First-in-human phase 1/2a trial of a macrocyclic ATR inhibitor (ATRN-119) in patients with advanced solid tumors

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INTRODUCTION

- DNA replication stress is caused by genomic alterations that promote tumorigenesis[1,2]
- ATR kinase, a member of the phosphatidylinositol kinase-related kinase family, stabilizes the genome in response to DNA replication stress[1,2]
- Thus, targeting ATR kinase may be a promising approach to treating cancer
- ATRN-119 is a potent inhibitor of the ATR kinase
- Preliminary studies demonstrate a high selectivity of ATRN-119 for the ATR kinase
- Improved selectivity correlates with increased tolerability, thereby permitting once-daily dosing[3]
- Both *in vitro* and *in vivo* studies show that ATRN-119 inhibits the growth of tumors harboring alterations in DNA damage repair genes in xenografts both alone and in combination with other targeted treatments, such as PARP and WEE1 inhibitors[3,4]

Figure 1. Macrocyclic structure of ATRN-119

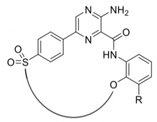

Figure 2. Study schema and study endpoints

Male or female patients aged 12 years or older with solid tumor harboring specific DDR mutations per NGS

Part 1. Dose escalation

3+3 dose escalation with once-daily dosing (up to 30* patients)

Total enrollment up to 60 patients

- Dose level 8: 1,300 mg
- Dose level 7: 1,100 mg
- Dose level 6: 800 mg
- Dose level 5: 550 mg (Currently enrolling)
- Dose level 4: 350 mg
- Dose level 3: 200 mg
- Dose level 2: 100 mg
- Dose level 1: 50 mg

✓ = cleared

*Planned protocol amendment to add dose levels 7 and 8

MTD/RP2D

Part 2. Dose expansion

Dose expansion of single-agent ATRN-119 after MTD/RP2D is established (up to 30 patients)

Potential indications: colorectal, prostate, gastric, endometrial

Mutations: undisclosed RepliBiom biomarkers

Primary objectives: Safety, MTD, RP2D, Pharmacokinetics

Secondary objectives: Antitumor activity (RECIST/PCWG3)

Exploratory objectives: Association between identified mutations and clinical outcomes

Key eligibility criteria

Inclusion criteria: ≥ 12 years old with advanced solid tumor harboring ≥ 1 documented DDR mutation per NGS; Measurable disease per RECIST v1.1 (PCWG3 criteria for mCRPC); Failed ≥ 1 approved SOC therapy; ECOG PS ≤ 1; Adequate bone marrow, renal, and liver function

Exclusion criteria: Cytotoxic chemotherapy, immunotherapy, radiotherapy, or targeted therapies within 4 weeks or ≥ 5 half-lives, and all prior therapy-related AEs are not at baseline/stable; Investigational agent within 5 half-lives or 30 days of study drug, whichever is longer; Known CNS involvement that is not stable; Concomitant treatment with strong inhibitors/inducers of CYP3A4 or CYP2D6

Figure 3. Summary of duration of treatment with daily ATRN-119

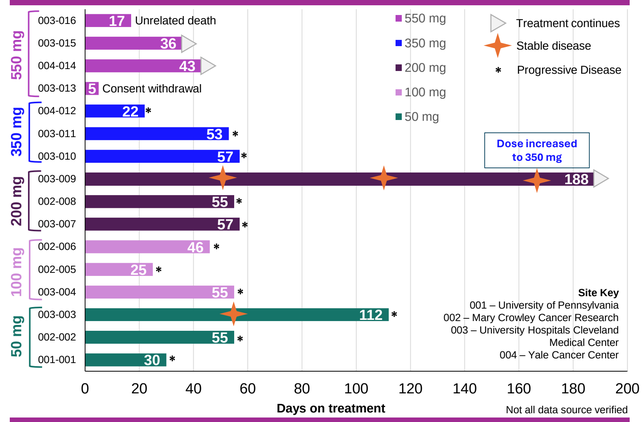

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Table 1. Baseline Demographics

Characteristic	Study patients (n=16)
Sex, n (%)	
Male	6 (38%)
Female	10 (63%)
Median age (range), years	62 (42 - 79)
Race, n (%)	
White	12 (75%)
Black or African American	4 (25%)
ECOG PS, n (%)	
0	3 (19%)
1	13 (81%)
Prior lines of systemic chemotherapies, n (%)	
Median (range)	3 (1 - 13)
< 2, n (%)	1 (6%)
2 - 3, n (%)	7 (44%)
≥ 4, n (%)	8 (50%)
Prior systemic therapy, n (%)	
Platinum-containing chemotherapy	14 (88%)
Immuno-oncology	3 (19%)
PARP inhibitor	1 (6%)
DDR deficiency, n (%)	
TP53	12 (75%)
CDKN2A	4 (25%)
CHEK2	3 (19%)
CDK12	2 (13%)
ARID1A	1 (6%)
RAD51D	1 (6%)
Rb1	1 (6%)
PALB2	1 (6%)
Tumor type, n (%)	
Colorectal carcinoma	4 (25%)
Breast cancer	2 (13%)
Pancreatic cancer	2 (13%)
Adenocarcinoma of unknown primary	1 (6%)
Adrenal cortical carcinoma	1 (6%)
Appendiceal adenocarcinoma	1 (6%)
Duodenal cancer	1 (6%)
Endometrial cancer	1 (6%)
Fallopian tube adenocarcinoma	1 (6%)
Prostate cancer	1 (6%)
Squamous NSCLC	1 (6%)

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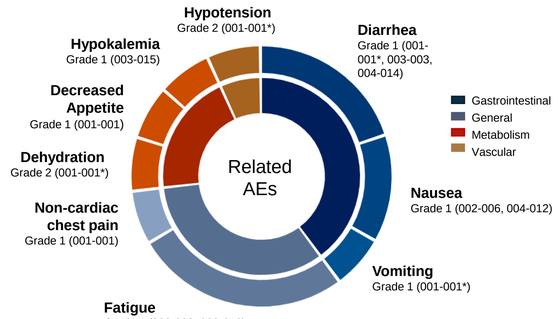
Figure 4. Adverse events at least possibly related to ATRN-119



*Resulted in treatment interruption

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All-cause treatment-emergent adverse events

- As of March 12, 2024, 10 of 16 patients experienced all-cause TEAEs
- No reported DLTs and no treatment-related Grade 4 or higher AEs
- Grade 1 (46%), Grade 2 (35%), Grade 3 (15%), Grade 4 (0%), and Grade 5 (4%, none were treatment-related) AEs were reported
- At doses up to 550 mg once-daily, there were no signs of hematological toxicity (no reported thrombocytopenia or leukopenia/neutropenia, one case of unrelated grade 1 anemia)
- Gastrointestinal disorders were the most common AEs (32%), e.g., nausea, vomiting, and diarrhea (all were Grade 1 or Grade 2)
- No target organ toxicity
- To date, the study data show no clear dose-relationship

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Figure 5. ATRN-119 Steady State Plasma Concentrations (Cycle 1 Day 7)

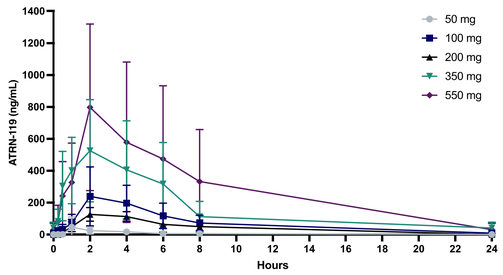


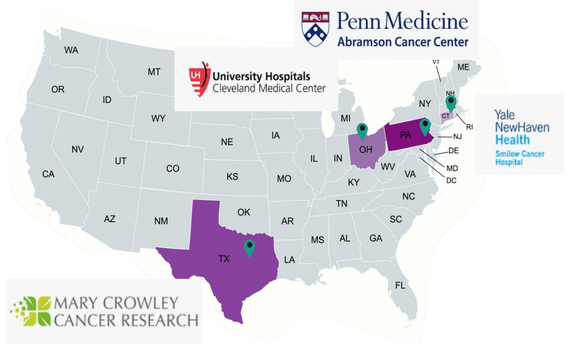
Table 2. ATRN-119 Cycle 1 Day 7 PK parameters (Steady state)

Dose Level (mg, once daily)	N	$AUC_{0\text{-}24hr}$ (ng*h/mL)	C_{max} (ng/mL)	Half-life (hours)
		Mean (SD)	Mean (SD)	Mean (SD)
50	3	180 (143)	94 (119)	1.4 (1.1)
100	3	1771 (920)	305 (171)	4.6 (0.5)
200	3	1024 (162)	179 (23)	4.3 (0.3)
350	3	5252 (4362)	605 (358)	6 (0.7)
550	3	6899 (6058)	797 (522)	4.5 (0.7)

SUMMARY

- This is an ongoing first-in-human phase 1 study of ATRN-119 in patients with advanced solid tumors harboring specific DDR mutations (NCT04905914)
- ATRN-119 is administered daily on a continuous schedule
- At the current dose level (550 mg), ATRN-119 is found to be safe and well tolerated with no DLTs
- Pharmacokinetic studies demonstrate:
  - ATRN-119 exhibits near-dose proportional exposure following oral administration
  - ATRN-119 has a half-life of 4-6 hours
  - ATRN-119 plasma concentrations are entering the expected therapeutic range at the current highest dose level (550 mg)
- The median number of prior lines of treatment was 3 (range: 1 to 13)
- Preliminary signs of clinical benefit have been observed in the early stages of development
  - One patient treated at dose level 1 (50 mg) had stable disease at Day 55 and disease progression at Day 112
  - One patient treated at dose level 3 (200 mg) had stable disease at Days 55, 112, and 168, and continues to be on treatment as of Day 188

Figure 6. Ongoing active enrollment at four participating sites



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ABBREVIATIONS

AE, adverse event; CNS, central nervous system; ATR, ataxia telangiectasia and Rad3 related; CYP, cytochrome P450; DDR, DNA damages response; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRPC, metastatic castration-resistant prostate cancer; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PARP, poly-ADP ribose polymerase; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; NGS, next generation sequencing; MTD, maximum tolerated dose; SAE, serious adverse event; SD, standard deviation; SOC, standard of care; TEAE, treatment-related adverse event

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