#495TIP: A phase 2 Study Evaluating the Safety and Efficacy of ENV-101 (Taladegib) in Patients With Advanced Solid Tumors Harboring PTCH1 Loss of Function Mutations

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ABSTRACT

Background

ENV-101 is a Hh pathway inhibitor (Smo inhibitor) originally developed as a treatment for patients with advanced solid tumors. Clinical responses have been reported in patients with gene mutations affecting PTCH1treated with other Hh pathway inhibitors. Endeavor is studying ENV-101 in advanced cancer patients with solid tumors harboring PTCH1 loss of function mutations. This study aims to evaluate dose as well as the efficacy and safety of ENV-101, a potent Hh pathway inhibitor, in patients with refractory advanced solid tumors characterized by loss of function mutations in the PTCH1 gene.

Two distinct mechanisms are responsible for inappropriate and uncontrolled Hh pathway activation in human malignancies: ligand-dependent, due to overexpression of Hh ligand, and ligand-independent, resulting from genetic mutations in pathway components such as Ptch and Smo. The ligand-dependent mediated Hh pathway activation is implicated in a number of malignancies, including basal cell carcinoma (BCC),medulloblastoma, rhabdomyosarcoma, breast cancer, esophageal cancer, gastric cancer, pancreatic cancer, prostate cancer, small cell lung cancer, bladder cancer, oral cancer, and melanoma. Hedgehog pathway activation due to the ligand-independent mechanism involving Ptch1 loss of heterozygosity (LOH) or Smo mutations are primarily reported in medulloblastoma and BCC. However, data indicate that these mutations may be present in other solid tumors as well. In addition, as the Hh pathway is known to be primarily active in embryonic development and is not required for survival in adults, this type of targeted therapy should provide improved outcomes to defined cancer patient populations.

Study design

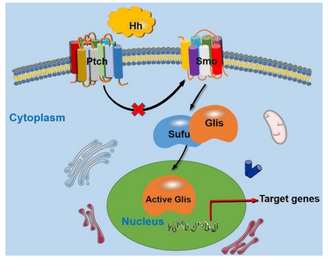
This is a Simon 2 stage design that aims to evaluate the efficacy and safety of ENV-101, a potent Hedgehog(Hh) pathway inhibitor, in patients with refractory advanced solid tumors characterized by loss of function(LOF) mutations in the PTCH1 gene. Stage 1 (Phase 2a) of this protocol will enroll a total of 44 patients randomized between two dose levels. In the presence of acceptable efficacy, stage 2 (Phase 2b) of this protocol will expand enrollment using a single dose level

Clinical trial identification

NCT05199584

INTRODUCTION

- ENV-101 is an oral Hh pathway inhibitor (Smo inhibitor) originally developed as a treatment for patients with advanced solid tumors
- Endeavor is continuing to study ENV-101 in advanced cancer patients with solid tumors harboring PTCH1 loss of function mutations
- This study aims to evaluate dose as well as the efficacy and safety of ENV-101, a potent Hh pathway inhibitor, in patients with refractory advanced solid tumors characterized by loss of function mutations in the PTCH1 gene
- In addition, taladegib exhibits an acceptable safety profile in nonclinical toxicology studies with effects that are considered to be monitorable, manageable, or acceptable in the intended patient population
- ENV-101 will be supplied as single dose, aquamarine-colored tablets, supplied at 100 mg doses.



KEY OBJECTIVES

1. To determine a recommended Phase 2 dose (RP2D) for ENV-101 in patients with advanced solid tumors.
2. To evaluate the efficacy of ENV-101 in patients with a solid tumor harboring PTCH1 LOF mutations as measured by tumor objective response rate (ORR) by independent review.

KEY INCLUSION AND EXCLUSION CRITERIA

- Females or males greater than or equal to 18 years of age.
- Has histologically or cytologically confirmed solid tumor that harbors a PTCH1 loss of function mutation
- Measurable disease as defined by RECIST v1.1
- ECOG performance score of 0 or 1
- No Concurrent administration of any anti-cancer therapies (e.g., chemotherapy, other targeted therapy) other than those administered in this study
- No Unresolved toxicity of ≥ CTCAE Grade 2 attributed to any prior therapies (

STUDY DESIGN

SCHEMA

PHASE 2A MONOTHERAPY

Enroll approximately 22 patients at 200 mg QD

PHASE 2A MONOTHERAPY

Enroll approximately 22 patients at 300 mg QD

If response is dose-dependent, expand if ≥ 4 responses in a single dose cohort; if response is not dose-dependent, expand if ≥ 6 responses total

PHASE 2B AGNOSTIC EXPANSION

Enroll approximately 60 or 82 patients, regardless of tumor histology

KEY MESSAGES

- The study is currently open and recruiting
- This is a multicenter, open label phase 2a study evaluating efficacy and safety of taladegib
- The trial consists of a Screening period (Visit window: -28 to -1 days from Baseline/Day 1), a treatment period comprised of Day 1, Day 14, monthly visits, and tumor assessments bi-monthly.
- During Phase 2a of the protocol, patients with PTCH1 LOF mutations will be enrolled and randomized (1:1) to either the 200 mg or 300 mg dose group. The Sponsor actively monitors enrollment in an attempt to achieve balance and diversity of histologies across dose groups and this may result in closing enrollment for certain tumor types.
- A single dose will be carried forward to Phase 2b of the protocol. The recommended dose will be based on safety, efficacy, PK and PD markers.
- Central review of tumor responses will be conducted by a central imaging vendor
- Enrolled patients will receive continuous oral dosing of ENV-101 at a dose of 200 or 300 mg once daily during 28-day treatment cycles, until the development of progressive disease (as per Investigator assessment), unacceptable toxicity, withdrawal of consent, death, decision by Investigator, or study termination by the Sponsor
- For more information, please contact Endeavor Biomedicines at ebmclinical@endeavorbiomedicines.com

Endpoints

Primary Endpoints

1. Phase 2a: Recommended dose is assessed by Objective Response Rate [Complete Response (CR) / Partial Response (PR) by RECIST 1.1] as determined by an independent review (confirmed CR or PR will be defined as a repeat assessment performed no less than 28 days after the criteria for response is first met), pharmacokinetic (PK) evaluation, safety and pharmacodynamic (PD) marker of mGli1.

2. Phase 2b: Objective Response Rate [Complete Response (CR) / Partial Response (PR)] by RECIST 1.1 as determined by an independent review. Confirmed CR or PR will be defined as a repeat assessment performed no less than 28 days after the criteria for response is first met.

Secondary Endpoints:

1. Adverse events (AE) and unacceptable toxicities (non-hematologic adverse events ≥ Grade 3 not including alopecia and fatigue).

2. ORR by Investigator: Best overall response of confirmed CR or PR as determined by the treating Investigator using RECIST 1.1.

3. CBR: The proportion of patients who achieved complete response, partial response, or stable disease as determined by the treating Investigator using RECIST 1.1.

4. OS: Number of months from initiation of ENV-101 to the date of death due to any cause or last follow up.

5. DOR: Defined as the number of months from the start of CR or PR, whichever response is recorded first and subsequently confirmed, to the first date that recurrent or progressive disease is documented or death.

6. PFS: Number of months from initiation of ENV-101 to the earlier of disease progression or death due to any cause or last follow up.

7. Phase 2a only: mGli1 message inhibition in skin.

8. Characterize the steady-state exposure (Ctrough) of ENV-101.

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