ETIC-LM : a multicenter, single-arm, phase 2 study evaluating the efficacy of oral tucatinib, oral capecitabine, and intrathecal trastuzumab in patients with HER2-positive metastatic breast cancer with leptomeningeal metastases, a UCBG study

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Background

Leptomeningeal metastases (LM) are a rare but devastating form of disease progression in HER2-positive (HER2+) metastatic breast cancer (MBC), occurring in 5–10% of patients.

Median overall survival (OS) historically ranges from 4 to 6 months, with poorer outcomes observed in type 1 LM (characterized by the presence of tumor cells in the cerebrospinal fluid (CSF)), and longer OS reported with newer therapies such as trastuzumab deruxtecan (T-DXd), brain-penetrant HER2 tyrosine kinase inhibitors, or intrathecal (IT) trastuzumab.

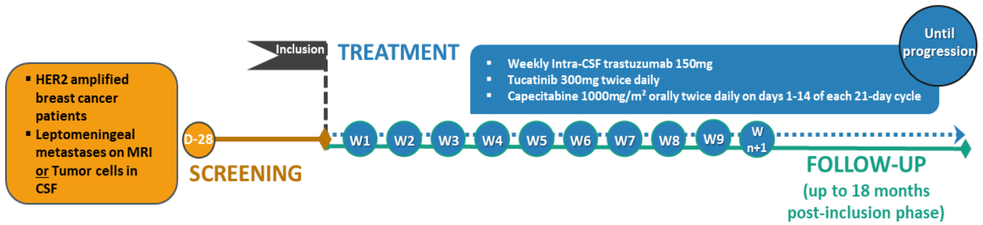
Tucatinib is a highly selective HER2 tyrosine kinase inhibitor that has demonstrated significant intracranial activity in HER2+ MBC with brain metastases, including in heavily pretreated patients, when combined with intravenous trastuzumab and oral capecitabine. IT trastuzumab has shown encouraging signs of efficacy without safety concerns in two prospective studies in HER2+ MBC with LM, offering one of the few targeted strategies capable of delivering anti-HER2 therapy directly into the CSF, thereby bypassing the blood-CSF barrier.

Based on the complementary pharmacological properties and mechanisms of action of these agents, the ETIC-LM trial was designed to evaluate the efficacy and safety of a triplet regimen composed of oral tucatinib, oral capecitabine and IT trastuzumab in patients with HER2+ MBC and LM, including those previously exposed to T-DXd and those presenting with the most severe form of LM: type 1 LM.

Study design

ETIC-LM is a **national, open-label, single-arm phase II study** enrolling patients with histologically confirmed HER2+ MBC and LM confirmed by MRI and/or presence of tumor cells in the CSF.
The investigational treatment consists of :

- oral tucatinib (300 mg twice daily, continuously)
- oral capecitabine (1000 mg/m²twice daily on days 1 to 14 of each 21-day cycle)
- intrathecal trastuzumab (150 mg weekly, administered via lumbar puncture or Ommaya reservoir).



=> Treatment is continued until disease progression, unacceptable toxicity, or patient withdrawal

Key study endpoints

Primary:

To evaluate the 12-month overall survival (12m-OS) rate defined as the proportion of patients alive 12 months after treatment initiation.

Secondary:

- Neurological symptom improvement and duration (NANO scale)
- Overall survival (OS).
- Progression-Free Survival (PFS), LM-specific and brain-specific PFS using RANO-LM,
- Overall Survival,
- CSF cytological response at 4 weeks,
- Quality of life (assessed by EORTC QLQ-C30 and BN20 questionnaires), and cognitive function (evaluated using the Montreal Cognitive Assessment (MoCA)).
- Safety endpoints include the incidence and severity of adverse events according to CTCAE version 5.0, as well as longitudinal cognitive evaluations.

Exploratory translational analyses :

- Pharmacokinetics of tucatinib, capecitabine, and CSF trastuzumab,
- Circulating biomarkers in CSF and plasma (ctDNA, CTCs).

Key inclusion/exclusion criteria

Inclusion Criteria

- **Age ≥18 years**
- **Histologically confirmed HER2-positive metastatic breast cancer**
- **Confirmed leptomeningeal metastasis by MRI and/or tumor cells in CSF**
- **Evaluable disease by RANO-LM (and RECIST 1.1 if applicable)**
- **ECOG performance status 0–2**
- **Adequate hematologic, hepatic, renal, and cardiac function**
- **Stable corticosteroid dose ≥5 days**
- **Prior local CNS therapy allowed if completed ≥2 weeks before inclusion**
- **Life expectancy ≥2 months**

Exclusion Criteria

- Prior treatment with tucatinib or capecitabine
- Severe organ dysfunction (hematologic, hepatic, renal)
- Active or uncontrolled infection
- Uncontrolled hypertension or severe cerebrovascular disorder
- HIV infection or active hepatitis B/C
- Pregnancy or breastfeeding
- Known hypersensitivity to study drugs
- DPD deficiency
- Inability to swallow oral medication

Study status

The trial began enrollment in February 2024.
Recruitment is ongoing.
About 12 French centers are currently participating or in the process of activation.
The trial is registered under NCT05800275 :
https://clinicaltrials.gov/study/NCT05800275

Contact

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