

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**

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: *Dr Abou-Alfa*

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

Endometrial Cancer Agenda

MODULE 1: “Biomarker”-Guided Therapy for Endometrial Cancer

MODULE 2: Targeted Therapy for Endometrial Cancer; New Directions

Endometrial Cancer Agenda

MODULE 1: “Biomarker”-Guided Therapy for Endometrial Cancer

MODULE 2: Targeted Therapy for Endometrial Cancer; New Directions

Lenvatinib and Pembrolizumab in Recurrent Endometrial Cancer

Shannon N. Westin, MD, MPH

Professor

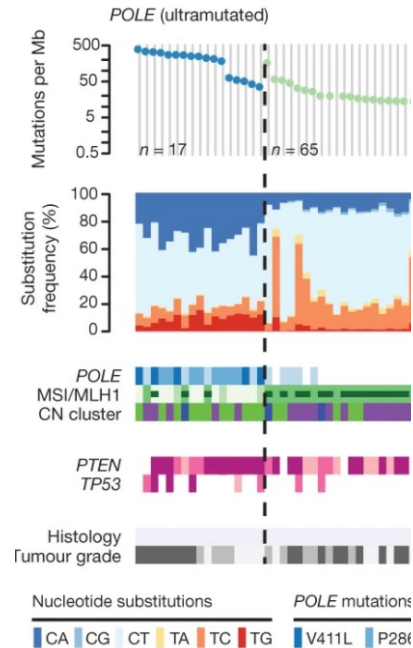
Department of Gynecologic Oncology and
Reproductive Medicine

THE UNIVERSITY OF TEXAS
MD Anderson
~~Cancer~~ Center

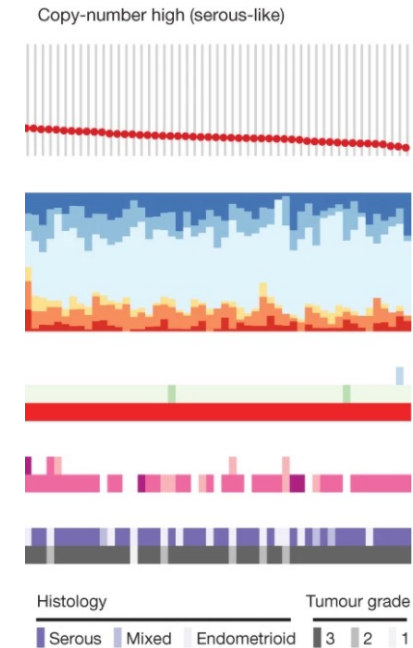
Making Cancer History®

One Size Fits All?

There are clear molecular differences in
endometrial cancer



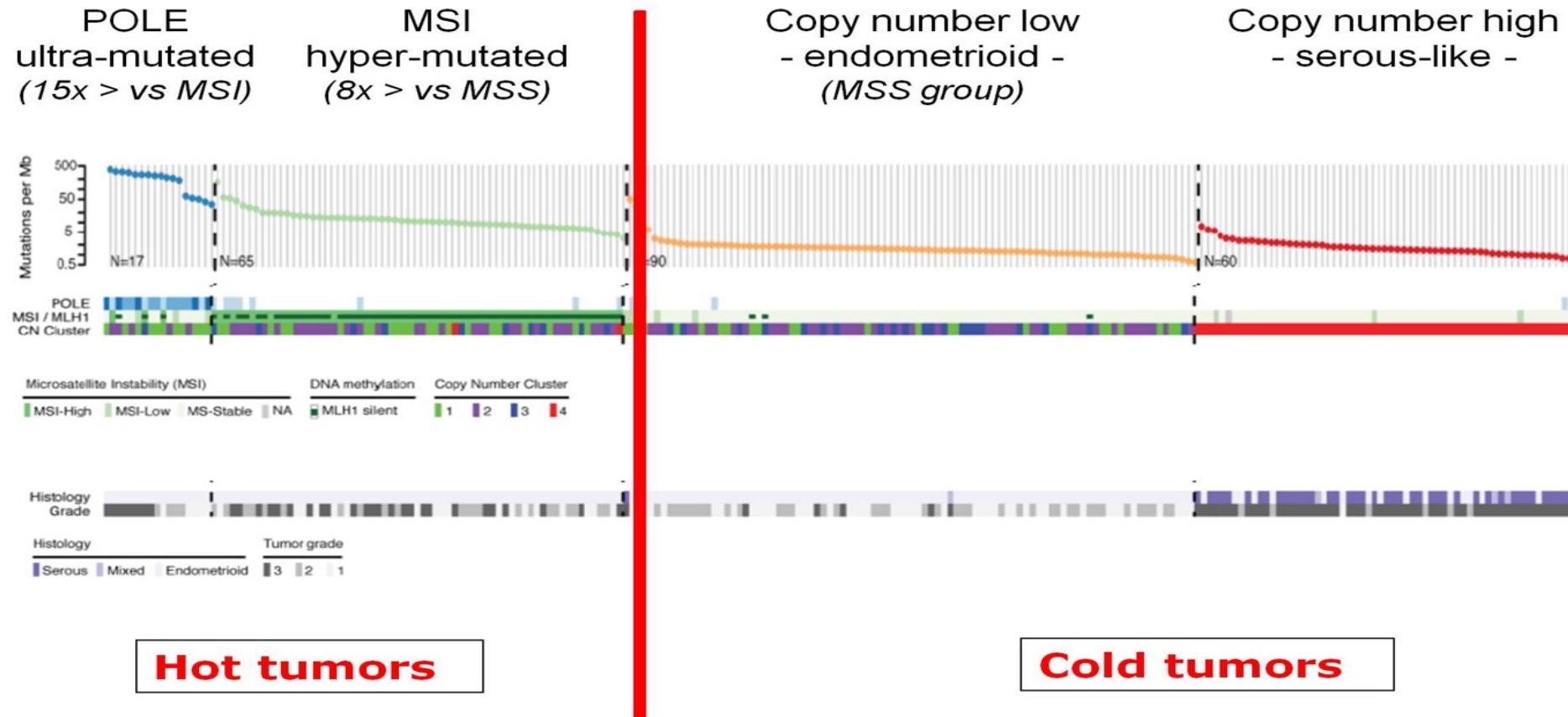
**Paclitaxel
and
Carboplatin**



Hot Tumors and IO

Endometrial Cancer (EC) – Four molecular subtypes

(Integrated genomic, transcriptomic and proteomic characterization)



Kandoth et al., Nature 2013

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.

“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)	–

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%

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

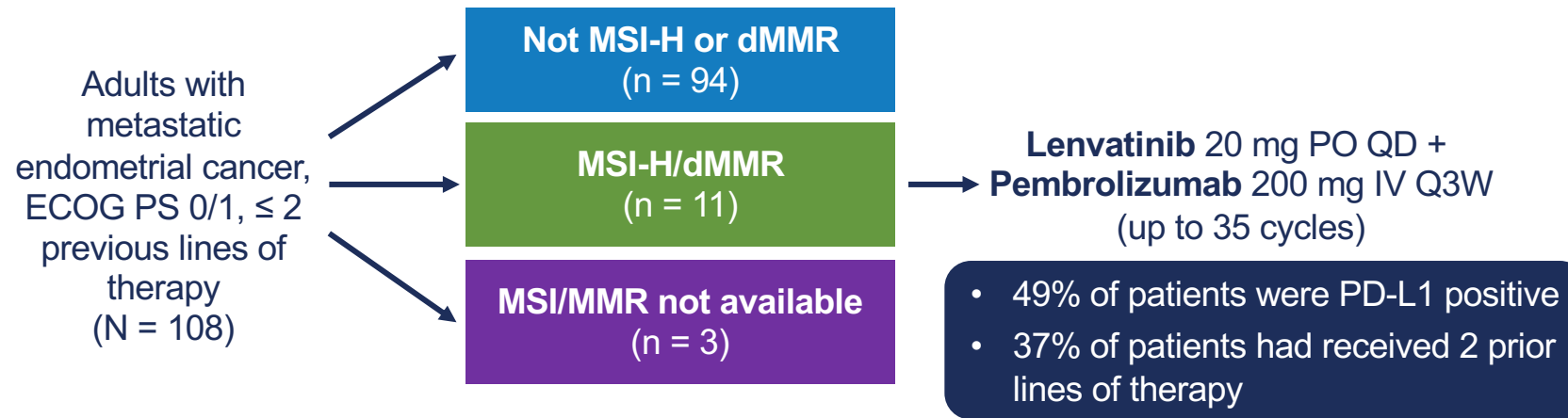
Ott PA et al. J Clin Oncol 2017

Antill PSK et al. J Clin Oncol 2019

Oaknin A et al. Gynecol Oncol 2019

Konstantinopoulos PA et al. J Clin Oncol 2019

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

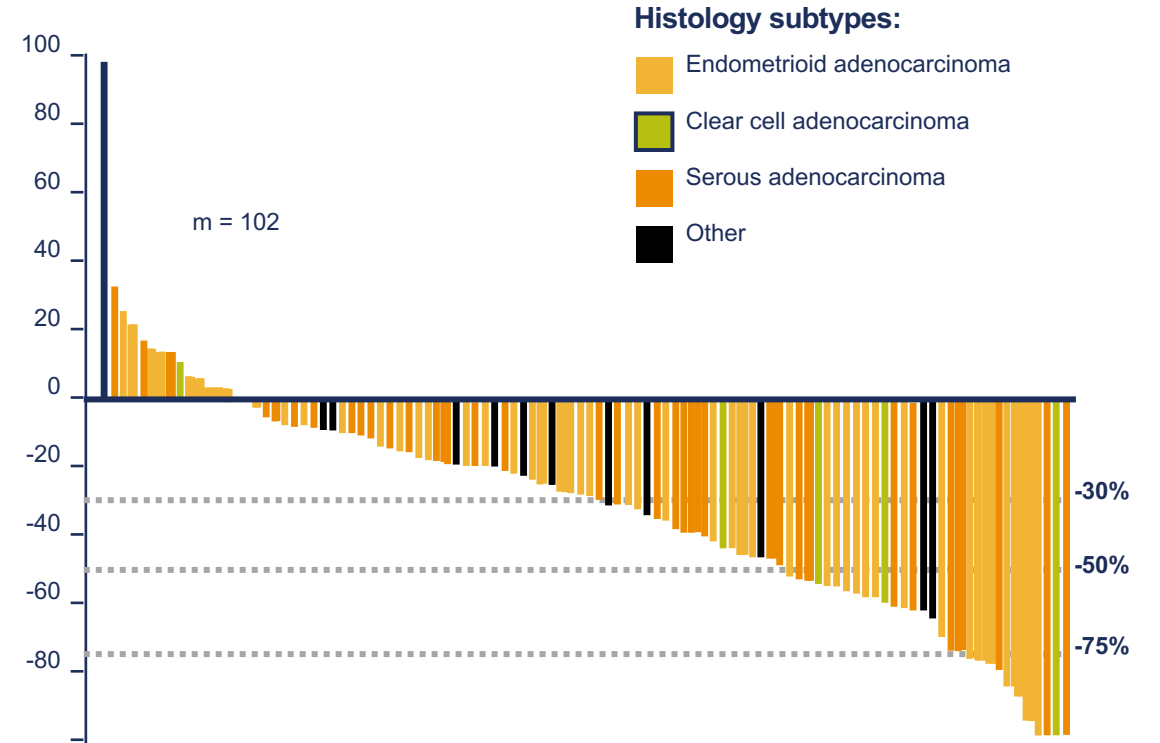
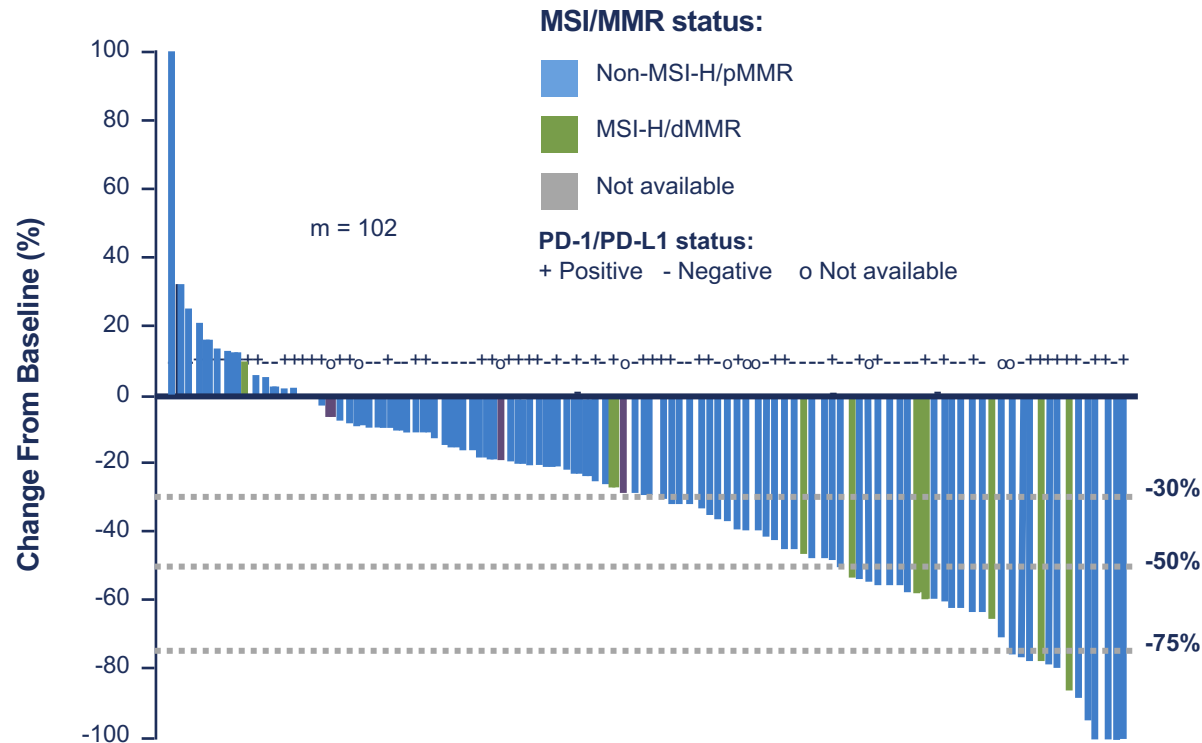


- Primary endpoint: ORR at Wk 24 (responses confirmed with secondary assessment > 4 wks later)
- Secondary endpoints: ORR, DoR, PFS, OS, DCR, CBR, safety

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)

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

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%)

KEYNOTE-775: Lenvatinib + Pembrolizumab vs SOC

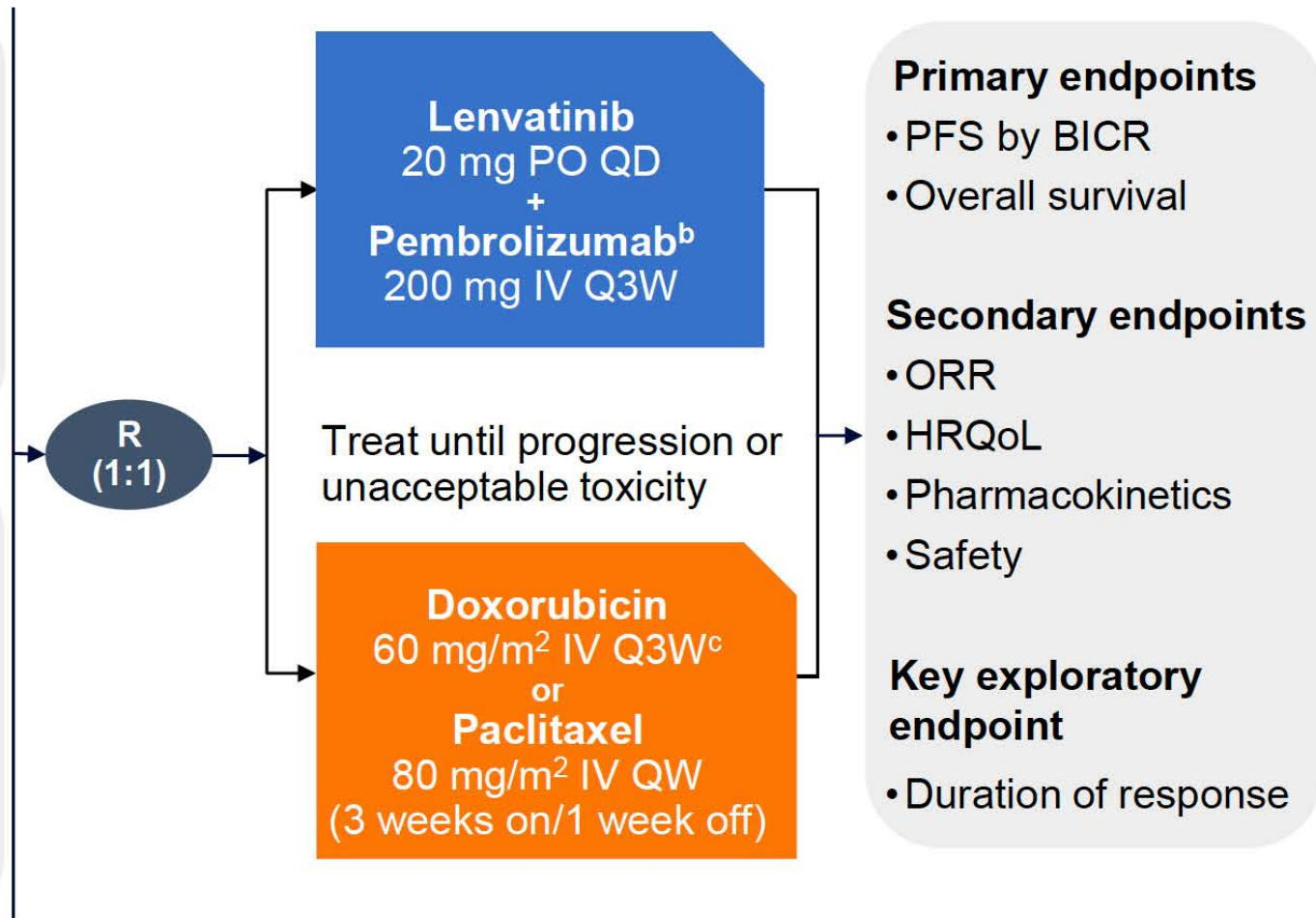
Key eligibility criteria

- 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

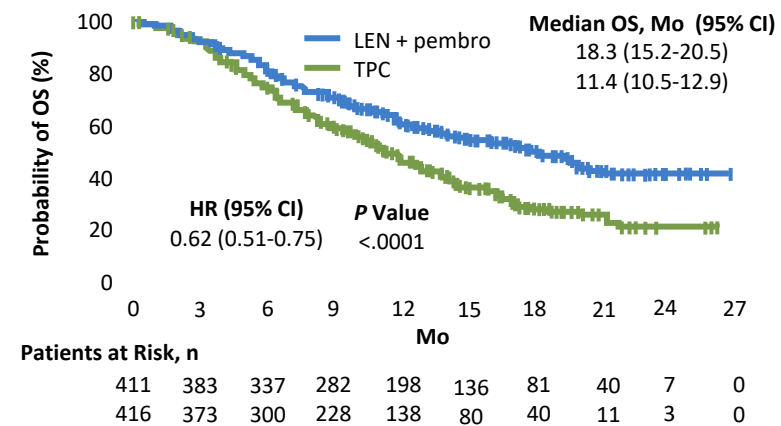
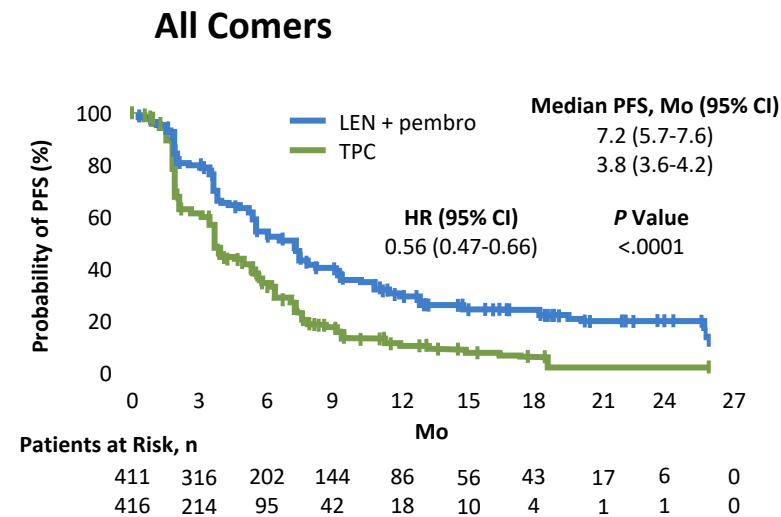
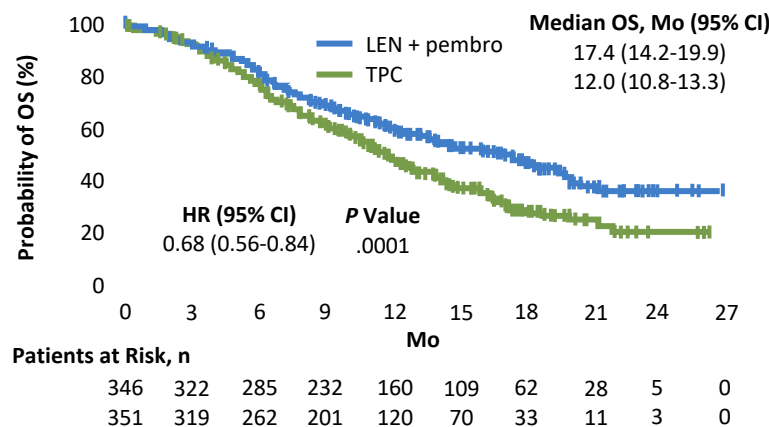
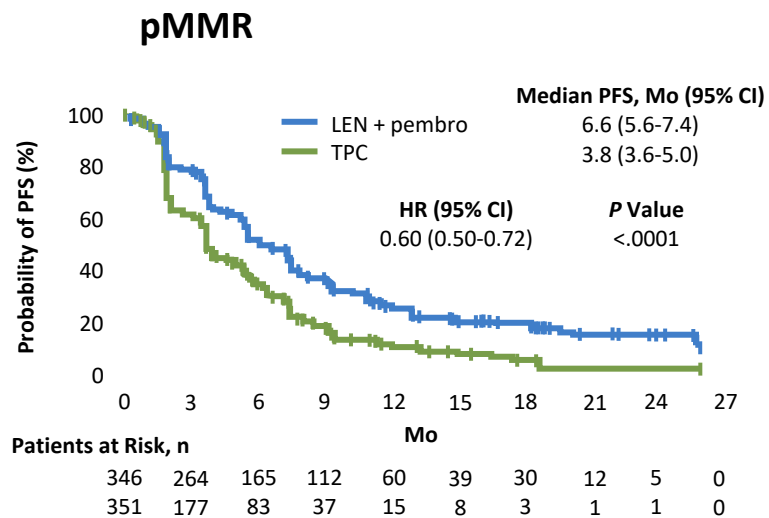
Stratification factors

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)



KEYNOTE-775: PFS and OS Benefit



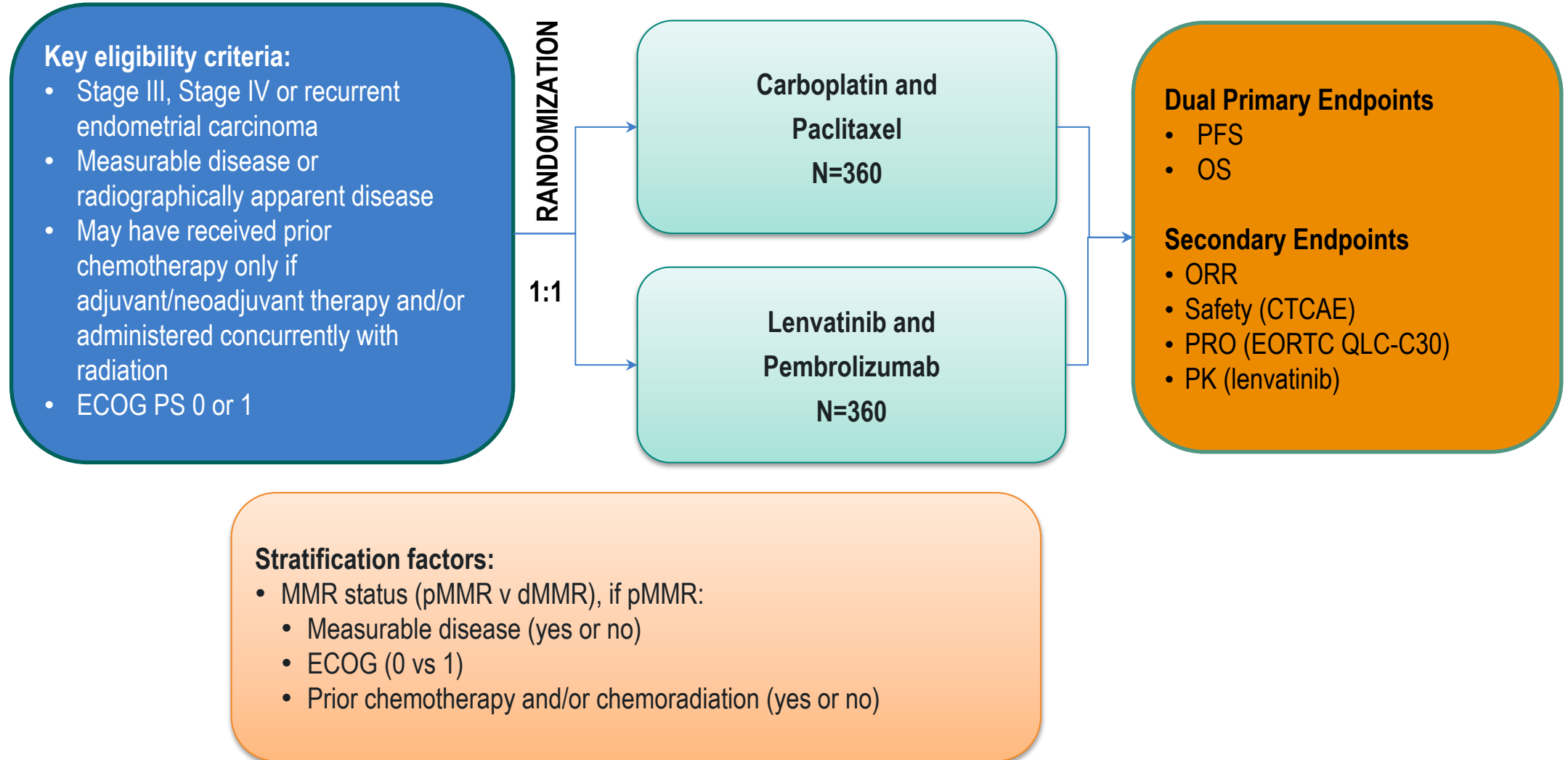
KEYNOTE-775: TEAEs

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%]).

LEAP-001: First line phase 3



Prevention of Treatment-Related AEs

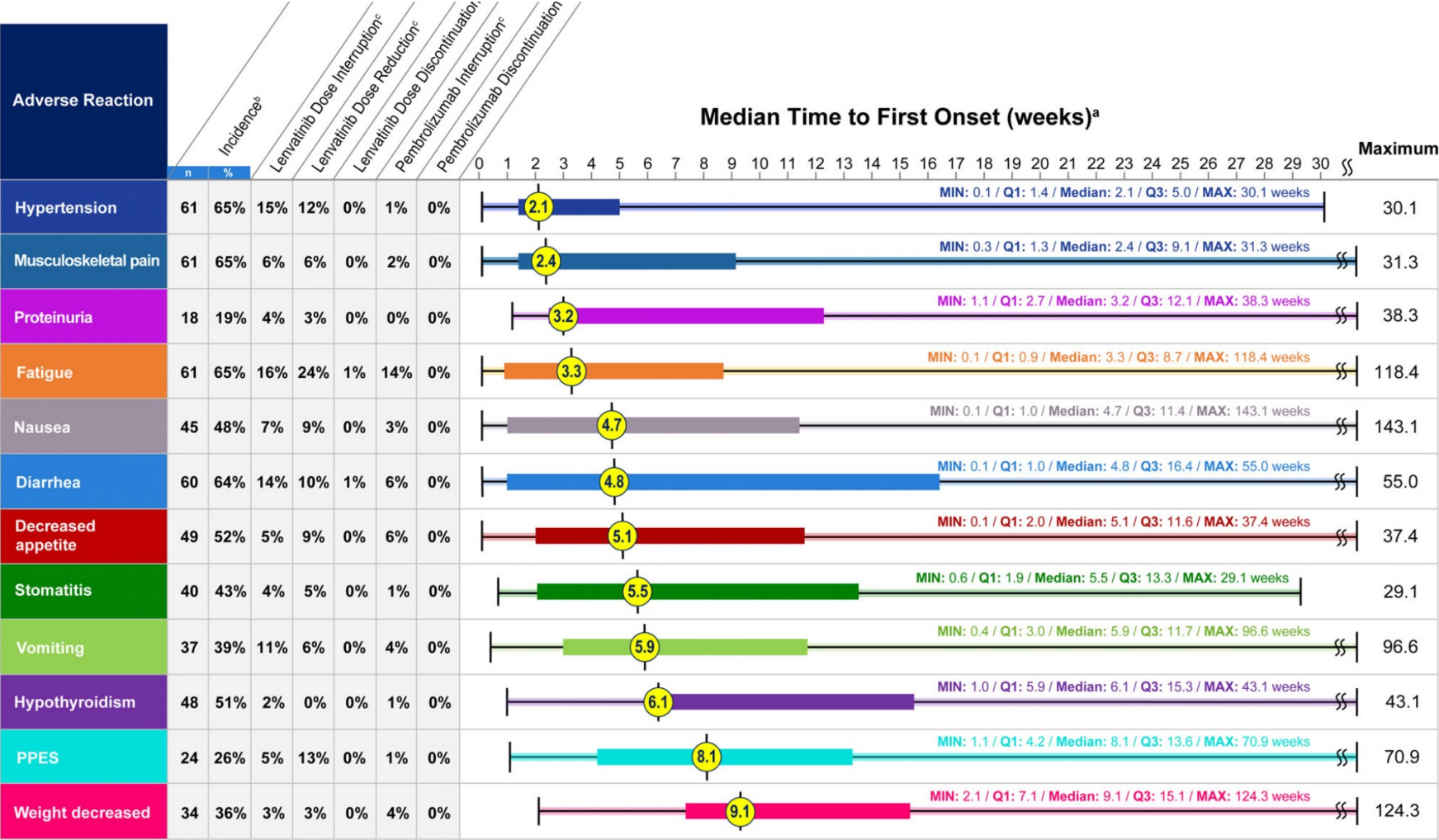
- Patient selection
- Treatment settings
- Clinical trial access
- Team education and communication
- Patient education and expectation setting
- Multidisciplinary care

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)	<ul style="list-style-type: none">▪ Symptomatic management▪ Continue therapy▪ Immunosuppression not needed
2 (mild to moderate)	<ul style="list-style-type: none">▪ Symptomatic management▪ Consider discontinuing until resolution to grade 1▪ Consider immunosuppression if intolerable or persistent▪ Involve consultants as needed
3 or 4 (severe)	<ul style="list-style-type: none">▪ Discontinue therapy▪ Start immunosuppression▪ Refer/involve consultants▪ At resolution, gradually taper off immunosuppression

Len/Pem Toxicity



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

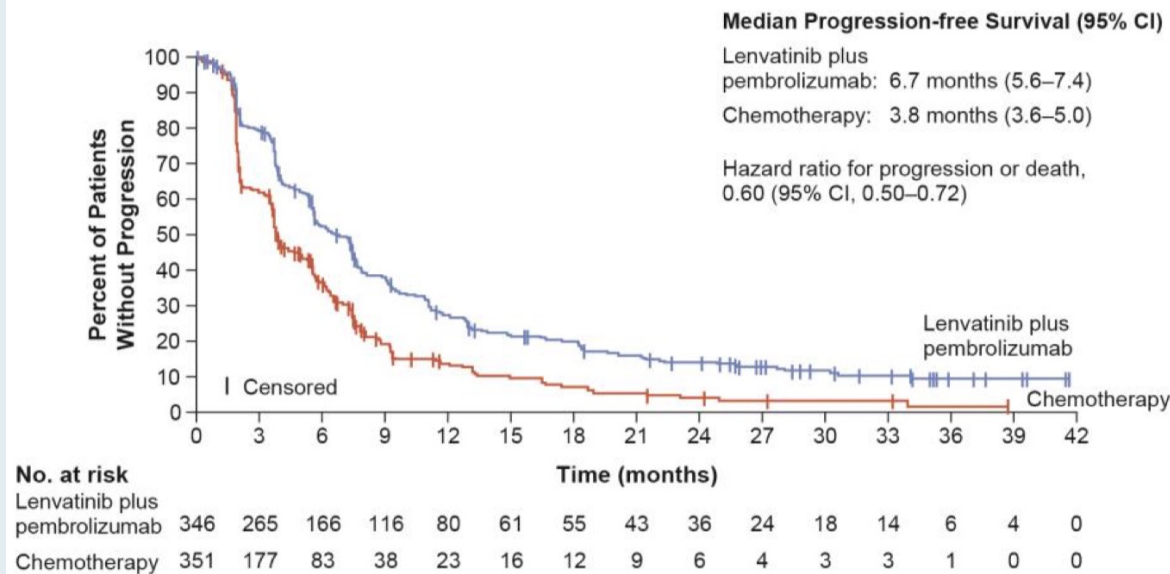
Immunotherapy in Advanced Endometrial Cancer

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

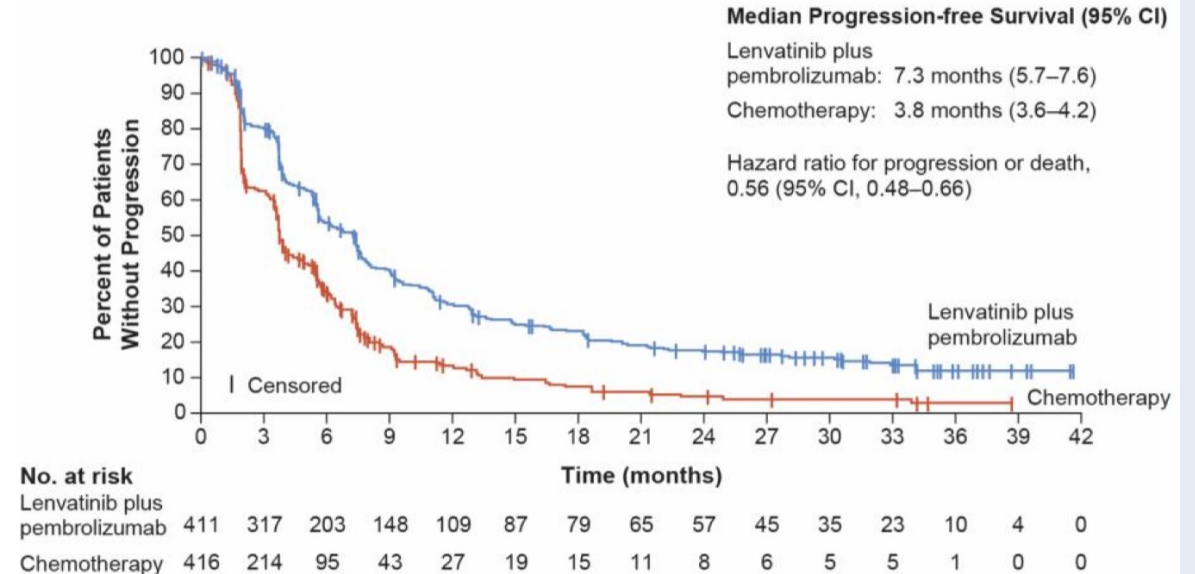
Vicky Makker¹, Nicoletta Colombo², Antonio Casado Herraiez³,
Bradley J. Monk⁴, Helen Mackay⁵, Alessandro D. Santin⁶,
David S. Miller⁷, Richard Moore⁸, Sally Baron-Hay⁹, Isabelle Ray-Coquard¹⁰,
Ronnie Shapira Frommer¹¹, Kimio Ushijima¹², Kan Yonemori¹³, Yong Man Kim¹⁴,
Eva M. Guerra Alia¹⁵, Ulus A. Sanli¹⁶, Jie Huang¹⁷, Jodi McKenzie¹⁸,
Gianmaria Barresi¹⁹, Domenica Lorusso²⁰

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

pMMR Population

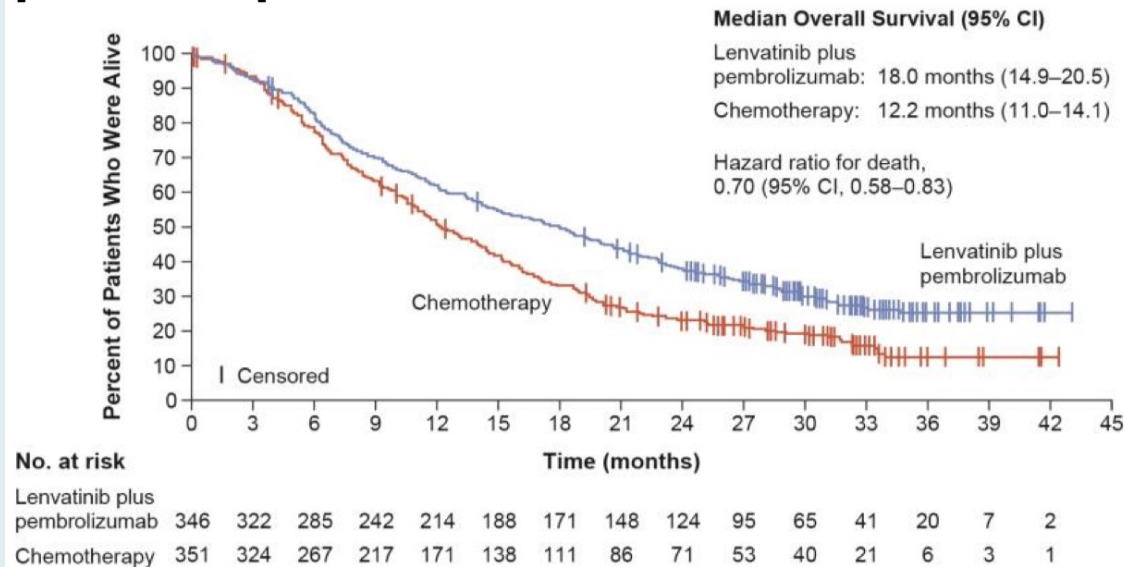


All-Comer Population

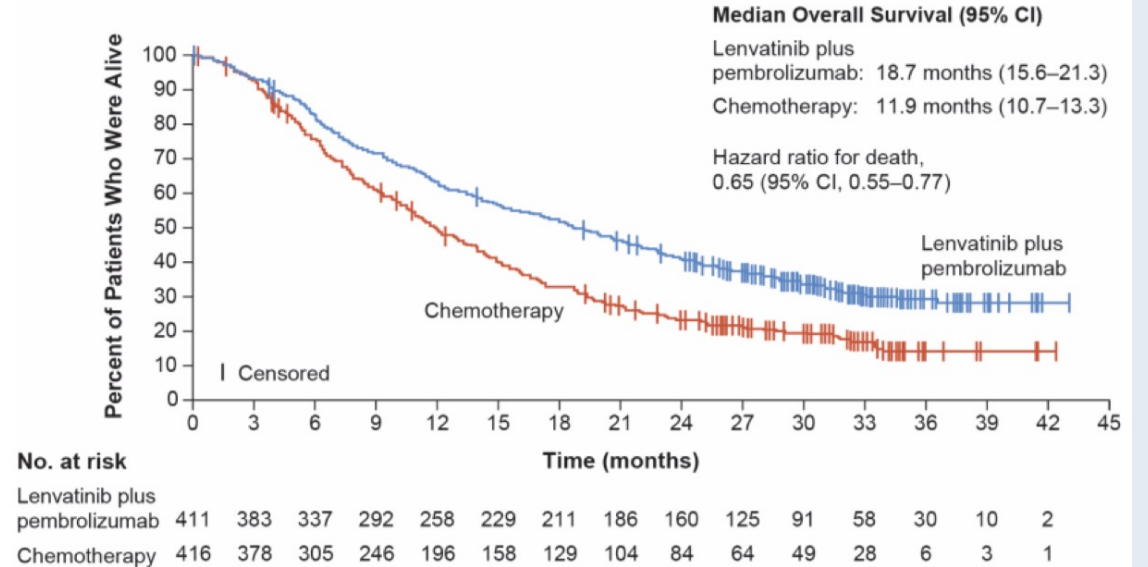


KEYNOTE-775: Overall Survival in pMMR and All-Comer Patient Populations

pMMR Population



All-Comer Population



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

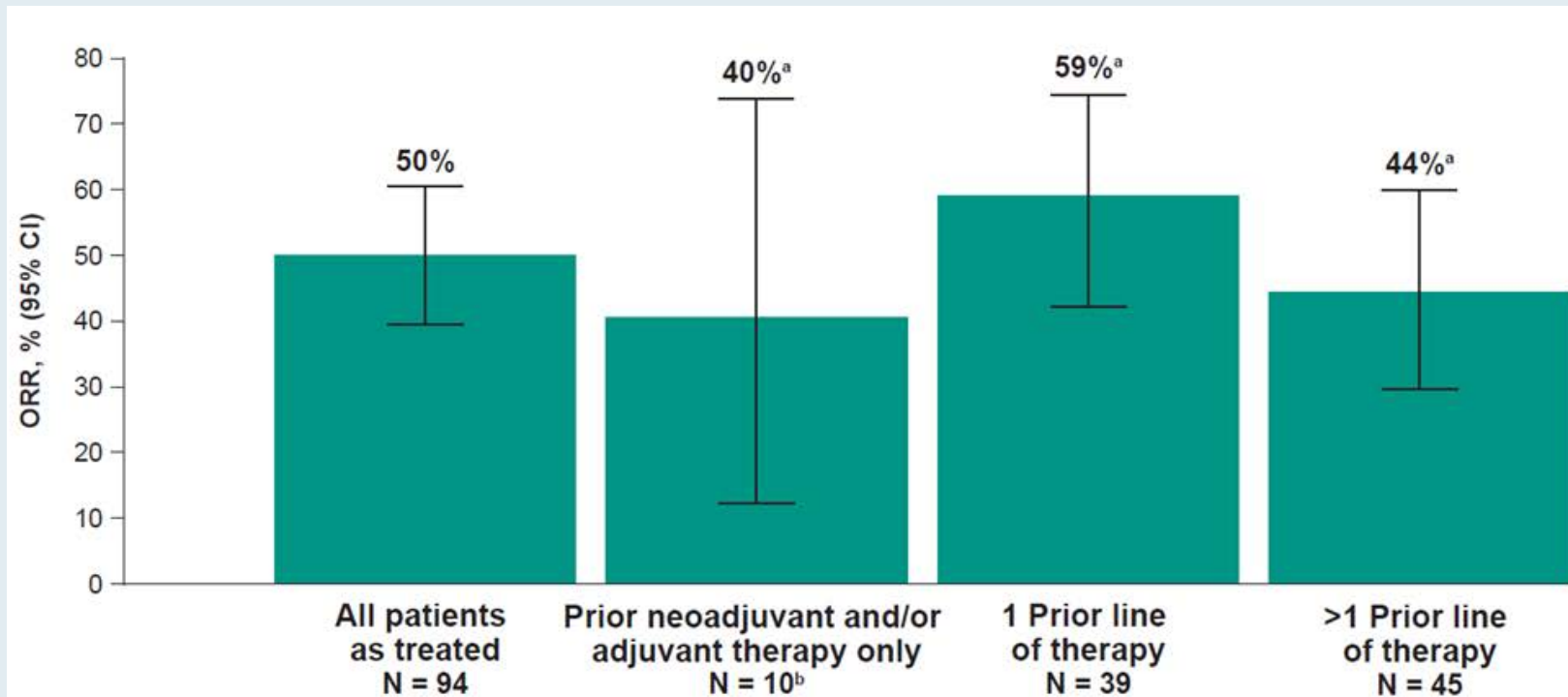
D.M. O'Malley¹; G.M. Bariani²; P.A. Cassier³; A. Marabelle⁴; A.R. Hansen⁵; A. De Jesus Acosta⁶; W.H. Miller, Jr⁷; T. Safrá⁸; A. Italiano⁹; L. Mileskin¹⁰; L. Yao¹¹; A. Gozman¹¹; F. Jin¹¹; M. Maio¹²

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

The following slides are intended for use as a full set for completeness and are a verbatim re-creation of the congress poster

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





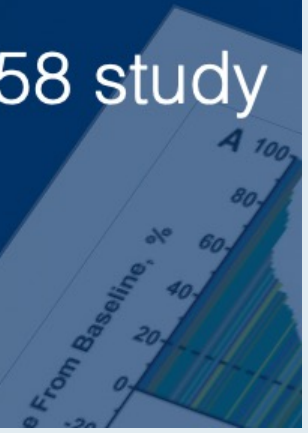
	N = 94
Median DoR	63.2 mo
Median PFS	13.1 mo
4-yr PFS rate	37%
Median OS	65.4 mo
4-yr OS rate	59%

ESMO 2022;Abstract 113P.

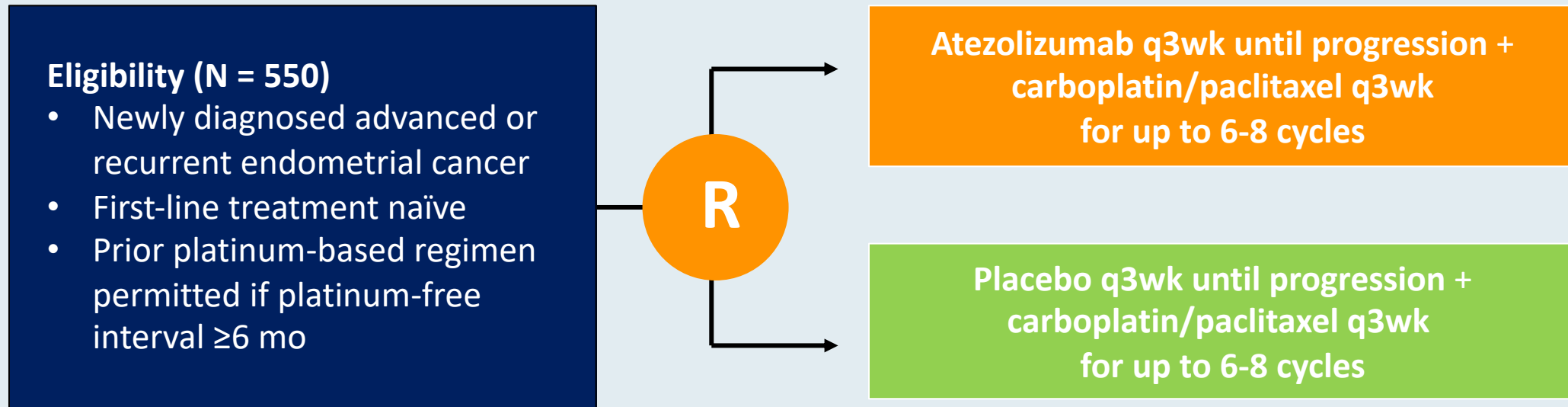
ORIGINAL ARTICLE | [VOLUME 33, ISSUE 9, P929-938, SEPTEMBER 01, 2022](#)

Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study

[M. Maio](#)   • [P.A. Ascierto](#) • [L. Manzyuk](#) • [D. Motola-Kuba](#) • [N. Penel](#) • [P.A. Cassier](#) • [G.M. Bariani](#) •
[A. De Jesus Acosta](#) • [T. Doi](#) • [F. Longo](#) • [W.H. Miller, Jr](#) • [D.-Y. Oh](#) • [M. Gottfried](#) • [L. Xu](#) • [F. Jin](#) • [K. Norwood](#) •
[A. Marabelle](#) • [Show less](#)



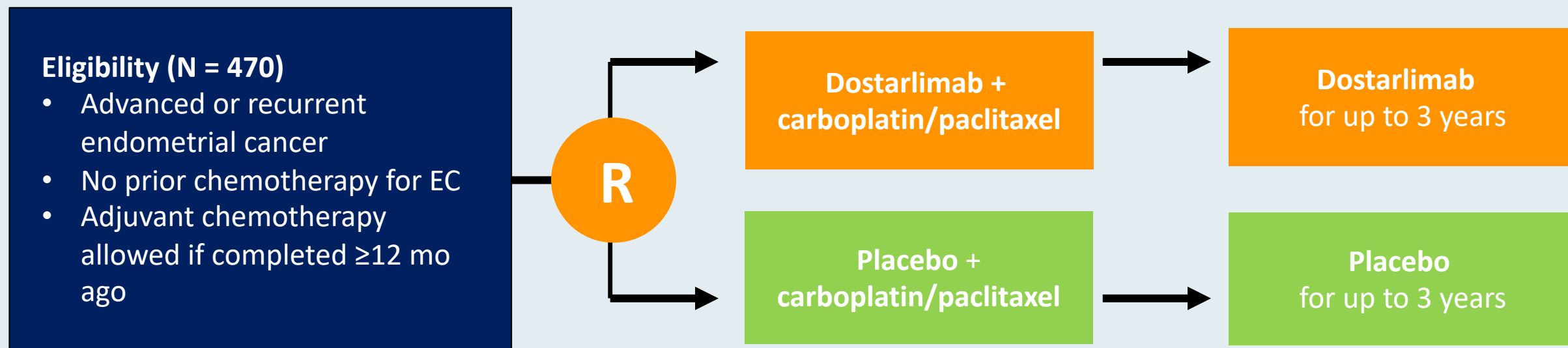
Phase III AtTEnD/ENGOT-EN7 Study Schema



Primary endpoints: OS, PFS

Secondary endpoints: Objective response rate, duration of response, safety

Phase III RUBY/ENGOT-EN6 Study Schema



Primary endpoint: PFS

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

Discussion Questions

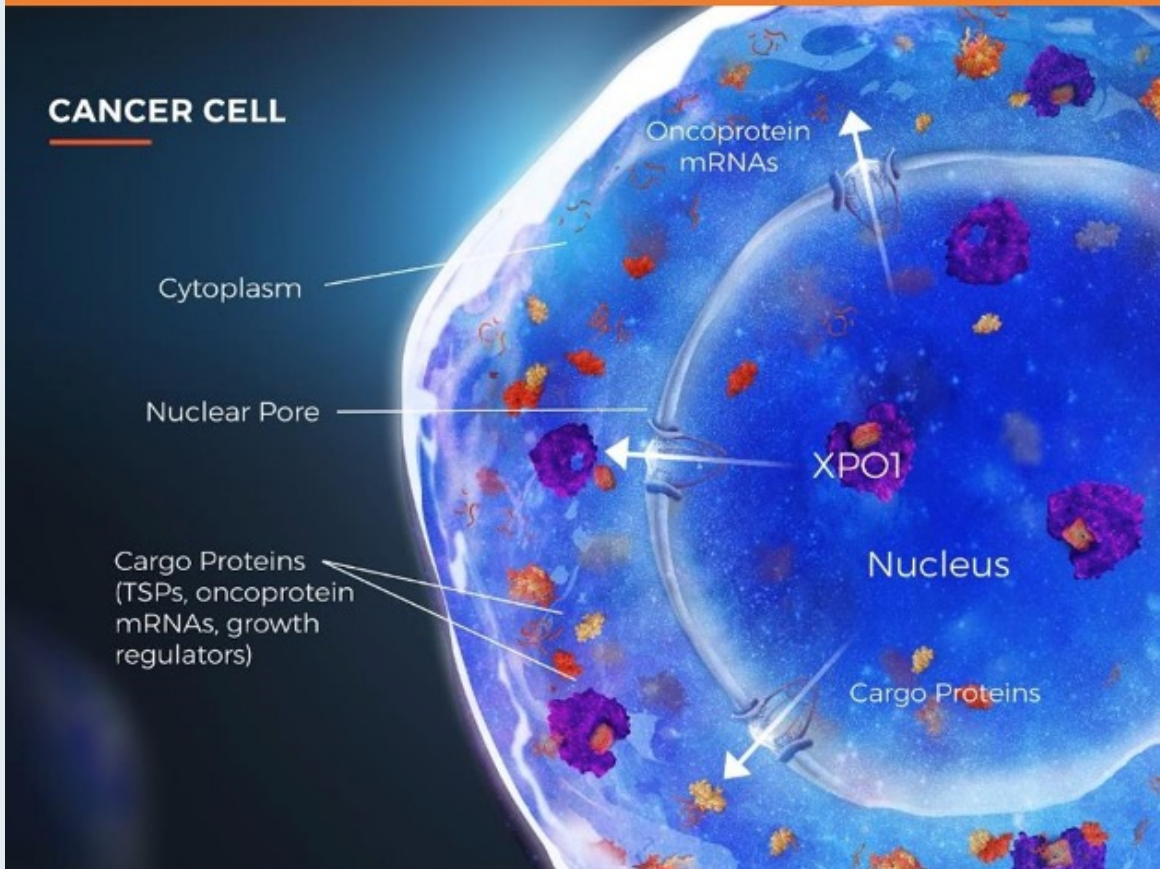
- Regulatory and reimbursement issues aside, what is your preferred use of immune checkpoint inhibitors in patients with metastatic endometrial cancer, and do you see integrating them in nonmetastatic disease?
- Do patients with metastatic endometrial cancer have a defined spectrum of immune-related toxicity?
- How do you prevent and ameliorate toxicity with pembrolizumab/lenvatinib?
- If there a role for pembrolizumab/lenvatinib in MSI-high disease? What about anti-PD-1/anti-CTLA-4 combinations?

Endometrial Cancer Agenda

MODULE 1: “Biomarker”-Guided Therapy for Endometrial Cancer

MODULE 2: Targeted Therapy for Endometrial Cancer; New Directions

Mechanism of Action of Selinexor



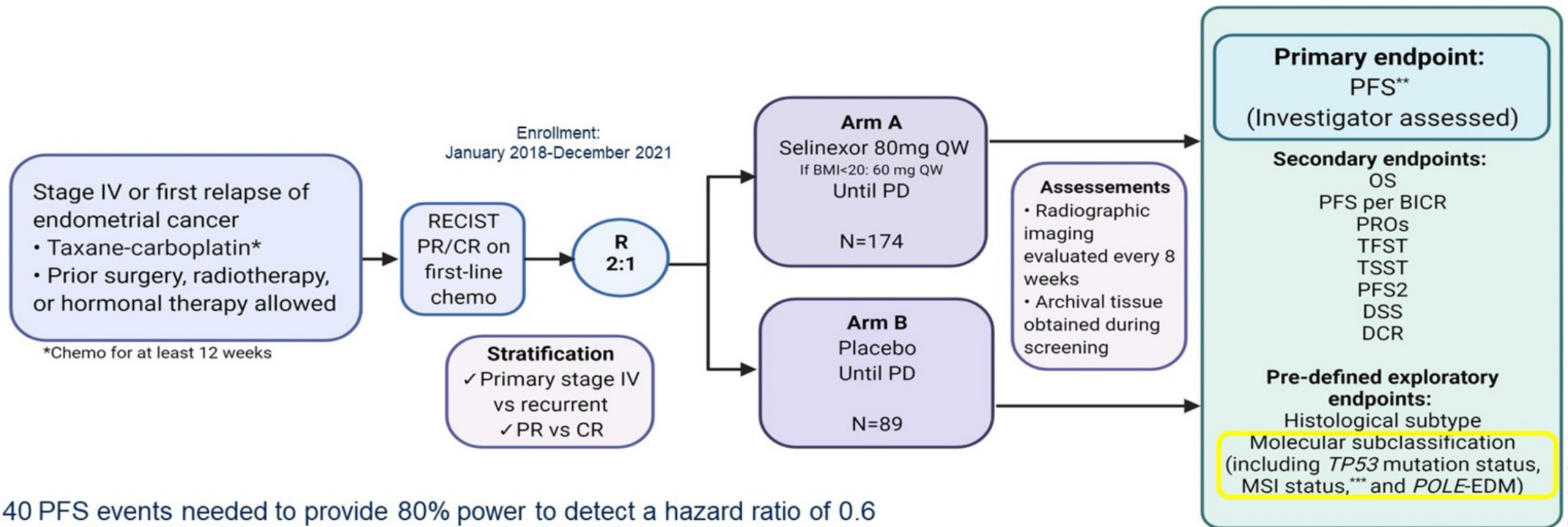
Selinexor is an oral selective inhibitor of XPO1-mediated nuclear export (SINE) compound

- 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

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 Makker¹, J Alejandro Pérez-Fidalgo², Alice Bergamini³, Daniel Spitz⁴, Toon Van Gorp⁵, Jalid Sehouli⁶, Jaroslav Klat⁷, Tamar Perri⁸, Amit Oza⁹, Estrid Høgda¹⁰, Jason Konner¹¹, Eva M Guerra-Alia¹², Francesco Raspagliesi¹³, Stéphanie Henry¹⁴, Bradley J. Monk¹⁵, Jerónimo Martínez¹⁶, Brian Slomovitz¹⁷, Sharon Shacham¹⁸, Mansoor Raza Mirza¹⁹, Ignace Vergote⁵

SIENDO/ENGOT-EN5 Phase III Study Design

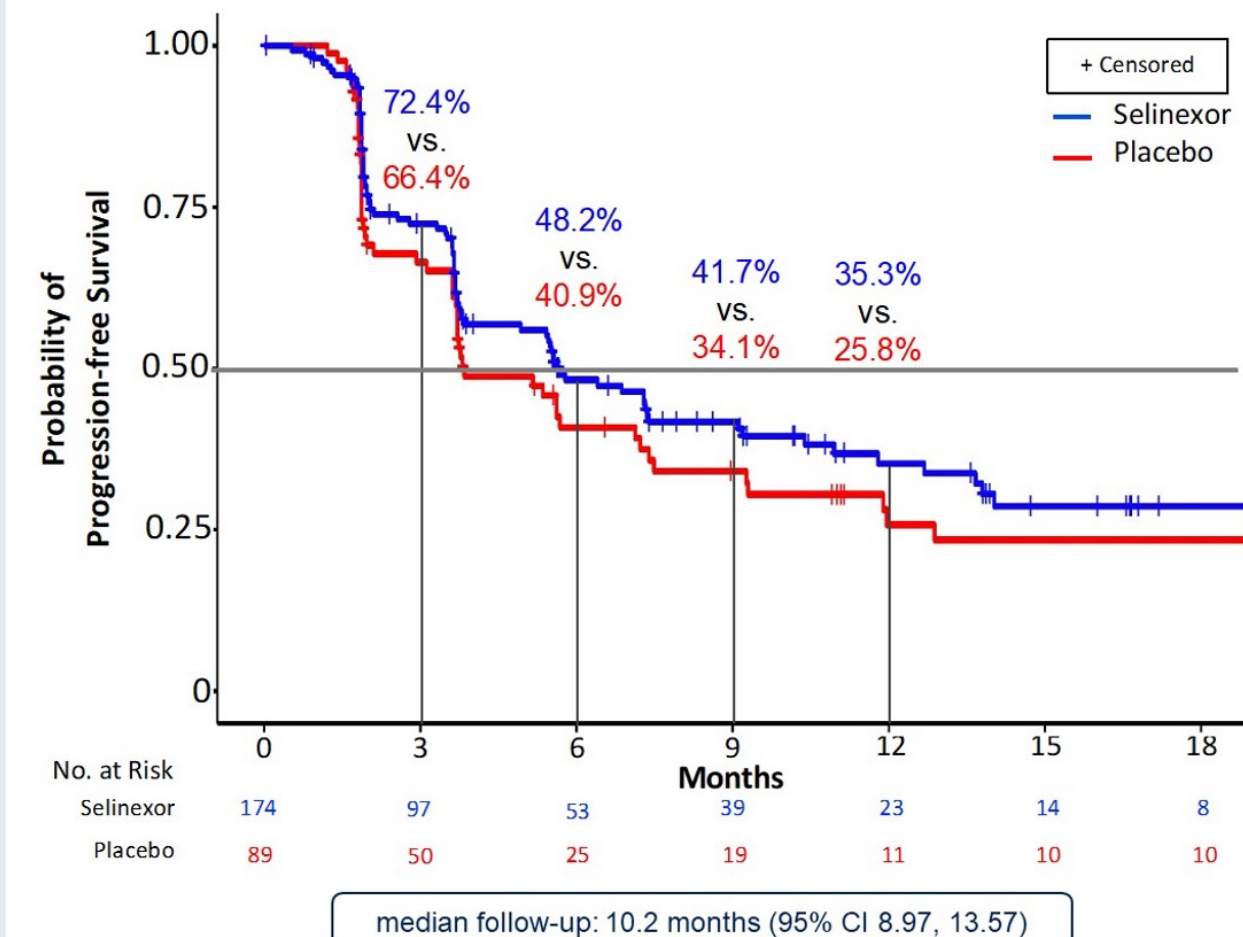


**140 PFS events needed to provide 80% power to detect a hazard ratio of 0.6 (median PFS 4.5 months for placebo and 7.5 months for selinexor) with a one-sided alpha of 0.025 and 2:1 randomization ratio favoring selinexor.

***Assessed by DNA sequencing and IHC
Data cutoff: January 18, 2022

Created with Biorender.com

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)

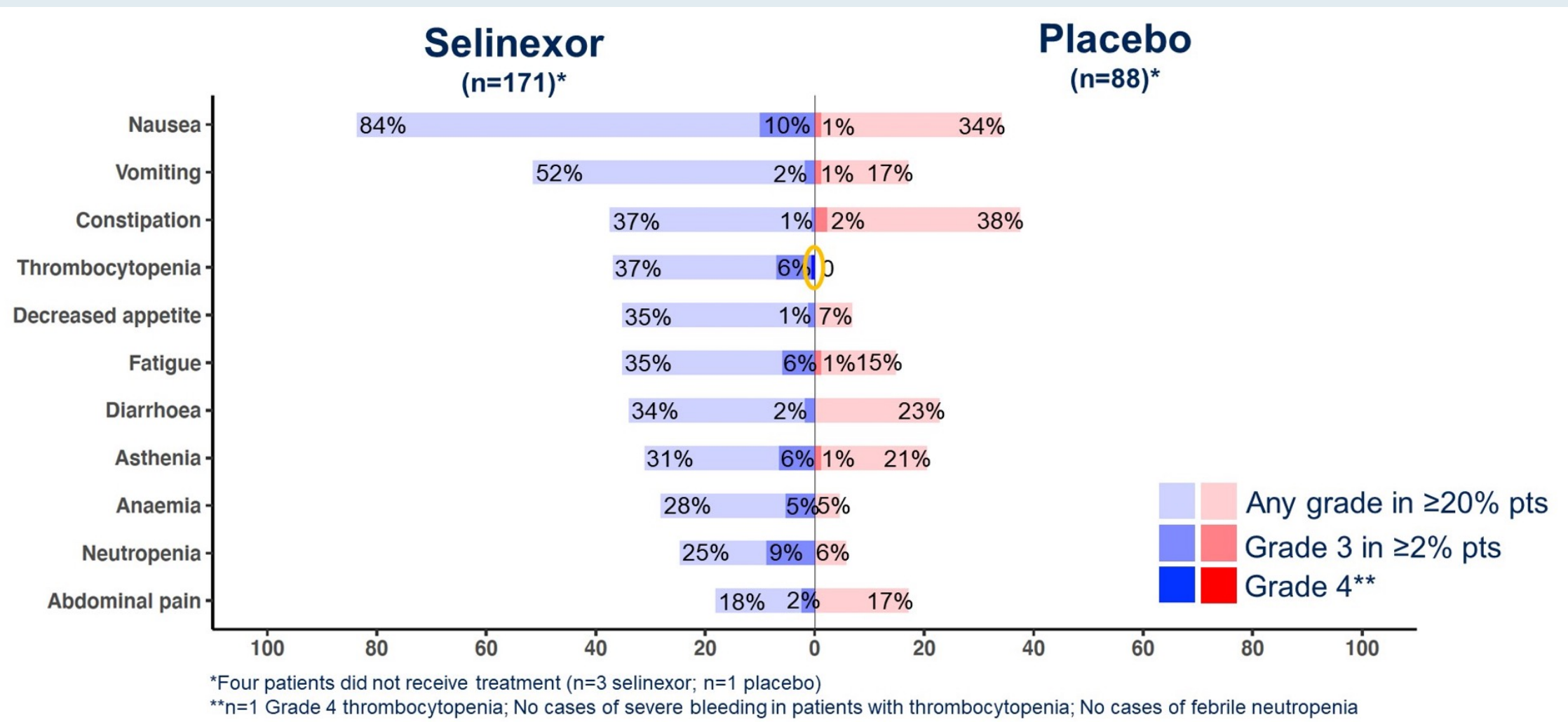
HR = 0.76 (95% CI 0.543-1.076)

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

SIENDO/ENGOT-EN5: Treatment-Emergent Adverse Events



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)

Thank you for joining us!

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

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**