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

Chapter	Page

. *Int J Gynecol Cancer* 2022;0:1–9. doi: 10.1136/ijgc-2022-004039

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.

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- 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).

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- 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

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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]

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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.

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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

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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.

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

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484 worthwhile in EC.[18] Patients will be recruited over 5 years with 3 years of additional follow-up to
485 observe 153 RFS events, for 80% power at the one-sided 5% significance level after allowing for up
486 to 5% dropout. As the planned recruitment period is relatively long, futility analyses are
487 incorporated into the study. Conditional power will be calculated and presented to the independent
488 data monitoring committee on an annual basis; if this drops below 15% then a further check will be
489 made after 6 months and if conditional power remains <15% then the IDMC may recommend closing
490 the trial.[19]
491
492 *The POLEmut-BLUE trial*
493 In the *POLE*mut-BLUE trial eligible patients with select stage I-II *POLE*mut EC in the main
494 study cohort (see Supplementary Data 1) will receive no adjuvant therapy. Patients will be recruited
495 over 36 months with 36 months of additional follow-up, which will give an expected total person-
496 years of 506. Assuming a 3-year pelvic recurrence rate of 1%, the upper 95% confidence limit for the
497 true 3-year pelvic recurrence rate would be 2.4%; a true 3-year pelvic recurrence rate of 5%, which is
498 considered an unacceptable high risk, can be ruled out with more than 95% confidence. If the
499 observed 3-year pelvic recurrence rate is higher at 2%, then the upper 95% confidence limit for the
500 true 3-year pelvic recurrence rate would be 3.7% and a rate of 5% or higher can still be rejected at
501 the one-sided 5% significance level. Interim analysis for futility will be carried out when half of the
502 person-years of follow-up have been observed, corresponding to approximately 253 person-years.
503 Final analysis will be performed when 506 person-years of follow-up are observed, which is foreseen
504 at 3 years after the inclusion of the last patient. In addition, higher-risk *POLE*mut EC patients will be
505 accrued into the exploratory cohort, offering observation or radiation alone (estimated sample size
506 25) for descriptive analysis.
507
508 *RAINBO overarching research program*
509 In the overarching RAINBO research program, predefined comparisons between
510 personalized molecular profile-based treatment and standard treatment will be made including all
511 participants of the four RAINBO sub-trials. To determine whether personalized treatment for EC is
512 more effective, less toxic and provides a better QoL than standard treatment, all patients who have
513 received molecular profile-directed adjuvant treatment (Group A) will be pooled and compared to
514 the pooled data of all patients who have received standard treatment (Group B). The projected
515 sample size of the overarching research program is around 1600. Power calculations for the different
516 endpoints were based on a sample size of 700 cases per group.
517

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.

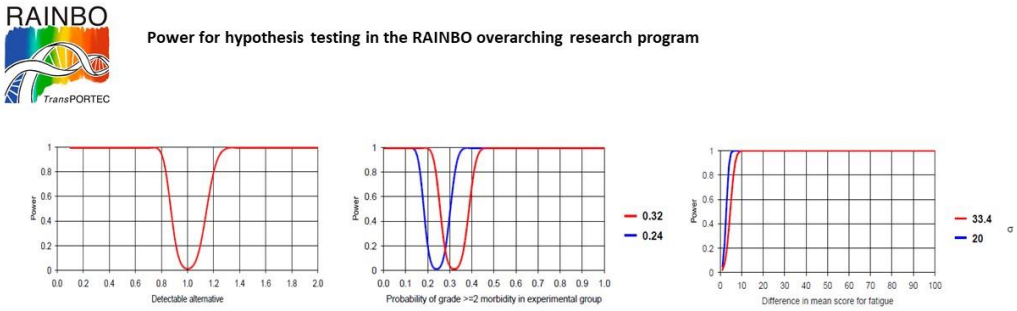
Health-related quality of life

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.

549 Cost-utility

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

558
559



Power graph 1: Detectable alternative in hazard ratio for RFS at 3 years

Power graph 2: Detectable alternative for grade >=2 morbidity at 3 years

Power graph 3: Detectable difference in the scale score for fatigue

560 **Supplemental figure 2. Power graphs RAINBO overarching research program**

561 *Definition of abbreviation: RFS = recurrence-free survival.*

562

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 $\chi 2$/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

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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:

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Statistical committee (alphabetical)
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Advisory committee (alphabetical)
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Country champions (alphabetical)
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