EVIDENCE AND PRACTICE CHANGING TREATMENTS IN FEMALE TUMORS

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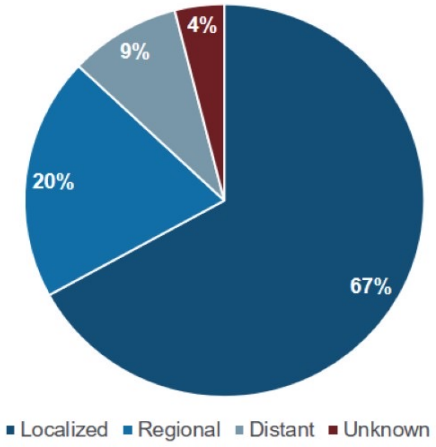
No conflict of interest

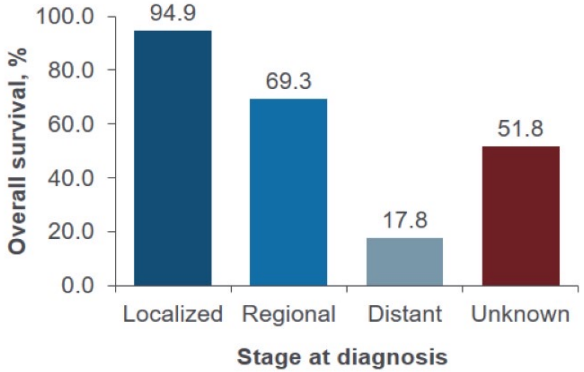
ENDOMETRIO	
Incidenza	Nel 2023, sono stati stimati 10.200 nuovi casi (Il 5,5% di tutti i tumori femminili; terza neoplasia più frequente nelle donne nella fascia di età 50-69 anni)
Mortalità	Nel 2022, sono stimati 2.500 decessi complessivi per i tumori dell'utero. Le stime per il 2023 non sono disponibili
Sopravvivenza netta a 5 anni dalla diagnosi	79%
Probabilità di vivere ulteriori 4 anni condizionata ad aver superato il primo anno dopo la diagnosi	86%
Prevalenza	Sono 122.600 le donne che vivono in Italia dopo una diagnosi di tumore del corpo dell'utero

Survival Rates of Uterine Cancer Are Associated With the Stage at Diagnosis

Percentage of cases by stage at diagnosis



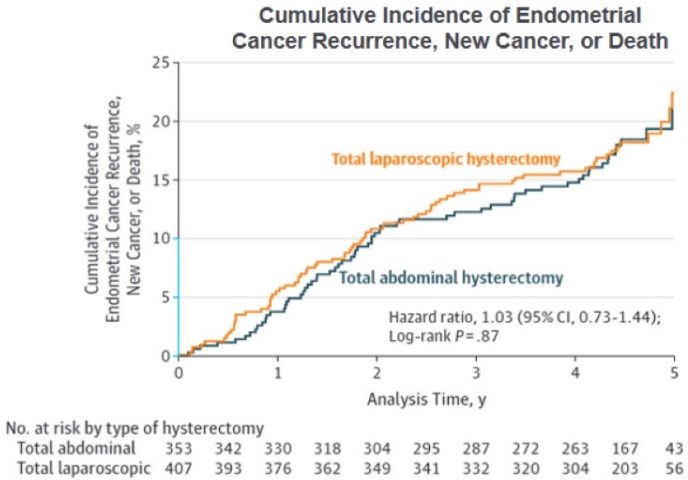
5-year relative survival by stage at diagnosis

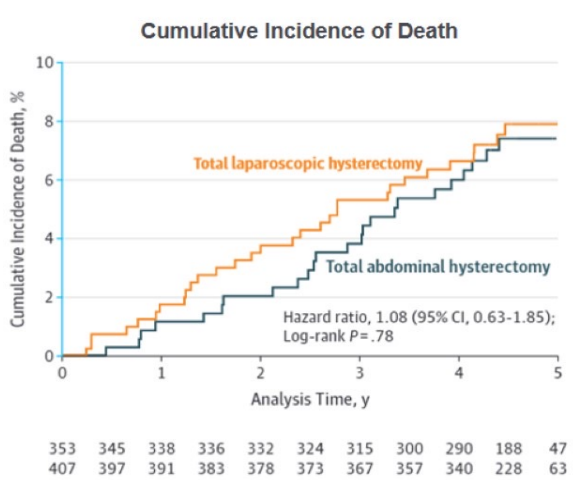


The Surveillance, Epidemiology, and End Results program (SEER). Cancer Stat Facts: Uterine Cancer. Accessed February 22, 2023. https://seer.cancer.gov/statfacts/html/corp.html.

Total Laparoscopic Hysterectomy vs Total Abdominal Hysterectomy
LACE Trial

Phase 3 randomized trial (2005-2010) involving patients with Stage 1 endometrioid histology





Comparable outcomes with total laparoscopic hysterectomy and total abdominal hysterectomy

Janda M, et al. JAMA. 2017;317:1224-1233.

No Reported Therapeutic Role for Lymphadenectomy

Non-inferiority of sentinel node mapping in comparison to lymphadenectomy

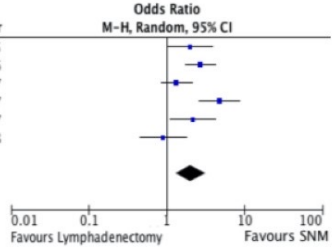
- 1249 (35.3%) sentinel node mapping
- 2287 (64.7%) lymphadenectomy
- Prevalence of recurrence (any site) and lymphatic specific recurrence is similar
- Superior to lymphadenectomy in detecting low volume disease (ultrastaging)

Bogani G, et al. Gynecol Oncol. 2019;153:676-683.

Detection on pelvic nodes

Study or Subgroup	SNM Events	SNM Total	Lymphadenectomy Events	Lymphadenectomy Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Eriksson 2015	33	642	13	493	15.6%	2.00 [1.04, 3.84]	2015
Holloway 2016	36	119	91	661	18.9%	2.72 [1.73, 4.26]	2016
Ducie 2017	54	202	45	210	18.8%	1.34 [0.85, 2.11]	2017
Buda 2017	23	145	25	657	16.4%	4.77 [2.62, 8.67]	2017
Baiocchi 2017	20	75	23	161	15.2%	2.18 [1.11, 4.29]	2017
Buda 2018	18	66	31	105	15.1%	0.90 [0.45, 1.78]	2018
Total (95% CI)		**1249**		**2287**	**100.0%**	**2.03 [1.30, 3.18]**	
Total events	184		228				

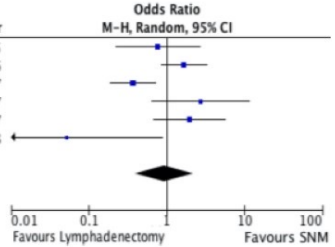
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 18.34$, df = 5 (P = 0.003); $I^2 = 73\%$
Test for overall effect: Z = 3.12 (P = 0.002)



Detection on paraortic nodes

Study or Subgroup	SNM Events	SNM Total	Lymphadenectomy Events	Lymphadenectomy Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Eriksson 2015	5	642	5	493	16.5%	0.77 [0.22, 2.66]	2015
Holloway 2016	12	119	42	661	21.9%	1.65 [0.84, 3.24]	2016
Ducie 2017	13	202	33	210	21.9%	0.37 [0.19, 0.72]	2017
Buda 2017	3	145	5	657	14.7%	2.75 [0.65, 11.66]	2017
Baiocchi 2017	7	75	8	161	18.3%	1.97 [0.69, 5.65]	2017
Buda 2018	0	66	13	105	6.7%	0.05 [0.00, 0.88]	2018
Total (95% CI)		**1249**		**2287**	**100.0%**	**0.93 [0.39, 2.18]**	
Total events	40		106				

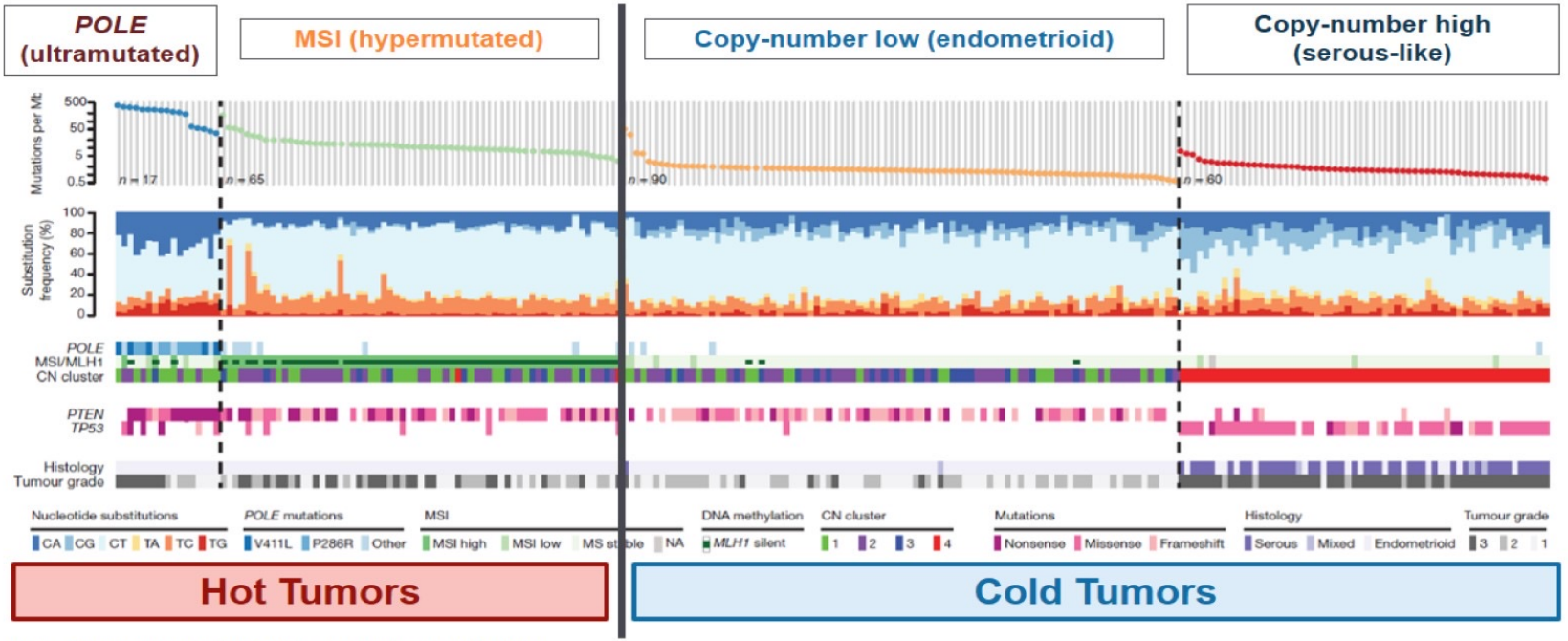
Heterogeneity: $Tau^2 = 0.76$; $Chi^2 = 19.13$, df = 5 (P = 0.002); $I^2 = 74\%$
Test for overall effect: Z = 0.18 (P = 0.86)



Molecular Profiling Is Recommended at Diagnosis of Endometrial Carcinoma

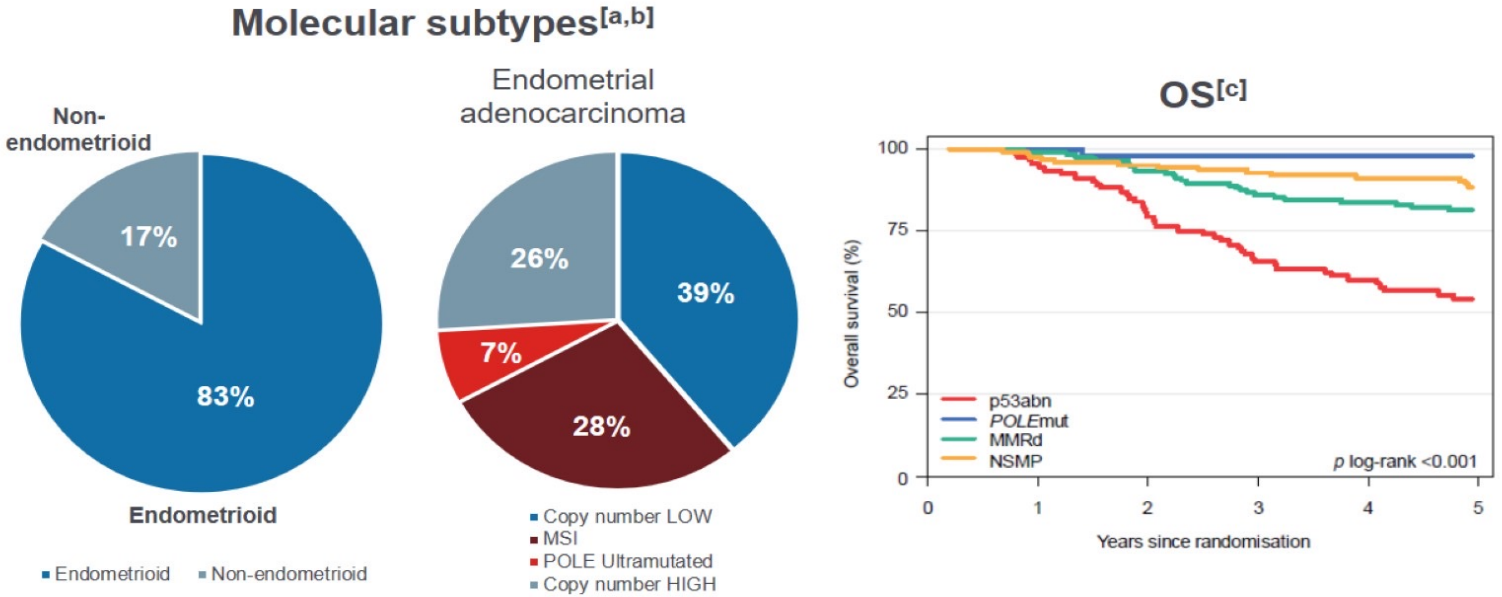
Concin N, et al. Int J Gynecol Cancer. 2021;31:12-39; Oaknin A, et al. Ann Oncol. 2022;33:860-877.

Integrated Genomic Characterization of Endometrial Carcinoma
TGCA Project



Cancer Genome Atlas Research Network, et al. Nature. 2013;497:67-73

Prognostic and Predictive Value of Molecular Subtyping in Endometrial Carcinoma: *TGCA Project*



MMRd, mismatch repair; MSI, microsatellite instability; NSMP, no specific molecular profile; OS, overall survival; p53abn, p53 abnormal; *POLE*mut, *POLE*-ultramutated.
a. Mahdy H, et al. StatPearls. Endometrial Cancer. Accessed March 6, 2023. www.ncbi.nlm.nih.gov/books/NBK525981/; b. Yen TT, et al. Int J Gynecol Pathol. 2020;39:26-35; c. León-Castillo A, et al. J Clin Oncol. 2020;38:3388-3397.

Original Article

Confirmation of ProMisE: A Simple, Genomics-Based Clinical Classifier for Endometrial Cancer

Aline Talhouk, PhD[1]; Melissa K. McConechy, PhD[2]; Samuel Leung, MSc[3]; Winnie Yang, BSc[1]; Amy Lum, BSc[1]; Janine Senz, BSc[1]; Niki Boyd, PhD[1]; Judith Pike, MD[4]; Michael Anglesio, PhD[1]; Janice S. Kwon, MD, MSc[4]; Anthony N. Karnezis, MD, PhD[1]; David G. Huntsman, MD[1]; C. Blake Gilks, MD[5]; and Jessica N. McAlpine, MD[4]

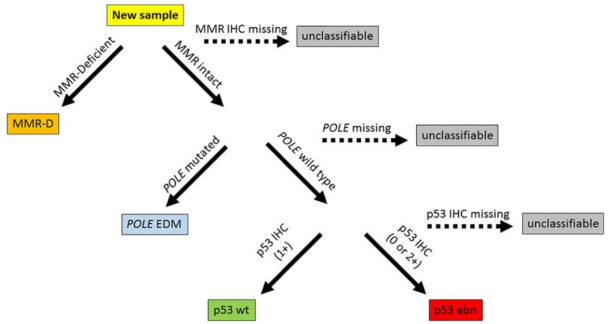


Figure 1. Steps in molecular classification with Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) are illustrated. The first assessment is immunohistochemistry for the presence of mismatch repair (MMR) proteins to identify women, enabling rapid referral to the hereditary cancer program and possibly directing surgical or therapeutic decisions. Tumors are assessed next for polymerase-ε (*POLE*) exonuclease domain mutations (EDMs) and finally for protein 53 (p53) IHC, yielding 4 subgroups: MMR-D, *POLE*, p53 wild type (wt), and p53 null/missense mutations (abn).

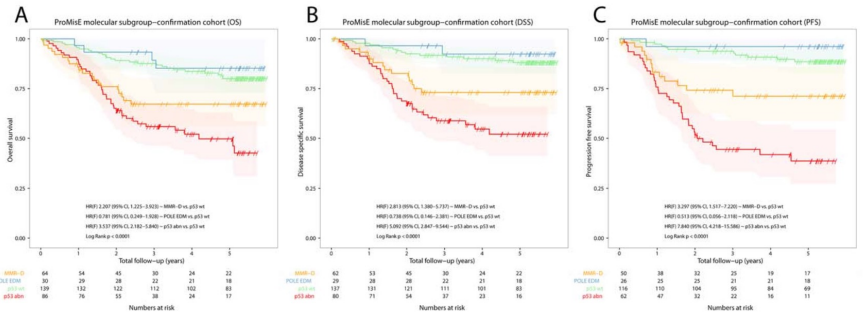
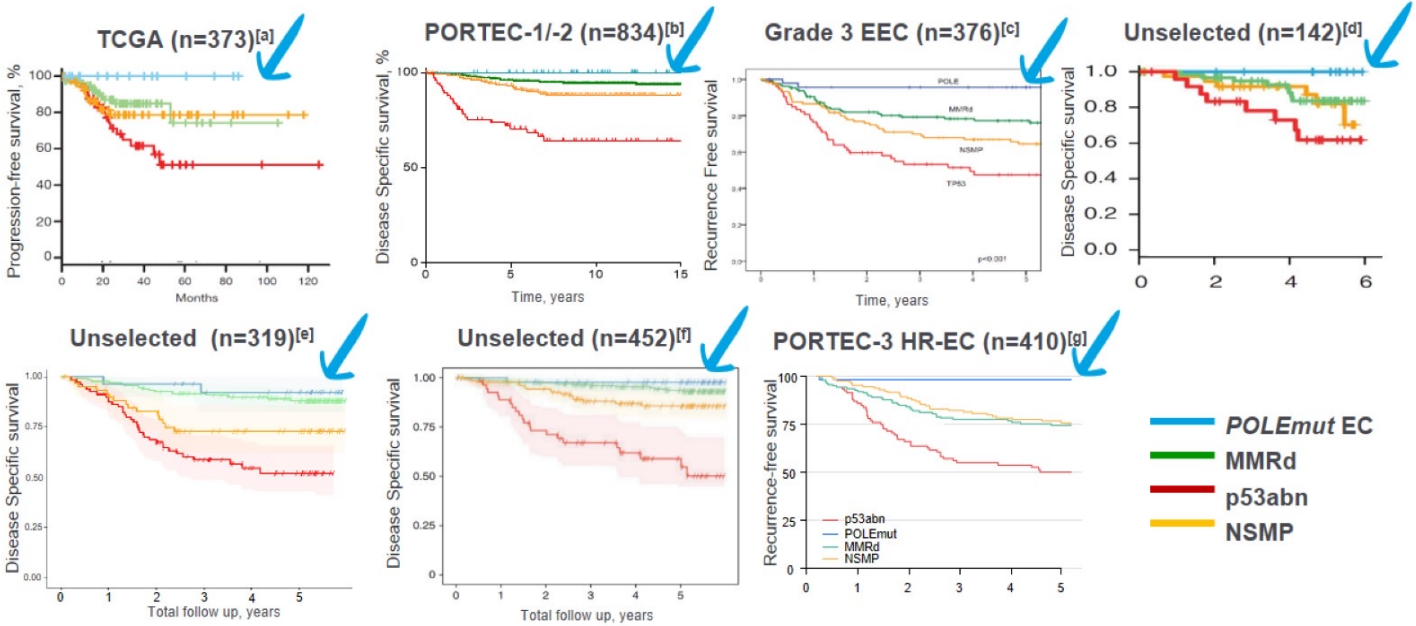


Figure 2. Kaplan-Meier survival analyses are illustrated for the confirmation cohort (n = 319) according to Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) molecular subgroups, including (A) overall survival (OS), (B) disease-specific survival (DSS), and (C) progression-free survival (PFS). CI indicates confidence interval; HR(F), hazard ratio using the Firth penalized maximum-likelihood bias-reduction method (with "F" indicating that the proportion of censored cases was >58% [corresponding confidence intervals were obtained using the profile likelihood]); MMR-D, mismatch repair-deficient; p53, tumor protein 53; p53 abn, null/missense p53 mutation; p53 wt, wild-type p53; *POLE* EDM, polymerase-ε exonuclease domain mutation.

POLE
MMR-D
P53
NSMP

High Prognostic Value of Molecular Characterization of Endometrial Cancer



a. Cancer Genome Atlas Research Network, et al. Nature. 2013;497:67-73; b. Stelloo E, et al. Clin Cancer Res. 2016;22:4215-4224; c. Bosse T, et al. Am J Surg Pathol. 2018;42:561-568; d. Talhouk A, et al. Br J Cancer. 2015;113:299-310; e. Talhouk A, et al. Cancer. 2017;123:802-813; f. Kommoss S, et al. Ann Oncol. 2018;29:1180-1188; g. León-Castillo A, et al. J Clin Oncol. 2020;38:3388-3397.

Endometrial Carcinoma Risk Groups

ESGO/ESTRO/ESP Guidelines[a]

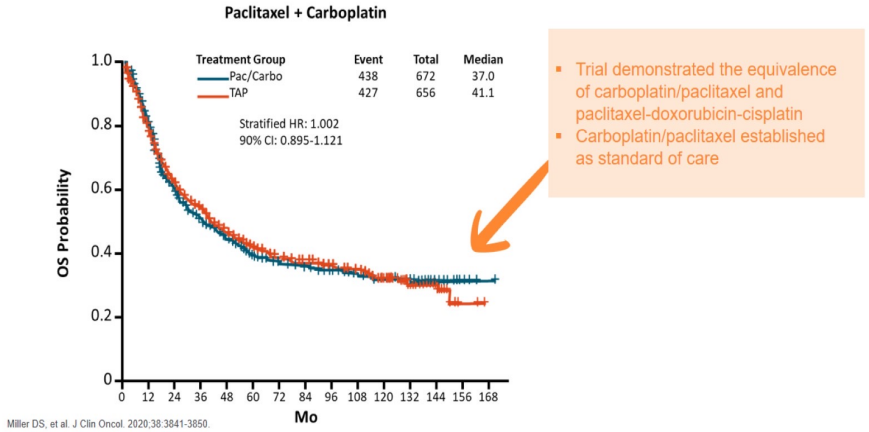
Risk Group	Molecular Classification Known
Low risk	▪ Stage I-II ***Pol*emut** endometrial carcinoma, no residual disease ▪ Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade + LVSI negative or focal
Immediate risk	▪ Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade + LVSI negative or focal ▪ Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade + LVSI negative or focal ▪ Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, mixed) without myometrial invasion
High-intermediate risk	▪ 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 risk	▪ Stage III-IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ▪ Stage I-IVA **p53abn** endometrioid carcinoma with myometrial invasion, with no residual disease ▪ Stage I-VA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	▪ Stage III-IVA with residual disease of any molecular type ▪ Stage IVB of any molecular type

ESMO Guidelines[b]

Risk Group	Description
Low risk	Stage IA (G1-G2) with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage I/II *POLE*mut cancer; stage III *POLE*mut cancers
Immediate risk	Stage IA G3 with endometrioid type (dMMR and NSMP) and no focal LVSI Stage IA non-endometrioid type (serous, clear-cell, undifferentiated carcinoma, carcinosarcoma, mixed) and/or p53-abn cancers without myometrial invasion and no or focal LVSI Stage IB (G1-G2) with endometrioid type (dMMR and NSMP) and no or focal LVSI Stage II G1 endometrioid type (dMMR and NSMP) and no or focal LVSI
High-intermediate risk	Stage I endometrioid type (dMMR and NSMP) any grade and any depth of invasion with substantial LVSI Stage IB G3 with endometrioid type (dMMR and NSMP) regardless of LVSI Stage II G1 endometrioid type (dMMR and NSMP) with substantial LVSI Stage II G2-G3 endometrioid type (dMMR and NSMP)
High risk	All stages and all histologies with p53-abn and myometrial invasion All stages with serous or undifferentiated carcinoma including carcinosarcoma with myometrial invasion All stage III and IVA with no residual tumour, regardless of histology and regardless of molecular subtype

ESGO, European Society of Gynaecological Oncology; ESMO, European Society for Medical Oncolyty; ESP, European Society of Pathology; ESTRO, European Sociey for Radiotherapy and Oncology.
a. Concin N, et al. Int J Gynecol Cancer. 2021;31:12-39; b. Oaknin A, et al. Ann Oncol. 2022;33:860-877.

Chemotherapy in Advanced/Recurrent Endometrial Cancer
GOG 209



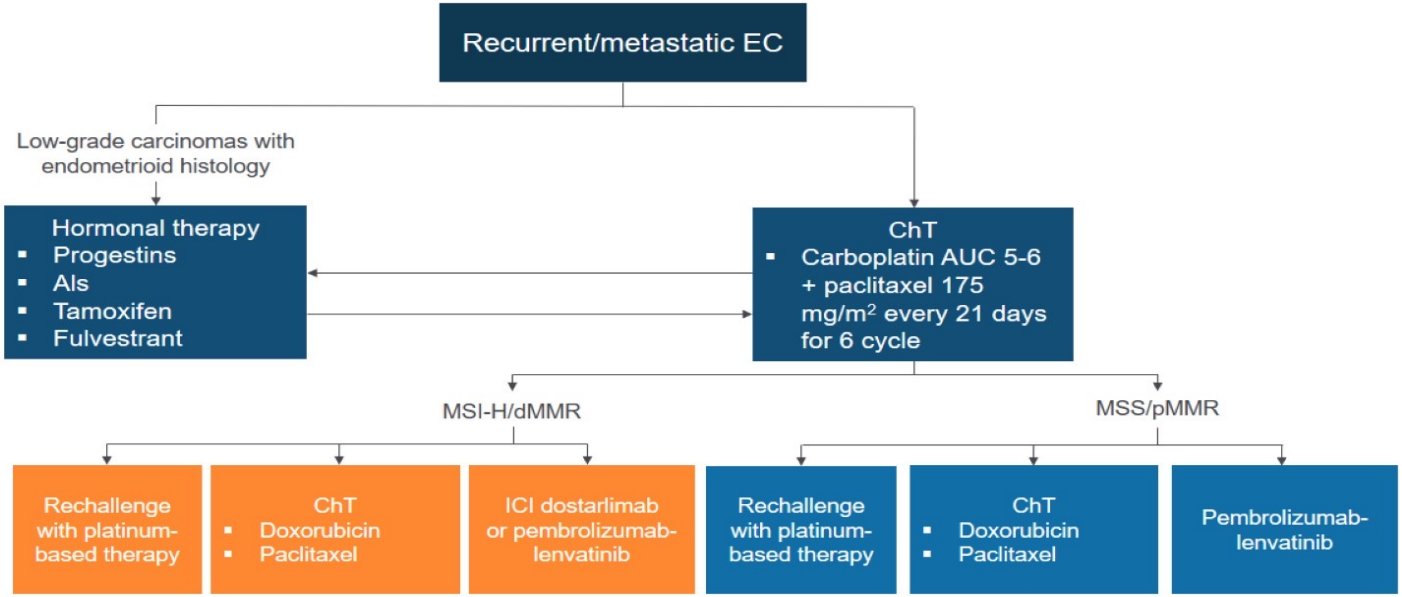
- Trial demonstrated the equivalence of carboplatin/paclitaxel and paclitaxel-doxorubicin-cisplatin
- Carboplatin/paclitaxel established as standard of care

Median FUP 124 mts
TAP 37 mts
TC 41 mts

Progression
Doxorubicin/taxane or endocrine therapy

JCO 2020

Management of Recurrent/Metastatic Endometrial Cancer
ESMO 2022 Guidelines



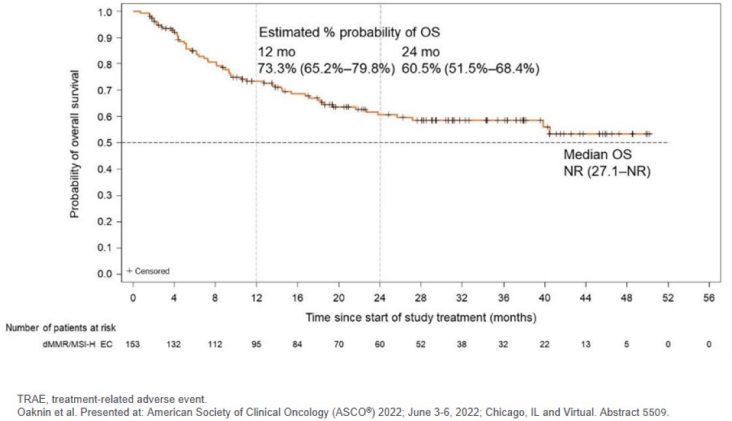
AI, aromatase inhibitor; AUC, area under the curve; ChT, chemotherapy; ICI, immune checkpoint inhibitor.
Oaknin A, et al. Ann Oncol. 2022;33:860-877.

Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET—a phase I, single-arm study

Ana Oaknin ,[1] Lucy Gilbert,[2] Anna V Tinker,[3] Jubilee Brown,[4] Cara Mathews,[5] Joshua Press,[6] Renaud Sabatier,[7] David M O'Malley,[8] Vanessa Samouelian,[9] Valentina Boni,[10] Linda Duska,[11] Sharad Ghamande,[12] Prafull Ghatage,[13] Rebecca Kristeleit,[14] Charles Leath III,[15] Wei Guo,[16] Ellie Im,[16] Sybil Zildjian,[16] Xinwei Han,[16] Tao Duan,[16] Jennifer Veneris,[16] Bhavana Pothuri[17]

I, single-arm study. *Journal for ImmunoTherapy of Cancer* 2022;**10**:e003777. doi:10.1136/jitc-2021-003777

Dostarlimab in Advanced/Recurrent dMMR/MSI-High Endometrial Cancer: *GARNET OS*



Safety:
Most common any grade TRAEs with dMMR EC vs dMMR non-EC vs overall dMMR solid tumors:
- Diarrhea (16.0% vs 14.1% vs 15.0%)
- Asthenia (16.0% vs 14.7% vs 15.2%)
- Pruritus (12.7% vs 13.6% vs 13.2%)

TRAE, treatment-related adverse event.
Oaknin et al. Presented at: American Society of Clinical Oncology (ASCO®) 2022; June 3-6, 2022; Chicago, IL and Virtual. Abstract 5509.

Conclusion Dostarlimab demonstrated durable antitumor activity in both dMMR/MSI-H (ORR 43.5%) and MMRp/MSS EC (ORR 14.1%) with a manageable safety profile.

original reports

Pembrolizumab in Patients With Microsatellite Instability–High Advanced Endometrial Cancer: Results From the KEYNOTE-158 Study

David M. O'Malley, MD[1]; Giovanni Mendonca Bariani, MD[2]; Philippe A. Cassier, MD[3]; Aurelien Marabelle, MD, PhD[4]; Aaron R. Hansen, MBBS[5]; Ana De Jesus Acosta, MD[6]; Wilson H. Miller Jr, MD, PhD[7,8]; Tamar Safra, MD[9,10]; Antoine Italiano, MD, PhD[11,12]; Linda Mileshkin, MBBS[13]; Lei Xu, PhD[14]; Fan Jin, MD[14]; Kevin Norwood, MD[14]; and Michele Maio, MD[15]

J Clin Oncol 40:752-761.

CONTEXT

Key Objective

Endometrial cancer is the second most prevalent gynecologic cancer in women worldwide; however, treatment options after failure of first-line therapy are limited. We evaluated the efficacy and safety of pembrolizumab, an antiprogrammed death-1 antibody, in patients with previously treated advanced endometrial cancer with tumors that had high levels of microsatellite instability/mismatch repair deficiency.

Knowledge Generated

Among patients who received pembrolizumab monotherapy, 48% had an objective response. Responses were durable, and the median duration of response was not reached after a median follow-up of 42.6 months. No new safety signals were identified.

Relevance

Pembrolizumab demonstrated durable antitumor activity with manageable toxicity in patients with advanced microsatellite instability–high or mismatch repair–deficient endometrial cancer. These findings support the use of pembrolizumab as a treatment option in this setting.

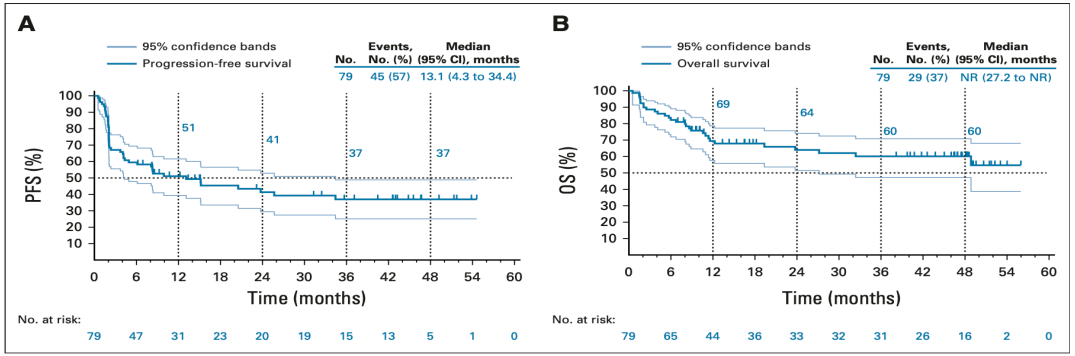
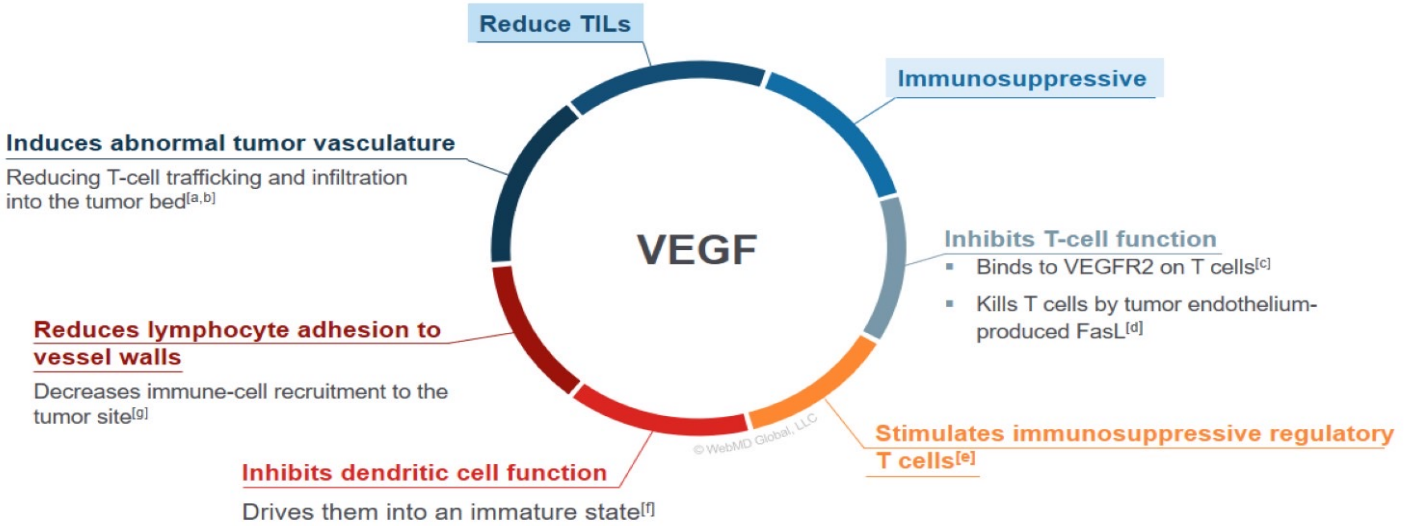


FIG 3. Kaplan-Meier analysis of (A) PFS per RECIST version 1.1 by independent central radiologic review in the efficacy analysis population and (B) OS in the efficacy analysis population. Light blue lines indicate 95% confidence bands. NR, not reached; OS, overall survival; PFS, progression-free survival.

Pembrolizumab and Dostarlimab are now reimbursed in dMMR EC previously exposed to platinum based Chemotherapy (no more than 2 previously lines) in Italy

Rationale for Combining Cancer Immunotherapy With Anti-VEGF

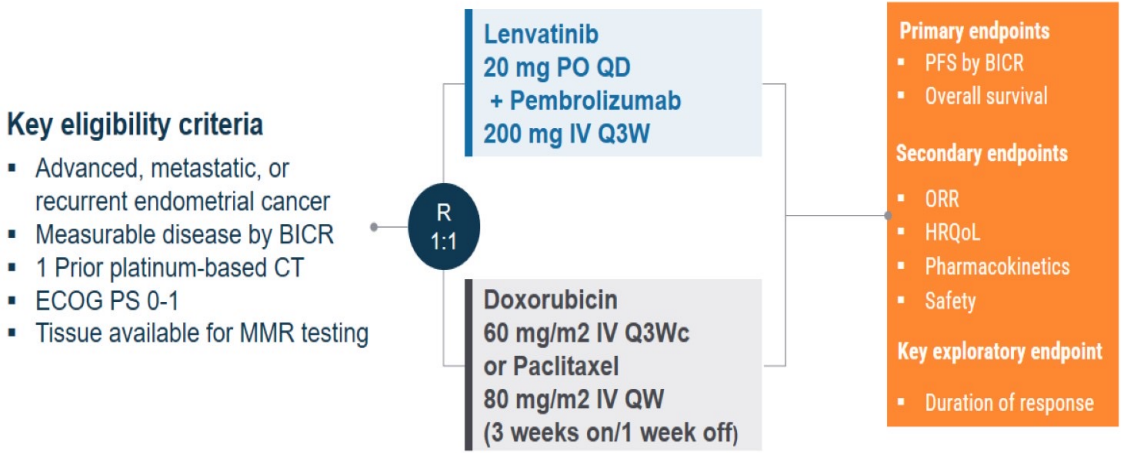


TIL, tumor-infiltrating lymphocyte; VEGF, vascular endothelial growth factor.
a. Shrimali RK, et al. Cancer Res. 2010;70:6171-6180; b. Chen DS, et al. Immunity. 2013;39:1-10; c. Gavalas NG, et al. Br J Cancer. 2012;107:1869-1875; d. Motz GT, et al. Nat Med. 2014;20:607-615; e. Terme M, et al. Cancer Res. 2013;73:539-549; f. Coukos G, et al. Br J Cancer. 2005;92:1182-1187; g. Bouzin C, et al. J Immunol. 2007;178:1505-1511.

Lenvatinib + Pembrolizumab in Advanced Endometrial Cancer

Study 309/KEYNOTE-775: Study Design

Multicenter, Open-label, Phase 3 Study



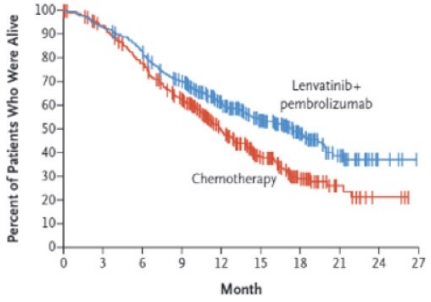
Stratification factors
MMR status(pMMR vs dMMR)
and further stratification within pMMR by
Region
ECOG PS
Pevic RT

BICR, blinded independent central review; HRQoL, health-related quality of ;life.
Makker V, et al. N Engl J Med. 2022;386:437-448.

Lenvatinib + Pembrolizumab in Advanced Endometrial Cancer

Study 309/KEYNOTE-775: OS

pMMR



No. at Risk										
Lenvatinib+pembrolizumab	346	322	285	232	160	109	62	28	5	0
Chemotherapy	351	319	262	201	120	70	33	11	3	0

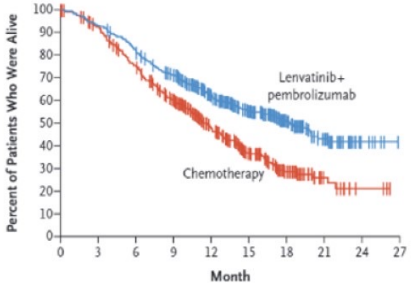
Median Overall Survival (95% CI)	*mo*
Lenvatinib+ Pembrolizumab	17.4 (14.2–19.9)
Chemotherapy	12.0 (10.8–13.3)

Hazard ratio for death, 0.68 (95% CI, 0.56–0.84)
P<0.001

Benefit in OS using lenvatinib + pembrolizumab also reported in dMMR population: NR vs 8.6 mos; *P* = .0001

Significant improvement in OS with lenvatinib + pembrolizumab vs chemotherapy in pMMR and all comers

All-comers



No. at Risk										
Lenvatinib+pembrolizumab	411	383	337	282	198	136	81	40	7	0
Chemotherapy	416	373	300	228	138	80	40	11	3	0

Median Overall Survival (95% CI)	*mo*
Lenvatinib+ Pembrolizumab	18.3 (15.2–20.5)
Chemotherapy	11.4 (10.5–12.9)

Hazard ratio for death, 0.62 (95% CI, 0.51–0.75)
P<0.001

Makker V, et al. N Engl J Med. 2022;386:437-448; EMA. Lenvatinib assessment report. Accessed March 2, 2023. https://www.ema.europa.eu/en/documents/variation-report/lenvima-h-c-003727-ii-0042-epar-assessment-report-variation_en.pdf

Table 3. Adverse Events of Any Cause with an Incidence of 25% or More among All the Patients in Either Treatment Group, According to Preferred Term.

Event	Lenvatinib plus Pembrolizumab (N=406)		Chemotherapy (N=388)	
	Any Grade	Grade ≥3*	Any Grade	Grade ≥3*
Any adverse event	405 (99.8)	361 (88.9)	386 (99.5)	282 (72.7)
Hypertension†	260 (64.0)	154 (37.9)	20 (5.2)	9 (2.3)
Hypothyroidism†‡	233 (57.4)	5 (1.2)	3 (0.8)	0
Diarrhea	220 (54.2)	31 (7.6)	78 (20.1)	8 (2.1)
Nausea	201 (49.5)	14 (3.4)	179 (46.1)	5 (1.3)
Decreased appetite	182 (44.8)	32 (7.9)	82 (21.1)	2 (0.5)
Vomiting	149 (36.7)	11 (2.7)	81 (20.9)	9 (2.3)
Weight decrease	138 (34.0)	42 (10.3)	22 (5.7)	1 (0.3)
Fatigue	134 (33.0)	21 (5.2)	107 (27.6)	12 (3.1)
Arthralgia	124 (30.5)	7 (1.7)	31 (8.0)	0
Proteinuria†	117 (28.8)	22 (5.4)	11 (2.8)	1 (0.3)
Anemia	106 (26.1)	25 (6.2)	189 (48.7)	57 (14.7)
Constipation	105 (25.9)	3 (0.7)	96 (24.7)	2 (0.5)
Urinary tract infection	104 (25.6)	16 (3.9)	39 (10.1)	4 (1.0)
Neutropenia	30 (7.4)	7 (1.7)	131 (33.8)	100 (25.8)
Alopecia	22 (5.4)	0	120 (30.9)	2 (0.5)

Discontinuation
33% of patients

THE REVOLUTION OF FIRST LINE TREATMENT:dMMR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

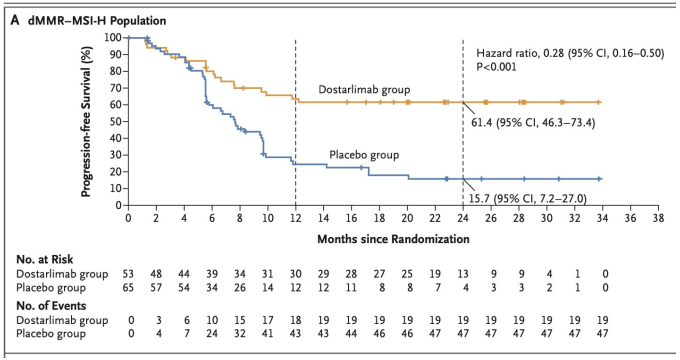
Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

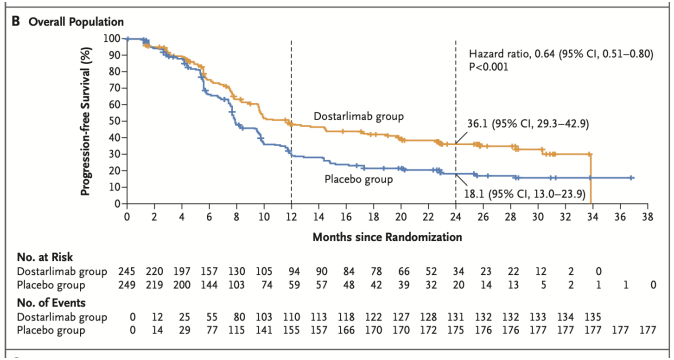
M.R. Mirza, D.M. Chase, B.M. Slomovitz, R. dePont Christensen, Z. Novák, D. Black, L. Gilbert, S. Sharma, G. Valabrega, L.M. Landrum, L.C. Hanker, A. Stuckey, I. Boere, M.A. Gold, A. Auranen, B. Pothuri, D. Cibula, C. McCourt, F. Raspagliesi, M.S. Shahin, S.E. Gill, B.J. Monk, J. Buscema, T.J. Herzog,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

CONCLUSIONS

Dostarlimab plus carboplatin–paclitaxel significantly increased progression-free survival among patients with primary advanced or recurrent endometrial cancer, with a substantial benefit in the dMMR–MSI-H population. (Funded by GSK; RUBY ClinicalTrials.gov number, NCT03981796.)

N ENGL J MED 388;23 NEJM.ORG JUNE 8, 2023





adverse events G3 or higher, 70.5% vs. 59.8%; serious adverse events, 37.8% vs. 27.6%).

Discontinuation of dostarlimab or placebo because of adverse events occurred in 17.4% of patients in the dostarlimab group and in 9.3% of patients in the placebo group.

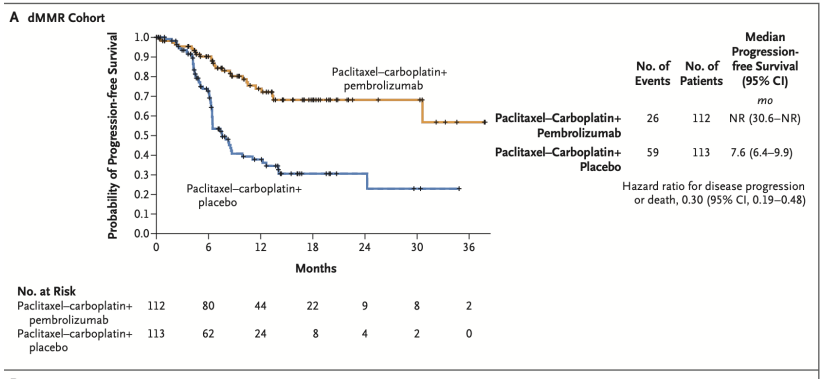
Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

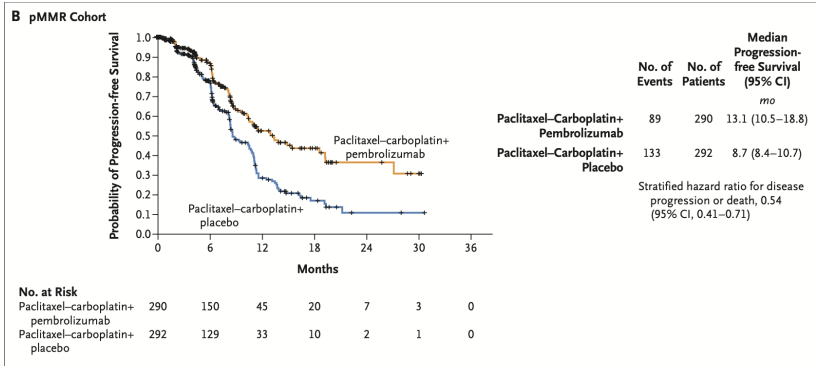
Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D., Richard G. Moore, M.D., Joanie M. Hope, M.D., Fernanda B. Musa, M.D., Robert Mannel, M.D., Mark S. Shahin, M.D., Guilherme H. Cantuaria, M.D., Eugenia Girda, M.D., Cara Mathews, M.D., Juraj Kavecansky, M.D., Charles A. Leath III, M.D., M.S.P.H., Lilian T. Gien, M.D., Emily M. Hinchcliff, M.D., M.P.H., Shashikant B. Lele, M.D., Lisa M. Landrum, M.D., Floor Backes, M.D., Roisin E. O'Cearbhaill, M.D., Tareq Al Baghdadi, M.D., Emily K. Hill, M.D., Premal H. Thaker, M.D., Veena S. John, M.D., Stephen Welch, M.D., Amanda N. Fader, M.D., Matthew A. Powell, M.D., and Carol Aghajanian, M.D.

CONCLUSIONS

In patients with advanced or recurrent endometrial cancer, the addition of pembrolizumab to standard chemotherapy resulted in significantly longer progression-free survival than with chemotherapy alone. (Funded by the National Cancer Institute and others; NRG-GY018 ClinicalTrials.gov number, NCT03914612.)

N Engl J Med 2023;388:2159-70.
DOI: 10.1056/NEJMoa2302312





In the dMMR cohort, grade 3 or higher adverse events were reported in 63.3% of patients in the pembrolizumab group and in 47.2% of those in the placebo group

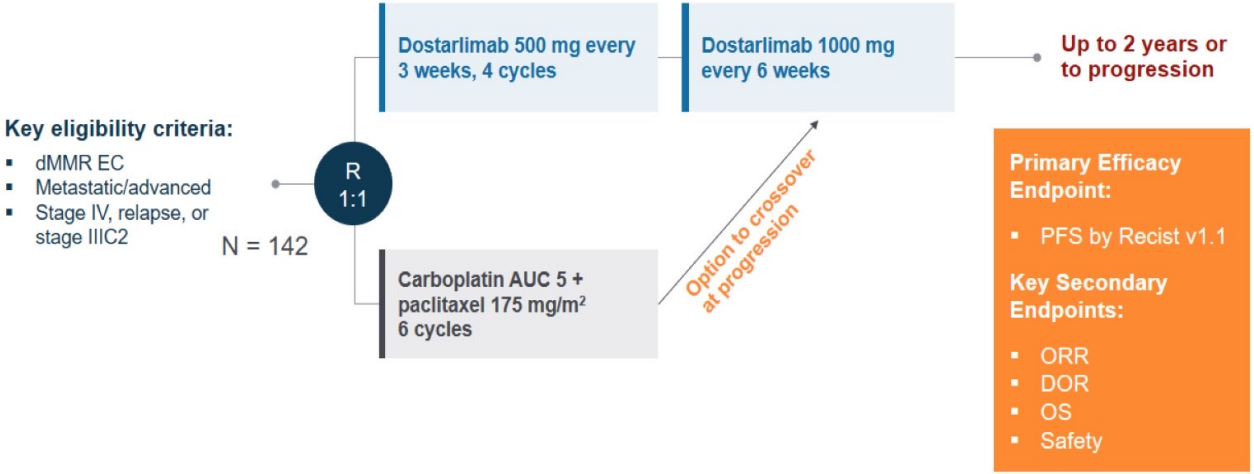
Paperwork for dostarlimab+cht
Approval in dMMR population submitted to EMA

Nominal use in ITALY currently available

Dostarlimab in First-Line dMMR Endometrial Cancer

ENGOT-en13/GINECO/DOMENICA

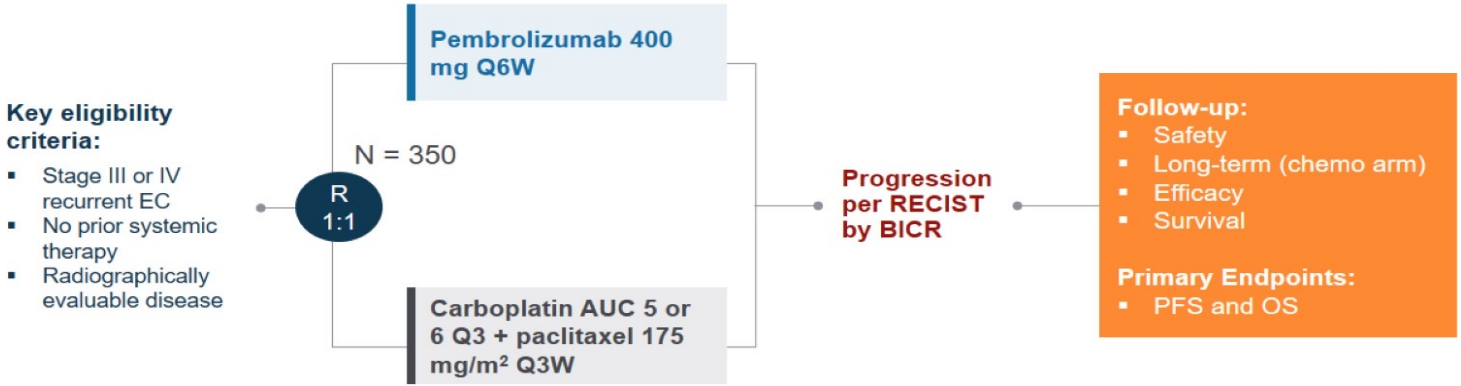
Randomized, Phase 3 trial



DOR, dursation of response.
Clinicaltrials.gov. Accessed February 23, 2023. https://clinicaltrials.gov/ct2/show/NCT05201547

Pembrolizumab in dMMR Advanced/Recurrent Endometrial Cancer
KEYNOTE-C93/ENGOT EN15

Randomized, Open-Label, Phase 3 trial



RECIST, Response Evaluation Criteria in Solid Tumors.
Clinicaltrials.gov. Accessed February 23, 2023. https://clinicaltrials.gov/ct2/show/NCT05173987

Adjuvant therapy

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

Nanda Horeweg, MD, PhD[1]; Remi A. Nout, MD, PhD[1,2]; Ina M. Jürgenliemk-Schulz, MD, PhD[3]; Ludy C.H.W. Lutgens, MD, PhD[4]; Jan J. Jobsen, MD, PhD[5]; Marie A.D. Haverkort, MD[6]; Jan Willem M. Mens, MD[2]; Annerie Slot, MD[7]; Bastiaan G. Wortman, MD, PhD[1,8]; Stephanie M. de Boer, MD, PhD[1]; Ellen Stelloo, PhD, MSc[9]; Karen W. Verhoeven-Adema, PhD[10]; Hein Putter, PhD[11]; Vincent T.H.B.M. Smit, MD, PhD[9]; Tjalling Bosse, MD, PhD[9]; and Carien L. Creutzberg, MD, PhD[1]; for the PORTEC Study Group

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J Clin Oncol 41:4369-4380

PORTEC-1. 484 pts
Pelvic EBRT vs no adj therapy
early stage intermediate risk EC
No BT

PORTEC-2 396 pts
BT vs EBRT
Early stage high-intermediate risk EC

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

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Accepted June 9, 2023
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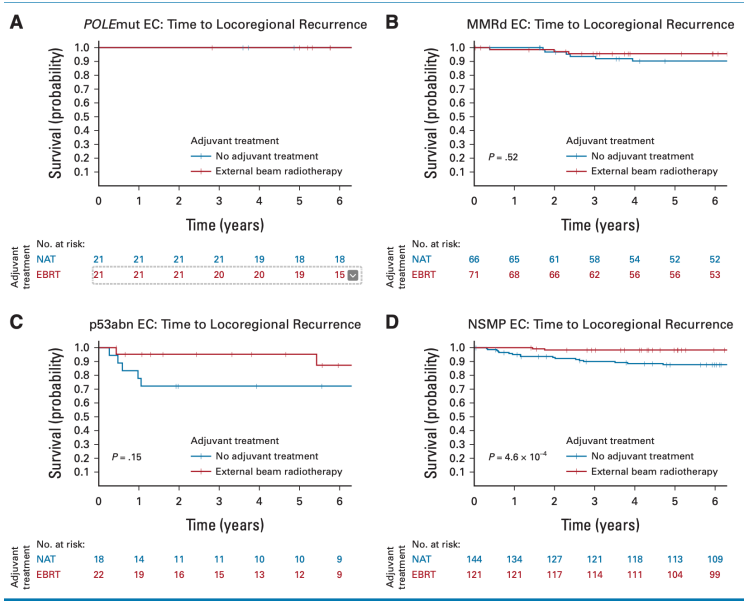
J Clin O

POLEmut
Omitting RT seems be safe



MMRd
EBRT and BT small benefit vs no treat

CONTEXT

Key Objective

To determine the predictiv… therapy (VBT) and pelvic external…

Knowledge Generated

Analyses of data from 880 women included in the randomized PORTEC-1 and PORTEC-2 radiotherapy trials showed at 5 years the following: (1) …dless of adjuvant radiotherapy; (2) similar locoregional recurrence-f… RT (94.2%), VBT (94.2%), and no adjuvant therapy (90.3%; $P = .74$)… survival in p53-abnormal EC with EBRT (96.9%), compared with V…); and (4) significantly better locoregional recurrence-free survival in… 98.3%) and VBT (96.2%) compared with no adjuvant therapy (87.7%; $P < .0001$).

Relevance ***(G.F. Fleming)***

Systemic therapy for EC … adds to our knowledge about also adapting radiotherapy fo…

P53abn
EBRT is recommended

NSMP
Advantage with adj treat
Better BT

PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer

OPEN ACCESS

Anne Sophie V M van den Heerik ,[1] Nanda Horeweg ,[1] Remi A Nout,[2] Ludy C H W Lutgens,[3] Elzbieta M van der Steen-Banasik,[4] G Henrike Westerveld,[5] Hetty A van den Berg,[6] Annerie Slot,[7] Friederike L A Koppe,[8] Stefan Kommoss,[9] Jan Willem M Mens,[2] Marlies E Nowee,[10] Stefan Bijmolt,[11] David Cibula,[12] Tanja C Stam,[13] Ina M Jurgenliemk-Schulz,[14] An Snyers,[15] Moritz Hamann,[16] Aleida G Zwanenburg,[17] Veronique L M A Coen,[18] Katrien Vandecasteele,[19] Charles Gillham,[20] Cyrus Chargari,[21] Karen W Verhoeven-Adema,[22] Hein Putter,[23] Wilbert B van den Hout,[24] Bastiaan G Wortman,[1] Hans W Nijman,[25] Tjalling Bosse,[26] Carien L Creutzberg[1]

Table 1 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 Stage I EEC, grade 1–2, LVSI unequivocally positive, any myometrial invasion	Vaginal brachytherapy Consider pelvic external beam radiotherapy if LVSI is unequivocally positive, especially if no lymph node dissection or sentinel node has been performed.
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

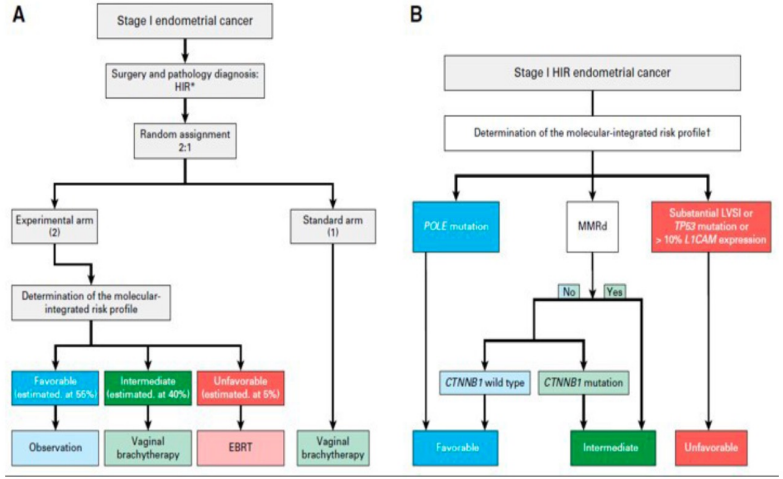
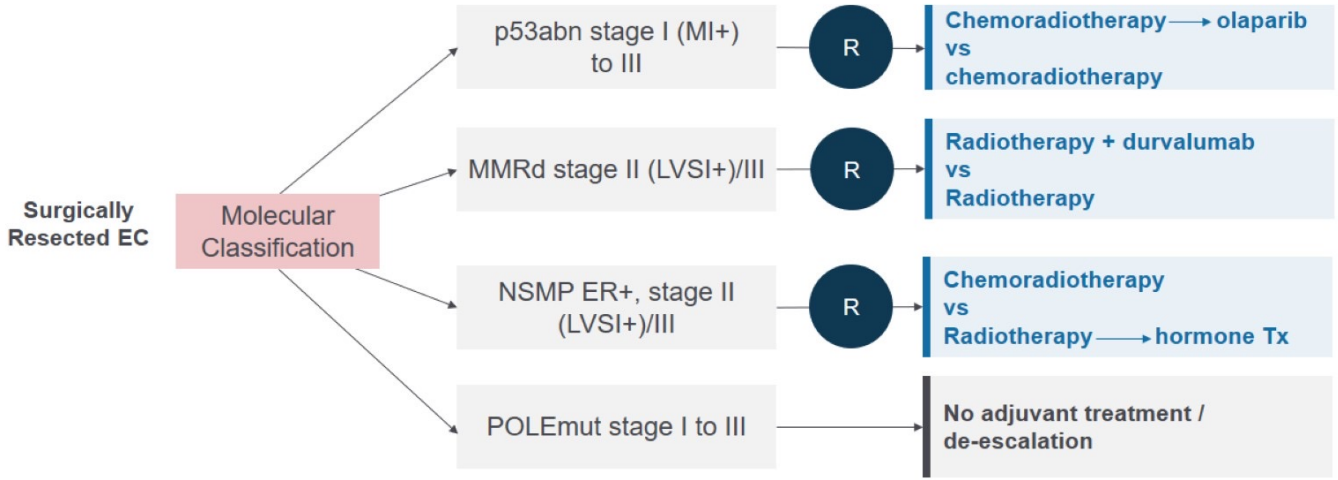


Figure 1 Study design PORTEC-4a trial. Reprinted from 'Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: evaluation of the pilot phase of the PORTEC-4a trial' by Wortman et al., 2018, *Gynecologic Oncology* 151; 69–75. A: trial design of the PORTEC-4a trial; B: decision tree for the molecular-integrated profile; *CTNNB1*, β-catenin; EBRT, external beam radiotherapy; LVSI; lymph-vascular space invasion; HIR, high-intermediate risk; L1-CAM, L1-cell adhesion molecule; *POLE*, polymerase-ε * stage I (with invasion) disease, grade 3 tumor; stage IB disease, grade 1 or 2 tumor, with either age 60 years or older or substantial LVSI; stage IB disease, grade 3 tumor, without LVSI; or stage II (microscopic) disease, grade 1 tumor.

Molecular Based Adjuvant Treatment in Endometrial Cancer

RAINBO ENGOT-EN1-4

Phase 2/3 trials



EEC, endometrioid endometrial carcinoma;
RFS, recurrence-free survival;
SER, serous endometrial carcinoma.

Primary endpoint: 3-year RFS

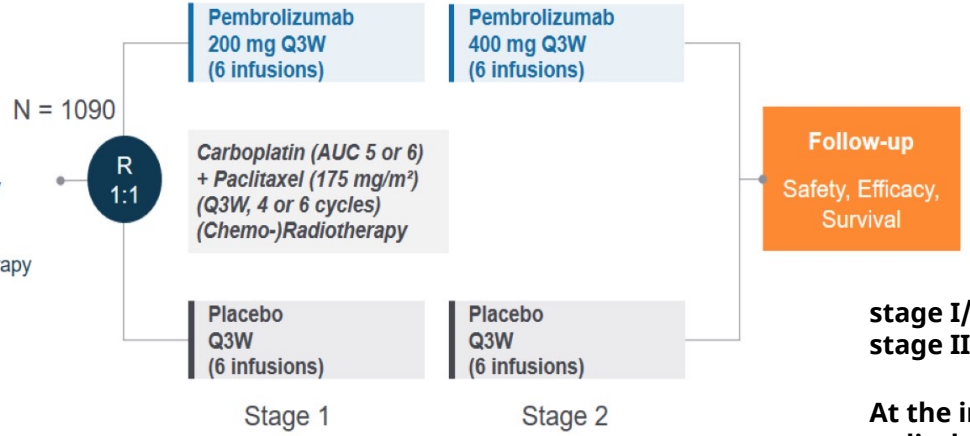
Clinicaltrials.gov. Accessed February 23, 2023. https://clinicaltrials.gov/ct2/show/NCT05255653; RAINBO Research Consortium. Int J Gynecol Cancer. 2022;33:109-117.

Pembrolizumab + Adjuvant Chemotherapy ± Radiotherapy in High-Risk Endometrial Cancer: *ENGOT-EN11/KEYNOTE-B21*

Randomized, Double blind, Phase 3 trial

Key eligibility criteria

- Newly diagnosed Endometrial Carcinoma or Carcinosarcoma
- Undergone curative intent surgery
- No residual disease
- At high risk for recurrence
- No prior radiation or systemic therapy

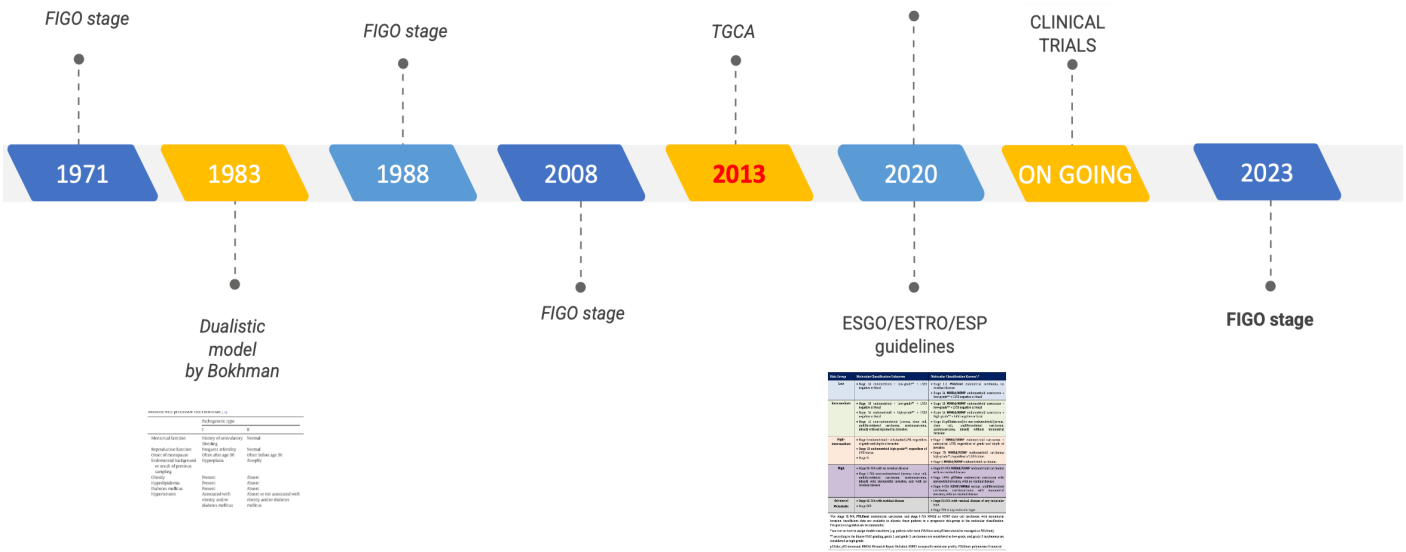


stage I/II non-endometrioid, stage III/IVa, p53 abnormality

At the investigator's discretion radiotherapy (EBRT and/or brachytherapy) ± radiosensitizing cisplatin 50 mg/m²

Clinicaltrials.gov. Accessed February 23, 2023. https://clinicaltrials.gov/ct2/show/NCT04634877.

ENDOMETRIAL CANCER HISTORY



FIGO staging 2009

14 years later

FIGO staging 2023

1. Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, et al. FIGO staging of endometrial cancer: 2023. International Journal of Gynecology & Obstetrics. 2023;n/a(n/a).
2. Creasman W. Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet. 2009;105(2):109.
3. Abu-Rustum NR, Zhou Q, Iasonos A, Alektiar KM, Leitao MM, Jr., Chi DS, et al. The revised 2009 FIGO staging system for endometrial cancer: should the 1988 FIGO stages IA and IB be altered? Int J Gynecol Cancer. 2011;21(3):511-6.

Histotype

Aggressive vs. non-aggressive

- Endometrioid → G1-2 → Non-aggressive
- Endometrioid → G3 → Aggressive
- Serous → Aggressive
- Clear cell → Aggressive
- Mixed → Aggressive
- Undifferentiated → Aggressive
- Carcinosarcoma → Aggressive
- Mesonephric-like → Aggressive
- Gastrointestinal mucinous → Aggressive

Grade

Low vs. High grade

- Low grade (G1-G2) → Non-aggressive
- High grade (G3) → Aggressive

Non-aggressive according to FIGO = low grade (G1-2) endometrioid

WHO Classification of Tumours Editorial Board. Female Genital Tumours, WHO Classification of Tumours. 5th ed2020.

Lymphovascular space invasion

Three-tiered system

- Absent (0 vessels) → Negative
- Focal (< 5 vessels) → Negative
- Substantial (≥ 5 vessels) → Positive

Adnexal involvement

Synchronous vs. metastatic

Low grade endometrioid involving both endometrium and ovary and:

- < 50% myometrial invasion
- Absent/focal LVSI
- Absence of additional metastases
- Ovarian tumor without capsule invasion/rupture T1a (TNM)

→ Synchronous primary (I

Remaining concomitants tumors → Metastatic (IIIA1)

Lymph node involvement

micrometastasis vs. macrometastasis

Micrometastasis (mM)	Macrometastasis (MM)
• 0.2-2mm in a single cross-section and/or more than 200 cells	• >2mm in a single cross-section

1. WHO Classification of Tumours Editorial Board. Female Genital Tumours, WHO Classification of Tumours. 5th ed2020.
2. Bosse T, Peters EE, Creutzberg CL, Jürgenliemk-Schulz IM, Jobsen JJ, Mens JW, et al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 Eur J Cancer. 2015;51(13):1742-50.
3. Barnes EA, Martell K, Parra-Herran C, Taggar AS, Donovan E, Leung E. Substantial lymphovascular space invasion predicts worse outcomes in early-stage endometrioid endometrial cancer. Brachytherapy. 2021;20(3):527-35.
4. Peters EEM, León-Castillo A, Smit V, Boennelycke M, Hogdall E, Hogdall C, et al. Defining Substantial Lymphovascular Space Invasion in Endometrial Cancer. Int J Gynecol Pathol. 2022;41(3):220-6.

Turashvili G, Gómez-Hidalgo NR, Flynn J, Gonen M, Leitao MM, Jr., Soslow RA, et al. Risk-based stratification of carcinomas concurrently involving the endometrium and ovary. Gynecol Oncol. 2019;152(1):38-45.

Unchanged definitions

Myometrial invasion: none (like in the 1988), <50%, ≥50%

Cervical stromal invasion: absent, present

Uterine serosal invasion: absent, present

Peritoneal washing: not considered for staging purposes

Stage I

Confined to the uterine corpus and ovary

FIGO 2023	Description	FIGO 2009
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	IA, **IIIA**
IA1	Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium	IA
IA2	Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI	IA
IA3	Low-grade endometrioid carcinomas limited to the uterus and ovary	**IIIA**
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI	IB
IC	Aggressive histological types limited to a polyp or confined to the endometrium	**IA**

Stage I

KEY CHANGES

- Re-introduction of superficial tumor involvement in a polyp or endometrium
- Stage restricted to:
  - Non-aggressive histological types
  - The absence of substantial/extensive LVSI
  - Aggressive histological types only if without myometrial invasion
- New distinction of synchronous low-grade endometrioid carcinomas involving the endometrium and the ovaries I vs III disease
  (based on molecular analysis that have established a common clonal origin associated with an overall good prognosis)

Stage II

Invasion of cervical stroma with extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion

FIGO 2023	Description	FIGO 2009
IIA	Invasion of the cervical stroma of non-aggressive histological types	II
IIB	Substantial LVSI of non-aggressive histological types	**IA, IB**, II
IIC	Aggressive histological types with any myometrial involvement	**IA, IB**, II

Stage II

KEY CHANGES

- The number of women with Stage II tumors will increase
- Cases with substantial LVSI, regardless other features (tumor spread or histoype)
- Stage IIC tumors represents aggressive histological subtype with myometrial invasion (any deep)

Remember: aggressive histology with NO myometrial invasion are classified Stage IC

Stage III

Local and/or regional spread of the tumor of any histological subtype

FIGO 2023	Description	FIGO 2009
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)	IIIA
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	IIIB, **IVB**
IIIB1	Metastasis or direct spread to the vagina and/or the parametria	IIIB
IIIB2	Metastasis to the pelvic peritoneum	**IVB**
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both	IIIC
IIIC1	Metastasis to the pelvic lymph nodes	
IIIC1i	Micrometastasis	IIIC1
IIIC1ii	Macrometastasis	
IIIC2	Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes	
IIIC2i	Micrometastasis	IIIC2
IIIC2ii	Macrometastasis	

Stage III

KEY CHANGES

- Further differentiation within the IIIA stage (IIIA1 vs IIIA2) to better reflect tumor behavior
- Introduction of IIIB2 for involvement of pelvic peritoneum (previous stage IV)
- Introduction of differentiation based on lymph node involvement : macro (IIICii) vs micrometastasis (IIICi) while isolated tumor cells (ITC) are not considered metastatic

This subcategorization also allows improved identification of low volume disease, including micrometastasis, in ultrastaged SLN.

Stage IV

Local and/or regional spread of the tumor of any histological subtype

FIGO 2023	Description	FIGO 2009
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa	IVA
IVB	Abdominal peritoneal metastasis beyond the pelvis	IVB
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone	**IIIC, IVB**

Stage IV

KEY CHANGES

- Addition of an extra substage for those presenting with extrapelvic peritoneal metastasis (Stage IVB)
- Distant metastasis have now become Stage IVC

Molecular classification

History and definition

TCGA	Surrogate	Abbreviation	Prognosis	Frequency
POLE ultramutated	*POLE* mutated	POLEmut	**Excellent**	5-15%
Microsatellite high/hypermutated	MMR deficient	MMRd	Intermediate	20-30%
Somatic copy-number alteration high	p53 abnormal	p53abn	**Poor**	10-25%
Somatic copy-number alteration low	No specific molecular profile	NSMP	Intermediate	30-60%

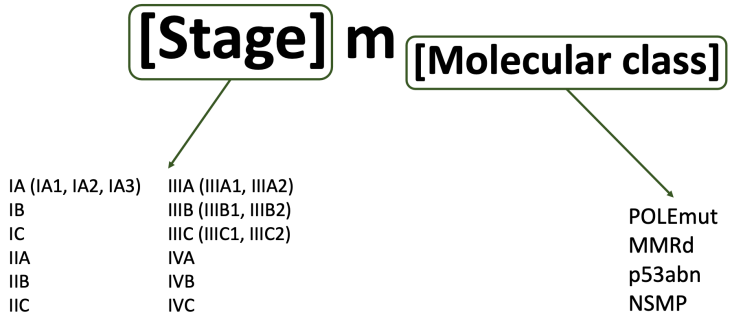
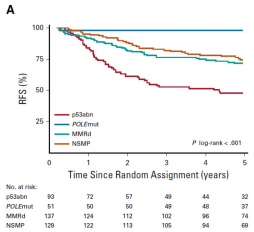


TABLE 2 FIGO endometrial cancer stage with molecular classification.[a]

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

IAm$_{POLEmut}$
WHY Downstage

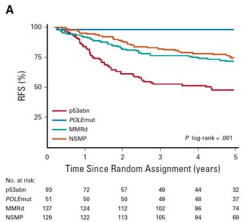


PORTEC-3 2020
51/410 high-risk POLEmut (1 recurrence)
76% early stages
5-year RFS POLEmut 98% – aHR 0.08 [95%CI 0.01-0.58]

McAlpine et al. 2021
109 POLEmut and no adjuvant treatment
Only 3 recurrences (all in high-risk patients)

Leon-Castillo et al. 2022
26 high-grade POLEmut (lymphadenectomy and no adjuvant treatment)
No recurrences recorded

IICm$_{p53abn}$
WHY Upstage



PORTEC-3 2020
93/410 high-risk p53abn
5-year RFS p53abn 48% – aHR 2.5 [95%CI 1.62-3.91]

66% early stages but only 4 low-grade endometrioid

Five-year RFS with CTRT versus RT for p53abn was 59% versus 36% (P=0.02)

León-Castillo A, de Boer SM, Powell ME, Mileshkin LR, Mackay HJ, Leary A, et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. 2020;38(29):3388-97.
Vrede SW, Kasius J, Bulten J, Teerenstra S, Huvila J, Colas E, et al. Relevance of Molecular Profiling in Patients With Low-Grade Endometrial Cancer. JAMA Network Open. 2022;5(12):e2247372-e.

Changes in stage

Advanced stages (Stage III-IV)

- **Advanced stages do not change with the molecular classification.**
- The FIGO Committee proposes using the new nomenclature for the purpose of data collection.
- The use of MMRd nomenclature is especially important due to the predictive value of MMRd for immune checkpoint inhibitor treatment.

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ejcancer.com
ELSEVIER
EJC

Original Research

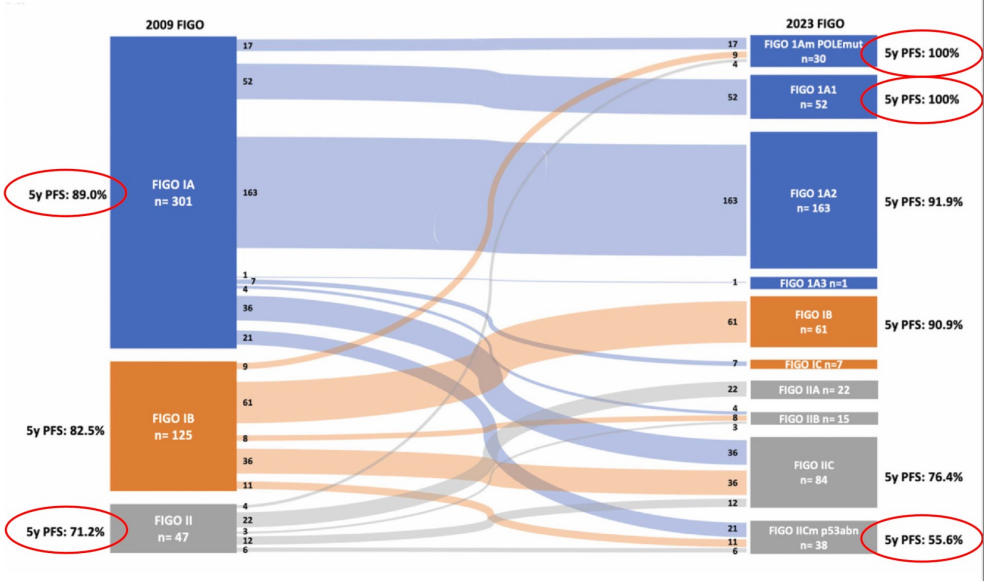
Verification of the prognostic precision of the new 2023 FIGO staging system in endometrial cancer patients – An international pooled analysis of three ESGO accredited centres

Richard Schwameis [a], Francesco Fanfani [b,c], Christoph Ebner [d], Naomi Zimmermann [a], Inge Peters [b,c], Camilla Nero [b,c], Christian Marth [d], Robin Ristl [e], Katharina Leitner [d], Christoph Grimm [a], Felicitas Oberndorfer [f], Ilaria Capasso [b,c], Alain G. Zeimet [d], Stephan Polterauer [a], Giovanni Scambia [b,c], Anna Fagotti [b,c], Nicole Concin [d,*]

- retrospective study of 519 EC patients
- primary treatment (and molecular characterisation) at 3 ESGO accredited centres

Gemelli — Fondazione Policlinico Universitario A. Gemelli Università Cattolica del Sacro Cuore
MEDICAL UNIVERSITY OF VIENNA
MEDIZINISCHE UNIVERSITÄT INNSBRUCK

Stage shifts between 2009 and 2023 FIGO in 473 patients with **early stage disease** (stages I/II)

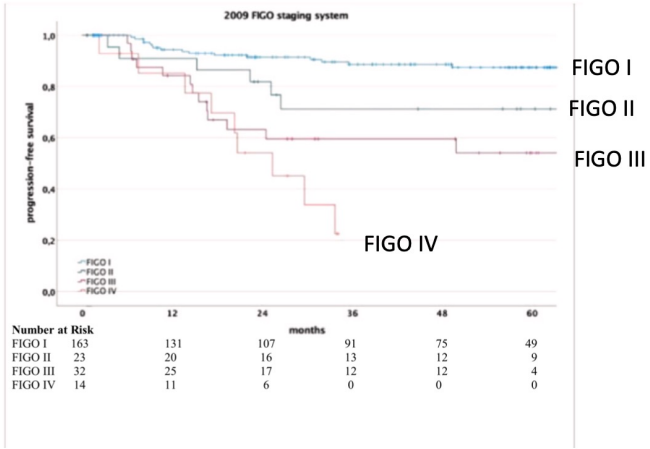


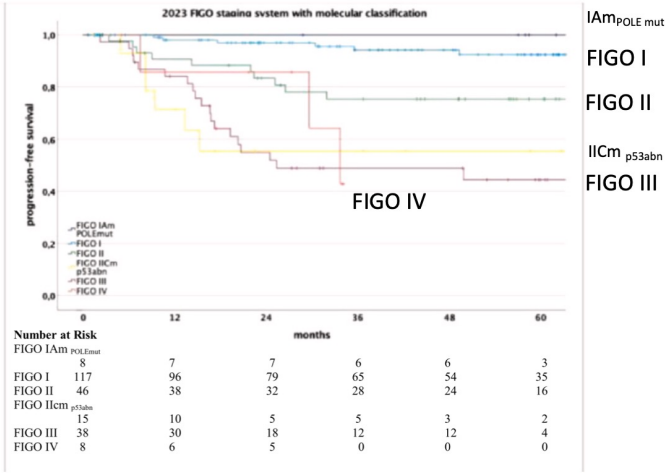
Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ejcancer.com

Original Research

Verification of the prognostic precision of the new 2023 FIGO staging system in endometrial cancer patients – An international pooled analysis of three ESGO accredited centres

Richard Schwameis [a], Francesco Fanfani [b,c], Christoph Ebner [d], Naomi Zimmermann [a], Inge Peters [b,c], Camilla Nero [b,c], Christian Marth [d], Robin Ristl [e], Katharina Leitner [d], Christoph Grimm [a], Felicitas Oberndorfer [f], Ilaria Capasso [b,c], Alain G. Zeimet [d], Stephan Polterauer [a], Giovanni Scambia [b,c], Anna Fagotti [b,c], Nicole Concin [g,a]





IAm$_{POLE\ mut}$

FIGO I

FIGO II

IICm $_{p53abn}$

FIGO III

More accurate prediction of PFS by the 2023 FIGO staging system compared to 2009

Contents lists available at ScienceDirect

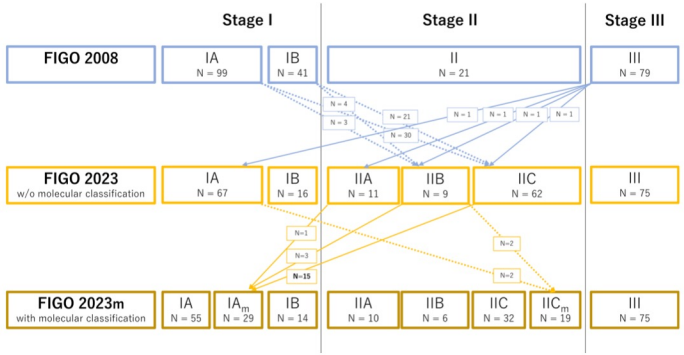
Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

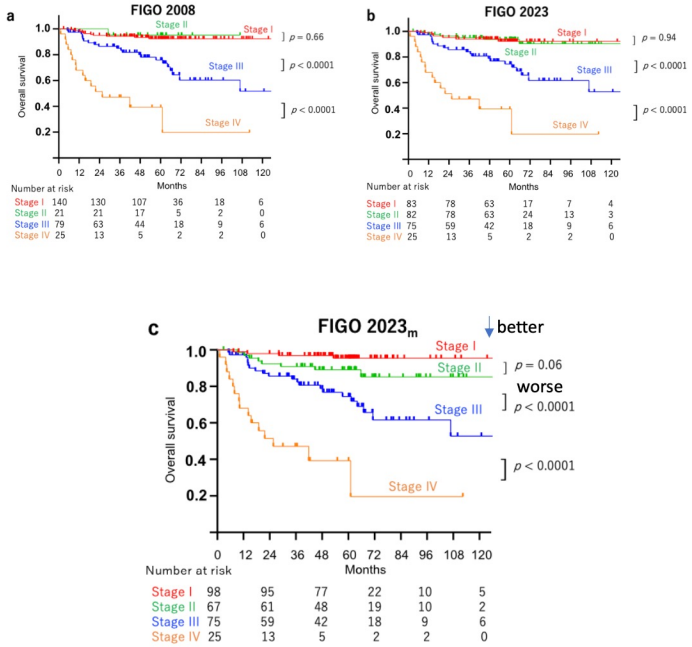
Utility of the revised FIGO2023 staging with molecular classification in endometrial cancer

Mayumi Kobayashi-Kato [a,b], Erisa Fujii [a,b], Yuka Asami [a,c], Yuka Ahiko [d], Kengo Hiranuma [a,e], Yasuhisa Terao [e], Koji Matsumoto [c], Mitsuya Ishikawa [b], Takashi Kohno [a], Tomoyasu Kato [b], Kouya Shiraishi [a,*], Hiroshi Yoshida [f,*]

265 patients



- **FIGO2023m classification had the best discriminatory ability** compared with FIGO2008 and FIGO2023.
- The presence of StageIAmPOLEmut, and Stage IICmp53abn impacts prognostic outcome.



Open questions/Controversies

- Only retrospective evidence (especially FOR MOLECULAR CLASSIFICATION SHIFT)
- Is the complete molecular analysis mandatory for all patients?
- In the absence of molecular classification, all high grade endometrioid endometrial cancers are considered high risk
- Integration of prognostic and anatomical factors in only one system
- Variability of LVSI assessment among pathologists

FIGO Stage should be an easy tool appliable worldwide!

Are we sure that we are using a common language universally?

CERVICE UTERINA	
Incidenza	Nel 2022, sono stimate circa 2.500 nuove diagnosi (1,3% di tutti i tumori incidenti nelle donne). Questa neoplasia è più frequente nella fascia giovanile (4% dei casi, quinta neoplasia più frequente). Stime non disponibili per il 2023
Mortalità	Nel 2022 sono state stimate 2.500 morti complessive per tutti i tumori dell'utero. Stime non disponibili per il 2023
Sopravvivenza netta a 5 anni dalla diagnosi	68%
Probabilità di vivere ulteriori 4 anni condizionata ad aver superato il primo anno dopo la diagnosi	75%
Prevalenza	Sono 51.100 le donne viventi in Italia dopo una diagnosi di tumore della cervice uterina

Table 1: International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging of Cancer of the Cervix Uteri (2018)

Stage		Description
I		The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded).
	IA	Invasive carcinoma that can be diagnosed only by microscopy with maximum depth of invasion ≤5 mm[a]
	IA1	Measured stromal invasion ≤3 mm in depth
	IA2	Measured stromal invasion >3 mm and ≤5 mm in depth
	IB	Invasive carcinoma with measured deepest invasion >5 mm (greater than stage IA); lesion limited to the cervix uteri with size measured by maximum tumor diameter[b]
	IB1	Invasive carcinoma >5 mm depth of stromal invasion and ≤2 cm in greatest dimension
	IB2	Invasive carcinoma >2 cm and ≤4 cm in greatest dimension
	IB3	Invasive carcinoma >4 cm in greatest dimension
II		The cervical carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
	IIA	Involvement limited to the upper two-thirds of the vagina without parametrial invasion
	IIA1	IIA1 Invasive carcinoma ≤4 cm in greatest dimension
	IIA2	Invasive carcinoma >4 cm in greatest dimension
	IIB	With parametrial invasion but not up to the pelvic wall
III		The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes
	IIIA	Carcinoma involves lower third of the vagina, with no extension to the pelvic wall
	IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
	IIIC	Involvement of pelvic and/or paraaortic lymph nodes (including micrometastases),[c] irrespective of tumor size and extent (with r and p notations).
	IIIC1	Pelvic lymph node metastasis only
	IIIC2	Paraaortic lymph node metastasis
IV		The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV
	IVA	Spread of the growth to adjacent organs
	IVB	Spread to distant organs

Early stage CC: radical surgery with tailored adjuvant therapy — 5-yrs OS 90%

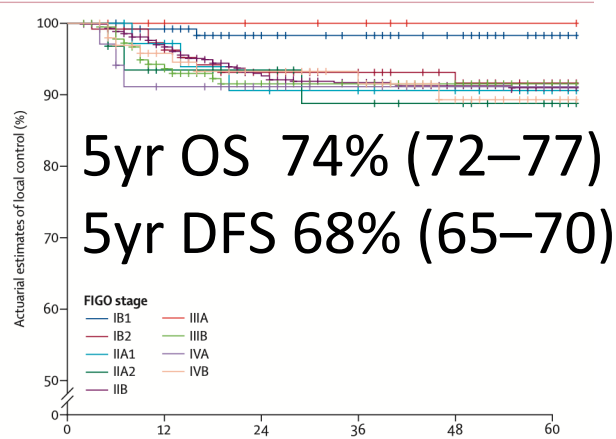
LACC (FIGO IB2-IVA): chemoradiation. 5-yrs OS 72-88%

Advanced (FIGO IVB) and recurrent: 5-yrs OS < 10%

MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study

Richard Pötter, Kari Tanderup, Maximilian Paul Schmid, Ina Jürgenliemk-Schulz, Christine Haie-Meder, Lars Ulrik Fokdal, Alina Emiliana Sturdza, Peter Hoskin, Umesh Mahantshetty, Barbara Segedin, Kjersti Bruheim, Fleur Huang, Bhavana Rai, Rachel Cooper, Elzbieta van der Steen-Banasik, Erik Van Limbergen, Bradley Rumwell Pieters, Li-Tee Tan, Remi Abubakar Nout, Astrid Agatha Catharina De Leeuw, Robin Ristl, Primoz Petric, Nicole Nesvacil, Kathrin Kirchheiner, Christian Kirisits, Jacob Christian Lindegaard, EMBRACE Collaborative Group*

Lancet Oncol 2021; 22: 538–47



5yr OS 74% (72–77)

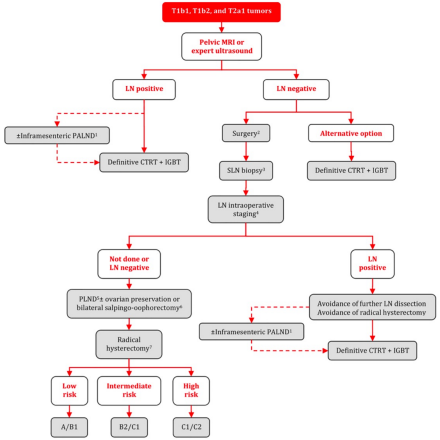
5yr DFS 68% (65–70)

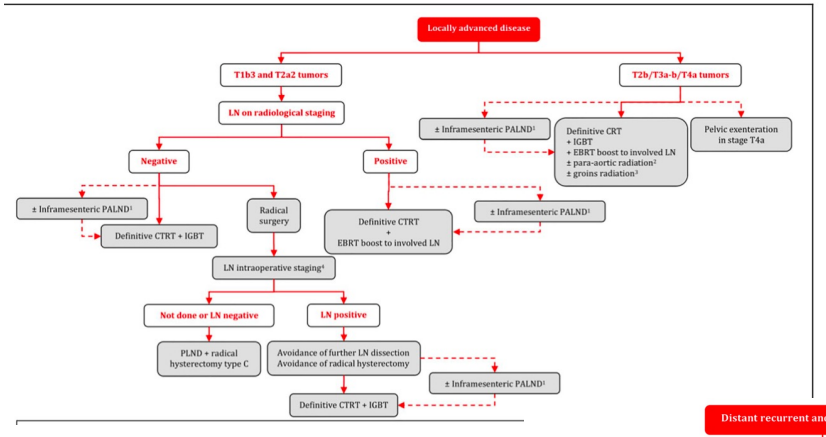
ORIGINAL ARTICLE

ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer – Update 2023*

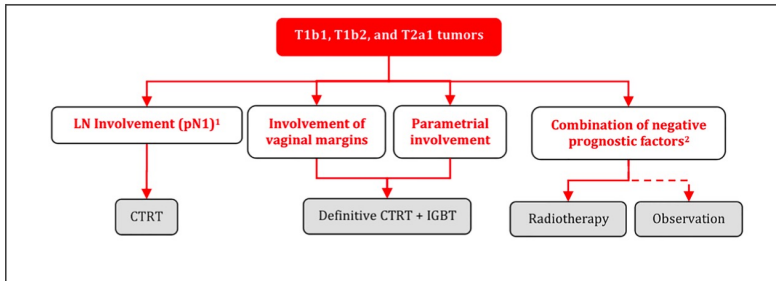
David Cibula[1,2] · Maria Rosaria Raspollini[3] · François Planchamp[4] · Carlos Centeno[5] · Cyrus Chargari[6] · Ana Felix[7,8] · Daniela Fischerová[1,2] · Daniela Jahnn-Kuch[9] · Florence Joly[10] · Christhardt Kohler[11,12] · Sigurd Lax[13,14] · Domenica Lorusso[15,16] · Umesh Mahantshetty[17] · Patrice Mathevet[18] · Raj Naik[19] · Remi A. Nout[20,21] · Ana Oaknin[22,23] · Fedro Peccatori[24] · Jan Persson[25,26] · Denis Querleu[15,27] · Sandra Rubio Bernabé[28] · Maximilian P. Schmid[29] · Artem Stepanyan[30] · Valentyn Svintsitskyi[31] · Karl Tamussino[32] · Ignacio Zapardiel[33] · Jacob Lindegaard[34]

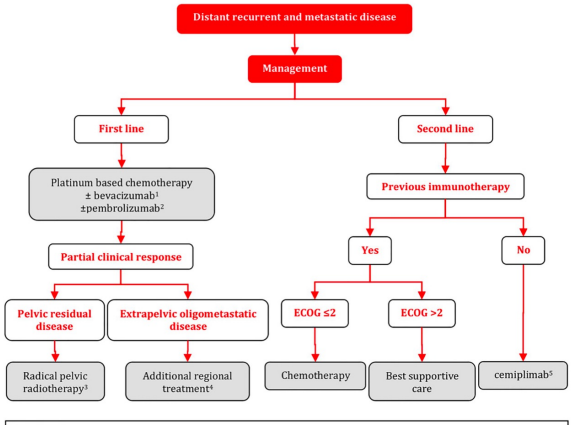
Received: 20 April 2023 / Revised: 20 April 2023 / Accepted: 24 April 2023





Adjuvant Treatment of T1b1, T1b2, and T2a1 Tumors





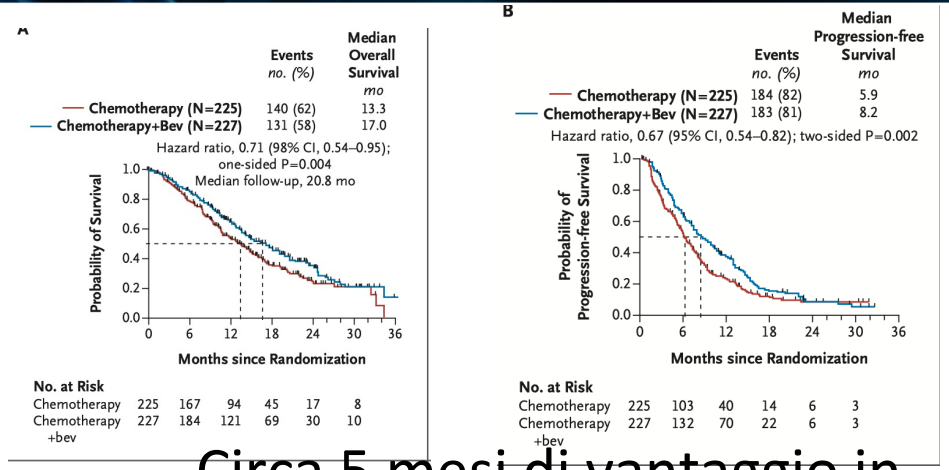
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Bevacizumab in Advanced Cervical Cancer

Krishnansu S. Tewari, M.D., Michael W. Sill, Ph.D., Harry J. Long III, M.D., Richard T. Penson, M.D., Helen Huang, M.S., Lois M. Ramondetta, M.D., Lisa M. Landrum, M.D., Ana Oaknin, M.D., Thomas J. Reid, M.D., Mario M. Leitao, M.D., Helen E. Michael, M.D., and Bradley J. Monk, M.D.

N Engl J Med 2014;370:734-43.
DOI: 10.1056/NEJMoa1309748



Circa 5 mesi di vantaggio in OS nel gruppo con Beva

Primary stage IVB
Recurrent /persistent
No prior CHT for recurrence

CONCLUSIONS

The addition of bevacizumab to combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer was associated with an improvement of 3.7 months in median overall survival. (Funded by the National Cancer Institute; GOG 240 ClinicalTrials.gov number, NCT00803062.)

Dopo carbo-taxo-Beva mediana di sopravvivenza circa 8 mesi

Regimi di II linea

Topotecan

Vinorelbina

Pemetrexed

Docetaxel

Gemcitabina

bevacizumab

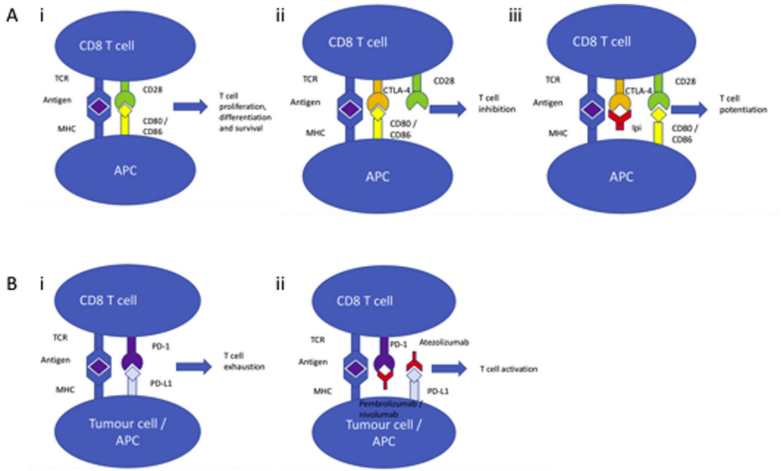
ORR circa 12%

OS 7 mesi

Overview

The Role of Biomarkers for the Prediction of Response to Checkpoint Immunotherapy and the Rationale for the Use of Checkpoint Immunotherapy in Cervical Cancer

S.J. Otter*†, J. Chatterjee*†, A.J. Stewart*†, A. Michael*†



HPV-related cancer

PD-L1 overexpressed (19% to 88%)

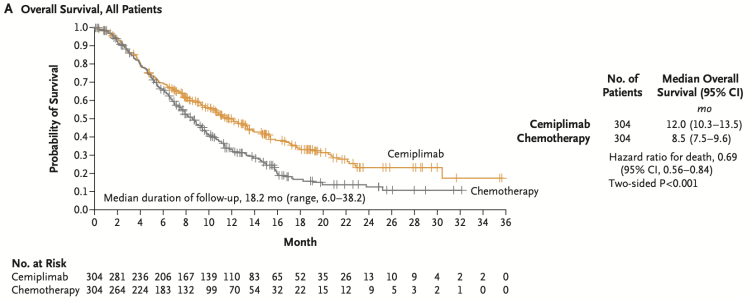
High TMB

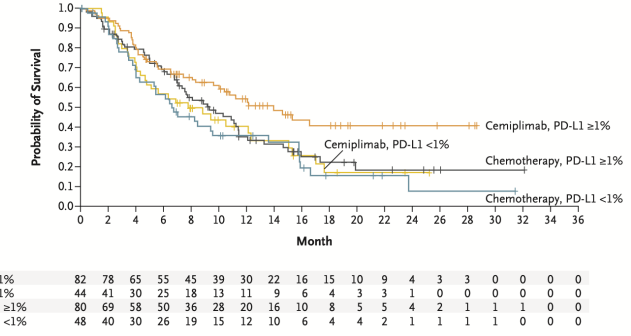
Keynote-158	Pembrolizumab
Checkmate 358	Nivolumab

Survival with Cemiplimab in Recurrent Cervical Cancer

K.S. Tewari, B.J. Monk, I. Vergote, A. Miller, A.C. de Melo, H.-S. Kim, Y.M. Kim, A. Lisyanskaya, V. Samouëlian, D. Lorusso, F. Damian, C.-L. Chang, E.A. Gotovkin, S. Takahashi, D. Ramone, J. Pikiel, B. Maćkowiak-Matejczyk, E.M. Guerra Alía, N. Colombo, Y. Makarova, D. Rischin, S. Lheureux, K. Hasegawa, K. Fujiwara, J. Li, S. Jamil, V. Jankovic, C.-I Chen, F. Seebach, D.M. Weinreich, G.D. Yancopoulos, I. Lowy, M. Mathias, M.G. Fury, and A. Oaknin, for the Investigators for GOG Protocol 3016 and ENGOT Protocol En-Cx9*

N Engl J Med 2022;386:544-55.





CONCLUSIONS

Survival was significantly longer with cemiplimab than with single-agent chemotherapy among patients with recurrent cervical cancer after first-line platinum-containing chemotherapy. (Funded by Regeneron Pharmaceuticals and Sanofi; EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 ClinicalTrials.gov number, NCT03257267.)

Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer

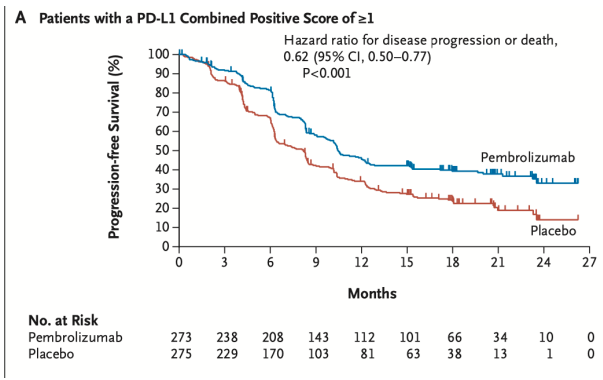
N. Colombo, C. Dubot, D. Lorusso, M.V. Caceres, K. Hasegawa, R. Shapira-Frommer, K.S. Tewari, P. Salman, E. Hoyos Usta, E. Yañez, M. Gümüş, M. Olivera Hurtado de Mendoza, V. Samouëlian, V. Castonguay, A. Arkhipov, S. Toker, K. Li, S.M. Keefe, and B.J. Monk, for the KEYNOTE-826 Investigators*

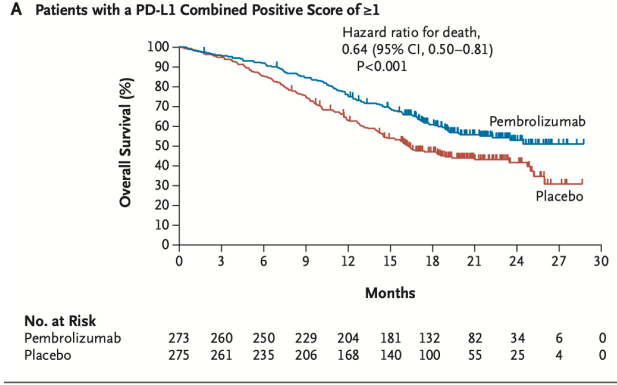
N Engl J Med 2021;385:1856-67.

First line treatment

Pembrolizumab
+
Paclitaxel+cisplatin or carboplatin
+- bevacizumab

placebo
+
Paclitaxel+cisplatin or carboplatin
+- bevacizumab





CONCLUSIONS

Progression-free and overall survival were significantly longer with pembrolizumab than with placebo among patients with persistent, recurrent, or metastatic cervical cancer who were also receiving chemotherapy with or without bevacizumab. (Funded by Merck Sharp and Dohme; KEYNOTE-826 ClinicalTrials.gov number, NCT03635567.)

AIFA: Solo per pts PL1 pos

Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer

N. Colombo, C. Dubot, D. Lorusso, M.V. Caceres, K. Hasegawa, R. Shapira-Frommer, K.S. Tewari, P. Salman, E. Hoyos Usta, E. Yañez, M. Gümüş, M. Olivera Hurtado de Mendoza, V. Samouëlian, V. Castonguay, A. Arkhipov, S. Toker, K. Li, S.M. Keefe, and B.J. Monk, for the KEYNOTE-826 Investigators*

	Gastrointestinal	Genitourinary	Vaginal	Fistula*	Overall (gastrointestinal, genitourinary, vaginal, and fistula)
Grade 3 adverse events					
Number of events	83	93	54	18	248
Number of patients	54 (4·3%)	59 (4·7%)	50 (4·0%)	13 (1·0%)	128 (10·2%)
Actuarial 5-year cumulative incidence of grade 3 or higher morbidity (95% CI)	8·5% (6·9–10·6)	6·8% (5·4–8·6)	5·7% (4·3–7·6)	3·2% (2·2–4·5)	18·4% (16·0–21·2)
Grade 4 adverse events					
Number of events	34	19	5	24	82
Number of patients	27 (2·2%)	16 (1·3%)	5 (0·4%)	21 (1·7%)	55 (4·4%)
Actuarial 5-year cumulative incidence of grade 4 or higher morbidity (95% CI)	3·0% (2·0–4·3)	1·0% (0·6–1·9)	0·5% (0·2–1·2)	2·1% (1·5–3·2)	5·2% (4·0–6·9)

Data are n, n (%), or actuarial cumulative incidence (95% CI). Adverse events were classified according to the Common Terminology Criteria for Adverse Events, version 3.0. Data were available for 1251 patients. Grade 5 events are not listed because they were not always allocated to a single organ system.
Eight gastrointestinal events, four genitourinary events, four fistulas, and five septic infections contributed to treatment-related death in 12 patients.
*15 vesico-vaginal, 10 recto-vaginal, 4 sigmoid-vagina, 13 other fistulas.

Table 4: **Grade 3–4 morbidity**

Interruzione del pembrolizumab
< 5% delle pts

BEATcc Trial

Open-label, multicentre, randomized, phase 3 trial in all-comer pts

Metastatic, Persistent Recurrent CC

1.1

410

Atezolizumab
+
Paclitaxel+cisplatin or carboplatin
+-bevacizumab

placebo
+
Paclitaxel+cisplatin or carboplatin
+-bevacizumab

38% risk of progression

PFS 36 months 26% vs 12%

Low toxicity profile

ESMO 2023

INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER
OPEN ACCESS

CALLA: Efficacy and safety of concurrent and adjuvant durvalumab with chemoradiotherapy versus chemoradiotherapy alone in women with locally advanced cervical cancer: a phase III, randomized, double-blind, multicenter study

Jyoti Mayadev,[1] Ana T Nunes,[2] Mary Li,[2] Michelle Marcovitz,[2] Mark C Lanasa,[2] Bradley J Monk[3]

Accepted 13 February 2020

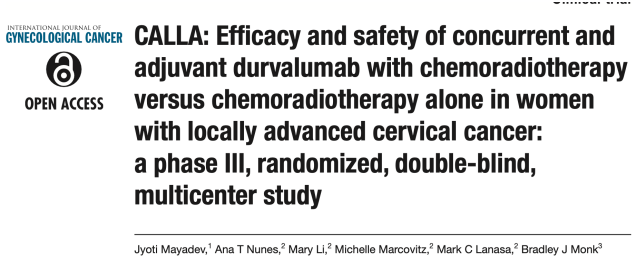
Primary LACC
IB2-IIB node positive
IIIA-IVA any nodal status

1.1
714 pts

CCRT +durvalumab
Up to 24 months or progression

CCRT +placebo
Up to 24 months or progression

2022: The CALLA trial did not achieve statistical Significance for PFS or OS


INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

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CALLA: Efficacy and safety of concurrent and adjuvant durvalumab with chemoradiotherapy versus chemoradiotherapy alone in women with locally advanced cervical cancer: a phase III, randomized, double-blind, multicenter study

Jyoti Mayadev,[1] Ana T Nunes,[2] Mary Li,[2] Michelle Marcovitz,[2] Mark C Lanasa,[2] Bradley J Monk[3]

Durvalumab :
lower distant metastasis

Advantage in pts ≥ IIIN+ or LALN
12% of patients

Pembrolizumab plus chemoradiotherapy for high-risk LACC: Randomized, double-blinded phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 study

Esmo 2023

Primary LACC
IB2-IIB node positive
IIIA-IVA any nodal status

1.1
1060 pts

CCRT +pembrolizumab
Pembro for 15 cycles

CCRT +placebo
Placebo for 15 cycles

<5% PDL1 neg
55% IIIA-IVA
N+ 84%
PALN 22%

136 Centers in
30 Countries

Pembrolizumab plus chemoradiotherapy for high-risk LACC: Randomized, double-blinded phase 3 ENGOT-cx11/GOG-3047/KEYNOTE-A18 study

Esmo 2023

IMRT or VMAT 89%
Cervix EQD2 dose 87 Gy
Overall treatment time within 56 days 80%

PFS 24 months 67.8% vs 57.3%
HR 0.70 (95% CI, 0.55-0.89)
P=0.0020

Practice changing

Low toxicity profile
Enteritis, diarrhea

Adjuvant chemotherapy following chemoradiotherapy as primary treatment for locally advanced cervical cancer versus chemoradiotherapy alone (OUTBACK): an international, open-label, randomised, phase 3 trial

Linda R Mileshkin, Kathleen N Moore*, Elizabeth H Barnes, Val Gebski, Kailash Narayan, Madeleine T King, Nathan Bradshaw, Yeh Chen Lee, Katrina Diamante, Anthony W Fyles, William Small Jr, David K Gaffney, Pearly Khaw, Susan Brooks, J Spencer Thompson, Warner K Huh, Cara A Mathews, Martin Buck, Aneta Suder, Thomas E Lad, Igor J Barani, Christine H Holschneider, Sylvia Van Dyk, Michael Quinn, Danny Rischin, Bradley J Monk†, Martin R Stockler†*

Lancet Oncol 2023; 24: 468–82

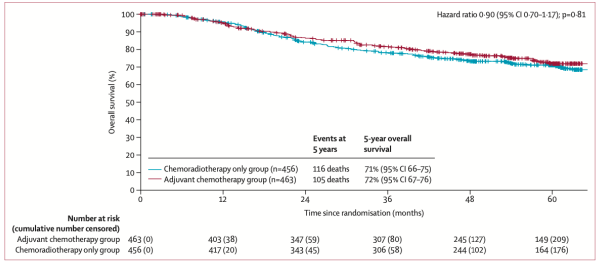


Figure 2: Kaplan-Meier estimates of overall survival

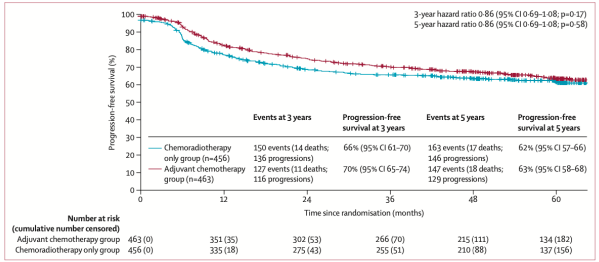


Figure 3: Kaplan-Meier estimates of progression-free survival

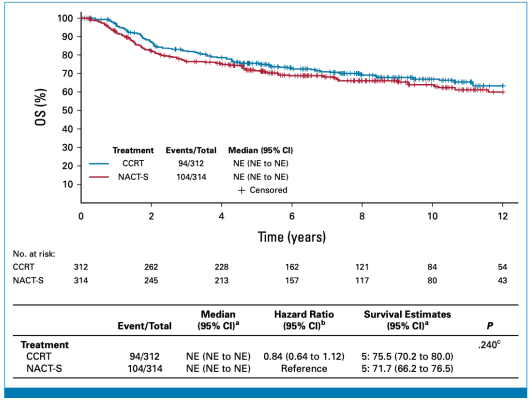
Interpretation Adjuvant carboplatin and paclitaxel chemotherapy given after standard cisplatin-based chemoradiotherapy for unselected locally advanced cervical cancer increased short-term toxicity and did not improve overall survival; therefore, it should not be given in this setting.

Randomized Phase III Study Comparing Neoadjuvant Chemotherapy Followed by Surgery Versus Chemoradiation in Stage IB2-IIB Cervical Cancer: EORTC-55994

Gemma G. Kenter, MD, PhD[1]; Stefano Greggi, MD, PhD[2]; Ignace Vergote, MD, PhD[3]; Dionyssios Katsaros, MD, PhD[4]; Juliusz Kobierski, MD[5]; Heleen van Doorn, MD, PhD[6]; Fabio Landoni, MD, PhD[7]; Jacobus van der Velden, MD, PhD[8]; Nicholas Reed, MD, PhD[9]; Corneel Coens, PhD[10]; Iske van Luijk, MD[11]; Nicoletta Colombo, MD, PhD[12]; Elzbietta van der Steen-Banasik, MD, PhD[13]; Nelleke Ottevanger, MD, PhD[14]; and Antonio Casado, MD, PhD[15]; on behalf of the EORTC-55994 Study Group

Accepted June 28, 2023
Published September 1, 2023

J Clin Oncol 41:5035-5043



	Event/Total	Median (95% CI)[a]	Hazard Ratio (95% CI)[b]	Survival Estimates (95% CI)[a]	P
Treatment					.240[c]
CCRT	94/312	NE (NE to NE)	0.84 (0.64 to 1.12)	5: 75.5 (70.2 to 80.0)	
NACT-S	104/314	NE (NE to NE)	Reference	5: 71.7 (66.2 to 76.5)	

Relevance *(G.F. Fleming)*
Additional radiotherapy was used for a substantial proportion of patients with stage IB2-IIB cervical cancer who were assigned to NACT + S on this trial. CCRT remains the standard of care in this setting.*

CONCLUSION This trial failed to demonstrate superiority in favor of the NACT-S arm but resulted in acceptable morbidity and HRQOL in both arms.

ESMO 2023

INTERLACE Trial Design

Randomized 500 pts

Induction cht

Carbo+pacli
For 6 weeks

Week 7

CRT
CHT CDDP for 5 weeks
RT EBRT+BT > 78 Gy EQD2

Stratified
Site
Stage
N
3DCRT vs IMRT
2D vs 3D BT
Tumor size

Primary endpoints
PFS
OS

Population

IIA 76%

IB1-IB2 10%

IIB-IVA 14%

N neg 60%

Discontinuation of CDDP

During RT 30% of pts

After neoCHT

Radiotherapy

IMRT 40%

IGABT 30%

PFS

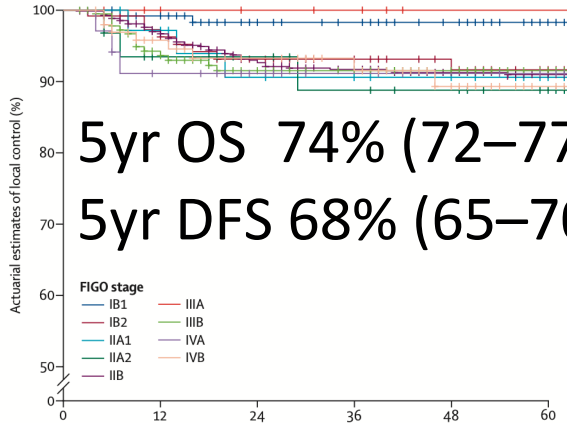
HR 065 (95% CI 0.46-0.91)

P=0.013

MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study

Richard Pötter, Kari Tanderup, Maximilian Paul Schmid, Ina Jürgenliemk-Schulz, Christine Haie-Meder, Lars Ulrik Fokdal, Alina Emiliana Sturdza, Peter Hoskin, Umesh Mahantshetty, Barbara Segedin, Kjersti Bruheim, Fleur Huang, Bhavana Rai, Rachel Cooper, Elzbieta van der Steen-Banasik, Erik Van Limbergen, Bradley Rumwell Pieters, Li-Tee Tan, Remi Abubakar Nout, Astrid Agatha Catharina De Leeuw, Robin Ristl, Primoz Petric, Nicole Nesvacil, Kathrin Kirchheiner, Christian Kirisits, Jacob Christian Lindegaard, EMBRACE Collaborative Group*

	Induction Chemo+CRT	CRT Alone
3yr	75%	72%
5yr	73%	64%



5yr OS 74% (72–77)

5yr DFS 68% (65–70;

OS

HR 0.61 (95% CI 0.40-0.91)

P=0.04

	Induction Chemo+CRT	CRT Alone
3yr	86%	80%
5yr	80%	72%

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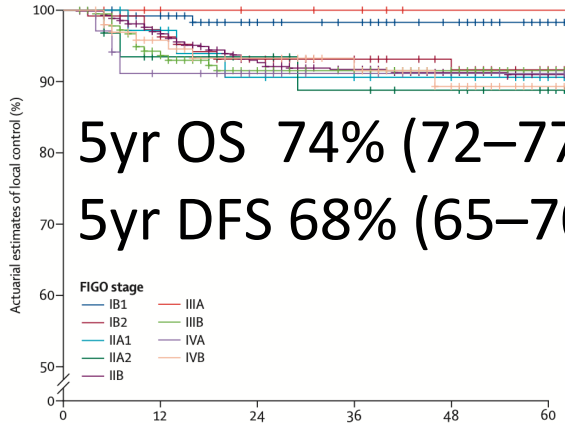


5yr OS 74% (72–77)

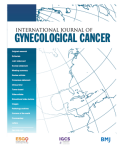
5yr DFS 68% (65–70;

Original research

ESTRO/ESGO/SIOPe Guidelines for the management of patients with vaginal cancer

Remi A Nout,[1] Gabriele Calaminus,[2] François Planchamp ,[3] Cyrus Chargari ,[4] Sigurd Lax,[5,6] Hélène Martelli,[7] W Glenn McCluggage,[8] Philippe Morice,[9] Maja Pakiz ,[10] Maximilian P Schmid,[11] Jonáh Stunt,[12] Beate Timmermann,[13,14] Christian Vokuhl,[15] Daniel Orbach,[16] Christina Fotopoulou [17]

et al. Int J Gynecol Cancer 2023;**33**:1185–1202.



OPEN ACCESS

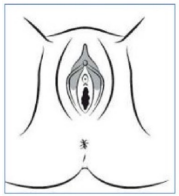
European Society of Gynaecological Oncology Guidelines for the Management of Patients with Vulvar Cancer - Update 2023

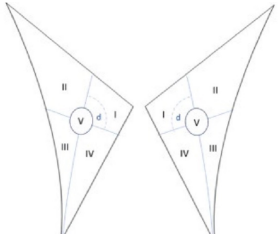
Maaike H M Oonk,[1] François Planchamp ,[2] Peter Baldwin,[3] Sven Mahner,[4] Mansoor Raza Mirza,[5] Daniela Fischerová ,[6,7] Carien L Creutzberg,[8] Eugénie Guillot,[9] Giorgia Garganese,[10,11] Sigurd Lax,[12,13] Andres Redondo,[14] Alina Sturdza,[15] Alexandra Taylor ,[16] Elena Ulrikh ,[17] Vincent Vandecaveye ,[18] Ate van der Zee, Linn Wölber,[19] Diana Zach,[20,21] Gian Franco Zannoni ,[10,11] Ignacio Zapardiel [14]

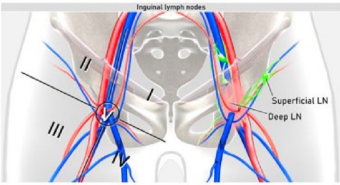
Int J Gynecol Cancer 2023;**0**:1–21.

Table 3 Study outcomes of IGABT for patients with primary vaginal cancer

	Years of inclusion	N	Median FU (months)	Dose to D90 CTV-T_{HR} (Gy)	2y-LC (%)	2y-DSS (%)	2y-OS (%)	Morbidity (%)
Dimopoulos *et al*[27]	1999–2006	13	43	86	92*	NA	85*	23
Fokdal *et al*[28]	2005–10	9	18	82	92†	59†	74†	4
Huertas *et al*[29]	2004–16	27	40	73	82	75	91	15
Gebhardt *et al*[30]	2011–16	16	39	77	93‡	64‡	67‡	3
Manuel *et al*[31]	1973–2014	47	24	81	93	86	82	2
Lee *et al*[32]	2005–11	10	17	74	86	60	62	13
Westerveld *et al*[33]	2001–16	148	29	80	86	73	79	17







Grazie per l'attenzione