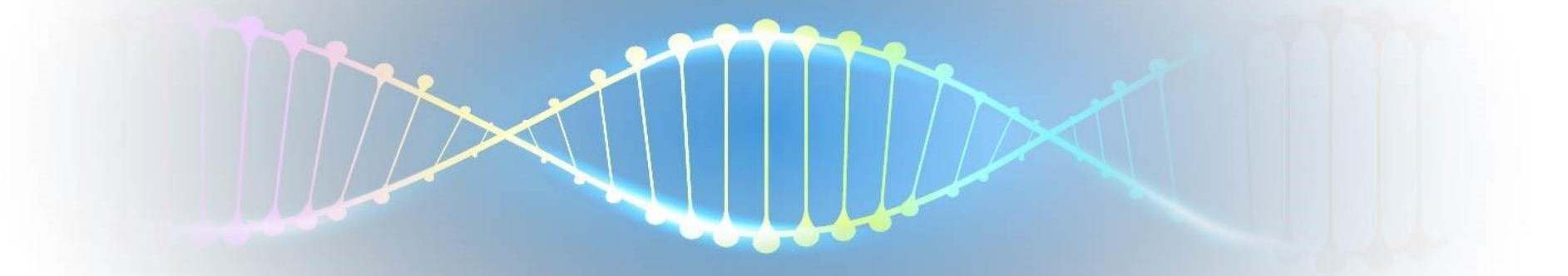
aprea therapeutics



Precision Oncology Through Synthetic Lethality

October 2023

Forward-Looking Statements

Certain information contained in this presentation includes “forward-looking statements”, within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, related to our clinical trials, regulatory submissions and strategic plans. We may, in some cases use terms such as “predicts,” “believes,” “potential,” “continue,” “anticipates,” “estimates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “likely,” “will,” “should” or other words that convey uncertainty of the future events or outcomes to identify these forward-looking statements. The forward-looking statements are based on current beliefs and expectations of our management team that involve risks, potential changes in circumstances, assumptions, and uncertainties. Any or all of the forward-looking statements may turn out to be wrong or be affected by inaccurate assumptions our management team might make or by known or unknown risks and uncertainties. These forward-looking statements are subject to risks and uncertainties including, without limitation, risks related to the success and timing of our clinical trials or other studies and the other risks set forth in our filings with the U.S. Securities and Exchange Commission, including our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q. Forward-looking statements regarding our product candidates are also subject to additional risks and uncertainties, including without limitation, with respect to: our dependence on additional financing to fund our operations and complete the development and commercialization of our product candidates, and the risks that raising such additional capital may restrict our operations or require us to relinquish rights to our technologies or product candidates; our limited history and preclinical status of the assets we acquired from Atrin Pharmaceuticals Inc.; our business plan or the likelihood of the successful implementation of such business plan; the timing of initiation of planned clinical trials for our product candidates; the future success of such trials; the successful implementation of our research and development programs and collaborations and the interpretation of the results and findings of such programs and collaborations and whether such results are sufficient to support the future success of our product candidates; the success, timing and cost of our anticipated clinical trials for our current product candidates; the timing of initiation, futility analyses, data presentation, reporting and publication and receipt of interim results (including, without limitation, any preclinical results or data); any statements about our understanding of product candidates mechanisms of action and interpretation of preclinical and early clinical results from its clinical development programs and any collaboration studies; and other factors, including legislative, regulatory, political and economic developments not within our control. For all these reasons, actual results and developments could be materially different from those expressed in or implied by our forward-looking statements. You are cautioned not to place undue reliance on these forward-looking statements, which are made only as of the date of this presentation. We undertake no obligation to update such forward-looking statements to reflect subsequent events or circumstances, except to the extent required by law or regulation.

Aprea Therapeutics (NASDAQ: APRE)

Precision Oncology via Synthetic Lethality in Defined Patient Populations

- Clinical stage precision medicine via novel synthetic lethality (SL) - based therapeutics
- All programs addressing significant unmet medical need

- ATR Inhibitor: ATRN-119
  - Clinical proof-of-concept
    - Phase 1/2a – Ongoing Dose Escalation
      - Patients 12 years of age or older with solid tumors harboring DDR mutation
      - Primary objective : Safety, MTD, RP2D and PK profile
  - Pre-clinical proof-of-principle
    - Demonstrated anti-tumor activity
    - Synergistic with anti-cancer therapies, including PARP inhibitors
  - Potential differentiation in safety and tolerability

Aprea Therapeutics (NASDAQ: APRE)

Precision Oncology via Synthetic Lethality in Defined Patient Populations

- WEE1 Inhibitor: ATRN-1051
  - IND enabling studies
    - Anticipate submitting an IND by the end of 2023
  - Pre-clinical proof-of-principle
    - Demonstrated anti-tumor activity
    - Ovarian cancer with Cyclin E over expression
    - Synergistic with anti-cancer therapies, including ATR inhibitor
  - Potential differentiation in safety and tolerability

- DDR Inhibitor: Undisclosed
  - Lead optimization
    - Target identified from our RepliBiom discovery platform

Experienced Leadership

Management

Oren Gilad, Ph.D.
President and CEO

John Hamill
CFO

Nadeem Mirza, M.D., MPH
Senior Medical Advisor

Ze'ev Weiss, CPA, B.Sc.
Chief Business Advisor

Mike Carleton, Ph.D.
Translational Medicine Advisor

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ATR Inhibitor : ATRN-119

ATR Inhibitor : ATRN-119

Clinical Proof-Of-Concept

Aprea Phase 1/2a - AR-276-01 - Study Overview

AR-276-01: A PHASE 1/2a, OPEN-LABEL, SAFETY, PHARMACOKINETIC, AND PRELIMINARY EFFICACY STUDY OF ORAL ATRN-119 IN PATIENTS WITH ADVANCED SOLID TUMORS

Sites: 4 US sites for dose escalation

- University of Pennsylvania
- Mary Crowley Cancer Research
- University Hospitals Cleveland Medical Center
- Yale Cancer Center

Patient enrollment: 48 patients in total

- Escalation phase: up to 18 patients
- Expansion phase: up to 30 patients

IMP: ATRN-119 is an oral ATR kinase inhibitor given daily

Aprea AR-276-01 Study Overview, Continued

Patient Population:

Male or female subjects 12 years of age or older with solid tumors harboring any DDR mutation per NGS

Part 1 (up to 18 patients)

Dose escalation (6 dose levels)

3+3 design

Part 2 (up to 30 patients)

Dose expansion, after MTD / RP2D established

Primary objectives:

- Safety, MTD, RP2D
- Pharmacokinetics (PK profile of oral ATRN-119 and its active metabolite ATRN-157)

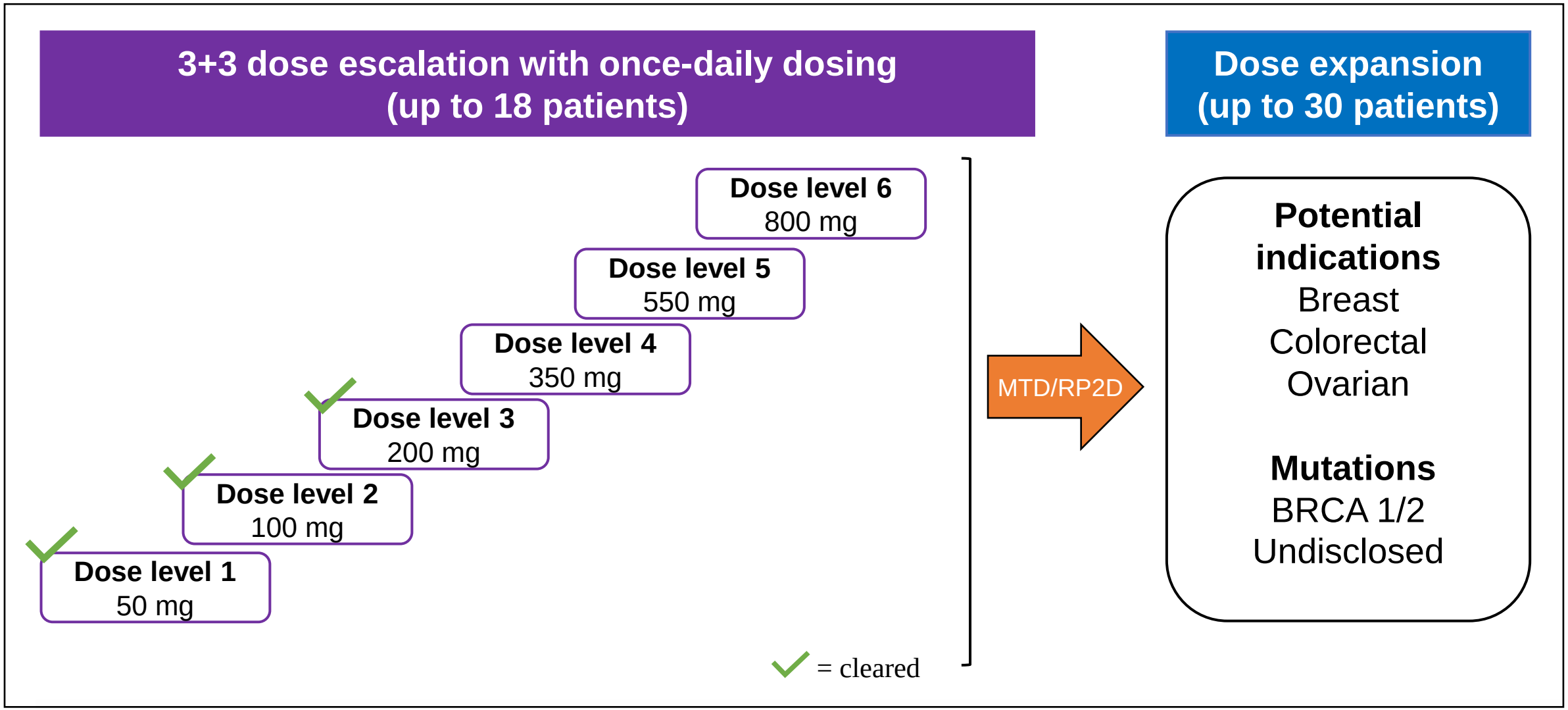
Secondary objectives:

- Antitumor activity (RECIST/PCWG3)

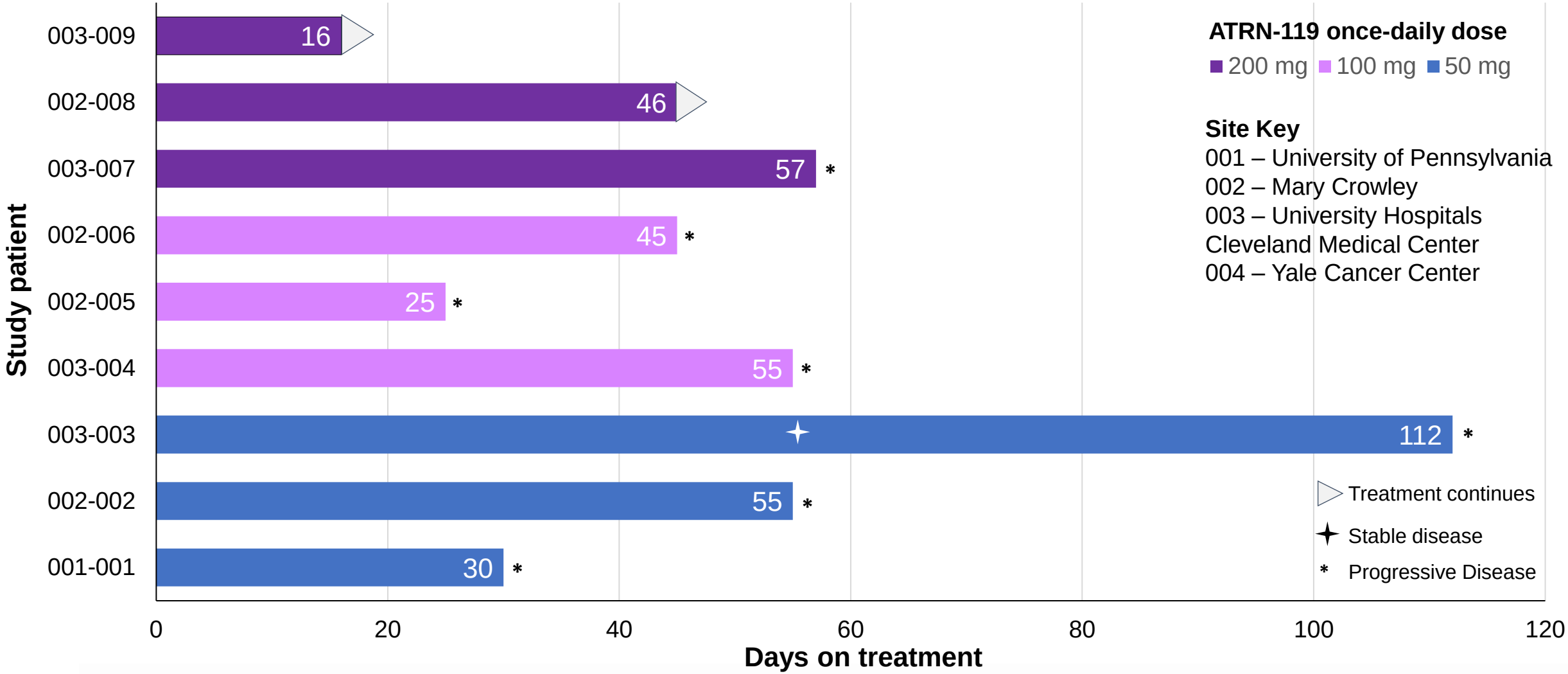
Exploratory objectives:

- Association between identified mutations and clinical outcomes

Aprea AR-276-01 Study Overview, Continued



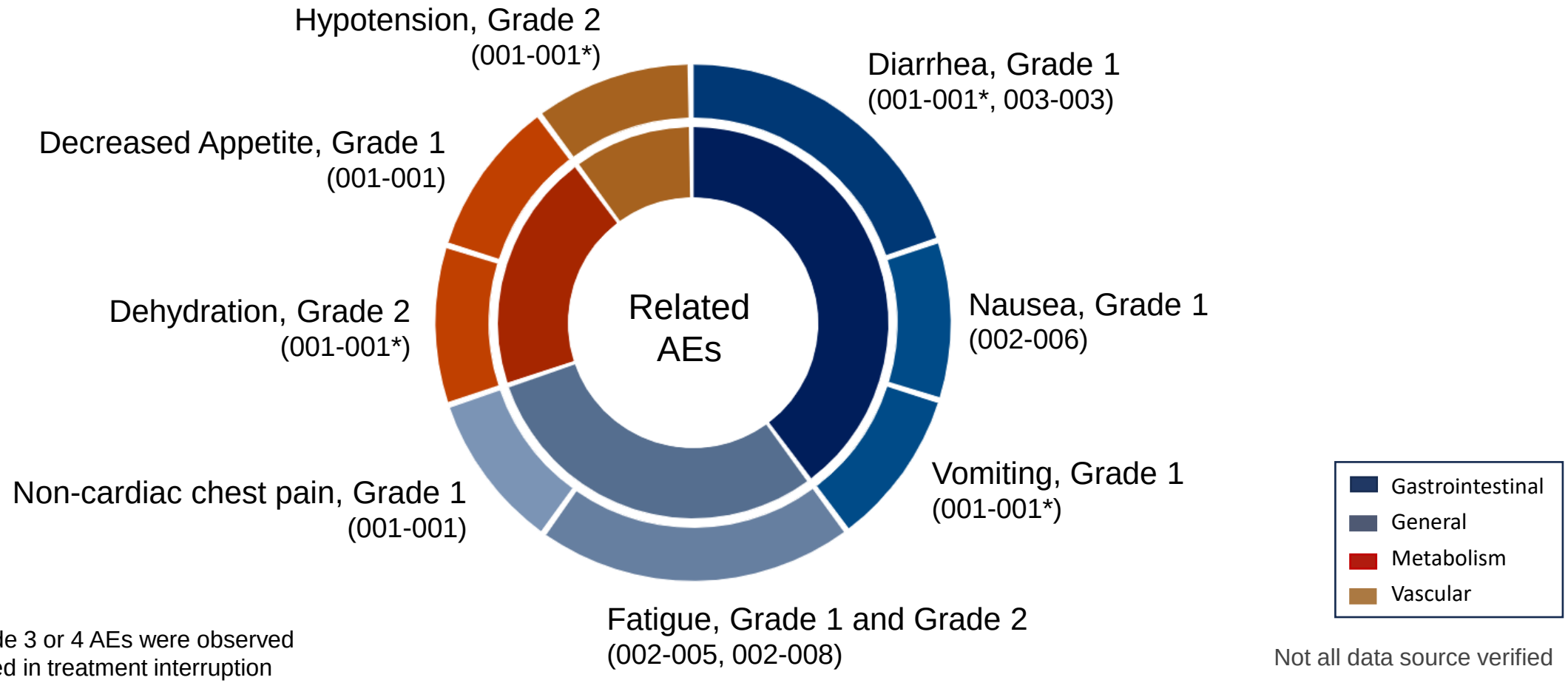
Summary of Duration of Treatment as of Sept 22, 2023



Not all data source verified

No ATRN-119 Related Grade 3 or 4 Adverse Events Reported

As of Sept 20, 2023: Five out of nine study patients have experienced AEs# assessed to be possibly/probably related to ATRN-119



No grade 3 or 4 AEs were observed
* Resulted in treatment interruption

Not all data source verified

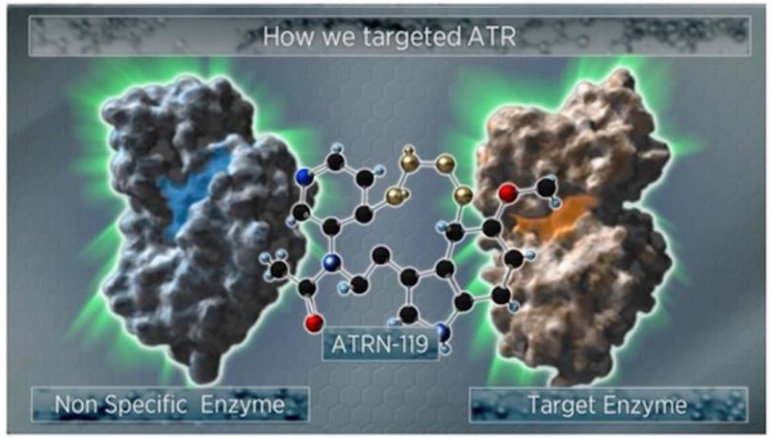
ATRN-119
2023-2025 Anticipated Clinical Milestones

Milestone	Timeline
Phase 1/2a – Monotherapy Dose Escalation	
Preliminary clinical data	4Q 2023
Last Patient Enrolled	1Q 2024
Phase 1/2a – Monotherapy Dose Expansion	
First Patient Enrolled	2Q 2024
Last Patient Enrolled	2Q 2025
Phase 1/2a – Combination	
First Patient Enrolled	1H 2024
Last Patient Enrolled	2H 2025

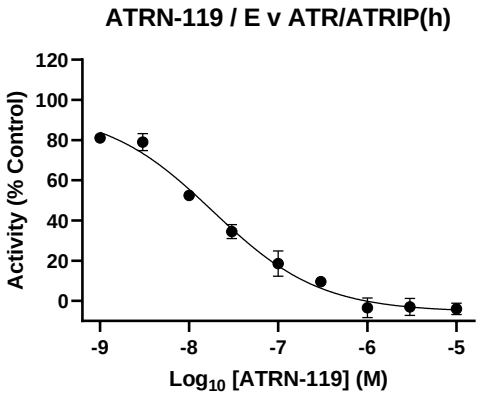
ATR Inhibitor : ATRN-119

Preclinical
Proof-Of-Principal

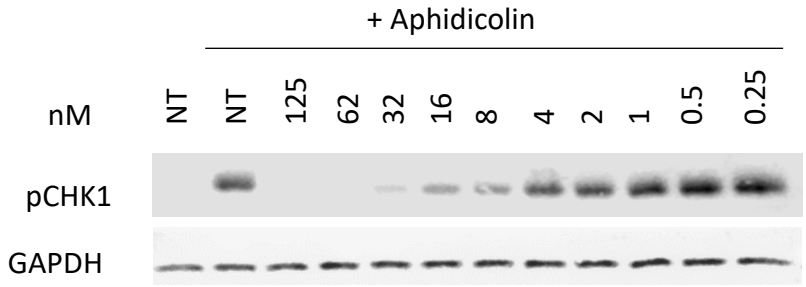
ATR Inhibitor - ATRN-119 Mechanism of Action



Replication fork collapse
+ Double Strand Breaks

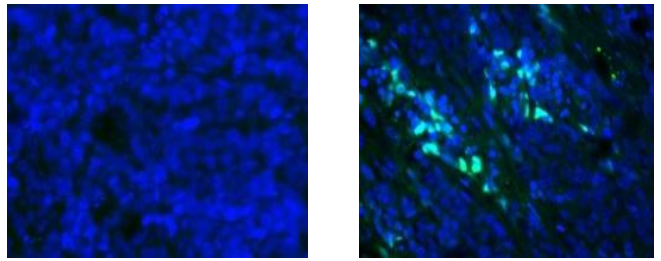


ATRN-119 binds to ATR



…inhibits its biological activity…

Tumor Samples Pharmacodynamics - γH2AX

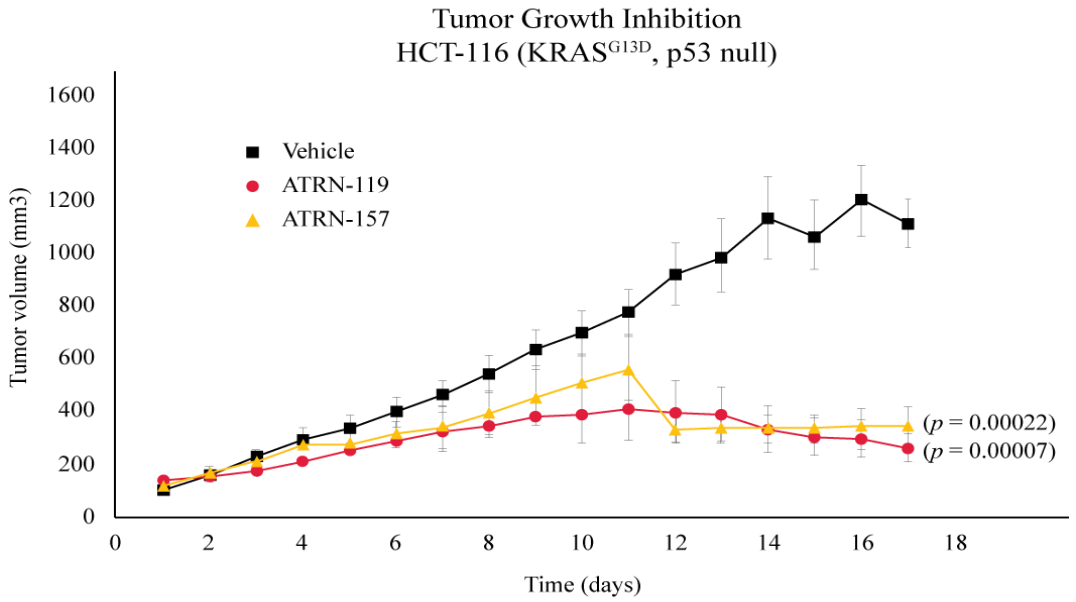


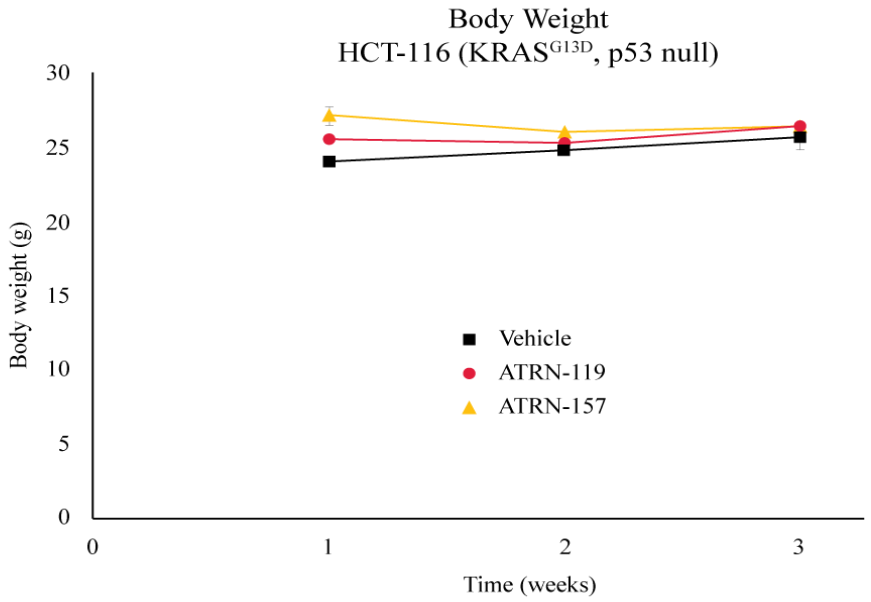
…and triggers replication fork collapse and Double Strand Breaks

Data on file

ATRN-119 Preclinical Profile

- Nanomolar potency in vitro across a broad spectrum of cancer cell lines
- Strong tumor control observed in vivo, including in challenging genetic backgrounds



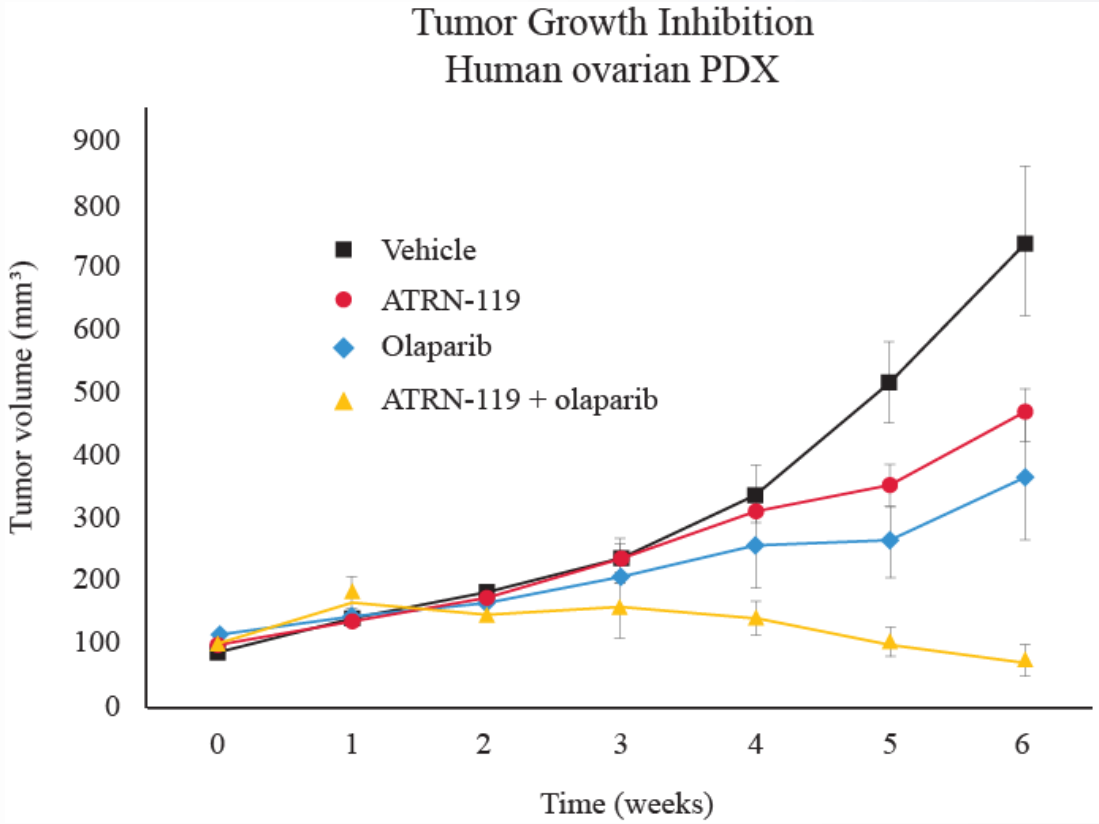


N=4 female mice per group, ATRN-119 - 100 mg/kg/day P.O, ATRN-157 - 20 mg/kg/day SQ.

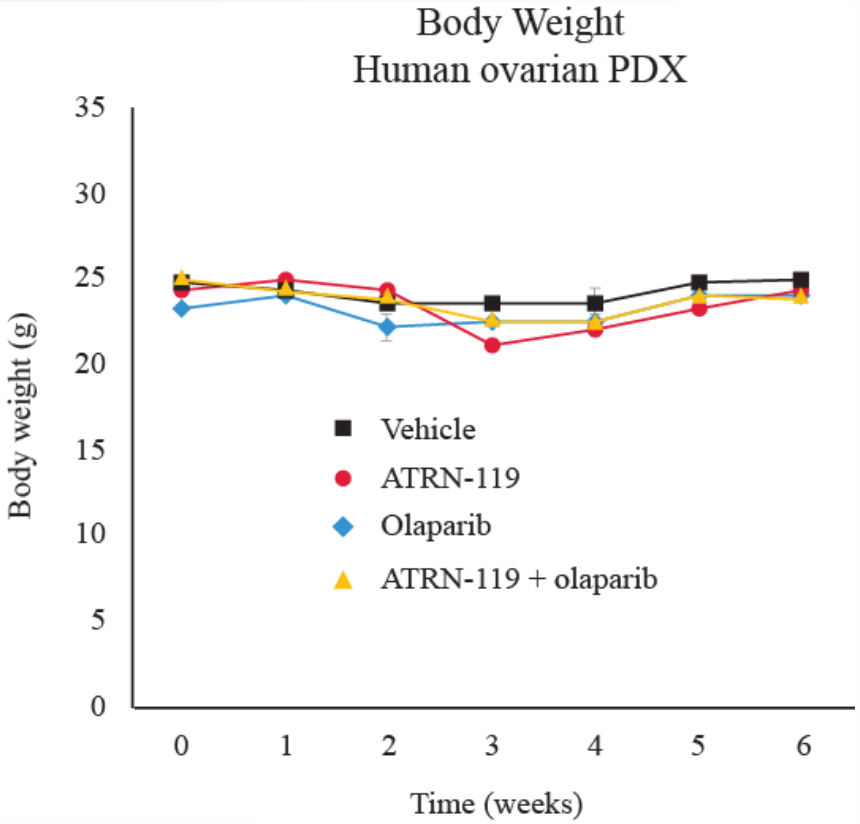
ATRN-157 is an active metabolite identified in dogs receiving ATRN-119 P.O.. In vitro metabolism studies in dog and human hepatocytes and liver microsomes indicated formation of ATRN-157 in both species. Potency and selectivity of ATRN-157 was comparable to ATRN-119.

ATRN-119 + Olaparib: Regression of BRCA2-Deficient Ovarian (HGSOC) Tumors

ATRN-119 + Olaparib Inhibits Ovarian Tumor Growth Over Time



ATRN-119 + Olaparib Shows Negligible Weight Loss Over Time



N=6-8 mice per group, ATRN-119 - 90 mg/kg P.O BID, Olaparib - 50 mg/kg/day P.O, ATRN-119+Olaparib at the same doses and schedules

Pre-clinical studies with ATRN-119

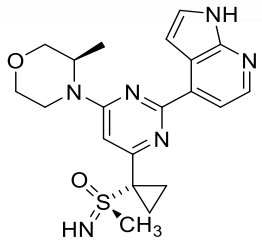
Data on file

ATR Inhibitor : ATRN-119

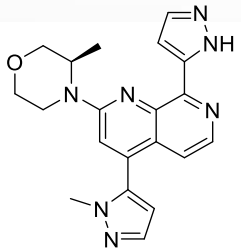
Potential Differentiation

ATR Landscape Drives Potential Competitive Advantage for ATRN-119

Current ATRs Structurally Similar in Core, Backbone, and Toxicity Profile



AZD-6738



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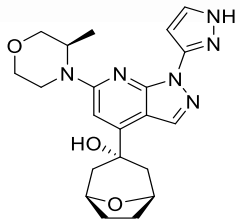


RP-3500

CAMOSERTIB

Parameter	AstraZeneca AZD6738 (1)(2)	Bayer BAY1895344 (3)	Repare / Roche(4) RP-3500 (5)
Route Of Administration	Oral	Oral	Oral
Clinical Studies Chosen (MTD/RP2D), Dose Schedule	160mg BID, 2-weeks-on, 2-weeks-off, or: Continuous dosing (1)	40mg BID, 3-days-on/4-days-off	160mg QD, 3-days-on/4-days-off
Main Grade ≥3 Hematological toxicities reported at Chosen Dose Schedule (MTD/RP2D), in clinical studies	Patriot 1, Escalation Phase, 160mg, BID (2): **Anemia** (1/6, 17%) Patriot 2, Expansion Phase (1): **Fatigue, anemia, nausea & thrombocytopenia (not differentiated)** (1): (4/6, 67%) with continuous dosing (3/15, 20%) with 2-week-on, 2-week-off	**Anemia** (2/2, 100%) **Neutropenia** (1/2, 50%)	**Anemia** (23/95, 24%) **Neutrophil count decreased** (10/95, 11%) **Platelet count decreased** (5/95, 5%)

Note: Head-to-head studies with ATRN-119 have not been conducted

(1) Phase I study of ATR inhibitor, AZD6738, as monotherapy in advanced solid tumors (PATRIOT part A, B), Dillon et al, Volume 30, October 2019, Pages v165-v166

(2) Poster CT084: A Phase I dose-escalation study of ATR inhibitor monotherapy with AZD6738 in advanced solid tumors (PATRIOT Part A), AACR 2017

(3) First-in-Human Trial of the Oral Ataxia Telangiectasia and RAD3-Related (ATR) Inhibitor BAY 1895344 in Patients with Advanced Solid Tumors, Yap et al, Cancer Discov 2021;11:80-91 and 2019 ASCO Poster, De-Bono et al.

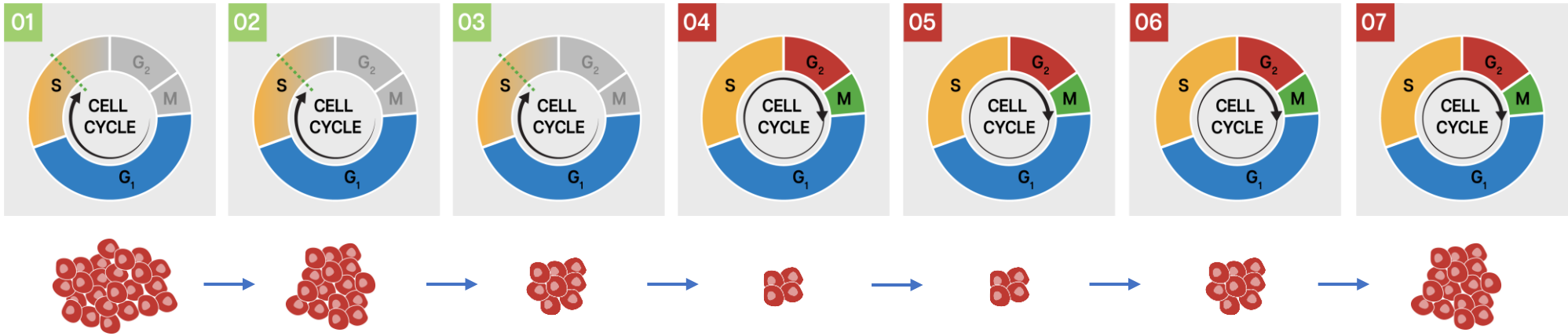
(4) Repare announced a worldwide license and collaboration agreement with Roche on June 1, 2022

(5) Preliminary Phase 1 Data From Ongoing First-in-Human Phase 1/2 TRESR Study of RP-3500, AACR 2022

ATRN-119 Daily Dosing Is Advantageous

Lack of daily dosing may contribute to formation of resistance

Drug "On" → **Drug "Off"** →



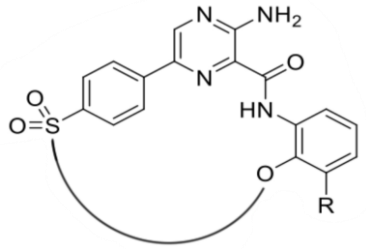
Tumor reduction and regrowth

Drug "On" →

Continuous tumor reduction

ATRN-119: Potential Best-in-Class Oral ATR Inhibitor

With Structurally Differentiated Core, Backbone, and Toxicity Profile



Parameter	ATRN-119 (1)
Route Of Administration	Oral
Clinical Studies Chosen (MTD/RP2D), Dose Schedule	continuous once-daily dosing (dose TBD in Phase 1) (1)
Hematological toxicities in preclinical studies	**Pre-Clinical, Toxicology Studies:** • In 28-day GLP tox study in dogs, hematological changes were of small magnitude with complete recovery • In a head-to-head comparative tolerability study, ATRN-119 demonstrated significantly less toxicity than another oral ATRi that is currently in clinical development (2)

ATRN-119 potential for reduced toxicity could make it a preferred ATR inhibitor as a single agent, as well as a candidate for combination with standard-of-care therapies.

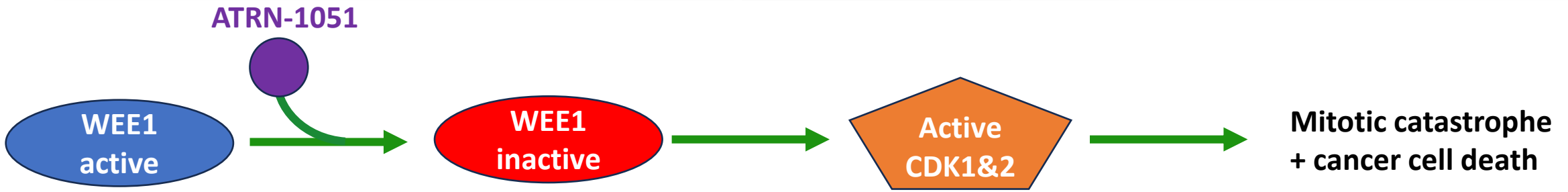
Note: ATRN-119 has not yet been tested clinically

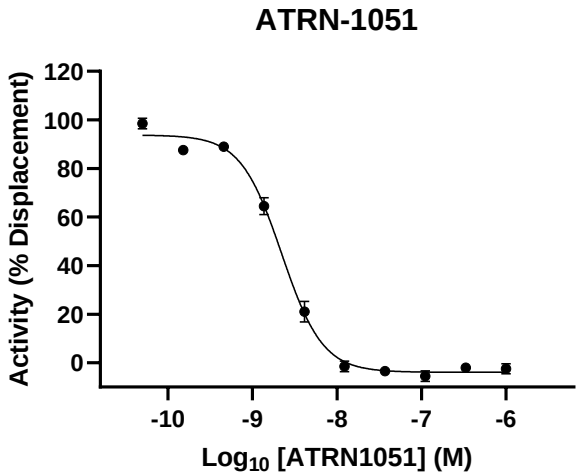
(1) ATRN-119, Phase 1/2a Clinical Study Protocol

(2) Internal pre-clinical head-to-head tolerability study in male beagle dogs. ATRN-119 - 20 mg/kg/day for 7 days, followed by 40 mg/kg/day for 7 days and finally 50 mg/kg/day for 7 days, all P.O. Competitor ATRi- administered at a clinically equivalent dose range during 21 days, P.O. By day 4 of dosing, the dog receiving the competitor ATRi exhibited severe reduction in multiple blood cell lineages including reticulocytes. Continued dosing of competitor ATRi for three weeks resulted in significant reduction of white blood cells, red blood cells and hemoglobin levels, and was accompanied by severe body weight loss (-15%). For the dog receiving ATRN-119, reduced levels of reticulocytes and neutrophils were noted with prolonged treatment but remained within normal ranges and body weight changes were negligible (-2% to +4%).

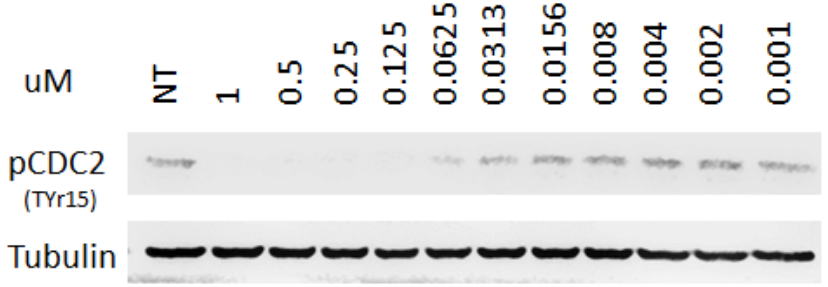
WEE1 Inhibitor : ATRN-1051
Preclinical proof-of-principle

WEE1 Inhibitor - ATRN-1051 Mechanism of Action

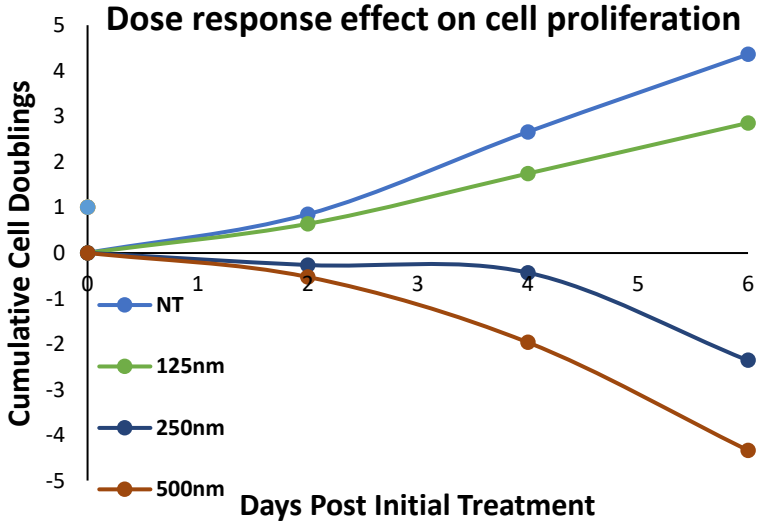




ATRN-1051 binds to WEE1



…inhibits its biological activity…

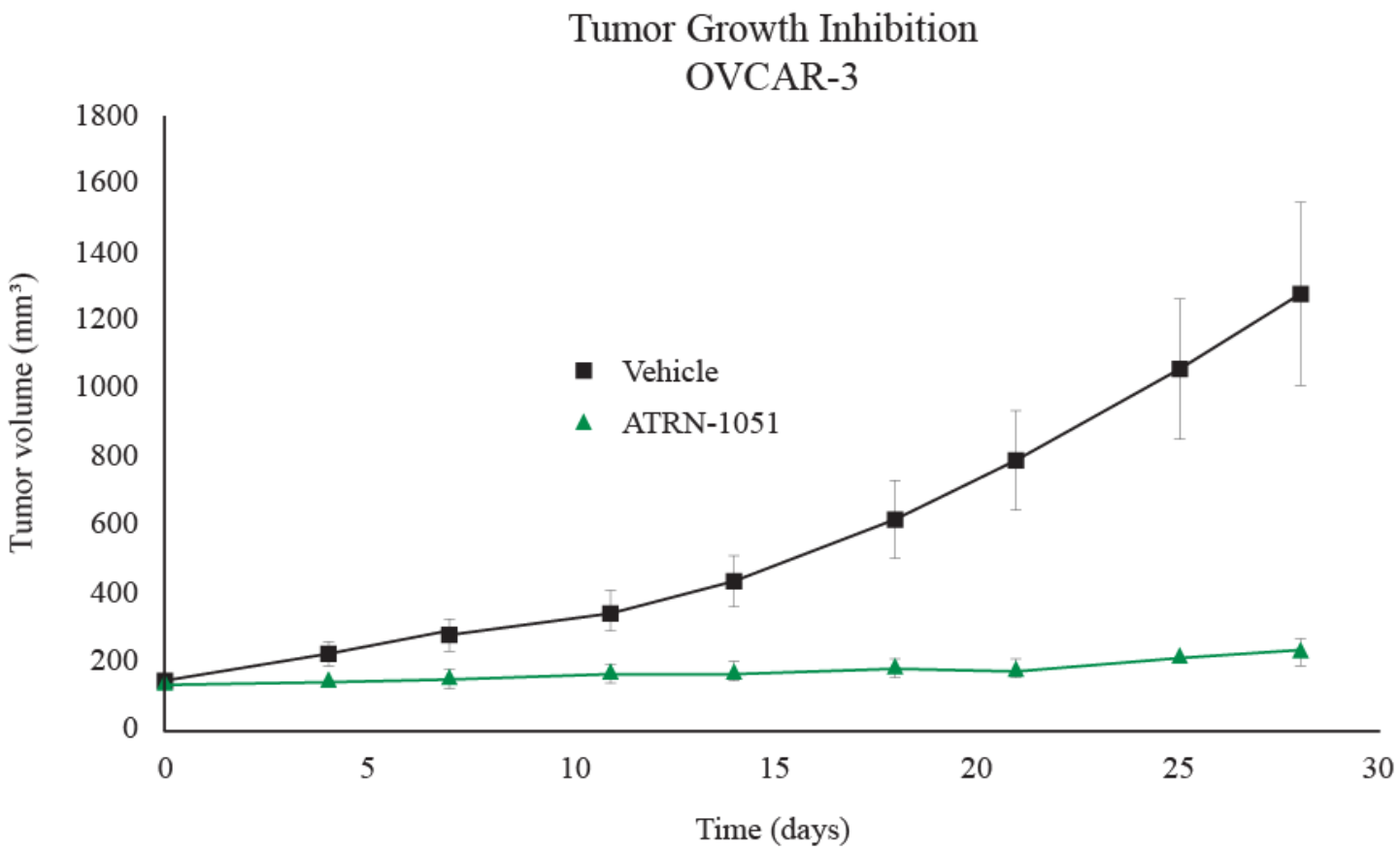


…and triggers mitotic catastrophe and cancer cell death

Data on file

ATRN-1051 Has Demonstrated Potentially Compelling Anti-tumor Activity

IND filing targeted by the end of 2023



N=7 mice per group, ATRN-1051, exploratory formulation - 30 mg/kg/day

Pre-clinical studies with ATRN-1051

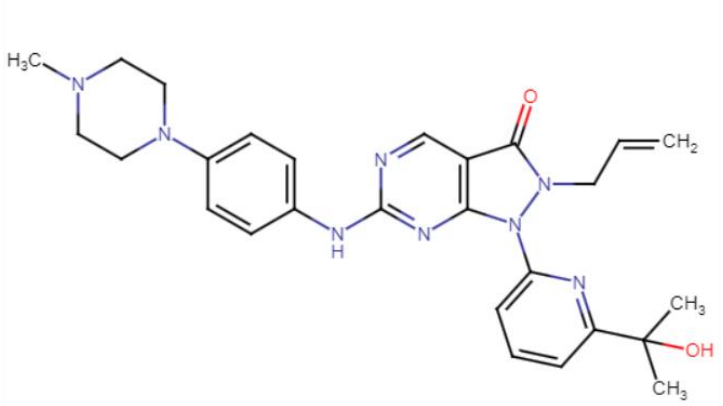
Data on file

WEE1 Inhibitor : ATRN-1051

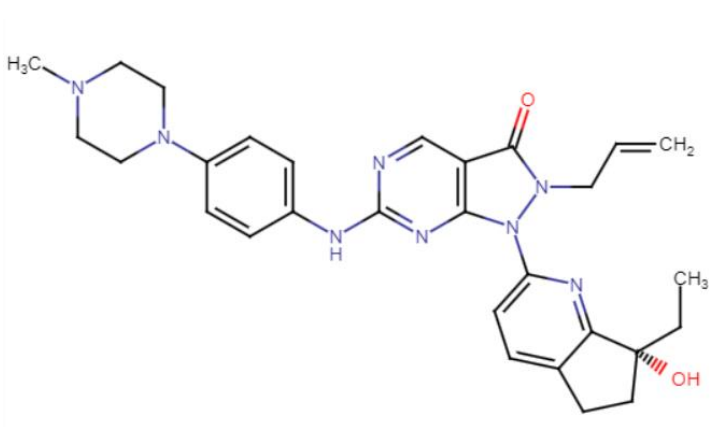
Potential Differentiation

ATRN-1051 is Potentially Differentiated from Other WEE1 Inhibitors

ATRN-1051 shows potential to be potent and structurally differentiated, with high selectivity to limit off-target toxicity



AZD-1775[(1)]



Azenosertib (ZN-c3)

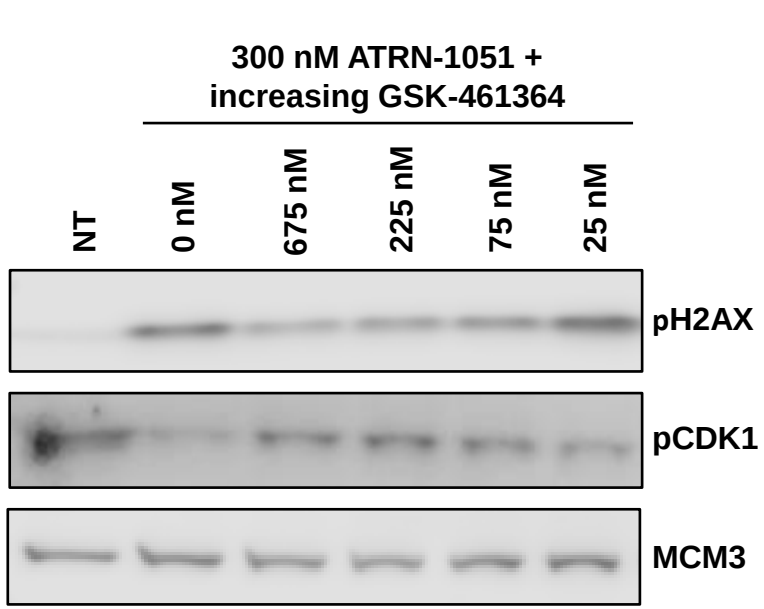
	On-Target IC_{50} (nM)	Off-Target Inhibition at 1 μM (%)		
	WEE1	**PLK1**	**PLK2**	**PLK3**
Aprea: ATRN-1051	2.2	17	33	12
Zentalis: Azenosetrib (ZN-c3) [(1)]	3.8	79	96	92
AstraZeneca: AZD-1775 [(1)(2)]	3.9	70	101	91

Note: Head-to-head studies have not been conducted

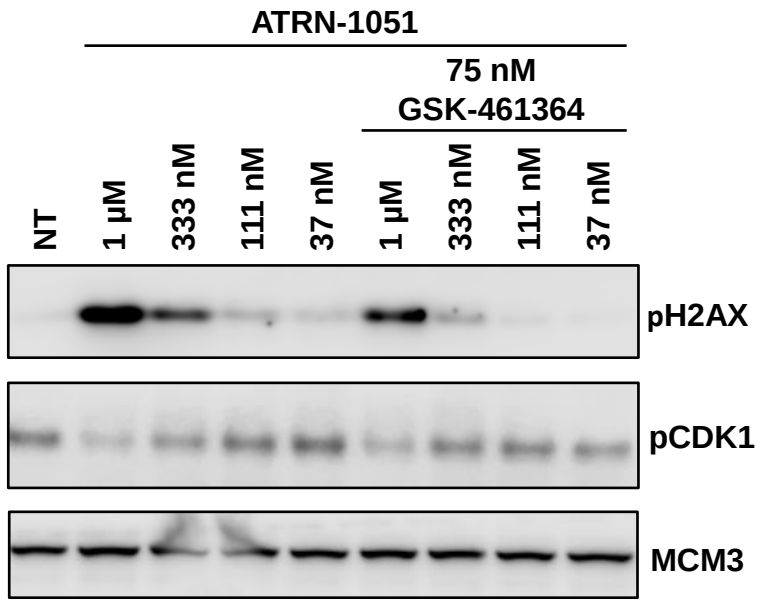
(1) Huang et al, (2021) J Med Chem

(2) AstraZeneca announced in July 2022 the discontinuation of development of AZD-1775

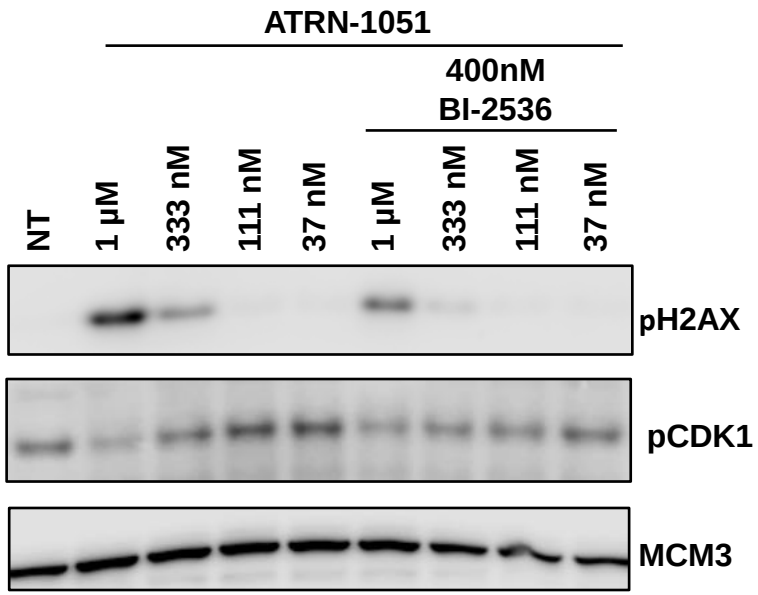
PLK1 Inhibition Limits The Genotoxic Effects of WEE1i



Dose range of PLK inhibitor GSK-461364 in combination with a single dose of ATRN-1051



PLK inhibitor, GSK-461364 interferes with ATRN-1051's ability to inhibit WEE1 in OVCAR3 cells.



PLK inhibitor, BI-2536, interferes with ATRN-1051's ability to inhibit WEE1 in OVCAR3 cells.

ATRN-1051 Preclinical Data Highlight Potentially Favorable PK Properties

Based on pre-clinical studies, ATRN-1051 shows potentially favorable drug exposure:

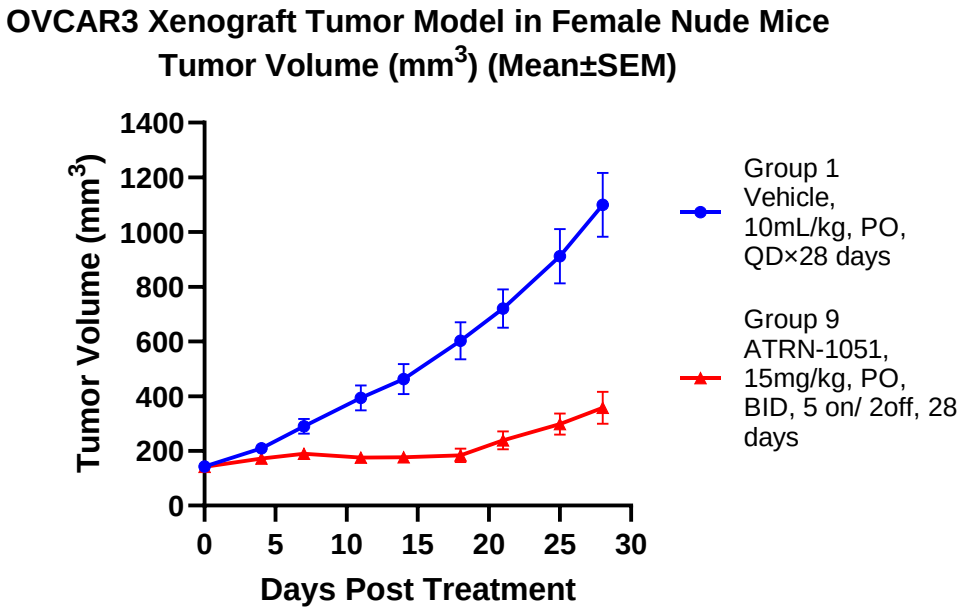
	ATRN 1051 (1)	Zentalis Azenosertib (ZN-c3) (2)			AstraZeneca AZD-1775 (2)		
Dose (mg/kg/d)	**10**	20	**40**	80	20	40	**80**
C_{max} ng/ml	1,460	1,167	1,997	5,100	635	2,460	4,703
T_{max} hr	3	1	1	1	1	1	1
AUC_{0-24}, ng*hr/ml	**16,739**	4,863	**17,088**	39,722	1,494	6,313	**13,408**

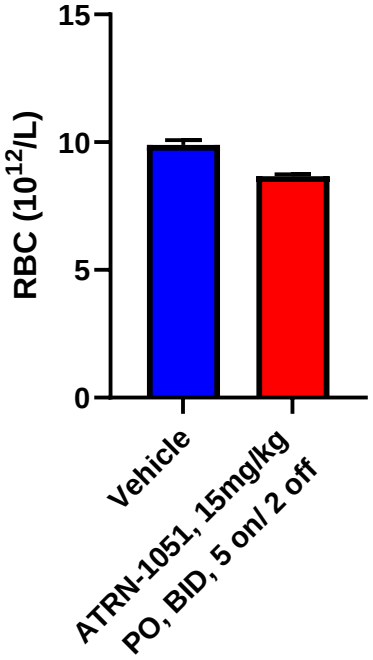
Note: Head-to-head studies have not been conducted

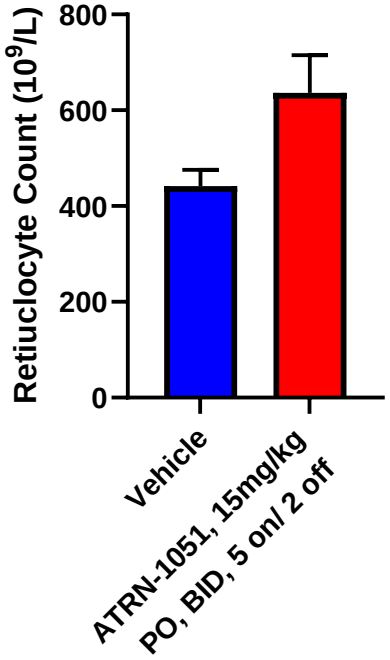
(1) Data from an exploratory formulation of ATRN-1051 administered to fasted Balb/c mice

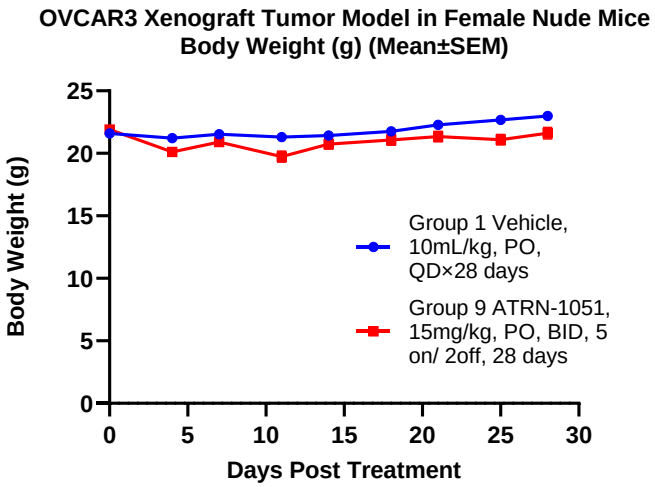
(2) Data from study in A-427 NSCLC xenograft model as reported in Zentalis Corporate Overview, March 2022

ATRN-1051 Suppresses Tumor Growth While Causing Little Effect on RBCs and Body Weight









ATRN-1051 Shows Negligible Inhibition of hERG Channels

In vitro kinase assays		Average WEE1 kinase IC50	hERG inhibition		Average hERG IC50	Fold difference between kinase and hERG inhibition
LanthaScreen (Thermo)	Hotspot (Reaction Biology)	21.8 nM	HEK293 cells (Medicilon)	CHO cells (WuXi)	4,750 nM	hERG inhibition over WEE1 kinase inhibition
2.2 nM	41.4 nM		8,840 nM	660 nM		218-fold (range 16- to 3,946-fold)

ATRN-1051
2023-2025 Anticipated Preclinical and Clinical Milestones

Milestone	Timeline
Preclinical proof-of-principle	
Additional differentiation data	4Q 2023
IND	
Submission	4Q 2023
Clearance	1Q 2024
Phase 1/2a – Monotherapy Dose Escalation	
First Patient Enrolled	1H 2024
Last Patient Enrolled	2H 2025
Phase 1/2a – Combination	
First Patient Enrolled	2H 2024
Last Patient Enrolled	2H 2025

Summary

Aprea Therapeutics (NASDAQ: APRE)
Financial Summary & Capitalization

- Cash & Equivalents of $27.7 million as of June 30, 2023
- Closed $4.9M (net) public offering in February 2023
- Obtained $2.0 million non-dilutive funding via research grant from National Cancer Institute (NCI)

Securities	Common Equivalents as of Aug. 10, 2023
Preferred Stock (as converted)	28,112
Common Stock	3,736,673
Options	558,141
Restricted Stock Units	20,870
Fully Diluted Equivalents	4,343,796

Summary

- Diversified portfolio with de-risked clinical and preclinical plans underway
- Opportunities in ovarian, CRC, prostate and breast cancers
  - Single agent and combination therapies
- Supportive follow-on strategy
  - IND submission by end of 2023
  - Undisclosed DDR asset
- Financed into Q4 2024
  - Reach short term inflection points and catalysts
  - Evaluate optimal strategic partnerships