Endometrial Cancer- Current Management and Emerging Therapies

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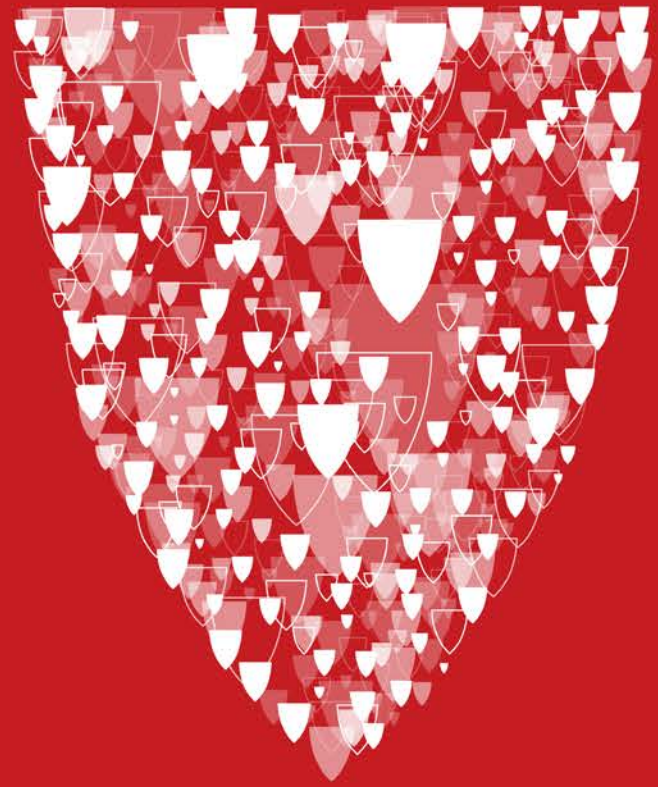


Disclosures

None

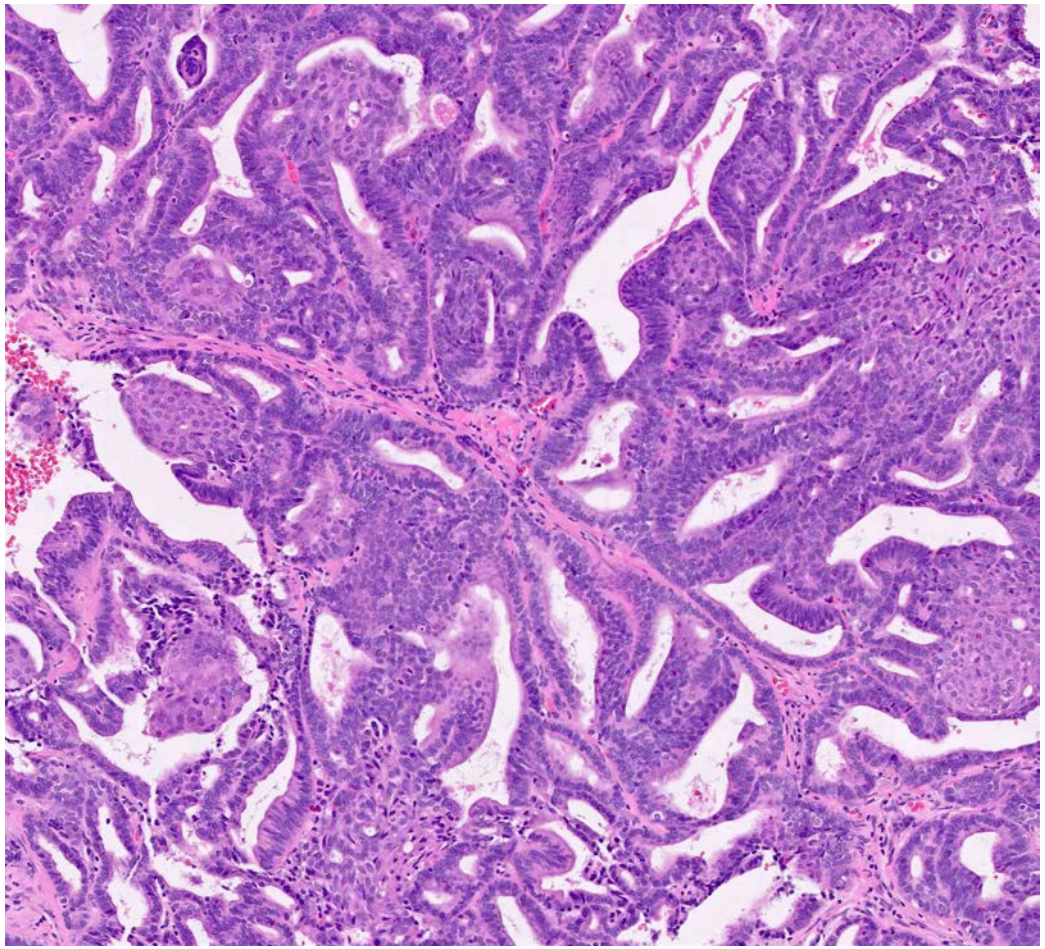
Objectives

Review current management for endometrial cancer

Review emerging therapies in endometrial cancer

Background

Uterine Cancer



Incidence: 67,880 cases in 2024, increasing!

Highest in Black patients

Mortality: 13,250 deaths in 2024

Almost twice as high for Black patients

3% lifetime risk

Median age 60-70 at diagnosis

90% of uterine cancers are endometrial

RFs: Excess estrogen, anovulation, obesity, tamoxifen, early menarche/late menopause, genetic syndromes

Uterine Cancer

Endometrial Cancer (90%)

- Endometrioid (75-80%)
- Serous (10%)
- Clear Cell (<5%)
- Carcinosarcoma (<5%)
- Undifferentiated/ Dedifferentiated

Uterine Sarcoma

- Leiomyosarcoma
- Endometrial Stromal Sarcoma
- Adenosarcoma

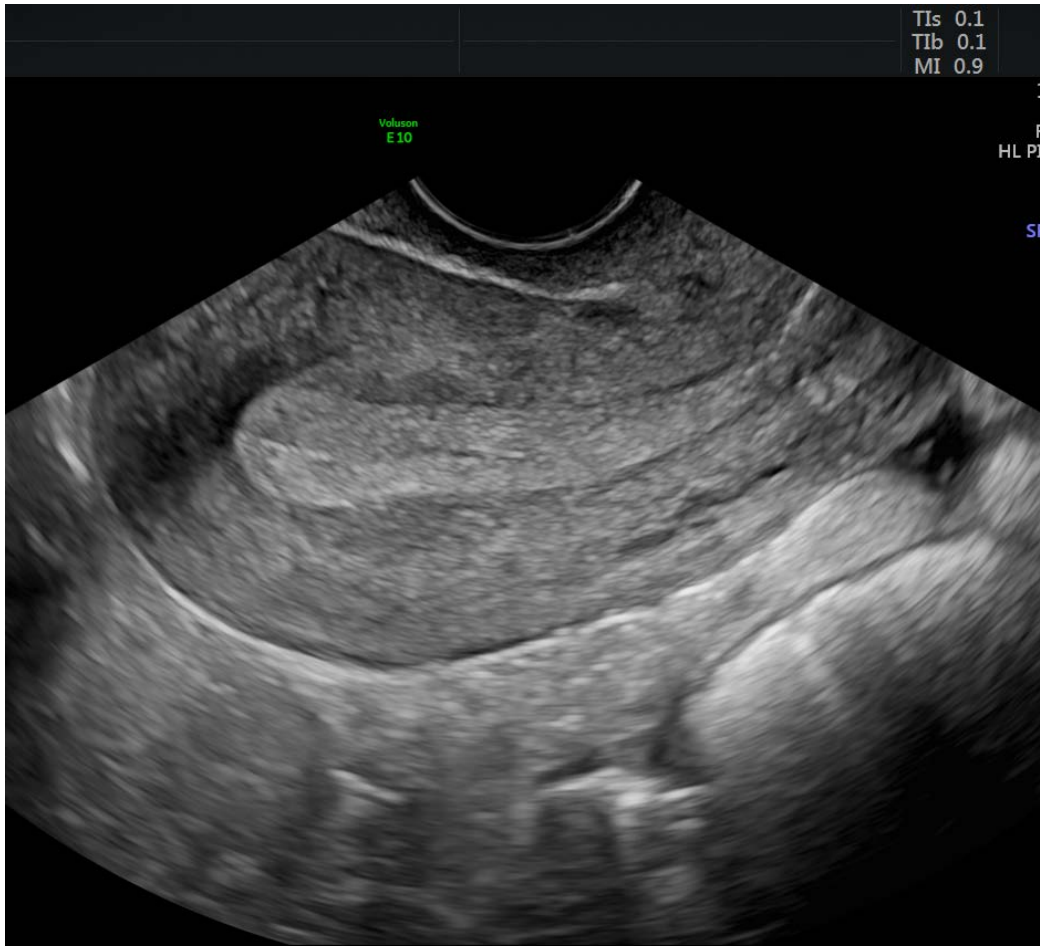
Uterine Cancer

Symptoms: Postmenopausal bleeding, abnormal uterine bleeding, abnormal cervical cytology, incidental finding on imaging, incidental finding after hysterectomy, pelvic radiation

NO SCREENING tests

~5% of endometrial cancers are genetic (Lynch syndrome, Cowden's)

Automatic testing for mismatch repair proteins



Uterine Cancer

Diagnosis

- Pelvic ultrasound (often displaying a thickened endometrial stripe, >4mm)
- Endometrial biopsy or Dilation and curettage
- Incidental after hysterectomy

Management

- Surgery
- Radiation
- Systemic Therapy

Recurrence

- Surgery
- Radiation
- Systemic Therapy

Uterine Cancer

Special Considerations

- Postmenopausal bleeding always needs evaluation (pelvic US +/- uterine sampling)
- Disparities noted in diagnosis of Black women
- For patients with significant vaginal bleeding could consider systemic progestins (megace, provera) or radiation to temporize, some require transfusion

Management

Presumed uterine confined disease

- TLH/BSO/Sentinel lymph nodes
- ChemoRT
- Endocrine therapy

Cervical involvement

- Radical hysterectomy, BSO, PLND

Disease outside of the uterus, surgically resectable

- Hysterectomy, BSO, tumor debulking

Disease outside of the uterus, not surgically resectable

- Neoadjuvant systemic therapy with possible interval debulking surgery

Distant Disease

- Systemic therapy

Systemic therapies for Uterine Cancer

Chemo vs Radiation

GOG 122 (2006)

- 388 pts RCT, Stage IIIA-IV no residual disease >2cm
- Compared WAR vs cis/adria
- Both arms had a 50% RR
- PFS 38% vs 50%
- OS 42% vs 55%

GOG 258 (Matei et al, NEJM 2019)

- 736 pts RCT, Stage IIIA-IV (all histologies), no residual disease >2cm, Stage I-II serous/ clear cell with positive washings
- Arms: CisRT followed by 4 cycles Carbo/taxol vs Carbo/taxol for 6 cycles
- PFS 59% vs 58% (non-significant)
- OS not achieved in either arm (2024 data)
- Fewer local recurrences with ChemoRT, both arms well tolerated

We often favor chemotherapy with brachytherapy over Chemo with pelvic radiation

Chemotherapy

GOG 209 (Miller, JCO, 2020)

- Established carbo/taxol as standard of care
- 1300 pts with stage III/IV/recurrent (chemo naive) RCT, non inferiority
- Carbo/Doxorubicin/Taxol (TAP) vs Carbo/taxol
- No difference in PFS or OS
- More G3/4 toxicity with TAP regimen

GOG 261 (Powell et al, JCO 2022)

Phase 3 RCT 637 pts with carcinosarcoma (uterine and ovarian) carbo/taxol vs ifos/taxol

536 uterine carcinosarcomas

Stage I-IV, recurrent chemo naïve

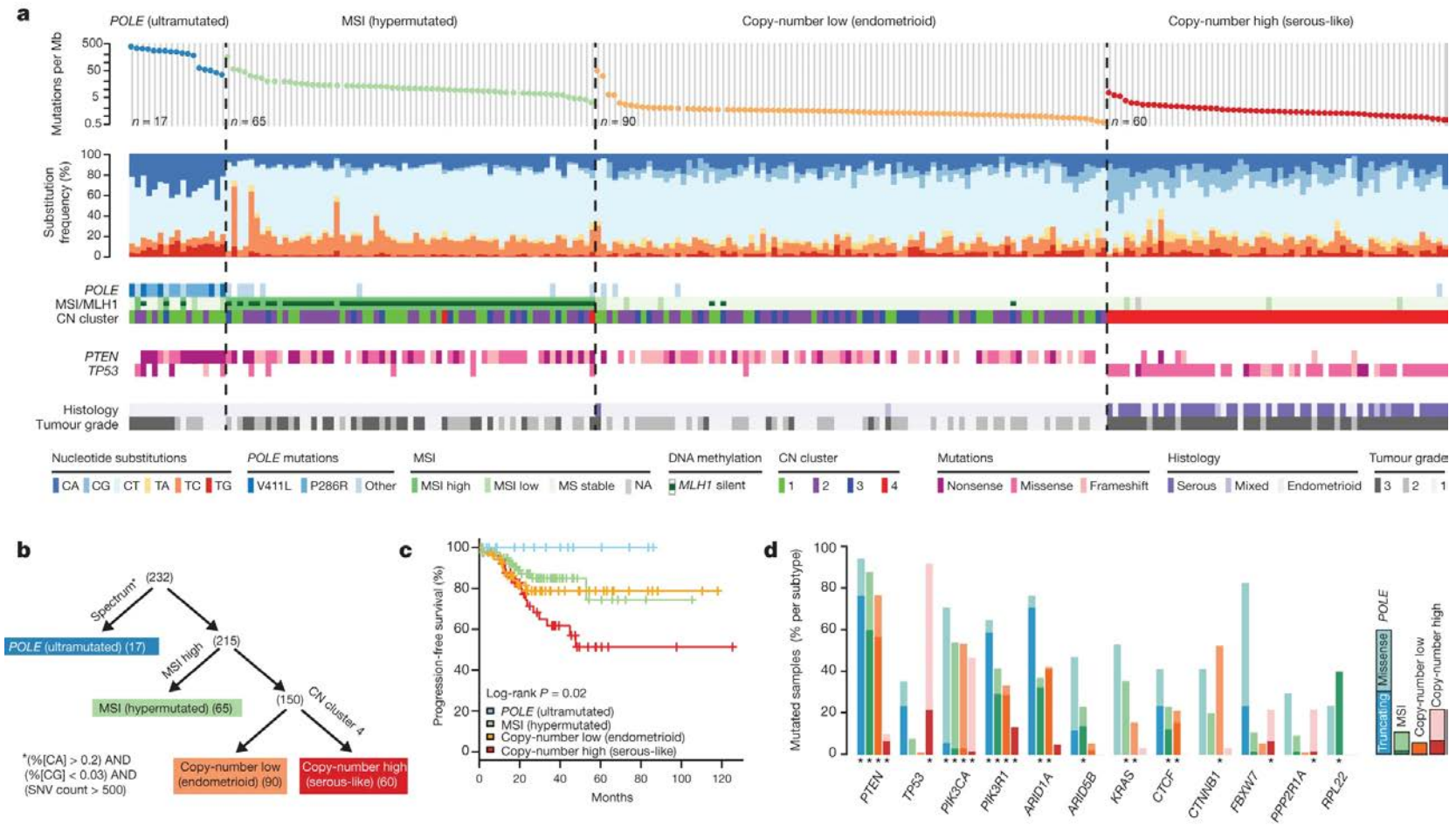
Carbo/taxol non-inferior to Ifos/taxol

PFS 16 vs 12m significant

OS 37 vs 29m non-significant

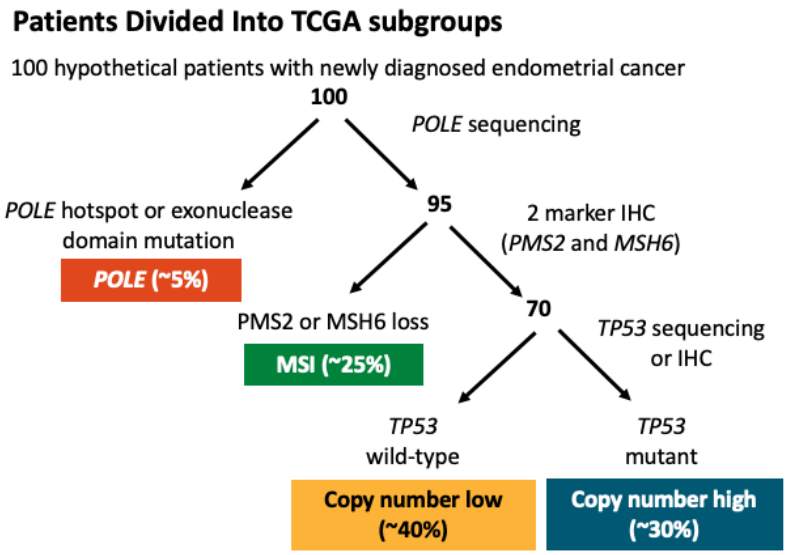
Less toxicity with carbo/taxol

Molecular Classifications, TCGA, Nature 2013

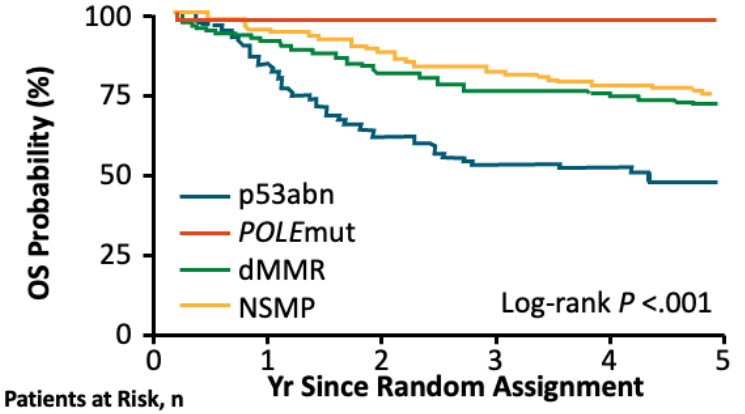


Molecular Classifications

TCGA Molecular Classification and Outcomes



- Prognostic value of molecular classification of high-risk endometrial cancer for benefit from chemotherapy



Patients at Risk, n						
p53abn	93	72	57	49	44	32
*POLE*mut	51	50	50	49	48	37
dMMR	137	124	112	102	96	74
NSMP	129	122	113	105	94	69

- 410 patients with successful molecular testing
  - 23% *p53*abn: *p53* abnormal
  - 12% *POLE*mut: *POLE* ultramutated
  - 33% dMMR: mismatch repair deficient
  - 32% NSMP: no specific molecular profile

MacKay. Oncotarget. 2017;8:84579. León-Castillo. JCO. 2020;38:3388.

Slide credit: clinicaloptions.com

NRG GY018, Eskander et al NEJM 2023

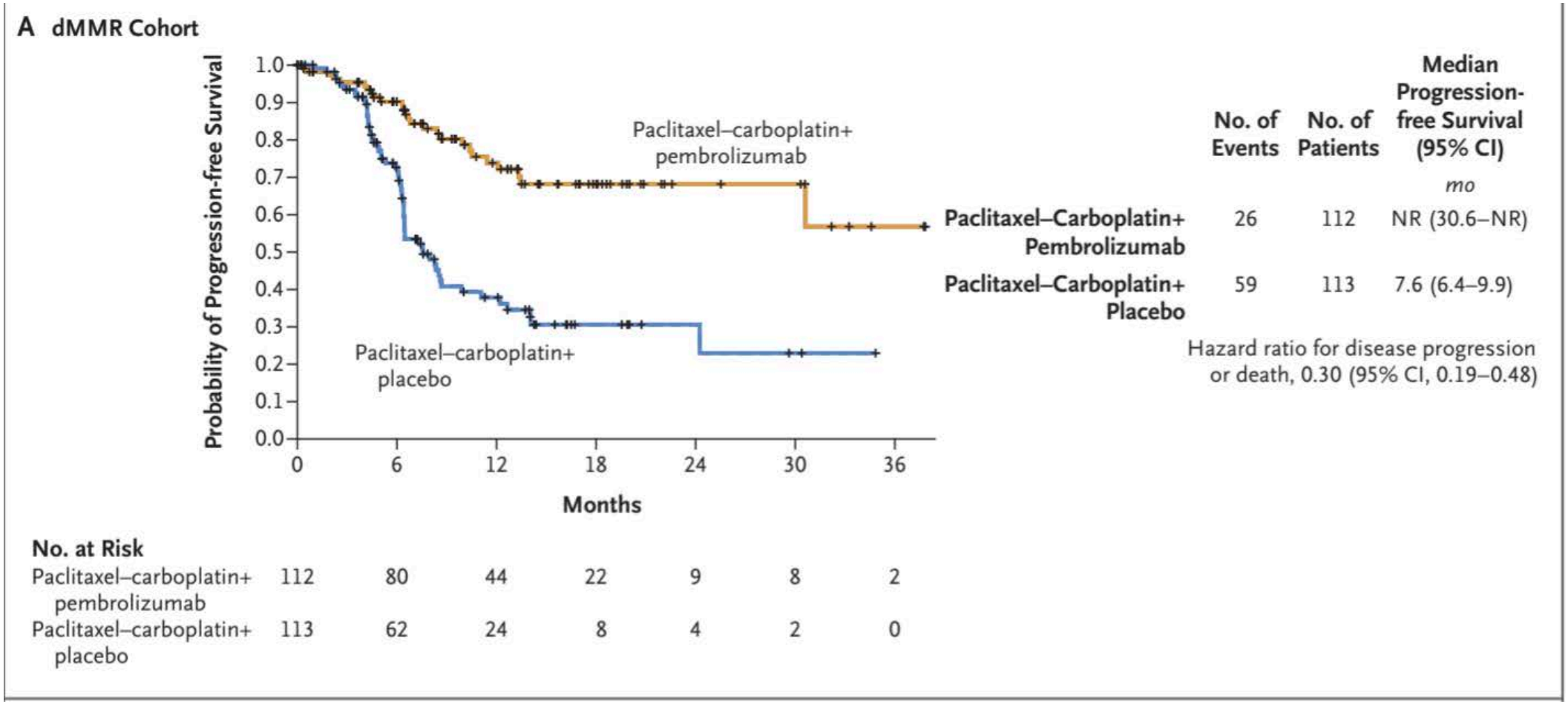
Phase 3 RCT 816pts

- Stage III-IVA with measurable disease
- Stage IVB or Recurrent with/without measurable disease
- Had to be 12m from last regimen if recurrent
- *Did not include carcinosarcoma*

Randomized to carbo/taxol/pembro with pembro maintenance vs carbo/taxol/placebo with placebo maintenance for up to 20 cycles (6 combined + 14 maintenance)

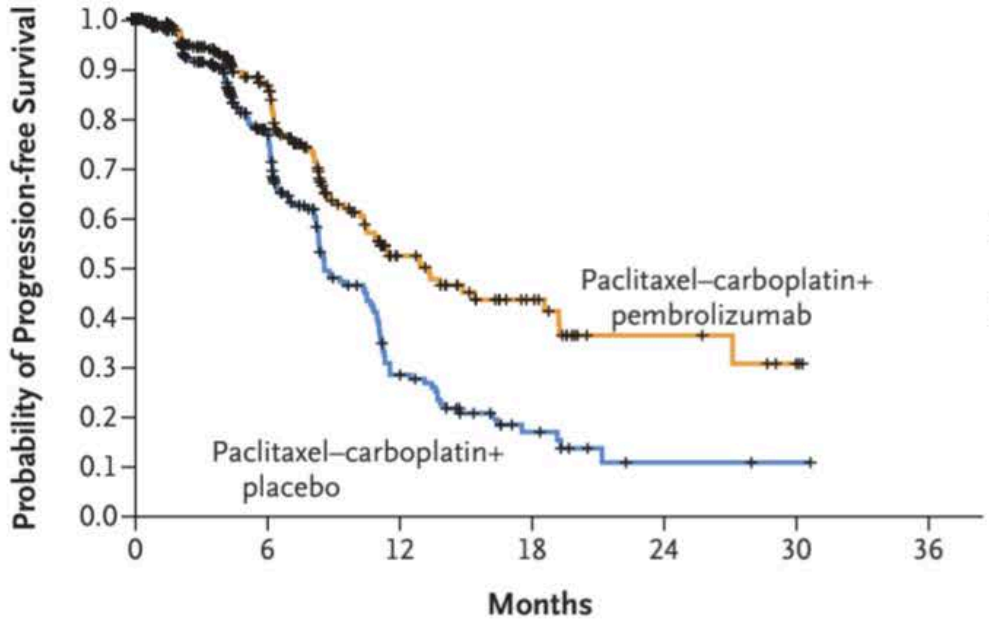
Primary outcome PFS

NRG GY018


A dMMR Cohort
Probability of Progression-free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Paclitaxel–carboplatin+ pembrolizumab
Paclitaxel–carboplatin+ placebo
0
6
12
18
24
30
36
Months
No. at Risk
Paclitaxel–carboplatin+ pembrolizumab 112 80 44 22 9 8 2
Paclitaxel–carboplatin+ placebo 113 62 24 8 4 2 0
No. of Events
No. of Patients
Median Progression-free Survival (95% CI)
mo
Paclitaxel–Carboplatin+ Pembrolizumab 26 112 NR (30.6–NR)
Paclitaxel–Carboplatin+ Placebo 59 113 7.6 (6.4–9.9)
Hazard ratio for disease progression or death, 0.30 (95% CI, 0.19–0.48)

NRG GY018

B pMMR Cohort



No. at Risk							
Paclitaxel–carboplatin+ pembrolizumab	290	150	45	20	7	3	0
Paclitaxel–carboplatin+ placebo	292	129	33	10	2	1	0

	No. of Events	No. of Patients	Median Progression-free Survival (95% CI)
			mo
Paclitaxel–Carboplatin+ Pembrolizumab	89	290	13.1 (10.5–18.8)
Paclitaxel–Carboplatin+ Placebo	133	292	8.7 (8.4–10.7)

Stratified hazard ratio for disease progression or death, 0.54 (95% CI, 0.41–0.71)

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RUBY, Mirza et al NEJM 2023

Phase 3 RCT 494pts

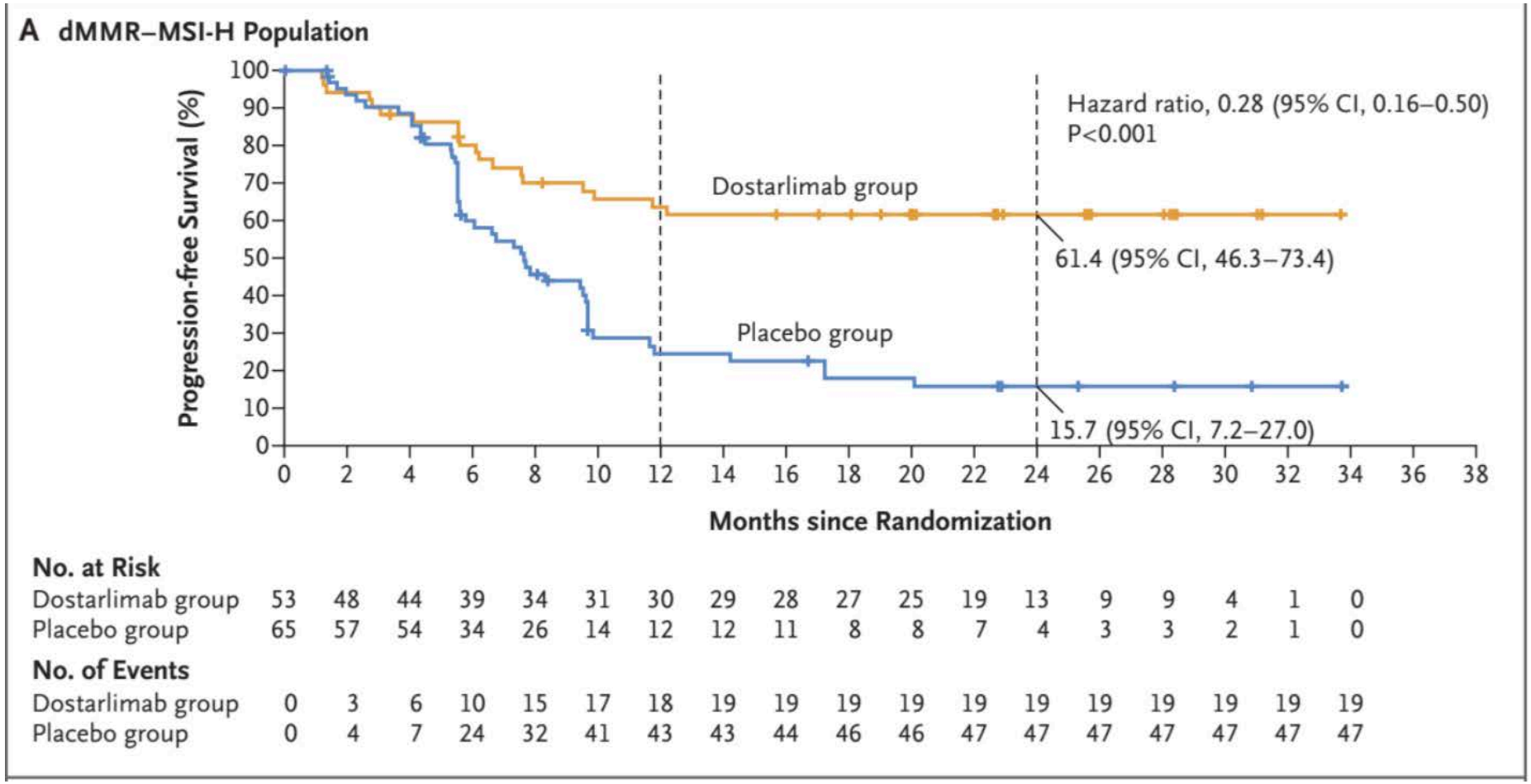
- Stage IIIA-C1 with measurable disease
- High risk histology (clear cell, serous, carcinosarcoma*, mixed histology) IIIC1 without measurable disease
- Stage IIIC2 or IV disease any histology
- Recurrent disease (if prior therapy at least 6m since last regimen)

Randomized to carbo/taxol/dostarlimab plus dostarlimab maintenance vs Carbo/taxol/placebo plus placebo maintenance for up to 3 years

Primary outcomes PFS and OS

~48% with recurrent disease, 9% with carcinosarcoma

Ruby



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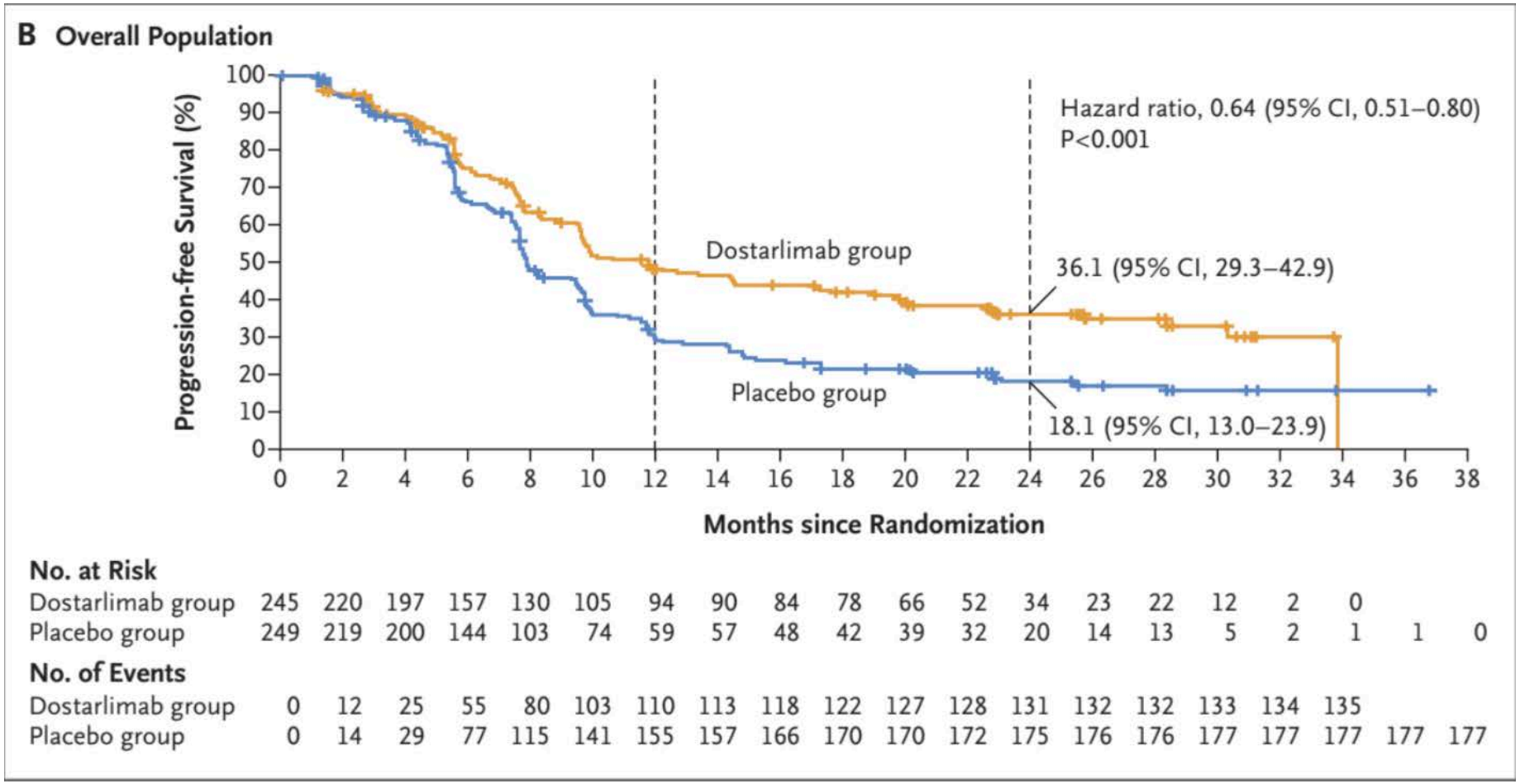
Ruby



No. at Risk																				
Dostarlimab group	245	220	197	157	130	105	94	90	84	78	66	52	34	23	22	12	2	0		
Placebo group	249	219	200	144	103	74	59	57	48	42	39	32	20	14	13	5	2	1	1	0
No. of Events																				
Dostarlimab group	0	12	25	55	80	103	110	113	118	122	127	128	131	132	132	133	134	135		
Placebo group	0	14	29	77	115	141	155	157	166	170	170	172	175	176	176	177	177	177	177	177

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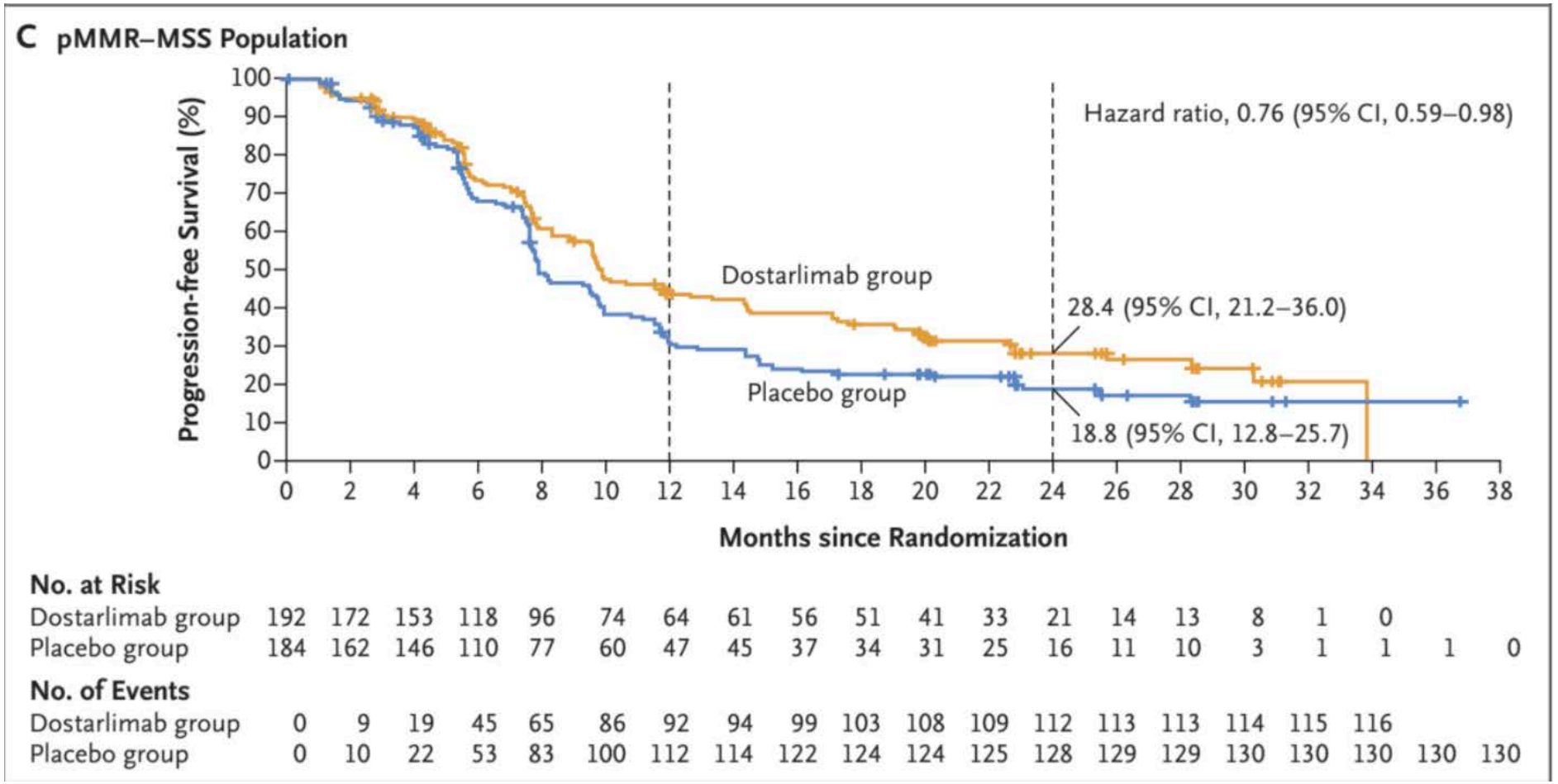

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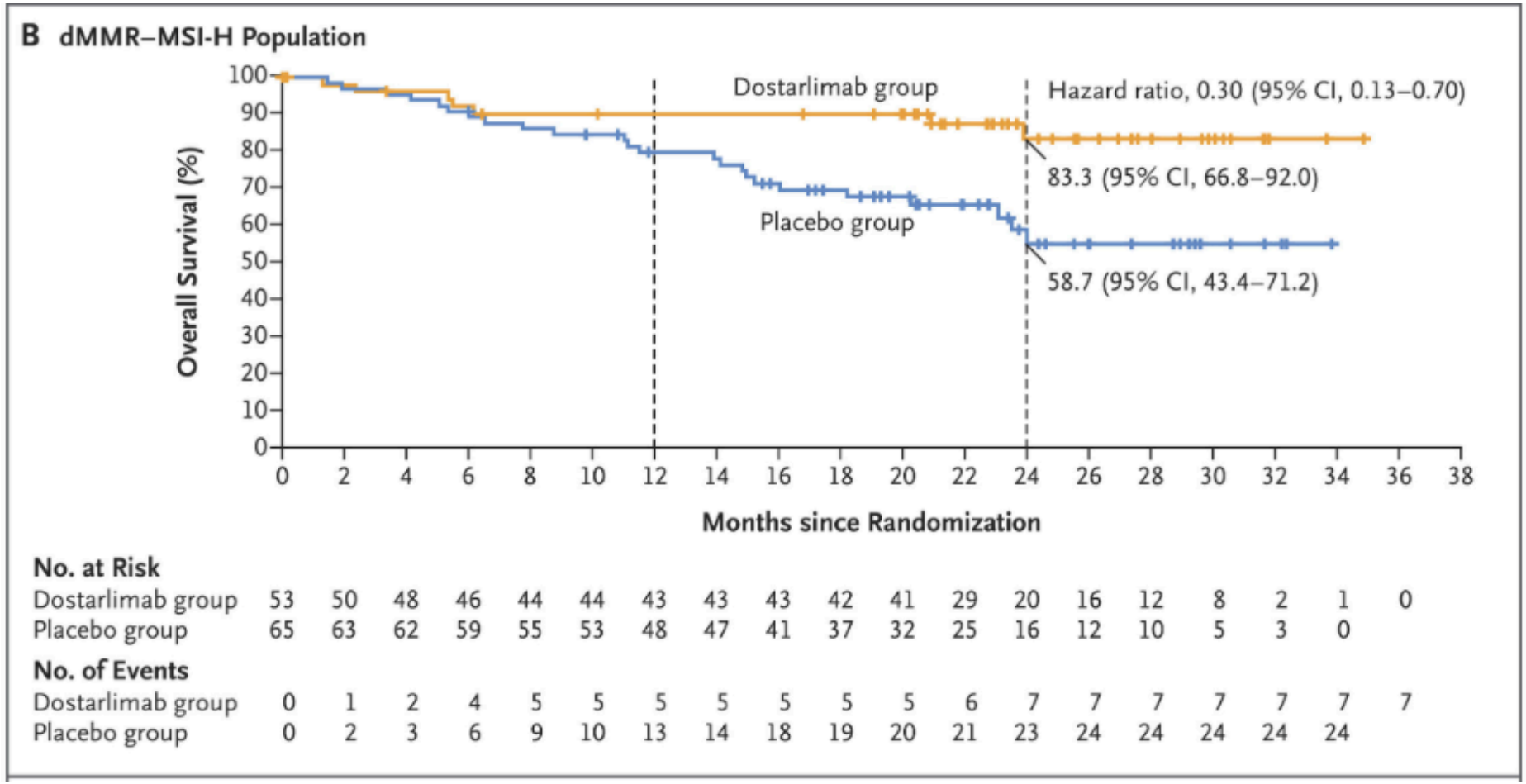

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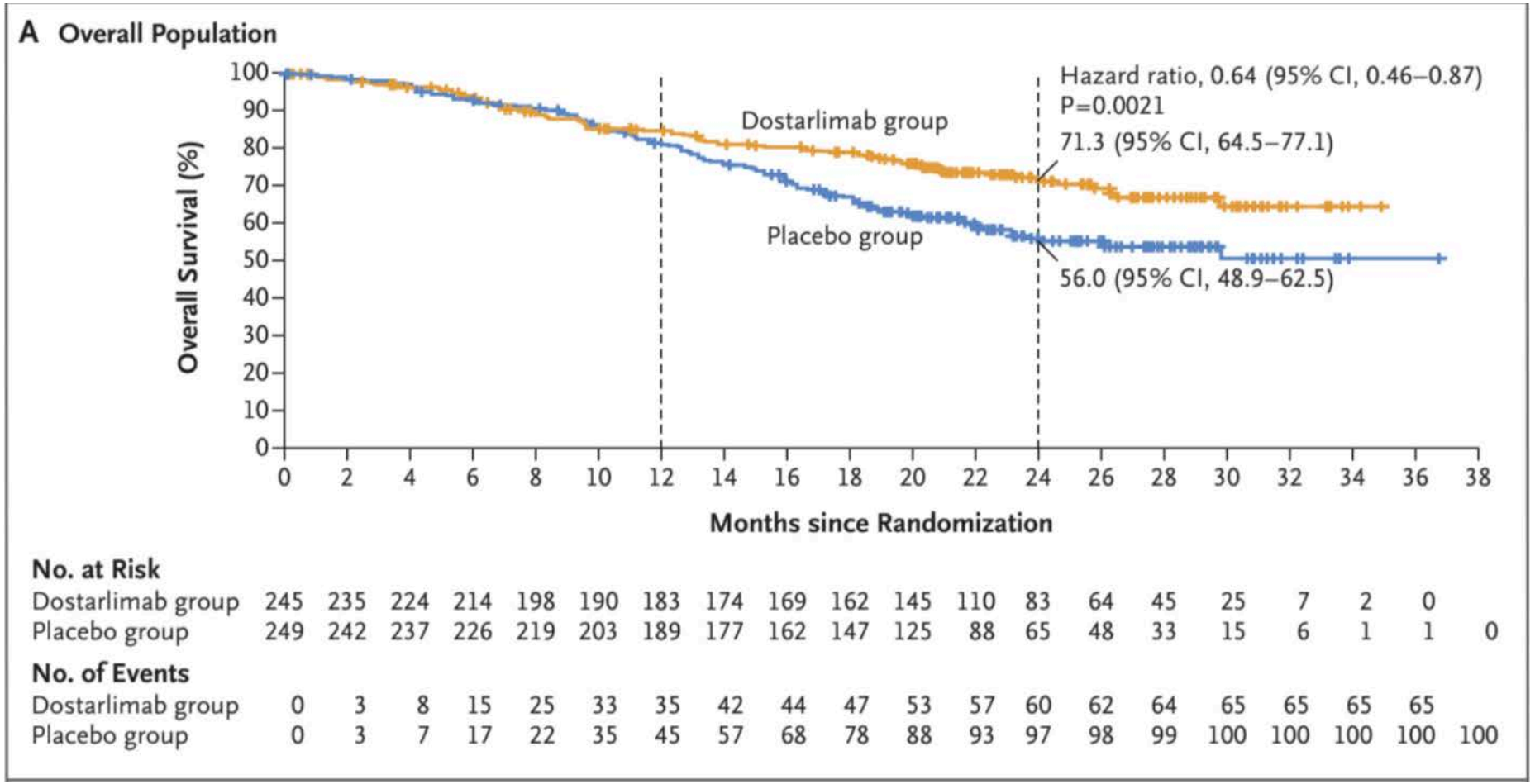

No. at Risk																			
Dostarlimab group	245	235	224	214	198	190	183	174	169	162	145	110	83	64	45	25	7	2	0	
Placebo group	249	242	237	226	219	203	189	177	162	147	125	88	65	48	33	15	6	1	1	0
No. of Events																				
Dostarlimab group	0	3	8	15	25	33	35	42	44	47	53	57	60	62	64	65	65	65	65	
Placebo group	0	3	7	17	22	35	45	57	68	78	88	93	97	98	99	100	100	100	100	100

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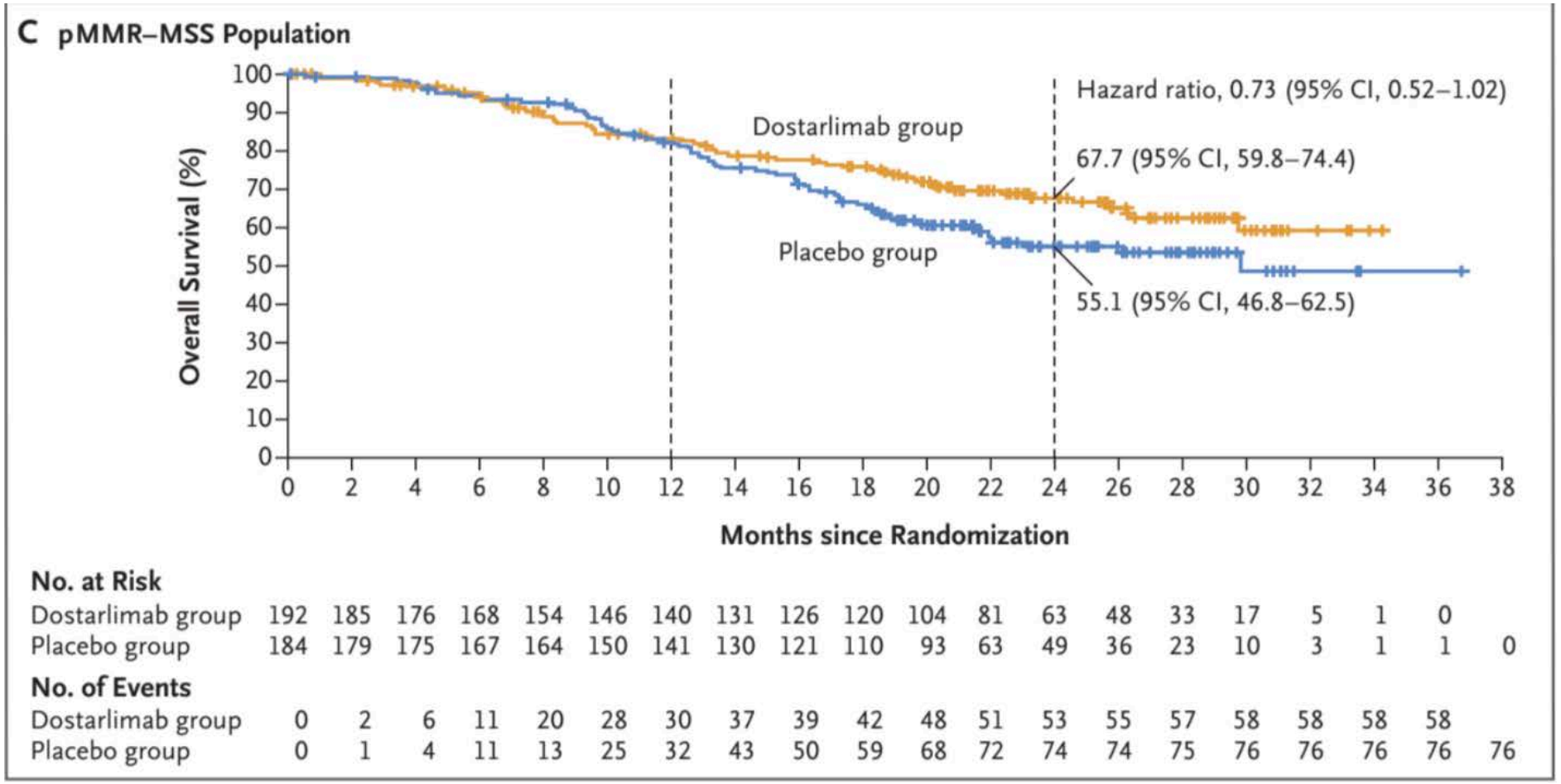
Ruby



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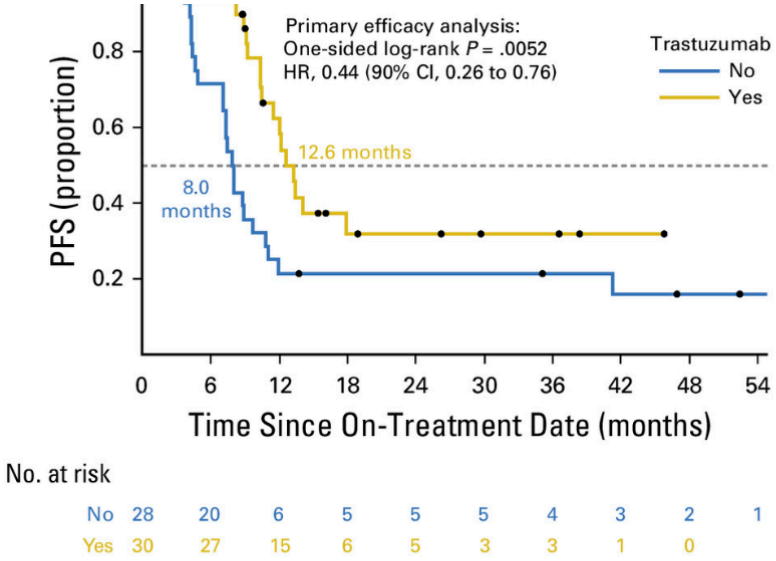
Trastuzumab, Fader et al., JCO 2018

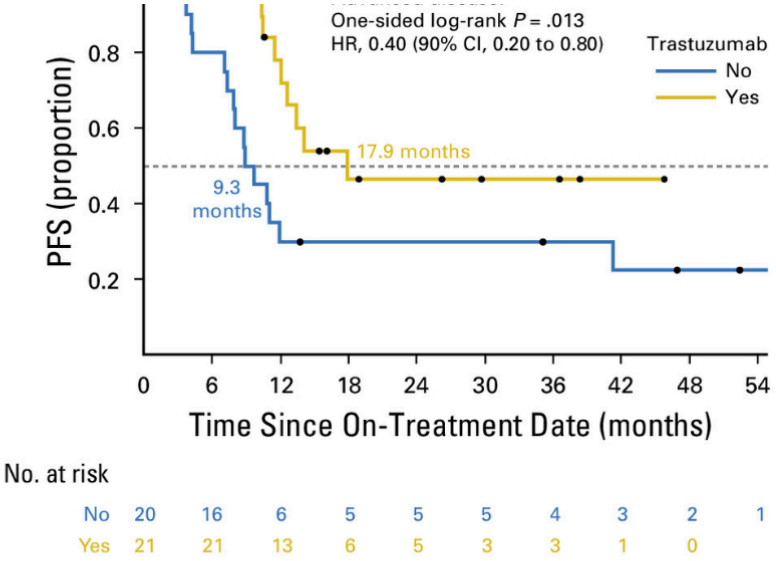
Phase II trial with 62 pts, stage III-IV or recurrent HER2 positive uterine serous

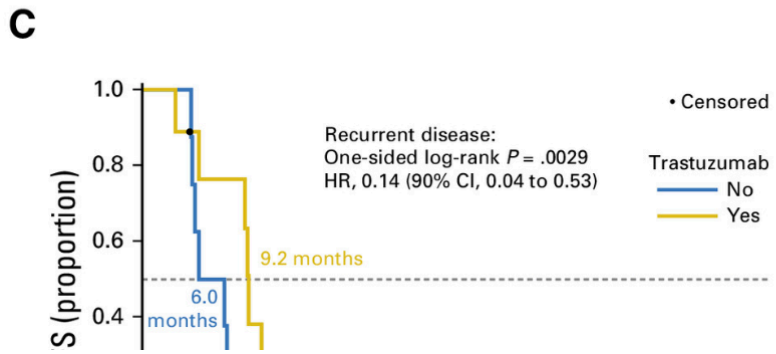
Carbo/taxol vs Carbo/taxol/trastuzumab + trastuzumab maintenance

PFS 9.3 vs 17.7m significant

OS 24.4 vs 29.6m significant







Recurrence

Keynote 775 (Makker et al, NEJM 2022)

Phase 3 RCT study of 827 pts with advanced, recurrent or metastatic endometrial cancer (at least 1 prior line of chemo)

697 pts MMRp, 130 MMRd

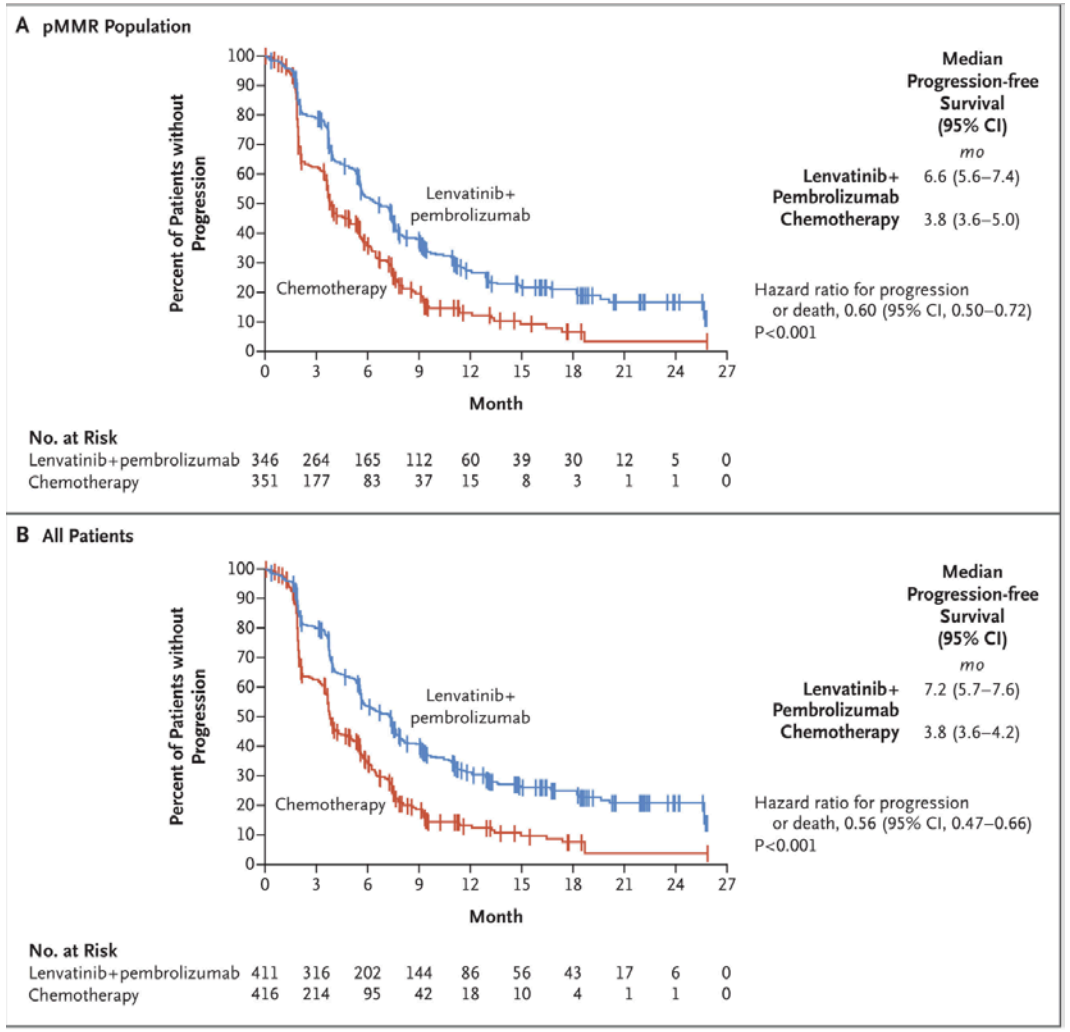
Randomized to Pembro/Lenvatinib vs physician choice (Adria or weekly taxol)

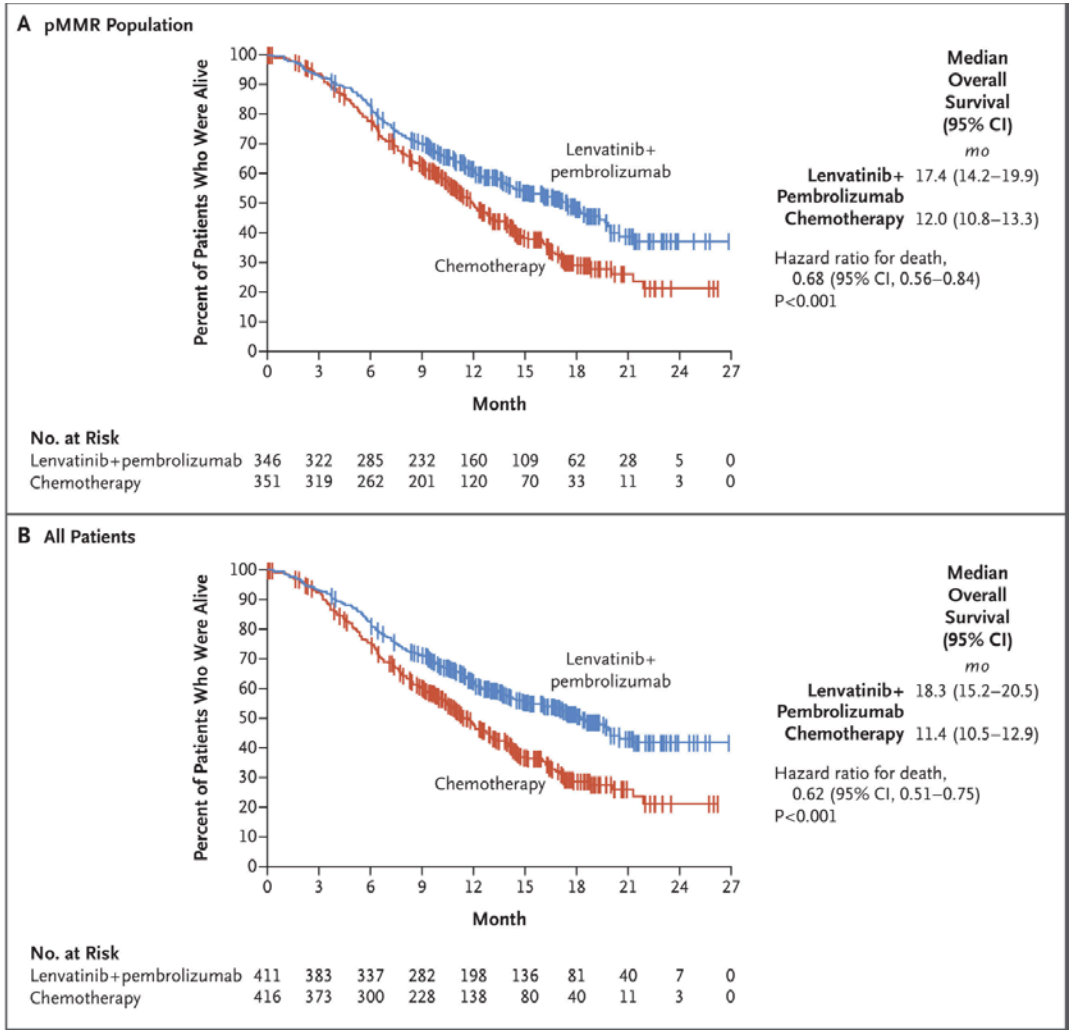
Primary endpoints PFS and OS

ORR 31.9% (5.2% CR) vs 14.7% (2.6% CR)

Median dose Lenvatinib 14mg

Keynote 775





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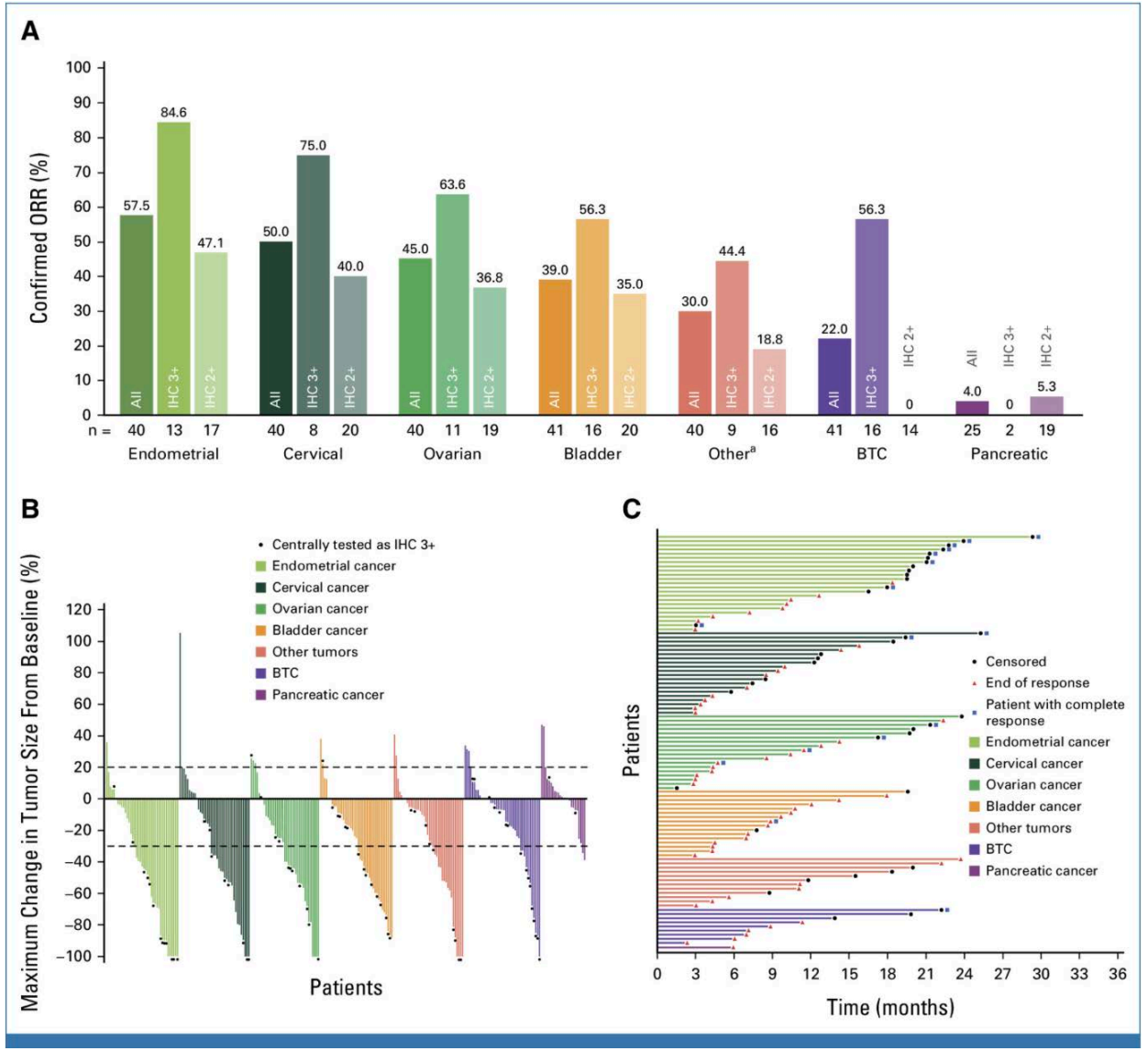
DESTINY- Pan tumor 02, Meric-Bernstam et al, JCO 2023

Phase II open-label trial of 267 pts (40 endometrial) with HER2+ advanced or recurrent solid tumors

Using ADC Trastuzumab deruxtecan (T-DXd)

Primary endpoint ORR

ORR in endometrial cohort 57.5%, Median DOR not reached in endometrial cohort


A
Confirmed ORR (%)
100
90
80
70
60
50
40
30
20
10
0
57.5
84.6
47.1
50.0
75.0
40.0
45.0
63.6
36.8
39.0
56.3
35.0
30.0
44.4
18.8
22.0
56.3
0
4.0
0
5.3
All
IHC 3+
IHC 2+
n = 40 13 17 40 8 20 40 11 19 41 16 20 40 9 16 41 16 14 25 2 19
Endometrial
Cervical
Ovarian
Bladder
Other[a]
BTC
Pancreatic
B
Maximum Change in Tumor Size From Baseline (%)
120
100
80
60
40
20
0
−20
−40
−60
−80
−100
Centrally tested as IHC 3+
Endometrial cancer
Cervical cancer
Ovarian cancer
Bladder cancer
Other tumors
BTC
Pancreatic cancer
Patients
C
Patients
Censored
End of response
Patient with complete response
Endometrial cancer
Cervical cancer
Ovarian cancer
Bladder cancer
Other tumors
BTC
Pancreatic cancer
0 3 6 9 12 15 18 21 24 27 30 33 36
Time (months)

ENGOT- EN3/PALEO, Mirza et al, Gyn Onc 2024

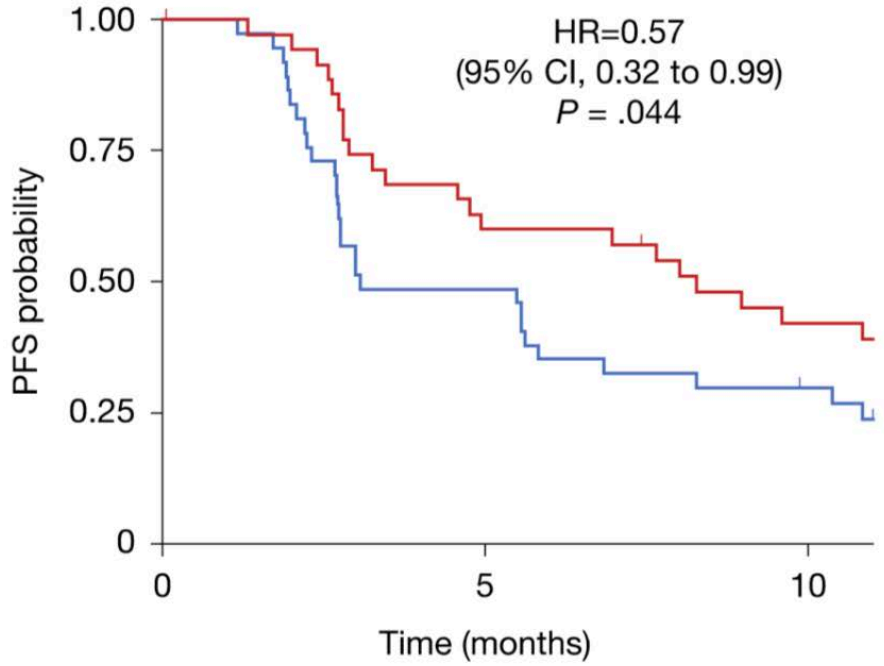
Phase II placebo-controlled RCT of letrozole + palbociclib or placebo in 77 patients

Endometrioid endometrial cancer, ER + (≥10%) advanced/recurrent

Primary endpoint PFS

PFS 8.3 vs 3.1m (palbociclib vs placebo), no OS benefit noted

A



No. at risk			
Palbociclib + letrozole	36	21	14
Placebo + letrozole	37	18	10

GOG 153 (Fiorica et al, Gyn Onc 2004)

Phase II trial 56 pts with recurrent or advanced endometrial cancer alternating Megace/ Tamoxifen

No prior systemic therapy (including hormones), 59% prior RT

80% recurrent, 56% endometrioid

27% ORR, 21% with CR

Median duration of response 28m

PFS 2.7m, OS 14m

9% with VTE

Everolimus and Letrozole (Slomovitz, JCO 2015)

38 pts Phase II with progressive or recurrent endometrial cancer

- Up to 2 prior lines of therapy
- 29% serous/clear cell/ mixed histology, excluded carcsarc

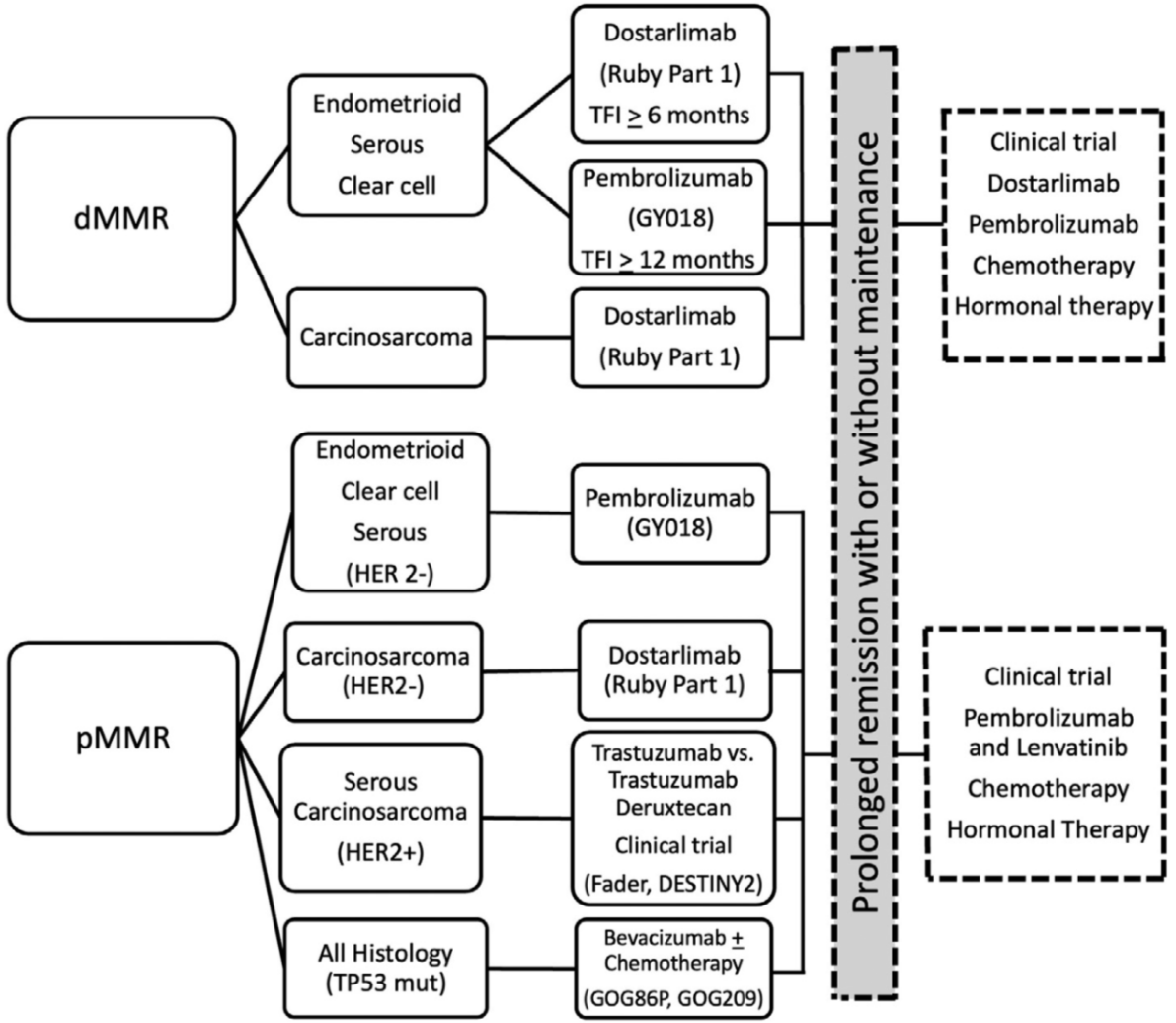
CBR 40%, ORR 32%, CR 26%

- No responses in serous carcinoma
- More effective in patients on metformin

Median OS 14m

Endocrine therapies

Treatment	ORR	Range
Hydroxyprogesterone (Delalutin)	29%	9-34%
Medroxyprogesterone (Provera)	25%	14-53%
Megesterol acetate (Megace)	20%	11-56%
Tamoxifen	18%	0-53%
Leuprolide	35%	
Everolimus + Letrozole	24-32%	
Megace + Tamoxifen	27%	
Temsirolimus	4%	
Temsirolimus + Bev	25%	



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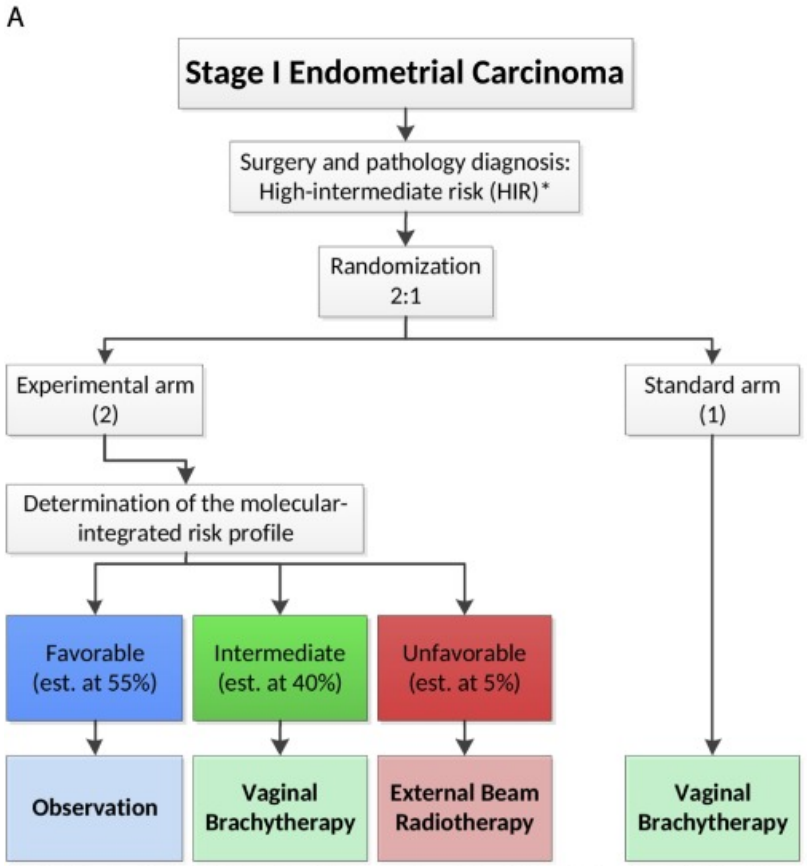
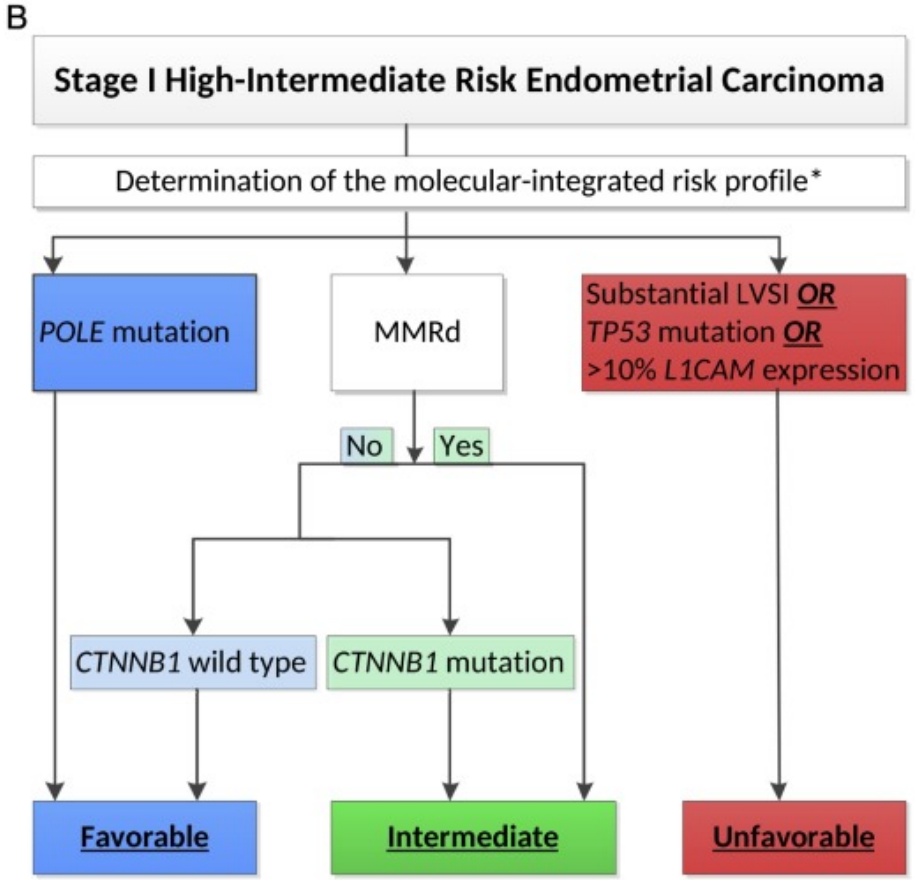
Emerging therapies

PORTEC 4a



High-intermediate risk (HIR) endometrial cancer: stage IA (with invasion) and grade 3; stage IB, grade 1 or 2; with either age ≥ 60 or substantial lymph-vascular space invasion (LVSI); stage IB, grade 3 without LVSI; or stage II (microscopic) with grade 1. Est = estimated.



*Patients with multiple characteristics (double classifiers) were designated intermediate risk. MMRd = Mismatch repair-deficiency. For details, see text.

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RAINBO

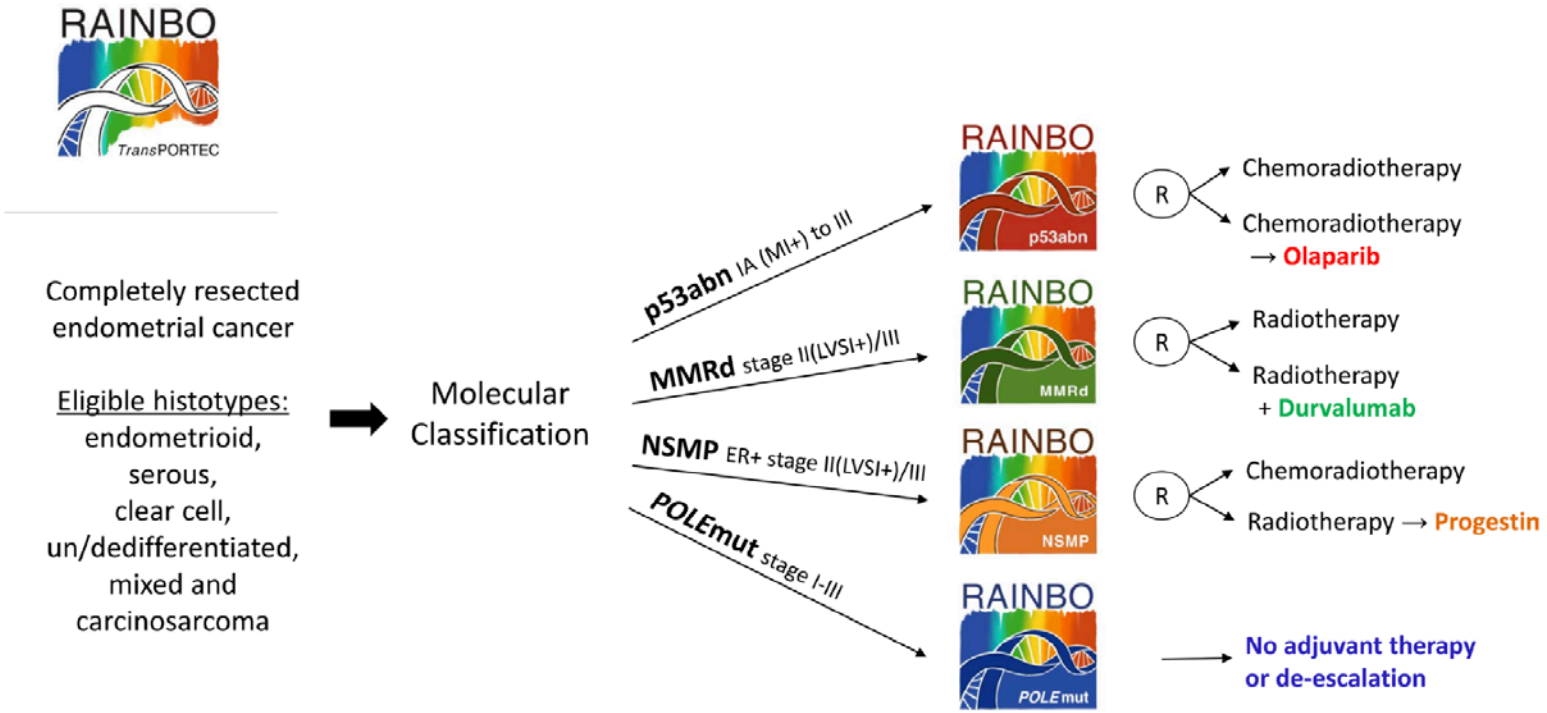

Figure 1 Design of the RAINBO program. ER, estrogen receptor status; LVSI, lymphovascular space invasion; MMRd, mismatch repair deficient; NSMP, no specific molecular profile; p53abn, p53 abnormal; POLEmut, DNA polymerase-ε mutated; R, randomization; RAINBO, Refining Adjuvant treatment IN endometrial cancer Based On molecular features.

Other upcoming therapy strategies

- Antibody-drug conjugates
- Immune checkpoint inhibition
- PARP inhibition
- CDK4/6 inhibition with aromatase inhibitors
- Exportin-1 inhibition in MMRp/p53wt patients

Questions?

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