LESS: Single-arm study to de-escalate adjuvant endocrine therapy duration in post-menopausal women with HR+ HER2- breast cancer at very low risk of metastasis

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Abstract ID: TPS615 (398984)

BACKGROUND

Adjuvant Endocrine Therapy (AET) is the cornerstone treatment of localized hormone-receptor positive (HR+) breast cancer, with demonstrated benefits on overall survival (30-40% relative decrease in mortality) but also on the risk of local and contralateral relapse (43-50% relative decrease).

While the relative benefit of 5 years of ET is identical for small tumors as compared to larger ones, the absolute benefit is much lower, and the risk-benefit ratio becomes questionable given the frequent and impactful side effects of ET which are associated with non-adherence.

If recent trials tested longer durations as compared to 5 years for high-risk cancers, older trials have tested shorter durations. Five years appeared at that time as the gold standard because of optimal benefit-risk ratios of tamoxifen among rather high-risk patients. However, **shorter treatments of 2-3 years** were already associated with **substantial benefits.**

→ The purpose of this study is to demonstrate that **AET limited to 2 years** of aromatase inhibitor (AI) in postmenopausal women at very low risk of recurrence as determined with a MammaPrint/BluePrint Ultra Low Risk test result can ensure very high survival without metastatic relapse and allows a **reduction of side effects and a better quality of life.**

POPULATION

MAIN INCLUSION CRITERIA

1. **Postmenopausal women**
2. ECOG performance status 0-1
3. Women with histologically proven invasive unilateral breast cancer (BC)
4. M0
5. Primary tumor completely resected and adequate axillary surgery performed according to current standards
6. HR positive (≥50%)
7. HER2 negative
8. No indication of adjuvant chemotherapy
9. Patient considered has having a Luminal A UltraLow risk of metastatic recurrence (i.e. less than 5% risk of metastatic relapse at 10 years) according to MammaPrint® and BluePrint® tests.

Note 1: MammaPrint test is indicated for patients with **pT1c-2, pN0/pN1mic and grade 2.**

Note 2: Up to 80 patients aged ≥ 65 years with: **pT1 (tumor ≤ 20 mm), pN0, grade 1 and Ki67 ≤10%** will be recruited

Note 3: To be eligible, MammaPrint index score should be > +0.355

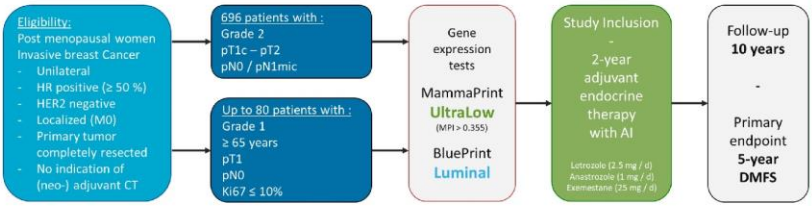
10. Patients eligible to receive or have recently started (with a maximum of 4 months) an adjuvant ET(letrozole, anastrozole, or exemestane)

MAIN EXCLUSION CRITERIA

1. Patients who received a neo-adjuvant ET, a neo-adjuvant or adjuvant CT or preoperative medical treatment
2. Any local or regional recurrence or metastatic disease
3. Non-invasive carcinoma
4. Bilateral breast cancer (except in case of contralateral DCIS), or history of other invasive ipsi- or contralateral breast cancer
5. Patients with a history of another malignancy without complete remission for more than 5 years
6. Women with high-risk BC predisposing deleterious germline mutations

DESIGN

LESS is a prospective, national, multicenter, single arm, interventional, non threshold crossing phase II study evaluating a therapeutic de-escalation that limits adjuvant ET to 2 years of Aromatase inhibitors



Legend: AI, Aromatase Inhibitors; CT, Chemotherapy; DMFS, Distant Metastasis Free Survival; ET, Endocrine Therapy; HR, Hormone Receptor; MPI: MammaPrint Index.

→ Genomic expression tests have been developed to better predict clinical outcome and to determine whether a patient does not benefit from chemotherapy and may safely de-escalate this treatment. MammaPrint® is a 70-gene prognostic test that, along with other clinicopathologic factors, determines a specific patient's breast cancer recurrence risk.

STUDY OBJECTIVES

PRIMARY OBJECTIVE:

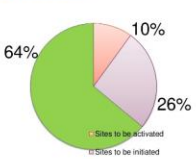
To prospectively demonstrate that an adjuvant aromatase inhibitor therapy duration limited to 2 years is associated with high **distant metastasis-free survival (DMFS) at 5 years** in a selected population with invasive breast cancer at low risk of metastatic recurrence

SECONDARY OBJECTIVES:

- Evaluate Invasive Disease-Free Survival (iDFS)
- Evaluate Invasive breast cancer-free survival (iBCFS)
- Evaluate breast cancer specific survival (BCSS)
- Evaluate overall survival (OS)
- Assess quality of life (QoL) at baseline and every year until 5 years after the start of the study in term of general QoL, fatigue, psychological, geriatric characteristics (in patients aged ≥ 75years) and cognitive functions
- Compare the survival and QoL endpoints with the breast cancer patients in the CANTO cohort who took 5 years of hormonal treatment
- Evaluate the safety of the treatment in the study population

PARTICIPATING SITES

50 French sites:



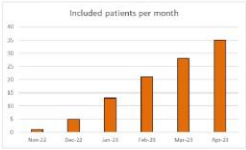
STUDY STATUS:

As of May 1, 2023, a total of 35 patients have been enrolled

- 15 in Grade 1 Cohort
- 20 in Grade 2 Cohort

First patient included in Nov. 2022

696 patients to be Included by Nov. 2025



STATISTICS

The null hypothesis that, in the study population after 2 years of adjuvant aromatase inhibitor, distant metastasis–free survival (DMFS) at 5 years is lower or equal to 94.5% will be tested against the alternative - that it is above 94.5%.

For an expected DMFS of 96.7% under the alternative hypothesis, a total of 37 DMFS evens are required in order to provide approximately 85% power at a one-sided significance level of 0.05 to reject the null hypothesis using a logrank test. For an estimated 2 years inclusion and 5 years follow-up, 696 ultralow risk patients are required.

For the QoL and cognition sub study we will primarily study physical (EORTC QLQ-C30, EORTC QLQ-BR23/45), psychological (IOCv2, HADS Anxiety and HADS Depression), neuropsychological impact (FACT-Cog), fatigue (EORTC QLQ-FA12) and G-CODE questionnaire (in patients aged >=75years) at baseline and subsequent years up to 5 years.

For the comparison with synthetic/historical control data from CANTO, inverse probability weighting techniques on a propensity score in a Cox model or in a mixed model will be used.

ACKNOWLEDGEMENTS

- Patients
- Agendia for funding
- The 50 French participating sites

CONTACTS

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ClinicalTrial.gov:
NCT05297617

QR Code : Less synopsis