ANNUAL MEETING ON WOMEN'S CANCER

TAMPA, FL • 2023

PATIENTS • PURPOSE • PROGRESS

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

Mansoor R. Mirza,[1] Dana Chase,[2] Brian Slomovitz,[3] René DePont Christensen,[4] Zoltán Novák,[5] Destin Black,[6] Lucy Gilbert,[7] Sudarshan Sharma,[8] Giorgio Valabrega,[9] Lisa M. Landrum,[10] Lars C. Hanker,[11] Ashley Stuckey,[12] Ingrid Boere,[13] Michael A. Gold,[14] Sarah E. Gill,[15] Bradley J. Monk,[16] Zangdong He,[17] Shadi Stevens,[18] Robert L. Coleman,[19] Matthew A. Powell[20]

[1]Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, and Nordic Society of Gynaecologic Oncology-Clinical Trial Unit, Copenhagen Denmark; [2]*David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [3]Department of Gynecologic Oncology, Mount Sinai Medical Center, and Department of Obstetrics and Gynecology, Florida International University, Miami Beach, FL, USA; [4]Research Unit for General Practice, University of Southern Denmark, Institute of Public Health, Odense, Denmark; [5]Department of Gynecology, Hungarian National Institute of Oncology, Budapest, Hungary; [6]Department of Obstetrics and Gynecology, LSU Health Shreveport, and Willis-Knighton Physician Network, Shreveport, LA, USA; [7]Division of Gynecologic Oncology, McGill University Health Centre, Montreal, Quebec, Canada; [8]Department of Obstetrics/Gynecology, AMITA Adventist Hinsdale Hospital, Hinsdale, IL, USA; [9]University of Torino, AO Ordine Mauriziano, Torino, Italy; [10]Indiana University Health and Simon Cancer Center, Indianapolis, IN, USA; [11]Department of Gynecology and Obstetrics, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; [12]Women and Infants Hospital, Providence, RI, USA; [13]Department of Medical Oncology, Erasmus MC Cancer Centre, Rotterdam, The Netherlands; [14]Oklahoma Cancer Specialists and Research Institute, Tulsa, OK, USA; [15]Division of Gynecologic Oncology, Nancy N. and J.C Lewis Cancer and Research Pavilion, Savannah, GA, USA; [16]HonorHealth Research Institute, University of Arizona College of Medicine, Phoenix, and Creighton University School of Medicine, Phoenix, AZ, USA; [17]GSK, Collegeville, PA, USA; [18]GSK, London, UK; [19]US Oncology Research, The Woodlands, TX, USA; [20]National Cancer Institute sponsored NRG Oncology, Washington University School of Medicine, St Louis, MO, USA;

*Current affiliation. Affiliation at time of study Arizona Center for Cancer Care, Creighton University School of Medicine Phoenix, AZ, USA

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Financial Disclosures

Dr Mirza reports consulting or advisory role at AstraZeneca, Biocad, GSK, Karyopharm, Merck, Roche, Zailab; speakers' bureau fees from AstraZeneca and GSK; research funding (to institution) from Apexigen, AstraZeneca, Deciphera (trial chair), GSK, and Ultimovacs; and personal financial interest in Karyopharm (stocks/shares, member of Board of Directors).

Other authors: **Dr Chase** reports speaker bureau fees and/or advisory roles from GSK, AstraZeneca, Clovis, and Genentech/Roche and consulting fees from GSK, AstraZeneca, Clovis, and Genentech/Roche. **Dr Slomovitz** reports advisory fees from AstraZeneca, Clovis, Genentech, GSK, GOG Foundation, Merck, Myriad, Jazz Pharma, Onconova, Nuvation Bio, EQRX, Regeneron, Eisai, and Incyte and Board of Director member for GOG Foundation and HOW: Hearing Ovarian Cancer Whispers. **Dr dePont Christensen** reports direct consulting payment from Nordic Society for Gynecologic Oncology for the RUBY P1 Primary manuscript; consulting fees from Karyopharm; payment for advisory board DMC participation from the Swiss GO Trial Group (MATAO trial); and stock options from Y-mAbs Therapeutics. **Dr Novak** reports honoraria from Sofmedica, AstraZeneca, and MSD; support for attending meetings from Sofmedica and Preglem; participation on a data safety monitoring board or advisory board from AstraZeneca and Richter Gedeon; leadership role as the President of Hungarian Society of Gynecologic Oncology; stock options from Richter Gedeon; and receipt of equipment, materials, drugs, medical writing, gifts or other services from AstraZeneca. **Dr Black** reports institutional grant fees from GSK; fees for being a Member of GOG Partners Investigational Council; and medical director/owner of Trials365, LLC. **Dr Gilbert** reports institutional grants from Alkermes, AstraZeneca, Clovis, Esperas, IMV, ImmunoGen Inc, Karyopharm, Merck Sharp & Dohme, Mersana, Novocure GmbH, OncoQuest Pharmaceuticals, Pfizer, Roche, and Tesaro; consulting fees from Merck; and honoraria from Alkermes, AstraZeneca, Eisai, Eisai-Merck, and GSK. **Dr Valabrega** reports consulting/advisory fees from Amgen, AstraZeneca, Clovis Oncology, GSK, PharmaMar, Roche, and Tesaro. **Dr Hanker** reports consulting/advisory fees from Amgen, AstraZeneca, Clovis Oncology, Eisai, GSK, Intuitive Surgery, Janssen, MSD, Novartis, Pfizer, PharmaMar, Roche, and Tesaro. **Dr Stuckey** reports royalties as an UptoDate reviewer. **Dr Boere** reports institutional research grant from GSK and institutional advisory board meeting fees from AstraZeneca and GSK. **Dr Monk** reports consulting fees from VBL, US Oncology Research, Sorrento, Regeneron, Puma, Pfizer, Myriad, Novocure, Novartis, Mersana, Macrogenics, Iovance, Karyopharm, ImmunoGen, Gradalis, GOG Foundation, Genmab/Seagen, EMD Merck, Elevar, Bayer, Aravive, Amgen, Akeso Bio, and Agenus and speakers' bureau honoraria from TESARO/GSK, Roche/Genentech, Merck, Easai, Clovis, and AstraZeneca. **Dr Coleman** reports grants or contracts from AstraZeneca, Clovis, Genelux, Genmab, Merck, Immunogen, and Roche/Genentech; consulting fees from AbbVie, Agenus, Alkermes, AstraZeneca, Clovis, Deciphera, Genelux, Genmab, GSK, Immunogen, Novocure, Merck, OncoQuest, Onxerna, Regeneron, and Roche/Genentech; honoraria from AstraZeneca, Clovis, Merck, and Roche/Genentech; and participation on a data safety monitoring board or advisory board from Eisai/BMS and VBL Therapeutics. **Dr Powell** reports consulting/advisory fees from GSK, Tesaro, Merck, Eisai, Seagen, Clovis Oncology, and AstraZeneca. **Dr Gill**, **Dr Gold**, **Dr Landrum**, and **Dr Sharma** have nothing to disclose. **Dr Stevens** and **Dr He** are employees of GSK.

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Unlabeled/Investigational Uses

I will be discussing the investigational use of dostarlimab plus carboplatin/paclitaxel in primary advanced or recurrent endometrial cancer

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Acknowledgments

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Study Sponsor: GSK

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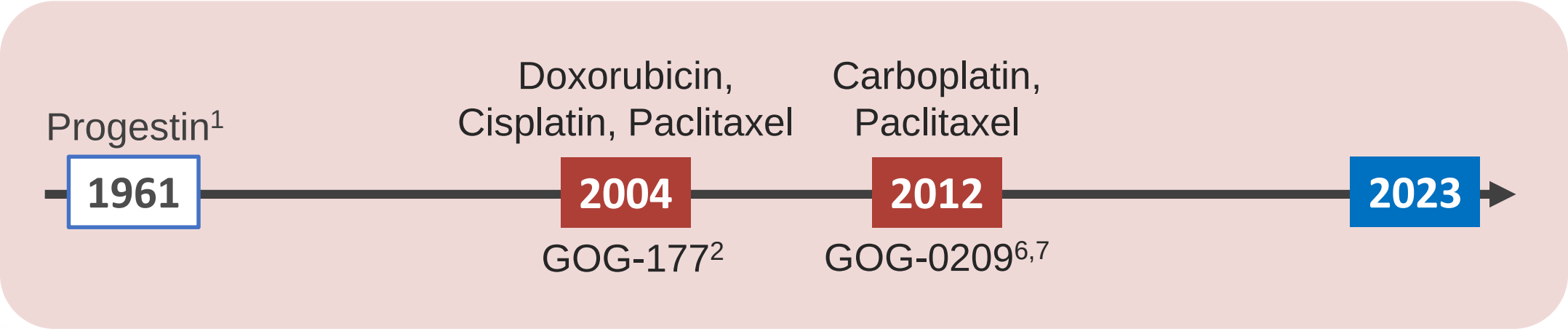
Background

- Carboplatin/paclitaxel (CP) is standard of care for first-line treatment of primary advanced or recurrent EC; however long-term outcomes remain poor, with median OS <3 years[1,2]
- Anti–PD-1 based therapy has transformed the management of EC post-platinum chemotherapy[3-5]
- Advances in first-line systemic treatment are urgently needed



CP, carboplatin-paclitaxel; EC, endometrial cancer; OS, overall survival.

1. Yang S, et al. *Discov Med.* 2011;12:205-212. 2. Fleming GF, et al. *J Clin Oncol*. 2004;22:2159-2166. 3. Oaknin A, et al. *J Immunother Cancer*. 2022;10(1):e003777. 4. O'Malley DM, et al. *J Clin Oncol.* 2022;40(7):752-761. 5. Makker V, et al. *N Engl J Med*. 2022;386:437-448 6. Miller DS, et al., *Gynecol Oncol*. 2012;125:771–773. 7. Miller DS, et al., *J Clin Oncol*. 2020;38:3841-3850.

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Study Rationale

Dostarlimab + **Chemotherapy**

- Durable activity in both dMMR/MSI-H and MMRp/MSS previously treated EC[1]
- dMMR/MSI-H EC is associated with:
  - High TMB/TILs[2]
  - Higher response rate to anti–PD-1[1]

- Enhances immunogenic cell-death[3,4]
- Reduces immunosuppression in TME[3,4]
- Broad clinical activity when combined with anti–PD-1 in several cancers[5–8]

Study Hypothesis

Dostarlimab + CP will improve outcomes in the **dMMR/MSI-H** and **OVERALL** primary advanced or recurrent EC patient populations vs CP alone

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.

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.

ENGOT-EN6-NSGO/GOG-3031/RUBY (NCT03981796)

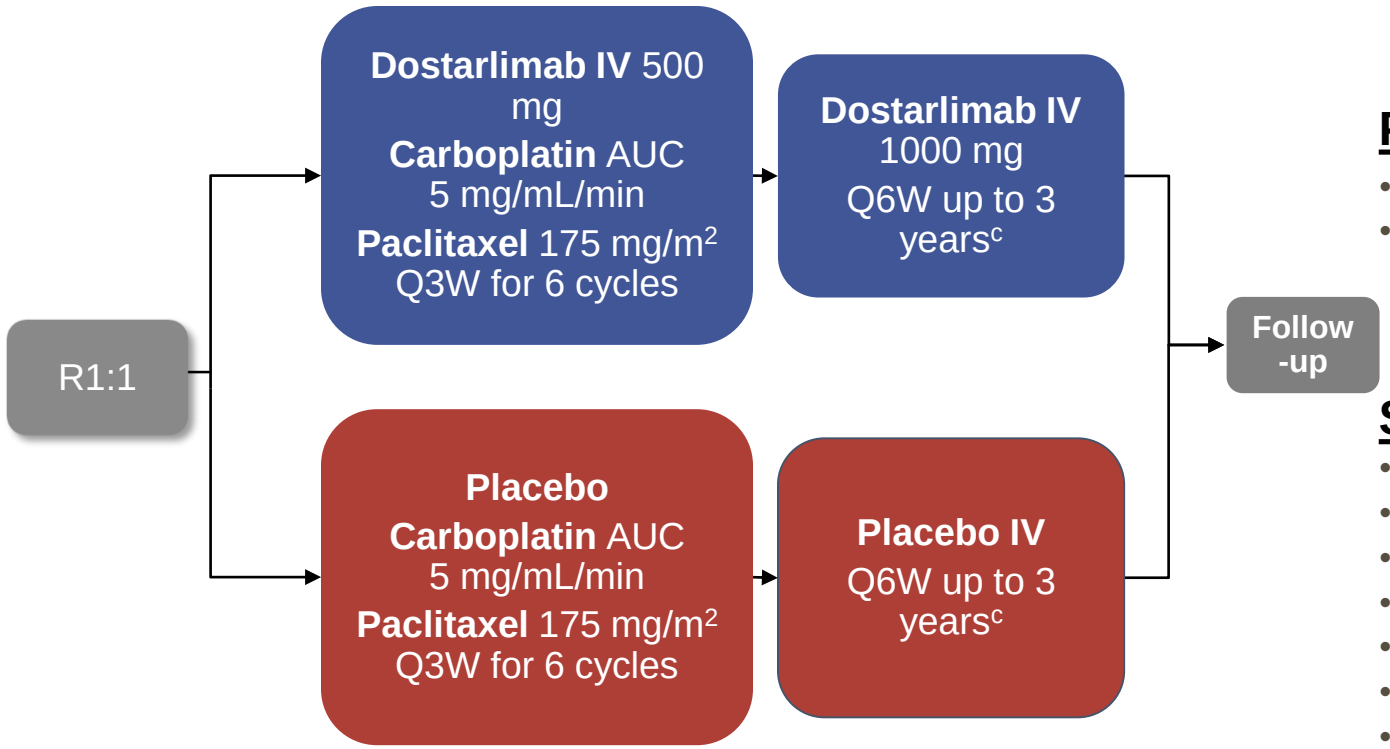
Phase 3, randomized, double-blind, multicenter study of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin/paclitaxel in patients with primary advanced or recurrent EC

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

On-study imaging assessments are to be performed Q6W (±7 days) from the randomization date until Week 25 (Cycle 8), followed by Q9W (±7 days) until Week 52. Subsequent tumor imaging is to be performed every 12 weeks (±7 days) until radiographic PD is documented by Investigator assessment per RECIST v1.1 followed by one additional imaging 4-6 weeks later, or subsequent anticancer therapy is started, whichever occurs first. Thereafter, scans may be performed per standard of care.

[a]Mixed histology containing at least 10% carcinosarcoma, clear cell, or serous histology. [b]Patients were randomized based on either local or central MMR/MSI testing results. Central testing was used with local results were not available. For local determination of MMR/MSI status, IHC, next generation sequencing, and polymerase chain reaction assays were accepted. For central determination of MMR/MSI status IHC per Ventana MMR RxDx panel was used. [c]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the Investigator. AUC, area under the plasma or serum concentration-time curve; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response, EC, endometrial cancer; IV, administered intravenously; INV, investigator assessment; MMR, mismatch repair; MSI, microsatellite instability; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome.

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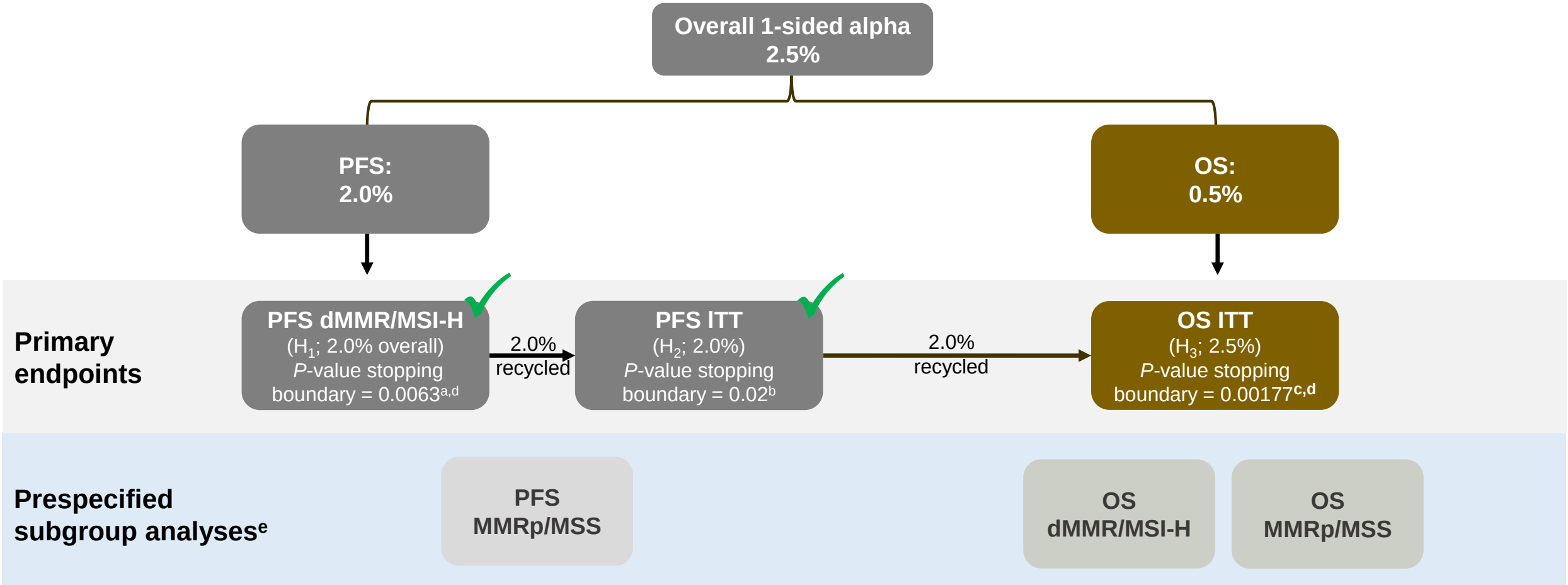
Statistical Testing and Multiplicity Control Strategy



Multiplicity control strategy is based on the graphical method (Maurer, 2013)

[a] Hypothesis for PFS dMMR/MSI (H_1) was tested at the IA with 0.63% alpha spent from the overall alpha level (2.0%) initially allocated. [b] Since null hypothesis (H_{01}) for H_1 was rejected at IA, the 2.0% alpha for (H_1) was recycled to hypothesis testing of PFS ITT (H_2). H_2 was tested at alpha level (2.0%)= 2.0% recycled + 0% initially allocated. [c] Since both null hypotheses (H_{01} and H_{02}) were rejected, 2.0% alpha for the family of hypothesis testing of PFS was recycled to testing of OS (H_3). H_3 was tested at alpha level (2.5%)= 2.0% recycled + 0.5% initially allocated. [d]Stopping boundaries and alpha spent at IA were adjusted based on the actual number of events/information fraction observed based on the prespecified alpha spending function at the time of analysis; *P*-value stopping boundary (IA)= 0.0063 for PFS dMMR/MSI-H; *P*-value stopping boundary (IA1)=0.00177 for OS ITT. [e]Not formally tested.

dMMR, mismatch repair deficient; FA, final analysis; H, hypothesis; IA, interim analysis; ITT, intent to treat; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; OS, overall survival; PFS, progression-free survival.

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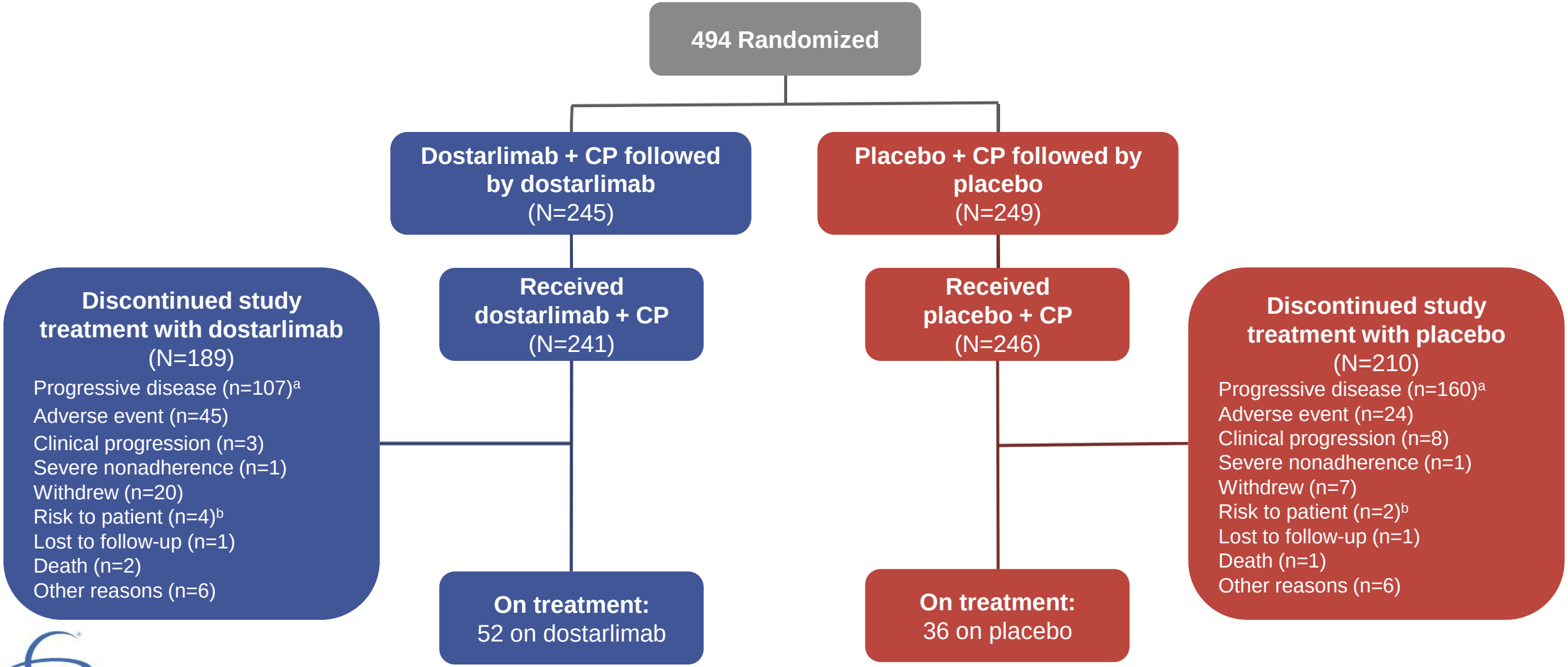
Patient Disposition



Data cutoff date: September 28, 2022.
[a]Progressive disease according to RECIST v1.1 by the investigator, sponsor, or both. [b]Risk to patient as judged by the investigator, sponsor, or both.
CP, carboplatin/paclitaxel.

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Patient Population and Baseline 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)
Disease status				
Primary stage III	10 (18.9)	14 (21.5)	45 (18.4)	47 (18.9)
Primary 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)

CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; MMR, mismatch repair; MMRp, mismatch repair proficient; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable.

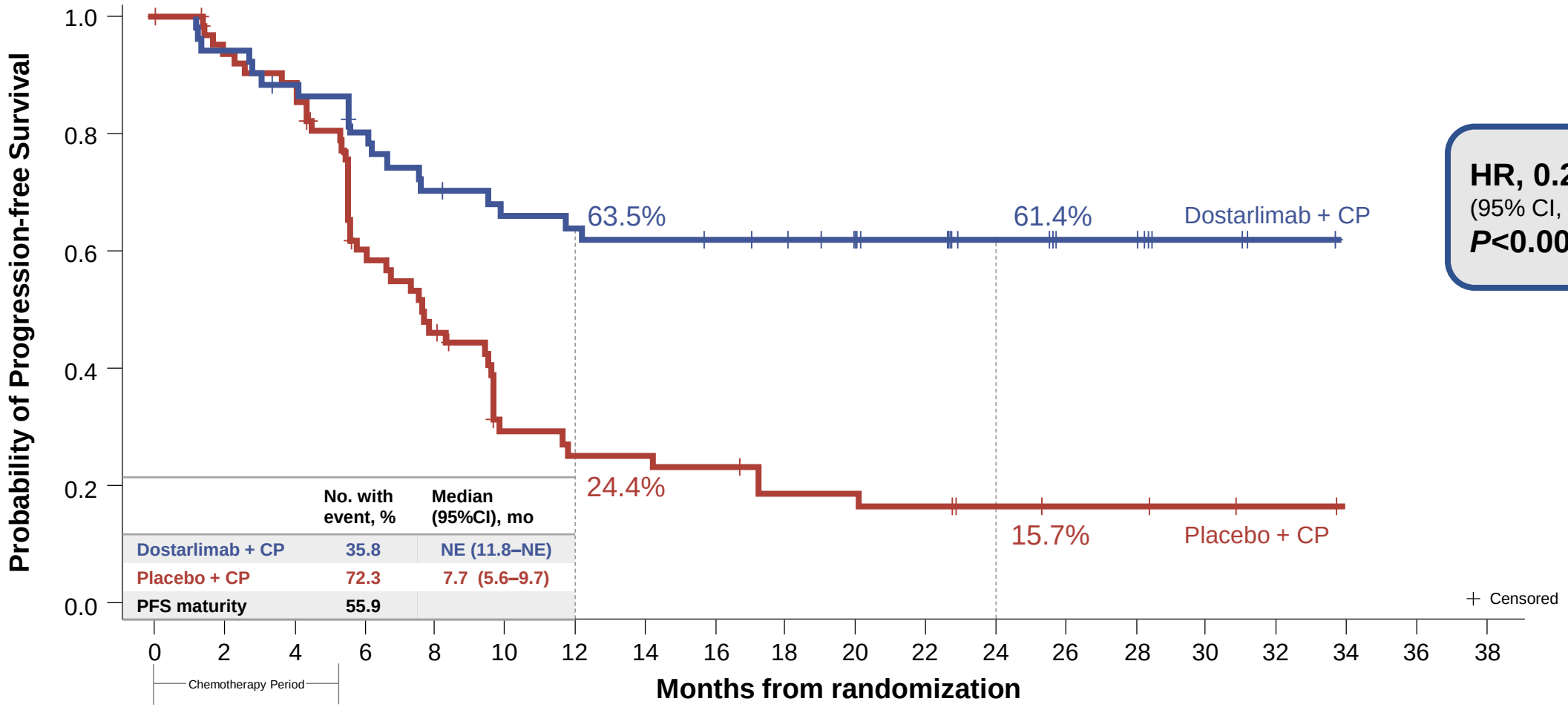
Baseline Characteristics

Variable, n (%)	dMMR/MSI-H		Overall	
	Dostarlimab + CP (N=53)	Placebo + CP (N=65)	Dostarlimab + CP (N=245)	Placebo + CP (N=249)
Age				
Median age, yr (range)	61 (45–81)	66 (39–85)	64 (41–81)	65 (28–85)
≥65	23 (43.4)	35 (53.8)	118 (48.2)	135 (54.2)
Race				
White	44 (83.0)	56 (86.2)	189 (77.1)	191 (76.7)
Black	4 (7.5)	6 (9.2)	28 (11.4)	31 (12.4)
Asian	2 (3.8)	0	7 (2.9)	8 (3.2)
Other[a]	3 (5.7)	3 (4.6)	21 (8.6)	19 (7.6)
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)
BMI				
Median BMI (range)	30.6 (20.1-54.4)	35.5 (17.9-58.1)	30.8 (17.6-60.6)	32.8 (17.7-68.0)
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)

[a]Other includes patients identifying as American Indian or Alaska native, native Hawaiian or other Pacific Islander, unknown, or not reported. [b]Patients with ECOG score: 52 dostarlimab+CP dMMR/MSI-H, 65 placebo+CP dMMR/MSI-H, 241 dostarlimab+CP overall, 246 placebo+CP overall. [b]Mixed carcinoma ≥10% of carcinosarcoma, clear cell, or serous histology.
BMI, body mass index; CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability-high.

Primary Endpoint: PFS in dMMR/MSI-H Population



HR, 0.28
(95% CI, 0.162–0.495)
***P*<0.0001**

At Risk(Events)

Dostarlimab + 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(19)
Placebo + 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(47)

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.

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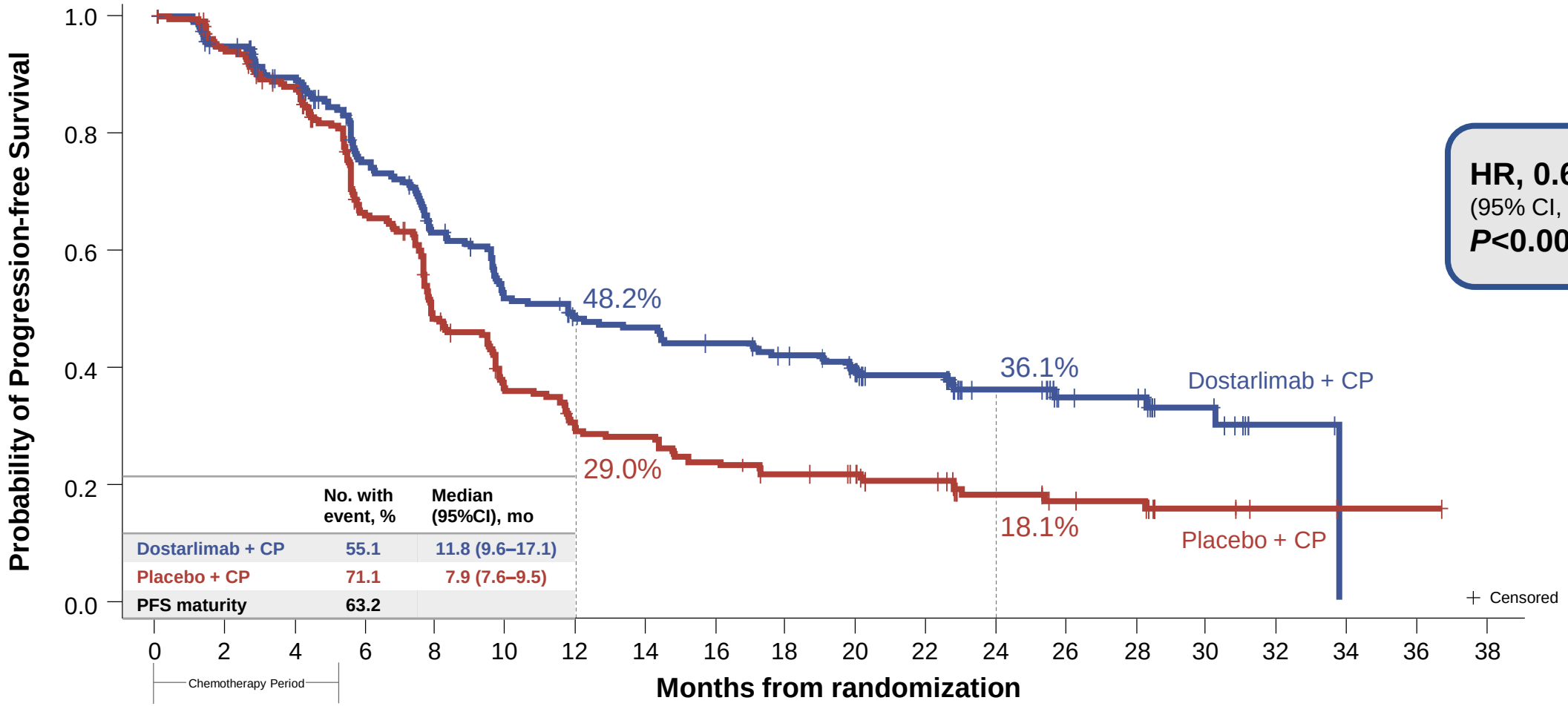
Primary Endpoint: PFS in Overall Population



HR, 0.64
(95% CI, 0.507–0.800)
***P*<0.0001**

At Risk(Events)

Dostarlimab + CP	245(0)	220(12)	197(25)	157(55)	130(80)	105(103)	94(110)	90(113)	84(118)	78(122)	66(127)	52(128)	34(131)	23(132)	22(132)	12(133)	2(134)	0(135)	
Placebo + CP	249(0)	219(14)	200(29)	144(77)	103(115)	74(141)	59(155)	57(157)	48(166)	42(170)	39(170)	32(172)	20(175)	14(176)	13(176)	5(177)	2(177)	1(177)	1(177)	0(177)

Median duration of follow-up 25.38 months.

CP, carboplatin/paclitaxel; HR, hazard ratio; PFS, progression-free survival.

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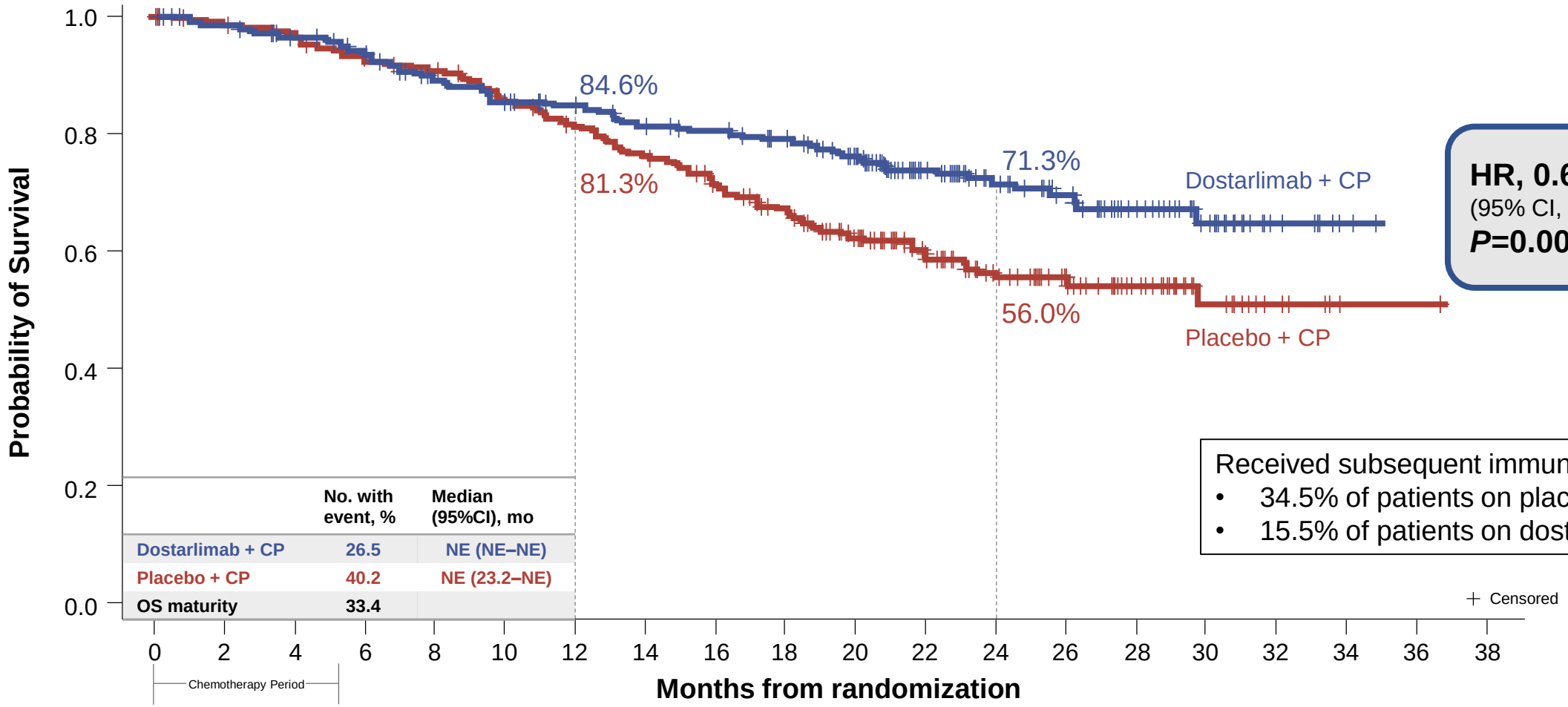
Primary Endpoint: OS in Overall Population (33% maturity)



	No. with event, %	Median (95%CI), mo
Dostarlimab + CP	26.5	NE (NE–NE)
Placebo + CP	40.2	NE (23.2–NE)
OS maturity	33.4	

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(3)	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)

Median duration of follow-up 25.38 months.

[a]P≤0.00177 required to declare statistical significance at first interim analysis.
CP, carboplatin/paclitaxel; HR, hazard ratio; NE, not estimable; OS, overall survival.

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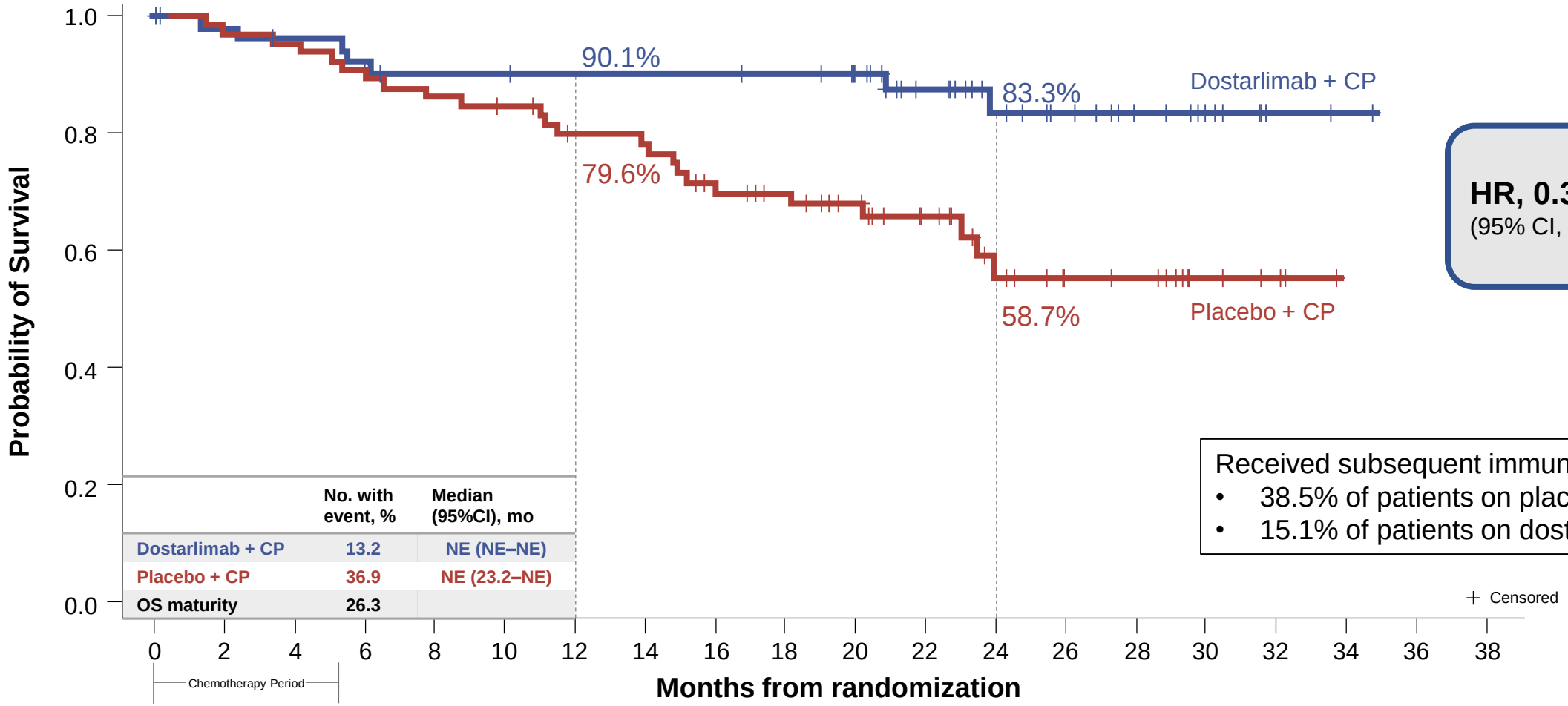
OS in dMMR/MSI-H Population



HR, 0.30
(95% CI, 0.127–0.699)

Received subsequent immunotherapy:
- 38.5% of patients on placebo arm
- 15.1% of patients on dostarlimab arm

At Risk(Events)

Dostarlimab + CP	53(0)	50(1)	48(2)	46(4)	44(5)	44(5)	43(5)	43(5)	43(5)	42(5)	41(5)	29(6)	20(7)	16(7)	12(7)	8(7)	2(7)	1(7)	0(7)
Placebo + CP	65(0)	63(2)	62(3)	59(6)	55(9)	53(10)	48(13)	47(14)	41(18)	37(19)	32(20)	25(21)	16(23)	12(24)	10(24)	5(24)	3(24)	0(24)	

CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; OS, overall survival.

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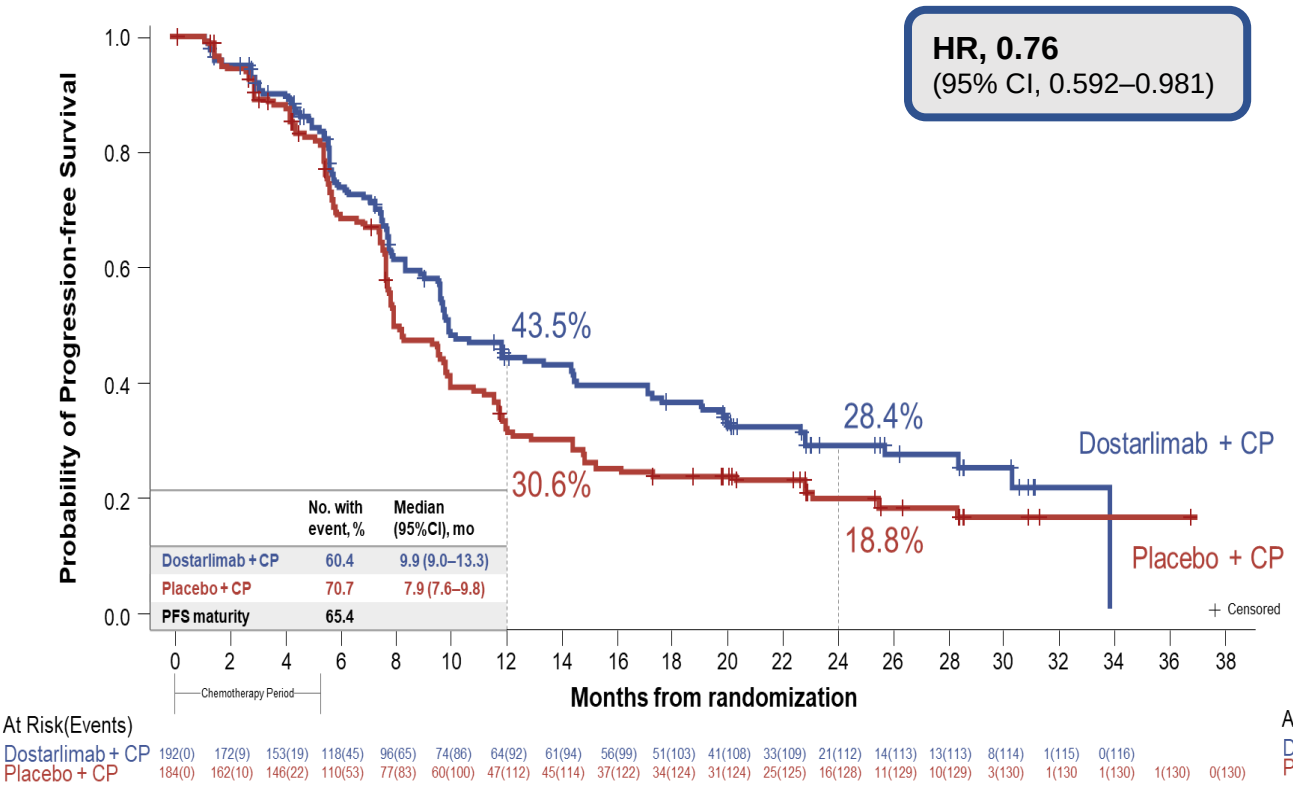
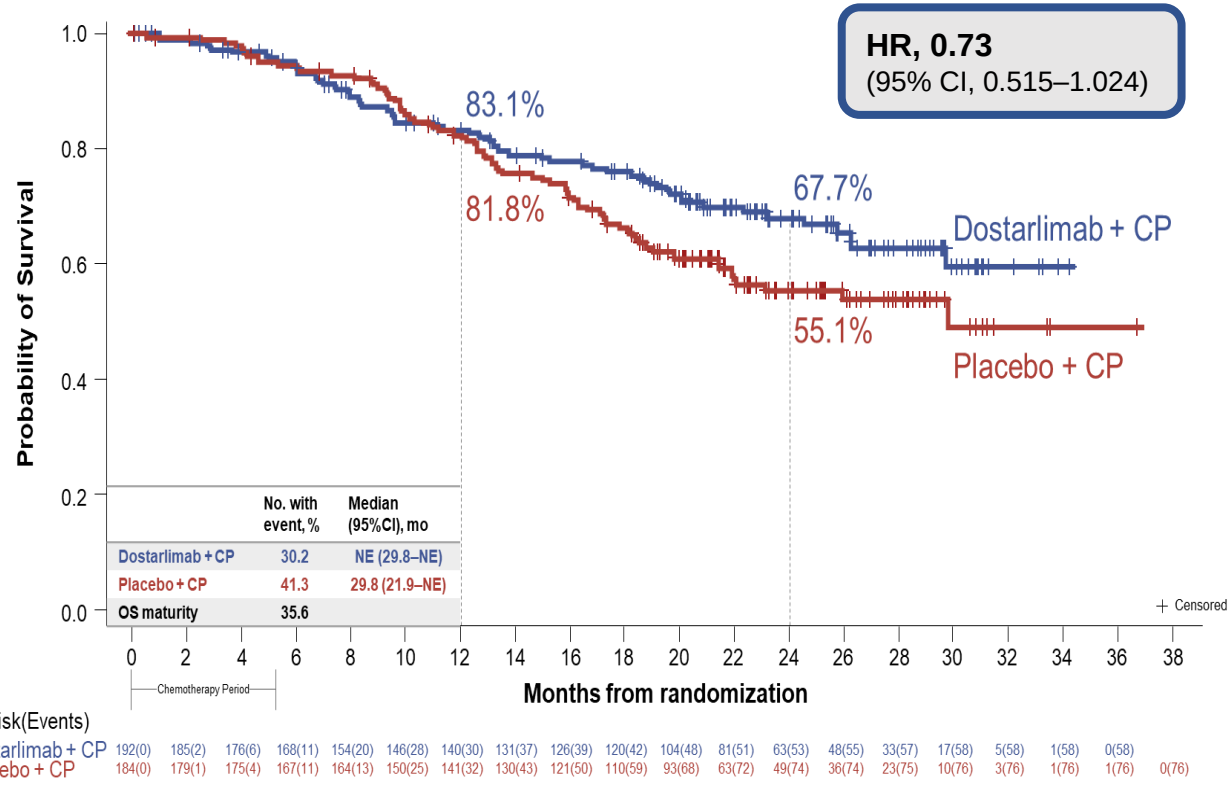
PFS and OS in MMRp/MSS Population

PFS



OS



Received subsequent immunotherapy:
- 33.2% of patients on placebo arm
- 15.6% of patients on dostarlimab arm

CP, carboplatin/paclitaxel; HR, hazard ratio; MMRp, mismatch repair proficient; MSS, microsatellite stable; NE, not estimable; OS, overall survival; PFS, progression-free survival.

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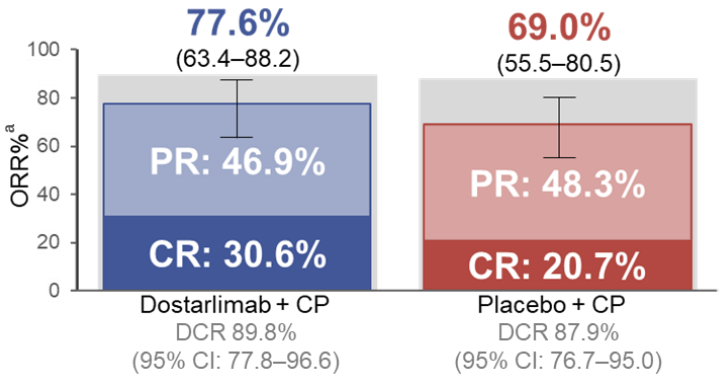
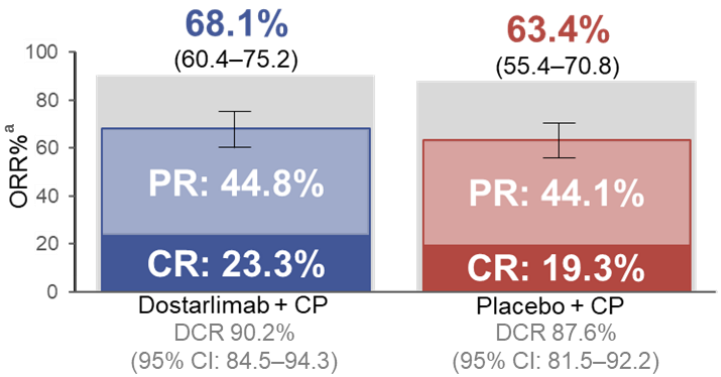
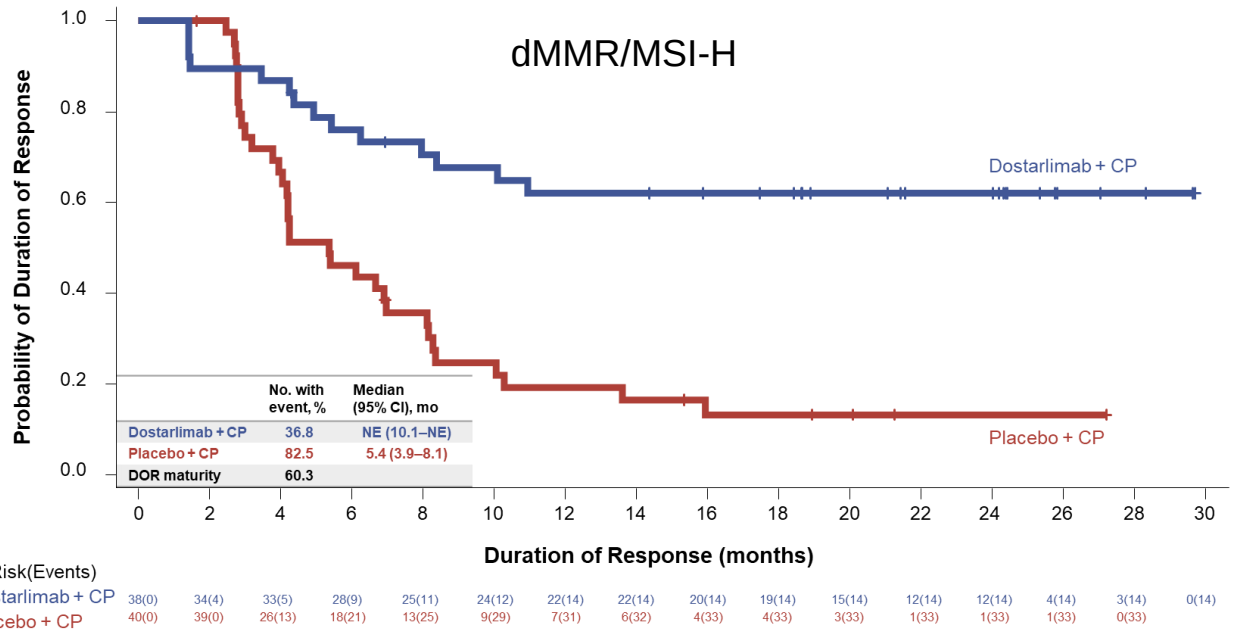
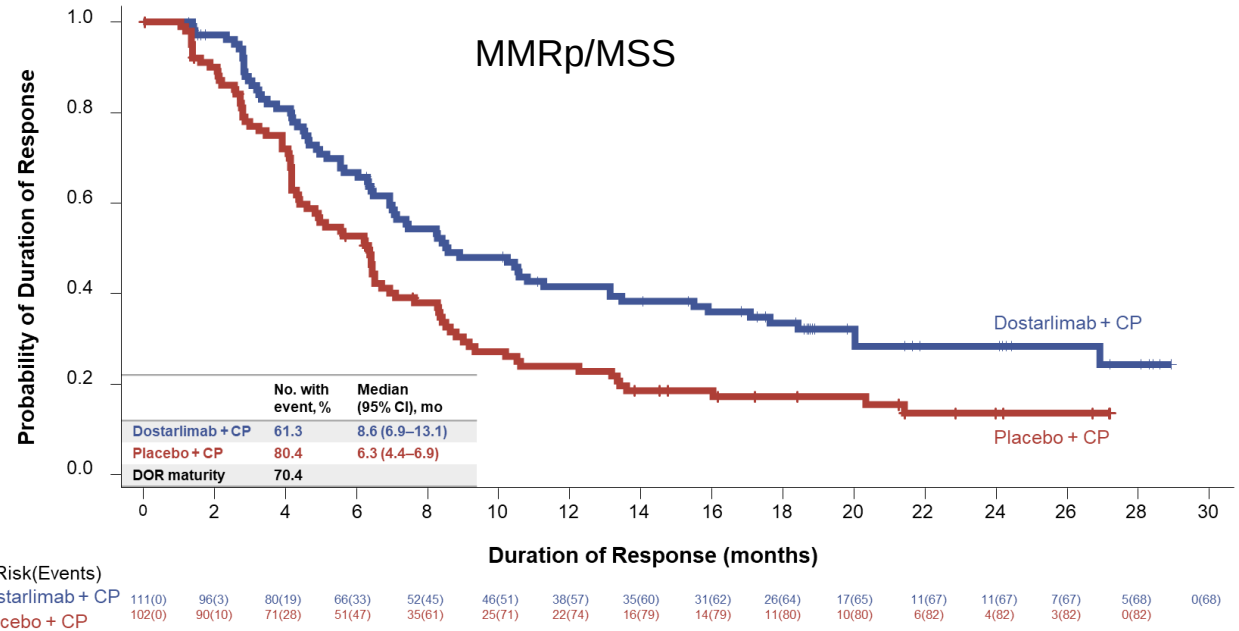
Objective Response Rate and Duration Of Response





Duration of Response[b]





[a]ORR assessed in patients with evaluable disease at baseline in the dMMR/MSI-H and MMRp/MSS populations were prespecified analyses. [b]DOR in the dMMR/MSI-H population was a prespecified analysis and in the MMRp/MSS population was a post hoc analysis. CP, carboplatin/paclitaxel; CR, complete response; DCR, disease control rate; dMMR, mismatch repair deficient; DOR, duration of response; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; ORR, objective response rate; PR, partial response.

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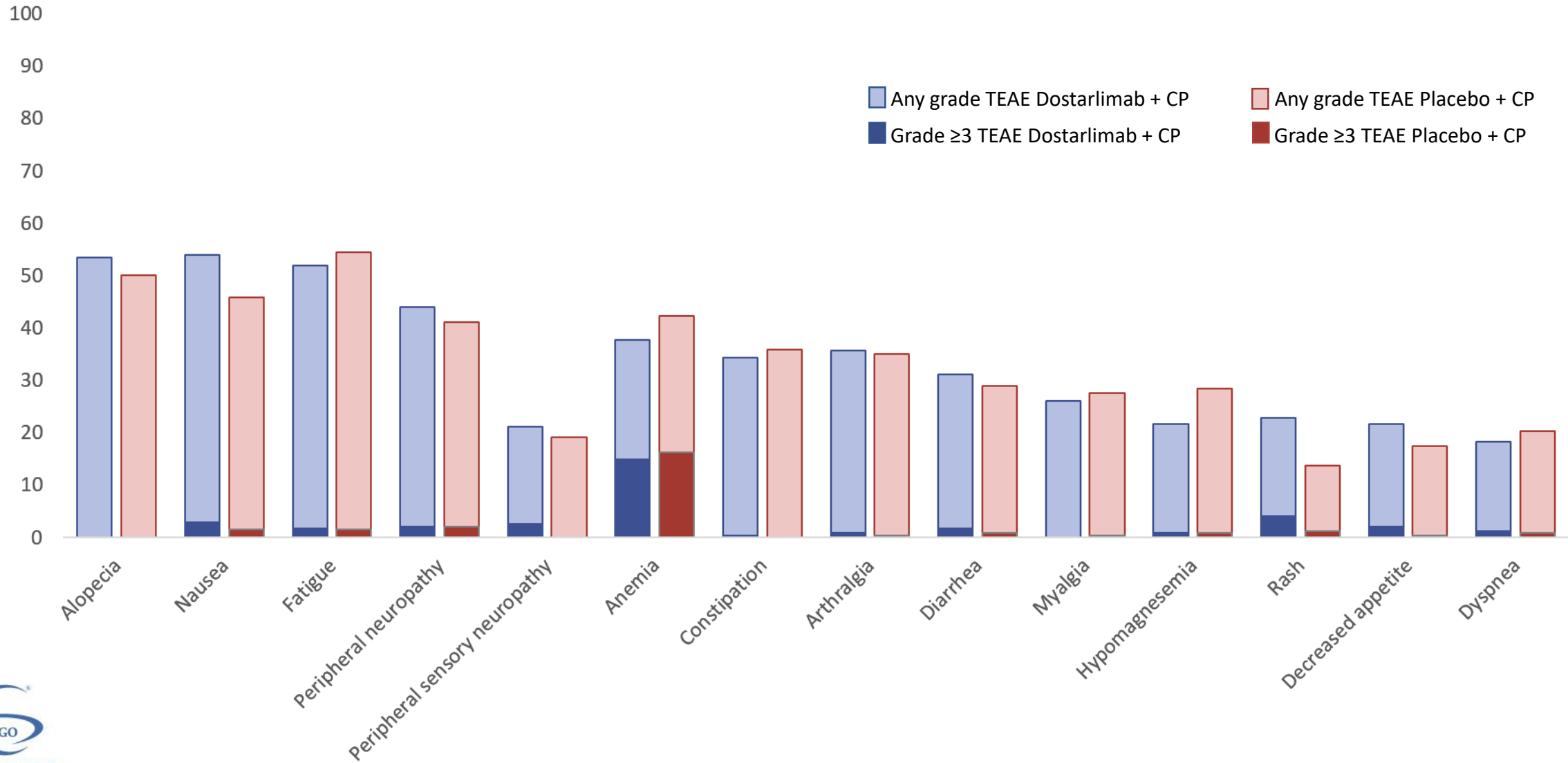
Safety Summary

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)

[a]3 deaths were not related to study treatment (opiate overdose, COVID-19, and general physical health deterioration). [b]One death was considered by the investigator as related to dostarlimab plus CP and occurred during the first 6 cycles (myelosuppression); one death was related to dostarlimab and occurred during the 90-day safety follow-up (hypovolemic shock).
CP, carboplatin/paclitaxel; irAE, immune-related adverse event; TEAE, treatment-emergent adverse event.

TEAEs in ≥20% of Either Arm



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

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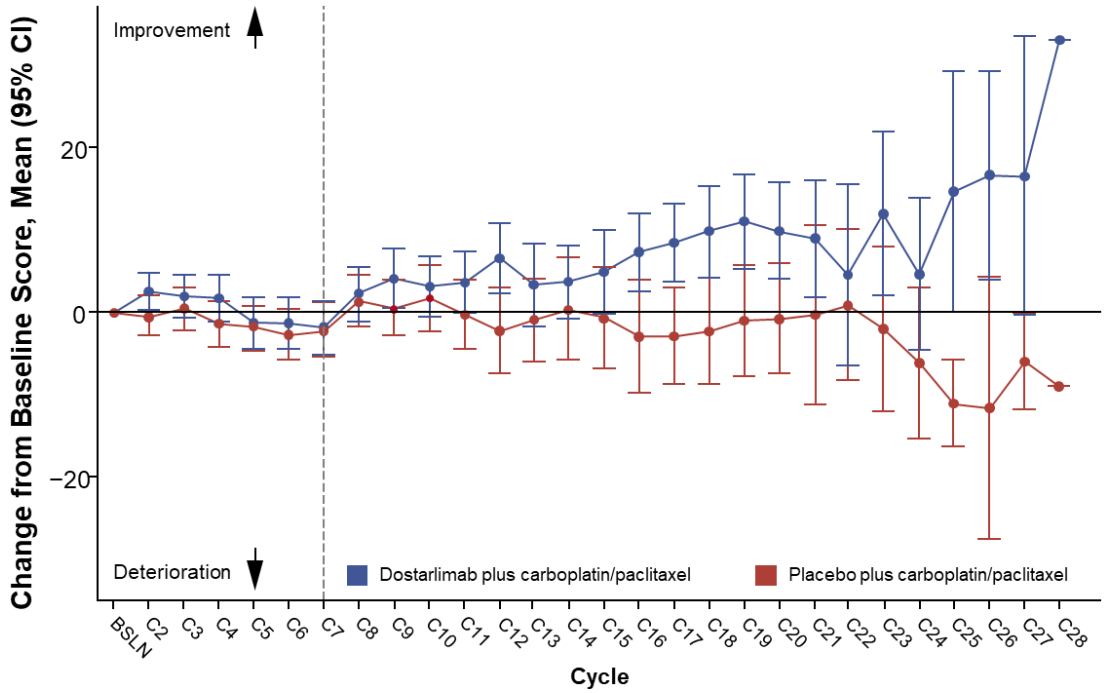
Patient-Reported Outcomes

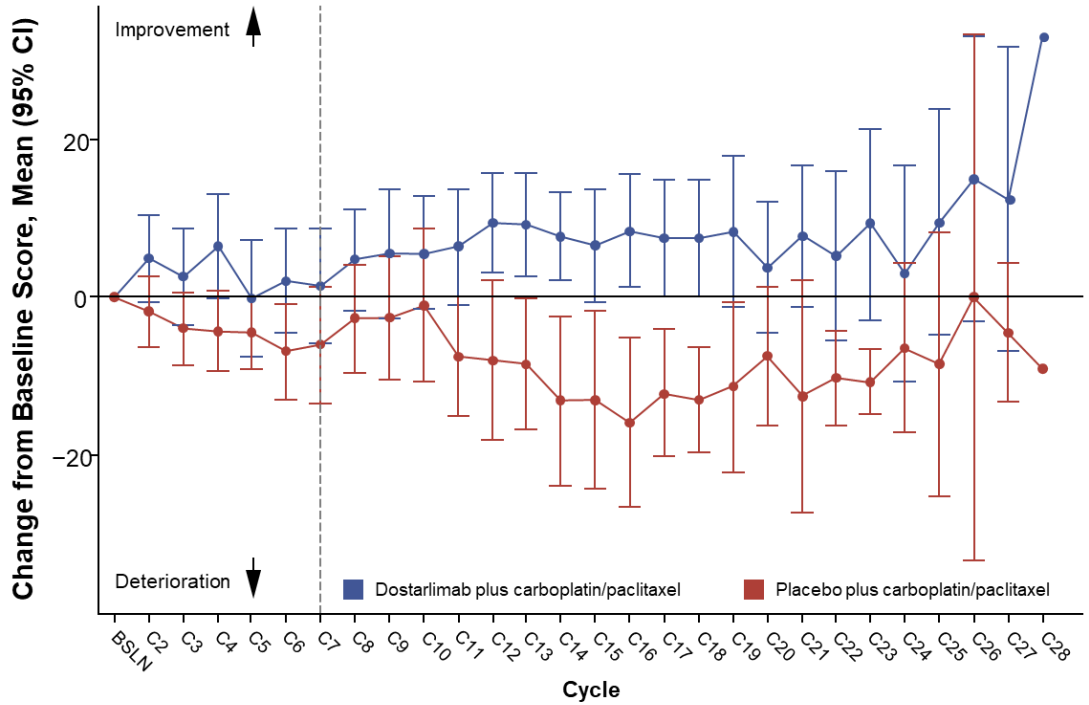
EORTC QLQ-C30 Global Quality of Life Score

Overall



No.	BSLN	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17	C18	C19	C20	C21	C22	C23	C24	C25	C26	C27	C28
Dostarlimab + CP	238	228	219	213	205	196	178	153	140	125	106	93	85	79	75	70	69	55	47	41	31	25	20	14	13	8	5	2
Placebo + CP	242	232	224	219	210	204	181	151	132	105	82	68	57	55	50	46	41	40	36	31	24	19	17	11	6	5	3	2

dMMR/MSI-H



No.	BSLN	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17	C18	C19	C20	C21	C22	C23	C24	C25	C26	C27	C28
Dostarlimab + CP	51	49	47	46	46	43	39	36	34	34	31	29	27	25	25	25	25	22	17	15	12	11	9	8	7	5	4	1
Placebo + CP	64	61	58	59	57	54	48	39	31	27	19	14	14	13	11	10	9	9	9	9	8	5	4	4	2	2	2	1

BSLN, baseline; C, cycle; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.

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Conclusions

- Dostarlimab + CP demonstrated statistically significant and clinically meaningful PFS benefit with an early OS trend in the overall population
  - Substantial, unprecedented benefit in dMMR/MSI-H patients
  - Clinically meaningful long-term benefit observed in MMRp/MSS patients
- Safety profile for dostarlimab + CP was manageable and generally consistent with that of the individual drugs
- **Dostarlimab plus carboplatin/paclitaxel represents a new standard of care for patients with primary advanced or recurrent endometrial cancer**

CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; OS, overall survival; PFS, progression-free survival.

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ORIGINAL ARTICLE

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

Mansoor R. Mirza, M.D., Dana M. Chase, M.D., Brian M. Slomovitz, M.D., René dePont Christensen, Ph.D., Zoltán Novák, Ph.D., Destin Black, M.D., Lucy Gilbert, M.D., Sudarshan Sharma, M.D., Giorgio Valabrega, M.D., Lisa M. Landrum, M.D., Ph.D., Lars C. Hanker, M.D., Ashley Stuckey, M.D., Ingrid Boere, M.D., Ph.D., Michael A. Gold, M.D., Annika Auranen, M.D., Bhavana Pothuri, M.D., David Cibula, M.D., Carolyn McCourt, M.D., Francesco Raspagliesi, M.D., Mark S. Shahin, M.D., Sarah E. Gill, M.D., Bradley J. Monk, M.D., Joseph Buscema, M.D., Thomas J. Herzog, M.D., Larry J. Copeland, M.D., Min Tian, Ph.D., Zangdong He, Ph.D., Shadi Stevens, M.D., Eleftherios Zografos, M.D., Robert L. Coleman, M.D., and Matthew A. Powell, M.D., for the RUBY investigators

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