Endometrial Cancer: Molecular Profiling and Other Updates

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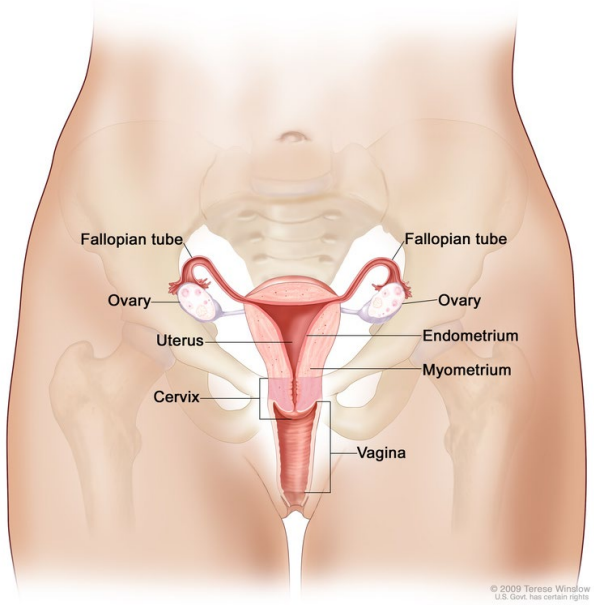
Disclosures

- None

Learning Objectives

- Demonstrate improved knowledge of current treatments for endometrial cancer.
- Appreciate how molecular profiling informs prognosis and treatment for endometrial cancer.
- Understand recent evidence for the treatment of uterine cancer.
- Perform screening for and discuss basic management strategies for immune checkpoint inhibitor toxicities.
- Provide cancer patients with additional resources and support.

Endometrial Cancer



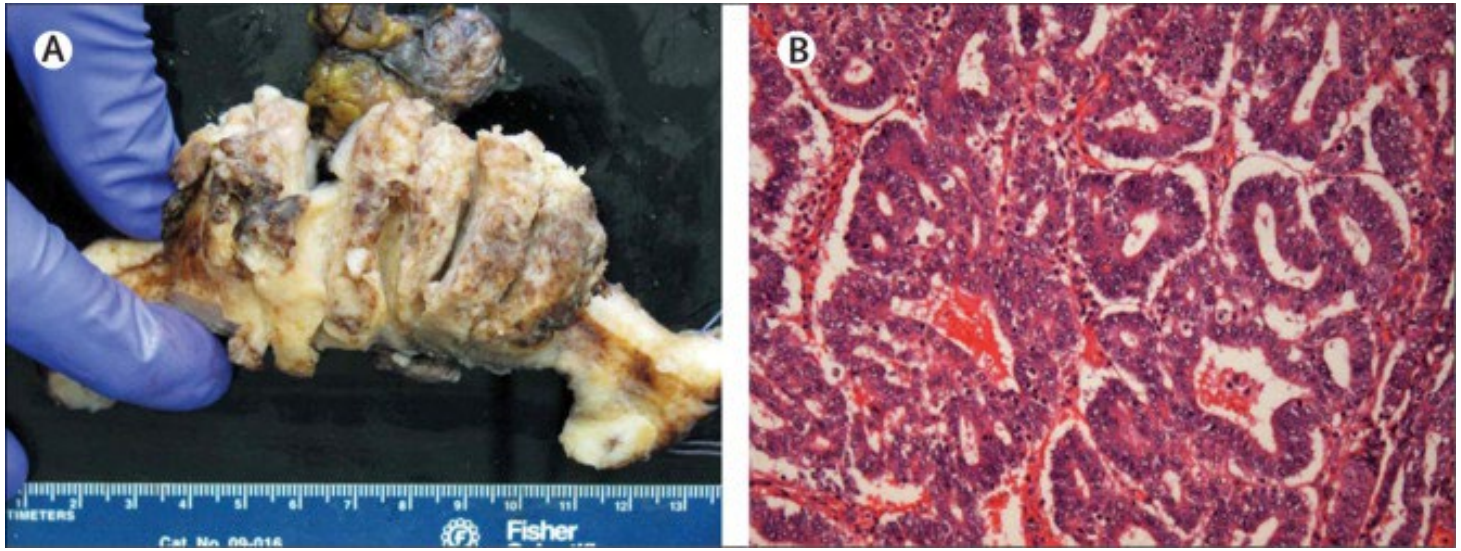
- Most common gynecologic cancer
- Risk factors include older age, obesity, unopposed estrogen
- Detected by endometrial biopsy
- Screening for symptoms occurs at well person exam

Symptoms:

- Abnormal bleeding, especially after menopause
- Pain, abnormal discharge

Incidence

- Uterine cancer each year
  - 65,620 cases
  - 12,590 deaths
- >90% are endometrial cancers
- 75% are early stage with excellent prognosis



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Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, Horner M-J (editors). SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics. National Cancer Institute, SEER Program, NIH Pub. No. 07-6215, Bethesda, MD, 2007.

Historical Classification of Endometrial Cancer

Feature	Type I	Type II
Demographics	Younger age High BMI	Older age Low BMI
Risk factors	Hyperestrogenism, DMII Hyperlipidemia	Breast cancer (?) *BRCA* mutation (?)
Precursor lesion	Atypical hyperplasia	Unclear, Dysplasia??
Histologic grade	Low, intermediate, or *high*	High
Histology	Endometrioid	Diverse Clear Cell, Papillary Serous, *High grade endometrioid*, Carcinosarcoma, Mucinous Undifferentiated, Mixed

Feature	Type I	Type II
Pattern of recurrence	Local	Distant
Stage at presentation	**I (73%)** **II (11%)** III (13%) IV (3%)	**I (54%)** **II (8%)** III (22%) IV (16%)
Survival by stage	I (85-90%) II (70%) III (40-50%) IV (15-20%)	I (50-80%) II (50%) III (20%) IV (5-10%)

Historical Perspectives

1960s treatment

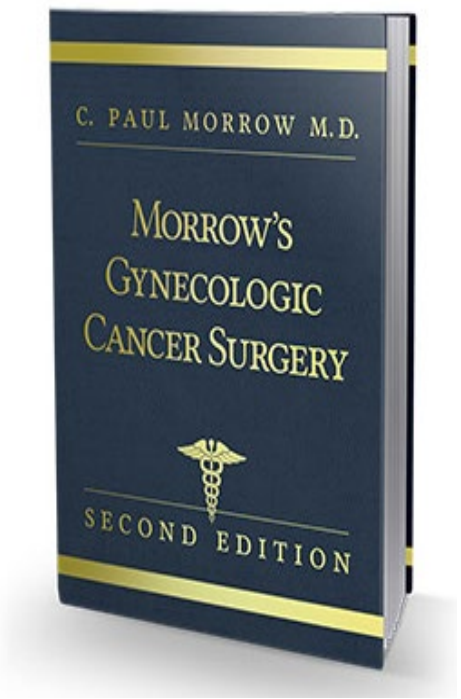
- TAH+BSO
- +/- pre-operative intra-cavitary radium
- +/- external beam radiation
- Lymph nodes were not thought to be important

1971: Lewis et al. report series of pts treated with radical hysterectomy and pelvic lymph node dissection

- 11.2% rate of lymph node involvement

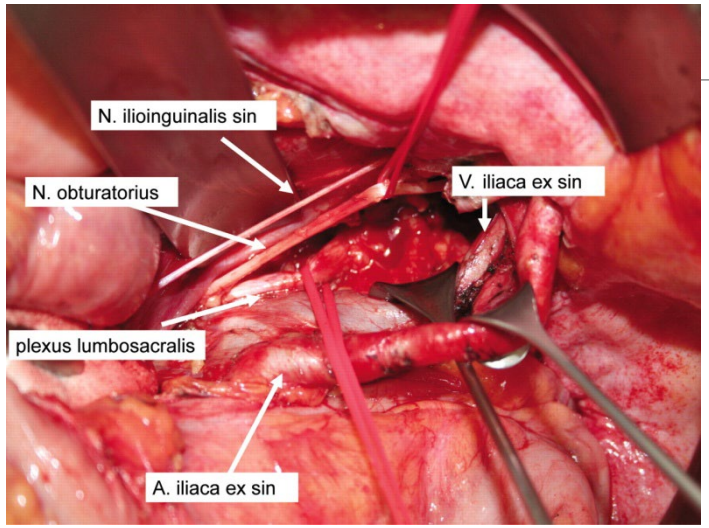
1973: Morrow et al.

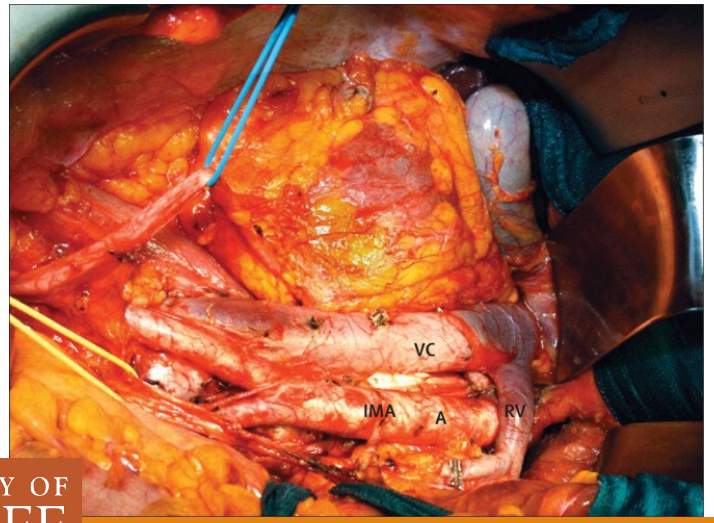
- ***5-year survival among patients with nodal involvement was ~30%***
- ***Argued for treatment of nodes in patients at high risk for nodal involvement***



Lewis BV, Stallworthy JA, Cowdell R. Adenocarcinoma of the body of the uterus. J Obstet Gynaecol Br Commonw. 1970 Apr;77(4):343-8.
Morrow CP, Di Saia PJ, Townsend DE.Current management of endometrial carcinoma. Obstet Gynecol. 1973 Sep;42(3):399-406

Lymph node involvement predicts prognosis





Morrow 1991: 895 women with endometrial cancer

- 5-year recurrence free survivals:
  - **Cancer confined to uterine corpus: 92.7%**
  - **+ Pelvic LN: 57.8 %**
  - **+ Para-aortic LN: 41.2%**

Morrow CP, Bundy BN, Kurman RJ, Creasman WT, Heller P, Homesley HD, Graham JE. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol. 1991 Jan;40(1):55-65.

Mayo Criteria: Who is really at risk for lymph node metastasis?

Proposed criteria to avoid lymphadenectomy among patients with very low risk of lymph node metastasis

Defined in observational study of 328 patients with

- Endometrioid histology
- Clinical Stage I / uterine confined
- Grade 1 or 2
- ≤50% invasive
- Treated at Mayo Clinic from 1984-1993

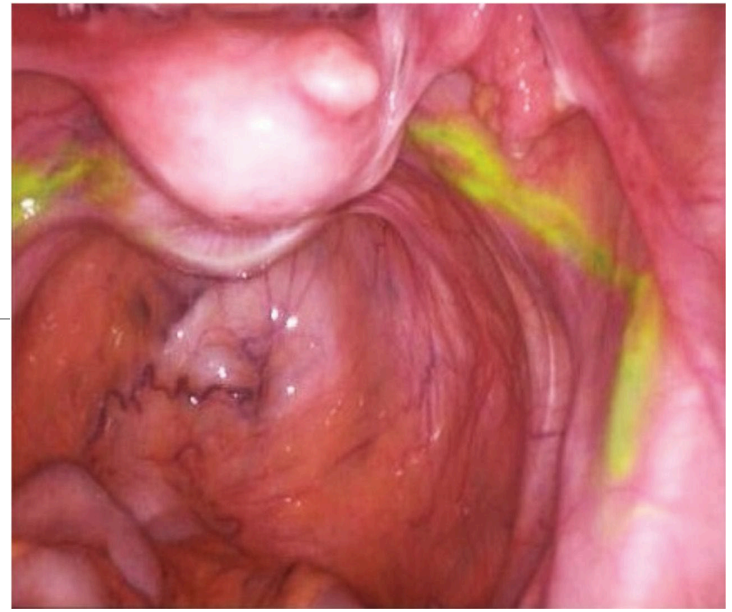
Table I. Surgical and pathologic characteristics of 328 patients with low-risk endometrial cancer (endometrioid histologic subtype, myometrial invasion ≤50%, and histologic grade 1-2)

Characteristic	*No.*	*%**
Stage		
IA	57	17
IB	239	73
IIIA	23	7
IIIC	9	3
FIGO grade		
1	223	68
2	105	32
Lymph-vascular invasion		
Yes	18	5
No	309	95
Not available	1	—
Histologic subtype		
Endometrioid	312	95
Areas of squamous differentiation	13	4
Adenosquamous	3	1
Myometrial invasion		
None	60	18
≤50%	268	82
Primary tumor diameter (cm)		
≤2	123	42
>2	169	58
Not available	36	—
Peritoneal cytologic results		
Positive	23	7
Negative	285	93
Not available	18	—
Unsatisfactory	2	—
Pelvic lymph nodes		
Positive	9	5
Negative	178	95
Not available	141	—

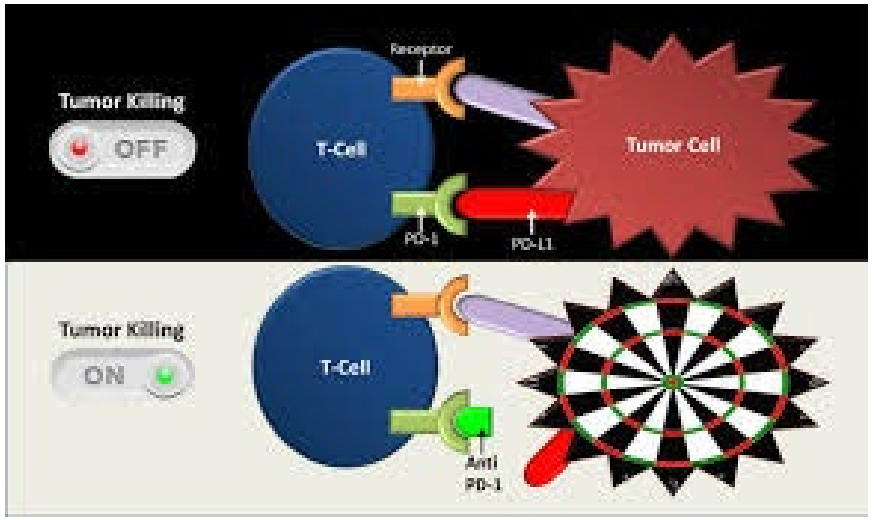
*Percentage calculations exclude missing cases.

Mariani A, Webb MJ, Keeney GL, et al. Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary? Am J Obstet Gynecol. 2000;182:1506–1519.

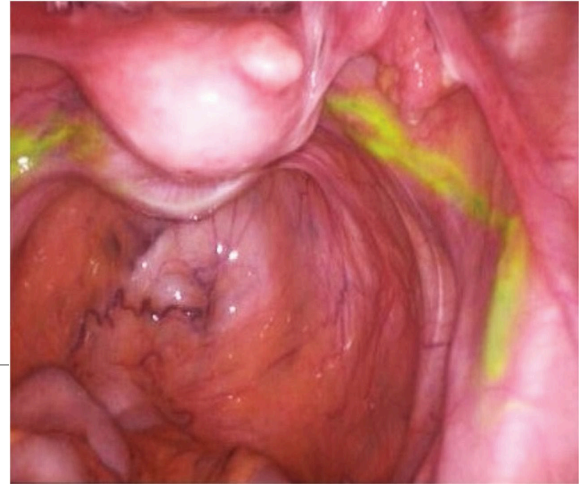
Endometrial cancer: Recent changes



- Sentinel Lymph Nodes
- Molecular Classification of Tumors
- Immunotherapy
- Maintenance Strategies
- Investigating Disparities



Validation of sentinel lymph nodes



Senti-Endo

- 133 patients from 9 centers in France
- Technetium colloid and blue dye injection.
- At least one SLN was detected in 111 of the 125 eligible patients.
- 17% had pelvic-lymph-node metastases.
- 5% had an associated SLN in the para-aortic area.
- Negative predictive value of 97%
- Sensitivity of 84%

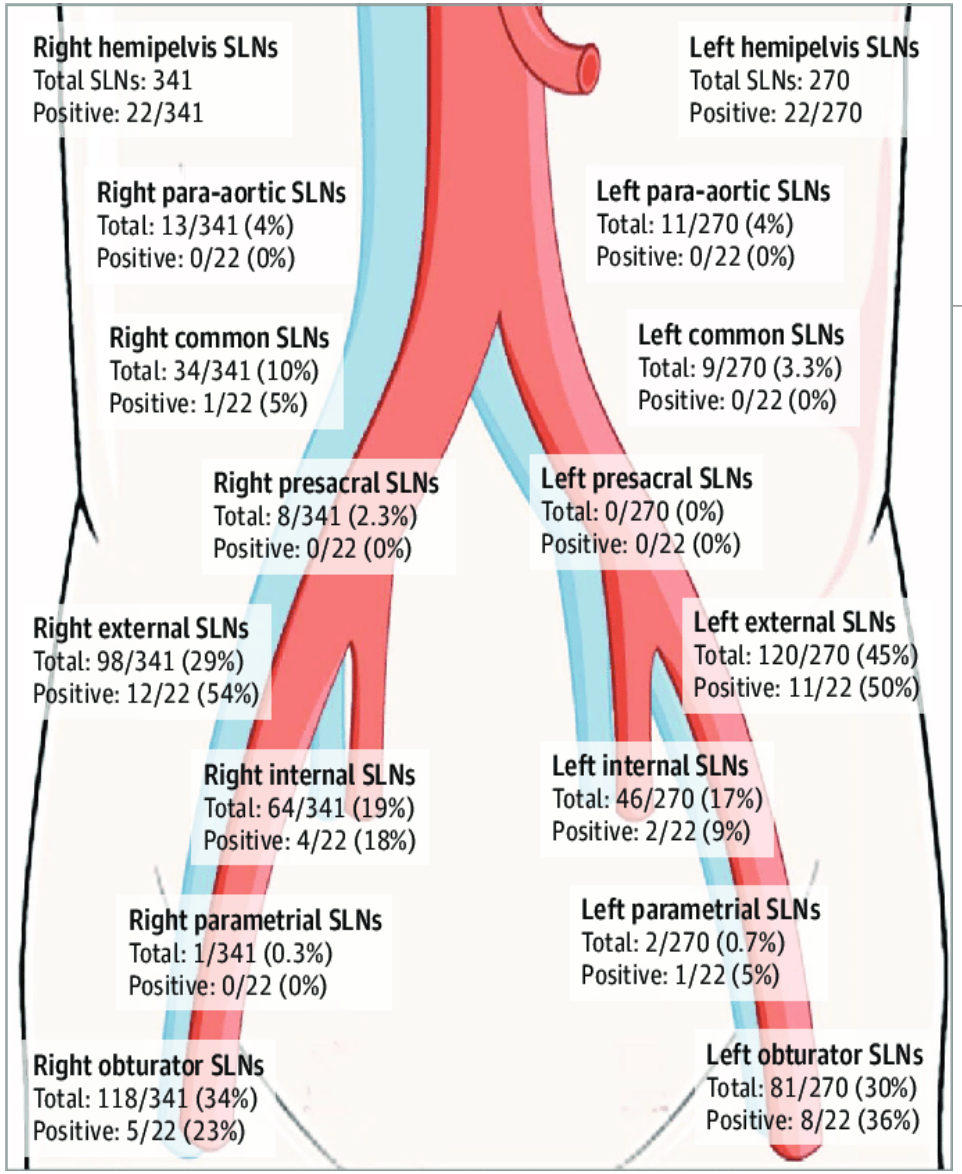
FIRES

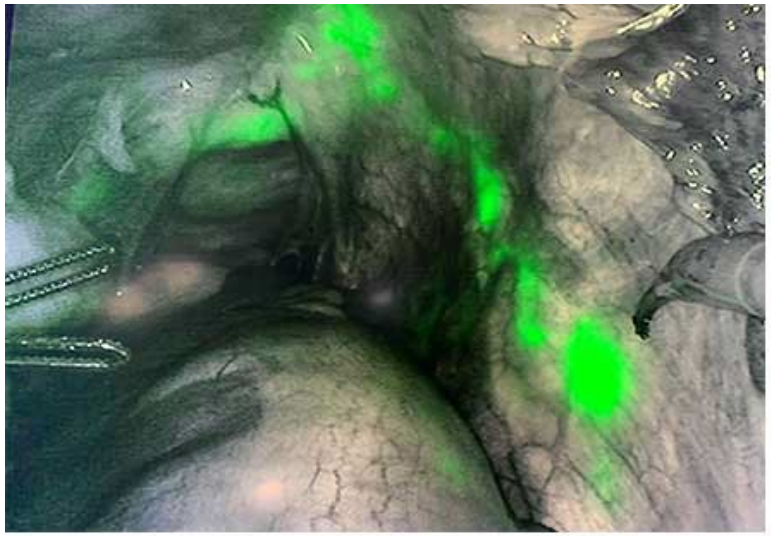
- 385 patients from 10 centers in the US
- Indocyanine green
- 29% of patients had high grade histology (g3 endometrioid, serous, carcinosarcoma, clear cell)
- 12% of patients had positive nodes
- Negative predictive 99.6%
- Sensitivity 97.2%

Ballester M, et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol. 2011 May;12(5):469-76.

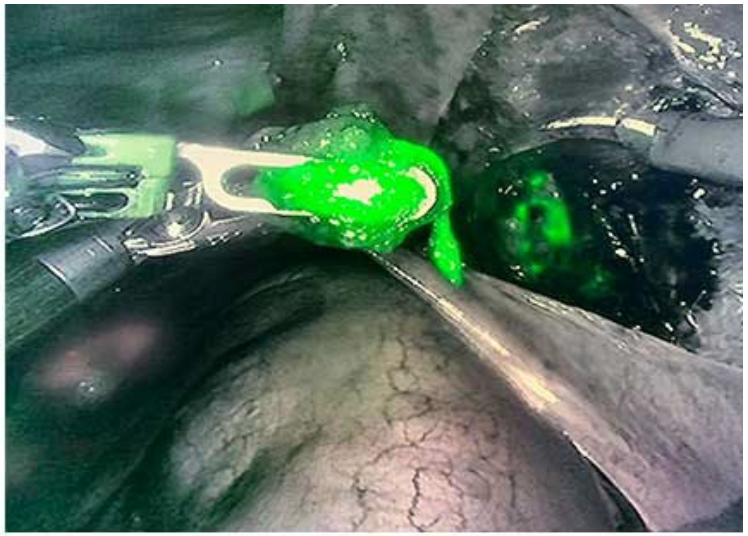
Rossi EC, Kowalski LD, Scalici J. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 2017 Mar;18(3):384-392.

Location of sentinel nodes





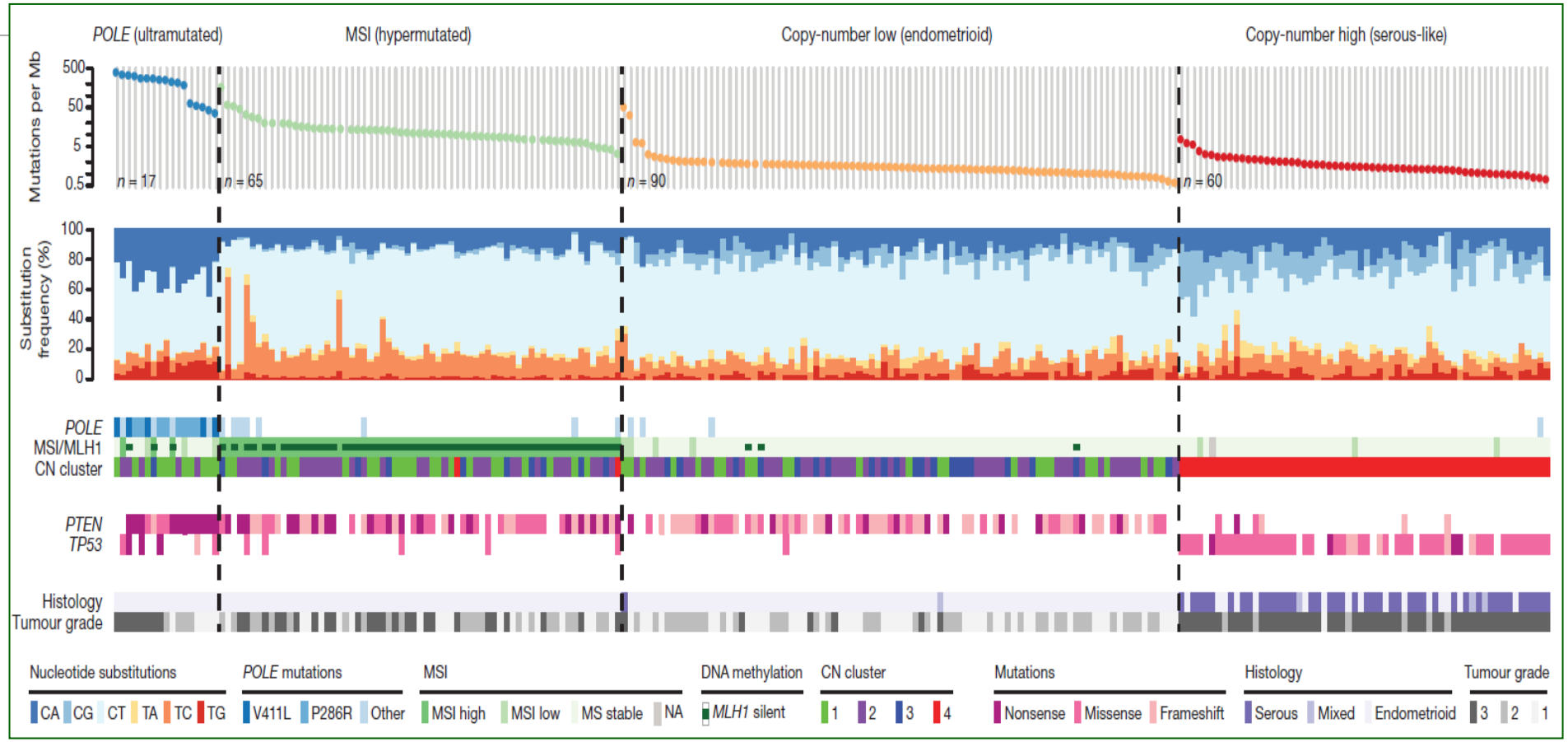
Before sentinel nodes removal



After sentinel nodes removal

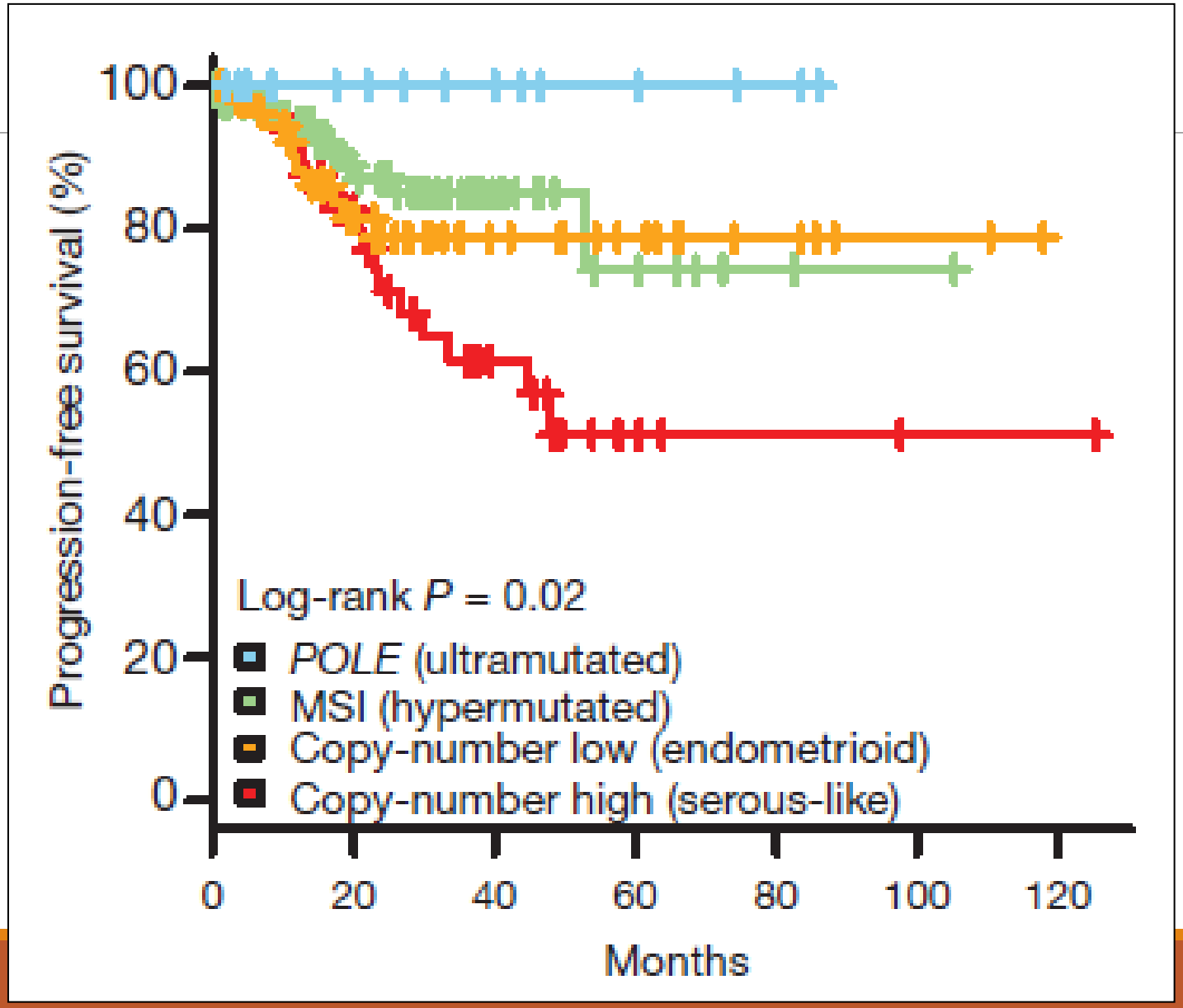
The Cancer Genome Atlas Project (TCGA) Genomic characterization highlights 4 distinct molecular categories

- POLE (ultramutated)
- MSI (hypermutated)
- Copy-number low (endometrioid)
- Copy-number high (serous-like)



TCGA Group Nature 2011

Molecular subtypes correlate with survival



TCGA Group Nature 2011

2023 FIGO Staging

- Non-aggressive histological types are composed of low-grade (grade 1 and 2) EECs. Aggressive histological types are composed of high-grade EECs(grade 3), serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, and carcinosarcomas.
- It should be noted that high-grade EECs (grade 3) are a prognostically, clinically, and molecularly heterogenous disease, and the tumor type that benefits most from applying molecular classification for improved prognostication and for treatment decision-making.

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 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[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 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 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

2023 FIGO Staging

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.

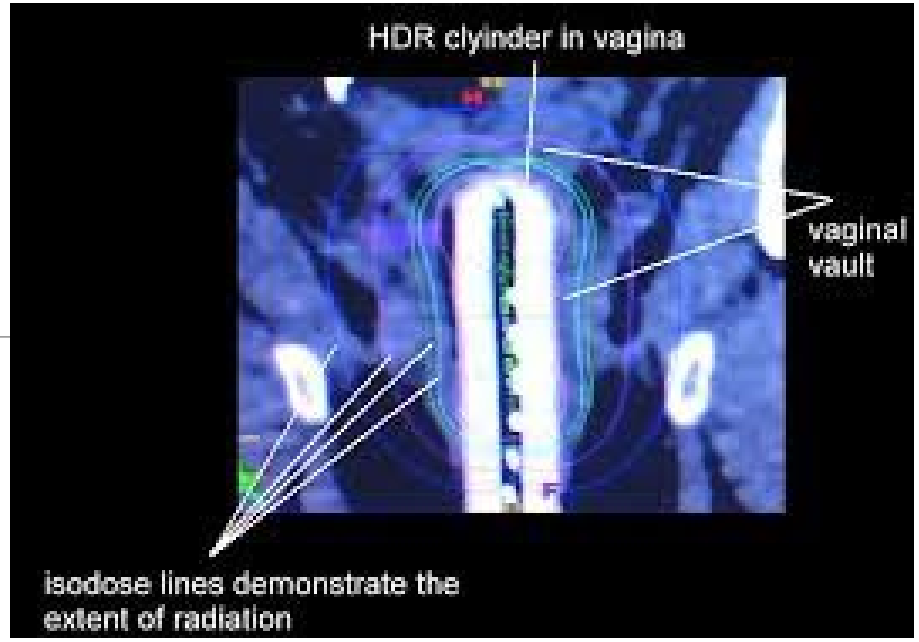
- Good prognosis: pathogenic *POLE* mutation (*POLEmut*)
- Intermediate prognosis: mismatch repair deficiency (MMRd)/microsatellite instability and no specific molecular profile (NSMP)
- Poor prognosis: p53 abnormal (p53abn)When the molecular classification is known:
- FIGO Stages I and II are based 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}.

Adjuvant Therapy in Endometrial Cancer

No RCT has demonstrated an overall survival benefit for ANY adjuvant therapy for early-stage endometrial cancer

Radiation therapy reduces risk of local recurrence

Chemotherapy is often given in high-risk histology groups like serous carcinoma and carcinosarcoma



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Ongoing Trials

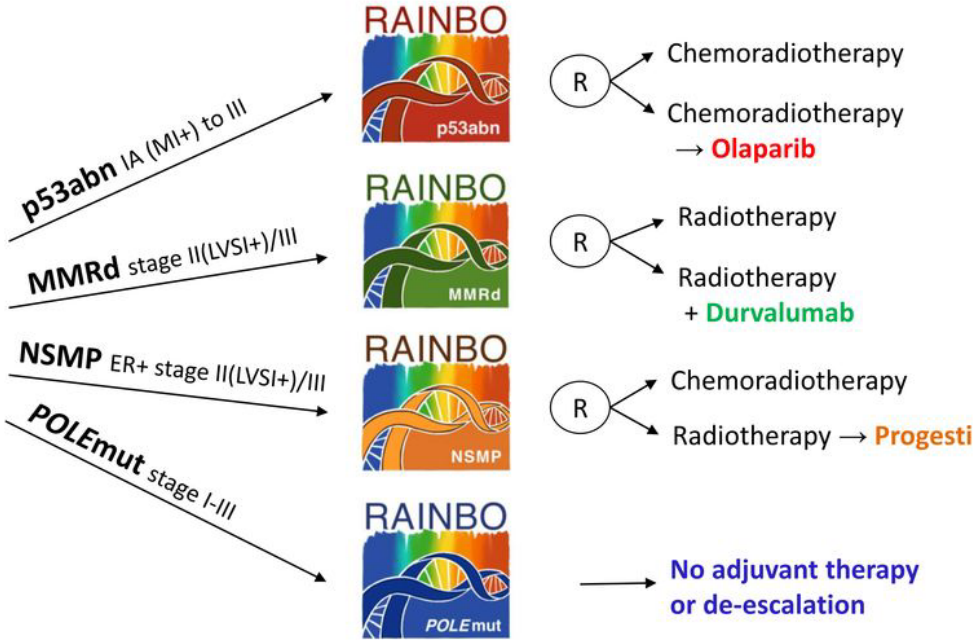
RAINBO

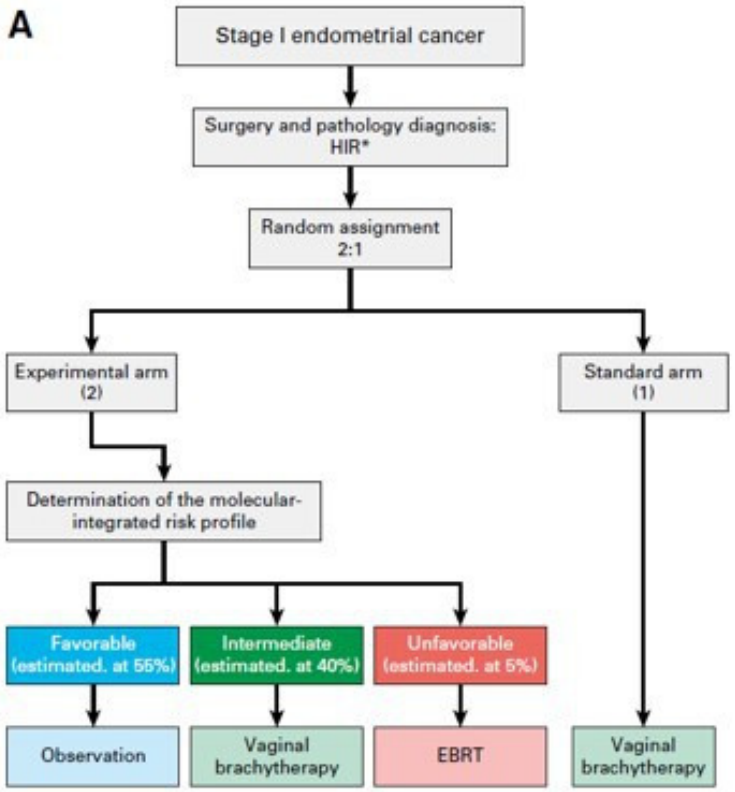
TransPORTEC

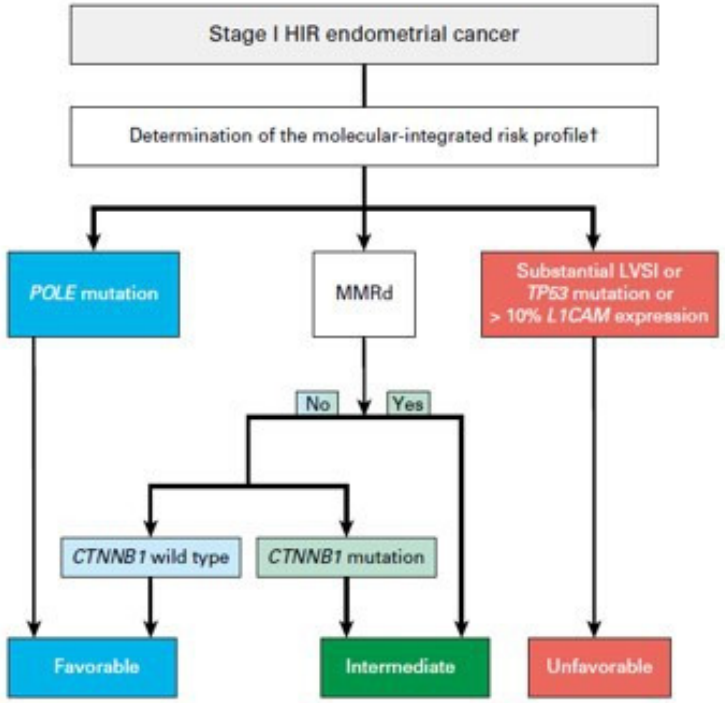
Completely resected endometrial cancer

Eligible histotypes:
endometrioid,
serous,
clear cell,
un/dedifferentiated,
mixed and
carcinosarcoma

➡ Molecular Classification







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Therapies for advanced and recurrent disease

- Longstanding standard of care – Carboplatin / Taxol
- Still considered first line standard of care → but often in combination with targeted agents

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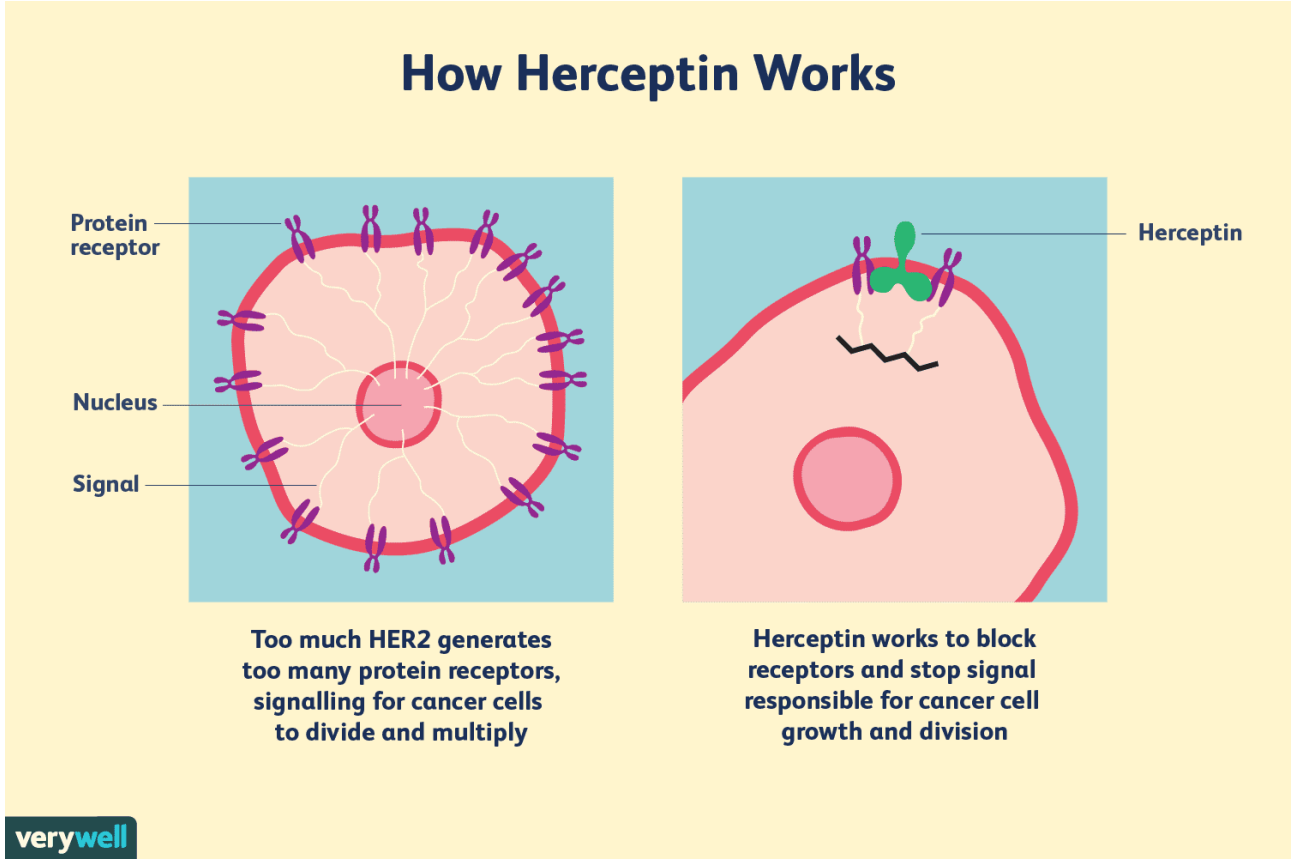
Trastuzumab (Herceptin)

- Monoclonal Ab to HER2 receptor
  - Blocks growth signaling for cell
- Useful in some endometrial cancers
- In one Phase II study when given in combination with chemotherapy – ORR (overall response rate) was 44%

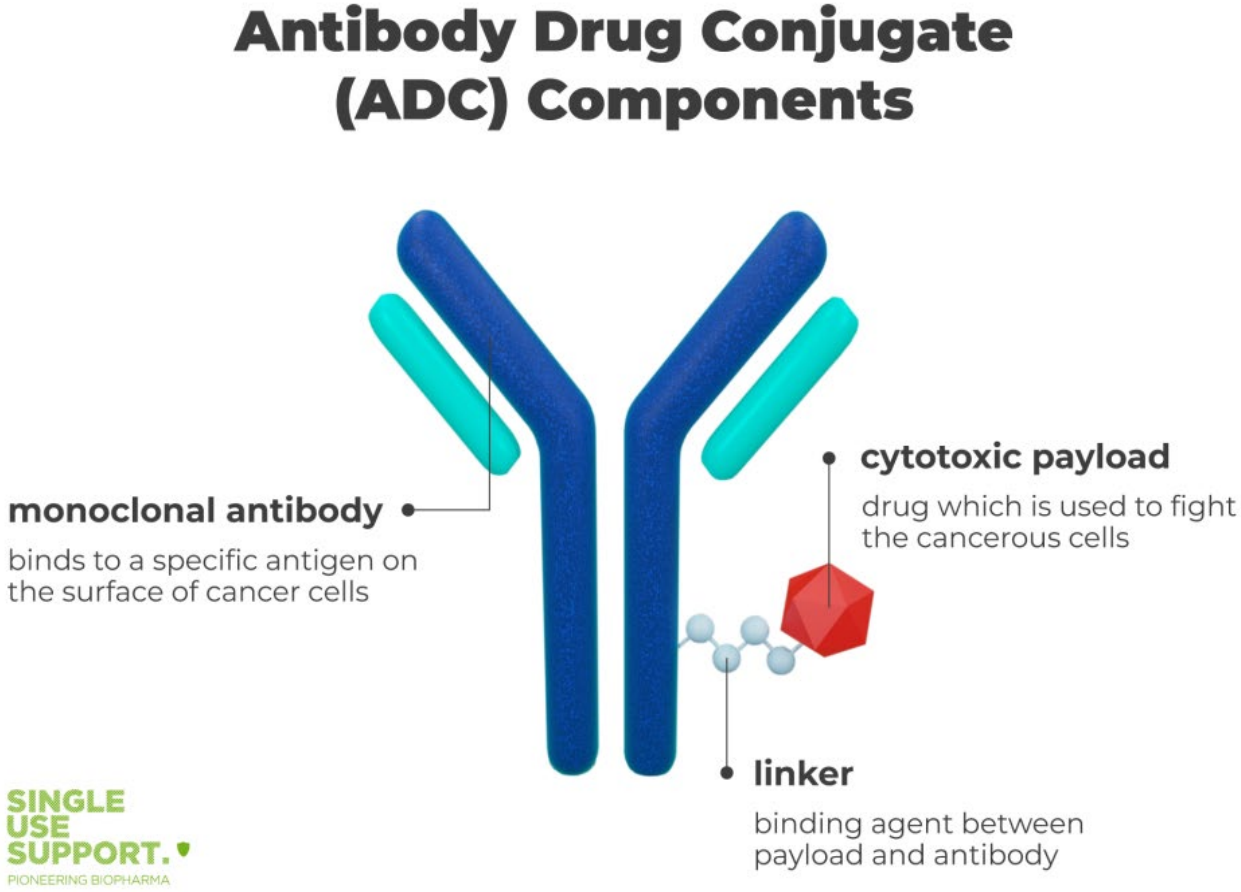


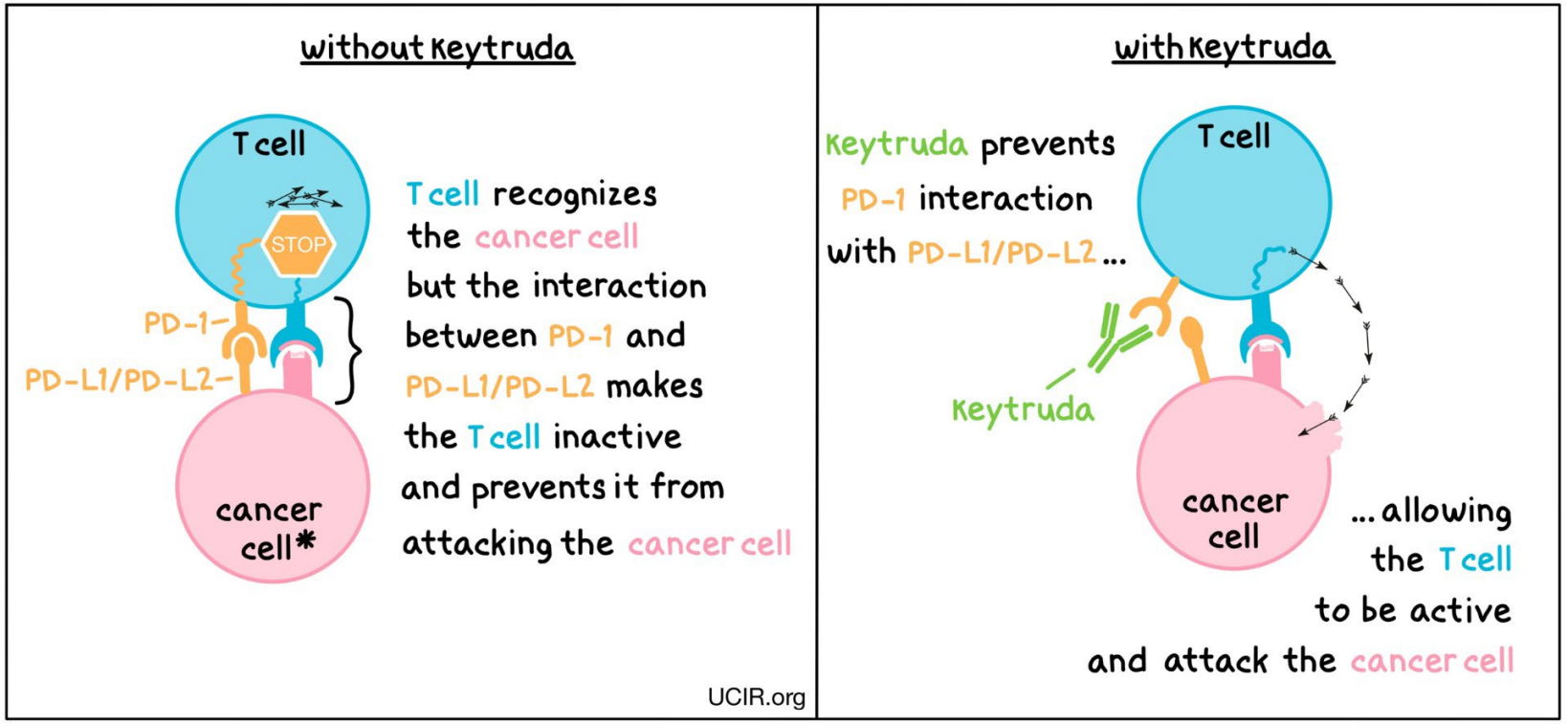
Fader AN, Clin Cancer Res 2020

Antibody – Drug Conjugates / Trastuzumab Deruxtecan

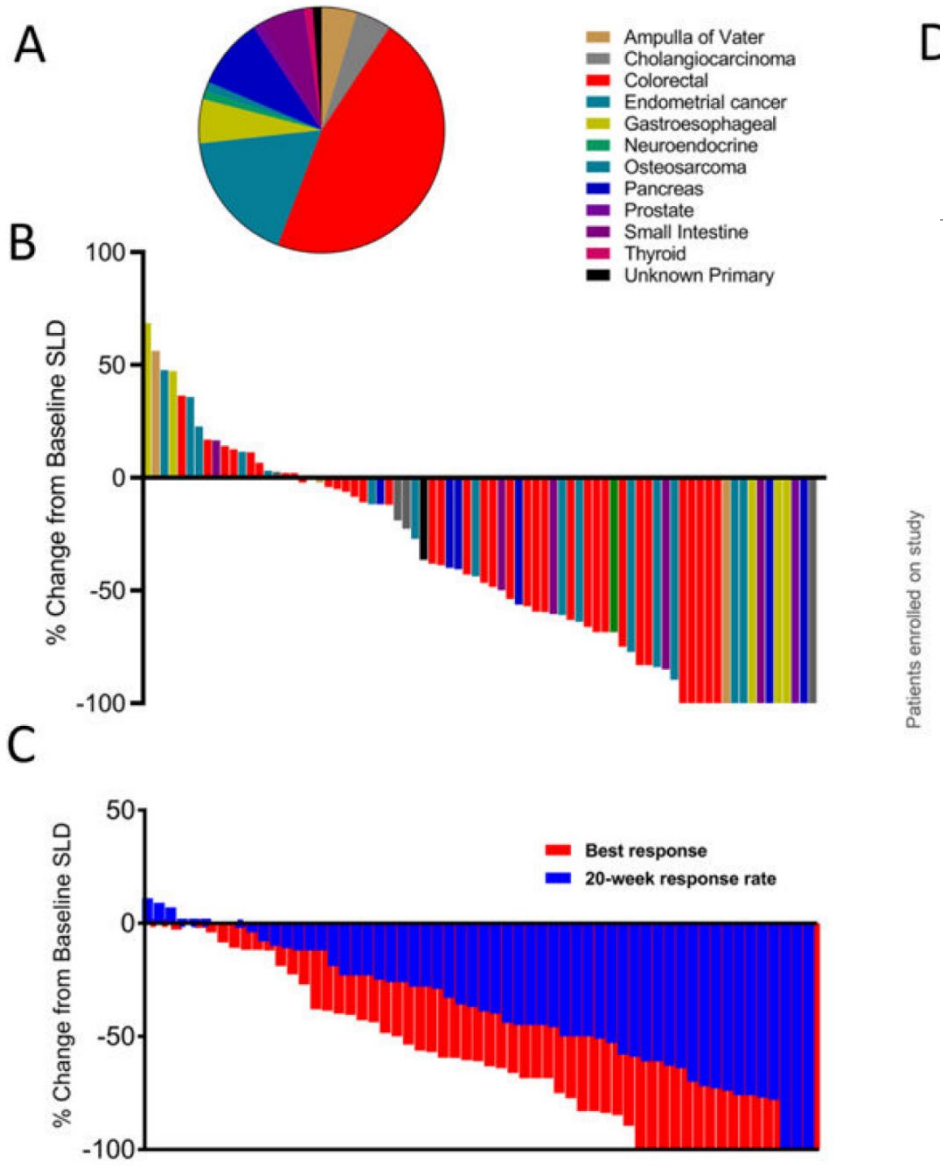
Trastuzumab Deruxtecan (Enhertu)

- Monoclonal antibody (trastuzumab) linked to topoisomerase I inhibitor (deruxtecan)
- Deruxtecan is internalized after binding with trastuzumab to the HER2 receptor → interferes with cell's ability to replicate DNA
- Ocular Toxicity**





- **Immune Checkpoint Inhibitors**
  Most likely to be helpful in mismatch repair deficient (MMRd), microsatellite instability – high (MSI-h) tumors



Pembrolizumab

- *FDA approved for any MSI-h solid tumors*
  - *30% of Endometrial cancer is MSI-h or MMRd*

First FDA approval for tissue site/agnostic indication

Type of response	Patients (n = 86)
Complete response	18 (21%)
Partial response	28 (33%)
Stable disease	20 (23%)
Progressive disease	12 (14%)
Not evaluable	8 (9%)
Objective response rate 95% CI	53% 42% to 64%
Disease control rate 95% CI	77% 66% to 85%
Median progression-free survival time 95% CI	NR 14.8 months to NR
2-year progression-free survival rate 95% CI	53% 42% to 68%
Median overall survival time 95% CI	NR NR to NR
2-year overall survival rate 95% CI	64% 53% to 78%

Targeting Tumors that are **not** MMRd or MSI-h (70%)

- Combination therapy → modify the tumor microenvironment

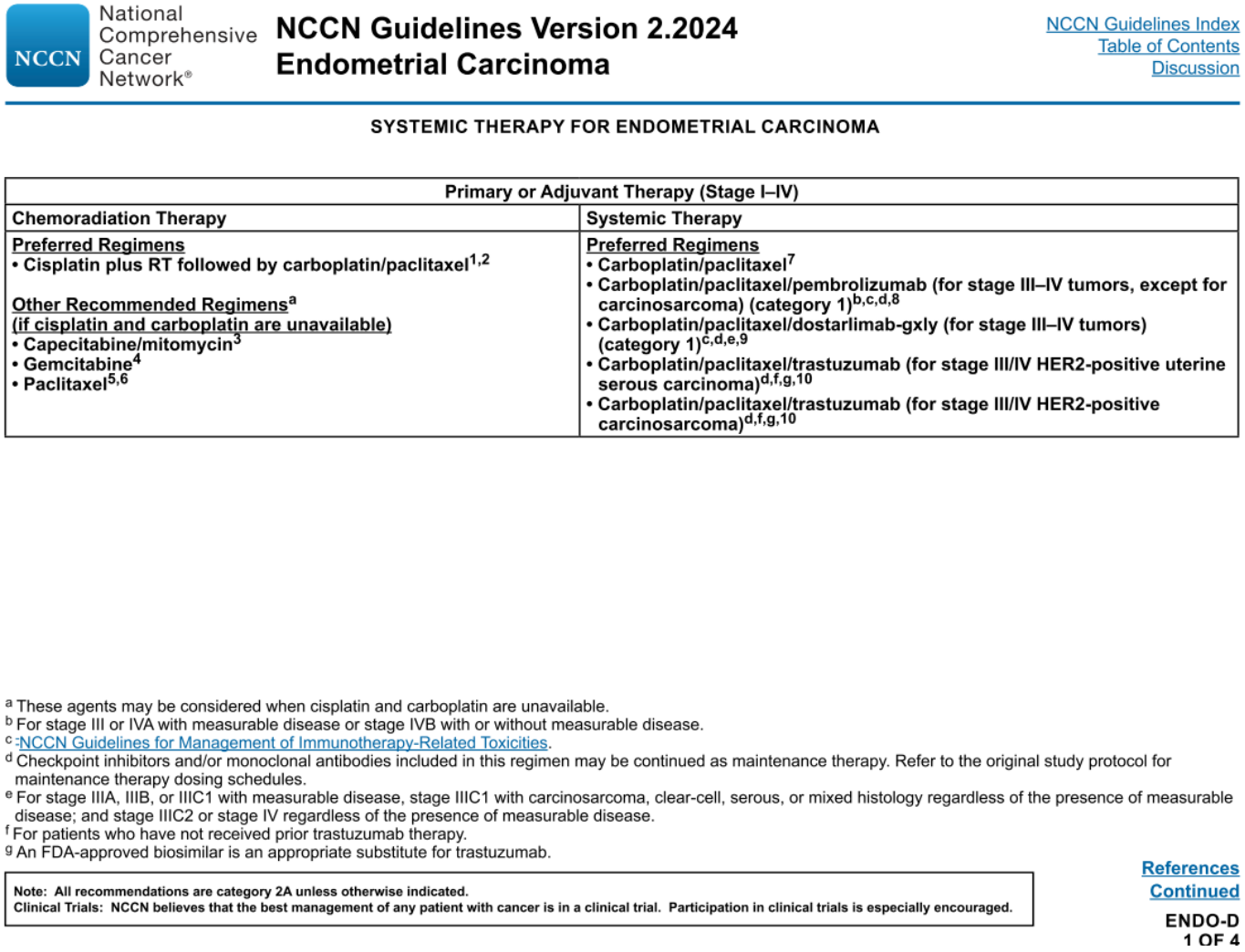
- Phase II trial of pembrolizumab in combination with Lenvatinib (VEGF inhibitor)
- **64% ORR in MSI tumors, 31% ORR in MSS tumors**
  - **Previous standard therapies in this setting, ORR about 15-20%**

Makker V et al Lancet Oncol 2019

Immunotherapy with Chemotherapy

- 2023
- 2 randomized phase III trials (NEJM)
- Improved PFS with addition of immunotherapy to chemotherapy
- Difference seen in all patients, but most pronounced in MMRd/MSI-h patients

- ***Both trials led to change in standard of care for endometrial cancer / update to NCCN guidelines***



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Endometrial Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Primary or Adjuvant Therapy (Stage I–IV)	
Chemoradiation Therapy	**Systemic Therapy**
Preferred Regimens • Cisplatin plus RT followed by carboplatin/paclitaxel[1,2] **Other Recommended Regimens[a]** **(if cisplatin and carboplatin are unavailable)** • Capecitabine/mitomycin[3] • Gemcitabine[4] • Paclitaxel[5,6]	**Preferred Regimens** • Carboplatin/paclitaxel[7] • Carboplatin/paclitaxel/pembrolizumab (for stage III–IV tumors, except for carcinosarcoma) (category 1)[b,c,d,8] • Carboplatin/paclitaxel/dostarlimab-gxly (for stage III–IV tumors) (category 1)[c,d,e,9] • Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive uterine serous carcinoma)[d,f,g,10] • Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive carcinosarcoma)[d,f,g,10]

[a] These agents may be considered when cisplatin and carboplatin are unavailable.
[b] For stage III or IVA with measurable disease or stage IVB with or without measurable disease.
[c] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[d] Checkpoint inhibitors and/or monoclonal antibodies included in this regimen may be continued as maintenance therapy. Refer to the original study protocol for maintenance therapy dosing schedules.
[e] For stage IIIA, IIIB, or IIIC1 with measurable disease, stage IIIC1 with carcinosarcoma, clear-cell, serous, or mixed histology regardless of the presence of measurable disease; and stage IIIC2 or stage IV regardless of the presence of measurable disease.
[f] For patients who have not received prior trastuzumab therapy.
[g] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References Continued

ENDO-D
1 OF 4

Mirza MR, Chase DM, Slomovitz BM, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med 2023; 388:2145

Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. N Engl J Med 2023; 388:2159.

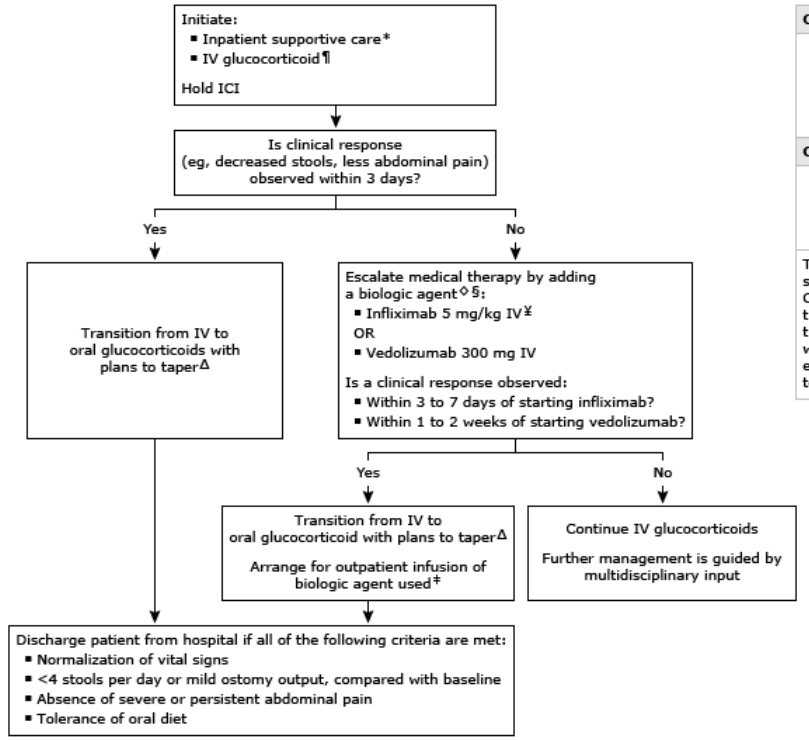
Maintenance Therapy

- Both Phase III trials with immune checkpoint inhibitors recommended 2 years of maintenance therapy
  - Cost
  - Toxicity
  - Emotional strain

Immune Checkpoint Inhibitor Toxicity

- Dermatologic / Mucosal toxicity
- Diarrhea / Colitis
- Hepatotoxicity
- Pneumonitis
- Thyroid Disease
- ***Hypophysitis***
- Adrenal Insufficiency
- ***Type I Diabetes***
- Rheumatologic
- ***Worsening of pre-existing autoimmune disease***

Inpatient therapy of grade 3 or 4 immune checkpoint inhibitor (ICI) colitis in adults



CTCAE grading for diarrhea[1]:

- Grade 3: ≥7 stools daily over baseline or severe increase in ostomy output compared to baseline; symptoms limit self-care ADL
- Grade 4: Grade 3 diarrhea with life-threatening consequences

CTCAE grading for enterocolitis[1]:

- Grade 3: Severe or persistent abdominal pain, fever, ileus, or peritoneal signs
- Grade 4: Grade 3 enterocolitis with life-threatening consequences

The management of ICI-mediated colitis is based on severity of disease using the CTCAE. Although the CTCAE categorizes ICI diarrhea and ICI colitis separately, these conditions (and their management) overlap and the terms are often used interchangeably. For patients with different grades for severity of diarrhea and enterocolitis, we use the symptom with the higher grade to guide treatment decisions.

In patients with grade 3 or 4 colitis due to ICI therapy, the goal of inpatient therapy is to decrease symptoms to the degree that they can be managed at home (fewer stools, resolution of severe abdominal pain). Hospitalized patients with ICI colitis require a multidisciplinary approach including medical oncology, gastroenterology, and surgery consultation.

This algorithm is intended for use in conjunction with other UpToDate content. Refer to UpToDate topics on the diagnosis and management of ICI colitis for additional details, including pretreatment evaluation and evidence supporting the efficacy of these therapies.

Disparities in endometrial cancer

- Higher incidence of high risk histologies
  - More likely to be copy number-high, p53 mutated
- More likely to be missed by TVUS screening
- Later stage at diagnosis
- Less likely to receive standard of care therapies
- Less likely to have MIS
- Less likely to have LN assessment
- Less likely to receive adjuvant treatment

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Endometrial Cancer: Molecular Profiling and Other Updates

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