Cancer de l'endomètre:

DUO-E et UTOLA

Que faut-il retenir de ces deux essais pour nos patientes ?

Pr Jean-Emmanuel Kurtz
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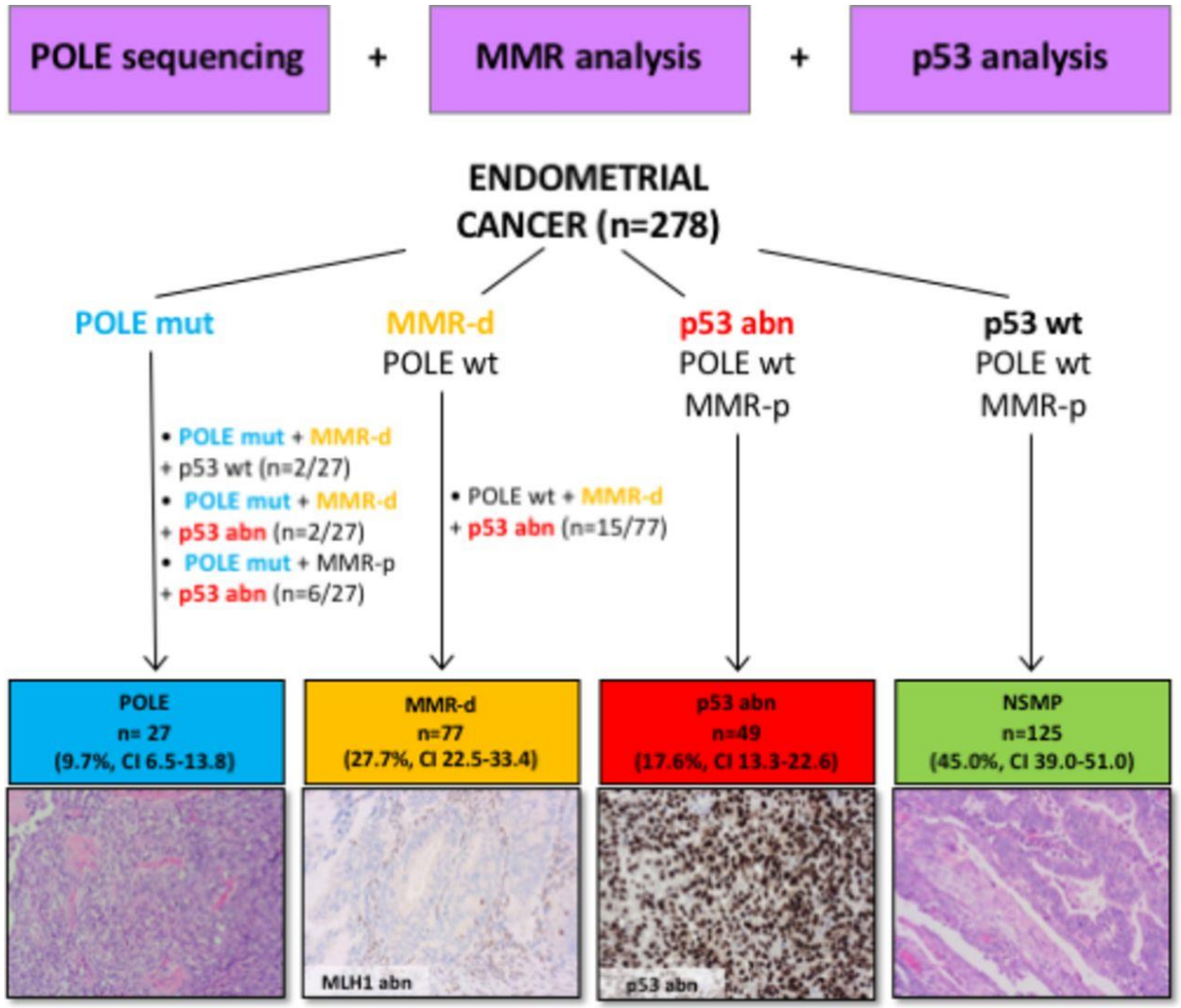
Le cancer de l’endomètre, before et now

Yves Klein. Inventation vitesse pure et stabilité monochrome, 1959

Le cancer de l'endomètre, before et now

	Type 1	Type 2
Clinical Features		
Risk factors	Unopposed estrogen	Age
Differentiation	Well differentiated	Poorly differentiated
Histology	Endometrioid	Serous, clear cell
Stage	I/II	III/IV
Prognosis	Favorable	Not favorable
Endometrial lining	Atrophic	Hyperplastic
Characteristic Molecular Features		
Ploidy	Diploid	Aneuploid
P53 overexpression	No	Yes
PTEN mutations	Yes	No
Microsatellite instability	Yes	No



Vers un traitement personnalisé du cancer de l'endomètre

- La chimiothérapie pour tous (sans discernement) n'est plus vraiment une option
- Au-delà de « hormonothérapie vs chimiothérapie »
- Recherche de cibles thérapeutiques
- Avènement de deux classes thérapeutiques majeures en oncologie gynécologique
- Inhibiteurs de PARP
  - Vers un traitement d'entretien comme dans le cancer de l'ovaire ?
- Inhibiteurs de checkpoints du système immunitaire
  - Un changement de paradigme dans les cancers MSI ?

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Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab ± olaparib as a first-line treatment for newly diagnosed advanced or recurrent endometrial cancer: results from the Phase III DUO-E/GOG-3041/ENGOT-EN10 trial

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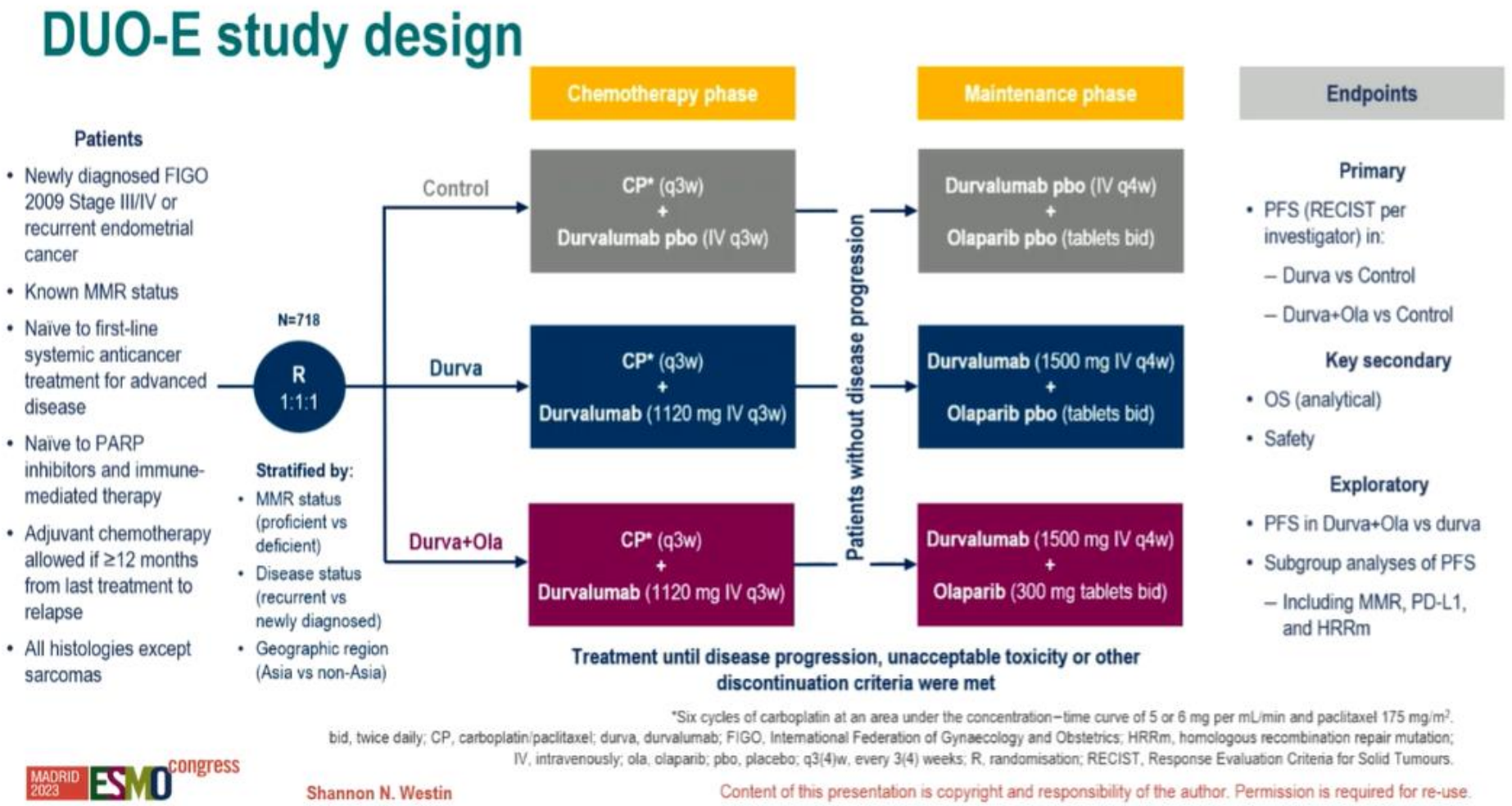
Conducted in partnership with the Gynecologic Oncology Group (GOG-3041) and the European Network for Gynaecological Oncological Trial groups (ENGOT-EN10). ClinicalTrials.gov identifier: NCT04269200. This study was sponsored by AstraZeneca.

Des inhibiteurs de PARP dans le cancer de l'endomètre



Patient characteristics

Characteristics		Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Age, years	Median (range)	64 (31–85)	64 (22–84)	63 (27–86)
Geographic region,* %	Asia	28	29	28
	Non-Asia	72	71	72
Race, %	White	59	57	56
	Asian	30	30	29
	Black/African American	4	5	6
	American Indian/Alaska Native	0	3	3
	Other or not reported	6	5	7
Ethnicity, %	Not Hispanic or Latino	90	87	86
	Hispanic or Latino	8	12	13
Disease status, %	Newly diagnosed*	48	47	48
	FIGO Stage III	5	7	5
	FIGO Stage IV	42	40	41
	Recurrent*	52	53	52
ECOG PS, %	(0) Normal Activity	65	66	69
	(1) Restricted Activity	35	34	31
Measurable disease at baseline, %		82	85	77

Characteristics		Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
MMR status,*†† %	Proficient	80	81	80
	Deficient	20	19	20
PD-L1 status,‡ %	Positive (TAP score ≥1%)	68	71	63
	Negative (TAP score <1%)	31	26	34
	Unknown	1	3	3
HRRm status,§ %	HRRm	13	11	16
	Non-HRRm	55	58	59
	Unknown	32	31	25
Histology type at diagnosis, %	Endometrioid	58	59	64
	Serous	22	24	18
	Carcinosarcoma	9	5	8
	Mixed, epithelial	5	4	4
	Clear cell	3	2	3
	Undifferentiated	1	2	2
	Mucinous or other	2	4	2
Previous chemotherapy, %		21	21	23
Previous radiotherapy, %		29	31	36
Prior surgery, %		84	86	87

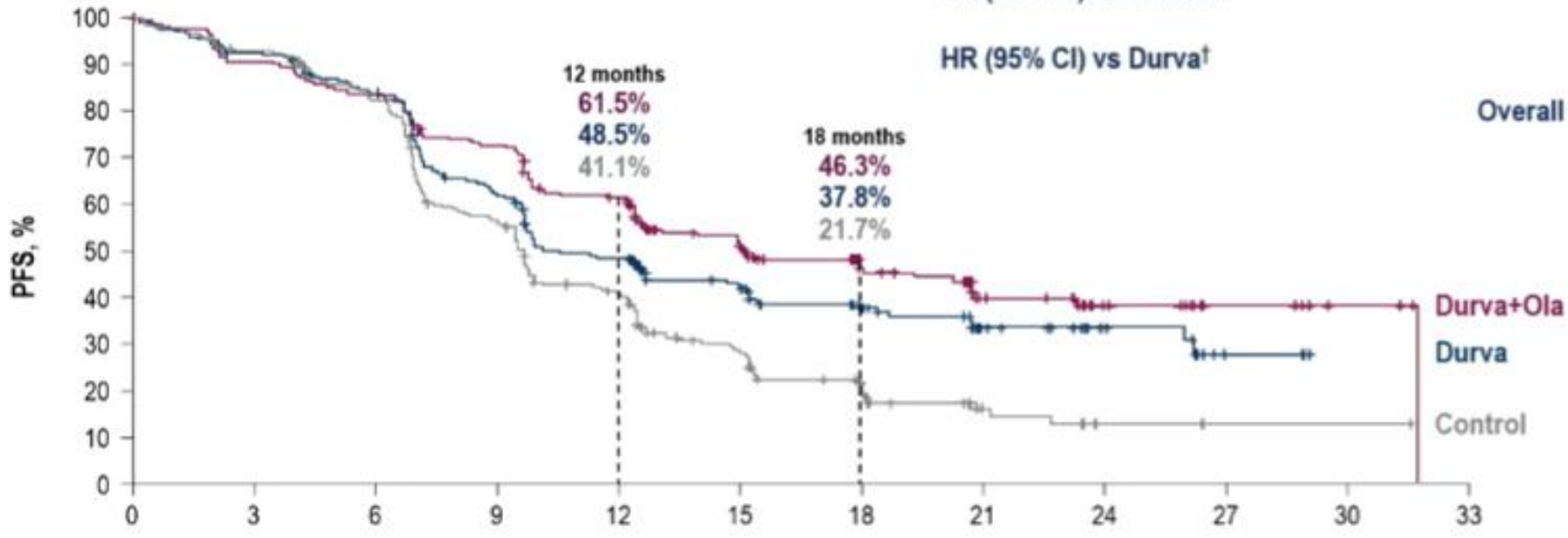
Percentages may not total 100 because of rounding. *Stratification factors (MMR status [proficient vs deficient], disease status [newly diagnosed vs recurrent], and geographic region [Asia vs non-Asia]) are per the randomisation code. Two patients with 'unknown' MMR status per central laboratory were randomised as 'deficient' per interactive voice response system, based on local testing. Asia included China, Hong Kong, India, Japan, Singapore and South Korea; †MMR status evaluated using the Ventana immunohistochemistry MMR panel; ‡PD-L1 expression evaluated using Ventana SP263; §HRRm status evaluated using the Foundation One CDx NGS assay and includes deleterious or suspected deleterious mutations in *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L*. HRRm status unknown includes patients recruited in China where HRR testing was not performed and patients with samples that were unavailable for testing. ECOG PS, Eastern Cooperative Oncology Group performance status; TAP, tumour area positivity.

PFS: ITT population

Primary endpoint

	Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS (95% CI),* months	9.6 (9.0–9.9)	10.2 (9.7–14.7)	15.1 (12.6–20.7)
HR (95% CI) vs Control†		**0.71** (0.57–0.89); *P*=0.003	**0.55** (0.43–0.69); *P*<0.0001
HR (95% CI) vs Durva†			0.78 (0.61–0.99)

Overall data maturity 61.0%



No. at risk

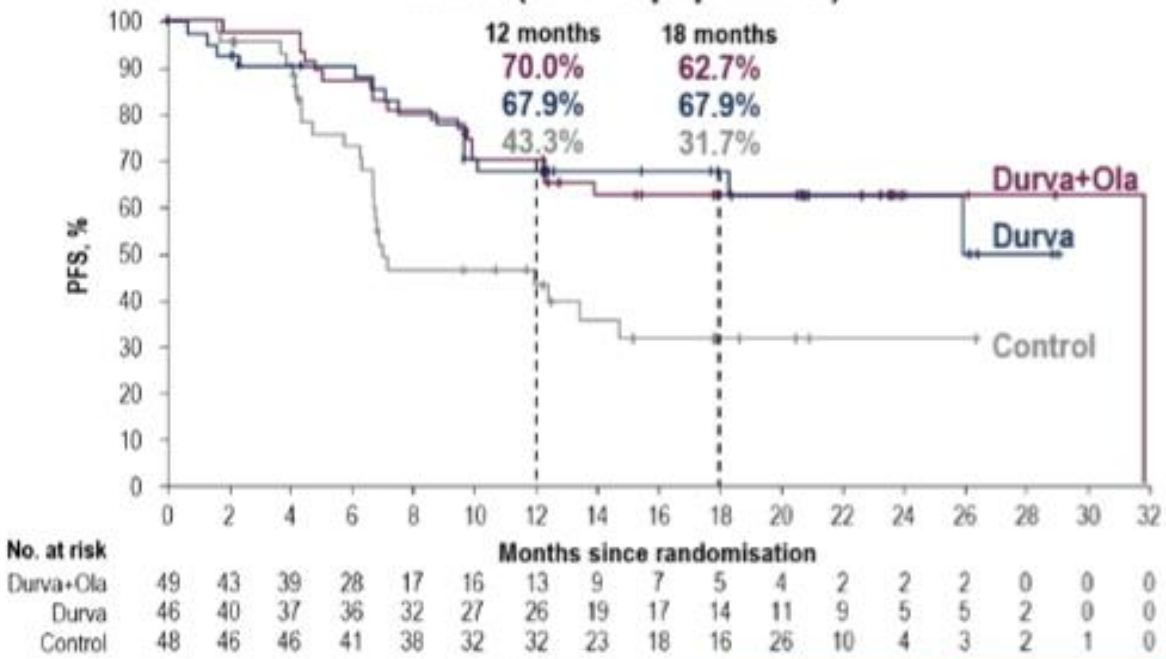
Durva+Ola	239	214	198	169	139	95	51	30	16	7	3	0
Durva	238	211	188	138	105	69	45	26	13	5	0	0
Control	241	213	184	125	86	45	26	10	3	1	1	0

The median (range) duration of follow-up for PFS was 12.6 (0.0–31.6), 15.4 (0.0–29.1), and 15.4 (0.0–31.7) months in censored patients for the Control, Durva, and Durva+Ola arms, respectively. PFS rates were estimated by the KM method. *CI for median PFS is derived based on the Brookmeyer–Crowley method; †The primary PFS analysis for each comparison was performed separately. The HR and CI were estimated from a Cox proportional hazards model stratified by MMR and disease status. The CI was calculated using a profile likelihood approach. The *P* value was calculated using a log-rank test stratified by MMR and disease status. ITT, intent-to-treat; KM, Kaplan–Meier.

Subgroup analysis of PFS by MMR status

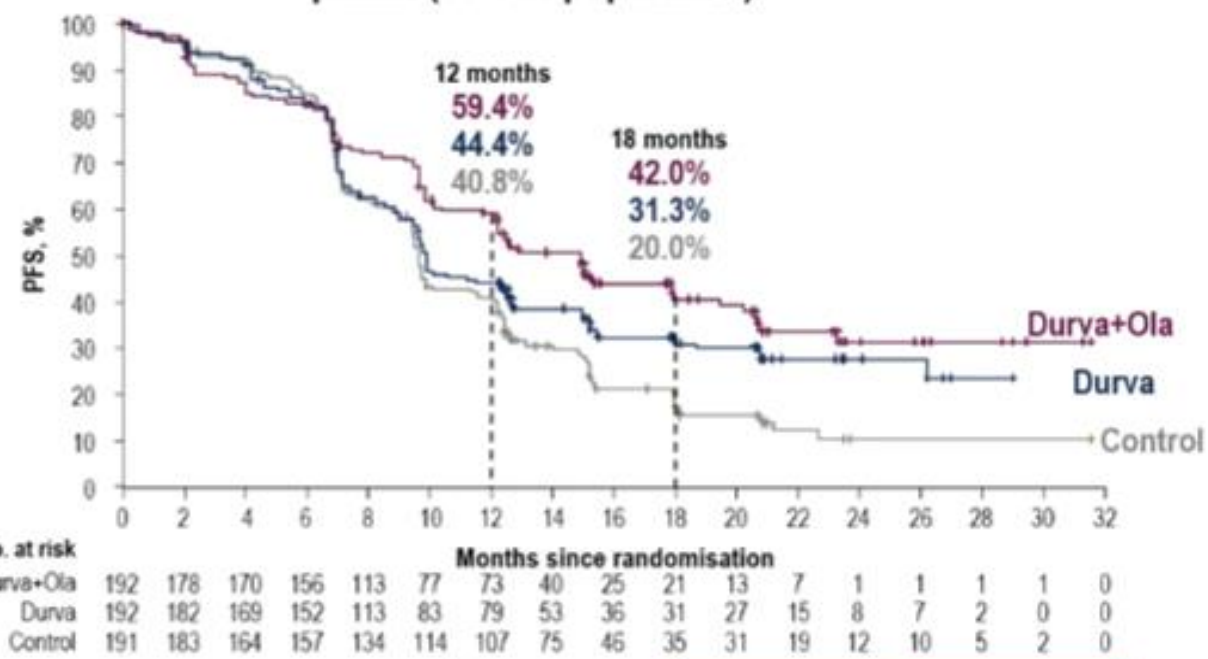
Prespecified exploratory analysis

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)
Median PFS (95% CI),* months	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)**

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)
Median PFS (95% CI),* months	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)**

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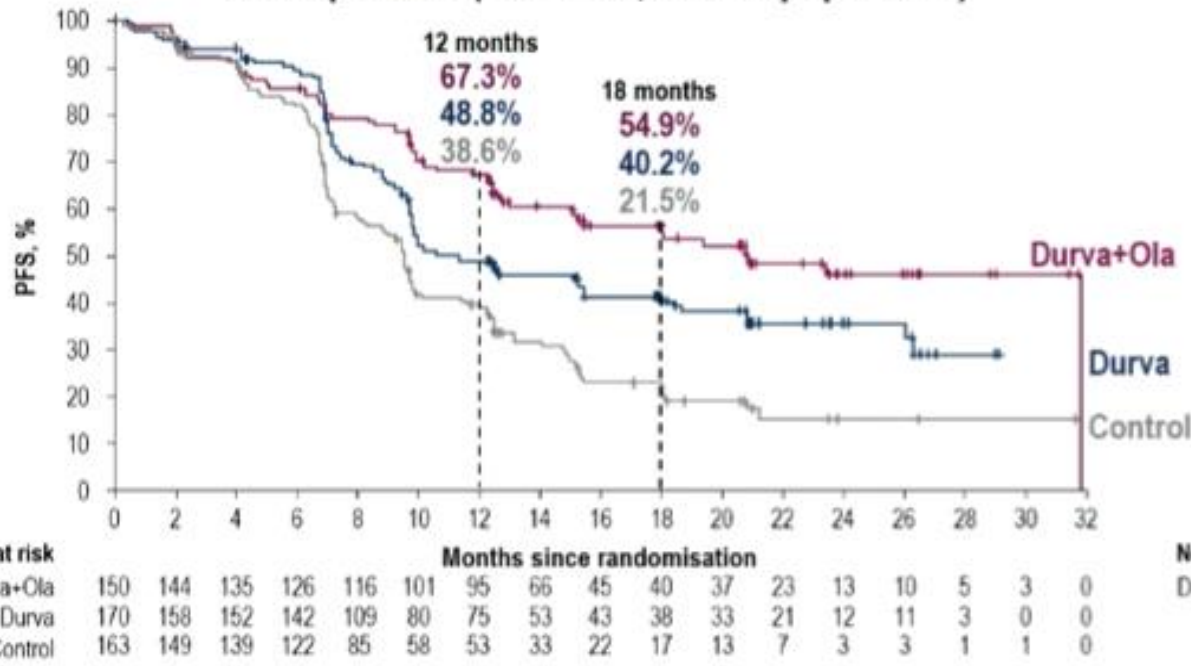
Exploratory subgroup analysis. MMR status evaluated using the Ventana immunohistochemistry MMR panel. Rates were estimated by the KM method.
*CI for median PFS was derived based on the Brookmeyer–Crowley method; †The HR and CI were estimated from an unstratified Cox proportional hazards model.

Subgroup analysis of PFS by PD-L1 status

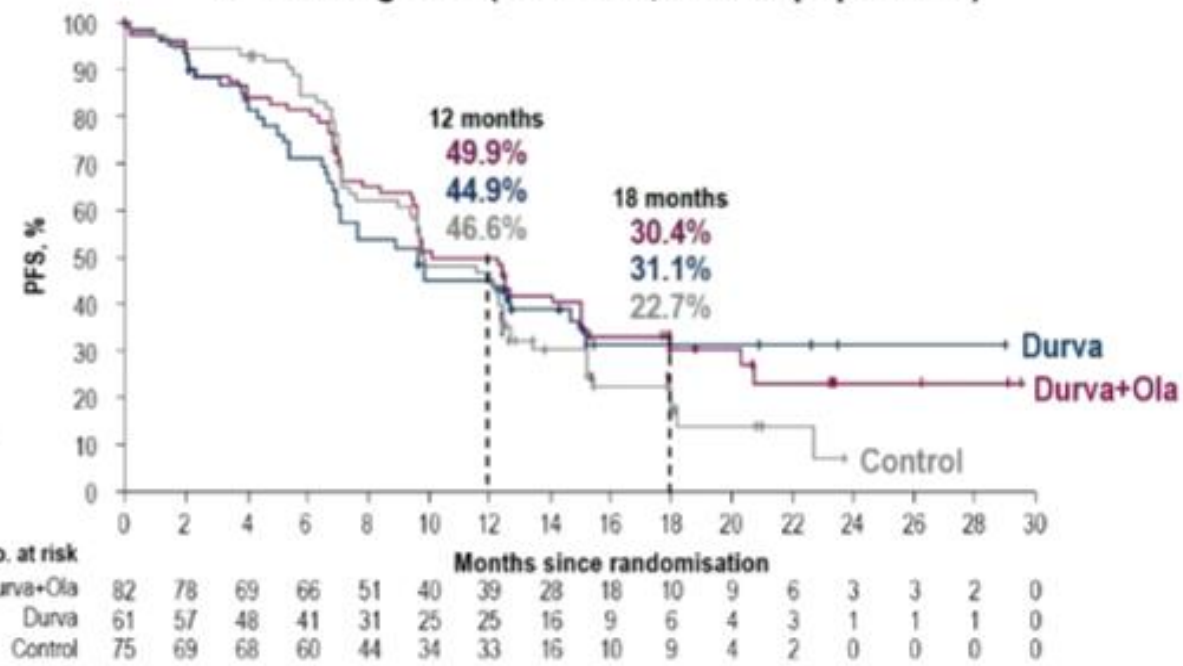
Prespecified exploratory analysis

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)
Median PFS (95% CI),* months	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)**

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)
Median PFS (95% CI),* months	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)**

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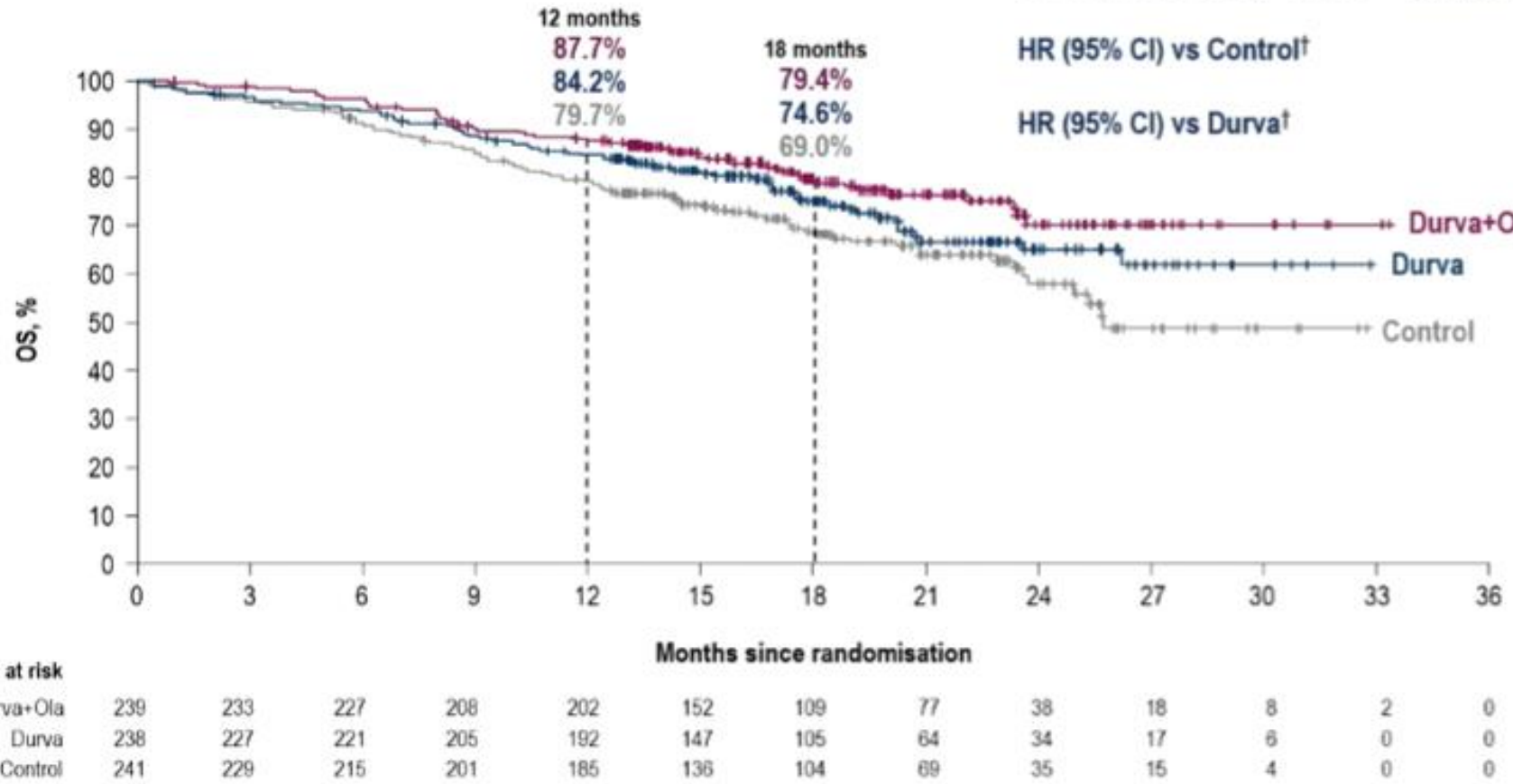
Exploratory subgroup analysis. PD-L1 expression evaluated using Ventana SP263. Prevalence shown is based on patients with known PD-L1 status. Rates were estimated by the KM method. *CI for median PFS was derived based on the Brookmeyer–Crowley method; †The HR and CI were estimated from an unstratified Cox proportional hazards model.

OS: ITT population

Secondary endpoint; interim analysis

	Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Events, n (%)	82 (34.0)	65 (27.3)	52 (21.8)
Median OS (95% CI),* months	25.9 (23.9–NR)	NR (NR–NR)	NR (NR–NR)
HR (95% CI) vs Control†		**0.77** (0.56–1.07); *P*=0.120	**0.59** (0.42–0.83); *P*=0.003
HR (95% CI) vs Durva†			**0.77** (0.53–1.10)

Overall data maturity 27.7%



No. at risk													
Durva+Ola	239	233	227	208	202	152	109	77	38	18	8	2	0
Durva	238	227	221	205	192	147	105	64	34	17	6	0	0
Control	241	229	215	201	185	136	104	69	35	15	4	0	0

The median (range) duration of follow-up for OS was 18.6 (0.5–32.9), 18.4 (2.1–33.0), and 18.7 (1.1–33.4) months in censored patients for the Control, Durva, and Durva+Ola arms, respectively. OS rates were estimated by the KM method. *CI for median OS is derived based on the Brookmeyer–Crowley method; †The HRs were estimated from an unstratified Cox proportional hazards model. The CI was calculated using a profile likelihood approach. *P* values were calculated using an unstratified log-rank test. *P* values failed to reach statistical significance. NR, not reached.

Que faut-il retenir de DUO-E ?

- Y a-t-il vraiment un apport de l'olaparib ?
- Pas d'analyse BRCA/HRD (pas de bénéfice dans la population dMMR)
- Vs NRG GY-018 (carboplatine paclitaxel + pembrolizumab)
- A venir: DOMENICA dans la population dMMR

Les questions qui restent en suspens

- Hétérogénéité du groupe NSMP (No Specific Mutation Profile)
- Quel test compagnon pour l'inhibiteur de PARP ?
  - Il n'est pas dit que les tests et seuils du cancer de l'ovaire soient applicables au cancer de l'endomètre
- Il faut résoudre une équation à plusieurs variables qui sont peut-être (dans une certaine proportion) interdépendantes:

  -HRD/HRP

  -P53mut/non mut

  -pMMR/dMMR

  -PD1 vs PDL1 Mab

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GINECO

Olaparib vs placebo as maintenance therapy after platinum based chemotherapy in advanced/metastatic endometrial cancer patients: The GINECO randomized phase IIb UTOLA trial

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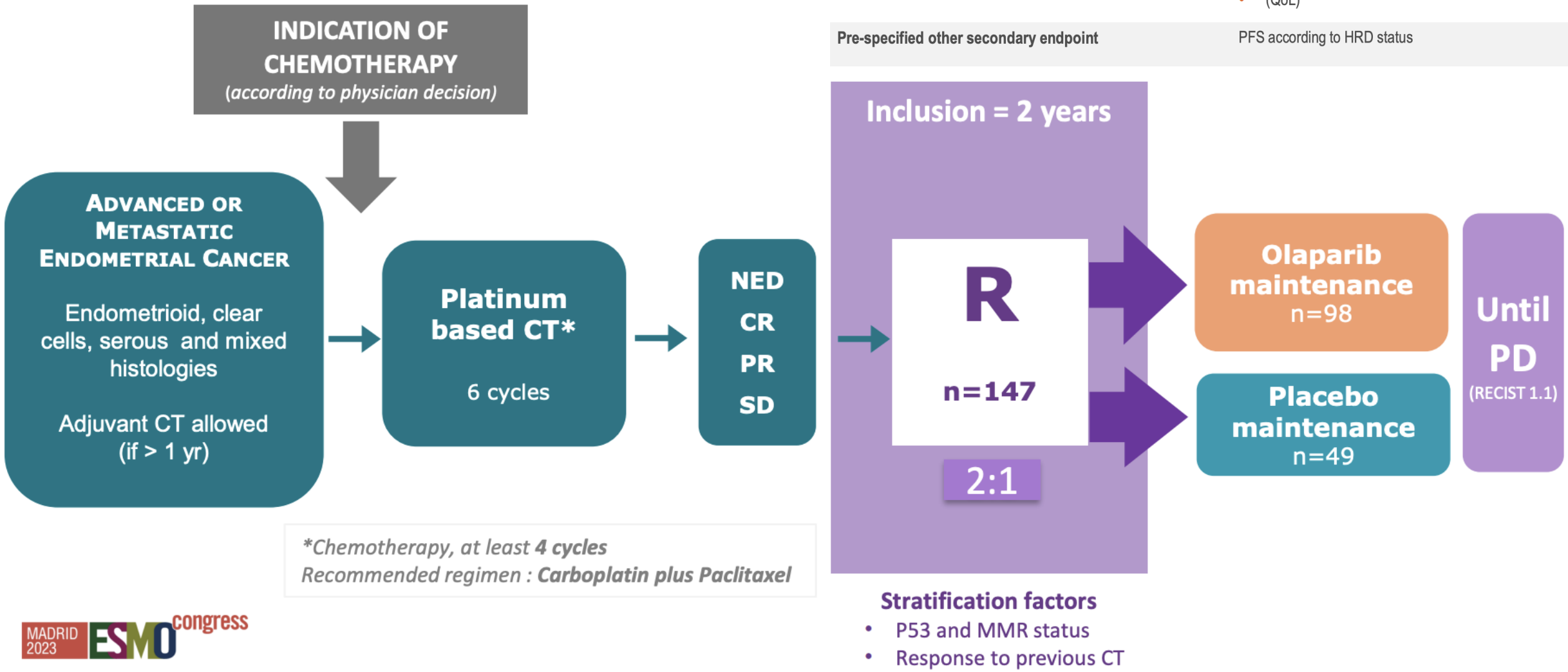
Pr Florence Joly, MD, PHD, Centre François Baclesse, Caen, GINECO, France, October, 2023

UTOLA study design

Randomized phase II trial

Primary endpoint : PFS in the ITT Population	Endpoint : Improvement of median PFS from 4.5 months to 7.5 months (from randomization)
Main secondary endpoints	• PFS according to P53 status • PFS according to response rate • OS in ITT and according to P53 status • Safety • (QoL)
Pre-specified other secondary endpoint	PFS according to HRD status



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Molecular characteristics

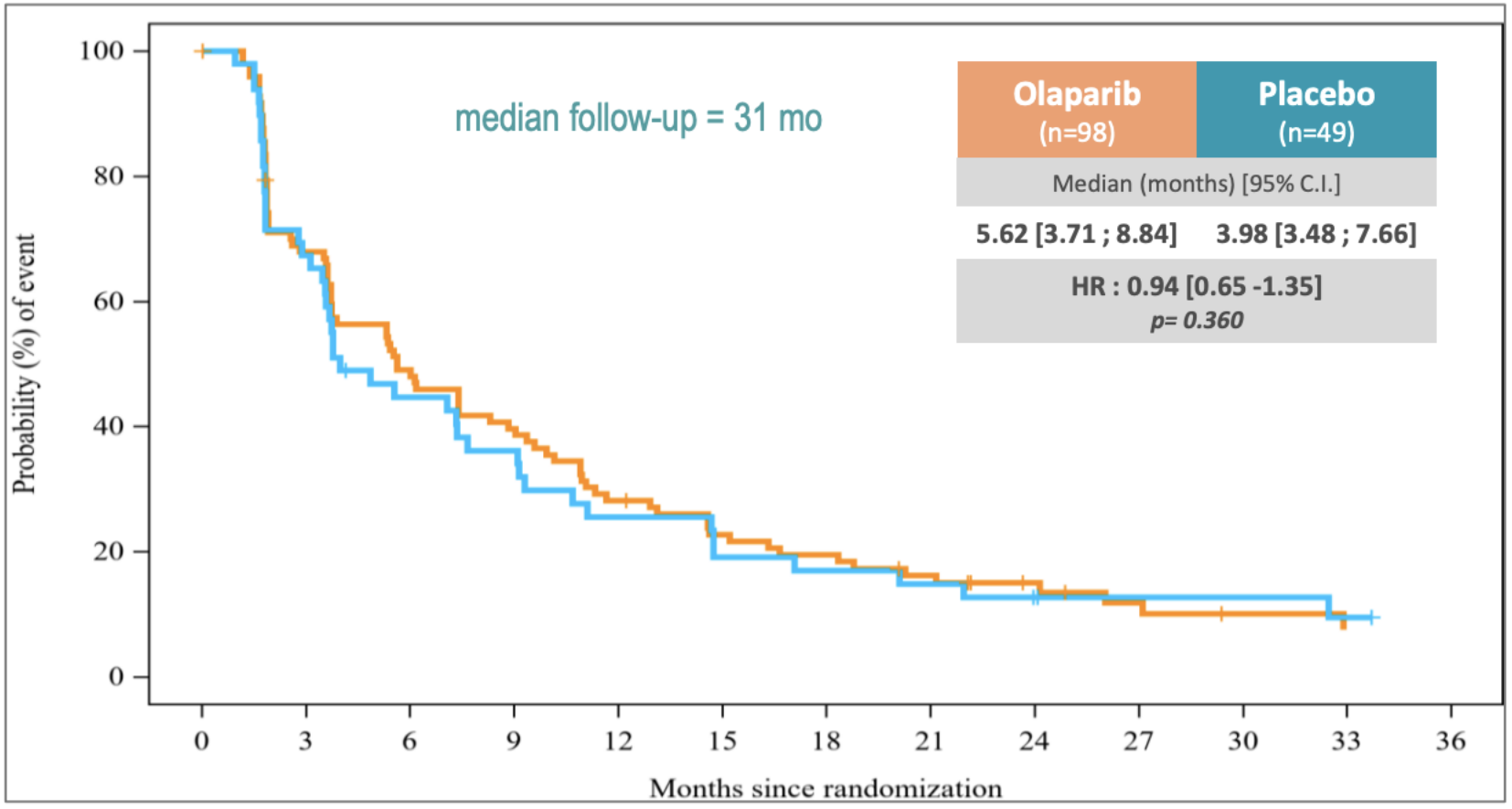
		Olaparib (n=98)	Placebo (n=49)	Total (n=147)
P53 status, n (%)	*Muted*	51 (52)	27 (55)	78 (53)
	Wild-type	46 (48)	22 (45)	68 (47)
	Not informative	1	0	1
MMR status, n (%)	*MMRp*	84 (88)	41(85)	125 (87)
	MMRd	11 (12)	7(15)	18 (13)
	MMRp/P53 mut	50 (51)	25 (51)	75 (51)
	Not informative	3	1	4
POLE mutation, n (%)*		1	0	1
BRCA1/2 mutation , n**		2	1	3
HRD status, n (%)***	*LGE ≥6*	51 (54)	22 (48)	73 (52)

**Pole E = pMMR, LGE<6,*
***one pt with BRCA 1 and 2,*
****HRD status (Large genomic event =LGE) available for 140 pts*

74% of P53 mut are HRD
79% of HRD are P53 mut

PFS* by investigator assessment: ITT

N=147

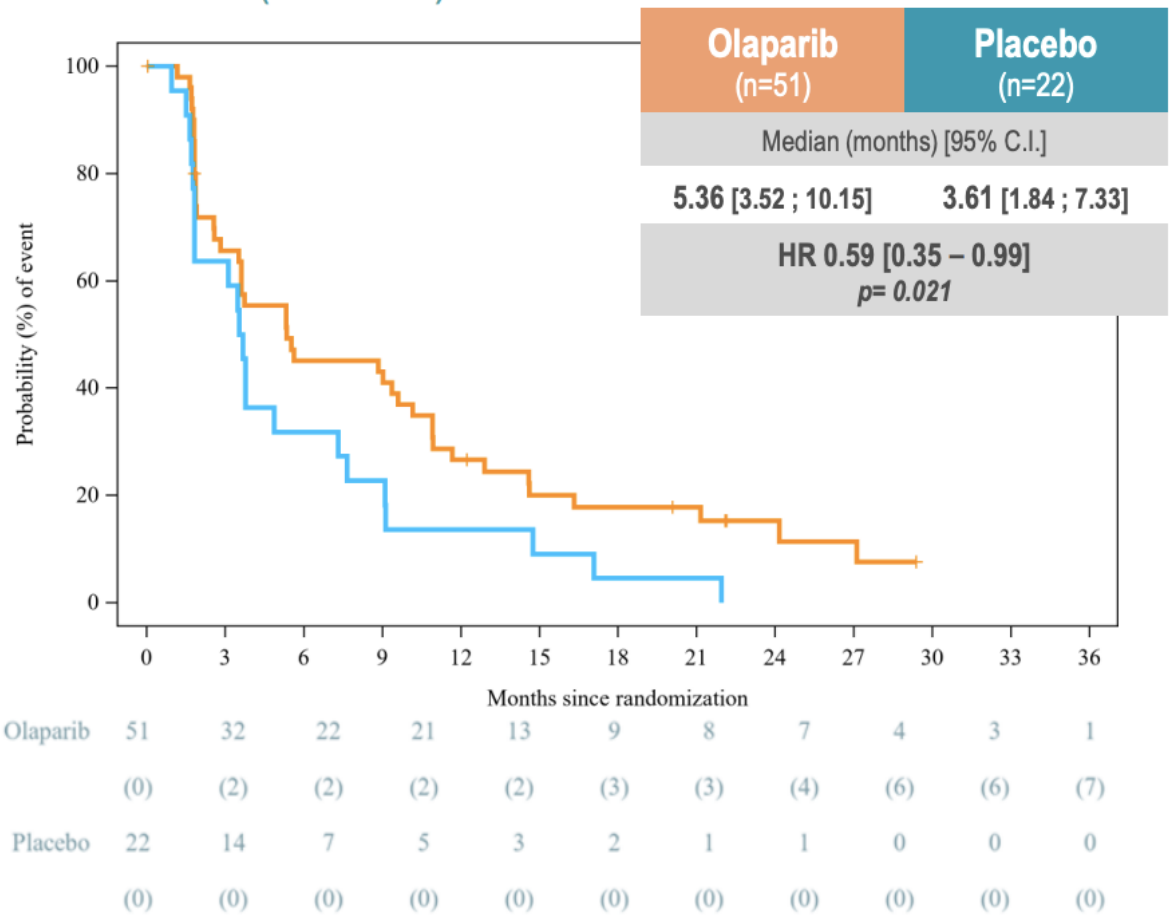


Olaparib	98	65	47	38	27	21	18	14	10	7	4	3	3
	(0)	(2)	(2)	(2)	(2)	(3)	(3)	(4)	(7)	(8)	(10)	(10)	(10)
Placebo	49	33	21	17	12	9	8	7	5	4	4	3	2
	(0)	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(2)	(3)	(3)	(3)	(4)

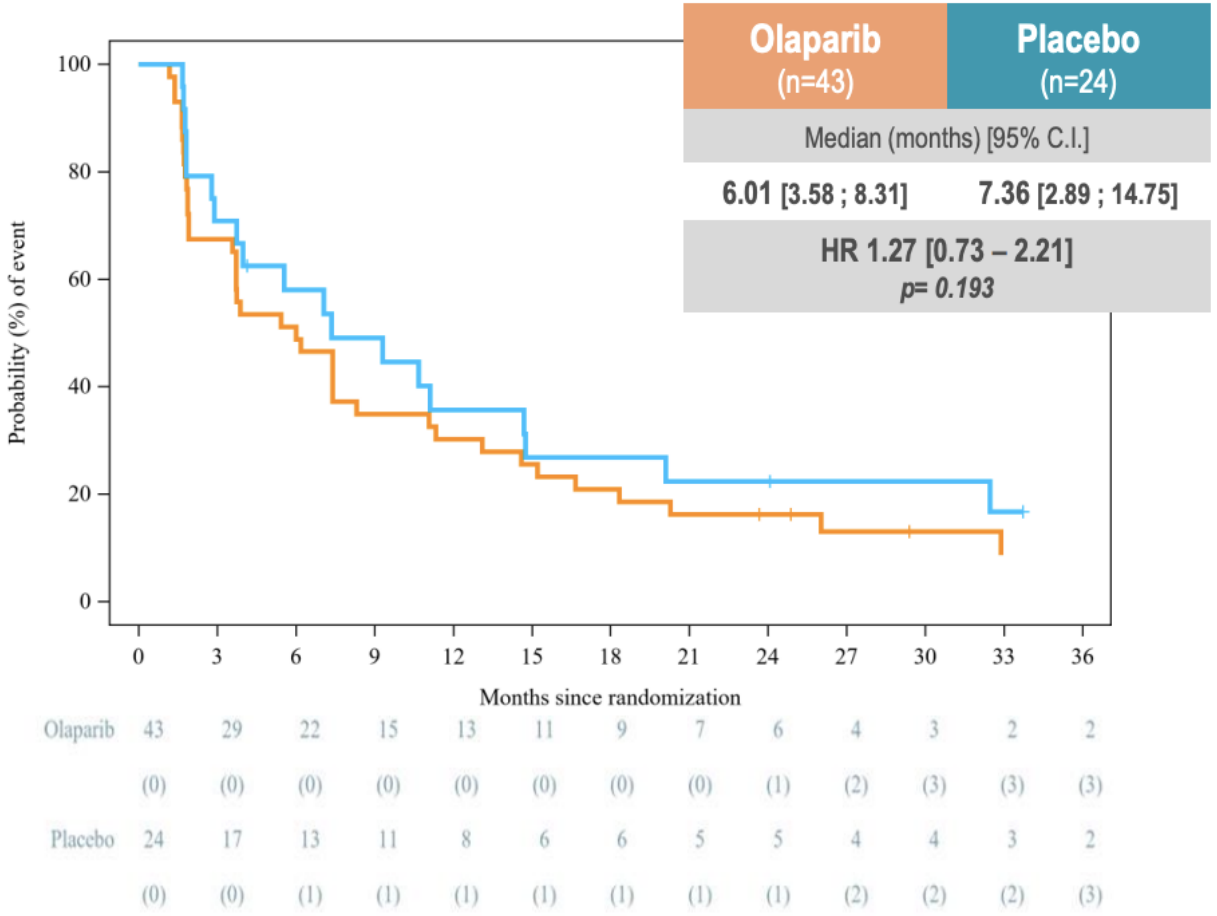
*PFS calculated from randomization (end of CT)

PFS: According to HRD status

HRD (LGE ≥6) n = 73

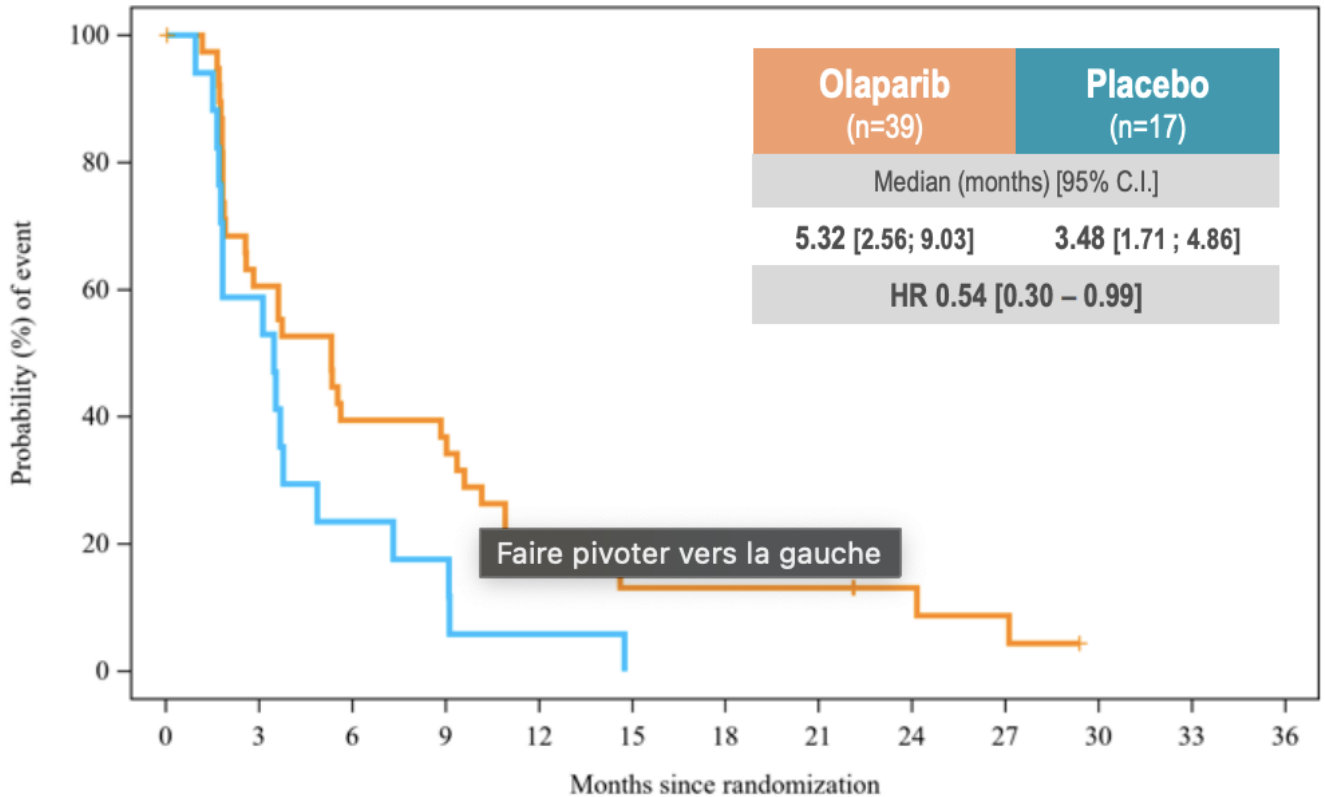


HRp (LGE <6) n = 67



PFS: HRD (LGE ≥6) and P53mut (exploratory analysis)

LGE ≥6, pMMR, P53 mut n=56



Que faut-il retenir de l'essai UTOLA ?

- Y a-t-il vraiment un apport de l'olaparib ?
- Certainement pas chez toutes les patientes
- Peut-être pour les patientes HRD/p53mut
- Séreux de haut grade ?
- Définition de HRD dans le cancer de l'endomètre (quelx test ?)