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

April 10, 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., April 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.

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