Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Endometrial Cancer

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2023 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

Monday, March 27, 2023

11:45 AM – 1:15 PM ET

Faculty

Robert L Coleman, MD

Matthew A Powell, MD

Brian M Slomovitz, MD

Moderator

Shannon N Westin, MD, MPH

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Faculty

Robert L Coleman, MD
Chief Medical Officer
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Gynecologic Oncology
The Woodlands, Texas

Brian M Slomovitz, MD
Professor, OB-GYN
Florida International University
Director, Gynecologic Oncology
Co-Chair, Cancer Research Committee
Mount Sinai Medical Center
Miami, Florida

Matthew A Powell, MD
Professor
Department of Obstetrics and Gynecology
Washington University School of Medicine
St Louis, Missouri

Moderator

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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Dr Coleman — Disclosures
Faculty

Advisory Committee and Consulting Agreements	AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, Genentech, a member of the Roche Group, GSK, ImmunoGen Inc, Merck, Myriad Genetic Laboratories Inc, Seagen Inc
Contracted Research	Clovis Oncology, Genentech, a member of the Roche Group, GSK, ImmunoGen Inc, Merck, Seagen Inc
Data and Safety Monitoring Board/Committee	Eisai Inc

Dr Powell — Disclosures
Faculty

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, GSK, Merck, Roche Laboratories Inc, Seagen Inc
Contracted Research	GSK

Dr Slomovitz — Disclosures
Faculty

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Clovis Oncology, EQRx, Genentech, a member of the Roche Group, Genmab US Inc, GSK, Incyte Corporation, Lilly, Merck, Novartis, Seagen Inc

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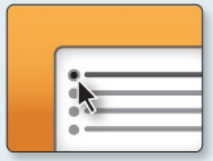
Dr Westin — Disclosures
Moderator

Consulting Agreements	Agenus Inc, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, EQRx, Genentech, a member of the Roche Group, GSK, ImmunoGen Inc, Lilly, Merck, Mereo BioPharma, Mersana Therapeutics Inc, NGM Bio, Nuvectis Pharma Inc, Seagen Inc, Vincerx Pharma, Zentalis Pharmaceuticals
Contracted Research	AstraZeneca Pharmaceuticals LP, Avenge Bio, Bio-Path Holdings, Clovis Oncology, Genentech, a member of the Roche Group, GSK, Mereo BioPharma, OncXerna Therapeutics Inc, Zentalis Pharmaceuticals

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and post-meeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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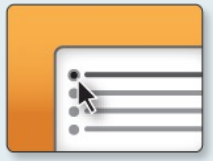
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and post-meeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Agenda

MODULE 1: Immune Checkpoint Inhibitors for Patients with Advanced Microsatellite Instability-High/Mismatch Repair-Deficient Endometrial Cancer — *Dr Powell*

MODULE 2: Immunotherapy-Based Strategies for Patients with MMR-Proficient Endometrial Cancer — *Dr Coleman*

MODULE 3: Diagnosis and Management of Adverse Events Associated with Immune Checkpoint Inhibitors Alone and in Combination for Endometrial Cancer — *Dr Westin*

MODULE 4: Novel Investigational Agents and Strategies Under Evaluation for Patients with Endometrial Cancer — *Dr Slomovitz*

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John K Chan, MD
Sutter Cancer Research Consortium
San Francisco, California

Kellie E Schneider, MD
Novant Health Cancer Institute
Charlotte, North Carolina

Dana M Chase, MD
David Geffen School of
Medicine at UCLA
Los Angeles, California

Lyndsay J Willmott, MD
Virginia G Piper Cancer
Care Network
Phoenix, Arizona

Thomas P Morrissey, MD
Lynn Cancer Institute
Boca Raton, Florida

Neil Love, MD
Research To Practice
Miami, Florida

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Module 1: Immune Checkpoint Inhibitors for Patients with Advanced Microsatellite Instability-High (MSI-H)/Mismatch Repair-Deficient (dMMR) Endometrial Cancer — Dr Powell

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Case Presentation: 60-year-old woman with MSI-high recurrent endometrioid adenocarcinoma of the uterus, s/p progression after minimal response to carboplatin/paclitaxel

Dr Lyndsay Willmott (Phoenix, Arizona)

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QUESTIONS FOR THE FACULTY

Lyndsay Willmott, MD

What is your usual first-line treatment for metastatic MSI-high endometrial cancer? Do you ever use anti-CTLA-4 antibodies combined with anti-PD-1/PD-L1 antibodies? How long do you continue treatment, and have you used ctDNA assays in this situation?

What is your experience with thyroid abnormalities with IOs?

Case Presentation: 51-year-old woman with MSI-high metastatic endometrial adenocarcinoma, s/p rapid, highly symptomatic PD on paclitaxel/carboplatin

Dr Kellie Schneider (Charlotte, North Carolina)

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QUESTIONS FOR THE FACULTY

Kellie Schneider, MD

How would you approach this patient? What second-line therapy would you likely recommend?

Do you use combination immunotherapy in these situations?

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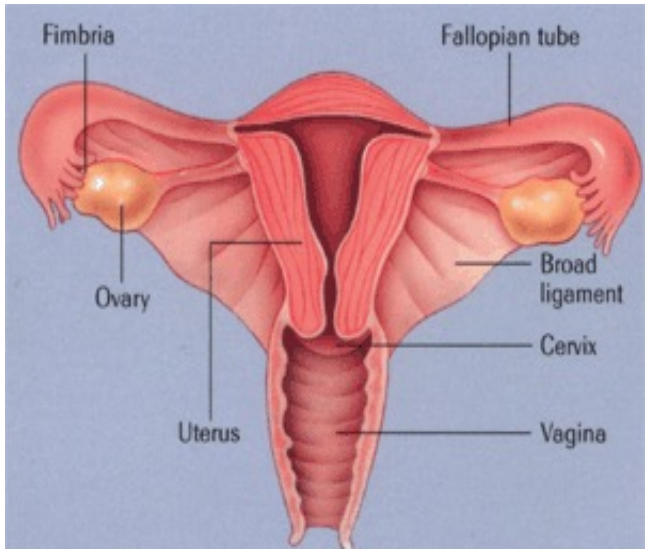
Immune Checkpoint Inhibitors for Patients with Advanced Microsatellite Instability-High (MSI-H)/Mismatch Repair-Deficient (dMMR) Endometrial Cancer

Matthew A. Powell, MD

Professor and Chief, Gynecologic Oncology

Washington University School of Medicine, Saint Louis, MO

Endometrial Cancer: Annual Incidence and Mortality

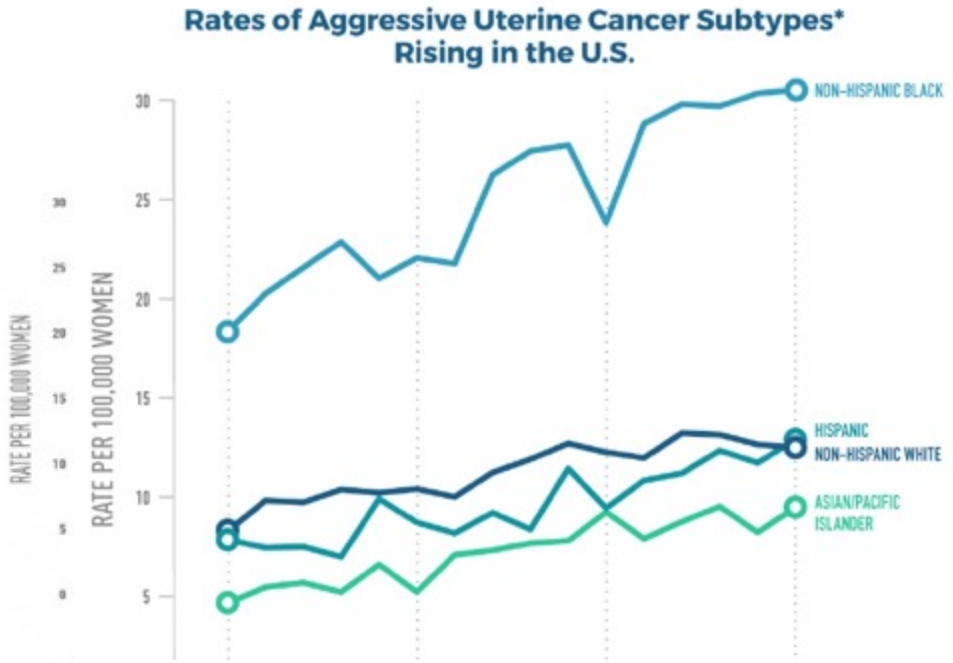


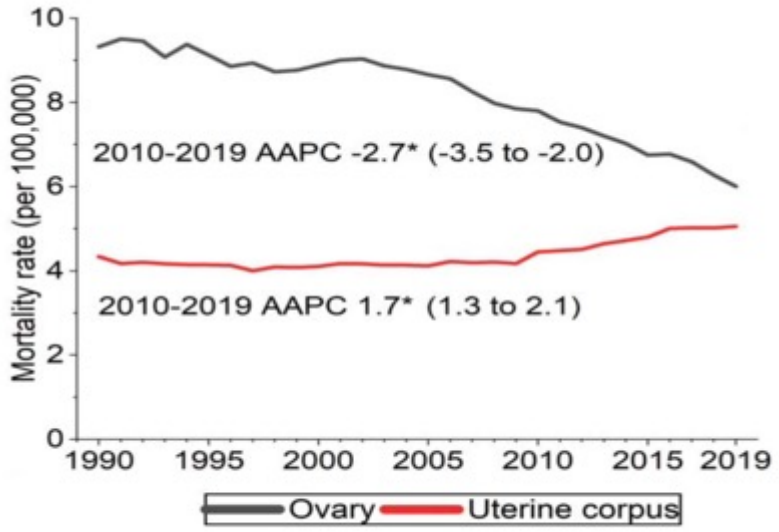
Year	Cases	Deaths
1987	35,000	2,900
2023	66,200	13,030

ACS, 2023.

Endometrial Cancer: US

- 65,950 estimated cases in 2022
- 12,550 deaths
- Fourth most common cancer in US
- Cumulative Lifetime risk in the general population is 3.1%
- Median Age 63
- Usually confined to the uterus at diagnosis
- 5-year cancer specific survival 81%
- **Increasing 1.7% (2010-2019)**
  - **Increasing 2% in Blacks annually!**
  - The uterine cancer mortality rate ratio for Black compared with White patients increased from 1.83 (95% CI 1.77–1.89) in 1990–1994 to 1.98 (95% CI 1.93–2.02) in 2015–2019

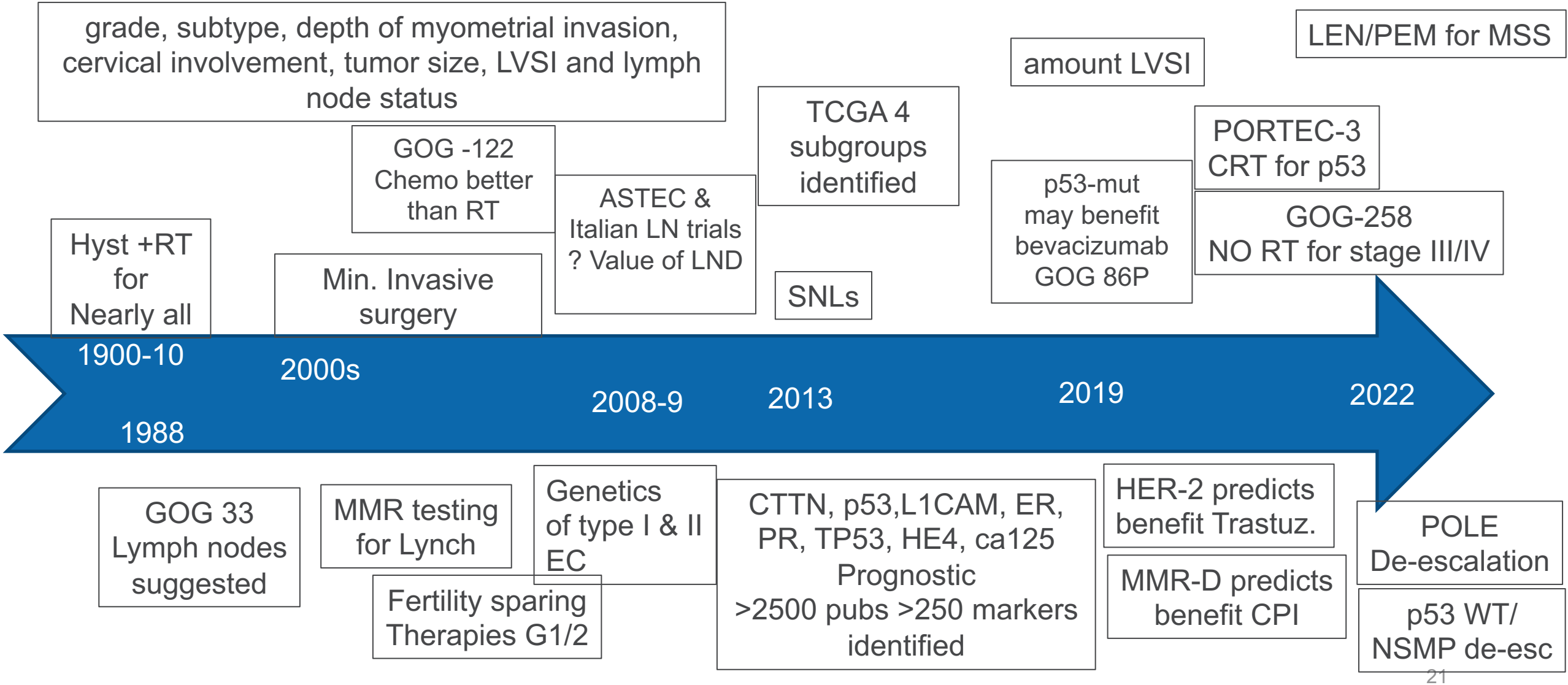




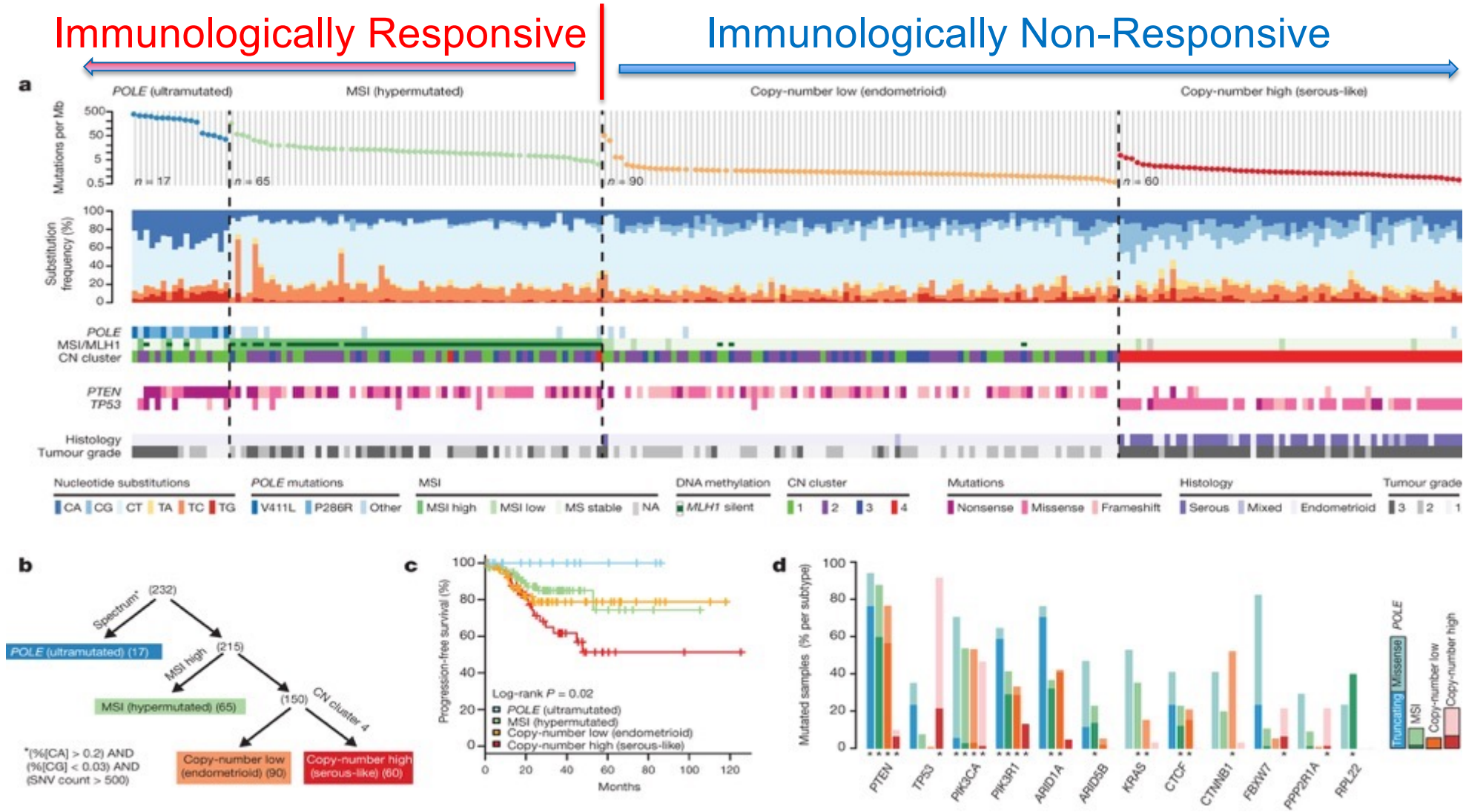
Giaquinto, A. Obstets & Gyn. 2022

NCI. SEER Program. www.seer.cancer.gov. ACS. cancer.org. Clarke MA et al. *J Clin Oncol*. 2019;37(22):1895-1908. Giaquinto AN et al. *Obstet Gynecol*. 2022;139(3):440-442.

History of management of Endometrial Cancer: Journey from prognostic to predictive markers



Disease Homogeneity to Molecular Granularity



G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

Endometrial Cancer: Molecular Subtypes

***POLE* ultramutated**	• Ultra-high somatic mutation frequency; MSS; frequent mutations in the exonuclease domain of *POLE*; high ASNS and CCNB1 expression • Represents ~4% of endometrioid tumors* • Best prognosis	Clear IO Efficacy
MSI hypermutated	• High mutation rate and few copy number alterations; high rate of *MLH1* promoter methylation; high phospho-AKT; low PTEN expression; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations • Represents ~39% of endometrioid tumors*†	Clear IO Efficacy
Copy-number low‡	• High frequency of mutations in *CTNNB1*, *KRAS*, *SOX17*; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations; elevated levels of progesterone receptor and RAD50 expression • Represents ~49% of endometrioid tumors*	Unclear IO Efficacy?
Copy-number high‡	• Greatest transcriptional activity; frequent *TP53* mutations; decreased levels of phospho-AKT; mutually exclusive *PIK3CA*, *PIK3R1,* and *PTEN* mutations • Represents ~9% of endometrioid tumors* • Worst prognosis	Unclear IO Efficacy?

G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

“Standard of Care”

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Primary or Adjuvant Therapy	
Chemoradiation Therapy	**Systemic Therapy**
Preferred Regimens • Cisplatin plus RT followed by carboplatin/paclitaxel[1,2]	**Preferred Regimens** • Carboplatin/paclitaxel[3] • Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive uterine serous carcinoma)[a,b,4] • Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive carcinosarcoma) (category 2B)[a,b,4]

No IO opportunity in the 1L (to date)

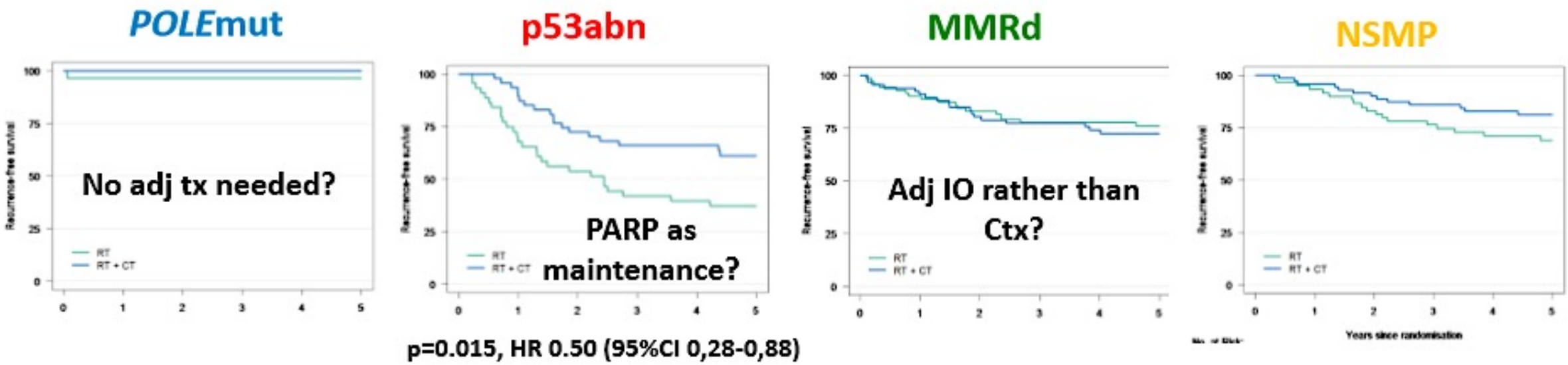
SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Recurrent Disease[c,d]	
First-Line Therapy[e]	**Second-Line or Subsequent Line Therapy**
Preferred • Carboplatin/paclitaxel (category 1 for carcinosarcoma)[3] • Carboplatin/paclitaxel/trastuzumab[b] (for recurrent HER2-positive uterine serous carcinoma)[a,4] • Carboplatin/paclitaxel/trastuzumab[b] (category 2B for HER2-positive carcinosarcoma)[a,4] **Other Recommended Regimens** • Carboplatin/docetaxel[f] • Carboplatin/paclitaxel/bevacizumab[g,h,5,6]	**Other Recommended Regimens** • Cisplatin/doxorubicin[10] • Cisplatin/doxorubicin/paclitaxel[g,m,10] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[11] • Albumin-bound paclitaxel[n] • Topotecan • Bevacizumab[h,o,12] • Temsirolimus[13] • Cabozantinib • Docetaxel[f] (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[14] • Cisplatin/ifosfamide (for carcinosarcoma)
Useful in Certain Circumstances (Biomarker directed: after prior systemic therapy) • Lenvatinib/pembrolizumab (category 1) for mismatch repair proficient (pMMR) tumors[i,j,7] • Pembrolizumab[j] (category 1) for TMB-H[k,8] or MSI-H/dMMR[l] tumors[9]	**Useful in Certain Circumstances (Biomarker directed: after prior systemic therapy)** • Lenvatinib/pembrolizumab (category 1) for mismatch repair proficient (pMMR) tumors[i,j,7] • Pembrolizumab[j] (category 1) for TMB-H[k,8] or MSI-H/dMMR tumors[l,9] • Dostarlimab-gxly for dMMR/MSI-H tumors (category 1)[j,p,15] • Larotrectinib or entrectinib for NTRK gene fusion-positive tumors (category 2B)[g] • Avelumab for dMMR/MSI-H tumors[j] • Nivolumab for dMMR/MSI-H tumors[j,16]

IO opportunities exist in the recurrent setting

PORTEC-3

Molecular classification predictive of differential benefit from adj Ctx



p=0.015, HR 0.50 (95%CI 0,28-0,88)

- P53abn: worst prognosis but greatest benefit from adj Ctx
- POLEmut: does not relapse regardless of tx
- MSI and NSMP: intermediate prognosis, but little benefit from Adj Ctx

Creutzberg, Leon-Castillo et al. ESMO 2019 and Leon-Castillo et al. ESGO 2019

Single Agent IO in pMMR/MSI-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: 13.9%**
Ph II Avelumab study (N= 16 pMMR)	Advanced stage or metastatic endometrial cancer	**ORR: 6.25%**

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
Pothuri et al. SGO Annual Meeting 2021

Single Agent IO in “biomarker” Selected Endometrial Cancer Populations (dMMR/MSI+)

- **Response to single agent IO in dMMR or MSI-high endometrial**

Study & Drug	Patient Population	Outcome
Keynote 158: Pembrolizumab (N=90)	Advanced stage or metastatic dMMR endometrial cancer	ORR: 48%
PHAEDRA trial: Durvalumab (N=35 dMMR)	Advanced stage or metastatic endometrial cancer	ORR in dMMR: 43%
GARNET study: Dostarlimab (N=129)	Previously treated, recurrent advanced stage endometrial cancer	ORR in dMMR: 43.5%
Ph II Avelumab study (N= 15 dMMR)	Advanced stage or metastatic endometrial cancer	ORR: 26.7%

O’Malley D, et al. J Clin Oncol, 2022, Maio M et. al ESMO 2022, Abstract 113P.
Antill PSK et al. J Clin Oncol 2019
Oaknin A et al. Journal for ImmunoTherapy of Cancer 2022
Konstantinopoulos PA et al. J Clin Oncol 2019

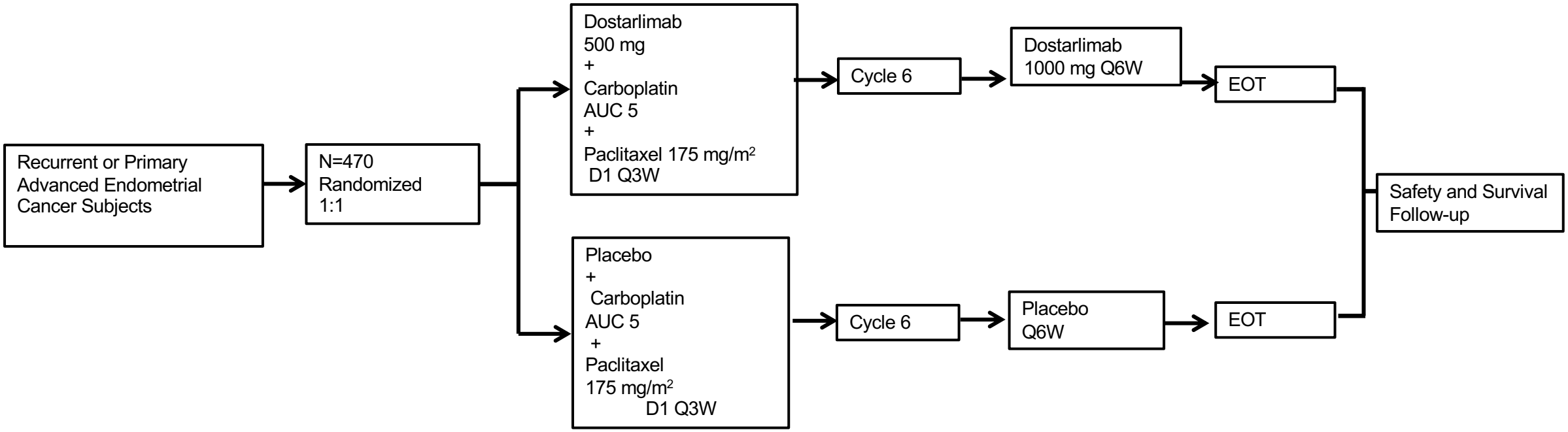
Endometrial Cancer: 1st line metastatic/recurrent

Front-line, metastatic or recurrent PI: Eskander	NRG-018	Testing the Addition of the Immunotherapy Drug Pembrolizumab to the Usual Chemotherapy Treatment (Paclitaxel and Carboplatin) in Stage III-IV or Recurrent Endometrial Cancer	**Active, Not Recruiting**
Front-line, metastatic or recurrent PI: Powell *ENGOT led	GOG-3031/RUBY	A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Patients With Recurrent or Primary Advanced Endometrial Cancer	**Active, Not Recruiting**
Front-line, metastatic or recurrent PI: Westin Co-PI: Moore *GOG led	GOG-3041/DUO-E	A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination With Durvalumab, Followed by Maintenance Durvalumab With or Without Olaparib in Patients With Newly Diagnosed Advanced or Recurrent Endometrial Cancer	**Recruiting**

Endometrial Cancer: 1st line metastatic/recurrent

Front-line, metastatic or recurrent PI: Marth	LEAP-001/ENGOT-en9	A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Advanced or Recurrent Endometrial Carcinoma	**Active, not recruiting**
Front-line, metastatic or recurrent	AtTEnd	Phase III Double-blind Randomized Placebo Controlled Trial of Atezolizumab in Combination With Paclitaxel and Carboplatin in Women With Advanced or Recurrent Endometrial Cancer	**Active, not recruiting**
Front-line metastatic or recurrent **(dMMR only)**	KEYNOTE-C93/GOG-3064/ENGOT-en15	A Phase 3 Randomized, Open-label, Active-comparator Controlled Clinical Study of Pembrolizumab versus Platinum Doublet Chemotherapy in Participants With Mismatch Repair Deficient (dMMR) Advanced or Recurrent Endometrial Carcinoma in the First-line Setting	**Recruiting**

Combinatorial IO approach: Chemotherapy + Dostarlimab (RUBY: NCT03981796)



Study Design

Population: Patients with primary Stage III or IV disease or first recurrent endometrial cancer
Treatment: Double-blind PD-1 inhibitor (dostarlimab) or placebo in combo with chemo (6 cycles); monotherapy for up to 3 years Stratification: MSI Status, Prior pelvic radiotherapy, Disease status
N Patients: 470 patients (235 patients – dostarlimab with chemo; 235 patients – placebo with chemo)
N Sites: Approximately 160 sites in 19 countries
Enrollment: 199 randomized to date
Primary Endpoint: Investigator assessed PFS per RECIST v1.1

Endometrial Cancer: 1st line metastatic/recurrent

Front-line, metastatic	NRG-018	Testing the Addition of the Immunotherapy Drug Pembrolizumab to the Usual Chemotherapy Treatment (Paclitaxel and Carboplatin) in Stage III-IV or Recurrent Endometrial Cancer	**Active, Not Recruiting**

02 December 2022

The manufacturer today announce positive headline results from the planned interim analysis of Part 1 of the RUBY/ENGOT-EN6/GOG3031/NSGO phase III trial investigating dostarlimab plus standard-of-care chemotherapy (carboplatin-paclitaxel) followed by dostarlimab compared to chemotherapy plus placebo followed by placebo in adult patients with primary advanced or recurrent endometrial cancer. The trial met its primary endpoint of investigator-assessed progression-free survival (PFS). It showed a statistically significant and clinically meaningful benefit in the prespecific mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) patient subgroup and in the overall population. A clinically relevant benefit in PFS was also observed in the mismatch repair proficient (MMRp)/microsatellite stable (MSS) patient subgroup.

Combinatorial IO approach: Chemotherapy + pembrolizumab
NRG GY018: Placebo controlled - 2 separate cohorts (NCT03914612)

- Measurable stage 3 or 4A endometrial cancer
- Stage 4B or recurrent endometrial cancer
- GOG PS 0-2

pMMR: N=590
dMMR: N=220

1:1

R

Carboplatin AUC 5 Q3wk
Paclitaxel 175 mg/m^2 Q3wk
Placebo q3w X up to 35 cycles

Carboplatin AUC 5 Q3wk
Paclitaxel 175 mg/m^2 Q3wk
Pembrolizumab 200mg q3w x up to 35 cycles

Stratification variables:
- **MMR status (by central laboratory assessment)**
- **GOG PS (0 or 1 vs. 2)**
- **Prior chemotherapy (yes vs. no)**

Primary endpoint: PFS

Eligible histologies:
- **Endometrioid, serous, clear cell, mixed, undifferentiated, adenocarcinoma NOS**

Dostarlimab in Combination with Chemotherapy for the Treatment of Primary Advanced or Recurrent Endometrial Cancer: A Placebo-Controlled Randomized Phase 3 Trial (ENGOT-EN6-NSGO/GOG-3031/RUBY)

Mirza MR et al.

SGO Annual Meeting 2023.

Scientific Plenary VI: Hot off the Press! Late-Breaking Abstracts Part 2

March 27, 2023

4:55 PM – 5:03 PM ET

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Pembrolizumab versus Placebo in Addition to Carboplatin and Paclitaxel for Measurable Stage 3 or 4a, Stage 4b or Recurrent Endometrial Cancer: The Phase 3, NRG GY018 Study

Eskander RN et al.

SGO Annual Meeting 2023.

Scientific Plenary VI: Hot off the Press! Late-Breaking Abstracts Part 2

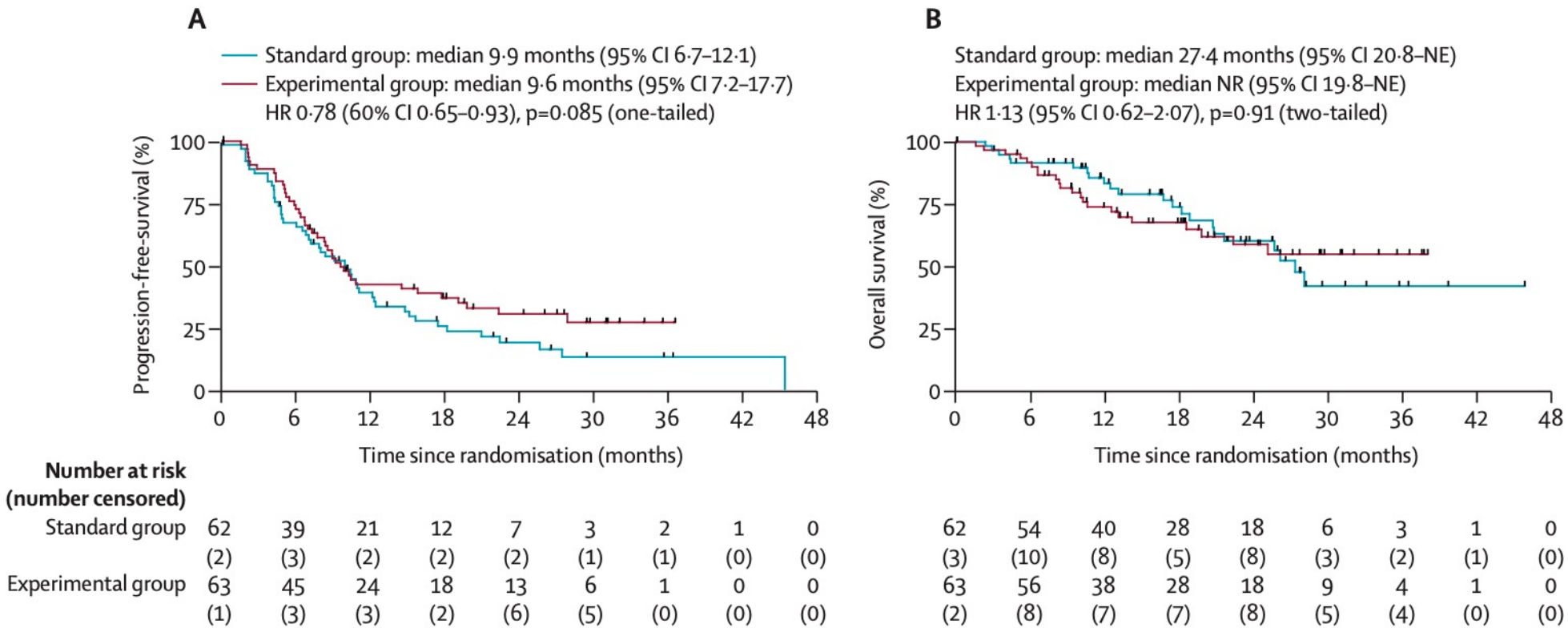
March 27, 2023

4:47 PM – 4:55 PM ET

Carboplatin and paclitaxel plus avelumab compared with carboplatin and paclitaxel in advanced or recurrent endometrial cancer (MITO END-3): a multicentre, open-label, randomised, controlled, phase 2 trial

Lancet Oncol 2023; 24: 286–96

*Sandro Pignata, Giovanni Scambia, Clorinda Schettino, Laura Arenare, Carmela Pisano, Davide Lombardi, Ugo De Giorgi, Claudia Andreetta, Saverio Cinieri, Carmine De Angelis, Domenico Priolo, Claudia Casanova, Marta Rosati, Filippo Greco, Elena Zafarana, Ilaria Schiavetto, Serafina Mammoliti, Sabrina Chiara Cecere, Vanda Salutari, Simona Scalone, Alberto Farolfi, Marilena Di Napoli, Domenica Lorusso, Piera Gargiulo, Daniela Califano, Daniela Russo, Anna Spina, Rossella De Cecio, Paolo Chiodini, Francesco Perrone, on behalf of the MITO investigators**



MITO END-3

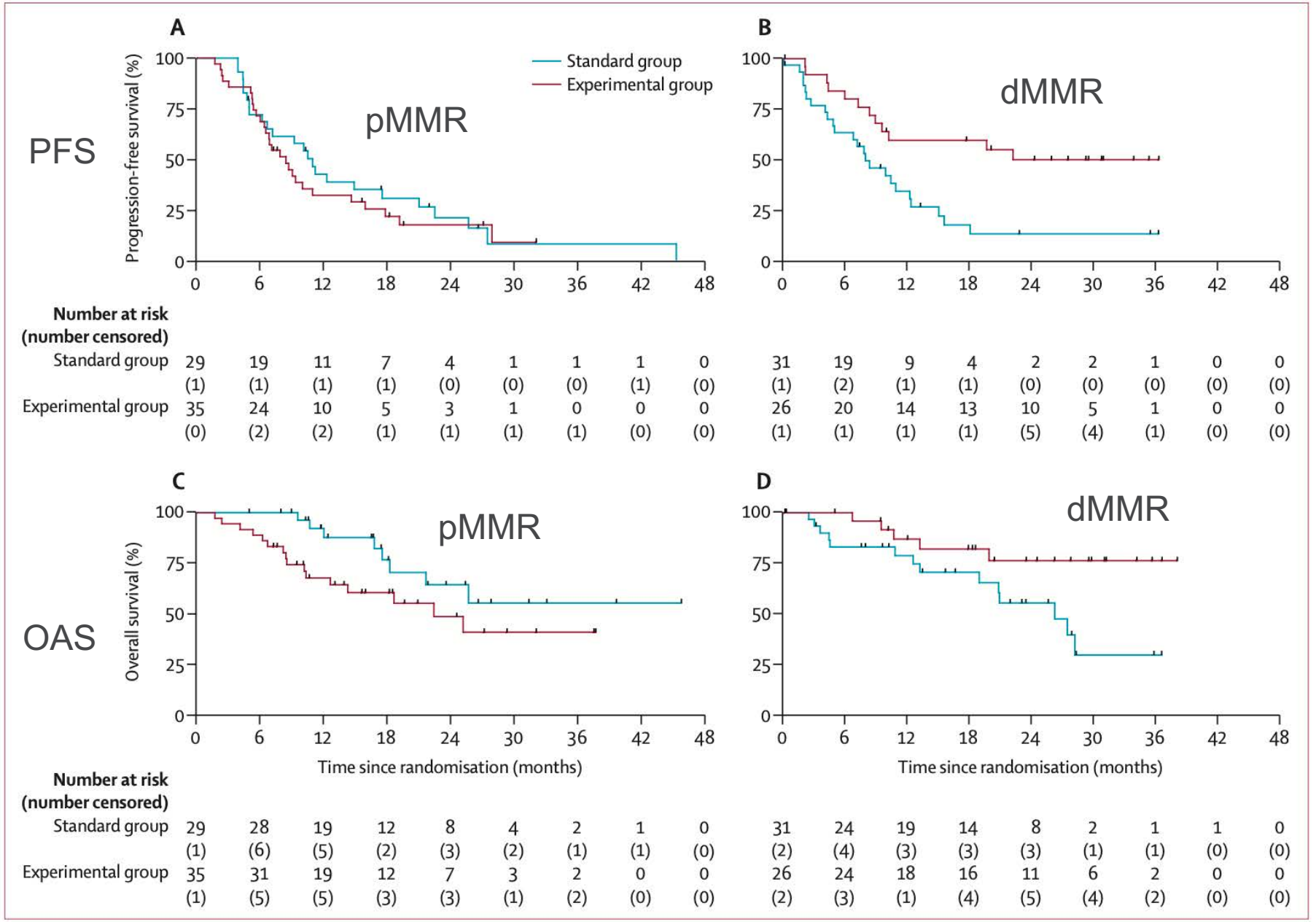


Figure 4: **Progression-free survival and overall survival curves by MMR status**
Progression-free survival in patients with pMMR (A) and dMMR (B). Overall survival in patients with pMMR (C) and dMMR (D). Vertical black lines represent censoring. Treatment groups are avelumab plus carboplatin and paclitaxel (experimental group) versus carboplatin and paclitaxel (standard group). pMMR=mismatch repair proficient. dMMR=mismatch repair deficient.

Lancet Oncol 2023; 24: 286–96

Combinatorial IO approach: Lenvatinib + Pembrolizumab Keynote 775 (NCT03517449)

- **Advanced, recurrent or metastatic endometrial**
- **Progressive disease 1-2 prior platinum regimens**
- **Measurable disease per RECIST 1.1**
- **Available archival tumor tissue**
- **Performance status of 0 to1**
- **Adequate organ function**

R

1:1

Pembrolizumab 200 mg IV q 3 weeks plus lenvatinib 20 mg PO once daily (QD) during each 21-day cycle for up to 35 cycles.

EITHER: Doxorubicin 60 mg/m2 IV q 3 weeks (max cumulative dose of 500 mg/m2) OR Paclitaxel 80 mg/m2 administered by IV on a 28-day cycle: 3 weeks receiving paclitaxel once a week and 1 week not receiving paclitaxel.

Stratification:
1. MMR status (pMMR or dMMR)
2. ECOG performance status (0 or 1)
3. Geographic region
4. Prior history of pelvic radiation (yes or no)

Primary endpoints:
1) Progression-free Survival (PFS) by RECIST 1.1 by BICR
2) Overall Survival (OS).

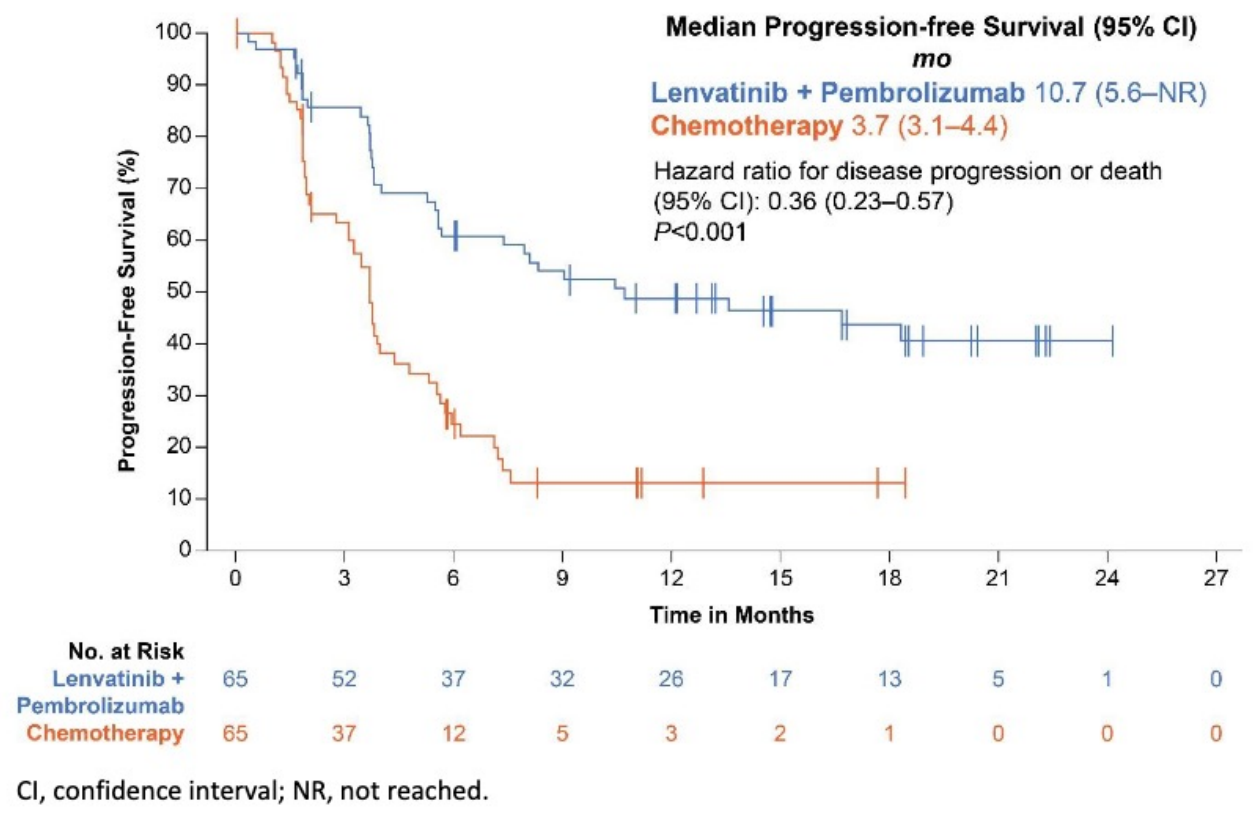
Secondary endpoints:
1) ORR, DOR, TTF, AEs, PK, PROs

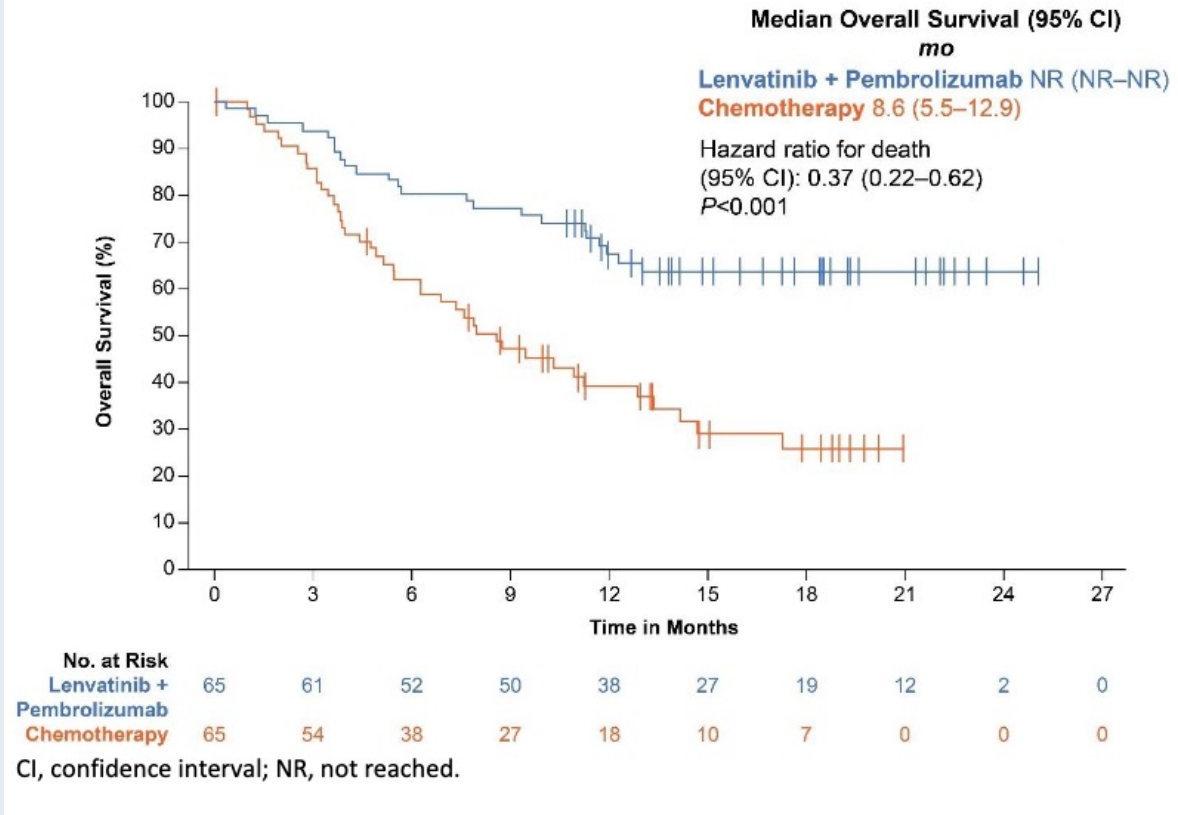
KEYNOTE-775: Confirmed Tumor Responses in dMMR Population

Endpoint	dMMR population		All patients	
	Lenvatinib/ pembrolizumab (n = 65)	Chemotherapy (n = 65)	Lenvatinib/ pembrolizumab (n = 411)	Chemotherapy (n = 416)
Objective response	40% (26) (28 to 53)	12% (8) (5 to 23)	31.9% (131) (27.4 to 36.6)	14.7% (61) (11.4 to 18.4)
Complete response	14% (9) (7 to 25)	3% (2) (<1 to 11)	6.6% (27) (4.4 – 9.4)	2.6% (11) (1.3 – 4.7)
Partial response	26% (17) (16 to 39)	9% (6) (3 to 19)	25.3% (104) (21.2 to 29.8)	12% (50) (9.1 – 15.5)
Median duration of response (range) — months	NR (2.1 to 20.4)	4.1 mo (1.9 to 15.6)	14.4 mo (1.6 to 23.7)	5.7 mo (0.0 to 24.2)

Makker et al. *NEJM* 2022;386:5(437-48).

KEYNOTE-775: Progression-Free and Overall Survival in dMMR Population





Makker et al. *NEJM* 2022;386:5(437-48).

Conclusions

- Importance of molecular subtypes in Endometrial Cancer
- Key trials of immunotherapy agents reporting
- dMMR/MSI+ tumors with robust response to CPIs
- pMMR/MSI- tumors may need dual therapy:
  - Chemo + CPI
  - TKI + CPI
- Not all CPIs may be the same. anti-PD-1 vs PDL-1?

Module 2: Immunotherapy-Based Strategies for Patients with MMR-Proficient (pMMR) Endometrial Cancer — Dr Coleman

RTP
RESEARCH
TO PRACTICE

Case Presentation: 61-year-old woman with a 10-cm right ovarian mass and right pelvic adenopathy; TAH-BSO and para-aortic lymph node dissection reveal MSS carcinosarcoma of the endometrium with right ovary and pelvic lymph node involvement (R0); adjuvant paclitaxel/carboplatin administered

Dr Thomas Morrissey (Boca Raton, Florida)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Thomas Morrissey, MD

Would you switch systemic treatment for this patient, and if so, to what? Or would you continue lenvatinib/pembrolizumab and use local therapy to the axillary disease?

RTP
RESEARCH
TO PRACTICE

Case Presentation: 68-year-old woman with Stage IB, Grade 1 endometrial cancer, s/p hysterectomy/SLNB

Dr Dana Chase (Phoenix, Arizona)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Dana Chase, MD

Do you generally treat patients with postoperative radiation therapy based on PORTEC/NCCN guidelines, or do you use GOG risk factors?

What treatment approach would you likely use at this point with the vaginal recurrence?

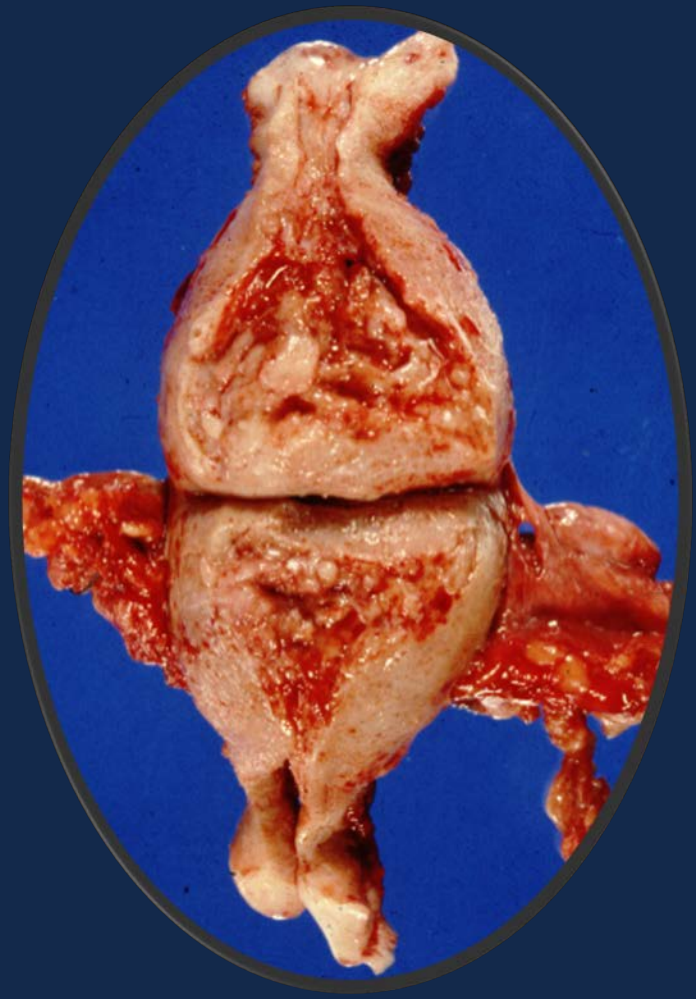
Immunotherapy-Based Strategies for Patients with MMR-Proficient (MMRp) Endometrial Cancer

Robert L. Coleman, MD, FACS, FACOG

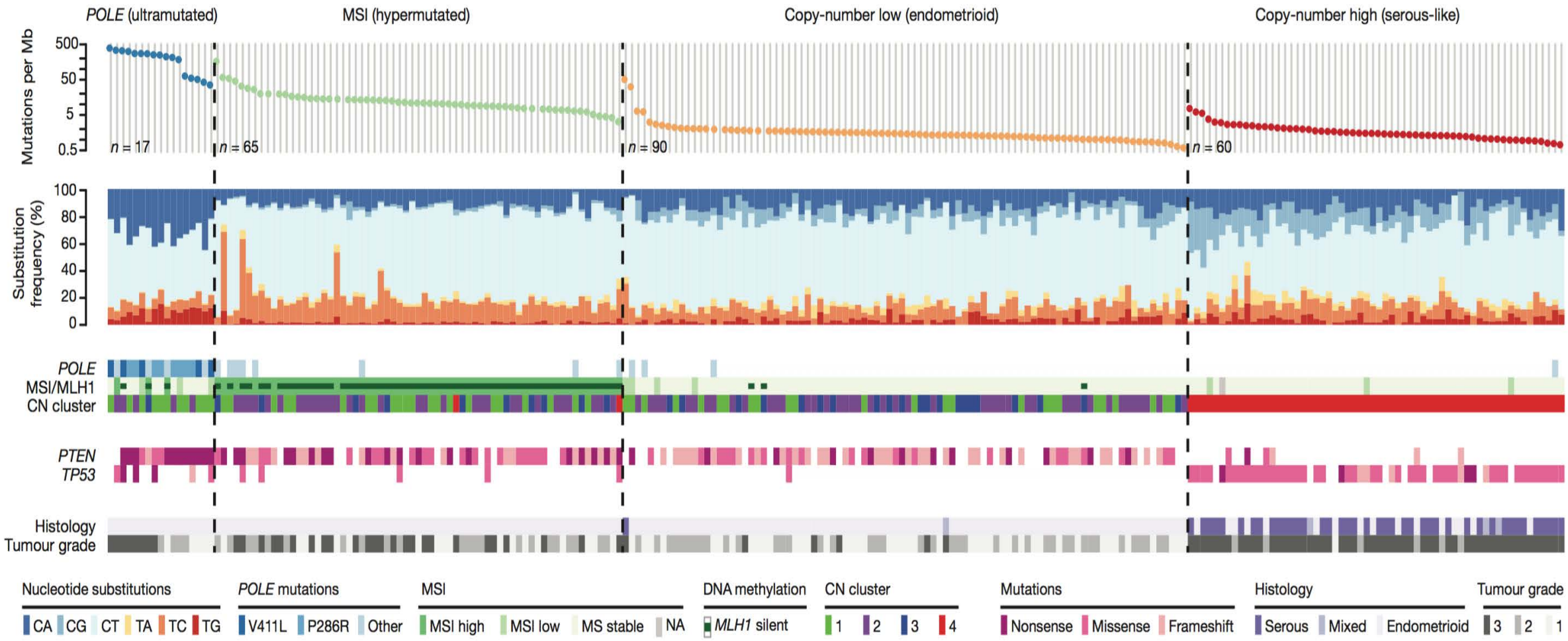
Chief Medical Officer, Sarah Cannon Research Institute

Gynecologic Oncologist, Texas Oncology

Co-Director GOG-Partners
Board of Directors, GOG-Foundation

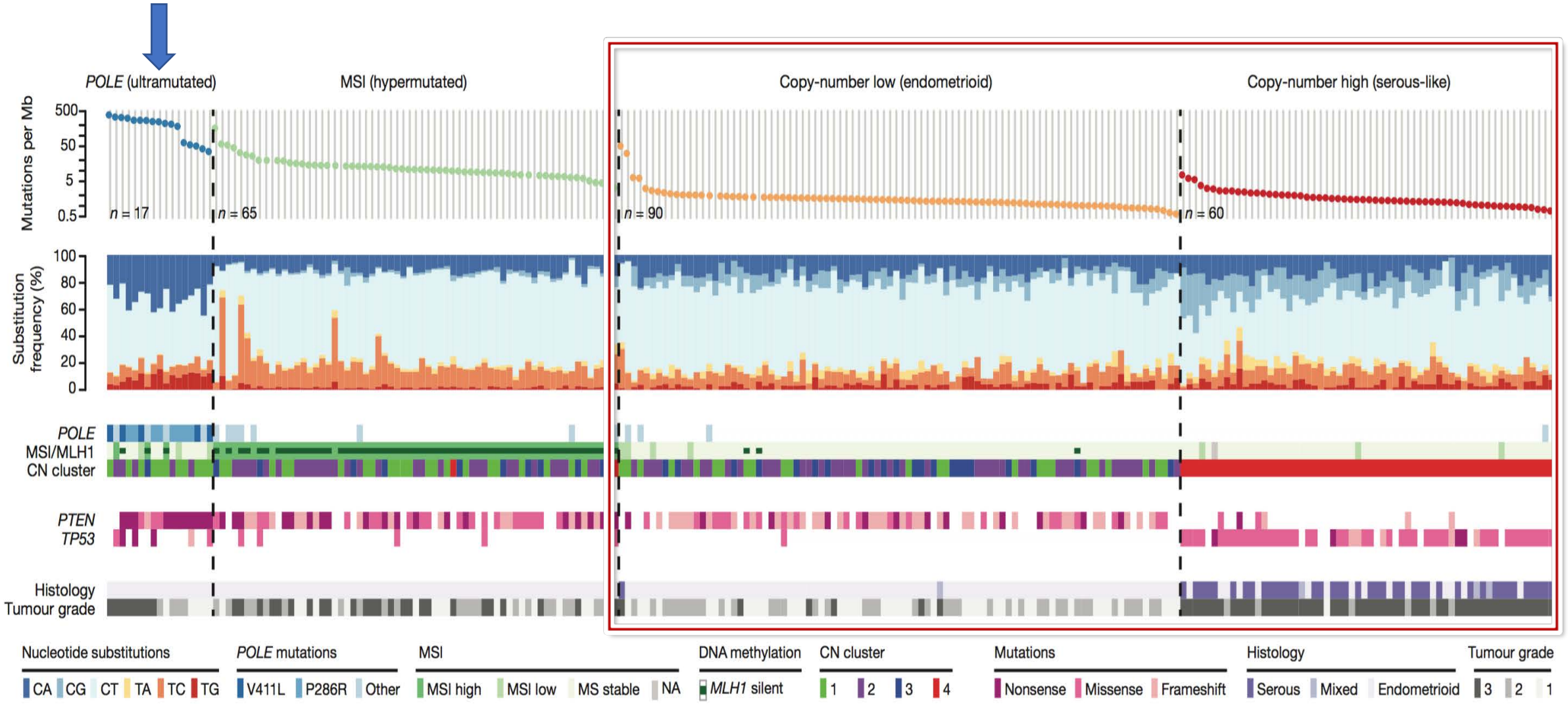


Molecular Profile of Endometrial Cancer



TCGA, Nature 2013

Molecular Profile of Endometrial Cancer: MSS/MMRp



TCGA, Nature 2013

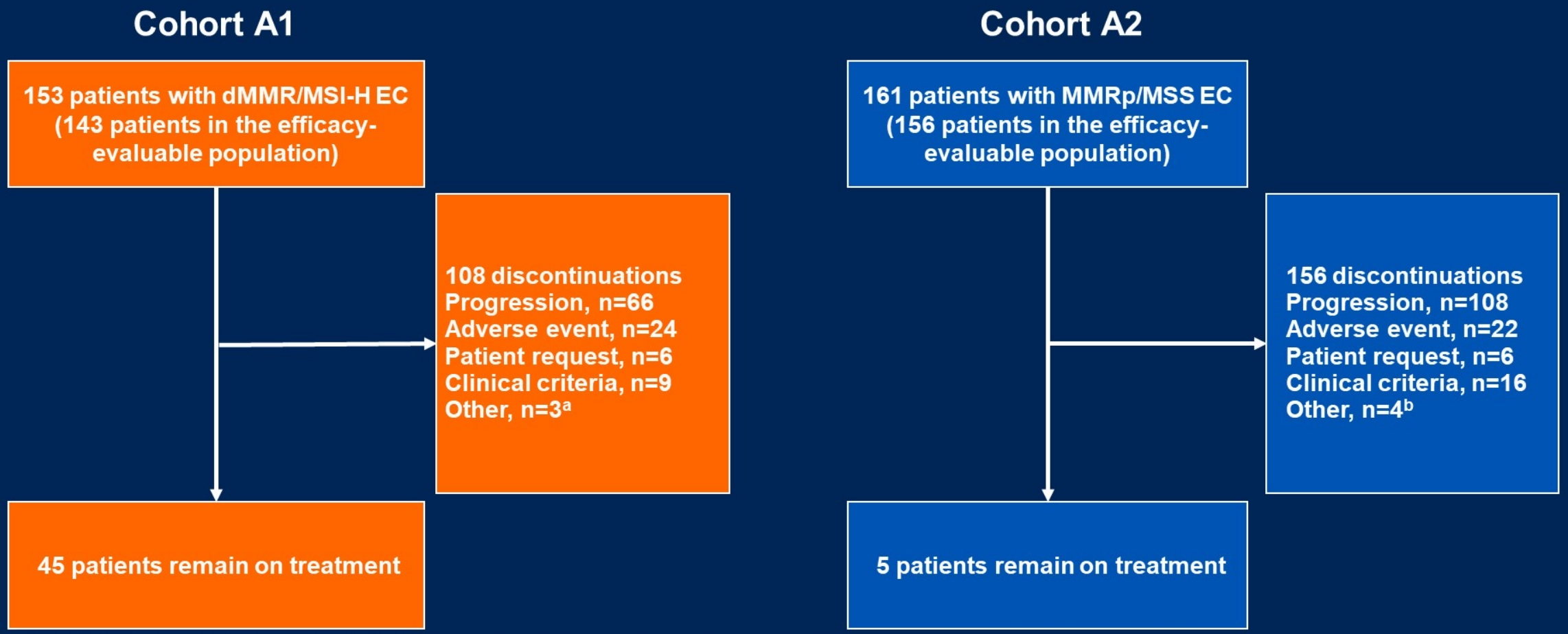
Single Agent IO Efficacy in Biomarker Selected Endometrial Cancer *(Cold Tumors)*

Study	Drug	N	Patient Selection	ORR (%)
GARNET[1,2]	Dostarlimab	143/156	Previously treated Recurrent/advanced dMMR/**pMMR**	46%/**15%**
PHAEDRA[3]	Durvalumab	35/36	Advanced/metastatic dMMR/**pMMR**	40%/**3%**

dMMR, deficient mismatch repair; IO, immunotherapy; ORR, overall response rate; pMMR, proficient mismatch repair

1. Oaknin A et al. ASCO 2022
2. Tinker AV et al. ESMO 2022
3. Antill Y et al. ASCO 2019

GARNET Trial Cohorts



10 (cohort A1) and 5 (cohort A2) patients were excluded from the efficacy-evaluable population because they had no measurable disease at baseline per BICR.
[a]3 patients in cohort A1 died of disease progression. [b]2 patients in cohort A2 died of disease progression, 1 patient was sent to hospice care, 1 patient discontinued because of a joint decision between patient and investigator.
BICR, blinded independent central review; dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; MSI-H, microsatellite instability–high; MSS, microsatellite stable.

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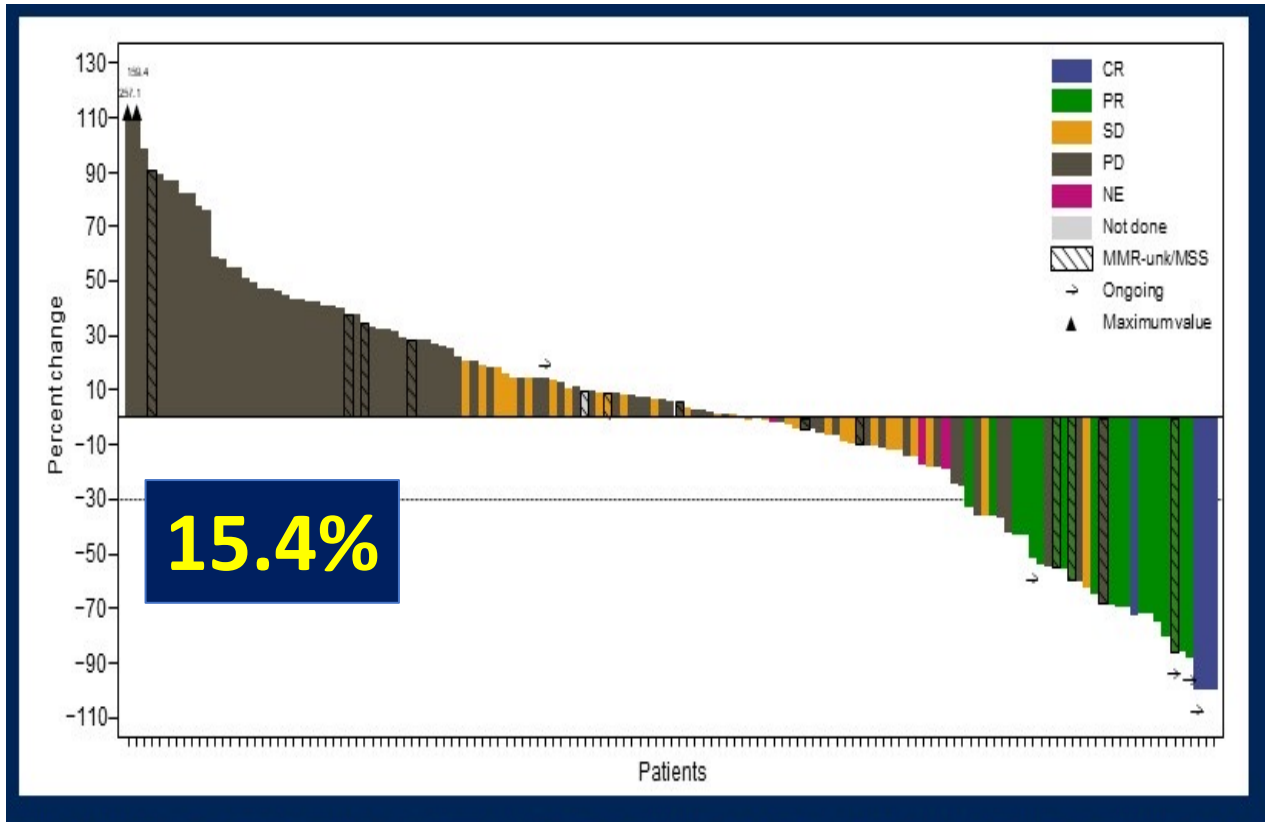
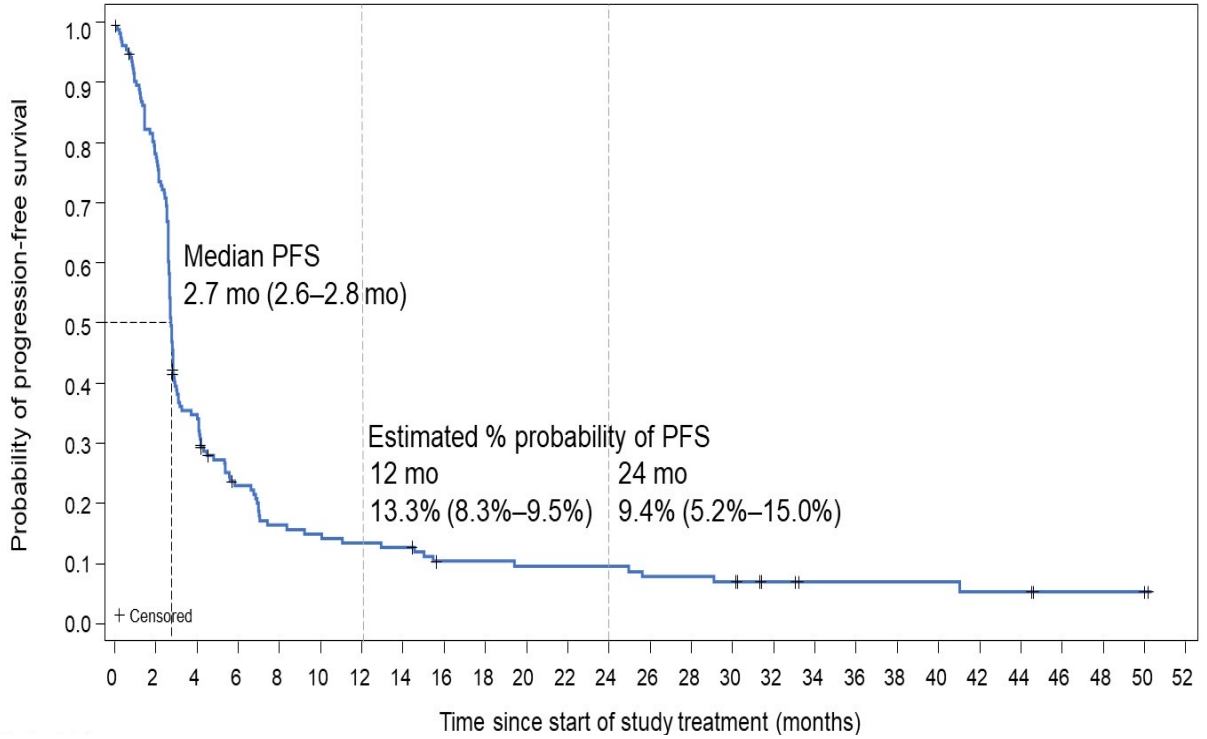
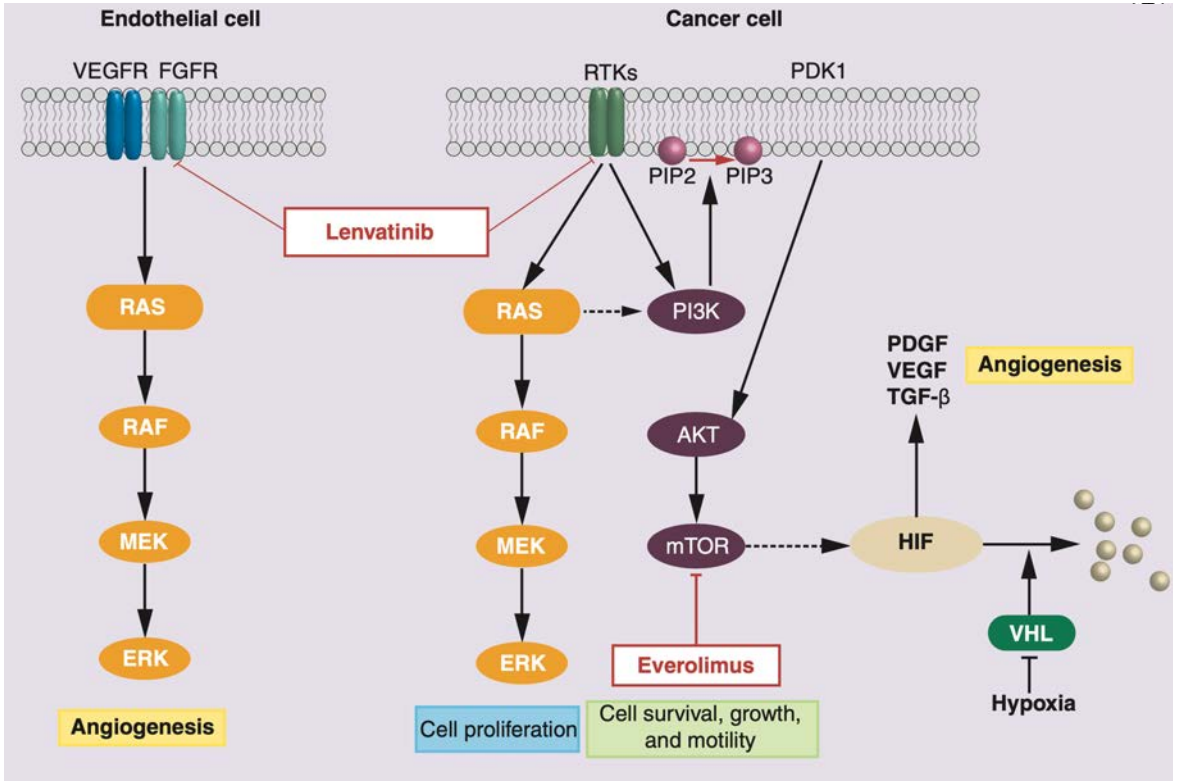
GARNET: Cohort A2 (MMRp/MSS)

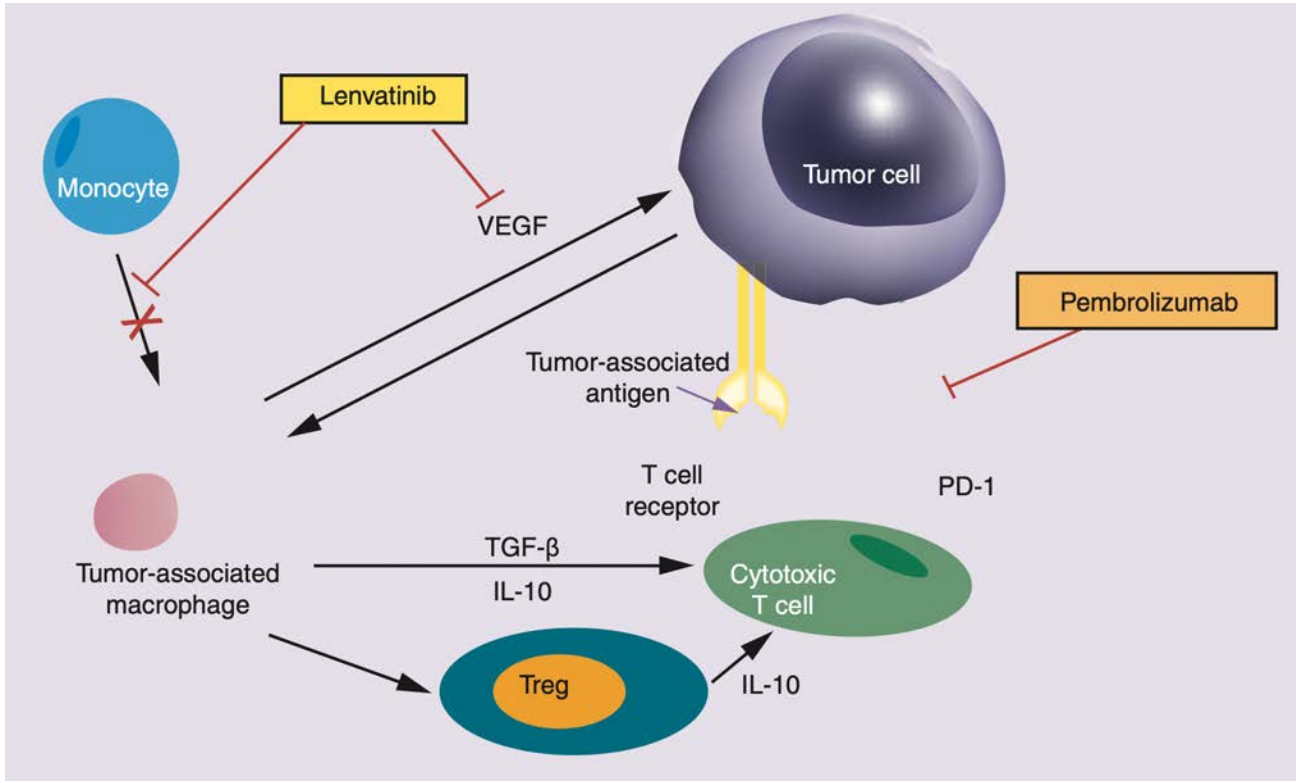




Oaknin, ASCO 2022

Rationale for Lenvatinib/Pembrolizumab





Keynote-146: Lenvatinib/Pembrolizumab

Articles

Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial

Vicky Makker, Drew Rasco, Nicholas J Vogelzang, Marcia S Brose, Allen L Cohn, James Mier, Christopher Di Simone, David M Hyman, Daniel E Stepan, Corina E Dutcus, Emmett V Schmidt, Matthew Guo, Pallavi Sachdev, Robert Shumaker, Carol Aghajanian, Matthew Taylor

Summary

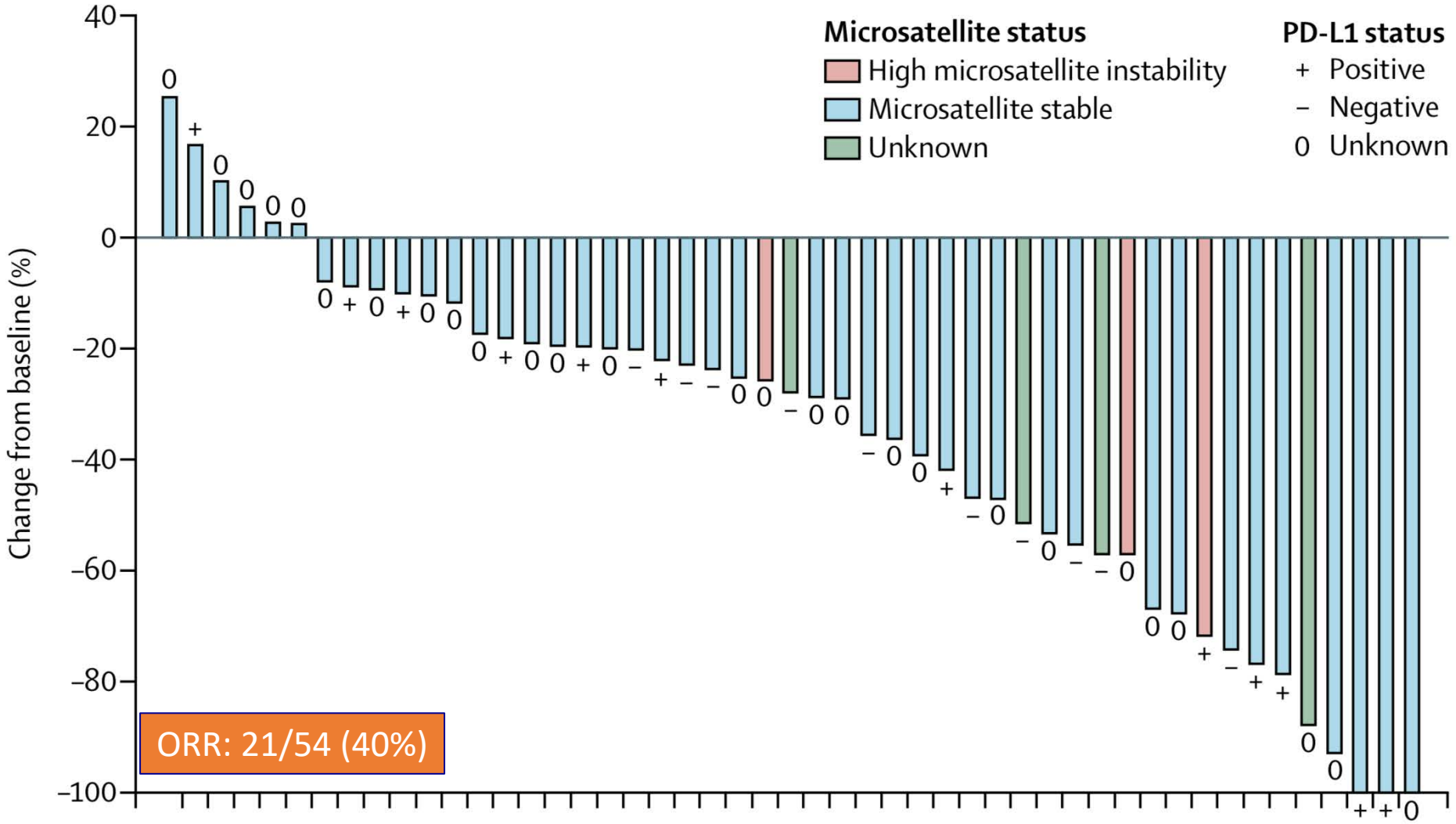
Background Lenvatinib is a multikinase inhibitor of VEGFR1, VEGFR2, and VEGFR3, and other receptor tyrosine kinases. Pembrolizumab, an antibody targeting PD-1, has moderate efficacy in biomarker-unselected endometrial cancer. We aimed to assess the combination of lenvatinib plus pembrolizumab in patients with advanced endometrial carcinoma, after establishing the maximum tolerated dose in a phase 1b study.

Lancet Oncol 2019

Published Online
March 25, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30020-8

Makker Lancet Oncol 2019

Keynote-146: Lenvatinib/Pembrolizumab



Makker Lancet Oncol 2019

Keynote-146: Lenvatinib/Pembrolizumab

	Patients With Previously Treated EC			
	Previous Data Cutoff Date: January 10, 2019[15]	Updated Data Cutoff Date: August 18, 2020[a]		
Investigator Assessment per irRECIST	Total (n = 108)	Total (n = 108)	Non–MSI-H/pMMR (n = 94)	MSI-H/dMMR (n = 11)
ORR, No. (%)	42 (38.9)	43 (39.8)	36 (38.3)	7 (63.6)
95% CI	29.7 to 48.7	30.5 to 49.7	28.5 to 48.9	30.8 to 89.1
Complete response, No. (%)	8 (7.4)	9 (8.3)[b]	8 (8.5)	1 (9.1)
Partial response, No. (%)	34 (31.5)	34 (31.5)	28 (29.8)	6 (54.5)
Stable disease, No. (%)	49 (45.4)	46 (42.6)	41 (43.6)	3 (27.3)
Durable stable disease rate,[c] No. (%)	21 (19.4)	18 (16.7)	17 (18.1)	1 (9.1)
Clinical benefit rate,[d] No. (%)	63 (58.3)	61 (56.5)	53 (56.4)	8 (72.7)
95% CI	48.5 to 67.7	46.6 to 66.0	45.8 to 66.6	39.0 to 94.0
Disease control rate,[e] No. (%)	91 (84.3)	89 (82.4)	77 (81.9)	10 (90.9)
95% CI	76.0 to 90.6	73.9 to 89.1	72.6 to 89.1	58.7 to 99.8
Median DOR, months (95% CI)[f]	21.2 (7.6 to NE)	22.9 (10.2 to NE)	23.0 (8.5 to NE)	21.2 (7.3 to NE)

Makker J Clin Oncol 2023

KEYNOTE-775: Ongoing Phase 3 Study of Pembrolizumab + Lenvatinib vs Chemotherapy in 2L EC

Enrollment & Eligibility

- N = ~780 2L advanced EC patients
  - Approximately 120 dMMR and 660 pMMR patients
- Measurable disease per RECIST v1.1
- ECOG PS ≤1
- Stratification factors:
  - dMMR vs MMRp
  - MMRp patients further stratified by ECOG PS, geographic region, and prior history of pelvic radiation

R 1:1

- Physician's choice chemotherapy (doxorubicin or paclitaxel)
- Pembrolizumab 200 mg IV Q3W + Lenvatinib 20 mg PO QD

Primary End Points

- PFS (BICR) and OS

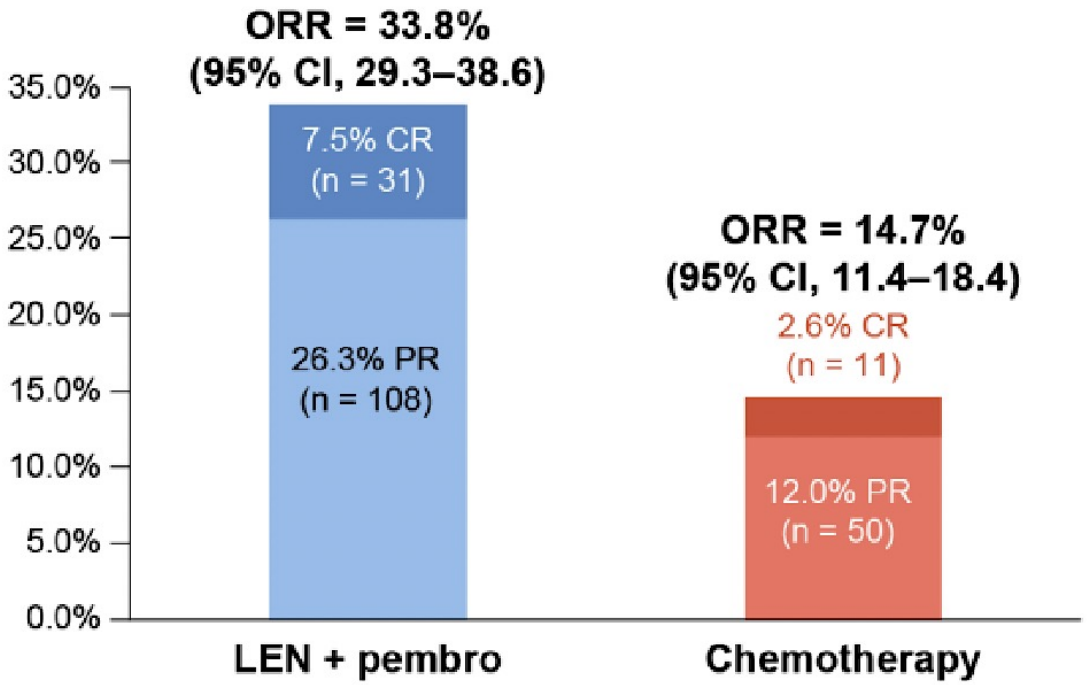
Secondary End Points

- ORR, HRQoL, safety and tolerability, PK

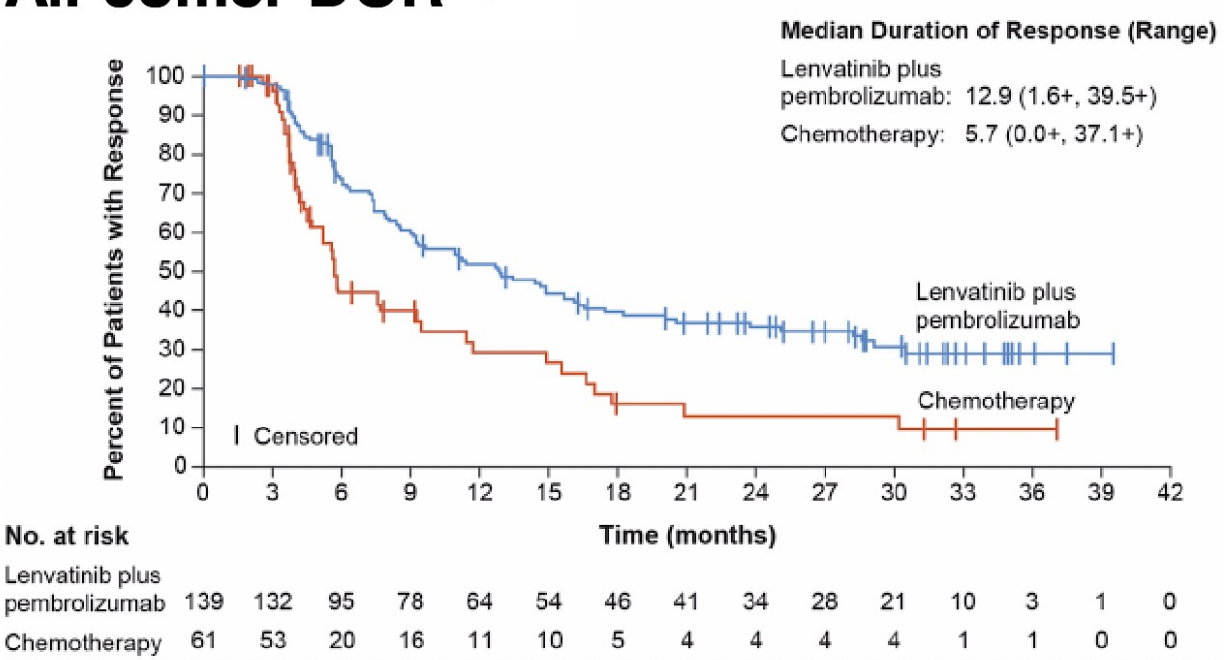
Makker V et al. *N Engl J Med* 2022: 386:437-448
Clinicaltrials.gov. NCT03517449

KEYNOTE-775: Continued Tumor Responses in pMMR and All-Comer Patients

All-comer ORR[a,c,d]



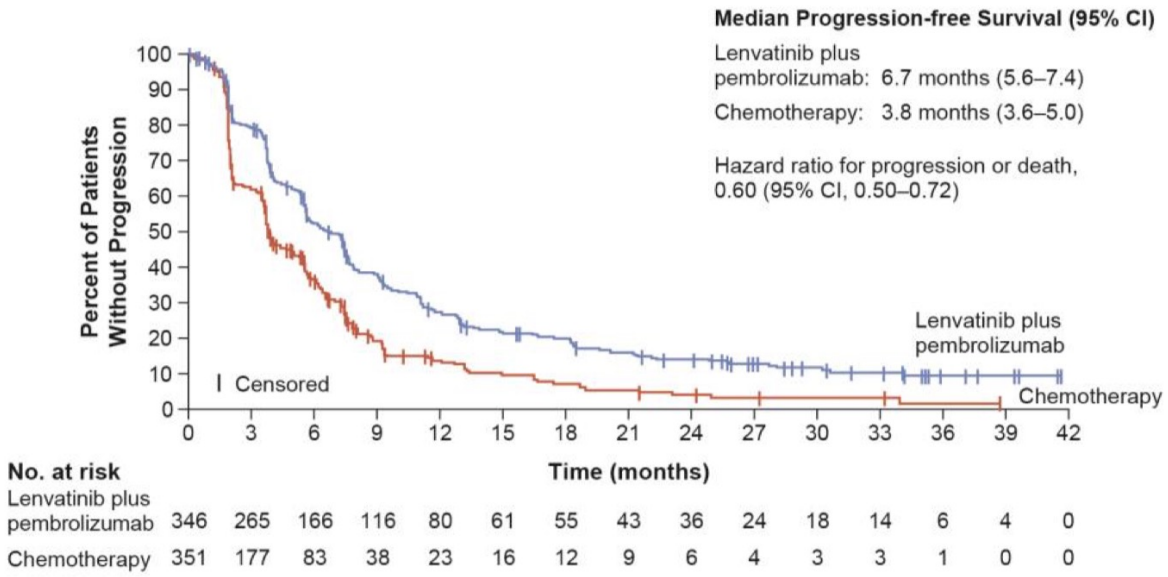
All-comer DOR[e,g]



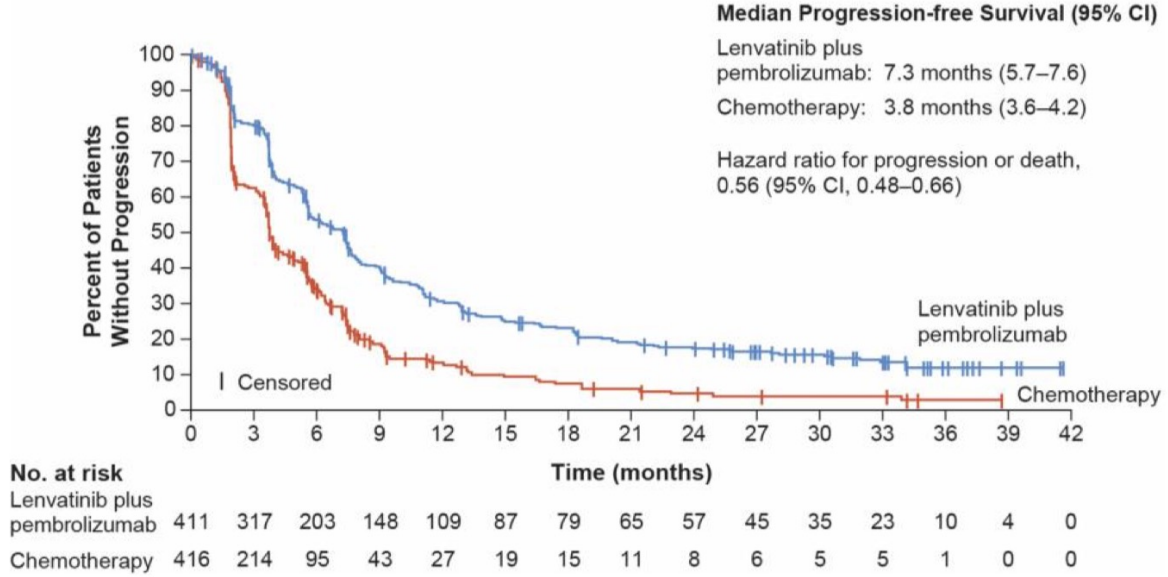
Makker V et al. ESMO 2022;Abstract 525MO.

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

pMMR Population



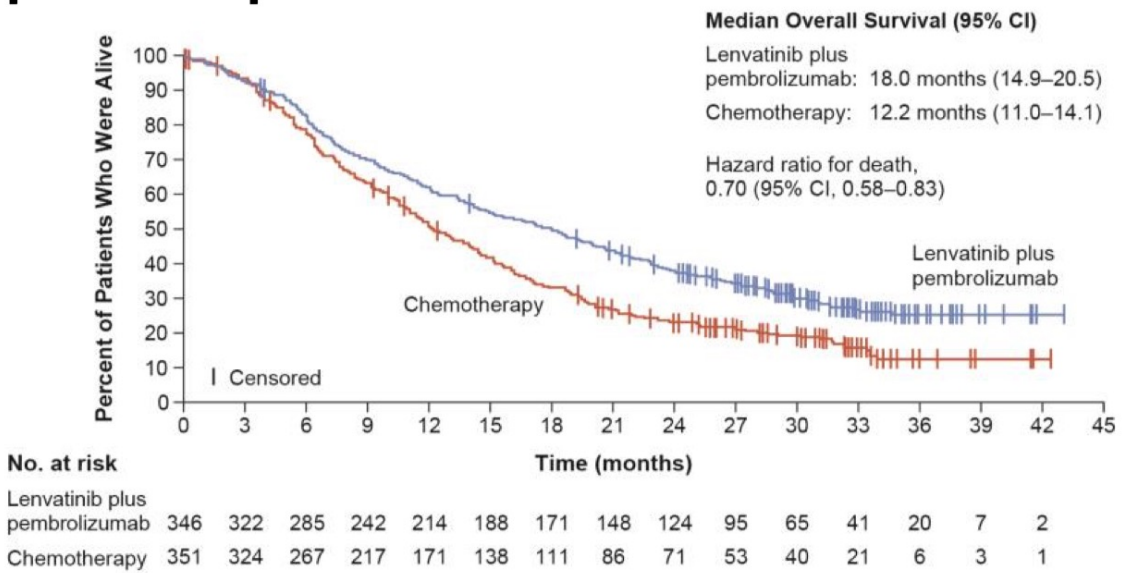
All-Comer Population



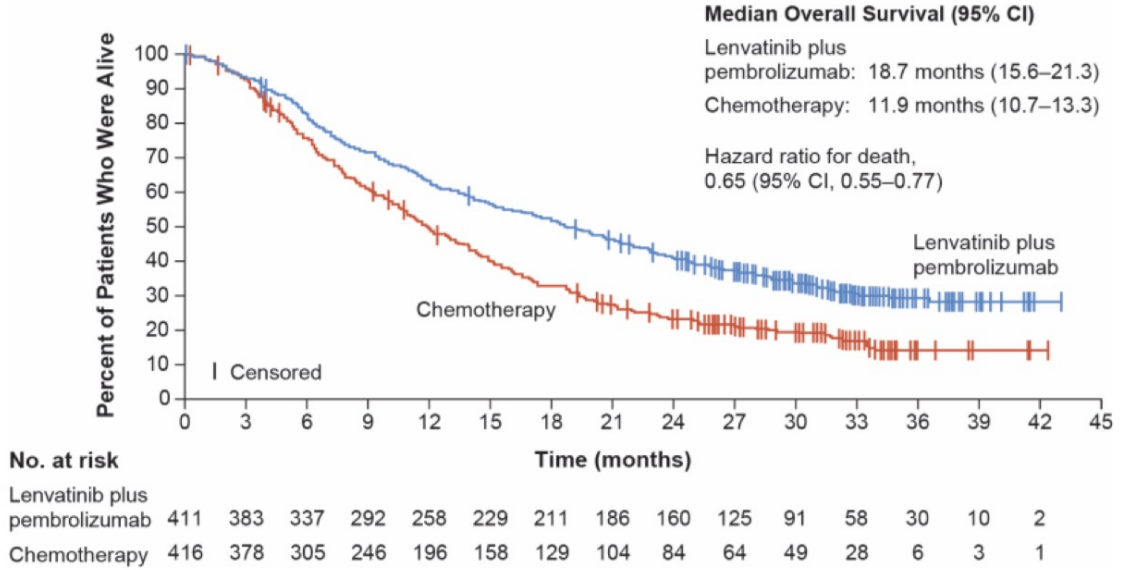
Makker V et al. ESMO 2022; Abstract 525MO.

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

pMMR Population



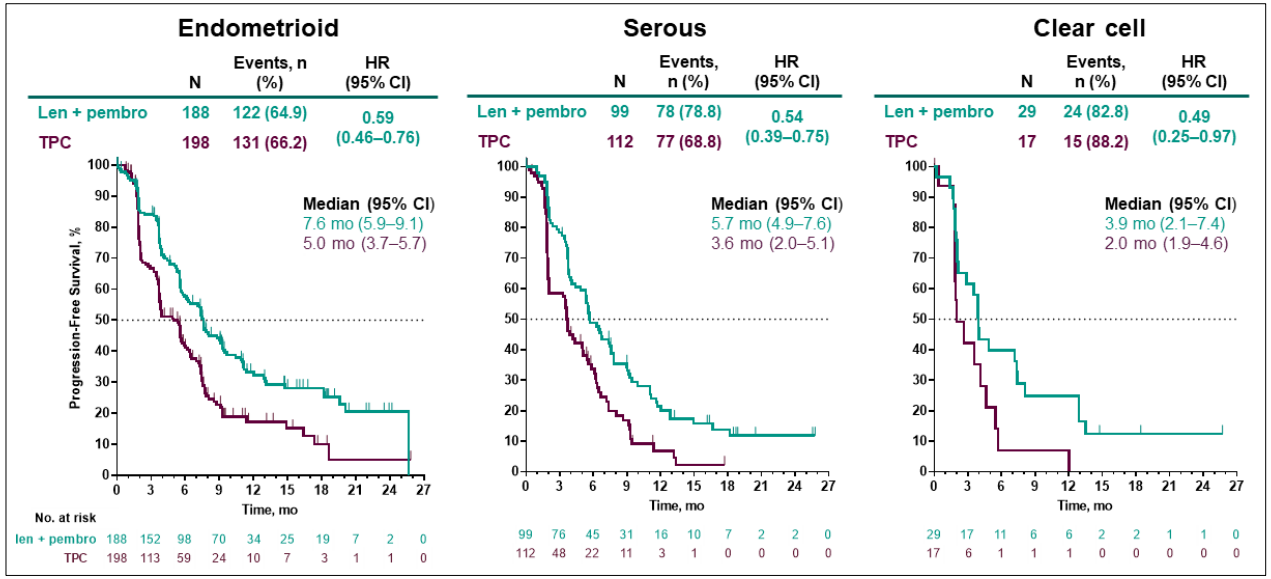
All-Comer Population



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

Additional Sub-Analyses (Non-Analytic)

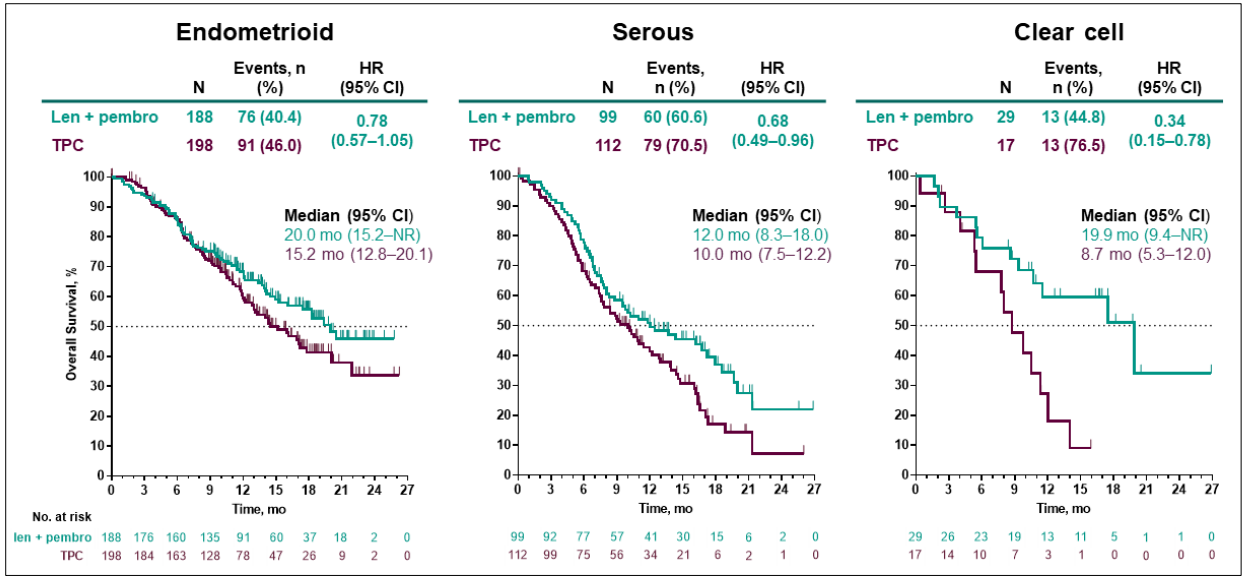
PFS[a] by Histology: pMMR



[a]Per RECIST v1.1 by BICR. Randomization was stratified by MMR status. HRs for other histologic types: mixed cell (n = 31): HR (95% CI), 0.90 (0.35-2.29); other (n = 23): HR (95% CI), 0.38 (0.12-1.19).
Data cutoff: Oct 26, 2020.

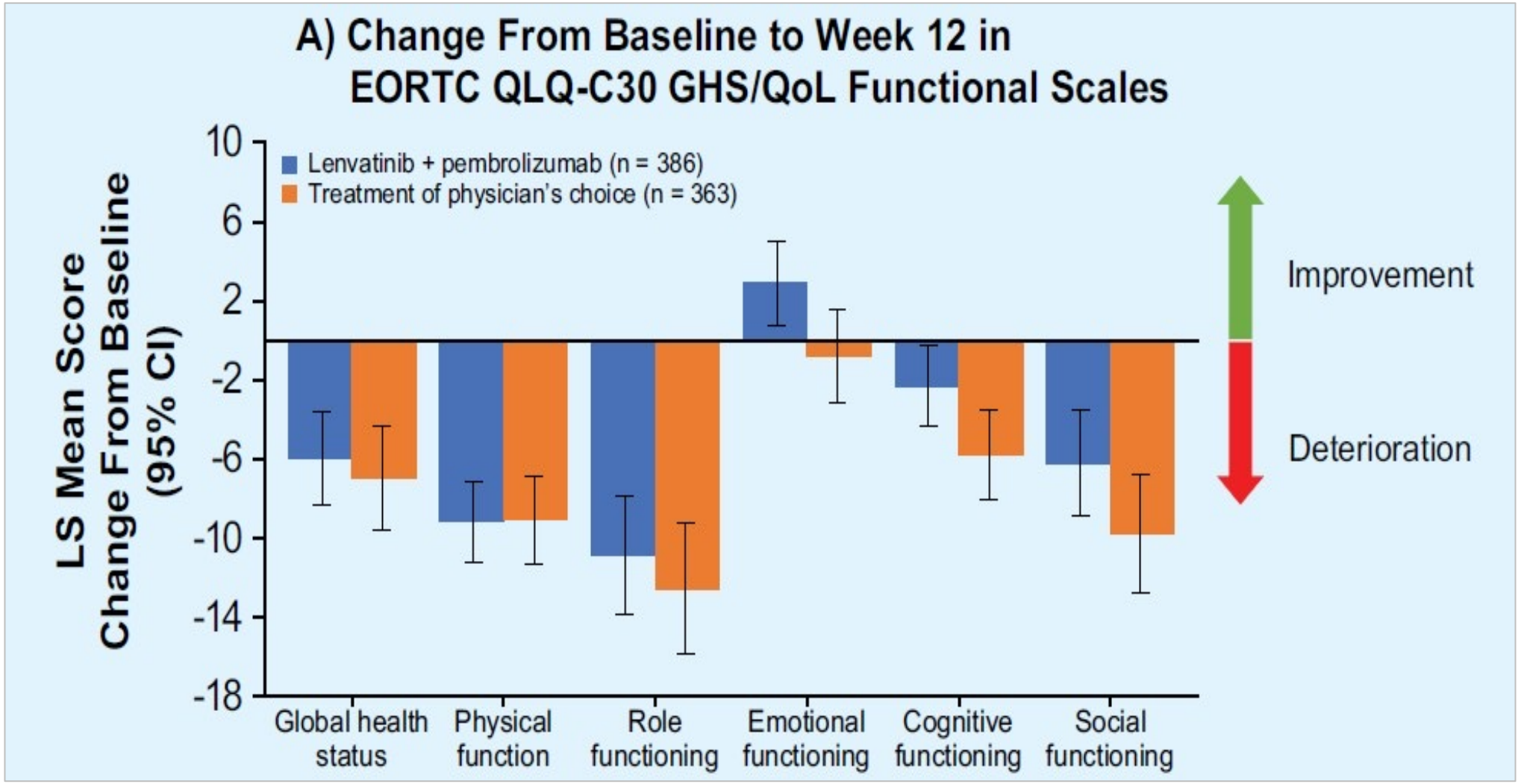
Colombo N, et al. *Ann Oncol*. 2021;32(suppl_5):S725-S772. doi:10.1016/annonc/annonc703

OS by Histology: pMMR



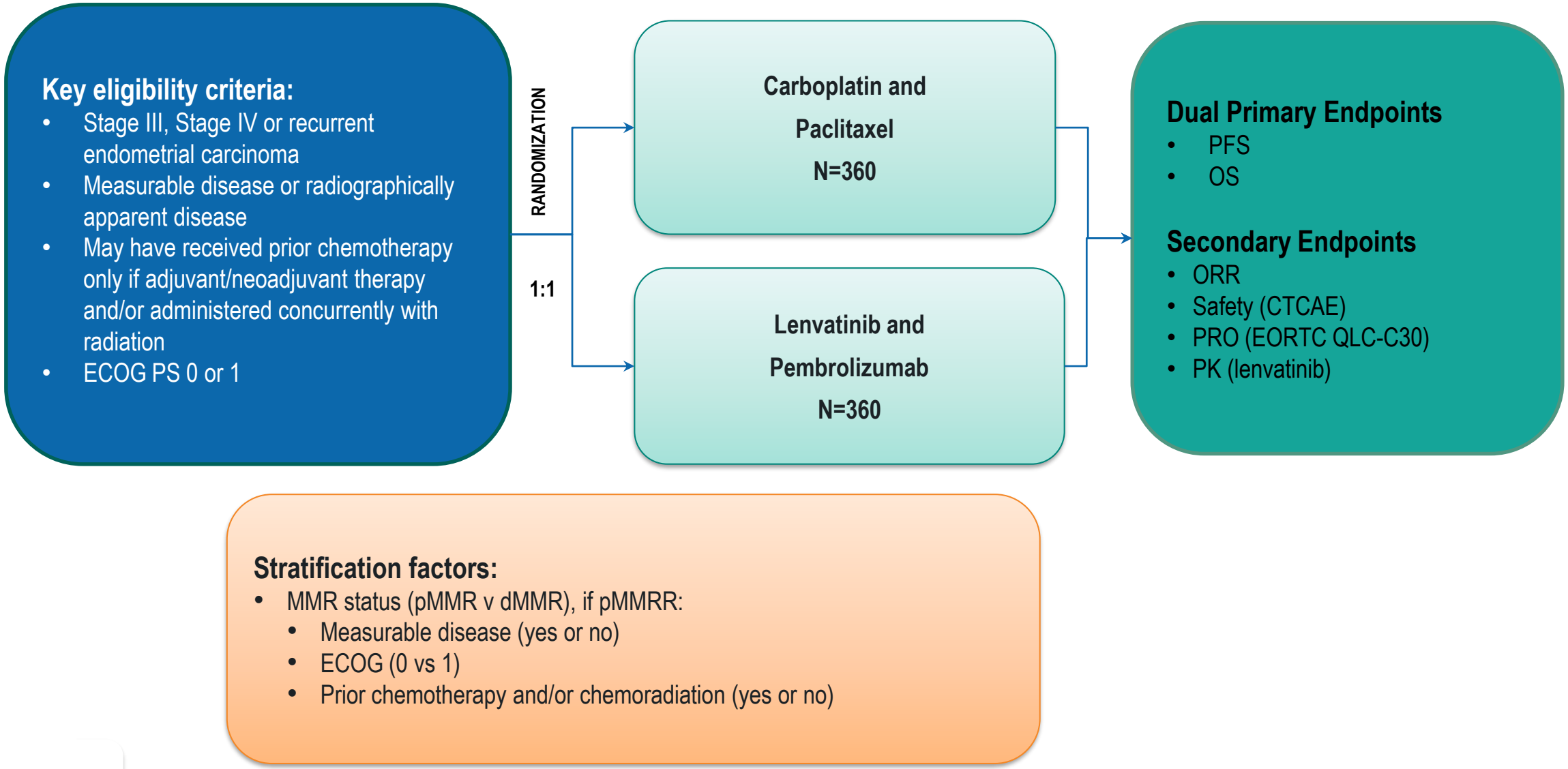
HRs for other histologic types: mixed cell (n = 31): HR (95% CI), 0.40 (0.17-0.99); other (n = 23): HR (95% CI), 0.32 (0.11-0.94).
Data cutoff: Oct 26, 2020.

Study 309/KEYNOTE-775: QoL (Week 12)



Makker V et al. NEJM 2022

LEAP-001: 1L phase 3 in endometrial cancer

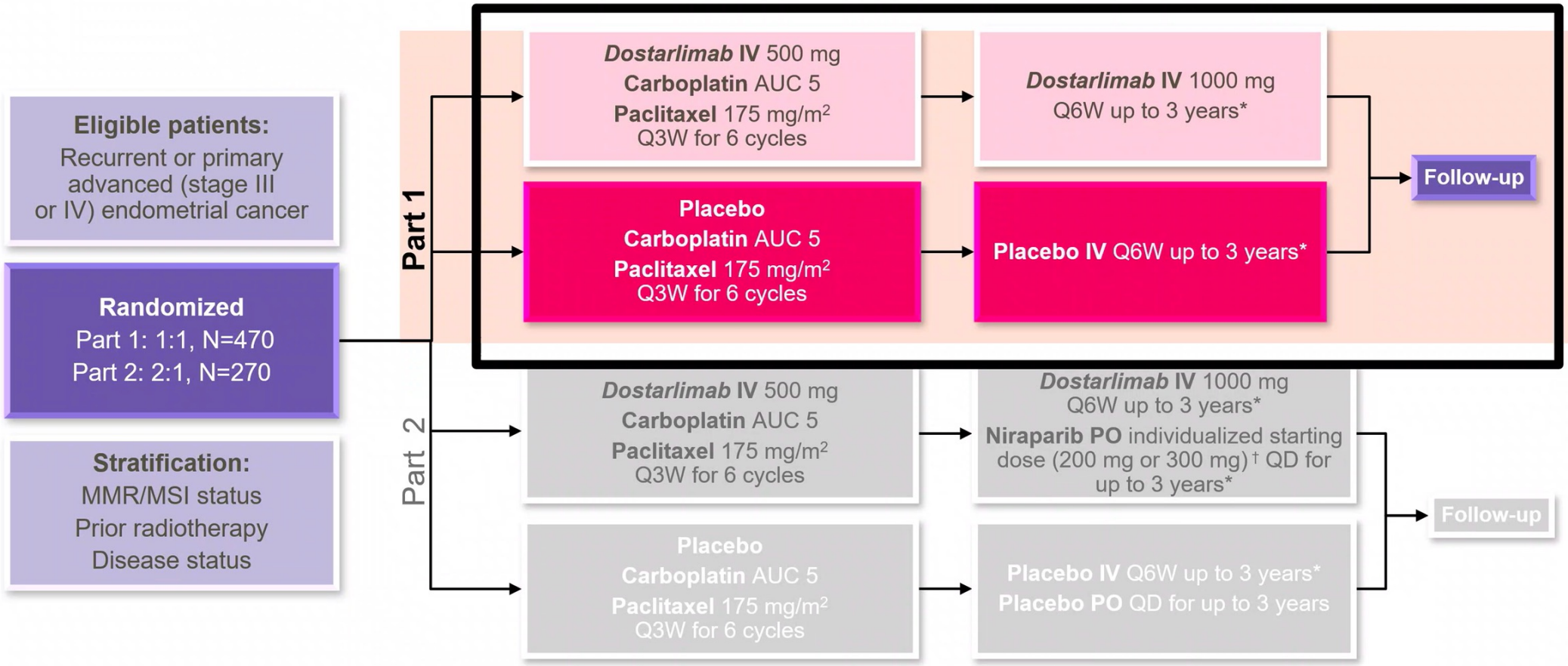


Stratification factors:

- MMR status (pMMR v dMMR), if pMMRR:
  - Measurable disease (yes or no)
  - ECOG (0 vs 1)
  - Prior chemotherapy and/or chemoradiation (yes or no)

RUBY Study Design

Phase 3, two-part, double-blind, randomized controlled registrational study in patients with primary advanced or recurrent endometrial cancer



Endpoints

Primary: PFS (inv. assessed), OS

Secondary: PFS (BICR), ORR, DOR, DCR, PROs, PFS2, safety and tolerability, Pharmacokinetics and immunogenicity of Dostarlimab

Primary: PFS (inv. assessed)

Secondary: PFS (BICR), OS, ORR, DOR, DCR, PROs, PFS2, safety and tolerability, PK and immunogenicity of Dostarlimab, PK of Niraparib

25% dMMR vs **75% pMMR**

Majority with no pelvic XRT

Most metastatic

Combinatorial IO approach: Chemotherapy + pembrolizumab
NRG GY018: Placebo controlled - 2 separate cohorts (NCT03914612)

- Measurable stage 3 or 4A endometrial cancer
- Stage 4B or recurrent endometrial cancer
- GOG PS 0-2

pMMR: N=590
dMMR: N=220

1:1
R

Carboplatin AUC 5 Q3wk
Paclitaxel 175 mg/m^2 Q3wk
Placebo q3w X up to 35 cycles

Carboplatin AUC 5 Q3wk
Paclitaxel 175 mg/m^2 Q3wk
Pembrolizumab 200mg q3w x up to 35 cycles

dMMR & pMMR
(α=0.0125 one-sided each)

Stratification variables:
- **MMR status (by central laboratory assessment)**
- **GOG PS (0 or 1 vs. 2)**
- **Prior chemotherapy (yes vs. no)**

Primary endpoint: PFS

Eligible histologies:
- **Endometrioid, serous, clear cell, mixed, undifferentiated, adenocarcinoma NOS**

	ENGOT EN-6/GOG-3031/RUBY Dostarlimab + TC (NCT03981796)	NRG-GY018 Pembrolizumab + TC (NCT03914612)
Target N	494	819
Investigational Treatment Duration	Up to 3 years	Up to 2 years
Chemotherapy duration	6 cycles	6 cycles, but can extend up to 10 cycles (if measurable and SD or PR after the 6th cycle)
Prior RT	Must be at least 3 weeks since	Must be at least 4 weeks since
Stratification factors	*Recurrent vs primary stage III vs primary stage IV disease *Prior radiotherapy *MMR status (central laboratory)	*ECOG PS (0 or 1 and 2) *Prior chemo (yes or no) *MMR status (local testing)
ECOG criteria	0–1	0–2
Time since chemotherapy for recurrent patients	≥6 months	≥12 months
Disease criteria	Primary stage IIIA to IIIC1 disease with presence of evaluable or measurable disease; primary stage IIIC2 or stage IV disease regardless of the presence of evaluable or measurable disease	Stage III, IV, or recurrent EC: Stage III or IVA, measurable disease; Stage IVB or recurrent whether there is measurable disease or not
Histology criteria	Includes carcinosarcoma	Excludes carcinosarcoma
Primary outcome(s)	PFS (IA), OS (all comers, dMMR)	PFS (Interim Analysis), dMMR and **MMRp (independent)**
Scan frequency	Every 6 weeks until week 25,then, every 9 weeks until week 52, then every 12 weeks	Every 9 weeks for the first 9 months, then every 12 weeks

New Wins…and in a pMMR – Analytical endpoint (GY018)

Dostarlimab RUBY phase III trial met its primary endpoint in a planned interim analysis in patients with primary advanced or recurrent endometrial cancer

- Results showed a statistically significant and clinically meaningful improvement in investigator-assessed progression-free survival
- RUBY is the only first-line trial to show improvement in progression-free survival for an immuno-oncology therapy in combination with standard-of-care chemotherapy in primary advanced or recurrent endometrial cancer
- Regulatory submissions based on the trial results are planned for the first half of 2023

The manufacturer today announce positive headline results from the planned interim analysis of Part 1 of the RUBY/ENGOT-EN6GOG3031/NSGO phase III trial investigation dostarlimab plus standard-of-care chemotherapy (carboplatin-paclitaxel) followed by dostarlimab compared to chemotherapy plus placebo followed by placebo in adult patients with primary advanced or recurrent endometrial cancer. The trial met its primary endpoint of investigator-assessed progression-free survival (PFS). It showed a statistically significant and clinically meaningful benefit in the prespecified mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) patient subgroup and in the overall population. A clinically relevant benefit in PFS was also observed in the mismatch repair proficient (MMRp)/microsatellite stable (MSS) patient subgroup

February 3, 2023

Dear Patient:

You are receiving this letter because you have participated in and are currently receiving treatment on NRG-GY018, **"A Phase III Randomized, Placebo-Controlled Study of Pembrolizumab (MK-3475, NSC #776864) in Addition to Paclitaxel and Carboplatin for Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer."**

The purpose of this letter is to inform you that a pre-planned interim analysis has just been completed. It reveals that the addition of pembrolizumab to chemotherapy (carboplatin and paclitaxel) slows the time to cancer progression. Now that these results are available, the use of the placebo infusions is no longer necessary.

Take Home Points: MMRp/MSS Endometrial Cancer

- Majority of endometrioid endometrial cancers are MMRp/MSS
- Molecular characterization reflects multiple potential options for care
- Immune checkpoint inhibitors have had disappointing results as single agents
  - Efficacy may be related to POL-E cases not demonstrating concomitant MSI
- Lenvatinib/pembrolizumab has robust level I evidence for efficacy in recurrent, previously treated patients (not previously ICI exposed)
- Trials are evaluating lenvatinib/pembrolizumab vs platinum-based combination in non-previously treated advanced stage/recurrent endometrial cancer
- Assessment of RUBY & GY018 may enable chemotherapy plus ICI in MMRp/MSS cancer

Module 3: Diagnosis and Management of Adverse Events Associated with Immune Checkpoint Inhibitors Alone and in Combination for Endometrial Cancer — Dr Westin

Case Presentation: 62-year-old woman with a family history of breast cancer

Dr Thomas Morrissey (Boca Raton, Florida)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Thomas Morrissey, MD

Is there a role for PARP inhibitors for patients with high-grade endometrial cancer and a germline BRCA mutation?

What is the role of hysterectomy, if any, in risk-reducing surgery for patients with germline BRCA mutations?

RTP
RESEARCH
TO PRACTICE

Case Presentation: 76-year-old woman who underwent hysterectomy, lymphadenectomy, omentectomy and 6 cycles of carboplatin/paclitaxel for a Stage IB MSS serous endometrial cancer; develops metastatic disease to the lungs 11 months later and is started on lenvatinib/pembrolizumab

Dr Dana Chase (Phoenix, Arizona)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Dana Chase, MD

How do you manage diarrhea in patients who are receiving lenvatinib/pembrolizumab? How do you determine whether it's due to the lenvatinib or the pembrolizumab?

For patients who experience autoimmune colitis while on a checkpoint inhibitor, would you rechallenge once symptoms have resolved? Would you consider observing this patient off therapy?

Diagnosis and Management of Adverse Events Associated with Immune Checkpoint Inhibitors Alone and in Combination for Endometrial Cancer

Shannon N. Westin, MD, MPH

Professor, Gynecologic Oncology Center Medical Director

Department of Gynecologic Oncology and Reproductive Medicine

USA

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

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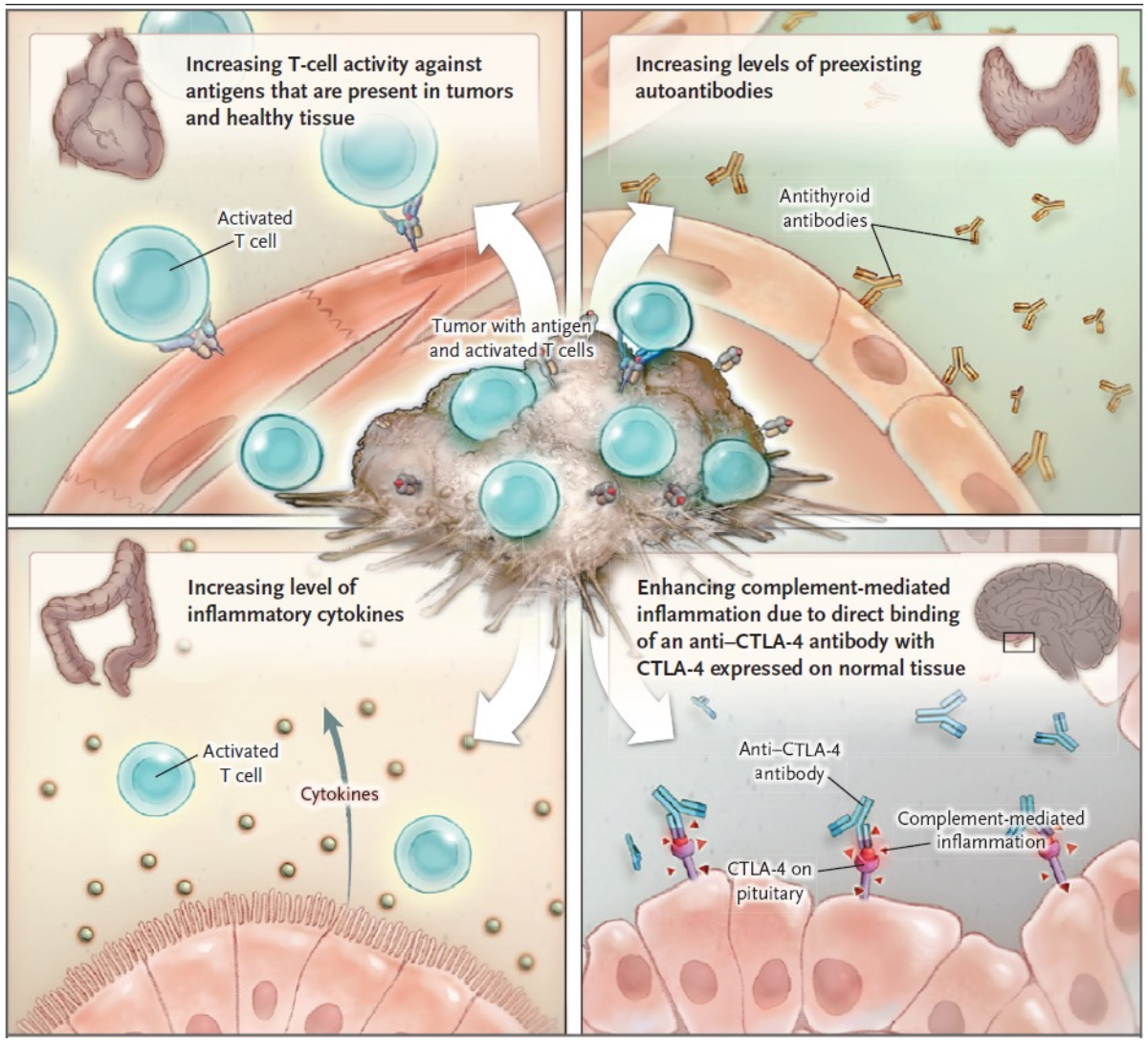
Why do irAEs occur?

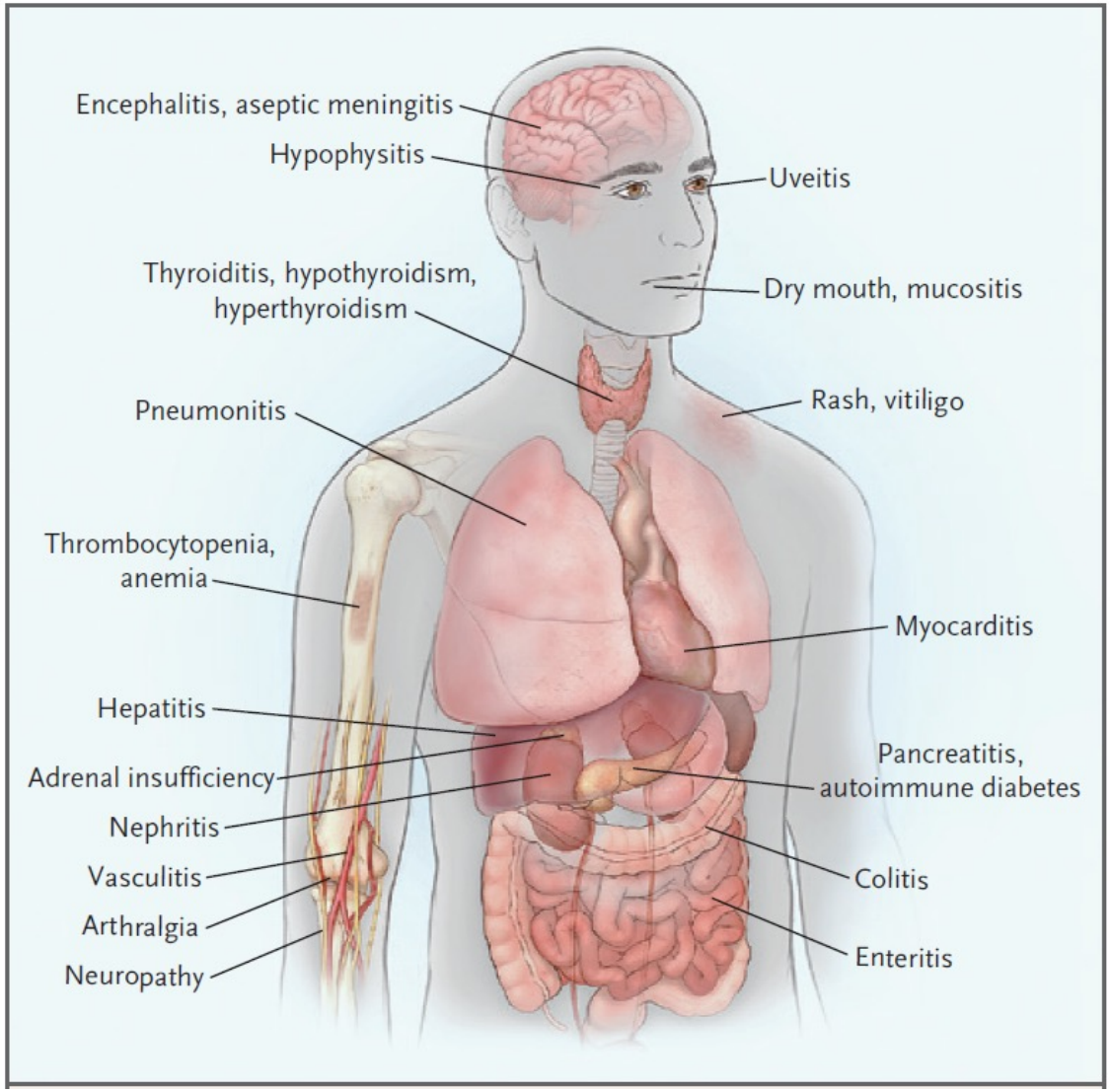
- Precise pathophysiology is unknown
- T-cell, antibody, and cytokine responses may be involved



Postow et al, *NEJM*, 2018

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Where do irAEs occur?



Postow et al, *NEJM*, 2018

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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

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
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General Principles for Managing AEs With Immunotherapy

- **Educate** patients about toxicities and to contact you immediately
  - Let other healthcare providers know that they are receiving IO
- **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

Grade	Management
1 (mild)	▪ Symptomatic management ▪ Continue therapy ▪ Immunosuppression not needed
2 (mild to moderate)	▪ Symptomatic management ▪ Consider discontinuing until resolution to grade 1 ▪ Oral/topical immunosuppression ▪ Involve consultants as needed
3 or 4 (severe)	▪ Discontinue therapy ▪ Intravenous immunosuppression ▪ Other agents as indicated: infliximab, vedolizumab ▪ Refer/involve consultants ▪ At resolution, gradually taper off immunosuppression ▪ Consideration of restart pending severity

Postow MA et al. *N Engl J Med*. 2018;378:158-168. Brahmer JR et al. *J Clin Oncol*. 2018;36:1714-1768. NCCN Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related Toxicities. Version 1.2022.

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Treatment of irAE: Side effects

- Glucocorticoid use: hyperglycemia, gastritis hypertension, edema, anxiety, and iatrogenic adrenal insufficiency
- Opportunistic infections
  - 13.5% of patients on glucocorticoids/infliximab developed serious infections
    - Pneumocystis jirovecii, pneumocystic carinii
  - Patients requiring >= 20mg prednisone / day
    - Sulfamethoxazole/trimethoprim, dapsone, atovaquone, pentamidine

Kyi C et. al, *J Immunother Cancer*. 2014;2:19.

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Immune Checkpoint + Tyrosine Kinase Inhibitors: TEAEs

KEYNOTE - 775

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%]).

Makker. NEJM 2022

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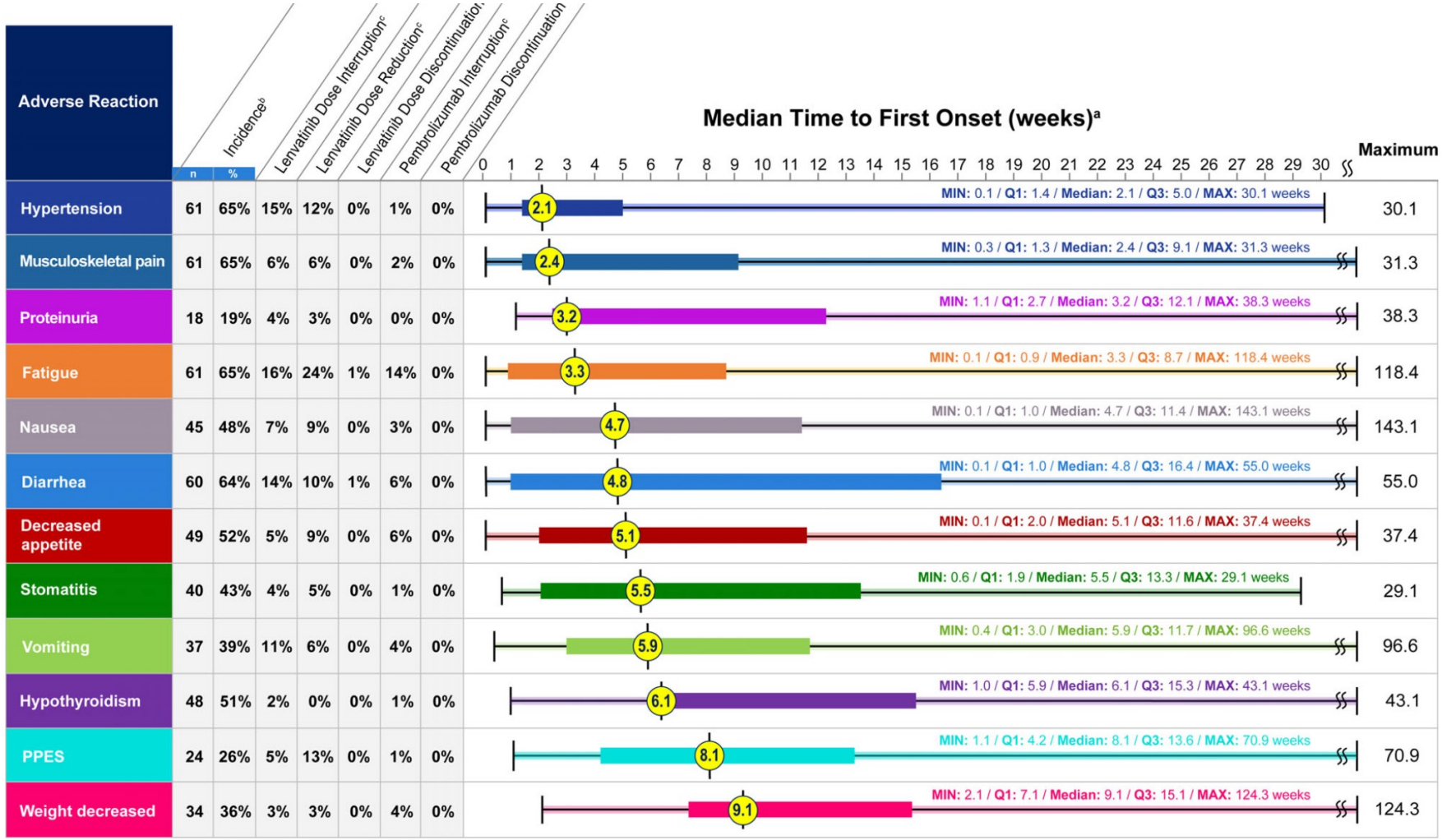
Len/Pem Toxicity Timing



Makker. Oncologist 2021

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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

Makker. Oncologist 2021

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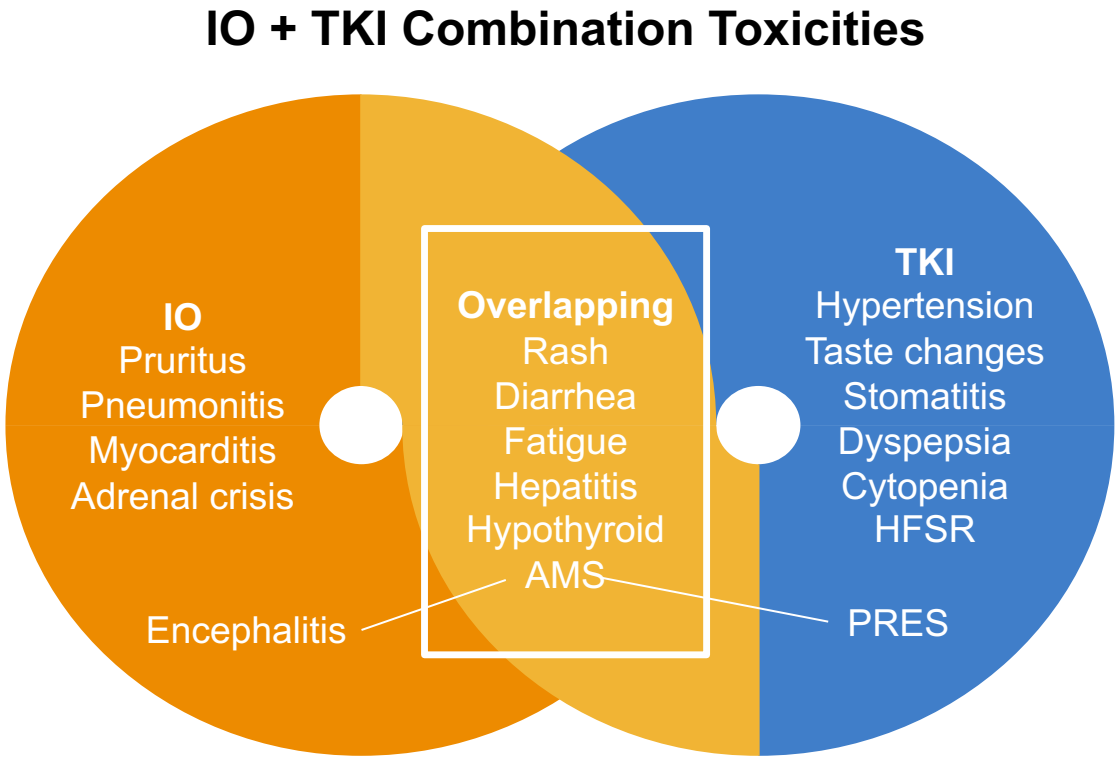
Management of AEs in IO Plus TKI Therapy

- Two mechanisms of action result in two sets of AE profiles that are not mutually exclusive
- It is important to determine which therapy is causing the AE in order to plan a management strategy



Makker V et al. *Oncologist*. 2021;26:e1599-e1608.
How JA et al. *Gynecol Oncol*. 2021;162:24-31.

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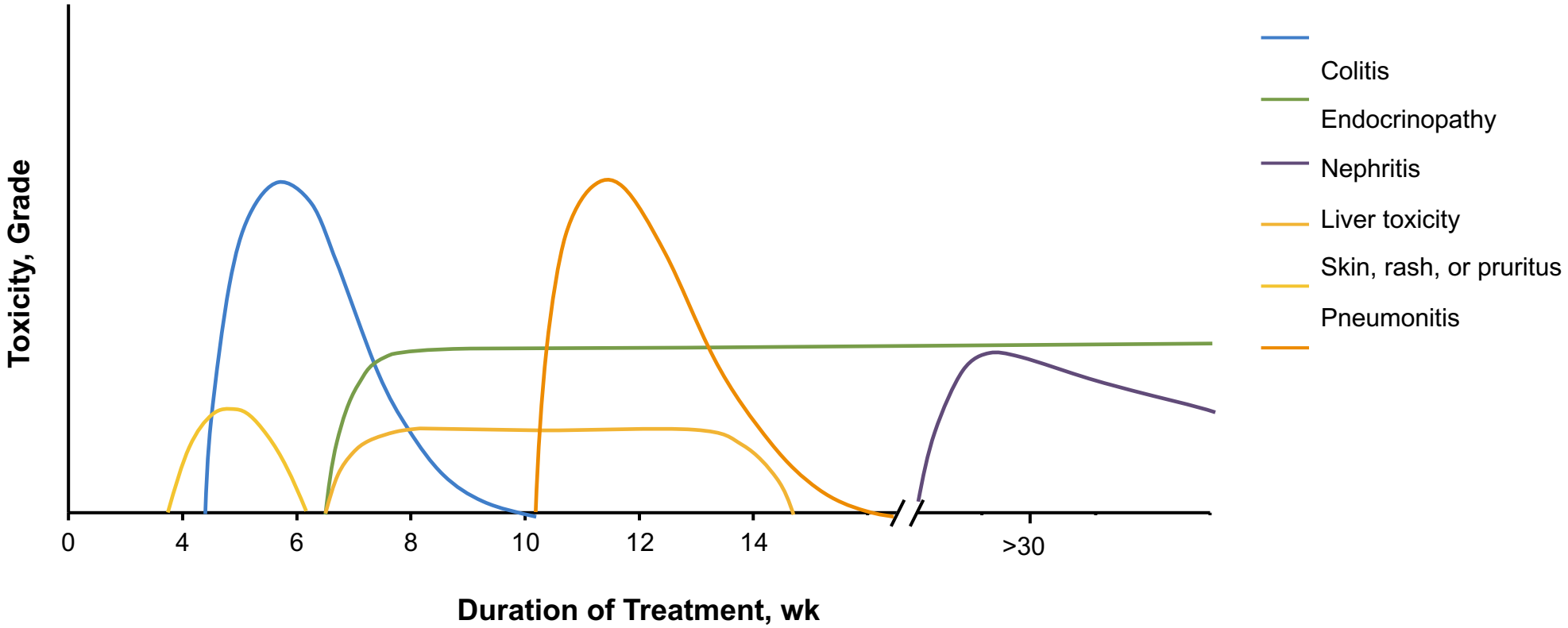
Variable Timing of irAEs



Martins F et al. *Nat Rev Clin Oncol*. 2019;16:563.

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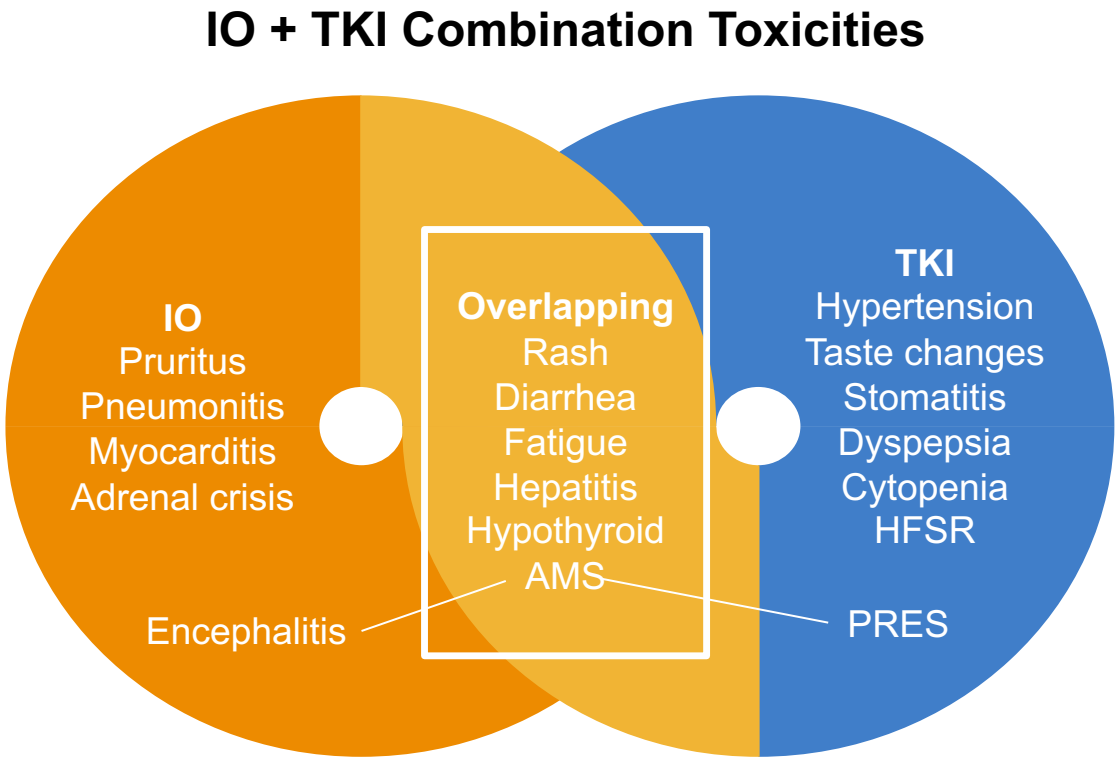
Management of AEs in IO Plus TKI Therapy

- Two mechanisms of action result in two sets of AE profiles that are not mutually exclusive
- It is important to determine which therapy is causing the AE in order to plan a management strategy
  - Hold TKI (shorter half-life than checkpoint inhibitor)
  - In certain cases, use appropriate supportive care
  - If symptoms resolve in a few days, TKI was likely the cause



Makker V et al. *Oncologist*. 2021;26:e1599-e1608.
How JA et al. *Gynecol Oncol*. 2021;162:24-31.

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Phase III IO Combo Trials

Name	EN6-RUBY[1]	EN7-ATTEND[2]	EN9-LEAP-1[3]	NRG018[4]	DUO-E[5]
Agent(s)	Dostarlimab	Atezolizumab	Pembrolizumab + lenvatinib	Pembrolizumab	Durvalumab + olaparib
Planned N	470	550	720	775	699
Concomitant CT	+	+	Pembrolizumab + lenvatinib vs chemotherapy	+	+
Maintenance	+	+		+	+
EU	+	+	+	–	+
US	+	–	+	+	+

1. NCT03981796. 2. NCT03603184. 3. NCT03884101. 4. NCT03914612. 5. NCT04269200.

NRG-GY018 Study demonstrates significantly improved progression free survival outcomes for women with advanced or recurrent endometrial cancer with the addition of pembrolizumab to chemotherapy

"The safety profile of pembrolizumab in this trial was consistent with that observed in previously reported studies; no new safety signals were identified. Results will be presented at an upcoming medical meeting and discussed with regulatory authorities."

RUBY Phase III trial met its primary endpoint in a planned interim analysis for patients with primary advanced or recurrent endometrial cancer

"The safety and tolerability profile of dostarlimab in the RUBY phase III trial was consistent with clinical trials of similar regimens. The most common treatment-emergent adverse events in patients receiving dostarlimab plus chemotherapy were nausea, alopecia, fatigue, peripheral neuropathy, anemia, arthralgia, constipation and diarrhea."

https://www.gog.org/news/nrg-gy018-press-release/

https://www.gsk.com/en-gb/media/press-releases/jemperli-dostarlimab-ruby-phase-iii-trial-met-its-primary-endpoint-in-a-planned-interim-analysis-in-patients-with-primary-advanced-or-recurrent-endometrial-cancer/

RTP RESEARCH TO PRACTICE

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Summary of Management AEs

- Early recognition
- Clarification of cause
  - Hold TKI
- Outpatient vs. inpatient
- Initiation of corticosteroid therapy (grade ≥ 2)
  - 1-2 mg/kg/day methylprednisolone
  - Slow steroid taper over 4-6 weeks
  - Prevention of adverse events
- Consultation

Module 4: Novel Investigational Agents and Strategies Under Evaluation for Patients with Endometrial Cancer — Dr Slomovitz

RTP
RESEARCH
TO PRACTICE

Case Presentation: 71-year-old woman with HER2-positive serous carcinoma of the uterus receives adjuvant carboplatin/paclitaxel and trastuzumab, now NED and receiving maintenance trastuzumab

Dr Lyndsay Willmott (Phoenix, Arizona)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Lyndsay Willmott, MD

Which patients with endometrial cancer should be tested for HER2 overexpression, when and how?

Is there the potential for future use of anti-HER2 therapies employed in breast cancer, including antibody-drug conjugates like trastuzumab deruxtecan? Is it possible these will be used in "HER2-low" disease?

RTP RESEARCH TO PRACTICE

Case Presentation: 82-year-old woman with MSI-high metastatic endometrial cancer, s/p PD on pembrolizumab after 4 cycles, receives talazoparib on the TAPUR clinical trial

Dr John Chan (San Francisco, California)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

John Chan, MD

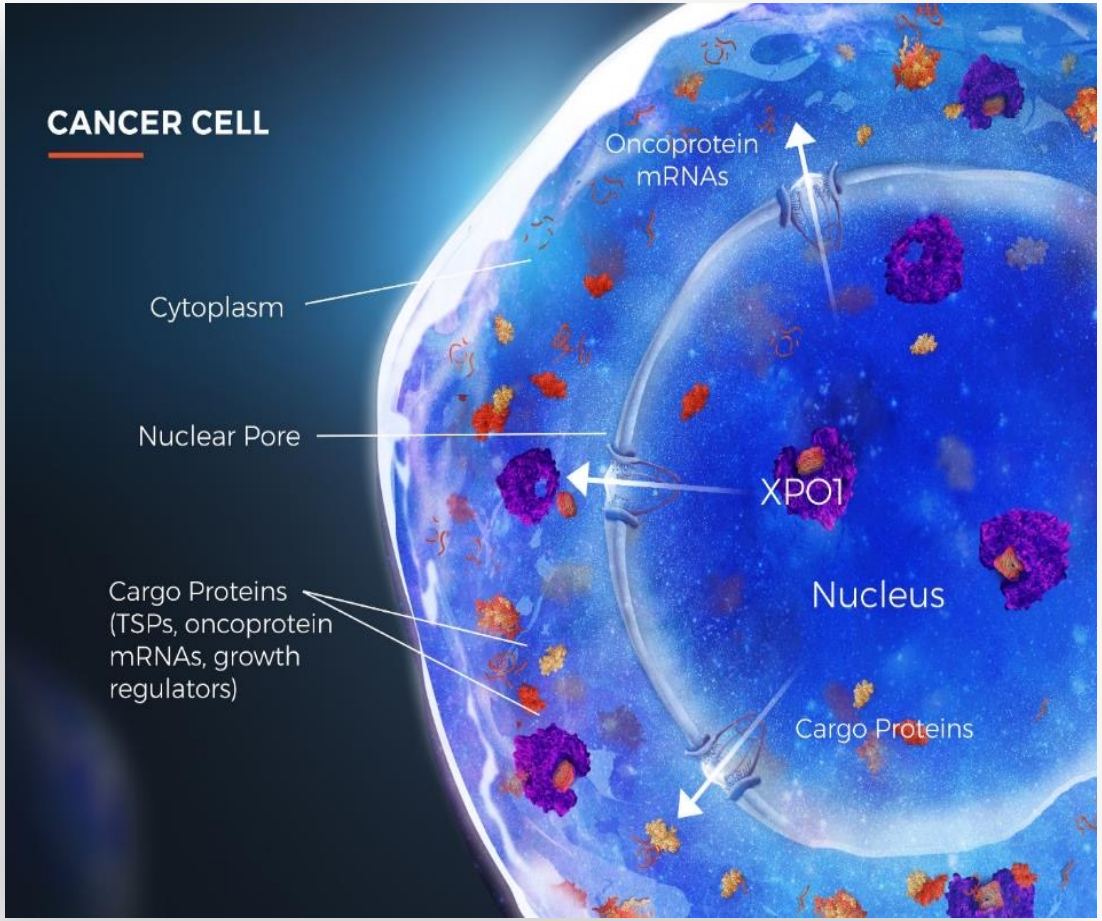
Would you consider adding ipilimumab or lenvatinib for a patient who has experienced disease progression on a checkpoint inhibitor for MSI-high endometrial cancer?

What are some of the compelling ongoing innovative clinical trials like the TAPUR study for patients with endometrial cancer?

Novel Investigational Agents and Strategies Under Evaluation for Patients with Endometrial Cancer

Brian M Slomovitz, MD
Professor, OB-GYN
Florida International University
Director, Gynecologic Oncology
Co-Chair, Cancer Research Committee
Mount Sinai Medical Center
Miami, Florida

Exportin 1 overexpression



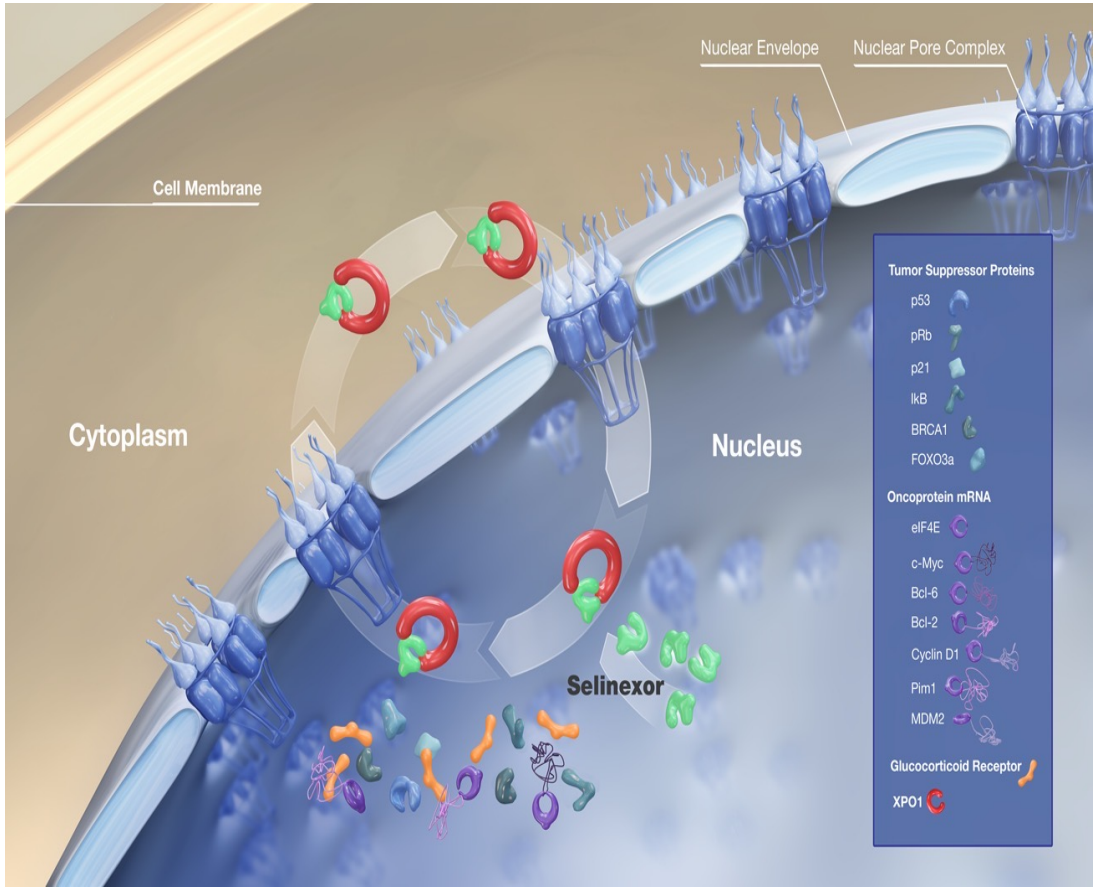
Exportin 1 (XPO1) is the major nuclear export protein for:

1. Tumor suppressor proteins (TSPs) – *functional inactivation (TSPs, e.g. p53, pRb, IκB, p27, p21, FOXOs)*
2. eIF4E-bound proto-oncogene mRNAs *(e.g. c-Myc, Bcl2, Bcl6, BclXL) – enhances translation*

Elevated XPO1 expression:

1. Inactivates TSPs by mislocalization
2. Enhances proto-oncoprotein translation
3. Correlates with poor patient prognosis

Selinexor



Selinexor is an oral selective inhibitor of XPO1 that:

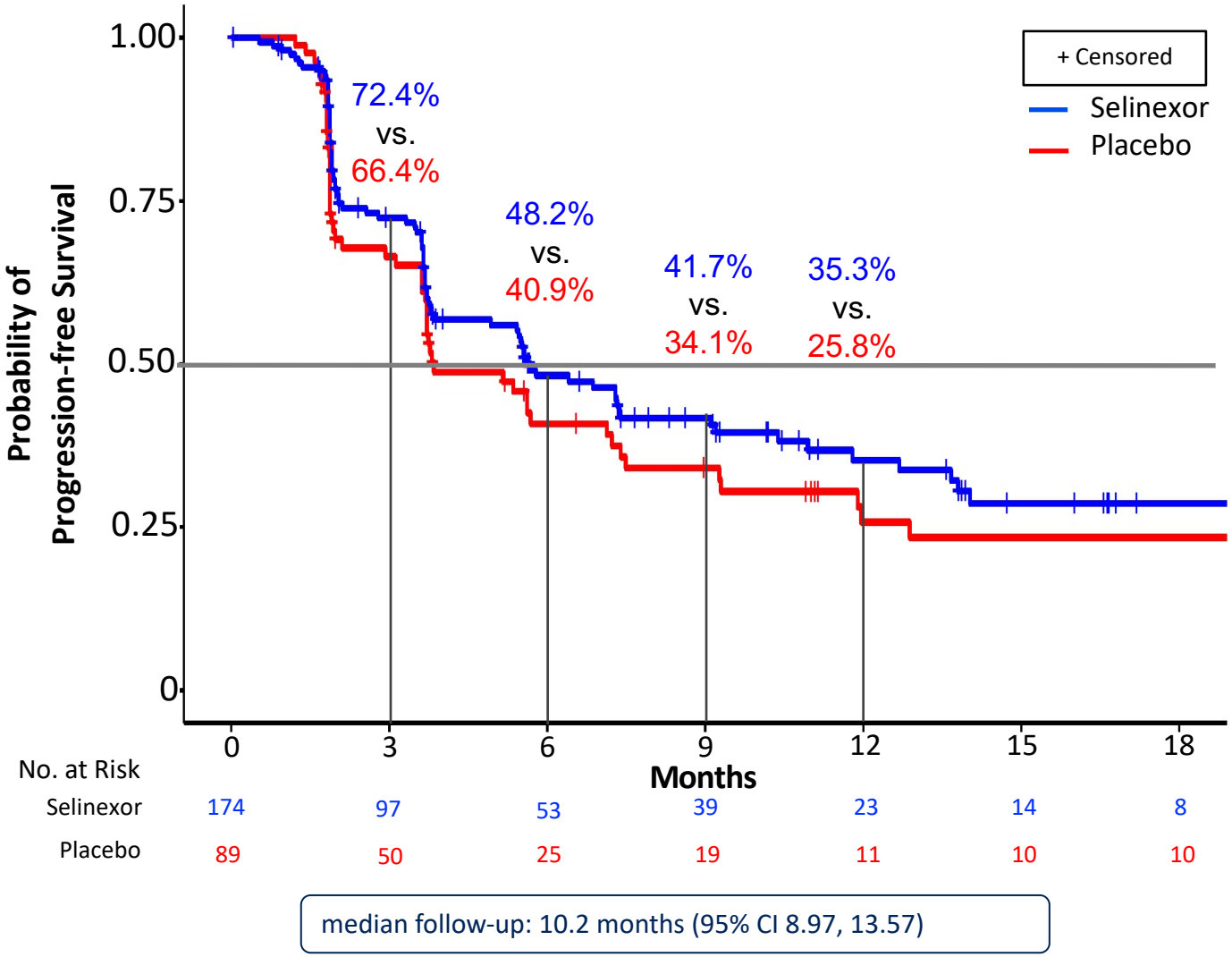
1. Reactivates TSPs and blocks proto-oncoprotein translation
2. Blocks DNA damage repair
3. Synergizes with DNA damage inducing therapies
4. Orally active against GCB and non GCB DLBCL *in vivo*

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

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

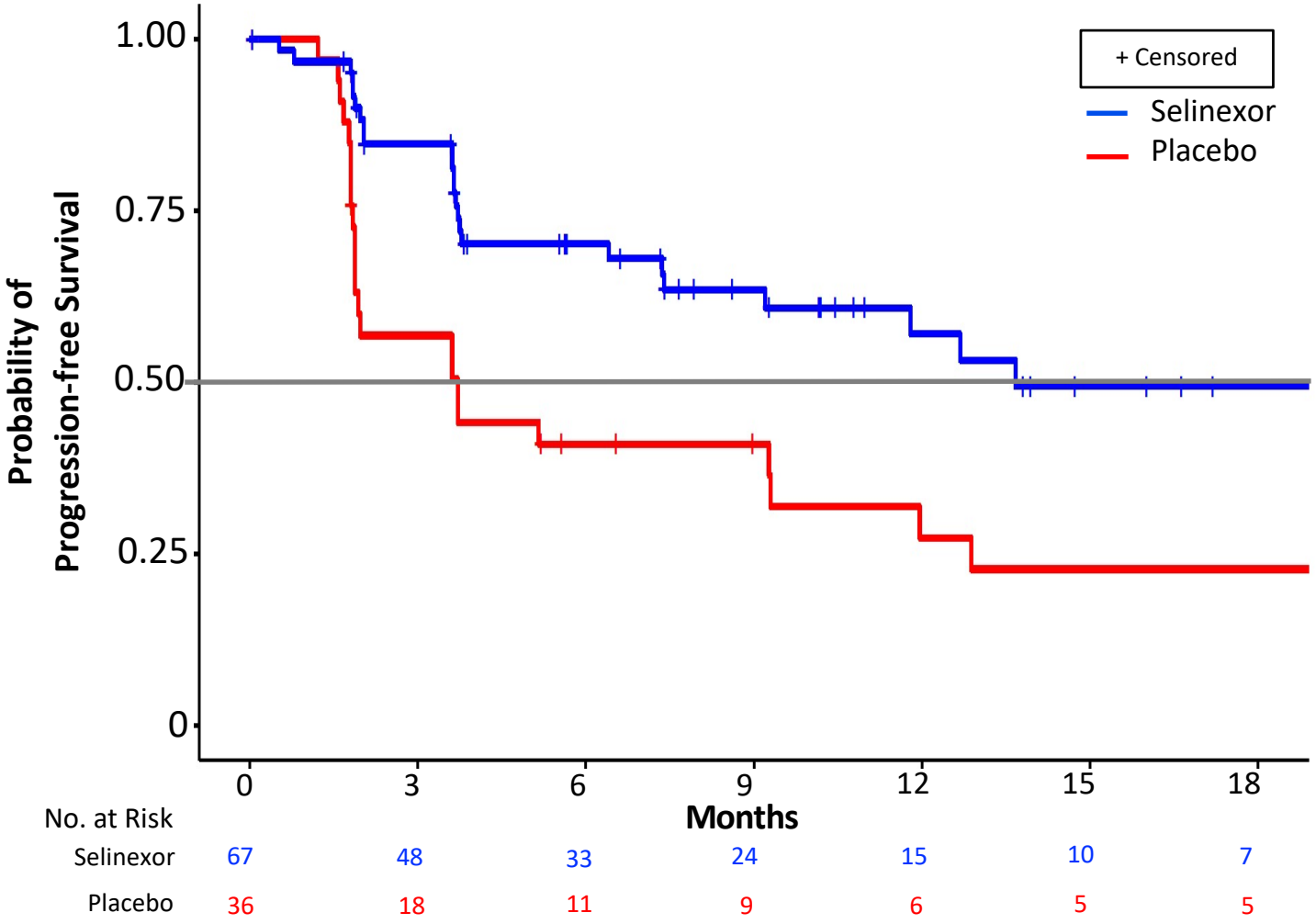
*In 7 patients (2.7% of 263), the stratification factor of CR/PR was incorrect and was corrected by the Investigators prior to database lock and unblinding. The statistical analysis was validated by the independent ENGOT statistician and approved by the IDMC.

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

Vicky Makker, M.D., ENGOT-EN5/GOG-3055/SIENDO

SGO 2022;Abstract LBA9.

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)

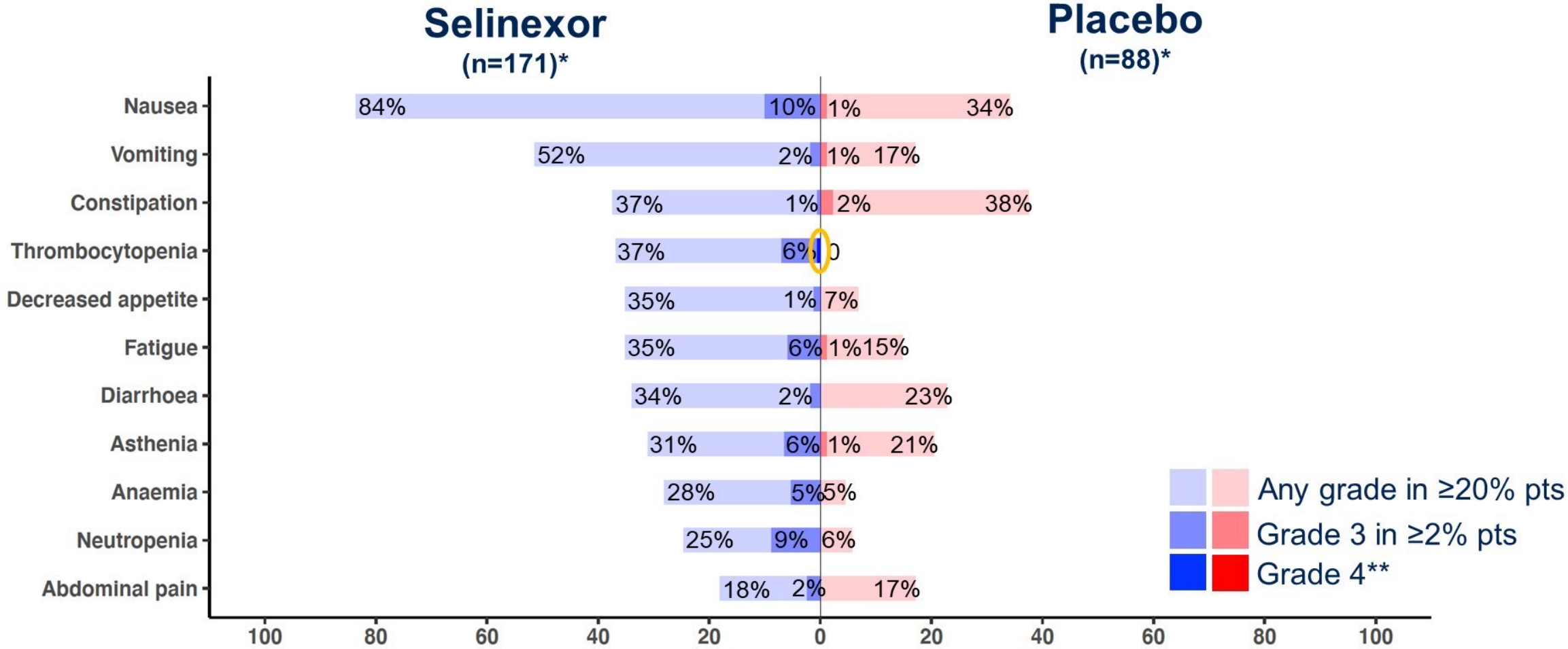
Nominal one-sided P value = 0.0008

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

Vicky Makker, M.D., ENGOT-EN5/GOG-3055/SIENDO

SGO 2022;Abstract LBA9.

Treatment-Emergent Adverse Events in ITT Population

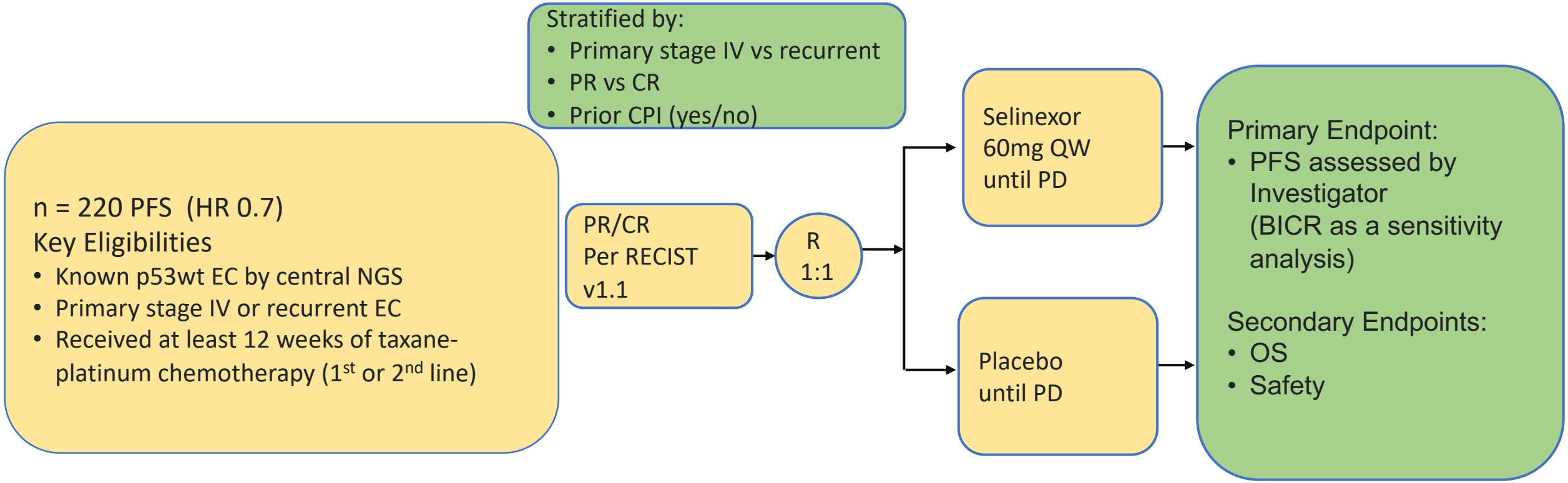


*Four patients did not receive treatment (n=3 selinexor; n=1 placebo)

**n=1 Grade 4 thrombocytopenia; No cases of severe bleeding in patients with thrombocytopenia; No cases of febrile neutropenia

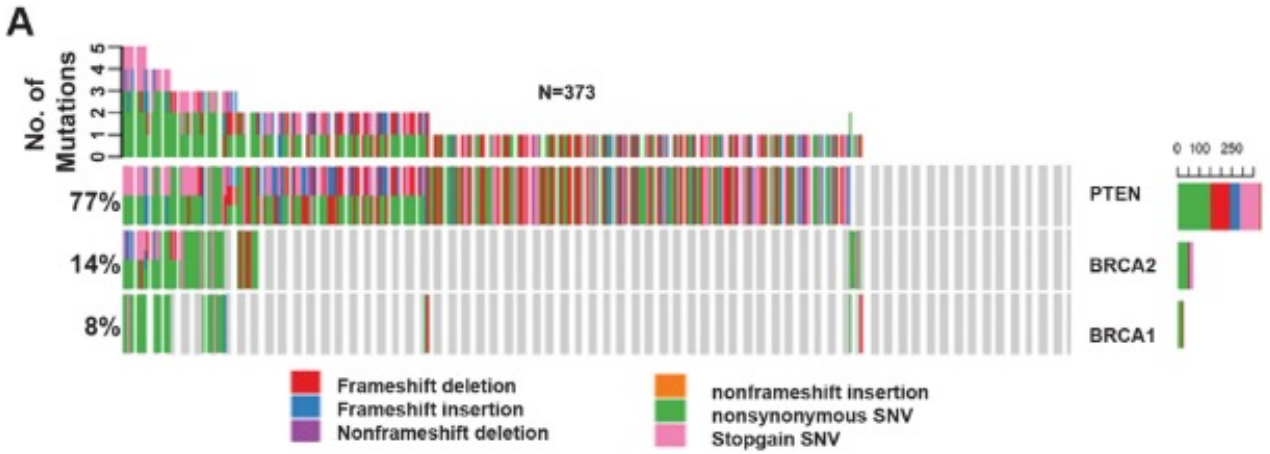
ENGOT-EN20/GOG3083/XPORT-EC-042 Randomized, blinded Phase 3 international study of oral Selinexor once weekly versus placebo for maintenance therapy in patients with p53wt endometrial carcinoma responding to front line chemotherapy

Primary Objective: To evaluate the efficacy of selinexor compared to placebo as maintenance therapy in patients with p53wt advanced or recurrent endometrial cancer

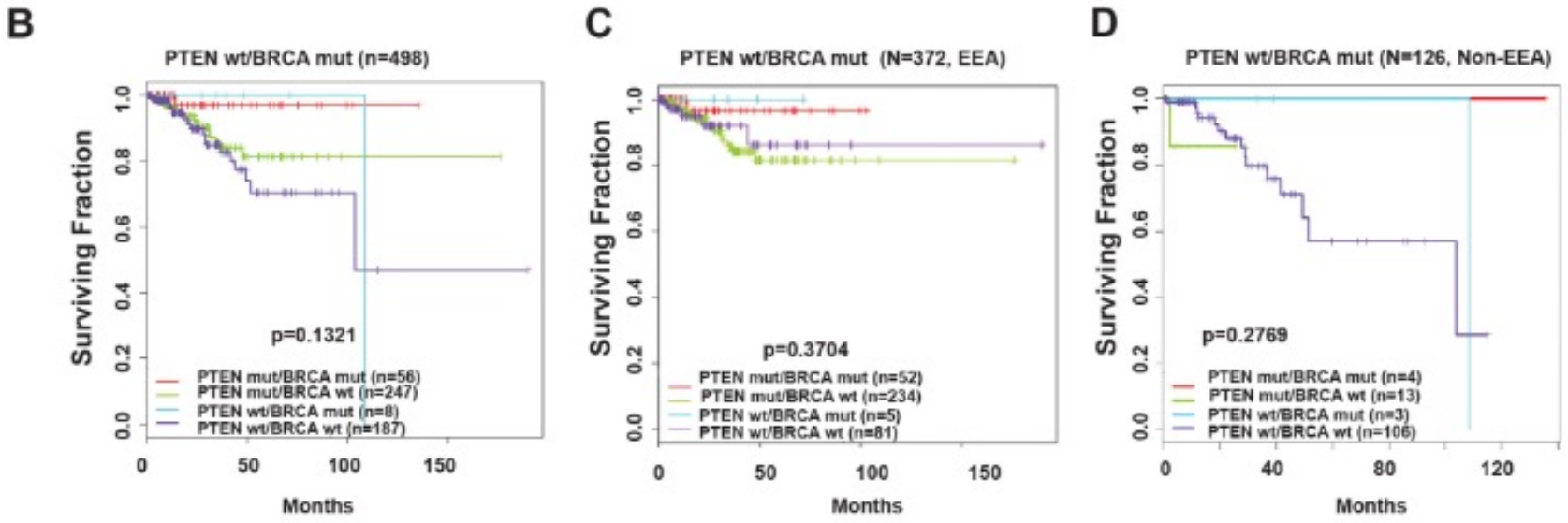


Homologous Recombination Deficiency

TCGA:
PTEN 77%
BRCA2 14%
BRCA1 8%



Presence of these molecular alterations were NOT prognostic for OS



EEA, endometrioid endometrial adenocarcinoma; mut, mutated; OS, overall survival; wt, wild-type

Siedel JH et al. *Gynecol Oncol.* 2021;160(3):777-785.

What About PARPI in Uterine Cancer ?

	Konstantinopoulos et al. N=35	**NRG GY012 N=40**	**NRG GY012 N=40**	**Gunderson et al. N=27**	**Westin et al. N=22**	**Westin et al N=9**	**You et al. N=14**	**Post et al. N=50**
Regimen	Talazoparib + Avelumab	Olaparib	Olaparib + Cediranib	Rucaparib + Bevacizumab	Olaparib + Vistusertib	Olaparib + Capivasertib	Olaparib + cyclo-phosphamide + metformin	Olaparib + Durvalumab
Population	Recurrent/ metastatic EC MSS/MMRp	Recurrent/ metastatic EC	Recurrent/ metastatic EC	Recurrent/ metastatic EC	Recurrent/ metastatic EC	Recurrent/ metastatic EC	Recurrent/ metastatic EC	Recurrent/met astatic EC
ORR	8.6%	< 1% endometrioid 19% serous	29% endometrioid 25% serous	14%	27%-31%	44%	20.8%	16%
PFS 6	25.3%	NR	NR	30%	NR	NR		34%
mPFS	3.65 mos	2.0 mos	5.5 mos	3.8 mos	NR	NR	5.1 mos	3.4 mos
Toxicity	G3: 45% anemia, 20% thrombocytopenia, 11% ANC	Any grade: 12% anemia, 10% VTE	Any grade: 33% HTN; 20% fatigue, 15% endocrine d/o		Any grade: 84% nausea, 83% anemia 76% hypergly 73% fatigue	Any grade: 76% nausea 63% anemia 53% fatigue 50% hyperglycemia	Any grade: 61% fatigue 54% nausea	TRAE grade $\geq$3 16%

Konstantinopoulos et al. ESMO 2020; Rimel et al. SGO 2021; Gunderson et al. ASCO 2021 Westin et al. ASCO 2018, Westin et al. CCR 2021 , Post et al Gynecol Oncol 2022

Moving IO & PARPi to Front Line Metastatic: Ongoing Phase 3 Trials

GOG 3031 Ruby Part 2: NCT03981796

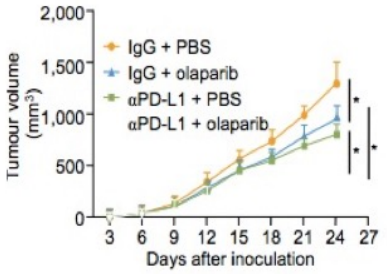
Population : Primary Stage III or IV or First Recurrent Endometrial Cancer

→ N=270 Randomized 2:1

- **Dostarlimab 500 mg + Carboplatin AUC 5 + Paclitaxel 175 mg/m² D1 Q3W**
- **Placebo + Carboplatin AUC 5 + Paclitaxel 175 mg/m² D1 Q3W**

Immunotherapy and PARPi

- Neoantigen load of HR defective tumors
  - Increased TILs
- PARPi:
  - Enhance DNA damage
  - DNA fragments induce a STING response
  - Increase peritoneal CD8+ T
- Xenograft models: Synergy b/w PARPi and checkpoint inhibition



Chen & Mellman. Immunity 2013; Galluzzi Nat Rev Drug Discov 2012; Jiao CCR 2017
Hannani Cancer J 2011; Vanneman and Dranoff. Nat Rev Cancer 2012; Kyle Immunology 2017

PRIMARY ENDPOINT
BICR assessed PFS per RECIST v1.1: 1) All Patients 2) MSI-H

Stratification:
MSI/MMR Status), WPRT, Disease Status (Primary Stage III, Stage IV, First Recurrent)

GOG 3041: DUO-E NCT04269200

Induction (6 cycles)	Maintenance (Cycles 7 and on)
Q3W Platinum CTX	Placebo for Olaparib
Q3W Placebo for Durvalumab	Q4W Placebo for Durvalumab
Q3W Platinum CTX	Placebo for Olaparib
Q3W Durvalumab at 1120mg (IV)	Q4W Durvalumab at 1500mg (IV)
Q3W Platinum CTX	Olaparib 300mg tablets (bd)
Q3W Durvalumab at 1120mg (IV)	Q4W Durvalumab at 1500mg (IV)

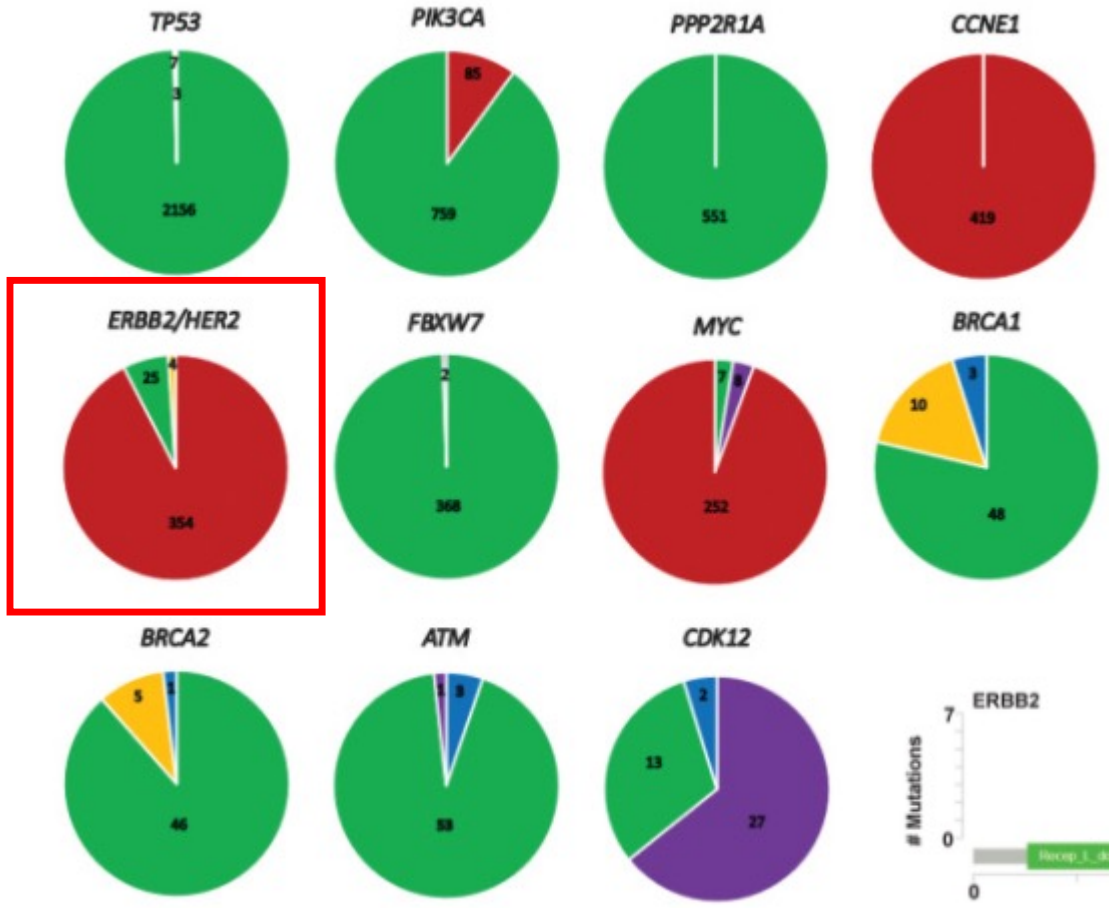
Study treatment will be administered until radiological disease progression per RECIST 1.1

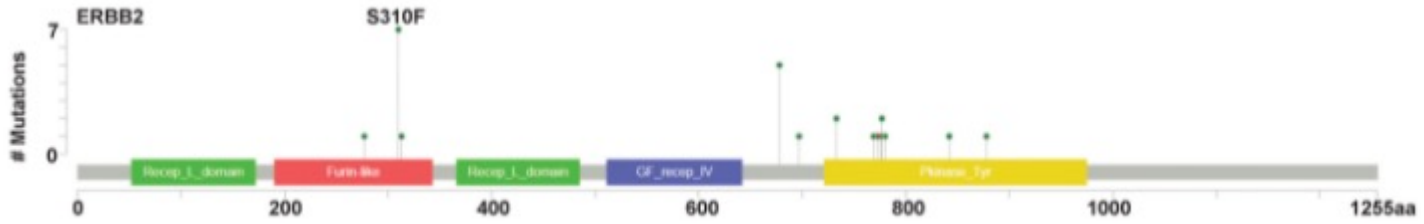
Primary endpoint
PFS (arm A vs B)

Secondary endpoints
PFS (arm A vs C), OS, PFS2, Safety, and PRO

Stratification:
- MMR status (proficient vs. deficient)
- Disease status (recurrent vs. newly diagnosed)
- Geographic Region (Asia vs. ROW)

Prevalence of ERBB2/HER2 molecular aberrations





Foundation Medicine Dataset:
2159 UPSC (central re-review) as compared to
2346 Endometrioid (predominantly adv stg)

UPSC:
92% TP53 mutations
99% MSS, 96% TMB <10mut/MB
17% ERBB2/HER2 amplification
ERBB2 missense mutations (S3104F, A232V, A245V)

Lin et al. Gynecol Oncol 2022

OU Health | Stephenson Cancer Center

Uterine Carcinosarcoma: HER2+ (~16%)

HER2 IHC Score ASCO/CAP 2007	Carcinoma component (total $n = 80$)	Sarcoma component (total $n = 44$)	FISH amplification per 2007 ASCO/CAP criteria (n positive/N performed)
0	20 uterine, 1 ovarian	22 uterine, 9 ovarian	0/0
1+	19 uterine, 6 ovarian	6 uterine, 2 ovarian	0/2
2+	20 uterine, 8 ovarian	5 uterine, 0 ovarian	5/28
3+	6 uterine, 0 ovarian	0 uterine, 0 ovarian	1/2
HER2 IHC Score ASCO/CAP 2013	**Carcinoma component (total $n = 80$)**	**Sarcoma component (total $n = 44$)**	**FISH amplification per 2013 ASCO/CAP criteria (n positive/N performed)**
0	25 uterine, 3 ovarian	22 uterine, 9 ovarian	0/0
1+	14 uterine, 4 ovarian	6 uterine, 2 ovarian	0/2
2+	18 uterine, 8 ovarian	5 uterine, 0 ovarian	5/26
3+	8 uterine, 0 ovarian	0 uterine, 0 ovarian	1/4

IHC immunohistochemistry, *FISH* fluorescent in situ hybridization, *ASCO* American Society of Clinical Oncology, *CAP* College of American Pathologists

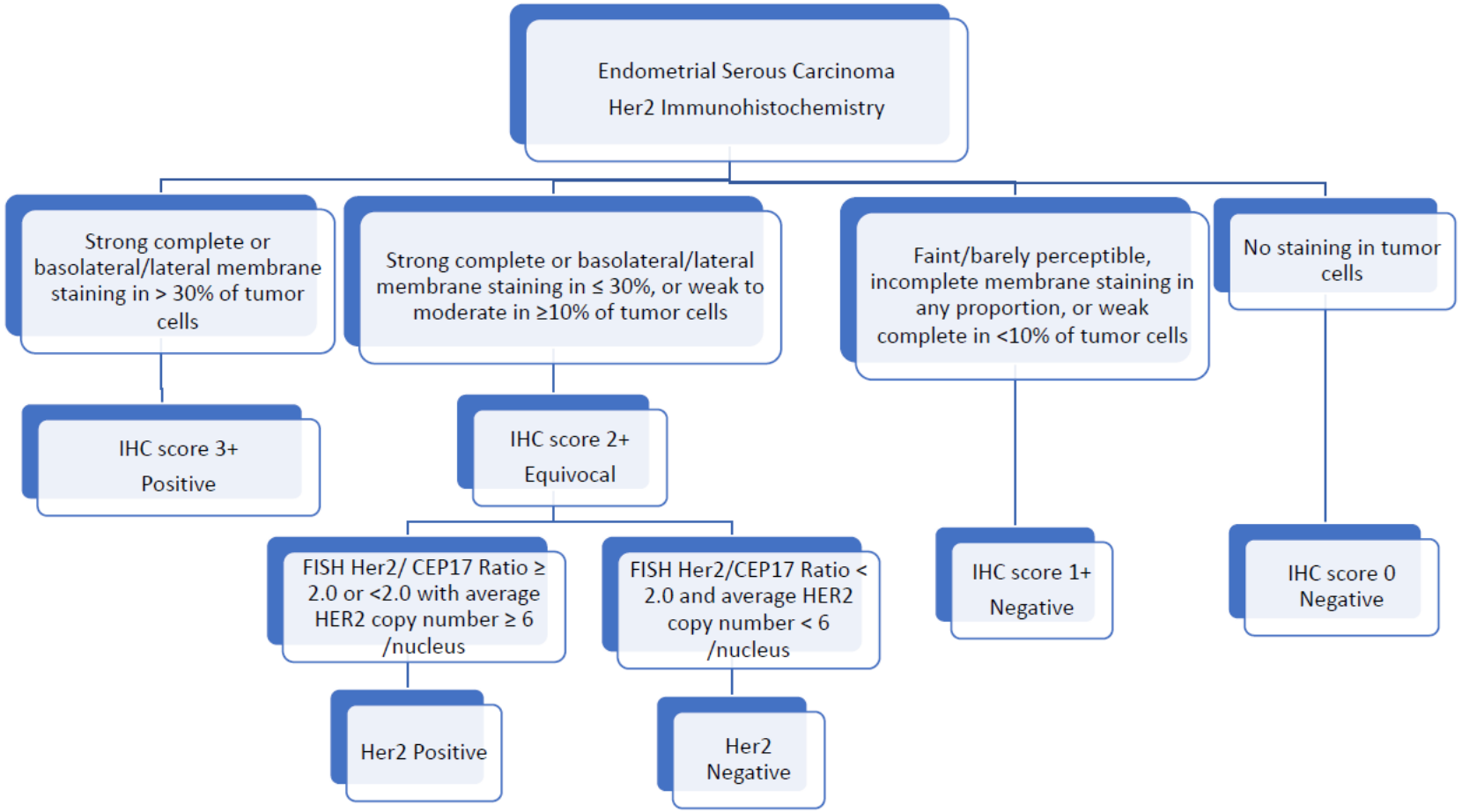
Rottman et al. Modern Pathology 2020

OU Health | Stephenson Cancer Center

IHC and FISH characterization of endometrial cancer

Addition of trastuzumab to paclitaxel and carboplatin was endorsed by the NCCN in 2019

Pathologic evaluation of tumor HER2 protein expression and gene amp is a critical part of therapeutic decision making



- HER2 IHC score incorporates both staining intensity and % of tumor cell staining
- Both complete and basolateral/ lateral staining patterns count towards % staining cut-off

Buza et al. Modern Pathology 2021

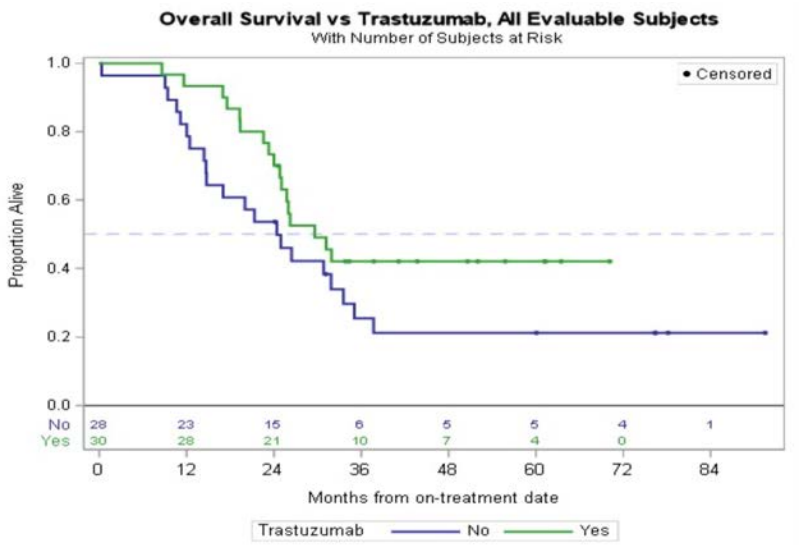
OU Health | Stephenson Cancer Center

Incorporation of anti-HER-2 treatment: Trastuzumab with Chemotherapy (Updated Survival Analysis)

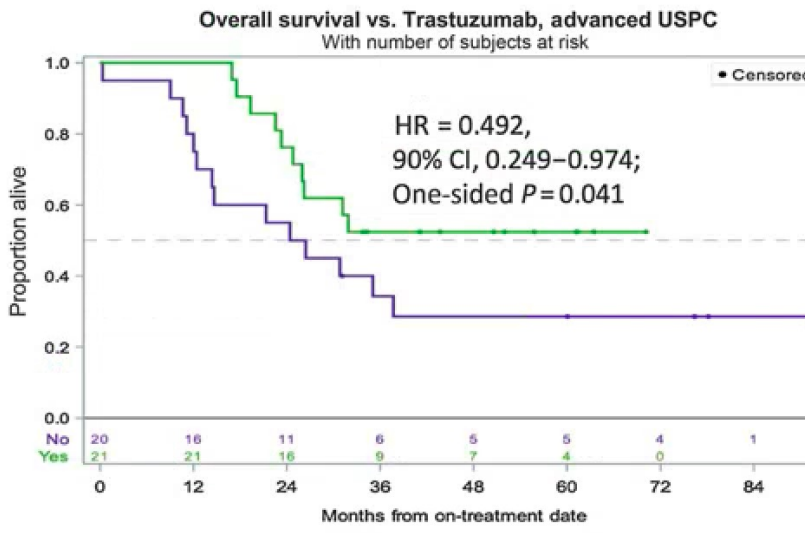
- Median OS of 24.4 (control) versus 29.6 (experimental) months (*P* = 0.046, HR = 0.58, 90% CI 0.34—0.99; Fig. 1).

- **<u>This benefit was particularly striking in stage III–IV patients, who had OS medians of 25.4 months (control) versus not reached (experimental, *P* = 0.041, HR = 0.49, 90% CI 0.25–0.97).</u>**

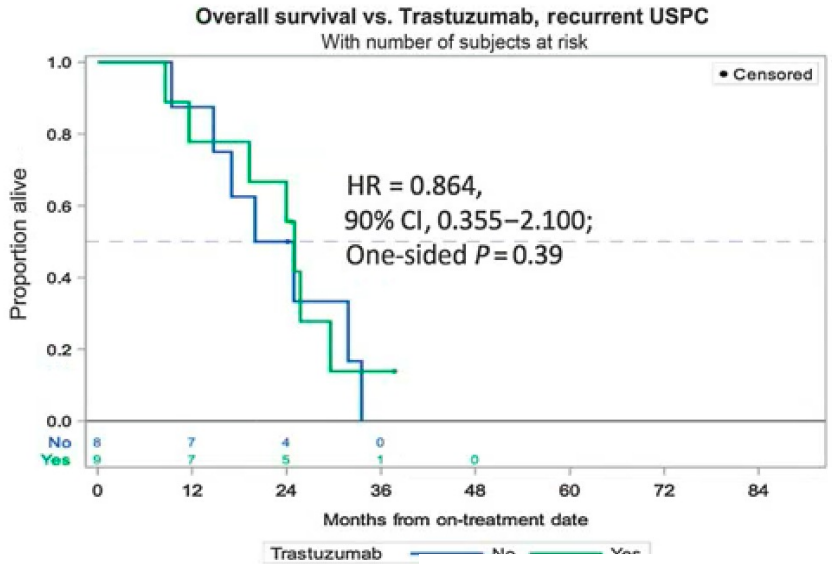
ITT Population



Advanced Stage Disease

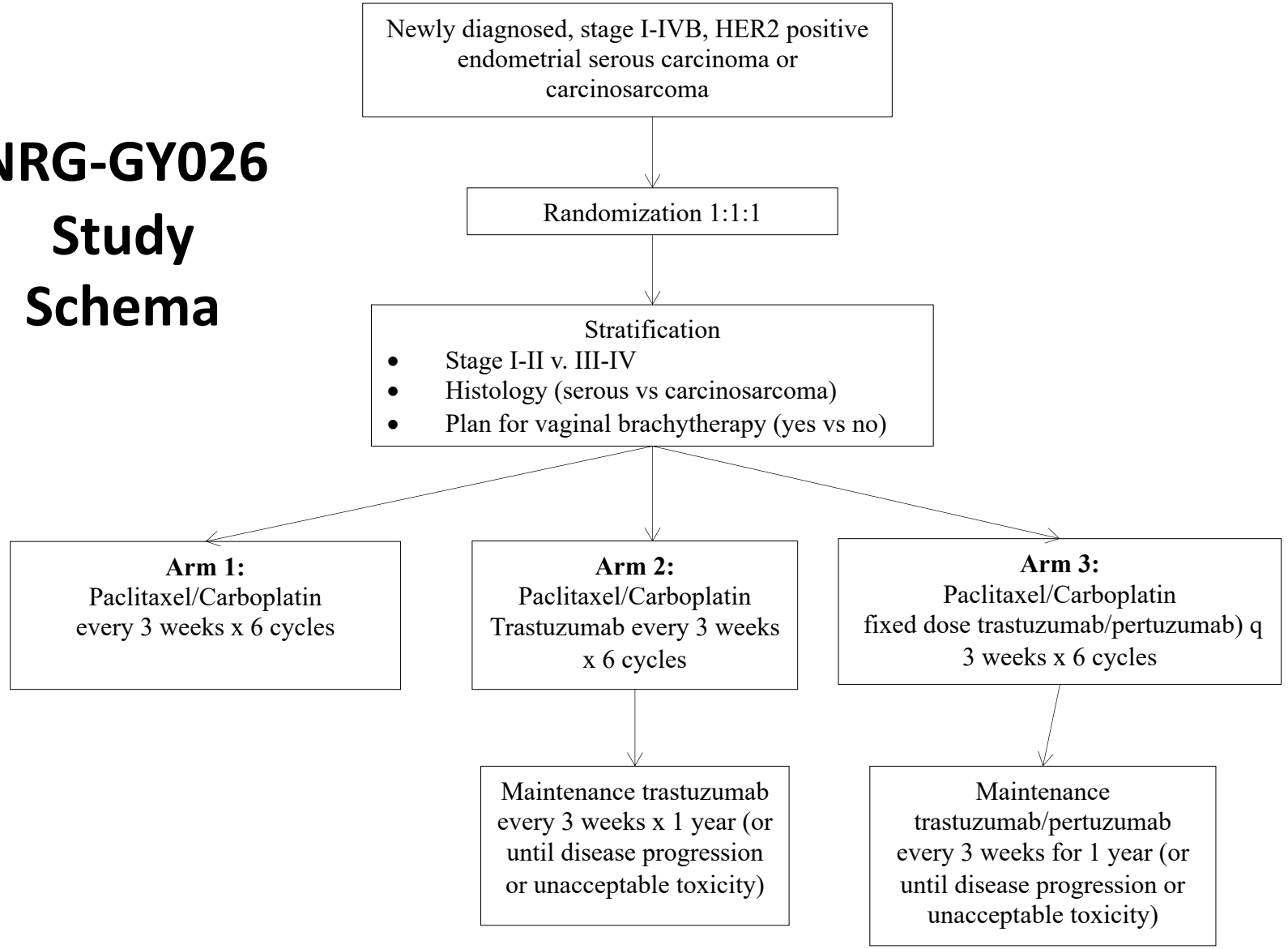


Recurrent Disease



Nickles-Fader Clin Cancer Research 2020

NRG-GY026 Study Schema

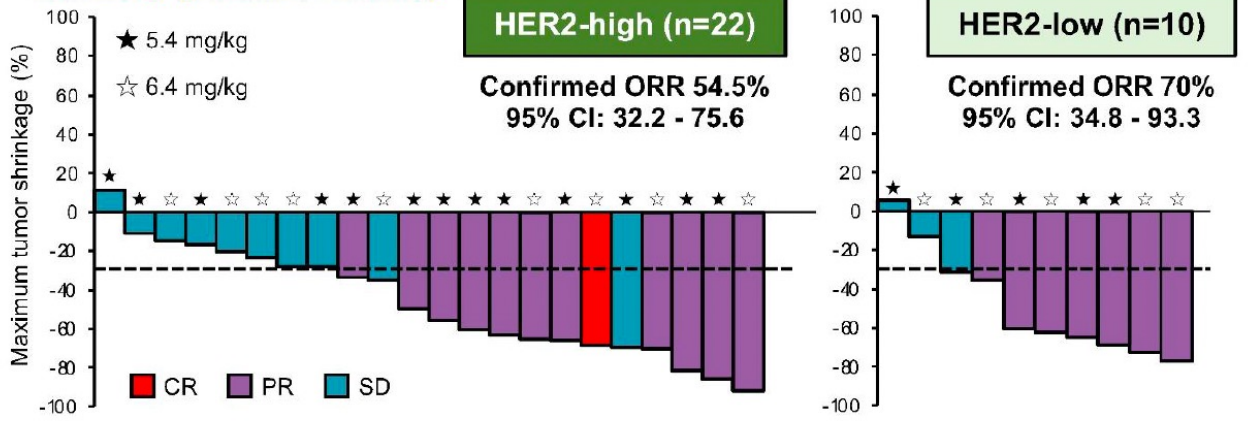


Activated

HER2-ADCs have shown promising preliminary clinical activity in HER2-expressing endometrial cancer

T-DXd in Uterine Carcinosarcoma[1]

Efficacy (Central review)



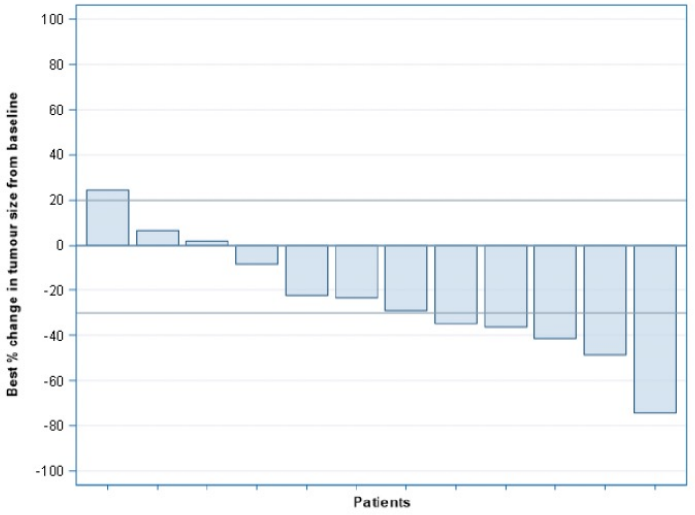
HER2-high (n=22)
Confirmed ORR 54.5%
95% CI: 32.2 - 75.6

HER2-low (n=10)
Confirmed ORR 70%
95% CI: 34.8 - 93.3

Confirmed Response Rate	CR (n, %)		PR (n, %)		SD (n, %)		PD (n, %)		ORR (%)
HER2-high (n=22)	1	(4.5)	11	(50)	10	(45.5)	0	(0)	54.5
HER2-low (n=10)	0	(0)	7	(70)	3	(30)	0	(0)	70

Median PFS 6.7 mos (95% CI 5.4-8.8 mos)

SYD985 in Endometrial Cancer (Her2 IHC≥1+)[2]



ORR: 39% (5 of 13 pts);
95% CI 13.9-68.4%

ADC, antibody drug conjugate; CI, confidence interval; CR, complete response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mo, month; ORR, objective response rate; PFS, progression-free survival; PR, partial response; pt, patient; SD, stable disease.

1. Hasegawa K et al. Presented at: ESMO 2021. September 16, 2021. Abs 813P. 2. Banerji U, et al. *Lancet Oncol* 2019; 20:1124–1135.

DESTINY-PanTumor02: trastuzumab deruxtecan met prespecified target for ORR across multiple HER2-expressing advanced solid tumors

06 March 2023 07:00 GMT

Trastuzumab deruxtecan meets prespecified criteria for objective response rate and duration of response

Positive high-level results from an analysis of the ongoing DESTINY-PanTumor02 Phase II trial showed that trastuzumab deruxtecan met the prespecified target for objective response rate (ORR) and demonstrated durable response across multiple HER2-expressing advanced solid tumours in heavily pretreated patients.

Trastuzumab deruxtecan is a specifically engineered HER2-directed antibody drug conjugate (ADC) being jointly developed and commercialised.

The DESTINY-PanTumor02 Phase II trial is evaluating the efficacy and safety of trastuzumab deruxtecan in patients with locally advanced, unresectable, or metastatic previously treated, HER2-expressing solid tumours not eligible for curative therapy, including biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, and rare cancers. The primary endpoint of the trial is investigator-assessed confirmed ORR and investigator-assessed duration of response (DoR) is a key secondary endpoint.

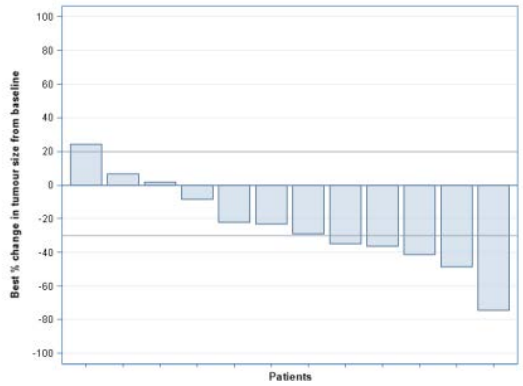
HER2, human epidermal growth factor receptor 2; ORR, objective response rate.

Press release. https://www.astrazeneca.com/media-centre/press-releases/2023/enhertu-destiny-pantumor02-shows-positive-results.html.

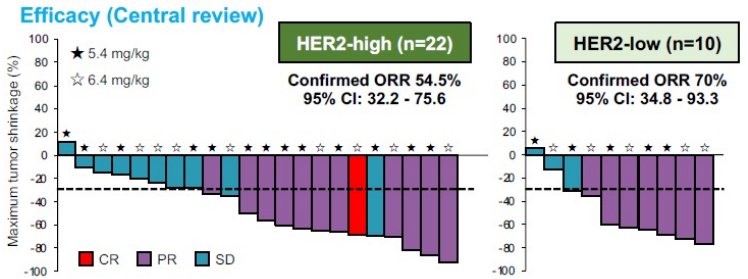
Strategies for EC post IO? ADCs

HER2 ≥ 1+

Trastuzumab Deruxtecan, Trastuzumab duocarmazine, DB 1303



Banerji et al. Lancet Oncol 2019

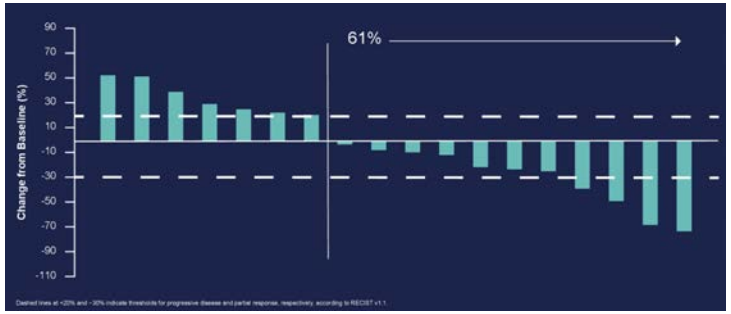


Confirmed Response Rate	CR (n, %)		PR (n, %)		SD (n, %)		PD (n, %)		ORR (%)
HER2-high (n=22)	1	(4.5)	11	(50)	10	(45.5)	0	(0)	54.5
HER2-low (n=10)	0	(0)	7	(70)	3	(30)	0	(0)	70

Hasegawa K et al. ESMO 2021 poster 813p

Non- HER2

TROP2: Sacituzumab Govitecan



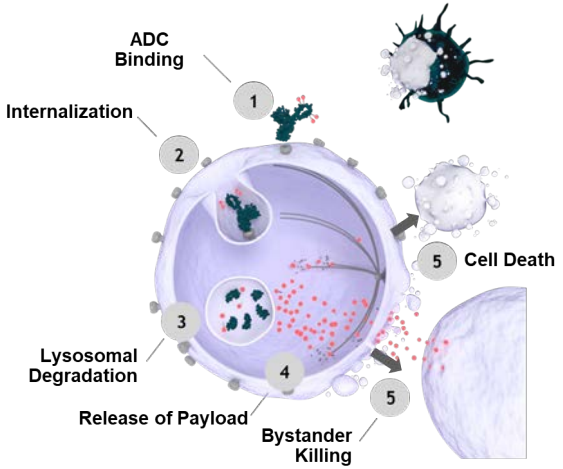
Reduction in tumor size from baseline observed in 61% (11/18)
DOR NR (9.1- 26.6 mos)
ORR 22% (95% CI 6.4, 47.6)

<u>TRAE All G/G > 3</u>
Nausea 83%/3.6%
Diarrhea 67%/7.9%
Neutropenia 56%/27.5%
FN 5.3%

Santin AD et la. ASCO 2020; Bardia et al. Ann Oncol. 2021 32(6): 746

Non- HER2

FRα: Mirvetuximab

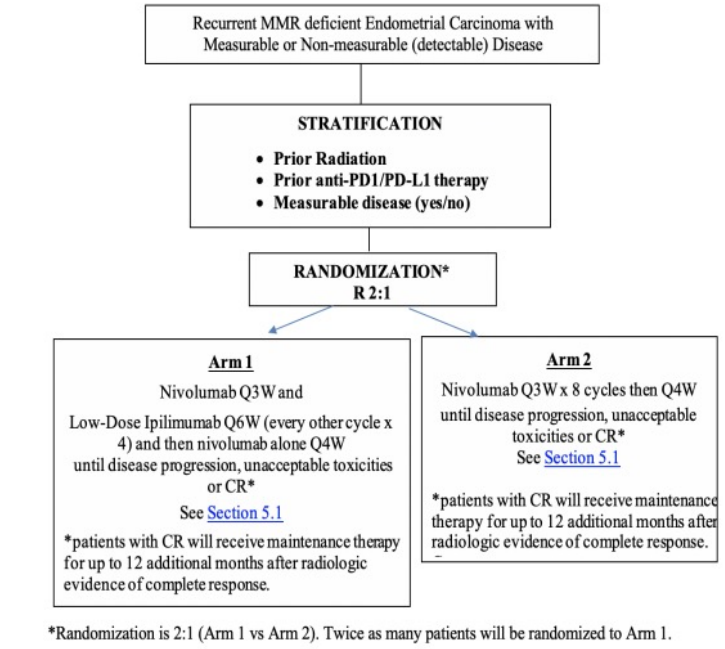


Phase 2 in FRα + EC: NCT03832361

Strategies for EC post IO? IO Combinations

PD-1/CTLA4

NRG GY025
RPH2 of Nivolumab and Ipilimumab vs Nivolumab in MMRd Recurrent EC

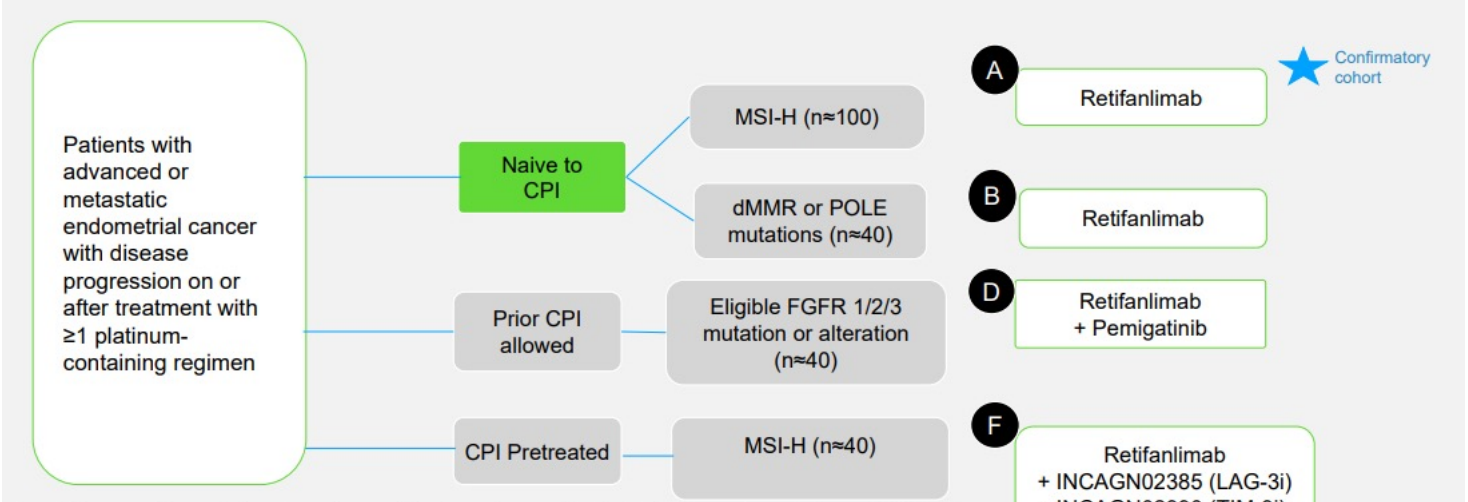


*Randomization is 2:1 (Arm 1 vs Arm 2). Twice as many patients will be randomized to Arm 1.

NCT05112601

PD-1 + LAG3

PODIUM 204/ GOG 3038 Novel CPI Combinations

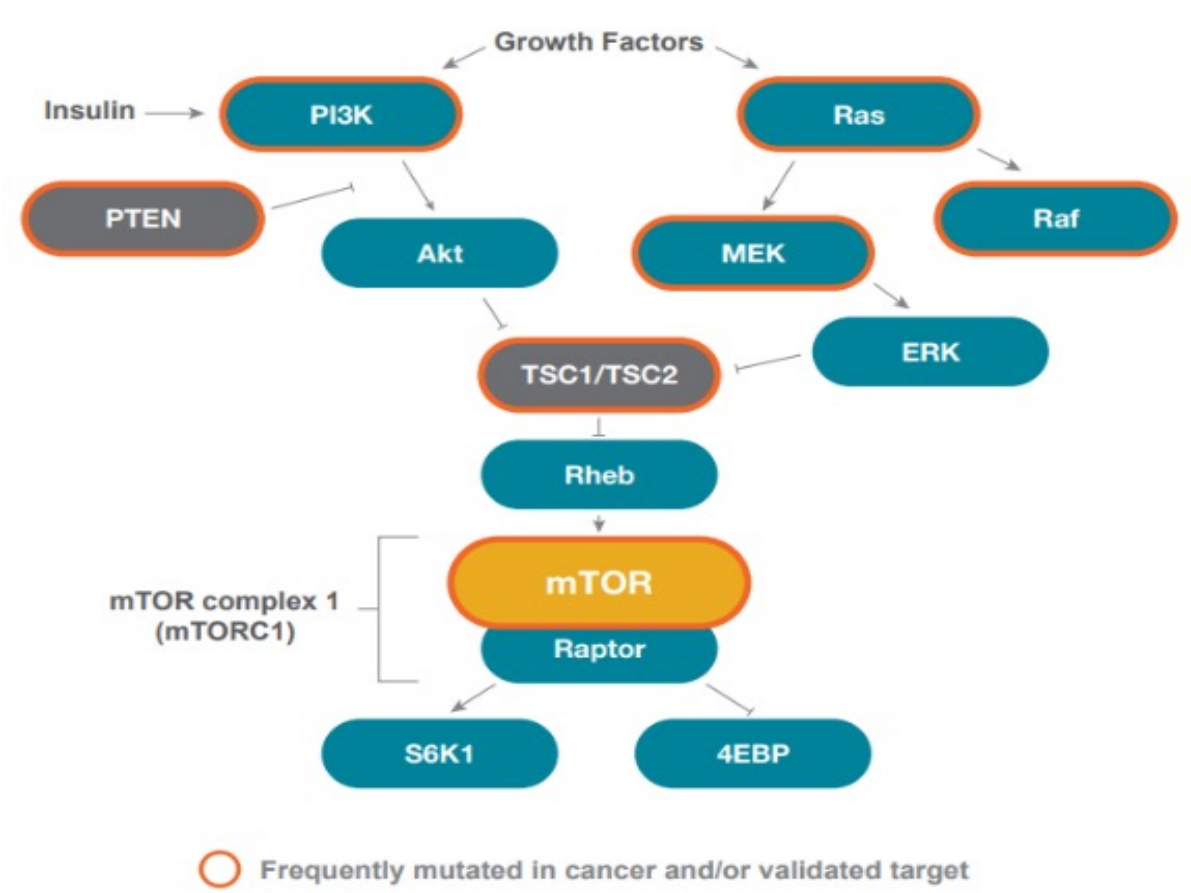


Closed Groups: *Group C (unselected): completed enrollment (Retifanlimab+Epacadostat), Group E (CPI Naïve, PD-L1+): enrollment closed (Retifanlimab+Epacadostat)

NCT04463771

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.

Contents lists available at ScienceDirect

Gynecologic Oncology

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

A randomized phase II trial of everolimus and letrozole or hormonal therapy in women with advanced, persistent or recurrent endometrial carcinoma: A GOG Foundation study

Brian M. Slomovitz [a,*], Virginia L. Filiaci [b], Joan L. Walker [c], Michael C. Taub [d], Karen A. Finkelstein [e], John W. Moroney [f], Aimee C. Fleury [g], Carolyn Y. Muller [h], Laura L. Holman [c], Larry J. Copeland [i], David S. Miller [j], Robert L. Coleman [k]

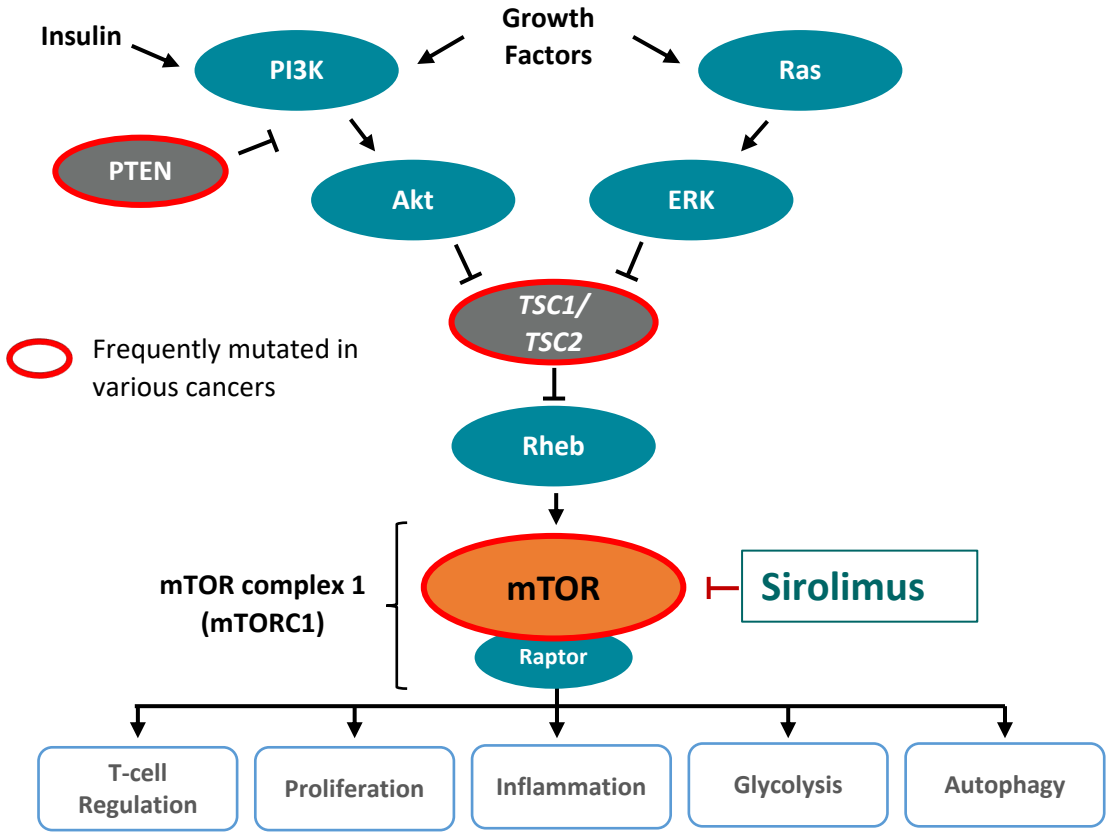
Regimen	N	Objective Response - ITT	Objective Response - NPC	CBR	PFS	OS
Everolimus/ Letrozole	37	24%	53%	78%	6.3 months	Not reached
MA/ Tamoxifen	36	22%	43%	69%	3.8 months	16.6 months

Regimen	RR -NPC	PFS -NPC
Everolimus/letrozole	47%	28 months
Tamoxifen/MA	43%	5 months
Carboplatin/paclitaxel	51%	14 months

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]

Mechanism of Action of mTOR Inhibitors[1]



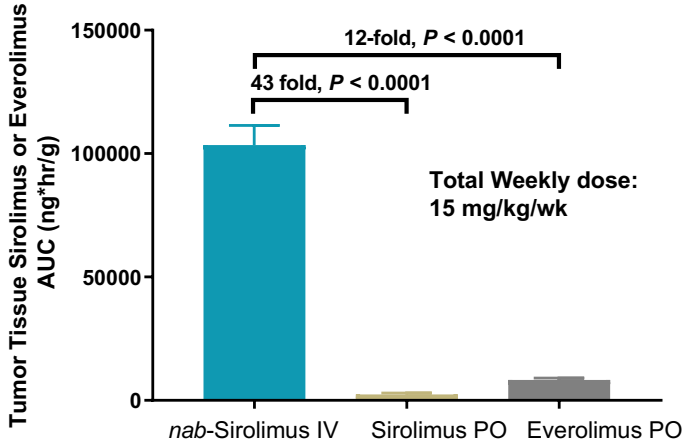
Akt, protein kinase B; ERK, extracellular signal-regulated kinases; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; *nab*, nanoparticle albumin-bound; PEComa, perivascular epithelioid cell tumor; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; Raptor, regulatory-associated 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.

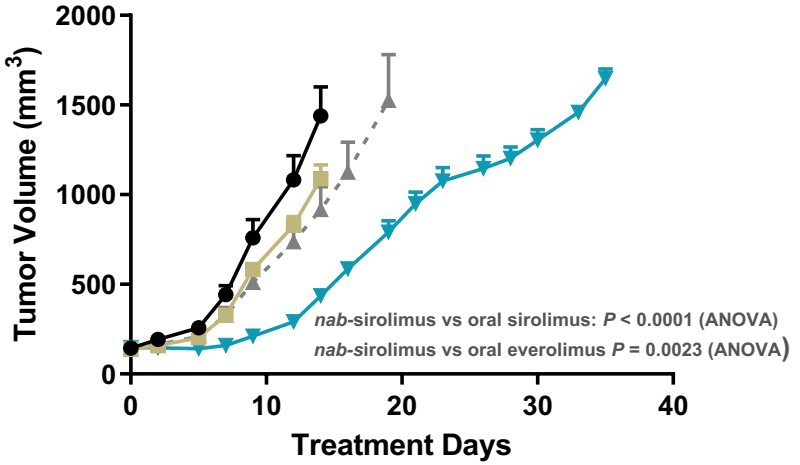
nab-sirolimus Combines Sirolimus with *nab* Technology

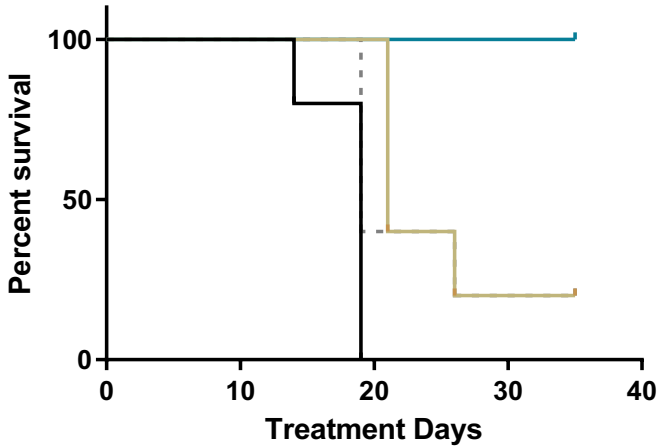
- *nab* technology is a proprietary method of binding therapies to albumin
  - achieves better tumor targeting and uptake than solvent-based treatment in preclinical models[1,2-4]
  - may translate to better efficacy and safety in clinical studies[2-4]
- *nab*-sirolimus adapts the *nab* process for sirolimus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

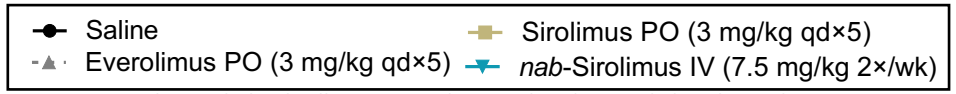
Significantly Higher Tissue Drug Accumulation with *nab*-Sirolimus[1]



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



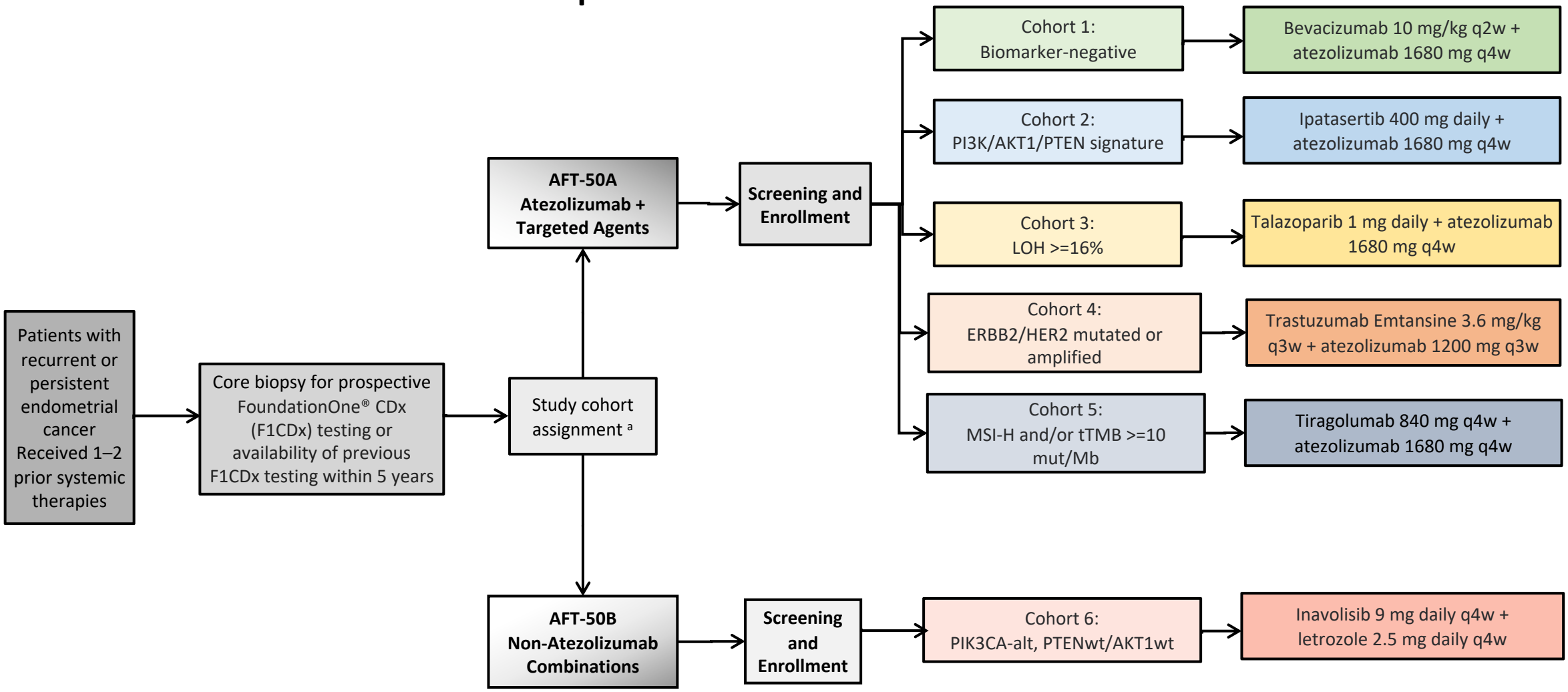




ANOVA, analysis of variance; IV, intravenous; *nab*, nanoparticle albumin-bound; NSCLC, non-small cell lung cancer; PEComa, perivascular epithelioid cell tumor; PO, by mouth; qd, once daily; wk, week.

1. Hou S et al. *Cancer Res*. 2019;79(13 Suppl):Abstract nr 348. 2. *Nab* pacitaxel 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.

AFT-50 Endomap



Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Endometrial Cancer

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2023 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

Monday, March 27, 2023

11:45 AM – 1:15 PM ET

Faculty

Robert L Coleman, MD

Matthew A Powell, MD

Brian M Slomovitz, MD

Moderator

Shannon N Westin, MD, MPH

RTP RESEARCH TO PRACTICE

John K Chan, MD
Sutter Cancer Research Consortium
San Francisco, California

Kellie E Schneider, MD
Novant Health Cancer Institute
Charlotte, North Carolina

Dana M Chase, MD
David Geffen School of
Medicine at UCLA
Los Angeles, California

Lyndsay J Willmott, MD
Virginia G Piper Cancer
Care Network
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