Hormonal receptor (HR)-positive HER2-negative breast cancer patients treated with preoperative ELacestrant and PULSAR adaptive radiotherapy: a proof-of-concept phase I-II study (HELP Trial)

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Background and rationale

Chemotherapy-based neoadjuvant treatment in HR-positive (HR+), HER2-negative (HER2-) breast cancer (BC) patients is related to lowest pathologic complete response (pCR) rate among all subtypes[1,2]. However, pCR rates after endocrine therapy are even lower.

Elacestrant, an oral selective estrogen receptor degrader (SERD), has recently demonstrated its efficacy in the metastatic setting[3].

The use of preoperative radiation therapy (RT) has been questioned due a potential immunosuppressive effect that may be detrimental for tumor control.

This potential negative aspect may be circumvented by the introduction of **Personalized Ultrafractionated Stereotactic Adaptive Radiotherapy (PULSAR)**, a novel concept with each fraction administrated at least 10-20 days apart from the other, resulting in excellent tolerability and may help to modulate tumor immunity [4].

ELIPSE was a window of opportunity trial evaluating the effect of 4 weeks of Elacestrant in postmenopausal women with HR+ HER2- BC amenable to surgery. It significantly reduced Ki67 expression and was associated with a shift towards a more endocrine sensitive and less proliferative phenotype, higher levels of tumor infiltrating lymphocytes (TILs) and expression of immuneresponse genes [5].

The combination with PULSAR can thus potentially lead to an enhanced immune response, and this may support the exploration of reduced elective nodal RT.

Trial design

This is a **proof-of-concept phase I-II trial to assess the safety (as primary endpoint)** and clinical efficacy of neoadjuvant therapy with Elacestrant and PULSAR **(Figure 1).** Secondary endpoints are nodal pathologic complete response ([n]pCR) rate and breast pCR rate, overall survival (OS) and invasive disease-free survival (iDFS) at 12 months.

An exploratory analysis will be performed including metabolomic and transcriptomic assessment and the evaluation of the immune environment on tissue samples before (diagnostic biopsy) and after treatment (surgical specimen), as well as ctDNA analysis on blood samples collected at baseline, at 12 weeks and at the end of preoperative treatment.

The study will enroll 21 postmenopausal patients with early HR+ HER2- node positive BC, clinically staged II-III. A **safety run in phase** will be conducted on the first 10 patients enrolled.

Mirroring the EMERALD trial to maintain pharmacologic continuity between settings, patients will receive Elacestrant 345 mg orally once daily for 20 weeks and PULSAR on the MRI based breast gross tumor volume (GTVt), consisting of 10 Gy “pulses” every 4 weeks for a maximum of 5 or less in case of radiologic complete response evaluated by breast MRI monthly

Surgery will be planned within 6 weeks from the last Elacestrant administration. Patients will then receive adjuvant systemic therapy as per standard of care and postoperative RT to the locoregional lymph nodes in case of nodal residual disease, if indicated.

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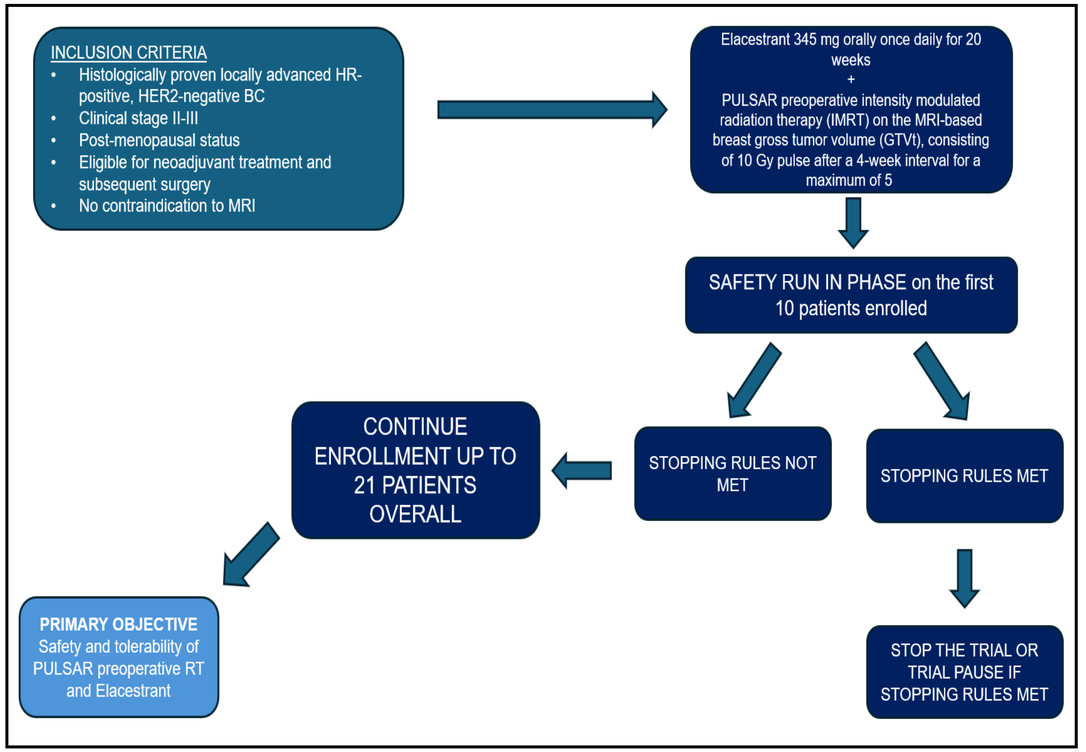


Figure 1. HELP trial design and flow chart

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