PB065

Safety and Preliminary Efficacy of APR-1051, a WEE1 Inhibitor, in a Phase 1 Study of Patients with Cancer-Associated Gene Alterations (ACESOT-1051)

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INTRODUCTION

WEE1 inhibition

- WEE1 tyrosine kinase is a key regulator of the G1-S and G2-M cell cycle checkpoints.[1] Inhibition of WEE1 can lead to aberrant cell cycle progression, premature entry into mitosis, and apoptosis[2]
- Clinical studies focusing on the inhibition of WEE1 as a single agent have demonstrated encouraging antitumor effects[3-5]
- However, myelosuppressive toxicity (e.g., anemia, thrombocytopenia, and neutropenia) has been limiting, including higher rates of Grade 3 toxicities in combination with standard treatments[1-5]

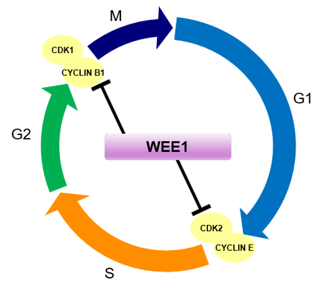


Figure 1. WEE1 activities in the DNA replication cell cycle

APR-1051

- APR-1051 is an orally bioavailable, small molecule inhibitor of WEE1 that has demonstrated *in vivo* anti-proliferative activity in several cancer models[5]
- APR-1051 may be a potential therapeutic anti-cancer agent. Its preclinical data showed high potency and selectivity with favorable drug exposure and tumor concentration[5]
- The low off-target inhibition of APR-1051 on the PLK family of kinases (PLK1, PLK2, PLK3) differentiates it from other WEE1 inhibitors and may confer an improved toxicity profile
- 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

STUDY METHODS

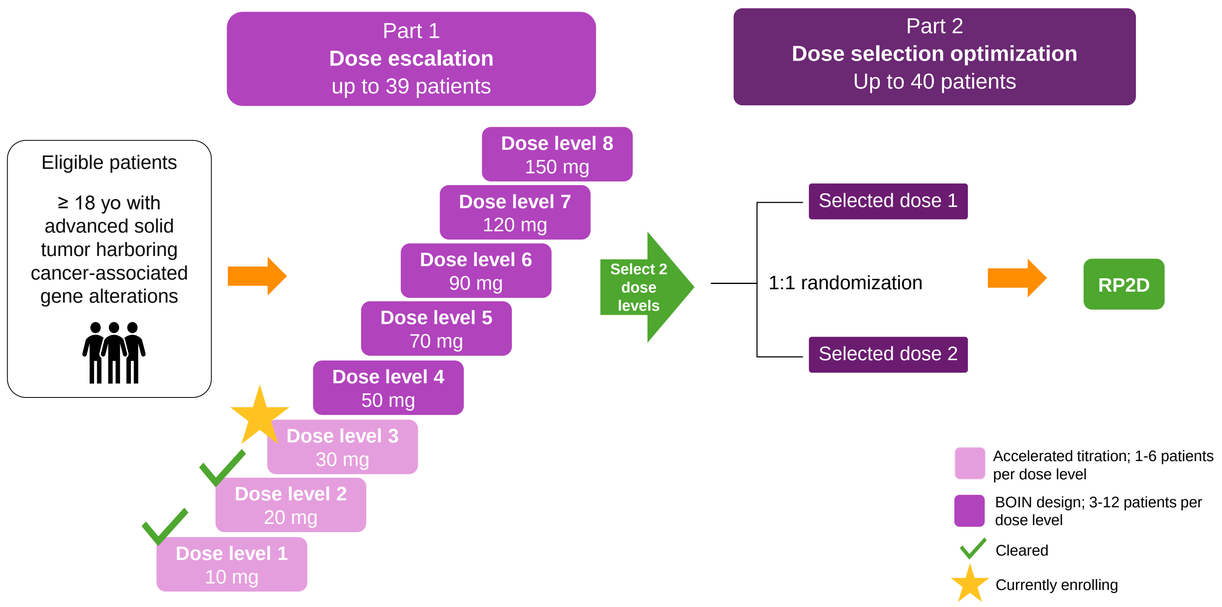
OBJECTIVES AND ENDPOINTS

	Objective	Endpoint
Primary	Characterize: • Safety • Dose-limiting toxicity (DLT) • Maximum tolerated dose (MTD) or maximum administered dose (MAD) • Recommended Phase 2 dose (RP2D)	• Adverse events (AE) • DLTs • Changes in physical exam, performance status, and clinical laboratory values from baseline
Secondary	Characterize: • Pharmacokinetics (PK) • Preliminary efficacy	• AUC_{0-T}, $AUC_{0-\infty}$, T_{max}, C_{max}, $t_{1/2}$, C_{min} • RECIST v1.1; Prostate Cancer Clinical Trials Working Group 3 (PCWG3) for metastatic castration-resistant prostate cancer (mCRPC)
Exploratory	Evaluate: • Pharmacodynamic (PD) effects	• *CCNE1* or *CCNE2* overexpression • *FBXW7* loss-of-function mutations • *PPP2R1A* loss-of-function mutations • *KRAS* GLY12 and *TP53* co-mutation

STUDY SCHEMA

Figure 2. Dose escalation and optimization using accelerated titration followed by BOIN design

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



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 specific gene alterations*
- 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

***Cancer-associated gene alterations**

- ❖ Amplification/overexpression of *CCNE1* or *CCNE2* regardless of tumor type
- ❖ Deleterious mutations in *FBXW7* or *PPP2R1A* regardless of tumor type
- ❖ Colorectal cancer with *KRAS* GLY12 and *TP53* co-mutation

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

PRELIMINARY RESULTS

PATIENT DEMOGRAPHICS

Table 1. Baseline demographics

Characteristic	Study patients (n=3)
Sex, n (%)	
Male	2 (67%)
Female	1 (33%)
Median age (range), years	70 (53 - 80)
Race, n (%)	
American Indian / Native Alaskan	1 (33%)
White	1 (33%)
Not reported	1 (33%)
ECOG PS, n (%)	
0	0 (0%)
1	3 (100%)
Prior lines of systemic chemotherapies, n (%)	
Median (range)	3 (3 - 5)
1 - 2	0 (0%)
3 - 4	2 (67%)
> 4	1 (33%)
Prior systemic therapy, n (%)	
Taxane	3 (100%)
Platinum-containing chemotherapy	2 (67%)
EGFR inhibitor	1 (33%)
VEGF inhibitor	1 (33%)
Topoisomerase inhibitor	1 (33%)
Investigational agent	1 (33%)
Gene alteration, n (%)	
CCNE1	3 (100%)
KRAS	2 (67%)
TP53	2 (67%)
Tumor type, n (%)	
Pancreatic cancer	2 (67%)
Gastric cancer	1 (37%)

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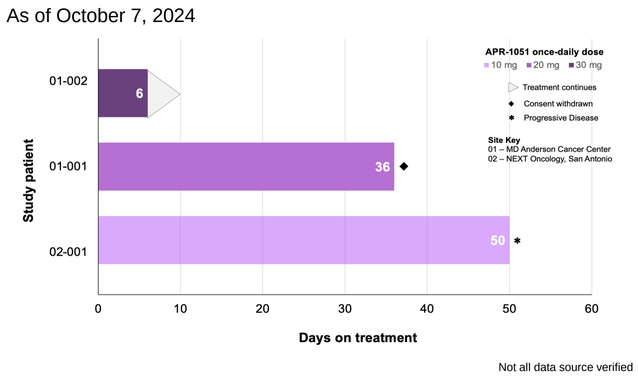
DURATION OF TREATMENT

Figure 3. Duration of treatment with APR-1051



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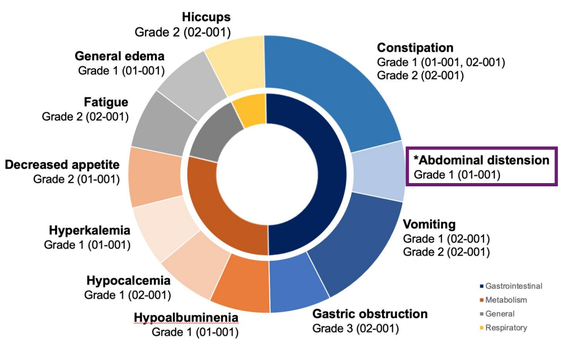
ADVERSE EVENTS

Figure 4. Summary of all-cause AEs

One AE possibly related to APR-1051*



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HEMATOLOGIC PROFILE

Figure 5. Complete blood count during the first cycle of treatment with APR-1051

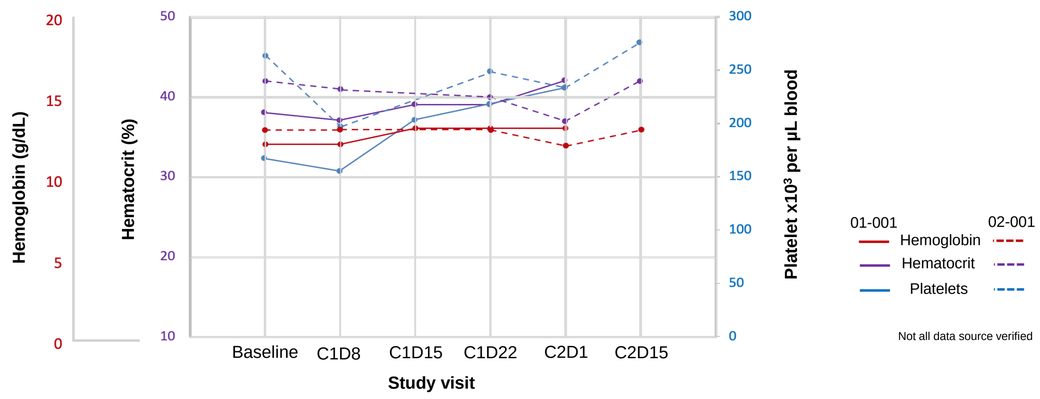

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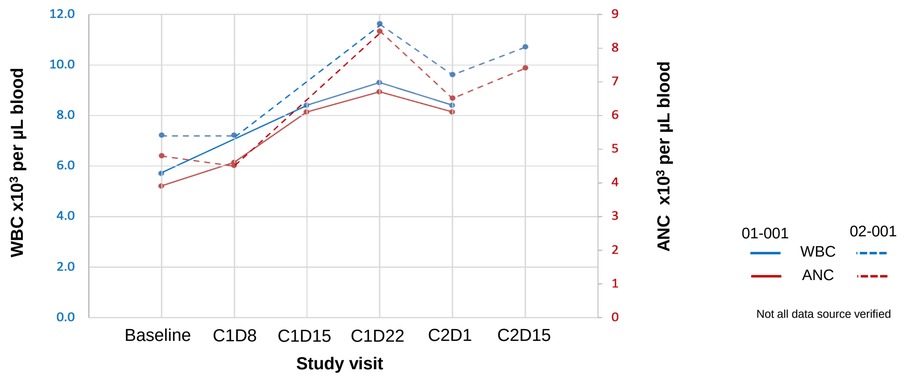
Figure 6. ANC and WBC during the first cycle of treatment with APR-1051



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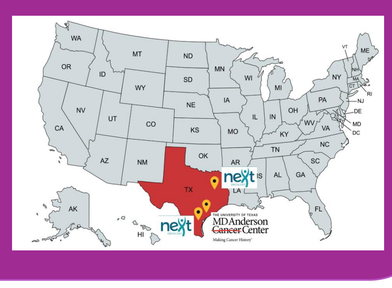
SUMMARY

- This is a first-in-human study of WEE1 inhibitor APR-1051 in patients with advanced solid tumors and specific cancer-associated gene alterations
- Preliminary results indicate APR-1051 is safe and well-tolerated with no hematologic toxicity and one possible treatment-related grade 1 AE at the dose levels assessed
- The study is currently enrolling into cohort 3 of the accelerated titration dose escalation
- Active enrollment is ongoing at three sites in the U.S. (NCT06260514) with additional sites planned



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Abbreviations

AE, adverse event; ANC, absolute neutrophil count; AUC, area under the curve; BOIN, Bayesian Optimal Interval Design; C, concentration; CCNE, Cyclin E; CTC, circulating tumor cell; ctDNA, circulating tumor DNA; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; FBXW7, F-box and WD repeat domain containing 7; KPS, Karnofsky Performance Scale; KRAS, Kirsten rat sarcoma viral oncogene homolog; MAD, maximum administered dose; MTD, maximum tolerated dose; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly (ADP-ribose) polymerase; PLK, Polo-like kinase 1; PBMC, peripheral blood mononuclear cell; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PD, pharmacodynamic; PPP2R1A, protein phosphatase 2 scaffold subunit Aalpha; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; T, time; TP53, tumor protein 53; WBC, white blood count; WEE1, Wee1-like protein kinase.

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