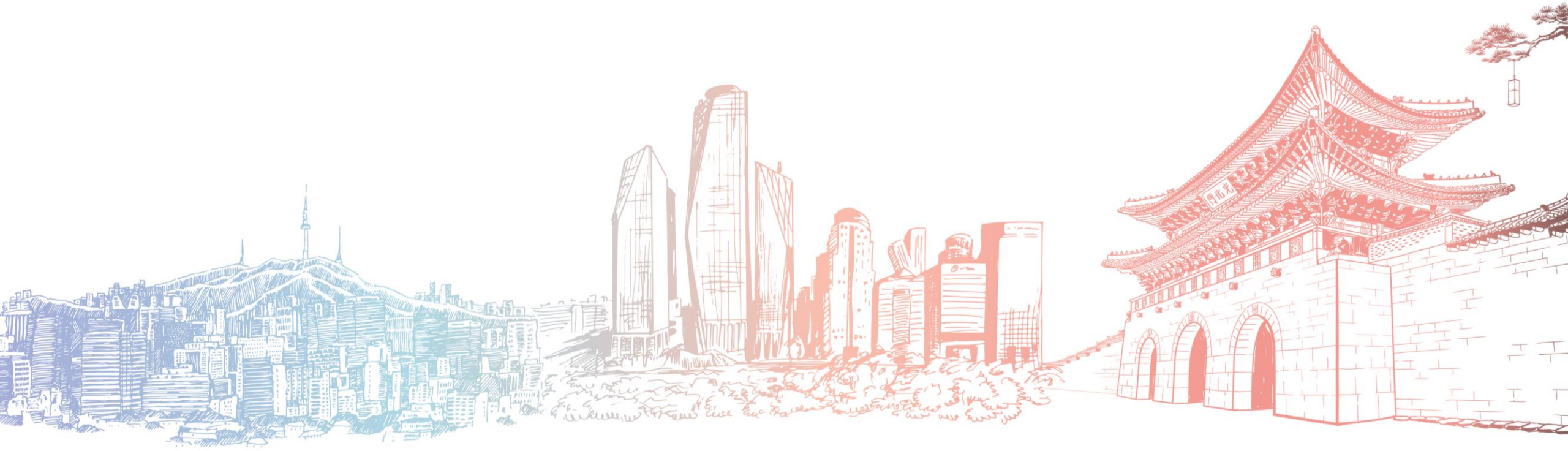
Evolution of ICI combinations: ICI + chemotherapy for treatment of primary advanced/recurrent EC

Dr. Mansoor Raza Mirza

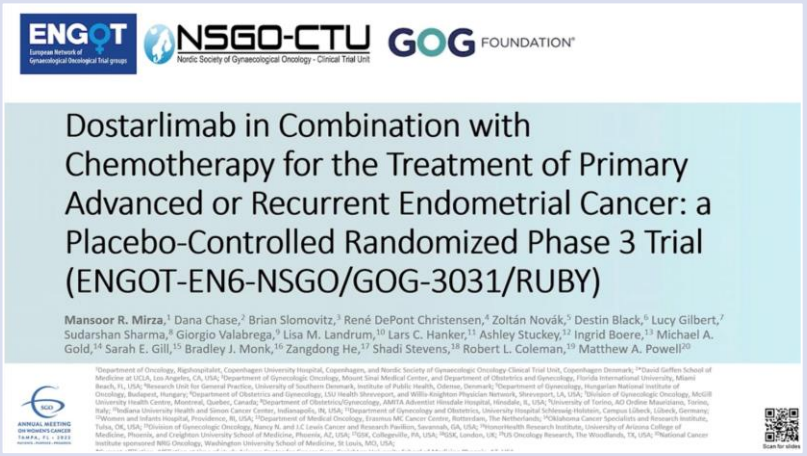


Disclosures

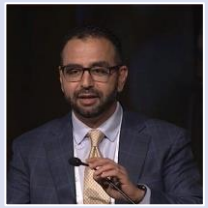
- Dr. Mirza reports consulting fees from AstraZeneca, Biocad, GSK, Karyopharm, Merck, Roche, Zailab; speakers' bureau fees from AstraZeneca and GSK; research funding (to institution) from Apexigen, AstraZeneca, Deciphera (trial chair), GSK, and Ultimovacs; and personal financial interest in Karyopharm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

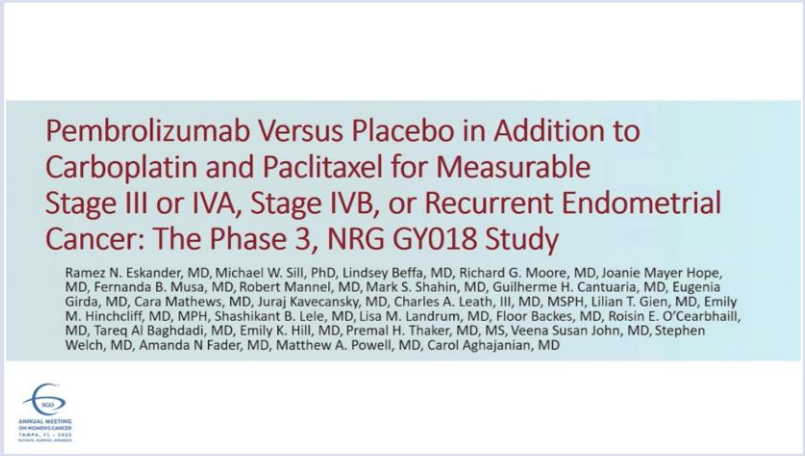
Paradigm-shifting data were presented at SGO[1-4]

Society of Gynecologic Oncology Annual Meeting | Tampa, Florida | March 2023



Dr. Mirza presented RUBY Part 1 data[a]





Dr. Eskander presented GY018 data

The treatment landscape for front-line EC has dramatically changed following the recent positive results from clinical trials and subsequent regulatory approvals have just begun

- The first approval for an immunotherapy (dostarlimab) in combination with chemotherapy for patients with advanced or first recurrent EC took place on July 31st, 2023 (FDA)[5]
- MHRA approval (October 2nd, 2023)[6,7]
- Positive CHMP opinion (October 12th, 2023)[8]

[a]RUBY Part 1 was also presented at ESMO virtual plenaries, March 2023.

C/P = carboplatin/paclitaxel; dMMR = mismatch repair deficient; EC = endometrial cancer; MSI-H = microsatellite instabilty-high.

1. Mirza MR et al. Presented at the Society of Gynecologic Oncology Annual Meeting on Women's Cancer (Oral presentation). March 25-28, 2023, Tampa, FL, USA. 2. Eskander RN et al. Presented at the Society of Gynecologic Oncology Annual Meeting on Women's Cancer (Oral presentation). March 25-28, 2023, Tampa, FL, USA. 3. Mirza MR et al. Mirza MR, et al. *N Engl J Med*. 2023;388:2145-2158. 4. Eskander RN et al. *N Engl J Med* 2023;388:2159-2170. 5. GSK Press Release. https://www.gsk.com/en-gb/media/press-releases/jemperli-plus-chemotherapy-approved-in-us-for-new-indication. Accessed August 23, 2023. 6. Jemperli (dostarlimab) [summary of product characteristics]. GlaxoSmithKline UK Limited. Brentford, Middlesex, UK; 2023. 7. Medicines and Healthcare products Regulatory Agency. MHRA authorises monoclonal antibody treatment, Jemperli, to be used with chemotherapy for endometrial cancer. Press release. Accessed 12 October 2023 at https://www.gov.uk/government/news/mhra-authorises-monoclonal-antibody-treatment-jemperli-to-be-used-with-chemotherapy-for-endometrial-cancer. 8. GSK Press Release. https://www.gsk.com/en-gb/media/press-releases/gsk-receives-positive-chmp-opinion-recommending-approval-of-jemperli-dostarlimab-plus-chemotherapy/. Accessed October 24, 2023

Immunotherapy combination Phase 3 trials: chemotherapy ± IO

Drug name	Dostarlimab	Pembrolizumab		Atezolizumab
	RUBY Part 1 | ENGOT-en6[1,2]	NRG-GY018[3,4]	KEYNOTE-B21 | ENGOT-en11[5,6]	AtTEnd | ENGOT-en7[7,8]
N	494	816	990	550
Study chair	Mirza	Eskander	Van Gorp	Colombo
Treatment arms	Dostarlimab + carboplatin/paclitaxel then dostarlimab **vs** Placebo + carboplatin/paclitaxel then placebo	Pembrolizumab + carboplatin/paclitaxel then pembrolizumab **vs** Placebo + carboplatin/paclitaxel then placebo	Pembrolizumab + carboplatin/paclitaxel **then** pembrolizumab ± RT ± cisplatin **vs** Placebo + carboplatin/paclitaxel **then** placebo ± RT ± cisplatin	Atezolizumab + carboplatin/paclitaxel then atezolizumab **vs** Placebo + carboplatin/paclitaxel then placebo
Stratification	MMR-MSI status, previous external pelvic radiotherapy, and disease status[2]	MMR status, ECOG PS, and previous chemotherapy[4]	MMR status, RT, histology, and FIGO surgical stage[6]	Histology, disease stage, MSI status, and country of experimental site[8]
Primary outcome(s)	PFS (INV), **OS**	PFS (INV)	DFS (INV), **OS**	PFS (INV), **OS**

There are no completed direct head-to-head trials of these products in EC. There are inherent limitations in cross-study comparisons; caution should be exercised in comparing trials. This slide is for information purposes only and is not intended to imply or infer the noninferiority or superiority of any product, in terms of efficacy or safety.

DFS = disease-free survival; EC = endometrial cancer; ECOG = Eastern Cooperative Oncology Group performance status; ENGOT = European Network of Gynecological Oncological Trial Groups; FIGO = International Federation of Gynecology and Obstetrics; INV = investigator assessed; IO = immuno-oncology; MMR = mismatch repair; MSI = microsatellite instability; OS = overall survival; PFS = progression-free survival; RT = radiotherapy.

1. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03981796. Accessed August 23, 2023. 2. Mirza MR, et al. *N Engl J Med.* 2023;388:2145-2158. 3. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03914612. Accessed August 23, 2023. 4. Eskander RN, et al. *N Engl J Med.* 2023. 388:2159-2170. 5. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT04634877. Accessed August 23, 2023. 6. Van Gorp T, et al. *J Clin Oncol.* 2021;39(Suppl_15):TPS5608. 7. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03603184. Accessed August 23, 2023. 8. Colombo N, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.

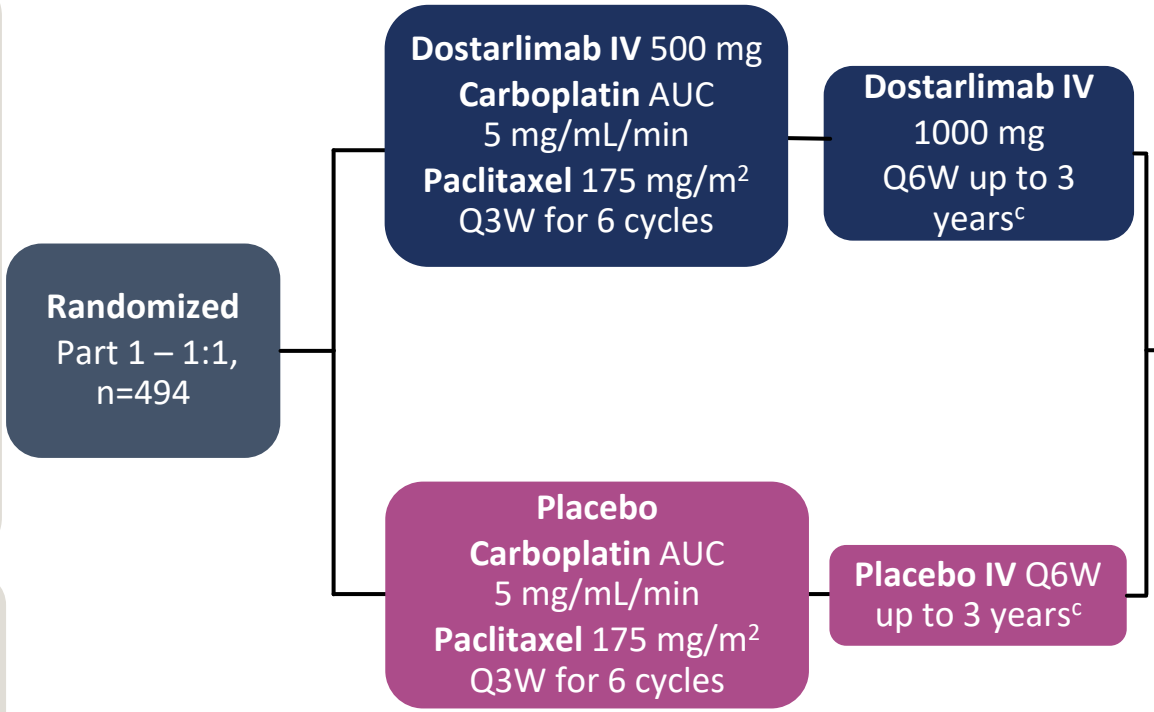
RUBY Part 1 | ENGOT-EN6 | GOG-3031 | NCT03981796[1]

Eligible patients:

- Histologically or cytologically proven EC with recurrent or advanced disease
- Stage III or 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]
- Naive to systemic therapy or systemic anticancer therapy or had a recurrence or PD ≥6 months after completing systemic anticancer therapy
- ECOG PS 0-1
- Adequate organ function

Stratification:

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



Primary end points: PFS by INV,[d] OS

Secondary end points: PFS by BICR,[e] PFS2, ORR,[f] DOR,[g] DCR,[h] HRQOL/PRO, safety[i]

Data cutoff: 28 September 2022

Median duration of follow-up: dMMR/MSI-H cohort: 24.8 mo (range, 19.2–36.9 mo), overall population: 25.4 mo (range, 19.2–37.8 mo)

Start date: July 18, 2019

Status: Active, not recruiting

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.

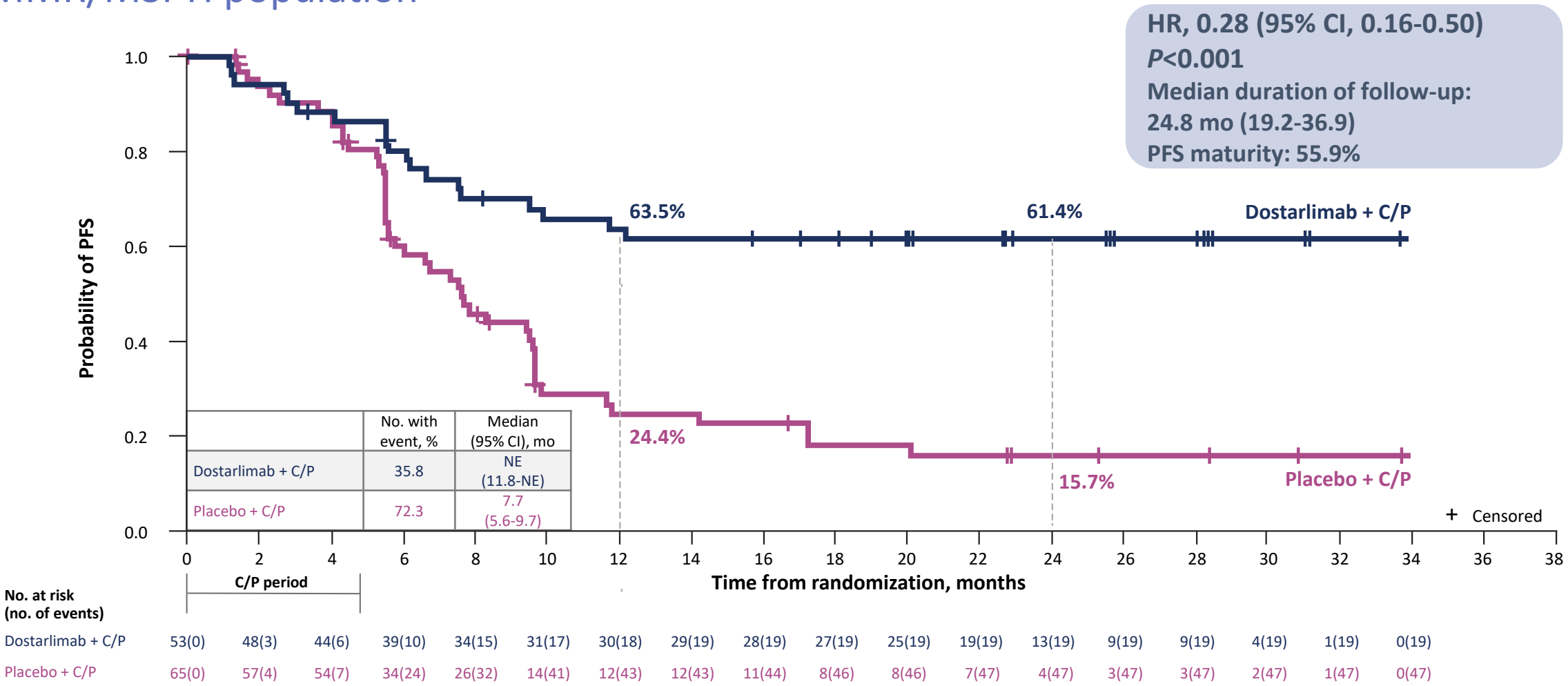
[a]Mixed histology containing at least 10% carcinosarcoma, clear cell, or serous histology. [b]Patients were randomized based on either local or central MMR/MSI testing results. Central testing was used with local results were not available. For local determination of MMR/MSI status, IHC, next generation 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. [d]PFS per IA – all patients with recurrent or primary advanced EC (ITT population). [e]PFS by BICR per RECIST v1.1 (not IA) – ITT population and dMMR/MSI-H population. [f]ORR by BICR and IA. [g]DOR by BICR and IA, [h]DCR by BICR and IA. [i]All AEs assessed for intensity according to CTCAE v4.03

AUC = area under the plasma or serum concentration-time curve; BICR = blinded independent central review; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; dMMR = mismatch repair deficient; DOR = duration of response, EC = endometrial cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; HRQOL = health-related quality of life; IA = investigator assessed; IV = administered intravenously; INV = investigator assessed; MMR = mismatch repair; mo = month; MSI = microsatellite instability; MSI-H = microsatellite instability-high; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PFS2 = time to second disease progression or death; PRO = patient-reported outcome; QxW = every x weeks.

1. Mirza MR, et al. *N Engl J Med* 2023. 388:2145-2158.

Primary end point: PFS by investigator per RECIST v1.1[1,2]

dMMR/MSI-H population



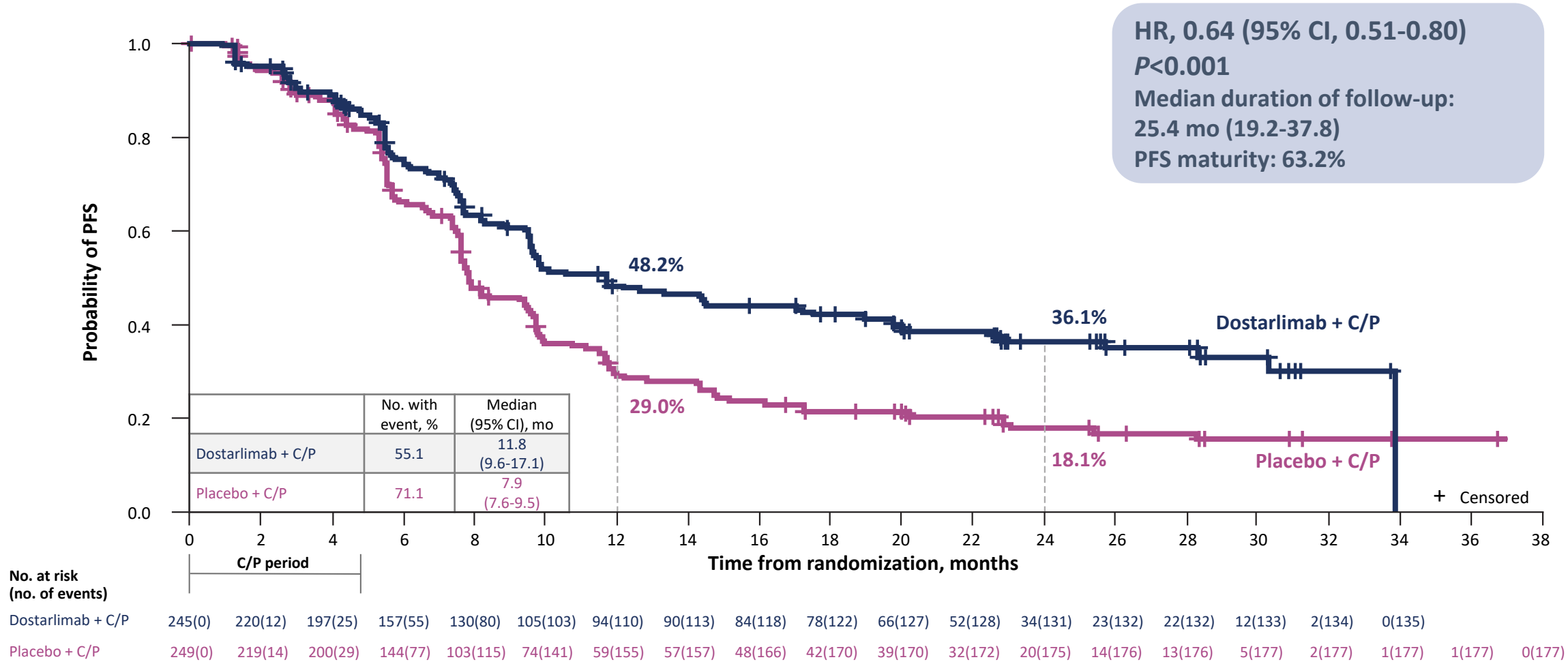
Adapted from Mirza MR, et al. *N Engl J Med*. 2023;388:2145-2158.

CI = confidence interval; C/P = carboplatin and paclitaxel; dMMR = mismatch repair deficient; HR = hazard ratio; mo = months; MSI-H = microsatellite instability-high; NE = not estimable; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours version 1.1.

1. Mirza MR, et al. *N Engl J Med*. 2023;388:2145-2158. 2. Mirza MR, et al. *Ann Oncol.* 2023;34:500-501.

Primary end point: PFS by investigator per RECIST v1.1[1,2]

Overall population (dMMR/MSI-H and MMRp/MSS)



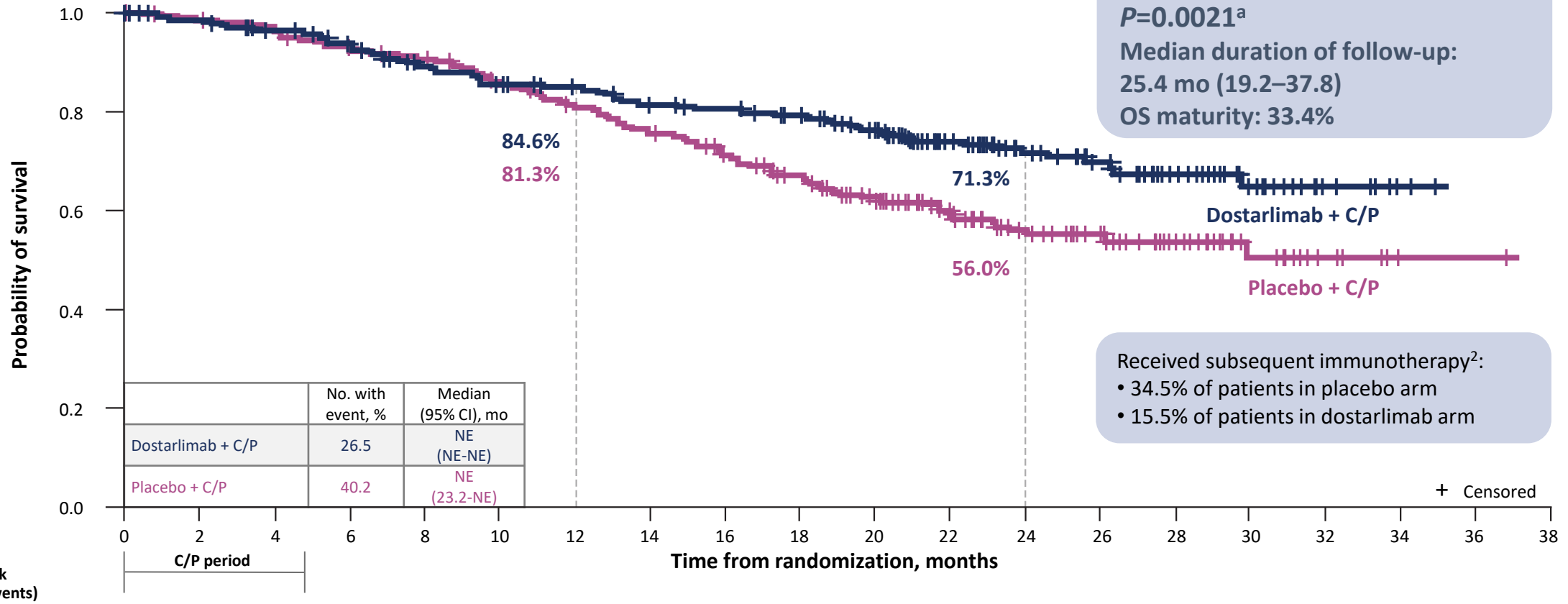
Adapted from Mirza MR, et al. *N Engl J Med*. 2023;388:2145-2158.

CI = confidence interval; C/P = carboplatin and paclitaxel; dMMR = mismatch repair deficient; HR = hazard ratio; MMRp= mismatch repair proficient; mo = months; MSI-H = microsatellite instability-high; MSS = microsatellite stable; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours version 1.1.

1. Mirza MR, et al. *N Engl J Med*. 2023;388:2145-2158. 2. Mirza MR, et al. *Ann Oncol.* 2023;34:500-501.

Primary end point: OS in overall population[1,2]

Overall population (dMMR/MSI-H and MMRp/MSS)



Received subsequent immunotherapy[2]:
- 34.5% of patients in placebo arm
- 15.5% of patients in dostarlimab arm

Adapted from Mirza MR, et al. *N Engl J Med*. 2023;388:2145-2158.

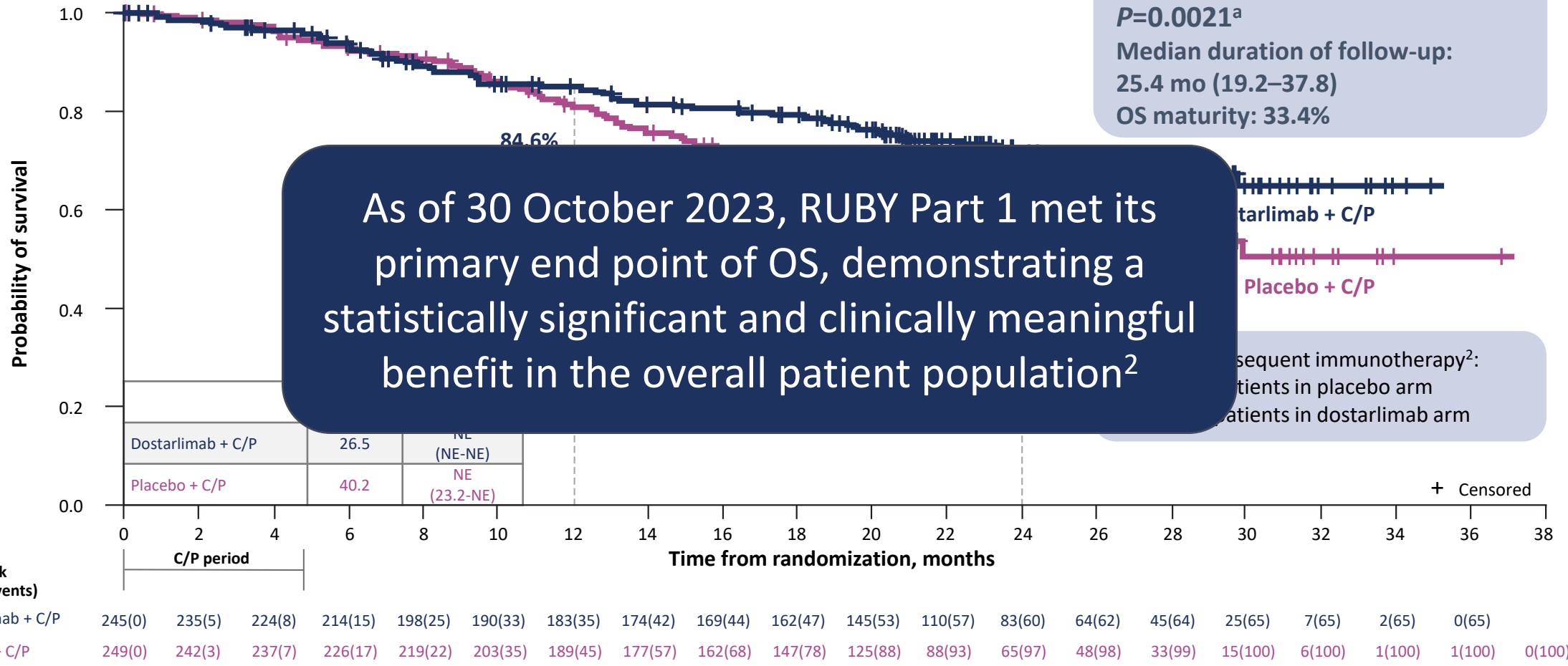
[a]*P*≤0.00177 required to declare statistical significance at first interim analysis.

CI = confidence interval; C/P = carboplatin and paclitaxel; dMMR = mismatch repair deficient; HR = hazard ratio; MMRp = mismatch repair proficient; mo = months; MSI-H = microsatellite instability-high; MSS = microsatellite stable; NE = not estimable; OS = overall survival.

1. Mirza MR, et al. *N Engl J Med*. 2023;388:2145-2158. 2. Mirza MR, et al. *Ann Oncol.* 2023;34:500-501.

Primary end point: OS in overall population[1,2]

Overall population (dMMR/MSI-H and MMRp/MSS)



Adapted from Mirza MR, et al. *N Engl J Med*. 2023;388:2145-2158.

[a]*P*≤0.00177 required to declare statistical significance at first interim analysis.

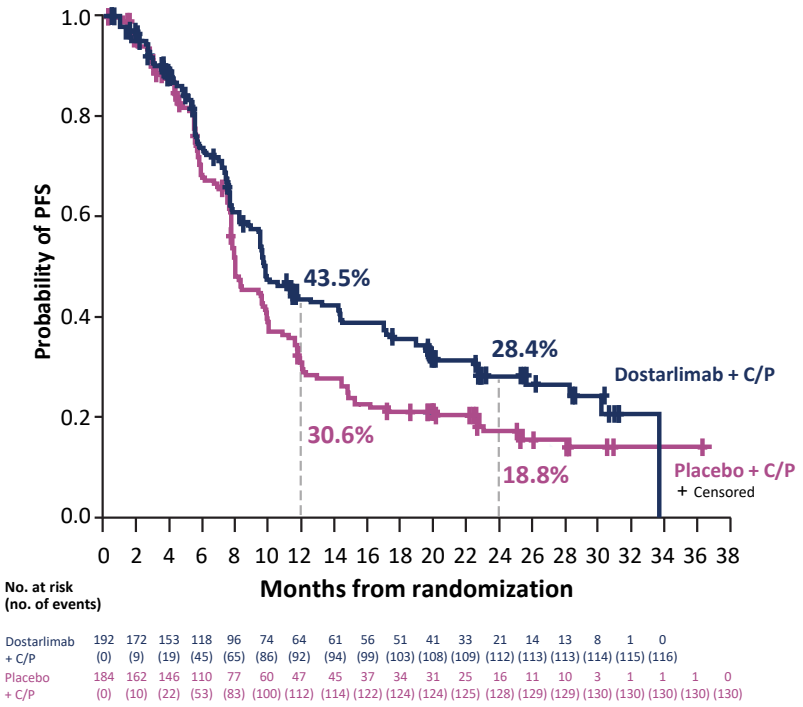
CI = confidence interval; C/P = carboplatin and paclitaxel; dMMR = mismatch repair deficient; HR = hazard ratio; MMRp = mismatch repair proficient; mo = months; MSI-H = microsatellite instability-high; MSS = microsatellite stable; NE = not estimable; OS = overall survival.

1. Mirza MR, et al. *N Engl J Med*. 2023;388:2145-2158. 2. Mirza MR, et al. *Ann Oncol.* 2023;34:500-501. 2. GSK. Phase III RUBY trial of Jemperli (dostarlimab) plus chemotherapy meets end point of overall survival in patients with primary advanced or recurrent endometrial cancer. https://www.gsk.com/en-gb/media/press-releases/phase-iii-ruby-trial-of-jemperli-dostarlimab-plus-chemotherapy-meets-endpoint-of-overall-survival-in-patients-with-primary-advanced-or-recurrent-endometrial-cancer. Accessed October 30, 2023.

Sustained and consistent long-term benefit across multiple efficacy end points in MMRp/MSS patients[1]

PFS

HR, 0.76
(95% CI, 0.59-0.98)

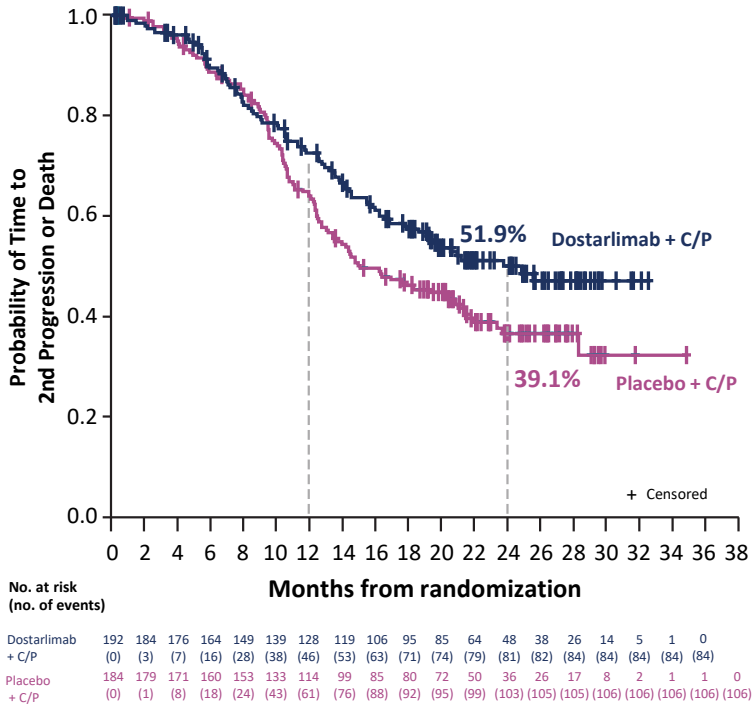


No. at risk (no. of events)

Dostarlimab + C/P	192 (0)	172 (9)	153 (19)	118 (45)	96 (65)	74 (86)	64 (92)	61 (94)	56 (99)	51 (103)	41 (108)	33 (109)	21 (112)	14 (113)	13 (113)	8 (114)	1 (115)	0 (116)	
Placebo + C/P	184 (0)	162 (10)	146 (22)	110 (53)	77 (83)	60 (100)	47 (112)	45 (114)	37 (122)	34 (124)	31 (124)	25 (125)	16 (128)	11 (129)	10 (129)	3 (130)	1 (130)	1 (130)	0 (130)

PFS2

HR, 0.71
(95% CI, 0.54-0.95)

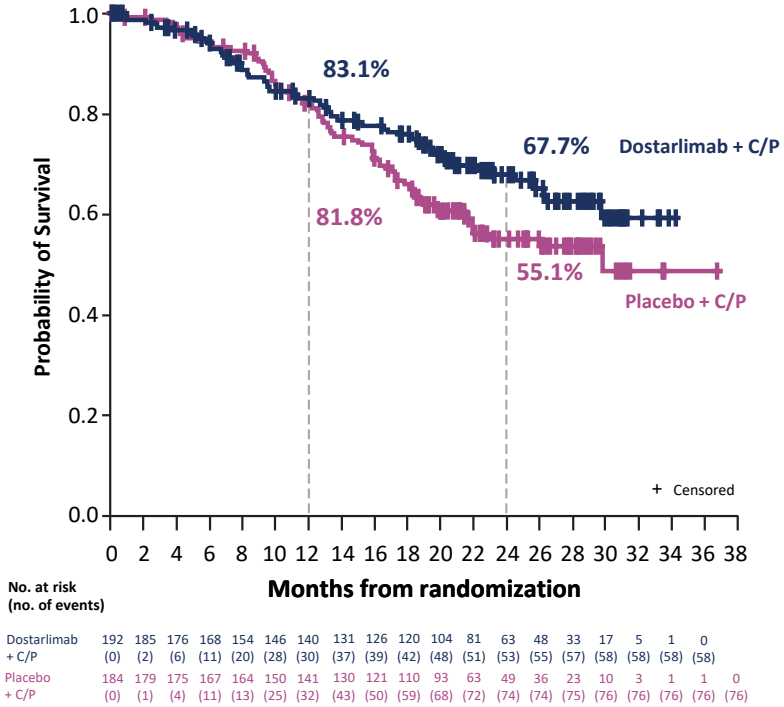


No. at risk (no. of events)

Dostarlimab + C/P	192 (0)	184 (3)	176 (7)	164 (16)	149 (28)	139 (38)	128 (46)	119 (53)	106 (63)	95 (71)	85 (74)	64 (79)	48 (81)	38 (82)	26 (84)	14 (84)	5 (84)	1 (84)	0 (84)
Placebo + C/P	184 (0)	179 (1)	171 (8)	160 (18)	153 (24)	133 (43)	114 (61)	99 (76)	85 (88)	80 (92)	72 (95)	50 (99)	36 (103)	26 (105)	17 (105)	8 (106)	2 (106)	1 (106)	0 (106)

OS

HR, 0.73
(95% CI, 0.52-1.02)



No. at risk (no. of events)

Dostarlimab + C/P	192 (0)	185 (2)	176 (6)	168 (11)	154 (20)	146 (28)	140 (30)	131 (37)	126 (39)	120 (42)	104 (48)	81 (51)	63 (53)	48 (55)	33 (57)	17 (58)	5 (58)	1 (58)	0 (58)
Placebo + C/P	184 (0)	179 (1)	175 (4)	167 (11)	164 (13)	150 (25)	141 (32)	130 (43)	121 (50)	110 (59)	93 (68)	63 (72)	49 (74)	36 (74)	23 (75)	10 (76)	3 (76)	1 (76)	0 (76)

Adapted from Mirza MR, et at. *N Engl J Med.* 2023;388:2145-2158.

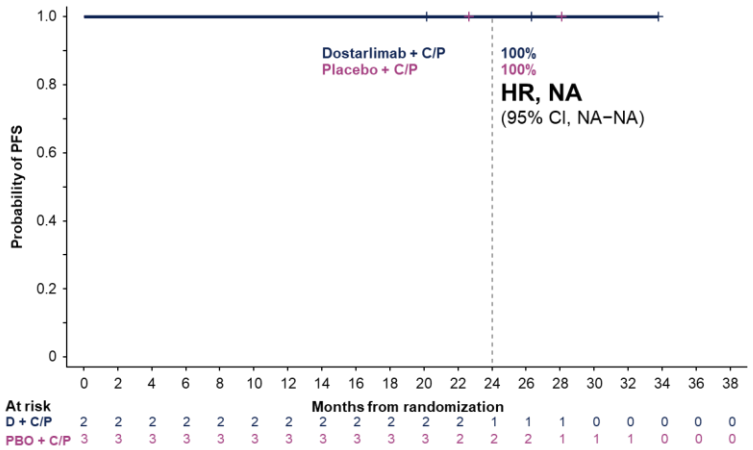
CI = confidence interval; C/P = carboplatin/paclitaxel; HR = hazard ratio; MMRp = mismatch repair proficient; MSS = microsatellite stable; PFS = progression-free survival; PFS2 = progression-free survival 2; OS = overall survival.

1. Mirza MR, et al. *N Engl J Med* 2023;388:2145-2158.

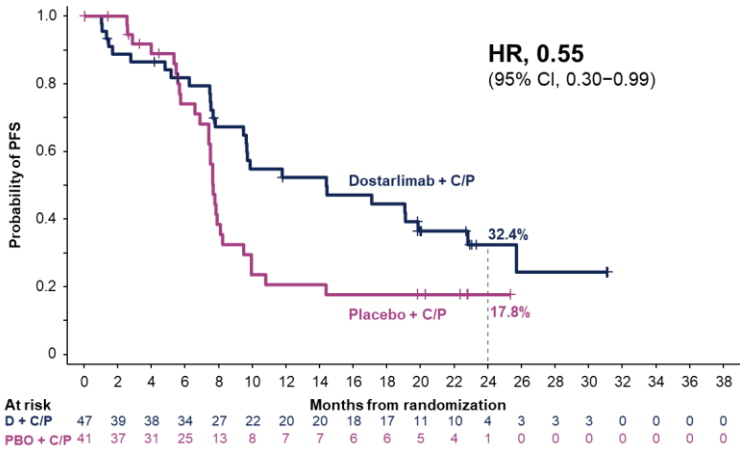
RUBY Part 1: PFS according to molecular subgroup

Based on 400/494 patients with known molecular classification per whole exome sequencing

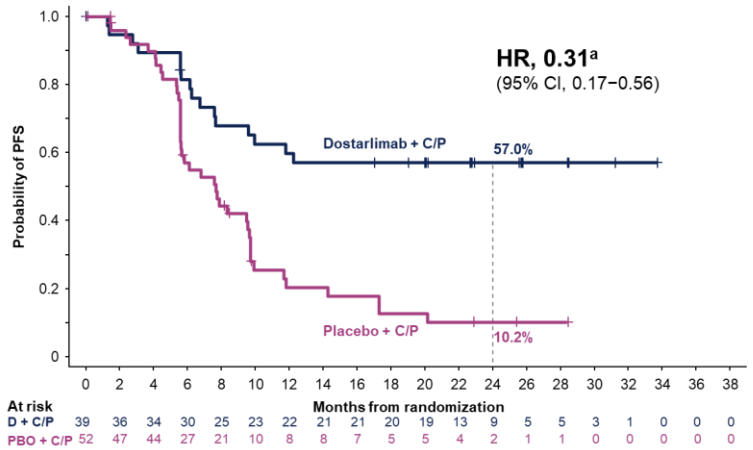
***POLE*mut**



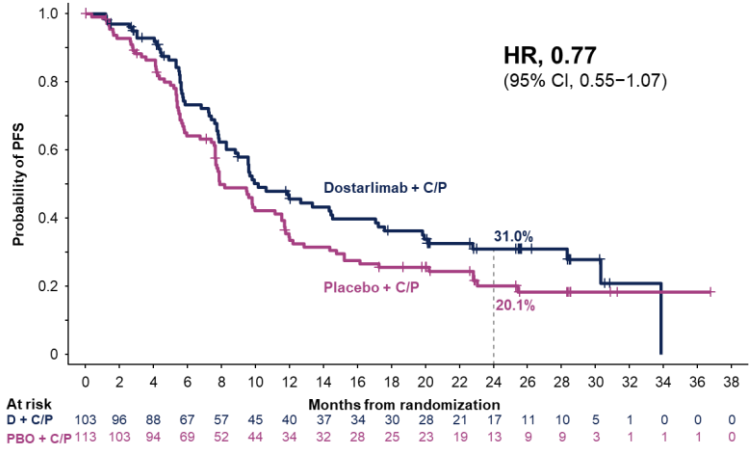
***TP53*mut**



dMMR/MSI-H



NSMP



Adapted from Mirza MR, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #740MO.

[a]Primary end point of PFS in dMMR/MSI-H patients (n=118) showed HR, 0.28; *P*<0.0001.

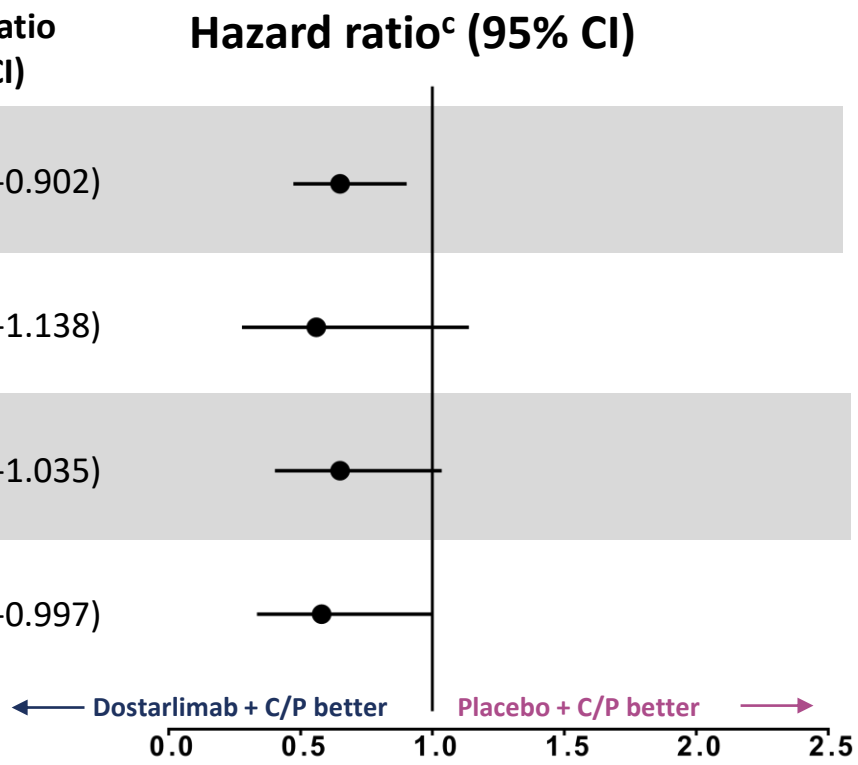
CI = confidence interval; C/P = carboplatin/paclitaxel; dMMR = mismatch repair deficient; HR = hazard ratio; MSI-H = microsatellite instability–high; mut = mutated; NA = not applicable; NSMP = no specific molecular profile; PFS = progression-free survival; POLε = polymerase epsilon; TP53 = tumor protein 53.

Mirza MR, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #740MO.

RUBY Part 1: PFS according to histological subgroups (ITT)[a]

Consistent benefit across histologic subtypes in the overall population

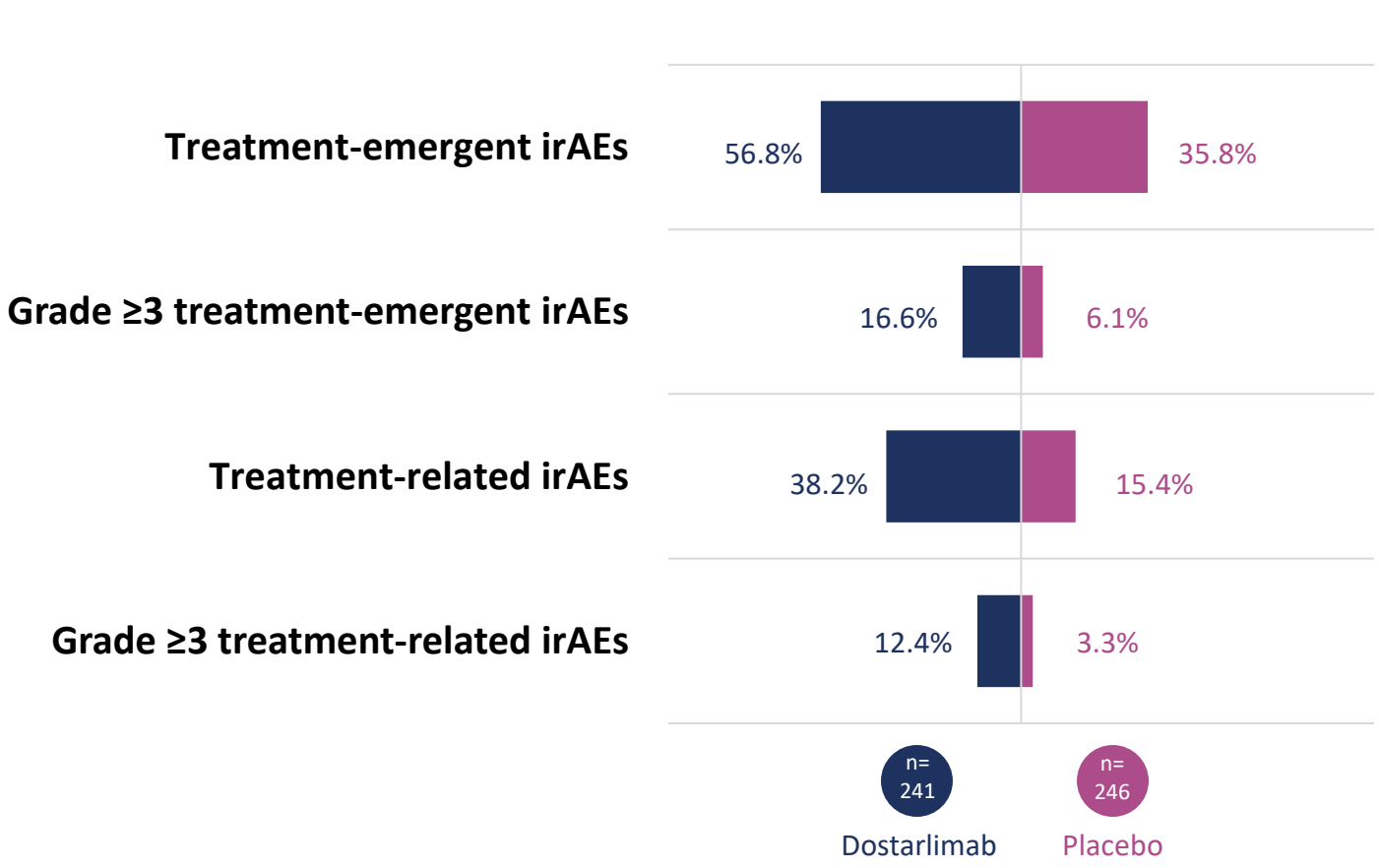
Histology	Dostarlimab + C/P (No. of events/no. of patients)	Placebo + C/P (No. of events/no. of patients)	Hazard ratio (95% CI)
Endometrioid carcinoma	64/130	89/136	0.65 (0.473-0.902)
Carcinosarcoma[b]	14/24	18/22	0.56 (0.278-1.138)
Serous adenocarcinoma	36/55	35/48	0.65 (0.403-1.035)
Other	21/36	35/43	0.58 (0.335-0.997)



Adapted from Mirza MR, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20–24, 2023; Madrid, Spain; Presentation #740MO.

[a]Data based on exploratory analysis by histological subgroups with more than 10 patients per treatment arm (overall population). [b]Total number of patients with carcinosarcoma was capped at approximately 10% of overall patient population. [c]Hazard ratios are based on unstratified Cox regression model.
CI = confidence interval; C/P = carboplatin/paclitaxel; ITT = intention to treat; PFS = progression-free survival.
Mirza MR, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20–24, 2023; Madrid, Spain; Presentation #740MO

RUBY Part 1 | Immune-related adverse events in the overall population

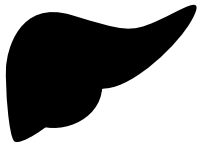


Any treatment-related irAE ≥5%

Arthralgia
5.8%
6.5%

Hypothyroidism
11.2%
2.8%

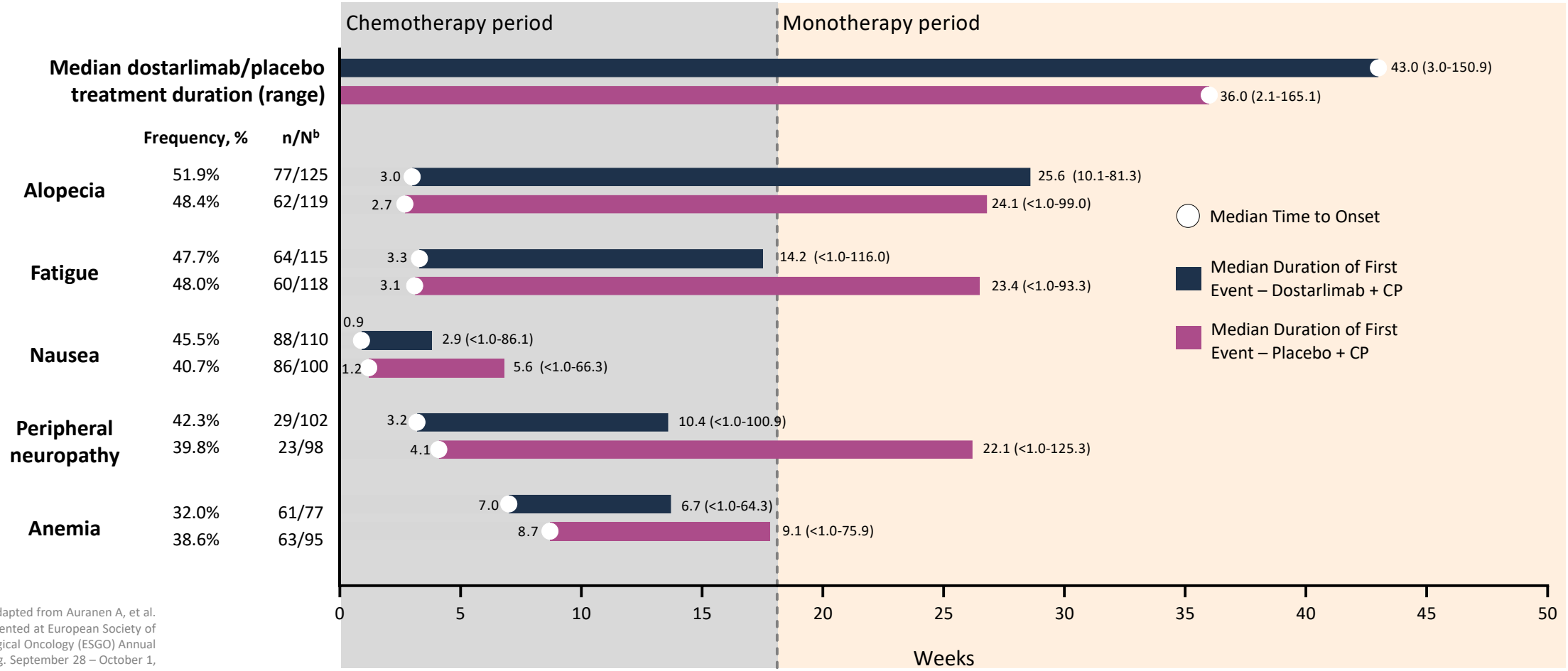
Rash
6.6%
2.0%



ALT increased
5.8%
0.8%

ALT = alanine aminotransferase; irAE = immune-related adverse event.
Mirza MR et al. *N Engl J Med* 2023; 388:2145-2158.

RUBY: Onset and duration of the most frequent TRAEs[a]

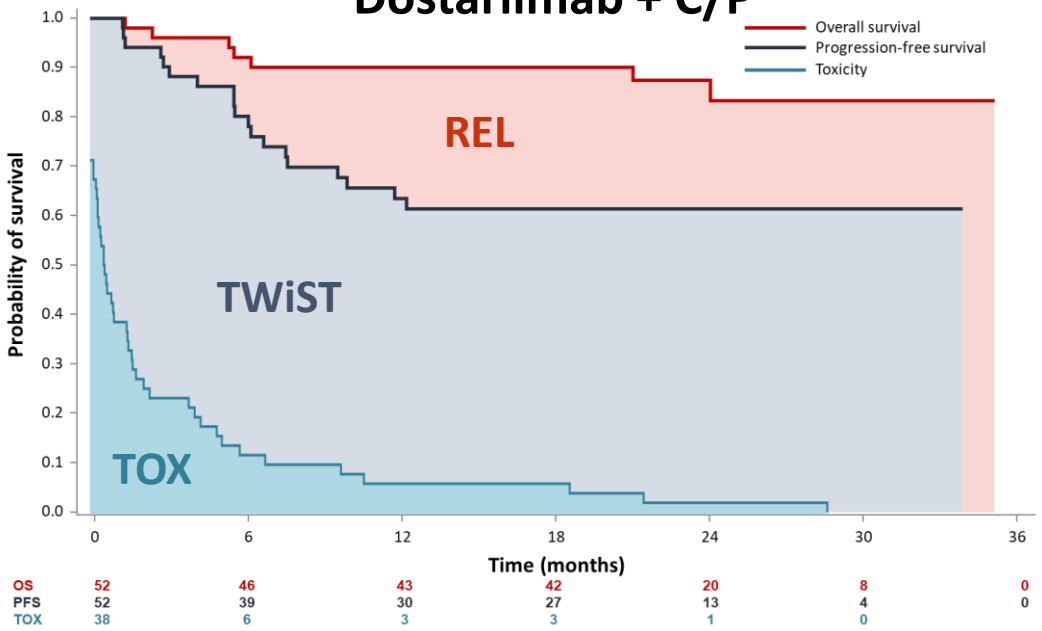


Adapted from Auranen A, et al. Presented at European Society of Gynecological Oncology (ESGO) Annual Meeting. September 28 – October 1, 2023; Istanbul, Türkiye; Poster #540.

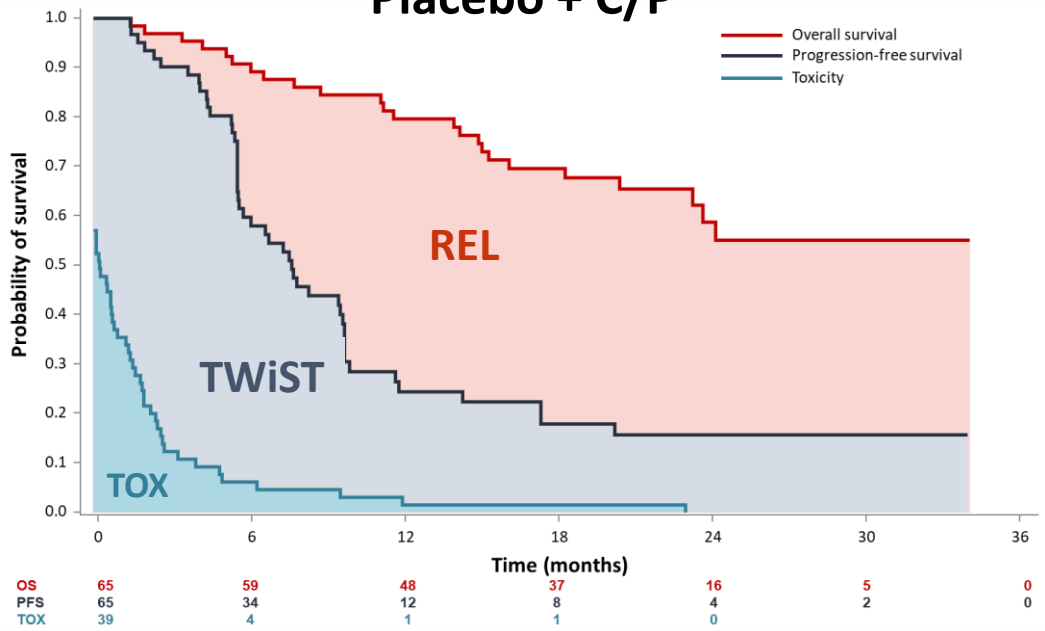
[a]TRAEs occurring in >30% in either arm. [b]n/N represents the number of patients with duration data over the number of patients with onset data.
The duration is defined as time from onset of any AE considered in this analysis to the first time the subject is free of any such event. It requires at least one day gap between the resolution of all events from first course to the onset of second course.
AE = adverse event; C/P = carboplatin/paclitaxel; TRAE = treatment-related adverse event.
Auranen A, et al. Presented at European Society of Gynecological Oncology (ESGO) Annual Meeting. September 28 – October 1, 2023; Istanbul, Türkiye; Poster #540.

RUBY Part 1: Significant increase in Q-TWiST with dostarlimab plus C/P in the dMMR/MSI-H population

Dostarlimab + C/P



Placebo + C/P



	TOX	TWiST	REL	Q-TWiST
Difference, months (95% CI)	**0.97** (−0.01 to 1.89), *P*<0.001[a]	**3.79** (1.43 to 6.01), *P*<0.001[a]	**2.72** (−0.63 to 5.73), *P*<0.001[a]	**5.44** (1.93 to 8.59), *P*<0.001[a]
D + C/P, months	3.19	11.67	16.60	22.67
PBO + C/P, months	2.22	7.89	13.88	17.23

Relative Q-TWiST gain of 21.99%[b]

Adapted from Chase DM, et al. Presented at European Society of Gynecological Oncology (ESGO) Annual Meeting. September 28 – October 1, 2023; Istanbul, Türkiye: Presentation #267

The relapse and the TWiST curves are Kaplan-Meier plots; the toxicity curve represents a step-down function describing the proportion of toxicity events over time.
[a]All results are nominal and not adjusted for multiple testing. [b]Calculated as the absolute difference divided by restricted mean survival time of OS in the placebo arm (5.44/24.74 months).
CI = confidence interval; C/P = carboplatin/paclitaxel; D = dostarlimab; dMMR = mismatch repair deficient; MSI-H = microsatellite instability–high; OS = overall survival; PBO = placebo; PFS = progression-free survival; Q-TWiST = quality-adjusted time without symptoms of disease progression or toxicity; REL = relapse; TOX = toxicity; TWiST = time without symptoms of disease progression or toxicity.
Chase DM, et al. Presented at European Society of Gynecological Oncology (ESGO) Annual Meeting. September 28 – October 1, 2023; Istanbul, Türkiye: Presentation #267.

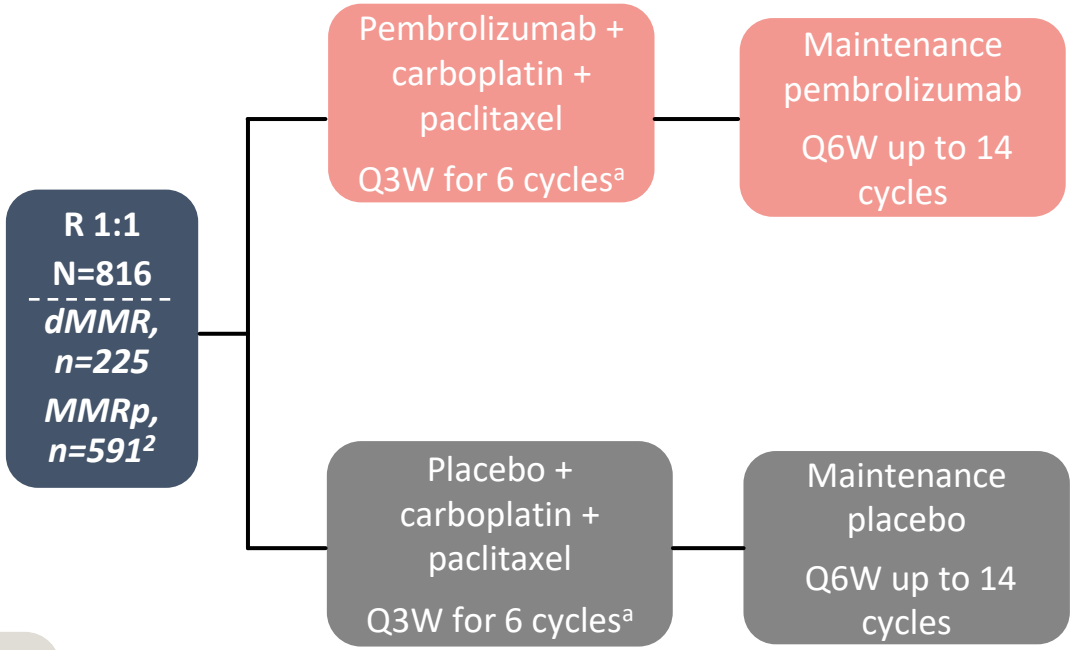
NRG-GY018 | NCT03914612[1,2]

Eligible patients:

- Histologically confirmed recurrent or advanced (stage III, IVA, or IVB) EC
- Performance status 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 prior to enrollment

Stratification:[2]

- MMR status
- Performance status (0 and 1-2)
- Prior chemotherapy (yes/no)



Primary end point: PFS per IA

Select secondary end points: AEs, ORR, DOR, OS, QOL, association between PD-L1 and MMR status, concordance between institutional MMR IHC and centralized MMR IHC

Start date: July 16, 2019

Status: Active, not recruiting

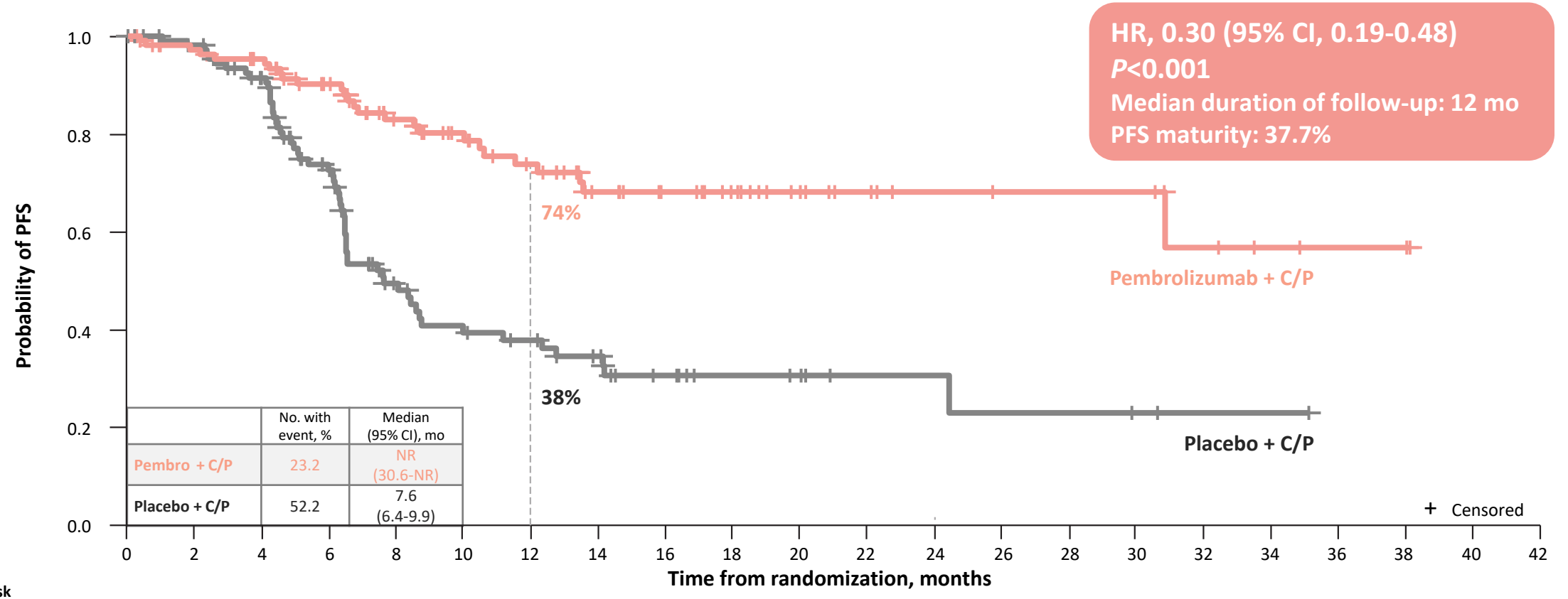
[a]Patients with SD or PR who still have measurable disease may continue treatment for up to a total of 10 cycles (if deemed necessary by the treating physician) in the absence of disease progression or unacceptable toxicity.

AE = adverse events; dMMR = mismatch repair deficient; DOR = duration of response; EC = endometrial cancer; IA = investigator assessment; IHC = immunohistochemistry; MMR = mismatch repair; MMRp = mismatch repair proficient; ORR = objective response rate; OS = overall survival; PD-L1 = programmed cell death-ligand 1; PFS = progression-free survival; PR = partial response; QOL = quality of life; QxW = every x weeks; R = randomized; SD = stable disease.

1. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03914612. Accessed May 17, 2023. 2. Eskander R et al. *N Engl J Med* 2023;388:2159-2170.

GY018 primary end point: PFS by investigator per RECIST v1.1

dMMR population[1-3]



No. at risk (no. of events)

Placebo + C/P	113(2)	62(24)	24(35)	8(47)	4(51)	2(52)	0(54)	
Pembro + C/P	112(1)	80(22)	44(46)	22(65)	9(78)	8(79)	2(84)	0(86)

Adapted from Eskander RN, et al. *N Engl J Med*. 2023;388:2159-2170.

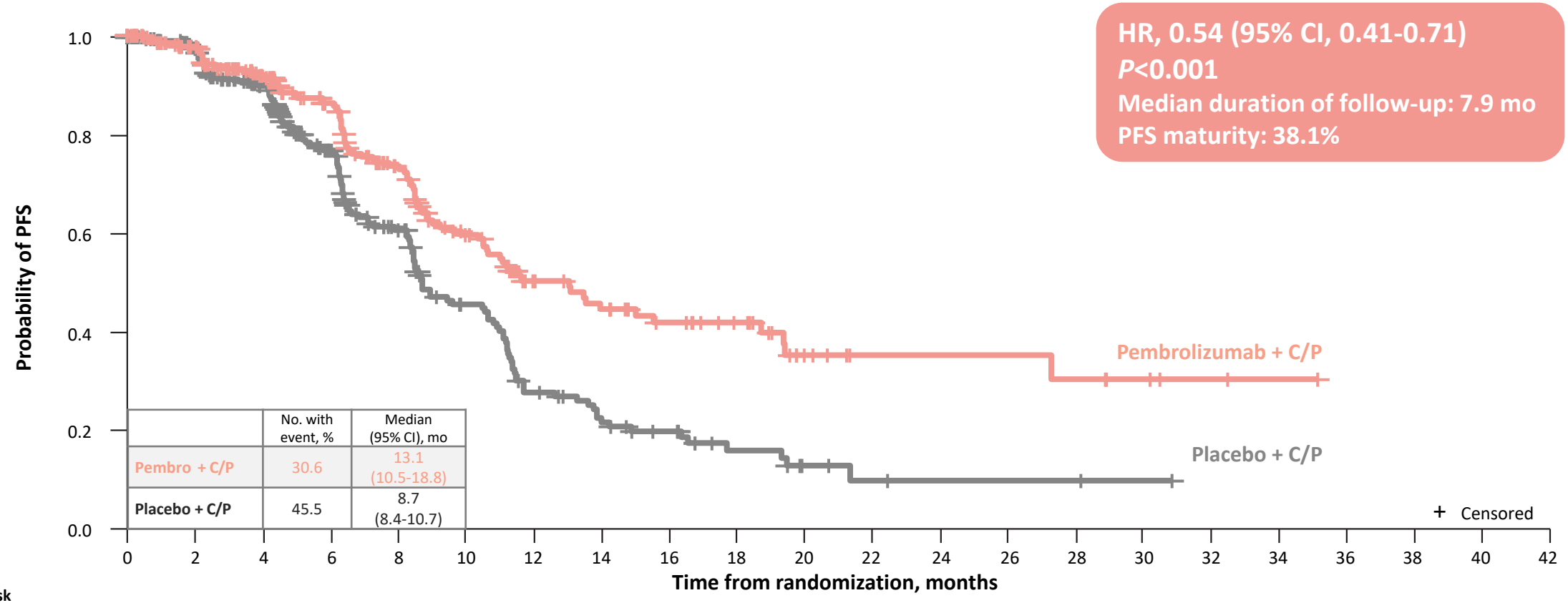
Data cutoff date: December 16, 2022.

CI = confidence interval; C/P = carboplatin and paclitaxel; dMMR = mismatch repair deficient; HR = hazard ratio; NR = not reached; Pembro = pembrolizumab; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

1. Eskander RN, et al. *N Engl J Med*. 2023;388:2159-2170. 2. Eskander RN, et al. Presented at: SGO; March 25-28 2023; Tampa, FL, USA. 3. Arend RC, et al. Presented at: SGO; March 25-28, 2023; Tampa, FL, USA.

GY018 primary end point: PFS by investigator per RECIST v1.1

MMRp population[1-3]



No. at risk (no. of events)

Placebo + C/P	292(14)	129(115)	33(141)	10(152)	2(157)	1 (158)	0(159)
Pembro + C/P	290(15)	150(112)	45(167)	20(185)	7(195)	3(198)	0(201)

Adapted from Eskander RN, et al. *N Engl J Med*. 2023;388:2159-2170.

Data cutoff date: December 16, 2022.

CI = confidence interval; C/P = carboplatin and paclitaxel; HR = hazard ratio; MMRp = mismatch repair proficient; NR = not reached; Pembro = pembrolizumab; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

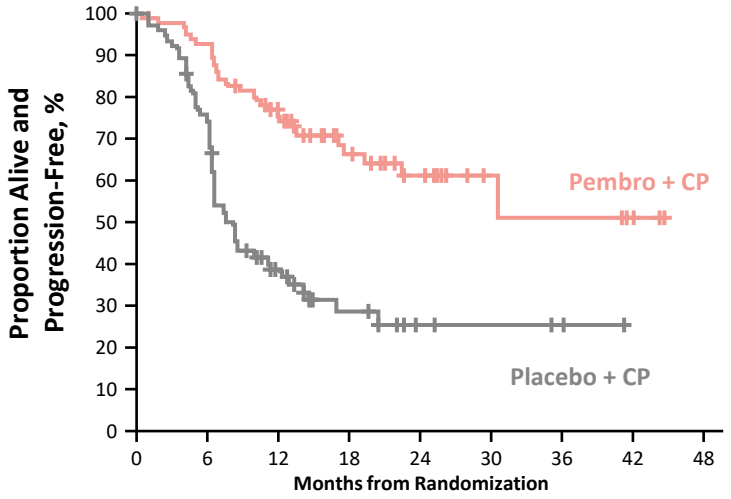
1. Eskander RN, et al. *N Engl J Med*. 2023;388:2159-2170. 2. Eskander RN, et al. Presented at: SGO; March 25-28 2023; Tampa, FL, USA. 3. Arend RC, et al. Presented at: SGO; March 25-28, 2023; Tampa, FL, USA.

GY018: PFS by methylation status in the dMMR population

No difference in PFS was identified in patients with dMMR EC based on mechanism of MMR loss

Methylation
Pembro + CP vs Placebo + CP

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

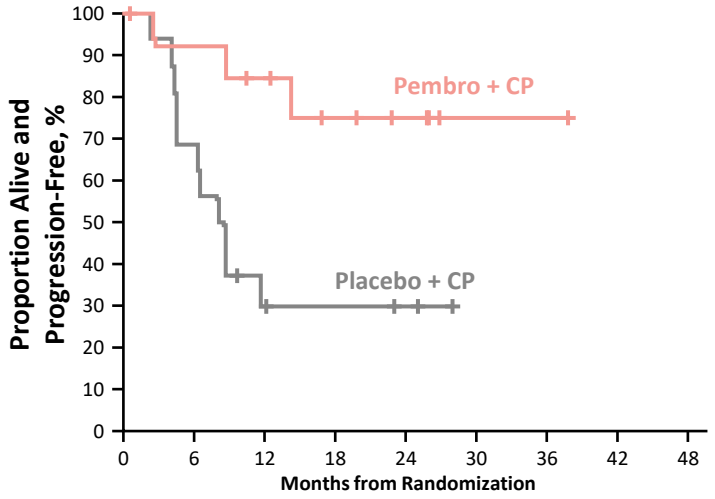


Number at risk (Cumulative number censored)

Placebo + CP	77 (2)	55 (3)	23 (9)	11 (16)	4 (22)	3 (23)	2 (24)	0 (26)
Pembro + CP	83 (0)	76 (1)	56 (7)	30 (28)	18 (38)	6 (50)	5 (50)	3 (52)	0 (55)

No Methylation
Pembro + CP vs Placebo + CP

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

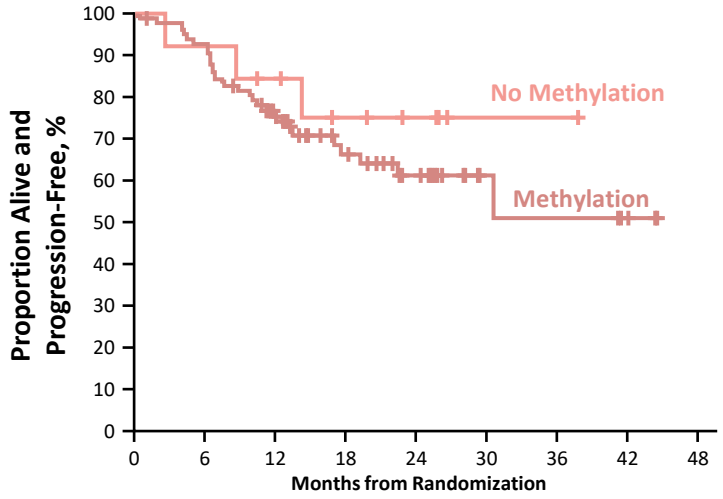


Number at risk (Cumulative number censored)

Placebo + CP	17 (0)	11 (1)	4 (2)	3 (3)	2 (4)	0 (6)		
Pembro + CP	13 (0)	12 (0)	10 (1)	6 (4)	4 (6)	1 (9)	1 (9)	0 (10)

Methylation Status
Pembro + CP Arm

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



Number at risk (Cumulative number censored)

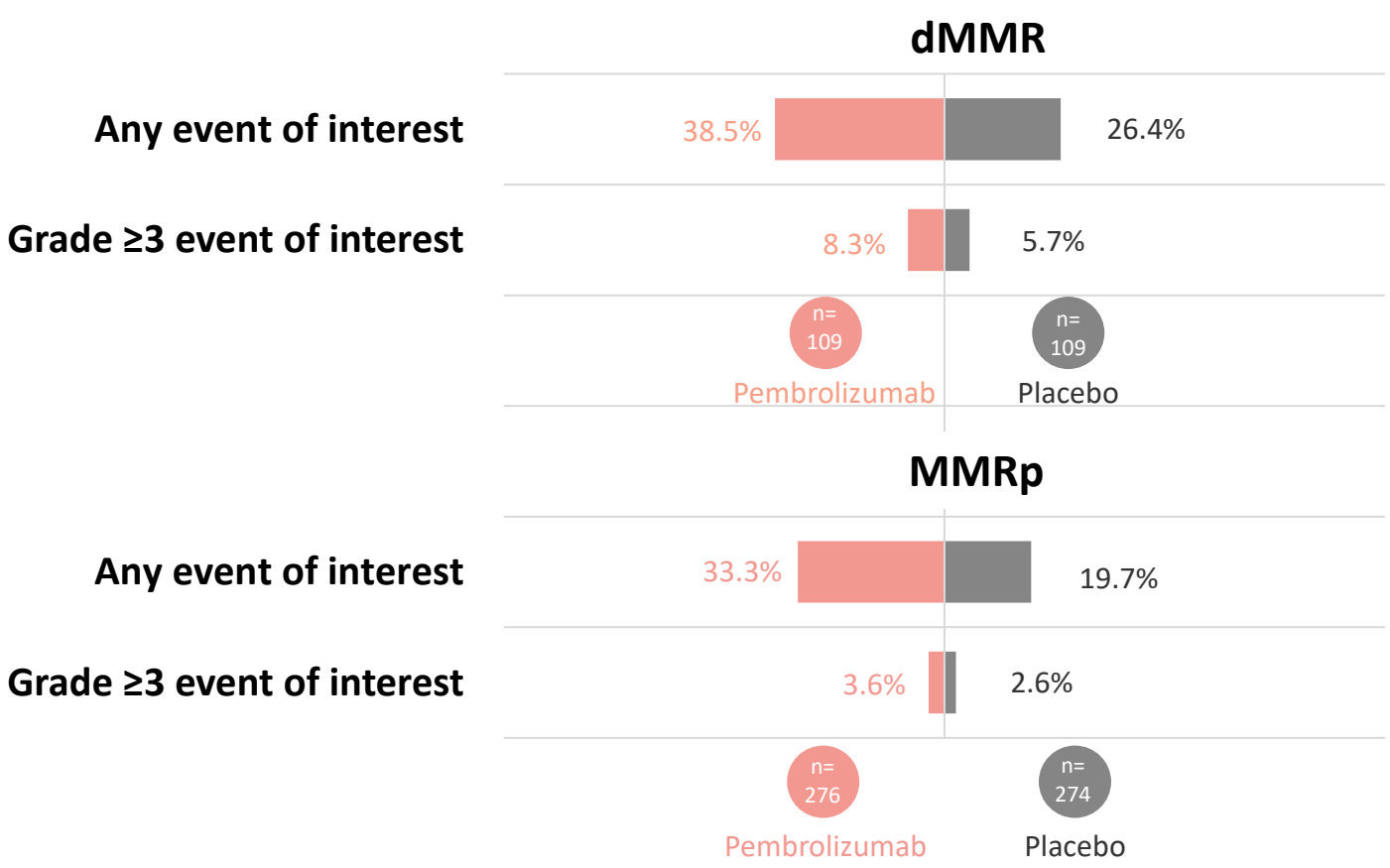
No Methylation	13 (0)	12 (0)	10 (1)	6 (4)	4 (6)	1 (9)	1 (9)	0 (10)	
Methylation	83 (0)	76 (1)	56 (7)	30 (28)	18 (38)	6 (50)	5 (50)	3 (52)	0 (55)

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

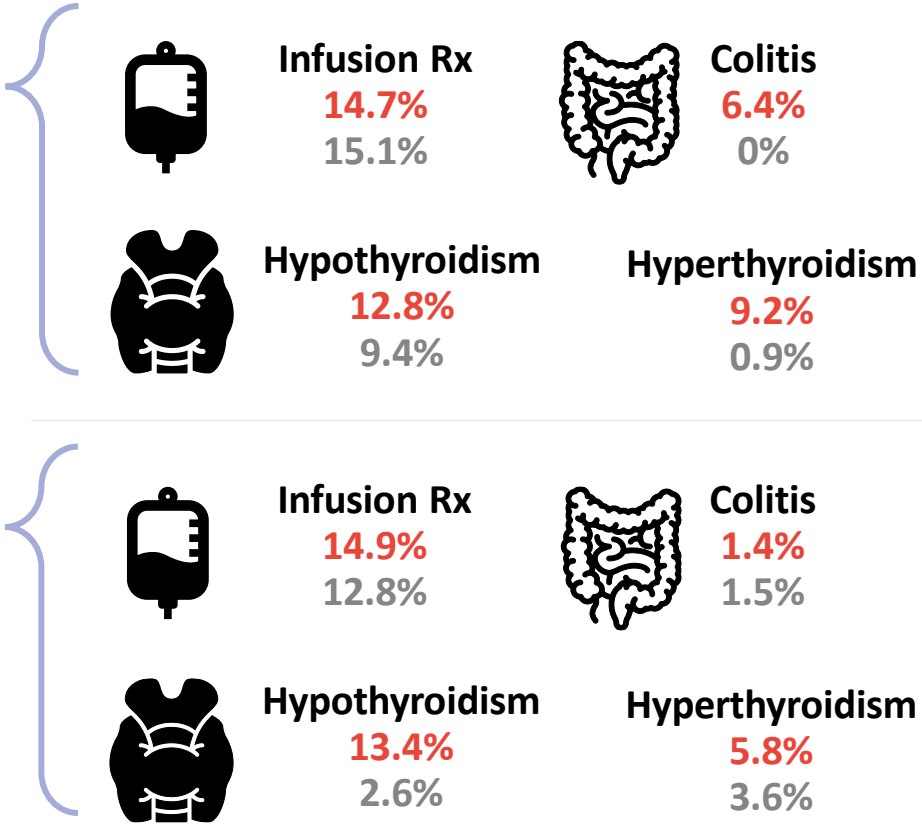
CP = carboplatin/paclitaxel; dMMR = mismatch repair deficient; MMR = mismatch repair; PFS = progression-free survival; OS = overall survival.
Data cut off date, August 18, 2023.

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

NRG-GY018 | Adverse events of interest in the dMMR and MMRp populations[a]



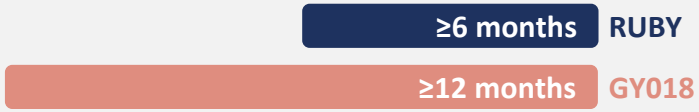
Adverse events of interest ≥5%



[a]Listed are AEs with a rounded incidence of at least 5% in all the patients in either trial group, according to preferred term. The events of interest are those with a possible immune-related cause and are considered regardless of attribution by the investigator. Some patients may have had more than one AE of interest.
AE = adverse event; dMMR = mismatch repair deficient; MMRp = mismatch repair proficient; Rx = reaction.
Eskander RN et al. *N Engl J Med* 2023; 388:2159-2170

RUBY Part 1 and NRG-GY018 | Key differences in study design[1-4]

Time since chemotherapy for recurrent disease



ECOG PS

RUBY	GY018
0-1	0-2

Histology – carcinosarcoma

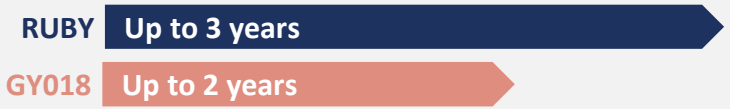
RUBY	GY018
~10%	Not included

Primary end points

RUBY	PFS by INV (dMMR/MSI-H and ITT), OS (ITT)
GY018	PFS by INV (dMMR and MMRp)

Chemotherapy duration

IO treatment duration



QOL measurement

	Instruments used	Assessed population
RUBY	EORTC QLQ-C30, EORTC QLQ-EN24, EQ-5D-5L	dMMR/MSI-H and ITT
GY018	FACT-En-TOI, FACT-GOG-NTX, PROMIS, single-item survey	MMRp[a]

There are no completed direct head-to-head trials of these products in EC. There are inherent limitations in cross-study comparisons; caution should be exercised in comparing trials. This slide is for information purposes only and is not intended to imply or infer the noninferiority or superiority of any product, in terms of efficacy or safety.

[a]Treatment information was unblinded February 3, 2023, and patients were asked to continue to complete PRO and QoL questionnaires.

dMMR = mismatch repair deficient; EC = endometrial cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC = European Organization for Research and Treatment of Cancer; EQ-5D-5L = European Quality of Life scale, 5-dimension, 5 level; FACT-En-TOI = Trial Outcome Index of the Functional Assessment of Cancer Therapy – Endometrial; FACT-GOG-NTX = Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity subscale; INV = Investigator assessed; IO = immuno-oncology; ITT = intention to treat; MMRp = mismatch repair proficient; MSI-H = microsatellite instability-high; OS = overall survival; PFS = progression free survival; PRO = patient reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; QLQ-C30 = Quality of Life Questionnaire Core 30; QLQ-EN24 = Quality of Life Questionnaire-Endometrial Cancer Module; QoL = quality of life.

1. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03981796. Accessed August 23, 2023. 2. Mirza MR, et al. *N Engl J Med.* 2023; 388:2145-2158. 3. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03914612. Accessed August 23, 2023. 4. Eskander RN, et al. *N Engl J Med*. 2023; 388:2159-2170.

RUBY Part 1 and NRG-GY018 | Summary of end points

	RUBY Part 1[1-3] N=494	GY018[3-5] N=816
Assessment	PFS (INV) and OS	PFS
Statistical design	Hierarchical	Two parallel cohorts
Primary end point and hierarchical end points [HR (95% CI); % maturity]	**PFS dMMR/MSI-H: 0.28 (0.16-0.50);** 55.9% maturity **PFS ITT: 0.64 (0.51-0.80);** 63.2% maturity **OS ITT: 0.64 (0.46-0.87);** 33.4% maturity	**PFS dMMR: 0.3 (0.19-0.48);** 37.7% maturity **PFS MMRp: 0.54 (0.41-0.71);** 38.1% maturity
Median duration of follow-up	**dMMR: 24.8 mo; ITT: 25.4 mo**	**dMMR: 12 mo; MMRp: 7.9 mo**
Prespecified subgroups [HR (95% CI)]	**PFS MMRp/MSS: 0.76 (0.59-0.98)** **OS dMMR/MSI-H: 0.30 (0.13-0.70)** **OS MMRp/MSS: 0.73 (0.52-1.02)**	-
Carcinosarcoma, clear cell, or serous histology, %	**33.0**	**23.7 [carcinosarcoma not allowed]**

There are no completed direct head-to-head trials of these products in EC. There are inherent limitations in cross-study comparisons; caution should be exercised in comparing trials. This slide is for information purposes only and is not intended to imply or infer the noninferiority or superiority of any product, in terms of efficacy or safety.

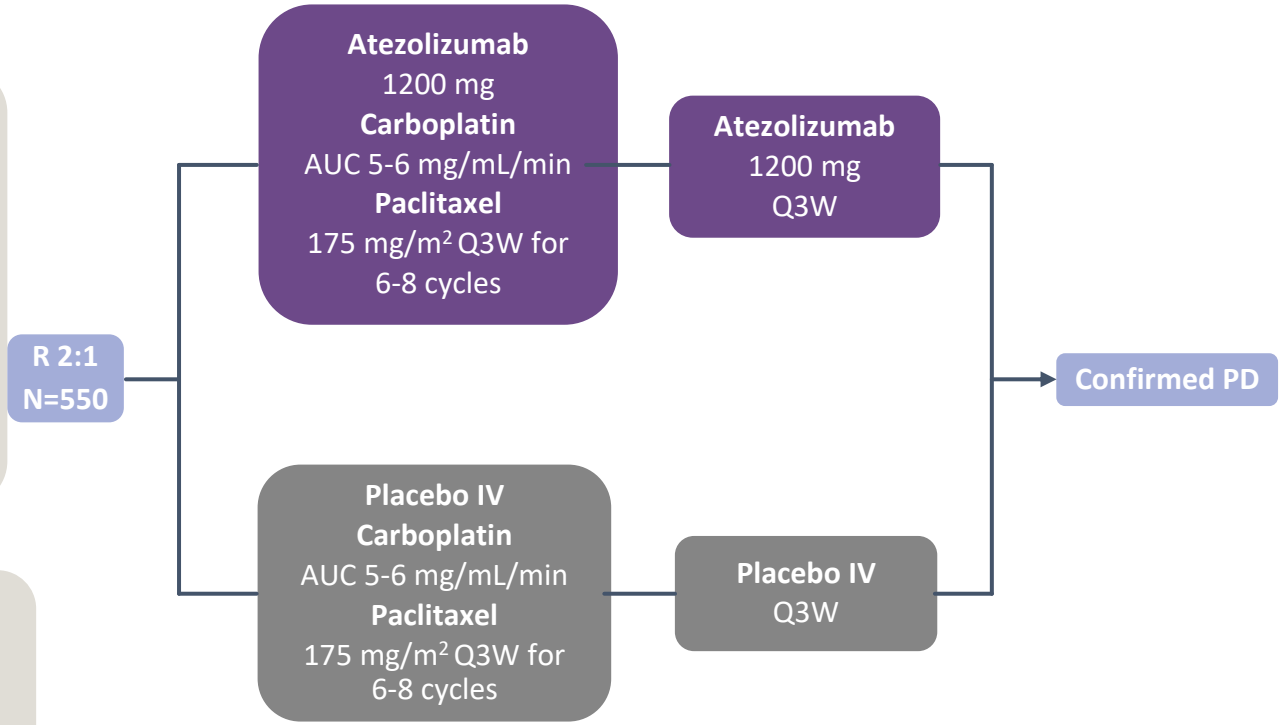
CI = confidence interval; dMMR = mismatch repair deficient; EC = endometrial cancer; HR = hazard ratio; ITT = intention-to-treat; MMRp = mismatch repair proficient; mo = months; MSI-H = microsatellite instability-high; MSS = microsatellite stable; NE = not evaluable; OS = overall survival; PFS = progression free survival.

1. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03981796. Accessed August 23, 2023. 2. Mirza MR, et al. *N Engl J Med*. 2023; 388:2145-2158. 3. Arend RC, et al. Presented at: SGO; March 25-28, 2023; Tampa, FL, USA. 4. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03914612. Accessed August 23, 2023. 5. Eskander RN, et al. *N Engl J Med*. 2023; 388:2159-2170. 6. Eskander RN et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA43.

AtTEnd | ENGOT-en7 | NCT03603184[1,2]

Eligible patients:
- Recurrent or primary advanced (stage III or IV) EC
- ECOG PS 0-2
- Age ≥18 years
- In recurrent patients, 1 prior line of systemic platinum-based regimen allowed with a platinum-free interval of ≥6 months
- Adequate organ and bone marrow function
- Prior RT allowed if completed more than 6 weeks ago

Stratification[2]:
- Country
- Histologic type
- Disease (recurrent and advanced)
- Microsatellite status



Primary end points:
PFS, OS

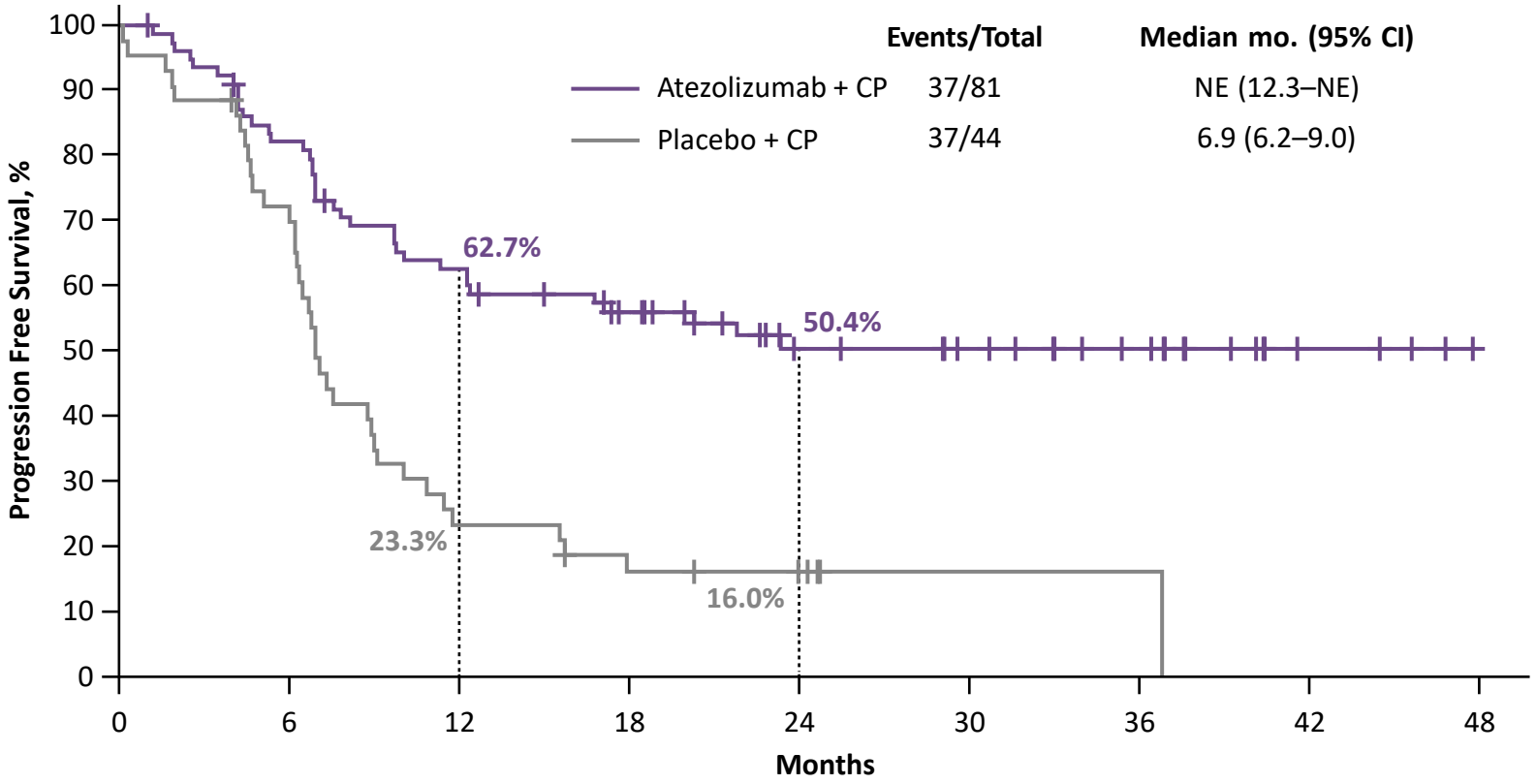
Select secondary end points:
ORR, DOR, safety, HRQoL

Status: Active, not recruiting

AUC = area under the curve; DOR = duration of response; EC = endometrial cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; HRQoL = health-related quality of life; IV = intravenous; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; Q3W = every 3 weeks; R = randomized; RT = radiotherapy.

1. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03603184. Accessed May 17, 2023. 2. Colombo N, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.

AtTEnd primary end point: PFS in dMMR population



Patients at Risk									
Atezolizumab + CP	81	64	48	37	23	20	13	4	0
Placebo + CP	44	31	10	6	4	1	1	0	

Median follow-up
26.2 months

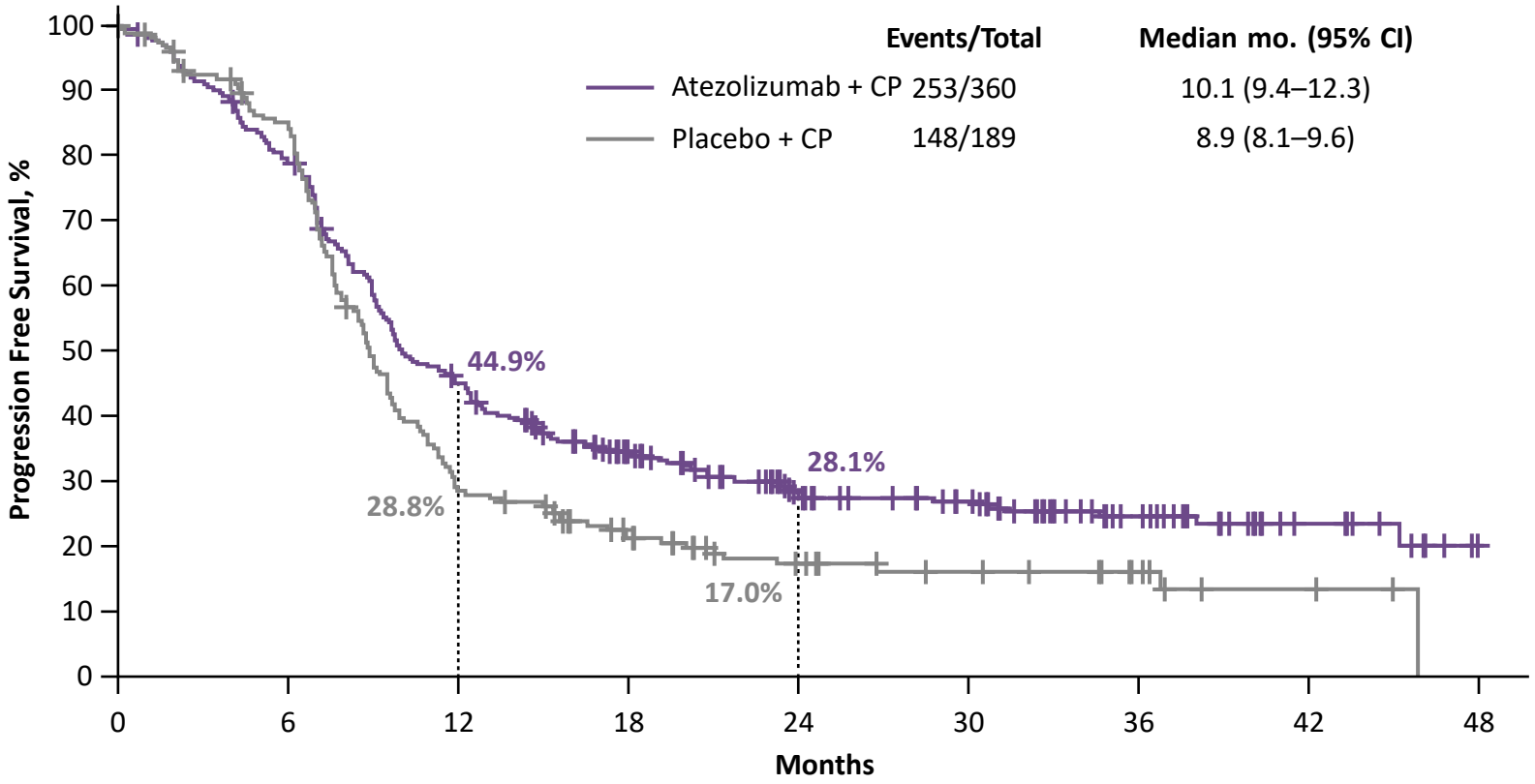
Logrank test
p=0.0005

HR 0.36
95% CI 0.23 to 0.57

Adapted from Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.

CI = confidence interval; CP = carboplatin/paclitaxel; dMMR = mismatch repair deficient; EC = endometrial cancer; HR = hazard ratio; mo = months; PFS = progression free survival.
Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.

AtTEnd primary end point: PFS in ITT population



Median follow-up
28.3 months

Logrank test
p=0.0219

HR 0.74
95% CI 0.61 to 0.91

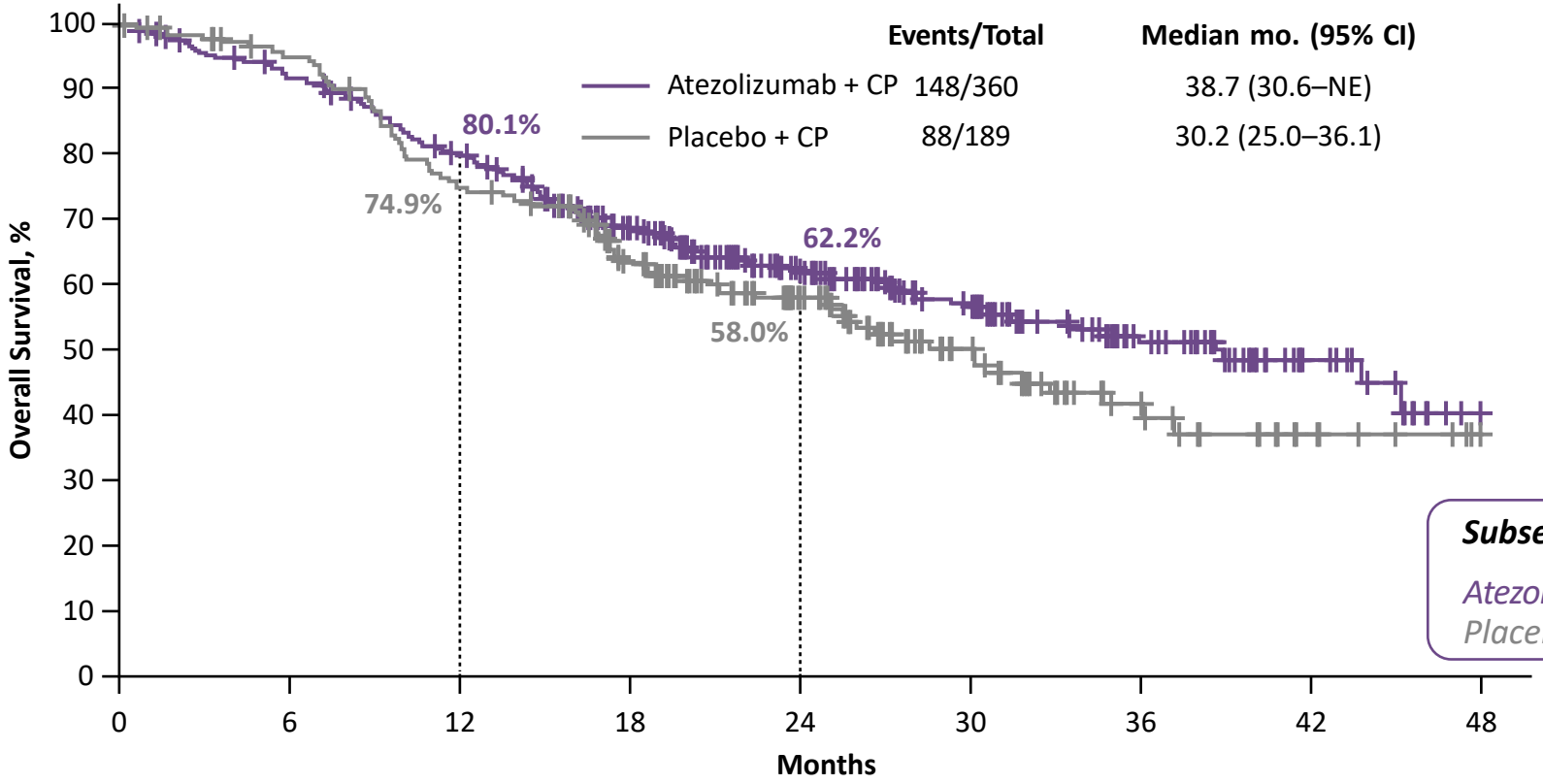
Patients at Risk

Atezolizumab + CP	360	278	155	101	65	53	31	10	2
Placebo + CP	189	152	51	32	19	12	8	3	0

Adapted from Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.

CI = confidence interval; CP = carboplatin/paclitaxel; EC = endometrial cancer; HR = hazard ratio; ITT = intention to treat; mo = months; PFS = progression free survival.
Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.

AtTEnd primary end point: OS in the ITT population



Patients at Risk

Atezolizumab + CP	360	320	273	212	147	104	61	18	3
Placebo + CP	189	171	133	100	70	41	22	8	2

INTERIM ANALYSIS

Data maturity: 43%

236 deaths/549 patients

Logrank test
p=0.0483[a]

HR 0.82
95% CI 0.63 to 1.07

Subsequent immunotherapy

Atezolizumab arm	*9.0%*
Placebo arm	*24.3%*

Adapted from Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.

[a]Critical *p*-value to state statistical significance at interim analysis is 0.024.

CI = confidence interval; CP = carboplatin/paclitaxel; EC = endometrial cancer; HR = hazard ratio; ITT = intention to treat; mo = months; OS = overall survival.

Colombo N, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.

AtTEnd | Summary of safety end points

Chemotherapy + atezolizumab in primary advanced/recurrent EC

	Atezolizumab + carboplatin/paclitaxel N=356	Placebo + carboplatin/paclitaxel N=185
Safety, n (%)		
Any AE	351 (98.6)	185 (100)
Any AE related to atezolizumab/placebo	269 (75.6)	118 (63.8)
Any Grade ≥3 AE related to atezolizumab/placebo	92 (25.8)	26 (14.1)
Fatal AE related to atezolizumab/placebo	1 (0.3)*	1 (0.5)*

*Pneumoniae assessed by investigators as related to treatment.
AE = adverse event; EC = endometrial cancer.
Colombo N, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.

Conclusions

- The addition of a PD-(L)1 inhibitor to standard of care chemotherapy in patients with primary advanced/recurrent EC resulted in substantial and unprecedented benefit in patients with dMMR/MSI-H EC (AtTEnd, RUBY, and NRG-GY018)
- Benefit was also observed in patients with MMRp with anti–PD-1 + chemotherapy, with meaningful improvements in PFS
- The tolerability profile of an anti-PD-(L)1 when combined with chemotherapy was predictable and consistent with established safety profiles for the individual regimens
- Immunotherapy (dostarlimab) in combination with chemotherapy has demonstrated survival gains with a higher quality of life vs chemotherapy alone in earlier treatment setting, as demonstrated by Q-TWiST
- Molecular data from RUBY (TCGA) and NRG-GY018 (mutational analyses) are building on our knowledge of EC and who may benefit from chemotherapy in combination with anti-PD-(L)1 therapies

C/P = carboplatin and paclitaxel; dMMR = mismatch repair deficient; ICI = immune checkpoint inhibitors; ITT = intent-to-treat; MMRp = mismatch repair proficient; MSI-H = microsatellite instability-high; PD-1 = programmed cell death protein 1.

Panel discussion

ICI monotherapy trials in primary advanced/recurrent EC

	Dostarlimab DOMENICA | ENGOT-en13[1]	Pembrolizumab ENGOT-en15 | KEYNOTE-C93[2,3]
N	260	280
Study chair	Joly	Slomovitz
Treatment arms	Dostarlimab vs carboplatin/paclitaxel	Pembrolizumab vs carboplatin/paclitaxel
Patient population	dMMR/MSI-H EC	dMMR EC
Primary outcome(s)	PFS (BICR)	PFS (BICR), OS

There are no completed direct head-to-head trials of these products in EC. There are inherent limitations in cross-study comparisons; caution should be exercised in comparing trials. This slide is for information purposes only and is not intended to imply or infer the noninferiority or superiority of any product, in terms of efficacy or safety.

BICR = blinded independent central radiology review; dMMR = mismatch repair deficient; EC = endometrial cancer; ENGOT = European Network of Gynaecological Oncological Trial Groups; ICI = immune check inhibitors; MSI-H = microsatellite instability high; OS = overall survival; PFS = progression-free survival.

1. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT05201547. Accessed August 29, 2023 . 2. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT05173987. Accessed January 31, 2023. 3. Slomovitz BM et al. *Journal of Clin Oncology*; 2022:50(16 supple).