A Phase Ib trial of xentuzumab and abemaciclib in patients with locally advanced or metastatic solid tumors, hormone receptor-positive, HER2-negative breast cancer (± endocrine therapy), or non-small cell lung cancer

Introduction

Study design
- Prospective, open-label, non-randomized, multiple dose-finding, Phase Ib study, followed by expansion cohorts (NCT03099174)

Mechanisms of action: Xentuzumab and abemaciclib

Xentuzumab
- A humanized IgG1 antibody
- Blocks with high affinity to IGF-IR and IGF-1R
- Inhibits IGFR autophosphorylation and downstream signaling triggered by both agonists

Abemaciclib
- A small molecule inhibitor of CDK4 and 6
- Greater selectivity for CDK4
- Greater selectivity for CDK4 compared with CDK6
- Inhibits Rb phosphorylation and arrests cells in the G1 phase
- Clinical activity in breast cancer and NSCLC

Objectives
- To determine the maximum tolerated dose (MTD/RP2D) of xentuzumab in combination with abemaciclib with or without hormonal therapy (letrozole, anastrozole, fulvestrant)
- To assess the antitumor activity of the triplet combination of xentuzumab, abemaciclib, and fulvestrant in patients with breast cancer who have progressed on prior endocrine therapy

Cohorts A, B, C, D, F

Cohort A: Xentuzumab + abemaciclib

Cohort B: Xentuzumab + abemaciclib + letrozole

Cohort C: Xentuzumab + abemaciclib + anastrozole

Cohort D: Xentuzumab + abemaciclib + fulvestrant

Cohort E: Xentuzumab + abemaciclib + letrozole + fulvestrant

Cohort F: Xentuzumab + abemaciclib + anastrozole + fulvestrant

Key inclusion criteria: All cohorts

1. Patients with HR+, HER2– disease
2. Inadequate bone marrow or organ function
3. Eastern Cooperative Oncology Group Performance Status 0–1
4. Inadequate bone marrow or organ function
5. Progressing disease or no therapeutic options available
6. Consented

Key endpoints
- Primary endpoints
- MTD
- Number of patients with DLT
- OR (95% CI, PDR)
- Duration of OR
- Duration of disease control
- PFS
- Progression-free survival

Secondary endpoints
- Inclusion criteria: Cohorts B, C, D, F

Key exclusion criteria: All cohorts
- Prior treatment with EGFR TKIs, VEGFR TKIs, or multitargeted tyrosine kinase inhibitors (excl. Crizotinib)
- Prior therapy for an HER2-positive breast cancer with trastuzumab, pertuzumab, and ado-trastuzumab emtansine
- Inadequate organ function
- Type I diabetes (or uncontrolled type II)
- Uncontrolled hyperglycemia or hypertension
- Chemotherapy, and PD-L1 expressing tumors
- Prior treatment with EGFR TKIs or ALK inhibitors is mandatory

Key points
- MTD/RP2D of xentuzumab in combination with abemaciclib with or without hormonal therapy
- Antitumor activity of xentuzumab in combination with abemaciclib in patients with NSCLC, and in a triplet therapy with abemaciclib plus fulvestrant in patients with HR+, HER2– disease

Study design
- Open-label, non-randomized, multiple dose-finding, Phase Ib study, followed by expansion cohorts

Endpoints
- Primary endpoints: MTD and the number of patients with DLTs (Cohorts A–D), OR (Cohorts E and F)
- Secondary endpoints (Cohorts E and F): disease control time, duration of OR, duration of disease control, PFS

Status
- Currently enrolling in Japan, USA, France, and Spain
- Target enrollment is ~88 patients

Current status

Patient screening started in May 2017

Recruitment is ongoing in Japan, USA, France, and Spain

Reference


Presented at the European Society for Medical Oncology Asia (ESMO Asia) congress, Singapore, November 17–19, 2017