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XENERA™-1: A phase II trial of 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

#TPS1103

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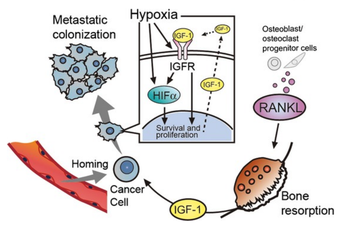
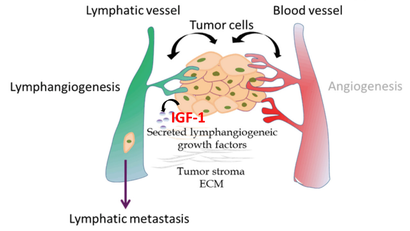
Introduction

- Resistance to standard first-line endocrine therapy is common in women with HR+, HER2- mBC, despite initial clinical benefit[1,2]
- 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,[3] and may be used in combination with endocrine therapy to prolong PFS[2]
  - However, the activity of mTOR inhibitors such as everolimus is limited by compensatory feedback mechanisms, involving reactivation of IGF/mTOR signaling[4,5]
- Combining everolimus with inhibition of IGF signaling abrogates this feedback, thus intensifying inhibition of tumor growth[4,5]
  - The effects are particularly pronounced in patients with non-visceral (e.g., bone and lymph node) metastases, in which IGF-1 plays a role in cancer cell proliferation[6,7]

Role of IGF in bone biology



Role of IGF in lymph node biology



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- Xentuzumab is a humanized IgG1 mAb that binds with high affinity to IGF-1 and IGF-2, and potently neutralizes their proliferative and anti-apoptotic cellular signaling[10,11]
- In a Phase II trial (NCT02123823) in HR+, HER2- BC, xentuzumab plus everolimus and exemestane demonstrated favorable PFS versus everolimus and exemestane alone in the prespecified subgroup without visceral metastases (HR 0.21 [0.05–0.98]; P_{int}=0.014)[12]
  - Given that randomization was stratified by presence/absence of visceral metastases, this is an important finding that led to the design of the present trial

HER2-, human epidermal growth factor receptor-2-negative; HR, hazard ratio; HR+, hormone receptor-positive; IGF, insulin-like growth factor; IGF-1R, insulin-like growth factor receptor 1; IgG1, immunoglobulin G1; INSR-A, insulin receptor isoform A; mAb, monoclonal antibody; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; NSAI, non-steroidal aromatase inhibitor; PFS, progression-free survival

Objectives

- The Phase II XENERA™-1 trial will assess the efficacy and safety of xentuzumab in combination with everolimus and exemestane, in post-menopausal women with HR+/HER2- locally advanced/mBC and non-visceral disease

Patients

- XENERA™-1 (NCT03659136) is a double-blind, placebo-controlled, randomized study

Key inclusion criteria

Female
≥18 years*

Histologically confirmed, locally advanced/mBC
HR+, HER2- disease
≥1 measurable non-visceral lesion and/or ≥1 non-measurable lytic or mixed bone lesion
Not amenable to curative surgery or radiation
ECOG PS 0–1 / Post-menopausal
Progression during/after prior aromatase inhibitor therapy† (and/or tamoxifen if adjuvant) / No more than 1 previous line of a NSAI ± a CDK 4/6 inhibitor
Prior fulvestrant allowed‡ / Provision of FFPE tissue biopsy

Key exclusion criteria

- Previous treatment with agents targeting the IGF, PI3K, AKT, or mTOR pathways
- Prior exemestane (except adjuvant)
- Cardiovascular abnormalities
- Visceral§/brain metastases
- Leptomeningeal carcinomatosis
- Previous chemotherapy for HR+/HER2- mBC
- Previous/concomitant malignancies
- Interstitial lung disease
- Concomitant systemic sex hormone therapy, growth hormones or growth hormone inhibitors
- Major surgery/radiotherapy within 4 weeks prior to start of study

*Or over the legal age of consent for each country; †Or prior endocrine treatment for advanced/metastatic breast cancer if pre- or peri-menopausal; ‡If ≥2 years in adjuvant setting or ≥6 months in metastatic setting; §Liver, lung, peritoneal, pleural metastases, pleural effusions, or peritoneal effusions. AKT, protein kinase B; CDK 4/6, cyclin-dependent kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; FFPE, formalin-fixed, paraffin-embedded; PI3K, phosphoinositide 3-kinase

Study design

- Post-menopausal women with HR+/HER2- mBC
- Non-visceral disease

Randomized (1:1)

Xentuzumab
1000 mg IV weekly
+
Everolimus + exemestane
(10 mg/day + 25 mg/day PO)

Placebo
IV weekly
+
Everolimus + exemestane
(10 mg/day + 25 mg/day PO)

Randomization stratified by presence of bone-only metastasis (Yes/No), and prior CDK 4/6 inhibitor treatment (Yes/No)

Treatment until disease progression, unacceptable toxicity or other reasons*

*Treatment may continue beyond progression in case of clinical benefit.
IV, intravenously; PO, orally

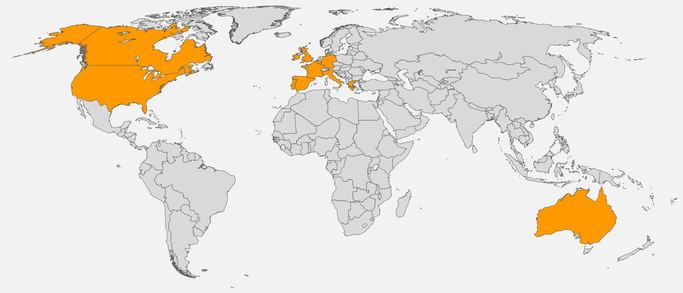
Endpoints and assessments

Primary	• PFS*† by independent assessment
Secondary	• OS; • DC†; duration of DC† • OR† • Time to progression of pain/intensification of pain palliation
Other	• Safety • Pharmacokinetics • Exploratory biomarkers

- Tumor imaging will be performed every 8 weeks up to Week 80 and every 12 weeks thereafter until progression, death or start of subsequent therapy
- PFS = time from the date of randomization to the date of PD or death, whichever occurs first
- OS = time from the date of randomization to death
- OR = best overall response of CR or PR
- DC = best overall response of CR, PR, or SD or non-CR/non-PD lasting ≥24 weeks
- Time to pain progression/increased requirement for pain palliation = time from randomization until the earliest of:
  - a clinically significant increase in pain (≥2-point increase from baseline in the BPI-SF Item 3) without a decrease in analgesic use,
  - increase in analgesic use (≥2-point increase in the 8-point AQA), or
  - death

*Independent assessment of PFS according to RECIST 1.1 will be completed in a treatment-blinded manner; †Tumor response will be assessed according to modified RECIST 1.1, with MD Anderson modifications for bone lesions; independent assessments will be considered primary with investigator assessment as supportive. AQA, Analgesic Quantification Algorithm; BPI-SF, Brief Pain Inventory – Short Form; CR, complete response; DC, disease control; OR, objective response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Current status



- Patient screening started in January 2019
- The first patient was enrolled in January 2019
- Target enrollment is 80 patients in 12 countries

Key Points

Objectives:
- Efficacy and safety of xentuzumab in combination with everolimus and exemestane in post-menopausal women with HR+, HER2- mBC and non-visceral disease

Study design:
- Double-blind, placebo-controlled, randomized, Phase II study

Endpoints:
- Primary: PFS by independent review
- Secondary: OS; DC; duration of DC; OR; time to progression of pain/intensification of pain palliation

Status: Currently enrolling across 12 countries

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