.cáncer. XII FORO DE ovario
Y OTROS TUMORES GINECOLÓGICOS

Necesidades no cubiertas: ¿cómo nos ayudará la evidencia en 1L?

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Disclosures of potential conflict of interest

- Speaker bureau: Astrazeneca-MSD, Clovis, GSK.
- Travel and accommodation fees: GSK, AstraZeneca-MSD, Merck.
- Honoraria: GSK.

I declare that this facts have no bearing on my prescribing as a physician.

AGENDA

1. Introduction

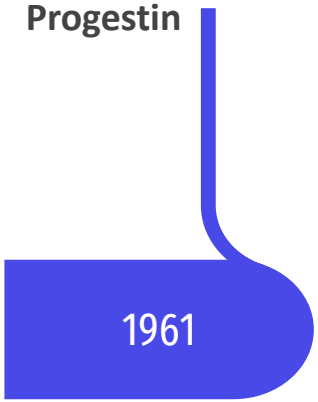
2. Evolution of the 1st line treatment in advanced/recurrent Endometrial Cancer:
    1. Progestin
    2. GOG 177 trial
    3. GOG 209 trial
    4. SIENDO trial
    5. RUBY trial
    6. NRG GY018 trial

3. Conclusions

Introduction

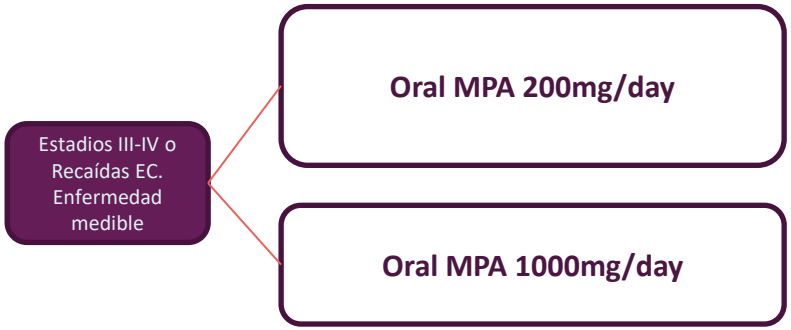
- Endometrial cancer (EC) is the most common gynecologic malignancy in women in the developed world and it is the only gynecological tumor with an increasing incidence.
- The overall prognosis is excellent for most patients diagnosed with early-stage EC. In contrast, the 5-years survival rate in stage IV EC is approximately 17%.
- In metastasic/recurrent EC, to date, there were limited therapeutic options mainly based on platinum-therapy or hormonotherapy.

Evolution of the 1st line treatment in advanced/recurrent Endometrial Cancer

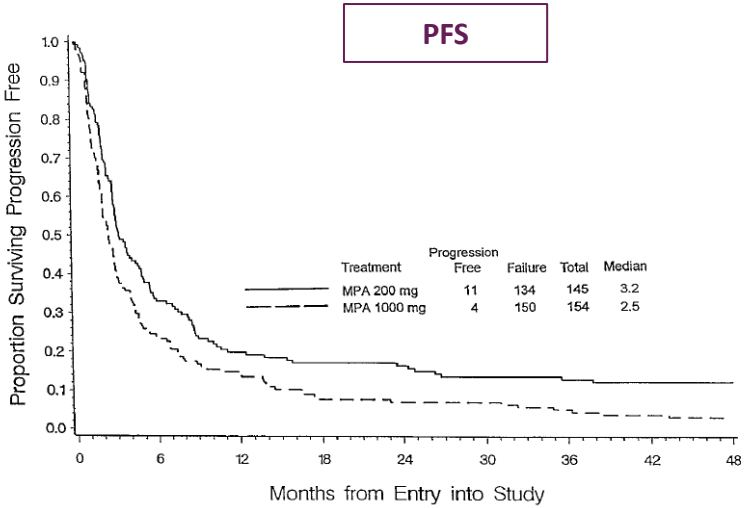


PROGESTIN

- Initial studies of progestins in endometrial carcinoma used parenteral forms.
- In 1961, a serie of 21 recurrent endometrial cancers treated with preparation of progestational agents were published. A third have shown objective responses with a duration of response ranging from 9 months to 4.5 years.
- In 1999, the GOG 81 trial evaluated the best dose of oral progestin.

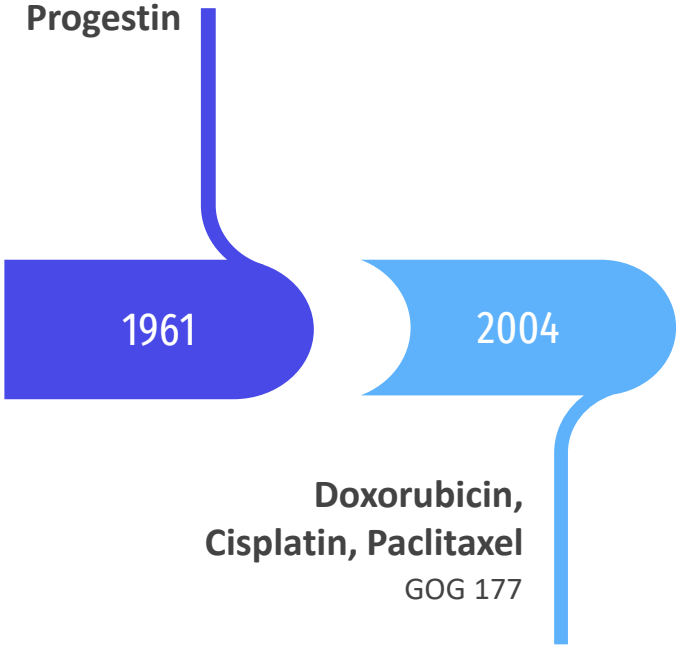


N: 324 patients



Kelley RM and Baker WH, N Engl J Med. 1961. Thigpen JT et al. JCO 1999

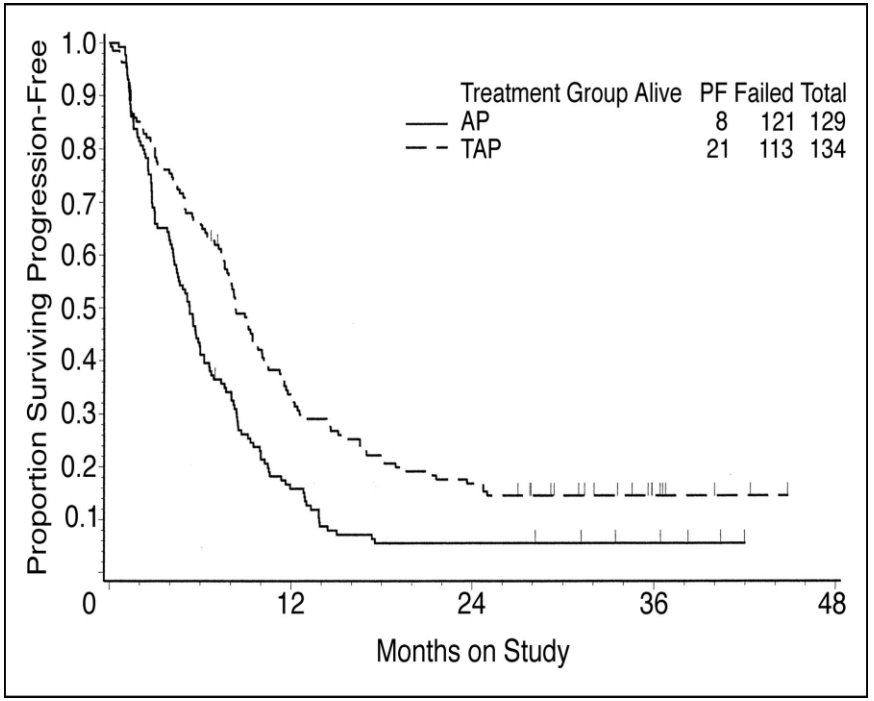
Evolution of the 1st line treatment in advanced/recurrent Endometrial Cancer



Advanced or Recurrent Disease
Limited Efficacy of Chemotherapy: GOG 177 trial

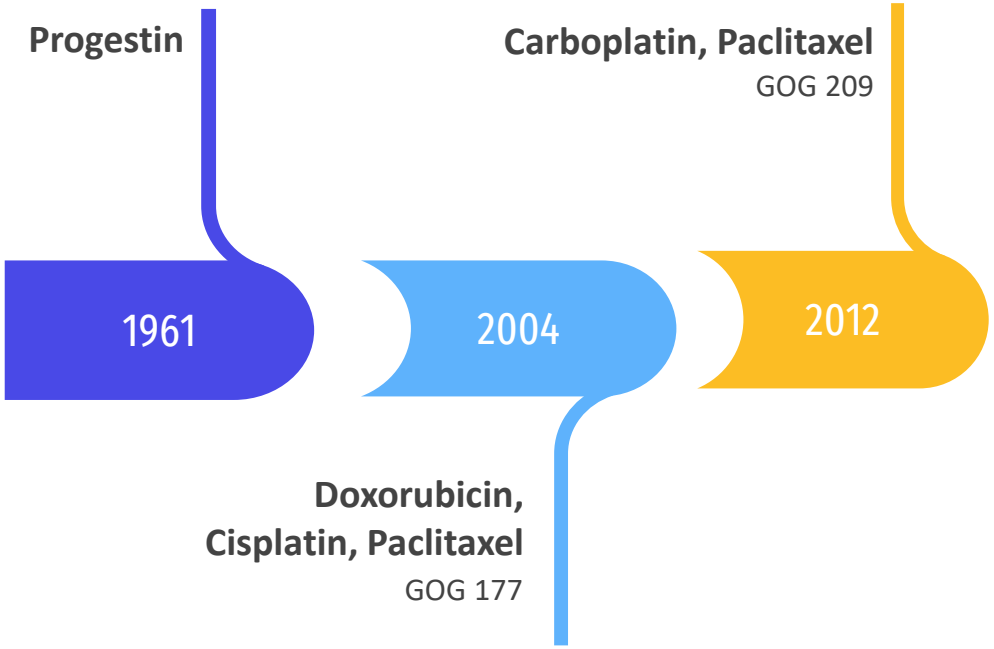
III-IV Stage or recurrent EC.

- **Doxorubicin 45 mg/m2 + cisplatin 50 mg/m2 (D1), paclitaxel 160 mg/m2 (D2) GCSF**
- **Doxorubicin 60 mg/m2 and cisplatin 50 mg/m2 every 3 weeks**



Fleming GF et al. J Clin Oncol. 2004

Evolution of the 1st line treatment in advanced/recurrent Endometrial Cancer



Advanced or Recurrent Disease
Limited Efficacy of Chemotherapy in 1st Line: GOG 209 trial

- Open-label, randomized, phase III noninferiority trial

Estadios III-IV o Recaídas
EC.
No tratamiento previo
Enfermedad medible
RE/P

Adriamcina 45mg/m2, CDDP 50mg/m2, D1 Paclitaxel 160mg/m2, D2 c/3 semanas
GSCF

Paclitaxel 175mg/m2, CBDCA AUC 6, D1 c/3 semanas

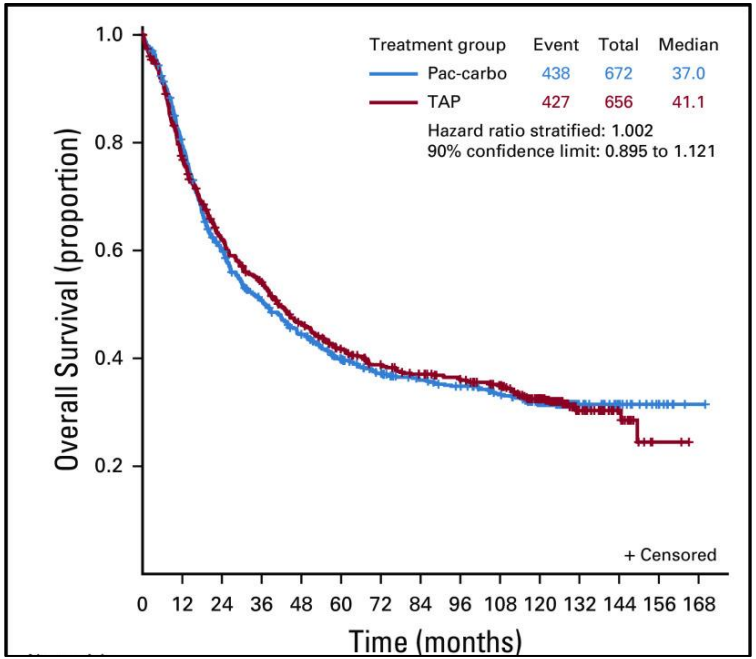
Stratification
- Performance status
- Disease status (measurable or recurrent)
- Adjuvant Radiotherapy (Y/N)

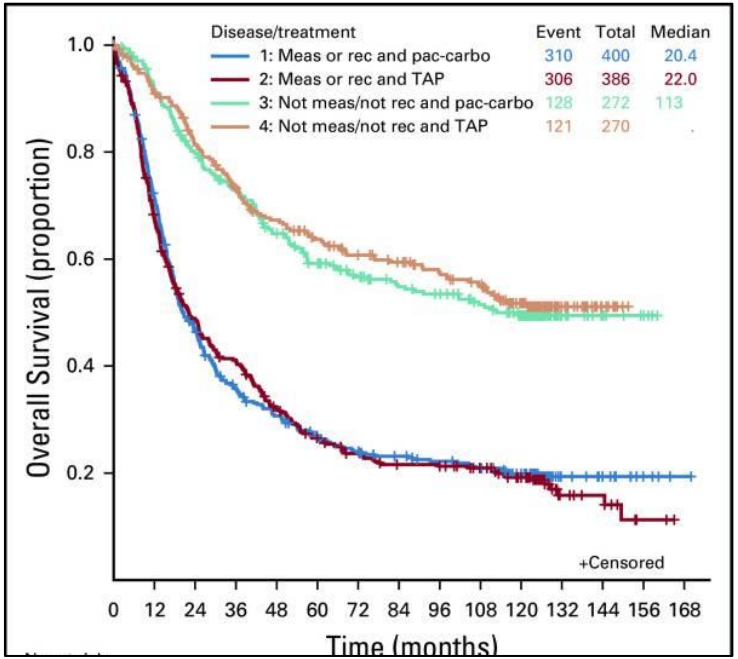
Objective: TC decreases survival time from study entry when compared with TAP.

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

Advanced or Recurrent Disease

Limited Efficacy of Chemotherapy in 1st Line: GOG 209 trial



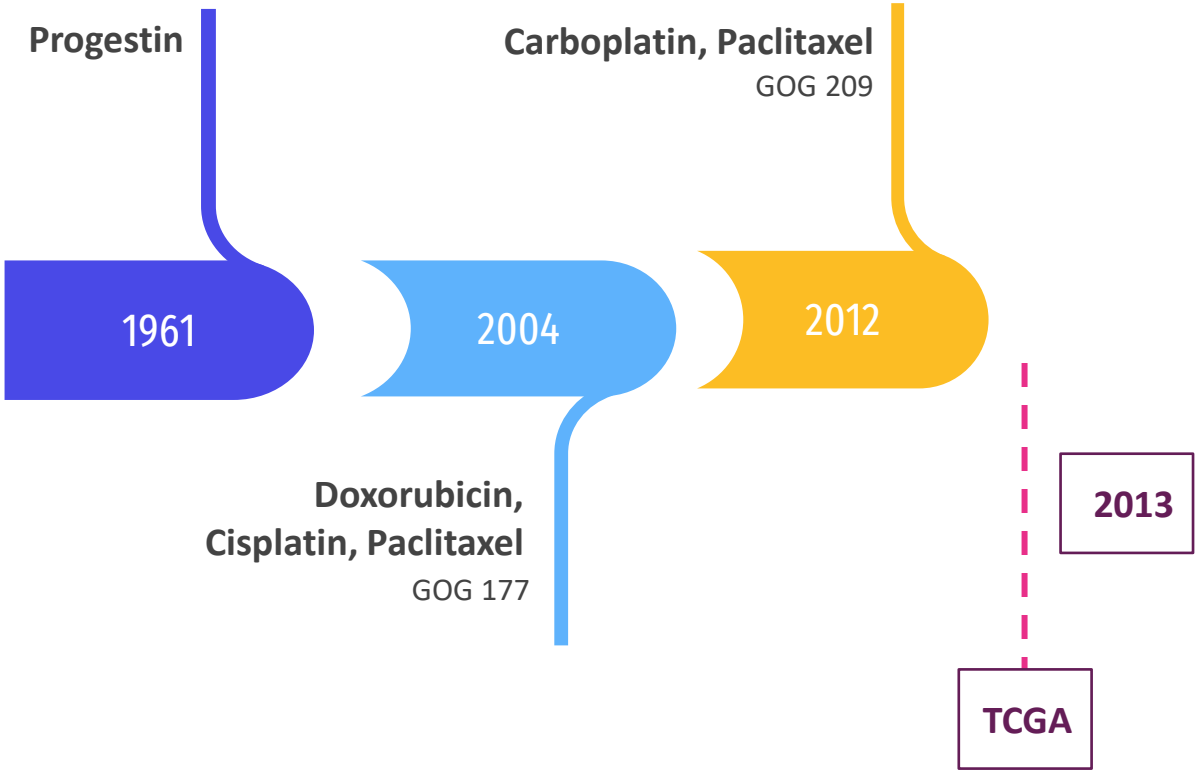


Median follow-up of 124 months:

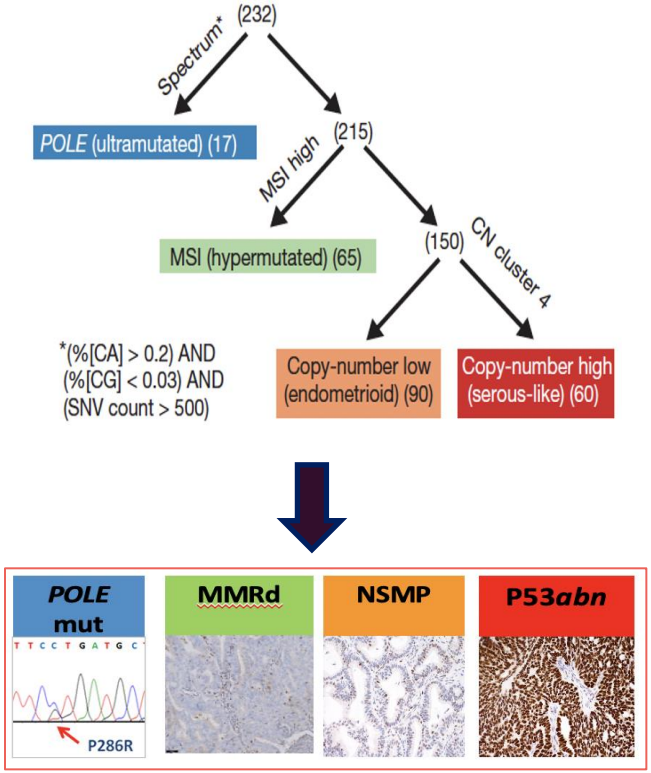
- More than 65% of the patients have died
- 28% remain alive without evidence of cancer.

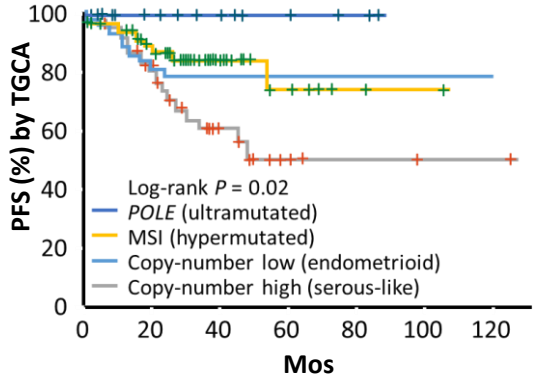
Miller DS et al. J Clin Oncol. 2020. 20;38(33):3841-3850

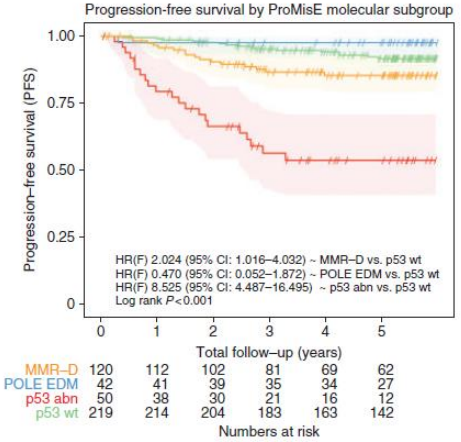
Evolution of the 1st line treatment in advanced/recurrent Endometrial Cancer



The “Modern” Molecular Classification: TCGA Classification



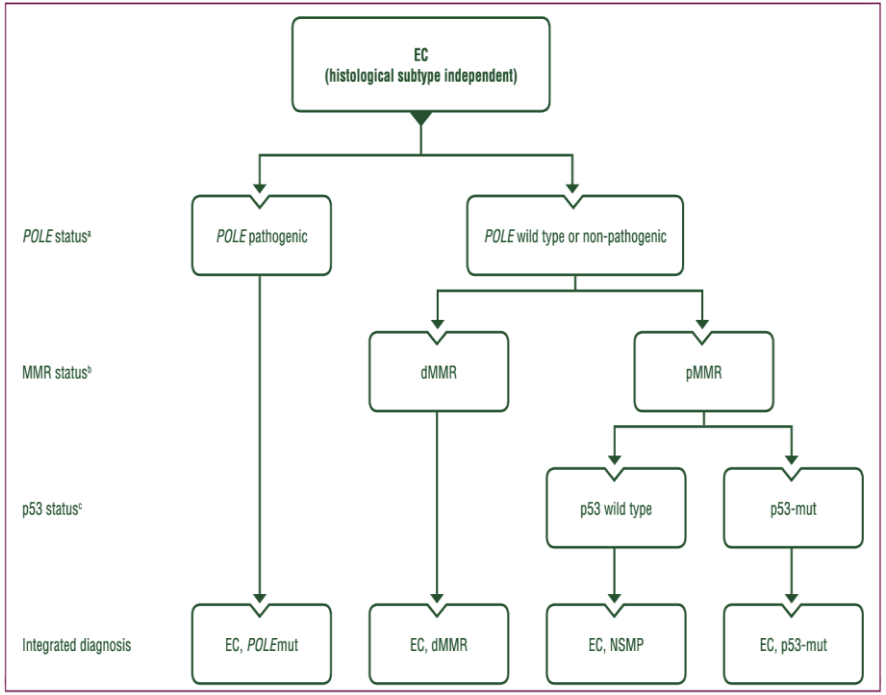




Cancer Genome Atlas Research Network. Nature. 2013;497:67. Talhouk, A. et al.Cancer 2017. McAlpine, J., Leon-Castillo, A et al. J. Pathol. 2018

The molecular classification is being included in International Guidelines

ESMO Guidelines



2023 FIGO Staging

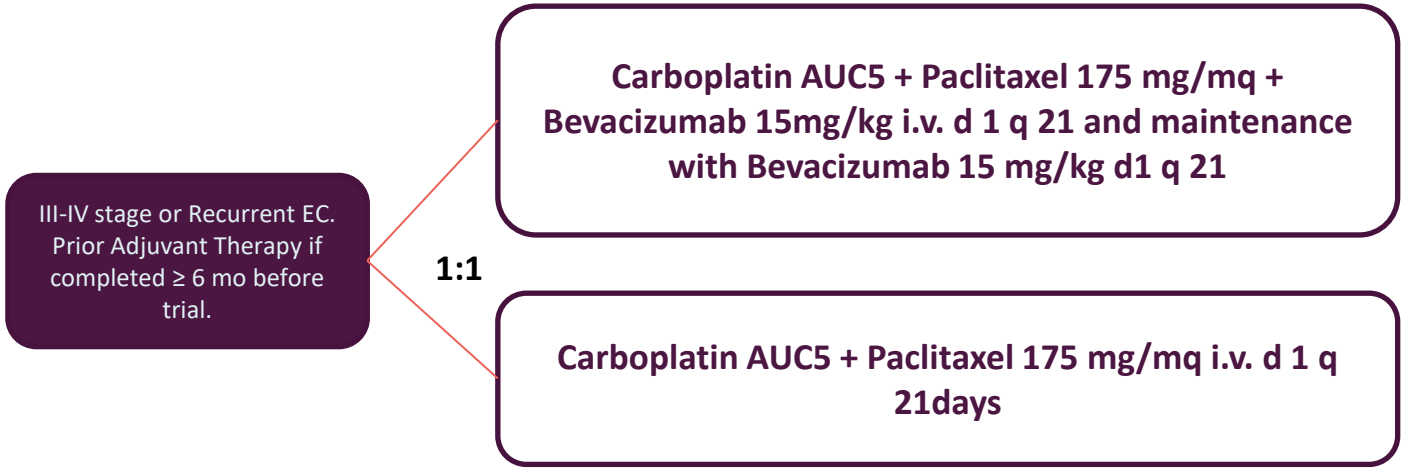
Molecular classification – When feasible, the addition of molecular subtype to staging criteria allows a better prediction of prognosis in a staging/prognosis scheme. The performance of complete molecular classification (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all endometrial cancer cases for prognostic risk-group stratification and as potential influencing factors of adjuvant treatment decisions. Molecular subtype assignment can be done on a biopsy, in which case it need not be repeated on the hysterectomy specimen.

- Good prognosis-- pathogenic *POLE* mutation (*POLEmut*)
- Intermediate prognosis: mismatch repair deficiency (MMRd) /microsatellite instability and no specific molecular profile (NSMP)
- Poor prognosis-- p53 abnormal (p53abn)

Oaknin A. et al Ann Oncol. 2022; Olawaiye AB. Presented at SGO 2023

Bevacizumab has not demonstrated benefit in PFS en advanced/recurrent Endometrial Cancer: MITO END-2 trial

- Open-label, multicenter, randomized phase II trial



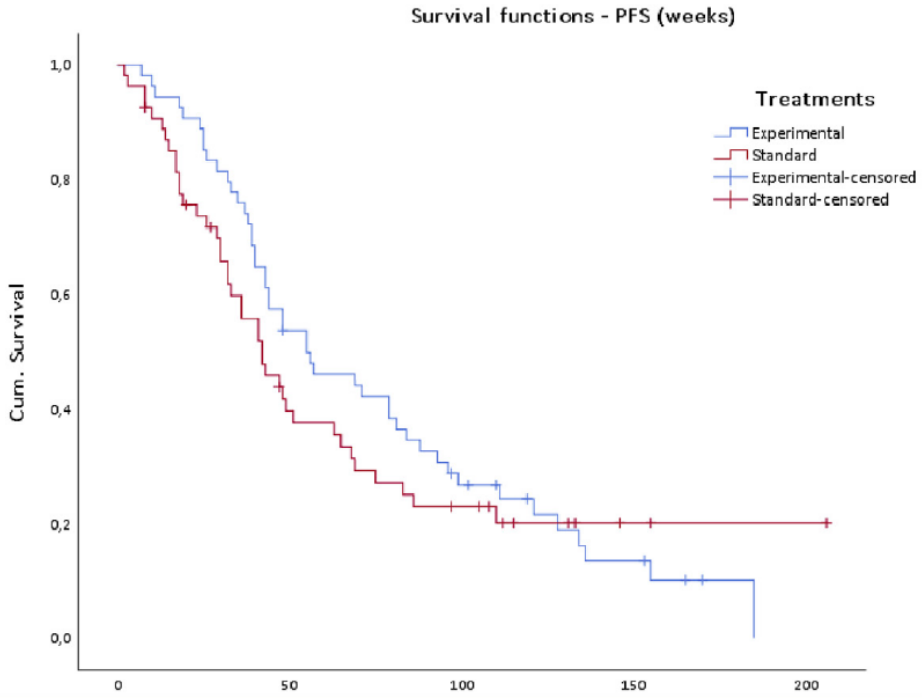
Stratification

- cancer type (endometrioid vs. non endometrioid EC)
- advanced versus recurrent disease
- Number of previous chemotherapy lines (0 vs 1).

- **Primary endpoints:** PFS
- **Secondary endpoints:** OS, ORR, Safety

Lorusso D et al. Gynecol. Oncol.. 2019

Bevacizumab has not demonstrated benefit in PFS in advanced/recurrent Endometrial Cancer: MITO END-2 trial



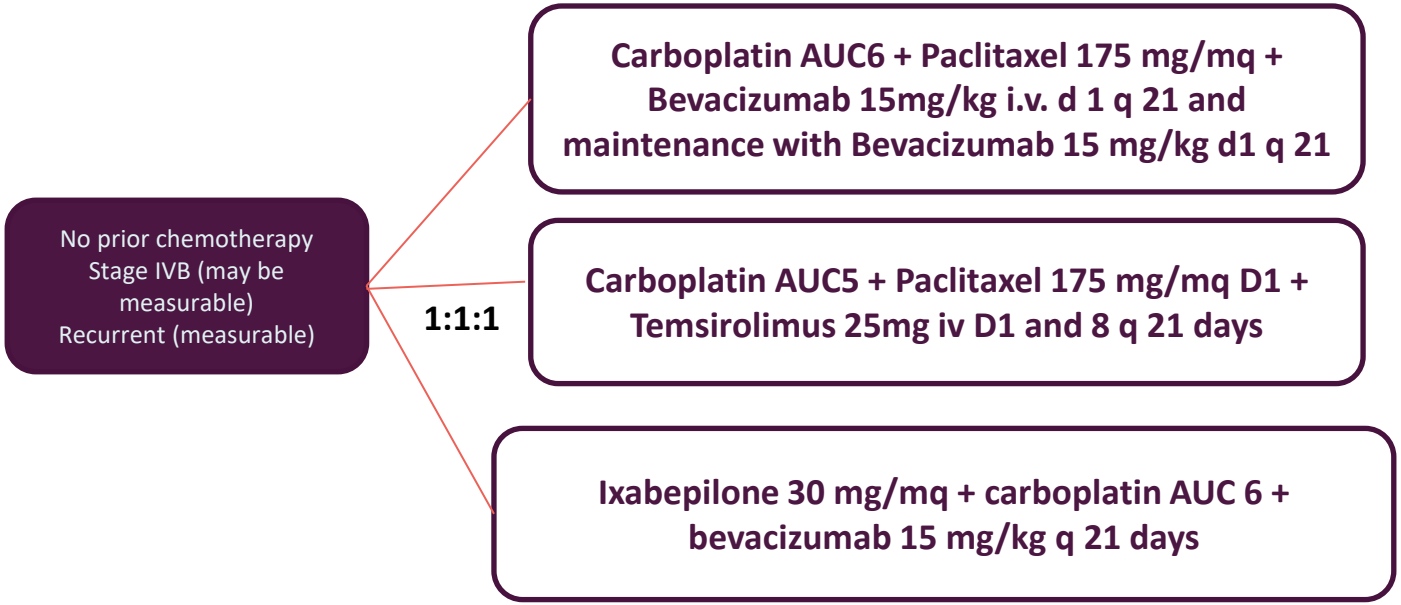
	CT (N=54)	CT-B (N=54)
Events, n	40	46
Median PFS, months **(95% CI)**	10,5 (7.2-13,5)	13.7 (7.5-20,0)
HR (stratified) (95% CI) 2-sided log-rank p-value 2-sided Breslow test p value	0.846 (0.5–1.3) 0.437 0.08*	

* p<0.20

Lorusso D et al. Gynecol. Oncol.. 2019

Bevacizumab has not demonstrated benefit in PFS in advanced/recurrent Endometrial Cancer: GOG-86P trial

- Three arm, single stage, historically controlled, randomized phase II study



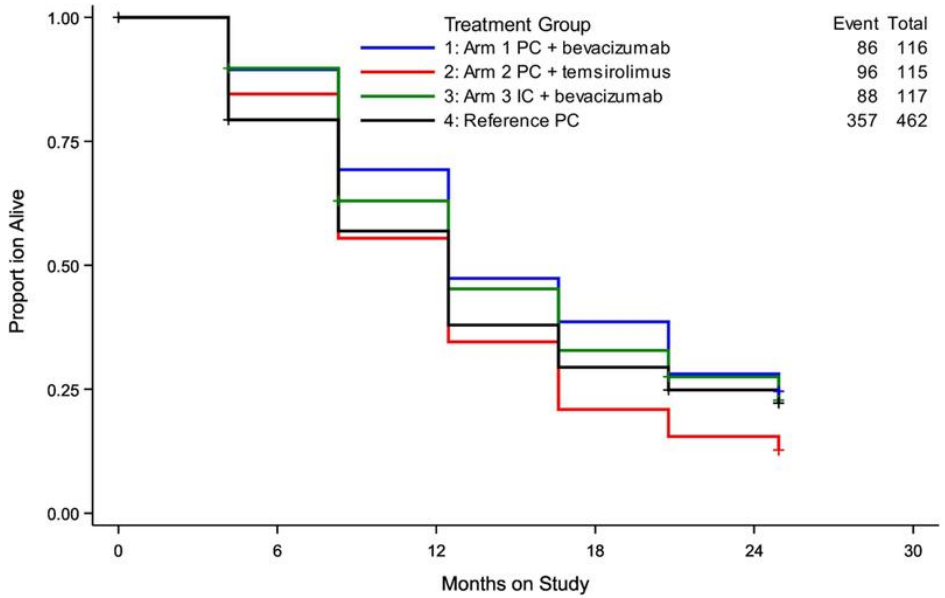
Stratification
- Measurable: Y/N
- Recurrent: Y/N
- Prior Radiotherapy: Y/N

- **Primary endpoints:** PFS
- **Secondary endpoints:** OS, ORR, Safety

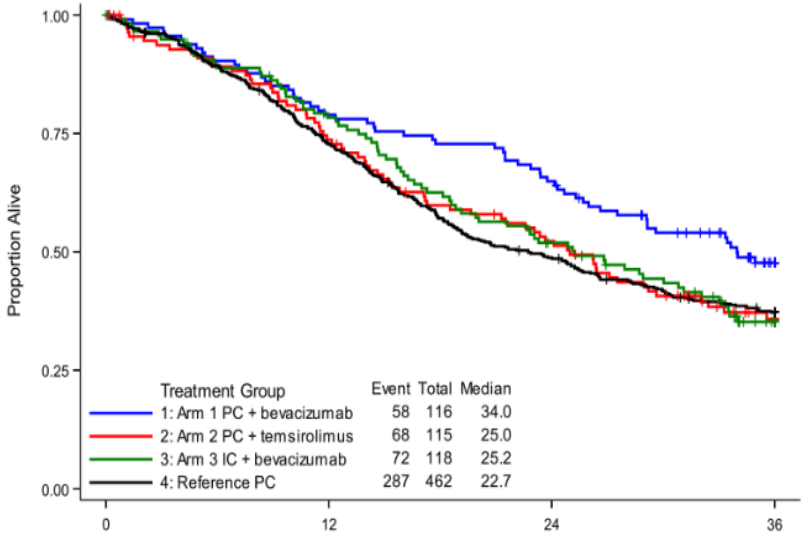
. Aghajanian et al.Gynecologic Oncology 150 (2018) 274–281

Bevacizumab has not demonstrated benefit in PFS en advanced/recurrent Endometrial Cancer: GOG-86P trial

PFS



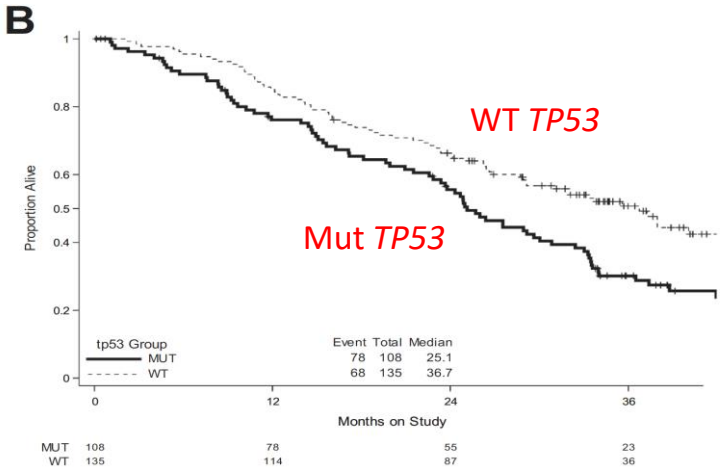
OS



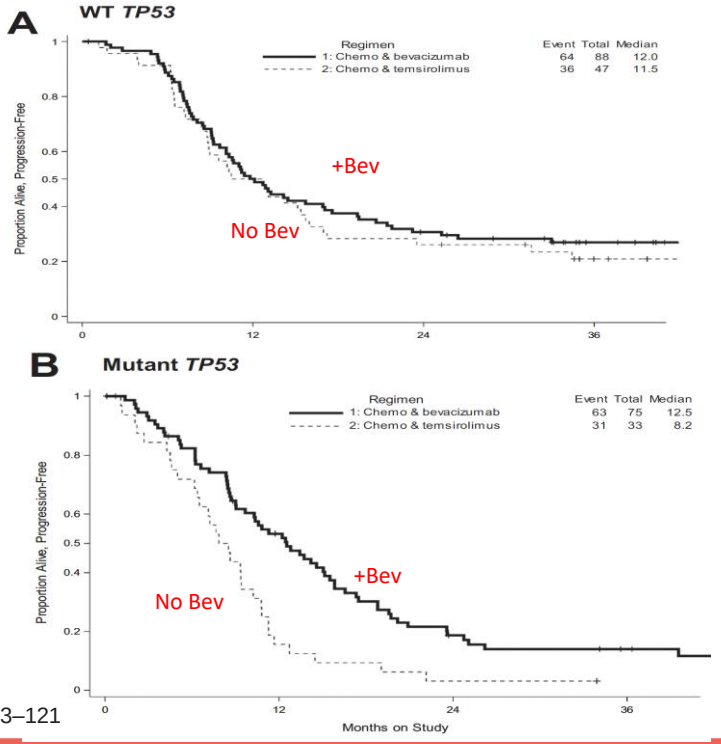
. Aghajanian et al.Gynecologic Oncology 150 (2018) 274–281

GOG-86P trial: Analysis according the presence or absence of a TP53 mutation

All patients

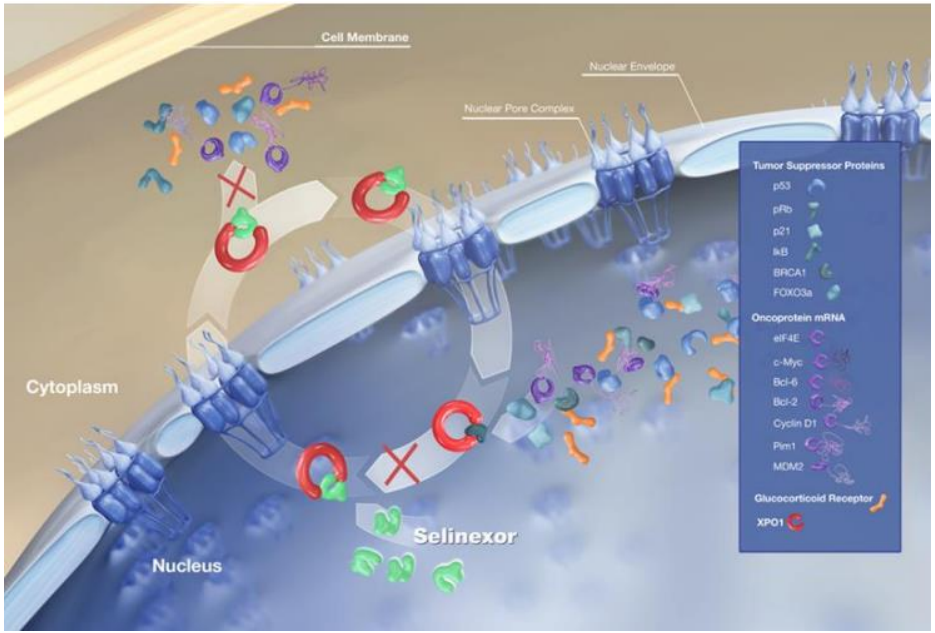


TP53 status and Bevacizumab



. Aghajanian et al.Gynecologic Oncology 150 (2018) 274–281; K.K. Leslie et al. Gynecologic Oncology 161 (2021) 113–121

SELINEXOR: inhibits exportin-1 (XPO1)



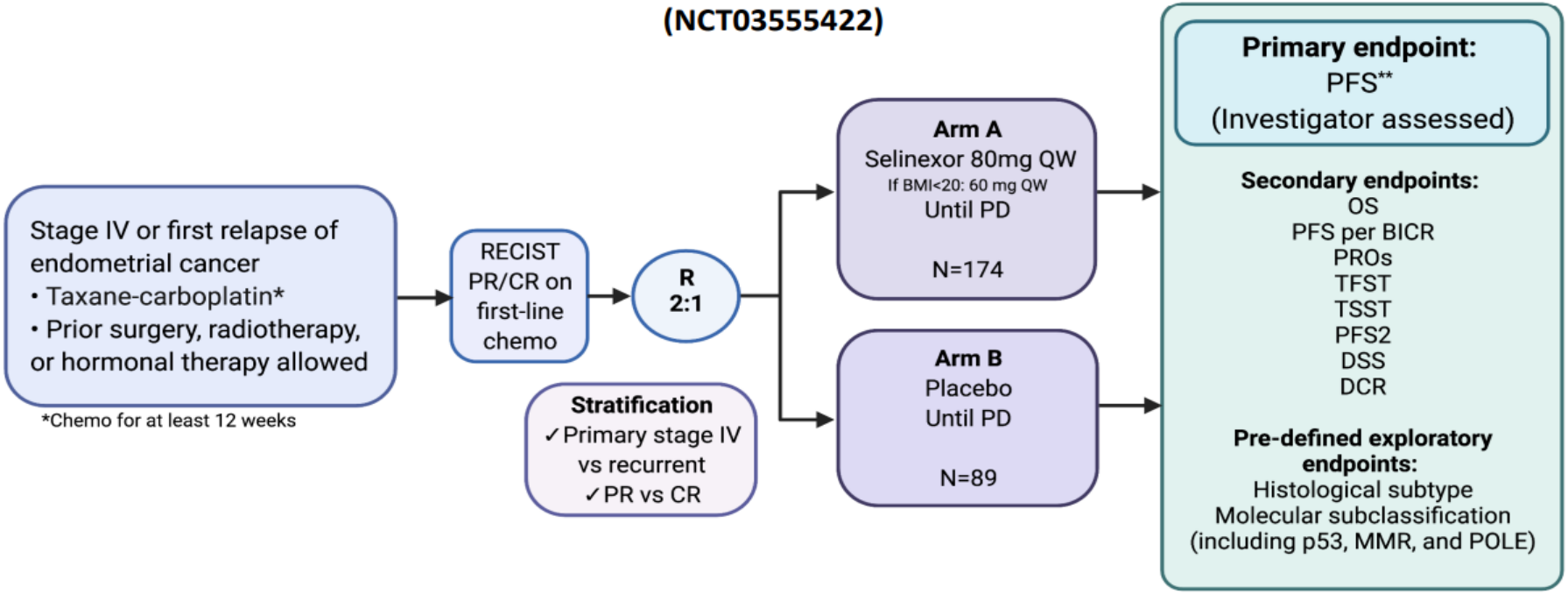
Inhibition of XPO1 impacts tumor cells via three mechanisms:

- Increases nuclear levels and activation of tumor suppressor proteins (p53, PTEN and FOXO1).
- Traps oncoprotein mRNA in the nucleus leading to reduced oncoprotein levels.
- Retains activated glucocorticoid receptor in the nucleus.

Presented by Vergote I. at SGO 2022

Selinexor has shown a benefit in PFS as maintenance treatment in advanced/recurrent EC

Stage IV or first relapse of endometrial cancer endometrioid, serous, undifferentiated, or carcinosarcoma (NCT03555422)

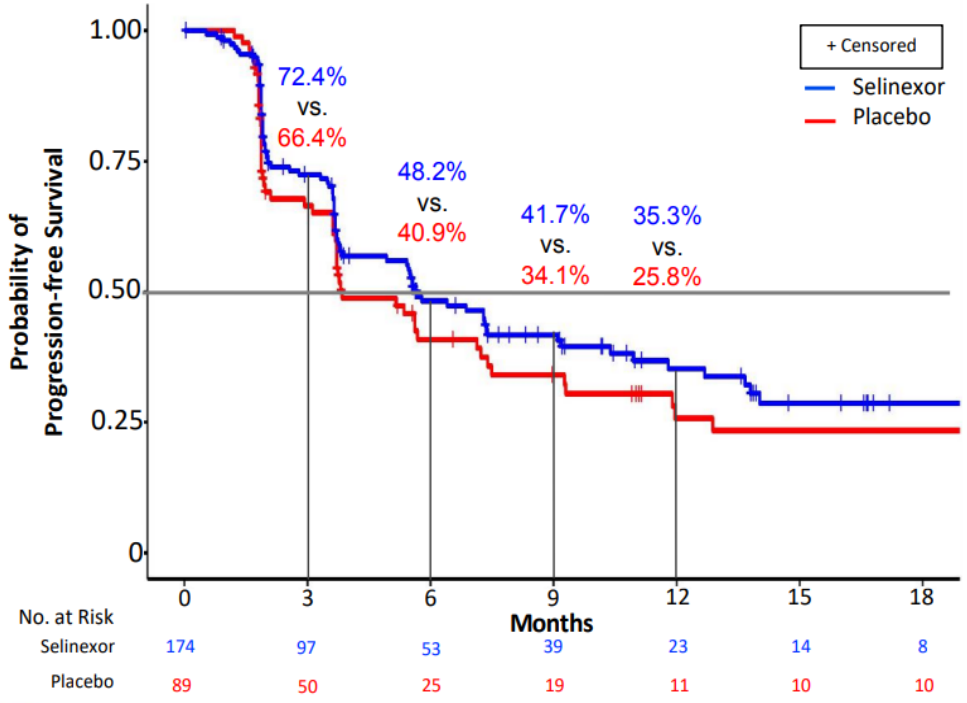


**140 PFS events needed to provide 80% power to detect a hazard ratio of 0.6 (median PFS 4.5 months for placebo and 7.5 months for selinexor) with a one-sided alpha of 0.025 and 2:1 randomization ratio favoring selinexor.

Selinexor has shown a benefit in PFS as maintenance treatment in advanced/recurrent EC

Primary Endpoint: PFS in ITT population

(based on audited stratification factors)*



Median PFS (Investigator assessed)

Selinexor (n=174): 5.7 mo (95% CI 3.81-9.20)

Placebo (n=89): 3.8 mo (95% CI 3.68-7.39)

HR* = 0.705 (95% CI 0.499-0.996)

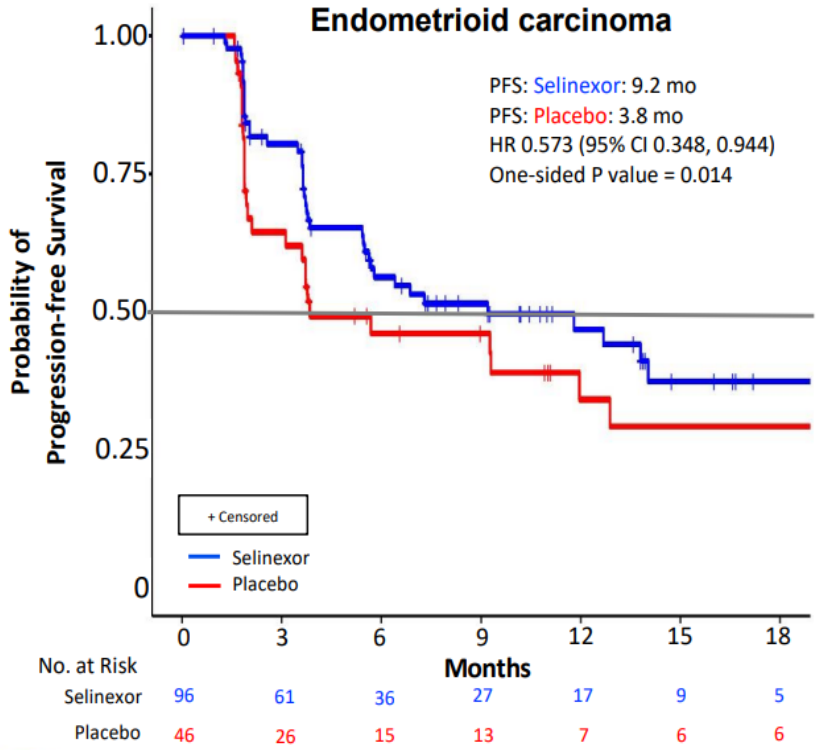
One-sided P value = 0.024

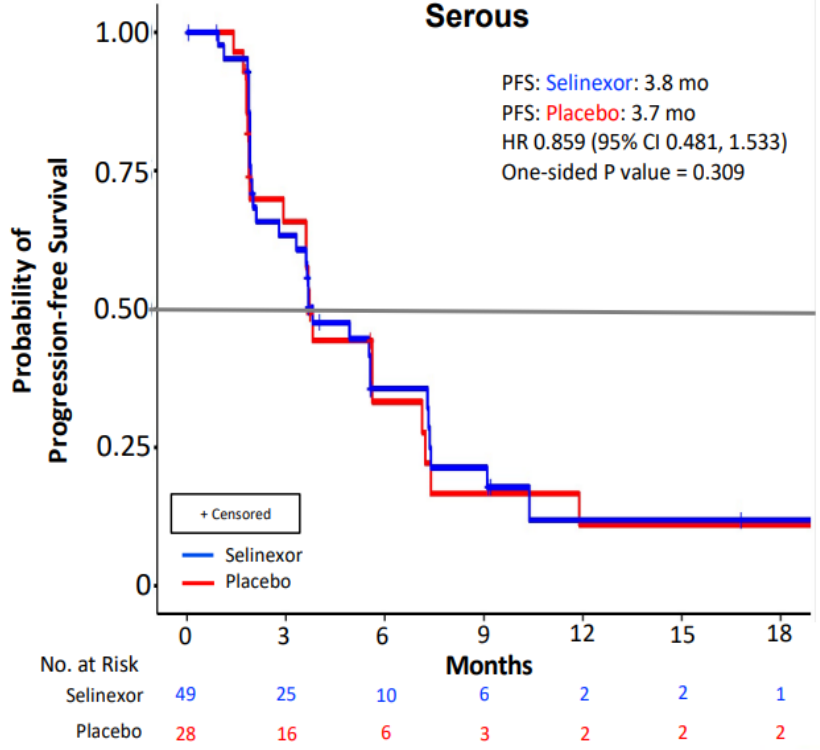
* In 7 patients (2.7% of 263), the stratification factor of CR/PR was incorrect and was corrected by the Investigators prior to database lock and unblinding.

The statistical analysis was validated by the independent ENGOT statistician and approved by the IDMC.

HR for ITT without correction of the stratification factors was 0.76 (95% CI: 0.543, 1.076).

Prespecified Exploratory Analyses: PFS according to Histological Subtype

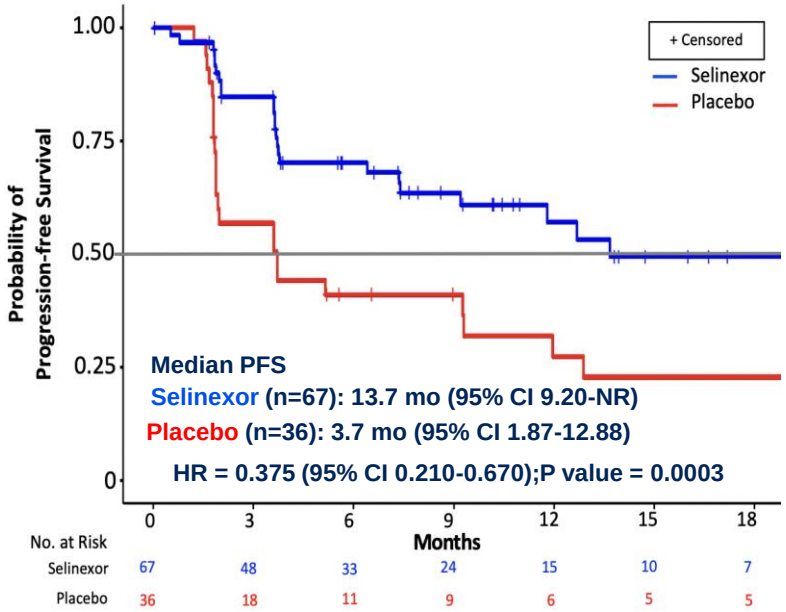




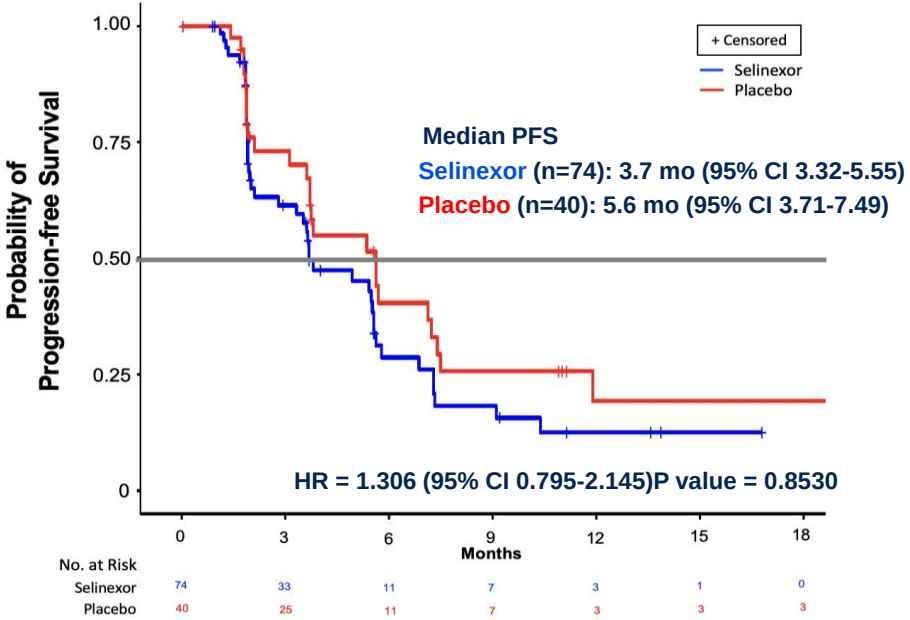
Presented by Vergote I. at SGO 2022

Prespecified Exploratory Analyses: PFS according to p53 status

p53 wild-type

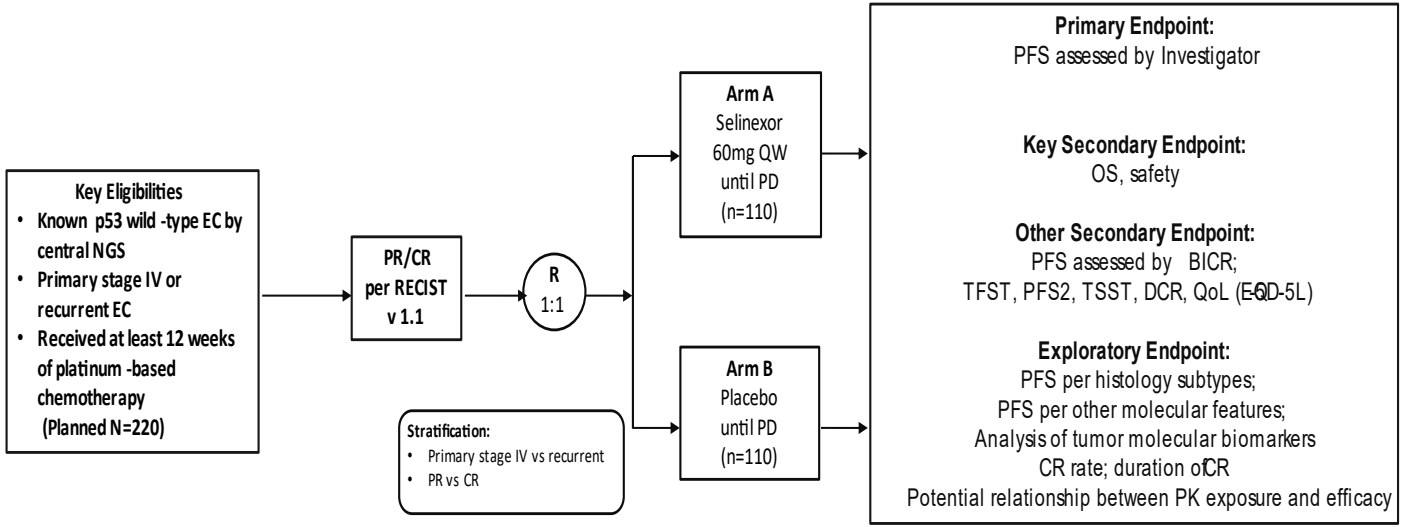


p53Mutant/Aberrant EC



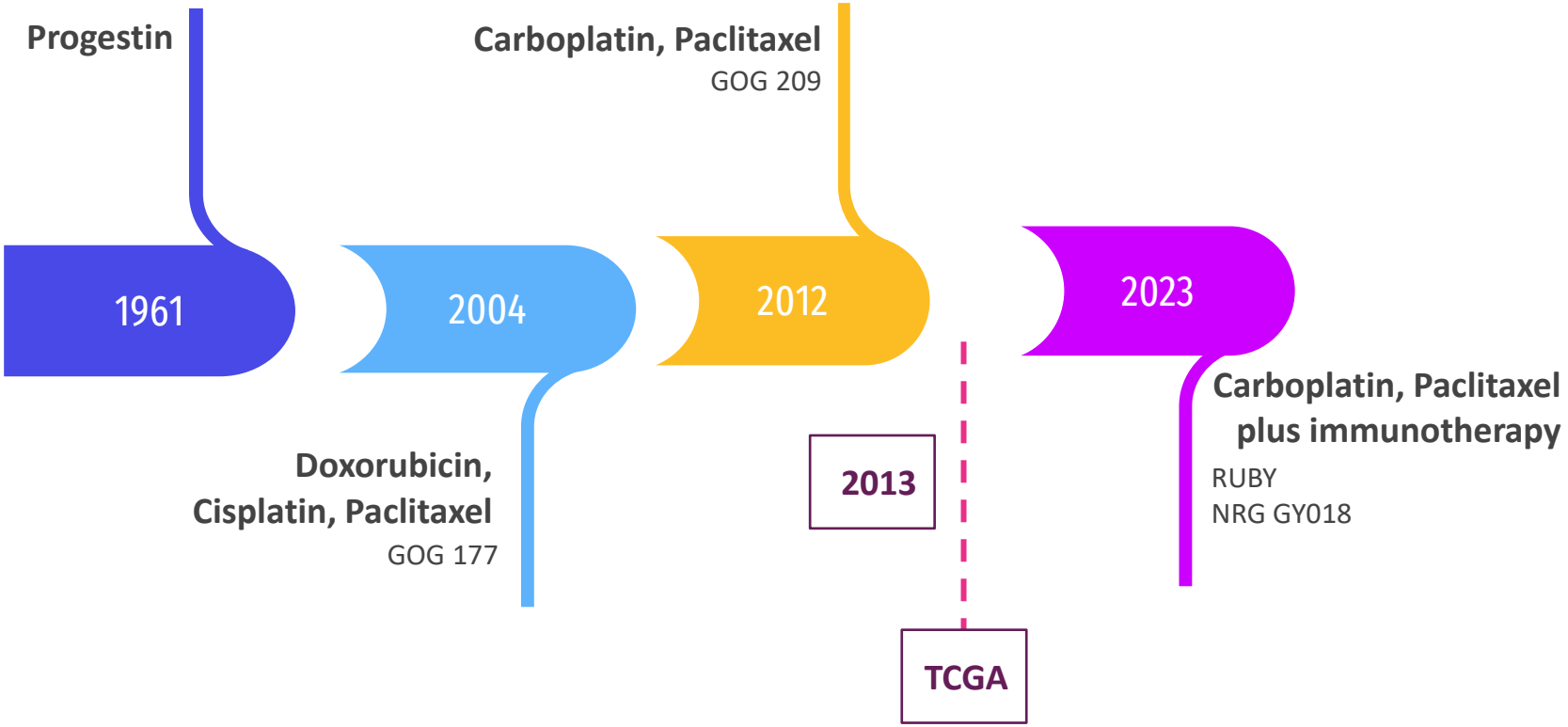
Vicky Makker, M.D. et al. Presented at ASCO Meeting 2022

Initiated Phase 3 study of selinexor as a maintenance therapy following systemic therapy in TP53wt advanced/recurrent EC: ENGOT-en20/BGOG/XPORT-EC-042



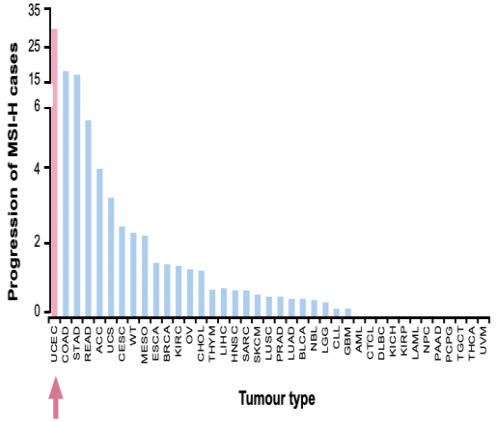
ClinicalTrials.gov Identifier: NCT03555422

Evolution of the 1st line treatment in advanced/recurrent Endometrial Cancer

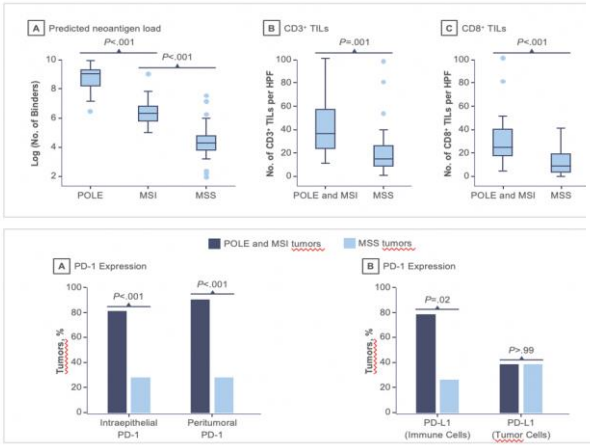


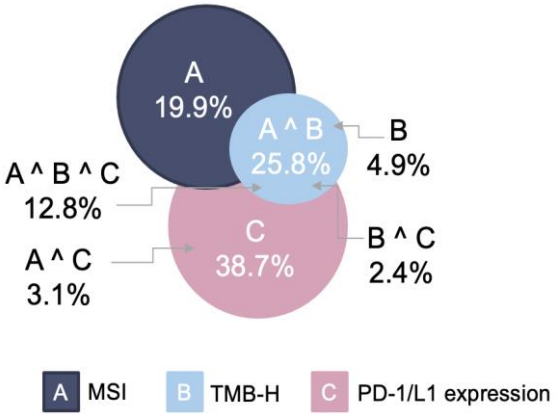
Rationale for checkpoint Inhibitors(ICI) in EC

EC is the solid tumour with the greatest percentage of MSI-H cases: 31%



Relationship between MSI, TMB and PD-1/L1 expression in EC





For patients with EC, the large overlap between MSI-H and TMB-H may indicate dMMR/MSI-H as a useful biomarker to identify those patients who will benefit most from ICI treatment

Howitt BE, *et al. JAMA Oncol* 2015; 1: 1319–1323; Luchini C, *et al. Ann Oncol* 2019; 30: 1232–1243

Immunotherapy has shown promise results after failure to platinum in dMMR/MSI-H EC

Treatment	Keynote-158[1] Pembrolizumab	NCT02912572[2] Avelumab	GARNET[3] Dostarlimab	PHAEDRA[4] Durvalumab
Phase	1/2	2	1/2	**2**
Population	Previously treated dMMR-recurrent or persistent EC	dMMR recurrent EC	Previously treated recurrent/advanced dMMR EC	Advanced dMMR EC, 0-3 prior therapies
Patients, n	79	15	143	35
ORR, %	48%	27%	45%	47%
mPFS	13.1 mo (95% CI, 4.3 to 34.4)	4.4 mo	6.0 mo (4.1–18.0 mo)	8.3 mo
mOS	NR (95% CI, 27.2 -NR).	—	NR (95% CI 27.1–NR)	NR

1.O'Malley D, *et al*. *J Clin Oncol* 2022; 40: 752–761.2. Konstantinopoulos et al. *J Clin Oncol. 2019;*37:2786-2794; 3. Oaknin A, et al. Presented at ASCO 2022, 4. Antill Y et al. *J Immunother Cancer.* 2021 Jun;9(6):e002255

Immunotherapy has shown modest results after failure to platinum in pMMR/MSS EC

	KEYNOTE-028[1]	NCT01375842[2]	GARNET[3]	NCT02912572[4]	PHAEDRA[5]
Treatment	**Pembrolizumab**	**Atezolizumab**	**Dostarlimab**	**Avelumab**	**Durvalumab**
Phase	**1b**	**1a**	**1/2**	**2**	**2**
Cohort	Previously treated locally advanced or metastatic PD-L1+ EC	Incurable or metastatic EC	Previously treated recurrent/advanced pMMR EC	pMMR recurrent EC	Recurrent pMMR EC
Patients, n	23 in efficacy analysis	15 (5 PD-L1high)	156	16	35
ORR, %	13.0*	13**	15.4	6	3
mPFS	1.8 mo	1.4 mo	2.7 mo (2.6–2.8 mo)	1.9 mo	—
mOS	NR	9.6 mo	16.9 mo (13.0–21.8 mo)	6.6 mo	—

1.O'Malley D, *et al*. *J Clin Oncol* 2022; 40: 752–761.2. Konstantinopoulos et al. *J Clin Oncol. 2019;*37:2786-2794; 3. Oaknin A, et al. Presented at ASCO 2022, 4. Antill Y et al. *J Immunother Cancer.* 2021 Jun;9(6):e002255

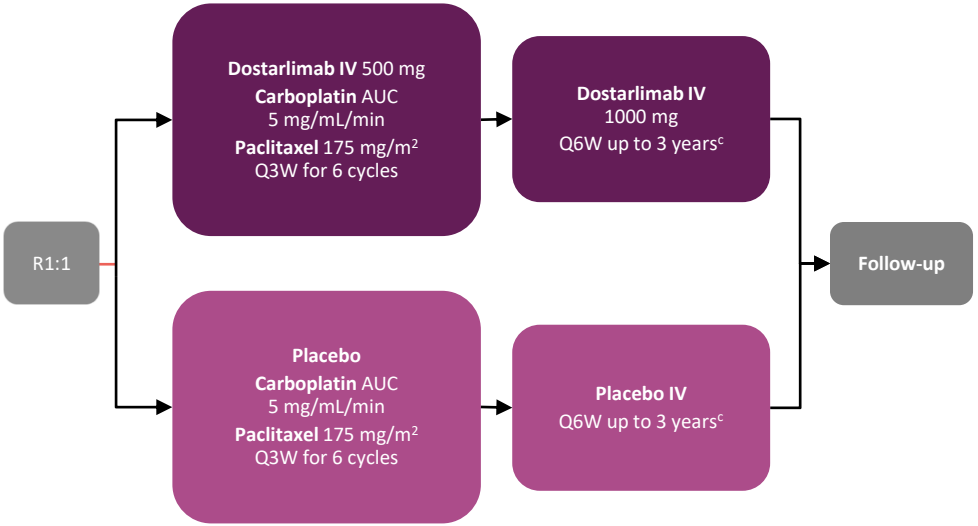
Dostarlimab in Combination with Chemotherapy for the Treatment of Primary Advanced/Recurrent EC: a Placebo-Controlled Randomized Phase 3 Trial (ENGOT-EN6-NSGO/GOG-3031/RUBY)

Eligible patients

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

Stratification

- MMR/MSI status[b]
- Prior external pelvic radiotherapy
- Disease status



Primary endpoint

- PFS by INV
- OS

Secondary endpoints

- PFS by BICR
- PFS2
- ORR
- DOR
- DCR
- HRQOL/PRO
- Safety

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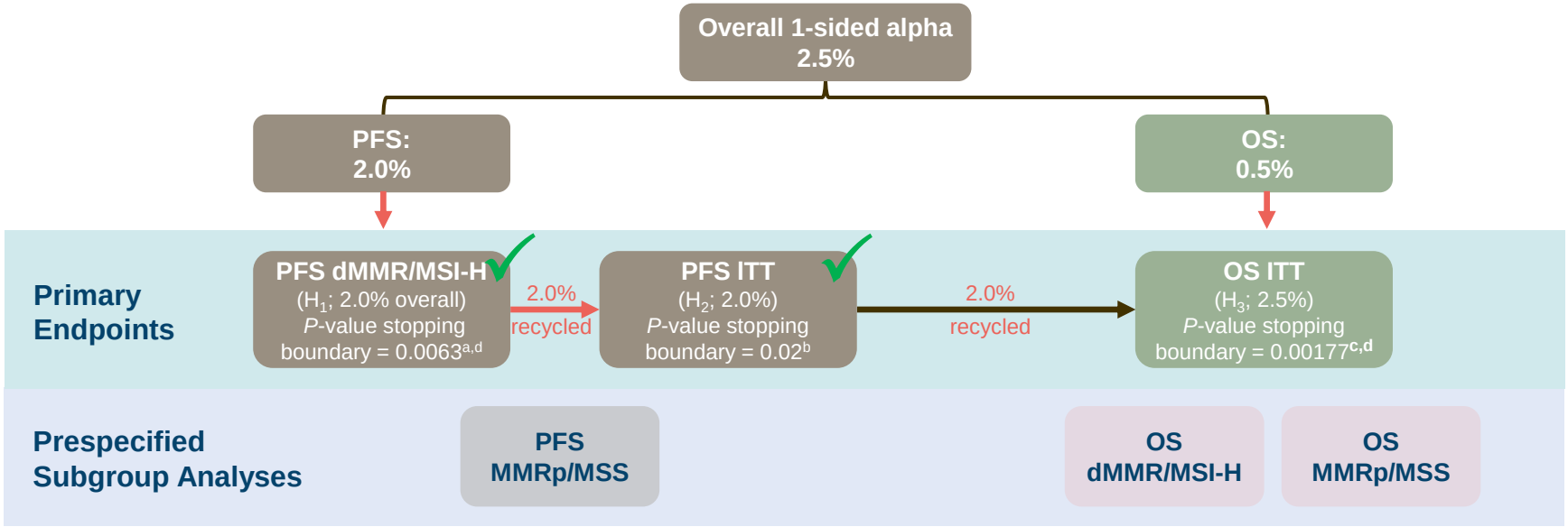
RUBY trial: Statistical testing



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RUBY trial: Basaline Characteristics

Variable, n (%)	dMMR/MSI-H		Overall	
	Dostarlimab + CP (N=53)	Placebo + CP (N=65)	Dostarlimab + CP (N=245)	Placebo + CP (N=249)
MMR/MSI status				
dMMR/MSI-H	53 (100)	65 (100)	53 (21.6)	65 (26.1)
MMRp/MSS	-	-	192 (78.4)	184 (73.9)
Prior external pelvic radiation				
Yes	8 (15.1)	13 (20.0)	41 (16.7)	45 (18.1)
No	45 (84.9)	52 (80.0)	204 (83.3)	204 (81.9)
ECOG[b]				
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)
Disease status				
Stage III	10 (18.9)	14 (21.5)	45 (18.4)	47 (18.9)
Stage IV	16 (30.2)	19 (29.2)	83 (33.9)	83 (33.3)
Recurrent	27 (50.9)	32 (49.2)	117 (47.8)	119 (47.8)
Measurable disease at baseline				
Yes	49 (92.5)	58 (89.2)	212 (86.5)	219 (88.0)
No	4 (7.5)	7 (10.8)	33 (13.5)	30 (12.0)

Variable, n (%)	dMMR/MSI-H		Overall	
	Dostarlimab + CP (N=53)	Placebo + CP (N=65)	Dostarlimab + CP (N=245)	Placebo + CP (N=249)
Prior Anticancer Treatment				
Yes	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)
Histology type				
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)
Mixed carcinoma[b]	2 (3.8)	4 (6.2)	10 (4.1)	9 (3.6)
Serous adenocarcinoma	1 (1.9)	1 (1.5)	50 (20.4)	52 (20.9)
Clear cell adenocarcinoma	0	0	8 (3.3)	9 (3.6)
Mucinous adenocarcinoma	0	0	0	1 (0.4)
Undifferentiated carcinoma	0	0	1 (0.4)	2 (0.8)
Other	2 (3.8)	3 (4.6)	17 (6.9)	21 (8.4)

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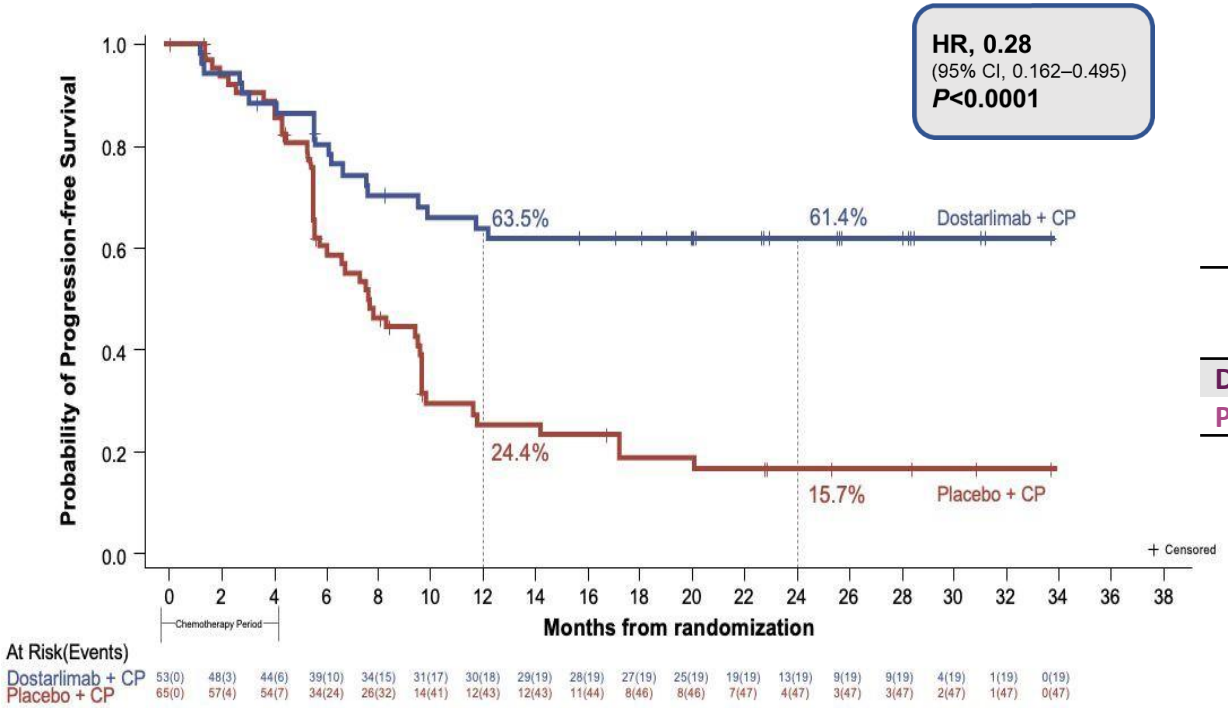
The addition of Dostarlimab has a meaningful Benefit in PFS in MMR-d/MSI-H EC



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

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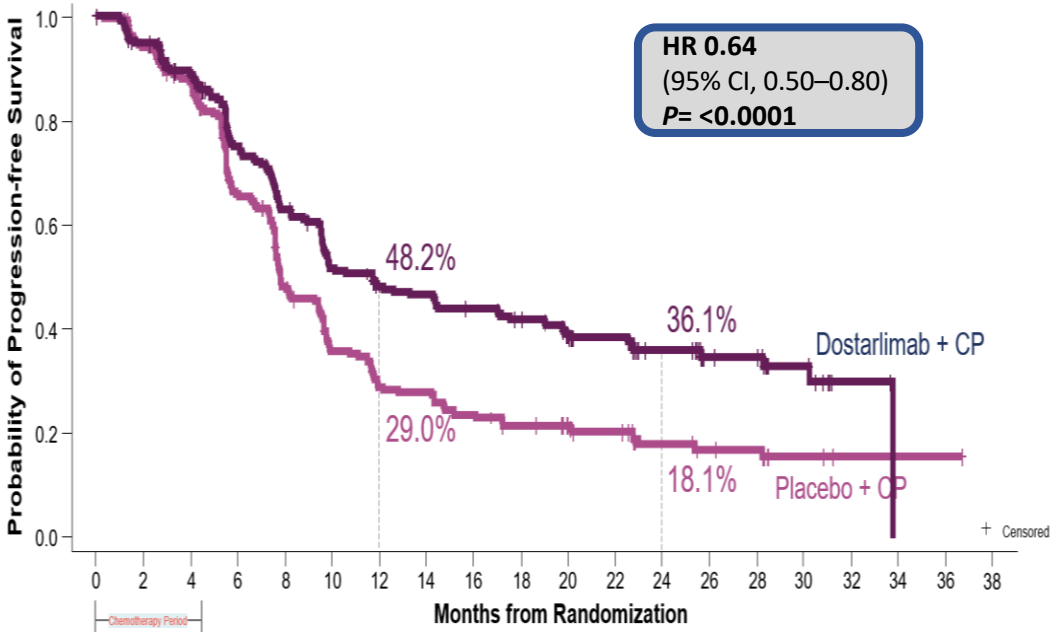
The addition of Dostarlimab has, also, a significant Benefit in PFS in overall population



	No. with event (%)	Median (95%CI),(mo)
Dostarlimab + CP	55.1	11.8 (9.6–17.1)
Placebo + CP	71.1	7.9 (7.6–9.5)

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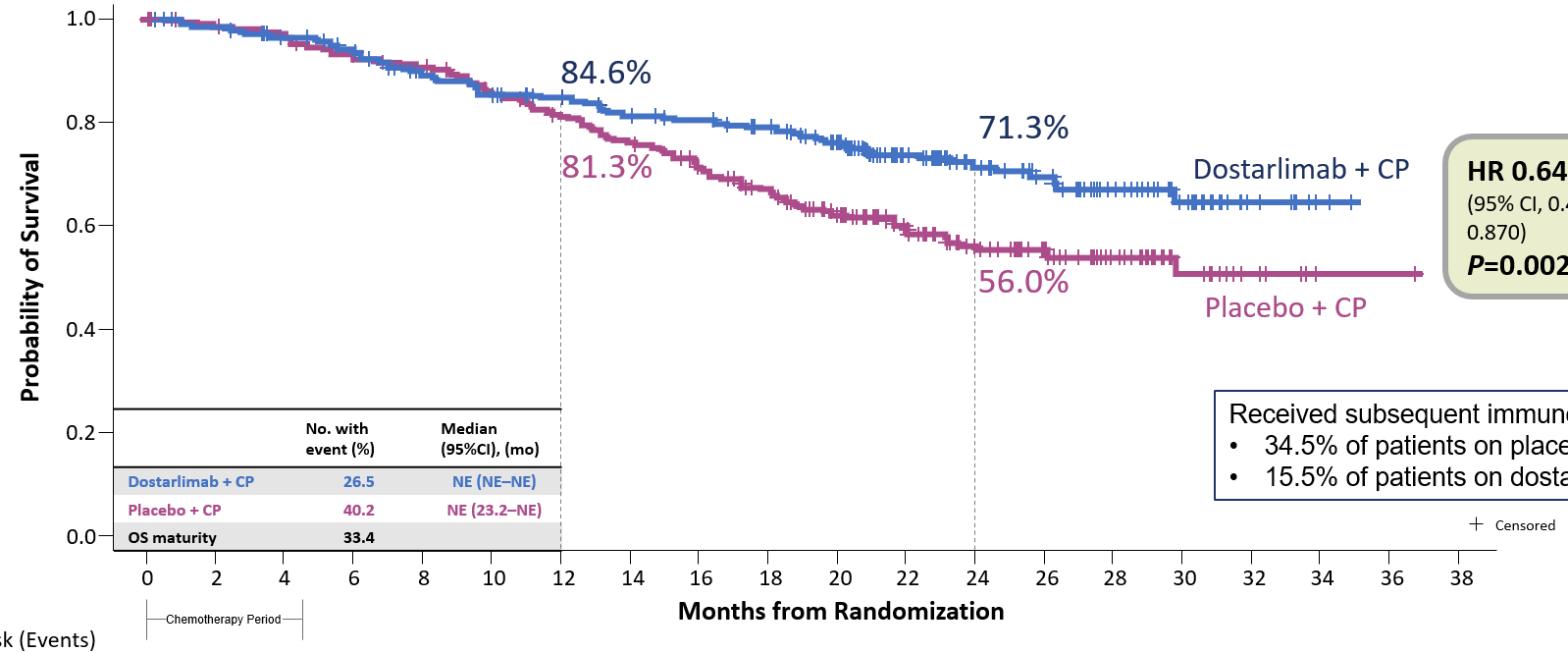
The addition of Dostarlimab shows a trends towards improved OS

OS in overall population (33% maturity)



HR 0.64
(95% CI, 0.464–0.870)
***P*=0.0021**[a]

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

At Risk (Events)

Dostarlimab + CP	245(0)	235(5)	224(8)	214(15)	198(25)	190(33)	183(35)	174(42)	169(44)	162(47)	145(53)	110(57)	83(60)	64(62)	45(64)	25(65)	7(65)	2(65)	0(65)	
Placebo + CP	249(0)	242(3)	237(7)	226(17)	219(22)	203(35)	189(45)	177(57)	162(68)	147(78)	125(88)	88(93)	65(97)	48(98)	33(99)	15(100)	6(100)	1(100)	1(100)	0(100)

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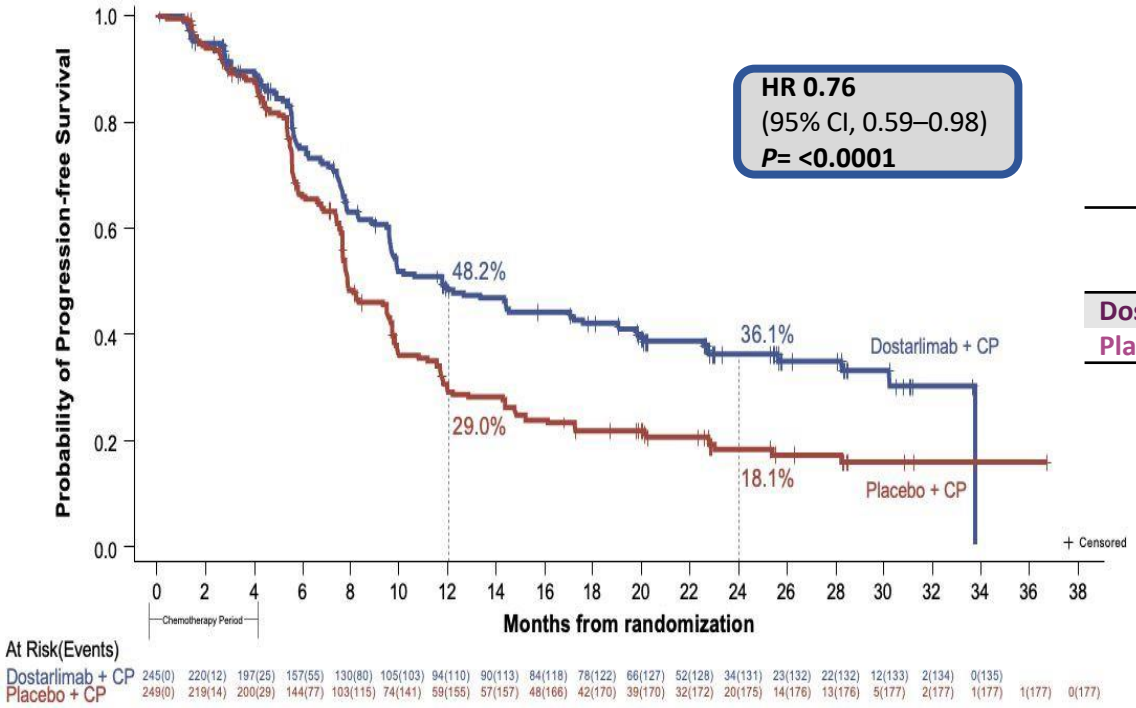
The addition of Dostarlimab has, also, a Benefit in PFS in MMR-p/MSS EC: Prespecified Subgroup Analyses



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

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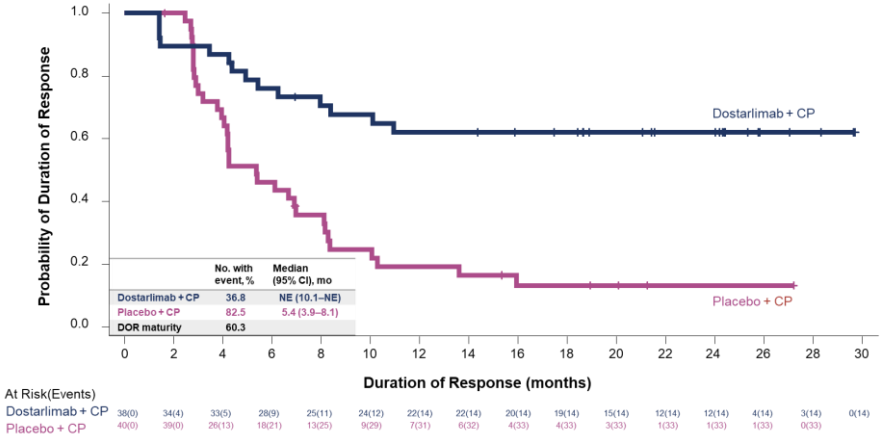
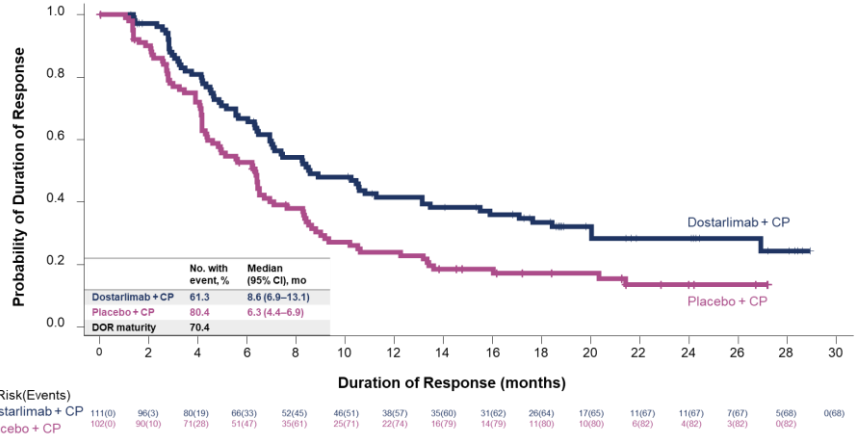
Objective Response Rate and Duration of response

dMMR/MSI-H



MMRp/MSS



	dMMR/MSI-H	
	Dostarlimab + CP (N=53)	**Placebo + CP (N=65)**
ORR, %[a,b] (n/N; 95% CI)	**77.6** (38/49; 63.4–88.2)	**69.0** (40/58; 55.5–80.5)
CR	15 (30.6)	12 (20.7)
PR	23 (46.9)	28 (48.3)

	MMRp/MSS	
	Dostarlimab + CP (N=192)	**Placebo + CP (N=184)**
ORR, %[a,b] (n/N; 95% CI)	**68.1** (111/163; 60.4–75.2)	**63.4** (102/161; 55.4–70.8)
CR	38 (23.3)	31 (19.3)
PR	73 (44.8)	71 (44.1)

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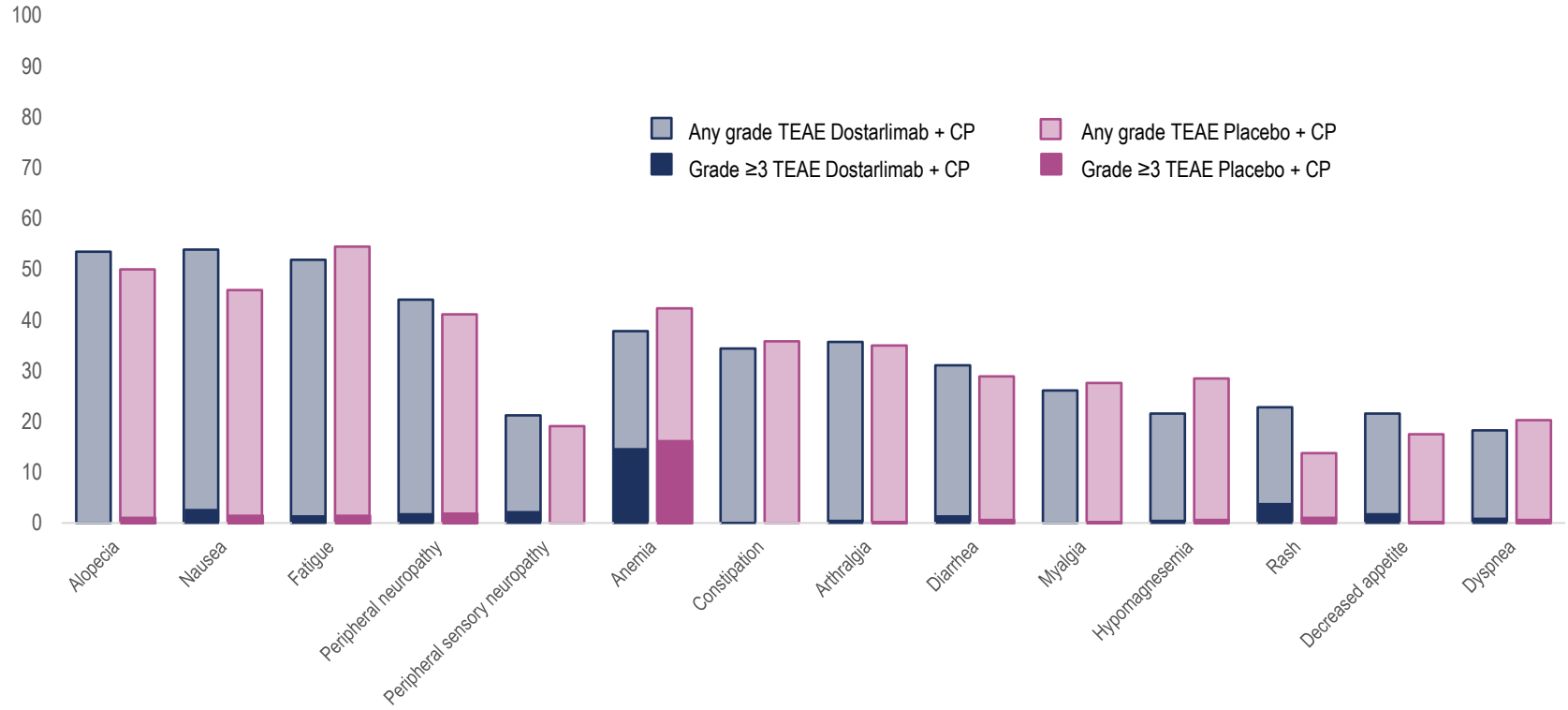
The safety profile of dostarlimab–carboplatin–paclitaxel was consistent with that of the individual components of the regimen



CP, carboplatin/paclitaxel; TEAE, treatment emergent adverse event.

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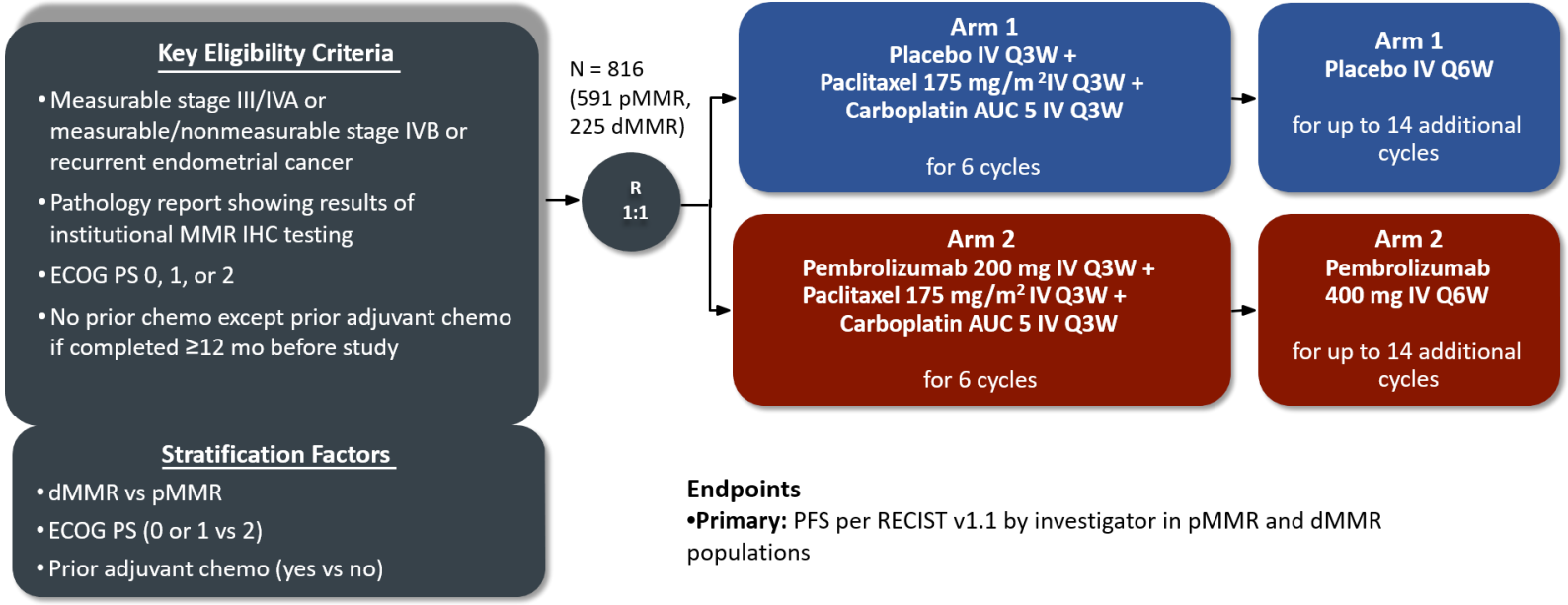
Pembrolizumab Versus Placebo in Addition to Carboplatin and Paclitaxel for Measurable Stage 3 or 4a, Stage 4b or Recurrent Endometrial Cancer: The Phase 3, NRG GY018 Study



Endpoints

•**Primary:** PFS per RECIST v1.1 by investigator in pMMR and dMMR populations

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NRG-GY018 trial: Statistical Consideration

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 of equal hazard rates tested at $\alpha = 0.0125$ using a stratified log-rank test

Protocol-Specified Interim PFS Analysis

- Objective: assess whether addition of pembrolizumab to standard-of-care prolongs PFS
- Timing: When both populations were closed for accrual and had reached at least half the information time[b]
  - ~196 PFS events for pMMR population
  - ~84 PFS events for dMMR population
- If null hypothesis for one population rejected, alpha forwarded to other population[c]
- Interim OS futility analysis planned at time of final or significant interim PFS analysis
- Data cutoff date: December 16, 2022

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NRG-GY018 trial: Basaline Characteristics in dMMR population

Characteristic	Pembro + CT (N = 112)	Placebo + CT (N = 113)
Age, median (range), y	67 (38-81)	66 (37-85)
Race, no. (%)		
White	92 (82.1)	86 (76.1)
Black/African-American	11 (9.8)	9 (8.0)
Asian	3 (2.7)	4 (3.5)
Other[a]	0	2 (1.8)
Unknown/Not reported	6 (5.4)	12 (10.6)
Ethnicity, no. (%)		
Non-Hispanic/non-Latino	106 (94.6)	99 (87.6)
Hispanic/Latino	5 (4.5)	6 (5.3)
Unknown/Not reported	1 (0.9)	8 (7.1)
ECOG PS, no. (%)		
0	72 (64.3)	73 (64.6)
1	39 (34.8)	35 (31.0)
2	1 (0.9)	5 (4.4)

Characteristic	Pembro + CT (N = 112)	Placebo + CT (N = 113)
Histology – no. (%)		
Adenocarcinoma, NOS	12 (10.7)	14 (12.4)
Clear cell	1 (0.9)	0 (0)
Dedifferentiated/ undifferentiated	4 (3.6)	4 (3.5)
Endometrioid, G1	21 (18.8)	35 (31.0)
Endometrioid, G2	52 (46.4)	41 (36.3)
Endometrioid, G3	15 (13.4)	16 (14.2)
Mixed epithelial	3 (2.7)	2 (1.8)
Serous	4 (3.6)	1 (0.9)
No prior chemotherapy, no. (%)	107 (95.5)	105 (92.9)
No prior radiotherapy, no. (%)	71 (63.4)	58 (51.3)
Received prior surgery, no. (%)	98 (87.5)	105 (92.9)

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NRG-GY018 trial: Basaline Characteristics in pMMR population

Characteristic	Pembro + CT (N = 293)	Placebo + CT (N = 295)
Age, median (range), y	66 (31–93)	65 (29–90)
Race, no. (%)		
White	212 (72.4)	212 (71.9)
Black/African-American	45 (15.4)	51 (17.3)
Asian	17 (5.8)	14 (4.7)
Other[a]	4 (1.4)	6 (2.0)
Unknown/Not reported	15 (5.1)	12 (4.1)
Ethnicity, no. (%)		
Non-Hispanic/non-Latino	263 (89.8)	273 (92.5)
Hispanic/Latino	21 (7.2)	16 (5.4)
Unknown/Not reported	9 (3.1)	6 (2.0)
ECOG PS, no. (%)		
0	196 (66.9)	198 (67.1)
1	88 (30.0)	88 (29.8)
2	9 (3.1)	9 (3.1)

Characteristic	Pembro + CT (N = 293)	Placebo + CT (N = 295)
Histology, no. (%)		
Adenocarcinoma, NOS	24 (8.2)	33 (11.2)
Clear cell	17 (5.8)	20 (6.8)
Dedifferentiated/ undifferentiated	7 (2.4)	6 (2.0)
Endometrioid, G1	54 (18.4)	46 (15.6)
Endometrioid, G2	51 (17.4)	58 (19.7)
Endometrioid, G3	53 (18.1)	42 (14.2)
Mixed epithelial	6 (2.0)	11 (3.7)
Serous	78 (26.6)	72 (24.4)
Pending	3 (1.0)	7 (2.4)
No prior chemotherapy, no. (%)	221 (75.4)	218 (73.9)
No prior radiotherapy, no. (%)	179 (61.1)	176 (59.7)
Received prior surgery, no. (%)	261 (89.0)	245 (83.0)

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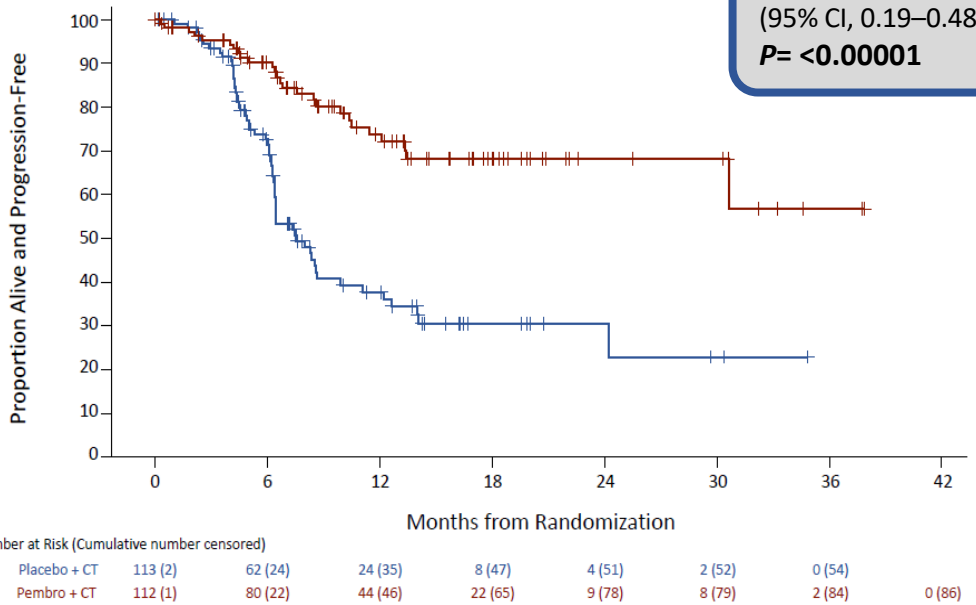
Pembrolizumab has improved PFS in MMR-d/MSI-H EC

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



	No. with event (%)	Median (95%CI), (mo)
Pembrolizumab + CP	23.21	NE (30.6–NE)
Placebo + CP	52.21	7.6 (6.4–9.9)

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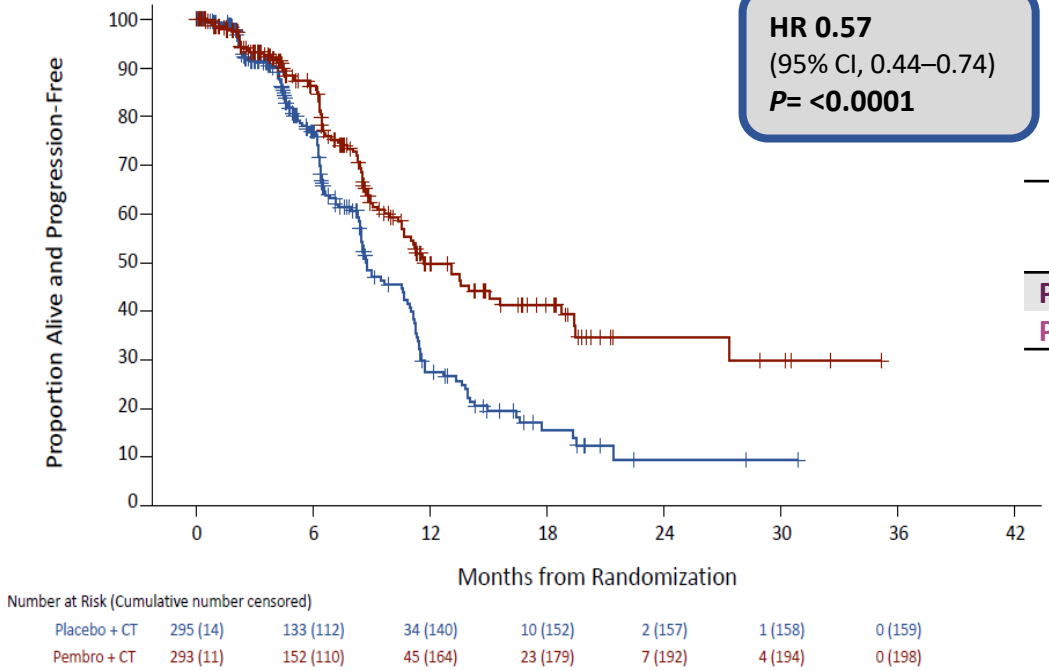
Pembrolizumab has improved PFS in MMR-p/MSS EC



HR 0.57
(95% CI, 0.44–0.74)
***P*= <0.0001**

	No. with event (%)	Median (95%CI), (mo)
Pembrolizumab + CP	**23.21**	**NE (30.6–NE)**
Placebo + CP	52.21	7.6 (6.4–9.9)

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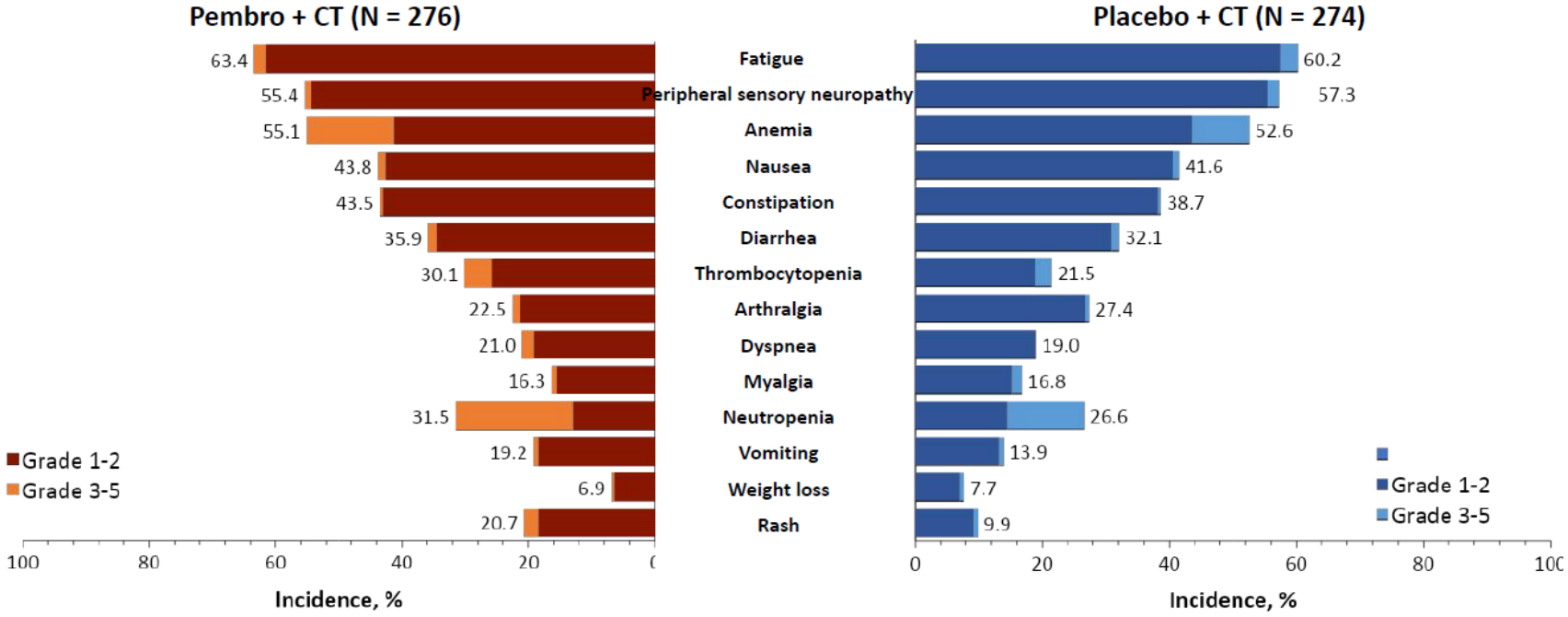
Adverse events were as expected for pembrolizumab and combination chemotherapy: pMMR Cohort



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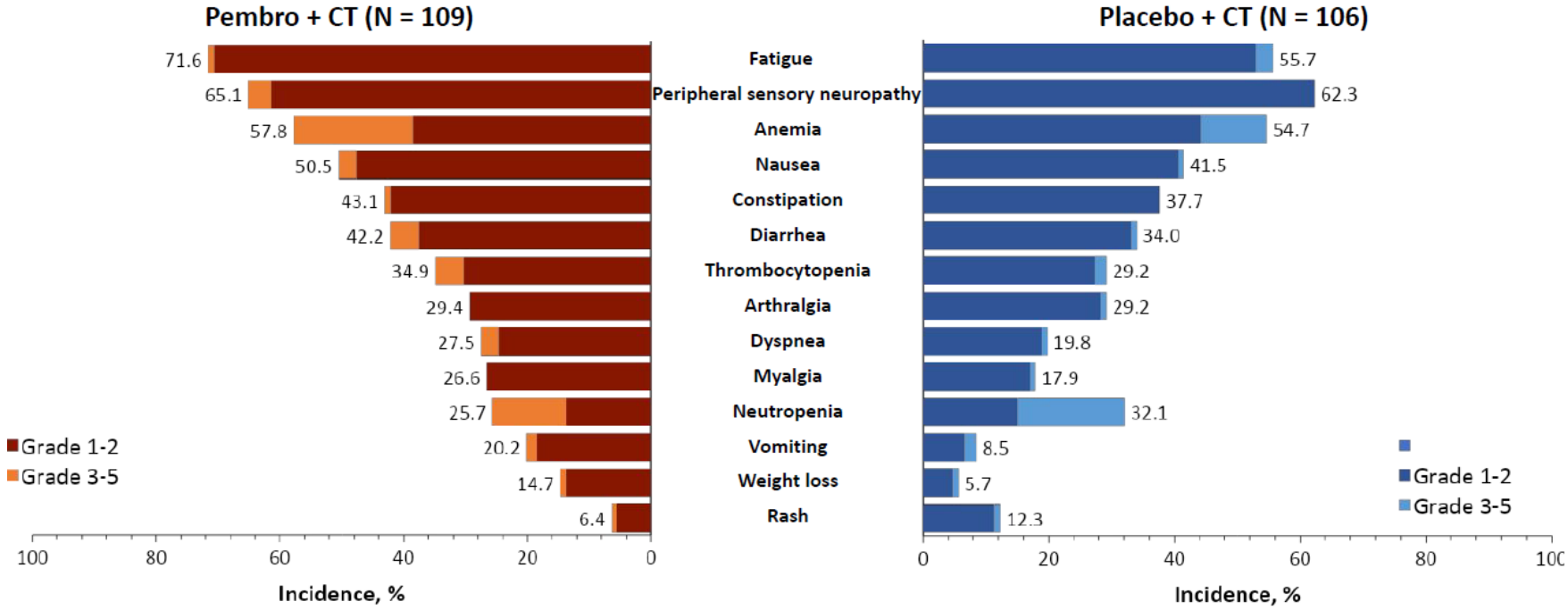
Adverse events were as expected for pembrolizumab and combination chemotherapy: dMMR Cohort



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CONCLUSIONS

- At the present time, it is mandatory to know the molecular profile of the endometrial cancer as prognostic factor.
- Endometrial cancers have relatively high proportions of TMB-H and MSI-H/dMMR tumors, providing rationale for treatment with checkpoint inhibitors:
  - The MSI-H/dMMR phenotype has emerged as a predictive biomarker for checkpoint inhibitor therapy.
- To the date, Paclitaxel plus Carboplatin is considered the standard of care.
- The addition of Bevacizumab to 1st line treatment has not demonstrated any benefit in PFS in advanced/recurrent Endometrial Cancer.
- Selinexor achieved a 62% decrease of risk for progression as maintenance treatment in p53 wt Endometrial Cancer. The phase 3 trial is ongoing.
- In 2023, the addition of checkpoint inhibitors to carboplatin/paclitaxel have changed the standard of care due to and statistically and clinically improved in the patients' outcomes:
  - Dostarlimab has improved PFS in dMMR/MSI-H (HR 0.28; CI 0.162–0.495) and in overall population (HR 0.64 (95%, 0.50–0.80) .
  - Pembrolizumab has improved PFS in dMMR/MSI-H (HR 0.30 (95%, 0.19–0.48) and in MMRp/MSS (HR 0.57 (95%, 0.44–0.74)

GRACIAS A TODOS