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

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Objectives
MTD/RPD 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– breast cancer

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
Secondary endpoints: disease control; time to OR; duration of OR; duration of disease control; PFS

Inclusion criteria
HR+, HER2– disease
Histologically or cytologically confirmed advanced breast cancer (± endocrine therapy), or non-small cell lung cancer
Progressed after platinum-based chemotherapy and immunotherapy, and received ≥2 prior chemotherapy regimens or be ineligible for further standard second-line chemotherapy

Exclusion criteria
– Adequate organ function
– Pre-existing renal or liver disease
– Hypersensitivity to study drugs (or similar compounds)
– Active infection
– Inadequate bone marrow or organ function
– Uncontrolled disease
– Inadequate bone marrow or organ function
– History of previous chemotherapy or radiation therapy
– Patients with: EGFR, ALK, or other sensitizing mutations
– Active infection
– Inadequate bone marrow or organ function
– History of previous chemotherapy or radiation therapy
– Patients with: EGFR, ALK, or other sensitizing mutations

Key endpoints
MTD and the number of patients with DLTs
Antitumor activity of triplet combination

Current status
Patient screening started in May 2017
Recruitment is ongoing in Japan, USA, France, and Spain
Target enrollment is >80 patients

References


Figure 1: Role of CDK4/6 and cyclin D in cell-cycle progression

Mechanisms of action: Xentuzumab and abemaciclib

Xentuzumab
– A humanized IgG1 mAb
– Blocks with high affinity to the IGF-1 and IGF-2 homodimer
– Strong dose-proportional and post-adoptive efficacy signal triggered by both proteins

Abemaciclib
– A small-molecule inhibitor of CDK4
– Greater selectivity for CDK4 compared with CDK6
– Induces G1-phase phosphorylation and cell-cycle arrest

Xentuzumab has clinical activity with breast cancer and NSCLC, as well as other solid tumors.

Trial

Cohorts A–D
– Xentuzumab + abemaciclib + fulvestrant
– MTD/RPD of xentuzumab in combination with abemaciclib
– To assess the antitumor activity of the triplet combination in breast cancer patients with HR+, HER2– disease
– To assess the antitumor activity of the triplet combination in patients with NSCLC

Cohorts E and F
– Xentuzumab + abemaciclib + letrozole
– To assess the antitumor activity of triplet combination in patients with HR+, HER2– disease
– To assess the antitumor activity of triplet combination in patients with HR-, HER2– breast cancer

Key inclusion criteria: All cohorts
– 18 years of age
– Eastern Cooperative Oncology Group performance status ≤2
– Adenocarcinoma of the breast, Stage IV NSCLC

Key exclusion criteria
– Patients with: EGFR, ALK, or other sensitizing mutations
– Active infection
– Inadequate bone marrow or organ function
– History of previous chemotherapy or radiation therapy
– Patients with: EGFR, ALK, or other sensitizing mutations

Radiology to 50% of bone metastases

Disease control
– Disease control
– OR
– Time to OR
– Duration of OR
– Duration of disease control

PFS
– progress of disease

References


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