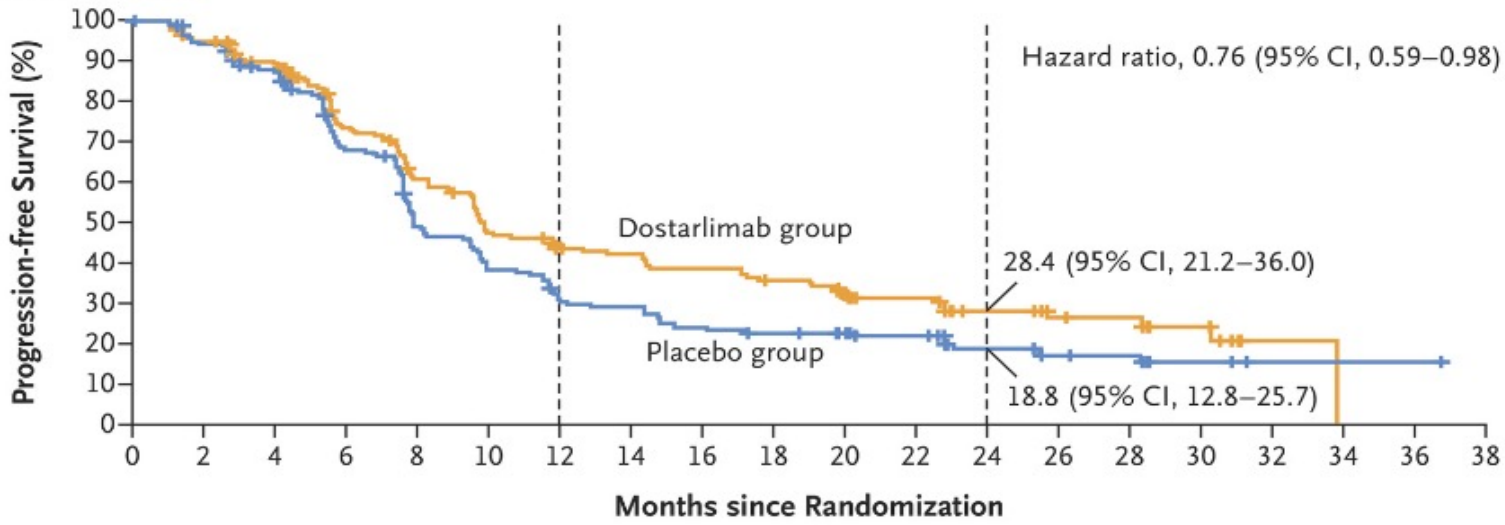
RUBY: PFS ITT and pMMR



pMMR



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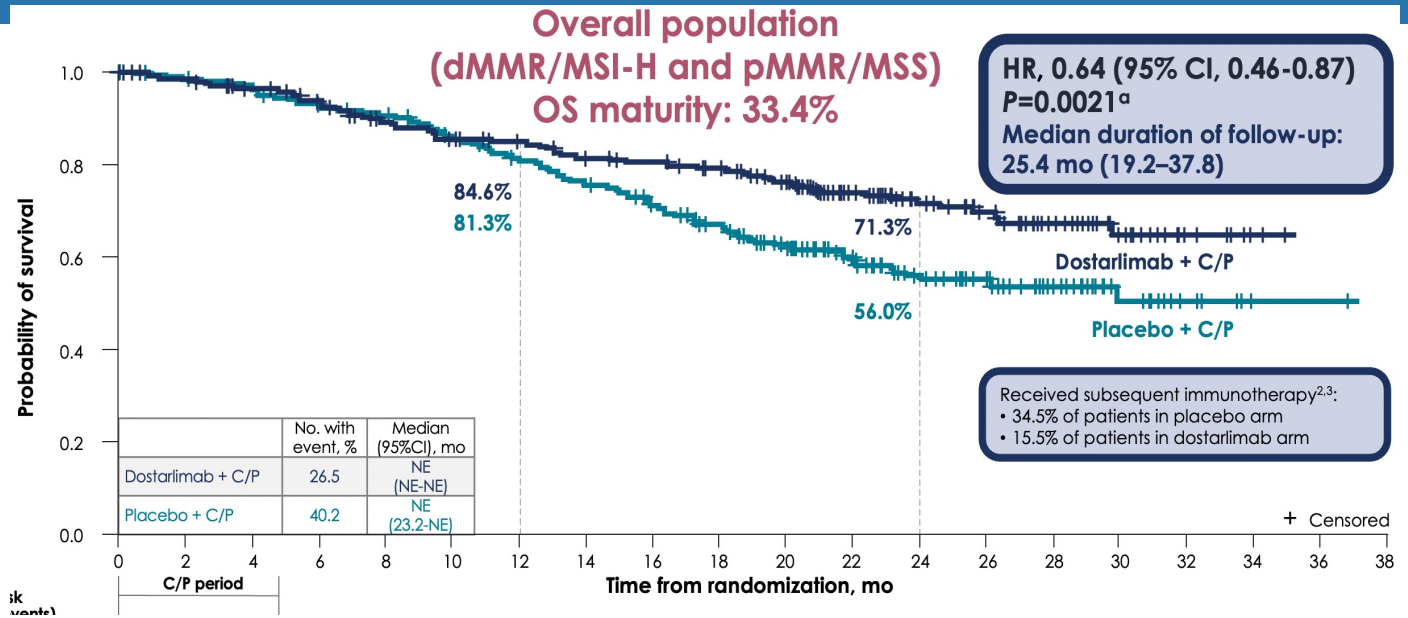
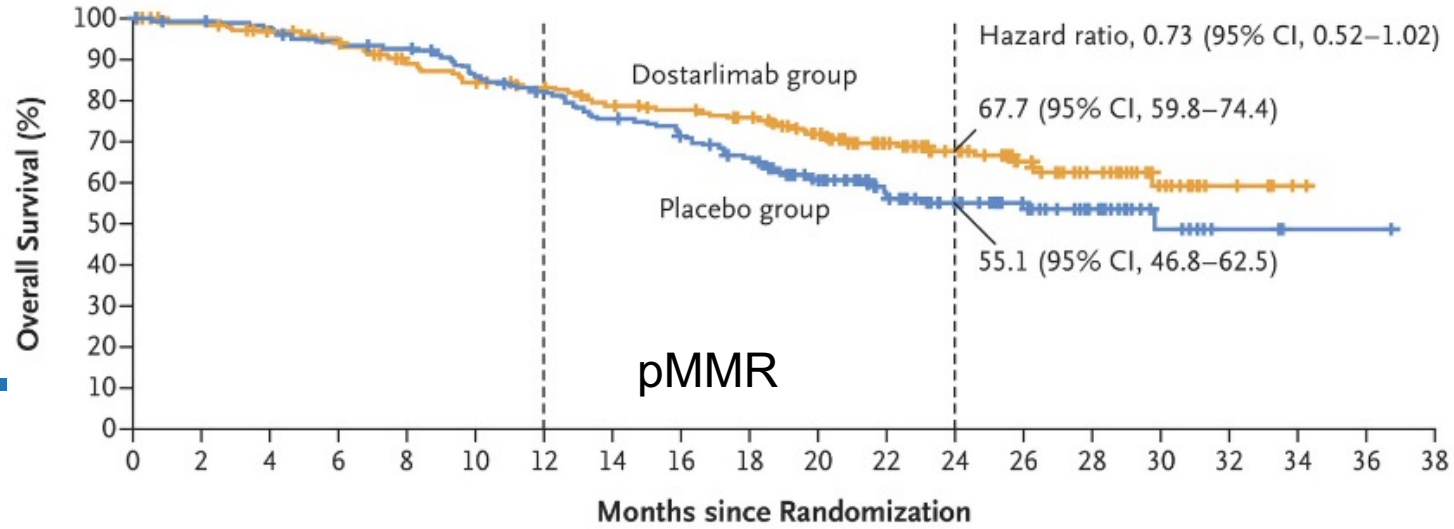
RUBY OS ITT and pMMR





Press Release 10/30/23

A clinically meaningful OS benefit was observed in both prespecified subpopulations in the trial: mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) and mismatch repair proficient (MMRp)/microsatellite stable (MSS) patient subgroups.

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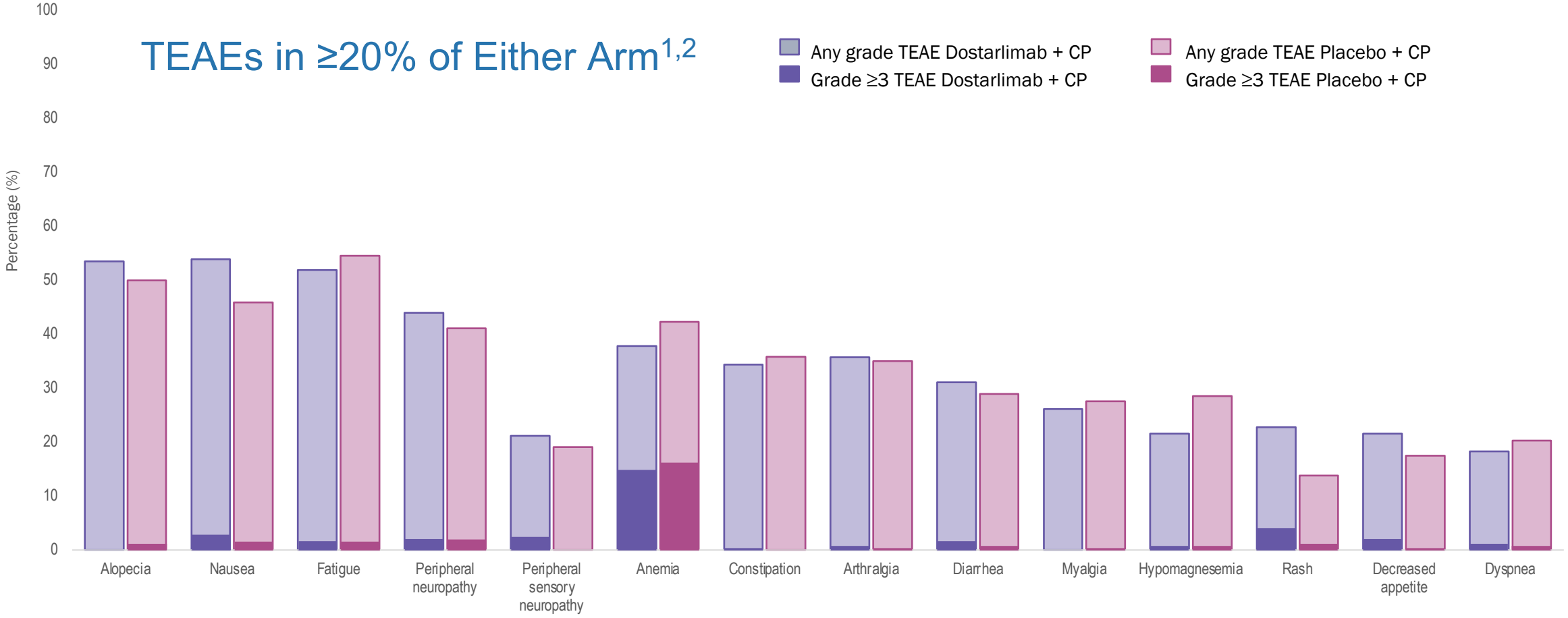
RUBY: Adverse Events



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RUBY: Safety Summary

Parameter, n (%)	Dostarlimab + CP (n=241)	Placebo + CP (n=246)
Any TEAE	241 (100)	246 (100)
Any grade ≥3 TEAE	170 (70.5)	147 (59.8)
Serious TEAE	91 (37.8)	68 (27.6)
Any treatment-related irAE	92 (38.2)	38 (15.4)
Any TEAE leading to discontinuation of dostarlimab or placebo	42 (17.4)	23 (9.3)
Any TEAE leading to discontinuation of carboplatin	24 (10.0)	19 (7.7)
Any TEAE leading to discontinuation of paclitaxel	24 (10.0)	23 (9.3)
Any TEAE leading to death	5 (2.1)[a]	0
Any TEAE related to dostarlimab leading to death	2 (0.8)[b]	—
Median duration of overall treatment (range), weeks	43.0 (3.0–150.9)	36.0 (2.1–165.1)

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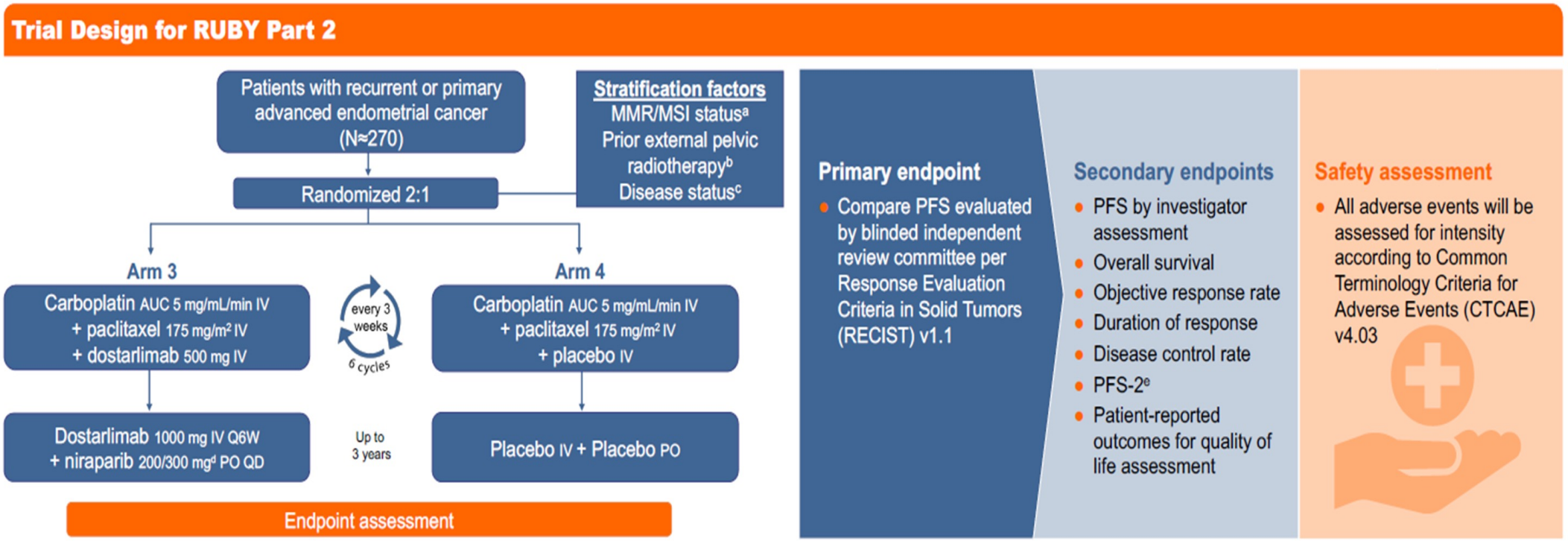
The Role of PARPi: RUBY Part 2

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



[a]MMR/MSI status: dMMR/MSI-H or MMRp/MSS; [b]Prior external pelvic radiotherapy: yes or no; [c]Disease status: recurrent, primary stage III, or primary stage IV; [d]Niraparib dosing is 200 mg PO QD for patients with baseline BW <77 kg or PC <150,000/μL or 300 mg QD for patients with baseline BW ≥77 kg and PC ≥150,000/μL; [e]PFS-2 is defined as the time from randomization to objective tumor progression on next-line treatment or death from any cause, whichever is earlier.

AUC, area under the curve; BW, body weight; dMMR, mismatch repair deficient; IV, intravenously; MMR, mismatch repair; MMRp, mismatch repair proficient; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSS, microsatelite stable; PC, platelet count; PFS, progression-free survival; PO, by mouth; Q3W, every 3 weeks; Q6W, every 6 weeks; QD, once daily.

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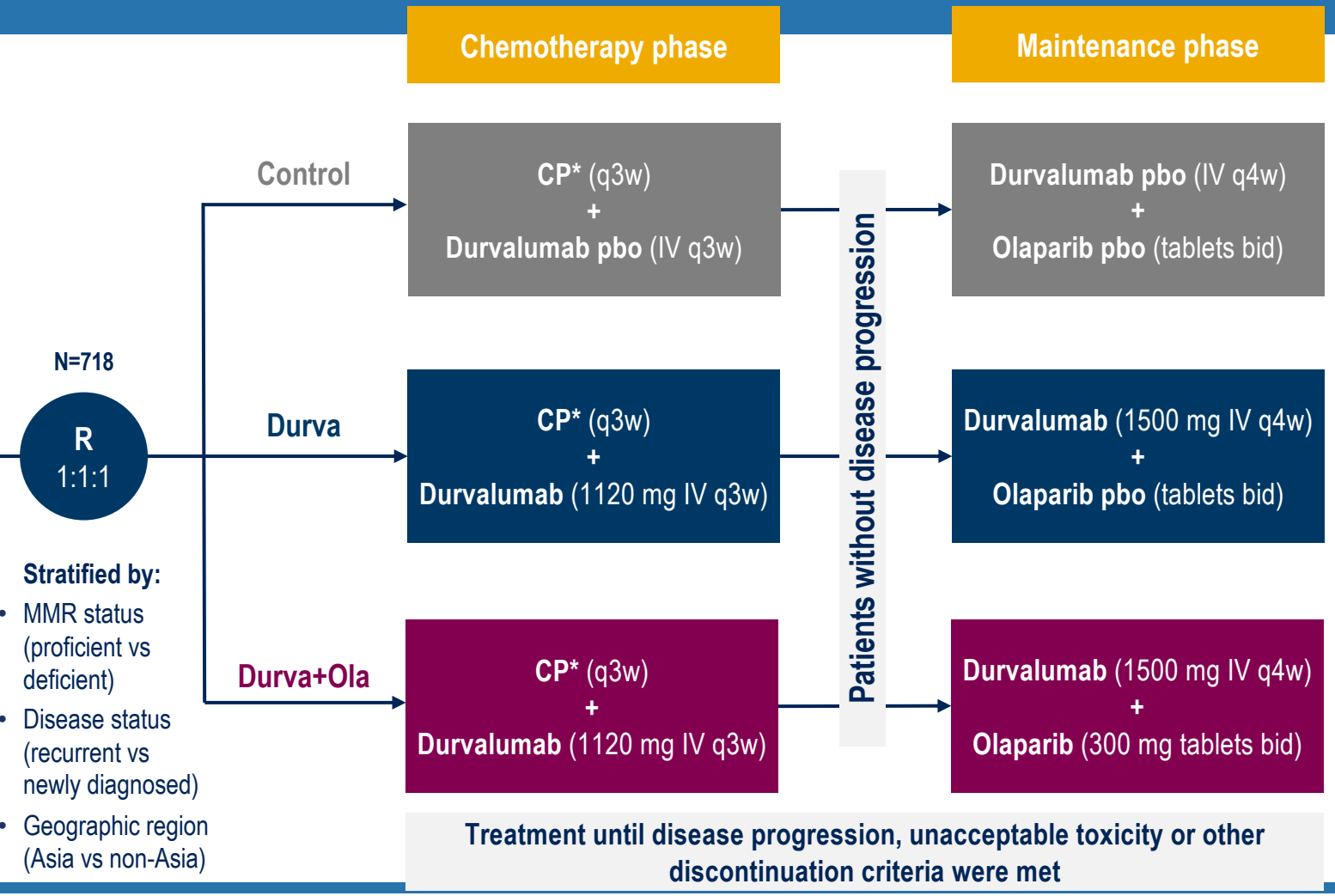
clinicaltrials.gov:01244789.

DUO-E: Study Schema

Patients

- Newly diagnosed FIGO 2009 Stage III/IV or recurrent endometrial cancer
- Known MMR status
- Naïve to first-line systemic anticancer treatment for advanced disease
- Naïve to PARP inhibitors and immune-mediated therapy
- Adjuvant chemotherapy allowed if ≥12 months from last treatment to relapse
- All histologies except sarcomas



Endpoints

Primary

- PFS (RECIST per investigator) in:
  - Durva vs Control
  - Durva+Ola vs Control

Key secondary

- OS (analytical)
- Safety

Exploratory

- PFS in Durva+Ola vs Durva
- Subgroup analyses of PFS
  - Including MMR, PD-L1, HRRm

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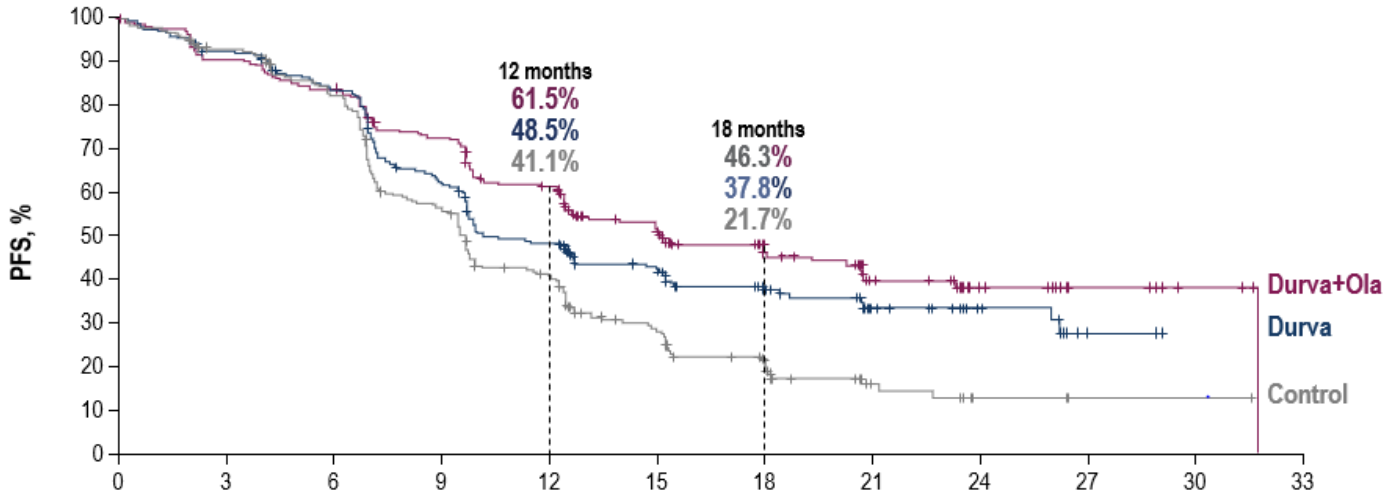
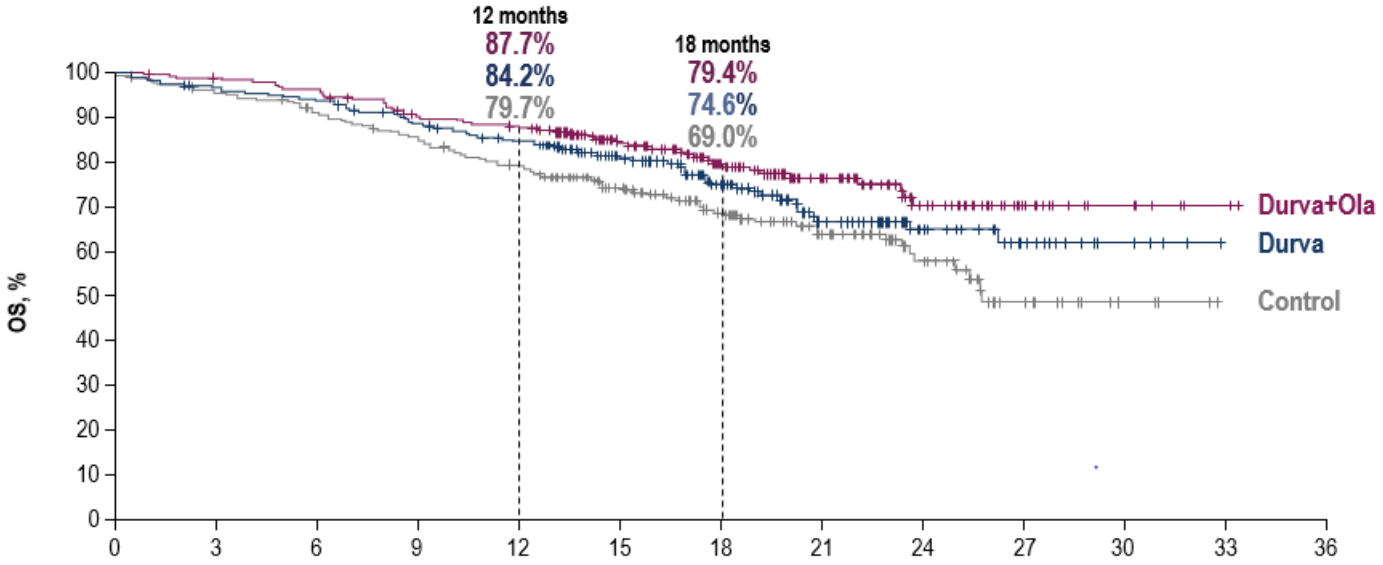
DUO-E Survival Outcomes: ITT Population



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

Overall data maturity 61.0%



	Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Events, n (%)	82 (34.0)	65 (27.3)	52 (21.8)
Median OS (95% CI),* months	25.9 (23.9–NR)	NR (NR–NR)	NR (NR–NR)
HR (95% CI) vs Control†		**0.77** (0.56–1.07); *P*=0.120	**0.59** (0.42–0.83); *P*=0.003
HR (95% CI) vs Durva†			**0.77** (0.53–1.10)

Overall data maturity 27.7%

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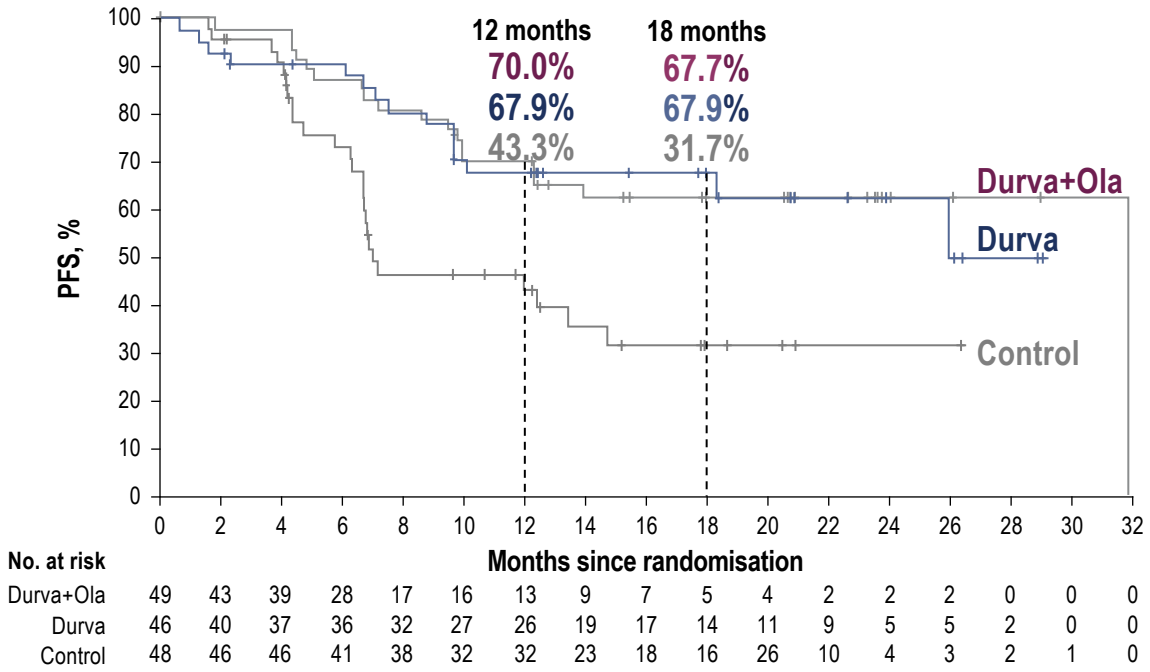
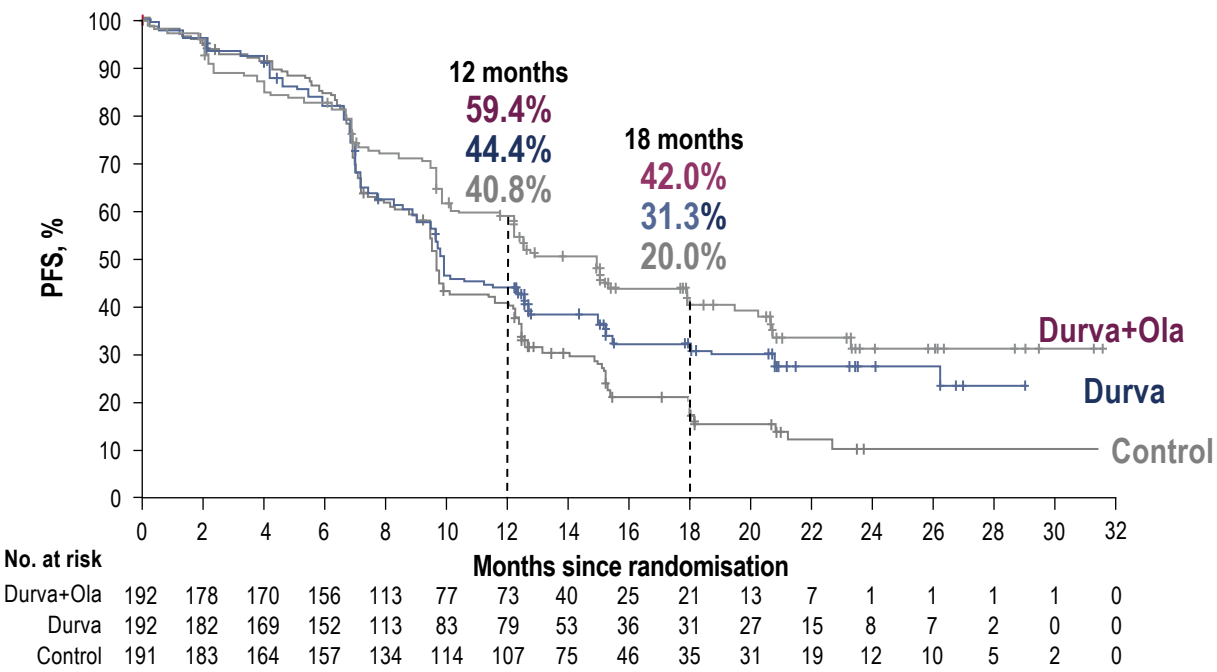
DUO-E: Subgroup Analysis of PFS by MMR Status

dMMR (20% of population)



	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)**

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)**

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Ongoing Trials: Is Chemotherapy Necessary?

	Pembrolizumab KEYNOTE-C93	Dostarlimab DOMENICA	Lenvatinib/Pembrolizumab LEAP-001
Study treatment	▪ Pembrolizumab 400 mg IV q6w for 18 cycles (2 years) ▪ Carboplatin AUC 5 or 6 mg/mL/min IV q3w + paclitaxel 175 mg/m^2 IV q3w for 6 cycles (with option for >6 cycles)	▪ Dostarlimab 500 mg q3w (cycles 1-4) then dostarlimab 1000 mg q6w (for up to 2 years) ▪ Carboplatin AUC 5-6 + paclitaxel 175 mg/m² q3w (for 6 cycles)	▪ Lenvatinib 20 mg orally qd + pembrolizumab 200 mg IV q3w ▪ Carboplatin AUC 6 IV q3w + paclitaxel 175 mg/m^2 IV q3w
Key eligibility criteria	▪ dMMR status ▪ Stage III/IV or recurrent EC including carcinosarcoma Radiographically evaluable disease (measurable or nonmeasurable per RECIST v1.1) ▪ No prior systemic therapy ▪ ECOG PS 0-1	▪ dMMR/MSI-H status ▪ Stage IIIC2/IV disease or first recurrence ▪ Prior neo/adjuvant chemotherapy allowed if ≥6 months from last treatment to relapse ▪ All histologic subtypes of endometrial adenocarcinoma included ▪ ECOG PS 0-1	▪ Stage III-IV or recurrent EC ▪ Prior adjuvant Chemo ≥6 months before study ▪ ECOG 0-1

12/8/23: LEAP-001 did not improve OS or PFS in the first-line treatment of certain patients with advanced or recurrent endometrial carcinoma versus a standard of care, platinum-based chemotherapy doublet (carboplatin plus paclitaxel).

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Recurrent Endometrial Cancer

dMMR

Parameter	KEYNOTE-158: Pembrolizumab	GARNET: Dostarlimab
ORR, % (95% CI)	**48 (37-60)**	**43.4 (33.8-53.4)**
▪ CR	11 (14)	11 (10.4)
▪ PR	27 (34)	35 (33.0)
▪ SD	14 (18)	13 (12.3)
▪ PD	23 (29)	39 (36.8)
Median DoR	NR (2.9-49.7+)	NR

pMMR

MMRp	Len Pem	Chemo
ORR	32.4%	15.1%
mDOR, Mo	9.3 (1.6-39.5)	5.7 (0-37.1)
mOS, mo	18.0 (14.2-19.9)	12.2 (11.0-14.1)
HR	0.70 (0.56-0.83)	

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O'Malley DM. J Clin Oncol. 2022 . Oaknin A. J Immunother Cancer. 2022.

Makker V. J Clin Oncol. 2023.

Conclusions

- Molecular testing has significant implications
  - Genetic testing
  - Treatment strategies
- Frontline treatment
  - Checkpoint inhibitors are the standard of care for dMMR
  - Data pending in pMMR, possible subsets
- Recurrent setting
  - Checkpoint inhibitors are used but unclear role if used previously

Thank you

"It's always Sit, Stay, Heel - never Think, Innovate, Be yourself."