Endometrial Cancer Frontiers: Understanding the Impact of Recent Approvals and Incorporating Precision Diagnostics for Your Patient

Ramez Eskander, MD
Moores Cancer Center, UC San Diego, San Diego, CA

GOG FOUNDATION®
Transforming the standard of care

Current Endometrial Cancer Treatment Landscape

GOG Highlight Reel

Immune Checkpoint Inhibition + CT is The New Standard of Care in Advanced Stage or Recurrent dMMR…& pMMR EC?

JULY 31, 2023[1]

FDA approves dostarlimab with chemotherapy for endometrial cancer (dMMR and MSI-H)

DECEMBER 11, 2023[2]

EC approves dostarlimab with chemotherapy for endometrial cancer (dMMR and MSI-H)

JUNE 14, 2024[3]

FDA approves durvalumab with chemotherapy for dMMR primary advanced or recurrent endometrial cancer

JUNE 17, 2024[4]

FDA approves pembrolizumab with chemotherapy for primary advanced or recurrent endometrial cancer

AUGUST 14, 2024[5]

EC approves durvalumab with chemotherapy for dMMR primary advanced or recurrent endometrial cancer

OCTOBER 24, 2024[6]

EC approves pembrolizumab with chemotherapy for primary advanced or recurrent endometrial cancer

JANUARY 17, 2025[7]

EC approves dostarlimab with chemotherapy, followed by single agent Dostarlimab for 1L treatment of primary advanced or recurrent endometrial cancer

1. Mirza MR, et al. *N Engl J Med.* 2023;388(23):2145-2158. doi:10.1056/nejmoa2216334; 2. GSK. 2023-12-22. *GSK's dostarlimab plus chemotherapy approved as the first and only frontline immuno-oncology treatment in the European Union for dMMR/MSI-H primary advanced or recurrent endometrial cancer* [Press Release]; 3. Westin SN, et al. *J Clin Oncol.* 2024;42(3):283-299. doi: 10.1200/JCO.23.02132; 4. Eskander RN, et al. *N Engl J Med.* 2023;388(23):2159-2170. doi:10.1056/NEJMoa2302312; 5.AstraZeneca. 2024-08-14. *Olaparib and durvalumab combination approved in the EU for patients with mismatch repair proficient advanced or recurrent endometrial cancer* [Press Release]; 6. Merck. 2024-10-24. *Merck's pembrolizumab receives 30th approval from European Commission with two new indications in gynecologic cancers* [Press Release].; 7. GSK Internal Communications

GOG Highlight Reel

GOG FOUNDATION

Immune Checkpoint Inhibition + CT is The New Standard of Care in Advanced Stage or Recurrent dMMR…& pMMR EC?

None of the FDA indications specify the requirement for measurable disease…?

Essentially all patients enrolled had measurable/evaluable or recurrent disease

JULY 31, 20

FDA approve
endometrial

mbrolizumab with
r primary advanced or recurrent
cer

DECEMBER

EC approves dostarlimab with chemotherapy for endometrial cancer (dMMR and MSI-H)

024[5]

EC approves durvalumab with chemotherapy for dMMR primary advanced or recurrent endometrial cancer

JUNE 14, 2024[3]

FDA approve
dMMR prim
cancer

Clinical Dilemma:
Stage 3C1, grade 3 endometrioid adenocarcinoma (dMMR), post-operative CT without radiographic evidence of residual disease…

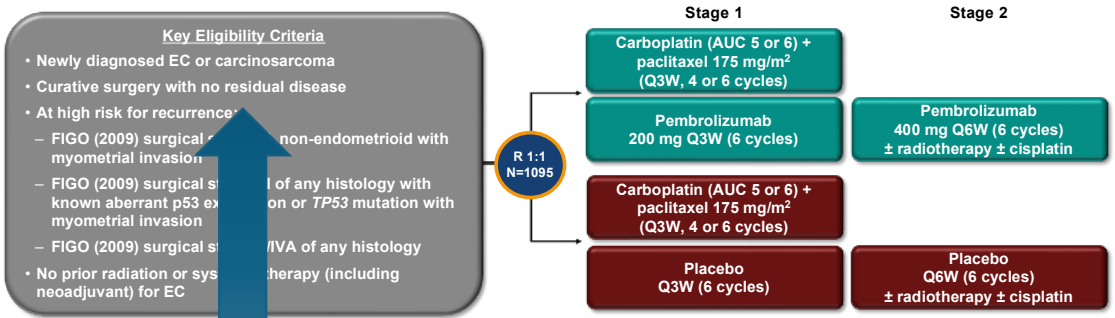
024[6]

brolizumab with
r primary advanced or
etrial cancer

arlimab

1. Mirza MR, et al. *N Engl J Med.* 2023;388(23):2145-2158. doi:10.1056/nejmoa2216334; 2. GSK. 2023-12-22. *GSK's dostarlimab plus chemotherapy approved as the first and only frontline immuno-oncology treatment in the European Union for dMMR/MSI-H primary advanced or recurrent endometrial cancer* [Press Release]; 3. Westin SN, et al. *J Clin Oncol.* 2024;42(3):283-299. doi: 10.1200/JCO.23.02132; 4. Eskander RN, et al. *N Engl J Med.* 2023;388(23):2159-2170. doi:10.1056/NEJMoa2302312; 5.AstraZeneca. 2024-08-14. *Olaparib and durvalumab combination approved in the EU for patients with mismatch repair proficient advanced or recurrent endometrial cancer* [Press Release]; 6. Merck. 2024-10-24. *Merck's pembrolizumab receives 30th approval from European Commission with two new indications in gynecologic cancers* [Press Release].; 7. GSK Internal Communications

ENGOT-en11/GOG-3053/KEYNOTE-B21: Phase 3 Study of Pembrolizumab or Placebo in Combination With Adjuvant Chemotherapy With or Without Radiotherapy in Patients With Newly Diagnosed, High-Risk Endometrial Cancer



No mandate for measurable disease…but a very heterogeneous population:

1A, G2 endometrioid, TP53mut vs.
3C1 serous endometrial cancer

ITT HR 1.02 (0.79-1.32)

Interaction *P* value for MMR status was 0.002

Who are these 281 dMMR patients?

91% White or Asian

50-60% stage 3C-4A

75% Endometrioid

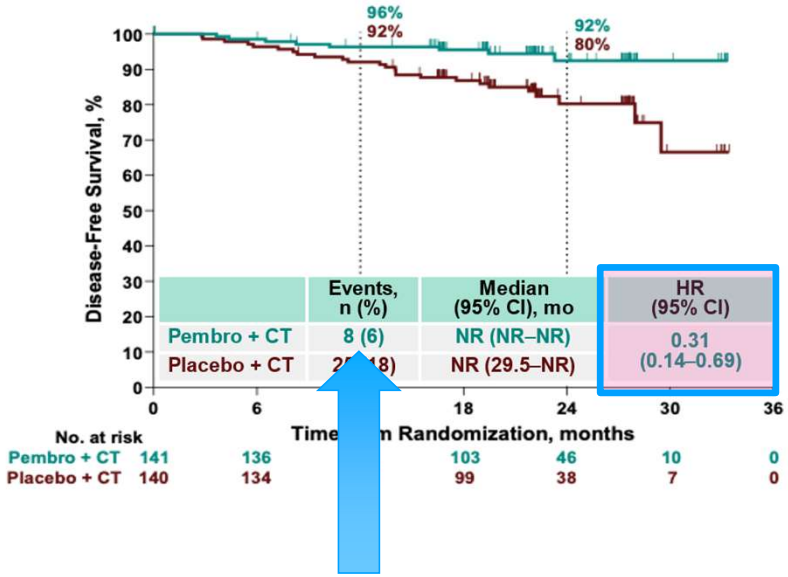
Imbalance in LN involvement (37 vs 50% LN-)

65-75% of patients treated with EBRT +/- cisplatin

NCT04634877

Slomovitz B, et al. Presented at: International Gynecologic Cancer Society (IGCS) Annual Global Meeting; 16-18 October 2024; Dublin, Ireland

ENGOT-en11/GOG-3053/KEYNOTE-B21 *cont.*



Only 8 recurrences in the pembrolizumab arm..

Although not a primary hypothesis tested analysis, the HR of 0.31 in dMMR EC is provocative and argues for use of pembrolizumab in combination with chemotherapy in adjuvant setting for dMMR patients

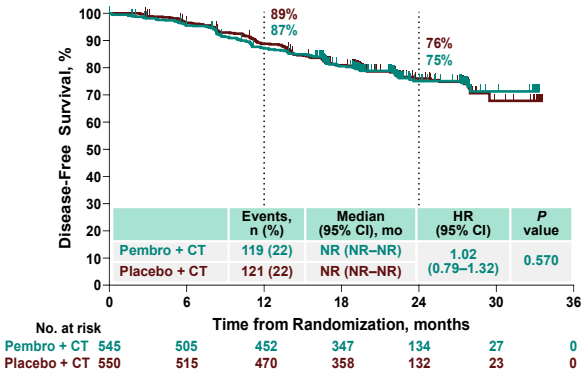
Analogous to expansion of PARPi in stage 2 EOC BRCAmut population

NCT04634877

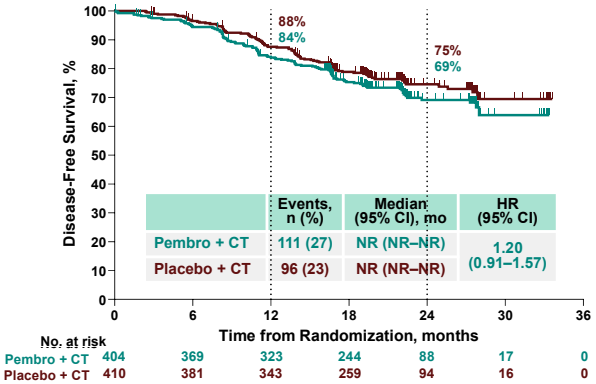
Slomovitz B, et al. Presented at: International Gynecologic Cancer Society (IGCS) Annual Global Meeting; 16-18 October 2024; Dublin, Ireland.

ENGOT-en11/GOG-3053/KEYNOTE-B21 *cont.*

ITT



pMMR



Do we have a definitive answer in the completely resected pMMR population?

Nearly 60% are stage 1 – stage 3B

HR in stage 3-4 is 0.91 (95% CI 0.68-1.22)

HR in LN positive cohort is 0.83 (95% CI 0.58-1.18)

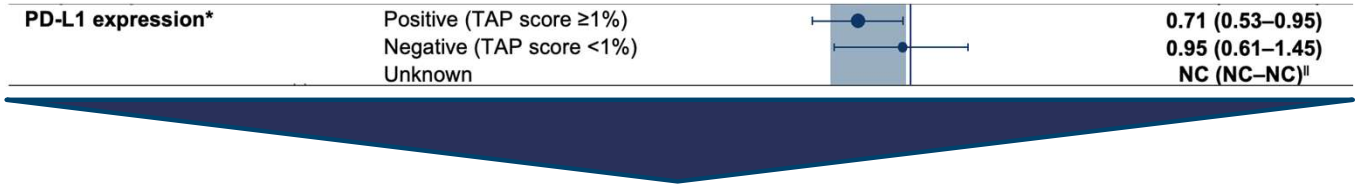
Completely resected, node + stage 3C1 or 3C2 patient?

NCT04634877

Slomovitz B, et al. Presented at: International Gynecologic Cancer Society (IGCS) Annual Global Meeting; 16-18 October 2024; Dublin, Ireland.

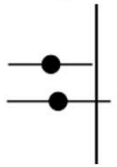
Durvalumab plus carboplatin/paclitaxel followed by durvalumab with/without olaparib in endometrial cancer: exploratory analyses of biomarker/histological heterogeneity and efficacy in the DUO-E mismatch repair proficient subpopulation (Westin et al.)

- 494 of 575 had *POLEm* and *TP53m* information available (~14% missing data)
- HRRm based on identified mutation in 14 pre-defined genes (~14% missing data)
- No data available for patients enrolled in China?



Discordant findings…

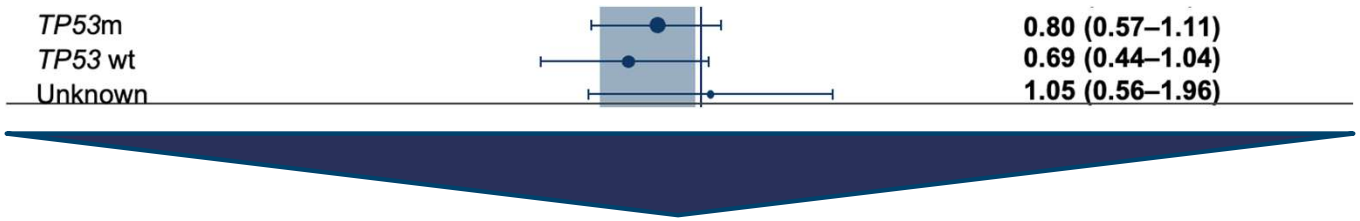
	Dostarlimab + niraparib + CP N=142	Placebo IV + placebo oral + CP N=74	HR (95%CI)
	No. of patients with events/No. of patients		
PD-L1 Status[a]			
PD-L1+	46/88	31/44	0.61 (0.38–0.96)
PD-L1-	32/53	20/26	0.66 (0.38–1.17)
Not evaluable[b]	1/1	2/4	NA



Westin et al. IGCS 2024; Mirza et al SGO 2024

Durvalumab plus carboplatin/paclitaxel followed by durvalumab with/without olaparib in endometrial cancer: exploratory analyses of biomarker/histological heterogeneity and efficacy in the DUO-E mismatch repair proficient subpopulation (Westin et al.)

- pMMR: CP+ durvalumab versus CP

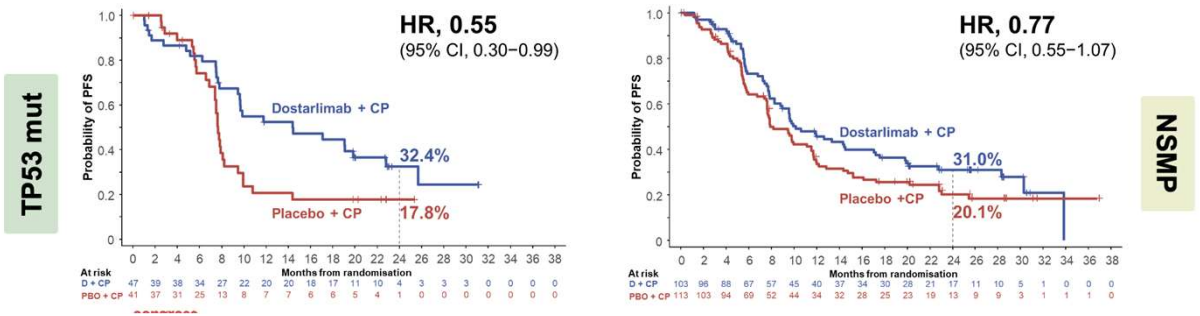


59% TP53mut

24% of TP53mut are serous histology

Discordant findings…

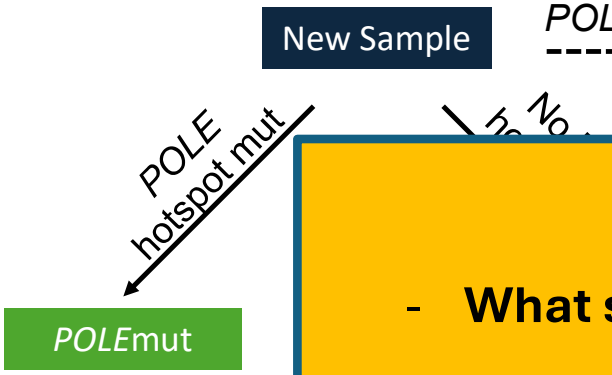
GOG-3031/RUBY



Westin et al. IGCS 2024; Mirza et al SGO 2024

Molecular Profiling in Newly Diagnosed EC

ProMisE Molecular Classification Algorithm[1]



Clinical Question:

- **What standard molecular testing are you performing and why?**
- **Are you acting on these results and if so, how?**
- **What are you doing with advanced stage, HER2 IHC 3+ in the adjuvant setting ?**

Recommended molecular profiling in newly diagnosed EC[2]

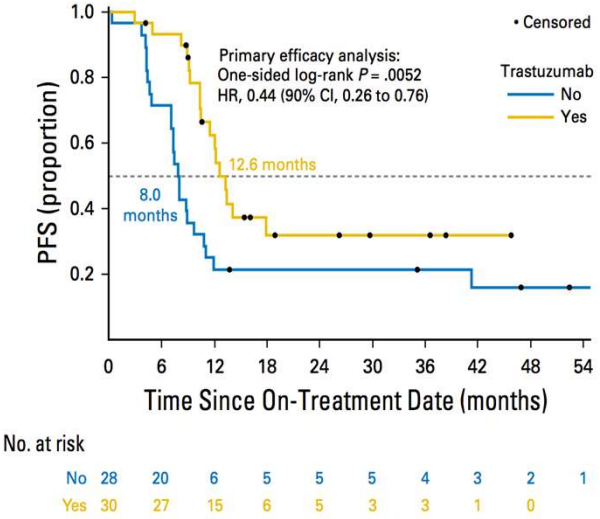
- MMR status[2] (presence or absence of MLH1, PMS2, MSH2, and MSH6 proteins[3])
- *POLE* status (if feasible)[2] or if status would influence adjuvant treatment[3]
  - May be lower priority for **very low-risk** EC[3]
- p53 status[2]
- ER/PR expression[2]
- HER2 amplification[2]

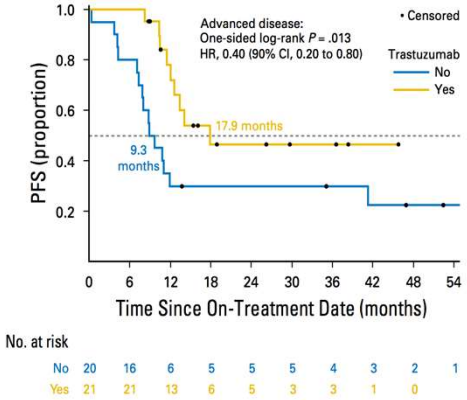
dMMR, mismatch repair deficient; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mut, mutated; NSMP, no specific molecular profile; pMMR, proficient MMR; PR, progesterone receptor; TMB-H, tumor mutational burden-high; wt, wild type. Walsh CS, et al. Gynecol Oncol. 2023;168:48-55; 2. NCCN®. Uterine Neoplasms (v1.2024). 2023. Accessed November 30, 2023. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf; 3. Berg HG, et al. Br J Cancer. 2023;128:647-655; 3. Jamieson A, et al. J Natl Compr Canc Netw. 2023;21:210-216.

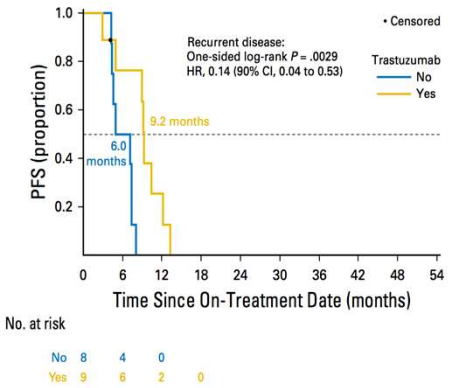
Incorporation of anti-HER-2 treatment: Trastuzumab with Chemotherapy

Key eligibility criteria

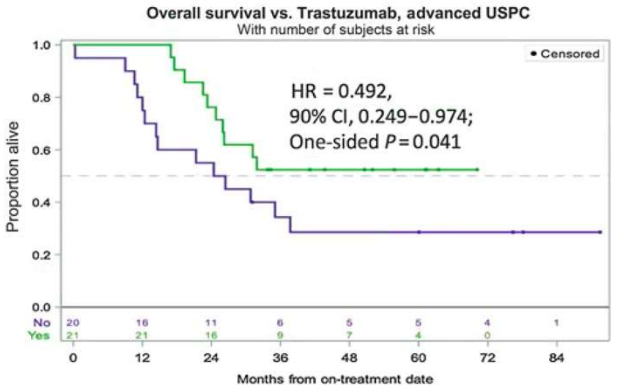
- Primary stage III or IV or recurrent HER2/neu-positive USC: IHC score 3+, or 2+ with + FISH
- ECOG 0-2
- ≤3 prior lines of therapy
- "platinum sensitive" recurrence (6 mo)

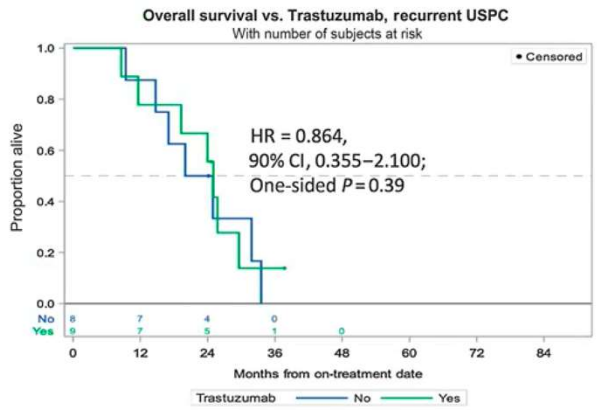






OS benefit particularly striking in stage III–IV patients, OS median of 25.4 months (control) versus NR (p = 0.041, HR = 0.49, 90% CI 0.25–0.97).





Nickles-Fader J Clin Oncol 2018

Opportunities for chemotherapy free treatment strategies?

GOG 3064 KN-C93

R → Pembrolizumab
R → Chemo

Primary endpoints:
PFS, OS

Key secondary endpoints:
ORR, DCR, DOR

Recruitment ongoing

dMMR patient population

NCT05173987

ENGOT-en13 DOMENICA

R → Dostarlimab
R → Chemo

Primary endpoint:
PFS

Key secondary endpoints:
OS, PROs, ORR, DOR

Recruitment ongoing

dMMR patient population

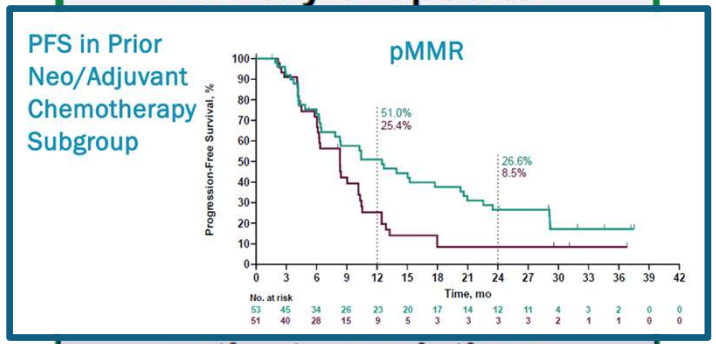
NCT05201547

ENGOT-en9 LEAP-001

R → Lenvatinib + pembrolizumab

Pembrolizumab/Lenvatinib Miss OS, PFS in Endometrial Cancer

December 8, 2023
Sabrina Serani



patient populations

NCT04865289

LEAP-001: Lenvatinib Plus Pembrolizumab vs Chemo

Key Eligibility Criteria

- Stage III, Stage IV or recurrent endometrial carcinoma[a]
- Radiographically apparent disease - either measurable or nonmeasurable
- No prior chemotherapy except in the neo/adjuvant setting[b]
- ECOG PS 0-1
- Tumor tissue sample for MMR testing

Stratification Factors

MMR status (pMMR vs dMMR),

- If pMMR
  - ECOG PS (0 vs 1)
  - Measurable disease (yes vs no)
  - Prior chemotherapy and/or chemoradiation (yes vs no)

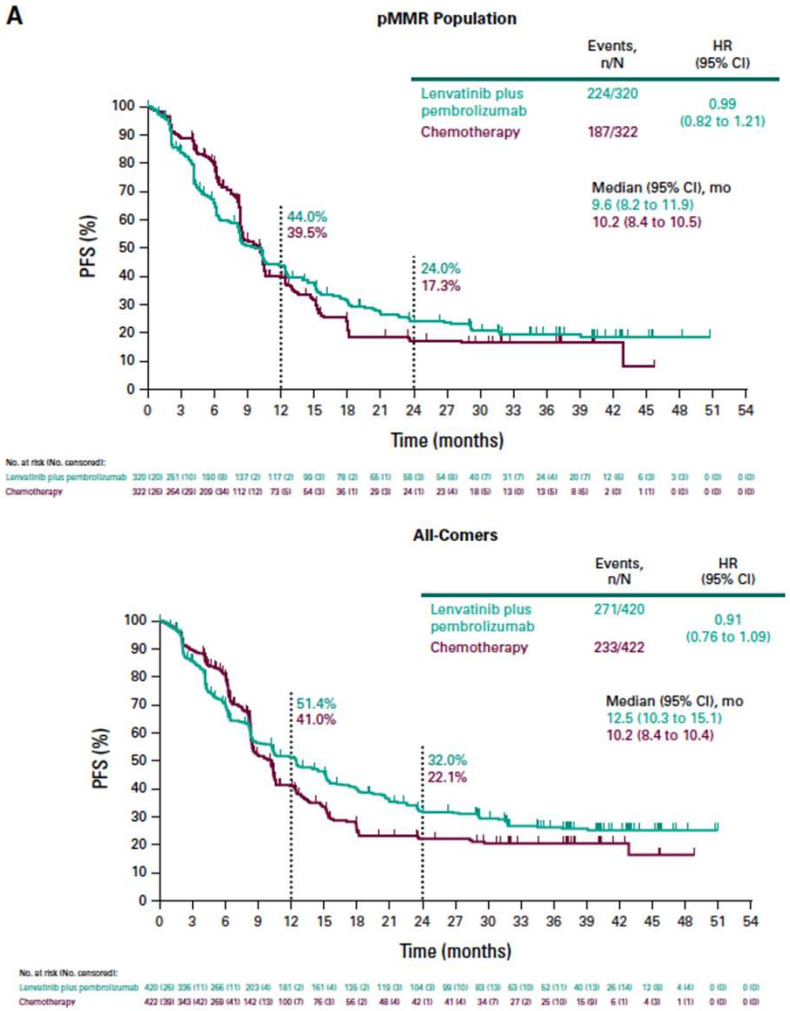
R (1:1)
N = 842

Lenvatinib 20 mg orally QD until PD
+
Pembrolizumab 200 mg IV Q3W
until PD or x35 cycles

Paclitaxel 175 mg/m^2 IV
+
Carboplatin AUC 6 IV Q3W
x7 cycles[c]

Endpoints

- **Dual primary:** PFS per RECIST v1.1 by BICR and OS
- **Secondary:** ORR per RECIST v1.1 by BICR, safety, and HRQoL
- **Exploratory:** Included DOR per RECIST v1.1 by BICR



NCT04865289

Marth C et al. J Clin Oncol 2024

LEAP-001: Lenvatinib Plus Pembrolizumab vs Chemo

OS - pMMR Population

	Events/Patients	HR (95% CI)
Overall	366/642	1.02 (0.83-1.26)
Prior neo/adjuvant chemo		
Yes	64/104	0.67 (0.41-1.11)
No	302/538	1.11 (0.88-1.39)

OS - All-comers

	Events/Patients	HR (95% CI)
Overall	442/842	0.93 (0.77-1.12)
Prior neo/adjuvant chemo		
Yes	70/121	0.64 (0.40-1.03)
No	372/721	0.96 (0.79-1.18)

PFS - pMMR Population

	Events/Patients	HR (95% CI)
Overall	411/642	0.99 (0.82-1.21)
Prior neo/adjuvant chemo		
Yes	72/104	0.60 (0.37-0.97)
No	339/538	1.09 (0.88-1.35)

PFS - All-comers

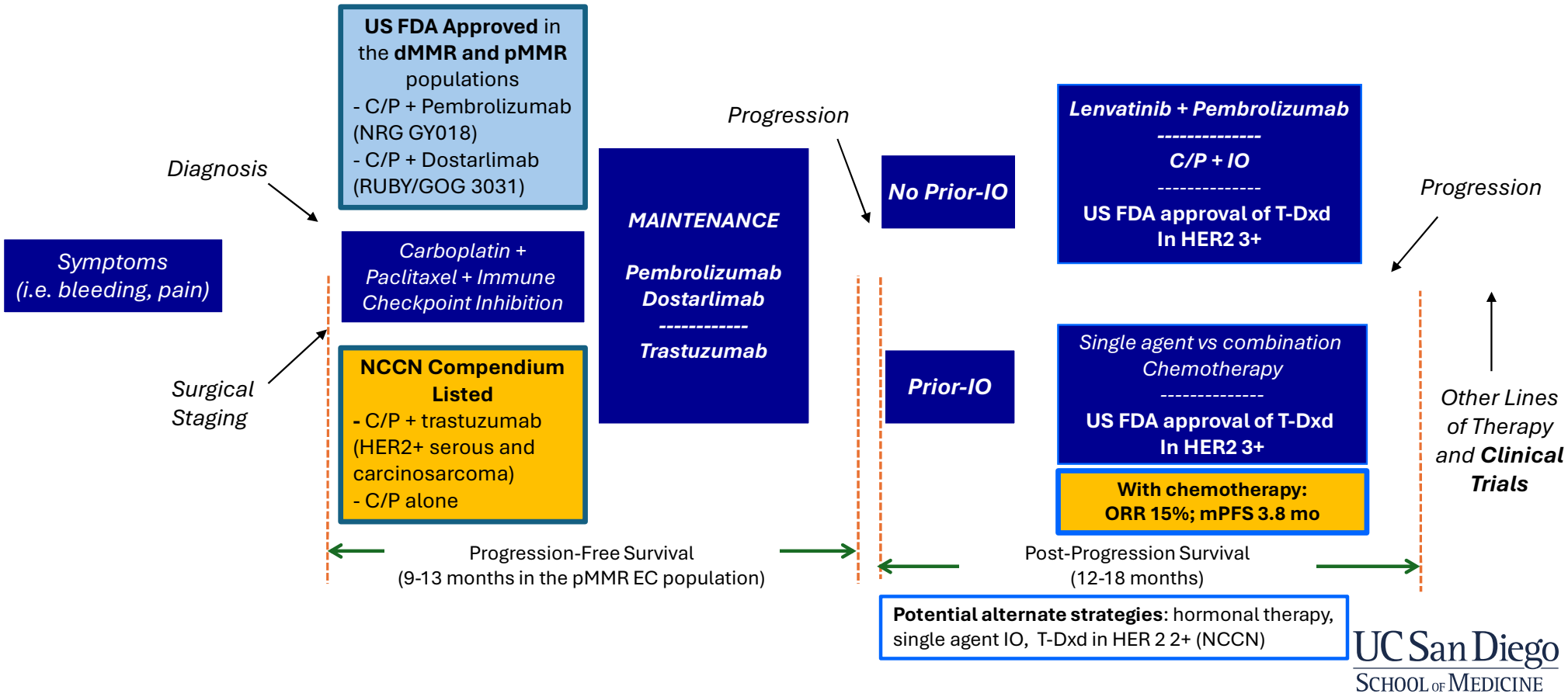
	Events/Patients	HR (95% CI)
Overall	504/842	0.91 (0.76-1.09)
Prior neo/adjuvant chemo		
Yes	81/121	0.52 (0.33-0.82)
No	423/721	0.94 (0.78-1.14)

- OS and PFS were similar between arms for the pMMR and All-Comer populations
- **Numerical increases in OS and PFS were observed with lenvatinib/pembrolizumab among patients with prior neoadjuvant/adjuvant chemotherapy**

NCT04865289

1. https://clinicaltrials.gov/study/NCT03884101. 2.Marth C et al. ESGO 2024. 3. Marth C et al. SGO 2024. 4. Pignata S et al ESMO-GYN 2024 Abstract 39O.

Evolving Treatment Landscape for the Management of Advanced Stage or Recurrent Endometrial Cancer



UC San Diego
School of Medicine