Where Science Becomes Hope

NEW THERAPIES IN ADVANCED/RECURRENT ENDOMETRIAL CANCER: WHERE ARE WE NOW?

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EMORY WINSHIP CANCER INSTITUTE

National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

DISCLOSURES

- I receive a stipend as EIC of *Gynecologic Oncology Reports*
- I have done one consulting board for Eisai and have received stipends for nonbranded talks for OncLive and Curio sponsored conferences
- Our division has received clinical trial funding support from multiple companies (Ergomed, Gilead, Corcept, and Mersana)
- Huge shout out to many of my national colleagues for sharing slides (Drs. Powell, Walsh and Slomovitz)

TALK OVERVIEW

- General GYN cancer numbers
  - Endometrial cancer treatment overview
  - Overall NCCN general guidelines for initial treatment of advanced cancers
- Overall recommendations for initial treatment of advanced cancer
  - MMR deficient endometrial cancer
  - MMR proficient endometrial cancer
- Beyond paclitaxel/carboplatin and immunotherapy
  - ADC's
  - Hormonal combinations
  - Other pipeline options

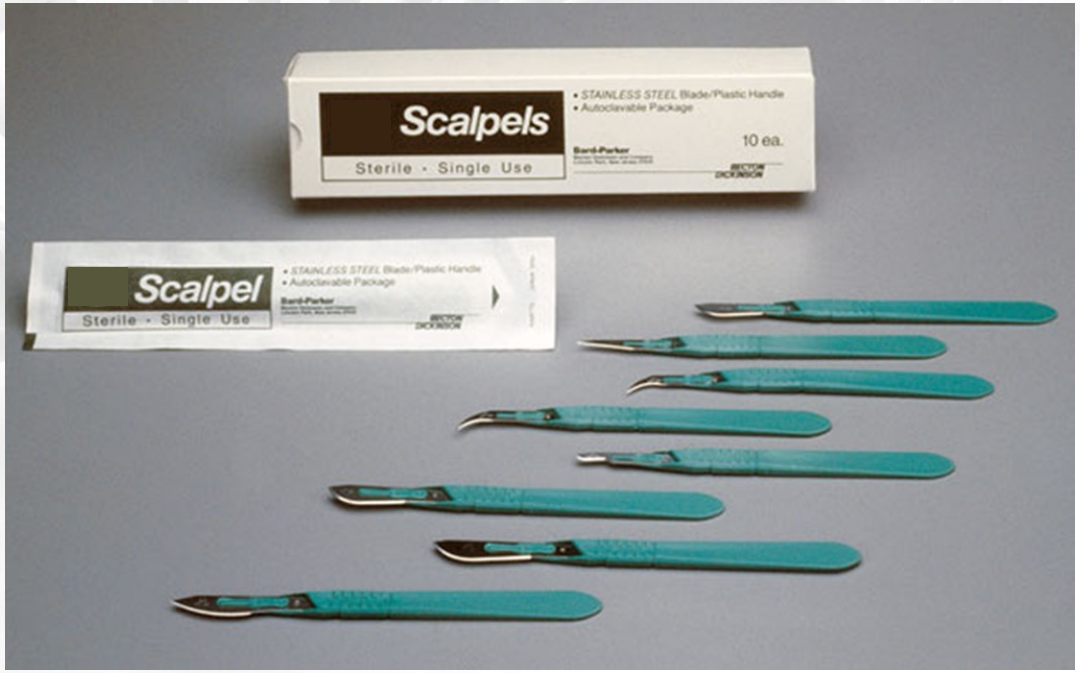
U.S. FEMALE CANCER STATISTICS 2025

Site	Number	Deaths
Breast	316,950	42,170
Uterus	69,120	13,860
Ovary	20,890	12,730
Cervix	13,360	4,320
Vulva	7,480	1,770

American Cancer Society. Cancer Facts and Figures 2025

ENDOMETRIAL CANCER INITIAL TREATMENT OPTIONS

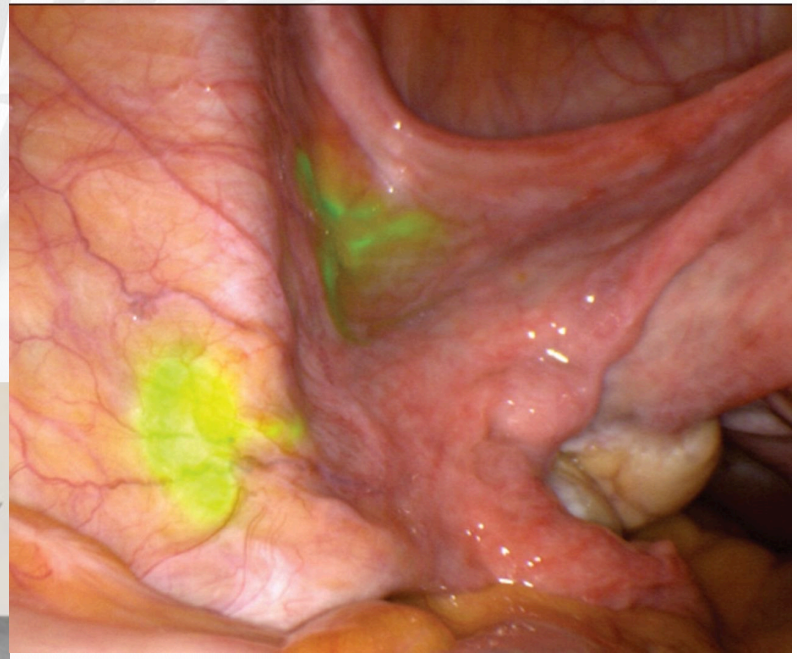
- Surgery
- Radiation
- Chemotherapy*



Surgery: A chance to cut is a chance to cure

***Includes standard cytotoxic chemotherapy, hormones, targeted therapy, immunotherapy etc.**

SURGERY STILL REIGNS SUPREME FOR EARLY STAGE DISEASE….DESPITE EVERYTHING THAT DR. LONIAL SAYS



A VARIETY OF "TARGETED" TREATMENT MODALITIES ARE USED IN THE TREATMENT OF ENDOMETRIAL CANCER

Surgery	• Hysterectomy with BSO • SNL vs. Pelvic and periaortic lymph node dissection vs NO NODES (level 1 data for NO nodes) • With a better understanding of the immune system interaction with EC should consider NO NODES
Radiotherapy	• Vaginal brachytherapy • External-beam radiation therapy • SBRT when oligo-metastatic recurrences happen

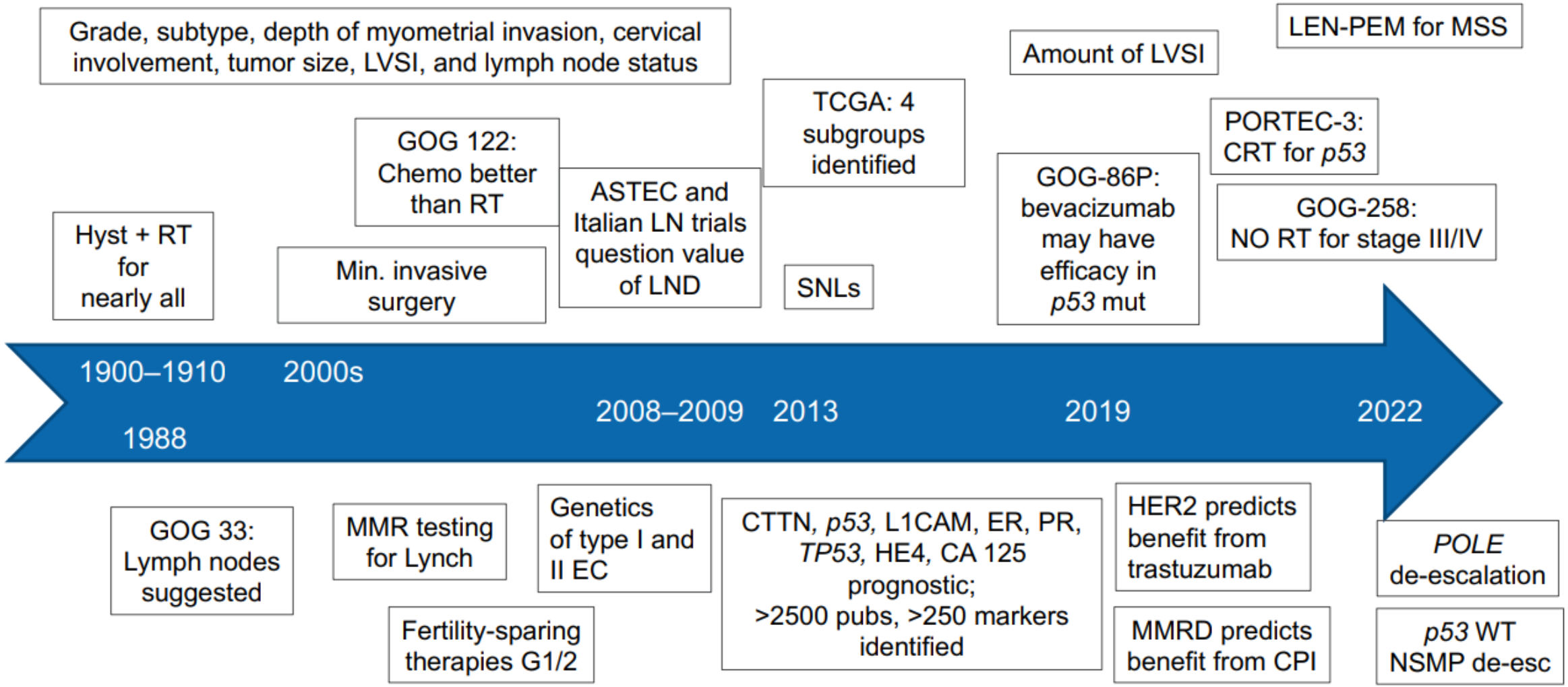
Chemotherapy	• Multiple regimens including
	  ○ Carboplatin and paclitaxel (including carcinosarcoma)
	  ○ Cyclophosphamide, doxorubicin, weekly paclitaxel and cisplatin

Hormone therapy	• Progestational agents (hydroxyprogesterone, medroxyprogesterone, or megestrol[a]) • Tamoxifen • Aromatase inhibitors, CD4/6, COMBINATIONS; NEED to develop further especially for NSMP
Biologic/ targeted therapy	• mTOR inhibitors, anti-VEGF (Bevacizumab, Lenvatinib, others), HER2 targeted therapies • Immune CPIs (including dual therapy, and combination with chemotherapy

[a] Megestrol acetate and pembrolizumab (for MSI-H/dMMR tumors) are the only systemic therapies with FDA approval for the treatment of endometrial cancer.[2,3]

BSO, bilateral salpingo-oophorectomy; dMMR, deficient mismatch repair; MSI-H, high microsatellite instability; FDA, US Food and Drug Administration; mTOR, mammalian target of rapamycin.

History of Management of Endometrial Cancer: Journey From Prognostic to Predictive Markers



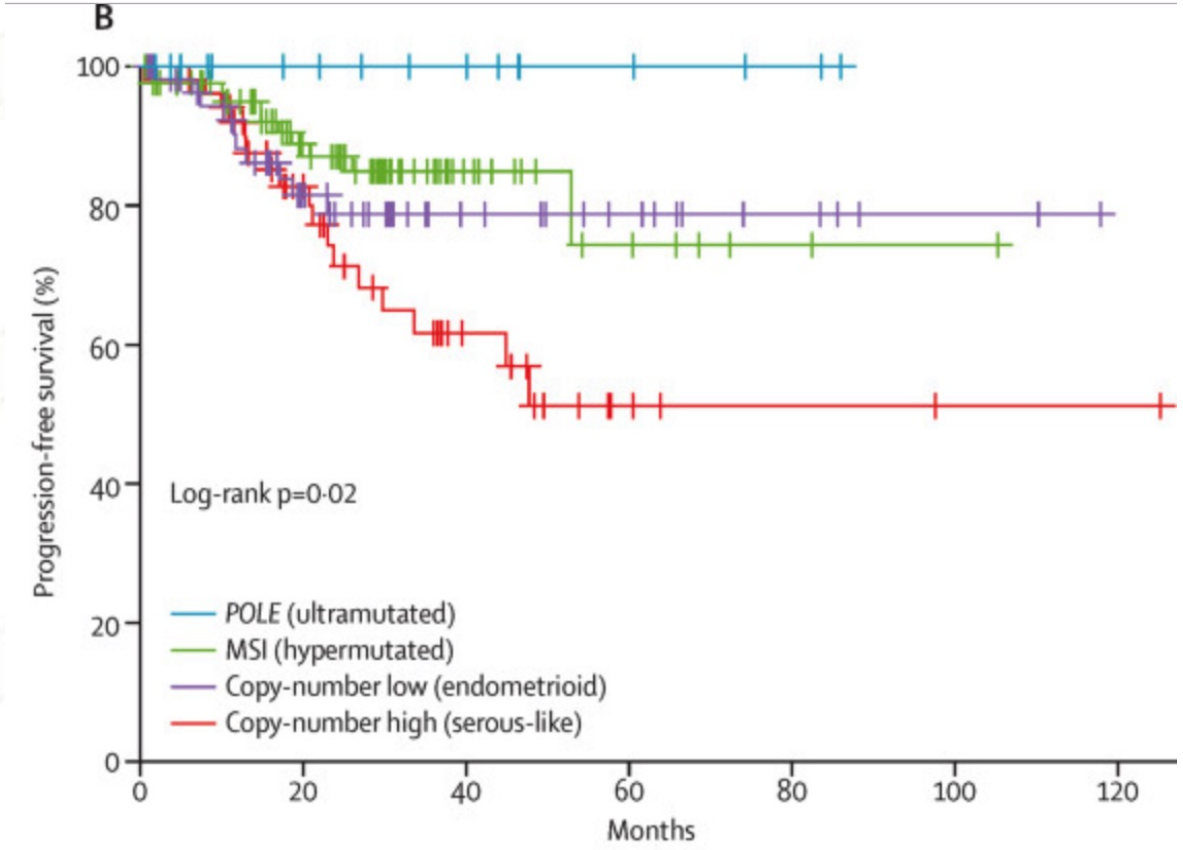
Courtesy of Matthew A Powell, MD

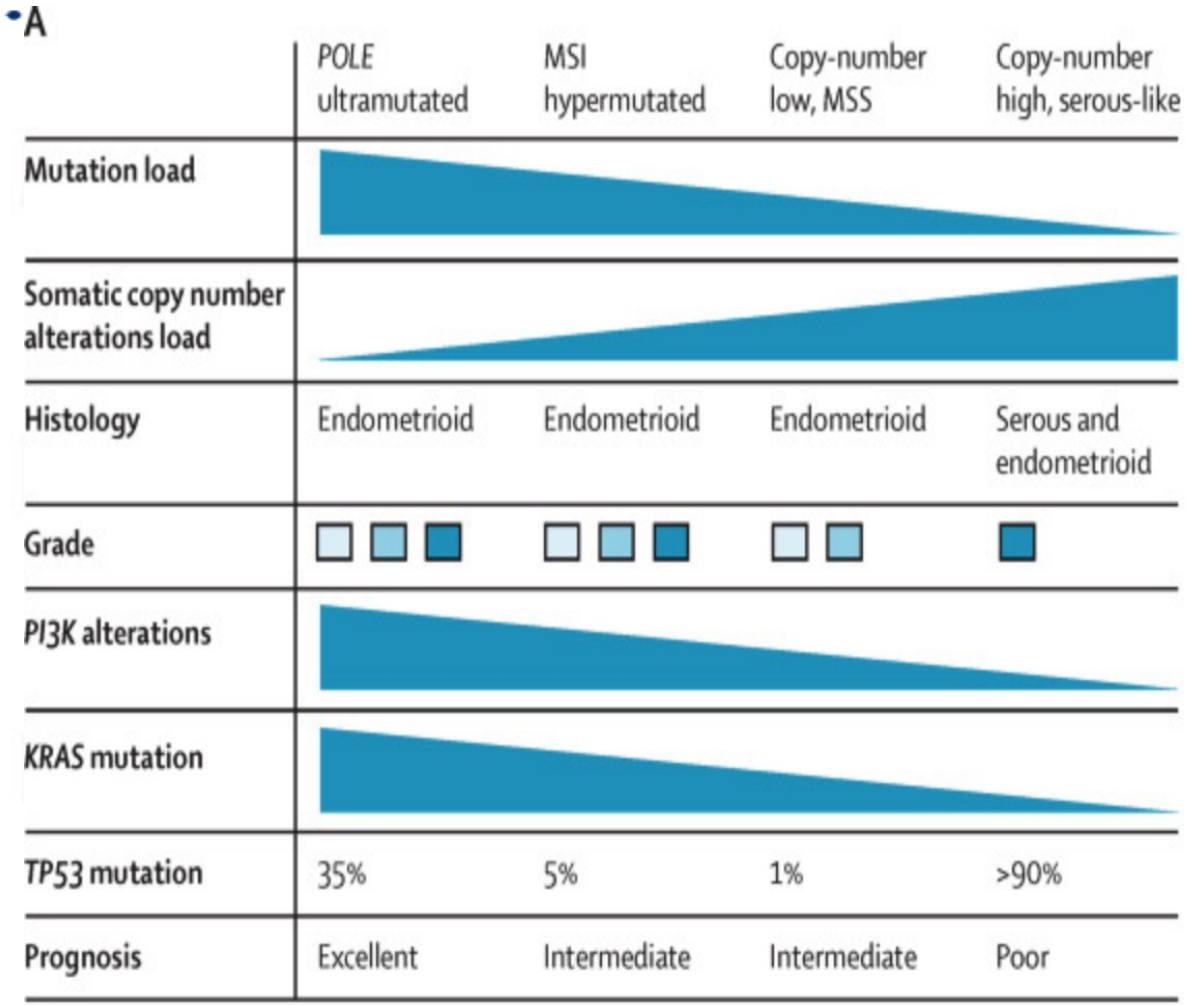
ARTICLE

OPEN
doi:10.1038/nature12113

Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*



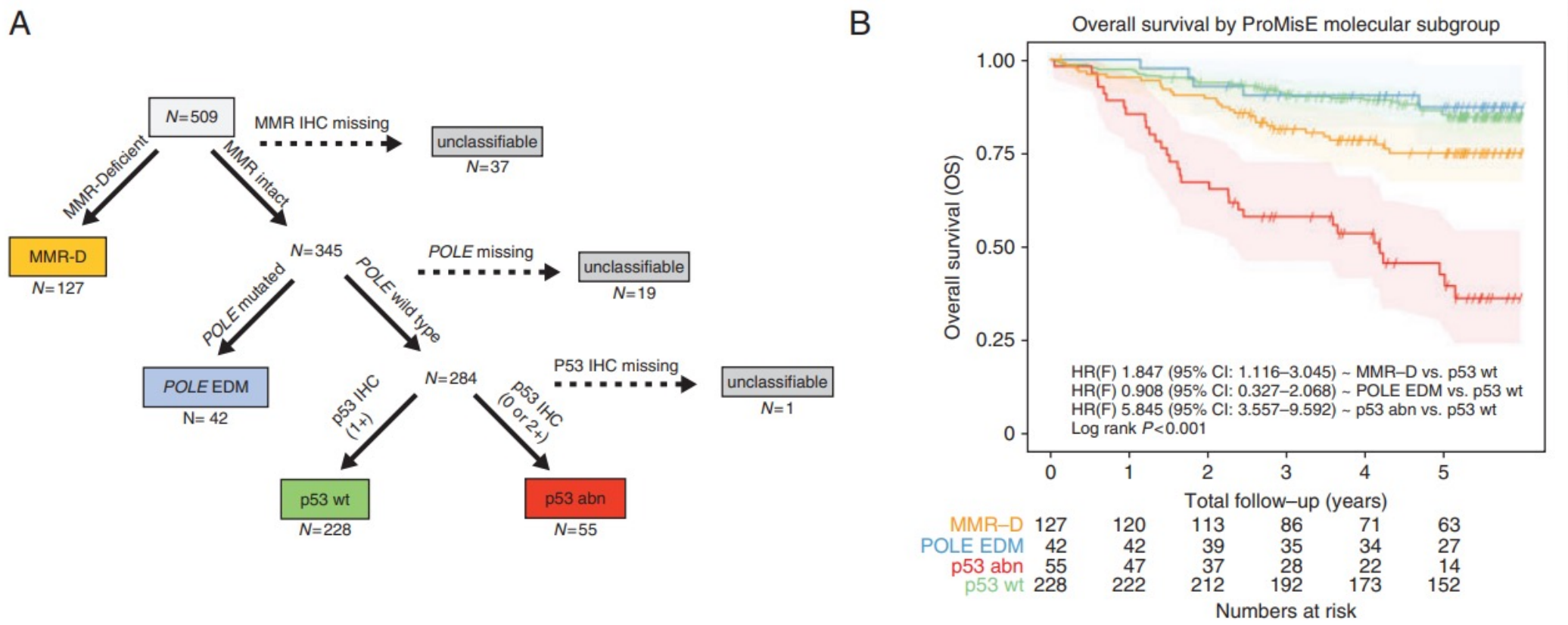


Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.

PROMISE MOLECULAR CLASSIFICATION

Proactive Molecular Risk Classifier for Endometrial Cancer

Four subtypes analogous to TCGA based on FFPE tissue analysis

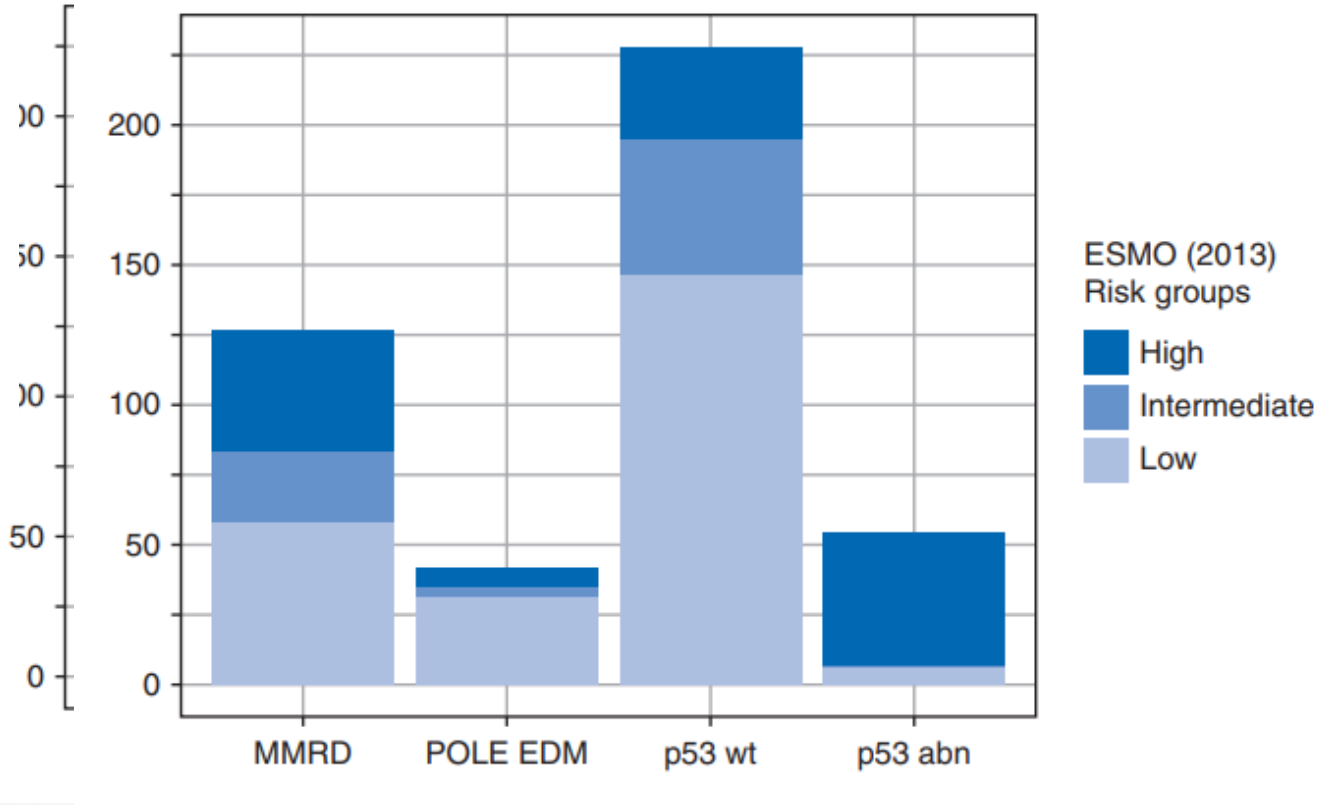


Kommoss et al., *Ann Onc* 2018

LACK OF OVERLAP BETWEEN LOW, INTERMEDIATE, AND HIGH RISK PATHOLOGY AND MOLECULAR CLASSIFICATIONS

ESMO 2013 Risk groups

Low risk:	Stage IA (G1 and G2) with endometrioid type
Intermediate risk:	Stage IA G3 with endometrioid type Stage IB (G1 and G2) with endometrioid type
High risk:	Stage IB G3 with endometrioid type all stages with non-endometrioid type



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Surgically staged[e]: Stage III, IV[r] → **Systemic therapy ± EBRT[s] ± vaginal brachytherapy[s]**

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA[a]

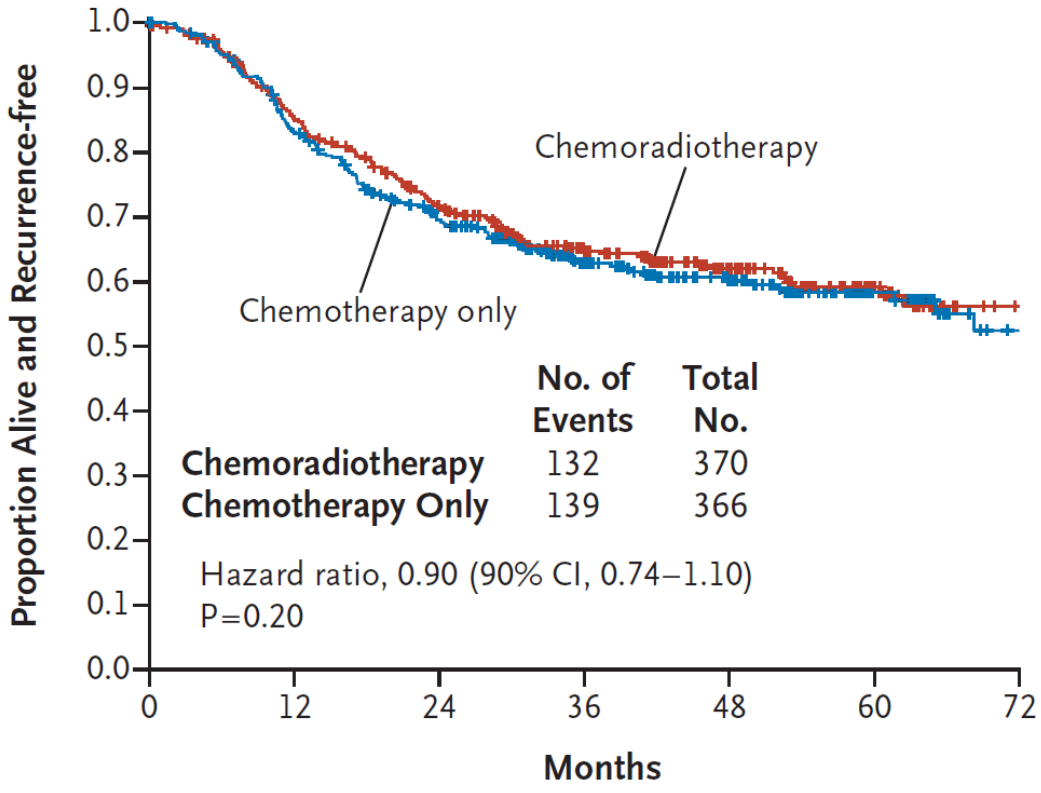
Primary or Adjuvant Therapy (Stage I–IV)	
Chemoradiation Therapy	**Systemic Therapy**
Preferred Regimen • Cisplatin plus RT followed by carboplatin/paclitaxel[1,2] **Other Recommended Regimens (if cisplatin and carboplatin are unavailable)** • Capecitabine/mitomycin[3] (category 2B) • Gemcitabine[4] (category 2B) • Paclitaxel[5,6] (category 2B)	**Preferred Regimens** • Carboplatin/paclitaxel/pembrolizumab (for stage III–IV tumors, except for carcinosarcoma) (category 1)[b,c,d,7,8] • Carboplatin/paclitaxel/dostarlimab-gxly (for stage III–IV tumors) (category 1)[c,d,e,9] • Carboplatin/paclitaxel/durvalumab (for stage III–IV dMMR tumors only) (category 1)[c,d,f,10] • Carboplatin/paclitaxel/trastuzumab (for stage III–IV HER2-positive uterine serous carcinoma or carcinosarcoma)[d,g,11] • Carboplatin/paclitaxel/bevacizumab (stage III–IV with measurable disease)[d,12,13] • Carboplatin/paclitaxel[14]

GOG 258: CHEMORADIOTHERAPY VS. CHEMOTHERAPY

Locally Advanced Endometrial Cancer

- Any Histology (except carcinosarcoma) – III, IVA
- Serous – I, II with positive cytology
- Clear Cell – I, II with positive cytology
- Gross residual disease < 2 cm ok (about 2%)

GOG-258	G1	G2	G3	serous	clear cell	CS
IA non-invasive				washings	washings	
IA invasive				washings	washings	
IB				washings	washings	
II				washings	washings	
IIIA - no residual	x	x	x	x	x	
IIIB - no residual	x	x	x	x	x	
IIIC1 - no residual	x	x	x	x	x	
IIIC2 - no residual	x	x	x	x	x	
IVA - no residual	x	x	x	x	x	
IVB - no residual						
IIIA - residual	x	x	x	x	x	
IIIB - residual	x	x	x	x	x	
IIIC1 - residual	x	x	x	x	x	
IIIC2 - residual	x	x	x	x	x	
IVA - residual	x	x	x	x	x	
IVB - residual						



Matei et al., *NEJM* 2019

GOG 258: MOLECULAR ANALYSIS

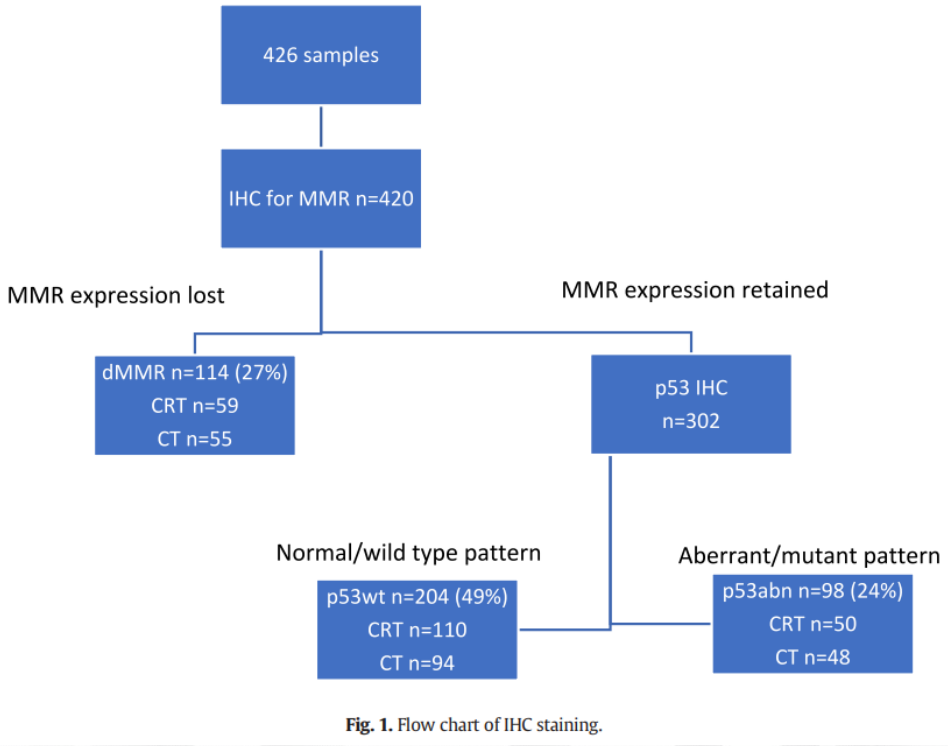
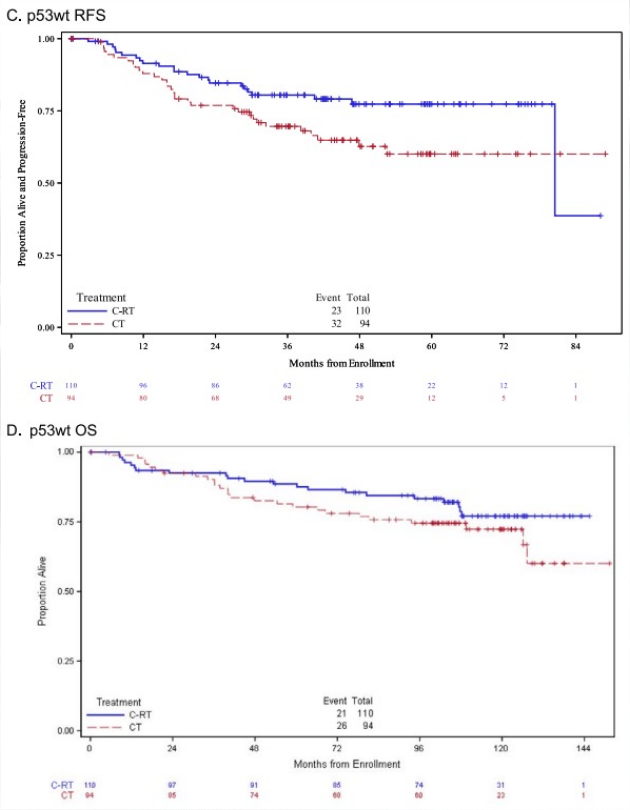
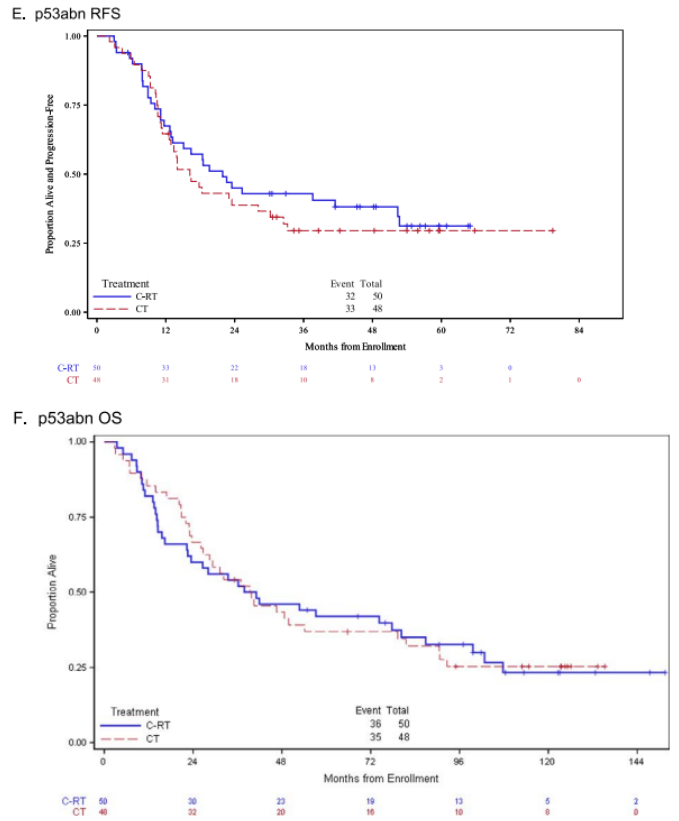


Fig. 1. Flow chart of IHC staining.

P53wt (49%)



P53abn (24%)



Clements et al., *Gynecol Oncol* 2025

Slight improvement in RFS with ChemoXRT in P53wt subgroup

77% vs 60%, HR 0.54 (95% CI, 0.32, 0.94)

IMMUNOTHERAPY IS NOW FIRMLY ESTABLISHED AS KEY THERAPY IN ENDOMETRIAL CANCER

First-line with chemotherapy

- GY018
- DUO-E
- Ruby
- Attend

First-line Chemo-free

- Leap 001 (previously received adj chemo??)

Second-line

dMMR:

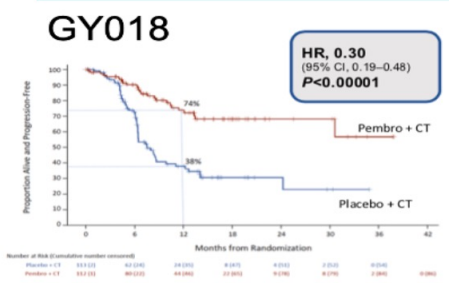
- Garnet
- KN 158

pMMR:

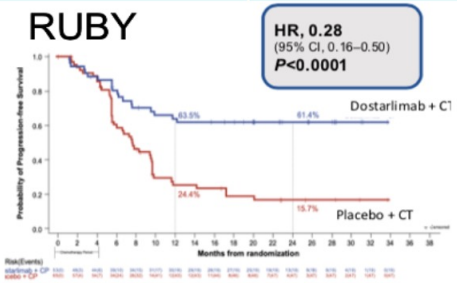
- KN 775

The Current Era: Chemotherapy and Immunotherapy for Advanced and/or Recurrent dMMR Endometrial Cancer

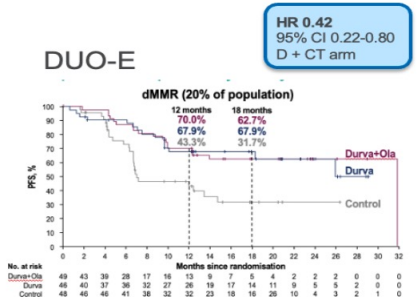
NRG-GY018[1]	RUBY Part 1[2]	RUBY Part 2[3]	DUO-E[4]	AtTEnd[5]
dMMR (mPFS, mo)	**dMMR (24-mo PFS)**	**dMMR (mPFS, mo)**	**dMMR (mPFS, mo)**	**dMMR (mPFS, mo)**
Pembro + CT (n=112): **NR (95% CI, 30.6-NR)** Placebo + CT (n=113): **7.6 (95% CI, 6.4-9.9) HR=0.30 (95% CI, 0.19-0.48); *P*<0.001**	Dostar + CP (n=53): **61.4% (95% CI, 46.3-73.4)** Placebo + CP (n=65): **15.7% (95% CI, 7.2-27.0) HR=0.28 (95% CI, 0.16-0.50); *P*<0.001**	Dostar + CP + Nira (n=50): **NE (95% CI, 11.8-NE)** Placebo + CP (n=25): **7.9 (95% CI, 5.4-NE) HR=0.48 (95% CI, 0.24-0.96); *P*=0.0174**	Durva + Ola (n=48): **31.8 (95% CI, 12.4-NR)** Durva (n=46): **NR (95% CI, NR-NR)** Control (n=49): **7.0 (95% CI, 6.7-14.8) HR (combo vs control) = 0.41 (95% CI, 0.21-0.75)**	Atezo + CP (n=81): **NE (95% CI, 12.3-NE)** Placebo + CP (n=44): **6.9 (95% CI, 6.2-9.0) HR=0.36 (95% CI, 0.23-0.57); *P*=0.0005**



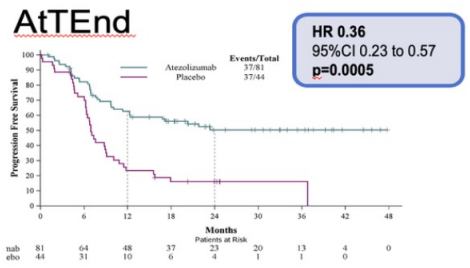
	No with events%	Median
Pembro + CT	23.2	NR (30.6-NR)
Placebo + CT	52.2	7.6 (6.4-9.9)



	No with events%	Median
Dorsta + CT	35.8	NR (11.8-NR)
Placebo + CT	72.3	7.7 (5.6-9.7)



	No with events %	Median
Durva + CT	32.6	NR (NR-NR)
Durva + O + CT	37.5	31.8 (12.4-NR)
Placebo + CT	51	7.0 (6.7-14.8)



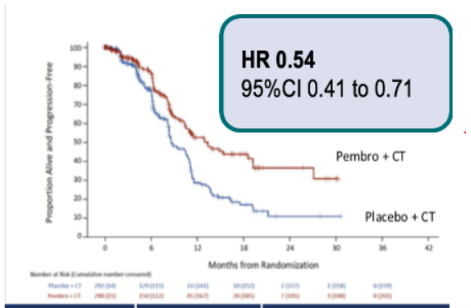
	No with events%	Median
Atezo + CT	45.7	NR (12.3-NR)
Placebo + CT	84.1	6.9 (6.2-9.0)

Eskander RN, et al. N Engl J Med 2023; Mirza MR, et al. N Engl J Med. 2023; Westin SN, et al. J Clin Oncol 2024. Colombo N, et al. ESMO 2023. Abstract LBA40. Annals Oncol

Chemotherapy and Immunotherapy for Advanced and/or Recurrent pMMR Endometrial Cancer

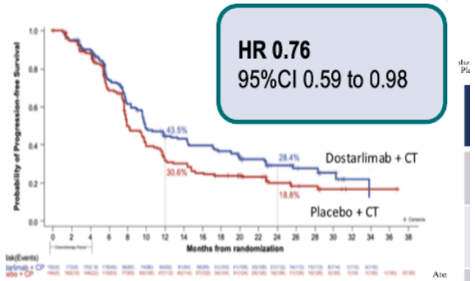
NRG-GY018[1]	RUBY Part 1[2]	RUBY Part 2[3]	DUO-E[4]	AtTEnd[5]
pMMR (mPFS, mo)	**pMMR (24-mo PFS)**	**pMMR (mPFS, mo)**	**pMMR (mPFS, mo)**	**pMMR (mPFS, mo)**
Pembro + CT (n=290): **13.1 (95% CI, 10.5-18.8)** Placebo + CT (n=292): **8.7 (95% CI, 8.4-10.7)** **HR=0.54 (95% CI, 0.41-0.71); *P*<0.001**	Dostar + CP (n=192): **28.4% (95% CI, 21.2-36.0)** Placebo + CP (n=184): **18.8% (95% CI, 12.8-25.7)** **HR=0.76 (95% CI, 0.59-0.98)**	Dostar + CP + Nira (n=142): **14.3 (95% CI, 9.7-16.9)** Placebo + CP (n=74): **8.3 (95% CI, 7.6-9.8)** **HR=0.63 (95% CI, 0. 44-0.91); *P*=0.0060**	Durva + Ola (n=191): **15.0 (95% CI, 12.4-18.0)** Durva (n=192): **9.9 (95% CI, 9.4-12.5)** Control (n=192): **9.7 (95% CI, 0.92-10.1)** **HR (combo vs control) = 0.57 (95% CI, 0.44-0.73)**	Atezo + CP (n=269): **9.5 (95% CI, 9.0-10.4)** Placebo + CP (n=140): **9.2 (95% CI, 8.5-9.9)** **HR=0.92 (95% CI, 0.73-1.16)**

GY018



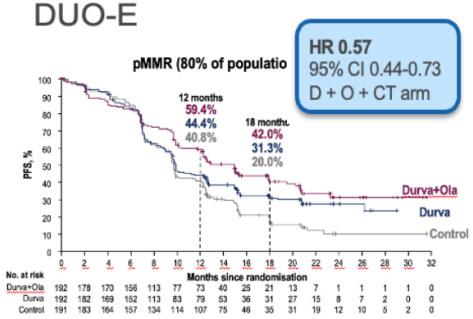
	No with events%	Median
Pembro + CT	30.6	13.1 (10.5-18.8)
Placebo + CT	45.5	8.7 (8.4-10.7)

RUBY



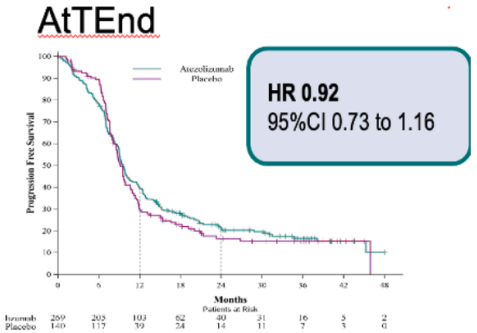
	No with events%	Median
Dorsta + CT	60.4	9.9 (9.0-13.3)
Placebo + CT	70.7	7.9 (7.6-9.8)

DUO-E



	No with events %	Median
Durva + CT	64.6	9.9 (9.4-12.5)
Durva + O + CT	56.5	15 (12.4-18)
Placebo + CT	77.1	9.7 (9.2-10.1)

AtTEnd

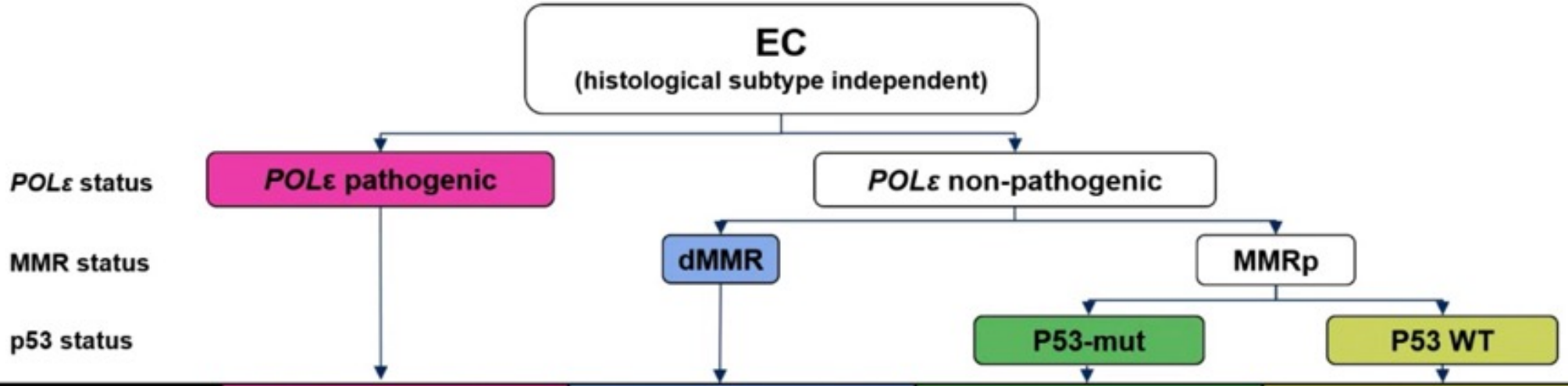


	No with events%	Median
Atezo + CT	78	9.5 (9.0-10.4)
Placebo + CT	77	9.2 (8.5-9.9)

Eskander RN, et al. N Engl J Med 2023; Mirza MR, et al. N Engl J Med. 2023; Westin SN, et al. J Clin Oncol 2024. Colombo N, et al. ESMO 2023. Abstract LBA40. Annals Oncol

RUBY Molecular Classification Algorithm

- In RUBY Part 1, molecular classification was performed for all participants with WES results – 400 of 494 patients

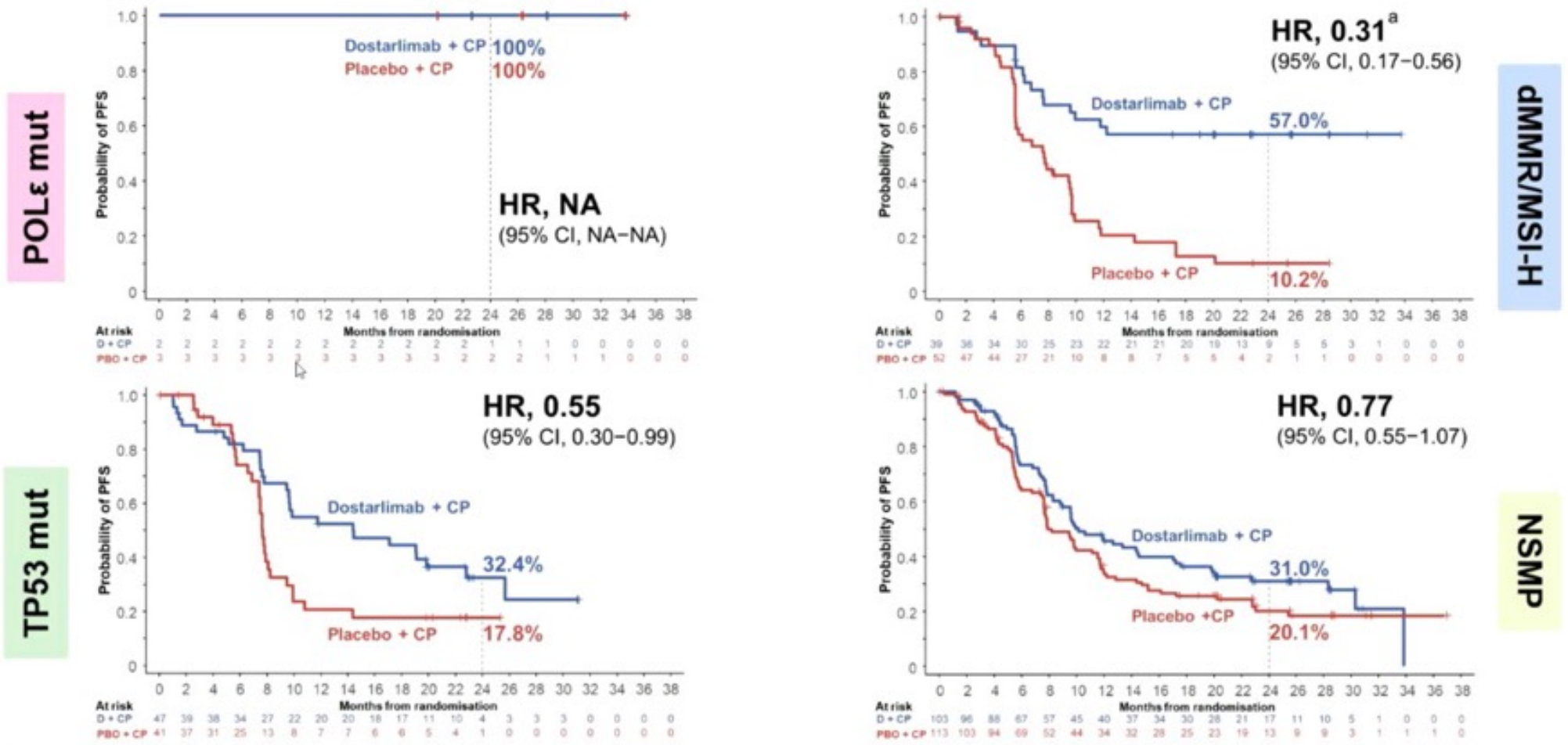


Integrated diagnosis	POLεmut (EDM)	dMMR (or MSI-H)	TP53 aberrant	NSMP
Prevalence in RUBY, % (n/N)	**1.25%** (5/400)	**22.75%** (91/400)	**22%** (88/400)	**54%** (216/400)
Diagnostic test	WES	Results of local (IHC, NGS, PCR) or central test (IHC) provided for RUBY at randomization	WES	

Efficacy per molecular classification was an exploratory analysis.
dMMR, mismatch repair deficient; EC, endometrial cancer; EDM, exonuclease domain; IHC, immunohistochemistry; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; mut, mutated; NGS, next generation sequencing; NSMP, no specific molecular profile; PCR, polymerase chain reaction; POLε, polymerase epsilon; TP53, tumor protein 53; WES, whole exome DNA sequencing; WT, wild type.

PFS According to Molecular Subgroup

Based on 400/494 patients with known molecular classification per whole exome sequencing

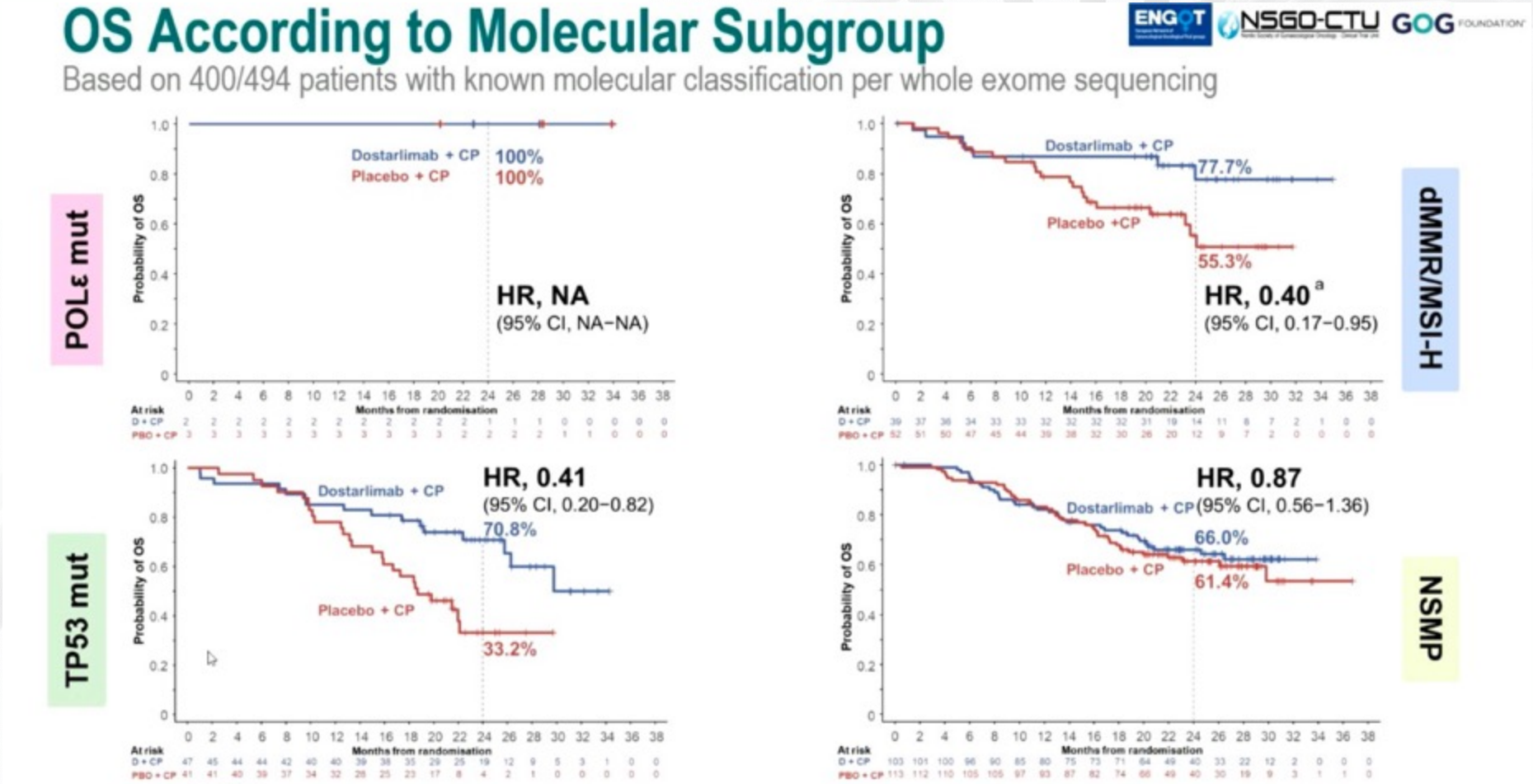


MADRID 2023 ESMO congress

[a]Primary endpoint of PFS in dMMR/MSI-H patients (n=118) showed HR, 0.28; *P*<0.0001

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; PBO, placebo; PFS, progression-free survival; POLε, polymerase epsilon; TP53, tumor protein 53

MMR PROFICIENT, P53 WILD TYPE TUMORS DON'T SEEM TO BENEFIT



[a]Prespecified OS analysis in dMMR/MSI-H patients (n=118) showed HR, 0.30.
CP, carboplatin-paclitaxel; D, dostarlimab; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability–high; mut, mutated; NA, not applicable; NR, not reached; NSMP, no specific molecular profile; OS, overall survival; PBO, placebo; POLε , polymerase epsilon; TP53, tumor protein 53.

GOG-3031/RUBY: PHASE 3 TRIAL OF DOSTARLIMAB + CHEMO FOR PRIMARY ADVANCED/RECURRENT EC – PFS

Categories	Dostarlimab + Carboplatin/Paclitaxel (no. of events/no. of patients)	Placebo + Carboplatin/Paclitaxel (no. of events/no. of patients)	Hazard Ratio (95% CI)
All patients	135/245	177/249	0.64 (0.507–0.800)
Age			
<65 yr	69/127	72/114	0.78 (0.559–1.083)
≥65 yr	66/118	105/135	0.51 (0.376–0.704)
Race			
White	101/189	135/191	0.62 (0.481–0.808)
Other	34/56	42/58	0.67 (0.422–1.050)
Region			
North America	91/171	133/187	0.55 (0.419–0.718)
Europe	44/74	44/62	0.91 (0.602–1.390)
Eastern Europe	11/16	12/14	0.86 (0.377–1.959)
Western Europe	33/58	32/48	0.95 (0.581–1.539)
Histology category			
Endometrioid carcinoma	64/130	89/136	0.65 (0.473–0.902)
Other	71/115	88/113	0.60 (0.439–0.823)
MMR/MSI status			
dMMR/MSI-H	19/53	47/65	0.33 (0.192–0.566)
MMRp/MSS	116/192	130/184	0.76 (0.595–0.982)
dMMR status (derived)	19/53	47/63	0.31 (0.182–0.539)
Prior external pelvic radiotherapy			
Yes	21/41	31/45	0.54 (0.303–0.956)
No	114/204	146/204	0.65 (0.508–0.831)
Disease status			
Recurrent	68/117	89/119	0.56 (0.408–0.775)
Primary stage III	21/45	21/47	1.03 (0.563–1.891)
Primary stage IV	46/83	67/83	0.57 (0.392–0.836)
No disease at baseline	12/33	12/30	1.16 (0.520–2.590)

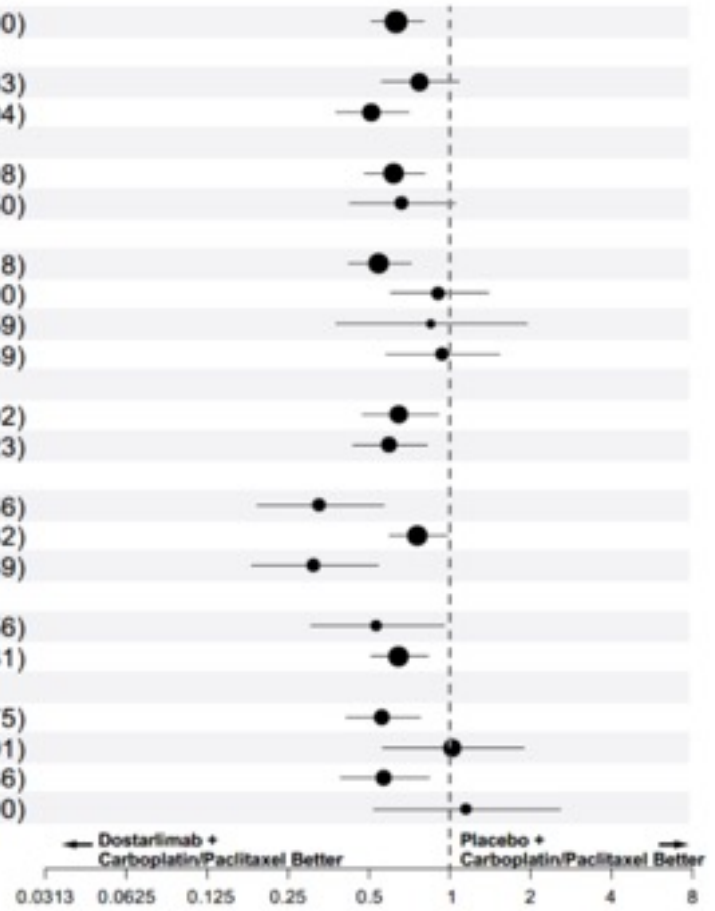


Figure S2. Forest Plot for Subgroup Analysis of PFS per Investigator Assessment

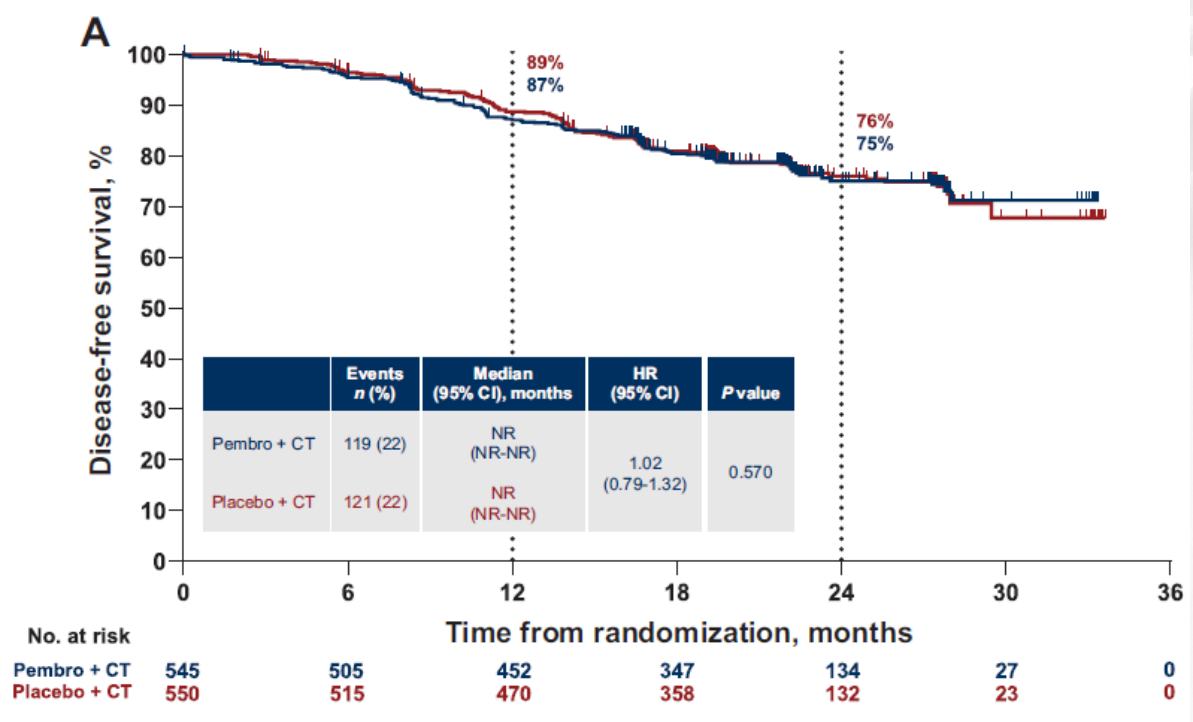
WHAT ABOUT HIGH RISK WITH NO RESIDUAL DISEASE AFTER SURGERY?

SHOULD WE ADD IMMUNOTHERAPY?

ENGOT-EN11/GOG-3053/KEYNOTE-B21: CHEMOTHERAPY WITH PLACEBO OR PEMBRO

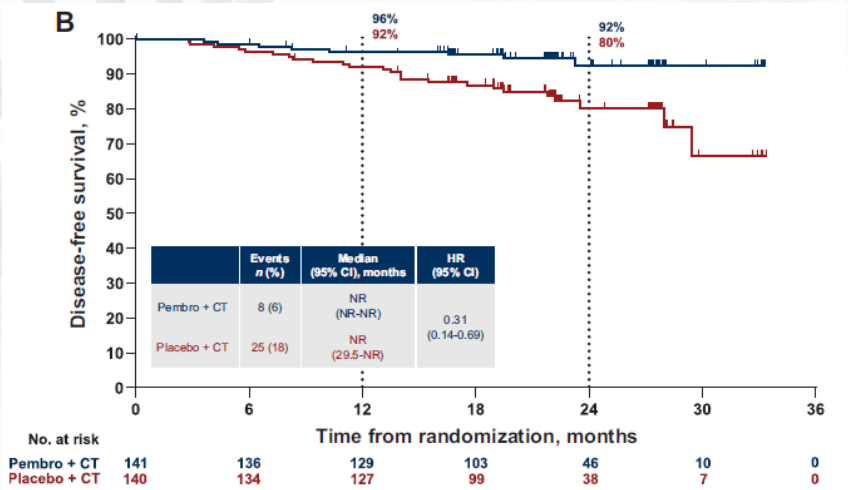
High Risk Endometrial Cancer

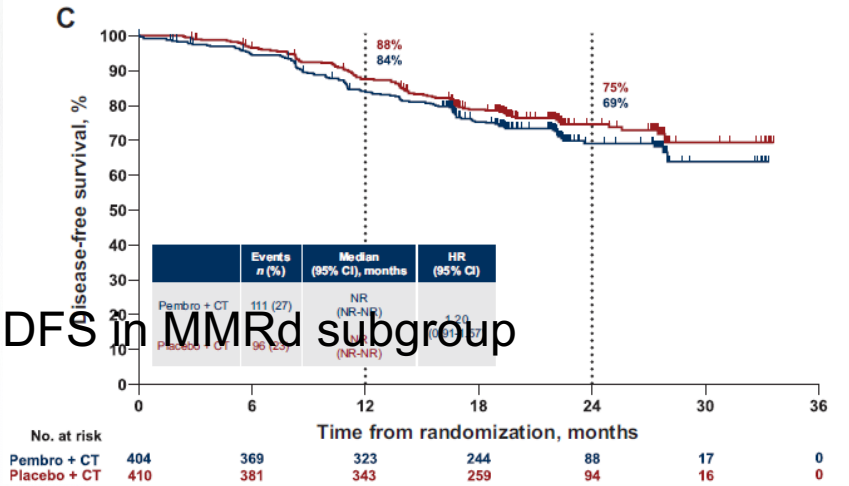
- Endometrioid - Stage I, II with myometrial invasion, abnormal P53
- Non-endometrioid – Stage I, II with myometrial invasion
- Any histology – Stage III, IVA without residual disease



Van Gorp et al., *Annals Oncol* 2024

DFS is not improved by adding pembrolizumab in ITT population or the MMRp group but was in MMRd HR 0.31 (95% CI, 0.14, 0.69)





Improved DFS in MMRd subgroup

SUMMARY: IMMUNOTHERAPY IN ENDOMETRIAL CANCER FIRST LINE (PLUS PARP)

- All studies need PROMIS+ (HER2,ER, type of p53mut, maybe HRD score, PDL-1) for all studies including 775-LEN/PEM (it's very suspicious they haven't released PROMIS for 775

- Anti-PD1 (pembrolizumab and dostarlimab) likely better than Anti-PDL-1(atezolizumab, avelumab and durvalumab) both in dMMR (trend) and pMMR (fairly convincing);
  - Trends are consistent with improved PFS, OS with anti-PD1 without significant increases in toxicity

- PARP therapy is NOT adding much
  - Small subgroup of HRD+/HRRm/p53mut may have a PFS signal but concerning OS may be showing harm.
  - Need OS from DUO-E and RUBY part 2 to consider moving forward with confirmatory + PARP trial?

- Acute need for HER2 assessment of the subgroups

TALK OVERVIEW

- General GYN cancer numbers
  - Endometrial cancer treatment overview
  - Overall NCCN general guidelines for initial treatment of advanced cancers
- Overall recommendations for initial treatment of advanced cancer
  - MMR deficient endometrial cancer
  - MMR proficient endometrial cancer
- Beyond paclitaxel/carboplatin and immunotherapy
  - Maintenance selinexor
  - ADC's
  - Hormonal combinations
  - Other clinical trial and pipeline options

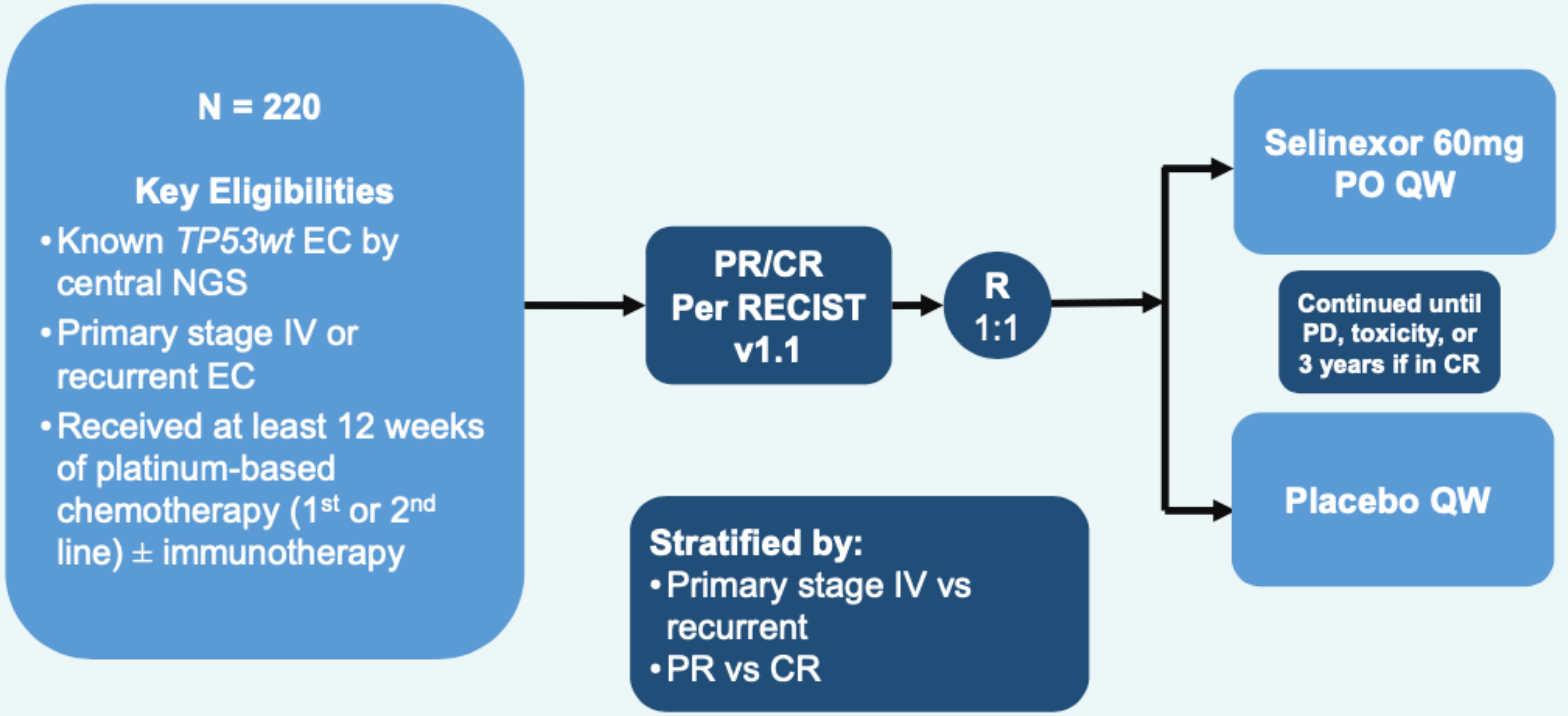
SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA[a]

RECURRENT DISEASE[h,i]

First-Line Therapy for Recurrent Disease[j]	Second-Line or Subsequent Therapy[j]
Preferred Regimens • Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1)[c,d,k,7] • Carboplatin/paclitaxel/dostarlimab-gxly (category 1)[c,d,k,9] • Carboplatin/paclitaxel/durvalumab (for dMMR only) (category 1)[c,d,k,10] • Carboplatin/paclitaxel/trastuzumab (for HER2-positive uterine serous carcinoma or carcinosarcoma)[d,g,11] • Carboplatin/paclitaxel (category 1 for carcinosarcoma)[l,14] **Other Recommended Regimens** • Carboplatin/docetaxel[m] • Carboplatin/paclitaxel/bevacizumab[d,12,13] **Useful in Certain Circumstances (Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant)** • MMR-proficient (pMMR) tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,15,16] • TMB-high (TMB-H) tumors[n] ▸ Pembrolizumab[c,17] • MSI-H/dMMR tumors[o] ▸ Pembrolizumab[c,18] ▸ Dostarlimab-gxly[c,19]	**Other Recommended Regimens** • Cisplatin/doxorubicin[20] • Cisplatin/doxorubicin/paclitaxel[p,20] • Cisplatin/gemcitabine[21] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[22] • Albumin-bound paclitaxel[q] • Topotecan • Bevacizumab[r,23] • Temsirolimus[24] • Cabozantinib • Lenvatinib[25] • Gemcitabine[26] • Docetaxel (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[27] • Cisplatin/ifosfamide (for carcinosarcoma) **Useful in Certain Circumstances (Biomarker-directed therapy)** • pMMR tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,15,16] • TMB-H tumors[n] ▸ Pembrolizumab[c,17] • MSI-H/dMMR tumors[o] ▸ Pembrolizumab[c,18] ▸ Dostarlimab-gxly[c,19] ▸ Avelumab[c] ▸ Nivolumab[c,s,28] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[29] • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib ▸ Repotrectinib[t,30]

ENGOT-EN20/GOG-3083/XPORT-EC-042 (NCT05611931)

A prospective, multicenter, double-blind, placebo-controlled, randomized Phase 3 study



Primary Objective: To evaluate the efficacy of selinexor compared to placebo as maintenance therapy in patients with *TP53*wt advanced or recurrent endometrial cancer

- Selinexor 60 mg QW dose was selected in this study to evaluate as a minimally effective dose.

CR, complete response; EC, endometrial cancer, HR, hazard ratio; NGS, next generation sequencing; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QW, once weekly; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; wt, wild type.

ENGOT-EN20/GOG-3083/XPORT-EC-042 (NCT05611931)

A prospective, multicenter, double-blind, placebo-controlled, randomized Phase 3 study

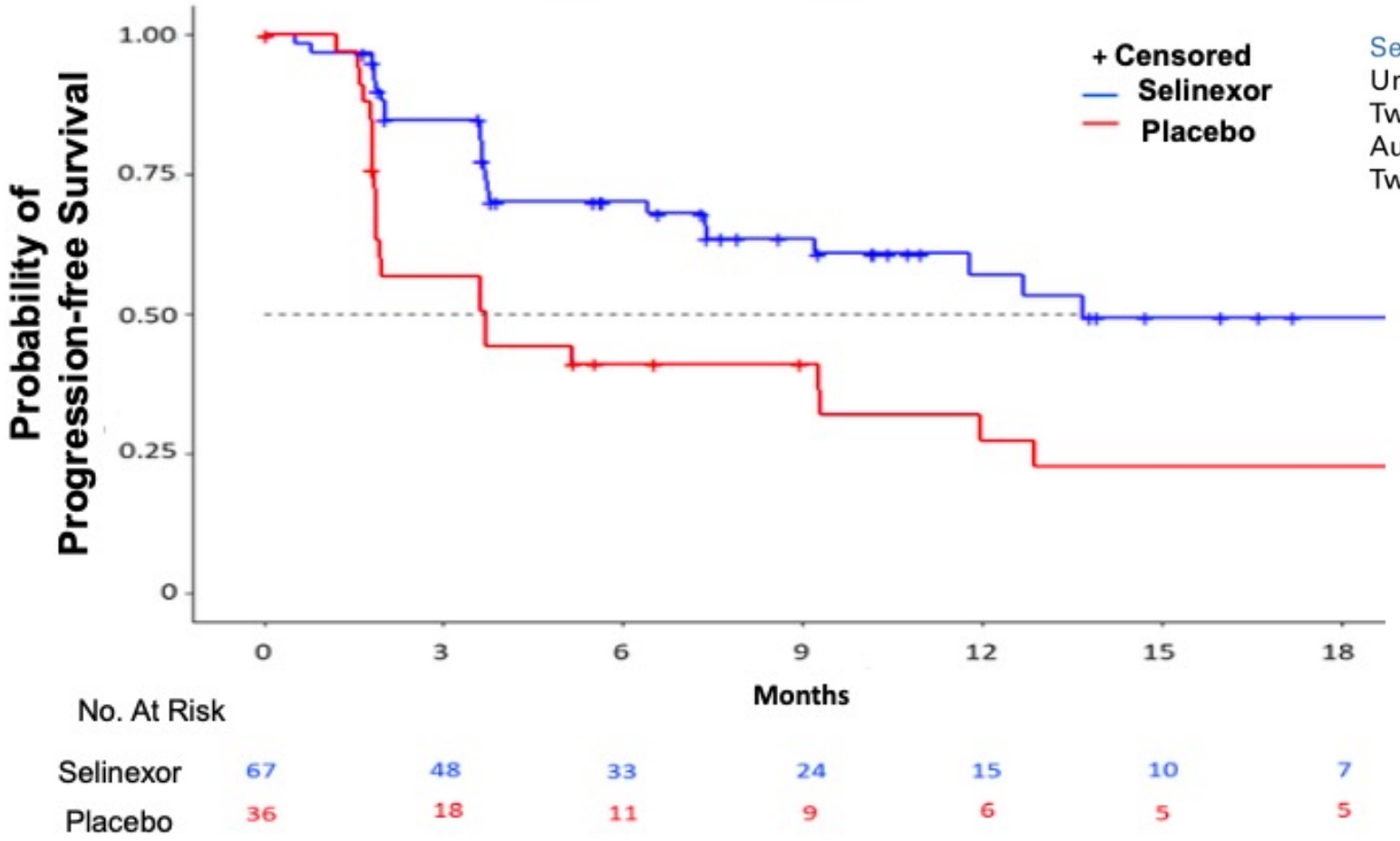


Figure 1. Progression-Free Survival of patients with wild type p53 endometrial cancer

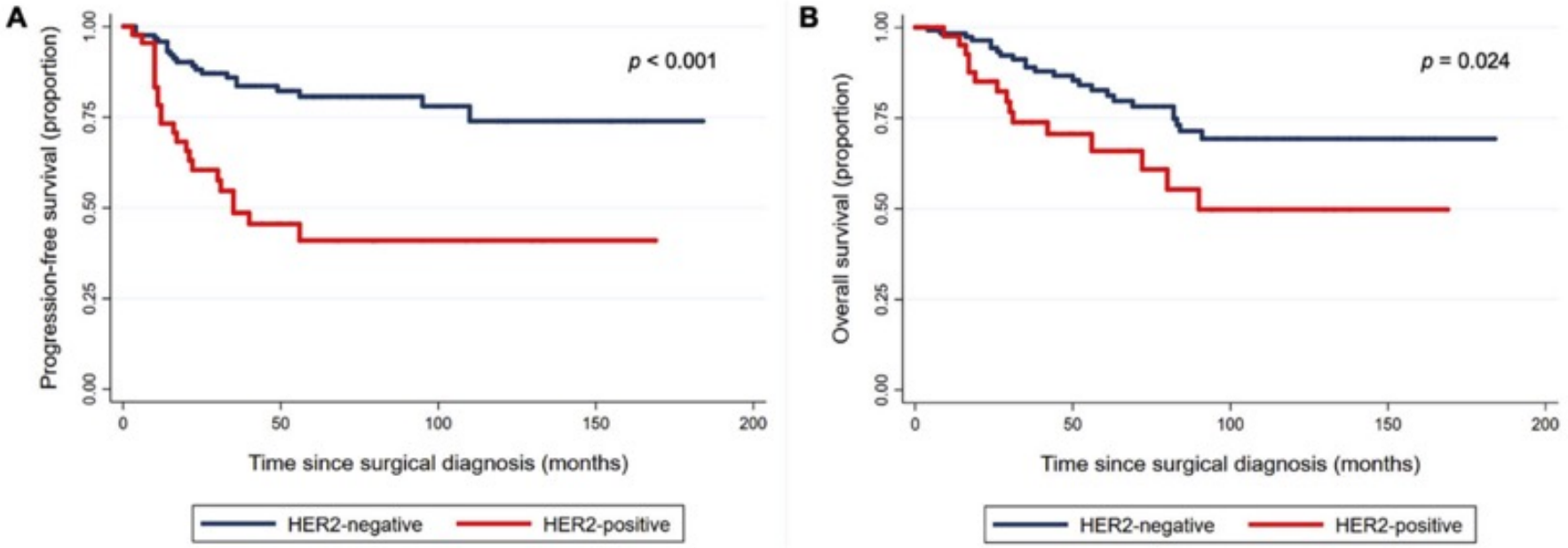
*This indication is approved under accelerated approval based on response rate. Continued approval may be contingent upon confirmatory trial(s).

HER-2 NEU EXPRESSION IN ENDOMETRIAL CANCERS

- HER2 overexpression ranges from 14-80%
- HER2 gene amplification from 21-47%
- Uterine papillary serous with 25-30% expression

Buza, N. HER2 testing in endometrial serous carcinoma: Time for standardized pathology practice to meet the clinical demand. Arch Pathol Lab Med 145(6):687-91, 2021

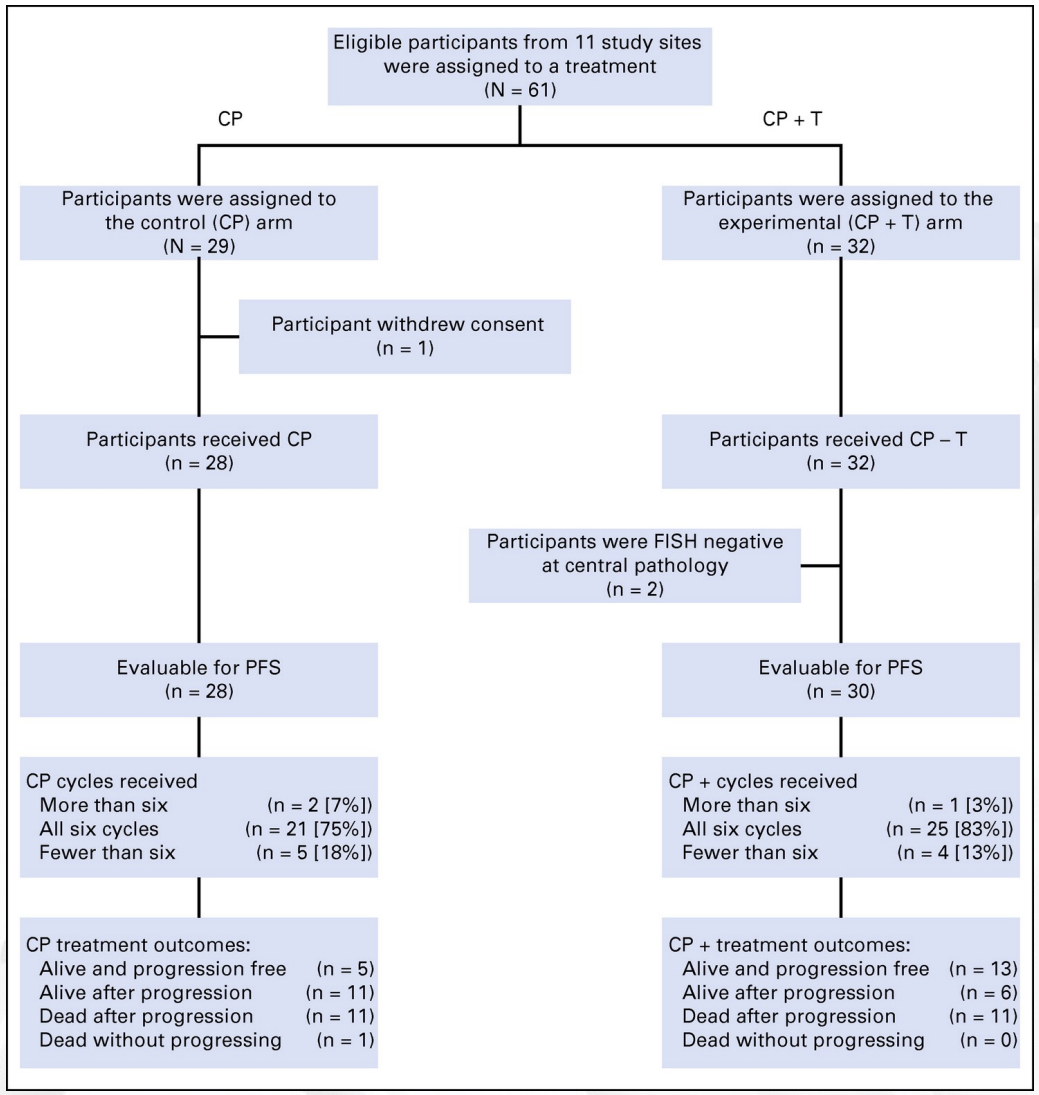
HUMAN EPIDERMAL GROWTH FACTOR 2 (HER2) IN STAGE1 UTERINE SEROUS CARCINOMA (OUTCOMES 2X WORSE!)

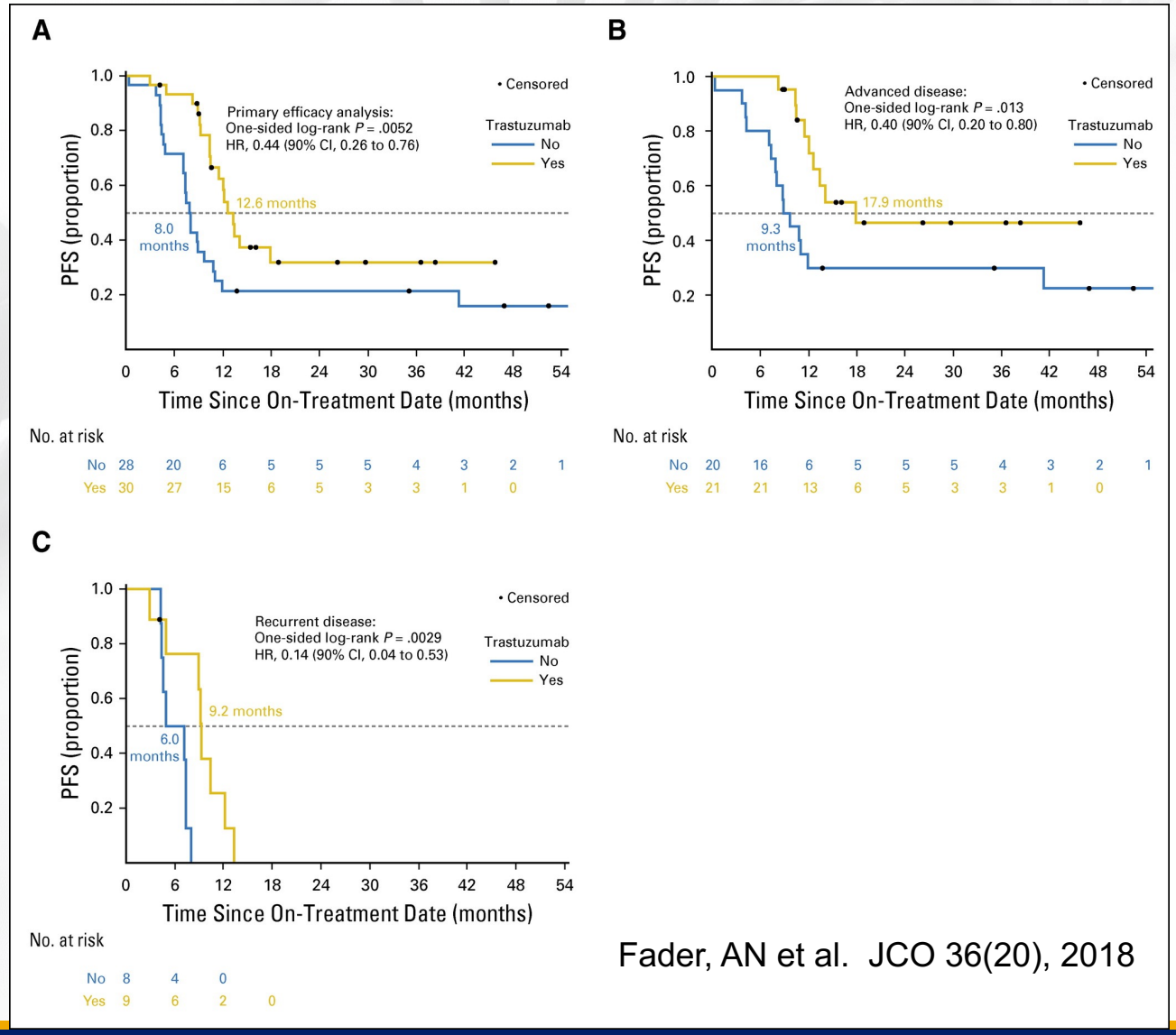


HER2 positive tumors were associated with inferior PFS (aHR 3.50, 95%CI 1.84-6.67; p < .001) and OS (aHR 2.00, 95%CI 1.04-3.88; p = .039) compared to HER2-negative tumors even when given Carbo/paclitaxel

Erickson et al *Gynecol Oncol* 2020.

RANDOMIZED PHASE II TRIAL OF TRASTUZUMAB IN UPSC

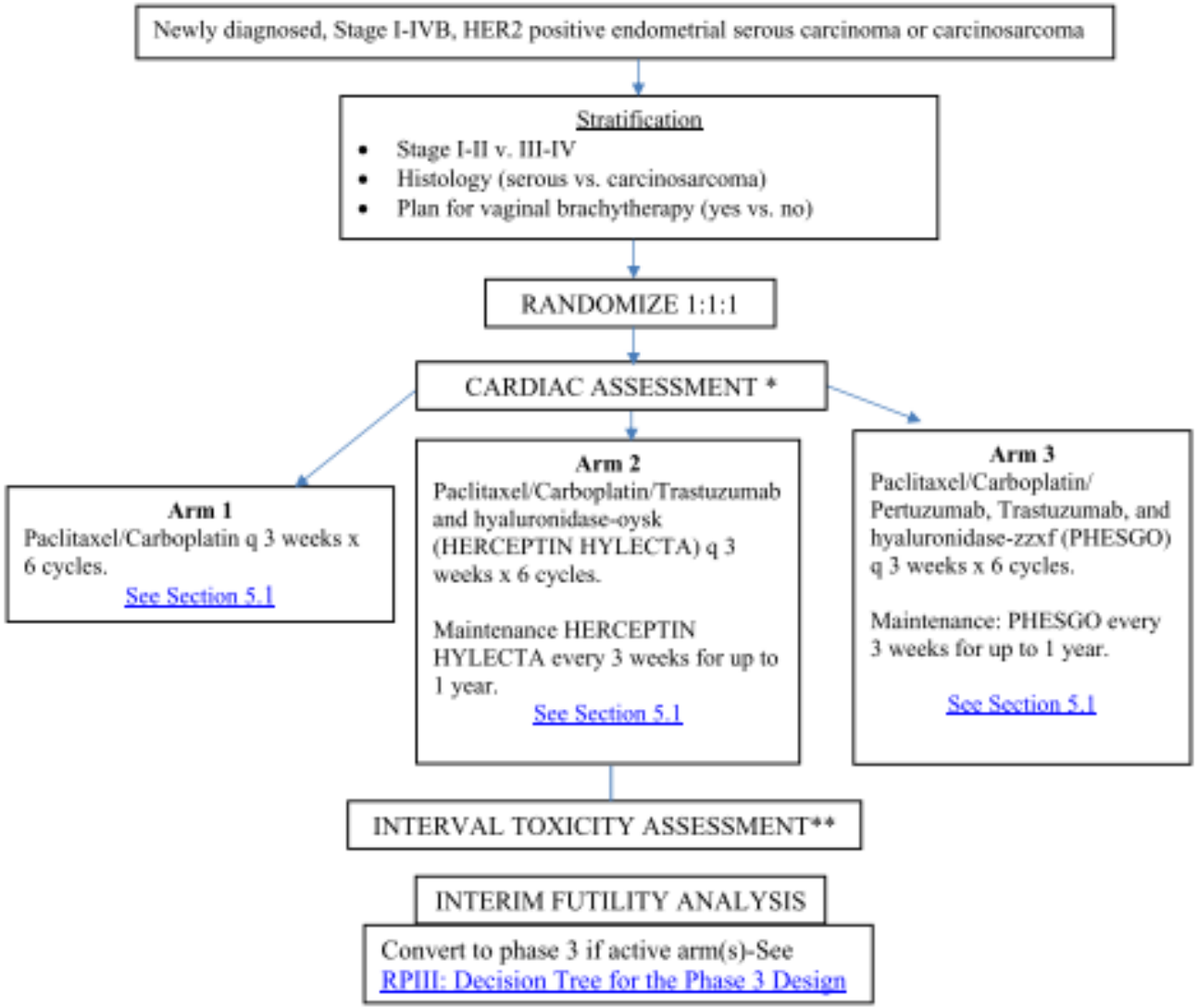




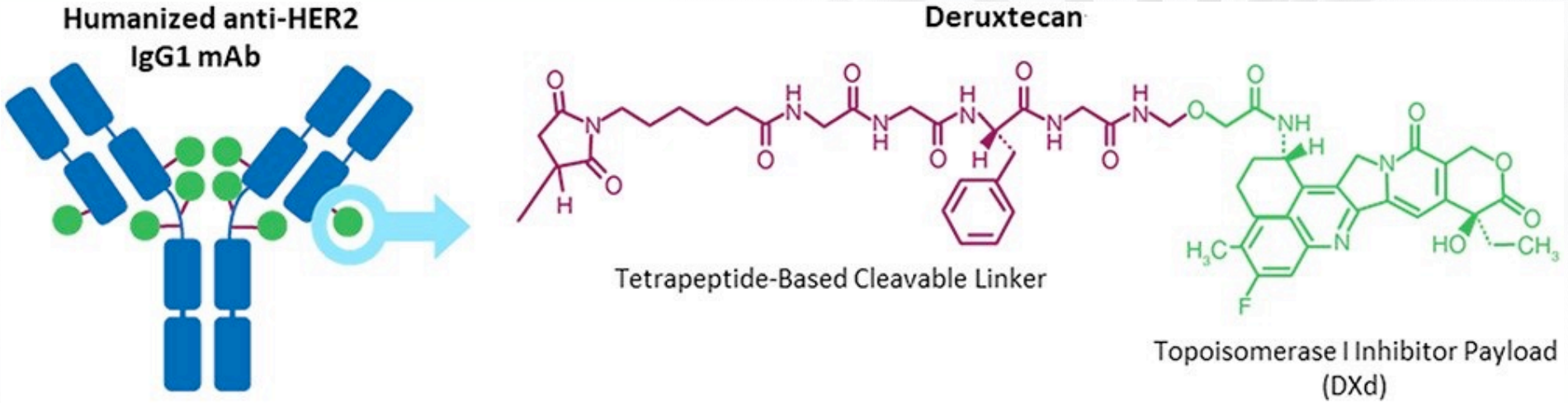
Fader, AN et al. JCO 36(20), 2018

NRG-GY026 SCHEMA

RPII: Paclitaxel/Carboplatin vs. Paclitaxel/Carboplatin/Trastuzumab and hyaluronidase-oysk (HERCEPTIN HYLECTA) vs. Paclitaxel/Carboplatin/ Pertuzumab, trastuzumab, and hyaluronidase-zzxf (PHESGO)→ drop inactive arm(s) to Phase III



TRASTUZUMAB DERUXTECAN



Unique features

- High potency payload
- High drug to antibody ratio (8ish)
- Payload with short systemic half-life
- Tumor selective (cleavable linker)
- Membrane permeable payload

Slide adapted with permission from Dr. Jane Meisel

Chem Pharm Bull (Tokyo). 2019; 67 (3): 173-185. Clin Cancer Res 2016; 22 (20): 5097-5108. Pharmacol Ther. 2018; 181:126-142. Cancer Sci 2016; 107 (7): 1039-1046.

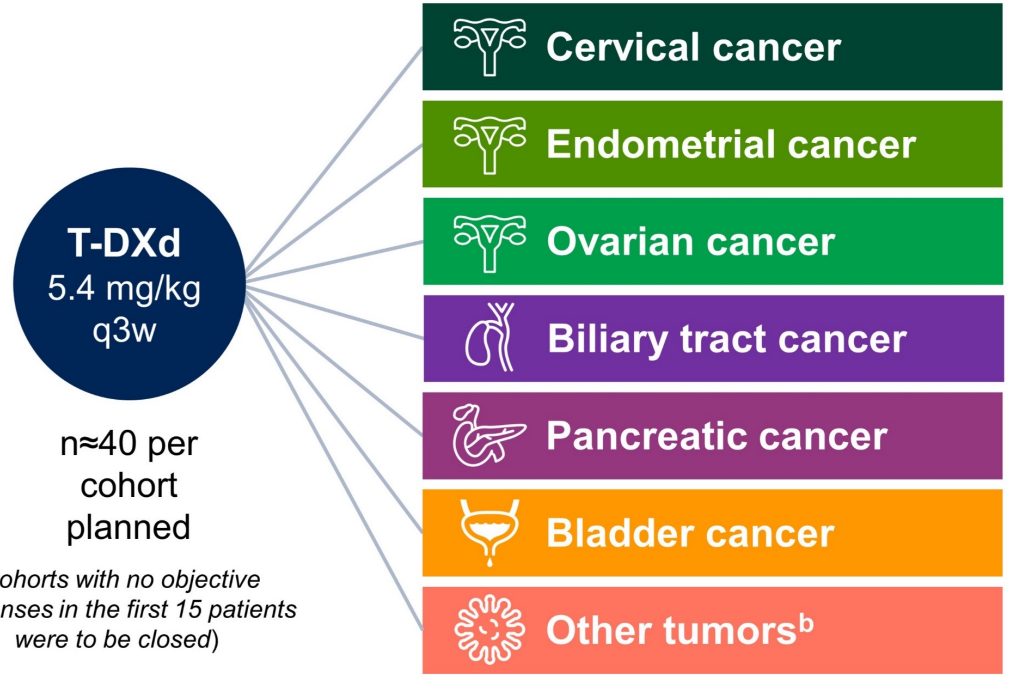
Original Reports | Gynecologic Cancer

Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial

Funda Meric-Bernstam, MD[1]; Vicky Makker, MD[2,3]; Ana Oaknin, MD[4]; Do-Youn Oh, MD[5]; Susana Banerjee, PhD[6]; Antonio González-Martín, MD[7]; Kyung Hae Jung, MD[8]; Iwona Ługowska, MD[9]; Luis Manso, MD[10]; Aránzazu Manzano, MD[11]; Bohuslav Melichar, MD[12]; Salvatore Siena, MD[13]; Daniil Stroyakovskiy, MD[14]; Anitra Fielding, MBChB[15]; Yan Ma, MSc[16]; Soham Puvvada, MD[15]; Norah Shire, PhD[15]; and Jung-Yun Lee, MD[17]

DOI https://doi.org/10.1200/JCO.23.02005

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

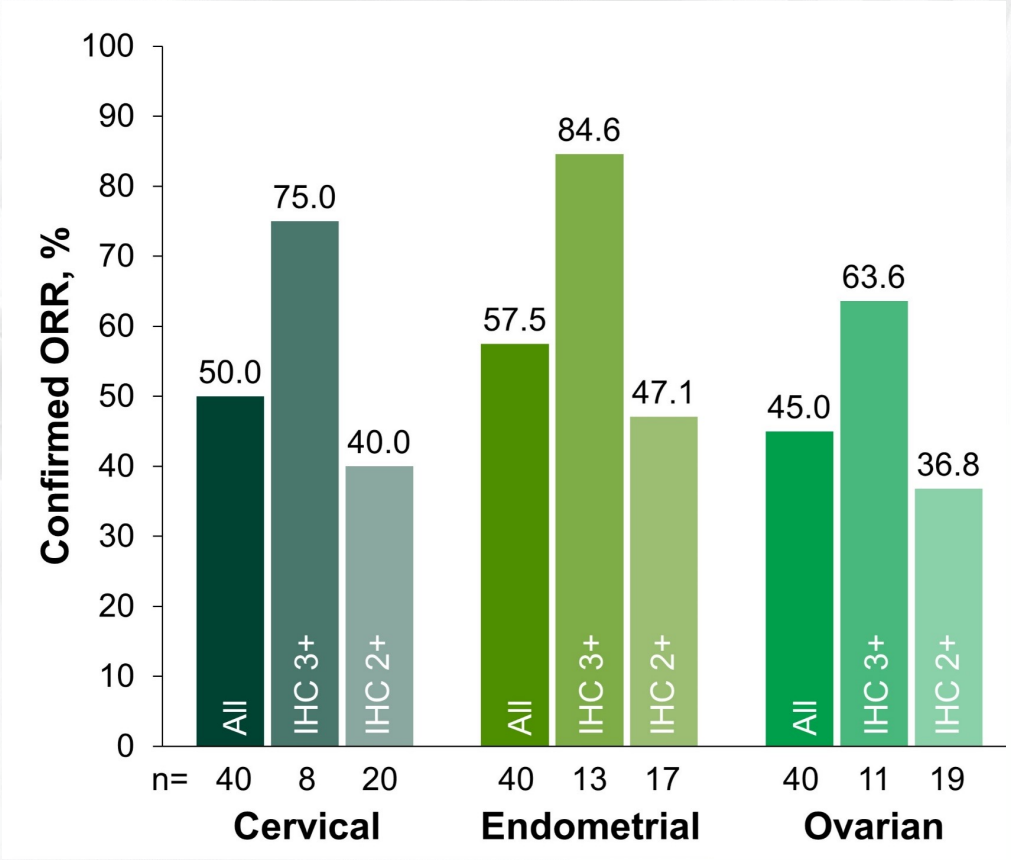
- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

- Nov 16, 2022

Efficacy

		Cervical (n=40)	Endometrial (n=40)	Ovarian (n=40)
Investigator assessment				
ORR, n (%)		**20 (50.0)**	**23 (57.5)**	**18 (45.0)**
Best overall response, n (%)	Complete response	2 (5.0)	7 (17.5)	4 (10.0)
	Partial response	18 (45.0)	16 (40.0)	14 (35.0)
	Stable disease	12 (30.0)	13 (32.5)	14 (35.0)
	PD	7 (17.5)	4 (10.0)	7 (17.5)
	Not evaluable	1 (2.5)	0	1 (2.5)
DCR[a] at 12 weeks, n (%)		27 (67.5)	32 (80.0)	28 (70.0)
Median DOR, months (95% CI)		9.8 (4.2–NE)	NR (9.9–NE)	11.3 (4.1–NE)
Independent central review: ORR, n (%)		16 (40.0)	21 (52.5)	17 (42.5)

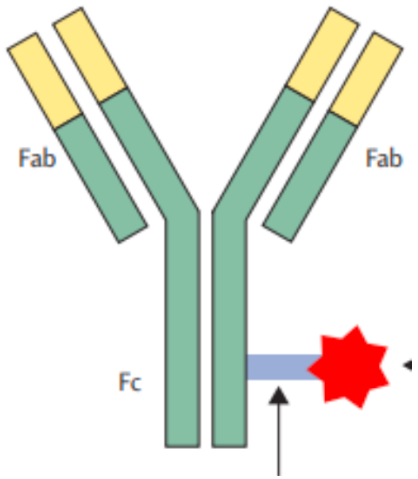


	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

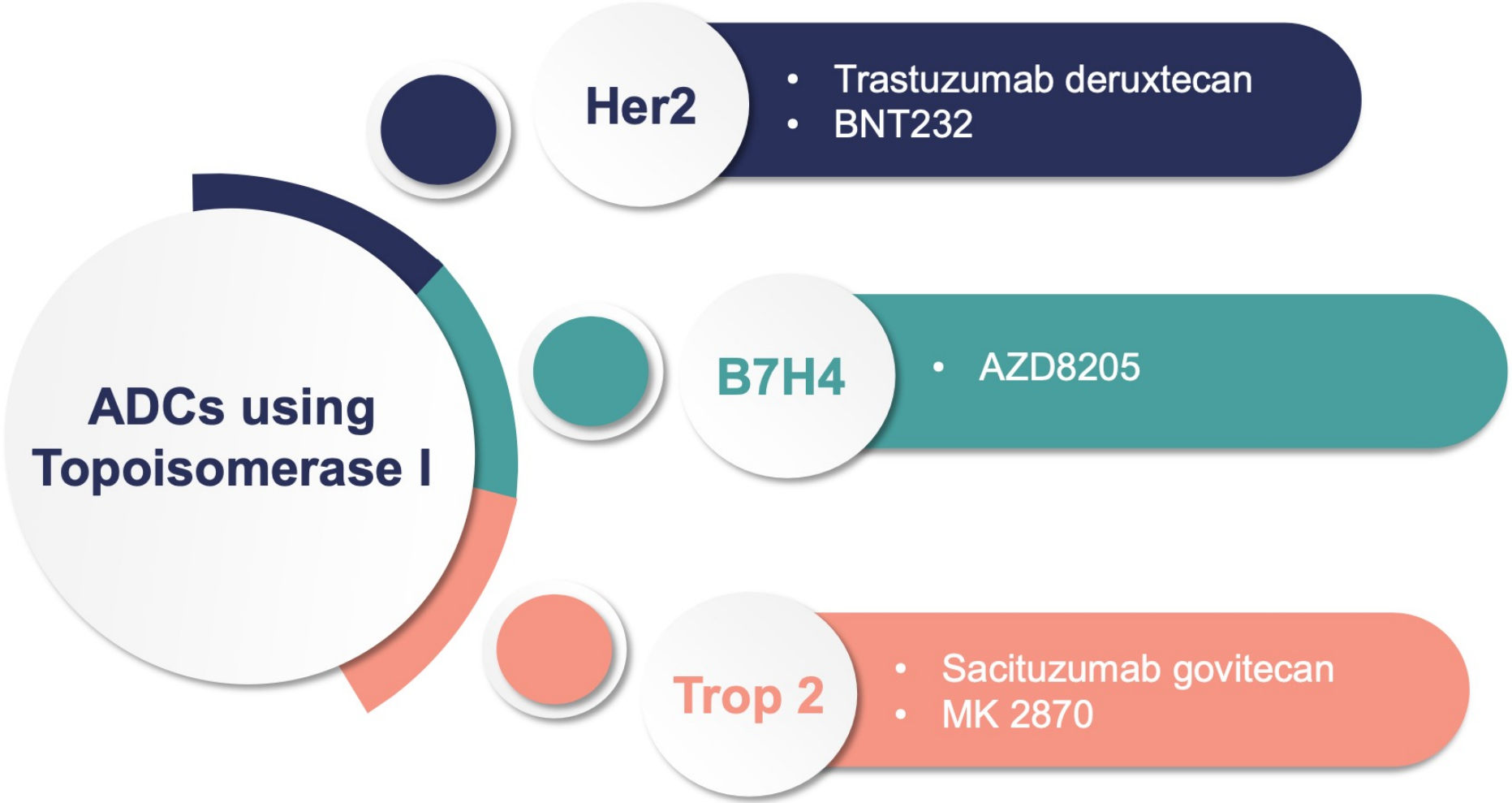
Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

PRESENTED BY: Funda Meric-Bernstam, MD

ADCs Under Development in Endometrial Cancer



Monoclonal antibody target	Drug Name	Payload	Ongoing trial
B7-H4	XMT-1660	Auristatin F-Hydroxypropylamide (microtubule inhibitor)	NCT05377996 (Phase I)
B7-H4	SGN-B7H4V (1 EC)	Monomethyl Auristatin E	NCT05194072 (Phase I)
B7-H4	AZD8205	Topoisomerase I inhibitor	NCT05123482 (Phase I)
Folate Receptor α	Farletuzumab ecteribulin (MORAb-202, FZEC) (3 EC)	Eribulin (microtubule inhibitor)	NCT04300556 (Phase I/II)
Folate Receptor α	Mirvetuximab Soravtansine	Maytansinoid (DM4)→ tubulin targeting	NCT03835819 (Phase II combination with pembro)
TROP2	Sacituzumab govitecan (IMMU-132) *approved in TNBC, urothelial	SN-38 (irinotecan metabolite) → Topoisomerase I inhibitor	NCT04251416 (Phase II) NCT03992131 (combination with rucaparib)
TROP2	SKB264/MK-2870	Belotecan derivative → Topoisomerase I inhibitor	NCT04152499 (Phase I/II) NCT06132958 (Phase III)



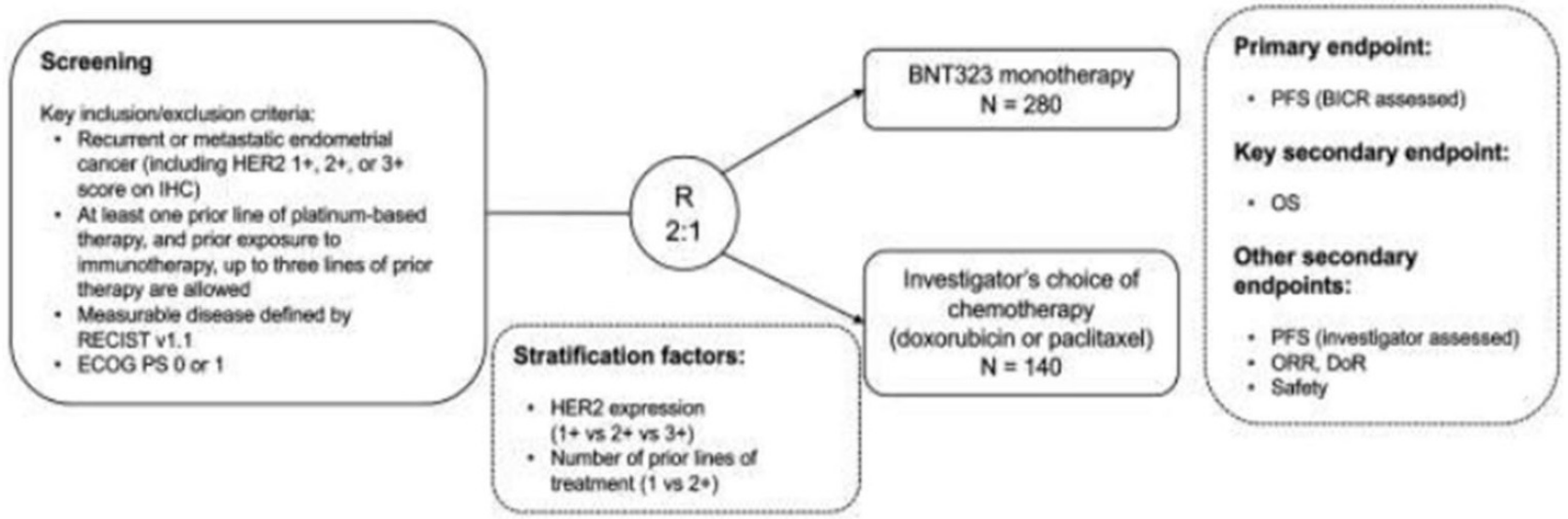
There is no efficacy data on Topo I after Topo I… and studies use prior Topo I as an exclusion criteria

GOG-3105/BNT323-01/ENGOT-en25:

A Phase III, Randomized, Multi-site, Open-label Trial of BNT323/DB-1303 Versus Investigator's Choice of Chemotherapy in Previously Treated Patients with HER2-Expressing Recurrent or Metastatic Endometrial Cancer

(GOG PI: Floor Backes, MD)

Cohort 1 (main cohort)

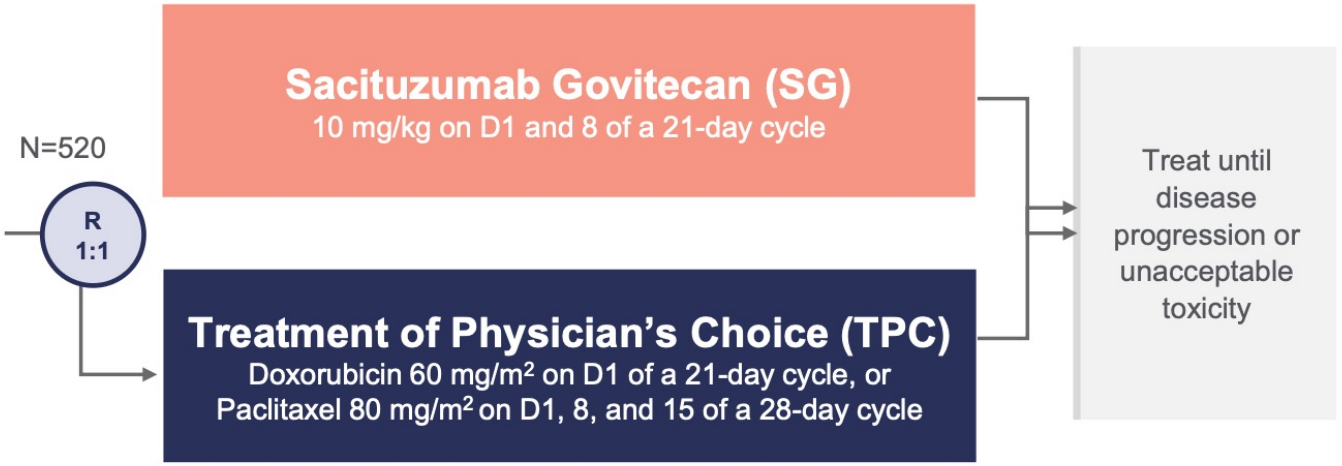


Abbreviations: BICR = blinded independent central review; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HER2 = human epidermal growth factor receptor 2;

ASCENT-GYN-01/GOG-3104/ENGOT-en26

A Randomized, Open-Label, Phase 3 Study of SG vs TPC in Participants With Endometrial Cancer Who Have Received Prior Platinum-Based Chemotherapy and Anti-PD-1/PD-L1 Immunotherapy

(GOG PI: Ramez Eskander, MD)



Primary Endpoints:
- PFS by BICR
- OS

Secondary Endpoints:
- ORR, DOR, CBR
- PFS by INV
- Safety
- QOL

Key Inclusion
- Recurrent or persistent endometrial cancer (endometrial carcinoma or carcinosarcoma)
- Up to 3 prior lines of systemic therapy for endometrial cancer, including systemic platinum-based chemotherapy and anti-PD-1/PD-L1 therapy, either in combination or separately
- Radiologically evaluable disease (either measurable or nonmeasurable) per RECIST v1.1
- ECOG Performance Status of 0-1

Partnership with Gynecologic Oncology Group Foundation

Expected FPI Q4 2024

BICR, blinded independent central review; CBR, clinical benefit rate; DOR, duration of response; ECOG, eastern cooperative oncology group; FPI, first patient in; INV, investigator; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; QOL, quality of life; RECIST, response evaluation criteria in solid tumors; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

GOG Highlight Reel

NCT06486441

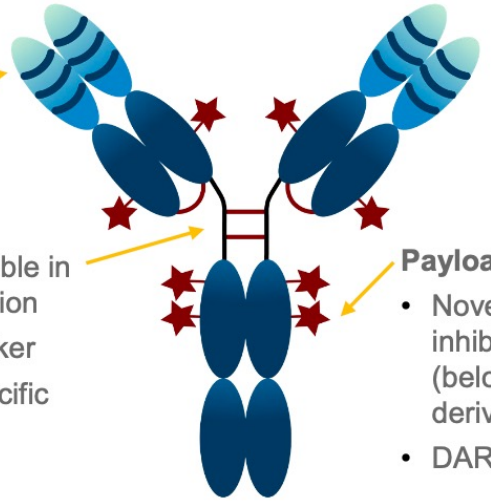
Trofuse: Phase 3 ENGOT-en23/GOG-3095/MK-2870-005[1]

TROP2: transmembrane glycoprotein overexpressed by several gynecologic tumor types

Primary endpoints: PFS, OS
Secondary endpoints: ORR, DOR, safety, HRQOL

R

- **MK-2870 4 mg/kg IV on day 1 of each 14-day cycle**
- **Doxorubicin 60 mg/m² IV on day 1 of each 21-day cycle**
  or
  Paclitaxel 80 mg/m² IV on days 1, 8, and 15 of each 28-day cycle



- MK-2870 employs the same antibody as sacituzumab govitecan
- Its linker was designed to have higher stability
- Novel TOPO I inhibitor payload (KL610023) is a belotecan derivative/topoisomerase inhibitor that has similar in vitro activity to belotecan and SN-38 (sacituzumab govitecan's payload)

GOG Highlight Reel

NCT06132958

Key Inclusion

- Histologically confirmed endometrial carcinoma or carcinosarcoma
- Radiographically evaluable disease, either measurable or nonmeasurable per RECIST v1.1 (by BICR)
- Must have received prior platinum-based chemo and anti–PD-1/anti–PD-L1 therapy, either separately or in combination
- No neuroendocrine tumors or endometrial sarcoma, including stromal sarcoma, leiomyosarcoma, adenosarcoma, or other types of pure sarcomas
- Has not received >3 prior lines of therapy for endometrial carcinoma or carcinosarcoma
- Has not had a recurrence of endometrial carcinoma or carcinosarcoma >180 days after completing platinum-based therapy administered in the curative-intent or adjuvant setting without any additional platinum-based therapy received in the metastatic or recurrent setting

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Hormonal Therapy for Recurrent or Metastatic Endometrial Carcinoma[t]		

Preferred Regimens
• Megestrol acetate/tamoxifen (alternating)
• Everolimus/letrozole
	Other Recommended Regimens
	• Medroxyprogesterone acetate/tamoxifen (alternating)
	• Progestational agents
	  ▸ Medroxyprogesterone acetate
	  ▸ Megestrol acetate
	• Aromatase inhibitors
	  ▸ Anastrozole
	  ▸ Letrozole
	  ▸ Exemestane
	• Tamoxifen
	• Fulvestrant
		Useful in Certain Circumstances
		• ER-positive tumors
		  ▸ Letrozole/ribociclib
		  ▸ Letrozole/abemaciclib

Hormonal Therapy for Uterine-Limited Disease Not Suitable for Primary Surgery or for Those Desiring Uterine Preservation for Fertility (ENDO-1)[t]	

Preferred Regimen
• Levonorgestrel IUD
	Other Recommended Regimens
	• Progestational agents
	  ▸ Megestrol acetate
	  ▸ Medroxyprogesterone acetate
	• Dual progestin agents
	  ▸ Megestrol acetate + levonorgestrel IUD
	  ▸ Medroxyprogesterone acetate + levonorgestrel IUD

HORMONAL TREATMENT OPTIONS IN RECURRENT ENDOMETRIAL CANCER

	ORR	CBR	PFS (months)	OS (months)	DOR (months)	ref
Progesterone single agent	25%	46%	7.6	8.9	8.9	Lentz, Thigpen
Progesterone/ tamoxifen	19-33%	69%	2.7-4	8.6-17	31	Pandya, Fiorica, Whitney, Slomovitz
SERM/SERD	10%	34%	1.9-2.3	8.8-18.9	1.9	Thigpen, Covens, Emons
Aromatase inhibitor	9-17%	17-44%	1-3.9	6-10.9	6.7	Rose, Heudel, Lindemann
Aromatase and mTOR inhibitor	22-32%	40-78%	3-6	14-31	30	Slomovitz, Heudel
Aromatase and CDK4/6 inhibitor	10-30%	64-73%	5.4-9.7	15.7-21.6	7.4	Colon-Otero, Konstantinopoulos, Mirza

GOG-3069

A Phase 2 Study of Alpelisib and Fulvestrant for PIK3CA-mutated Estrogen Receptor (ER)-positive Endometrioid Endometrial Cancers

(PI: Stéphanie Gaillard, MD PhD)

BACKGROUND

- The PI3K/PTEN/PIK3CA pathway is altered in 93% of endometrioid endometrial cancer with PIK3CA activating mutations in 53%1
- Recent data have shown promising responses in patients with ER positive endometrial cancer treated with endocrine therapy plus mTOR inhibitors or CDK4/6 inhibitors2-5.
- The combination of alpelisib and fulvestrant was FDA approved for treatment of ER+ PIK3CA-mutated Breast Cancer on May 24, 2019, based on the SOLAR-1 study6.
- GOG3069 is evaluating the efficacy of alpelisib and fulvestrant for the treatment of ER+ PIK3CA-mutated Endometrioid Endometrial Cancer

METHODS

- Conditional stratified Phase 2 study
- Stratified by prior chemotherapy exposure
- Target accrual 50 patients

FAST FACTS ABOUT GOG-3069

- Sponsor: GOG Foundation
- Planned Enrollment: 50 patients
- GOG Accrual: 0
- GOG Activated Sites: 6/15
- Countries: US

Screening/Registration

↓

TREATMENT
Alpelisib 300mg orally daily
+
Fulvestrant 500mg IM Day 1 and Day 15 of Cycle 1, then Day 1 each 28-day cycle

↓

Disease evaluations every 8 weeks for the first 3 evaluations then every 12 weeks until PD

Primary Outcome:
ORR
Secondary Outcomes:
safety/toxicity, PFS, OS, DoR

Eligibility

- Advanced, persistent, recurrent endometrial cancer
- Endometrioid histology
- PIK3CAmutated (CLIA-certified testing)
- ER+ (≥ 1% of tumor cells)
- Measurable disease by RECISTv1.1
- Up to 1 prior line of chemotherapy and no more than 1 additional systemic therapy
- Prior endocrine therapy allowed
- No prior mTOR, PIK3CA, PI3K, or AKT inhibitors allowed

GOG Highlight Reel

NCT05154487

REFERENCES: [1]Levine, Nature. 2013; [2]Slomovitz. Gyn Onc. 2022; [3]Konstantinopolous. JCO 2022; [4]Colon-Otero. ESMO Open; 2020;[5]Mirza. ESCO 2020 [6]André. NEJM 2019

GOG-3111/FTH-PIK-201

A Randomized, Open-label, Multi-Center, Phase 2 Clinical Trial Evaluating Sapanisertib and Serabelisib (PIKTOR) with Paclitaxel, Serabelisib with Paclitaxel, and Paclitael Alone in Patients with Advanced or Recurrent Endometrial Cancer

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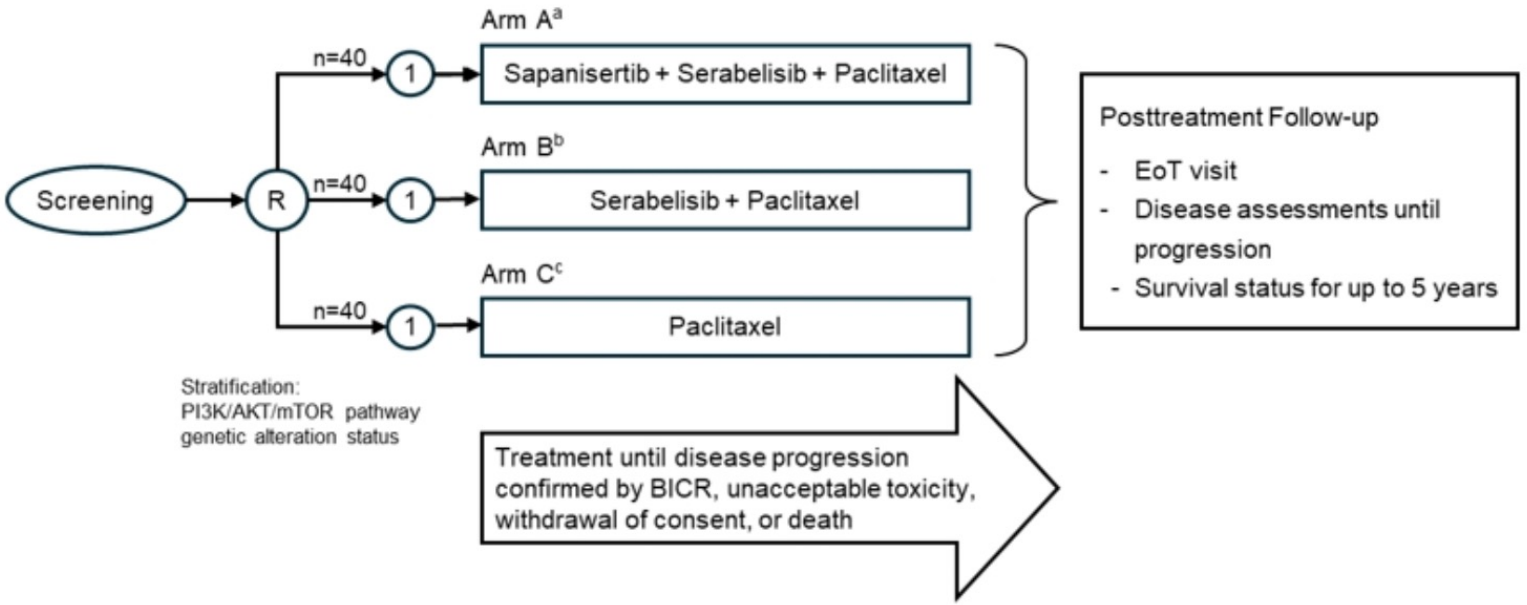
1.2 Schema



AKT = protein kinase B; BICR = blinded independent central review; EoT = end of treatment; mTOR = mechanistic target of rapamycin; PI3K =phosphoinositide 3-kinase; R = randomization

a. Sapanisertib 3 mg taken orally QD on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle; serabelisib 200 mg taken orally QD on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle; paclitaxel 80 mg/m^2 IV infusion once weekly on Days 1, 8, and 15 of a 28-day cycle

b. Serabelisib 200 mg taken orally QD on Days 2-4, 9-11, 16-18, and 23-25 of a 28-day cycle; paclitaxel 80 mg/m^2 IV infusion once weekly on Days 1, 8, and 15 of a 28-day cycle

c. Paclitaxel 80 mg/m^2 IV infusion once weekly on Days 1, 8, and 15 of a 28-day cycle

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NCT06463028

Key Inclusion

- Histologically confirmed diagnosis of endometrioid endometrial carcinoma
- Documented evidence of advanced or recurrent endometrial cancer that is not amenable to surgery/radiation for curative intent
- Participant has received at least 1 but not more than 3 prior systemic therapies
- PI3K/AKT/mTOR pathway gene alteration status available
- At least 1 measurable target lesion according to RECIST v1.1
- ECOG performance status of <1 at screening

QUESTIONS?