

# DGOG symposium

18 januari 2023

*Studies*

*Endometrium*

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LUMC



## Studies Endometrium

- *Ongoing trials*
  - Adjuvant:
    - MMRd-GREEN
  - Recurrent/Metastatic:
    - RUBY, Keynote-B93, PROMOTE-P
- *Pipeline /Startup*
  - RAINBO program



# MMRd-GREEN

Phase 3 trial on the addition of Durvalumab to standard adjuvant radiotherapy in patients with stage II/LVSI+III MMRd EC

**Primair eindpunt: 3 yr EFS**

**Benodigd aantal patiënten: 316**

**Aantal geïncludeerde patiënten per datum Jan2023: 2**

Netherlands		International
<b>AUMC</b>	Catharina ZH	IGR France
<b>Amphia-Verbeeten</b>	UMCN	CCTG Canada
<b>EMC</b>	UMCM	NCRI UK
<b>LUMC</b>	MST	Germany
NKI-AvL		MITO/gemelli Italy
UMCG		BGOG Belgium
MCL-RIF		India
		Brazilië

*Bold: open per 5 jan 2023*



## RUBY studie

**Studie opzet & behandeling:** Gerandomiseerde fase III studie Dostarlimab (TSR-042) + Carboplatin-paclitaxel versus Placebo + Carboplatin-paclitaxel bij patiënten met recidief of primair gevorderd endometriumcarcinoom

**Primair eindpunt:** PFS (RECIST) alle ptn en bij ptn met MSI-H

**Secundair:** OS, ORR, DOR, DCR, PROs, safety, exploratief

**Aantal geïnccludeerde patiënten:** 494 part 1 (33 carcinosarcoma) + 291 part 2

**Duur van de inclusie:** 7/2019- 4/2022

**Reden van sluiting:** inclusie behaald

**Publicaties:** SGO part 1 (25-28mrt '23)

# Prediction of Response Of horMOnal Treatment in advanced and recurrent Endometrial cancer (PROMOTE-P)

**Studie opzet & Behandeling:** Prospectieve, observationele studie van patiënten met gevorderd of recidief endometriumcarcinoom die starten met hormonale therapie.

**Primair eindpunt:** Validation of the response prediction algorithm to hormonal therapy defined as response rate, progression free survival (PFS) and clinical benefit rate (CBR).

**Benodigd aantal patiënten:** 150

**Aantal geïncludeerde patiënten per 1-1-2023:** 1

**Deelnemende centra:** 16 centra (incl. 3 buitenlandse centra)

## Voortgang inclusie

In oktober 2022 is de eerste patiënt geïncludeerd in de PROMOTE-P studie.

Momenteel zijn er:

- 5 centra waar lokale goedkeuring is verkregen (en patiënten kunnen includeren)
  - Radboudumc, Erasmus, MMC, CZE, Amphia
- 9 centra waar gewerkt wordt aan de lokale goedkeuringsprocedure en dus spoedig patiënten kunnen worden geïncludeerd.

## KEYNOTE-B93 / ENGOT-en15

### **Studie opzet & behandeling:**

Phase 3 trial of Pembrolizumab vs Platinum-based doublet chemotherapy in advanced MMRd-EC in the 1st line

**Primair eindpunt: PFS**

**Aantal benodigde patiënten: 350**

**Deelnemende centra:**

- AUMC
- CZE
- EMC
- LUMC
- MUMC
- UMCG
- UMCN
- UMCU

# Stand van zaken

## KEYNOTE-B93 / ENGOT-en15

Inclusion worldwide: >36/350

Inclusion Netherlands: 1

Site #	Hospital	# Subjects Screened	# Subjects Randomized
1701	EMC	0	0
1702	LUMC	2	1
1703	RUMC	0	0
1704	CZE	1	0
1705	UMCU	0	0
1706	AUMC	0	0
1707	UMCG	0	0
1709	MUMC	0	0

## Pipeline / studies in Opstart

- **ENGOT-EN20/GOG-3083/XPORT-EC-042:**

Phase 3, RCT, placebo-controlled trial of Selinexor (selective inhibitor of nuclear export) in maintenance therapy after systemic therapy for p53-WT, Stage IV or recurrent EC.

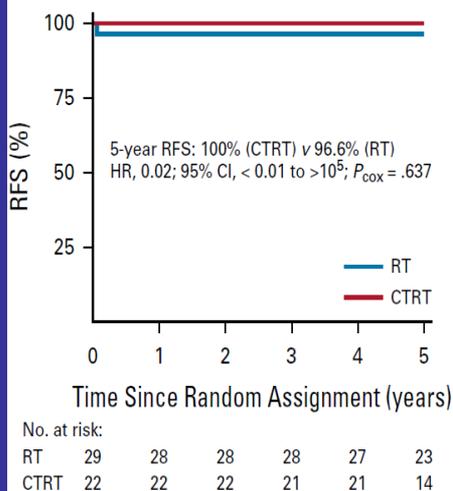
- **ENGOT EQRX GINECO trial:**

Phase 3 study proposal for Lerociclib (CDK4/6i) plus letrozole vs Letrozol in low grade (gr 1/2) EC.

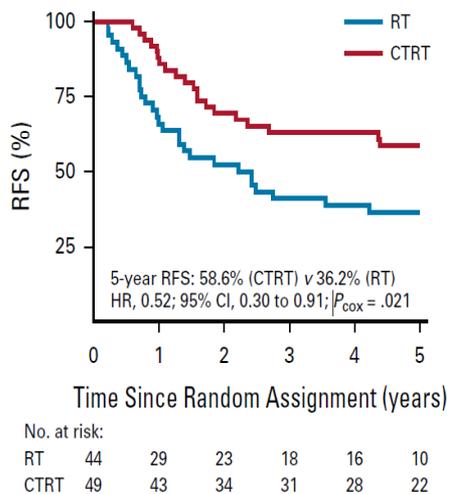
- **RAINBO Program**

# RAINBO Background, Molecular data from PORTEC-3

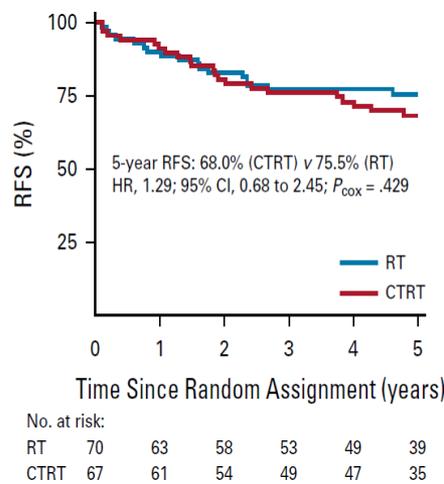
## POLEmut



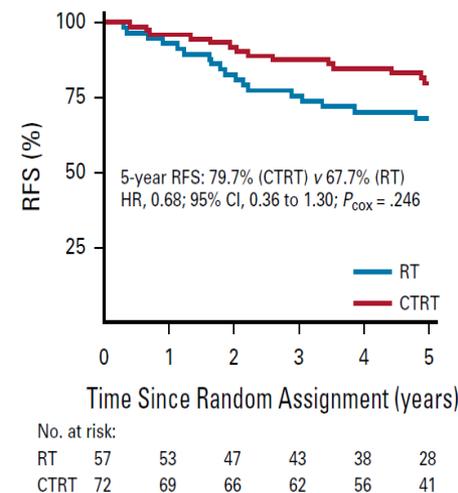
## p53abn



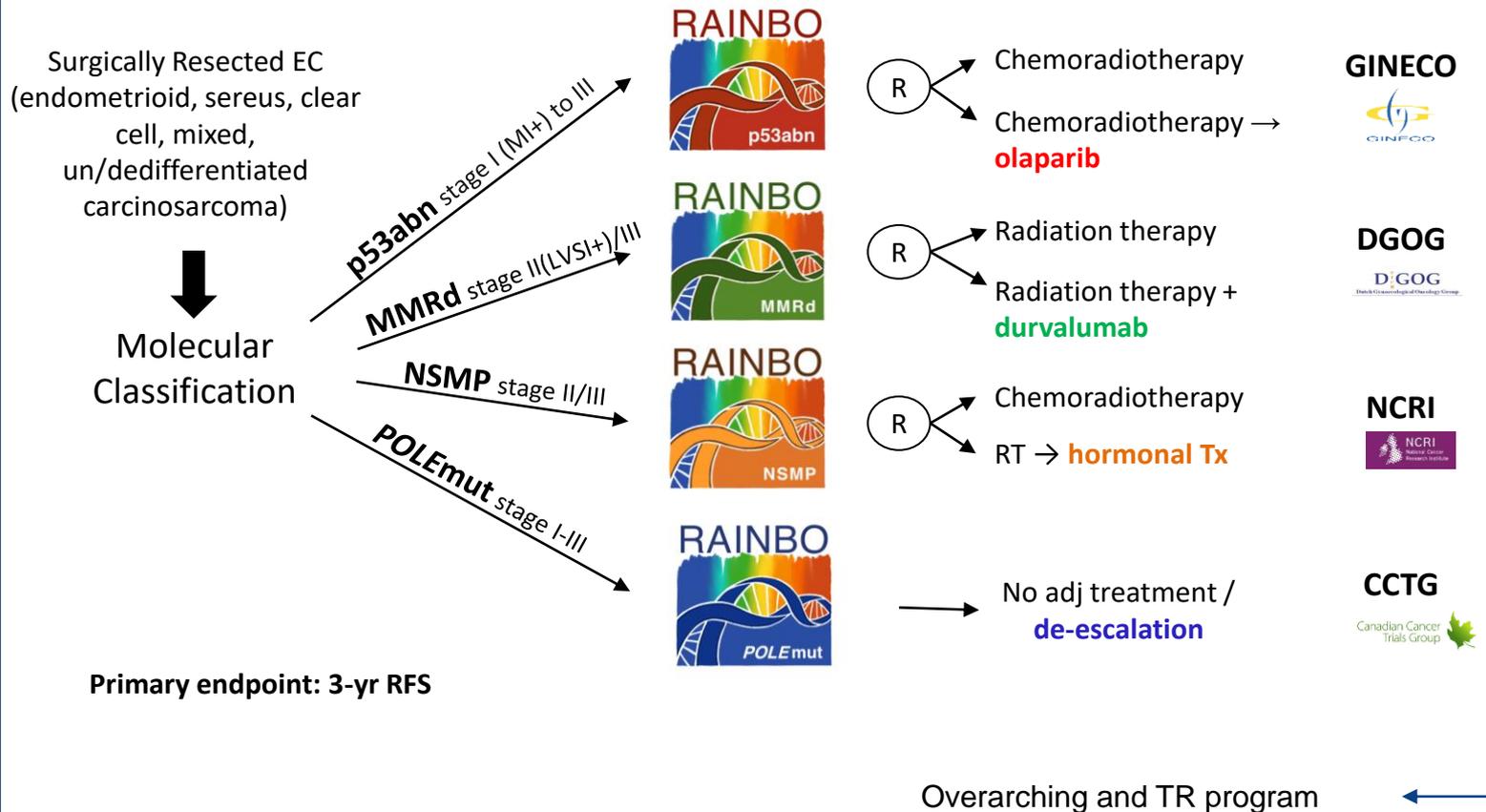
## MMRd



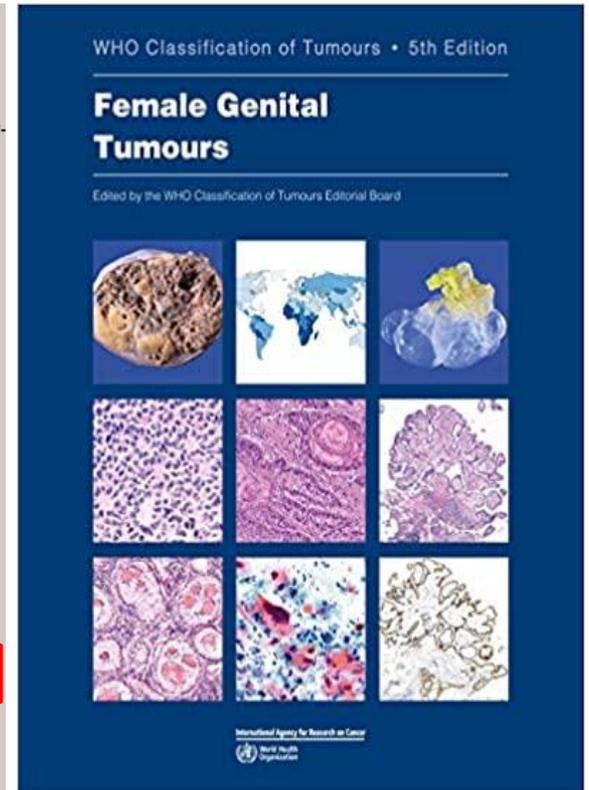
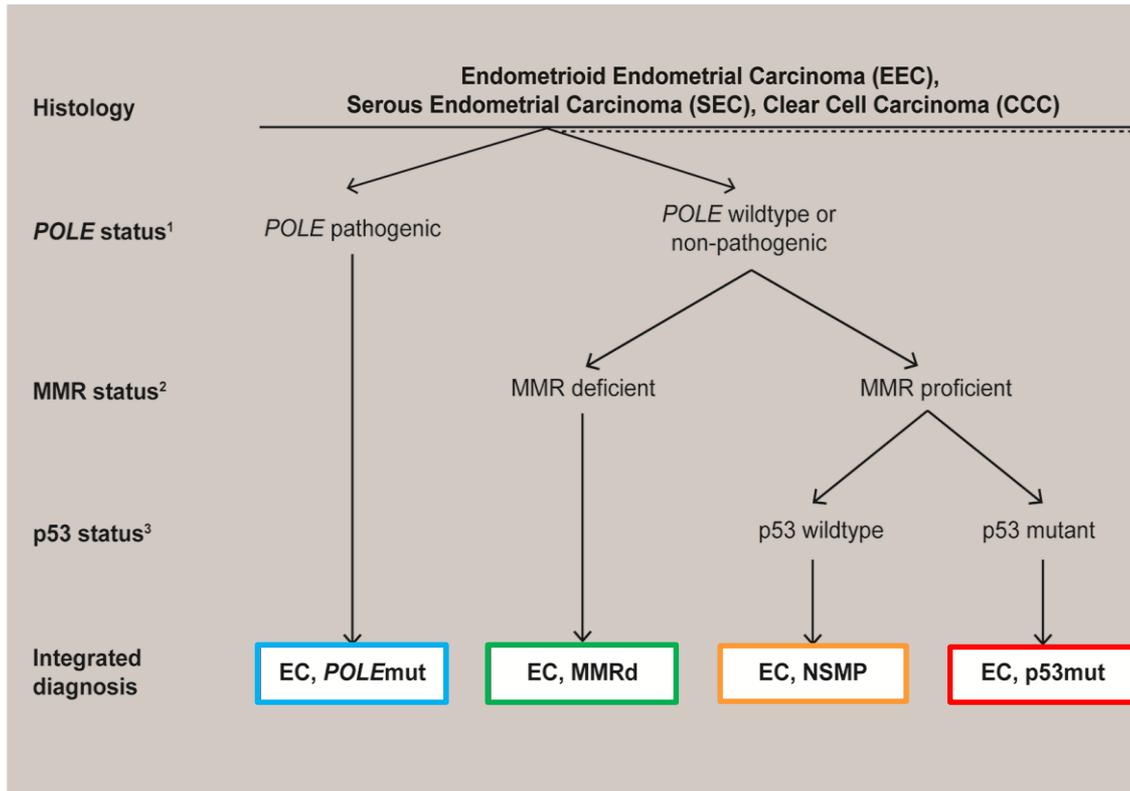
## NSMP



# TransPORTEC/GCIG/ENGOT-EN14<sup>1-4</sup> - RAINBO



# Molecular classification of endometrial cancer

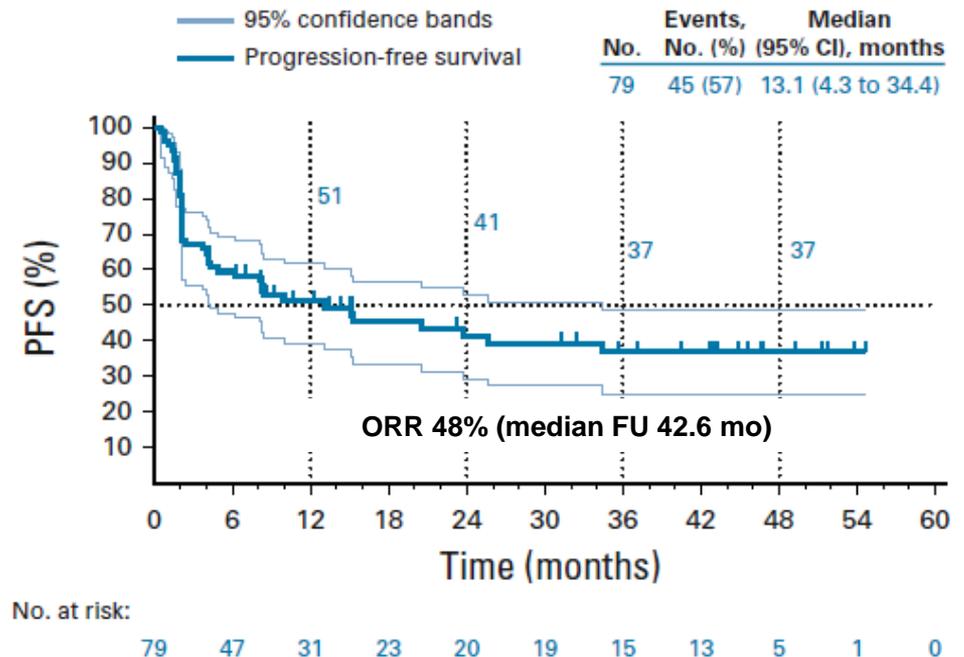


# MMRd endometrial cancer

## *Molecular rationale for immunotherapy*

- High TMB (10-100 mut/mb)
- Dense intra-tumoral CD8+ T cells & tertiary lymphoid structures
- High PD-1/PD-L1
- No sensitivity of chemotherapy added to radiotherapy (León-Castillo, de Boer et al. 2020)

## *Clinical evidence for chemotherapy-free immunotherapy in advanced/recurrent MMRd EC*



## **Pembrolizumab KEYNOTE-158**

1) TCGA Nature 2013, 2) Horeweg et al. Nature 2022, 3) van Gool et al. CCR 2015, 4) Howitt et al. JAMA 2015, 5) León-Castillo et al. JCO 2020

O'Malley et al. 2022



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Merve Kaya  
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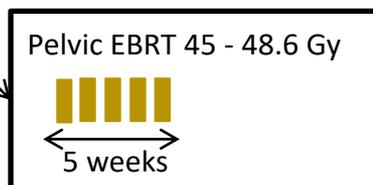
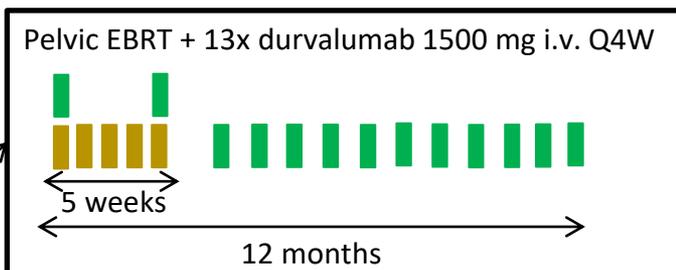
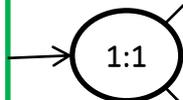
# MMRd-GREEN trial

Sponsor: LUMC



### MMRd-GREEN inclusion criteria:

- MMRd (*POLE* wildtype)
- Stage II with substantial LVSI or stage III EC
- WHO 0-1
- TLH-BSO/TAH-BSO regardless of lymph node staging
- No prior pelvic irradiation



### Primary objective:

- 3-yr RFS

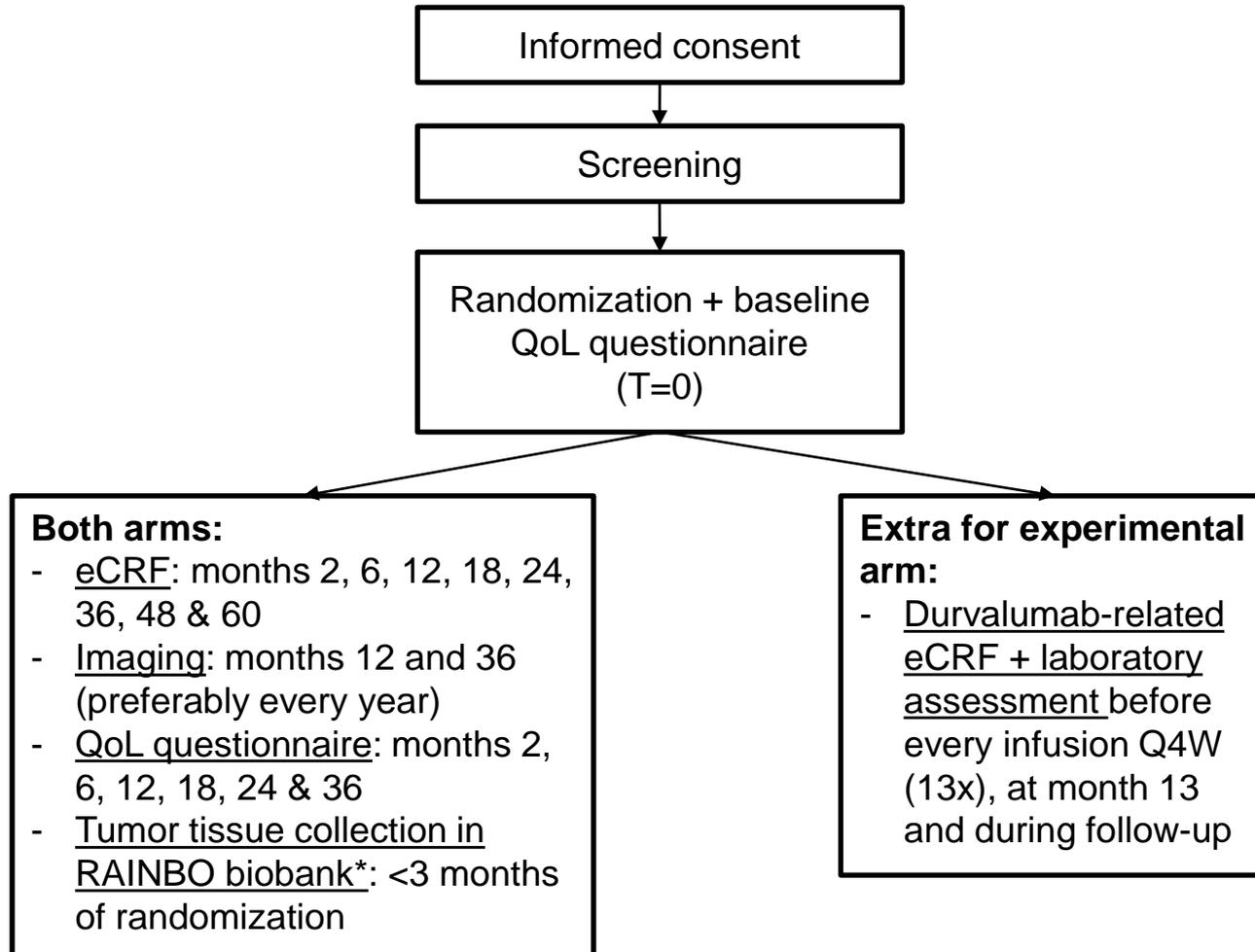
### Secondary objectives:

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

**Sample size: 316 patients**

*Treatment initiated within 6-8 weeks (max 10 weeks) after surgery  
Durvalumab initiated within the 1<sup>st</sup> week of adjuvant EBRT*

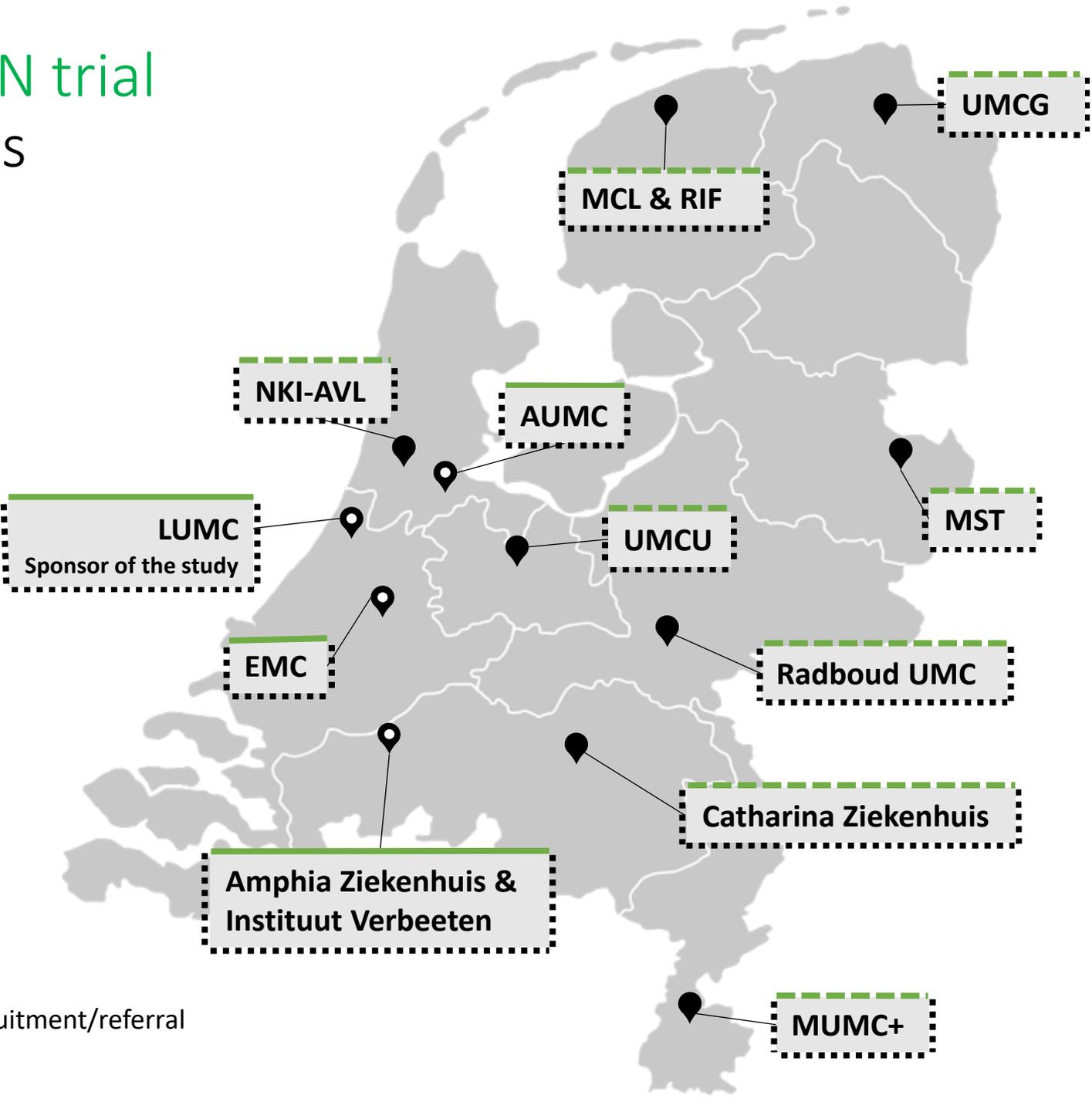
# Study procedures



*\*Located at the department of Pathology, LUMC*

# MMRd-GREEN trial

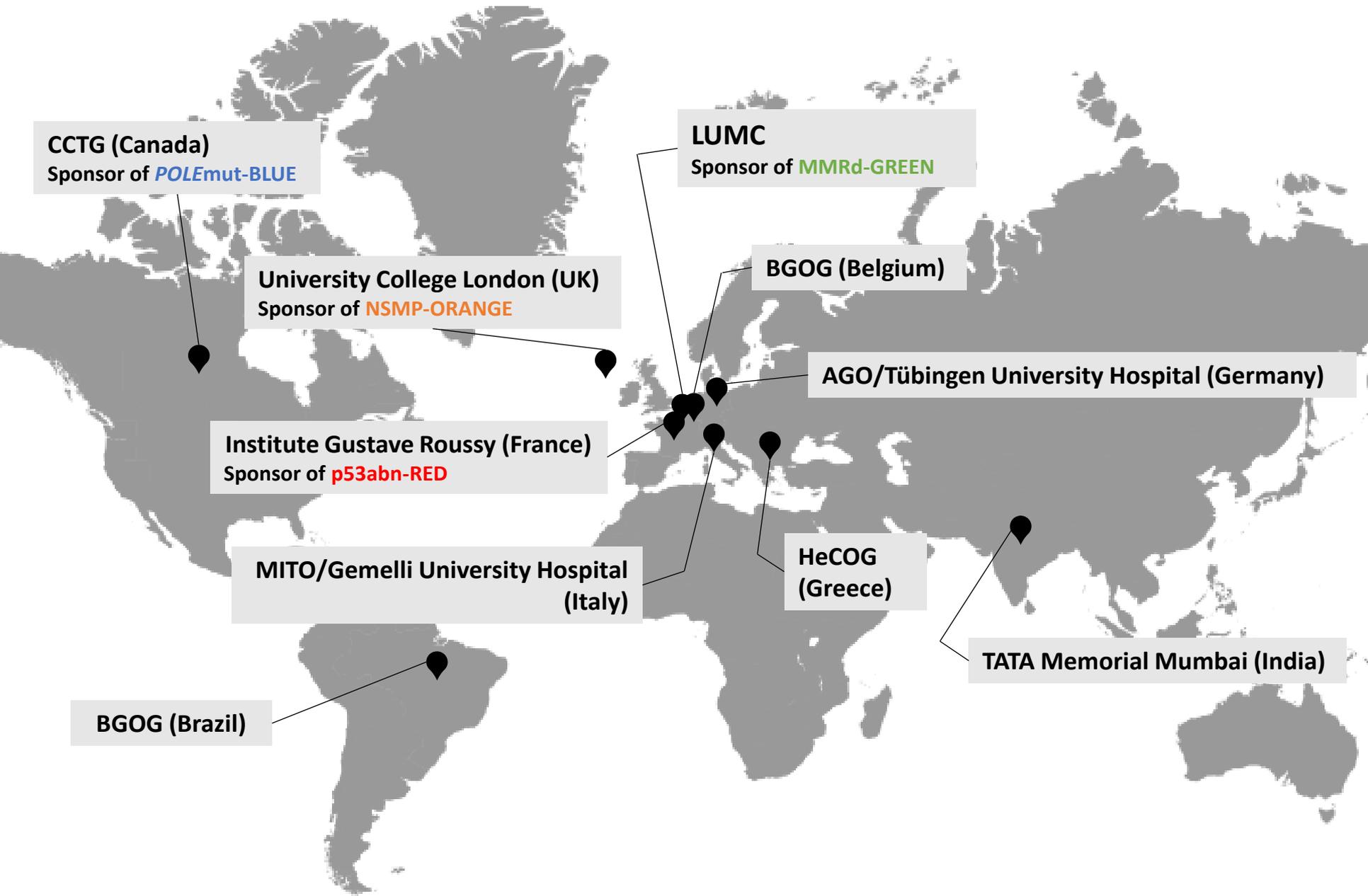
## Current status



### Legend

-  Trial active, open for recruitment/referral
-  Trial not yet active

# Worldwide interest in the RAINBO program

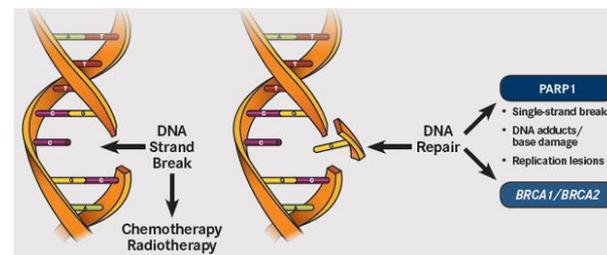




# Rationale for the p53abn-RED trial

- 5-year RFS with chemoradiation only 59%<sup>1</sup>
- p53abn EC have chromosomal instability and copy number alterations<sup>2</sup>
- p53 in several DNA repair pathways → ~ 50% HRD<sup>3</sup>
- PARPi prevent repair of SSBs → accumulation → DBSs → lethal for HRD cells<sup>4</sup>
- PARPi effective in genetically similar cancers<sup>5-8</sup>
- No results in EC yet, UTOLA maintenance trial ongoing<sup>9</sup>

1) León-Castillo et al. JCO 2020, 2) TCGA Nature 2013, 3) de Jonge et al. Clin Cancer Res 2019, 4) Lim et al. Cancers 2017, 5) Mirza et al. N Engl J Med 2016, 6) Moore et al. Gyn Onc 2018, 7) González-Martín et al. N Engl J Med 2019, 8) Tutt et al. N Engl J Med 2021, 9) NCT03745950





Alexandra Leary  
Institut Gustave Roussy

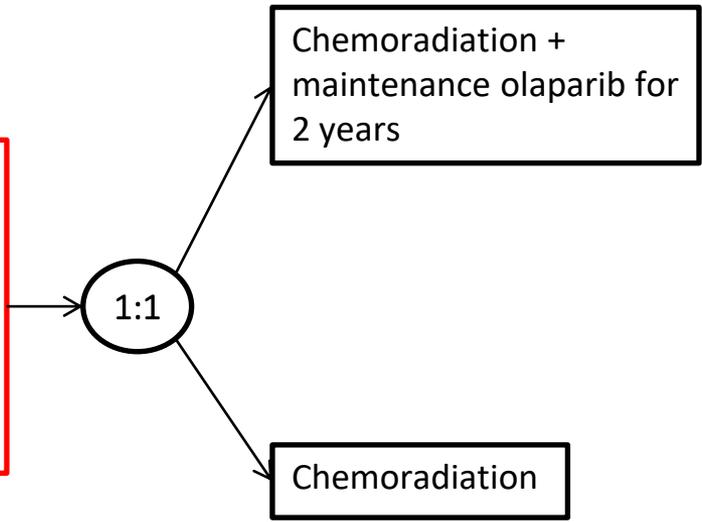
# p53abn-RED trial

Sponsor: Institute Gustave Roussy



**p53abn-RED inclusion criteria:**

- p53abn (*POLE* wildtype, MMR proficient)
- Stage IA with myometrial invasion to stage III EC
- WHO 0-1



**Primary objective:**

- 3-yr RFS

**Secondary objectives:**

- OS, DSS
- RFS and OS in HRD+
- Vaginal, pelvic, distant recurrences
- HRQoL
- Safety & tolerability
- Exploratory translational research

**Sample size: 575 patients**



Anneke Westermann  
Amsterdam UMC

*Olaparib initiated within 10 wks of completion of CRT*





## p53abn-RED: Current status

- Sponsored by AZ and French Cancer Research
  - *Some* reimbursement for non-French centers as well
- Protocol all but finalized (final check by AZ)
- Ethics submission in France expected February 2023
- DGOG on board



**Discussion:** study underfunded in the NL

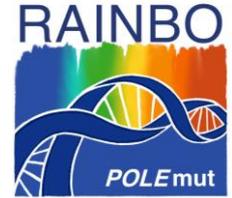
- Assess projected cost of running the trial (Protocol not yet distributed)
- Negotiate with international sponsor (Flat fee/start-up fee and small per-patient-fee, or per-patient-fee only)
- Find funding (Existing KWF-RAINBO grant: for translational/pathology or new KWF grant for running the RAINBO-trials)

# p53abn-RED: Conclusions



- Novel targeted treatment for EC pts with poorest prognosis
- Some start-up funding already obtained, application for more Q1 2023
- Approval of DGOG med-oncology
- 'First patient in' expected Q4 '23 – Q1 '24





# Rationale for the *POLEmut*-BLUE trial

- Evidence for excellent clinical outcome
  - Meta-analysis (n=294) → 4% recurrence, 1% EC death<sup>1</sup>
  - PORTEC-3 (n=51) → 2% recurrence, 2% EC death<sup>2</sup>
  - Danish cohort without adjuvant therapy (n=26) → 0% recurrence, 0% EC-death<sup>3</sup>
- No benefit of adjuvant treatment<sup>1-3</sup>
- De-escalation of adjuvant therapy to reduce morbidity and costs
- No recommendations in guidelines for stage III *POLEmut* EC

1) McAlpine et al. *Cancer* 2021, 2) León-Castillo et al. *JCO* 2020, 2) León-Castillo et al. *Gyn Onc* 2022

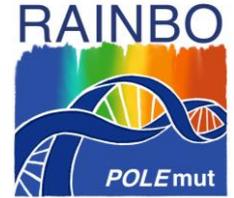




Jessica Mc Alpine  
Vancouver



Kathy Han  
Toronto



# POLEmut-BLUE trial

Sponsor: Canadian Cancer Trials Group

## **POLEmut-BLUE inclusion criteria:**

- *POLEmut*
- Stage IA (not confined to polyp) to stage III EC
- WHO 0-2



No adjuvant treatment for stage I and II (if microscopic and gr 1-2 without LVSI)

No adjuvant treatment or adjuvant RT according to institutional practice for stage II non-microscopic, stage II microscopic G3 and/or LVSI, stage III

## **Primary objective:**

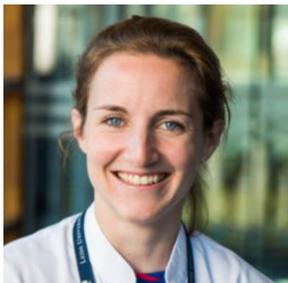
- 3-yr pelvic recurrence

## **Secondary objectives:**

- OS, DSS
- Vaginal, distant recurrences
- HRQoL
- Health economic impact
- Change in level of patient conflict

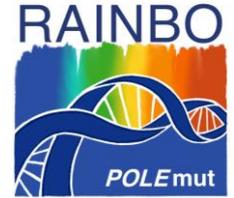
**Sample size stage I/II: 120**

**Sample size stage III: ±25**



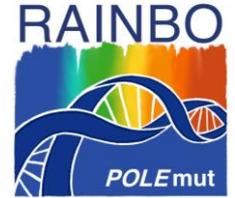
Stephanie de Boer  
LUMC





## POLEmut-BLUE: Current status

- Open for inclusion in Canada
- Ethics submission in the Netherlands expected in Q1-2 2023
- First Dutch participant expected Q2-3 2023
- Funding needed
  - Consider applying for new KWF grant for running the RAINBO-trials
  - Additional grants?



## POLEmut-BLUE: Conclusions

- De-escalation of adjuvant treatment
- Excellent prognosis regardless of adjuvant treatment
- Application for more funding Q1-2023
- Trial is open for inclusion in Canada



Carien Creutzberg



Nanda Horeweg

# Overarching and TR project



Vincent Smit



Tjalling Bosse



Inclusion of:	Stage IA (MI+) - III	Stage 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