XXII ASSEMBLEA MaNGO MILANO

STANDARD TREATMENTS AND NEW DIRECTIONS IN GYNAECOLOGICAL CANCERS

MILANO June 26th-28th, 2025

Responsabili Scientifici:
NICOLETTA COLOMBO, FRANCESCO RASPAGLIESI

GSK SPONSORED SYMPOSIUM

The new therapeutic algorithm for Endometrial Cancer

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Direttore UOC Ginecologia Oncologia Medica IEO

Financial Disclosures

I have the following ongoing financial relationships with ACCME defined ineligible companies to report over the past 24 months:

- Employee: University of Milan-Bicocca and European Institute of Oncology IRCCS, Milan
- Consultant/Advisor: Roche; PharmaMar; AstraZeneca; Clovis Oncology; MSD; GlaxoSmithKline; Tesaro; Pfizer; Immunogen; Mersana; Eisai; Oncxerna, Nuvation Bio, Gilead, Regeneron
- Promotional Speaker: AstraZeneca, Tesaro, Novartis, Clovis, MSD, GlaxoSmithKline, Eisai
- Investigator/Researcher: AstraZeneca, PharmaMar, Roche
- Nonfinancial interests: Steering Committee Member for ESMO Clinical Guidelines, Chair Scientific Committee ACTO onlus

- Per questo incarico/relazione ho ricevuto un compenso/trasferimento di valore (TOV) da GSK.
- Negli ultimi 12 mesi ho svolto altri incarichi promozionali/non-promozionali per conto del Gruppo GlaxoSmithKline.

MaNGO
Mario Negri Gynecologic Oncology

GSK

Endometrial cancer is not one disease!!!

Bokhman : a dualistic model for endometrial tumorigenesis

TCGA molecular model

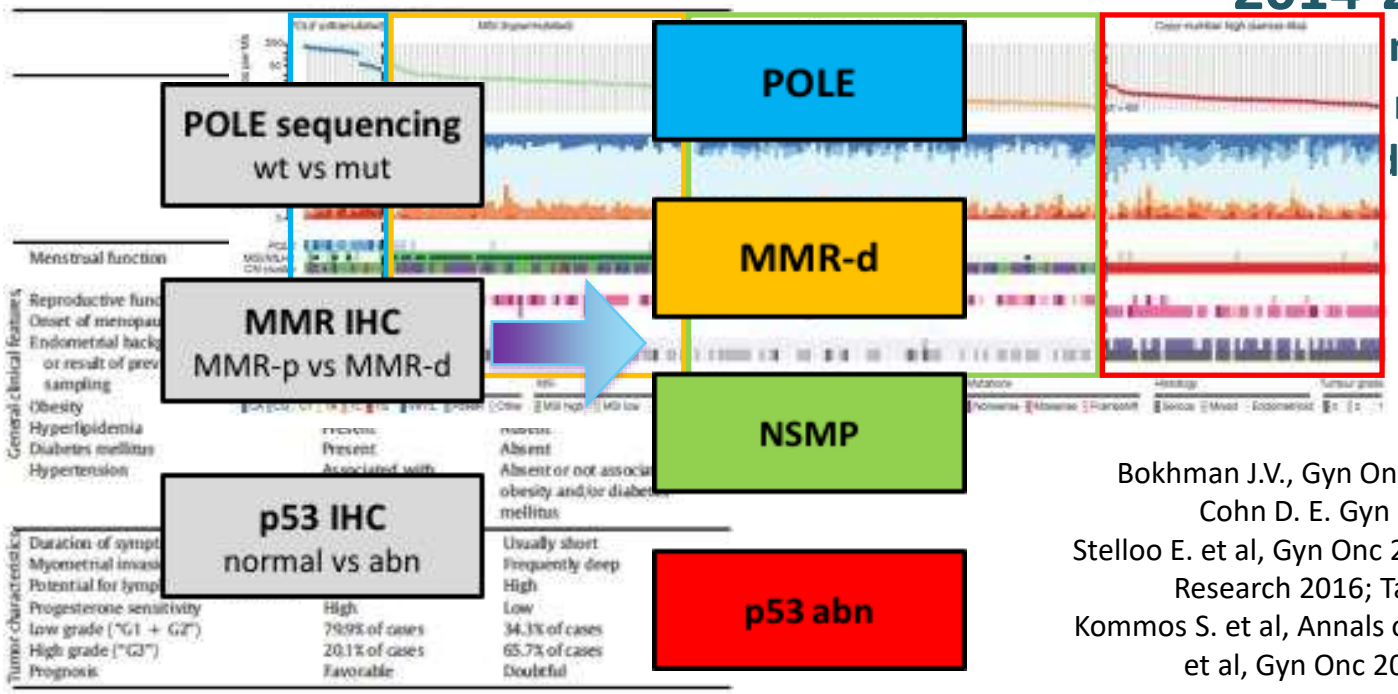
1983

2013

2014-2018

nsPORTEC: molecular

lel



Bokhman J.V., Gyn Onc 1983. Suarez A.A., Felix A.S., Cohn D. E. Gyn Onc 2017. TGCA, Nature 2013 Stelloo E. et al, Gyn Onc 2014; Stelloo et al, Clin Cancer Research 2016; Talhouk A. et al, Gyn Onc 2016; Kommos S. et al, Annals of Oncology, 2018: Abdulfatah et al, Gyn Onc 2019. Concin N. et al, IJGC 2021

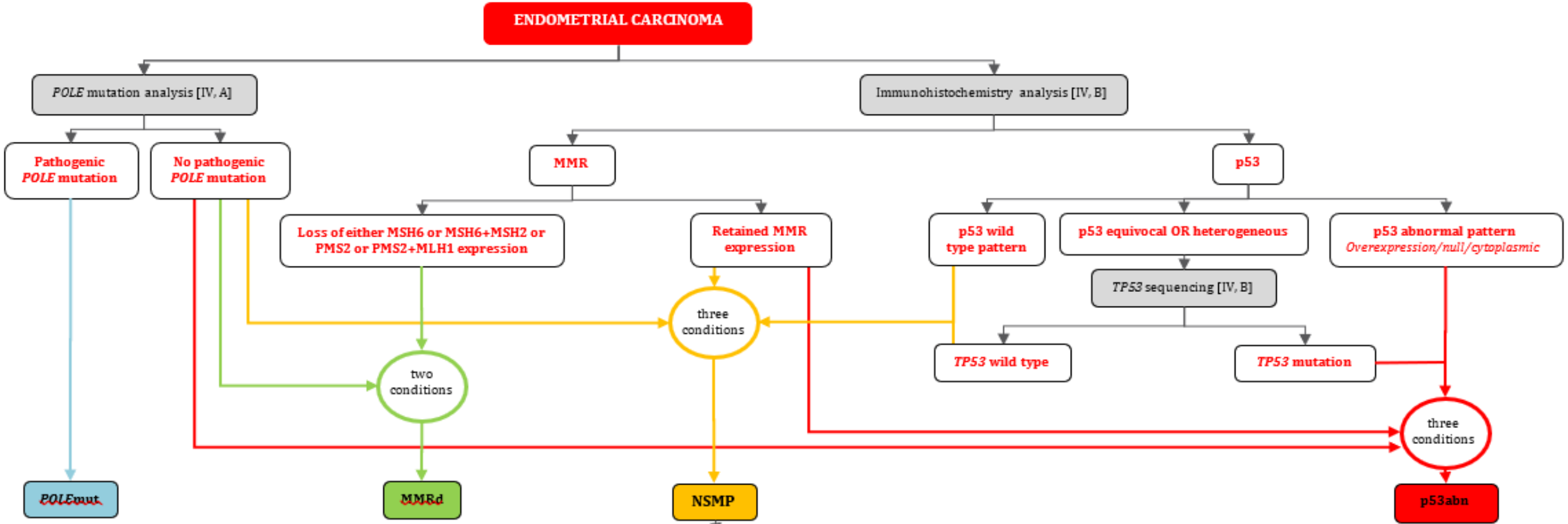
31 Members of multidisciplinary European Working Group

Project Chairs

ESGO
European Society of Gynaecological Oncology

European Society of Pathology

ESTRO
European Society for RADIOTHERAPY & ONCOLOGY



MULTIPLE CLASSIFIERS [IV, B]

- *POLEmut + MMRd ⇨ Classify as POLEmut*
- *POLEmut + p53abn ⇨ Classify as POLEmut*
- *MMRd + p53abn ⇨ Classify as MMRd*
- *POLEmut + MMRd + p53abn ⇨ Classify as POLEmut*

ER oestrogen receptor; neg negative; pos positive; MMR mismatch repair; MMRd mismatch repair deficient; NSMP no specific molecular profile; p53abn p53 abnormal.

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Systemic Therapy For Advanced and Recurrent Disease

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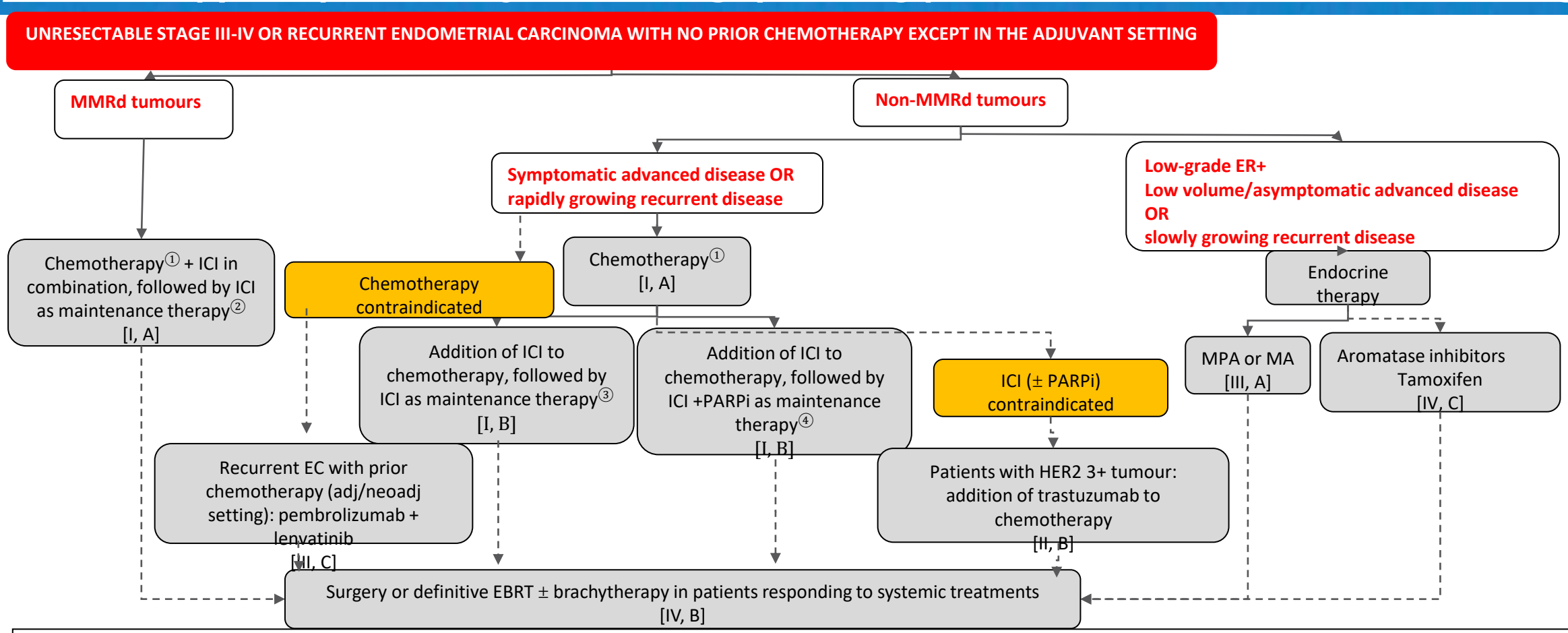
The European Voice of Gynaecological Oncology

First line systemic therapy in unresectable stage III-IV or recurrent endometrial carcinoma with no prior chemotherapy except in the adjuvant setting (including patients with residual disease after surgery)



①The standard chemotherapy regimen is carboplatin + paclitaxel.
②Immune checkpoint inhibitor (ICI): dostarlimab or durvalumab or pembrolizumab (drugs in alphabetical order).
③ICI: dostarlimab or pembrolizumab.
④ICI + poly(ADP-ribose) polymerase inhibitor (PARPi): durvalumab + olaparib.
Adj/neoadj adjuvant/neoadjuvant; EBRT external beam radiotherapy; ER+ estrogen receptor positive; MA megestrol acetate; MMRd mismatch repair deficiency, MPA medroxyprogesterone acetate; non-MMRd non-mismatch repair deficiency; NSMP non-specific molecular profile.

Endocrine Therapy of Endometrial Cancer

Drug	Reference	Number Patients	Median OR (%)	PFS	OS
Progestin	Piver (1980), Podratz (1984), Thigpen (1999)	568 (114-155)	24 (16-37)	3	11
Tamoxifen		179 (17-68)	23 (17-68)	2-12	6-16
Other SERM/ SERD		117 (29-53)	16 (10-31)	2-4	13
Aromatase inhibitor		106 (23-51)	9 (9-10)	1-3	6-11
Progestin + Tamoxifen	Kendina (1984), Pandya (2001), Fiorica (2004), Withney (2004)	245 (42-89)	30 (19-37)	3-12	9-16
Endocrine plus mTORi	Fleming (2014), Slomovitz (2015)	56 (21-35)	25 (14-32)	3-4	10-14
Endocrine plus Cdk4/6i	Mirza (2020)	77	64 DCR	8	-

ORR: 9-25%
PFS: 1-12 months
OS: 6-16 months

Modified from Willem Jan Van Weelden, et al., Front. Oncol., 2019, and Gaducci and Cosio, Cancers 2021

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DOI: 10.1111/1471-0528.17331

BJOG An International Journal of Obstetrics and Gynaecology

SYSTEMATIC REVIEW

The effect of progestin therapy in advanced and recurrent endometrial cancer: A systematic review and meta-analysis

Willem Jan van Weelden[1] | Philine B. Birkendahl[1] | Roy I. Lalisang[2,3] | Joanna IntHout[4] | Roy F. P. M. Kruitwagen[3,5] | Andrea Romano[3] | Johanna M. A. Pijnenborg[1]

- Twenty- six studies (1639 patients)
- ORR of progestin therapy was 30% (95% CI 25– 36)
- The clinical benefit rate was 52% (95% CI 42– 61)
- In PR- positive EC, the ORR was 55%, compared with 12% in PR- negative disease (risk difference 43%, 95% CI 15– 71).
- Severe toxicity occurred in 6.5%.

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SYSTEMIC THERAPY

FIRST LINE SYSTEMIC THERAPY

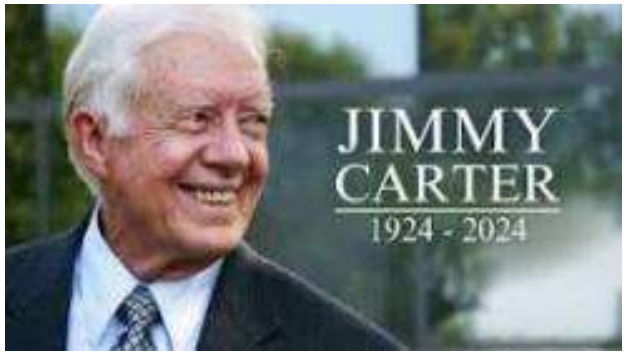
in unresectable stage III/IV or recurrent EC with no prior chemotherapy except in the adjuvant setting (including patients with residual disease after surgery)

- The MMR status should be taken into consideration to determine the choice of first line therapy:

  - Patients with MMRd tumours should be offered an ICI e.g. dostarlimab or durvalumab or pembrolizumab (drugs mentioned in alphabetical order) in combination with carboplatin-paclitaxel chemotherapy followed by ICI as maintenance therapy [I, A].

The immunotherapy «Miracle»

Bob Marley died at the age of 36, **in 1981**, of lung and brain metasases from melanoma



Jimmy Carter was diagnosed with melanoma, with liver and brain metasases **in 2015**, at the age 90. He received immunotherapy and died 10 years later at age 100

ENDOMETRIAL CANCER: A CINDERELLA STORY

Once upon a time…

Carboplatin

and paclitaxel

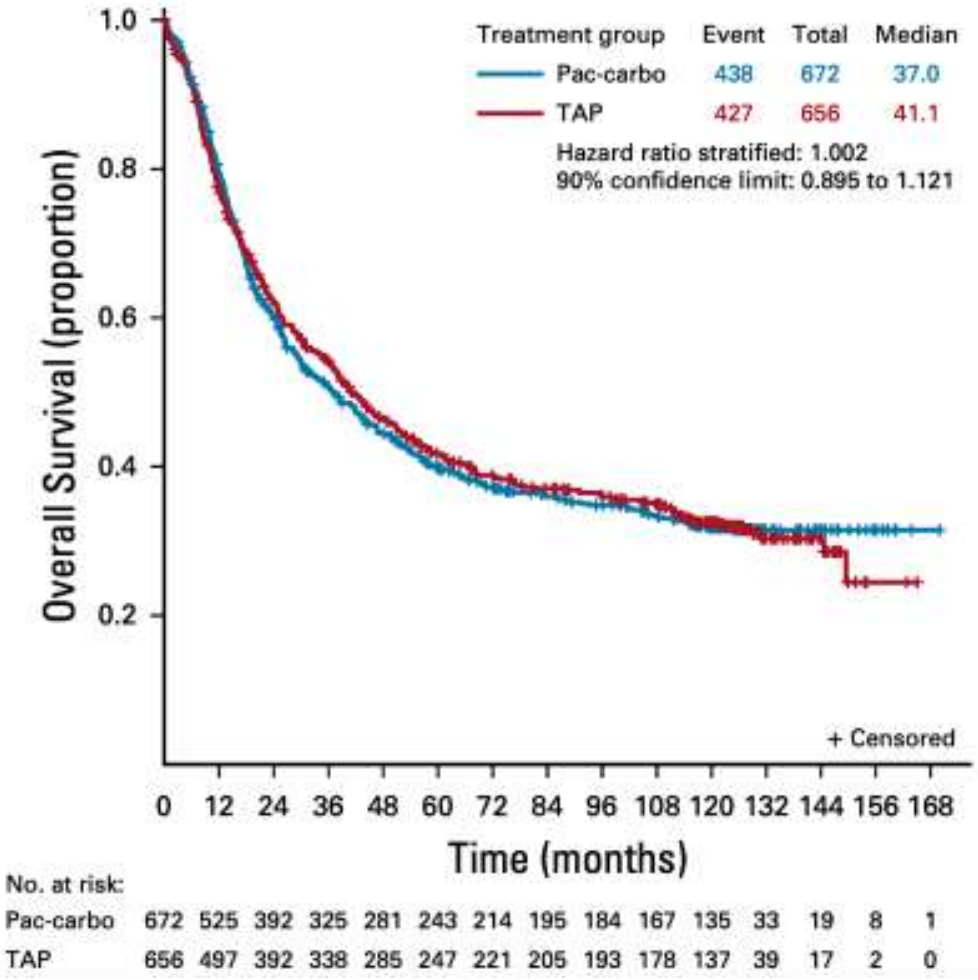
Hormone therapy

Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209)

David S. Miller, MD[1]; Virginia L. Filiaci, PhD[2]; Robert S. Mannel, MD[3]; David E. Cohn, MD[4]; Takashi Matsumoto, MD[5]; Krishnansu S. Tewari, MD[6]; Paul DiSilvestro, MD[7]; Michael L. Pearl, MD[8]; Peter A. Argenta, MD[9]; Matthew A. Powell, MD[10]; Susan L. Zweizig, MD[11]; David P. Warshal, MD[12]; Parviz Hanjani, MD[13]; Michael E. Carney, MD[14]; Helen Huang, MS[2]; David Cella, PhD[15]; Richard Zaino, MD[16]; and Gini F. Fleming, MD[17]

Journal of Clinical Oncology
An American Society of Clinical Oncology Journal

2020

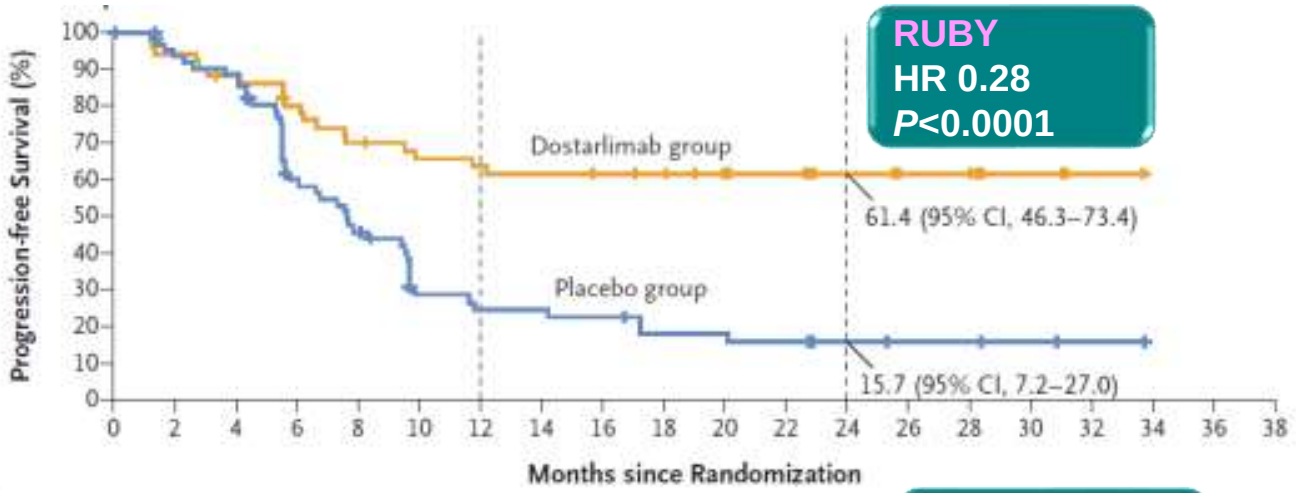


- **For decades**, the standard 1L therapy for advanced or recurrent EC has been carboplatin and paclitaxel with **LIMITED EFFICACY (5-year OS: 15-20%)**.

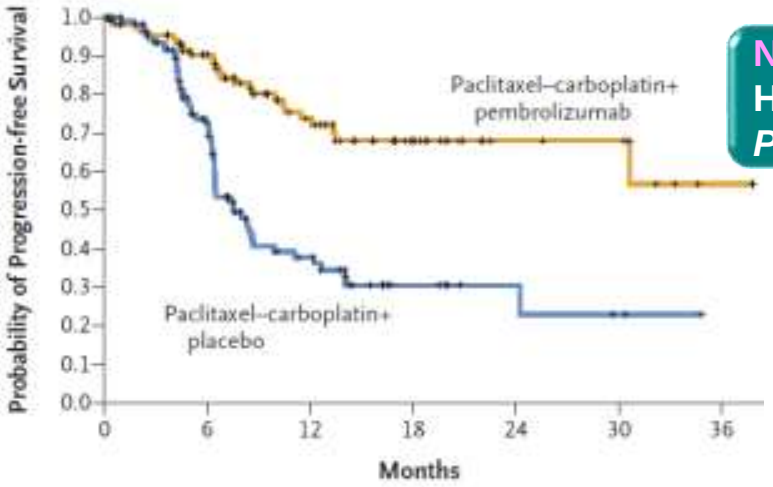
- The GOG-209 study was a non-inferiority study. First presented in 2012 and then published in 2020.

First-line Treatment

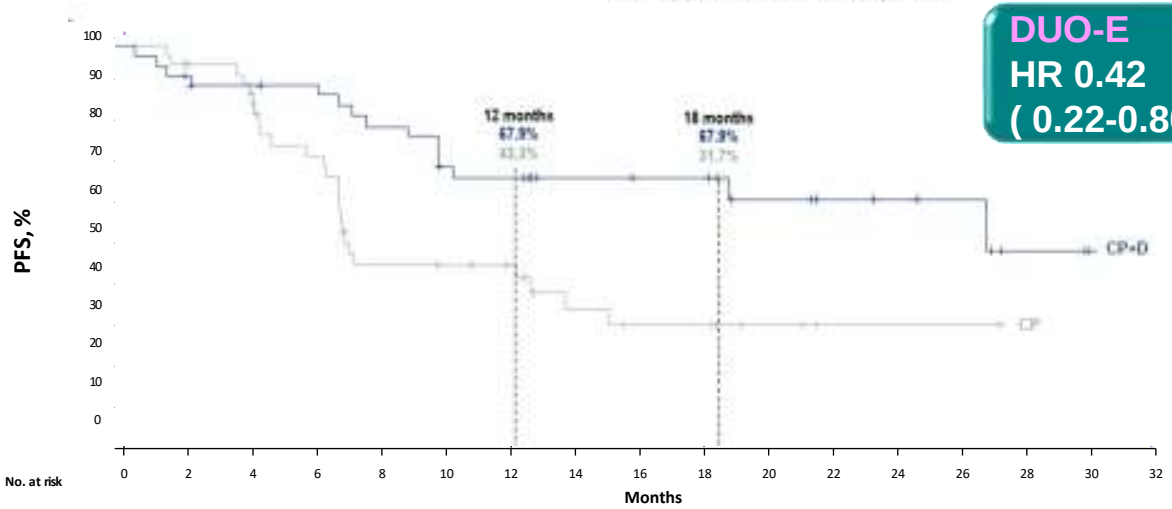
Immune Checkpoint Inhibitor plus Chemotherapy in First-line Endometrial Cancer: PFS in dMMR Tumors



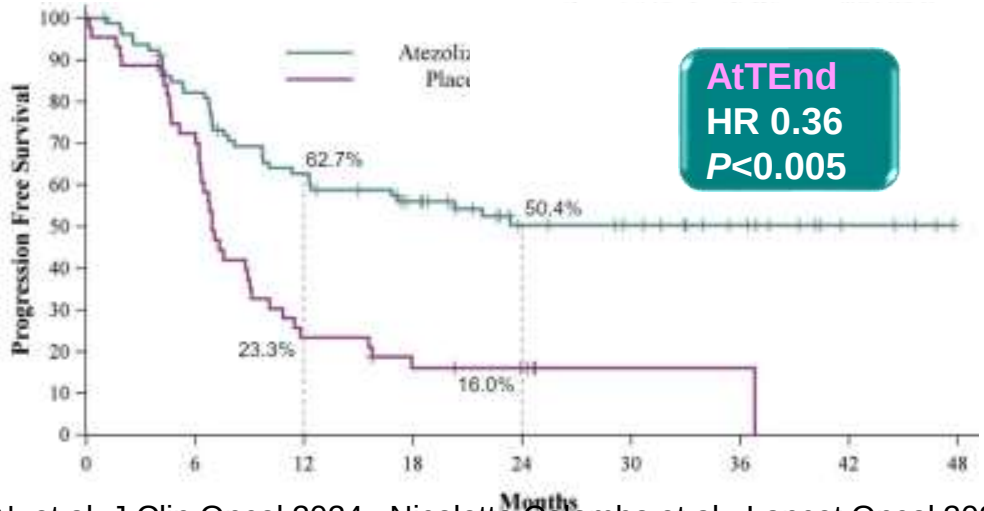
RUBY
HR 0.28
***P*<0.0001**



NRG-GY018
HR 0.30
***P*<0.0001**



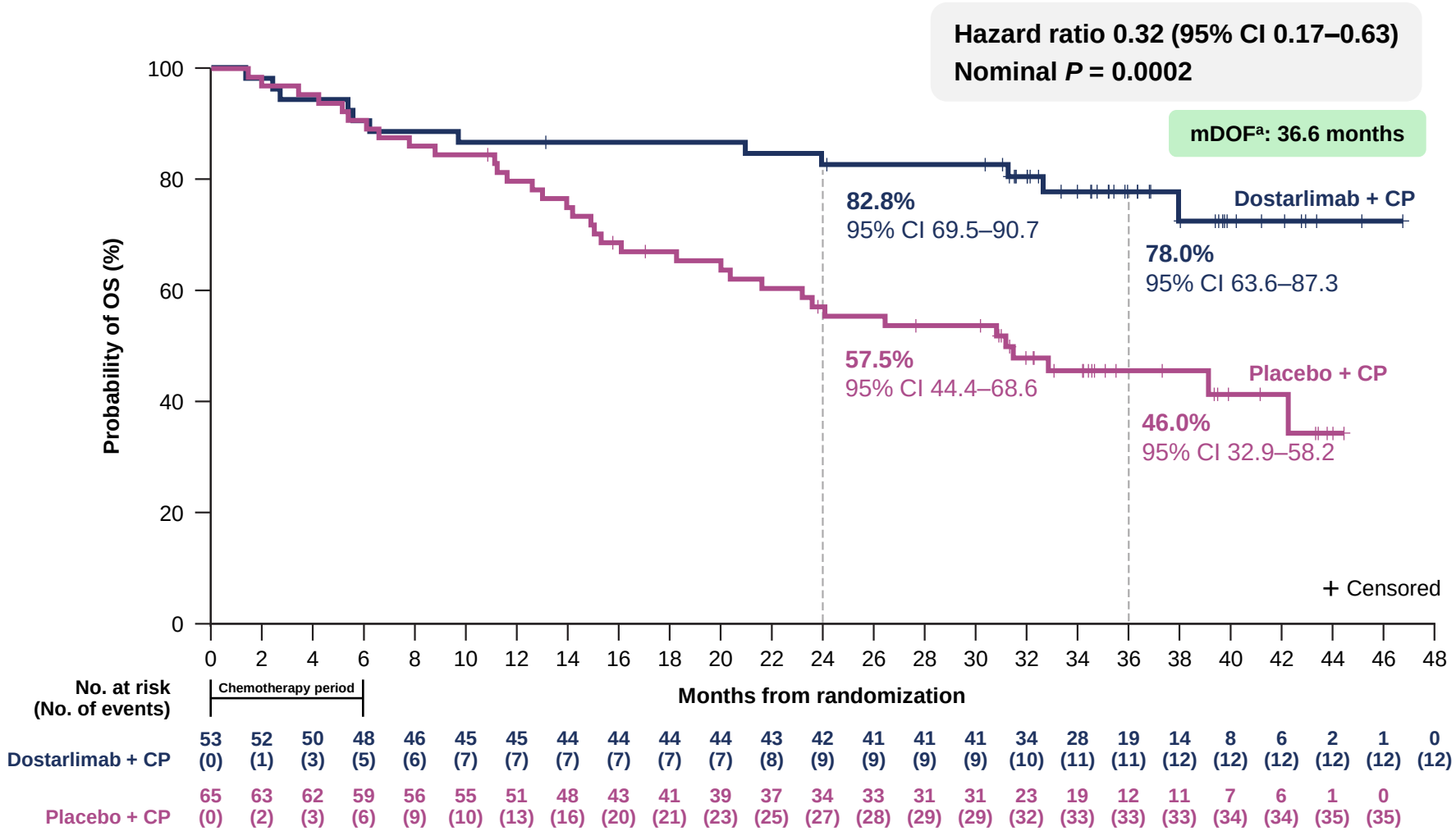
DUO-E
HR 0.42
(0.22-0.80)



AtTEnd
HR 0.36
***P*<0.005**

Mansoor R. Mirza et al. NEJM August 2023, Ramez N. Eskander et al. NEJM August 2023, Westin SN, et al. J Clin Oncol 2024, Nicoletta Colombo et al., Lancet Oncol 2024

OS (dMMR/MSI-H population) – prespecified exploratory subgroup analysis[1,2]



	No. with event, %	Median (95% CI), mo
Dostarlimab + CP	22.6	NE (NE–NE)
Placebo + CP	53.8	31.4 (20.3–NE)
OS maturity, %		40

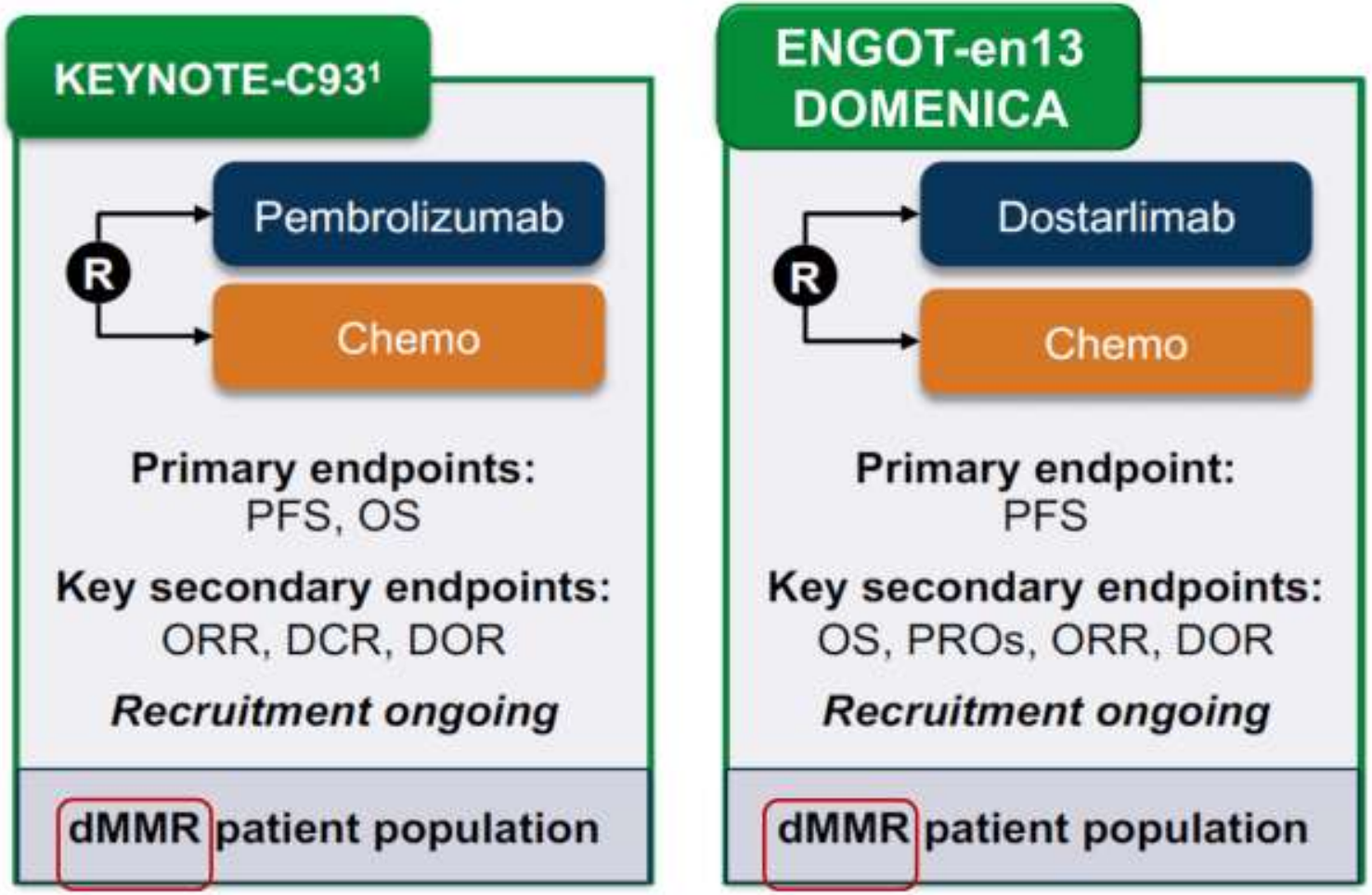
%, (n/N)	Dostarlimab + CP	Placebo + CP
Received any FUACT	28.3 (15/53)	60.0 (39/65)
Received subsequent IO	15.1 (8/53)	41.5 (27/65)
Proportion of FUACT that was IO	53.3 (8/15)	69.2 (27/39)

[a]mDOF, median duration of follow-up, is defined as time in months from randomization to data cutoff date; expected mDoF: 31.0–48.7 months.
CI = confidence interval; CP = carboplatin-paclitaxel; dMMR = mismatch repair deficient; FUACT = follow-up anticancer therapy; IA1 = interim analysis 1; IO = immunotherapy, mOS = median overall survival; MSI-H = microsatellite instability-high; MSS = microsatellite stable;
MMRp = mismatch repair proficient; mo = months; NE = not estimable; No. = number; OS = overall survival.

1. Used with permission of The Authors, from Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial, Powell MA, et al., 35, 2024; permission conveyed through Copyright Clearance Center, Inc. 2. Powell MA, et al. presented at the SGO Annual Meeting on Women's Cancer 2024 (Oral Presentation), 16–18 Mar, San Diego, CA.

WILL ICIs alone replace chemotherapy in the front line setting of dMMR EC ?

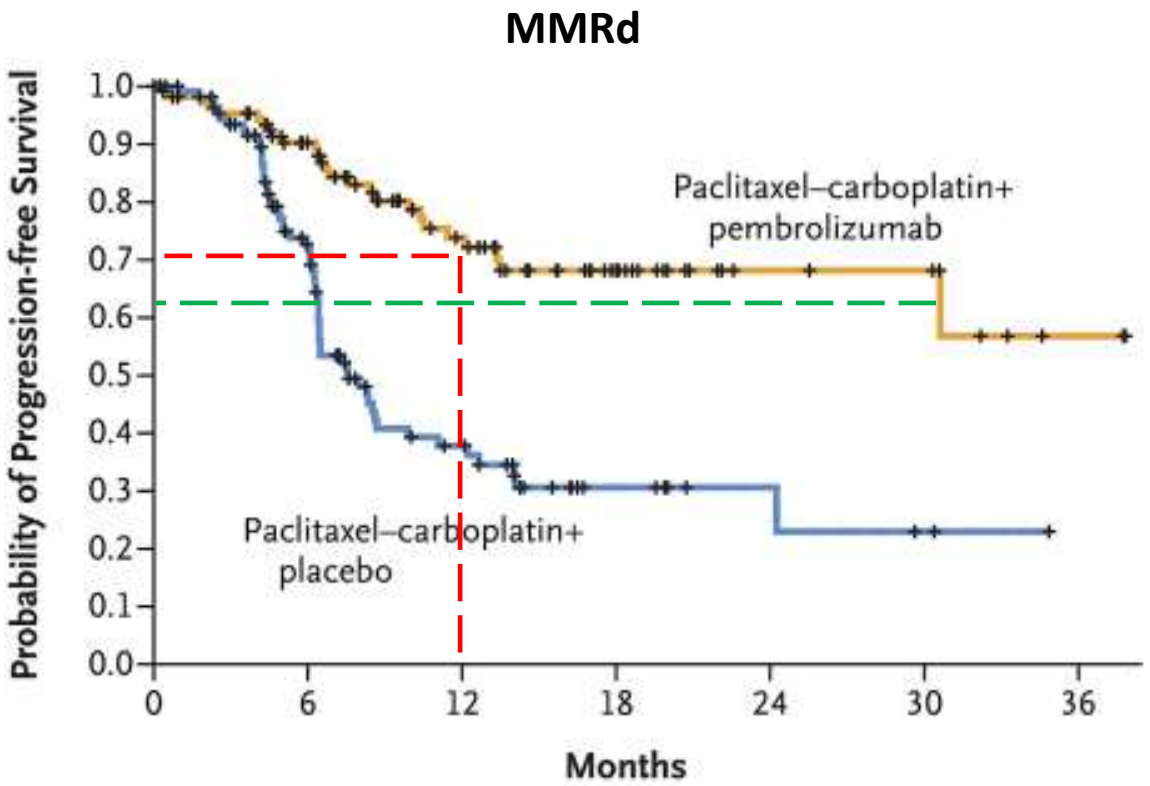
dMMR EC :Do wee need chemo in this group?



I contenuti si riferiscono a prodotti p disegni di studi clinici investigazionali

Can we do better?

How to personalize?

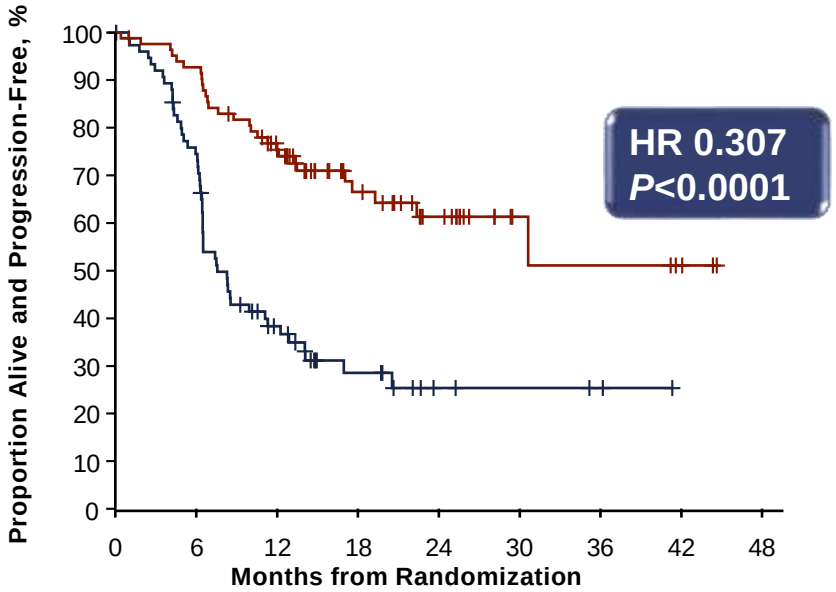


~30% "bad MMRd" **~70% "good MMRd"**

NRG 018: PFS by Methylation Status in dMMR Population

Methylation
Pembro + CP vs Placebo + CP

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

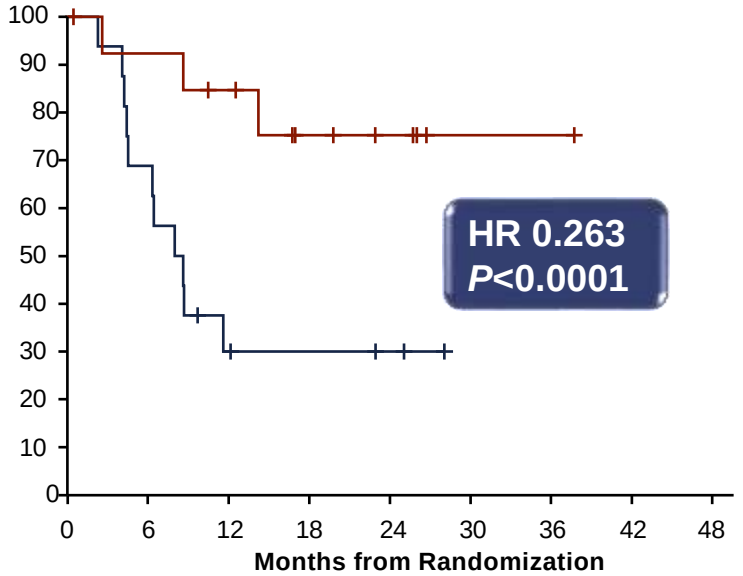


Number at risk (Cumulative number censored)

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

No Methylation
Pembro + CP vs Placebo + CP

	Events n/N	Median (95% CI), mo	HR (95% CI)
Placebo + CP	11/17	8.3 (4.4–NR)	0.263 (0.07–0.99) *P* = 0.0172
Pembro + CP	3/13	NR (14.2–NR)	

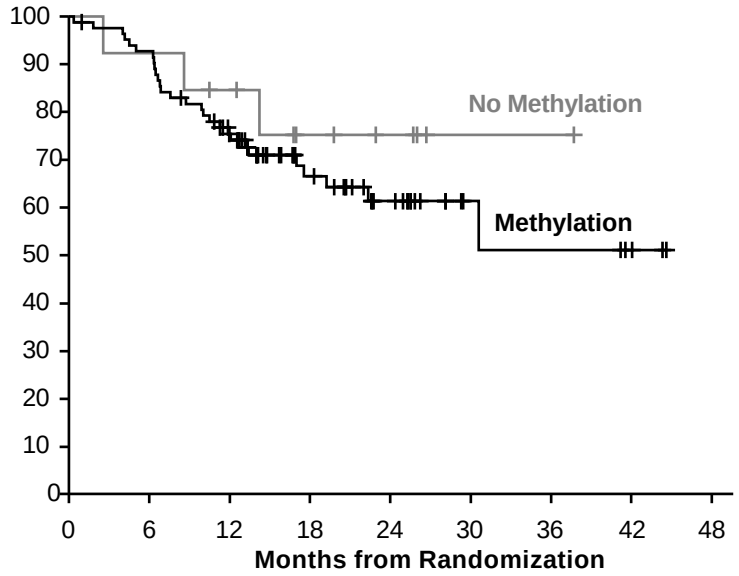


Number at risk (Cumulative number censored)

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

Methylation Status
Pembro + CP Arm

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



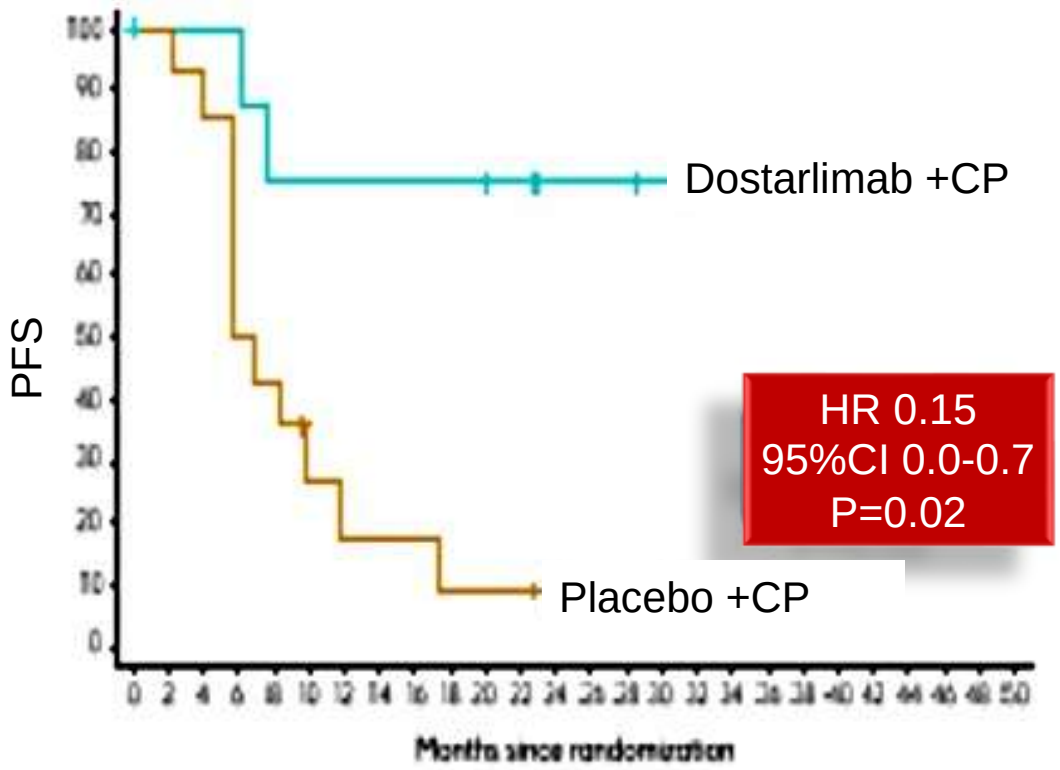
Number at risk (Cumulative number censored)

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

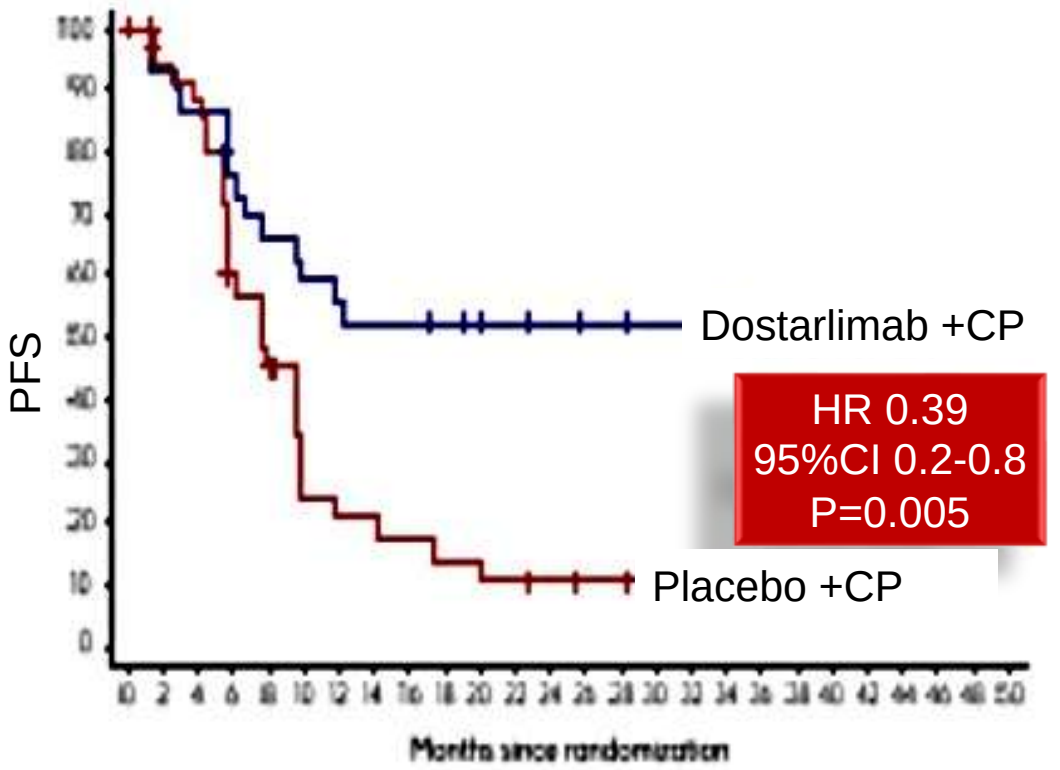
Eskander, ESGO 2023

RUBY: Dostarlimab response among Hypermethylated and Mutated dMMR Endometrial Carcinoma

Mutated-dMMR

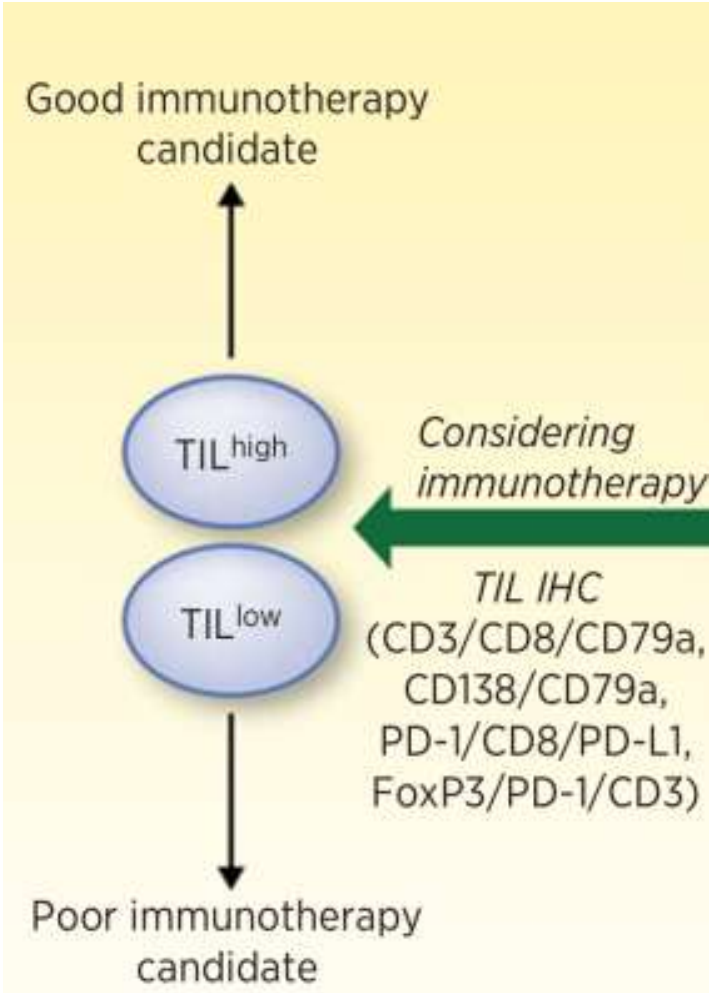


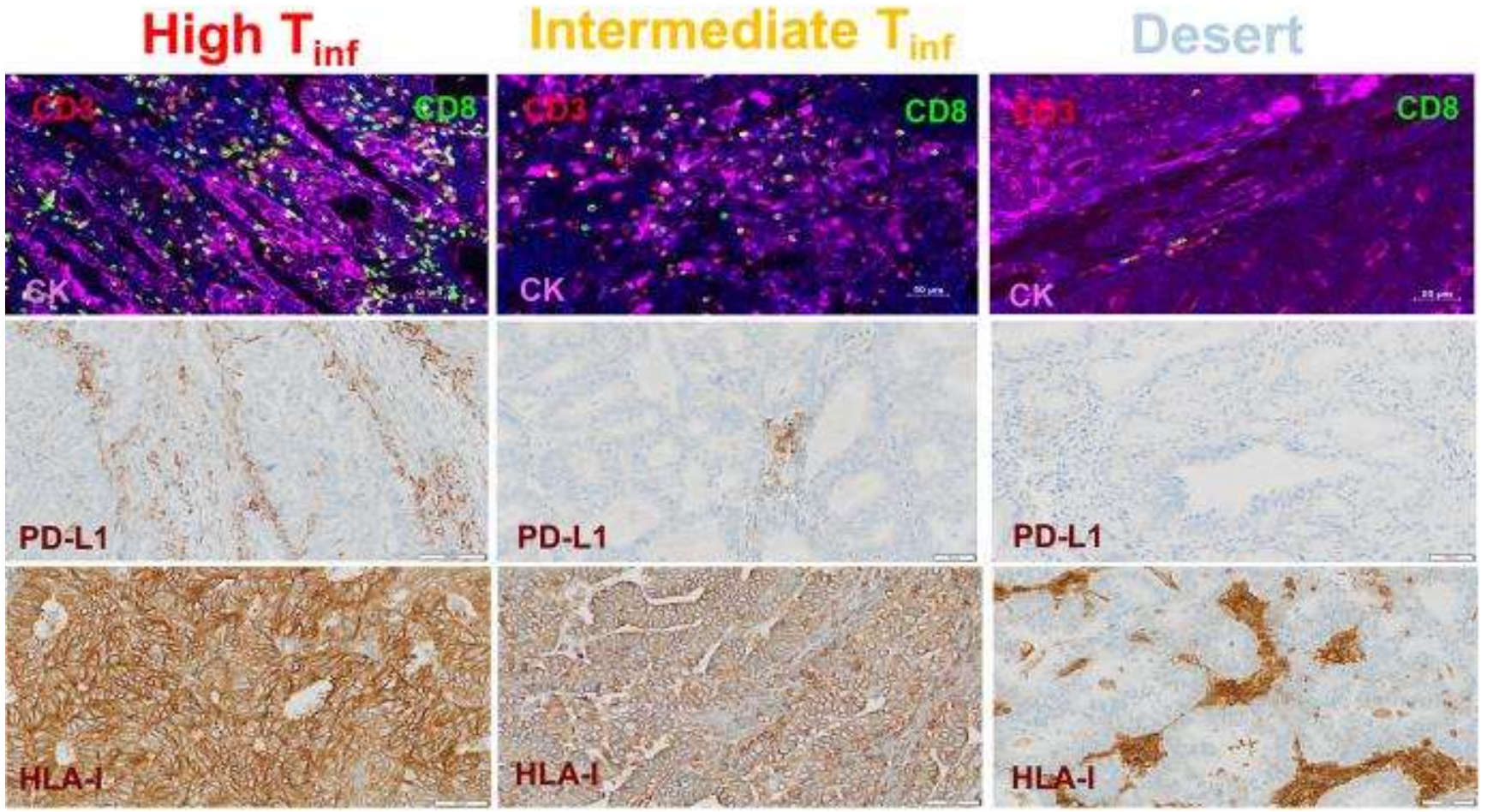
Methylated-dMMR



Mansoor Mirza et al. ASCO 2024

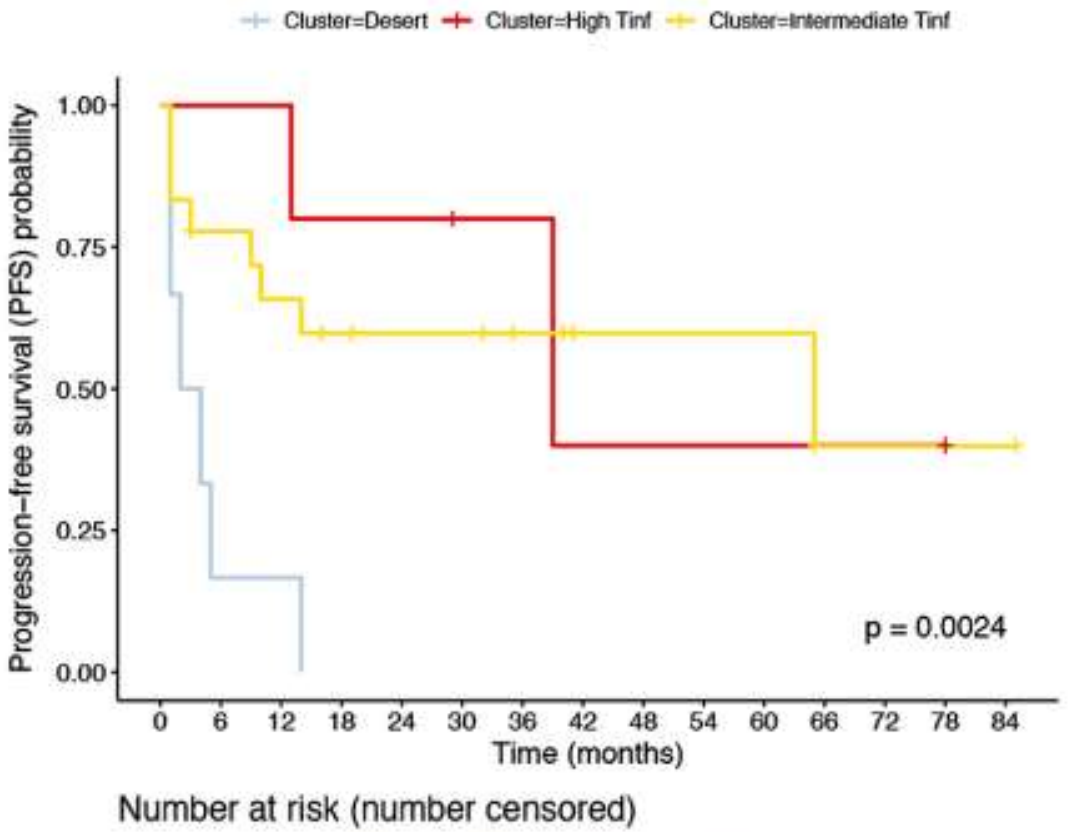
Immune predictors of response to immune checkpoint inhibitors in MMRd EC

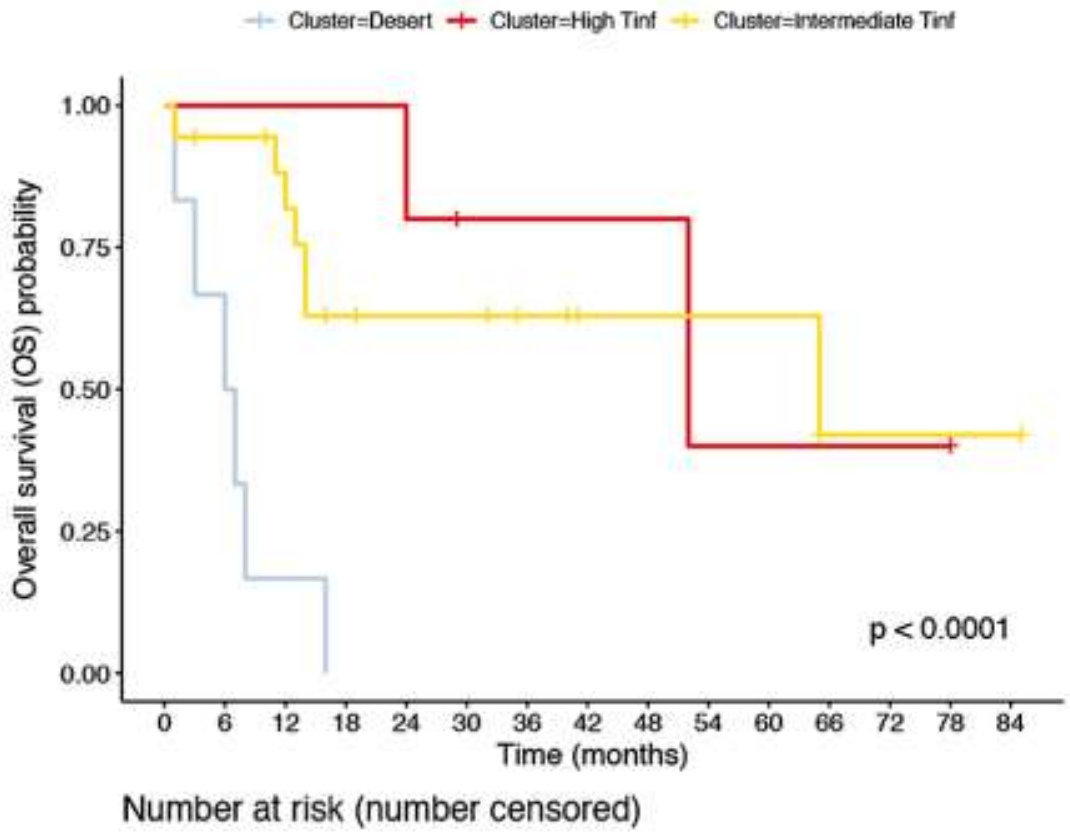




Grau Bejar JF, Alexandra Leary, et al. Journal for ImmunoTherapy of Cancer 2024; Mary M. Mullen and David G. Mutch, Clin Cancer Res 2019

Immune predictors of response to immune checkpoint inhibitors in MMRd EC





Assessment of immune response (rather than molecular subtype) may better predict response to immunotherapy

Grau Bejar JF, Alexandra Leary, et al. Journal for ImmunoTherapy of Cancer 2024

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SYSTEMIC THERAPY

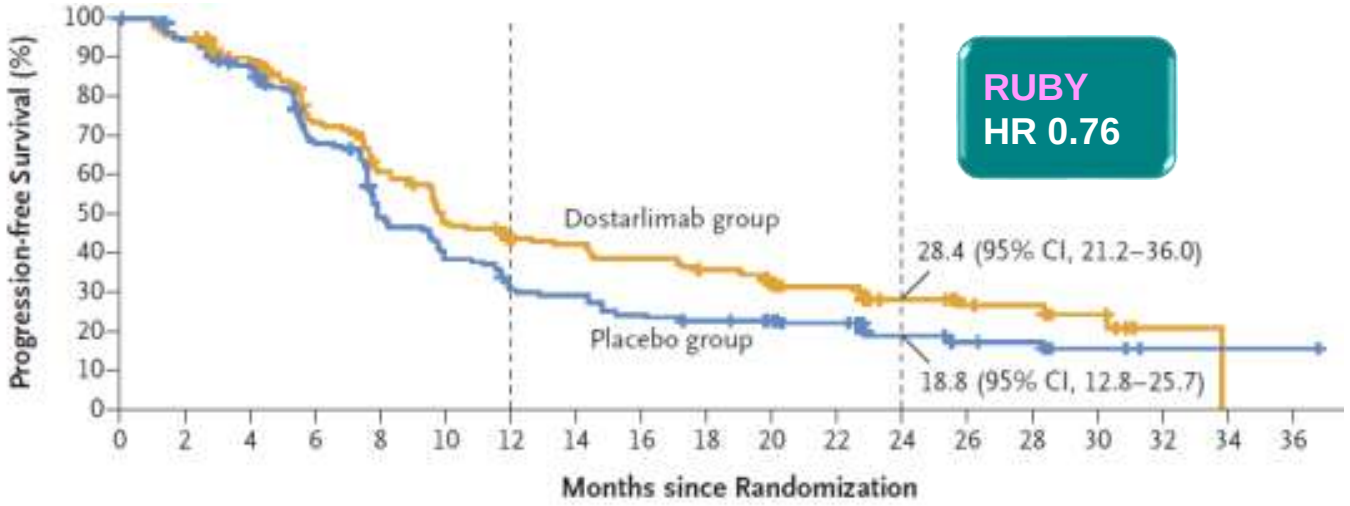
FIRST LINE SYSTEMIC THERAPY

in unresectable stage III/IV or recurrent EC with no prior chemotherapy except in the adjuvant setting (including patients with residual disease after surgery)

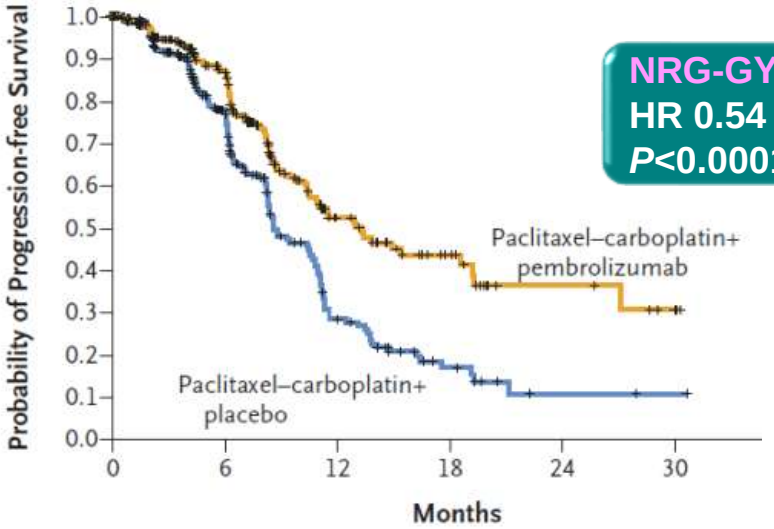
- Patients with non-MMRd tumours with rapidly growing/symptomatic disease should be offered carboplatin- paclitaxel chemotherapy [I, A]. The addition of ICI to chemotherapy followed by ICI as maintenance therapy, e.g. dostarlimab or pembrolizumab (drugs mentioned in alphabetical order), or the addition of ICI followed by a combination of ICI and PARPi as maintenance therapy, i.e. durvalumab and olaparib, can be considered [I, B].

www.esgo.org

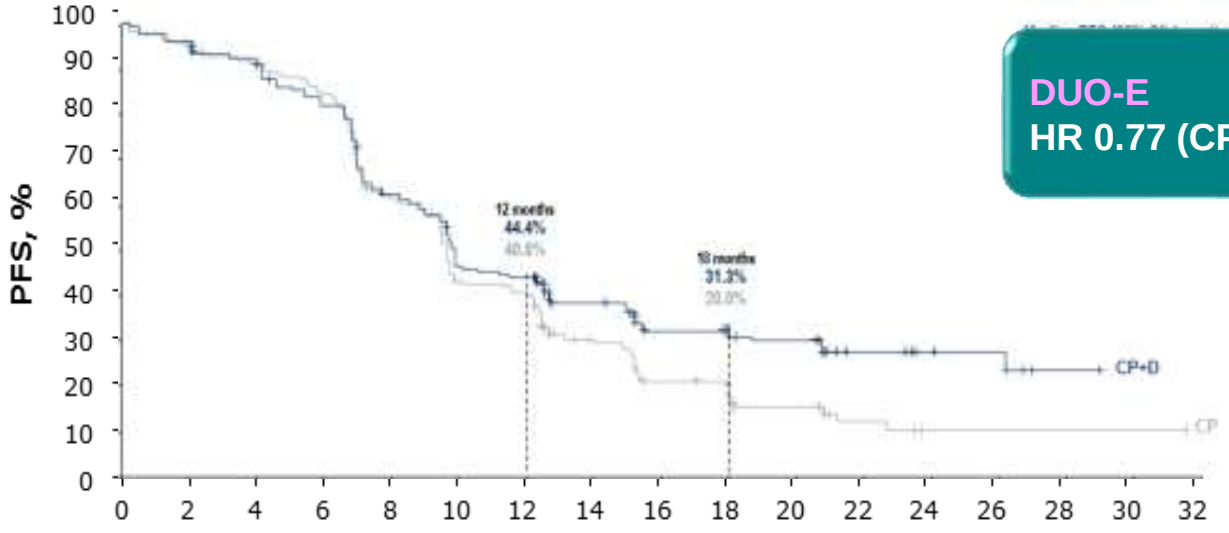
Immune Checkpoint Inhibitor plus Chemotherapy in First-line Endometrial Cancer: PFS non-**MMRd** Tumors



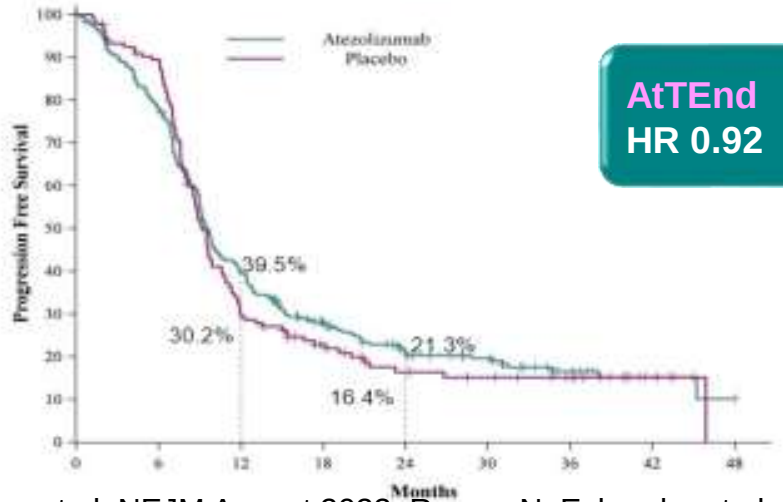
RUBY
HR 0.76



NRG-GY018
HR 0.54
***P*<0.0001**



DUO-E
HR 0.77 (CP↔CP+D)



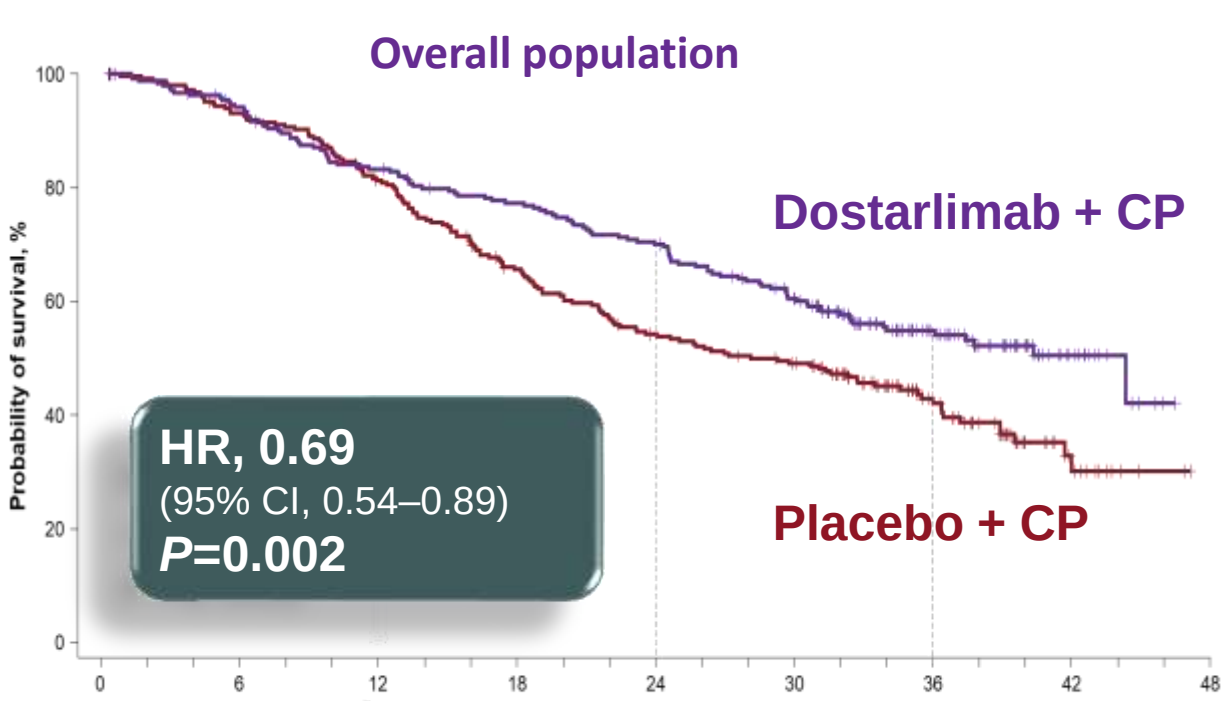
AtTEnd
HR 0.92

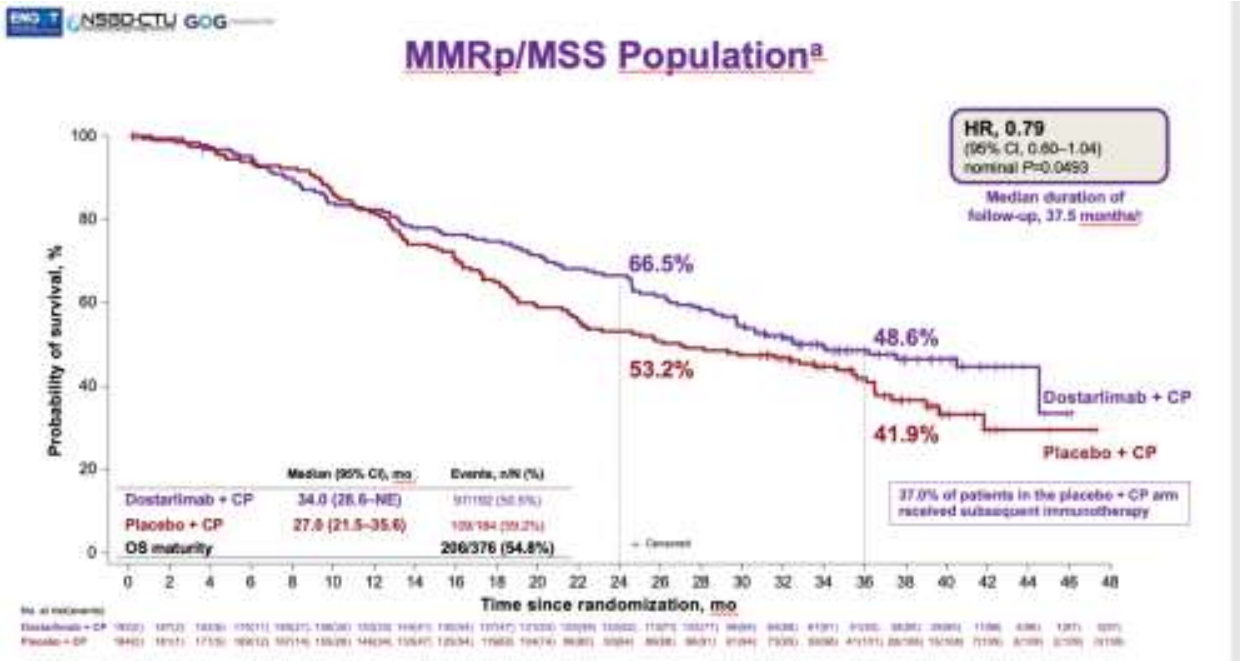
Mansoor R. Mirza et al. NEJM August 2023, Ramez N. Eskander et al. NEJM August 2023, Nicoletta Colombo et al., Lamnvet Oncology 2024, Shannon N. Westin, et al. ESGO 2023

*JEMPERLI è attualmente approvato in Europa (dalla European Medicines Agency, EMA) in associazione a carboplatino e paclitaxel per il trattamento di prima linea di pazienti adulte affette da CE primario avanzato o ricorrente e che sono candidate per la terapia sistemica. Tuttavia, in Italia, questa indicazione non è rimborsata per le pazienti con CE primario avanzato o ricorrente in assenza di deficit del sistema di mismatch repair (MMR proficient, MMRp)/con stabilità dei microsatelliti (Microsatellite Stable, MSS) e che sono candidate per la terapia sistemica.

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer: OS

RUBY/ENGOT-en6



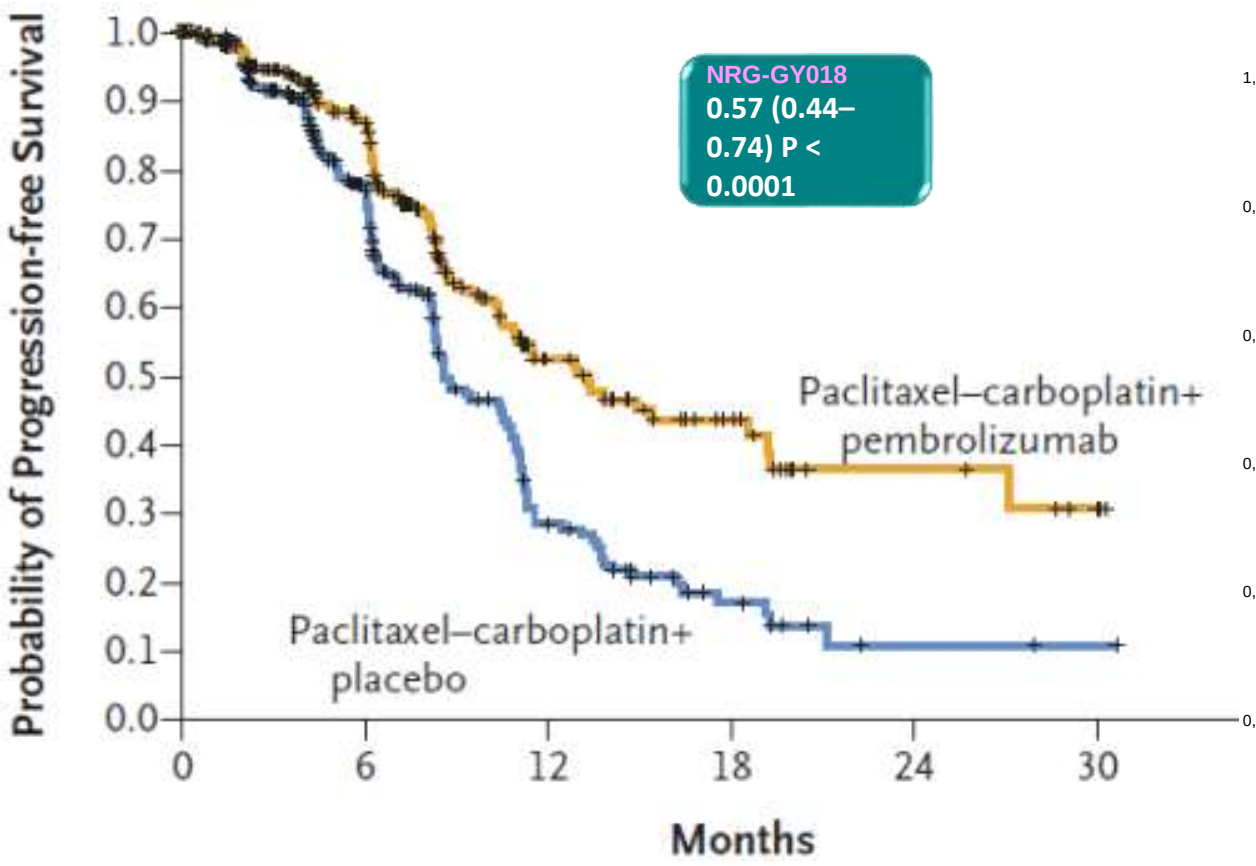


Powell, M.A. et al. Annals of Oncology, Volume 35, Issue 8, 728 – 738, 2024;

A clear trend favoring dostarlimab was observed, suggesting a **21% reduction in the risk of death.** This analysis was exploratory , so the P value less than 0.05 is **not formally considered statistically significant**

*JEMPERLI è attualmente approvato in Europa (dalla European Medicines Agency, EMA) in associazione a carboplatino e paclitaxel per il trattamento di prima linea di pazienti adulte affette da CE primario avanzato o ricorrente e che sono candidate per la terapia sistemica. Tuttavia, in Italia, questa indicazione non è rimborsata per le pazienti con CE primario avanzato o ricorrente in assenza di deficit del sistema di mismatch repair (MMR proficient, MMRp)/con stabilità dei microsatelliti (Microsatellite Stable, MSS) e che sono candidate per la terapia sistemica.

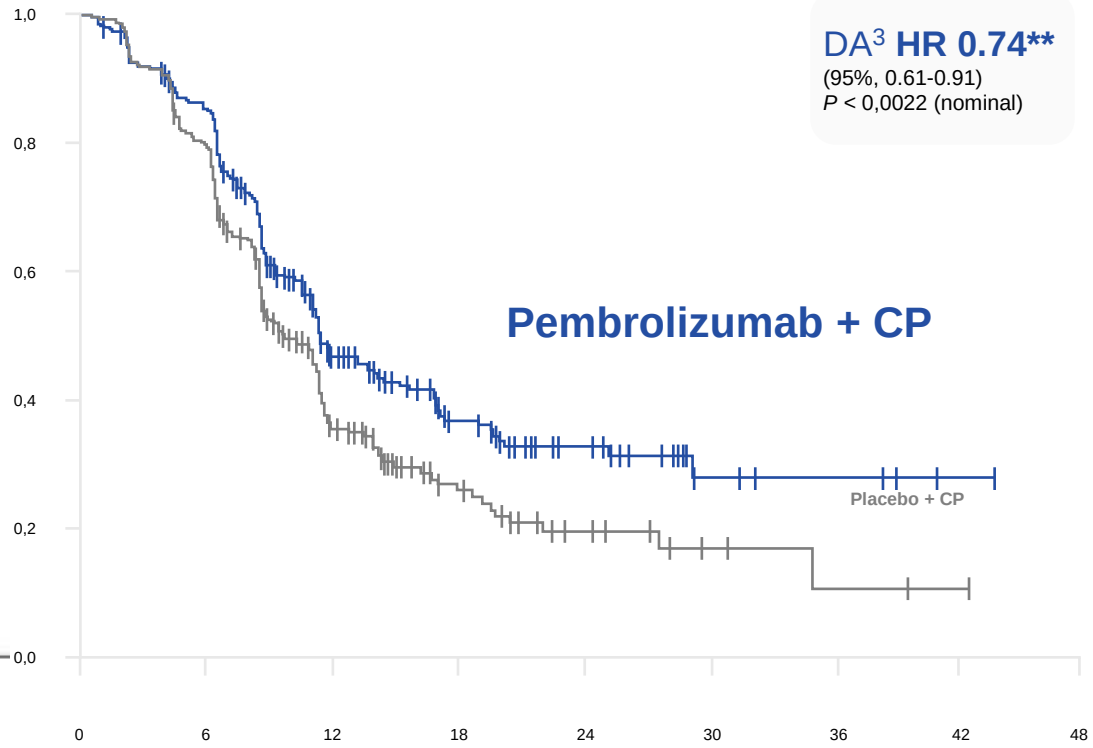
NRG-018: non-MMRd population



Ramez N. Eskander et al. NEJM August 2023

NRG-GY018[2,3] – Data maturity: NA

Updated Descriptive Analysis (DA)**. Median follow-up: **15.3 months**

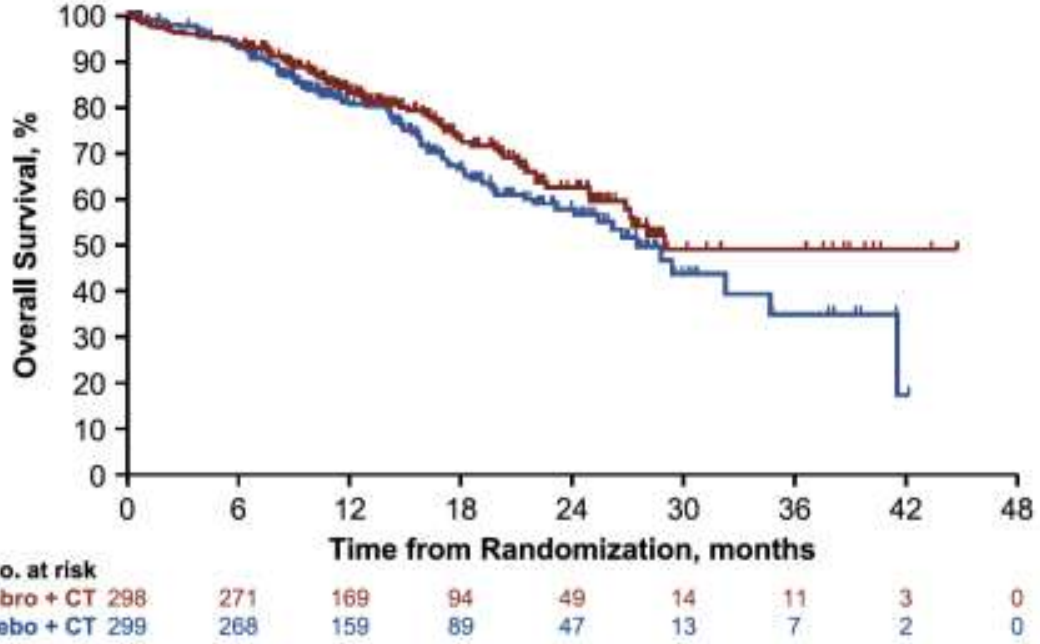


DA, descriptive analysis at the request of the European Regulatory Authority after unblinding. DCO 18.08.2023

NRG-018: OS in non-MMRd population

A)

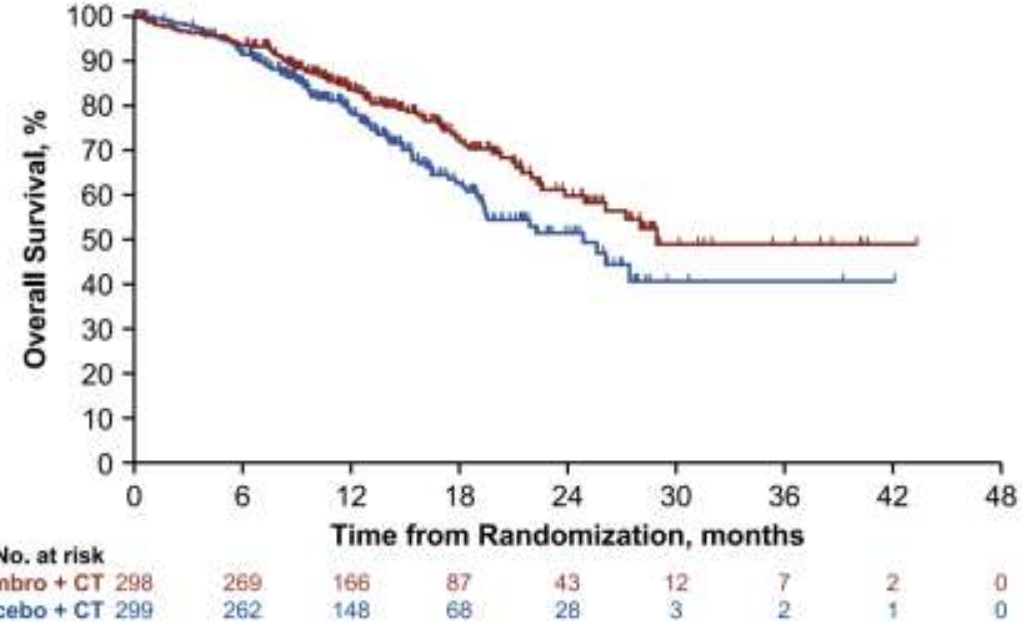
	Events, n/N	Follow-up Duration[a], median (range), mo	Median OS (95% CI), mo	HR (95% CI)[b], *P*-value[c]
Pembro + CT	77/298	15.7 (0.5–45.4)	28.9 (26.8–NR)	**0.80 (0.59–1.08)**
Placebo + CT	92/299	15.0 (0.9–45.6)	28.7 (24.0–34.6)	***P* = 0.0683**



Sensitivity analysis in the pMMR population at ad hoc analysis

C)

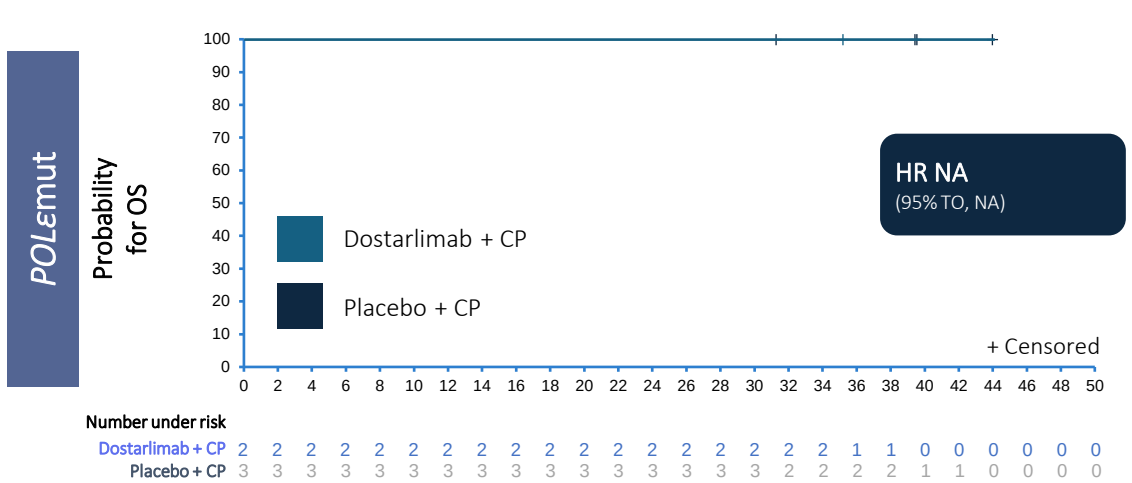
	Events, n/N	Median OS (95% CI), mo	HR (95% CI)[b]
Pembro + CT	77/298	28.9 (24.9–NR)	**0.70 (0.50–0.98)**
Placebo + CT	92/299	24.8 (19.3–NR)	

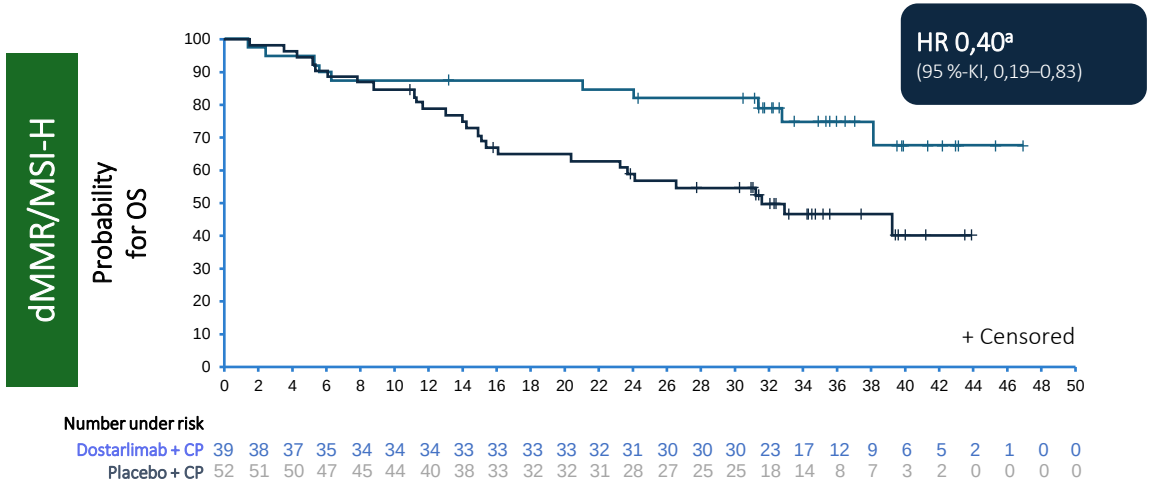


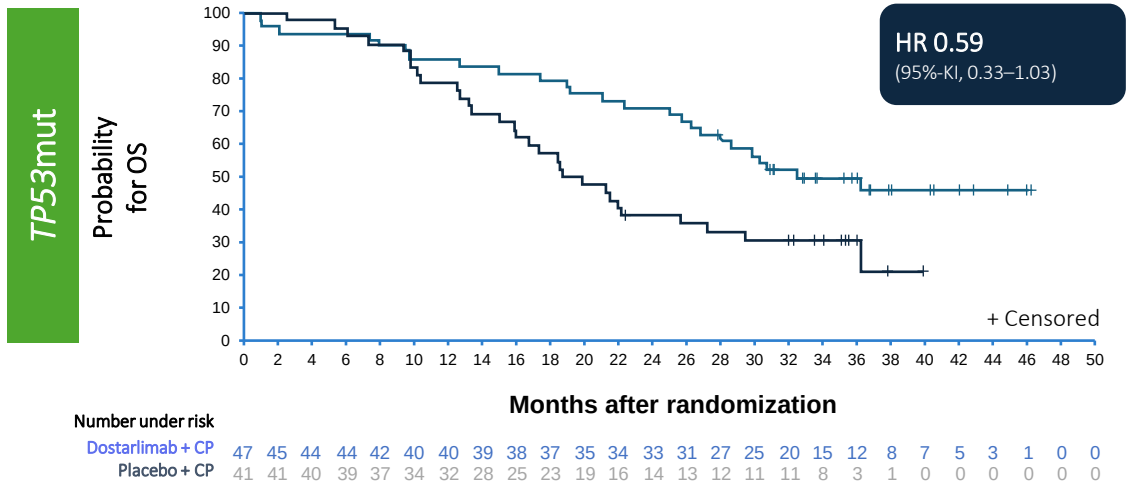
Ramez Eskander et al. Nat Med. 2025 May;31(5):1539-1546.

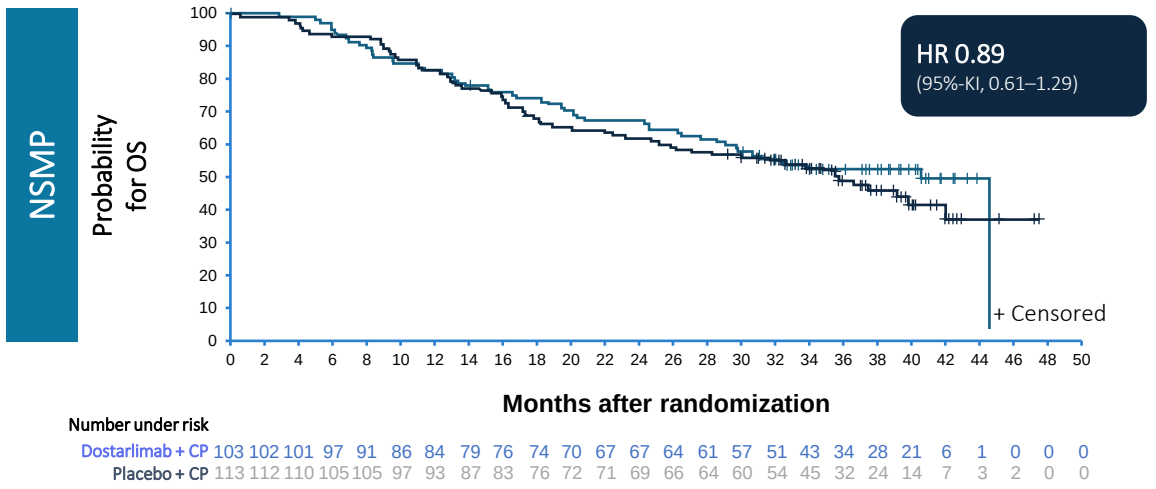
Can we identify the best responders among the non-MMRd patients?

RUBY: OS according to molecular subgroup









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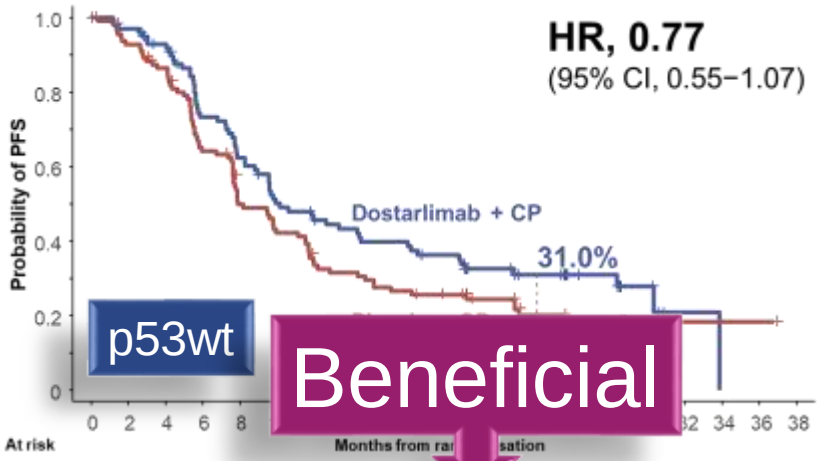
[a]Analysis shown on this slide is post hoc exploratory analysis of 91 patients with dMMR/MSI-H EC and WES results. In the prespecified OS analysis of the dMMR/MSI-H population (n=118), shown earlier, HR was 0.32.
CI, confidence interval; CP, carboplatin-paclitaxel; Dost, dostarlimab; dMMR, mismatch repair deficient; EC, endometrial cancer; HR, hazard ratio; MSI-H, microsatellite instability-high; mut, mutated; NA, not applicable; NSMP, no specific molecular profile; OS, overall survival; PBO, placebo; POLε, polymerase epsilon; TP53, tumor protein 53; WES, whole-exome sequencing.
Powell MA, et al. Presented at the ESMO Gynaecological Cancers Meeting 2024. Presentation 37MO.

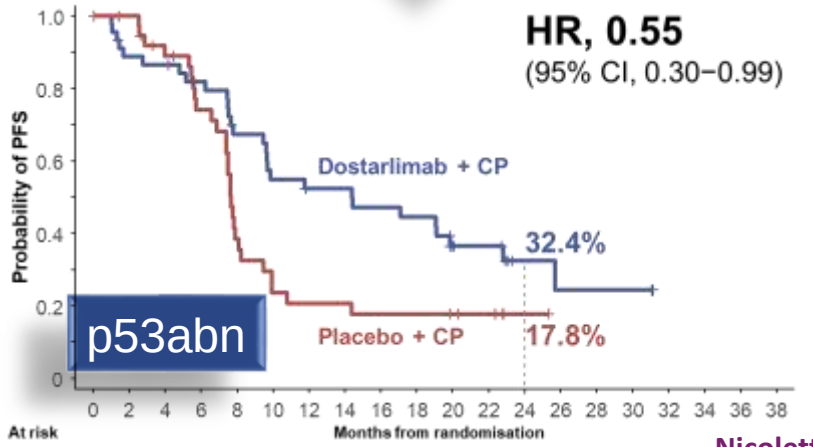
IO and PFS in non-dMMR TP53mut and TP53wt

ENGOT-en6/RUBY



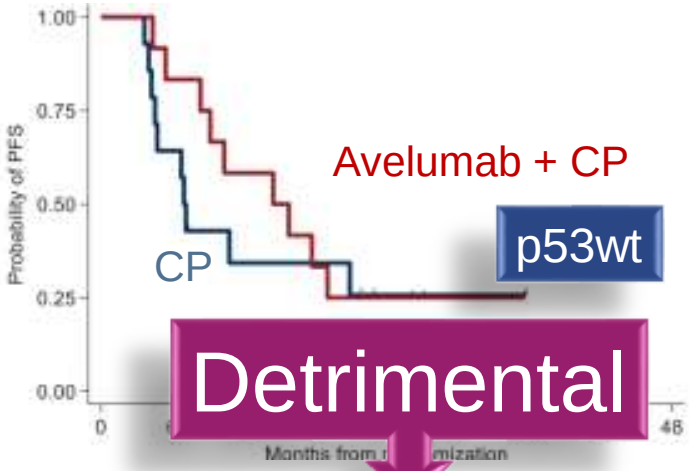
p53wt

Beneficial



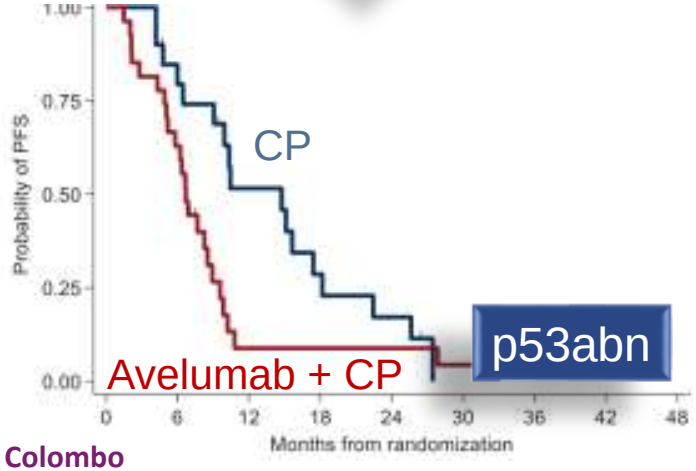
p53abn

MITO END-3



p53wt

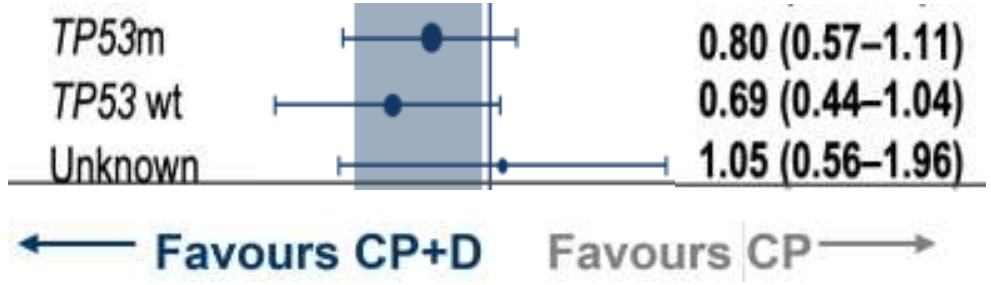
Detrimental



p53abn

DUO-E

Indifferent



Nicoletta Colombo

*JEMPERLI è attualmente approvato in Europa (dalla European Medicines Agency, EMA) in associazione a carboplatino e paclitaxel per il trattamento di prima linea di pazienti adulte affette da CE primario avanzato o ricorrente e che sono candidate per la terapia sistemica. Tuttavia, in Italia, questa indicazione non è rimborsata per le pazienti con CE primario avanzato o ricorrente in assenza di deficit del sistema di mismatch repair (MMR proficient, MMRp)/con stabilità dei microsatelliti (Microsatellite Stable, MSS) e che sono candidate per la terapia sistemica.

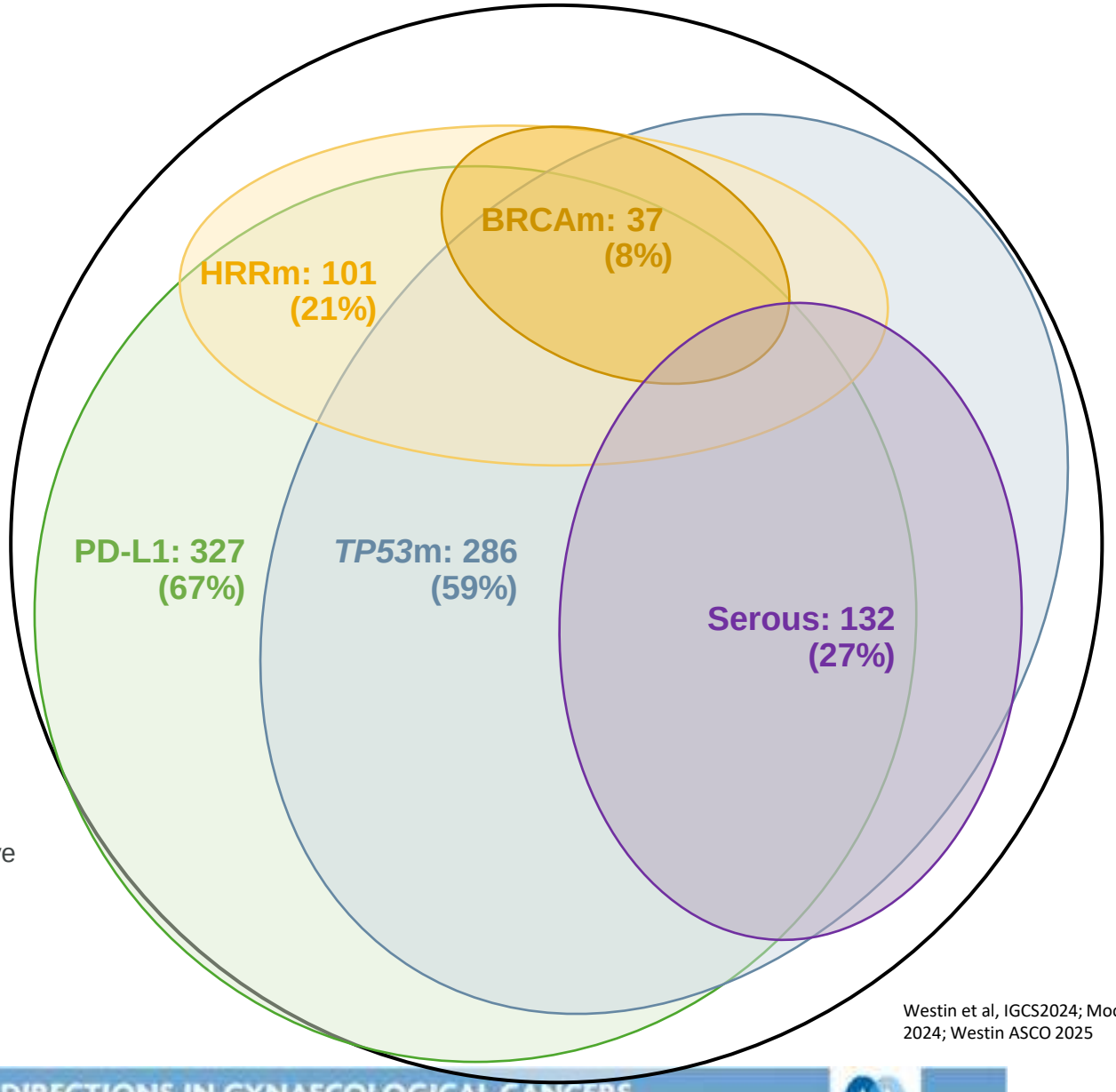
Mansoor Mirza, et al. ESMO 2023; Sandro Pignata, et al. Ann Oncol 2024, Westin et al. IGCS 2024

DUO-E :pMMR biomarker-known subpopulation: co-prevalence of HRRm, *TP53*m and BRCAm.

The pMMR biomarker-known (n=486) subpopulation was heterogeneous, with a large overlap of biomarkers:

- 84% of patients were positive for one or more biomarkers
- PD-L1 positive and *TP53*m were the most prevalent biomarkers

	PD-L1 positive	*TP53*m	HRRm	BRCAm	*POLE*m	Serous
PD-L1 positive	67%	44%	16%	6%	2%	20%
*TP53*m	44%	59%	14%	6%	2%	24%
HRRm	16%	14%	21%	8%	2%	6%
BRCAm	6%	6%	8%	8%	1%	3%
*POLE*m	2%	2%	2%	1%	2%	0%
Serous	20%	24%	6%	3%	0%	27%

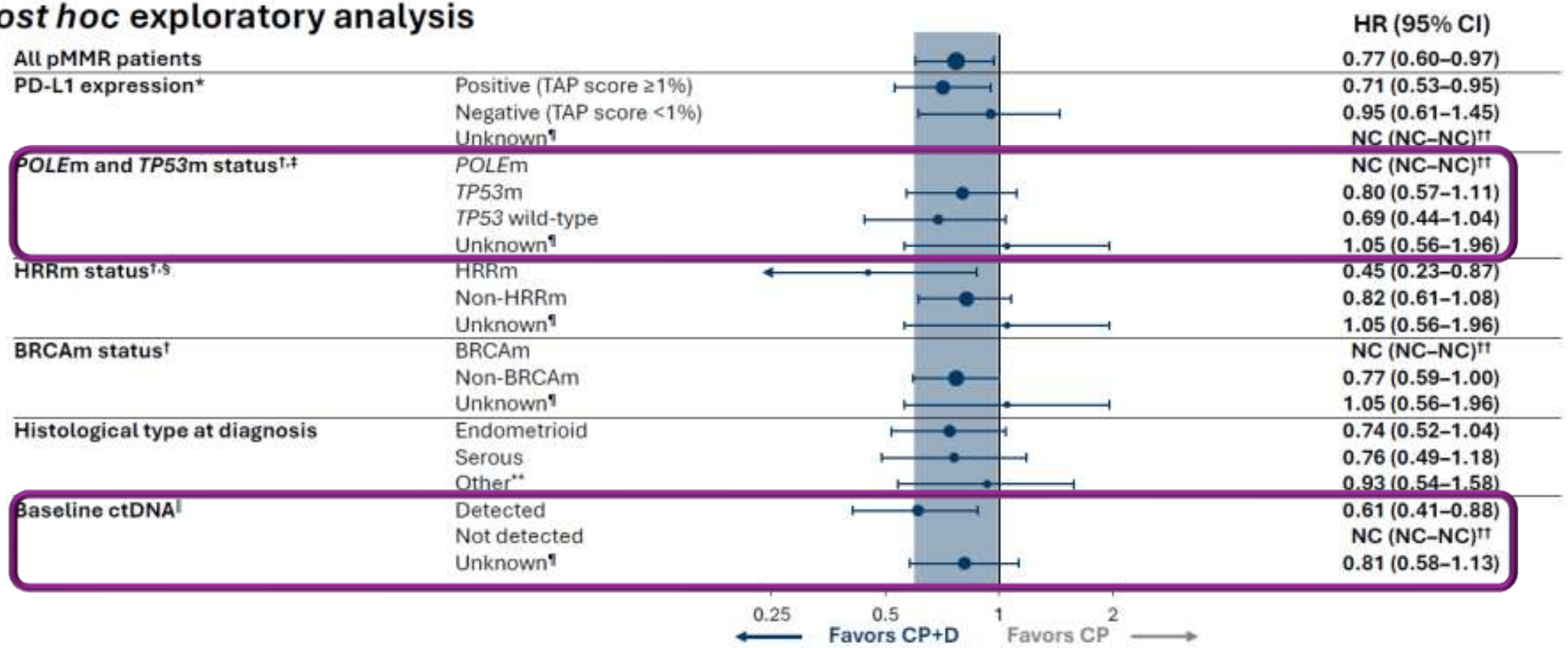


Westin et al, IGCS2024; Moore SC 2024; Westin ASCO 2025

pMMR subpopulation: PFS by biomarker subgroup

CP + durvalumab vs CP

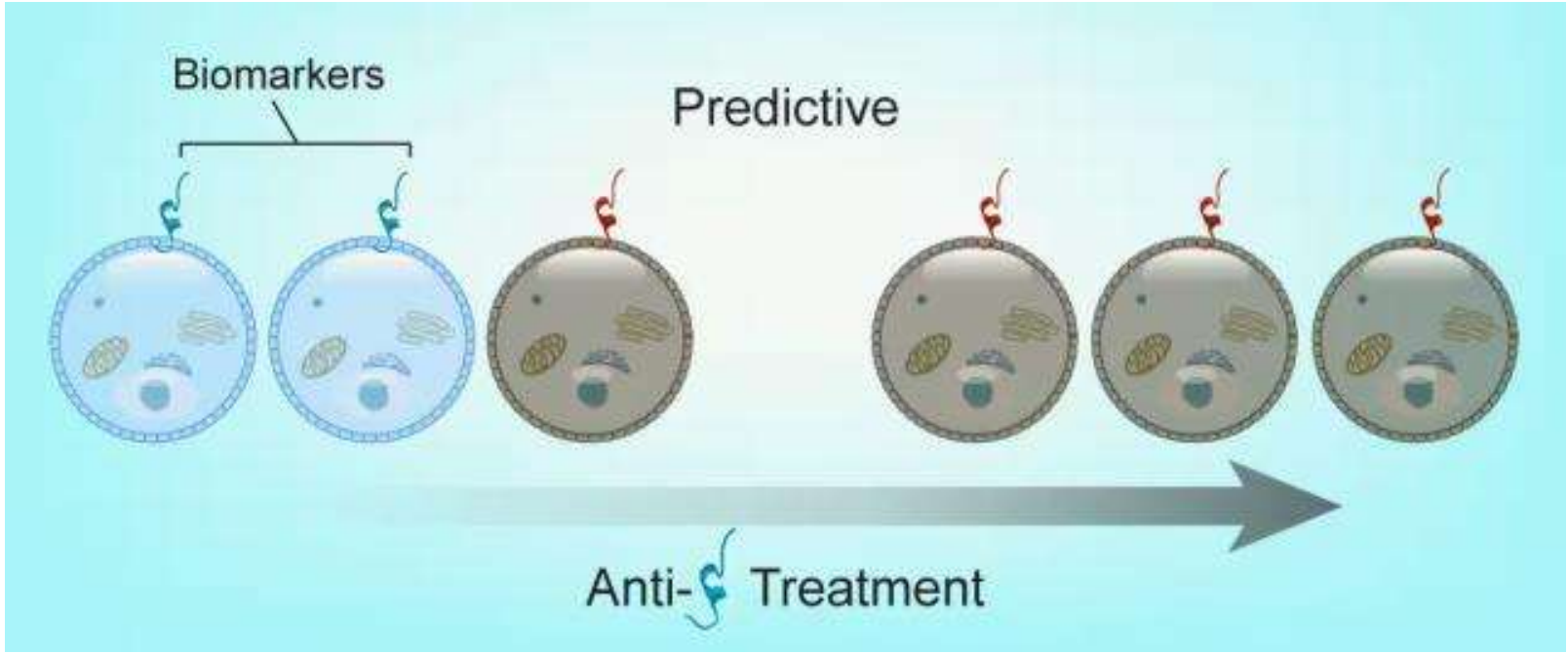
Post hoc exploratory analysis



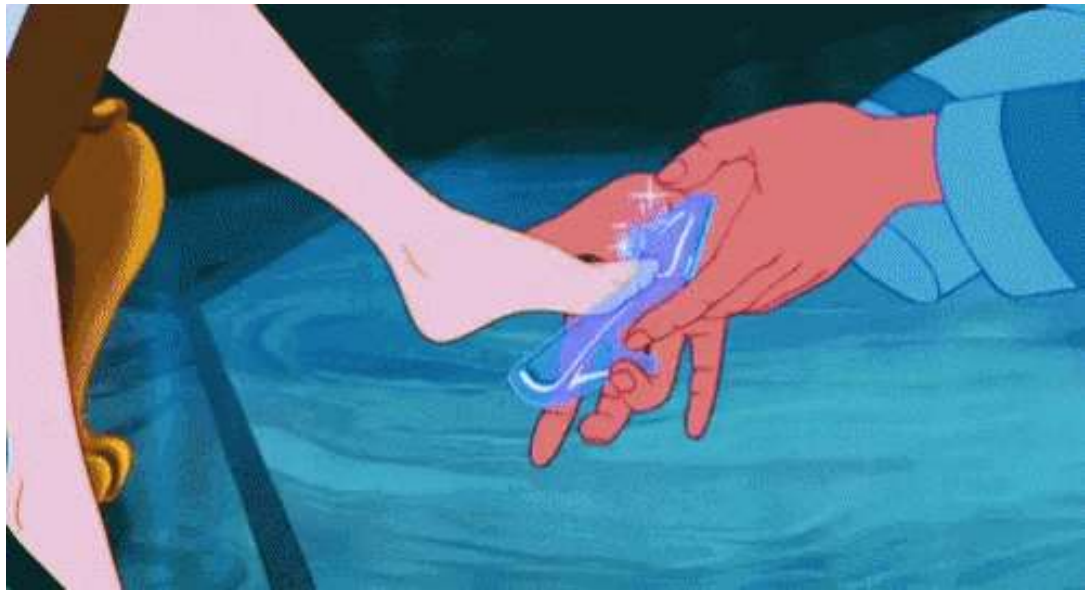
DCO: April 12, 2023. *PD-L1 expression was evaluated using the VENTANA PD-L1 (SP263) assay. PD-L1 positive defined as TAP ≥1%, PD-L1 negative defined as TAP <1%; †Status determined retrospectively in two ways: from tissue samples (FoundationOne®CDx assay; Foundation Medicine, Inc.), and by molecular profiling of ctDNA (FoundationOne®Liquid CDx; Foundation Medicine, Inc.) from blood samples; ‡*TP53*m status defined as a sample with a deleterious or suspected deleterious mutation in *TP53* excluding samples with a deleterious or suspected deleterious mutation in *POLE*; *TP53* wild-type status defined as a sample with no deleterious or suspected deleterious mutation in *TP53* excluding samples with a deleterious or suspected deleterious mutation in *POLE*; §Positive HRRm status defined as a sample with a deleterious or suspected deleterious mutation in any of the following prespecified genes: *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D,* and *RAD54L*; negative HRRm status (non-HRRm) defined as a sample with no deleterious or suspected deleterious mutations in any of the prespecified genes; ‖ctDNA was analyzed using the methylation-based Guardant Infinity™ assay (Guardant Health, Palo Alto, CA); ¶'Unknown' status included patients recruited in China (where molecular testing was not performed) and/or patients who withdrew consent and/or those without available samples; **'Other' includes carcinosarcoma, mixed epithelial, clear cell, undifferentiated, mucinous, and other; ††Not calculated due to low event numbers. NC, not calculable.

Moore et al, SGO 2025

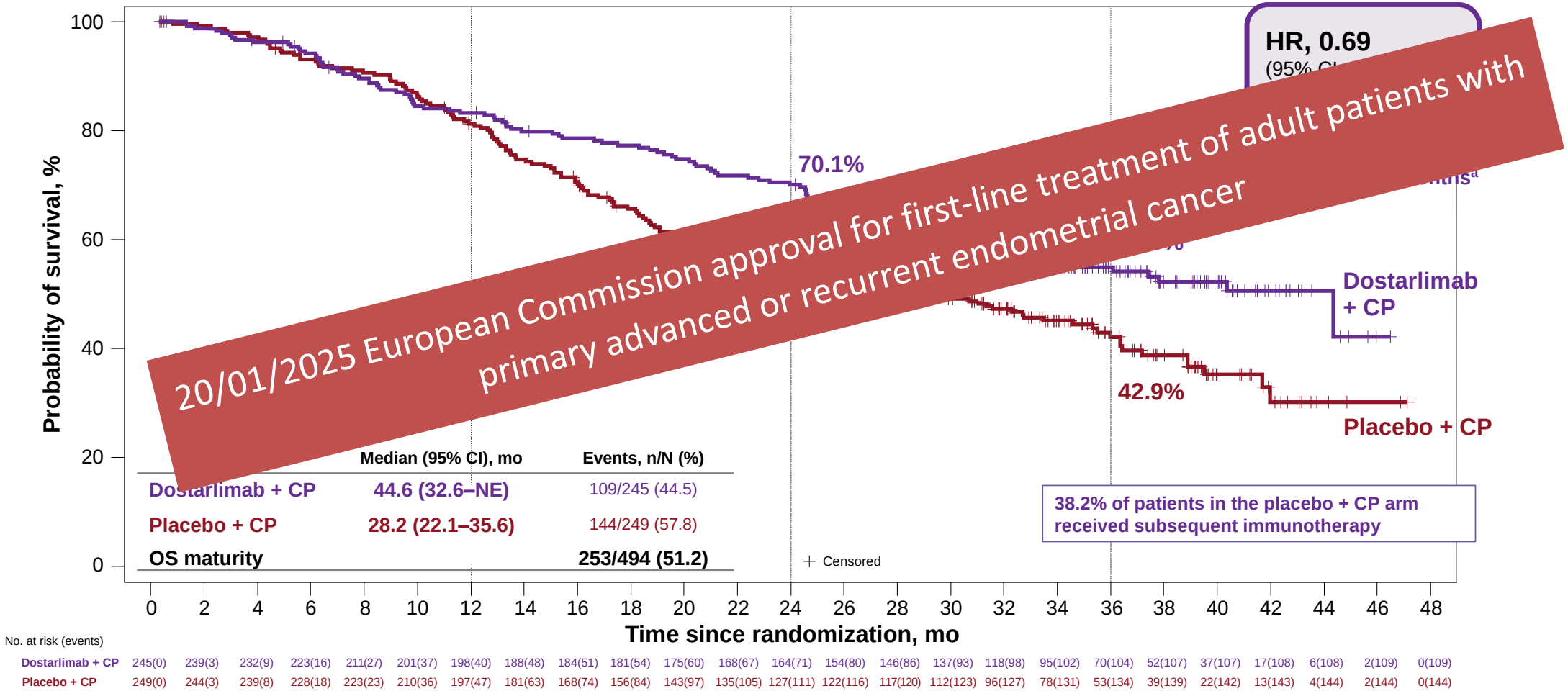
No predictive biomarkers to predict the benefit of ICIs+ chemotherapy in the non-MMRD population



Like the Duke with Cinderella's glass slipper, we aim to find the perfect fit—for every woman, the right treatment…



IO + chemotherapy
RUBY 1° endpoint: Statistically significant OS benefit in overall population



20/01/2025 European Commission approval for first-line treatment of adult patients with primary advanced or recurrent endometrial cancer

*JEMPERLI è attualmente approvato in Europa (dalla European Medicines Agency, EMA) in associazione a carboplatino e paclitaxel per il trattamento di prima linea di pazienti adulte affette da CE primario avanzato o ricorrente e che sono candidate per la terapia sistemica. Tuttavia, in Italia, questa indicazione non è rimborsata per le pazienti con CE primario avanzato o ricorrente in assenza di deficit del sistema di mismatch repair (MMR proficient, MMRp)/con stabilità dei microsatelliti (Microsatellite Stable, MSS) e che sono candidate per la terapia sistemica.

Powell, M.A. et al. Annals of Oncology, Volume 35, Issue 8, 728 – 738, 2024

DUO-E study design

Patients

- Newly diagnosed FIGO 2009 Stage III/IV or recurrent endometrial cancer
- 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

N=718

R
1:1:1

Stratified by:

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

	Chemotherapy phase	Maintenance phase
CP arm	**CP*** (q3w) + **Durvalumab pbo** (IV q3w)	**Durvalumab pbo** (IV q4w) + **Olaparib pbo** (tablets bid)
CP+D arm	**CP*** (q3w) + **Durvalumab** (1120 mg IV q3w)	**Durvalumab** (1500 mg IV q4w) + **Olaparib pbo** (tablets bid)
CP+D+O arm	**CP*** (q3w) + **Durvalumab** (1120 mg IV q3w)	**Durvalumab** (1500 mg IV q4w) + **Olaparib** (300 mg tablets bid)

Patients without disease progression

Treatment until disease progression, unacceptable toxicity or other discontinuation criteria were met

Endpoints

Primary

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

Key secondary

- OS (analytical)
- Safety

Exploratory

- PFS in CP+D+O arm vs CP+D arm
- Subgroup analyses of PFS
  - Including MMR, PD-L1, and HRRm

*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; D, durvalumab; FIGO, International Federation of Gynaecology and Obstetrics; HRRm, homologous recombination repair mutation; IV, intravenously; O, olaparib; pbo, placebo; q3(4)w, every 3(4) weeks; R, randomisation; RECIST, Response Evaluation Criteria for Solid Tumours.

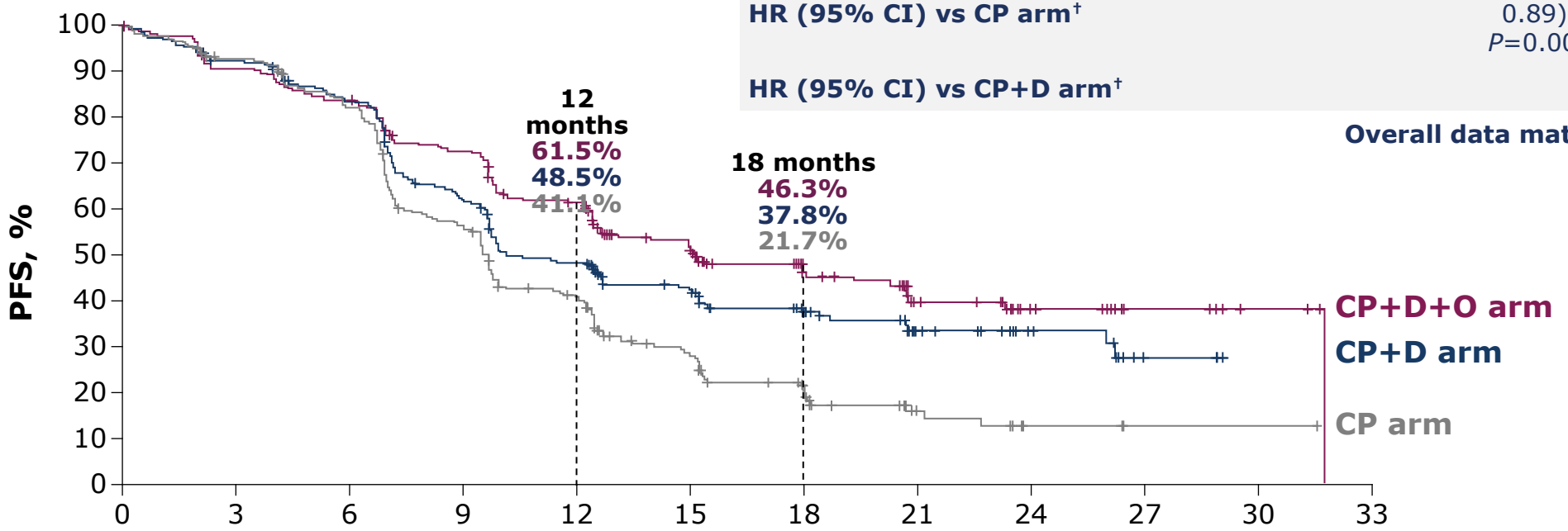
Westin SN *et al. J Clin Oncol* 2024;42:283–99

PFS: ITT population

Dual primary endpoints

	CP arm (N=241)	CP+D arm (N=238)	CP+D+O arm (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 CP arm†		**0.71** (0.57–0.89); *P*=0.003	**0.55** (0.43–0.69); *P*<0.0001
HR (95% CI) vs CP+D arm†			0.78 (0.61–0.99)

Overall data maturity 61.0%



No. at risk

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

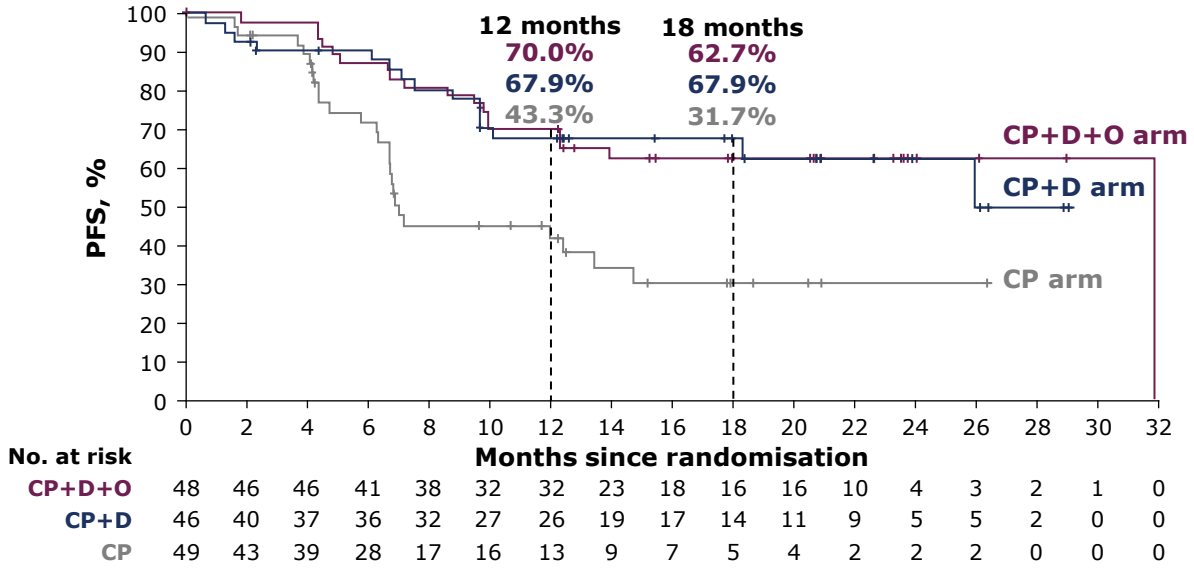
The median (range) duration of follow-up for PFS was 12.6 (0.0–31.6), 15.4 (0.0–29.1), and 15.4 (0.0–31.7) months in censored patients for the CP, CP+D, and CP+D+O arms, respectively. PFS rates were estimated by the KM method. *CI for median PFS is derived based on the Brookmeyer–Crowley method;

†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.

Westin SN *et al. J Clin Oncol* 2024;42:283–99

Subgroup analysis of PFS by MMR status

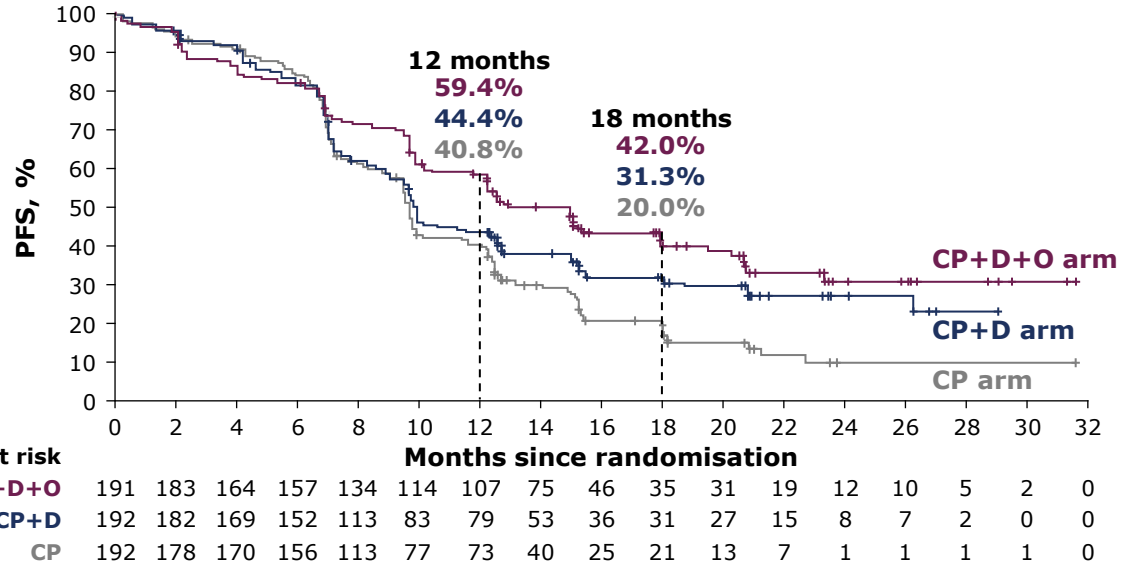
dMMR (20% of population)



No. at risk																	
CP+D+O	48	46	46	41	38	32	32	23	18	16	16	10	4	3	2	1	0
CP+D	46	40	37	36	32	27	26	19	17	14	11	9	5	5	2	0	0
CP	49	43	39	28	17	16	13	9	7	5	4	2	2	2	0	0	0

	CP arm (N=49)	CP+D arm (N=46)	CP+D+O arm (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 CP arm†		**0.42 (0.22–0.80)**	**0.41 (0.21–0.75)**
HR (95% CI) vs CP+D arm†			**0.97 (0.49–1.98)**

pMMR (80% of population)



No. at risk																	
CP+D+O	191	183	164	157	134	114	107	75	46	35	31	19	12	10	5	2	0
CP+D	192	182	169	152	113	83	79	53	36	31	27	15	8	7	2	0	0
CP	192	178	170	156	113	77	73	40	25	21	13	7	1	1	1	1	0

	CP arm (N=192)	CP+D arm (N=192)	CP+D+O arm (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 CP arm†		**0.77 (0.60–0.97)**	**0.57 (0.44–0.73)**
HR (95% CI) vs CP+D arm†			**0.76 (0.59–1.99)**

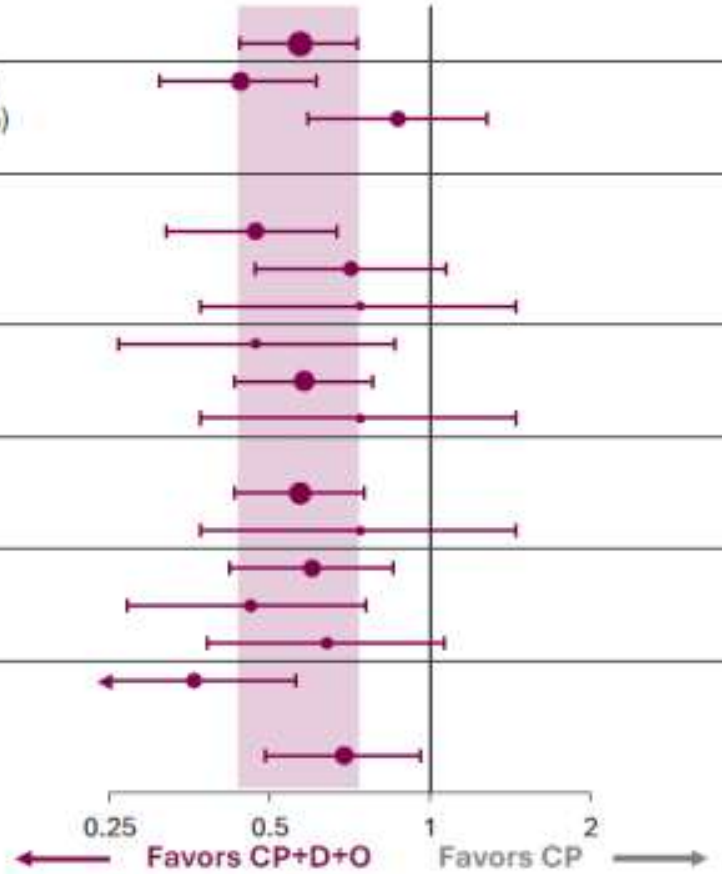
Westin SN *et al. J Clin Oncol* 2024;42:283–99

pMMR subpopulation: PFS by biomarker subgroup

CP + durvalumab + olaparib vs CP

Post hoc exploratory analysis

		HR (95% CI)
All pMMR patients		0.57 (0.44–0.73)
PD-L1 expression*	Positive (TAP score ≥1%)	0.44 (0.31–0.61)
	Negative (TAP score <1%)	0.87 (0.59–1.28)
	Unknown¶	NC (NC–NC)††
*POLE*m and *TP53*m status†,‡	*POLE*m	NC (NC–NC)††
	*TP53*m	0.47 (0.32–0.67)
	TP53 wild-type	0.71 (0.47–1.07)
	Unknown¶	0.74 (0.37–1.45)
HRRm status†,§	HRRm	0.47 (0.26–0.86)
	Non-HRRm	0.58 (0.43–0.78)
	Unknown¶	0.74 (0.37–1.45)
BRCAm status†	BRCAm	NC (NC–NC)††
	Non-BRCAm	0.57 (0.43–0.75)
	Unknown¶	0.74 (0.37–1.45)
Histological type at diagnosis	Endometrioid	0.60 (0.42–0.85)
	Serous	0.46 (0.27–0.76)
	Other**	0.64 (0.38–1.06)
Baseline ctDNA‖	Detected	0.36 (0.23–0.56)
	Not detected	NC (NC–NC)††
	Unknown¶	0.69 (0.49–0.96)



DCO: April 12, 2023. *PD-L1 expression was evaluated using the VENTANA PD-L1 (SP263) assay. PD-L1 positive defined as TAP ≥1%, PD-L1 negative defined as TAP <1%; †Status determined retrospectively in two ways: from tissue samples (FoundationOne®CDx assay; Foundation Medicine, Inc.), and by molecular profiling of ctDNA (FoundationOne®Liquid CDx; Foundation Medicine, Inc.) from blood samples; ‡*TP53*m status defined as a sample with a deleterious or suspected deleterious mutation in *TP53* excluding samples with a deleterious or suspected deleterious mutation in *POLE*; §Positive HRRm status defined as a sample with a deleterious or suspected deleterious mutation in any of the following prespecified genes: *ATM*, *BRCA1*, *BRCA2*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*; negative HRRm status (non-HRRm) defined as a sample with no deleterious or suspected deleterious mutations in any of the prespecified genes; ‖ctDNA was analyzed using the methylation-based Guardant Infinity® assay (Guardant Health, Palo Alto, CA); ¶'Unknown' status included patients recruited in China (where molecular testing was not performed) and/or patients who withdrew consent and/or those without available samples; **'Other' includes carcinosarcoma, mixed epithelial, clear cell, undifferentiated, mucinous, and other; ††Not calculated due to low event numbers. NC, not calculable.

Moore et al, SGO 2025

SYSTEMIC THERAPY

FIRST LINE SYSTEMIC THERAPY

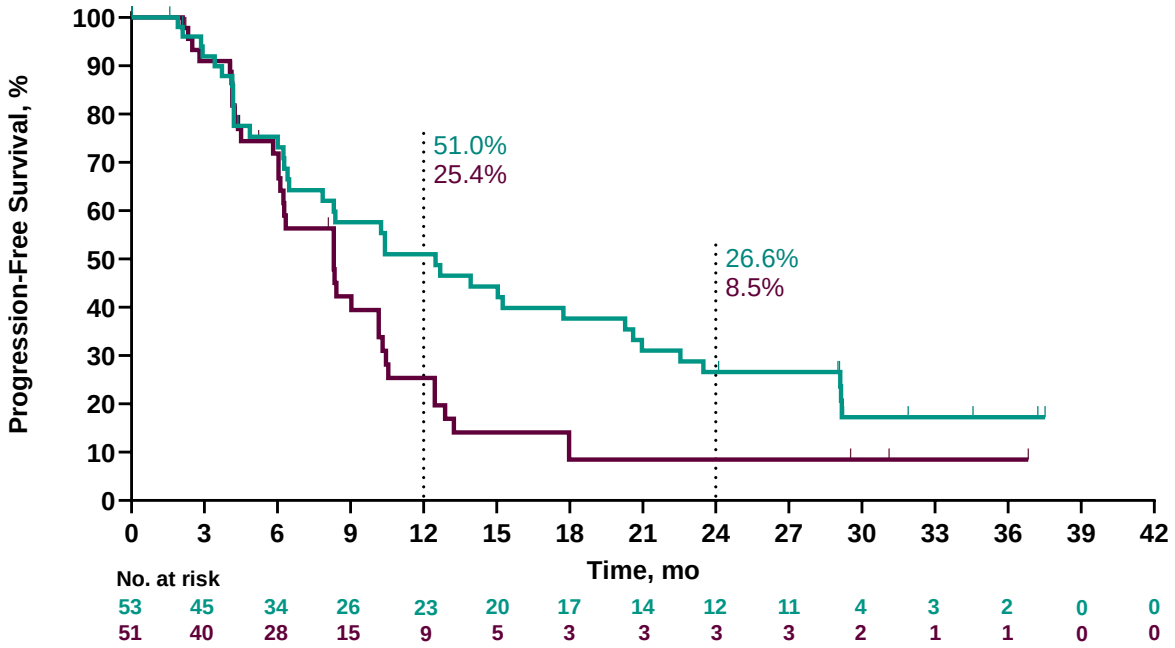
in unresectable stage III/IV or recurrent EC with no prior chemotherapy except in the adjuvant setting (including patients with residual disease after surgery)

- If chemotherapy is contraindicated, in patients with non-MMRd relapsed disease and with prior chemotherapy in the adjuvant/neoadjuvant setting, a combination of pembrolizumab and the multi-tyrosine-kinase inhibitor lenvatinib may be considered [III, C].

ENGOT-en9/LEAP-001 Progression-Free Survival[a] Improved With LEN/PEMBRO vs TC in Prior Neoadjuvant/Adjuvant Chemotherapy Subgroup

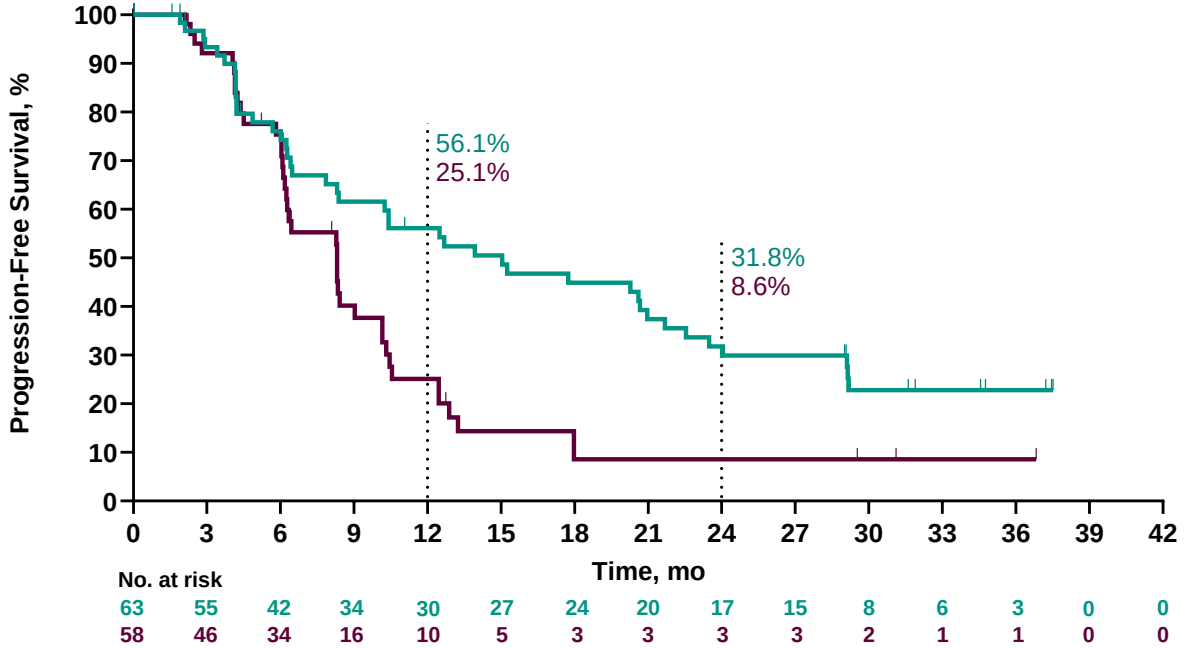
pMMR Population

	Events, n/N	Median (95% CI), mo	HR (95% CI)
LEN/PEMBRO	37/53	12.5 (6.5–20.3)	0.60 (0.37–0.97)
TC	35/51	8.3 (6.1–10.2)	



All-comers

	Events, n/N	Median (95% CI), mo	HR (95% CI)
LEN/PEMBRO	42/63	15.0 (8.3–21.0)	0.52 (0.33–0.82)
TC	39/58	8.3 (6.2–10.2)	



Christian Marth et al. J Clin Oncol 2025 Mar 20;43(9):1083-1100

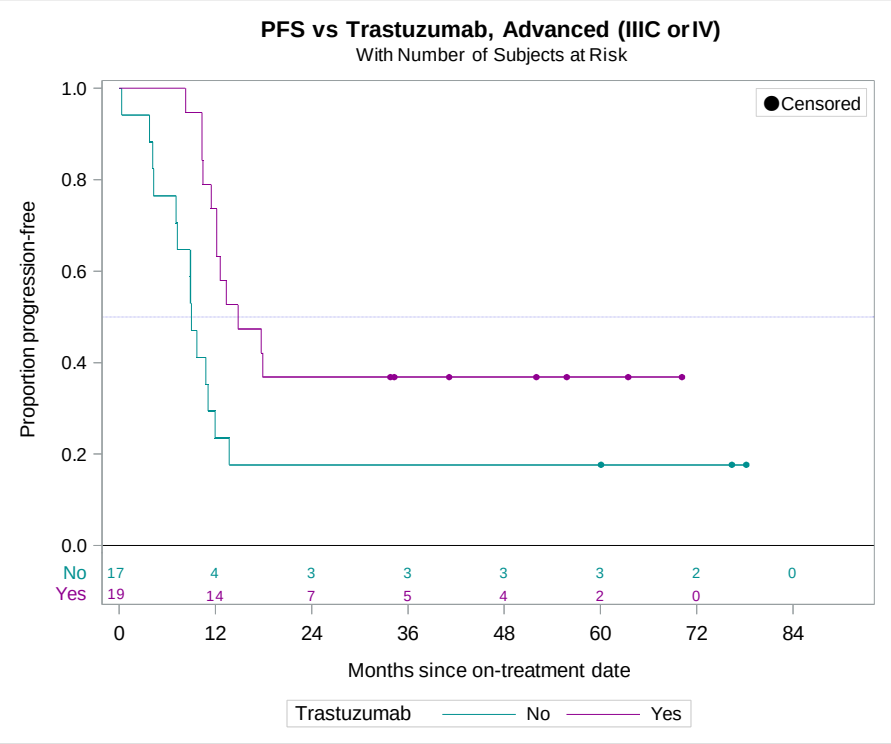
SYSTEMIC THERAPY

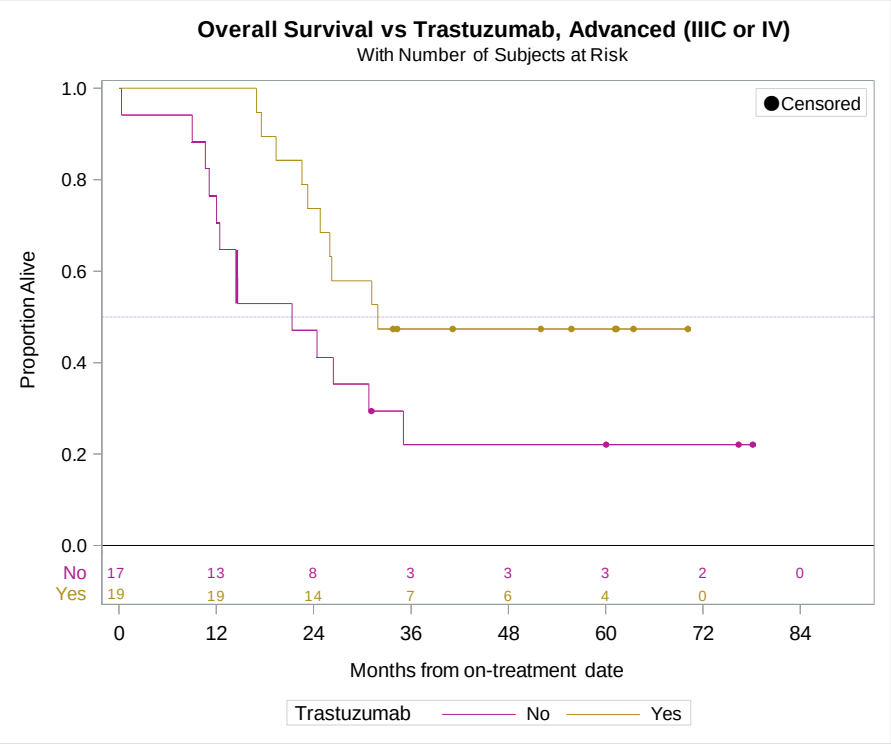
FIRST LINE SYSTEMIC THERAPY

in unresectable stage III/IV or recurrent EC with no prior chemotherapy except in the adjuvant setting (including patients with residual disease after surgery)

- If ICI (± PARPi) is contraindicated, for patients with a HER2 3+ tumour, a combination of carboplatin-paclitaxel plus trastuzumab may be considered [II, B].
- The standard chemotherapy regimen is 6 cycles of carboplatin-paclitaxel [I, A].

Carboplatin/paclitaxel+/-Trastuzumab (NCT01367002)
Updated Survival analysis stage III/IV





In a subset analysis of pts restricted to stage IIIC/IV disease, the addition of trastuzumab (n=17) continued to provide both (*left*) PFS benefit over control (n=19) and OS benefit over control (21.1 versus 31.9 months, HR 0.440 90% CI 0.219-0.882 p=0.0230).

Amanda N. Fader et al.,J Clin Oncol. 2018 Jul 10;36(20):2044-2051
Amanda N. Fader et al. , JCO 2020

First line treatment endometrial cancer

The MMR status should be taken into consideration to determine the choice of first line therapy:

- MMRd: ***should be offered*** chemotherapy + ICI (dostarlimab or durvalumab or pembrolizumab) followed by ICI as maintenance therapy
- Non-MMRd tumours with rapidly growing/symptomatic disease: ***can be considered*** chemotherapy +/-ICI followed by ICI as maintenance therapy, e.g. dostarlimab or pembrolizumab or durvalumab. All patients can be considered since there are no predictive biomarkers to select a particular group of patients.
- NON-MMRd: ***can be considered*** Chemotherapy +ICI followed by a combination of ICI and PARPi as maintenance therapy, ie durvalumab and Olaparib.
- In patients with prior chemotherapy in the adjuvant or neoadjuvant setting, a combination of lenvatinib and pembrolizumab ***may be considered***
- If ICI (± PARPi) is contraindicated, for patients with a HER2 3+ tumour, a combination of carboplatin-paclitaxel plus trastuzumab ***may be considered***
- In low-grade ER-positive, low volume/asymptomatic advanced or slowly growing recurrent tumours, endocrine therapy is the preferred systemic therapy

Endometrial Cancer

GRAZIE

XXII ASSEMBLEA MaNGO MILANO