C034

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 (RS) in tumorigenesis
- RS is a hallmark cause of genomic instability in cancer cells[1,2]
- Genomic alterations associated with RS have been characterized in many cancer types using large-scale genomic analyses[3]

Ataxia Telangiectasia and Rad3-related (ATR) kinase
- ATR kinase is a member of the phosphoinositide 3-kinase related kinase family **(PIKK)** and a principal regulator of the DNA damage response (DDR) to RS[1]
- Activated upon DNA single strand formation, ATR kinase is essential for stabilizing stressed DNA replication forks and preventing their collapse into DNA double-strand breaks
- Exploiting RS vulnerability with ATR inhibition may be a promising strategy in cancer therapeutics[1,2]

ATRN-119
- ATRN-119 is an oral, highly specific ATR kinase inhibitor
- Preliminary studies have shown that:
  - The high specificity for ATR kinase correlates with increased tolerability, daily dosing, and reduced dose-limiting hematologic toxicity[6]
  - Single agent ATRN-119 *in vitro* increased cytotoxicity against a broad spectrum of cancer cell lines harboring DDR gene alterations and *in vivo* inhibited tumor growth in cell line-derived and patient-derived xenografts
  - Combination studies *in vivo* demonstrated significant synergy between ATRN-119 and poly (ADP-ribose) polymerase (PARP) inhibition[5,6]

Preclinical Studies

Figure 1. ATRN-119 is an orally bioavailable, potent, and selective macrocyclic small molecule inhibitor of ATR kinase

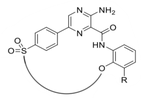


Figure 2. ATRN-119 binds to ATR (A), inhibits its biological activity (B), and triggers DNA replication fork collapse and DS breaks (C)

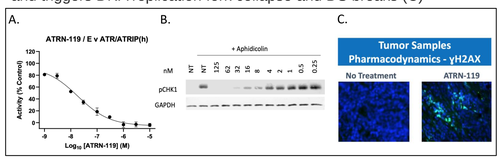
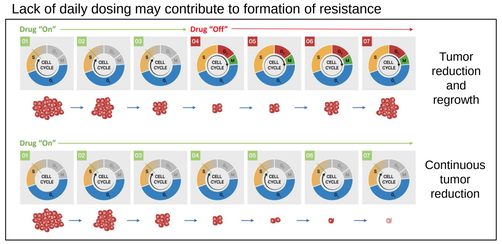


Figure 3. ATRN-119 daily dosing Is desirable

Lack of daily dosing may contribute to formation of resistance



Study Methods

Objectives

Primary objectives
- To evaluate the safety profile of escalating doses of daily oral ATRN-119 and to determine the MTD and RP2D
- To characterize the PK profile of oral ATRN-119 and its active metabolite ATRN-157

Secondary objective
- To evaluate antitumor activity of oral ATRN-119 in various solid tumors

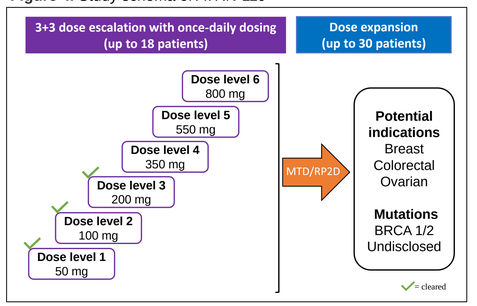
Exploratory objective
- To explore the association between mutations identified in tumor tissue and clinical outcome

Key Eligibility Criteria

Inclusion criteria
- ≥ 12 years old with advanced solid tumor harboring ≥ 1 documented DDR mutation (e.g., ARID1A) 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 metastases or CNS involvement that is not stable for previous 1 month
- Concomitant treatment with strong inhibitors or inducers of CYP3A4 or CYP2D6

Figure 4. Study schema of ATRN-119



Preliminary Results

Table 1. Patient demographics

Characteristic	Study patients (n=9)
Sex, n (%)	
Male	4 (44%)
Female	5 (56%)
Median age (range), years	62 (48 - 79)
Race, n (%)	
White	6 (67%)
Black or African American	3 (33%)
ECOG PS, n (%)	
0	3 (33%)
1	6 (67%)
Prior lines of systemic chemotherapies, n (%)	
< 2	1 (11%)
2 - 3	5 (56%)
≥ 4	3 (33%)
Prior systemic therapy, n (%)	
Platinum-containing chemotherapy	9 (100%)
Immuno-oncology	1 (11%)
PARP inhibitor	1 (11%)
DDR deficiency, n (%)	
TP53	7 (78%)
CDKN2A	3 (33%)
ARID1A	1 (11%)
RAD51D	1 (11%)
Rb1	1 (11%)
Tumor type, n (%)	
Colorectal carcinoma	2 (22%)
Adrenal cortical carcinoma	1 (11%)
Appendiceal adenocarcinoma	1 (11%)
Duodenal cancer	1 (11%)
Endometrial cancer	1 (11%)
Fallopian tube adenocarcinoma	1 (11%)
Pancreatic cancer	1 (11%)
Adenocarcinoma of unknown primary	1 (11%)

Not all data source verified

Figure 5. Summary of duration of treatment

As of Sept 22, 2023

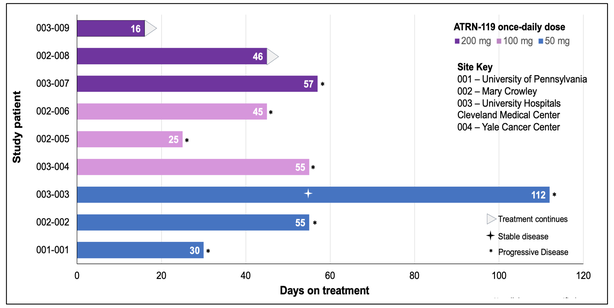


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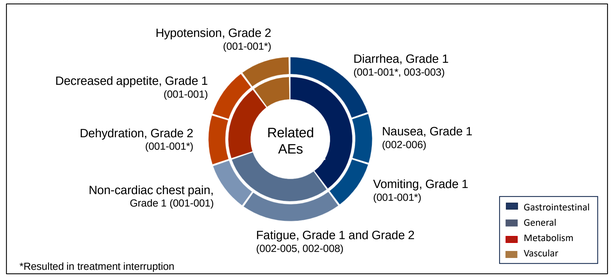
Figure 6. Adverse events at least possibly related to ATRN-119

As of Sep 20, 2023: Five study patients have experienced AEs assessed as possibly/probably related to ATRN-119



*Resulted in treatment interruption

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Preliminary Results (cont'd)

Table 2. All-cause treatment-emergent adverse events

As of Sept 20, 2023: no Grade 4 events, no significant hematologic toxicity, and no liver function test toxicity have been reported

	Total (n=9)		Dose Level 1 (n=3)		Dose Level 2 (n=3)		Dose Level 3 (n=3)	
TEAE* by system organ class	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)
Gastrointestinal								
Diarrhea	3 (33%)	0	2 (67%)	0	1 (33%)	0	0	0
Nausea	2 (22%)	0	0	0	2 (67%)	0	0	0
Abdominal discomfort	1 (11%)	0	1 (33%)	0	0	0	0	0
Abdominal distension	1 (11%)	0	0	0	1 (33%)	0	0	0
Abdominal pain	1 (11%)	0	1 (33%)	0	0	0	0	0
Flatulence	1 (11%)	0	1 (33%)	0	0	0	0	0
Hemorrhoidal hemorrhage	1 (11%)	0	0	0	0	0	1 (33%)	0
Rectal hemorrhage	1 (11%)	0	1 (33%)	0	0	0	0	0
Stomatitis	1 (11%)	0	1 (33%)	0	0	0	0	0
Vomiting	1 (11%)	0	1 (33%)	0	0	0	0	0
Ascites	0	1 (11%)	0	0	0	1 (33%)	0	0
Metabolism and nutrition								
Blood phosphorus decreased	1 (11%)	0	0	0	1 (33%)	0	0	0
Decreased appetite	1 (11%)	0	1 (33%)	0	0	0	0	0
Dehydration	1 (11%)	0	1 (33%)	0	0	0	0	0
Hyperglycemia	1 (11%)	0	1 (33%)	0	0	0	0	0
Nervous system								
Asthenia	1 (11%)	0	0	0	1 (33%)	0	0	0
Headache	1 (11%)	0	1 (33%)	0	0	0	0	0
Syncope	0	1 (11%)	0	1 (33%)	0	0	0	0
Infections								
Candida infection	1 (11%)	0	1 (33%)	0	0	0	0	0
Upper respiratory tract infection	1 (11%)	0	1 (33%)	0	0	0	0	0
Musculoskeletal and connective tissue								
Arthralgia	1 (11%)	0	0	0	1 (33%)	0	0	0
Back pain	1 (11%)	0	1 (33%)	0	0	0	0	0
Renal and urinary								
Dysuria	1 (11%)	0	0	0	1 (33%)	0	0	0
Pollakiuria	1 (11%)	0	0	0	1 (33%)	0	0	0
Respiratory								
Dyspnea	1 (11%)	0	1 (33%)	0	0	0	0	0
Hemoptysis	1 (11%)	0	1 (33%)	0	0	0	0	0
Vascular								
Hypotension	1 (11%)	0	1 (33%)	0	0	0	0	0
Other								
Fatigue	4 (44%)	0	1 (33%)	0	2 (67%)	0	1 (33%)	0
Chest pain (non-cardiac)	1 (11%)	1 (11%)	1 (33%)	0	0	1 (33%)	0	0
Fall	1 (11%)	0	0	0	1 (33%)	0	0	0

*Excludes progressive disease

Not all data source verified

Summary

- Daily dosing of ATRN-119 may result in persistent tumor-reducing effect
- No dose-limiting toxicities have been reported to date in patients treated with ATRN-119
- ATRN-119 appears to be well tolerated with a manageable toxicity profile
- Pharmacokinetic data analysis is ongoing and results will be presented in future publications
- This phase 1/2a study is currently enrolling eligible study patients at four U.S. sites (NCT04905914)
- The dose expansion cohort in select cancers is on track to be initiated in 2Q 2024

Abbreviations: 2Q, second quarter; AE, adverse event; ATR, Ataxia Telangiectasia and Rad3-related; CNS, central nervous system; DDR, DNA damage response; ECOG, Eastern Cooperative Oncology Group; MTD, maximum tolerated dose; NGS, next generation sequencing; PARPi, poly ADP ribose polymerase inhibitor; mCRPC, metastatic castration-resistant prostate cancer; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; RS, replication stress; SOC, standard of care; TEAE, treatment-emergent adverse event

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