CANCÉROPÔLE Est
Régions Bourgogne-Franche-Comté / Grand Est

Actualité en immuno-oncologie
Cancers gynécologiques

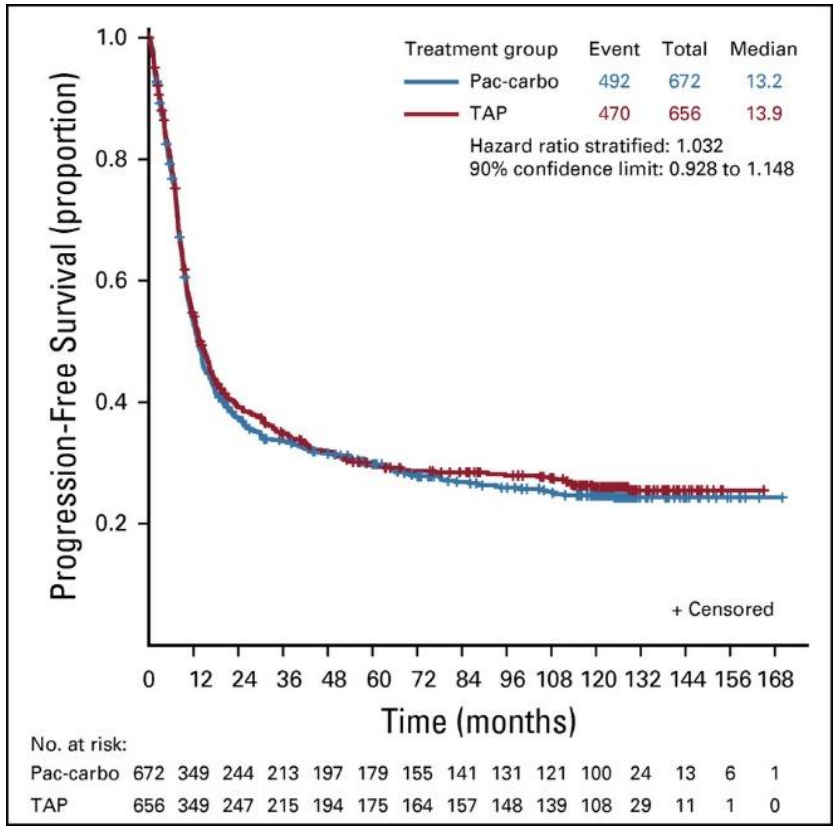
Dr Jean-David Fumet, MD, PhD
Département d'oncologie médicale
CLCC Georges-François Leclerc – Dijon
13/03/2025

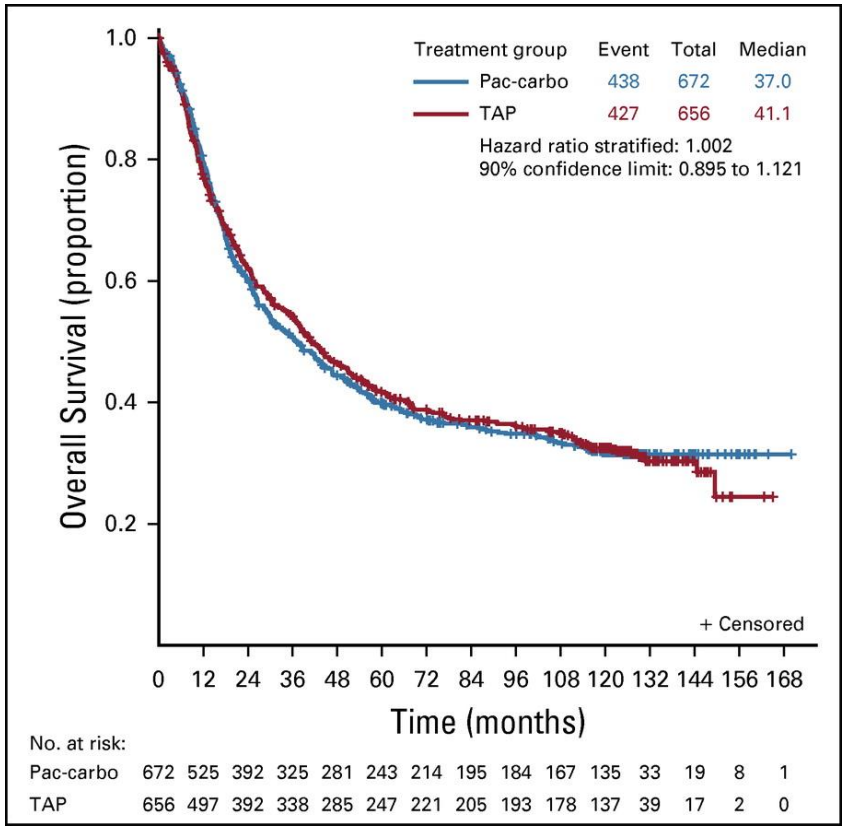
CGFL CENTRE GEORGES FRANÇOIS LECLERC Ensemble, dépassons le cancer

Le cancer de l’endomètre

CARBOPLATINE TAXOL : un long règne

GOG0209





- Miller DS, Filiaci VL, Mannel RS, et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). *J Clin Oncol*. 2020;38(33):3841-3850. doi:10.1200/JCO.20.01076

Fin 2023 : le pouvoir a « changé »

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

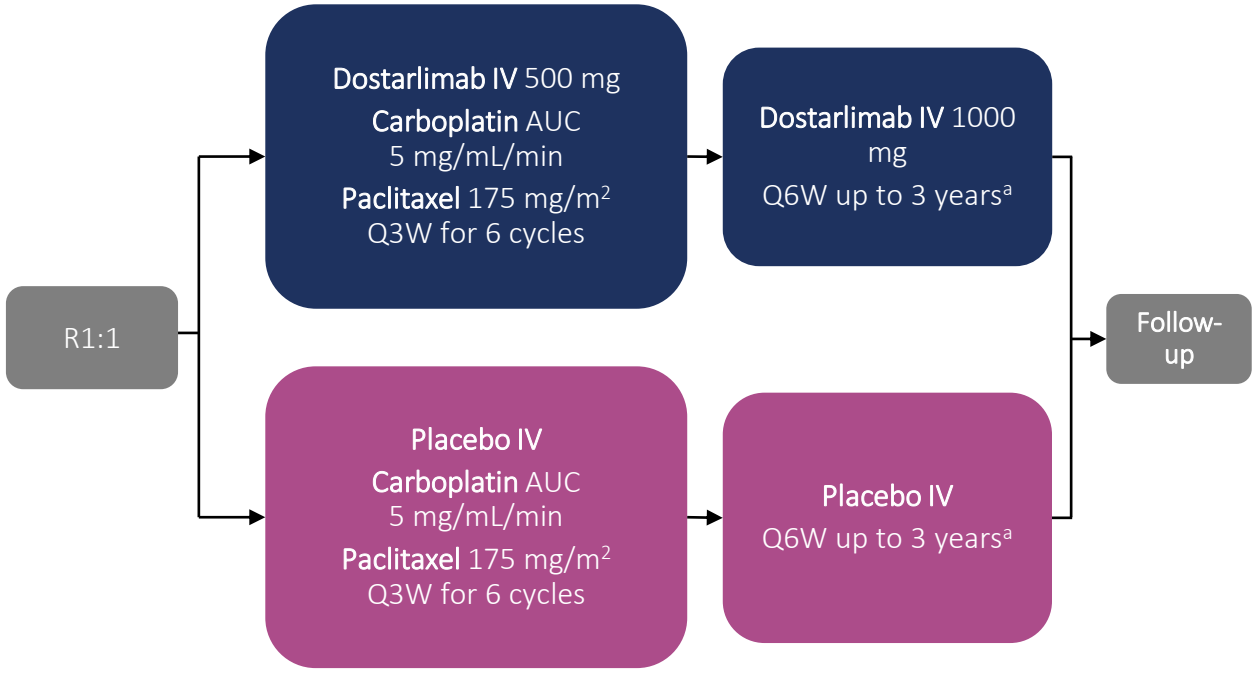
Phase 3, randomized, double-blind, multicenter study of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel in patients with primary advanced or recurrent EC

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
- 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
- Prior external pelvic radiotherapy
- Disease status



End points

Primary end point: PFS by INV per RECIST v1.1, OS

Secondary end points: PFS by BICR per RECIST v1.1, PFS2, ORR, DOR, DCR, HRQOL/PRO, Safety

Further study details can be found at Mirza MR, et al. N Engl J Med. 2023 Jun 8;388(23):2145-2158.

[a]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; ECOG PS = Eastern Cooperative Oncology Group performance score; ENGOT = The European Network for Gynecological Oncological Trial groups; GOG = Gynecologic Oncology Group; HRQOL = health-related quality of life; INV = investigator assessment; IV = intraveneous; MMR = mismatch repair; MSI = microsatellite instability; NSGO = Nordic Society of Gynecologic Oncology; 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; R = randomisation; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours version 1.1.

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

Patient Population and Baseline Characteristics

Variable, n (%)	Overall	
	Dostarlimab + CP (N=245)	Placebo + CP (N=249)
MMR/MSI status		
dMMR/MSI-H	53 (21.6)	65 (26.1)
MMRp/MSS	192 (78.4)	184 (73.9)
Prior external pelvic radiation		
Yes	41 (16.7)	45 (18.1)
No	204 (83.3)	204 (81.9)
Disease status		
Primary stage III	45 (18.4)	47 (18.9)
Primary stage IV	83 (33.9)	83 (33.3)
Recurrent	117 (47.8)	119 (47.8)

Data cutoff date: September 28, 2022.
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.
Powell MA, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation # LBA1.

Baseline Characteristics

Variable	Overall	
	Dostarlimab + CP (N=245)	Placebo + CP (N=249)
Age		
Median (range), y	64 (41–81)	65 (28–85)
≥65 y, n (%)	118 (48.2)	135 (54.2)
Race, n (%)		
White	189 (77.1)	191 (76.7)
Black	28 (11.4)	31 (12.4)
Asian	7 (2.9)	8 (3.2)
Other[a]	21 (8.6)	19 (7.6)
ECOG PS, n (%)[b]		
0	145 (60.2)	160 (65.0)
1	96 (39.8)	86 (35.0)
BMI		
Median (range)	30.8 (17.6–60.6)	32.8 (17.7–68.0)
Measurable disease at baseline, n (%)		
Yes	212 (86.5)	219 (88.0)
No	33 (13.5)	30 (12.0)

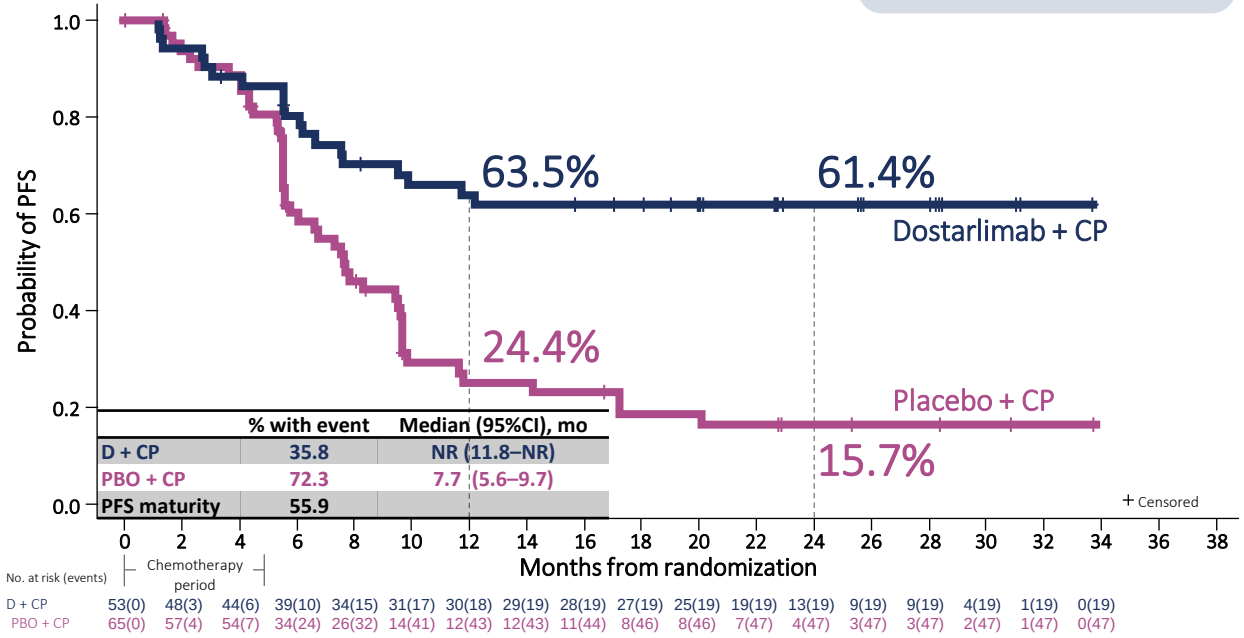
Variable	Overall	
	Dostarlimab + CP (N=245)	Placebo + CP (N=249)
Prior anticancer treatment, n (%)		
Yes	48 (19.6)	52 (20.9)
Carboplatin-paclitaxel	36 (14.7)	39 (15.7)
Histology type, n (%)		
Carcinosarcoma	25 (10.2)	19 (7.6)
Endometrioid	134 (54.7)	136 (54.6)
Mixed carcinoma[c]	10 (4.1)	9 (3.6)
Serous adenocarcinoma	50 (20.4)	52 (20.9)
Clear cell adenocarcinoma	8 (3.3)	9 (3.6)
Mucinous adenocarcinoma	0	1 (0.4)
Undifferentiated carcinoma	1 (0.4)	2 (0.8)
Other	17 (6.9)	21 (8.4)

Data cutoff date: September 28, 2022.
[a]Other includes patients identifying as American Indian or Alaska native, native Hawaiian or other Pacific Islander, unknown, or not reported. [b]Number of patients with ECOG PS score: 52 dostarlimab + CP dMMR/MSI-H, 65 placebo + CP dMMR/MSI-H, 241 dostarlimab + CP overall, 246 placebo + CP overall. [c]Mixed carcinoma ≥10% of carcinosarcoma, clear cell, or serous histology.
BMI, body mass index; CP, carboplatin-paclitaxel; dMMR, mismatch repair deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; MSI-H, microsatellite instability high.
Powell MA, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA1.

Statistically significant improvements in PFS in patients with primary advanced or recurrent EC[1-3]

dMMR/MSI-H

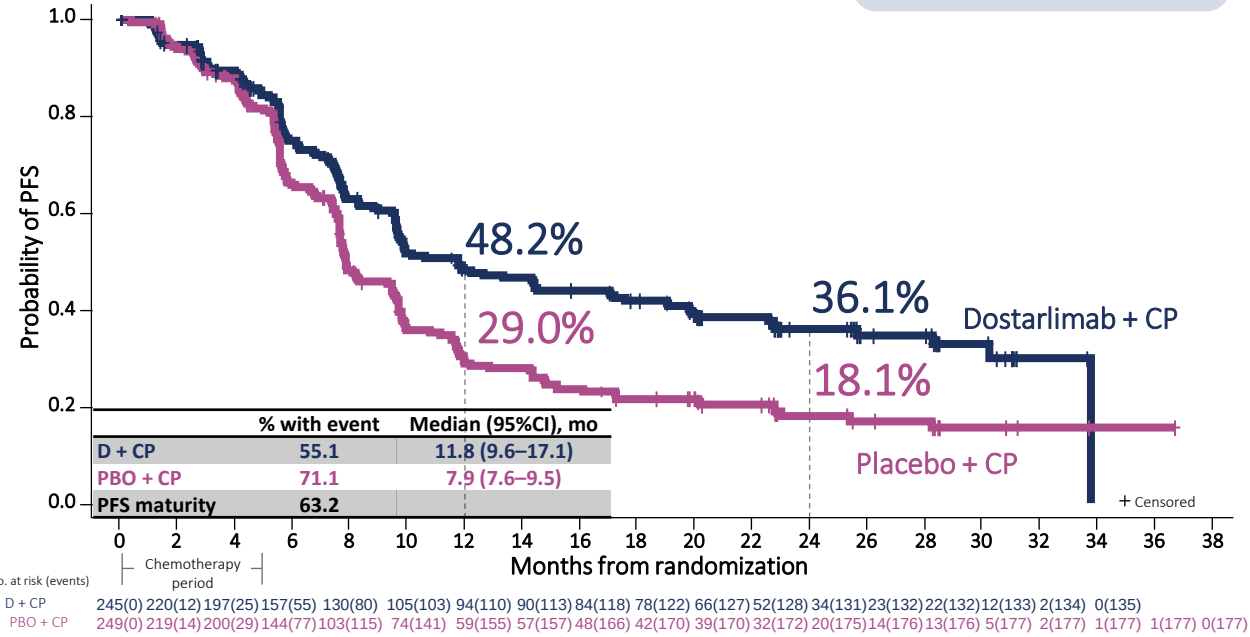
HR, 0.28
(95% CI, 0.162–0.495)
P<0.0001



Median duration of follow-up: 24.8 mo

Overall

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



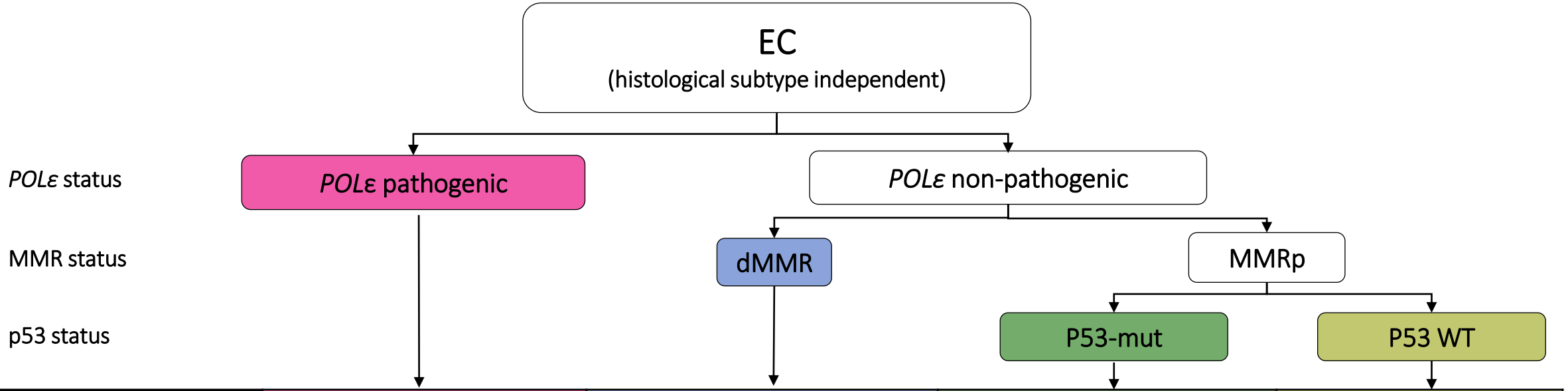
Median duration of follow-up: 25.4 mo

CI = confidence interval; CP = carboplatin-paclitaxel; D = dostarlimab; dMMR = mismatch repair deficient; EC = endometrial cancer; HR = hazard ratio; mo = month; MSI-H = microsatellite instability–high; NR = not reached; PBO = placebo; PFS = progression-free survival.

1. Mirza MR, et al. N Engl J Med. 2023;388:2145-2158. 2. 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, US. 3. Mirza MR, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #740MO.

RUBY molecular classification algorithm

In RUBY Part 1, molecular classification was performed for all participants with WES results – 400 of 494 patients



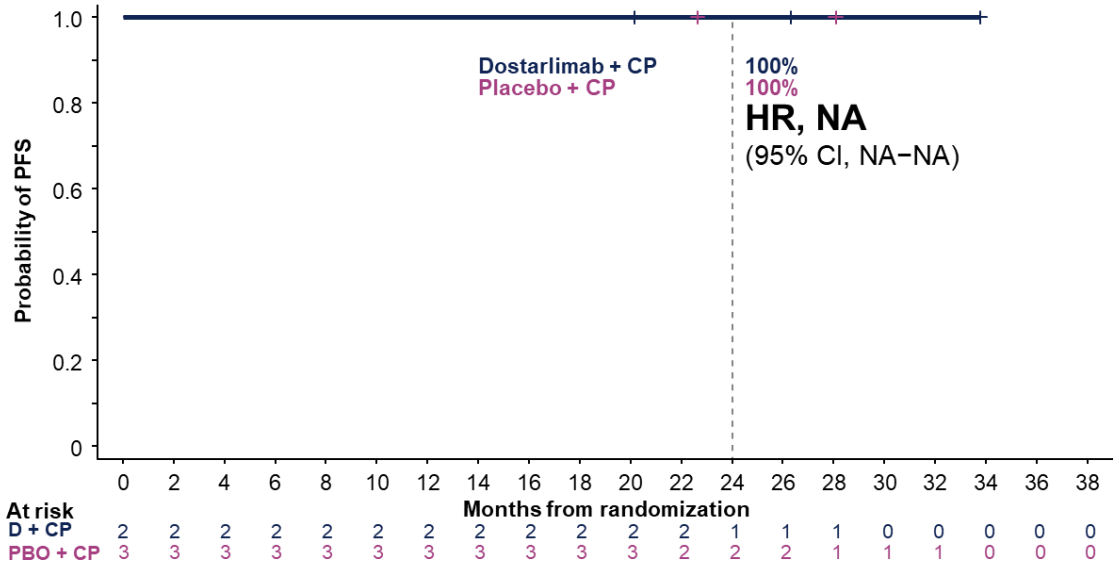
Integrated diagnosis	*POLε*mut (EDM)	dMMR (or MSI-H)	TP53 aberrant	NSMP
Prevalence in RUBY, % (n/N)	**1.25%** (5/400)	**22.75%** (91/400)	**22%** (88/400)	**54%** (216/400)
Diagnostic test	WES	Results of local (IHC, NGS, PCR) or central test (IHC) provided for RUBY at randomization	WES	

Efficacy per molecular classification was an exploratory analysis.
dMMR = mismatch repair deficient; EC = endometrial cancer; EDM = exonuclease domain; IHC = immunohistochemistry; MMR = mismatch repair; MMRp = mismatch repair proficient; MSI-H = microsatellite instability-high; mut = mutated; NGS = next generation sequencing; NSMP = no specific molecular profile; P53 = protein 53; PCR = polymerase chain reaction; POLε = polymerase epsilon; TP53 = tumor protein 53; WES = whole exome DNA sequencing; WT = wild type.
Mirza MR, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #740MO.

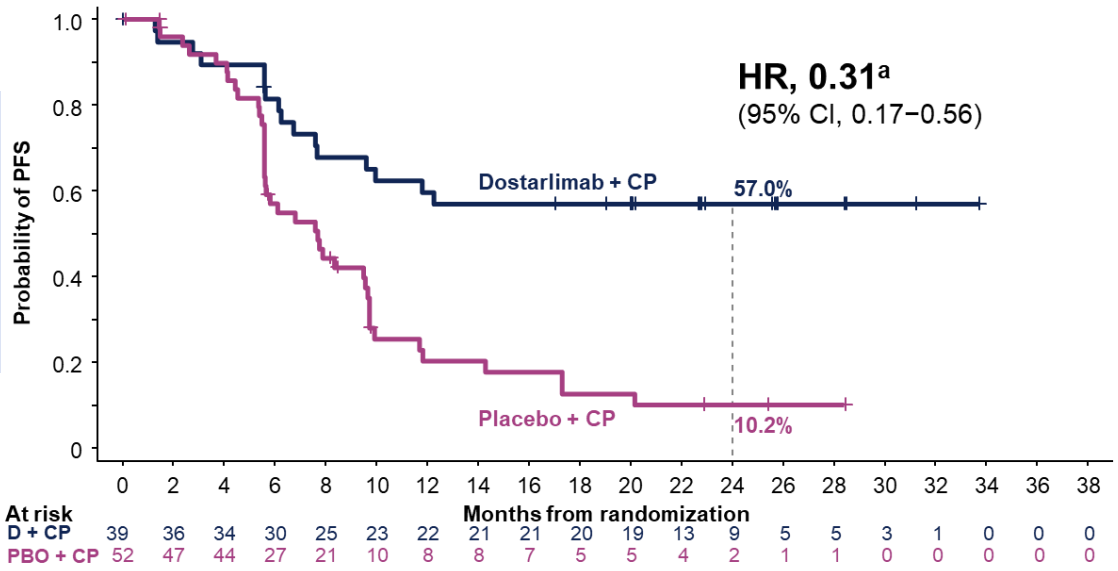
PFS according to molecular subgroup

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

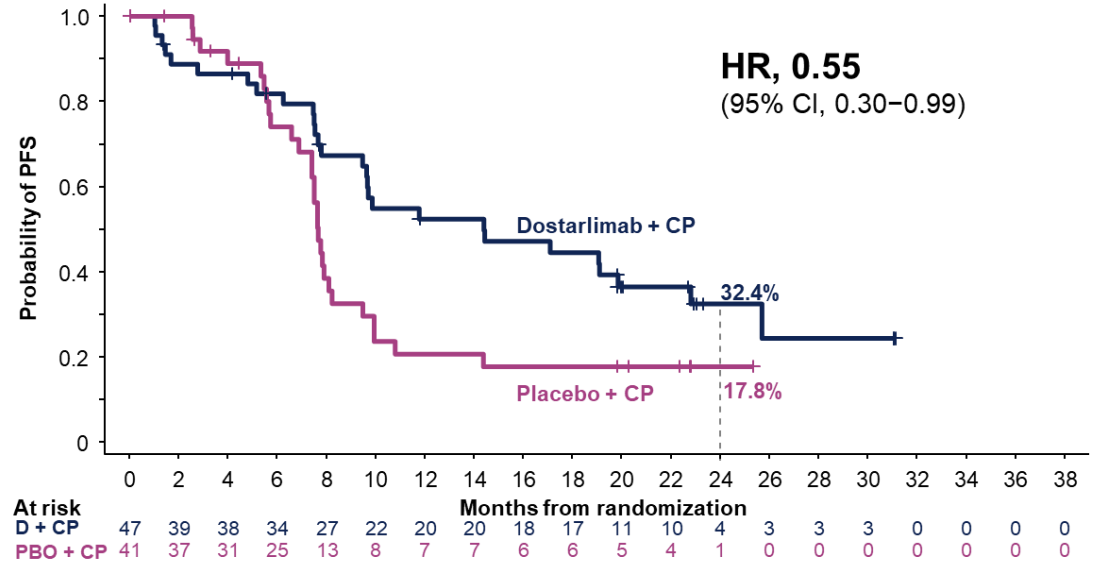
POLε mut



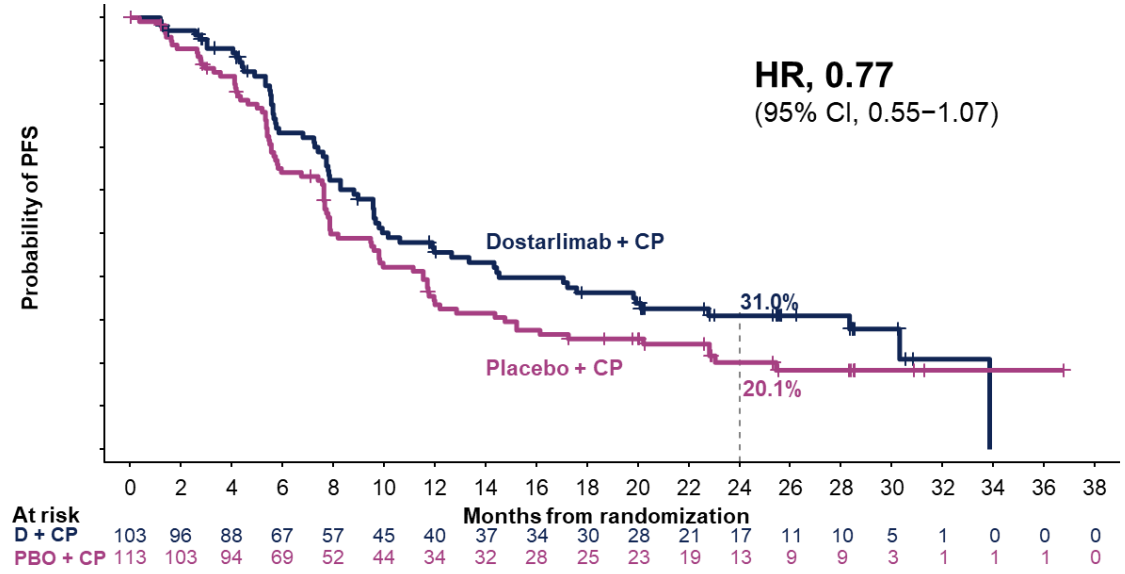
dMMR/MSI-H



TP53 mut



NSMP

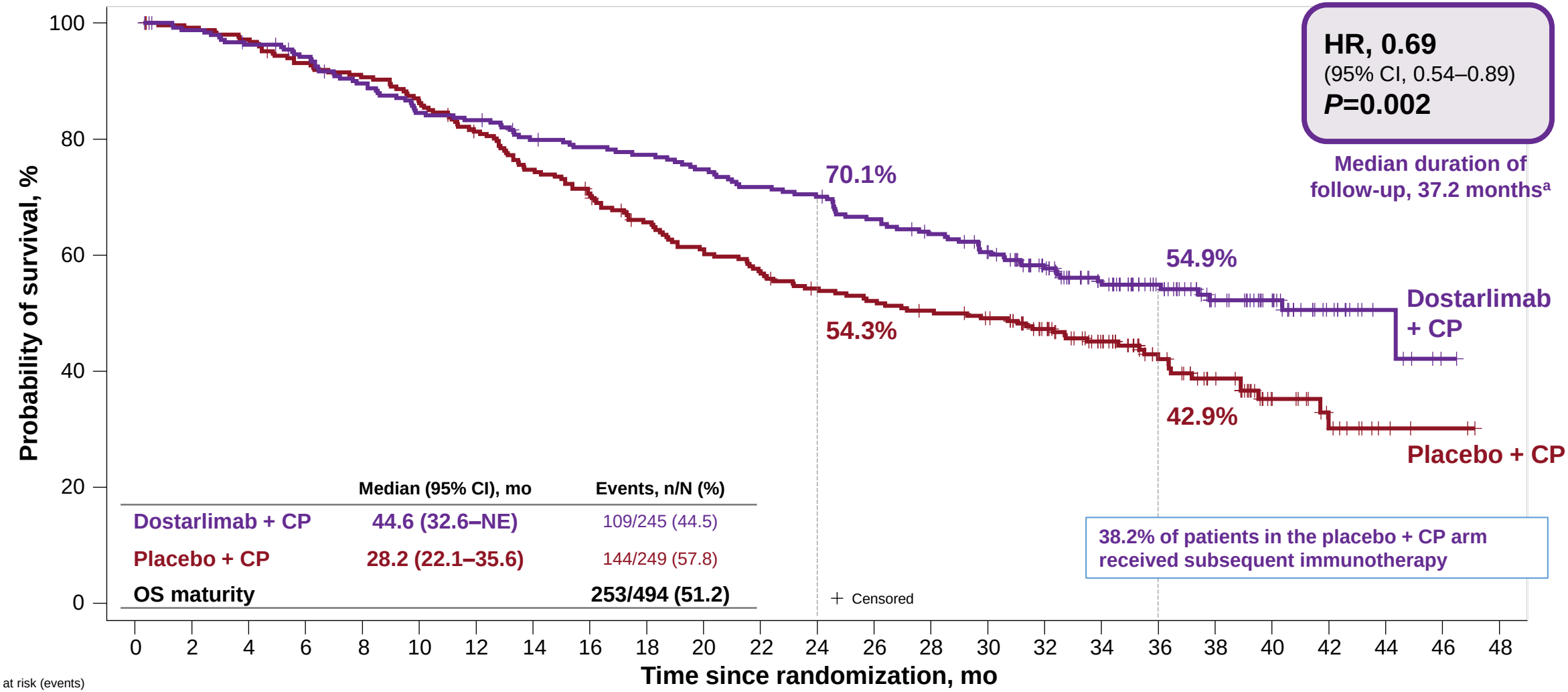


[a]Primary endpoint of PFS in dMMR/MSI-H patients (n=118) showed HR, 0.28; *P*<0.0001.

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

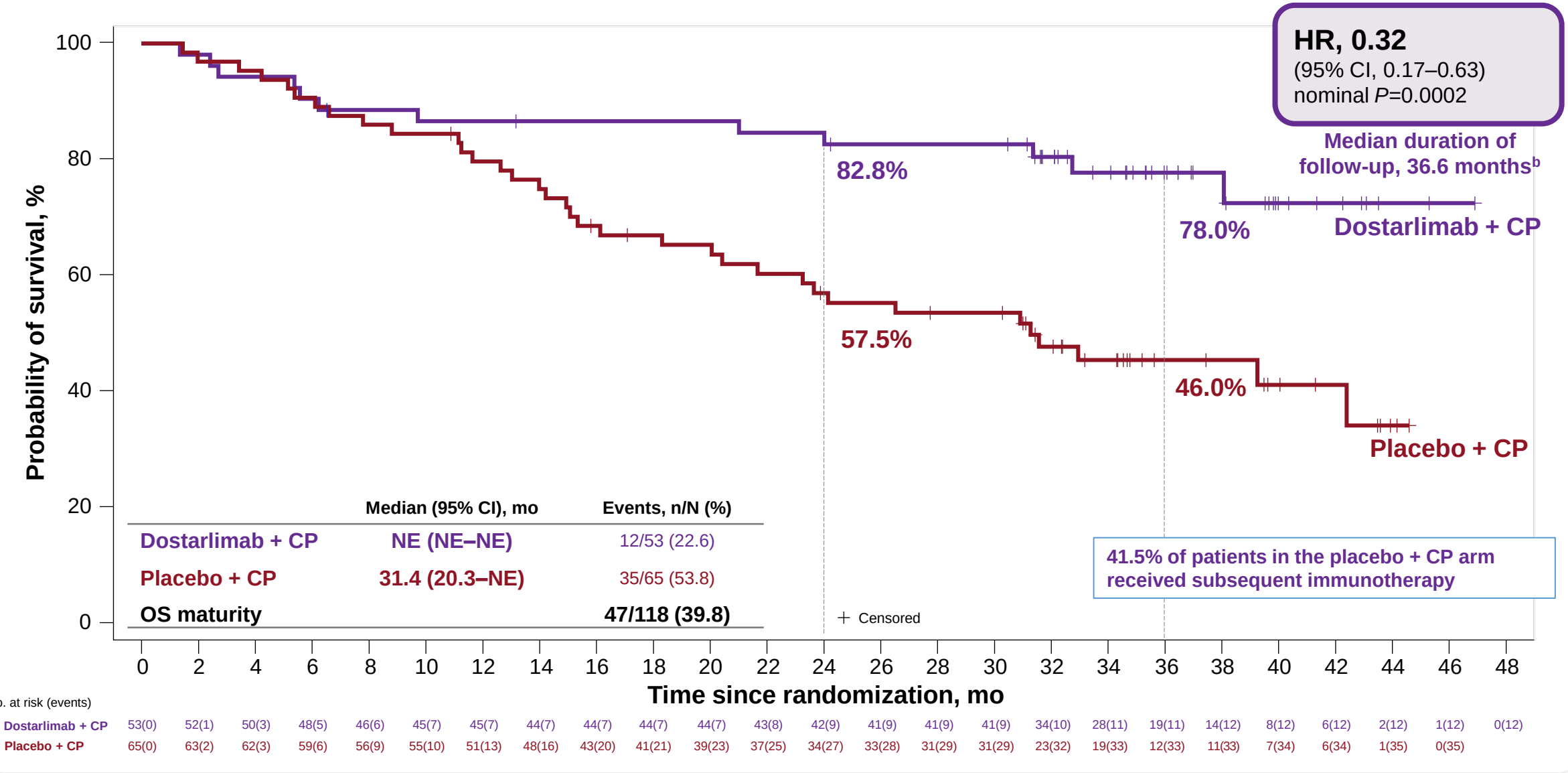
Mirza MR, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #740MO.

Statistically Significant OS Benefit in Overall Population – Primary Endpoint



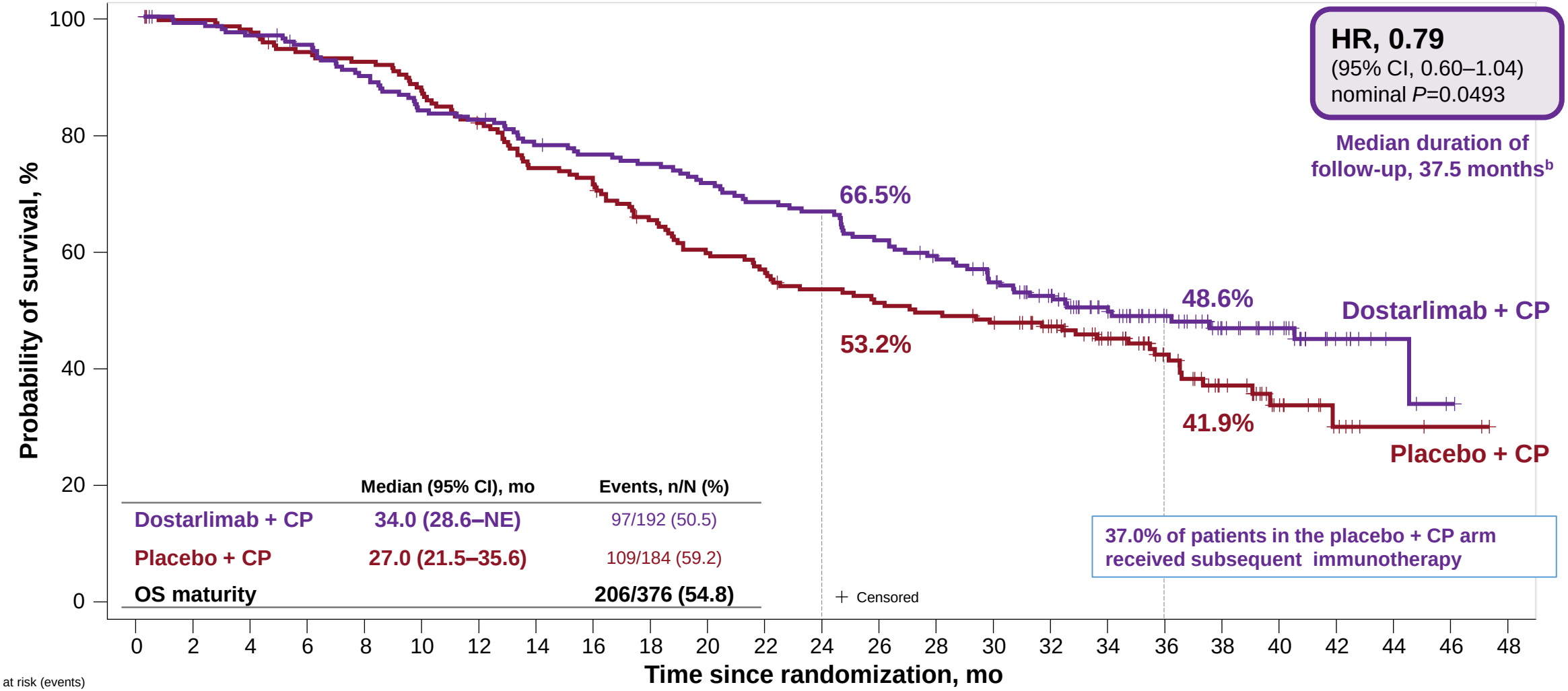
[a]Median expected duration of follow-up.
CI, confidence interval; CP, carboplatin-paclitaxel; HR, hazard ratio; mo, month; NE, not estimable; No, number; OS, overall survival.
Powell MA, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA1.

Substantial OS Benefit in dMMR/MSI-H Population[a]



[a]Overall survival in the dMMR/MSI-H and MMRp/MSS populations was a prespecified exploratory endpoint [b]Median expected duration of follow-up.
CI, confidence interval; CP, carboplatin-paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; mo, month; MSI-H, microsatellite instability-high; NE, not estimable; No, number; OS, overall survival.
Powell MA, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA1.

Clinically Meaningful OS Difference in MMRp/MSS Population[a]

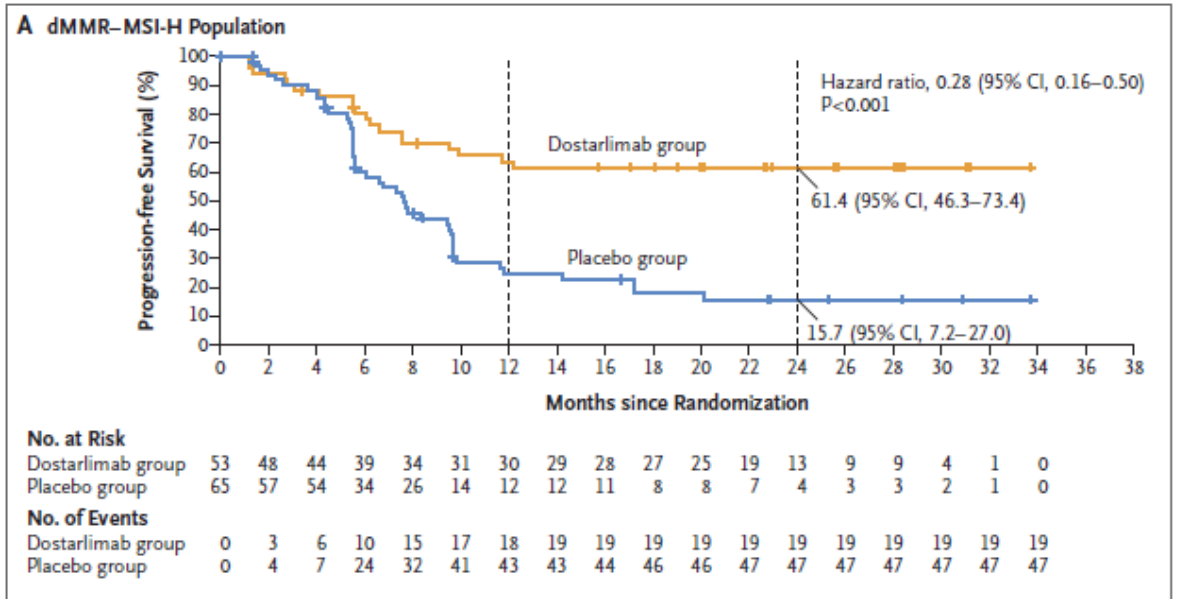


[a]Overall survival in the dMMR/MSI-H and MMRp/MSS populations was a prespecified exploratory endpoint. [b]Median expected duration of follow-up.
CI, confidence interval; CP, carboplatin-paclitaxel; HR, hazard ratio; MMRp, mismatch repair proficient; mo, month; MSS, microsatellite stable; NE, not estimable; No, number; OS, overall survival.
Powell MA, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA1.

Safety Summary[a]

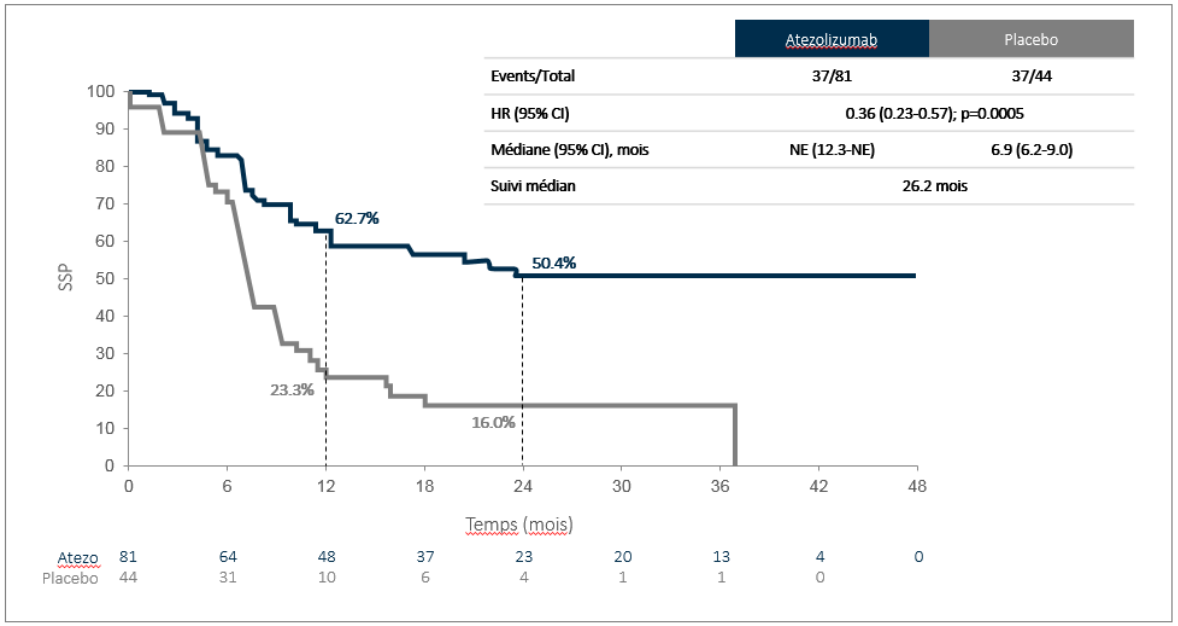
Parameter	Dostarlimab + CP (N=241)	Placebo + CP (N=246)
Any TEAE, n (%)	241 (100)	246 (100)
Any grade ≥3 TEAE, n (%)	174 (72.2)	148 (60.2)
Serious TEAE, n (%)	96 (39.8)	69 (28.0)
Any treatment-related irAE, n (%)	98 (40.7)	40 (16.3)
Any TEAE leading to discontinuation of dostarlimab or placebo, n (%)	46 (19.1)	20 (8.1)
Any TEAE leading to discontinuation of carboplatin, n (%)	20 (8.3)	15 (6.1)
Any TEAE leading to discontinuation of paclitaxel, n (%)	26 (10.8)	25 (10.2)
Any TEAE leading to death, n (%)	5 (2.1)[b]	0
Any TEAE related to dostarlimab leading to death, n (%)	2 (0.8)[c]	—
Duration of overall treatment, median (range), weeks	43.0 (3.0–192.6)	36.0 (2.1–193.1)

[a]Data are based on the safety analysis set, which consists of patients who received ≥1 dose of study treatment. [b]Three deaths were not related to study treatment (opiate overdose, COVID-19, and general physical health deterioration). [c]One death was considered by the investigator as related to dostarlimab, carboplatin, and paclitaxel 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.
Powell MA, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA1.

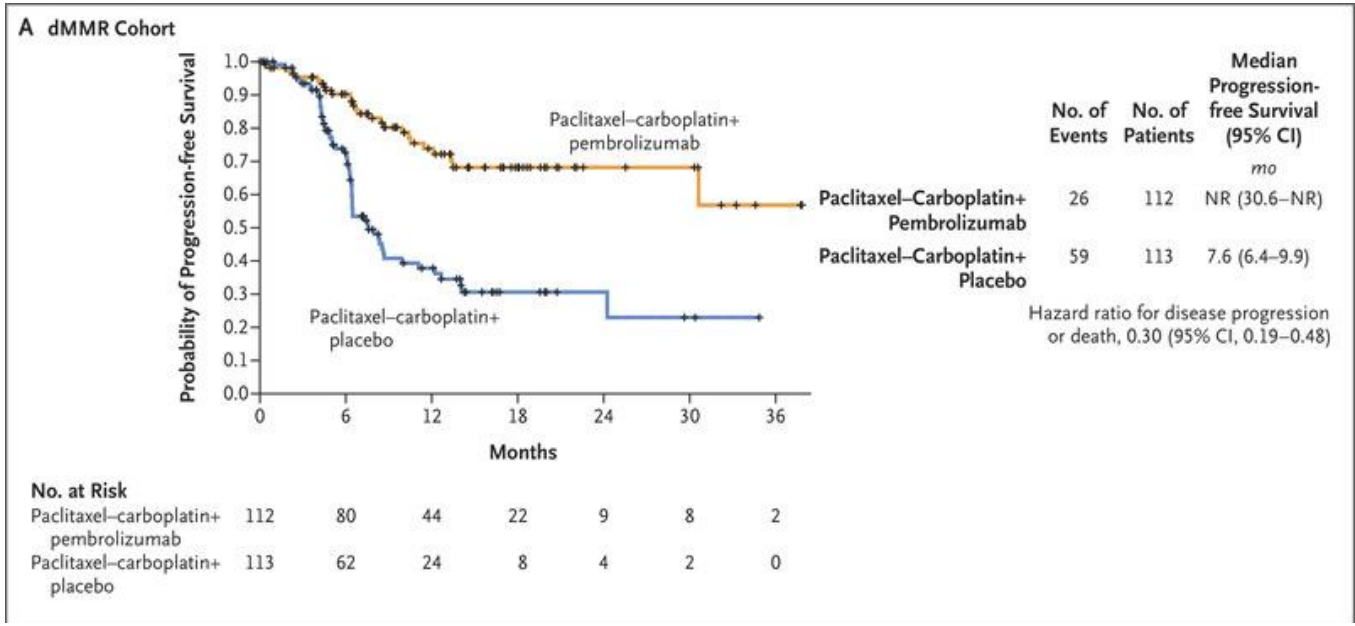


Mirza MR, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #740MO

Chimiothérapie + anti PD(L)1 chez les dMMR : HR = 0,3

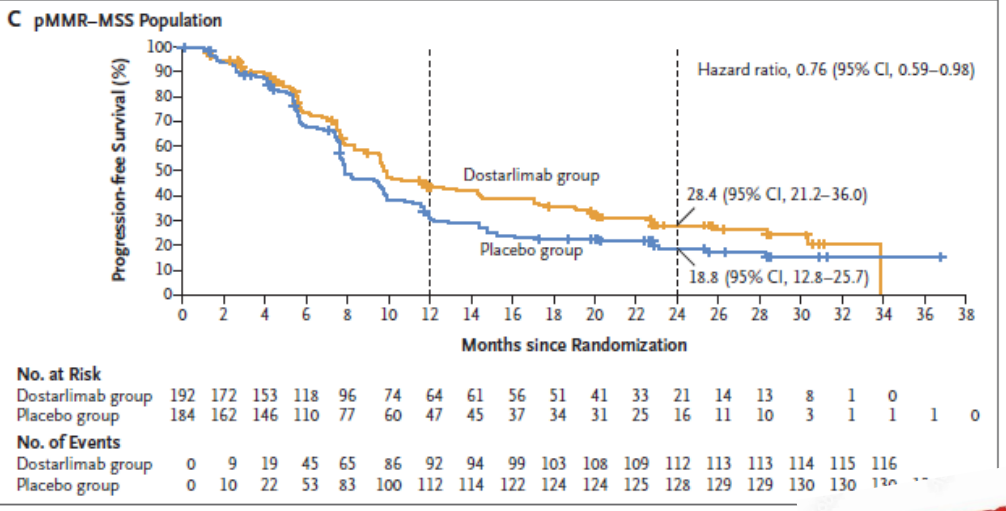


Colombo et al, Annals of Oncology 2023



Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. *N Engl J Med*. 2023;388(23):2159-2170. doi:10.1056/NEJMoa2302312

Chimiothérapie + anti PD1 chez les pMMR : HR = 0,6-0,7
Anti PD-L1 moins efficace ?



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2023; Madrid, Spain; Presentation #740MO

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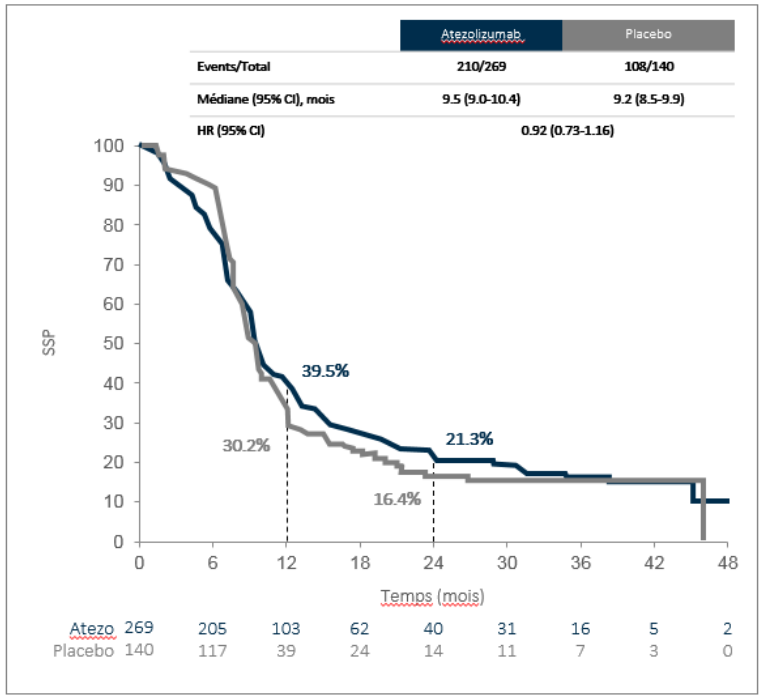
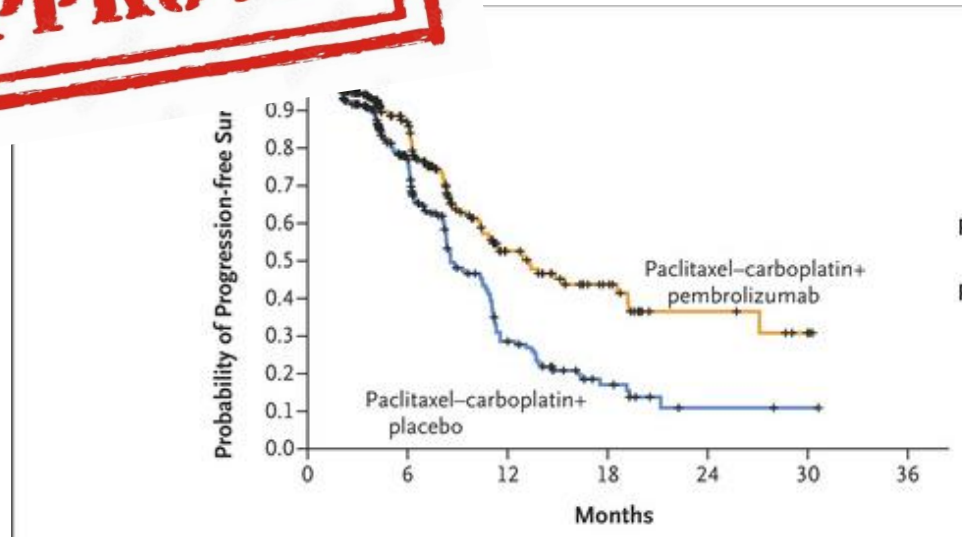


Colombo et al, Annals of Oncology 2023



	No. of Events	No. of Patients	Median Progression-free Survival (95% CI)
			mo
Paclitaxel–Carboplatin+ Pembrolizumab	89	290	13.1 (10.5–18.8)
Paclitaxel–Carboplatin+ Placebo	133	292	8.7 (8.4–10.7)

Stratified hazard ratio for disease progression or death, 0.54 (95% CI, 0.41–0.71)

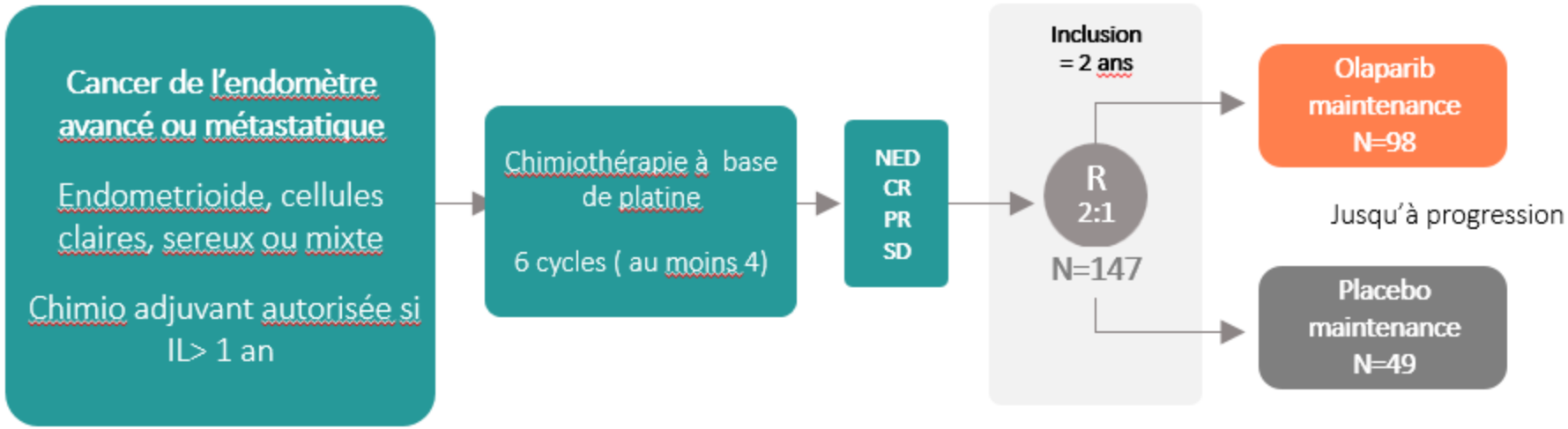
Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. *N Engl J Med*. 2023;388(23):2159-2170. doi:10.1056/NEJMoa2302312

Perspective : Une place pour les inhibiteurs de PARP ?

UTOLA (GINECO)

Olaparib vs placebo comme traitement d'entretien après une chimiothérapie à base de platine chez des patientes atteintes d'un cancer de l'endomètre avancé/métastatique

Olaparib vs placebo en maintenance après chimiothérapie à base de platine dans le cancer de l'endomètre advancé/metastatique : Etude GINECO UTOLA : Phase IIB randomisée



Objectif principal :

- SSP en ITT

Objectif secondaires principaux

- SSP selon statut p53
  SSP selon réponse
  SG en ITT et selon p53 s
- Tolérance
- (QoL)

Facteurs de strafication :

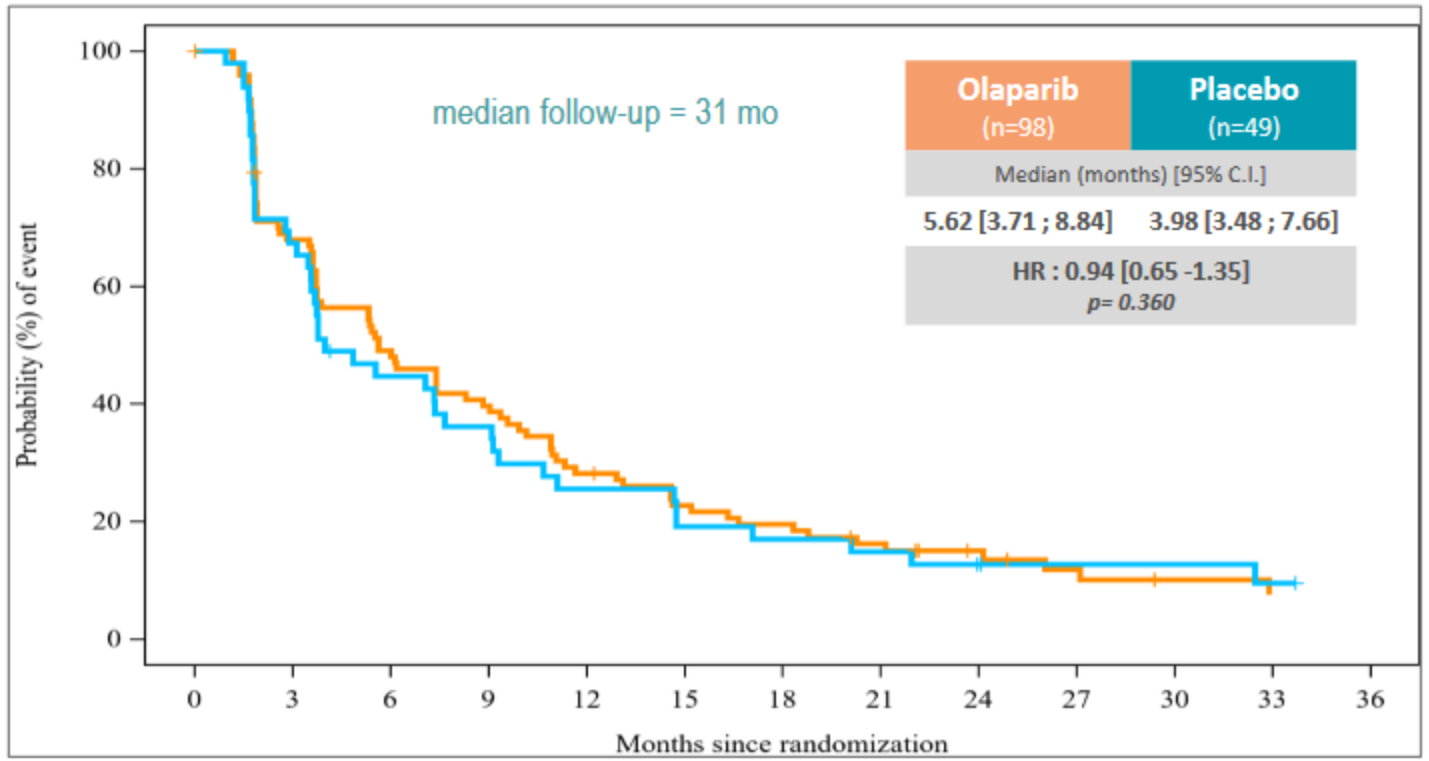
- P53 et statut MMR
- Réponse à la CT antérieure

147 patientes incluses
75% endométrioïde
20% séreux
30% en RC, 45% en RP

* *Chemotherapy, at least* ***4 cycles***
Recommanded Regimen: ***Carboplatin plus Paclitaxel***

PFS* by investigator assessment: ITT

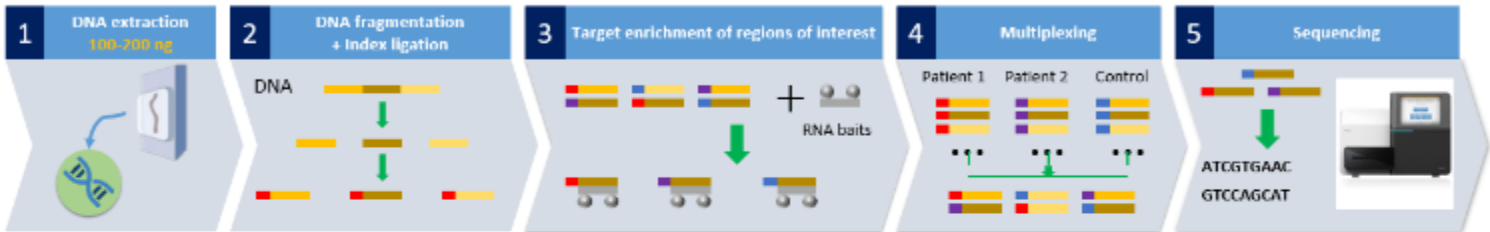
N=147



Olaparib	98	65	47	38	27	21	18	14	10	7	4	3	3
	(0)	(2)	(2)	(2)	(2)	(3)	(3)	(4)	(7)	(8)	(10)	(10)	(10)
Placebo	49	33	21	17	12	9	8	7	5	4	4	3	2
	(0)	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(2)	(3)	(3)	(3)	(4)

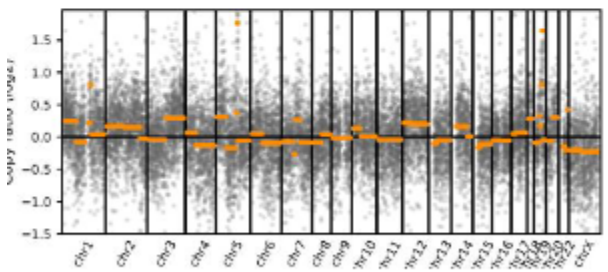
**PFS calculated from randomization (end of CT)*

- Definition of **HRD** status - NGS methods : Chromosomic instability

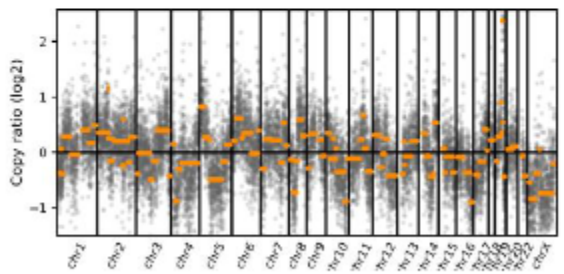


Genes Panel (127 genes) [1]
➔ LGE*

Stable



Instable



- **Large Genomic Event (LGE)***
- Structurale Instability Score (SIS)
- Allelic Imbalance (AI)

Cut-off for HRD status :
Median

LGE ≥ 6 ➡ HRD

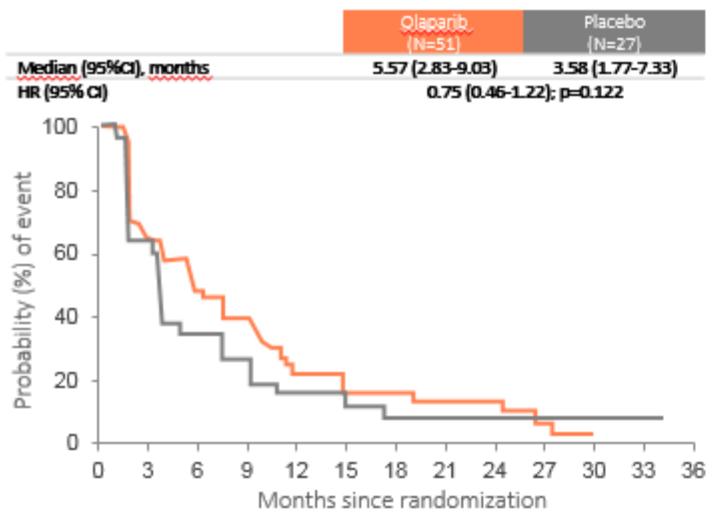
MADRID 2023 ESMO congress

** LGE = LST = large-scale state transition*

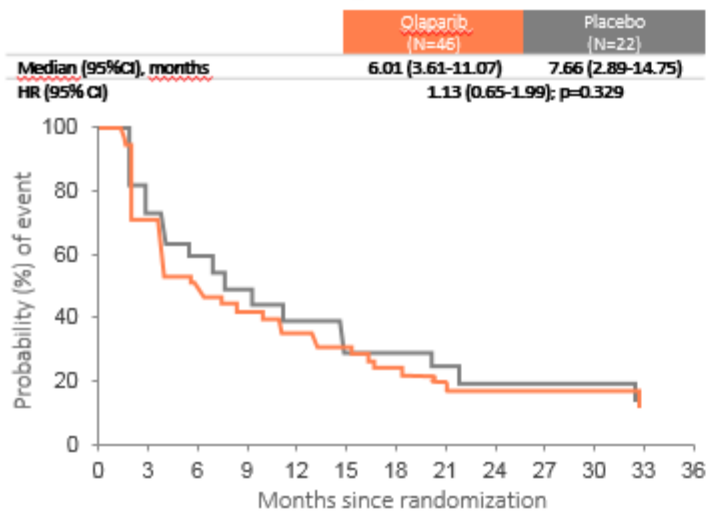
1.Leman et al clin cancer Res 2023

SSP / investigateur en fonction de p53

P53 mut – N=78

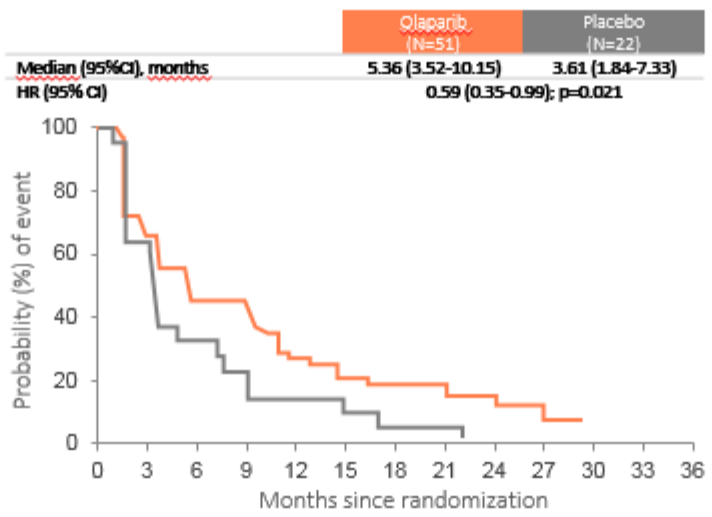


P53 sauvage – N=68

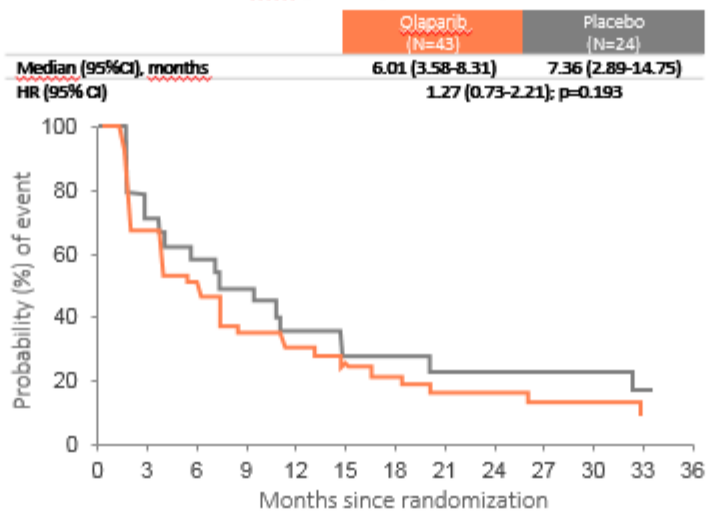


SSP: selon statut HRD

HRD (LGE≥6) N=73

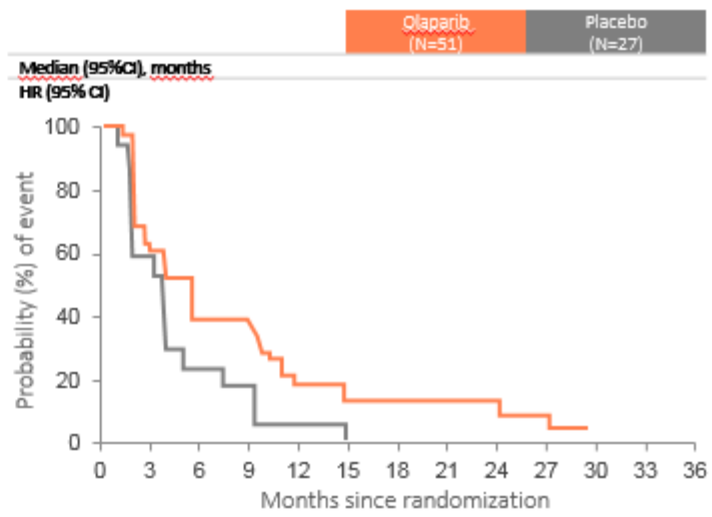


HRp (LGE<6) N=67



Analyse exploratoire : p53 muté et HRD

P53 mut – N=78



- En ITT, pas de bénéfice sur la SSP avec l'olaparib en maintenance
- On note une amélioration de la SSP avec l'olaparib dans la sous-population mutée p53 et surtout dans la population HRD

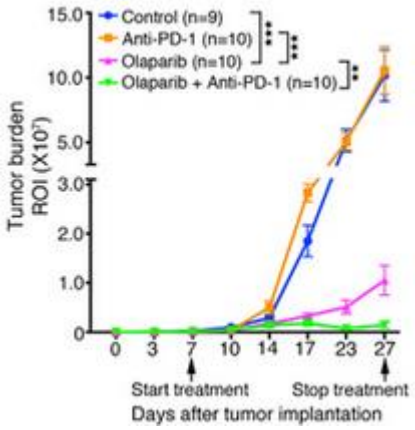
Next step ?
Une place pour les inhibiteurs de PARP + immunothérapie ?

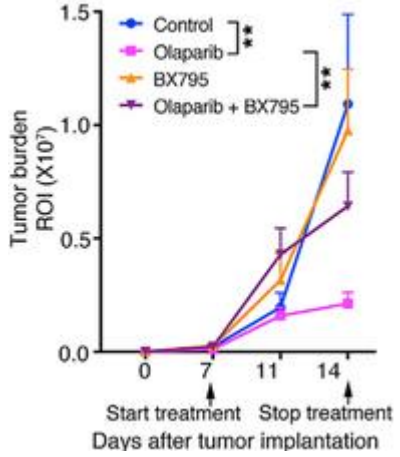
Effets immunogéniques des PARPi

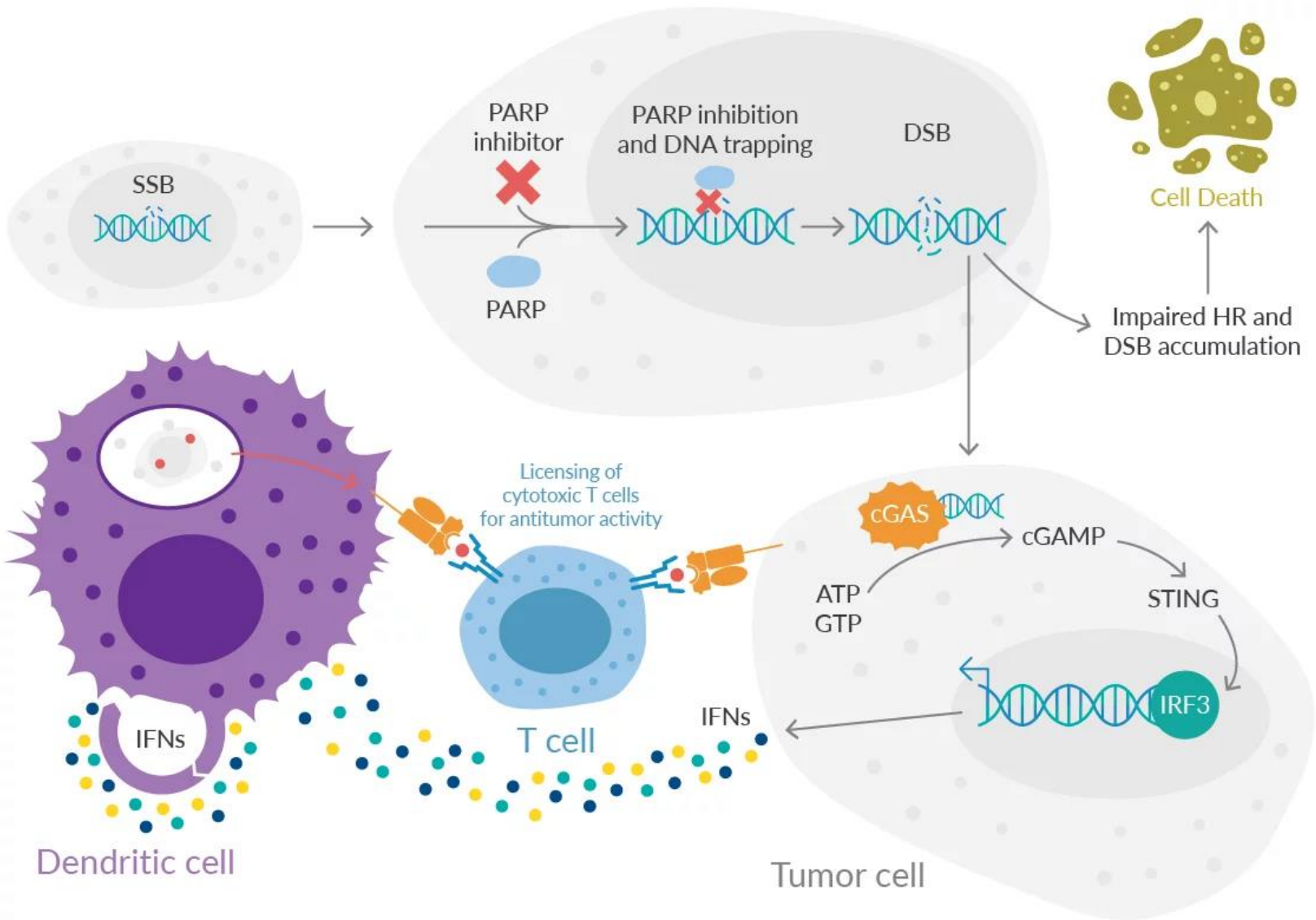
- **La génétique influence l'infiltrat immunitaire**
  - Tumeurs HRD/BRCAm : plus immuno-infiltrées *(Strickland et al 2016, Nolan et al 2017)*
  - Tumeurs MSI/TMB high : plus immuno-infiltrées *(Llosa et al 2015, Rizvi et al 2015)*

- **Les inhibiteurs de PARP agissent sur l'infiltrat immunitaire dans des modèles murins**
  - *via* la voie cGAS/STING *(Pantelidou et al 2019)*
  - Favorise le recrutement lymphocytaire T et l'expression de PD-L1 *(Pantelidou et al 2019)*

- **La combinaison PARPi + immunothérapie est synergique dans des modèles murins** *(Jiao et al 2017, Ding et al 2018)*







https://www.caymanchem.com/news/helping-recruit-immune-cells-to-cancer

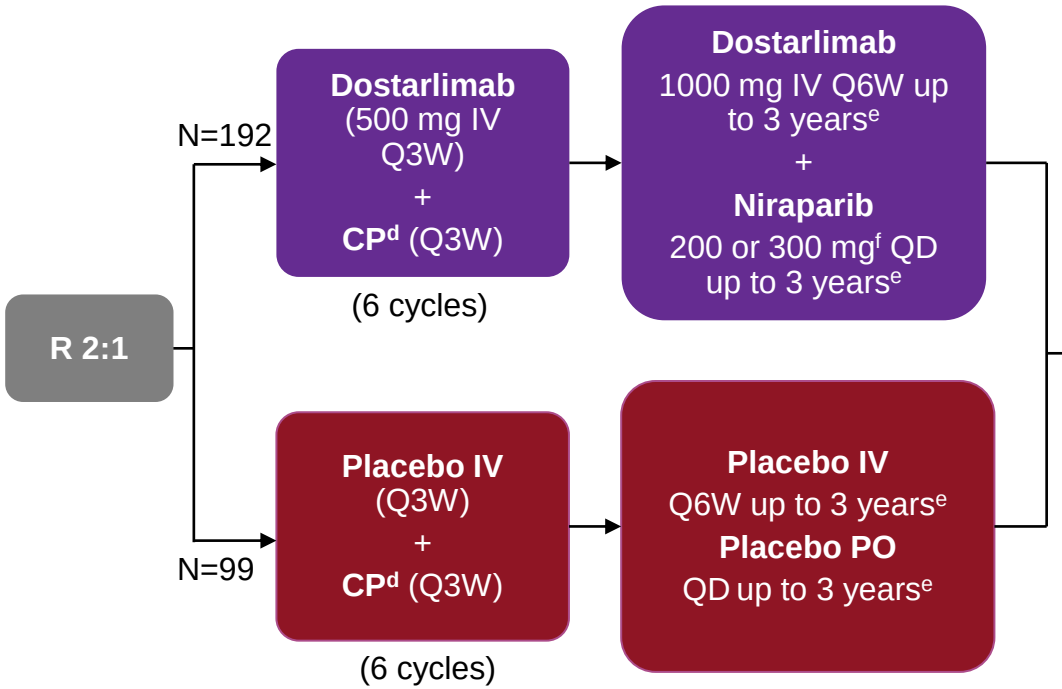
ENGOT-EN6-NSGO/GOG-3031/RUBY Part 2

Eligible patients

- Stage III/IV disease or first recurrent EC[a]
  - All histologies except sarcomas[b]
- Naive to systemic anticancer therapy or had a recurrence or PD ≥6 months after completing systemic anticancer therapy
- Naive to PARP inhibitor therapy

Stratification

- MMR/MSI status[c]
  - 25% dMMR/MSI-H
  - 75% MMRp/MSS
- Prior external pelvic radiotherapy
- Disease status



Primary endpoint

- PFS by INV per RECIST v1.1
  - Overall
  - MMRp/MSS

Secondary endpoints

- OS
- PFS by BICR
- ORR
- DOR
- DCR (BOR of CR, PR, or SD)
- PFS2
- HRQOL/PRO
- PK
- Safety

On-study imaging assessments were performed Q6W (±7 days) from the randomization date until week 25 (cycle 8), followed by Q9W (±7 days) until week 52. Subsequent tumor imaging was performed every 12 weeks (±7 days) until radiographic PD was documented by investigator assessment per RECIST v1.1 followed by 1 additional imaging 4–6 weeks later, or subsequent anticancer therapy was started, whichever occurred first. Thereafter, scans were performed per standard of care.
[a]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. [b]Carcinosarcoma, clear cell, serous, or mixed histology permitted (mixed histology containing ≥10% carcinosarcoma, clear cell, or serous histology). [c]Patients were randomized based on either local or central MMR/MSI testing results. Central testing was used when 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. [d]Carboplatin AUC 5 mg/mL/min and paclitaxel 175 mg/m^2. [e]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. [f]Dose of 300 mg in patients with body weight ≥77 kg and platelet count ≥150,000/μL and 200 mg in patients with body weight <77 kg or platelet count <150,000/μL or both.
AUC, area under the plasma or serum concentration-time curve; BICR, blinded independent central review; BOR, best overall response; CP, carboplatin-paclitaxel; CR, complete response; DCR, disease control rate; dMMR, MMR deficient; DOR, duration of response; EC, endometrial cancer; HRQOL, health-related quality of life; IHC, immunohistochemistry; INV, investigator assessment; IV, intravenous; MMR, mismatch repair; MMRp, MMR proficient; MSI, microsatellite instability; MSI-H, MSI high; MSS, microsatellite stable; ORR, objective response rate; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetic; PO, by mouth; PR, partial response; PRO, patient-reported outcome; Q3W, every 3 weeks; Q6W, every 6 weeks; Q9W, every 9 weeks; QD, once daily; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2.

Patient Population and Baseline Characteristics

Variable, % (n)	Overall		MMRp/MSS	
	Dostar + CP followed by Dostar + nira (N=192)	Placebo + CP followed by placebo (N=99)	Dostar + CP followed by Dostar + nira (N=142)	Placebo + CP followed by placebo (N=74)
MMR/MSI status				
dMMR/MSI-H	26.0 (50)	25.3 (25)	0	0
MMRp/MSS	74.0 (142)	74.7 (74)	100 (142)	100 (74)
Prior external pelvic radiation				
Yes	15.6 (30)	16.2 (16)	14.8 (21)	16.2 (12)
No	84.4 (162)	83.8 (83)	85.2 (121)	83.8 (62)
Disease status				
Primary stage III	16.1 (31)	17.2 (17)	14.1 (20)	16.2 (12)
Primary stage IV	32.8 (63)	31.3 (31)	34.5 (49)	32.4 (24)
Recurrent	51.0 (98)	51.5 (51)	51.4 (73)	51.4 (38)

CP, carboplatin-paclitaxel; dMMR, MMR deficient; dostar, dostarlimab; MMR, mismatch repair; MMRp, MMR proficient; MSI, microsatellite instability; MSI-H, MSH high; MSS, microsatellite stable; nira, niraparib.
Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2.

Baseline Characteristics

Variable	Overall		MMRp/MSS	
	Dostar + CP followed by dostar + nira (N=192)	Placebo + CP followed by placebo (N=99)	Dostar + CP followed by dostar + nira (N=142)	Placebo + CP followed by placebo (N=74)
Age				
Median (range), y	65.0 (36–86)	64.0 (40–83)	65.0 (36–84)	64.5 (40–83)
≥65 y, % (n)	54.7 (105)	49.5 (49)	52.8 (75)	50.0 (37)
Race, % (n)				
White	84.9 (163)	77.8 (77)	85.2 (121)	77.0 (57)
Black	8.9 (17)	9.1 (9)	9.9 (14)	10.8 (8)
Asian	1.6 (3)	1.0 (1)	1.4 (2)	1.4 (1)
Other[a]	4.7 (9)	12.1 (12)	3.5 (5)	10.8 (8)
ECOG PS, % (n)[b]				
0	62.2 (117)	65.7 (65)	65.5 (91)	71.6 (53)
1	37.2 (70)	34.3 (34)	34.5 (48)	28.4 (21)
2	0.5 (1)[c]	0	0	0
BMI				
Median (range), kg/m^2	30.1 (17.0–56.2)	30.7 (1.6–70.2)	30.1 (17.4–56.2)	30.5 (1.6–70.2)

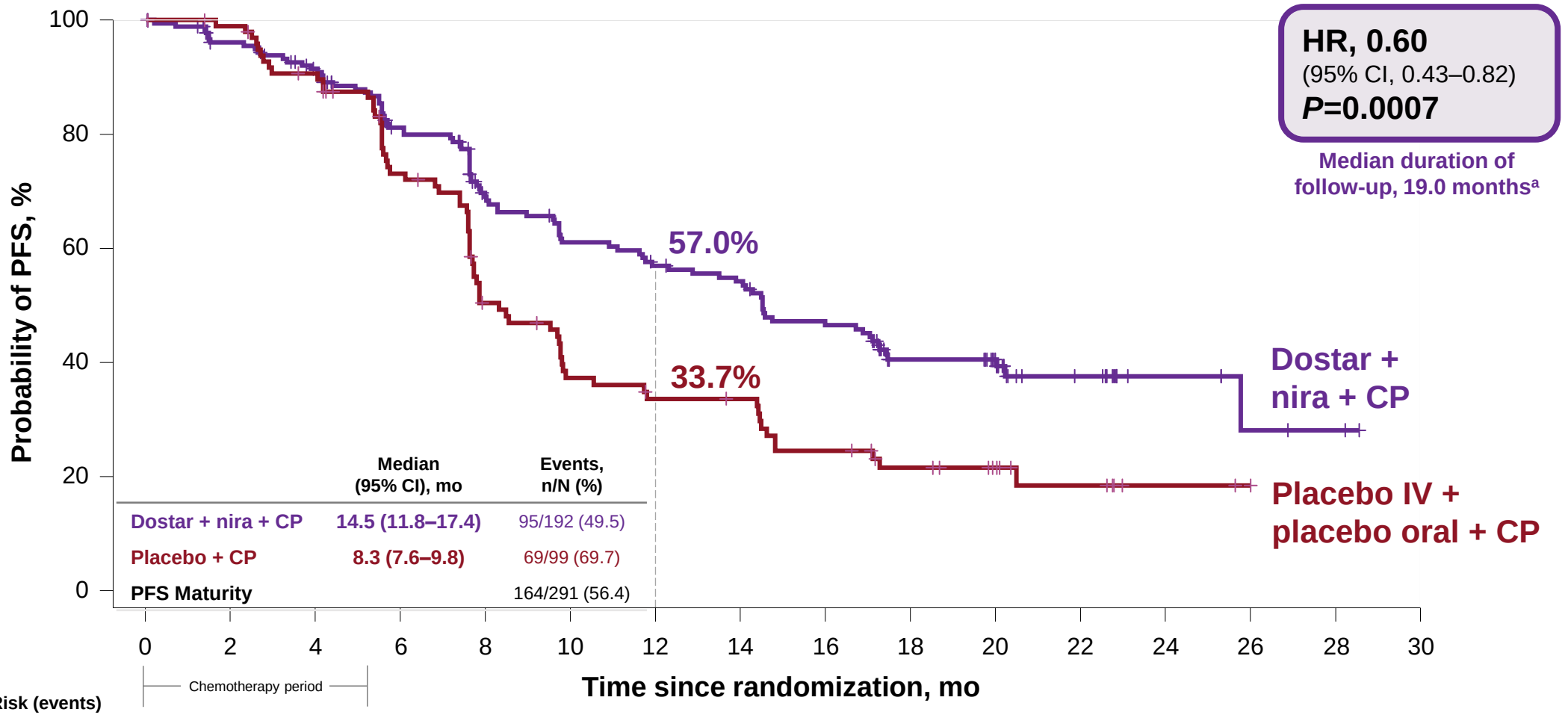
Variable	Overall		MMRp/MSS	
	Dostar + CP followed by dostar + nira (N=192)	Placebo + CP followed by placebo (N=99)	Dostar + CP followed by dostar + nira (N=142)	Placebo + CP followed by placebo (N=74)
Histology type, % (n)[d]				
Carcinosarcoma	9.4 (18)	10.1 (10)	12.0 (17)	12.2 (9)
Endometrioid[e]	63.0 (121)	69.7 (69)	54.2 (77)	62.2 (46)
Mixed carcinoma[f]	5.2 (10)	3.0 (3)	7.0 (10)	4.1 (3)
Serous adenocarcinoma	15.1 (29)	13.1 (13)	19.7 (28)	16.2 (12)
Clear cell adenocarcinoma	4.2 (8)	3.0 (3)	5.6 (8)	4.1 (3)
Mucinous adenocarcinoma	0.5 (1)	0	0	0
Undifferentiated carcinoma	1.6 (3)	0	0.7 (1)	0
Other	1.0 (2)	1.0 (1)	0.7 (1)	1.4 (1)
Evaluable disease at baseline, % (n)[g]				
Patients	84.4 (162)	86.9 (86)	84.5 (120)	85.1 (63)

[a]Other includes patients identifying as mixed race, unknown, or not reported. [b]Patients with ECOG score: 188 dostar + CP followed by dostar + nira overall, 99 placebo + CP followed by placebo overall, 139 dostar + CP followed by dostar + nira MMRp/MSS, 74 placebo + CP followed by placebo MMRp/MSS. [c]One patient had an ECOG PS of 2, and 1 patient had an ECOG PS of 2 or greater. [d]At diagnosis. [e]Adenocarcinoma or adenocarcinoma variants. [f]Mixed carcinoma ≥10% of carcinosarcoma, clear cell, or serous histology. [g]Includes patients with target or non-target lesions.

BMI, body mass index; CP, carboplatin-paclitaxel; dostar, dostarlimab; ECOG PS, Eastern Cooperative Oncology Group performance status; MMRp, mismatch repair proficient; MSS, microsatellite stable; nira, niraparib.

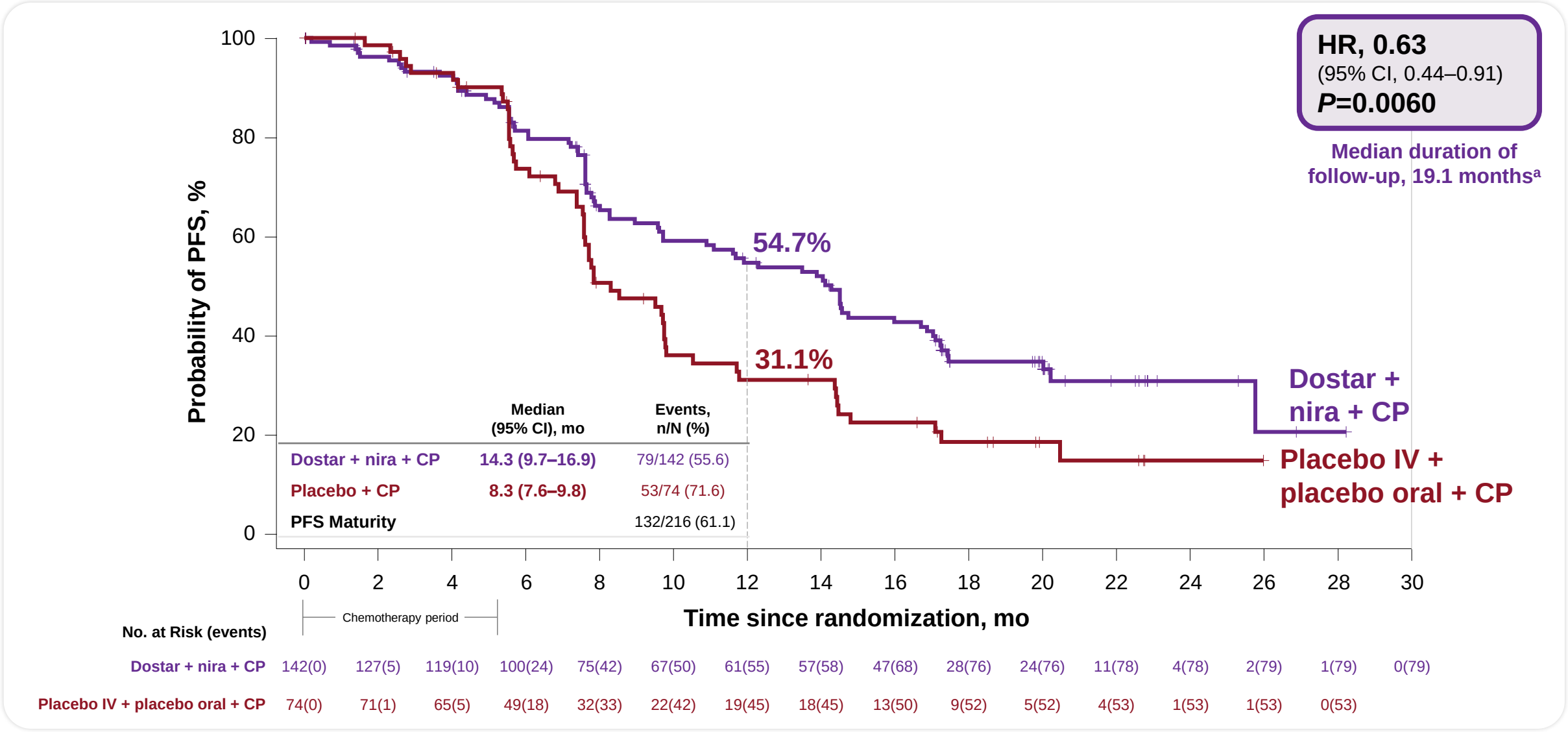
Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2.

Statistically Significant PFS Benefit in Overall Population – Primary Endpoint



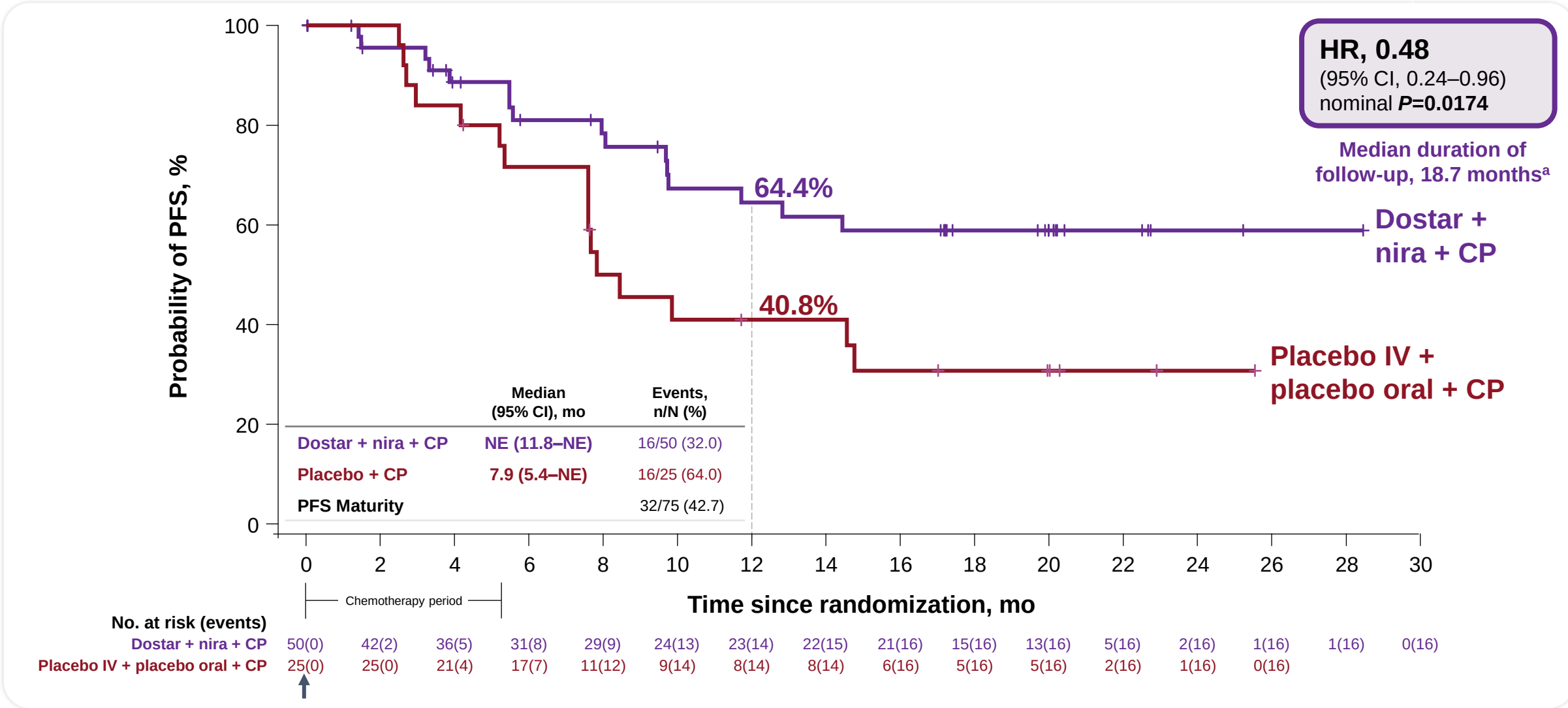
[a]Median expected duration of follow-up.
CI, confidence interval; CP, carboplatin-paclitaxel; dostar, dostarlimab; HR, hazard ratio; IV, intravenous; mo, month; nira, niraparib; No, number; PFS, progression-free survival.
Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2.

Statistically Significant PFS Benefit in MMRp/MSS Population – Primary Endpoint



[a]Median expected duration of follow-up.
CI, confidence interval; CP, carboplatin-paclitaxel; dostar, dostarlimab; HR, hazard ratio; IV, intravenous; MMRp, mismatch repair-proficient; mo, month; MSS, microsatellite stable; nira, niraparib; No, number; PFS, progression-free survival.
Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2.

Clinically Relevant PFS Difference in dMMR/MSI-H Population – Exploratory Endpoint



[a]Median expected duration of follow-up.
CI, confidence interval; CP, carboplatin-paclitaxel; dMMR, mismatch repair deficient; dostar, dostarlimab; HR, hazard ratio; IV, intravenous; mo, month; MSI-H, microsatellite instability high; NE, not estimable; nira, niraparib; No, number; PFS, progression-free survival.
Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2.

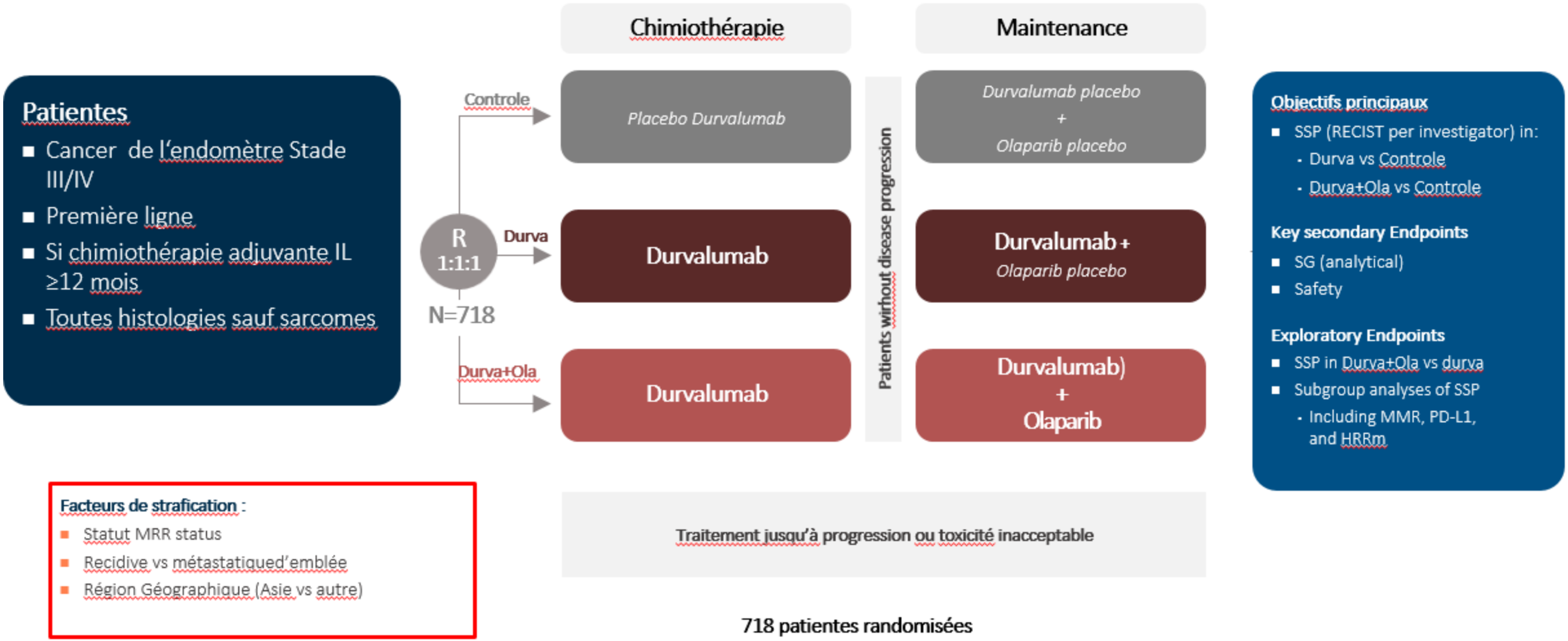
DUO-E/GOG-3041/ENGOT-EN10

Durvalumab (durva) plus carboplatine/paclitaxel (CP) suivi d'un traitement d'entretien (mtx) durva ± olaparib (ola) comme traitement de première ligne (1L) du cancer de l'endomètre (CE) avancé ou récurrent nouvellement diagnostiqué.

MADRID 2023 ESMO congress

Westin SN, Moore K, Chon HS, et al. Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial. J Clin Oncol. 2024

phase III DUO-E/COG-3041/ENGOT-EN10 trial
Intérêt du durvalumab ± olaparib associé à la chimiothérapie dans le cancer de l'endomètre récidivant ou métastatique

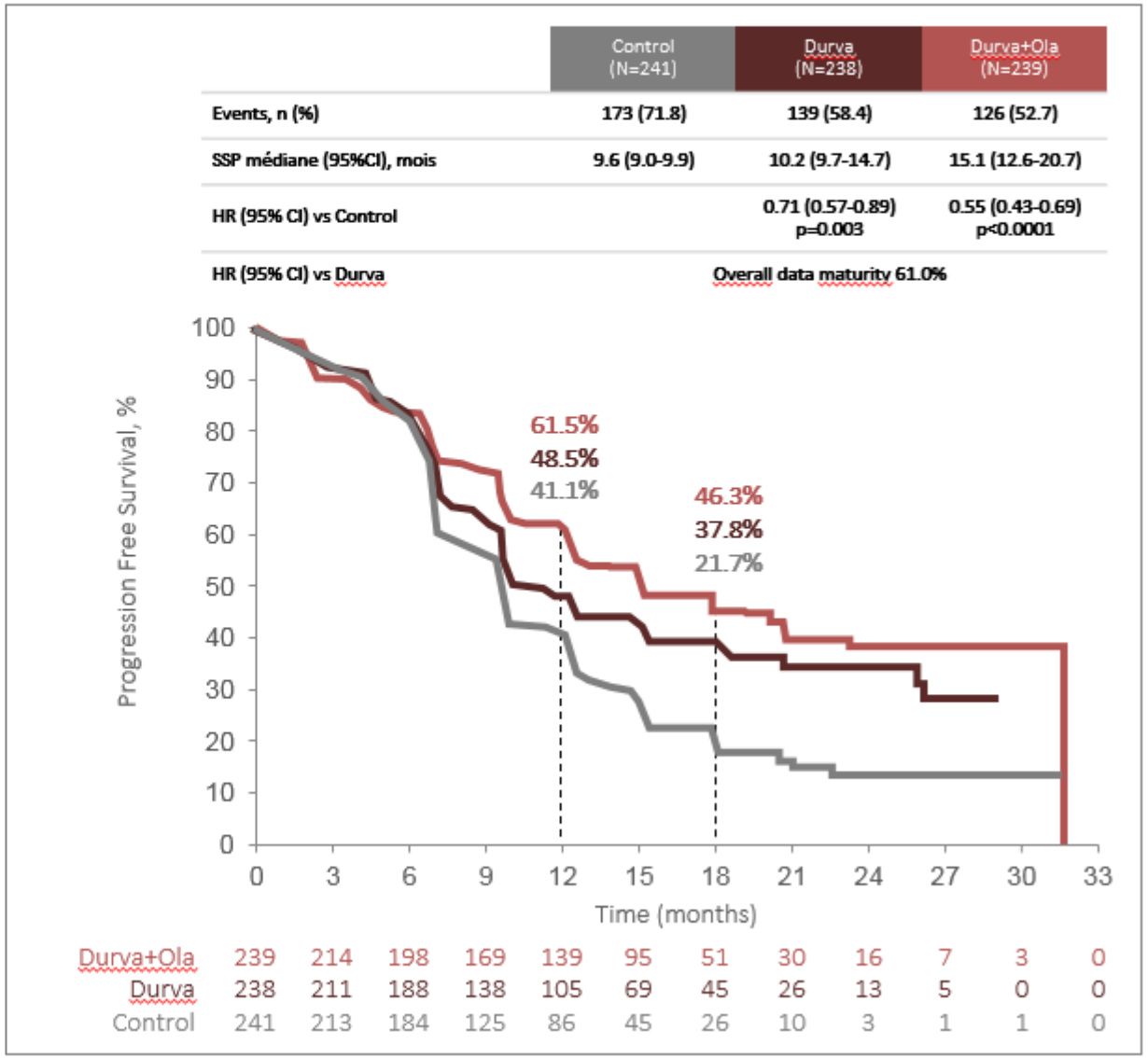


Westin SN, Moore K, Chon HS, et al. Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial. J Clin Oncol. 2024

Caractéristiques des patientes

	Control N=241	Durva N=238	Durva+Ola N=239
Age, ans, médiane	64 (31-85)	64 (22-84)	63 (27-86)
Statut de la maladie, %			
Nouvellement diagnostiqué	48	47	48
FIGO Stade III	5	7	5
FIGO Stade IV	42	40	41
Récidive	52	53	52
Histologie au diagnosic			
Endometriode	58	59	64
Sereux	22	24	18
Carcinosarcome	9	5	8
Mixte, epithelial	5	4	4
Cellules claires	3	2	3
Indifférenciés	1	2	2
Mucineux ou autre	2	4	2
Mesurable%	82	85	77
Statut MMR %			
Proficient	80	81	80
Deficient	20	19	20
PD-L1 statut, %			
Positif (TAP score ≥1%)	68	71	63
Negatif (TAP score <1%)	31	26	34
Indéterminé	1	3	3
HRRm statut, %			
HRRm	13	11	16
Non-HRRm	55	58	59
Unknown	32	31	25
Previous chemotherapy, %	**21**	**21**	**23**
Previous radiotherapy, %	**29**	**31**	**36**
Prior surgery, %	**84**	**86**	**87**

SSP en ITT

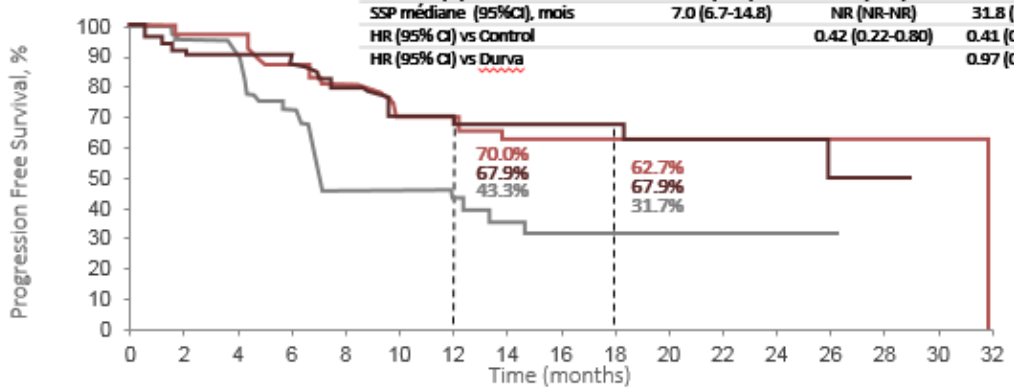


Westin SN, Moore K, Chon HS, et al. Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial. J Clin Oncol. 2024

SSP selon statut MMR

dMMR (20% of population)

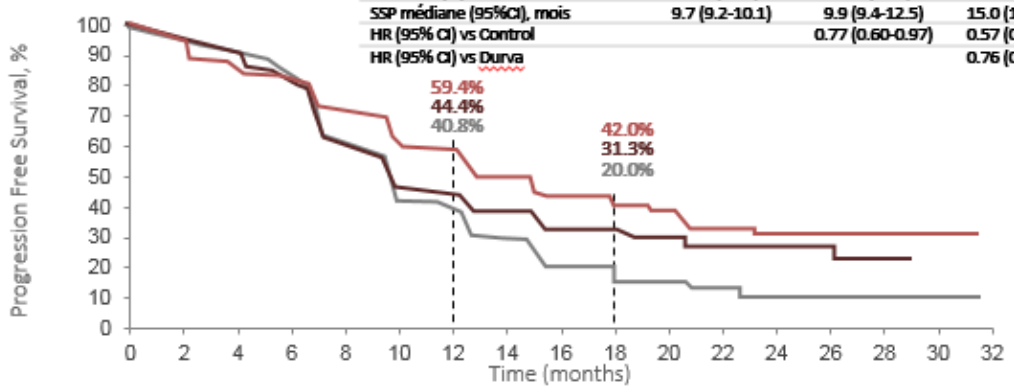
	Control (N=49)	Durva (N=46)	Durva+Ola (N=48)
Events, n (%)	25 (51.0)	15 (32.6)	18 (37.5)
SSP médiane (95%CI), mois	7.0 (6.7-14.8)	NR (NR-NR)	31.8 (12.4-NR)
HR (95% CI) vs Control		0.42 (0.22-0.80)	0.41 (0.21-0.75)
HR (95% CI) vs Durva			0.97 (0.49-1.98)



Durva+Ola	49	43	39	28	17	16	13	9	7	5	4	2	2	2	0	0	0
Durva	46	40	37	36	32	27	26	19	17	14	11	9	5	5	2	0	0
Control	48	46	46	41	38	32	32	23	18	16	26	10	4	3	1	1	0

pMMR (80% of population)

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

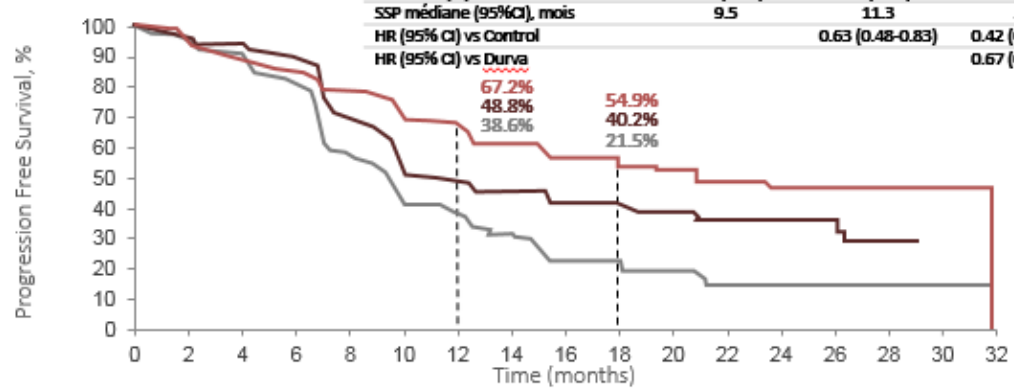


Durva+Ola	192	178	170	156	113	77	73	40	25	21	13	7	1	1	1	1	0
Durva	192	182	169	152	113	83	79	53	36	31	27	15	8	7	2	0	0
Control	191	183	164	157	134	114	107	75	46	35	31	19	12	10	5	2	0

SSP selon statut PD-L1

PD-L1 positive (TAP ≥1%; 69% of population)

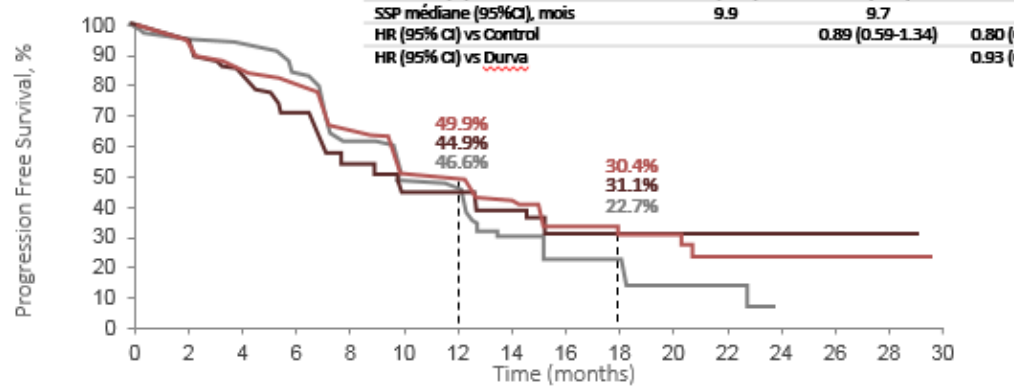
	Control (N=163)	Durva (N=170)	Durva+Ola (N=150)
Events, n (%)	114 (69.9)	97 (57.1)	68 (45.3)
SSP médiane (95%CI), mois	9.5	11.3	20.8
HR (95% CI) vs Control		0.63 (0.48-0.83)	0.42 (0.31-0.57)
HR (95% CI) vs Durva			0.67 (0.49-0.91)



Durva+Ola	150	144	135	126	116	101	95	66	45	40	37	23	13	10	5	3	0
Durva	170	158	152	142	109	80	75	53	43	38	33	21	12	11	3	0	0
Control	163	149	139	122	85	58	53	22	22	17	13	7	3	3	1	1	0

PD-L1 negative (TAP <1%; 31% of population)

	Control (N=75)	Durva (N=61)	Durva+Ola (N=82)
Events, n (%)	57 (76.0)	38 (62.3)	55 (67.1)
SSP médiane (95%CI), mois	9.9	9.7	10.1
HR (95% CI) vs Control		0.89 (0.59-1.34)	0.80 (0.55-1.16)
HR (95% CI) vs Durva			0.93 (0.61-1.41)



Durva+Ola	82	78	69	66	51	40	39	28	18	10	9	6	3	3	2	0
Durva	61	57	48	41	31	25	25	16	9	6	4	3	1	1	1	0
Control	75	69	68	60	44	34	33	16	10	9	4	2	0	0	0	0

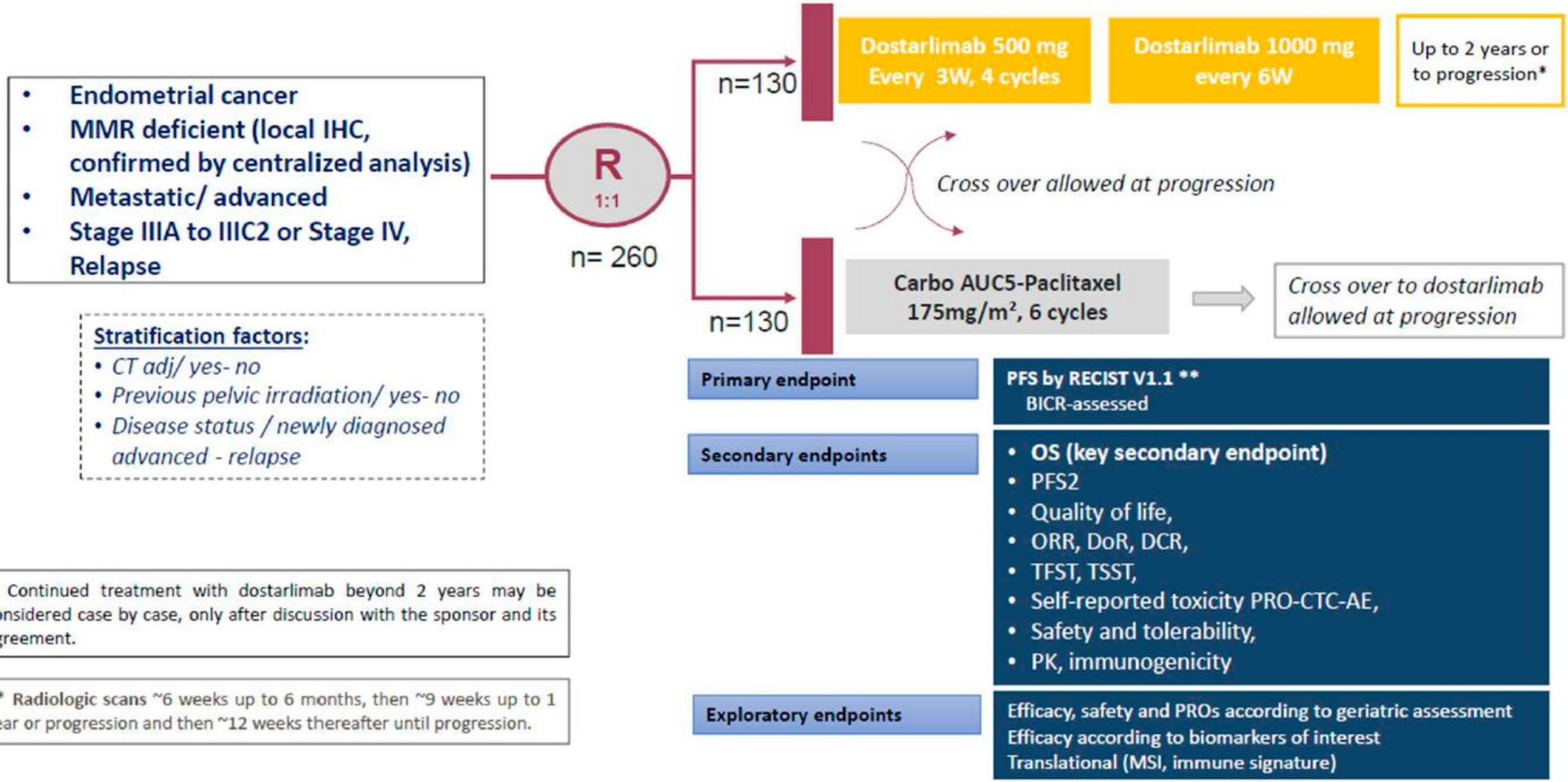
Westin SN, Moore K, Chon HS, et al. Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial. J Clin Oncol. 2024

Conclusion

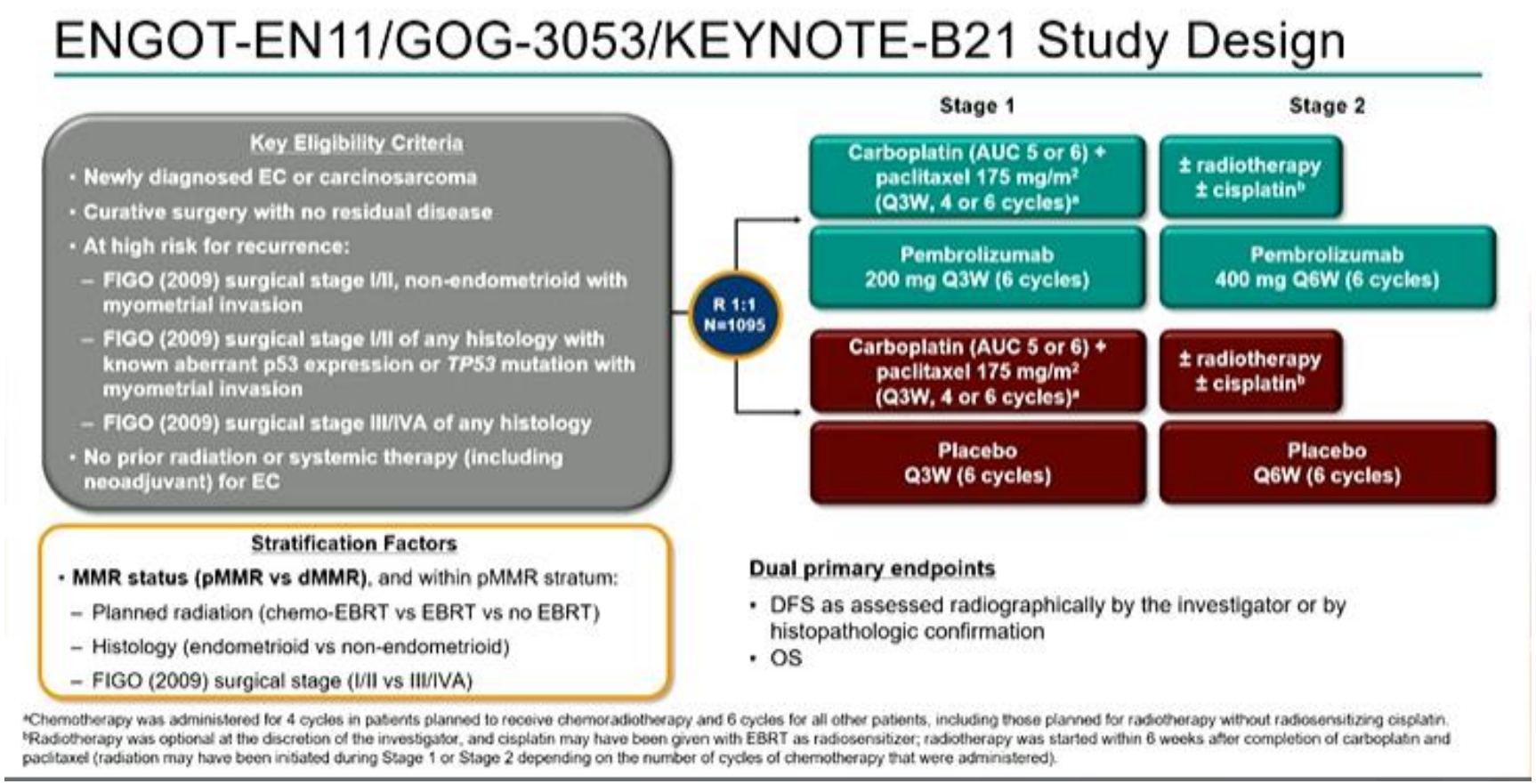
- **Chimiothérapie + anti-PD(L)1 en 1ere ligne : 5 études de phase III positives = un standard validé**
  - Bénéfice +++ chez les dMMR : ***HR = 0,3***
  - Bénéfice ++ chez les pMMR (anti PD-1 > anti PD-L1) : ***HR = 0,6***

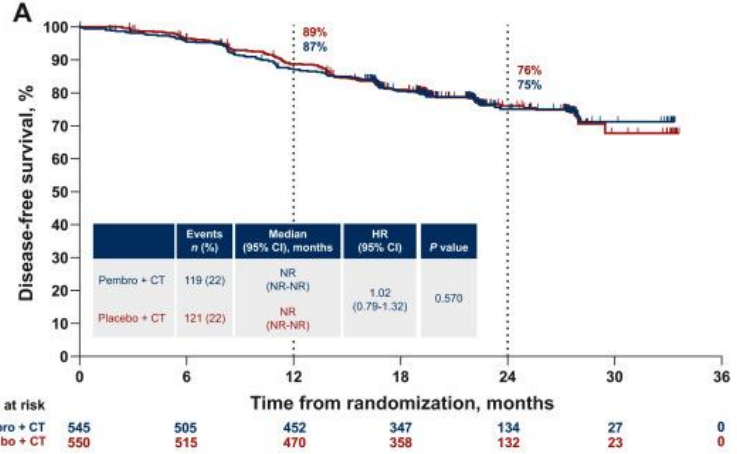
Nécessité de la chimiothérapie chez les dMMR ?

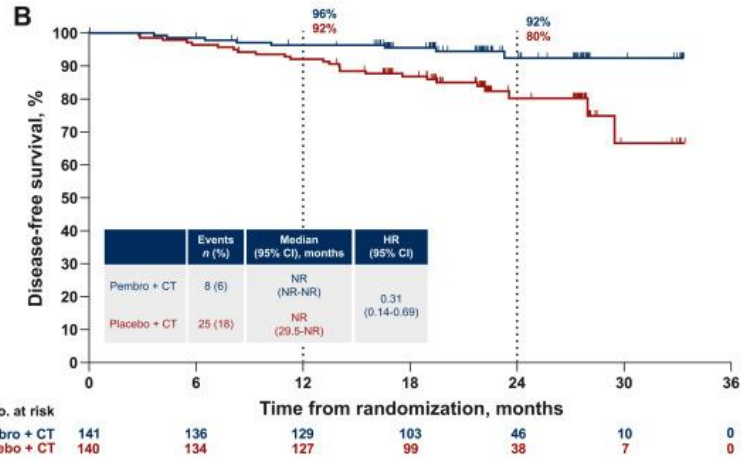
DOMENICA

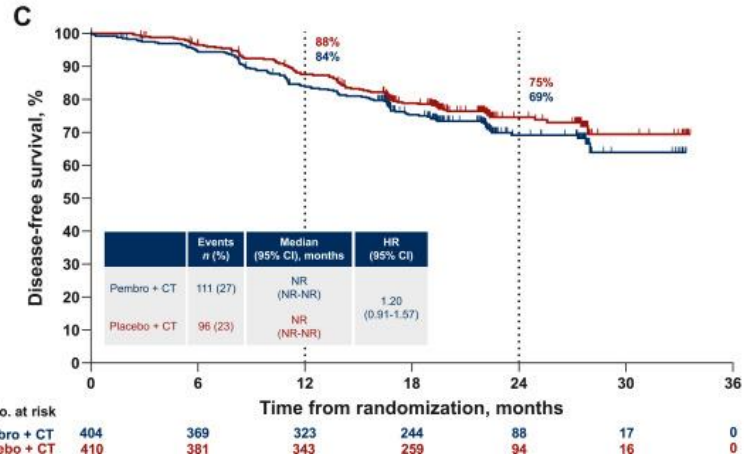

Endometrial cancer
MMR deficient (local IHC, confirmed by centralized analysis)
Metastatic/ advanced
Stage IIIA to IIIC2 or Stage IV, Relapse
Stratification factors:
CT adj/ yes- no
Previous pelvic irradiation/ yes- no
Disease status / newly diagnosed advanced - relapse
R
1:1
n= 260
n=130
n=130
Dostarlimab 500 mg Every 3W, 4 cycles
Dostarlimab 1000 mg every 6W
Up to 2 years or to progression*
Cross over allowed at progression
Carbo AUC5-Paclitaxel 175mg/m², 6 cycles
Cross over to dostarlimab allowed at progression
Primary endpoint
PFS by RECIST V1.1 **
BICR-assessed
Secondary endpoints
OS (key secondary endpoint)
PFS2
Quality of life,
ORR, DoR, DCR,
TFST, TSST,
Self-reported toxicity PRO-CTC-AE,
Safety and tolerability,
PK, immunogenicity
Exploratory endpoints
Efficacy, safety and PROs according to geriatric assessment
Efficacy according to biomarkers of interest
Translational (MSI, immune signature)
* Continued treatment with dostarlimab beyond 2 years may be considered case by case, only after discussion with the sponsor and its agreement.
** Radiologic scans ~6 weeks up to 6 months, then ~9 weeks up to 1 year or progression and then ~12 weeks thereafter until progression.

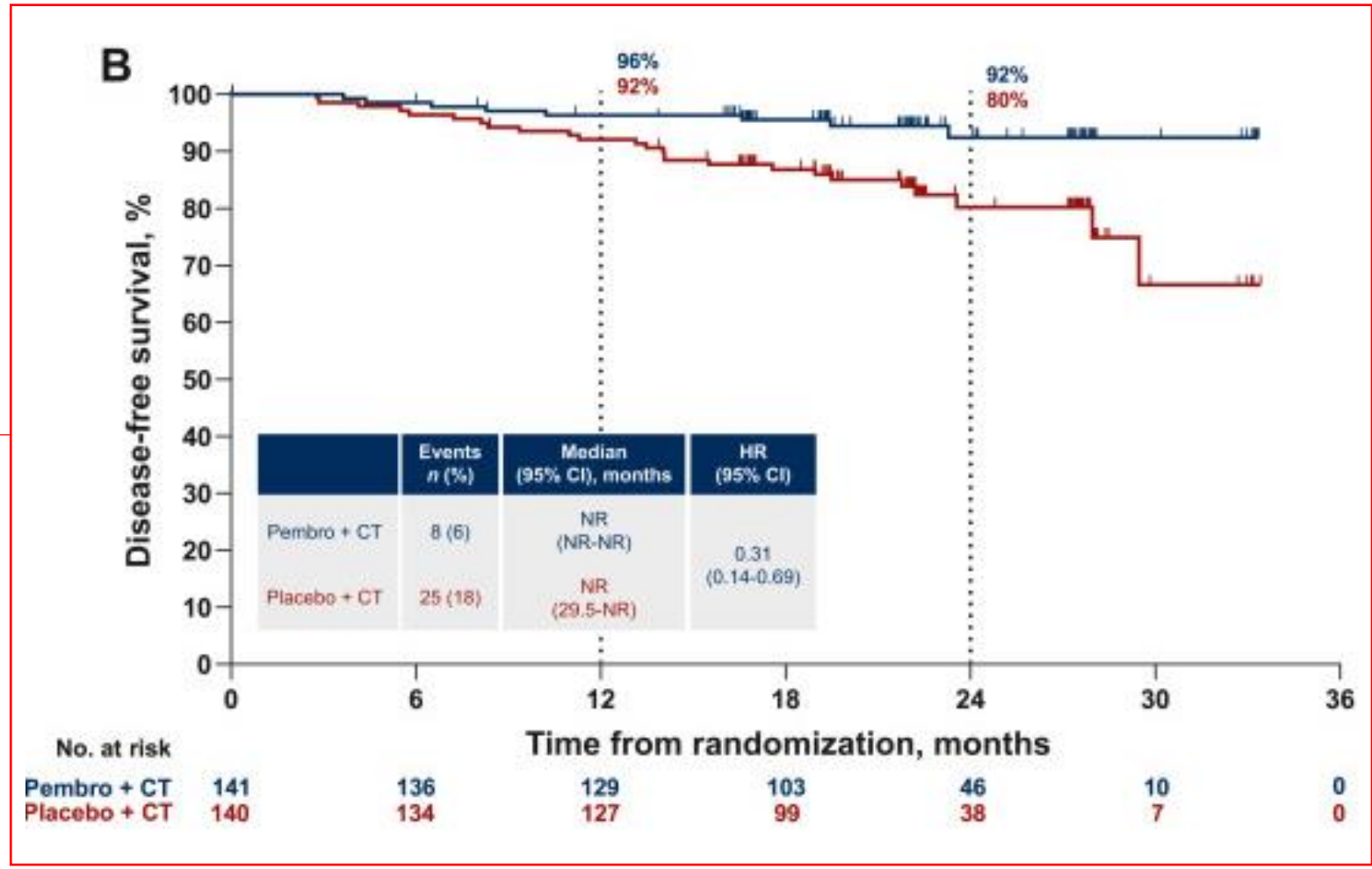
Une place en adjuvant ?











Peut être chez les dMMR

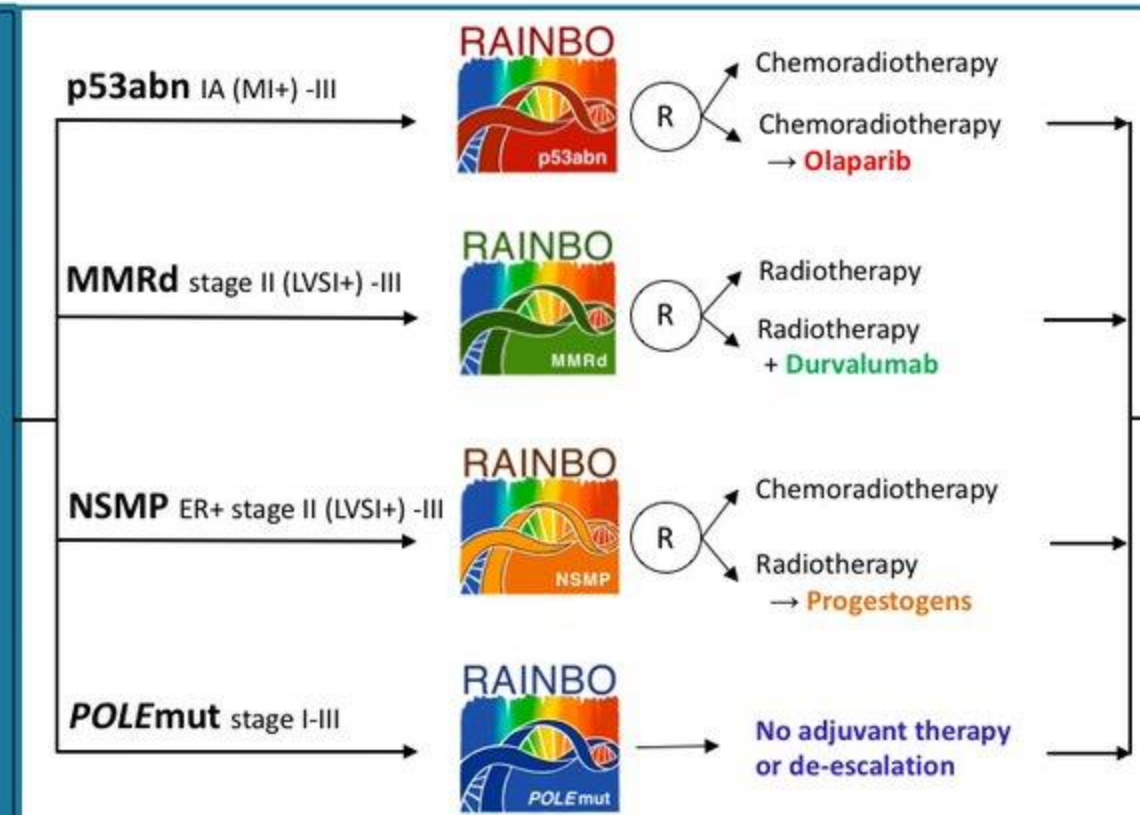
INTERNATIONAL JOURNAL OF
GYNECOLOGICAL CANCER

Refining Adjuvant treatment IN endometrial cancer Based On molecular features: the RAINBO clinical trial program

Women with completely resected stage I-III endometrial cancer

Eligible histotypes: endometrioid, serous, clear cell, un/dedifferentiated, mixed and carcinosarcoma

Molecular profiling according to the WHO 2020 classification



Uniform data registration and central tumor tissue biobanking

RAINBO

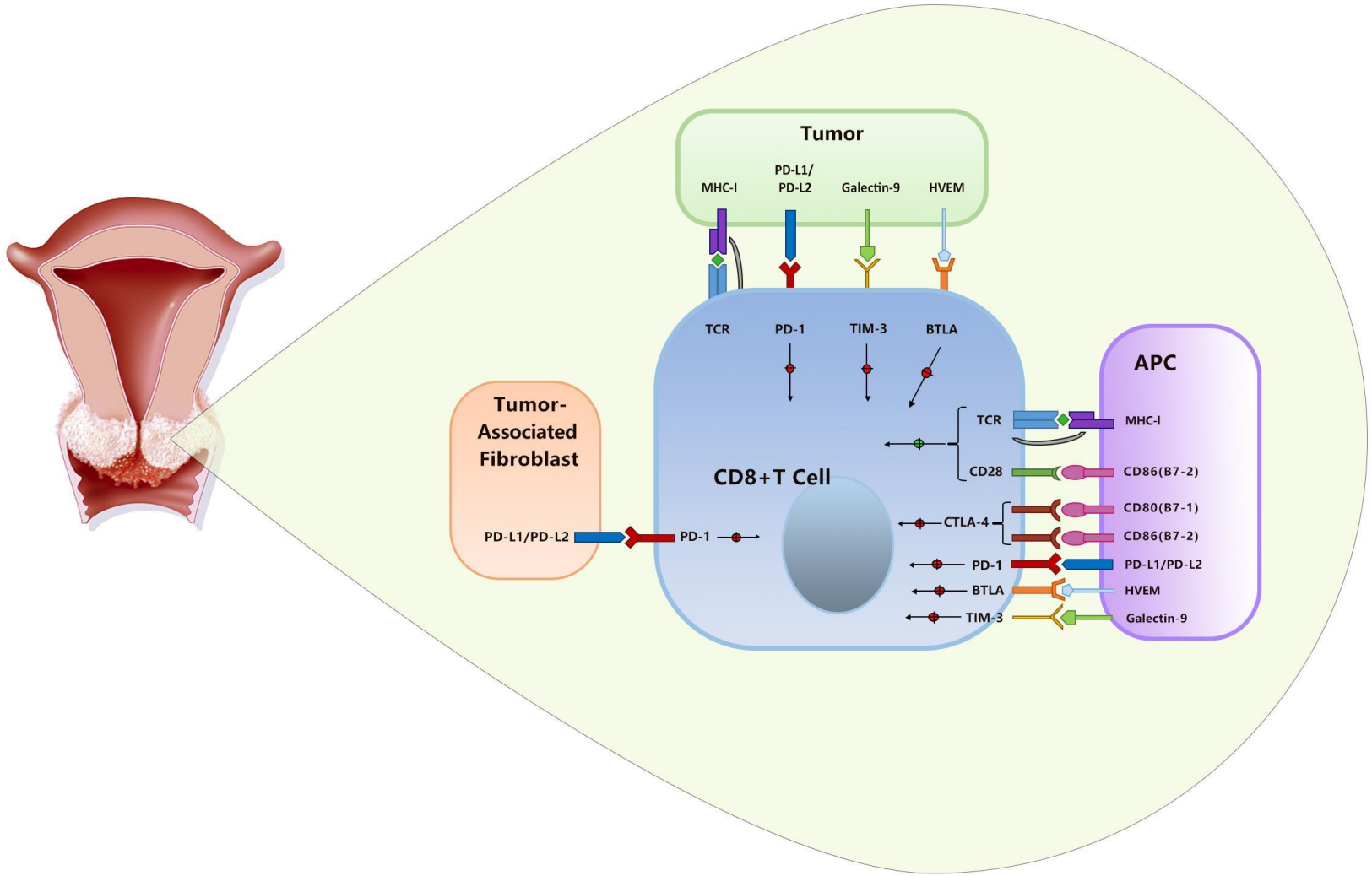
Overarching and translational research program

@IJGConline

The RAINBO Research Consortium

@RAINBOprogram

Le cancer du col utérin



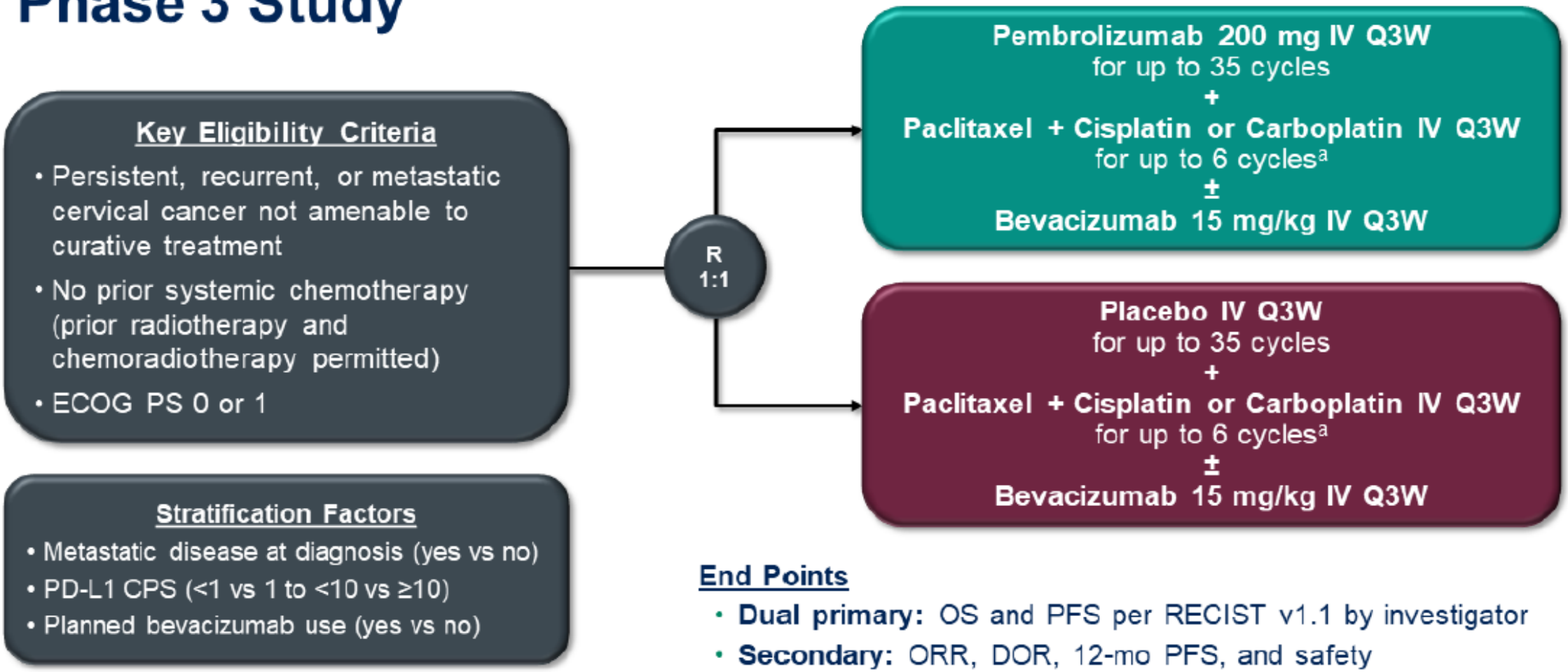
2023 ASCO ANNUAL MEETING

Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy for Persistent, Recurrent, or Metastatic Cervical Cancer: Final Overall Survival Results of KEYNOTE-826

Bradley J. Monk,[1] Nicoletta Colombo,[2,3] Krishnansu S. Tewari,[4] Coraline Dubot,[5] M. Valeria Caceres,[6] Kosei Hasegawa,[7] Ronnie Shapira-Frommer,[8] Pamela Salman,[9] Eduardo Yañez,[10] Mahmut Gümüş,[11] Mivael Olivera Hurtado de Mendoza,[12] Vanessa Samouëlian,[13] Vincent Castonguay,[14] Alexander Arkhipov,[15] Cumhur Tekin,[16] Kan Li,[16] Stephen M. Keefe,[16] Domenica Lorusso,[17] on behalf of the KEYNOTE-826 Investigators

[1]HonorHealth Research Institute, University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, AZ, USA; [2]Gynecologic Oncology, European Institute of Oncology IRCCS and [3]Università degli Studi di Milano Bicocca, Milan, Italy; [4]Obstetrics & Gynecology, University of California, Irvine, Orange, CA, USA; [5]Oncologie Médicale, Institut Curie Saint Cloud, and GINECO, Paris, France; [6]Medical Oncology, Instituto de Oncologia Angel H. Roffo, Buenos Aires, Argentina; [7]Gynecologic Oncology, Saitama Medical University International Medical Center, Hidaka, Japan; [8]Ella Lemelbaum Institute for Immuno-Oncology, Sheba Medical Center, Ramat Gan, Israel; [9]Medical Oncology, Oncovida Cancer Center, Providencia, Santiago, Chile; [10]Medical Oncology, Universidad de la Frontera, Temuco, Chile; [11]Medical Oncology, Istanbul Medeniyet University Hospital, Istanbul, Turkey; [12]Medical Oncology, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; [13]Gynecologic Oncology, Centre Hospitalier de l'Université de Montréal (CHUM), Centre de Recherche de l'Université de Montréal (CRCHUM), Université de Montréal, Montreal, QC, Canada; [14]Medical Oncology, Centre Hospitalier Universitaire de Québec, Université Laval, Quebec City, QC, Canada; [15]Oncology and Chemical Therapy, Medical Rehabilitation Center under the Ministry of Health of Russian Federation, Moscow, Russian Federation; [16]Oncology, Merck & Co., Inc., Rahway, NJ, USA; [17]Gynaecology Oncology Unit, Fondazione Policlinico Universitario A Gemelli IRCCS and Catholic University of Sacred Heart, Rome, Italy

KEYNOTE-826: Randomized, Double-Blind, Phase 3 Study

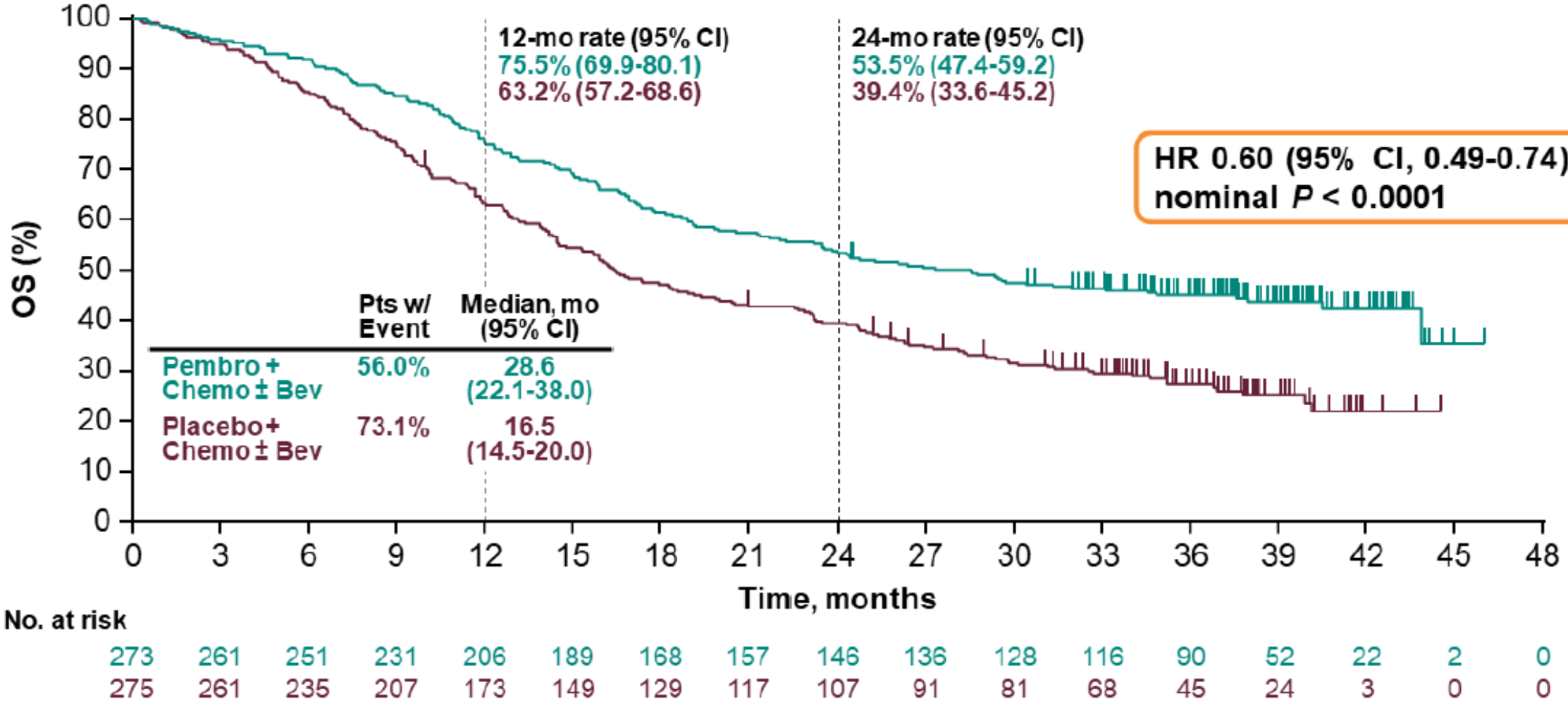


End Points

- **Dual primary:** OS and PFS per RECIST v1.1 by investigator
- **Secondary:** ORR, DOR, 12-mo PFS, and safety

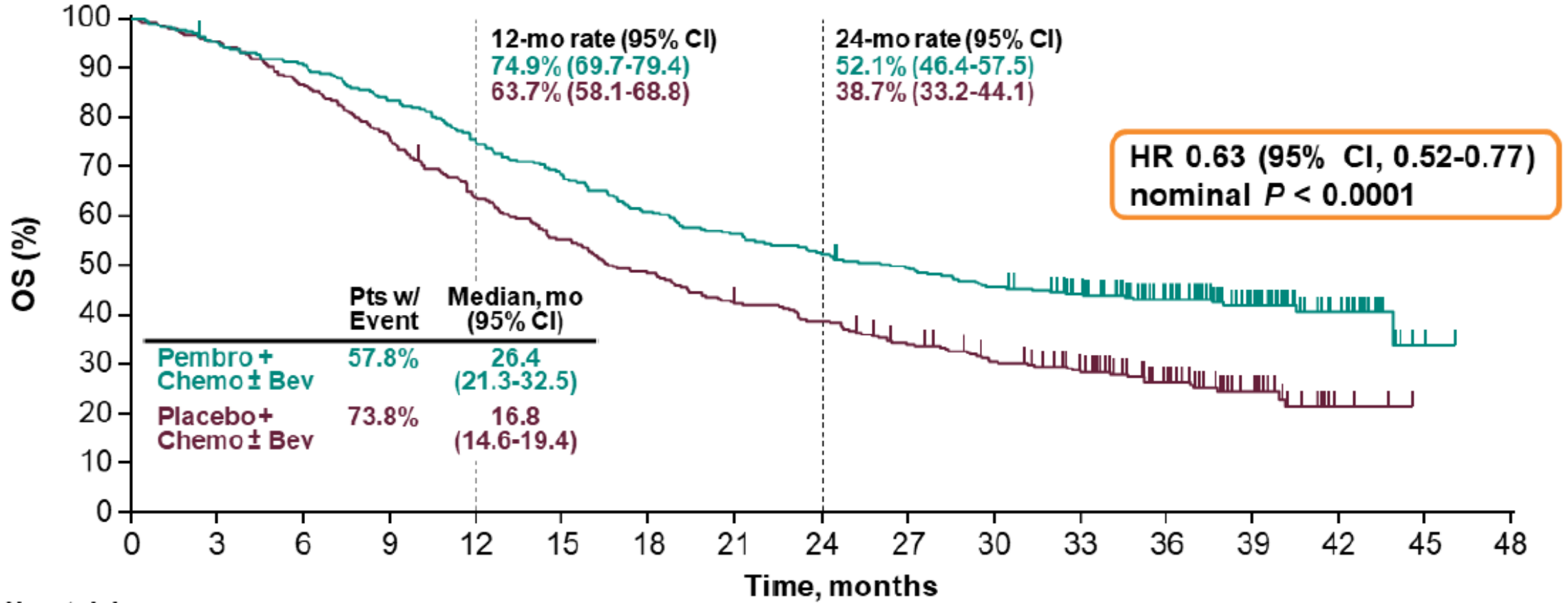
[a]Paclitaxel: 175 mg/m^2. Cisplatin: cisplatin 50 mg/m^2. Carboplatin: AUC 5 mg/mL/min. The 6-cycle limit was introduced with protocol amendment 2, although participants with ongoing clinical benefit who were tolerating chemotherapy could continue beyond 6 cycles after sponsor consultation. CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100). KEYNOTE-826 ClinicalTrials.gov identifier, NCT03635567.

Protocol-Specified Final OS: PD-L1 CPS ≥1 Population



Data cutoff date: October 3, 2022.

Protocol-Specified Final OS: All-Comer Population

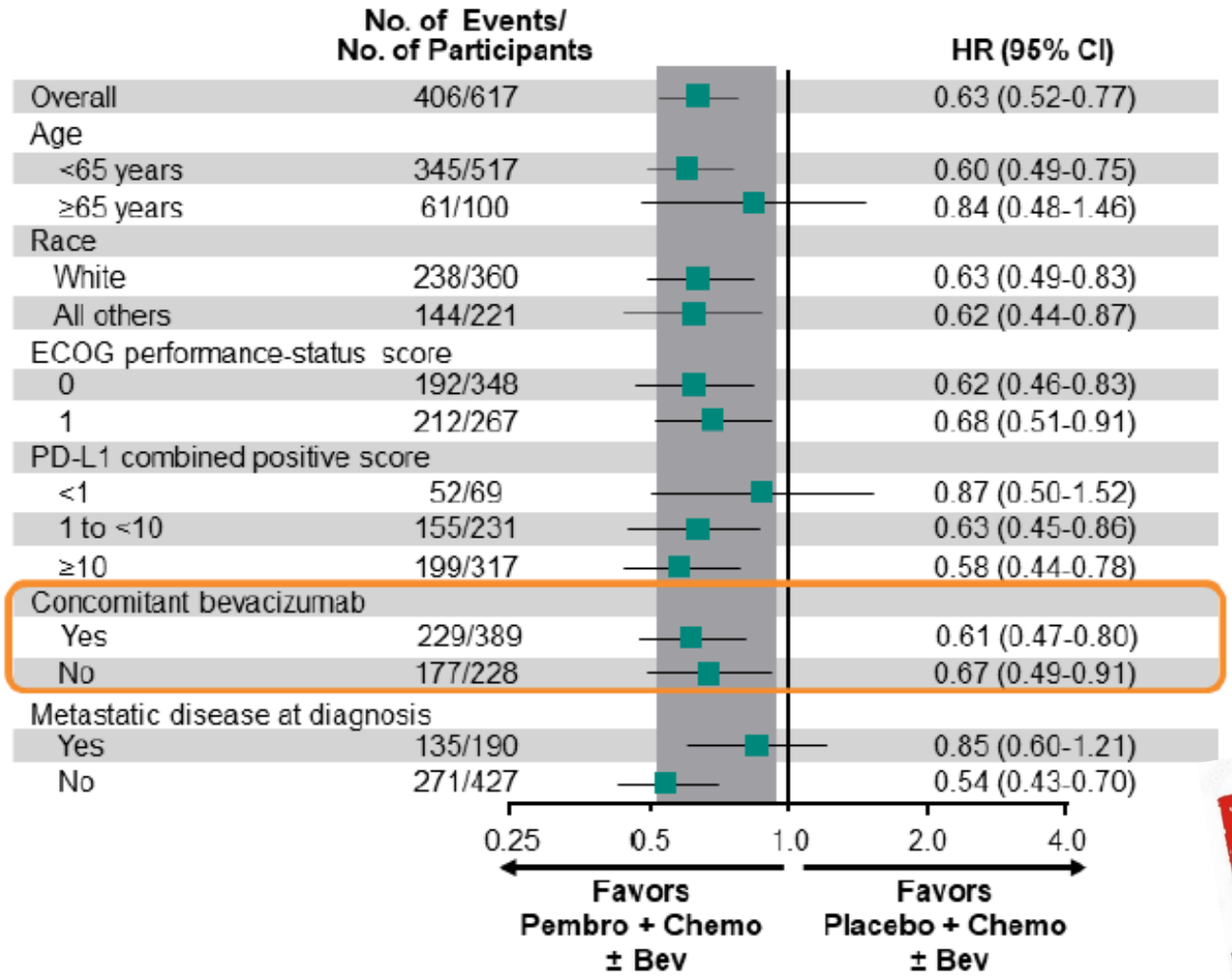


No. at risk

308	292	278	256	230	210	187	173	160	150	138	125	95	55	22	2	0
309	295	268	235	196	170	149	130	118	101	87	72	48	26	3	0	0

Data cutoff date: October 3, 2022.

Protocol-Specified Final OS in Subgroups, All-Comer Population



Data cutoff date: October 3, 2022.

En 2e ligne ?

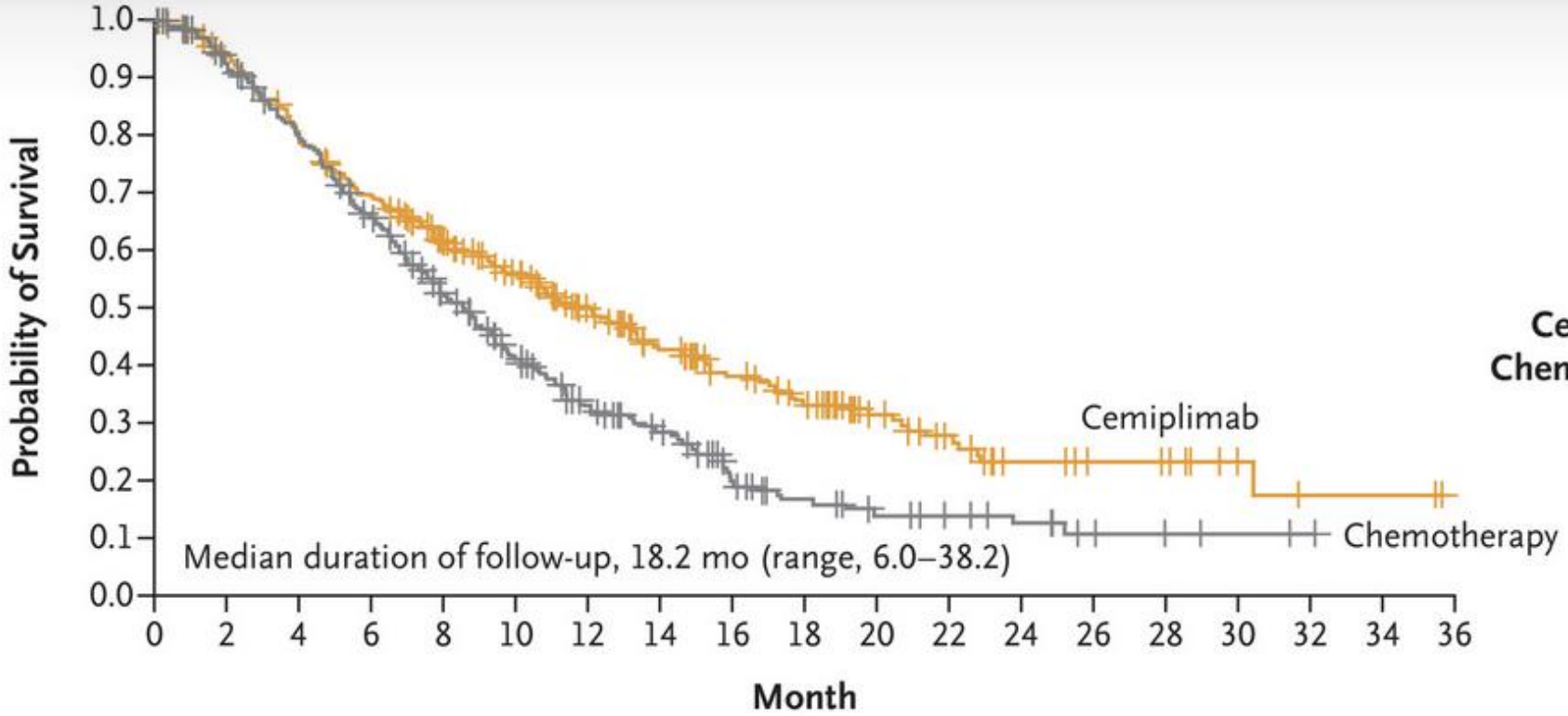
ORIGINAL ARTICLE

Survival with Cemiplimab in Recurrent Cervical Cancer

Authors: Krishnansu S. Tewari, M.D., Bradley J. Monk, M.D., Ignace Vergote, M.D., Austin Miller, Ph.D., Andreia C. de Melo, M.D., Ph.D. , Hee-Seung Kim, M.D., Yong Man Kim, M.D., Ph.D., +28 , for the Investigators for GOG Protocol 3016 and ENGOT Protocol En-Cx9* Author Info & Affiliations

Published February 9, 2022 | N Engl J Med 2022;386:544-555 | DOI: 10.1056/NEJMoa2112187 | VOL. 386 NO. 6

A Overall Survival, All Patients

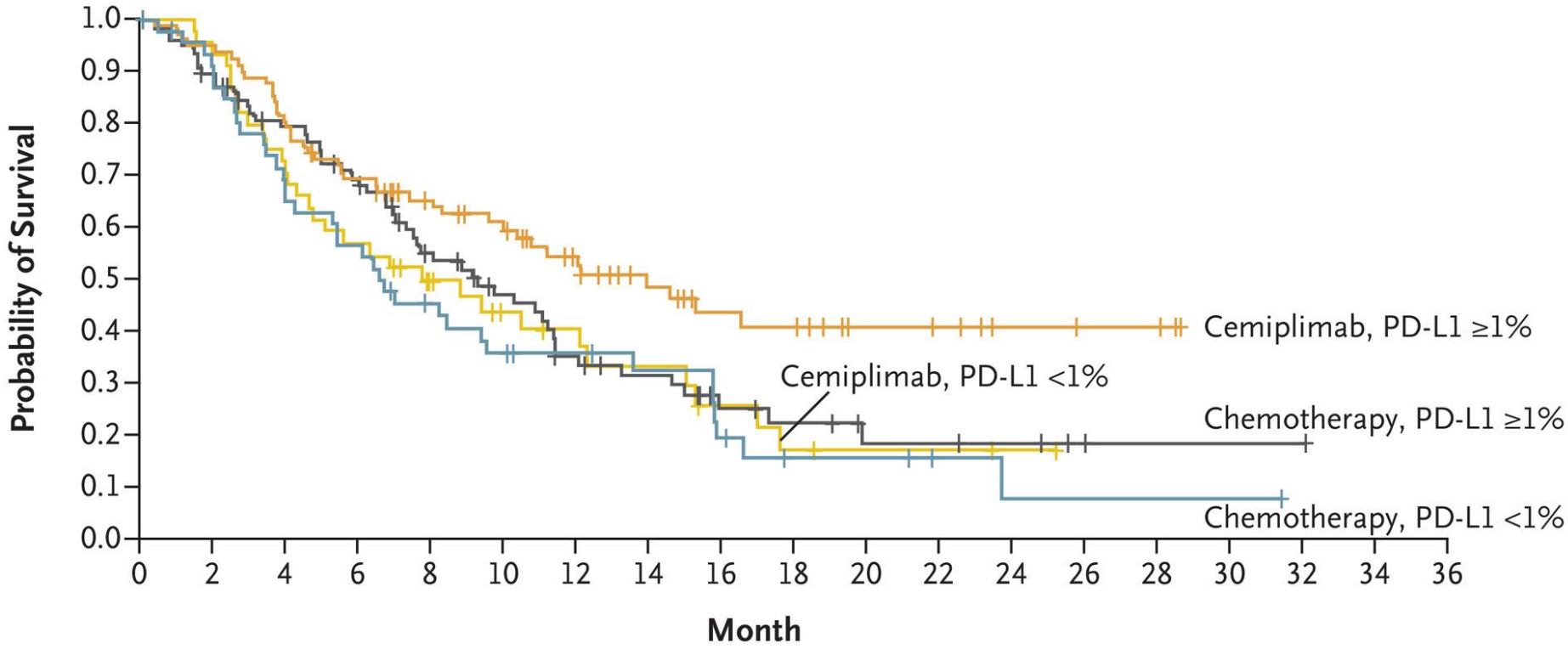


	No. of Patients	Median Overall Survival (95% CI)
		mo
Cemiplimab	304	12.0 (10.3–13.5)
Chemotherapy	304	8.5 (7.5–9.6)

Hazard ratio for death, 0.69
(95% CI, 0.56–0.84)
Two-sided P<0.001

No. at Risk

Cemiplimab	304	281	236	206	167	139	110	83	65	52	35	26	13	10	9	4	2	2	0
Chemotherapy	304	264	224	183	132	99	70	54	32	22	15	12	9	5	3	2	1	0	0



No. at Risk

Cemiplimab, PD-L1 ≥1%	82	78	65	55	45	39	30	22	16	15	10	9	4	3	3	0	0	0	0
Cemiplimab, PD-L1 <1%	44	41	30	25	18	13	11	9	6	4	3	3	1	0	0	0	0	0	0
Chemotherapy, PD-L1 ≥1%	80	69	58	50	36	28	20	16	10	8	5	5	4	2	1	1	1	0	0
Chemotherapy, PD-L1 <1%	48	40	30	26	19	15	12	10	6	4	4	2	1	1	1	1	0	0	0

Une place pour les tumeurs localisées/localement avancées ?

EDITORIAL

Improved Treatment for Cervical Cancer — Concurrent Chemotherapy and Radiotherapy

Author: Gillian M. Thomas, M.D. Author Info & Affiliations

Published April 15, 1999 | N Engl J Med 1999;340:1198-1200 | DOI: 10.1056/NEJM199904153401509
VOL. 340 NO. 15 | Copyright © 1999

Radiochimiothérapie concomitante :

- *Chimiothérapie* — *Radiothérapie*

Platine hebdo (40 mg/m2) — *pelvis +/- LA 45 Gy / 25 fc*

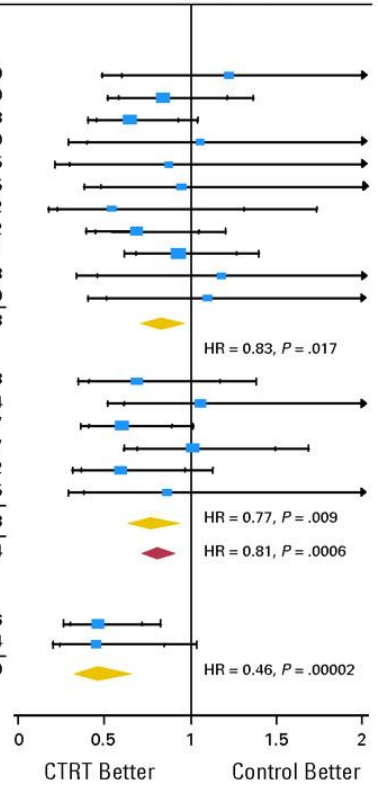
+

Curiethérapie utérovaginale guidée par image (IGBT)

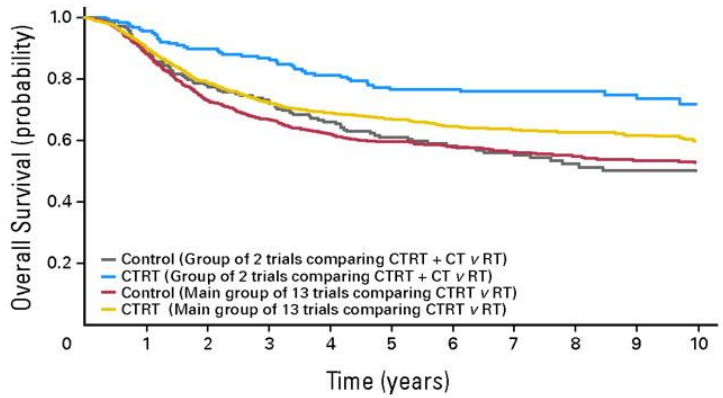
Etalement: = *55 jours* *(Mazeron,Radioth Oncol, 2015)*

A

Trial ID	CTRT events	CTRT pts.	Control events	Control pts.	O-E	Variance
Trials of Chemoradiation *v* radiotherapy						
(a) Platinum-based CTRT						
Onishi[44] (CDDP or CDBCA)	16	26	15	23	1.52	7.59
Pearcey[43] (CDDP)	53	130	60	129	-5.00	28.20
GOG0123[6] (CDDP)	49	185	69	189	-12.90	29.38
Chen[23] (a) (CDDP FU VCR)	8	30	8	30	0.21	4.00
Chen[23] (b) (CDDP FU VCR)	6	30	7	30	-0.45	3.25
Pras (CDBCA FU)	17	28	16	26	-0.47	8.15
GOG0165[26] (a) (CDDP)	8	26	12	24	-3.03	4.92
Cikaric[47] (CDDP)	37	100	48	100	-8.02	21.12
Leborgne (CDDP FU)	75	170	85	170	-3.07	39.91
Gariapagaoglu[48] (CDDP)	9	22	8	22	0.70	4.23
Lal[50] (CDDP)	14	94	12	86	0.62	6.49
Sub-total	292	841	340	829	-29.89	157.23
(b) Non–platinum-based CTRT						
Thomas[24] (a) (FU)	24	57	32	58	-5.16	13.83
Thomas[24] (b) (FU)	26	58	25	60	0.71	12.74
Lorvidhaya[25] (a) (MMC FU)	40	233	59	242	-12.52	24.57
Lorvidhaya[25] (b) (MMC FU)	54	230	49	221	0.31	25.67
Roberts[49] (MMC)	25	124	39	124	-8.39	15.92
GOG0165[26] (b) (FU)	11	27	12	24	-0.82	5.55
Sub-total	180	729	216	729	-25.87	98.28
Total	472	1,570	544	1,534	-54.56	251.54
Trials of CTRT + adjuvant chemotherapy *v* radiotherapy						
SWOG8797[8,46] (CDDP FU)	28	135	54	133	-15.61	20.36
Kantardzic[45] (CDDP BLM)	15	40	25	40	-7.74	9.74
Sub-total	43	175	79	173	-23.35	30.10



B



No. at risk

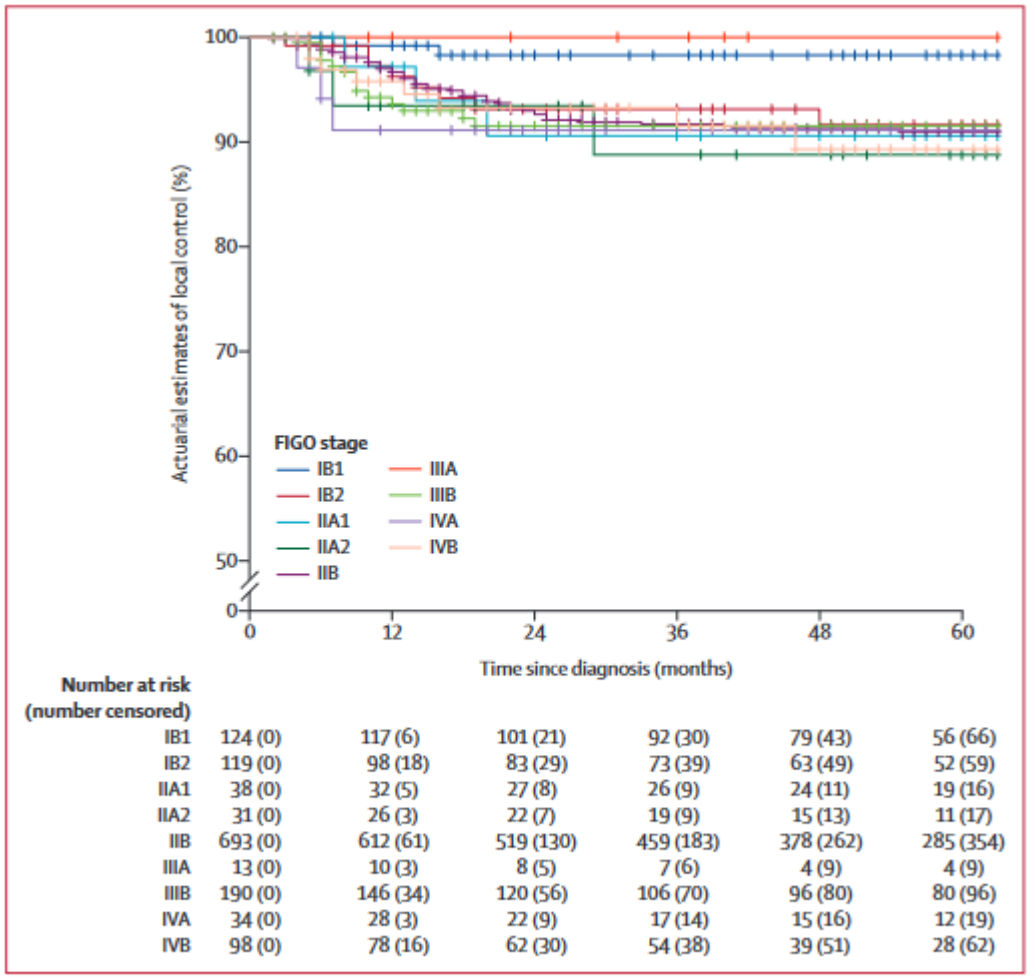
Main group of 13 trials (Additional numbers at risk on control arm due to double counting of control arm from one three-arm trial[26])

Control	1,558	1,244	921	760	610	499	350	274	192	131	81
CTRT	1,570	1,285	1,019	836	694	582	401	309	223	158	101
Group of two trials comparing CTRT + CT *v* RT											
Control	173	155	133	121	106	95	82	67	51	35	21
CTRT	175	165	155	144	129	115	106	89	74	58	37

Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials, JCO 2008

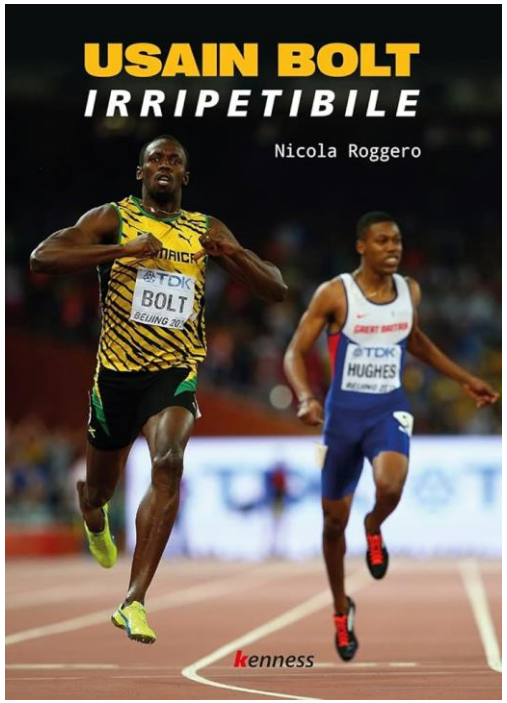
IMRT / VMAT

- Controle local à 5 ans >90%
- Survie globale à 5 ans : 75%
- Profil de toxicité diminué



Number at risk (number censored)						
IB1	124 (0)	117 (6)	101 (21)	92 (30)	79 (43)	56 (66)
IB2	119 (0)	98 (18)	83 (29)	73 (39)	63 (49)	52 (59)
IIA1	38 (0)	32 (5)	27 (8)	26 (9)	24 (11)	19 (16)
IIA2	31 (0)	26 (3)	22 (7)	19 (9)	15 (13)	11 (17)
IIB	693 (0)	612 (61)	519 (130)	459 (183)	378 (262)	285 (354)
IIIA	13 (0)	10 (3)	8 (5)	7 (6)	4 (9)	4 (9)
IIIB	190 (0)	146 (34)	120 (56)	106 (70)	96 (80)	80 (96)
IVA	34 (0)	28 (3)	22 (9)	17 (14)	15 (16)	12 (19)
IVB	98 (0)	78 (16)	62 (30)	54 (38)	39 (51)	28 (62)

Figure 2: **Kaplan-Meier estimates of local control and FIGO$_{2009}$ stage**
FIGO=The International Federation of Gynaecology and Obstetrics.



MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study
Pötter, RichardChargari, Cyrus et al.
The Lancet Oncology, Volume 22, Issue 4, 538 - 547

ENGOT-cx11/GOG-3047/KEYNOTE-A18: Randomized, Double-Blind, Phase 3 Study

Key Eligibility Criteria

- FIGO 2014 stage IB2-IIB (node-positive disease) or FIGO 2014 stage III-IVA (either node-positive or node-negative disease)
- RECIST 1.1 measurable or non-measurable disease
- Treatment naïve

Stratification Factors

- Planned EBRT type (IMRT or VMAT vs non-IMRT or non-VMAT)
- Stage at screening (stage IB2-IIB N+ vs III-IVA)
- Planned total radiotherapy dose (<70 Gy vs ≥70 Gy [EQD2])

R
1:1
N = 1060

Cisplatin 40 mg/m^2 QW for 5 cycles[a] + EBRT followed by brachytherapy
+
Pembrolizumab 200 mg Q3W for 5 cycles

Pembrolizumab 400 mg Q6W for 15 cycles

Cisplatin 40 mg/m^2 QW for 5 cycles[a] + EBRT followed by brachytherapy
+
Placebo Q3W for 5 cycles

Placebo Q6W for 15 cycles

[a]A 6th cycle was allowed per investigator discretion. ENGOT-cx11/GOG-3047/KEYNOTE-A18 ClinicalTrials.gov identifier, NCT04221945.

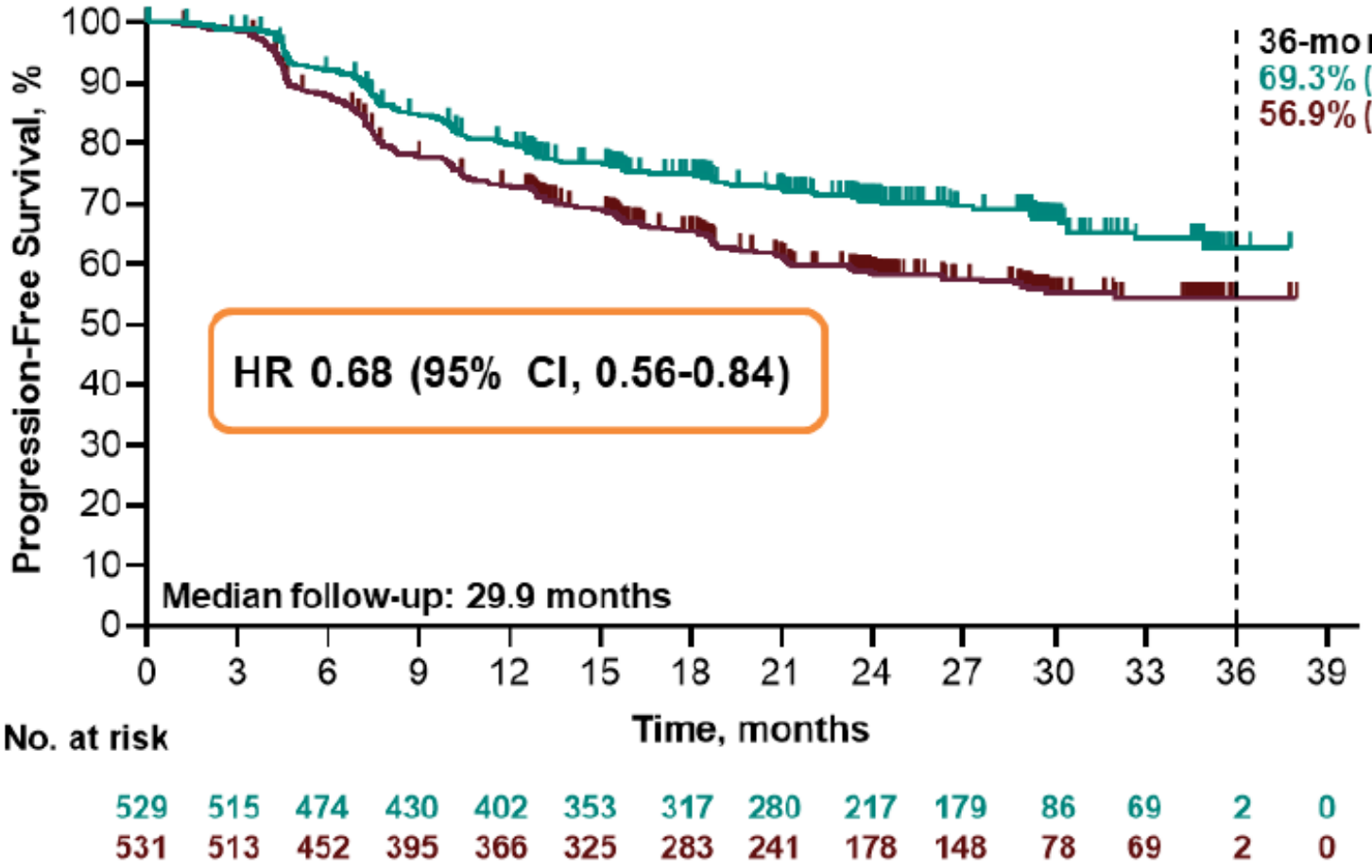
Baseline Characteristics

	Pembro Arm (N = 529)	Placebo Arm (N = 531)
Age, median (range)	49 y (22-87)	50 y (22-78)
Race[a]		
White	254 (48.0%)	264 (49.7%)
Asian	156 (29.5%)	148 (27.9%)
Multiple	78 (14.7%)	86 (16.2%)
American Indian or Alaska Native	24 (4.5%)	22 (4.1%)
Black or African American	14 (2.6%)	8 (1.5%)
Native Hawaiian or Other Pacific Islander	2 (0.4%)	1 (0.2%)
PD-L1 CPS		
<1	22 (4.2%)	28 (5.3%)
≥1	502 (94.9%)	498 (93.8%)
Missing	5 (0.9%)	5 (0.9%)
ECOG PS 1	149 (28.2%)	133 (25.0%)
Squamous cell carcinoma	434 (82.0%)	451 (84.9%)

134	Pembro Arm (N = 529)	Placebo Arm (N = 531)
Stage at screening (FIGO 2014 criteria)		
IB2-IIB	233 (44.0%)	226 (42.6%)
III-IVA	296 (56.0%)	305 (57.4%)
Lymph node involvement[b]		
Positive pelvic only	327 (62.2%)	324 (61.0%)
Positive para-aortic only	14 (2.6%)	10 (1.9%)
Positive pelvic and para-aortic	104 (19.7%)	104 (19.6%)
No positive pelvic or para-aortic	84 (15.9%)	93 (17.5%)
Planned type of EBRT		
IMRT or VMAT	469 (88.7%)	470 (88.5%)
Non-IMRT and non-VMAT	60 (11.3%)	61 (11.5%)
Planned total radiotherapy dose (EQD2)		
<70 Gy	47 (8.9)	46 (8.7)
≥70 Gy	482 (91.1)	485 (91.3)

[a]3 patients (0.3%) had missing information for race, 1 (0.2%) in the pembro arm and 2 (0.4%) in the placebo arm. [b]Per protocol, a positive lymph node is defined as ≥1.5 cm shortest dimension by MRI or CT.
Data cutoff date: January 8, 2024.

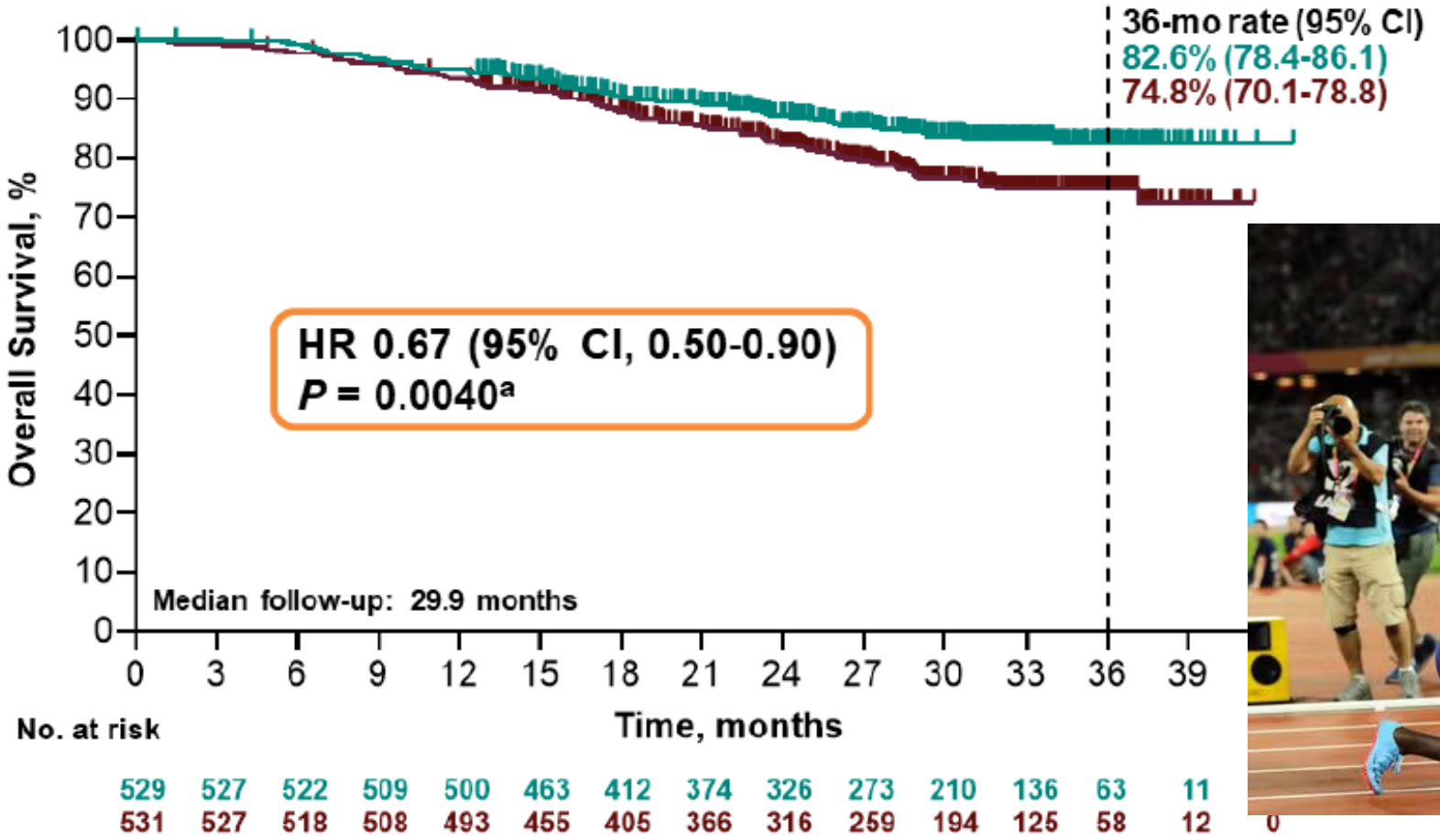
Updated Progression-Free Survival at IA2



	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	29.3%	NR (NR-NR)
Placebo Arm	39.5%	NR (32.0-NR)

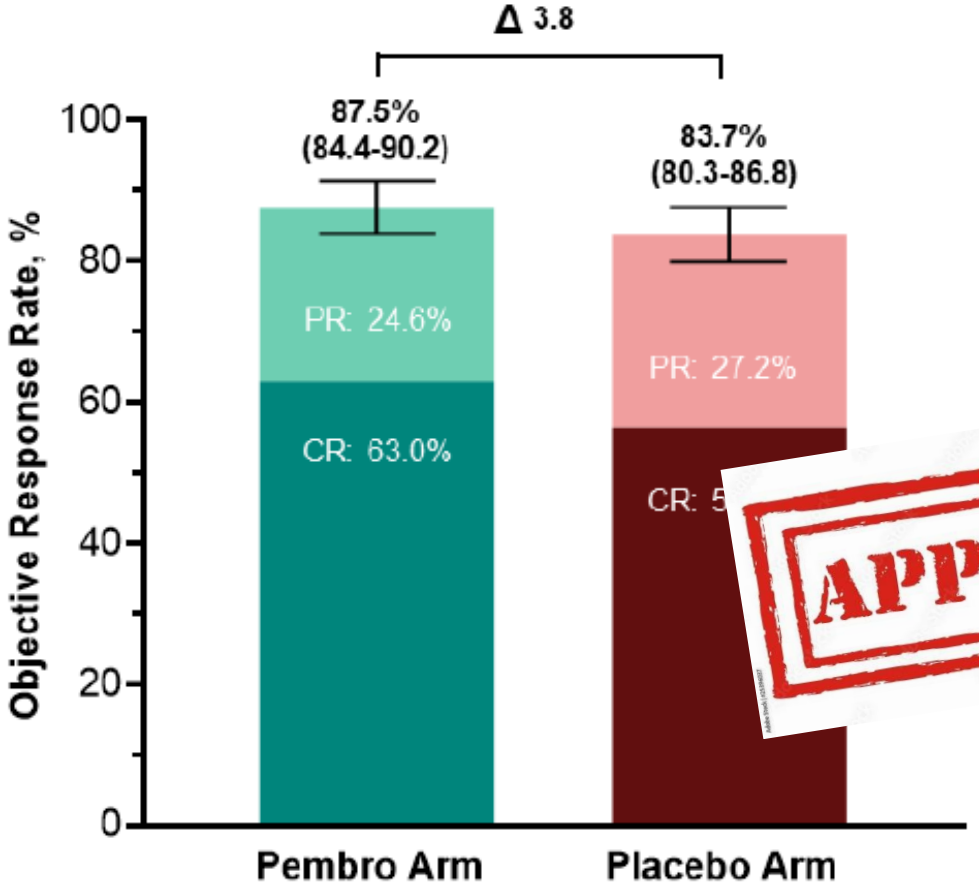
Response assessed per RECIST v1.1 by investigator review or histopathologic confirmation. Since the success criterion of the PFS hypothesis was met at IA1, no formal testing of PFS was performed at IA2.
Data cutoff date: January 8, 2024.

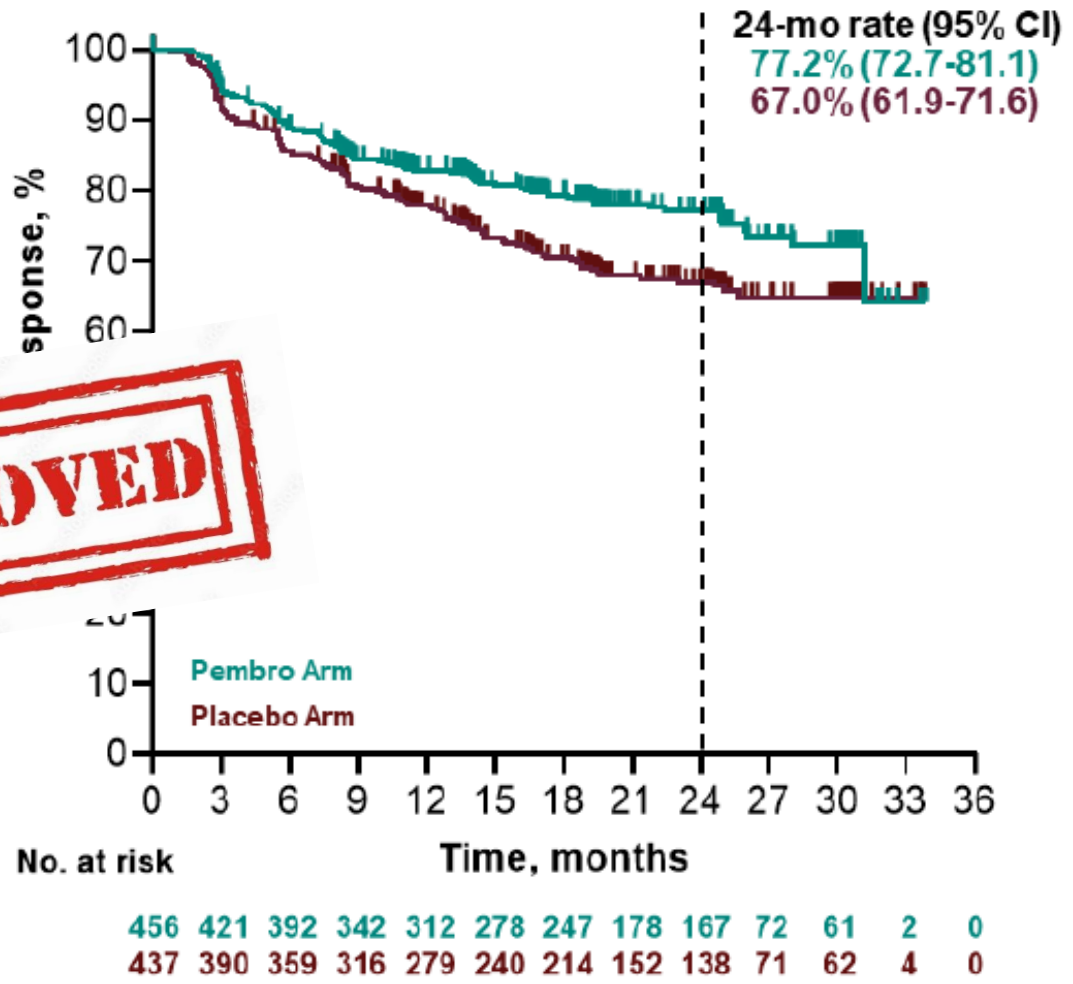
Primary Endpoint: Overall Survival at IA2



[a]With 184 of the 240 deaths expected at the final analysis (76.7% information fraction), the observed $P = 0.0040$ (1-sided) crossed the prespecified nominal boundary of 0·01026 (1-sided) at this planned second interim analysis. At this time, 66 patients had received immunotherapy as post-progression treatment, including 15/138 patients (10.9%) in the pembro arm and 51/193 patients (26.4%) in the placebo arm; of those, 10 (7.2%) and 41 (21.2%), respectively, had received pembro. Data cutoff date: January 8, 2024.

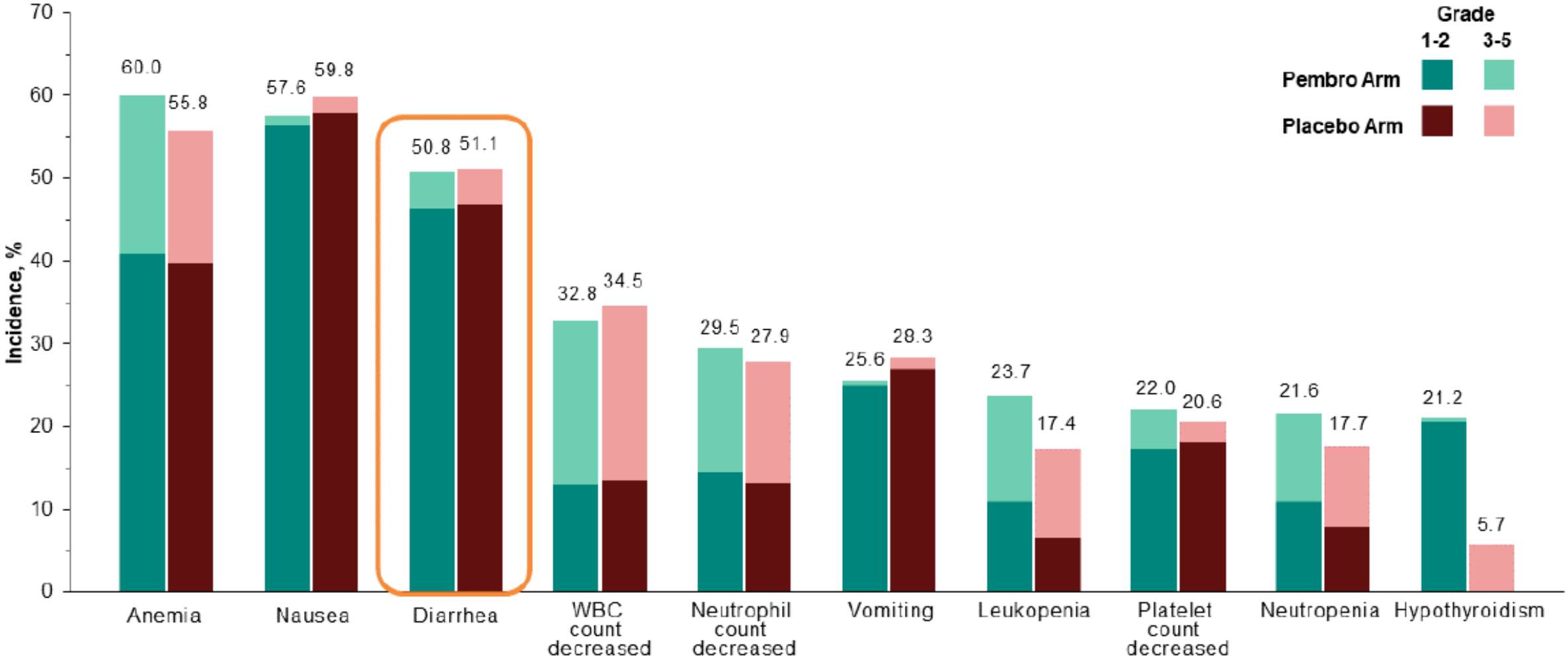
Secondary End Points: Overall Response Rate and Response Duration





Response assessed per RECIST v1.1 by investigator review. Data cutoff date: January 8, 2024.

Treatment-Related Adverse Events, Incidence ≥20% in Either Arm



Data cutoff date: January 8, 2024.

Et les anti-PD-L1 ?

Immunotherapy in Locally Advanced Cervical Cancer
CALLA Study

Concurrent CRT ± durvalumab (anti-PD-L1) in locally advanced cervical cancer

- Primary locally advanced carcinoma of the cervix (Ib2-IIB node positive or IIIA-IVA any nodal status)
- Measurable disease by RECIST v1.1
- ECOG-PS: 0-1

Enrolling 714 patients

R 1:1

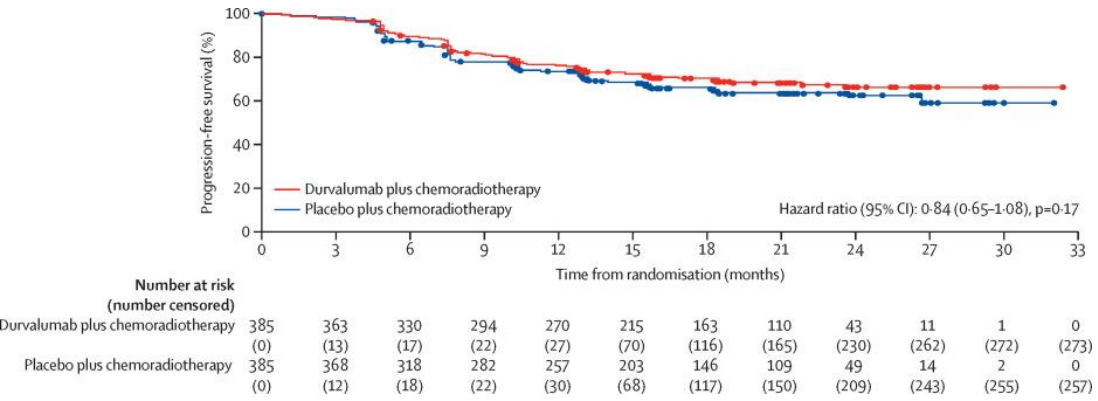
CRT + durvalumab up to 24 months or until progression

CRT + placebo up to 24 months or until progression

Primary Endpoint: PFS

Secondary Endpoints:
- OS
- ORR
- DOR
- Safety
- HRQoL

Monk BJ, et al. J Clin Oncol. 2019;37: Abstract TPS5597.



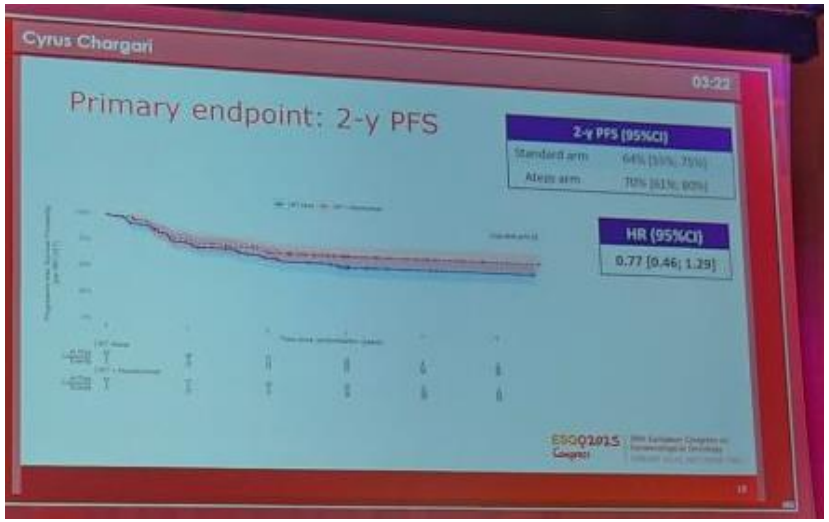
Number at risk (number censored)												
Durvalumab plus chemoradiotherapy	385 (0)	363 (13)	330 (17)	294 (22)	270 (27)	215 (70)	163 (116)	110 (165)	43 (230)	11 (262)	1 (272)	0 (273)
Placebo plus chemoradiotherapy	385 (0)	368 (12)	318 (18)	282 (22)	257 (30)	203 (68)	146 (117)	109 (150)	49 (209)	14 (243)	2 (255)	0 (257)

ATEZOLACC trial (ESGO2025)

RANDOMISATION (1:1)
N=190

Arm A:
Week 1 to 5: IMRT 45 Gy in 25 fractions + Cisplatin 40 mg/m² IV (or carboplatin AUC2*)
Week 7: Uterovaginal Brachytherapy

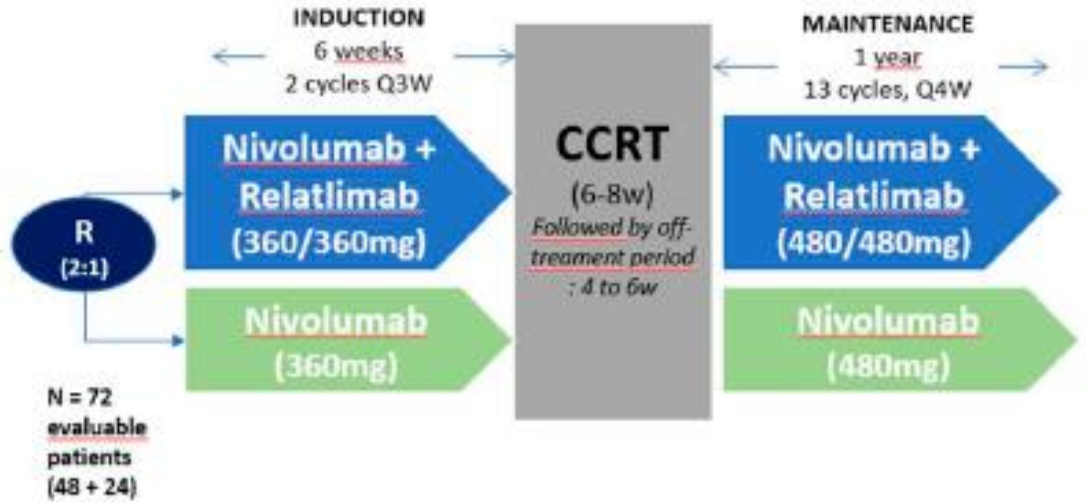
Arm B:
Week 1 to 5: IMRT 45 Gy in 25 fractions Cisplatin 40 mg/m² IV (or carboplatin AUC2*)
Week 7: Uterovaginal Brachytherapy
Week 1 to 57: atezolizumab 1200 mg IV Q3W



Next step ? COLIBRI-2

Key inclusion criteria

- Patients >18y with locally advanced cervical squamous or adenosquamous carcinoma
- FIGO 2018 stage IB3 if N≥1 or II to IVA with any N stage and no evidence of metastatic disease (M0)
- Naïve of any anti-cancer treatment and to be treated by standard CCRT
- PS ECOG 0-2



Primary endpoint

ORR post-induction

Secondary endpoints

- Efficacy : PFS, Time to local progression, Time to metastatic progression, ORR after CCRT and end of maintenance therapy & OS
- Safety : Incidence of adverse events as per NCI-CTCAE V5.0

Exploratory endpoints

- Tumor : Gene expression profile (RNASeq), genomic profile (WES), TME dynamic changes (IHC/Multi-IF)
- Blood : Serum LAG3 level (Elisa), ctDNA (WES), HPV ddPCR

CCRT: concurrent chemoradiotherapy R: randomisation, Q3W : every 3 weeks, Q4W : every 4 weeks, w: weeks, PFS: progression free survival, OS: overall survival, N= sample size.

Le cancer de l'ovaire

ESMO
Annals of Oncology 30: 1080–1087, 2019
doi:10.1093/annonc/mdz135
Published online 2 May 2019

ORIGINAL ARTICLE

Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study

U. A. Matulonis[1*], R. Shapira-Frommer[2], A. D. Santin[3], A. S. Lisyanskaya[4], S. Pignata[5], I. Vergote[6], F. Raspagliesi[7], G. S. Sonke[8], M. Birrer[9], D. M. Provencher[10], J. Sehouli[11], N. Colombo[12], A. González-Martín[13], A. Oaknin[14], P. B. Ottevanger[15], V. Rudaitis[16], K. Katchar[17], H. Wu[18], S. Keefe[19], J. Ruman[19] & J. A. Ledermann[20]

Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study

Eric Pujade-Lauraine, Keiichi Fujiwara, Jonathan A Ledermann, Amit M Oza, Rebecca Kristeleit, Isabelle-Laure Ray-Coquard, Gary E Richardson, Cristiana Sessa, Kan Yonemori, Susana Banerjee, Alexandra Leary, Anna V Tinker, Kyung Hae Jung, Radoslaw Madry, Sang-Yoon Park, Charles K Anderson, Fabian Zohren, Ross A Stewart, Caimiao Wei, Samuel S Dychter, Bradley J Monk

Article | Open access | Published: 16 July 2024

Neoadjuvant and adjuvant pembrolizumab in advanced high-grade serous carcinoma: the randomized phase II NeoPembrOV clinical trial

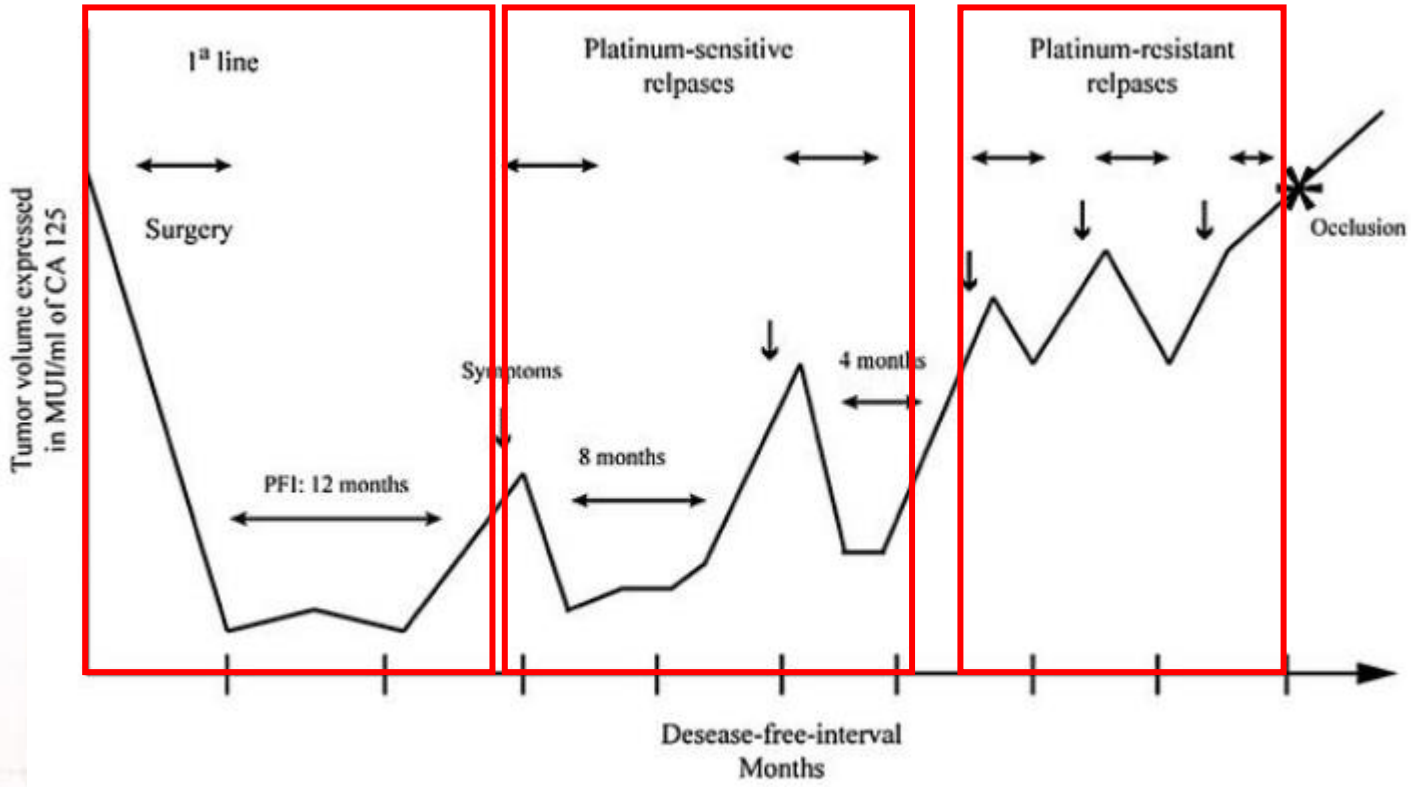
Isabelle L. Ray-Coquard, Aude-Marie Savoye, Camille Schiffler, Marie-Ange Mouret-Reynier, Olfa Derbel, Elsa Kalbacher, Marianne LeHeurteur, Alejandra Martinez, Corina Cornila, Mathilde Martinez, Leila Bengrine Lefevre, Frank Priou, Nicolas Cloarec, Laurence Venat, Frédéric Selle, Dominique Berton, Olivier Collard, Elodie Coquan, Olivia Le Saux, Isabelle Treilleux, Sophie Gouerant, Antoine Angelergues, Florence Joly & Olivier Tredan

rapid communications

Atezolizumab, Bevacizumab, and Chemotherapy for Newly Diagnosed Stage III or IV Ovarian Cancer: Placebo-Controlled Randomized Phase III Trial (IMagyn050/GOG 3015/ENGOT-OV39)

Kathleen N. Moore, MD[1,2]; Michael Bookman, MD[3]; Jalid Sehouli, MD[4]; Austin Miller, PhD[5]; Charles Anderson, MD[6]; Giovanni Scambia, MD[7]; Tashanna Myers, MD[8]; Cagatay Taskiran, MD[9,10]; Katina Robison, MD[11]; Johanna Mäenpää, MD[12]; Lyndsay Willmott, MD[13]; Nicoletta Colombo, MD[14]; Jessica Thomes-Pepin, MD[15]; Michalis Lionios, MD[16]; Michael A. Gold, MD[17]; Yolanda Garcia, MD[18]; Sudarshan K. Sharma, MD[19]; Christopher J. Darus, MD[20]; Carol Aghajanian, MD[21]; Aikou Okamoto, MD[22]; Xiaohua Wu, MD[23]; Rustem Safin, MD[24]; Fan Wu, MS[25]; Luciana Molinero, MD[26]; Vidya Maiya, MD[26]; Victor K. Khor, PhD[26]; Yvonne G. Lin, MD[26]; and Sandro Pignata, MD[27]

Let's not throw the baby out with the bath water.



atural history of ovarian cancer evolution

Chemotherapy with or without avelumab followed by avelumab maintenance versus chemotherapy alone in patients with previously untreated epithelial ovarian cancer (JAVELIN Ovarian 100): an open-label, randomised, phase 3 trial

Bradley J Monk*, Nicoletta Colombo, Amit M Oza, Keiichi Fujiwara, Michael J Birrer, Leslie Randall, Elena V Poddubskaya, Giovanni Scambia, Yaroslav V Shparyk, Myong Cheol Lim, Snehalkumar M Bhoola, Joohyuk Sohn, Kan Yonemori, Ross A Stewart, Xiaoxi Zhang, Julia Perkins Smith, Carlos Linn, Jonathan A Ledermann*

original reports

Randomized Phase II Trial of Nivolumab Versus Nivolumab and Ipilimumab for Recurrent or Persistent Ovarian Cancer: An NRG Oncology Study

Dmitriy Zamarin, MD, PhD[1]; Robert A. Burger, MD[2]; Michael W. Sill, PhD[3]; Daniel J. Powell Jr, PhD[4]; Heather A. Lankes, PhD, MPH[3]; Michael D. Feldman, MD, PhD[4]; Oliver Zivanovic, MD, PhD[1]; Camille Gunderson, MD[5]; Emily Ko, MD, MSCR[2]; Cara Mathews, MD[7]; Sudarshan Sharma, MD[8]; Andrea R. Hagemann, MD[9]; Samir Khleif, MD[10]; and Carol Aghajanian, MD[1]

GYNAECOLOGICAL CANCERS · Volume 35, Supplement 2, S546, September 2024

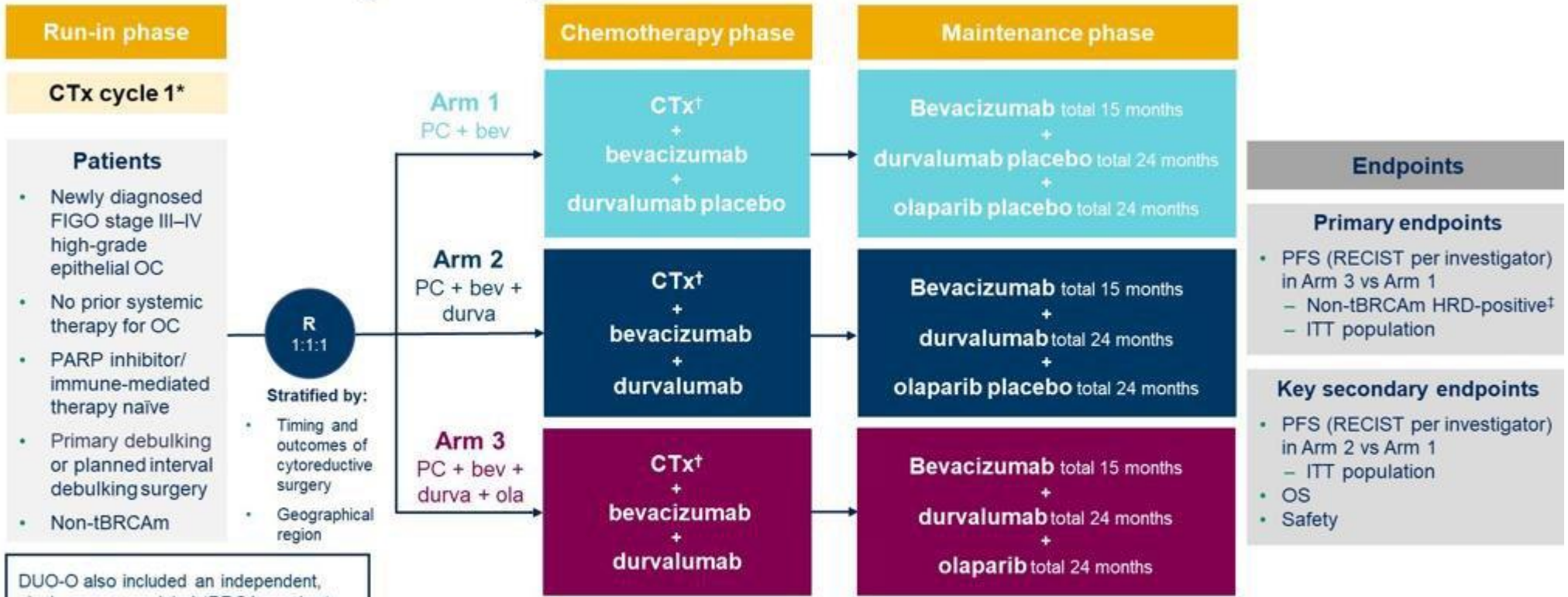
712MO Final overall survival (OS) from the phase III ATALANTE/ENGOT-ov29 trial evaluating atezolizumab (Atz) versus placebo with standard chemotherapy (Cx) plus bevacizumab (bev) in ovarian cancer (OC) patients (pts) with platinum-sensitive relapse (PSR)

J.E. Kurtz[1] · E. Pujade-Lauraine[2] · A. Oaknin[3] · ... · N. Bonichon Lamichhane[18] · E. Kalbacher[19] · F. Heitz[20] ... Show more

Affiliations & Notes · Article Info

Draft

DUO-O study design



DUO-O also included an independent, single-arm, open-label tBRCAm cohort – results are not presented

Endpoints

Primary endpoints

- PFS (RECIST per investigator) in Arm 3 vs Arm 1
  - Non-tBRCAm HRD-positive‡
  - ITT population

Key secondary endpoints

- PFS (RECIST per investigator) in Arm 2 vs Arm 1
  - ITT population
- OS
- Safety

Treatment continued until disease progression, study treatment was complete or other discontinuation criteria were met

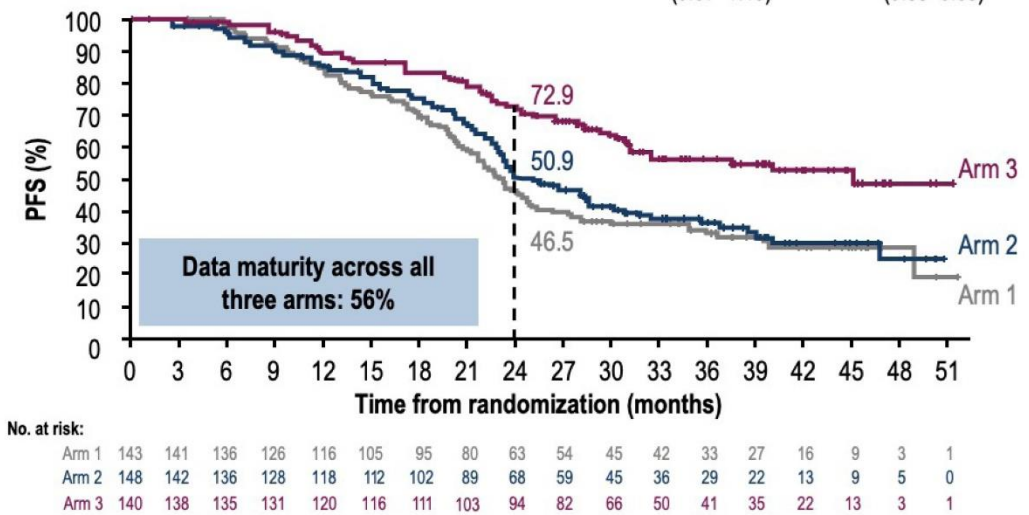
Dosing and schedule: bevacizumab (15 mg/kg IV q3w); durvalumab (1120 mg IV q3w); olaparib (300 mg po bid); chemotherapy: paclitaxel 175 mg/m² IV q3w and carboplatin at AUC5 or AUC6 IV q3w. PFS interim analysis DCO: December 5, 2022.
*With or without bevacizumab according to local practice; †Cycles 2–6; ‡Genomic instability score ≥42 assessed prospectively by Myriad MyChoice CDx assay.
AUC, area under the curve; bev, bevacizumab; bid, twice daily; CTx, chemotherapy; DCO, data cutoff; durva, durvalumab; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intent-to-treat; IV, intravenous; ola, olaparib; OS, overall survival; PC, paclitaxel/carboplatin; po, by mouth; q3w, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria for Solid Tumors.

PRESENTED BY: Dr Philipp Harter

Final PFS

Non-tBRCAm HRD-positive

	Arm 1 CP + B N=143	Arm 2 CP + B + D N=148	Arm 3 CP + B + D + O N=140
Median follow-up,* months	38.4	33.1	34.6
Events, n (%)	94 (66)	89 (60)	57 (41)
mPFS,† months	**23.3**	**25.1**	**45.1**
HR (95% CI) vs Arm 1‡		**0.89** (0.67–1.19)	**0.46** (0.33–0.65)

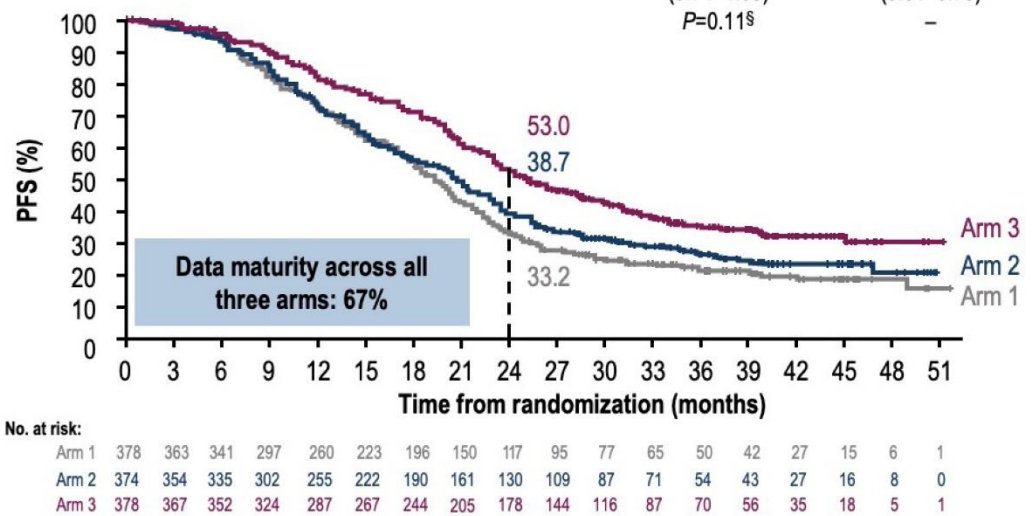


No. at risk:

Arm 1	143	141	136	126	116	105	95	80	63	54	45	42	33	27	16	9	3	1
Arm 2	148	142	136	128	118	112	102	89	68	59	45	36	29	22	13	9	5	0
Arm 3	140	138	135	131	120	116	111	103	94	82	66	50	41	35	22	13	3	1

Non-tBRCAm ITT

	Arm 1 CP + B N=378	Arm 2 CP + B + D N=374	Arm 3 CP + B + D + O N=378
Median follow-up,* months	34.5	33.1	32.0
Events, n (%)	283 (75)	257 (69)	221 (58)
mPFS,† months	**19.3**	**20.6**	**25.1**
HR (95% CI) vs Arm 1‡		**0.87** (0.74–1.03) *P*=0.11§	**0.61** (0.51–0.73) –



No. at risk:

Arm 1	378	363	341	297	260	223	196	150	117	95	77	65	50	42	27	15	6	1
Arm 2	374	354	335	302	255	222	190	161	130	109	87	71	54	43	27	16	8	0
Arm 3	378	367	352	324	287	267	244	205	178	144	116	87	70	56	35	18	5	1

DCO2 = 18 Sep 2023. *In censored patients; †Medians and rates were estimated by the KM method (medians are unstable in arms with <50% maturity); ‡HRs and CIs were estimated from a stratified Cox PH model. Model was stratified by timing and outcome of cytoreductive surgery for the non-tBRCAm HRD-positive population, and by timing and outcome of cytoreductive surgery and geographic region for the non-tBRCAm ITT population; §P value was calculated from a stratified log-rank test. Statistical significance for Arm 3 versus Arm 1 was achieved at the interim PFS analysis in both the non-tBRCAm HRD-positive (DCO1 = 5 Dec 2022; HR 0.49 [95% CI 0.34–0.69]; P<0.0001) and non-tBRCAm ITT (DCO1 = 5 Dec 2022; HR 0.63 [95% CI 0.52–0.76]; P<0.0001) populations; the updated analysis (DCO2) is descriptive in nature for Arm 3 versus Arm 1, so no P value is reported. The comparison of Arm 2 versus Arm 1 in the non-tBRCAm HRD-positive population was not part of the predefined MTP and so was not formally tested. The comparison of Arm 2 versus Arm 1 was not statistically significant at the time of the interim PFS analysis and so was retested at the final PFS analysis; the boundary for declaring statistical significance at the final PFS analysis was 0.0248 (Arm 2 vs Arm 1) for 2.5% alpha.
MTP, multiple-testing procedure.

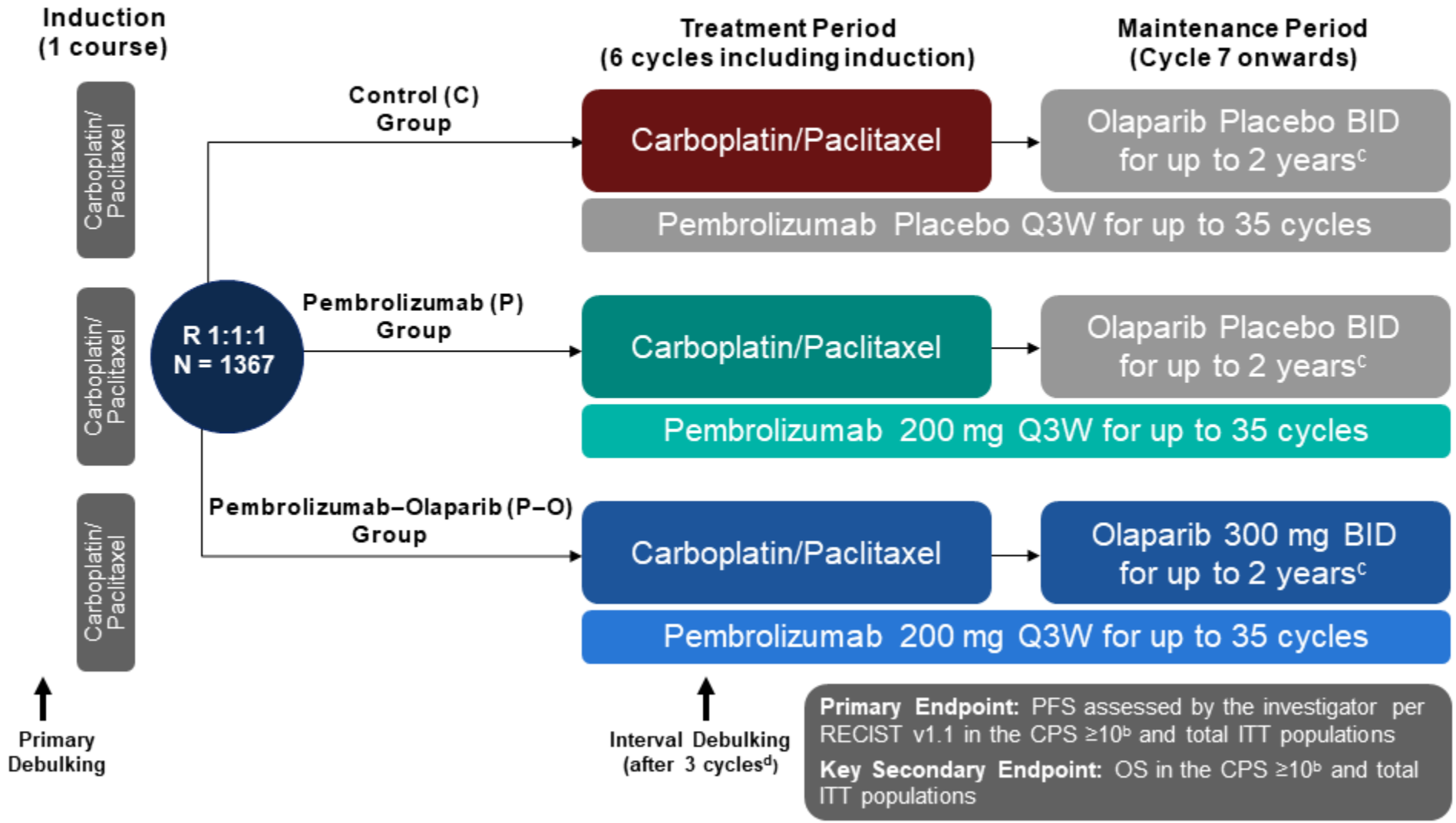
ENGOT-OV43/GOG-3036/KEYLYNK-001 Study Design (NCT03740165)

Key Eligibility Criteria

- Advanced (FIGO Stage ≥III) epithelial ovarian cancer
- *BRCA1/2*-nonmutated
- No prior systemic therapy
- Candidate for carboplatin + paclitaxel[a] as adjuvant or neoadjuvant therapy
- Bevacizumab permitted per investigator discretion

Stratification Factors

- PD-L1 expression[b] (CPS ≥10 vs <10)
- Planned bevacizumab use (yes vs no)
- Surgery status (no residual tumor [R0] after primary debulking vs residual tumor [R1] after primary debulking vs planned interval debulking)



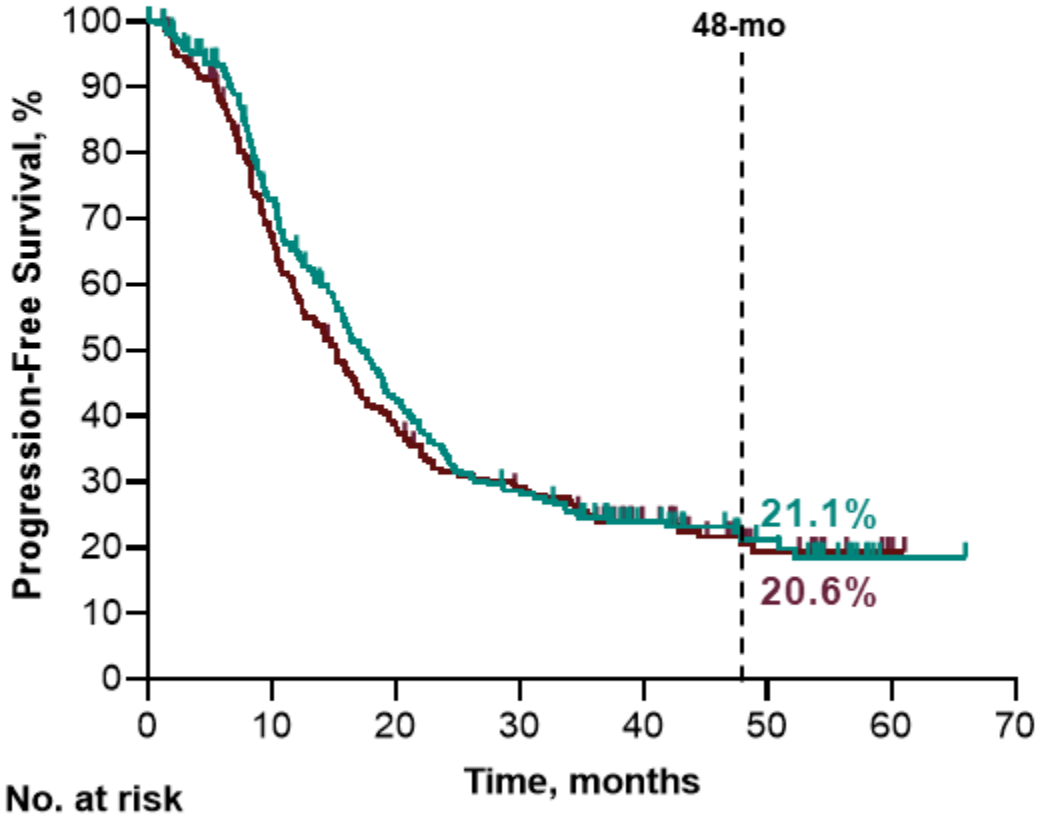
Primary Endpoint: PFS assessed by the investigator per RECIST v1.1 in the CPS ≥10[b] and total ITT populations

Key Secondary Endpoint: OS in the CPS ≥10[b] and total ITT populations

[a]Docetaxel may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an adverse event requiring discontinuation of paclitaxel. [b]Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100). [c]Only participants with no evidence of disease at start of maintenance and no progression stopped after 2 years. [d]Including induction cycle.

H3-4: Progression-Free Survival P vs C at FA in CPS ≥10 and Total ITT Populations

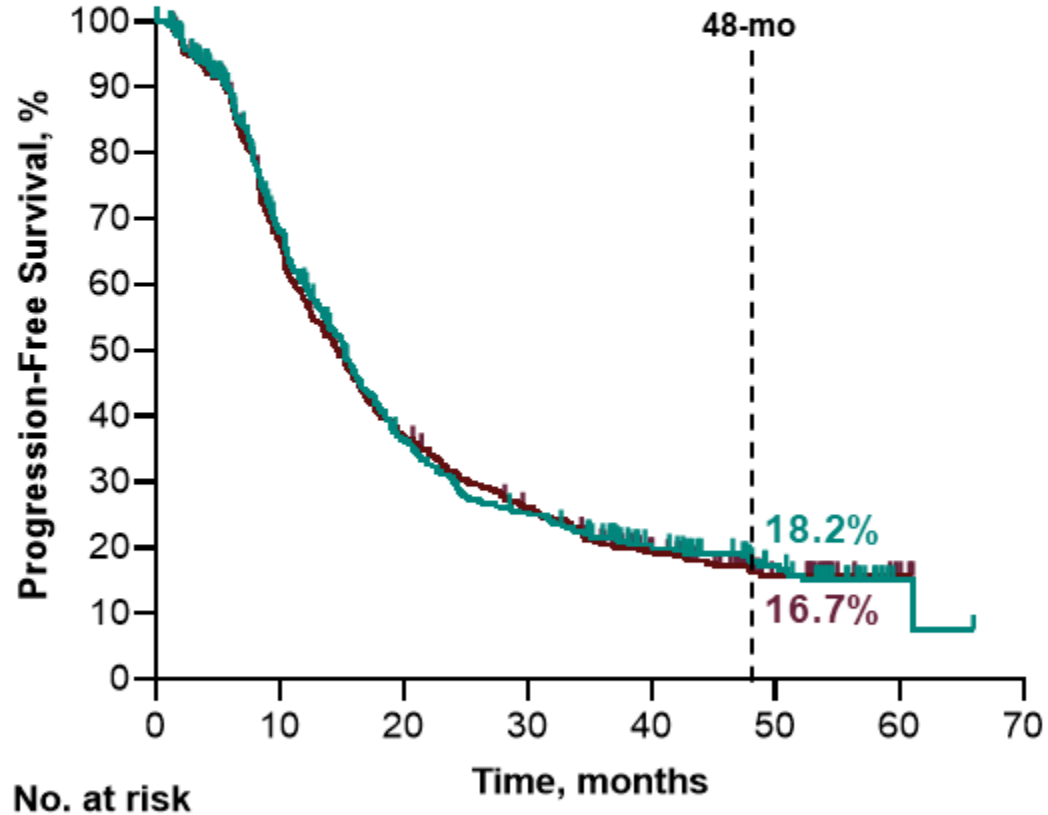
CPS ≥10 Population	Median, months	Events	HR (95% CI)	*P*-value
P Group	17.3	69.6%	0.95[a] (0.77-1.19)	0.3339[b]
C Group	15.2	72.4%		



No. at risk

230	150	85	56	33	17	1	0
228	142	81	58	37	14	2	0

Total ITT Population	Median, months	Events	HR (95% CI)
P Group	15.2	73.8%	1.01[a] (0.87-1.18)
C Group	14.6	77.5%	



No. at risk

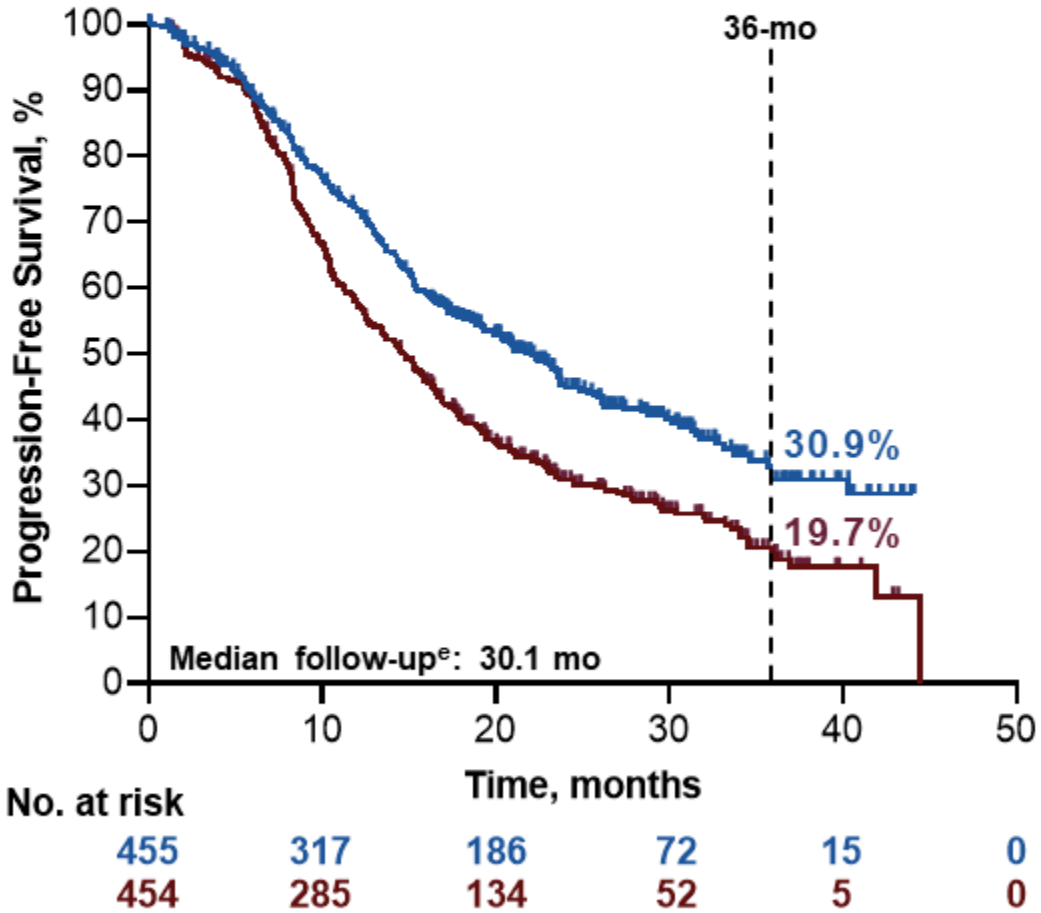
458	279	144	99	61	32	2	0
454	285	157	106	64	26	3	0

Median follow-up[c]: 49.6 mo

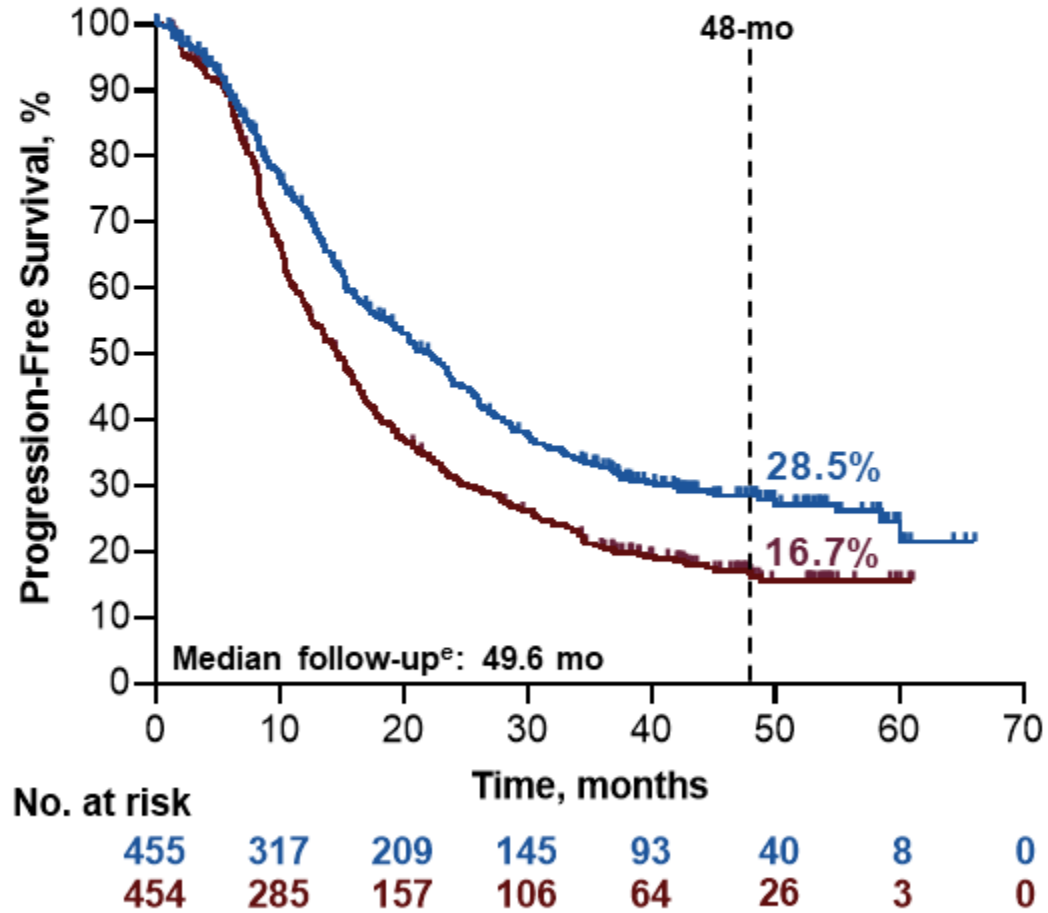
Response assessed per RECIST v1.1 by investigator review. aHazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. bPrespecified P-value boundary not met. cDefined as the time from randomization to the data cutoff date. Data cutoff date: August 26, 2024.

H2: Progression-Free Survival P–O vs C, Total ITT Population at IA1 and FA

IA1[a]	Median, months	Events	HR (95% CI)	*P*-value
P–O Group	22.1	53.0%	0.68[c] (0.58-0.81)	<0.0001[d]
C Group	14.6	69.2%		



FA[b]	Median, months	Events	HR (95% CI)
P–O Group	22.2	64.0%	0.71[c] (0.61-0.84)
C Group	14.6	77.5%	



Response assessed per RECIST v1.1 by investigator review. aData cutoff date: January 9, 2023. bData cutoff date: August 26, 2024. cHazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. dPrespecified P-value boundary met. eDefined as the time from randomization to the data cutoff date.

Etude FIRST

Stock exchange announcement

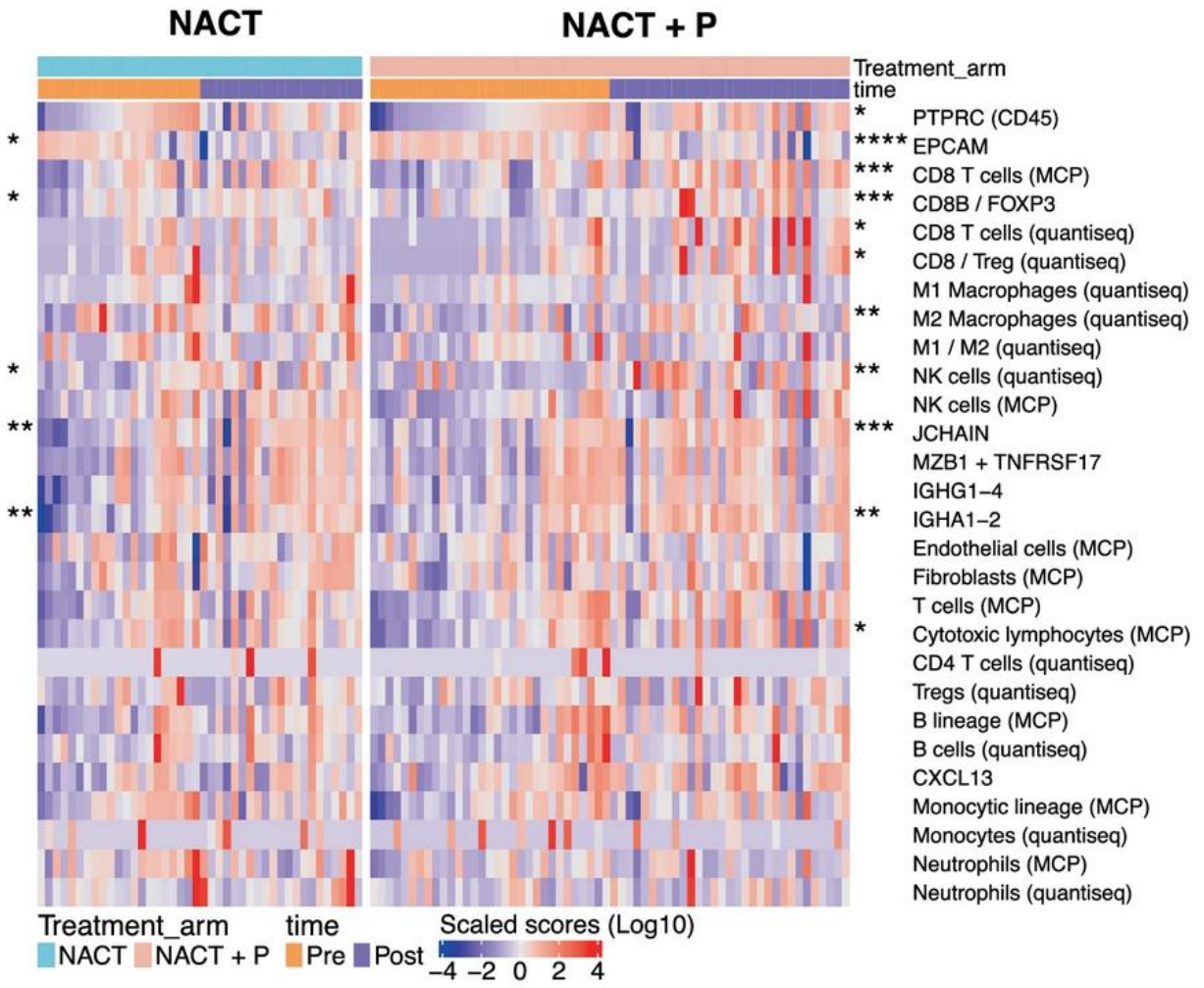
For media and investors only

Issued: 20 December 2024, London UK

GSK announces FIRST trial met its primary endpoint of progression free survival in first line advanced ovarian cancer

- Addition of *Jemperli* (dostarlimab) to both platinum-based chemotherapy and *Zejula* (niraparib) maintenance, with or without bevacizumab, demonstrated a statistically significant effect on progression free survival (PFS) versus active comparator arm

Perspective : cibler au-dela de PD-1/PD-L1



Le Saux O, Ardin M, Berthet J, et al. Immunomic longitudinal profiling of the NeoPembrOv trial identifies drivers of immunoresistance in high-grade ovarian carcinoma. Nat Commun. 2024;15(1):5932.

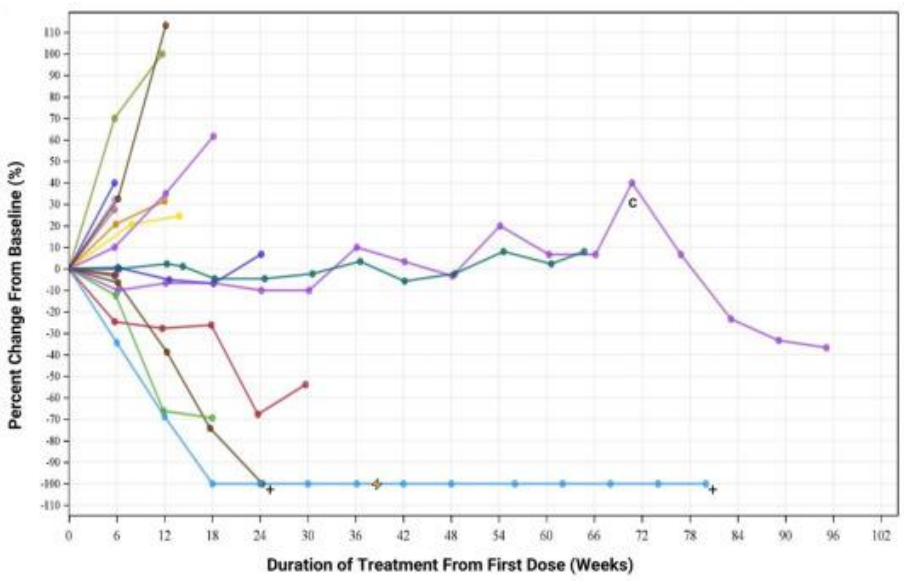
Perspective : cibler au-dela de PD-1/PD-L1

ABSTRACT ONLY · Volume 176, Supplement 1, S35-S36, September 2023

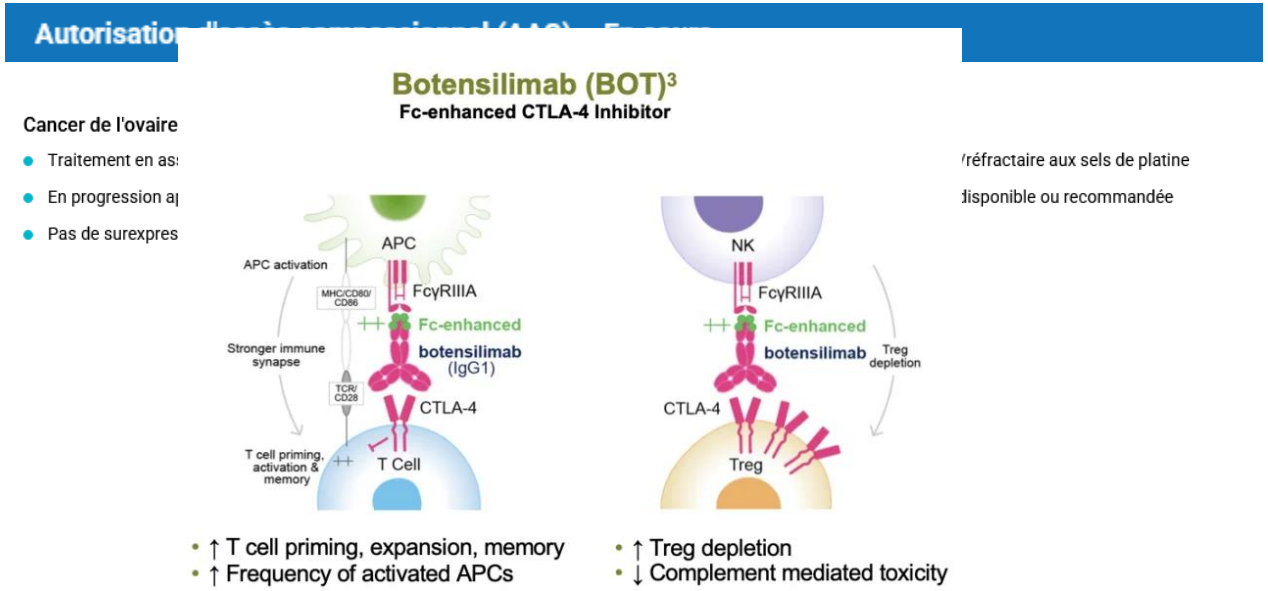
Botensilimab, a novel innate/adaptive immune activator, plus balstilimab (anti-PD-1) in patients with recurrent platinum refractory/resistant ovarian cancer (041)

Bruno Bockorny [a] · Ursula Matulonis [b] · Steven O'Day [c,l] · ... · Xin (James) Song [i] · Daruka Mahadevan [j] · Michael Gordon [k] ... Show more

Affiliations & Notes Article Info



ORR = 29%



Conclusion

- **Cancer de l'endomètre** :
  - Carboplatine paclitaxel + anti-PD(L)1 = standard 1ere ligne
  - DOMENICA pour les populations dMMR
  - Une place pour PARP + IO chez les pMMR ?

- **Cancer du col de l'utérus**
  - Radiochimiothérapie – pembrolizumab = standard pour les stades III-IVA
  - COLIBRI-2

- **Cancer de l'ovaire**
  - FIRST attendu (ASCO 2025)
  - Recherche de biomarqueurs et nouvelles cibles (immune checkpoints, cellules immunosupressibe, combinaisons…)

CANCÉROPÔLE Est
Régions Bourgogne-Franche-Comté / Grand Est

Actualité en immuno-oncologie
Cancers gynécologiques

Dr Jean-David Fumet, MD, PhD
Département d'oncologie médicale
CLCC Georges-François Leclerc – Dijon
13/03/2025

CGFL CENTRE GEORGES FRANÇOIS LECLERC Ensemble, dépassons le cancer