Endometrial Cancer – Highlight Reel

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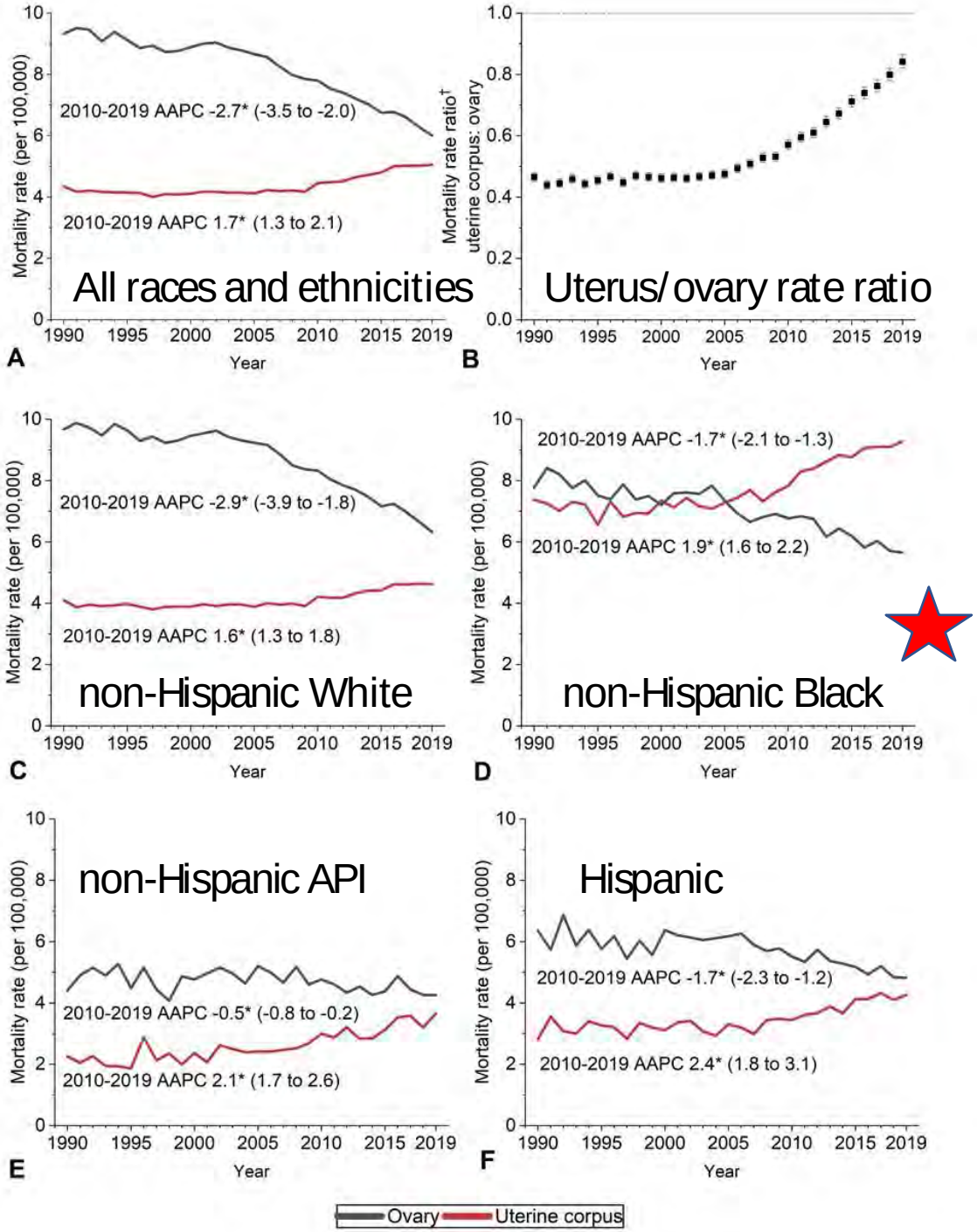
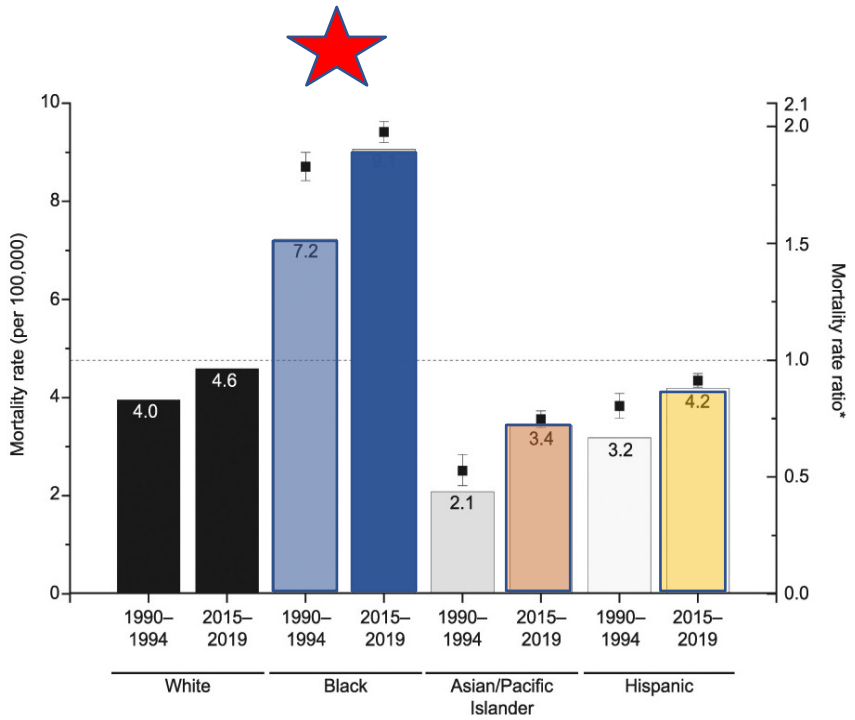
Objectives

- Diversity
- Selinexor
- CDK 4/6
- HER2 ADC (even for HER-low tumors)
- mTOR ADC
- First-line I/O in dMMR patient

Trends in uterine and ovarian cancer mortality rates by race and ethnicity, US 1990–2019.





Giaquinto *Obstet & Gynecol* Feb 2022

New FDA Guidance on "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry", April 13 2022

- Diverse groups need to be a part of the study to evaluate whether the study drug is effective and safe for everyone who will be administered study drug, or what side effects might emerge in one ethnic group or another
- Sponsors must present effectiveness and safety data by gender, age, and ethnic group (eg, race, ethnicity, ancestry) and must identify any modifications of dose or dose interval needed for a specific subgroup, as applicable
- Sponsors should discuss their strategy to enroll a diverse study population at any time throughout the medical product's development
- A Diversity Plan is required for clinical studies intended to support a marketing submission for a stand alone BLA

https://www.fda.gov/media/157635/download

Real World Data from Endometrial Cancer Molecularly Targeted Consortium: Portrait of Advanced/Recurrent Endometrial Cancer

		White (N=668), n (%)	Black (N=226), n (%)	*P*
NGS or IHC tumor testing	Yes	527 (78.9)	175 (77.4)	0.23
	No	112 (16.8)	47 (20.8)	
Mutations	PI3K	228 (34.1)	51 (22.6)	<0.001
	PTEN	200 (29.9)	27 (11.9)	<0.001
	TP53	178 (26.6)	94 (41.6)	<0.001
	Beta-catenin	56 (8.4)	9 (4)	0.02
	AKT	13 (1.9)	8 (3.5)	0.15
	mTOR	8 (1.2)	2 (0.9)	1.00
	ESR	11 (1.6)	3 (1.3)	1.00
	POLE	5 (0.7)	1 (0.4)	1.00
	TSC2	5 (0.7)	1 (0.4)	1.00
ERBB2	Amplification/overexpression	29 (4.3)	12 (5.3)	0.56
ERBB3	Amplification/overexpression	19 (2.8)	4 (1.8)	0.42
TMB status	High	47 (7)	7 (3.1)	0.001
	Intermediate	69 (10.3)	15 (6.6)	
	Low	134 (20.1)	67 (29.6)	

		White	Black	*P*
NGS	Yes	48.4%	49.6%	0.75
	No	51.6%	50.4%	
IHC	Yes	49%	45.6%	0.21
	No	46.1%	52.2%	

- MSI and dMMR more common in white patients ($p<0.001$)
- Based on all patients who had NGS testing by Foundation One and CARIS
- Testing status unknown for 4.3% of white (29) and 1.8% of black (4) patients

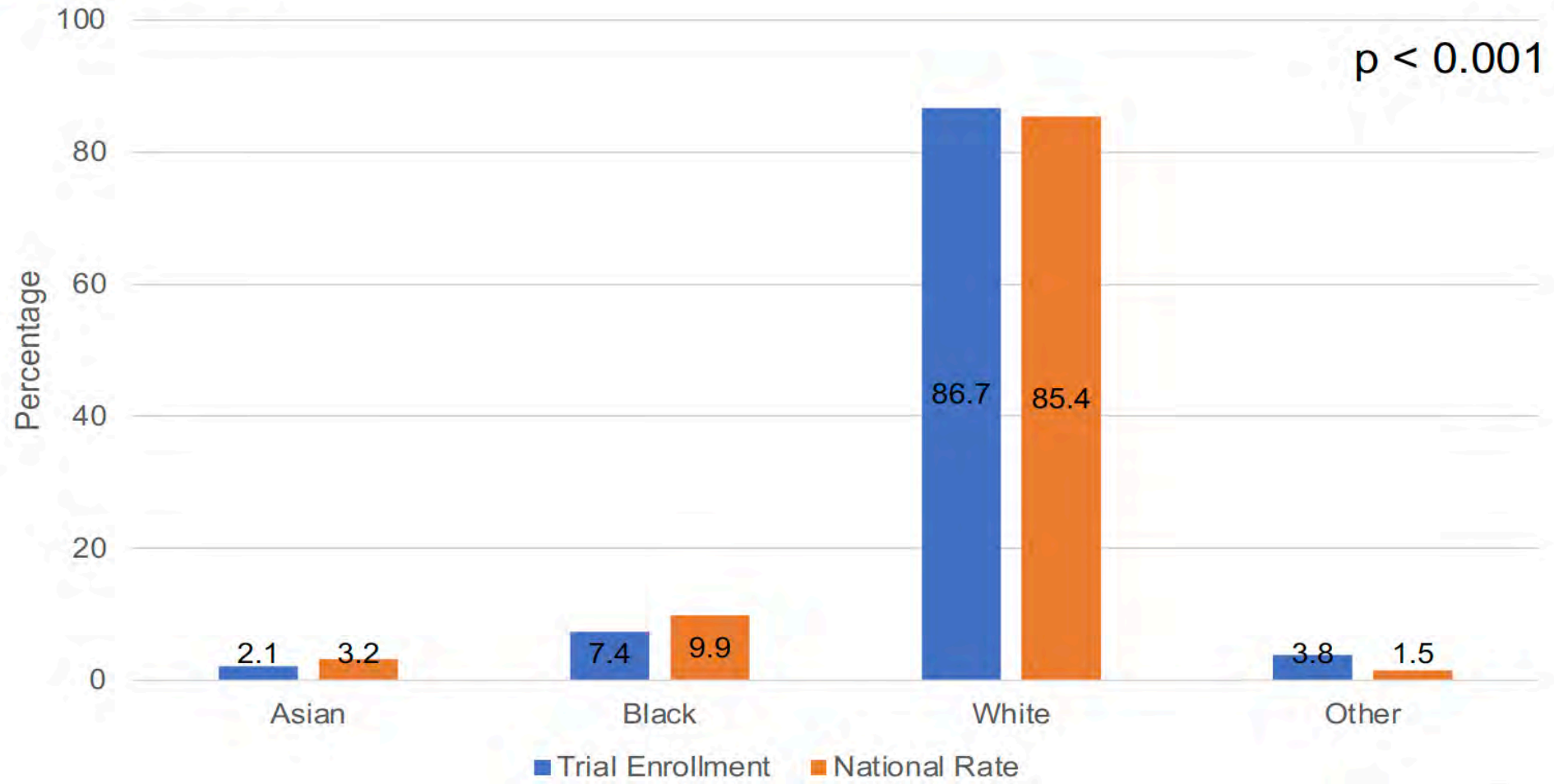
Secord et al, SGO, 2022

Black and Hispanic patient representation in NCCN-recommended systemic therapy regimens for endometrial cancer

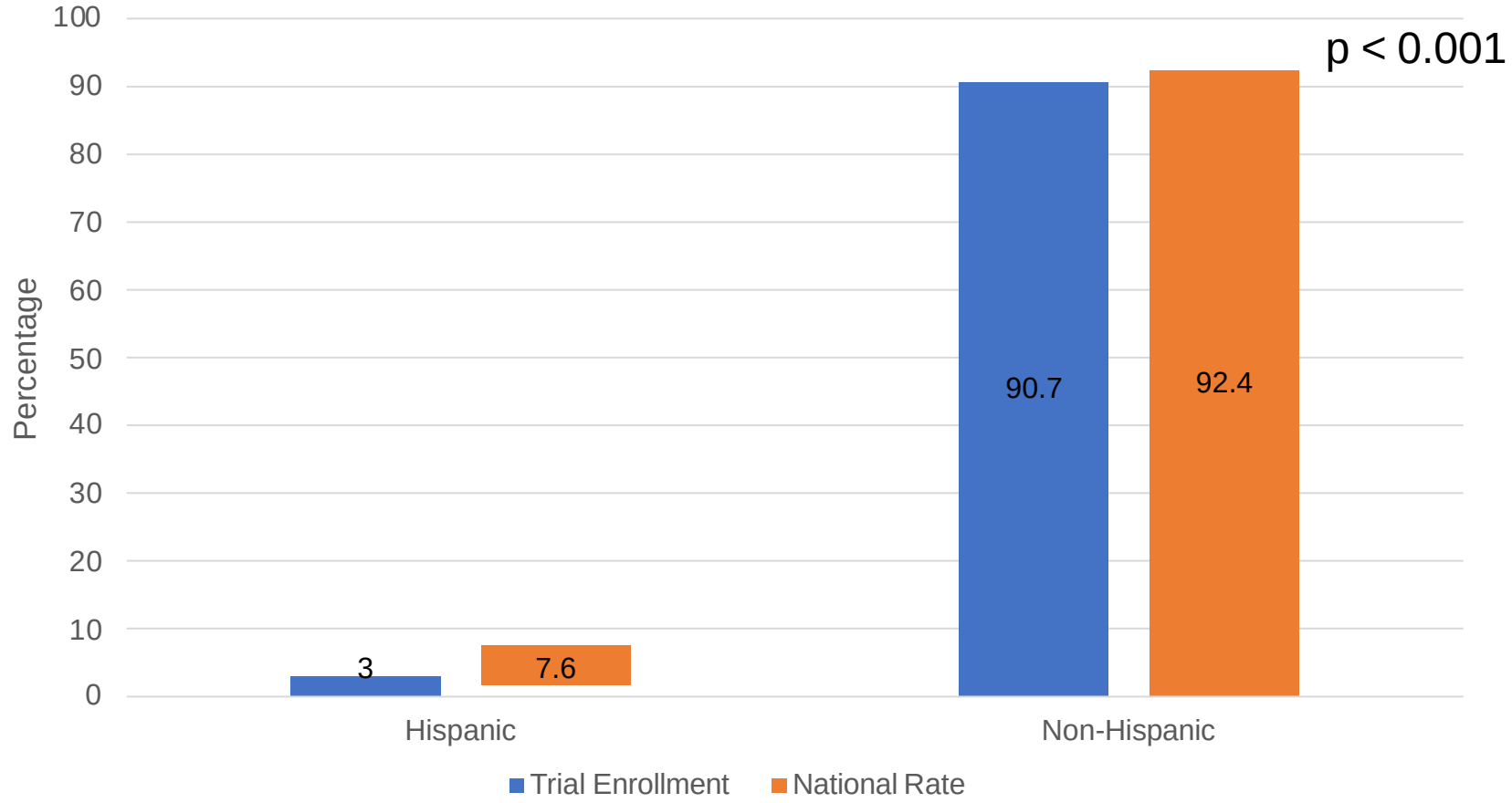
Amita Kulkarni MD, Helen Daifotis MD, Alexander Melamed MD, MPH, Joseph Dottino MD, Jason Wright MD, Fady Khoury Collado MD, June Hou MD, Caryn St Clair MD, Allison Gockley MD

Columbia University Irving Medical Center, New York, NY

Patient representation in NCCN endometrial cancer guidelines compared to the CDC's US Cancer Statistics Database, by race



Patient representation in NCCN endometrial cancer guidelines compared to the CDC's US Cancer Statistics Database, by ethnicity



Conclusion

- Racial ethnic minority patients were commonly under-represented in cited NCCN studies when compared to national rates of endometrial cancer among these groups

- Continuing to improve minority recruitment as well as transparency with reporting on race and ethnicity in therapeutic trials will help to ensure generalizability of treatment guidelines

Future Direction: Diversity

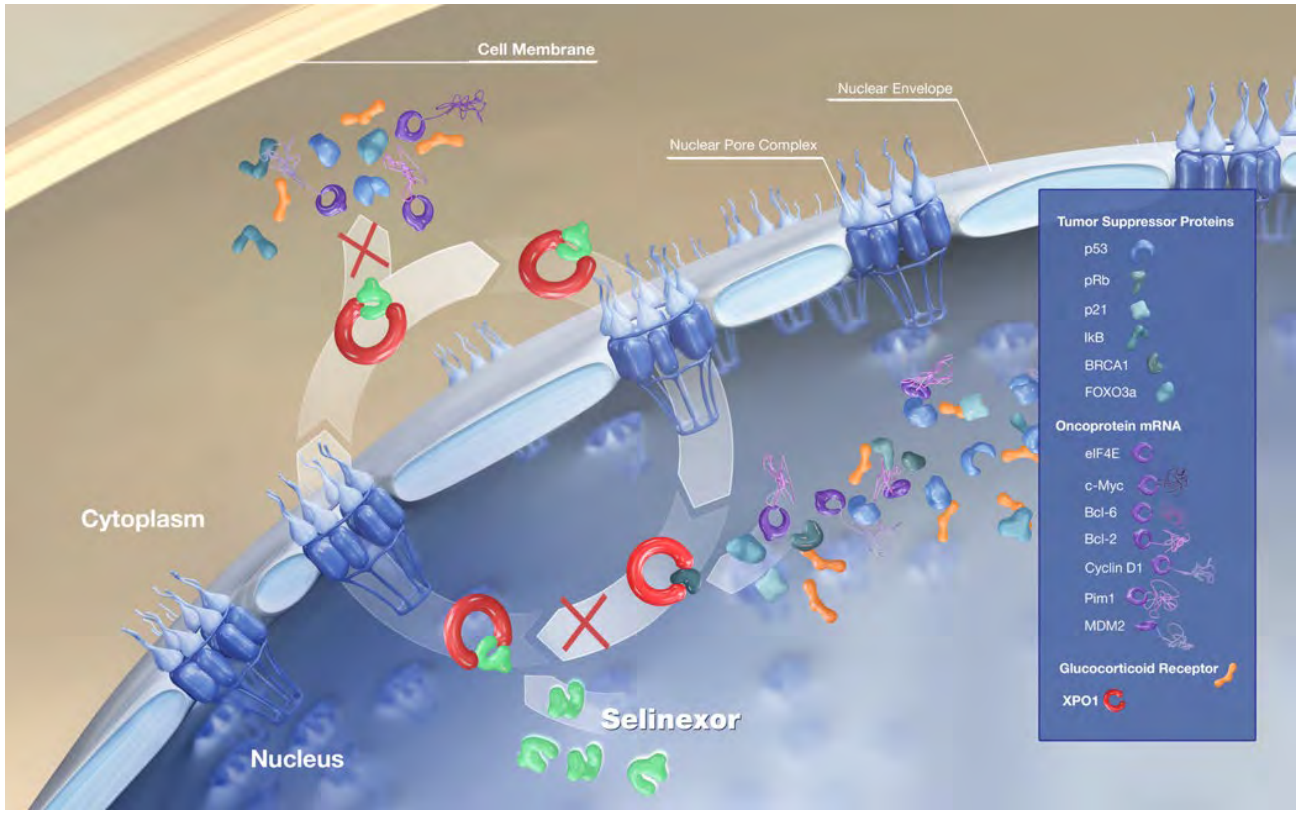
- Identifying solutions
- Working within our communities to overcome barriers to research
- Ensuring that all trials have equal representation
- Takes a team!

Prospective double-blind, randomized phase III ENGOT-EN5/GOG-3055/SIENDO study of oral selinexor/placebo as maintenance therapy after first-line chemotherapy for advanced or recurrent endometrial cancer

Ignace Vergote,[1] Alejandro Pérez Fidalgo,[2] Erika Hamilton,[3] Giorgio Valabrega,[4] Toon Van Gorp,[1] Jalid Sehouli,[5] David Cibula,[6] Tally Levy,[7] Stephen Welch,[8] Debra Richardson,[9] Eva Maria Guerra Alía,[10] Giovanni Scambia,[11] Stéphanie Henry,[12] Pauline Wimberger,[13] David Miller, [14] Jerónimo Martínez,[15] Bradley Monk,[16] Sharon Shacham,[17] Mansoor Raza Mirza,[17,18] **Vicky Makker**[19]

[1]Catholic University Leuven, Cancer Institute at University Hospitals, Belgium, European Union, [2]Hospital Clinico Universitario de Valencia, Spain, [3]Sarah Cannon Research Institute USA, [4]University of Torino, Candiolo Cancer Institute, FPO-IRCCS, Italy, [5]European Competence Center for Ovarian Cancer, Charité Comprehensive Cancer Center, Charité–Berlin University of Medicine, Germany, [6]Charles University and General Faculty Hospital Prague, Czech Republic, [7]Wolfson Medical Center, Holon, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Israel, [8]London Health Sciences Centre, UK [9]University of Oklahoma Medical Center, USA, [10]Hospital Universitario Ramón y Cajal, Spain, [11]Fondazione Policlinico Universitario A. Gemelli IRCCS, Italy, [12]Centre de Maternité Sainte Elisabeth, Namur, Belgium, [13]Technische Universitat Dresden, University Hospital Carl Gustav Carus, Germany, [14]University of Texas Southwestern Medical Center; Harold C. Simmons Comprehensive Cancer Center, USA, [15]Hospital Universitario Virgen de la Arrixaca, Spain, [16]Biltmore Cancer Center, USA, [17]Karyopharm Therapeutics, USA, [18]Rigshospitalet, Copenhagen University Hospital, Denmark, [19]Memorial Sloan Kettering Cancer Center, USA

Selenixor: XPO1 Inhibition



Exportin 1 (XPO1) is the major nuclear export protein for:

-Tumor suppressor proteins (TSPs, e.g., p53, IkB, and FOXO)

Inhibition of XPO1 results in:

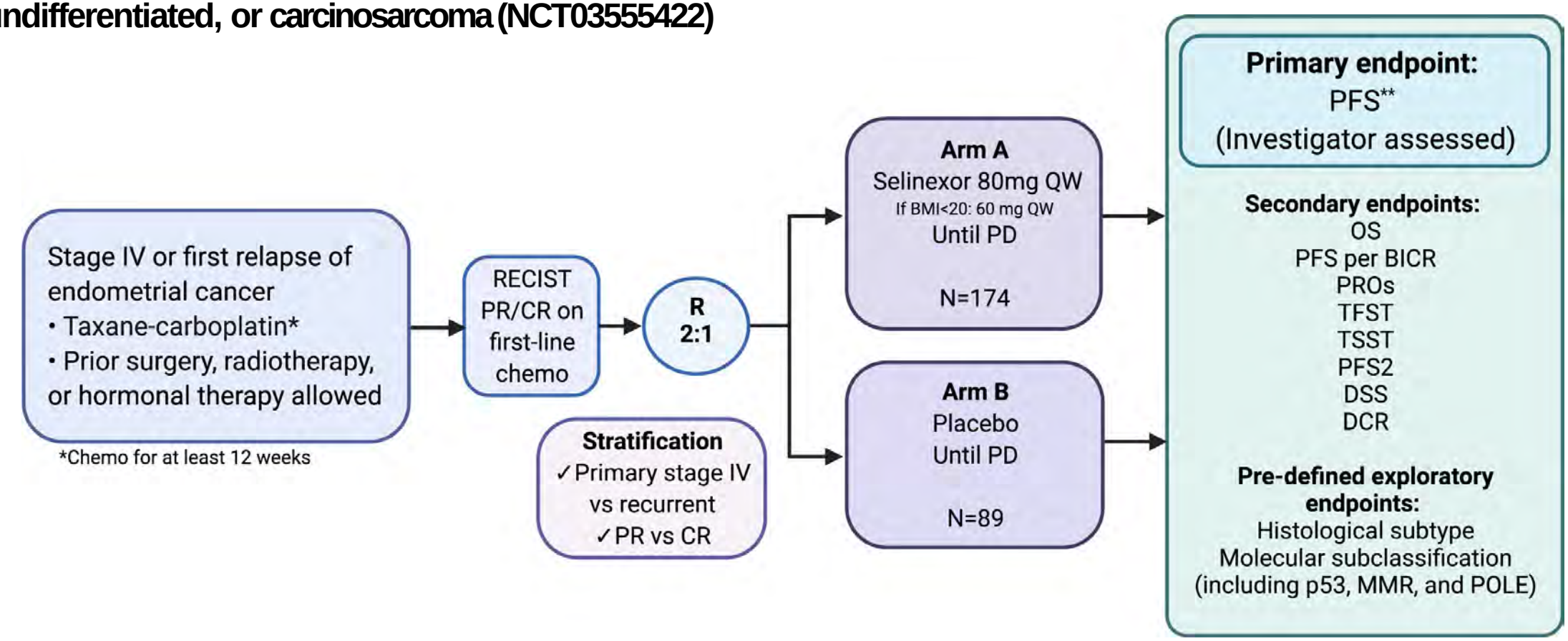
-Tumor by reactivating multiple TSPs by preventing nuclear export

-Reduction of oncoprotein levels

Selinexor is an oral selective **XPO1 inhibitor**

GOG-3055/ENGOT-EN5/SIENDO

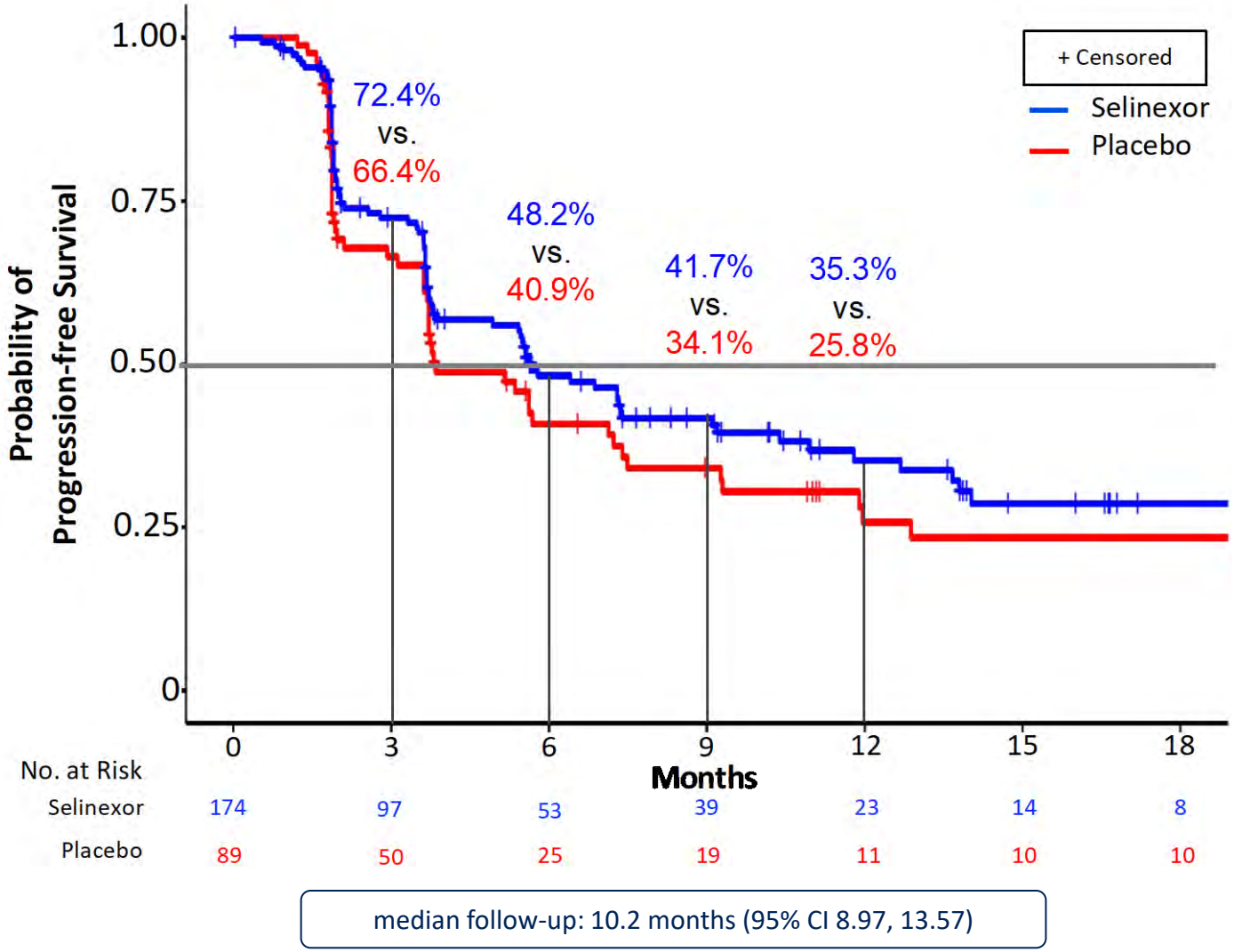
Stage IV or first relapse of endometrial cancer endometrioid, serous, undifferentiated, or carcinosarcoma (NCT03555422)



**140 events needed to provide 80% power to detect a hazard ratio of 0.6 (median 4.5 months for placebo and 7.5 months for selinexor) with a one-sided alpha of 0.025 and 2:1 randomization ratio favoring selinexor.

BMI, body mass index; DCR, disease control rate; DSS, disease-specific survival; QW, once weekly; CR, complete response; OS, overall survival; PFS, progression- free survival; PFS2, progression-free survival on subsequent therapy; PR, partial response; PROs, patient-reported outcomes ; R, randomized; TFST, time to first subsequent therapy; TSST, time to second subsequent treatment

Primary Endpoint: PFS in ITT Population



median follow-up: 10.2 months (95% CI 8.97, 13.57)

Median PFS

Selinexor (n=174): 5.7 mo (95% CI 3.81-9.20)

Placebo (n=89): 3.8 mo (95% CI 3.68-7.39)

Audited* (by electronic case report form)

HR = 0.705 (95% CI 0.499-0.996)

One-sided P value = 0.024

Unaudited* (by interactive response technology)

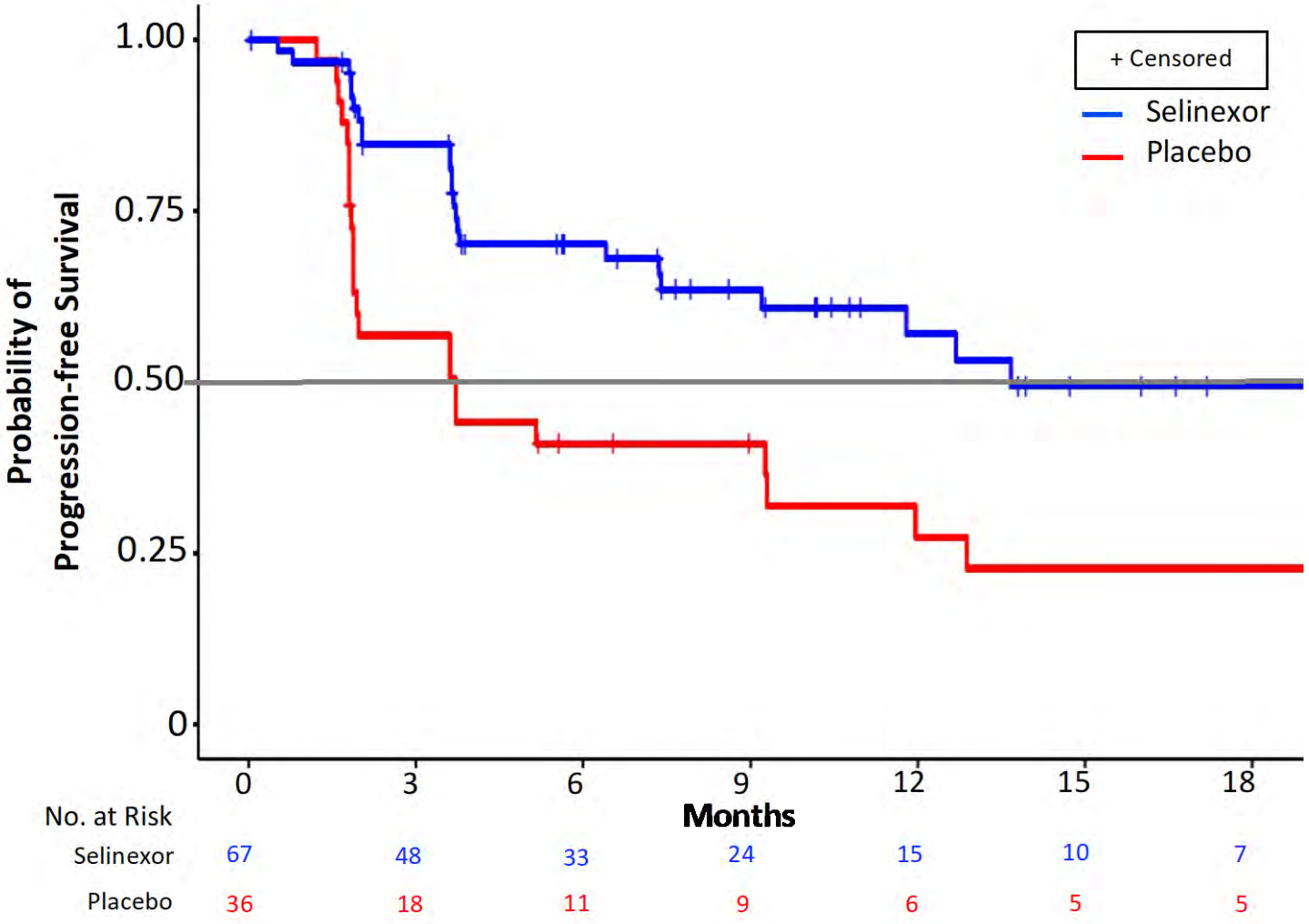
HR = 0.76 (95% CI 0.543-1.076)

One-sided P value = 0.063

*In 7 patients (2.7% of 263), the stratification factor of CR/PR was incorrect and was corrected by the Investigators prior to database lock and unblinding. The statistical analysis was validated by the independent ENGOT statistician and approved by the IDMC.

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

Preliminary Analysis of a Prespecified Exploratory Subgroup PFS: Patients with p53 wild-type EC



Median PFS

Selinexor (n=67): 13.7 mo (95% CI 9.20-NR)

Placebo (n=36): 3.7 mo (95% CI 1.87-12.88)

Audited

HR = 0.375 (95% CI 0.210-0.670)

Nominal one-sided P value = 0.0003

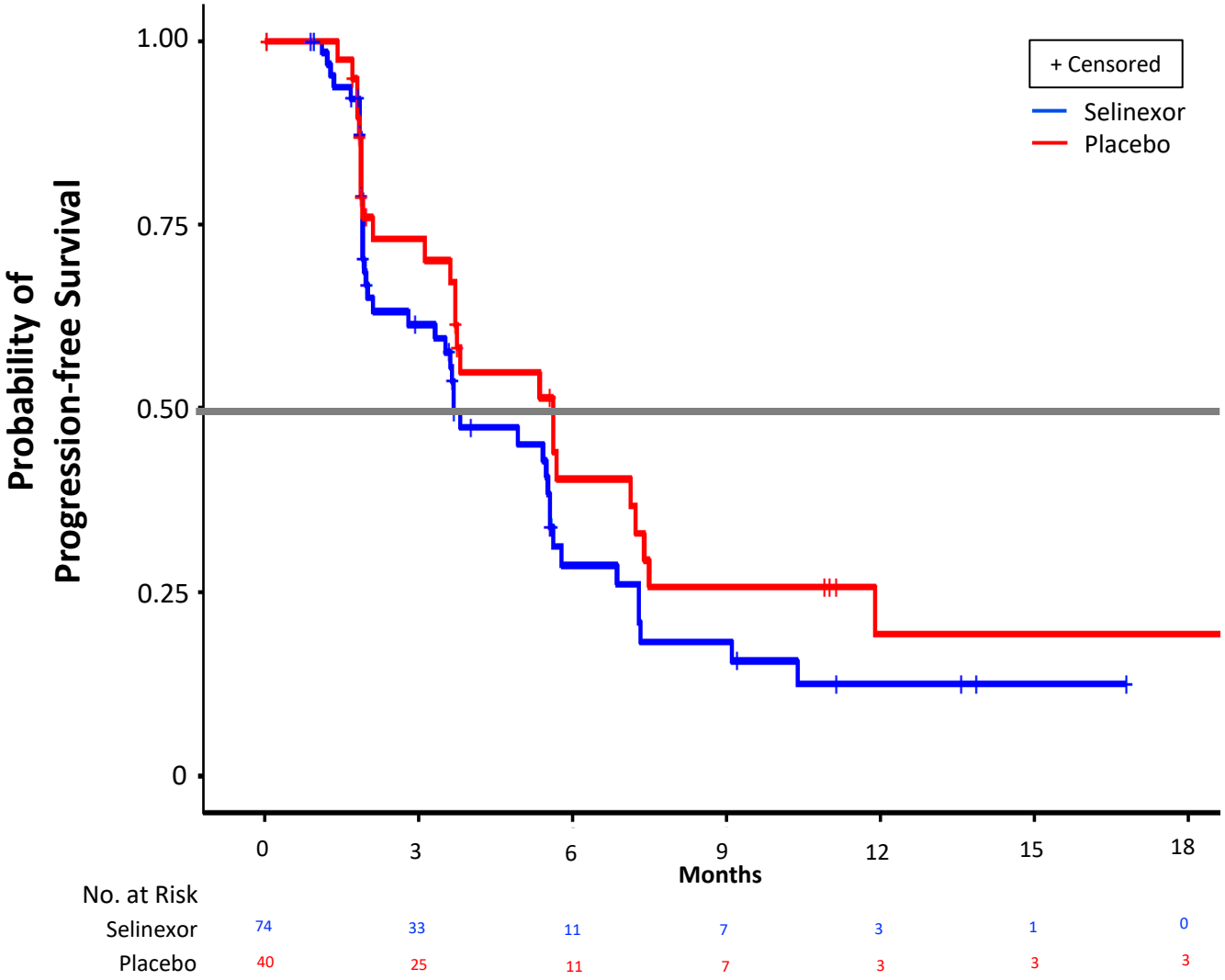
Unaudited

HR = 0.407 (95% CI 0.229-0.724)

Nominal one-sided P value = 0.0008

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

Preliminary Analysis of a Prespecified Exploratory Subgroup PFS: Patients with p53 Mutant/Aberrant EC



Median PFS

Selinexor (n=74): 3.7 mo (95% CI 3.32-5.55)

Placebo (n=40): 5.6 mo (95% CI 3.71-7.49)

Audited

HR = 1.306 (95% CI 0.795-2.145)

Nominal one-sided P value = 0.8530

Unaudited

HR = 1.345 (95% CI 0.819-2.208)

Nominal one-sided P value = 0.8785

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

SIENDO: Summary and Conclusions

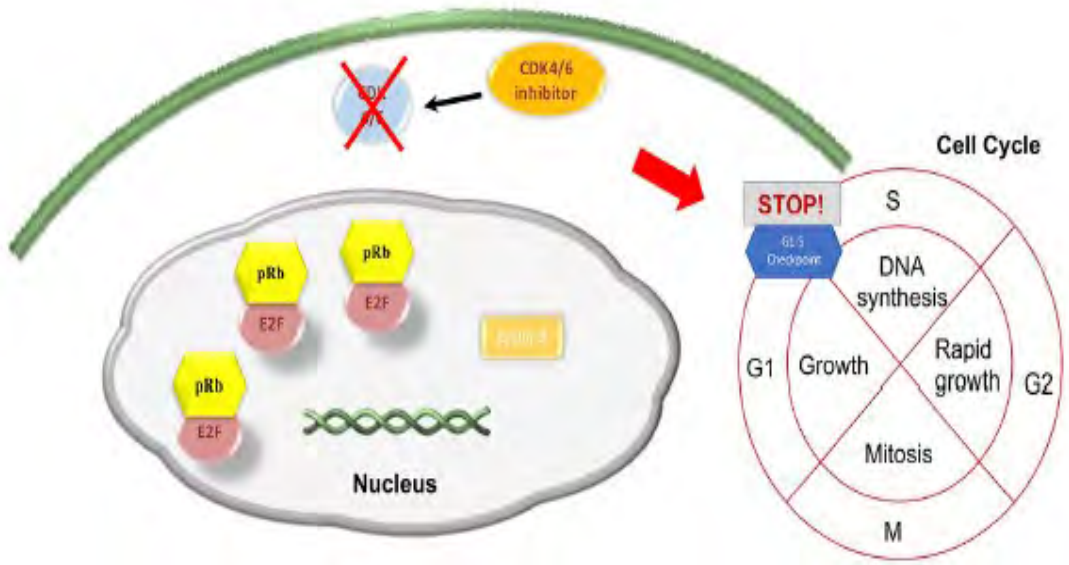
- Once-weekly oral selinexor may prolong progression-free survival compared to placebo in patients with advanced or recurrent endometrial cancer; the audited ITT population had a 30% decrease of risk for progression and/or death compared to placebo
- Pre-specified exploratory subgroup analyses identified p53 wild-type as a potential predictor of efficacy of selinexor, with 10-month PFS improvement over placebo; no benefit for selinexor was seen in patients with p53 mutant/aberrant tumors
- In this small, exploratory subgroup analysis, potential benefit may be observed for selinexor over placebo in the patients with p53 wild-type including MSS and Copy-Number Low endometrial cancer
- Further investigation is warranted for selinexor as a maintenance treatment for patients with p53 wt endometrial cancer

Future Direction: Selinexor

- Evaluate OS in Siendo
- Better understand role of p53 WT and mutant to predict response
- Siendo 2?

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.**



ENGOT-EN3/NSGO-PALEO Trial Design

Inclusion criteria:

- Measurable/evaluable endometrial cancer
- Primary stage 4 or relapsed disease
- ≥1 prior systemic therapy
- ER+ (≥10%) endometrioid adenocarcinoma
- ECOG PS 0/1
- No prior endocrine therapy except MPA and megestrol acetate
- No prior CDK inhibitor

Stratification:

- No. of prior lines (primary advanced disease vs 1st relapse vs ≥2 relapses)
- Measurable vs evaluable disease per RECIST
- Prior use of MPA/megestrol acetate

1:1 randomization

Placebo 125 mg days 1–21
Letrozole 2.5 mg days 1–28

Repeated every 28 days until progression

Palbociclib 125 mg days 1–21
Letrozole 2.5 mg days 1–28

Primary endpoint: Investigator-assessed PFS (target HR 0.625, 80% power, 15% 1-sided α)

Secondary endpoints:

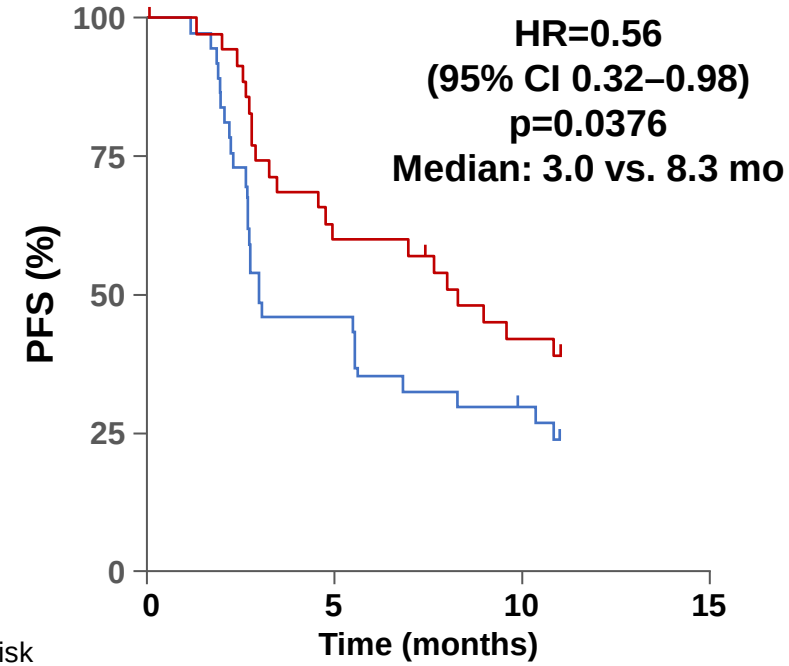
- PFS in subgroups
- Objective response rate, disease control rate, PFS2, overall survival
- PROs
- Safety and tolerability

CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HR, hazard ratio; MPA, medroxyprogesterone acetate; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status

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

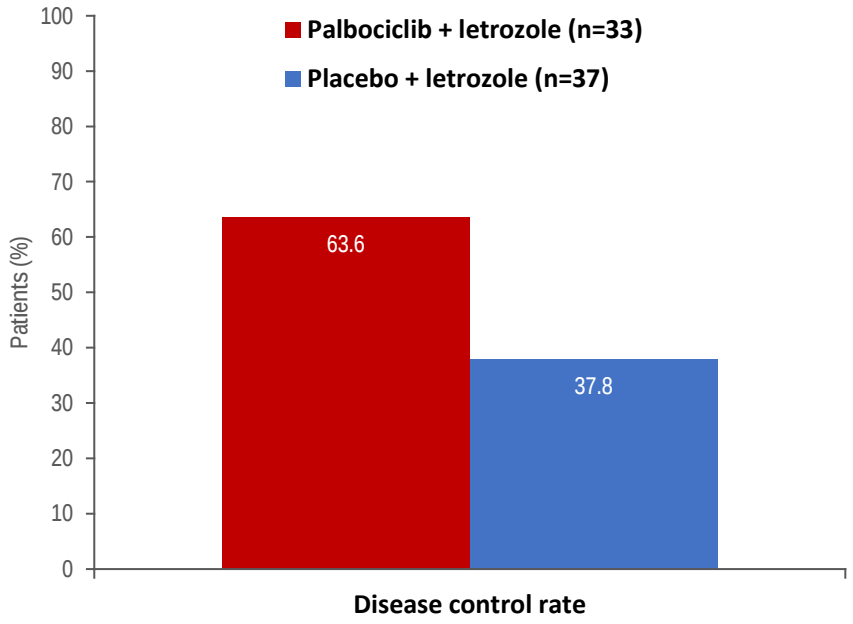
ENGOT-EN3/NSGO-PALEO: Efficacy (ITT population)

Primary endpoint: PFS



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

Secondary endpoint: Disease control rate*



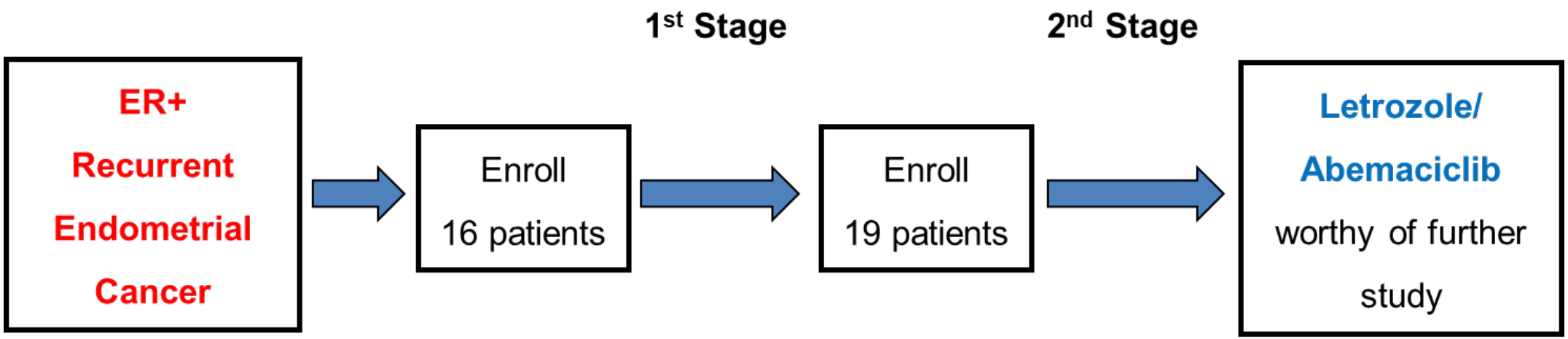
* = at 24 weeks

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

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

Phase 2, two-stage study of letrozole and abemaciclib in estrogen receptor (ER) positive recurrent or metastatic endometrial cancer (EC)

- **Regimen:** Letrozole 2.5mg PO daily and Abemaciclib 150 mg PO BID until progression or toxicity
- **H0: true ORR ≤ 5% AND PFS6 ≤ 10%** whereas **improvement to a 20% ORR or 30% PFS6 rate**



Panagiotis A. Konstantinopoulos et al, SGO 2022

Objective Response Rate

RESPONSE	Patients (N=30) n (%)
Best Overall Response	
Complete Response (CR)	0
Partial Response (PR)	**9 (30%)** **(1 unconfirmed,** **all PRs in endometrioid tumors)**
Stable Disease (SD)	13 (43.3%)
Progressive Disease (PD)	7 (23.3%)
Not evaluable	1 (3.3%)
ORR, % (95% CI)	**30% (14.7-49.4)**

Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice in patients with HER2-low unresectable and/or metastatic breast cancer: Results of DESTINY-Breast04, a randomized, phase 3 study

Shanu Modi Memorial Sloan Kettering Cancer Center, Memorial Hospital, New York, NY, USA

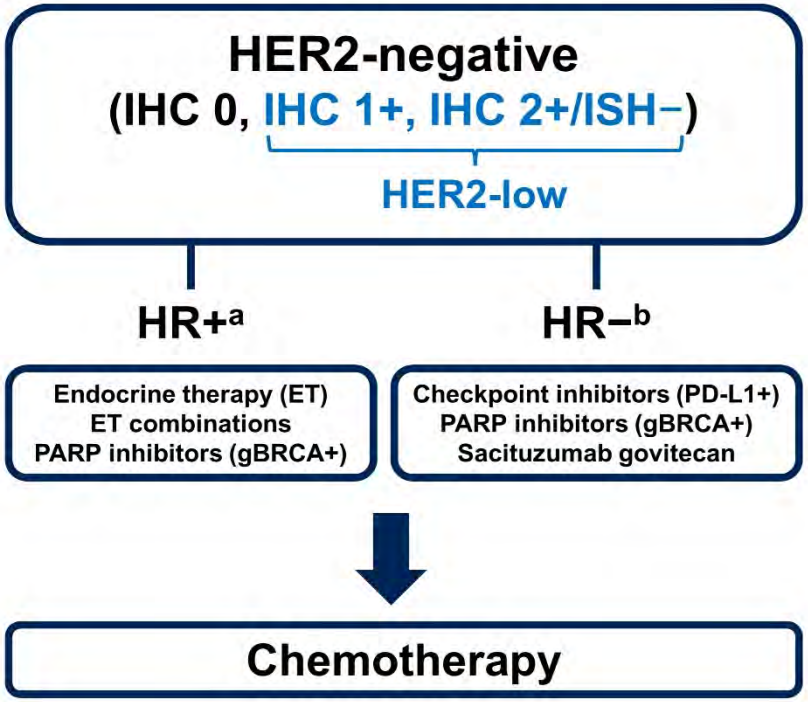
June 5, 2022

Additional authors: William Jacot, Toshinari Yamashita, Joo Hyuk Sohn, Maria Vidal, Eriko Tokunaga, Junji Tsurutani, Naoto Ueno, Yee Soo Chae, Keun Seok Lee, Naoki Niikura, Yeon Hee Park, Xiaojia Wang, Binghe Xu, Dhiraj Gambhire, Lotus Yung, Gerold Meinhardt, Yibin Wang, Nadia Harbeck, David Cameron

On behalf of the DESTINY-Breast04 investigators

HER2-low mBC: Unmet Clinical Need

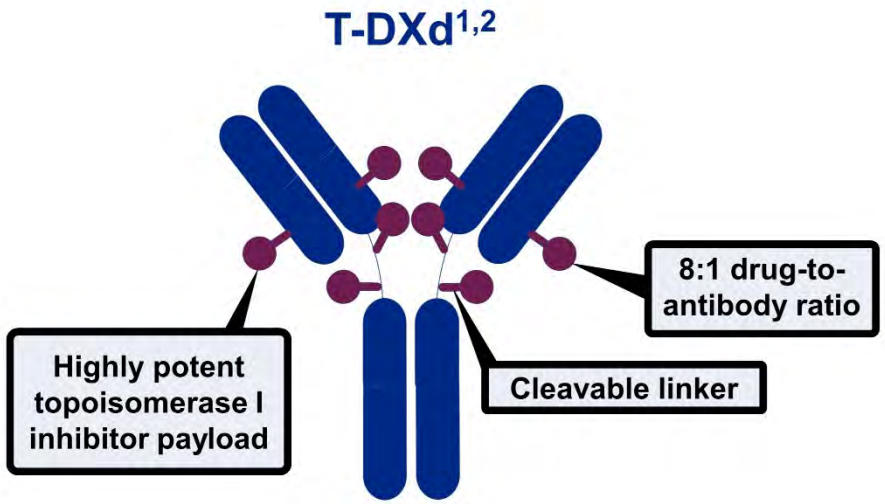
Current Standard of Care



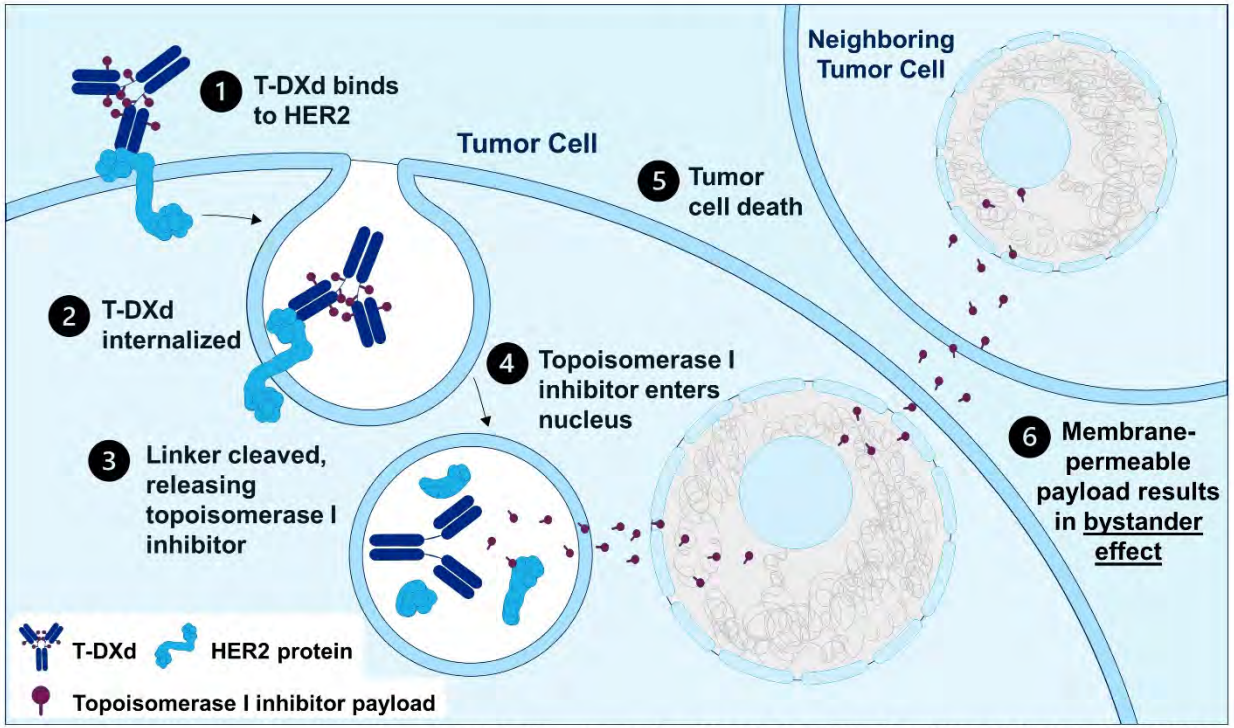
- **HER2-low mBC is defined by IHC scores of 1+ or 2+/ISH−**
  - This is a heterogenous population with a high prevalence of HR coexpression and without a distinct biology
- **HER2-low mBC is treated as HER2− mBC, with limited options for later lines of therapy[1-4]**
  - Current HER2-targeted therapies are not effective for patients with tumors that express lower levels of HER2
- **Therapeutic options for patients with HR+/HER2− mBC after CDK4/6i progression have limited efficacy**
  - Real-world studies suggest a PFS of <4 months after progressive disease with CDK4/6i[5]
- **Limited benefit exists for patients who progress after multiple lines of chemotherapy**
  - In a pooled analysis of patients with HER2− mBC, eribulin and capecitabine provide minimal benefit, with a mPFS of ~4 months and mOS of ~15 months[6]

CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; gBRCA+, germline breast cancer gene positive; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; mOS, median overall survival; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death ligand 1; mPFS, median progression-free survival; T-DXd, trastuzumab deruxtecan.
[a]Immunoreactive for estrogen or progesterone receptor in ≥1% tumor cell nuclei. [b]Immunoreactive for estrogen or progesterone receptor in <1% tumor cell nuclei.
1. Tarantino P, et al. *J Clin Oncol.* 2020;38(17):1951-1962. 2. Aogi K, et al. *Ann Oncol.* 2012;23:1441-1448. 3. Eiger D, et al. *Cancers (Basel).* 2021;13(5):1015. 4. Fehrenbacher L, et al. *J Clin Oncol.* 2019;38(5):444-453. 5. Mo H, et al. *Clin Breast Cancer.* 2022;22:143-148. 6. Kaufman PA, et al. *J Clin Oncol.* 2015;33:594-601.

T-DXd MOA, Bystander Effect, and Rationale for Targeting HER2-low mBC



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]



Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

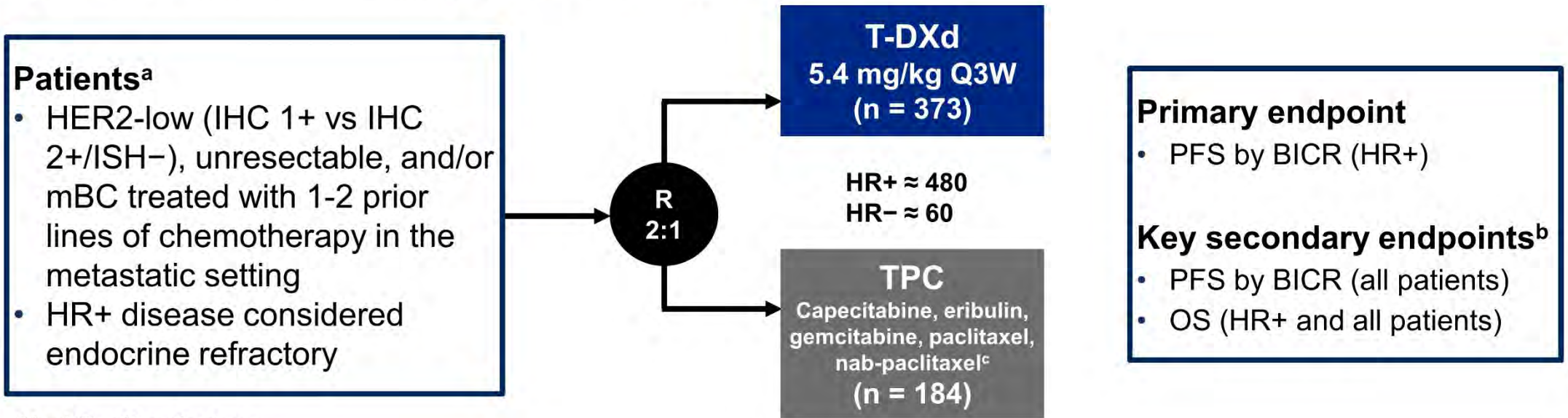
- **Results from a phase 1b study have reported efficacy of T-DXd in heavily pretreated patients (N = 54) with HER2-low mBC, with a mPFS of 11.1 months and an ORR of 37.0%[3]**

HER2, human epidermal growth factor receptor 2; MOA, mechanism of action; mBC, metastatic breast cancer; mPFS, median progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

1. Nakada T, et al. *Chem Pharm Bull*. 2019;67:173-185. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22:5097-5108. 3. Modi S, et al. *J Clin Oncol.* 2020;38:1887-1896.

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)



Stratification factors

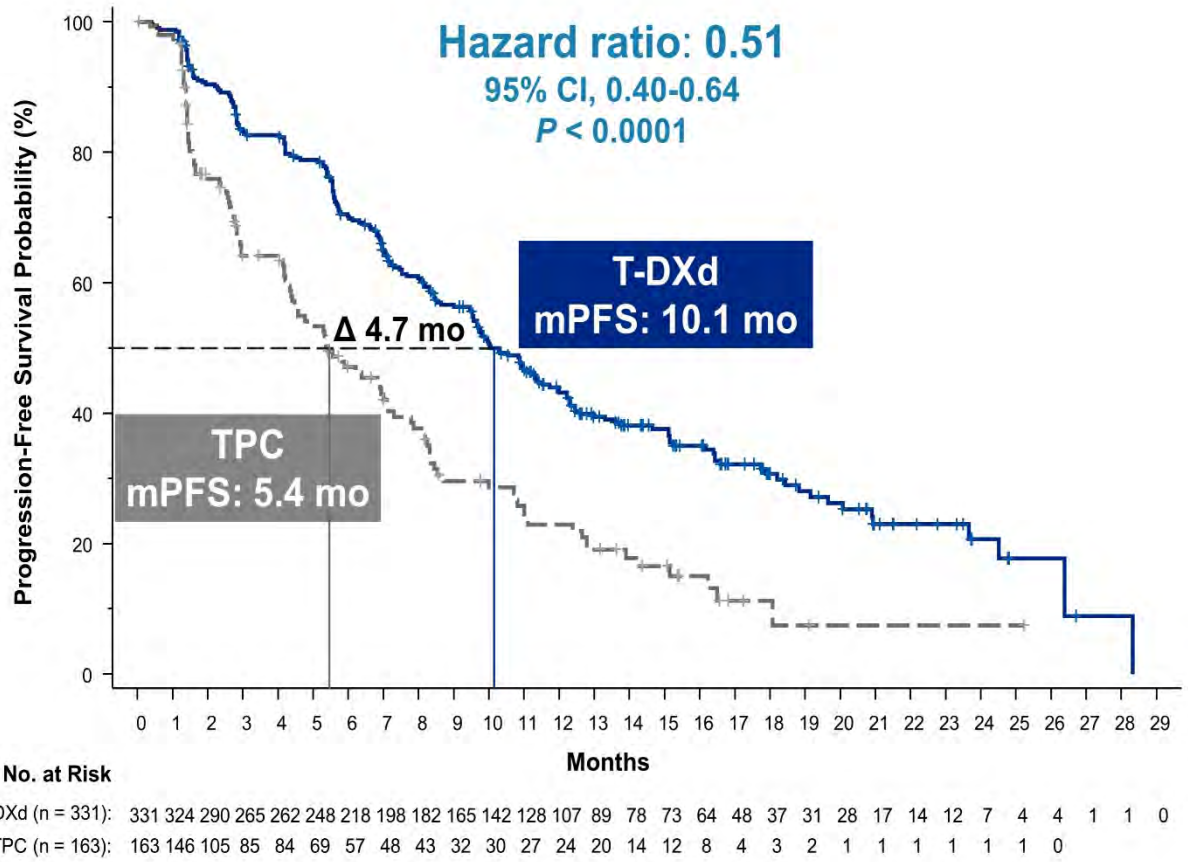
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

PFS in HR+ and All Patients

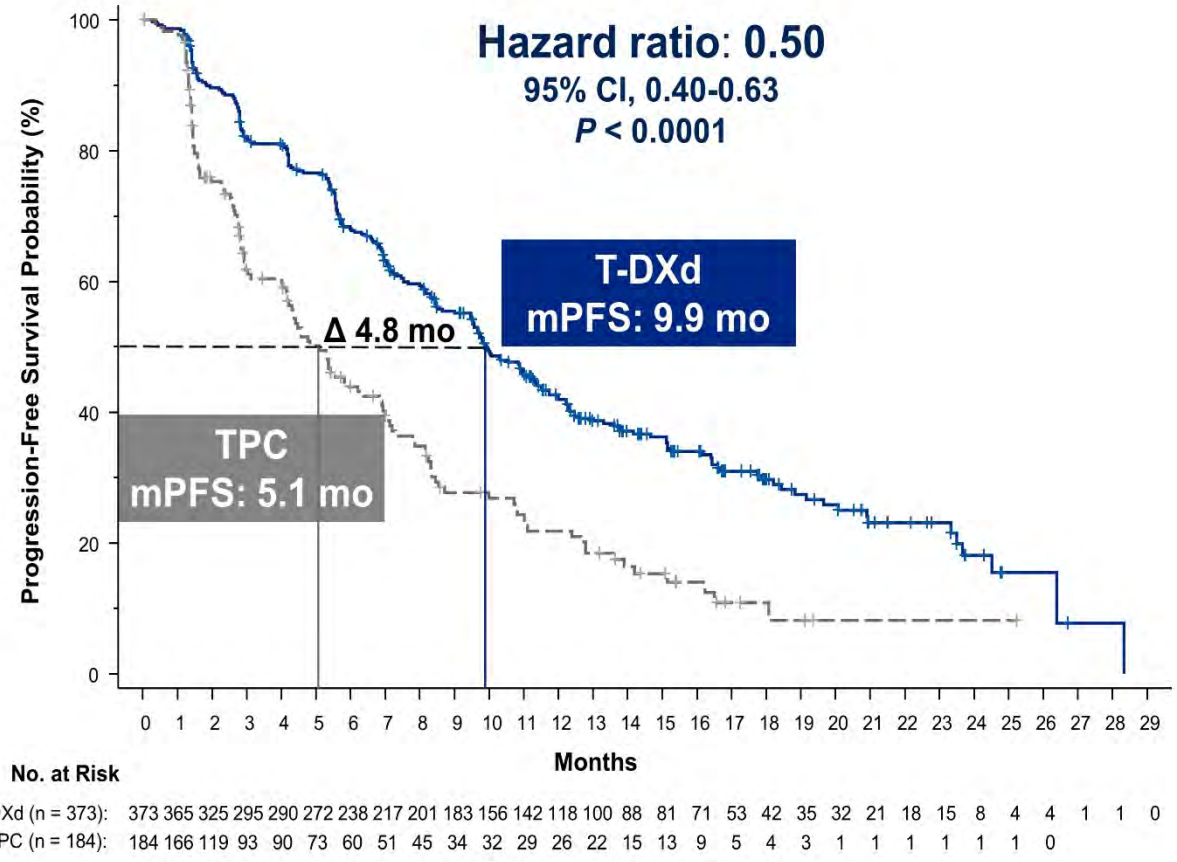
Hormone receptor–positive



No. at Risk

T-DXd (n = 331):	331	324	290	265	262	248	218	198	182	165	142	128	107	89	78	73	64	48	37	31	28	17	14	12	7	4	4	1	1	0
TPC (n = 163):	163	146	105	85	84	69	57	48	43	32	30	27	24	20	14	12	8	4	3	2	1	1	1	1	1	1	0			

All patients



No. at Risk

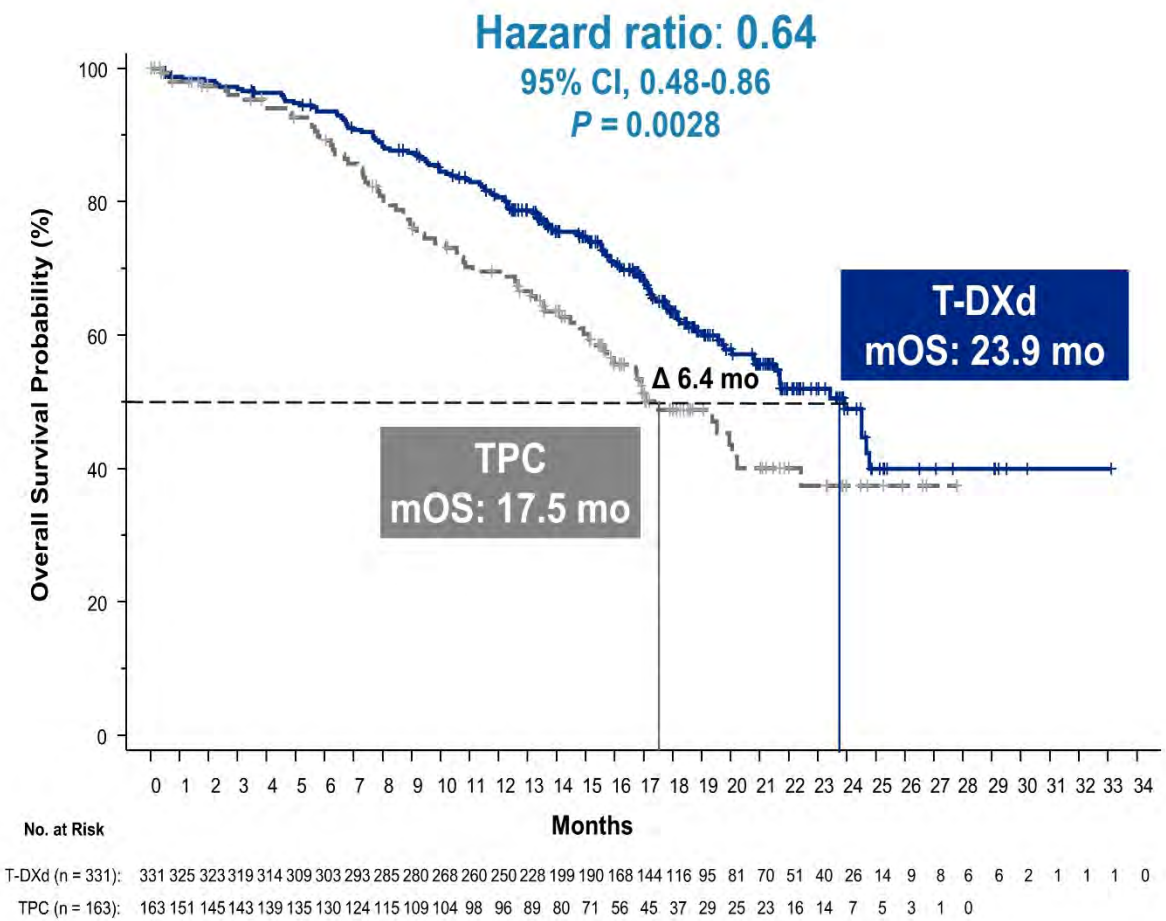
T-DXd (n = 373):	373	365	325	295	290	272	238	217	201	183	156	142	118	100	88	81	71	53	42	35	32	21	18	15	8	4	4	1	1	0
TPC (n = 184):	184	166	119	93	90	73	60	51	45	34	32	29	26	22	15	13	9	5	4	3	1	1	1	1	1	1	0			

PFS by blinded independent central review.

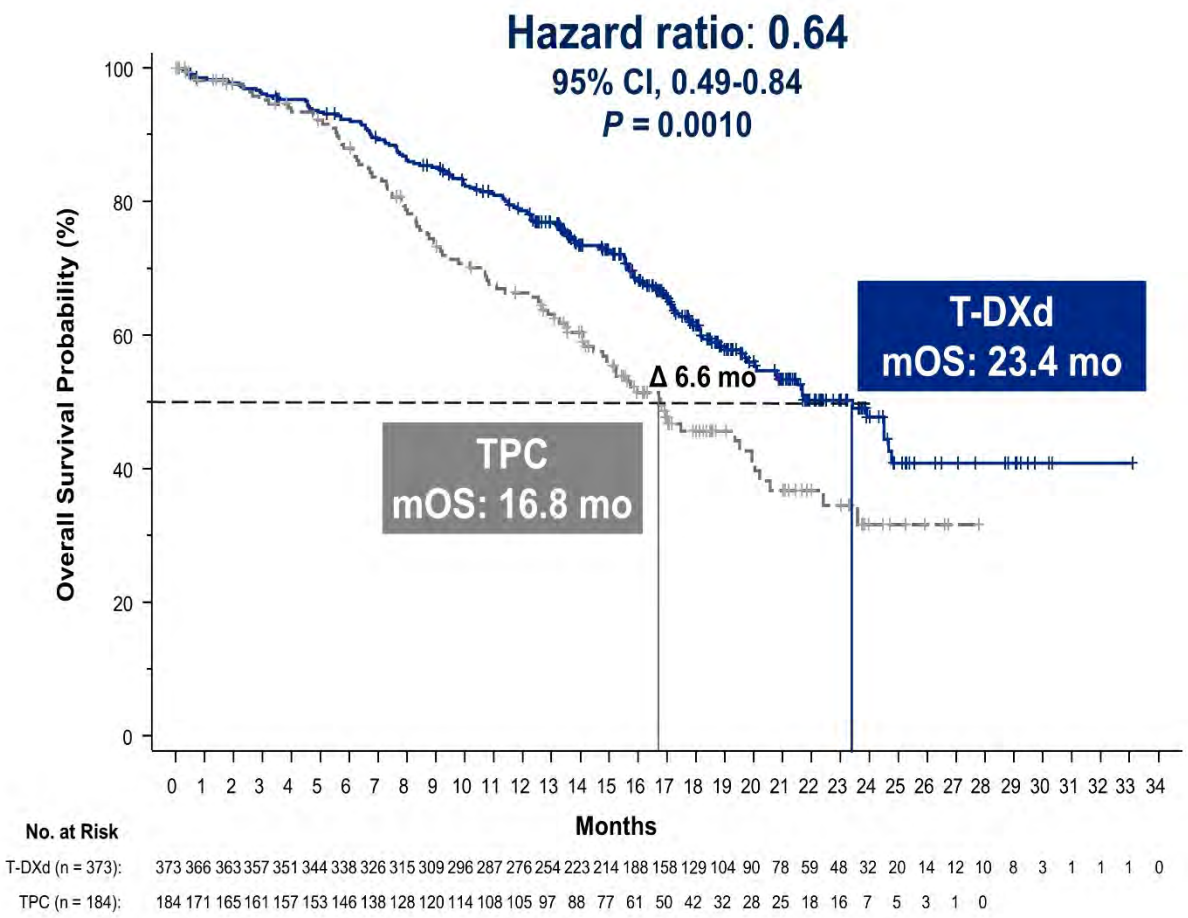
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS in HR+ and All Patients

Hormone receptor–positive



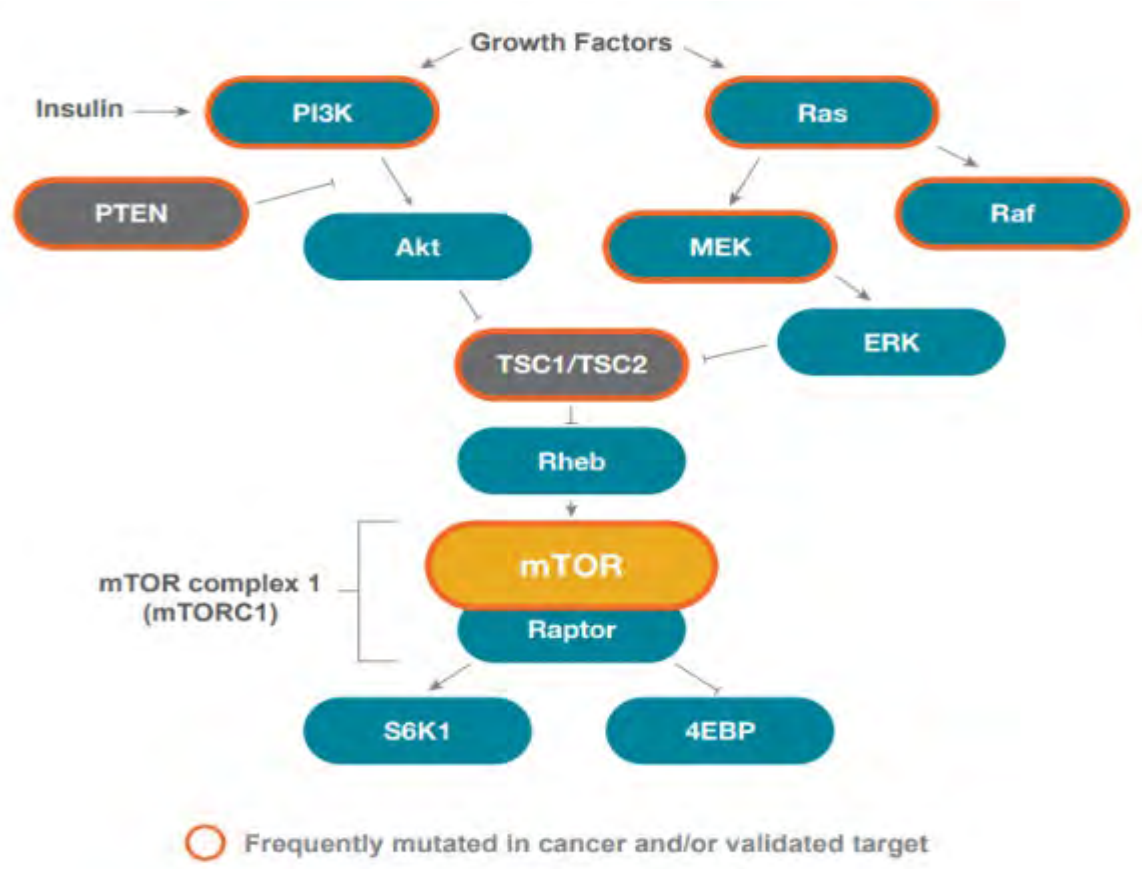
All patients



HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

The mTOR Pathway Integrates Environmental Signals to Regulate Cellular Growth and Homeostasis

- The mTOR signaling pathway **coordinates cell growth and metabolism with environmental cues** such as growth factors and nutrients
- mTOR activation ultimately regulates cell growth through the **phosphorylation of p70S6 kinase 1 (S6K1) and eIF4E binding protein (4EBP)** and cell proliferation



4EBP, eIF4E binding protein; Akt, protein kinase B; eIF4E, eukaryotic translation initiation factor 4E; ERK, extracellular signal-regulated kinases; MEK, mitogen-activated protein kinase kinase; mTOR, mechanistic target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; Raf, rapidly accelerated fibrosarcoma protein; Raptor, regulatory-associated protein of mTOR; Ras, rat sarcoma virus homolog; Rheb, Ras homolog enriched in brain; S6K, p70S6 kinase; *TSC1/2*, tuberous sclerosis complex subunit 1/2.

Saxton RA, et al. *Cell*. 2017;169(2):361-371.

GOG 3007: Results

Regimen	N	Objective Response	Objective Response - NPC	CBR	CBR-NPC	PFS	OS
Everolimus/ Letrozole	37	22%, (95%CI, 11% to 37%)	53%	78%	87%	6 mos (95% CI, 4-18)	31 mos(95% CI 14-40)
MPA/ Tamoxifen	37	25%, (95%CI, 14% to 41%)	43%	69%	86%	4 mos (95% CI, 3-6)	17 Mos (95% CI 9-289)

Median follow-up: 37 mos

CBR, clinical benefit response; MPA, medroxyprogesterone acetate; NPC, no prior chemotherapy; OS, overall survival; PFS, progression-free survival

Slomovitz BM et al. *Gynecol Oncol*. March 2022.

GOG 3007: Outcomes in Patients Who Did Not Receive Prior Chemotherapy

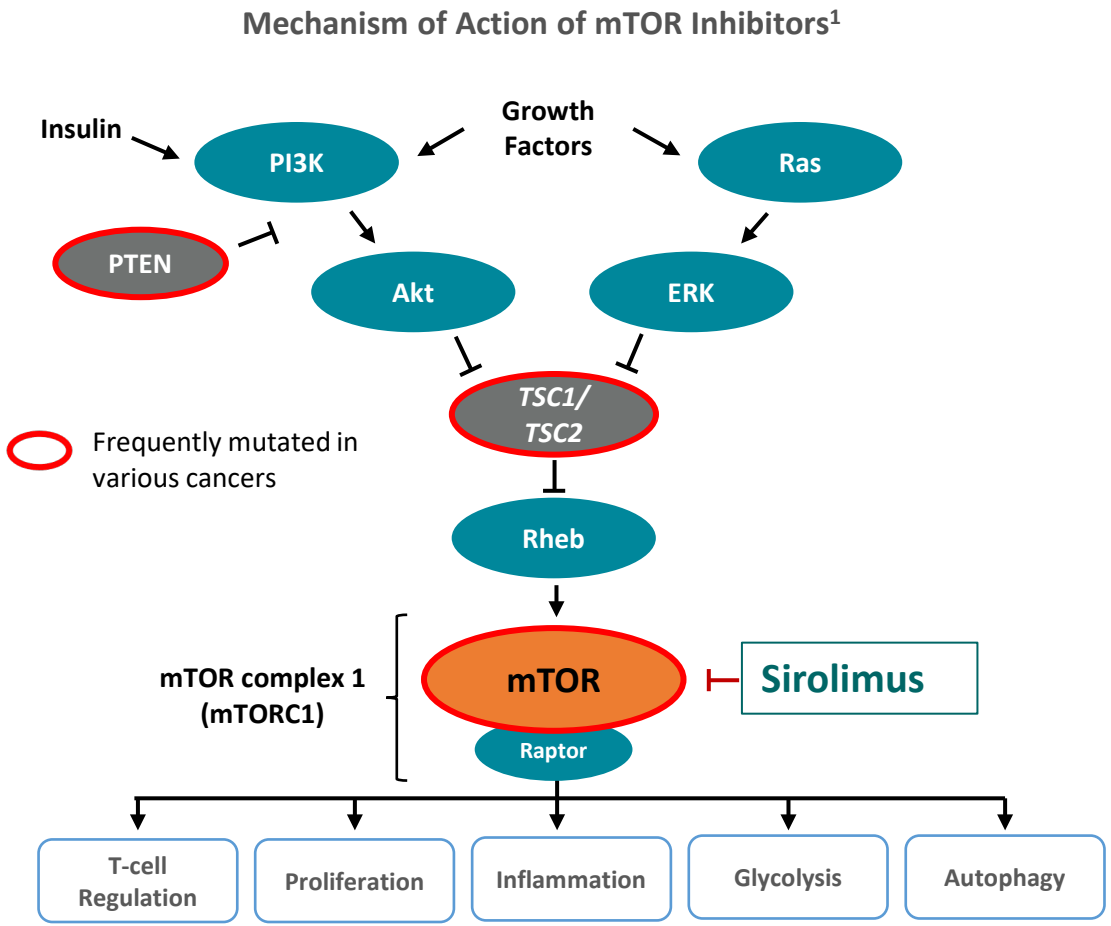
Regimen	RR	PFS
Everolimus/letrozole	47%	28 months
Tamoxifen/MPA	43%	6.1 months
Carboplatin/paclitaxel (GOG 209)	51%	14 months

MPA, medroxyprogesterone acetate; PFS, progression-free survival; RR, response rate

Slomovitz BM et al. *Gynecol Oncol*. March 2022

nab-Sirolimus Mechanism of Action

- **mTOR pathway activation is prevalent in PEComas[1]**
  - mTOR pathway controls cell proliferation, division, and numerous metabolic pathways
  - Mutations of mTOR inhibitory genes (eg, *PTEN*, *TSC1*, and *TSC2*) can lead to their inactivation, which triggers mTORC1 formation and uncontrolled cell division[2]
  - mTOR inhibitors bind to mTORC1 and halt cancer cell proliferation and division[1]
- **mTOR inhibitors such as sirolimus have shown clinical benefit in malignant PEComa[3-5]**
  - However, currently available mTOR inhibitors are limited by poor solubility, low bioavailability, and incomplete target inhibition[6]
- Nanoparticle albumin-bound (*nab*) technology enhances bioavailability and tumor targeting of chemotherapeutic agents (eg, paclitaxel, sirolimus)[7]
- ***nab* technology complexes sirolimus to human albumin, leveraging natural albumin-based transport mechanisms to enhance intra-tumoral drug accumulation[7-8]**
- *nab* platform improves drug bioavailability, tumor targeting, and efficacy[7-8]



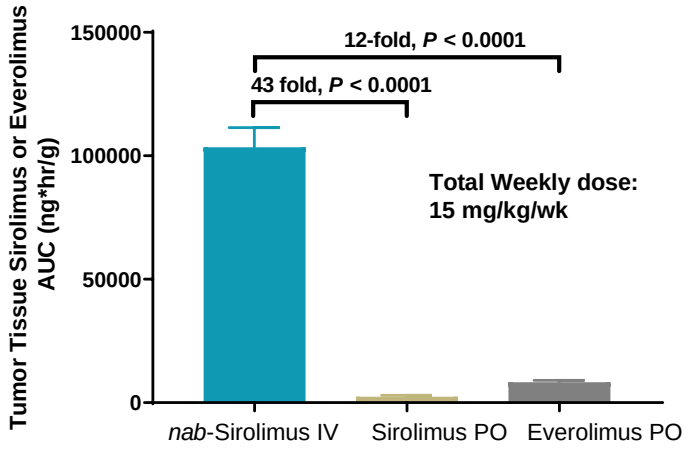
Akt, protein kinase B; ERK, extracellular signal-regulated kinases; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; *nab*, nanoparticle albumin-bound; PEComa, perivascular epithelioid cell tumor; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; Raptor, regulatory-associated protein of mTOR; Ras, rat sarcoma virus homolog; Rheb, Ras homolog enriched in brain; *TSC1/2,* tuberous sclerosis complex subunit1/2.

1. Akumalla S et al. Oncology. 2020;98(12):905-912. 2. Bleeker JS, et al. Sarcoma. 2012;2012:541626. 3. Benson C et al. Anticancer Res. 2014;34(7):3663-3668. 4. Dickson MA et al. Int J Cancer. 2013;132(7):1711-1717. 5. Italiano A et al. Ann Oncol. 2010;21(5):1135-1137. 6. Hou S et al. Cancer Res. 2019;79(13 Suppl):Abstract nr 348. 7. Desai N et al, Clin Cancer Res. 2006;12(4):1317-1324. 8. Shahzad Y et al, Curr Cancer Drug Targets. 2014;14(8):752-63.

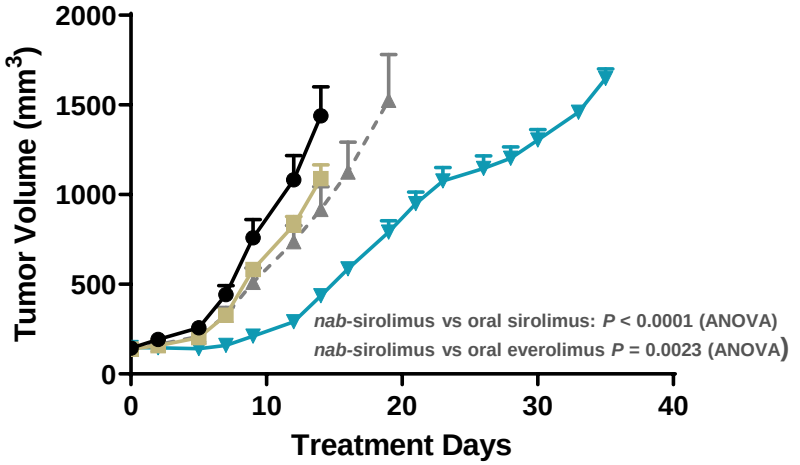
nab-sirolimus Combines Sirolimus with *nab* Technology

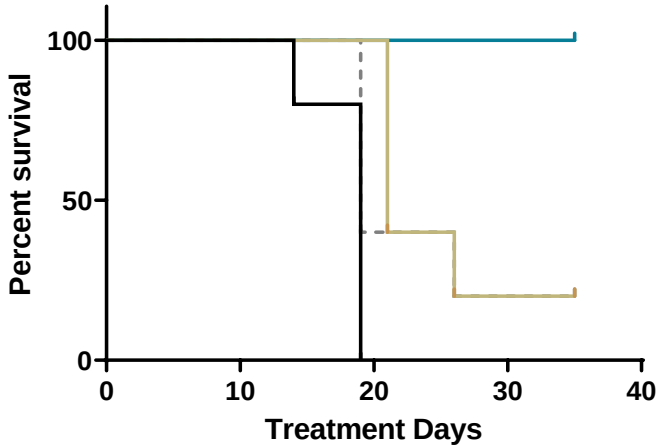
- *nab* technology is a proprietary method of binding therapies to albumin
  - achieves better tumor targeting and uptake than solvent-based treatment in preclinical models[1,2-4]
  - may translate to better efficacy and safety in clinical studies[2-4]
- *nab*-sirolimus adapts the *nab* process for sirolimus to enhance anti-tumor activity compared with currently approved mTOR inhibitors and is currently FDA approved for adult patients with advanced malignant PEComa[1]

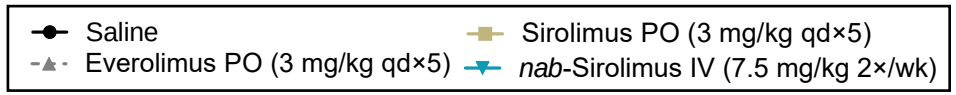
Significantly Higher Tissue Drug Accumulation with *nab*-Sirolimus[1]



Stronger Inhibition of Tumor Growth and Longer Survival in Animals with *nab*-Sirolimus[1]







ANOVA, analysis of variance; IV, intravenous; *nab*, nanoparticle albumin-bound; NSCLC, non-small cell lung cancer; PEComa, perivascular epithelioid cell tumor; PO, by mouth; qd, once daily; wk, week.

1. Hou S et al. *Cancer Res*. 2019;79(13 Suppl):Abstract nr 348. 2. ABRAXANE prescribing information. 3. Desai N et al, *Clin Cancer Res*. 2006;12(4):1317-1324. 4. Gradishar WJ, et al. *J Clin Oncol*. 2005;23(31):7794-7803.

AMPECT: Best Response, Duration of Response by Independent Review

	N = 31*
Confirmed Overall Response Rate	**39%** (12/13, 95% CI: 22, 58)
CR	**7%** (2/31)
PR	**32%** (10/31)
SD	52%
Progressive Disease	10%
Disease Control Rate (CR, PR, SD ≥12 weeks)	71%
Median DOR (n=12 responders)†	Not Reached
Range: min–max, months	5.6–55.5+
DOR rate at 6 months	92%
DOR rate at 12 months	75%
DOR rate at 24 months	66%
DOR rate at 36 months	66%

Total may exceed 100% due to rounding.

- 2 patients converted from a PR to CR after 11 months and 34 months of treatment, respectively
- Median DOR has not been reached; 50% of patients had a DOR of 36.1+ months (range, 5.6–55.5+ months)

*3/34 treated patients were not evaluable: 2 patients confirmed as "not PEComa" (misdiagnosis), 1 pt had no tissue for central confirmation of PEComa. †DOR median and rates are based on KM estimates; "+" indicates ongoing value.
CI, confidence interval; CR, complete response; DOR, duration of response; KM, Kaplan-Meier; max, maximum; min, minimum; PEComa, perivascular epithelioid cell tumor; PR, partial response; SD, stable disease.
Wagner et al. Connective Tissue Oncology Society Annual Meeting. 2021; Abstract 1080747.

Future Direction: Biomarker directed

- CDK 4/6
- Her 2
- mTOR

ORIGINAL ARTICLE FREE PREVIEW

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

Andrea Cercek, M.D., Melissa Lumish, M.D., Jenna Sinopoli, N.P., Jill Weiss, B.A., Jinru Shia, M.D., Michelle Lamendola-Essel, D.H.Sc., Imane H. El Dika, M.D., Neil Segal, M.D., Marina Shcherba, M.D., Ryan Sugarman, M.D., Ph.D., Zsofia Stadler, M.D., Rona Yaeger, M.D., et al.

June 5, 2022

RESULTS A total of 12 patients have completed treatment with dostarlimab and have undergone at least 6 months of follow-up. All 12 patients (100%; 95% confidence interval, 74 to 100) had a clinical complete response, with no evidence of tumor on magnetic resonance imaging, ^{18}F-fluorodeoxyglucose–positron-emission tomography, endoscopic evaluation, digital rectal examination, or biopsy. At the time of this report, no patients had received chemoradiotherapy or undergone surgery, and no cases of progression or recurrence had been reported during follow-up (range, 6 to 25 months). No adverse events of grade 3 or higher have been reported.

2022 ASCO® ANNUAL MEETING

Dostarlimab in Advanced/Recurrent Mismatch Repair Deficient/Microsatellite Instability–High or Proficient/Stable Endometrial Cancer: the GARNET study

Ana Oaknin,[1] Bhavana Pothuri,[2] Lucy Gilbert,[3] Renaud Sabatier,[4] Sharad Ghamande,[5] Adriano Gravina,[6] Emiliano Calvo,[7] Susana Banerjee,[8] Rowan E. Miller,[9] Joanna Pikiel,[10] Mansoor R. Mirza,[11] Tao Duan,[12] Sybil Zildjian,[13] Eleftherios Zografos,[14] Jennifer Veneris,[13] Anna V. Tinker[15]

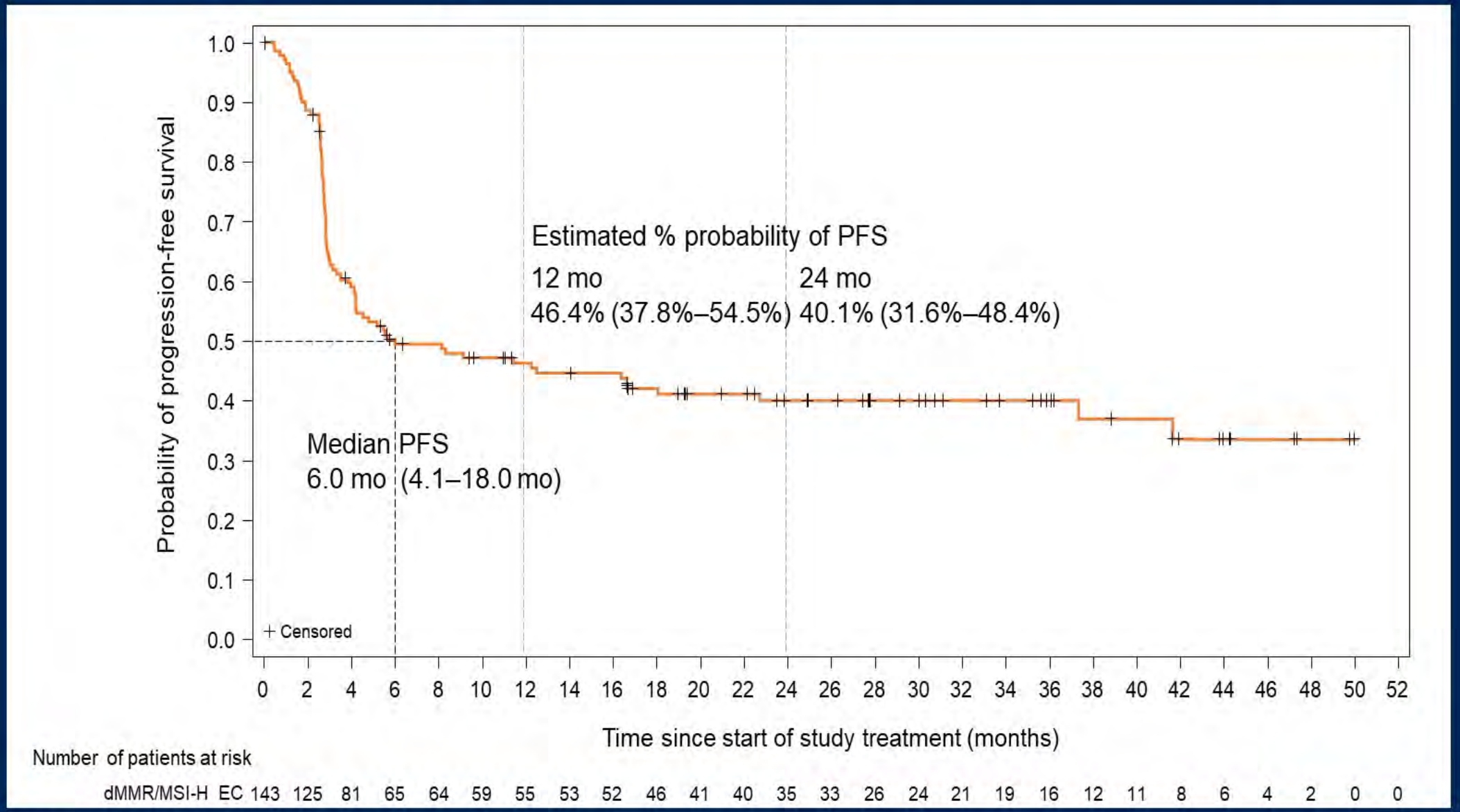
[1]Gynaecologic Cancer Programme, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [2]Gynecologic Oncology Group (GOG) and Department of Obstetrics/Gynecology, Laura & Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; [3]Division of Gynecologic Oncology, McGill University Health Centre, Montreal, Quebec, Canada; [4]Department of Medical Oncology, Institut Paoli Calmettes, Aix-Marseille University, Marseille, France; [5]Department of Obstetrics & Gynecology, Georgia Cancer Center, Augusta University, Augusta, GA, USA; [6]Clinical Trial Unit, Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy; [7]START Madrid–CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; [8]Gynaecology Unit, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK; [9]University College London, St. Bartholomew's Hospitals London, London, UK; [10]Department of Chemotherapy, Regional Center of Oncology, Gdansk, Poland; [11]Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Denmark, Nordic Society of Gynaecologic Oncology–Clinical Trial Unit, Copenhagen, Denmark; [12]GlaxoSmithKline, Pennington, NJ, USA; [13]GlaxoSmithKline, Waltham, MA, USA; [14]GlaxoSmithKline, London, UK; [15]Department of Medicine, British Columbia Cancer, Vancouver Centre, University of British Columbia, Vancouver, British Columbia, Canada

Primary Endpoint Analysis

	dMMR/MSI-H EC N=143	MMRp/MSS EC N=156
Median follow-up time, months	**27.6**	**33.0**
ORR, % (95% CI; n/N)	**45.5%** (37.1–54.0; 65/143)	**15.4%** (10.1–22.0; 24/156)
Complete response, n (%)	**23** (16.1)	**4** (2.6)
Partial response, n (%)	**42** (29.4)	**20** (12.8)
Stable disease, n (%)	21 (14.7)	29 (18.6)
Progressive disease, n (%)	51 (35.7)	88 (56.4)
Not evaluable, n (%)	6 (4.2)	15 (9.6)
Median time from cycle 1 day 1 to best overall response, mo		
Complete response	2.79	2.81
Partial response	2.69	2.79
Disease control rate, % (95% CI; n/N)	60.1% (51.6–68.2; 86/143)	34.0% (26.6–42.0; 53/156)
Response ongoing, n (%)	54 (83.1)	9 (37.5)
Median duration of response (range), months	**NR** (1.18+ to 47.21+)	**19.4** (2.8 to 47.18+)
Probability of maintaining response, %		
6 months	96.8	82.6
12 months	93.3	60.3
24 months	83.7	44.2

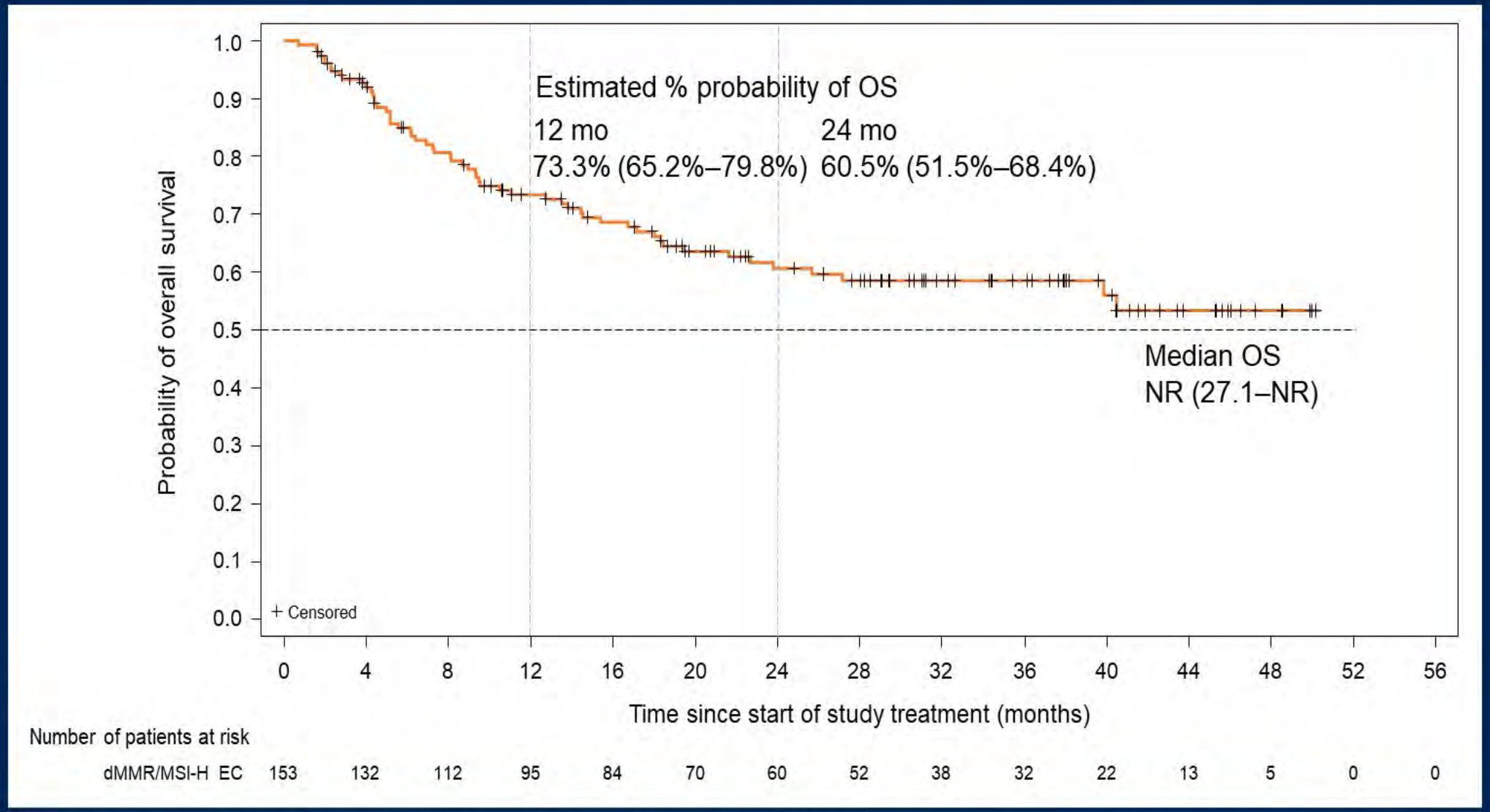
dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; MSI-H, microsatellite instability–high; MSS, microsatellite stable; NR, not reached; ORR, objective response rate.

Probability of Progression-Free Survival: dMMR/MSI-H



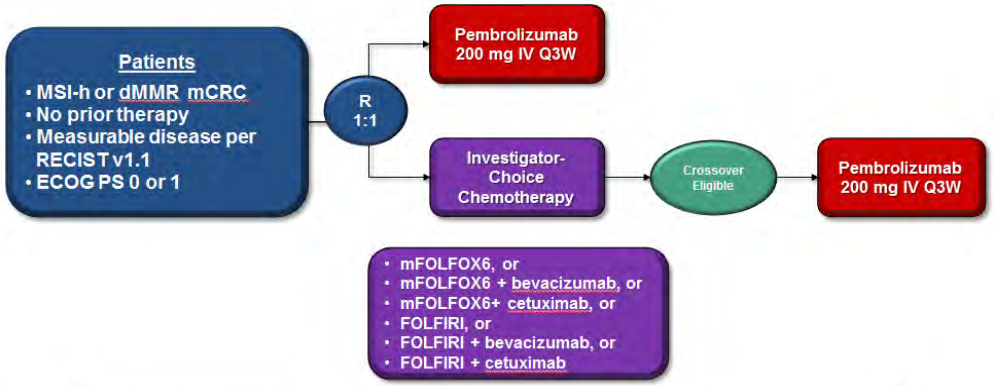
dMMR, mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability–high; PFS, progression-free survival.

Probability of Overall Survival: dMMR/MSI-H



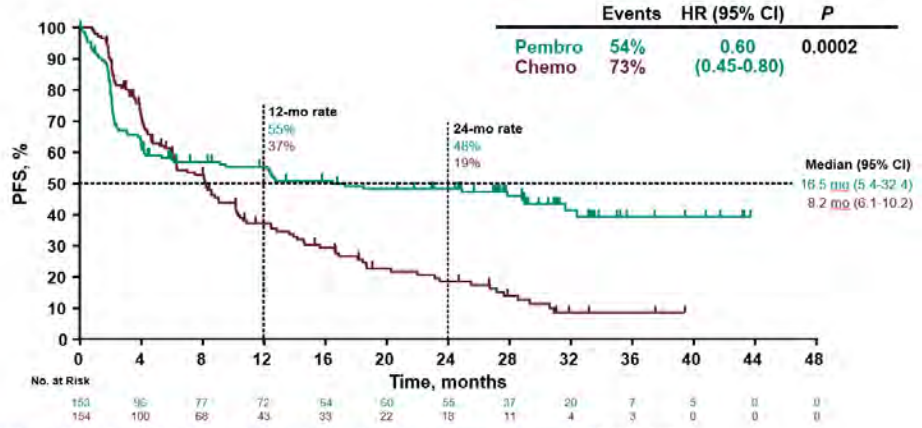
dMMR, mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability–high; NR, not reached; OS, overall survival.

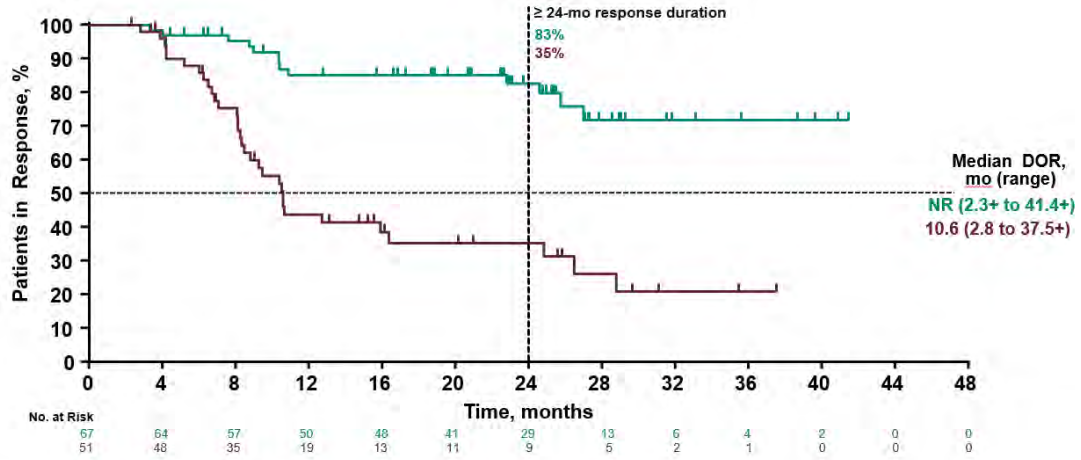
KEYNOTE-177: Robust Activity of Pembro Monotx Compared to SOC in Stage IV MSI-H/dMMR CRC



	Pembrolizumab N = 153	Chemotherapy N = 154
ORR, n (%)	**67 (43.8)**	**51 (33.1)**
Difference, estimate (95% CI)	10.7 (-0.2-21.3)	
P-value	0.0275	
Best Overall Response, n (%)		
Complete response	17 (11.1)	6 (3.9)
Partial response	50 (32.7)	45 (29.2)
Stable disease	32 (20.9)	65 (42.2)
Disease control rate (CR+PR+SD)	99 (64.7)	116 (75.3)
Progressive disease	45 (29.4)	19 (12.3)
Not evaluable	3 (2.0)	2 (1.3)
No assessment	6 (3.9)	17 (11.0)
Median time to response (range), mo	2.2 (1.8-18.8)	2.1 (1.7-24.9)

t-off: 19Feb2020; Response assessed per RECIST v1.1 by BICR.

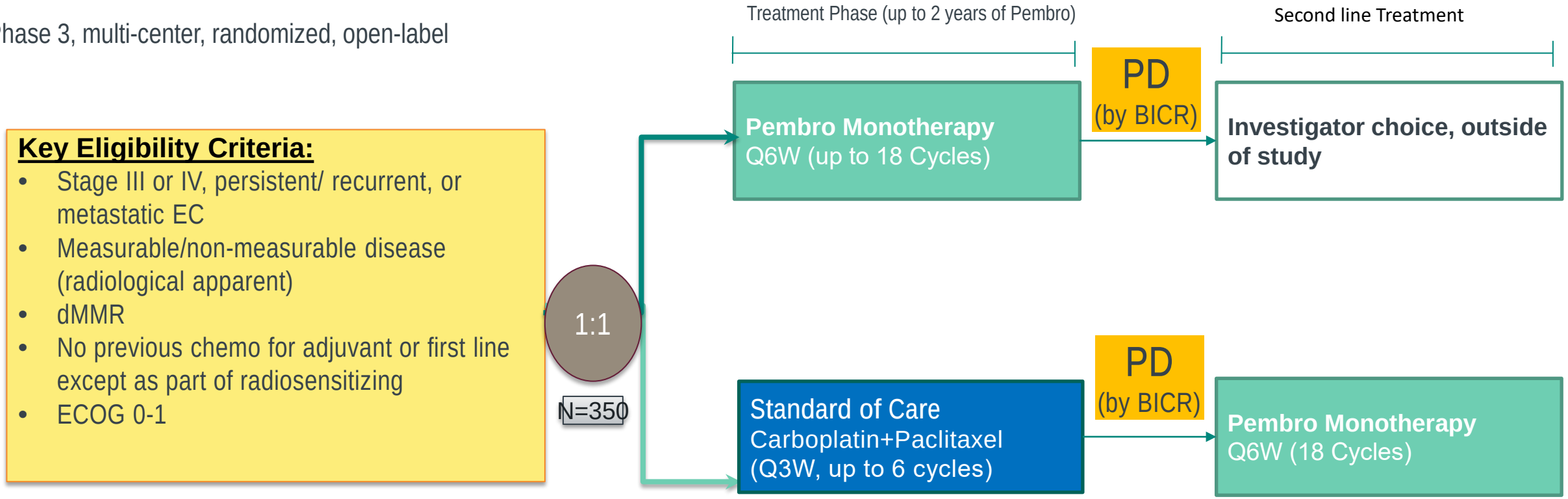




Duration of Response assessed per RECIST v1.1 by BICR; Data cut-off: 19Feb2020.

GOG-3064/ENGOT en15/KN-C93: A phase 3, randomized, open-label study of first-line pembrolizumab versus platinum-doublet chemotherapy in mismatch repair deficient advanced or recurrent endometrial carcinoma

Phase 3, multi-center, randomized, open-label



Stratification:
- Newly diagnosed advanced EC vs Recurrent EC
- Histology – endometrioid vs. non-endometrioid

*Participants who were randomized to Arm 2 (chemotherapy) and experience BICR-assessed disease progression per RECIST 1.1, will have an opportunity to participate in the Crossover Phase to receive up to 18 cycles of pembrolizumab 400 mg Q6W, upon Sponsor consultation

Dual Primary Endpoints
- *PFS (by BICR)*
- *OS*

Key Secondary Endpoint
- *ORR (by BICR)*

The Future is Bright