XXXIII CONGRESSO NAZIONALE AIRO

AIRO2023

BOLOGNA,
27-29 OTTOBRE 2023
PALAZZO DEI CONGRESSI

Radioterapia Oncologica: l'evoluzione al servizio dei pazienti

Profilazione genomica e radioterapia Endometrio

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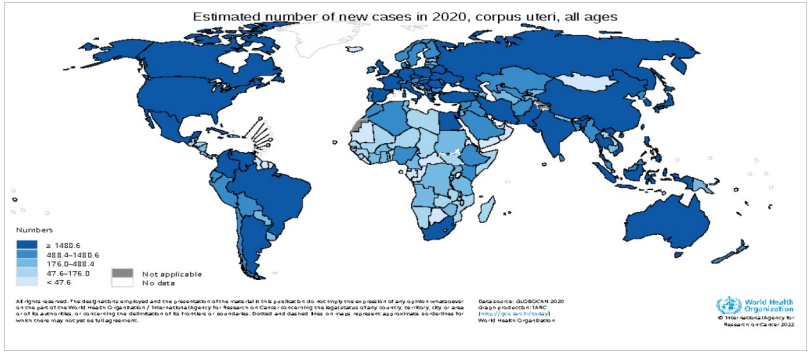
Radioterapia e Oncologia clinica

DISCLOSURE

No conflict of interest to disclose.

ENDOMETRIAL CANCER

- The most common gynaecological tumor in developed countries
- The only gynaecologic cancer with rising incidence and mortality
- The increased of mortality could be caused by an inaccurate risk stratification
- While patients diagnosed at an early stage have an excellent prognosis, those diagnosed at a late stage have a 5-year survival rate of only 17%

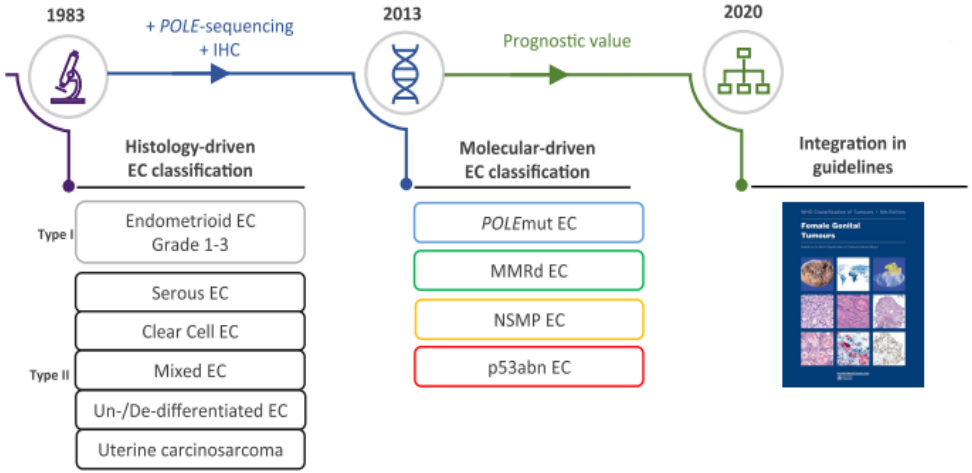


Bokhman's classification

The Cancer Genome Atlas Research Network

ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

FIGO Staging System for EC



2021

2023

Table 2 Definition of prognostic risk groups

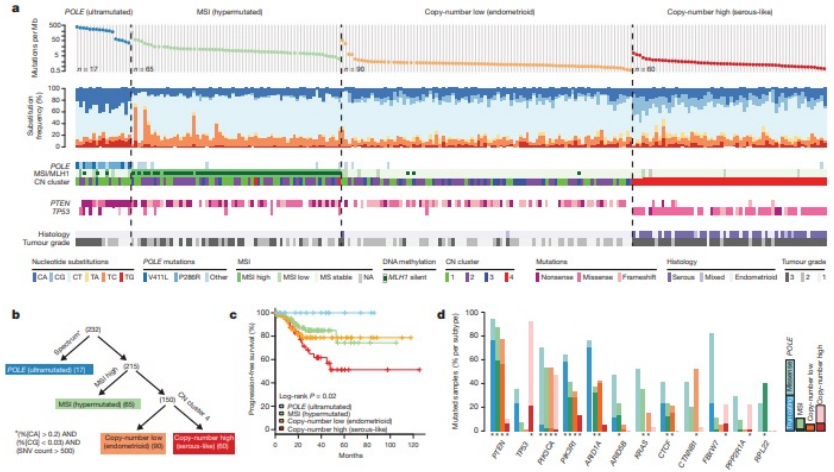
Risk group	Molecular classification unknown	Molecular classification known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II ***POLE*mut** endometrial carcinoma, no residual disease ► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	► 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, undifferentiated 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

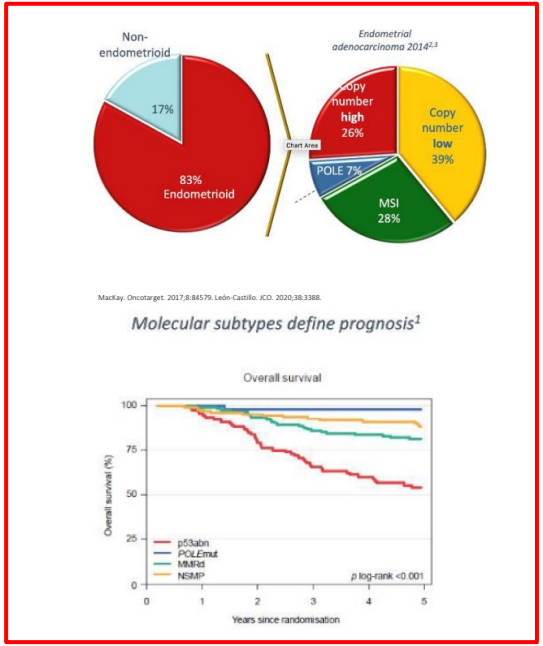
Stage	Description
Stage I	Confined to the uterine corpus and ovary[a]
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometrioid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[a]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[a]
IC	Aggressive histological types[b] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[a] of non-aggressive histological types
IIC	Aggressive histological types[b] with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[d] IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIIC1i Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2i Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

TGCA PROJECT: NEW OPPORTUNITIES IN EC

Integrated Genomic Characterization of Endometrial Carcinoma

Nature. 2013 May 2; 497(7447): 67–73.





TCGA: **not feasible** in a clinical context or single patient setting!!
ProMisE (Proactive Molecular Risk Classifier for endometrial cancer)
Trans PORTEC international consortium

- Vermij 2020: IHC p53, MSH-6, PMS-2, + somatic mut POLE (exons 9,11,13,14)
More reproducibile, using Immunohistochemistry and NGS

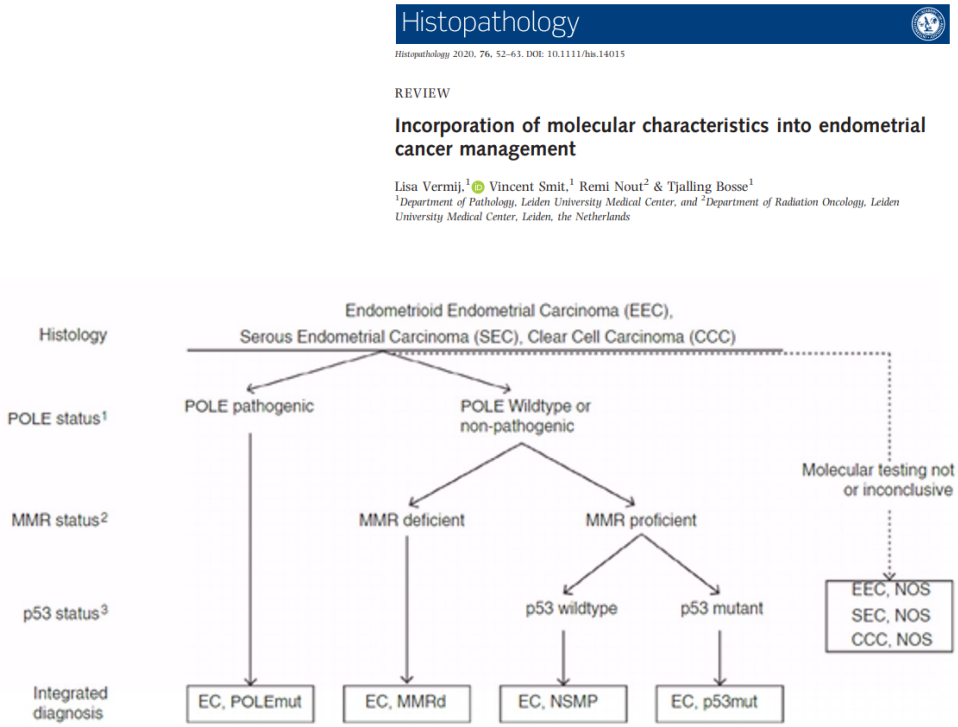
- TCGA, ProMisE and TransPORTEC validated **retrospectively!**
Ongoing PORTEC 4|a study (randomized trial of molecular-profile-based vs standard recommendations for adjuvant RT in early stages EC)
- **Combine traditional pathologic and molecular results seems ideal.**

POLE (ultramutated) mutation pathogenic variants in the catalytic subunit of DNA Polymerase epsilon, performed using NGS

Mismatch repair deficient (MMRd) abnormal expression of one or more mismatch repair proteins by IHC, which is highly concordant with MSI-instabily status

p53 abnormal (p53abn) exhibiting aberrant p53 . This group largely corresponds to the "**copy number-high/serous-like**" TCGA group

No specific molecular profile (NSMP) exhibiting normal p53 and MMR expression by IHC and no mutations in the exonuclease domain of POLE, analogous to the "**copy number low**" subgroup in the TCGA


Histopathology

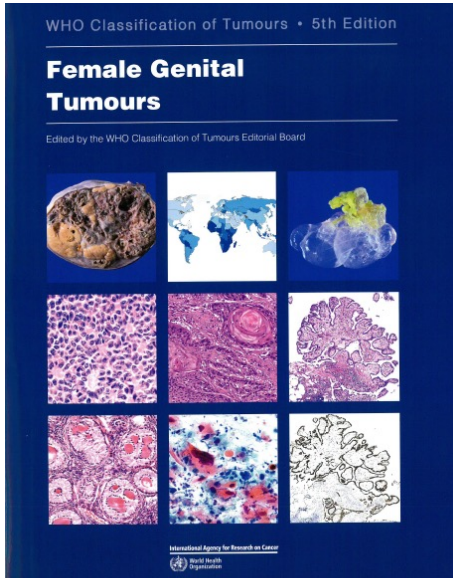
Histopathology 2020, 76, 52–63. DOI: 10.1111/his.14015

REVIEW

Incorporation of molecular characteristics into endometrial cancer management

Lisa Vermij,[1] Vincent Smit,[1] Remi Nout[2] & Tjalling Bosse[1]
[1]Department of Pathology, Leiden University Medical Center, and [2]Department of Radiation Oncology, Leiden University Medical Center, Leiden, the Netherlands

WHO classification 2020



Endometrial epithelial tumours and precursors

	Endometrial hyperplasia without atypia
8380/2	Atypical hyperplasia of the endometrium
8380/3	Endometrioid adenocarcinoma NOS
	POLE-ultramutated endometrioid carcinoma
	Mismatch repair–deficient endometrioid carcinoma
	p53-mutant endometrioid carcinoma
	No specific molecular profile (NSMP) endometrioid carcinoma
8441/3	Serous carcinoma NOS
8310/3	Clear cell adenocarcinoma NOS
8020/3	Carcinoma, undifferentiated, NOS
8323/3	Mixed cell adenocarcinoma
9110/3	Mesonephric adenocarcinoma
8070/3	Squamous cell carcinoma NOS
8144/3	Mucinous carcinoma, intestinal type
9111/3*	Mesonephric-like adenocarcinoma
8980/3	Carcinosarcoma NOS

MOLECULAR SUBTYPING OF EC

Most favorable prognosis

POLE — PTEN 94% KRAS 53% PIK3CA 71% PIK3R1 65% ARID1A 76% FBXW7 82% ARID5B 47% — <10%

NSMP — PTEN 77% CTNNB1 52% PI3KCA 53% PI3KR1 33% ARID1A 42% — 30-40%

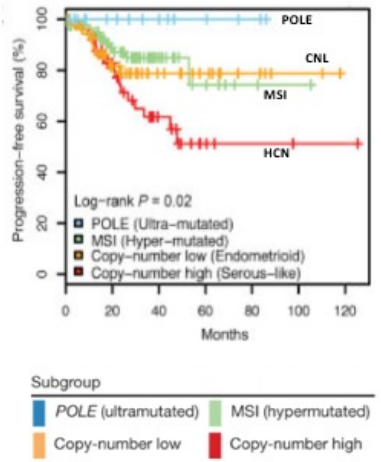
MSI — PTEN 88% KRAS 35% PIK3CA 71% RPL22 33% PI3KCA 54% PIK3R1 40 % ARID1A 37% — 25-30%

HCN — Tp53 92% PPP2R1A 22% PI3KCA 47% Chromosomal Instability (MYC, erb-B2, CCNE1, FGFR3, SOX17) — 15-25%

Worst prognosis

TGCA, Nature 2013

PFS

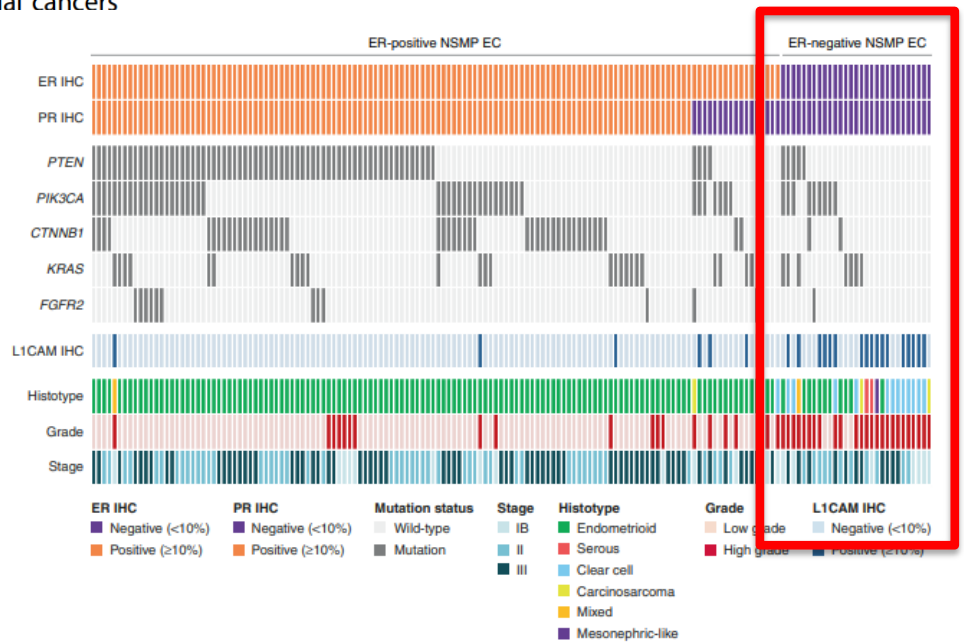


Copy Number Low

Prognostic refinement of NSMP high-risk endometrial cancers using oestrogen receptor immunohistochemist

648 high-risk EC

Assesment of the prognostic value of ER, PR, L1CAM and CTNNB1 mutations

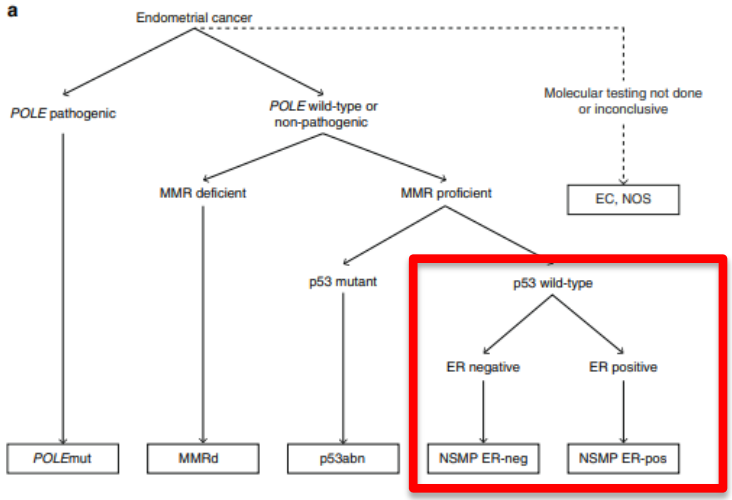


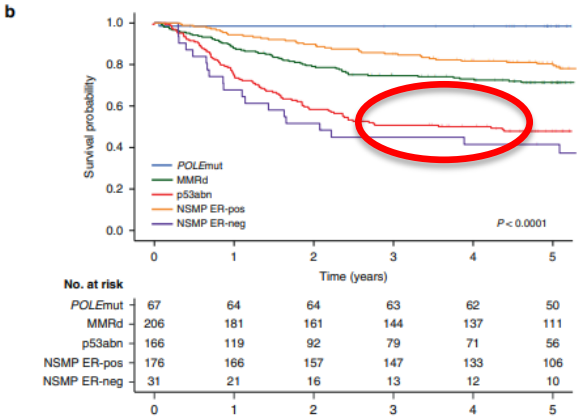
Vermij L. et al.Br J Cancer (2023) 128:1360-1368

Incorporation of ER status in the molecular classification of endometrial cancer

Assessment of ER status in high-risk NSMP EC is **feasible** in clinical practice and has the potential **to improve risk stratification** and **treatment** of patients with NSMP EC

Hormone tx
Inhibition of cyclin D-CDK4/6 (palbociclib)
ENGOT-EN3/NSGO-PALEO: Letrozolo + Palbociclib increase PFS and disease control rate





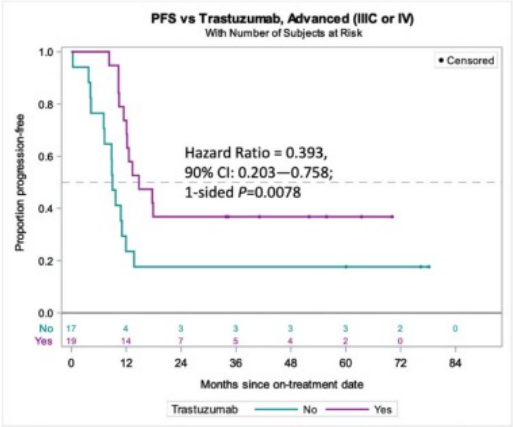
British Journal of Cancer (2023) 128:1360 – 1368

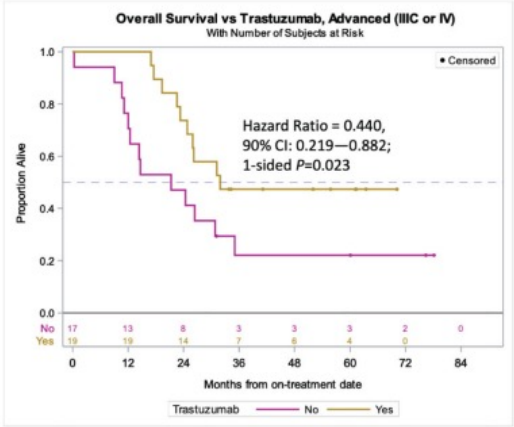
Copy Number High

Randomized phase II trial of carboplatin-paclitaxel compared to carboplatin-paclitaxel-trastuzumab in advanced (stage III-IV) or recurrent uterine serous carcinomas that overexpress Her2/Neu (NCT01367002): updated overall survival analysis

HER2

In a subset analysis of patients restricted to stage IIIC/IV disease, the addition of trastuzumab (n=17) continued to provide both: **progression-free survival** benefit over control (n=19) (9.0 versus 14.8 months, HR 0.393,) and **overall survival** benefit over control (21.1 versus 31.9 months, HR 0.440) undergoing primary therapy after surgery

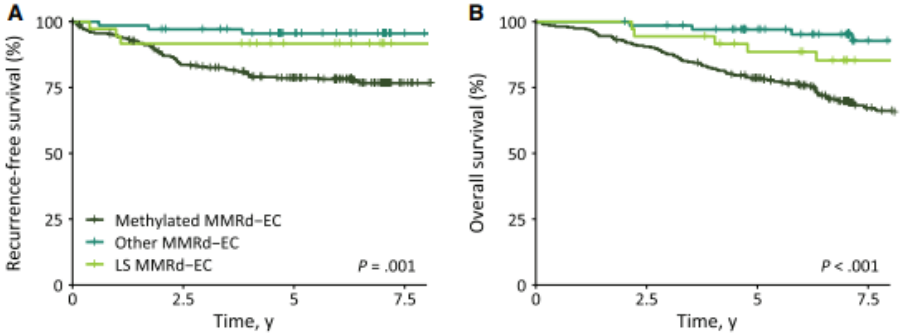


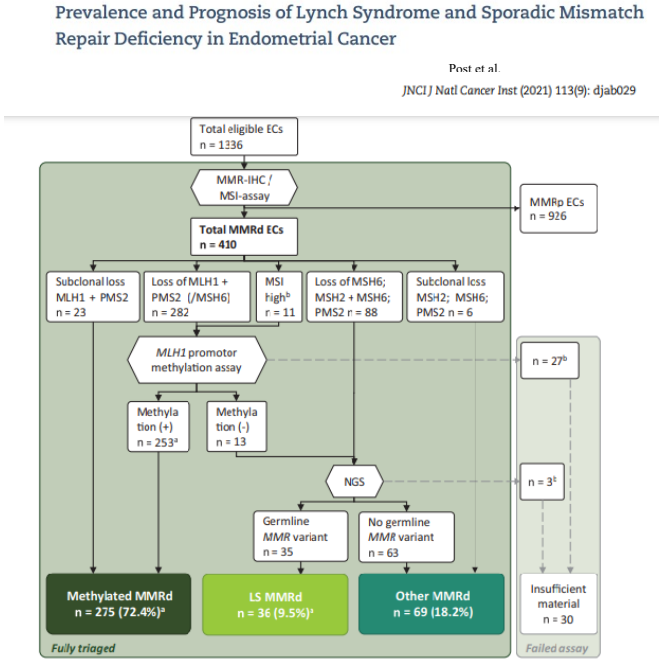


Amanda N. Fader1Clin Cancer Res. 2020 August 01; 26(15): 3928–3935

MSI High

Mismatch repair deficient subgroup (MMRd)



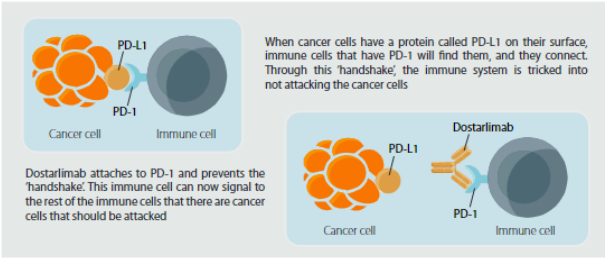


Related to <u>germline</u> mutations of **MMR genes**

- 3% of all EC
- 10% of MMRd/MSI EC

Single agent IO efficacy?

Study	Drug	N	Patient Selection	ORR(%)
Keynote 158:	Pembrolizumab	49	Advanced/metastatic dMMR	57%
Garnet :Oaknin (2020)	Dostarlimab	71	Previously treated Recurrent/advanced d-MMR	45%
PHAEDRA: Antill (2019)	Durvalumab	35	Advanced /metastatic p-MMR	43%
Konstantinopoulos (2019)	Avelumab	15	Advanced /metastatic d-MMR	27%



Oaknin A, *et al. J Immunother Cancer* 2022;**10**:e003777.

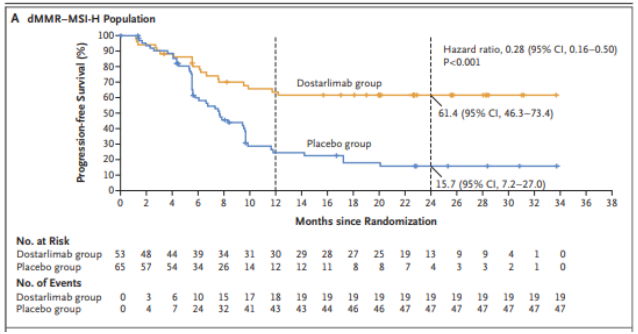
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

M.R. Mirza, D.M. Chase, B.M. Slomovitz, R. dePont Christensen, Z. Novák, D. Black, L. Gilbert, S. Sharma, G. Valabrega, L.M. Landrum, L.C. Hanker, A. Stuckey, I. Boere, M.A. Gold, A. Auranen, B. Pothuri, D. Cibula, C. McCourt, F. Raspagliesi, M.S. Shahin, S.E. Gill, B.J. Monk, J. Buscema, T.J. Herzog, L.J. Copeland, M. Tian, Z. He, S. Stevens, E. Zografos, R.L. Coleman, and M.A. Powell, for the RUBY Investigators*

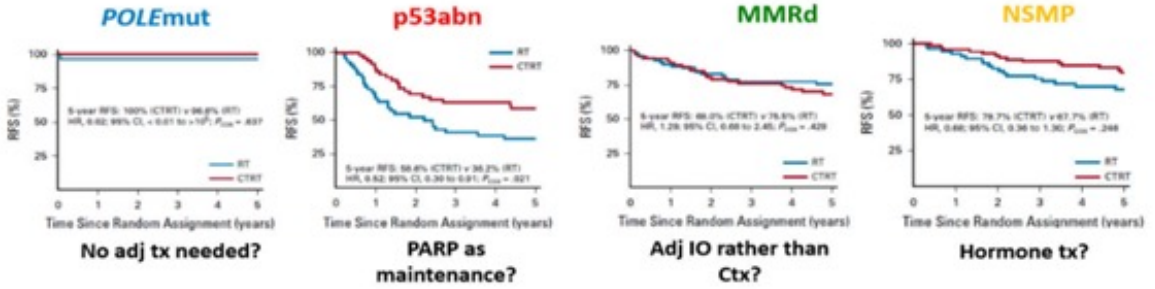
RUBY trial: Dostarlimab is an immune-checkpoint inhibitor that targets the programmed cell death 1 receptor. The combination of **CT (carboplatin-paclitaxel)** and immunotherapy may have synergistic effects in the treatment of endometrial cancer



June 8,2023

MOLECULAR SUBTYPING OF EC

PORTEC-3 Trial



- POLEmut: does not relapse regardless of tx
- P53abn: worst prognosis but greatest benefit from adj Ctx
- MSI and NSMP: intermediate prognosis , but little benefit from Adj Ctx

Prognostic and predictive value of benefit from adj treatment

Alicia León-Castillo et al *Journal of Clinical Oncology* 2020 383388-3397


What else?

ESGO/ESTRO/ESP guidelines

ESTRO European Society of Pathology

ESGO European Society of Gynaecological Oncology

- Integration of molecular markers with traditional pathologic features
- **Quantification LVI negative-focal-substantial** (tumor in 5 or more cells in lymphovascular spaces)
- **Bynary FIGO grading** Grade **1** and **2 low-grade**; Grade **3 high-grade**
- **Sentinel lymph node biopsy** can be considered for staging in patients with **low-risk/intermediate-risk disease**. It can be omitted in cases without myometrial invasion
- **Surgical lymph node staging** should be performed in patients with **high intermediate risk/high risk disease**

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 ***POLEmut*** 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

Concin N, *et al. Int J Gynecol Cancer* 2021;**31**:12–39. doi:10.1136/ijgc-2020-002230

Low risk

Risk group	Molecular classification unknown	Molecular classification known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease ► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal

NO ADJUVANT TREATMENT

Recommendations

- For patients with low-risk EC no adjuvant treatment is recommended [I,A]
- <u>When molecular classification is known</u>:
  - **Stage I–II**, low-risk based on pathogenic POLE-mutation, omission of adjuvant treatment should be considered [III,A]
  - **Stage III–IVA** and POLE-mutation: no data with the omission of the adjuvant treatment [IV,C] (all pts in PORTEC3 treated with EBRT)

Intermediate risk

No substantial **LVSI is crucial prognostic factor** for both local and distant recurrence and for OS (PORTEC trial)

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

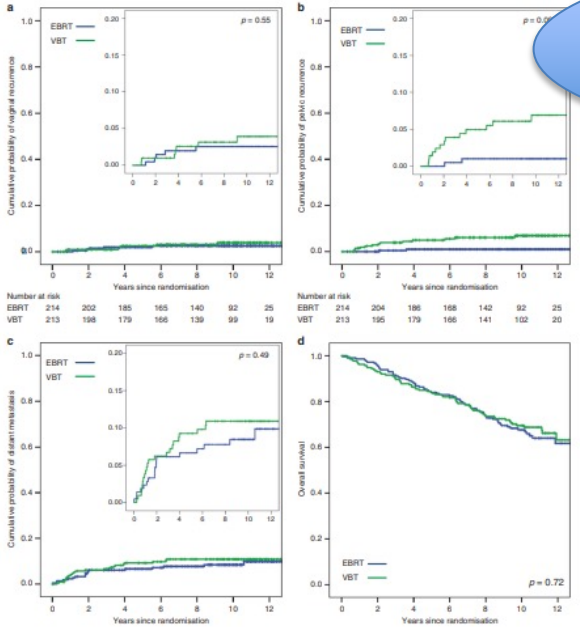
Recommendations

- Adjuvant BT recommended to decrease vaginal recurrence [I,A]
- Omission of adjuvant BT can be considered for patients <60y [II,A]
- When molecular classification is known, POLE mut and p53abn with myometrial invasion have specific recommendations
- For p53abn carcinomas restricted to a polyp or without myometrial invasion, adjuvant therapy is generally **not recommended** [III,C]

- EBRT versus BT (PORTEC II): BT alone recommended to decrease vaginal recurrence. No decrease in OS with omission of BT, > 14% risk of local recurrence (Danish Study)
- No benefit in OS→ no adjuvant treatment is an option in this group (<60y)

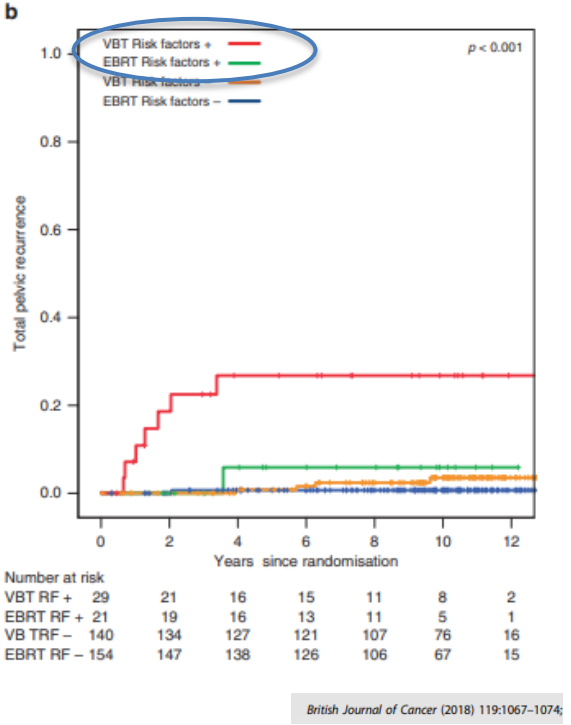
Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy

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



substantial LVSI, L1CAM expression or p53-mutant expression

EBRT provided better pelvic control in patients with **unfavourable risk factors**: substantial LVSI, p53abn or L1CAM overexpression (higher risk of pelvic recurrence)



British Journal of Cancer (2018) 119:1067–1074;

High-intermediate risk (pN0 after lymph node staging)

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

Recommendations

- Adjuvant BT is recommended to decrease vaginal recurrence [II,B]
- EBRT can be considered for substantial LVSI and 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

SN ultrastaging

- No difference between adjuvant chemo alone and EBRT alone in DFS and OS *(Maggi et al, 2006 and Susumu et al, 2008)*
- Combination of chemo and radiotherapy provide better DFS and OS than radiotherapy alone *(NSGO/EORTC trial and PORTEC-3 trials)*
- No benefit in DFS or OS from 3 cycles of chemo with BCT compared with EBRT alone *(GOG-249 trial)*
- No benefit of chemotherapy for MMRd carcinomas *(Molecular analysis of PORTEC-3)*

High-intermediate risk cN0/pNx (lymph node staging not performed)

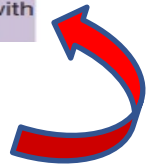
High–intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ► Stage II **MMRd/NSMP** endometrioid carcinoma

Recommendations

- Adjuvant EBRT is recommended, especially for substantial LVSI and/or for stage II [I,A]
  (GOG-249, PORTEC-3 and GOG-99 trials)
- Additional adjuvant chemotherapy can be considered, especially for high-grade and/or substantial LVSI [II,B]
  (PORTEC-3 trial)
- Adjuvant BT alone can be considered for high-grade LVSI negative and for stage II G1 endometrioid carcinomas [II,B]
- When molecular classification is known, POLEmut and p53abn have specific recommendations

High risk

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

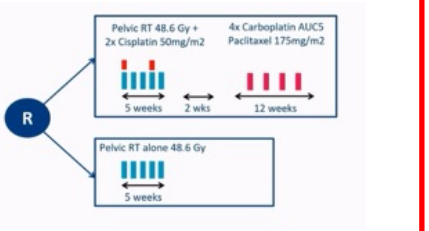


Recommendations

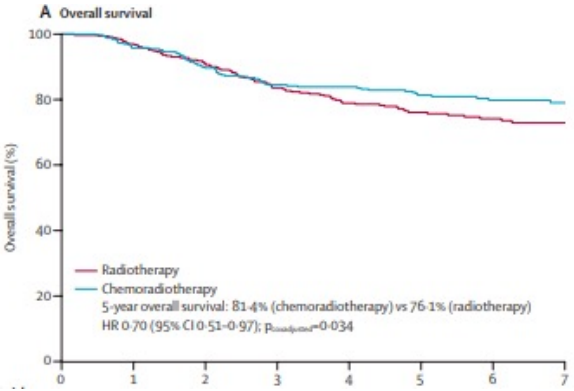
- EBRT with concurrent and adjuvant chemotherapy [I,A] or alternatively sequential chemotherapy and radiotherapy is recommended [I,B]
- Chemotherapy alone is an alternative option [I,B]
- **Carcinosarcomas** should be treated as high-risk carcinomas (not as sarcomas) [IV,B]
- When the molecular classification is known, p53abn carcinomas without myometrial invasion and POLEmut have specific recommendations

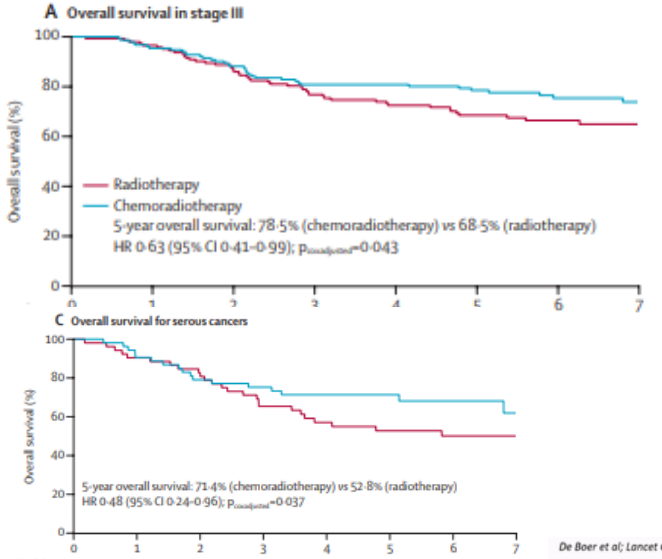
PORTEC 3 trial results 5ys

- Chemo + EBRT (2 cycles of cisplatin during EBRT followed by 4 cycles of carboplatin-paclitaxel) vs EBRT alone: improve in 5% OS benefit at 5y
- The greatest OS difference seen in <u>stage III</u> endometrioid ECs and in <u>serous</u> ECs



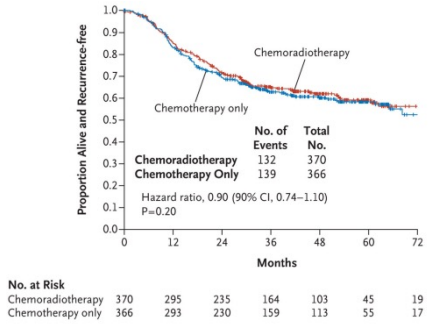
- N=660, median FU 6 yrs
- 28% non-endometrioid
- 32% grade 3
- 45% stage III



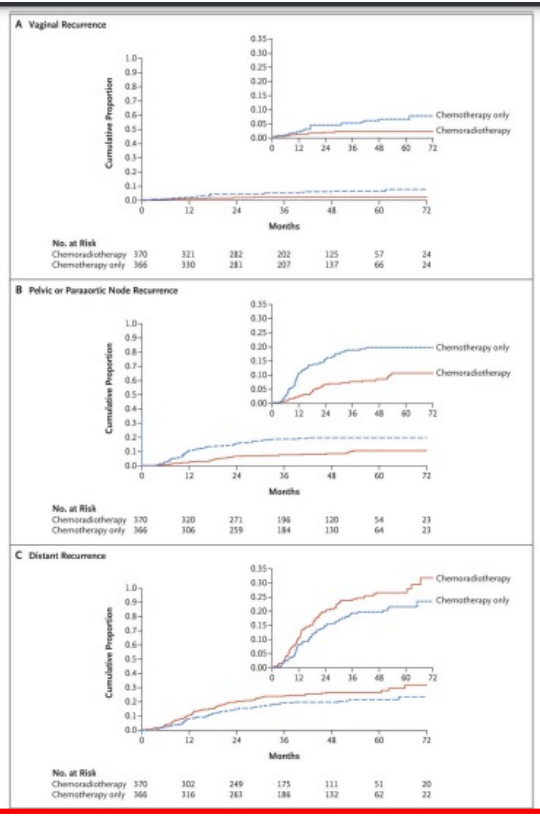


De Boer et al; Lancet Oncology 2019

GOG 258 trial



At 60 months, the percentage of patients alive and relapse-free was 59% in the chemoradiotherapy group and 58% in the chemotherapy-only group (HR: 0.90)



Chemoradiotherapy was associated with a **lower 5-year incidence** of **vaginal recurrence** (2% vs. 7%; HR: 0.36;)

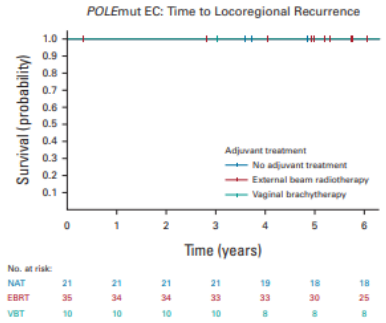
pelvic and paraaortic lymph-node recurrence (11% vs. 20%; HR: 0.43;) than chemotherapy alone

Distant recurrence was more common in association with chemoradiotherapy (27% vs. 21%; HR:1.36)

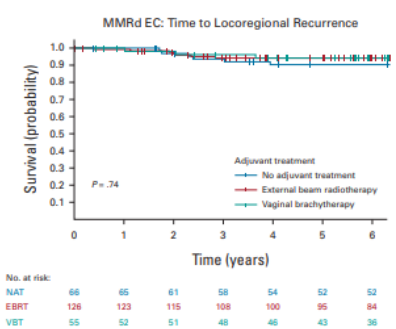
Matei D et al. N Engl J Med. 2019 June 13; 380(24): 2317–2326.

Molecular Classification Predicts Response to Radiotherapy in the Randomized PORTEC-1 and PORTEC-2 Trials for Early-Stage Endometrioid Endometrial Cancer

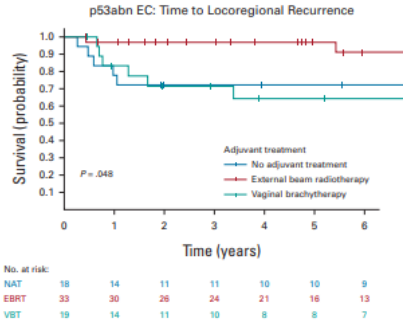
POLEmut



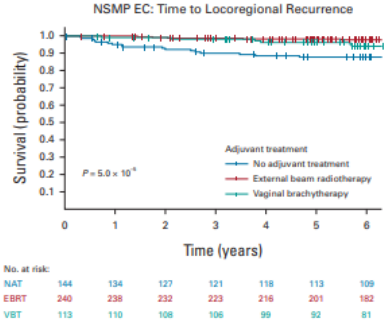
MMRd



p53abn



NSMP



- **POLE mut**: Omitting radiotherapy is safe (at 5 ys, no locoregional recurrences)
- **MMRd**: EBRT and VBT make a small, non significant benefit compared with no adjuvant therapy (should be prospectively validated)
- **P53abn:** locoregional recurrence-free survival was excellent after EBRT, but poor after VBT or no adjuvant therapy (seem to be particularly radiosensitive). EBRT is recommended
- **NSMP** stage I have significant benefit from adjuvant radiotherapy. VBT was as effective as EBRT and both yielded a significantly better locoregional control than no adjuvant therapy.

Horeweg et al, JCOVol.41, Issue 27, 2023

New 2023 FIGO Staging System for Endometrial Cancer

2023 FIGO stages based on surgical/anatomical and histological findings

Stage	Description
Stage I	Confined to the uterine corpus and ovary[c]
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
	IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d]
IC	Aggressive histological types[e] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma with extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[d] of non-aggressive histological types
IIC	Aggressive histological types[e] with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[f]
	IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIICii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

Integration of molecular markers (when Known)

Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage IAm$_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage IICm$_{p53abn}$	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

Abbreviation: LVSI, lymphovascular space involvement.

[a]When feasible, the addition of molecular subtype to the staging criteria allows a better prediction of prognosis in a staging/prognosis scheme. The performance of complete molecular classification (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all cases of endometrial cancer for prognostic risk-group stratification and as potential influencing factors of adjuvant or systemic treatment decisions. Molecular subtype assignment can be done on a biopsy, in which case it need not be repeated on the hysterectomy specimen. When performed, these molecular classifications should be recorded in all stages.

- Good prognosis: pathogenic *POLE* mutation (*POLEmut*)
- Intermediate prognosis: mismatch repair deficiency (MMRd)/microsatellite instability and no specific molecular profile (NSMP)
- Poor prognosis: p53 abnormal (p53abn)When the molecular classification is known:
- FIGO Stages I and II are based on surgical/anatomical and histological findings. In case the molecular classification reveals *POLEmut* or p53abn status, the FIGO stage is modified in the early stage of the disease. This is depicted in the FIGO stage by the addition of "m" for molecular classification, and a subscript is added to denote *POLEmut* or p53abn status, as shown below. MMRd or NSMP status do not modify early FIGO stages; however, these molecular classifications should be recorded for the purpose of data collection. When molecular classification reveals MMRd or NSMP, it should be recorded as Stage Im$_{MMRd}$ or Stage Im$_{NSMP}$ and Stage IIm$_{MMRd}$ or Stage IIm$_{NSMP}$.
- FIGO Stages III and IV are based on surgical/anatomical findings. The stage category is not modified by molecular classification; however, the molecular classification should be recorded if known. When the molecular classification is known, it should be recorded as Stage IIIm or Stage IVm with the appropriate subscript for the purpose of data collection. For example, when molecular classification reveals p53abn, it should be recorded as Stage IIIm$_{p53abn}$ or Stage IVm$_{p53abn}$.

Berek J.S et al. Int J Gynecol Obstet. 2023;162:383–394.

KEY CHANGES

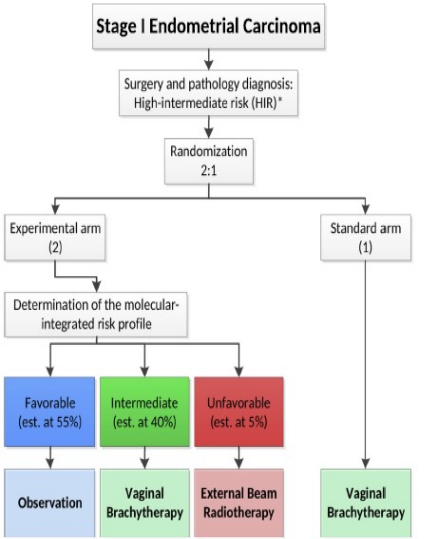
#ESGO 2023

- Incorporation of **histological sybtype** (**Non-aggressive histological types**: low grade EC vs **Aggressive histological types**: high grade EC and aggressive histological types as serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, and carcinosarcomas)
- Incorporation of degree of **LVI** : *"LVSI negative" (0 vessels); "LVSI focal" (<5 vessels); or "LVSI substantial/extensive" (≥5 vessels)*
- Incorporation of **molecular profile** into the staging
- Distinction between synchronous and metastatic cancer (In the case of high grade tumors, ovarian involvement is almost always categorized as metastatic)
- Adaptation of anatomical spread in regards to the stage (*adnexal vs (sub)serosa, cervix, pelvic vs extrapelvic peritoneum*)
- More detailed description of LN involvement- impact on SLN classification **(micro vs macrometastasis)**

PORTEC 4a

The first randomised trial using the molecular risk factors **to assign adjuvant treatment** for women with stage I-II high-intermediate risk endometrial cancer

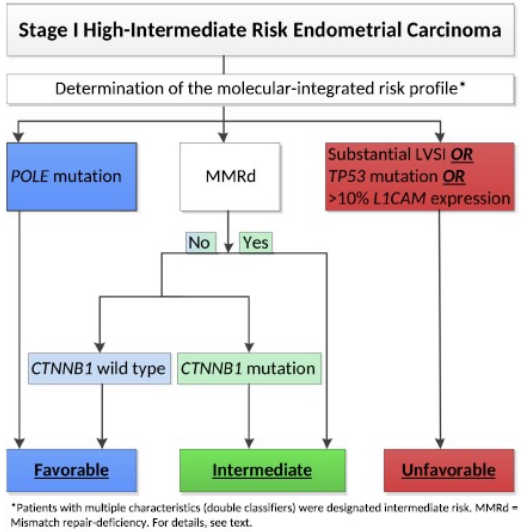
Trial design



*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.

On going

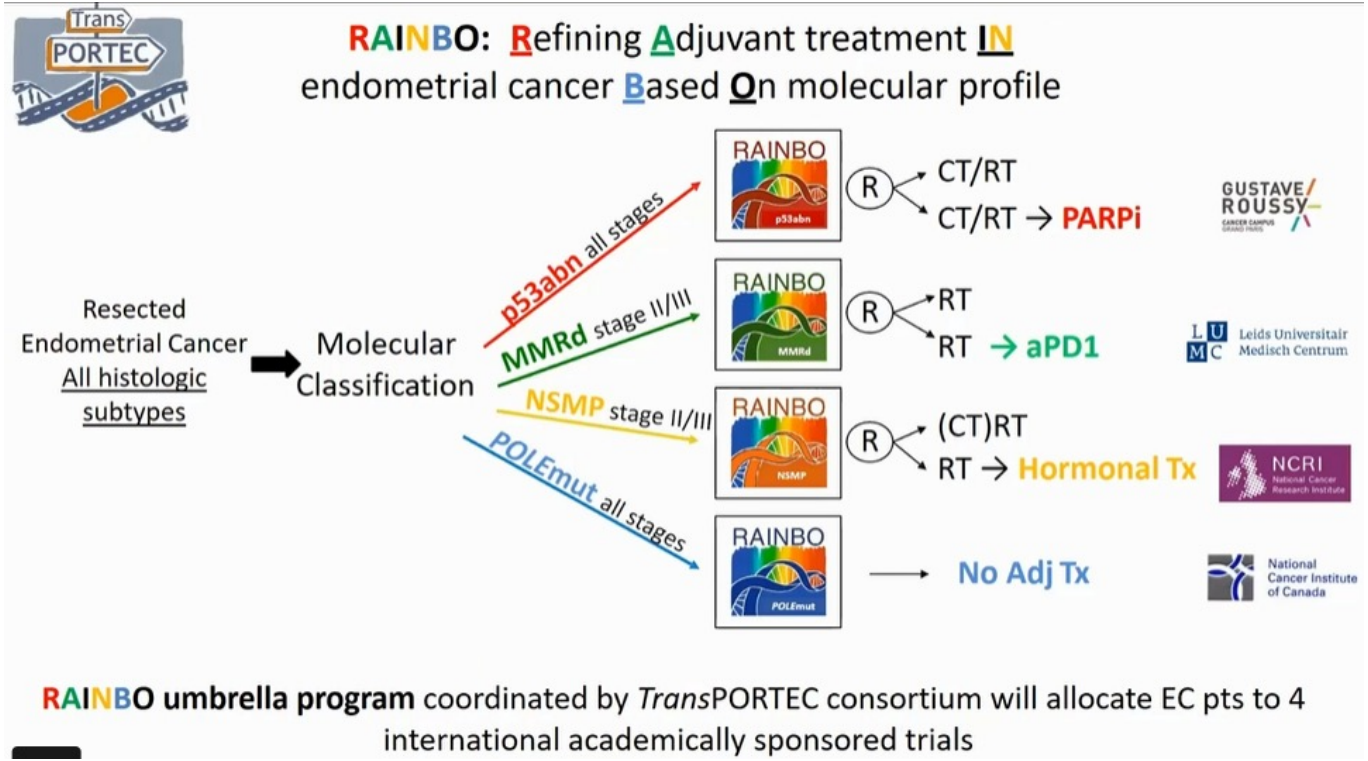
Profile



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

Wortman et al, Gyn Oncol 2018

On going


Trans PORTEC
RAINBO: Refining Adjuvant treatment IN endometrial cancer Based On molecular profile
Resected Endometrial Cancer All histologic subtypes
Molecular Classification
p53abn all stages
MMRd stage II/III
NSMP stage II/III
POLEmut all stages
RAINBO
R
CT/RT
CT/RT → PARPi
RT
RT → aPD1
(CT)RT
RT → Hormonal Tx
No Adj Tx
GUSTAVE ROUSSY
Leids Universitair Medisch Centrum
NCRI National Cancer Research Institute
National Cancer Institute of Canada
RAINBO umbrella program coordinated by TransPORTEC consortium will allocate EC pts to 4 international academically sponsored trials

Take Home Messages

- Endometrial cancers is represented by at least **4 different tumors** with different prognosis requiring different treatments
- **POLEmut EC**, which is associated with an excellent prognosis and should lead to consideration of **de-escalation** of adjuvant therapy
- **p53abn EC**, which reclassifies these women to the high-risk group. VBT alone is not sufficient for locoregional and distant disease control and chemotherapy and **EBRT** should be considered
- Novel treatment strategies and trials are biomarker-based and biomarker-driven, will be needed


ESGO
European Society of Gynaecological Oncology

ESGO Centre Accreditation in Endometrial Cancer Surgery

Accreditation for Endometrial Cancer Surgery

Azienda Sanitaria Friuli Centrale - ASUFC, Udine, Italy
Department of Obstetrics and Gynaecology

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Prof. Nicole Concin
ESGO President

Dr. Ane Gerda Zahl Eriksson
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Geneva, Switzerland
September 25, 2023

The European Voice of Gynaecological Oncology

Grazie per l'attenzione