ACESOT-1051: First-in-human phase 1 study of WEE1 inhibitor APR-1051 in patients with advanced solid tumors harboring cancer-associated gene alterations

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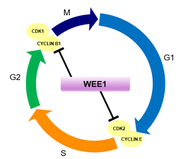
INTRODUCTION

- 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[1-3]
- DNA damage-induced cell cycle checkpoint activation of WEE1 slows G1-S and G2-M phase transitions and stabilizing replication forks, particularly in CCNE1 overexpressing cells[1-4]
- Clinical studies focusing on the inhibition of WEE1 as a single agent have demonstrated encouraging antitumor effects[1,5,6]
- 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[1,3,5-7]
- There are currently no FDA-approved WEE1 inhibitors

Figure 1. WEE1 activities in the DNA replication cell cycle



APR-1051

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

PRECLINICAL STUDIES

PHARMACOLOGY

- *In vitro* pharmacology studies have shown that APR-1051 inhibited WEE1 with an IC_{50} of 2.25 nM (cell-free LanthaScreen™ Eu Kinase Binding Assay)
- *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%

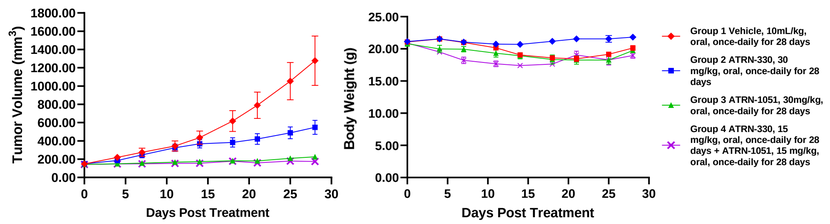
PHARMACOKINETICS/ADME

- Studies in healthy mice orally dosed APR-1051 10 mg/kg/day resulted in a C_{max} of 1,219 ng/mL, T_{max} of 2 hrs, and AUC_{0-24} of 14,211 ng*hr/mL which would allow for 3 to 8 times lower dosing than other WEE1 inhibitors in xenograft models to achieve comparable exposure (AUC_{0-24}) 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 toxicology studies were performed in rats and dogs to inform 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

Figure 2. Tumor volumes and body weights of human ovarian cancer (OVCAR-3) xenografted into female nude mice (mean ± SEM) following treatment with APR-1051 (WEE1i) with and without APR-330 (ATRi)



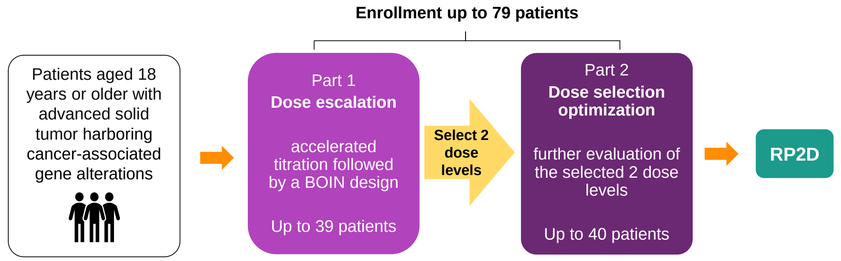
STUDY RATIONALE

- 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

Figure 3. Study design: Multi-center, open-label Phase I single-agent APR-1051 dose escalation and dose selection optimization



Oral APR-1051 will be administered once-daily for 28-day cycles

Primary objectives: Safety, DLT, MTD/MAD, RP2D

Secondary objectives: Pharmacokinetics, Antitumor activity (RECIST/PCWG3)

Exploratory objectives: Pharmacodynamics

Figure 4a. Single-agent APR-1051 dose escalation study schema

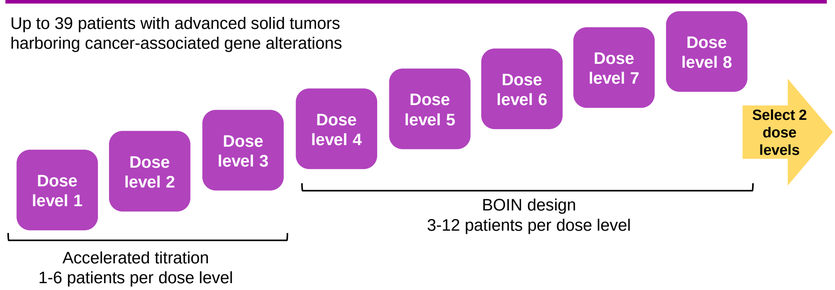
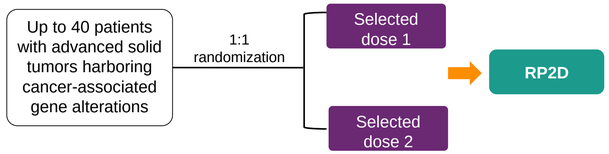


Figure 4b. Single-agent APR-1051 dose selection optimization study schema



KEY ELIGIBILITY CRITERIA

INCLUSION CRITERIA

- Age 18 years or older with ECOG PS 0 or 1 (or KPS ≥ 70)
- Diagnosis of advanced/metastatic solid tumor that is either locally advanced and not amenable to curative therapy or stage 4 disease with:
  - Amplification/overexpression of *CCNE1* or *CCNE2* regardless of tumor type, or
  - Deleterious mutations in *FBXW7* or *PPP2R1A* regardless of tumor type, or
  - Colorectal cancer with *KRAS-GLY12* and *TP53* co-mutation, or
  - Uterine serous carcinoma regardless of biomarker status
- Measurable disease per RECIST version 1.1 (PCWG3 criteria for patients with mCRPC)
- Recovered to Grade 1 or baseline from prior treatment-related toxicity/AEs
- Adequate bone marrow and organ function

EXCLUSION CRITERIA

- Prior systemic anti-cancer therapy within 3 weeks or at least 5 half-lives prior to the first of day of treatment
- Investigational agent within 30 days or 5 half-lives before the first day of treatment
- Prior therapy with a WEE1 inhibitor
- Concomitant treatment with other anti-cancer therapy (endocrine therapy for breast and prostate cancer permitted)

CORRELATIVE SCIENCE

- Molecular profiles for cancer-associated gene alterations will be recorded for each patient
- ctDNA obtained via blood samples will be collected at designated time points
- Evaluations of CTC for protein modifications and/or PBMC will be performed at designated time points

SUMMARY

- ACESOT-1051 first-in-human study has received FDA approval
- This biomarker-driven study will include patients with advanced/metastatic solid tumor harboring cancer-associated gene alterations, such as *CCNE1* or *CCNE2*, *FBXW7, PPP2R1A,* or *KRAS GLY12*
- Enrollment is anticipated to begin in Q2 2024
- MD Anderson Cancer Center is the lead site, and the study will be conducted at 3 to 10 sites in the U.S (NCT06260514)

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ABBREVIATIONS

AE, adverse event; AUC, area under the curve; BCRP, breast cancer resistance protein; BOIN, Bayesian optimal interval; *BRCA*, breast cancer gene; CDK, cyclin-dependent kinase; C_{max}, maximum plasma concentration; CTC, circulating tumor cell; ctDNA, circulating tumor DNA; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; GLP, Good Laboratory Practice; H2RA, H2 receptor antagonist; IC_{50}, half-maximal inhibitory concentration; KPS, Karnofsky Performance Scale; MAD, maximum administered dose; mCRPC, metastatic castration-resistant prostate cancer; MDR1, multidrug resistance 1; MTD, maximum tolerated dose; mVAF, mean variant allele frequency; NOAEL, no observed adverse effect level; PARP, poly-ADP ribose polymerase; PBMC, peripheral blood mononuclear cells; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PD, pharmacodynamics; P-gp, P-glycoprotein; PK, pharmacokinetics; PLK, polo-like kinase; PPI, proton pump inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SEM, standard error of mean; SOC, standard of care; T_{max}, time to maximum plasma concentration.

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