Emerging Therapies and Clinical Trials

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Objectives

- Discuss current trials by line of therapy
  - First-line adjuvant
  - First-line metastatic or recurrent
  - Second or third line recurrent
- Explore unmet needs and areas of opportunity

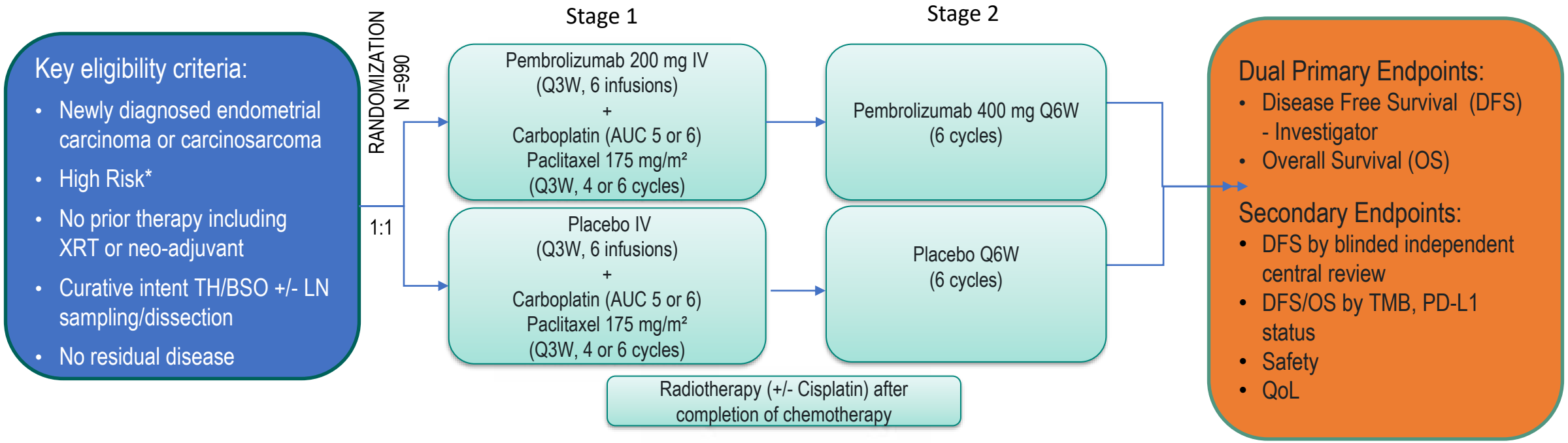
“The best way to predict the future is to create it”

Abraham Lincoln

Endometrial Cancer: Active Trials Adjuvant

Front-line Adjuvant PI: Slomovitz Co-PI: Barber	GOG-3053/KEYNOTE-B21 NCT04634877	A Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Adjuvant Chemotherapy With or Without Radiotherapy for the Treatment of Newly Diagnosed High-Risk Endometrial Cancer After Surgery With Curative Intent	Recruiting

Study Diagram



* High Risk:
- FIGO (2009) Surgical Stage I or II with myometrial invasion
  of non-endometrioid histology
  or
  of any histology with known aberrant p53 expression or p53 mutation
- FIGO (2009) Surgical Stage III or IVA of any histology

Stratification factors:
- MMR status (if pMMR then further stratification by:
  - Stage (I/II vs III/IVA)
  - Planned radiation (EBRT vs Chemo-EBRT vs no EBRT)
  - Histology (non-endometrioid vs endometrioid)

Endometrial Cancer: 1st line metastatic recurrent

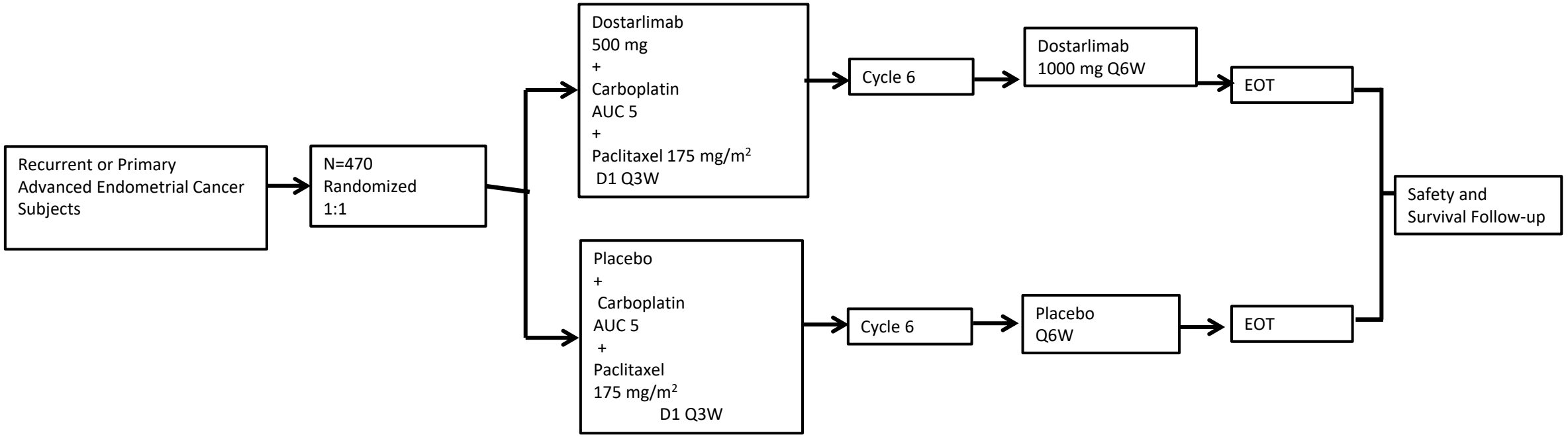
Front-line, metastatic or recurrence PI: Powell *ENGOT led	GOG-3031/RUBY NCT03981796	A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Patients With Recurrent or Primary Advanced Endometrial Cancer	Recruiting
Front-line, metastatic or recurrence PI: Westin Co-PI: Moore *GOG led	GOG-3041/DUO-E NCT04269200	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
Front-line, maintenance PI: Makker *ENGOT led	GOG-3055/SIENDO NCT03555422	A Randomized, Double-Blind, Phase 3 Trial Of Maintenance With Selinexor/ Placebo After Combination Chemotherapy For Patients With Advanced Or Recurrent Endometrial Cancer	Recruiting

Endometrial Cancer: 1st line metastatic recurrent

Front-line, metastatic or recurrence PI: Marth	LEAP -001 NCT04865289	Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for Endometrial Carcinoma (ENGOT-en9/MK-7902-001)	Active, not recruiting
Front-line, metastatic or recurrence	Attend NCT03603184	Phase III Double-blind Randomized Placebo Controlled Trial of Atezolizumab in Combination With Paclitaxel and Carboplatin in Women With Advanced/Recurrent Endometrial Cancer	Active, recruiting
Front-line, metastatic or recurrence PI: Eskander	NRG-GY-018 NCT03914612	Testing the Addition of the Immunotherapy Drug Pembrolizumab to the Usual Chemotherapy Treatment (Paclitaxel and Carboplatin) in Stage III-IV or Recurrent Endometrial Cancer	Recruiting

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 (RUBY)
(4010-03-001 / ENGOT EN-6 / GOG-3031)

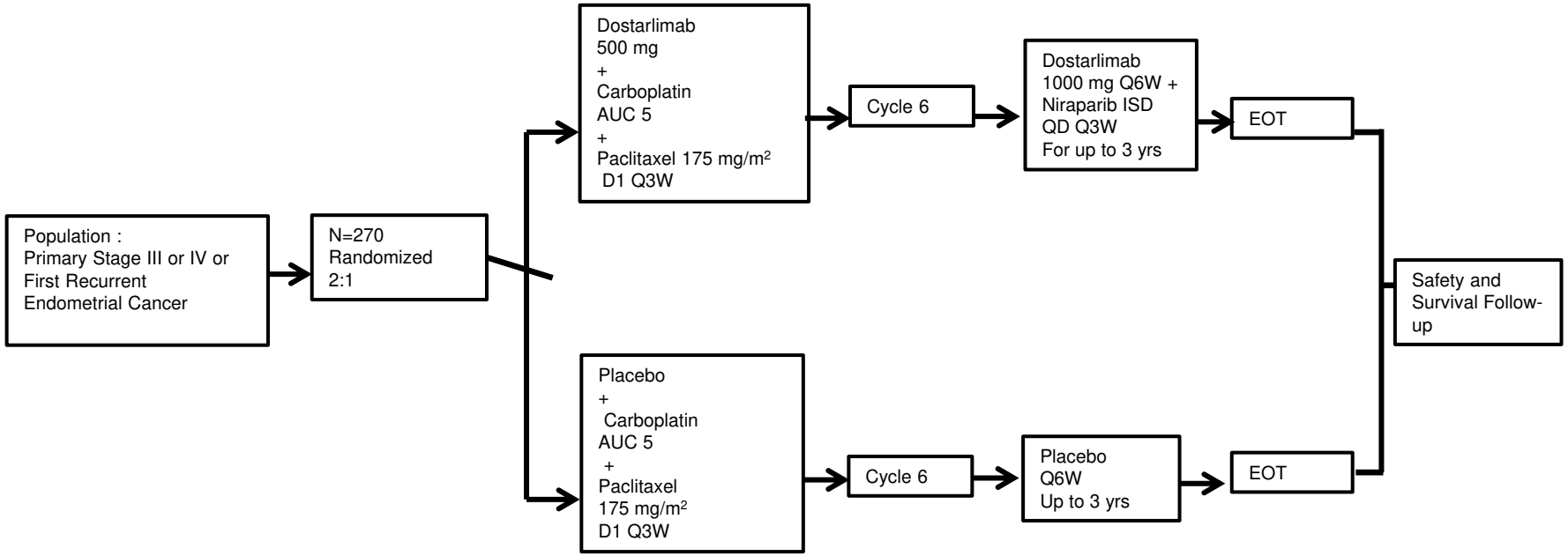
RUBY
CARESTONE CLINICAL TRIAL



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

Study Design – Part 2



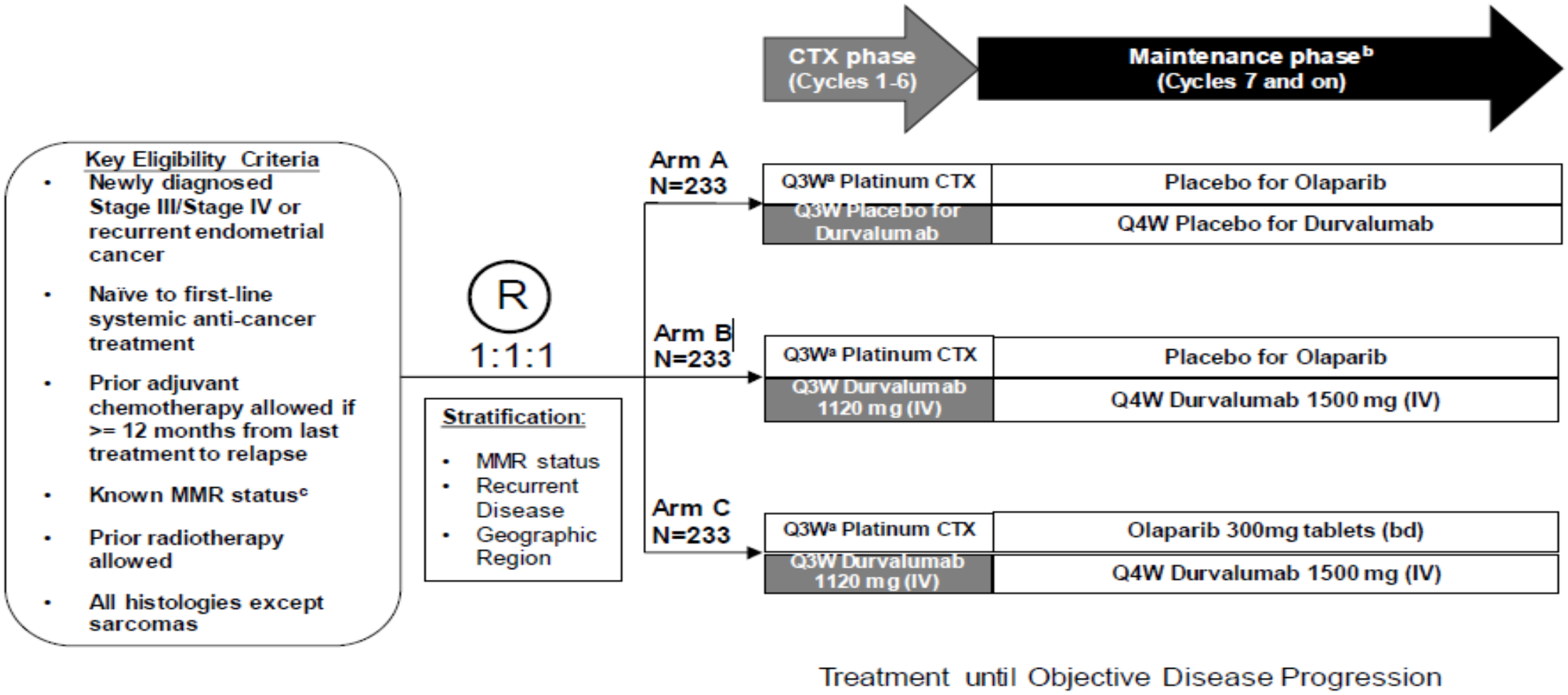
STRATIFICATION

MSI/MMR Status (MSI-H or MSS), Prior External Pelvic Radiotherapy (Yes or No), Disease Status (Primary Stage III or IV, First Recurrent)

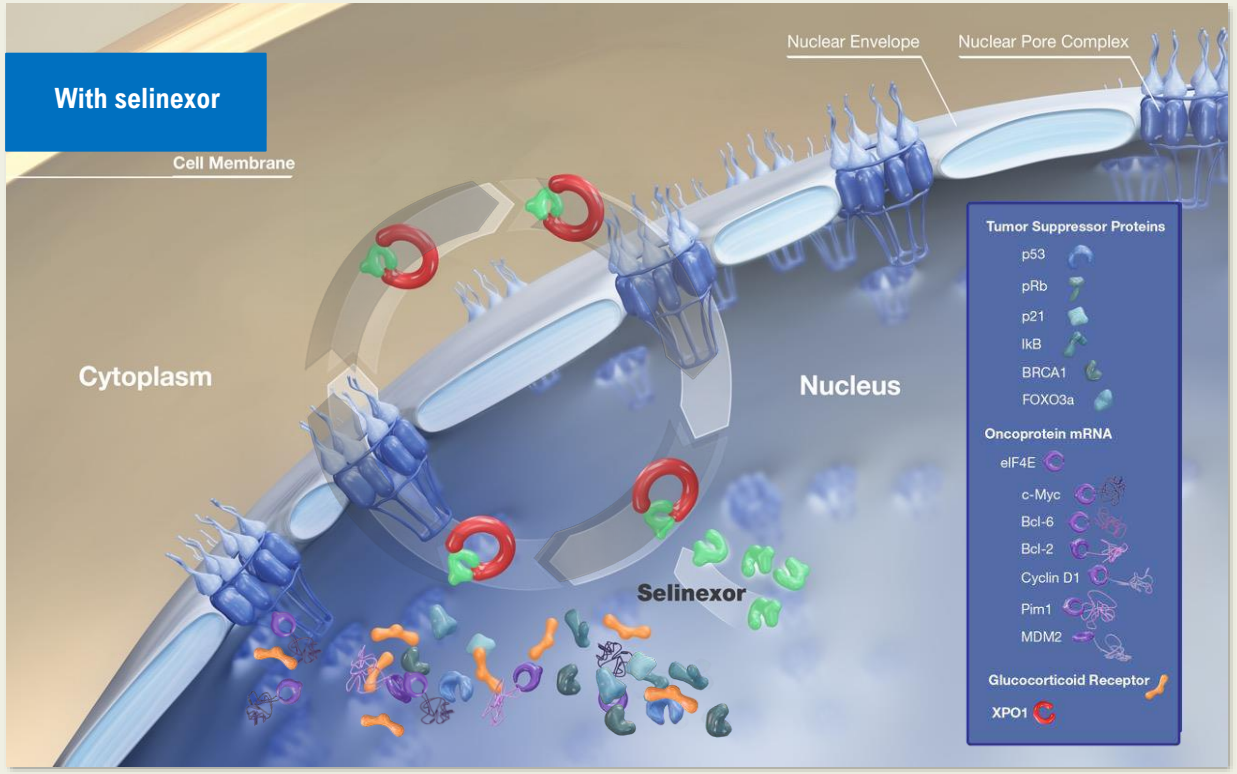
PRIMARY ENDPOINT

BICR assessed PFS per RECIST v1.1

GOG-3041/DUO-E: Schema



Selinexor Inhibits XPO1 and Induces Cancer Cell Death



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 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*

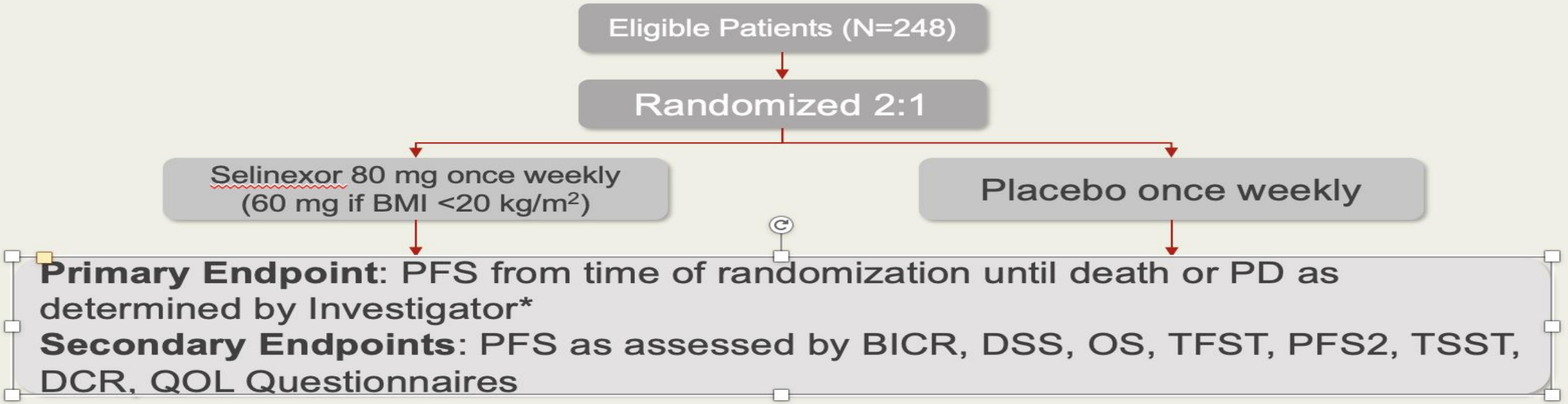
Ranganathan Blood 2012; Etchin BJH 2013; Tai Blood 2014; Ranganathan Blood 2015; Etchin Leukemia, 2015; Ranganathan Clin Can Res 2016; Gu., JCI, 2018; Luedtke, J Cell Mol Med 2018; Brunetti Cancer Cell 2018.

KCP-330-024-ENGOT-EN5/SIENDO Trial Overview

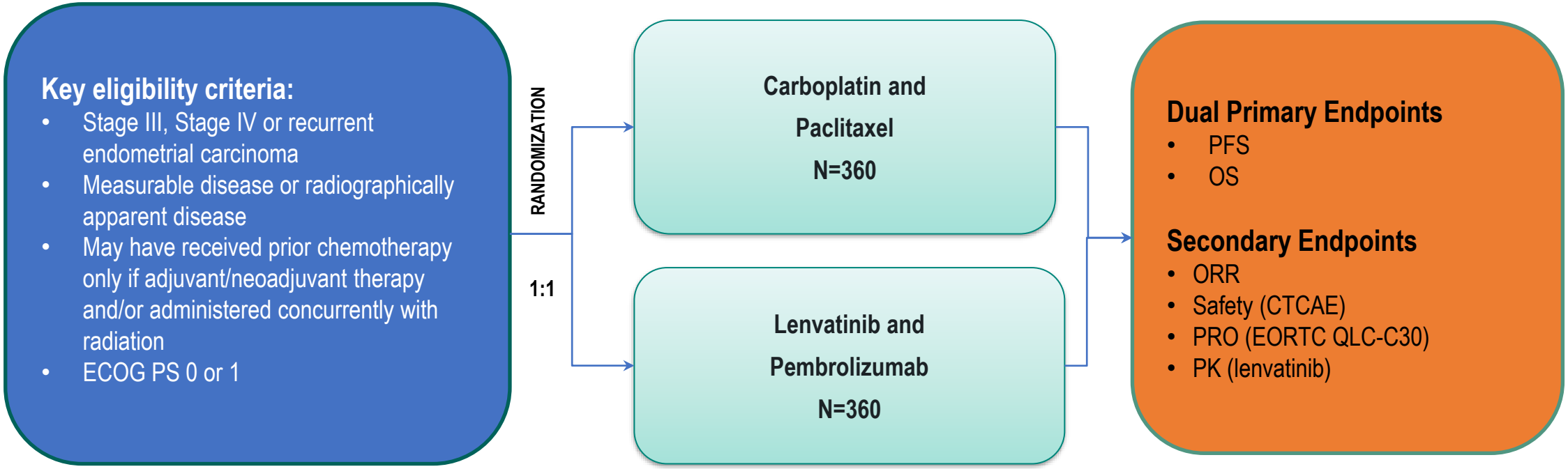
Eligibility

Patients who completed a single line of at least 12 weeks of taxane-platinum combination therapy including patients who received taxane-platinum combination therapy for:

- Primary Stage IV disease
- First Relapse (i.e., relapse after primary therapy including surgery and/or adjuvant therapy for Stage I-IV disease)



LEAP-001: 1L phase 3 in endometrial cancer

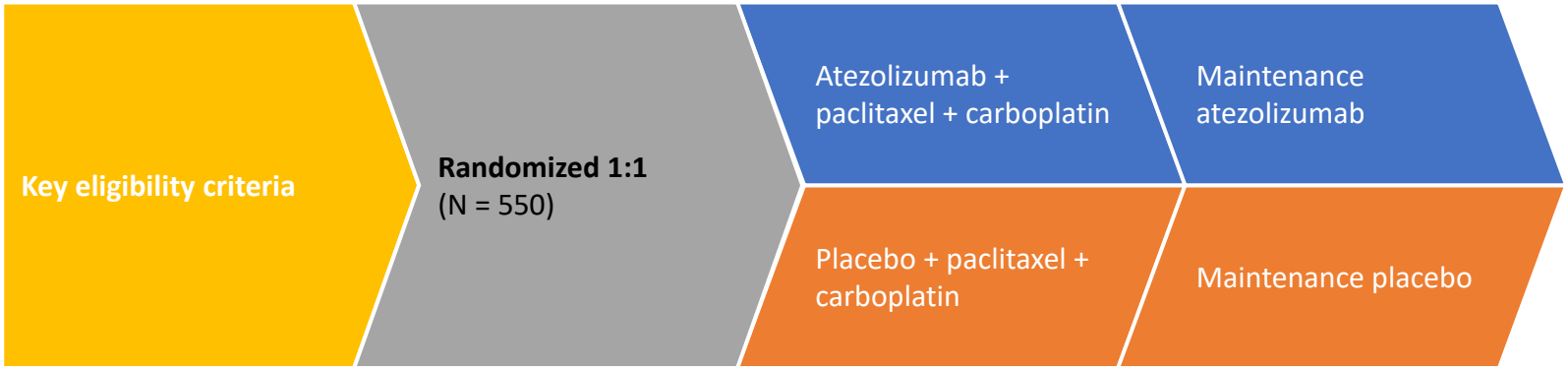


Stratification factors:

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

AtTEnd (ENGOT-en7): atezolizumab + carboplatin/paclitaxel clinical trials[1]

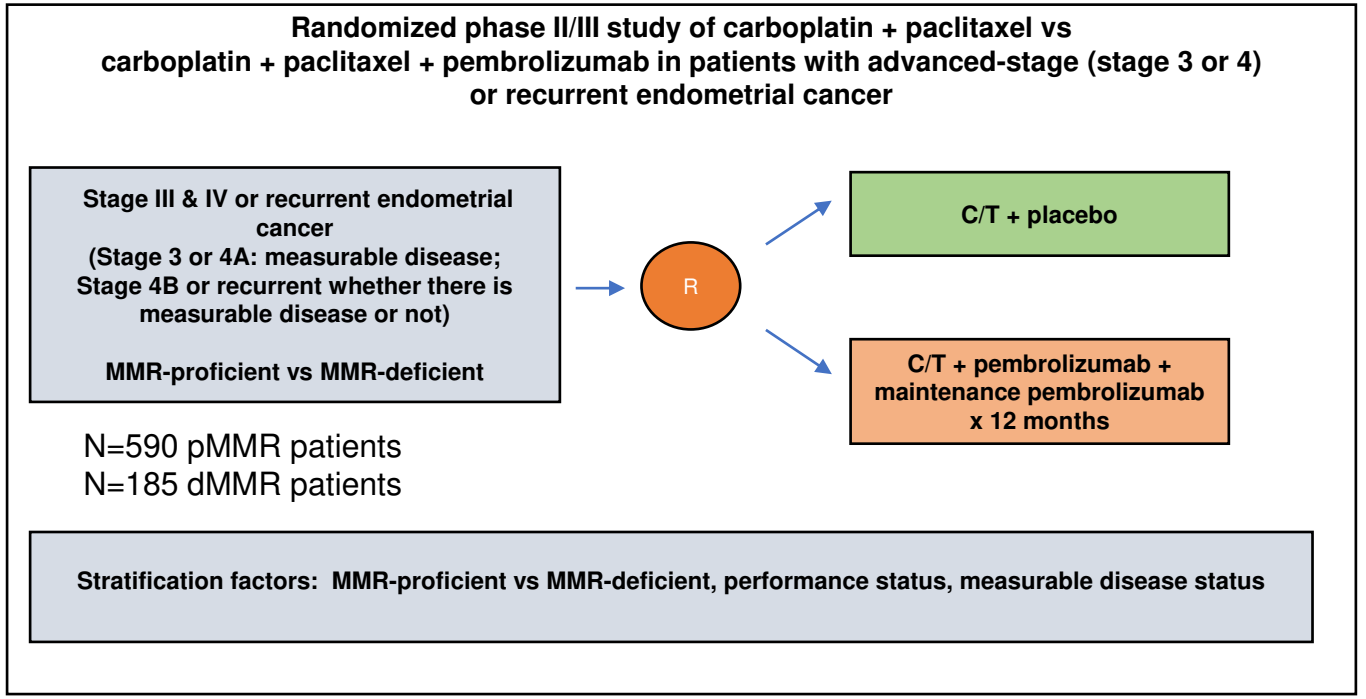
- AtTEnd (ENGOT-en7) is an international (no US patients), multicenter, phase 3, double-blind, randomized, controlled trial of atezolizumab in combination with paclitaxel and carboplatin in women with advanced/recurrent endometrial cancer
- 550 patients with newly diagnosed, advanced stage III/IV, or recurrent endometrial cancer will be accrued during a period of 24 months with a 1:2 randomization ratio into 2 arms:
  - Control group: standard chemotherapy plus placebo IV every 21 days up to 6/8 cycles followed by placebo until progression
  - Experimental group: standard chemotherapy plus 1200 mg atezolizumab IV every 21 days up to 6/8 cycles followed by atezolizumab until progression
- Standard chemotherapy will consist of 175 mg/m² paclitaxel plus AUC5/6 carboplatin. Patients will be stratified by histology, disease stage, microsatellite status, and country of experimental site
- Primary endpoints are OS and PFS. Secondary endpoints include ORR, duration of response, PFS2, quality of life, adverse events, and compliance



Primary endpoint:
PFS expected July 2021

1. www.clinicaltrials.gov, NCT03603184.

Hot & Cold: NRG-GY018



Patients may have received prior radiation therapy or hormonal therapy. Patients in whom both radiation and chemotherapy are planned must receive radiation prior to entry on study. C = carboplatin; T = paclitaxel.

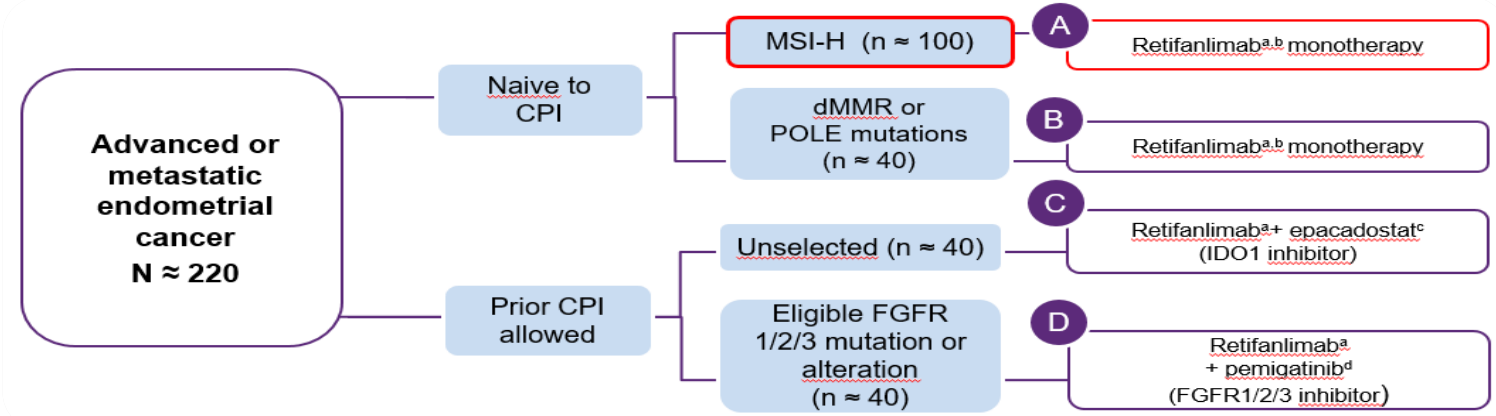
Endometrial Cancer: Active Trials
2nd Line

Recurrent, 2nd line, CPI pretreated or naive PI: Slomovitz Co-PI: Moxley	GOG-3038/POD1UM-204 NCT04463771	An Umbrella Study of INCMGA00012 Alone and in Combination with Other Therapies in Participants with Advanced or Metastatic Endometrial Cancer Who Have Progressed on or After Platinum-Based Chemotherapy	Recruiting Selection closed Sites: 23/30 Total: 40 (215) GOG:26
Recurrent, 2nd line PI: Huang Co-PI: Huang, Slomovitz	GOG-3039 NCT04393285	A Phase II Study of Abemaciclib in Combination with Letrozole in Advanced, Recurrent or Metastatic Endometrioid Endometrial Cancer	Recruiting Selection closed Sites: 19/25 Total: 5/50
Recurrent 2nd line, CPI naive PI: Slomovitz Co-PI: Moroney, Alvarez, Cantillo, Secord, LIu	AFT-50 EndoMap NCT04486352	A Phase IB/II Multi-Cohort Study of Targeted Agents With Atezolizumab for Patients With Recurrent or Persistent Endometrial Cancer	Not yet recruiting

GOG3038/ENGOT-en12

PODIUM 204
PD1 Clinical Program in Multiple Malignancies

Phase 2, Open-Label, Non-Randomized, Umbrella Study of Retifanlimab (PD-1 Inhibitor) Alone or With Other Therapies in Patients With Advanced or Metastatic Endometrial Cancer Who Have Progressed on or After Platinum-Based Chemotherapy



Primary Endpoint
- Group A: ORR (per RECIST 1.1, by ICR)

Secondary Endpoints
- A & B: DOR, DCR, PFS, OS
- C & D: ORR
- All groups: safety and tolerability

Key Inclusion Criteria
- Women > 18 years of age (or as applicable per local country requirements)
- Histologically confirmed diagnosis of advanced or metastatic endometrial cancer
- Disease progression on or after treatment with > 1 platinum-containing regimen
- > 1 measurable tumor lesion per RECIST v1.1
- ECOG PS of 0 to 1
- Willingness to provide tumor tissue sample (fresh or archived)

Key Exclusion Criteria
- Histologically confirmed diagnosis of sarcoma of the uterus
- Toxicity of prior therapy that has not recovered to < grade 1
- Active autoimmune disease requiring systemic immunosuppression with corticosteroids or immunosuppressive drugs within 14 days before the first dose of study treatment
- Known active hepatitis B or C
- HIV positive, unless viral load undetectable,CD4+ count ≥ 300/µL
- Groups C and D: Limiting immune-related toxicity during prior checkpoint inhibitor therapy

a Retifanlimab administered IV on day 1 of each 28-day cycle for up to 26 cycles.
b Epacadostat administered orally BID.
c Pemigatinib administered orally QD.

NCT04463771

GOG 3039: Study Schema

Metastatic, persistent or recurrent **endometrioid** endometrial cancer

Abemaciclib 150mg PO BID

+

Letrozole 2.5mg PO Daily

28- Day Cycle Until Progression or Toxicity

Objectives* (Recently changed)

- Primary: 6 month PFS

- Secondary: response rate, to estimate time to disease progression.
  - To describe toxicities of combination therapy

AFT-50 Study Overview

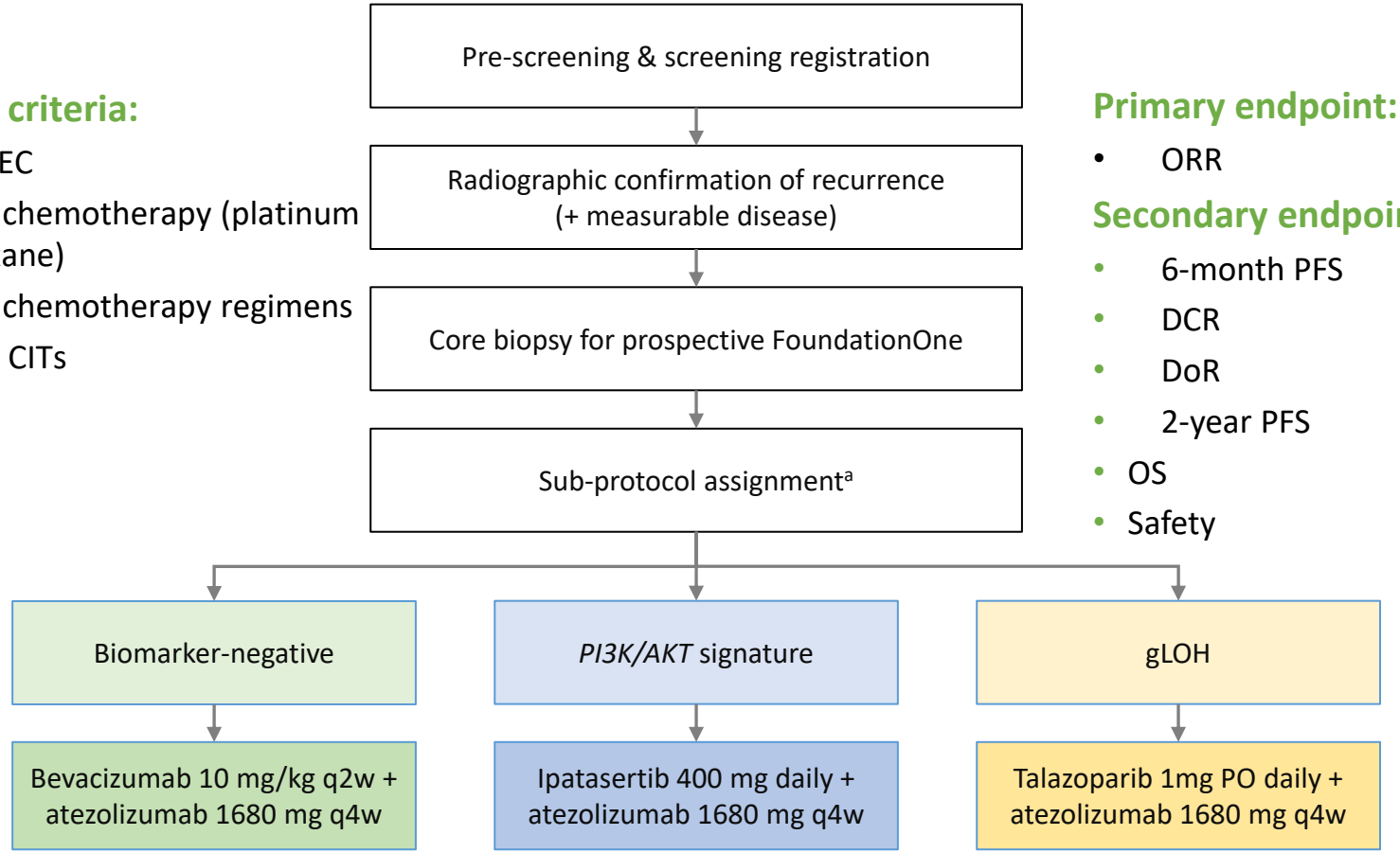
Study Chair	Brian Slomovitz, MD (Cell: 646-706-2463)
Study Type/Phase	Phase IB/II
Clinical Indication	Endometrial Cancer
Study Drugs	Atezolizumab Bevacizumab Ipatasertib Talazoparib
Pharma Partner(s)	Genentech Pfizer (one treatment arm)
# Initial Study Subjects	60 (20 per study arm)
# Sites	25
Estimated Duration	48 Months
ClinicalTrials.Gov	https://clinicaltrials.gov/ct2/show/NCT04486352 Identifier: NCT04486352

AFT-50 EndoMap: Study Goals & Obligations - Design

Eligibility criteria:

Recurrent EC

- ≥1 prior chemotherapy (platinum &/or taxane)
- ≤2 prior chemotherapy regimens
- No prior CITs



Primary endpoint:

- ORR

Secondary endpoints:

- 6-month PFS
- DCR
- DoR
- 2-year PFS
- OS
- Safety

EndoMAP. NCT04486352. Updated April 21, 2021. Accessed June 6, 2021. https://clinicaltrials.gov/ct2/show/NCT04486352

Areas of Opportunity

- First line adjuvant
  - Biomarker driven (ER, PR, what else)
  - Better identify high risk patients
  - Non-chemotherapy based regimens
  - I/O?

- First-line metastatic or recurrent
  - I/O with or without chemo
  - Hormonal therapy
  - Other biomarker driven therapy
  - Treatment differences MSI v MSS (dMMR v pMMR)
  - Role of radiation combinations?

Areas of Opportunity

- Second line metastatic or recurrent
  - I/O after I/O??
  - Biomarker driven (ER, PR, what else)
  - Future of second line chemo for endometrial cancer
  - Role of re-challenging with platinum therapy
  - Other ideas

Thank you!