2023 ASCO ANNUAL MEETING

Post-ASCO 2023 en gynécologie

Dr Elise deluche
MCU-PH
Oncologie Médicale
Chu de limoges

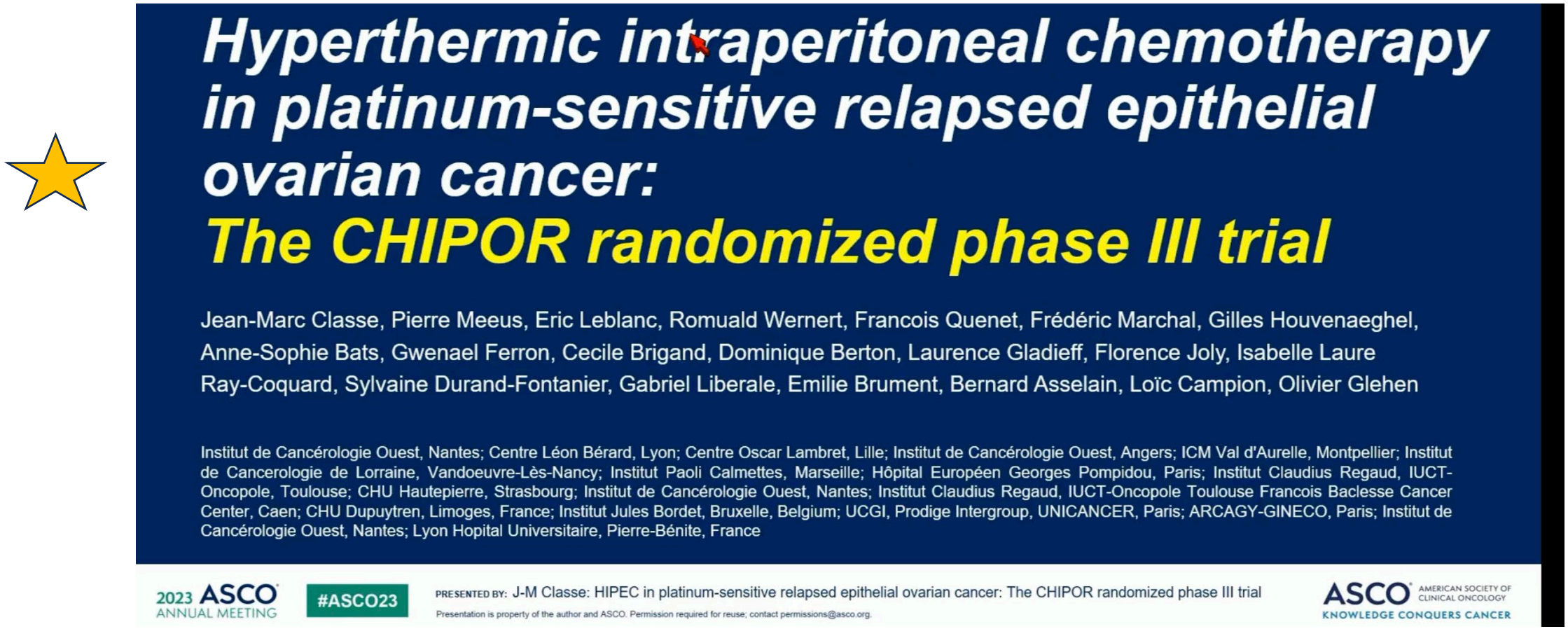
CHU Centre hospitalier universitaire Limoges

Liens d’intérêts

- Advisory Boards : Novartis, Pfizer, GSK, Lilly, MSD
- Congrès : Pfizer, Amgen, Roche, Novartis, GSK
- Honoraires: Astrazeneca-Daiichi, Lilly, Novartis, Pfizer, Fresubin, GSK, MSD, BMS, MENARINI - STEMLINE

2023 ASCO ANNUAL MEETING

CHIPOR : CHIP en rechute platine sensible

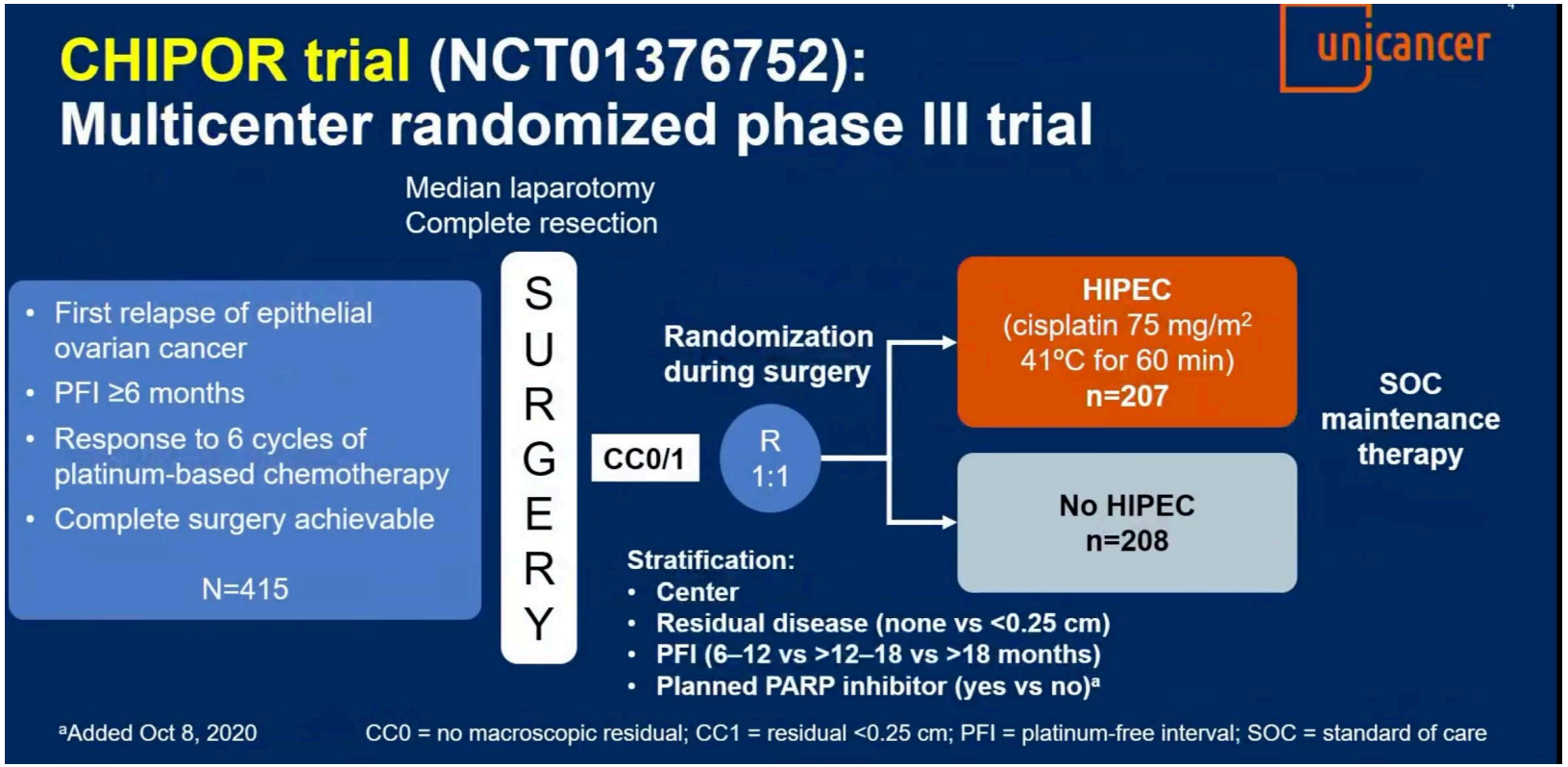


CHIPOR : CHIP en rechute platine sensible

1ère grande étude de grande ampleur

Patientes très sélectionnées

- Platine sensible
- 6 cycles de tt
- RC après la chimiothérapie
- CC0-CC1 en per-opératoire



Début en 2011 ° Fin en 2021

- **Primary endpoint: Overall Survival**
  - 80% power at 2-sided alpha = 5% to detect a HR of 0.71 with vs without HIPEC after 268 events
  - Univariate stratified Cox model
- **Secondary endpoints**: PFS, TTST, safety (morbidity and mortality within 30 days after surgery), surgical outcome, QoL
- Data cutoff: 8 January 2023, 268 events observed (median follow-up: 6.2 years)

HR = hazard ratio; OS = overall survival; PFS = progression-free survival; QoL = quality of life; TTST = time to subsequent treatment

Characteristics	No HIPEC (n=208)	HIPEC (n=207)
Median age (IQR), years	**59** (53–67)	**62** (55–68)
FIGO stage III/IV at primary treatment, %	84%	88%
Bevacizumab (first-line setting), n (%)	73 (35%)	64 (31%)
Median PFI (IQR), months	**17.8** (11.8–25.3)	**17.4** (10.6–26.6)
High-grade serous or grade 3 endometrioid, n (%)[a]	**165 (82%)**	**159 (79%)**
Completed 6 cycles of chemotherapy, n (%)	189 (91%)	188 (91%)
Surgery to CC0, n (%)	**180 (87%)**	**180 (87%)**

No. of patients (%)	No HIPEC (n=208)	HIPEC (n=207)
Severe kidney failure	3 (1.4%)	21 (10%)
Before thiosulfate amendment[a]	1/154 (0.7%)	19/156 (12%)
After thiosulfate amendment[a]	2/54 (3.7%)	2/51 (3.9%)

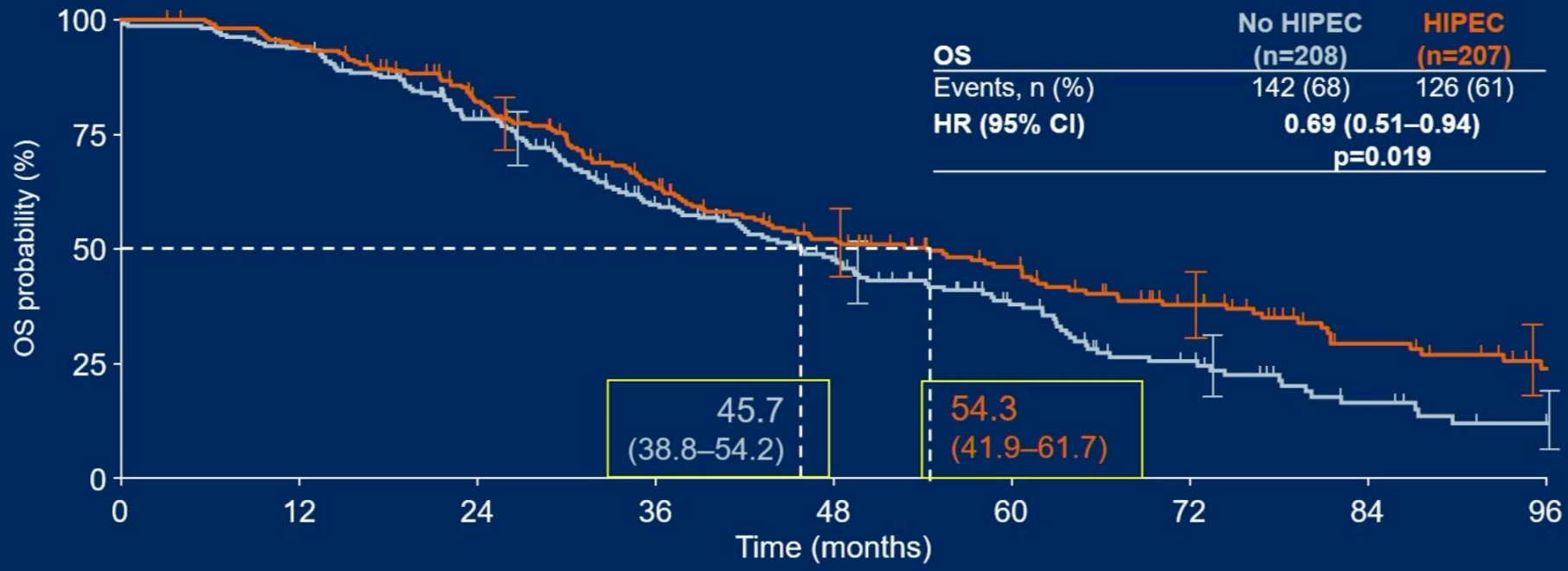
CHIPOR trial: Severe morbidity and mortality (within 30 days after surgery)*

No. of patients (%)	No HIPEC (n=208)	HIPEC (n=207)
Median duration of surgery (IQR), min	218 (160–282)	337 (272–407)
Digestive tract resection	78 (38%)	85 (41%)
Stoma diversion	10 (4.8%)	20 (9.7%)
Grade ≥3 morbidity	41 (20%)	82 (40%)
Blood disorders	16 (8%)	28 (14%)
Digestive tract disorders	14 (7%)	18 (9%)
Mortality	3 (1.4%)	0

No. of patients (%)		No HIPEC (n=208)	HIPEC (n=207)
Maintenance bevacizumab		16 (8%)	7 (3%)
BRCA mutation status	Known	164 (79%)	167 (81%)
	Mutated	51/164 (31%)	48/167 (29%)
Maintenance PARP inhibitor *		46 (22%)	35 (17%)

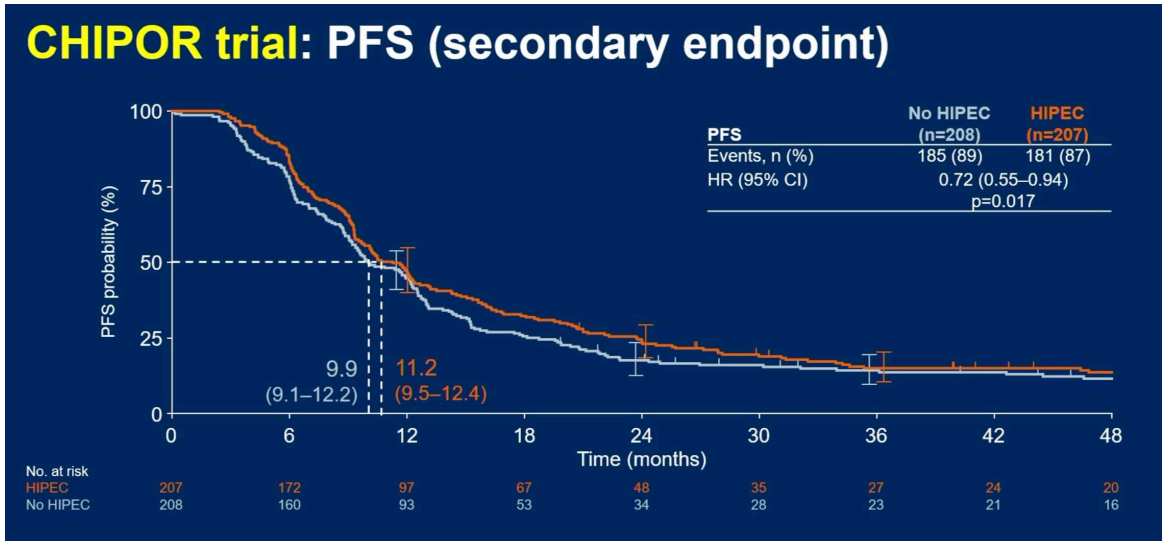
2023 ASCO ANNUAL MEETING

CHIPOR trial: Primary endpoint (OS, ITT population)



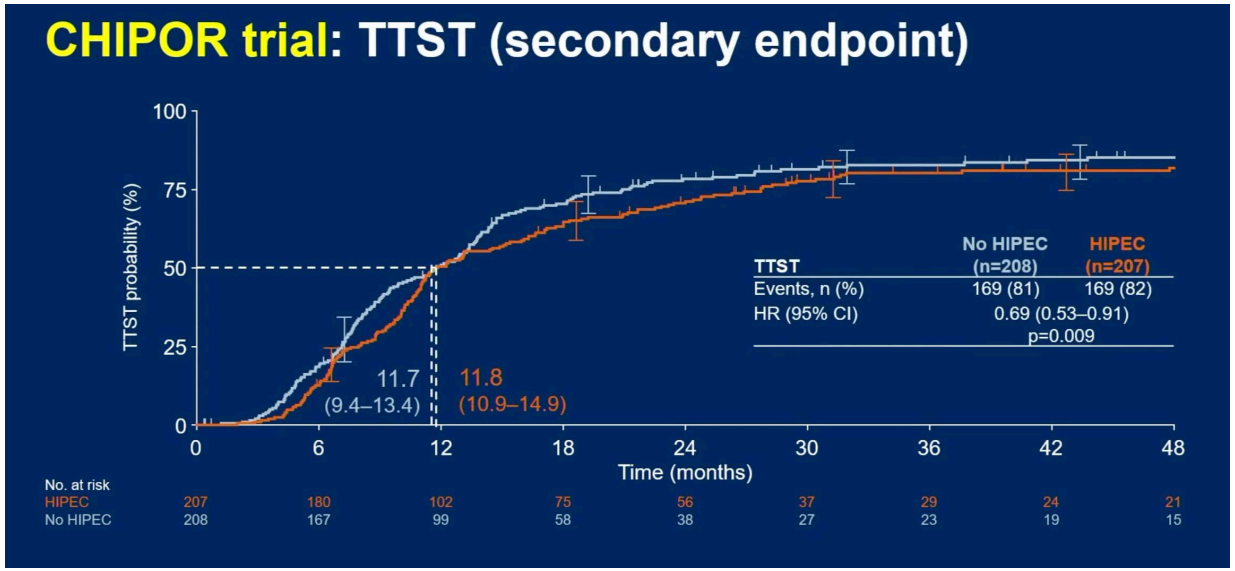
OS	No HIPEC (n=208)	HIPEC (n=207)
Events, n (%)	142 (68)	126 (61)
HR (95% CI)	**0.69 (0.51–0.94)**	
	p=0.019	

CHIPOR trial: PFS (secondary endpoint)



PFS	No HIPEC (n=208)	HIPEC (n=207)
Events, n (%)	185 (89)	181 (87)
HR (95% CI)	0.72 (0.55–0.94) p=0.017	

CHIPOR trial: TTST (secondary endpoint)



TTST	No HIPEC (n=208)	HIPEC (n=207)
Events, n (%)	169 (81)	169 (82)
HR (95% CI)	0.69 (0.53–0.91) p=0.009	

CONCLUSION : Pas de changement de pratique dans l'immédiat mais affaire à suivre…

+

- 1ère étude aussi large
- Bien conduite
- Bénéfice sur la SG

-

- Pas de validation de la chirg à après chimio à la rechute
- Est-ce que cela fait mieux que la chirg première:
  - 2 essais randomisés chirg à la rechute:
    - DESKTOP III :+
    - GOG-0213 : -
- Traitement de maintenance ne correspond pas à la routine
- Manque données de qualité de vie (tox sous platine)
- Quid du résultat dans les BRCA ?
- Attention aux tox
- Centre de référence

2023 ASCO ANNUAL MEETING

SHAPE : hystérectomie simple vs radicale

An international randomized phase III trial comparing radical hysterectomy and pelvic node dissection vs simple hysterectomy and pelvic node dissection in patients with low-risk early-stage cervical cancer

A Gynecologic Cancer Intergroup study led by the Canadian Cancer Trials Group

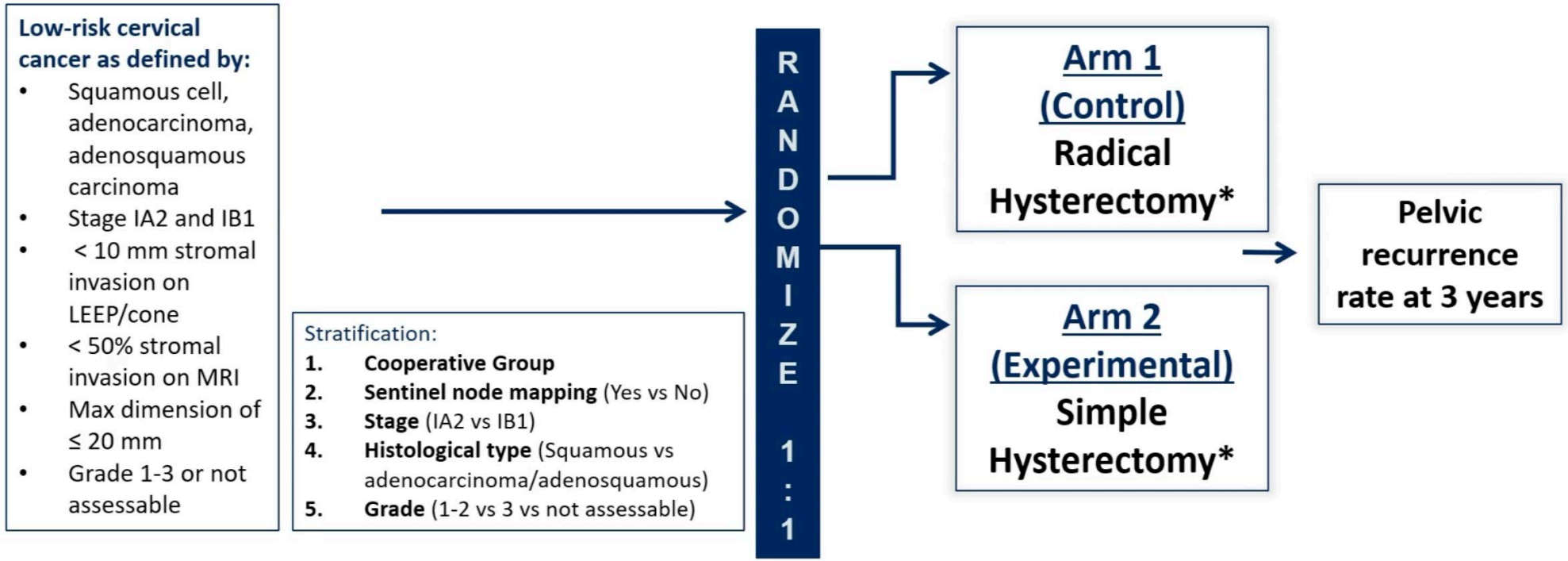
CCTG CX.5 - SHAPE

NCT01658930

Marie Plante, Janice Kwon, Sarah Ferguson, Vanessa Samouelian, Gwenael Ferron, Amandine Maulard, Cor de Kroon, Willemien Van Driel, John Tidy, Sven Mahner, Stefan Kommoss, Frederic Goffin, Christian Marth, Karl Tamussino, Brynhildur Eyjolfsdottir, Jae-Weon Kim, Noreen Gleeson, Juliana Ubi, Lori Brotto, Dongsheng Tu, Lois Shepherd

On behalf of the SHAPE investigators

Etude de non -infériorité



Carcinoma of the cervix uteri.

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≥7 mm
IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
IB	Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA *
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension
IB2	Clinically visible lesion >4.0 cm in greatest dimension

2009

VS

2018

- **IA** Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
  - **IA1** Measured stromal invasion <3 mm in depth
  - **IA2** Measured stromal invasion ≥3 mm and <5 mm in depth
- **IB** Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri[b]
  - **IB1** Invasive carcinoma ≥5 mm depth of stromal invasion and <2 cm in greatest dimension
  - **IB2** Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
  - **IB3** Invasive carcinoma ≥4 cm in greatest dimension

Plus de prise en compte de l'horizontale

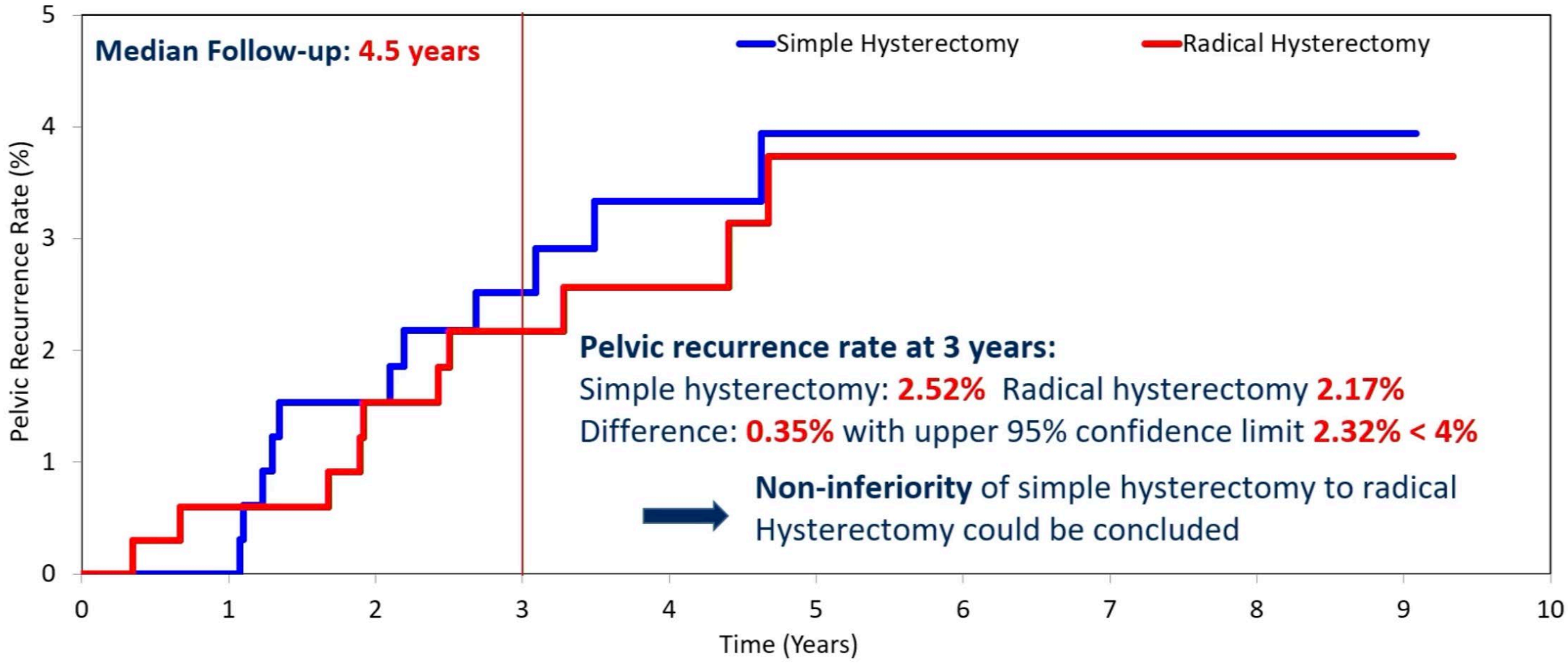
Stage II:

Characteristics	Simple Hysterectomy N=350 (%)	Radical Hysterectomy N=350 (%)	Total N=700
FIGO Stage:			
• IA2	30 (8.6)	28 (8.0)	58 (8.3)
• IB1	320 (91.4)	322 (92.0)	642 (91.7)
Histology			
• Squamous	218 (62.3)	214 (61.1)	432 (61.7)
• Adenocarcinoma	114 (32.6)	131(37.4)	245 (35.0)
• Adenosquamous	18 (5.1)	5 (1.4)	23 (3.3)
Grade:			
• 1 or 2	205 (58.6)	210 (60.0)	415 (58.2)
• 3	49 (14)	49 (14)	98 (14)
• Not assessed	96 (27.4)	91 (26)	187 (26.7)

Key post surgical findings on final pathology	Simple hysterectomy N=338 (%)	Radical hysterectomy N=344 (%)	P-value
• Residual cervical cancer detected	154 (45.6)	163 (47.4)	0.65
• Lymphovascular space invasion (LVSI)	45 (13.3)	45 (13.1)	1.00
• Positive nodes (from sentinel or non sentinel nodes)	11 (3.3)	15 (4.4)	0.55
• Positive vaginal margins	7 (2.1)	10 (2.9)	0.62
• Positive parametrium	0	6 (1.7)	0.03
• Lesions > 2cm	15 (4.4)	14 (4.1)	0.85

Adjuvant Treatment	Simple hysterectomy N=338 (%)	Radical hysterectomy N=344 (%)	P-value
• Adjuvant Post Operative Treatment	31 (9.2)	29 (8.4)	0.79
• Chemotherapy only	1	0	
• Radiation therapy only	15	11	
• Chemoradiation	15	18	

Pelvic Recurrence Rate (ITT)



Simple	350	328	311	273	204	133	61	31	14	4	0
Radical	350	329	315	286	208	132	66	31	16	2	0

Secondary Efficacy Endpoints (ITT)

Endpoints	Simple Hysterectomy N=350	Radical Hysterectomy N=350		
	3 year outcomes		Hazard Ratio (90% confidence interval)	P-value
Pelvic Recurrence Free survival	97.5%	97.8%	1.12 (0.54-2.32)	0.79
Extra-Pelvic Recurrence Free survival	98.1%	99.7%	3.82 (0.79-18.4)	0.10
Relapse Free Survival	96.3%	97.8%	1.54 (0.69-3.45)	0.30
Overall survival	99.1%	99.4%	1.09 (0.38-3.14)	0.87

Surgery-related Adverse Events (All Grades with incidence ≥ 5% in one of the Arms)

Adverse Event	Simple Hysterectomy N=338 (%)	Radical Hysterectomy N=344 (%)	P value	Simple Hysterectomy N=338 (%)	Radical Hysterectomy N=344 (%)	P value
	Within 4 weeks of surgery (acute)			After 4 weeks of surgery (late)		
Any adverse event	144 (42.6)	174 (50.6)	**0.04**	181 (53.6)	208 (60.5)	**0.08**
• Abdominal pain	33 (9.8)	42 (12.2)	0.33	36 (10.7)	47 (13.7)	0.24
• Constipation	16 (4.7)	22 (6.4)	0.40	13 (3.8)	19 (5.5)	0.37
• Fatigue	19 (5.6)	23 (6.7)	0.63	19 (5.6)	28 (8.1)	0.23
• Paresthesia	14 (4.1)	22 (6.4)	0.23	17 (5.0)	22 (6.4)	0.51
• Peripheral sensory neuropathy	- (-)	- (-)	- (-)	21 (6.2)	13 (3.8)	0.16
• Urinary incontinence	8 (2.4)	19 (5.5)	**0.048**	16 (4.7)	38 (11.0)	**0.003**
• Urinary retention	2 (0.6)	38 (11.0)	**<0.0001**	2 (0.6)	34 (9.9)	**<0.0001**
• Dyspareunia	- (-)	- (-)	- (-)	21 (6.2)	19 (5.5)	0.75
• Pelvic pain	19 (5.6)	9 (2.6)	0.054	23 (6.8)	17 (4.9)	0.33
• Lymphedema	- (-)	- (-)	- (-)	35 (10.4)	36 (10.5)	1.00
• Hot flashes	- (-)	- (-)	- (-)	14 (4.1)	20 (5.8)	0.38

All Treated Patients Post Surgery

Intraoperative complications	Simple Hysterectomy N=338 (%)	Radical Hysterectomy N=344 (%)	P-value
Intraoperative Injury	24 (7.1)	22 (6.4)	0.77
• Bladder	3	9	0.14
• Ureter	3	5	0.73
• Nerve	5	2	0.28
• Bowel	2	2	1.00
• Vein	4	1	0.21
• Other	7	3	0.22

Quality of Life and Sexual Health

Scale	Effect Estimate*	P-value
EORTC QLQ-C30 pain scale	-4.53	p=0.02
EORTC QLQ-CX24 • Symptom experiences	-2.12	p=0.02
• Body Image	-5.22	p=0.02
• Sexual Worry	-6.67	p=0.04
• Sexual Activities	-7.59	p=0.003
• Sexual Enjoyment	-7.67	p=0.049
FSFI Desire	0.37	p=0.002
FSFI Arousal	0.38	p=0.003
FSFI Lubrication	0.36	p=0.008
FSFI Total Score	1.82	p=0.006
FSDS Total Score	-2.47	p=0.02

Significant differences were seen between the 2 groups over time and **all were in favor of the simple hysterectomy group**

*From linear mixed models for change scores from baseline over time

Quality of Life and Sexual Health

Sexual-Vaginal Functioning (EORTC QLQ-CX24): Lower is Better			
	SH (Mean change score)	RH (Mean change score)	P-value
Month 3	4.41	16.03	p<0.0001
Month 6	0.93	11.85	p<0.0001
Month 12	0.94	9.16	p<0.0001
Sexual Pain (FSFI Pain Scale): Higher is Better			
	SH (Mean change score)	RH (Mean change score)	P-value
Month 3	0.03	-0.78	p=0.003
Month 6	0.10	-0.56	p=0.02
Month 12	0.35	-0.22	p=0.002

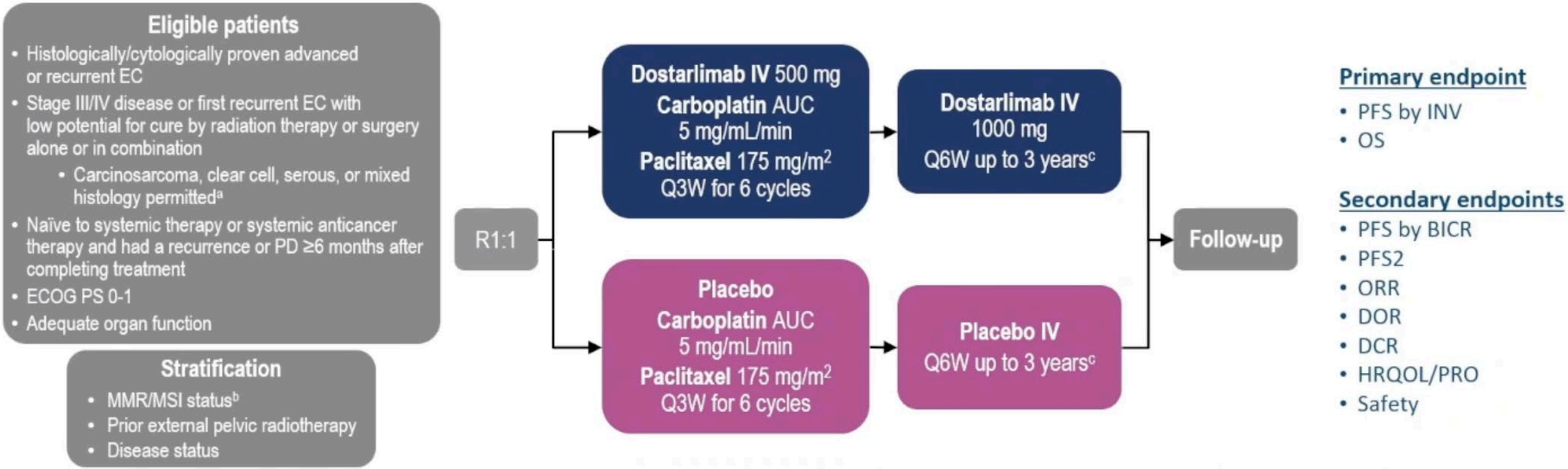
Conclusion

- L’hystérectomie simple présente une efficacité similaire, avec une moindre morbidité urologique et une meilleure qualité de vie sexuelle à long terme.
  - <ou = 2 cm
  - <1 cm invasion stromale
  - <50% invasion à l’IRM
  - Evaluation GG indispensable

Changement de pratique

2023 ASCO ANNUAL MEETING

RUBY (ENGOT-EN6; GOG-3031) : presentation ESMO plénière mars 2023
Dostarlimab + Chemotherapy → nouvelle presentation à l'ASCO 2023



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 per standard of care.

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

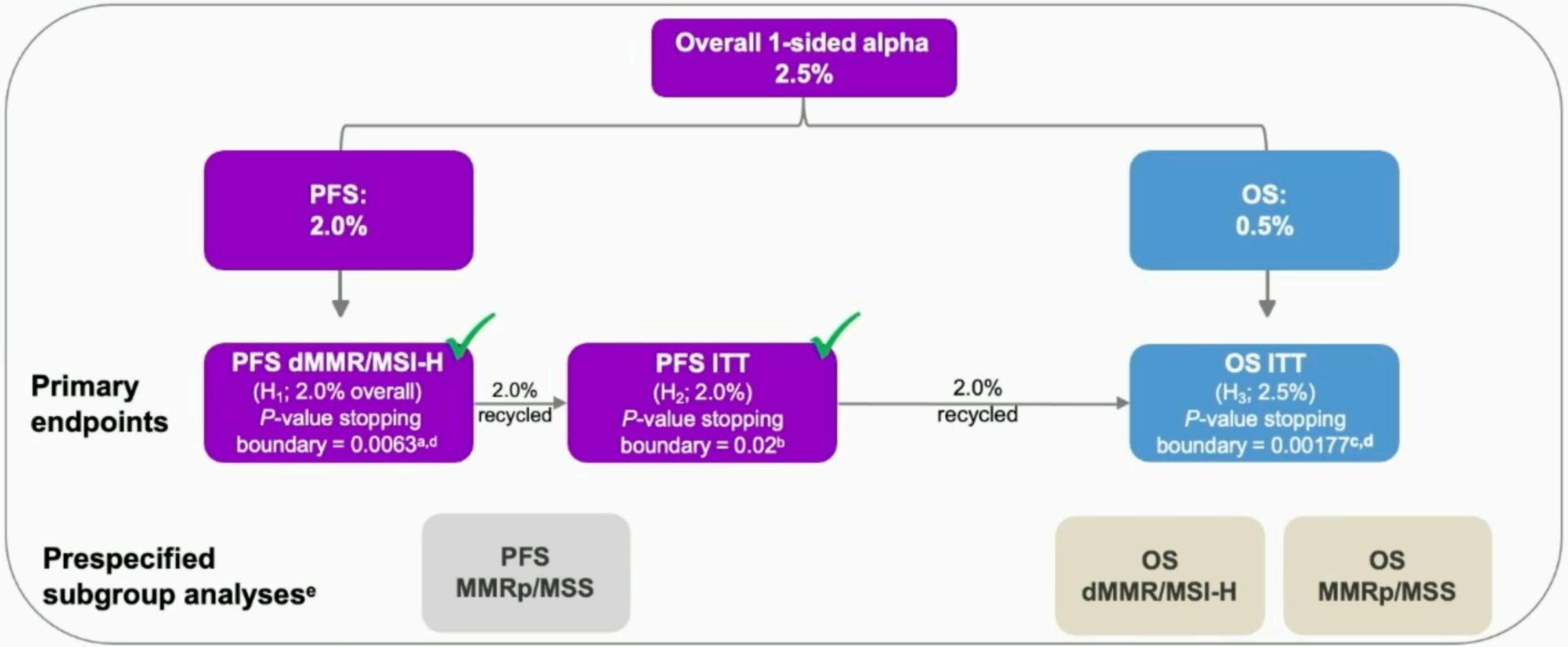
Caractéristiques de la population

Variable, n (%)	dMMR/MSI-H (n=118)		Overall (n=494)	
	Dostarlimab + CP (N=53)	Placebo + CP (N=65)	Dostarlimab + CP (N=245)	Placebo + CP (N=249)
MMR/MSI status				
dMMR/MSI-H	53 (100)	65 (100)	53 (21,6)	65 (26,1)
MMRp/MSS	—	—	192 (78,4)	184 (73,9)
Prior external pelvic radiation				
Yes	8 (15,1)	13 (20,0)	41 (16,7)	45 (18,1)
No	45 (84,9)	52 (80,0)	204 (83,3)	204 (81,9)
Disease status				
Primary stage III	10 (18,9)	14 (21,5)	45 (18,4)	47 (18,9)
Primary stage IV	16 (30,2)	19 (29,2)	83 (33,9)	83 (33,3)
Recurrent	27 (50,9)	32 (49,2)	117 (47,8)	119 (47,8)

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

M. R. Mirza, et al., SGO® 2023, Abs #265

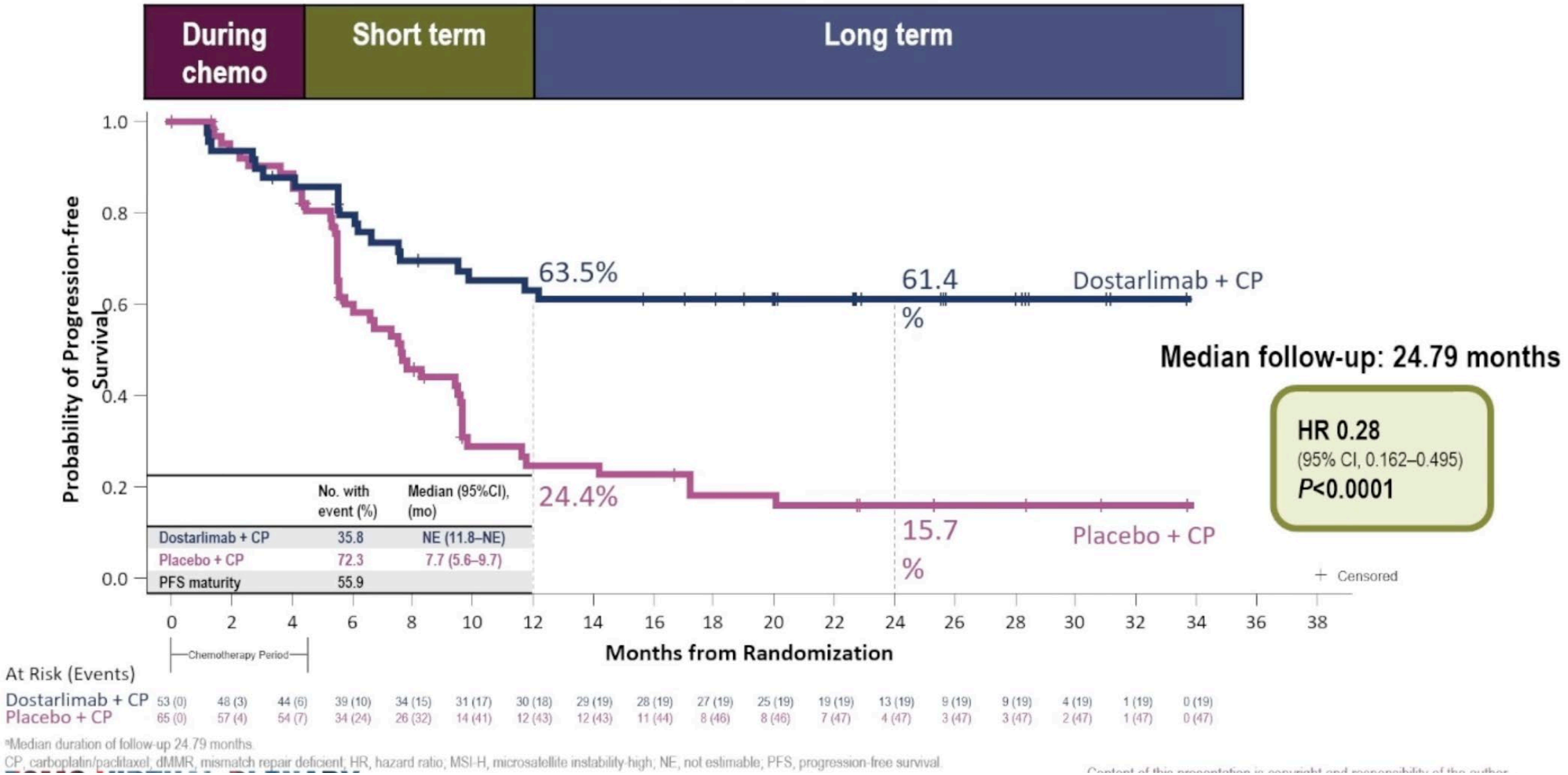
Tests statistiques pour la stratégie d'analyse



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

[a] Hypothesis for PFS dMMR/MSI (H1) was tested at the IA with 0.63% alpha spent from the overall alpha level (2.0%) initially allocated. [b] Since null hypothesis (H01) for H1 was rejected at IA, the 2.0% alpha for (H1) was recycled to hypothesis testing of PFS ITT (H2). H2 was tested at alpha level (2.0%)= 2.0% recycled + 0% initially allocated. [c] Since both null hypotheses (H01 and H02) were rejected, 2.0% alpha for the family of hypothesis testing of PFS was recycled to testing of OS (H3). H3 was tested at alpha level (2.5%)= 2.0% recycled + 0.5% initially allocated. dStopping boundaries and alpha spent at IA were adjusted based on the actual number of events/information fraction observed based on the prespecified alpha spending function at the time of analysis; P-value stopping boundary (IA)= 0.0063 for PFS dMMR/MSI-H; P-value stopping boundary (IA1)=0.00177 for OS ITT. eNot formally tested. dMMR, mismatch repair deficient; FA, final analysis; H, hypothesis; IA, interim analysis; ITT, intent to treat; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; OS, overall survival; PFS, progression-free survival.

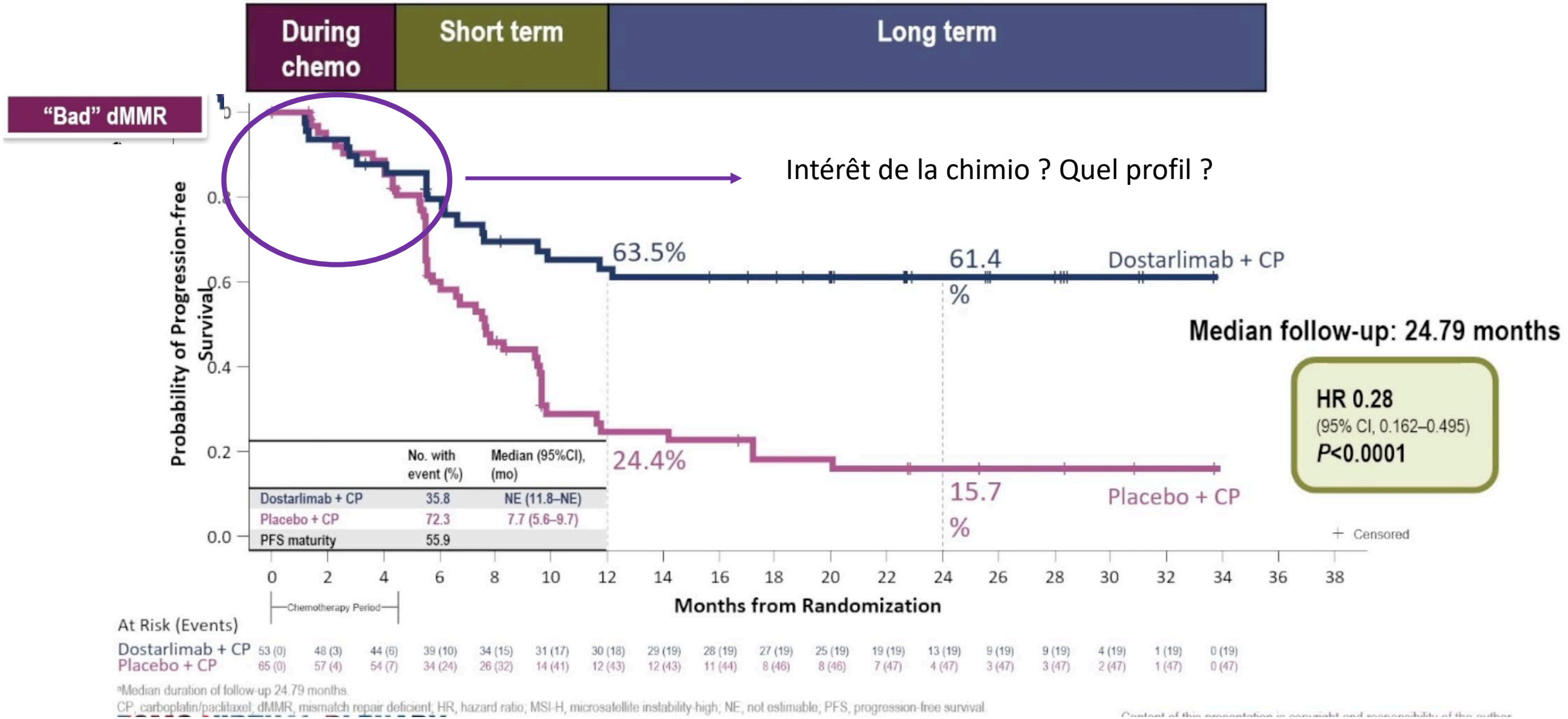
PRIMARY ENDPOINT: PFS IN dMMR/MSI-H POPULATION



[a]Median duration of follow-up 24.79 months.

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

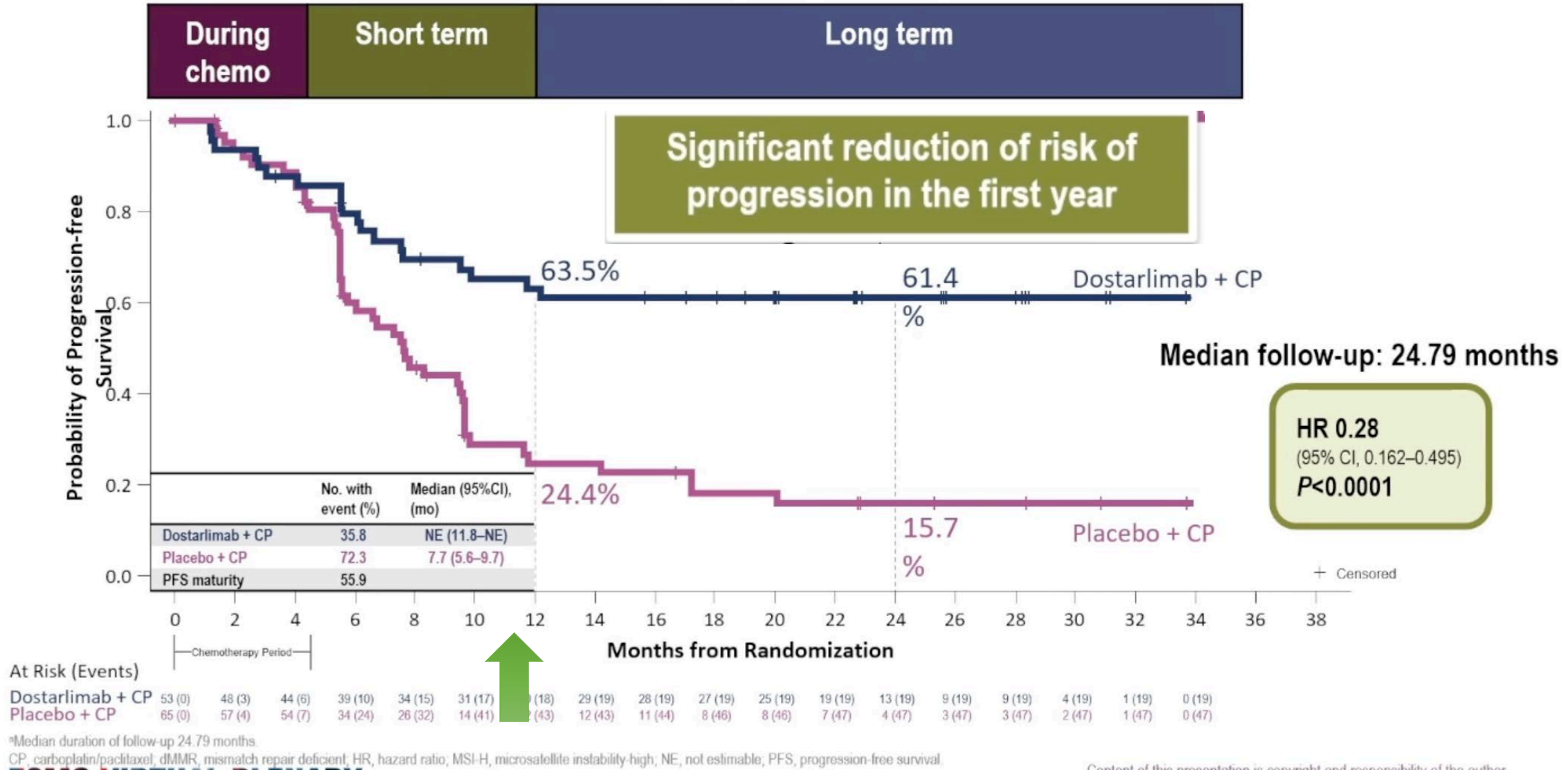
PRIMARY ENDPOINT: PFS IN dMMR/MSI-H POPULATION



[a]Median duration of follow-up 24.79 months.

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

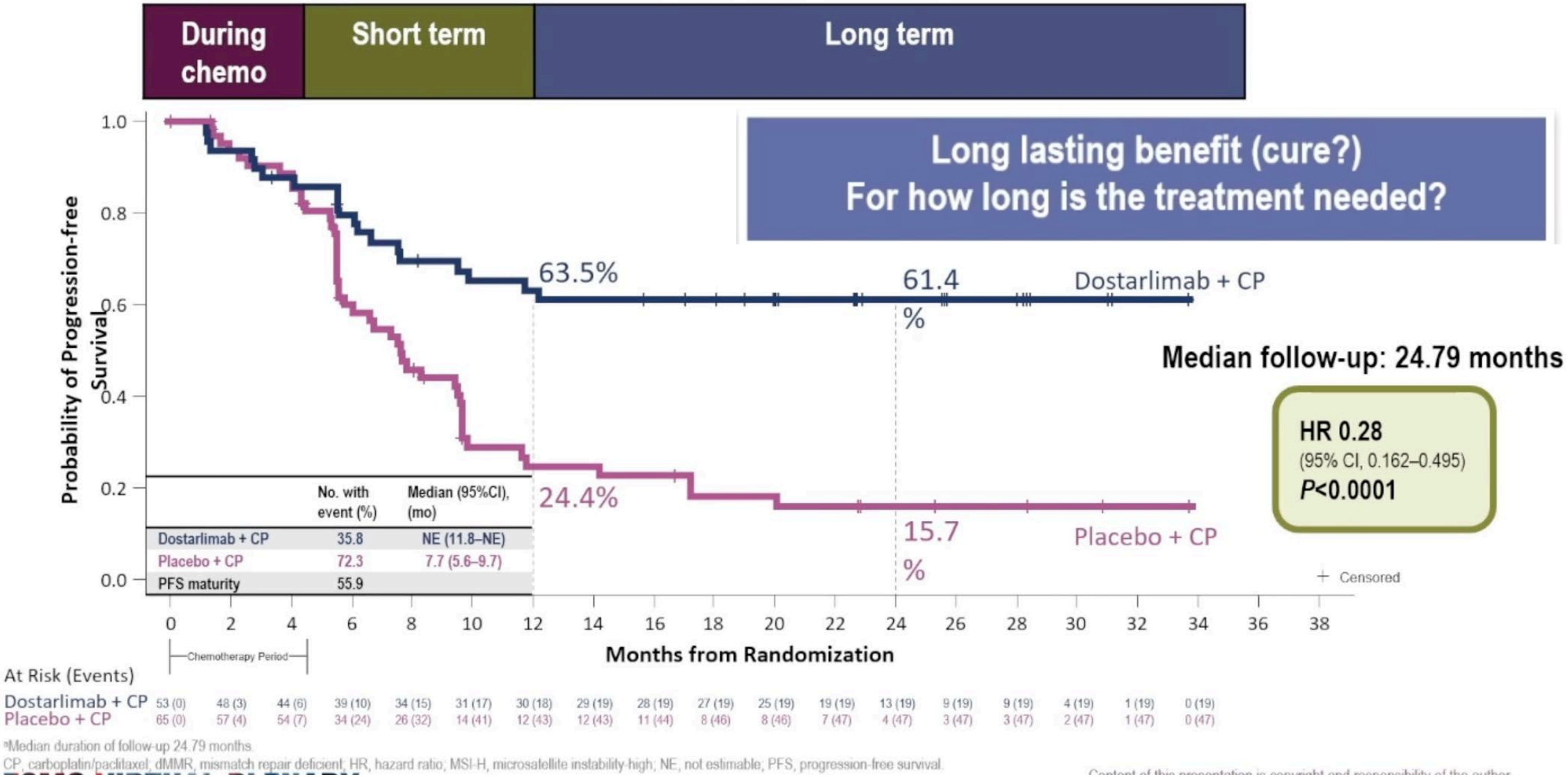
PRIMARY ENDPOINT: PFS IN dMMR/MSI-H POPULATION



[a]Median duration of follow-up 24.79 months.

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

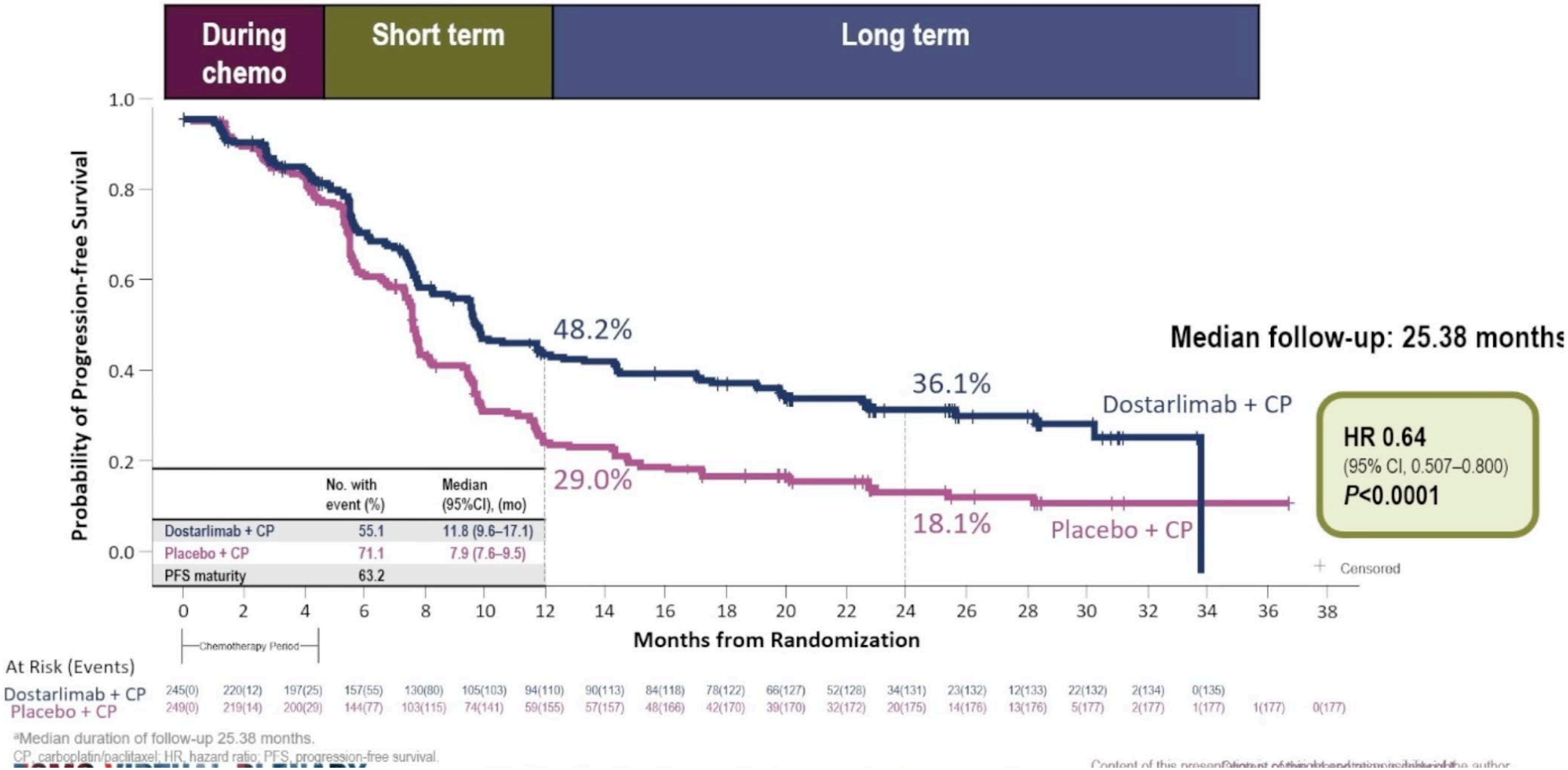
PRIMARY ENDPOINT: PFS IN dMMR/MSI-H POPULATION



[a]Median duration of follow-up 24.79 months.

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

PRIMARY ENDPOINT: PFS IN OVERALL POPULATION



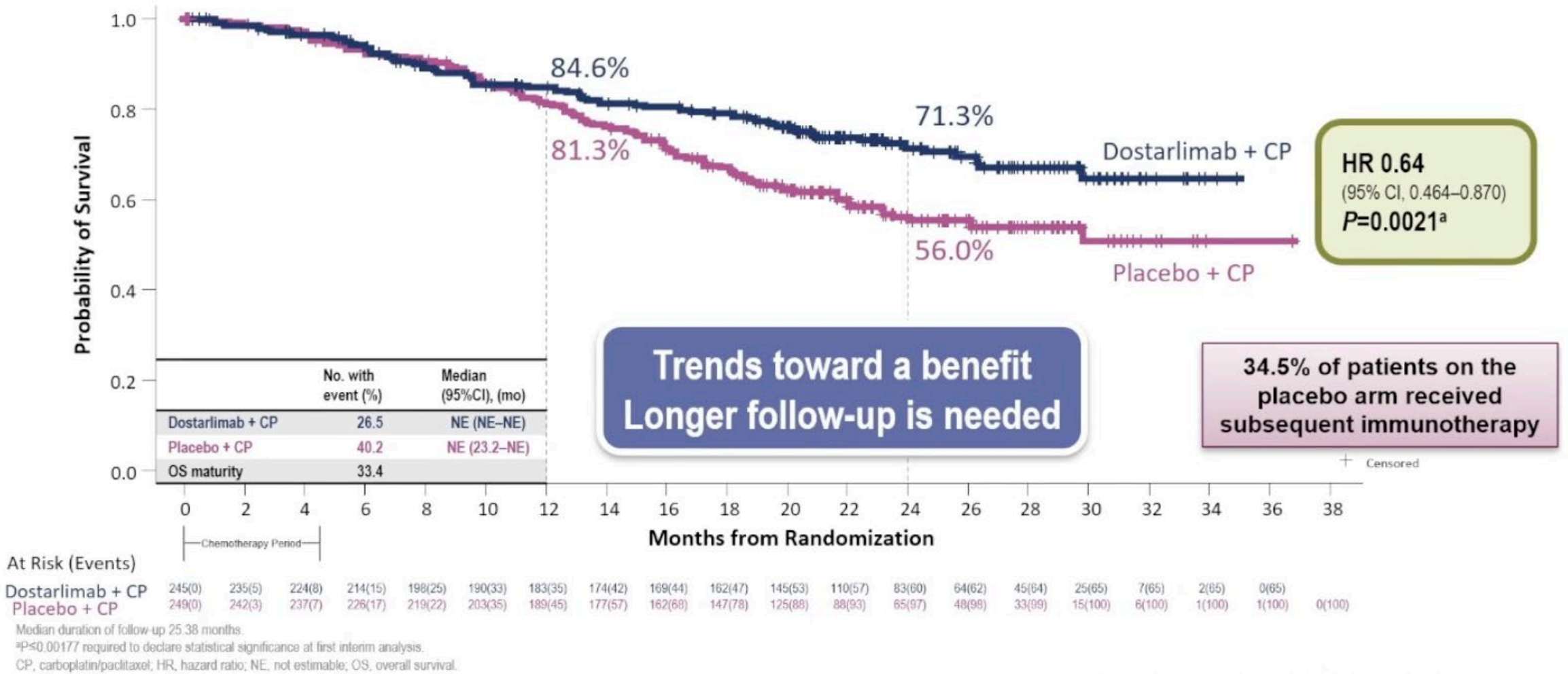
[a]Median duration of follow-up 25.38 months.
CP, carboplatin/paclitaxel; HR, hazard ratio; PFS, progression-free survival.

Statistically and clinical significant PFS benefit in dMMR/MSI-H and overall population

Statistically significance PFS benefit in the MMRp/MSS population could not be proven

Role of chemotherapy in dMMR/MSI-H still to be proven (no arm with dostarlimab alone)

CO-PRIMARY ENDPOINT: OS IN OVERALL POPULATION (33% MATURITY)



Median duration of follow-up 25.38 months.

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

CP, carboplatin/paclitaxel; HR, hazard ratio; NE, not estimable; OS, overall survival.

PRO Assessments

- The EORTC QLQ-C30 and QLQ-EN24 questionnaires were used to collect patient HRQoL data[a]
- PRO assessments were completed before treatment on day 1 of each treatment cycle, at the end of treatment visit, and at safety and survival follow-up visits
  - Cycle 1, Day 1 was the baseline value
  - Cycle 7, Day 1 is the start of the monotherapy phase
  - Cycle 13, Day 1 is the start of the first cycle in the second year of treatment cycles

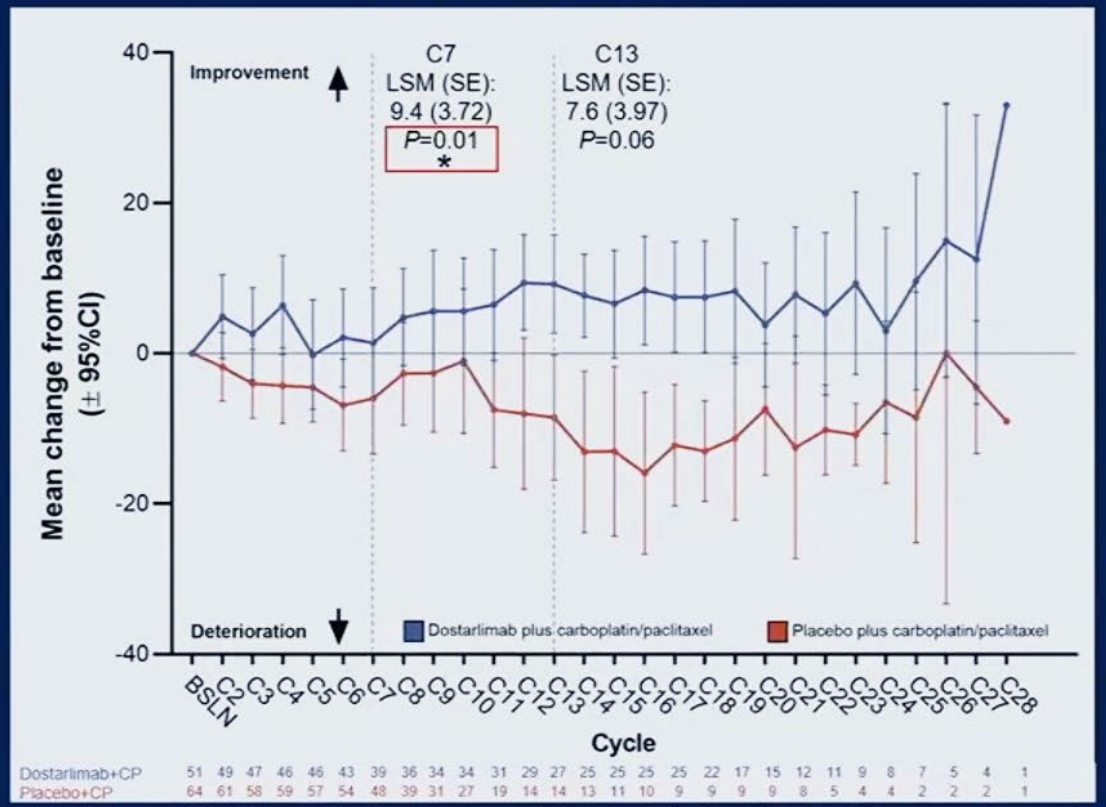
Instrument	Domains assessed	Score	Higher score indicates
EORTC QLQ-C30	**Global health status/QoL**	0–100	Better HRQoL
	Functional scales: Physical, role, emotional, cognitive, social	0–100	Better functioning
	Symptoms: Fatigue, nausea & vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties	0–100	Worse symptoms
EORTC QLQ-EN24	**Functional scales**: Sexual interest, sexual activity, sexual enjoyment	0–100	Better functioning
	Symptoms: lymphoedema, urological, gastrointestinal, poor body image, vaginal, pain in back and pelvis, tingling/numbness, muscular pain, hair loss, taste change	0–100	Worse symptoms

[a]EQ-5D-5L was also administered. EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQoL 5-dimensions 5-levels; HRQoL, health-related quality of life; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire-Core 30; QLQ-EN24, Quality of Life Questionnaire-Endometrial Cancer Module; QoL, Quality of Life.

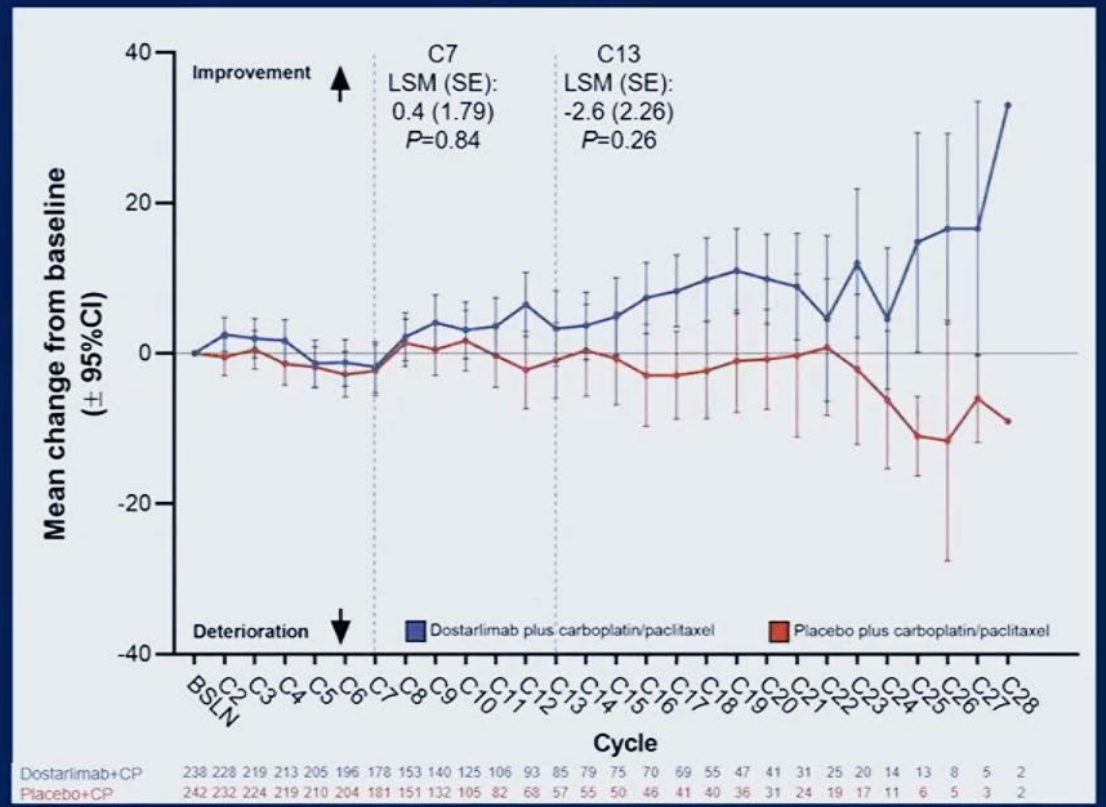
PRESENTED BY: Dr Mansoor Raza Mirza

Significant Difference Seen at Cycle 7 in Global QoL Between Arms in dMMR/MSI-H Population

dMMR/MSI-H



Overall

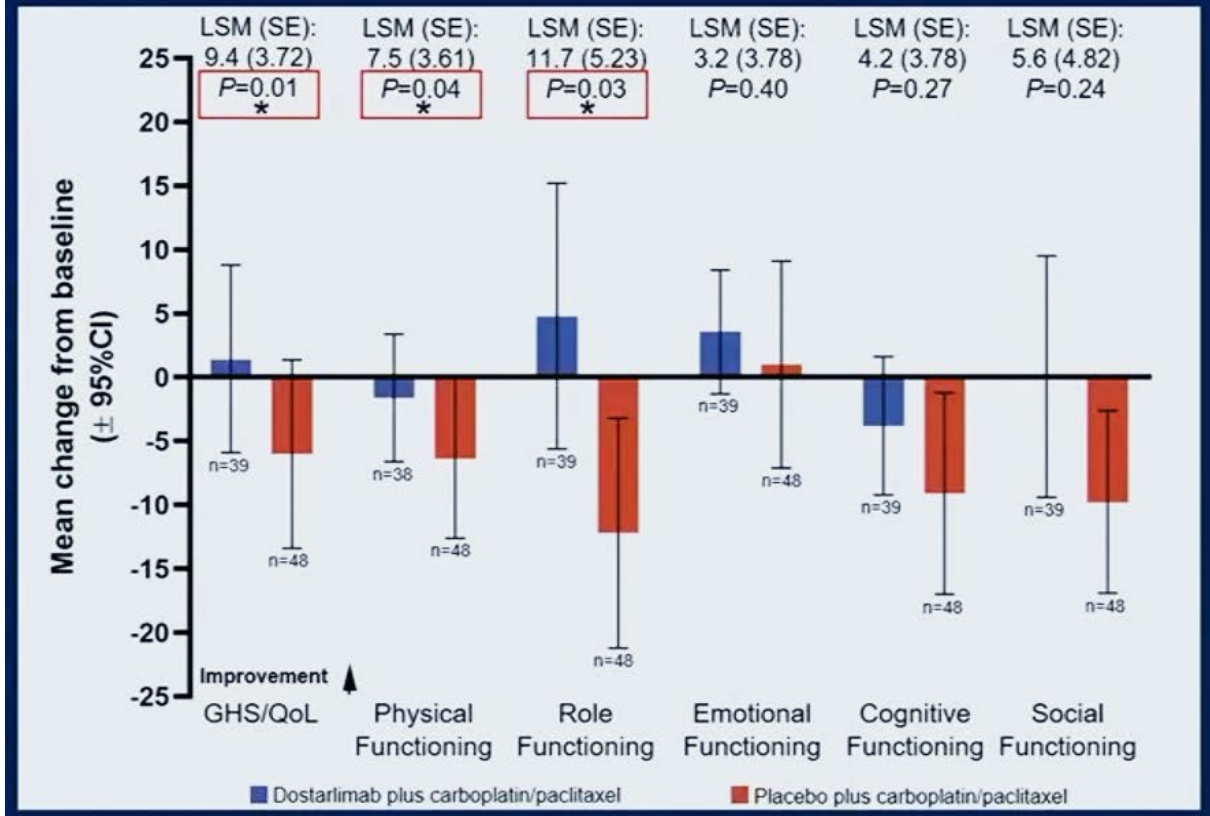


*Indicates nominal significance. P-values shown are nominal p-values. Mixed models for repeated measures were used to generate least-square means, adjusting for within-patient correlations across time points within a patient and controlling for baseline values.

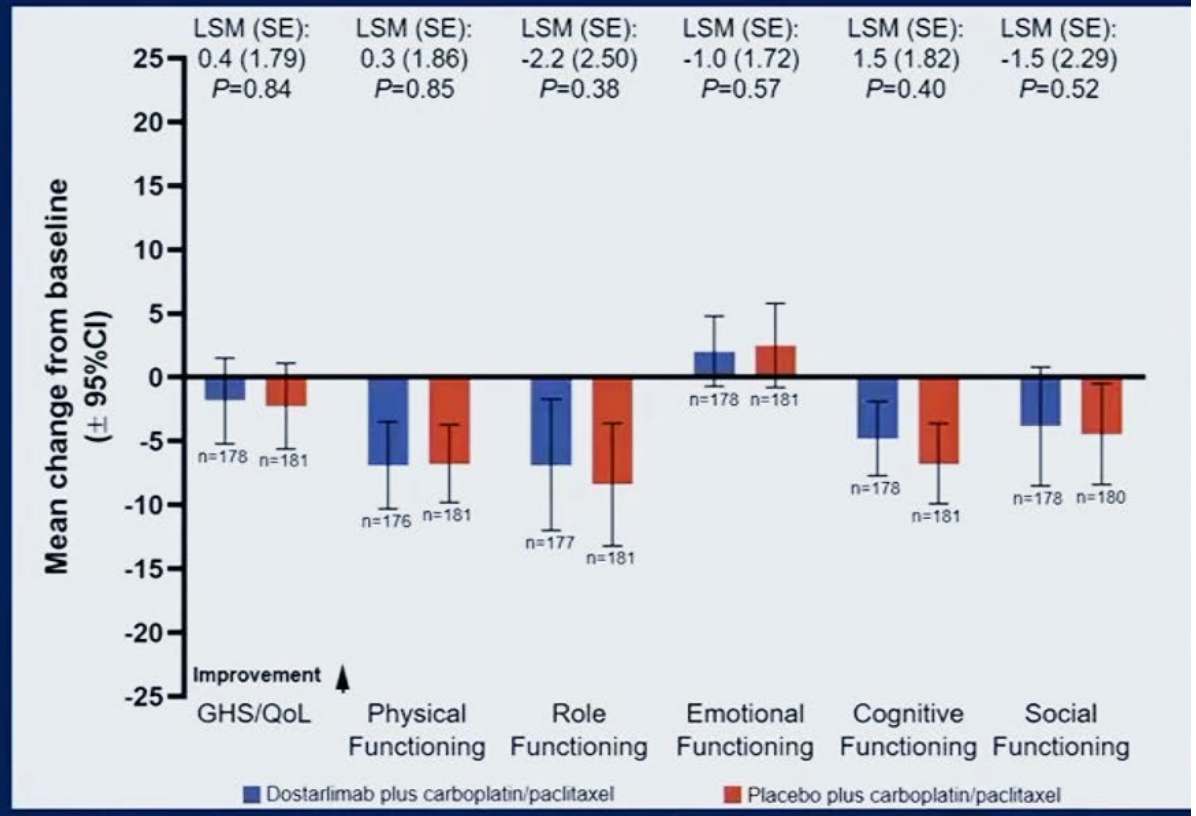
BSLN, baseline; C, cycle; CP, carboplatin-paclitaxel; dMMR, mismatch repair deficient; LSM, least square mean; MSI-H, microsatellite instability-high.

Significant Differences Seen at Cycle 7 Between Arms in dMMR/MSI-H Population for GHS/QoL, Physical Functioning, and Role Functioning

dMMR/MSI-H



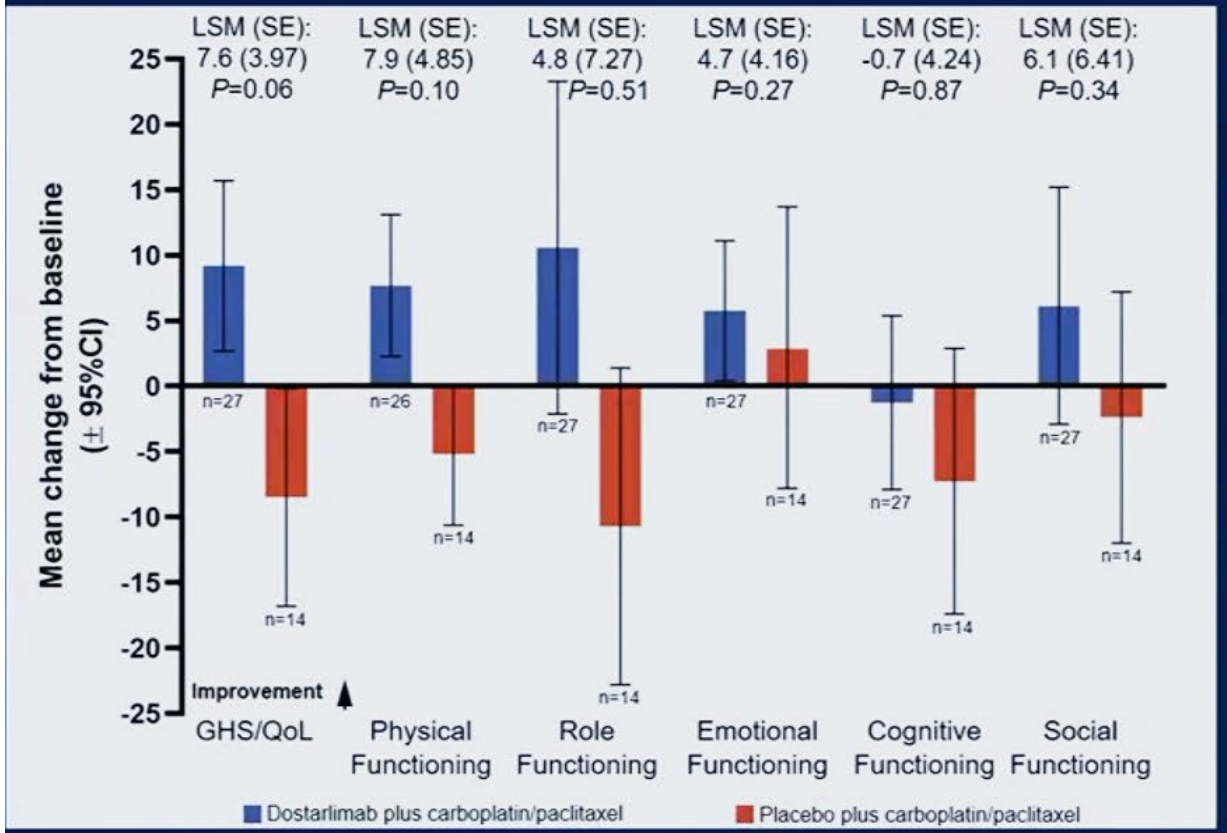
Overall



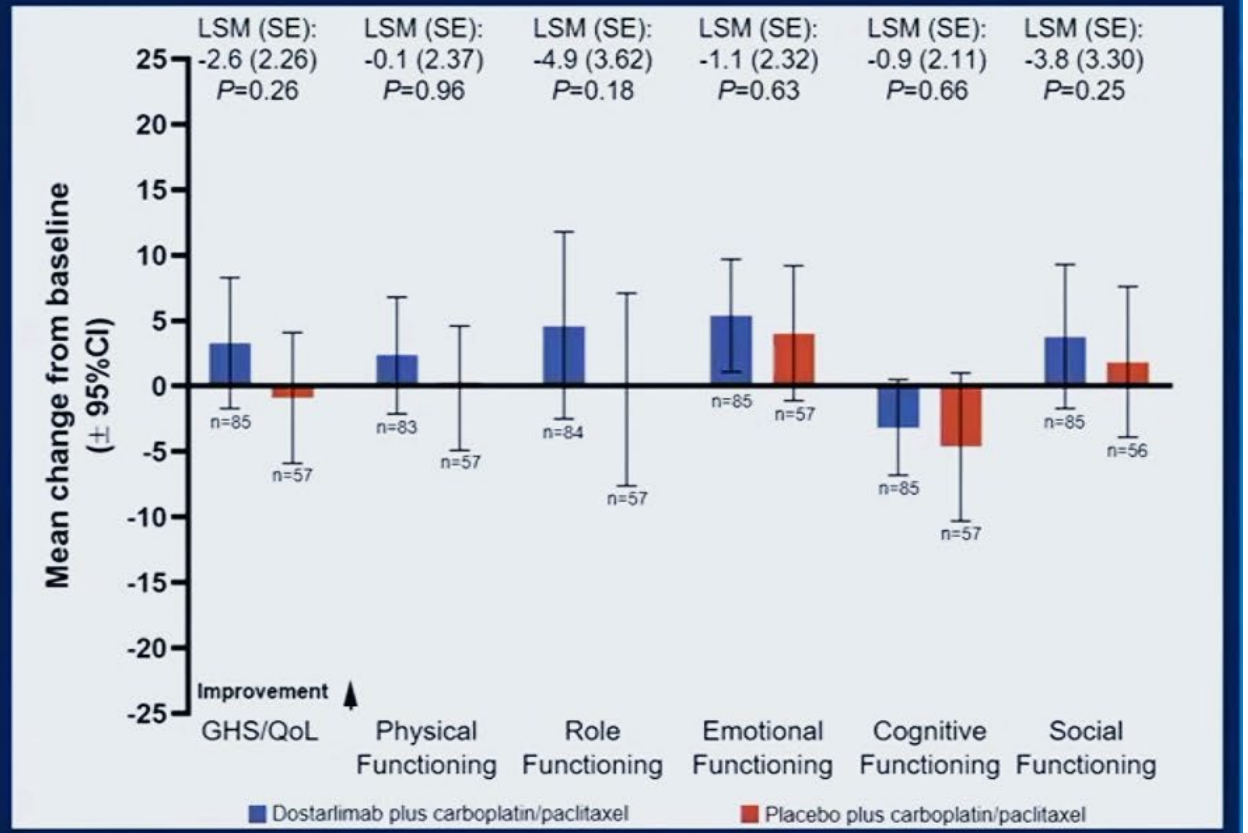
* Indicates nominal significance. P-values shown are nominal p-values. Mixed models for repeated measures were used to generate LSM, adjusting for within-patient correlations across time points within a patient and controlling for baseline values. dMMR, mismatch repair deficient; GHS, global health score; LSM, least square mean; MSI-H, microsatellite instability-high; QoL, quality of life.

No Significant Differences Seen at Cycle 13 Between Arms

dMMR/MSI-H



Overall



Conclusion

- Etude de changement de pratique
- Nouveau standard : bénéfice important du dostarlimab en combinaison avec une chimiothérapie par carboplatine et paclitaxel dans les cancers de l'endomètre dMMR en 1re ligne de traitement.
- Accès précoce fin de l'année en France pour proposer ce traitement.
- En attendant, essai DOMENICA
- Attente résultat de l'étude : Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for Endometrial Carcinoma (ENGOT-en9 / MK-7902-001) (LEAP-001)

ETUDE DOMINCA EN COURS