Early safety and efficacy of APR-1051, a novel WEE1 inhibitor, in patients with cancer-associated gene alterations: Updated data from ACESOT-1051 phase 1 trial

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INTRODUCTION

- WEE1 tyrosine kinase is a key regulator of the G1-S and G2-M cell cycle checkpoints[1,2]
- Inhibition of WEE1 can lead to cell death[1,2]
- WEE1 inhibitors have shown promise in treating several types of cancers in human studies[3-5]
- However, limiting myelosuppressive toxicity, such as anemia, thrombocytopenia, and neutropenia, has been observed, including higher rates of Grade 3 toxicities in combination with standard treatments[1-5]
- APR-1051 is an orally bioavailable, potent, and selective small molecule inhibitor of WEE1
- APR-1051 may be a potential therapeutic anti-cancer agent, demonstrating in vivo anti-proliferative activity with favorable drug exposure and tumor concentration in several cancer models[5]
- As of September 17, 2025, 16 patients with advanced solid tumors and specific cancer-associated gene alterations have been enrolled up to dose level 100 mg once daily in this first-in-human study of oral, WEE1 inhibitor APR-1051
- Here, we update on the ongoing first-in-human phase 1 study to assess the safety, pharmacokinetic, pharmacodynamic, and preliminary efficacy of single-agent APR-1051 in advanced solid tumors harboring cancer-associated gene alterations

Figure 1. WEE1 activities in the DNA replication cell cycle

METHODS

Key eligibility criteria

Inclusion criteria

- Age ≥ 18 years
- Advanced/metastatic solid tumor that is either locally advanced and not amenable to curative therapy or stage 4 disease with specific cancer-associated gene alterations, such as:
  - Amplification/overexpression of CCNE1 or CCNE2 regardless of tumor type
  - Deleterious mutations in FBXW7 or PPP2R1A regardless of tumor type
  - Colorectal cancer with KRAS GLY12/13 and TP53 co-mutation
- HPV-related OPSCC, defined as either p16+ SCC with a base of tongue or tonsil primary site or unknown primary p16+ SCC presenting as neck nodal metastases for which high risk HPV mRNA was confirmed by in situ hybridization
- p16+ cervical, vaginal, or vulvar SCC regardless of biomarker status
- Uterine serous carcinoma regardless of biomarker status
- Measurable disease per RECIST v1.1 (PCWG3 criteria for patients with mCRPC)
- ECOG PS 0 or 1 (or KPS ≥ 70)
- Recovered to Grade 1 or baseline from prior treatment-related toxicity/adverse events
- 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)

Presented at AACR NCI EORTC International Conference on Molecular Targets and Cancer Therapeutics
October 22 - 26, 2025, Boston, Massachusetts, USA
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METHODS (continued)

Study objectives

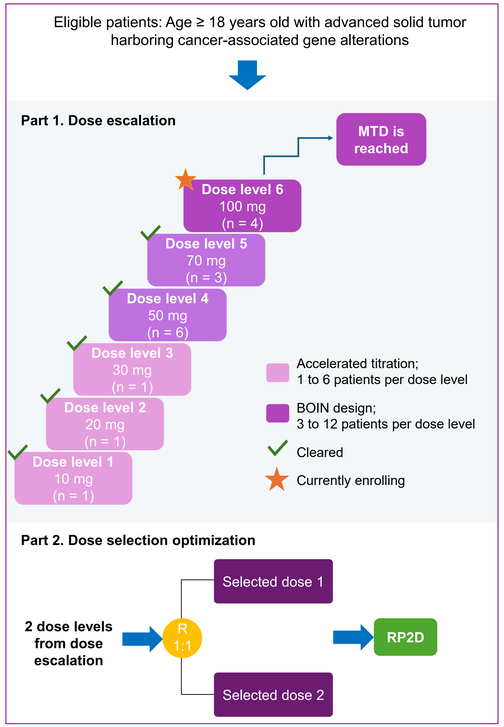
Primary objective

- To characterize the safety profile, dose-limiting toxicity, maximum tolerated dose or maximum administered dose, and recommended phase 2 dose of APR-1051

Secondary objective

- To characterize the pharmacokinetics of APR-1051 and the major metabolites and active metabolites of APR-1051
- To assess preliminary efficacy of APR-1051

Figure 2. Study schema



Abbreviations

AE, adverse event; AUC, area under the curve; BOIN, Bayesian Optimal Interval Design; C, concentration; C1D1, Cycle 1 Day 1; CCNE, Cyclin E; CTCAE v5.0, Common Terminology Criteria for Adverse Events, version 5.0; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; FBXW7, F-box and WD repeat domain containing 7; GLY, glycine; HPV, human papillomavirus; KPS, Karnowski Performance Scale; KRAS, Kirsten rat sarcoma viral oncogene homolog; mCRPC, metastatic castration-resistant prostate cancer; MedDRA, Medical Dictionary for Regulatory Activities; mRNA, messenger ribonucleic acid; MTD, maximum tolerated dose; OPSCC, oropharyngeal squamous cell carcinoma; PARP, poly (ADP-ribose) polymerase; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PD, pharmacodynamic, PK, pharmacokinetic; PPP2R1A, protein phosphatase 2 scaffold subunit alpha; R, randomized; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; RP2D, recommended phase 2 dose; SCC, squamous cell carcinoma; SD, standard deviation; t, time; TP53, tumor protein 53; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; WEE1, Wee1-like protein kinase

RESULTS

Figure 3. Summary of duration of treatment (N = 16)

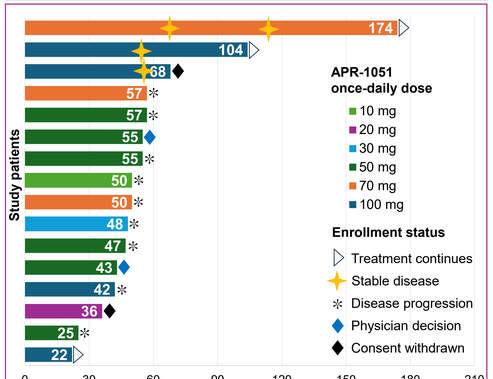


Table 1. Baseline demographics

Characteristic[a]	Study patients (N = 16)
Sex	
Male	9 (56)
Female	7 (44)
Median age (range), years	57 (40 to 86)
Race	
White	8 (50)
Asian	2 (13)
Black or African American	2 (13)
American Indian or Alaska Native	1 (6)
Unknown	3 (18)
ECOG PS	
0	5 (31)
1	11 (69)
Tumor types	
Colorectal	11 (69)
Pancreatic	2 (13)
Gastric	1 (6)
HPV+ OPSCC	1 (6)
Uterine	1 (6)
Prior lines of systemic therapy	
1	1 (6)
2 or 3	9 (56)
≥ 4	6 (38)

[a] n (%) unless otherwise indicated

Not all data source verified

Safety

- As of September 17, 2025, 15 (94%) patients experienced any treatment-emergent adverse event
- Common treatment-emergent adverse events were gastrointestinal effects (constipation, nausea, vomiting [each n = 4; 25%]), fatigue (n = 4; 25%), and anemia (n = 4; 25%)
- A total of 8 (50%) patients experienced adverse events assessed to be possibly or probably related to APR-1051, which were mostly Grade 1 or 2 gastrointestinal effects (n = 7; 44%)
- There was one treatment-related adverse event of ALT/AST increased (n = 1; 6%) considered serious and assessed as a dose-limiting toxicity (dose level 50 mg) (**Table 2**)
- No Grade 4 or 5 treatment-related adverse events have been observed

Table 2. TRAEs reported in patients treated with APR-1051

MedDRA Preferred Term	APR-1051 all dose levels (N = 16)	
Treatment-related AE[a], n	**All Grades**	**Grade ≥ 3[b]**
Nausea	4 (25)	0 (0)
Alanine aminotransferase increased	3 (19)	1 (6)[c]
Aspartate aminotransferase increased	3 (19)	1 (6)[c]
Fatigue	2 (13)	0 (0)
Anemia	1 (6)	0 (0)
Blood bilirubin increased	1 (6)	0 (0)
Constipation	1 (6)	0 (0)
Dysgeusia	1 (6)	0 (0)
Dyspepsia	1 (6)	0 (0)
Gastroesophageal reflux disease	1 (6)	0 (0)
Lymphocyte count decreased	1 (6)	0 (0)
Vomiting	1 (6)	0 (0)

[a] A patient may have more than one AE and/or have the same AE more than once
[b] Grade 3 unless otherwise indicated based on CTCAE v5.0
[c] Alanine aminotransferase increased and aspartate aminotransferase increased was one DLT event

Pharmacokinetics

- Data indicate APR-1051 t_{max} is an average of 4 hours and its half-life averages 16.7 hours (Cycle 1 Day 1), supporting once-daily administration (**Table 3**)
- There is a strong trend for dose proportionality with oral exposure increasing with rising dose levels (**Figures 4 and 5**)
- APR-1051 accumulation is present between Cycle 1 Day 1, and steady-state with accumulation ratios average 2.4 (SD 1.2) for $AUC_{0\text{-}24}$ and 2.1 (SD 0.7) for C_{max}

Table 3. $AUC_{0\text{-}24}$ by dose level at Cycle 1 Day 1

Dose Level mg, once daily	N	Cycle 1, Day 1			
		$AUC_{0\text{-}24hr}$ (ng*h/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)
		Geo Mean (SD)	Geo Mean (SD)	Geo Mean (SD)	Geo Mean (SD)
10	1	128	8.2	6	17
20	1	120	9.7	4	20
30	1	497	33.5	4	15
50	6	707 (682)	46 (41)	3 (1.5)	20 (9)
70	3	799 (322)	52 (23)	4 (0)	16 (3)
100	3	1456 (780)	124 (85)	2 (1.5)	13 (1)

RESULTS (continued)

Figure 4. APR-1051 concentration vs time at Cycle 1 Day 1

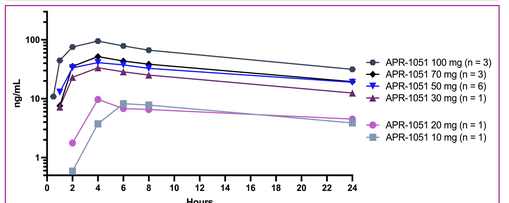
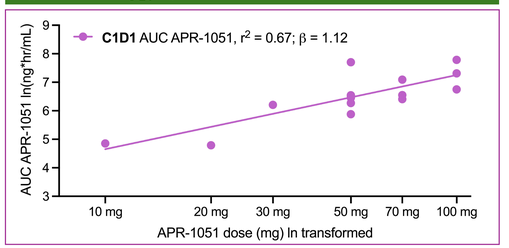


Figure 5. $AUC_{0\text{-}24}$ by dose level at Cycle 1 Day 1



CONCLUSION

Summary

- This ongoing phase 1 study is currently enrolling at three sites in the U.S. (NCT06260514)
- As of September 17, 2025, 16 patients with advanced solid tumors and specific cancer-associated gene alterations have been enrolled up to dose level 100 mg once daily in this first-in-human study of oral WEE1 inhibitor APR-1051
- APR-1051 was manageable with mostly Grade 1 or 2 adverse events, which were mainly gastrointestinal events and fatigue
- Pharmacokinetic studies support once-daily dosing, and oral exposure is dose proportional
- Preliminary signs of clinical benefit have been observed in 3 (19%) patients with disease stabilization

Acknowledgments

- The patients and their families who make this study possible
- The clinical study teams who are participating in the study
- This study is sponsored by Aprea Therapeutics, Inc.

References

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