Applicazione delle ESGO/ESTRO/ESP guidelines nella terapia adiuvante e novità nella terapia sistemica

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ESGO-ESTRO-ESP Endometrial Cancer Guidelines

27 Members of multidisciplinary European Working Group

Balance between “OLD“ and “ NEW“ working group members

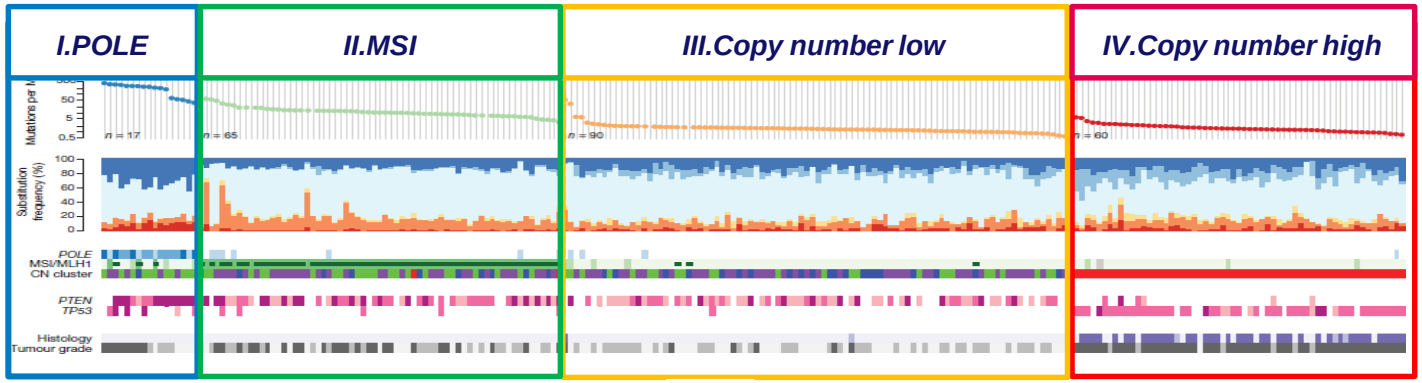
Risk classification and adjuvant treatment

Definition of prognostic risk groups integrating molecular markers

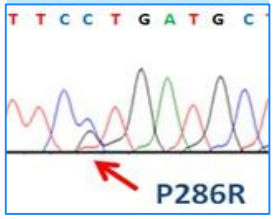
Classical risk factors

- Grade
- Myometrial invasion
- Histologic subtype
- LVSI
- Stage
- Age

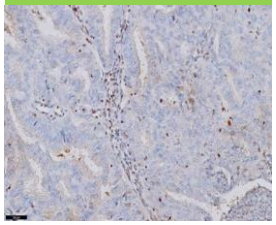
TCGA molecular groups by surrogate markers
ProMisE molecular classifier



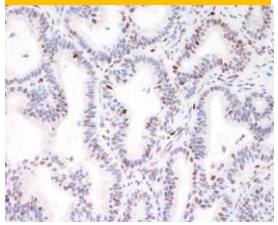
Mol Class 1
POLE mut



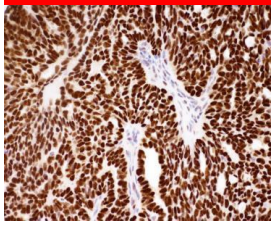
Mol Class 2
MMRd



Mol Class 3
NSMP



Mol Class 4
p53abn

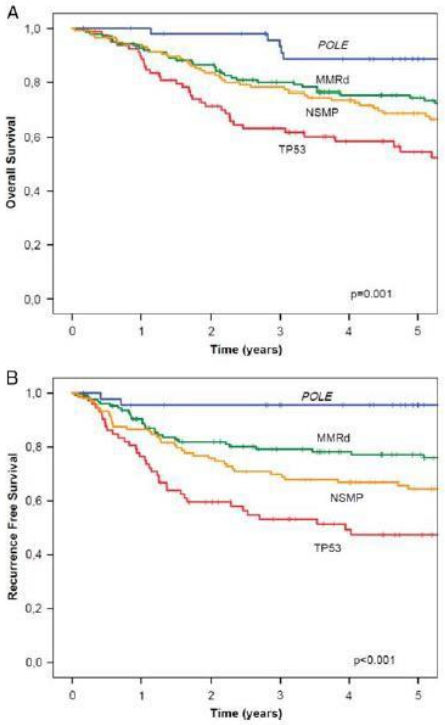


TGCA, Kandoth et al, Nature 2013; Stelloo et al, Clin Cancer Research 2016, Kommos et al, Annals of Oncology 29: 1180–1188, 2018

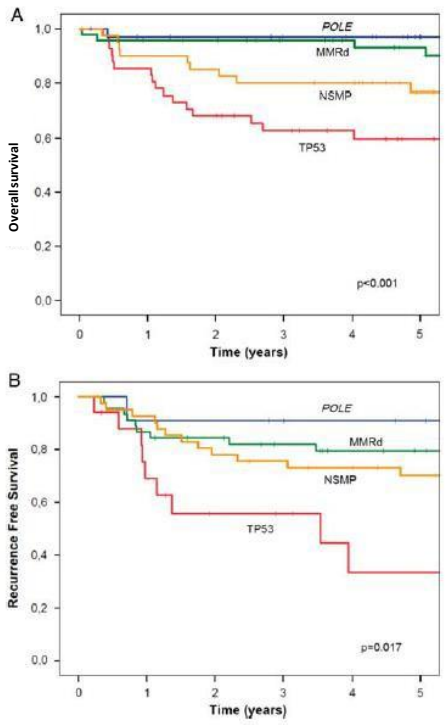
Risk category and prognosis may change according to molecular classification: the case of grade 3

N=381; international collaboration

Grade 3, all stages



Grade 3, stage I

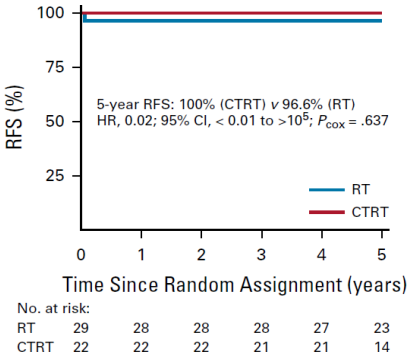


- Grade 3 endometrial cancer is **not** a homogeneous 'high risk' cohort
- TGCA molecular groups have clear prognostic impact in high-risk EC
- Prognostic strength of molecular classification is independent of stage

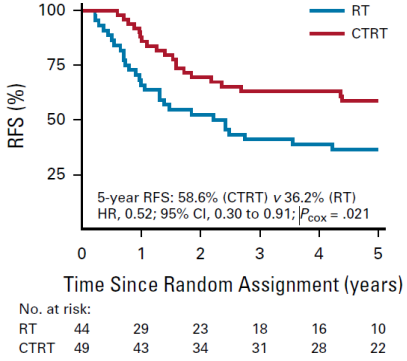
Bosse et al, Am J Surg Pathol 2018

PORTEC-3
Molecular classification predictive of benefit from adjuvant chemotherapy?

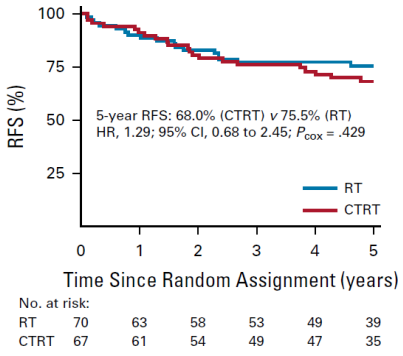
*POLE*mut



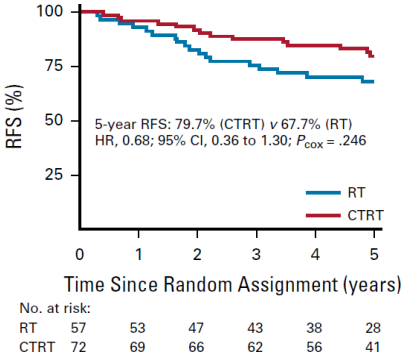
p53abn



MMRd



NSMP



Leon-Castillo et al; JCO 2020

Pathology and molecular pathology: take home message

- Conventional pathologic analysis remains an important tool for tumor stratification, but suffers from interobserver variation.
- A simplified pragmatic molecular classification using immunohistochemical markers (p53, MSH-6 and PMS-2) and one molecular test (mutation analysis of the exonuclease domain of polymerase Ɛ (*POLE*) has been shown to identify groups analogous to the TCGA genomic-based classification. A large number of publications reported the feasibility of this approach and confirmed its prognostic relevance.
- **The definition of prognostic risk groups to inform adjuvant treatment should now integrate the surrogate molecular classification with conventional morphologic features**

The ESGO-ESTRO-ESP guidelines (2020)

ESGO European Society of Gynaecological Oncology

ESTRO

European Society of Pathology

MaNGO Marie Negri Gynecology Oncology

Risk Group	Molecular Classification Unknown	Molecular Classification Known[Δ],*
Low	• Stage IA endometrioid + low-grade** + LVSI negative or focal	• Stage I-II ***POLE*mut** endometrial carcinoma, no residual disease • Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade** + LVSI negative or focal
Intermediate	• Stage IB endometrioid + low-grade** + LVSI negative or focal • Stage IA endometrioid + high-grade** + LVSI negative or focal • Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	• Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade** + LVSI negative or focal • Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade** + LVSI negative or focal • Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High-intermediate	• Stage I endometrioid + substantial LVSI, regardless of grade and depth of invasion • Stage IB endometrioid high-grade**, regardless of LVSI status • Stage II	• Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI, regardless of grade and depth of invasion • Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade**, regardless of LVSI status • Stage II **MMRd/NSMP** endometrioid carcinoma
High	• Stage III-IVA with no residual disease • Stage I-IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	• Stage III-IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease • Stage I-IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease • Stage I-IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced Metastatic	• Stage III-IVA with residual disease • Stage IVB	• Stage III-IVA with residual disease of any molecular type • Stage IVB of any molecular type

[Δ]For stage III-IVA ***POLE*mut** endometrial carcinoma, and stage I-IVA MMRd or NSMP clear cell carcinoma with myometrial invasion, insufficient data are available to allocate these patients to a prognostic risk-group in the molecular classification. Prospective registries are recommended

* see text on how to assign double classifiers (e.g. patients with both *POLE*mut and p53abn should be managed as *POLE*mut)

** according to the binary FIGO grading, grade 1 and grade 2 carcinomas are considered as low-grade, and grade 3 carcinomas are considered as high-grade.

p53abn: p53 abnormal, MMRd: Mismatch Repair Deficient, NSMP: nonspecific molecular profile, *POLE*mut: polymerase Ɛ mutated

Adjuvant treatment: low risk

Low risk:

- **Stage IA (G1 and G2) with endometrioid ([a]MMRd and NSMP) type and no or focal LVSI**
- **Stage I/II POLEmut cancer**
- **Stage IA non-endometrioid type and/or P53 abnormal restricted to polyps + no or focal LVSI**

No adjuvant treatment

POLEmut cancers stage III: no adjuvant treatment is an option, but no data available, so preferably treat within the scope of prospective registry

Adjuvant treatment: Intermediate risk

Intermediate risk:

- **Stage IA G3 with endometrioid type (MMRd and NSMP) + no or focal LVSI**
- **Stage IB (G1 and G2) with endometrioid type (MMRd and NSMP) + no or focal LVSI**
- **Stage IA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) and/or p53 abn cancers without myometrial invasion and no or focal LVSI**

- **Adjuvant brachytherapy can be recommended to decrease vaginal recurrence**
- **Omission of adjuvant brachytherapy can be considered especially for patients aged <60 years**

Adjuvant treatment: High intermediate risk ,node negative

High Intermediate risk:

- Stage I endometrioid (MMRd and NSMP) any grade and depth of invasion with substantial LVSI
- **Stage IB G3 with endometrioid type (MMRd and NSMP) + no or focal LVSI**
- **Stage II endometrioid cancer (MMRd and NSMP) and no high risk criteria**

- Adjuvant brachytherapy is recommended to decrease vaginal recurrence.
- External beam radiotherapy can be considered for substantial LVSI, IBG3 and for stage II.
- Adjuvant chemotherapy can be considered, especially for grade 3 and/or substantial LVSI.
- Omission of any adjuvant treatment is an option after shared decision making and with close follow-up.

Adjuvant treatment: High intermediate risk , node unknown

High Intermediate risk:

- Stage I endometrioid (MMRd and NSMP) any grade and depth of invasion with substantial LVSI
- **Stage IB G3 with endometrioid type (MMRd and NSMP) + no or focal LVSI**
- **Stage II endometrioid cancer (MMRd and NSMP) and no high risk criteria**

- Adjuvant external beam radiotherapy is recommended, especially for substantial LVSI. stage IBG3 and/or for stage II
- Additional (concomitant or sequential) adjuvant chemotherapy can be considered, especially for grade 3 and/or substantial LVSI
- Adjuvant brachytherapy alone can be considered for grade 3 LVSI negative or focal and for stage II grade 1 endometrioid cancers

Adjuvant treatment: High risk

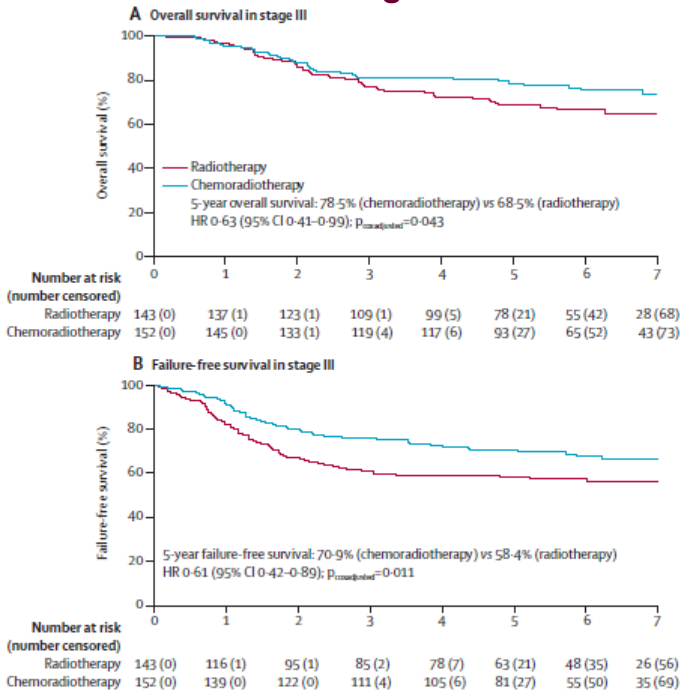
High risk:

- **All stages and all histologies with p53abn and myometrial invasion**
- **All stages with serous or undifferentiated carcinoma including carcinosarcoma with myometrial invasion**
- **All Stage III-IV with no residual tumor, regardless of histology and regardless of molecular subtype**

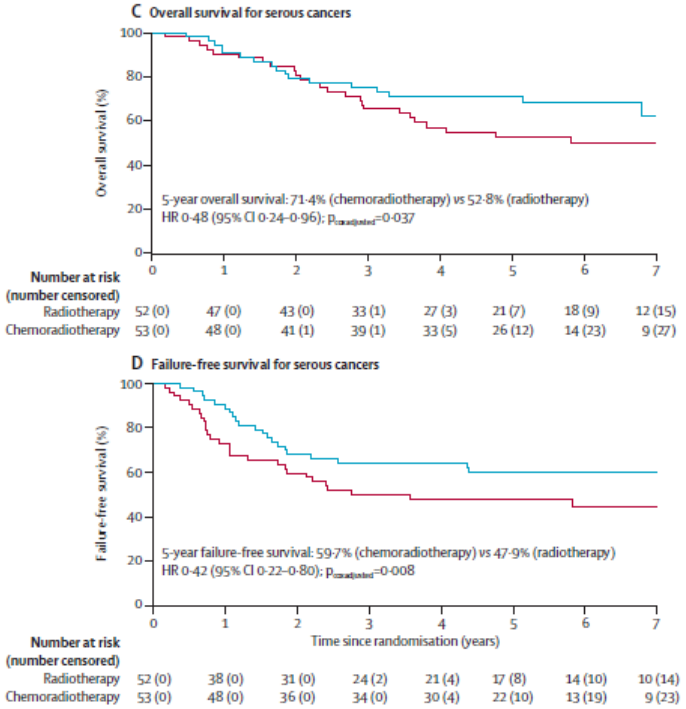
- EBRT with concurrent and adjuvant chemotherapy is recommended
- Sequential chemotherapy and radiotherapy
- Chemotherapy alone is an alternative option

PORTEC 3: updated results (72 months median F-UP)

Stage III



Serous



The Lancet Oncology July 22, 2019

GOG 158 : C-RT vs CT

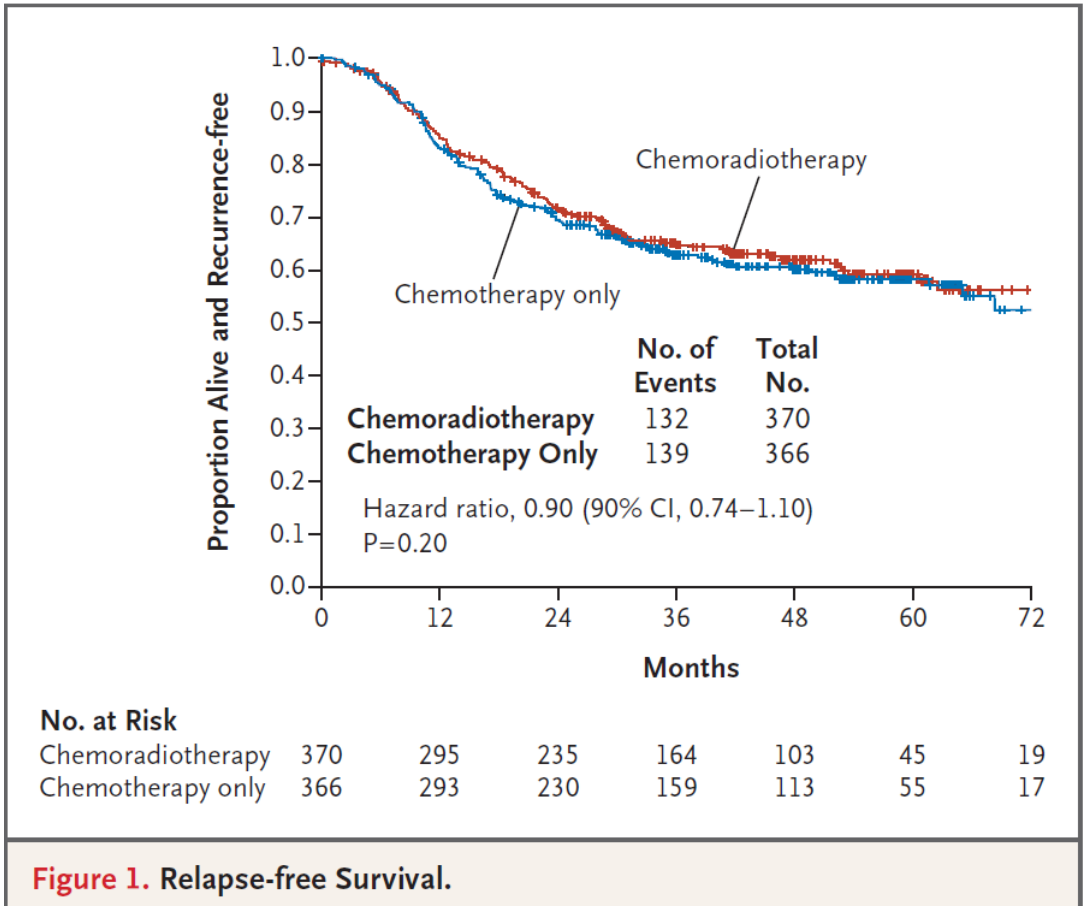


Figure 1. Relapse-free Survival.

Daniela Matei et al. N Engl J Med, June 13, 2019

Adjuvant treatment: take home message

- **All POLE tumors**, irrespective of stage and grade are **Low risk**
  - **No adjuvant treatment**
- **All P53 abn tumors,** irrespective of stage and grade are **High risk**
  - **EBRT with concurrent and adjuvant chemotherapy, sequential chemotherapy and EBRT, chemotherapy**
- **IB G3 tumors,** in the absence of P53 abn (high risk) or POLE (low risk) are **high intermediate risk**
  - **Brachytherapy (EBRT or chemotherapy if LVSI +)**
  - **Observation**

Clinical Case #1

56-year old, BMI= 22, no comorbidities.

Surgery: Hysterectomy + BSO + SLN biopsy (Robotic-assisted)

Pathology: endometrioid adenocarcinoma of the endometrium, grade 3, MI>50% (6mm/10mm). No LVSI. Negative SLN bilaterally.

Stage FIGO IB G3

Molecular analysis:

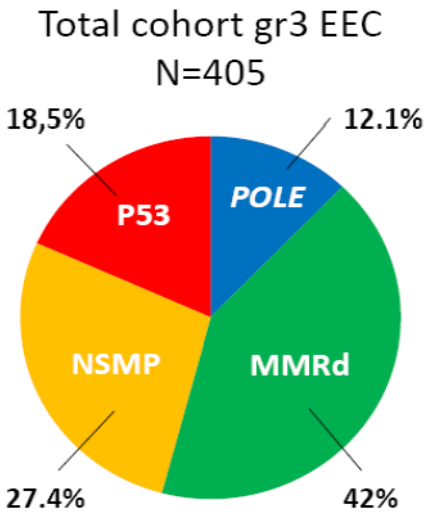
MSS: microstability stable. IHC for MLH1, PMS2, MSH2, MSH6 present.

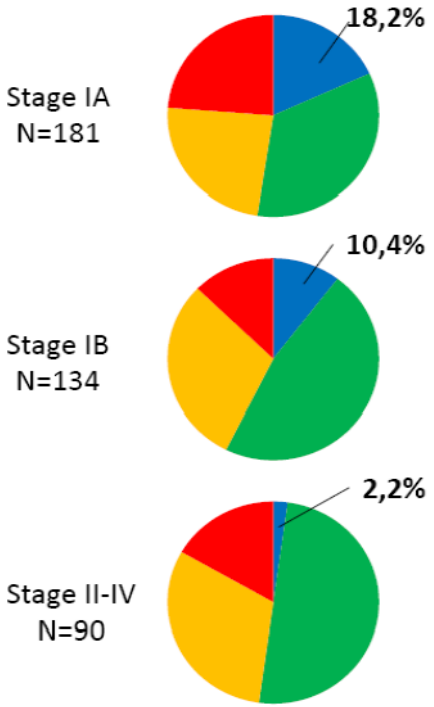
NGS POLE: mutated (percentage of mutated allels: 19%)

NGS TP53: wild-type

Clinical Case #1

Subgroups in which molecular subtyping is particularly helpful…Grade 3 endometrioid endometrial cancer



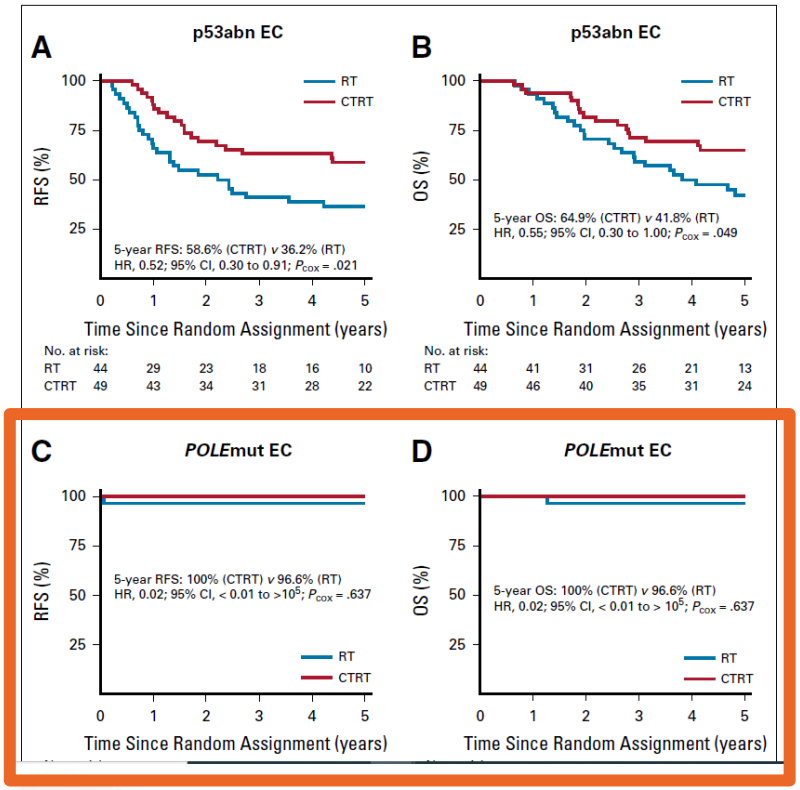


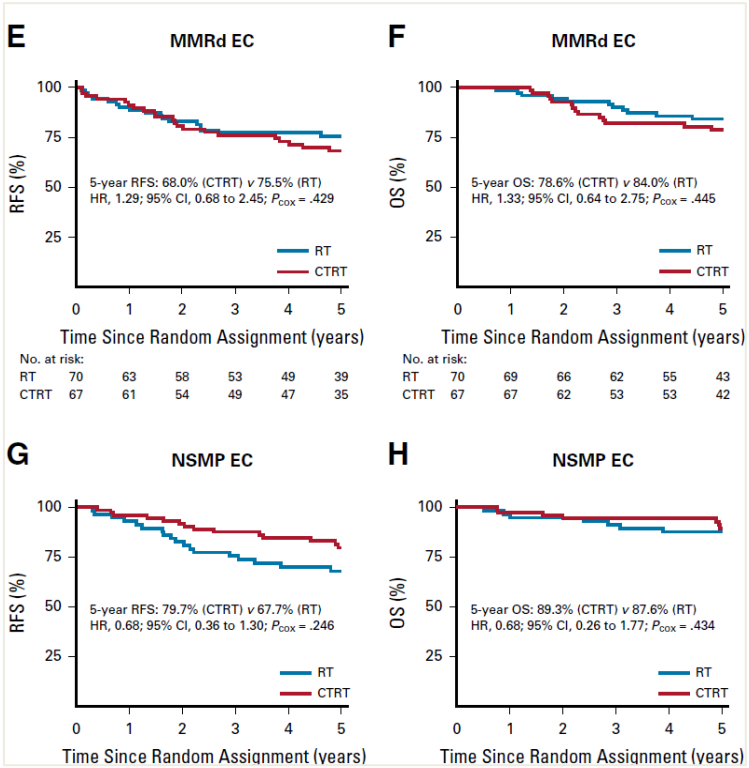
Frequency of POLEmut is relatively high in grade 3 EEC, **and it's associated with early stage**

Bosse, Soslow, Am J Surg Path 2018

PORTEC-3

Molecular classification predictive of benefit from adjuvant chemotherapy?





Leon de Castillo et al. , JCO 2020

Clinical Case #1

Suggested treatment based on clinicopathologic risk factors (high-intermediate risk):

- Radiotherapy or Chemoradiation (PORTEC 3)

Suggested treatment based on the molecular classification:

- **Observation.**

Clinical Case #2

61-year old, BMI= 27,no comorbidities.

Surgery: Hysterectomy + BSO + SLN biopsy (Robotic-assisted)

Pathology: endometrioid adenocarcinoma of the endometrium, grade 3, MI<50% (3.5mm/11mm), no LVSI, associated with complex iperplasia with atypia. Negative SLN bilaterally.

Stage FIGO IA G3

Molecular analysis:

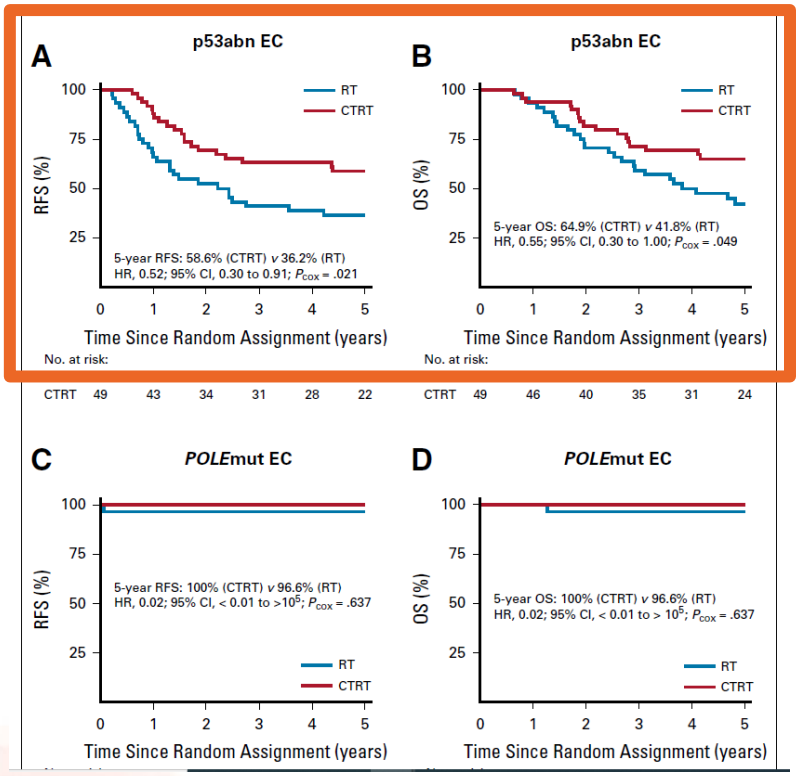
MSS: microstability stable. IHC for MLH1, PMS2, MSH2, MSH6 present.

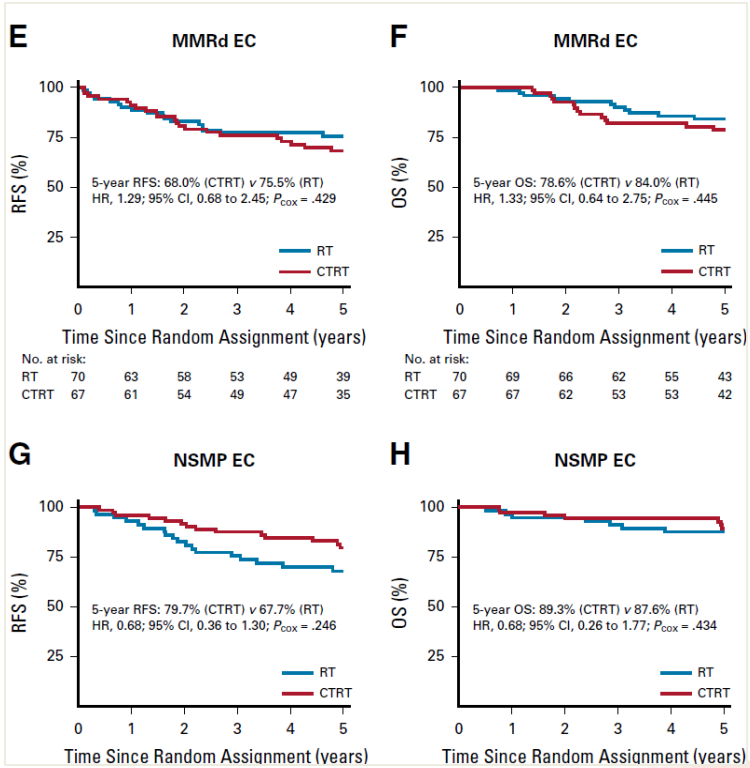
NGS POLE: wild-type

NGS TP53: mutated (percentage of mutated allels: 17%)

PORTEC-3

Molecular classification predictive of benefit from adjuvant chemotherapy?





Leon de Castillo et al. , JCO 2020

Clinical Case #2

Suggested treatment based on the ESGO Guidelines following the classical risk factors (Intermediate-risk):

- Vaginal brachitherapy vs. Observation

Suggested treatment based on the molecular classification (High-risk):

- EBRT with concurrent and adjuvant chemotherapy (PORTEC 3)
- Sequential chemotherapy and radiotherapy
- Chemotherapy alone is an alternative option (GOG 258)

Clinical Case #3

75-year old, BMI= 23.

Surgery: Hysterectomy + BSO + SLN biopsy (Robotic-assisted)

Pathology: endometrioid adenocarcinoma of the endometrium, grade 3, MI<50% (2.3mm/16mm). No LVSI. Negative SLN bilaterally. IHC for p53: absent.

Stage FIGO IA G3

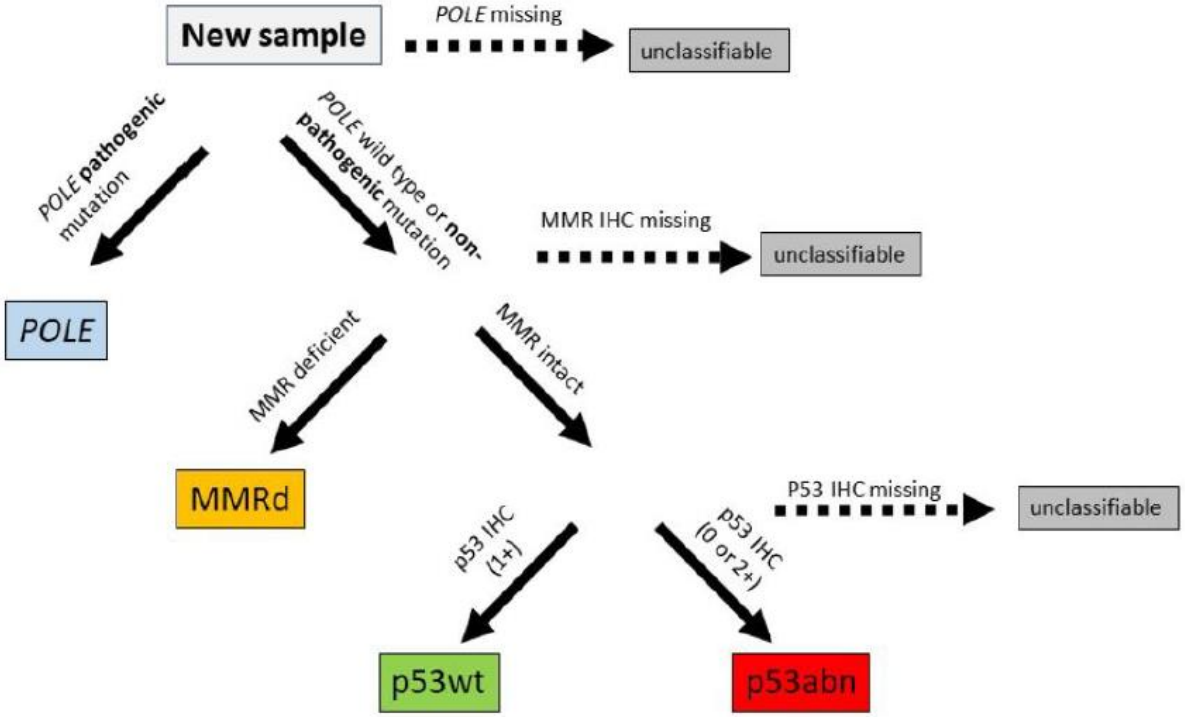
Molecular analysis:

MSI High (microstability). Absence of expression of MLH1 e PMS2 at IHC. Methylation of MLH1 gene promoter.

NGS POLE: wild-type

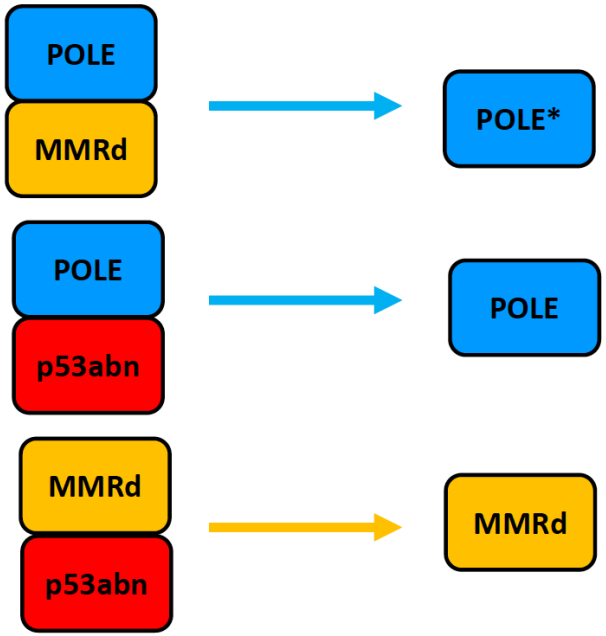
NGS TP53: mutated

Molecular classification algorithm



Clinical Case #3

How to categorize the ≅ 3% of ECs that harbour > 1 molecular feature

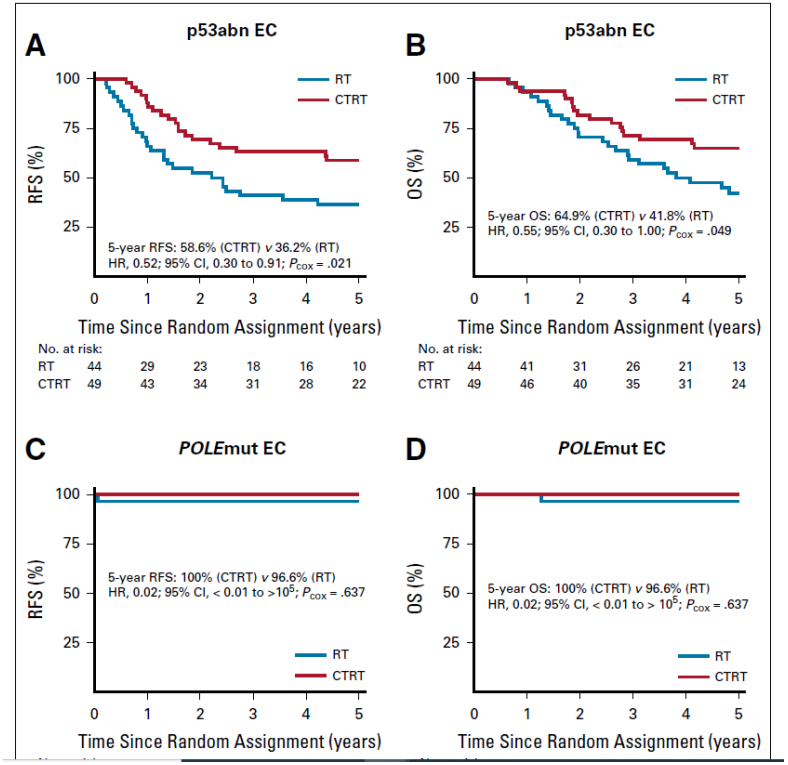


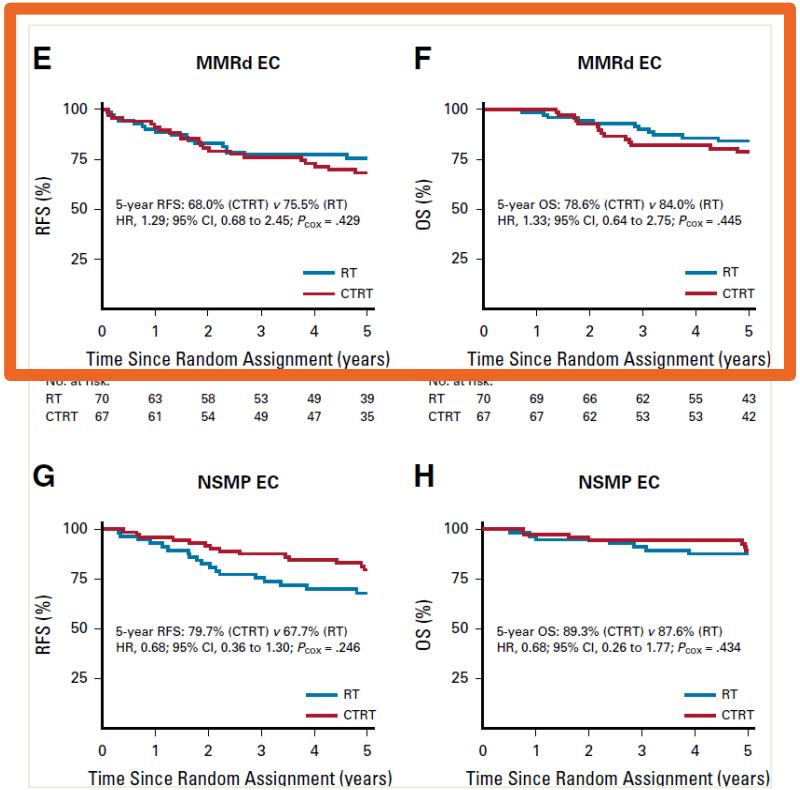
Leon-Castillo et al, J Path, Dec 2019

NB. Majority of ECs with more than one molecular feature are MMRd-p53abn, next POLE mut-p53abn. POLE -MMRd with pathogenic POLE mutation appears to follow prognostic outcomes of POLE but *would still refer to HCP. ECs with all 3 molecular features (MMRd-POLE-p53abn) are rare.
Critical that confirmed pathogenic *POLE* mutations (León-Castillo et al, J Path 2019, accepted- under final revisions)
p53 subclonal expression.....think MMRd or POLE.....or progression? (Singh et al, J Path 2019, accepted- revision)

PORTEC-3

Molecular classification predictive of benefit from adjuvant chemotherapy?





Leon de Castillo et al. , JCO 2020

Clinical Case #3

Suggested treatment based on the ESGO Guidelines following the classical risk factors (Intermediate risk):

Vaginal brachitherapy vs. Observation

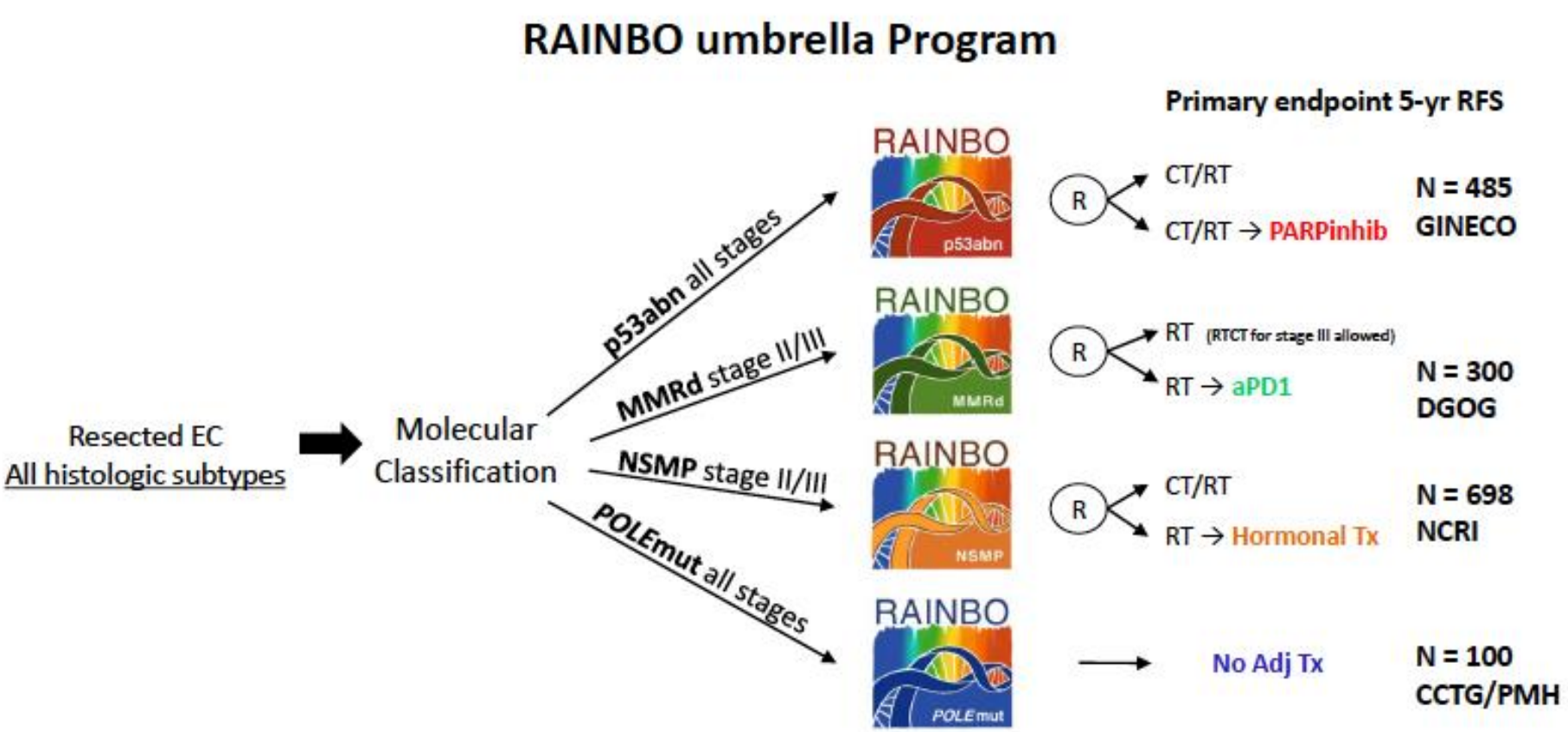
Suggested treatment based on molecular classification (Intermediate risk):

- Vaginal brachitherapy vs. Observation

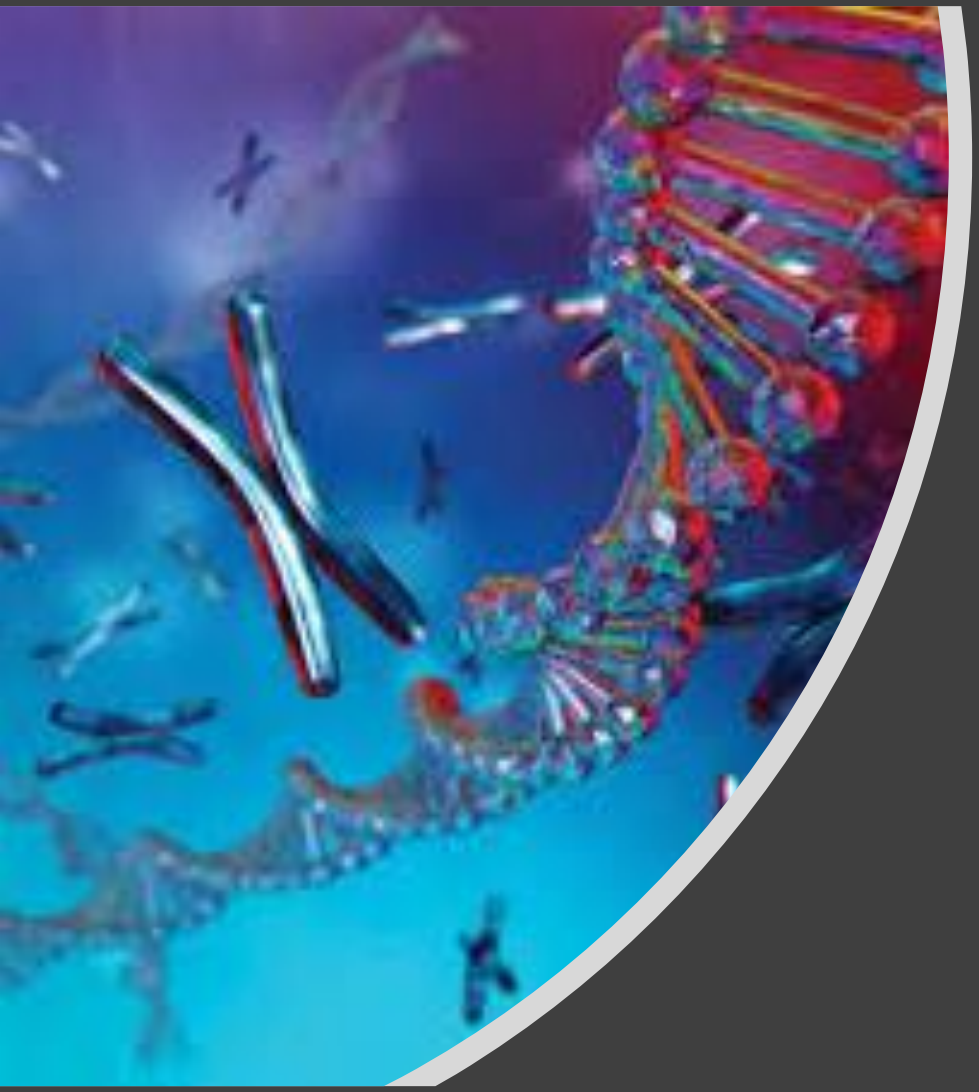
Summary – Molecular profiling for risk startification and adjuvant treatment decision of women with early stage EC.

- Classification is essential
  - Need to distinguish GOOD tumor from BAD (p53abn low grade endometrioid, MMRd) and recognize what appear BAD tumors but are GOOD (POLEmut, early stage p53wt)
- Prognostic
  - Value for patients. Early information.
- Predictive
  - Design appropriate clinical trials to define treatment strategies.

Future directions



RAINBO umbrella program supported by GCIG and coordinated by *Trans*PORTEC will allocate EC pts to 4 international academic sub-trials each led by one Gyn-Onc national clinical trial group



Can Molecular profiling improve the systemic treatment of endometrial cancer ?

Potential Therapeutic Impact of TGCA Classification of Endometrial Cancer

	POLE	MSI	Copy Number Low	Copy Number High
MSI/MLH methylation	Mixed MSI high, low, stable	MSI high	MSI stable	MSI stable
Molecular profile	*POLE* (100%) *PTEN* (94%) *PIK3CA* (71%) *FBXW7* (82%) *ARID1A* (76%) *KRAS* (53%) PD1/PD-L1 overexpression	*PTEN* (88%) *RPL22* (37%) *KRAS* (35%) *PIK3CA* (54%) *ARID1A* (37%) PD-1/PD-L1 overexpression	*PTEN* (77%) *CTNNB1* (52%) *PIK3CA* (53%) *ARID1A* (42%) *FGFR2* (10.9%)	*TP53* (92%) *PPP2R1A* (22%) *FBXW7* (22%) *PIK3CA* (47%) *PTEN* (11%) *FGFR* (7%) *HER2* (25%)
Potential drugs	• PI3K/PTEN/AKT/ mTOR pathway • Anti-PD-1/PD-L1 • Hormones	• PI3K/PTEN/AKT/mTOR pathway • Anti-PD-1/PD-L1 • Hormones	• PI3K/PTEN/AKT/mTOR pathway • Hormones • FGFR-I	• HER2- I • PI3K- I • PARP-I • Wee-1 I • FGFR-I

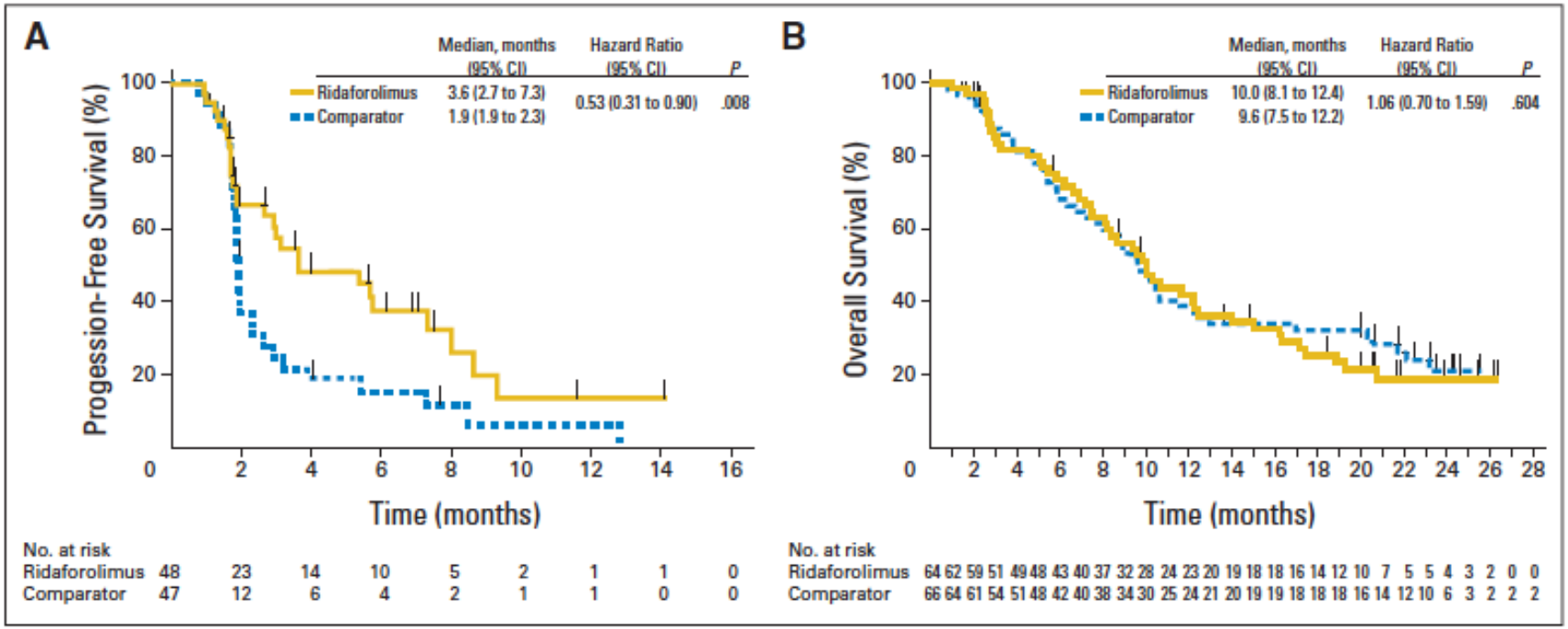
Stelloo E, et al. *Clin Cancer Res.* 2016;22;4215-4224.

Published Ahead of Print on June 15, 2015 as 10.1200/JCO.2014.58.8871
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2014.58.8871

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Randomized Phase II Trial of Ridaforolimus in Advanced Endometrial Carcinoma

Amit M. Oza, Sandro Pignata, Andres Poveda, Mary McCormack, Andrew Clamp, Benjamin Schwartz, Jonathan Cheng, Xiaoyun Li, Kristy Campbell, Pierre Dodion, and Frank G. Haluska

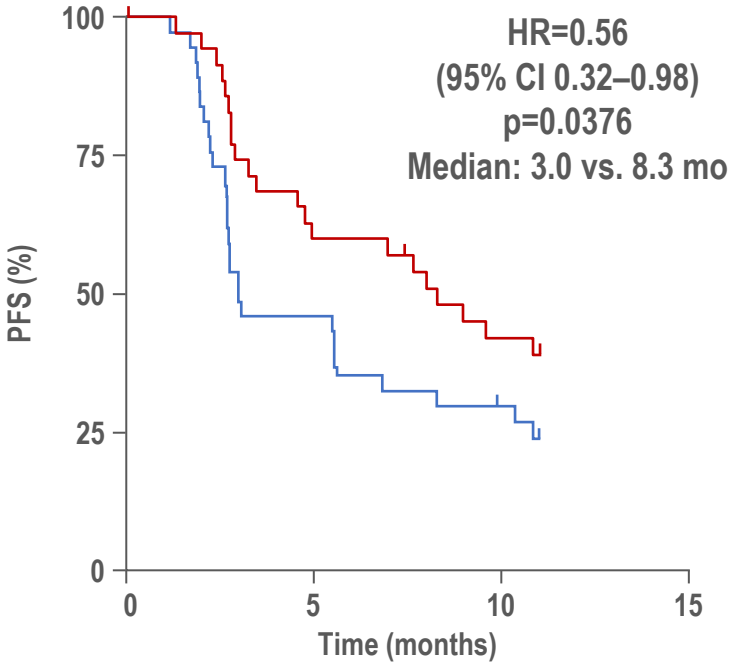


Oza AN, et al. *J Clin Oncol.* 2015;33(31):3576-3582.

ENGOT-EN3 / NSGO-PALEO

Mirza et al. ESMO 2020

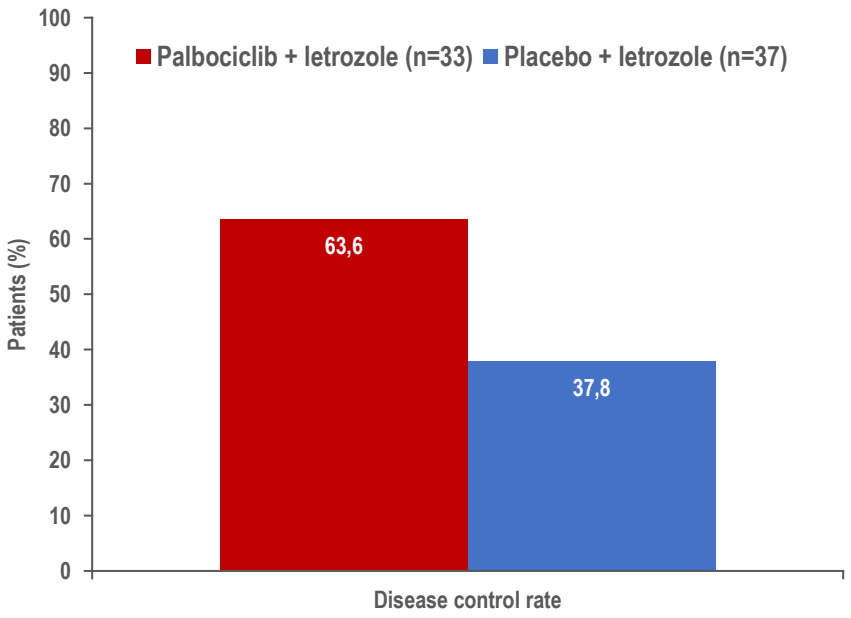
Primary endpoint: PFS



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

CI = confidence interval; HR = hazard ratio

Secondary endpoint: Disease contro



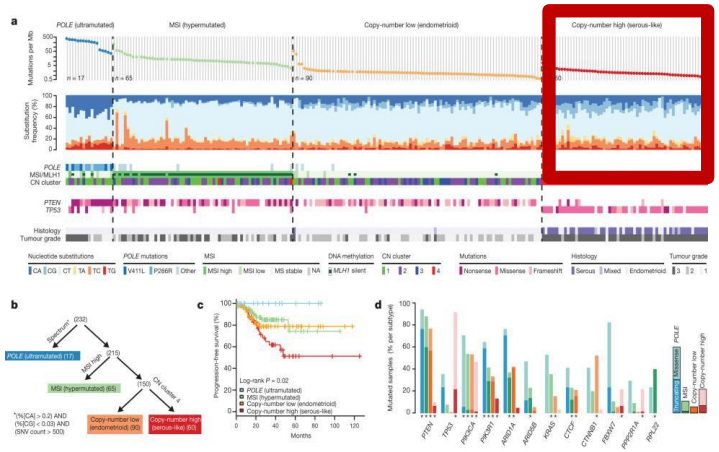
* = at 24 weeks

Potential Therapeutic Impact of TGCA Classification of Endometrial Cancer

	POLE	MSI	Copy Number Low	Copy Number High
MSI/MLH methylation	Mixed MSI high, low, stable	MSI high	MSI stable	MSI stable
Molecular profile	*POLE* (100%) *PTEN* (94%) *PIK3CA* (71%) *FBXW7* (82%) *ARID1A* (76%) *KRAS* (53%) PD1/PD-L1 overexpression	*PTEN* (88%) *RPL22* (37%) *KRAS* (35%) *PIK3CA* (54%) *ARID1A* (37%) PD-1/PD-L1 overexpression	*PTEN* (77%) *CTNNB1* (52%) *PIK3CA* (53%) *ARID1A* (42%) *FGFR2* (10.9%)	*TP53* (92%) *PPP2R1A* (22%) *FBXW7* (22%) *PIK3CA* (47%) *PTEN* (11%) *FGFR* (7%) *HER2* (25%)
Potential drugs	• PI3K/PTEN/AKT/ mTOR pathway • Anti-PD-1/PD-L1 • Hormones	• PI3K/PTEN/AKT/mTOR pathway • Anti-PD-1/PD-L1 • Hormones	• PI3K/PTEN/AKT/mTOR pathway • Hormones • FGFR-I	• **HER2- I** • PI3K- I • PARP-I • **Wee-1 I** • FGFR-I

Stelloo E, et al. *Clin Cancer Res.* 2016;22;4215-4224.

Differences between USC and Endometrioid Tumors

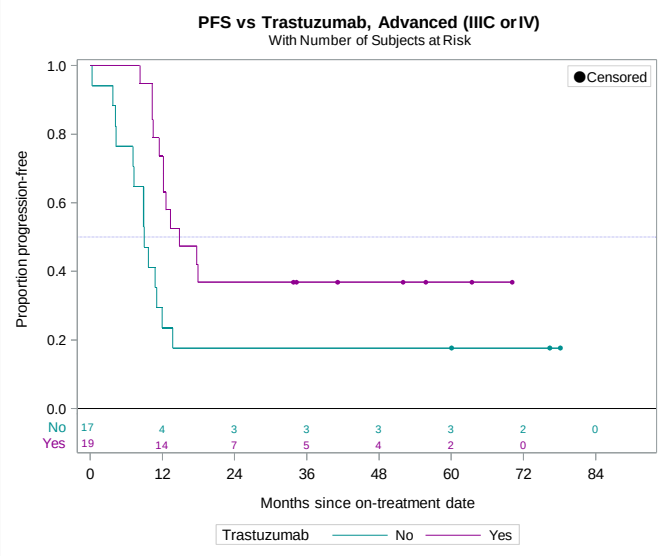


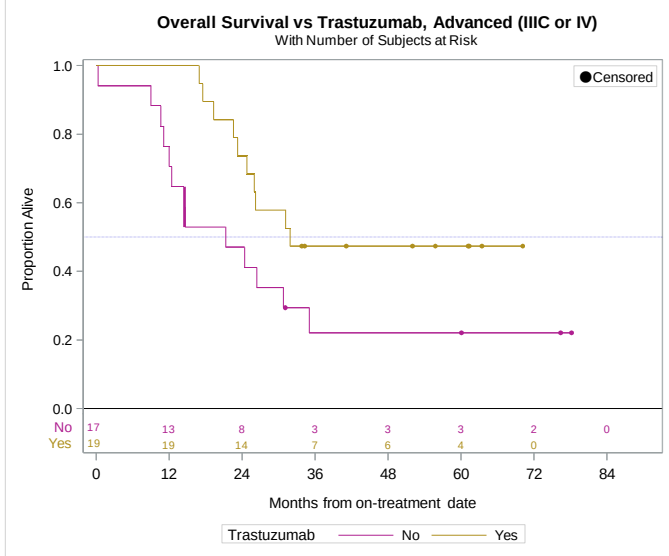
TCGA Data and USC

- High genomic instability
- Low tumor mutation burden
- *TP53* alterations in over 90% of cases

Molecular alterations	ECC	UPSC
ER/PR	ER/PR positive	ER/PR negative
p53	p53 mutation are rare	90% with p53 mutations
PTEN	80% PTEN mutations	PTEN mutations are rare
HER-2/neu	Over expressed in 10–30%	Over-expressed in 45–60%
Claudin 3/4	N/A	Over-expressed
Bcl-2	N/A	Over-expressed

Carboplatin/paclitaxel+/-Trastuzumab (NCT01367002) Updated Survival analysis stage III/IV

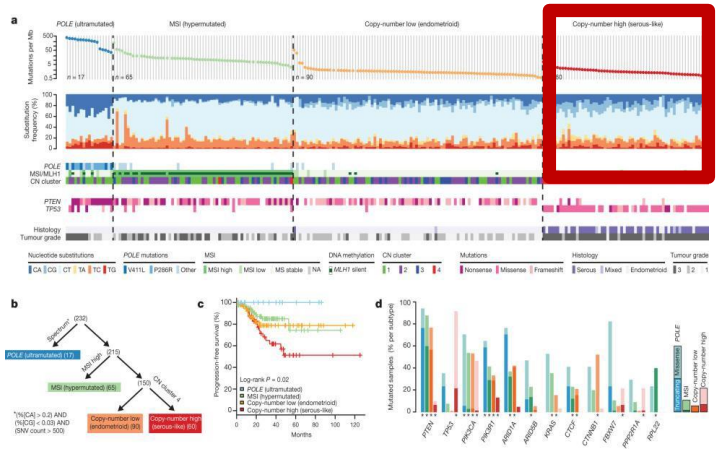




In a subset analysis of pts restricted to stage IIIC/IV disease, the addition of trastuzumab (n=17) continued to provide both (*left*) PFS benefit over control (n=19) and OS benefit over control (21.1 versus 31.9 months, HR 0.440 90% CI 0.219-0.882 p=0.0230).

Amanda N. Fader et al.,J Clin Oncol. 2018 Jul 10;36(20):2044-2051
Amanda N. Fader et al. , JCO 2020

Differences between USC and Endometrioid Tumors



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Claudin 3/4	N/A	Over-expressed
Bcl-2	N/A	Over-expressed

Adavosertib (AZD1775) inhibits WEE1 and may be most active in p53-mutant background

Cell cycle checkpoints slow down the cell cycle

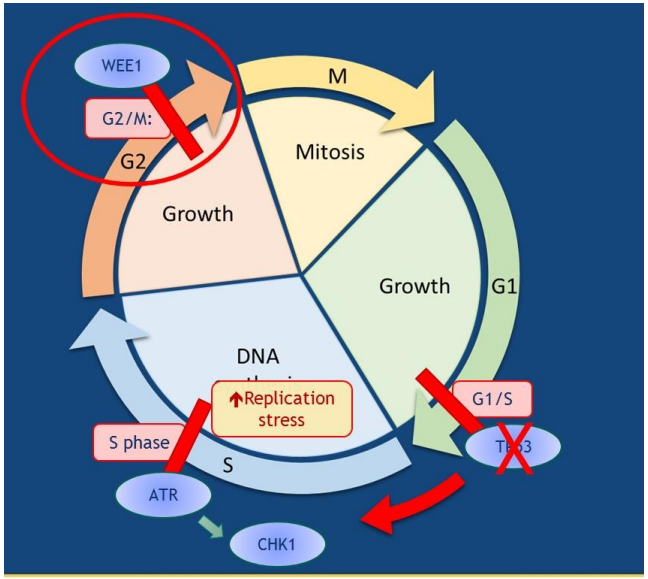
- **Allow time for appropriate DNA replication**
- **Prevent progression to mitosis with DNA damage or underreplicated DNA**

Cells with TP 53 mutation/loss lose their G1/S checkpoint

- **Leads to early entry into S phase**
- **Increases replication stress**
- **Increases dependency on the G2/M checkpoint**

WEE1 is a Key regulator of G2/M checkpoint

- **WEE1 inhibition leads to disregulation of the G2/M checkpoint and to mitotic catastrophy**

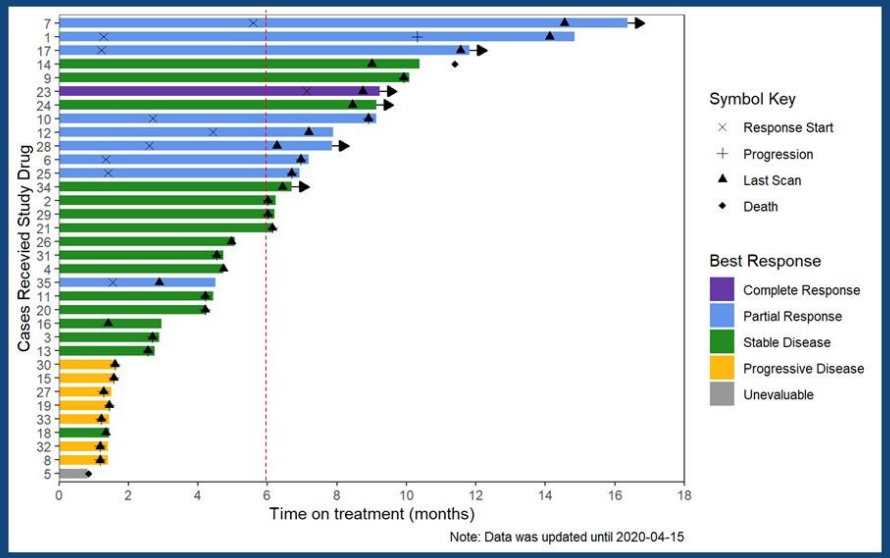


Adavosertib (AZD1775) in serous endometrial cancer

Clinical Activity: response rate

Best Overall Response	Overall N=34
Complete response (confirmed)	1 (2.9%)
Partial response Confirmed Unconfirmed	 8 (23.5%) 1 (2.9%)
Stable disease ≥ 6 months < 6 months	 7 (20.6%) 9 (26.5%)
Progressive disease	7 (20.6%)
Unevaluable	1 (2.9%)
Objective response rate (confirmed and unconfirmed)	**10 (29.4%)**
Clinical benefit rate (CR + PR + SD≥6 mos)	**17 (50.0%)**

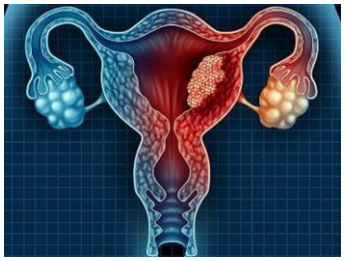
Clinical activity is durable in many patients



Median duration of response: 9.03 months (95% CI 5.29-NA)

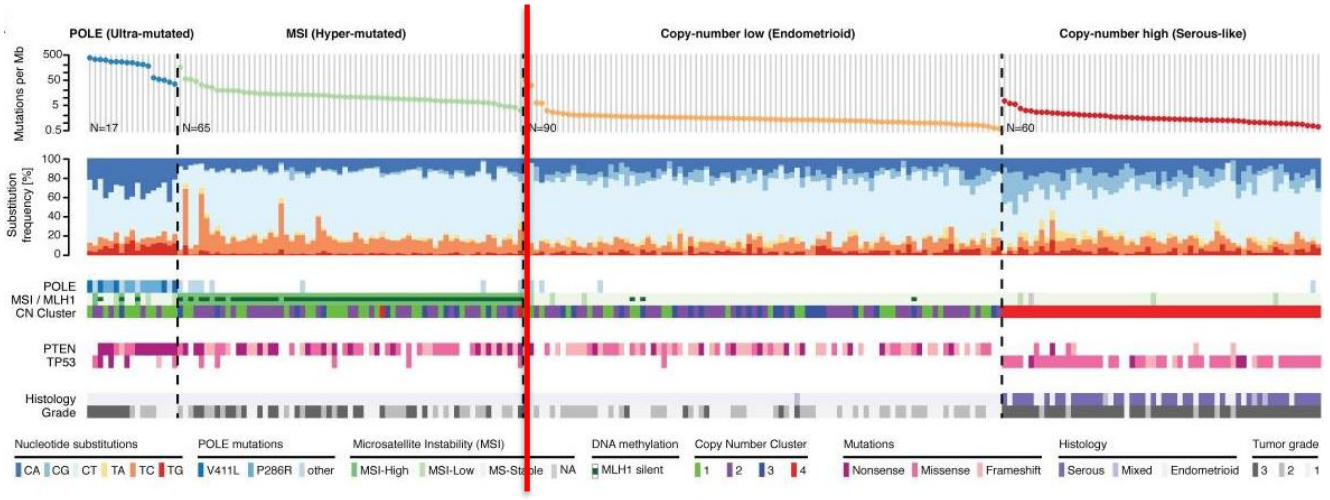
#6009, ASCO 2020

Endometrial carcinoma



Integrated Genomic Characterization of Endometrial Carcinoma

The Cancer Genome Atlas Research Network



Hot tumors

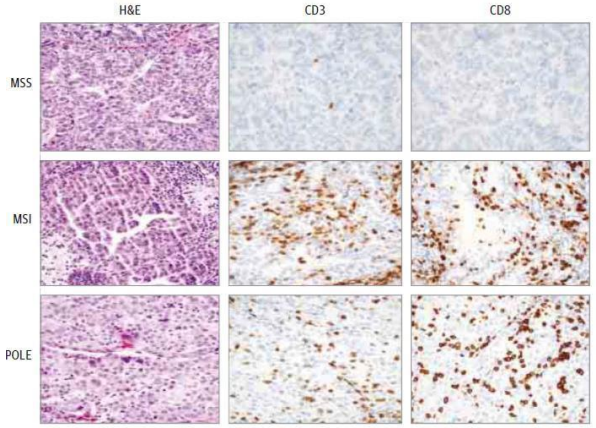
Good Response to Immunotherapy

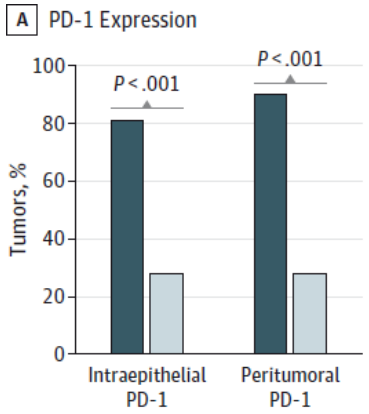
Cold tumors

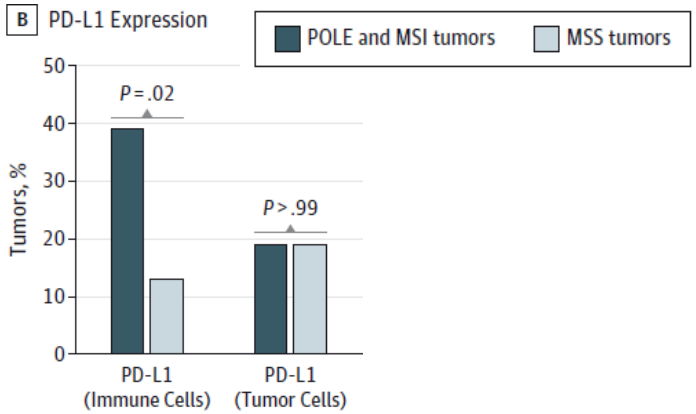
Poor Response to Immunotherapy

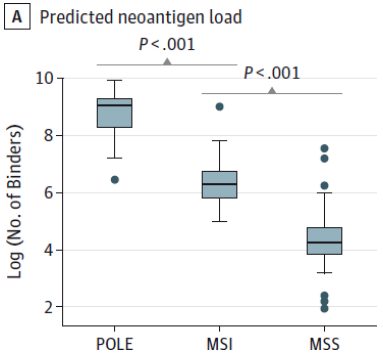
Nature. May 2,2013;497(7447): 67-73

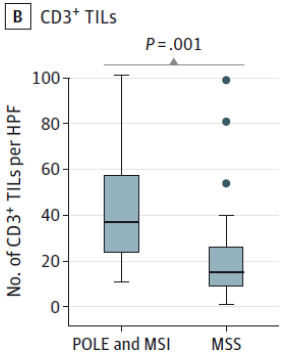
MSI high and POLE mutated Endometrial Cancers display increased Neoantigen load, more TILs, and higher PD1/PD-L1 Expression

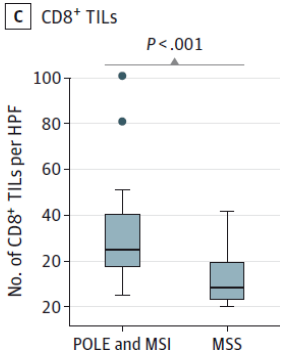












Howitt BE, Konstantinopoulos PA. Association of Polymerase e-Mutated and Microsatellite-Instable Endometrial Cancers With Neoantigen Load, Number of Tumor-Infiltrating Lymphocytes, and Expression of PD-1 and PD-L1. JAMA Oncol. 2015 Dec;1(9):1319-23

MSI/dMMR: Concept and Incidence

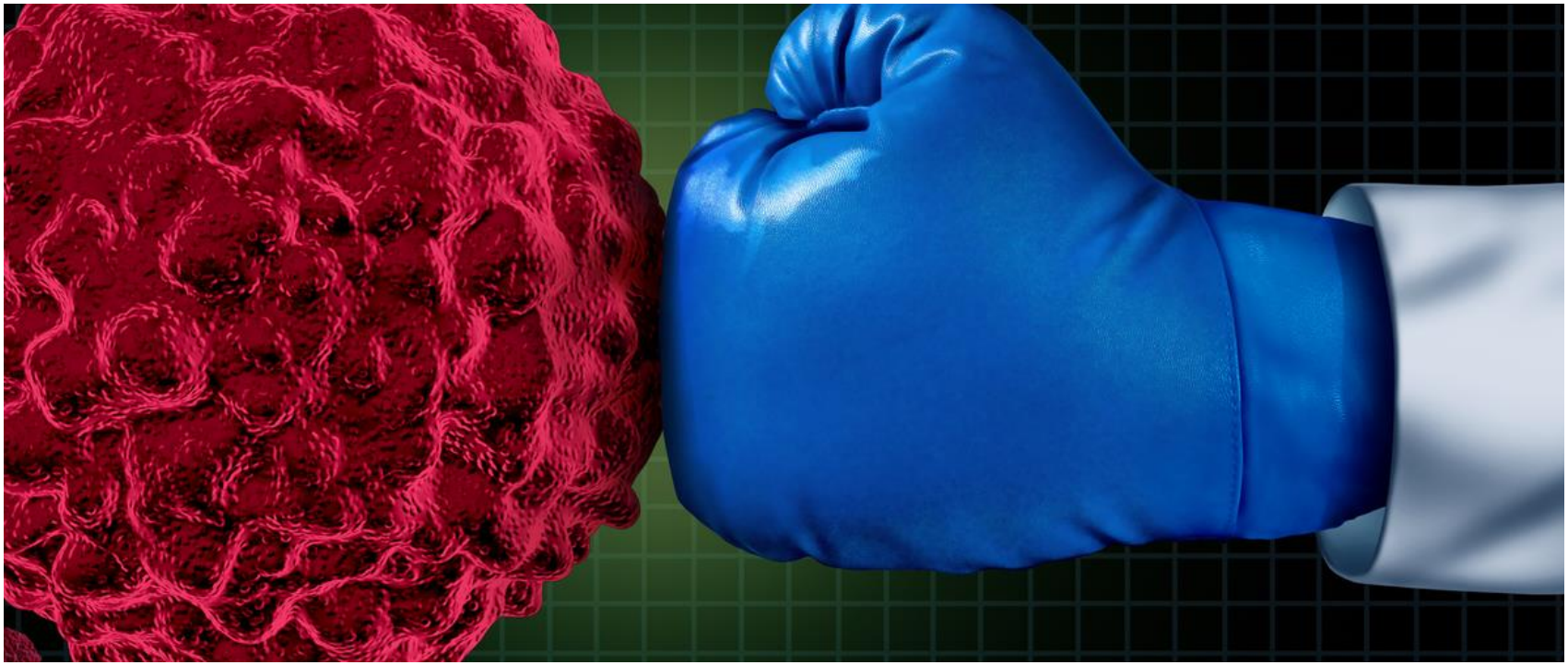
- **DNA MMR:** Highly conserved mechanism used to restore DNA integrity after the occurrence of mismatching errors, including single-base mismatches or short insertions and deletions
  - 4 genes that play a critical role in this process include: MLH1 ,MSH2, MSH6 and PMS2
- **MSI:** Condition of genetic hypermutability resulting from defective DNA MMR
- **MSI/dMMR tumor:** A tumor that accumulates thousands of mutations, particularly clustered in microsatellites and consisting in repeat length alterations, resulting in MSI

Tumor Type*	MSI-High, %
Uterine corpus endometrial	28.3
Stomach adeno	21.9
Colon adeno	16.6
Rectal adeno	9.2
Adrenal cortical	5.4
Esophageal	3.3
Ovarian	3.2
Hepatocellular	2.9
Cervical squamous	2.3

*At least 2% MSI-High incidence

Luchini. Annals Oncol. 2019;30:1232. Cortes-Ciriano. Nat Commun. 2017;8:15180.

Can Immunotherapy improve the systemic treatment of advanced/recurrent endometrial cancer ?



Single-Agent IO Efficacy in Biomarker-Selected Endometrial Cancer

Study	Drug	N	Patient Selection	ORR, %
KEYNOTE-158[a]	Pembrolizumab	49	Advanced/metastatic dMMR	57
GARNET[b]	Dostarlimab	103	Previously treated Recurrent/advanced d-MMR	44.7
PHAEDRA[c]	Durvalumab	35	Advanced /metastatic p-MMR	43
Konstantinopoulos[d]	Avelumab	15	Advanced /metastatic d-MMR	26.7

a. Marabelle et al. *J Clin Oncol.* 2020;38:1-10; b. Oaknin A, et al. Ann Oncol 2020; c. Antill Y, et al. ASCO®. 2019; d. Konstantinopoulos PA, et al. ASCO®. 2019;

Dostarlimab in ovarian Cancer: Garnet study

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

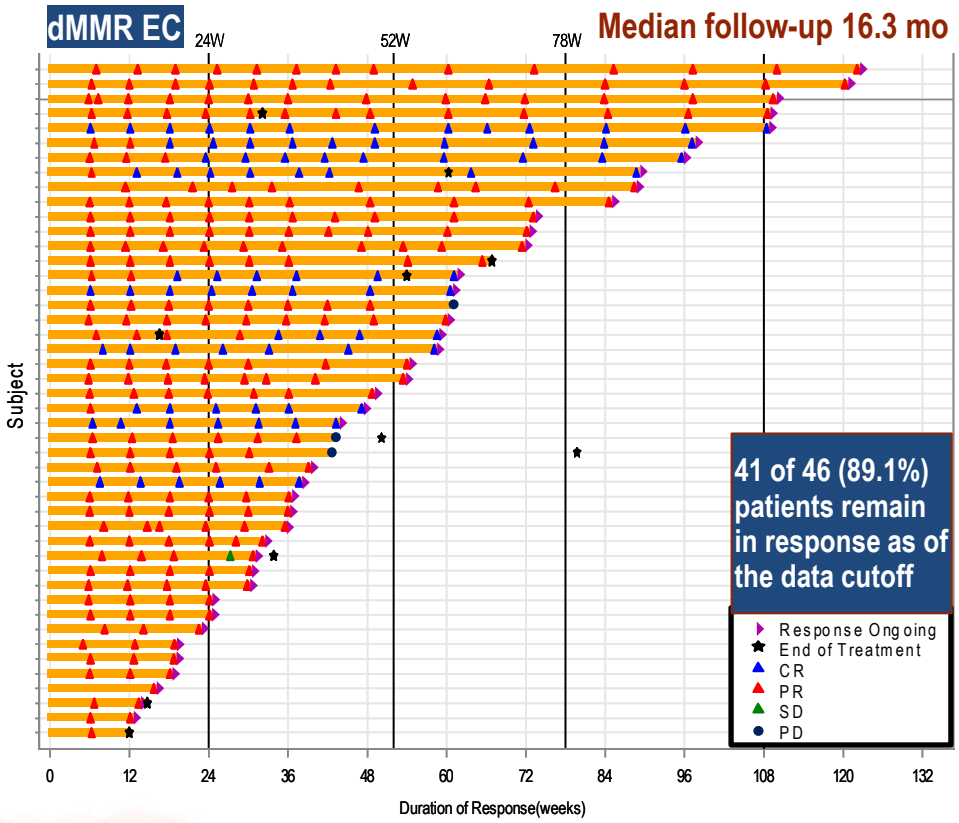
*Responses required confirmation at a subsequent scan; SD had to be observed at ≥12 weeks on study to qualify as SD; †Includes confirmed CR, PR or SD at ≥12 weeks.

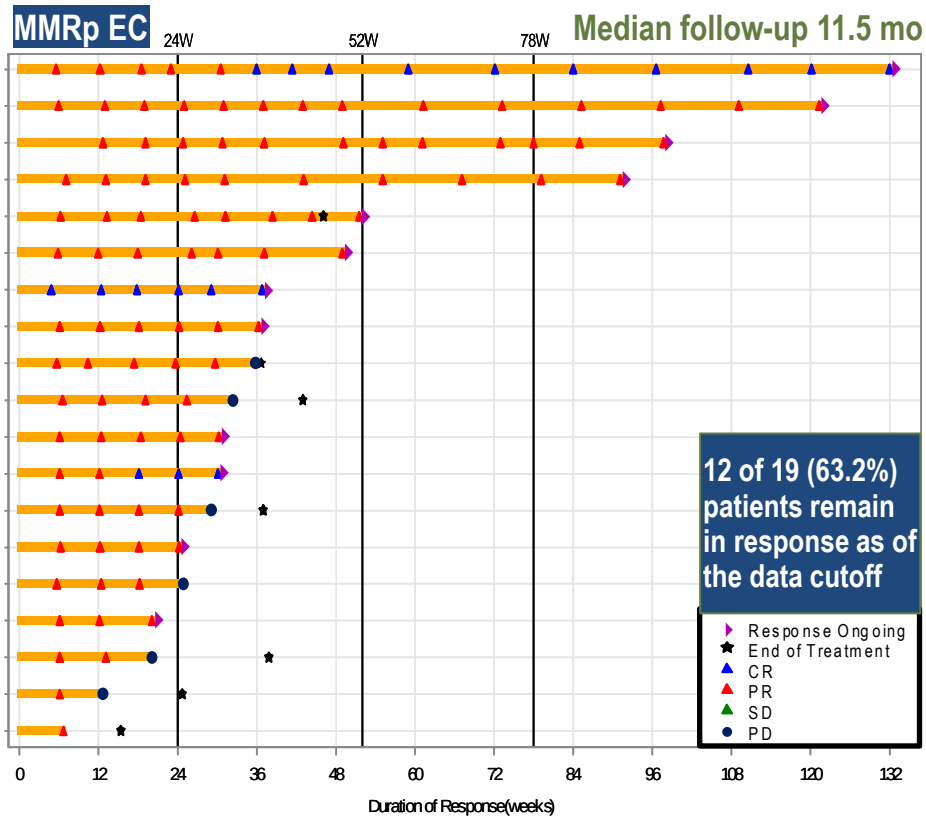
CR, complete response; dMMR, mismatch mutation repair deficient; EC, endometrial cancer; MMRp, mismatch mutation repair proficient, ORR, objective response rate; PR, partial response; SD, stable disease.

Oaknin A, et al. Ann Oncol 2020

Dostarlimab in ovarian Cancer: Garnet study

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.

Oaknin A, et al. Ann Oncol 2020

Single agent IO efficacy in non-biomarker selected in Endometrial Cancer

Study	Drug	N	Patient Selection	ORR(%)
Keynote 28: Ott (2017)	Pembro	24	Advanced/metastatic PDL1+	13%
Garnet :Oaknin (2020)	Dostarlimab	142	Previously treated Recurrent/advanced p-MMR	13,4%
PHAEDRA: Antill (2019)	Durvalumab	36	Advanced /metastatic p-MMR	3%
Konstantinopoulos (2019)	Avelumab	16	Advanced /metastatic p-MMR	6%

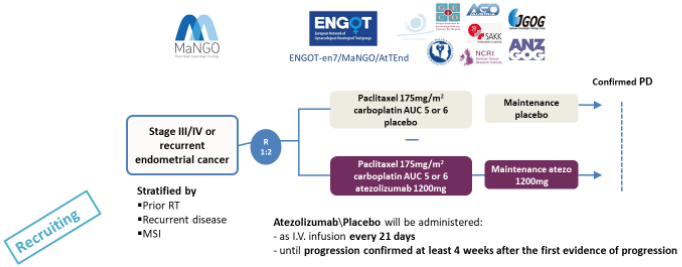
Ott et al. J Clin Oncol. 2017; 35(22):2535-41; Oaknin, Ann Onco 2020; Antill ASCO 2019 ; Konstantinopoulos ASCO 2019

How can we expand Treatment Beyond the “biomarker” Selected Population?

Combination	Rational
IO+Chemotherapy	Immune cell stimulation Immunogenic cell death Enhanced presentation of tumor specific antigens Increased T-cell activation

Ongoing First line Phase III trials

A phase III double-blind randomised placebo-controlled trial of atezolizumab in combination with paclitaxel/carboplatin in women with advanced/ recurrent endometrial cancer: AtTEnd / ENGOT-en7/MaNGO

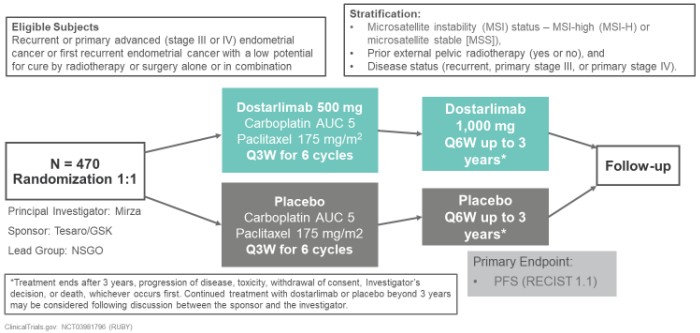


FPI: October 2018
LPI: Q4 2020

Primary Endpoint: OS and PFS
Secondary Endpoints: PFS in MSI, PFS2, RR, QoL, safety
Translational Endpoints: PD1, PDL1, TILs, blood based biomarkers
Study Duration: accrual 2 years; **Follow-up:** 2 years

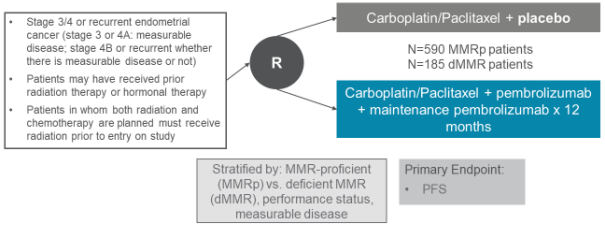
ClinicalTrials.gov : NCT03603184
Global ENGOT PI on behalf of MaNGO: Nicoletta Colombo MD

ENGOT-EN6/NSGO-RUBY



ClinicalTrials.gov: NCT03981796 (RUBY)

NRG-GY018: Randomized, phase 2/3 study of carboplatin + paclitaxel vs. carboplatin + paclitaxel + pembrolizumab in patients with advanced stage or recurrent endometrial cancer



dMMR, deficient mismatch repair; MMRp, mismatch repair proficient. ClinicalTrials.gov: NCT03914612 (NRG-GY018)

How can we expand Treatment Beyond the “biomarker” Selected Population?

Combination	Rational
IO+Chemotherapy	Immune cell stimulation Immunogeneic cell death Enhanced presentation of tumor specific antigens Increased T-cell activation
IO+Antiangiogenic Therapy	Reduction in T-reg activity Reversal of immunosuppressive effects of VEGF Improved T-cell trafficking and infiltration into tumor bed Increased Immune cell recruitment

Rationale for Combining Cancer Immunotherapy with Anti-VEGF

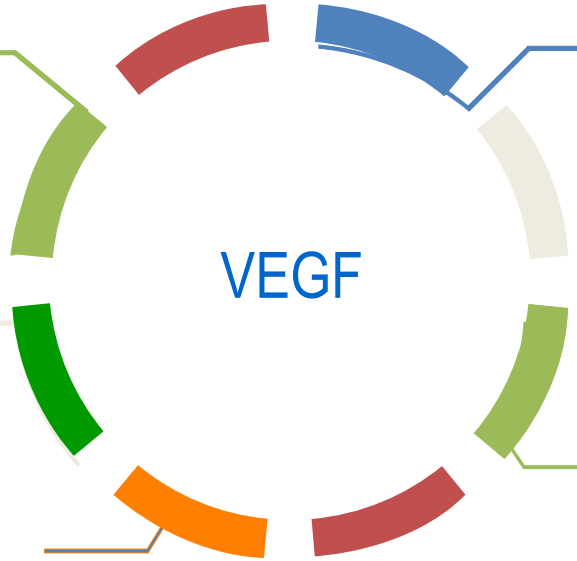
Reduce TILs

Induces abnormal tumor vasculature

Reducing T-cell trafficking and infiltration into the tumor bed[5,6]

Reduces lymphocyte adhesion to vessel walls

Decreases immune-cell recruitment to the tumor site[4]



Immunosuppressive

Inhibits T-cell function

Binds to VEGFR2 on T cells[1]

Kills T cells by tumor endothelium-produced FasL[2]

Stimulates immunosuppressive regulatory T cells[2]

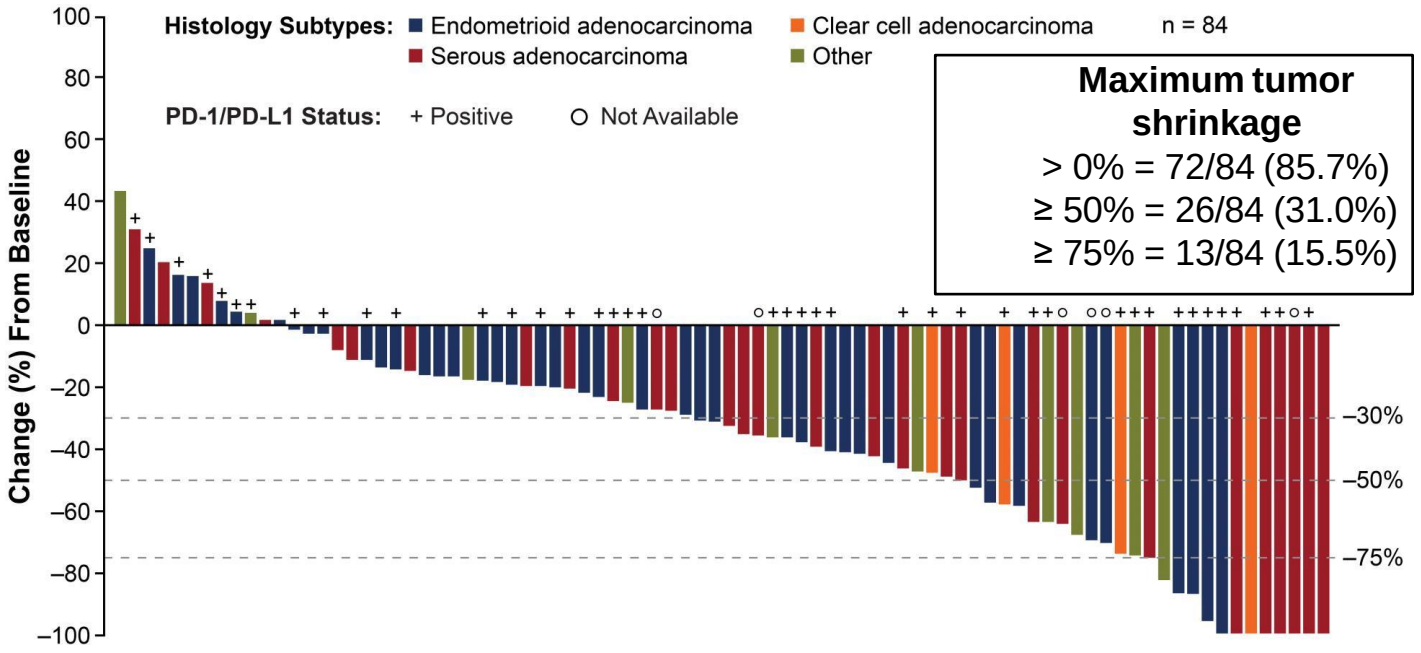
Inhibits dendritic cell function

Drives them into an immature state[3]

1. Gavalas NG, et al. *Br J Cancer.* 2012;107(11):1869-1875. 2. Terme M, et al. *Cancer Res.* 2013;73(2):539-549. 3. Coukos G, et al. *Br J Cancer.* 2005;92(7):1182-1187 4. Bouzin C, et al. *J Immunol.* 2007;178(3):1505-1511. 5. Shrimali RK, et al. *Cancer Res.* 2010;70(15):6171-6180. 6. Chen DS, et al. *Immunity.* 2013;39(1):1-10.

Final primary efficacy analysis results of the KEYNOTE-146/Study 111: advanced endometrial cancer cohort

Lenvatinib-Pembrolizumab
38.3% response rate in not dMMR or MSI-H endometrial cancer

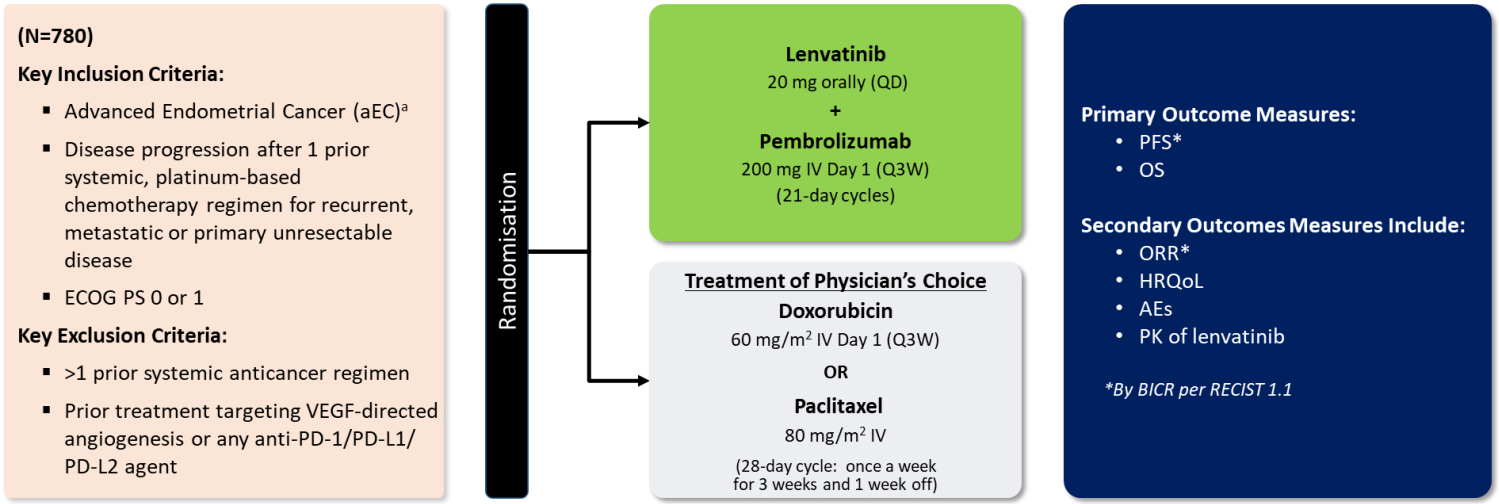


n = the number of previously treated not-MSI-H or dMMR patients with both baseline and at least 1 postbaseline target lesion assessment.

Maker et al. , SGO 2020

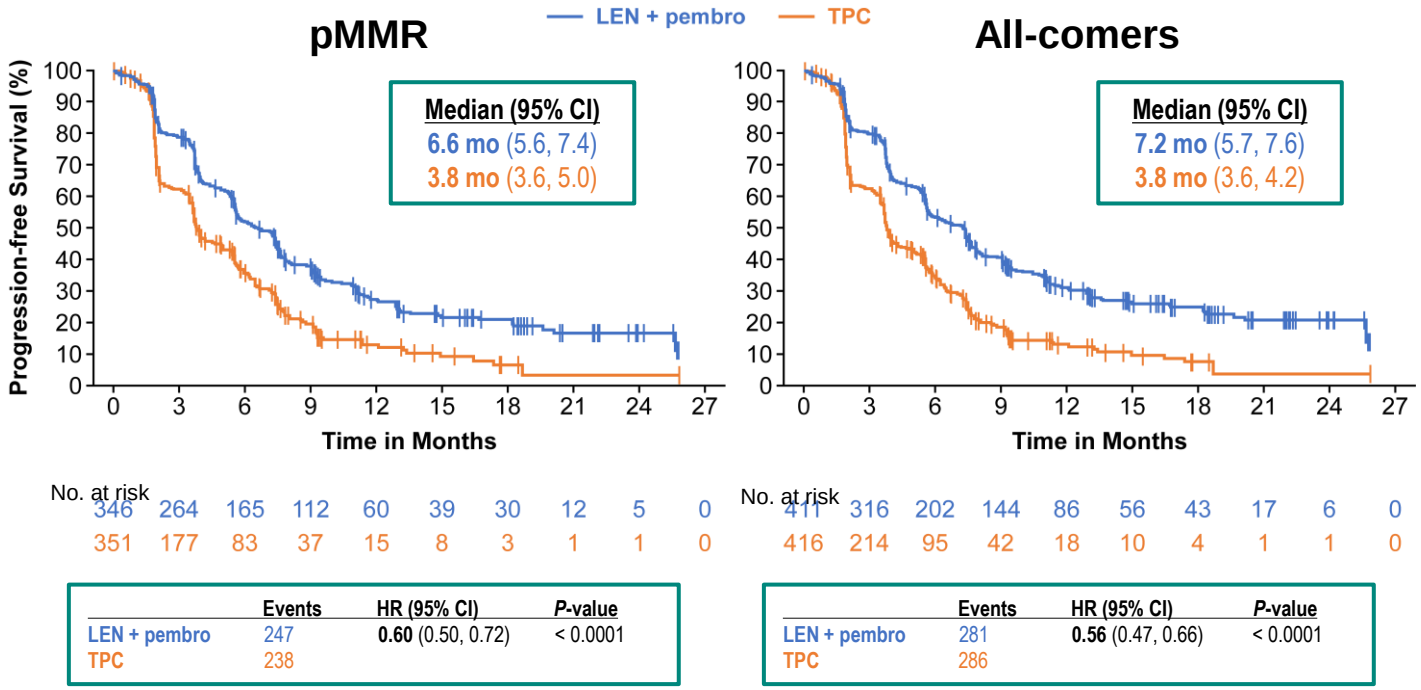
Study 309 / KEYNOTE-775: Phase 3 Study of Lenvatinib Plus Pembrolizumab vs Treatment of Physician's Choice in Advanced Endometrial Cancer

A Phase 3, randomized, open-label study



Study 309 / KEYNOTE-775: Phase 3 Study of Lenvatinib Plus Pembrolizumab vs Treatment of Physician's Choice in Advanced Endometrial Cancer

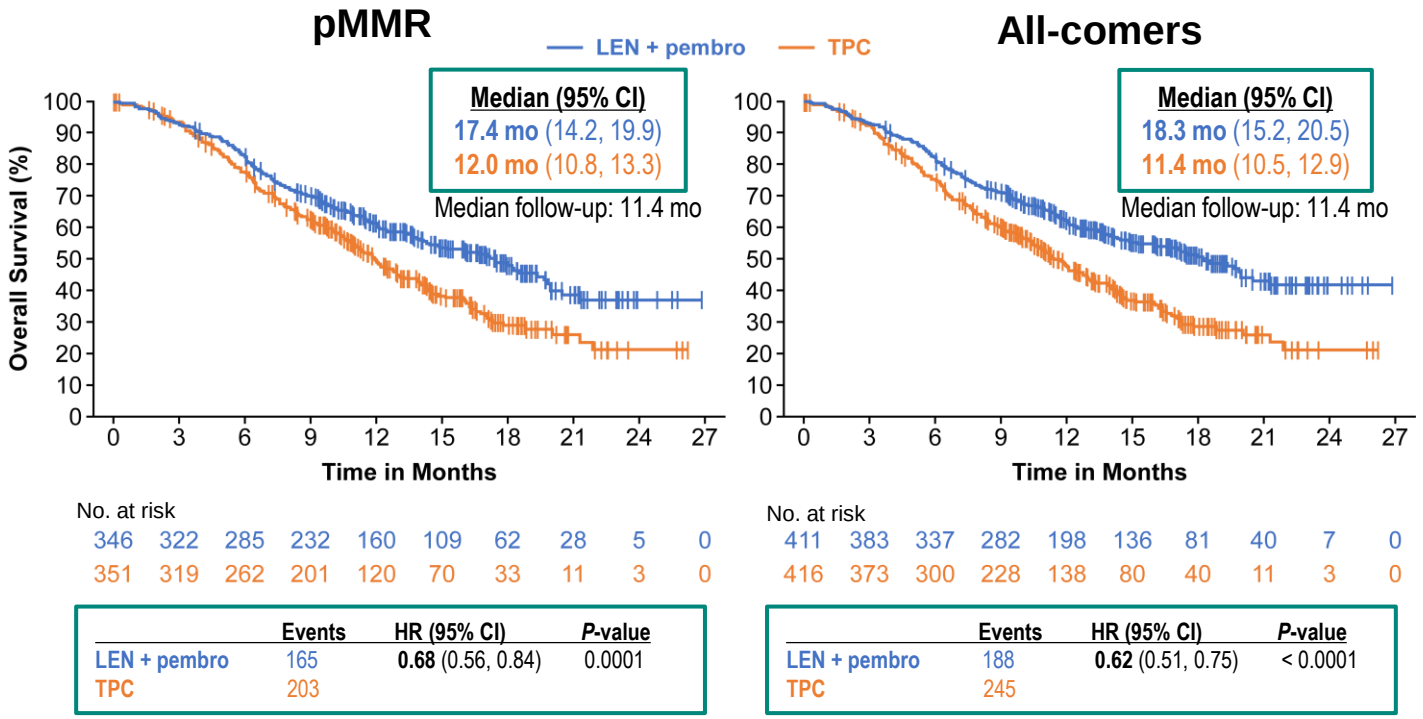
Progression-free Survival[a]



[a]By BICR per Response Evaluation Criteria in Solid Tumors version 1.1.

Study 309 / KEYNOTE-775: Phase 3 Study of Lenvatinib Plus Pembrolizumab vs Treatment of Physician's Choice in Advanced Endometrial Cancer

Overall Survival



Study 309 / KEYNOTE-775: Phase 3 Study of Lenvatinib Plus Pembrolizumab vs Treatment of Physician's Choice in Advanced Endometrial Cancer

Objective Responses

	pMMR		All-comers	
	LEN + pembro	TPC	LEN + pembro	TPC
Patients, n	346	351	411	416
Objective response rate, % (95% CI)	30.3 (25.5–35.5)	15.1 (11.5–19.3)	31.9 (27.4–36.6)	14.7 (11.4–18.4)
Difference vs TPC, % *P*-value	15.2 < 0.0001	--	17.2 < 0.0001	--
Best overall response, %				
Complete response	5.2	2.6	6.6	2.6
Partial response	25.1	12.5	25.3	12.0
Stable disease	48.6	39.6	47.0	40.1
Progressive disease	15.6	30.8	14.8	29.6
Not evaluable / assessed	0.6 / 4.9	2.0 / 12.5	1.2 / 5.1	1.9 / 13.7
Median duration of response (range), months	9.2 (1.6[a]–23.7[a])	5.7 (0.0[a]–24.2[a])	14.4 (1.6[a]–23.7[a])	5.7 (0.0[a]–24.2[a])
Median time to response (range), months	2.1 (1.5–9.4)	3.5 (1.0–7.4)	2.1 (1.5–16.3)	2.1 (1.0–7.4)

[a]No progressive disease reported at the last disease assessment.

Study 309 / KEYNOTE-775: Phase 3 Study of Lenvatinib Plus Pembrolizumab vs Treatment of Physician's Choice in Advanced Endometrial Cancer

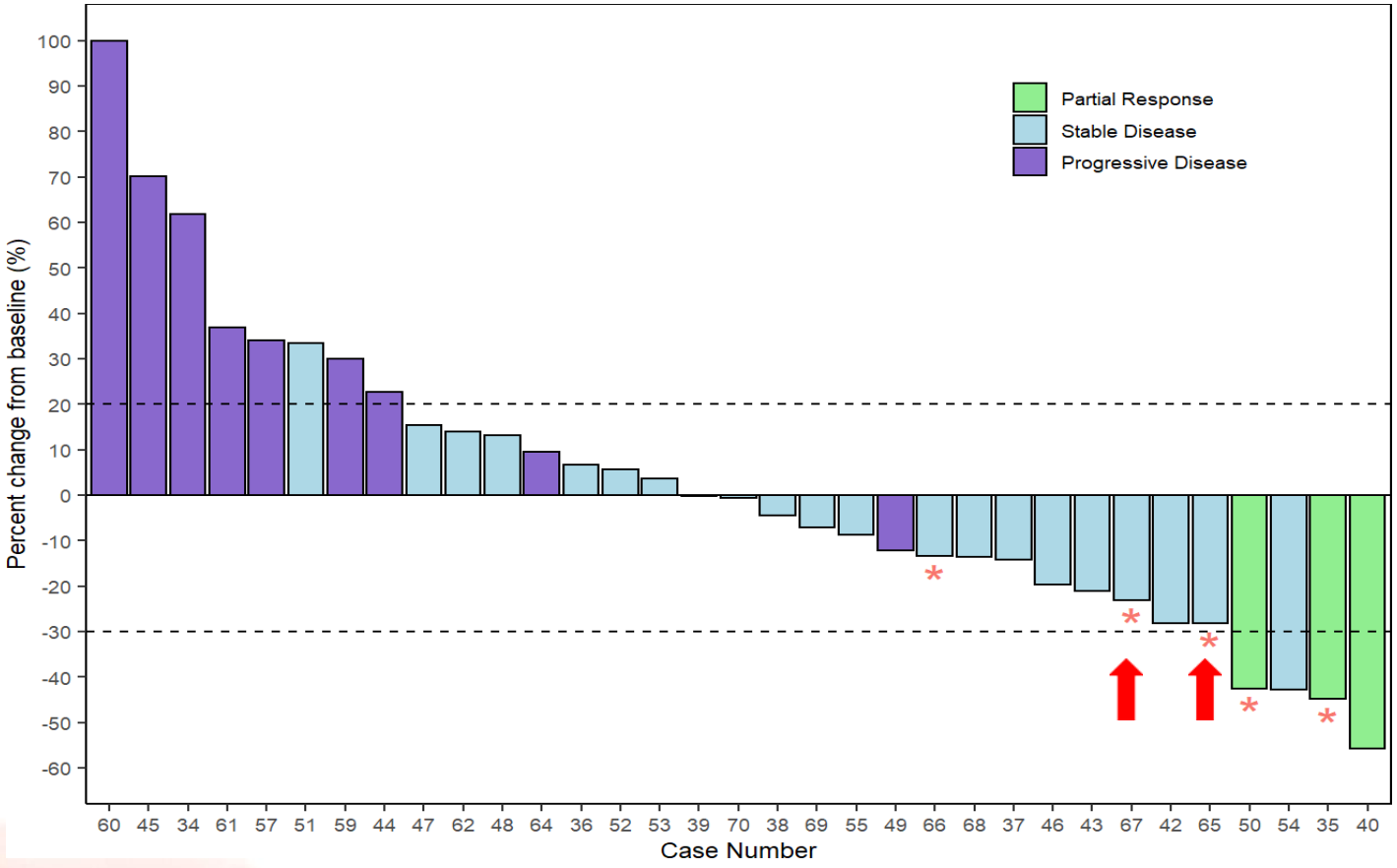
Success Criterion Achieved for Primary and Key Secondary Hypotheses

Primary Hypothesis	Observed HR (95% CI)	Number of Events	p-value observed	Outcome
H1: PFS (pMMR)	0.60 (0.50, 0.72)	485	<0.0001	Positive
H2: OS (pMMR)	0.68 (0.56, 0.84)	368	0.0001	Positive
H4: PFS (all-comer)	0.56 (0.47, 0.66)	567	<0.0001	Positive
H5: OS (all-comer)	0.62 (0.51, 0.75)	433	<0.0001	Positive
Key Secondary Hypothesis	**Difference, %**		**p-value observed**	**Outcome**
H3: ORR (pMMR)	15.2		<0.0001	Positive
H6: ORR (all-comer)	17.2		<0.0001	Positive

How can we expand Treatment Beyond the “biomarker” Selected Population?

Combination	Rational
IO+Chemotherapy	Immune cell stimulation Immunogeneic cell death Enhanced presentation of tumor specific antigens Increased T-cell activation
IO+Antiangiogenic Therapy	Reduction in T-reg activity Reversal of immunosuppressive effects of VEGF Improved T-cell trafficking and infiltration into tumor bed Increased Immune cell recruitment
IO+PARPi	Increased TILs Enhance DNA damage, with increased CD8+ T cells

Talazoparib-Avelumab in Endometrial Cancer
35 patients, median n.prior lines:3



3 PR :8.6% (1.8-23.1)

5 patients still on treatment **(*)**

2 patients **(red arrows)** still on treatment with near PR (23%, 28% reduction)

PFS at 6 months: 25.3%
(95% CI: 11.5 - 41.7)

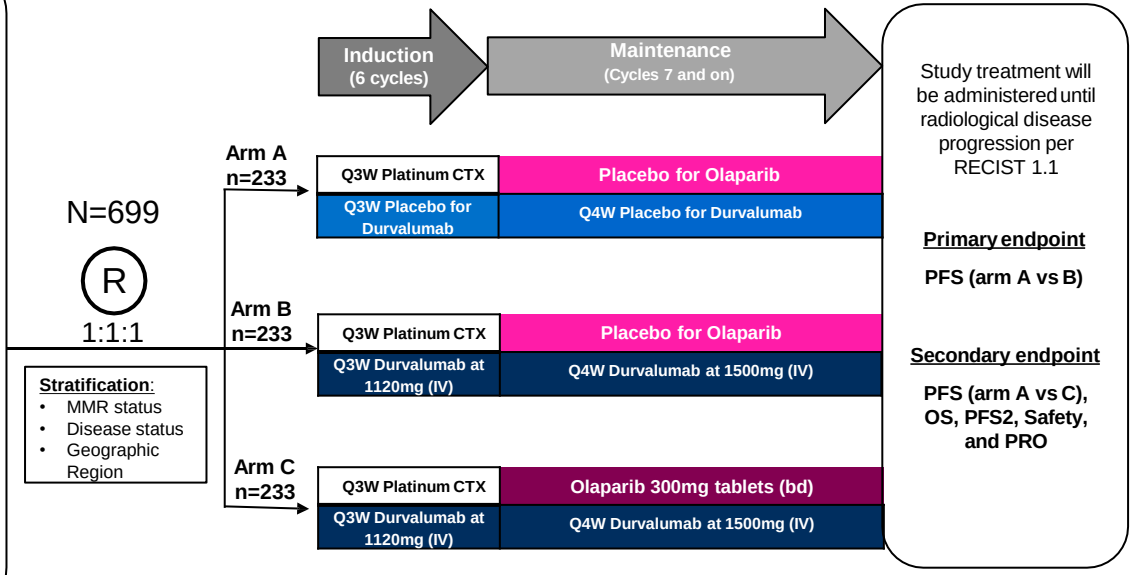
Panagiotis Konstantinopoulos et al., ESMO 2020

ENGOT-EN10/DUO-E: Durvalumab-Olaparib in endometrial cancer

STUDY DESIGN

Key Eligibility

- **Female Pts aged>18 yrs.**
- **Histology confirmed diagnosis of epithelial endometrial carcinoma.**
- **EC –Newly diagnosed stage III, IV, recurrent where potential for cure with surgery or combination is poor.**
- **Naïve to 1st line systemic anti-cancer treatment.**
- **Adjuvant chemo allowed if >= 12 months from last treatment to relapse**
- **Known MMR status**



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

Primary endpoint

PFS (arm A vs B)

Secondary endpoint

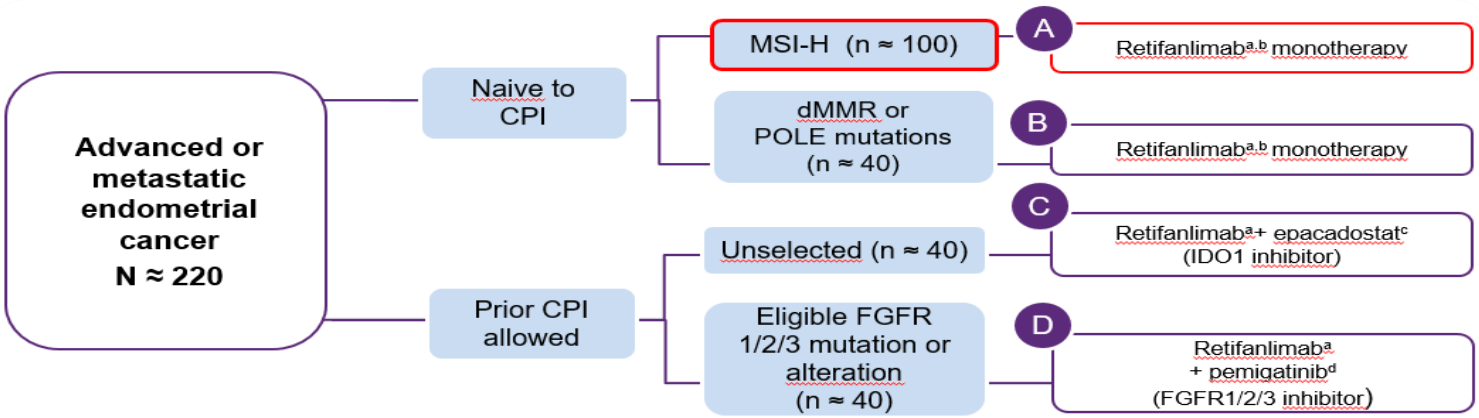
PFS (arm A vs C), OS, PFS2, Safety, and PRO

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

ENGOT Model: C Sponsor: AstraZeneca
Planned No. of patients: 699
No. of already recruited patients: 35
Trial Status: recruiting

PODIUM 204
PD1 Clinical Program in Multiple Malignancies

GOG3038/ENGOT-en12



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 for advanced/metastatic disease
- > 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
- Group A and B: carcinosarcoma histology
- 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 (see exception for groups A/B)
- HIV positive, unless viral load undetectable,CD4+ count ≥ 300/µL
- Groups C and D: Limiting immune-related toxicity during prior checkpoint inhibitor therapy

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

Summary

- Different types of endometrial cancer have specific histological and molecular features, precursor lesions and natural histories.
- Letrozole/palbociclib showed promising results in a phase II study of ER positive endometrial adenocarcinomas
- HER2/neu, P53 and HRD are promising targets for serous uterine cancer and preliminary clinical data with agents targeting these pathways are encouraging
- ICIs have clear efficacy in MMRd/MSI endometrial cancers.
- The combination of lenvatinib and pembrolizumab is effective in non MMRd/MSI endometrial cancers, including serous uterine cancers.
- Several ongoing trials integrating ICIs in the first line treatment have the potential to change the current standard of care of advanced/recurrent endometrial cancer.

Immunotherapy has changed the face of many cancers in the past decade and finally this is happening also for endometrial cancers!!!