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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Main Inclusion Criteria
- 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 Exclusion Criteria
- HER2-positive status (positivity defined as IHC3+ and/or FISH amplification >2);
- Other concurrent malignancies;
- Active brain metastases or leptomeningeal disease;
- Previous treatment with: capecitabine, first generation (bicalutamide) or second generation;
- Previous treatment with AR inhibitors (enzalutamide, ARN-509, darolutamide) or other investigational AR inhibitors.

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 response or sensitivity to the treatment.
- cDNA evaluation
- Pharmacokinetic analysis
- Additional analyses not listed above could be planned

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.

Trial Overview

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

**Statistical Analysis**
Darolutamide is a novel AR antagonist with a unique chemistry. It is a full and high-affinity AR antagonist that, similar to second-generation antianidrogens enzalutamide and ARN-509, inhibits testosterone-induced nuclear translocation of AR. Importantly, darolutamide also blocks the tested mutant ARs activity in response to antianidrogens therapies, including the F876L mutation that confers resistance to enzalutamide and ARN-509. Results from a phase II-I 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 in September 2018**

Centers

23 French and 2 Belgium centers newly declared to competent authorities

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