PB336

ATRN-119, a Novel Macrocyclic ATR Inhibitor, in Patients with Advanced Solid Malignancies: A Phase 1/2a Trial (ABOYA-119)

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INTRODUCTION

DNA damage and response (DDR) and Ataxia Telangiectasia and Rad3-related (ATR) kinase

- DDR is key to a cell's ability to maintain genomic stability, and its deficiency has been characterized in many cancer types[1,2]
- ATR kinase is a principal regulator of DDR; when activated, it stabilizes stressed DNA replication forks and prevents their collapse into DNA double-strand breaks
- ATR inhibition may be a promising strategy in cancer therapeutics[1,3]
- Advanced solid tumors with dysregulated DDR or oncogenic stress may be more susceptible to ATR kinase inhibition

ATRN-119

- ATRN-119 is a differentiated macrocyclic and highly selective, potent, oral ATR inhibitor with antitumor activity correlated with specific DDR, tumor suppressor, or oncogene alterations
- Preliminary studies showed improved selectivity correlated with increased tolerability[2]
- Both *in vitro* and *in vivo* studies of ATRN-119 demonstrate significant anticancer effects in DDR deficient models, both alone and in combination with other targeted treatments, such as PARP inhibitors and WEE1 inhibitors[2,4]
- Here, we summarize preliminary results of this ongoing first-in-human study of ATRN-119

STUDY OBJECTIVES

Primary objectives and endpoints

- Evaluate the safety profile of escalating doses of ATRN-119
- Determine the MTD and RP2D
- Characterize the PK profile of ATRN-119 and its active metabolite ATRN-157

Secondary objectives and endpoints

- Evaluate antitumor activity of ATRN-119 in various solid tumors

Exploratory objective

- Explore the association between mutations identified in tumor tissue and clinical outcomes

KEY ELIGIBILITY CRITERIA

Inclusion criteria

- ≥ 12 years old with advanced solid tumor harboring ≥ 1 NGS-confirmed specific DDR mutation:
  - Any mutation in *ARID1A*
  - Any missense mutation in KRAS at *Gly12* or *Gly13*
  - Probable loss of function mutation in select genes
  - Amplification (>4 genomic copies in total) of *MYC*, *CCNE1* or *CCNE2*
- Merkel cell carcinoma regardless of known mutation status
- Measurable disease per RECIST v1.1 (PCWG3 criteria for mCRPC)
- Failed ≥ 1 approved SOC therapy
- ECOG PS ≤ 1

Exclusion criteria

- Known additional malignancy that is progressing or requires active treatment (with some exceptions)
- Known CNS metastases/involvement that is not treated and stable for the previous 1 month
- 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
- Concomitant treatment with strong inhibitors or inducers of CYP3A4 or CYP2D6

PATIENT DEMOGRAPHICS

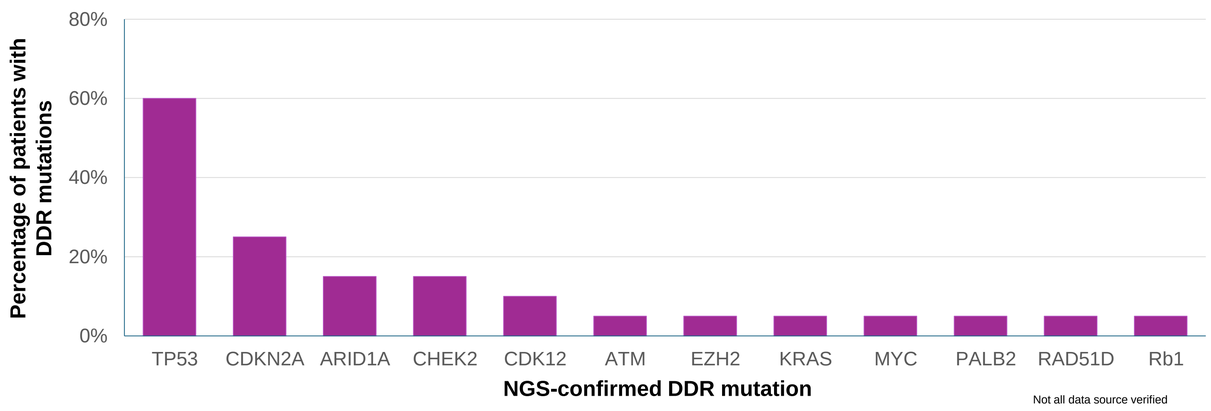
Table 1. Baseline demographics

Characteristic	Study patients (n=20)
Sex, n (%)	
Male	7 (35%)
Female	13 (65%)
Median age (range), years	62 (42 - 79)
Race, n (%)	
White	15 (75%)
Black or African American	5 (25%)
ECOG PS, n (%)	
0	5 (25%)
1	15 (75%)
Prior lines of systemic chemotherapies, n (%)	
< 2	2 (10%)
2 - 3	9 (45%)
≥ 4	9 (45%)
Prior systemic therapy, n (%)	
Platinum-based chemotherapy	16 (80%)
Immuno-oncology	4 (20%)
PARP inhibitor	2 (10%)

Characteristic	Study patients (n=20)
Tumor type, n (%)	
Colorectal carcinoma	5 (25%)
Breast cancer	3 (15%)
Lung cancer	2 (10%)
Pancreatic cancer	2 (10%)
Adrenal cortical carcinoma	1 (5%)
Appendiceal adenocarcinoma	1 (5%)
Duodenal cancer	1 (5%)
Endometrial cancer	1 (5%)
Fallopian tube adenocarcinoma	1 (5%)
Ovarian cancer	1 (5%)
Prostate cancer	1 (5%)
Adenocarcinoma of unknown primary	1 (5%)

Not all data source verified

Figure 1. DDR mutations at study enrollment



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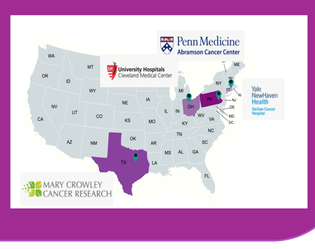
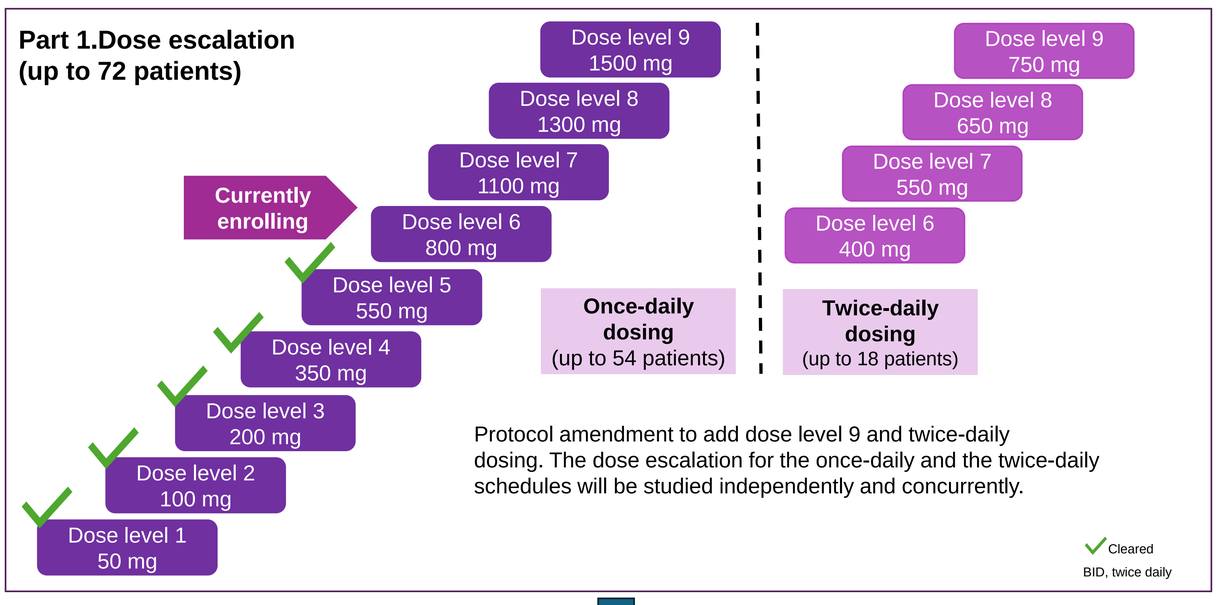
SUMMARY

- In this ongoing first-in-human study of oral ATRN-119 in patients with advanced solid tumors harboring ≥ 1 specific DDR mutation, continuous daily administration up to and including 800 mg is shown to be safe and tolerable
- As of Oct 2, 2024, most AEs are Grade 1 or 2 and there are no DLTs, no SAEs, and no ATRN-119-related AEs ≥ Grade 4
- PK studies demonstrate increasing exposure with escalating doses
- Preliminary signs of clinical benefit have been observed in two patients treated at the 50 mg and 200 mg dose level
- This study is currently in the dose escalation phase with planned addition of a twice-daily ATRN-119 dosing regimen
- Active enrollment is ongoing at four sites in the U.S. (NCT04905914)



STUDY SCHEMA

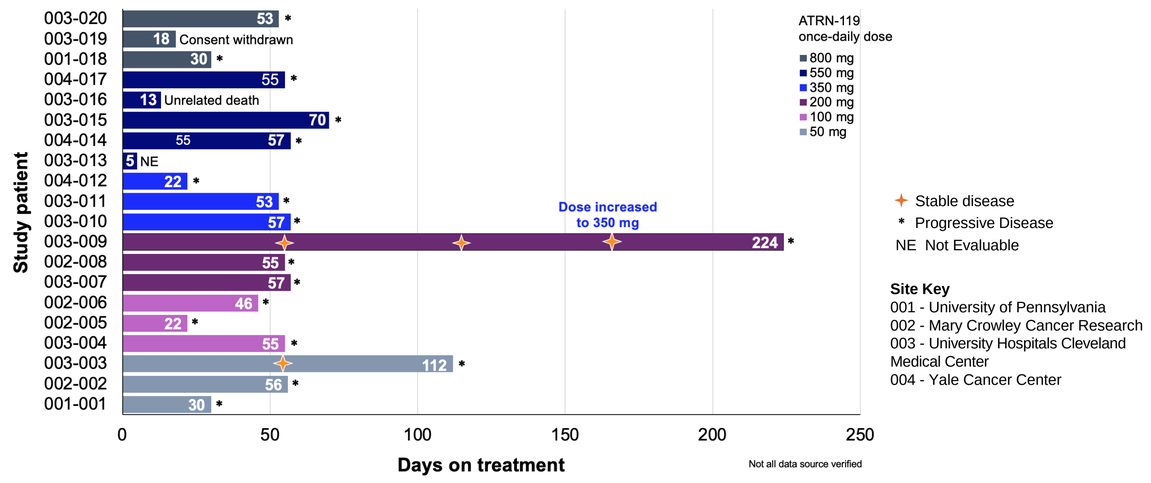
Figure 2. 3+3 dose escalation and dose expansion (up to 132 patients)



DURATION OF TREATMENT

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

As of October 7, 2024



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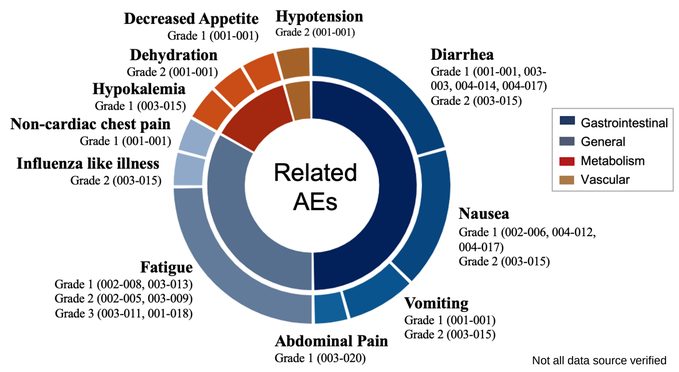
ADVERSE EVENTS

Figure 4. AEs at least possibly related to ATRN-119



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All-cause TEAEs reported at ATRN-119 dose levels 50-800 mg once-daily

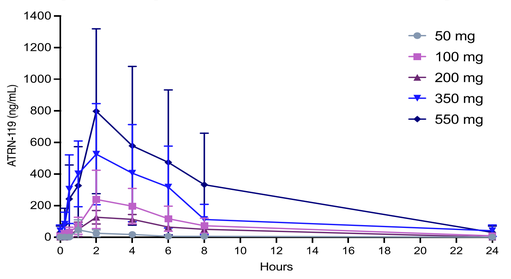
- As of Oct 2, 2024, 14 of 20 patients experienced AEs considered to possibly/probably related to ATRN-119
- No related SAE or grade 4-5 AEs have been observed
- There is no clear dose-relationship in AE
- There is no clear target organ toxicity
- No signs of hematological toxicity have been registered and no DLTs have been observed to date

PHARMACOKINETICS

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

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)	57 (56)	2.1 (1.4)
100	3	1771 (920)	277 (151)	3.8 (1.6)
200	3	1024 (162)	149 (9.2)	3.2 (0.5)
350	3	5252 (4362)	525 (320)	5.9 (0.5)
550	3	6899 (6058)	797 (522)	5.5 (1.4)

Figure 5. ATRN-119 Cycle 1 Day 7 (steady state) mean plasma concentration by dose



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Abbreviations AE, adverse event; ARID1A, AT-rich interactive domain 1A; ATR, Ataxia Telangiectasia and Rad3-related; **AUC, area under the curve; BID, twice daily; CHEK, checkpoint kinase;** DDR, DNA damage response; CCNC, Cyclin C; CCNE, Cyclin E; CDK, cyclin-dependent kinase; **CDKN2A, cyclin dependent kinase inhibitor 2A;** C_{max}, maximum serum concentration; **CNS, central nervous system; CYP, Cytochrome P450; DLT, dose-limiting toxicity; DDR,** DNA damage and response; ECOG PS, Eastern Cooperative Oncology Group performance status; **EZH2,** enhancer of zeste 2 polycomb repressive complex 2 subunit; Gly, glycine; KRAS, Kirsten rat sarcoma viral oncogene homolog; **mCRPC,** metastatic castration-resistant prostate cancer; MTD, maximum tolerated dose; MYC, myelocytomatosis oncogene; NGS, next-generation sequencing; PALB2, partner and localizer of BRCA2; PARP, poly (ADP-ribose) polymerase; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PK, pharmacokinetic; RAD51D, **RAD51 paralog D; Rb1,** retinoblastoma 1; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SD, standard deviation; SOC, standard of care; TP53, tumor protein 53; WEE1, Wee1-like protein kinase.

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