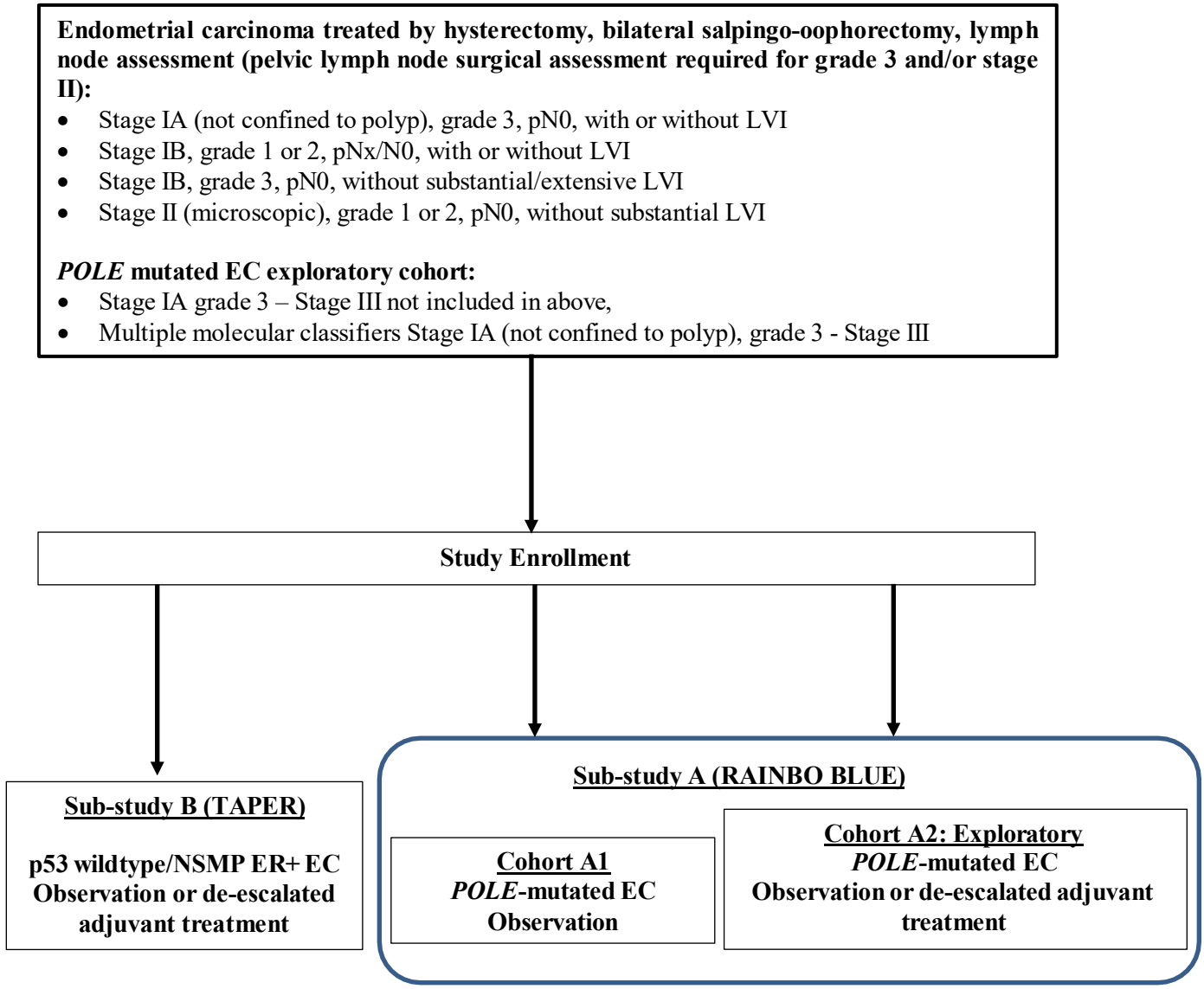
TREATMENT SCHEMA

This protocol tests de-escalated adjuvant treatment in patients with *POLE*-mutated or p53wt/NSMP (p53 wildtype/no specific molecular profile) early-stage endometrial cancer (EC). Patients may be enrolled to one of two sub-studies (EN10.A/RAINBO BLUE or EN10.B/TAPER) as shown below:



N = 120 *POLE*-mutated (Sub-study A, Cohort A1)
180 p53 wildtype/NSMP (Sub-study B)
~25 *POLE*-mutated exploratory cohort (Sub-study A, Cohort A2)

4.0 STUDY POPULATION

This is a multi-centre, molecularly driven study of de-escalated adjuvant treatment in patients with *POLE*-mutated or p53wt/NSMP early-stage endometrial cancer (EC). Patients may be enrolled to one of two sub-studies EN.10A (RAINBO BLUE *POLE*-mutated) or EN.10B (TAPER p53wt/NSMP). Sub-study A includes two cohorts, A1 and A2. Sub-study A cohort A1 and sub-study B further group patients based on disease stage and treatment (see Section 7 and the sub-study specific sections at the end of the protocol).

A patient must pass both the general (Section 4.1 below) and additional sub-study specific eligibility criteria to be enrolled to an appropriate treatment group. The sub-study specific additional criteria are described in the sub-study sections at the end of this protocol.

4.1 Eligibility Criteria

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy and to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar disease(s).

These eligibility criteria are expected to be followed. Any proposed variance must be discussed with CCTG prior to patient enrollment:

4.1.1 Patients must have had surgery consisting of hysterectomy (total abdominal, laparoscopic or robotic-assisted) and bilateral salpingo-oophorectomy. Lymph node dissection can be performed as per institutional standards (sentinel or full lymphadenectomy). There must be no macroscopic residual disease after surgery.

4.1.2 Patients must have histologically confirmed Stage I to III endometrial carcinoma which can be endometrioid, serous, clear cell, un/dedifferentiated, carcinosarcoma or mixed.

4.1.3 Patients' Eastern Cooperative Group (ECOG) performance status must be 0, 1, or 2.

4.1.4 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

4.1.5 Patients' age must be ≥ 18 years.

4.1.6 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrollment 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.

4.1.7 Patient is able (i.e. sufficiently fluent) and willing to complete the patient reported outcomes (PRO) questionnaires in either English, French or a validated language. The baseline assessment must be completed within required timelines, prior to enrollment. 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.

4.1.8 Patients must be accessible for treatment and follow-up. Patients enrolled on this trial must be treated and followed at the participating centre. This implies there must be reasonable geographical limits placed on patients being considered for this trial. The patient's city of residence may be required to verify their geographical proximity. (Call the CCTG office (613-533-6430) if questions arise regarding the interpretation of this criterion.) Investigators must assure themselves the patients enrolled on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

Patients must agree to return to their primary care facility for any adverse events which may occur through the course of the trial.

4.1.9 Protocol treatment is to begin within 10 weeks of hysterectomy/bilateral salpingo-oophorectomy.

4.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

4.2.1 Prior Neoadjuvant chemotherapy for current endometrial cancer diagnosis.

4.2.2 Prior pelvic radiation.

4.2.3 Patients with a history of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for $\geq$ 5 years.

4.2.4 Clinical evidence of distant metastasis as determined by pre-surgical or post-surgical imaging (CT scan of chest, abdomen and pelvis or whole-body PET-CT scan) (see the radiology timeline outlined in Section 5).