



## OPEN ACCESS

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/ijgc-2022-004039>).

Leiden University Medical Center, Leiden, The Netherlands

### Correspondence to

RAINBO Research Consortium, Leiden University Medical Center, Leiden, Netherlands; n.horeweg@lumc.nl

Accepted 31 October 2022



© IGCS and ESGO 2022. Re-use permitted under CC BY-NC. No commercial re-use. Published by BMJ.

**To cite:** RAINBO Research Consortium. *Int J Gynecol Cancer* Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2022-004039

# 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](http://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.<sup>1</sup> 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.<sup>1</sup> About 15–20% of patients have a high risk of recurrence and disease-related death.<sup>1</sup> For these patients, radiotherapy and/or adjuvant chemotherapy is recommended.<sup>2</sup>

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- $\epsilon$ , 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

## Clinical trial

has no single identifying molecular feature and tumor stage- and grade-dependent outcomes.<sup>3</sup> 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.<sup>2</sup>

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.<sup>4</sup> 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,  $p=0.021$ ).<sup>5</sup> 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.<sup>6</sup> 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.<sup>7</sup> We recently confirmed using a functional assay that HRD is present in about half the cases of p53abn endometrial cancer.<sup>8</sup> 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,  $p=0.43$ ).<sup>5</sup> MMRd endometrial cancer is hypermutated and frequently has dense intra-tumoral CD8+ T cell infiltrates and tertiary lymphoid structures.<sup>9</sup> 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.<sup>10</sup> 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.<sup>11</sup>

#### 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.<sup>5</sup> 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.<sup>12</sup> For example, in PORTEC-3, grade  $\geq 3$  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.<sup>4,12</sup> 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%).<sup>13</sup> 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,<sup>2</sup> and yield an objective response in about a quarter of patients and clinical benefit in about half of patients.<sup>14</sup> 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.<sup>15</sup> 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.<sup>16</sup> 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.<sup>17</sup> 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.<sup>17</sup> There was no apparent benefit in clinical outcomes from receiving adjuvant therapy.<sup>17</sup> An *in vitro* study showed that pathogenic *POLE* mutations did not increase sensitivity to radiotherapy or chemotherapeutics.<sup>18</sup> 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.<sup>5</sup> 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.

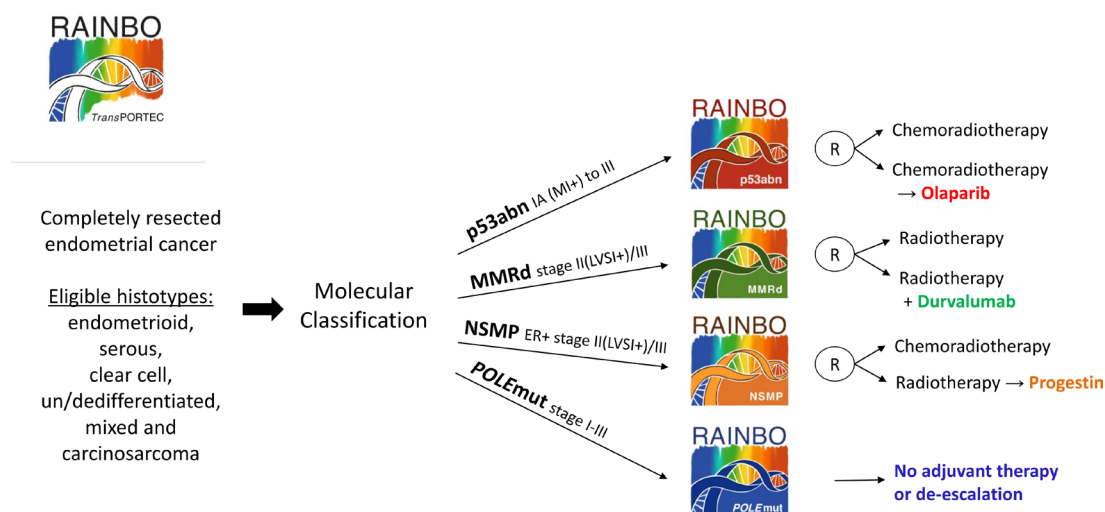
Funding for the RAINBO program has been obtained from the French Cancer Institute (Institut National du Cancer), the Dutch Cancer Society (KWF Kankerbestrijding), the Canadian Institutes for Health Research and AstraZeneca. Ethical approval will be obtained from the Institutional Review Board at each 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.

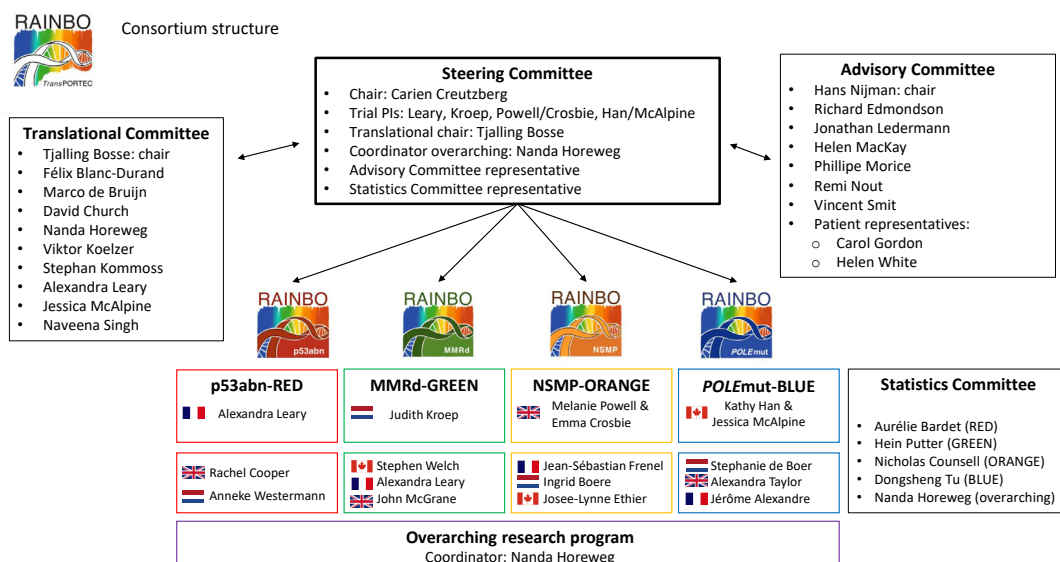
The NSMP-ORANGE trial is an international phase III non-inferiority trial in which patients with stage II (LVSI+) or stage III NSMP endometrial cancer are randomized (1:1) to adjuvant radiotherapy followed by progesterone tablets (either medroxyprogesterone acetate or megestrol acetate) for 2 years or 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 CTG 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; *POLE*mut, DNA polymerase- $\epsilon$  mutated; R, randomization; RAINBO, Refining Adjuvant treatment IN endometrial cancer Based On molecular features.

## Clinical trial



**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

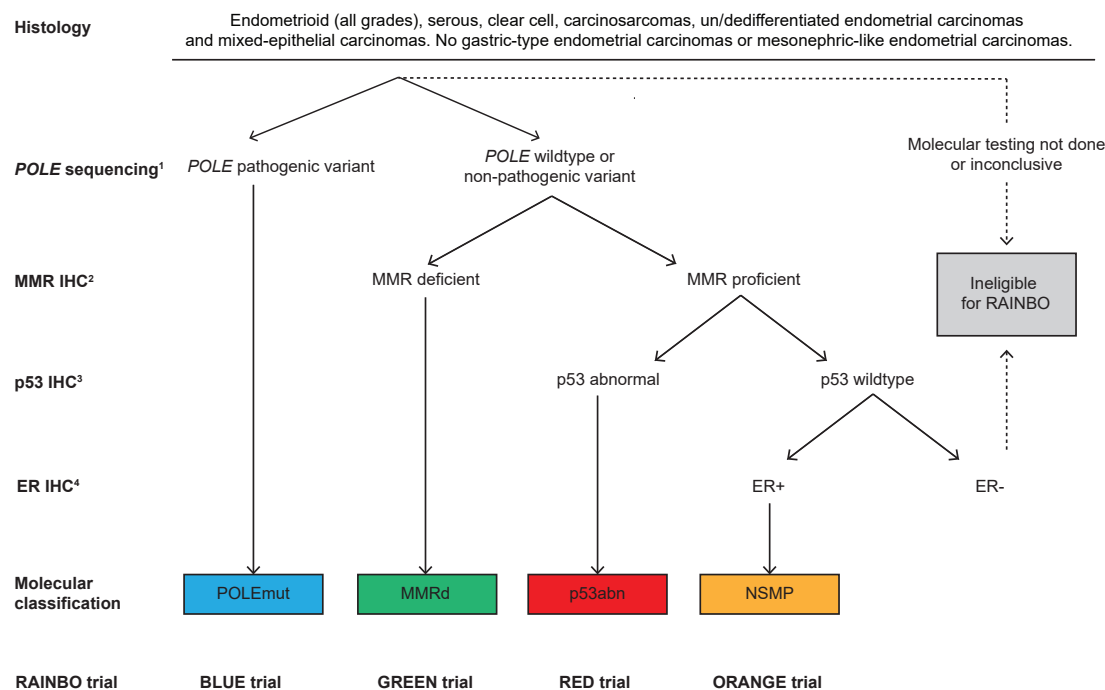
enables a combination of the data and tumor material of the four trials for the overarching program and translational studies.

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

|   | Baseline  | Tx | Time since registration in months |    |    |    |    |    |    |
|---|---|----|-----------------------------------|----|----|----|----|----|----|
|   |   |    | 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.<sup>3</sup>

<sup>1</sup>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 León-Castillo et al<sup>16</sup> which are considered pathogenic. <sup>2</sup>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). <sup>3</sup>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. <sup>4</sup>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.<sup>3</sup>
- ▶ 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.

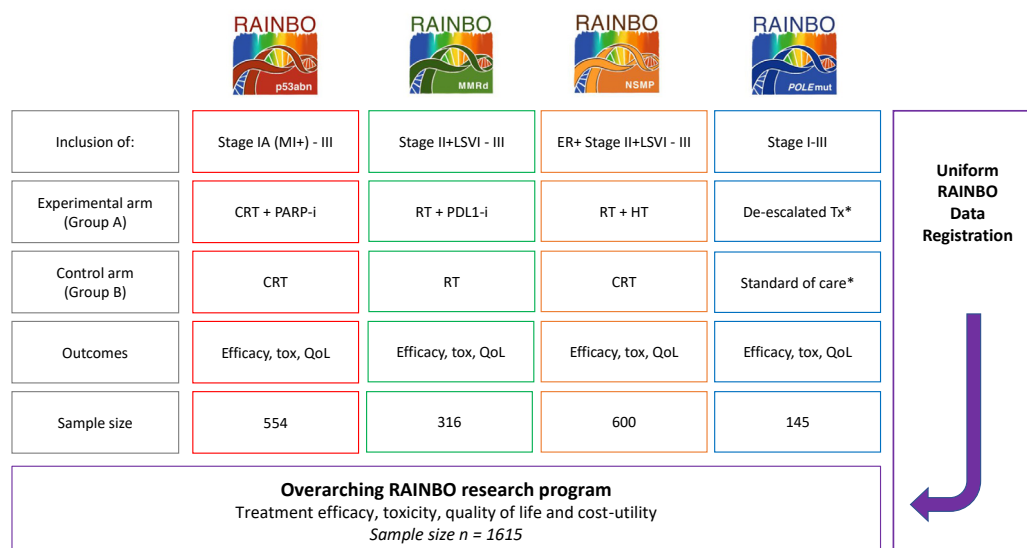
### Exclusion Criteria

- ▶ 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

## Clinical trial



**Figure 4** Sample size of the RAINBO clinical trials and overarching research program. CRT, chemoradiotherapy; ER, estrogen receptor; HT, hormonal therapy; LSVI, 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 *POLEmut-BLUE* trial participants will be pooled in Group A or B depending on tumor characteristics and received adjuvant treatment strategy.

the *POLEmut-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 *POLEmut-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 *POLEmut-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  $\alpha=0.05$ ) to detect a HR of  $\leq 0.67$  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  $\alpha=0.05$ ) to detect a HR  $\leq 0.58$  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  $\leq 75\%$  (ie, HR 1.495) with 80% power (one-sided  $\alpha=0.05$ ). 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 *POLEmut-BLUE* trial will recruit 120 patients with select stage I-II *POLEmut* 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  $\alpha=0.05$ ). 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' *POLEmut* 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.<sup>5</sup> Moreover, many patients will suffer from treatment-related morbidity impacting on quality of life.<sup>4,12</sup> 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.

**Twitter** RAINBO Research Consortium @RAINBOprogram

**Acknowledgements** We gratefully acknowledge the patient advocacy group ‘Olijf’; the Institute Gustave Roussy Trial Center, Comprehensive Cancer Center the Netherlands (IKNL); Cancer Research UK and UCL Cancer Trials Centre and L Hughes and K Chan; the Canadian Clinical Trials Group (CCTG) and A Fyles, F Huang, M Carey, M Barkati, S Ferguson, and A Urton; the PORTEC-3 Trial Group; and the TransPORTEC Research Consortium.

**Collaborators** RAINBO Research Consortium: Individual names of the members of the collaborator group: Steering Group (alphabetical): T Bosse,<sup>1</sup> CL Creutzberg,<sup>2</sup> EJ Crosbie,<sup>3</sup> K Han,<sup>4</sup> N Horeweg,<sup>2</sup> A Leary,<sup>5</sup> JR Kroep,<sup>6</sup> JN McAlpine,<sup>7</sup> ME Powell.<sup>8</sup> Translational Committee (alphabetical): F Blanc-Durand,<sup>5</sup> T Bosse,<sup>1</sup> M de Bruyn,<sup>9</sup> DN Church,<sup>10,11</sup> N Horeweg,<sup>2</sup> VH Koelzer,<sup>12,13</sup> S Kommos,<sup>14</sup> A Leary,<sup>5</sup> JN McAlpine,<sup>7</sup> N Singh,<sup>15</sup> Statistical Committee (alphabetical): A Bardet,<sup>16,17</sup> N Counsell,<sup>18</sup> N Horeweg,<sup>2</sup> H Putter,<sup>19</sup> D Tu,<sup>20</sup> Advisory Committee (alphabetical): R Edmondson,<sup>3</sup> C Gordon,<sup>21</sup> J Ledermann,<sup>22</sup> P Morice,<sup>23</sup> H MacKay,<sup>24</sup> H Nijman,<sup>9</sup> RA Nout,<sup>25</sup> VTHBM Smit,<sup>1</sup> H White.<sup>26</sup> Country Champions (alphabetical): J Alexandre,<sup>27,28</sup> SM de Boer,<sup>2</sup> I Boere,<sup>29</sup> R Cooper,<sup>30</sup> JL Ethier,<sup>31,32</sup> JS Frenel,<sup>33</sup> J McGrane,<sup>34</sup> A Taylor,<sup>35</sup> S Welch,<sup>36</sup> AM Westermann.<sup>37</sup> Trial Management (alphabetical): H Dijkstra-van der Linden,<sup>38</sup> L Farrelly,<sup>18</sup> A Feeney,<sup>18</sup> M Kaya,<sup>2</sup> W Liu,<sup>20</sup> A Melis,<sup>39</sup> F Ngadjieu-Tchouatieu,<sup>39</sup> W Parulekar,<sup>20</sup> K Verhoeven-Adema.<sup>38</sup> Writing Committee: N Horeweg,<sup>2</sup> ME Powell,<sup>8</sup> K Han,<sup>4</sup> JR Kroep,<sup>6</sup> F Blanc-Durand,<sup>5</sup> S Welch,<sup>34</sup> A Bardet,<sup>16,17</sup> N Counsell,<sup>18</sup> H Putter,<sup>19</sup> D Tu,<sup>20</sup> N Singh,<sup>15</sup> DN Church,<sup>10,11</sup> S Kommos,<sup>14</sup> M de Bruyn,<sup>9</sup> H Nijman,<sup>9</sup> CL Creutzberg,<sup>2</sup> JN McAlpine,<sup>7</sup> T Bosse,<sup>1</sup> EJ Crosbie,<sup>3</sup> H MacKay,<sup>24</sup> A Leary.<sup>5</sup>

Affiliations of the participants of the RAINBO research consortium: <sup>1</sup>Department of Pathology, Leiden University Medical Center, the Netherlands. <sup>2</sup>Department of Radiation Oncology, Leiden University Medical Center, the Netherlands. <sup>3</sup>Department of Obstetrics and Gynaecology, Manchester Academic Health Science Centre, St Mary’s Hospital, Manchester, UK. <sup>4</sup>Department of Radiation Oncology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Radiation Oncology, Toronto, Canada. <sup>5</sup>Department of Medical Oncology, Gustave Roussy Cancer Center, Université Paris Saclay, Cancer Medicine and Gynecological Tumor Translational Research Lab, Villejuif, France. <sup>6</sup>Department of Medical Oncology, Leiden University Medical Center, the Netherlands. <sup>7</sup>Department of Obstetrics and Gynecology, University of British Columbia, Vancouver, Canada. <sup>8</sup>Department of Clinical Oncology, Barts Health NHS Trust, London, UK. <sup>9</sup>Department of Gynaecology, University Medical Center Groningen, Groningen University, Groningen, the Netherlands. <sup>10</sup>Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK. <sup>11</sup>Oxford NIHR Comprehensive Biomedical Research Centre, Oxford, UK. <sup>12</sup>Department of Pathology and Molecular Pathology, University Hospital Zürich, University of Zürich, Zürich, Switzerland. <sup>13</sup>Department of Oncology and Nuffield Department of Medicine, University of Oxford, Oxford, UK. <sup>14</sup>Department of Women’s Health, University of Tübingen, Tübingen, Germany. <sup>15</sup>Department of Cellular Pathology, Barths Health NHS Trust, London, UK. <sup>16</sup>Bureau of Biostatistics and Epidemiology, University Paris-Saclay, Gustave-Roussy, Villejuif, France. <sup>17</sup>Oncostat U1018, Inserm, University Paris-Saclay, Ligue Contre le Cancer, Villejuif, France. <sup>18</sup>Cancer Research UK and University College London Cancer Trials Centre, University College London, London, UK. <sup>19</sup>Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands. <sup>20</sup>Canadian Cancer Trials Group, Queen’s University, Kingston, Ontario, Canada. <sup>21</sup>Patient Representative, Canadian Cancer Clinical Trials Group, Queen’s University, Kingston, Ontario, Canada. <sup>22</sup>Cancer Research UK and UCL Cancer Trials Centre, UCL Cancer Institute and UCL Hospitals, London, UK. <sup>23</sup>Department of Gynaecologic Surgery, Gustave Roussy Cancer Center, Université Paris Saclay, Villejuif, France. <sup>24</sup>Department of Medical Oncology, Odette Cancer Center, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada. <sup>25</sup>Department of Radiotherapy, Erasmus MC Cancer Institute, Rotterdam, the Netherlands. <sup>26</sup>Patient Representative, Peaches Patient Voices, Manchester, UK. <sup>27</sup>Centre de Recherche des Cordeliers, Equipe labélisée Ligue Contre le Cancer, Sorbonne Université, Université de Paris, INSERM, Paris, France. <sup>28</sup>Department of Medical Oncology, Hôpital Cochin, Institut du Cancer Paris, Paris, France. <sup>29</sup>Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, the

## Clinical trial

Netherlands.<sup>30</sup>Department of Clinical Oncology, Leeds Teaching Hospitals NHS Trust, Leeds, UK. <sup>31</sup>Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute, Kingston, Ontario, Canada. <sup>32</sup>Department of Oncology, Queen's University, Kingston, Ontario, Canada. <sup>33</sup>Department of Medical Oncology, Institut de Cancerologie de l'Ouest-Centre Rene Gauducheau, Saint-Herblain, France. <sup>34</sup>Sunrise Oncology Centre, Royal Cornwall Hospital, Truro, UK. <sup>35</sup>Department of Gynaecological Oncology, The Royal Marsden NHS Foundation Trust, London, UK. <sup>36</sup>Division of Medical Oncology, Western University, London, Ontario, Canada. <sup>37</sup>Department of Oncology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands. <sup>38</sup>Comprehensive Cancer Center the Netherlands (KNL), Leiden, the Netherlands. <sup>39</sup>Clinical Research Department, Institute Gustave Roussy, Chevilly-Larue, France.

**Contributors** The current work is the result of the collaborative effort of the RAINBO Research Consortium. The Consortium is led by the Steering Group consisting of the following members (in alphabetical order): T Bosse, CL Creutzberg, EJ Crosbie, K Han, N Horeweg, A Leary, JR Kroep, JN McAlpine, ME Powell. The Translational Committee is responsible for the design and conduct of translational studies with the tumor materials obtained from the participants of the RAINBO program and consists of the following members (in alphabetical order): F Blanc-Durand, T Bosse, M de Bruyn, DN Church, N Horeweg, VH Koelzer, S Kommos, A Leary, JN McAlpine, N Singh. The Statistical Committee is responsible for the design and analyses of the outcomes of the four RAINBO clinical trials and the overarching research program and consists of the following members (in alphabetical order): A Bardet, N Counsell, N Horeweg, H Putter, D Tu. The Advisory Committee with representation from international experts and patient advocates provides the Steering Group with independent advice and consists of the following members (in alphabetical order): R Edmondson, C Gordon, J Ledermann, P Morice, H MacKay, H Nijman, RA Nout, VTHBM Smit, H White. The Country Champions are responsible for the execution of the RAINBO clinical trials in the non-leading countries (in alphabetical order): J Alexandre, SM de Boer, I Boere, R Cooper, JL Ethier, JS Frenel, J McGrane, A Taylor, S Welch, AM Westermann. The RAINBO clinical trials are managed by (in alphabetical order): H Dijcker-van der Linden, L Farrelly, A Feeney, M Kaya, W Liu, A Melis, F Ngadjjeu-Tchouatieu, W Parulekar, K Verhoeven-Adema. The current manuscript has been written collaboratively by all the Writing Committee members: N Horeweg, ME Powell, K Han, JR Kroep, F Blanc-Durand, S Welch, A Bardet, N Counsell, H Putter, D Tu, N Singh, DN Church, S Kommos, M de Bruyn, H Nijman, CL Creutzberg, JN McAlpine, T Bosse, EJ Crosbie, H MacKay, A Leary. NH acts as guarantor for this publication and takes responsibility for its content. The sponsors are responsible for the conduct of the clinical trials of the RAINBO program.

**Funding** A research project grant from the Dutch Cancer Society (KWF 13403) was awarded for partial funding of the MMRd-GREEN trial and the RAINBO overarching research program. An unrestricted educational grant from the French Institut National du Cancer was awarded for partial funding of the p53abn-RED trial and French participation in the RAINBO program. An unrestricted educational grant was provided by AstraZeneca for partial funding of the p53abn-RED trial. Two grants from the Canadian Institutes for Health Research were awarded for, respectively, the POLEmut-BLUE trial (CCTG EN.10 TAPER arm A POLE) and Canadian participation in the MMRd-GREEN trial. Durvalumab and olaparib were provided by AstraZeneca.

**Competing interests** J Alexandre reports grants paid to his institution by MSD and Janssen; consulting fees to him by MSD, AstraZeneca, GSK, Eisai, and Janssen; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events to him by MSD, AstraZeneca, GSK, Clovis, and Novartis; support for attending meetings and/or travel to him by AstraZeneca and Novartis. SM de Boer reports a research grant paid to her institution by Varian Medical Systems. T Bosse reports research project funding by the Dutch Cancer Society (KWF). DN Church has participated in an advisory board for MSD and has received research funding from HalioDx (on behalf of the TransSCOT consortium). CL Creutzberg reports research grants from the Dutch Cancer Society (KWF) for the conduct of the PORTEC trials and the RAINBO program. JL Ethier reports payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events by Merck, GSK and AstraZeneca and participation in these companies' Advisory Boards. JS Frenel reports having personally received consulting fees and support for attending meetings and/or travel by Pfizer, Lilly, Novartis, AstraZeneca, Clovis Oncology, GSK, Gilead, Daiichi Sankyo, and Seagen. Payment or honoraria were personally received for lectures, presentations, speaker bureaus, manuscript writing or educational events from Lilly, Novartis, AstraZeneca, Gilead, Daiichi Sankyo, and Seagen. C Gordon reports being a member of the Canadian Cancer Clinical Trials Group as member of the Patients' Representatives Committee on a volunteer basis. K Han reports research grants from the Canadian

Institutes of Health Research Project Grant and Princess Margaret Hospital Foundation, participating on the AstraZeneca Cervical Cancer Radiation Oncology Advisory Board (October 2021), and being Endometrial Cancer Working Group Co-Chair of the Canadian Cancer Trials Group. N Horeweg reports research grants paid to her institution from the Dutch Cancer Society (KWF) and an unrestricted research grant by Varian for the RAINBO program and other unrelated research projects. VH Koelzer is principal investigator in a public-private partnership with Roche unrelated to the topic of this manuscript, received research funding from the Image Analysis Group unrelated to the topic of this manuscript, served as an invited speaker on behalf of Indica Labs, and is participant of a patent application co-owned by the Netherlands Cancer Institute (NKI-AVL) and the University of Basel on the assessment of cancer immunotherapy biomarkers by digital pathology. JR Kroep reports having received study drugs and an unrestricted research grant from AstraZeneca for the conduct of the MMRd-GREEN trial, as well as a research grants from the Dutch Cancer Society and WCRF. Consulting fees were paid to the researcher's institution by AstraZeneca, MSD, GSK, Novartis and Eisai, as well as payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events by MSD and GSK. Participation on a Data Safety Monitoring Board or Advisory Board without payment for the TEIPP trial and the ALISON trial were reported. J McGrane reports having received consulting fees for participation in advisory boards of GSK, MSD and Ipsen and honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events, and for attending meetings and/or travel. A Taylor reports participation in the advisory board of MSD.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and ethical approval will be obtained in each country and/or at each participating center according to the local regulations. The first approval was given by the Medisch-Ethische Toetsingscommissie Leiden, Den Haag, Delft (registration number P21.074). All participants will give written informed consent to participate in one of the four RAINBO trials and the overarching and translational research program before taking part.

**Provenance and peer review** Commissioned; internally peer reviewed.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, an indication of whether changes were made, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

## REFERENCES

- Crosbie EJ, Kitson SJ, McAlpine JN, *et al*. Endometrial cancer. *Lancet* 2022;399:1412–28.
- Concin N, Matias-Guiu X, Vergote I, *et al*. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *Int J Gynecol Cancer* 2021;31:12–39.
- WHO Classification of Tumours Editorial Board. *WHO classification of tumours, 5th Edition, Volume 4: Female genital tumours*, 2020: 252–66. <https://www.iarc.who.int/news-events/publication-of-the-who-classification-of-tumours-5th-edition-volume-4-female-genital-tumours/>
- Post CCB, de Boer SM, Powell ME, *et al*. Long-term toxicity and health-related quality of life after adjuvant chemoradiation therapy or radiation therapy alone for high-risk endometrial cancer in the randomized PORTEC-3 trial. *Int J Radiat Oncol Biol Phys* 2021;109:975–86.
- León-Castillo A, de Boer SM, Powell ME, *et al*. Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on prognosis and benefit from adjuvant therapy. *J Clin Oncol* 2020;38:3388–97.
- Kandoth C, McLellan MD, Vandin F, *et al*. Mutational landscape and significance across 12 major cancer types. *Nature* 2013;502:333–9.



- 7 Marquard AM, Eklund AC, Joshi T, *et al.* Pan-cancer analysis of genomic scar signatures associated with homologous recombination deficiency suggests novel indications for existing cancer drugs. *Biomark Res* 2015;3.
- 8 de Jonge MM, Auguste A, van Wijk LM, *et al.* Frequent homologous recombination deficiency in high-grade endometrial carcinomas. *Clin Cancer Res* 2019;25:1087–97.
- 9 Horeweg N, Workel HH, Loiero D, *et al.* Tertiary lymphoid structures critical for prognosis in endometrial cancer patients. *Nat Commun* 2022;13:1373.
- 10 Antill Y, Kok P-S, Robledo K, *et al.* Clinical activity of durvalumab for patients with advanced mismatch repair-deficient and repair-proficient endometrial cancer. A nonrandomized phase 2 clinical trial. *J Immunother Cancer* 2021;9.
- 11 Deng L, Liang H, Xu M, *et al.* STING-dependent cytosolic DNA sensing promotes radiation-induced type I interferon-dependent antitumor immunity in immunogenic tumors. *Immunity* 2014;41:843–52.
- 12 de Boer SM, Powell ME, Mileskin L, *et al.* Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol* 2016;17:1114–26.
- 13 Vermij L, Jobsen JJ, León-Castillo A. Prognostic refinement of NSMP high-risk endometrial cancers using oestrogen receptor immunohistochemistry. *MedRxiv* 2022 <https://www.medrxiv.org/content/10.1101/2022.09.13.22279853v1>
- 14 Ethier J-L, Desautels DN, Amir E, *et al.* Is hormonal therapy effective in advanced endometrial cancer? A systematic review and meta-analysis. *Gynecol Oncol* 2017;147:158–66.
- 15 Martin-Hirsch PP, Bryant A, Keep SL. Adjuvant progestagens for endometrial cancer. *Cochrane Database Syst Rev* 2011;6.
- 16 León-Castillo A, Britton H, McConechy MK, *et al.* Interpretation of somatic POLE mutations in endometrial carcinoma. *J Pathol* 2020;250:323–35.
- 17 McAlpine JN, Chiu DS, Nout RA, *et al.* Evaluation of treatment effects in patients with endometrial cancer and POLE mutations: an individual patient data meta-analysis. *Cancer* 2021;127:2409–22.
- 18 Van Gool IC, Rayner E, Osse EM, *et al.* Adjuvant treatment for *POLE* proofreading domain-mutant cancers: sensitivity to radiotherapy, chemotherapy, and nucleoside analogues. *Clin Cancer Res* 2018;24:3197–203.