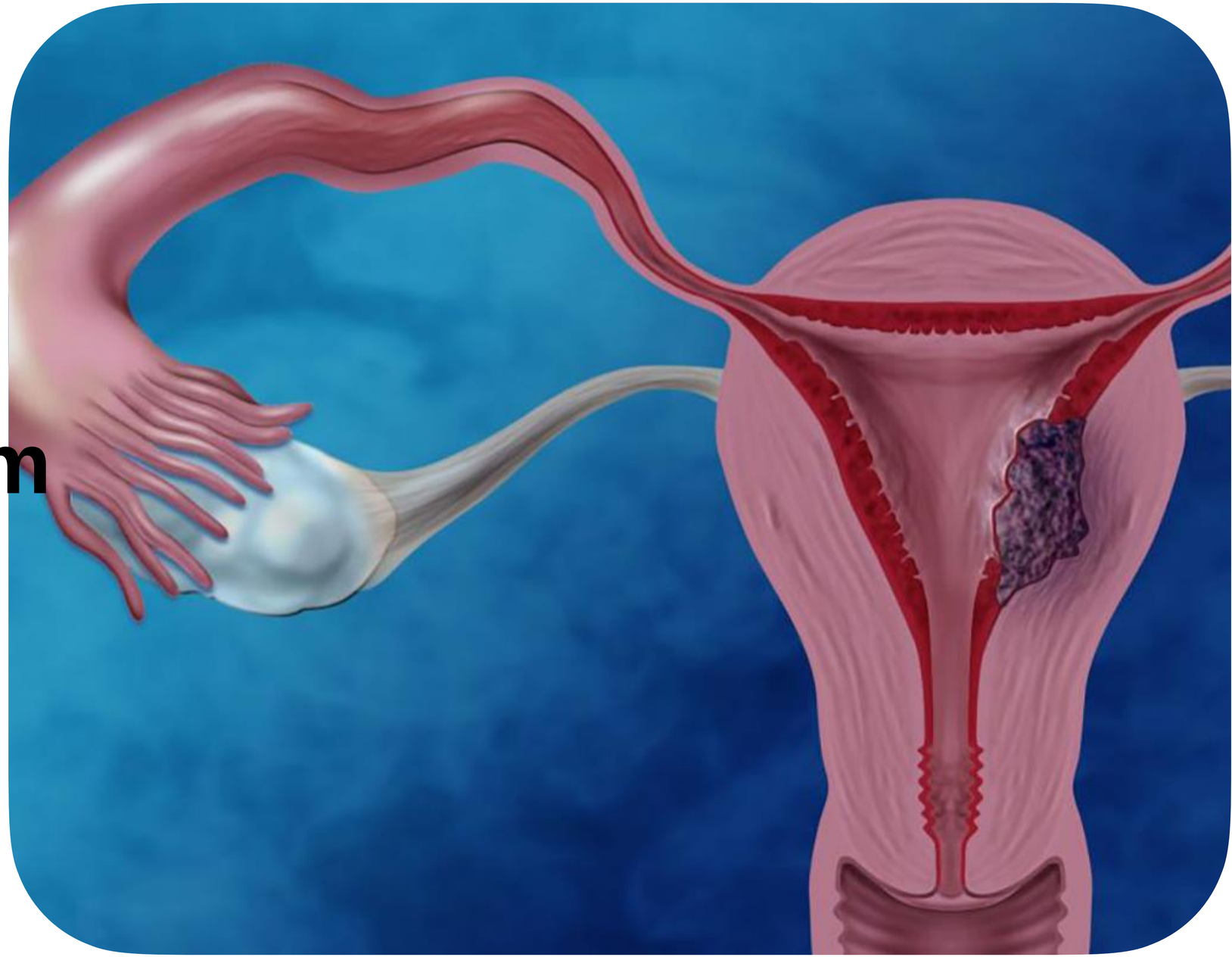
PORTEC 3

Wise decisions in molecular profiling

Dr Shraddha Raj, Associate professor, Radiation Oncology, State Cancer Institute, Indira Gandhi Institute of Medical sciences, Patna

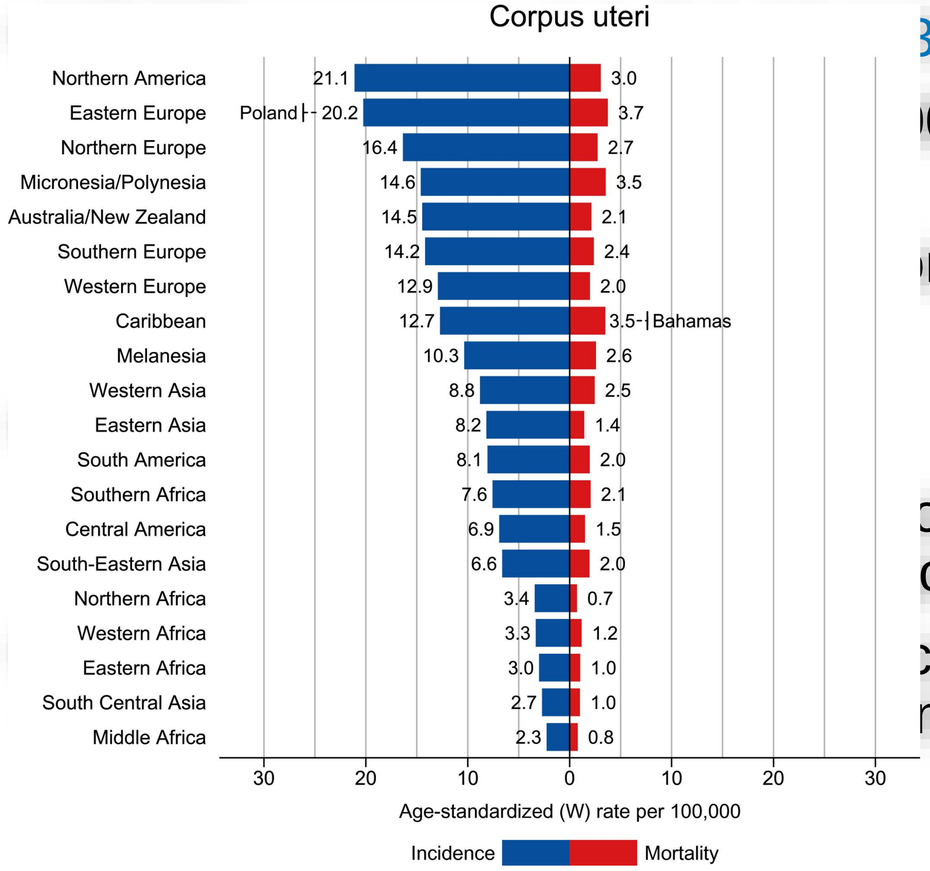
Ca Endometrium

Background



Ca Endometrium

Background



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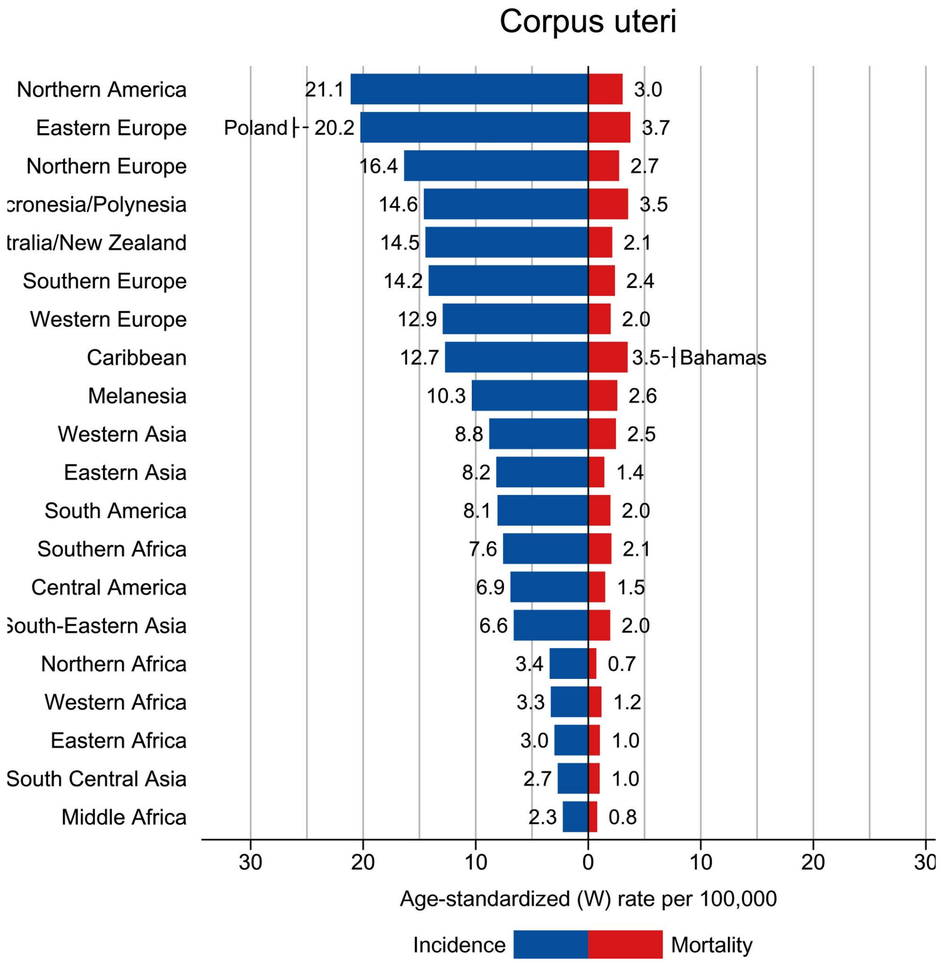
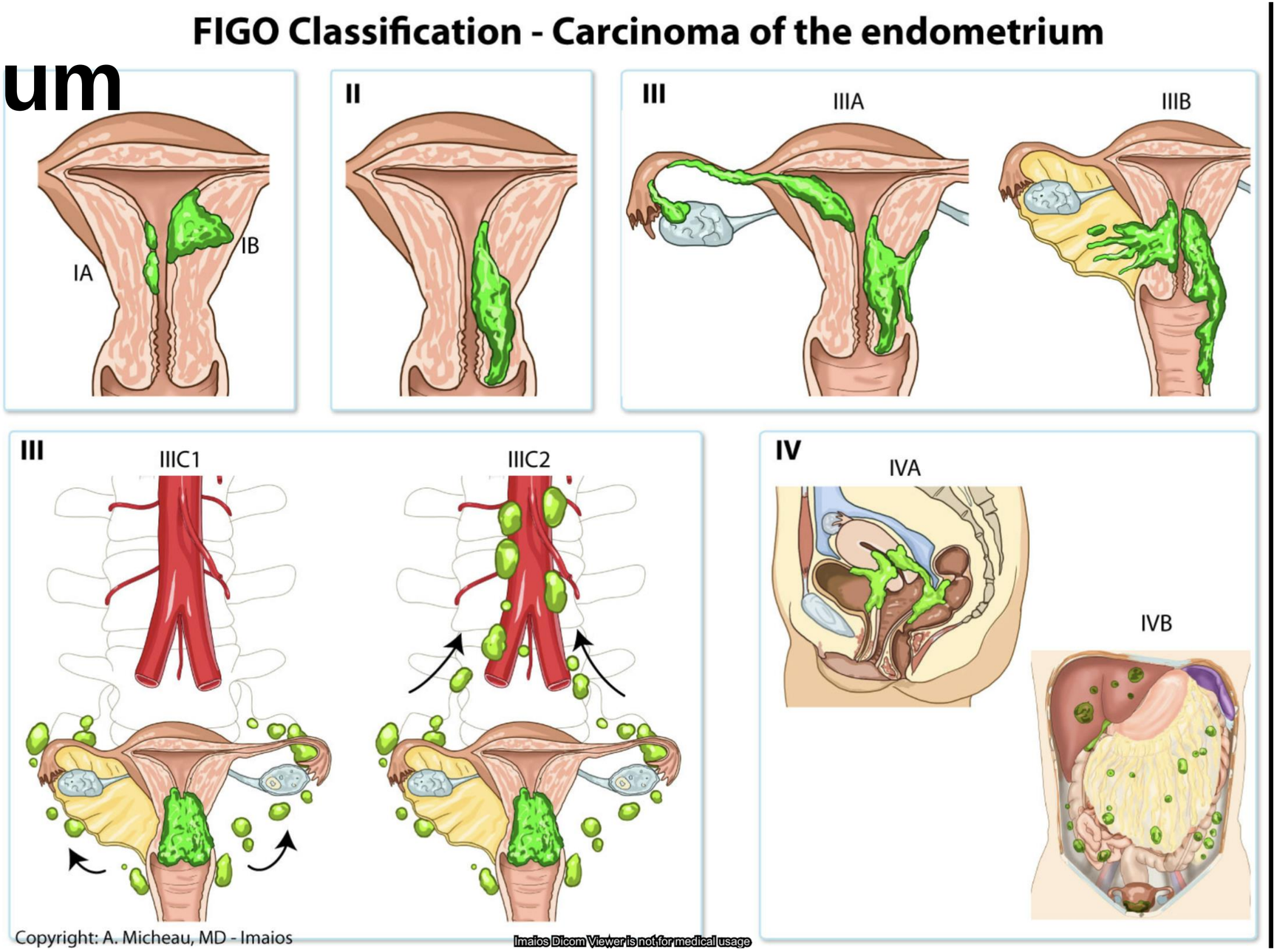


*https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf

Ca Endometrium

Staging

2018



https://www.imaios.com/en/e-Cases/Channels/Radiology/Radiological-classifications-commonly-used-in-medical-imaging/Carcinoma-of-the-endometrium

Ca Endometrium

Conventional risk stratification

Ca Endometrium

Conventional risk stratification

- Bokhman(1983)# classified into two types:
  - Type 1(65%):
    - obesity, hyperlipidemia, and signs of hyperestrogenism
    - Less or mod differentiation
    - Better prognosis
  - Type 2(35%):
    - no such signs, not clearly defined
    - Poor differentiation
    - Poorer prognosis

#Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983 Feb;15(1):10-7. doi: 10.1016/0090-8258(83)90111-7. PMID: 6822361.

Ca Endometrium

Known prognostic factors

- Stage
- Histology
- Grade
- Myometrial invasion
- Lymph-vascular invasion
- Age
- Lynch syndrome

Portec 1

Lancet 2000

Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial

*Carien L Creutzberg, Wim L J van Putten, Peter C M Koper, Marnix L M Lybeert, Jan J Jobsen, Carla C Wárlám-Rodenhuis, Karin A J De Winter, Ludy C H W Lutgens, Alfons C M van den Bergh, Elzbieta van de Steen-Banasik, Henk Beerman, Mat van Lent, for the PORTEC Study Group**

Summary

Background Postoperative radiotherapy for International Federation of Gynaecology and Obstetrics (FIGO) stage-1 endometrial carcinoma is a subject of controversy due to the low relapse rate and the lack of data from randomised trials. We did a multicentre prospective randomised trial to find whether postoperative pelvic radiotherapy improves locoregional control and survival for patients with stage-1 endometrial carcinoma

Methods Patients with stage-1 endometrial carcinoma (grade 1 with deep [⩾50%] myometrial invasion, grade 2 with any invasion, or grade 3 with superficial [<50%] invasion) were enrolled. After total abdominal hysterectomy and bilateral salpingo-oophorectomy, without lymphadenectomy, 715 patients from 19 radiation oncology centres were randomised to pelvic radiotherapy (46 Gy) or no further

complications were seen in eight patients, of which seven were in the radiotherapy group (2%). 2-year survival after vaginal recurrence was 79%, in contrast to 21% after pelvic recurrence or distant metastases. Survival after relapse was significantly ($p=0{\cdot}02$) better for patients in the control group. Multivariate analysis showed that for locoregional recurrence, radiotherapy and age below 60 years were significant favourable prognostic factors.

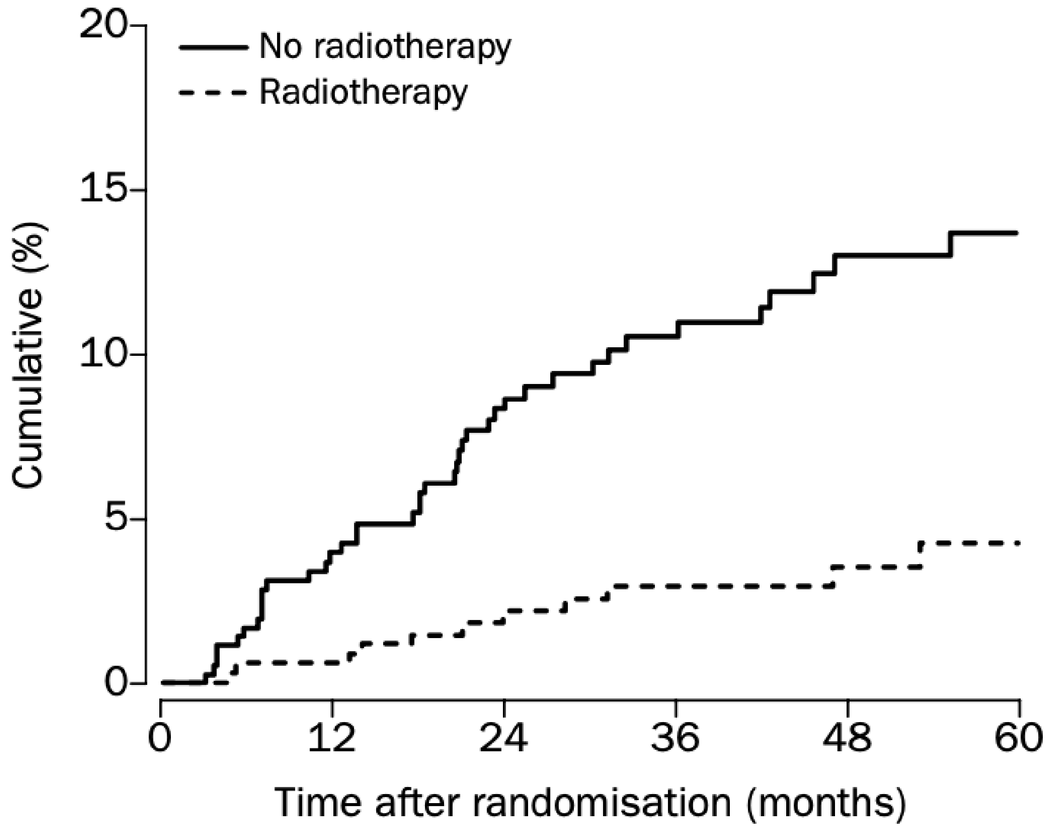
Interpretation Postoperative radiotherapy in stage-1 endometrial carcinoma reduces locoregional recurrence but has no impact on overall survival. Radiotherapy increases treatment-related morbidity. Postoperative radiotherapy is not indicated in patients with stage-1 endometrial carcinoma below 60 years and patients with grade-2 tumours with superficial invasion.

Lancet 2000; **355:** 1404–11

Outcomes(PORTEC-1)

Outcome	Radiotherapy (n=354)			Control (n=360)		
	Number	5-year %	SE	Number	5-year %	SE
Locoregional relapse	11	4·2	1·3	40	13·7	2·1
Vaginal vault	5	1·6	0·7	19	6·4	1·4
Vagina	2	0·7	0·5	11	3·8	1·2
Pelvic	4	2·0	1·0	10	3·4	1·1
Distant metastasis	24	7·9	1·7	20	7·0	1·6
Death	57	19·3	2·7	48	14·9	2·2
Endometrial cancer	23	9·2	2·0	18	6·0	1·4
Locoregional relapse	3	2·0	1·1	4	1·1	0·6
Distant metastasis	18	6·4	1·6	13	4·5	1·3
Complications	2	0·8	0·6	1	0·3	0·3
Secondary cancer	11	3·4	1·2	8	1·9	0·8
Other causes	23	6·7	1·6	22	7·0	1·6
First failure type						
Locoregional relapse	11	3·9	1·2	40	13·1	2·0
Distant metastasis	19	5·5	1·3	11	4·1	1·3
Death without relapse	35	10·4	2·0	26	7·5	1·6
Secondary cancer	22	8·2	1·9	23	8·0	1·8
GI-tract	9	3·4	1·2	8	2·6	1·0
Breast	5	1·5	0·8	9	3·0	1·1
Other	8	3·3	1·4	6	2·4	1·1

GI-gastrointestinal.



Numbers at risk

Radiotherapy	354	338	284	219	161	109
No radiotherapy	360	328	271	210	159	115

Figure 2: **Probability of locoregional (vaginal or pelvic) relapse**

Outcomes (PORTEC-1)

- significant benefit with post operative radiotherapy in loco regional relapse however no benefit in overall survival

- led to the next level of research question: whether vaginal brachytherapy alone could have reduced the isolated local recurrences without toxicities and other concerns of pelvic RT?

	Locoregional relapse		Death due to endometrial cancer	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Age ⩾60	3·2 (1·3–7·5)	0·003	3·1 (1·2–8·0)	0·02
Invasion ⩾50%	1·8 (0·9–3·8)	0·11	1·9 (0·8–4·4)	0·16
Grade 1	0·77 (0·4–1·6)	0·50	0·45 (0·2–1·3)	0·15
Grade 3	2·2 (0·8–5·8)	0·11	4·9 (1·9–12·5)	0·0008
No radiotherapy	3·9 (2·0–7·6)	<0·0001	0·76 (0·4–1·4)	0·37

Hazard ratio describes relative hazard of failure per unit time, for age ⩾60 years compared with <60 years; for myometrial invasion ⩾50% compared with <50%; for grade 1 and 3 compared with grade 2; for no radiotherapy compared with postoperative radiotherapy.

Table 3: **Cox-regression analysis**

Portec 2

Lancet
March 2010

Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial

R A Nout, V T H B M Smit, H Putter, I M Jürgenliemk-Schulz, J J Jobsen, L C H W Lutgens, E M van der Steen-Banasik, J W M Mens, A Slot, M C Stenfert Kroese, B N F M van Bunningen, A C Ansink, W L J van Putten, C L Creutzberg, for the PORTEC Study Group

Lancet 2010; 375: 816–23

See Comment page 781

Departments of Clinical Oncology (R A Nout MD, C L Creutzberg MD), Pathology (V T H B M Smit MD), and Medical Statistics (H Putter PhD), Leiden University Medical Center, Leiden, Netherlands; Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, Netherlands (I M Jürgenliemk-Schulz MD); Department of Radiotherapy, Medisch Spectrum Twente, Enschede, Netherlands (J J Jobsen MD); MAASTricht

Summary

Background After surgery for intermediate-risk endometrial carcinoma, the vagina is the most frequent site of recurrence. This study established whether vaginal brachytherapy (VBT) is as effective as pelvic external beam radiotherapy (EBRT) in prevention of vaginal recurrence, with fewer adverse effects and improved quality of life.

Methods In this open-label, non-inferiority, randomised trial undertaken in 19 Dutch radiation oncology centres, 427 patients with stage I or IIA endometrial carcinoma with features of high-intermediate risk were randomly assigned by a computer-generated, biased coin minimisation procedure to pelvic EBRT (46 Gy in 23 fractions; n=214) or VBT (21 Gy high-dose rate in three fractions, or 30 Gy low-dose rate; n=213). All investigators were masked to the assignment of treatment group. The primary endpoint was vaginal recurrence. The predefined non-inferiority margin was an absolute difference of 6% in vaginal recurrence. Analysis was by intention to treat, with competing risk methods. The study is registered, number ISRCTN16228756.

Findings At median follow-up of 45 months (range 18–78), three vaginal recurrences had been diagnosed after VBT and four after EBRT. Estimated 5-year rates of vaginal recurrence were 1·8% (95% CI 0·6–5·9) for VBT and 1·6% (0·5–4·9) for EBRT (hazard ratio [HR] 0·78, 95% CI 0·17–3·49; p=0·74). 5-year rates of locoregional relapse (vaginal

PORTEC 2

Outcomes

	Events/total	Estimated 5-year (%; 95% CI)	Hazard ratio (95% CI)*	Log-rank p value*
Vaginal recurrence				
EBRT	4/183	1·9% (0·6–5·8)	1·00	0·39
VBT	2/183	1·5% (0·4–6·5)	0·48 (0·09–2·64)	
Pelvic recurrence				
EBRT	1/183	0·6% (0·1–4·0)	1·00	0·06
VBT	6/183	3·3% (1·5–7·3)	6·10 (0·73–50·7)	
Locoregional recurrence				
EBRT	5/183	2·4% (0·9–6·5)	1·00	0·42
VBT	8/183	4·8% (2·4–9·7)	1·58 (0·52–4·86)	
Distant metastases				
EBRT	10/183	5·0% (2·6–9·4)	1·00	0·79
VBT	11/183	6·4% (3·6–11·5)	1·12 (0·48–2·64)	
Disease-free survival				
EBRT	24/183	80·2% (71·4–89·0)	1·00	0·89
VBT	25/183	84·5% (78·6–90·4)	1·04 (0·59–1·82)	
Overall survival				
EBRT	19/183	82·1% (73·5–90·7)	1·00	0·66
VBT	22/183	86·2% (80·5–91·9)	1·15 (0·62–2·13)	

EBRT=external beam radiotherapy. VBT=vaginal brachytherapy. *Both log-rank tests and Cox proportional hazards models are stratified for FIGO (International Federation of Gynecology and Obstetrics) stage.

Table 4: **Recurrence and survival for patients at true high-intermediate risk after pathology review (n=366)**

ESGO ESTRO ESP 2015

TABLE 2. New risk groups to guide adjuvant therapy use

Risk group	Description	LOE
Low	Stage I endometrioid, grade 1–2, <50% myometrial invasion, LVSI negative	I
Intermediate	Stage I endometrioid, grade 1–2, ≥50% myometrial invasion, LVSI negative	I
High-intermediate	Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status	I
	Stage I endometrioid, 1–2, LVSI unequivocally positive, regardless of depth of invasion	II
High	Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status	I
	Stage II	I
	Stage III endometrioid, no residual disease	I
	Non endometrioid (serous or clear cell or undifferentiated carcinoma, or carcinosarcoma)	I
Advanced	Stage III residual disease and stage IVA	I
Metastatic	Stage IVB	I

FIGO 2009 staging used; molecular factors were considered but not included; tumour size was considered but not included; nodal status may be considered for treatment recommendations.

LOE, level of evidence; LVSI, lymphovascular space invasion.

Risk groups of endometrial cancer and current treatment recommendations

Risk group	ESMO-ESGO-ESTRO consensus[1]	Common treatment recommendations
Low risk	Stage I EEC, grade 1–2,<50% myometrial invasion, LVSI negative	No adjuvant treatment
Low-intermediate risk	Stage I EEC, grade 1–2,≥50% myometrial invasion, LVSI negative	Vaginal brachytherapy (consider observation if age <60 years)
High-intermediate risk	Stage I EEC, grade 3, <50% myometrial invasion, any LVSI	Vaginal brachytherapy Consider pelvic external beam radiotherapy if LVSI is unequivocally positive, especially if no lymph node dissection or sentinel node has been performed.
	Stage I EEC, grade 1–2, LVSI unequivocally positive, any myometrial invasion	
High risk	Stage I EEC, grade 3, ≥50% myometrial invasion, any LVSI	External beam radiotherapy Consider vaginal brachytherapy if no LVSI
	Stage II EEC Stage III EEC	Vaginal brachytherapy if grade 1–2 and LVSI negative Pelvic radiotherapy if : • **Stage II, grade 3** • **LVSI unequivocally positive** • **Stage III** Stage III: combined adjuvant radiotherapy and chemotherapy (PORTEC-3 schedule or sequential)
	NEEC stage I–III (serous, clear cell or undifferentiated cancers; carcinosarcoma)	Vaginal brachytherapy if serous/clear cell, stage IA after full surgical staging, LVSI negative Stage IB–III: combined adjuvant pelvic radiotherapy and chemotherapy

- **EEC, endometrioid endometrial cancer; ESGO, European Society of Gynecological Oncology; ESMO, European Society for Medical Oncology; ESTRO, European Society; LVSI, lymph-vascular space invasion; NEEC, non-endometrioid endometrial cancer; PORTEC, post operative radiation therapy endometrial cancer**

Portec 3

Lancet

February 2018

Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial

*Stephanie M de Boer, Melanie E Powell, Linda Mileshkin, Dionyssios Katsaros, Paul Bessette, Christine Haie-Meder, Petronella B Ottevanger, Jonathan A Ledermann, Pearly Khaw, Alessandro Colombo, Anthony Fyles, Marie-Helene Baron, Ina M Jürgenliemk-Schulz, Henry C Kitchener, Hans W Nijman, Godfrey Wilson, Susan Brooks, Silvestro Carinelli, Diane Provencher, Chantal Hanzen, Ludy C H W Lutgens, Vincent T H B M Smit, Naveena Singh, Viet Do, Romerai D'Amico, Remi A Nout, Amanda Feeney, Karen W Verhoeven-Adema, Hein Putter, Carien L Creutzberg, on behalf of the PORTEC study group**

Summary

Background Although women with endometrial cancer generally have a favourable prognosis, those with high-risk disease features are at increased risk of recurrence. The PORTEC-3 trial was initiated to investigate the benefit of adjuvant chemotherapy during and after radiotherapy (chemoradiotherapy) versus pelvic radiotherapy alone for women with high-risk endometrial cancer.

Lancet Oncol 2018; 19: 295–30

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February 12, 2018
http://dx.doi.org/10.1016/
S1470-2045(18)30079-2

Caption

Lancet Oncol 2018; 19: 295–309

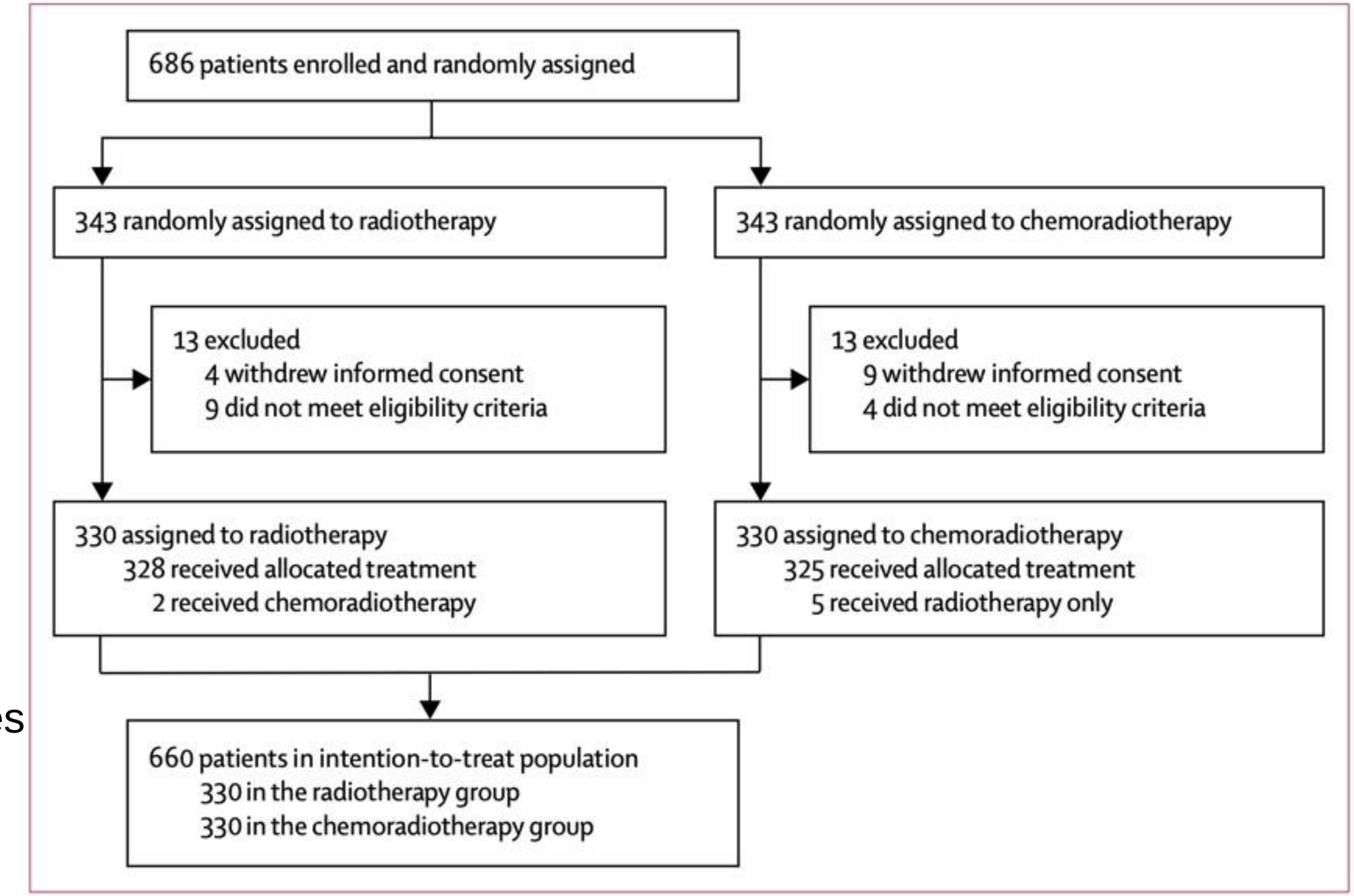
PORTEC 3

Methods

- Arm1:EBRT
- Arm2: EBRT+ Chemotherapy:

Cisplatin 40mg/m2 wk1 & wk4

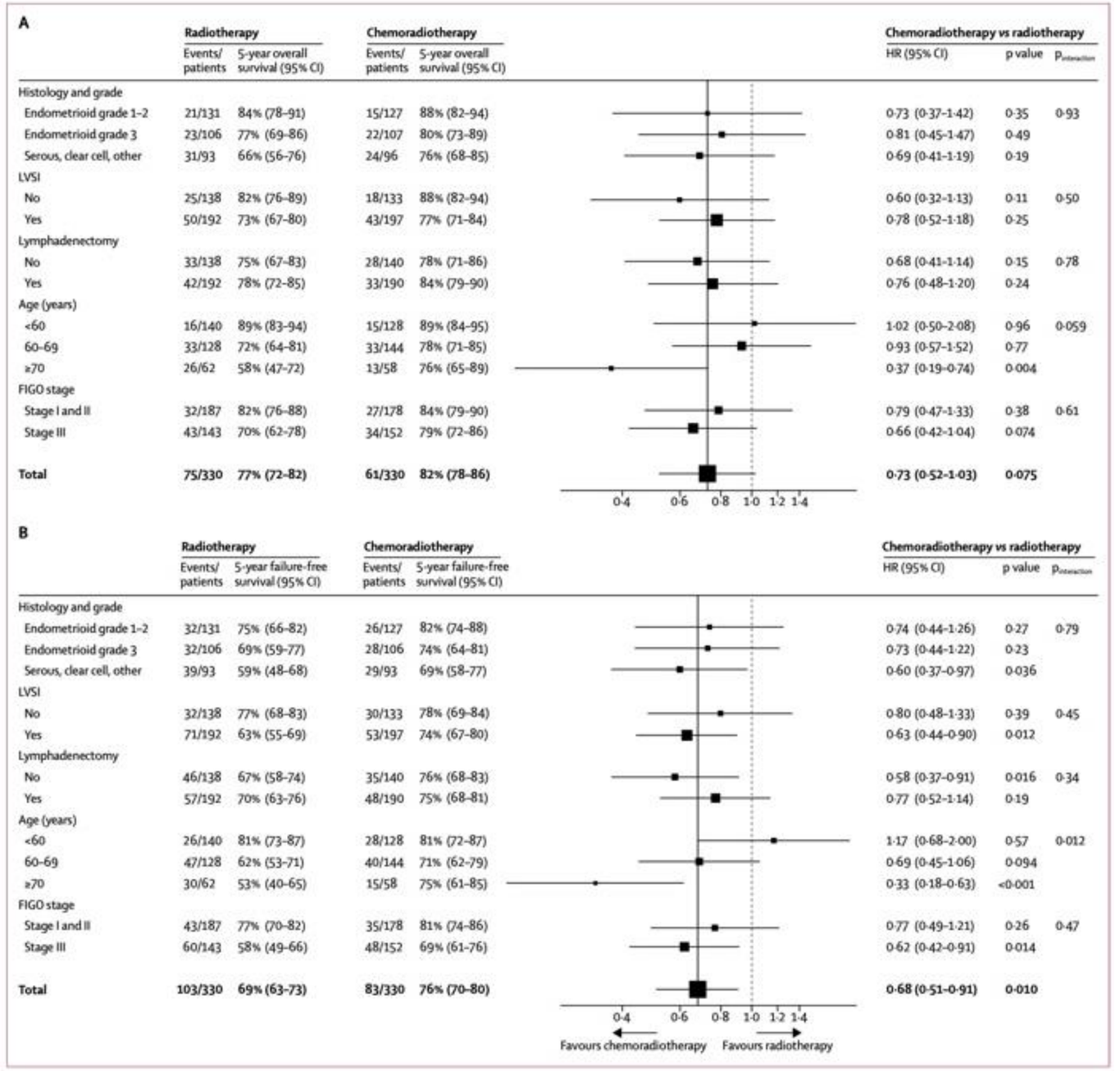
Pacli(175mg/m2)+ Carbo(AUC5) X 4 cycles



Lancet Oncol 2018; 19: 295–309

PORTEC 3

Results



A

	Radiotherapy Events/ patients	Radiotherapy 5-year overall survival (95% CI)	Chemoradiotherapy Events/ patients	Chemoradiotherapy 5-year overall survival (95% CI)	Chemoradiotherapy vs radiotherapy HR (95% CI)	p value	$p_{interaction}$
Histology and grade							
Endometrioid grade 1–2	21/131	84% (78–91)	15/127	88% (82–94)	0·73 (0·37–1·42)	0·35	0·93
Endometrioid grade 3	23/106	77% (69–86)	22/107	80% (73–89)	0·81 (0·45–1·47)	0·49	
Serous, clear cell, other	31/93	66% (56–76)	24/96	76% (68–85)	0·69 (0·41–1·19)	0·19	
LVSI							
No	25/138	82% (76–89)	18/133	88% (82–94)	0·60 (0·32–1·13)	0·11	0·50
Yes	50/192	73% (67–80)	43/197	77% (71–84)	0·78 (0·52–1·18)	0·25	
Lymphadenectomy							
No	33/138	75% (67–83)	28/140	78% (71–86)	0·68 (0·41–1·14)	0·15	0·78
Yes	42/192	78% (72–85)	33/190	84% (79–90)	0·76 (0·48–1·20)	0·24	
Age (years)							
<60	16/140	89% (83–94)	15/128	89% (84–95)	1·02 (0·50–2·08)	0·96	0·059
60–69	33/128	72% (64–81)	33/144	78% (71–85)	0·93 (0·57–1·52)	0·77	
≥70	26/62	58% (47–72)	13/58	76% (65–89)	0·37 (0·19–0·74)	0·004	
FIGO stage							
Stage I and II	32/187	82% (76–88)	27/178	84% (79–90)	0·79 (0·47–1·33)	0·38	0·61
Stage III	43/143	70% (62–78)	34/152	79% (72–86)	0·66 (0·42–1·04)	0·074	
Total	**75/330**	**77% (72–82)**	**61/330**	**82% (78–86)**	**0·73 (0·52–1·03)**	**0·075**	

B

	Radiotherapy Events/ patients	Radiotherapy 5-year failure-free survival (95% CI)	Chemoradiotherapy Events/ patients	Chemoradiotherapy 5-year failure-free survival (95% CI)	Chemoradiotherapy vs radiotherapy HR (95% CI)	p value	$p_{interaction}$
Histology and grade							
Endometrioid grade 1–2	32/131	75% (66–82)	26/127	82% (74–88)	0·74 (0·44–1·26)	0·27	0·79
Endometrioid grade 3	32/106	69% (59–77)	28/106	74% (64–81)	0·73 (0·44–1·22)	0·23	
Serous, clear cell, other	39/93	59% (48–68)	29/93	69% (58–77)	0·60 (0·37–0·97)	0·036	
LVSI							
No	32/138	77% (68–83)	30/133	78% (69–84)	0·80 (0·48–1·33)	0·39	0·45
Yes	71/192	63% (55–69)	53/197	74% (67–80)	0·63 (0·44–0·90)	0·012	
Lymphadenectomy							
No	46/138	67% (58–74)	35/140	76% (68–83)	0·58 (0·37–0·91)	0·016	0·34
Yes	57/192	70% (63–76)	48/190	75% (68–81)	0·77 (0·52–1·14)	0·19	
Age (years)							
<60	26/140	81% (73–87)	28/128	81% (72–87)	1·17 (0·68–2·00)	0·57	0·012
60–69	47/128	62% (53–71)	40/144	71% (62–79)	0·69 (0·45–1·06)	0·094	
≥70	30/62	53% (40–65)	15/58	75% (61–85)	0·33 (0·18–0·63)	<0·001	
FIGO stage							
Stage I and II	43/187	77% (70–82)	35/178	81% (74–86)	0·77 (0·49–1·21)	0·26	0·47
Stage III	60/143	58% (49–66)	48/152	69% (61–76)	0·62 (0·42–0·91)	0·014	
Total	**103/330**	**69% (63–73)**	**83/330**	**76% (70–80)**	**0·68 (0·51–0·91)**	**0·010**	

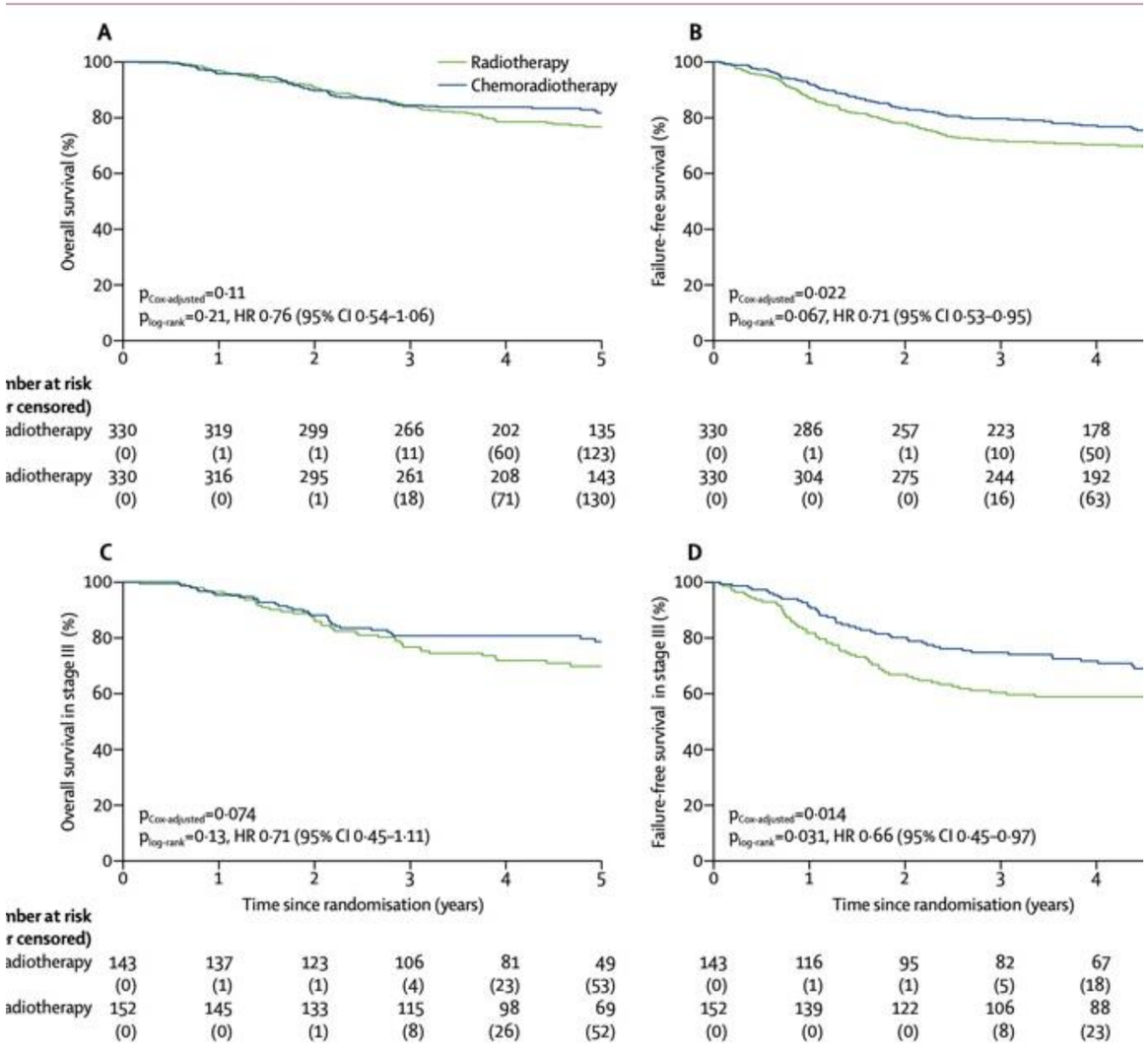
***Figure 3*: Forest plot of multivariable analysis (treatment by covariate interaction) of overall survival (A) and failure-free survival (B)**
For the multivariable analysis the stratification factors (participating group, lymphadenectomy, stage of cancer, and histological type), lymphovascular space invasion, and age were used. HR=hazard ratio. LVSI=lymphovascular space invasion. FIGO=International Federation of Gynecology and Obstetrics.

Lancet Oncol 2018; 19: 295–309

PORTEC 3

Outcomes

Stage I-II: Combined adjuvant CT and RT can't be recommended as no survival diff
High pelvic control with RT alone
Stage III: Chemoradiotherapy should be considered to maximise failure free survival.
Individualised,discussing benefits and risks for each patient



Overall survival and failure-free survival
eier survival curves for overall survival (A) and failure-free survival (B) in all patients, and for overall survival (C) and failure-free survival (D) of patie
ndometrial cancer. $P_{log\text{-}rank}$=unadjusted log-rank p value. $P_{Cox\text{-}adjusted}$=p value adjusted for stratification factors. HR=hazard ratio.

Lancet Oncol 2018; 19: 295–309

Portec 2

10 yr update with pathological review

Nature 2018

Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy

B. G. Wortman[1], C. L. Creutzberg[1], H. Putter[2], I. M. Jürgenliemk-Schulz[3], J. J. Jobsen[4], L. C. H. W. Lutgens[5], E. M. van der Steen-Banasik[6], J. W. M. Mens[7], A. Slot[8], M. C. Stenfert Kroese[9], B. van Triest[10], H. W. Nijman[11], E. Stelloo[12], T. Bosse[12], S. M. de Boer[1], W. L. J. van Putten[13], V. T. H. B. M Smit[12] and R. A. Nout[1] for the PORTEC Study Group

BACKGROUND: PORTEC-2 was a randomised trial for women with high-intermediate risk (HIR) endometrial cancer, comparing pelvic external beam radiotherapy (EBRT) with vaginal brachytherapy (VBT). We evaluated long-term outcomes combined with the results of pathology review and molecular analysis.

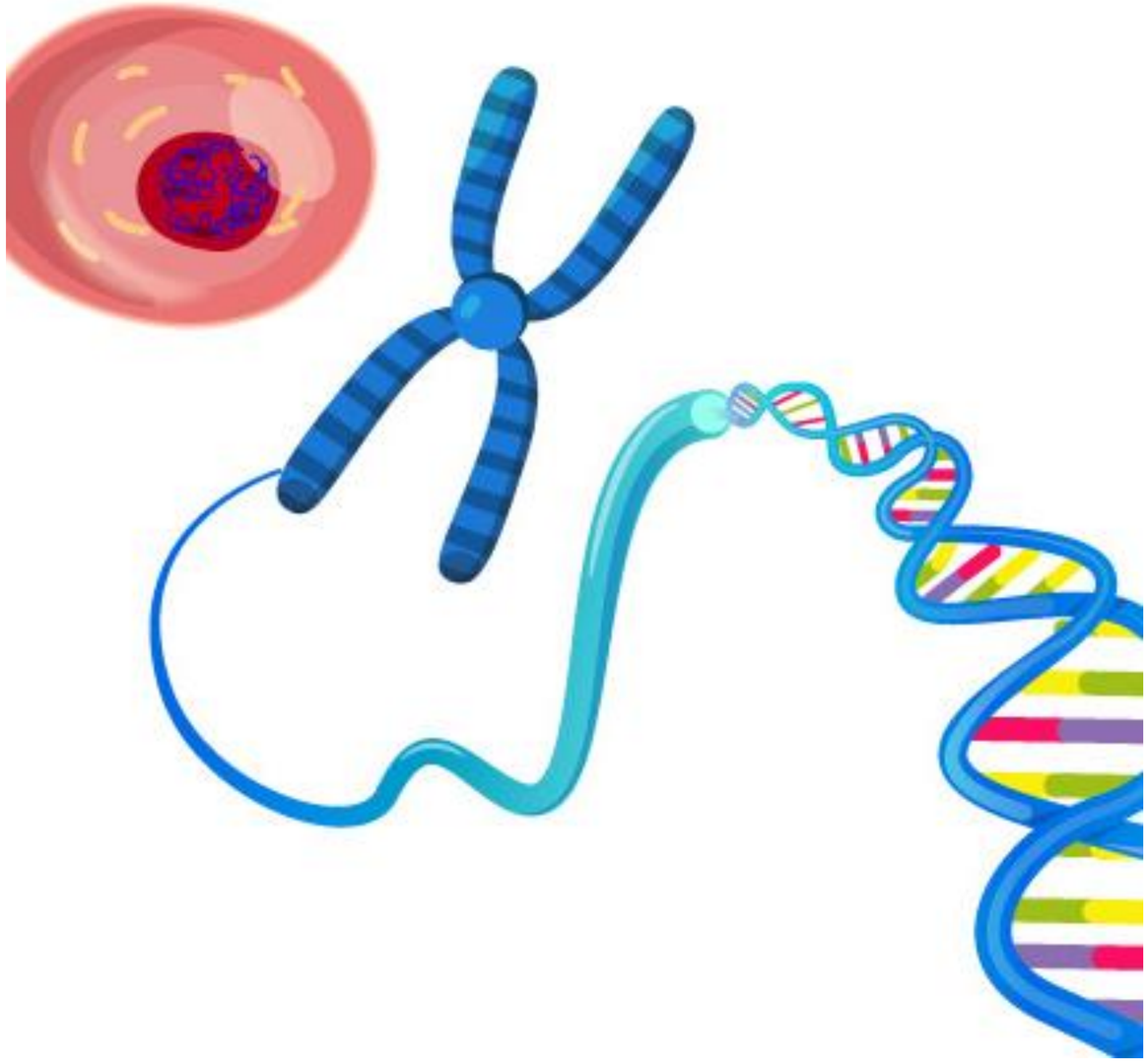
METHODS: 427 women with HIR endometrial cancer were randomised between 2002–2006 to VBT or EBRT. Primary endpoint was vaginal recurrence (VR). Pathology review was done in 97.4%, combined with molecular analysis.

RESULTS: Median follow-up was 116 months; 10-year VR was 3.4% versus 2.4% for VBT vs. EBRT ($p = 0.55$). Ten-year pelvic recurrence (PR) was more frequent in the VBT group (6.3% vs. 0.9%, $p = 0.004$), mostly combined with distant metastases (DM). Ten-year isolated PR was 2.5% vs. 0.5%, $p = 0.10$, and DM 10.4 vs. 8.9% ($p = 0.45$). Overall survival for VBT vs. EBRT was 69.5% vs. 67.6% at 10 years ($p = 0.72$). L1CAM and p53-mutant expression and substantial lymph-vascular space invasion were risk factors for PR and DM. EBRT reduced PR in cases with these risk factors.

CONCLUSION: Long-term results of the PORTEC-2 trial confirm VBT as standard adjuvant treatment for HIR endometrial cancer. Molecular risk assessment has the potential to guide adjuvant therapy. EBRT provided better pelvic control in patients with unfavourable risk factors.

Ca Endometrium

Molecular classification



Why molecular risk stratification?

Why molecular risk stratification?

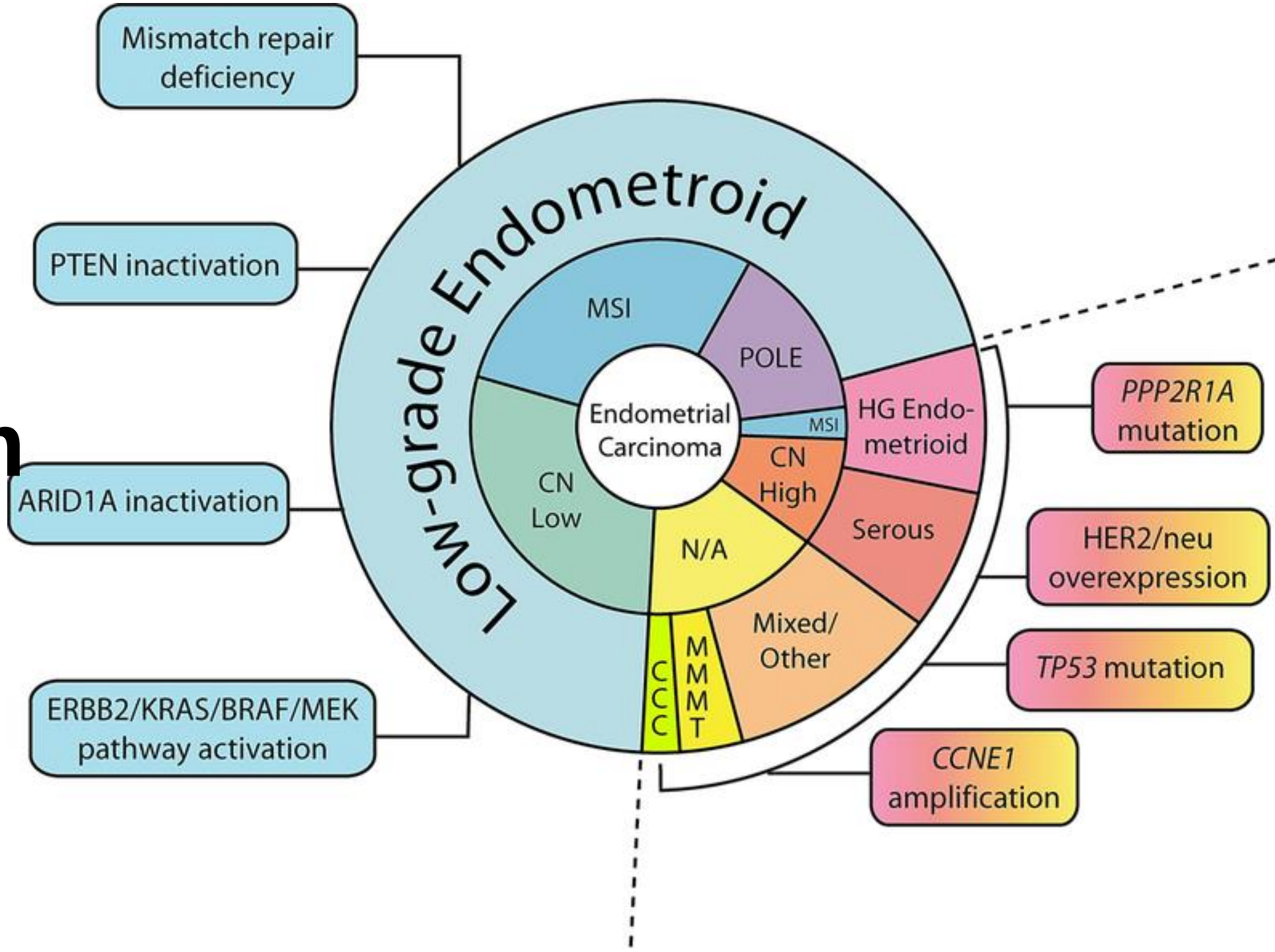
- Existing FIGO classification may have discrepancies upto 38% in pathological determinants

- Molecular subtype assignment is highly reproducible and can be done on diagnostic endometrial biopsies or curettings, showing high concordance with classification performed on the subsequent hysterectomy specimen.

- Prognostic value of molecular classification has consistently been demonstrated
- Predictive value emerging with respect to response to radiotherapy chemotherapy and targeted treatment

Ca Endometrium

TGCA



Yen TT, Wang TL, Fader AN, Shih IM, Gaillard S. Molecular Classification and Emerging Targeted Therapy in Endometrial Cancer. International Journal of Gynecological Pathology : Official Journal of the International Society of Gynecological Pathologists. 2020 Jan;39(1):26-35. DOI: 10

TCGA

Nature 2013

ARTICLE

OPEN

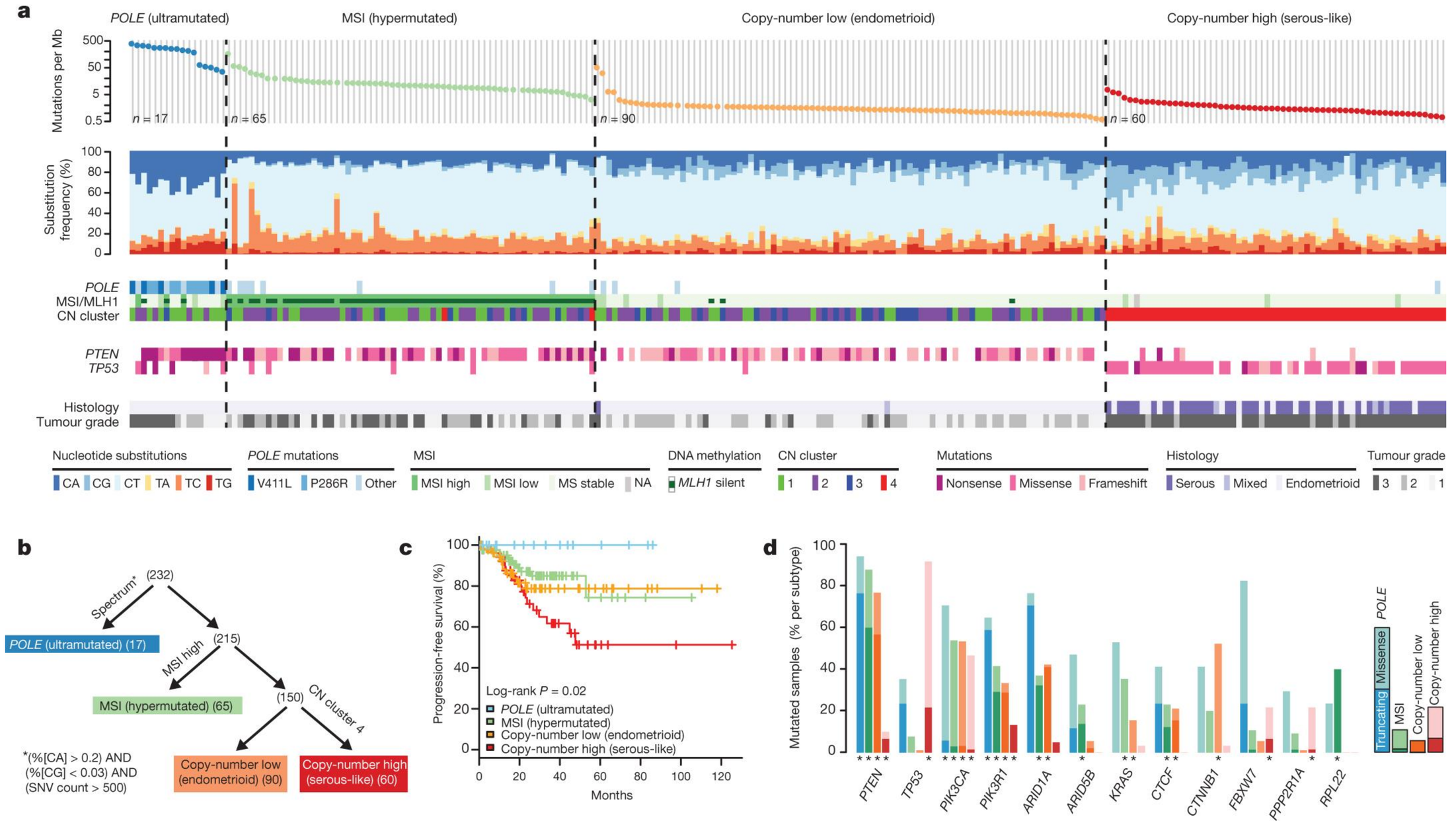
doi:10.1038/nature12113

Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*

We performed an integrated genomic, transcriptomic and proteomic characterization of 373 endometrial carcinomas using array- and sequencing-based technologies. Uterine serous tumours and ~25% of high-grade endometrioid tumours had extensive copy number alterations, few DNA methylation changes, low oestrogen receptor/progesterone receptor levels, and frequent *TP53* mutations. Most endometrioid tumours had few copy number alterations or *TP53* mutations, but frequent mutations in *PTEN*, *CTNNB1*, *PIK3CA*, *ARID1A* and *KRAS* and novel mutations in the SWI/SNF chromatin remodelling complex gene *ARID5B*. A subset of endometrioid tumours that we identified had a markedly increased transversion mutation frequency and newly identified hotspot mutations in *POLE*. Our results classified endometrial cancers into four categories: *POLE* ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high. Uterine serous carcinomas share genomic features with ovarian serous and basal-like breast carcinomas. We demonstrated that the genomic features of endometrial carcinomas permit a reclassification that may affect post-surgical adjuvant treatment for women with aggressive tumours.

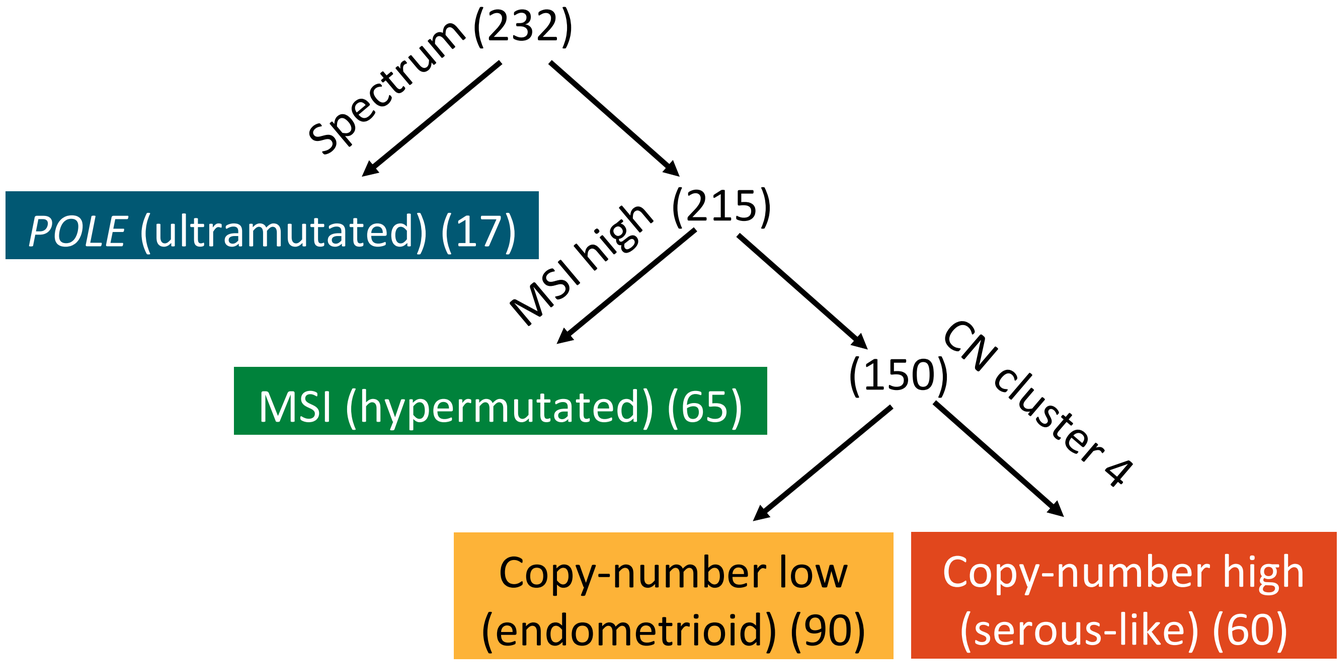
- In 2013, The Cancer Genome Atlas (TCGA) used genomic, transcriptomic, and proteomic analy

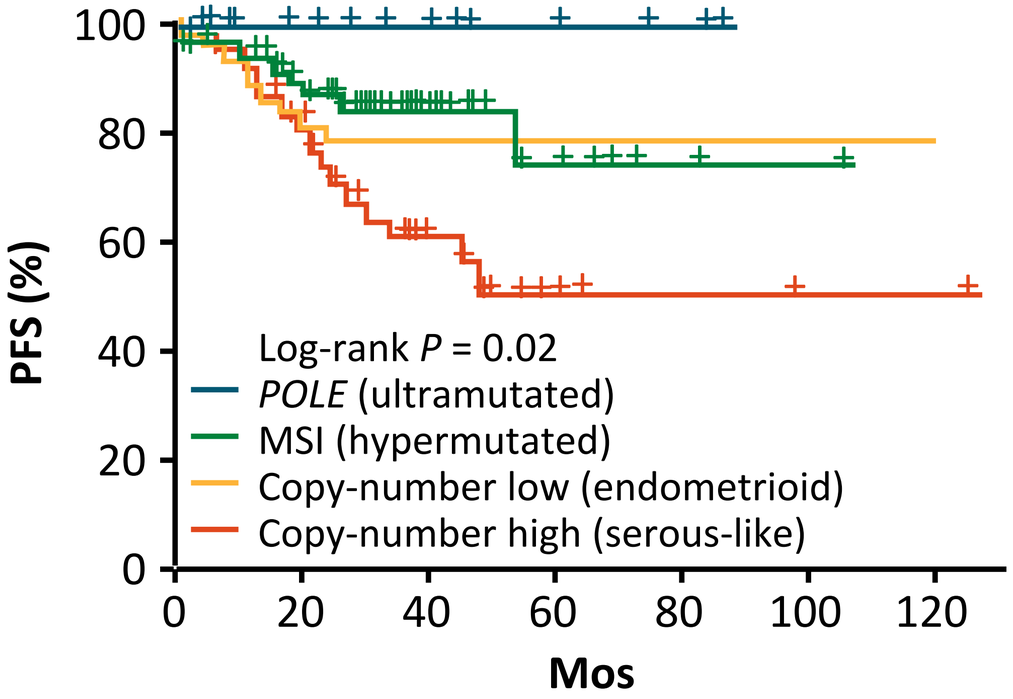


G Getz *et al. Nature* **497**, 67-73 (2013) doi:10.1038/nature12113

nature

The “Modern” Molecular Classification: TCGA Classification





- **POLE (ultramutated malignancies):**
  - Their hallmark are mutations in the exonuclease domain of POLE
  - POLE encodes the catalytic subunit of DNA polymerase epsilon which plays a relevant role in DNA repair.
- **MSI-High: Tumors that harbor a high rate of mutations resulting from impaired DNA MMR pathway:**
  - A DNA repair system that corrects errors such as single-base mismatches or short insertions and deletions that spontaneously occur during DNA replications
  - The most implicated genes are: MLH1, MSH2, MSH6, PMS2

Cancer Genome Atlas Research Network. Nature. 2013;497:67.

Slide credit: clinicaloptions.com

Beyond TCGA

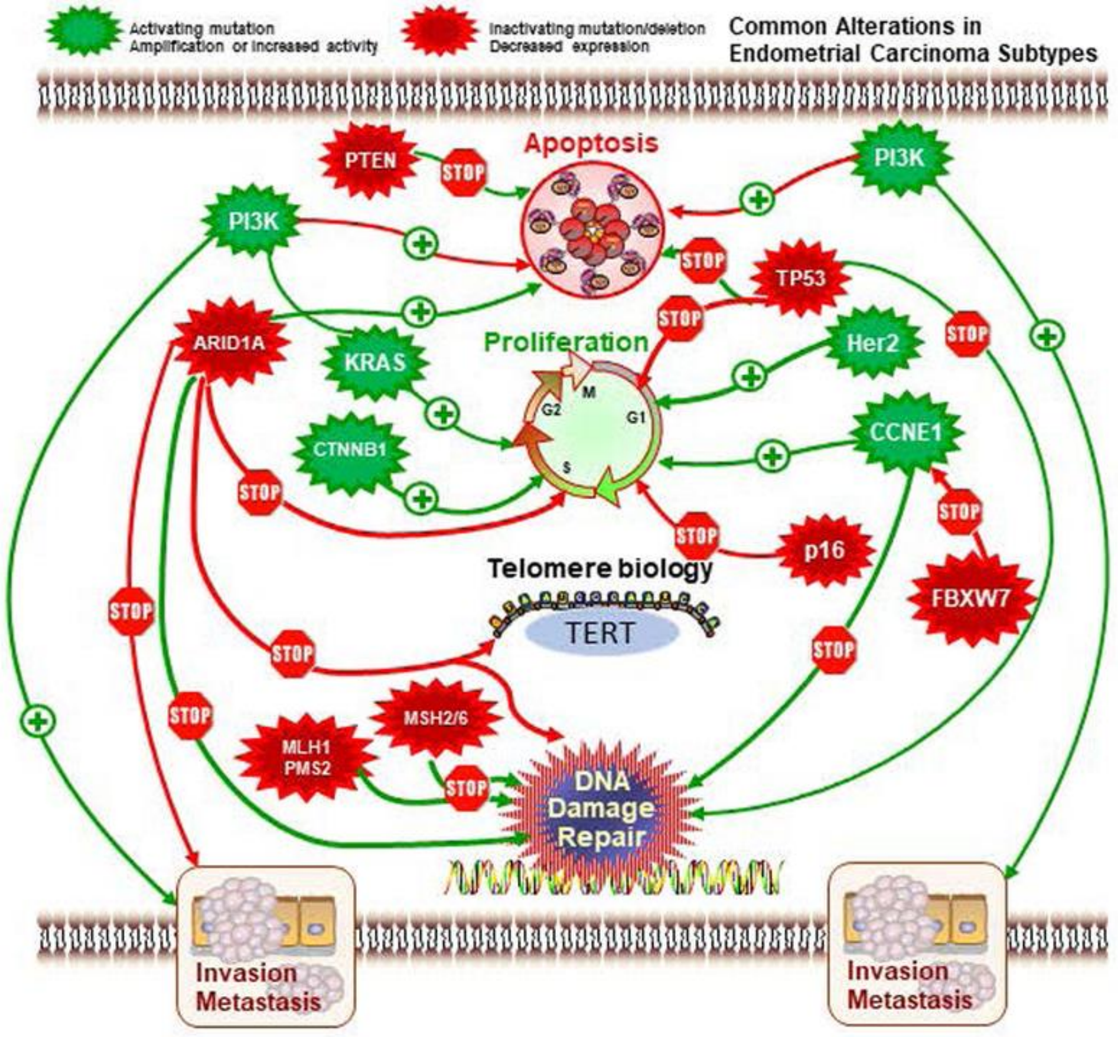
ProMise

- These four molecular subtypes provide insight into the pathogenesis of ECs and a framework for subclassification of ECs for interpretation of research endeavors and clinical trials but were not fully integrated into routine clinical practice due to concerns about cost and applicability.

- Subsequently, a clinically applicable molecular classification system that can be performed on standard formalin-fixed, paraffin-embedded material and serve as a surrogate for diagnosis of the four TCGA molecular subtypes was developed

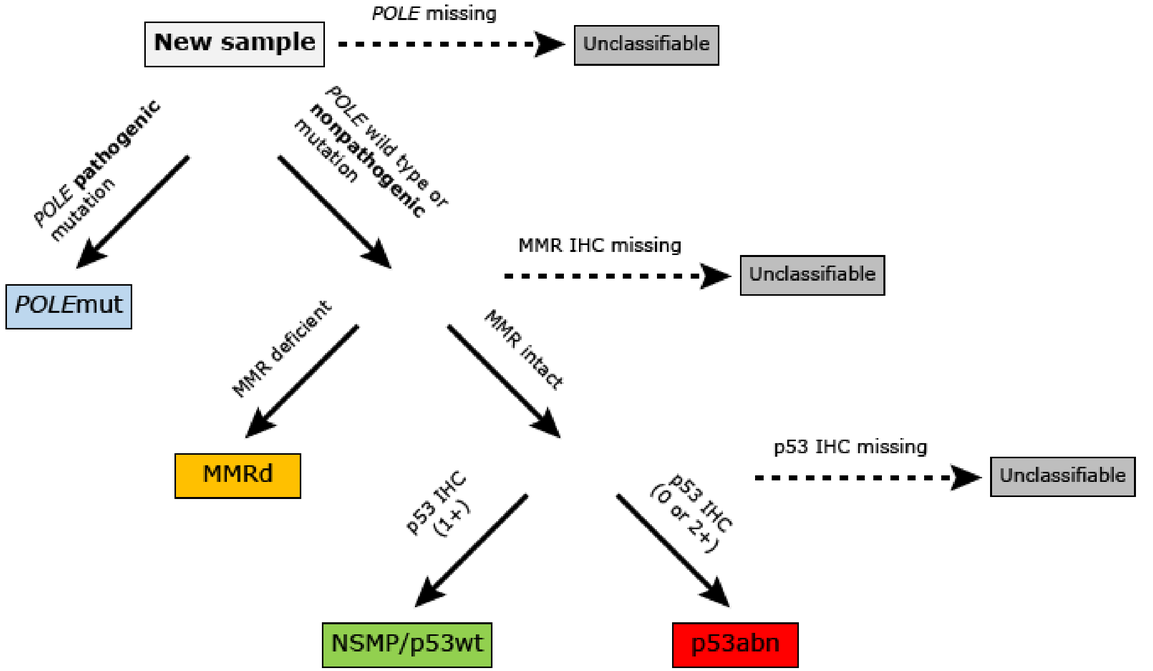
Ca Endometrium

PROMISE classification



Yen TT, Wang TL, Fader AN, Shih IM, Gaillard S. Molecular Classification and Emerging Targeted Therapy in Endometrial Cancer. International Journal of Gynecological Pathology : Official Journal of the International Society of Gynecological Pathologists. 2020 Jan;39(1):26-35. DOI: 10

Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) molecular classification figure [1-3]



ProMisE molecular classification figure. It is anticipated that all molecular tests will be performed on newly diagnosed ECs: diagnostic biopsies or hysterectomy specimens. Order of classification begins with first pulling out ECs with pathogenic *POLE* mutations,[1] next identifying women with mismatch repair deficiency (loss of MMR proteins on IHC), and finally identifying women with aberrant versus wild type p53 IHC staining.[2] Approximately 3% of ECs have more than one molecular classifying feature ("multiple-classifier" ECs). This order of segregation appropriately defines the predominant tumor biology and clinical behavior.[3]

POLE: DNA polymerase epsilon; mut: mutation; MMR: mismatch repair; IHC: immunohistochemistry; MMRd: mismatch repair deficient; NSMP: no specific molecular profile; wt: wildtype; abn: abnormal expression; EC: endometrial carcinoma.

References:

1. *León-Castillo A, Britton H, McConechy MK, et al. Interpretation of somatic POLE mutations in endometrial carcinoma. J Pathol 2020; 250:323.*
2. *Singh N, Piskorz AM, Bosse T, et al. p53 immunohistochemistry is an accurate surrogate for TP53 mutational analysis in endometrial carcinoma biopsies. J Pathol 2020; 250:336.*
3. *León-Castillo A, Gilvazquez E, Nout R, et al. Clinicopathological and molecular characterisation of 'multiple-classifier' endometrial carcinomas. J Pathol 2020; 250:312.*

PORTEC 3

J Clin Oncol

Aug 2020

original reports abstract

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

Alicia León-Castillo, MD[1]; Stephanie M. de Boer, MD[2]; Melanie E. Powell, MD[3]; Linda R. Mileshkin, MBBS[4]; Helen J. Mackay, MD[5]; Alexandra Leary, MD, PhD[6]; Hans W. Nijman, MD, PhD[6,7]; Naveena Singh, MD, MBBS[8]; Pamela M. Pollock, PhD[9]; Paul Bessette, MD[10]; Anthony Fyles, MD[11]; Christine Haie-Meder, MD[12]; Vincent T. H. B. M. Smit, MD, PhD[1]; Richard J. Edmondson, MD[13]; Hein Putter, MD[14]; Henry C. Kitchener, MD[13]; Emma J. Crosbie, MD, PhD[13]; Marco de Bruyn, PhD[7]; Remi A. Nout, MD[2]; Nanda Horeweg, MD, PhD[2]; Carien L. Creutzberg, MD, PhD[2]; and Tjalling Bosse, MD, PhD[1] on behalf of the TransPORTEC consortium

PURPOSE The randomized Adjuvant Chemoradiotherapy Versus Radiotherapy Alone in Women With High-Risk Endometrial Cancer (PORTEC-3) trial investigated the benefit of combined adjuvant chemotherapy and radiotherapy (CTRT) versus radiotherapy alone (RT) for women with high-risk endometrial cancer (EC). Because The Cancer Genome Atlas defined an EC molecular classification with strong prognostic value, we investigated prognosis and impact of chemotherapy for each molecular subgroup using tissue samples from PORTEC-3 trial participants.

METHODS Paraffin-embedded tissues of 423 consenting patients were collected. Immunohistochemistry for p53 and mismatch repair (MMR) proteins, and DNA sequencing for *POLE* exonuclease domain were done to classify tumors as p53 abnormal (p53abn), *POLE*-ultramutated (*POLE*mut), MMR-deficient (MMRd), or no specific molecular profile (NSMP). The primary end point was recurrence-free survival (RFS). Kaplan-Meier method, log-rank test, and Cox model were used for analysis.

Caption

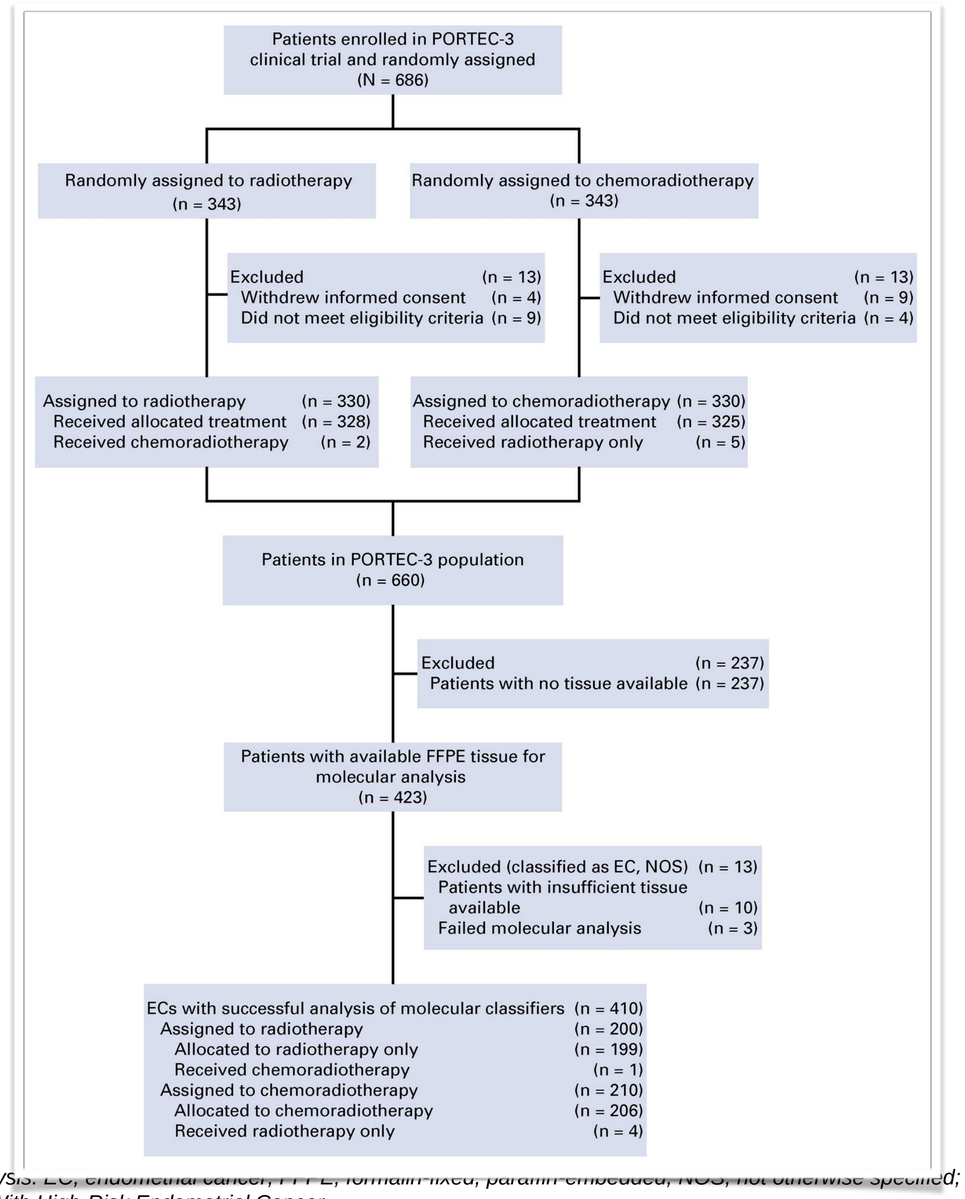


FIG 1. Flowchart of sample analysis. EC, endometrial cancer; FFPE, formalin-fixed, paraffin-embedded; NOS, not otherwise specified; PORTEC-3, Adjuvant Chemoradiotherapy Versus Radiotherapy Alone in Women With High-Risk Endometrial Cancer.

Published in: Alicia León-Castillo; Stephanie M. de Boer; Melanie E. Powell; Linda R. Mileshkin; Helen J. Mackay; Alexandra Leary; Hans W. Nijman; Naveena Singh; Pamela M. Pollock; Paul Bessette; Anthony Fyles; Christine Haie-Meder; Vincent T. H. B. M. Smit; Richard J. Edmondson; Hein Putter; Henry C. Kitchener; Emma J. Crosbie; Marco de Bruyn; Remi A. Nout; Nanda Horeweg; Carien L. Creutzberg; Tjalling Bosse; *Journal of Clinical Oncology* 2020 383388-3397.
DOI: 10.1200/JCO.20.00549

TABLE 1. Clinicopathological Features by Molecular Subgroup in High-Risk Endometrial Cancers

Characteristic	Total	p53abn	*POLE*mut	MMRd	NSMP	*P*
No. of patients	410 (100)	93 (22.7)	51 (12.4)	137 (33.4)	129 (31.5)	
Age, years						< .001
Mean (range)	61.2 (26.7-80.5)	65.8 (47.3-80.5)	57.2 (42.7-72.3)	60.6 (33.5-76.5)	60.1 (26.7-78.6)	
Histotype						< .001
EEC grade 1-2	161 (39.3)	4 (4.3)	4 (7.8)	59 (43.1)	94 (72.9)	
EEC grade 3	113 (27.6)	21 (22.6)	29 (56.9)	47 (34.3)	16 (12.4)	
Serous carcinoma	65 (15.9)	46 (49.5)	6 (11.8)	7 (5.1)	6 (4.7)	
Clear-cell carcinoma	39 (9.5)	12 (12.9)	6 (11.8)	12 (8.8)	9 (7.0)	
Mixed carcinoma	19 (4.6)	6 (6.5)	3 (5.9)	7 (5.1)	3 (2.3)	
Other	13 (3.2)	4 (4.3)	3 (5.9)	5 (3.6)	1 (0.8)	
Stage						< .001
IA	54 (13.2)	23 (24.7)	12 (23.5)	13 (9.5)	6 (4.7)	
IB	73 (17.8)	14 (15.1)	20 (39.2)	26 (19.0)	13 (10.1)	
II	105 (25.6)	24 (25.8)	7 (13.7)	33 (24.1)	41 (31.8)	
IIIA	46 (11.2)	8 (8.6)	2 (3.9)	10 (7.3)	26 (20.2)	
IIIB	29 (7.1)	4 (4.3)	4 (7.8)	13 (9.5)	8 (6.2)	
IIIC	103 (25.1)	20 (21.5)	6 (11.8)	42 (30.7)	35 (27.1)	
LVSI						.283
Absent	155 (37.8)	35 (37.6)	18 (35.3)	45 (32.8)	57 (44.2)	
Present	255 (62.2)	58 (62.4)	33 (64.7)	92 (67.2)	72 (55.8)	
Surgery						.398
TAH-BSO	135 (32.9)	29 (31.2)	12 (23.5)	39 (28.5)	55 (42.6)	
TAH-BSO + LND	162 (39.5)	38 (40.9)	24 (47.1)	57 (41.6)	43 (33.3)	
Laparoscopic	52 (12.7)	13 (14.0)	7 (13.7)	19 (13.9)	13 (10.1)	
Laparoscopic+ LND	61 (14.9)	13 (14.0)	8 (15.7)	22 (16.1)	18 (14.0)	
Lymphadenectomy						.199
No	187 (45.6)	42 (45.2)	19 (37.3)	58 (42.3)	68 (52.7)	
Yes	223 (54.4)	51 (54.8)	32 (62.7)	79 (57.7)	61 (47.3)	
Treatment						.424
RT	200 (48.8)	44 (47.3)	29 (56.9)	70 (51.1)	57 (44.2)	
CTRT	210 (51.2)	49 (52.7)	22 (43.1)	67 (48.9)	72 (55.8)	

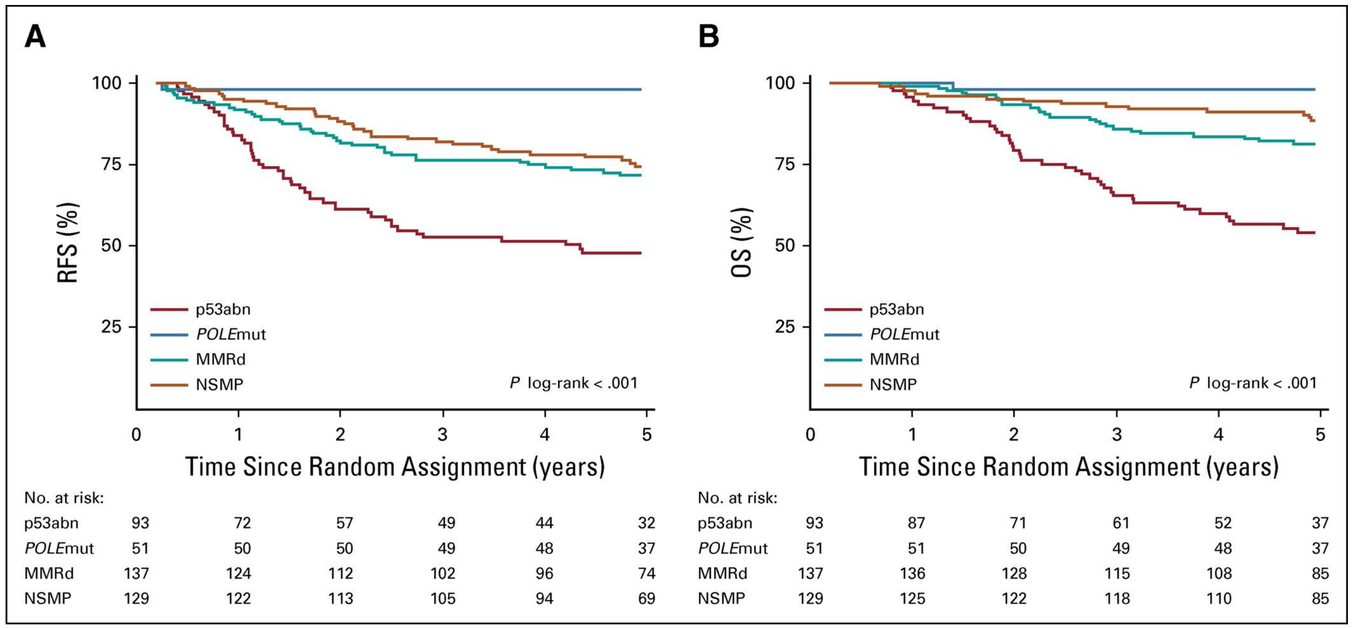
NOTE. Data reported as No. (%) unless otherwise indicated.

Abbreviations: CTRT, combined adjuvant chemotherapy and radiotherapy; EEC, endometrioid endometrial carcinoma; LND, lymph node dissection; LVSI, lymphovascular space invasion; MMRd, MMR-deficient; NSMP, no specific molecular profile; p53abn, p53-abnormal; *POLE*mut, POLE-ultramutated; RT, external beam radiotherapy alone; TAH-BSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy.

TABLE 2. Univariable and Multivariable Analysis of Molecular Subgroups and Clinicopathological Features in High-Risk Endometrial Cancers (N = 410)

		Recurrence-Free Survival (n = 127 events)						Overall Survival (n = 92 events)					
		Univariable Analysis			Multivariable Analysis			Univariable Analysis			Multivariable Analysis		
Parameter	Total No.	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age		1.052	1.028 to 1.075	< .001	1.037	1.013 to 1.061	.002	1.078	1.049 to 1.108	< .001	1.060	1.029 to 1.091	< .001
Molecular subgroups													
MMRd	137	1			1			1			1		
p53abn	93	2.448	1.607 to 3.728	< .001	2.517	1.621 to 3.907	< .001	2.622	1.647 to 4.173	< .001	2.298	1.418 to 3.726	.001
*POLE*mut	51	0.060	0.008 to 0.441	.006	0.079	0.011 to 0.576	.012	0.083	0.011 to 0.606	.014	0.118	0.016 to 0.868	.036
NSMP	129	0.993	0.632 to 1.562	.977	0.976	0.620 to 1.537	.917	0.581	0.320 to 1.053	.073	0.547	0.302 to 0.993	.047
Histology and grade													
Endometrioid, grade 1-2	161	1			1			1			1		
Endometrioid, grade 3	132	0.956	0.626 to 1.461	.837	1.067	0.646 to 1.762	.800	1.571	0.936 to 2.636	.087	1.463	0.814 to 2.628	.203
Nonendometrioid	117	1.239	0.816 to 1.882	.314	0.822	0.465 to 1.453	.500	1.997	1.198 to 3.328	.008	0.982	0.503 to 1.919	.958
Stage													
I-II	232	1			1			1			1		
III	178	1.868	1.315 to 2.654	< .001	2.186	1.518 to 3.148	< .001	1.545	1.026 to 2.328	.037	1.914	1.256 to 2.919	.003
LVSI													
Absent	155	1			1			1			1		
Present	255	1.492	1.023 to 2.175	.038	1.299	0.878 to 1.921	.191	1.560	0.996 to 2.444	.052	1.219	0.753 to 1.974	.420
Treatment													
RT	200	1			1			1			1		
CTRT	210	0.824	0.582 to 1.168	.277	0.700	0.493 to 0.993	0.046	0.817	0.542 to 1.230	0.333	0.726	0.481 to 1.096	.127

Abbreviations: CTRT, combined adjuvant chemotherapy and radiotherapy; HR, hazard ratio; LVSI, lymphovascular space invasion; MMRd, MMR-deficient; NSMP, no specific molecular profile; p53abn, p53-abnormal; POLEmut, POLE-ultramutated; RT, external beam radiotherapy alone.



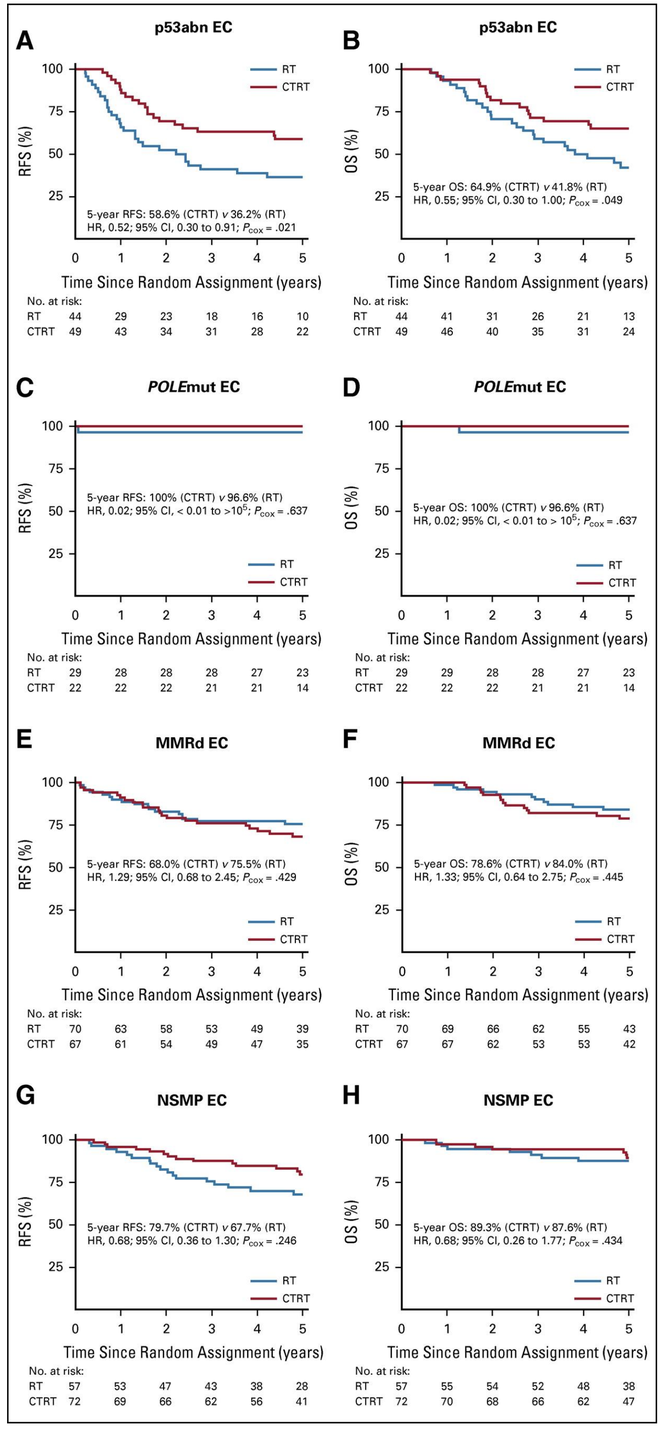


FIG 3. Kaplan-Meier survival curves for (A) recurrence-free survival (RFS) and (B) overall survival (OS) among patients with p53abn endometrial cancer (EC); (C) RFS and (D) OS among patients with POLEmut EC; (E) RFS and (F) OS among patients with MMRd EC; and (G) RFS and (H) OS among patients with NSMP EC. CTRT, combined adjuvant chemotherapy and radiotherapy; HR, hazard ratio; MMRd, MMR-deficient; NSMP, no specific molecular profile; p53abn, p53-abnormal; Pcox, P value by Cox regression analysis; POLEmut, POLE-ultramutated tumor; RT, external beam radiotherapy alone.

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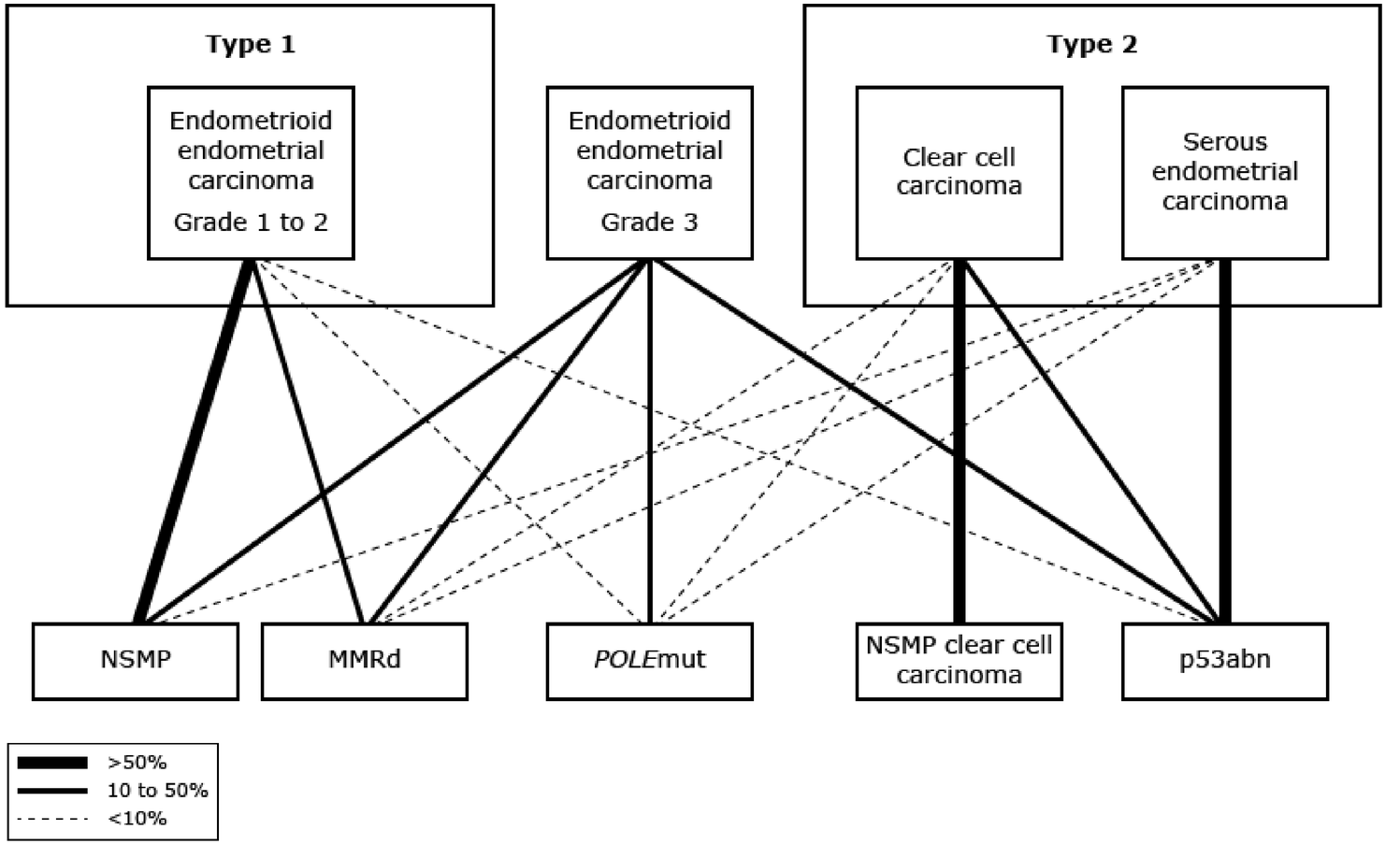
DOI: 10.1200/JCO.20.00549

Type 1 and 2 classification and relationship to histomorphologic and molecular endometrial carcinoma classification



The relationship between type 1/2 endometrial carcinoma, histomorphologic classification, and molecular classification. The thickness of the lines between boxes indicates the percentage of type 1 or type 2 carcinomas that are of the corresponding molecular subtypes below. Note that grade 3 endometrioid endometrial carcinoma is considered to be type 1 by some authors and type 2 by others and has therefore been left separate from either of these categories.

NSMP: no specific molecular profile; MMRd: mismatch repair deficient; *POLE*: DNA polymerase epsilon; mut: mutation; abn: abnormal expression.

Courtesy of Jessica N McAlpine, MD, and Jutta Huvila, MD, PhD.

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Table 2

Definition of prognostic risk groups

Risk group	Molecular classification unknown	Molecular classification known*†
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

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Recommendations (Adjuvant treatment)

LOW RISK	• No adjuvant treatment is recommended (I, A).	• ► When molecular classification is known: – 1.For patients with endometrial carcinoma stage I–II, low-risk based on pathogenic POLE-mutation, omission of adjuvant treatment should be considered (III, A). – 2.For the rare patients with endometrial carcinoma stage III–IVA and pathogenic POLE-mutation, there are no out-come data with the omission of the adjuvant treatment. Prospective registration is recommended (IV, C).
INTERMEDIATE RISK	• Adjuvant brachytherapy can be recommended to decrease vaginal recurrence (I, A). • Omission of adjuvant brachytherapy can be considered (III, C), especially for patients aged <60 years (II, A).	• ► When molecular classification is known, POLEmut and p53abn with myometrial invasion have specific recommendations (see respective recommendations for low- and high-risk). • ► For p53abn carcinomas restricted to a polyp or without myome- trial invasion, adjuvant therapy is generally not recommended (III, C).
HIGH INTERMEDIATE RISK(pN0)	• Adjuvant brachytherapy can be recommended to decrease vaginal recurrence (II, B). • EBRT can be considered for substantial LVSI and for stage II (I, B). • Adjuvant chemotherapy can be considered, especially for high- grade and/or substantial LVSI (II, C). • Omission of any adjuvant treatment is an option (IV, C).	• When molecular classification is known, POLEmut and p53abn have specific recommendations (see respective recommenda- tions for low- and high-risk).
HIGH INTERMEDIATE RISK(cN0,pNx)	• Adjuvant EBRT is recommended, especially for substantial LVSI and/or for stage II (I, A). • ► Additional adjuvant chemotherapy can be considered, espe- cially for high-grade and/or substantial LVSI (II, B). • ► Adjuvant brachytherapy alone can be considered for high-grade LVSI negative and for stage II grade 1 endometrioid carcinomas (II, B).	• When molecular classification is known, POLEmut and p53abn have specific recommendations (see respective recommenda- tions for low- and high-risk).
HIGH RISK	• EBRT with concurrent and adjuvant chemotherapy (I, A) or alternatively sequential chemotherapy and radiotherapy is recommended (I, B). • ► Chemotherapy alone is an alternative option (I, B). • ► Carcinosarcomas should be treated as high-risk carcinomas (not as sarcomas) (IV, B).	• When the molecular classification is known, p53abn carci- nomas without myometrial invasion and POLEmut have specific recommendations (see respective recommendations for low- and intermediate-risk) (III, C).

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Recommendations (Molecular classification)

- The decision to use molecular classification in all endometrial carcinoma cases in the subse
- Molecular classification is recommended to be performed by the TCGA surrogate using the

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Summary

Five categories of tumors are recognized:
(1) ultramutated/with pathogenic POLE mutations;
(2) hypermutated with MSI/MMRd (loss of MMR protein immunoreactivity);
(3) high copy number/p53abn (p53 mutant immunoreactive pattern);
(4) low copy number/NSMP (retained MMR protein immunoreactivity, and p53 wild-type immunoreactive pattern);
(5) multiple classifier (any combination of markers included in the previous categories).

Molecular subtypes of endometrial carcinoma: Molecular, pathologic, and clinical features[1-19]

TCGA category	Molecular classification	Molecular features (diagnostic tests)	Pathology features	Clinical features	Outcomes	Treatment options
***POLE* "ultramutated"** (approximately 7% of TCGA)	***POLE*mut** (approximately 7 to 9% of all ECs)	▪ Markedly high TMB ▪ >100 mut/Mb ▪ SCNA very low ▪ *PTEN* mutations (94%) ▪ (*POLE* EDM or hotspot sequencing)	Commonly high grade, LVSI, aggressive features, "ambiguous morphology" prominent TIL, EEC G3-2-1* but can be any	Presents in younger, often thinner women	Highly favorable (>96% five-year survival)	▪ Observation only may be reasonable, even if high-risk features. Clinical trials are needed to establish safety and efficacy. ▪ Checkpoint inhibitors for rare advanced/recurrent
MSI "hypermutated" (approximately 28% of TCGA)	**MMRd** (26 to 30% of all ECs)	▪ 10 to 100 mut/Mb ▪ SCNA low ▪ *PTEN* (88%), *PIK3CA* (54%), *ARID1A* (37%) mutations ▪ (MMR IHC: PMS2, MSH6, ±MSH2, and MLH1; or MSI assay)	LVSI and higher grade, prominent TIL, MELF, EEC G2/3-1* but can be any	Lynch syndrome association	Intermediate	▪ Radiation ▪ Checkpoint inhibitors if advanced/recurrent
Copy-number low (approximately 39% of TCGA)	**p53wt/NSMP** (45 to 50% of all ECs)	▪ Low TMB (<10 mut/Mb) ▪ SCNA low ▪ *PTEN* (77%), *PIK3CA* (53%), *CTNNB1* (52%), *ARID1A* (42%) mutations ▪ ER+ PR+ ▪ (p53 IHC: wt [normal expression] and absence of *POLE*mut or MMRd)	Squamous differentiation, low TIL, mostly low-grade EEC G1-2-3*	Often presents in younger individuals with higher BMI or exogenous estrogen	Intermediate-favorable	▪ Hormonal therapy ▪ PI3K/mTOR inhibitors?
Copy-number high (approximately 26% of TCGA)	**p53abn** (13 to 18% of all ECs)	▪ Low TMB (<10 mut/Mb) ▪ SCNA high ▪ *PIK3CA* (47%), *PPP2R1A* (22%), *FBXW7* (22%) mutations ▪ (p53 IHC: abnormal or *TP53* mutation)	LVSI, high cytonuclear atypia, mostly high grade, mostly serous but approximately 25% EEC G3	Presents in older, thinner, women; commonly advanced stage	Poor (approximately 50% five-year survival)	▪ Chemotherapy ▪ *HER2*-targeted or *HRD*-targeted therapy?

Molecular subtypes

Ultramutated/DNA polymerase epsilon (*POLE*) mutated group (*POLE*mut)

– These are copy number (CN) stable ECs with recurrent mutations in the exonuclease domain of *POLE*, a gene involved in DNA replication and repair [59-62]. These tumors have one of the highest somatic mutation frequencies of any solid tumors, frequently exceeding 100 mutations per megabase (Mb). Often, but not exclusively, of endometrioid histologic type, *POLE*mut ECs have prominent tumor-infiltrating lymphocytes (TILs).

Patients with *POLE*mut ECs tend to be younger and thinner, and despite often having seemingly aggressive pathologic features (eg, high-grade, lymphovascular space invasion), they have highly favorable outcomes (>96 percent five-year survival) confirmed across multiple studies [63-67].

In an individual patient data meta-analysis of all *POLE*mut ECs, adjuvant therapy was not associated with improved outcomes for women with pathogenic *POLE* mutations, supporting de-escalation of therapy in clinical trials [67]. Two prospective studies assessing the possibility of de-escalation of therapy are ongoing: (1) PORTEC-4a is a multicenter randomized phase III trial in patients with high-intermediate risk EC [68-70], and (2) Tailored Adjuvant Therapy in *POLE*-mutated and p53-wildtype/no specific molecular profile (NSMP) Early Stage Endometrial Cancer (TAPER) is a prospective cohort study in early-stage EC [67,70].

Immunotherapy may be an option in these rare cases of recurrent *POLE*mut ECs given the high observed TIL [71-73].

Molecular subtypes

- **Hypermutated/microsatellite unstable group (MMRd)**

- These tumors have low levels of somatic CN alterations but a very high mutational burden and high TIL secondary t
- Epigenetic silencing of MLH1 is responsible for the majority of this subgroup, but it also includes both somatic and g

- The receptor tyrosine kinase (RTK)/RAS/beta-catenin pathways and phosphatase and tensin homolog (*PTEN*)/phos

Molecular subtypes

- **Copy number low group (NSMP)**

- A third group of genomically stable, MMR proficient, moderate mutational load ECs (frequently involving PI3K/Akt and Wnt/catenin beta 1 [*CTNNB1*] signaling pathways) was identified with intermediate to favorable outcomes.
- These lack tumor protein 53 (*TP53*) mutation and are also referred to as p53-wildtype (p53wt).
- This group encompasses mostly endometrioid neoplasms with estrogen and progesterone receptor (ER, PR) positivity and high response rates to hormonal therapy.

Molecular subtypes

Copy number high (serous-like) group (p53abn)

- The fourth molecular subgroup had high somatic CN alterations and mutational profiles, similar to high-grade serous ovarian and basal-like breast carcinomas*. TP53* mutations are characteristic for this group. The p53abn cases are associated with a poor prognosis and responsible for 50 to 70 percent of endometrial cancer mortality.
- Human epidermal growth factor receptor 2 (*HER2*) amplification was reported in approximately 20 to 25 percent of CN high ECs, and subsequently, >40 percent of CN high ECs were found to have homologous recombination deficiency (HRD) based on *RAD51* foci formation, with a lower percentage showing HRD based on mutational signatures
- . Antiangiogenic agents may also add value in advanced or recurrent p53abn EC

- The proportion of p53abn ECs for each histologic type are as follows: serous carcinoma (93 percent), carcinosarcoma (85 percent), clear cell carcinoma (38 percent), type II EC (grade 3; 22 percent), and type I EC (grade 1 or 2; 5 percent) [81].
- Data from patients enrolled in the PORTEC-3 trial suggest that ECs with p53 abnormalities are associated with superior outcomes when treated with chemotherapy in addition to radiation as compared with radiation alone [47]. Attempts to capitalize on other molecular features within this molecular subclass (eg, *HER2* amplification, HRD) are ongoing [54,55,82].

- Breast cancer susceptibility genes (*BRCA1/2*) mutation carriers have an increased risk for p53abn EC, with the highest risk for *BRCA1* mutation carriers [83].

Ca Endometrium

Implications of molecular classification

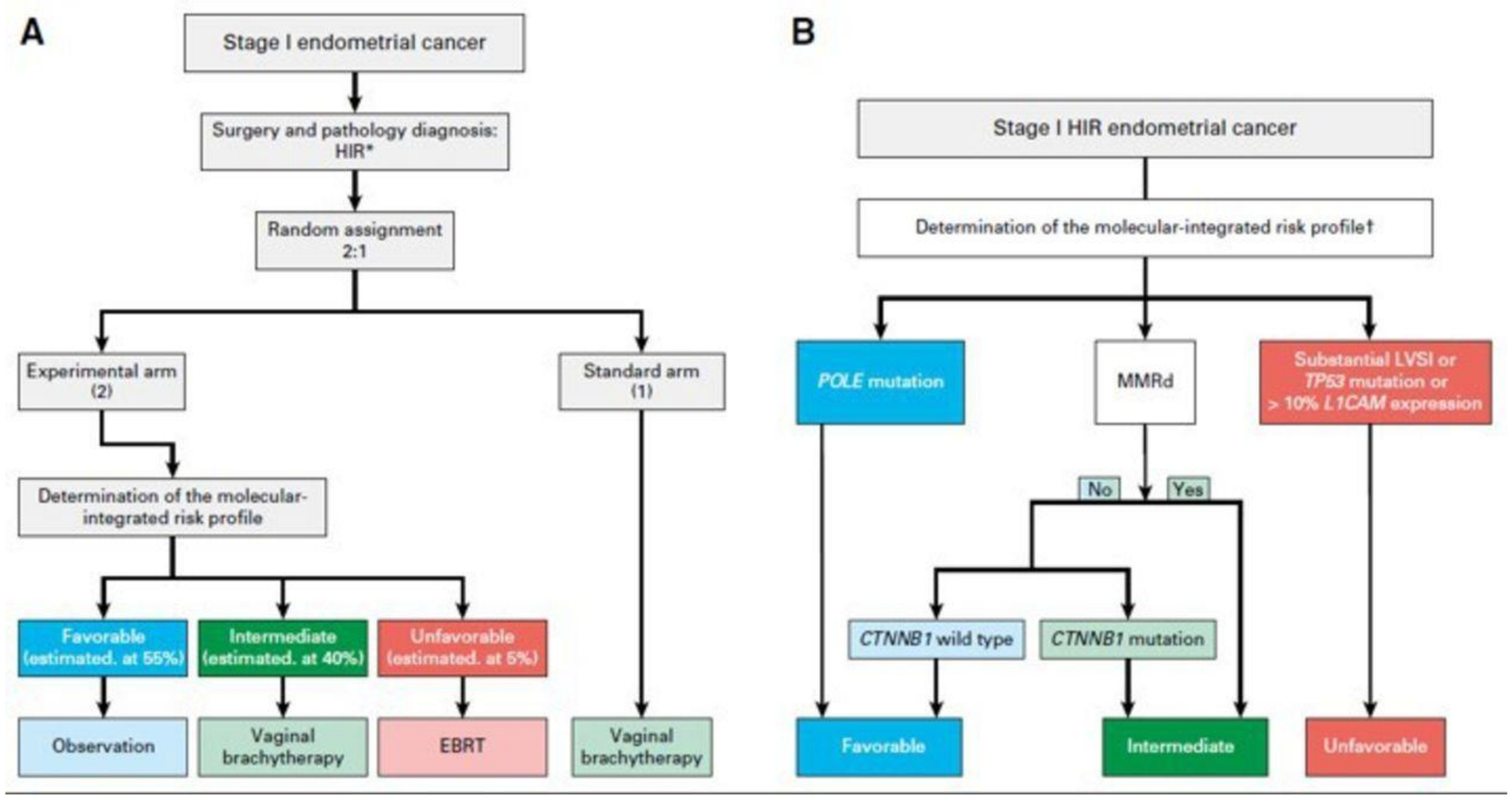
Prognosis

Adjuvant treatment

Ca Endometrium

PORTEC 4a

Study design PORTEC-4a trial.



Anne Sophie V M van den Heerik et al. Int J Gynecol Cancer 2020;30:2002-2007

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

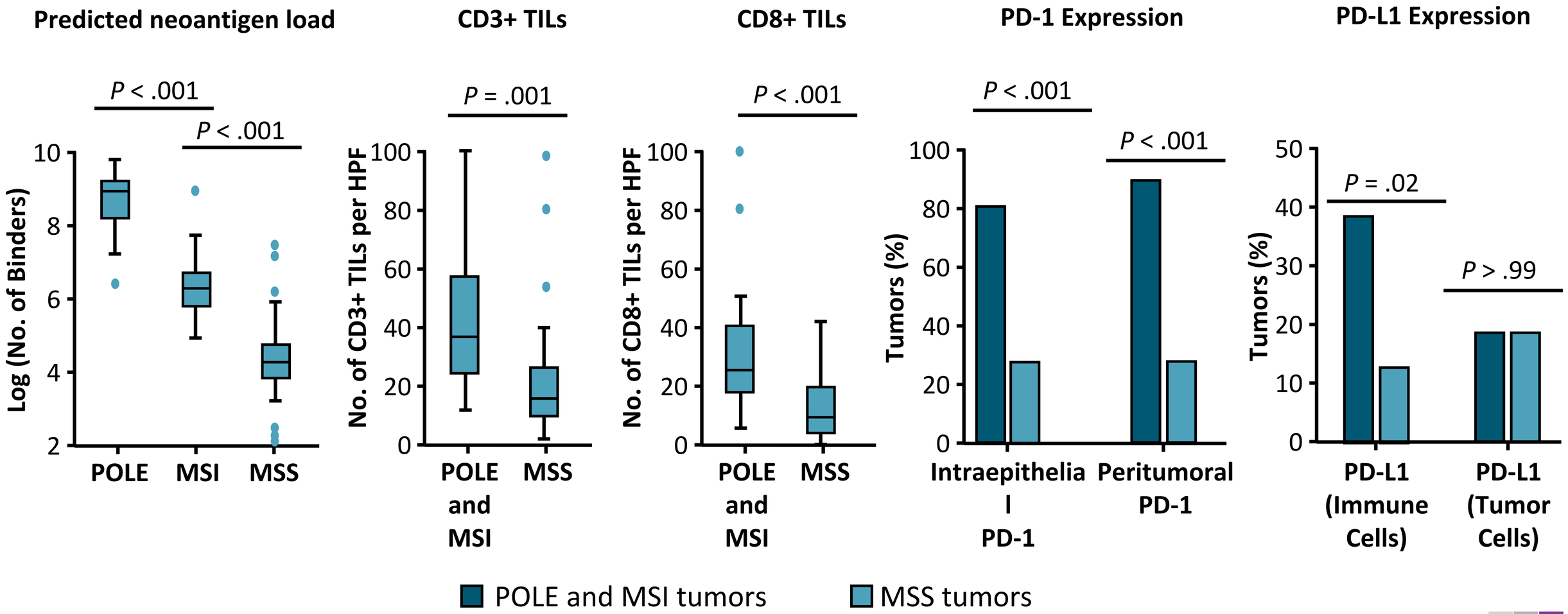
Tumor Type*	MSI-High, %
Uterine corpus endometrial	28.3
Stomach adeno	21.9
Colon adeno	16.6
Rectal adeno	9.2
Adrenal cortical	5.4
Esophageal	3.3
Ovarian	3.2
Hepatocellular	2.9
Cervical squamous	2.3

*At least 2% MSI-High incidence

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

Slide credit: clinicaloptions.com

Rationale for Immunotherapy in Endometrial Carcinoma



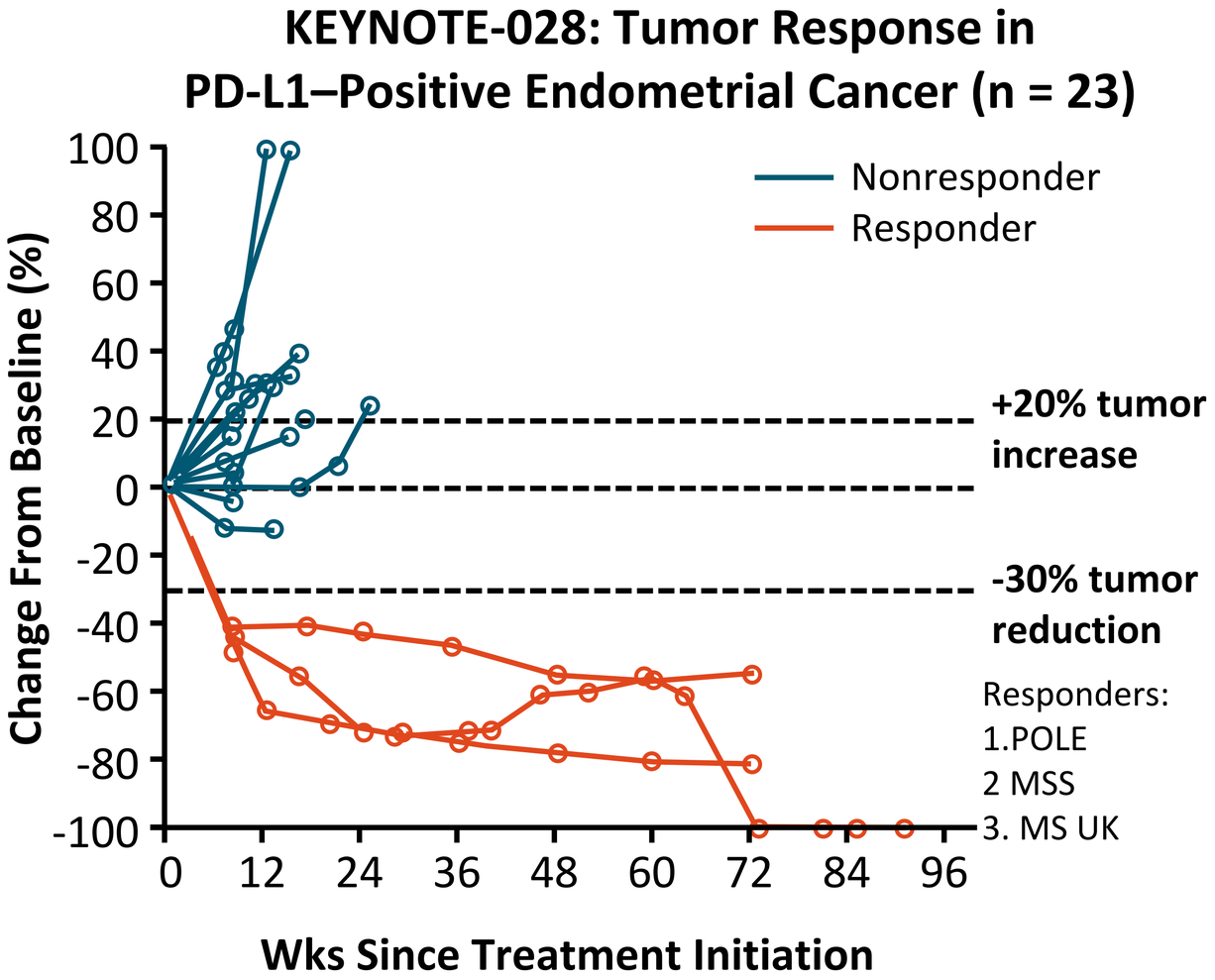
Howitt. JAMA Oncol. 2015;1:1319.

Slide credit: clinicaloptions.com

Clinical Data of Immunotherapy in Advanced/Recurrent Endometrial Cancer

Preliminary Evidence of Pembrolizumab Activity in Endometrial Carcinoma

- KEYNOTE-016: ORR of 71% in dMMR noncolorectal cancer cohort (n = 7, including 2 patients with endometrial cancer)
- Pooled analysis of 5 multicohort, single-arms trials of pembrolizumab that enrolled patients with previously treated MSI-H/dMMR solid tumors
  - ORR of 36% in 14 patients with endometrial cancer



Le. NEJM. 2015;372:2509. Pembrolizumab. PI. Ott. .JCO. 2017; 35:2535.

Slide credit: clinicaloptions.com

KEYNOTE-158: Pembrolizumab for Advanced Endometrial Cancer

Patients with unresectable or metastatic endometrial cancer with progression on or intolerance to standard therapy; ECOG PS 0 or 1; evaluable tumor for biomarker assay; no autoimmune disease or noninfectious pneumonitis

→ **Pembrolizumab 200 mg IV Q3W** →

Up to 35 cycles or until PD, unacceptable toxicity, consent withdrawal

Cohort D: endometrial cancer
Cohort K: non-CRC, MSI-H solid tumor

- Primary endpoint: ORR by central review using RECIST v1.1 criteria
  - Response assessed every 9 wks in Yr 1; every 12 wks thereafter
- Secondary endpoints: PFS, OS, DoR, safety

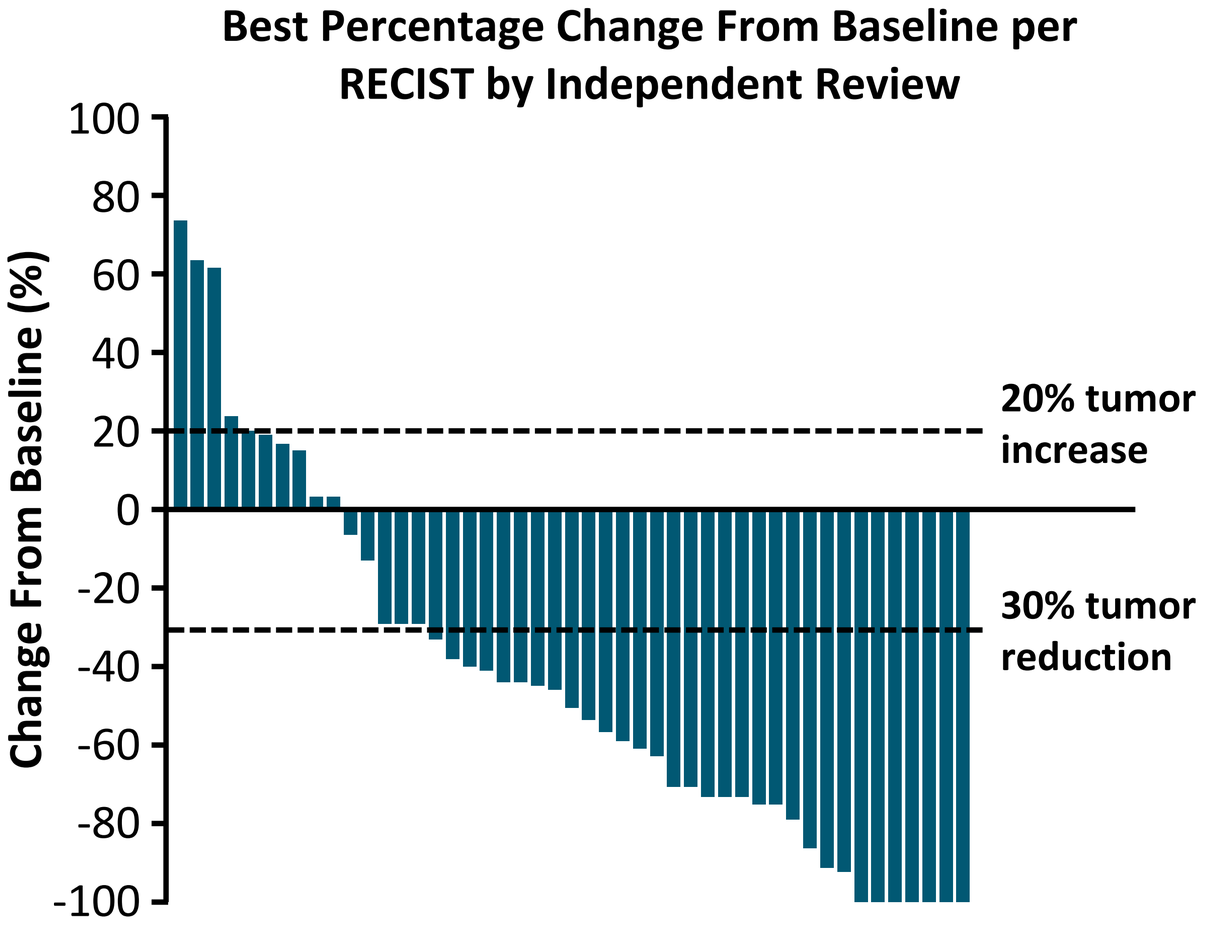
O'Malley ESMO 2019. Abstr 3394.

Slide credit: clinicaloptions.com

KEYNOTE-158: Antitumor Activity in Patients With MSI-H Advanced EC

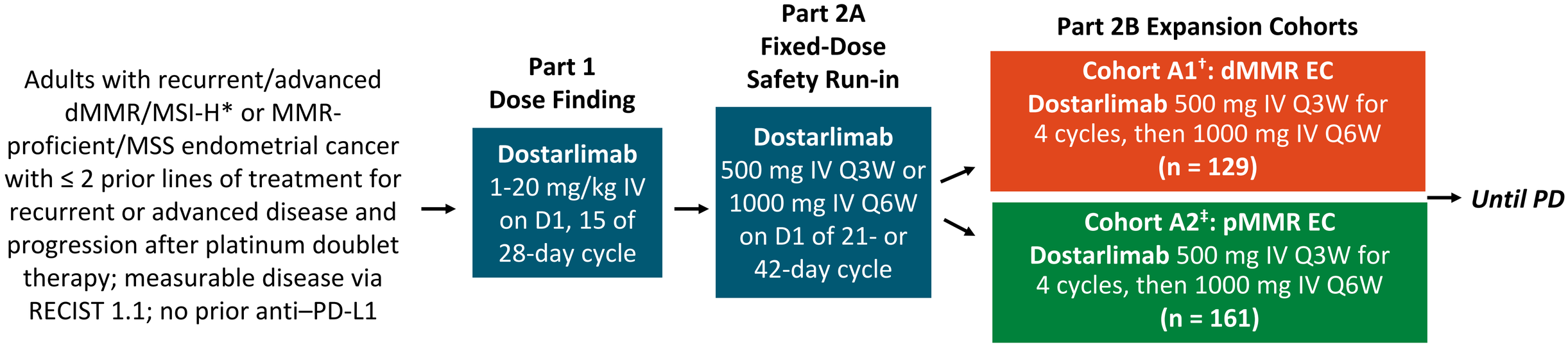
Confirmed Objective Response per RECIST v1.1 by IRC	MSI-H EC, N = 49 (Cohorts D + K)	EC, N = 107 (Cohort D, biomarker unselected)
ORR, % (95% CI)	57.1 (42.2-71.2)*	11.2 (5.9-18.8)
Best overall response n (%)		
CR	8 (16.3)	0
PR	20 (40.8)	12 (11.2)
Stable disease	8 (16.3)	26 (24.3)
Progressive disease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

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



GARNET: Dostarlimab (TSR-042) Monotherapy in Endometrial Cancer

- Multicenter, open-label, single-arm phase I study



- Primary endpoint: ORR
- Secondary endpoints: DoR, DCR

*Tumor MMR/MSI screening based on local MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but patient eligibility needs to be confirmed by MMR IHC results.
†Includes 3 patients with MMRunk/MSI-H disease.
‡Includes 16 patients with MMRunk/MSS disease.

Oaknin. ESMO 2020. Abstr LBA36. Oaknin. JAMA Oncol. 2020;6:1. NCT02715284.

GARNET: Response Outcomes

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

Variable
Median follow-up time, mos
Objective response rate,* n (%, 95% CI)
CR, n (%)
PR, n (%)
Stable disease, n (%)
Progressive disease, n (%)
Not evaluable, n (%)
Not done, n (%)
Disease control rate,† n (%, 95% CI)
Response ongoing, n (%)
Median duration of response, mos (range)
Kaplan-Meier estimated probability of remaining in response, %
At 6 mos
At 12 mos
At 18 mos

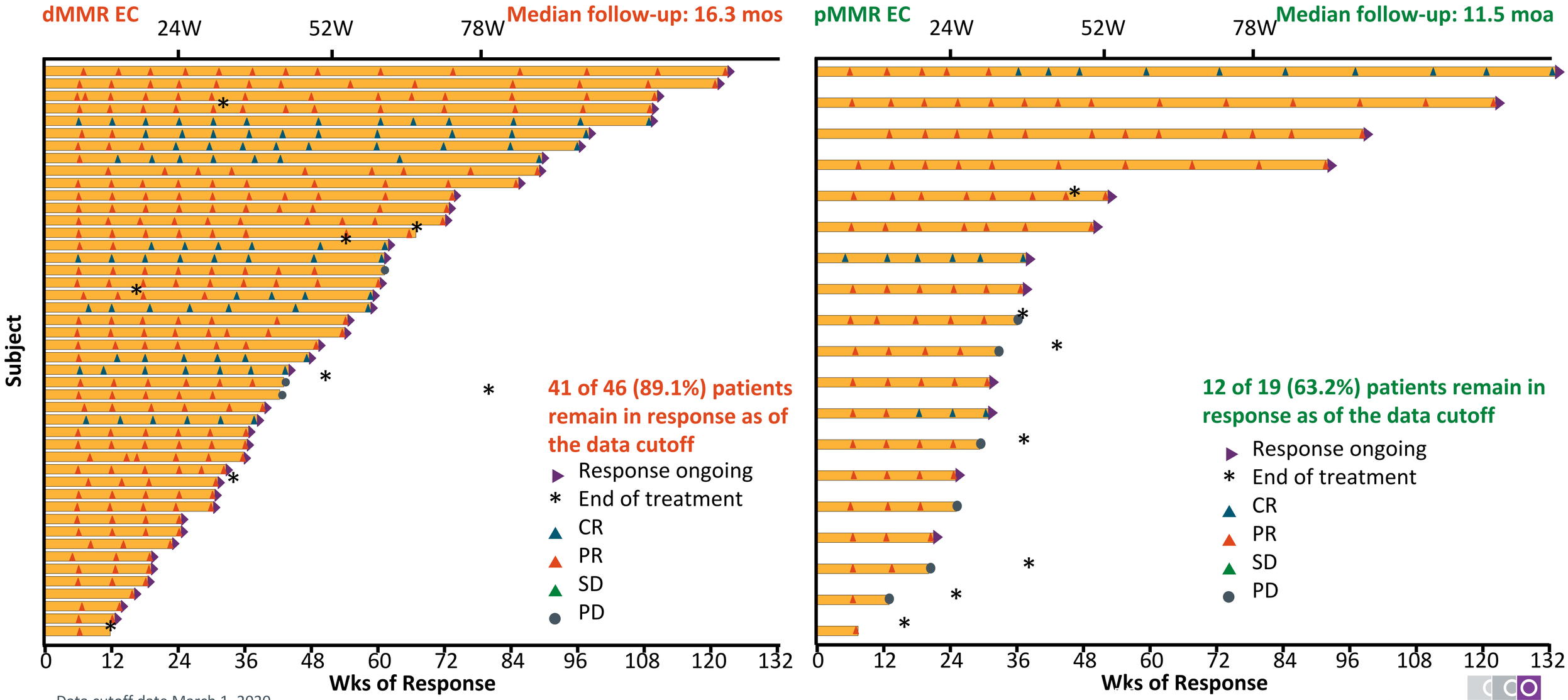
*Responses required confirmation at a subsequent scan; SD had to be observed at ≥ 12 wks on study to qualify as SD; †Includes confirmed CR, PR, or SD at ≥ 12 wks.

Oaknin. ESMO 2020. Abstr LBA36.

Slide credit: clinicaloptions.com

GARNET: Duration of Response

- Measured from first observed response (PR or CR), this response is not shown on the figure



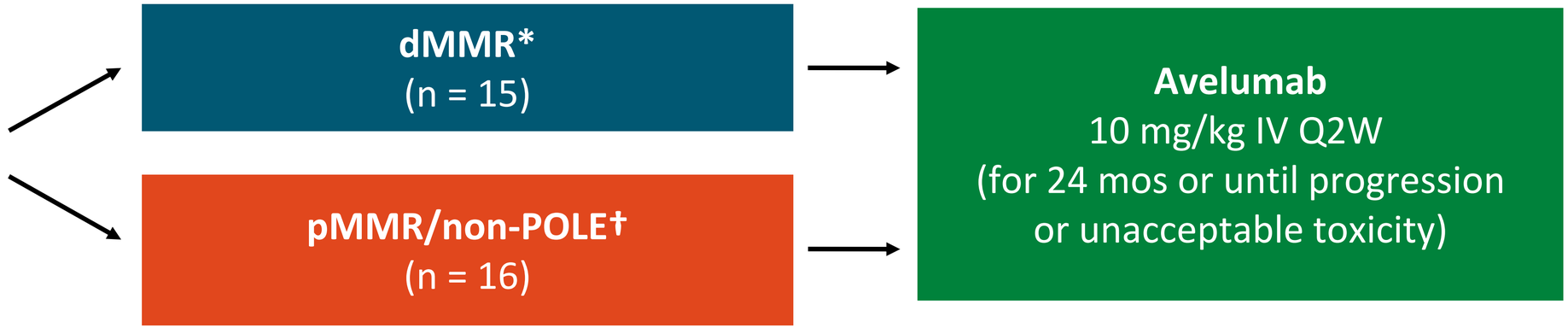
Data cutoff date March 1, 2020.

Oaknin. ESMO 2020. Abstr LBA36.

Slide credit: clinicaloptions.com

Phase II Trial of Avelumab in Patients With dMMR and pMMR Recurrent/Persistent EC

Recurrent/persistent endometrial cancer of any histology, ≥ 1 previous chemotherapy regimen, ECOG PS 0/1, no previous ICI, no brain metastases



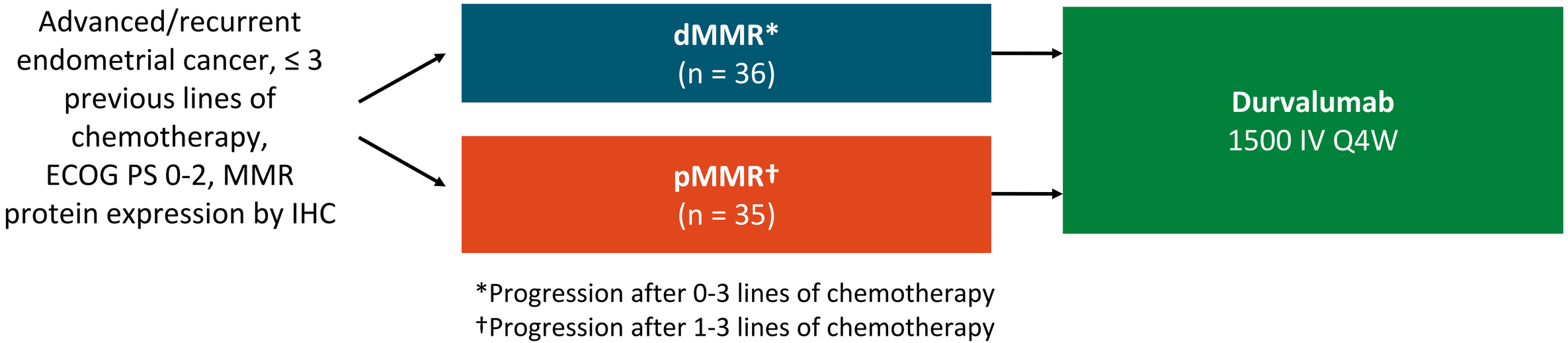
*Complete loss of 1 or more MMR proteins determined by IHC and/or POLE-mutated tumors; no patients had a documented POLE mutation.

†Normal IHC for all MMR proteins; pMMR with unknown POLE status; a 2-stage trial design allowed for early stop due to futility for each cohort; the pMMR cohort was closed after the first stage after accrual of 16 patients.

Primary endpoint: ORR, PFS at 6 mos

Konstantinopoulos. JCO. 2019;37:2786.

PHAEDRA Phase II Trial of Durvalumab in Patients With Advanced EC and dMMR or pMMR



Primary endpoint: OTR by iRECIST

Secondary endpoints: PFS, OS, ORR by RECIST 1.1, safety, QoL

Antill. ASCO 2019. Abstr 5501. Antill. ESMO 2019. Abstr LBA12.

Slide credit: clinicaloptions.com

Combination Checkpoint Inhibitor Studies in Advanced/Recurrent Endometrial Cancer

Checkpoint Inhibitors Plus Antiangiogenic Agents

KEYNOTE-146[1]

KEYNOTE-775 (phase III)[2]

ENGOT-en9/LEAP-001 (phase III)[3]

Pembrolizumab + Lenvatinib

NCT03367741[4]:

Nivolumab + Cabozantinib

Checkpoint Inhibitors Plus Chemotherapy

NRG-GY018[5]:

Pembrolizumab + Paclitaxel/Carboplatin

AtTEnd/ENGOT-en7[6]:

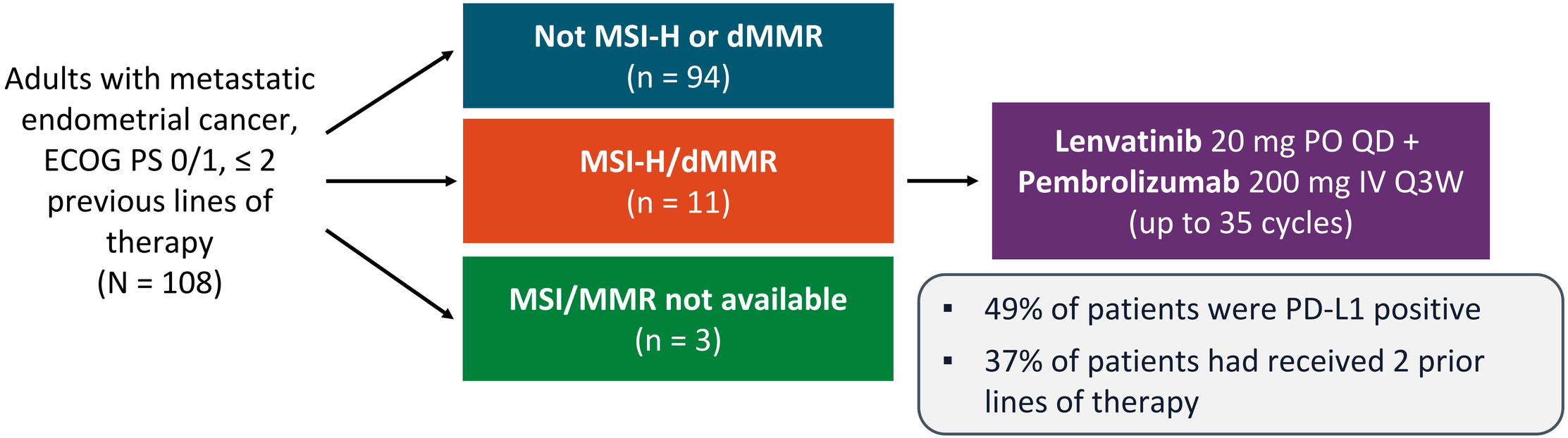
Atezolizumab + Paclitaxel/Carboplatin

RUBY (ENGOT-EN6; GOG-3031)[7]:

Dostarlimab + Chemotherapy

1. Makker. JCO. 2020; 38: 2981. 2. NCT03517449. 3. NCT03884101. 4. NCT03367741. 5. NCT03914612. 6. NCT03603184. 7. NCT03981796.

Phase Ib/II KEYNOTE-146: Pembrolizumab + Lenvatinib in Patients With Previously Treated EC



Primary endpoint: ORR at Wk 24 (responses confirmed with secondary assessment > 4 wks later)

Secondary endpoints: ORR, DoR, PFS, OS, DCR, CBR, safety

Makker. JCO. 2020; 38: 2981.

Slide credit: clinicaloptions.com

KEYNOTE-146: ORR at Wk 24 (Primary Endpoint)

Investigator Assessment per irRECIST	Total (n = 108)	Not MSI-H or dMMR (n = 94)	MSI-H/dMMR (n = 11)
ORR_{WK24}, n (%)	41 (38.0)	34 (36.2)	7 (63.6)
ORR, n (%)	42 (38.9)	35 (37.2)	7 (63.6)
CR	8 (7.4)	7 (7.4)	1 (9.1)
PR	34 (31.5)	28 (29.8)	6 (54.5)
Median DoR, mos (95% CI)	21.2 (7.6-NE)	NE (7.4-NE)	21.2 (7.3-NE)
Median PFS, mos (95% CI)	7.4 (5.3-8.7)	7.4 (5.0-7.6)	18.8 (4.0-NE)
Median OS, mos (95% CI)	16.7 (15.0-NE)	16.4 (13.5-25.9)	NE (7.4-NE)

Makker. JCO. 2020; 38: 2981.

Slide credit: clinicaloptions.com

FDA Approval of Pembrolizumab + Lenvatinib for Advanced EC That Is Not MSI-H or dMMR

- Pembrolizumab plus lenvatinib is indicated for the treatment of advanced endometrial carcinoma that is not MSI-high or dMMR[1]
- FDA, Australian Therapeutic Goods Administration, and Health Canada collaborated on review, allowing simultaneous decision in all 3 countries[1]
- Approval based on data from KEYNOTE-146[1]
  - 94 (87%) patients had tumors that were not MSI-high or dMMR[2]
  - Of these, most patients were aged ≥ 65 yrs and 49% were PD-L1 positive[2]

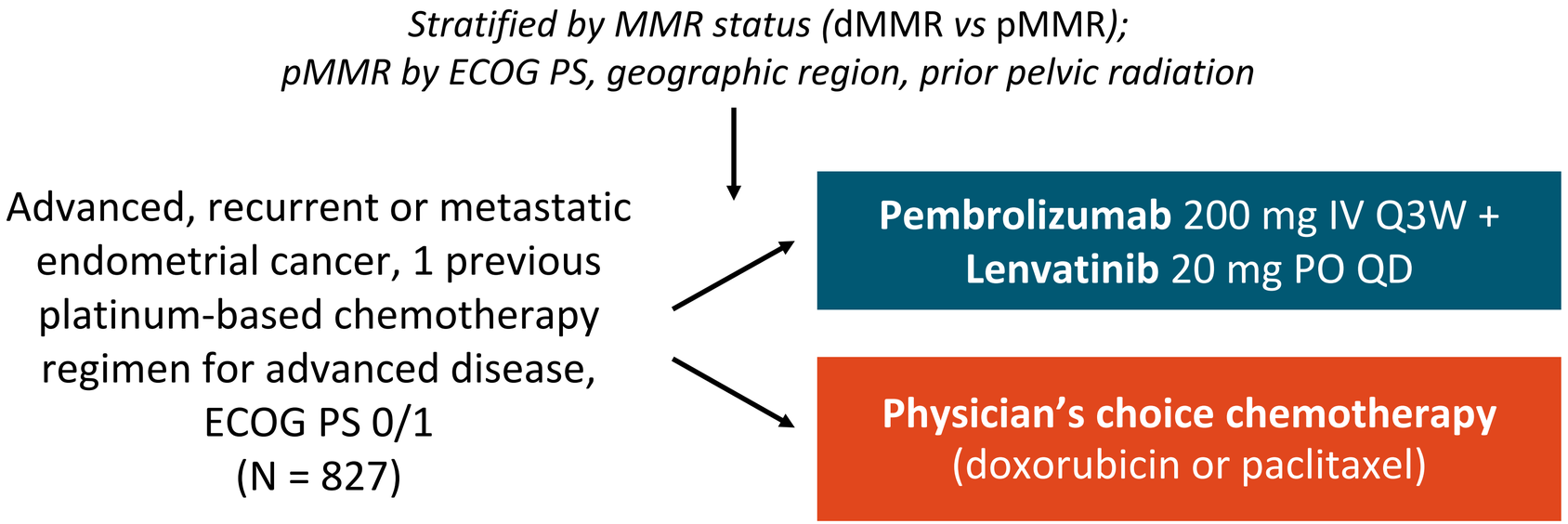
	N = 108[2]
Objective Response Rate	
ORR (95% CI)	40.3% (31.6-49.5)
CR rate	8 (6.5)
PR rate	43 (33.9)
Response duration	
Median in mos (range)	NE (8.5-NE)
no. with duration ≥ 6 mos	36

Treatment is associated with any-grade AEs (>50%): hypertension (59.7%), diarrhea (52.4%)

1. US Food and Drug Administration. Press Release. September 17, 2019. 2. Makker. JCO. 2020;38: 2981.

Slide credit: clinicaloptions.com

Phase III KEYNOTE-775: Second-line Pembrolizumab + Lenvatinib vs Chemotherapy in Advanced EC



Primary endpoints: PFS, OS

Secondary endpoints: ORR, HRQoL, safety and tolerability, PK

NCT03517449.

Slide credit: clinicaloptions.com

Combination Checkpoint Inhibitor Studies in Advanced/Recurrent Endometrial Cancer

Checkpoint Inhibitors Plus Antiangiogenic Agents

KEYNOTE-146[1]

KEYNOTE-775 (phase III)[2]

ENGOT-en9/LEAP-001 (phase III)[3]

Pembrolizumab + Lenvatinib

NCT0336774[4]:

Nivolumab + Cabozantinib

Checkpoint Inhibitors Plus Chemotherapy

NRG-GY018[5]:

Pembrolizumab + Paclitaxel/Carboplatin

AtTEnd/ENGOT-en7[6]:

Atezolizumab + Paclitaxel/Carboplatin

RUBY (ENGOT-EN6; GOG-3031)[7]:

Dostarlimab + Chemotherapy

1. Makker. JCO. 2020; 38: 2981. 2. NCT03517449. 3. NCT03884101. 4. NCT03367741. 5. NCT03914612. 6. NCT03603184. 7. NCT03981796.

Conclusion

- Carcinoma endometrium is an important malignancy in the western countries.
- Molecular profiling is subject to availability of resources. It is recommended wherever feasible as it is highly reproducible and has strong prognostic implications.
- POLE-mut is favourable type mostly requiring no adjuvant treatment.
- P53 abn is most unfavourable requiring adjuvant radiotherapy as well as chemotherapy.
- NSMP and MMRd are intermediate prognosis groups.
- Immunotherapy is evolving with favourable outcomes.

Future directions

Thank you