Xentuzumab in combination with everolimus and exemestane in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer and non-visceral involvement (XENERTM™-1)

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Introduction

- Resistance to standard first-line endocrine therapy is common in women with HR+, HER2- breast cancer, despite initial clinical benefit.8
- The mTOR inhibitor everolimus is approved in combination with exemestane to treat post-menopausal women with advanced HR+HER2- BC after failure on a NSAI.9 and may be used in combination with endocrine therapy to prolong PFS.10
- However, the activity of mTOR inhibitors such as everolimus is limited by compensatory feedback mechanisms, involving reactivation of IGF/mTOR signalling.11
- Combining everolimus with IGF signalling abrogates this feedback, thus interfering inhibition of tumour growth.12
- The effects are more substantial in patients with non-visceral (e.g., bone and lymph node) metastases, in which IGF-1 plays a role in cancer cell proliferation.13

Objectives

- Efficacy and safety of xentuzumab in combination with everolimus and exemestane in women with HR+, HER2- and non-visceral disease.
- Study design: Double-blind, placebo-controlled, randomised Phase II study
- Endpoints: Primary: PFS by independent assessment

Key findings and conclusions

- Patients
  - Female patients (≥18 years old) of any race
  - HR+, HER2- metastatic breast cancer
  - Eligible for combination treatment with everolimus and exemestane

- Key exclusion criteria
  - >1 prior treatment line with a CDK4/6 inhibitor
  - Leptomeningeal disease
  - History of or clinical benefit to systemic treatments targeting the IGF, AKT or mTOR pathways

- Phase II XENERA™ trial

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Design

- **XENERA™-1** (NC03659136) is a double-blind, placebo-controlled, randomised study

Trial

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<tr>
<th>Patients</th>
<th>Key inclusion criteria</th>
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| Female patients (18 years or legal age of consent) | Histologically confirmed, locally advanced/metastatic breast cancer in patients with HR+ and HER2- status, and non-visceral involvement (pulmonary, liver, bone).
| HR+, HER2- disease | Premenopausal status (and patient on ovarian suppression therapy) for HR+ breast cancer.
| Disease progression over 12 months of completion of endocrine therapy or within 1 month of completion of endocrine therapy for advanced breast cancer or non-visceral disease.
| | Presence of visceral metastases.

Endpoints and assessments

- **Primary**
  - PFS by independent assessment

- **Secondary**
  - Overall survival
  - Disease control duration of disease control
  - Objective response
  - Time to progression of pain
  - Treatment until disease progression, unacceptable toxicity or other reasons

- **Other**
  - Safety
  - Pharmacokinetics
  - Exploratory biomarkers

- Tumour imaging will be performed every 8 weeks up to Week 80 and every 12 weeks thereafter until progression, death, or start of subsequent therapy.
- Treatment response will be assessed according to modified RECIST 1.1 with MD Anderson criteria for patients with target and/or non-targeted lesions.
- The effect of treatment on the primary endpoint will be analysed via a stratified (bone-only metastases, prior CDK4/6 inhibitor treatment, menopausal status, log-rank test and Cox-proportional hazards model.

Endpoints and assessments

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<th>Patient screening started in January 2019</th>
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<td>The first patient was enrolled in January 2019</td>
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<td>Target enrolment is 88 patients in 12 countries</td>
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**Key findings and conclusions**

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**References**