The Current Therapeutic Landscape in Endometrial Cancer

Tashanna K. Myers, MD, FACOG, FACS
Associate Professor of Obstetrics and Gynecology
University of Massachusetts Medical School-Baystate
Chief, Division of Gynecologic Oncology
Springfield, Massachusetts, USA

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Endometrial Cancer Statistics in the US and Globally 2020

	New cases	Deaths
Globally	417,000	97000
USA	65,620	12590
	Endometrioid 41000 (Grade 1-2) 14000 (Grade 3) Serous 8000 Clear Cell 1000 Sarcoma/Carcinosarcoma 1620	 3700 (Grade 1-2) 3790 (Grade 3) 4000 300 800

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Sung HS, et al. Global Cancer Statistics 2020: GLOBOCAN Estimated of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries
Siegel et al. Cancer Statistics 2020

HISTORIC ENDOMETRIAL CANCER CLASSIFICATION

Characteristic	Type I	Type II
Histology	Endometrioid	Non-endometrioid (serous, clear-cell, undifferentiated including carcinosarcomas)
Grade	Usually low	Usually high
Stage	Often early	Often advanced
Etiology	Unopposed estrogen	Sporadic
Hormone receptor expression	Positive	Negative
Genomic stability	Diploid, frequent MSI	Aneuploid
Common mutations	*PTEN, k-RAS,*	*P53.ERBB2*

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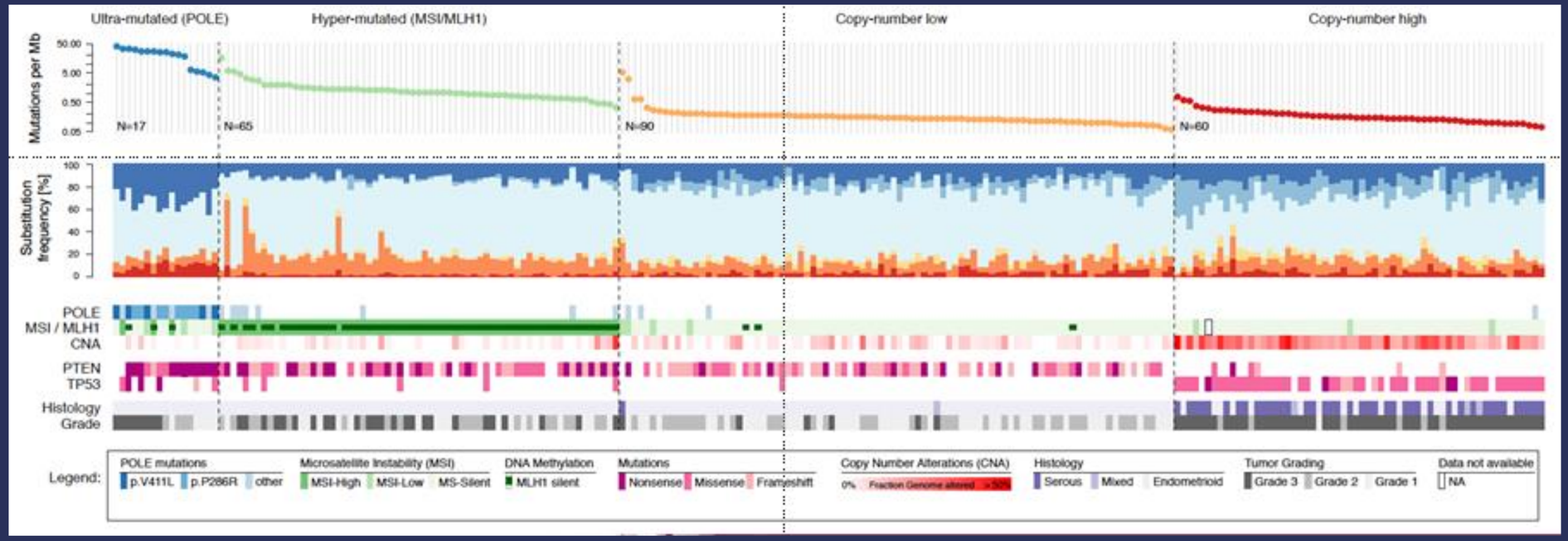
Colombo N, et al. *Ann Oncol*. 2016;27:16-41; Llobet D, et al. *J Clin Pathol*. 2009;62:777-785.
Binder PS, et al. *Womens Health (Lond)*. 2014;10:277-288.

Molecular classification of endometrial cancer: TCGA



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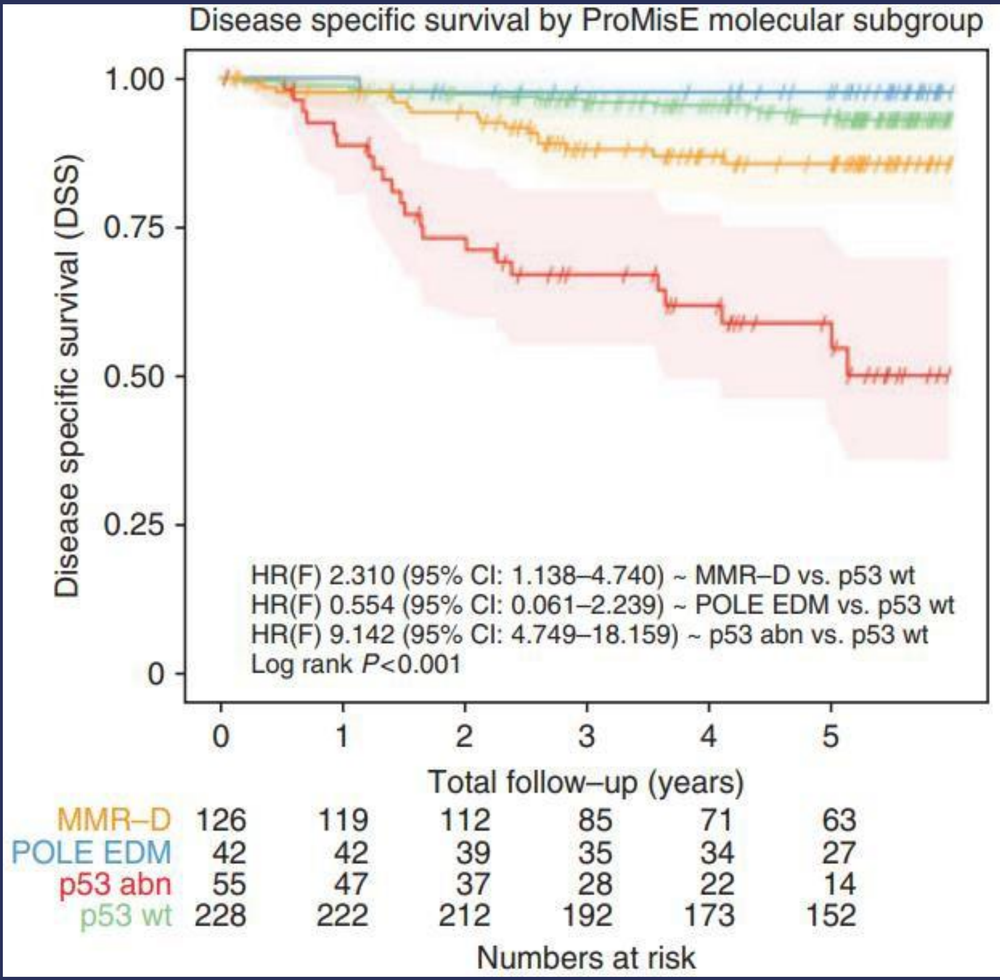
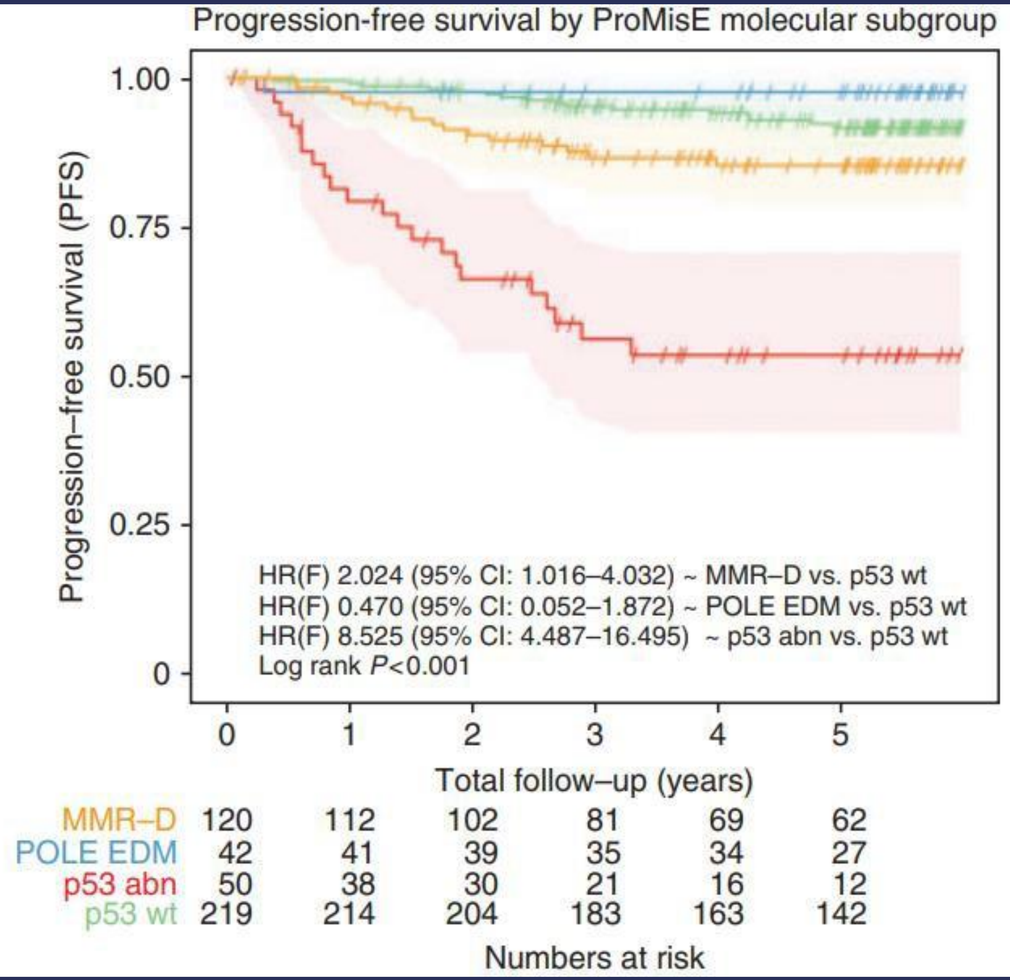
TCGA Nature. 2013 22;500:415-21

ProMisE Molecular Classifier Subtypes





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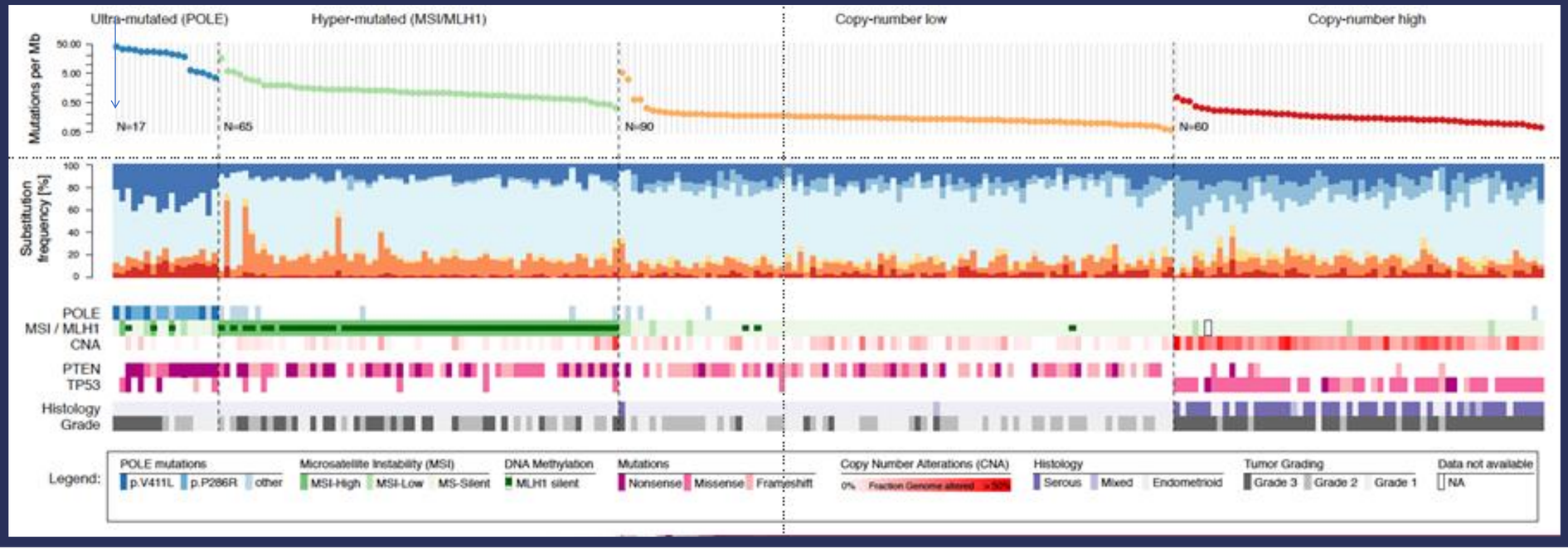
Kommoss S, et al. *Ann Oncol*. 2018;29:1180-1188.

Molecular classification of endometrial cancer: TCGA

POLE mutations are ultra-mutated, 100-500 mutations/Mb, endometrioid, PTEN



TCGA Nature. 2013 22;500:415-21

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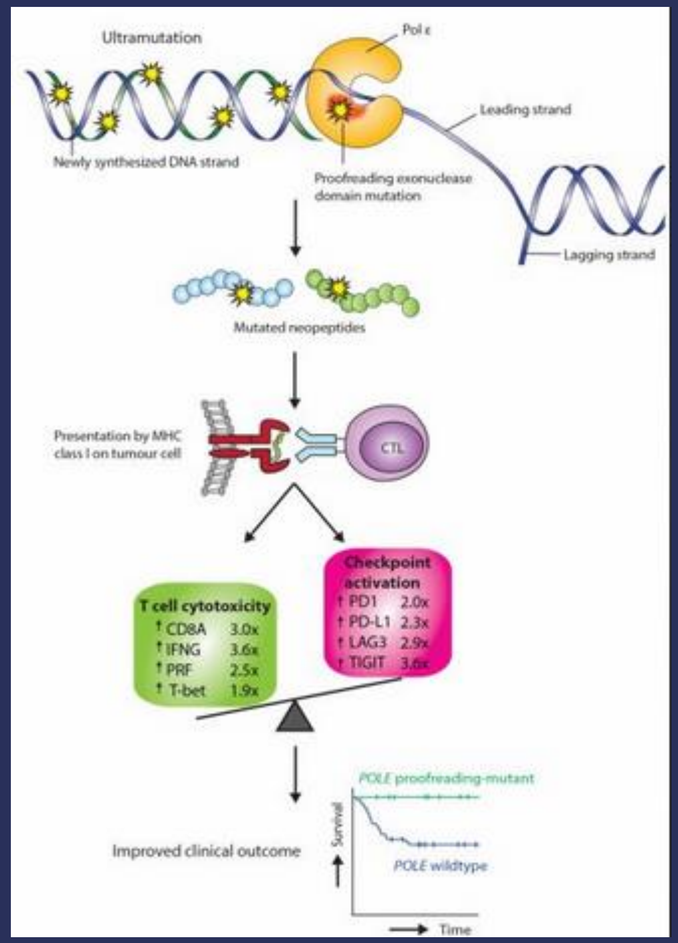
POLE Ultra-mutated Group

- POLE is a DNA polymerase responsible for replicating & repairing DNA sequences
- Mutations in the exonuclease domain = ultramutated status
- 6% (G1-2), 15-22% of G3/HG
- PORTEC-1 & PORTEC-2 analysis found
  - *POLE* mutant fewer recurrences & death
    - (6.2 vs. 14.1%) & (2.3 vs. 9.7%)
  - Strong association with HG tumors
  - 0/15 G3 POLE mutant tumors recurred vs. 31% (29/94) G3 non-POLE (HR 0.09, p=0.01)
  - <u>Identification of POLE mutation carriers may allow stratification to no treatment</u>



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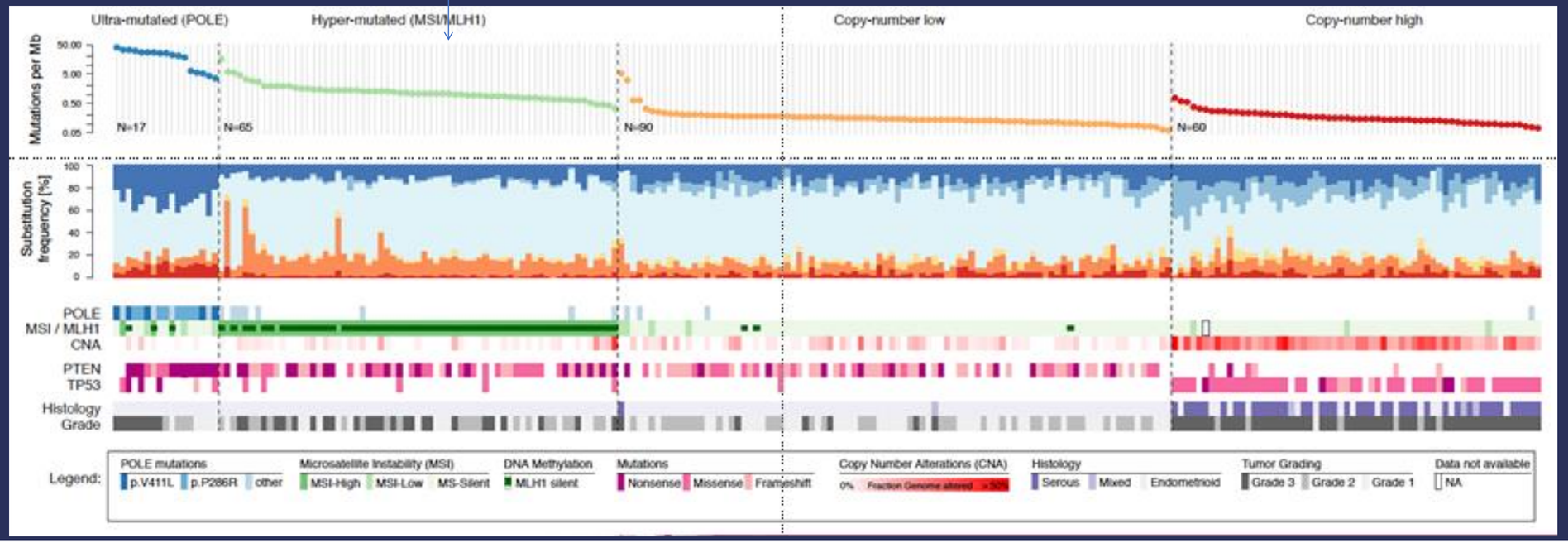
J Natl Cancer Inst 2015; 107:402; Curr Opinion Obst Gynecol. 29(1): 35-39

Molecular classification of endometrial cancer: TCGA

MSI high group with 10-20mut/Mb, endometrioid, PTEN mutations, mixed grade



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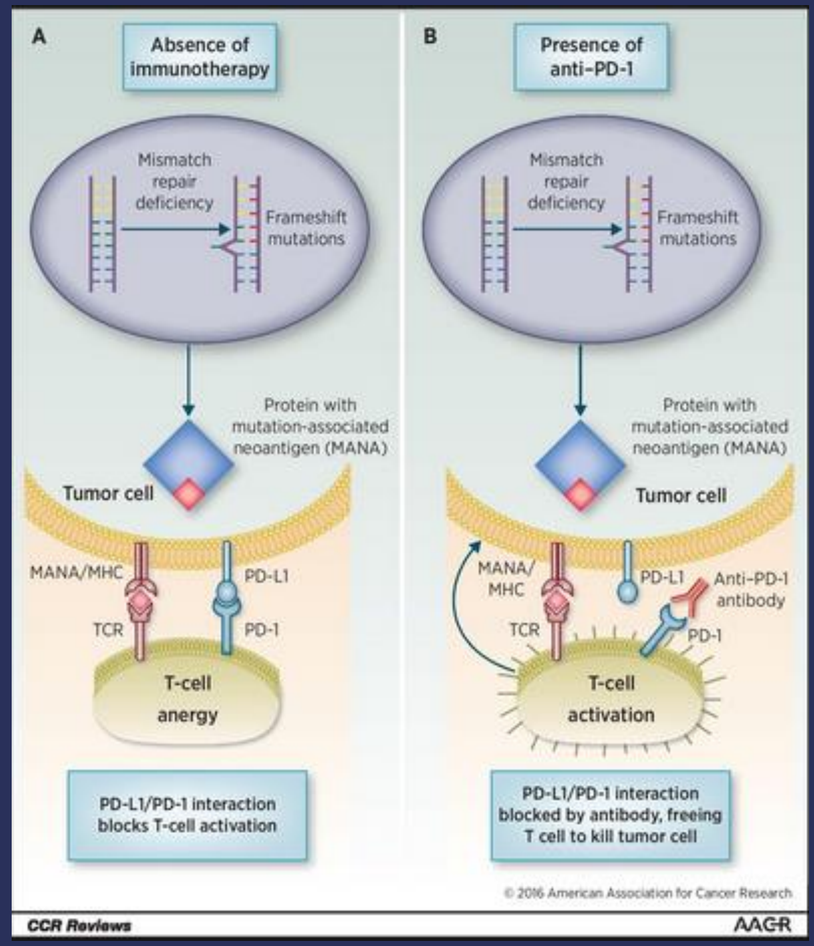
TCGA Nature. 2013 22;500:415-21

MSI-H Group

- Loss of function in the DNA mismatch repair proteins (MSH2, MLH1, MSH6, PMS2) leads to mutations in genes that have microsatellite repeats
- 28 % of all endometrial cancer
- This can be targeted with immune checkpoint inhibitors



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KEYNOTE-158: Efficacy of Pembrolizumab in MSI-H/dMMR Noncolorectal Cancers

Tumor Type	N	CR, n	PR, n	ORR, % (95% CI)	Median PFS, Mos (95% CI)	Median OS, Mos (95% CI)	Median DoR, Mos (Range)
Endometrial	49	8	20	57.1 (42.2-71.2)	25.7 (4.9-NR)	NR (27.2-NR)	NR (2.9-27.0+)
Gastric	24	4	7	45.8 (25.6-67.2)	11.0 (2.1-NR)	NR (7.2-NR)	NR (6.3-28.4+)
Cholangiocarcinoma	22	2	7	40.9 (20.7-63.6)	4.2 (2.1-NR)	24.3 (6.5-NR)	NR (4.1+ to 24.9+)
Pancreatic	22	1	3	18.2 (5.2-40.3)	2.1 (1.9-3.4)	4.0 (2.1-9.8)	13.4 (8.1-16.0+)
Small intestine	19	3	5	42.1 (20.3-66.5)	9.2 (2.3-NR)	NR (10.6-NR)	NR (4.3+ to 31.3+)
Ovarian	15	3	2	33.3 (11.8-61.6)	2.3 (1.9-6.2)	NR (3.8-NR)	NR (4.2-20.7+)
Brain	13	0	0	0 (0-24.7)	1.1 (0.7-2.1)	5.6 (1.5-16.2)	--

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Marabelle A, et al. J Clin Oncol. 2020;38:1-10.

KEYNOTE-158: Pembrolizumab in Advanced EC

Response Rates by Cohort

Confirmed Objective Response per RECIST v1.1 by IRC	MSI-H EC, N = 49 (Cohorts D + K)	EC, N = 107 (Cohort D, biomarker unselected)
ORR, % (95% CI)	57.1 (42.2-71.2)*	11.2 (5.9-18.8)
Best overall response n (%)		
CR	8 (16.3)	0
PR	20 (40.8)	12 (11.2)
Stable disease	8 (16.3)	26 (24.3)
Progressive disease	11 (22.4)	56 (52.3)

***ORR 45.5% in cohort D (n = 11)and 60.5% in Cohort K (n = 38)**

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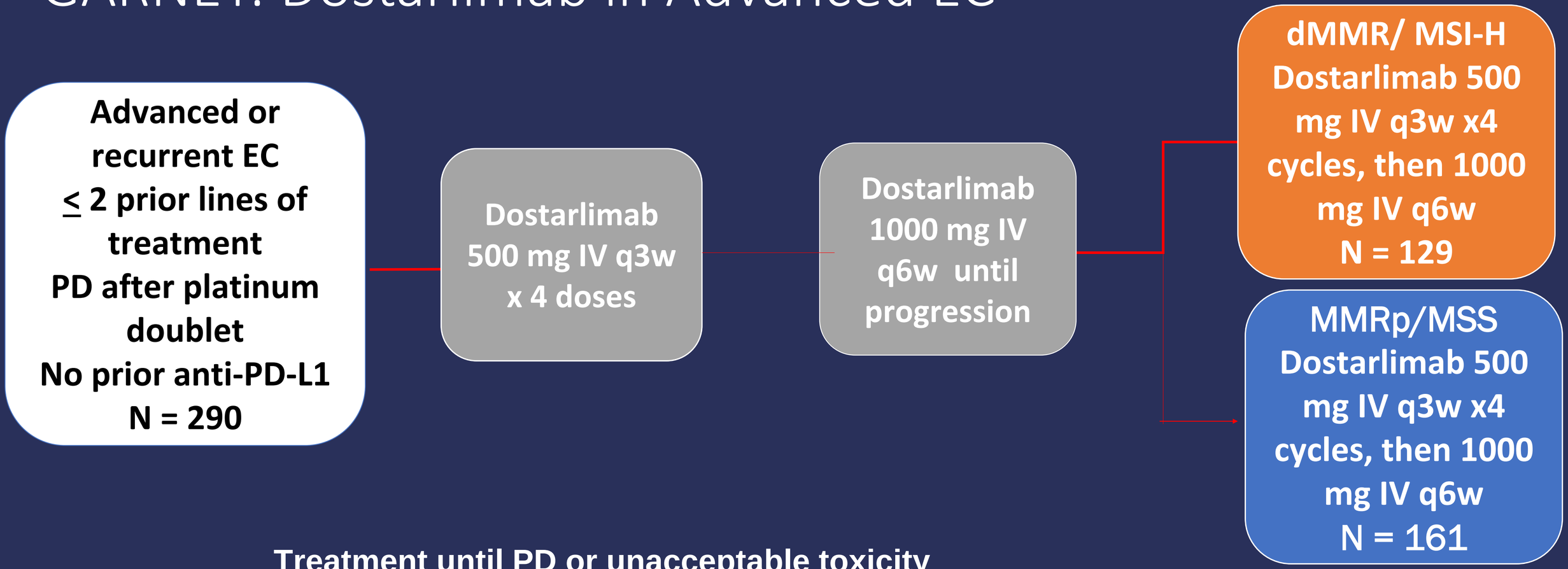
O'Malley DM. ESMO 2019. Abstract 3394.

GARNET: Dostarlimab in Advanced EC



Treatment until PD or unacceptable toxicity
Primary endpoint: ORR and DoR

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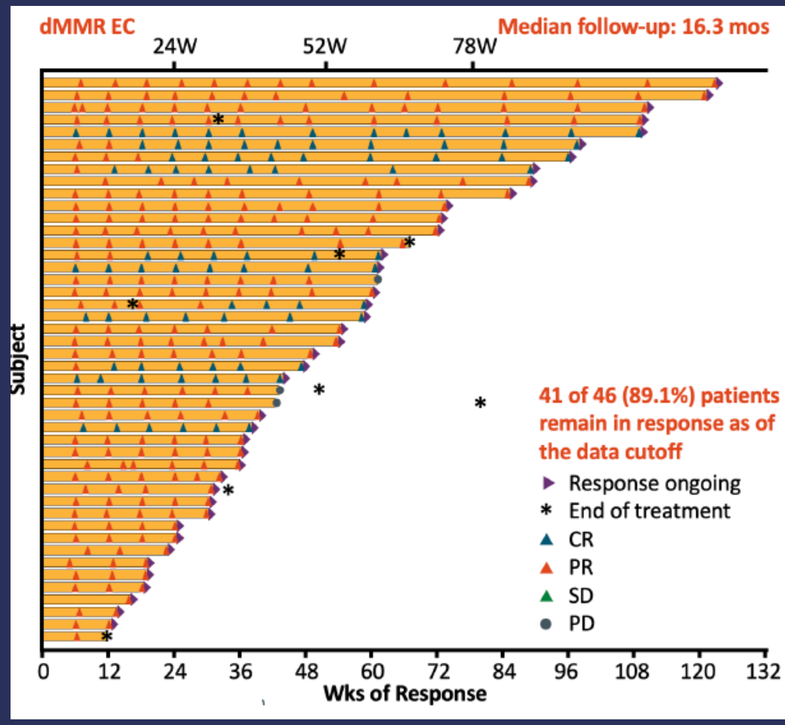
Oaknin A. ESMO 2020. Abstract LBA36.

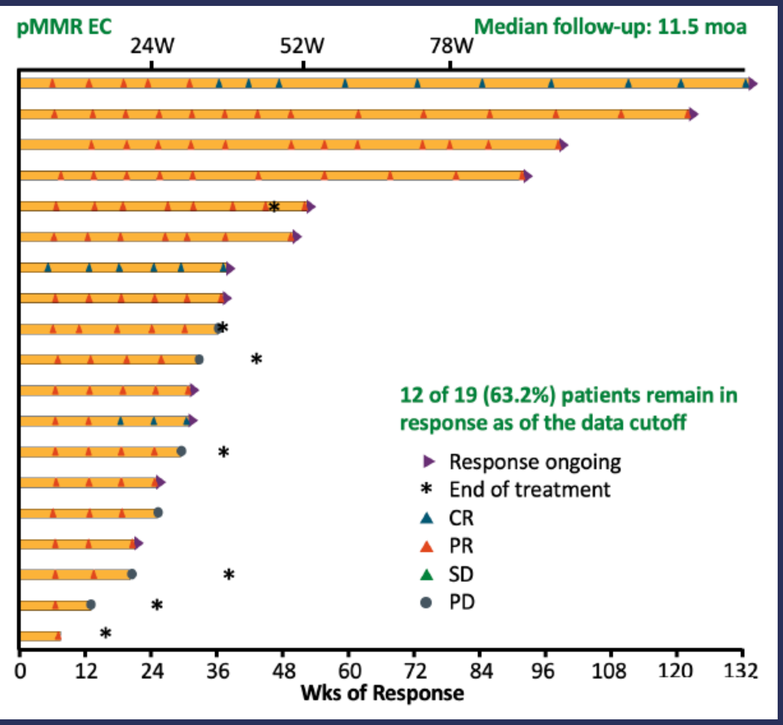
GARNET: Dostarlimab in Advanced EC

	dMMR N = 103	pMMR N = 142
CR, n	11	3
PR, n	35	16
ORR, %	44.7	13.4
DCR, %	57.3	35.2

DoR dMMR cohort



DoR pMMR cohort



Feb 26, 2021: Dostarlimab granted Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency conditional authorization for certain types of recurrent/advanced EC

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Oaknin A. ESMO 2020. Abstract LBA36; EMA. Meeting highlights from the CHMP 22-25 February 2021.

Phase II Trial of Avelumab in Patients with Mismatch Repair Deficient and Mismatch Repair Proficient Recurrent/ Persistent Endometrial Cancer

Recurrent or persistent EC of any histology
≥ 1 previous chemotherapy regimen
PS 0 – 1
No previous ICI

dMMR/POLEm
N = 15

pMMR/non-POLE
N = 16

Avelumab
10mg/kg IV q2w

Treatment until PD or unacceptable toxicity
Primary endpoint: ORR/6 mo. PFS
Secondary endpoints: PFS, OS, safety

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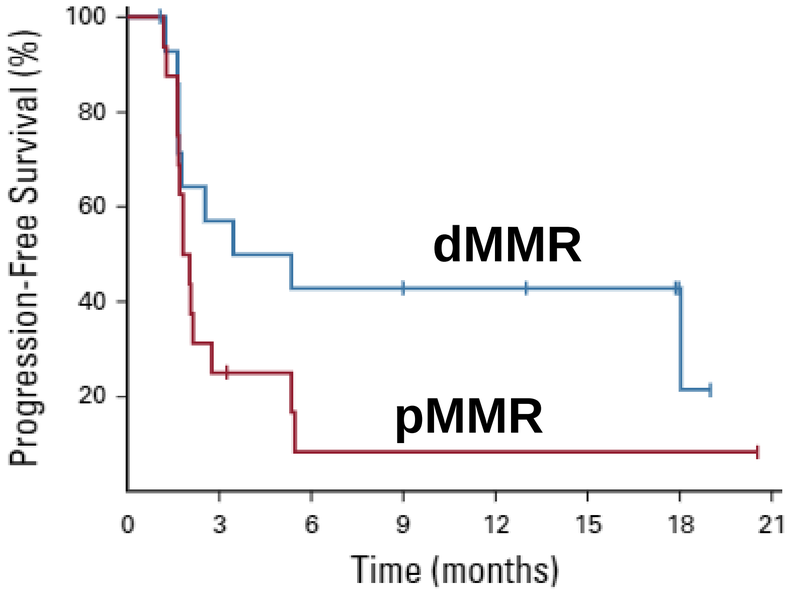
• Konstantinopoulos PA, et al. *J Clin Oncol*. 2019;37:2786-2794.

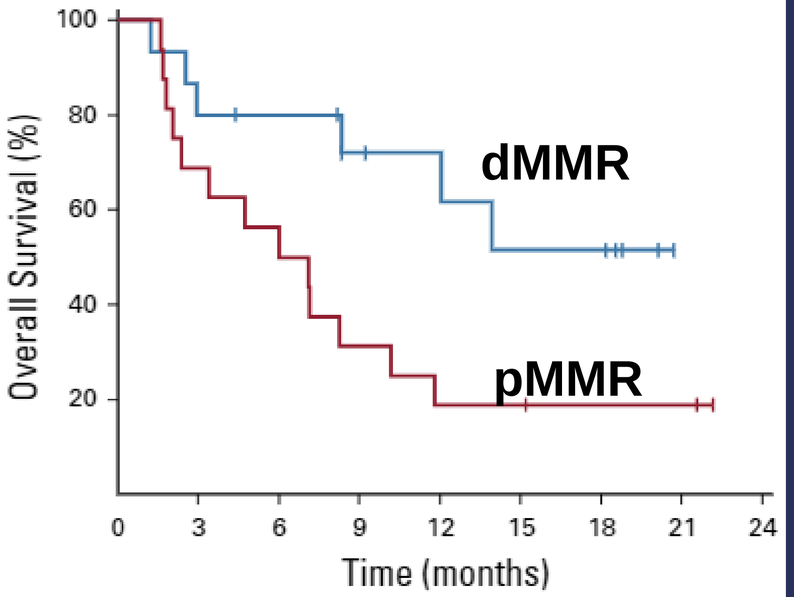
Avelumab in Persistent/Recurrent Endometrial Cancer

	dMMR N = 15	pMMR N = 16
CR, n	1	0
PR, n	3	1
ORR, %	26.7	6.25
PFS6, %	40	6.25

PFS



OS



Conclusion: Avelumab exhibited promising activity in mismatch repair deficient endometrial cancer regardless of PD-L1 status. IHC for MMR assessment was a useful tool for patient selection.

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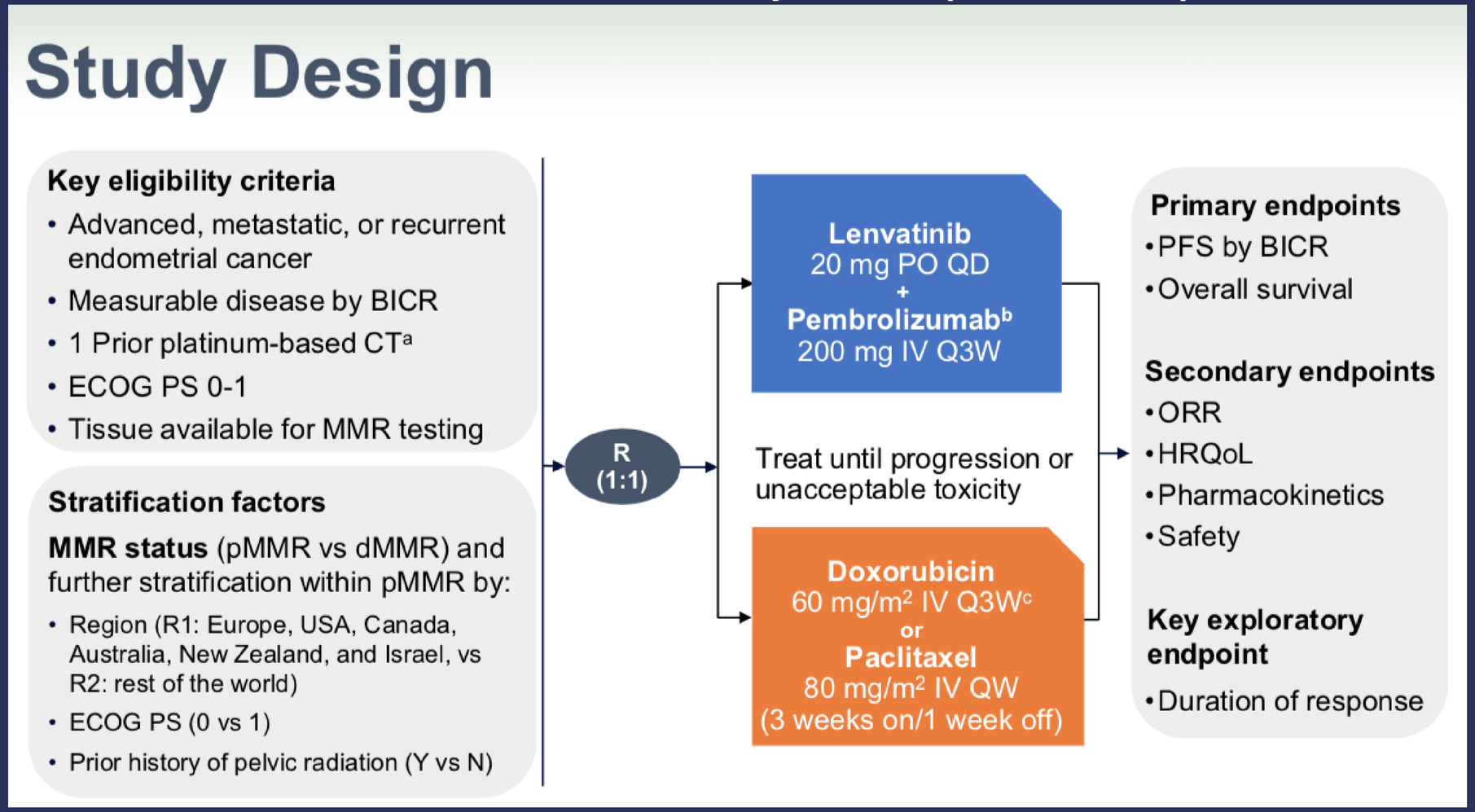
Konstantinopoulos PA, et al. *J Clin Oncol*. 2019;37:2786-2794.

A phase 3 trial evaluating efficacy and safety of lenvatinib in combination with pembrolizumab in patients with advanced endometrial cancer. Keynote 775 (NCT03517449)

Study Design



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V. Makker et al. A multicenter, open-label, randomized, phase 3 study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab vs treatment of physician's choice in patients with advanced endometrial cancer: Study 309/KEYNOTE-775
SGO 2021 Virtual Annual Meeting

A phase 3 trial evaluating efficacy and safety of lenvatinib in combination with pembrolizumab in patients with advanced endometrial cancer. Keynote 775 (NCT03517449)

Baseline Characteristics

	LEN + pembro (n = 411)	TPC (n = 416)
Median age (range), years	64 (30-82)	65 (35-86)
MMR status: pMMR / dMMR, %	84.2 / 15.8	84.4 / 15.6
Prior history of pelvic radiation, %	40.9	41.6
ECOG 0 / 1, %[a]	59.9 / 39.9	57.9 / 42.1
Race: White / Black / Asian / other, %[b]	63.5 / 4.1 / 20.7 / 2.9	59.1 / 3.4 / 22.1 / 4.8
Histology at diagnosis, %[c]		
Endometrioid carcinoma High-grade / low-grade / not specified[d]	22.9 / 14.4 / 21.9	21.6 / 13.0 / 26.4
Serous carcinoma	25.1	27.6
Clear cell carcinoma	7.3	4.1
Mixed	5.4	3.8
Prior lines of systemic treatment 1 / ≥ 2, %	72.3 / 27.7	66.6 / 33.4
Prior lines of platinum-based treatment 1 / 2, %[e]	79.3 / 20.2	75.7 / 24.3
Prior neo-adjuvant and/or adjuvant treatment, %	54.5	60.3

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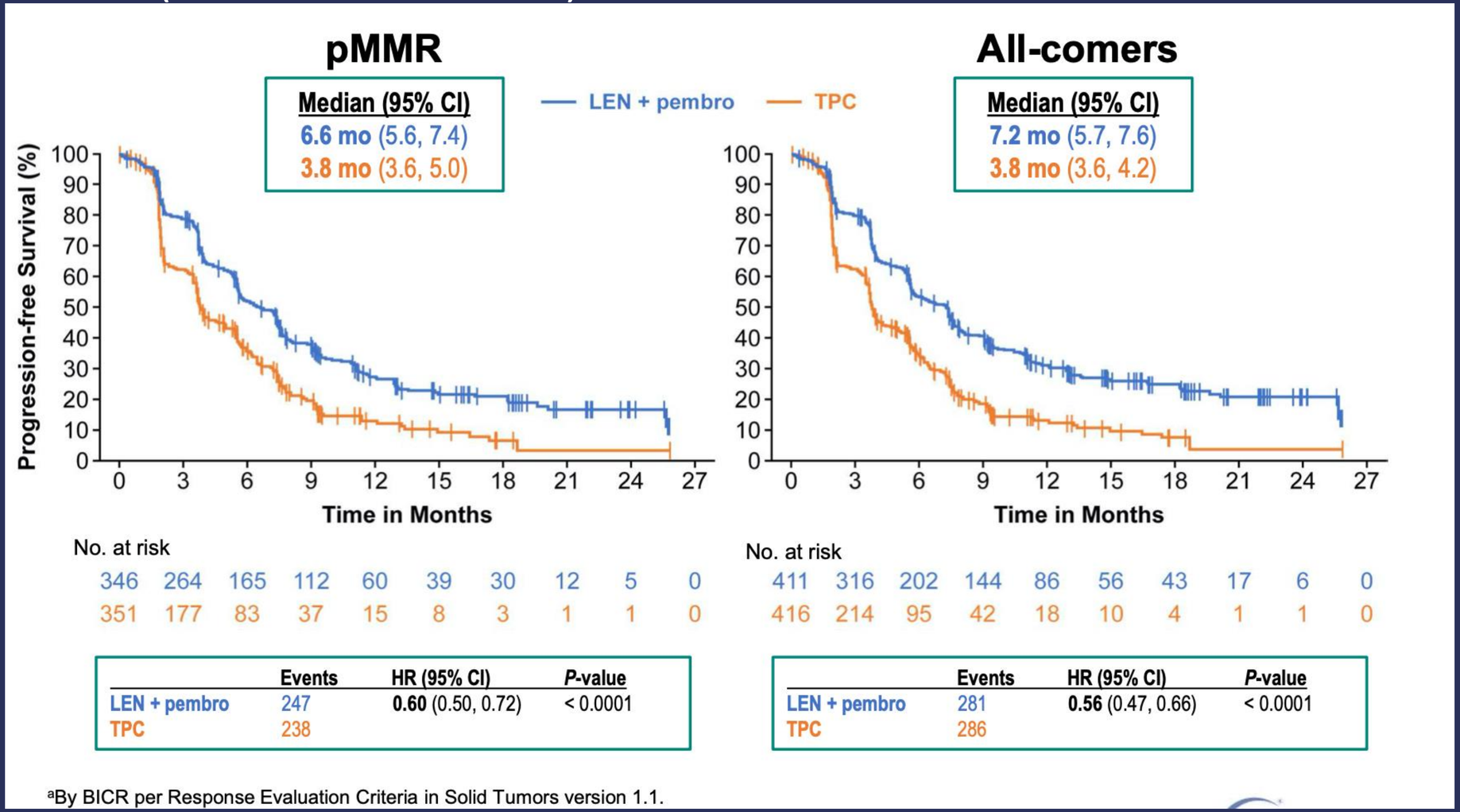
V. Makker et. SGO Virtual Annual Meeting 2021

Keynote 775 (NCT03517449)



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

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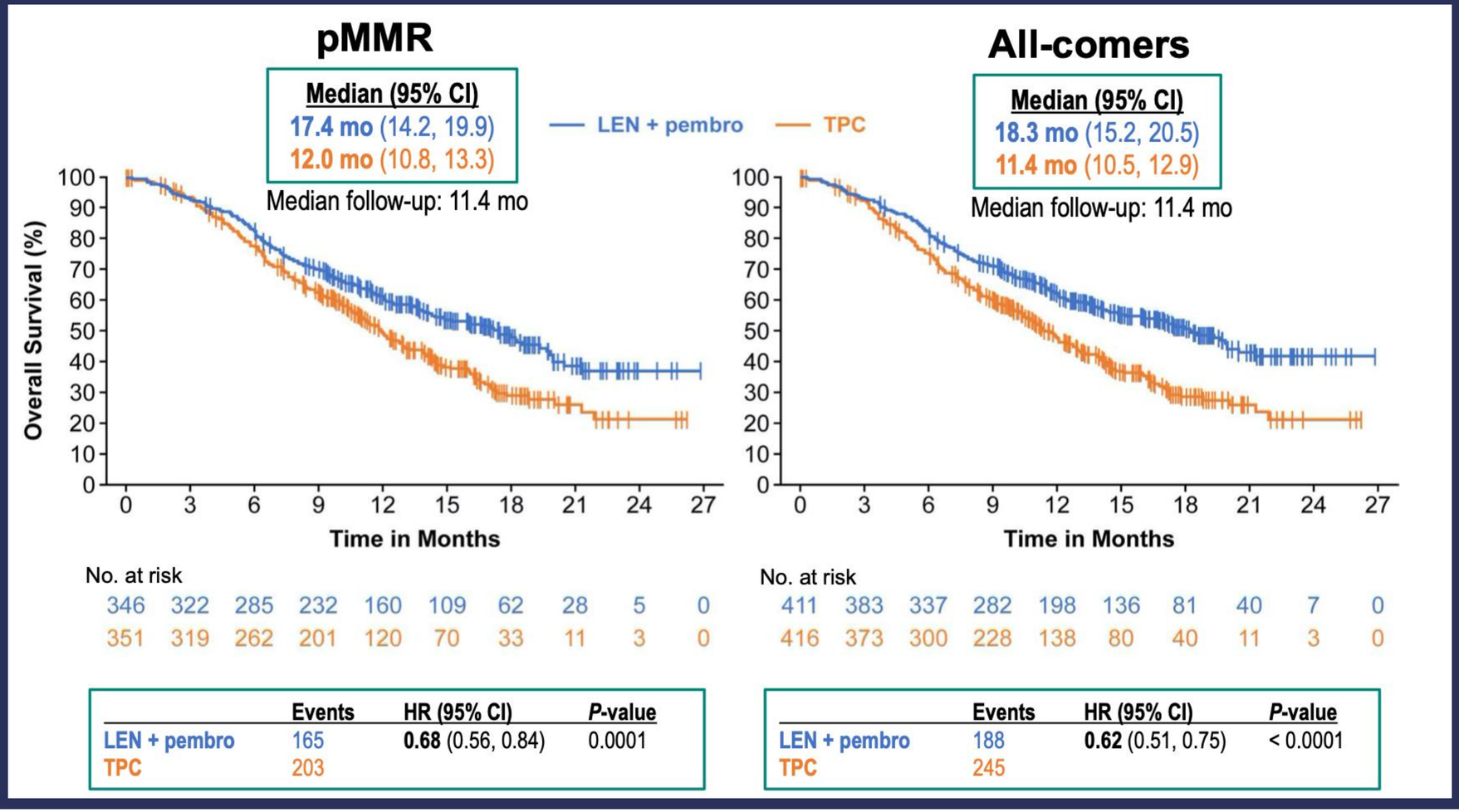
V. Makker et. SGO Virtual Annual Meeting 2021

Lenvatinib + Pembrolizumab Keynote 775 (NCT03517449)



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V. Makker et. SGO Virtual Annual Meeting 2021

A phase 3 trial evaluating efficacy and safety of lenvatinib in combination with pembrolizumab in patients with advanced endometrial cancer Keynote 775 (NCT03517449)

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, %	15.2	--	17.2	--
P-value	< 0.0001		< 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)

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A phase 3 trial evaluating efficacy and safety of lenvatinib in combination with pembrolizumab in patients with advanced endometrial cancer. Keynote 775 (NCT03517449)

TEAEs With Frequency ≥ 25% in All-comers

	LEN + pembro (n = 406)		TPC (n = 388)	
	Any Grade	Grade ≥3[a]	Any Grade	Grade ≥3[a]
Patients with any TEAEs, %	99.8	88.9	99.5	72.7
Hypertension	64.0	37.9	5.2	2.3
Hypothyroidism[b]	57.4	1.2	0.8	0.0
Diarrhea	54.2	7.6	20.1	2.1
Nausea	49.5	3.4	46.1	1.3
Decreased appetite	44.8	7.9	21.1	0.5
Vomiting	36.7	2.7	20.9	2.3
Weight decrease	34.0	10.3	5.7	0.3
Fatigue	33.0	5.2	27.6	3.1
Arthralgia	30.5	1.7	8.0	0.0
Proteinuria	28.8	5.4	2.8	0.3
Anemia	26.1	6.2	48.7	14.7
Constipation	25.9	0.7	24.7	0.5
Urinary tract infection	25.6	3.9	10.1	1.0
Headache	24.9	0.5	8.8	0.3
Asthenia	23.6	5.9	24.5	3.9
Neutropenia	7.4	1.7	33.8	25.8
Alopecia	5.4	0.0	30.9	0.5

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A phase 3 trial evaluating efficacy and safety of lenvatinib in combination with pembrolizumab in patients with advanced endometrial cancer. Keynote 775 (NCT03517449)

Treatment Exposure, Safety, and Discontinuation in All-comers

	LEN + pembro (n = 406)	TPC (n = 388)
Median duration of treatment (range), days	231 (1-817)	104.5 (1-785)
Patients with any TEAEs, %	99.8	99.5
Grade ≥ 3	88.9	72.7
Patients with any TEAEs leading to dose reductions, %[a]	66.5	12.9
Patients with any-grade TEAEs leading to interruption, %[b]	69.2	27.1
LEN[c]	58.6	--
Pembro[c]	50.0	--
LEN + pembro	30.8	--
Patients with any-grade TEAEs leading to discontinuation, %[b]	33.0	8.0
LEN[c]	30.8	--
Pembro[c]	18.7	--
LEN + pembro	14.0	--

[a]Includes LEN only or TPC. [b]Includes LEN or pembro or LEN + pembro or TPC. [c]Regardless of action taken with the other drug in the combination arm.

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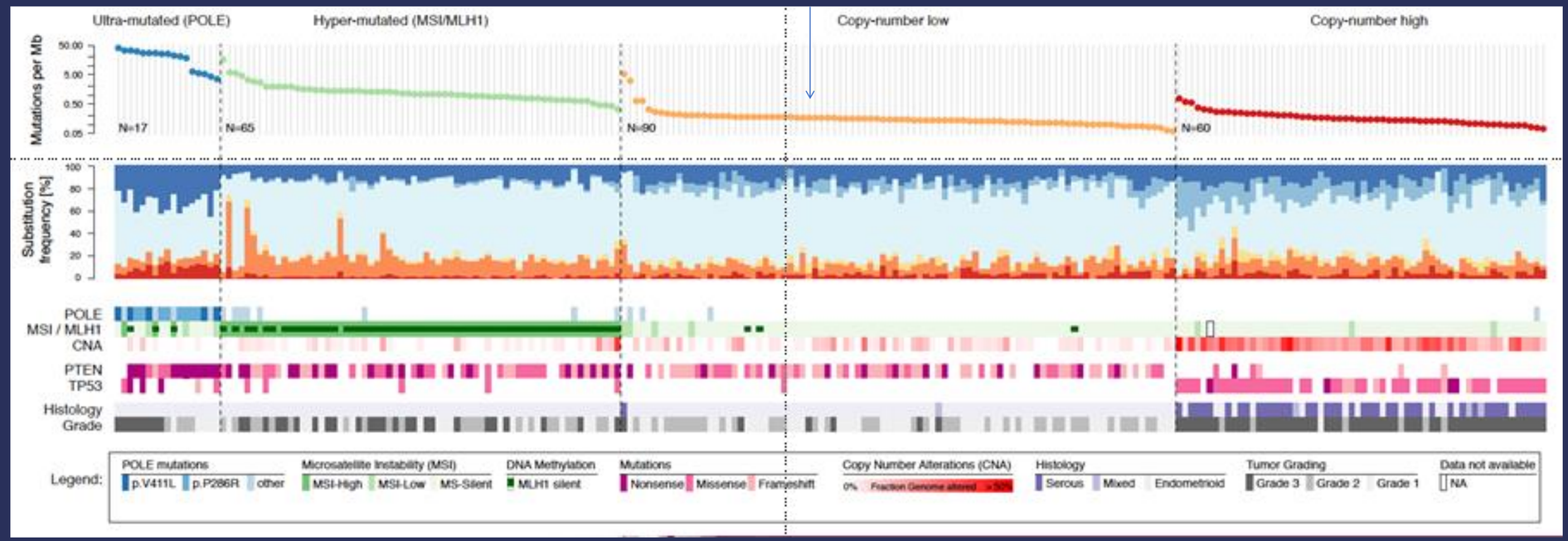
Molecular classification of endometrial cancer: TCGA

CN Low: 2-3 mutations/Mb, endometrioid, PTEN & CTNNB1 mutations, G1



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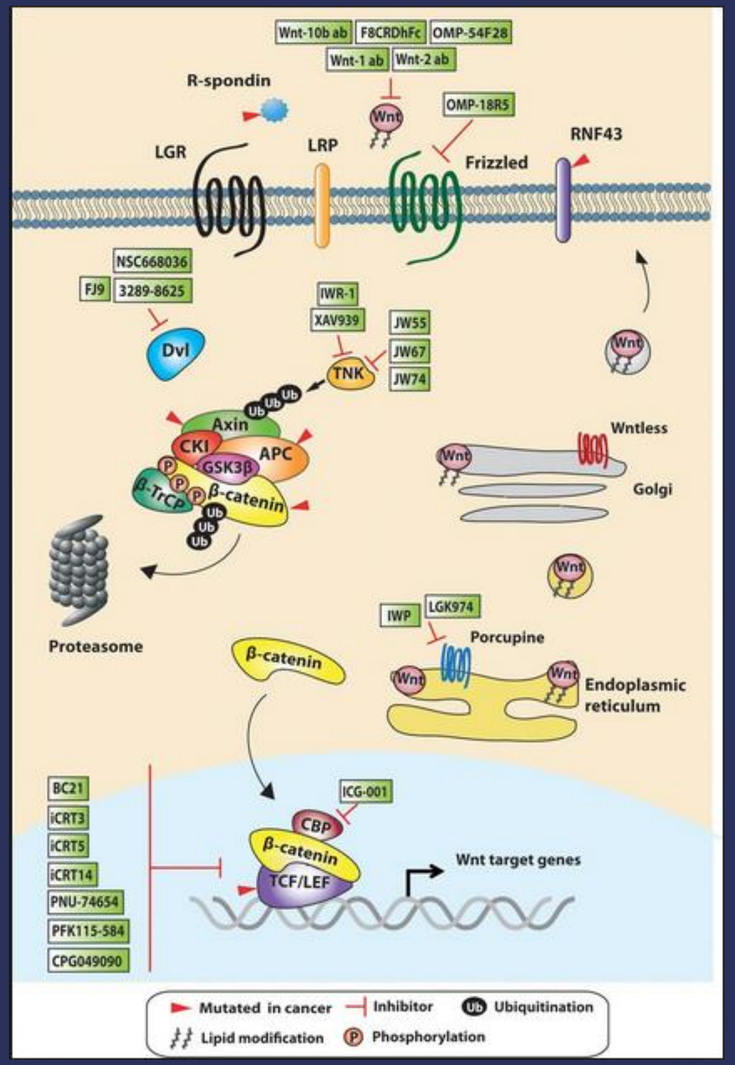
TCGA Nature. 2013 22;500:415-21

Copy Number Low/MSS

- Characterized by PTEN loss, mutations in PI(3)K pathway and ARID1A
- Increased progesterone receptor expression
  - Suggesting responsiveness to hormonal therapy
- Uniquely characterized by mutations in genes involved in the Wingless-related integration site (WNT) signaling
- The majority of copy number low patients have altered WNT
  - *CTNNB1* (β catenin) mutations 53%
  - *SOX17* (mediates proteolysis of β catenin) 8%
- Promotes cellular proliferation and progression
- One study has demonstrated benefit in targeting *CTNNB1* mutations…



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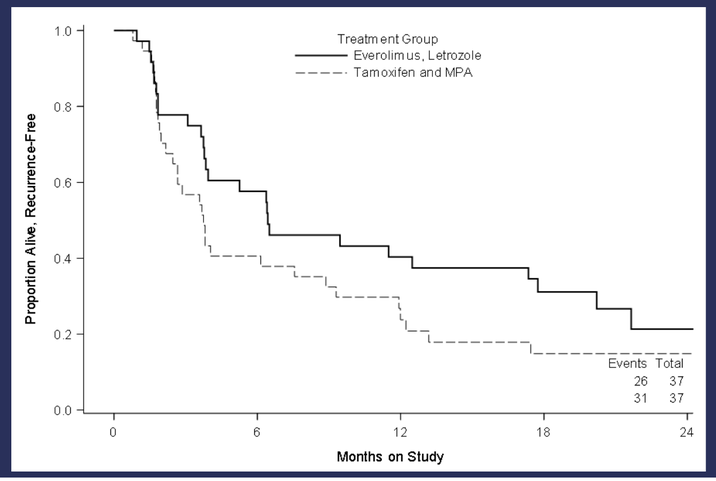
Slomovitz, J Clin Oncol 2013

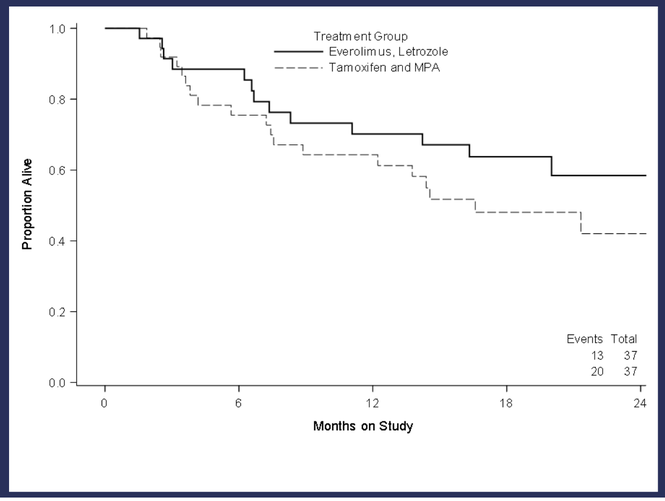
GOG 3007: A randomized Phase II trial of everolimus and letrozole (EL) or hormonal therapy (medroxyprogesterone acetate/tamoxifen)(PT) in women with advanced, persistent or recurrent endometrial cancer: A GOG Foundation Study

Regimen	N	Objective Response - ITT	Objective Response - NPC	CBR	PFS	OS
Everolimus/ Letrozole	37	24%	53%	78%	6.3 months	Not reached
MA/ Tamoxifen	36	22%	43%	69%	3.8 months	16.6 months

PFS by Regimen



Overall Survival by Regimen



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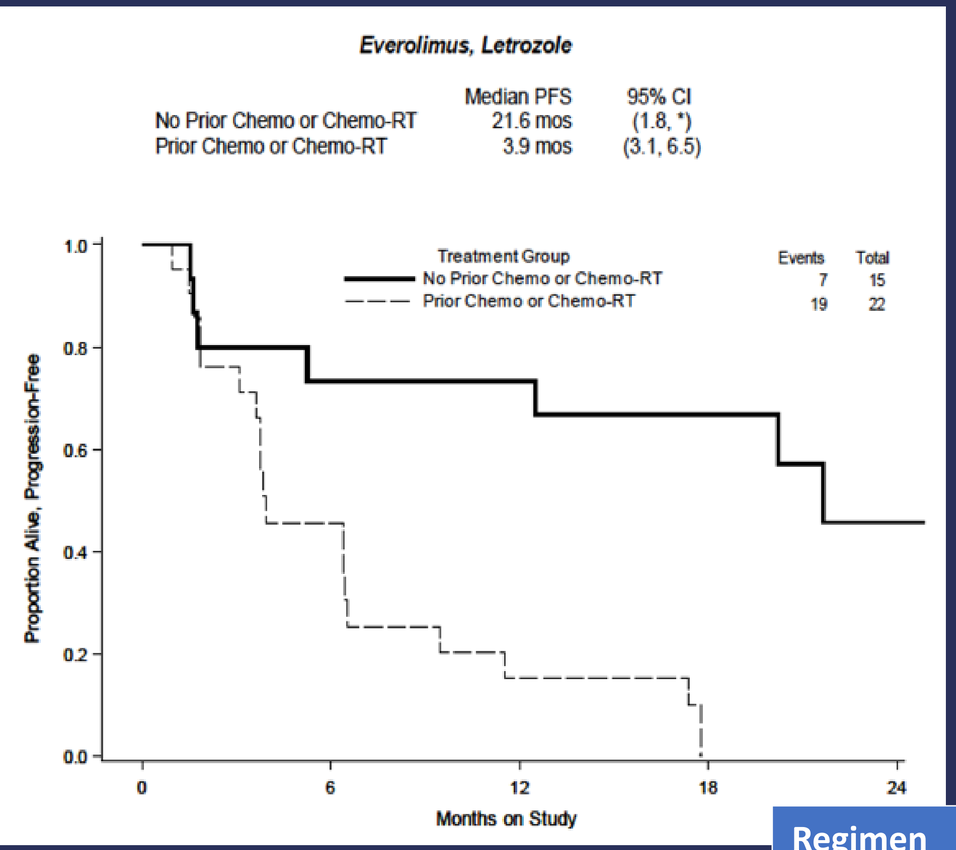
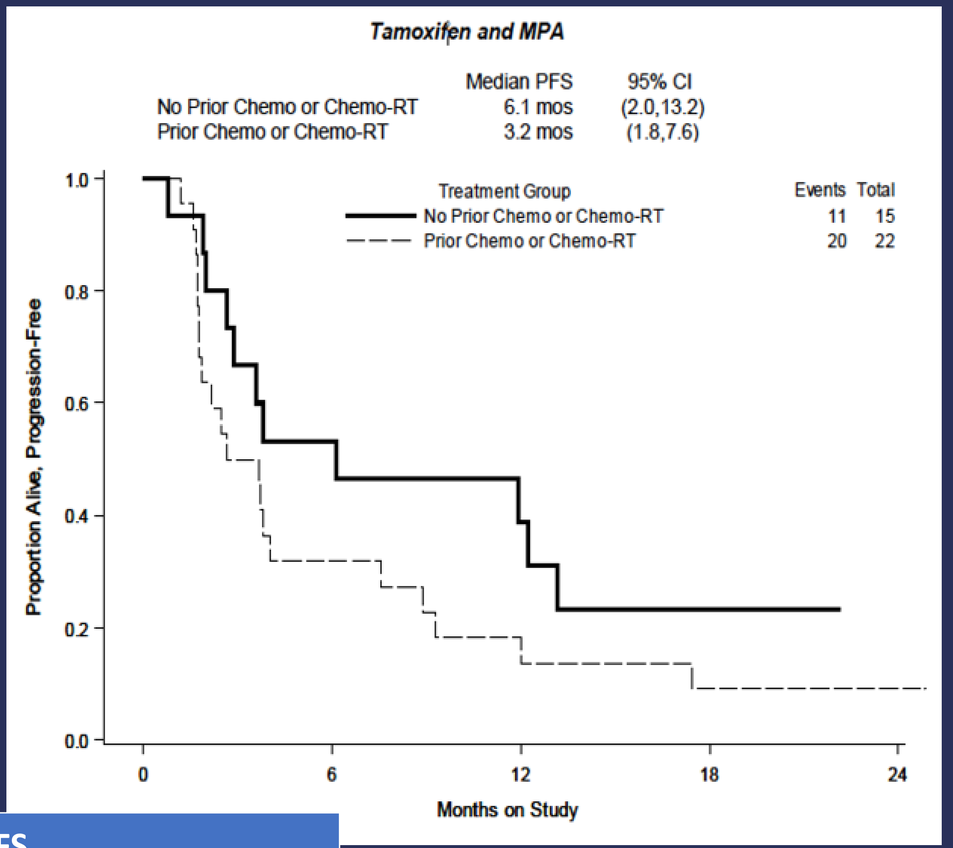
Slomovitz BM et al. SGO Scientific Plenary 2018. Abstract 1. Gyn Onc 2018;149:2-247

GOG 3007: PFS & OS by prior treatment





Regimen	RR	PFS
Everolimus/letrozole	53%	21.6 months
Tamoxifen/MA	43%	6.1 months
Carboplatin/paclitaxel	51%	14 months

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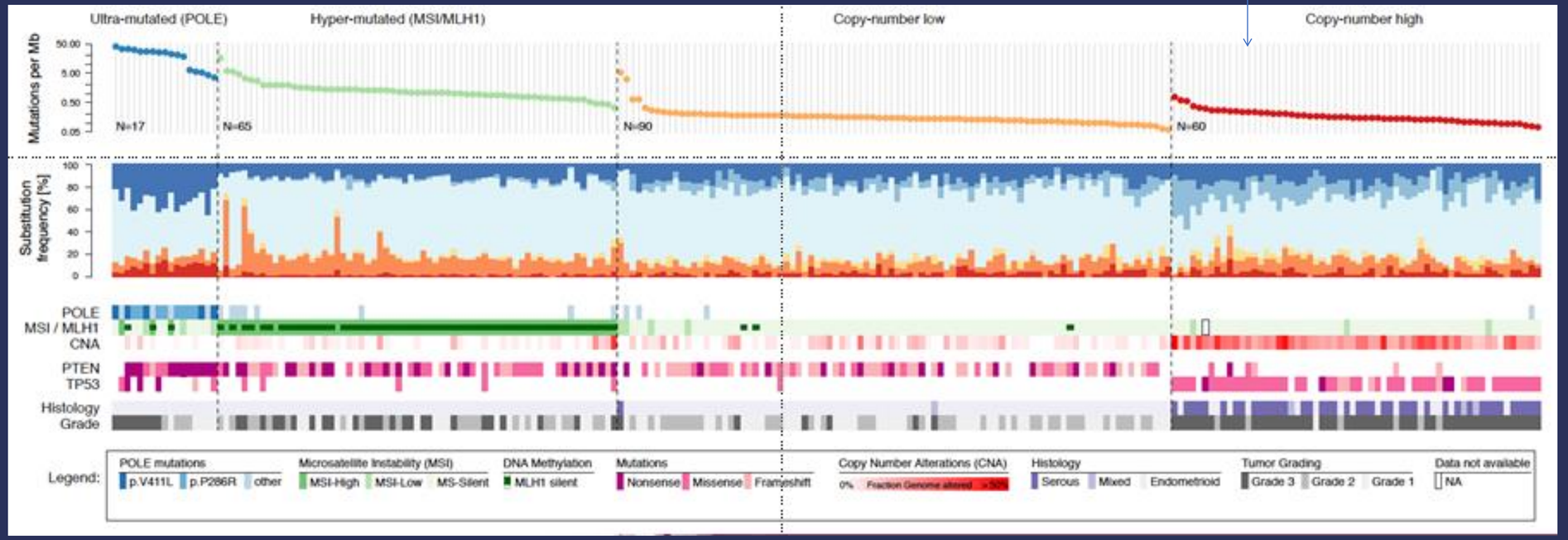
Slomovitz BM et al. SGO Scientific Plenary 2018. Abstract 1. Gyn Onc 2018;149:2-247

Molecular classification of endometrial cancer: TCGA

CN high: 2-3 mutations/Mb, TP53 mutations, high grade



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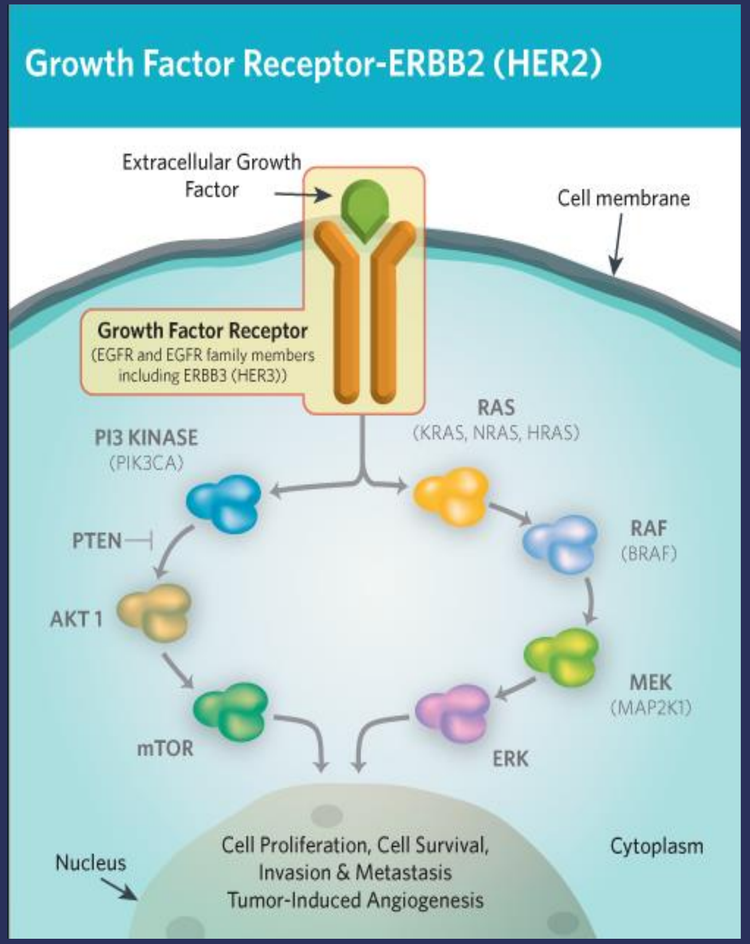
TCGA Nature. 2013 22;500(7463):415-21

Copy Number High

- Comprised of serous and 25% high grade endometrioid cancers
- Other than *TP53* (>90%) we see 45% *PI3K*, 25% *ERBB2*, 20% *BRCA1* (10% somatic and 10% epigenetic silencing)
- *ERBB2* mutation/overexpression has been targeted with trastuzumab as a single agent in GOG 181B with little activity
  - Many patients did not express Her2-Neu



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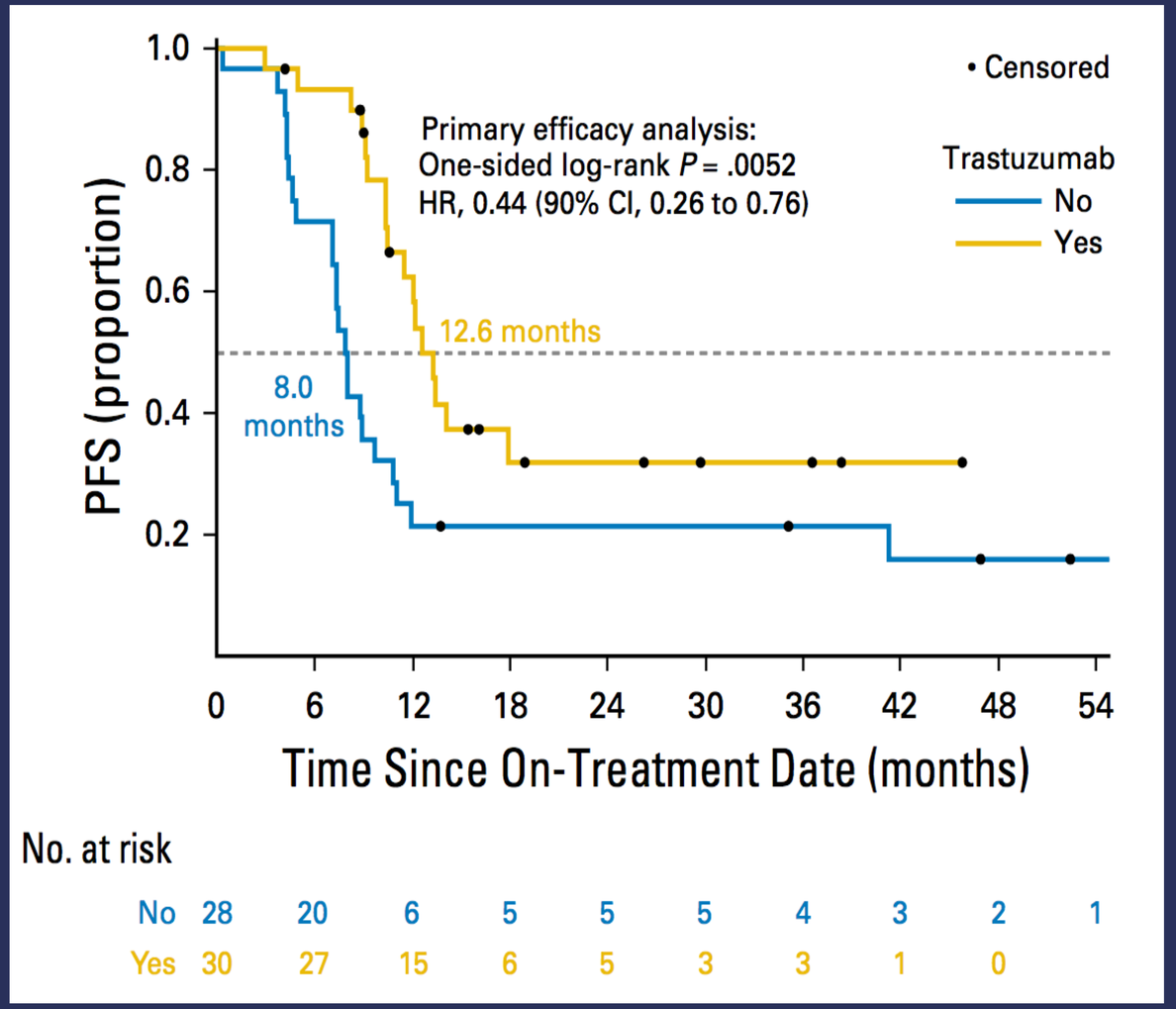
Fleming et al. Gynecol Oncol 2010; 116:15-20

Incorporation of anti-HER-2 treatment: Trastuzumab with Chemotherapy

Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu

Amanda N. Fader, Dana M. Roque, Eric Siegel, Natalia Buza, Pei Hui, Osama Abdelghany, Setsuko K. Chambers, Angeles Alvarez Secord, Laura Havrilesky, David M. O'Malley, Floor Backes, Nicole Nevadunsky, Babak Edraki, Dirk Pikaart, William Lowery, Karim S. ElSahwi, Paul Celano, Stefania Bellone, Masoud Azodi, Babak Litkouhi, Elena Ratner, Dan-Arin Silasi, Peter E. Schwartz, and Alessandro D. Santin

- **Key eligibility** criteria
- **Primary stage III or IV or recurrent HER2/neu-positive disease**
- **HER2/neu-positive USC as defined by an immunohistochemistry score of 3+, or 2+ with gene amplification confirmed by fluorescence in situ hybridization (FISH)**
- **ECOG 0-2**
- **≤3 prior lines of therapy**
- **"platinum sensitive" recurrence (6 mo.)**



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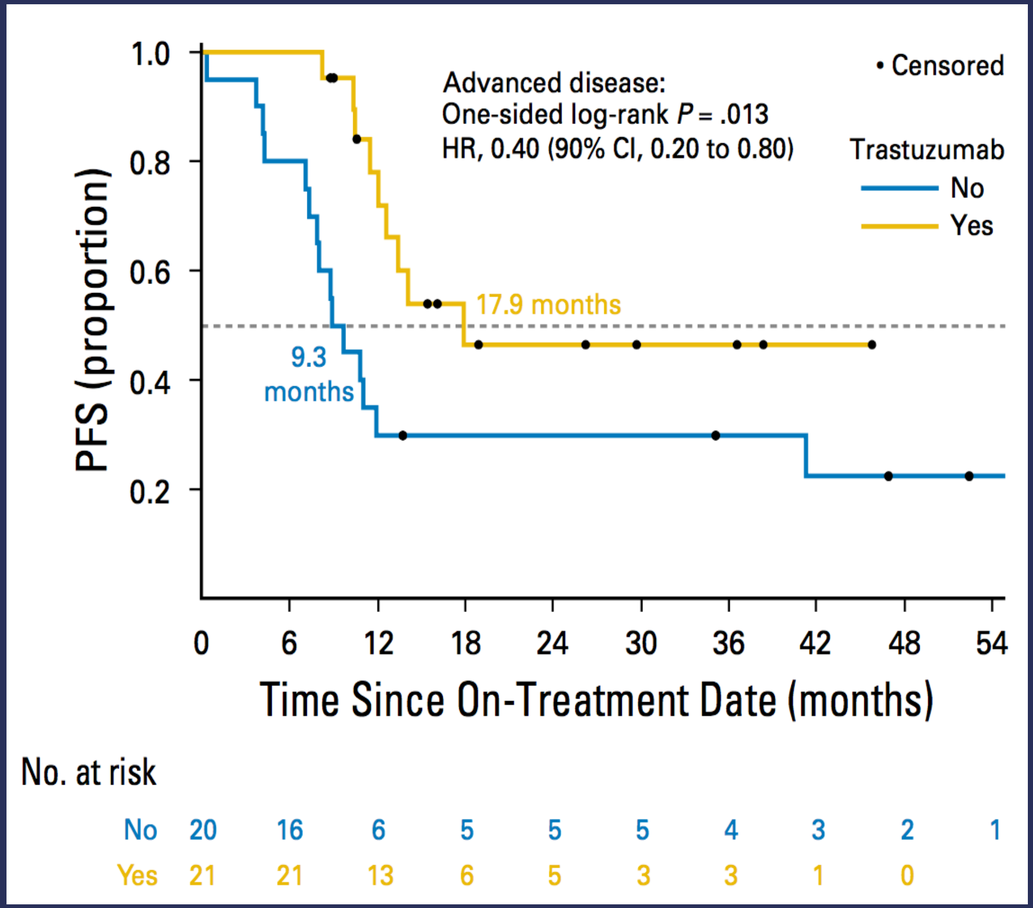
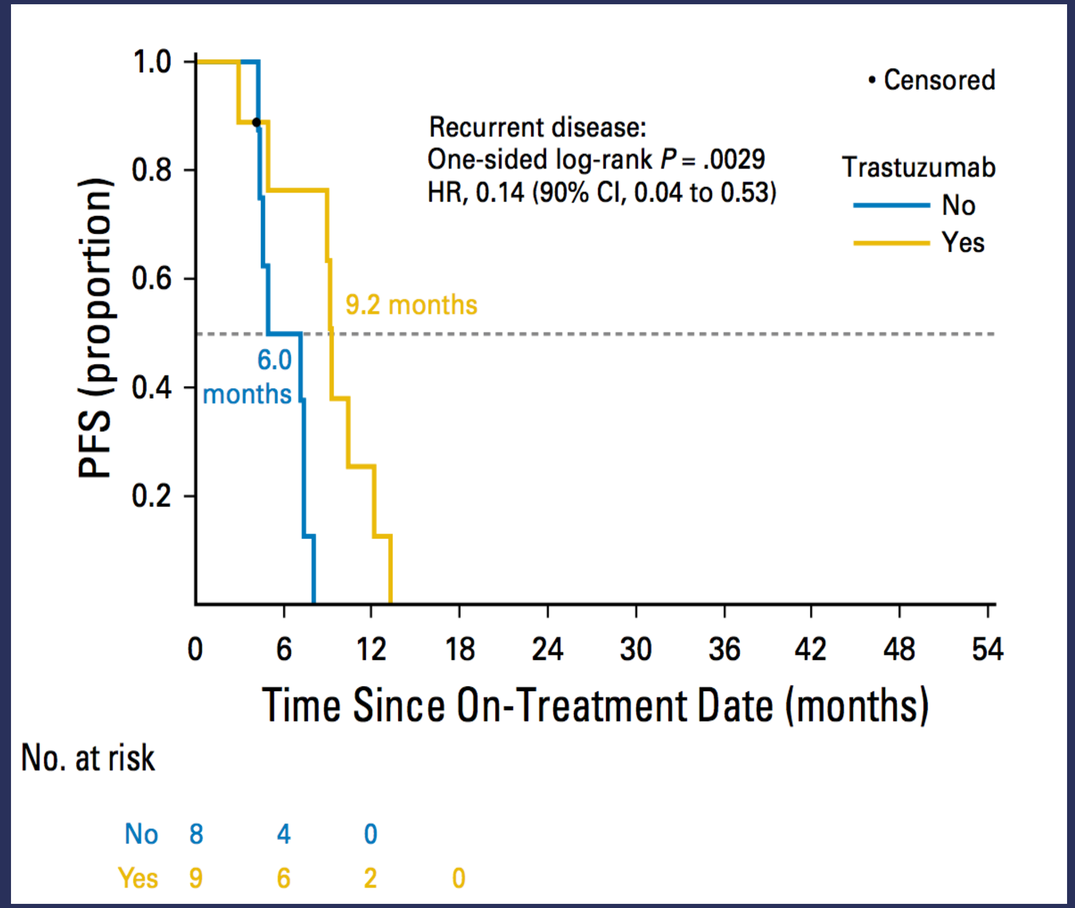
Nickles-Fader J Clin Oncol 2018

Incorporation of anti-HER-2 treatment: Trastuzumab with Chemotherapy





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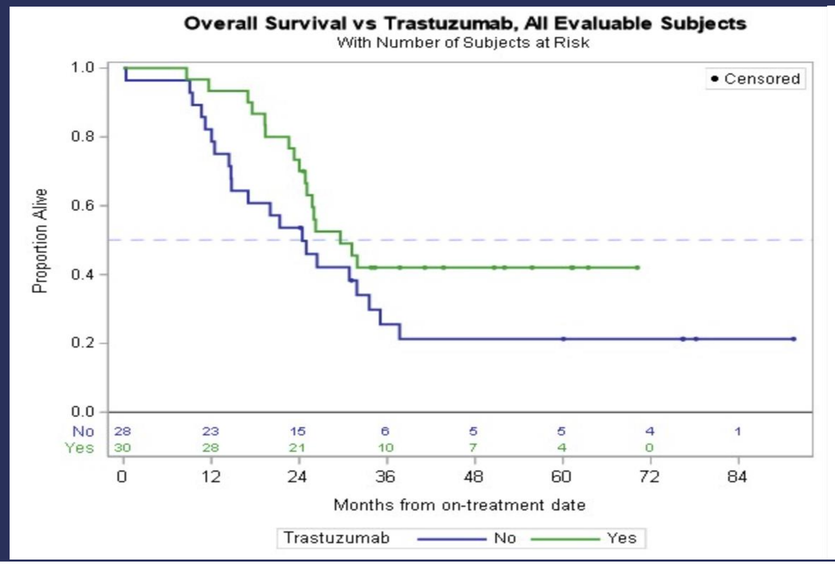
Nickles-Fader J Clin Oncol 2018

Incorporation of anti-HER-2 treatment: Trastuzumab with Chemotherapy (Updated Survival Analysis)

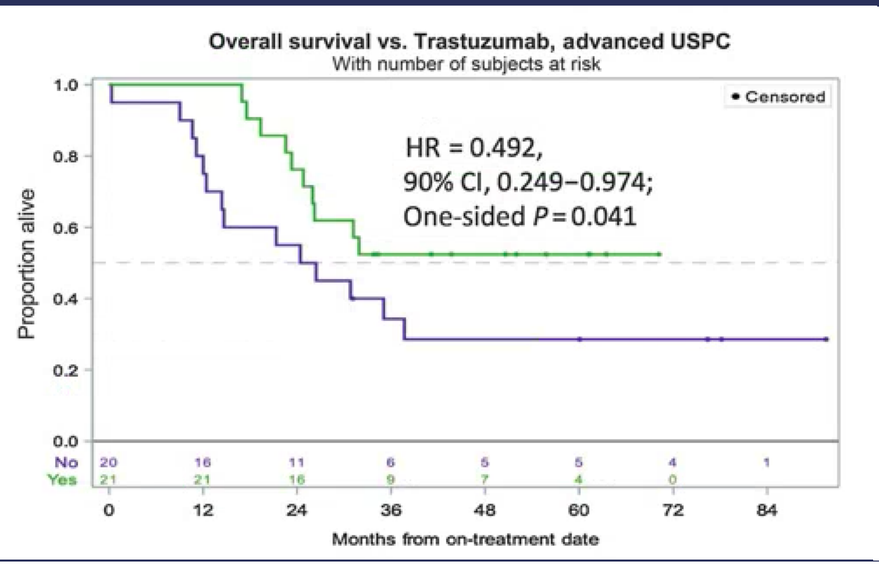
- Median OS of 24.4 (control) versus 29.6 (experimental) months (*P* = 0.046, HR = 0.58, 90% CI 0.34—0.99; Fig. 1).

  This benefit was particularly striking in stage III–IV patients, who had OS medians of 25.4 months (control) versus not reached (experimental, *P* = 0.041, HR = 0.49, 90% CI 0.25–0.97).

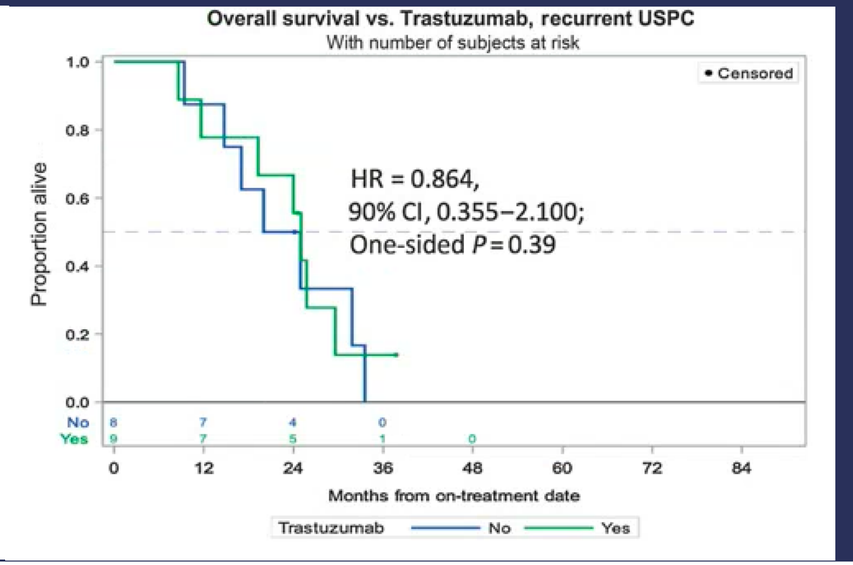
ITT Population



Advanced Disease



Recurrent Disease



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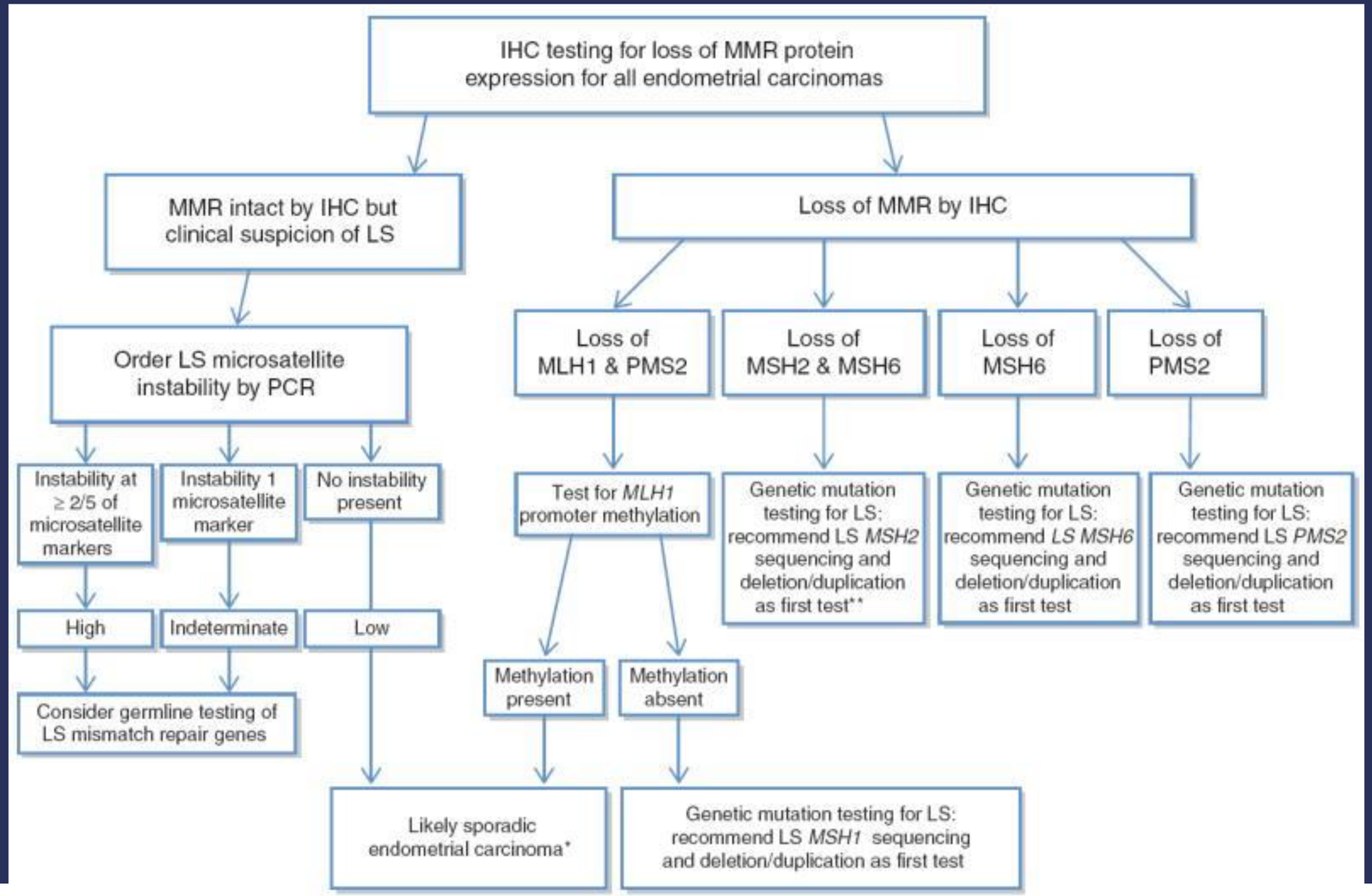
Nickles-Fader Clin Cancer Research 2020

Molecular Profiling in Endometrial Cancer … Now

Estrogen receptor (ER) Progesterone receptor (PR) should also be included in the initial profiling of the tumor



IHC testing is inexpensive and readily available in most institutions. This is where you begin precision medicine.

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Mills AM, et al. *Am J Surg Pathol*. 2014;38:1501-1509.

Molecular changes with targeted therapies

PTEN
PI3KCA
ARID1A (clear cell)
HER2 (serous)
KRAS
MMR
ER
PR

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2021
Endometrial Carcinoma

NCCN Guidelines Index
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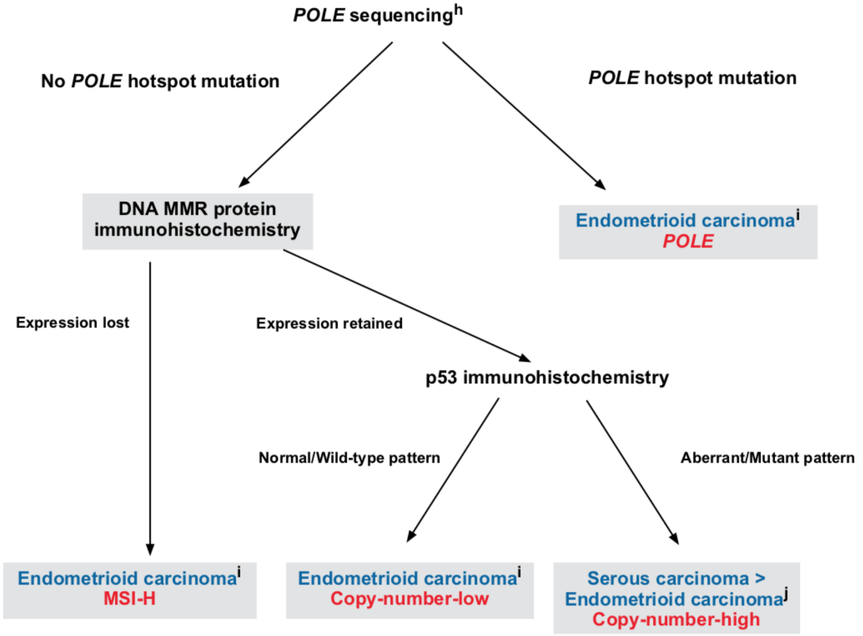
PRINCIPLES OF MOLECULAR ANALYSIS

FIGURE 1: PATHOLOGY AND GENOMICS IN ENDOMETRIAL CARCINOMA[f,g]



[f]Adapted with permission from Murali R, Delair DF, Bean SM, et al. Evolving roles of histologic evaluation and molecular/genomic profiling in the management of endometrial cancer. J Nat Compr Canc Netw 2018;16:201-209.
[g]Diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinomas (blue represents histotype; red represents TCGA genomic class).
[h]*POLE* sequencing made by mutational analysis may not be available at all institutions.
[i]May also apply to clear cell carcinomas.
[j]This algorithm does not distinguish between high-grade tumors that cannot otherwise be classified (ie, high-grade carcinoma, serous carcinoma, clear cell carcinoma).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References

PROGNOSTIC MARKERS

POLE
TP53

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Thank you

Baystate Health | University of Massachusetts Medical School