MiRaDor: A proof-of-concept study of treatment efficacy by monitoring Minimal Residual Disease (MRD) using circulating tumor DNA (ctDNA) in hormone receptor-positive/HER2-negative (HR[+]/HER2[-]) early breast cancer (EBC)

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BACKGROUND

- Liquid biopsy methods based on analysis of ctDNA represent an alternative to invasive tumor biopsy procedures [1]
- ctDNA can be detected in plasma of patients with advanced cancers and can be used to track disease progression [2]
- MRD is the small number of tumor cells that remain in the bloodstream during and after treatment and has been used as a prognostic biomarker in hematological malignancies [3]
- Subsequently, MRD has also been associated with increased risk of recurrence in patients with solid tumors, including breast cancer [4]
- Because MRD through ctDNA detection is associated with high risk of future relapse, it could potentially allow for physicians to start new/additional treatments earlier based on molecular relapse and before incurable symptomatic metastatic disease develops [5]

TRIAL DESIGN

- MiRaDor (NCT05708235) is a multicenter, open-label, non-comparative, phase II trial aiming to evaluate treatment efficacy by monitoring MRD using ctDNA in high-risk, HR[+]/HER2[-] EBC
- Analysis will be exploratory without hypothesis testing, based on 95% Clopper-Pearson confidence intervals
- ctDNA will be analyzed with the FoundationOne® Tracker
- Screening 1,260 patients will provide a precision rate of 3.2% of patients with ctDNA detected and 10 patients per arm will provide a precision rate of 30% of patients with 90% decrease in ctDNA after 3 months
- An overview of the trial design is shown in **Figure 1** and efficacy assessments are shown in **Figure 2**

STUDY ENPOINTS

- The **primary endpoint** is the proportion of patients with at least a 90% decrease or clearance in baseline ctDNA at 3 months after randomization
- **Secondary endpoints** include: (1) Total ctDNA detection and breakdown; (2) Proportion of patients with at least 90% decrease in baseline ctDNA at 3 months and maintained at 6, 9, and 12 months, (3) Proportion of patients with 50% and 70% decrease in baseline ctDNA at 3, 6, 9, and 12 months; (4) Time to first ctDNA increase; (5) Duration of at least a 90% decrease in baseline ctDNA; (6) Best percentage of ctDNA decrease at 3, 6, 9, and 12 months; (7) Safety and toxicity profile
- **Exploratory endpoints** include: (1) Time from initiation of study treatment to invasive local/regional recurrence or distant recurrence or death of any cause, (2) Biomarker association with clinical outcomes, (3) Validation of FoundationOne® Tracker

STUDY DESIGN

Figure 1. MiRaDor Trial Design

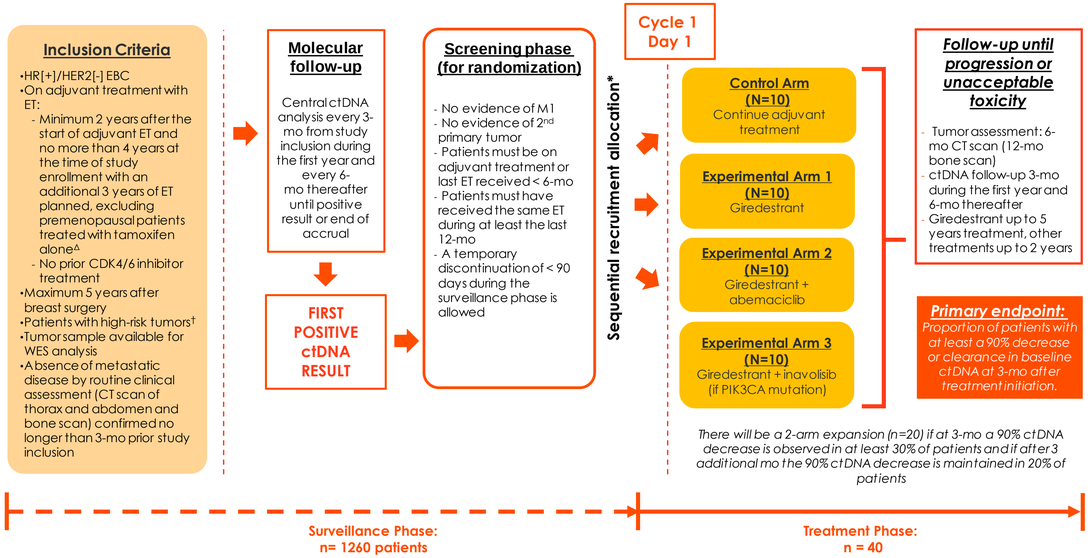
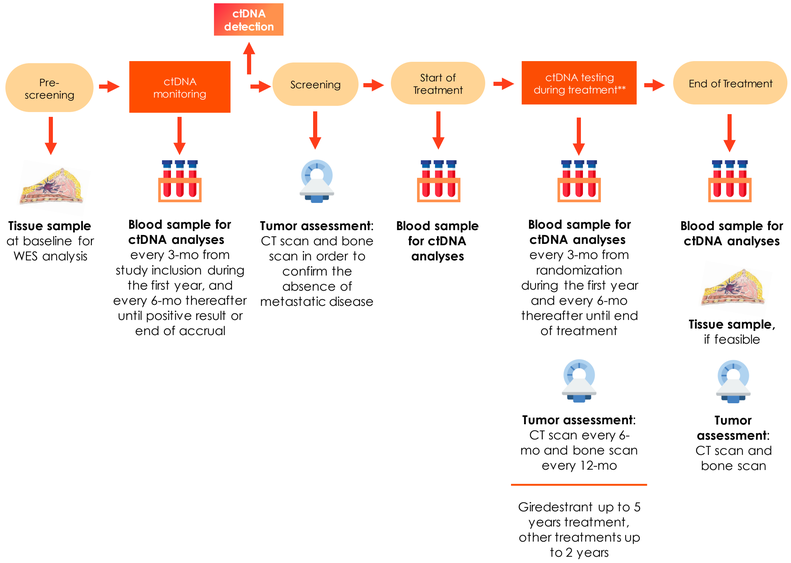


Figure 2. MiRaDor Efficacy Assessments



^ΔLHRH agonist will be maintained after randomization in men and peri- and pre-menopausal women.
†If no previous neoadjuvant chemotherapy: pN2/N3, or pN1 if: pT3/T4, and/or pN1 and high genomic risk (Mammaprint®, Oncotype®, or similar), and/or pN1, with histological grade II/III and Ki67>20%;
If previous chemotherapy, must have significant residual invasive disease defined by one of the following: residual invasive disease in the breast ypT3 or ypT4 and/or any macroscopic, ≥ 2mm, lymph node involvement regardless of primary tumor site involvement (includes no residual disease in the breast)
*Treatment allocation will vary depending on *PI3KCA* status, which will be assessed to all patients during screening. If positive, patients could be allocated in any arm. In case of negativity, patient could be allocated in any arm, except for arm 3.
** In addition to blood samples collected for periodic ctDNA analyses, blood samples will also be collected at C1D15 and at D1 of each subsequent cycle.

CDK4/6: cyclin-dependent kinase 4/6; **CT scan**: computed tomography scan; **ctDNA**: circulating tumor DNA; **EBC:** early breast cancer; **ET**: Endocrine therapy; **HR[+]/HER2[-]:** hormone receptor positive/HER2-negative **LHRH**: Luteinizing hormone-releasing hormone; **mo:** months; **WES:** whole-exome sequencing

AUTHOR DISCLOSURE

Antonio Llombart-Cussac Disclosure:

Consulting/Advisor: Roche, AstraZeneca, Seagen, Daiichi Sankyo, Eli Lily, Merck Sharp&Dohme, GSK, Gilead, Menarini, Exact Sciences, Novartis, Pfizer, Gilead; **Honararia**: Roche, Novartis, Pfizer, Lilly, Daiichi Sankyo; **Research funding to the Institution**: Roche, AstraZeneca, Eisai, F. Hoffman-La Roche, Guardant Health, Merck Sharp&Dohme, Pfizer, Piqur Therapeutics, Puma C, Queen Mary University London; **Stock**: Initia Research; **Travel, accomodations, expenses**: Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, AstraZeneca, Gilead; **Patents**: HER2 as a predictor of response to dual HER2 blockade in the absense of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/0338368 A1

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Scan here to view a plain language summary of this trial.