A Phase III, Randomized, Double blind, Placebo controlled, Multi centre, Global Study of Volrustomig in Women with High Risk Locally Advanced Cervical Cancer Who Have Not Progressed Following Platinum based, Concurrent Chemoradiation Therapy (eVOLVE-Cervical)

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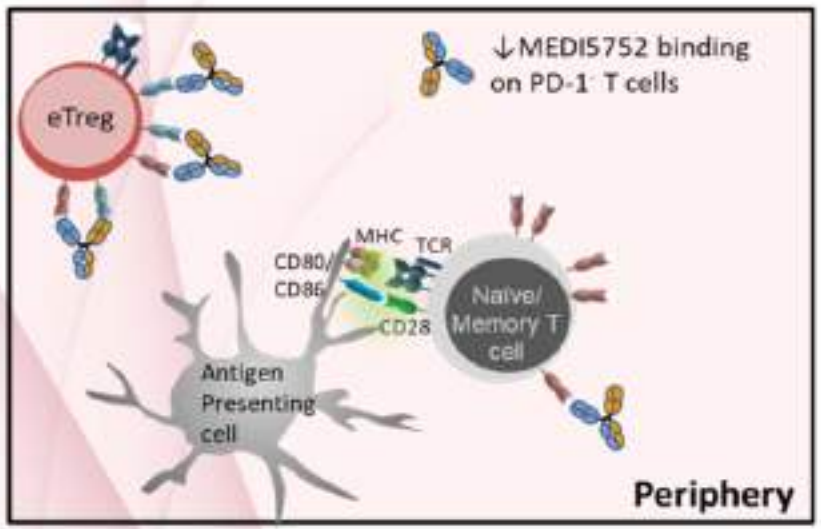
Geographical Distribution

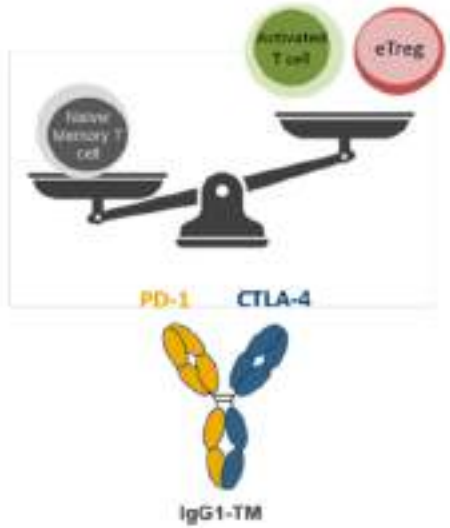
eVOLVE cervical

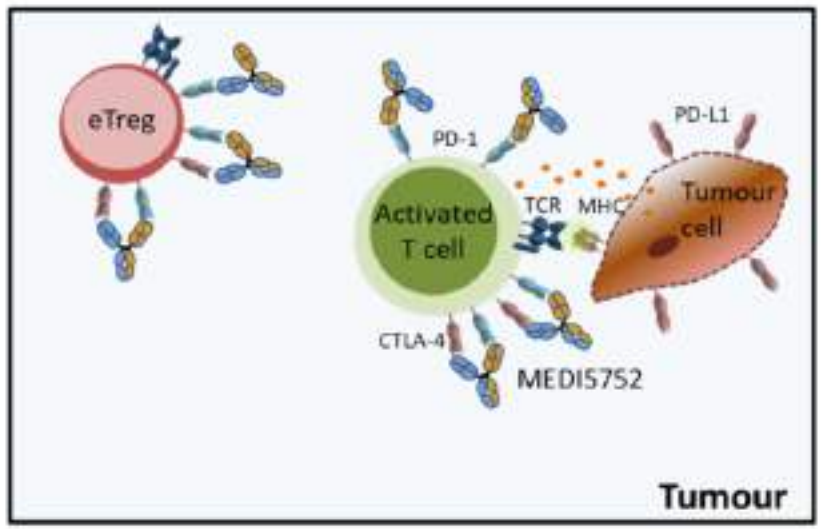
18 Countries / Regions, around 200 sites, 1000 randomized subjects

Volrustomig (MEDI5752) is designed to enhance CTLA-4 blockade on PD-1+ activated T cells

eVOLVE cervical







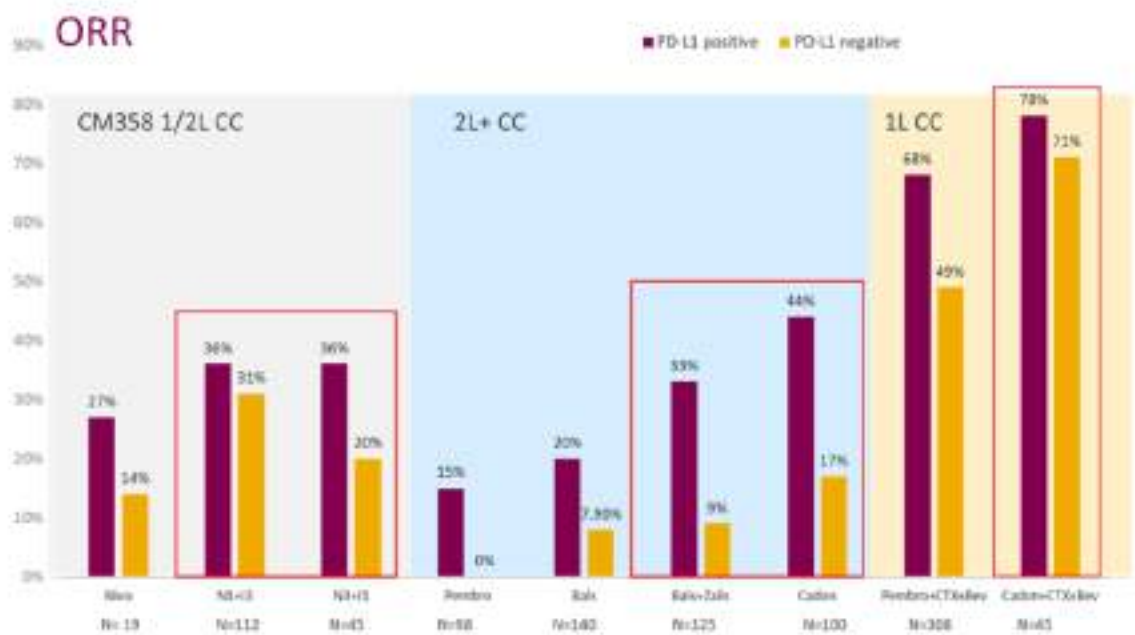
Volrustomig uses **PD-1** as an anchor to direct **CTLA-4 blockade** to **activated PD1+ T cells**

Volrustomig builds on CTLA-4 sensitivity in cervical cancer

eVOLVE cervical

- **Cervical cancer is an immunosensitive tumor** with anti-PDx monotherapy approved in 1L/2L recurrent or metastatic cervical cancer, but efficacy is limited to PD-L1 positive population[1,2]

- **With addition of anti-CTLA-4 to anti-PDx, response rates was higher** in PD-L1 positive population and an uplift in PD-L1 negative population in 1L/2L recurrent or metastatic cervical cancer[3,4,5,6]



1 Chung et al 2019 JCO, 2 N. Colombo et al 2021 NEJM, 3 Oaknin et al ESMO 2022, 4 O'Malley et al 2020 ESMO 5 Wu et al 2022 SGO; 6 Wang et al 2022 ASCO.

Patient Population

eVOLVE cervical

Newly diagnosed FIGO 2018 IIIC-IVA cervical cancer

LN Involvement

PS 0-1

Available tumor samples collection (retrospective PD-L1 testing)

Before Randomization- completed SOC CCRT (concurrent cisplatin + EBRT + brachytherapy) and must not have progressed following CCRT

No evidence of metastatic disease (M0)

Study design – eVOLVE-Cervical

eVOLVE cervical

Screening period FIGO 2018 IIIC-IVA cervical cancer (LN involvement)	Randomization	Treatment period	Follow-up

Part I: **Diagnosis (Day-154) to Day-1**

Patient consenting process step 1:

- Tumor sample submission and analysis
  - PD-L1 expression by VENTANA PD-L1 (SP263) Assay
- **Initial staging procedures** completed prior to any component of definitive treatment

Part II: **Day -56 to -1**

Patient consenting process step 2:

- After completion of SOC CCRT (≥4 cycles)
- No progression after SOC CCRT
- Grade > 1 toxicities resolved prior to randomization
- ECOG 0 or 1

Max **56** days after the end of CCRT

N=1000

R 1:1

Arm A

Volrustomig 750mg IV Q3W for 24 months

Arm B

Placebo IV Q3W for 24 months

Stratification factors

- PD-L1 expression (PD-L1 high expression vs. low/negative)
- **FIGO stage (IIIC1 vs. IIIC2 vs. IVA) – to be entered by the site staff during randomization transaction in IRT.**
- Region (Asia vs. non-Asia)

Primary Endpoint:

- PFS in PD-L1 high population (Inv)

Key Secondary Endpoint:

- PFS in ITT (Inv)
- OS in PD-L1 high population/ITT

PFS (BICR) - sensitivity analysis

Key Inclusion Criteria for Screening Part I

eVOLVE cervical

- Participant must be ≥ 15 years at the time of screening.

  Note: Participants < 18 years of age: Physical changes should be aligned with Tanner stage III.
- Participants must have histologically confirmed **cervical adenocarcinoma**, **cervical squamous carcinoma**, or **cervical adenosquamous carcinoma** and the following requirements:
  - Participants must have histologically documented **FIGO 2018 Stage IIIC to IVA** cervical cancer **(CSP Appendix G)**; only participants **with lymph node involvement** will be included.
  - Nodal involvement confirmation may be either histological (eg, biopsy) or by imaging (PET-CT, CT or MRI) with pathological lymph node size defined by a short axis diameter of ≥ 10 mm (axial plane).
  - No evidence of metastatic disease (M0).
- Initial staging procedures performed prior to initiation of any component of definitive treatment (CCRT) should include:
  - Pelvic MRI (preferred) or CT with IV contrast.
  - Chest and abdomen CT (preferred) or MRI with IV contrast.
  - PET CT is recommended in addition but not mandatory.
  - Brain MRI (preferred) or CT with IV contrast only if symptomatic.
  - The above scans for initial staging procedures must have been performed no more than 42 days prior to the first dose of CCRT.
- **Provision of FFPE tumor sample** to assess the PD-L1 expression as determined by a central laboratory using the VENTANA PD-L1 (SP263) Assay prior to randomization. Patients with unknown PD-L1 expression are not eligible for study: Tumor sample requirements as follows: FFPE sample must be collected less than 3 months prior to CCRT.

Key Inclusion Criteria for Screening Part II

eVOLVE cervical

- Participants must have completed **concurrent chemoradiotherapy** as defined below:
  a. Completed within 1 to **56 days** prior to randomization.
  b. Received **weekly cisplatin 40 mg/m²** for 5 to 6 cycles as concurrent chemotherapy with radiation therapy. If participants cannot tolerate toxicity, must have received **at least 4 cycles of cisplatin**.
  c. The last dose of cisplatin must be administered prior to, or concurrently with, the final dose of radiation. Consolidation chemotherapy after radiation is not permitted.
  d. Received EBRT and brachytherapy as part of the chemoradiation therapy, and brachytherapy can only be omitted if there is a medical contraindication. Prescription doses of radiotherapy are requested as below:
     (i) A total dose of **≥ 45 Gy for EBRT to the pelvis**
     (ii) If brachytherapy is used, normal tissues should be limited **with 2 cc rectal dose ≤ 75 Gy, sigmoid 2 cc dose ≤ 75 Gy, and 2 cc bladder dose ≤ 90 Gy**.
  e. It is strongly preferred that participants complete CCRT within 8 weeks.

- Participants **must not have progressed following CCRT** as demonstrated by the following imaging studies performed after completion of CCRT:
  - RECIST 1.1 imaging of the chest/abdomen by CT (preferred) or MRI with IV contrast, pelvic MRI (preferred) or CT with IV contrast.
  - **The participants with persistent disease must not be amenable to other available therapies with curative intent after definitive CCRT, consistent with local treatment guideline based on individualized benefit risk assessments by the Investigator.**

Key Exclusion Criteria

eVOLVE cervical

- Diagnosis of **small cell (neuroendocrine)** or **mucinous adenocarcinoma** of cervical cancer (ie, mucinous NOS, intestinal type, signet ring cell type, invasive stratified mucin-producing carcinoma and gastric type) based on **2020 WHO classification** of cervical cancer.
- Evidence of metastatic disease (including metastasis to inguinal lymph nodes, intraperitoneal disease, lung liver, or bone; excluding metastasis to pelvic or paraaortic lymph nodes or vagina) prior to CCRT
- Unresolved toxicities from previous CCRT, defined as toxicities not yet resolved due to NCI CTCAE 5.0 Grade ≤ 1 or baseline. Participants with irreversible toxicity that is not reasonably expected to be exacerbated by the study intervention in the opinion of the Investigator may be included (e.g., hearing loss, alopecia and NCI CTCAE 5.0 Grade 2 peripheral neuropathy).
- Active or prior documented autoimmune or inflammatory disorders including inflammatory bowel disease (eg, colitis or Crohn's disease), diverticulitis (with the exception of diverticulosis), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis), Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, pneumonitis (past medical history of ILD, drug induced ILD, or radiation pneumonitis requiring steroid treatment, or any evidence of clinically active ILD), etc.

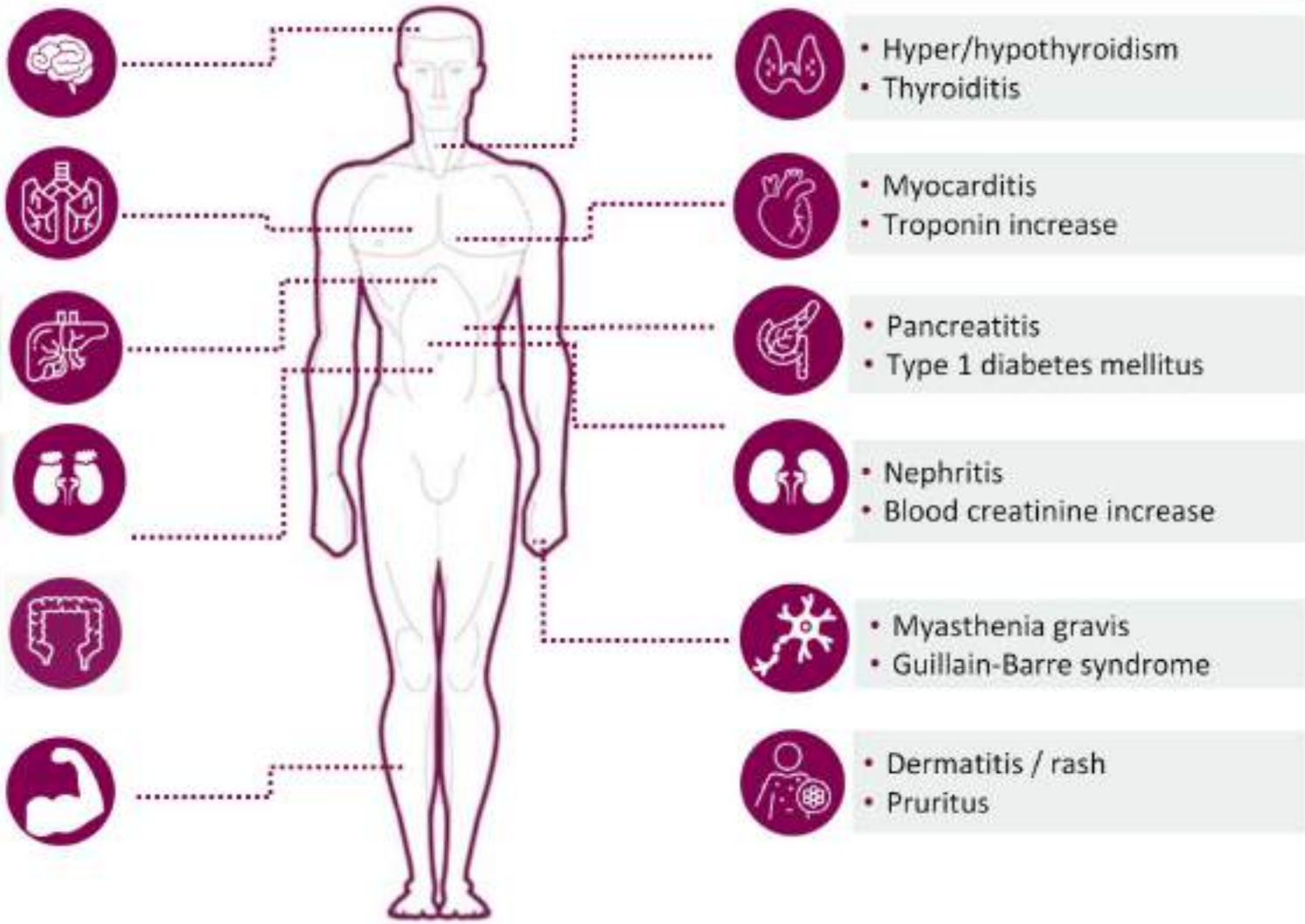
Key Exclusion Criteria

eVOLVE cervical

- Current or prior use of immunosuppressive medication within 14 days before the first dose of the study intervention is excluded
- Patients who have undergone a previous hysterectomy, including a supracervical hysterectomy, or will have a hysterectomy as part of their initial cervical cancer therapy.
- **Any prior (besides prior CCRT) or concurrent treatment for cervical cancer**. Concurrent use of hormonal therapy for noncancer related conditions (eg, insulin for diabetes and HRT) is acceptable.
- **Exposure to immune mediated therapy** prior to the study for any indication including, but not limited to, other anti- CTLA-4, anti-PD-1, and anti-PD-L1 antibodies, or therapeutic anti-cancer vaccines.

Immune-Mediated Adverse Events (imAEs)

eVOLVE cervical



Key Study Assessments

eVOLVE cervical

Before CCRT

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- PET-CT is recommended in addition but not mandatory.
- Brain MRI (preferred) or CT with IV contrast only if symptomatic.
- The above scans for initial staging procedures must have been performed up to 42 days prior to the first dose of CCRT.

Screening

- **Part I:Tumour FFPE blocks and/or slides** for PD-L1 central testing for stratification and primary endpoint purpose
- **Part II: Tumour scan** post CCRT within 56-day before randomization: chest, abdomen and pelvic CT/MRI, PET-CT (if needed)
- Vital signs, demographics, physical exam, ECOG PS, medical history, ECG, ECHO/MUGA
- **Safety** laboratory parameters

Treatment Period

- Dispensation of IP (Q3w)
- Safety lab parameters
- ECOG PS, vital signs
- ECG
- Targeted physical exam
- Chest, abdomen and pelvic CT/MRI, PET-CT (if needed)
- Adverse event
- Concomitant medication
- ePRO
- PK and immunogenicity assessments

Post Treatment

Treatment discontinuation visit, 30-day and 90-day safety follow-up

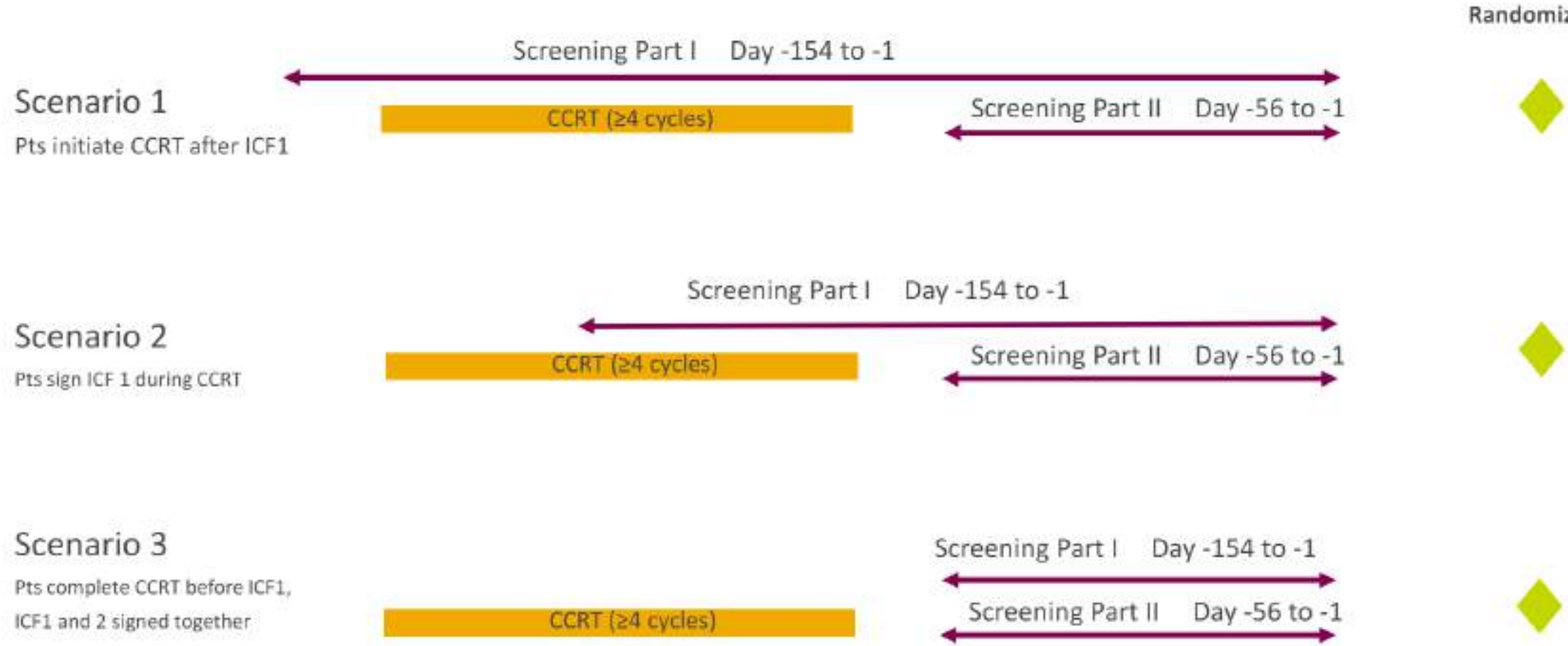
- AE, ECG, targeted physical exam, vital signs, ECOG PS
- Safety lab parameters
- Adverse event follow-up
- ePRO

Survival follow-up (every 12 weeks)

- PFS2
- Subsequent anticancer therapy
- Survival status

Screening Period – 3 scenarios

eVOLVE cervical



Grazie per l'attenzione

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