A Phase 1 Study of ARRY-382, an Oral Inhibitor of Colony-stimulating Factor-1 Receptor (CSF1R), in Patients with Advanced or Metastatic Cancers

Introduction

ARRY-382 is a highly selective and small-molecule inhibitor of CSF1R (colony-stimulating factor-1 receptor) with an IC50 for CSF1R autophosphorylation inhibition of 9 nM. CSF1R is a receptor tyrosine kinase normally expressed on the surface of mononuclear phagocytes. Within the tumor microenvironment, CSF1R signaling is thought to play an important role in recruitment and differentiation of tumor-associated macrophages (TAMs) and osteoclasts, promoting disease progression through stimulation of both tumor cell immune resistance, promotion of angiogenesis, and modulation of the tumor stroma.

In cell-based models, ARRY-382 has demonstrated potent inhibition of osteoclast differentiation (IC50 = 4 nM) and bone resorption (IC50 = 58 nM). In mice tumor models using HEK-293 cells, ARRY-382 inhibited CSF1R activity (ED50 = 3 mg/kg). In tumor-bearing rats, ARRY-382 inhibited CSF1R activity (ED50 = 9 mg/kg) and tartrate-resistant acid phosphatase (TRAP) serum levels.

Safety

Dose-limiting Toxicities (DLTs) and Maximum Tolerated Dose

- 200 mg QD
- 500 mg QD
- 400 mg QD (N=6)
- Non-Tolerated Dose
- MT0 400 mg QD (N=11)
- 500 mg QD

The 200 mg QD cohort was expanded to monitor further evaluation of ARRY-382 treatment-related changes of Day 1. (Dose-dependent dose modification: *Decreased dose interruption and subsequent reduction for DLTs.*)

Pharmacokinetics

Concentration-Time Profiles

- Consistent concentration-time profiles with increasing dose and repeated dosing.
- Low peak-to-trough supporting QD is suitable.
- The exposure (AUC0-24 and Cmax) of ARRY-382 increased with increasing dose.
- Appears dose proportional for AUC0-24 and Cmax.
- Good target coverage around the clock with a 200 mg QD dosing. At the MT0 (400 mg QD), ARRY-382 plasma concentrations were continuously above the cell-based IC50 for CSF1R inhibition.

Pharmacodynamic Parameters

- Good reproducibility in exposure in this cancer population at the MTD of 400 mg QD.
- Efficacy was confirmed by reductions in baseline-derived NTX, a bone metabolism biomarker.
- Biologically relevant increases in the number of classical monocytes (CM) and decreases in nonclassical monocytes (NCM).
- Inhibition of CSF1R may be expected to affect CSF1 (the ligand of CSF1R), decrease NCM counts and decrease urinary collagen type 1 cross-linked N-telopeptide (NTX).

Pharmacodynamic Endpoints

- NTX decreased by 62% at baseline, with a ~40% reduction in the overall study population. No evidence of histological changes or organ damage.
- Decreases were observed regardless of tumor type.

Pharmacodynamic Endpoints

- Urinary collagen type 1 cross-linked N-telopeptide (NTX).
- AUCtau (hr*mg/mL): Days 1, 8, 22 pre-dose.
- Urine NTX: Days 1, 15 pre-dose.
- AUC0-24 (hr*mg/mL): Day 1 pre-dose.
- AUC0-24 (hr*mg/mL): Days 1, 15 post-dose.
- Valsalva ratio 1.24:1 (Cycle 1).
- No changes from baseline were observed in NTX and NTX/cre.

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