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Refining adjuvant treatment in endometrial cancer based on molecular features: the RAINBO clinical trial program

RAINBO Research Consortium

ABSTRACT

Background The endometrial cancer molecular classification has been integrated into the 2020 World Health Organization (WHO) diagnostic classification and European treatment guidelines, and provides direction towards more effective and less toxic adjuvant treatment strategies for women with endometrial cancer.

Primary objective(s) The RAINBO program of clinical trials will investigate four molecular class-directed adjuvant treatment strategies following surgical resection to either increase cure rates through the addition of novel targeted therapies or safely reduce toxicity and improve quality of life through treatment de-escalation.

Study hypothesis Molecular-directed adjuvant treatment strategies will improve clinical outcomes and reduce toxicity of unwarranted therapies in women with endometrial cancer. The overarching and translational research RAINBO program will advance knowledge of predictive and prognostic (bio)markers that will improve prognostication and treatment allocation.

Trial design The RAINBO program is a platform of four international clinical trials and an overarching research program. The randomized phase III p53abn-RED trial for women with invasive stage I–III p53abn endometrial cancer compares adjuvant chemoradiation followed by olaparib for 2 years with adjuvant chemoradiation alone. The randomized phase III MMRd-GREEN trial for women with stage II (with lymphovascular space invasion (LVSI)) or stage III mismatch repair-deficient (MMRd) endometrial cancer compares adjuvant radiotherapy with concurrent and adjuvant durvalumab for 1 year to radiotherapy alone. The randomized phase III NSMP-ORANGE trial is a treatment de-escalation trial for women with estrogen receptor positive stage II (with LVSI) or stage III no specific molecular profile (NSMP) endometrial cancer comparing radiotherapy followed by progestin for 2 years to adjuvant chemoradiation. The *POLE*mut-BLUE trial is a phase II trial in which the safety of de-escalation of adjuvant therapy is investigated for women with stage I–III *POLE*mut endometrial cancer: no adjuvant therapy for lower-risk disease and no adjuvant therapy or radiotherapy alone for higher-risk disease. The overarching RAINBO program will combine data and tumor material of all participants to perform translational research and evaluate molecular class-based adjuvant therapy in terms of efficacy, toxicity, quality of life, and cost-utility.

Major inclusion/exclusion criteria Inclusion criteria include a histologically confirmed diagnosis of endometrial cancer treated by hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy or sentinel lymph node biopsy, with no macroscopic residual disease after surgery and no distant metastases, and molecular classification according to the WHO 2020 algorithm.

Primary endpoint(s) Recurrence-free survival at 3 years in the p53abn-RED, MMRd-GREEN, and NSMP-ORANGE trials and pelvic recurrence at 3 years in the *POLE*mut-BLUE trial.

Sample size The p53abn-RED trial will include 554 patients, the MMRd-GREEN trial 316, the NSMP-ORANGE trial 600, and the *POLE*mut-BLUE trial 145 (120 for lower-risk disease and approximately 25 for higher-risk disease). The overarching research program will pool the four sub-trials resulting in a total sample size of around 1600.

Estimated dates for completing accrual and presenting results The four clinical trials will have different completion dates; main results are expected from 2028.

Trial registration number The RAINBO program is registered at clinicaltrials.gov (NCT05255653).

INTRODUCTION

Endometrial cancer is the most common gynecological cancer in high-income countries and its incidence and mortality are rising, at least in part, due to increased obesity and aging of the population.[1] Primary treatment for endometrial cancer is total hysterectomy with bilateral salpingo-oophorectomy with or without staging by a sentinel lymph node biopsy, systematic lymphadenectomy or additional biopsies.[1] About 15–20% of patients have a high risk of recurrence and disease-related death.[1] For these patients, radiotherapy and/or adjuvant chemotherapy is recommended.[2]

Endometrial cancer is classified into four distinct molecular subtypes: (1) '*POLE*mut' endometrial cancer, characterized by pathogenic mutations in the exonuclease domain of DNA polymerase-ε, resulting in an ultra-high tumor mutational burden and an excellent clinical outcome; (2) mismatch repair-deficient (MMRd) endometrial cancer, which has loss of mismatch repair proteins, resulting in microsatellite instability and an intermediate prognosis; (3) p53abn endometrial cancer, with a low tumor mutational burden and high somatic copy-number alterations resulting in poor clinical outcomes; and (4) no specific molecular profile (NSMP) endometrial cancer, which has no single identifying molecular feature and tumor stage- and grade-dependent outcomes.[3] The four molecular classes have been implemented in the latest ESGO/ESTRO/ESP and ESMO and guidelines, and when available are used in addition to standard clinicopathological risk factors to classify patients with endometrial cancer into risk groups that form the basis for endometrial cancer treatment recommendations.[2]

Although these guidelines are expected to improve prognostication and decisions on adjuvant treatment, challenges remain. First, risks of recurrence and death are high in some sub-groups—for example, in p53abn endometrial cancer and stage III MMRd endometrial cancer. Second, the currently recommended treatments lead to substantial morbidity for patients.[4] Last, insufficient data are available for some sub-groups to allocate the patient to a prognostic risk group and provide treatment recommendations. Examples are stage III *POLE*mut endometrial cancer and stage II–III MMRd and NSMP endometrial cancer with clear cell histology. Prospective clinical trials of molecular class-directed adjuvant treatment strategies are urgently needed to optimize tumor control, reduce toxicity, improve quality of life, and collect outcome data on the rarer subtypes of endometrial cancer.

Applying the molecular framework in endometrial cancer, the RAINBO Consortium has designed a platform of clinical trials to prospectively investigate different treatment strategies for each of the four molecular classes: the RAINBO program. These clinical trials have been designed to assess adjuvant therapy regimens specific to the molecular classes, examining efficacy or toxicity and quality of life.

Rationale for the Four Clinical Trials of the RAINBO Program

p53abn-RED Trial

Twenty-three percent of women participating in PORTEC-3 had p53abn endometrial cancer, and their prognosis was poor despite the benefit of the addition of concurrent and adjuvant chemotherapy to radiotherapy (5-year recurrence-free survival (RFS) 59% vs 36%, hazard ratio (HR) 0.52, 95% CI 0.30 to 0.91, p=0.021).[5] The Cancer Genome Atlas study described remarkable genomic similarities between p53abn endometrial cancer and high-grade serous ovarian cancer. They both harbor high genomic instability, low mutation loads and almost universal *TP53* mutations, suggesting opportunities for overlapping treatment paradigms.[6] A more recent evaluation by the Cancer Genome Atlas study showed that 25% of endometrial cancer cases had genomic instability scores suggestive of homologous recombination deficiency (HRD), and these were almost exclusively *TP53*-mutated tumors.[7] We recently confirmed using a functional assay that HRD is present in about half the cases of p53abn endometrial cancer.[8] PARP inhibitors have been developed in high-grade ovarian cancer because of the high frequency of molecular alterations in the homologous recombination DNA damage repair pathway, and are now part of standard of care. We hypothesize that 2 years of PARP inhibition as maintenance therapy after chemoradiation will improve RFS compared with chemoradiation only in patients with p53abn stage I–III endometrial cancer.

MMRd-GREEN Trial

Thirty-three percent of women participating in PORTEC-3 had MMRd endometrial cancer, and no benefit of the addition of chemotherapy to radiotherapy was observed (5-year RFS 68% vs 76%, HR 1.29, 95% CI 0.68 to 2.45, p=0.43).[5] MMRd endometrial cancer is hypermutated and frequently has dense intra-tumoral CD8+ T cell infiltrates and tertiary lymphoid structures.[9] Counterbalancing this active immune phenotype, high levels of immune checkpoint molecules such as PD-1 and PD-L1 are expressed. Several immune checkpoint inhibitors have shown benefit and are now approved in advanced MMRd endometrial cancer. In patients with advanced microsatellite unstable/MMRd endometrial cancer, PD-(L)1 inhibitors have shown objective response rates of around 45% and durable anti-tumor activity and manageable toxicity.[10] We therefore hypothesize that adjuvant radiotherapy combined with and followed by a year of immune checkpoint inhibition will reduce the risk of recurrence in patients with high-risk MMRd endometrial cancer compared with radiotherapy alone.[11]

NSMP-ORANGE Trial

Thirty-two percent of woman included in PORTEC-3 had NSMP endometrial cancer, and a 5-year RFS of 80% after chemoradiation and 68% after radiotherapy was found.[5] This apparent improvement in RFS did not reach statistical significance (HR 0.68, 95% CI 0.36 to 1.30, p=0.25). This leaves some uncertainty as to the clinical benefit of chemotherapy, particularly when considering the potential negative impact on functioning and symptoms.[12] For example, in PORTEC-3, grade ≥3 toxicity was observed in 61% after chemoradiation compared with 13% after radiotherapy alone (p<0.0001) and, even 5 years after chemoradiation, women still reported significantly more grade 2 toxicity.[4,12] Therefore, research into less toxic alternatives for chemotherapy is of importance. Hormonal treatment has a relatively mild toxicity profile and is an attractive alternative because the majority of high-risk NSMP endometrial cancers are of the endometrioid histotype and hormone receptor positive (estrogen receptor 85%, progesterone receptor 73%).[13] Hormonal treatment is currently the first-line systemic therapy in patients with recurrent and metastatic endometrial cancer without rapidly progressive disease. Progestins are generally recommended,[2] and yield an objective response in about a quarter of patients and clinical benefit in about half of patients.[14] There are no modern era trials of adjuvant hormone therapy in endometrial cancer. A meta-analysis of seven randomized studies carried out mainly in the 1980s showed no significant impact on overall survival.[15] However, most of the participants had low- and intermediate-risk disease. It is also likely that about half of the patients included in these trials had molecular profiles less likely to benefit from hormonal treatment (p53abn, MMRd, *POLE*mut). By selecting patients with tumors likely to respond to hormone manipulation, we will test the hypothesis that, in patients with hormone receptor positive high-risk NSMP endometrial cancer, radiotherapy with maintenance progesterone tablets for 2 years will be as effective as chemoradiation while reducing toxicity and improving quality of life.

*POLE*mut-BLUE Trial

*POLE*mut endometrial cancer is the least common molecular class of endometrial cancer (~10%), and excellent patient outcomes are consistently demonstrated with this tumor feature, regardless of adjuvant therapy. *POLE*mut endometrial cancer is characterized by a high tumor mutational burden and has one of the 11 pathogenic mutations in the exonuclease domain of the *POLE* gene.[16] Endometrial cancer with non-pathogenic *POLE* mutations has been shown to have significantly more disease-related events and is often associated with mismatch-repair deficiency.[17] A meta-analysis of 294 patients with pathogenic *POLE* mutations showed that 4.1% had disease recurrence or progression and only 1.0% died due to their disease.[17] There was no apparent benefit in clinical outcomes from receiving adjuvant therapy.[17] An *in vitro* study showed that pathogenic *POLE* mutations did not increase sensitivity to radiotherapy or chemotherapeutics.[18] Women with high-risk *POLE*mut endometrial cancer included in PORTEC-3 had excellent outcomes regardless of the addition of chemotherapy (5-year RFS 100% vs 97%, p=0.64). A recent Danish population-based study confirmed that the prognosis of women with *POLE*mut endometrial cancer is excellent even in the absence of adjuvant treatment.[5] These data support a phase II clinical trial on treatment de-escalation for *POLE*mut endometrial cancer. In the RAINBO *POLE*mut-BLUE trial, omission of adjuvant therapy will be investigated in lower-risk disease and de-escalation of treatment (observation or radiotherapy, but not chemoradiation) in higher-risk disease.

In the RAINBO trial program we aim to improve clinical outcomes and reduce toxicity of unwarranted therapies in women with endometrial cancer by molecular-directed adjuvant treatment strategies. In addition, we aim to discover and validate predictive and prognostic (bio)markers to improve prognostication and treatment allocation.

METHODS

Trial Design

The RAINBO program is a platform of four clinical trials where patients are included according to the molecular class of their tumor (Figure 1). The RAINBO Consortium structure is provided in Figure 2 and shows how the four trials are managed by a Central Steering Committee and connected to a common Advisory Committee, Statistics Committee, and Translational Research Committee. The RAINBO program is designed according to the ENGOT model D, with Leiden University Medical Center in the Netherlands as the sponsor of the RAINBO program and the MMRd-GREEN trial. The p53abn-RED trial is led from France by the sponsor Institute Gustave Roussy. The NSMP-ORANGE trial will be led from the UK and sponsored by University College London pending funding applications. The *POLE*mut-BLUE trial is led from Canada and sponsored by the Canadian Cancer Trials Group.

Funding for the RAINBO program has been obtained from the French Cancer Institute (Institut National du Cancer), the Dutch Cancer Society (KWF Kankerbestrijding), the Canadian Institutes for Health Research and AstraZeneca. Ethical approval will be obtained from the Institutional Review Board at each participating center and/or via Clinical Trials Information System of the European Medicines Agency in European Union member states before start of accrual.

The p53abn-RED trial is an international phase III superiority trial in which patients with invasive stage I–III p53abn endometrial cancer are randomized (1:1) to adjuvant chemoradiation followed by olaparib (300 mg twice daily, orally) for 2 years or adjuvant chemoradiation alone. Patients will be recruited at 20 participating centers in France and at international sites.

The MMRd-GREEN trial is an international phase III superiority trial in which women with stage II with substantial lymphovascular space invasion (LVSI) or stage III MMRd endometrial cancer are randomized (1:1) to adjuvant pelvic radiotherapy combined with and followed by the PD-L1 inhibitor durvalumab (13 cycles of 1500 mg intravenously, every 4 weeks) for 1 year or radiotherapy alone. Patient accrual has started; activation of 12 centers in the Netherlands and international sites is ongoing.

The NSMP-ORANGE trial is an international phase III non-inferiority trial in which patients with stage II (LVSI+) or stage III NSMP endometrial cancer are randomized (1:1) to adjuvant radiotherapy followed by progesterone tablets (either medroxyprogesterone acetate or megestrol acetate) for 2 years or adjuvant chemoradiation alone. Patients will be included in 25–30 centers in the UK and international sites.

The *POLE*mut-BLUE trial (also known as CCTG EN.10 TAPER arm A POLE) is an international phase II trial investigating the safety of de-escalation of adjuvant therapy: no adjuvant therapy for select stage I–II disease (main cohort, see online supplemental data 1) and

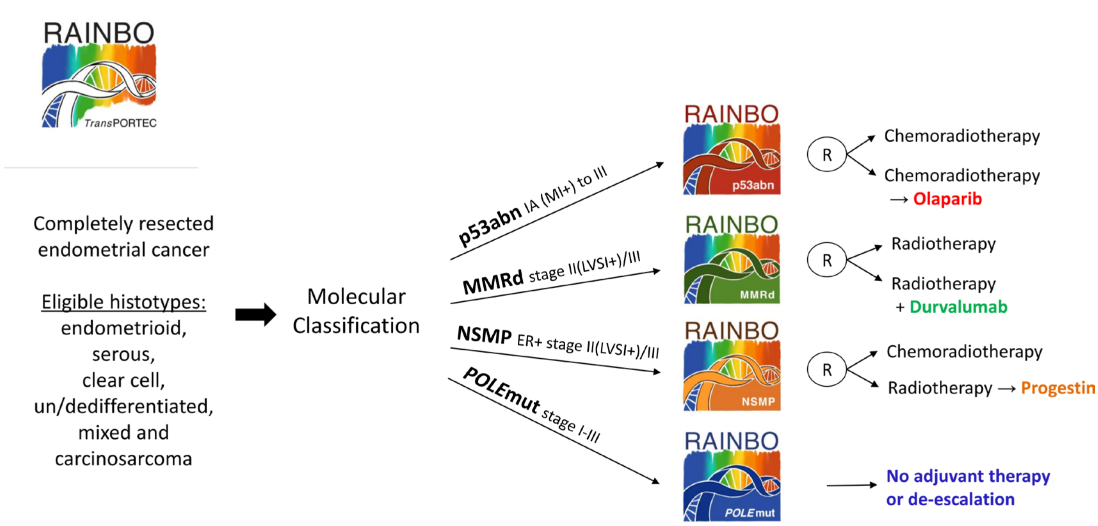

Figure 1 Design of the RAINBO program. ER, estrogen receptor status; LVSI, lymphovascular space invasion; MMRd, mismatch repair deficient; NSMP, no specific molecular profile; p53abn, p53 abnormal; POLEmut, DNA polymerase-ε mutated; R, randomization; RAINBO, Refining Adjuvant treatment IN endometrial cancer Based On molecular features.

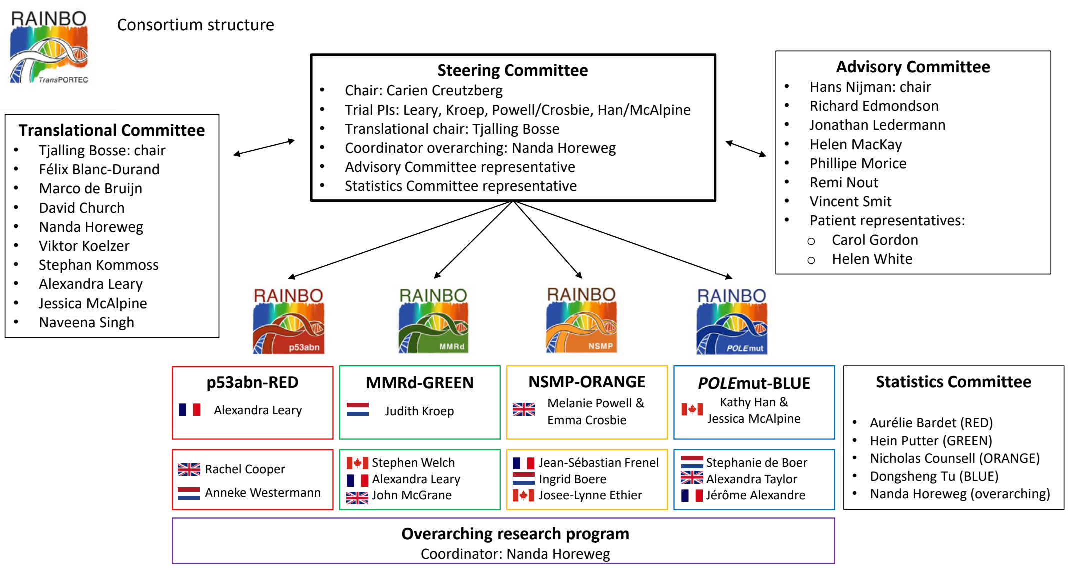

Figure 2 RAINBO Consortium structure. MMRd, mismatch repair deficient; NSMP, no specific molecular profile; p53abn, p53 abnormal; POLEmut, DNA polymerase-ε mutated; RAINBO, Refining Adjuvant treatment IN endometrial cancer Based On molecular features.

no adjuvant therapy or radiotherapy only for higher-risk stage I–III disease (exploratory cohort). Patient accrual has started in Canada, where >15 centers will open in addition to international sites.

The four clinical trials have common inclusion and exclusion criteria, synchronized measurements, and uniform prospective registration of a set of common data elements (Table 1). This enables a combination of the data and tumor material of the four trials for the overarching program and translational studies.

In the RAINBO overarching research program, personalized molecular profile-direct treatment (Group A) and standard treatment (Group B) will be assessed in terms of efficacy, toxicity, quality of life, and cost-utility. Data of all participants of the p53abn-RED,

Table 1 Registration of common data elements in the RAINBO program

			Time since registration in months						
	Baseline	Tx	2–3	6	12	18	24	36	60
Informed consent	x								
Tumor tissue collection	x								
Patient age, height	x								
Patient weight, WHO performance status	x				x*		x*	x	x*
Comorbidity (NCI)	x								
Chest/abdominal/pelvic CT/MRI and/or PET-CT	x			x*	x*	x*	x*	x	
Pathology assessment	x								
Molecular classification	x								
Treatment characteristics (if applicable)		x							
Selected toxicities (CTCAE v5.0)	x		x	x	x	x*	x*	x	x*
PR-QoL (EORTC QLQ C30 and EN24)	x		x*	x*	x	x*	x*	x	x*
Follow-up endpoints	Vaginal, pelvic, para-aortic lymph node and abdominal/distant recurrences and death, and cause of death								
Off study	Date and reason (eg, IC withdrawal, lost to follow-up, death)								

*Optional, the trial-specific protocol will indicate whether time point is included or not.
CTCAE, Common Terminology Criteria for Adverse Events; EORTC, European Organization for Research and Treatment of Cancer; IC, informed consent; NCI, National Comorbidity Index; PET, positron-emission tomography; PR-QoL, patient reported quality of life; QLQ C30 and EN24, quality of life questionnaire common and endometrial cancer-specific modules; Tx, treatment.

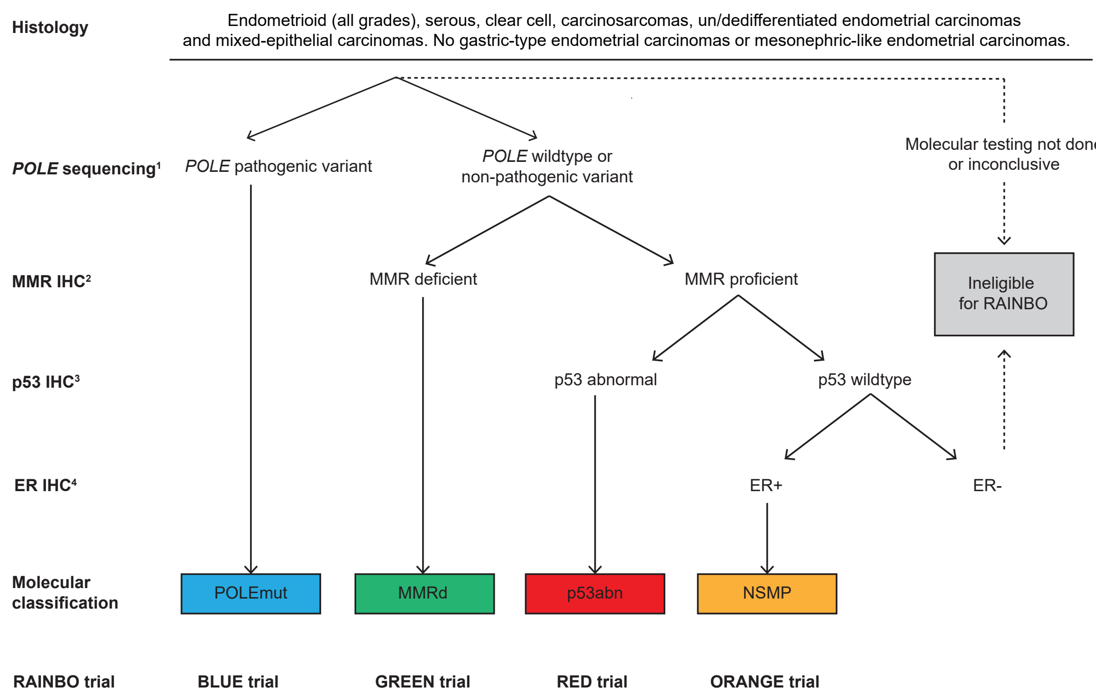

Figure 3 Inclusion algorithm of the RAINBO program. Assessment of the molecular classification must be performed according to the World Health Organization 2020 classification of endometrial cancer.[3]

[1]POLE status is assessed by DNA sequencing of the POLE gene and at least the five most common (but preferably all) 11 variants as described by Léon-Castillo et al[16] which are considered pathogenic. [2]MMR deficiency is assessed by IHC and is defined by loss of one or more of the four MMR proteins (MLH1, PMS2, MSH2 and MSH6). [3]p53 status is assessed by IHC and three abnormal patterns are defined: mutant overexpression, null pattern, and cytoplasmatic expression. DNA sequencing of the entire *TP53* gene to detect pathogenic variants is an accepted alternative. [4]ER status is assessed by IHC and is considered positive if expression is observed in >10% of the tumor tissue. ER, estrogen receptor; IHC, immunohistochemistry; MMRd, mismatch repair deficient; p53abn, p53 abnormal; POLEmut, DNA polymerase-ε mutant; RAINBO, Refining Adjuvant treatment IN endometrial cancer Based On molecular features.

MMRd-GREEN, and NSMP-ORANGE sub-trials will be investigated by treatment (Figure 3).

The central RAINBO tumor tissue repository will form a strong basis for future translational research studies directed at identifying biomarkers that can further refine the molecular classification and predict targeted therapy benefit.

Participants

The inclusion and exclusion criteria of the RAINBO program apply to all women included in the four RAINBO clinical trials. In addition, trial-specific inclusion and exclusion criteria are provided in online supplemental data 1. Assessment of the *POLE*, MMR, p53, and estrogen receptor status are mandatory to determine for which trial women are eligible. The inclusion algorithm of the RAINBO program is shown in Figure 3. The protocol for the assessment of the molecular classification is provided in online supplemental data 2. The requirements for surgery, radiotherapy and chemotherapy are set out in online supplemental data 3.

Inclusion Criteria

- Histologically confirmed diagnosis of endometrial cancer with one of the following histotypes: endometrioid endometrial carcinoma, serous endometrial carcinoma, uterine clear cell carcinoma, dedifferentiated and undifferentiated endometrial carcinoma, uterine carcinosarcoma, and mixed endometrial carcinomas of the aforementioned histotypes.
- Full molecular classification performed according to the WHO 2020 diagnostic algorithm.[3]
- Hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy or sentinel node biopsy, without macroscopic residual disease after surgery.
- No distant metastases as determined by pre-surgical or post-surgical imaging (CT scan of chest, abdomen and pelvis or whole-body PET-CT scan).
- Age ≥18 years.
- WHO performance status 0, 1 or 2.
- Expected start of adjuvant treatment (if applicable) within 10 weeks after surgery.
- Patients must be accessible for treatment and follow-up.
- Written informed consent for participation in one of the RAINBO trials, permission for the contribution of a tissue block for translational research, and permission for the use and sharing of data for the overarching research program.

Exclusion Criteria

- History of another primary malignancy, except for non-melanoma skin cancer, in the past 5 years.
- Prior pelvic radiation.

Primary Endpoints

The primary endpoint of the p53abn-RED, MMRd-GREEN, and NSMP-ORANGE trials is 3-year RFS. The primary endpoint of

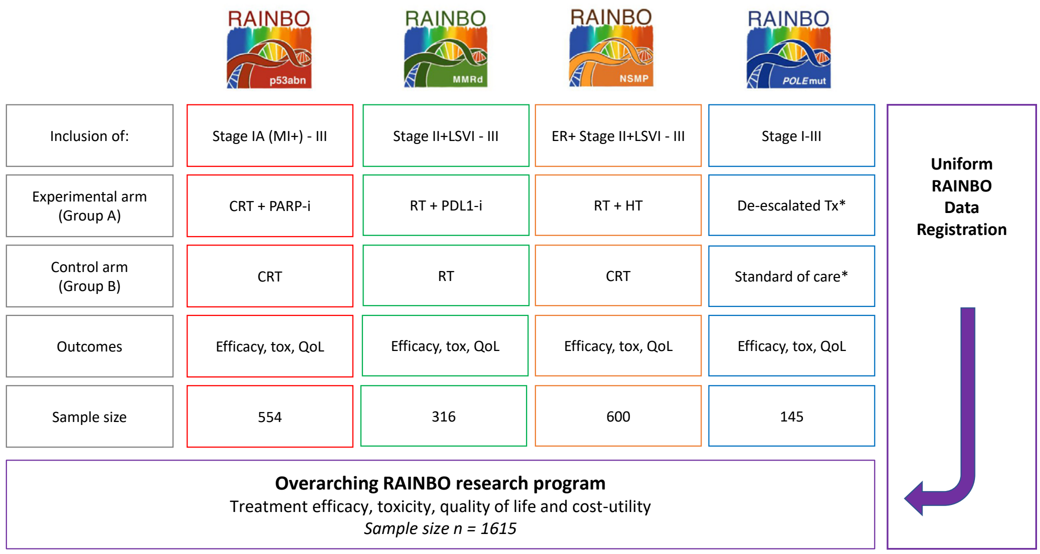

Figure 4 Sample size of the RAINBO clinical trials and overarching research program. CRT, chemoradiotherapy; ER, estrogen receptor; HT, hormonal therapy; LVSI, lymphovascular space invasion; MI, myometrial invasion; RAINBO, Refining Adjuvant treatment IN endometrial cancer Based On molecular features; RT, radiotherapy; Tx, therapy; tox, toxicity; QoL, quality of life. *Data on *POLE*mut-BLUE trial participants will be pooled in Group A or B depending on tumor characteristics and received adjuvant treatment strategy.

the *POLE*mut-BLUE trial is 3-year pelvic recurrence. Secondary endpoints of the p53abn-RED, MMRd-GREEN, and NSMP-ORANGE trials are 5-year RFS, 3- and 5-year pelvic recurrence-free survival. Secondary endpoints of the *POLE*mut-BLUE trial are 5-year pelvic recurrence, 3- and 5-year RFS, decisional conflict, and fear of recurrence. Other secondary endpoints of all four RAINBO trials include 3- and 5-year vaginal recurrence-free survival, distant recurrence-free survival, endometrial cancer-specific survival, overall survival, treatment-related toxicity (using the Common Terminology Criteria for Adverse Events (CTCAE) version 5) and health-related quality of life (using the common and endometrial cancer European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires C30 and EN24). Endpoints of the overarching RAINBO research program are 3 year RFS, vaginal, pelvic, and distant recurrence-free survival, endometrial cancer-specific and overall survival, treatment-related toxicity, quality of life and cost-utility. The p53abn-RED, MMRd-GREEN, NSMP-ORANGE, and *POLE*mut-BLUE trials each have predefined biomarker studies directed at, respectively, HRD status, immune phenotype, hormone receptor expression, and *POLE* mutations. In addition, formalin-fixed paraffin-embedded tumor tissue from all four trials will be collected to establish a central biobank including DNA and RNA repositories and scanned histological images for translational studies.

Sample Size

A detailed description of the sample size calculations and the underlying assumptions for all four clinical trials is provided in online supplemental data 4.

The p53abn-RED trial will randomize (1:1) 554 patients. The trial will have 80% power (two-sided α=0.05) to detect a HR of ≤0.67 from a 3-year RFS rate of 64.6% in the control arm using a log-rank test, with an interim analysis for efficacy at 70% information, assuming accrual duration of 36 months with an additional follow-up of 30 months and a drop-out rate of 5%.

The MMRd-GREEN trial will randomize (1:1) 316 patients. The trial will have 80% power (two-sided α=0.05) to detect a HR ≤0.58 from a 3-year RFS rate of 65% in the control arm using a log-rank test, assuming accrual duration of 30 months with a 30-month follow-up period and a drop-out rate of 2%. No interim analysis is planned; an independent data monitoring committee (IDMC) will routinely monitor recurrences and adverse events.

The NSMP-ORANGE trial will randomize (1:1) 600 patients. Assuming a 3-year RFS rate of 82.5% in the control arm, a non-inferiority margin of 7.5 percentage points is of interest, to exclude a rate ≤75% (ie, HR 1.495) with 80% power (one-sided α=0.05). Patients will be recruited over 5 years with 3 years of additional follow-up, allowing for 5% dropout. Futility analyses are incorporated; conditional power will be routinely presented to the IDMC.

The *POLE*mut-BLUE trial will recruit 120 patients with select stage I–II *POLE*mut endometrial cancer in the main ‘lower risk’ study cohort (criteria provided in online supplemental data 1). A 3-year pelvic recurrence rate of 1% (upper 95% CI 2.4%) is assumed. If the upper 95% CI is <5%, it will be concluded that no adjuvant therapy has an acceptable low risk of pelvic recurrence (one-sided α=0.05). Patients will be recruited over 36 months with 36 months of additional follow-up. Interim analysis for futility will be carried out when half of the person-years of follow-up have been observed. In addition, patients with ‘higher-risk’ *POLE*mut endometrial cancer will be accrued into an exploratory cohort (approximately 25 patients) for descriptive analysis (criteria provided in online supplemental data 1).

The sample size of the overarching RAINBO research program will be around 1600 patients (Figure 4). Power calculations and graphs for efficacy, toxicity and quality of life are provided in online supplemental data 4.

Randomization and Blinding

In the p53abn-RED trial, patients will be allocated to the one of the two treatment arms using stratified randomization via an interactive web response system. Stratification factors are country, tumor stage (I–II vs III), and staging lymphadenectomy (yes vs no). In the MMRd-GREEN trial, central randomization is done by a web-based randomization application with stratification for participating center, tumor grade (1–2 vs 3), and staging lymphadenectomy (yes vs no) using a biased coin minimization procedure. In the NSMP-ORANGE trial, patient randomization is done by a remote data capture system using a minimization algorithm which will adjust the probability of treatment assignment to minimize imbalance within the stratification factors (center, stage, and lymphadenectomy/sentinel node biopsy) as well as incorporating a random element. In the *POLE*mut-BLUE trial, patients are not randomized. Blinding will not be applied in any of the RAINBO clinical trials.

Statistical Methods

Time-to-event analysis using the Kaplan–Meier method and Cox proportional hazards models will be performed to analyze the primary endpoint of the p53abn-RED, MMRd-GREEN, and NSMP-ORANGE trials. Competing risk analysis will be performed for the primary endpoint of the *POLE*mut-BLUE trial. Detailed descriptions of the statistical methods of the primary and secondary endpoints of the four RAINBO sub-trials and the overarching research program are given in online supplemental data 5.

DISCUSSION

The recent integration of the molecular classes in the risk stratification and treatment recommendations of patients with endometrial cancer is expected to improve prognostication, shared decision-making, and reduce over- and under-treatment. Nonetheless, subgroups with a poor prognosis remain, even with multimodality treatment.[5] Moreover, many patients will suffer from treatment-related morbidity impacting on quality of life.[4 12] To further improve treatment of patients with endometrial cancer, clinical trials are needed that investigate more effective treatments in those at highest risk, and less toxic, safe alternative treatment strategies in those who do not benefit from the current standard of care.

RAINBO is an innovative practice-defining program consisting of three randomized clinical trials of novel adjuvant treatment strategies for women with high-risk p53abn endometrial cancer, MMRd endometrial cancer, and NSMP endometrial cancer and one clinical trial of treatment de-escalation for women with *POLE*mut endometrial cancer. In each trial, oncological outcomes, survival, toxicity, and quality of life will be uniformly registered to enable pooling for the overarching research program. As such, RAINBO will give a comprehensive answer to the question whether molecular-directed treatment is more effective, less toxic, and yields better quality of life than the current standard of care for women with endometrial cancer. Formalin-fixed paraffin-embedded tumor tissue blocks will be prospectively collected to create a biobank for trial-specific and overarching translational research. The translational research program of RAINBO is expected to contribute to better patient stratification, both for risk assessment and for precision treatment allocation through identification and validation of new prognostic and predictive (bio)markers. Further, we anticipate that this work will provide an insight into the (molecular) biology of endometrial cancer and its interaction with the immune system. In short, the RAINBO program will deliver unique results that will shape the future of endometrial cancer research and management.

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Refining Adjuvant treatment IN endometrial cancer Based On molecular features: the RAINBO clinical trial program

RAINBO research consortium*

** Lists of participants and their affiliations appear at the end of the paper.*

Supplemental data

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1. In- and exclusion criteria

The p53abn-RED trial

Inclusion criteria:

- Molecular classification: p53 abnormal (p53abn) endometrial cancer (EC).
- Histologically confirmed Stage III EC or stage II EC with substantial lymph vascular space invasion (LVSI).
- World Health Organization (WHO) performance score 0-1.
- Body weight > 30 kg.
- Adequate systemic organ function:
  - Creatinine clearance (> 40 cc/min): Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance.
- Adequate bone marrow function: hemoglobin >9.0 g/dl, absolute neutrophil count ≥1.0 x 109/l, platelet count ≥75 x 109/l.
- Adequate liver function:
  - bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
  - ALT (serum glutamic-pyruvic transaminase) and/or AST (serum glutamic-oxaloacetic transaminase) ≤2.5 x ULN.

Exclusion criteria:

- Pathogenic polymerase-ε mutations (*POLE*mut).
- Mismatch-repair deficiency (MMRd)
- Major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of the investigational medicinal product.
- History of allogenic organ transplantation.
- Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring adverse events or compromise the ability of the patient to give written informed consent.

- Any previous treatment with a PARP inhibitor, including olaparib.
- History of active primary immunodeficiency.
- History or evidence of hemorrhagic disorders within 6 months prior to randomization
- Patients with myelodysplastic syndrome/acute myeloid leukemia history or with features suggestive of myelodysplastic syndrome/acute myeloid leukemia.
- Previous allogenic bone marrow transplant or double umbilical cord blood transplantation.
- Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive Hepatitis B Virus [HBV] surface antigen (HBsAg) result), hepatitis C, or human immuno-deficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Concomitant use of known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks.
- Concomitant use of known strong (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.
- Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.
- A medical or psychological condition which, in the opinion of the investigator, would not permit the patient to complete the study or sign meaningful informed consent.

The MMRd-GREEN trial

Inclusion criteria:

- Molecular classification: MMRd EC.
- Histologically confirmed stage III EC or stage II EC with substantial LVSI.
- WHO performance score 0-1.
- Body weight > 30 kg.
- Adequate systemic organ function:

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  - Creatinine clearance (> 40 cc/min): measured creatinine clearance (CL) >40 mL/min or
  - Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance.
- Adequate bone marrow function: hemoglobin >9.0 g/dl. Absolute neutrophil count >1.0 X 109/1, platelet count >75 x 109/1.
- Adequate liver function:
  - Bilirubin <1.5 x Institutional upper limit of normal (ULN). «This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
  - ALT (serum glutamic-pyruvic transaminase) and/or AST (serum glutamic-oxaloacetic transaminase) <2.5 x ULN.

Exclusion criteria

- Pathogenic *POLE* mutations
- Major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of the investigational medicinal product.
- History of allogenic organ transplantation.
- Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness or social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
- Any previous treatment with a PD(L)1 inhibitor, including durvalumab.
- Receipt of live attenuated vaccine within 30 days prior to the first dose of durvalumab. Note: patients, if enrolled, should not receive a live vaccine whilst receiving the investigational medicinal product or up to 30 days after the last dose of the investigational medicinal product.
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab with the exceptions of:
  - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection).
  - Systemic corticosteroids at physiologic doses not to exceed «10 mg/day» of prednisone or its equivalent.
  - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

- History of active primary immunodeficiency.
- Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [except for diverticulosis], systemic lupus erythematosus, Sarcoidosis, or Wegener syndrome. The following are exceptions to this criterion:
  - Patients with vitiligo or alopecia.
  - Patients with hypothyroidism (e.g., following Hashimoto's thyroiditis) stable on hormone replacement.
  - Any chronic skin condition that does not require systemic therapy.
  - Patients without active disease in the last 5 years may be included but only after consultation with the study physician.
- Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immuno-deficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- A medical or psychological condition which, in the opinion of the investigator, would not permit the patient to complete the study or sign meaningful informed consent.

The NSMP-ORANGE trial

Inclusion criteria

- Non-specific molecular profile (NSMP) EC.
- Histologically confirmed stage II EC with substantial LVSI or stage III EC.
- Estrogen receptor (ER) positive EC.

Exclusion criteria

- Pathogenic *POLE* mutations
- Mismatch-repair deficiency
- p53 abnormality (IHC or sequencing of the entire *TP53* gene)

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The POLEmut-BLUE trial

Inclusion criteria

- Pathogenic *POLE* mutation(s).
- For the low-risk group, patients must have one of the following combinations of FIGO stage, grade, and LVSI:
  - Stage IA (not confined to polyp), grade 3, pN0*, with or without LVSI.
  - Stage IB, grade 1 or 2, pNx/N0, with or without LVSI.
  - Stage IB, grade 3, pN0*, without substantial LVSI^.
  - Stage II (microscopic), grade 1 or 2, pN0*, without substantial LVSI.
- For the higher-risk group, patients must have one of the following combinations of FIGO stage, grade, and LVSI:
  - Stage IA (not confined to polyp), grade 3, pNx, with or without LVSI
  - Stage IB, grade 3, pNx, with or with LVSI.
  - Stage IB, grade 3, pN0, with substantial LVSI^.
  - Stage II (microscopic), grade 1 or 2, pNx, with or without LVSI.
  - Stage II (microscopic), grade 1 or 2, pN0, with substantial LVSI^.
  - Stage II (microscopic), grade 3, pNx/N0, with or without LVSI.
  - Stage II non-microscopic, any grade, pNx/N0, with or without LVSI.
  - Stage III, any grade, pNx/N0-2, with or without LVSI.
- Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrolment in the trial to document their willingness to participate. A similar process must be followed for sites outside of Canada as per their respective cooperative group's procedures.
- Patient is able (i.e., sufficiently fluent) and willing to complete the QOL and/or health utility questionnaires in either English, French or a validated language. The baseline assessment must be completed within the required timelines, prior to enrolment. Inability (lack of comprehension in English or French, or other equivalent reason such as cognitive issues or lack of competency) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible.
- Patients must be accessible for treatment and follow up. Patients enrolled on this trial must be treated and followed at the participating center. Investigators must assure themselves the patients enrolled on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

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- Patients must agree to return to their primary care facility for any adverse events which may occur through the course of the trial.
- In accordance with CCTG policy, protocol treatment is to begin within 10 weeks of hysterectomy/bilateral salpingo-oophorectomy.

* Pelvic lymph node surgical assessment (sentinel or full lymphadenectomy) is required for grade 3 or stage II. Para-aortic lymphadenectomy is not mandated.

^ Substantial LVSI is defined as ≥ 3 foci as per College of American Pathologists' reporting guidelines.

Exclusion criteria

- Prior chemotherapy for EC
- Isolated tumor cells identified in lymph node(s) for the low risk group

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2. Requirements for surgery, radiotherapy and chemotherapy

The RAINBO program imposes some requirements on participating centers for surgery, external beam radiotherapy and/or vaginal brachytherapy and chemotherapy if these treatments are given in the four clinical trials.

Surgery

The standard surgical procedure is i) open, ii) laparoscopic, or iii) robot-assisted total abdominal hysterectomy with bilateral salpingo-oophorectomy (BSO) and biopsy of any clinically suspicious lesions (such as peritoneal deposits or lymph nodes) with histological examination. Performance of diagnostic staging lymphadenectomy and/or sentinel node biopsy are at the discretion of the participating center or group.

Lymph node debulking with or without para-aortic lymph node sampling is recommended in case of macroscopic positive pelvic nodes and/or para-aortic nodes, as detected on pre-surgical CT or MRI scans or intra-operatively. Other extra-uterine tumor deposits should also be completely removed.

At the completion of the operation there should be no remaining macroscopic tumor.

External beam radiotherapy

The dose schedule for adjuvant EBRT should range between 45-48.6 Gy, with fraction size of 1.8-2.0 Gy per fraction, 5 fractions a week. Treatment should preferably be started within 6 to 8 weeks after surgery, but no later than 10 weeks. Treatment breaks should be avoided, and treatment time for EBRT should be kept within 5-6 weeks. Treatment prolongation due to public holidays and machine maintenance should not exceed 2-4 days.

External beam radiotherapy will be given according to the center's standard policy and technique. Pelvic or pelvic and para-aortic radiotherapy is used according to the extent of the tumor involvement. The clinical target volume (CTV) includes the proximal half of the vagina, the paravaginal / parametrial soft tissues, and the internal and external iliac lymph node regions, as well as the distal third to half of the common iliac lymph node region. Inclusion of the subaortic pre-sacral nodes is recommended for tumors with pelvic lymph node involvement, cervical stromal involvement, or vaginal involvement.

Contouring of the CTV should be done according to literature data and atlases and taking institutional preferences and practices into account. Useful guidelines and contouring atlas can be found at: RTOG website (NRG Oncology/RTOG consensus guidelines), and in the publication by

Small.[1] The organs at risk to be contoured are the bladder, rectum, sigmoid, bowel bag (excluding sigmoid, according to the EMBRACE-II recommendations), and the femoral heads.[2]

In case of external or internal iliac lymph node involvement, the common iliac lymph node regions are to be included up to the aortic bifurcation. In case of common iliac node involvement, the target volume should include at least the lower para-aortic region. In case of para-aortic involvement, the para-aortic lymph node region should be extended to include the higher para-aortic region at least 1 cm above the renal vessels (margin of at least 2 cm above the highest lymph node region involved).[1] If a complete bilateral lymphadenectomy has been performed with at least 12 lymph nodes (with nodes from all sites: left and right external, internal and common iliac regions and lower para-aortic nodes) and all lymph nodes are free of tumor at histopathologic evaluation, the upper border of the CTV is at the start of the (common) iliac bifurcation.

CT planning will be used with individual target volume and organ-at-risk contouring for all patients. Treatment planning will be done using intensity-modulated radiotherapy (IMRT) or volumetric arc therapy (VMAT) or tomotherapy with appropriate QA. CT planning scans in treatment position with (comfortably) full bladder should be obtained; preferably also an empty bladder scan is obtained and merged to determine an internal target volume (ITV) accounting for movement of the vaginal vault region.[1] The full bladder scan should be used for treatment planning. Dose specification, planning and homogeneity requirements should be done according to ICRU-report 83.[3] The dose in the CTV, PTV and organs at risk should be recorded and DVHs should be generated. At least 95% of the prescribed dose should cover >98% of the PTV (aiming for >99%). The maximum dose received by 2% of the PTV should not exceed 107 % of the prescribed dose. Dose constraints for the organs at risk are provided below in Supplemental Table 1.

The Planning Target Volume (PTV) consists of the CTV/ITV with a 5-7 mm margin, depending on the type of position verification and institutional practices. Daily position verification using cone beam CT is strongly recommended. A ‘library of plans’ technique with daily selection of the most appropriate treatment plan is permitted if standard for the treating center.

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Supplemental Table 1. RAINBO dose aims and constraints for external beam radiotherapy

Organ at risk	Dose volume	Limit	Type
Bowel			
- RT pelvic area	V30Gy	< 500 cc	constraint
- RT pelvic + PAO area	V30Gy	< 650 cc	constraint
	V30Gy	< 350 cc	aim
	V40Gy	< 250 cc	aim
Sigmoid	V45Gy	< 60%	aim
	V50Gy	< 50%	aim
Bladder	V40Gy	< 75%	aim
	V30Gy	< 85%	aim
Rectum	V30Gy	< 95%	aim
	V40Gy	< 85%	aim
Spinal canal	V48Gy	< 0.03 cc	constraint
Femur head	Dmax	< 50 Gy	aim
Kidney	Dmean	< 15 Gy	constraint
		< 10 Gy	aim
	V12Gy	< 55%	constraint
Body	Dmax	107%	constraint

Definition of abbreviations: D = dose; PAO = para-aortic; RT = radiotherapy; V = volume

Vaginal brachytherapy

A brachytherapy boost is to be considered in patients with documented cervical stromal involvement and/or substantial LVSI. Brachytherapy should be either incorporated within the last week of EBRT (not giving both on the same day) or be given in the first week after completion of EBRT (HDR sessions ideally immediately following completion of EBRT). Overall treatment time for radiotherapy (EBRT and brachytherapy) should not exceed 50 days.

Brachytherapy is given with a vaginal cylinder or vaginal ovoids or ring applicator, according to the center's standard technique. When using a cylinder, the active length will ideally be 2-3 cm, with the reference isodose covering the proximal 2.5-3 cm of the vagina. High-dose-rate (HDR) and pulse-dose-rate (PDR) schedules are permitted, which deliver an EQD2 equivalent dose of 10-14 Gy at 5 mm from the vaginal mucosa (to obtain a cumulative EDQ2 of 60 Gy at 5 mm). Example of a schedule: HDR 8-10 Gy in 2 fractions.

Radiotherapy quality control

The participating centers of the RAINBO program have extensive experience with quality assessment of external beam radiotherapy and brachytherapy in clinical trials for EC because of the proceeding series of PORTEC trials.[4-6] In addition, many centers have participated in the EMBRACE[2 7] and INTERLACE trials (NCT0566240) on cervical cancer which are renowned for their stringent EBRT and brachytherapy planning criteria and intensive assessments. This protocol is based on those experiences and provides the participating centers with a detailed description of the requirements for EBRT and brachytherapy that should fit current practices. Therefore, there will be no formal radiotherapy quality assessment control in the RAINBO trials.

Chemotherapy

Chemotherapy in the RAINBO program is preferably given concurrent and adjuvant according to the PORTEC-3 schedule: two cycles of intravenous cisplatin 50mg/m² in the first and fourth week of the pelvic external beam radiotherapy followed by four cycles of intravenous carboplatin AUC 5 and paclitaxel 175 mg/m² at 21-day intervals.[6]

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3. Histopathology and molecular testing

Histopathology

One of the unique aspects of the RAINBO program is that all histological grades and almost all histological subtypes of endometrial cancer can enter the program. Histologic subtypes that are eligible for the RAINBO program are: endometrioid (all grades), serous, clear cell, carcinosarcomas, un-/dedifferentiated endometrial carcinomas and mixed-epithelial carcinomas. Histologic subtypes that are excluded are: gastric-type endometrial carcinomas and mesonephric-like endometrial carcinomas. Central histopathological review is not a requirement for entering into the RAINBO program.

Assessment of cervical stromal tumor invasion must be performed by microscopy as part of the pathological staging of the surgical resection specimen; only cases with unequivocal stromal involvement should be classified as stage II.

Substantial LVSI can be diagnosed on H&E slides without the need for additional immunostains. Substantial LVSI is defined as widespread invasion of tumor emboli into vascular spaces at and beyond the invasive front of the tumor. It is most often identified in a spray-like pattern in the myometrium and frequently accompanied by vascular-associated immune-infiltrate. Although the extent of LVSI may vary per H&E slide, LVSI foci are often found in multiple slides. If the extent of LVSI is limited to <4 vessels, it is regarded as focal LVSI. For some of the RAINBO trials at least substantial LVSI must be present for some tumor stages. Substantial LVSI is defined as LVSI in 4 or more vessels.[8]

Molecular classification

Prior to inclusion in one of the RAINBO trials complete assessment of the molecular classification must be performed on the EC specimen. This can be either the tumor containing hysterectomy (preferred) specimen or the preoperative specimen. Molecular classification includes mutational status assessment of the exonuclease domain of DNA polymerase epsilon (*POLE*), MMR immunohistochemistry (IHC) and p53 IHC or TP53 sequencing. These tests should be performed in a (pathology) laboratory with ISO-15189 accreditation (or equivalent certification). For molecular class assignment the algorithm of the WHO 2020 classification is used.[9] Cases with more than one classifying feature (sometimes referred to as multiple or double classifiers) should be classified as follows:

i) EC with pathogenic *POLE* mutations are classified as *POLE*mut EC regardless of the MMR and p53 status,

ii) EC without pathogenic POLE mutations and mismatch repair deficiency are classified as MMRd EC, regardless of the p53 status,

iii) EC without pathogenic POLE mutations that are mismatch repair proficient and have p53 an abnormal IHC pattern and/or pathogenic *TP53* mutations are classified as p53abn EC, and

iv) EC without pathogenic POLE mutations that are mismatch repair proficient and have no p53 abnormalities are classified as NSMP.

POLE status

There is a variety of validated technologies available to assess the status of *POLE* in EC. Acceptable technologies for RAINBO include: 1) targeted NGS covering exon 9-14, 2) Sanger sequencing covering exon 9-14. Use of other technologies such as *POLE* hotspot analysis by for example (multiplex) qPCR or SnAPShot could be granted by the RAINBO steering committee after proper validation against golden standard NGS. For all techniques, adequate assessment of preferably the mutational status of all 11 hotspots, but at least the five most frequent hotspots within the exonuclease domain of *POLE* are required (Table 2.1). *POLE* variants outside the exonuclease domain are not considered.

Supplemental table 1. Pathogenic *POLE* EDM mutations in the exonuclease domain

Order of frequency	Protein change	Nucleotide substitution	Assessment for RAINBO program	Interpretation molecular class
1.	P286R	c.857C > G	Mandatory	*POLE*-mutant
2.	V411L	c.1231G > T or C	Mandatory	*POLE*-mutant
3.	S297F	c.890C > T	Mandatory	*POLE*-mutant
4.	S459F	c.1376C > T	Mandatory	*POLE*-mutant
5.	A456P	c.1366G > C	Mandatory	*POLE*-mutant
6.	F367S	c.1100T > C	Strongly recommended	*POLE*-mutant
7.	L424I	c.1270C > A	Strongly recommended	*POLE*-mutant
8.	M295R	c.884T > G	Strongly recommended	*POLE*-mutant
9.	P436R	c.1307C > G	Strongly recommended	*POLE*-mutant
10.	M444K	c.1331T > A	Strongly recommended	*POLE*-mutant
11.	D368Y	c.1102G > T	Strongly recommended	*POLE*-mutant

According to Léon-Castillo et al. J Pathol 2020[10]

Besides the pathogenic *POLE* mutations in the exonuclease domain listed in Supplemental table 1, Léon-Castillo et al. (J Pathol 2020[10]) also defined a list of non-pathogenic *POLE* mutations and variants of unknown significance in the exonuclease domain of *POLE*. These neither affect the assessment of the *POLE* status nor assignment of the molecular class. In case of the detection of a novel *POLE* variant within the exonuclease domain that is not described by Léon-Castillo et al. (J Pathol, 2020), the case should be regarded as *POLE* wildtype.

For the inclusion into the *POLE*mut-BLUE trial, the EC must contain a pathogenic variant in the exonuclease domain of *POLE*. If the assessment of the *POLE* status has failed or is not available, the patient cannot enter the RAINBO program. Assignment of an EC as being *POLE*mut EC is independent of any of the other test results as described in Supplemental figure 1.

In the unlikely case that a patient has a pathogenic *POLE* mutation but assessment of MMR status and/or p53 status has failed, the patient is not eligible for participation in the RAINBO program either, even though such patients can be classified into the *POLE*mut molecular class according to the WHO 2020 algorithm.

MMR status

For the purpose of all RAINBO trials MMR status must be determined by IHC. When MMR-IHC is performed, MSH6 and PMS2 (two-antibody approach) is the minimal requirement. Cases with positive nuclear staining of MSH6 and PMS2 can be regarded MMR proficient. In all cases with ambiguous MSH6 and/or PMS2 staining, MLH1 and MSH2 are required for final MMR status assignment. A cancer is considered MMR deficient when at least one of the MMR proteins show loss of expression with positive internal control. In most MMR deficient cases, the complete tumor will show loss of expression; infrequently a sub-clonal loss of MMR expression can be observed. In cases of sub-clonal/partial MMR protein loss there might be a pathogenic driver mutation in POLE. If the EC appears to be POLE-wild type, the cancer is considered MMR deficient when >10% of the tumor volume shows sub-clonal loss.

In ambiguous MMR-IHC cases or in case of failed MMR IHC, it is recommended to perform an analysis of MSI status for definitive assignment. MSI-high is then considered equal to MMRd. If both tests failed, then MMR status and final molecular class cannot be assigned, and the patient is not eligible for inclusion in the RAINBO trials. For the assignment of an EC as MMR deficient, POLE status must be wildtype as can be deducted from Supplemental Figure 1.

The RAINBO program encourages to execute the Lynch Syndrome triage following international guidelines.[11] It is therefore recommended to perform MLH1 methylation assay in cases with loss of MLH1/PMS2 expression in order to pre-screen patients for germline testing. The MLH1 methylation assay is however not a requirement for entering in one of the RAINBO trials, as it has no impact on the molecular EC classification.

p53 status

p53 status is preferably determined by IHC. Abnormal p53 IHC is defined as 1) complete loss of expression with positive internal control or 2) strong nuclear and/or 3) cytoplasmic overexpression. When the p53-IHC stain is well interpretable, TP53 sequencing is not required for molecular subgroup assignment. In cases with an ambiguous IHC result, p53 status cannot be assigned by p53 IHC alone. In these instances, it is recommended to use sequencing (NGS or Sanger) to assign p53 status. Upfront assessment of p53 status by *TP53* mutational analyses (e.g., by NGS or Sanger) instead of IHC is allowed under the condition that 1) the complete *TP53* gene is covered by the sequencing panel and 2) only pathogenic p53 mutations are considered. We refer to the following two public databases to determine the pathogenicity of any detected TP53 mutations:

- International Agency for Research on Cancer (IARC) TP53 database[12] (https://p53.iarc.fr/TP53GeneVariations.aspx)
- ClinVar database[13] (https://erepo.clinicalgenome.org/evrepo/ui/classifications?matchMode=exact&gene=TP53)

Sometimes sequencing detects *TP53* mutations that are not present in these two databases. Often these are secondary mutations in a MMRd or *POLE*mut EC that can be disregarded. If the tumor is MMR proficient and *POLE* wild type, we recommend performing p53 IHC and rely on the IHC result to classify the EC.

If both IHC and sequencing of the whole TP53 gene are performed upfront, discordance between these two techniques can be observed in 7.7-9.3% across all EC molecular types and in 4.9-5.5% in *POLE*-wild type and MMR-proficient EC.[14 15] The majority of these discordant cases can be resolved by reviewing the p53 IHC (missed sub-clonal areas, missed “null=pattern”?) and reviewing the sequencing data (is the variant truly pathogenic, has there not been a mix-up, what is the allele-frequency?). If in such cases IHC shows convincing abnormality and sequencing did not detect a pathogenic variant, the cases should be considered p53 abnormal. If sequencing shows a pathogenic *TP53* variant but IHC shows a convincing wild type staining pattern, other aspects can be considered for final molecular subgroups assignment. One can for example look at the other molecular alterations (Her2 amplification, PTEN status, histologic subtype) to support a subgroup assignment. We estimate that this will only be needed in ~1% of cases and we advise to send these specific cases out for consult to the national RAINBO pathology expert for assistance with the interpretation and assignment of molecular class.

Abnormal p53 patterns may be observed in only a part of the tumor while the remaining tissue shows wild type p53 staining; this is called sub-clonal abnormal p53 expression and has been observed in 5-7% of high-risk EC.[14 15] This phenomenon is often the result of secondary p53 mutations and usually occurs in *POLE* mutant or MMRd EC. According to the WHO 2020 guideline, those cases must be assigned to respectively the *POLE*mut or MMRd EC molecular class. Hence, sub-clonal p53 abnormality in *POLE*mut and MMRd EC does not affect eligibility for respectively the

RAINBO-BLUE and RAINBO-GREEN trials. However, in *POLE*-wild type and MMR proficient EC, the presence of sub-clonal p53 abnormality will determine whether the EC is classified as a p53abn EC or a NSMP EC. Because this situation is very rare (<1% of EC) current literature does not provide solid evidence for a threshold for the percentage of sub-clonal p53 abnormality.[15] For the RAINBO program, it was decided based on consensus that *POLE*-wild type, MMR-proficient EC with sub-clonal p53 abnormality in >50% of the tumor should be regarded as p53abn EC and are eligible for participation in the RAINBO-RED trial. *POLE* wild type, MMR-proficient EC with sub-clonal p53 abnormality in <10% of the tumor should be regarded as NSMP EC and are eligible for participation in the RAINBO NSMP-ORANGE trial. The very small group of patients who have a *POLE* wild type, MMR proficient EC with 10-50% sub-clonal p53 abnormality cannot be assigned to a molecular class and are not eligible for participation in any of the 4 RAINBO clinical trials. Nonetheless, collection of data on clinical outcome and FFPE tumor blocks of this specific subgroup is encouraged to enable future research on molecular class assignment.

For further details on the interpretation of p53-IHC we refer to the following publications: Köbel et al. 2016[16], Singh et al. 2020[14] and Vermij et al. 2022.[15] To finally assign an EC as p53abn EC the EC must show abnormal p53 expression and be MMR proficient and *POLE* wild type.

ER status

ER should be assessed using immunohistochemistry of a whole tumor slide in women who have NSMP EC (hence POLE wild type and MMR proficient and p53 wild type) to determine eligibility for the NSMP-ORANGE trial. ER is considered positive if expression is observed in >10% of the tumor tissue. Women with NSMP EC with ER positivity can be considered for inclusion in the RAINBO NSMP-ORANGE trial.

Allocation to molecular class-based trial

EC patients that are eligible based on the in- and exclusion criteria of the RAINBO program (listed in the main text of the article), and who are molecularly classified as described above should be considered for inclusion in the RAINBO trial of their molecular type. The patients should be screened according to the inclusion- and exclusion criteria of the appropriate trial (Supplementary Data 1) and be counselled and asked for informed consent if eligible.

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4. Sample size and power

The p53abn-RED trial

The trial has a superiority design wherein eligible patients will be randomized (1:1) to olaparib (300 mg per day, orally) starting after chemoradiation for a total of 2 years vs. chemoradiation only. Based on an expected RFS rate of 64.6% at 3 years in control group (PORTEC-3[17]), 197 events will allow to test for a hazard ratio of at least 0.67 (i.e., RFS rate of 74.6% at 3 years in treatment group) with a power of 80% or more, based on a 5%-bilateral log rank test, and including an interim analysis for efficacy. An interim analysis will be performed with group-sequential design when 70% of the information will be accrued, i.e., after 139 RFS events.. Considering an exponential survival, an accrual duration of 36 months and an additional follow-up period of 30 months, 526 patients will need to be included overall. Considering a potential dropout rate of 5%, the number of patients to include is set to 554.

The MMRd-GREEN trial

The trial has a superiority design wherein eligible patients will be randomized (1:1) to either external beam radiotherapy concurrent with the PD-L1 inhibitor durvalumab (AstraZeneca) up to one year or external beam radiotherapy only. A two-sided log-rank test with an overall sample size of 309 subjects (154 in the control group and 155 in the experimental group) achieves 80.0% power at a 0.05 significance level to detect a hazard ratio of 0.58 when the proportion surviving in the control group is 0.65 and in the experimental group is 0.78. After correction for drop-out, the required sample size is 316 subjects. Accrual duration is projected to be 30 months with a 30-month additional follow-up period. No interim analysis is planned, but an independent data monitoring committee will continuously monitor recurrences and adverse events in the trial.

The NSMP-ORANGE trial

The trial has a non-inferiority design wherein eligible patients will be randomized (1:1) to radiotherapy with hormone therapy (medroxyprogesterone or medroxyprogesterone acetate) for 2 years or chemoradiation. The sample size calculation is based on the stage III NSMP EC patients participating in the PORTEC-3 trial who had a 3-year RFS of 82.5% after chemoradiation.[17] A non-inferiority margin of 7.5 percentage points is of interest, to exclude a 3-year RFS rate of below 75% in the experimental arm, representing a hazard ratio (HR) of 1.495. This margin was chosen after considering outcomes through RT alone in PORTEC-3 and is in-line with the perspectives of both patients and clinicians with regards to the required benefits for adjuvant chemotherapy to be worthwhile in EC.[18] Patients will be recruited over 5 years with 3 years of additional follow-up to observe 153 RFS events, for 80% power at the one-sided 5% significance level after allowing for up to 5% dropout. As the planned recruitment period is relatively long, futility analyses are incorporated into the study. Conditional power will be calculated and presented to the independent data monitoring committee on an annual basis; if this drops below 15% then a further check will be made after 6 months and if conditional power remains <15% then the IDMC may recommend closing the trial.[19]

The POLEmut-BLUE trial

In the *POLE*mut-BLUE trial eligible patients with select stage I-II *POLE*mut EC in the main study cohort (see Supplementary Data 1) will receive no adjuvant therapy. Patients will be recruited over 36 months with 36 months of additional follow-up, which will give an expected total person-years of 506. Assuming a 3-year pelvic recurrence rate of 1%, the upper 95% confidence limit for the true 3-year pelvic recurrence rate would be 2.4%; a true 3-year pelvic recurrence rate of 5%, which is considered an unacceptable high risk, can be ruled out with more than 95% confidence. If the observed 3-year pelvic recurrence rate is higher at 2%, then the upper 95% confidence limit for the true 3-year pelvic recurrence rate would be 3.7% and a rate of 5% or higher can still be rejected at the one-sided 5% significance level. Interim analysis for futility will be carried out when half of the person-years of follow-up have been observed, corresponding to approximately 253 person-years. Final analysis will be performed when 506 person-years of follow-up are observed, which is foreseen at 3 years after the inclusion of the last patient. In addition, higher-risk *POLE*mut EC patients will be accrued into the exploratory cohort, offering observation or radiation alone (estimated sample size 25) for descriptive analysis.

RAINBO overarching research program

In the overarching RAINBO research program, predefined comparisons between personalized molecular profile-based treatment and standard treatment will be made including all participants of the four RAINBO sub-trials. To determine whether personalized treatment for EC is more effective, less toxic and provides a better QoL than standard treatment, all patients who have received molecular profile-directed adjuvant treatment (Group A) will be pooled and compared to the pooled data of all patients who have received standard treatment (Group B). The projected sample size of the overarching research program is around 1600. Power calculations for the different endpoints were based on a sample size of 700 cases per group.

Treatment efficacy

It is estimated that we will have 80% power (alpha 0.01) to detect a true hazard ratio of 0.833 or 1.201 based on 700 participants in each group; and 90% power to detect a true HR of .814 or 1.229. Assumptions: accrual time of 4 years, additional follow-up time of 3 years and a median RFS with the standard treatment of 5.04 years (based on the PORTEC-3 trials' pooled estimate). The relation between the power and detectable difference is presented in power graph 1 of Supplemental figure 2.

Treatment toxicity

It is estimated that we will have 80% or more power (alpha 0.01) to detect a true difference in grade ≥2 morbidity at 3 years if it occurs in less than 23.7% or more than 40.9% of the patients in group B. Assumptions: 700 patients are included in each group, the cumulative incidence of grade >=2 morbidity is 32% at 3 years with the standard treatment (based on the chemoradiation group in PORTEC-3), using Fisher's exact test to evaluate this null hypothesis. Alternatively, if the cumulative incidence of grade ≥2 morbidity is assumed to be 24% at 3 years with the standard treatment (based on the radiotherapy group in PORTEC-3), we will have at least 80% power to detect a true difference if it occurs in less than 16.5% or more than 32.4% of the patients in group B. The relation between the power and detectable difference is presented in power graph 2 of Supplemental figure 2.

Health-related quality of life

It is estimated that we will have 80% or more power (alpha 0.01) to detect a true difference in the EORTC QLQ-C30 scale score for fatigue at 3 years if the difference between group A and B is 6.1 points (scale of 0 to 100) or more. Assumptions: 700 patients are included in each group, the standard deviation of the scale score for fatigue in the control population is 33.4 (based on the reference values for cervical cancer patients of the EORTC-QLQ) and the t-test is used to evaluate this null hypothesis. Alternatively, we have 80% or more power to detect a true difference in fatigue of 3.7 points or more if the SD in the control population is assumed to be equal to the Dutch reference population (SD=20, according to van de Poll et al. 2011).[20] The relation between the power and detectable difference is presented in power graph 3 of Supplemental figure 2.

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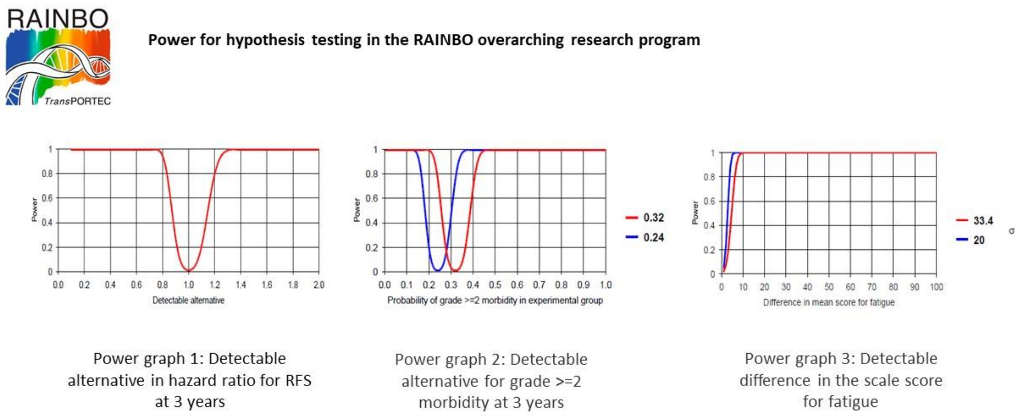
Cost-utility

Disease-related health care costs will be estimated for Group A and B based on the collected data on received adjuvant treatment, treatment for first recurrence and severe toxicity. Costs of molecular profiling will only be included in group B. Quality-adjusted life years will be estimated with individual follow-up times corrected for quality by linear interpolation of utility values deduced from the EORTC QLQ-C30 questionnaires using the EORTC QLU-C10D.[21 22] Cost-effectiveness acceptability curves will be used to plot the probability that tailored treatment is more cost-effective than standard treatment as a function of willingness to pay. Sensitivity analysis will include alternative methodology for utility value assessment by the EORTC 8D.[23 24]



Supplemental figure 2. Power graphs RAINBO overarching research program

Definition of abbreviation: RFS = recurrence-free survival.

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5. Statistical methods

The p53abn-RED trial

The primary endpoint, 3-year RFS, will estimated according to Kaplan-Meier's method and compared between the two treatment groups using a Cox' proportional hazards model, with adjustment for randomization stratification factors. Secondary endpoints will be analyzed using competing risk models except for OS, which will be analyzed using the same methodology as RFS.

The MMRd-GREEN trial

The primary endpoint, 3-year RFS will be assessed according to Kaplan-Meier's methodology and compared between groups using a log-rank test when a median follow-up of three years has accrued. Other time-to-event analysis, including toxicity will be performed using similar methods. Health-related quality of life of patients will be analyses using linear mixed models and generalized estimating equations. Cross-sectional analysis of QoL will be performed at 6 months, 12 months, and 36 months using linear regression for scale scores and logistic regression for item scores after dichotomization.

The NSMP-ORANGE trial

The primary endpoint will be described using Kaplan-Meier's method and analyzed using a Cox' proportional hazards model. The interpretation of non-inferiority will be based on the 95% confidence interval. Similar methods will be used for other time-to-event endpoints. Toxicity will be described using proportions and exact 95% confidence intervals and compared between groups using χ^2/Fisher's exact tests as appropriate. Quality of life outcomes will be analyzed using mixed models.

The POLEmut-BLUE trial

In the *POLE*mut-BLUE trial, the primary endpoint 3-year pelvic recurrence will be derived from a competing risk analysis with death due to any cause as competing event and censoring of alive patients without pelvic recurrence. If the upper 95% confidence limit is less than 5% it will be concluded that the risk of pelvic recurrence at 3 years with molecular-tailored de-escalated adjuvant treatment is acceptable. The same competing risk-based approach is also used to estimate isolated vaginal recurrence and distant metastasis rates at 3 years and associated 90% confidence intervals. Kaplan-Meier method will be used to estimate 3-year rates of recurrence-free, EC-specific, and overall survivals and associated 90% confidence interval. In all these analyses, only those who have complied with the recommendation for no or de-escalated adjuvant treatment will be included. Patients' quality of life mean score for each subscale will be calculated at each time of assessment from all patients who are assessed and compared to that observed in PORTEC-2[25], as a historical control by a 2-sided one-sample t-test.

The overarching RAINBO research program

In the overarching research program, the oncological, survival and toxicity outcomes will be analyzed according to Kaplan-Meier's methodology and compared using log-rank tests and multivariable Cox' proportional hazards models. Longitudinal analysis of toxicity and quality of life across the first 3 years after randomization will be done using linear mixed models and generalized estimating equations. Cross-sectional analysis will be performed at 2-3 months, 6, 12 and 36 months using linear and logistic regression. Disease-related health care costs will be estimated for Group A and B based on the collected data on received adjuvant treatment, treatment for first recurrence and severe toxicity. Costs of molecular profiling will only be included in group A. Quality-adjusted life years will be estimated with individual follow-up times corrected for quality by linear interpolation of utility values deduced from the EORTC QLQ-C30 questionnaires using the EORTC QLU-C10D[21 22]. Cost-effectiveness acceptability curves will be used to plot the probability that tailored treatment is more cost-effective than standard treatment as a function of willingness to pay.

6. RAINBO Research Consortium

The RAINBO Research Consortium decided to publish this paper as a group, without any individual authorships. This is because of the ensemble of 4 clinical trials and an overarching and translational research program are the result of the interaction between experts of different disciplines; as opposed to the efforts of the individuals. Selecting a limited number of individuals for an authorship would not do justice to the efforts of all contributors that qualify for an authorship. Moreover, using individual authorships implies that only a handful of individuals will be assigned the most valued (first, second and last) authorships, which is incompatible with the number of lead investigators of the RAINBO program. The members of the RAINBO Research consortium on October 4th 2022 are:

Steering group (alphabetical)
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Statistical committee (alphabetical)
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Advisory committee (alphabetical)
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