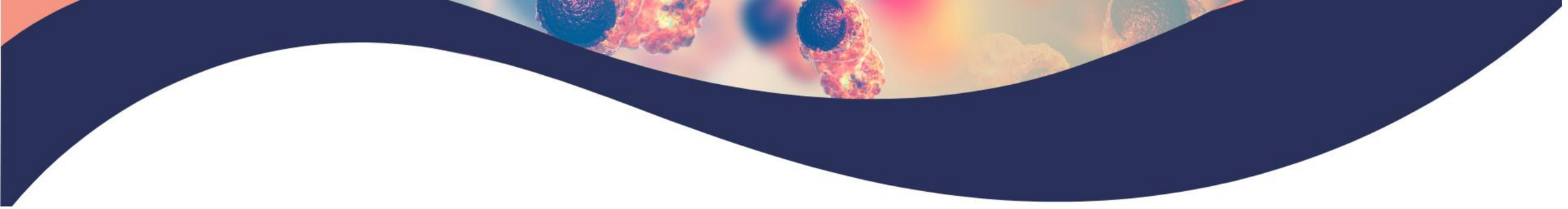


Emerging Novel Therapies and Clinical Trials, 2nd Line & Beyond

Floor Backes, MD
The Ohio State University,
Wexner Medical Center and James Cancer Hospital
Columbus, Ohio, USA

2024 SGO Winter Meeting

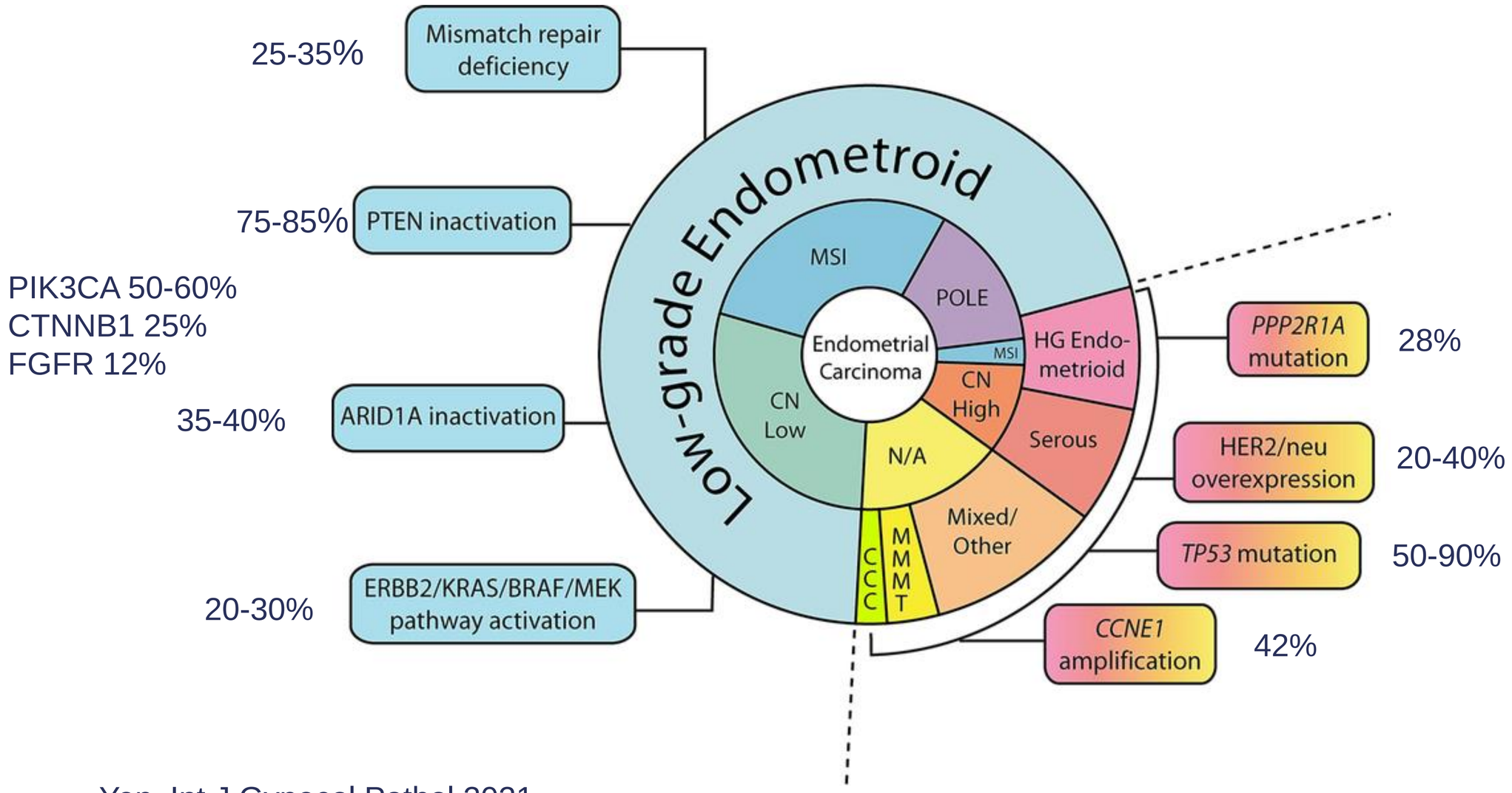
January 25, 2024

GOG FOUNDATION®
Transforming the standard of care™

NCCN Guidelines Version 1.2024
Endometrial Carcinoma

RECURRENT DISEASE[h,i]	
First-Line Therapy for Recurrent Disease[j]	**Second-Line or Subsequent Therapy**
Preferred • Carboplatin/paclitaxel (category 1 for carcinosarcoma)[k,7] • Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1)[b,c,d,8] • Carboplatin/paclitaxel/dostarlimab-gxly (category 1)[c,d,e,9] • Carboplatin/paclitaxel/trastuzumab[d,g] (for HER2-positive uterine serous carcinoma)[d,10] • Carboplatin/paclitaxel/trastuzumab[d,g] (for HER2-positive carcinosarcoma)[f,10] **Other Recommended Regimens** • Carboplatin/docetaxel[l] • Carboplatin/paclitaxel/bevacizumab[d,m,11,12] **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,13] • TMB-H tumors[n] ▸ Pembrolizumab[c,14] • MSI-H/dMMR tumors[o] ▸ Pembrolizumab[c,15] ▸ Dostarlimab-gxly[c,16]	**Other Recommended Regimens** • Cisplatin/doxorubicin[17] • Cisplatin/doxorubicin/paclitaxel[p,14] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[14] • Albumin-bound paclitaxel[q] • Topotecan • Bevacizumab[m,r,19] • Temsirolimus[20] • Cabozantinib • Docetaxel (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[21] • Cisplatin/ifosfamide (for carcinosarcoma) **Useful in Certain Circumstances (Biomarker-directed therapy)** • pMMR tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,13] • TMB-H tumors[n,12] ▸ Pembrolizumab[c] • MSI-H/dMMR tumors[o] ▸ Pembrolizumab[c,15] ▸ Dostarlimab-gxly[c,16] ▸ Avelumab[c] ▸ Nivolumab[c,22] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[23] • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib

Changing Molecular Landscape



Other factors
TROP2 (>90%)
FRα (64%)
HRD (22%)
PD-L1
B7-H4
CLDN6

Yen, Int J Gynecol Pathol 2021

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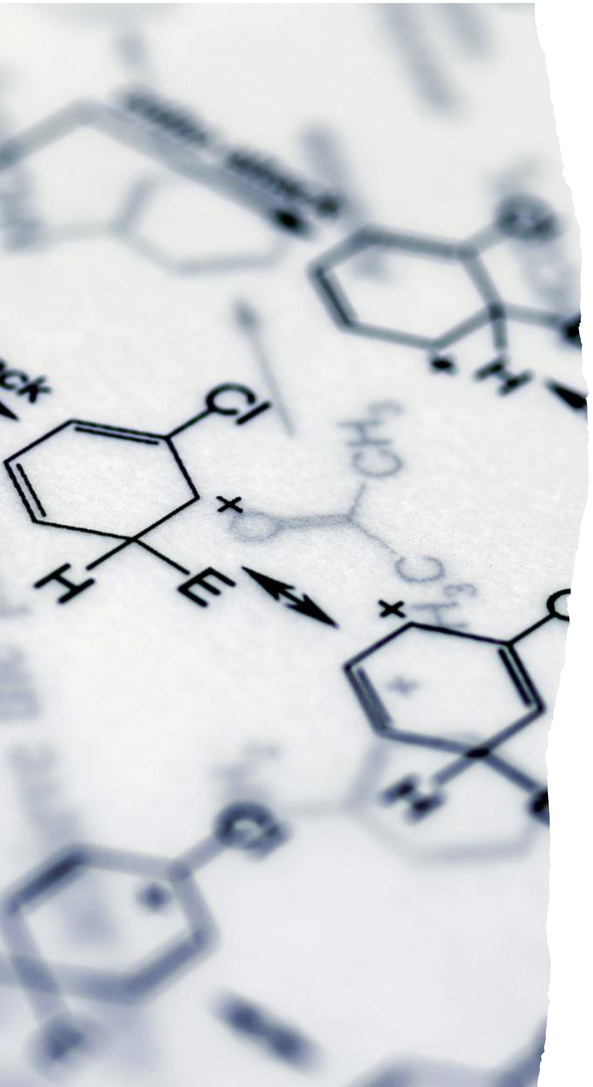
Novel Agents and combinations for Recurrent Endometrial Cancer



- Immunotherapy
  - IO combinations (FGFR, TIGIT, LAG3,TIM3)
- Antibody Drug Conjugates
  - HER2
  - TROP2
  - FRα
- Targeting cell cycle regulation and DNA repair
  - PI3K inhibitors (eg, alpelisib)
  - CHK1 inhibitor (eg, afuresertib)
  - WEE1 inhibitor (eg, adavosertib, ZN-c312)
  - PARP inhibitor
- Hormonal therapy
  - Anti-estrogen, antiprogesterone, SERM/SERD
  - Combinations: mTOR, PIK3CA inhibitor, CDK4/6 inhibitor

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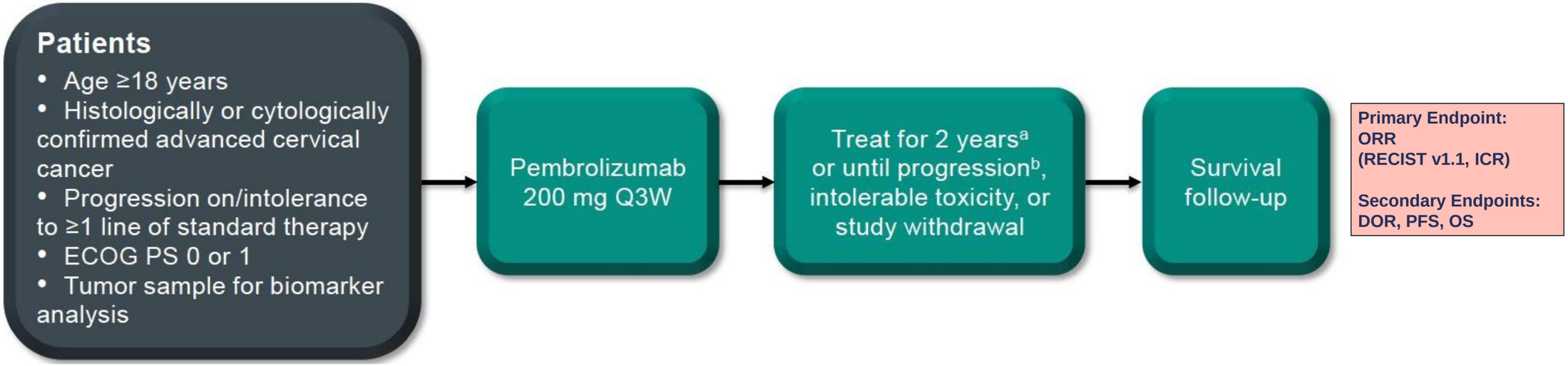
Phase 2 KEYNOTE-158 Trial: Study Design

- Ongoing, international, multicohort, open-label phase 2 study of pembrolizumab in select advanced solid tumors that have progressed on SOC therapy
- Patients with previously treated, MSI-H/dMMR advanced endometrial cancer enrolled in cohorts D and K



- Efficacy/safety assessed in all pts who received ≥1 dose pembro (all pts as treated)
  - DOR assessed in all pts who had a CR or PR

O'Malley D, et al. ESMO 2022. Abstract 546P. JCO 2022

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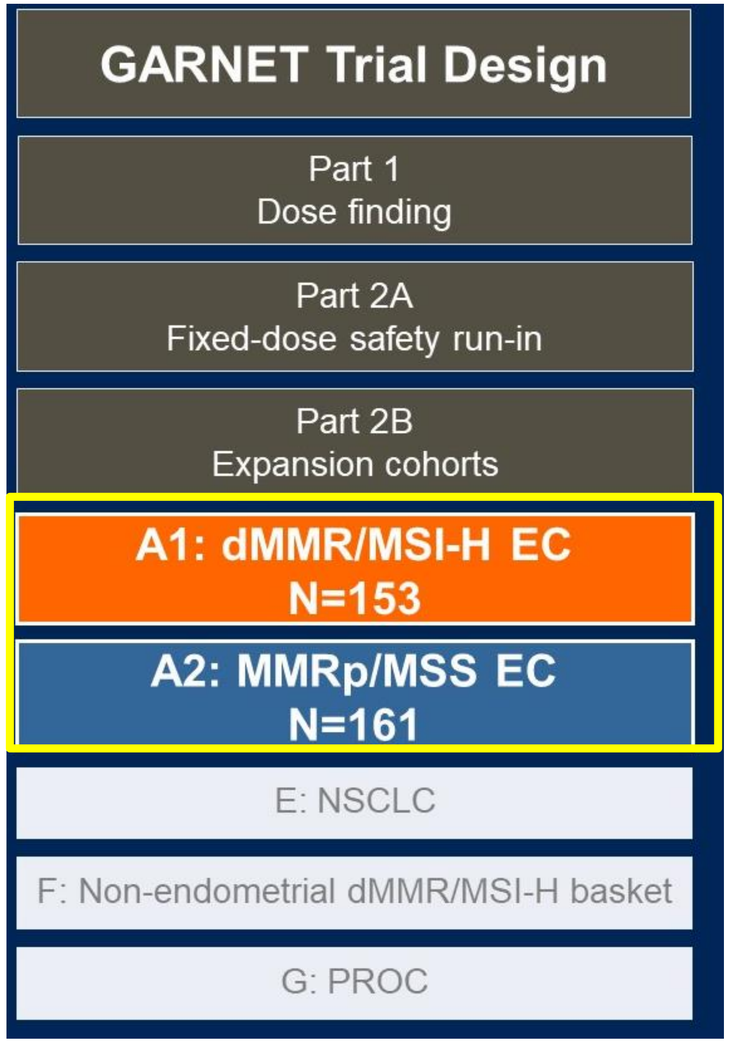
Phase 1 GARNET Study of Dostarlimab: Endometrial Cancer Cohorts



- **Dostarlimab 500 mg Q3W x 4 cycles → dostarlimab 1000 mg Q6W to PD**
- **Until disease progression**

- **Primary endpoints:** ORR and DOR per RECIST V.1.1 (BICR assessment)

- **Key inclusion criteria:**
  - Progression on or after platinum doublet therapy
  - ≤ 2 prior lines of treatment for recurrent/adv disease
  - Measurable disease at baseline
  - Anti-PD-(L)1 naïve
  - Screening via local MMR/MSI testing (IHC, PCR, or NGS) in certified local laboratory; patient cohort assignment was by MMR IHC results
  - 2 scans demonstrating PD on or after latest systemic therapy

- **Cohort A1 – Dostarlimab treatment disposition at DCO: 70.5 (n=108)**
- **Discontinued: 29.4% (n=45) on treatment**
- **Efficacy/safety assessed in all patients with measurable disease at baseline and had received ≥6 months dostarlimab (efficacy-evaluable population)**

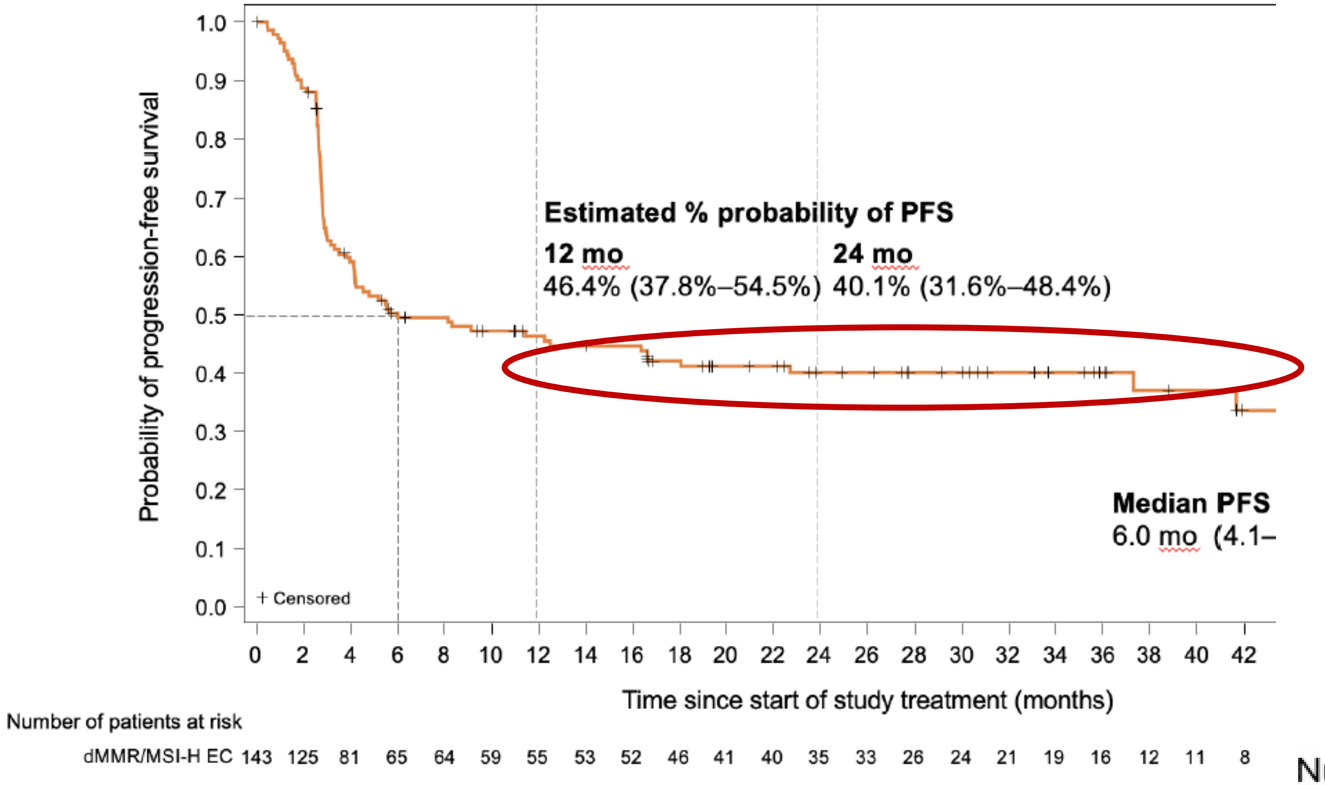
Oaknin A, et al. JAMA Oncol. 2020;6(11):1766-1772;
Oaknin A, et al. J Immunother Cancer. 2022;10:e003777; Tinker A, et al. ESMO 2022. Abstract 548P.

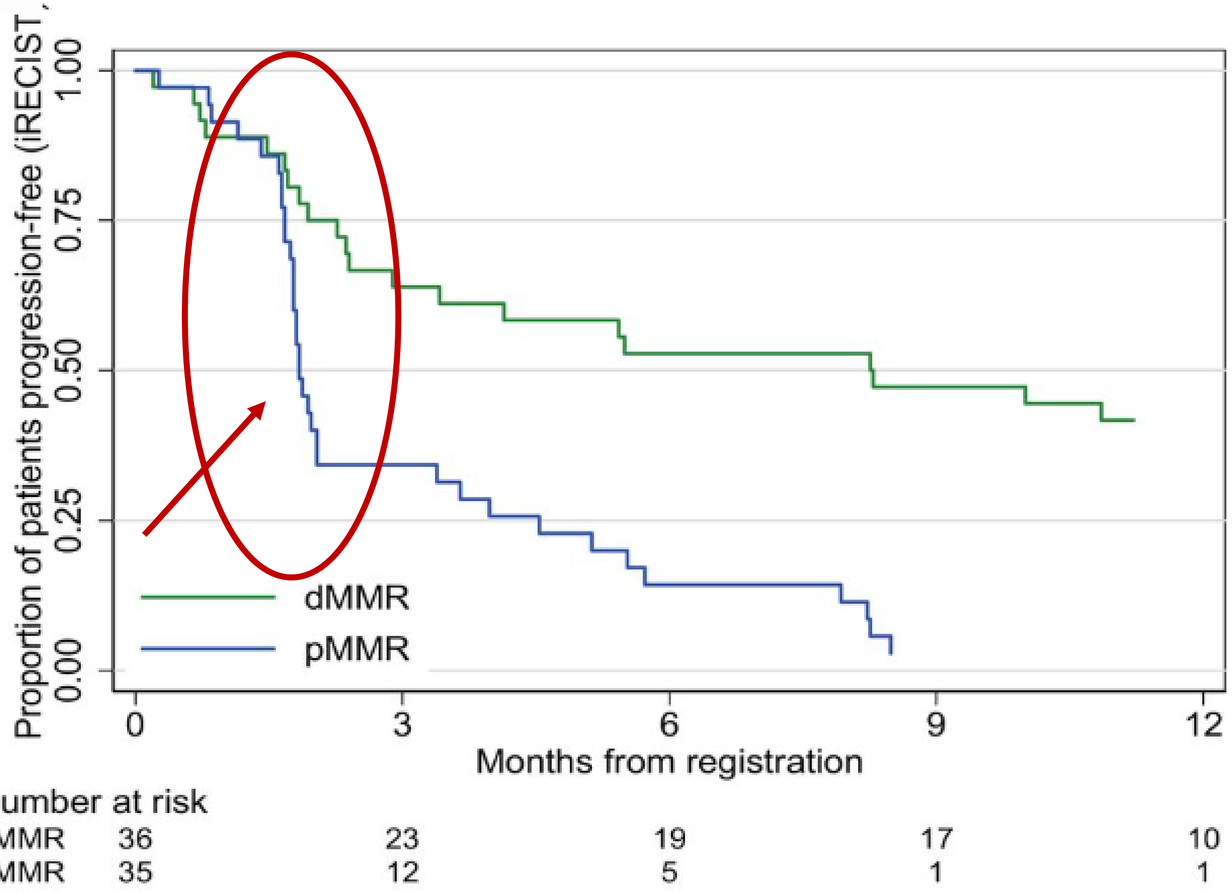
Single Agent Immunotherapy

	Keynote-158[1]	GARNET MSI-H/dMMR	PHAEDRA	GARNET MSS/pMMR	KEYNOTE-028[2]	NCT01375842[2]
Phase / type	2	2	2	2	1b	1a
Population	Previously treated MSI-H	Previously treated MSI-H	dMMR	Previously treated MSS	Previously treated PD-L1+ MSS/pMMR	Recurrent EC MSS/pMMR
Patients, n	90	108	35	156	24	15
Treatment	Pembrolizumab	Dostarlimab	Durvalumab	Dostarlimab	Pembrolizumab	Atezolizumab
Prior lines	0 - >5	1-3		1-3		
ORR, %	48%*	43.5%	47%	14.1%	13%	13
DCR, %	66%	56%		35%	26%	27%
DOR	NR (3-50+)	NR		NR	—	—
mPFS	13.1 mo	Immature	8.3		1.8 mo	1.7 mo
mOS	@12-mo : 69%	NR	@12-month: 71%		NR	9.6 mo
Safety summary (TRAE grade ≥3)	12%	13%	3%	19%	16.7%	Any TRAE: 47%

Antill, J for ImmunoTher of Cancer 2021, Oaknin A, et al. J Immunother Cancer. 2022, O'Malley, JCO 2022

We need better!





GARNETT. Oaknin A at al. ASCO 2022

PHAEDRA Trial. Antill, J for ImmunoTher of Cancer 2021

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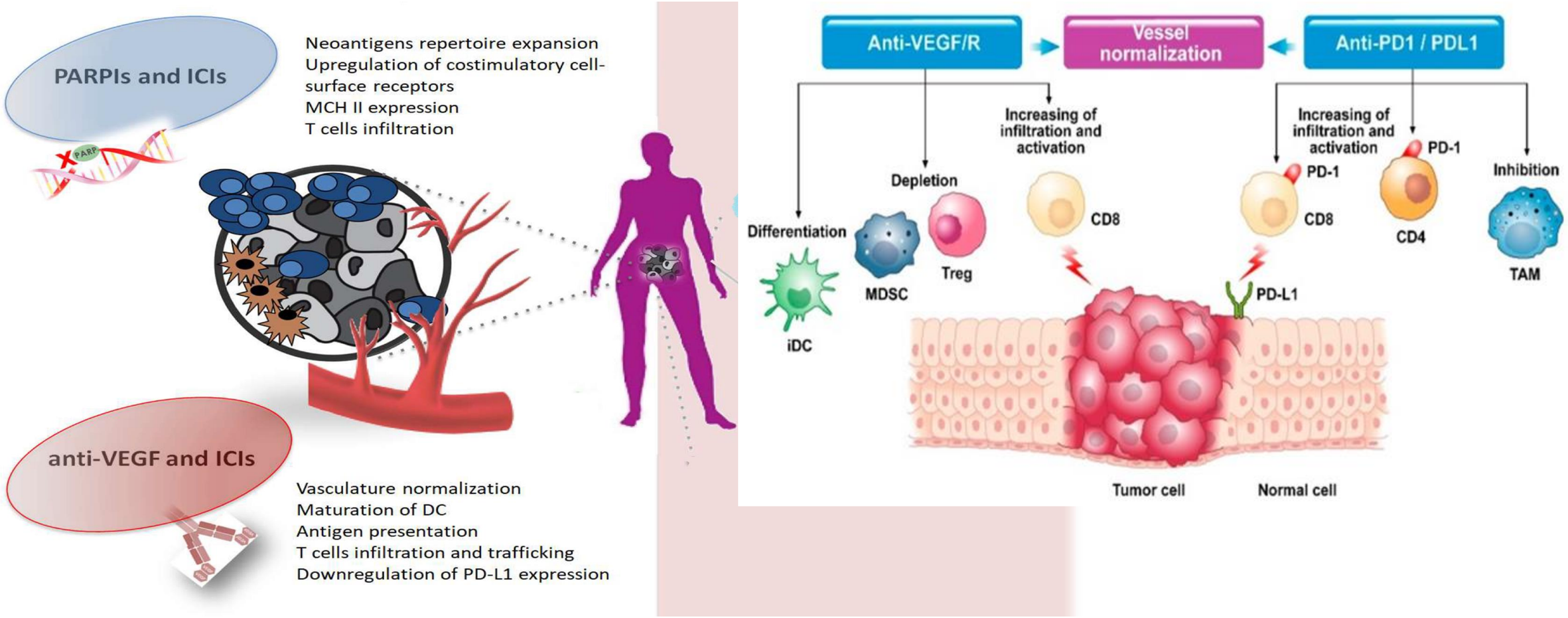
Options for Combinations



Ciciola P, et al. J Clin Med. 2020

Study 309/KEYNOTE 775 Design

VEGFR1-3, FGRF1-4, PDGFR, RET, KIT

Key eligibility criteria
- Advanced, metastatic, or recurrent endometrial cancer
- Measurable disease by BICR
- 1 Prior platinum-based CT[a]
- ECOG PS 0–1
- Tissue available for MMR testing

Stratification factors

MMR status (pMMR vs dMMR) and further stratification within pMMR by:
- Region (R1: Europe, USA, Canada, Australia, New Zealand, and Israel, vs R2: rest of the world
- ECOG PS (0 vs 1)
- Prior history of pelvic radiation (yes vs no)

R (1:1)

Lenvatinib 20 mg PO QD + Pembrolizumab[b] 200 mg IV Q3W

Treat until progression or unacceptable toxicity

Doxorubicin 60 mg/m² IV Q3W[c] or Paclitaxel 80 mg/m² IV QW (3 weeks on/1 week off)

Primary endpoints
- PFS by BICR
- Overall survival

Secondary endpoints
- Objective response rate
- HRQoL
- Pharmacokinetics
- Safety

Key exploratory endpoint
- Duration of response

aPatients may have received up to 2 prior platinum-based CT regimens if 1 is given in the neoadjuvant or adjuvant treatment setting.
bMaximum of 35 doses. cMaximum cumulative dose of 500 mg/m2.

Makker et al, NEJM 2022

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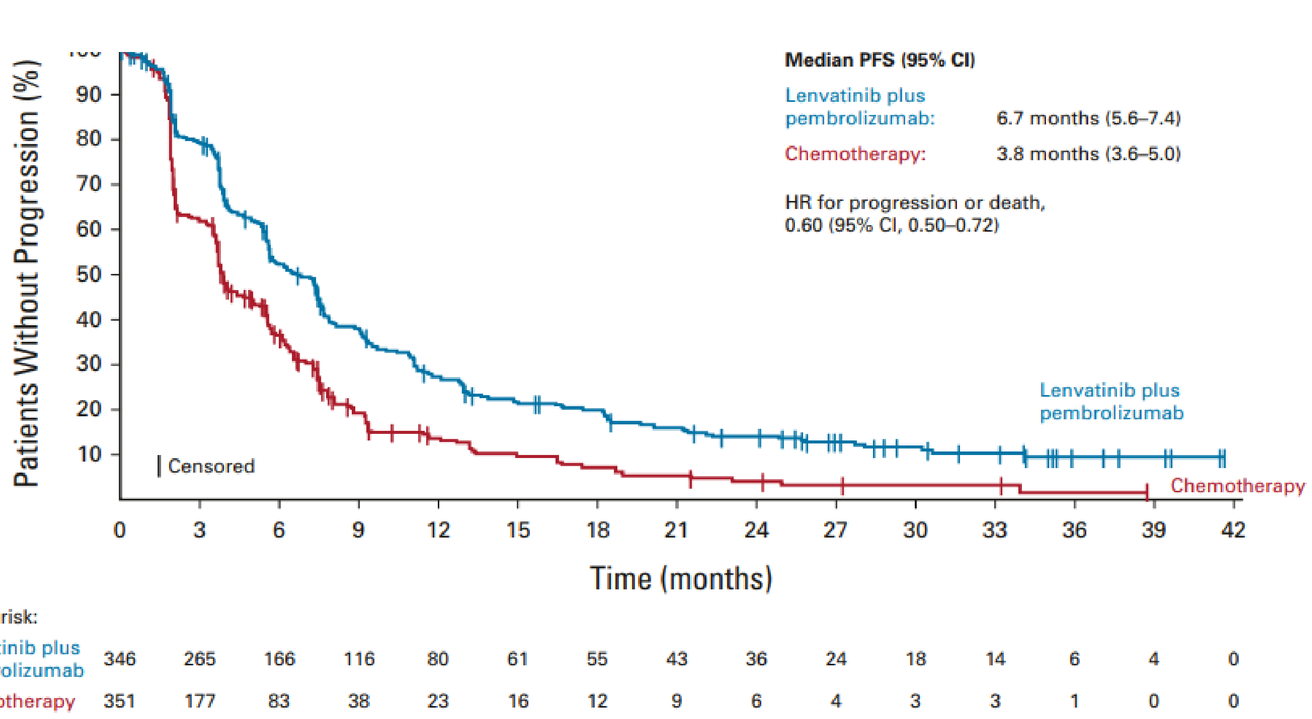
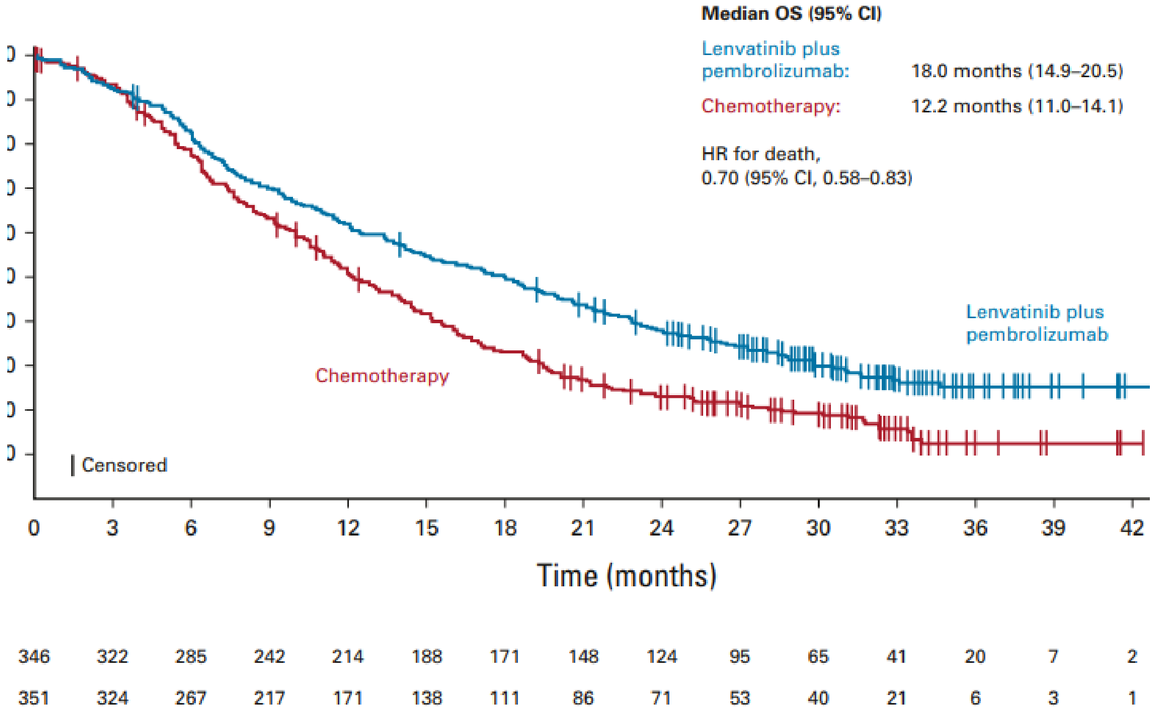
Study 309 / Keynote-775

FDA approved for pMMR (July 2021)
EMA approved for pMMR/dMMR (Nov 2021)





No. at risk:

Lenvatinib plus pembrolizumab	346	265	166	116	80	61	55	43	36	24	18	14	6	4	0
Chemotherapy	351	177	83	38	23	16	12	9	6	4	3	3	1	0	0

Lenvatinib plus pembrolizumab	346	322	285	242	214	188	171	148	124	95	65	41	20	7	2
Chemotherapy	351	324	267	217	171	138	111	86	71	53	40	21	6	3	1

ORR: 30.3% vs 15.1% in pMMR; 40% vs 12% in dMMR
DOR: 9.2 vs 5.7 months in pMMR; NR (2.1-20.4) vs 4.1 in dMMR

Makker et al, NEJM 2022, Makker JCO 2023

Study 309/Keynote 775 Safety/Adverse Events

Table 3. Adverse Events of Any Cause with an Incidence of 25% or More among All the Patients in Either Treatment Group, According to Preferred Term.

Event	Lenvatinib plus Pembrolizumab (N=406)		Chemotherapy (N=388)	
	Any Grade	Grade ≥3*	Any Grade	Grade ≥3*
Any adverse event	405 (99.8)	361 (88.9)	386 (99.5)	282 (72.7)
Hypertension†	260 (64.0)	154 (37.9)	20 (5.2)	9 (2.3)
Hypothyroidism†‡	233 (57.4)	5 (1.2)	3 (0.8)	0
Diarrhea	220 (54.2)	31 (7.6)	78 (20.1)	8 (2.1)
Nausea	201 (49.5)	14 (3.4)	179 (46.1)	5 (1.3)
Decreased appetite	182 (44.8)	32 (7.9)	82 (21.1)	2 (0.5)
Vomiting	149 (36.7)	11 (2.7)	81 (20.9)	9 (2.3)
Weight decrease	138 (34.0)	42 (10.3)	22 (5.7)	1 (0.3)
Fatigue	134 (33.0)	21 (5.2)	107 (27.6)	12 (3.1)
Arthralgia	124 (30.5)	7 (1.7)	31 (8.0)	0
Proteinuria†	117 (28.8)	22 (5.4)	11 (2.8)	1 (0.3)
Anemia	106 (26.1)	25 (6.2)	189 (48.7)	57 (14.7)
Constipation	105 (25.9)	3 (0.7)	96 (24.7)	2 (0.5)
Urinary tract infection	104 (25.6)	16 (3.9)	39 (10.1)	4 (1.0)
Neutropenia	30 (7.4)	7 (1.7)	131 (33.8)	100 (25.8)
Alopecia	22 (5.4)	0	120 (30.9)	2 (0.5)

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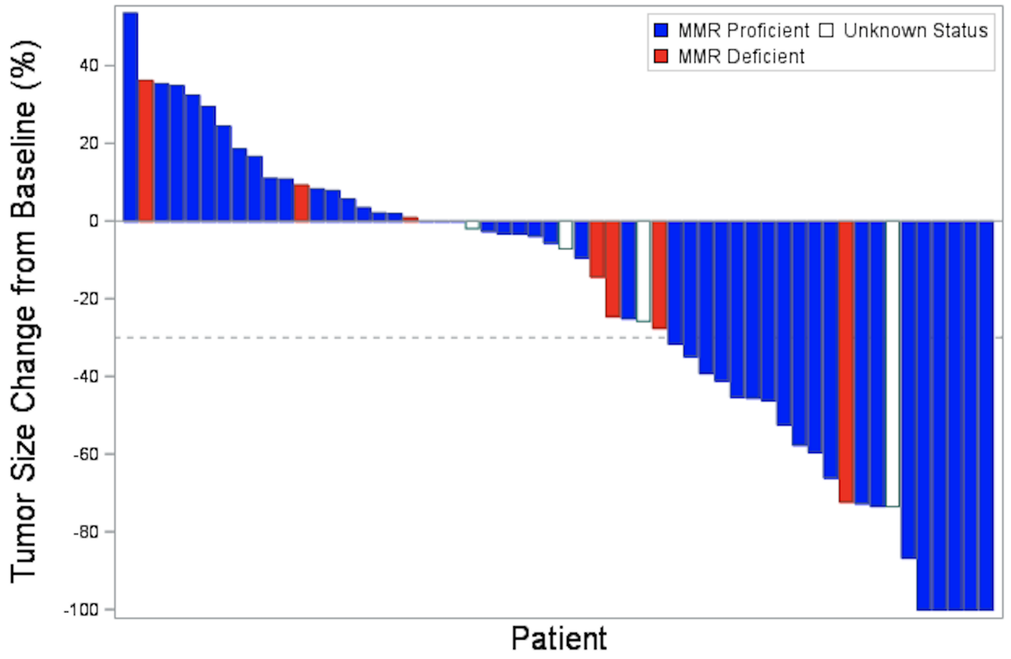
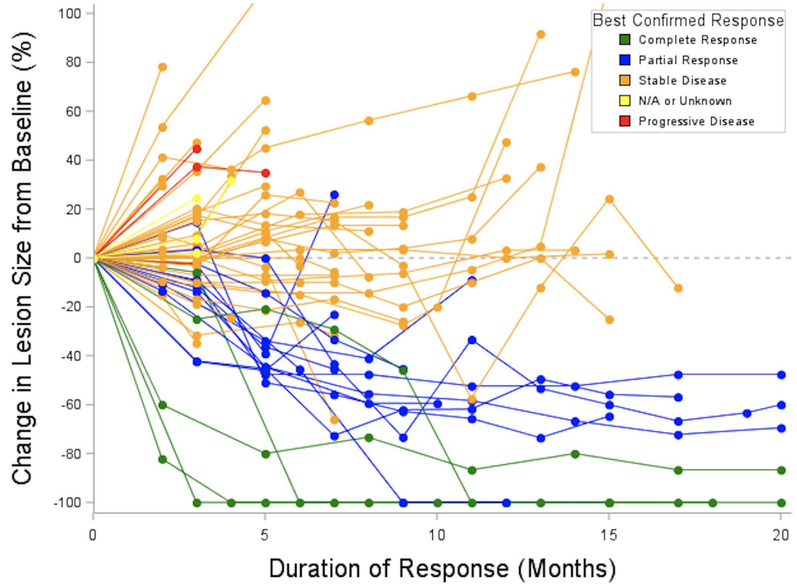
Atezolizumab and Bevacizumab in Recurrent Endometrial Cancer

Total Number of Subjects	n=57
Clinical Activity	
ORR for all	30% (95% CI 18-43)
ORR for MMRp	33% (95% CI 20-48)
Median DOR (months)	15 (95% CI 2.9-34)
Median PFS (months)	7.87 (95% CI 5.5-11.7)





No grade 4 AEs occurred.
Dose interruptions, reductions, and discontinuations due to AEs occurred in :
79%, 4%, and 16% of patients

Fuh, IGCS 2022

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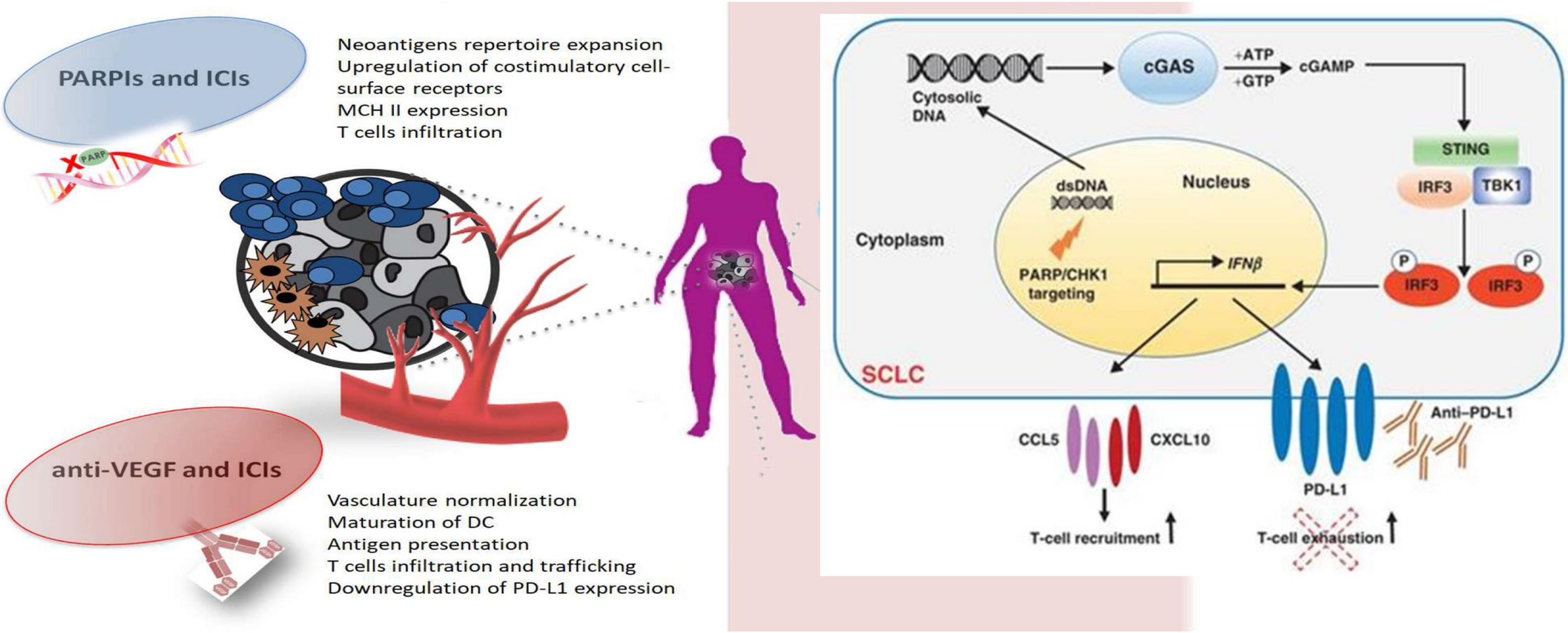
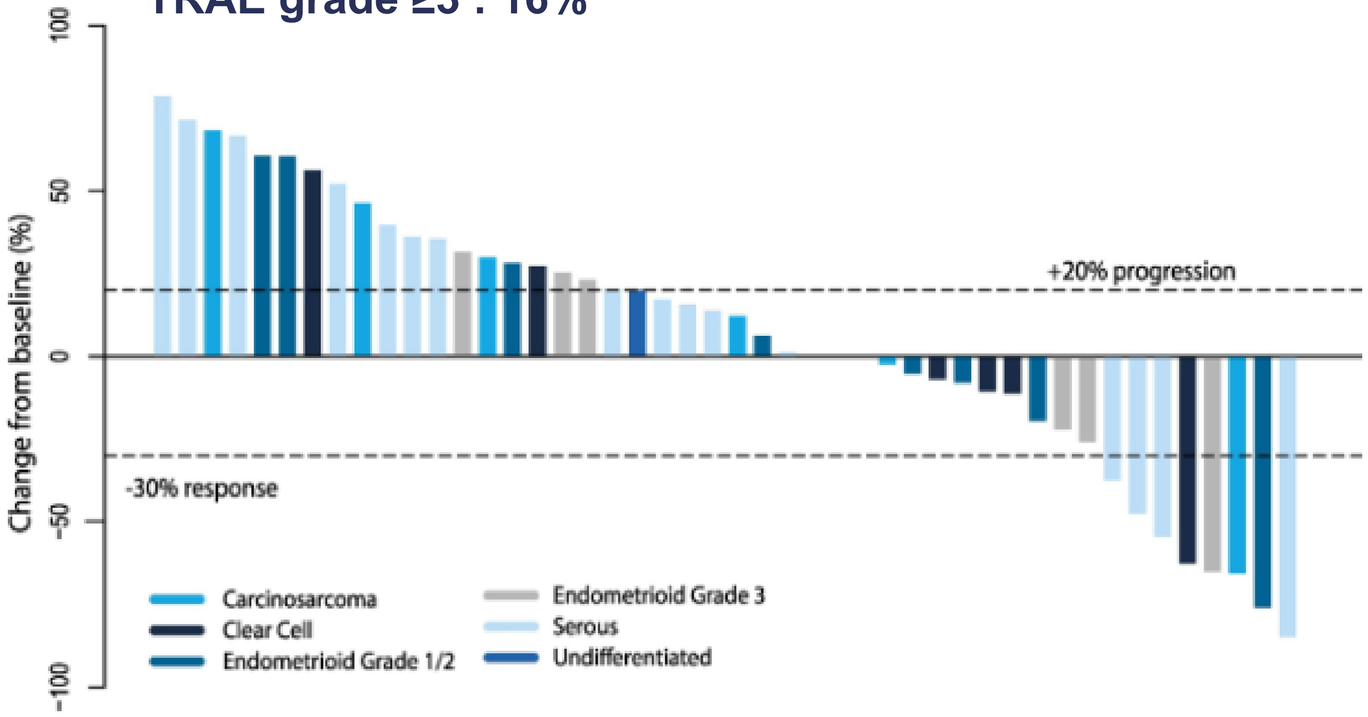
Options for Combinations

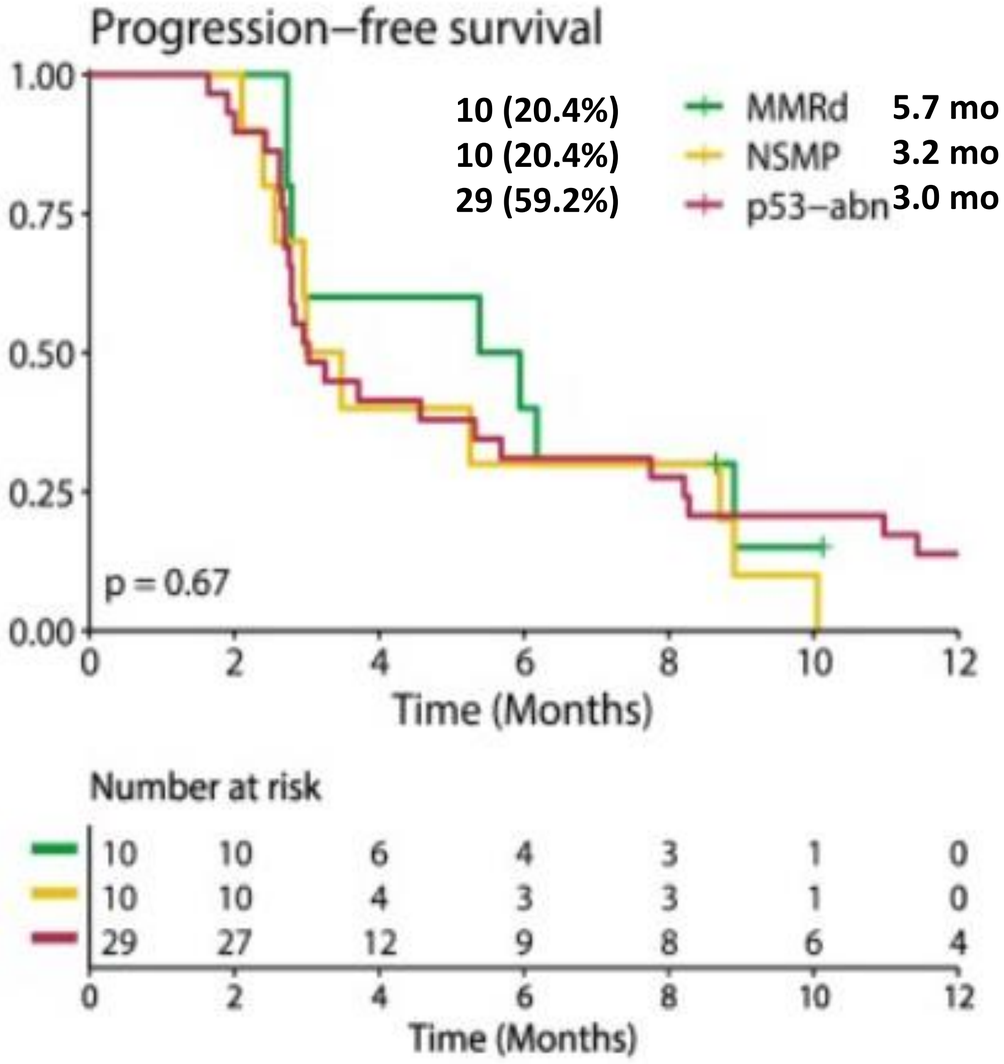


DOMEC trial

Phase II; N=50
Durvalumab 1500 mg IV q4w + olaparib 300 mg BID
Primary endpoint PFS 6 months

6-month PFS: 34%; Median PFS 3.4 months; ORR 16%
TRAE grade ≥3 : 16%

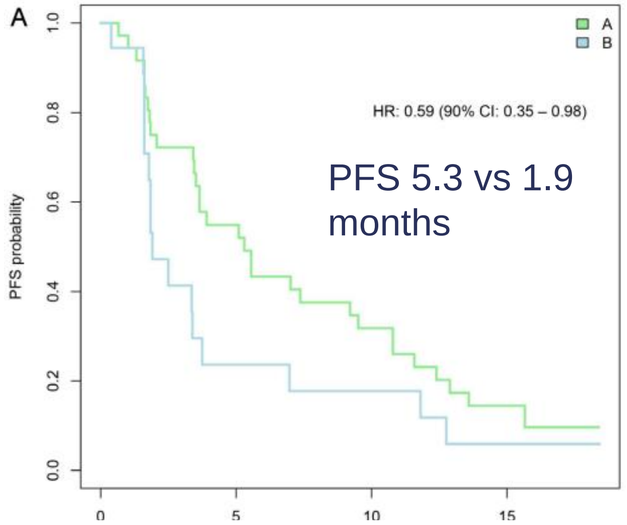


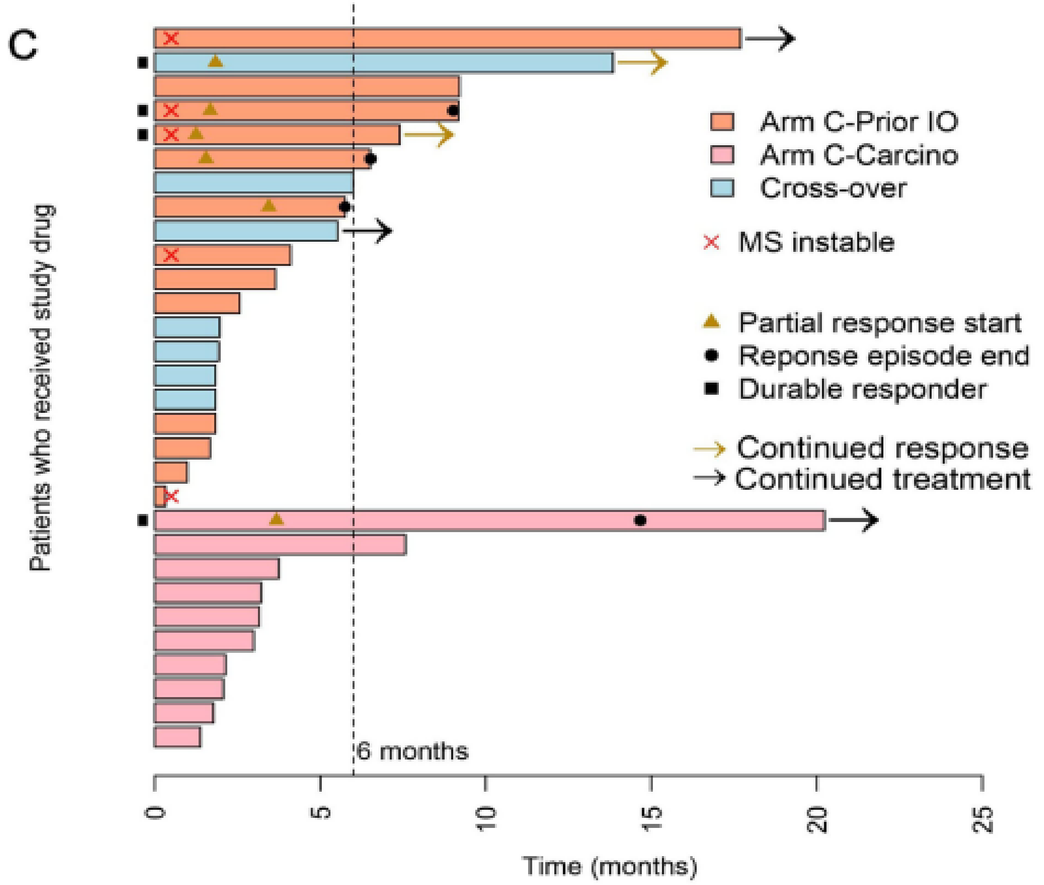


Post, Gynecol Oncol 2022

IO after IO

- Arm A: Nivolumab 240 mg IV D1+15 with cabozantinib 40 mg daily (TKI - MET, VEGFR2, RET, AXL) q 28 days
- Arm B: Nivolumab
- Cross-over allowed.
- 94 vs 100% MSS tumors
- ORR 25 vs 11%
- Post-IO: N=20
  - MSI-H: 22% .
  - 61% ≥3 prior lines
  - ORR 25%





Llheureux, S, et al. J Immunother Cancer 2022

Lenvatinib/pembrolizumab after IO

- Renal cell cancer
  - 104 patients with prior IO: ORR 62.5%
- Melanoma
  - LEAP-004: PD on or <12 weeks from last CPI
  - ORR 21.4%, OS 14 months
- Endometrial cancer
  - Rose: 8 dMMR patients: Lenvatinib/pembrolizumab : ORR 75%
  - Morton: 11 endometrial patients (8 dMMR, 3 pMMR): ORR 54.5%
    - Variety of single agent and combination therapy

Lee, Lancet Oncol 2021. Arance, JCO 2021. Rose, Gynecol Oncol Rep 2023. Morton Obstet Gynecol 2023.

Recurrent dMMR: DUAL Immunotherapy NRG-GY025

Recurrent MMR deficient Endometrial Carcinoma with Measurable or Non-measurable (detectable) Disease

STRATIFICATION

- **Prior Radiation**
- **Prior anti-PD1/PD-L1 therapy**
- **Measurable disease (yes/no)**

RANDOMIZATION*
R 2:1

Activation Date: 2/7/22
Accrual: 16/90

Arm 1

Nivolumab Q3W and

Low-Dose Ipilimumab Q6W (every other cycle x 4) and then nivolumab alone Q4W until disease progression, unacceptable toxicities or CR*

See Section 5.1

*patients with CR will receive maintenance therapy for up to 12 additional months after radiologic evidence of complete response.

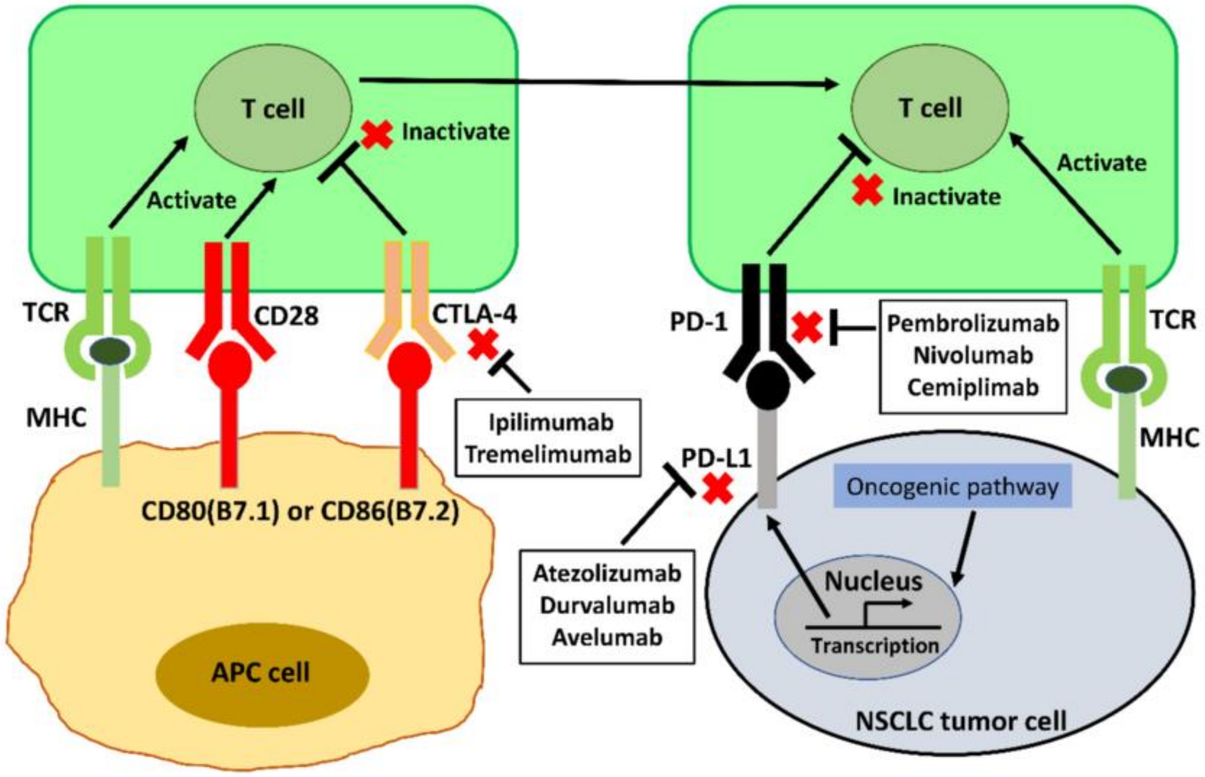
Arm 2

Nivolumab Q3W x 8 cycles then Q4W until disease progression, unacceptable toxicities or CR*

See Section 5.1

*patients with CR will receive maintenance therapy for up to 12 additional months after radiologic evidence of complete response.

*Randomization is 2:1 (Arm 1 vs Arm 2). Twice as many patients will be randomized to Arm 1.



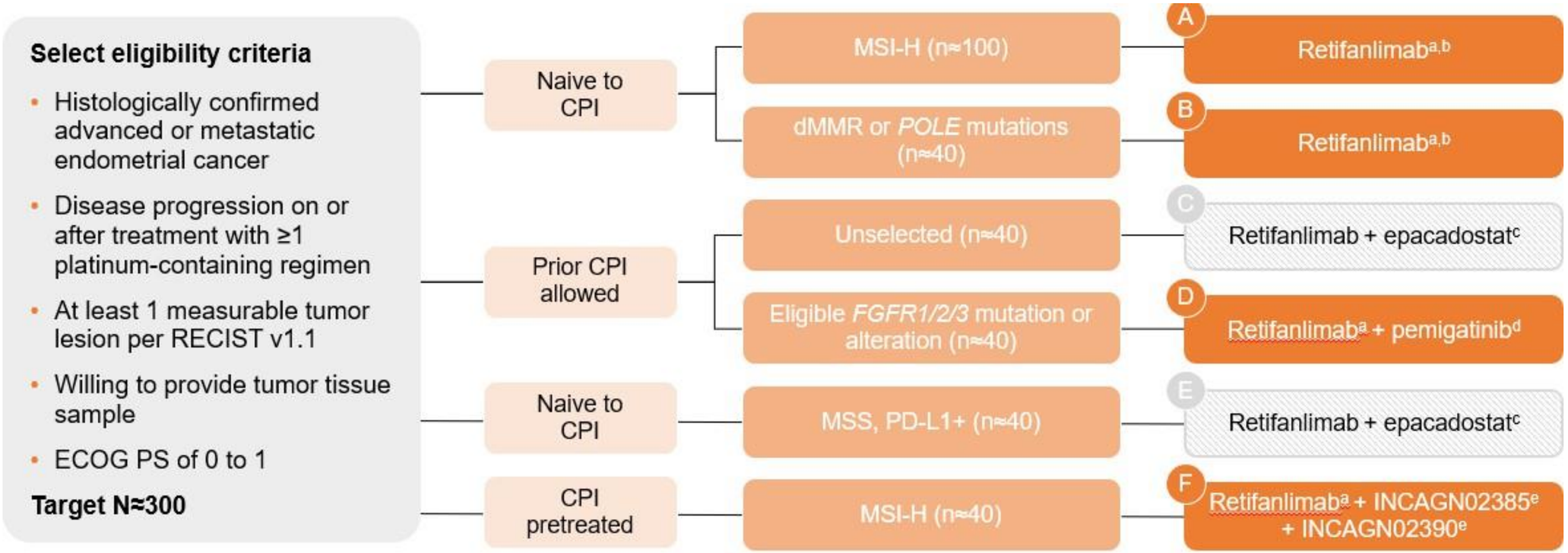
Li-Chung, Vaccines 2021

NCT05112601. Updated April 28, 2022. Accessed May 10, 2022. https://clinicaltrials.gov/ct2/show/NCT05112601

Study Chairs: Haider Mahdi, MD, MPH; K. Moore, MD; Matthew Powell, MD; Stephanie Gaillard, MD, PhD.

GOG-3038/POD1UM-204

An Umbrella Study of INCMGA00012 Alone and in Combination With Other Therapies in Participants With Advanced or Metastatic Endometrial Cancer Who Have Progressed on or After Platinum-Based Chemotherapy (PI: Brian Slomovitz, MD)

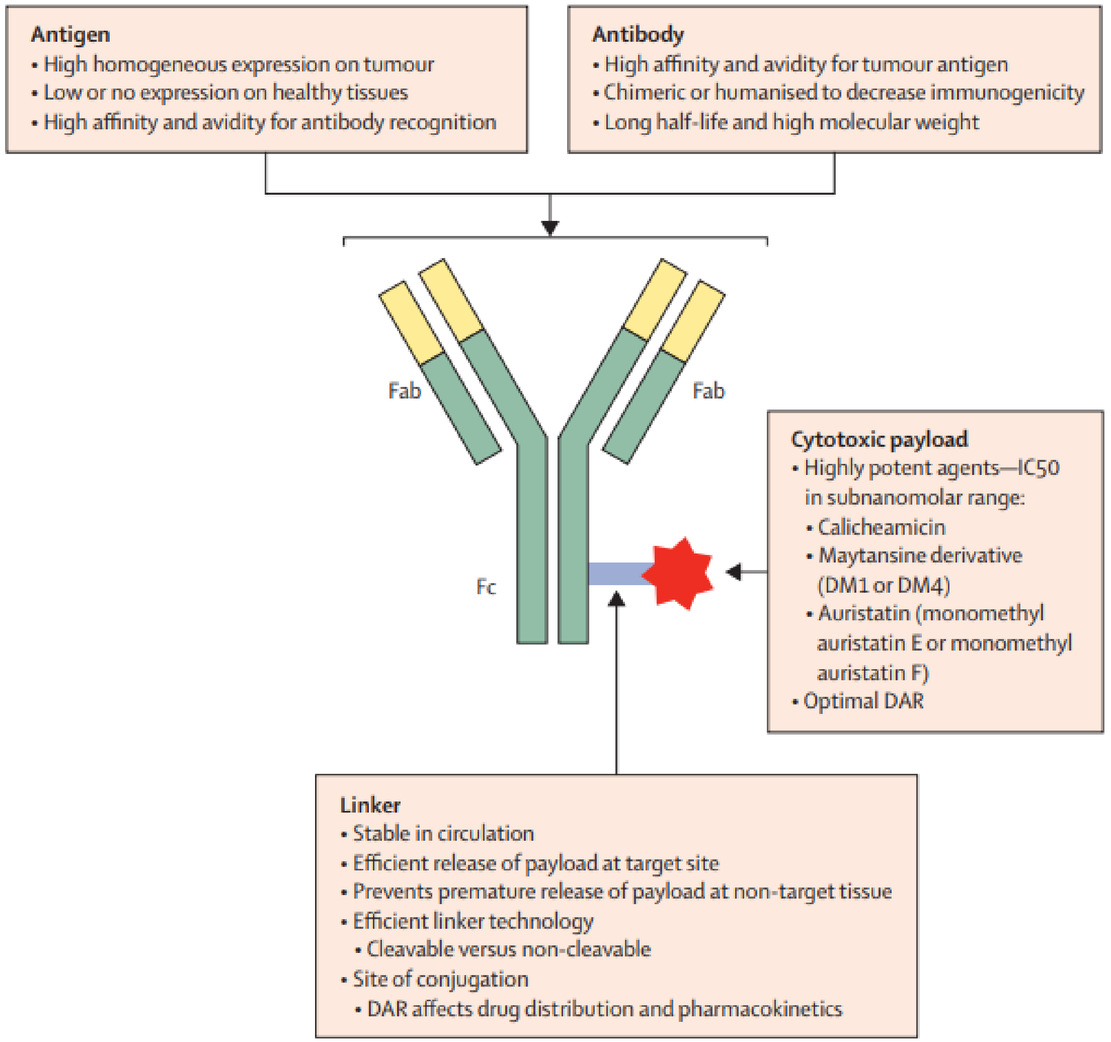


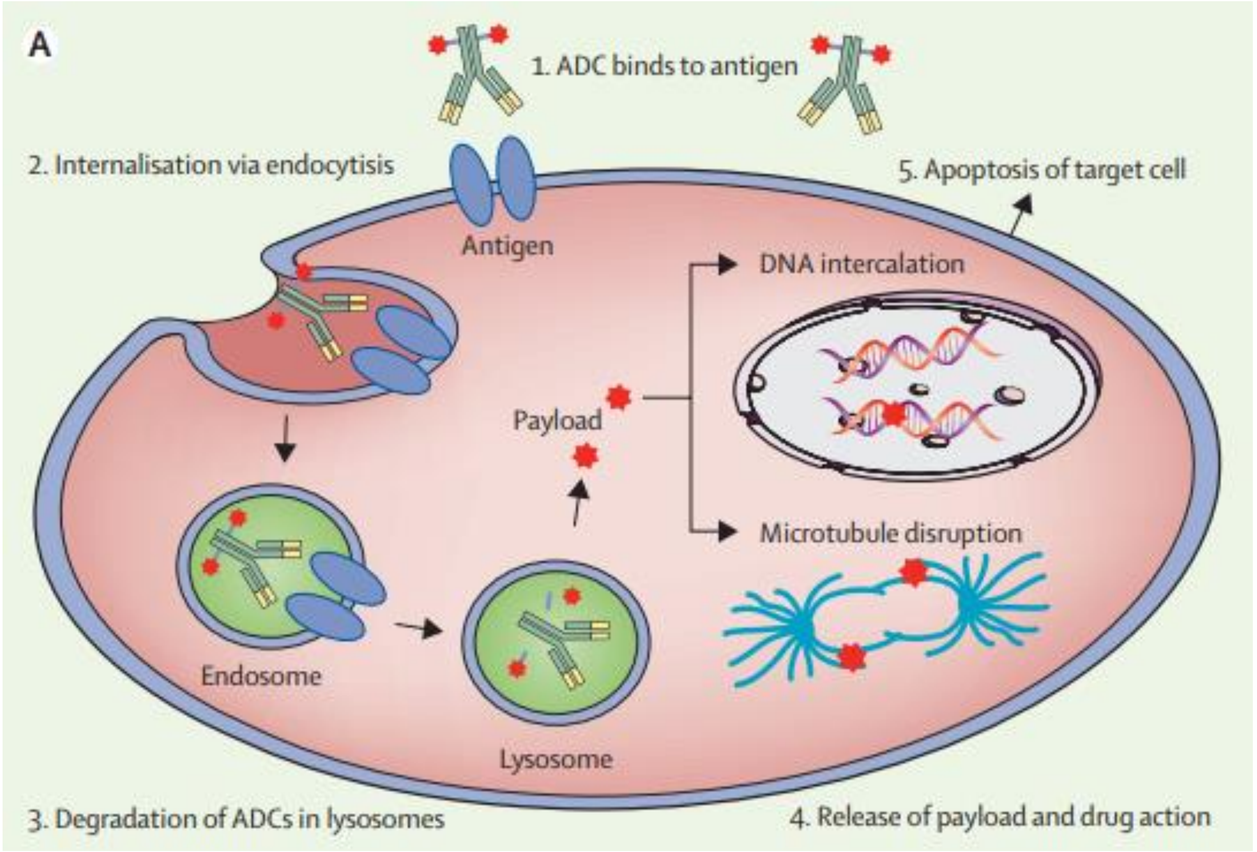
Primary endpoint: ORR, per RECIST v1.1 and determined by ICR (group A)[1,2]
Secondary objectives: DoR, DCR, PFS, OS (groups A-B); ORR (groups B-F); safety (all groups)[1,2]

a Patients eligible to receive retifanlimab monotherapy will first be considered for group A until fully enrolled, unless they do not meet MSI-H criteria. Retifanlimab administered iv on day 1 of each 28-day cycle for up to 26 cycles, if patients continue to derive benefit and do not meet any study treatment discontinuation criteria. b Patients in group A or group B who experience disease progression on retifanlimab monotherapy may be eligible for further treatment with one of the combination regimens in groups D or F. c Closed enrollment groups. d Pemigatinib (FGFR1/2/3 inhibitor) administered orally qd. e INCAGN02385 and INCAGN02390 administered iv q2w.
dMMR, deficient mismatch repair; ICR; independent central review; MSI-H, microsatellite instability-high; MSS, microsatellite stable; POLE, DNA polymerase epsilon.
1. Slomovitz BM, et al. IGCS 2022. Poster 1455. 2. ClinicalTrials.gov. Accessed May 2023. https://clinicaltrials.gov/ct2/show/NCT04463771

NCT04463771

Antibody Drug Conjugates in Endometrial Cancer





Chau C, Lancet 2019

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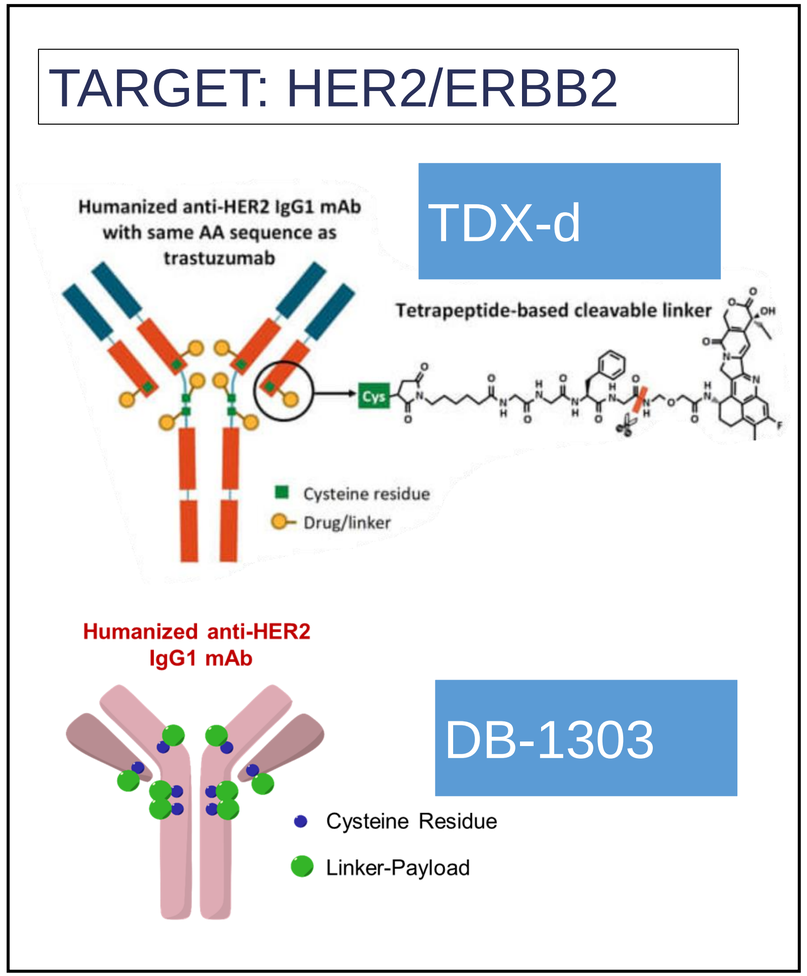
Targeting HER2



- Prevalence in uterine cancer ~25%
  - 75% of uterine serous carcinoma have TP53 alteration
  - No standard testing (NGS, IHC, FISH)

Drug Name	Payload
Trastuzumab deruxtecan (DS-8201a or T-DXd)	Topoisomerase I inhibitor
BNT323/DB-1303	Topoisomerase I inhibitor
Ado-trastuzumab emtansine (T-DM1)	Microtubule inhibitor derived from maytansine

IHC = immunohistochemisty.

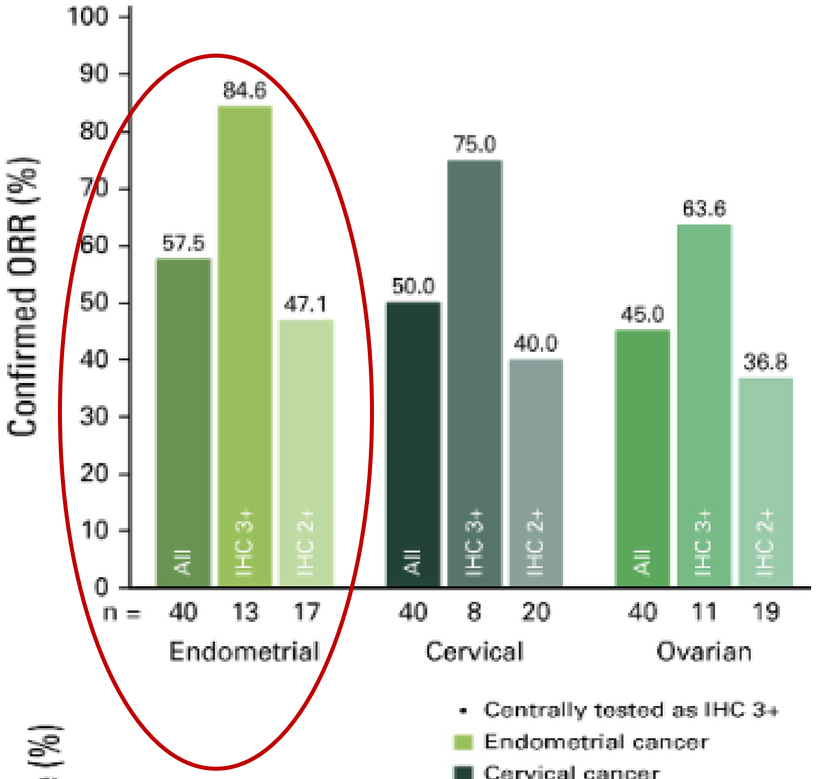
Erickson BK, et al. *Gynecol Oncol*. 2020;159(1):17-22. Erickson BK, et al. *Curr* Opin Obstet Gynecol. 2020;32(1):57-64.
Lin et al. Gynecol Oncol 2022.

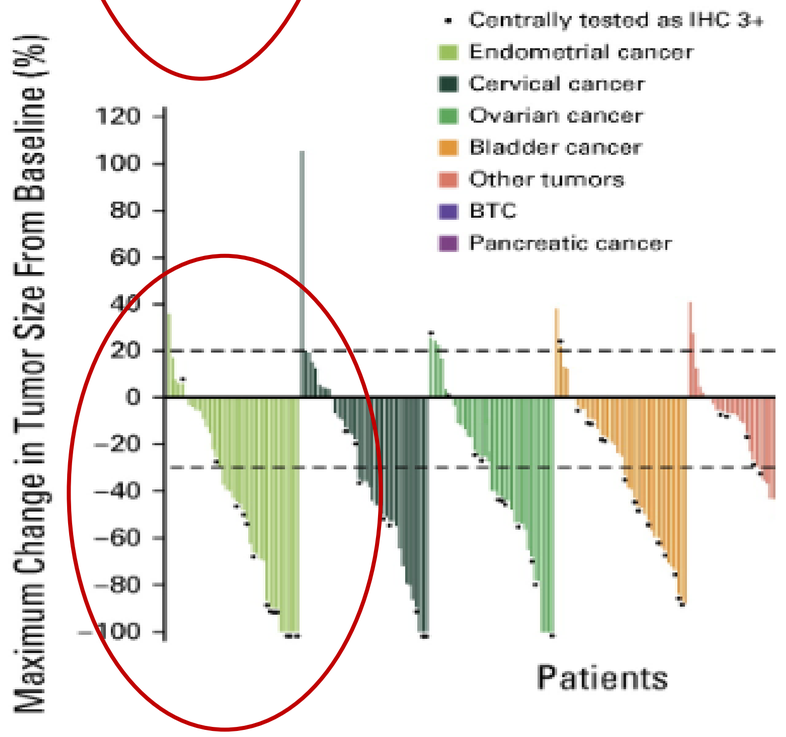
Trastuzumab Deruxtecan (TDxd) DESTINY-PanTumor02 Phase II Trial

- N=40 endometrial cancer
- 22% prior Anti-HER2
- 1/3 ≥ 3 prior lines (median 2)
- 10% Black, 25% Asian
- IHC: 3+ 33%, 2+ 43%, 1+ 10%, 0/uk 15%
- ORR 57.5%, DCR 94%

- The most frequent TEAEs of any grade were nausea, vomiting, diarrhea, fatigue.
- Grade 3 or greater was rare (neutropenia, anemia). ILD/pneumonitis 10.5% (0.4% grade 3, 1.1% grade 5)
- Alopecia 22%

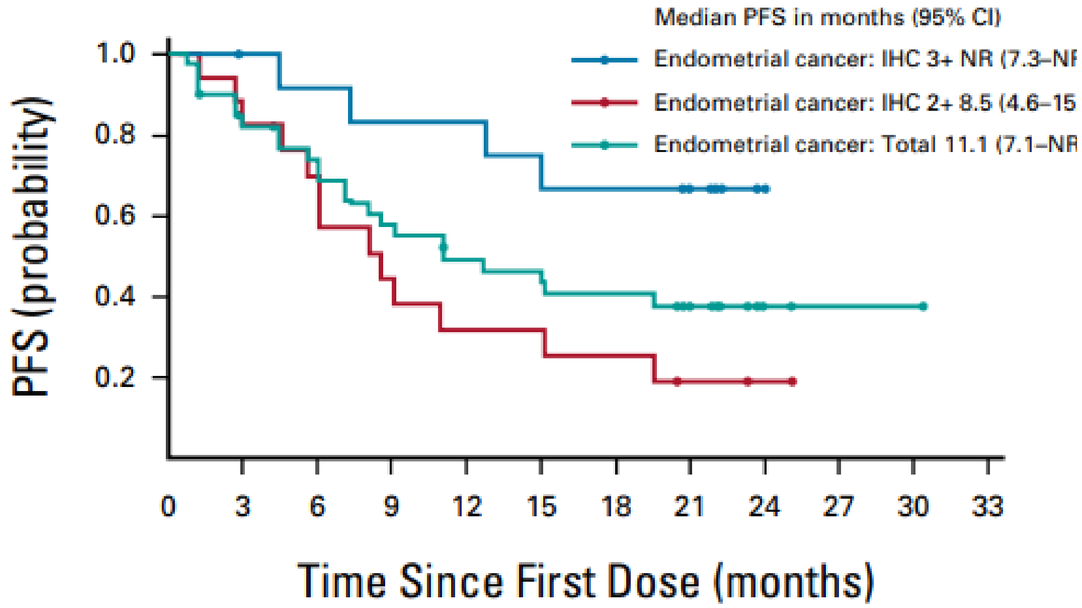
Meric-Bernstam, F. JCO 2023





Trastuzumab Deruxtecan (TDxd): DESTINY-PanTumor02 Phase II Trial

A



No. at risk:

Endometrial cancer: IHC 3+	13	12	11	10	10	9	8	5	0			
Endometrial cancer: IHC 2+	17	14	11	7	5	5	4	2	1	0		
Endometrial cancer: Total	40	31	27	21	17	16	14	8	2	1	1	0

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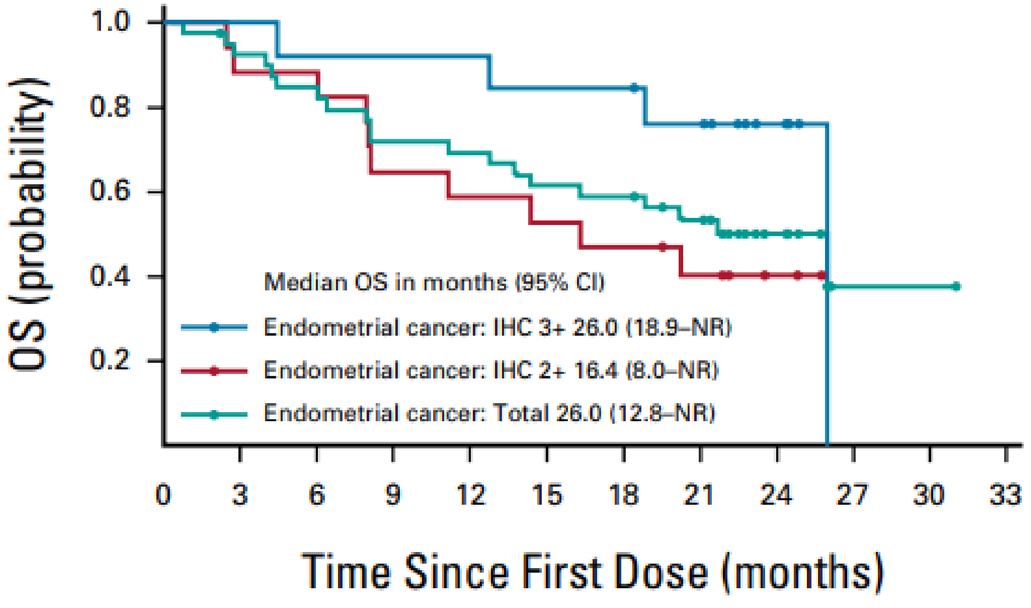


No. at risk:

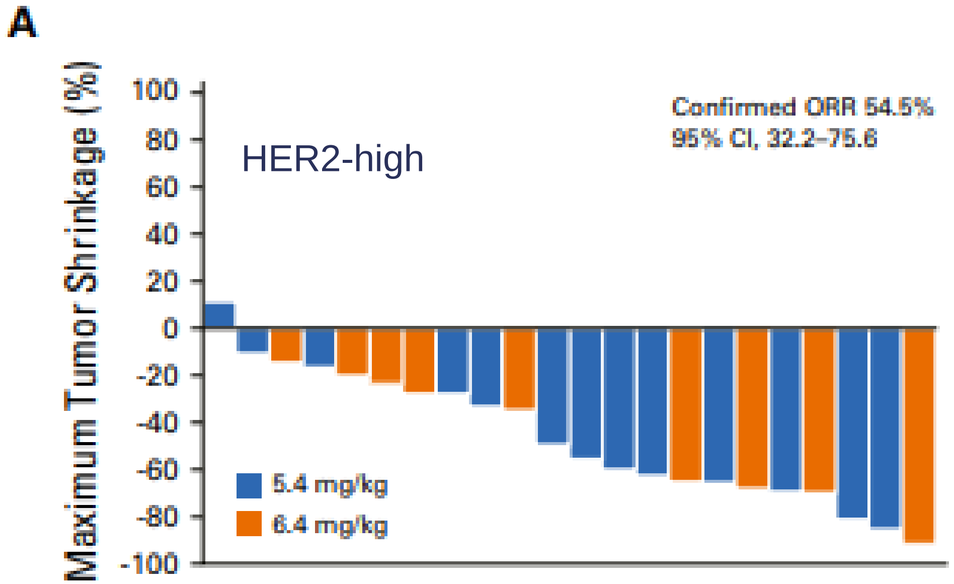
Endometrial cancer: IHC 3+	13	13	12	12	12	11	11	9	4	0		
Endometrial cancer: IHC 2+	17	15	15	11	10	9	8	6	3	0		
Endometrial cancer: Total	40	36	33	28	27	24	23	19	9	1	1	0

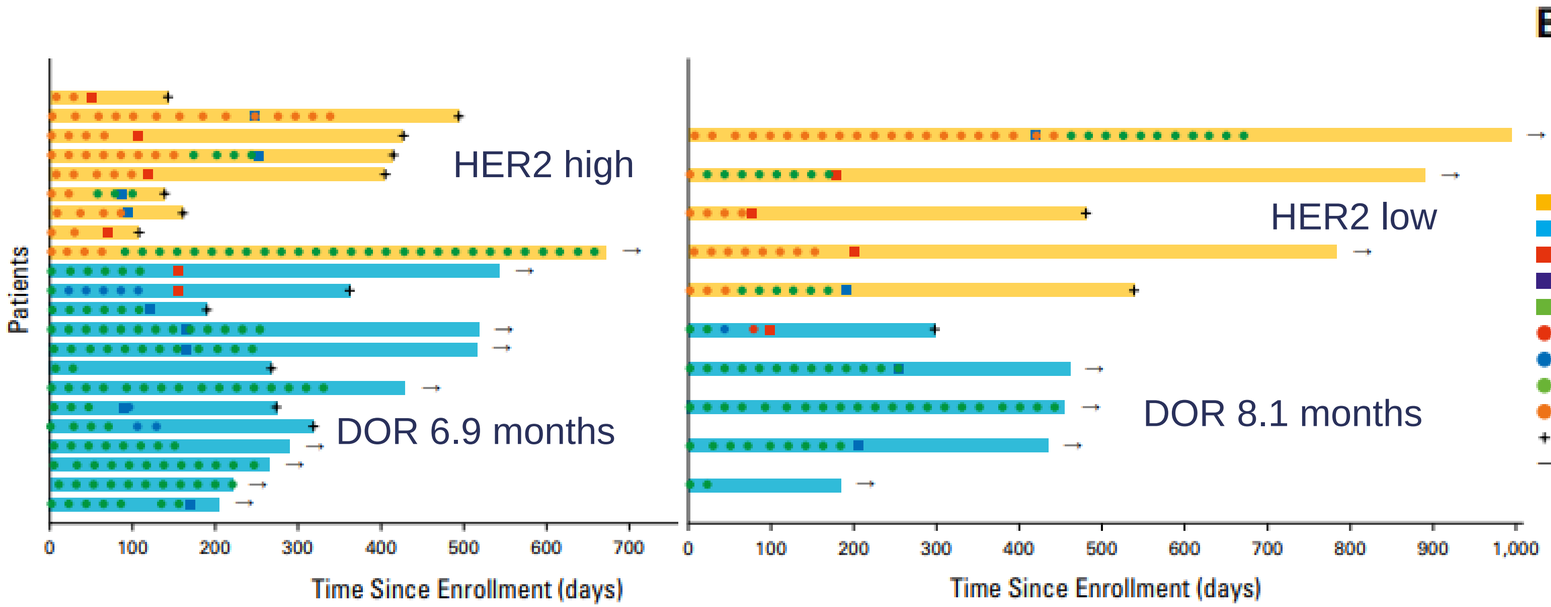
Meric-Bernstam, F. JCO 2023

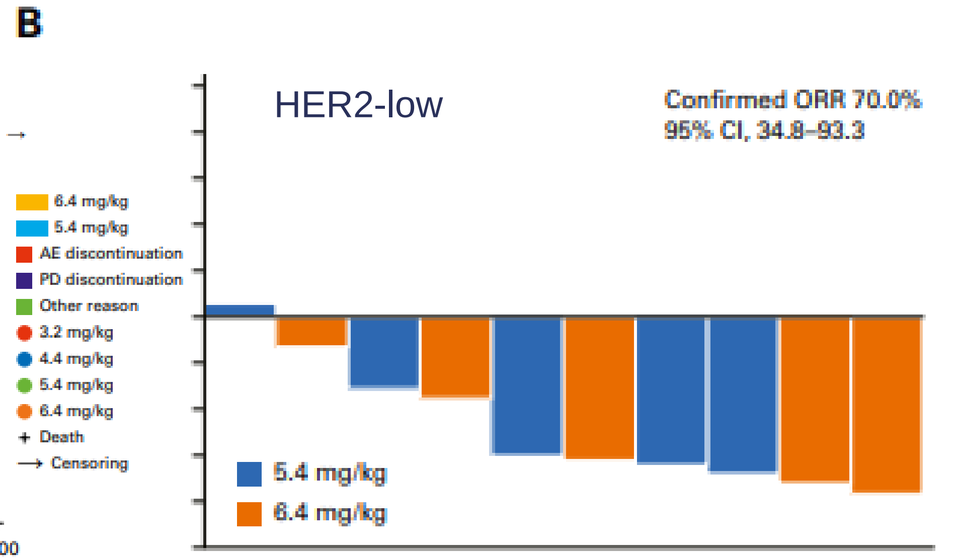
GOG FOUNDATION®

STATICE TRIAL: Trastuzumab deruxtecan (DS-8201a or T-DXd)

- HER2 targeting; topoisomerase I inhibitor
- Phase II, N= 34 (22 high, 10 low), Japan
- Carcinosarcoma, HER2 IHC score ≥1+ , >1 prior line
- 6.4 mg/kg → 5.4 mg/kg
- Median PFS 6.7 months (95% CI, 5.4 to 8.8)
- Pneumonitis/ILD in 9 (27%)



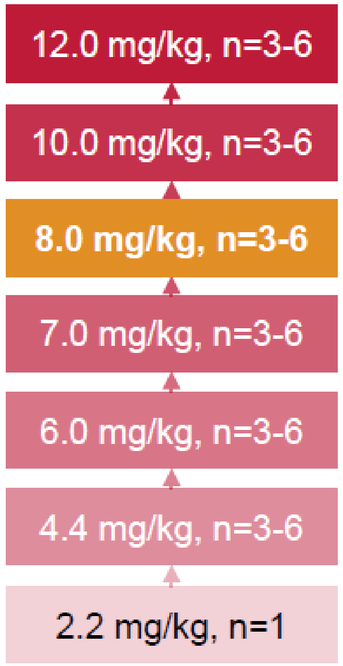




Nishikawa T, JCO 2023

BNT323/DB-1303: Phase I/2a

Phase 1 (Dose Escalation)
(HER2 IHC 3+, IHC 2+, IHC 1+ or ISH +, or HER2 amplification by NGS, or HER2 mutation by NGS)



Additional dose finding cohorts
(A total of up to 20 participants)

RP2D/MTD
(RP2D=8 mg/kg)

Dose extension
If a dose is confirmed to have a tolerable safety profile by the SMC, the cohort size may be backfilled to a maximum of 15-21 at any dose level ≥4.4mg/kg. Up to 57 additional participants (HER2 low BC, HER2+ BC, HER2+/low endometrial carcinoma, and HER2 activation mutation NSCLC) will be enrolled.

Phase 2a (Dose Expansion)

Cohort 2a Trastuzumab-treated HER2+ (IHC3+, IHC2+/ISH positive) gastric or gastroesophageal junction adenocarcinoma (N=30), HER2+ esophageal carcinoma (N=10), and HER2+ CRC (N=15)

Cohort 2b Both HER2 overexpression and HER2 low (IHC3+,2+,1+ or ISH positive) endometrial carcinoma, including UC and USC (N=30-60)

Cohort 2c HR+/HER2 Low (IHC2+ /ISH negative, or IHC1+) BC (N=30-50)

Cohort 2d HER2+ (IHC3+, IHC2+/ISH positive) BC (N=20-40)

Cohort 2e NSCLC with activating HER2 mutation (N=15-30)

Cohort 2f HER2+ or HR+/HER2-low BC with treatment failure of trastuzumab deruxtecan (N=10, HER2+ BC; N=10, HR+/HER2-low BC)

Objectives

Dose Escalation
- **Primary:** safety and tolerability, MTD or RP2D
- **Secondary:** efficacy, PK, and immunogenicity
- **Exploratory:** biomarker and ER relationship

Dose Expansion
- **Primary:** safety and tolerability, efficacy
- **Secondary:** PK, antidrug antibodies, efficacy
- **Exploratory:** biomarker, ER relationship, population PK, neutralizing antibody, efficacy

>1 prior line. NCT05150691

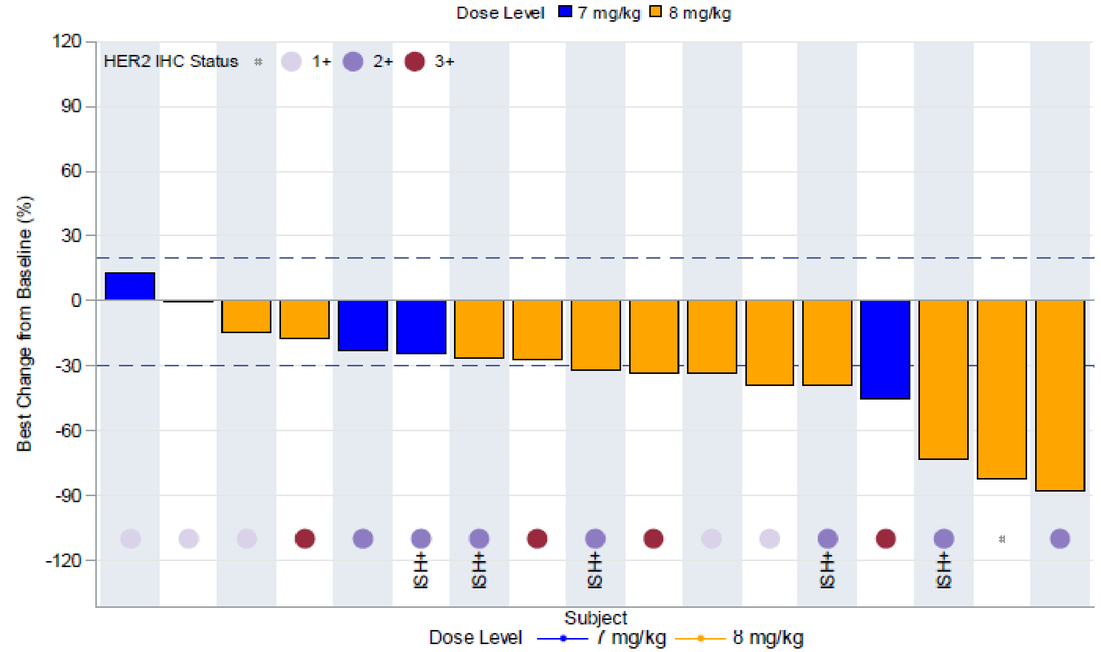
Moore, K. ESGO 2023

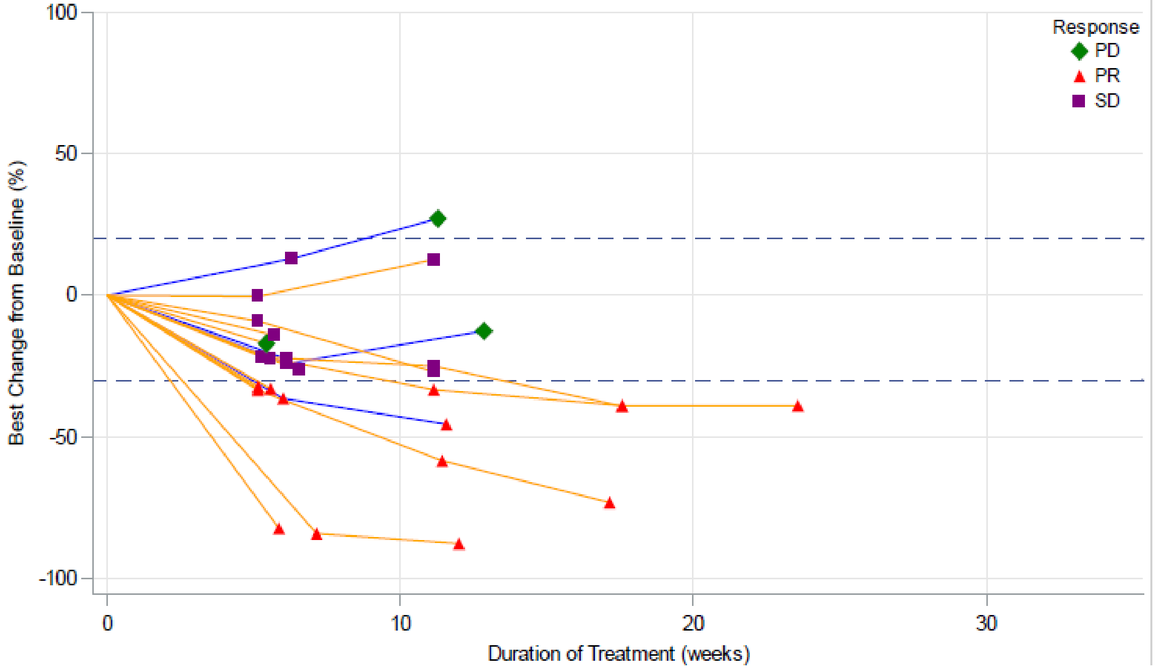
GOG FOUNDATION

DB-1303/BNT323

- HER2 targeting; topoisomerase I inhibitor
- N=32
- 59% prior IO
- 38% prior Anti-HER2
- 1/3≥3 prior lines
- 34% Black, 6% Asian
- ORR 10/17 (58.8%) (unconfirmed), DCR 94%

- The most frequent TEAEs of any grade were nausea, fatigue, and vomiting, grade 3 or greater was rare.
- Alopecia 3.1%

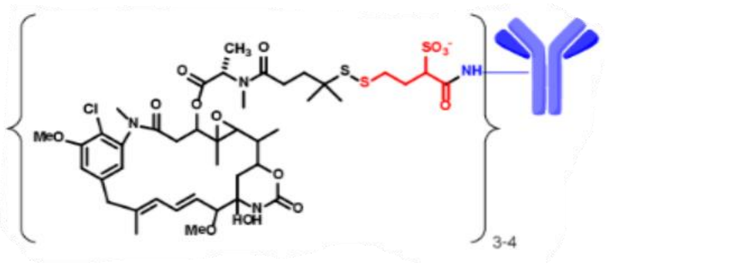


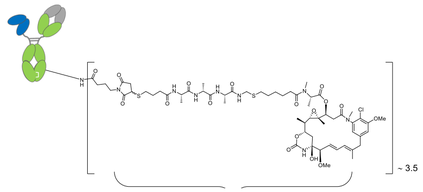


Moore, K. ESGO 2023

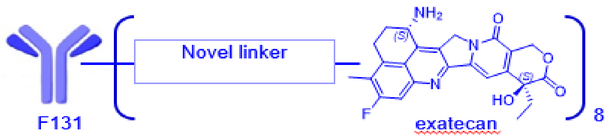
Targeting Folate Receptor (FR)-α

TARGET: Folate Receptor α

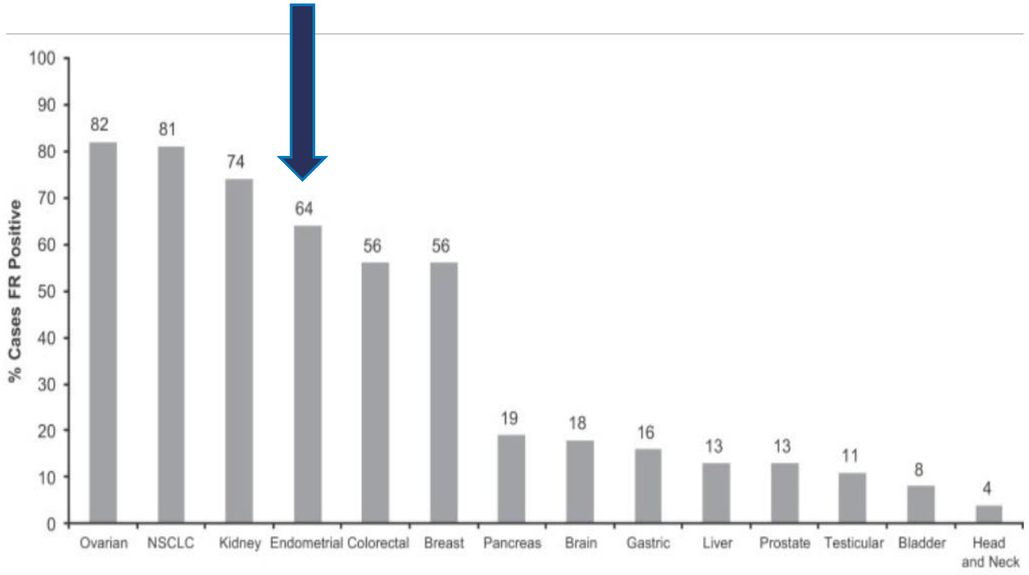




PRO1184 Structure



- FRα overexpression in ~64% of endometrial tumors



Drug Name	Payload
Luveltamab tazivibulin (STRO-002)	Hemiasterlin-derivative Tubulin-inhibitor
Mirvetuximab Soravtansine	Maytansinoid (DM4)→ tubulin targeting
Farletuzumab ecteribulinm (MORAb-202, FZEC)	Eribulin → microtubule-depolymerizing

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

STRO-002-GM1: Phase 1 Dose-Expansion Cohort of Luveltamab tazevibulin (luvelta) in Recurrent EC

Key Inclusion and Exclusion Criteria

- Endometrial cancer
  - Excluded: leiomyosarcoma, stromal sarcomas and carcinosarcomas
- **≥1% FolRα expression by central IHC**
- Recurrent disease
  - **≥1 platinum-based chemotherapy or 1 immunotherapy-based regimen**
  - **≤3 prior regimens**
- At least 1 target lesion

17 Patients Enrolled

Luveltamab tazevibulin Dosing Schedule

- Q3W cycles
- **5.2 mg/kg** unless prior pelvic XRT, then **4.3 mg/kg** X 2 cycles with option to dose escalate to 5.2 mg/kg

Endpoints

- Safety
- PK
- Anti-tumor activity assessed by ORR, DOR and PFS by RECIST v1.1
- CA-125

Most common TEAEs, n (%)	Any grade	Grade ≥3
Anemia	13 (76.5)	4 (23.5)
Arthralgia	12 (70.6)	3 (17.6)
Neutropenia†	11 (64.7)	9 (52.9)
Nausea	10 (58.8)	1 (5.9)
Decreased appetite	10 (58.8)	0

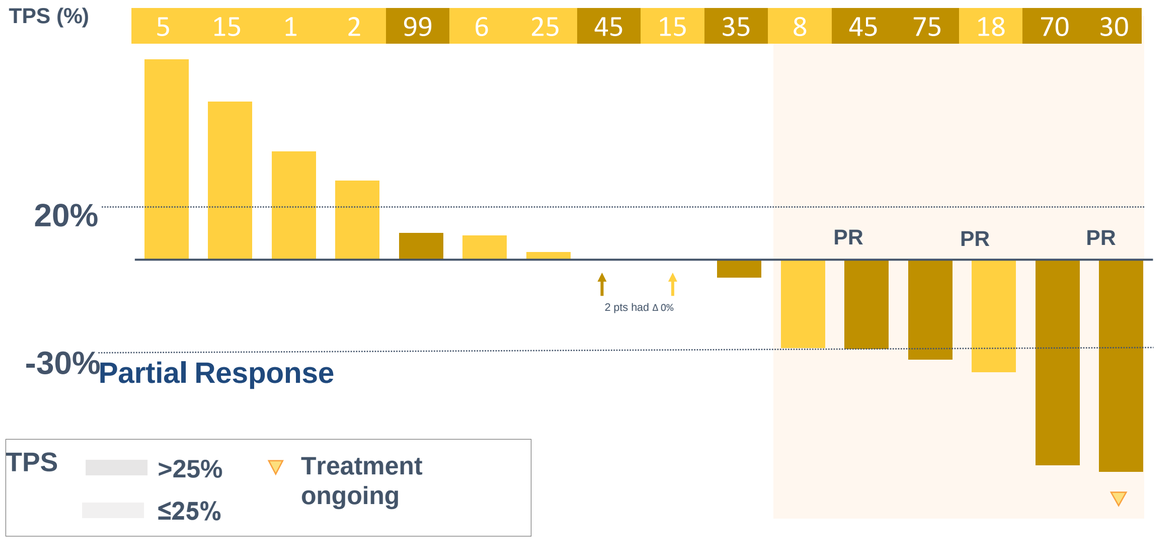
DOR, duration of response; IHC, immunohistochemistry; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; XRT, radiotherapy.

ClinicalTrials.gov NCT03748186

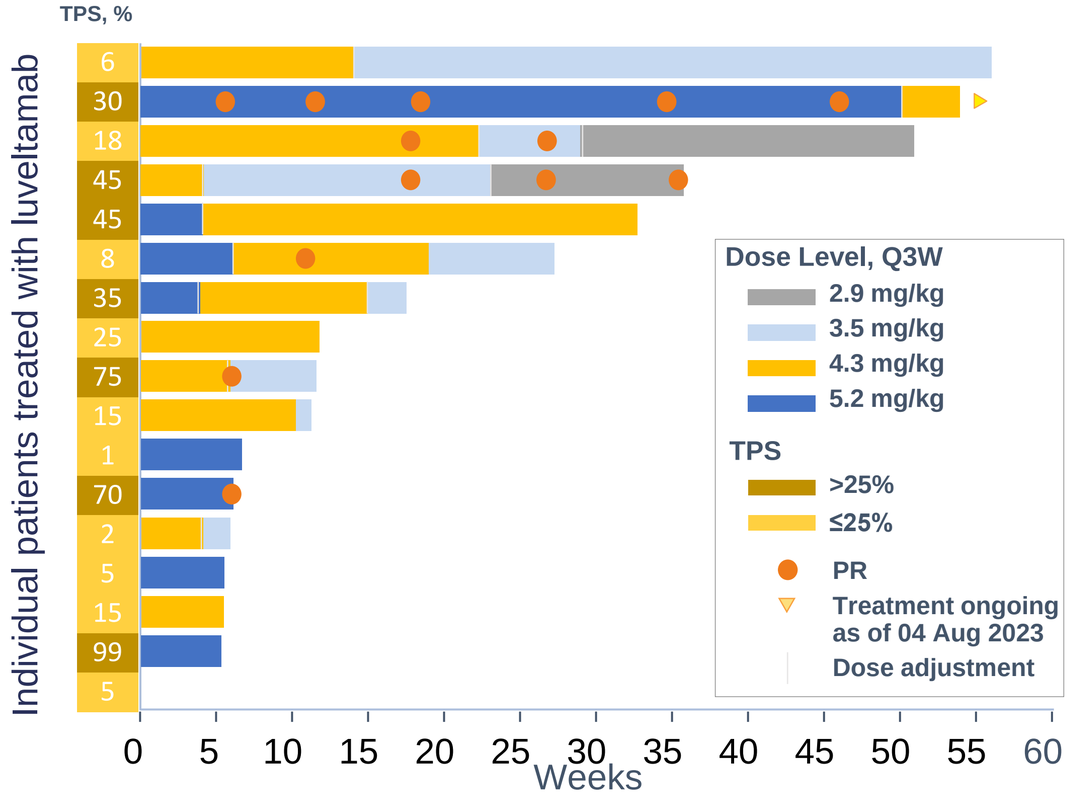
Pothuri B. ESMO 2023

Luveltamab tazevibulin Showed Early Evidence Of Anti-tumor Activity in FolRα Expressing EC

Maximum Reduction in Target Lesions*



Treatment Duration and Dose Modifications



- Median exposure (range): 12 (3–53) weeks
- 5 of 17 (29%) patients received ≥5 cycles
- Median follow-up: 10.1 months

Anti-tumor Activity*

n (%)	Overall FolRα ≥1% (n=16)	FolRα ≤25% (n=9)	FolRα >25% (N=7)
PR	3 (19)	1 (11)	2 (29)
SD†	8 (50)	4 (44)	4 (57)
PD	5 (31)	4 (44)	1 (14)
DCR	11 (69)	5 (56)	6 (86)

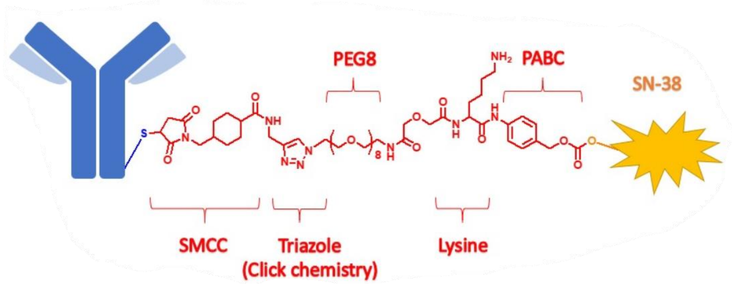
†3 unconfirmed PRs

Data cutoff: 04 August 2023. *n=16 response evaluable patients. DCR, disease control rate; EC, endometrial cancer; PR, partial response; Q3W, every 3 weeks; TPS, tumor proportion score.

Pothuri B. ESMO 2023

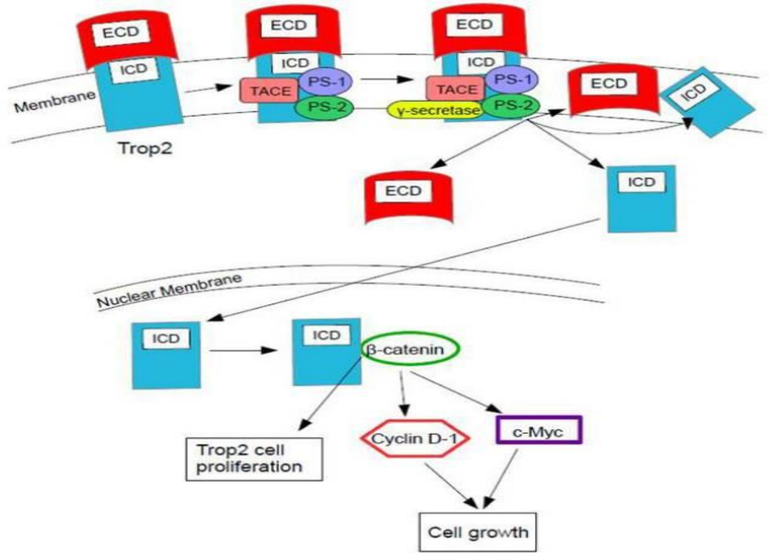
Targeting TROP2

TARGET: TROP2



TROP 2

- **Overexpression in endometrial cancer is common**
  - Present in 90+% of samples
    - 62% with expression in at least 50% of tumor cells
  - Implicated in intracellular signaling pathways
  - May be a modulator of EpCAM-induced cell signaling
  - Fosters cell migration



Drug Name	Payload
Sacituzumab govitecan (IMMU-132) *approved in TNBC, urothelial	SN-38 (irinotecan metabolite) → Toiposomerase I inhibitor
SKB264/MK-2870	Belotecan derivative → Topoisomerase I inhibitor

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

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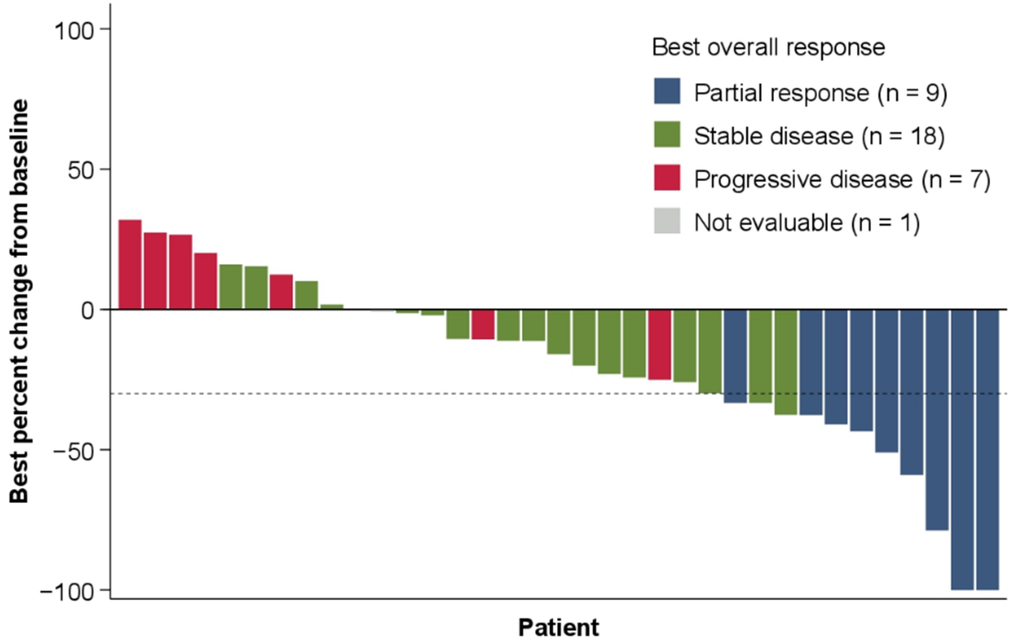
TROP2 Targeting: IMMU-132/Sacituzumab govitecan-hziy

- ORR 33% in 21 patients with persistent or recurrent endometrial cancer with at least 2+TROP2 by IHC (IMMU-132 study)
- ORR 22% and median PFS 5.7 months in an endometrial cancer cohort (n=28) with progression after prior platinum-based chemotherapy and anti-PD-1/PD-L1-directed therapy (TROPiCS-03 study NCT03964727)
- AE's: neutropenia (58%), diarrhea (56%), anemia

TROPiCS-03: Endometrial Cancer Cohort



Bardia, A., et al 2021. Santin, ASCO 2023

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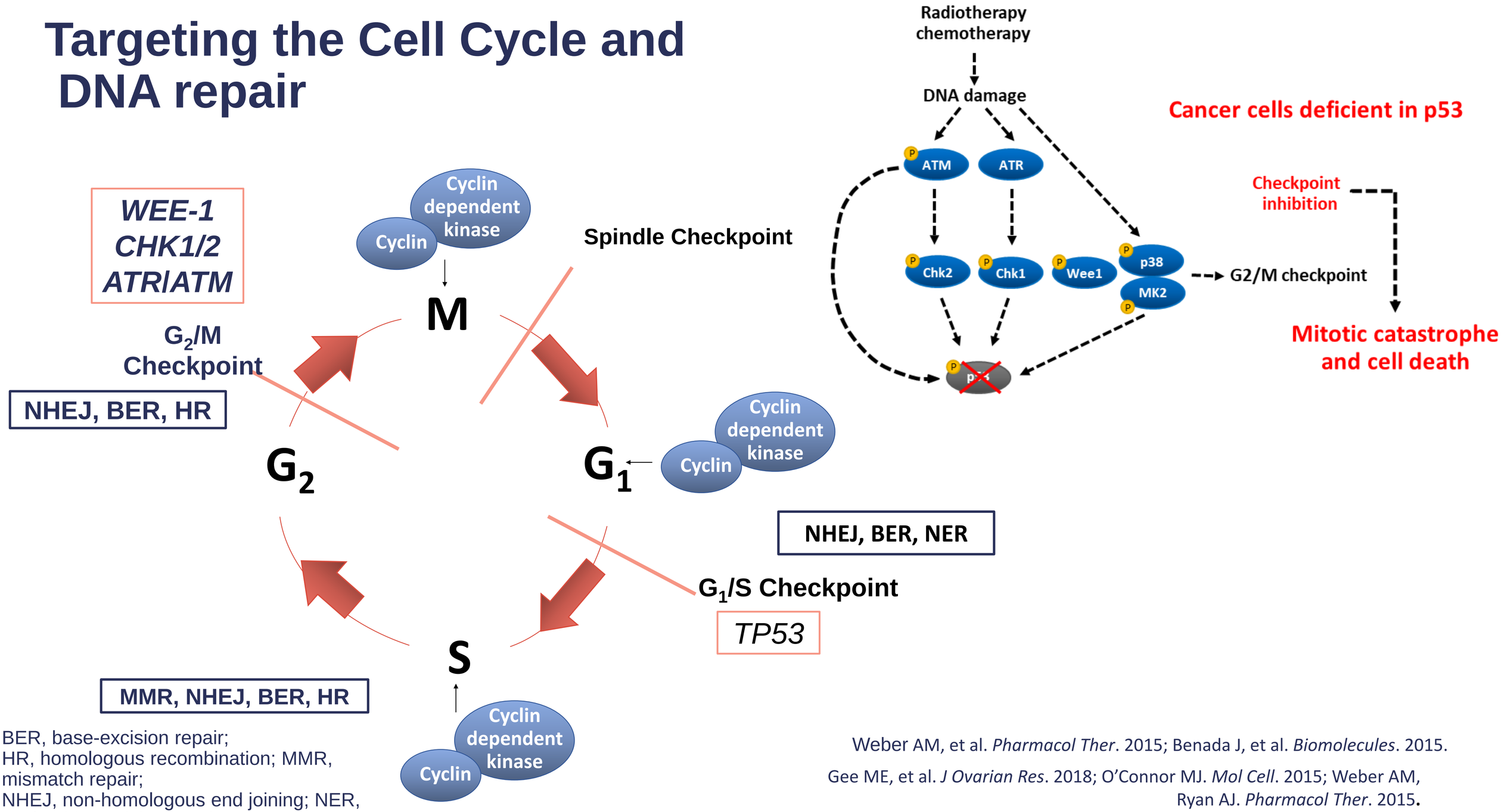
ADCs under Development in Endometrial Cancer

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) → Toiposomerase 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)

Targeting the Cell Cycle and DNA repair



BER, base-excision repair;
HR, homologous recombination; MMR, mismatch repair;
NHEJ, non-homologous end joining; NER, nucleotide-excision repair.

Weber AM, et al. *Pharmacol Ther*. 2015; Benada J, et al. *Biomolecules*. 2015.

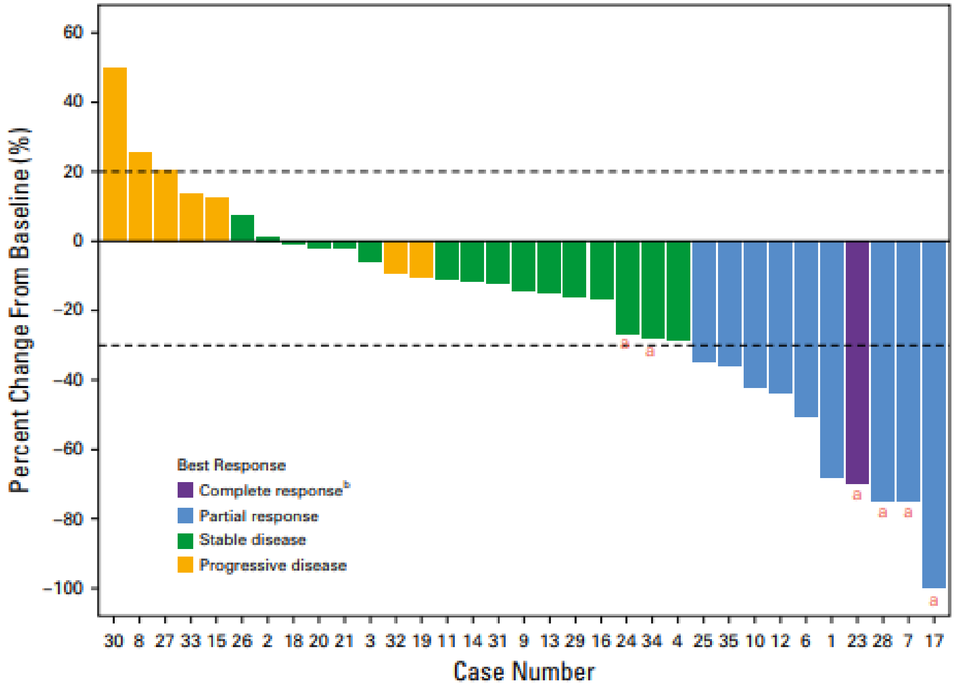
Gee ME, et al. *J Ovarian Res*. 2018; O'Connor MJ. *Mol Cell*. 2015; Weber AM, Ryan AJ. *Pharmacol Ther*. 2015.

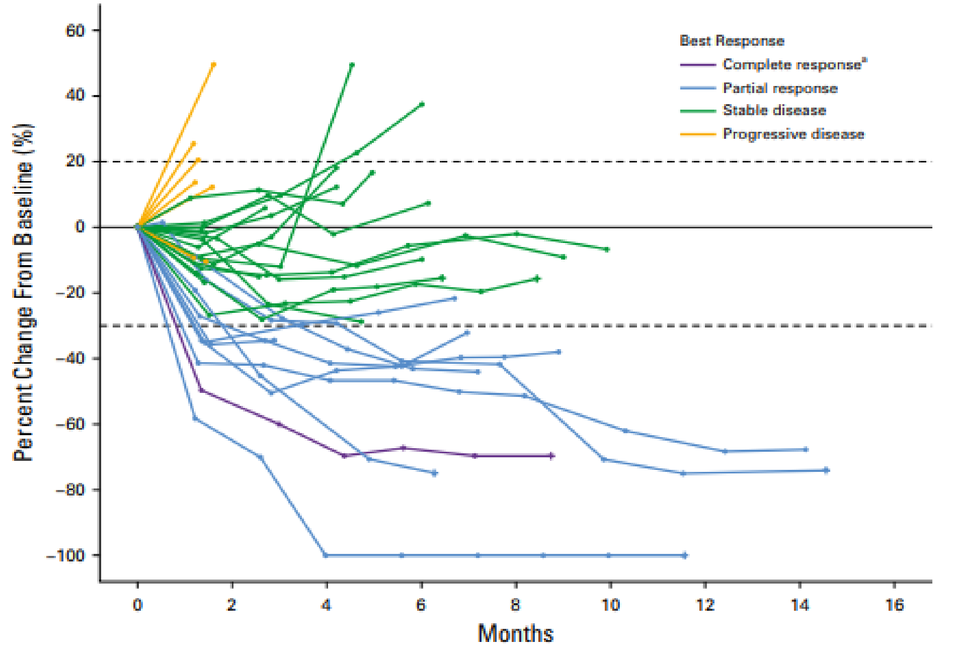
Adavosertib (WEE-1 inhibitor)

- WEE1 kinase, regulator G2/M and S phase checkpoints
- 2-stage Phase II, N=34
- Uterine serous carcinoma
- Adavosertib 300 mg PO D1-5 and D8-12 every 21 days
- ORR 29.4%
- 6-month PFS 47.1%, median PFS 6.1 months
- DOR 9.0 months
- AE: diarrhea, fatigue, nausea, hematologic – 75% of patients required dose hold and 50% reduction, 2 patients discontinued

→ADAGIO: phase II, N=109 – pending final results

→ORR 28%, DOR 4.7 months, PFS 2.8 months





Liu, JCO 2021. Liu, ASCO 2023

TETON / GOG-3065 / ZN-c3-004 (version 3)

Evaluating Azenosertib in Uterine Serous Carcinoma

Key Eligibility: Recurrent or persistent USC; ≥1 prior platinum-based chemotherapy regimen; Prior HER-2 directed therapy for known HER2+; Prior anti-PD(L)1[i]; Measurable disease per RECIST; ECOG PS 0-1

All Comers Enrollment

Cohort 1 (N=30)[ii]
Azenosertib 400 mg QD 5:2

All Comers Enrollment

Cohort 2 (N=60)[ii]
Azenosertib 400 mg QD 5:2

Endpoints (ICR)

ORR
DOR

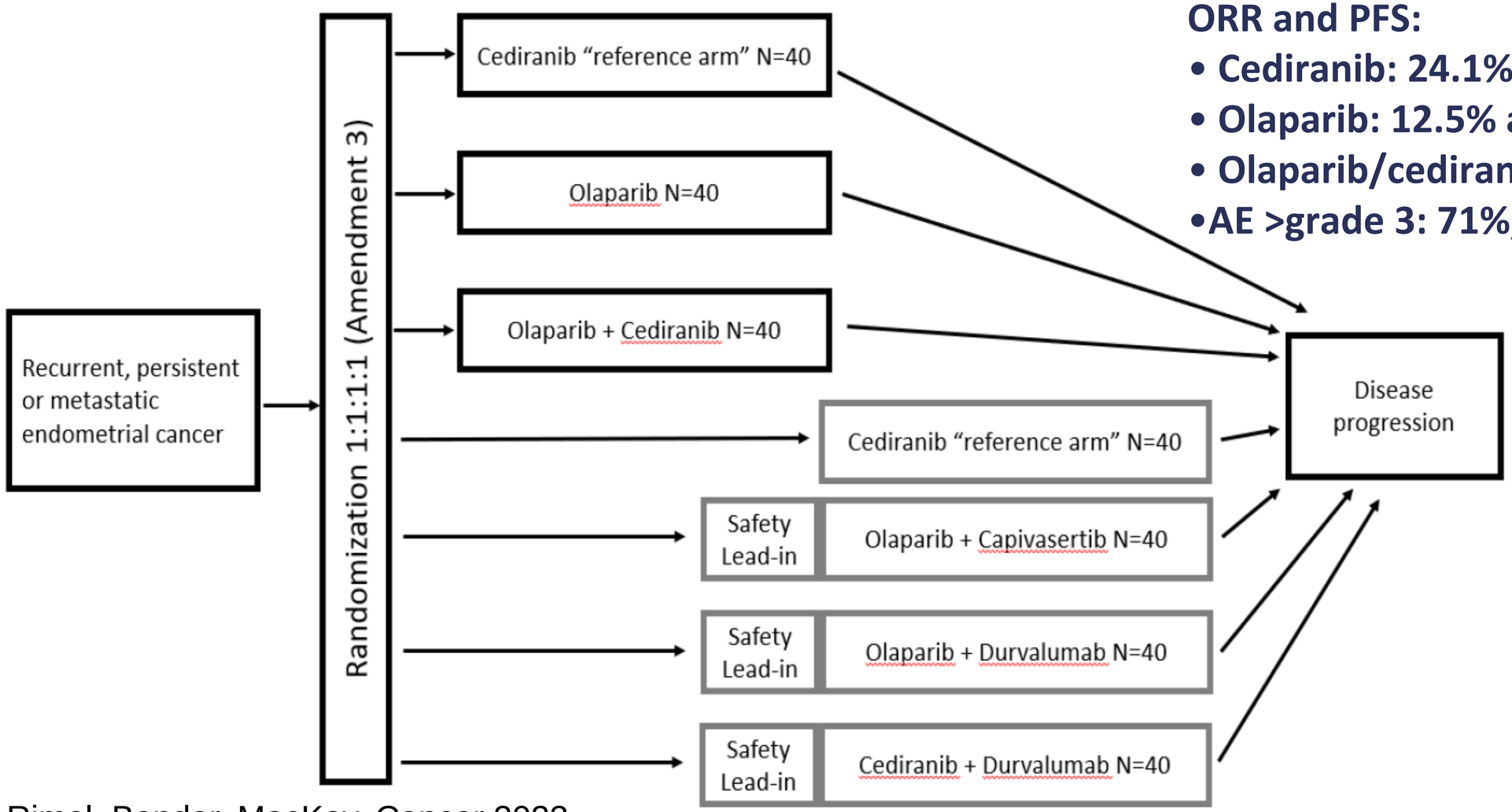
ClinicalTrials.gov NCT04814108

[i] Except for sites outside the US where aPD1 is not available, or for subjects ineligible for aPD(L)1
[ii] Response-evaluable subjects
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; RECIST, response evaluation criteria in solid tumors; ORR, objective response rate; DOR, Duration of Response

GOG FOUNDATION®

PARP combinations: NRG-GY012

22% of endometrial cancer have mutations in HR pathway (ATM, ATR)



ORR and PFS:

- **Cediranib: 24.1% and 3.8 months**
- **Olaparib: 12.5% and 2.0 months**
- **Olaparib/cediranib: 31.4% and 5.5 months**
- **AE >grade 3: 71%, 48%, 80%, respectively**

Rimel, Bender, MacKay. Cancer 2023

GOG FOUNDATION

Other Ongoing Studies

EAY191-N4: A Randomized trial of selumetinib (MEKi) and Olaparib or selumetinib alone in patients with recurrent or persistent RAS pathway mutant ovarian and endometrial cancers (ComboMATCH treatment trial) (Westin)

Hormonal Therapy

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Endometrial Carcinoma

Hormonal Therapy for Recurrent or Metastatic Endometrial Carcinoma[s]		

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

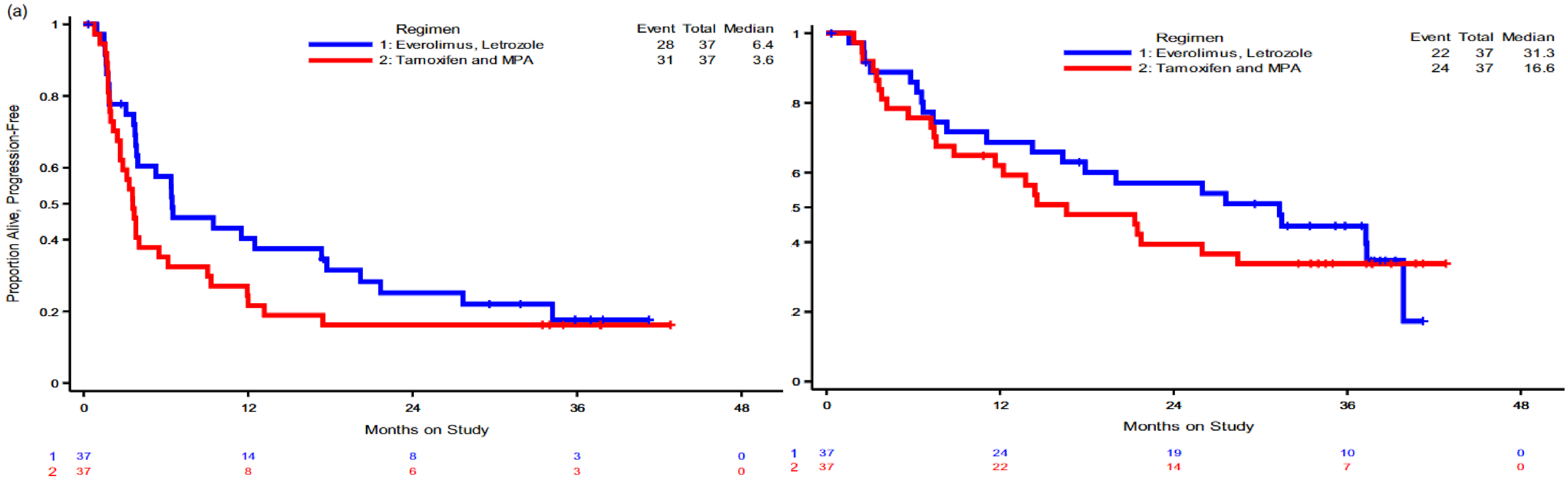
Hormonal Therapy

	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

Hormonal therapy with mTOR inhibitors: GOG-3007

Everolimus 10 mg daily with letrozole 2.5 mg daily versus
Medroxyprogesterone acetate (MPA) 200 mg daily alternating weekly with tamoxifen 20 mg BID

ORR 22% vs 25%

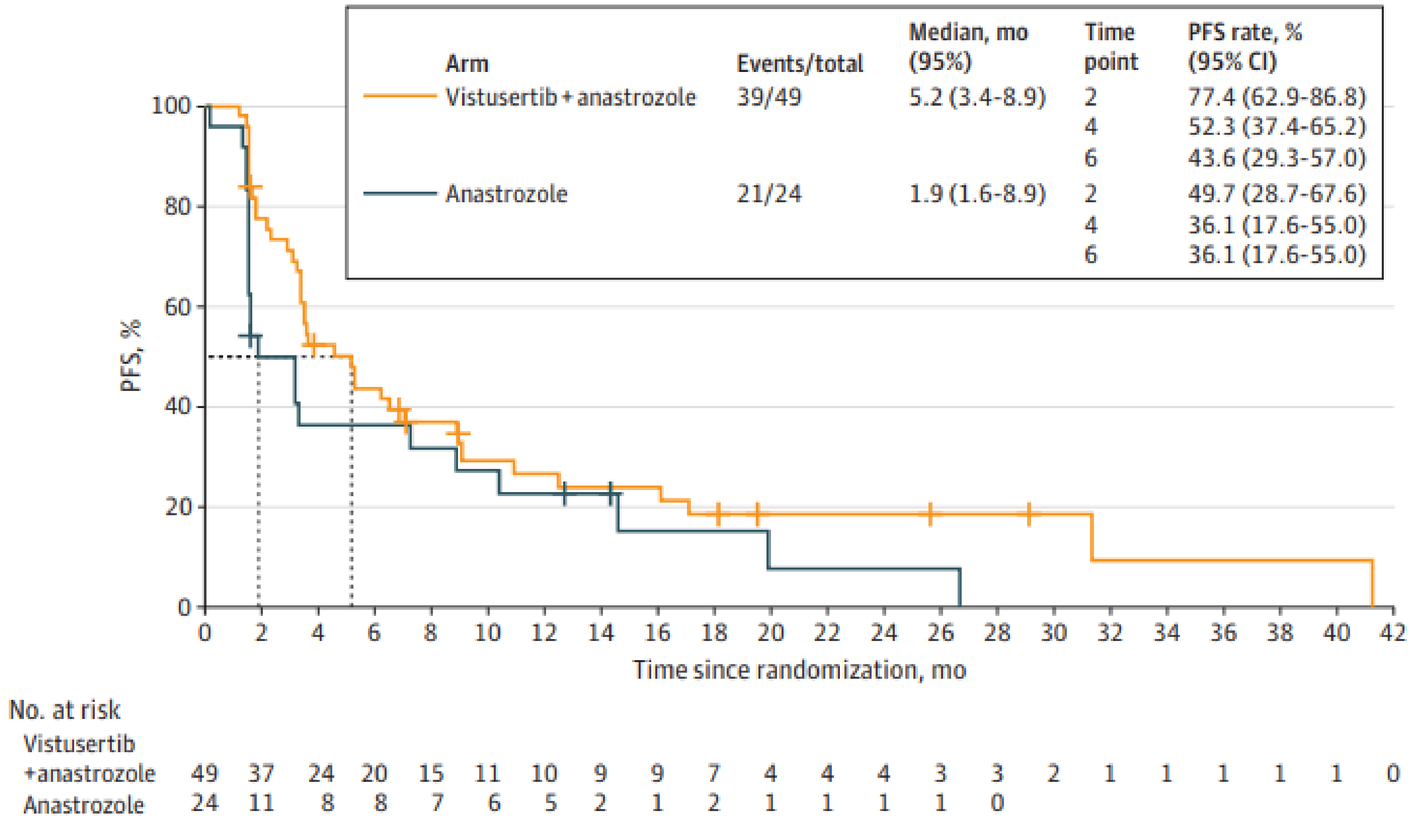


TRAE Grade 3 or > anemia, mucositis, hyperglycemia, fatigue and pneumonitis in the everolimus/letrozole group; versus hypertension and thromboembolic events in the hormonal therapy group

Slomovitz Gynecol Oncol 2022

GOG FOUNDATION

VICTORIA: mTOR Inhibitor, Vistusertib, Combined With Anastrozole in Patients With Hormone Receptor−Positive Recurrent or Metastatic Endometrial Cancer



ORR: 24.5 vs 17.4%

Most common grade 3/4 AE

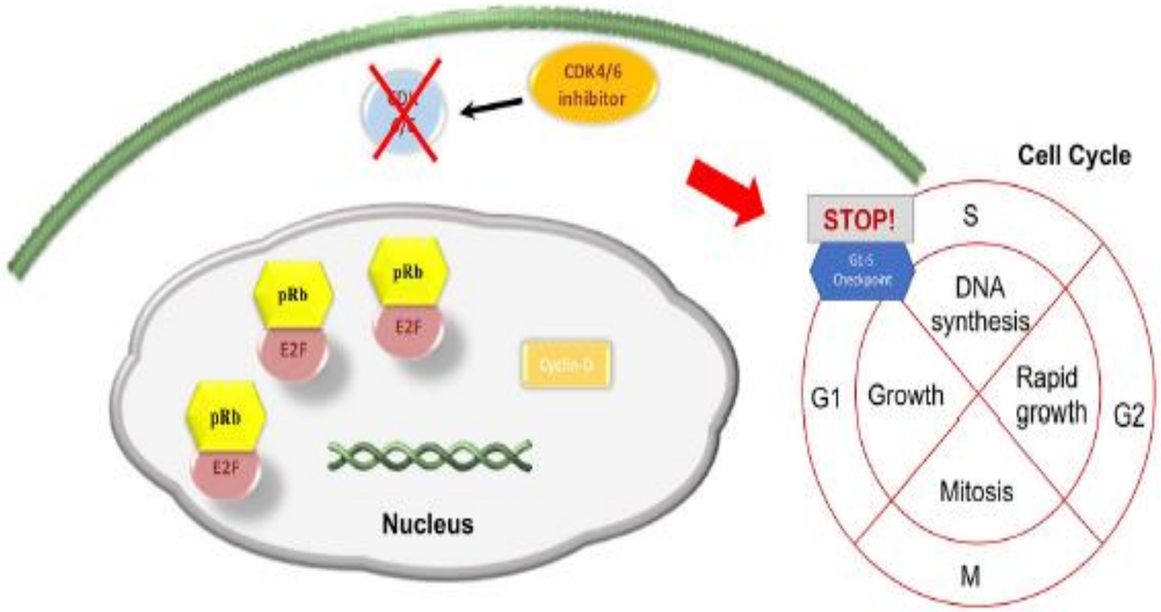
- V+A arm lymphopenia (20%), hyperglycemia (12%), and fatigue (8%)

Heudel, JAMA Oncol 2022

GOG FOUNDATION®

CDK 4/6 Inhibitors

- Hormonally driven malignancies are known to have actionable therapeutic targets.
- CDK 4/6 inhibitors induce cell-cycle arrest via G1 to S cell cycle checkpoint
- Cyclin D/CDK complex is downstream of estrogen signaling, representing potential synergic antitumor activity when combined with aromatase inhibitor.

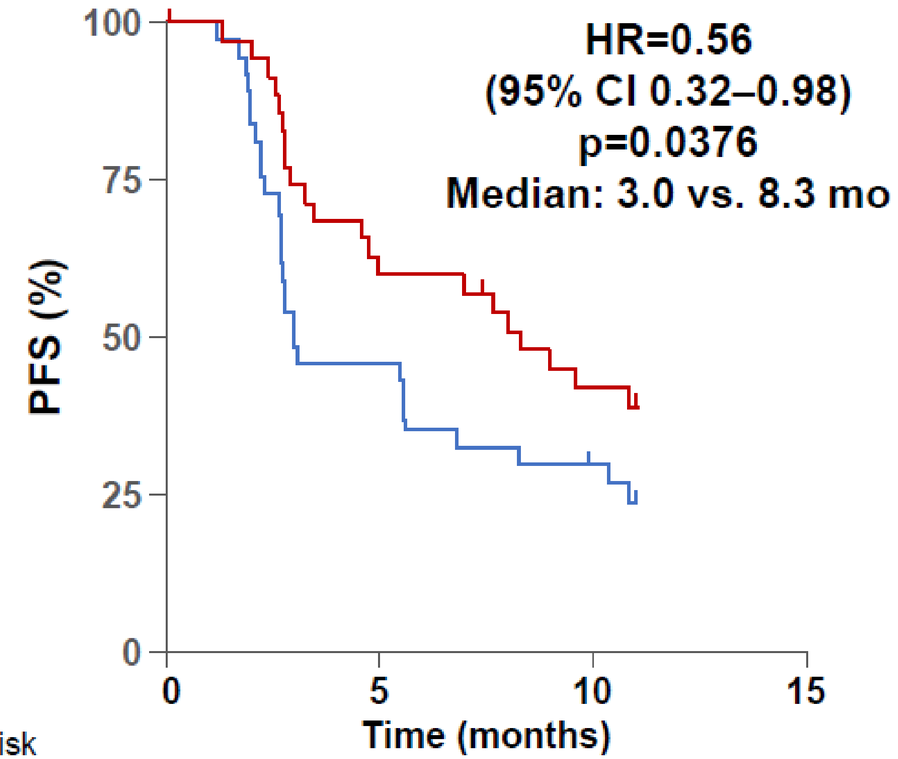


Palbociclib
Ribociclib
Abemaciclib

GOG FOUNDATION

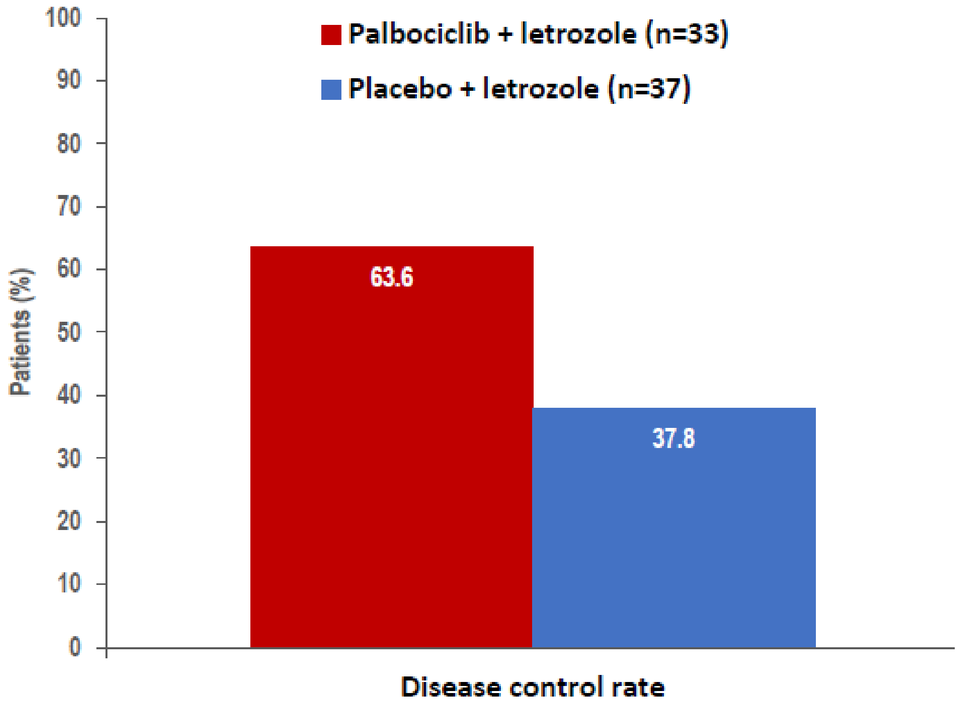
ENGOT-EN3/NSGO-PALEO: letrozole +/- palbociclib, a CDK 4/6 inhibitor

Primary endpoint: PFS



Number at risk			
Palbociclib + letrozole	36	21	14
Placebo + letrozole	37	17	10

Secondary endpoint: Disease control rate*



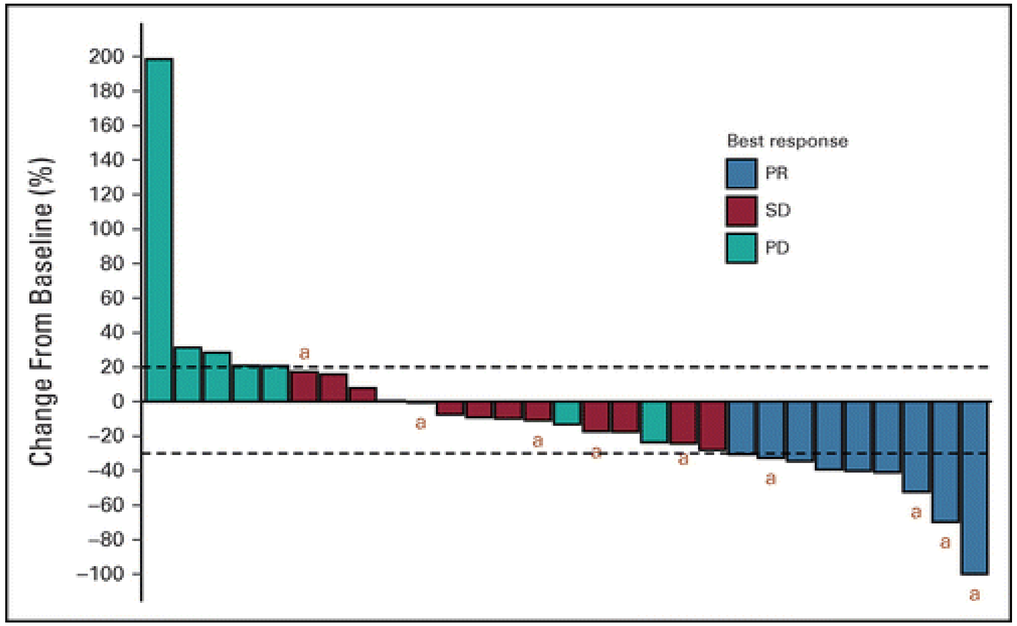
* = at 24 weeks

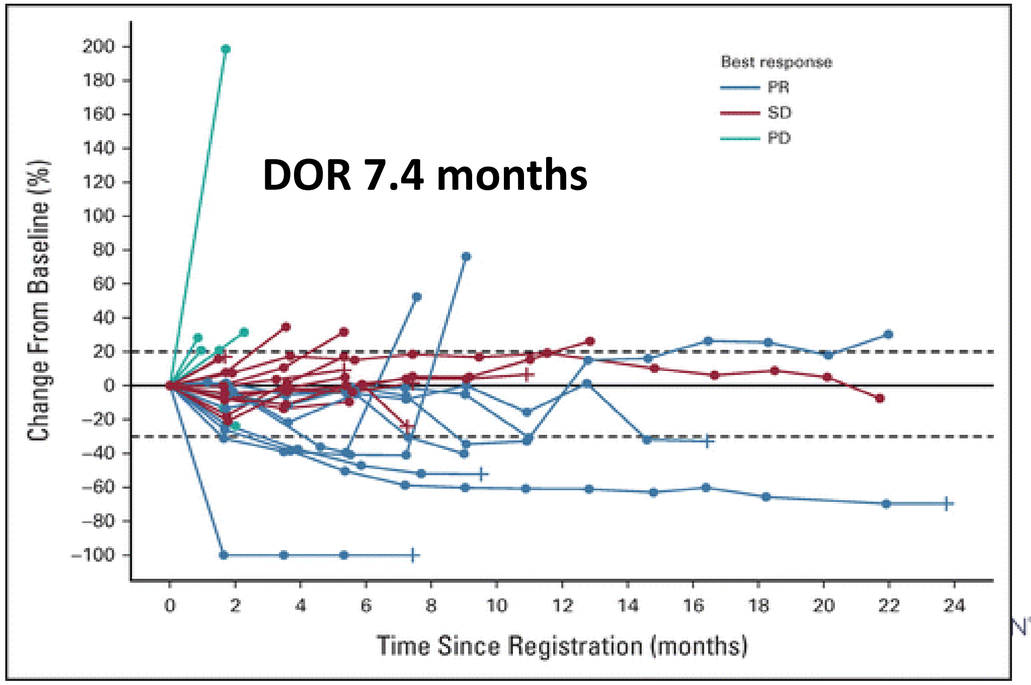
Mirza MR et al. *Ann Oncol*. 2020;31(suppl 4). Abstract LBA28.

GOG FOUNDATION®

Letrozole+Abemaciclib

- Phase II, N=30
- Abemaciclib 150 mg PO BID and letrozole 2.5 mg PO daily
- ORR 9/30 (30%) (only in endometrioid)
- Most common ≥ grade 3 TRAE:
  - Neutropenia (20%) and anemia (17%)
- Responses independent of grade, prior hormonal therapy, MMR status, PR
- Possible biomarkers: CTNNB1, KRAS, CDKN2A, TP53





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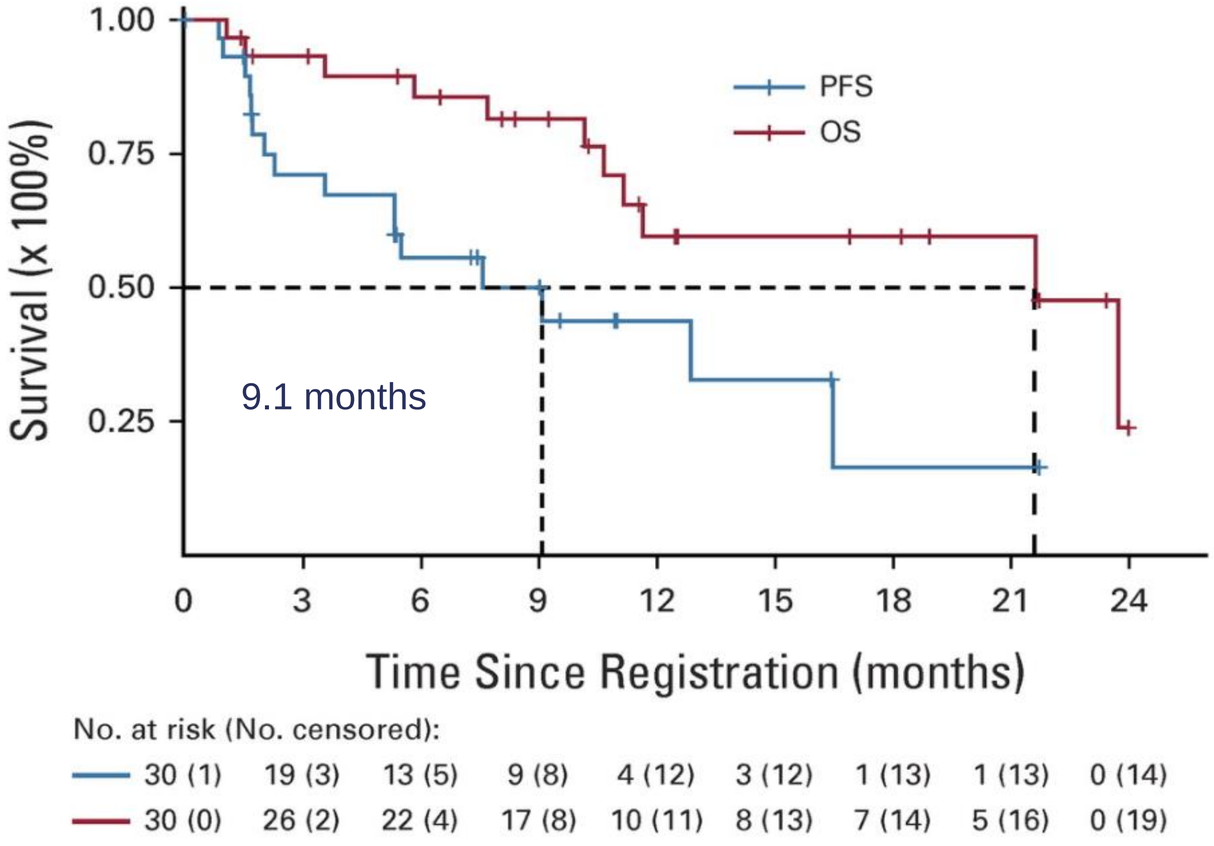
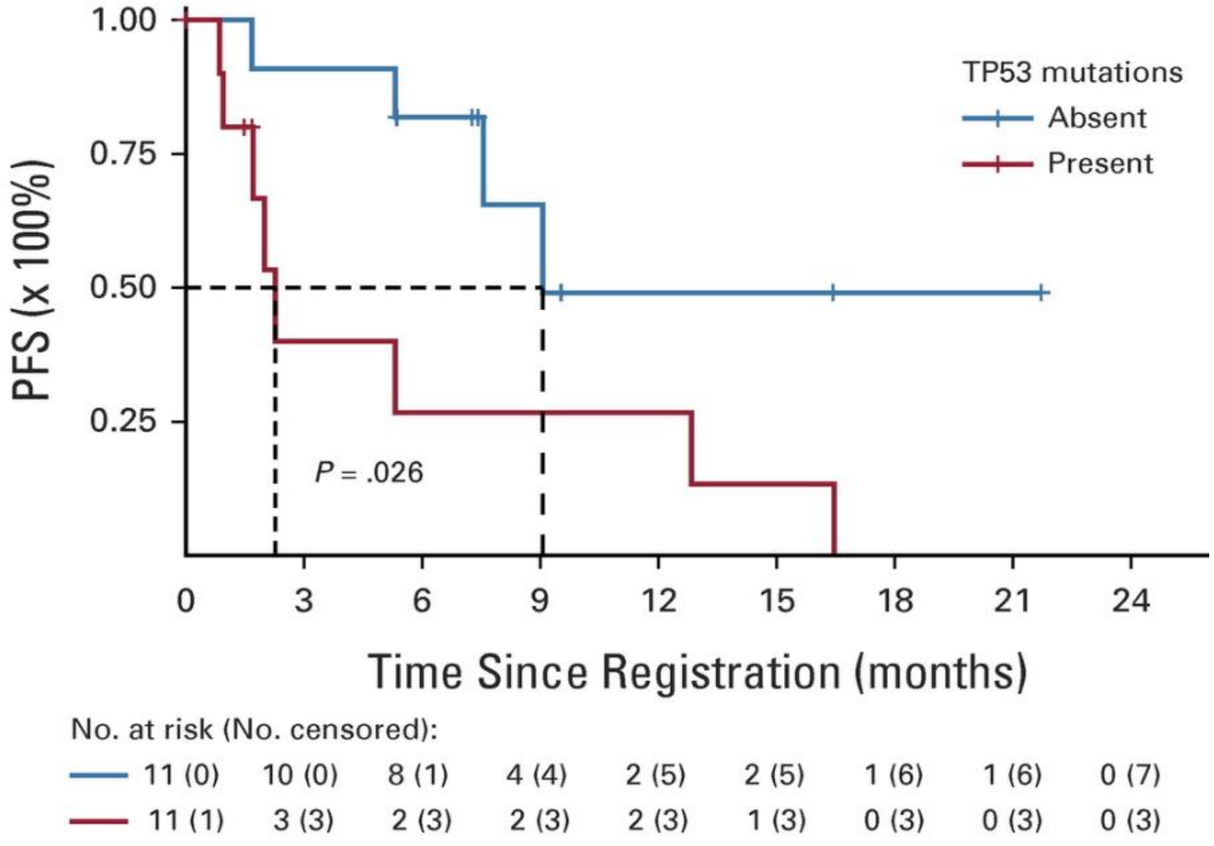
Letrozole Abemaciclib





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Ongoing Trials

- **NRG GY028:** Phase IB and randomized phase II trial of medroxyprogesterone acetate +/- ipatasertib (**AKT inhibitor**) in recurrent /metastatic endometrioid endometrial cancer (Onstad Grinsfelder/Westin)

- **GOG-3069:** A Phase 2 Study of Alpelisib (**PIK3CA inhibitor**) and Fulvestrant for PIK3CA-mutated Estrogen Receptor (ER) Positive Endometroid Endometrial Cancer (Gaillard)

Conclusion

- Subclassification of endometrial cancer is complex
- Molecular profiling, including NGS and IHC, is critical and opens up new opportunities for targeted therapy
- The new landscape will need options for treatment after IO
  - Without progression on IO
  - With progression on IO
- Antibody Drug Conjugates are effective in delivering high potency chemotherapy
  - New toxicity management strategies
- Hormonal therapy and combinations can provide significant clinical benefit