The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

A CME/MOC- and NCPD-Accredited Event

Saturday, October 22, 2022
7:30 AM – 5:30 PM ET

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — Lung Cancer: *Drs Langer and Lovly*

Module 2 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs LaCasce and Smith*

Module 3 — Prostate and Bladder Cancers: *Drs Morgans and Yu*

Module 4 — Renal Cell Carcinoma: *Prof Powles*

Module 5 — Multiple Myeloma: *Dr Usmani*

Module 6 — Hepatobiliary Cancers: *Prof Abou-Alfa*

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Agenda

Module 7 — Breast Cancer: *Drs Goetz and Krop*

Module 8 — Endometrial Cancer: *Dr Westin*

Module 9 — Ovarian Cancer and PARP Inhibitors: *Dr O'Malley*

Module 10 — Gastrointestinal Cancers: *Drs Messersmith and Strickler*

Module 11 — Melanoma: *Prof Long*

Endometrial Cancer Faculty

Shannon N Westin, MD, MPH
Professor
Director, Early Drug Development
Department of Gynecologic Oncology
and Reproductive Medicine
The University of Texas
MD Anderson Cancer Center
Houston, Texas

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Lenvatinib and Pembrolizumab in Recurrent Endometrial Cancer

Shannon N. Westin, MD, MPH

Professor

Department of Gynecologic Oncology and Reproductive Medicine

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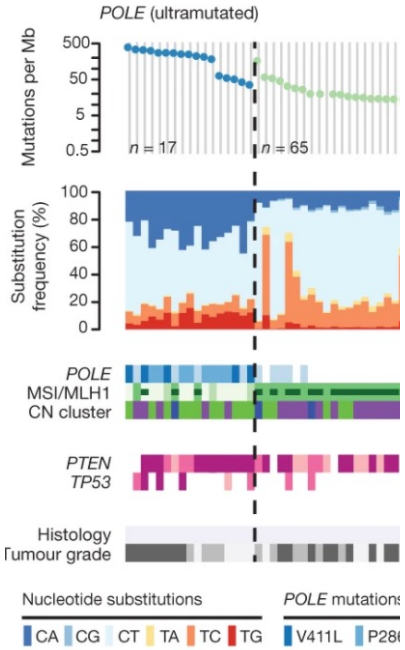
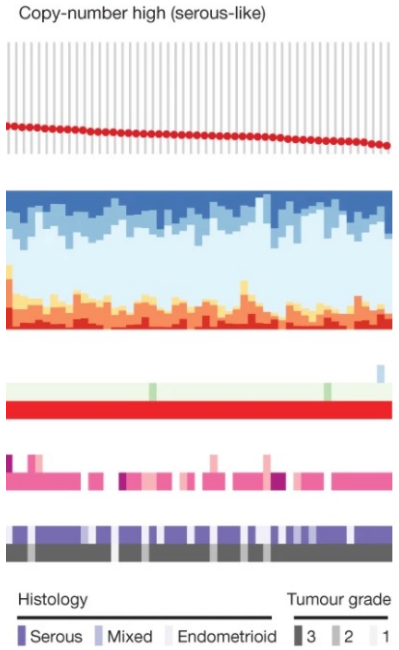
One Size Fits All?

There are clear molecular differences in endometrial cancer



Paclitaxel and Carboplatin



Kandoth Nature 2013; Miller JCO 2020

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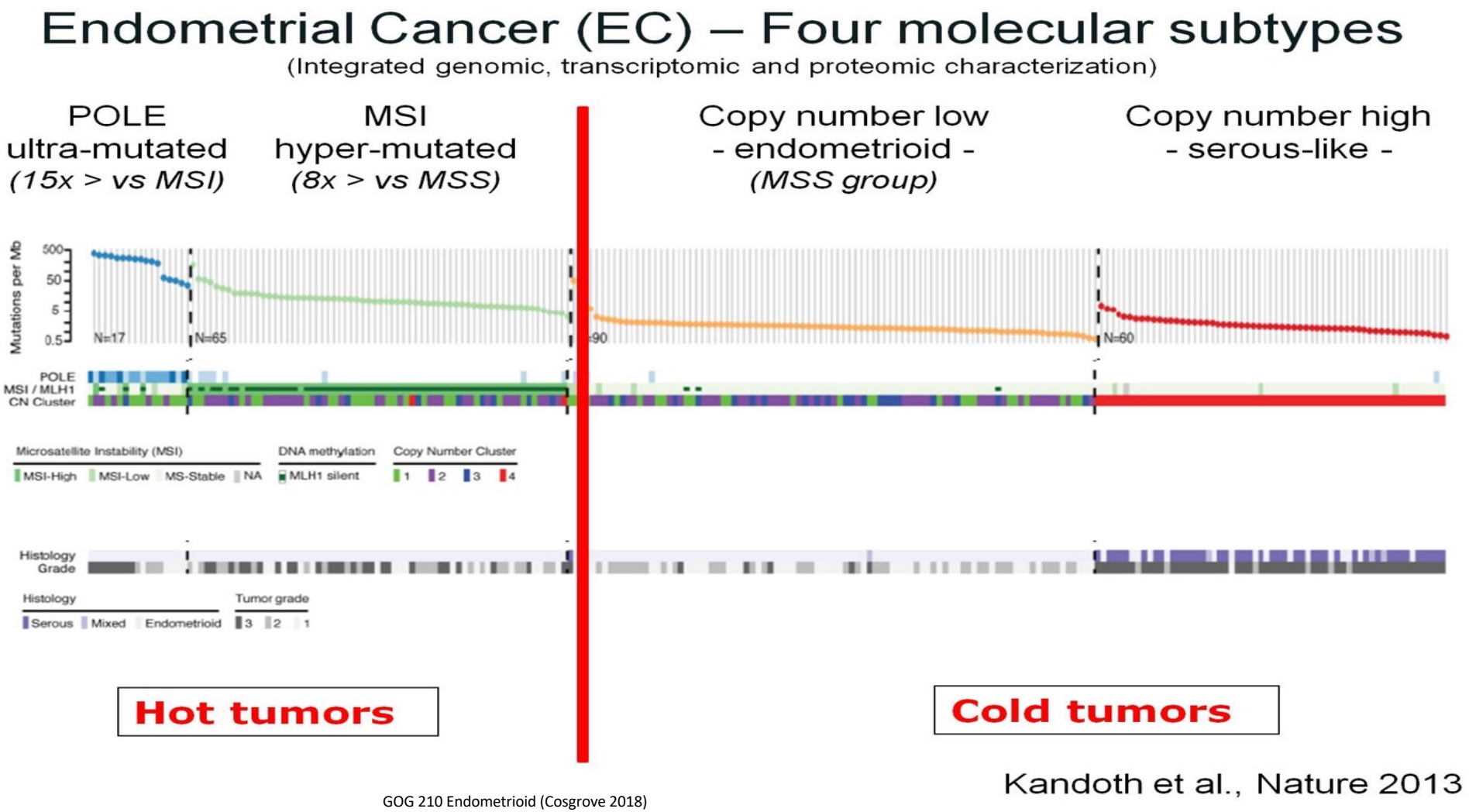
Hot Tumors and IO



GOG 210 Endometrioid (Cosgrove 2018)

Incidence: 49% CNS, 4% POLE mutant, 39% MMR deficient, 8% copy number altered (CNA).
Cancer-specific mortality: 5%=CNS ; 2.6% =POLE tumors; 7.6%=MMR deficient tumors; 19% with CNA tumors.

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"Biomarker" Guided Therapy in Endometrial Cancer

MMR deficient & MSI-H population

- Harbor hundreds to thousands of somatic mutations that encode potential neoantigens and are thus immunogenic

Phase II KEYNOTE-158 Study (27 independent tumor types)

- Endometrial (n=49), gastric (n=24), cholangiocarcinoma and pancreatic cancer most common
- In the entire cohort: ORR 34.3%, (95% CI, 28.3% to 40.8%). Median PFS 4.1 months (95% CI, 2.4 to 4.9 months) and median OS 23.5 months (95% CI, 13.5 months to not reached).

TABLE 3. Antitumor Activity for Tumor Types With Greatest Enrollment

Tumor Type	No.	CR, No.	PR, No.	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Median DOR, Months (range)
Endometrial	49	8	20	57.1 (42.2 to 71.2)	25.7 (4.9 to NR)	NR (27.2 to NR)	NR (2.9 to 27.0+)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)	NR (6.3 to 28.4+)
Cholangiocarcinoma	22	2	7	40.9 (20.7 to 63.6)	4.2 (2.1 to NR)	24.3 (6.5 to NR)	NR (4.1+ to 24.9+)
Pancreatic	22	1	3	18.2 (5.2 to 40.3)	2.1 (1.9 to 3.4)	4.0 (2.1 to 9.8)	13.4 (8.1 to 16.0+)
Small intestine	19	3	5	42.1 (20.3 to 66.5)	9.2 (2.3 to NR)	NR (10.6 to NR)	NR (4.3+ to 31.3+)
Ovarian	15	3	2	33.3 (11.8 to 61.6)	2.3 (1.9 to 6.2)	NR (3.8 to NR)	NR (4.2 to 20.7+)
Brain	13	0	0	0.0 (0.0 to 24.7)	1.1 (0.7 to 2.1)	5.6 (1.5 to 16.2)	–

Marabelle A, et al. J Clin Oncol, 2019

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Single Agent IO in "Biomarker" Selected Endometrial Cancer Populations (dMMR)

Study & Drug	Patient Population	Outcome
KEYNOTE-158: Pembrolizumab (N=49)	Advanced stage or metastatic dMMR endometrial cancer	ORR: 57.1%
PHAEDRA trial: Durvalumab (N=35 dMMR)	Advanced stage or metastatic endometrial cancer	ORR in dMMR: 43%
GARNET study: Dostarlimab (N=70)	Previously treated, recurrent advanced stage endometrial cancer	ORR in dMMR: 45%
Ph II Avelumab study (N= 15 dMMR)	Advanced stage or metastatic endometrial cancer	ORR: 26.7%

Marabelle A, et al. J Clin Oncol, 2019
Antill PSK et al. J Clin Oncol 2019
Oaknin A et al. SGO virtual meeting 2020
Konstantinopoulos PA et al. J Clin Oncol 2019

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Single Agent IO in "Non-biomarker" Selected Endometrial Cancer Populations

Study & Drug	Patient Population	Outcome
KEYNOTE-28: Pembrolizumab (N=24)	Advanced stage or metastatic PD-L1+ endometrial cancer	ORR: 13%
PHAEDRA trial: Durvalumab (N=36 pMMR)	Advanced stage or metastatic endometrial cancer	ORR in pMMR: 3%
GARNET study: Dostarlimab (N=94)	Previously treated, recurrent advanced stage endometrial cancer	ORR in pMMR: 13%
Ph II Avelumab study (N=16 pMMR)	Advanced stage or metastatic endometrial cancer	ORR: 6.25%

PD-L1 positive endometrial cancer is not approved indication of Pembrolizumab in China, Taiwan, Korea, Singapore, Philippines, and HK

Ott PA et al. J Clin Oncol 2017
Antill PSK et al. J Clin Oncol 2019
Oaknin A et al. Gynecol Oncol 2019
Konstantinopoulos PA et al. J Clin Oncol 2019

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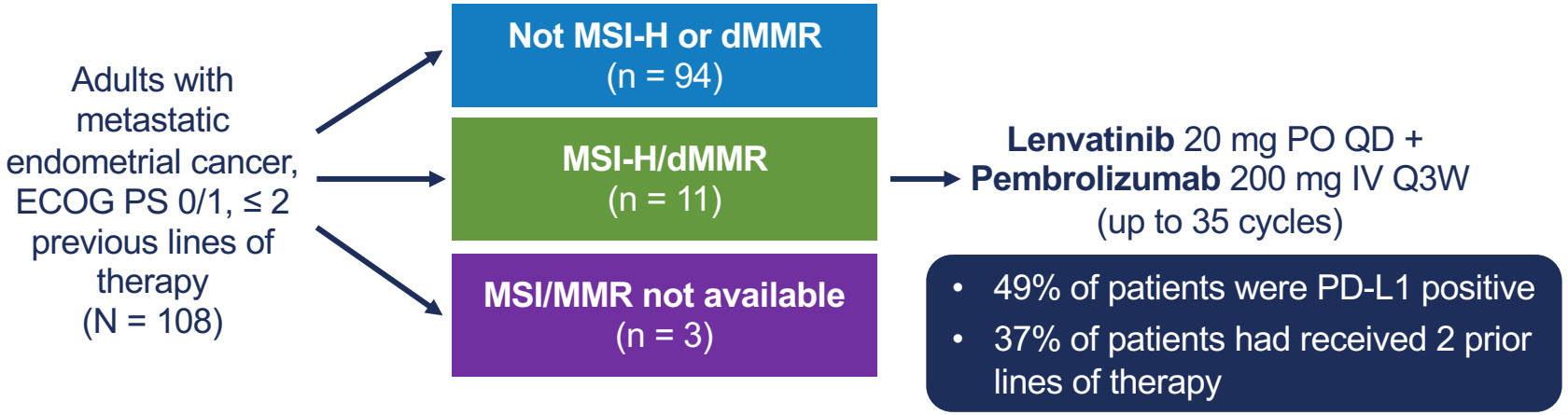
Phase Ib/II KEYNOTE-146: Pembrolizumab + Lenvatinib in Patients With Previously Treated EC



- Primary endpoint: ORR at Wk 24 (responses confirmed with secondary assessment > 4 wks later)
- Secondary endpoints: ORR, DoR, PFS, OS, DCR, CBR, safety

Makker. JCO. 2020; 38: 2981.

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KEYNOTE-146: ORR at Wk 24 (Primary Endpoint)

Investigator Assessment per irRECIST	Total (n = 108)	Not MSI-H or dMMR (n = 94)	MSI-H/dMMR (n = 11)
ORR_{WK24}, n (%)	41 (38.0)	34 (36.2)	7 (63.6)
ORR, n (%)	42 (38.9)	35 (37.2)	7 (63.6)
CR	8 (7.4)	7 (7.4)	1 (9.1)
PR	34 (31.5)	28 (29.8)	6 (54.5)
Median DoR, mos (95% CI)	21.2 (7.6-NE)	NE (7.4-NE)	21.2 (7.3-NE)
Median PFS, mos (95% CI)	7.4 (5.3-8.7)	7.4 (5.0-7.6)	18.8 (4.0-NE)
Median OS, mos (95% CI)	16.7 (15.0-NE)	16.4 (13.5-25.9)	NE (7.4-NE)

Makker. JCO. 2020; 38: 2981.

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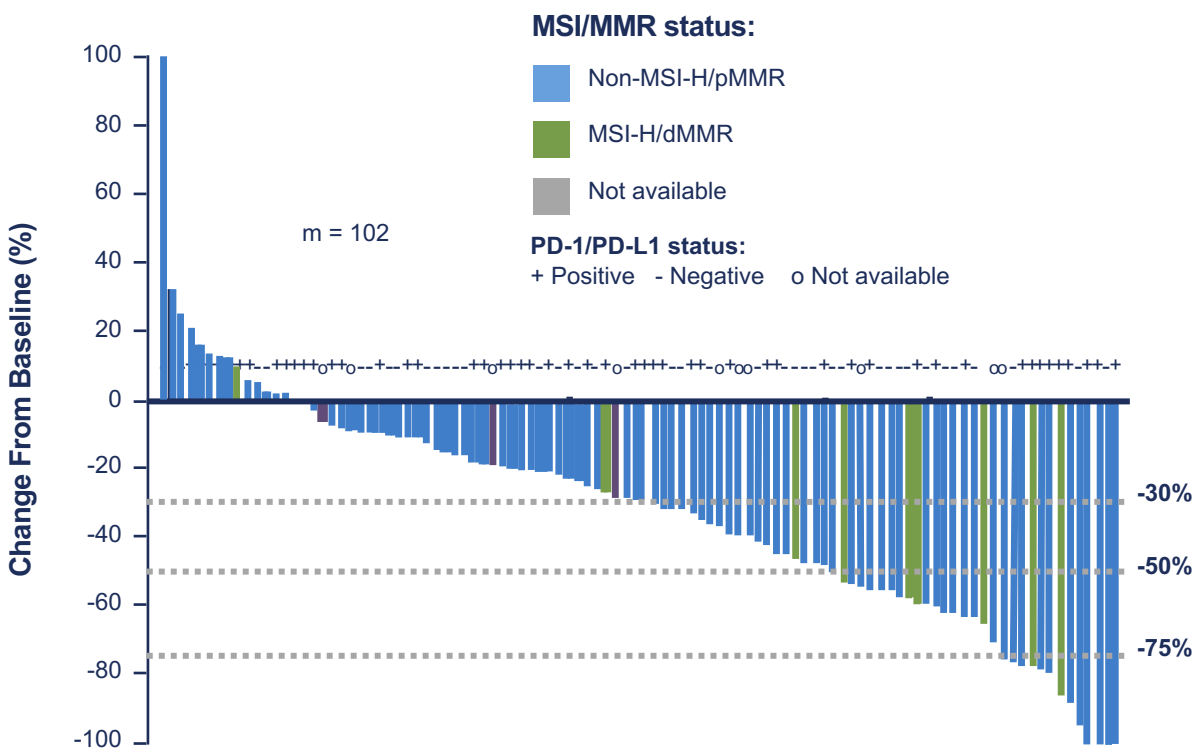
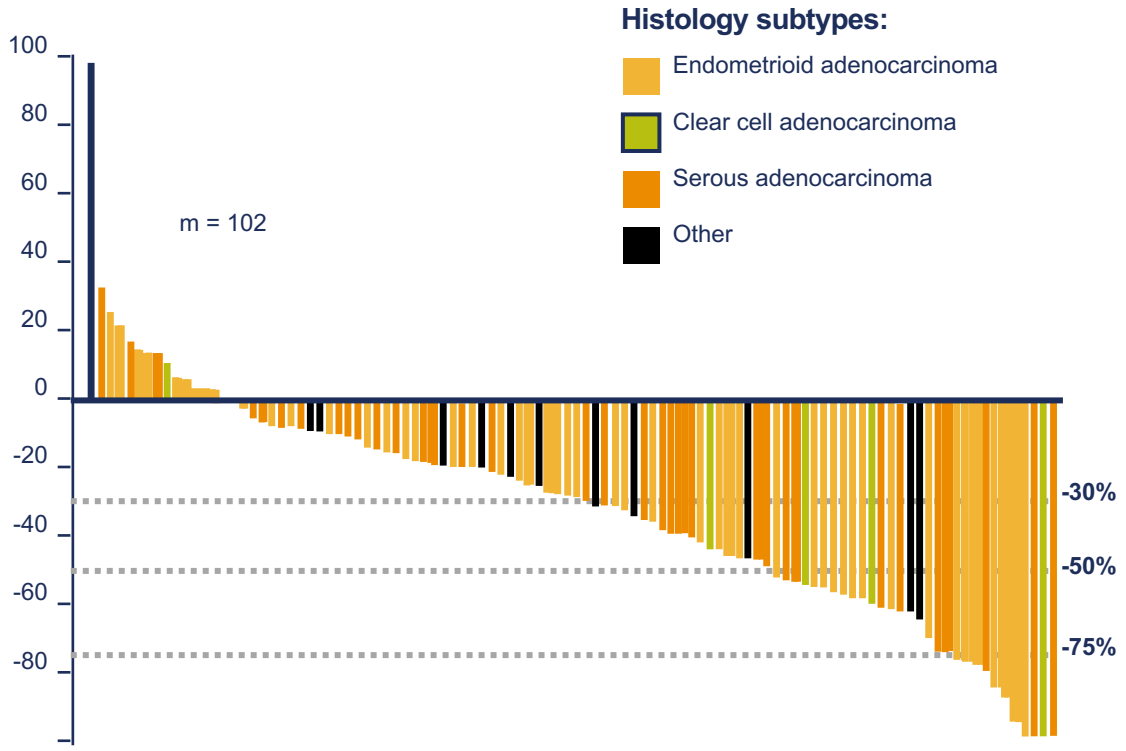
KEYNOTE-146: Response by MSI Status and Histology





- Percentage change in sum diameters of target lesions from baseline to post-baseline nadir.
- m denotes the number of previously treated patients with both baseline and at least 1 postbaseline target lesion assessment

Makker. JCO. 2020; 38: 2981.

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KEYNOTE-146: Safety

Parameter	Previously Treated EC (n = 108), n (%)
Patients with any treatment-related TEAEs	105 (97.2)
Patients with treatment-related TEAEs leading to study drug discontinuation	20 (18.5)
Both lenvatinib and pembrolizumab	10 (9.3)
Lenvatinib	17 (15.7)
Pembrolizumab	14 (13.0)
Patients with treatment-related TEAEs leading to study drug dose reduction of lenvatinib	70 (64.8)
Patients with treatment-related TEAEs leading to study drug interruption	78 (72.2)
Both lenvatinib and pembrolizumab	30 (27.8)
Lenvatinib	73 (67.6)
Pembrolizumab	43 (39.8)

- Most common grade ≥3 TEAEs were:
  - Hypertension (32.4%)
  - Fatigue (8.3%)
  - Diarrhea (6.5%)
- Any-grade irAEs occurred in 57.4% of patients; most common was hypothyroidism (47.2%)
- Most common grade ≥3 irAE was severe skin reactions (4.6%)

Makker. JCO. 2020; 38: 2981.

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KEYNOTE-775: Lenvatinib + Pembrolizumab vs SOC

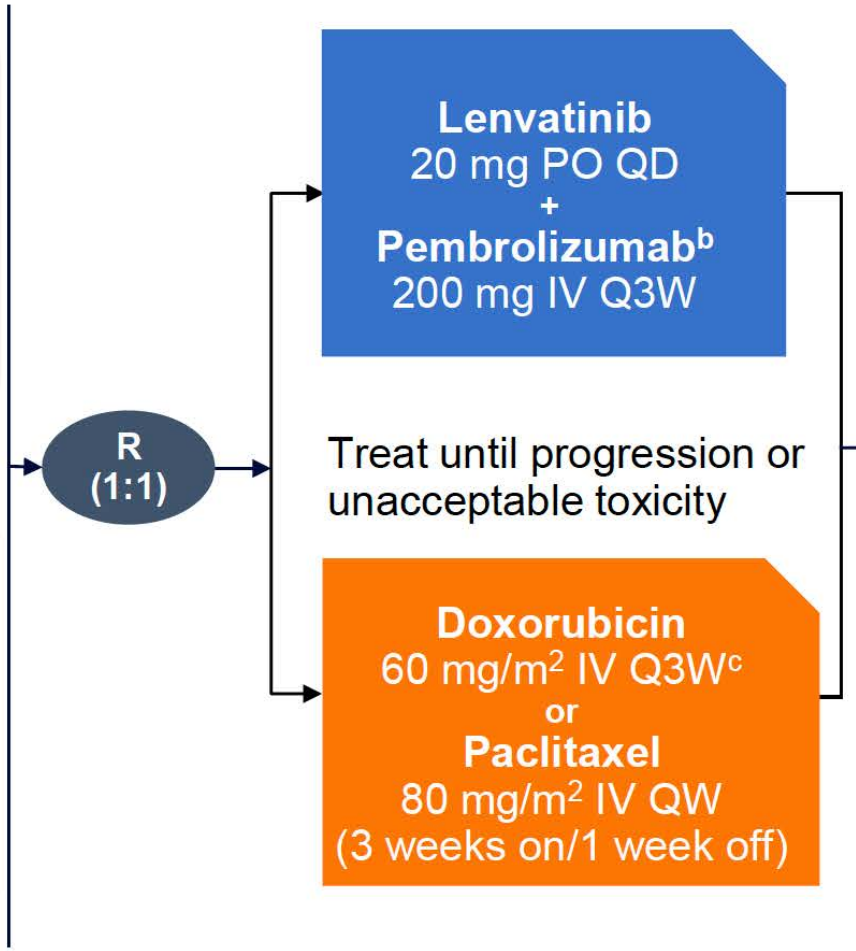
Key eligibility criteria

- 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 (Y vs N)



Primary endpoints

- PFS by BICR
- Overall survival

Secondary endpoints

- ORR
- HRQoL
- Pharmacokinetics
- Safety

Key exploratory endpoint

- Duration of response

Makker. NEJM 2022

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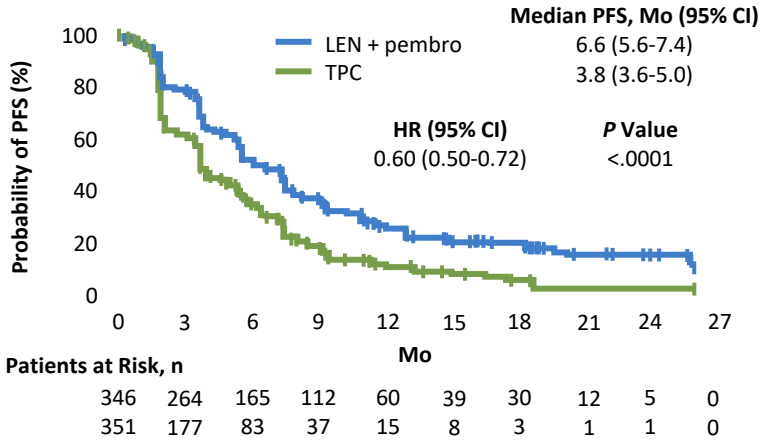
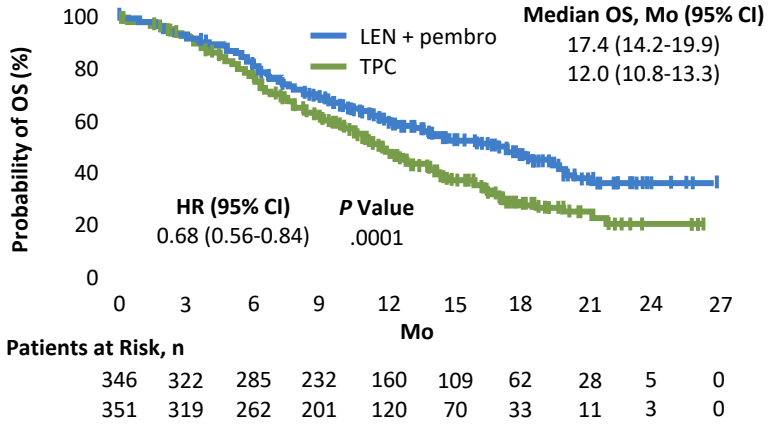
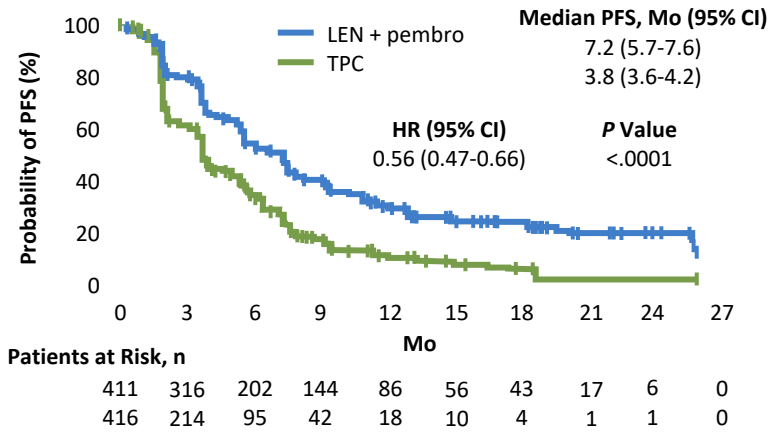
KEYNOTE-775: PFS and OS Benefit

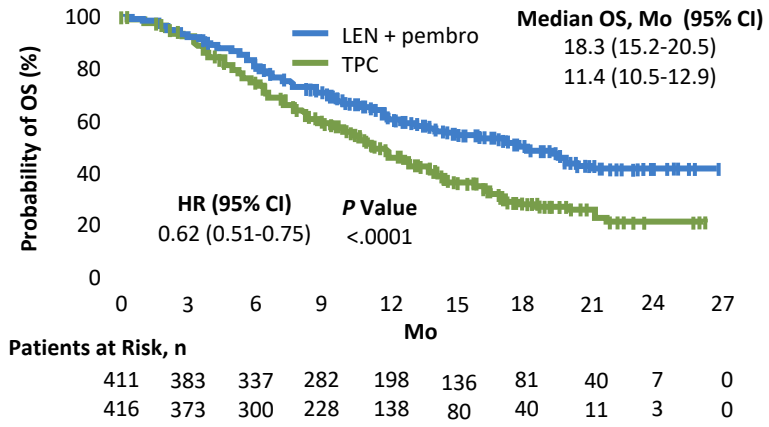
pMMR





All Comers





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KEYNOTE-775: TEAEs

TEAE, %	Lenvatinib + Pembrolizumab (n = 406)		Doxorubicin or Paclitaxel (n = 351)	
	Any Grade	Grade ≥3*	Any Grade	Grade ≥3*
Hypertension	64.0	37.9	5.2	2.3
Hypothyroidism	57.4	1.2	0.8	0
Diarrhea	54.2	7.6	20.1	2.1
Nausea	49.5	3.4	46.1	1.3
Decreased appetite	44.8	7.9	21.1	0.5
Vomiting	36.7	2.7	20.9	2.3
Weight decrease	34.0	10.3	5.7	0.3
Fatigue	33.0	5.2	27.6	3.1
Arthralgia	30.5	1.7	8.0	0

TEAE, %	Lenvatinib + Pembrolizumab (n = 406)		Doxorubicin or Paclitaxel (n = 351)	
	Any Grade	Grade ≥3*	Any Grade	Grade ≥3*
Proteinuria	28.8	5.4	2.8	0.3
Anemia	26.1	6.2	48.7	14.7
Constipation	25.9	0.7	24.7	0.5
UTI	25.6	3.9	10.1	1.0
Headache	24.9	0.5	8.8	0.3
Asthenia	23.6	5.9	24.5	3.9
Neutropenia	7.4	1.7	33.8	25.8
Alopecia	5.4	0	30.9	0.5

*In the lenvatinib and pembrolizumab arm, 5.7% of patients suffered grade 5 AEs (including events of gastrointestinal disorder [1.2%], cardiac disorder [0.5%], general disorder [1.5%], and infections [0.7%]), and 4.9% of patients in the TPC arm suffered grade 5 AEs (including cardiac disorder [1%], general disorder [1.3%], infections [1.5%], and subdural hematoma [0.3%]).

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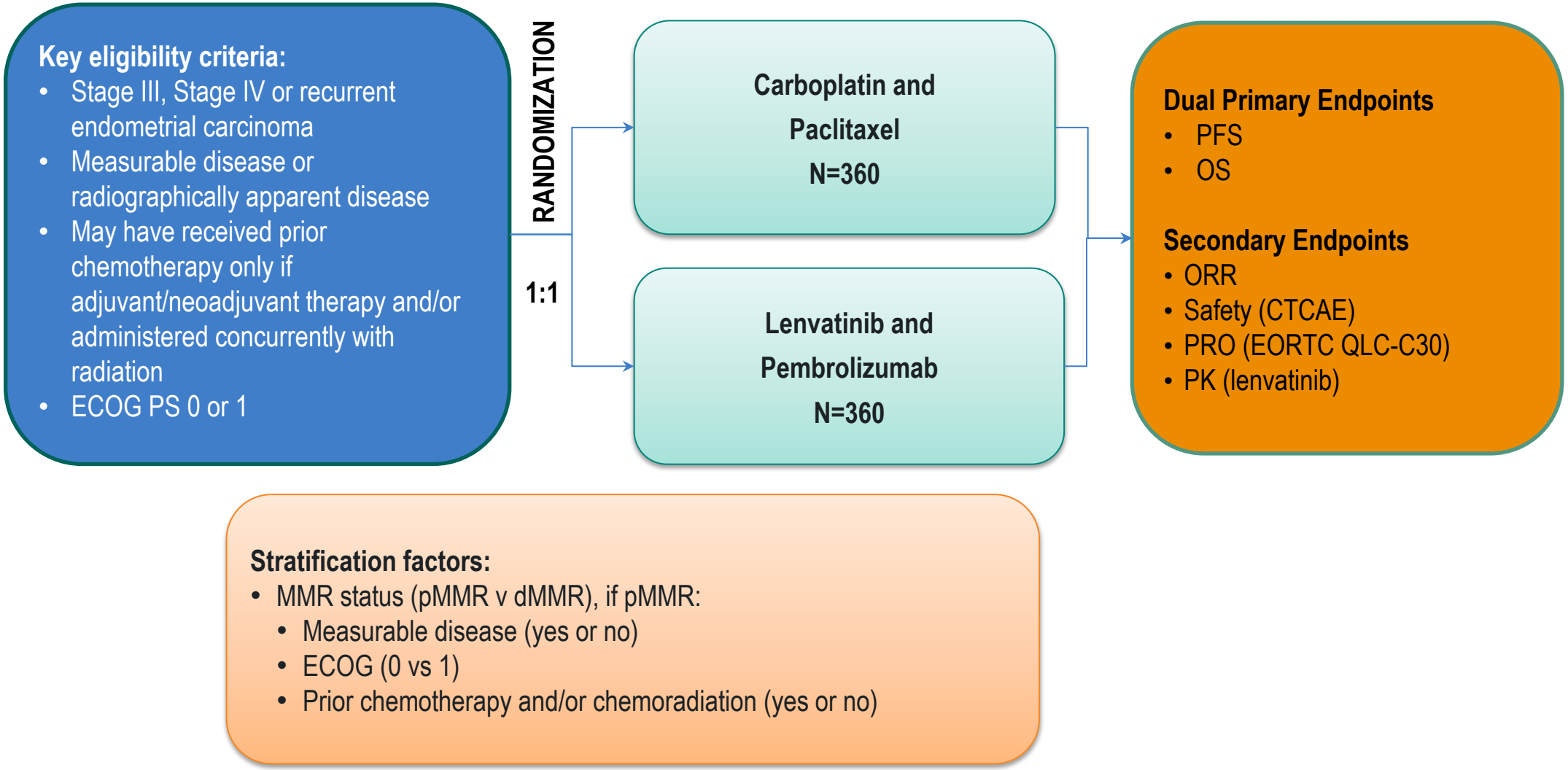
LEAP-001: First line phase 3



ClinicalTrials.gov: NCT04865289

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Prevention of Treatment-Related AEs

- Patient selection
- Treatment settings
- Clinical trial access
- Team education and communication
- Patient education and expectation setting
- Multidisciplinary care

Menderes G *Expert Opin Biol.* 2016; Minion LE, Tewari KS. *Gynecol Oncol.* 2018

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General Principles for Managing AEs With Immunotherapy

- Educate patients about toxicities and to contact you immediately if they occur
  - Let other healthcare providers know that they are receiving immunotherapy
- Assess for irAEs at each cycle for the first 3 mo, including laboratory tests
- Thyroid tests every cycle for first 3 mo, and then every 2 to 3 cycles
- Maintain low threshold for steroids or immunosuppression if irAE is concerning

Grade	Management
1 (mild)	▪ Symptomatic management ▪ Continue therapy ▪ Immunosuppression not needed
2 (mild to moderate)	▪ Symptomatic management ▪ Consider discontinuing until resolution to grade 1 ▪ Consider immunosuppression if intolerable or persistent ▪ Involve consultants as needed
3 or 4 (severe)	▪ Discontinue therapy ▪ Start immunosuppression ▪ Refer/involve consultants ▪ At resolution, gradually taper off immunosuppression

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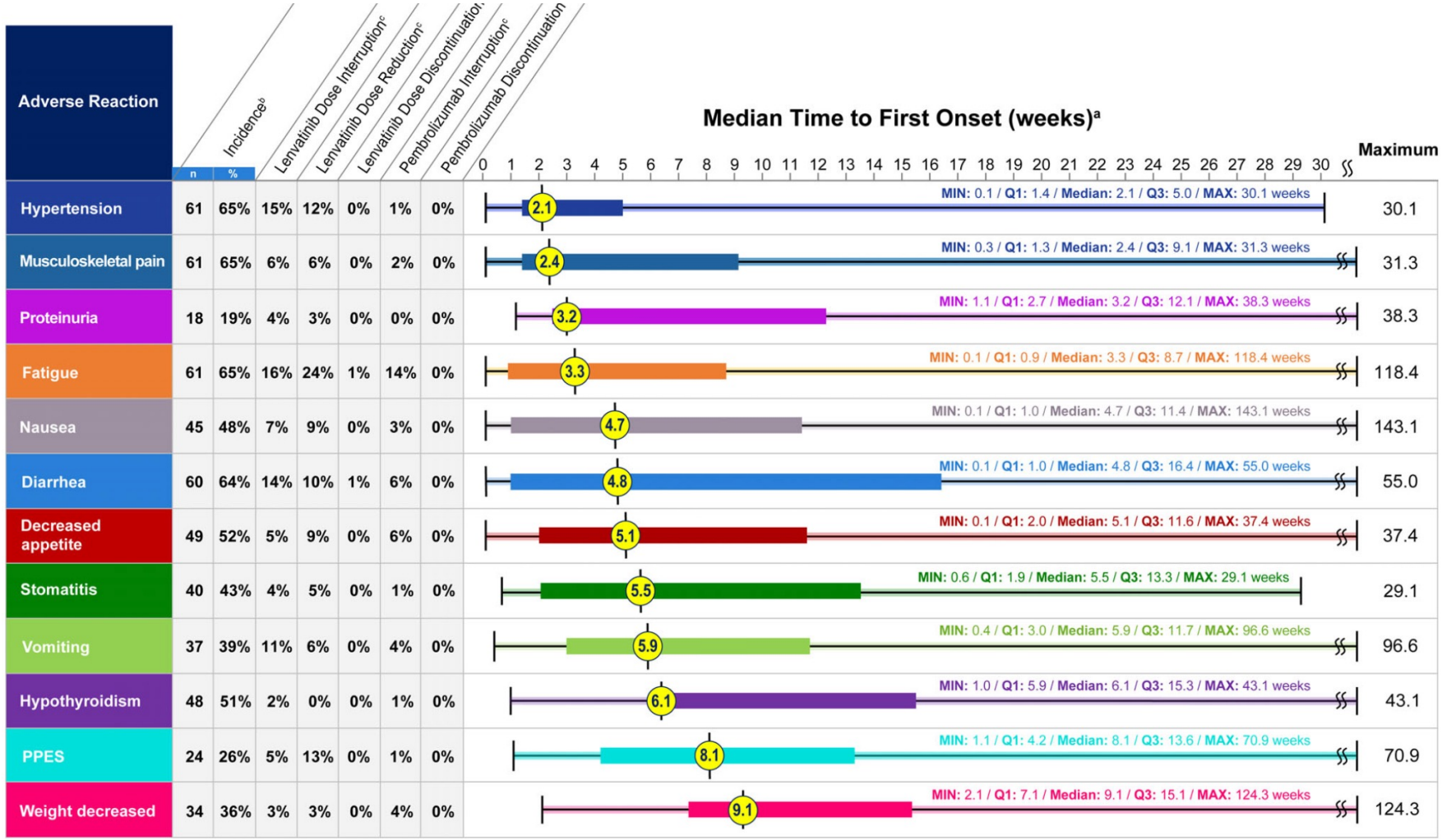
Len/Pem Toxicity



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Specific Guidelines for Toxicity Management for Len/Pem

Hypertension

- Daily monitoring
- Consideration of antihypertensive Rx

Diarrhea

- Reporting
- Antimotility agents
- Consider the timeline
- Dose interruption

Fatigue

- Rule out other causes
- Exercise
- Dose interruption/reduction

Nausea

- Prophylactic antiemetics
- High fat foods
- Small frequent meals

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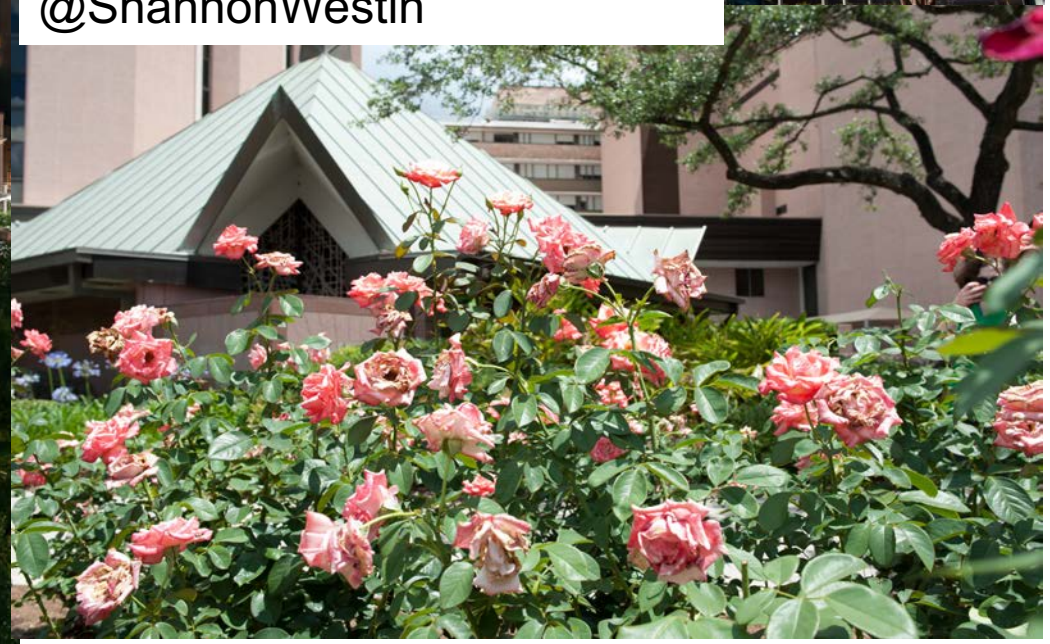
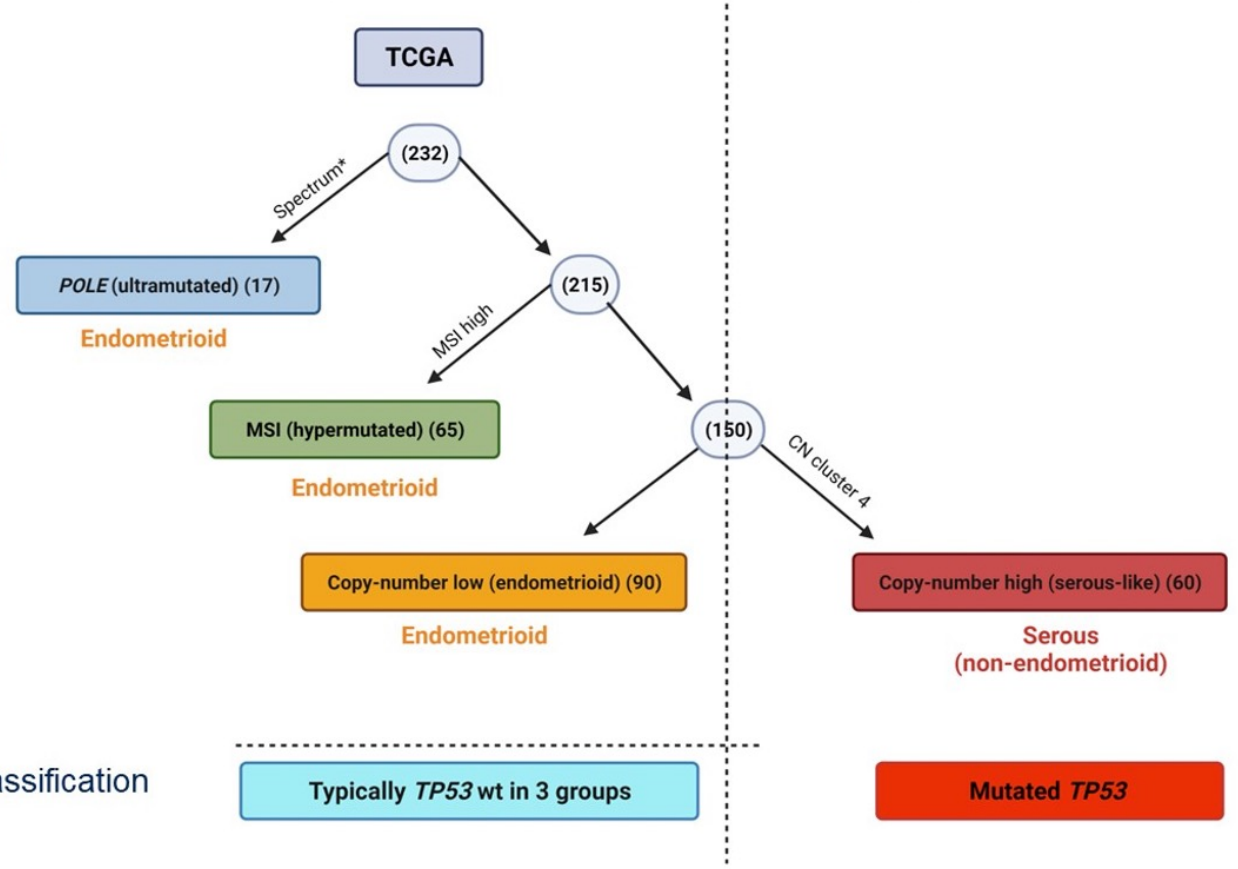
Thank you

swestin@mdanderson.org
@ShannonWestin



Molecular Subclassification of Endometrial Cancer by the TCGA System of Four Independent Subtypes

- TCGA and others identified and validated 4 distinct molecular subtypes in endometrial cancer with each having its own prognostic significance:[1,2]
  - *POLE*-exonuclease domain mutant (ultramutated)
  - MSI-H (hypermutated)
  - Serous-like (copy-number high)
  - No specific molecular profile (copy-number low)



Four mutually exclusive groups assigned according to this classification system, ordered from top to bottom

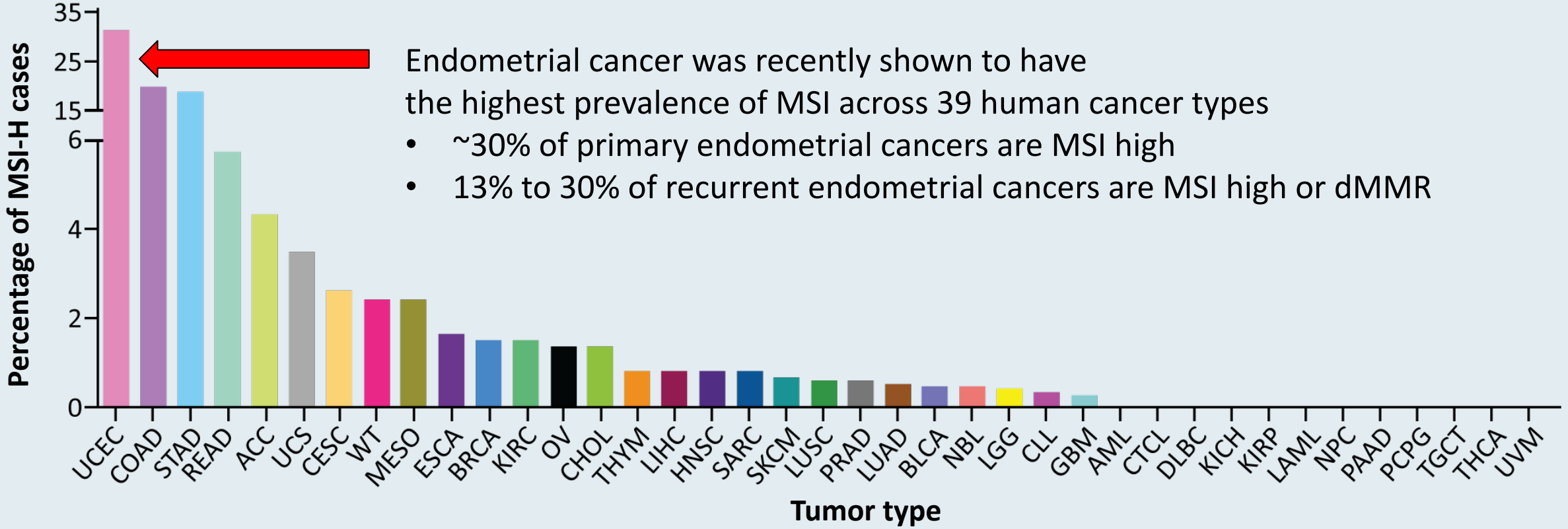
[1]Abu-Rustum NR, Yashar CM, Bradley K, et al. NCCN Guidelines® Insights: Uterine Neoplasms, Version 3.2021: Featured Updates to the NCCN Guidelines. J Natl Compr Cancer Netw [Internet] 2021;19(8):888–95
[2]Getz G, Gabriel SB, Cibulskis K, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497(7447):67

Makker V et al. ASCO 2022;Abstract 5511.

RTP RESEARCH TO PRACTICE

High Microsatellite Instability (MSI) Across 39 Cancer Types

Whole-exome data from 11,139 tumor-normal pairs from the Cancer Genome Atlas and Therapeutically Applicable Research to Generate Effective Treatments projects



Endometrial cancer was recently shown to have the highest prevalence of MSI across 39 human cancer types

- ~30% of primary endometrial cancers are MSI high
- 13% to 30% of recurrent endometrial cancers are MSI high or dMMR

MSI-H = MSI-high; dMMR = mismatch repair deficient; UCEC = uterine corpus endometrial carcinoma

Bonneville R et al. *JCO Precis Oncol* 2017;2017:10.1200/PO.17.00073; Green AK et al. *ASCO Educational Book* 2020.

RTP RESEARCH TO PRACTICE

Single-Agent IO in "Biomarker" Selected Endometrial Cancer Populations (dMMR)

Study and drug	Patient population	Outcome
KEYNOTE-158: Pembrolizumab (N = 49)	Advanced-stage or metastatic dMMR endometrial cancer	ORR: 48%
PHAEDRA: Durvalumab (N = 35 dMMR)	Advanced-stage or metastatic endometrial cancer	ORR in dMMR: 47%
GARNET: Dostarlimab (N = 70)	Previously treated, recurrent advanced-stage endometrial cancer	ORR in dMMR: 45.5%
Ph II avelumab study (N = 15 dMMR)	Advanced-stage or metastatic endometrial cancer	ORR: 26.7%

IO = immuno-oncology therapy

O'Malley DM et al. *J Clin Oncol* 2022;40:752-61; Antill Y et al. *J Immunother Cancer* 2021;9(6):e002255; Oaknin A et al. ASCO 2022;Abstract 5509; Konstantinopoulos PA et al. *J Clin Oncol* 2019;37(30):2786-94.

2022 ASCO® ANNUAL MEETING

Abstract 5509

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

PRESENTED BY:
Ana Oaknin, MD

GARNET: 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

Oaknin A et al. ASCO 2022;Abstract 5509.

ABSTRACT ONLY | VOLUME 33, SUPPLEMENT 7, S798-S799, SEPTEMBER 01, 2022

ESMO 2022;Abstract 548P.

548P Progression-free survival (PFS) and overall survival (OS) in advanced/recurrent (AR) mismatch repair deficient/microsatellite instability–high or proficient/stable (dMMR/MSI-H or MMRp/MSS) endometrial cancer (EC) treated with dostarlimab in the GARNET study

A.V. Tinker • B. Pothuri • L. Gilbert • R. Sabatier • J. Brown • S. Ghamande • C. Mathews • D. O'Malley • V. Boni • A. Gravina • S. Banerjee • R. Miller • J. Pikiel • M.R. Mirza • T. Duan • G. Antony • S. Zildjian • E. Zografos • J. Veneris • A. Oaknin • Show less

GARNET: Secondary Endpoint Analysis

Variable	dMMR/MSI-H EC N=143	MMRp/MSS EC N=156
Median follow-up time, months	27.6	33.0
PFS events observed, n (%)	83 (58.0)	136 (87.2)
Median PFS (95% CI), months	6.0 (4.1–18.0)	2.7 (2.6–2.8)
Estimated probability of PFS, % (95% CI)		
6 months	49.5 (41.0–57.5)	22.9 (16.5–30.0)
12 months	46.4 (37.8–54.5)	13.3 (8.3–19.5)
24 months	40.1 (31.6–48.4)	9.4 (5.2–15.0)
36 months	40.1 (31.6–48.4)	6.8 (3.3–12.0)
OS events observed, n (%)	57 (37.3)	111 (68.9)
Median OS (95% CI), months	NR (27.1–NR)	16.9 (13.0–21.8)
Estimated probability of survival, % (95% CI)		
6 months	84.9 (78.0–89.8)	74.3 (66.6–80.6)
12 months	73.3 (65.2–79.8)	60.6 (52.3–67.9)
24 months	60.5 (51.5–68.4)	38.4 (30.5–46.2)
36 months	58.4 (49.2–66.5)	22.2 (14.9–30.5)

dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; MSI-H, microsatellite instability–high; MSS, microsatellite stable; NR, not reached; OS, overall survival; PFS, progression-free survival.

Tinker A et al. ESMO 2022;Abstract 548P.

ESMO 2022;Abstract 546P.

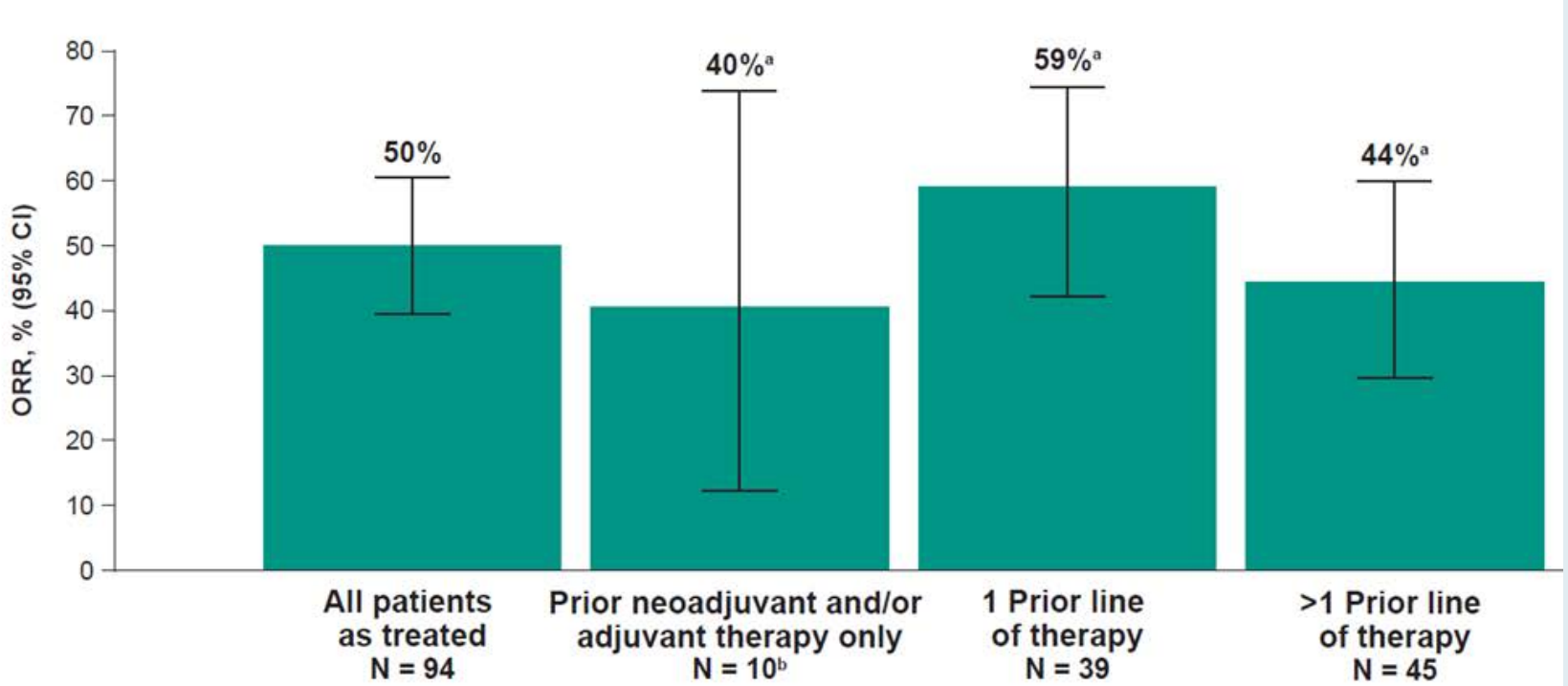
Pembrolizumab for Microsatellite Instability-High or Mismatch Repair Deficient Advanced Endometrial Cancer: Long-Term Follow-Up Results From KEYNOTE-158

D.M. O'Malley[1]; G.M. Bariani[2]; P.A. Cassier[3]; A. Marabelle[4]; A.R. Hansen[5]; A. De Jesus Acosta[6]; W.H. Miller, Jr[7]; T. Safra[8]; A. Italiano[9]; L. Mileshkin[10]; L. Yao[11]; A. Gozman[11]; F. Jin[11]; M. Maio[12]

[1]The Ohio State University Wexner Medical Center and The James Comprehensive Cancer Center, Columbus, OH, USA; [2]Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil; [3]Centre Léon Bérard, Lyon, France; [4]Gustave Roussy, Institut National de la Santé et de la Recherche Médicale (INSERM) U1015, Université Paris Saclay, Villejuif, France; [5]Princess Margaret Cancer Centre, Toronto, ON, Canada; [6]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [7]Segal Cancer Centre, Jewish General Hospital, Rossy Cancer Network and Departments of Oncology and Medicine, McGill University, Montreal, QC, Canada; [8]Tel Aviv Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [9]Institut Bergonie, Bordeaux, France; [10]Peter MacCallum Cancer Centre and the Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, VIC, Australia; [11]Merck & Co., Inc., Rahway, NJ, USA; [12]University of Siena and Center for Immuno-Oncology, Department of Oncology, University Hospital, Siena, Italy

Presented at the European Society for Medical Oncology Virtual Congress 2022 (ESMO 2022)
September 9 – 13, 2022
Paris, France (and online)

KEYNOTE-158: Objective Response Rate (ORR) and Best ORR by Independent Central Radiologic Review



	N = 94
Median DoR	63.2 mo
Median PFS	13.1 mo
4-yr PFS rate	37%
Median OS	65.4 mo
4-yr OS rate	59%

O'Malley DM et al. ESMO 2022;Abstract 546P.

RTP RESEARCH TO PRACTICE

Single-Agent IO in "Non-biomarker" Selected Endometrial Cancer Populations

Study and drug	Patient population	Outcome
KEYNOTE-28: Pembrolizumab (N = 24)	Advanced-stage or metastatic PD-L1+ endometrial cancer	ORR: 13%
PHAEDRA: Durvalumab (N = 36 pMMR)	Advanced-stage or metastatic endometrial cancer	ORR in pMMR: 3%
GARNET: Dostarlimab (N = 94)	Previously treated, recurrent advanced-stage endometrial cancer	ORR in pMMR: 15.4%
Ph II avelumab study (N = 16 pMMR)	Advanced-stage or metastatic endometrial cancer	ORR: 6.25%

Ott PA et al. *J Clin Oncol* 2017;35(22):2535-41; Antill Y et al. *J Immunother Cancer* 2021;9(6):e002255; Oaknin A et al. ASCO 2022;Abstract 5509; Konstantinopoulos PA et al. *J Clin Oncol* 2019;37(30):2786-94.

Immunotherapy in Mismatch Repair-Proficient Endometrial Cancer

Study	Drug	N	Patient selection	ORR
GARNET[1]	Dostarlimab	156	Previously treated Recurrent/advanced MMRp	15%
PHAEDRA[2]	Durvalumab	36	Advanced/metastatic MMRp	3%
NCT02912572[3]	Avelumab + talazoparib	35	Advanced/metastatic MMRp	11%
KEYNOTE-775[4,5]	Pembrolizumab + lenvatinib	346	Previously treated Recurrent/advanced MMRp	30%

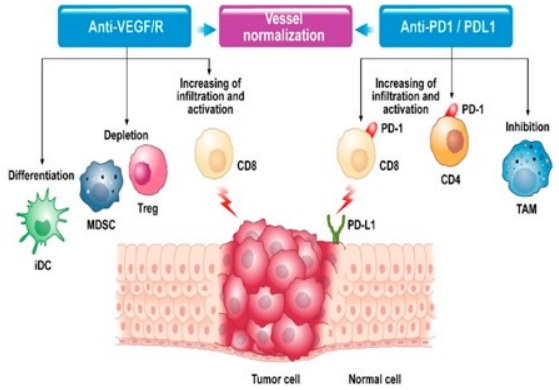
MMRp = mismatch repair-proficient; ORR = overall response rate.

1. Oaknin A et al. ASCO 2022;Abstract 5509; 2. Antill Y et al. *J Immunother Cancer* 2021;9(6):e002255; 3. Konstantinopoulos PA et al. *JAMA Oncology* 2022;8(9):1317-22; 4. Makker V et al. SGO 2021;Abstract 37; 5. Makker V et al. *N Engl J Med* 2022 February 3;386(5):437-48.

Combination Approaches: Leveraging Immune Checkpoint Inhibitor Activity

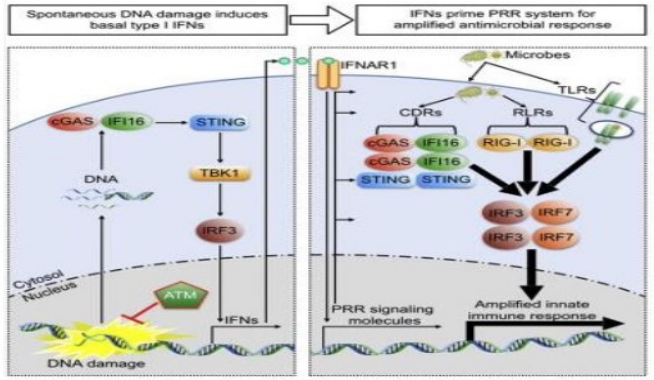
Antiangiogenic Agents

- Reduction in Treg activity
- Reversal of immunosuppressive effects of VEGF
- Improved T-cell trafficking and infiltration of CD8+ into the tumor bed



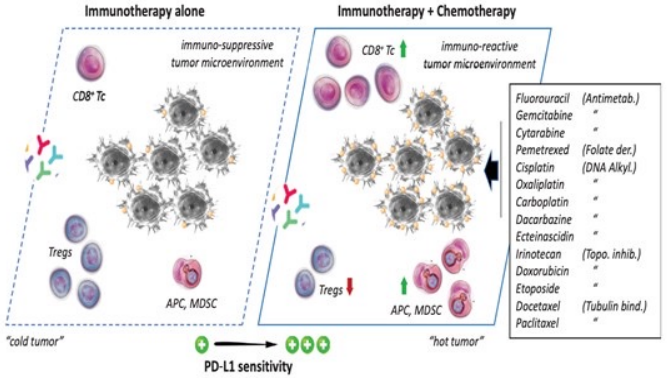
PARP inhibitors

- Enhanced DNA Damage with increased CD8+T Cells
- Potential Synergistic antitumor activity partly mediated by STING pathway



Chemotherapy

- Immunogenic cell death
- Enhanced presentation of tumor specific antigens
- Increased T-Cell activation by DC



DC: Dendritic Cells
STING: Stimulator of Interferon Genes

Ciciola P, et al. J Clin Med. 2020; Bailly C, et al. NAR Cancer. 2020;Huang J.,et al. *Biochem and Biophy Res Comm*. 2015; 463:551-6; Sen et al. Cancer Discov 2019

Updated efficacy and safety of lenvatinib plus pembrolizumab versus treatment of physician's choice in patients with advanced endometrial cancer: Study 309/KEYNOTE-775

Vicky Makker[1], Nicoletta Colombo[2], Antonio Casado Herraez[3], Bradley J. Monk[4], Helen Mackay[5], Alessandro D. Santin[6], David S. Miller[7], Richard Moore[8], Sally Baron-Hay[9], Isabelle Ray-Coquard[10], Ronnie Shapira Frommer[11], Kimio Ushijima[12], Kan Yonemori[13], Yong Man Kim[14], Eva M. Guerra Alia[15], Ulus A. Sanli[16], Jie Huang[17], Jodi McKenzie[18], Gianmaria Barresi[19], Domenica Lorusso[20]

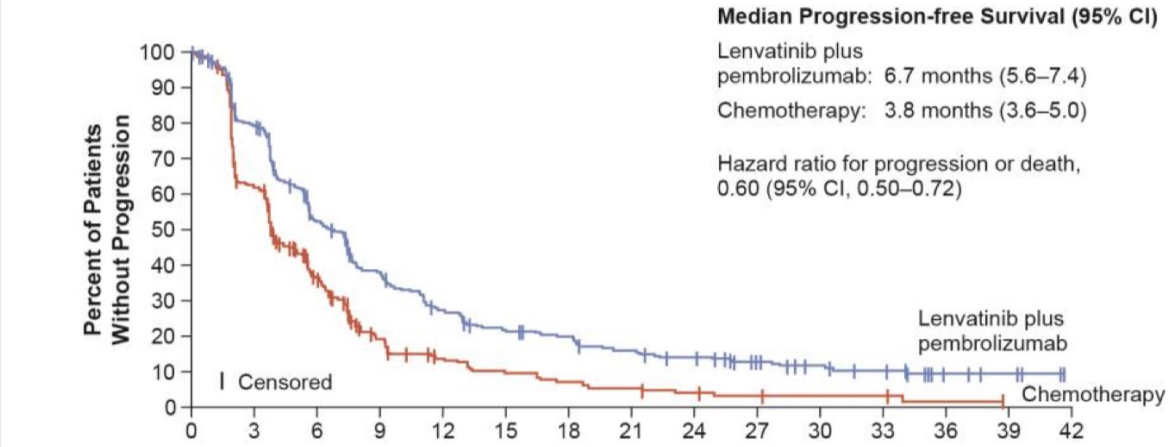
PARIS 2022 ESMO congress

ESMO 2022;Abstract 525MO.

RTP RESEARCH TO PRACTICE

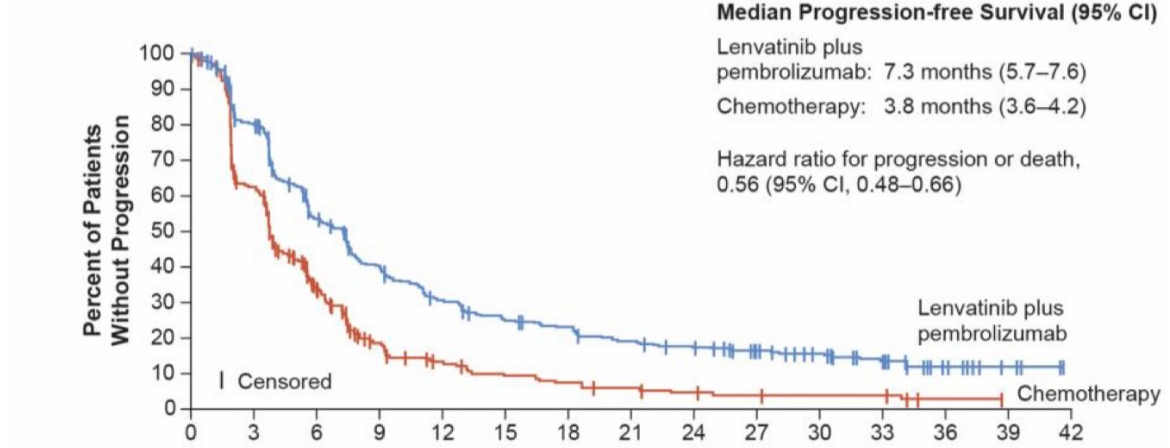
KEYNOTE-775: Progression-Free Survival in pMMR and All-Comer Patient Populations

pMMR Population



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

All-Comer Population

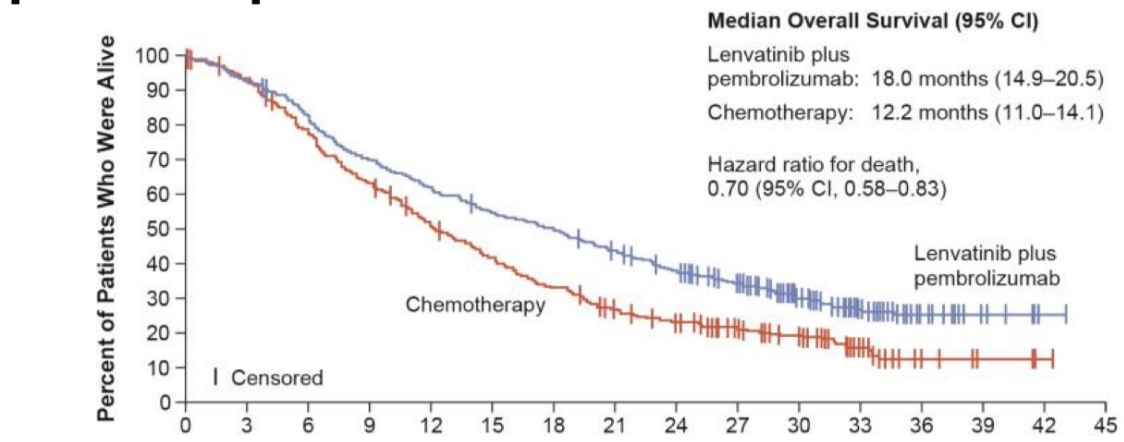


No. at risk															
Lenvatinib plus pembrolizumab	411	317	203	148	109	87	79	65	57	45	35	23	10	4	0
Chemotherapy	416	214	95	43	27	19	15	11	8	6	5	5	1	0	0

Makker V et al. ESMO 2022;Abstract 525MO.

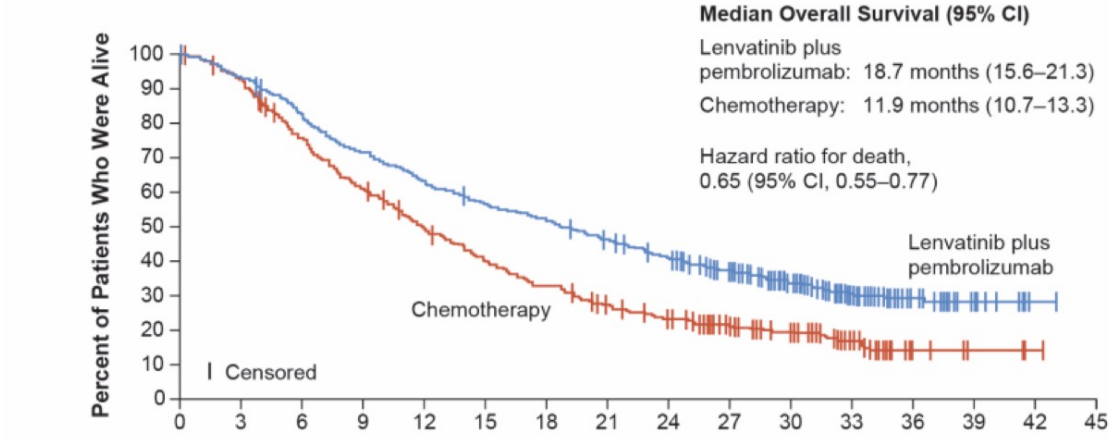
KEYNOTE-775: Overall Survival in pMMR and All-Comer Patient Populations

pMMR Population



No. at risk															
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

All-Comer Population



No. at risk															
Lenvatinib plus pembrolizumab	411	383	337	292	258	229	211	186	160	125	91	58	30	10	2
Chemotherapy	416	378	305	246	196	158	129	104	84	64	49	28	6	3	1

Makker V et al. ESMO 2022;Abstract 525MO.

RTP RESEARCH TO PRACTICE

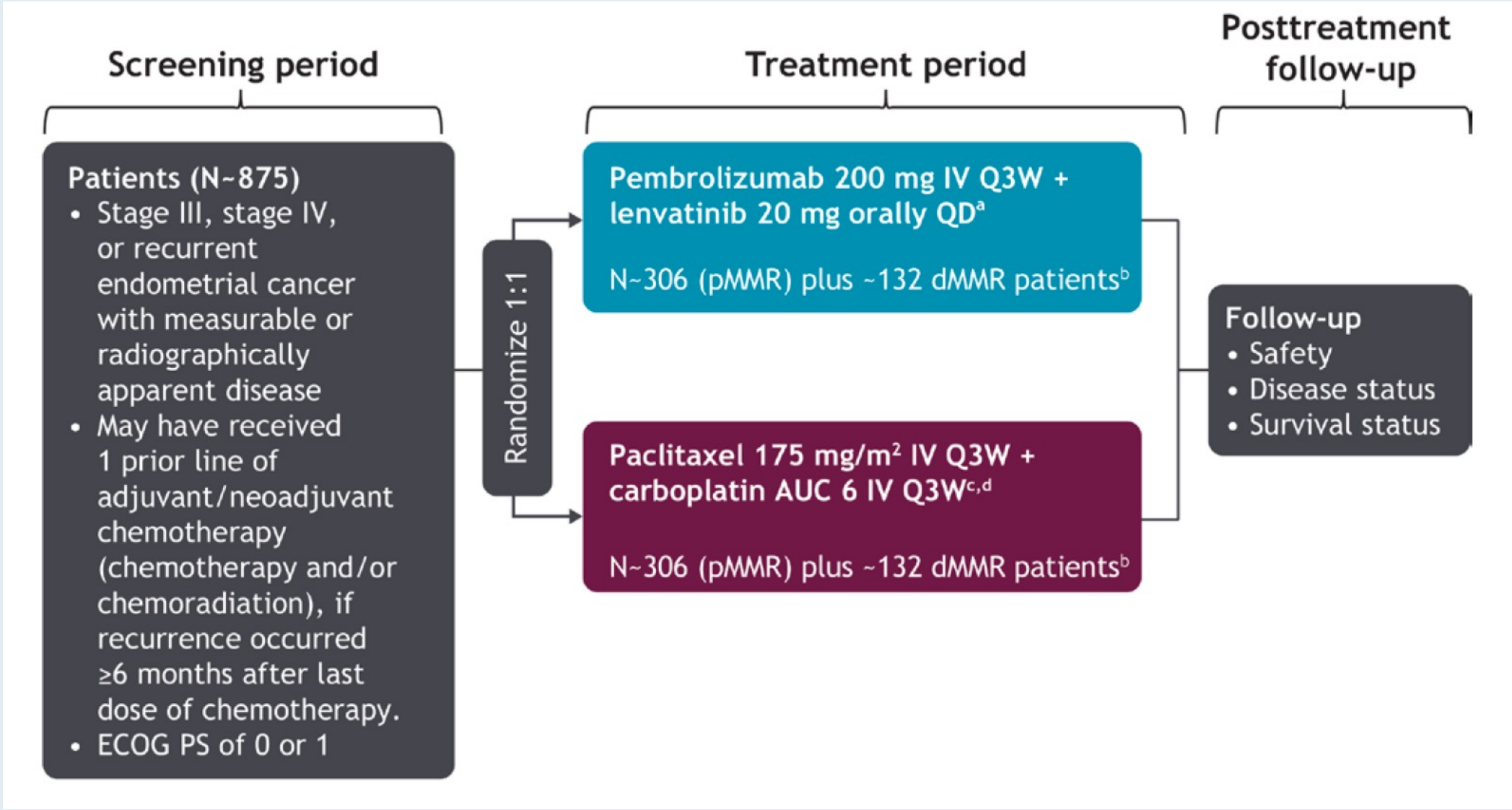
KEYNOTE-775: Treatment-Emergent Adverse Events (TEAEs)

Preferred Term[a]	LEN + pembro (n = 406)		Chemotherapy (n = 388)	
	Any grade	Grade ≥ 3[b]	Any grade	Grade ≥ 3[b]
TEAEs, n (%)	405 (99.8)	366 (90.1)	386 (99.5)	286 (73.7)
Hypertension	264 (65.0)	159 (39.2)	20 (5.2)	10 (2.6)
Hypothyroidism	239 (58.9)	6 (1.5)	3 (0.8)	0 (0.0)
Diarrhea	226 (55.7)	33 (8.1)	79 (20.4)	8 (2.1)
Nausea	210 (51.7)	14 (3.4)	180 (46.4)	5 (1.3)
Decreased appetite	189 (46.6)	31 (7.6)	83 (21.4)	2 (0.5)
Vomiting	153 (37.7)	12 (3.0)	82 (21.1)	10 (2.6)
Weight decreased	144 (35.5)	44 (10.8)	23 (5.9)	1 (0.3)
Fatigue	138 (34.0)	22 (5.4)	107 (27.6)	12 (3.1)
Arthralgia	131 (32.3)	7 (1.7)	31 (8.0)	0 (0.0)
Proteinuria	124 (30.5)	21 (5.2)	13 (3.4)	1 (0.3)
Treatment-related TEAEs, n (%)[c]	395 (97.3)	320 (78.8)	364 (93.8)	233 (60.1)
Adverse events of special interest (for pembro), n (%)[d]	279 (68.7)	54 (13.3)	17 (4.4)	1 (0.3)
Clinically significant adverse events (for LEN), n (%)[d]	386 (95.1)	227 (55.9)	149 (38.4)	51 (13.1)
Dose interruption due to TEAE[e]	292 (71.9)	---	110 (28.4)	---
Dose reduction due to TEAE[f]	273 (67.2)	---	49 (12.6)	---
Treatment discontinuation due to TEAE[g]	159 (39.2)	---	31 (8.0)	---
Discontinuation of LEN	145 (35.7)	---	---	---
Discontinuation of pembro	90 (22.2)	---	---	---
Discontinuation of both LEN and pembro	65 (16.0)	---	---	---

Makker V et al. ESMO 2022;Abstract 525MO.

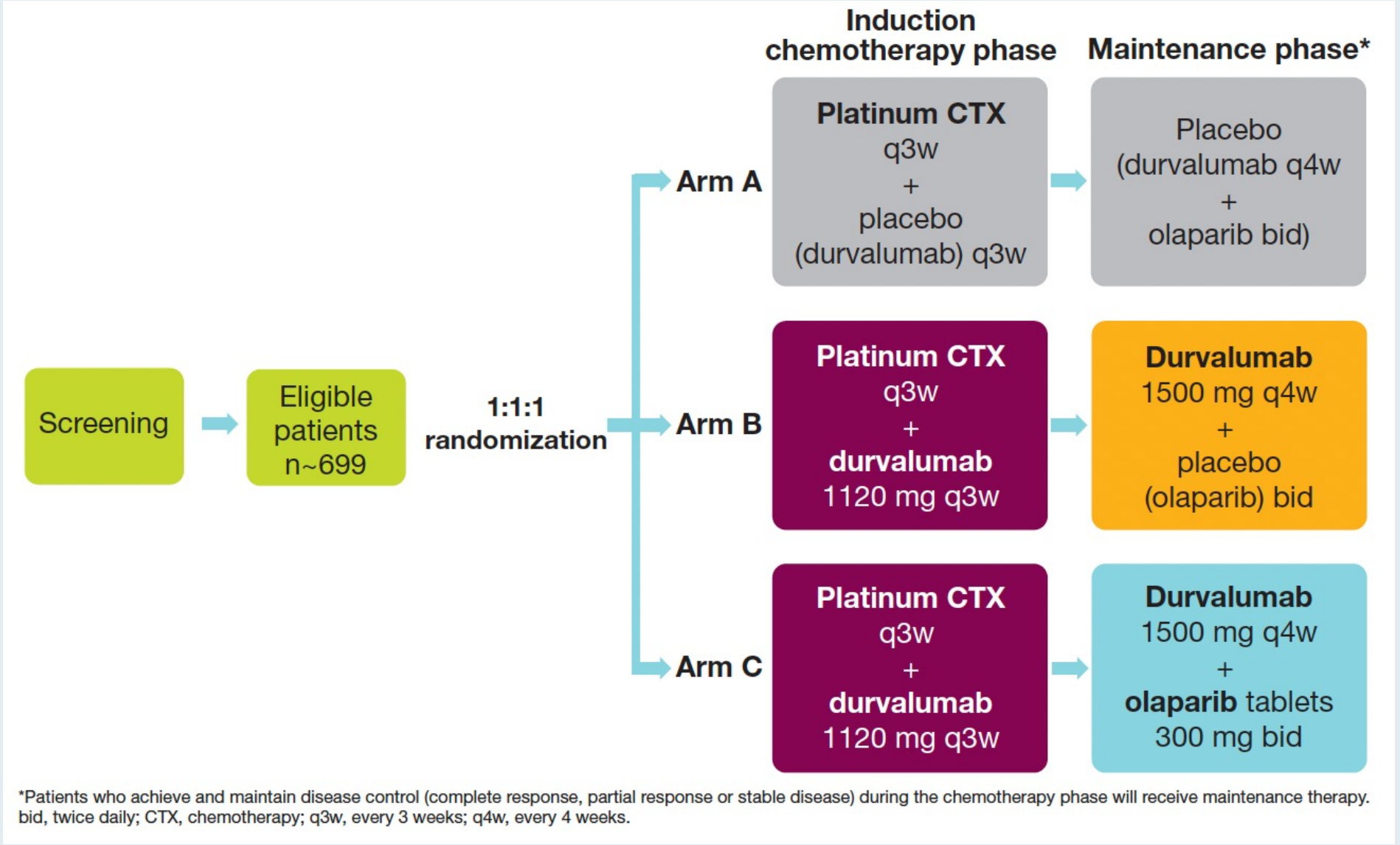
RTP RESEARCH TO PRACTICE

ENGOT-EN9/LEAP-001 Phase III Study Design



Marth et al. *Int J Gynecol Cancer* 2022;32(1):93-100.

DUO-E Study Design

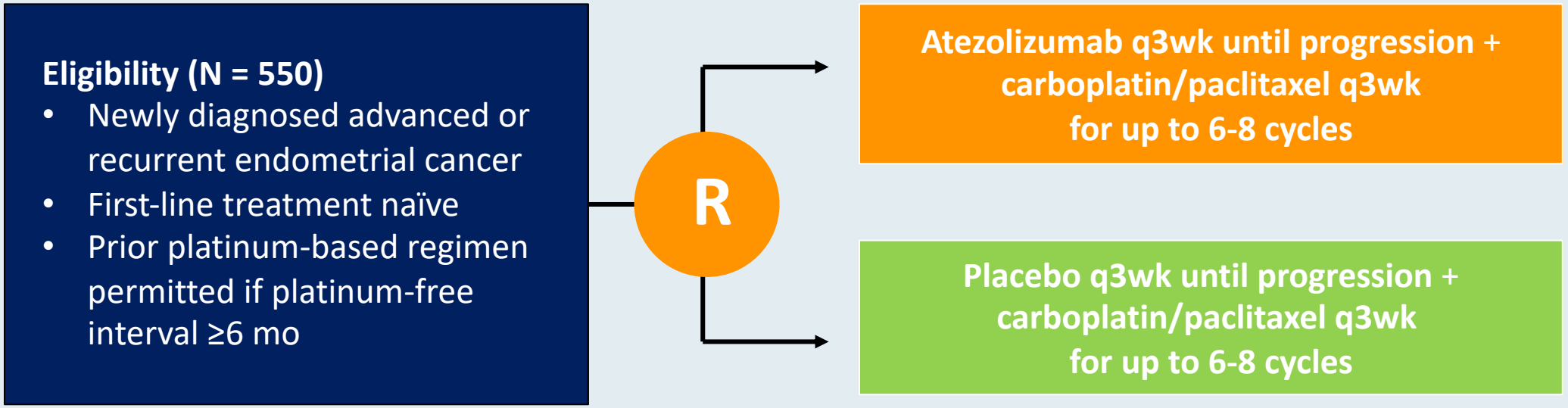


*Patients who achieve and maintain disease control (complete response, partial response or stable disease) during the chemotherapy phase will receive maintenance therapy.
bid, twice daily; CTX, chemotherapy; q3w, every 3 weeks; q4w, every 4 weeks.

Westin SN et al. ASCO 2020;Abstract TPS6108.

RTP RESEARCH TO PRACTICE

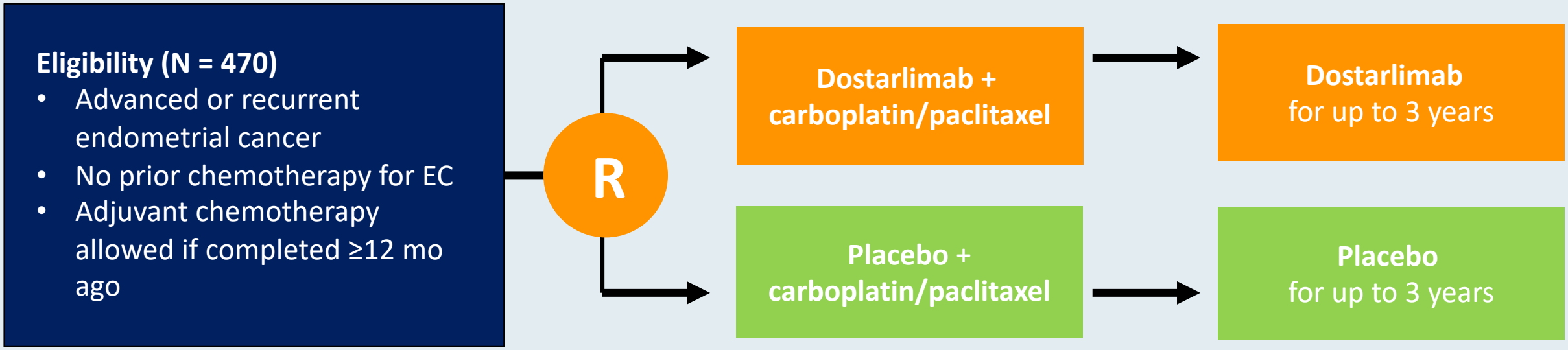
Phase III AtTEnD/ENGOT-EN7 Study Schema



Primary endpoints: OS, PFS
Secondary endpoints: Objective response rate, duration of response, safety

www.clinicaltrials.gov. NCT03603184. Accessed October 2022.

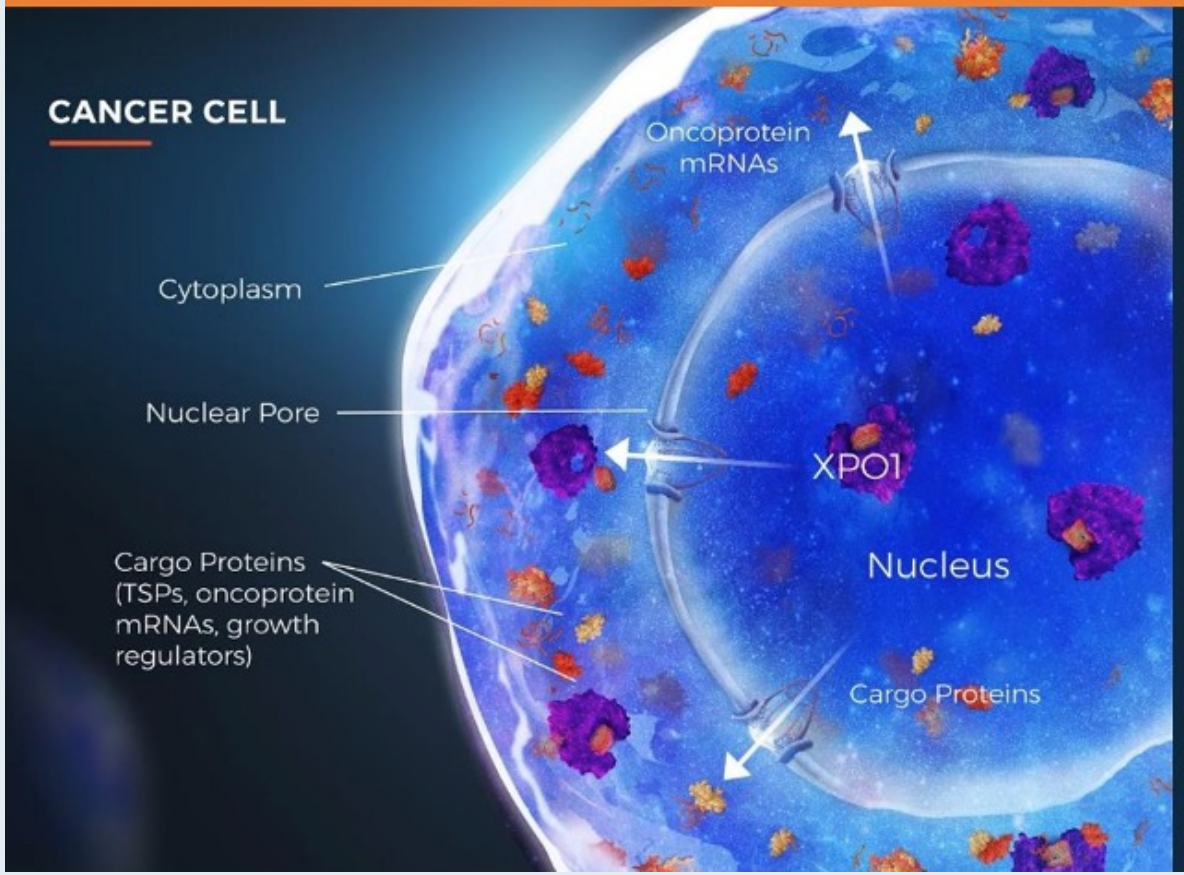
Phase III RUBY/ENGOT-EN6 Study Schema



Primary endpoint: PFS
Secondary endpoints: OS, ORR (objective response rate), DoR, Safety, PRO

www.clinicaltrials.gov. NCT03981796. Accessed October 2022.

Mechanism of Action of Selinexor



Selinexor is an oral selective inhibitor of XPO1-mediated nuclear export (SINE) compound

- XPO1 exports the major tumor suppressor proteins (TSPs) including p53 away from the nucleus, where TSPs carry out their function
- Tumor cells overexpress XPO1
- Tumor cells inactivate cytoplasmic *p53* through protein degradation
- Selinexor inhibits XPO1 nuclear export, leads to retention / reactivation of TSPs in the nucleus and stabilization of p53
- Retention of wild-type *p53* (p53wt) and other TSPs in the cell nucleus leads to selective killing of cancer cells, while largely sparing normal cells

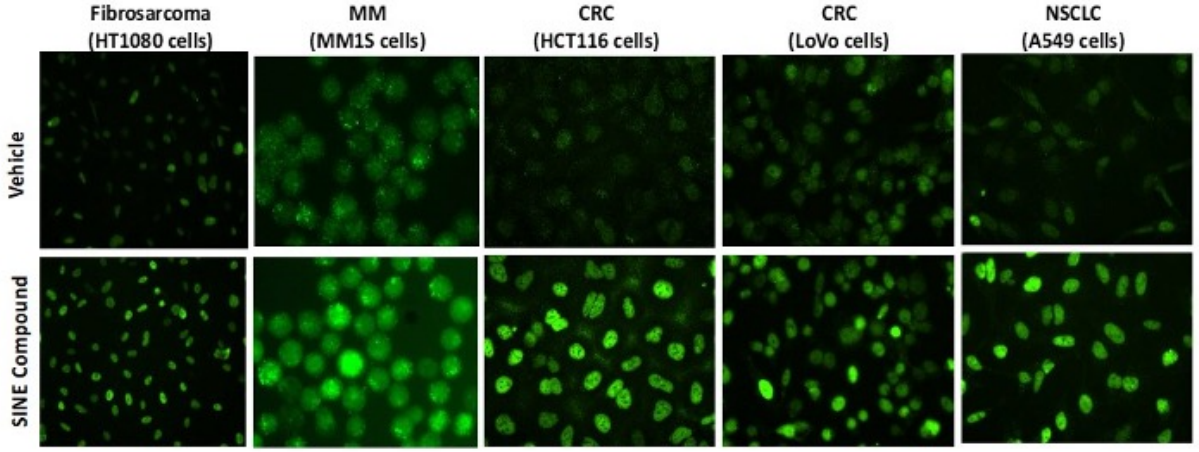
Makker V et al. ASCO 2022;Abstract 5511.

RTP RESEARCH TO PRACTICE

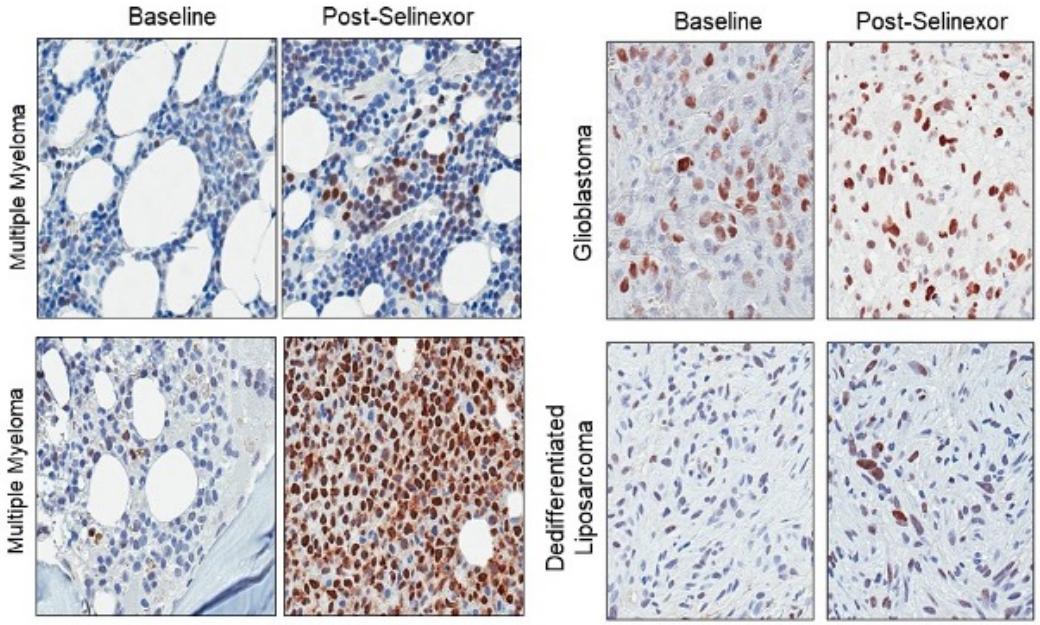
Selinexor Induces Nuclear Accumulation of p53

- Aberrant XPO1 mediated nuclear export of p53 is a mechanism by which cancer cells can inhibit p53
- Inhibition of XPO1 leads to nuclear accumulation of p53 across cancer types, as demonstrated in cell lines and patient samples
- p53 wild-type tumors account for 45-65% of all endometrial cancers
  - Generally, endometrioid in histology and occurs in younger patients

p53 IF in cell lines



p53 IHC in human patient samples



Oncogenic signaling pathways in The Cancer Genome Atlas. Cell. 2018; 173: 321-37
Pan-cancer analysis of whole genomes. Nature. 2020; 578: 82-93
Soumerai et al. Clin Cancer Res. 2018; 24: 5939-47

Makker V et al. ASCO 2022;Abstract 5511.

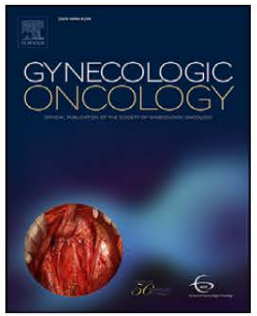
RTP RESEARCH TO PRACTICE

Gynecologic Oncology 156 (2020) 308–314

Contents lists available at ScienceDirect

Gynecologic Oncology

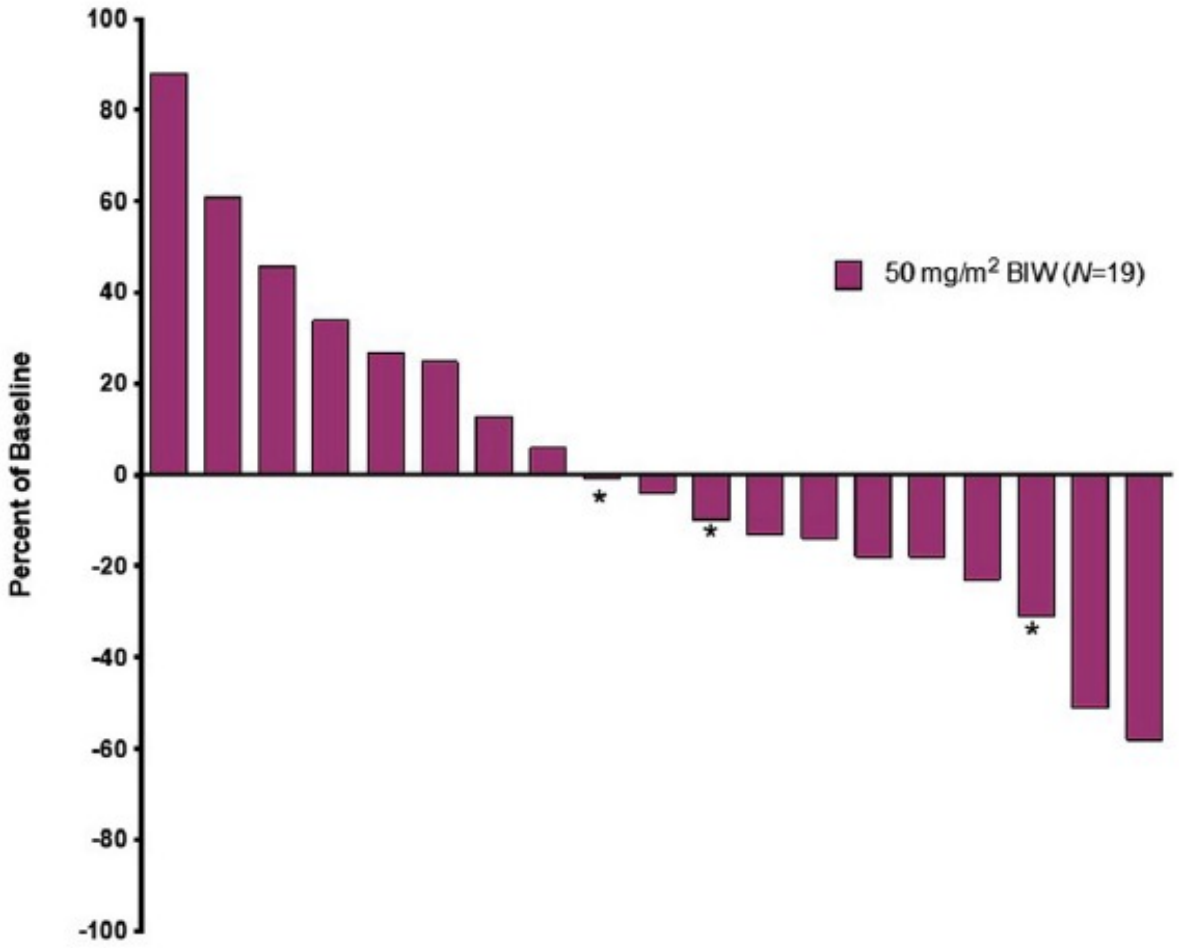
journal homepage: www.elsevier.com/locate/ygyno



Phase 2 study of the Exportin 1 inhibitor selinexor in patients with recurrent gynecological malignancies

I.B. Vergote [a, *], B. Lund [b], U. Peen [c], Z. Umajuridze [d], M. Mau-Sorensen [d], A. Kranich [e], E. Van Nieuwenhuysen [a], C. Haslund [b], T. Nottrup [d], S.N. Han [a], N. Concin [a], T.J. Unger [f], Y. Chai [f], N. Au [f], T. Rashal [f], A. Joshi [f], M. Crochiere [f], Y. Landesman [f], J. Shah [f], S. Shacham [f], M. Kauffman [f], M.R. Mirza [f]

Efficacy of Selinexor in a Phase II Study Among Patients with Recurrent Endometrial Cancer



Efficacy endpoints	N =23
Disease control rate (DCR)	35%
Median duration of DCR	6.3 mo
Partial response rate	9%
Median PFS	2.8 mo
Median OS	7.0 mo

Median prior regimens (range): 2 (1-5)

Vergote IB et al. *Gynecol Oncol* 2020;156(2):308-14.

2022 ASCO® ANNUAL MEETING

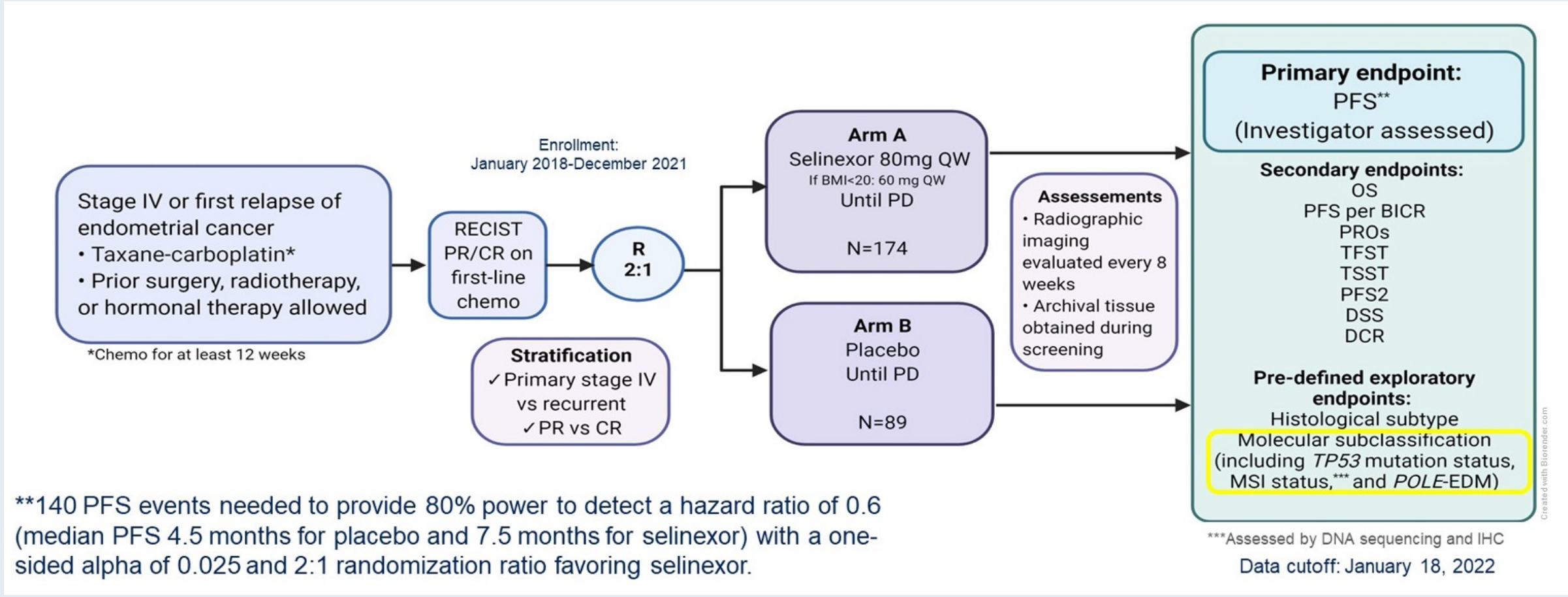
Abstract 5511.

Randomized Phase III Study of Maintenance Selinexor vs Placebo in Endometrial Cancer (ENGOT-EN5/GOG-3055/SIENDO): Impact of Subgroup Analysis and Molecular Classification

Vicky Makker[1], J Alejandro Pérez-Fidalgo[2], Alice Bergamini[3], Daniel Spitz[4], Toon Van Gorp[5], Jalid Sehouli[6], Jaroslav Klat[7], Tamar Perri[8], Amit Oza[9], Estrid Høgdall[10], Jason Konner[11], Eva M Guerra-Alia[12], Francesco Raspagliesi[13], Stéphanie Henry[14], Bradley J. Monk[15], Jerónimo Martínez[16], Brian Slomovitz[17], Sharon Shacham[18], Mansoor Raza Mirza[19], Ignace Vergote[5]

RTP RESEARCH TO PRACTICE

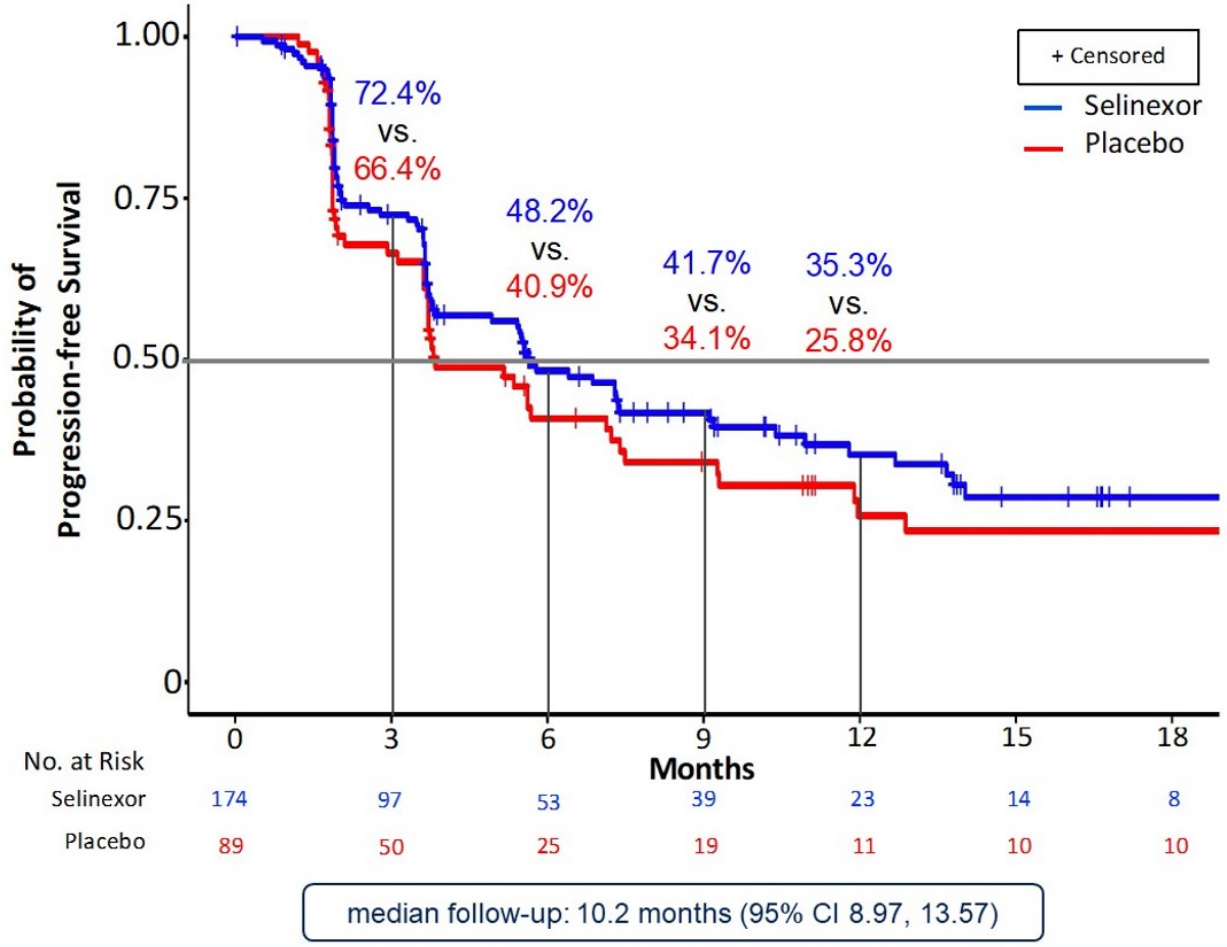
SIENDO/ENGOT-EN5 Phase III Study Design



Makker V et al. ASCO 2022;Abstract 5511.

RTP RESEARCH TO PRACTICE

SIENDO/ENGOT-EN5 Primary Endpoint: PFS (Intent-to-Treat Population)



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)

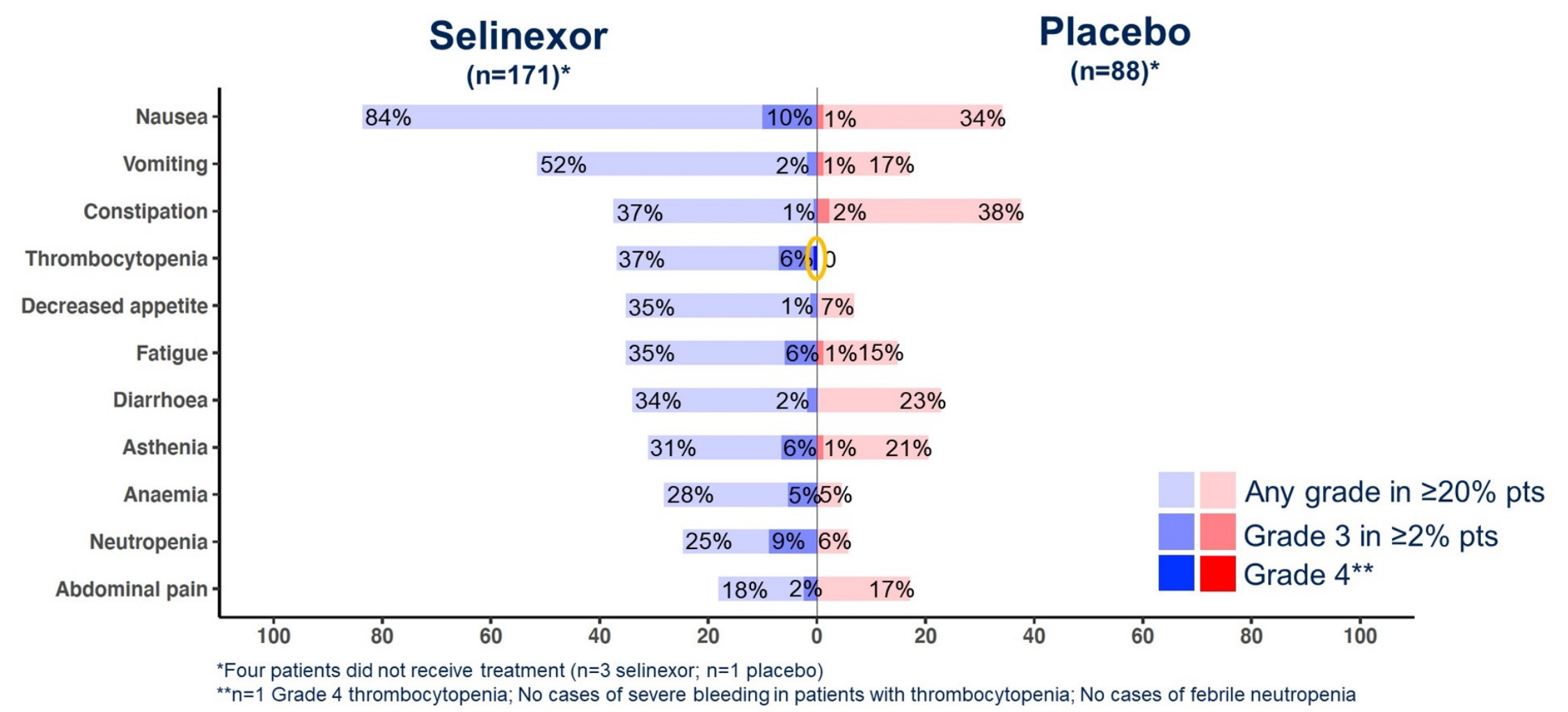
One-sided P value = 0.063

*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

Makker V et al. ASCO 2022;Abstract 5511.

SIENDO/ENGOT-EN5: Treatment-Emergent Adverse Events



*Four patients did not receive treatment (n=3 selinexor; n=1 placebo)
**n=1 Grade 4 thrombocytopenia; No cases of severe bleeding in patients with thrombocytopenia; No cases of febrile neutropenia

Makker V et al. ASCO 2022;Abstract 5511.

SIENDO/ENGOT-EN5: Preliminary Exploratory Analysis of Mutually-Exclusive TCGA Subgroups

	Selinexor	Placebo	*One-sided p-value* (nominal)	HR (95% CI)
	Progression-free survival — median, (months)			
POLE mutated (selinexor n=2, placebo n=4)				
Stratification-adjusted, audited	3.8	1.9	0.404	0.71 (0.04-11.79)
Stratification-adjusted, unaudited			0.404	0.71 (0.04-11.79)
MSI-H (selinexor n=18, placebo n=8)				
Stratification-adjusted, audited	6.4	NR	0.685	1.41 (0.35-5.67)
Stratification-adjusted, unaudited			0.685	1.41 (0.35-5.67)
Copy number low (selinexor n=37, placebo n=20)				
Stratification-adjusted, audited	NR	3.7	<0.0001	0.16 (0.06-0.44)
Stratification-adjusted, unaudited			0.0004	0.22 (0.09-0.58)
Copy number high (selinexor n=50, placebo n=33)				
Stratification-adjusted, audited	3.7	5.6	0.820	1.31 (0.74-2.31)
Stratification-adjusted, unaudited			0.860	1.37 (0.77-2.41)

Makker V et al. ASCO 2022;Abstract 5511.

Thank you for joining us!

CME, MOC and NCPD credit information will be emailed to each participant within 5 business days.

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We are taking a short break!

The program will resume at 3:50 PM ET

Up Next…

Dr O'Malley discusses PARP inhibitors and the management of ovarian cancer

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