3ª Jornada de Actualización EN CÁNCER GINECOLÓGICO

Bilbao
12-13 junio 2025

TRATAMIENTO DEL CANCER DE ENDOMETRIO SEGÚN EL SUBTIPO MOLECULAR

Estibaliz Iza Rodríguez
ONCOLOGÍA MÉDICA
HOSPITAL UNIVERSITARIO DE CRUCES

ÍNDICE

1. Introducción
2. Tratamiento d MMR
3. Tratamiento p53 mutado
4. Tratamiento NSMP
5. Conclusiones

INTRODUCCIÓN

- El cáncer de endometrio es el tumor ginecológico **más frecuente**.
- Generalmente se detectan en estadíos tempranos (80%) y tienen un pronóstico excelente pero las pacientes diagnosticadas con enfermedad avanzada tienen una supervivencia estimada a 5 años de un 17-20%.
- **25-30% son dMMR/MSI-H**. >90% son esporadicos.
- Estadificación **FIGO 2023**
- FR: obesidad, HTA, hiperinsulinemia, nuliparidad, menarquia precoz, menopausia tardía, tamoxifeno, sdmes hereditarios.

Two Pathogenetic Types of Endometrial Carcinoma

JAN V. BOKHMAN, M.D.

Department of Gynecology, N. N. Petrov Research Institute of Oncology, USSR Ministry of Health, Leningrad, USSR

Received May 6, 1981

2 subtipos principales:

- **Tipo 1**: endometrioide bajo grado (grado 1 y 2), RH +, precedido de hiperplasia atípica. 80%, pronóstico excelente. Mutaciones + Frec: PTEN, PI3KCA, KRAS, FGRF2, CTNNB1, MSI y ARID1A.

- **Tipo 2**: alto grado, histología no endometrioide (serosos, céls claras,..), RH -, peor pronóstico. Mutaciones + Frec: p53, HER2, CDH

	Type I	Type II
Associated clinical features	Metabolic syndrome: obesity, hyperlipidaemia, hyperglycaemia, and increased oestrogen concentrations	None
Grade	Low	High
Hormone receptor expression	Positive	Negative
Histology	Endometrioid	Non-endometrioid (serous, clear-cell carcinoma)
Genomic stability	Diploid, frequent microsatellite instability (40%)	Aneuploid
TP53 mutation	No	Yes
Prognosis	Good (overall survival 85% at 5 years)	Poor (overall survival 55% at 5 years)

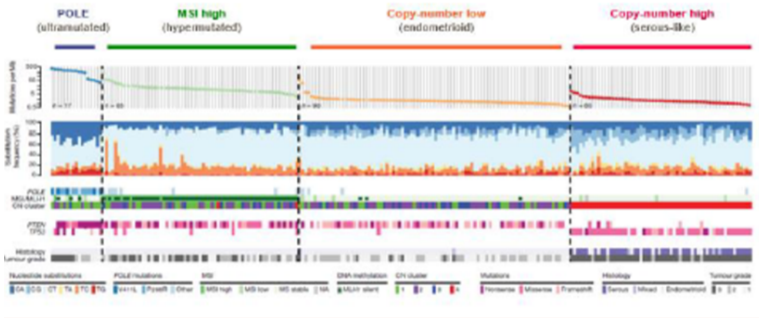
Table 1: Dualistic classification of endometrial cancers, by Bokhman subtype

ARTICLE OPEN

doi:10.1038/nature12113

Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*



Proteomic-based molecular characterization

Image adapted from Cancer Genome Atlas Research Network, et al. *Nature*. 2013;497:67-73.

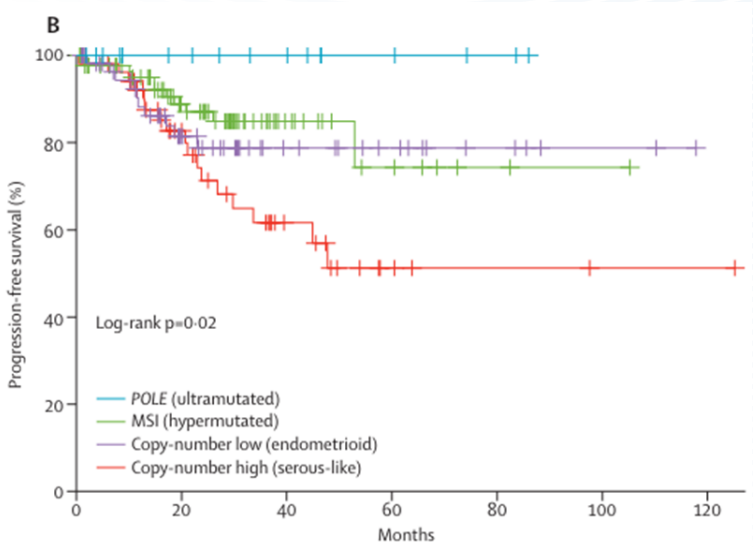
Paso del modelo dualista (Bokhman) a la caracterización molecular del TCGA

SUBTIPOS MOLECULARES TCGA

A

	POLE ultramutated	MSI hypermutated	Copy-number low, MSS	Copy-number high, serous-like
Mutation load				
Somatic copy number alterations load				
Histology	Endometrioid	Endometrioid	Endometrioid	Serous and endometrioid
Grade				
PI3K alterations				
KRAS mutation				
TP53 mutation	35%	5%	1%	>90%
Prognosis	Excellent	Intermediate	Intermediate	Poor

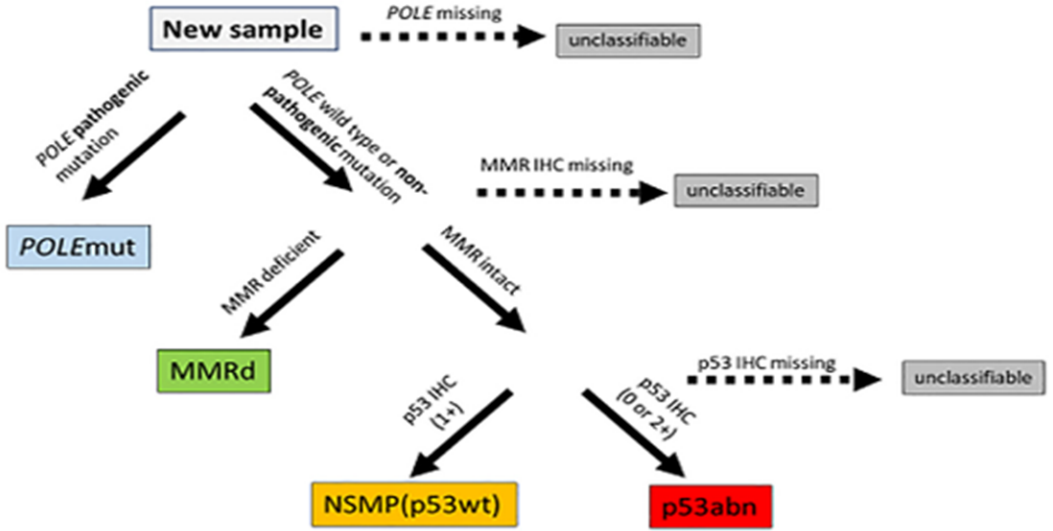
B



Los subtipos moleculares se correlacionan con el pronóstico

Morice P et al Endometrial Cancer. Lancet 2016; 387: 1094–108

SUBTIPOS SUBROGADOS (ProMisE Y TRANSPORTEC)



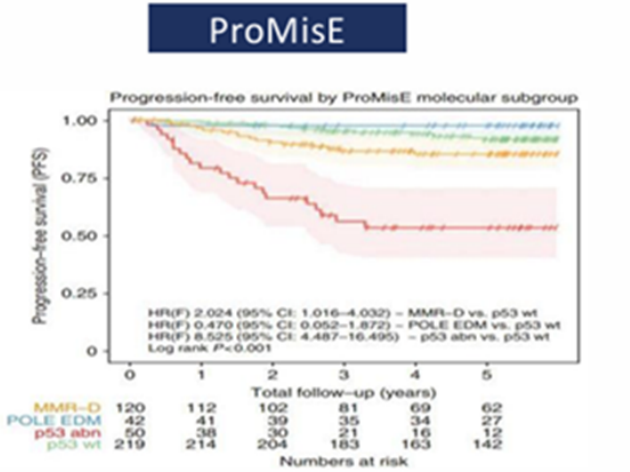
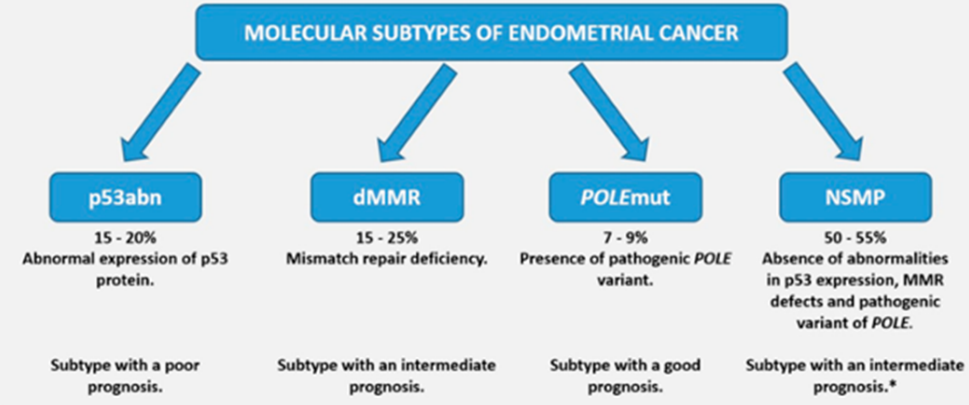
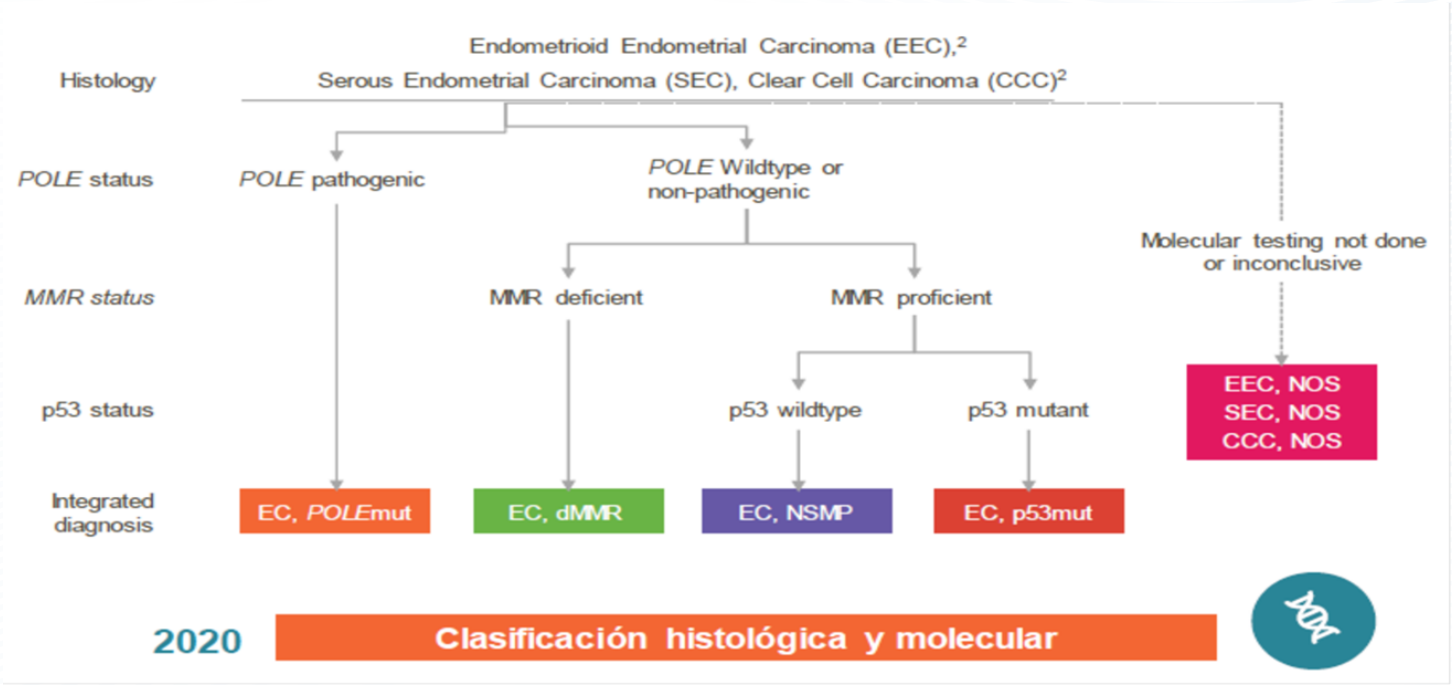


Fig. 2. The ProMisE algorithm divides endometrial cancers into four distinct molecular subgroups that are similar to TCGA.
Jamieson, A., Molecular classification in endometrial cancer: opportunities for precision oncology in a changing landscape. Cancer, 2022;128(5):2853–2857.



Galant N, et al Molecular Classification of Endometrial Cancer and Its Impact on Therapy Selection Int. J. Mol. Sci. 2024, 25, 5893

ESGO/ESTRO/ESP (2021) RECOMIENDAN USAR SUBTIPOS SUBROGADOS DE LA CLASIFICACIÓN MOLECULAR DEL TCGA



ESMO Y NCCN

ESMO

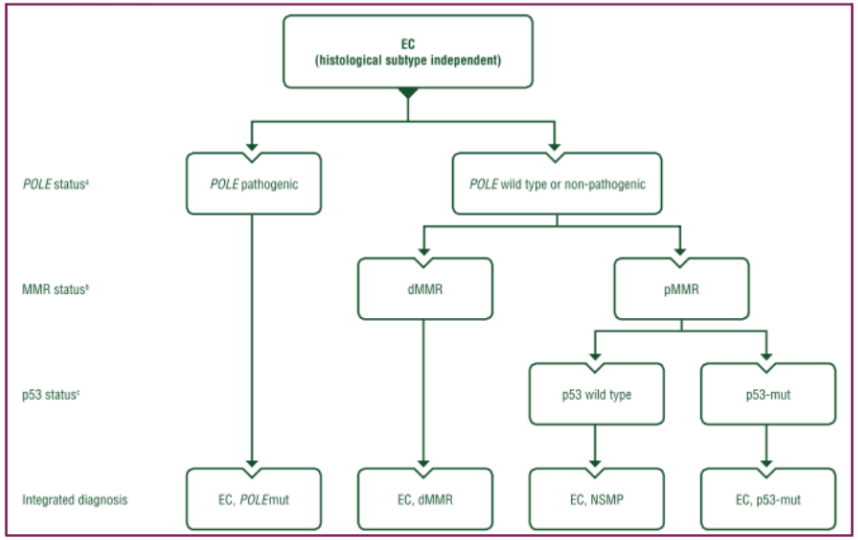
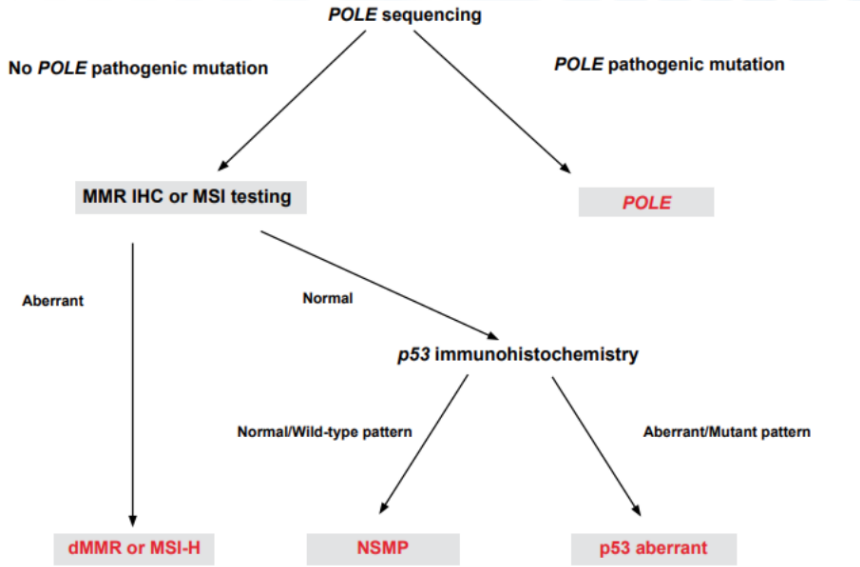


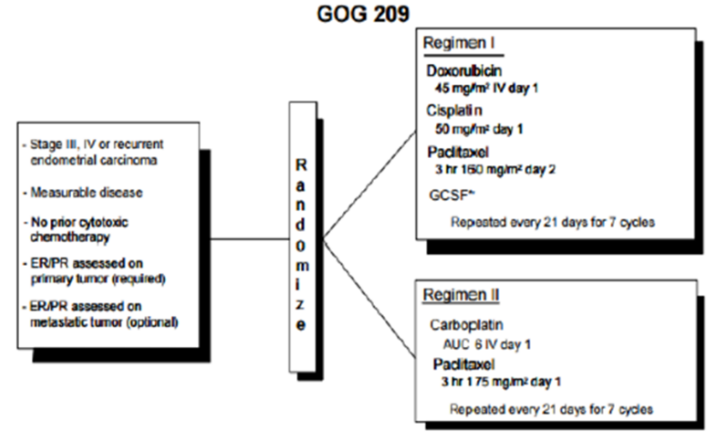
Figure 1. Diagnostic algorithm for the integrated molecular EC classification.

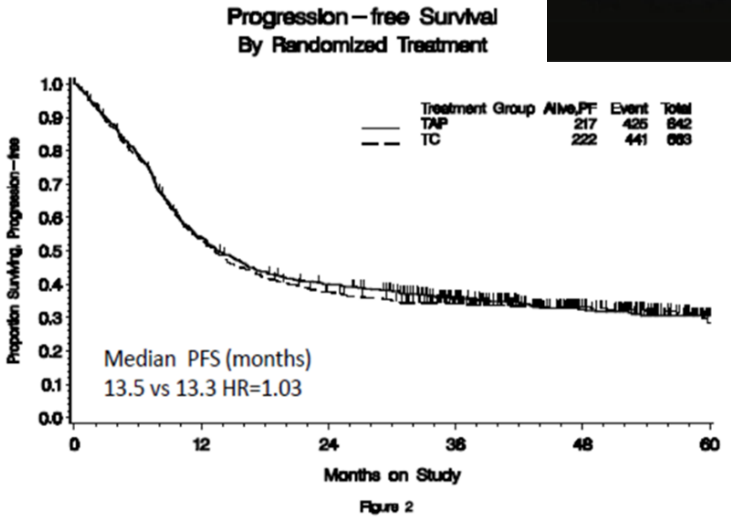
NCCN



GOG 209

Carboplatin-Paclitaxel is standar of care in 1st line endometrial cancer



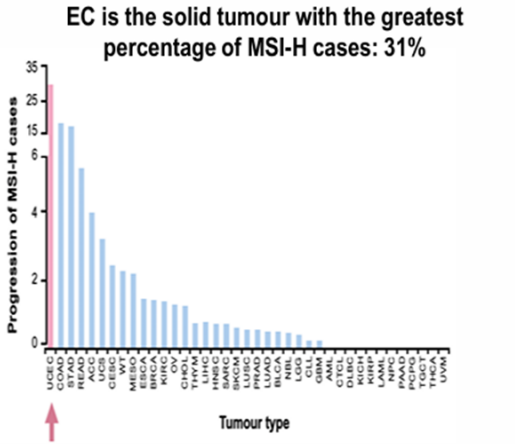


ESTUDIO DE NO INFERIORIDAD->NUEVO ESTÁNDAR DE TRATAMIENTO CBDCA-PACLITAXEL

Miller et al, Gynecol Oncol 2012; 125: 771-773

d MMR/ MSI-H

d MMR/MSI-H CARACTERÍSTICAS



- 25-30% d MMR
- >90% esporádicos.Sdm de Lynch
- IHQ:pérdida de expresión de MMR

	Keynote-158	NCT02912572	GARNET	PHAEDRA
Treatment	**Pembrolizumab**	**Avelumab**	**Dostarlimab**	**Durvalumab**
Phase	1/2	2	1/2	**2**
Population	Previously treated dMMR-recurrent or persistent EC	dMMR recurrent EC	Previously treated recurrent/advanced dMMR EC	Advanced dMMR EC, 0-3 prior therapies
Patients, n	94	15	143	35
ORR, %	**50%**	**27%**	**45%**	**47%**
mPFS	13.1 mo (95% CI, 4.3 to 25.7)	4.4 mo	6.0 mo (4.1–18.0 mo)	8.3 mo
mOS	65.4 (95% CI, 29.5 -NR).	—	NR (95% CI 27.1–NR)	NR

Galant N, et al Molecular Classification of Endometrial Cancer and Its Impact on Therapy Selection Int. J. Mol. Sci. 2024, 25, 5893

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

M.R. Mirza, D.M. Chase, B.M. Slomovitz, R. dePont Christensen, Z. Novák, D. Black, L. Gilbert, S. Sharma, G. Valabrega, L.M. Landrum, L.C. Hanker, A. Stuckey, I. Boere, M.A. Gold, A. Auranen, B. Pothuri, D. Cibula, C. McCourt, F. Raspagliesi, M.S. Shahin, S.E. Gill, B.J. Monk, J. Buscema, T.J. Herzog, L.J. Copeland, M. Tian, Z. He, S. Stevens, E. Zografos, R.L. Coleman, and M.A. Powell, for the RUBY Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D., Richard G. Moore, M.D., Joanie M. Hope, M.D., Fernanda B. Musa, M.D., Robert Mannel, M.D., Mark S. Shahin, M.D., Guilherme H. Cantuaria, M.D., Eugenia Girda, M.D., Cara Mathews, M.D., Juraj Kavecansky, M.D., Charles A. Leath III, M.D., M.S.P.H., Lilian T. Gien, M.D., Emily M. Hinchcliff, M.D., M.P.H., Shashikant B. Lele, M.D., Lisa M. Landrum, M.D., Floor Backes, M.D., Roisin E. O'Cearbhaill, M.D., Tareq Al Baghdadi, M.D., Emily K. Hill, M.D., Premal H. Thaker, M.D., Veena S. John, M.D., Stephen Welch, M.D., Amanda N. Fader, M.D., Matthew A. Powell, M.D., and Carol Aghajanian, M.D.

ASCO Journal of Clinical Oncology®

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

Shannon N. Westin, MD, MPH[1]; Kathleen Moore, MD[2]; Hye Sook Chon, MD[3]; Jung-Yun Lee, MD[4]; Jessica Thomes Pepin, MD[5]; Michael Sundborg, MD[6]; Ayelet Shai, MD, PhD[7]; Joseph de la Garza, MD[8]; Shin Nishio, MD[9]; Michael A. Gold, MD[10]; Ke Wang, MD[11]; Kristi McIntyre, MD[12]; Todd D. Tillmanns, MD[13]; Stephanie V. Blank, MD[14]; Ji-Hong Liu, MD[15]; Michael McCollum, MD[16]; Fernando Contreras Mejia, MD[17]; Tadaaki Nishikawa, MD[18]; Kathryn Pennington, MD[19]; Zoltan Novak, MD, PhD[20]; Andreia Cristina De Melo, MD[21]; Jalid Sehouli, MD[22]; Dagmara Klasa-Mazurkiewicz, MD[23]; Christos Papadimitriou, MD[24]; Marta Gil-Martin, MD[25]; Birute Brasiuniene, MD, PhD[26]; Conor Donnelly, PhD[27]; Paula Michelle del Rosario, MD[28]; Xiaochun Liu, MD, PhD[29]; and Els Van Nieuwenhuysen, MD[30]; on behalf of the DUO-E Investigators

DOI https://doi.org/10.1200/JCO.23.02132

MADRID 2023 ESMO congress

Phase III double-blind randomized placebo controlled trial of atezolizumab in combination with carboplatin and paclitaxel in women with advanced/recurrent endometrial carcinoma: ENGOT-en7/MaNGO/AtTEnd study

Nicoletta Colombo, Milan, Italy

On behalf of K. Harano (JGOG, Japan), E. Hudson (NCRI, United Kingdom), F. Galli (MaNGO, Italy), Y. Antill (ANZGOG, Australia-New Zealand), C. H. Choi (KGOG, Korea), M. Rabaglio (SAKK, Switzerland), F. Marmé (AGO, Germany), E. Petru (AGO-A, Austria), C.-H. Lai (TGOG, Taiwan), E. Biagioli (MaNGO, Italy), L. Fariñas-Madrid (GEICO, Spain), K. Takehara (JGOG, Japan), K. Allan (NCRI, United Kingdom), Y. C. Lee (ANZGOG, Australia-New Zealand), E. Piovano (MaNGO, Italy), C. Zamagni (MaNGO, Italy), G. Tasca (MaNGO, Italy), A. Ferrero (MaNGO, Italy), M.-

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

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

Eligible patients

- Histologically/cytologically proven advanced or recurrent EC
- Stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination
  - **Carcinosarcoma, clear cell, serous, or mixed histology permitted**[a]
- Naïve to systemic therapy or systemic anticancer therapy and had a recurrence or PD **≥6 months after completing treatment**
- ECOG PS 0-1
- Adequate organ function

Stratification

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

N=494
R1:1

Dostarlimab IV 500 mg
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m²
Q3W for 6 cycles

→ **Dostarlimab IV** 1000 mg Q6W up to 3 years[c]

Placebo
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m²
Q3W for 6 cycles

→ **Placebo IV** Q6W up to 3 years[c]

→ Follow-up

Primary endpoint

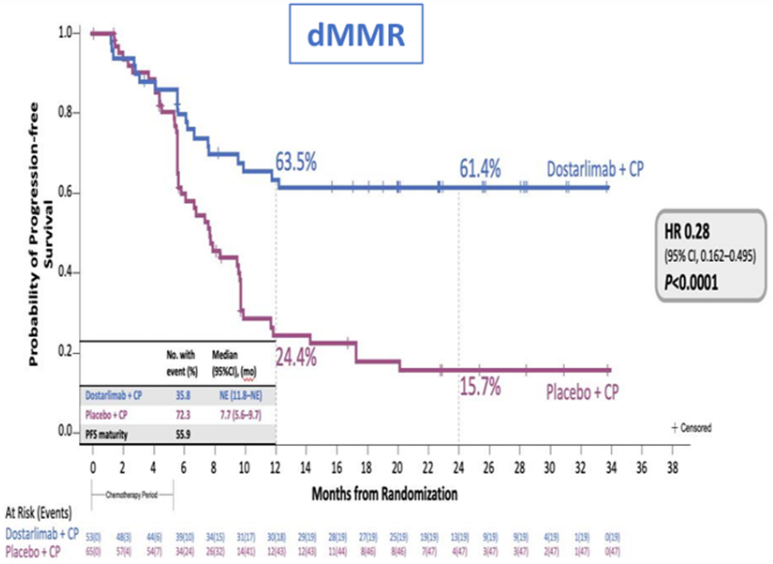
- PFS by INV
- OS

Secondary endpoints

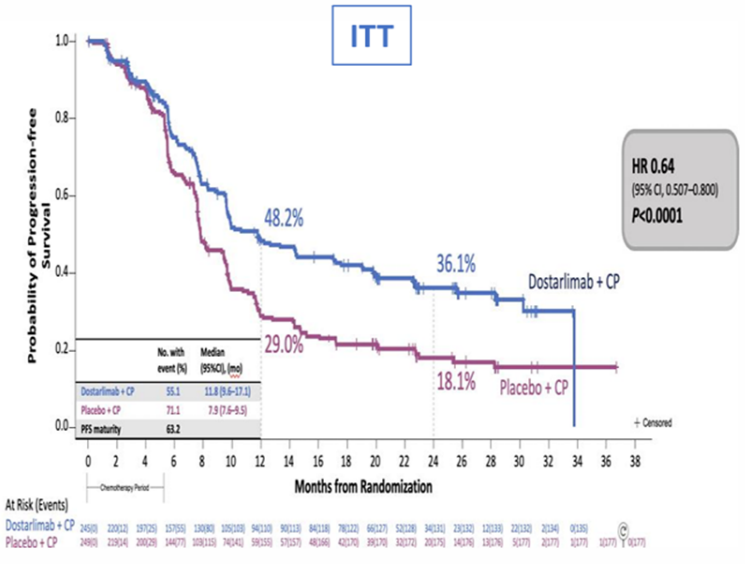
- PFS by BICR
- PFS2
- ORR
- DOR
- DCR
- HRQOL/PRO
- Safety

Mirza et al, NEJM 2023; 388: 2145-2158

RESULTADOS PFS



Median duration of follow-up 24.79 months.

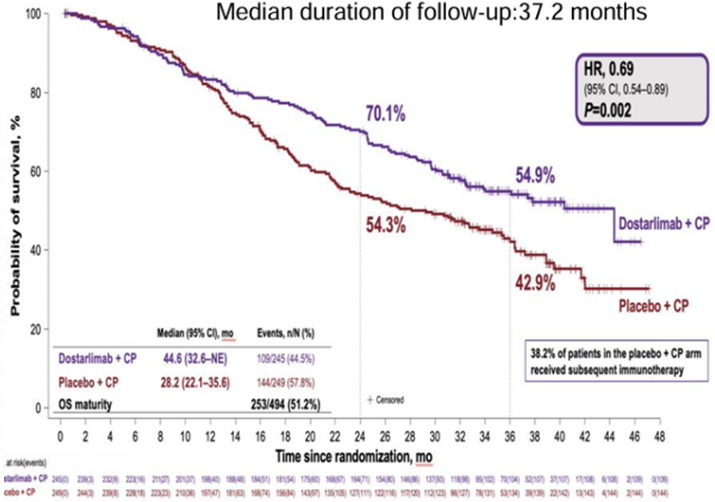


Median duration of follow-up 25.38 months.

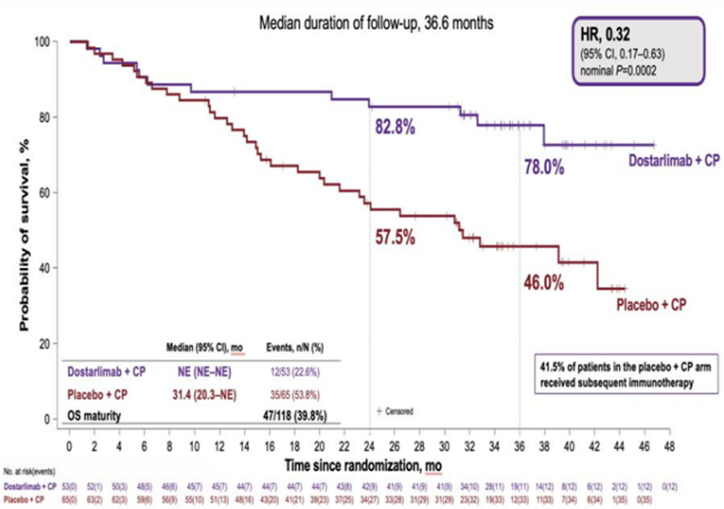
Mirza et al, NEJM 2023; 388: 2145-2158

RESULTADOS OS

ITT

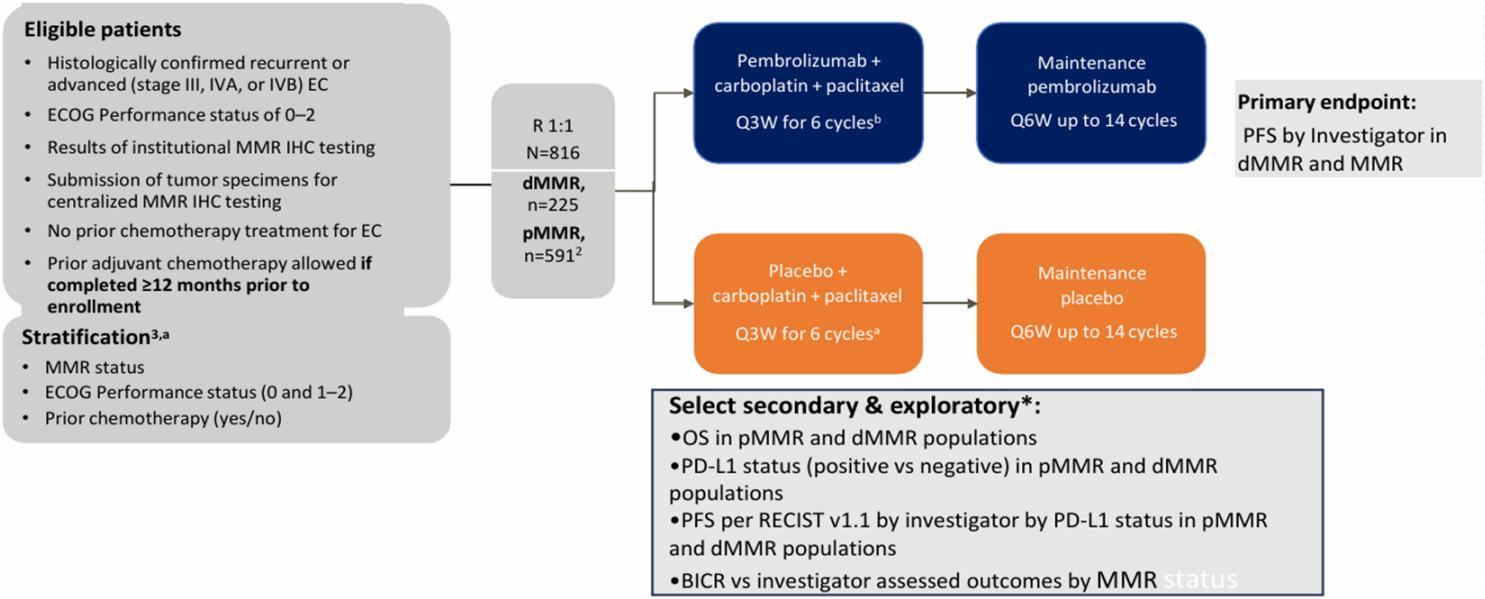


dMMR



Mirza et al, NEJM 2023; 388: 2145-2158

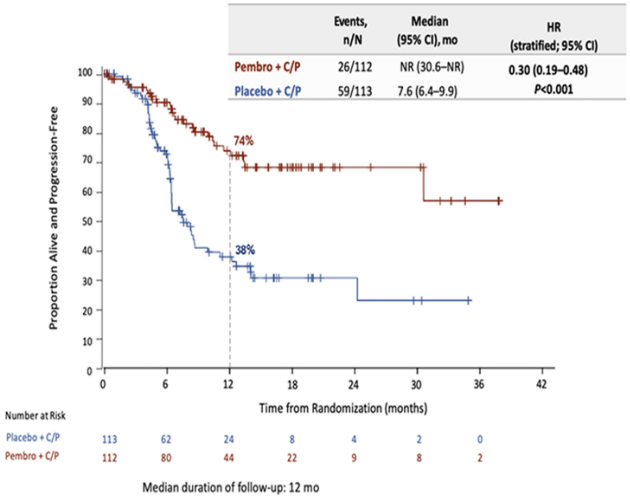
NRG-GY018: pembrolizumab plus carboplatin-paclitaxel vs placebo plus carboplatin-paclitaxel in patients with advanced/recurrent endometrial cancer



Eskander et al, NEJM 2023; 388: 2159-2170

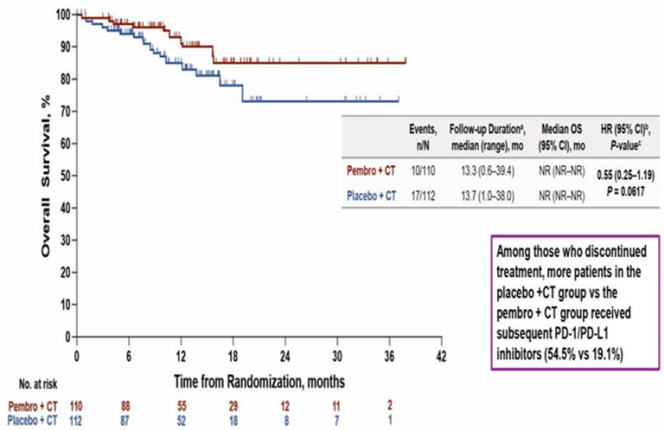
RESULTADOS PFS Y OS

Primary End-Point: PFS in dMMR cohort



Median duration of follow-up: 12 mo

Secondary End-Point: OS dMMR EC*



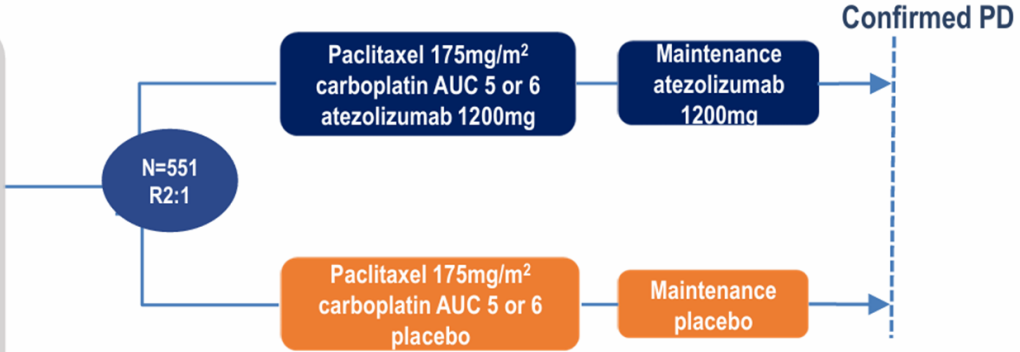
Among those who discontinued treatment, more patients in the placebo +CT group vs the pembro + CT group received subsequent PD-1/PD-L1 inhibitors (54.5% vs 19.1%)

*Immature at IA ;18% information fraction

Eskander et al, NEJM 2023; 388: 2159-2170

AtTEnd: Study Design

- Endometrial carcinoma or **carcinosarcoma**
- Patients with advanced (stage III-IV) newly diagnosed or recurrent disease with no prior systemic chemotherapy for recurrence.
- In recurrent patients, one prior line of systemic platinum-based regimen is permitted with a **platinum-free interval ≥ 6 months.**
- ECOG 0-2
- Normal organ and bone marrow function



Stratified by:

- Country
- Endometrioid vs. other histotypes
- Recurrent disease vs newly diagnosed
- pMMR vs dMMR vs non evaluable *(centrally evaluated)*

Endpoints

Hierarchical order

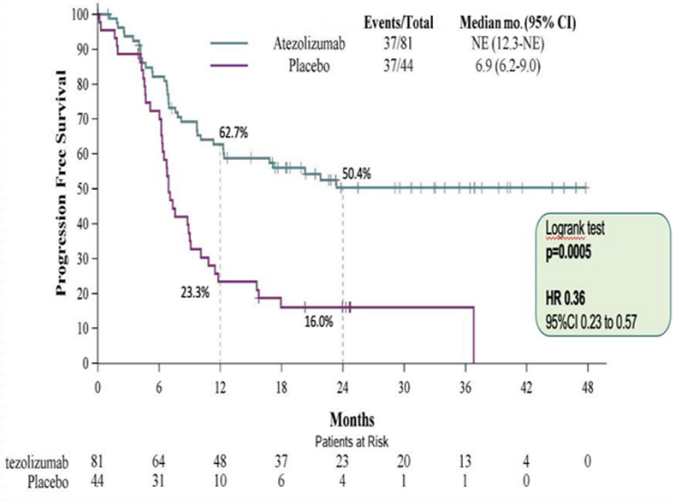
PFS dMMR	IF POSITIVE	PFS All comers	IF POSITIVE	OS* All comers
α (two-sided) 4%	α=4%	α (two-sided) 4%	α=4%	α (two-sided) 5%
HR: 0.5		HR: 0.7		HR: 0.7

ECOG: Eastern Cooperative Oncology Group. pMMR: mismatch repair proficient. dMMR: mismatch repair deficient. AUC: area under the curve. PD: progressive disease. PFS: Progression free survival. OS: overall survival. HR: hazard ratio.

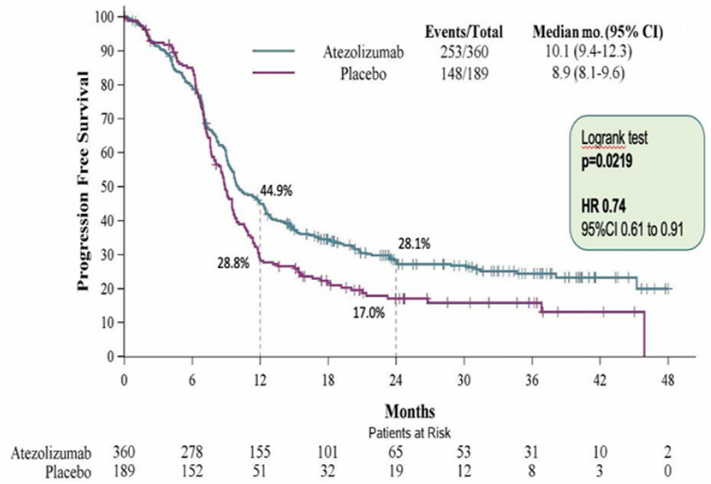
*OS interim analysis planned with a 63% power

Colombo et al, The Lancet 2024; 25: 1135-1146

Primary End-Point: PFS in dMMR → All-Comers



Median follow-up 26.2 months

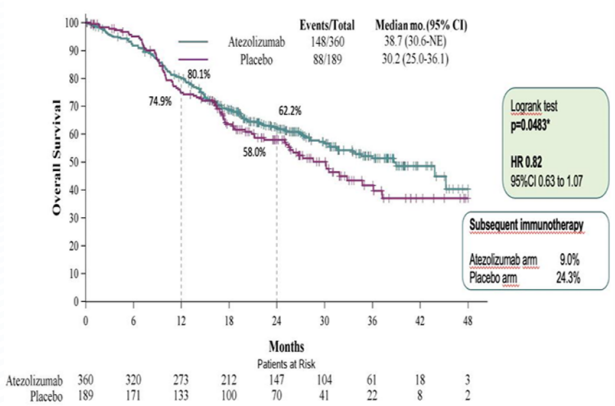


Median follow-up 28.3 months

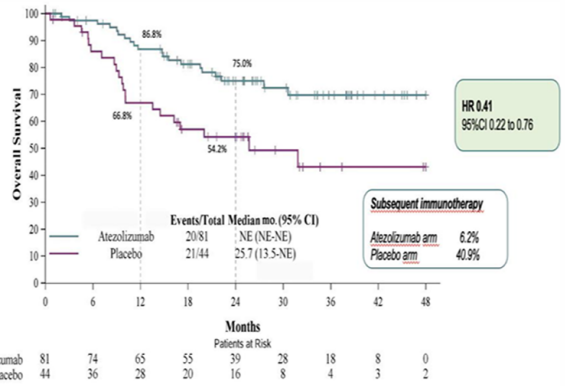
Colombo et al, The Lancet 2024; 25: 1135-1146

Prespecified Subgroup Analyses: OS in the dMMR/MSI-H (43% of Maturity)

ITT

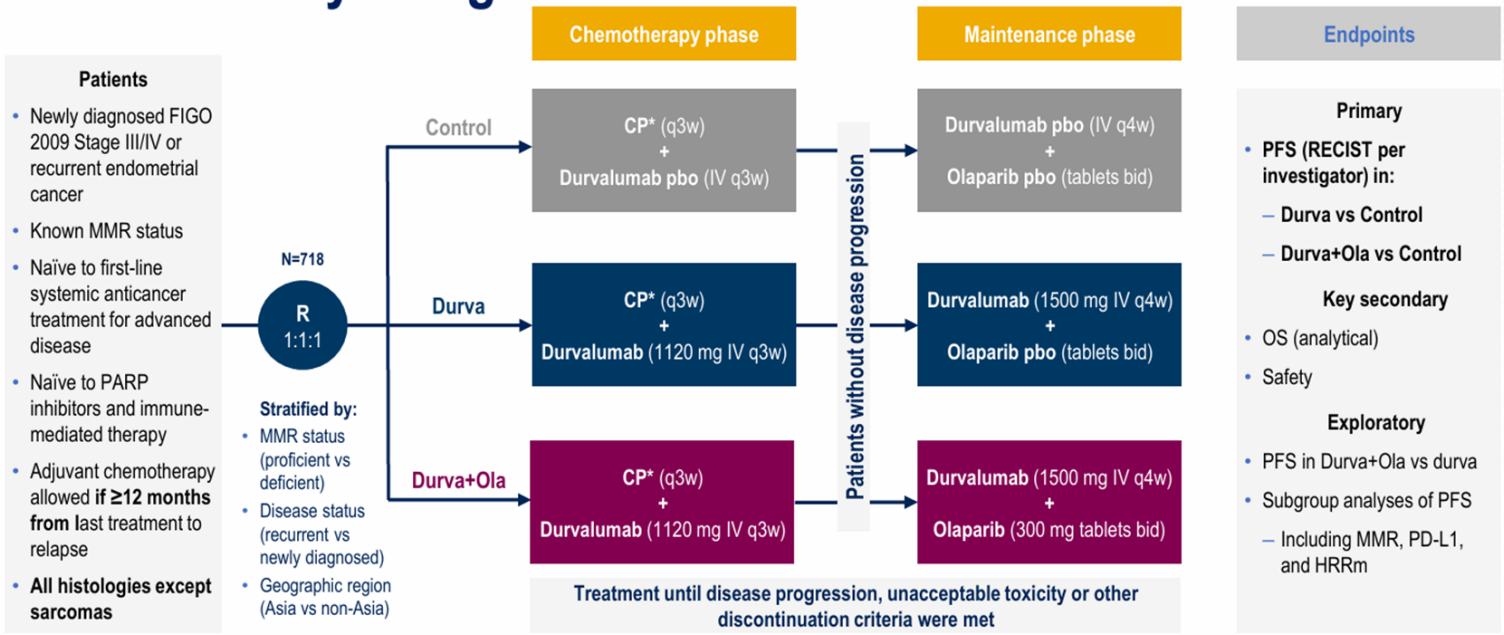


dMMR



Colombo et al, The Lancet 2024; 25: 1135-1146

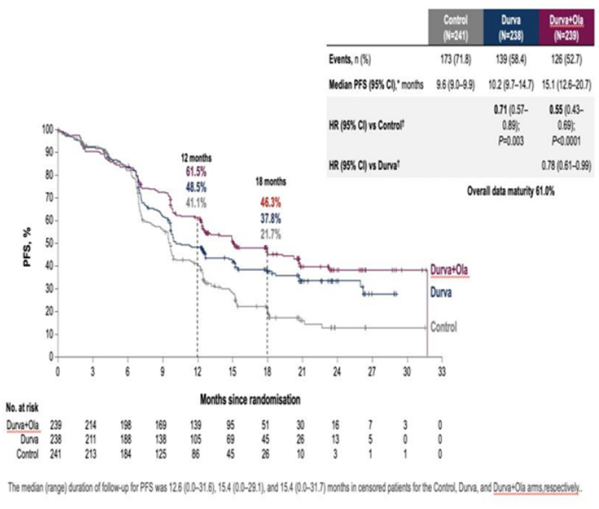
DUO-E study design



*Six cycles of carboplatin at an area under the concentration–time curve of 5 or 6 mg per mL/min and paclitaxel 175 mg/m^2.
bid, twice daily; CP, carboplatin/paclitaxel; durva, durvalumab; FIGO, International Federation of Gynaecology and Obstetrics; HRRm, homologous recombination repair mutation; IV, intravenously; ola, olaparib; pbo, placebo; q3(4)w, every 3(4) weeks; R, randomisation; RECIST, Response Evaluation Criteria for Solid Tumours.

Westin et al, JCO 2023; 42: 283-299

Prespecified Exploratory Subgroup analysis of PFS by MMR status

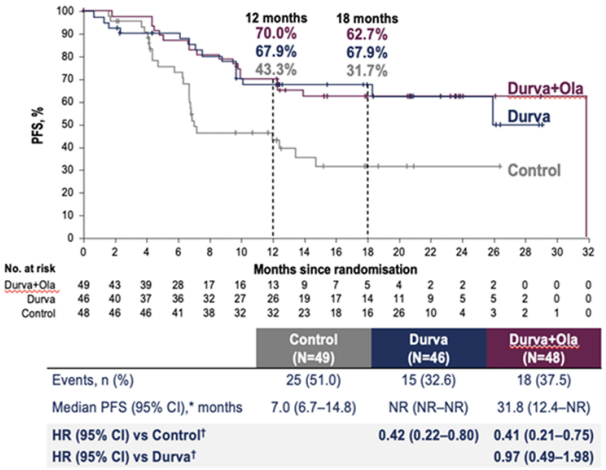


	Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS (95% CI),* months	9.6 (9.0–9.9)	10.2 (9.7–14.7)	15.1 (12.6–20.7)
HR (95% CI) vs Control†		0.71 (0.57–0.89); P=0.003	0.55 (0.43–0.69); P<0.0001
HR (95% CI) vs Durva†			0.78 (0.61–0.99)

Overall data maturity 61.0%

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.

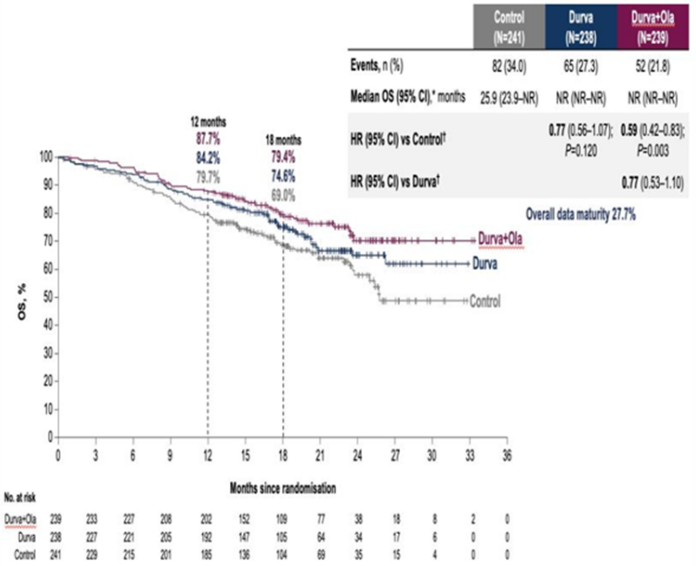
dMMR (20% of population)



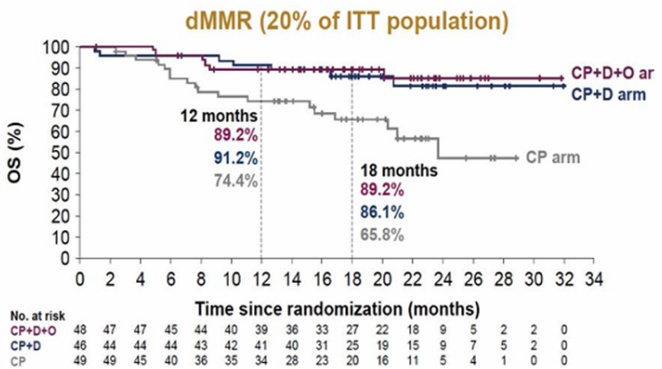
	Control (N=49)	Durva (N=46)	Durva+Ola (N=48)
Events, n (%)	25 (51.0)	15 (32.6)	18 (37.5)
Median PFS (95% CI),* months	7.0 (6.7–14.8)	NR (NR–NR)	31.8 (12.4–NR)
HR (95% CI) vs Control†		**0.42 (0.22–0.80)**	**0.41 (0.21–0.75)**
HR (95% CI) vs Durva†			**0.97 (0.49–1.98)**

Westin et al, JCO 2023; 42: 283-299

Post-hoc Exploratory Analyses: OS in MMR subpopulations:



	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)



	CP arm (n=49)	CP+D arm (n=46)	CP+D+O arm (n=48)
Events, n (%)	18 (36.7)	7 (15.2)	6 (12.5)
Median OS (95% CI), months	23.7 (16.9–NR)	NR (NR–NR)	NR (NR–NR)
HR (95% CI) vs CP arm*		**0.34 (0.13–0.79)**	**0.28 (0.10–0.68)**
HR (95% CI) vs CP+D arm*			0.84 (0.27–2.52)

Overall data maturity: 21.7%

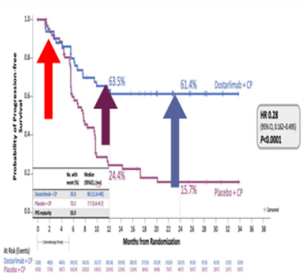
Westin et al, JCO 2023; 42: 283-299

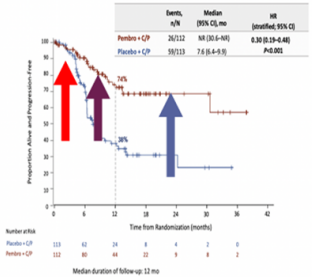
¿ DEBERÍAN TODAS LAS PACIENTES d MMR LLEVAR ICI EN PRIMERA LÍNEA?

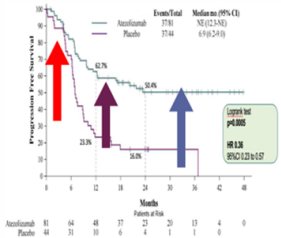
Tailoring First Line Therapy: dMMR/MSI-H*

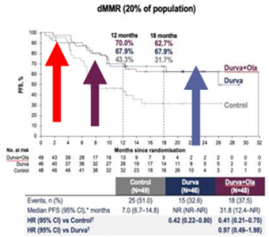
TRIAL	ICI	HR PFS
RUBY-Part 1	Dostarlimab	**0.28** (95% CI 0.16-0.49)
NRG-GY018	Pembrolizumab	**0.30** (95% CI 0.19-0.48)
AtTEnd	Atezolizumab	**0.36** (95% CI 0.23-0.57)
DUO-E – Arm 2	Durvalumab	**0.42** (95% CI 0.22-0.80)

*Different studies, cross-trial comparisons are not appropriate





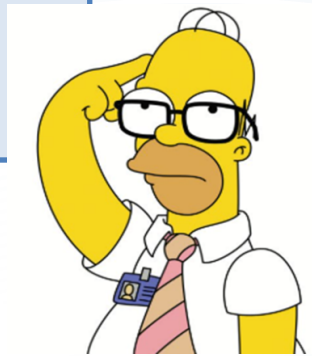




Mirza MR. et al N Engl J Med. 2023 Jun 8;388(23):2145-2158. Eskander RN et al; N Engl J Med. 2023 Jun 8;388(23):2159-2170
Nicoletta Colombo et al. Presented at ESMO Meeting , Madrid 2023 ; Westin SN et al J Clin Oncol. 2023 Oct 21:JCO2302132

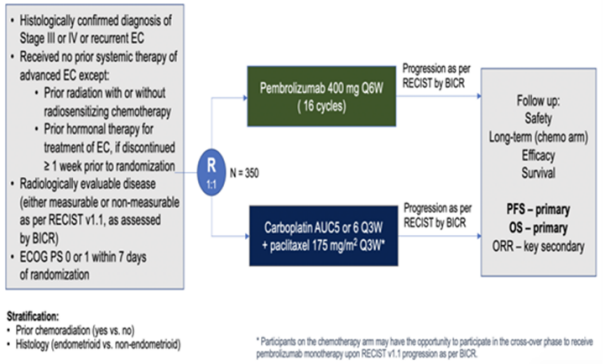
SÍ, debería usarse ICI en 1º línea en dMMR

¿ PODEMOS ELIMINAR LA QUIMIOTERAPIA DEL ESQUEMA TERAPEÚTICO EN ESTAS PACIENTES d MMR ?



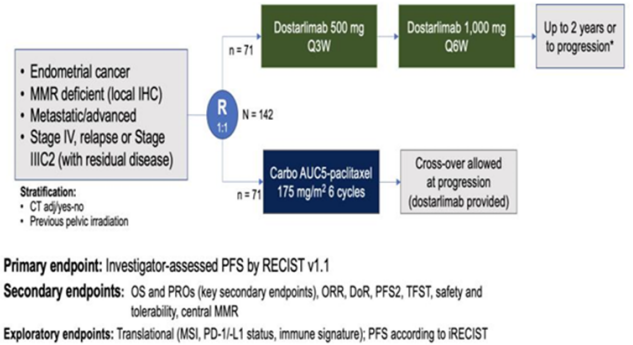
KEYNOTE-C93/GOG-3064/ENGOT-en 15
Study design

Phase III randomized trial of pembrolizumab vs. platinum doublet chemotherapy in first-line dMMR advanced or recurrent EC



ENGOT-en13/GINECO/DOMENICA
Study design

Phase III randomized trial comparing chemotherapy alone vs.dostarlimab in first-line dMMR EC advanced/metastatic



Primary endpoint: Investigator-assessed PFS by RECIST v1.1

Secondary endpoints: OS and PROs (key secondary endpoints), ORR, DoR, PFS2, TFST, safety and tolerability, central MMR

Exploratory endpoints: Translational (MSI, PD-1/-L1 status, immune signature); PFS according to iRECIST

HABRÁ QUE ESPERAR A RESULTADOS PARA RESPONDER ESTA PREGUNTA

CONCLUSIONES dMMR

- Los ICI están cobrando mucha relevancia en el tratamiento del cancer de endometrio recurrente/metastásico.
- En las pacientes con tumores **dMMR/MSI-H la combinación de QT + inmunoterapia** ha demostrado un **aumento clínicamente significativo en SG y SLP**, y debe considerarse el **nuevo SOC.**
- Hay que seguir investigando para identificar aquellas pacientes dMMR que no se benefician de los ICI.
- A la espera de los resultados de los estudios Domenica y Keynote C-93 para ver si es posible omitir la QT en estas pacientes.

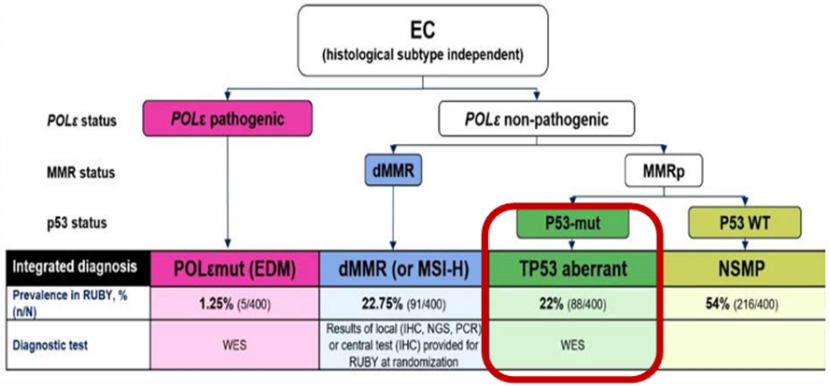
P53 MUTADO

P53 mutado CARACTERÍSTICAS

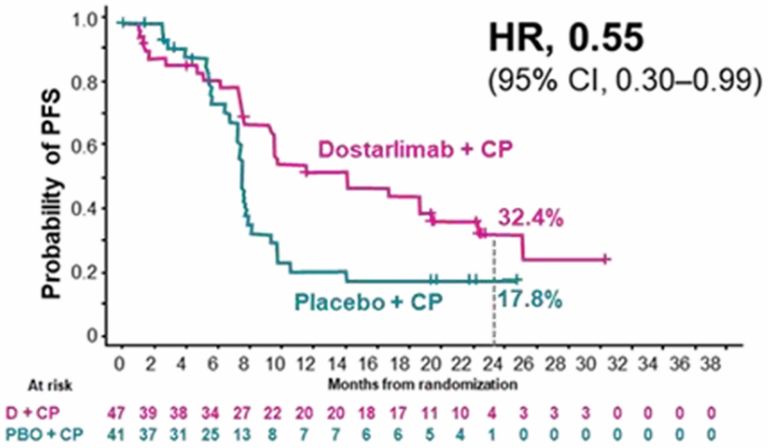
- Subtipo de **peor pronóstico**, 15% de los cánceres de endometrio pero supone el 50-70% de la mortalidad.
- **Más agresivos** y enfermedad más avanzada al diagnóstico
- Aprox **20% sobreexpresión de HER2**
- Tiene un alto número de alteraciones somáticas.
- El p53 mutado es más frecuente en determinadas histologías: 93% seroso, 85% carcinosarcomas y 38% células claras.
- Se detecta por **IHQ**: mutado implica la sobreexpresión del p53 así como la ausencia de tinción del mismo.
- **HRD** es más prevalente en los tumores p53 mutados.

Galant N, et al Molecular Classification of Endometrial Cancer and Its Impact on Therapy Selection Int. J. Mol. Sci. 2024, 25, 5893

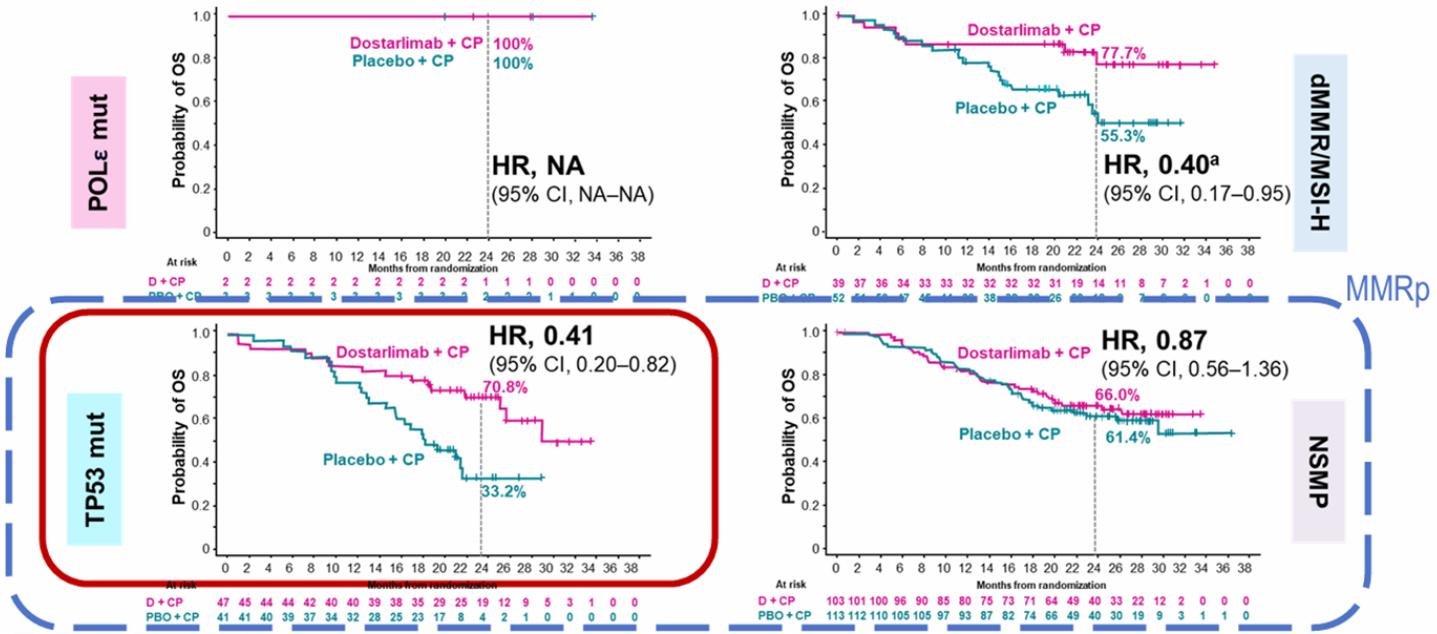
PFS RUBY SUBGRUPO p53



Integrated diagnosis	POLεmut (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	



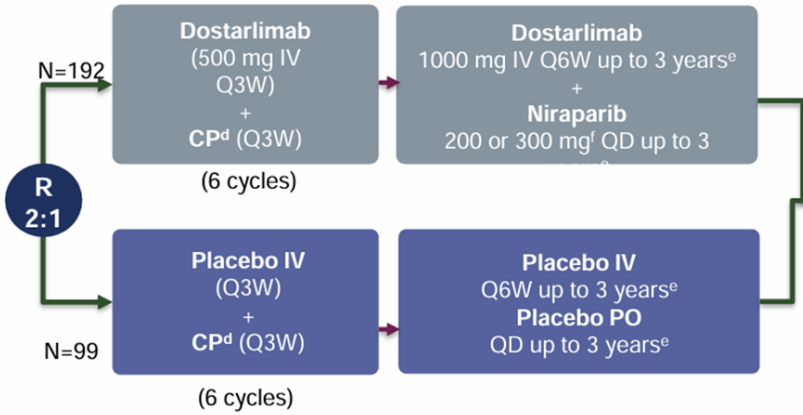
OS RUBY


POLε mut
Probability of OS
Dostarlimab + CP
Placebo + CP
100%
100%
HR, NA
(95% CI, NA–NA)
Months from randomization
At risk
D + CP 2 2 2 2 2 2 2 2 2 2 2 2 1 1 1 0 0 0 0 0
dMMR/MSI-H
Dostarlimab + CP
Placebo + CP
77.7%
55.3%
HR, 0.40ª
(95% CI, 0.17–0.95)
D + CP 39 37 36 34 33 33 32 32 32 32 31 19 14 11 8 7 2 1 0 0
MMRp
TP53 mut
HR, 0.41
(95% CI, 0.20–0.82)
70.8%
33.2%
D + CP 47 45 44 44 42 40 40 39 38 35 29 25 19 12 9 5 3 1 0 0
PBO + CP 41 41 40 39 37 34 32 28 25 23 17 8 4 2 1 0 0 0 0 0
NSMP
HR, 0.87
(95% CI, 0.56–1.36)
66.0%
61.4%
D + CP 103 101 100 96 90 85 80 75 73 71 64 49 40 33 22 12 2 0 0 0
PBO + CP 113 112 110 105 105 97 93 87 82 74 66 49 40 30 19 9 3 1 1 0

RUBY PARTE 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

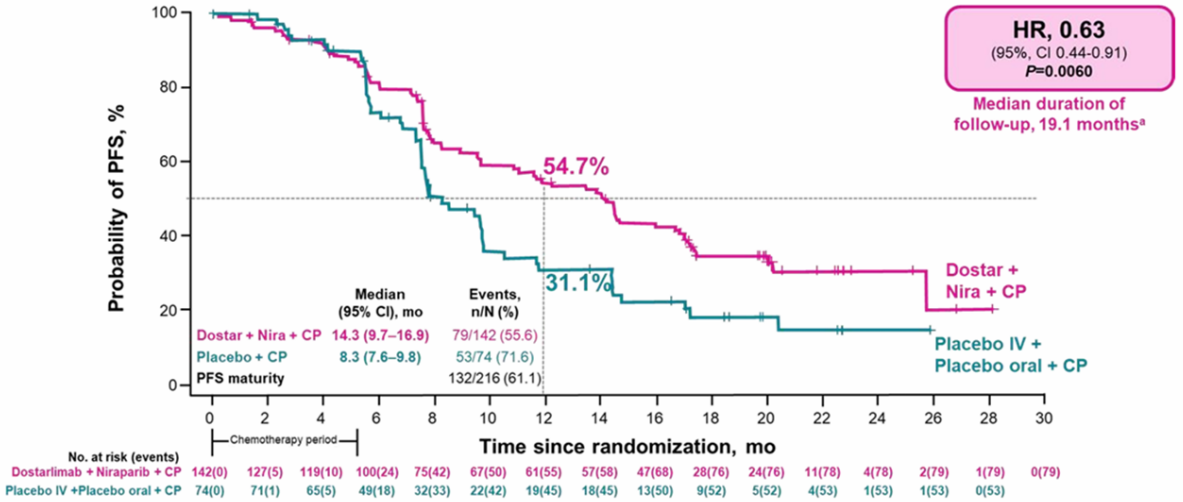


Primary endpoint
- PFS by INV per RECIST v1.1
  - Overall
  - MMRp/MSS

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

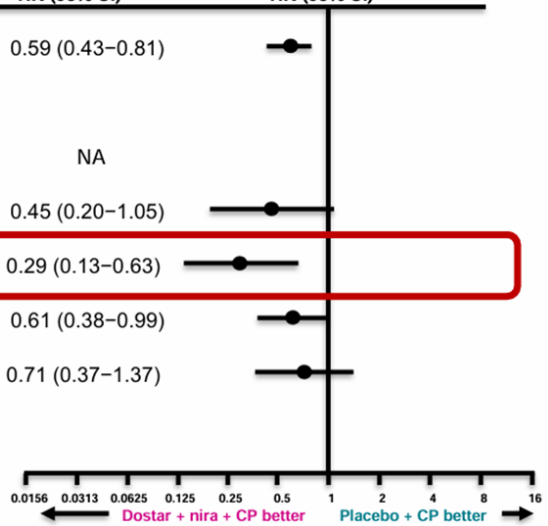
RUBY PARTE 2

PFS outcome in MMRp



Exploratory PFS Molecular Subgroup Analyses in Overall Population

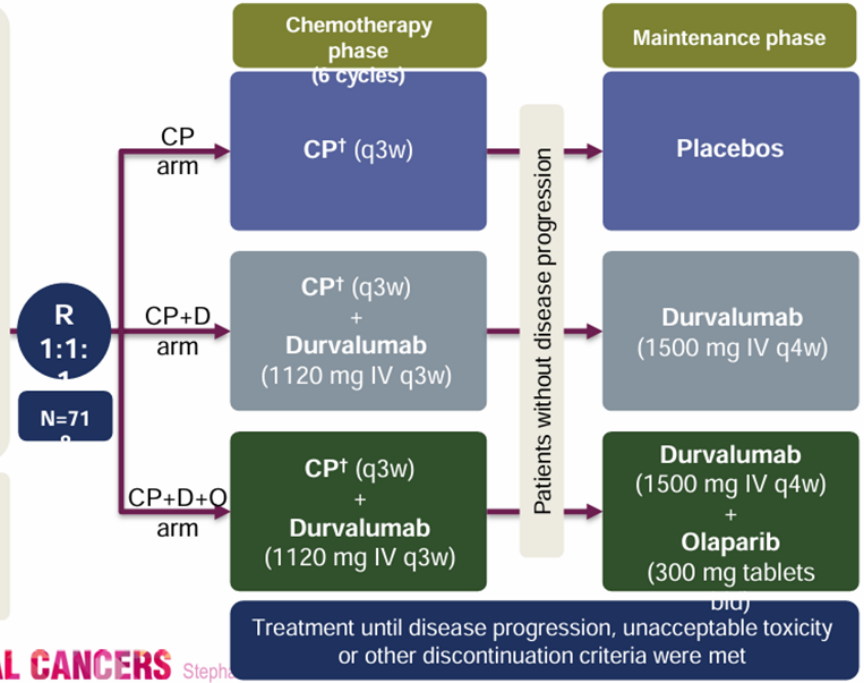
	Dostarlimab + Niraparib + CP N=192	Placebo IV + Placebo oral + CP N=99	HR (95% CI)
	No. of patients with events/No. of patients		
All patients	95/192	69/99	0.59 (0.43–0.81)
Molecular subgroup[a]			
POLEmut	0/3	1/2	NA
dMMR/MSI-H	12/37	10/17	0.45 (0.20–1.05)
TP53mut	27/39	10/10	0.29 (0.13–0.63)
NSMP	37/75	31/46	0.61 (0.38–0.99)
Not evaluable[b]	19/38	17/24	0.71 (0.37–1.37)



Front Line Metastatic OR Recurrent – DUO-E

Patients
- Newly diagnosed FIGO 2009 Stage III/IV or recurrent endometrial cancer (measurable disease if newly diagnosed Stage III disease)
- Known MMR status
- Naïve to first-line systemic anticancer treatment for advanced disease
- Naïve to PARP inhibitors and immune-mediated therapy
- Adjuvant chemotherapy allowed if ≥12 months from last treatment to relapse
- All histologies except sarcomas

Stratified by:
- MMR status (proficient vs deficient)
- Disease status (recurrent vs newly diagnosed)
- Geographic region (Asia vs non-Asia)

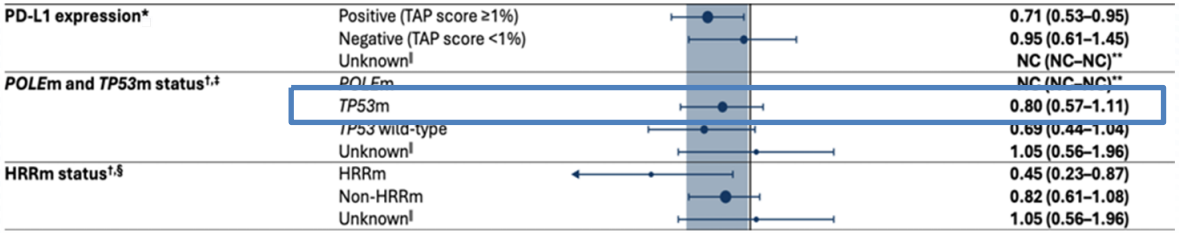


Primary
- PFS (RECIST per investigator) in:
  - CP+D arm vs CP arm
  - CP+D+O arm vs CP arm

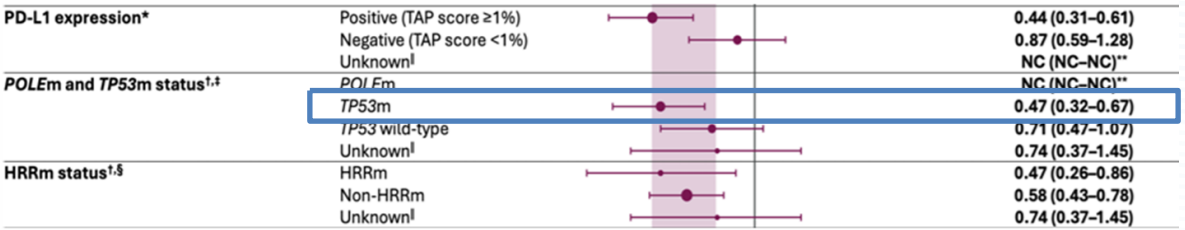
Secondary
- OS (key secondary)
- TFST, PFS2 and TSST
- Safety

***Post hoc* exploratory analyses**
- MMR subpopulation analyses of OS, TFST, PFS2 and TSST (DCO1)

CP + durvalumab vs CP



CP + durvalumab + olaparib vs CP

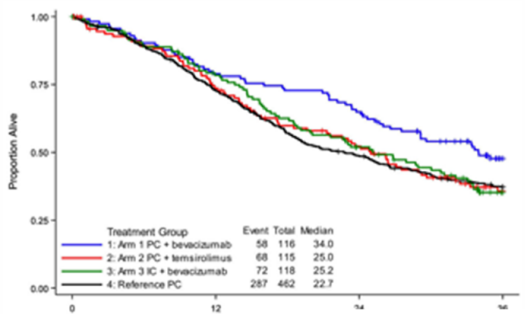


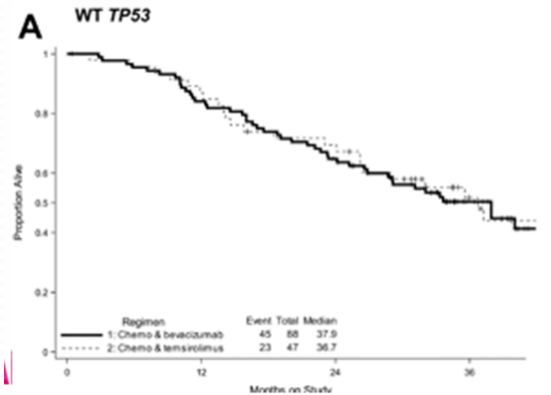
Bevacizumab

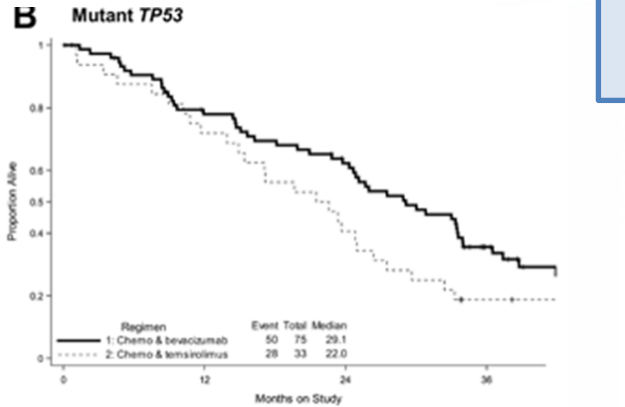
GOG 86P

A Phase II Study of Frontline Paclitaxel/Carboplatin/ Bevacizumab, Paclitaxel/Carboplatin/Temsirolimus, or Ixabepilone/Carboplatin/Bevacizumab in Advanced/Recurrent Endometrial Cancer

Carol Aghajanian, MD[1], Virginia Filiaci, PhD[2], Don S. Dizon, MD[3], Jay W. Carlson, DO[4], Matthew A. Powell, MD[5], Angeles Alvarez Secord, MD[6], Krishnansu S. Tewari, MD[7], David P. Bender, MD[8], David M. O'Malley, MD[9], Ashley Stuckey, MD[10], JianJiong Gao, PhD[11], Fanny Dao, MS[12], Robert A. Soslow, MD[1], Heather A. Lankes, PhD,MPH[13], Kathleen Moore, MD[14], and Douglas A. Levine, MD[12]







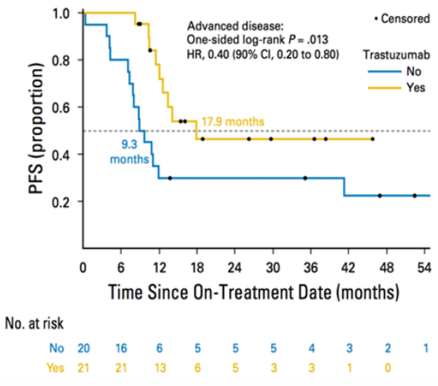
P53 como marcador predictivo de beneficio del Bevacizumab

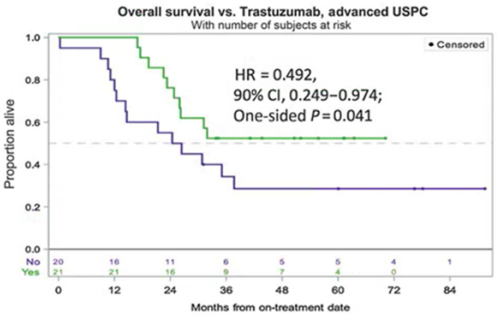
Trastuzumab

Chemotherapy +/- Trastuzumab
Key eligibility criteria

- **Primary stage III or IV** or recurrent HER2/neu-positive USC: IHC score 3+, or 2+ with + FISH
- ECOG 0-2
- ≤3 prior lines of therapy
- "platinum sensitive" recurrence (6 mths)

20% de los tumores serosos de endometrio tienen sobreexpresión de Her2





CONCLUSIONES P53 mutado

- El **pronóstico** de estas pacientes es especialmente **pobre**, sería recomendable la realización de ensayos clínicos en este subtipo específico.
- **Beneficio en SLP y SG en las pacientes p53 mutado** que recibían QT+ Dostarlimab en el ensayo RUBY, así como en el DUO-E la combinación de Durvalumab-Olaparib.
- Dada la sobre-expresión de **HER2** (20%) valorar antiHER2.
- Se podría valorar asociar **Bevacizumab** en estas pacientes (p53 mutado tiene valor predictivo de respuesta).
- Es importante entender el subtipo p53 mutado de cara a diseñar nuevas estrategias terapéuticas (inhibidores de ciclo celular, ADC, …)

NSMP

NSMP CARACTERÍSTICAS

- Es un subgrupo **muy heterogéneo**, y el subgrupo **más frecuente** (50% aprox).
- Se caracterizan por p MMR, p53 wild type y ausencia de mutaciones en POLE y suelen expresar RH (con una expresión variable).
- Subtipo de **pronóstico intermedio**.
- Marcadores como L1CAM (sobreexpresión), negatividad de los RH, mutaciones en CTNNB1 o la amplificación del cromosoma 1q, se están proponiendo como marcadores para una mejor estratificación del riesgo del subtipo NSMP.
- También el grado, estadío e invasión linfovascular se usan de cara a la elección del mejor tratamiento.

GRUPO LEIDEN subdivide en 3 categorías:

1. **ALTO RIESGO**: presencia de ILVS y/o sobreexpresión de L1CAM (+ > 10% de las células).
2. **RIESGO INTERMEDIO**: no ILVS ni sobreexpresión de L1CAM, pero mutación en exón 3 del CTNNB1.
3. **BAJO RIESGO**: CTNNB1 wild type, sin ILVS ni sobreexpresión de L1CAM.

Estas categorías de riesgo se están estudiando en el PORTEC4a.

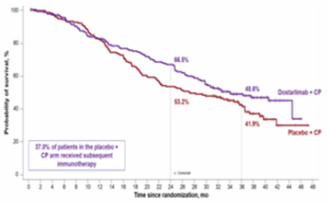
Otros: presencia de marcadores de daño del DNA, PTEN, AKT, PI3KCA, KRAS,…

Galant N, et al Molecular Classification of Endometrial Cancer and Its Impact on Therapy Selection Int. J. Mol. Sci. 2024, 25, 5893

MMRp EC

Clinically meaningful <u>though modest</u> PFS and OS benefit of ICI + chemotherapy

EN6-RUBY Part 1[1–3]

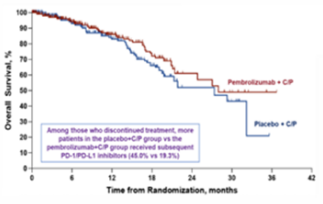


OS Data	Events, %	Median (95% CI), mo
Dostarlimab + C/P	50.5	34.0 (28.6-NE)
Placebo + C/P	59.2	27.0 (21.5-35.6)
OS data maturity	54.8%	
Median follow-up, mo	37.5	

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

OS **HR 0.79** (95% CI, 0.60-1.04); *Nominal p*=0.0493

NRG-GY018[4–5]

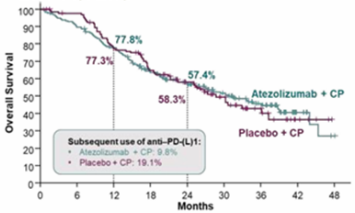


OS Data	Events, %	Median (95% CI), mo
Pembrolizumab + C/P	15.3	28.0 (21.4-NR)
Placebo + C/P	18.3	27.4 (19.5-NR)
OS data maturity	27.2%	
Median follow-up, mo	8.4-8.8	

PFS HR 0.54 (95% CI, 0.41-0.71); *P*<0.001

OS **HR 0.79** (95% CI, 0.53-1.17) *Nominal p=0.1157*

EN7-AtTEnd[6]

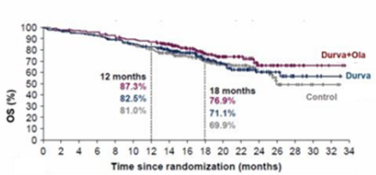


OS Data	Events, %	Median (95% CI), mo
Atezolizumab + C/P	47.2	31.5 (25.0-38.9)
Placebo + C/P	46.4	28.6 (22.4-37.2)
OS data maturity	--	
Median follow-up, mo	--	

PFS HR 0.92 (95% CI, 0.73-1.16);

OS **HR 1.00** (95% CI, 0.74-1.35)

DUO-E[7–8]



OS Data	Events, %	Median (95% CI), mo
Durvalumab + C/P	30.2	NR (NR-NR)
Placebo + C/P	33.3	25.9 (25.1-NR)
OS data maturity	29.2%	
Median follow-up, mo	--	

PFS HR 0.77 (95% CI, 0.60-0.97); *Durva + C/P arm*

OS **HR 0.91** (95% CI, 0.64-1.30) *Durva + C/P arm*

1. Mirza MR, et al. N Engl J Med. 2023;388:2145-2158. 2. Mirza MR, et al. Ann Oncol. 2023;34:500-501; 3. Eskander RN, et al. N Engl J Med. 2023;388:2159-2170. 4. Eskander RN, et al. Presented at: SGO; March 25-28 2023; Tampa, FL, USA. 5. Arend RC, et al. Presented at: SGO; March 25-28, 2023; Tampa, FL, USA.; 6. Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.; 7. Westin SN, et al. J Clin Oncol. 2023; DOI: 10.1200/JCO.23.02132.; 6. Powell MA, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA1; 7. Eskander RN, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2; 8. Baurain JF, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Scientific Plenary V

¿ QUÉ PACIENTES pMMR NSMP (P53WT) PUEDEN BENEFICIARSE MÁS DE LA COMBINACIÓN QT + ICI +/- iPARP ?

HABRÁ QUE SEGUIR INVESTIGANDO BIOMARCADORES QUE NOS AYUDEN A ESTRATIFICAR EL NSMP

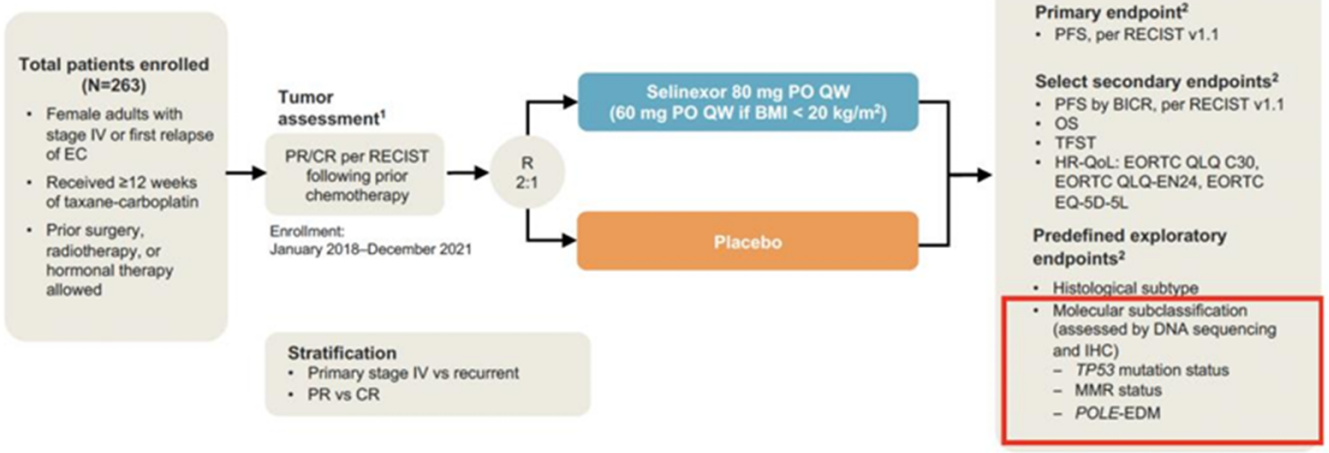
Molecular profile of endometrial cancers

Histology	Endometrioid			Serous and high grade endometrioid	Carcinosarcoma	Clear cell
TCGA subtype	'POLE-ultramutated'	'MSI-hypermutated	'MSS copy-number low'	'copy-number high serous-like'	NA	NA
Mutation load						
SCNA load						
Grade	1, 2, 3	1,2,3**	1,2	3	High	High
ER status	ER- ; ER+	ER+ ; ER-	ER+			
TP53 mutation	35%	low	low	>90%	60-90%	35%
PI3K alterations	PTEN M+ (94%) PIK3CA M+ (71%) PIK3R1 M+(65%)	PTEN M+ (75-85%) PIK3CA M+(50-55%) PIK3R1 M+(30-40%)		PTEN (11%) PIK3CA A+ (45%) PIK3CA M+ (35%) PIK3R1 M+ (12%)	PTEN M+ (19%) PIK3CA M+ (35%) PIK3CA A+ (14%)	PTEN loss (80%) PIK3CA (18%)
KRAS mutation	>50%	35%			17%	0%
Erbb alterations	0	low	low	ErbB2 A+ 30-40% (serous)	ErbB2 A+ (13%) ErbB3 A+/M+ (13%)	ErbB2 M+ (12%)
FGFR amplification or mutation	FGFR1 A+/M+ (7%) FGFR2 A+/M+ (13%) FGFR3 A+/M+ (5%)				FGFR3 A+ (20%)	
Wnt/βcatenin			CTNNB1 M+ (>50%)			
Other	ARID1A M+ (75%) PD1/PD-L1 overexpr. Mutation(s) in the exonuclease domain of the POLE gene	ARID1A M+(35-40% PD1/PD-L1 overexpr.	ARID1A M+(35-40%)	PPP2R1A M+(20%) FBXW7 M+(20% of UC) HER-2 (25%)	ARID1A (25%) PPP2R1A (28%) FBXW7 M+(35%) CCNE1 A+ (42%) Sox17 A+ (25%)	ARID1A (25%) TERT promoter mutations

2024 ESMO GYNAECOLOGICAL CANCERS

Mansoor Raza Mirza

ENGOT-EN5/GOG-3055/SIENDO (NCT03555422): A Randomized Double-Blind, Phase 3 Trial of Maintenance With Selinexor/Placebo After Combination Chemotherapy for Patients With Advanced or Recurrent Endometrial Cancer[1,2]

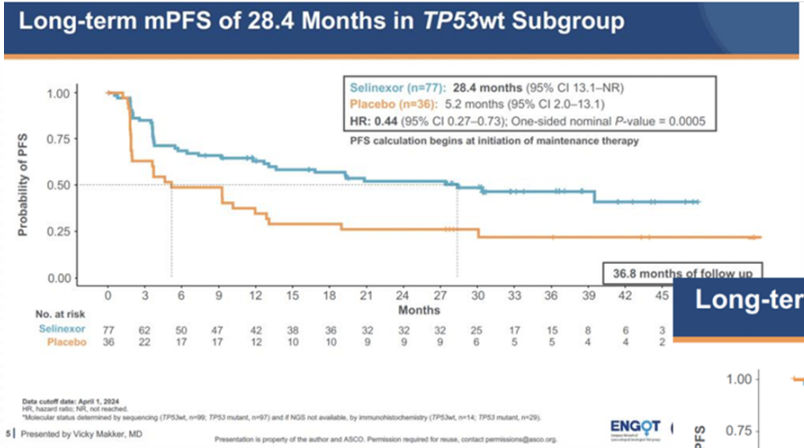


BICR, blinded independent central review; CR, complete response; EDM, exonuclease domain mutation; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, Quality of Life Questionnaire EuroQol-5 Dimensions-5 Levels; HR-QoL, health-related quality of life; MMR, mismatch repair; OS, overall survival; PD, progressive disease; PO, by mouth; POLE, polymerase epsilon; PR, partial response; PROs, patient-reported outcomes; QLQ, quality of life questionnaire; QW, once weekly; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; TFST, time to first subsequent therapy

1. ClinicalTrials.gov. NCT03555422. https://www.clinicaltrials.gov/study/NCT03555422?term=NCT03555422. Accessed April 1 2024. 2. Vergote I, *et al.* Presentation at: European Society for Medical Oncology Virtual Plenary; March 17-18, 2022; Abstract VP2-2022.
Primary study results previously published in Vergote I, *et al J Clin Oncol.* 2023;41(35):5400-5410.

SELINEXOR: inhibidor de la XPO1, produce un arresto celular porque no se puede exportar el p53 del núcleo al citoplasma

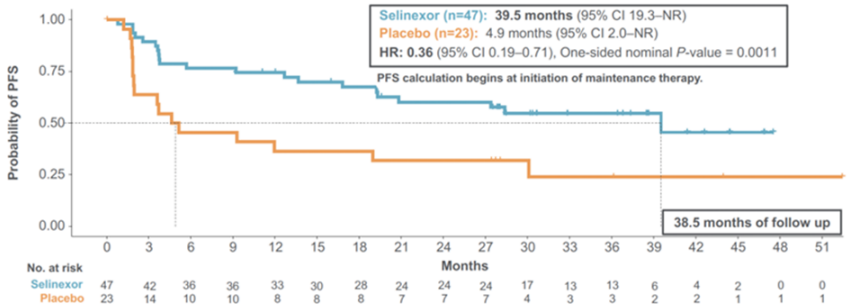
Long-term mPFS of 28.4 Months in *TP53*wt Subgroup



Data cutoff date: April 1, 2024.
HR, hazard ratio; NR, not reached.
*Molecular status determined by sequencing (*TP53*wt, n=99; *TP53* mutant, n=97) and if NGS not available, by immunohistochemistry (*TP53*wt, n=14; *TP53* mutant, n=29).

5 | Presented by Vicky Makker, MD

Long-term mPFS of 39.5 Months in *TP53*wt/pMMR* Subgroup

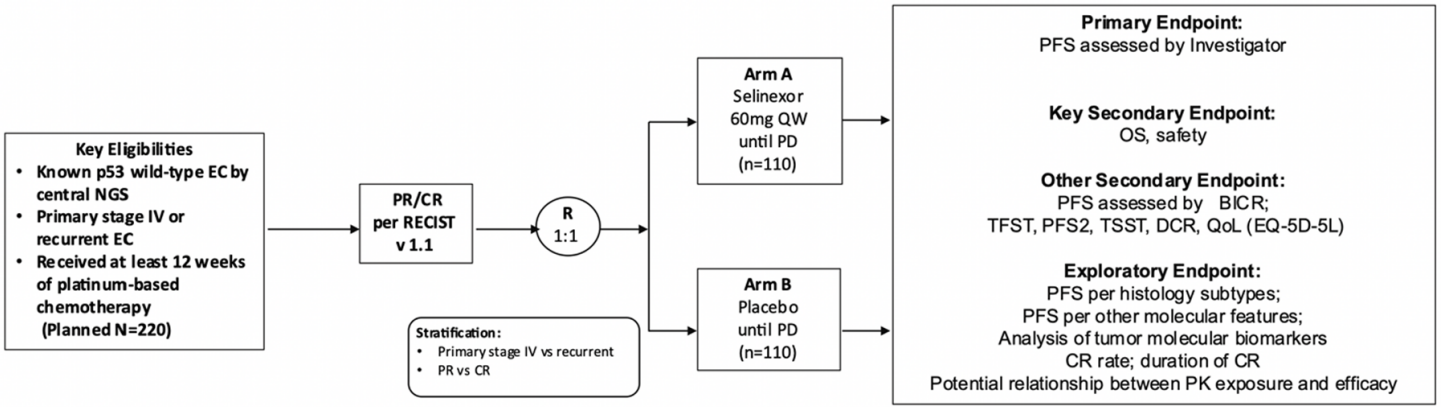


Data cutoff date: April 1, 2024
*Molecular status determined by sequencing (*TP53*wt, n=99; *TP53* mutant, n=97; pMMR, n=164) and if NGS not available, by immunohistochemistry (*TP53*wt, n=14; *TP53*wt mutant, n=29; pMMR, n=20).

6 | Presented by Vicky Makker, MD

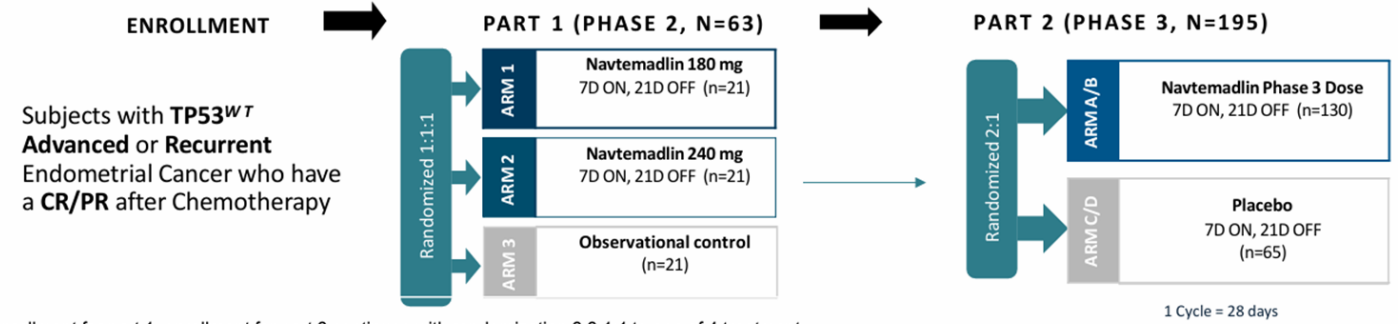
<u>1º análisis</u>: SLP en ITT NO fue estadísticamente significativo. En el análisis exploratorio pre-especificado se observó eficacia prometedora en p53wt

ENGOT-EN20 / XPORT



ENGOT-EN21/KRT-232-118

A Two-part, Randomized Phase 2/3 Study of Navtemadlin in Subjects with TP53WT Advanced or Recurrent Endometrial Cancer Who Responded after Chemotherapy



After enrollment for part 1, enrollment for part 2 continues with randomization 2:2:1:1 to one of 4 treatment arms:

1. Navtemadlin 180 mg
2. Navtemadlin 240 mg
3. Placebo 180 mg
4. Placebo 240 mg

Once the SRC determines the navtemadlin Phase 3 dose, enrollment will continue with 2:1 randomization to the navtemadlin Phase 3 dose and matching placebo dose for Part 2

ENGOT model: C
Status: Recruiting
Planned number of patients: Phase 2+3: 258
Sponsor: Kartos Therapeutics,
ENGOT Lead Group: AGO-Austria
NSGO-CTU Lead PI: Kristina Lindemann
NSGO-CTU Contacts: Henriette Watson Hansen, Line Jensen and Kristine Madsen
Primary Endpoint: Progression Free Survival (PFS)

NAVTEMADLIN: inhibidor MDM2, que regula negativamente el p53, promueve la apoptosis porque restaura la actividad de p53

A randomized phase II trial of everolimus and letrozole or hormonal therapy in women with advanced, persistent or recurrent endometrial
carcinoma

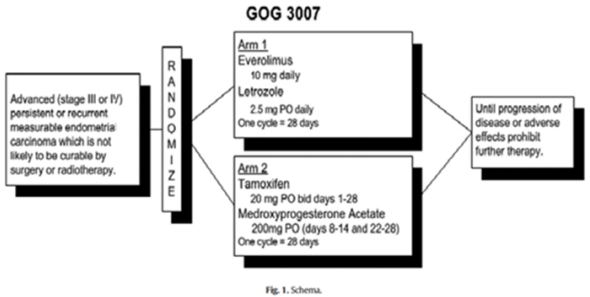


Fig. 1. Schema.

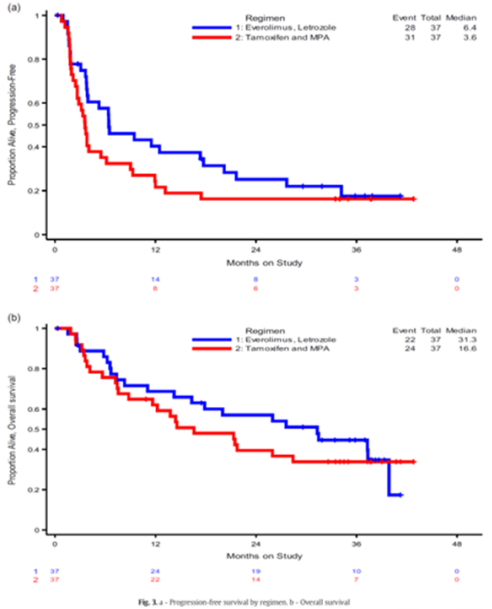


Fig. 3. a - Progression-free survival by regimen. b - Overall survival

El tratamiento hormonal suele ser bien tolerado y es una opción en pacientes frágiles o enfermedad de bajo volúmen y lento crecimiento.
En pacientes con RE/RP +:

- Tasas de Respuesta de los progestágenos de > 35%.
- IA suelen usarse Tambien en este contexto con beneficio clínico de aprox 40-45% con tasas de respuesta de aprox 10%.

ENGOT model A, sponsor NSGO-CTU, NCT02730429

- Measurable/evaluable endometrial cancer
- Primary stage 4 or relapsed disease
- ≥1 prior systemic therapy
- ER+ (≥10%) endometrioid adenocarcinoma
- ECOG PS 0/1
- No prior endocrine therapy except MPA and megestrol acetate
- No prior CDK inhibitor

Stratification:
- No. of prior lines (primary advanced disease vs 1st relapse vs ≥2 relapses)
- Measurable vs evaluable disease per RECIST
- Prior use of MPA/megestrol acetate

1:1 randomisation

Placebo 125 mg days 1–21
Letrozole 2.5 mg days 1–28

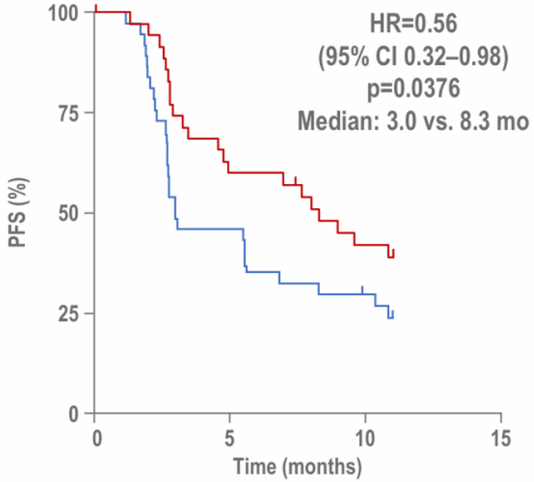
Repeated every 28 days until progression

Palbociclib 125 mg days 1–21
Letrozole 2.5 mg days 1–28

Primary endpoint: Investigator-assessed PFS (target HR 0.625, 80% power, 15% 1-sided α)
Secondary endpoints:
- PFS in subgroups
- Objective response rate, disease control rate, PFS2, overall survival
- PROs
- Safety and tolerability

HR = hazard ratio; MPA = medroxyprogesterone acetate; PROs = patient-reported outcomes

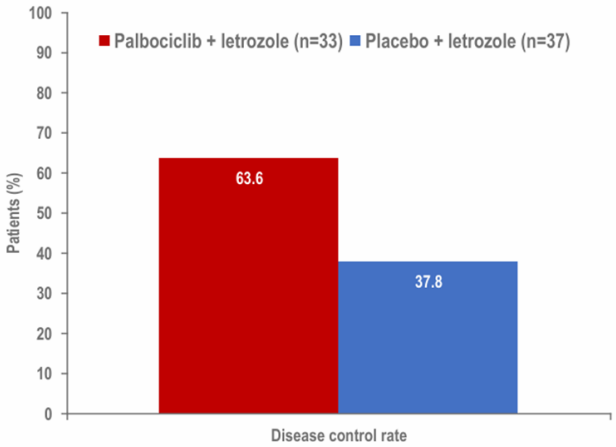
Primary endpoint: PFS



Number at risk

Palbociclib + letrozole	36	21	14
Placebo + letrozole	37	17	10

Secondary endpoint: Disease control rate*

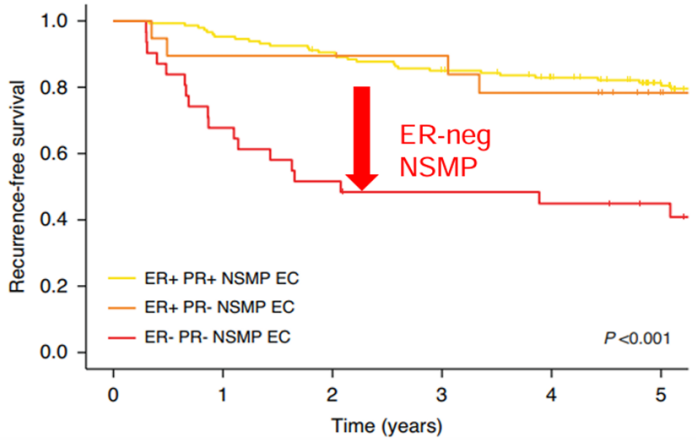


CI = confidence interval; HR = hazard ratio

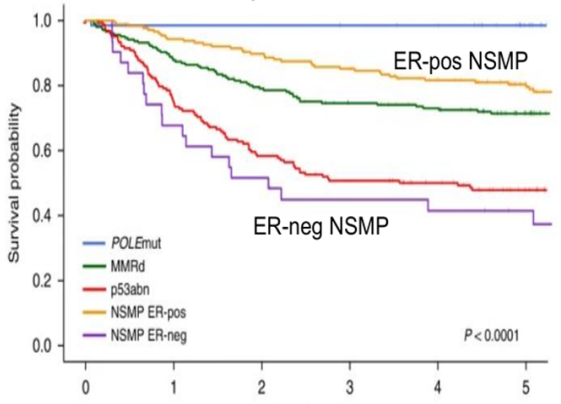
* = at 24 weeks

RH EN NSMP

Within the NSMP subclass, ER-neg stand out



Within molecular classified EC, ER-neg NSMP behave like p53abn…



CONCLUSIONES NSMP

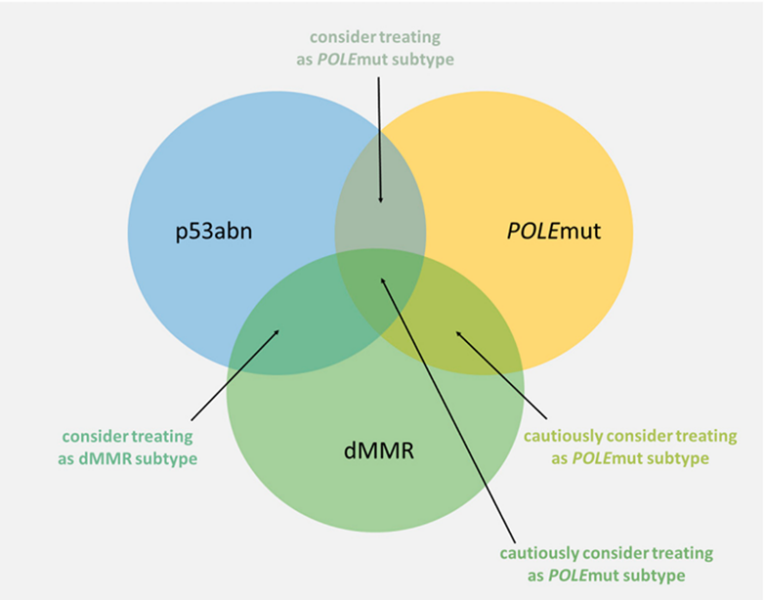
- Subgrupo **muy heterogéneo**.
- Beneficio discreto del subtipo NSMP en ensayos en primera línea de combinación QT + ICI
- Una opción puede ser tratamiento de mantenimiento con **Selinexor** (p53 wt).
- Otra opción es tratamiento **hormonal** (enfermedad de bajo volumen, lento crecimiento, pacientes mayores,…) Ensayos de hormonterapia en combinación (palbociclib / everolimus,…) aumento del beneficio.
- **Importancia de descubrir BIOMARCADORES predictivos de respuesta y pronósticos**. Hay que estratificar el subtipo NSMP de cara a tratamiento más individualizado.

MULTIPLE CLASSIFIERS

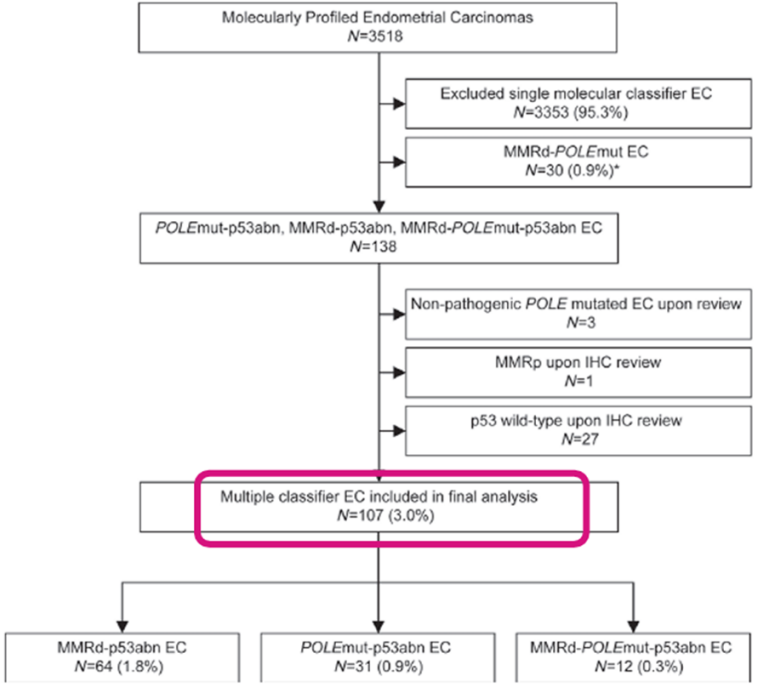
2.5. Multiple Classifiers

It is important to remember that a small percentage of EC patients (approximately 3–6%) may harbor more than one genetic condition. These cases are called "multiple classifiers" [16,97]. De Vitis et al. suggested that the percentage of "multiple classifiers" may be even higher (about 11% of EC cases) if, instead of p53 immunostaining, *TP53* mutation analysis is performed [98].

The most problematic aspect of therapy decision-making seems to be the abnormal expression of p53 and *POLE* mutations; thus, the p53abn subtype is known as a subtype with a poor prognosis, while *POLE*mut has a favorable prognosis. However, it has been suggested that patients with *POLE*mut-p53abn endometrial cancer have outcomes similar to the *POLE*mut subtype and, as a result, they should be treated as patients with the *POLE*mut subtype [16,98–100]. Similarly, it is suggested that patients with MMR deficiency and abnormal p53 expression should be classified as the dMMR subtype [16,100]. Information on the simultaneous occurrence of *POLE*mut and dMMR (including triple-classifiers, i.e., dMMR-*POLE*mut-p53abn subtype) is scarce and should be considered cautiously [16,97]. It was tentatively propounded to classify dMMR-*POLE*mut patients as *POLE*mut if a pathogenic *POLE* mutation is detected using NGS or if the mutation corresponds to one of the eleven most common pathogenic *POLE* variants [97] (Figure 2).

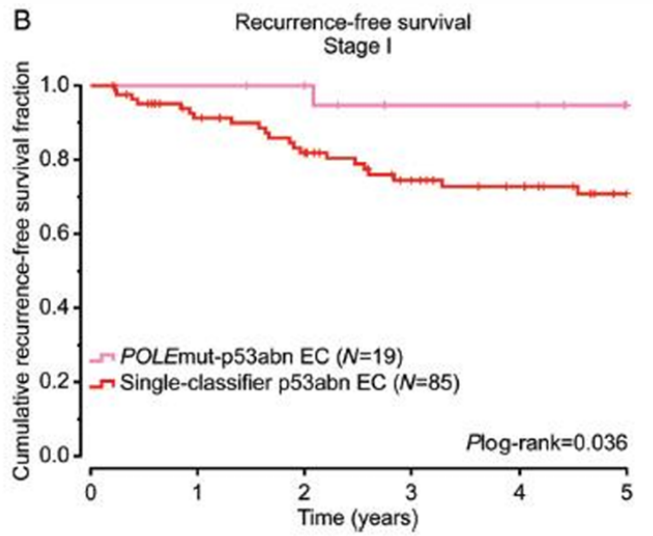


- **Se recogieron > 3000 casos de cancer de endometrio clasificados molecularmente en estudios previos.**
- **3% eran multiple classifiers.**

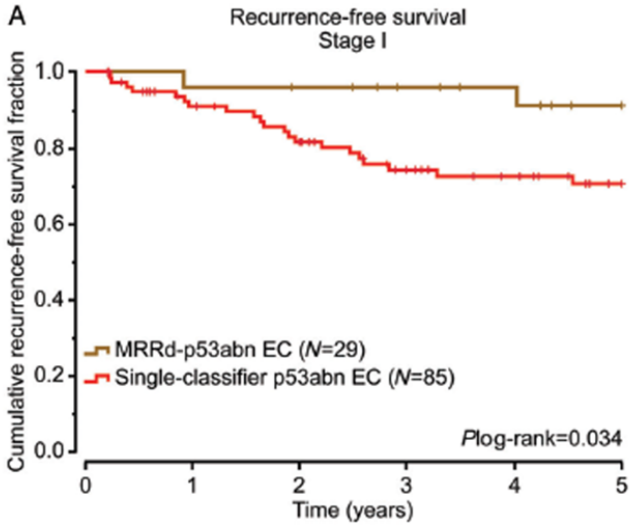


Leon castillo et al J Path 2020

POLEm/p53abn se comporta como POLEm, no p53abn

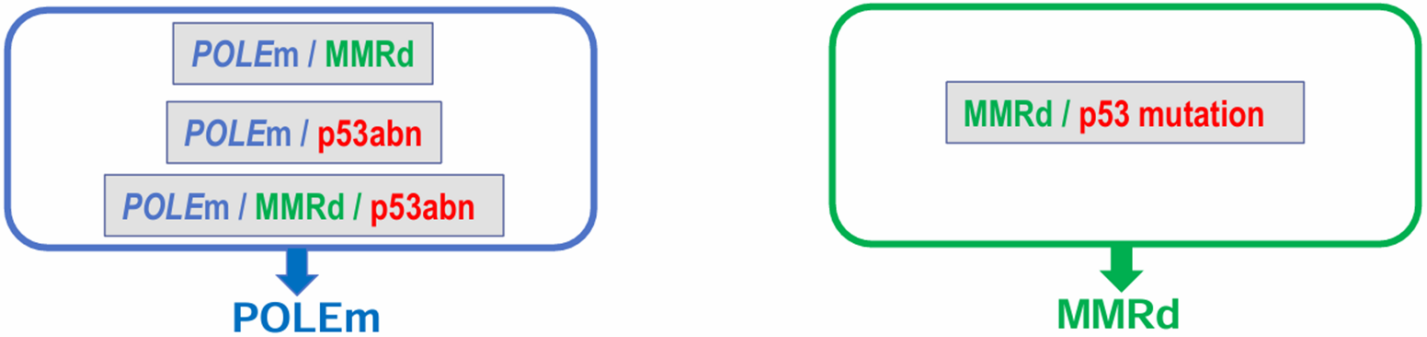


d MMR/p53abn se comporta como d MMR, no p53abn



Leon castillo et al J Path 2020

Double classifiers should be classifed as:



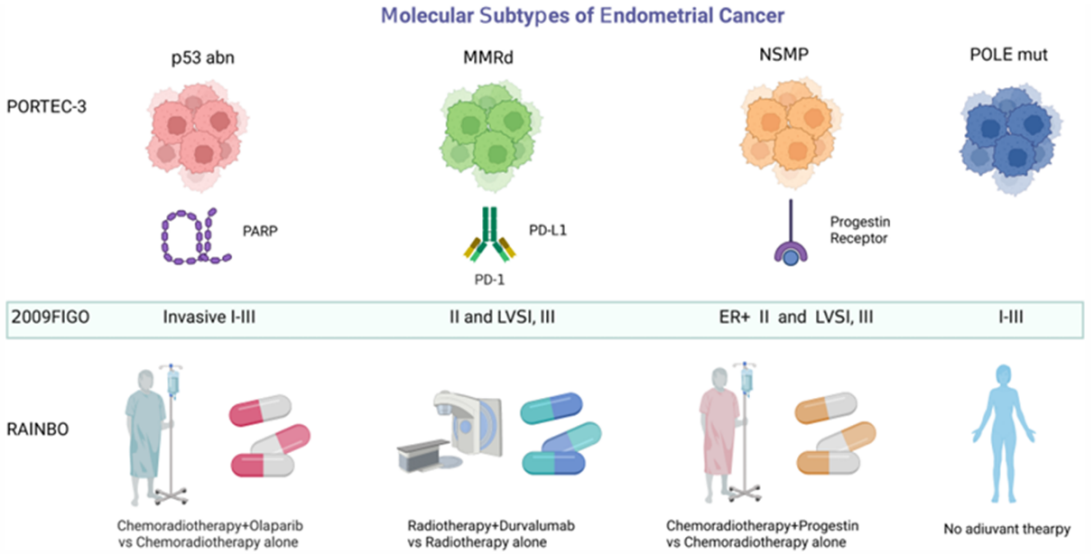


FIGURE 1 Molecular subtypes of the endometrial cancer associated with the randomized Phase 3 TransPORTEC RAINBO program. The p53abn-RED trial for women with invasive Stage I–III p53 abnormality (p53 abn) endometrial cancer compares adjuvant chemoradiation followed by olaparib for 2 years to adjuvant chemoradiation alone. The mismatch repair-deficient (MMRd)-GREEN trial for women with Stage II (with lymphovascular space invasion [LVSI]) or Stage III MMRd endometrial cancer compares adjuvant radiotherapy with concurrent and adjuvant durvalumab for 1 year to radiotherapy alone. The NSMP-ORANGE trial is a treatment de-escalation trial for women with estrogen receptor-positive Stage II (with LVSI) or Stage III non-specific molecular profile (NSMP) endometrial cancer comparing radiotherapy followed by progestin for 2 years to adjuvant chemoradiation. The POLEmut-BLUE trial is a Phase 2 trial in which the safety of de-escalation of adjuvant therapy is investigated for women with Stage I–III polymerases epsilon exonuclease domain mutated (POLE mut) endometrial cancer: no adjuvant therapy for lower-risk disease and no adjuvant therapy or radiotherapy alone for higher-risk disease.

CONCLUSIONES FINALES

- La **clasificación molecular** ha demostrado ser una **herramienta valiosa** para guiar el manejo terapeútico y la correcta estratificación de las pacientes en cuanto a pronóstico.
- Se están realizando múltiples análisis y ensayos clínicos que sugieren nuevos caminos en el tratamiento del cáncer de endometrio según el subtipo molecular.
- Debido al pronóstico diferente de cada subtipo molecular y respuesta a los diferentes tratamientos, el **subtipo molecular debe guiarnos a la hora de elegir una terapia u otra**:

1. Beneficio de ICI en d MMR
2. Beneficio de ICI +/- iPARP en p53 (Bevacizumab, Trastuzumab,..)
3. Diferentes opciones en el NSMP (Selinexor, tratamiento hormonal, …)

- Hay que **seguir investigando en los <u>biomarcadores</u>**.

GRACIAS