Uterine Cancer Trials in Progress

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Clinical Trial Lead, Uterine Cancer
GOG Partners
March 24, 2021

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Front Line

- **Ongoing**
  - GOG-3031 RUBY (Mirza, Powell)
  - GOG-3041 DUO-E (Westin, Moore)
  - GOG-3055 SIENDO (Makker)

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

Study Chair: Mirza Mansoor, MD
GOG Study Chair: Matthew Powell, MD

ClinicalTrials.gov Identifier: NCT03981796

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Study Background

RUBY Study Rationale

Endometrial cancer accounts for > 90% of all uterine cancer, and approximately 20% of patients are diagnosed with advanced or metastatic disease (Stage III or IV) for which surgical cure is not likely.

There is currently no approved anticancer therapy for these patients. Although radiotherapy (external beam radiotherapy and/or brachytherapy), chemoradiation, or adjuvant systemic platinum-based chemotherapy is recommended, an unmet medical need in this patient population remains high.

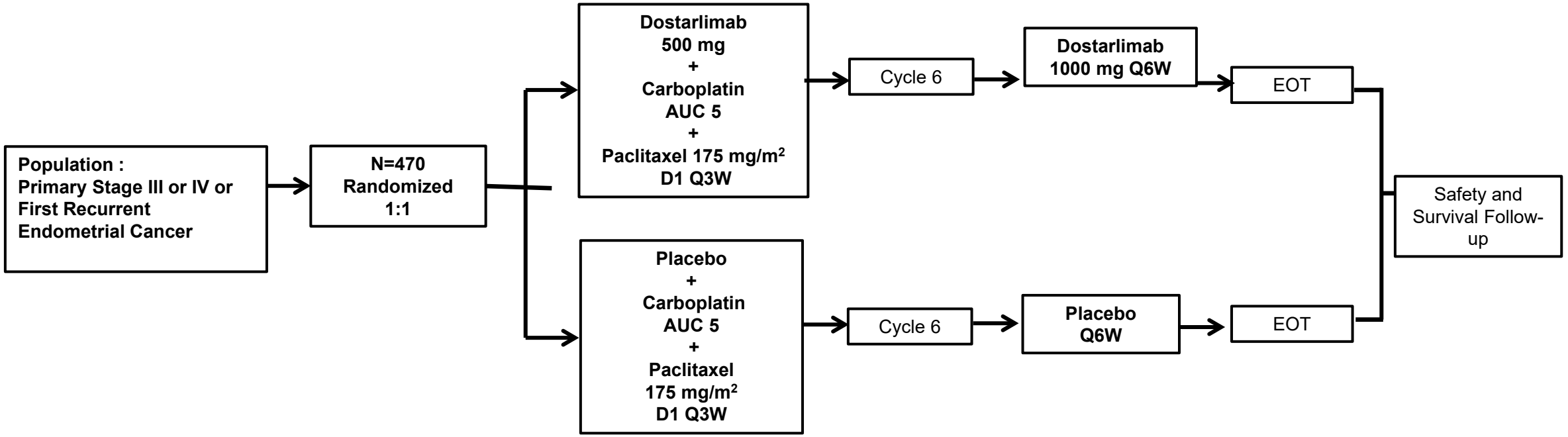
Preliminary data from Study 4010-01-001 suggest that dostarlimab monotherapy provides benefit in subjects with recurrent or advanced endometrial cancer who have progressed from platinum containing regimen, in both MSI-H/dMMR or MSS/MMRp patients.

There is accumulating evidence that, in addition to direct cytostatic and cytotoxic effects, the mechanism of action of conventional chemotherapies may involve activation of tumor-targeted immune responses, including increasing the immunogenicity of cancer cells and reducing immunosuppression of tumors.

Carboplatin binds efficiently to DNA, thereby inhibiting replication and transcription and inducing cell death. Repair of carboplatin induced DNA damage is reduced by PARP inhibition.

The ability of the PARP inhibitor niraparib to synergistically increase the activity of PD-1/PD-L1 pathway inhibitors in nonclinical syngeneic models makes niraparib an appealing addition to dostarlimab for a population of all comers with advanced endometrial cancer who have been treated with platinum-containing chemotherapy.

Study Design – Part 1



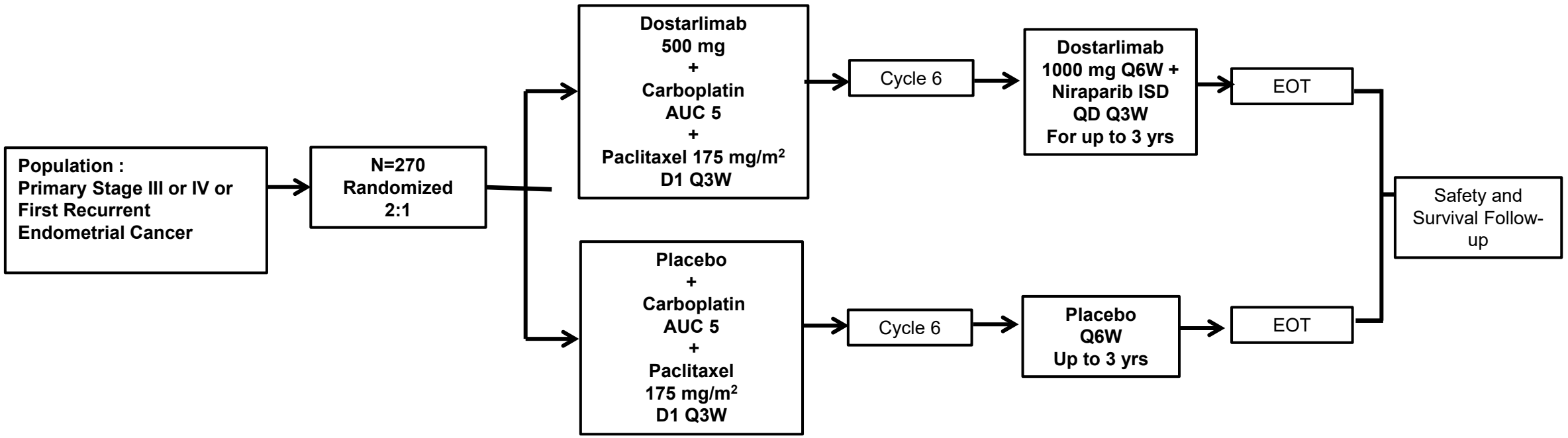
STRATIFICATION

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

PRIMARY ENDPOINT

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

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

Sample Size

Part 2

Approximately 270 patients enrolled

To maintain the natural distribution of dMMR/MSI-H (25%) and MMRp/MSS (75%) patients in the overall endometrial cancer population the number of patients will be capped:

- dMMR/MSI-H: 70 patients
- MMRp/MSS: 200 patients

To prevent over-representation of patients with carcinosarcoma* the number carcinosarcoma patients will be capped at 30 (~10%)

*Inclusion Criteria 4b.

Study Objectives

Part 2 - Primary & Secondary Objectives

Primary

To compare the progression-free survival **(PFS)** of treatment with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab plus niraparib to treatment with placebo plus carboplatin-paclitaxel followed by placebo, as **assessed by Blinded Independent Central Review (BICR)** per Response Evaluation Criteria in Solid Tumors version 1.1 **(RECIST v.1.1),** in:

- **All patients** with recurrent or primary advanced endometrial cancer

Secondary

To evaluate the following measures of clinical benefit of treatment with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab plus niraparib compared to treatment with placebo plus carboplatin-paclitaxel followed by placebo in subjects with recurrent or primary advanced endometrial cancer:

KEY secondary endpoint: **OS** Overall Survival

PFS based on Investigator Assessment

PFS2

ORR (Objective Response Rate) BICR/IA

DOR (Duration of Response) BICR/IA

DCR (Disease Control Rate) BICR/IA

Patient-reported Outcomes **(PROs):** EQ-5D-5L, EORTC-QLQ-C30, EORTC-QLQ-EN24

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Study Objectives

Part 2 - Exploratory Objectives

To **assess biomarkers in tumor tissue** that **may be predictive of response to treatment** with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab plus niraparib compared to treatment with placebo plus carboplatin-paclitaxel followed by placebo, including markers of DNA damage/DNA repair (eg, TMB and homologous recombination deficiency [HRD]) and PDL1 expression.

To **characterize circulating biomarkers in the blood** that **may be predictive of response to treatment** with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab plus niraparib compared to placebo plus carboplatin-paclitaxel followed by placebo.

To explore **if MSI status assessed in blood may be predictive of response to treatment** with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab plus niraparib compared to placebo plus carboplatin-paclitaxel followed by placebo. The **concordance between blood-based** MSI assessment and **tumor tissue-based** MMR IHC will also be explored.

OPTIONAL Whole blood draw for **genetics research** **(**germline genetic testing), to understand disease genetics or investigate drug responses and clinical outcomes. Retrospective, based on study outcome and warranted scientific rationale

Key Inclusion Criteria

Protocol Section 8.1

Female ≥18 years of age

Adequate tumor tissue sample provided at Screening for MSI/MMR status testing.

Subject must have primary Stage III or Stage IV disease or first recurrent endometrial cancer with a low potential for cure by radiation therapy or surgery alone or in combination, and meet at least one of the following criteria:

a. Subject has primary Stage IIIA to IIIC1 disease with presence of evaluable or measurable disease per RECIST v.1.1 based on Investigator's assessment. Lesions that are equivocal or can be representative of post-operational change should be biopsied and confirmed for the presence of tumor.

b. Subject has primary Stage IIIC1 disease with carcinosarcoma, clear cell, serous, or mixed histology (containing ≥ 10% carcinosarcoma, clear cell, or serous histology) regardless of presence of evaluable or measurable disease on imaging.

c. Subject has primary Stage IIIC2 or Stage IV disease regardless of presence of evaluable or measurable disease.

d. Subject has first recurrent disease and is naïve to systemic anticancer therapy.

e. Subject has received prior neo-adjuvant/adjuvant systemic anticancer therapy and had a recurrence or PD ≥ 6 months after completing treatment (first recurrence only).

Note: Subjects with uterine sarcoma are not allowed.

See Protocol Section 8.1 for full list of Inclusion Criteria

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Key New Exclusion Criteria

Protocol Section 8.2

Subject has received prior therapy with a PARP inhibitor.

Subject has clinically significant cardiovascular disease (eg, significant cardiac conduction abnormalities, uncontrolled hypertension, myocardial infarction, uncontrolled cardiac arrhythmia or unstable angina <6 months to enrollment, New York Heart Association Grade ≥2 congestive heart failure, serious cardiac arrhythmia requiring medication, Grade ≥2 peripheral vascular disease, and history of cerebrovascular accident within 6 months).

Subject has any known history or current diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

Subject is at increased bleeding risk due to concurrent conditions (eg, major injuries or major surgery within the past 28 days prior to start of study treatment, history of hemorrhagic stroke, transient ischemic attack, subarachnoid hemorrhage, or clinically significant hemorrhage within the past 3 months).

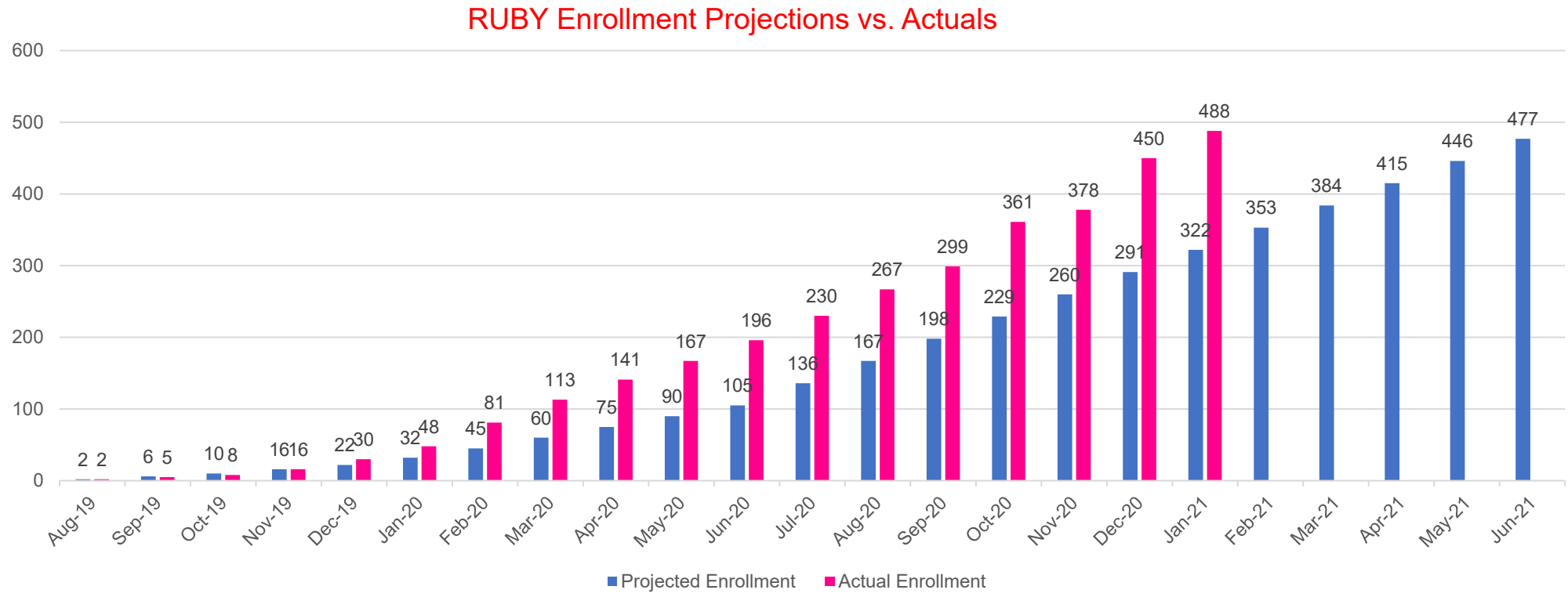
Subject has a known hypersensitivity to niraparib components or excipients.

Subject has participated in Part 1 of this study.

See Protocol Section 8.2 for full list of Exclusion Criteria

Patient Enrollment Actual vs. Projections

(as of 28-Jan-21)



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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

Study Chair: Shannon Westin, MD
Co-study Chair: Kathleen Moore, MD

ClinicalTrials.gov Identifier:

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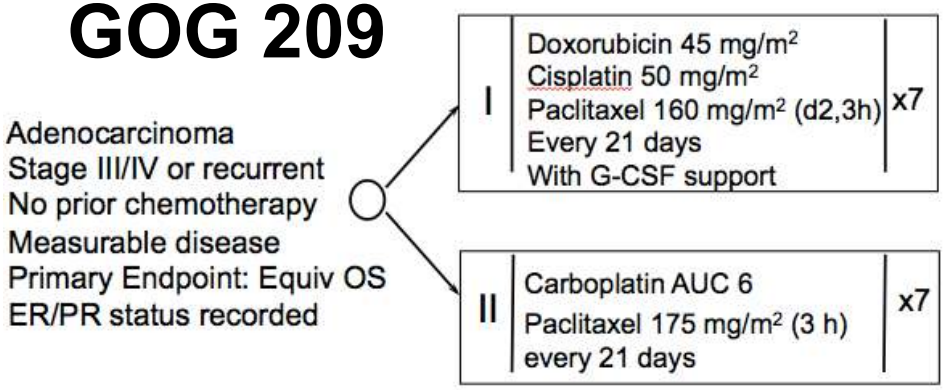
Background/Rationale

GOG 209



Outcome Measure	TAP	TC	HR
Median PFS	14 mos	14 mos	1.03
Median OS	38 mos	32 mos	1.01
OS (90% CI, Test for Non-inferiority)		1.16	P>0.1

Inhibition of PD-L1 is of interest in endometrial cancer, especially in combination with chemotherapy

- increased immunogenicity
- up-regulation of PD-L1
- increased antigen presentation

Durvalumab: PD-L1 inhibitor

- tolerable in combination with paclitaxel, carboplatin

AstraZeneca

Miller JCO 2020

Westin, AACR 2019

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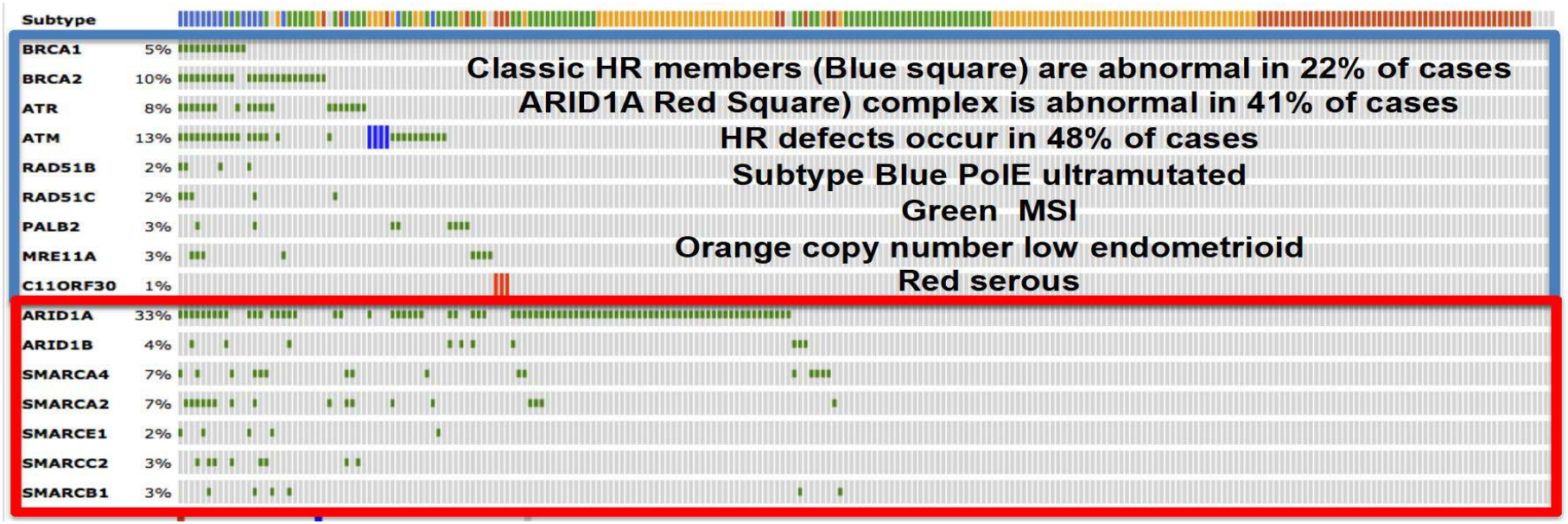
Background/Rationale



- **<u>HRD is present in endometrial cancer</u>**
  - **Classic HRD members: 22%**
  - **ARID1A: 41%**
  - **HRD + ARID1A: 48%**

G. Mills

Study Design

Global Study / ≈ 25 Countries / ≈ 210 Sites

Key Eligibility

- Newly diagnosed Stage III/Stage IV or Recurrent Endometrial Cancer
- Adjuvant chemo allowed if ≥ 12 months from last treatment to relapse
- All histologies except sarcomas

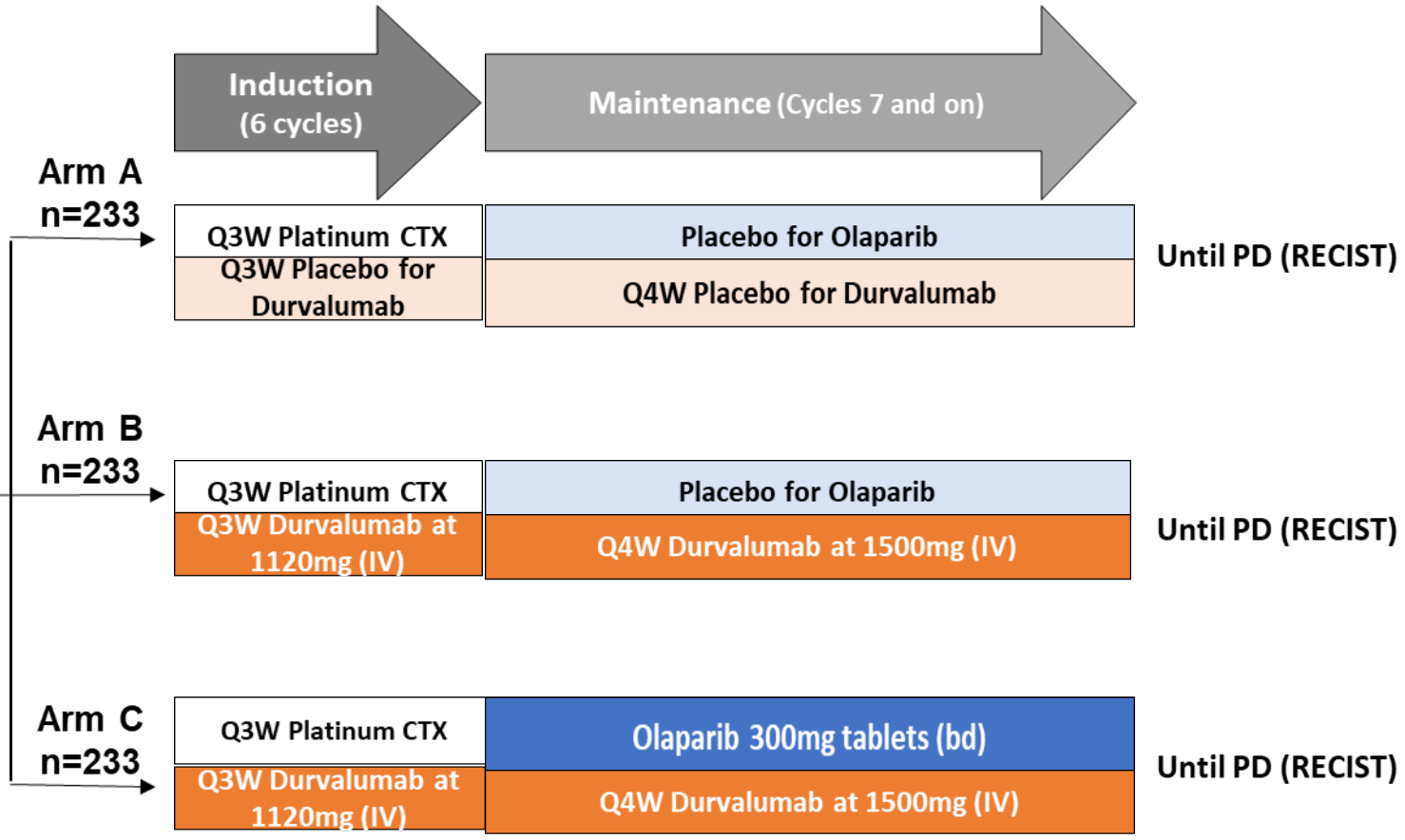
N=699

R

1:1:1

Stratification:

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



Only patients with no evidence of PD allowed to continue on maintenance

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DURVALUMAB PLUS OLAPARIB DUO-E ENDOMETRIAL CANCER

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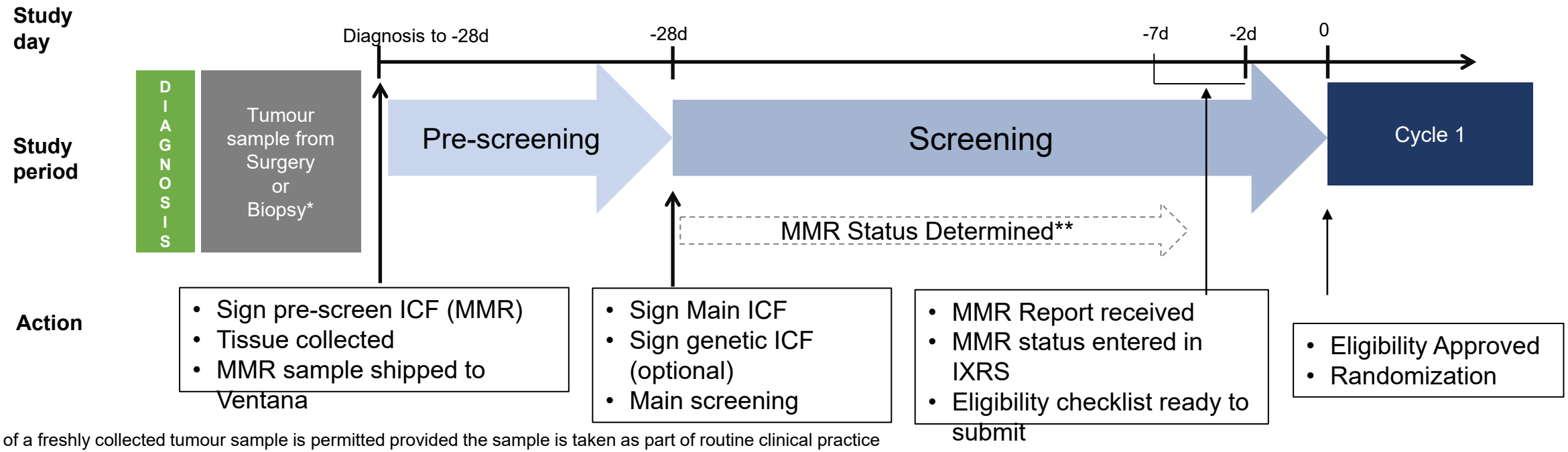
Screening and Enrollment



* Use of a freshly collected tumour sample is permitted provided the sample is taken as part of routine clinical practice

** Patients with unknown MMR status prior to randomisation will be considered screen failures and will not be eligible. If the 28 day screening period cannot be completed due to a delay in receiving MMR test result, the sponsor may be contacted for approval for MMR re-test (please see section 5.4). Sample must be shipped to the Ventana and MMR results must be available prior to dosing. Submission and testing of new samples can only be performed if the original testing failed due to technical failure. Please refer to the laboratory manual for further details regarding retesting procedures

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DURVALUMAB PLUS OLAPARIB DUO-E ENDOMETRIAL CANCER

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KEY INCLUSION / EXCLUSION CRITERIA

- Histologically confirmed diagnosis of epithelial endometrial carcinoma (excluding sarcomas)
  - Newly diagnosed Stage III measurable disease per RECIST 1.1 following surgery or diagnostic biopsy, OR
  - Newly diagnosed Stage IV with/without disease following surgery or diagnostic biopsy, OR
  - Recurrence of disease - measurable or non-measurable disease per RECIST 1.1
- **Naïve to first-line systemic anti-cancer treatment**
  - For patients with recurrent disease only, prior chemo is allowed **only** if given in the adjuvant setting (as part of the upfront/adjuvant anti-cancer treatment, which may be concurrent or followed with chemo radiation) and there is at least 12 months from date of last dose of chemo administered to date of subsequent relapse
- Adequate bone marrow and organ function
- No unresolved toxicity NCI CTCAE version 5.0 Grade ≥2 from previous anticancer therapy with exception of alopecia, vitiligo, and laboratory values defined in the inclusion criteria
  - Consideration will be made for ≥2 neuropathy
- No active or prior documented autoimmune or inflammatory disorders or uncontrolled intercurrent illness
- **No prior PARP inhibitor or immune checkpoint inhibitor**
- **Must be able to swallow oral medications**

GOG-3041/DUO-E: Current Status as of 3/10/21

All sites selected
GOGF Sites Activated: 53
Total enrolled: 269
- GOGF enrolled: 148

Total randomized: 149
- GOGF randomized: 83
- First enrollment 6/2020

Thanks to top enrolling sites
- Moffitt: Dr. Chon
- USOR Minnesota Oncology: Dr. Thomas-Pepin
- NYU: Dr. Blank
- USOR Oregon Oncology: Dr. Anderson
- West Cancer Center: Dr. El-Naggar
- FirstHealth of Carolinas: Dr. Sundborg
- USOR Texas Oncology – Dallas: Dr. McIntyre
- MDACC: Dr. Westin
- USOR Texas Oncology – Tyler: Dr. Priebe
- USOR Rocky Mountain Cancer Center: Dr. Fox
- Oklahoma Cancer Specialists - Dr. Gold

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DURVALUMAB PLUS OLAPARIB DUO-E ENDOMETRIAL CANCER

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GOG-3055/SIENDO

A Randomized, Double-Blind, Phase 3 Trial of Maintenance With Selinexor/ Placebo After Combination Chemotherapy for Patients With Advanced or Recurrent Endometrial Cancer

Study Chair: Vicky Makker, MD

ClinicalTrials.gov Identifier: NCT03555422

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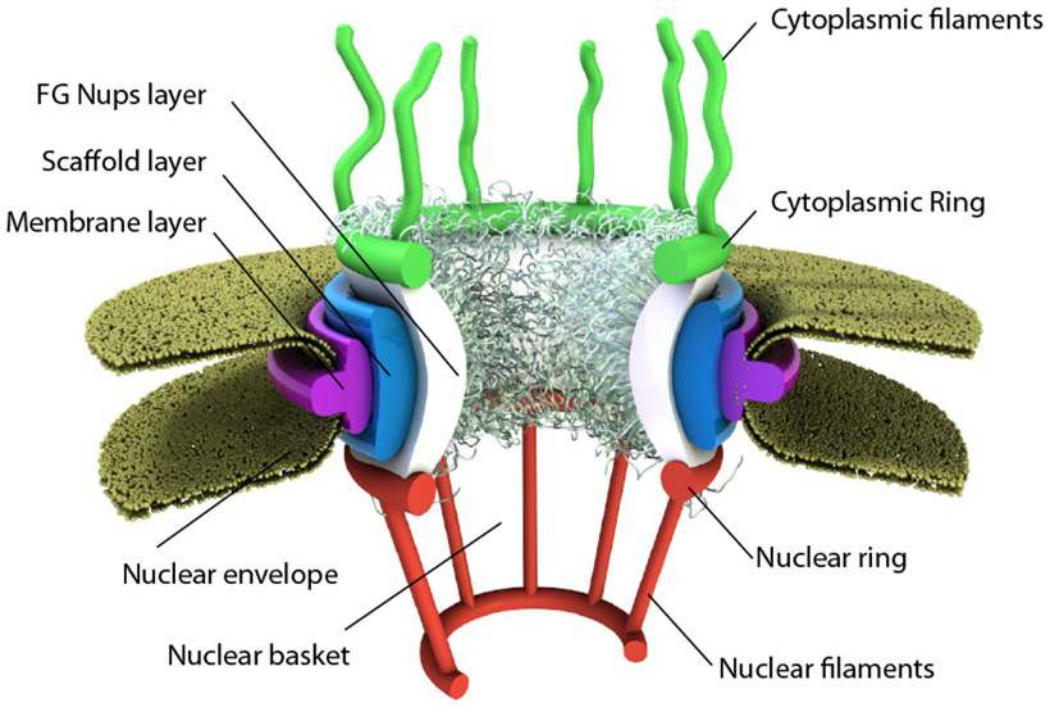
Overview of Nuclear Transport

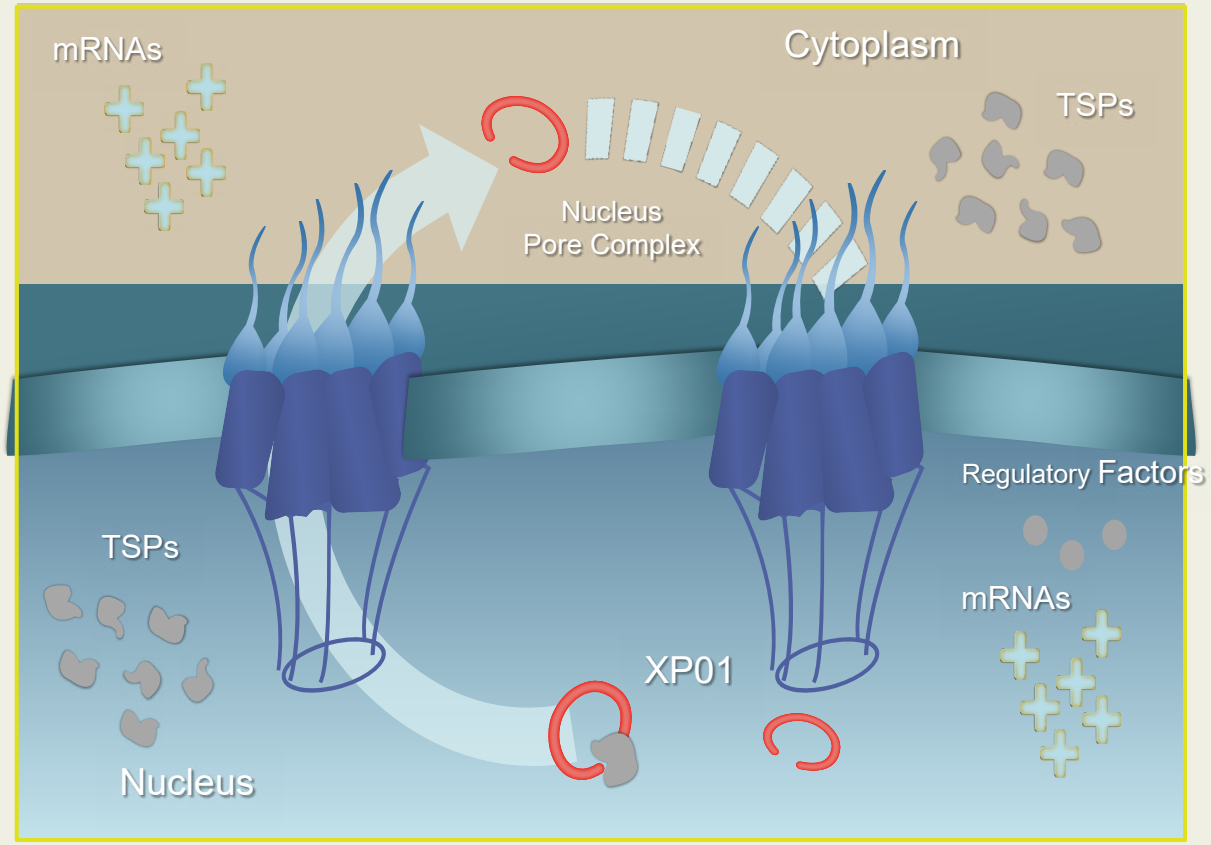


Nuclear Pore

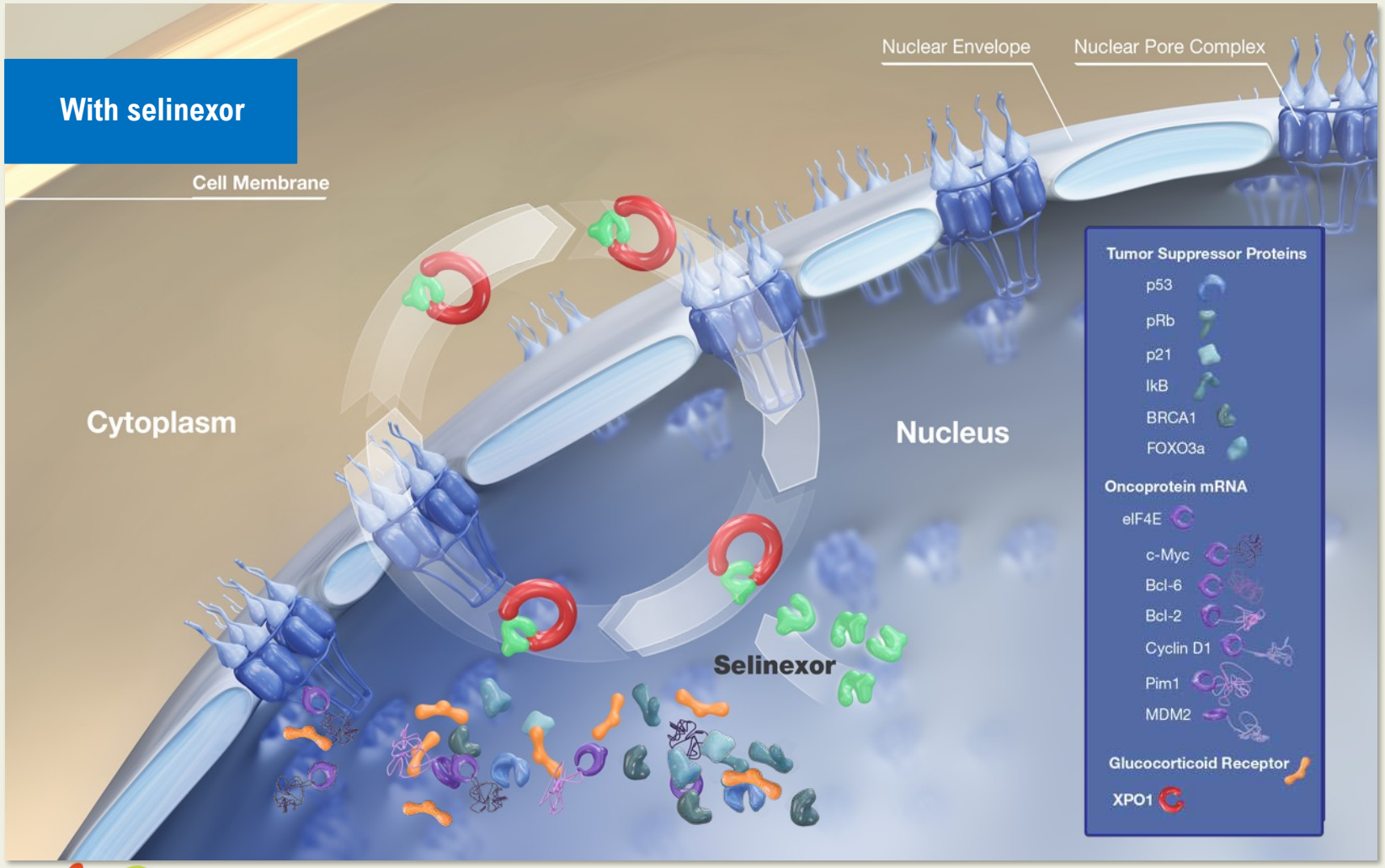
- The **nuclear pore** is a complex gate between the nucleus and cytoplasm, closely regulating the import and export of most large molecules into and out of the nucleus
- Importins are a family of proteins that facilitate the transport of large proteins from the cytoplasm into the nucleus
- Exportins are a family of proteins that facilitate the transport of large molecules from the nucleus to the cytoplasm
- In humans, there are 7 known exportins (XPO1-7)

XPO1 Shuttles Proteins Between the Nucleus and Cytoplasm Selectively Regulating Distribution

- **Exportin 1** (XPO1) is a karyopherin, a family of proteins that transport molecules between the nucleus and cytoplasm
- In normal cells, XPO1 maintains **homeostatic** levels of proteins and mRNAs
- XPO1 exports >200 cargo proteins, including tumor suppressor proteins (TSPs), eIF4E-bound mRNAs, and others
- Plays key role in the control of several cancer-related processes: cell-cycle progression, apoptosis, metastasis, and drug resistance



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:

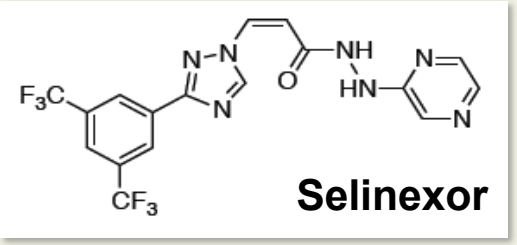
1. Inactivates TSPs by mislocalization
2. Enhances proto-oncoprotein translation
3. Correlates with poor patient prognosis

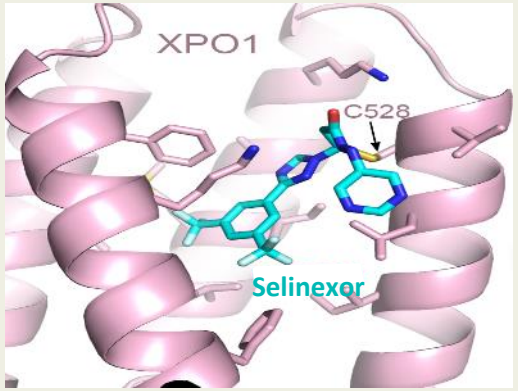
Selinexor is an oral selective inhibitor of XPO1 that:

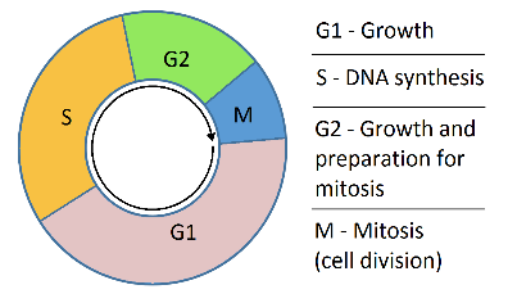
1. Reactivates TSPs and blocks proto-oncoprotein translation
2. Blocks DNA damage repair
3. Synergizes with DNA damage inducing therapies
4. Orally active against GCB and non GCB DLBCL *in vivo*

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.

Selinexor: Novel, First-in-Class, Small Molecule, Selective Inhibitor of Nuclear Export (SINE) XPO1



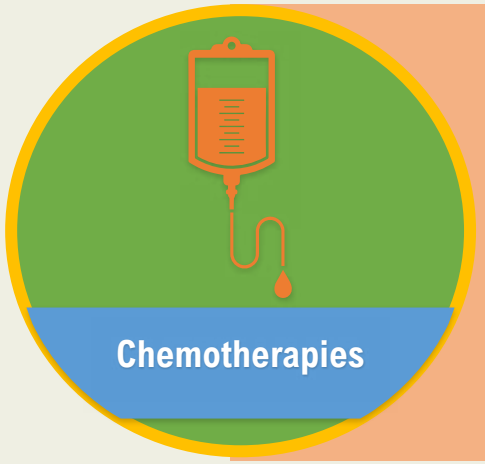




- Oral drug given 1-2 times per week (PDn $t_{1/2}$ ~48 hrs)
- No known drug-drug interactions
  - None through CYP450s or other enzymes
  - No effect on QTc intervals
- Forms a covalent adduct at cysteine 528 (C528) in the XPO1 cargo binding pocket
- Inhibits XPO1-mediated nuclear export of TSPs and oncogenic mRNAs resulting in G1/G2 arrest and apoptosis
- Potent anti-myeloma, lymphoma, leukemia and solid tumor effects in preclinical models
- Preclinical evidence of therapeutic window between cancer cells and normal cells
- Randomized Phase II/III studies ongoing in advanced hematologic and solid tumors
- Over 3,200 patients dosed alone or in combination

Selinexor Synergizes with Chemotherapies and Targeted Agents

Therapies that have been shown to synergize with selinexor include:



- Cytarabine
- Platinum compounds
- Topoisomerase I and II inhibitors
- Taxanes
- Doxorubicin
- Melphalan

- Lenalidomide
- Pomalidomide
- Dexamethasone
- Bortezomib
- Tyrosine kinase inhibitors

- Selinexor may restore apoptotic pathways and tumor cell sensitivity
- Selinexor reduces expression of many DNA damage repair (DDR) proteins

Study Design

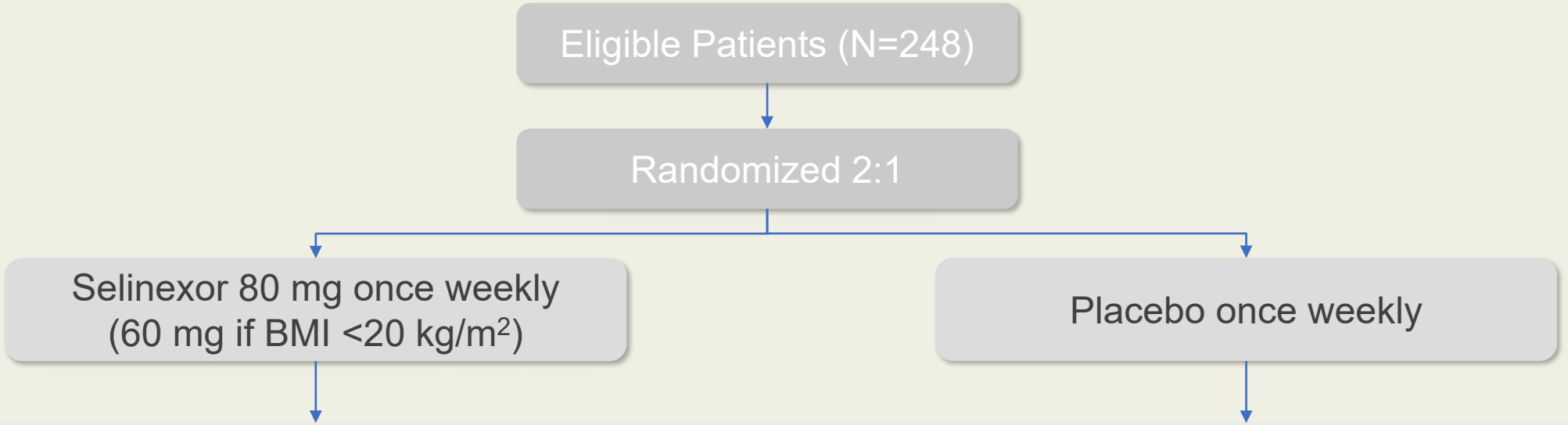
- Trial Design: Prospective, multicenter, double-blind, placebo-controlled, randomized Phase 3 study designed to evaluate maintenance treatment with selinexor compared with placebo in patients with endometrial cancer in **partial or complete remission** according to RECIST v1.1 who have completed a single line of **at least 12 weeks of taxane-platinum** combination therapy.
  - This includes patients who received taxane-platinum combination therapy for **primary Stage IV disease** and patients who received taxane-platinum combination therapy at **first relapse** (i.e., relapse after primary therapy for early stage disease including surgery and/or adjuvant therapy for Stage I-IV disease)
- Patients will be randomized after at least 12 weeks of chemotherapy AND achieved a PR or CR in a **2:1 manner** to maintenance therapy with either **selinexor or placebo**, respectively
- Treatment arms will be stratified by:
  - **Primary Stage IV disease** versus **recurrent disease** at the time of taxane-platinum combination therapy
  - Disease status after chemotherapy (partial response [**PR**] vs. complete response [**CR**])

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)



Primary Endpoint: PFS from time of randomization until death or PD as determined by Investigator*
Secondary Endpoints: PFS as assessed by BICR, DSS, OS, TFST, PFS2, TSST, DCR, QOL Questionnaires

Inclusion Criteria

1. Histological confirmed endometrial cancer of the endometrioid, serous, or undifferentiated type. Carcinosarcoma of the uterus is also allowed

2. Completed a single line of at least 12 weeks of taxane-platinum combination therapy (not including adjuvant or neoadjuvant therapy), and achieved PR or CR according to RECIST 1.1 for:

    A. Primary Stage IV disease, defined as:

        i. had a primary or later debulking surgery during first-line taxane-platinum therapy with R0 resection (R0 resection indicates a macroscopic complete resection of all visible tumor) and achieved CR after at least 12 weeks taxane-platinum chemotherapy OR

        ii. had a primary or later debulking surgery during first-line taxane-platinum therapy with R1 resection (R1 resection indicates incomplete removal of all macroscopic disease,) and achieved PR or CR after at least 12 weeks taxane-platinum chemotherapy, OR

        iii. c. had no surgery and achieved PR or CR after at least 12 weeks taxane-platinum chemotherapy.

Inclusion Criteria

B. At first relapse (i.e., relapse after primary therapy including surgery and/or chemotherapy therapy for Stage I-IV disease), defined as:

   i. had Stage I – III disease at diagnosis and received at initial diagnosis adjuvant chemotherapy and relapsed later. Patients should have PR or CR after at least 12 weeks of taxane-platinum chemotherapy compared with the start of this chemotherapy at the time of relapse, OR

   ii. had Stage I-III disease at diagnosis and did not receive adjuvant chemotherapy at initial diagnosis and relapsed later. Patients should have PR or CR after at least 12 weeks of taxane-platinum chemotherapy compared with the start of this chemotherapy at the time of relapse, OR

   iii. had Stage IV disease at diagnosis and received initially chemotherapy with or without surgery and relapsed later. At the time of relapse, patients should have PR or CR after at least 12 weeks of taxane-platinum chemotherapy compared with the start of this chemotherapy at the time of relapse.

4. Must be able to **initiate study drug 5 to 8 weeks** after completion of their final dose of chemotherapy

5. Eastern Cooperative Oncology Group (**ECOG**) performance status of **0-1**

Exclusion Criteria

1. Has any sarcomas, small cell carcinoma with neuroendocrine differentiation, or clear cell carcinomas.
2. Received a blood or platelet **transfusion** during **4 weeks prior to randomization**.
3. Being treated with a concurrent cancer therapy.
4. Previous treatment with an exportin 1 (XPO1) inhibitor.
5. Previous treatment with anti-PD-1 or anti-PD-L1 immunotherapy (e.g., pembrolizumab).
6. Concurrent treatment with an investigational agent or participation in another clinical trial.
7. Patients who received any systemic anticancer therapy including **investigational agents** or **radiation ≤3 weeks** (or ≤5 half-lives of the drug [whichever is shorter]) prior to C1D1. Palliative radiotherapy may be permitted for symptomatic control of pain from bone metastases in extremities, provided that the radiotherapy does not involve target lesions, and the reason for the radiotherapy does not reflect progressive disease (PD).

Recurrent Disease

- **Ongoing**
  - GOG-3038 POD1UM-204 (Slomovitz, Moxley)
  - GOG-3039 (Huang M, Huang G, Slomovitz)

GOG-3038/POD1UM-204

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

PI: Brian Slomovitz, MD
Co-PI: Katherine Moxley, MD
ENGOT PI: Jalid Sehouli, MD

ClinicalTrials.gov Identifier: NCT04463771

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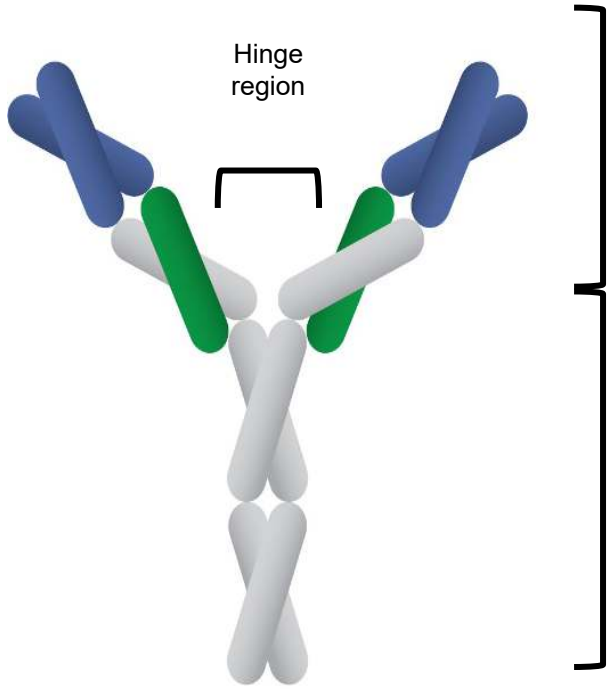
INCMGA00012, an Investigational PD-1 Inhibitor in Clinical Development

INCMGA00012 is a humanized, hinge-stabilized IgG4 monoclonal antibody[a]

INCMGA00012 structure



Fab region
Antigen-binding

Fc region
Binds to Fc receptors on immune cells to activate them

Preclinical Setting

- In preclinical studies, INCMGA00012:
  - Bound to PD-1
  - Blocked PD-1/PD-L1 and PD-1/PD-L2 binding
  - Enhanced antigen-induced IFN-γ secretion

with potency and binding characteristics comparable to replicas of nivolumab and pembrolizumab[a]

[a] Developed by Incyte as part of a collaboration agreement with MacroGenics, Inc. Lakhani N, et al. Poster presented at SITC 2017 [abstract P249].

[a] Republished with permission of The American Society for Clinical Investigation, from: "Anti–PD-1/PD-L1 therapy of human cancer: past, present, and future." Chen L and Han X. Vol 125, No 9, 2015; permission conveyed through Copyright Clearance Center, Inc.
APC, antigen-presenting cell; NK, natural killer; PD-1, programmed cell death protein 1; PD-L, programmed cell death ligand; RGMb, repulsive guidance molecule BMP co-receptor B; T_{eff}, effector T cell; T_{reg}^{33}, regulatory T cell.
3. Chen L, Han X. *J Clin Invest.* 2015;125:3384-3391.

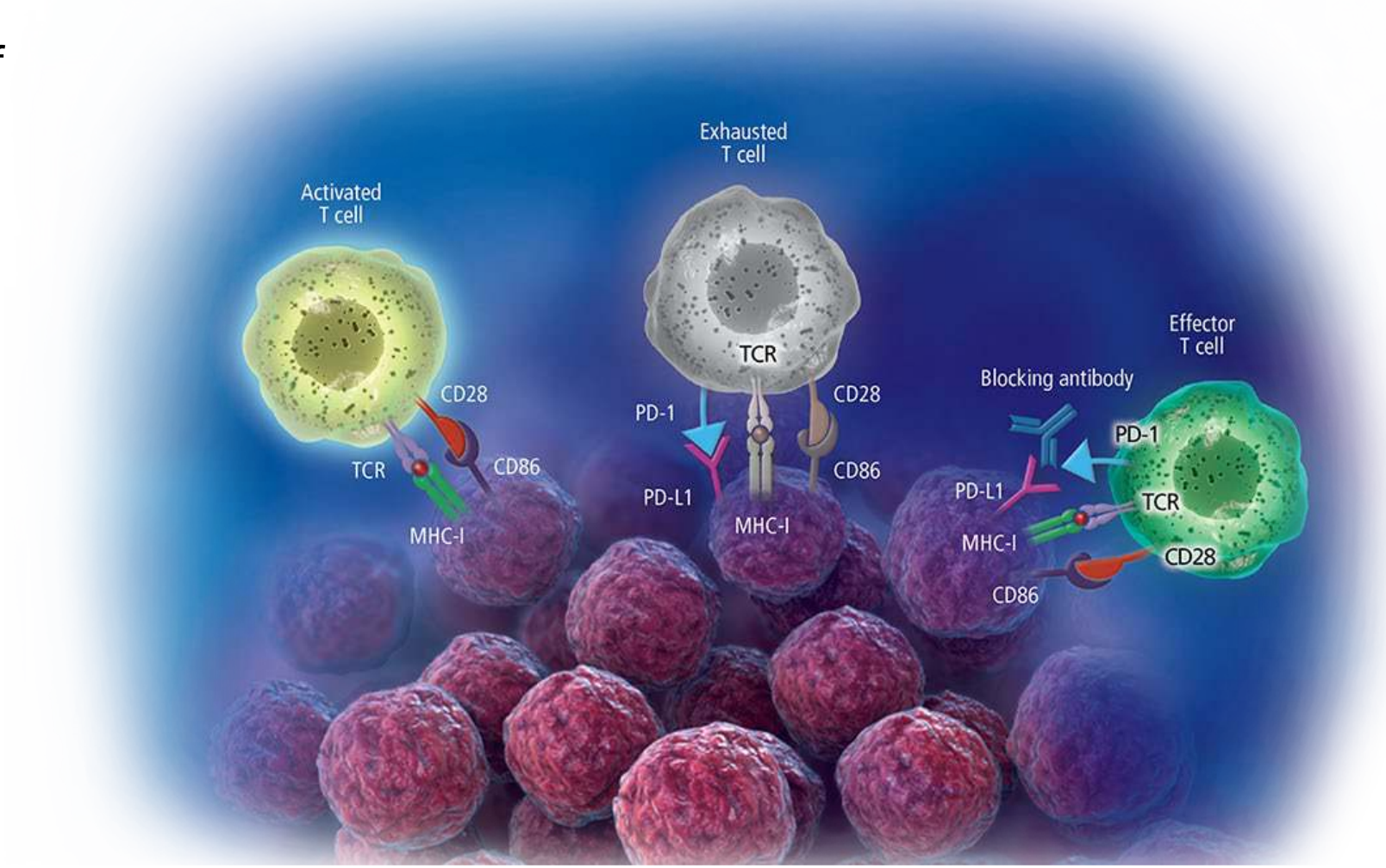
The PD-1 Pathway Is a Key Immunosuppressor in the TME

Tumor cells express high levels of PD-L1[1]

- Interaction of PD-1 with PD-L1 suppresses host immunity

Elevated PD-L1 expression levels have been observed in multiple tumor types and are associated with a poor prognosis[2]

Several anti–PD-(L)1 mAbs that block PD-1/PD-L1 interactions have been approved to treat various cancers and are used as a backbone in a number of combination trials[3,4]



mAb, monoclonal antibody; MHC, major histocompatibility complex; TCR, T cell receptor; TME, tumor microenvironment.

1. Chen L, Han X. *J Clin Invest.* 2015;125:3384-3391; 2. Wu P, et al. *PLoS One.* 2015;10:e0131403; 3. Martin-Liberal J, et al. *Cancer Treat Rev.* 2017;54:74-86; 4. Tang J, et al. *Ann Oncol.* 2018;29:84-91.

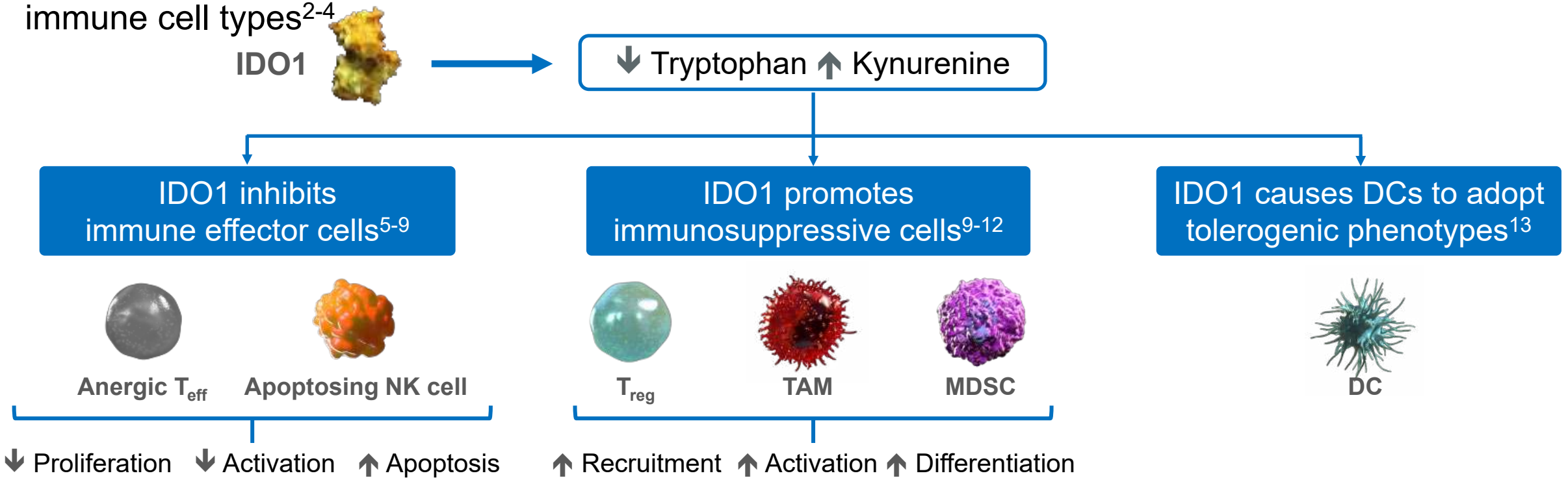
Overview of Ongoing Studies

Study	Phase	Condition	Regimen	Dosing	Status
POD1UM-303	3	Locally recurrent or metastatic SCAC	Combined with chemotherapy	375 mg Q3W	Not yet recruiting
POD1UM-304	3	Metastatic NSCLC	Combined with chemotherapy	375 mg q3w	Recruiting
POD1UM-202	2	Anal cancer	Monotherapy	500 mg q4w	Active, not recruiting Preliminary results available
POD1UM-201	2	Merkel cell carcinoma	Monotherapy	500 mg q4w	Recruiting
POD1UM-203	2	NSCLC, UC, melanoma, RCC	Monotherapy	500 mg q4w	Active, not recruiting
fight-101	1/2	Solid tumors	Combined with pemigatinib (FGFR1/2/3 inhibitor)	500 mg q4w	Recruiting
POD1UM-101	1	Solid tumors, including MSI-H endometrial cancer	Monotherapy	Various	MSI-H endometrial cancer cohort recruiting Preliminary results available
POD1UM-102	1b	Solid tumors	Combined with epacadostat (IDO1 inhibitor) or parsaclisib (PI3Kδ inhibitor)	500 mg q4w	Active, not recruiting
POD1UM-104	1b	Solid tumors (Japanese patients)	Monotherapy or combined with INCB001158 (arginase inhibitor)	500 mg q4w	Recruiting
INCB 81776-101	1	Solid tumors	Combined with INCB081776 (AXL/MER inhibitor)	500 mg q4w	Recruiting

Epacadostat MOA - IDO1 inhibitor

IDO1 catalyzes the first, rate-limiting step of tryptophan degradation in the kynurenine pathway.

In cancer, through depletion of tryptophan and production of downstream metabolites, like kynurenine, IDO1 contribute to a local immunosuppressive TME through actions on multiple immune cell types[2-4]



1. Moon YW, et al. *J Immunother Cancer*. 2015;3:51. 2. Mbongue JC, et al. *Vaccines*. 2015;3:703-729. 3. Munn DH, et al. *J Clin Invest*. 2007;117:1147-1154. 4. Brochez L, et al. *Eur J Cancer*. 2017;76:167-182. 5. Pietra G, et al. *Cancer Res*. 2012;72:1407-1415. 6. Fallarino F, et al. *Cell Death Differ*. 2002;9:1069-1077. 7. Song H, et al. *Intl Immunopharmacol*. 2011;11:932-938. 8. Frumento G, et al. *J Exp Med*. 2002;196:459-468. 9. Fallarino F, et al. *J Immunol*. 2006;176:6752-6761. 10. Brody JR, et al. *Cell Cycle*. 2009;8:1930-1934. 11. Holmgaard RB, et al. *Cell Rep*. 2015;13:412-424. 12. Zhao Q, et al. *J Immunol*. 2012;188:1117-1124. 13. Mellor AL, et al. 2017. *Front Immunol*. 2017;8:1360.

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Epacadostat – IDO1 (indoleamine 2,3-dioxygenase 1) Inhibitor

Epacadostat Was Shown To Be a Potent, Highly Selective Inhibitor of the IDO1 Enzyme in Preclinical Studies[1]

- Epacadostat was more selective for IDO1 than for IDO2 or TDO (both IC50 >5,000 nM)[1]

Epacadostat Reduced Kynurenine Levels in the TME, Plasma and Lymph Nodes in Mouse Model[2]

- In tumor-bearing mice, epacadostat reduced Kyn levels by 78–87% in all three tissues

Epacadostat reverses the tryptophan/kynurenine ratio, thereby[3-5]:

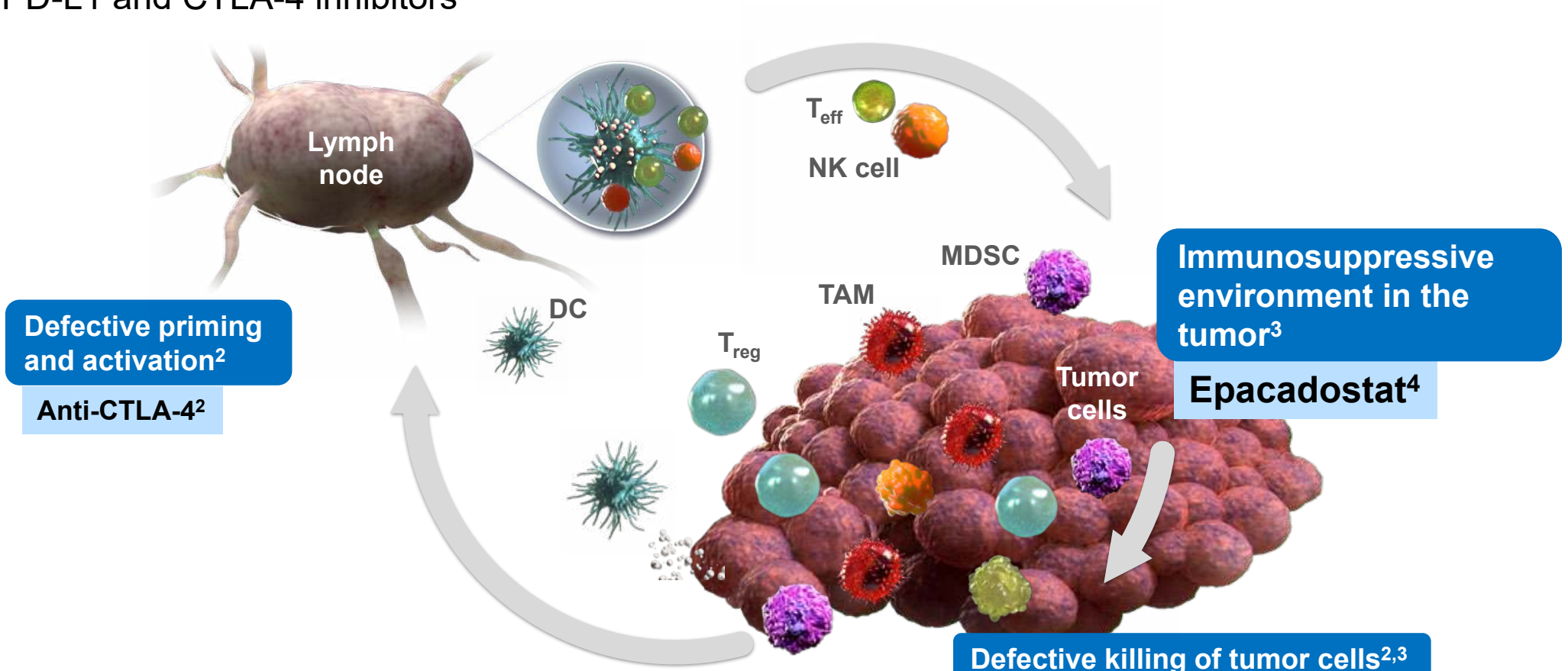
- Decreases activity of immunosuppressive cells such as Treg -> removing the local mediated immune suppression.
- Increased activity of dendritic cells, Teff and NK cells -> enabling the immune system to locally attack the tumor through

Epacadostat helps disrupt IDO1-mediated immunosuppression in the TME[3,6,7]

1. Liu X, et al. Blood. 2010;115:3520-3530. 2. Koblish HK, et al. Mol Cancer Ther. 2010;9;489-498. 3. Liu X, et al. Blood. 2010;115:3520-30; 4. Jochems C, et al. Oncotarget. 2016;7:37762-72;
5. Koblish HK, et al. Mol Cancer Ther. 2010;9;489-98; 6. Munn DH, et al. J Clin Invest. 2007;117:1147-54; 7. Timosenko E, et al. Immunotherapy. 2017;9,83-97.

Rationale for Combination Treatment with Epacadostat

The role of epacadostat in regulating the TME away from an immunosuppressive state provides the rationale for investigating its use with anti-cancer treatments that have complementary modes of action, such as PD-1/PD-L1 and CTLA-4 inhibitors[1]



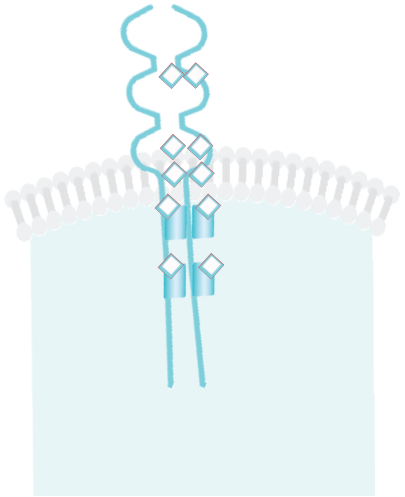
1. Jochems C, et al. *Oncotarget.* 2016;7:37762-37772. 2. Chen DS, Mellman I. *Immunity*. 2013;39:1-10.
3. Wu AA, et al. *Oncoimmunology*. 2015;4:e1016700. 4. Liu X, et al. *Blood*. 2010;115:3520-3530.

Pemigatinib - FGFR Inhibitor

Pemigatinib (INCB054828) is an inhibitor of the FGFR family of receptor tyrosine kinases that is proposed for the treatment of malignant diseases

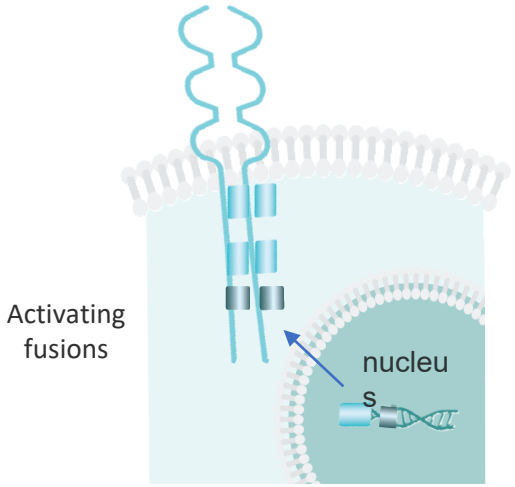
Activating mutations

Leading to constitutive activation of the kinase domain or ligand-independent receptor dimerization



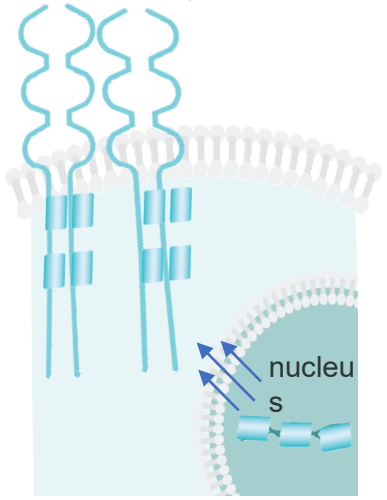
Chromosomal rearrangements

e.g. Translocations resulting in gene fusions that allow ligand-independent receptor dimerization



Gene amplification

Inducing protein overexpression, receptor accumulation and activation of downstream signaling pathways



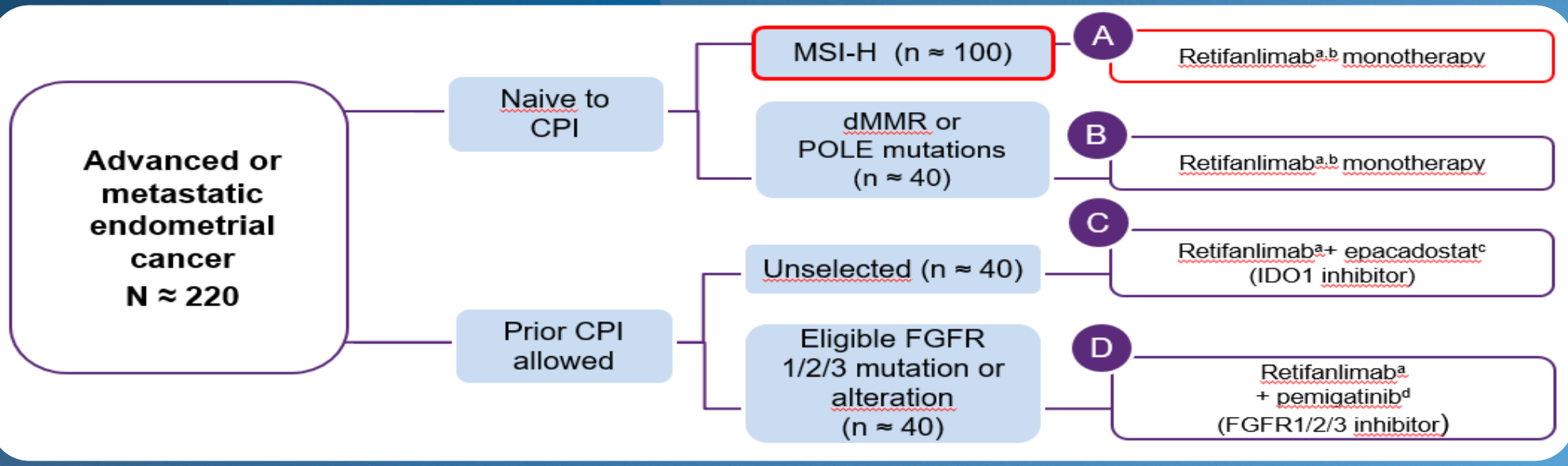
Genetic alterations in *FGFR*s or *FGF*s leading to dysregulated signal transduction can stimulate tumor cell proliferation, angiogenesis, metastasis, and survival[2]
These alterations have been shown in preclinical models to be driver mutations

FGFR2 mutation is associated with more aggressive disease and FGFR2 mutations were more common in patients initially diagnosed with Stage III/IV endometrial cancer. Patients with FGFR2 mutation had significantly shorter PFS and OS. Therefore, the combination of an FGFR inhibitor may provide added benefit to a checkpoint inhibitor.

PODIUM 204
PD1 Clinical Program in Multiple Malignancies

GOG3038/ENGOT-en12

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

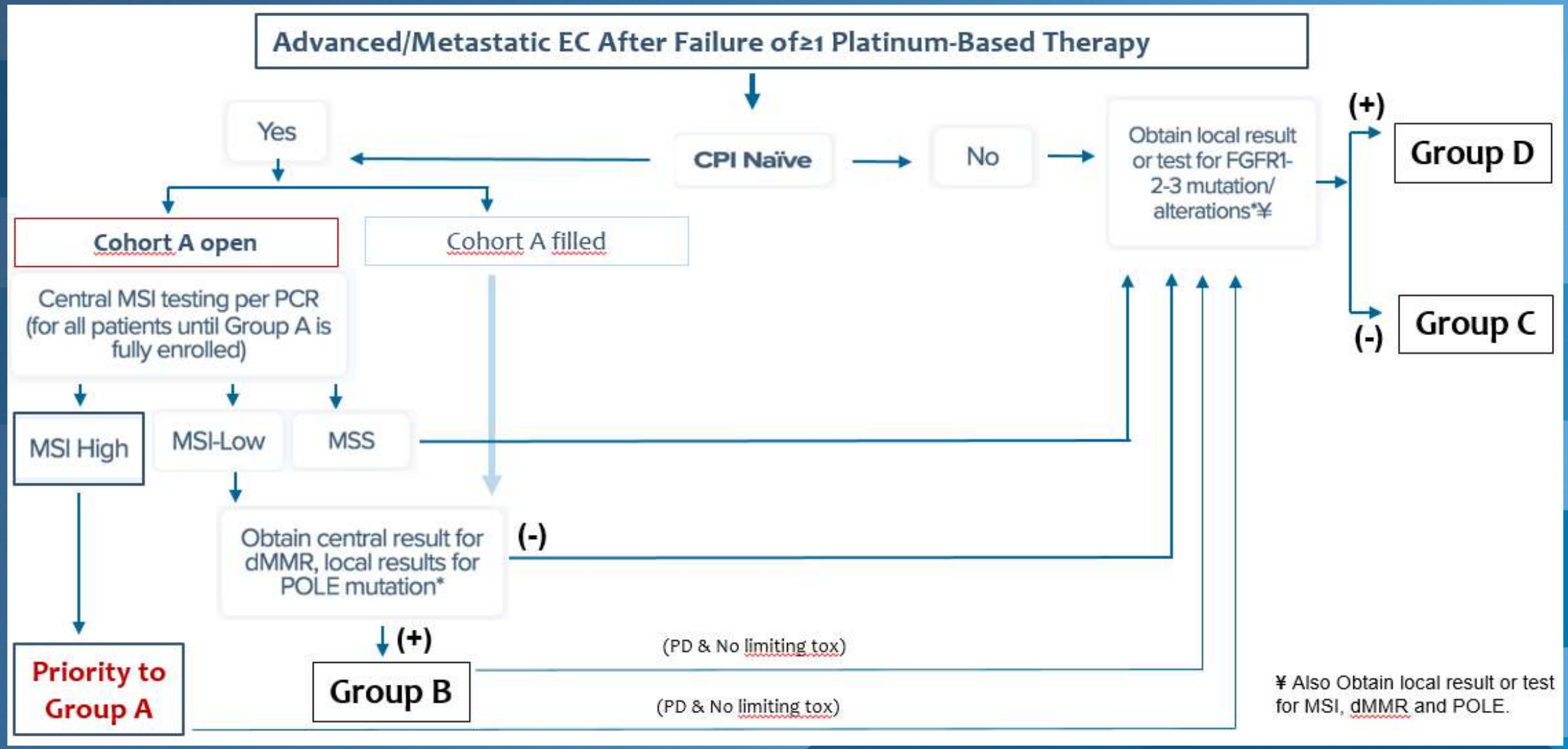
- Histologically confirmed diagnosis of sarcoma of the uterus
- Toxicity of prior therapy that has not recovered to < grade 1
- Active autoimmune disease requiring systemic immunosuppression with corticosteroids or immunosuppressive drugs within 14 days before the first dose of study treatment
- Known 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

Slomovitz BM, et al. SITC 2020 [poster 644];

Patient Enrollment Decision Diagram



Testing Scenarios to consider

CPI naive patient that has MSS results confirmed by local test -> no need to test centrally, patient considered not eligible for Group A.

CPI naive patient that has pMMR results confirmed by local test -> advise the site to test centrally for MSI (discordance between MMR/MSI is not rare).

CPI naive patient that has dMMR results confirmed by local test -> advise the site to test centrally for MSI – Group A is a priority.

CPI naive patient with locally obtained MSI-H results -> patient should have MSI test confirmed centrally (companion diagnostic).

Note: For CPI naive patients decisions for MSI/MMR testing have to be considered also in context of any possible exclusion criteria (eg. CPI naive patient with carcisosarcoma diagnosis will not be testes for MSI/MMR as carcinosarcoma histology is an exlusion criterion for Group A and B.

CPI treated patient with known/unknown MSI/MMR status -> patient can be considered for Group C, locally obtained MMR/MSI/POLE results to be recorded in eCRF. Until Group D is open for enrollment no need to perform FGFR test.

GOG 3039
A Phase II Study of Abemaciclib in Combination with Letrozole in Advanced, Recurrent or Metastatic Endometrioid Endometrial Cancer

Study Chair: Marilyn Huang, MD
Co-study Chairs: Gloria Huang, MD
Brian Slomovitz, MD, MS

ClinicalTrials.gov Identifier: NCT04393285

Sponsors: GOG Foundation/Lilly

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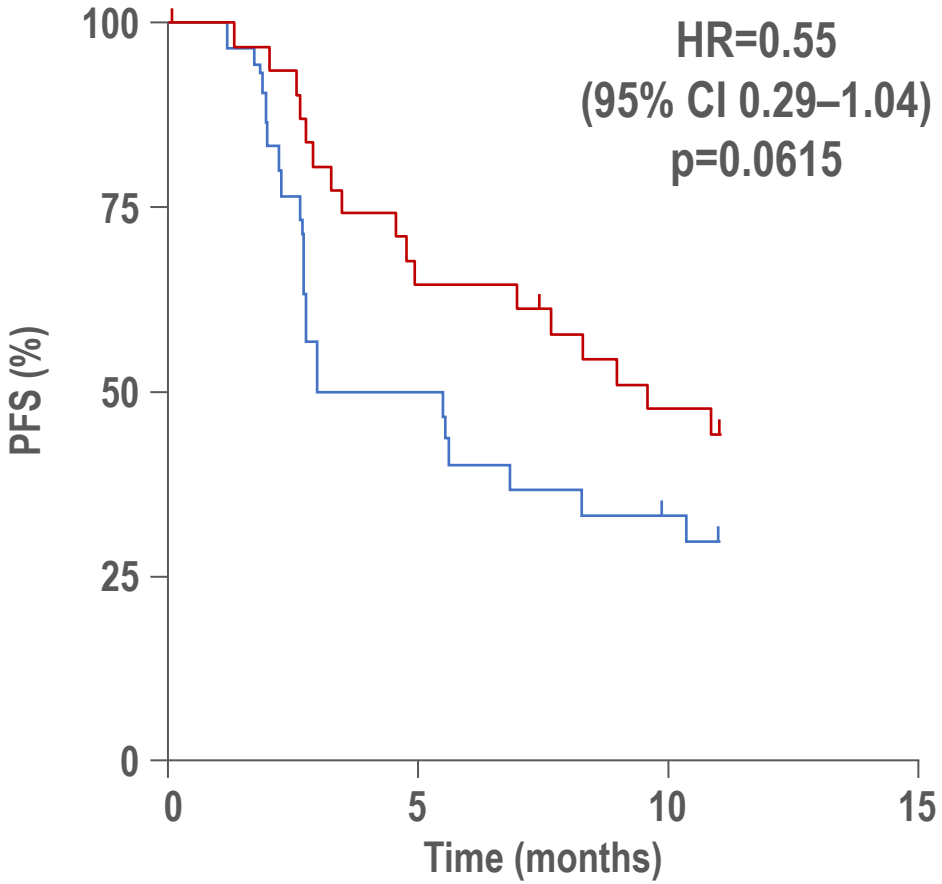
Background

- Hormonally driven malignancies are known to have actionable therapeutic targets.
- CDK 4/6 inhibitors induce cell-cycle arrest via G1 to S cell cycle checkpoint
- Cyclin D/CDK complex is downstream of estrogen signaling, representing potential synergic antitumor activity when combined with aromatase inhibitor.

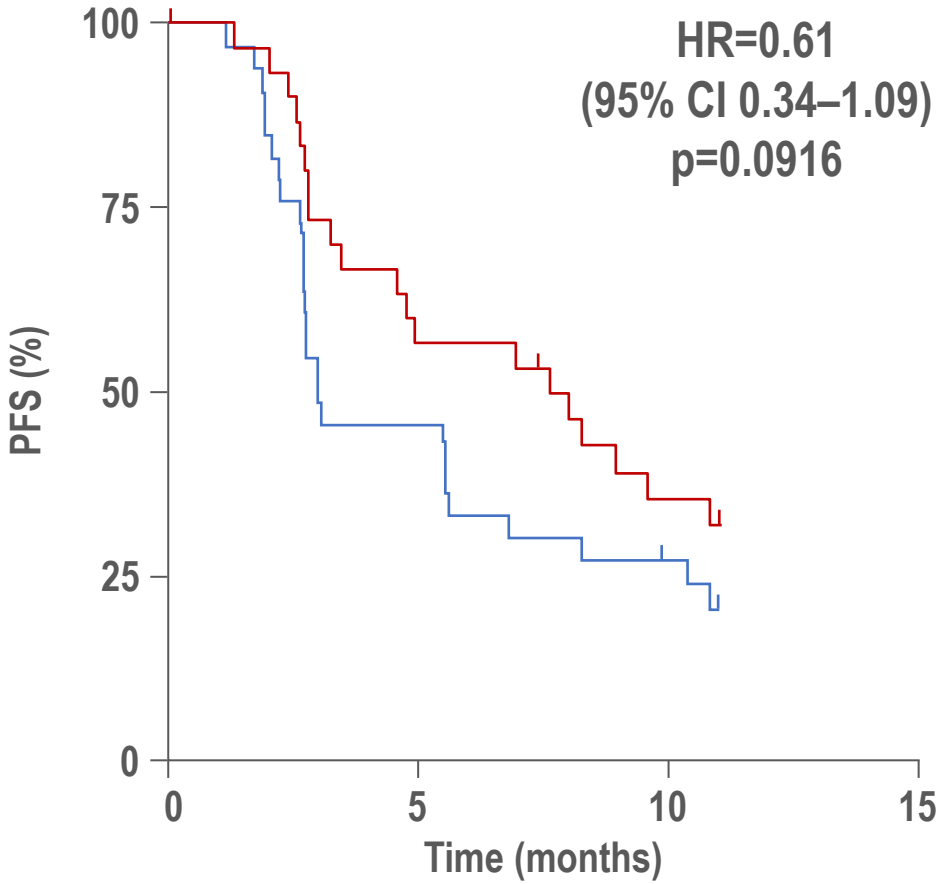
PFS by stratification factors

No prior MPA/megestrol acetate



Number at risk			
Palbociclib + letrozole	32	20	14
Placebo + letrozole	30	15	9

Patients with relapsed disease



Number at risk			
Palbociclib + letrozole	31	17	10
Placebo + letrozole	33	15	8

Schema

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

Abemaciclib 150mg PO BID

+

Letrozole 2.5mg PO Daily

28- Day Cycle Until Progression or Toxicity

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Objectives

Primary: to determine the objective response rate in patients with advanced, persistent, or recurrent endometrioid endometrial cancer.

Secondary: to estimate time to disease progression.

- To describe toxicities of combination therapy

Key Eligibility Criteria

- Advanced (FIGO 2014 Stage III or IV), persistent, or recurrent endometrial carcinoma
- Must have endometrioid histology (all grades allowed) (Hormone receptor status is not required for enrollment).
- Must have measurable disease by RECIST v1.1.
- Prior chemotherapy in the adjuvant setting for Stage I, II, or III is permitted.
- Prior chemoradiotherapy for a pelvic recurrence is permitted.
- Regardless of circumstances, no more than one prior chemotherapy regimen (including chemo-radiotherapy) is permitted.
- ECOG performance status of 0 to 1.