Future Perspectives on Personalized Medicine for Endometrial Cancer

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Disclosures

Advisory Board/Consultant

- Merck
- Eisai
- Seagen
- Karyopharm
- GSK

Endometrial Cancer Recurrence Risk

- Median PFS is ~8 months
- 80% will recur within first two years.

Study (control arm)	Median PFS (months)
GY-018	8.7m
RUBY	7.9m
GOG 209 (TC arm)	13m
MITO END-2	10.5m
FANDANDO	7.2m

Trends in Overall Survival

Overall survival in MMRp advanced/recurrent EC is ~30 months

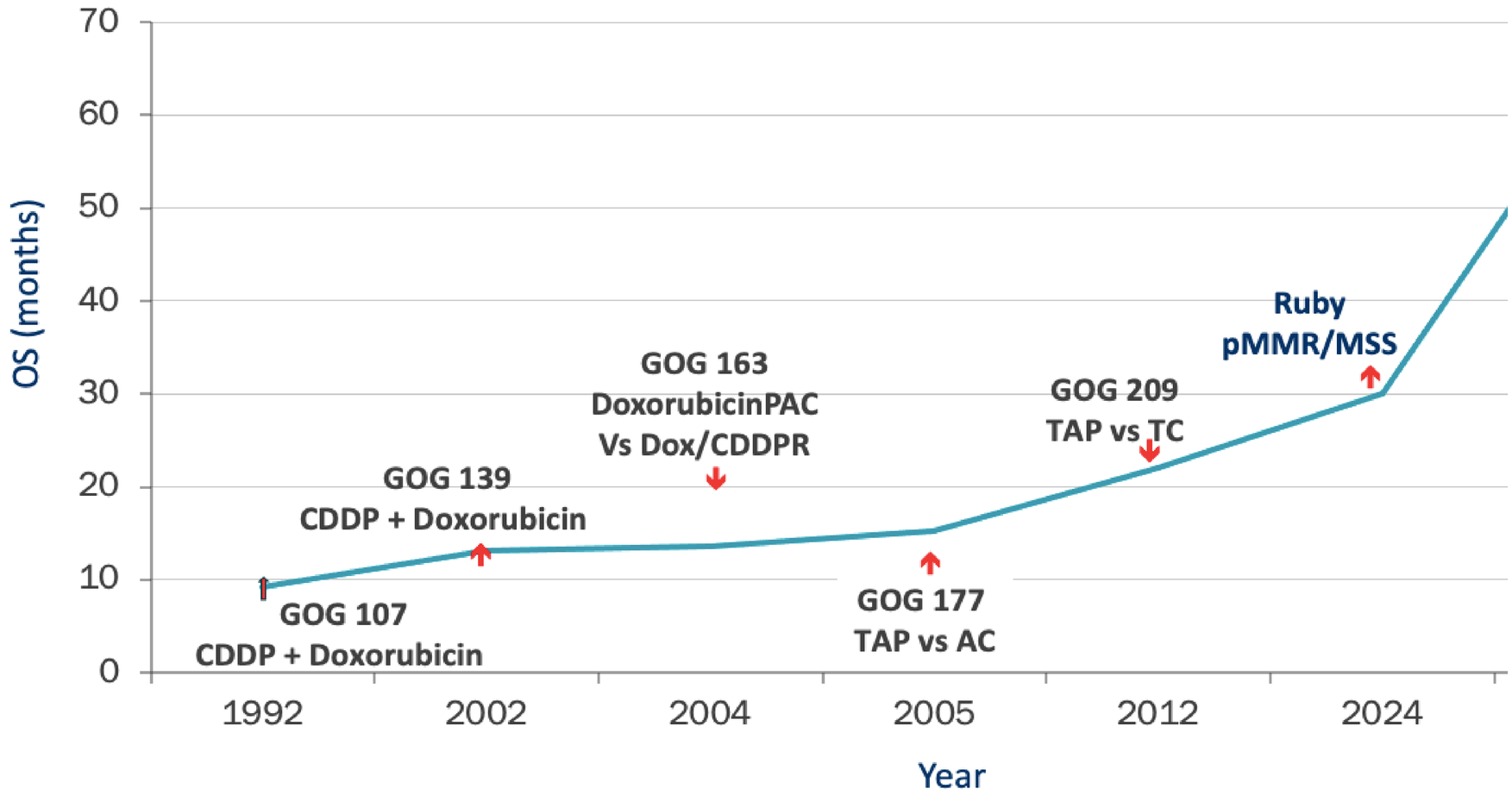

Figure adapted from K. Moore WAGO 2023

Clinical Trial Overview
Endometrial cancer MMRp, P53wt

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Clinical trials in dMMR EC-Can we eliminate chemotherapy?

	Pembrolizumab	Dostarlimab
	KEYNOTE-C93	DOMENICA
Study treatment	▪Pembrolizumab 400 mg IV q6w for 18 cycles (2 years) ▪Carboplatin AUC 5 or 6 mg/mL/min IV q3w + paclitaxel 175 mg/m^2 IV q3w for 6 cycles (with option for >6 cycles)	▪Dostarlimab 500 mg q3w (cycles 1-4) then dostarlimab 1000 mg q6w (for up to 2 years) ▪Carboplatin AUC 5-6 + paclitaxel 175 mg/m^2 q3w (for 6 cycles)
Key eligibility criteria	▪dMMR status ▪Stage III/IV or recurrent EC including carcinosarcoma Radiographically evaluable disease (measurable or nonmeasurable per RECIST v1.1) ▪No prior systemic therapy ▪ECOG PS 0-1	▪dMMR/MSI-H status ▪Endometrial adenocarcinoma with primary advanced stage IIIC2 or stage IV disease or first recurrence ▪Prior neo/adjuvant chemotherapy allowed if ≥6 months from last treatment to relapse ▪All histologic subtypes of endometrial adenocarcinoma included if dMMR/MSI-H ▪ECOG PS 0-1

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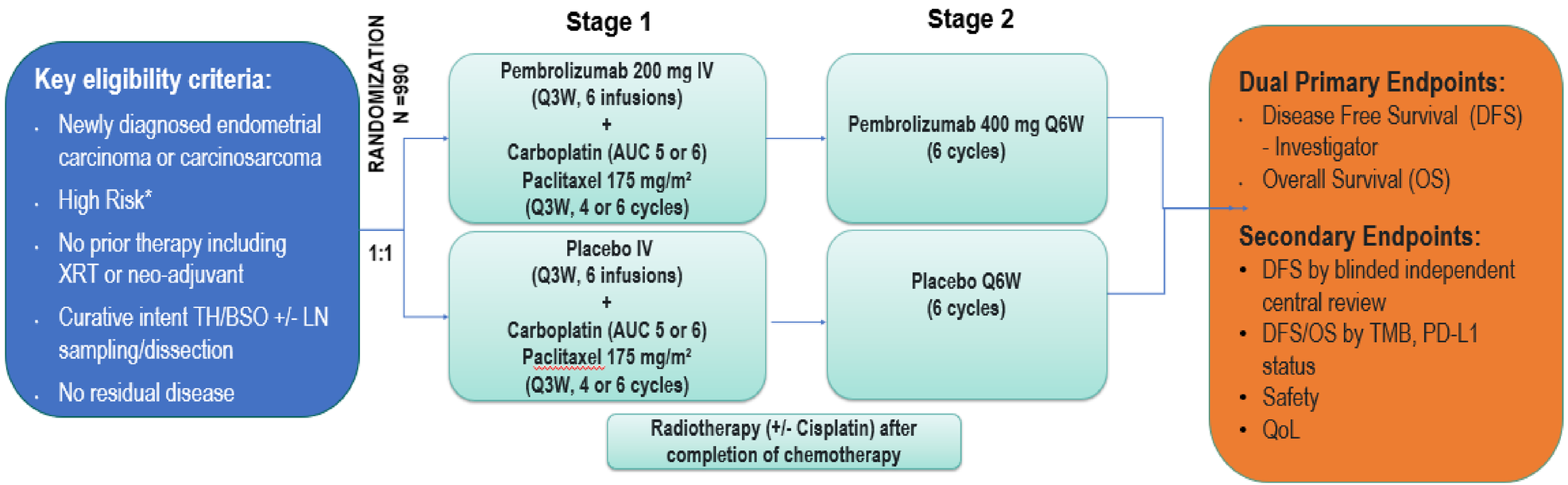
Slomovitz BM, et al. *J Clin Oncol.* 2022;40(Suppl 16):TPS5623. ClinicalTrials.gov. Accessed April 19, 2023. https://clinicaltrials.gov/ct2/show/NCT05173987ClinicalTrials.gov. Accessed April 19, 2023. https://clinicaltrials.gov/ct2/show/NCT05201547

MK-3475-B21/ENGOT-en11/GOG-3053: KEYNOTE-B21

A Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Adjuvant Chemotherapy With or Without Radiotherapy for the Treatment of Newly Diagnosed High-Risk Endometrial Cancer After Surgery With Curative Intent



*** High Risk:**

- **FIGO (2009) Surgical Stage I or II with myometrial invasion**
  - of non-endometrioid histology
  - **or** of any histology with known aberrant p53 expression or p53 mutation
- FIGO (2009) Surgical Stage **III or IVA of any histology**

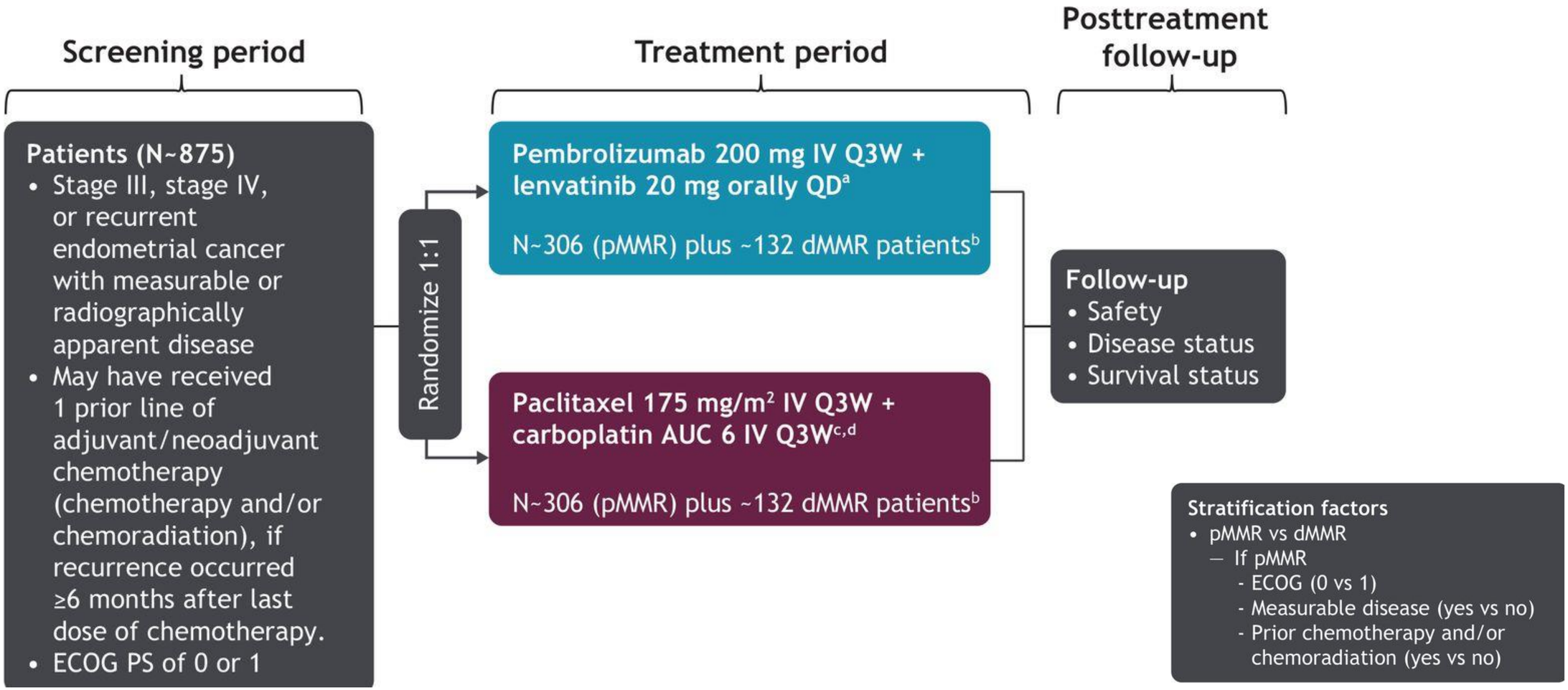
Stratification factors:

- MMR status (if pMMR then further stratification by:
  - Stage (I/II vs III/IVA)
  - Planned radiation (EBRT vs Chemo-EBRT vs no EBRT)
  - Histology (non-endometrioid vs endometrioid)

NCT04634877

ENGOT-en9/LEAP-001

A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Advanced or Recurrent EC



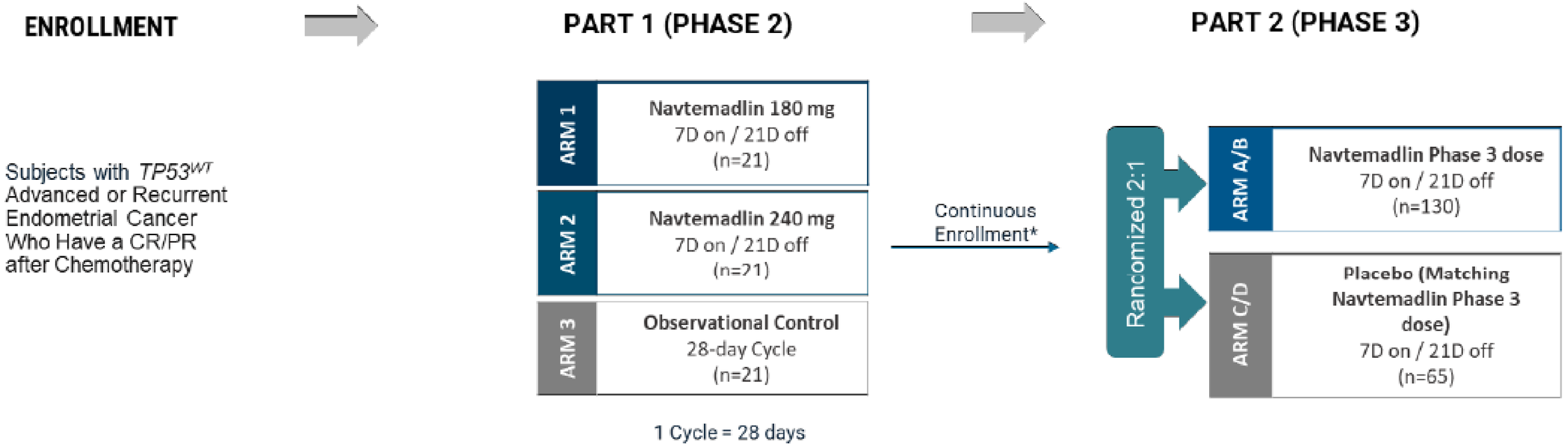
NCT03884101

Marth C. Int J Gynecol Cancer 2022.

KRT-232-118/GOG-3089

A Phase 2/3 Study of Navtemadlin as Maintenance Therapy in Subjects with TP53WT Advanced or Recurrent Endometrial Cancer Who Responded to Chemotherapy

Figure 1: Study Schema

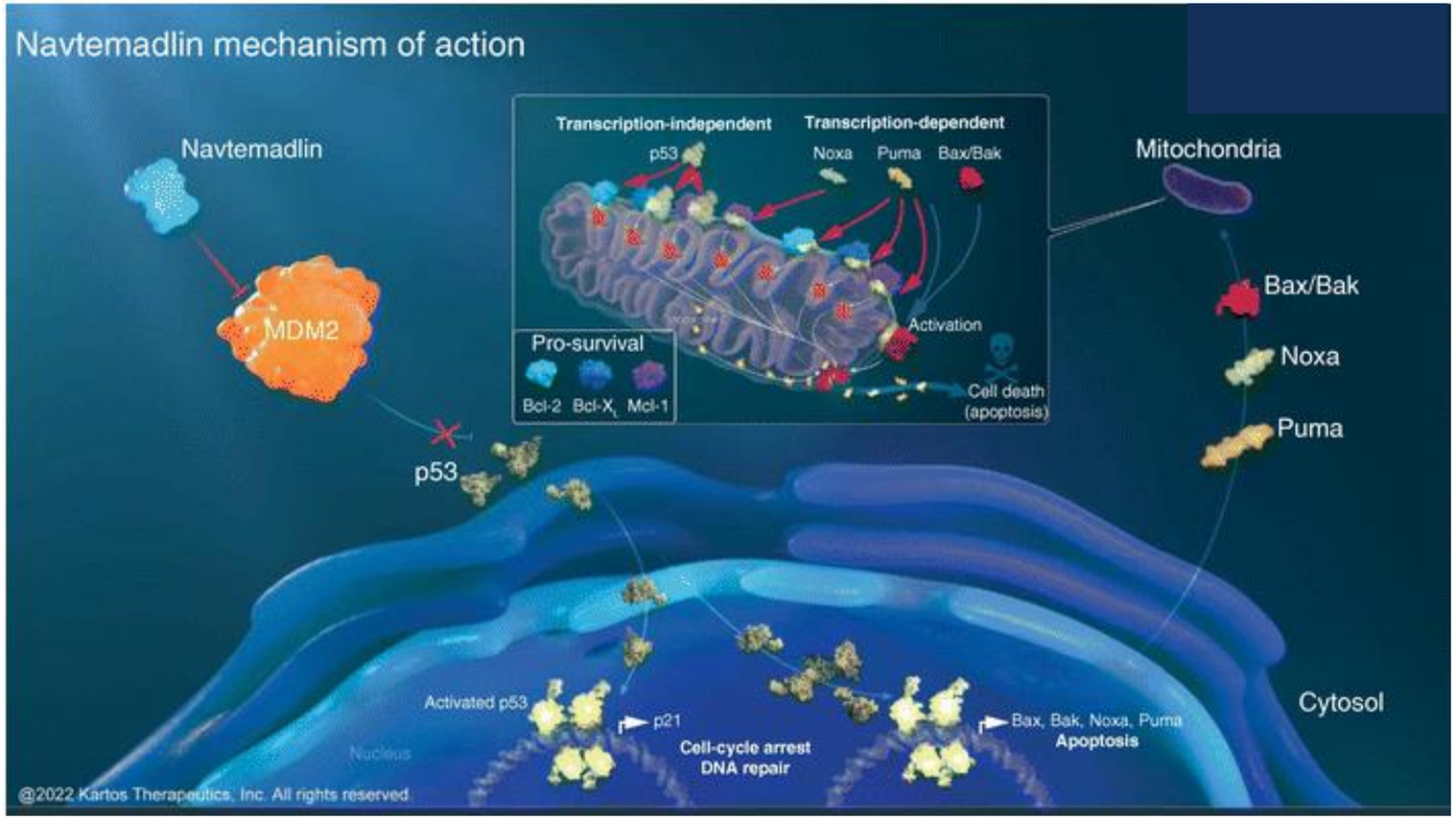


NCT05797831

KRT-232-11: Navtemadlin

Phase 2/3 Study of Navtemadlin as Maintenance Therapy in Subjects with TP53WT Advanced or Recurrent Endometrial Cancer Who Responded to Chemotherapy 8/GOG-3089

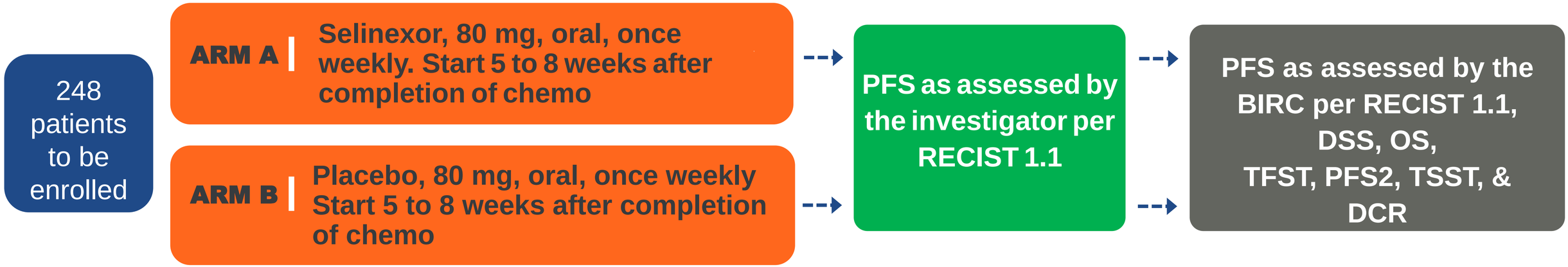
- Oral MDM2 inhibitor
- Restores p53 activity to drive apoptosis of wild type TP53 cells
  - Expression of pro-apoptotic Bcl-2 family proteins



NCT05797831; Verstovsek S. BOREAS. Future Oncology 2022.

KCP-330-024/BGOG-EN5/ENGOT-EN5/SIENDO/GOG-3055

Randomized, Double-blinded, Phase 3 Trial of Maintenance with Selinexor/Placebo After Combination Chemotherapy for Participants with Advanced or Recurrent EC



KEY INCLUSION CRITERIA:

- Histological confirmed endometrial cancer of the endometrioid, serous, or undifferentiated type. Carcinosarcoma of the uterus is also allowed.
- Completed a single line of at least 12 weeks of taxane-platinum combination therapy (not including adjuvant or neoadjuvant therapy), and achieved partial or complete remission (PR or CR) according to RECIST version 1.1 for:
  - Primary Stage IV disease, OR
  - At first relapse (i.e., relapse after primary therapy including surgery and/or chemotherapy therapy for Stage I-IV disease).
- Must be able to initiate study drug 5 to 8 weeks after completion of their final dose of chemotherapy.

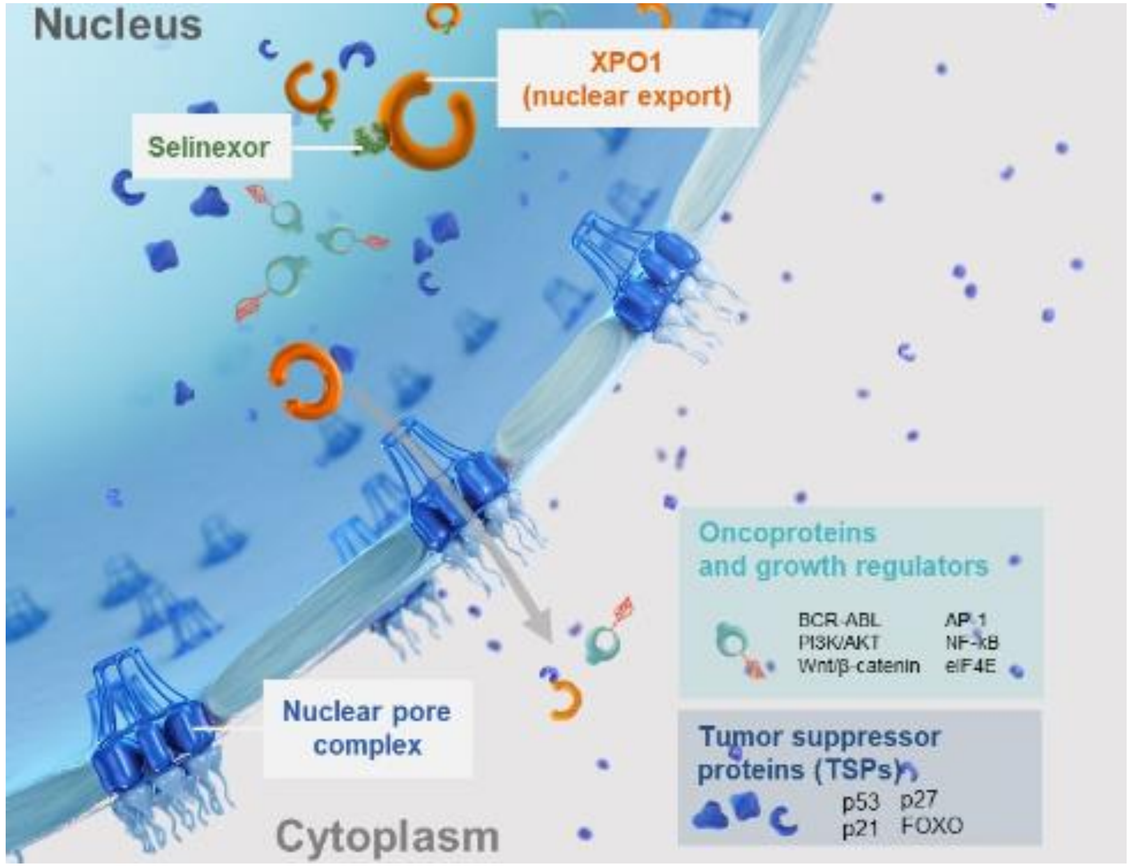
KEY EXCLUSION CRITERIA:

- Previous treatment with an exportin 1 (XPO1) inhibitor or with anti-PD1 or anti-PD-L1 immunotherapy (e.g., pembrolizumab).

NCT03555422

Selinexor

- XPO1 exports the major tumor suppressor proteins away from the nucleus
- Cancer cells
  - Overexpress XPO1
  - Inactivate cytoplasmic p53 through protein degradation
- Selinexor inhibits XPO1 nuclear export
  - Leads to retention and reactivation of TSPs in the nucleus and stabilization of p53
  - Results in selective killing of cancer cells

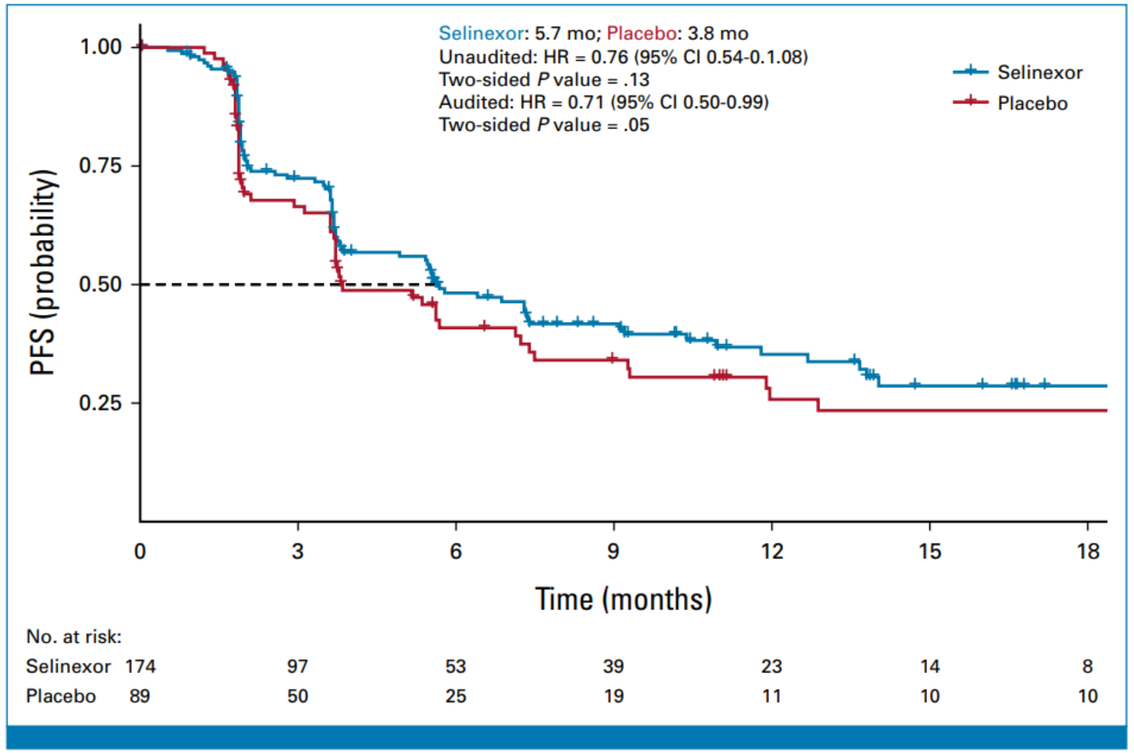


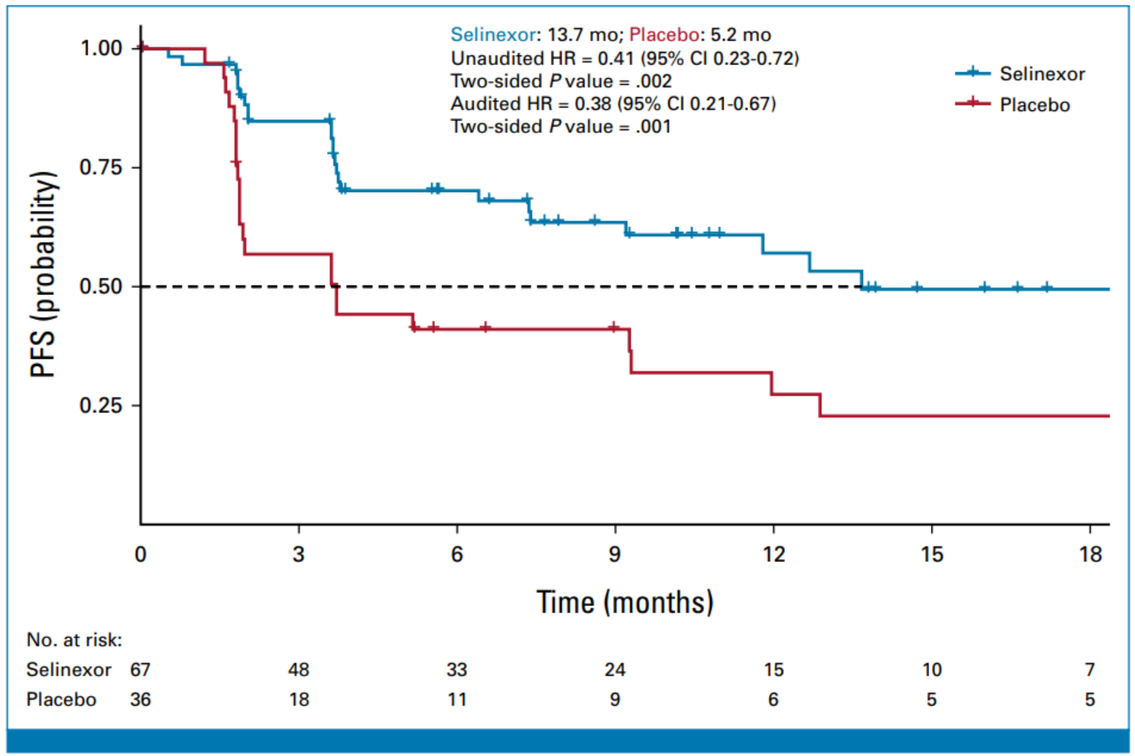
Patient Characteristics

Characteristic	Selinexor (n = 174)	Placebo (n = 89)
Age, years, median (range)	65.5 (40-81)	64.0 (33-81)
<70	116 (66.7)	61 (68.5)
≥70	58 (33.3)	28 (31.5)
Race, No. (%)		
Asian	4 (2.3)	4 (4.5)
Black or African American	7 (4.0)	2 (2.2)
Native Hawaiian or other Pacific Islander	1 (0.6)	0
White	158 (90.8)	81 (91.0)
Others	4 (2.3)	2 (2.2)
Ethnicity, No. (%)		
Hispanic or Latino	9 (5.2)	5 (5.6)
Not Hispanic or Latino	160 (92.0)	83 (93.3)
Not reported	1 (0.6)	0
Unknown	4 (2.3)	1 (1.1)
ECOG performance status,[a] No. (%)		
0	99 (56.9)	54 (60.7)
1	71 (40.8)	35 (39.3)
2	1 (0.6)	0
Histology, No. (%)		
Endometrioid	96 (55.2)	48 (53.9)
Serous	49 (28.2)	28 (31.5)
Undifferentiated	4 (2.3)	1 (1.1)
Carcinosarcoma	10 (5.7)	6 (6.7)
Endometrial adenocarcinoma[b]	15 (8.6)	6 (6.7)
Molecular characterization of *TP53* mutation status,[c] No. (%)		
Wild type	67 (38.5)	36 (40.4)
Mutant/aberrant	74 (42.5)	40 (44.9)
Unknown	33 (19)	13 (14.6)
Molecular characterization of microsatellite instability status,[c] No. (%)		
MSS/pMMR	113 (64.9)	59 (66.3)
MSI-H/dMMR	22 (12.6)	13 (14.6)
Unknown	39 (22.4)	17 (19.1)
Disease at the time of taxane-platinum combination therapy, No. (%)		
Unaudited stratification factors		
Primary stage IV disease	82 (47.1)	41 (46.1)
Recurrent disease	83 (47.7)	41 (46.1)
Missing[d]	9 (5.2)	7 (7.9)
Audited stratification factors[e]		
Primary stage IV disease	78 (44.8)	43 (48.3)
Recurrent disease	96 (55.2)	46 (51.7)
Disease status after the most recent chemotherapy, No. (%)		
Unaudited stratification factors		
Complete response	72 (41.4)	37 (41.6)
Partial response	102 (58.6)	52 (58.4)
Audited stratification factors[e]		
Complete response	70 (40.2)	40 (44.9)
Partial response	104 (59.8)	49 (55.1)

Vergote I. J Clin Oncol 2023.

KCP-330-024/BGOG-EN5/ENGOT-EN5/SIENDO/GOG-3055





PFS: ITT population

PFS: *TP53* status

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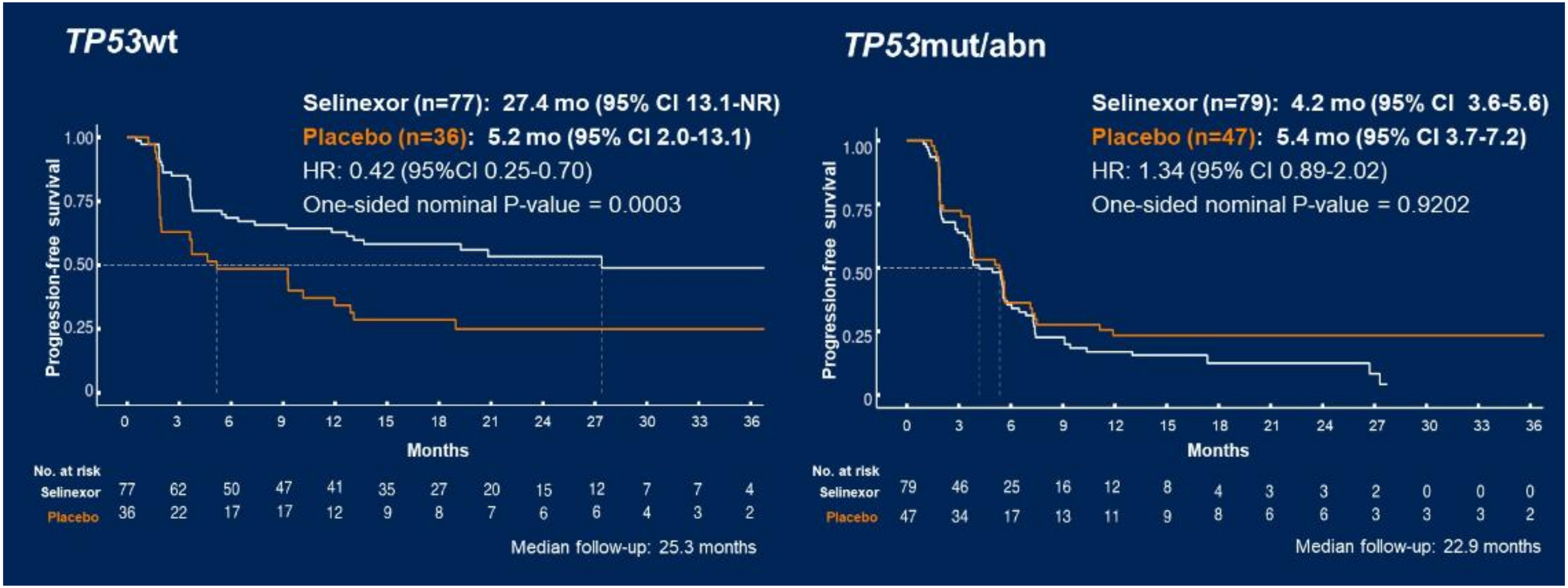
Vergote I. J Clin Oncol 2023.

SIENDO TEAEs

	Selinexor n = 171[a] (per patient), No. (%)		Placebo n = 88[a] (per patient), No. (%)	
Event	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Hematologic AEs				
Thrombocytopenia	61 (35.7)	12 (7.0)	0	0
Anemia	42 (24.6)	4 (2.3)	2 (2.3)	0
Neutropenia	41 (24.0)	15 (8.8)	5 (5.7)	0
Leukopenia	15 (8.8)	2 (1.2)	1 (1.1)	0
Nonhematologic AEs				
Nausea	137 (80.1)	16 (9.4)	25 (28.4)	0
Vomiting	86 (50.3)	2 (1.2)	8 (9.1)	0
Constipation	32 (18.7)	0	13 (14.8)	2 (2.3)
Diarrhea	46 (26.9)	1 (0.6)	12 (13.6)	0
Fatigue	53 (31.0)	10 (5.8)	10 (11.4)	1 (1.1)
Asthenia	48 (28.1)	10 (5.8)	15 (17.0)	1 (1.1)
Decreased appetite	52 (30.4)	2 (1.2)	4 (4.5)	0
Dysgeusia	28 (16.4)	0	7 (8.0)	0
Dizziness	20 (11.7)	2 (1.2)	6 (6.8)	0
Abdominal pain	15 (8.8)	2 (1.2)	7 (8.0)	0
Decreased weight	15 (8.8)	0	1 (1.1)	0
Headache	11 (6.4)	0	4 (4.5)	0
Dose reduction	84 (49.1)		3 (3.4)	
Dose interruption	78 (45.6)		5 (5.7)	
Discontinuation because of AE	17 (9.9)	**15.8%**	1 (1.1)	

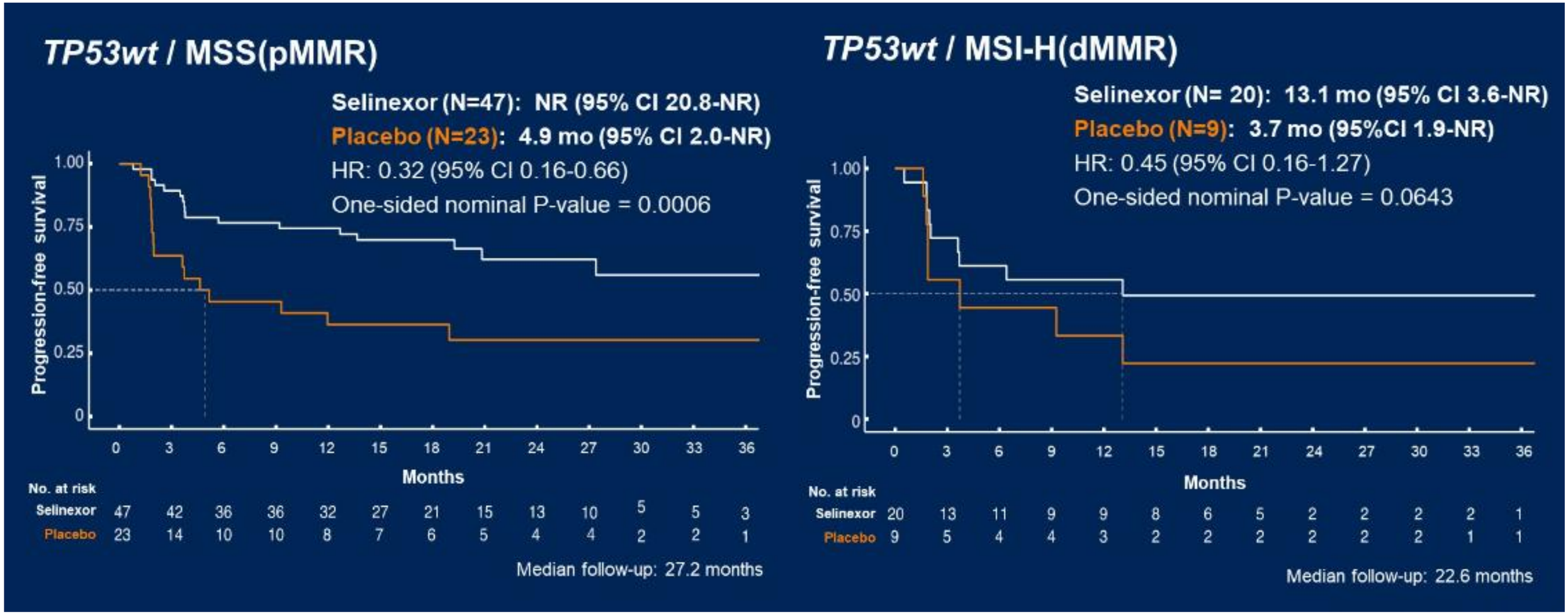
Vergote I. J Clin Oncol 2023.

GOG 3055/SIENDO: Long-term PFS follow up, *TP53*

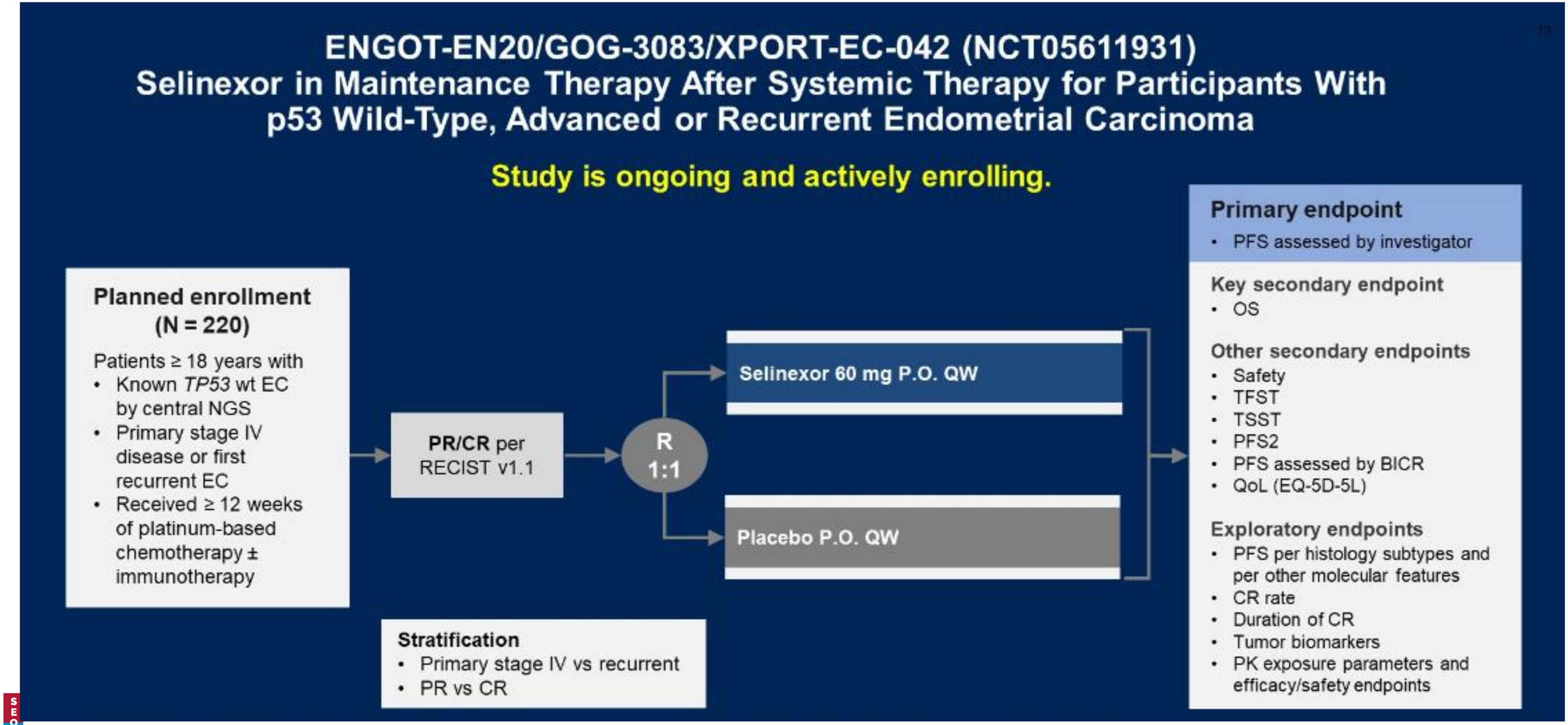


Pre-specified subgroups

GOG 3055/SIENDO: Long-term PFS follow up, *TP53, MMR*



ENGOT-EN20/GOG 3083/XPORT-EC-042



Impact on future treatment algorithm: How to approach frontline and subsequent therapies for advanced endometrial cancer

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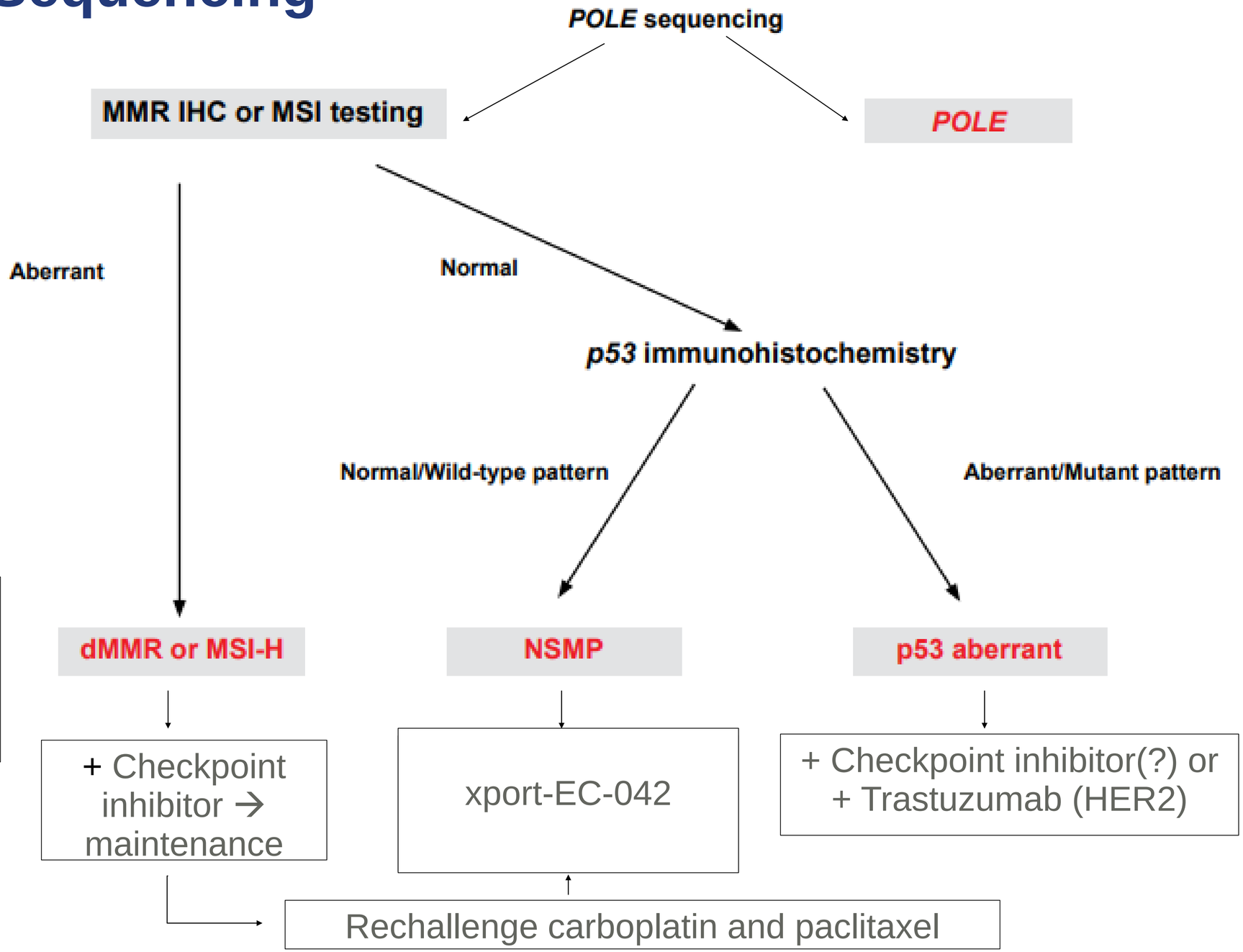
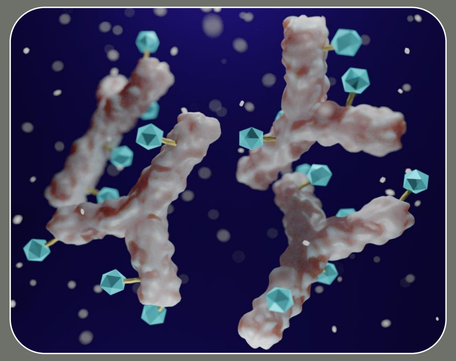
Treatment Sequencing



Advanced disease: carboplatin and paclitaxel

What is on the Horizon?

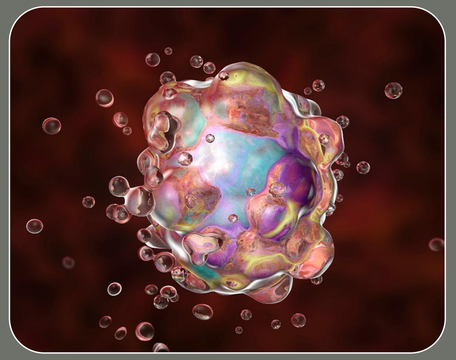
Targeting HER2



Trastuzumab deruxtecan:
DESTINY (phase 2)[1]

Trastuzumab ± C/P:
NCT01367002 (phase 2)[2]

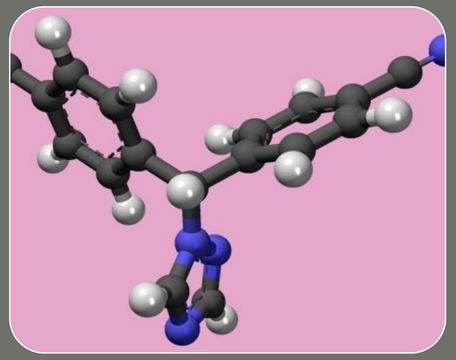
Kickstarting apoptosis



Selinexor:
SIENDO (phase 3)[3]; xport-EC-042 (phase 3)[4]

Navtemadlin:
EURUS (phase 2/3)[5]

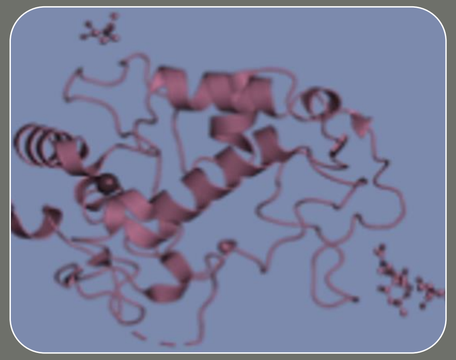
Revisiting endocrine therapy



Letrozole + palbociclib:
PALEO (phase 2)[6]

Letrozole + abemaciclib:
GOG-3039 (phase 2)

FR-α inhibition



Mirvetuximab soravtansine + gemcitabine:
NCT02996825 (phase 1)[8]

Farletuzumab ecteribulin:
NCT03386942 (phase 1)[9]

Inhibiting TROP-2

Sacituzumab govitecan:
NCT04251416 (phase 2)[10]

FR-α = folate receptor alpha; HER2 = human epidermal growth factor 2; TROP-2 = Trophoblast cell surface antigen 2.

1. Meric-Bernstam F, et al. *J Clin Oncol.* 2023;41(suppl_17):LBA3000. 2. Fader AN, et al. *Clin Cancer Res*. 2020;26:3928-3935. 3. Makker V, et al. *J Clin Oncol.* 2022;40:5511-5511. 4. Vergote IB, et al. *J Clin Oncol*. 2023;41(16_suppl):TPS5627-TPS5627. 5. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT05797831. Accessed August 23, 2023. 6. Mirza MR, et al. *Ann Oncol*. 2020;31(s4):S1160. 7. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT05712941. Accessed August 23, 2023. 8. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT02996825. Accessed August 23, 2023. 9. National Library of Medicine. https://clinicaltrials.gov/ct2/show/NCT03386942. Accessed August 23, 2023. 10. Santin A, et al. *J Clin Oncol.* 2023;41(suppl_16):abst 5599.

Endocrine therapy

Progestin therapy

- Response rates in recurrent disease: 11-24%
  - 1st line, positive ER/PR status, lower grade, and younger age
  - Often reserved for fertility preservation or palliative therapy

Everolimus and Letrozole

- Response rate 24% (53% if no prior chemotherapy)
- Clinical benefit rate 78%

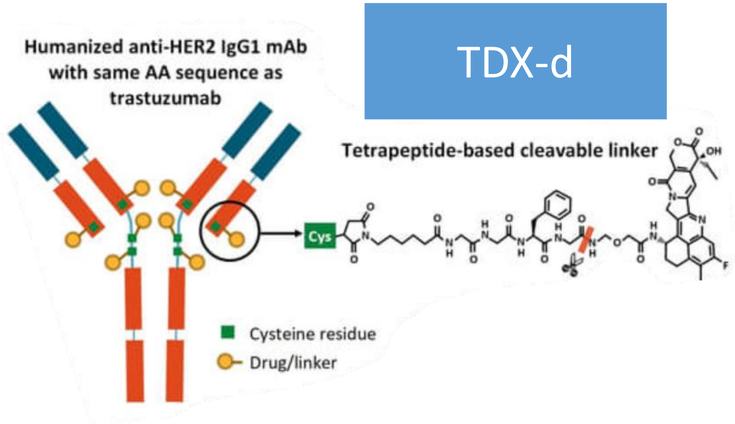
Aromatase and CDK 4/6 inhibitors

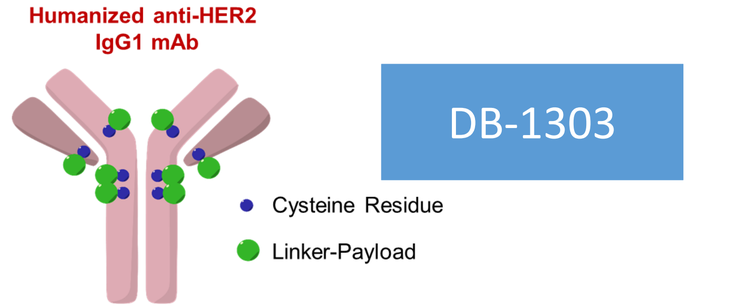
- PALEO (palbociclib + letrozole v letrozole)
  - DCR 63.6% vs 37.8%; PFS 8.3 vs 3.0 months
- Abemaciclib + letrozole
  - ORR 30%; PFS 9.1 m (no response in *TP53*m)

MacKay HJ. 2020 ASCO Educational Book; Ethier. Gyn Oncol 2017; Singh M. Gyn Oncol 2007. Pijnenborg JMA. JCO. 2023. Slomovitz Gyn Onc 2022. Slomovitz BM. SGO 2018. Mirza MR. Ann Oncol 2020. Konstantinopoulos P. JCO 2023.

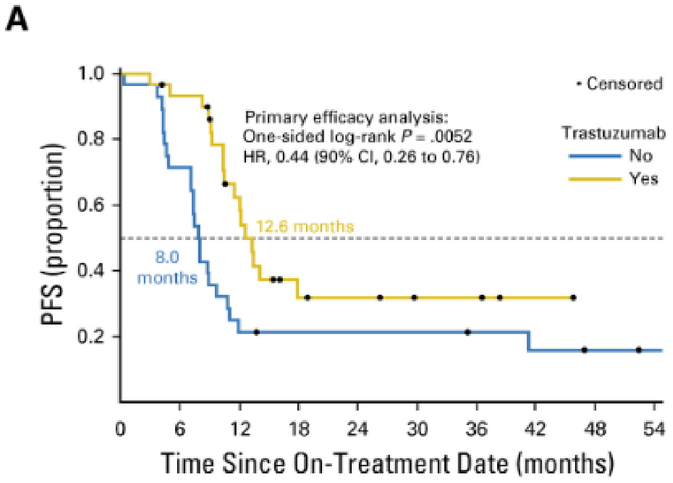
Targeting HER2

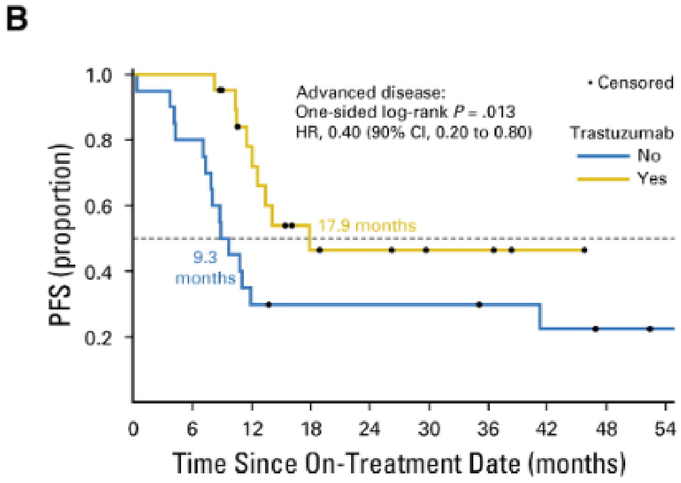
TARGET: HER2/ERBB2





- HER2 is a negative prognostic marker
- Prevalence in uterine cancer ~20%
  - No standard testing
- Phase II trial of trastuzumab + chemotherapy
  - Improved PFS in UPSC with HER2 overexpression

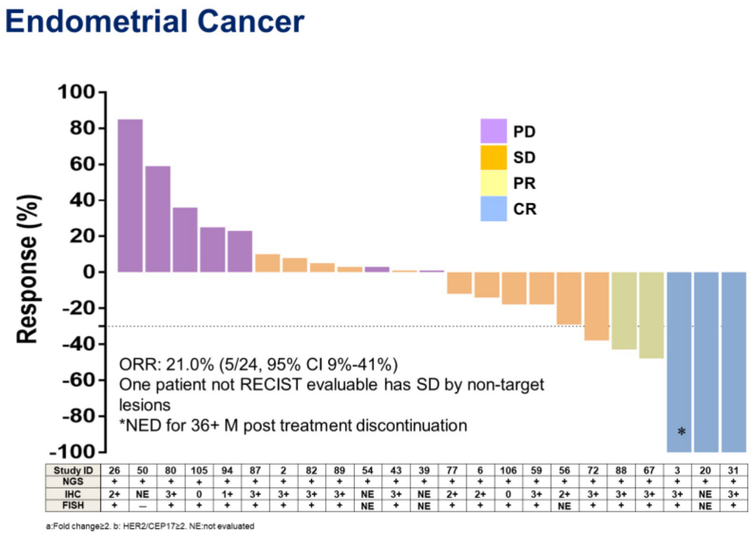




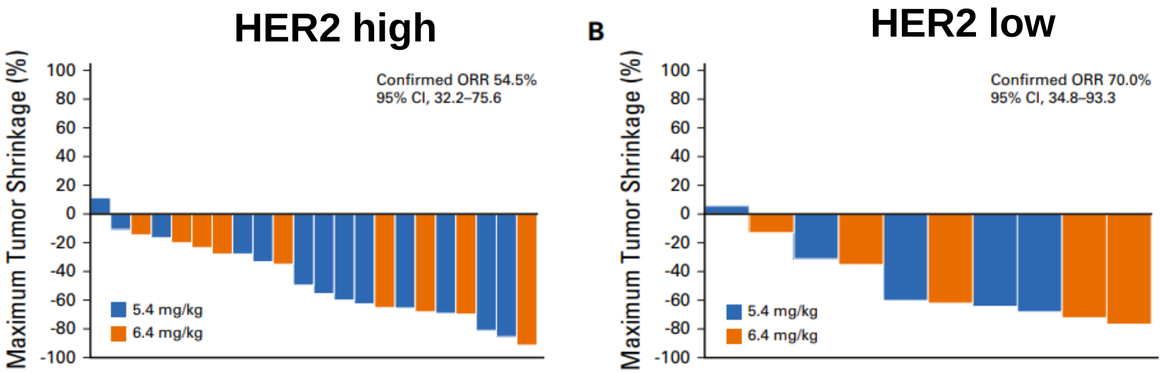
Lin et al. Gynecol Oncol 2022. Fader AN. J Clin Oncol 2018.

Trastuzumab ADCs in Endometrial Cancer

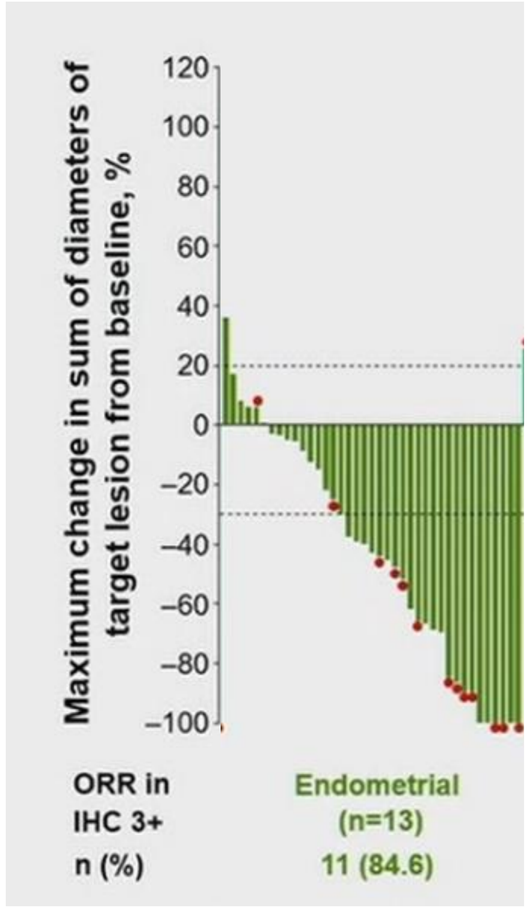
- Ado-trastuzumab emtansine (T-DM1)
  - HER2 Amplified Tumors (Basket Trial)

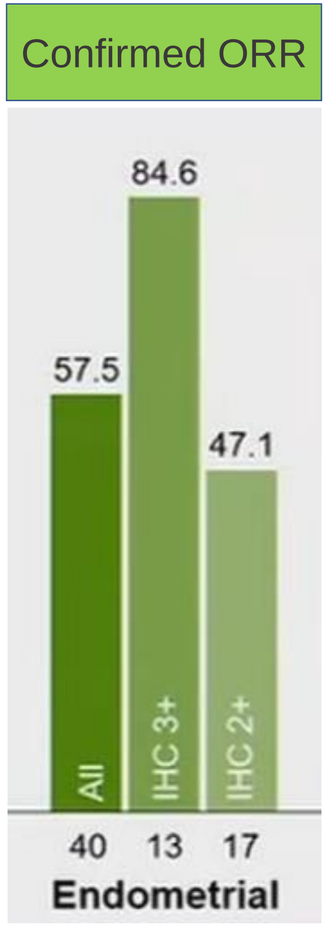


- Trastuzumab Deruxtecan (T-Dxd): STATICE
  - HER2 Expressing Uterine Carcinosarcoma



- Trastuzumab Deruxtecan (T-Dxd): DESTINY PanTumor 02
  - HER2 expression (2-3+)
  - 2L population
  - 40 patients/cohort



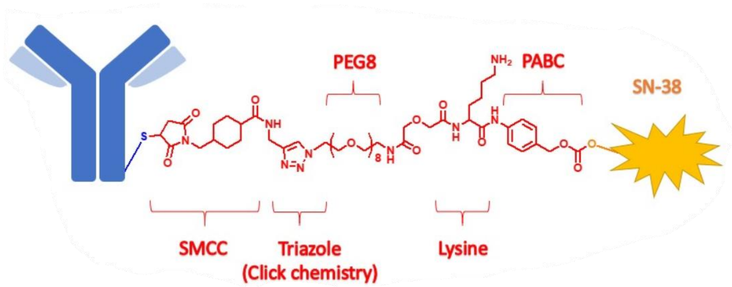


Breakthrough designation

Jhaveri Annals of Oncol 2019. Meric-Berstram. J Clin Oncol 2023; abstr 3025. Nishikawa. J Clin Oncol 2023.

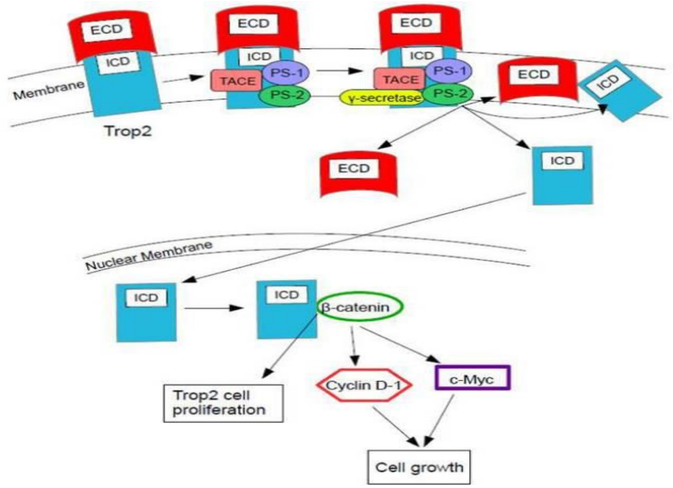
Inhibiting TROP2

TARGET: TROP2



Sacituzumab Govitecan

- TROP 2
  - Implicated in intracellular signaling pathways
  - May be a modulator of EpCAM-induced cell signaling
  - Fosters cell migration



- Overexpression in endometrial cancer is common
  - Present in 90+% of samples
    - 62% with expression in at least 50% of tumor cells

Santin. J Clin Oncol 2023 (abstract 5599). Bignotti Int J Gyencol Cancer 2011.

TROP2 Inhibition in Endometrial Cancer

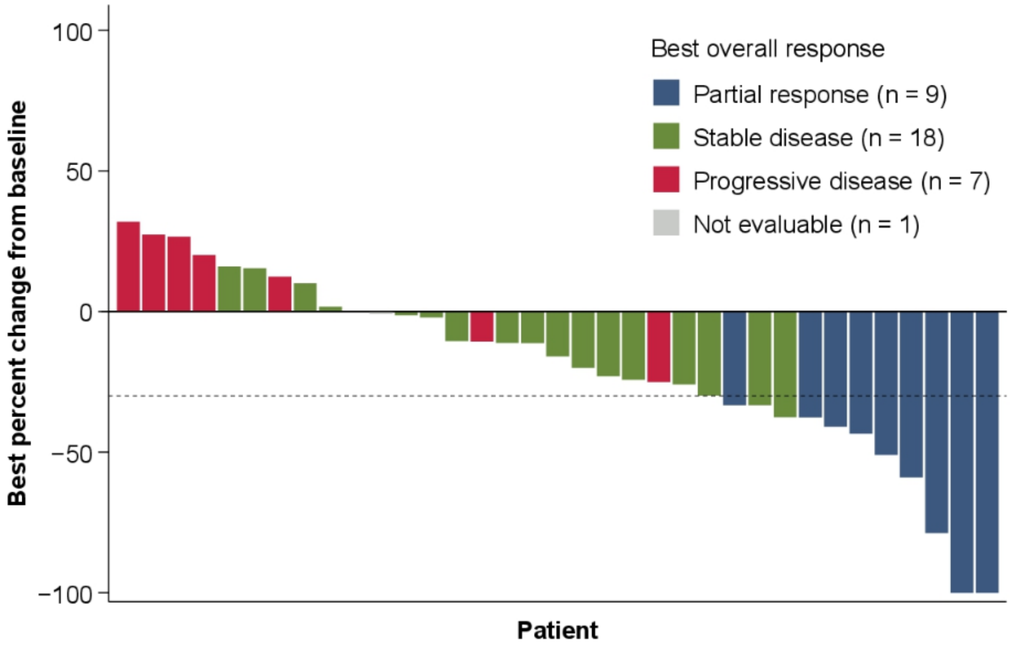
- 2+ TROP 2 IHC staining
  - Median 3 prior lines

Table 2. Overall response rate and durable disease control	**SG (n = 21) n (%)**
Best overall response	
Confirmed complete response (CR)	1 (4.8)
Confirmed partial response (PR)	6 (28.5)
Stable disease	11 (47.6)
Progressive disease	3 (14.3)
Objective response rate (confirmed CR + PR)	7 (33.3)
Durable disease control (confirmed CR + PR + SD ≥ 6 months)	7 (35.0)*

*Out of 20 patients evaluable for durable disease control

- Median PFS 5.7 months; OS 22.5 months

- TROPiCS-03: Endometrial Cancer Cohort
  - Prior anti PD(L)1 therapy in 61%
  - 20 patients



- 25% ORR; clinical benefit rate 35%
- Median PFS 5.6 months

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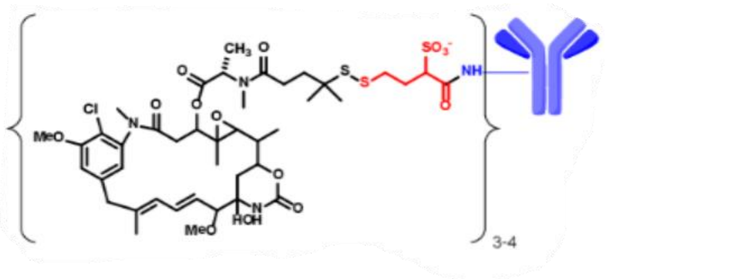
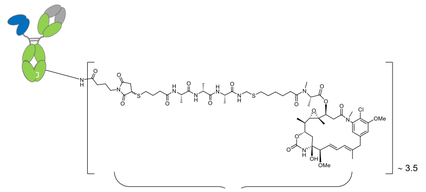
Santin. J Clin Oncol 2023 (abstract 5599). Santin J Clin Oncol 2023 (abstract 5610).

Clinical trial NCT03964727.

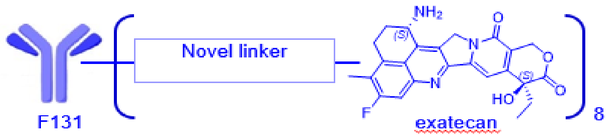
FR-α Inhibition: ADCs

TARGET: Folate Receptor α

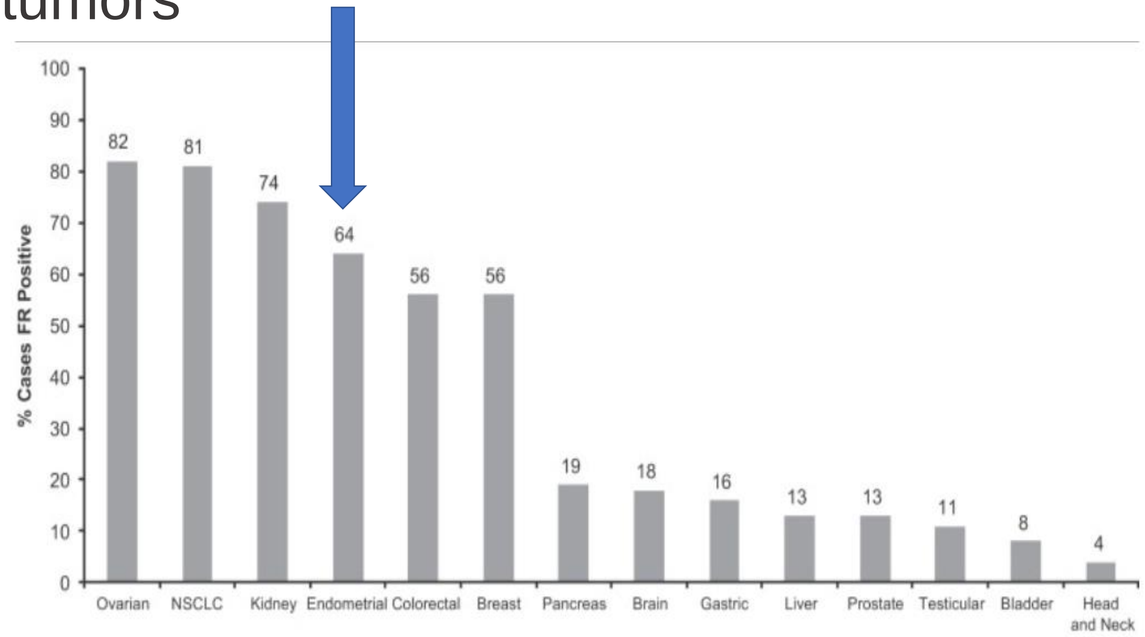




PRO1184 Structure



- FRα overexpression in ~64% of endometrial tumors



- Ongoing trials:
  - Mirvetuximab soravtansine in MSS EC (NCT03835819)
  - STRO-002 in recurrent EC (NCT03748186)

Assaraf et al. Drug Resistance Updates (2014); Moore et al. Cancer 2017

Take-Aways

- Molecular profiling is critical in EC treatment selection
- Maintenance strategies being utilized for high risk patients
- Emerging therapies with novel targets being explored

Thank you!

"It's always Sit, Stay, Heel - never Think, Innovate, Be yourself."

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