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)

*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.

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

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BIBLIOGRAPHY

** 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.

AUTHOR DISCLOSURE

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Antonio Llombart-Cussac Disclosure:

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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, noncomparative, 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 Cycle 1 Day 1 Follow-up until **Molecular** Screening phase **Inclusion Criteria** progression or (for randomization) follow-up ctDNA •HR[+]/HER2[-] EBC unacceptable **Control Arm** screening On adjuvant treatment with toxicity CentralctDNA No evidence of M1 Continue adjuvant analysis every 3-- Minimum 2 years after the No evidence of 2nd treatment mo from study Tumor assessment: 6start of adjuvant ET and primary tumor inclusion during mo CT scan (12-mo no more than 4 years at Patients must be on the first year and bone scan) the time of study adjuvant treatment or ctDNA follow-up 3-mo Experimental Arm 1 every 6enrollment with an last ET received < 6-mo mo thereafter during the first year and additional 3 years of ET Patients must have until positive 6-mothereafter planned, excluding Giredestrant received the same ET Blood sample for Blood sample for Tissue sample **Blood sample** Blood sample for Tumor assessment: result or end of Giredestrant up to 5 premenopausal patients during at least the last ctDNA analyses ctDNA analyses for ctDNA ctDNA analyses at baseline for CT scan and bone years treatment, other treated with tamoxifen accrual every 3-mo from WES analysis every 3-mo from scan in order to treatments up to 2 years **Experimental Arm 2** A temporary randomization study inclusion during confirm the No prior CDK4/6 inhibitor discontinuation of < 90 during the first year the first year, and absence of treatment days during the Giredestrant + every 6-mo thereafter metastatic disease and every 6-mo Maximum 5 years after surveillance phase is abemaciclib thereafter until end until positive result or breast surgery Primary endpoint: **FIRST** allowed Tissue sample of treatment Patients with high-risk tumors end of accrual roportion of patients wi **POSITIVE** if feasible Tumor sample available for **Experimental Arm 3** at least a 90% decrease **ctDNA** WES analysis or clearance in baselin (N=10) Absence of metastatic **RESULT** ctDNA at 3-mo after Giredestrant + inavolisib disease by routine clinical treatment initiation. (if PIK3CA mutation) assessment (CT scan of thorax and abdomen and bone scan) confirmed no CT scan every 6assessment There will be a 2-arm expansion (n=20) if at 3-mo a 90% ctDNA longer than 3-mo prior study CT scan and mo and bone scan decrease is observed in at least 30% of patients and if after 3 inclusion every 12-mo bone scan additional mothe 90% ctDNA decrease is maintained in 20% of patients Giredestrant up to 5 years treatment other treatments up **Treatment Phase:** Surveillance Phase: to 2 years n= 1260 patients n = 40^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, ≥ 2 mm, lymph node involvement regardless of primary tumor site involvement (includes no residual disease in the breast)

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