A Phase Ib trial of xentuzumab and abemaciclib in advanced or metastatic solid tumors, including advanced NSCLC

**Introduction**

Unmet need for treatment options in advanced NSCLC
- NSCLC accounts for over 85% of all lung cancers, the majority (55%) of which are diagnosed at an advanced stage, with a 5-year survival rate of only 16%.
- Despite multiple advances in anticancer therapy, many patients with advanced NSCLC are refractory to immunotherapy, chemotherapy, and targeted agents (such as EGFR and ALK inhibitors), presenting an unmet need for novel treatment options against additional molecular targets.

**Rationale for dual inhibition**
- The IGF and the CDK4/6-retinoblastoma pathways have been implicated in the pathogenesis and resistance mechanisms of various cancers, including NSCLC.
- CDK4 and 6 are key regulatory components of the cell cycle.
- Phosphorylation of Rb by CDK4/6 results in decreased cell proliferation through disruption of cell-cycle progression.

**Objectives for the NSCLC cohort (Cohort E)**
- To assess the anti-tumor activity of xentuzumab in combination with abemaciclib in patients with NSCLC.
- To further characterize the safety, tolerability, and pharmacokinetics of xentuzumab in combination with abemaciclib.

**Endpoints for the NSCLC cohort (Cohort E)**
- **Primary endpoint:**
  - Time to clinical response (TTR).
- **Secondary endpoints:**
  - Duration of objective response.
  - Duration of disease control.
  - PFS.
  - Pharmacokinetic parameters.
  - Immunogenicity.

**Exploratory biomarker and pharmacogenomic analyses will also be performed**

**Study Design**

- Prospective, open-label, non-randomized, multiple-dose-finding. Phase Ib study followed by expansion cohorts (NCT030939174).
- Xentuzumab + abemaciclib + hormonal therapy (letrozole, anastrozole, and fulvestrant, respectively).

**Key inclusion criteria: all cohorts**
- ≥ 18 years.
- ≥ 20 years.
- Measurable/evaluable disease.
- Adequate organ function.

**Key Exclusion criteria: all cohorts**
- Active infection.
- Uncontrolled hypertension.
- Severe or uncontrolled systemic disease.
- Type 1 diabetes, or uncontrolled type 2 diabetes.
- Inadequate bone marrow reserve or organ function.

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**Key inclusion criteria: NSCLC cohort (Cohort E)**
- Histologically or cytologically confirmed stage IV NSCLC.
- Progressed after platinum-based chemotherapy and immunotherapy.
- and received ≤2 other prior lines of chemotherapy or be ineligible for further standard second-line chemotherapy.
- Patients with EGFR-activating mutations or ALK translocations, prior treatment with EGFR-TKIs and ALK inhibitors is mandatory.

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- Active infection.
- Uncontrolled hypertension.
- Severe or uncontrolled systemic disease.
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**Treatment within 21 days and/or 3 half-lives for immunotherapy**

**Previous treatments**
- IGF-1R targeting compounds.
- Major surgery ≥ 120 days prior.
- Radiotherapy to ≥25% of bone marrow.
- Relinquish ≥12 of bone marrow.

**Key points**

- To assess the anti-tumor activity of xentuzumab in combination with abemaciclib in patients with NSCLC.
- To further characterize the safety, tolerability, and pharmacokinetics of xentuzumab in combination with abemaciclib.

**Current status**

- **Objective:**
  - Patient screening started in May 2017.
- Recruitment is ongoing in Japan, US, France and Spain.
- Target enrollment is ~88 patients, including ~20 patients with stage IV NSCLC.