

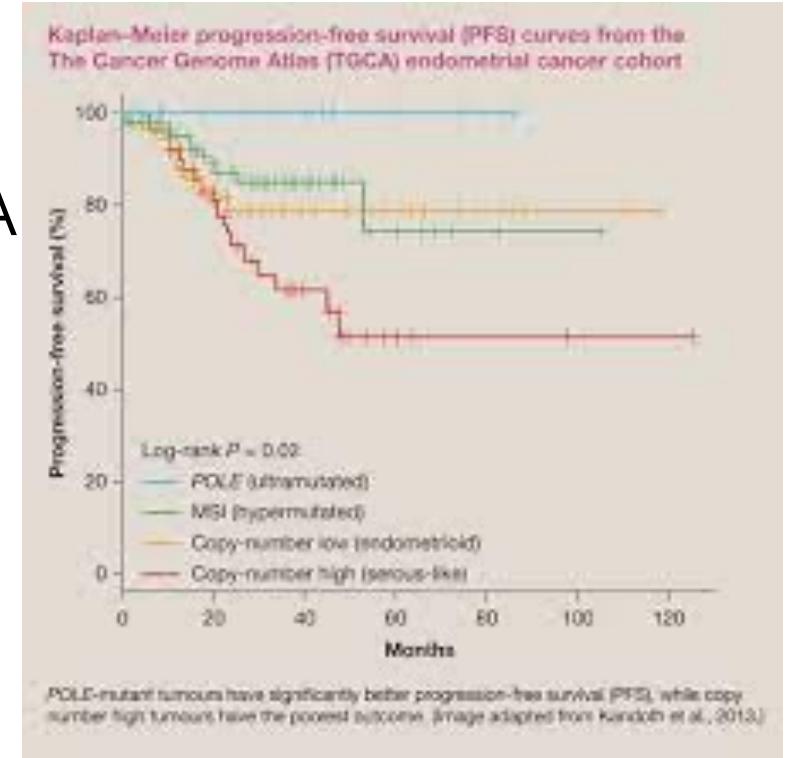
# Advancing Precision in Endometrial Cancer: Molecular classification and its impact on prognosis and treatment. Are we ready?

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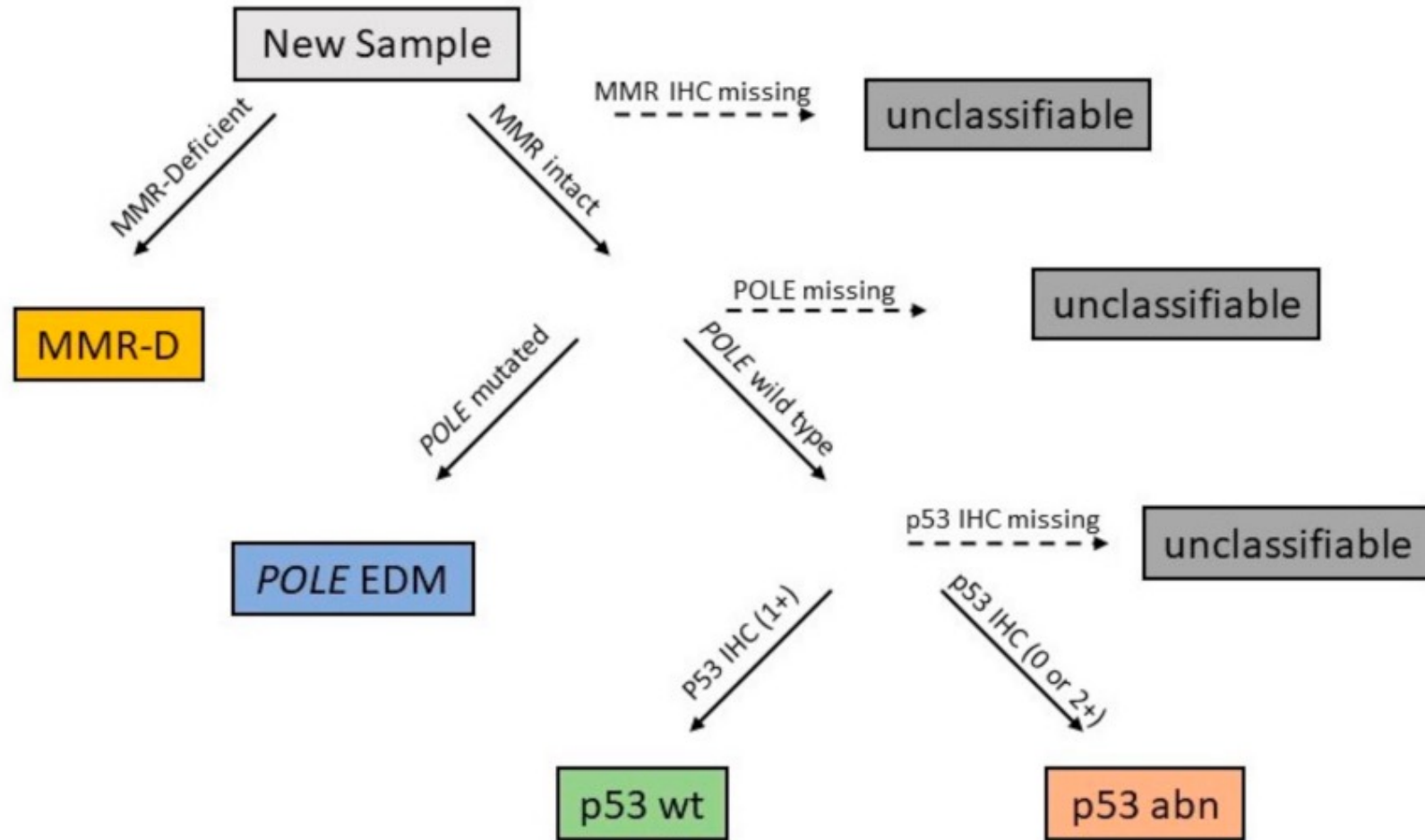
# 2013 Integrated genomic characterization of endometrial cancer. TCGA

- Identified 4 molecular classifications
  - POLE -7% Ultramutated often high grade
  - MMRd 30% Germline + Somatic loss, PTEN, PIK3CA
  - P53 abnormal 20% High grade and serous
  - NSMP 40% ER PR positive



Validated in over 4000 pts

# Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE)



Talhok et al Cancer 2017

Molecular classification predicts response to radiotherapy in the randomized PORTEC1 and PORTEC-2 trials for early stage endometrioid endometrial cancer

- PORTEC 1 n=714
  - EBRT vs Observation
  - Grade 1 or 2 with outer half myoinvasion
  - Grade 2 or 3 up to middle third invasion
- PORTEC 2 n=427 HIR
  - EBRT vs VBT
  - Stage 1B > age 60, grade 3
  - Stage 1C >age 60 grade 1-2
  - Stage IIA, except grade 3 with deep myoinvasion

Horewege et al. PORTEC Study Group  
JCO 2023

# Molecular Analysis of PORTEC 1&2

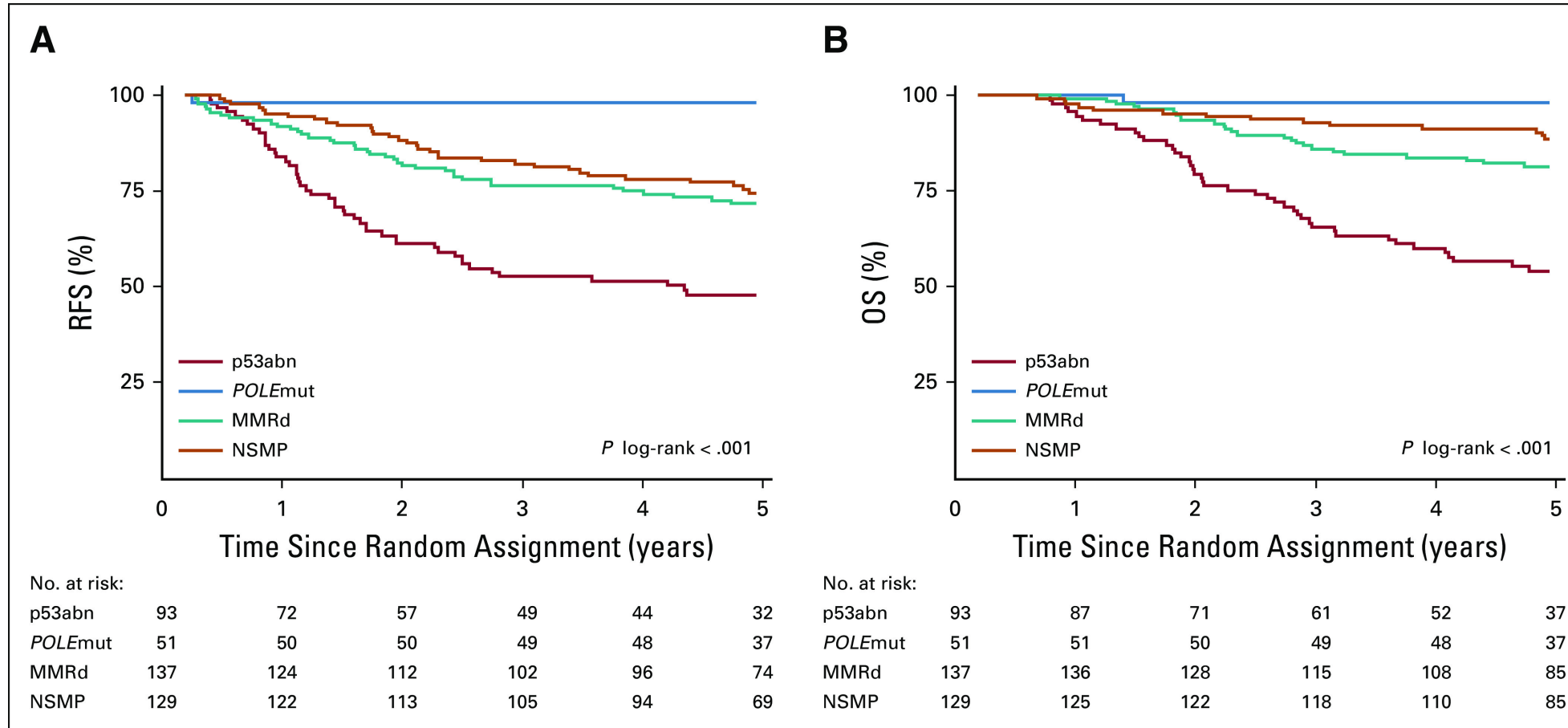
880 patients

POLE 7.5% (n=66) dMMR 28.1% (n=247) p53 8% (n=70) NSMP 56.5% (n=497)

- POLE: no recurrence regardless of radiation
- dMMR: EBRT or VBT not associated with improved RFS  
94.2% EBRT, 94.2% VBT, 90.3% Observation. (p= .74)
- P53 abnormal: EBRT improves RFS  
96.9% EBRT, 64.3% VBT, 72.2% Observation. (p= .048)
- NSMP: Local regional control better with EBRT or VBT  
98.3% EBRT, 96.2% VBT, 87.7% Observation. (p< .0001)

The molecular classification of EC predicts response to radiation in stage I EEC and may guide treatment decisions

# Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy



# Molecular Classification of PORTEC III

High risk disease (stage III and/or high risk histology): EBRT vs CTRT

5 year RFS

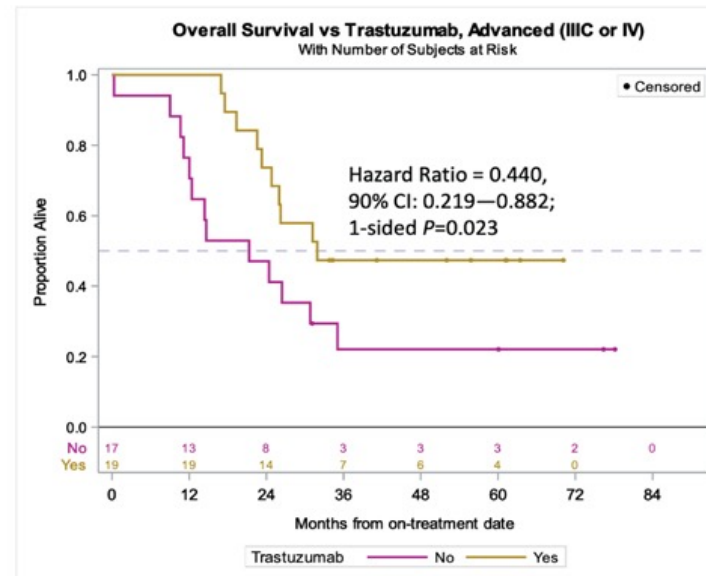
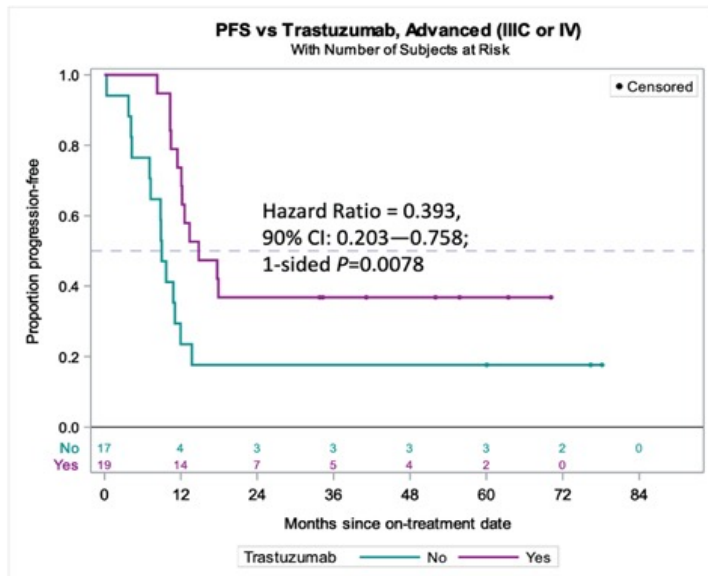
POLE	12%(51)	98%
MMRd	33%(137)	72%
P53	23%(93)	48%
NSMP	32%(129)	74%

5 year RFS

	EBRT	CTRT	p
POLE	97%	100%	.64
dMMR	76%	68%	.42
P53	36%	59%	.019
NSMP	68%	80%	.24

# Her 2 neu

- Expressed in 30% of Uterine Serous Tumors
- Poor prognostic factor associated with worse survival
- Trial of pts with 3+ Her2neu or 2+ with FISH amplification randomized to paclitaxel/carbo vs paclitaxel/carbo/transtuzumab with with maintenance showed the addition of transtuzumab improved OS



Fader et al. JCO 2018



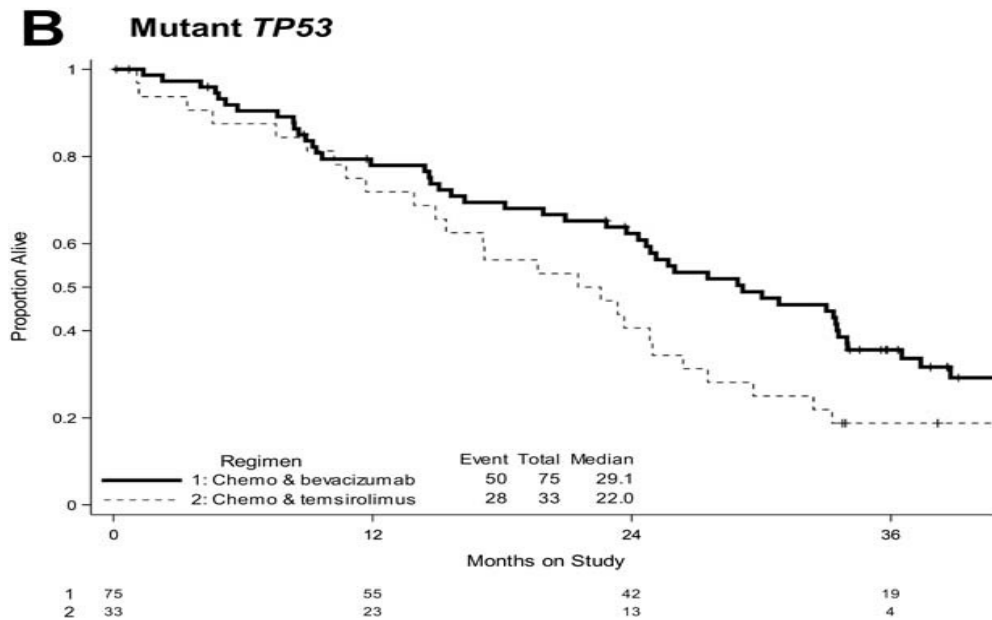
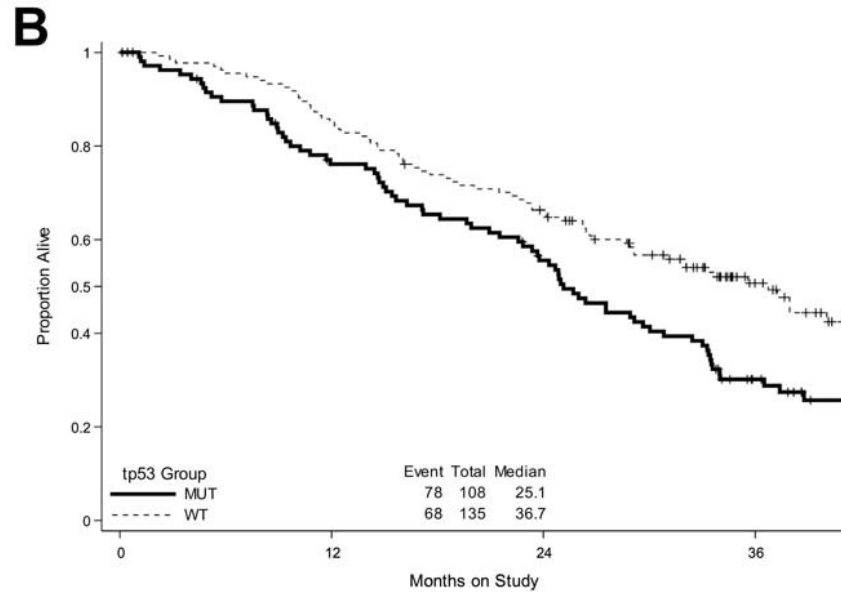
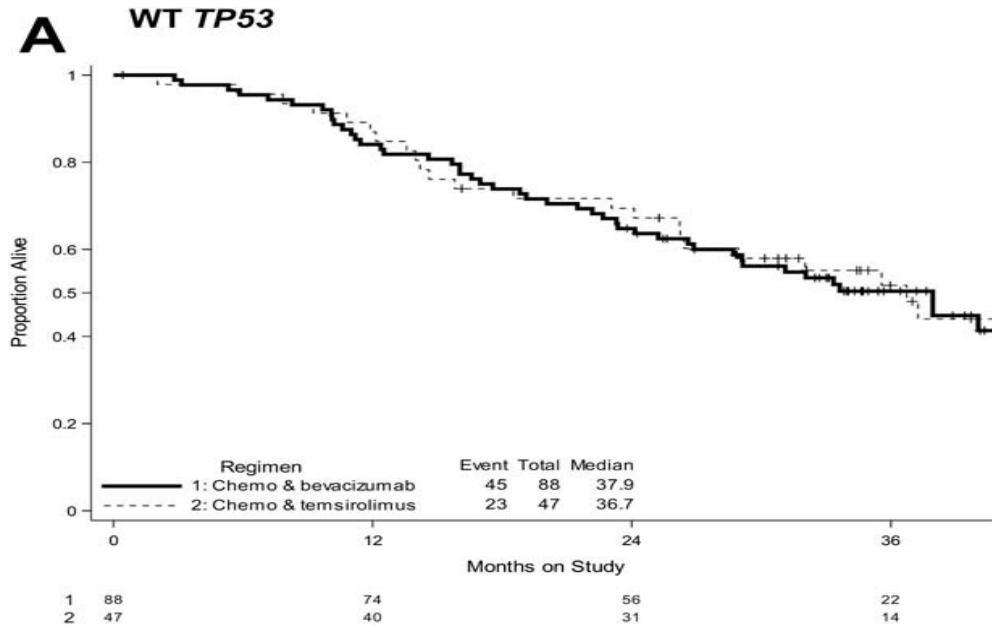
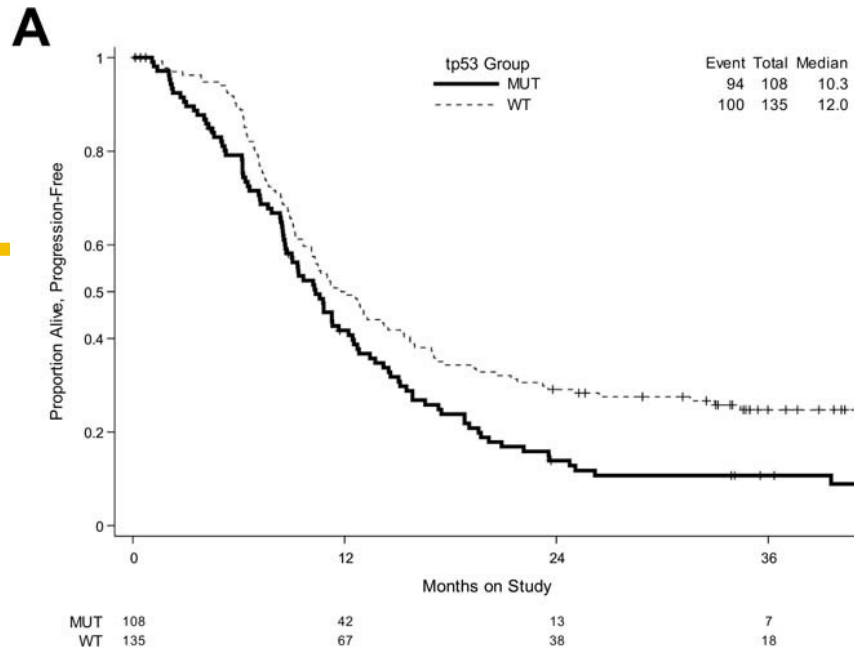
# 2023 FIGO Endometrial Cancer Staging

Stage designation	Molecular findings in patients with early endometrial cancer (stages I and II after surgical staging)
Stage IAm <sup>POLEmut</sup>	<i>POLEmut</i> endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage IICm <sup>p53abn</sup>	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

# Mutated p53 portends improvement in outcome when bevacizumab is combined with chemo. An NRG study

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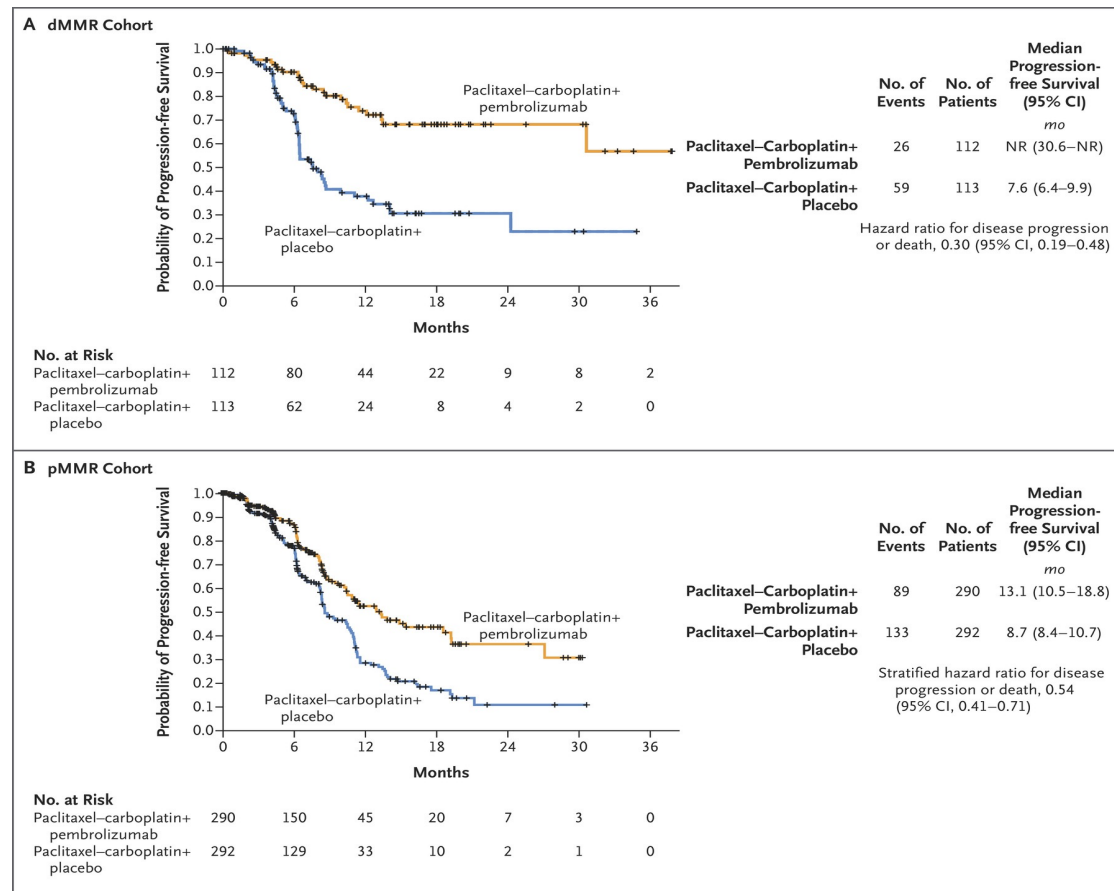
- GOG study 86P
- Stage III/IV/recurrent
- PC bev, PC temsirolimus, ixabepilone/C bev
- 243 has p53 mutational analysis done
- 44% mp53 and 56% wtp53
- Those with p53 mutation had worse prognosis PFS 10 vs 12 month
- PFS bev vs temsirolimus 12.5 vs 8.2 in mp53 (HR 0.48 CI 0.31-0.75)
- PFS and OS for wtp53 no difference



# MMRd/MSIh Endometrial cancer

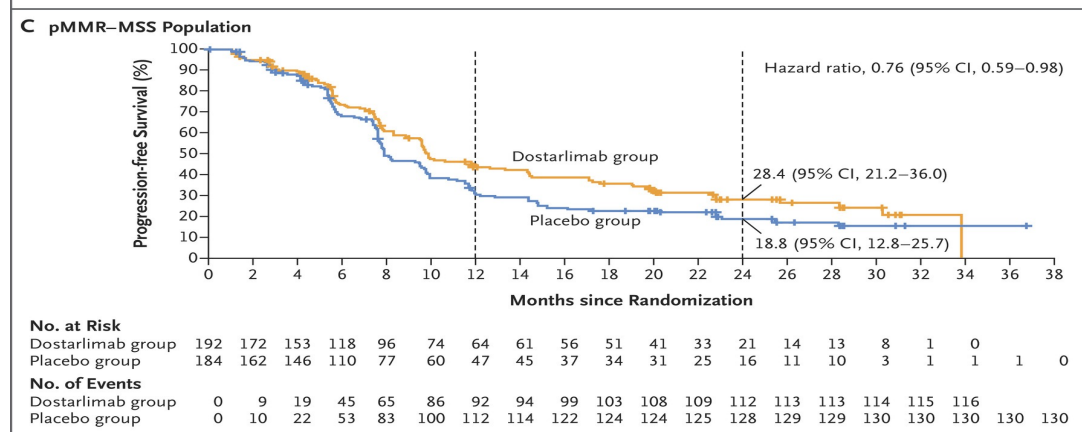
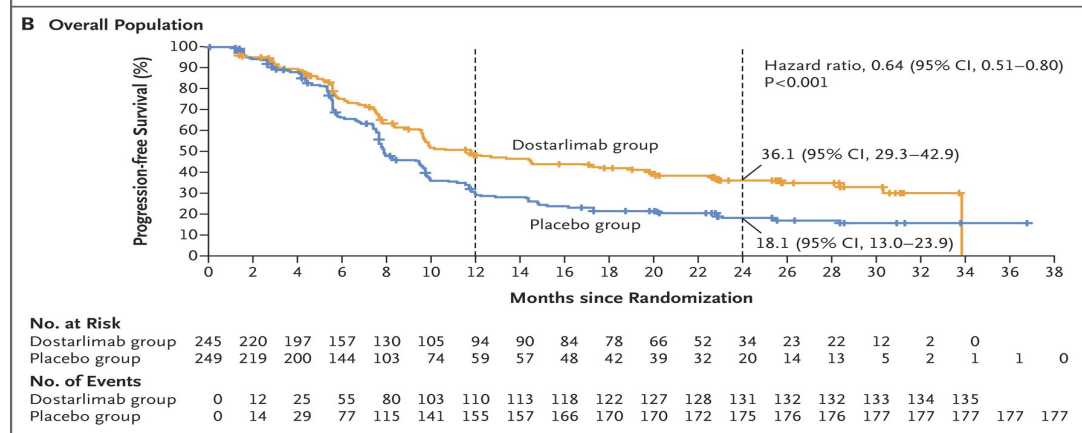
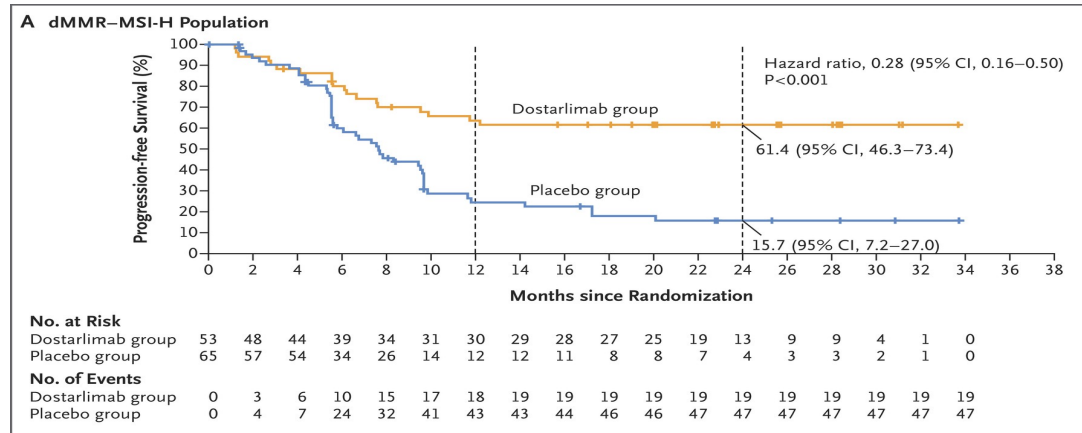
- Initial indication for immune checkpoint inhibitors (pembrolizumab, dostarlimab) for second line therapy.
- 2 trials, GY 2018 and RUBY evaluated addition of PD-1 inhibition in first line treatment followed by 2-3 years of maintenance treatment

GY2018



Eskander et al. NEJM 2023

# RUBY Trial with dostarlimab



Mirza et al. NEJM 2023

# DUO-E: durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab +/- olaparib

Control arm: C/T/D followed by placebo

Durvalumab arm: C/T/D followed by durvalumab maintenance

Durvalumab Olaparib arm: C/T/D followed by durvalumab and Olaparib maintenance

Westin et al  
JCO 2023

MMRd Cohort PFS 18mo

67.9% O+D 62% D 43.4% Control

- The addition of Olaparib did not substantially improve PFS outcomes
- HR for PFS C vs D 0.42 (0.22 -0.80) D-O vs C 0.41 (0.21-0.75)

MMRp Cohort PFS

15 mo O+D 9.9 mo D 9.7mo C

Olaparib did improve PFS in MMRp cohort HR 0.57 (0.44-0.73)

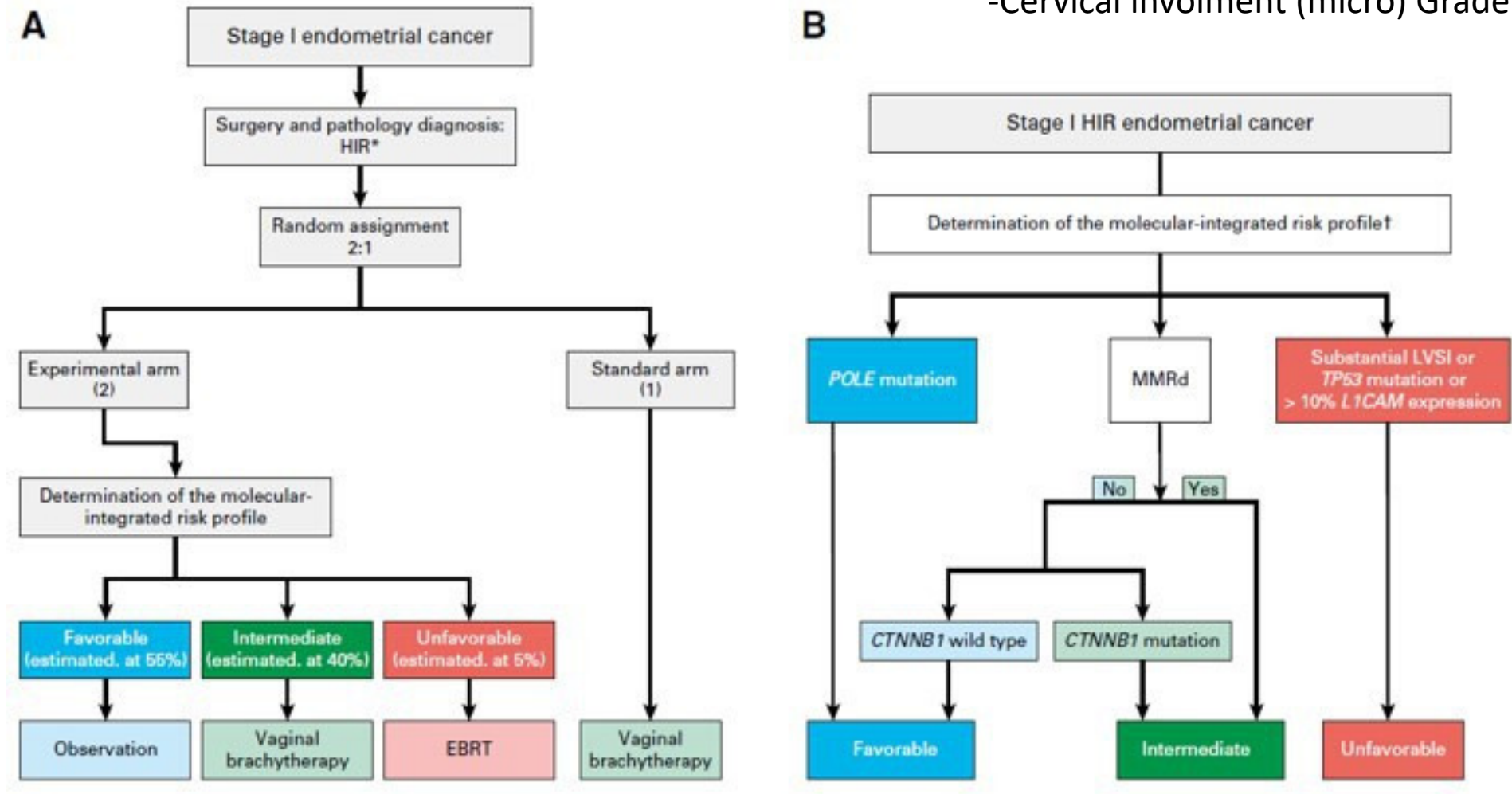
# Other molecular targeted therapies

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- PTEN and PI3K/AKT/mTOR pathway: MTOR inhibitors PI3KCA inhbitors
- KRAS,BRAF, NRAS: MEK inhibitors
- HRD pathway, somatic Rad51 mutations: PARPi
- ARID1A :EZH2 inhibitors and PARPi
- CTNNB1 mutations can lead to activation of VEGF: Bev with chemo
- FGFR2 mutations: FGFR inhibitors
- ER/ PR: Hormones, CDK4/6 inhibitors, Evirolimus and letrozole
- Her2neu: Trastuzumab and ADCs targeting Her2neu
- dMMR MSIh: PDL-1 inhibitors
- pMMR MSIs: Pembro with lenvatatinib

# Ongoing Studies: PORTEC 4a

- Grade 3 less than 50% myoinvasion
- Grade 1-2 greater than 50% myoinvasion and age 60+ or LVSI
- Grade 3 greater than 50% myoinvasion no LVSI
- Cervical involvement (micro) Grade 1

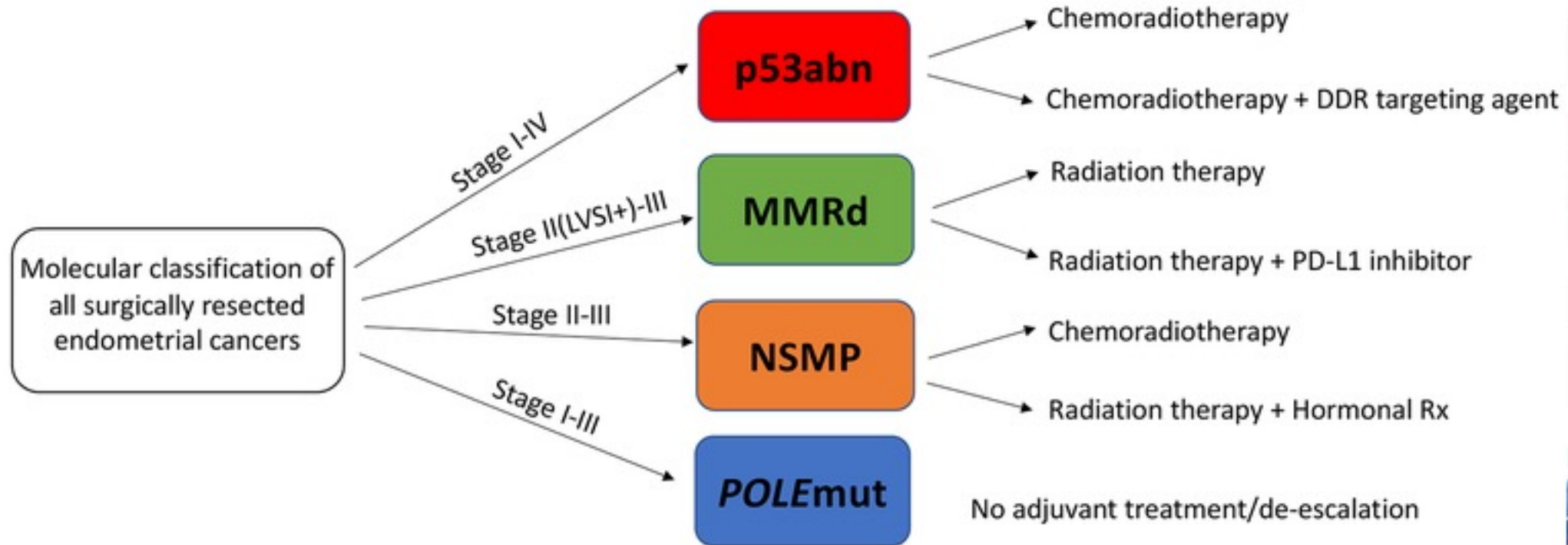




# Ongoing studies: RAINBO



## TransPORTEC RAINBO Umbrella Trial



France



DGOG



NCRI



Canada

# Conclusion

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Molecular profiling in endometrial cancer is important for prognosis and treatment

As of 2024

- POLE: retrospective studies suggest that de-escalation of treatment is possible. Ongoing studies evaluating observation only in these patients
- P53 abn: More aggressive treatment is needed. EBRT vs VBT and chemo possibly w bev
- dMMR: unclear if radiation is beneficial in HIR but addition of PD-L1 is essential in advanced and recurrent disease to chemo
- NSMP: Vaginal Brachytherapy beneficial in HIR
- Her 2 neu: Addition of trastuzumab is associate with improvement in OS