Brian Slomovitz

- Immunotherapy combinations in the future

Immunotherapy combinations in the future

Brian M. Slomovitz, MD, MS, FACOG

Director, Gynecologic Oncology, Mount Sinai Medical Center, Miami Beach

Professor, Florida International University

Member, Board of Directors, GOG Foundation

Clinical Trial Lead, Uterine Cancer, GOG-Partners Foundation

bslomovitz@gog.org

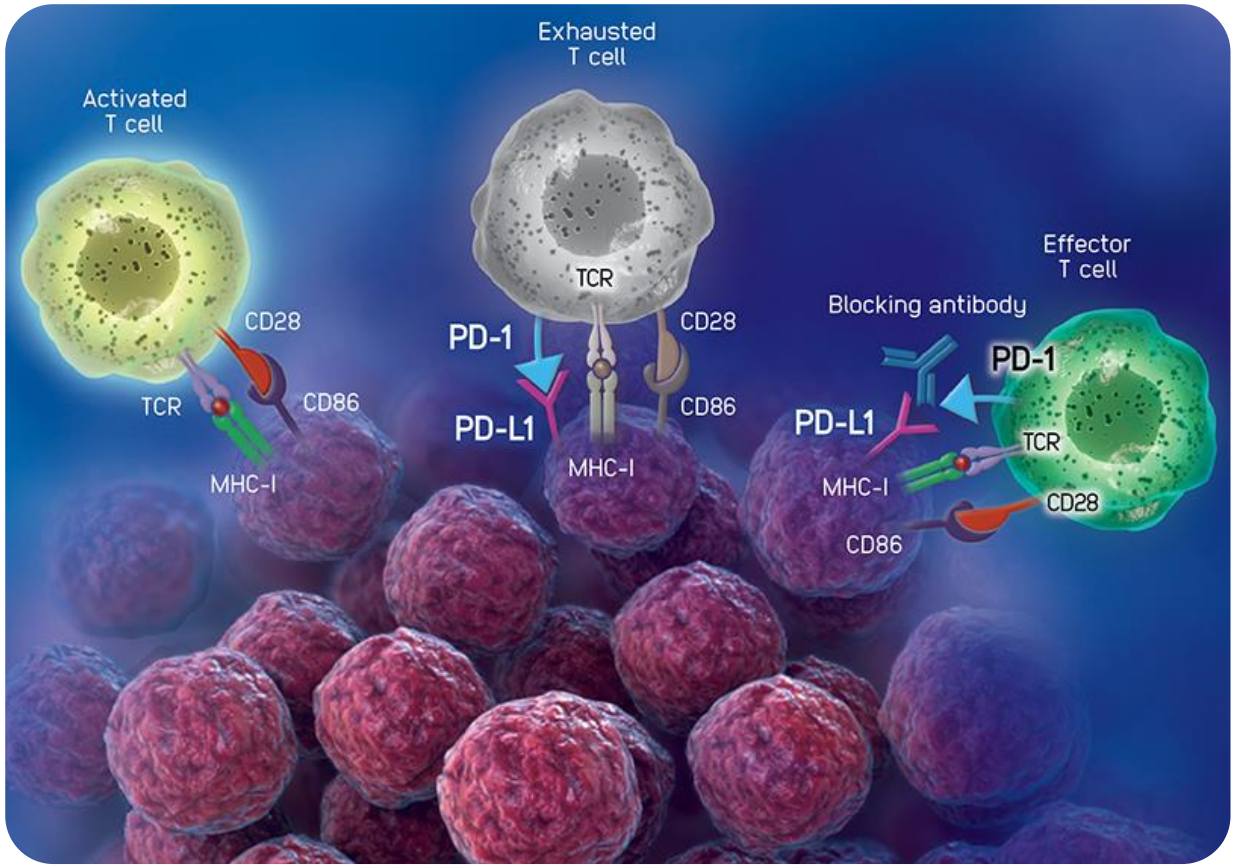
Disclosures

- **GOG Foundation**
- **Merck**
- **Astra-Zeneca**
- **Seagen**
- **Clovis**
- **GSK**
- **Genentech**
- **Myriad**
- **Incyte**

The combination of targeting with PD/PDL-1 and molecularly targeted agents against known biological processes in endometrial tumors is hypothesized to more comprehensively deliver improved clinical benefit.

The PD-1 Pathway Is a Key Immunosuppressor in the Tumor Microenvironment

- The PD-1 immune checkpoint is a negative regulator of T-cell activity through its interaction with its 2 ligands, PD-L1 and PD-L2[1-3]
- Activation of PD-1 can reduce effector T-cell function[1-3]
- High PD-L1 expression, which suppresses host immunity, has been observed in multiple tumor types and is associated with a poor prognosis[4]

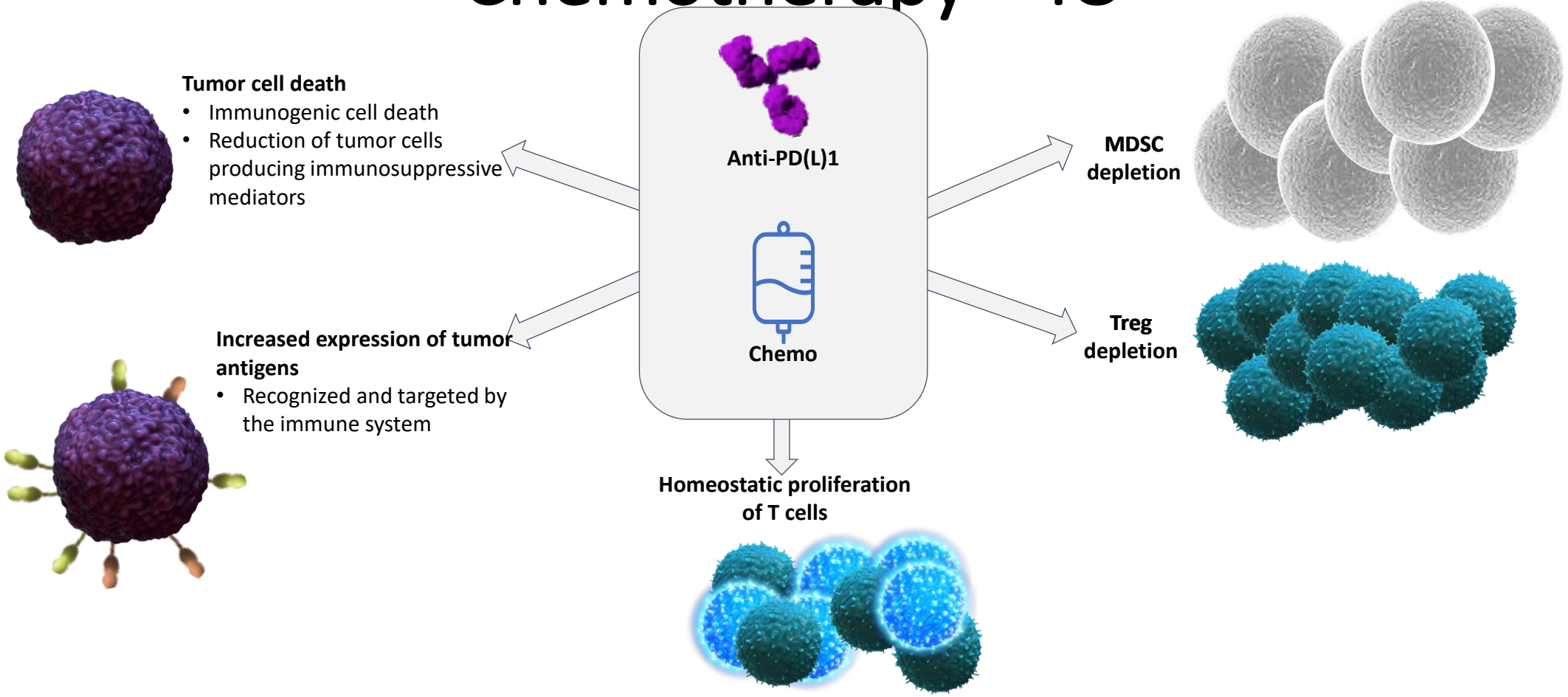


Adapted from McDermott DF, Atkins MB. *Cancer Med.* 2013;2(5):662-673.

CD, cluster of differentiation; MHC, major histocompatibility complex; TCR, T-cell receptor.

1. McDermott DF, Atkins MB. *Cancer Med.* 2013;2:662-673. 2. Zheng P, Zhou Z. *Biomark Cancer*. 2015;7:S15-18. 3. Chen L, Han X. *J Clin Invest.* 2015;125:3384-3391. 4. Wu P, et al. *PLoS One*. 2015;10:e0131403.

Rational for Combinatorial Approach with Chemotherapy + IO



Chemo, chemotherapy; ICI, immune checkpoint inhibitors; IO, immunotherapy; MDSC, myeloid-derived suppressor cell; Treg, regulatory T cells.

1. Hato SV et al. *Clin Cancer Res.* 2014. 2. Chen Y et al. *Am J Cancer Res*. 2021. 3. Pfannenstiel T et al. *Cell Immunol*. 2010. 4. Sevko A et al. *J Immunol*. 2013.

Combination Checkpoint Inhibitor Studies in Advanced/Recurrent Endometrial Cancer

Checkpoint Inhibitors Plus Antiangiogenic Agents

KEYNOTE-146[1]

KEYNOTE-775 (phase III)[2]

ENGOT-en9/LEAP-001 (phase III)[3]

Pembrolizumab + Lenvatinib

NCT03367741[4]:

Nivolumab + Cabozantinib

Checkpoint Inhibitors Plus Chemotherapy

NRG-GY018[5]:

Pembrolizumab + Paclitaxel/Carboplatin

AtTEnd/ENGOT-en7[6]:

Atezolizumab + Paclitaxel/Carboplatin

RUBY (ENGOT-EN6; GOG-3031)[7]:

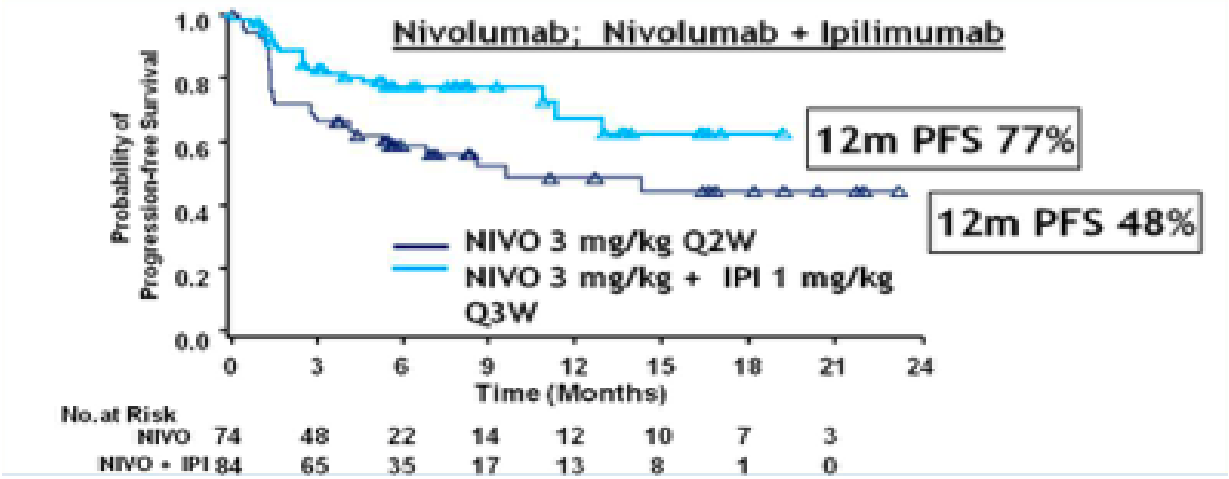
Dostarlimab + Chemotherapy

. Makker. JCO. 2020; 38: 2981. 2. NCT03517449. 3. NCT03884101. 4. NCT03367741. 5. NCT03914612. 6. NCT03603184. 7. NCT03981796

Dual blockade with anti PD1/CTLA4 therapy is superior to anti-PD1 monotherapy in dMMR CRC

CheckMate 142
Nivolumab with low dose Ipilimumab vs Nivolumab alone

- ORR 46% vs. 28%
- Response > 6 mo
  - 89% vs. 67%
- Data support synergistic activity
- Regimen well tolerated
- Rate of adverse events 32%
- FDA just approved Nivo/Ipi in dMMR mCRC

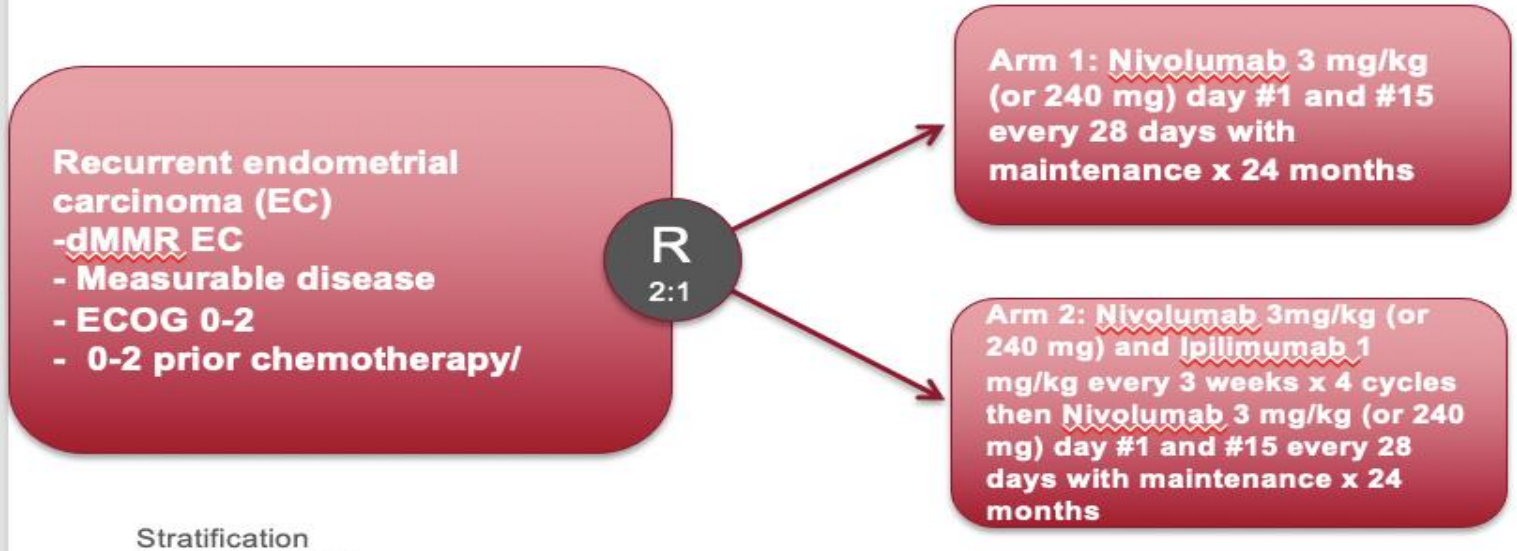


Overman et al 2017 Lancet Oncology; Overman et al 2018 JCO

Dual CPI

NRG-GY025

Design and Schema



Stratification
1. Prior radiation
2. Prior PD1 exposure
3. Evaluable vs. measurable disease

NRG ONCOLOGY™

AFT-50 EndoMap: A Phase IB/II Multi-Cohort Study of Targeted Agents With Atezolizumab for Patients With Recurrent or Persistent Endometrial Cancer (NCT04486352)

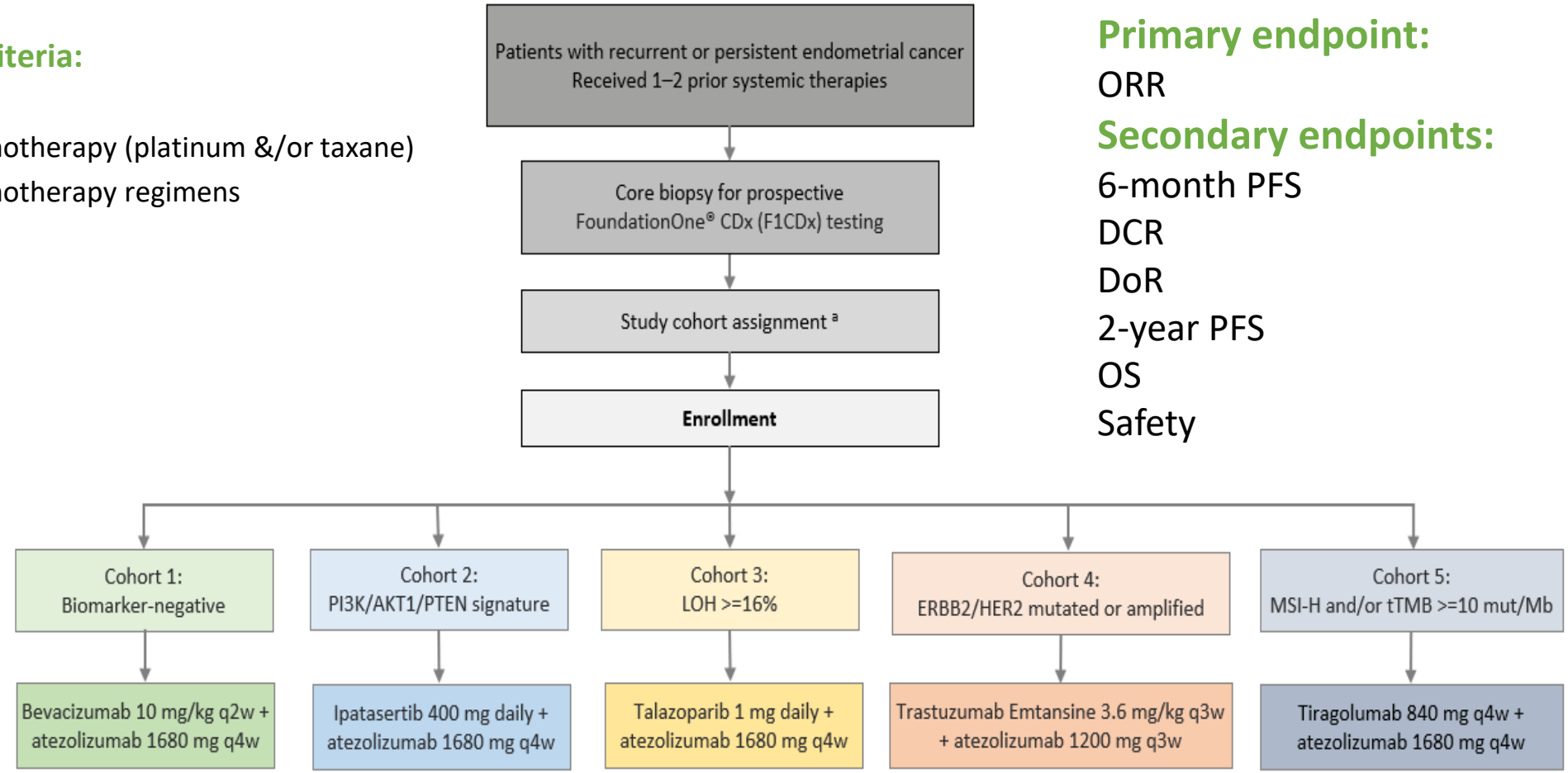
Eligibility criteria:

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
PI: B Slomovitz, Co-PI: E Cantillo, A Secord, J Moroney, E Alvarez

AFT-50
Study Goals & Obligations – **Design**

- This is a Phase IB/II multi-cohort study designed to evaluate the efficacy and safety of targeted agents plus cancer immune checkpoint therapy with atezolizumab in patients with recurrent and/or persistent endometrial cancer.
- The study provides a platform whereby patients will be placed into study cohorts evaluating atezolizumab plus a targeted agent, selected on the basis of the tumor’s specific genomic profile.

Study Goals & Obligations

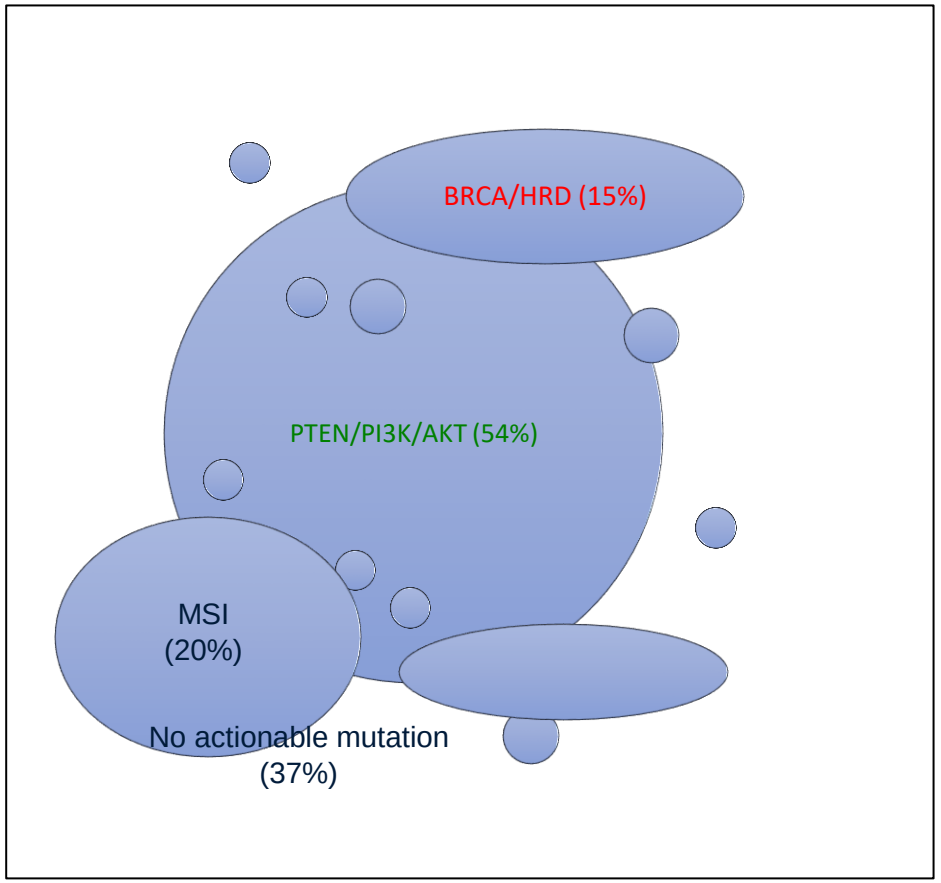
Primary Objective

To evaluate the investigator-assessed overall response rate (ORR) of each biomarker cohort

Eligibility – **Inclusion** Criteria

- Recurrent or persistent endometrial carcinoma which has progressed or recurred after at least 1, but no more than 2, prior lines of therapy. Prior therapies may include chemoradiation, chemotherapy and/or biologic therapy, maintenance/consolidation therapy) for the treatment of endometrial cancer. radiosensitizer will be counted as a systemic therapeutic regimen.
- **Prohibits prior I/O**
- May eventually have to be updated based on RUBY, GY018, DUO-E
- Allows for carcinosarcomas

Actionable mutations occur at different frequencies



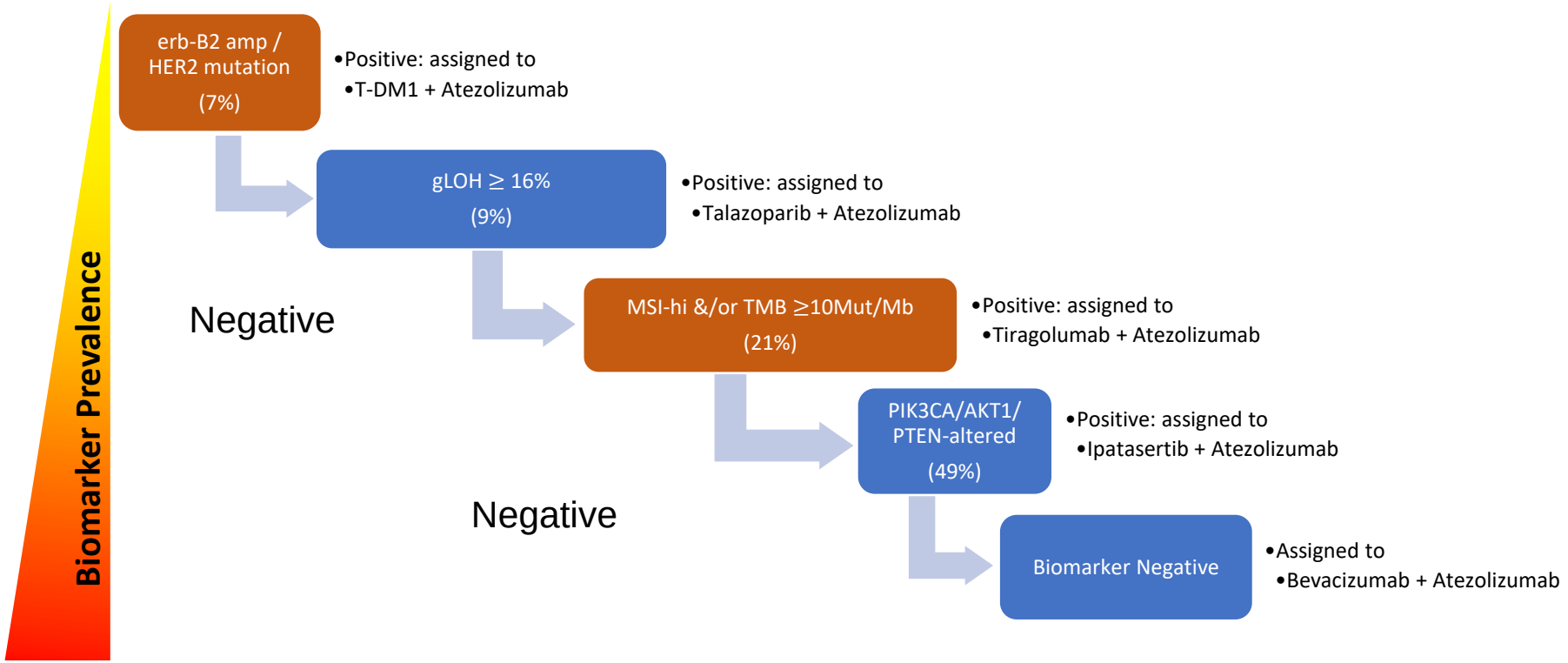
Potential Biomarker Overlap*
- **PI3K:Clovis-15 ~ 9%**

* Internal GNE data

- Treatment arm assignment will be weighted to favor the less prevalent mutation
- Projected # of patients to be screened to fill all treatment arms: ~120 patients

Biomarkers for Cohort Assignment

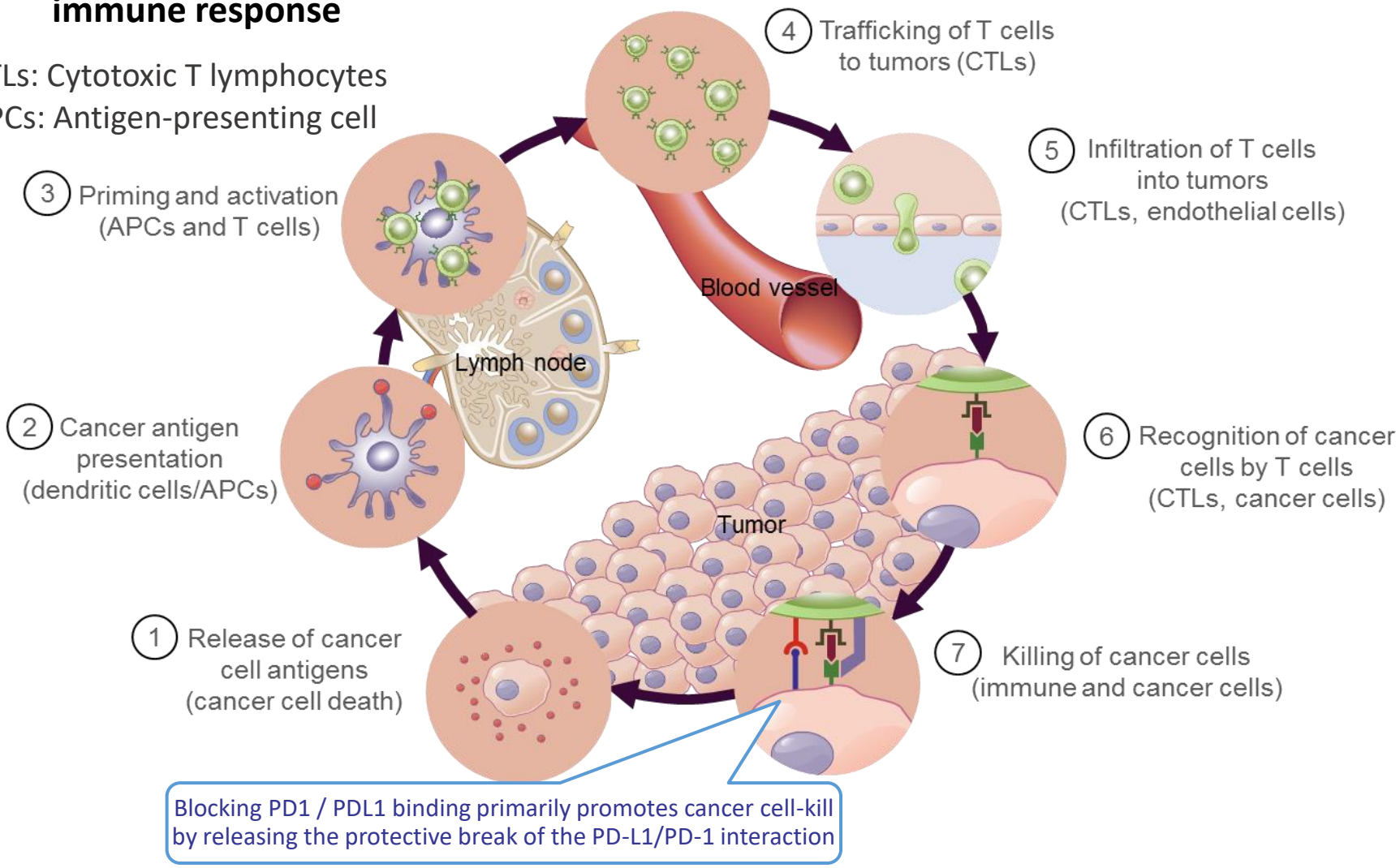
- All patients tumors undergo a prospective testing with the FoundationOne® CDx assay
- Ipatasertib + Atezolizumab: *PIK3CA/AKT1/PTEN*-altered tumors
- Talazoparib + Atezolizumab: Tumors with genomic LOH ≥16%
  - gLOH ≥16% will be used as a surrogate for HRD
- Tiragolumab + Atezolizumab: Tumors that are MSI-Hi &/or have a tumor mutational burden (TMB) ≥10 Mut/Mb
- T-DM1 + Atezolizumab: Tumors with amplified &/or mutated *erb-B2/*HER2
- Bevacizumab + Atezolizumab: Tumors negative for the alterations listed above



Cancer-Immunity Cycle

A series of stepwise events occur and expand iteratively for a successful antitumor immune response

CTLs: Cytotoxic T lymphocytes
APCs: Antigen-presenting cell

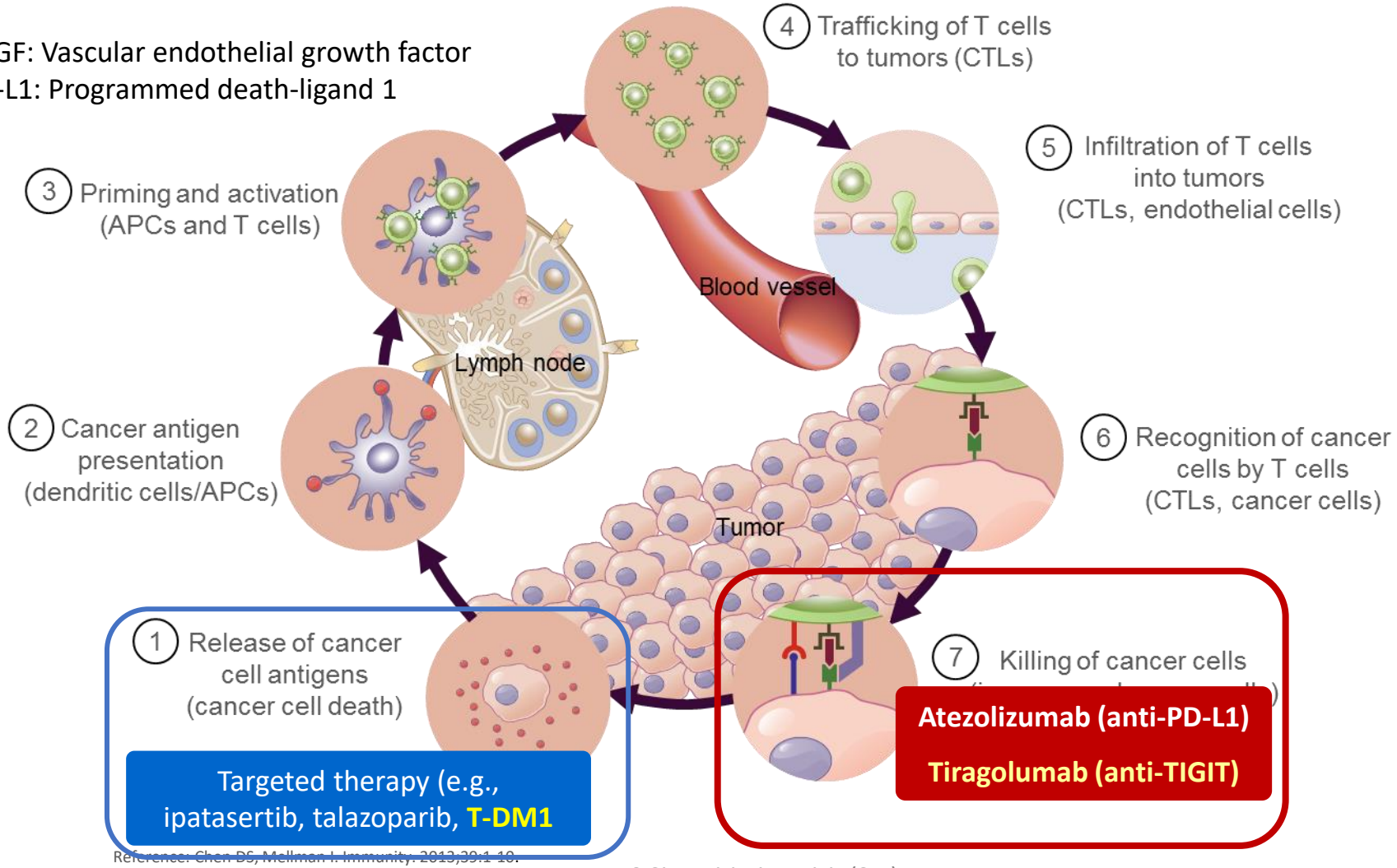


ALLIANCE FOUNDATION TRIALS

Cancer-Immunity Cycle:

Rationale for combinations with atezolizumab

VEGF: Vascular endothelial growth factor
PD-L1: Programmed death-ligand 1

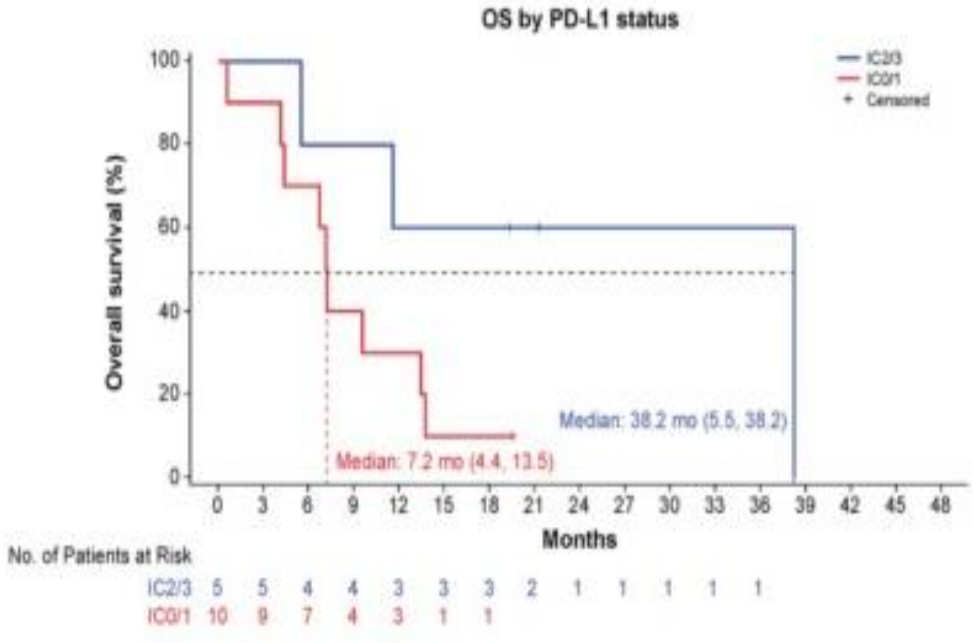


Reference: Chen DS, Mellman I. Immunity. 2013;39:1-10.

Atezolizumab monotherapy has clinical activity in EC

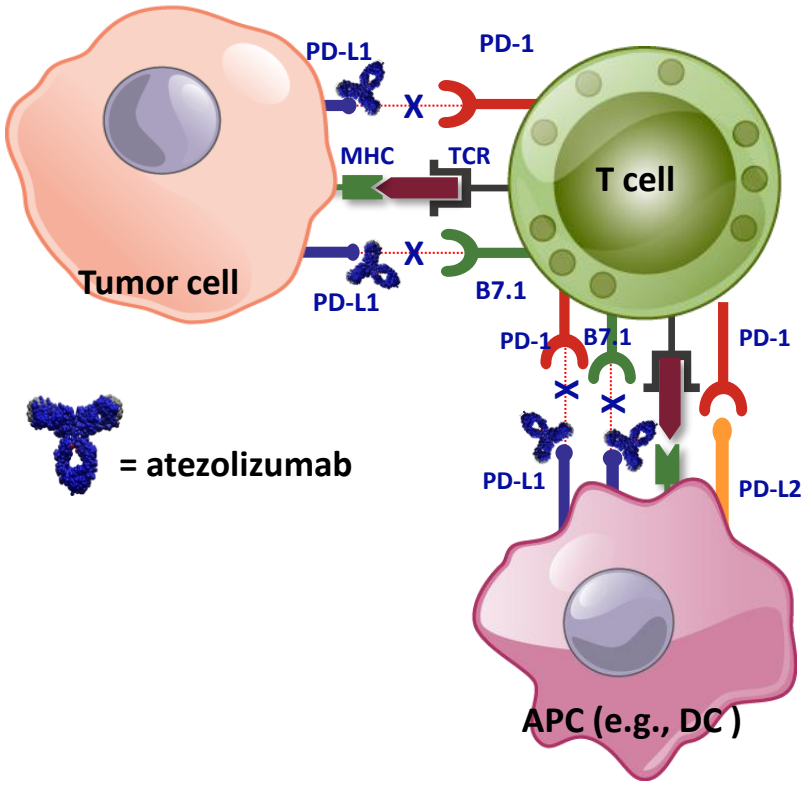
	IC0/1 (n=10)	IC2/3 (n=5)	All patients (n=15)
ORR per RECIST, n (%) (95% CI)	0 (0, 30.9)	2 (40.0) (5.3, 85.3)	2 (13.3) (1.7, 40.5)
CR PR SD PD NE	0 0 1 (10.0) 7 (70.0) 2 (20.0)	0 2 (40.0) 1 (20.0) 2 (40.0) 0	0 2 (13.3) 2 (13.3) 9 (60.0) 2 (13.3)
Disease control rate, n (%)	0	2 (40.0)	2 (13.3)
Median PFS (95% CI), mon	1.4 (1.3–1.7)	4.2 (1.2–NE)	1.4 (1.3–4.0)
1y PFS (95% CI), mon	NE	20.0 (0, 55.1)	6.7 (0, 19.3)
Median OS (95% CI), mon	7.2 (4.4–13.5)	38.2 (5.5–38.2)	9.6 (6.8–13.8)
1y OS (95% CI), mon	30.0 (1.6, 58.4)	60.0 (17.1, 100.0)	40.0 (15.2, 64.8)

PCD4989g: Phase Ia atezolizumab in advanced/recurrent EC



Liu JF *et al.*, Gyn Onc 2019

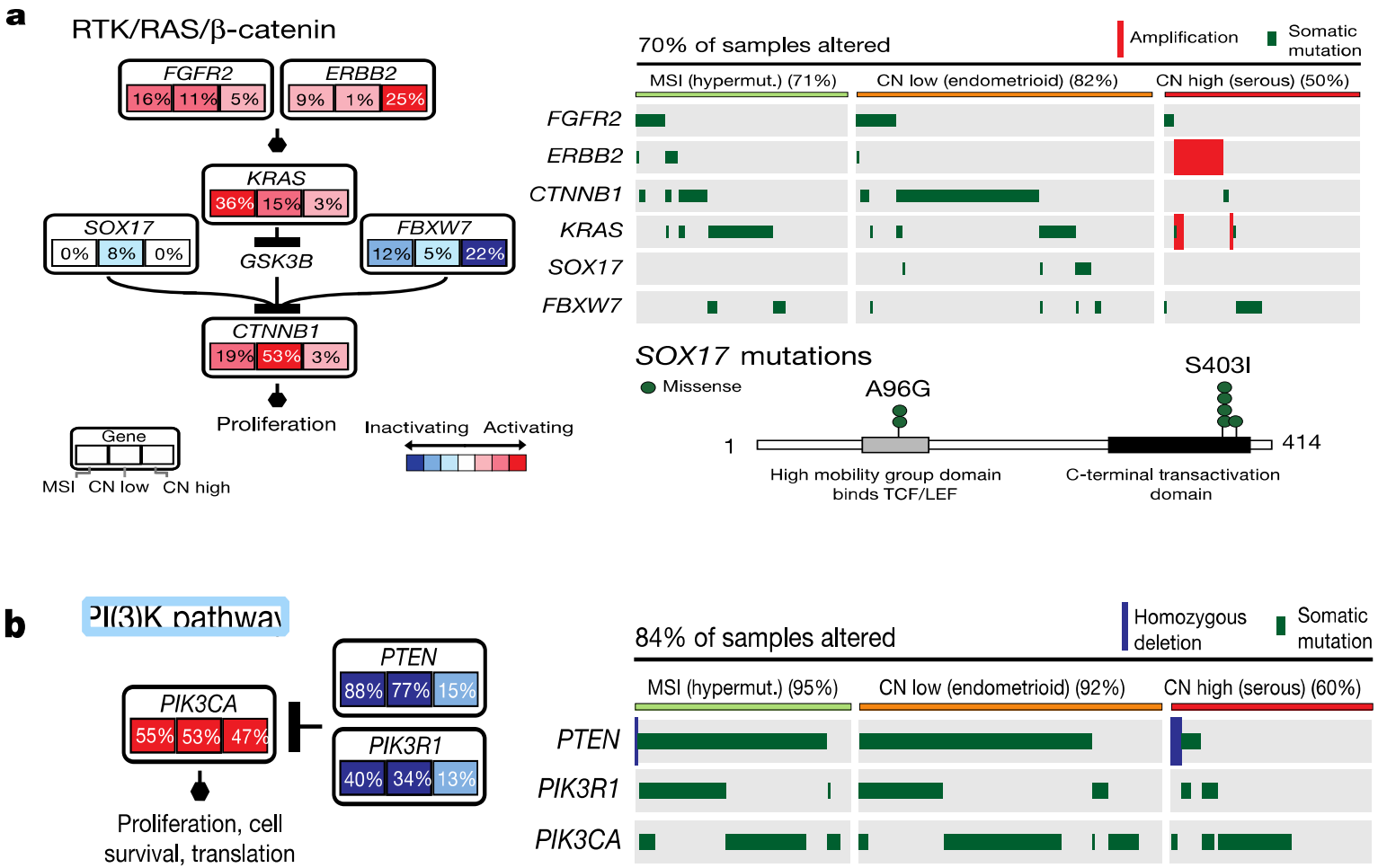
Atezolizumab



- Restores Antitumor T-Cell Activity
- Humanized anti–PD-L1 monoclonal antibody
- Inhibits PD-L1 from binding to PD-1 and B7.1 CD80, on activated T cells, thus relieving immune suppression and promoting an antitumor response[1,4,5]
- Currently approved in urothelial cancer, NSCLC and small cell lung cancer (SCLC), triple negative breast cancer (TNBC), and HCC
- Associated risks include - infusion-related reactions; immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypo/hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, and myositis.

1. Chen DS, et al. Clin Cancer Res 2012;18:6580-6587. 2. Brown JA, et al. J Immunol 2003;170:1257-1266.
3. Park JJ, et al. Blood 2010;116:1291-1298. 4. Herbst RS, et al. Nature 2014;515:563-567. 5. Zou W, Chen L. Nat Rev Immunol 2008;8:467-477.

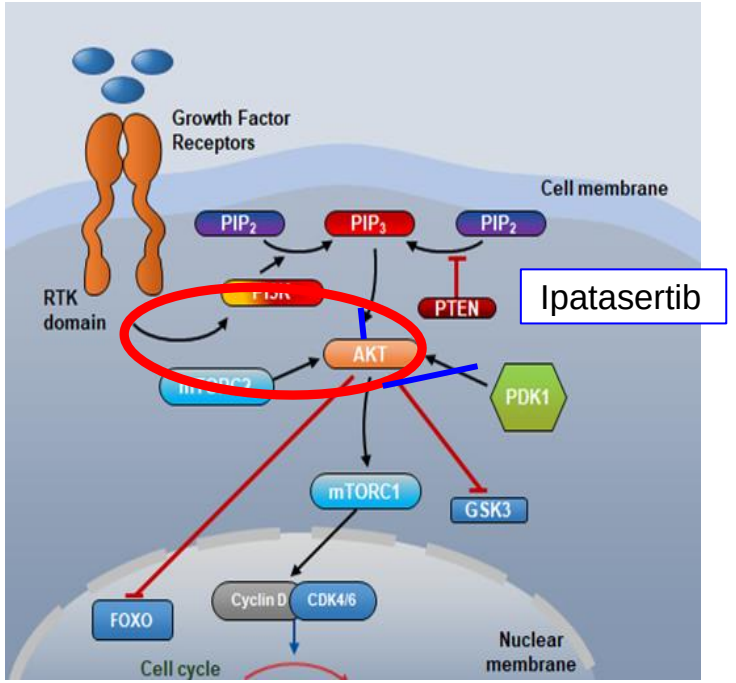
Endometrial cancers harbor multiple actionable mutations



TCGA, Nature 2013

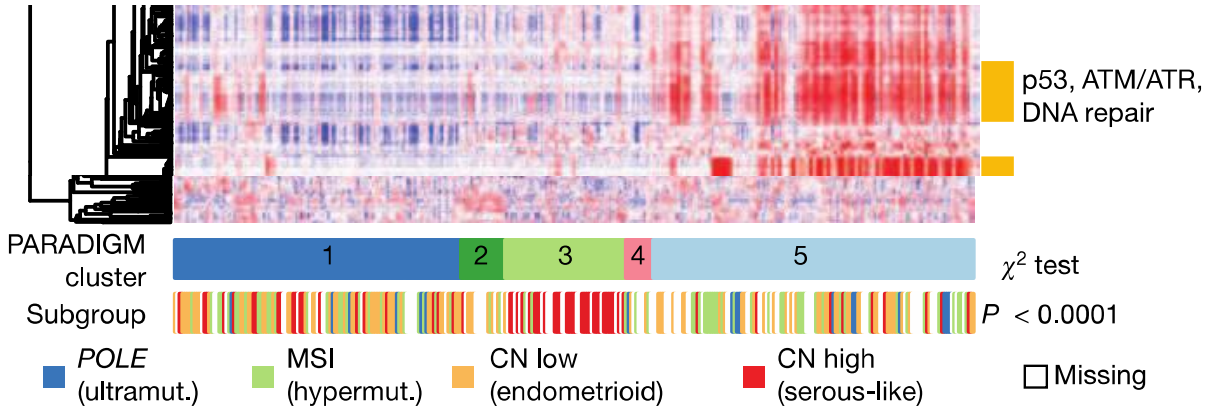
Ipatasertib

- Ipatasertib is an oral, selective ATP-competitive AKT inhibitor
- Activated AKT regulates downstream signals (e.g., mTOR) and increases cell growth & survival
- Ipatasertib decreases growth & proliferation in cancer cell lines & xenografts, including those with PTEN-loss, oncogenic *PIK3CA* mutations, HER2 amplification
- Associated Risks: nausea, vomiting, diarrhea, stomatitis/mucosal inflammation, asthenia/fatigue, hyperglycemia, erythema multiforme, and rash
- Potential Risks: hematologic or immunosuppressant effects, hyperlipidemia, hepatotoxicity, pneumonitis, colitis, and developmental toxicity
- Potential overlapping toxicities with atezolizumab: gastrointestinal, dermatologic, hepatic, pulmonary, and hyperglycemia events

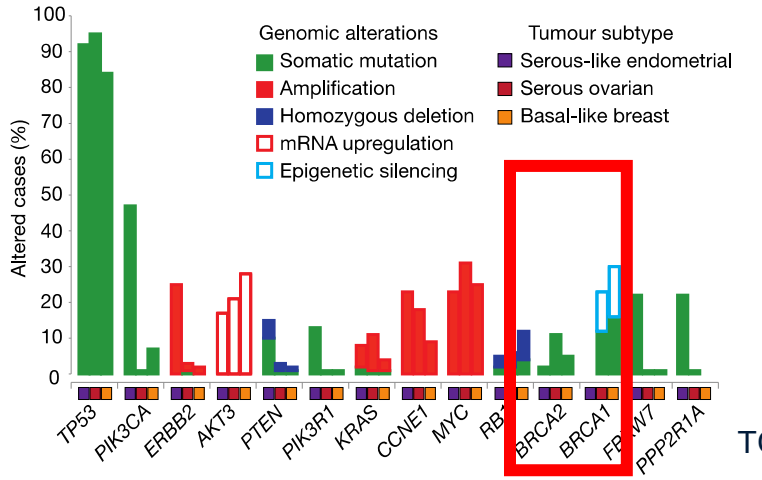


Blake JF, et al. *J Med Chem*. 2012;55:8110-8127.; Brown JS, Banerji U. *Pharmacol Ther*. 2017;172:101-115.; Lin K, et al. *Sci Signal. 2012;5:ra37.* Yan Y, et al. *Clin Cancer Res. 2013;19(24):6976-6986.*

Homologous Recombination (incl. BRCA1/2) alterations in EC



Candidates for PARP inhibition



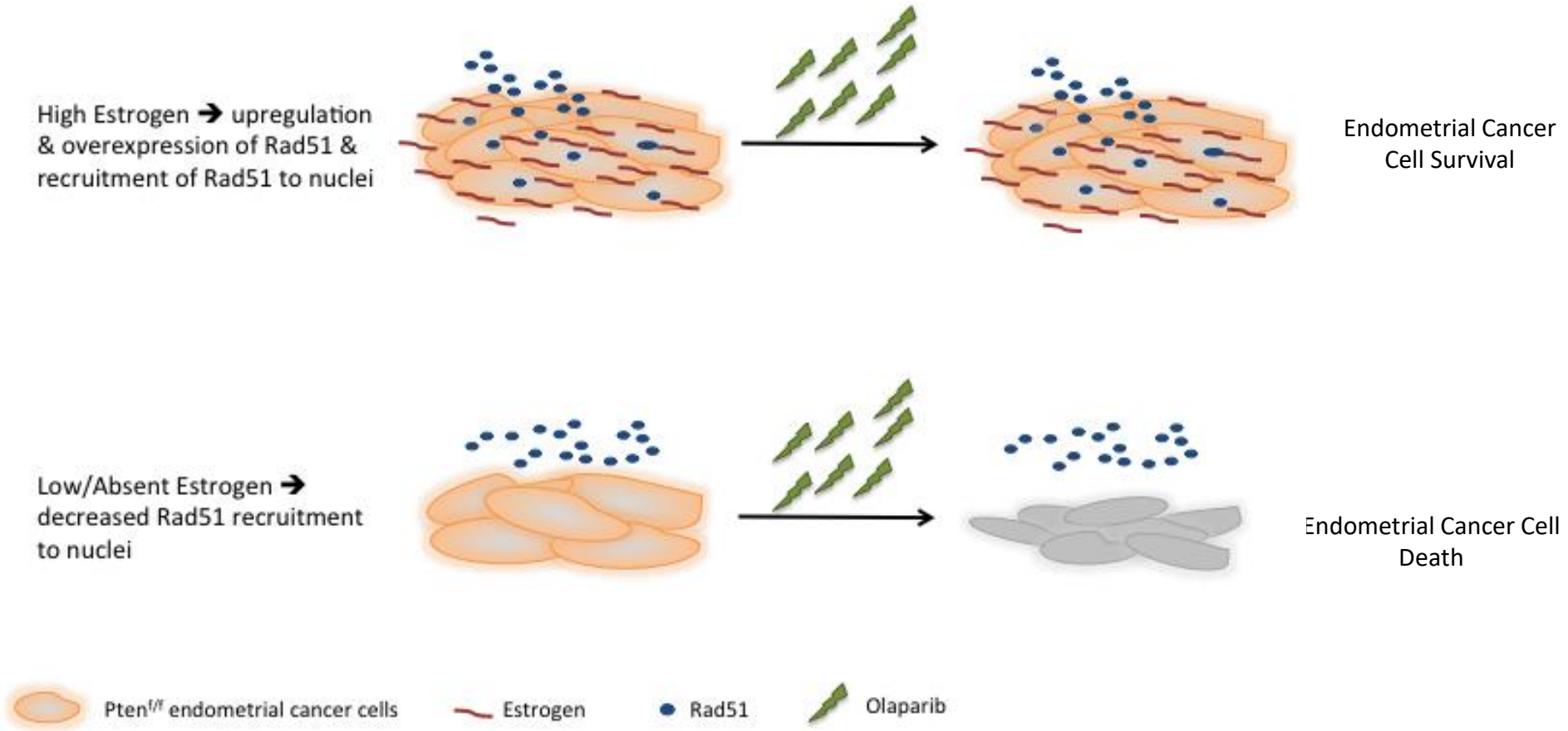
TCGA, Nature 2013

Do you like PARPs?

- HRD definition is yet to be defined in EC
- We cannot make assumption that HRD score in ovarian cancer = endometrial cancer
- *BRCA* mutations are more frequent in type 2 cancers and evidence of LOH in EC has been described
- Clinical trials with PARP use in EC are ongoing…

PARP inhibition in Endometrial Cancer:

Low estrogen states (e.g., post-menopausal, serous histology) compromises homologous recombination pathways & leads to Endometrial cancer cell death with Olaparib



Janzen et al., *MCT.* 2013.

Endometrial Cancer: 1L/Metastatic or

Setting	Trial Name	Study Intent	Update
		Dostarlimab (TSR-042) Plus Carboplatin-paclitaxel Versus	

Imfinzi plus Lynparza and Imfinzi alone both significantly improved progression-free survival in advanced endometrial cancer when added to chemotherapy

DUO-E is the first global Phase III trial of immunotherapy plus PARP inhibition to demonstrate clinical benefit in this setting

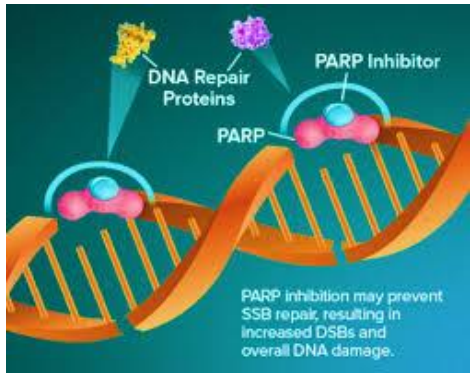
Positive high-level results from the DUO-E Phase III trial showed *Imfinzi* (durvalumab) in combination with platinum-based chemotherapy followed by either *Imfinzi* plus *Lynparza* (olaparib) or *Imfinzi* alone as maintenance therapy both demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to standard-of-care chemotherapy alone in patients with newly diagnosed advanced or recurrent endometrial cancer. There was a greater clinical benefit observed with the combination of *Imfinzi* and *Lynparza* as maintenance treatment.

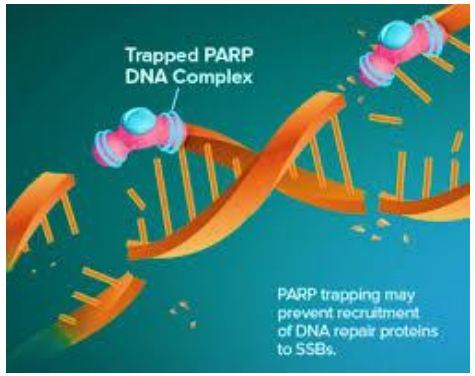
- Press Release: May 26, 2023

Talazoparib

Talazoparib is a Poly (ADP-ribose) polymerase (PARP) Inhibitor that induces cancer cell death via 2 complementary mechanisms:

- PARP enzyme inhibition (top) → Prevents PARP-mediated DNA damage repair
- Trapping of PARP-DNA complexes (bottom) → inhibits PARP



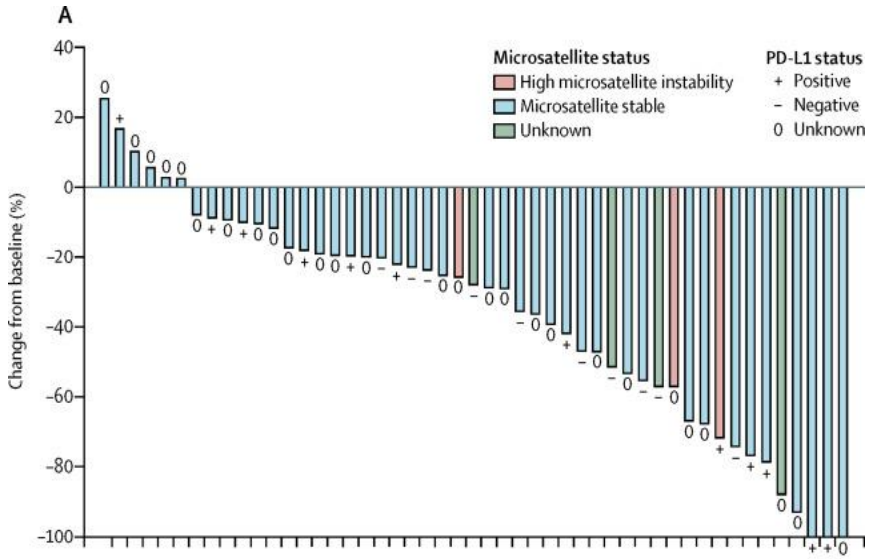


- Preclinical experiments implicate low/absent estrogen states with a phenotypic HRD (↓Rad51 recruitment) & PARP sensitivity (Janzen et al., MCT 2013)
- Associated: Fatigue, anemia, nausea, neutropenia, headache, thrombocytopenia, vomiting, alopecia, diarrhea, decreased appetite.
- Most common laboratory abnormalities (≥25%) were: Decreases in hemoglobin, platelets, neutrophils, lymphocytes, leukocytes, and calcium. Increases in glucose, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase.
- <u>Potential</u> overlapping toxicities with atezolizumab: gastrointestinal and hepatic events

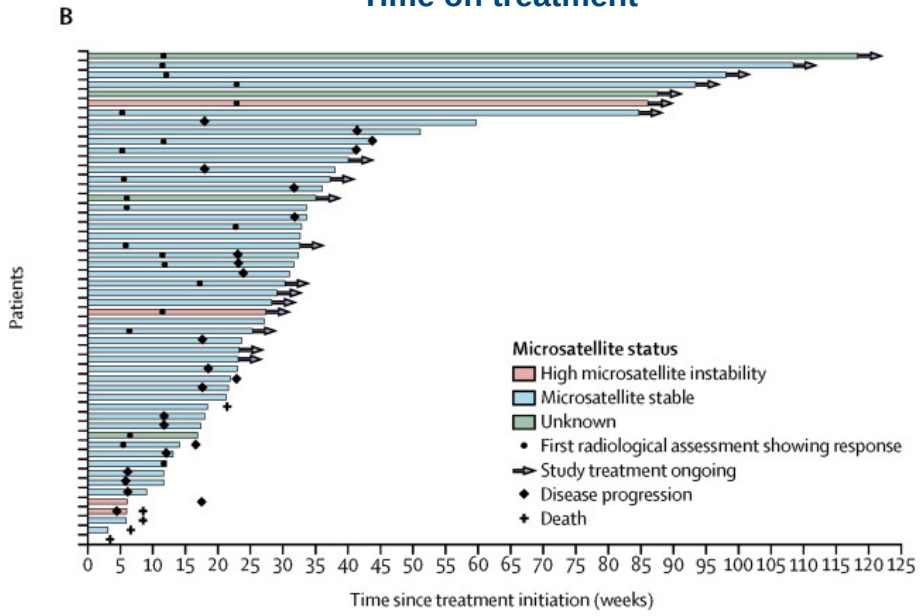
Blocking VEGF & PD1 with lenvatinib & pembrolizumab

- N=53
- ORR 39.6% (26.5, 54.0)
  - 45 (85%) MSS: ORR 35.6% (21.9, 51.2)
  - 4 (8%) MSI-H: ORR 50% (6.8, 93.2)
- 83% (55.9, 94.2) with responses ≥ 6 months
- 64.5% (32.8, 84.2) with responses ≥ 12 months

Maximum % change



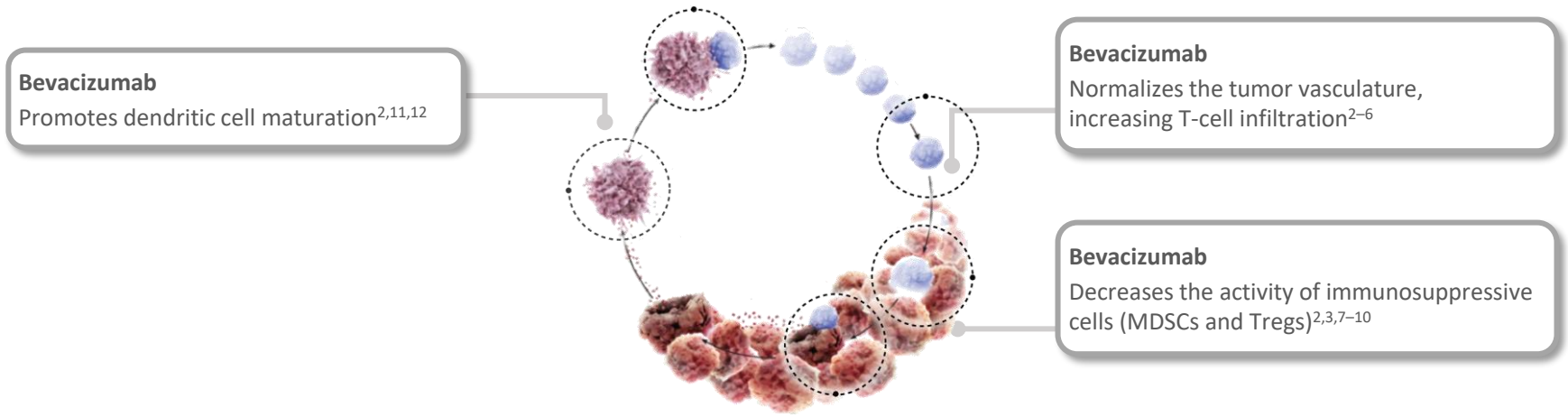
Time on treatment



Makker V et al. Lancet Oncol. 2019

Bevacizumab

- Bevacizumab is an Anti-VEGF Antibody and recognizes all VEGF isoforms
- Direct anti angiogenic effect by binding to and clearing VEGF from the tumor microenvironment
- Additional antitumor activity may be on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).
- Approved in multiple indications: metastatic colorectal cancer, NSCLC, renal cell carcinoma, ovarian cancer, cervical cancer, recurrent glioblastoma multiforme.
- Bevacizumab is approved in combination with atezolizumab for the treatment of hepatocellular carcinoma.
- Associated risks: GI perforations, hemorrhage, acute toxic encephalopathy, fistulae, wound-healing complications, hypertension, venous thromboembolism, and proteinuria.



2. Hegde PS, et al. Semin Cancer Biol. 2018. 3. Wallin JJ, et al. Nat Commun. 2016. 4. Goel S, et al. Physiol Rev. 2011. 5. Motz GT, et al. Nat Med. 2014. 6. Hodi FS, et al. Cancer Immunol Res. 2014. 7. Gabrilovich DI & Nagaraj S. Nat Rev Immunol. 2009. 8. Roland CL, et al. PLoS One. 2009. 9. Facciabene A, et al. Nature. 2011. 10. Voron T, et al. J Exp Med. 2015. 11. Gabrilovich DI, et al. Nat Med. 1996. 12. Oyama T, et al. J Immunol. 1998.

Bevacizumab is active in recurrent EC GOG229E

- N=54 (52 evaluable patients) with recurrent EC
- Intervention: Bevacizumab 15mg/kg q21d
- Efficacy
  - Overall response rate = 13.5% (90% CI 6.5% - 27%)
    - 1 CR
    - 6 PR
  - Median DOR = 6 mon
  - PFS^{6m} = 40.4% (90%CI 29% - 53%)
  - mPFS = 4.17m
  - mOS = 10.55m

Aghajanian et al., JCO 2011

Atezolizumab and Bevacizumab in Recurrent Endometrial Cancer: A Phase II, Multi-institutional Trial

Inclusion criteria:

- Advanced, recurrent endometrial cancer
- Endometrioid, serous, mixed adenocarcinoma, clear-cell, or carcinosarcoma
- 1-2 prior lines for endometrial cancer
- Measurable disease at time of recurrence
- Prior carboplatin/paclitaxel acceptable
- Archival tissue or tissue biopsy

Pre-treatment blood collection

Treatment

Bevacizumab 15mg/kg IV D1 +
Atezolizumab 1200mg D1
Q 21 day cycle

Post-treatment blood collection

Primary Endpoint:
Objective response rate (ORR)

Secondary Endpoints:

1) PFS
2) OS
3) Safety using CTCAE v4.0
4) ORR by immune related response criteria (irRC)

Exploratory Endpoint:

1) Immune subpopulations by CyToF
2) Multiparametric fluorescent imaging by CODEX

OU Health | Stephenson Cancer Center

O'NEAL COMPREHENSIVE CANCER CENTER AT UAB

Washington University in St. Louis
SITEMAN CANCER CENTER

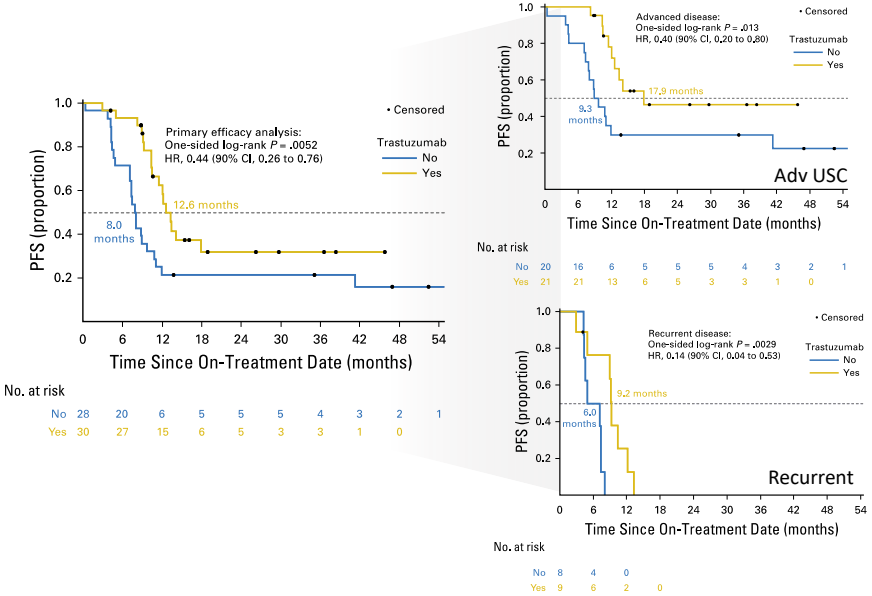
NCT03526432

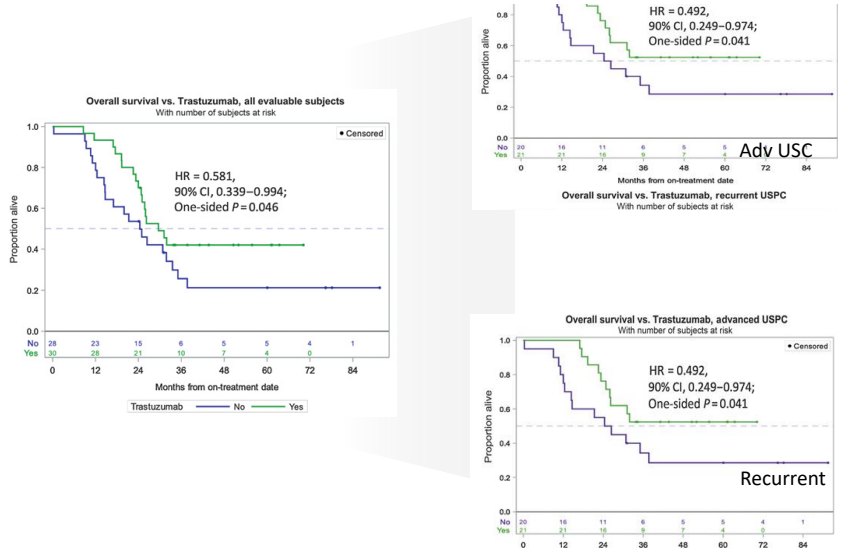
Results: Overall Adverse events and Clinical Activity

Total Number of Subjects	n=57
Adverse events	n (%)
Grade 3 due to atezolizumab	4 (7%)
Grade 3 due to bevacizumab	12 (22%)
Grade 4	0
Dose interruption	45 (79%)
Dose reduction	2 (4%)
Discontinued due to toxicity	9 (16%)
Clinical Activity	
ORR for all	30% (95% CI 18-43)
ORR for MMRp	33% (95% CI 20-48)
Median DOR (months)	15 (95% CI 2.9-34)
Median PFS (months)	7.87 (95% CI 5.5-11.7)

Trastuzumab Emtansine (T-DM1)

- T-DM1 is a HER2-targeting Antibody Drug Conjugate (ADC)
  - Trastuzumab is covalently linked to the anti-microtubule disrupter, DM1 (emtansine)
- Preclinical data show T-DM1 ↑IFNγ production in T-cells & ↑PD-L1 expression in TAMs in HER2+ transgenic breast cancer models
- Uterine serous carcinomas (USC) frequently show HER2 amplification/overexpression (Mutations are rare, but possible)
  - Prevalence ~25% USC.
  - Also seen in carcinosarcoma, rarely in endometrioid (usually Gr3)
- NCCN Guidelines recommend HER2 testing in endometrial cancer





Fader et al., JCO 2018

Fader et al., CCR. 2020

Tiragolumab

- Therapeutic blockade of TIGIT by tiragolumab may enhance the magnitude and qualityof the the tumor-specific T-cell responses and to enhance NK cell mediated anti-tumor immunity, which may result in improved meaningful anti-tumor activity

- The rationale for combination therapy with atezolizumab and tiragolumab is based on unmet clinical need, highly correlated co-expression of TIGIT and PD-1 on infiltrating T-cells, and preclinical/clinical data demonstrating enhance anti-tumor activity and progression-free survival.

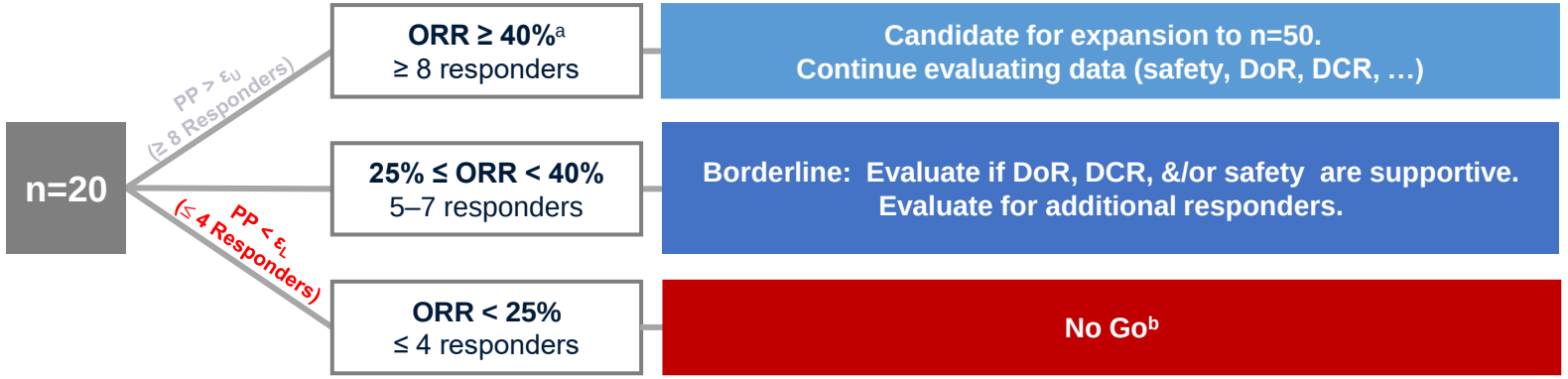
- Tiragolumab prevents TIGIT from binding to its ligand, and restores anti-tumor response and complements the activity of anti-PD-L1/PD-1 antibodies.(IB)

- In addition to preclinical findings, targeting TIGIT and PD-L1 has shown anti-tumor activity in cancer patients in a phase I study. Tiragolumab was well-tolerated in combination with atezolizumab in a Phase Ia/b study in multiple solid tumors (Study GO30103, NCT02794571) tumors

Gating criteria (n=20; each arm evaluated independently)

ORR of 30% gate set as aggressive goal

- Rationale: Historical ORR ~15%. Doubling of the historical ORR in a single arm with high unmet medical need is clinically significant
- Efficacy & Futility Boundaries



[a] Initial review estimated at ~16 weeks to provide time to establish earliest rate of confirmed responses (i.e., 2 tumor assessment intervals q8w to allow delayed responses + 1 interval for confirmation)
[b] Combinations that do not meet Go criteria may be elevated upon review of above factors and totality of efficacy benefit

POD1UM-204 GOG 3038
Phase 2, Open-Label, Nonrandomized, Umbrella Study of Retifanlimab Alone or Combined With Other Therapies in Recurrent Advanced/Metastatic Endometrial Cancer[1,2]

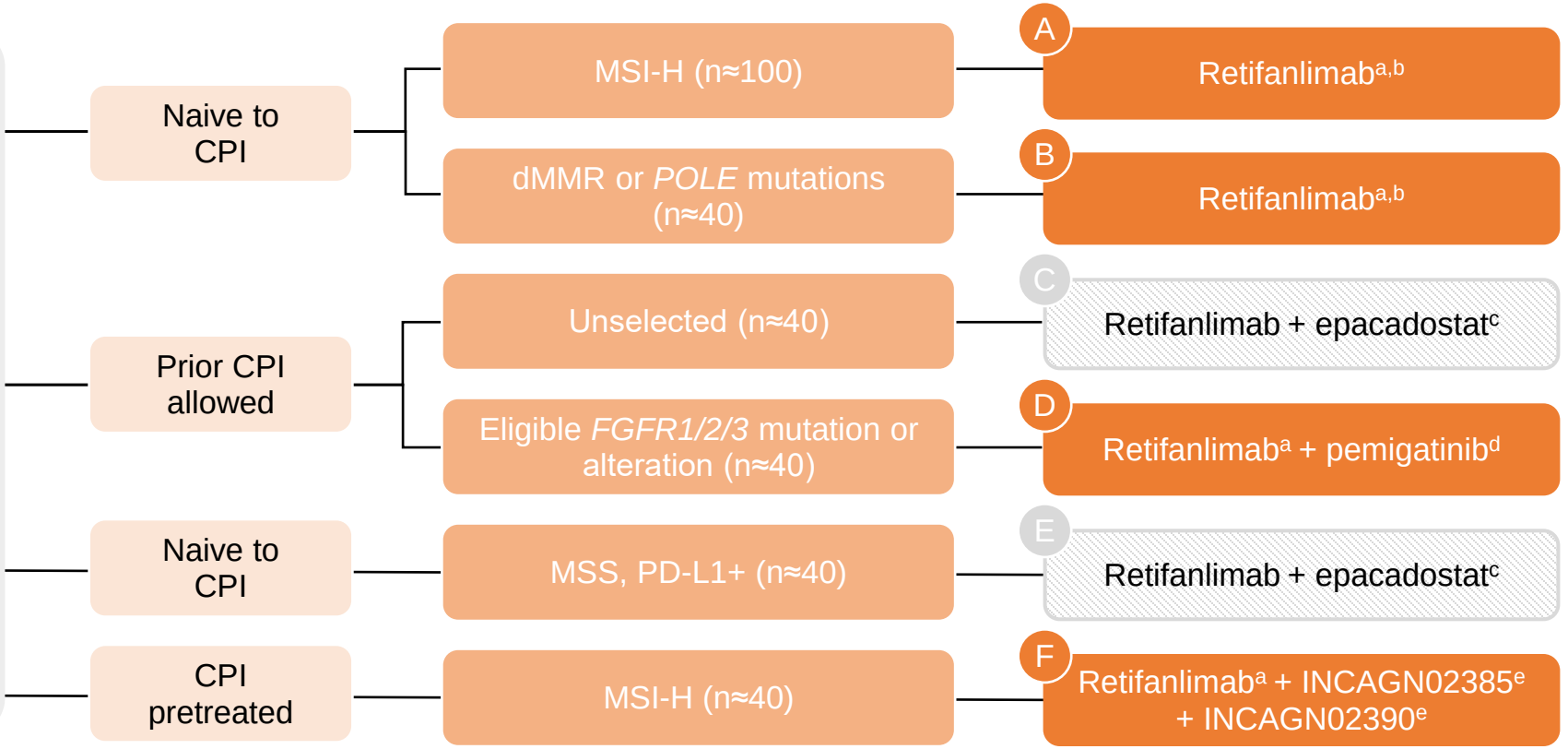
POD1UM-204

Phase 2, Open-Label, Nonrandomized, Umbrella Study of Retifanlimab Alone or Combined With Other Therapies in Recurrent Advanced/Metastatic Endometrial Cancer[1,2]

Select eligibility criteria

- Histologically confirmed advanced or metastatic endometrial cancer
- Disease progression on or after treatment with ≥1 platinum-containing regimen
- At least 1 measurable tumor lesion per RECIST v1.1
- Willing to provide tumor tissue sample
- ECOG PS of 0 to 1

Target N≈300



Primary endpoint: ORR, per RECIST v1.1 and determined by ICR (group A)[1,2]

Secondary objectives: DoR, DCR, PFS, OS (groups A-B); ORR (groups B-F); safety (all groups)[1,2]

a Patients eligible to receive retifanlimab monotherapy will first be considered for group A until fully enrolled, unless they do not meet MSI-H criteria. Retifanlimab administered iv on day 1 of each 28-day cycle for up to 26 cycles, if patients continue to derive benefit and do not meet any study treatment discontinuation criteria. b Patients in group A or group B who experience disease progression on retifanlimab monotherapy may be eligible for further treatment with one of the combination regimens in groups D or F. c Closed groups. d Pemigatinib (FGFR1/2/3 inhibitor) administered orally qd. e INCAGN02385 and INCAGN02390 administered iv q2w.

dMMR, deficient mismatch repair; ICR; independent central review; MSI-H, microsatellite instability-high; MSS, microsatellite stable; POLE, DNA polymerase epsilon.

1. Slomovitz BM, et al. IGCS 2022. Poster 1455. 2. ClinicalTrials.gov. Accessed May 2023. https://clinicaltrials.gov/ct2/show/NCT04463771

Incyte 1801 Augustine Cut-Off
Wilmington, DE 19803
302.498.6700

Date: 03Jun2022

Protocol: INCMGA 0012-204 (POD1UM-204), umbrella study
Protocol Title: 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

Subject: **Notification Letter for Stopping Enrollment in Group E (Combination of INCMGA00012 and epacadostat in CPI Naïve, MSS, PD-L1+, n=40) as per Protocol Section 4.1: Overall Design**

Dear POD1UM-204 Investigators,

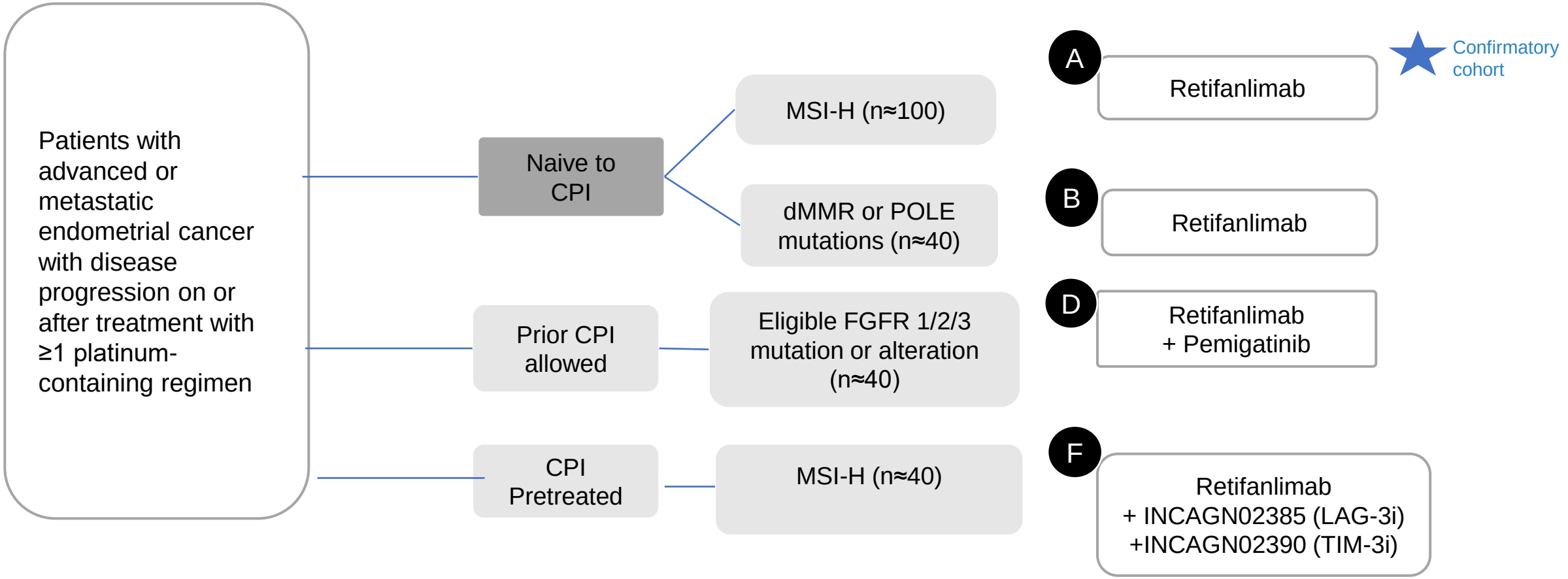
This letter is to inform you that we recently conducted a review of the data from INCMGA00012 and epacadostat Groups in the POD1UM-204 study (Group E and previously enrolled Group C) as part of regular study data review surveillance, and a strategic decision was taken following this review. We have enrolled 7 participants onto Group E and 5 of these participants had at least 1 postbaseline tumor assessment or discontinued study treatment. There were 6 participants previously enrolled in Group C that met the main eligibility criteria for Group E. There has been 1 response in these 11 participants. The overall incidence of Grade 3 rash in Groups C (unselected) and E that led to epacadostat dose interruptions or discontinuations in Cycle 1 was 16/45 (36%).

Although Group E has not completed enrolling all 14 participants for the planned interim analysis that was to also include the 6 participants from Group C, based on the totality of the data observed with the epacadostat and retifanlimab combination, Incyte brought forward the data and the strategic decision to stop further enrollment onto Group E due to lack of efficacy to the independent DMC. The option to terminate any Group combination therapy before completion of enrollment based on available safety, efficacy or translational data is described in Protocol Section 4.1. Upon evaluation, the independent DMC recommended and agreed to stop further enrollment into Group E.

Participants enrolled onto Group E prior to stopping the enrollment and ongoing participants in Group C will be allowed to continue as per the protocol at 600 mg BID of epacadostat if they derive benefit as per investigator's assessment and participant's decision. Investigators may reduce the dose to 400 mg BID for managing adverse events as described in the current protocol (Section 6.5, Dose Modifications). If a participant cannot tolerate epacadostat 400 mg BID then they must be discontinued from treatment with epacadostat also as described in the protocol.

This decision has no impact on enrollment onto other Groups in this umbrella study.

POD1UM-204: Phase 2, open-label, nonrandomized, umbrella study of retifanlimab alone or combined with other therapies in recurrent advanced/metastatic endometrial cancer*



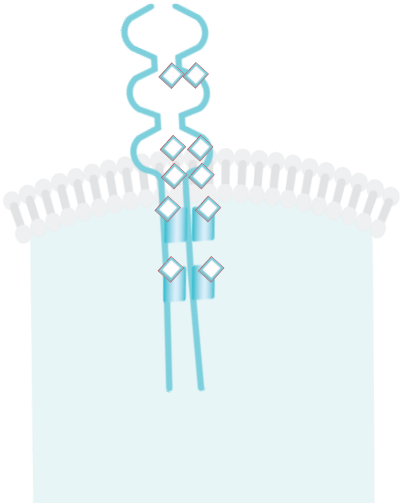
Closed Groups: ***Group C (unselected): completed enrollment (Retifanlimib+Epacadostat), Group E (CPI Naïve, PD-L1+): enrollment closed (Retifanlimab+Epacadostat)**

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

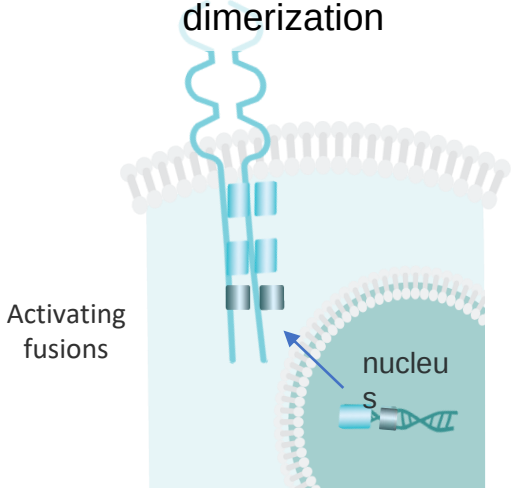
Activating mutations

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



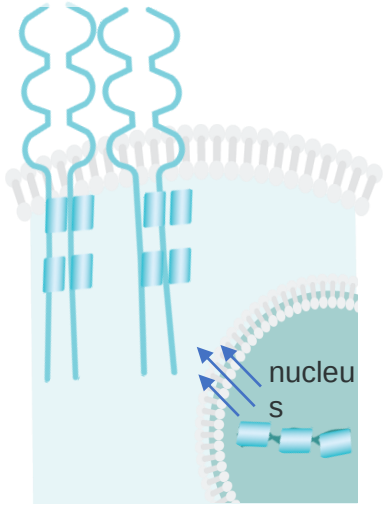
Chromosomal rearrangements

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

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

LAG-3 Co-Inhibitory Receptor Limits Antigen-

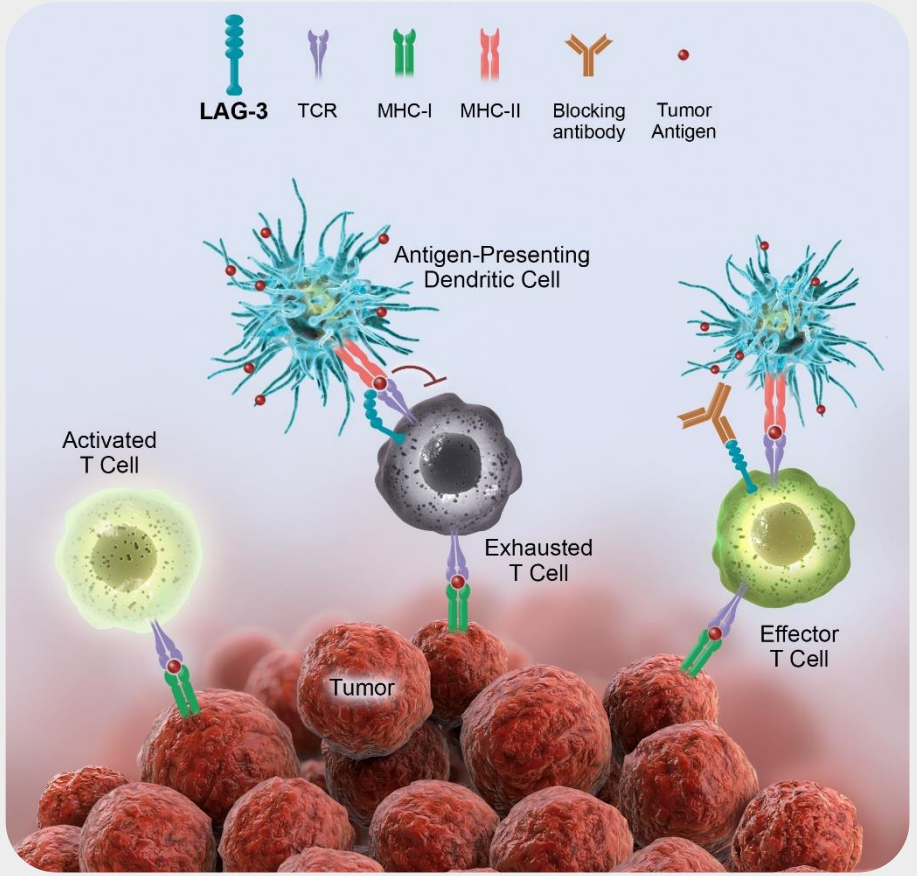
LAG-3 expression[1-3]
- Cell surface of activated T cells and other lymphocytes

LAG-3 binding partners[1,3]
- Major ligand: MHC class II (MHC-II)
- Other: galectin-3, LSECtin, and FGL-1

LAG-3 signaling[1-3]
- Limits antigen-specific T-cell responses

LAG-3/PD-1 co-expression[1,2]
- Frequently co-expressed on CD4+ and CD8+ T cells, and particularly TILs
- Correlated with intratumoral T cell dysfunction in human tumor samples

Example of LAG-3 MoA through MHC-II interaction[4,5]



FGL-1, fibrinogen-like protein 1; LAG-3, lymphocyte activation gene-3; LSECtin, liver sinusoidal endothelial cell lectin; MHC, major histocompatibility complex; MoA, mechanism of action; PD-1, programmed cell death protein 1; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte.

1. Andrews LP, et al. *Nat Immunol.* 2019;20:1425-1434. 2. Solinas C, et al. *Cancers (Basel).* 2019;11:1213. 3. Chocarro L, et al. *Int J Mol Sci.* 2021;22:5282. 4. Hannier S, et al. *J Immunol.* 1998;161:4058-4065. 5. Grosso JF, et al. *J Clin Invest.* 2007;117:3383-3392.

TIM-3 May Also Promote Immunosuppression

TIM-3 expression[1-3]
- Differentiated type-1 CD4+ and CD8+ T cells, T_{regs}, and innate immune cells

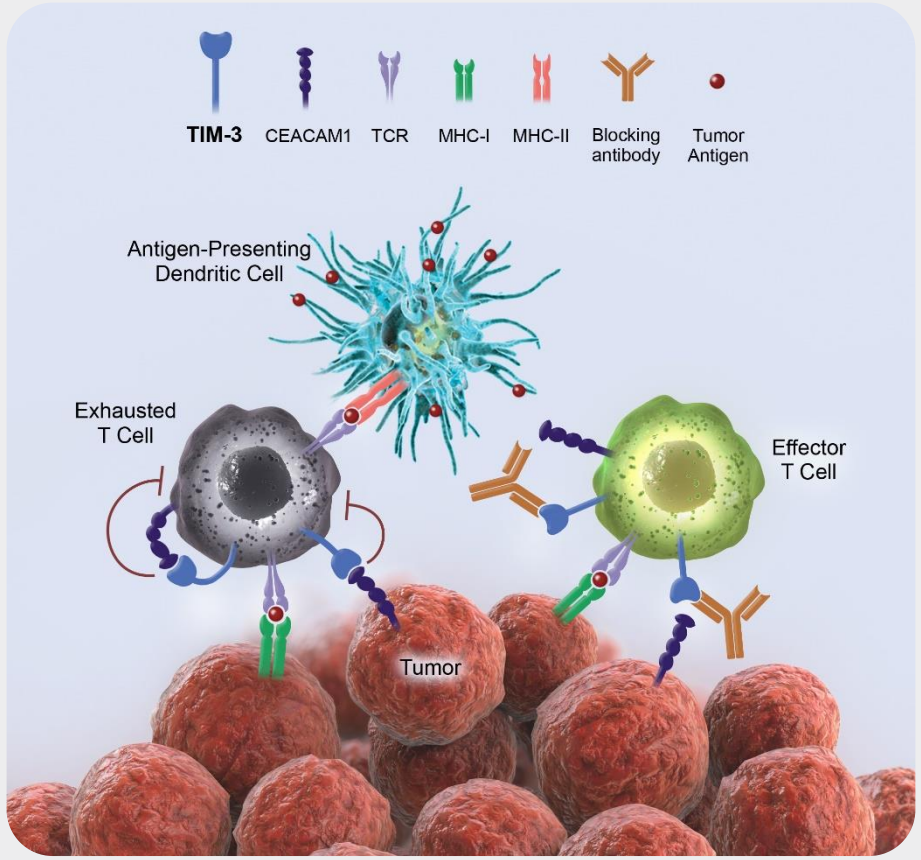
TIM-3 binding partners[1-3]
- PS, galectin-9, CEACAM1, and HMGB1

TIM-3 signaling[2,3]
- Negative intracellular signal promoting immunosuppression

TIM-3/PD-1 co-expression[2]
- Marks highly dysfunctional T cells in multiple cancer types

TIM-3 expression in T_{regs}[2]
- Expressed in more than half of T_{regs} from lung cancer tissues
- Potential role in T_{reg}-mediated immunosuppression

Example of TIM-3 MoA through CEACAM1 binding[4]



CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1; HMGB1, high mobility group box 1; PS, phosphatidylserine; TIM-3, T-cell immunoglobulin and mucin domain-3; T_{reg} cell, regulatory T cell.

1. Andrews LP, et al. *Nat Immunol.* 2019;20:1425-1434. 2. Tang R, et al. *Semin Immunol.* 2019;42:101302. 3. Acharya N, et al. *J*

Combination Therapy

- Some combinations work
- Role of I/O after I/O needs to be further characterized
- Further investigation needed

The Future is Bright

Thank you