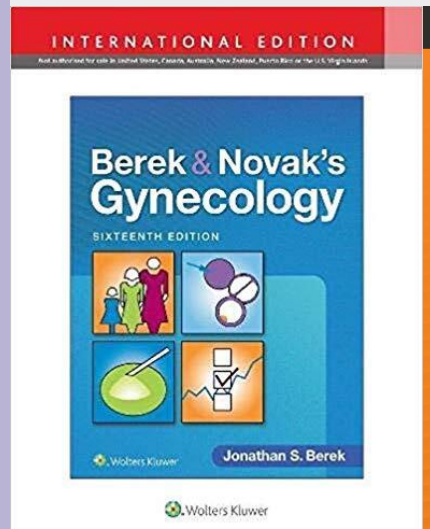
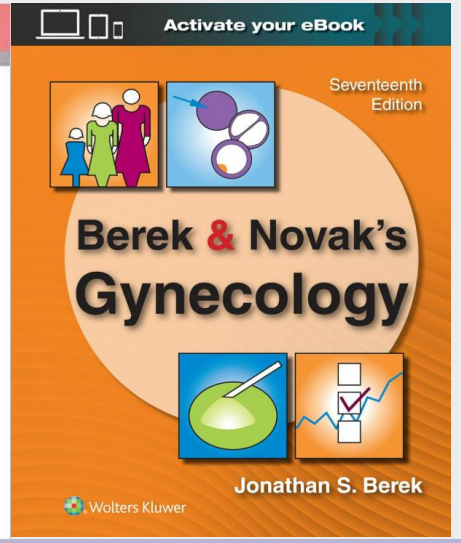
Updates on Endometrial Cancer





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DECLARATION OF INTERESTS

Nothing to declare

Low TMB / Cold Tumor / pMMR

CD8+ T cells infiltration ↓

Immune Exclusion

High TMB / Hot Tumor / MSI-H

CD8+ T cells infiltration↑

PD-1/PD-L1: T cell exhaustion

ICI (+): Tumor Clearance

Why endometrial cancer is changing fast

- Most common gynecologic malignancy in high-income countries — with rising incidence and rising mortality, a trend opposite to most cancers.
- Driven by aging populations, obesity, and metabolic disease.
- Historically staged by anatomy alone (FIGO 2009); adjuvant decisions rested on grade, depth of invasion, and LVSI.
- The TCGA molecular framework revealed four biologically distinct subtypes anatomy could not capture.

- **Three shifts redefining practice**
  - **Molecular classification** Now embedded directly in FIGO 2023 staging.
  - **Molecular-directed adjuvant therapy** De-escalation and escalation by subtype.
  - **Chemo-immunotherapy** New first-line standard in advanced / recurrent disease.

KEY POINTS

1. The most common risk factors for the development of endometrial carcinoma are related to prolonged, unopposed estrogen stimulation.
2. Office endometrial aspiration biopsy is the accepted first step in evaluating a woman with abnormal uterine bleeding or suspected endometrial pathology.
3. Serous and clear cell endometrial carcinomas make up less than 10% of endometrial cancers, yet account for more than one-half of all endometrial cancer deaths.
4. Most patients with endometrial cancer should undergo surgical treatment including hysterectomy, bilateral salpingo-oophorectomy, sentinel lymph node biopsy when possible, and peritoneal cytology.
5. The most important adverse prognostic variables in endometrial cancer are advancing patient age, nonendometrioid or grade 3 histology, deep myometrial invasion, lymphovascular invasion, large tumor size, cervical extension, lymph node metastasis, and intraperitoneal spread.
6. Postoperative adjuvant radiotherapy and chemotherapy in selected patients with endometrial cancer decreases the risk of local vaginal/pelvic recurrence and improves disease-free survival.
7. Overall 5-year survival rate in endometrial cancer is approximately 75%.
8. Radiotherapy is the best treatment option for patients with isolated local–regional recurrences who have not received prior radiation. Isolated vaginal recurrences may be successfully treated in as many as 80% of patients.
9. The molecular classification of endometrial tumors is rapidly evolving and helps direct targeted treatment in the primary and recurrent setting.
10. Uterine sarcomas are, in general, the most malignant group of uterine tumors and differ from endometrial cancers with regard to risk factors, diagnosis, clinical behavior, pattern of spread, and management.

FIGO 2023 STAGING

Biology enters the staging system

FIGO 2009 was purely anatomic; the 2023 update integrate s histologic type, grade, LVSI, and molecular classification.

Aggressive (non-endometrioid) histologies are staged differ ently from low-grade endometrioid tumors at the same dept h.
Substantial LVSI and lymph node metastasis size are now f ormally incorporated.

Complete molecular classification is encouraged in all cases .

The molecular modifier "m"

In Stages I–II, POLEmut and p53abn status can change the stage:

↓ POLEmut early disease is down-staged → **IAmPOLEmut**

↑ p53abn early disease is up-staged → **IICmp53abn**

~27%

of cases reclassified under FIGO 2023m in a 720-patient cohort — with better prognostic discrimination than FIGO 2009.

Surgical foundation: *sentinel lymph node mapping has largely replaced full lymphadenectomy in apparent early-stage disease.*

Table 37-7A FIGO Staging of Endometrial Cancer 2023[a,b]

Stage	Description
Stage I	Confined to the uterine corpus and ovary[c]
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d]
IC	Aggressive histological types[e] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma with extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[d] of non-aggressive histological types
IIC	Aggressive histological types[e] with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[f] IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIICii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

Table 37-7B Molecular Findings in Patients with Early Endometrial Cancer

Optional Stage Designation	Molecular Findings in Patients with Early Endometrial Cancer (Stages I and II After Surgical Staging)
Stage IAm^{POLEmut}	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage IICm^{p53abn}	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

Table 37-6 Carcinoma of the Endometrium (2009)

Stage I[a]	Tumor confined to the corpus uteri
IA[a]	No or less than half myometrial invasion
IB[a]	Invasion equal to or more than half of the myometrium
Stage II[a]	Tumor invades cervical stroma, but does not extend beyond the uterus[b]
Stage III[a]	Local and/or regional spread of the tumor
IIIA[a]	Tumor invades the serosa of the corpus uteri and/or adnexae[c]
IIIB[a]	Vaginal and/or parametrial involvement[c]
IIIC[a]	Metastases to pelvic and/or para-aortic lymph nodes[c]
IIIC1[a]	Positive pelvic nodes
IIIC2[a]	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV[a]	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA[a]	Tumor invasion of bladder and/or bowel mucosa
IVB[a]	Distant metastases, including intraabdominal metastases and/or inguinal lymph nodes

The four TCGA-derived molecular subtypes

POLEmut

POLE ultramutated

~5–10%

Pathogenic POLE exonuclease mutation
Very high tumor mutational burden
Often young, early stage

Excellent prognosis

MMRd / MSI-H

Mismatch-repair deficient

~25–30%

Loss of MLH1/PMS2/MSH2/MSH6
Mostly MLH1 hypermethylation
Screen for Lynch syndrome

Intermediate prognosis

NSMP

No specific molecular profile

~40–50%

"Copy-number low"
Often ER/PR+, endometrioid
Heterogeneous group

Intermediate prognosis

p53abn

p53 abnormal

~15%

"Copy-number high"
Serous-like; akin to HGSOC
Most recurrences & deaths

Poor prognosis

MMR / MSI TESTING

Universal IHC screening of tumor for MMR defects (MSI testing if inconclusive). **Reflex MLH1 promoter-methylation** testing with MLH1 loss → germline testing for **Lynch syndrome**. **MSH2 / MSH6 / PMS2 loss** → also offer germline testing. Address disparities in access to counseling & targeted therapy.

FRAMEWORK & DIRECTION

ProMisE algorithm provides a clinically applicable testing framework — predictive & prognostic. **1.8–9.8%** of tumors carry >1 classifier (multiple-classifier). Endometrial MSI arises via **MLH1 hypermethylation** vs MMR-gene mutation in colon cancer. **Trials ongoing** on treatment escalation / de-escalation by molecular class.

ADJUVANT THERAPY

Tailoring adjuvant treatment by molecular class

Subtype	Early-stage direction	Rationale & evidence
POLEmut	**De-escalate / observe**	Excellent outcomes even at higher stage; adjuvant therapy generally omitted in st age I–II.
MMRd	Standard; immunotherapy under study	Highly responsive to checkpoint blockade; adjuvant IO being tested in high-risk di sease.
NSMP	Risk-adapted (often hormone-driven)	ER/PR-positive tumors may benefit from endocrine strategies; treat by clinicopath ologic risk.
p53abn	**Intensify**	Poor prognosis; PORTEC-3 showed chemoradiotherapy benefit; HGSOC-like bio logy supports chemo ± targeted agents.

RAINBO program: *a platform of trials prospectively testing class-specific adjuvant strategies for each of the four molecular subtypes.*

1

MOLECULAR-DRIVEN THERAPY

Immune Checkpoint Inhibitors

MSI-H subtype (TCGA) arises from sporadic/inherited **mismatch-repair** defects. MSI status is a surrogate for CPI response — pembrolizumab received **site-agnostic FDA approval (2017)**.

RUBY

dostarlimab + carboplatin/paclitaxel

dMMR — median PFS

30.3 mo vs 7.7 mo placebo

HR 0.29, P < .0001

24-mo overall survival: **71.3% vs 56.0%** (HR 0.64)

Included advanced / first-recurrence disease and carcinosarcomas.

NRG-GY018

pembrolizumab + CP → maintenance

Improved PFS in **both dMMR and pMMR** cohorts

dMMR benefit **> pMMR**

Rationale: chemotherapy boosts tumor-antigen production and induces PD-L1 expression, driving immune stimulation.

Measurable stage III/IVA, IVB or recurrent disease; carcinosarcoma excluded.

2

TARGETED RECEPTOR THERAPY

Her-2/neu–Directed Agents

Her-2/Neu — a tyrosine-kinase receptor central to cancer signaling, growth, and survival — is overexpressed in uterine **serous carcinoma** and **carcinosarcoma**.

Fader et al. — Phase II

Advanced or recurrent serous endometrial carcinoma

Regimen: **trastuzumab** (anti–Her2/Neu mAb) added to carboplatin/paclitaxel, followed by **trastuzumab maintenance**.

Outcome: **improved progression-free and overall survival.**

ELIGIBILITY

Her-2/Neu–positive tumors

IHC 3+

IHC 3+

Strong, complete membrane staining

2+

IHC 2+ with FISH

Equivocal IHC confirmed by gene amplification

3

SUSTAINING RESPONSE

Maintenance Therapy

SIENDO

ENGOT-EN5 / GOG-3055

Maintenance **selinexor** after CR/PR to carbo/paclitaxel. A **XPO-1 inhibitor** — drives nuclear accumulation and reactivation of tumor suppressors (e.g. **p53**).

TP53-wildtype — median PFS

13.7 mo vs 3.7 mo placebo

FDA-approved in relapsed/refractory multiple myeloma and DLBCL; a potential future option for TP53wt tumors.

GOG 86P

targeted agents + chemotherapy

Investigated targeted agents combined with chemotherapy in advanced/recurrent endometrial cancer.

Exploratory analysis — mutated p53

Improved PFS & OS

when **bevacizumab** was added to chemotherapy and continued as maintenance.

Biomarker takeaway: TP53 status is emerging to guide maintenance selection — **TP53wt → selinexor** | **mutated p53 → bevacizumab**.

ADJUVANT THERAPY · KEY TRIAL

PORTEC-4a: molecular-profile-based treatment

A randomized phase 3 non-inferiority trial in high-intermediate risk early-stage endometrial cancer.

- 564 patients randomized 2:1 to molecular-integrated risk-profile-based treatment vs standard vaginal brachytherapy.
- Profile group: favorable → observation; intermediate → brachytherapy; unfavorable → external-beam radiotherapy.
- Distribution: 46% favorable · 40% intermediate · 14% unfavorable.
- The molecular-profile strategy met the pre-defined non-inferiority margin for vaginal control.

Non-inferior

Met pre-defined non-inferiority margin for vaginal control.

~46%

of patients had a favorable profile and could safely be spared adjuvant radiotherapy.

Take-home: *molecular stratification enables safe de-escalation for many women — reducing treatment morbidity without compromising locoregional control.*

KEYNOTE-B21: adjuvant pembrolizumab in high-risk EC

Phase 3 ENGOT-en11/GOG-3053 (N=1095): pembrolizumab vs placebo added to adjuvant chemotherapy ± radiotherapy after curative surgery for newly diagnosed high-risk EC.

Primary endpoint negative overall

DFS in the ITT population showed **no benefit**: HR 1.02 (0.79–1.32), p = 0.570.

But the dMMR subgroup (~25%)

HR 0.31

95% CI 0.14–0.69
for disease-free survival

Disease-free survival by MMR status

Population	HR (95% CI)	Direction
ITT (all-comers)	1.02 (0.79–1.32)	**No benefit**
pMMR	1.20 (0.91–1.57)	**No benefit**
dMMR	0.31 (0.14–0.69)	**Favors pembro**

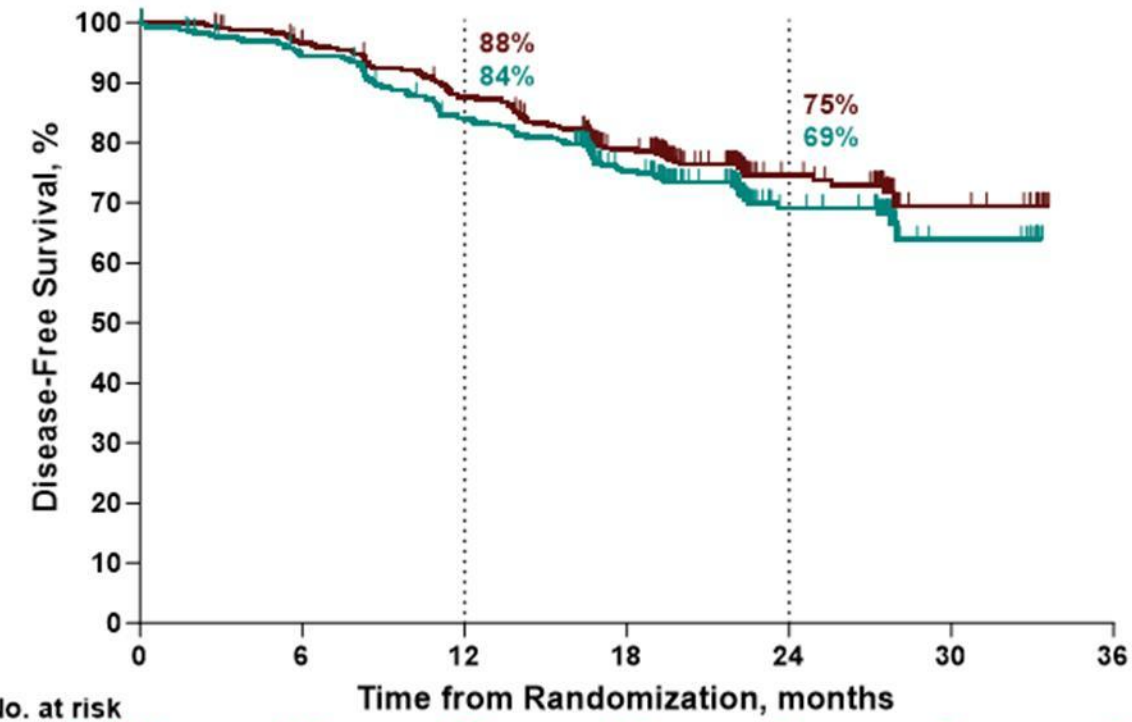
OS immature at interim; combination safety manageable with no treatment-related deaths.

Clinical message: *adjuvant checkpoint benefit is confined to dMMR — MMR testing should drive patient selection in the curative setting.*

Pembrolizumab Plus Chemotherapy Improved DFS[a] in dMMR Subgroup

pMMR Subgroup

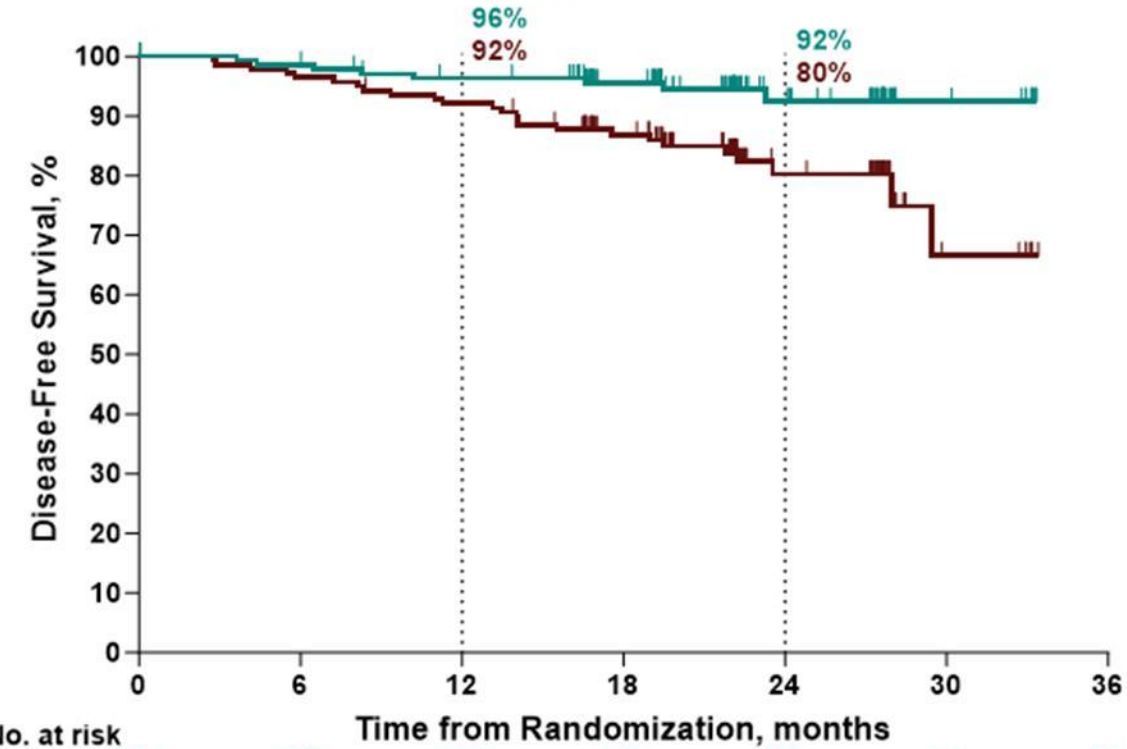
	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembro + CT	111 (27)	NR (NR–NR)	1.20 (0.91–1.57)
Placebo + CT	96 (23)	NR (NR–NR)	



No. at risk							
Pembro + CT	404	369	323	244	88	17	0
Placebo + CT	410	381	343	259	94	16	0

dMMR Subgroup

	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembro + CT	8 (6)	NR (NR–NR)	0.31 (0.14–0.69)
Placebo + CT	25 (18)	NR (29.5–NR)	



No. at risk							
	141	136	129	103	46	10	0
	140	134	127	99	38	7	0

[a]DFS was defined as the time from randomization to local or distant recurrence of EC (assessed radiographically by the investigator or by histopathologic confirmation) or death from any cause.
Data cutoff date: March 4, 2024.

Why the dMMR benefit is biologically expected

Exploratory analysis of disease-specific survival (DSFS, death due to EC) from KEYNOTE-B21, by biomarker.

Disease-specific survival

dMMR

HR 0.17

0.06–0.49 · substantial benefit

pMMR

HR 1.11

0.83–1.47 · no benefit

In dMMR, benefit held **regardless of PD-L1 or TMB** (PD-L1 CPS ≥1: HR 0.14). In pMMR, no benefit was seen across any PD-L1 or TMB stratum.

dMMR EC is an inflamed phenotype

- **High PD-L1 expression** — CPS ≥1 in 91% of dMMR vs 80% of pMMR tumors
- **High tumor mutational burden** — TMB ≥10 mut/Mb in 88% of d MMR vs 16% of pMMR
- **Basis for checkpoint response** — Immunogenic biology drives durable anti–PD-1 activity

Takeaway: *the DSFS signal and tumor biology align — dMMR is the biomarker that unlocks adjuvant immunotherapy benefit.*

ADVANCED / RECURRENT DISEASE

First-line chemo-immunotherapy: pivotal trials

Trial	Added to carbo–paclitaxel	Population	Key result
NRG-GY018 (KEYNOTE-868)	Pembrolizumab → maintenance	Stage III–IV / recurrent; dMMR & pMMR cohorts	Significant PFS benefit in BOTH cohorts; OS benefit confirmed.
RUBY (Part 1)	Dostarlimab → maintenance	Primary advanced / first recurrence	Marked PFS gain (greatest in dMMR); significant OS benefit overall.
DUO-E	Durvalumab ± olaparib → maintenance	Newly diagnosed advanced / recurrent	PFS benefit; added PARP inhibitor explored, esp. in pMMR.

Effect is largest in dMMR / MSI-high tumors, *but benefit extends to pMMR disease — establishing chemo-IO as the new first-line backbone.*

NRG-GY018 (KEYNOTE-868): mature overall survival

Long-term follow-up of first-line pembrolizumab + carboplatin/paclitaxel vs placebo + CP in advanced / recurrent EC.

Updated overall survival by MMR cohort

Cohort	OS HR (95% CI)	Key OS metric
dMMR (n=223)	**0.56 (0.34–0.92)**	48-mo OS 78.6% vs 60.4%
pMMR (n=586)	0.86 (0.69–1.08)	Median 44.4 vs 35.1 mo

Sustained OS benefit despite heavy crossover — **93.2% (dMMR) and 81.1% (pMMR)** of control-arm patients received a subsequent checkpoint inhibitor.

dMMR overall survival

HR 0.56

44% lower risk of death vs chemotherapy alone (95% CI 0.34–0.92).

Approved US/EU 2024, regardless of MMR status.

Bottom line: *mature survival data cement first-line chemo-immunotherapy as standard of care, with the deepest effect in dMMR.*

Study 309/KEYNOTE-775: durable 5-year benefit

Lenvatinib + pembrolizumab vs treatment of physician's choice after prior platinum (N=827) — 5-year outcomes.

Outcomes at ~5 years of follow-up

Population	OS HR	PFS HR	ORR (len+pem vs TPC)
All-comers	0.66	0.56	33.8% vs 14.4%
pMMR	0.70	0.60	32.4% vs 14.8%
dMMR	**0.44**	**0.39**	41.5% vs 12.3%

Median OS in all-comers 18.7 vs 11.9 months. Benefit was durable and consistent with the primary analysis despite crossover, with a manageable safety profile and no new signals.

5-year overall survival (dMMR)

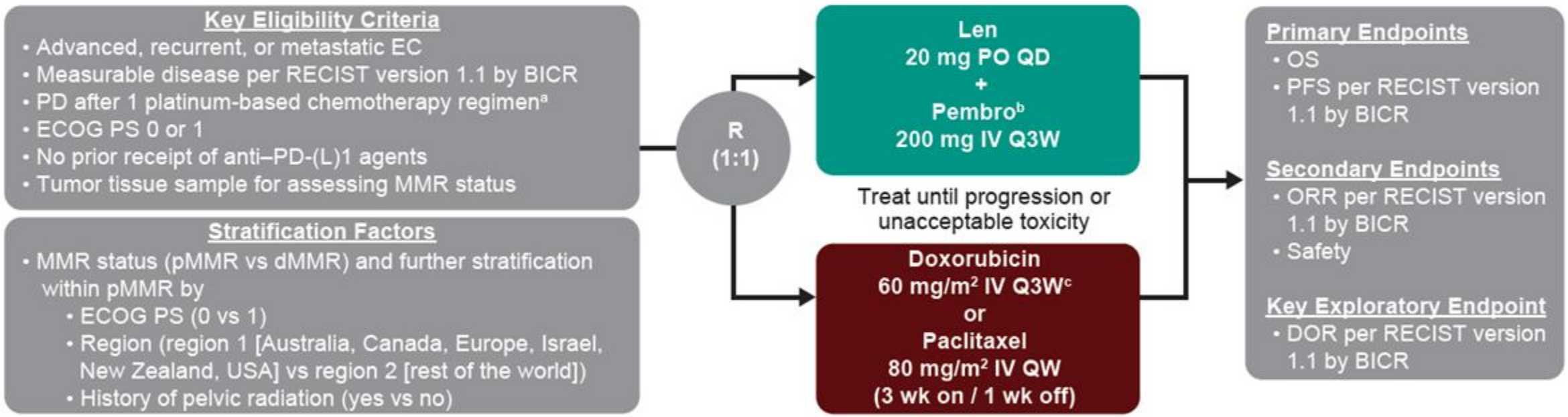
36.5%

vs **9.8%** with physician's choice

Now a standard of care for previously treated advanced / recurrent EC.

Second-line anchor: *len + pembro delivers durable long-term survival across MMR groups, deepest in dMMR.*

Study 309/KEYNOTE-775 Study Design



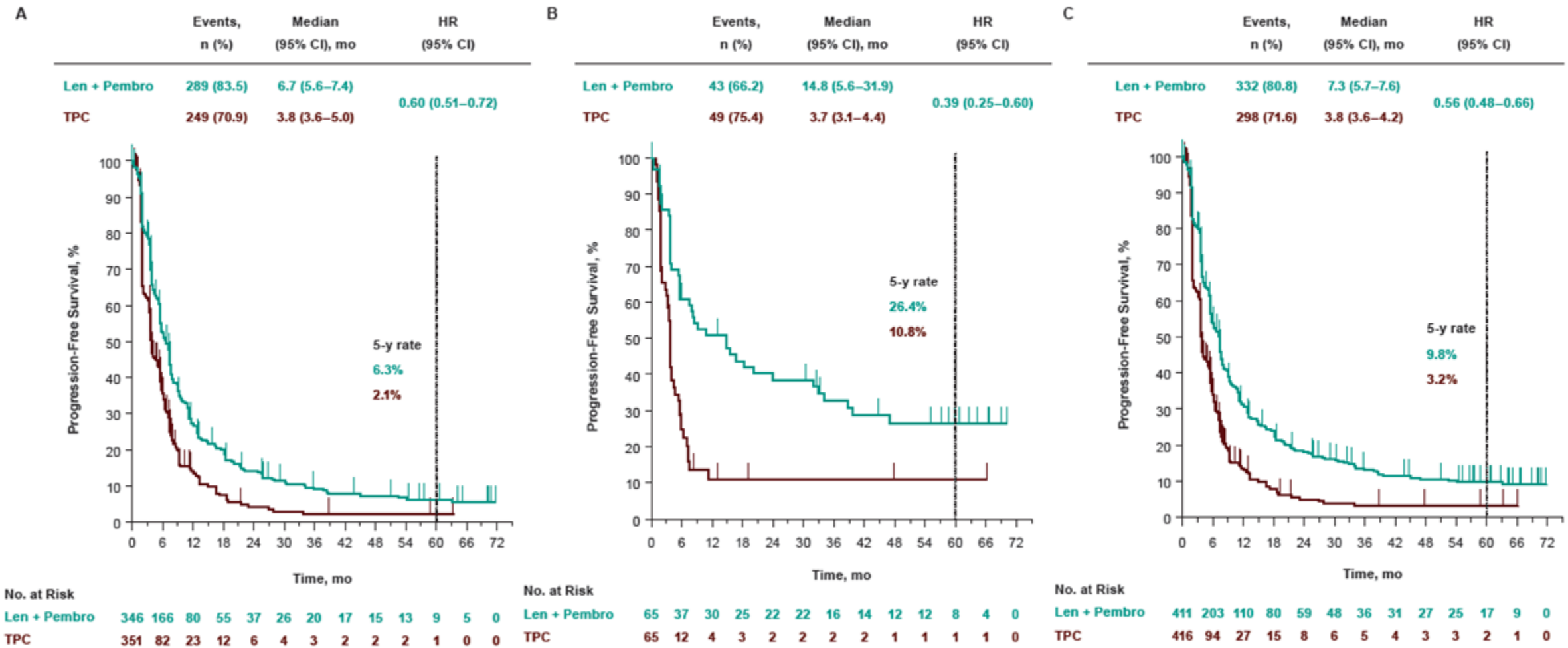
BICR, blinded independent central review; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MMR, mismatch repair; PD-(L)1, programmed cell death protein 1 or programmed cell death ligand 1; PO, oral; Q3W, every 3 weeks; QD, once daily; QW, once weekly.

[a]Participants may have received up to 2 prior platinum-based chemotherapy regimens if 1 was given in the neoadjuvant or adjuvant treatment setting.

[b]Maximum of 35 cycles.

[c]Maximum cumulative dose of 500 mg/m^2.

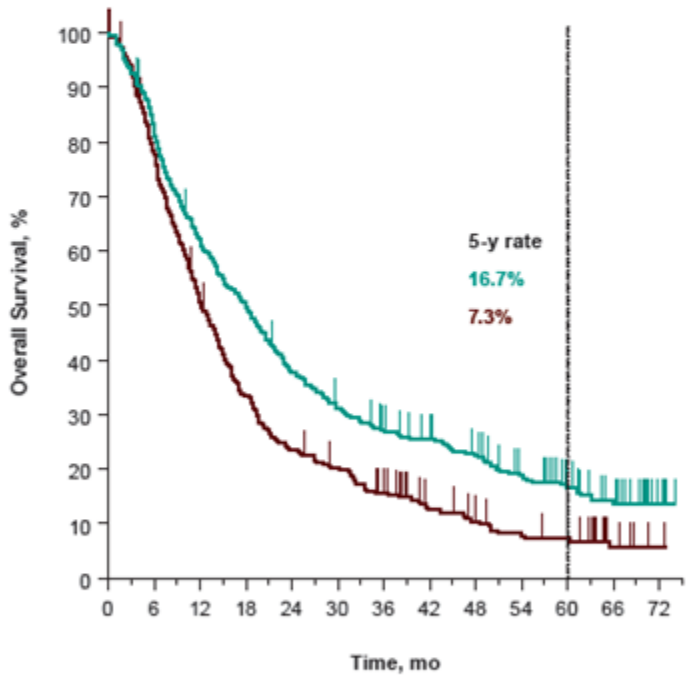
PFS per RECIST Version 1.1 by BICR in the (A) pMMR, (B) dMMR, and (C) All-Comer Populations at 5 Years of Follow-Up



OS in the (A) pMMR, (B) dMMR, and (C) All-Comer Populations at 5 Years of Follow-Up

A

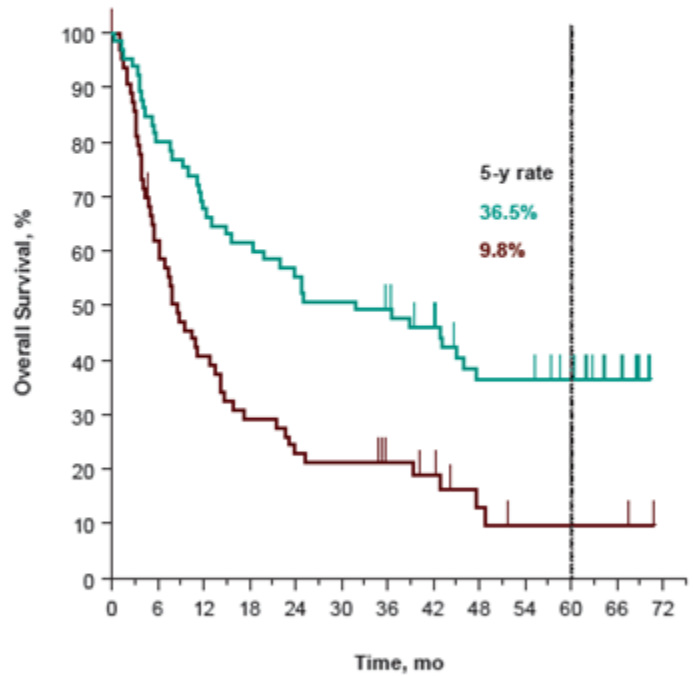
	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Len + Pembro	285 (82.4)	18.0 (14.9–20.5)	0.70 (0.60–0.83)
TPC	310 (88.3)	12.2 (11.0–14.1)	



No. at Risk													
Len + Pembro	346	285	213	171	129	105	89	79	66	48	36	21	4
TPC	351	268	173	113	80	67	49	32	24	18	15	5	1

B

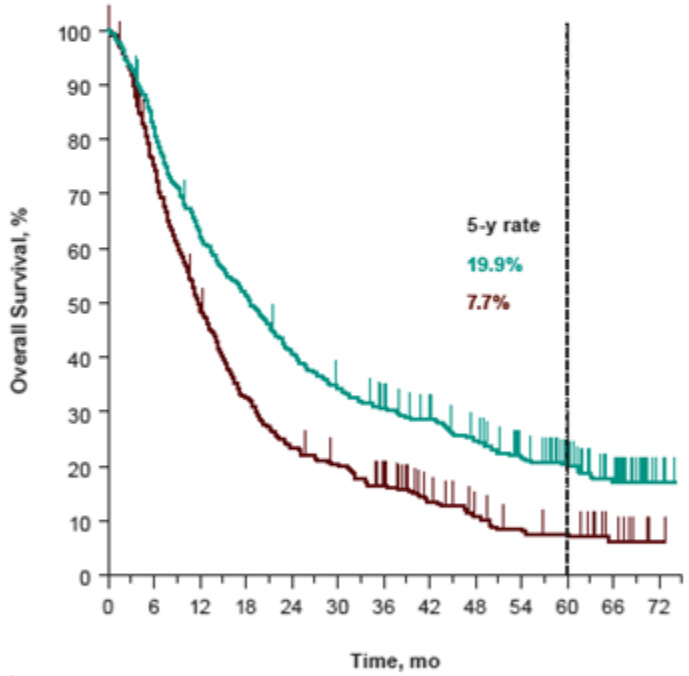
	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Len + Pembro	40 (61.5)	31.9 (15.6–47.7)	0.44 (0.29–0.67)
TPC	53 (81.5)	8.6 (5.5–13.4)	



No. at Risk													
Len + Pembro	65	52	44	40	36	33	31	27	19	19	15	8	0
TPC	65	38	25	18	14	13	10	8	4	2	2	2	0

C

	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Len + Pembro	325 (79.1)	18.7 (15.6–21.3)	0.66 (0.57–0.77)
TPC	363 (87.3)	11.9 (10.6–13.3)	



No. at Risk													
Len + Pembro	411	337	257	211	165	138	120	106	85	67	51	29	4
TPC	416	306	198	131	94	80	59	40	28	20	17	7	1

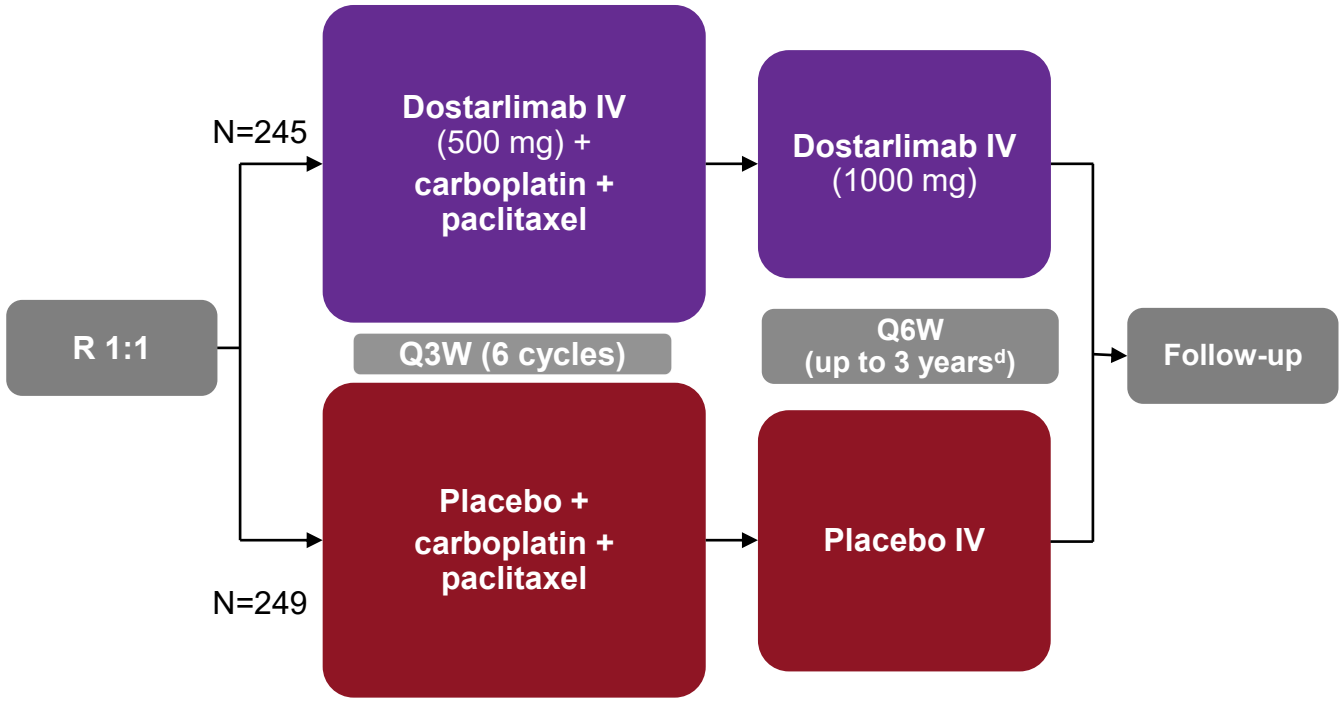
RUBY Trial - Study design

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**

Stratification

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



Primary endpoint

- PFS by INV[e] (IA1)
- **OS (IA1 & IA2)**

Secondary endpoints

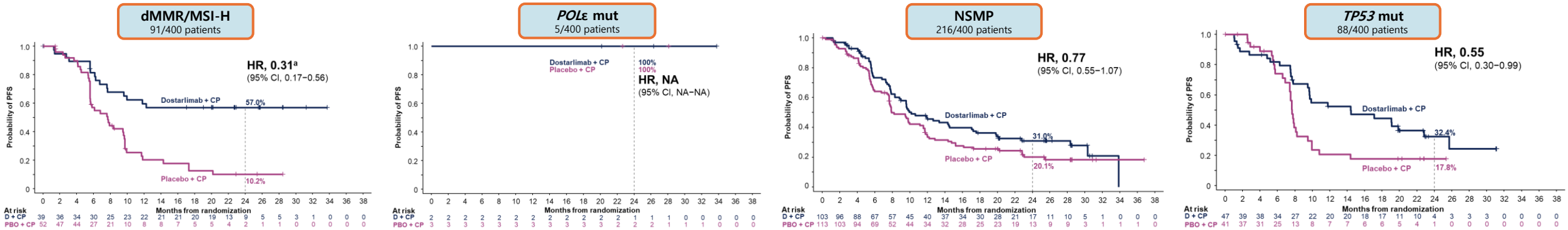
- PFS by BICR (IA1)
- PFS2 (IA1 & IA2)
- ORR (IA1)
- DOR (IA1)
- DCR (IA1)
- HRQOL/PRO (IA1)
- Safety (IA1 & IA2)

On-study imaging assessments were performed Q6W (±7 days) from the randomization date until week 25 (cycle 8), followed by Q9W (±7 days) until week 52. Subsequent tumor imaging was performed every 12 weeks (±7 days) until radiographic PD was documented by investigator assessment per RECIST v1.1 followed by one additional imaging 4–6 weeks later, or subsequent anticancer therapy was started, whichever occurred first. Thereafter, scans may have been performed per standard of care.
aHistologically/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. bCarcinosarcoma, clear cell, serous, or mixed histology permitted (mixed histology containing at least 10% carcinosarcoma, clear cell, or serous histology). cPatients were randomized based on either local or central MMR/MSI testing results. Central testing was used when local results were not available. For local determination of MMR/MSI status, IHC, next-generation sequencing, and polymerase chain reaction assays were accepted. For central determination of MMR/MSI status, IHC per Ventana MMR RxDx panel was used. dTreatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the sponsor and the investigator. eThe threshold for the primary endpoint of PFS was crossed at IA1. Therefore, IA1 was considered the final analysis for PFS.
BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; EC, endometrial cancer; HRQOL, health-related quality of life; IA, interim assessment; IHC, immunohistochemistry; INV, investigator assessment; IV, intravenous; MMR, mismatch repair; MSI, microsatellite instability; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRO, patient-reported outcome; Q3W, every 3 weeks; Q6W, every 6 weeks; Q9W, every 9 weeks; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.
Powell MA, et al. Ann Oncol. 2024;35(8):728-738.

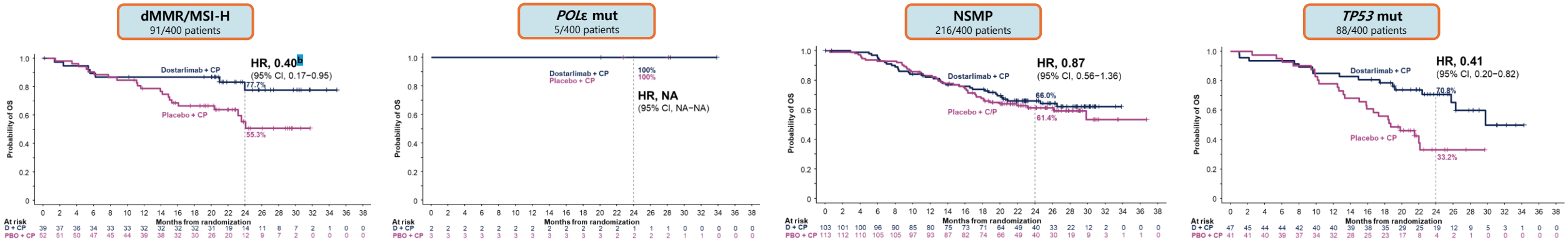
PFS and OS in RUBY Part 1 According to Molecular Subgroup[1]

dMMR/MSI-H, POLε mut, NSMP, and TP53 mut

Progression Free Survival (PFS)



Overall Survival (OS)



- Figures derived from 400/494 patients with known molecular classification per whole exome sequencing.

[a]Primary endpoint of PFS in dMMR/MSI-H patients (n=118) showed hazard ratio 0.28; P < 0.0001. [b]Prespecified OS analysis in dMMR/MSI-H patients (n=118) showed HR, 0.30.

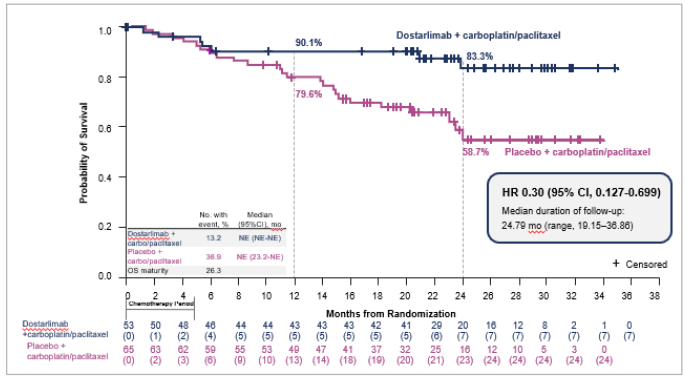
CI, confidence interval; **CP**, carboplatin-paclitaxel; **D**, dostarlimab; dMMR, mismatch repair deficient; **HR**, hazard ratio; **MSI-H**, microsatellite instability-high; **mut**, mutated; **NA**, not applicable; **NSMP**, no specific molecular profile; **OS**, overall survival; **PBO**, placebo; **PFS**, progression-free survival; **POLε**, polymerase epsilon; **TP53**, tumor protein 53.

1. . Mirza MR, et al. Annals of Oncology, Volume 34, Supplement 2, S507, October 2023. 2. Mirza MR, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023 Jun 8;388(23):2145-2158.

Up-to-date RUBY OS Data

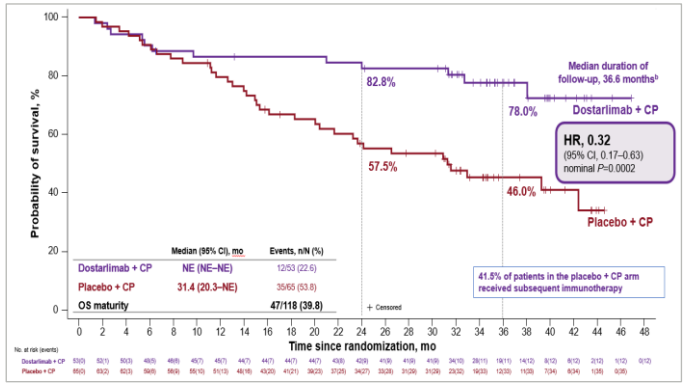
2023 SGO[1] (2-year)

- RUBY Part 1 IA1 OS
- Median duration of follow-up: 24.8 mo.
- dMMR/MSI-H: HR 0.30



2024 SGO[2] (3-year)

- RUBY Part 1 IA2 OS
- Median duration of follow-up: 36.6 mo.
- dMMR/MSI-H: HR 0.32



2026 SGO[3] (4-year)

Overall Survival	dMMR/MSI-H	
	Dostarlimab + CP (N=53)	Placebo + CP (N=65)
Median OS (95% CI), mo	NR (NR-NR)	32.8 (21.6-NR)
OS maturity, % (n/N)	44.9 (53/118)	
HR (95% CI)	0.34 (0.19-0.63)	
4-y OS rate, % (95% CI)	72.8 (58.5-82.9)	40.3 (28.2-52.1)

1. Mirza MR, et al. N Engl J Med. 2023;388:2145-2158 2. Powell MA, et al. Ann Oncol. 2024;35(8):728-738. 3. Abstracts / Gynecologic Oncology 208 (2026) S30–S67

ADVANCED / RECURRENT DISEASE

Why MMR status now drives every decision

Regulatory landscape

- 2023 — Dostarlimab + chemotherapy approved for advanced / recurrent disease.
- June 2024 — Pembrolizumab + chemotherapy approved regar dless of MMR status, with maintenance.
- NCCN recommends checkpoint-inhibitor-containing first-line re gimens broadly.

Clinical workflow

- Test MMR/MSI on every endometrial cancer — it guides syste mic therapy and flags Lynch syndrome.
- dMMR: exceptional checkpoint-inhibitor responses, including in later lines.
- pMMR: chemo-IO still beneficial; PARP and antibody–drug conj ugates under active study.

Beyond first line: *lenvatinib + pembrolizumab remains an option for previously treated pMMR disease; HER2-directed and folate-rec eptor ADCs are emerging.*

RECENT CONGRESS UPDATE · EMERGING

ESMO 2025

Sacituzumab tirumotecan: a TROP2 ADC after platinum

2870-001/KL264-01 phase 1/2 (N=158): sacituzumab tirumotecan (Sac-TMT) monotherapy in advanced / metastatic EC after ≥1 prior platinum line.

31.6%
Confirmed ORR

74.7%
Disease control rate

9.3 mo
Median duration of response

TROP2-directed ADC

Anti-TROP2 antibody + topoisomerase-I payload

TROP2 near-ubiquitously expressed in EC

A chemotherapy-free option after platinum

Median PFS 6.0 months and median OS 14.4 months (4 mg/kg cohort); the 4 and 5 mg/kg doses had similar efficacy with a manageable safety profile.

On the horizon: *phase 3 TroFuse-005 (monotherapy) and TroFuse-033 (with pembrolizumab maintenance in pMMR) are now testing Sac-TMT prospectively.*

SUMMARY

Key takeaways for practice

1 **Molecular classification on every case.** POLE, MMR/MSI, and p53 status now drive staging, prognosis, and treatment — FIGO 2023 down-stages POLEmut and up-stages p53abn.

2 **Adjuvant immunotherapy is dMMR-specific.** KEYNOTE-B21 was negative overall yet showed a strong dMMR signal (D FS HR 0.31; DSFS HR 0.17). De-escalate POLEmut, intensify p53abn (PORTEC-4a spares radiotherapy in many).

3 **Chemo-immunotherapy is the first-line standard.** NRG-GY018, RUBY, and DUO-E — and mature NRG-GY018 OS (d MMR HR 0.56; ASCO 2026) confirms a durable survival gain, deepest in dMMR.

4 **Recurrent disease keeps expanding.** Lenvatinib + pembrolizumab shows durable 5-year benefit (KEYNOTE-775), and t he TROP2 ADC sacituzumab tirumotecan is an emerging post-platinum option.

Korean Society of
Gynecologic Oncology

2026년
대한부인종양학회 하계학술대회
제20차 젊은의사 워크숍
제9차 분과전문의 연수강좌
제1차 부인종양간호사 연수강좌
& 카데바 워크숍

일자 2026년 8월 8일(토) - 9일(일)

장소 위례 밀리토피아 마린 호텔 / 가톨릭대학교 응용해부연구소

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