INTRODUCTION

- WEE1 is a protein kinase that catalyzes the inhibitory phosphorylation of CDK1 and CDK2, which delays cell cycle progression from S/G2 to M phase and G1 to S phase, respectively. 1,4
- DNA damage-induced cell cycle checkpoint activation of WEE1 slows G1-S and G2-M phase transitions and stabilizes replication forks, particularly in CNE1 overexpressing cells.2
- Clinical studies focusing on the inhibition of WEE1 as a single agent have demonstrated encouraging antitumor effects.1,4
- However, limiting myelosuppressive toxicity (e.g., anemia, neutropenia, and thrombocytopenia) has been reported, including higher rates of Grade 3 toxicities in combination with standard treatments.1-4
- There are currently no FDA-approved WEE1 inhibitors.

APR-1051

- APR-1051 is an orally bioavailable, highly potent, and selective small molecule inhibitor of WEE1.5
- APR-1051 has demonstrated in vivo antiproliferative activity in multiple cancer cell lines.7
- Pharmacodynamic properties of APR-1051 included lower off-target inhibition of three members of the PLK family of kinases (PLK1, PLK2, and PLK3).7

PRECLINICAL STUDIES

- In vitro pharmacology studies have shown that APR-1051 inhibited WEE1 with an IC50 of 2.25 nM (cell-free LanthaScreenTM EU Kiiase Binding Assay).8
- In vivo studies in a murine model of ovarian cancer (OVCAR3) demonstrated that APR-1051 30 mg/kg daily or 15 mg/kg twice daily has acceptable pharmacology effectiveness and effect on body weight (Figure 2).
- APR-1051 exhibited favorable selectivity against PLK kinases 1, 2, and 3 where activity never exceeded 9% of full activity (Figure 3).
- In healthy mice orally dosed APR-1051 10 mg/kg/day resulted in a Cmax of 1.219 ng/mL, T1/2 of 2 hrs, and AUC0-24 of 14.21 ng*h/ml which would allow for 3 to 6 times lower dosing than other WEE1 inhibitors in xenograft models to achieve comparable exposure (AUC0-24) levels.
- Administration, distribution and metabolism studies in animals have shown that APR-1051 has limited potential for accumulation, has moderate permeability across Caco-2 cells, is not a potential P-gp substrate, undergoes no apparent degradation or metabolism, is metabolized by CYP3A4/5 enzymes (major), and is a substrate for MDR1 and BCRP export transporters.

TOXICOLOGY

- GLP toxicity studies were performed in rats and dogs to determine the initial starting dose of APR-1051 in humans.
- No significant and APR-1051-related changes were noted in body weight, food consumption, ophthalmology, bone marrow smear evaluation, electrocardiogram, clinical pathology, or gross and histopathology.

STUDY RATIONALE

- APR-1051 preclinical data showed high potency and selectivity with favorable drug exposure and tumor concentration.
- The low off target inhibition of APR-1051 on PLK1, PLK2, and PLK3 differentiates it from other WEE1 inhibitors and may confer an improved toxicity profile.
- APR-1051 may be a potential therapeutic anti-cancer agent.

STUDY OBJECTIVE

- The aim of this first-in-human phase 1 study is to assess the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of single-agent APR-1051 in advanced solid tumors harboring cancer-associated gene alterations.

APR-1051 treatment schedule:

- Group 1: Vehicle, 10mL/kg, oral, once-daily for 28 days
- Group 2: ATRN-330, 30mg/kg, oral, once-daily for 28 days + ATRN-1051, 15mg/kg, oral, once-daily for 28 days
- Group 3: ATRN-330, 15mg/kg, oral, once-daily for 28 days + ATRN-1051, 15mg/kg, oral, once-daily for 28 days
- Group 4: ATRN-330, 15mg/kg, oral, once-daily for 28 days + ATRN-1051, 15mg/kg, oral, once-daily for 28 days

Inclusion criteria:

- Age 18 years or older with ECOG PS 0 or 1 (kPS 0-70)
- Diagnosis of advanced/metastatic solid tumor that is either locally advanced and not amenable to curative therapy or stage 4 disease:
  - G1-S and G2-M phase transitions and stabilizing replication forks, particularly in CNE1 overexpressing cells.
  - Clinical studies focusing on the inhibition of WEE1 as a single agent have demonstrated encouraging antitumor effects.
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