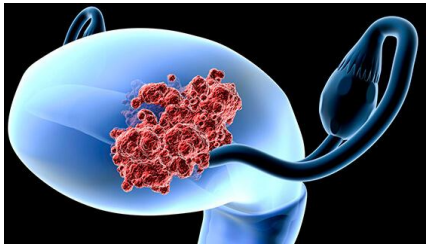
Leiden University Medical Center

DUTCH GOG
Dutch Gynaecological Oncology Group

Systeemtherapie voor endometrium carcinoom (EC)

2 december 2025

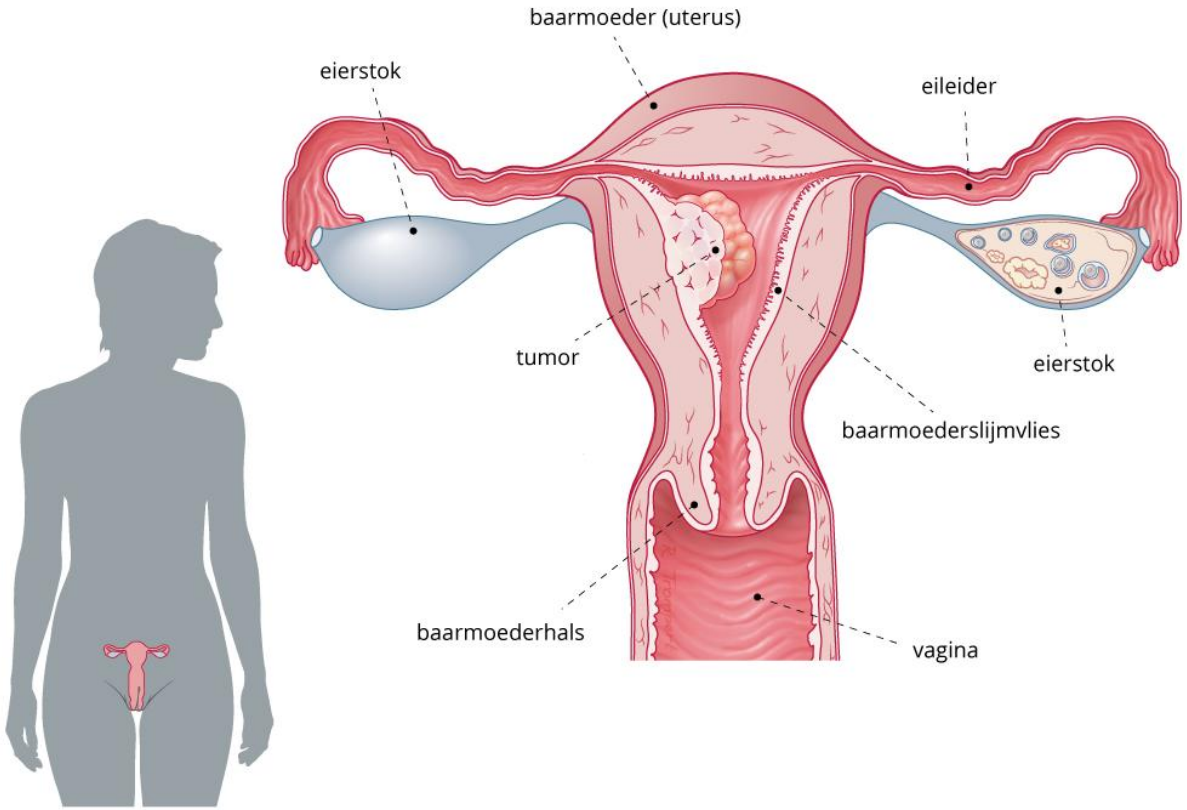


Prof. dr. Judith Kroep, MD, PhD

Dept Medical Oncology

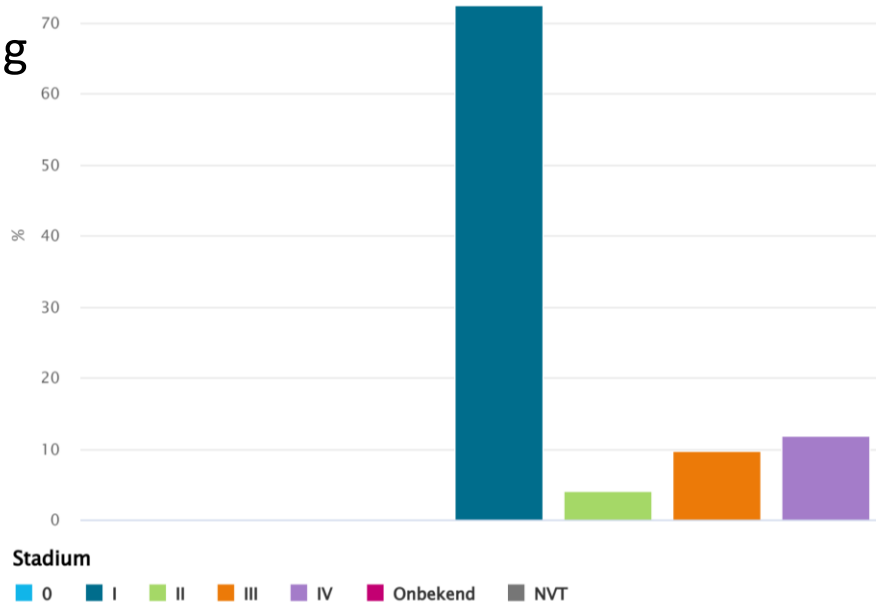
LUMC

Endometrial cancer



IKNL/NKR data Endometrium Carcinoom (EC)

- Jaarlijkse incidentie ±2000
- Incidentie stijgt obesitas en vergrijzing
- > 50% is 60 tot 79 jaar
- ±80% heeft stadium I
- Relatieve 5-jaarsoverleving hoog
  - Endometrioid 87%
  - Non-endometrioid 52%
- ±10% presenteert met stadium IV:



MMRd

What is DNA mismatch repair deficiency (MMRd)?

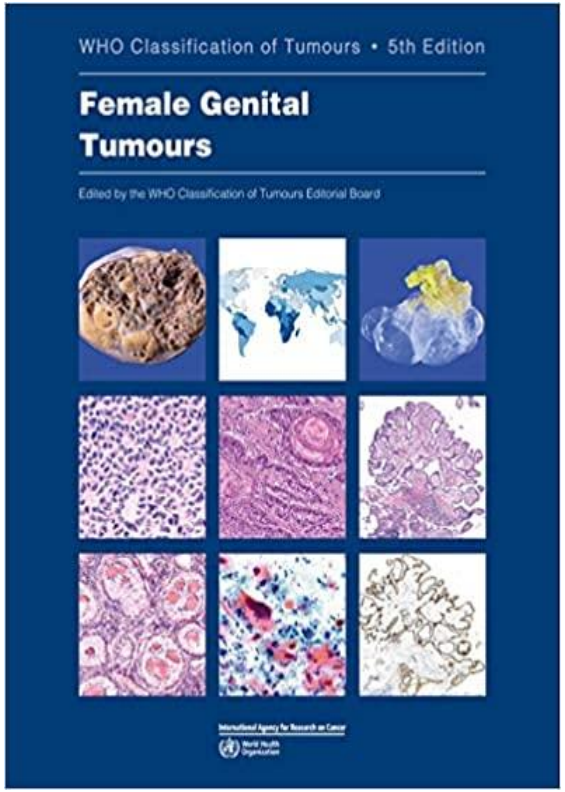
When a cell divides it must make a copy of its DNA. Mistakes can happen during that copying process. Our cells have ways of fixing these copying errors: DNA mismatch repair. When the mismatch repair does not work, these cells are mismatch repair deficient (MMRd). If a cell cannot fix the mistakes it can become cancer.

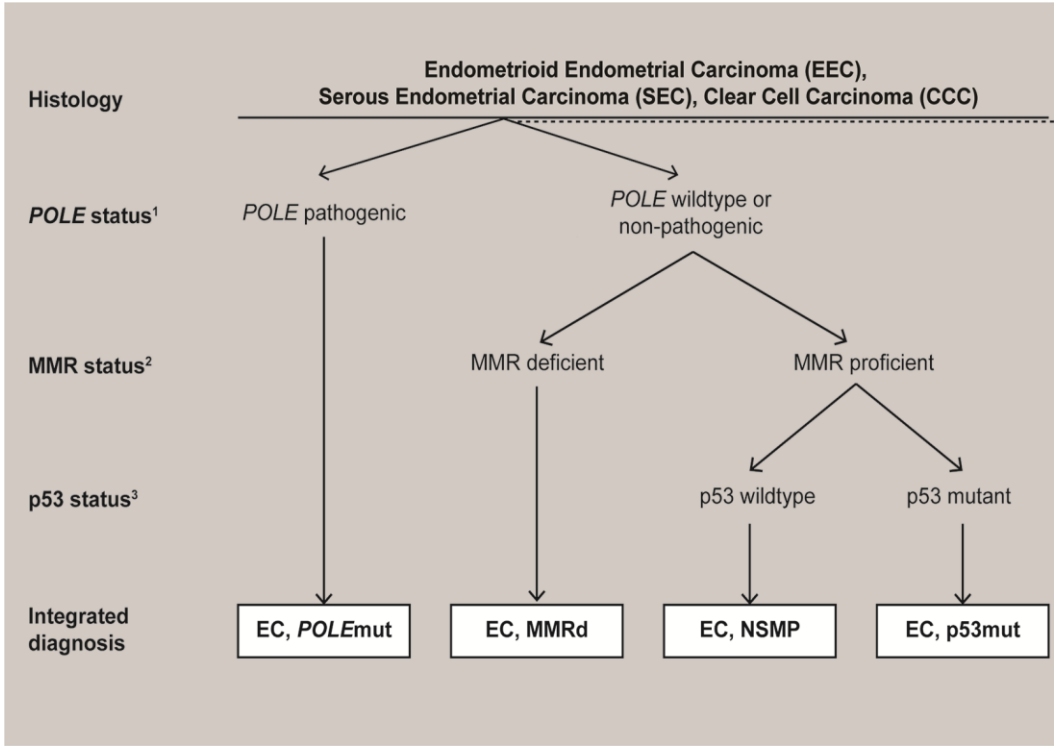
What is high microsatellite instability (MSI-H)?

MSI-H, is a type of MMRd. MMRd and MSI-H are often used to describe the same thing. Microsatellites are short, repeated pieces of DNA. The number of microsatellites in a cell can become unstable when a cell cannot fix mistakes. This instability can cause cancer.

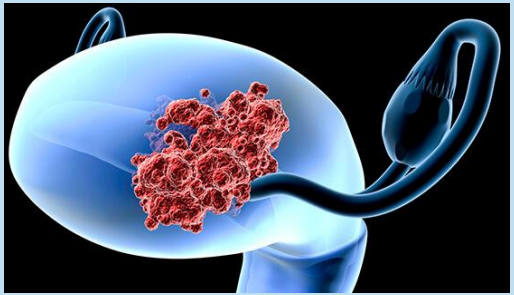
Tumor type	MSI-high, %
Uterine	**28.3**
Stomach adenocarcinoma	21.9
Colon adenocarcinoma	16.6
Rectal adenocarcinoma	9.2
Adrenal cortical	5.4
Esophageal	3.3
Ovarian	3.2
Hepatocellular	2.9
Cervical squamous	2.3

Diagnostic algorithm for the molecular classification of EC

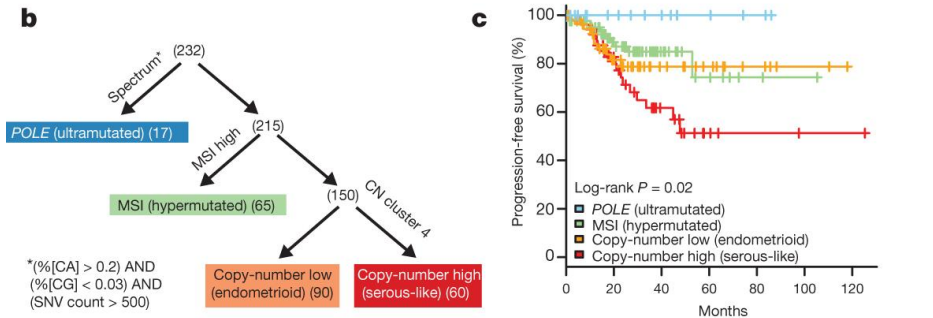


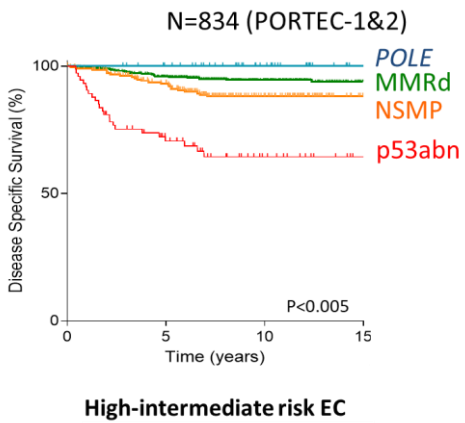


EC Adjuvant therapy

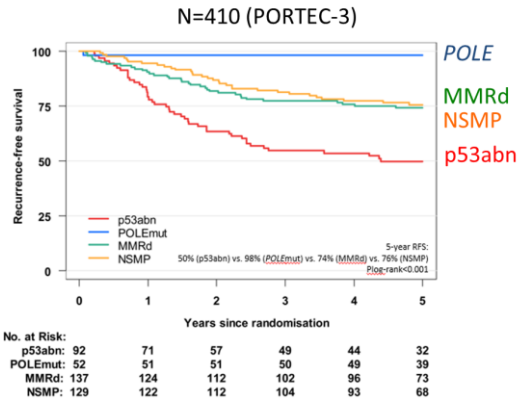


Molecular classification is Prognostic (TCGA and PORTEC data)





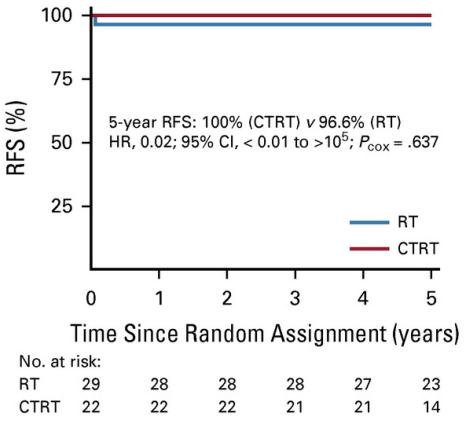
High-intermediate risk EC



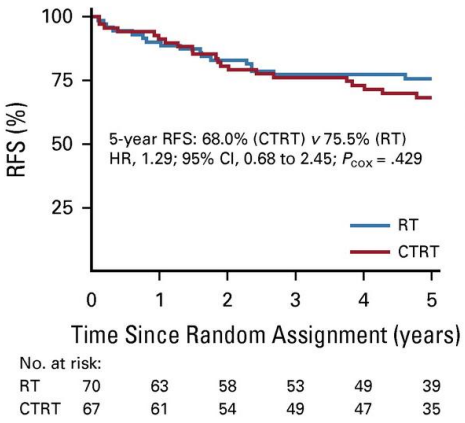
Levine Nature 497, 67-73, 2013; Stelloo Clin Cancer Res 2016; Leon-Castillo J Clin Oncol 2020

Molecular classification is Predictive - RFS in PORTEC-3 cohort -

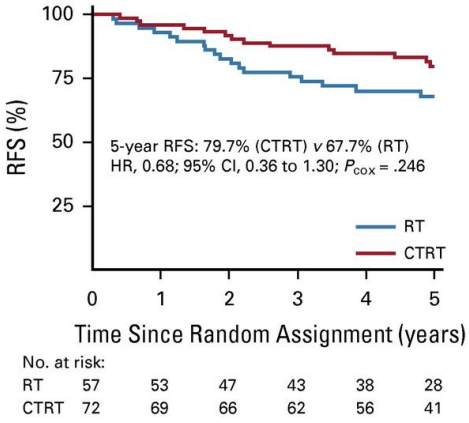
All stages *POLE*mut EC



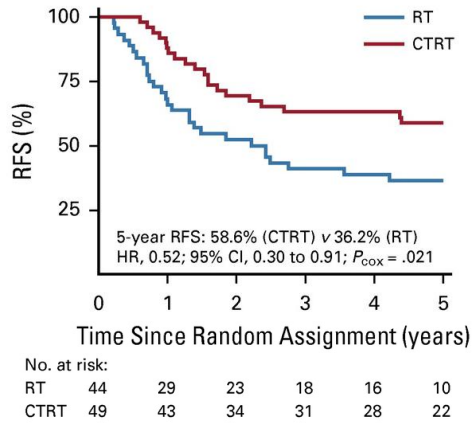
All stages MMRd EC



All stages NSMP EC



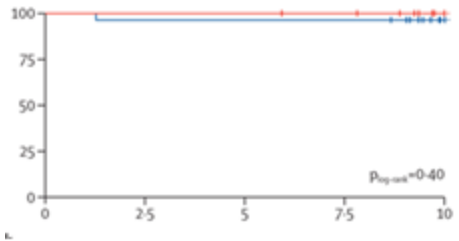
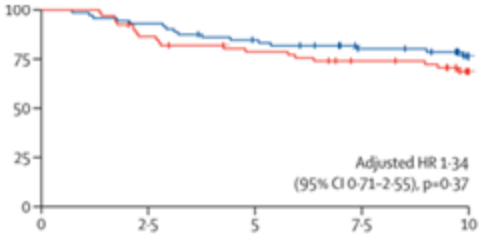
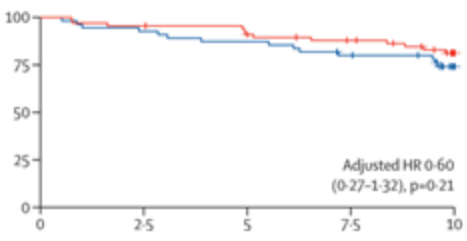
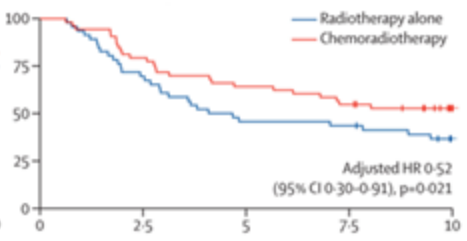
All stages p53abn EC



Excellent RFS, regardless of treatment arm.	No benefit from CRT	Inconclusive benefit from CRT	Significant benefit from CRT

Léon-Castillo, de Boer et al. 2020

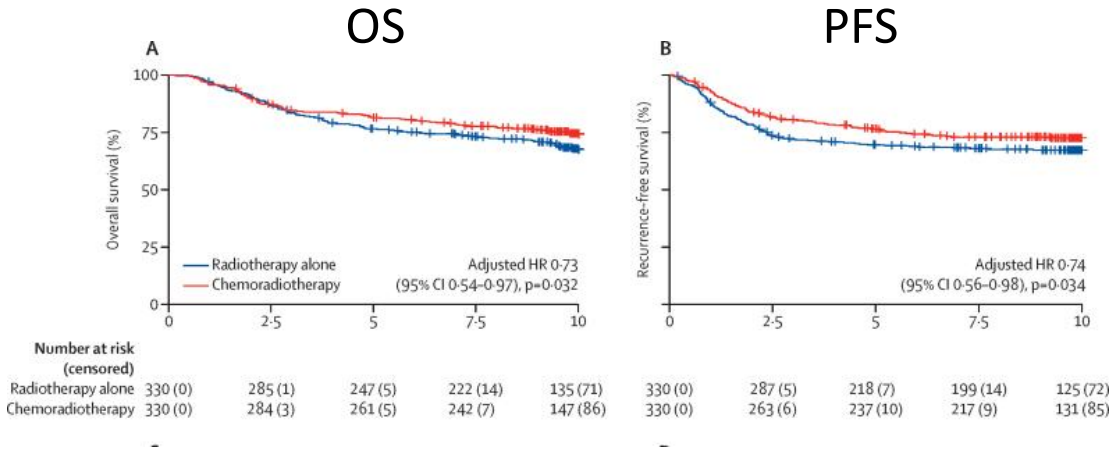
Molecular classification is predictive - OS in PORTEC-3 cohort -

All stages *POLE*mut EC	All stages MMRd EC	All stages NSMP EC	All stages p53abn EC
			
Excellent RFS, regardless of treatment arm.	No benefit from CRT	Inconclusive benefit from CRT	Significant benefit from CRT

Post CCB, Lancet Oncol 2025

Can Molecular classification help select adjuvant therapy

PORTEC-3 data 10 yr FUP



Largest benefit from chemoradiotherapy in patients with:

- Stage III: HR 0.66, p=0.02
- Stage I-III Serous EC: HR=0.55, p=0.044

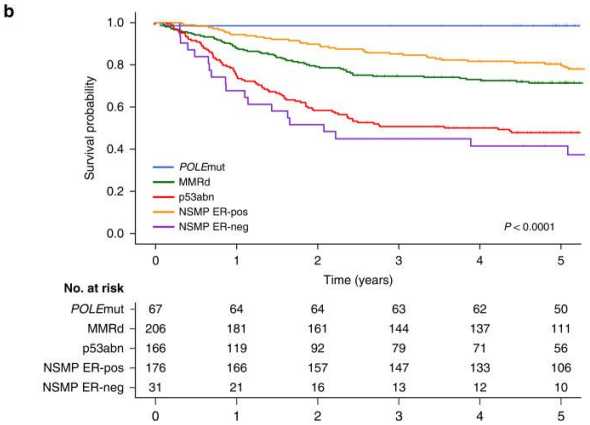
De Boer Lancet Oncology 2019; Post et al, Lancet 2025

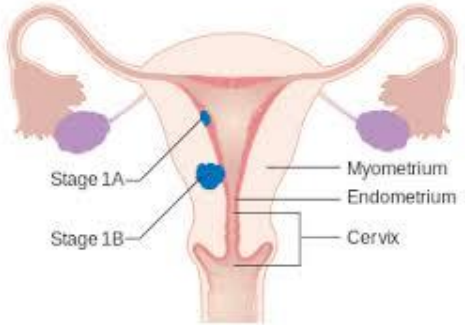
Molecular Classification helps which HR-EC needs adj Chemo

P53-abd: YES, regardless of stage (except stage IA without myometrial invasion)

Stage I/II POLE-mut, MMRd, NSMP ER+: NO

Unsure for NSMP ER-:





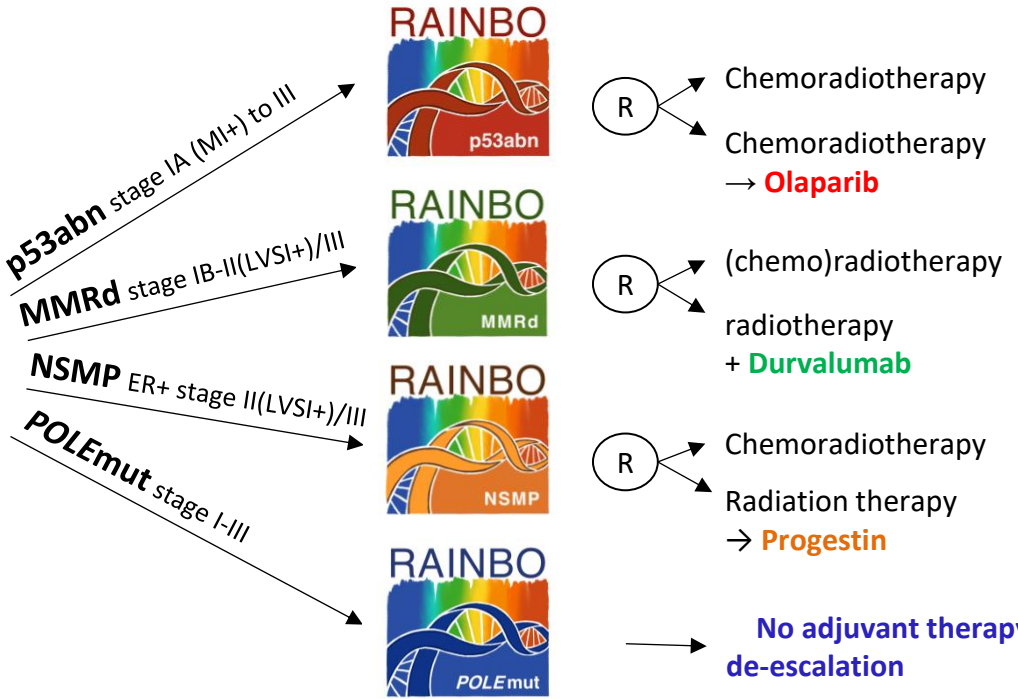
Vermij, BJC 2023

RAINBO program

Surgically resected EC

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

⇨ Molecular Classification

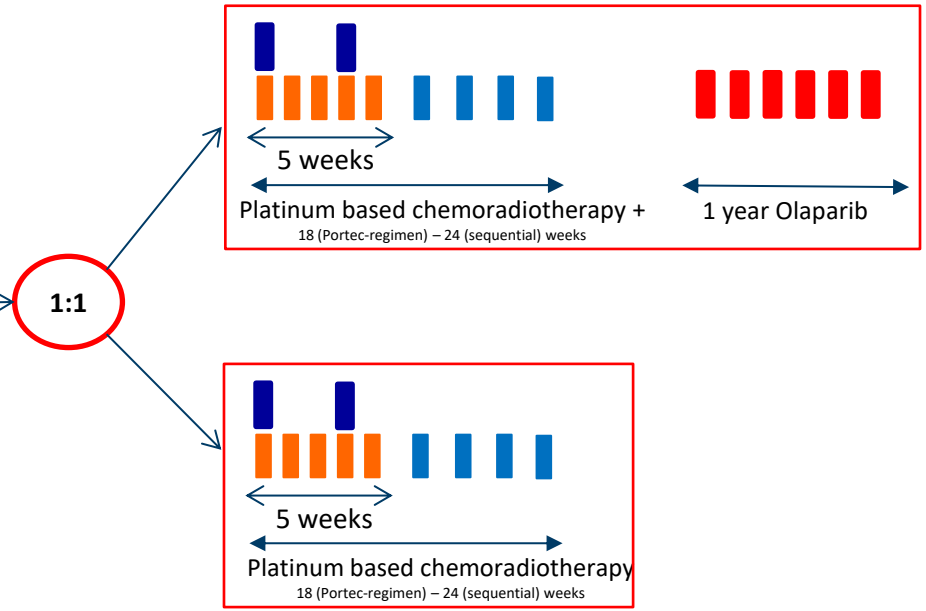


RAINBO program supported by GCIG and coordinated by *Trans*PORTEC will allocate EC pts to 4 international academic sub-trials each led by one Gyn-Onc national clinical trial group

RAINBO Research Consortium, 2022

RAINBO p53abn-RED

Inclusion criteria:
- P53abn (*POLE* wildtype)
- FIGO 2009 Stage Ia with myometrial invasion-III
- Eligible histotypes: endometrioid, serous, clear cell, un/dedifferentiated, mixed and carcinosarcoma
- WHO 0-1
- TLH-BSO/TAH-BSO regardless of lymph node staging
- No prior pelvic irradiation



Primary objective:
- 3-yr RFS

Secondary objectives:
- OS, DSS
- Vaginal, pelvic, distant recurrences
- HRQoL
- Safety & tolerability
- Exploratory translational research

Sample size: 554 patients

- Chemoradiotherapy initiated within max 10 weeks after surgery
- Olaparib initiated within 8 weeks after completion of chemoradiotherapy

RAINBO MMRd-GREEN

Inclusion criteria:
- MMRd (*POLE* wildtype)
- FIGO 2009 Stage IB/II with LVSI or stage IIIA-C EC plus FIGO 2023 stage III
- WHO 0-1
- TLH-BSO/TAH-BSO regardless of lymph node staging
- No prior pelvic irradiation

1:1

Pelvic RT 45-48.6 Gy + 13x durvalumab 1500 mg **Q4W**

or

Primary objective:
- 3-yr RFS

Secondary objectives:
- OS, DSS
- Vaginal, pelvic, distant recurrences
- HRQoL
- Safety & tolerability
- Exploratory translational research

Sample size: 316 patients

Treatment initiated within max 10 weeks after surgery
Durvalumab initiated within the 1st week of adjuvant radiotherapy

RAINBO

MMRd

Netherlands
Sponsor of MMRd-GREEN

Canada
Sponsor of *POLE*mut-BLUE

United Kindom
Sponsor of NSMP-ORANGE

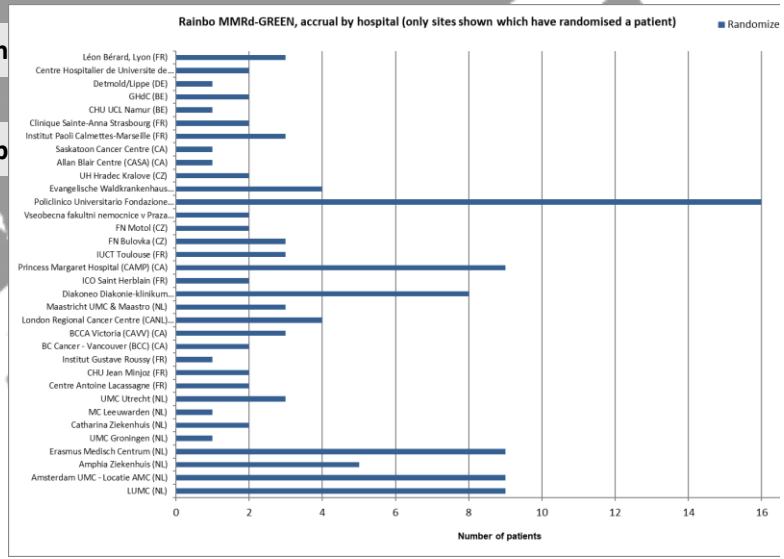
Belgium

German

France
Sponsor of p53abn-RED

Czech Repub

Italy



MMRd-GREEN

Design:
Randomized phase III adjuvant
durvalumab (1 yr) plus radiotherapy
vs (chemo) radiotherapy
Amendment accepted

Recruitment: 128/316 patients randomized
Primary Endpoint: 3-year RFS
Sponsor: LUMC/DGOG

Participating Country	status	Patient inclusion
Netherlands (DGOG)	Open 10 sites	42
France (GR/GINECO)	Open 10 sites	20
Germany (SH/AGO)	Open 7 sites	14
Belgium (BGOG)	Open 6 sites	4
Czech Republic (CEEGOG)	Open 4 sites	9
Italy (Gemelli/MITO)	Open 1 site	16
Canada (CCTG)	Open 8 sites	23
UK (NRCI)	Start up	
India (KolGO)	Start up	

RAINBO *POLE*mut-BLUE trial

Sponsor: Canadian Cancer Trials Group
International, multicenter, phase II

***POLE*mut-BLUE inclusion criteria**:
- *POLE*mut
- Stage IA (not confined to polyp) to stage III EC
- TLH-BSO/TAH-BSO regardless of lymph node staging
- No prior pelvic irradiation
- With treatment of interest as follows →

NOT randomized

A1 - Very low risk (n=120)

No treatment

IA gr 3 pN0
IB gr 1-2 +/- LVSI
IB gr 3 pN0 +/- LVSI
II gr 1-2 pN0

A2 - Low risk (n=25)

Alle hogere stadia t/m III of pNx

Pelvic RT 48.6 Gy (27x) OR Vaginal BT 21 Gy (3x)

OR no adjuvant treatment
NO chemotherapy

Primary objective:
- 3-yr pelvic recurrence

Secondary objectives:
- OS, DSS
- Vaginal, distant recurrences
- HRQoL
- Health economic impact
- Fear of cancer recurrence

Sample size: 145 patients

** Recommendation of treatment according to institutional practice. Treatment initiated within 6-8 weeks (max 10 weeks) after surgery;*

ENGOT-en14 *POLE*mut-BLUE

- ✓ CCTG central activation Dec 19, 2022
- ✓ 72/145 patients accrued
- ✓ **Participating countries**:

Participating Country	status	Patient inclusion
Canada (CCTG)	Open 13 sites	44
Netherlands (DGOG)	Open 6 sites	17
France (GR)	Open 1 site	0
Australia & New Zealand (ANZGOG)	Open 11 sites	0
United States (NRG)	Open 52 sites	8
Italy (MaNGO)	Open 2 sites	3
Norway	Open 1 site	0
Germany (AGO)	Start up	
UK (NRCI)	Start up	

Overarching and translational research project

	RAINBO p53abn	RAINBO MMRd	RAINBO NSMP	RAINBO *POLE*mut
Inclusion of:	Stage IA (MI+) - III	Stage Ib/II+LSVI - III	Stage II+LSVI - III	Stage I-III
Experimental Tx	CRT + PARP-i	EBRT + PDL1-i	EBRT + HT	De-escalated Tx
Control Tx	CRT	EBRT	CRT	Standard of care
Outcomes	RFS, OS, tox/QoL	RFS, OS, tox/QoL	RFS, OS, tox/QoL	RFS, OS, tox/QoL
Sample size	575	316	600	145

Uniform RAINBO Data Registration

Overarching RAINBO research project

Treatment efficacy, toxicity, quality of life and cost-utility

Translational research

Tumor micro-environment, molecular features, tumor immunology, AI

CONCLUSION

Risk stratification and molecular profiling matter more than ever

- Move prognosis beyond traditional stage + grade assessment

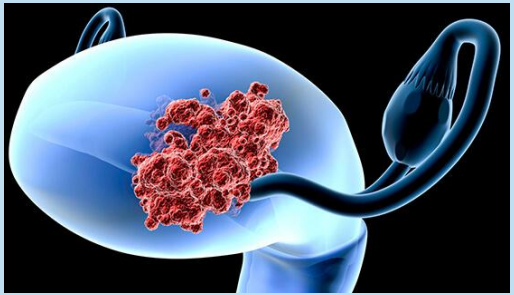
Molecular profiling is now central to adjuvant therapy decisions

- Key biomarkers: POLE, MMR/dMMR, p53abn
- Enables de-escalation in favorable subtypes and escalation in high-risk groups

RAINBO program

- International, molecularly driven initiative
- Aligns adjuvant therapy with tumor molecular subtype
- Aims to optimize outcomes and reduce overtreatment

Recurrent EC therapy



Systemic therapy recurrent EC

Praktijk veranderende studies

1e lijn:

RUBY PART 1: C/T ± Dostarlimab → onderhoud dostarlimab

NRG-GY018: C/T ± Pembrolizumab → onderhoud pembrolizumab

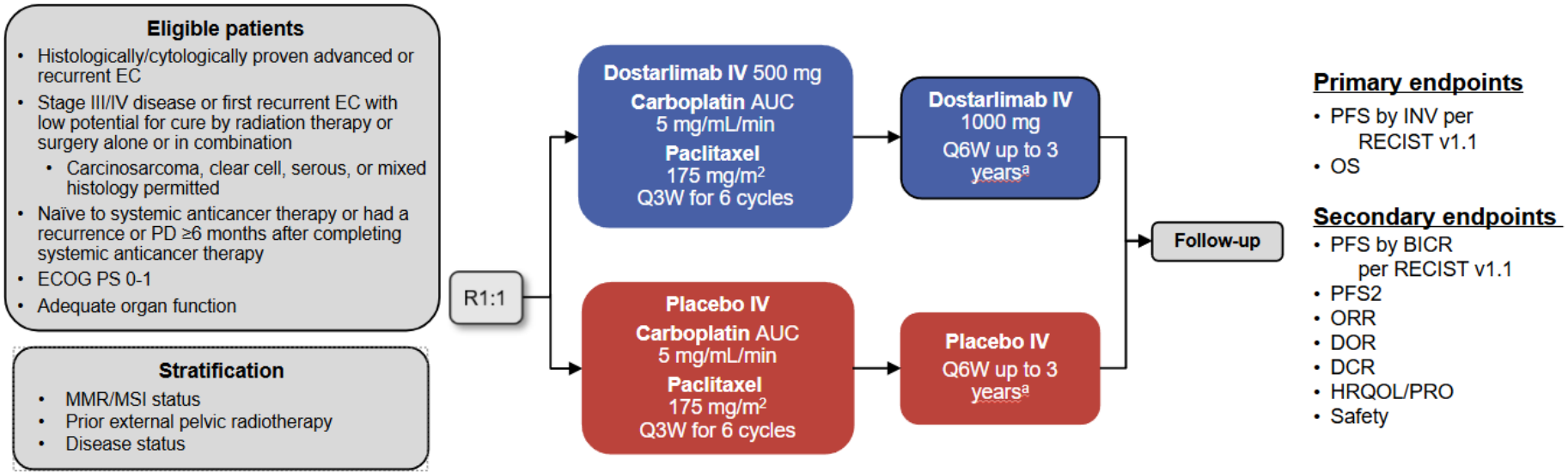
DUO-E: C/T ± Durvalumab → onderhoud durvalumab ± olaparib

AtTEnd: C/T ± Atezolizumab + → onderhoud atezoluzimab

≥2e lijn:

KEYNOTE-775: Pembrolizumab + lenvatinib

RUBY PART 1: C/T ± dostarlimab (n=494)

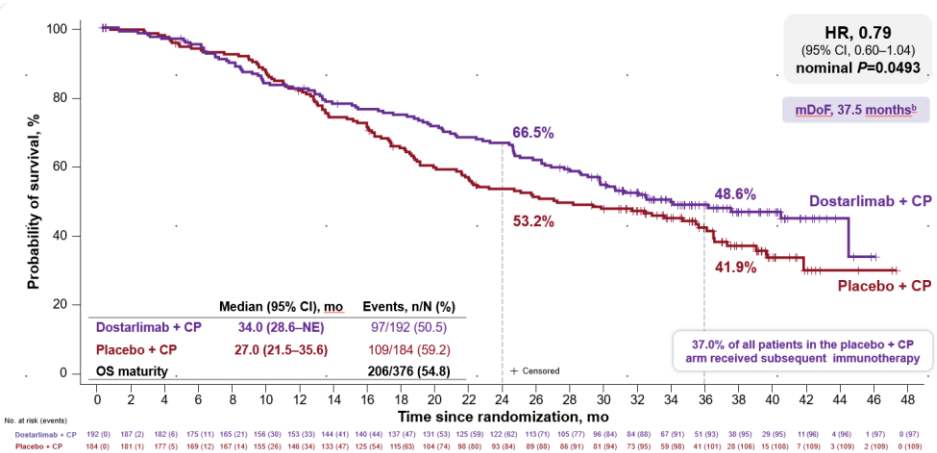


Further study details can be found at Mirza MR, et al. N Engl J Med. 2023 Jun 8;388(23):2145-2158.
[a]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the Investigator. AUC, area under the plasma or serum concentration-time curve; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response, EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQOL, health-related quality of life; INV, investigator assessment; MMR, mismatch repair; MSI, microsatellite instability; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, second progression-free survival; PRO, patient-reported outcome; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

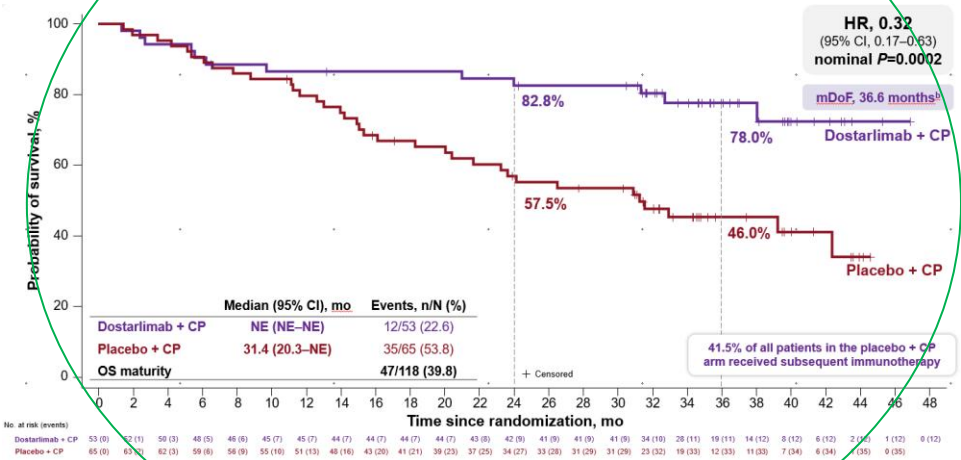
Powel et al, ESMO GYN 2024

RUBY PART 1: dMMR vs pMMR

MMRp (exploratory)

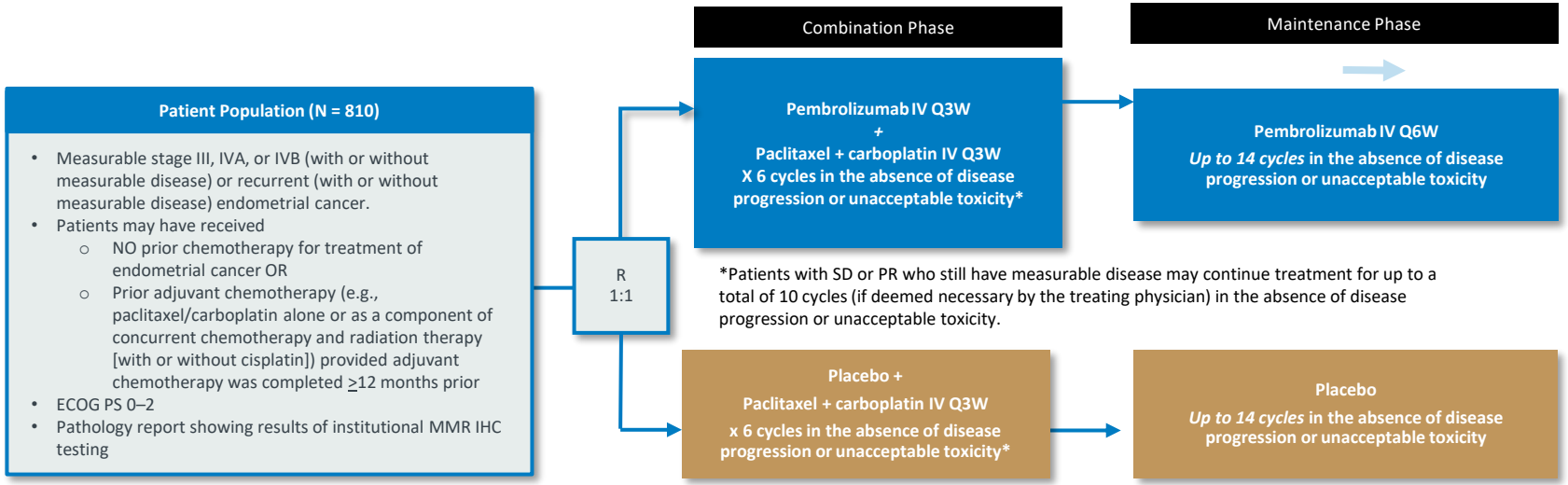


MMRd primary endpoint



Powel et al, ESMO GYN 2024

NRG-GY018: C/P ± pembrolizumab (n=816)



*MMR status as randomized

1. https://clinicaltrials.gov/ct2/show/NCT03914612. Eskander R.N. et al. Presented at ESMO 2023. Eskander RN, et al. NEJM. 27 March 2023 Eskander RN, et al.

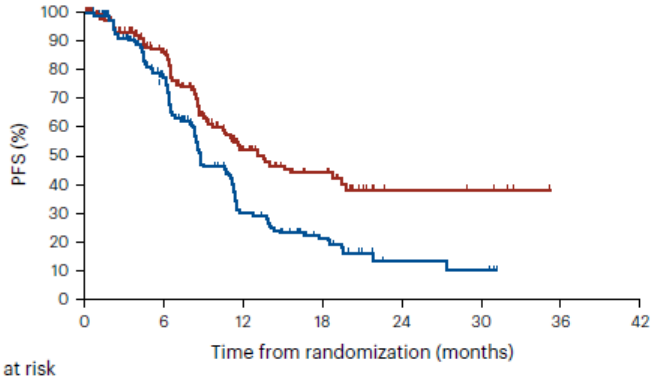
Eskander, Nature Medicine 2025

NRG-GY018: C/P ± pembrolizumab PFS

MMRp

a

	Events, n/N	Median PFS (95% CI), months	HR (95% CI)[a], P value[b]
Pembrolizumab + CT	95/294	13.1 (10.6–19.5)	0.57 (0.44–0.74)
Placebo + CT	138/294	8.7 (8.4–11.0)	P < 0.0001

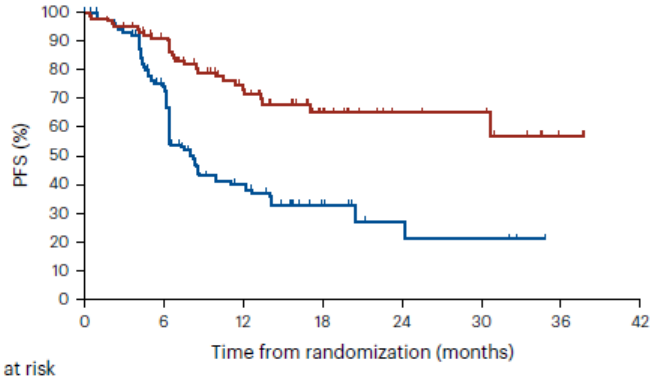


Number at risk								
Pembrolizumab + CT	294	162	57	29	7	6	0	0
Placebo + CT	294	144	36	15	4	3	0	0

MMRd

b

	Events, n/N	Median PFS (95% CI), months	HR (95% CI)[a], P value[b]
Pembrolizumab + CT	29/110	NR (30.7–NR)	0.34 (0.22–0.53)
Placebo + CT	60/112	8.3 (6.5–12.3)	P < 0.0001



Number at risk								
Pembrolizumab + CT	110	85	45	24	10	9	2	0
Placebo + CT	112	69	25	9	4	3	0	0

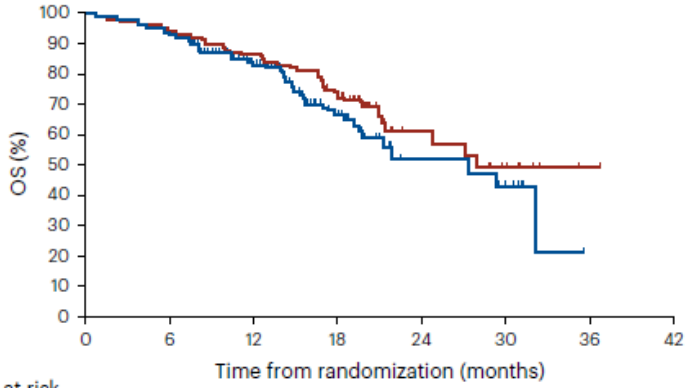
Eskander, Nature Medicine 2025

NRG-GY018: C/P ± pembrolizumab OS

MMRp

a

	Events, n/N	Follow-up Duration[a], median (range), months	Median OS (95% CI), months	HR (95% CI)[b], P value[c]
Pembrolizumab + CT	45/294	8.8 (0.1–37.0)	27.96 (21.42–NR)	0.79 (0.53–1.17)
Placebo + CT	54/294	8.4 (0.1–37.2)	27.37 (19.52–NR)	P = 0.1157

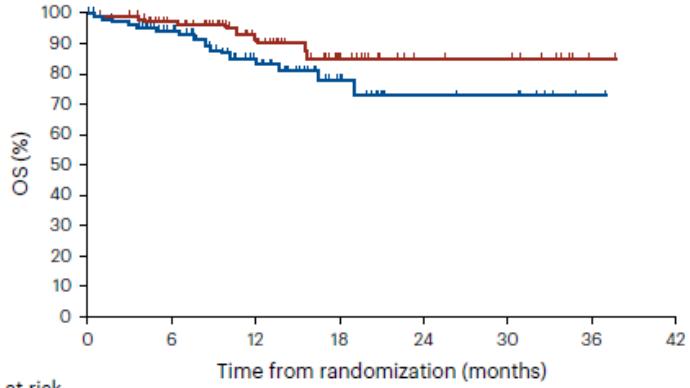


Number at risk								
Pembrolizumab + CT	294	179	97	51	16	10	1	0
Placebo + CT	294	174	94	46	11	7	0	0

MMRd

b

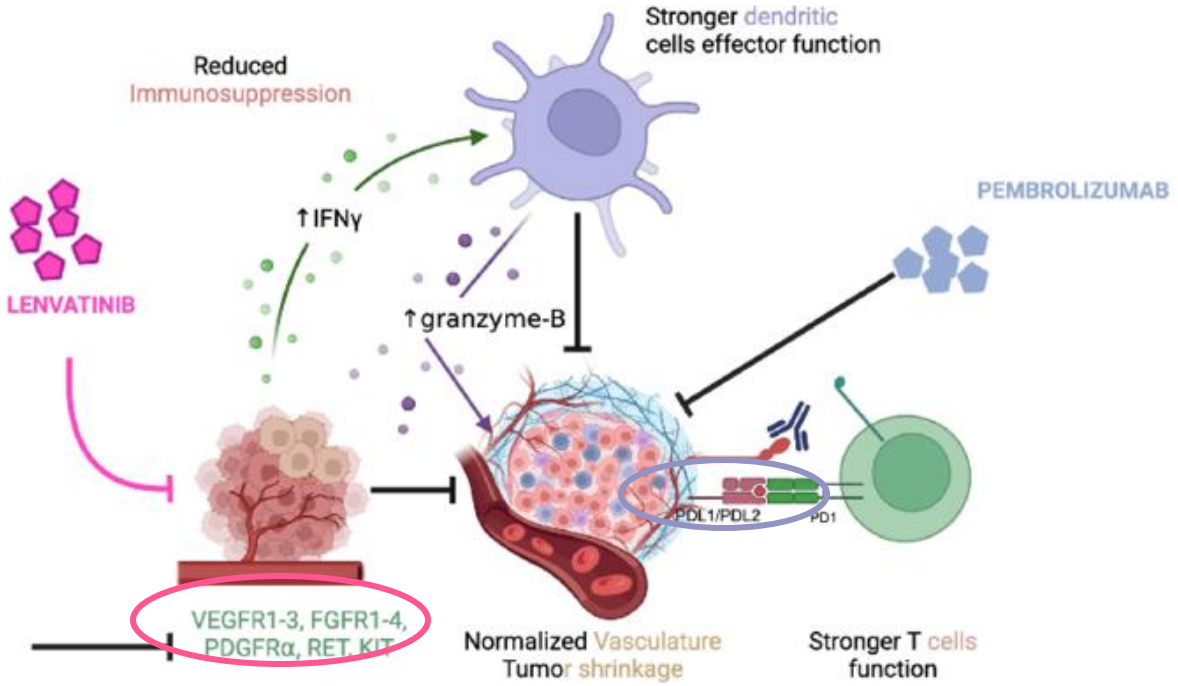
	Events, n/N	Follow-up Duration[a], median (range), months	Median OS (95% CI), months	HR (95% CI)[b], P value[c]
Pembrolizumab + CT	10/110	13.3 (0.6–39.4)	NR (NR–NR)	0.55 (0.25–1.19)
Placebo + CT	17/112	13.7 (1.0–38.0)	NR (NR–NR)	P = 0.0617



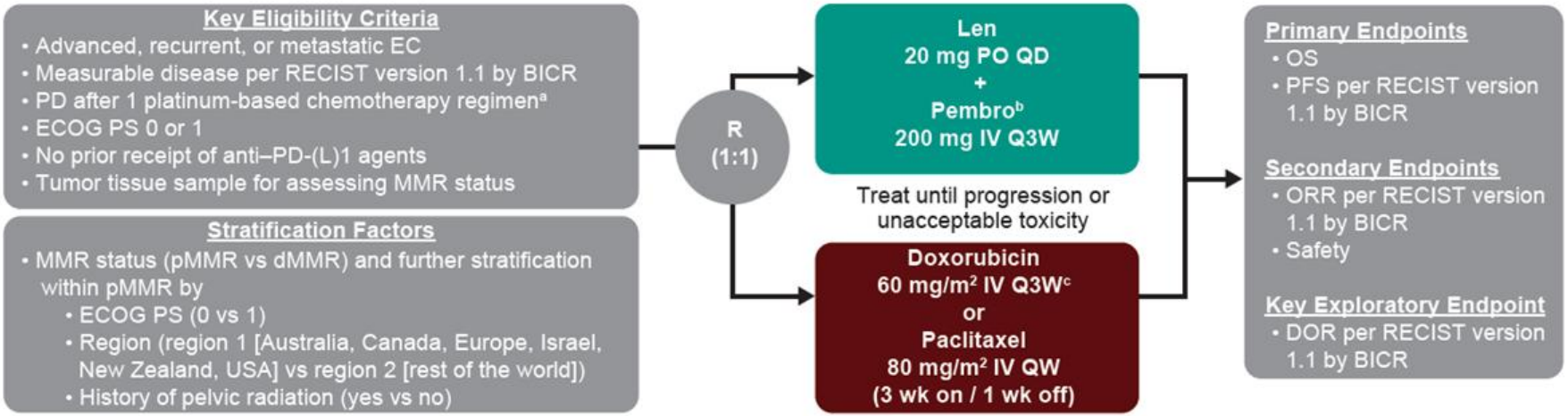
Number at risk								
Pembrolizumab + CT	110	88	55	29	12	11	2	0
Placebo + CT	112	87	52	18	8	7	1	0

Eskander, Nature Medicine 2025

2e lijn Pembrolizumab en Lenvatinib mechanism



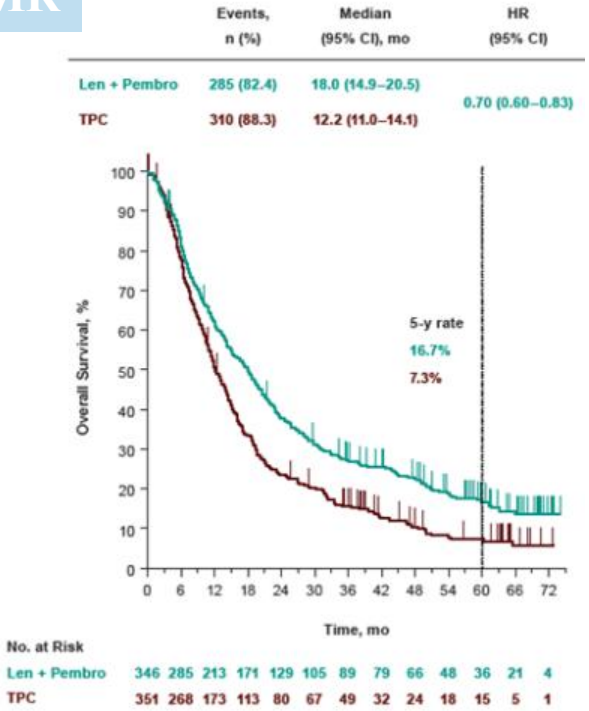
KN-775: >1L: lenvatinib/pembrolizumab (n=827)



Makker et al, ESMO 2025

KN-775: >1L lenvatinib/pembrolizumab OS en PFS

pMMR

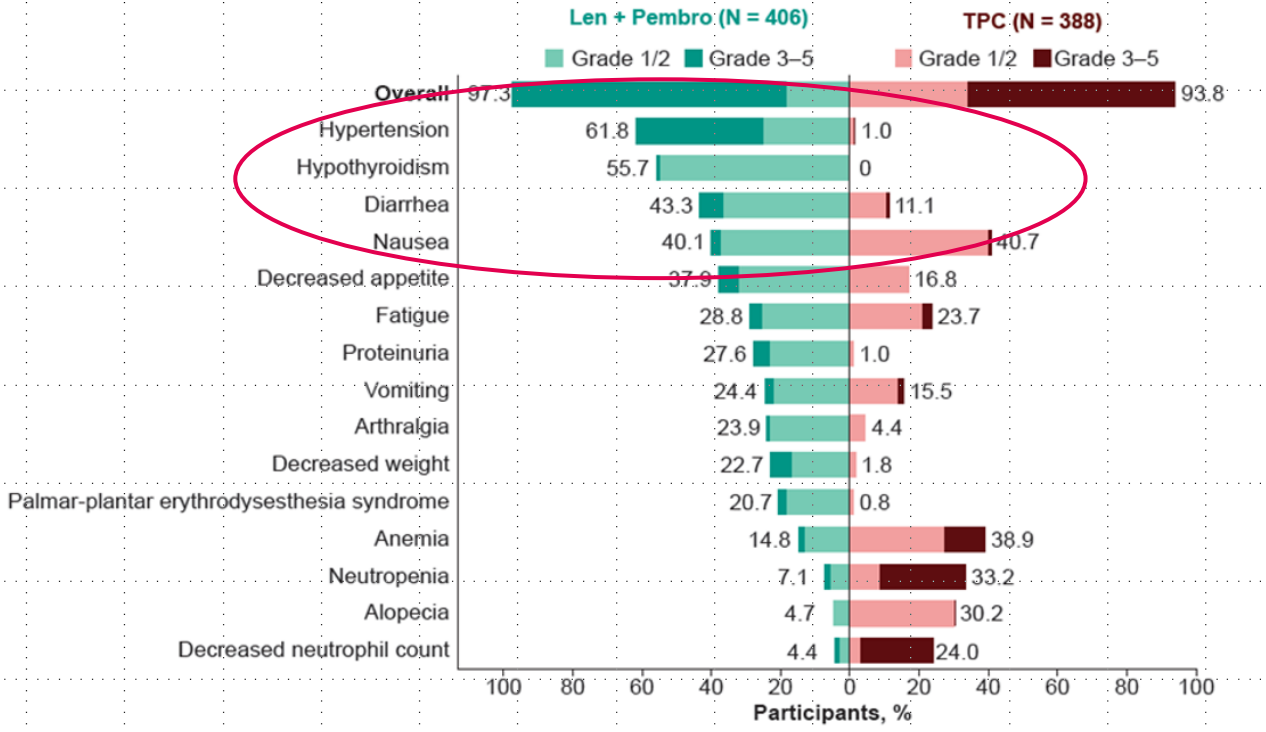


84% was pMMR !

Makker et al, ESMO 2025

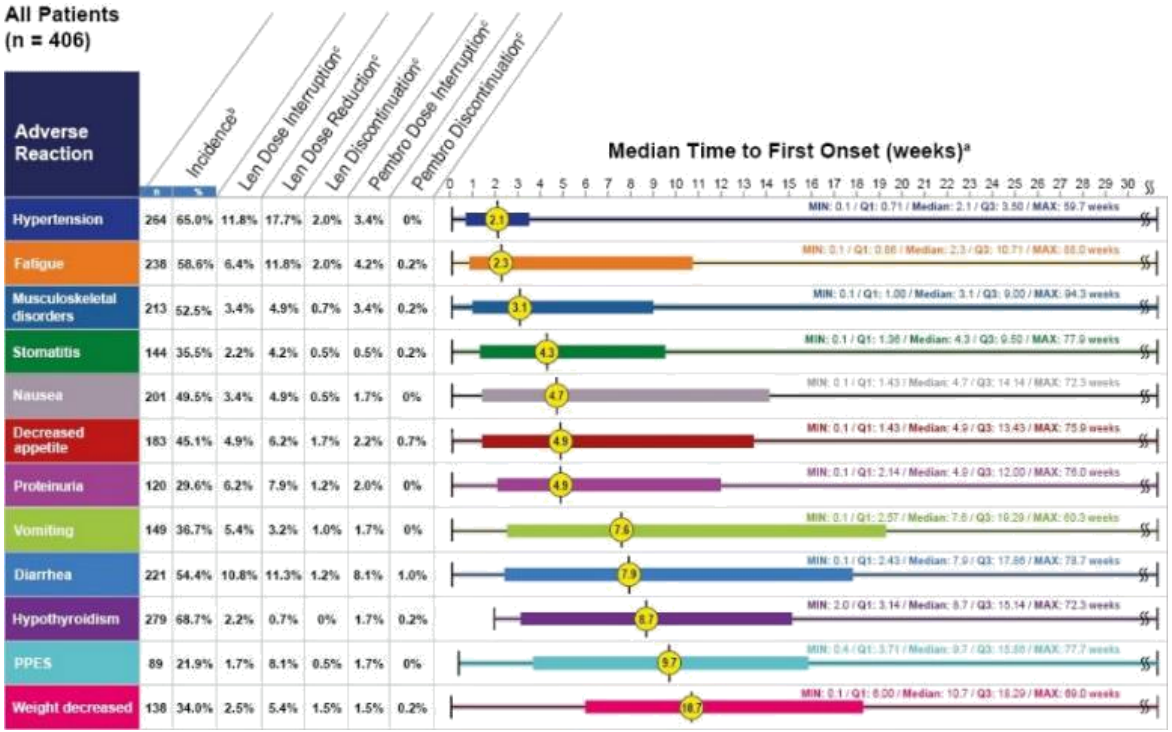
Hoe toxisch is Lenvatinib?

Toxiciteit lenvatinib



Colombo et al, The Oncologist, 2024; Makker et al, ESMO 2025

Toxiciteit lenvatinib



Colombo et al, The Oncologist, 2024; Makker et al, ESMO 2025

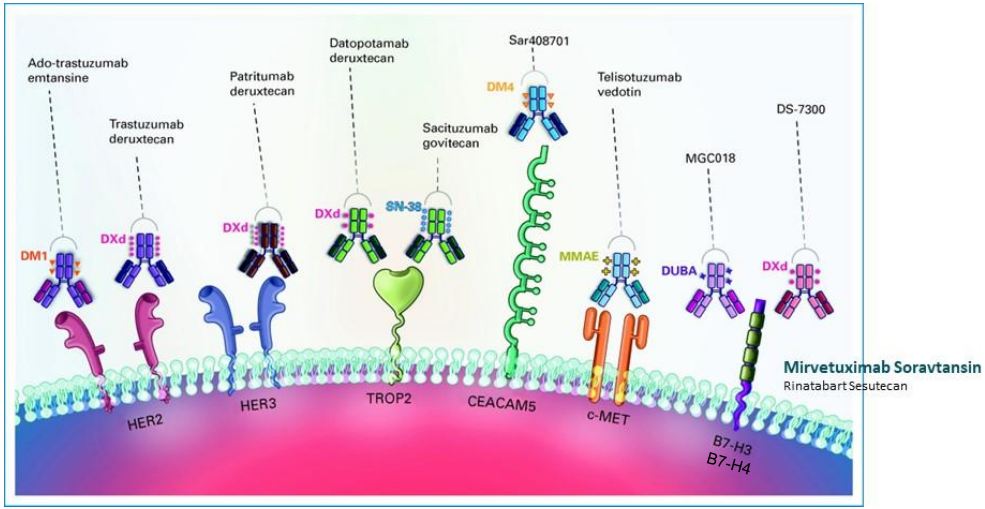
Plaatsbepaling immunotherapie CieBOM

Type/conclusie	Behandeling	Opmerking
MMRd: duidelijke consistente winst	1L: Carboplatin-paclitaxel + IO >1L: nivolumab**	Pembrolizumab* (2jr) en dostarlimab (3jr) vergoed, durvalumab (nog) niet.
pMMR: geringer voordeel, advies terughoudend counselen	1L: Carboplatin-paclitaxel+ pembrolizumab)*** >1L: lenvatinib/pembrolizumab**	Subgroep data NRG-GY018 volgt 2026 waarschijnlijk. NB. pembrolizumab wordt wel vergoed in 1L; cave zeer heterogeen effect in pMMR groep

* Doseringsadviezen cf NVMO
** indien IO naief
*** conform plaatsbepaling NVMO op basis van moleculair profiel: bv. NSMP ER-/PR-, zeldzame subtypen (clear cell carcinoom, carcinosarcoom). POLE heeft uitstekende prognose ± IO. p53abn?

Future Developments

- Further refining therapy based on molecular markers
- Trials on ADC, bispecific antibodies and others



Summary Systemic therapy EC

- Immunotherapy is added in the 1st and 2nd line therapy of metastatic / recurrent EC
- The role of molecular based therapy in the adjuvant setting is currently studied (rainbo program)
- Future developments

Leiden University Medical Center

Thank You

Olijf
Netwerk voor vrouwen met gynaecologische kanker

Gemelli
Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

GINECO

DGOG
The Dutch Gynaecological Oncology Group

KWF

RAINBO
TransPORTEC

Diakoneo
DIAK KLINIKUM

GTG-UK
Gynae-oncology Trials Group UK

ENGOT
European Network of Gynaecological Oncological Trial groups

Bontius Stichting

BGOG
Belgian Gynaecological Oncology Group

Canadian Cancer Trials Group

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CEEGOG
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mayapada hospital
Experience Better Care

GCIG
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