Updated data from ABOYA-119: A phase 1/2a trial of ATRN-119, a novel macrocyclic ATR inhibitor, in patients with advanced solid tumors harboring DNA damage repair alterations

B010

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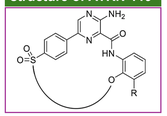
INTRODUCTION

- Replication stress is a major contributor to cellular genomic instability driving tumorigenesis[1,2]
- In response to replication stress-induced DNA damage, ataxia telangiectasia and rad3-related (ATR) kinase is activated to preserve genomic integrity[1,2]
- Genomic alterations associated with replication stress have been characterized in several cancer types[3]
- ATR kinase inhibitors disrupt cellular DNA damage repair (DDR) pathways and are emerging as promising targeted therapies for solid tumors[1,2]
- ATRN-119 is an oral, differentiated macrocyclic, highly specific ATR kinase inhibitor with demonstrated antitumor activity that correlates with specific DDR, tumor suppressor, or oncogene alterations in pre-clinical studies[4]
- In pre-clinical studies, the high specificity for ATR kinase correlates with increased tolerability, daily dosing, and reduced dose-limiting hematologic toxicity[5]

Figure 1. Macrocyclic structure of ATRN-119



METHODS

Study objectives

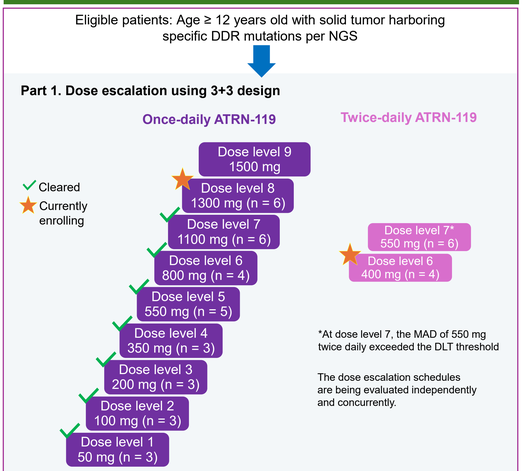
Primary objectives

- To evaluate the safety profile of escalating doses of oral ATRN-119 and to determine the maximum tolerated dose and recommended phase 2 dose
- To characterize the pharmacokinetic 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

Figure 2. Study schema



METHODS (continued)

Key eligibility criteria

Inclusion criteria

- Age ≥ 12 years old
- 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 standard-of-care 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 adverse events 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

RESULTS

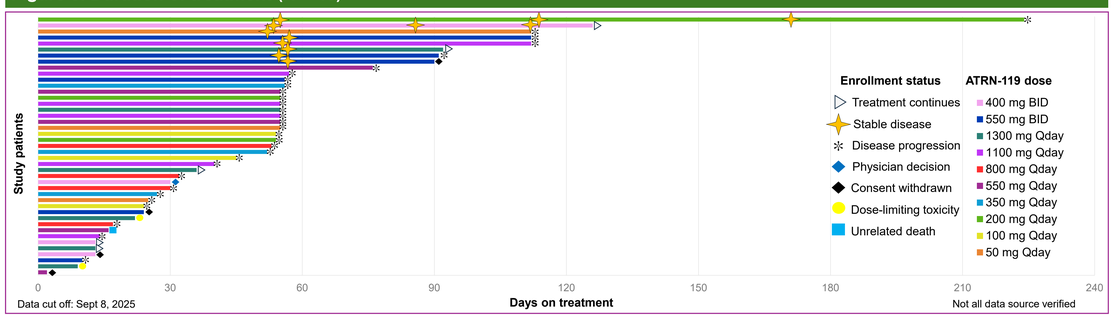
Table 1. Baseline demographics

Characteristic[a]	Study patients (N = 43)
Sex	
Male	22 (51)
Female	21 (49)
Median age (range), years	65 (41 to 81)
Race	
White	33 (77)
Black or African American	8 (19)
American Indian or Alaska native	1 (2)
Asian	1 (2)
ECOG PS	
0	16 (37)
1	27 (63)
Tumor types	
Colorectal	11 (25)
Pancreatic	8 (19)
Breast	4 (9)
Prostate	4 (9)
Endometrial	3 (7)
Ovarian	3 (7)
Lung	2 (5)
Other[b]	8 (19)
Prior lines of systemic therapy	
1	4 (9)
2 or 3	16 (37)
≥ 4	23 (54)

[a] n (%) unless otherwise indicated
[b] Other: adrenal, appendiceal, duodenal, esophageal, fallopian, leiomyosarcoma, renal, unknown (each n = 1; 2%)

RESULTS (continued)

Figure 3. Duration of treatment (N = 43)



Safety

- A total of 40 (93%) patients experienced any treatment-emergent adverse event
- Gastrointestinal toxicity, including diarrhea, nausea, and vomiting, was the most frequently reported adverse events
- As of September 8, 2025, 31 (72%) patients experienced adverse events assessed to be possibly or probably related to ATRN-119, and most of these events were gastrointestinal effects (n = 23; 53%) and fatigue (n = 10; 23%) (**Table 2**)
- One (2%) patient had a serious treatment-related adverse event of Grade 3 anemia at dose level 550 mg BID
- Four (9%) patients had dose-limiting toxicities, including diarrhea (n = 2; 5%) at dose levels 550 mg BID (Grade 3) and 1300 mg Qday (Grade 3); blood bilirubin increased (n = 1; 2%) at dose level 1100 mg Qday (Grade 3); transaminase increased (n = 1; 2%) at dose level 550 mg BID (Grade 2)
- No Grade 4 or 5 adverse events have been observed

Table 2. TRAEs reported in ≥ 2 patients and/or any Grade ≥ 3

MedDRA Preferred Term	ATRN-119 All dose levels (N = 43)	
Treatment-related AEs[a], n (%)	**All Grades**	**Grade ≥ 3[b]**
Diarrhea	17 (40)	2 (5)
Nausea	12 (28)	0 (0)
Fatigue	10 (23)	2 (5)
Vomiting	6 (14)	0 (0)
Decreased appetite	4 (9)	0 (0)
Abdominal pain	3 (7)	0 (0)
Dehydration	3 (7)	0 (0)
Abdominal distension	2 (5)	0 (0)
Constipation	2 (5)	0 (0)
Dysgeusia	2 (5)	0 (0)
Hypotension	2 (5)	0 (0)
Anemia	1 (2)	1 (2)[c]
Blood bilirubin increased	1 (2)	1 (2)

[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] Assessed to be a serious adverse event

Pharmacokinetics

- The half-life (median) of ATRN-119 is 5.1 hours (IQR 3.7-6.6), and the median t_{max} is 4 hours. There was a strong trend for dose proportionality based on AUC (**Figure 4**)
- Twice-daily administration provides higher steady-state exposures compared to equivalent total daily doses administered once daily (**Table 3**)

Figure 4. ATRN-119 AUC_{0-24} at steady-state by dose level

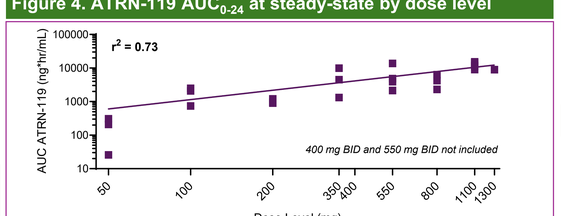


Table 3. ATRN-119 PK parameters at steady-state by dose level

Dose Level (mg)	N	AUC_{0-24hr} (ng*h/mL) Mean (SD)	C_{max} (ng/mL) Mean (SD)	$t_{1/2}$ (h) Mean (SD)
50 Qday	3	180.3 (142.8)	56.5 (56)	2.1 (1.4)
100 Qday	3	1771 (920)	277 (151)	3.8 (1.6)
200 Qday	3	1024 (162.1)	149 (9.2)	3.2 (0.5)
350 Qday	3	5252 (4362)	525 (320)	5.9 (0.5)
550 Qday	4	6152 (5167)	727 (449)	5.4 (1.1)
800 Qday	3	4285 (2014)	432 (496)	8.6 (5.1)
1100 Qday	5	12413 (2519)	999 (209)	7 (2.9)
1300 Qday	1	8880 (.)	717 (.)	4.8 (.)
400 BID[a]	2	15770 (7692)	976 (430)	4 (0.3)
550 BID[a]	4	16598 (8071)	973 (457)	7.2 (3.4)

[a] For BID administration, the Cycle 2 Day 1 AUC_{0-24hr} is estimated by doubling the AUC_{0-12hr}

CONCLUSION

Summary

- This ongoing phase 1/2a study is currently enrolling eligible study patients at seven U.S. sites (NCT04905914)
- As of September 8, 2025, 43 patients with advanced solid tumors and ≥ 1 DDR mutation have been enrolled in this first-in-human study of oral ATRN-119
- ATRN-119 appears to be manageable with mostly Grade 1 or 2 adverse events
- Gastrointestinal adverse events, including diarrhea, nausea, and vomiting, were most frequently reported followed by fatigue
- Pharmacokinetic studies demonstrated proportional increase in exposure with ascending doses
- Twice-daily administration of ATRN-119 provides increased exposure compared to the equivalent total daily doses administered once daily
- Preliminary signs of clinical benefit have been observed in 8 (18.6%) patients at various dose levels
- Additional dosing regimens may be explored

Acknowledgments

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- The clinical study teams who are participating in the study
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Abbreviations

AE, adverse event; ATR, Ataxia Telangiectasia and Rad3-related; AUC, area under the curve; BID, twice daily; C, concentration; CNS, central nervous system; CTCAE v5.0, Common Terminology Criteria for Adverse Events, version 5.0; DDR, DNA damage response; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; mCRPC, metastatic castration-resistant prostate cancer; MedDRA, Medical Dictionary for Regulatory Activities; MTD, maximum tolerated dose; NGS, next generation sequencing; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PK, pharmacokinetic; Qday, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended phase 2 dose; SD, standard deviation; SBIR, Small Business Innovation Research; SOC, standard of care; t, time; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

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