START: A randomized phase II study in patients with triple negative, androgen receptor positive locally recurrent (unresectable) or metastatic breast cancer treated with darolutamide or capecitabine (UCBG-306)

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Background

- Up to 36% of triple-negative breast cancer (TNBC) are androgen receptor (AR)-positive (≥ 10% by IHC).
- Several clinical trials assessing antagonists of the AR or androgen synthesis suppressor showed promising clinical benefit rates (CBR) in the metastatic setting.
- Darolutamide is a novel, effective and well tolerated AR antagonist tested in prostate cancer clinical trials. Thus we aim to assess clinical activity and safety of darolutamide in AR-positive TNBC.

Main Inclusion Criteria

1) Histologically confirmed locally recurrent (unresectable) or metastatic breast cancer ;
2) Triple-negative breast cancer:

   Estrogen receptor (ER)-negative and Progesterone receptor (PgR)-negative by IHC; HER2 negative status confirmed centrally before inclusion with FFPE tissue from the primary tumour ;

3) Androgen receptor (AR)-positive, as defined centrally by a ≥ 10% by IHC ;
4) Patients chemotherapy naïve or have received a maximum of one line of chemotherapy for advanced disease ;
5) Presence of measurable or evaluable disease according to RECIST v1.1.

Main Exclusion Criteria

1) HER2-positive status (positivity defined as IHC3+ and/or FISH amplification >2) ;
2) Other concurrent malignancies ;
3) Active brain metastases or leptomeningeal disease ;
4) Previous treatment with: capecitabine, first generation (bicalutamide) or second–generation ;
5) Previous treatment with AR inhibitors (enzalutamide, ARN–509, darolutamide) or other investigational AR inhibitors CYP17 enzyme inhibitor such as abiraterone …

Methodology

This is an open-label, multicenter, randomized, two-arm non-comparative phase II trial (NCT03383679). Women with locally recurrent (unresectable) or metastatic and centrally confirmed AR-positive TNBC are eligible. Patients should be chemotherapy naïve or have received a maximum of one line of chemotherapy for advanced disease. Eligible patients are randomized (2:1) between darolutamide experimental arm (600 mg twice daily) and capecitabine control arm (according to each center policy, minimum 1000 mg/m2 twice daily, 2 weeks on and 1 week off). Randomization (minimization) is stratified by number of previous lines of chemotherapy (0 versus 1). Tumour biopsies and sequential circulating tumour DNA are collected as part of a translational research program. A total of 90 patients will be randomized.

Objectives

PRIMARY OBJECTIVES:

Primary objective:

To evaluate the antitumour activity of darolutamide or capecitabine in each arm among patients with triple-negative androgen receptor positive advanced/metastatic breast cancer, as measured by the clinical benefit rate at 16 weeks.

SECONDARY OBJECTIVES:

Efficacy :

- Clinical benefit rate at 24 weeks: CR, PR or SD at 24 weeks
- Objective response rate (ORR) at 16 and 24 weeks
- Duration of overall response (DoR) at 16 and 24 weeks
- Overall survival (OS) at 1 and 2 years
- Progression-free survival (PFS) at 1 and 2 years

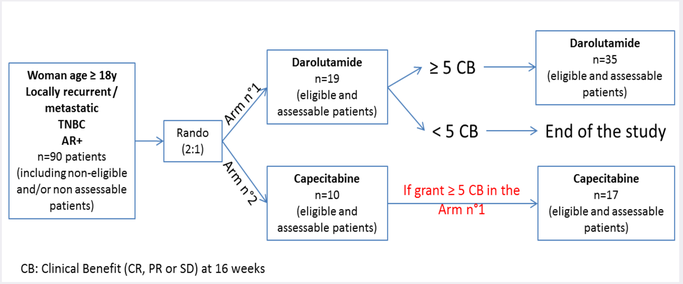
Safety :

- Tolerance and safety

Translational research program :

- Identification of predictive factors of resistance or sensitivity to the treatment.
- ctDNA evaluation
- Pharmacokinetic analysis
- Additional analyses not listed above could be planned

Trial Overview



CB: Clinical Benefit (CR, PR or SD) at 16 weeks

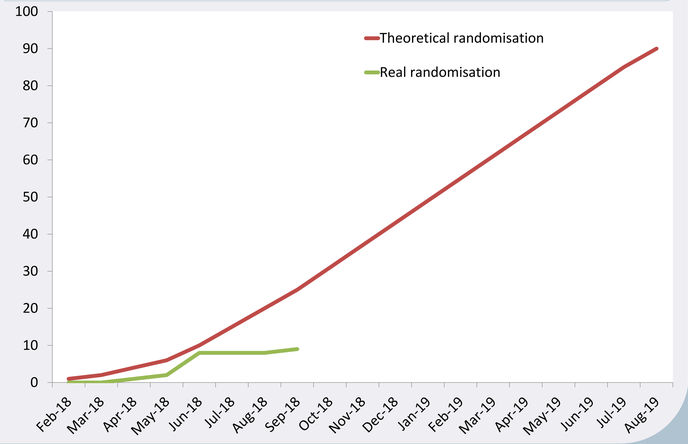
Randomization with a ratio 2:1 in favour of the Darolutamide arm

Stratification : Number of previous chemotherapy line (1 versus 0)

Darolutamide

Darolutamide is a novel AR antagonist with a unique chemistry. It is a full and high-affinity AR antagonist that, similar to second-generation antiandrogens enzalutamide and ARN-509, inhibits testosterone-induced nuclear translocation of AR. Importantly, darolutamide also blocks the tested mutant ARs activity in response to antiandrogen therapies, including the F876L mutation that confers resistance to enzalutamide and ARN-509. Results from a phase I-II trial in patients with progressive metastatic castration-resistant prostate cancer suggest that darolutamide provides disease suppression with a favorable safety profile (Fizazi et al, 2014).

Inclusions status in September 2018



Statistics

Arm n°1: Darolutamide

CBR at 16 weeks with abiraterone acetate has been shown to be 20%. We aim to increase the CBR from 20% (H0) to 40% (H1) in the experimental group.

- Two-stage optimal Simon's design
- Primary endpoint : clinical benefit rate at 16 weeks

A total of **54 eligible and assessable patients** are required. **Stage 1 (19 patients):** If ≤ 4 patients achieve a CBR at 16 weeks among the 19 patients, the study will be terminated early. Otherwise, the second group of 35 subjects will be recruited.

Stage 2 (35 patients): If at the end of recruitment, 16 patients or more achieve a clinical benefit at 16 weeks (of the 54 assessable patients), then the null hypothesis will be rejected and the experimental arm will be deemed interesting for further research.

Arm n°2: capecitabine (standard arm)

Standard arm: No statistical hypothesis. The aims is to evaluate the CBR and tolerance of this chemotherapy in this particular subgroup of breast cancers.

To account for non-eligible and/or non-assessable patients (+/- 10%), 90 patients will be randomized.

Centers

22 French centers are open

Institut Bergonié, Centre Francois Baclesse, Gustave Roussy, Centre Léon Bérard, Centre Antoine Lacassagne, Institut CURIE - Hôpital R. Huguenin, Institut de Cancérologie Lucien Neuwirth, Hôpitaux du leman, CH Pau, Centre Jean Perrin, CHU Dupuytren, L'Hôpital privé du confluent, CHD Vendee, Institut Claudius Regaud, CH Mont-de-Marsan, Centre Paul Strauss, Clinique Tivoli Ducos, Clinique Victor Hugo, ICM Val d'Aurelle, Hopital Saint Louis, CH Alpes Leman, Centre Hospitalier Lyon Sud

9 French centers will open soon

23 French and 2 Belgium centers newly declared to competent authorities

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