Invasive lobular breast cancer (ILBC) is the most common histologic subtype (5-15%) after invasive ductal BC (IDBC) [1]. It is characterized by a distinct clinical course including presentation, with metastases of relapse and response rates to conventional therapies [2]. Despite clinical and pathologic differences, ILBC is still treated like IDBC.

Toxicity of E-cadherin (CDH1) expression is the most frequent oncogenic event (90% of cases) [3,4]. In vivo studies investigating synthetic lethality approaches, have shown profound antitumor effects of ROS1 inhibitors in models of E-cadherin-defective BC, providing the preclinical rationale for assessing their activity in this disease [4,5].

A study is currently investigating this hypothesis in ER+/HER2- metastatic lobular breast cancer (NCT03620643).

Entrectinib is a potent small-molecule tyrosine kinase inhibitor that targets TRK, ROS1 and ALK tyrosine kinases, that are constitutively active in tumours with NTRK, ROS1 and ALK gene fusions [6].

We aim to evaluate the combination of neoadjuvant entrectinib and endocrine therapy (ET) in women with estrogen receptor (ER) positive, HER2-negative early ILBC.

**Trial Design**

- **Phase II, single-arm study**
- **Target population**: pre and post-menopausal women with stage IIA to stage IIIB ER-positive/HER2-negative invasive lobular breast cancer
- **Study treatment**: 4x 28-day cycles of letrozole (2.5 mg daily) in combination with entrectinib (600 mg daily). Pre-menopausal women will receive goserelin (3.6 mg every 28 days).
- **C Jurative breast surgery to be performed according to local guidelines, at least 16 weeks of treatment, during weeks 17–18.
- **Length of the study**:
  - Planned recruitment period: 18 months
  - Planned treatment period for a patient: 4 months
  - Planned follow-up period for a patient: 1 month

**Statistical Plan**

- Simon 2-stage design, one-sided alpha =beta=10%
- Power of 3% residual cancer burden (RCB) 0/1 rate as minimal required level activity
- **Interim Analysis** on the first 17 pts: if RCB 0/1 ≥ 2/17 pts, the study will continue until 39 evaluable subjects are enrolled. If RCB 0/1 ≤ 2/39 pts, the combination will be considered worthy for further investigation.
- If a clear radiologic benefit (PR or CR) is observed for subjects by the pre-surgery MRI in absence of RCB 0/1, then enrollment into Stage 2 can be allowed for this cohort after discussion with the Sponsor.

**Background and Aim**

- **Invasive lobular breast cancer (ILBC)** is the most common histologic subtype (5-15%) after invasive ductal BC (IDBC) [1]. It is characterized by a distinct clinical course including presentation, with metastases of relapse and response rates to conventional therapies [2]. Despite clinical and pathologic differences, ILBC is still treated like IDBC.

- **LC**, loss of E-cadherin (CDH1) expression is the most frequent oncogenic event (90% of cases) [3,4]. In vivo studies investigating synthetic lethality approaches, have shown profound antitumor effects of ROS1 inhibitors in models of E-cadherin-defective BC, providing the preclinical rationale for assessing their activity in this disease [4,5].

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- **Entrectinib** is a potent small-molecule tyrosine kinase inhibitor that targets TRK, ROS1 and ALK tyrosine kinases, that are constitutively active in tumours with NTRK, ROS1 and ALK gene fusions [6].

- We aim to evaluate the combination of neoadjuvant entrectinib and endocrine therapy (ET) in women with estrogen receptor (ER) positive, HER2-negative early ILBC.

**Study Design**

- **Key Inclusion Criteria**
  - Female: age ≥ 18 years, ECOG PS 0-1
  - Histological diagnosis of invasive lobular breast adenocarcinoma ER-positive and HER2-negative
  - T size ≥ 20 mm (by local MRI)
  - No N1 or L1
  - No prior treatment for breast cancer

- **Primary Endpoint**
  - RCB 0/1 rate by local assessment

- **Secondary Endpoint**
  - pCR rate (ypT0/Tis ypN0) by local assessment
  - ORR by locally-assessed breast MRI via modified RECIST
  - Safety (NCI CTCAE, v5.0)

- **Exploratory Endpoints**
  - Translational Analyses
  - Peripheral neuropathy
  - Hyperuricemia

**Key Exclusion Criteria**

- Clinical T4 disease including inflammatory breast cancer, cT2 or cT3 disease
- Prior history of invasive cancer in past 5 years
- LVEF ≤ 55% measured by echo or MUGA
- Concurrent treatment with strong/moderate CYP3A inhibitors/inducers
- Significant cardiac disease (e.g. recent myocardial infarction, or unstable angina)
- GTR ≤ 450 ms
- Known interstitial lung disease, interstitial fibrosis, or history of TKI-induced pneumonitis
- Known gastrointestinal disease (e.g., Crohn’s disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes
- Peripheral neuropathy ≥ Grade 2

**Translational Research**

- The aim is to identify differences between responders versus non responders in terms of genomic aberrations, transcriptional programs and transcription factors at baseline (pre-treatment) and surgery (post-treatment)
- Tumour biopsies and plasma samples before (baseline) and after (surgery) 4 months of neoadjuvant hormone therapy and entrectinib will be collected, and a comprehensive analysis of genomic and transcriptional landscape will be performed:
  - IHC for CDH1 expression
  - RNA seq on pre- and post-treatment samples for gene expression profiles, immune profiles and gene rearrangements detection
  - Plasma samples for cRNA extraction (bio banking, low pass whole genome sequencing, Foundation Medicine assay performance)

**Current status and participating centres**

- Ten participating centres in Belgium (Institut Jules Bordet, Brussels; UZ Leuven, Leuven; CHU UCL Namur Saint Elisabeth, Namur; UZ Brussels, Brussels; Cliniques universitaires Saint-Luc, Brussels; Grand Hôpital de Charleroi, Charleroi; UZ Gent, Gent; France (Institut Curie, Paris; Institut Bergonie, Bordeaux; Institut Gustave Roussy, Villejuif).

- Eight patients are currently enrolled in the ROSALINE study (3 patients included in Cliniques universitaires Saint-Luc, 2 in Jules Bordet Institute, 2 in CHU UCL Namur, and 1 in Grand Hôpital de Charleroi).

**Acknowledgements**

This study is supported by Roche.

We thank the Clinical Trials Supporting Unit (CTSU) team, the patients and their families.

**References**