Endometrial Cancer – Highlight Reel

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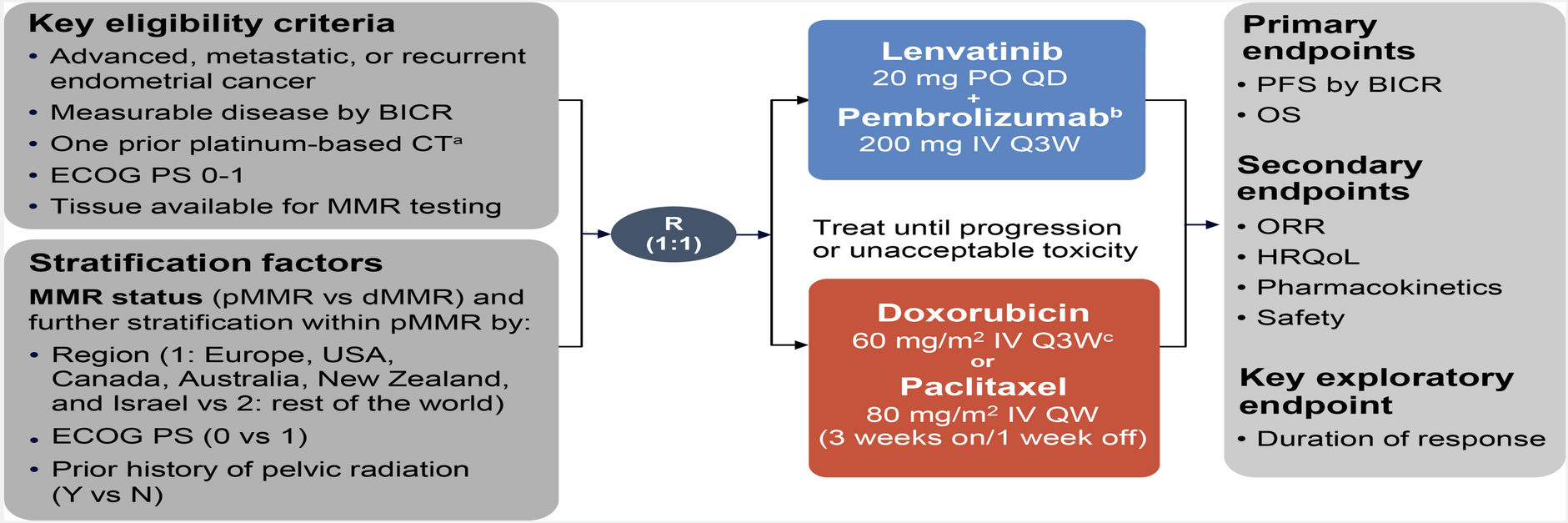
GOG Highlight Reel

Objectives

- Review key studies from fall meetings
- Discuss ongoing endometrial cancer trials in GOG Partners
- Predict changes in standard of care after first-line studies report

Review of Key Studies

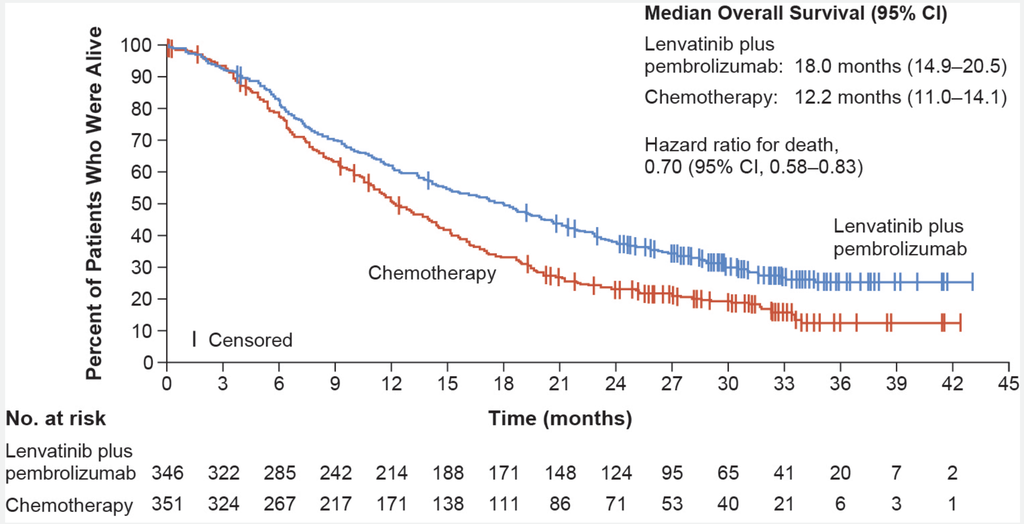
Study 309/K775:Updated efficacy and safety



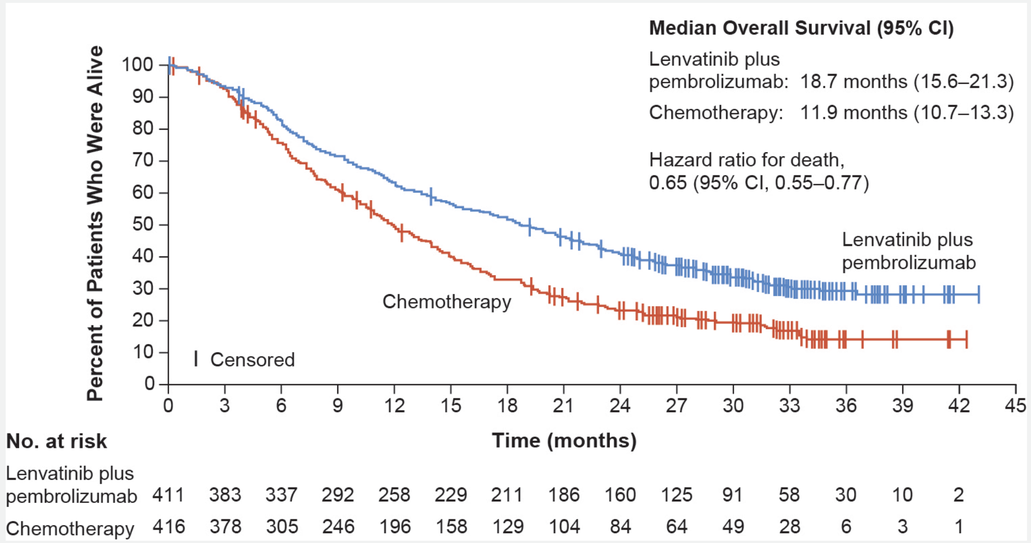
- PFS, OS, and ORR were statistically significant with lenvatinib plus pembrolizumab vs chemotherapy at the primary analysis (Makker 2022, *NEJM)*.
- Median follow-up time: 14.7 months (data cutoff date: 1 March 2022; >16 months of additional follow-up time from the interim analysis for OS).
- PFS and ORR (by BICR per RECIST v1.1) are also presented at this data cutoff; all analyses are descriptive.

Continued OS benefit of lenvatinib plus pembrolizumab vs chemotherapy with follow-up extended by over 16 months

pMMR Population



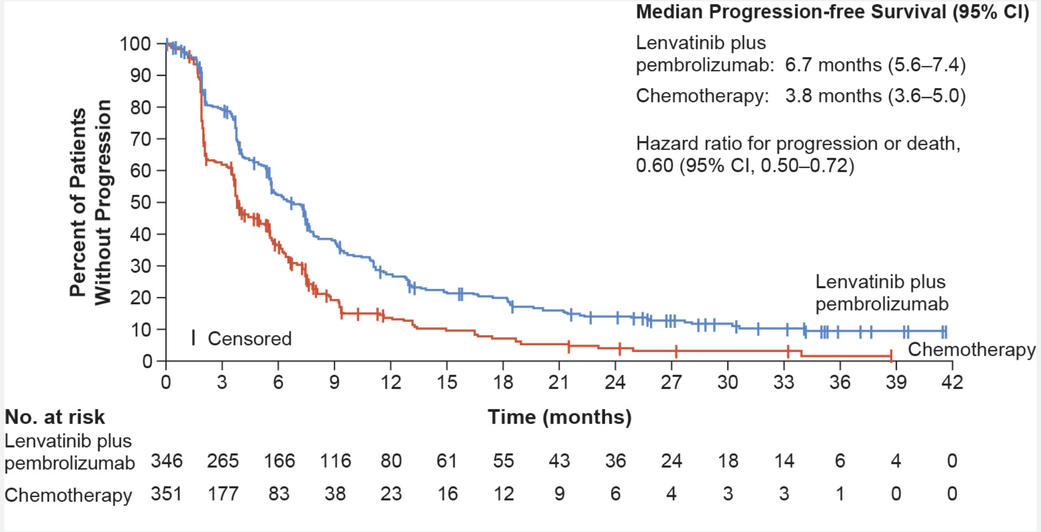
All-Comer Population



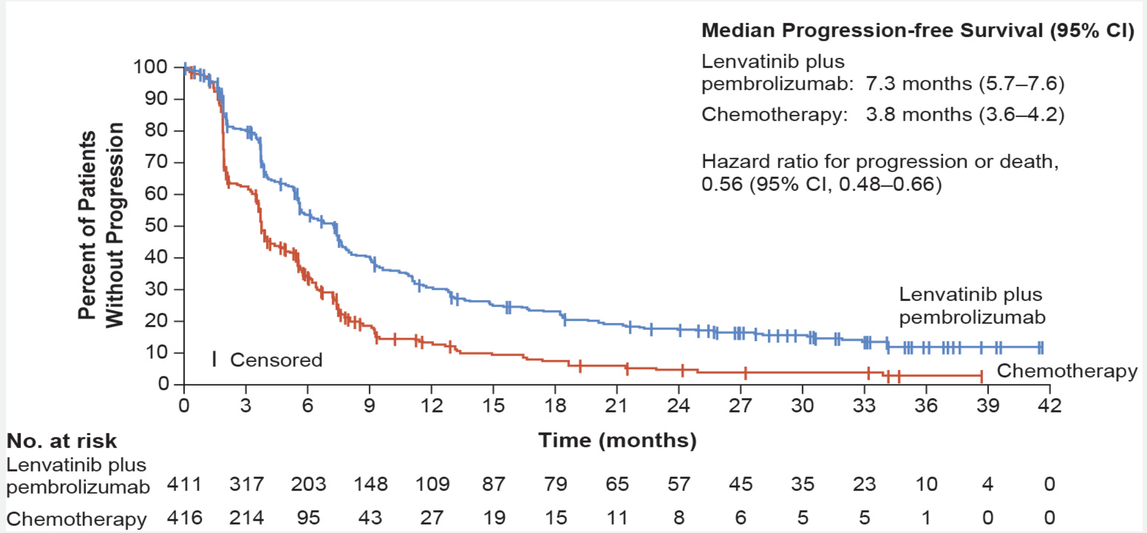
- OS favored lenvatinib plus pembrolizumab despite some pts in the chemotherapy arm receiving subsequent lenvatinib plus pembrolizumab. (In the chemotherapy arm, 10.0% of pts in the pMMR population and 8.7% of pts in the all-comer population).
  - After excluding these pts, the pMMR OS HR was 0.64 (95% CI, 0.54, 0.76); the all-comer OS HR was 0.60 (95% CI, 0.51, 0.71).

Continued PFS[a] benefit of lenvatinib plus pembrolizumab vs chemotherapy with follow-up extended by over 16 months

pMMR Population

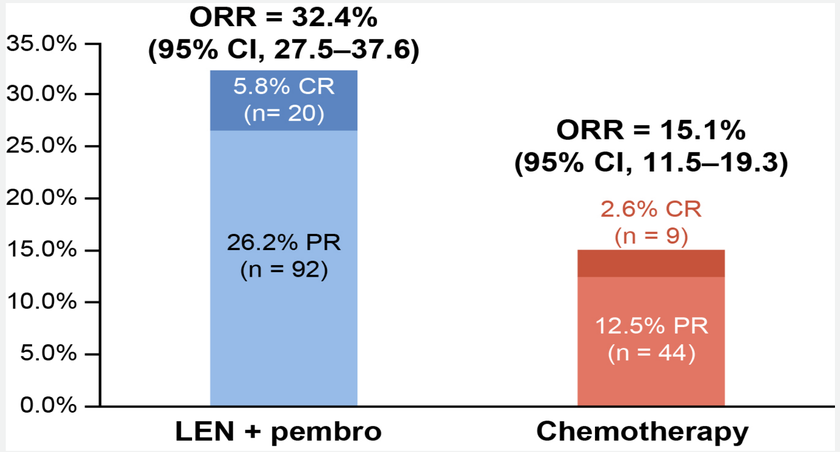


All-Comer Population

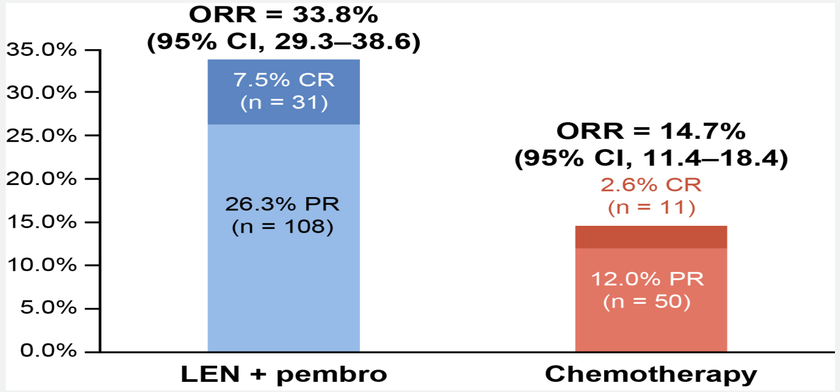


Continued tumor responses in pMMR and all-comer pts by BICR per RECIST v1.1

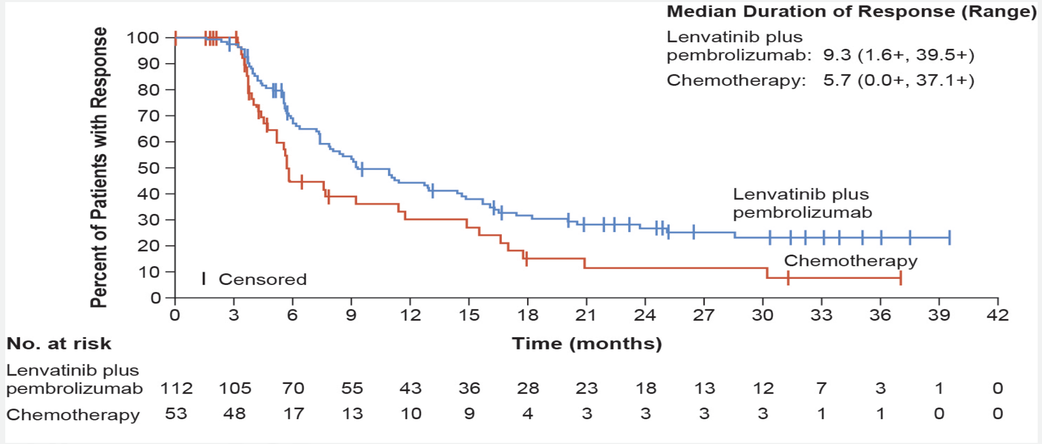
pMMR ORR



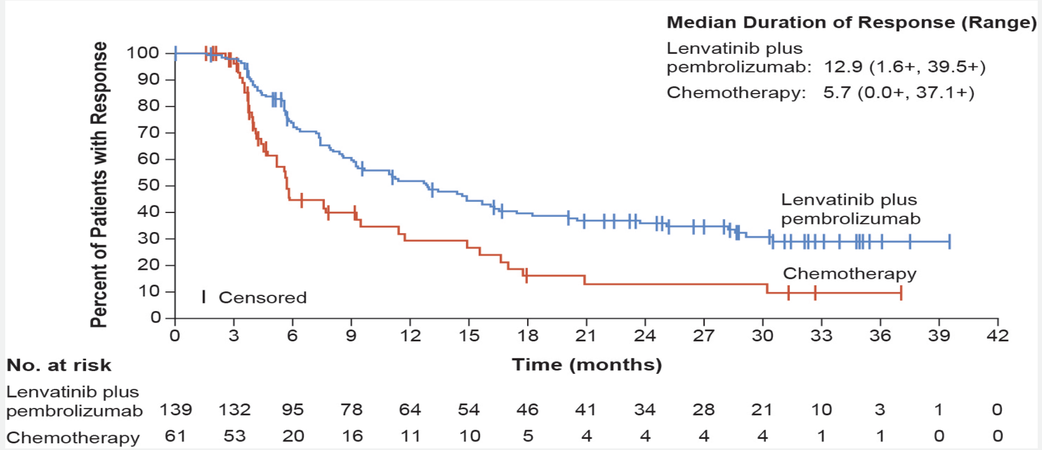
All-comer ORR



pMMR DOR



All-comer DOR

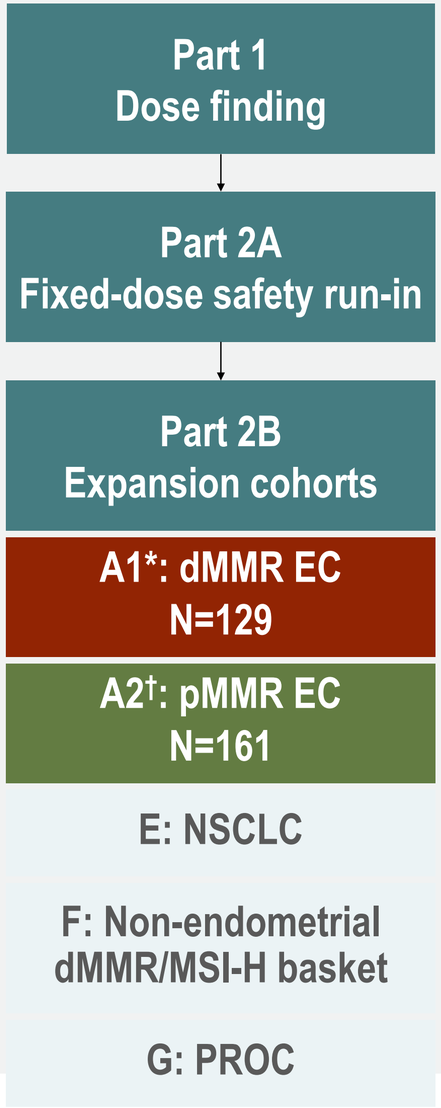


Conclusions

- At the interim analysis, lenvatinib plus pembrolizumab led to statistically significantly improved PFS (pMMR HR: 0.60; all-comer HR: 0.56), OS (pMMR HR: 0.68; all-comer HR: 0.62), and ORR (pMMR ORR: 30.3% vs 15.1%; all-comer ORR: 31.9% vs 14.7%) compared to chemotherapy (Makker 2022, *NEJM*).
- At the final prespecified analysis of OS, lenvatinib plus pembrolizumab continued to demonstrate clinically meaningful improvement in OS, PFS, and ORR vs chemotherapy in pts with aEC (pMMR and all-comer populations) who received prior platinum therapy, supporting the robustness of the treatment effect observed at the interim analysis (Makker 2022, *NEJM*).
- OS KM curves for lenvatinib plus pembrolizumab and chemotherapy arms separated early and remained separated, despite some pts in the chemotherapy arm receiving subsequent lenvatinib plus pembrolizumab.
- No new safety signals were observed, and safety results were consistent with the interim analysis (Makker 2022, *NEJM*) and with the established safety profile of each agent.
- Results continue to support the use of lenvatinib plus pembrolizumab as a standard therapy in pts with previously treated aEC.

GARNET: Safety and antitumor activity of dostarlimab in dMMR or pMMR endometrial cancer

- GARNET (NCT02715284) is a phase 1, single-arm study of dostarlimab (TSR-042) monotherapy in multiple tumor types
- In part 2B, dostarlimab was dosed at the RTD determined from Part 1 and 2A
  - 500 mg IV Q3W for 4 cycles, then 1000 mg IV Q6W until disease progression
- MMR status was determined by local immunohistochemistry
- Primary endpoint: ORR and DOR

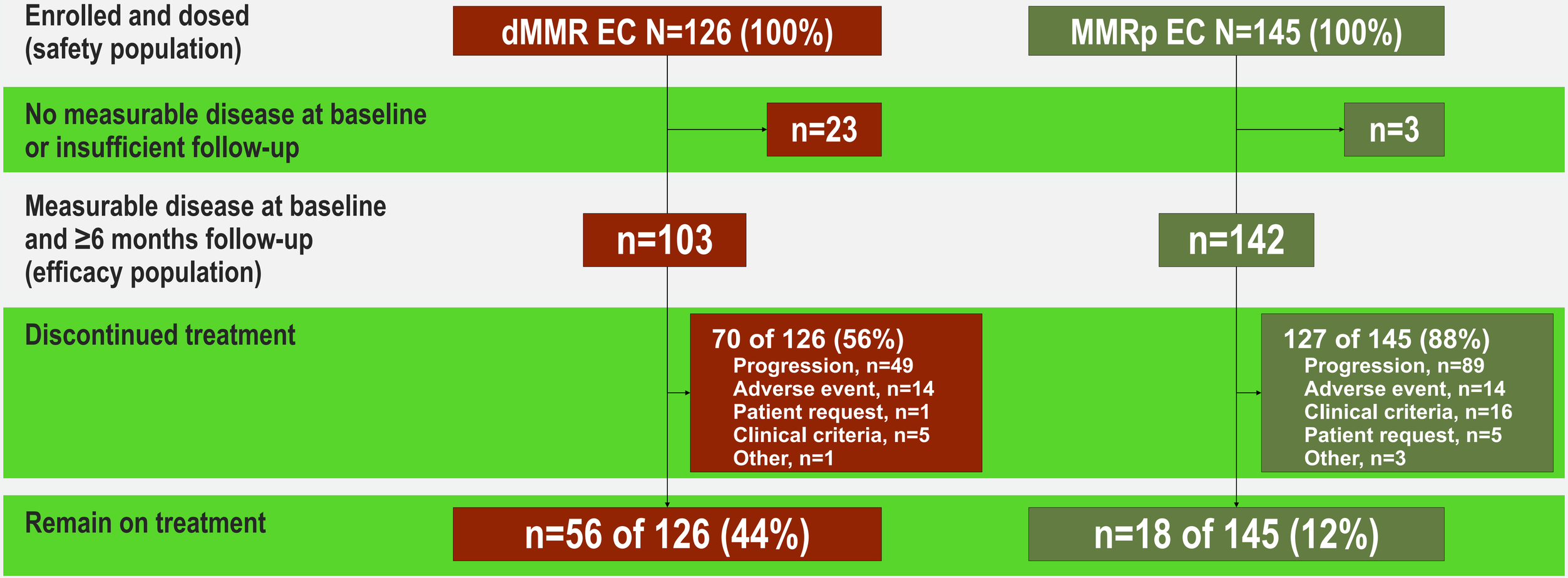


Key inclusion/exclusion criteria for cohorts A1 and A2:

- Patients must have progressed on or after platinum doublet therapy
- Patients must have received ≤2 prior lines of treatment for recurrent or advanced disease
- Patients must have measurable disease at baseline
- Patients must be anti–PD-(L)1 naïve
- Patients could be screened based on local MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but patient eligibility needs to be confirmed by MMR IHC results

*Cohort enrollment includes 3 patients with MMRunk/MSI-H disease; †Cohort enrollment includes 16 patients with MMRunk/MSS disease

Enrollment and Outcomes



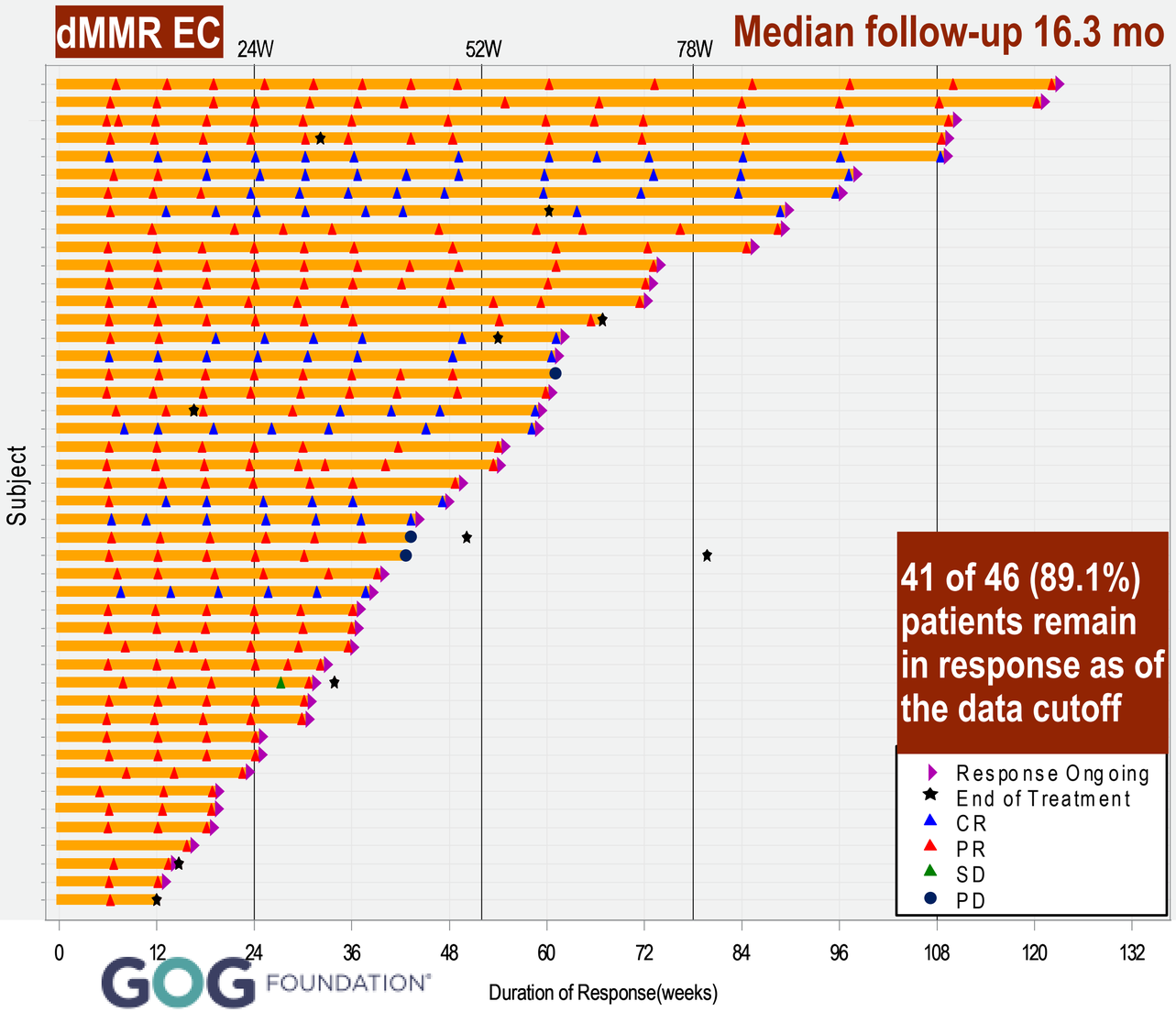
Data cut-off date March 1, 2020. dMMR, mismatch mutation repair deficient; EC, endometrial cancer; MMRp, mismatch mutation repair proficient.

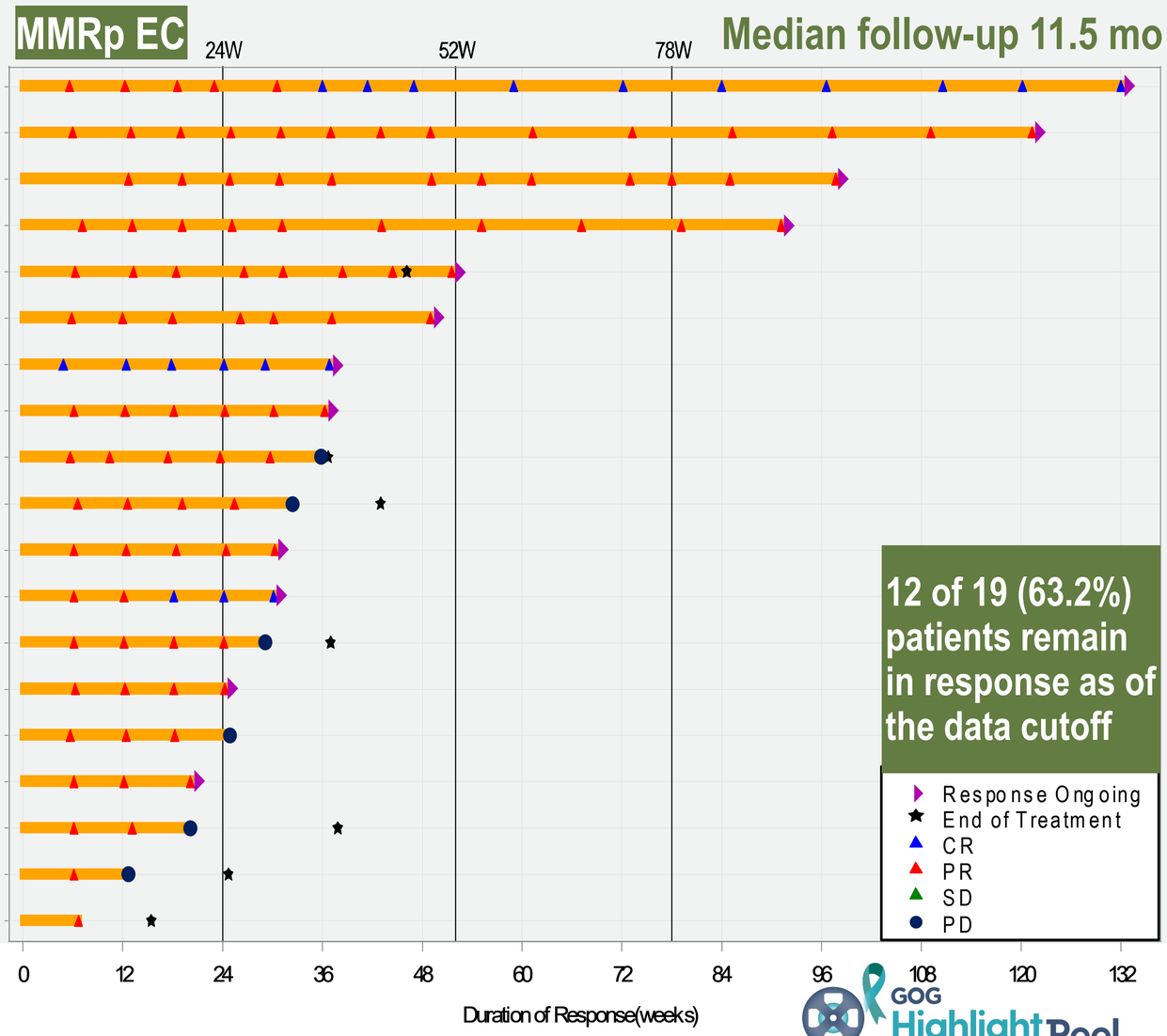
Primary Endpoint Analysis

- ORR was 44.7% in patients with dMMR EC, and 13.4% in patients with MMRp EC

Variable	dMMR EC, n=103	MMRp EC, n=142
Median follow-up time, mo	**16.3**	**11.5**
Objective response rate*, n (%, 95% CI)	**46 (44.7%, 34.9–54.8)**	**19 (13.4%, 8.3–20.1)**
Complete response, n (%)	11 (10.7)	3 (2.1)
Partial response, n (%)	35 (34.0)	16 (11.3)
Stable disease, n (%)	13 (12.6)	31 (21.8)
Progressive disease, n (%)	39 (37.9)	77 (54.2)
Not evaluable, n (%)	3 (2.9)	0
Not done, n (%)	2 (1.9)	15 (10.6)
Disease control rate†, n (%, 95% CI)	**59 (57.3%, 47.2–67.0)**	**50 (35.2%, 27.4–43.7)**
Response ongoing, n (%)	**41 (89.1)**	**12 (63.2)**
Median duration of response, (range) mo	**Not reached (2.63–28.09+)**	**Not reached (1.54+–30.36+)**
Kaplan–Meier estimated probability of remaining in response		
at 6 mo, %	97.8	83.0
at 12 mo, %	90.6	61.3
at 18 mo, %	79.2	61.3

Duration of Response





Data cut-off date March 1, 2020. CR, complete response; dMMR, mismatch mutation repair deficient; EC, endometrial cancer; MMRp, mismatch mutation repair proficient; PD, progressive disease; PR, partial response; SD, stable disease.

Conclusions

- Dostarlimab demonstrated durable antitumor activity in both dMMR and MMRp advanced/recurrent EC

- dMMR status by IHC was associated with a higher response rate

- Dostarlimab demonstrated a notable disease control rate (35.2%; 2.1% CR, 11.3% PR, 21.8% SD) in patients with MMRp EC, was comprised of a higher percentage of patients with Type II EC which is historically associated with a worse prognosis

- No new safety signals were detected, and only 5.5% of patients discontinued dostarlimab due to a TRAE

    - Most adverse events were grade 1 or 2

    - Safety was consistent between dMMR and MMRp cohorts

CR, complete response; dMMR, mismatch mutation repair deficient; EC, endometrial cancer; IHC, immunohistochemistry MMRp, mismatch mutation repair proficient; PD-(L)1, programmed cell death (ligand) 1; PR, partial response; SD, stable disease.

Post Hoc Analysis of Objective Response Rate by Mismatch Repair Protein Dimer Loss/Mutation Status in Patients with Mismatch Repair Deficient Endometrial Cancer Treated with Dostarlimab

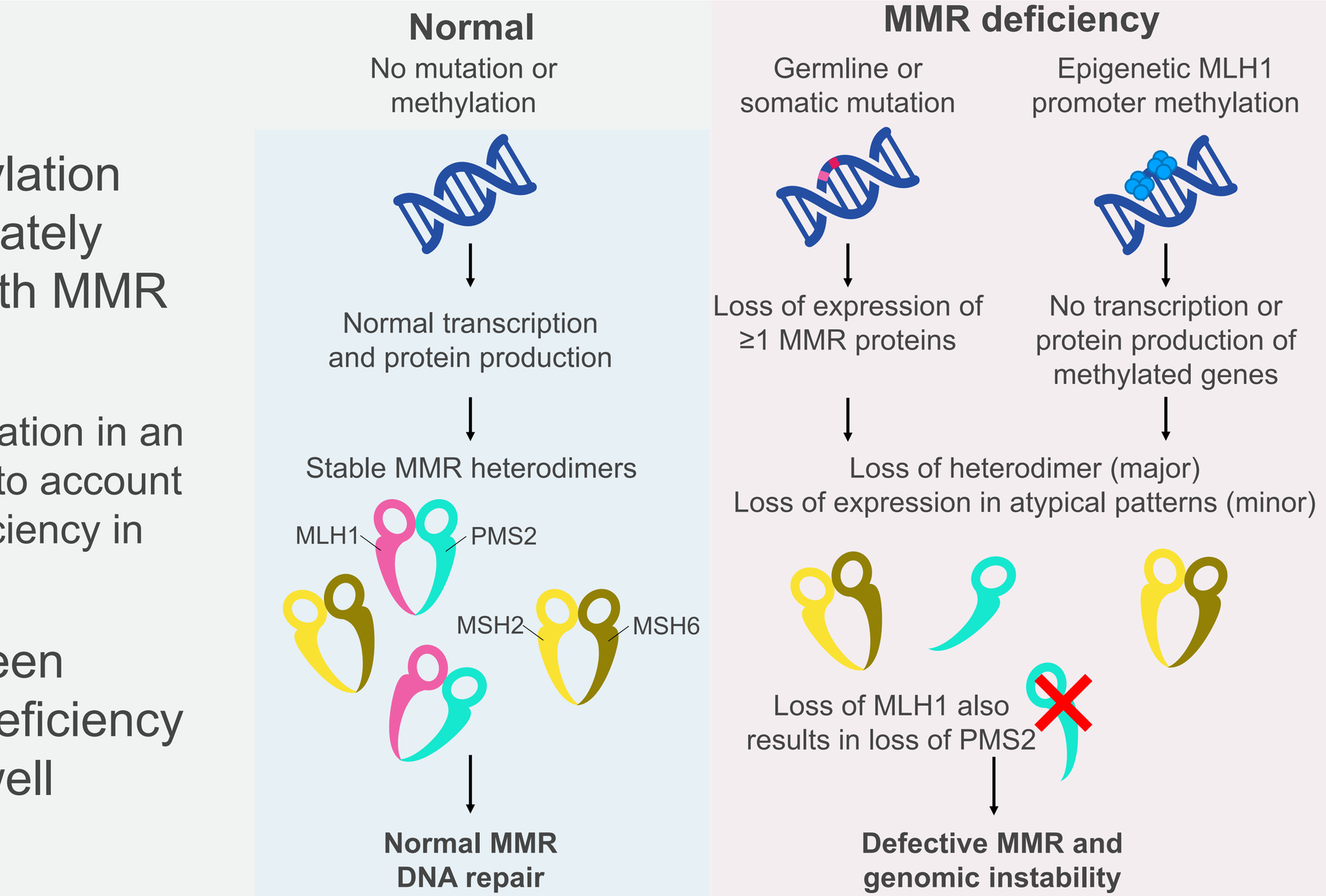
- MMR deficiency is caused by loss of expression of the MMR proteins MLH1, PMS2, MSH2, and/or MSH6[1]
  - These proteins function as heterodimers (MLH1–PMS2 and MSH2–MSH6) to mediate DNA repair
- Loss of expression is caused primarily by 2 mechanisms

  Germline (Lynch syndrome) or somatic mutation of MLH1, PMS2, MSH2, and/or MSH6

  Epigenetic methylation of the MLH1 promoter
- Gene mutation or epigenetic silencing of 1 gene typically leads to loss of expression of the heterodimer (most common dMMR staining pattern) and results in defective MMR and genomic instability[1]
  - Other patterns of loss are possible (loss of only 1 protein; loss of 3 proteins; or loss of atypical combinations of 2 proteins, eg, PMS2 and MSH6, etc)

Background

- MLH1 promoter methylation accounts for approximately 75%–80% of cases with MMR deficiency in EC[1-4]
  - Somatic or germline mutation in an MMR gene is estimated to account for 10-20% of MMR deficiency in EC[1-4]
- The relationship between mechanism of MMR deficiency and outcomes is not well understood



dMMR, MMR deficient; EC, endometrial cancer; MMR, mismatch repair.

1. Pasanen, A, et al. *Mod Pathol* **33**, 1443–1452 (2020). 2. Kurpiel, B, et al. *Int J of Gyn Path* 41:1:1-11 (2022).
3. Buchanan, D, et al. *JCO* 2014 32:2, 90-100, 4. Kahn, RM et al. *Cancer*, 125: 3172-3183.

No difference in ORR or DOR by pattern of MMR protein loss

- MMR protein loss is similar to the estimated ratios in the dMMR EC population[1-4]

MMR protein staining pattern (IHC)	Patients, N	Responders, n	ORR, % (95% exact CI)	DOR median (95% CI), mo
Cohort A1 (dMMR/MSI-H EC)	143	65	45.5 (37.1–54.0)	NR (38.9–NR)
MLH1–PMS2 dimer loss	94 (66%)	46	48.9 (38.5–59.5)	NR (34.7–NR)
MSH2–MSH6 dimer loss	16 (11%)	9	56.3 (29.9–80.2)	NR (13.9–NR)
Other[a]	33 (23%)	10	30.3 (15.6–48.7)	NR (13.7–NR)

1. Pasanen, A, et al. *Mod Pathol* **33**, 1443–1452 (2020). 2. Kurpiel, B, et al. *Int J of Gyn Path* 41:1:1-11 (2022). 3. Buchanan, D, et al. *JCO* 2014 32:2, 90-100, 4. Kahn, RM et al. *Cancer*, 125: 3172-3183.

[a]Other: any other pattern of loss that is not exclusively MLH1–PMS2 or MSH2–MSH6 dimer loss. This group includes 17 patients with loss of expression of 1 MMR protein, 13 with loss of 3 proteins, 1 with loss of 2 proteins that are not a canonical dimer, and 2 with MMR unknown/MSI-H status.
dMMR, MMR deficient; DOR, duration of response; EC, endometrial cancer; IHC, immunohistochemistry; MMR, mismatch repair; MSI-H, microsatellite instability–high; ORR, objective response rate.

No difference in ORR or DOR in those with MLH1 loss by mutation status

- Most MLH1 loss was not accompanied by mutations, consistent with the estimated rate in the dMMR population[1-4]

	Patients, N	Responders, n	ORR, % (95% exact CI)	DOR median (95% CI), mo
Cohort A1 (dMMR/MSI-H EC)	143	65	45.5 (37.1–54.0)	NR (38.9–NR)
Cohort A1 patients with available mutation data	101	—	—	—
MLH1 loss by IHC (any pattern)[a]	78	31	39.7 (28.8–51.5)	NR (38.9–NR)
MLH1 loss by IHC (any pattern) and mutation in *MLH1* or *PMS2* genes	7 (9%)	3	42.9 (9.9–81.6)	NR (NR–NR)
MLH1 loss by IHC (any pattern) and no mutation in *MLH1* or *PMS2* genes	71 (91%)	28	39.4 (28.0–51.7)	NR (38.9–NR)

1. Pasanen, A, et al. *Mod Pathol* **33**, 1443–1452 (2020). 2. Kurpiel, B, et al. *Int J of Gyn Path* 41:1:1-11 (2022). 3. Buchanan, D, et al. *JCO* 2014 32:2, 90-100, 4. Kahn, RM et al. *Cancer*, 125: 3172-3183.

[a]This group includes 66 patients with loss of the MLH1–PMS2 dimer and 12 with another pattern.
dMMR, MMR deficient; DOR, duration of response; EC, endometrial cancer; IHC, immunohistochemistry; MMR, mismatch repair; MSI-H, microsatellite instability–high; ORR, objective response rate.

Conclusions

- Consistent with the literature, the most common pattern of MMR protein loss was the MLH1–PMS2 heterodimer (66% of patients in the GARNET cohort A1 vs ≈75% in the general EC population)[1-4]
- Tumors with loss of MLH1 and no mutation identified in *MLH1* or *PMS2* are likely to have MLH1 promoter methylation; however, direct testing of methylation would be the most accurate means to identify these patients
  - There were no noticeable differences observed in ORR by pattern of MMR protein loss or MMR gene methylation/mutation status
  - This data set is the largest to explore the response rate by mechanism leading to MMR deficiency
- These data are hypothesis generating
  - GARNET was not powered to study the effect of MMR protein pattern or mutation status on response to dostarlimab
- **The data suggest the route to MMR deficiency does not influence response to dostarlimab (ORR of 39.4% in patients with presumed MLH1 promoter methylation)**

1. Pasanen, A, et al. *Mod Pathol* **33**: 1443–1452 (2020). 2. Kurpiel, B, et al. *Int J of Gyn Path* **41(1):** 1-11 (2022). 3. Buchanan, D, et al. *JCO* 2014 **32(2)**, 90-100, 4. Kahn, RM et al. *Cancer*, **125**: 3172-3183.

dMMR, MMR deficient; EC, endometrial cancer; MMR, mismatch repair; ORR, objective response rate.

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

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O'NEAL COMPREHENSIVE CANCER CENTER AT UAB

Washington University in St. Louis
SITEMAN CANCER CENTER

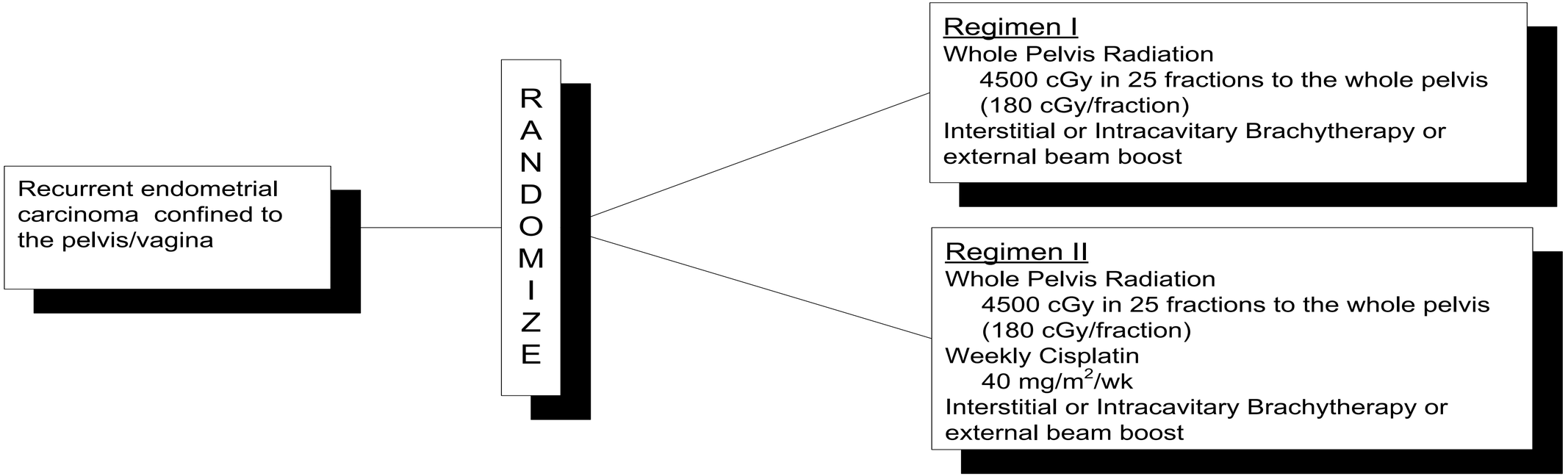
NCT03526432

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)

RANDOMIZED TRIAL OF PELVIC RADIATION WITH AND WITHOUT CONCURRENT CISPLATIN IN PATIENTS WITH A PELVIC ONLY RECURRENCE OF ENDOMETRIAL CANCER

GOG 238



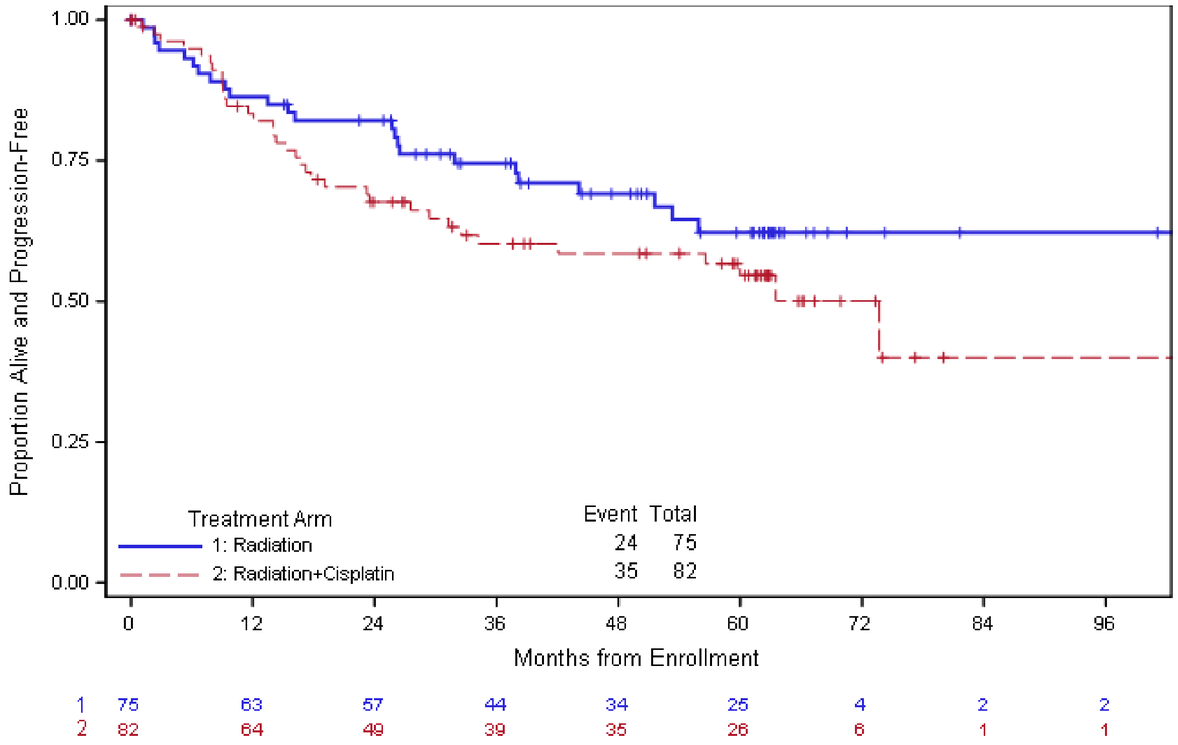
Institution IMRT Credentialing is required when IMRT is to be used before registering any patient on this trial. A Knowledge Assessment for this study must be completed by the treating radiation oncologist before registering patients on this trial.

For patients with tumors involving the distal vagina and clinically negative groins, the bilateral inguino-femoral lymph node regions should be treated to 4500 cGy.

3-D conformal or IMRT boost is allowed for patients who are not candidates for brachytherapy.

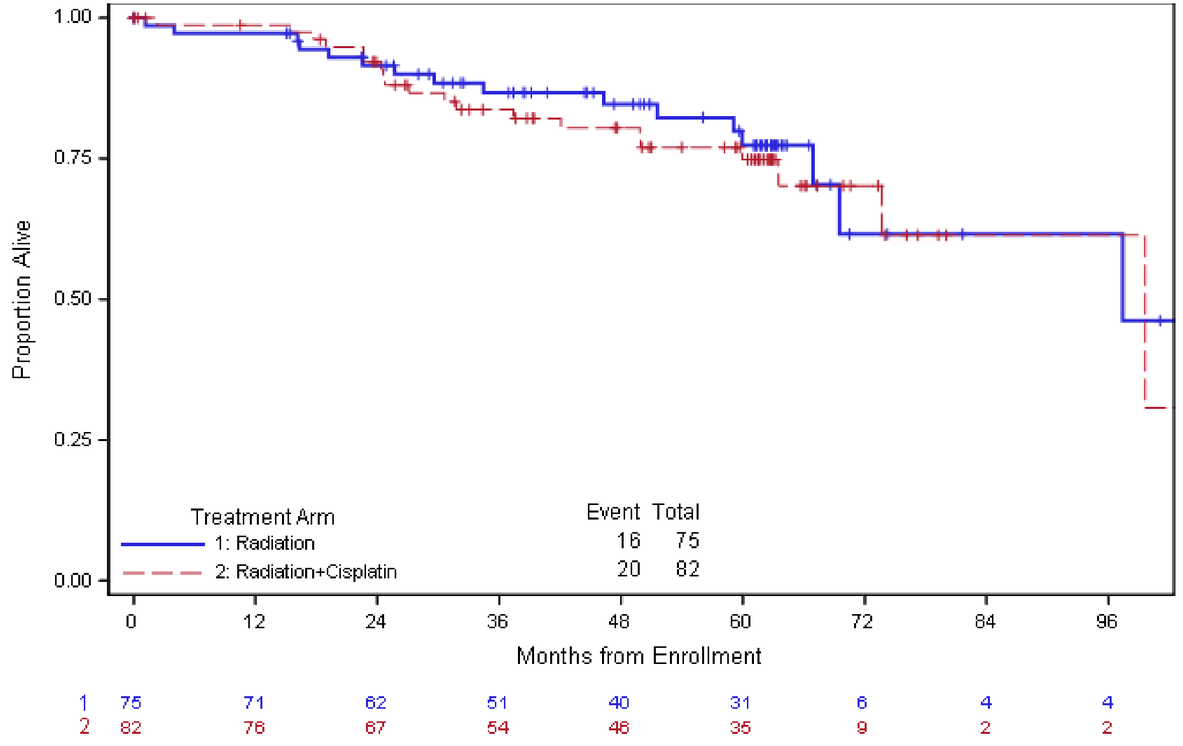
GOG-0238

PFS



HR 1.5 (95% CI: 0.88 – 2.55)

OS



HR 1.14 (95% CI: 0.57 – 2.28)

Radiation therapy remains the standard of care for pelvic only/vaginal cuff recurrences
Low grade endometrioid cancers highly represented (81.5%)
32% of patients treated with radiation therapy recurred

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Ongoing Trials

First Line:

I/O

CDK 4/6 inhibition

Nuclear export inhibition

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 (KEYNOTE-C93/GOG-3064/ENGOT-en15)

Global lead: GOG (PI: Slomovitz co-PI: Backes)

ENGOT PI: S.Pignata

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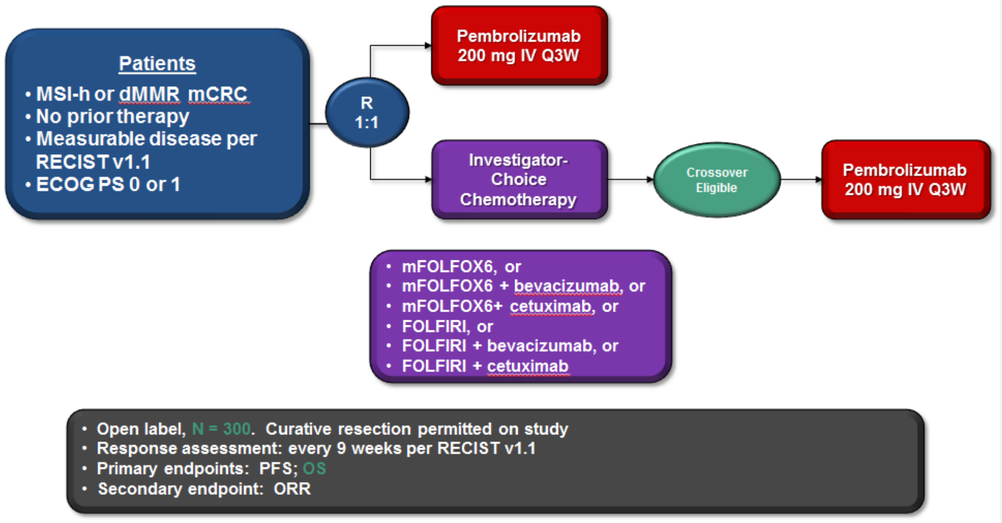
Transforming the standard of care™

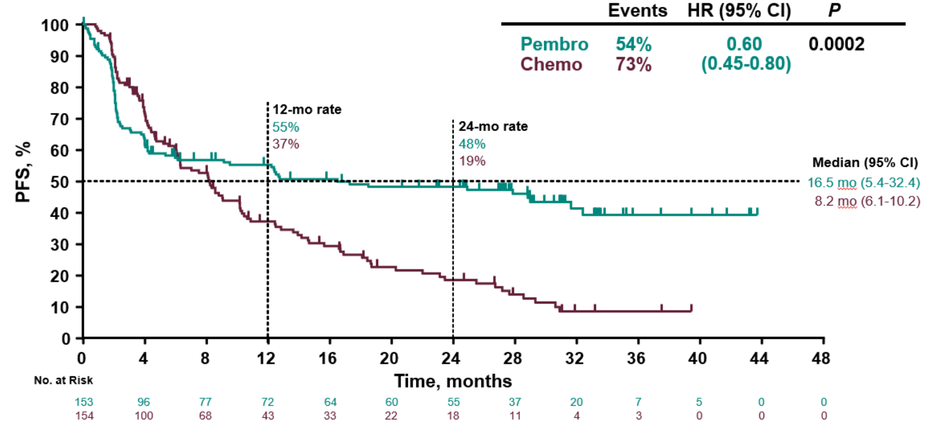
ENGOT
European Network of Gynaecological Oncological Trial groups

KEYNOTE-177: Robust Activity of Pembro Monotx Compared to SOC in Stage IV MSI-H/dMMR CRC

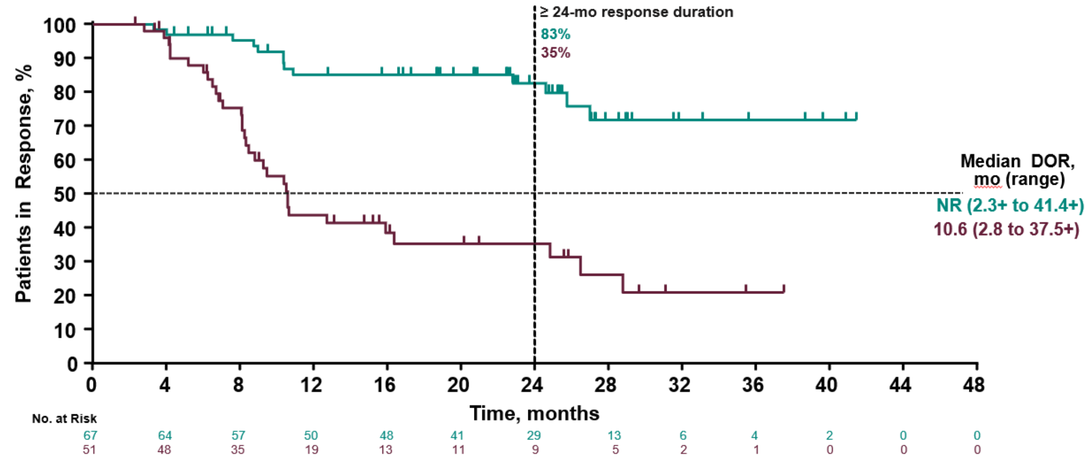


	Pembrolizumab N = 153	Chemotherapy N = 154
ORR, n (%)	**67 (43.8)**	**51 (33.1)**
Difference, estimate (95% CI)	10.7 (-0.2-21.3)	
P-value	0.0275	
Best Overall Response, n (%)		
Complete response	17 (11.1)	6 (3.9)
Partial response	50 (32.7)	45 (29.2)
Stable disease	32 (20.9)	65 (42.2)
Disease control rate (CR+PR+SD)	99 (64.7)	116 (75.3)
Progressive disease	45 (29.4)	19 (12.3)
Not evaluable	3 (2.0)	2 (1.3)
No assessment	6 (3.9)	17 (11.0)
Median time to response (range), mo	2.2 (1.8-18.8)	2.1 (1.7-24.9)

t-off: 19Feb2020; Response assessed per RECIST v1.1 by BICR.



Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR.
Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.



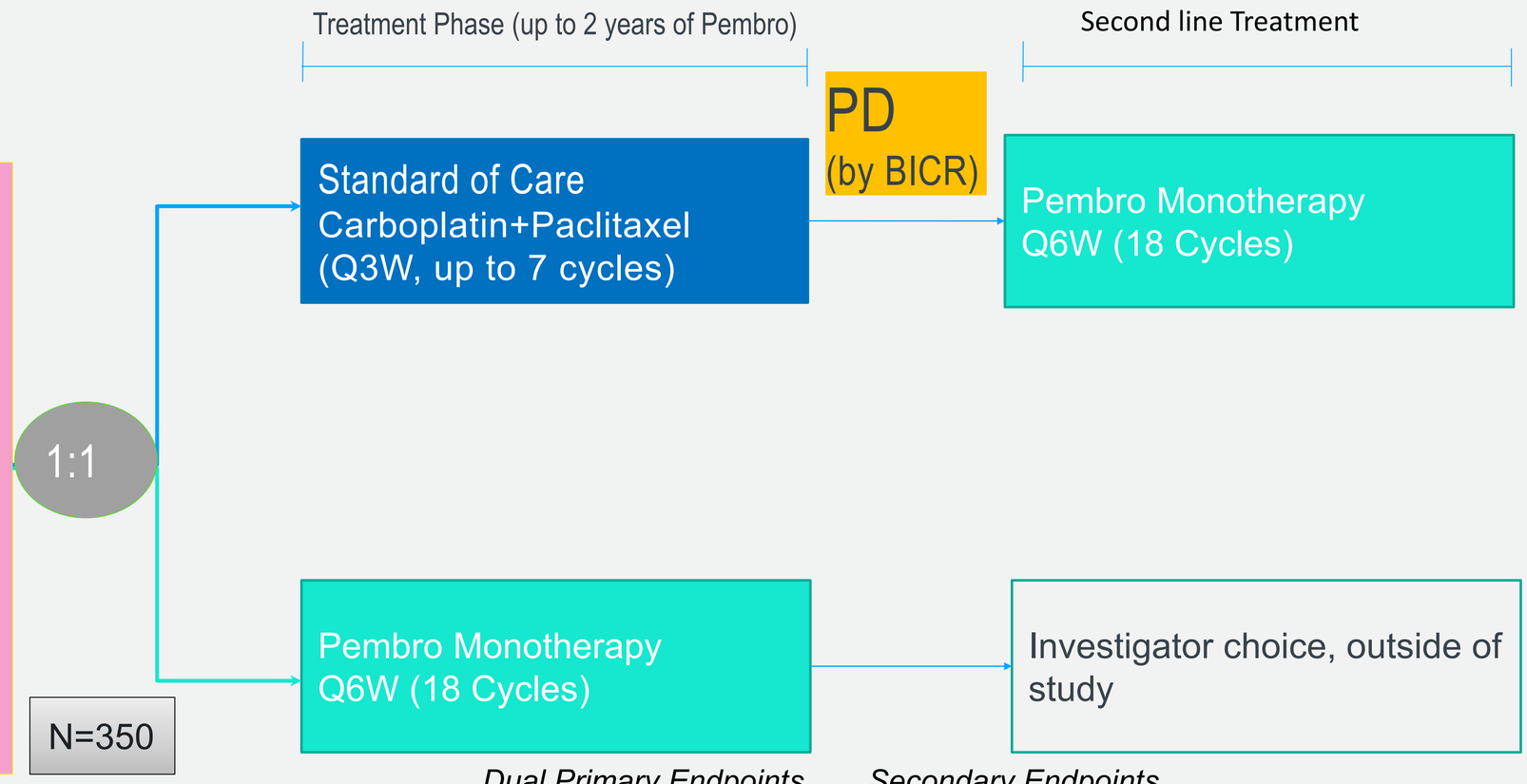
Duration of Response assessed per RECIST v1.1 by BICR; Data cut-off: 19Feb2020.

GOG 3064/ ENGOT–en15/MK KN-C93: 1L dMMR platinum-doublet chemotherapy vs pembro (with formal cross over)

Phase 3, multi-center, randomized, open-label

<u>Key Eligibility Criteria:</u>

- Stage III or IV, persistent/ recurrent, or metastatic EC
- Measurable/non-measurable disease (radiological apparent)
- dMMR/MSI-H
- No previous chemo for first line except as part of chemoradiation
- Prior adjuvant/neoadjuvant chemotherapy allowed, as long as completed > 6 mths before recurrence
- ECOG 0-1



Dual Primary Endpoints

- *PFS (by BICR)*
- *OS*

Secondary Endpoints

- *ORR (by BICR)*
- *PFS2*
- *HRQOL*
- *Safety*

<u>Potential Stratification:</u>

- Previous radiation and/or adj chemotherapy
- Histology – endometrioid vs. non-endometrioid

Background on CDK 4/6 Inhibition

- Most endometrial tumors are hormonally driven (type 1 endometrioid adenocarcinoma); estrogen signaling through estrogen receptor acts as an oncogenic signal

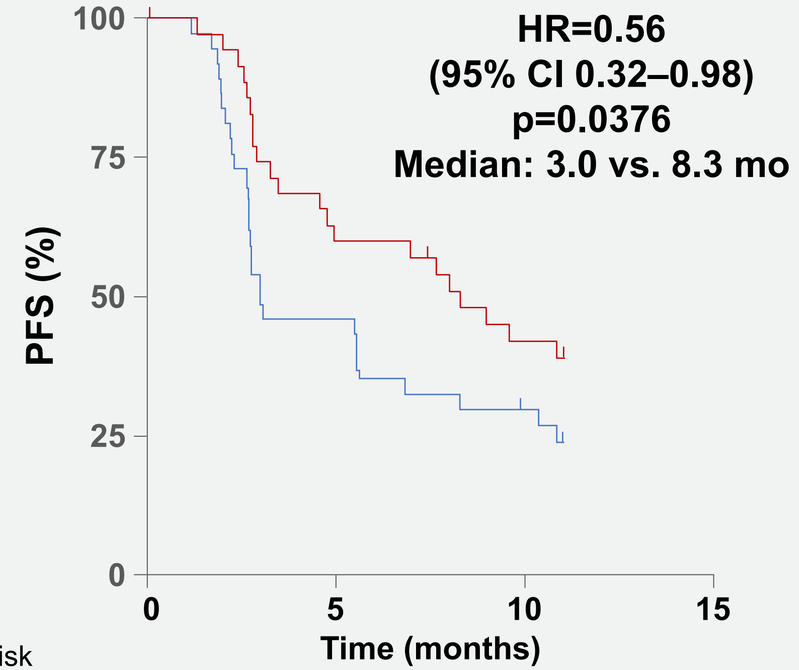
- Not all patients can handle more toxic treatments; low grade endometrioid cancer should be treated with endocrine therapy in the 1L, leaving cytotoxic options for later lines

- There is established clinical proof of concept for CDK 4/6i in metastatic endometrial cancer

- Endometrial cancer endocrine sensitivity and frequent cell cycle deregulation suggest that coupling mechanisms of CDKi and estrogen blockade could result in enhanced efficacy

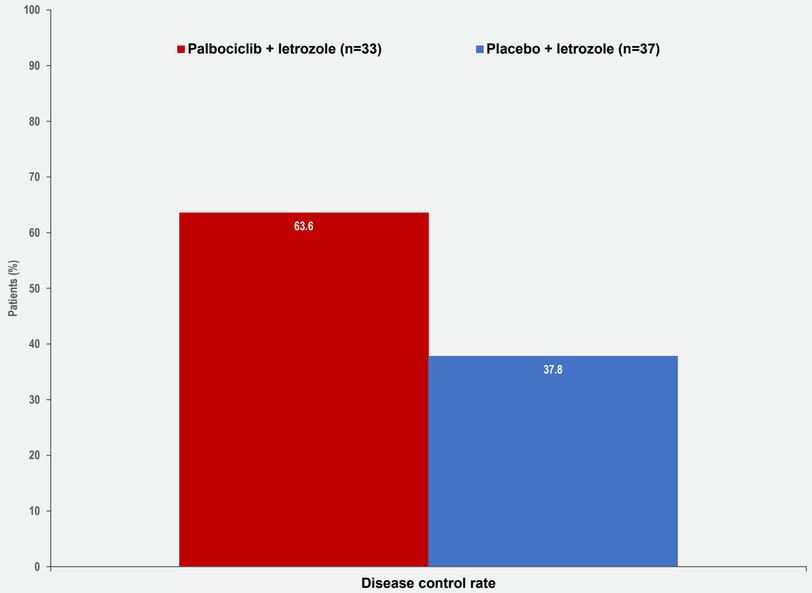
ENGOT-EN3/NSGO-PALEO: Efficacy (ITT population)

Primary endpoint: PFS



Number at risk			
Palbociclib + letrozole	36	21	14
Placebo + letrozole	37	17	10

Secondary endpoint: Disease control rate*



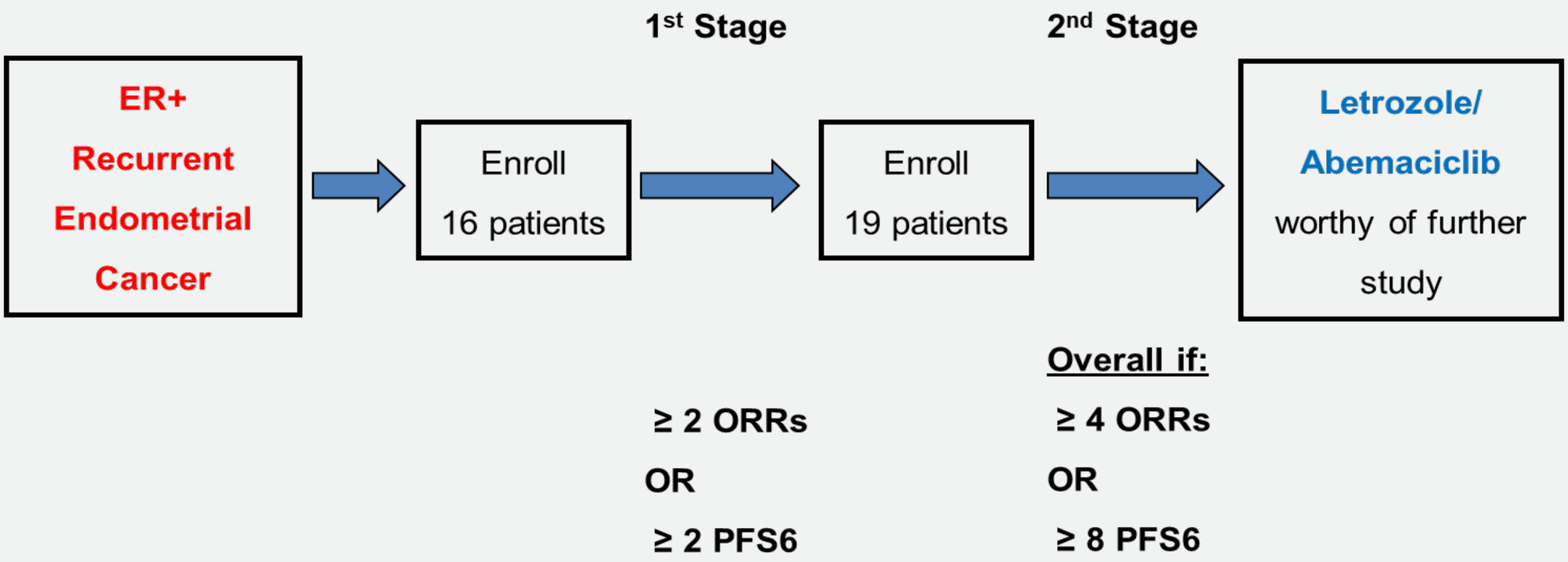
* = at 24 weeks

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

Mirza MR et al. *Ann Oncol*. 2020;31(suppl 4). Abstract LBA28.

Phase 2, two-stage study of letrozole and abemaciclib in estrogen receptor (ER) positive recurrent or metastatic endometrial cancer (EC)

- **Regimen:** Letrozole 2.5mg PO daily and Abemaciclib 150 mg PO BID until progression or toxicity



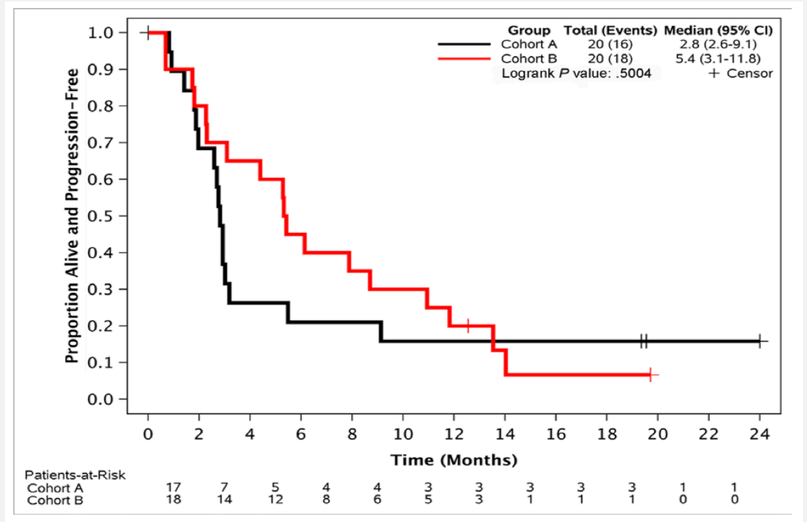
Objective Response Rate

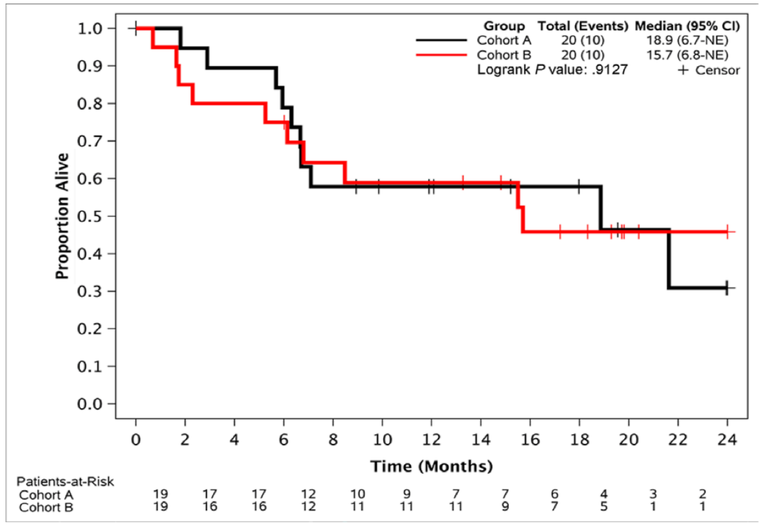
RESPONSE	Patients (N=30) n (%)
Best Overall Response	
Complete Response (CR)	0
Partial Response (PR)	**9 (30%)** **(1 unconfirmed,** **all PRs in endometrioid tumors)**
Stable Disease (SD)	13 (43.3%)
Progressive Disease (PD)	7 (23.3%)
Not evaluable	1 (3.3%)
ORR, % (95% CI)	**30% (14.7-49.4)**

Promising Early signal with combined AI and CDK4/6 inhibition in ER+ EC

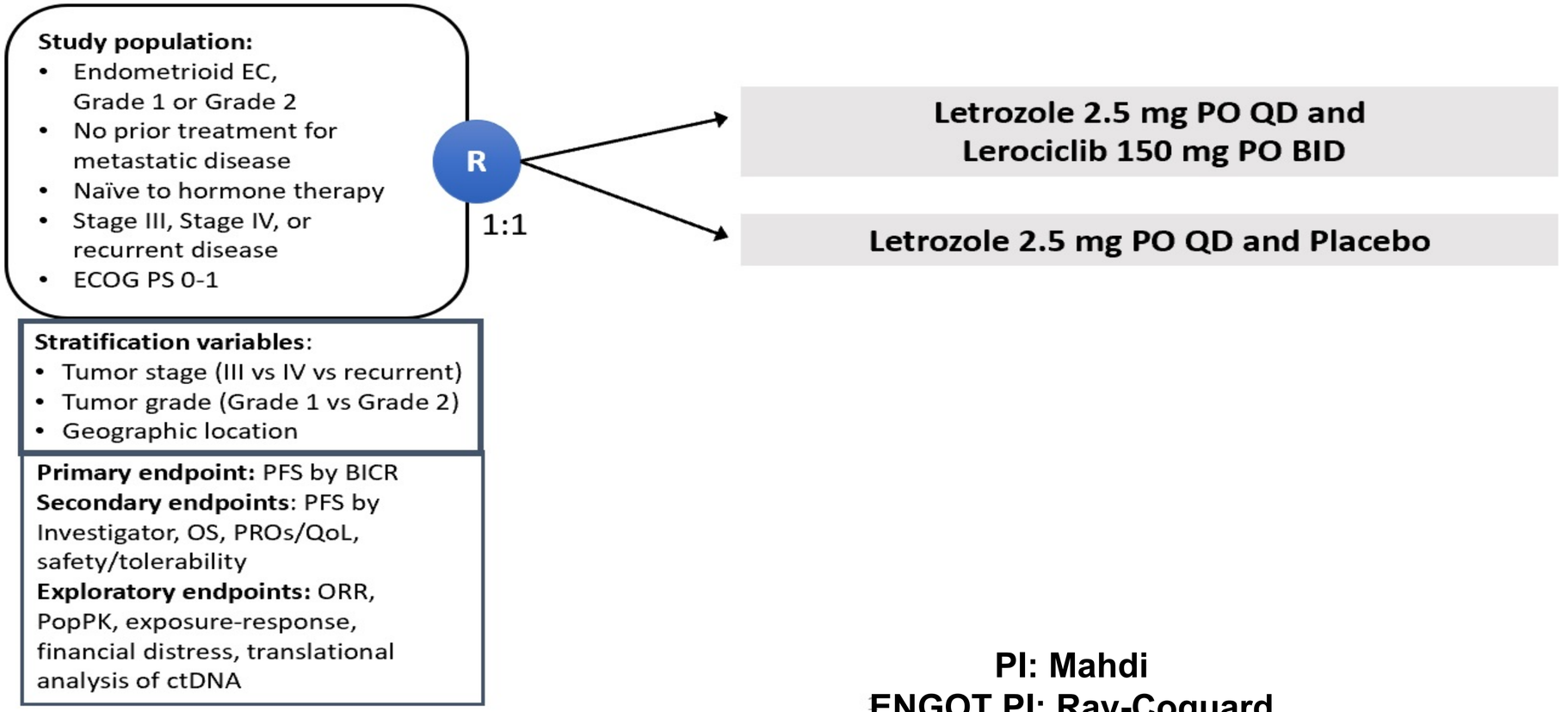
- Colon-Otero et al ESMO 2020
  - Letrozole 2.5 mg oral +Ribociclib 400 mg oral QD
  - PFS12 weeks 55%
  - PFS24 weeks 35%
  - PFS24 weeks in grade 1-2 EC 45%
  - Median PFS and OS 5.4 and 16

Table 2 Subset analysis of PFS	
Total Patients PFS ≥24 **weeks**	**11/40 (27.5%)**
Ovarian group	4/20 (20.0%)
Low-grade serous	3/3 (100.0%)*
High-grade serous	1/17 (5.9%)
Endometrial group	7/20 (35.0%)
Grade 1 to 2	5/11 (45.5%)
High-grade	2/9 (22.2%)





EQ132-303/GOG-3075/ENGOT en-17: A Randomized, Double-Blinded, Placebo-Controlled Phase 3 Study of Lerociclib with Letrozole, versus Placebo in Combination with Letrozole, in Participants with Advanced or Recurrent Grade 1 or Grade 2 Endometrioid



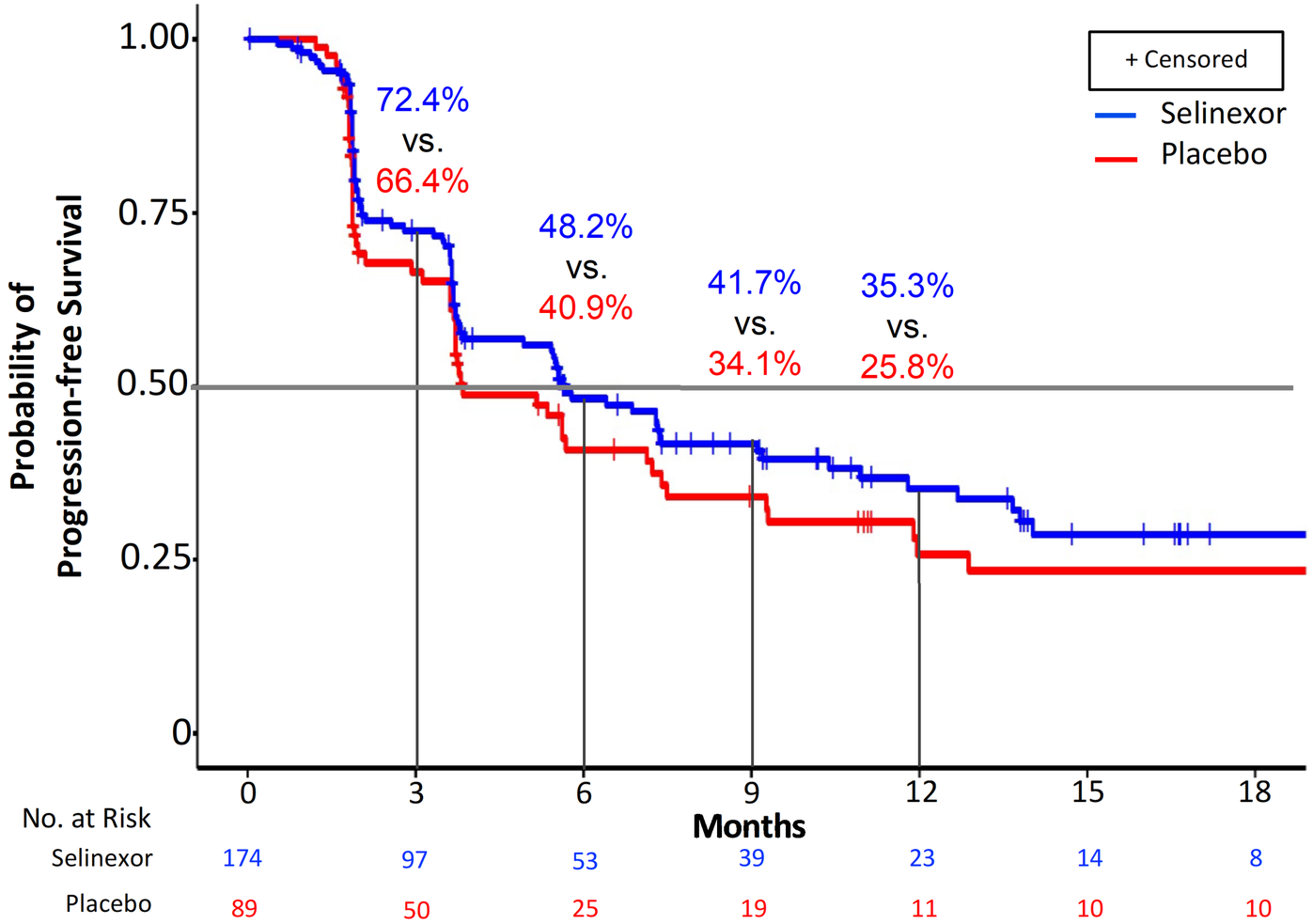
PI: Mahdi
ENGOT PI: Ray-Coquard

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)

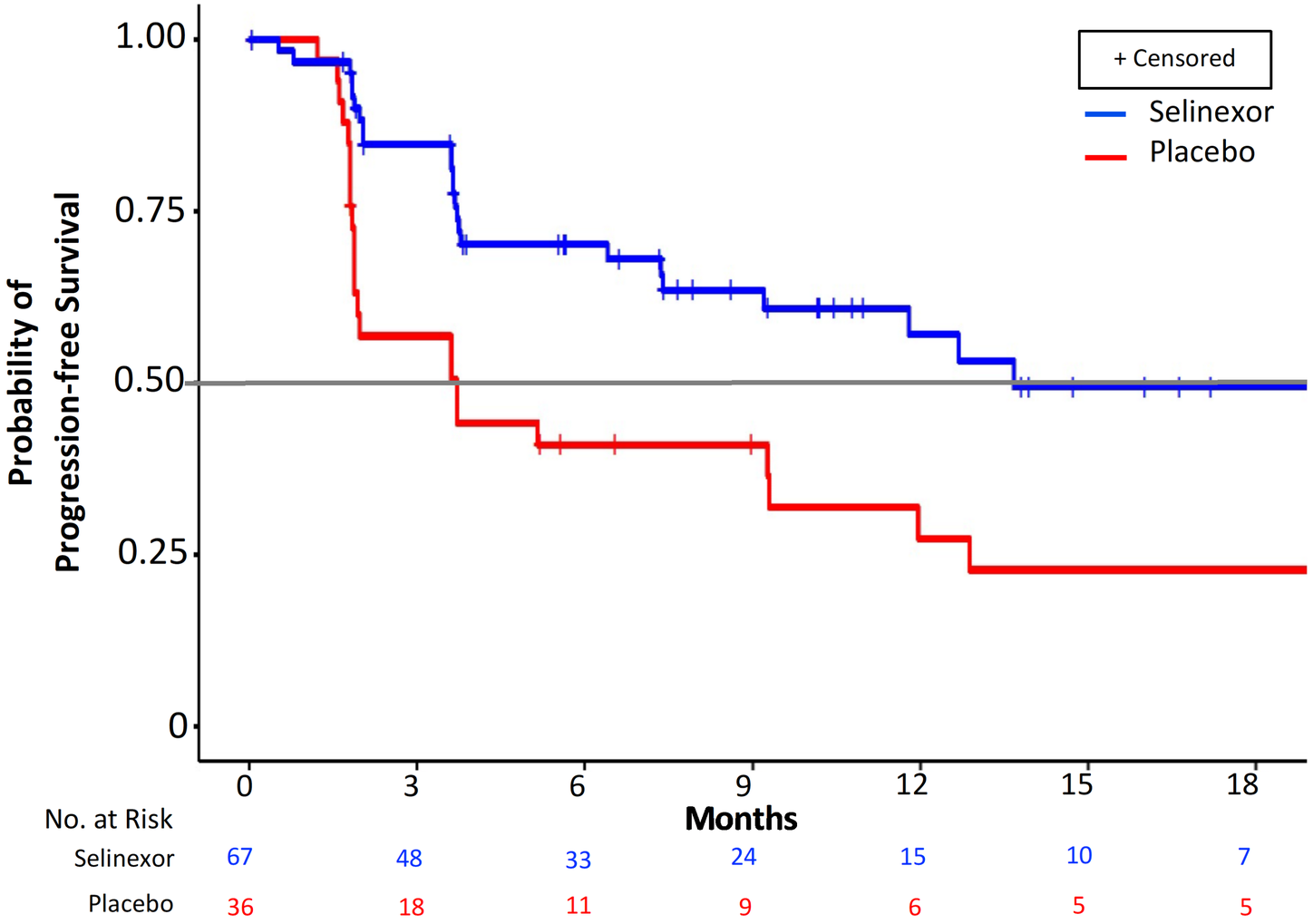
HR = 0.76 (95% CI 0.543-1.076)

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

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

GOG FOUNDATION

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

GOG Highlight Reel

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

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

Stratified by:
- Primary stage IV vs recurrent
- PR vs CR
- Prior CPI (yes/no)

n = 220 PFS (HR 0.7)
Key Eligibilities
- Known p53wt EC by central NGS
- Primary stage IV or recurrent EC
- Received at least 12 weeks of taxane-platinum chemotherapy (1st or 2nd line)

PR/CR Per RECIST v1.1

R 1:1

Selinexor 60mg QW until PD

Placebo until PD

Primary Endpoint:
- PFS assessed by Investigator (BICR as a sensitivity analysis)

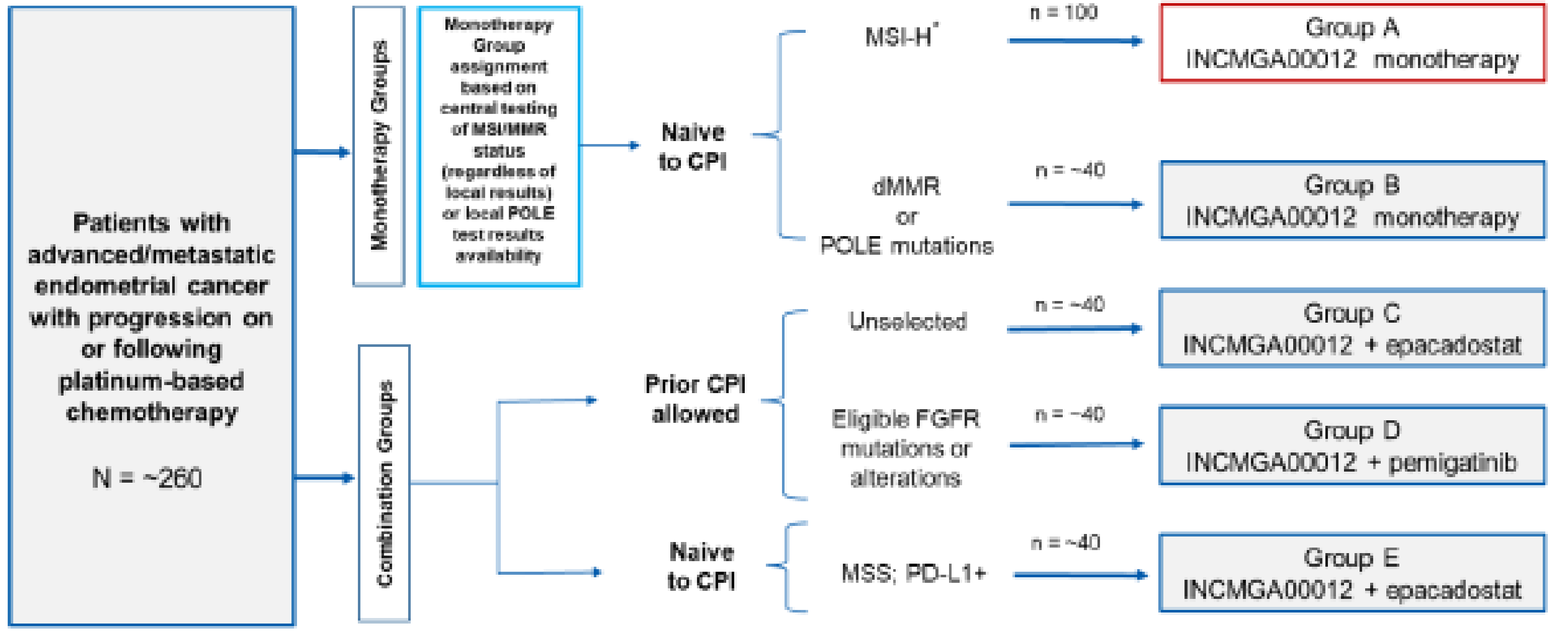
Secondary Endpoint:
- OS
- Safety

Second Line:
I/O

Primary Endpoint = ORR
PI: Slomovitz, B

INCMGA 0012-204/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



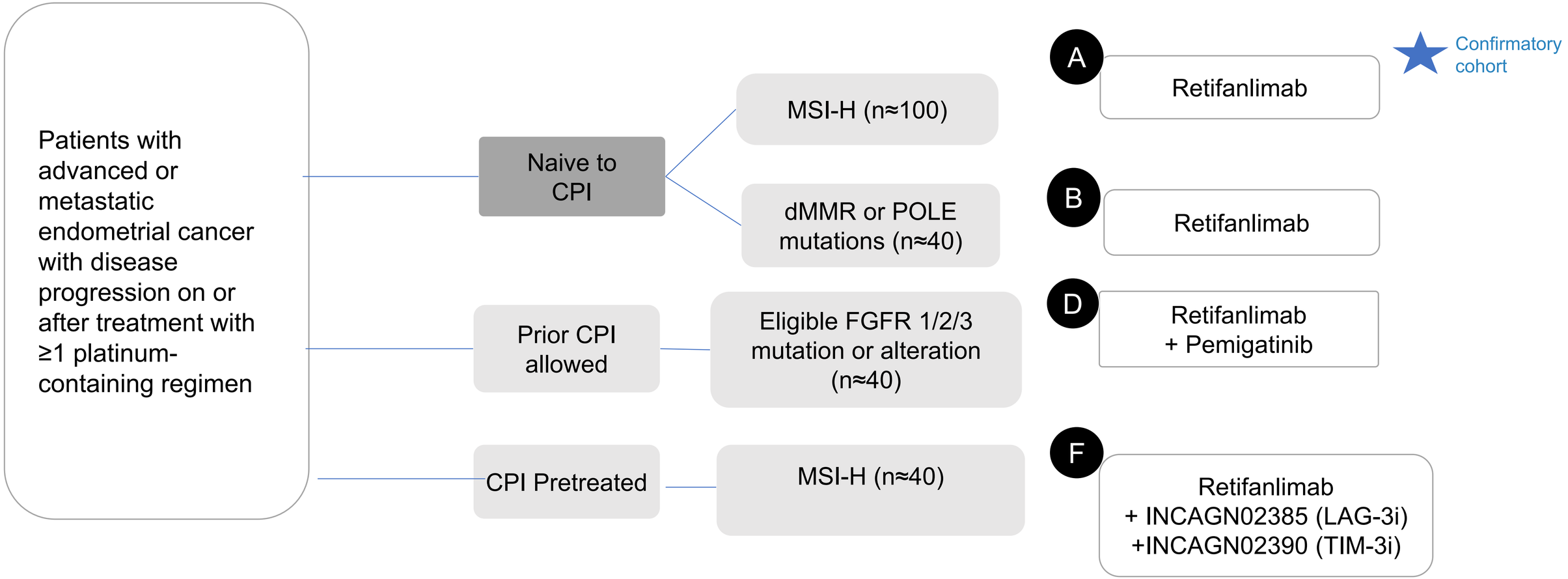
CLOSED

CPI = checkpoint inhibitor therapy.

Note: Participants in Group A or Group B who experience disease progression on INCMGA00012 monotherapy may be eligible for further treatment with 1 of the combination regimens.

*Participants naive to CPI therapy will be prioritized for central MSI testing to confirm eligibility for Group A, regardless of dMMR status.

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)**

GOG FOUNDATION

GOG Highlight Reel

MSI-H Endometrial Cancer - anti-LAG-3/anti-TIM-3/anti-PD-1 combination rationale

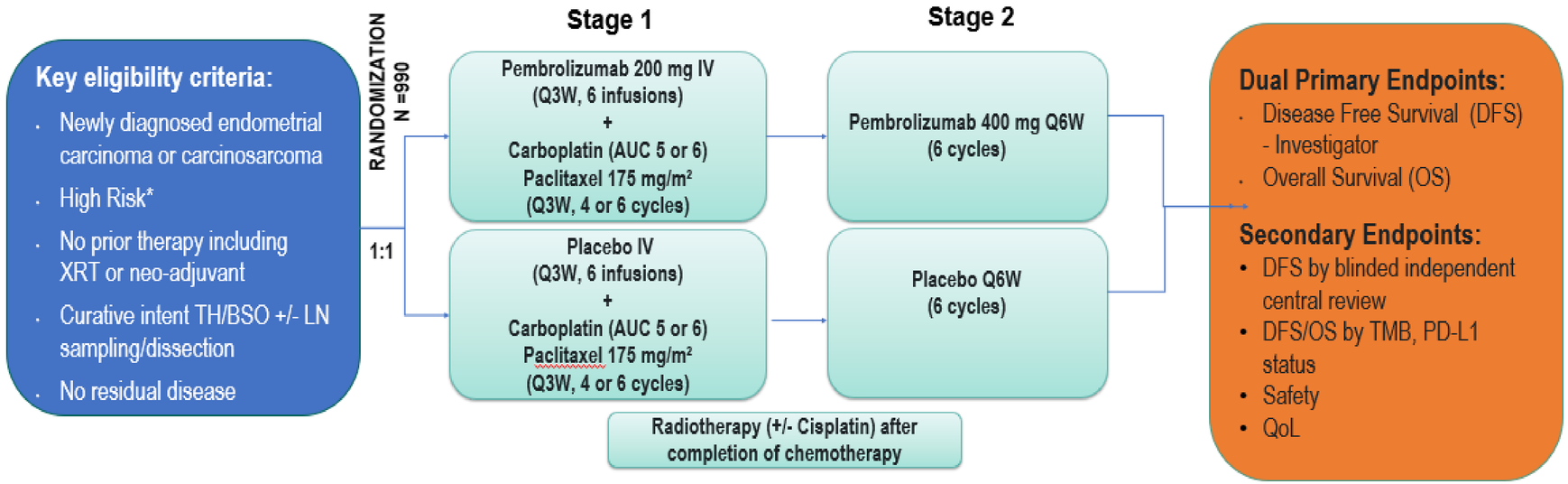
- Analysis of LAG-3 expression in the The Cancer Genome Atlas dataset showed a wide range of expression among different cancer types. Multiple solid tumors, including endometrial cancer, have considerably high expression of LAG-3 (Panda et al 2020).
- high LAG-3 expression measured by mRNA sequencing correlates significantly with high TMB
- tumor associated LAG-3+ lymphocytes are higher in MMR-deficient tumors compared with intact tumors
- TIM-3 and LAG-3 are frequently co-expressed with PD-1 in TILs
- rationale for PD-1, LAG 3, and TIM-3 combination blockade support exploring the clinical activity of the triplet combination approach in MSI-H/dMMR advanced endometrial cancer with evidence of disease progression on or after prior PD-(L)1 therapy

Predicting the Future

N=990
Closed to accrual
PI: Slomovitz, B, Barber, E

MK-3475-B21/ENGOT-en11/GOG-3053 KEYNOTE-B21

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



*** 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)

GOG FOUNDATION

NCT04634877

GOG Highlight Reel

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	CLOSED TO ACCRUAL
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	CLOSED TO ACCRUAL
Front-line, metastatic or recurrent PI: Slomovitz, Backes *GOG led	GOG-3064/c93 NCT05173987	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

Endometrial Cancer: 1st line metastatic recurrent

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	CLOSED
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

Predicting Future in First Line Recurrent-dMMR

	Chemo + I/O +/- PARP	LEAP-001	
Scenario #1	Positive	Positive	Either regimen or C93
Scenario #2	Positive	Negative	Chemo I/O; C93??
Scenario #3	Negative	Positive	Pembro/Len or C93
Scenario #4	Negative	Negative	Chemo; EXPORT; CDK4/6

Predicting Future in First Line Recurrent-dMMR

	Chemo + I/O +/- PARP	LEAP-001	
Scenario #1	Positive	Positive	
Scenario #2	Positive	Negative	
Scenario #3	Negative	Positive	
Scenario #4	Negative	Negative	
Scenario #5	Positive or Negative	Positive or Negative	B21: Positive

Predicting Future in First Line Recurrent-pMMR

	Chemo + I/O +/- PARP	LEAP-001	
Scenario #1	Positive	Positive	Chemo+I/O or Pem/Len
Scenario #2	Positive	Negative	Chemo+I/O
Scenario #3	Negative	Positive	Pem/Len; EXPORT, CDK4/6
Scenario #4	Negative	Negative	Chemo; EXPORT, CDK4/6

Predicting Future in First Line Recurrent-pMMR

	Chemo + I/O +/- PARP	LEAP-001	
Scenario #1	Positive	Positive	
Scenario #2	Positive	Negative	
Scenario #3	Negative	Positive	
Scenario #4	Negative	Negative	
Scenario #5	Positive or Negative	Positive or Negative	Positive

The Future is Bright