UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

April 10, 2024
Date of Report (Date of earliest event reported)

Aprea Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**001-39069**	**84-2246769**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

3805 Old Easton Road **Doylestown, PA**	**18902**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: **(617) 463-9385**

(Former name or former address, if changed since last report): Not applicable

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common stock, par value $0.001 per share	APRE	The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Item 8.01 Other Events.

On April 10, 2024, Aprea Therapeutics, Inc. (the "Company") issued a press release which provided details about four poster presentations the Company plans to present at the ongoing American Association of Cancer Research (AACR) Annual Meeting. A copy of the press release is filed as Exhibit 99.1 hereto and incorporated herein by reference.

On April 10, 2024, the Company updated its corporate presentation slide deck. A copy of the corporate presentation slide deck is filed as Exhibit 99.2 hereto and incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit Number	Description
99.1	Press release issued by Aprea Therapeutics, Inc. dated April 10, 2024.
99.2	Corporate Presentation (April 2024).
104	Cover Page Interactive Data File (embedded within the inline XBRL document).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Aprea Therapeutics, Inc.

Dated: April 10, 2024

By: /s/ Oren Gilad
Name: Oren Gilad, Ph.D.
Title: President and Chief Executive Officer

Aprea Therapeutics Announces Presentations on its Next Generation WEE1 Inhibitor, APR-1051, and A Novel Macrocyclic ATR Inhibitor, ATRN-119, at AACR Annual Meeting 2024

Pre-clinical findings underscore the potential of APR-1051, a next-generation WEE1 kinase inhibitor, to be a well-tolerated and effective treatment for Cyclin E-overexpressing cancers
IND for APR-1051 has been cleared; details on planned Phase 1 first in human trial (ACESOT-1051) presented
ATRN-119, a novel macrocyclic ATR inhibitor, continues to appear safe and well tolerated with no Dose Limiting Toxicities observed in ongoing Phase 1/2a study; preliminary signs of clinical benefit reported; enrollment in the study continues

DOYLESTOWN, PA, Apr. 10, 2024 (GLOBE NEWSWIRE) – Aprea Therapeutics, Inc. (Nasdaq: APRE) ("Aprea", or the "Company"), a clinical-stage biopharmaceutical company focused on precision oncology through synthetic lethality, today released details about four poster presentations at the ongoing American Association of Cancer Research (AACR) Annual Meeting, taking place April 5 to 10, 2024 in San Diego, CA. The posters feature APR-1051, Aprea's next-generation inhibitor of WEE1 kinase, as well as a clinical update on ATRN-119, its novel macrocyclic ATR inhibitor. The Company also presented a poster highlighting a new set of preclinical data in glioblastoma with a next-generation macrocyclic ATR inhibitor, ATRN-333.

"The four poster presentations at this prestigious conference highlight our growing pipeline and commitment to help cancer patients in need," said Dr. Oren Gilad, President and CEO of Aprea. "We are pleased to share the strong pre-clinical data and future clinical strategy for our promising next-generation WEE1 kinase inhibitor, APR-1051. We are also very excited to provide an encouraging update on the ongoing clinical study of our novel macrocyclic ATR inhibitor, ATRN-119."

Copies of the posters will be available on the Aprea corporate website here, at the conclusion of the AACR meeting.

APR-1051

The novel WEE1i, APR-1051, is a potentially well tolerated and effective treatment for cyclin E-overexpressing cancers

Lead Author and Presenter: Molly Hansbarger
Abstract Number: 7121

- This poster summarizes the pre-clinical data of APR-1051
- APR-1051 exhibits high potency for WEE1 inhibition in vitro
  - Selectivity is key for success. APR-1051 shows low off-target inhibition of the PLK family of kinases.
    - To measure the potential for off-target inhibition of the PLK family of enzymes, in vitro experiments were conducted to determine the IC50s of APR-1051 vs ZN-c3 (Zentalis Pharmaceuticals)
    - The results showed significantly lower off-targeting of PLK1, PLK2 and PLK3 as indicated by higher IC50 values for APR-1051 compared to ZN-c3.
      IC50 of APR-1051 over IC50 of ZN-c3
      - PLK1: > 150-fold
      - PLK2: > 50-fold
      - PLK3: > 600-fold
    - Off-targeting of PLK1 by other WEE1 inhibitors may compromise the efficacy of these drugs.
    - Off-targeting of the PLK family may increase the risk of producing PLKi-associated adverse effects.
- Cyclin E as a potential biomarker for APR-1051 treatment
    - APR-1051 demonstrated effectiveness in suppressing the growth of Cyclin E-overexpressing breast and ovarian cancer cell lines.
    - The dose and scheduling of APR-1051 that causes significant suppression of CCNE1-amplified high-grade serous ovarian cancer tumors in mice is well tolerated.
    - Red blood cell and platelet counts remained within non-pathogenic ranges after a 28-day treatment period, consistent with proposed minimal off target PLK1 inhibition
- APR-1051 will potentially exhibit low cardiotoxicity.

- Inhibition WEE1 by APR-1051 occurs at an IC50 that is 200-fold lower on average than the IC50 of hERG potassium channel inhibition.
- Strong evidence for combination therapy
  - APR-1051 was evaluated in combination with Aprea's second-generation ATR inhibitors (ATRN-330 and ATRN-354) in xenografted tumors. The results showed higher anti-tumor activity for the combinations, compared with vehicle or monotherapy.
- APR-1051 received U.S. FDA clearance for a clinical trial, now with plans to dose the first patient in June 2024

ASECOT-1051: First-in-human phase 1 study of WEE1 inhibitor APR-1051 in patients with advanced solid tumors harboring cancer-associated gene alterations.

Presenter: Nadeem Q. Mirza, M.D., MPH
Lead author: Timothy Yap, M.D.
Abstract Number: CT196

- This poster summarizes the strategy for the upcoming clinical trial of APR-1051
- The aim of this first-in-human Phase 1 study (*ACESOT-1051: **A** Multi-**C**enter **E**valuation of WEE1 Inhibitor in Patients with Advanced **So**lid **T**umors, APR-**1051)*** is to assess the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of single-agent APR-1051 in advanced solid tumors harboring cancer-associated gene alterations (NCT06260514)
- This biomarker-driven study will include patients with advanced/metastatic solid tumors harboring cancer-associated gene alterations, such as *CCNE1* or *CCNE2*, *FBXW7, PPP2R1A,* or $KRAS^{G12}$
- Oral APR-1051 will be administered once daily for 28-day cycles.
- The study will consist of two parts.
  - Part 1 will be dose escalation and is expected to enroll up to 39 patients with advanced solid tumors harboring cancer-associated gene alterations. In the dose escalation phase the first three dose levels will use accelerated titration followed by Bayesian Optimal Interval (BOIN) design for the remaining dose levels
  - Part 2 (up to 40 patients) is designed for dose optimization, with the goal of selecting the Recommended Phase 2 Dose (RP2D)
- The primary objectives are to measure safety, dose-limiting toxicities (DLTs), maximum tolerated dose or maximum administered dose (MTD/MAD), RP2D; Secondary objectives are to evaluate pharmacokinetics, preliminary efficacy according to RECIST or PCWG3 criteria; Pharmacodynamics is an exploratory objective.
- Enrollment is anticipated to begin in Q2 2024
- MD Anderson Cancer Center is the lead site, and the study will be performed at between 3 and 10 sites in the U.S

ATRN-119

Nadeem Mirza, MD, MPH, Senior Medical Advisor to Aprea commented, "Enrollment of patients continues in the dose escalation portion of our Phase 1/2a clinical trial evaluating ATRN-119 in patients with advanced solid tumors having mutations in defined DDR-related genes. We are now enrolling patients in the 550 mg cohort (Cohort 5). ATRN-119 continues to be safe and well tolerated, with no dose-limiting toxicities and no signs of significant hematological toxicity reported. We are encouraged by the preliminary signs of clinical benefit. Stable disease has been reported in two patients, one of which continues to be on treatment out to Day 188. Dose escalation will proceed throughout 2024."

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

Presenter: Nadeem Q. Mirza, M.D., MPH
Lead author: Fiona Simpkins, M.D.
Abstract Number: CT195

- This poster reports on the ongoing first-in-human Phase 1 study of ATRN-119 in patients with advanced solid tumors harboring specific DDR mutations (NCT04905914)
- As of March 12, 2024, 16 patients were enrolled in the first five cohorts of the dose escalation stage (50 mg/day, 100 mg/daily, 200 mg/daily, 350 mg/daily, and 550 mg/daily)
- ATRN-119 is being administered daily on a continuous schedule
- ATRN-119 has been found to be safe and well tolerated.
  - No reported DLTs and no treatment-related Grade 4 or higher AEs have been reported.

    - At doses up to 550 mg once daily, there have been no signs of hematological toxicity.
- Pharmacokinetic studies show ATRN-119 serum concentrations are entering the expected therapeutic range at the current highest dose level (550 mg). The Company currently has FDA clearance to evaluate doses up to 800mg, with a planned protocol amendment to add doses up to 1300 mg.
- Preliminary signs of clinical benefit have been observed.
    - Two patients have achieved stable disease (SD) – one each in the 50 mg and 200 mg cohorts.
    - The latter patient at 200 mg/day had SD at Days 55, 112, and 168, and continues to be on treatment as of Day 188 without significant adverse events reported. This patient is now receiving 350 mg daily, as per the trial protocol, and is tolerating treatment well.

ATRN-333

Convection-enhanced delivery of a novel ATR inhibitor synergizes with systemic lomustine for improved treatment of glioblastoma.

Presenter: Teresa Lee, Ph.D.
Lead Authors: Alexander Josowitz Ph.D., Teresa Lee Ph.D.
Abstract Number: 7117

- This poster describes a combination approach using a next-generation macrocyclic ATR inhibitor, ATRN-333, to sensitize glioblastoma (GBM) tumors to lomustine, an oral DNA alkylating agent.
- The DNA damage response and DNA repair mechanisms such as the ataxia telangiectasia and Rad3-related (ATR) pathway are key mediators of therapeutic responses in glioblastoma (GBM). Recent studies have shown that targeting DNA repair proteins alongside standard-of-care options is a promising anti-tumor strategy for this disease.
- To overcome difficulties associated with drug delivery to the brain, a convection-enhanced delivery (CED) system in conjunction with nanoparticle (NP) technology was used for direct intracranial administration of ATRN-333 to orthotopic GBM tumors.
- Both free and NP-encapsulated ATRN-333 showed high potency in inhibiting ATR function in cell-based assays.
- There was a clear synergistic effect between lomustine and ATRN-333 in GBM cell lines.
- ATRN-333 effectively sensitized both flank and intracranial tumors to lomustine *in vivo*.
- When administered via CED, ATRN-333 showed favorable intracranial retention and was well tolerated in mice when combined with lomustine.
- These results suggest that ATR inhibitor/lomustine combination therapy, used in conjunction with a CED platform, is a powerful avenue for GBM treatment.
- The results support further investigation and potential clinical implementation of ATRN-333 and other macrocyclic ATR inhibitors as chemosensitizers for glioblastoma.

About Aprea

Aprea Therapeutics, Inc. is a clinical-stage biopharmaceutical company headquartered in Doylestown, Pennsylvania, focused on precision oncology through synthetic lethality. The Company's lead program is ATRN-119, a clinical-stage small molecule ATR inhibitor in development for solid tumor indications. Aprea has completed all IND-enabling studies for its oral, small molecule WEE1 inhibitor, APR-1051, and recently received FDA clearance of its IND. For more information, please visit the company website at www.aprea.com.

The Company may use, and intends to use, its investor relations website at https://ir.aprea.com/ as a means of disclosing material nonpublic information and for complying with its disclosure obligations under Regulation FD.

Forward-Looking Statement
Certain information contained in this press release 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 study analyses, clinical trials, regulatory submissions, and projected cash position. We may, in some cases use terms such as "future," "predicts," "believes," "potential," "continue," "anticipates," "estimates," "expects," "plans," "intends," "targeting," "confidence," "may," "could," "might," "likely," "will," "should" or other words that convey uncertainty of the

future events or outcomes to identify these forward-looking statements. Our forward-looking statements are based on current beliefs and expectations of our management team and on information currently available to management that involve risks, potential changes in circumstances, assumptions, and uncertainties. All statements contained in this press release other than statements of historical fact are forward-looking statements, including statements regarding our ability to develop, commercialize, and achieve market acceptance of our current and planned products and services, our research and development efforts, including timing considerations and other matters regarding our business strategies, use of capital, results of operations and financial position, and plans and objectives for future operations. Any or all of the forward-looking statements may turn out to be wrong or be affected by inaccurate assumptions we 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, timing, and cost of our ongoing clinical trials and anticipated clinical trials for our current product candidates, including statements regarding the timing of initiation, pace of enrollment and completion of the trials (including our ability to fully fund our disclosed clinical trials, which assumes no material changes to our currently projected expenses), futility analyses, presentations at conferences and data reported in an abstract, and receipt of interim or preliminary results (including, without limitation, any preclinical results or data), which are not necessarily indicative of the final results of our ongoing clinical trials, our understanding of product candidates mechanisms of action and interpretation of preclinical and early clinical results from its clinical development programs, and the other risks, uncertainties, and other factors described under "Risk Factors," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere in the documents we file with the U.S. Securities and Exchange Commission. 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 press release. We undertake no obligation to update such forward-looking statements for any reason, except as required by law.

Investor Contact:

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LifeSci Advisors
mmoyer@lifesciadvisors.com

APREA THERAPEUTICS

APREA THERAPEUTICS

Precision Oncology Through Synthetic Lethality

April 2024

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 amend 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 ca use terms such as “predicts,” “believes,” “potential,” “continue,” “anticipates,” “estimates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “likely,” “will,” “should other words that convey uncertainty of the future events or outcomes to identify these forward-looking statements. The forward-looking statements are based current beliefs and expectations of our management team that involve risks, potential changes in circumstances, assumptions, and uncertainties. Any or all of 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 uncertainties. These forward-looking statements are subject to risks and uncertainties including, without limitation, risks related to the success and timing of our clin 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 Quarterly Reports on Form 10-Q. Forward-looking statements regarding our product candidates are also subject to additional risks and uncertainties, including with limitation, with respect to: our dependence on additional financing to fund our operations and complete the development and commercialization of our proc 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; limited history and preclinical status of the assets we acquired from Atrin Pharmaceuticals Inc.; our business plan or the likelihood of the successful implementatio 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 research and development programs and collaborations and the interpretation of the results and findings of such programs and collaborations and whether such res 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 candida the timing of initiation, futility analyses, data presentation, reporting and publication and receipt of interim results (including, without limitation, any preclinical result data); any statements about our understanding of product candidates mechanisms of action and interpretation of preclinical and early clinical results from its clin development programs and any collaboration studies; and other factors, including legislative, regulatory, political and economic developments not within our cont For all these reasons, actual results and developments could be materially different from those expressed in or implied by our forward-looking statements. You 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 obligatio 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 Novel Synthetic Lethality Therapeutics

All programs address significant unmet medical need, are synergistic with other anticancer therapies, and potentially differentiated in safety and tolerability

ATR Inhibitor: ATRN-119

- First macrocyclic ATR inhibitor
- Highly selective with continuous daily dosing targeted
- Phase 1/2a – Ongoing Dose Escalation
  - Readout 1Q 2025
  - Solid tumor with DDR mutation
- Pre-clinical proof-of-principle
  - Anti-tumor activity at nanomolar concentration
  - Preserved hematologic safety profile

WEE1 Inhibitor: APR-1051

- Best in class, next generation
- Pre-clinical proof-of-principle
  - Highly potent and selective anti-tumor activity
  - Limited off target effect
  - Ovarian cancer with Cyclin E over expression (OVCAR-3)
  - Stable hematologic function
  - Favorable pharmacokinetics
- IND cleared March 2024
- Phase 1 planned for 1H 2024

DDR Inhibitor: Undisclosed

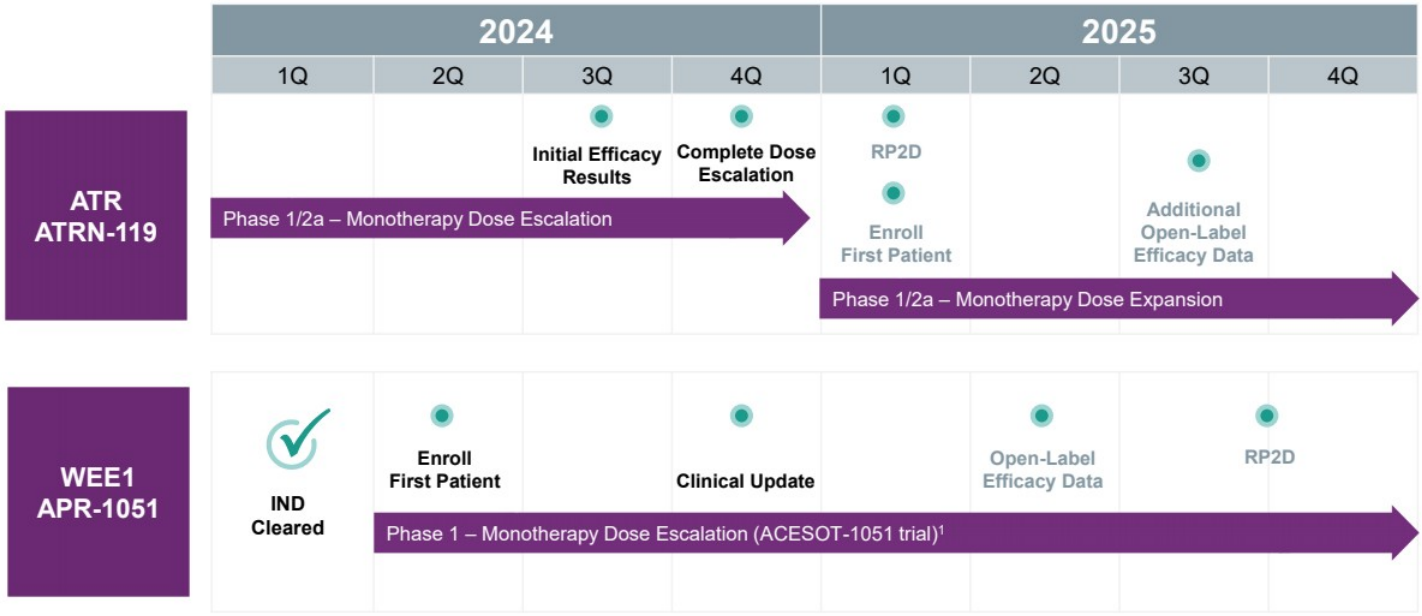
- Lead optimization
- Target identified from our RepliBior discovery platform

APREA THERAPEUTICS

ATR - Ataxia telangiectasia and Rad3-related
DDR – DNA Damage Response

Robust DDR Development Pipeline Milestones

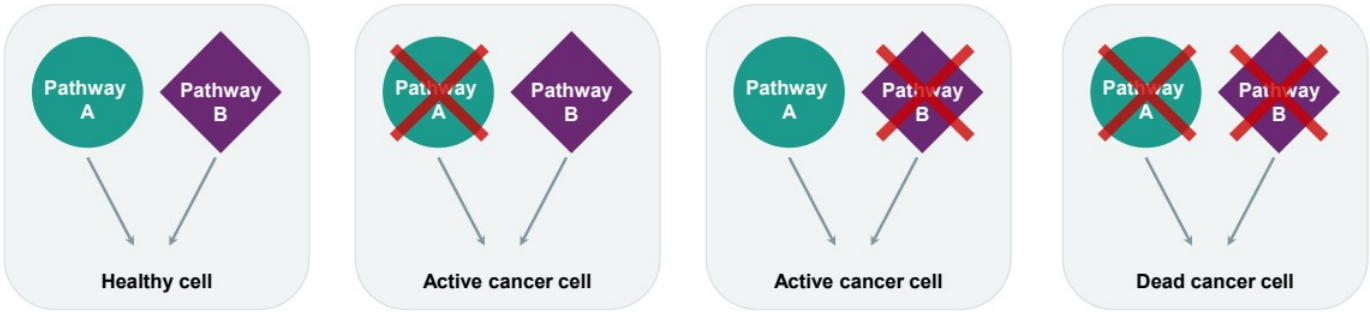
2024-2025 Anticipated Clinical Milestones



APREA THERAPEUTICS

1. **A** Multi-**C**enter **E**valuation of WEE1 Inhibitor in Patients with Advanced **So**lid **T**umors, APR-**1051**

Synthetic Lethality



- Cancer cell death only upon the loss of function of two codependent pathways
- DNA Damage Response (DDR) allows cells to pause and self repair during replication (mitosis)
- Inhibition of DDR leads to mitotic catastrophe and cell death
- ATR and WEE1 inhibitors are integral to stopping DDR and are emerging targets for cancer cell death
- Builds on scientific innovation led by Aprea founder and key personnel[1]

APREA THERAPEUTICS

[1] Gilad et al, (2010) Cancer Res.

Leadership with Strong Drug Development and Commercial Expertise

Pioneers in Synthetic Lethality

Management

Oren Gilad, Ph.D. President and CEO	John Hamill Sr. Vice President and 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	Brian Wiley SVP, Corporate Strategy
ATRIN Pharmaceuticals Perelman School of Medicine	WINDTREE THERAPEUTICS Trevena SAVIENT PHARMACEUTICALS, INC. NephroGenex pharmanet	Salarius PHARMACEUTICALS TRIGR THERAPEUTICS Verastem Oncology abbvie sanofi	ATRIN Pharmaceuticals INTEC PHARMA pwc	iniphorm ATRIN Pharmaceuticals MERCK Bristol Myers Squibb presage Mavu PHARMA	Boston BioConsulting Gloucester MILLENNIUM

Board of Directors

Richard Peters, M.D., Ph.D. Chairman of the Board	**Oren Gilad, Ph.D.** President and CEO	**Jean-Pierre Bizzari, M.D.** Director
Marc Duey Director	**Michael Grissinger** Director	**Gabriela Gruia, M.D.** Director
John Henneman Director	**Rifat Pamukcu, M.D.** Director	**Bernd R. Seizinger, M.D., Ph.D.** Director

ATR Inhibitor: ATRN-119

Clinical Proof-of-Concept

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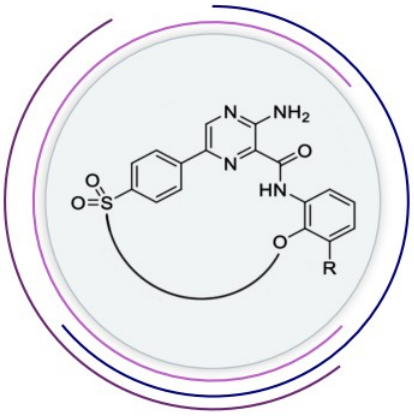
ATRN-119: First and Only Macrocyclic ATR Inhibitor[1]

Macrocycles: A Well-Evolved Approach for PIK-Related Kinase Inhibition (e.g., rapamycin and mTOR)[2-4]



Benefits of Unique Cyclic Skeleton Structure vs Competitors' First-Generation Acyclic Structure

Macrocycles restrict the number of conformations that can be formed, which can:

- Increase potency
- Increase selectivity

These effects can then promote:

- Increased tolerability by decreasing off-targeting
- Permit more efficacious dosing

[1] Based on company knowledge
[2] Brown, EJ et al, (1994) Nature
[3] Brown, EJ et al, (1995) Nature
[4] Brown, EJ and SL Schreiber, (1996) Cell

APREA THERAPEUTICS

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

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

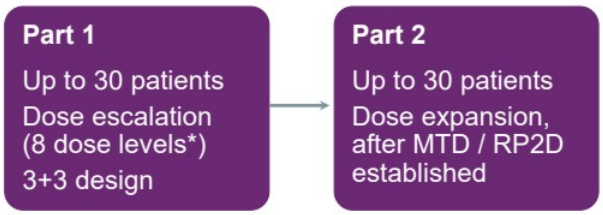
Patient enrollment:
60 patients in total

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

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

Patient Population:

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



Primary objectives:

- Safety, MTD, RP2D
- Pharmacokinetics

Secondary objectives:

- Antitumor activity (RECIST/PCWG3)

Exploratory objectives:

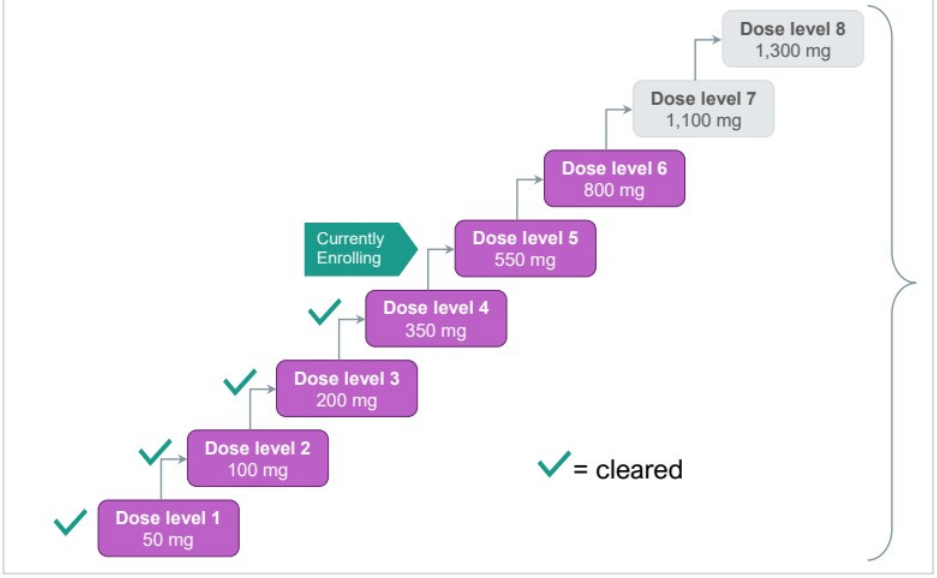
- Association between identified mutations and clinical outcomes

APREA THERAPEUTICS

*Planned protocol amendment adding cohorts 7 and 8

Aprea AR-276-01 Study

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



MTD/RP2D

Dose expansion (up to 30 patients)

Potential indications
Colorectal
Prostate
Gastric
Endometrial

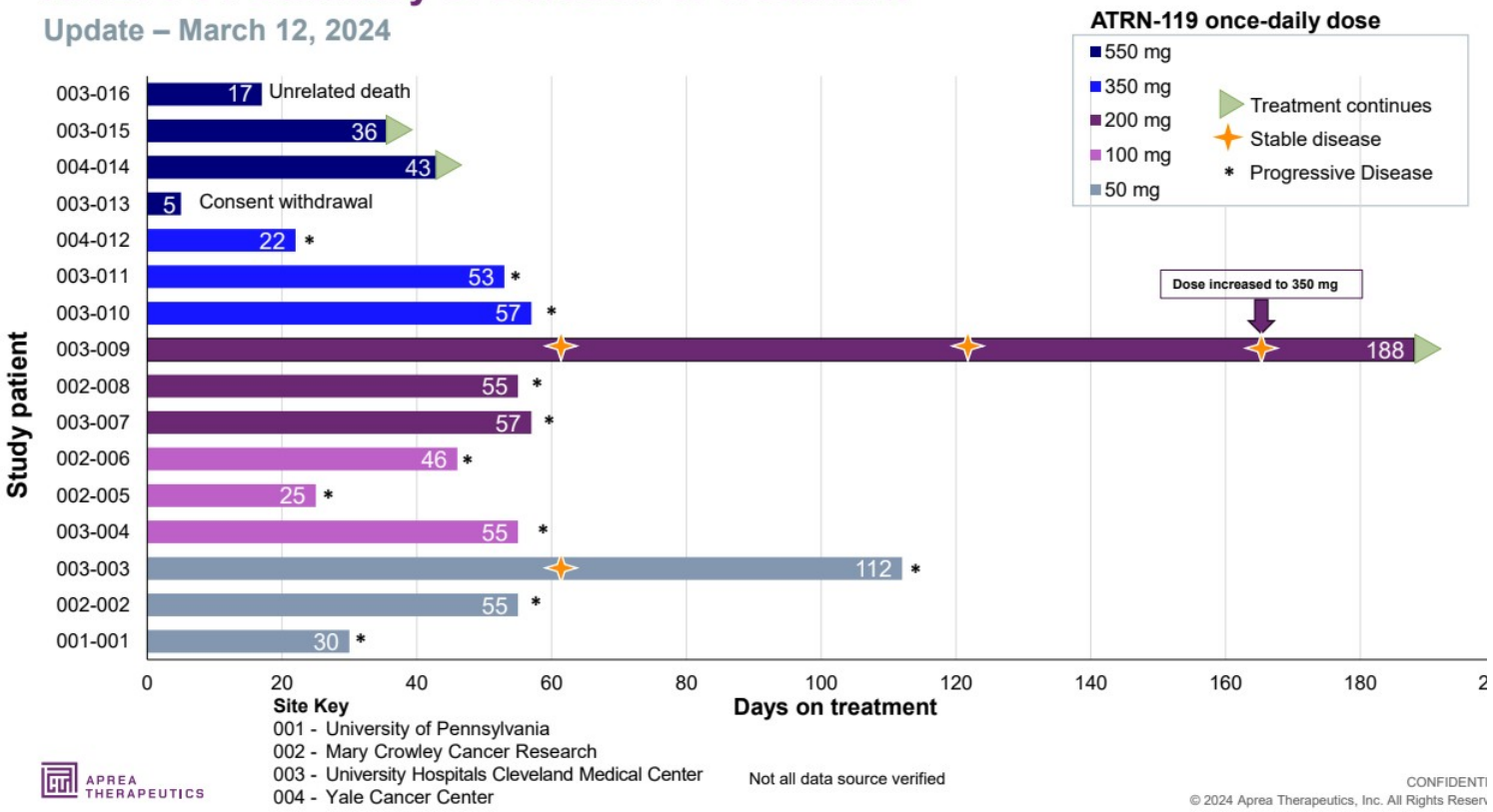
Mutations
Undisclosed RepliBion biomarkers

APREA THERAPEUTICS

*Planned protocol amendment adding cohorts 7 and 8

AR-276-01 Summary of Duration of Treatment

Update – March 12, 2024



Site Key

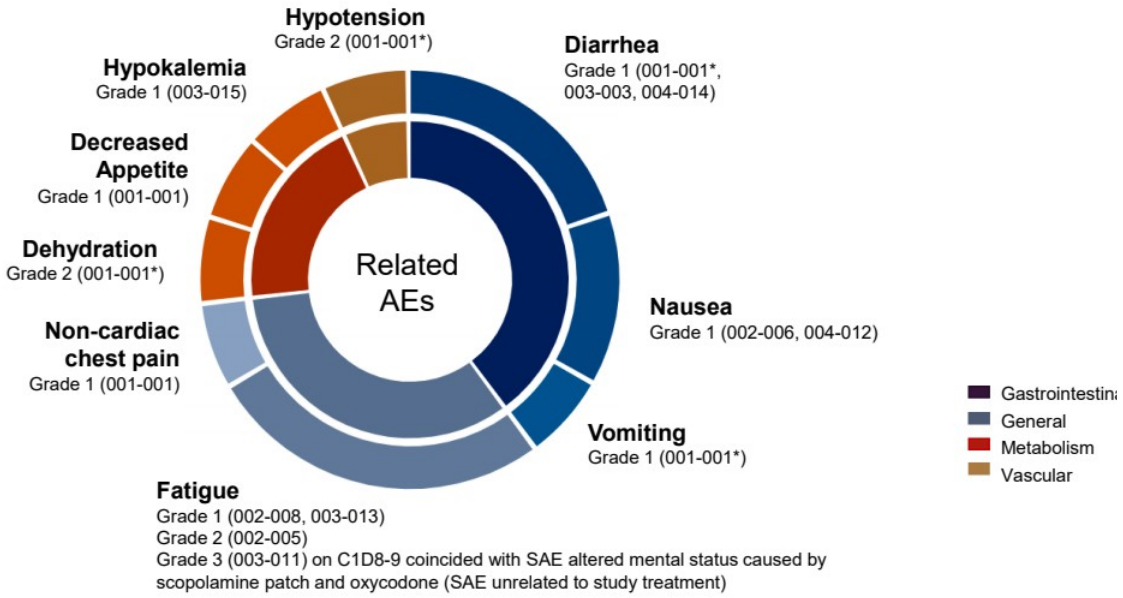
001 - University of Pennsylvania
002 - Mary Crowley Cancer Research
003 - University Hospitals Cleveland Medical Center
004 - Yale Cancer Center

Not all data source verified

APREA THERAPEUTICS

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

As of March 12, 2024: Ten Of Sixteen Patients Experienced AEs[#] Possibly/probably Related to ATRN-1



APREA THERAPEUTICS

No grade 4 AEs were observed
* Resulted in treatment interruption
Not all data source verified

ATRN-119
2024-2025 Anticipated Clinical Milestones

Milestone	Timeline
Phase 1/2a – Monotherapy Dose Escalation	
Potential efficacy data	2H 2024
Complete Dose Escalation	4Q 2024
RP2D	1Q 2025
Phase 1/2a – Monotherapy Dose Expansion	
First Patient Enrolled	1Q 2025
Additional Open-Label Efficacy Data	3Q 2025

APREA THERAPEUTICS

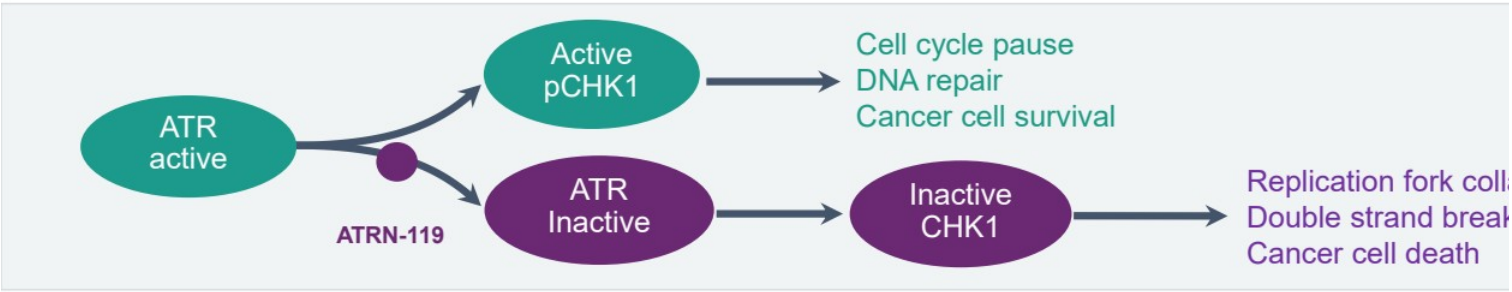
Planned protocol amendment adding cohorts 7 and 8 to monotherapy dose escalation 1Q2024

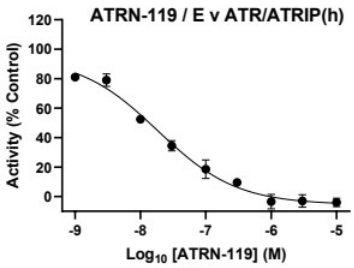
ATR Inhibitor: ATRN-119

Preclinical
Proof-of-Principal

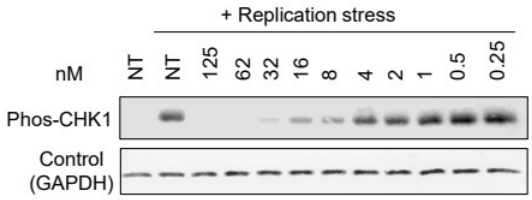
APREA THERAPEUTICS

ATR Inhibitor – ATRN-119
Mechanism of Action – Prevent CHK1 Phosphorylation by ATR Kinase



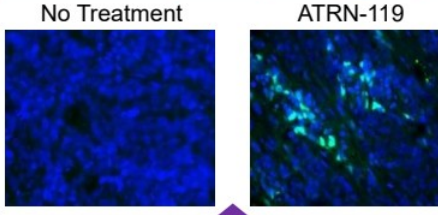


ATRN-119 binds to ATR



…inhibits its biological activity…

Tumor Samples
Pharmacodynamics - γH2AX (green)



…and triggers replication fork collapse and double-strand breaks (γH2AX)

APREA THERAPEUTICS

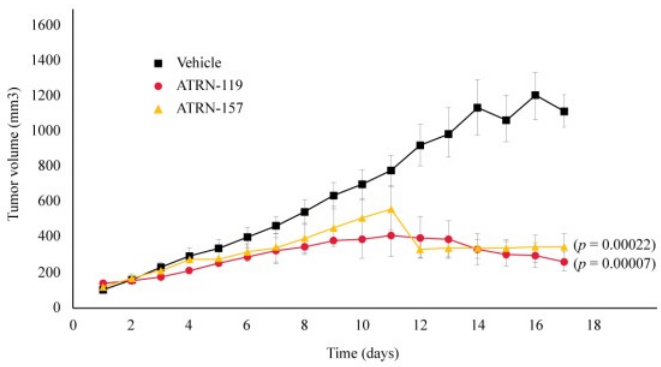
pCHK1 – Phosphorylated Checkpoint kinase 1
Data on file

ATRN-119 Preclinical Profile

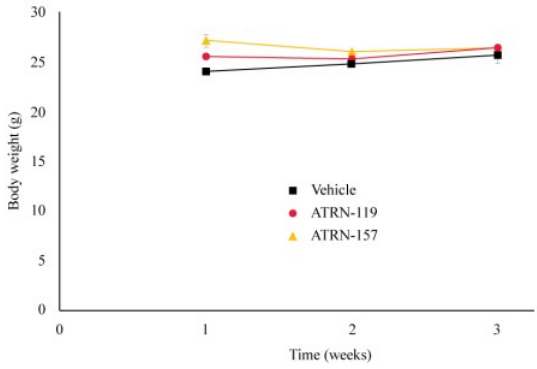
Nanomolar potency in vitro across a broad spectrum of cancer cell lines

Strong tumor control observed in vivo, including in challenging genetic backgrounds

Tumor Growth Inhibition
HCT-116 ($KRAS^{G13D}$, p53 null)



Body Weight
HCT-116 ($KRAS^{G13D}$, p53 null)

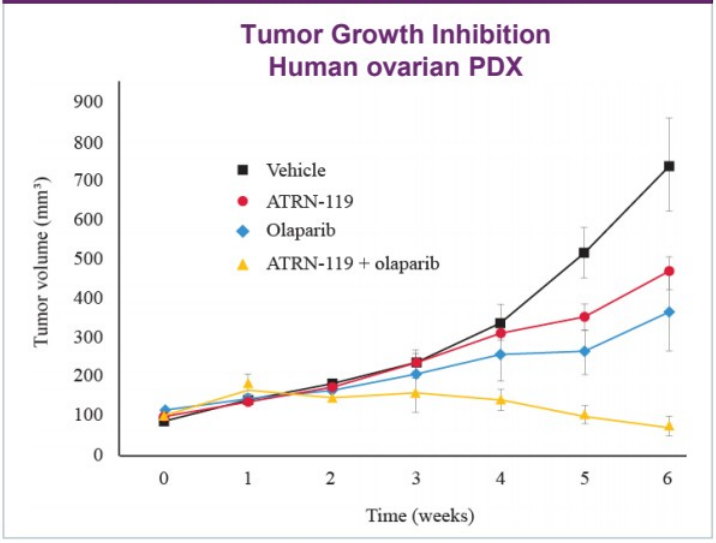


APREA THERAPEUTICS

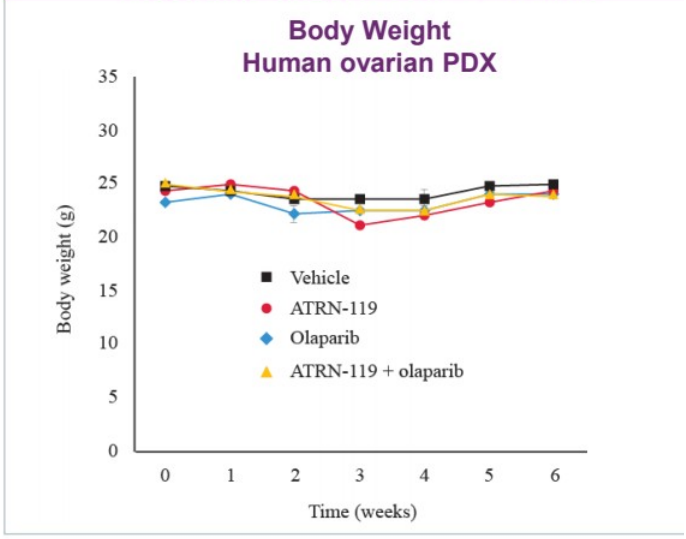
N=4 female mice per group, ATRN-119 - 100 mg/kg/day P.O, ATRN-157 - 20 mg/kg/day SQ.
ATRN-157 is an active metabolite identified in dogs receiving ATRN-119 P.O.. In vitro metabolism studies in dog and human hepatocytes and liver microsomes indicated formation of ATRN-157 in both species. Potency and selectivity of ATRN-157 was comparable to ATRN-119.
Pre-clinical studies with ATRN-119 and ATRN-157.

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



APREA THERAPEUTICS

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

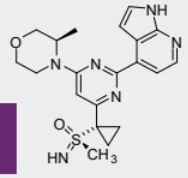
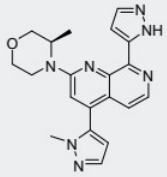
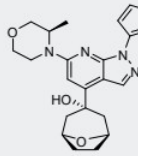
ATR Inhibitor: ATRN-119

A Potentially Differentiated ATRi

APREA THERAPEUTICS

Reported Challenges with Other ATR Inhibitors

First Generation Compounds Share Similar Core, Backbone, Toxicity, and Intermittent Dosing Schedu

Parameter	AstraZeneca AZD6738[1,2] 	Bayer BAY1895344[3] 	Repare / Roche[4] RP-3500[5] 
Route of Administration	**Oral**	**Oral**	**Oral**
MTD/RP2 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	Patriot 1, Escalation Phase, 160mg, BID[2]: **Anemia** (1/6, 17%) Patriot 2, Expansion Phase[1]: **Fatigue, anemia, nausea, and thrombocytopenia (not differentiated)** (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

APREA THERAPEUTICS

ATRN-119 Daily Dosing Means Continuous Tumor Reduction

Intermittent Dosing May Lead to Tumor Resistance

APREA THERAPEUTICS

Daily Dosing Is Clinically Superior Based on Other ATRi in Development

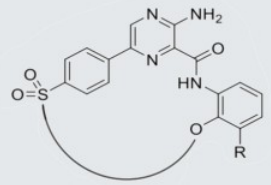
Artios ATR Inhibitor: ART0380
Initial Results From Phase 1 Dose Escalation[1]

Dose Escalation Phase	• 49 patients • Continuous dosing: QD; Range 200-400mg, (n=10) • Intermittent dosing: 3D on/4D off; Range 100 - 1,200mg, (n=39)
RP2D	• Continuous = 200mg • Intermittent dosing = 600mg
Efficacy Among Measurable Patients	• Continuous – **ORR 29%** (2/7). One of two responders treated at twice the RP2D. • Intermittent – **ORR 8%** (2/26). One of two responders treated at twice the RP2D.
Safety	• 36% Anemia Grade 3 at doses considered tolerable

APREA THERAPEUTICS

[1]ART0380-ESMO-Poster-2023

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 daily dosing (RP2D 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 and within normal ranges • 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.

APREA THERAPEUTICS

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.

WEE1 Inhibitor: APR-1051

ACESOT-1051:

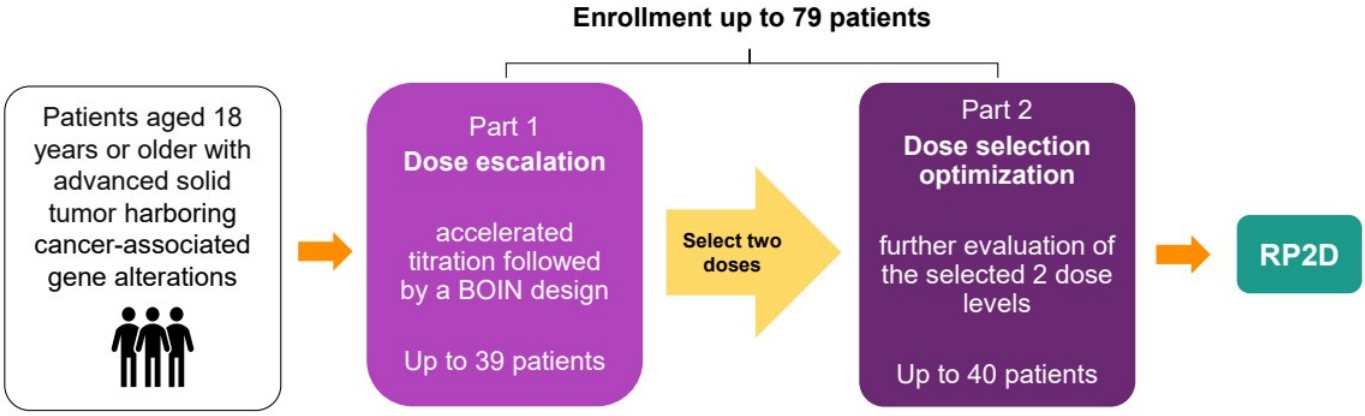
First-in-human phase 1 study of WEE1 inhibitor APR-1051 in patients with advanced solid tumors harboring cancer-associated gene alterations

APREA THERAPEUTICS

APR-1051: Study Design

Multi-center, open-label Phase 1 single-agent APR-1051 dose escalation and dose selection optimizati

Assess the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of single-agent APR-1051 in advanced solid tumors harboring cancer-associated gene alterations



Oral APR-1051 will be administered once-daily for 28-day cycles

Primary objectives: Safety, DLT, MTD/MAD, RP2D

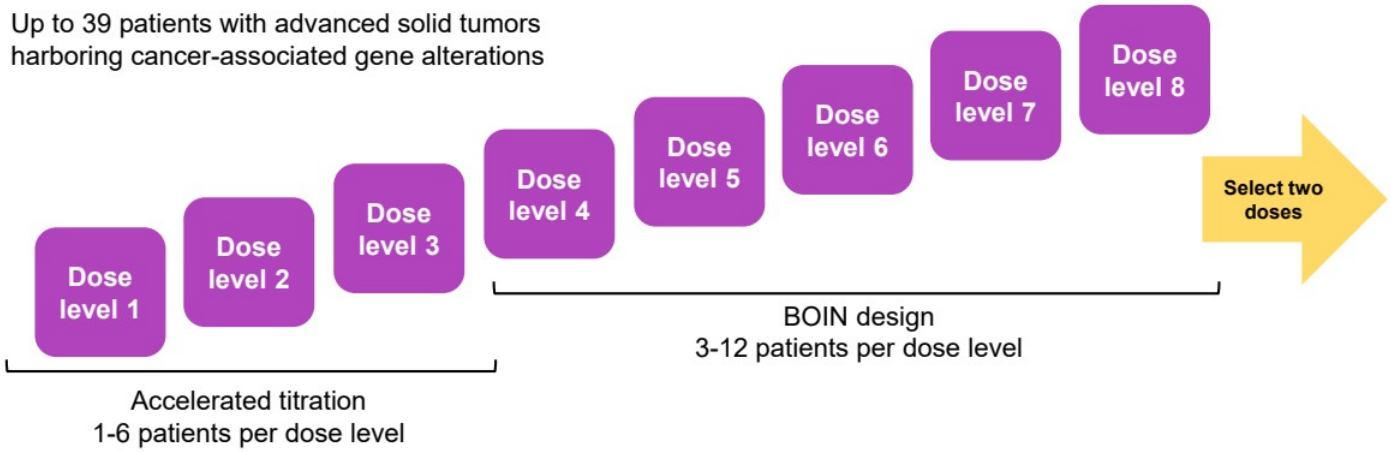
Secondary objectives: Pharmacokinetics, Antitumor activity (RECIST/PCWG3)

Exploratory objectives: Pharmacodynamics

APREA THERAPEUTICS

APR-1051: Study Design

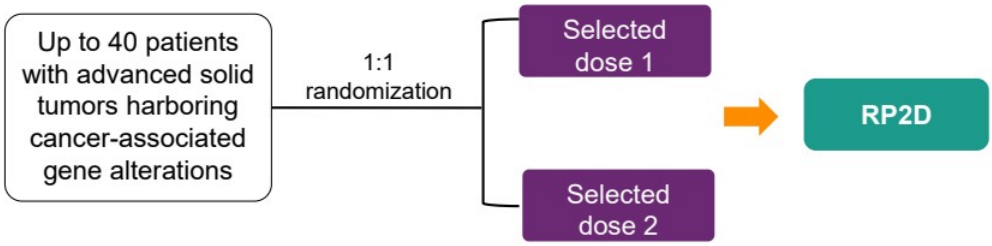
Single-agent APR-1051 dose escalation study schema



APREA THERAPEUTICS

APR-1051: Study Design

Single-agent APR-1051 dose selection optimization study schema & key eligibility criteria



INCLUSION CRITERIA

- Age 18 years or older with ECOG PS 0 or 1 (or KPS ≥ 70)
- Diagnosis of advanced/metastatic solid tumor that is either locally advanced and not amenable to curative therapy or stage 4 disease with:
  - Amplification/overexpression of *CCNE1* or *CCNE2* regardless of tumor type, or
  - Deleterious mutations in *FBXW7* or *PPP2R1A* regardless of tumor type, or
  - Colorectal cancer with *KRAS-GLY12* and *TP53* co-mutation, or
  - Uterine serous carcinoma regardless of biomarker status
- Measurable disease per RECIST version 1.1 (PCWG3 criteria for patients with mCRPC)
- Recovered to Grade 1 or baseline from prior treatment-related toxicity/AEs
- Adequate bone marrow and organ function

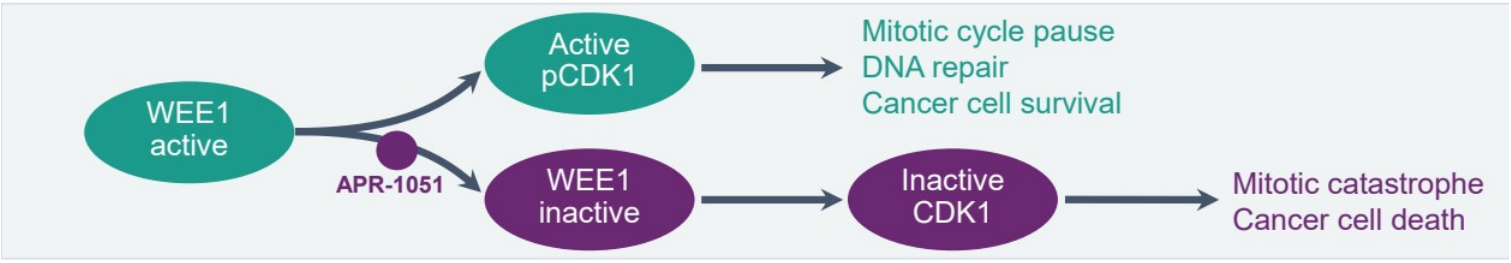
APREA THERAPEUTICS

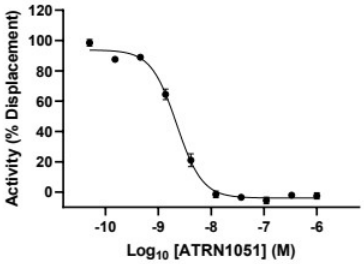
WEE1 Inhibitor: APR-1051

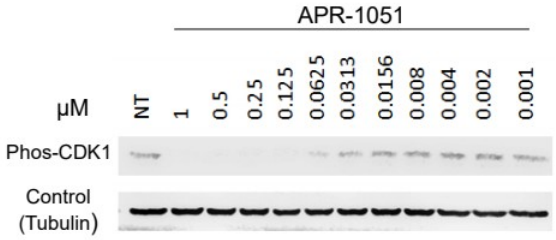
Preclinical Proof-of-Principle

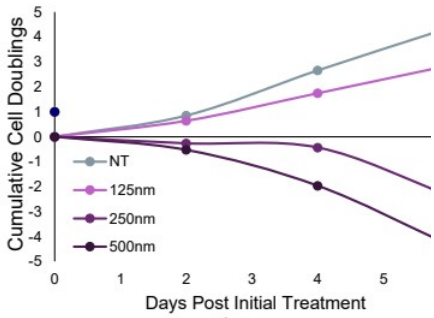
APREA THERAPEUTICS

WEE1 Inhibitor – APR-1051
Mechanism of Action – Prevent CDK1 Phosphorylation by WEE1 Kinas









APR-1051 binds to WEE1

…inhibits its biological activity…

…and triggers mitotic catastrophe and cancer cell death

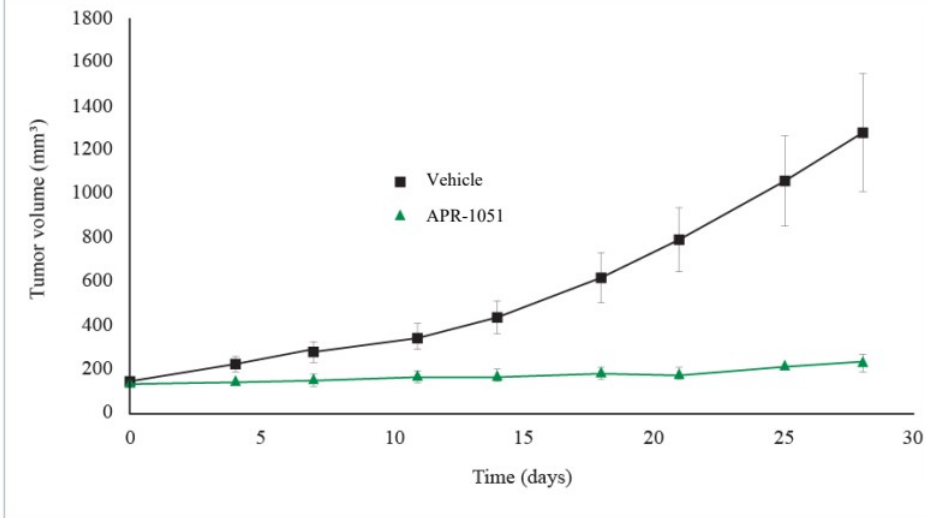
APREA THERAPEUTICS

pCDK1- Phosphorylated Cyclin Dependent Kinase 1
Data on file

APR-1051 Demonstrated Potentially Compelling Anti-tumor Activity

IND Cleared March 2024

Tumor Growth Inhibition
OVCAR-3



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

APREA THERAPEUTICS

Pre-clinical studies with APR-1051
Data on file

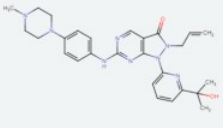
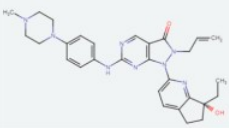
WEE1 Inhibitor: APR-1051

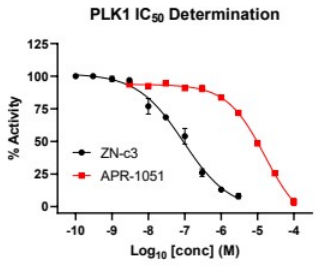
A Potentially Differentiated Wee1i

APREA THERAPEUTICS

APR-1051 Potentially Differentiated from Other WEE1 Inhibitors

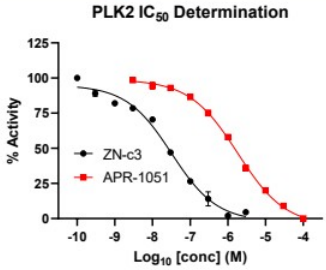
APR-1051 Potent and Structurally Differentiated, with High Selectivity to Limit Off-target Toxicity

		 AstraZeneca Adavosertib (AZD-1775)[1,2]	 Zentalis Azenosetrib (ZN-c3)[1]	 Aprea APR-1051
On-Target IC_{50} (nM)	**WEE1**	3.8	3.8	1.9



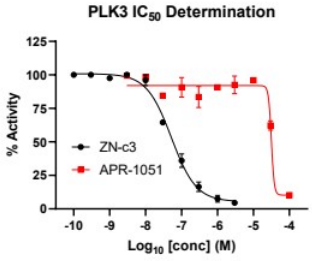
ZN-c3 = 92.1 nM
APR-1051 = 15,900 nM

PLK1 Inhibition
IC50 values show >150-fold



ZN-c3 = 32.0 nM
APR-1051 = 1,800 nM

PLK2 Inhibition
IC50 values show >50-fold



ZN-c3 = 52.2 nM
APR-1051 = 31,600 nM

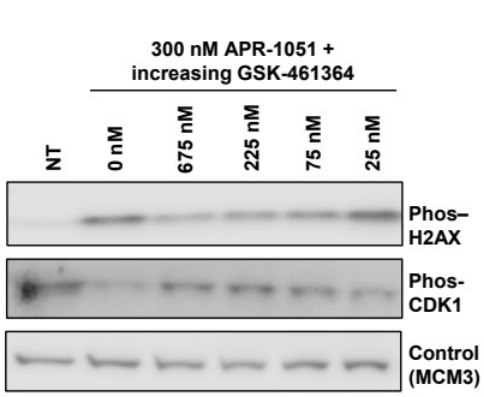
PLK3 Inhibition
IC50 values show >600-fold

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

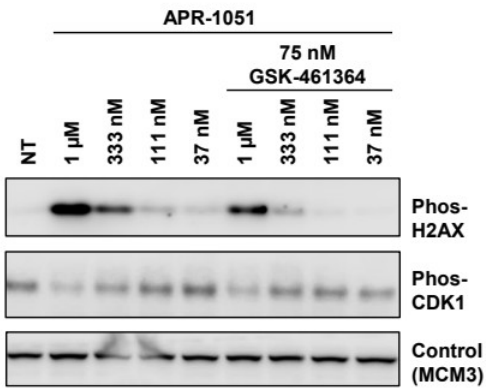
AACR-NCI-EORTC Meeting, Poster C147, 2023

PLK1 Inhibition Reduces Cytotoxic Effects of WEE1 Inhibitors

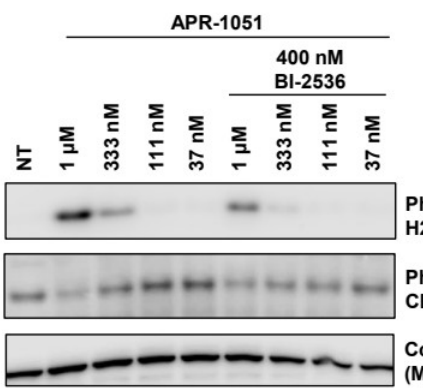
Minimal PLK1 Co-inhibition Enables Full Therapeutic Potential APR-1051



Dose range of PLK inhibitor GSK-461364 in combination with a single dose of APR-1051 in OVCAR-3 cells



PLK inhibitor, GSK-461364 interferes with the effects of APR-1051 in OVCAR-3 cells



PLK inhibitor, BI-2536, interferes with the effects of APR-1051 in OVCAR-3 cells

APREA THERAPEUTICS

AACR-NCI-EORTC Meeting, Poster C147, 20

APR-1051 Preclinical Data Highlight Potentially Favorable PK Properties

Based on Pre-clinical Studies, APR-1051 Shows Potentially Favorable Drug Exposure

	APR-1051[1]	Zentalis Azenosertib (ZN-c3)[2]			AstraZeneca Adavosertib (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 APR-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

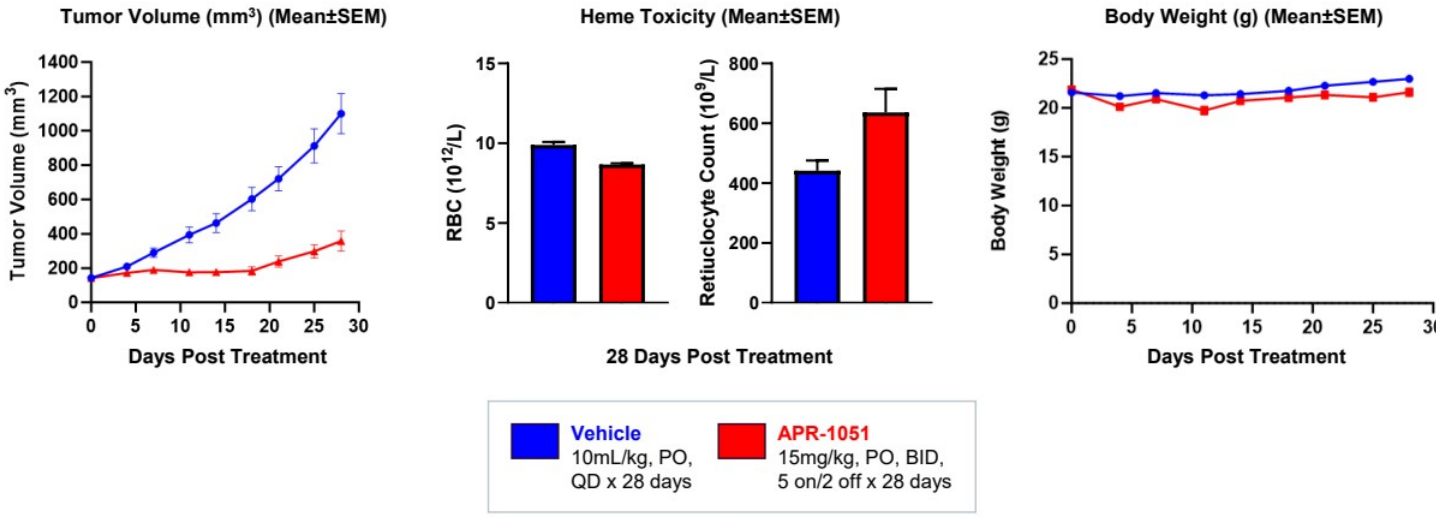
APR-1051 Shows Negligible Inhibition of hERG Channels

QT prolongation AEs were reported with some competitor WEE1 inhibitors

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

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

OVCAR Xenograft Tumor Model in Female Nude Mice



Vehicle
10mL/kg, PO,
QD x 28 days

APR-1051
15mg/kg, PO, BID,
5 on/2 off x 28 days

APREA THERAPEUTICS

AACR-NCI-EORTC Meeting, Poster C147, 20

APR-1051
2024-2025 Anticipated Clinical Milestones

Milestone	Timeline
Phase 1 – Monotherapy Dose Escalation	
Enroll first patient	1H 2024
Clinical Update	4Q 2024
Open-Label Efficacy Data	2Q 2025
RP2D	2H 2025

APREA THERAPEUTICS

Strong Intellectual Property Portfolio

Family 1: Ataxia Telengiectasia and Rad3-Related (ATR) Protein Kinase Inhibitors

- Macrocyclic inhibitors of ATR & methods of using them to treat various cancers, filed on Oct. 13th, 2015
- Patents granted in AU, CA, CN, EP, IL, JP, MX, HK. National phase examinations ongoing in BR, IN, KR
- 1.1: Issued on May 30, 2017 as U.S. Patent 9,663,535
- 1.2: Issued on May 29, 2018 as U.S. Patent 9,981,989
- 1.3: Issued on Feb. 5, 2019 as U.S. Patent 10,196,405

Family 2: ATR Inhibitors and Methods of Use

- Carboxylic acid-containing macrocyclic ATR inhibitors, and prodrugs; methods of using these inhibitors to treat various cancers; filed on Apr. 12th, 2017
- Issued on May 28th, 2019 as U.S. Patent 10,301,324

Family 3: ATR Inhibitor Pharmaceutical Composition and Methods

- International application filed on Apr. 14th, 2023
- Pharmaceutical formulation and composition of our lead molecule in the clinic

Family 4: WEE1 Inhibitor Pharmaceutical Compositions and Methods

- International Application filed on Jun. 3rd, 2022
- Composition of our lead WEE1 inhibitor compounds

Family 5: Methods of Treating Cancer

- U.S. Provisional Application filed on Oct. 20th, 2023
- Clinical methods of treating advanced solid cancer tumors using lead molecule

Aprea Therapeutics (NASDAQ: APRE)
Financial Summary & Capitalization

Cash & Equivalents of $21.6M as of December 31, 2023

Closed approximately $16.0M (before deducing placement agent fees and offering costs of approximately $1.4 million) from our private placement of our common stock in March 2024 with the potential to receive up to an additional $18.0 million upon cash exercise of accompanying warrants at the election of the investors.

Securities	Common Equivalents as of April 8, 2024
Preferred Stock (as converted)	28,112
Common Stock	5,430,215
Warrants:	
Pre-Funded	507,076
Tranche A	1,097,394
Tranche B	1,097,394
Total	2,701,864
Options	682,101
Restricted Stock Units	28,130
Fully Diluted Equivalents	8,870,422

APREA THERAPEUTICS

Investment Highlights

Technology developed by pioneers in synthetic lethality

- Management with strong drug development and commercial expertise

Diversified portfolio with best in class, de-risked clinical and preclinical programs

- Highly potent and selective ATR and WEE1 inhibitors
- Opportunities in ovarian, colorectal, prostate, and breast cancers
- Single agent and combination therapies

Near term catalysts

- Phase 1/2a ATRN-119 potential efficacy 2H 2024; complete dose escalation 4Q 2024
- Initiate Phase 1 for APR-1051 1H 2024

Financed into 3Q 2025

- Reach short term inflection points and catalysts
- Evaluate optimal strategic partnerships

APREA THERAPEUTICS