ARTS-021-1001: Phase1/2 Study of ARTS-021, an Oral Administrated, Highly Potent and Selective CDK2 Inhibitor, in Advanced or Metastatic Solid Tumors

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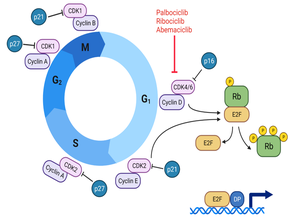
Background

- Cyclin E1 (CCNE1) is frequently upregulated in human cancer either through amplification or over-expression (**Figure 1**). High CCNE1 level is associated with a worse prognosis and has been reported to mediate resistance to both targeted- and chemotherapies [1].
- Genome wide loss of function screens reveal cyclin dependent kinase 2 (CDK2) addiction in CCNE1 aberrant tumor cells, suggesting CDK2 is an ideal target for tumors with CCNE1 amplification/over-expression.
- ARTS-021 is an investigational, reversible, orally administrated CDK2 selective inhibitor that inhibits CDK2 at nanomolar potency and with over 600-fold selectivity against CDK1 (**Table 1**).
- ARTS-021 has shown promising preclinical data, including strong single agent antitumor activity in CCNE1 amplified patient derived xenografts (PDX) (**Figure 2**).
- Consistent with the hypothesis that CDK2 activity may mediate resistance to CDK4/6 inhibitors, ARTS-021 significantly enhanced Palbociclib anti-tumor activity in an estrogen positive (ER+) breast cancer xenograft model (**Figure 2**).
- The results from pre-clinical research support the clinical development of ARTS-021 as a monotherapy in CCNE1-amplified cancers and in combination with CDK4/6 inhibitors in ER+ breast cancer.
- Furthermore, CCNE1 amplification is a common and distinct driver of tumorigenesis in epithelial ovarian cancer (EOC) that is associated with poor response to standard of care upfront chemotherapeutic agents [2]. Therefore, we propose the innovation strategy of ARTS-021 to meet the clinical needs of EOC patients with CCNE1 amplification.

Figure 1. CDK2 and Cell Cycles



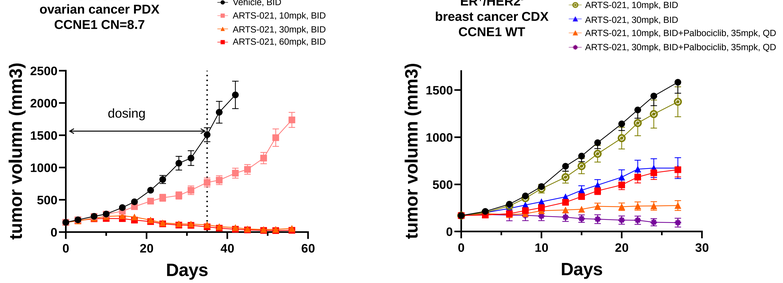
Adapted from Bai et al., Cancer Bio & Med, 2017; Knudsen., Nature Review Cancer 2018; graph generated with Biorender

Table 1. ARTS-021 is a Highly Potent and Selective CDK2 Inhibitor

Enzyme Activity IC_{50} (nM) [a]						Kinome S(10)
CDK2	CDK1	CDK4	CDK6	CDK7	CDK9	
1.4	942	477	1,237	2,834	7,440	0.022
Nano Bret Assay IC_{50} (nM) [b]						
CDK2	CDK1	CDK4	CDK6	CDK7	CDK9	
0.22*	107.4	788.9	412	5073	>10,000	

a: Enzymatic assay: Caliper Assay; ATP concentration used at 1mM; CDK1, CDK2, CDK4, CDK6, CDK7 and CDK9 are in complex with cyclin B1, Cyclin E1, Cyclin D1, Cyclin D3, Cyclin H/MAT1and Cyclin T1 respectively. Kinome S(10): fraction of kinases with <10 percentage of control at 1uM compound among 403 non-mutant kinases tested, Eurofins Discovery KinomeScan;
b: HEK-293T cells were transfected with canonical CDK/cyclin pairs as in the enzyme assay and treated with compound and a tracer for 1 hour before measurements were taken; *: below low limit of quantification (<0.5nM).

Figure 2. ARTS-021 Induced Tumor Regression as a Single Agent in CCNE1-amplified Ovarian PDX Model and Enhanced Palbociclib Activity in ER+/HER2- Breast Cancer Xenograft Model

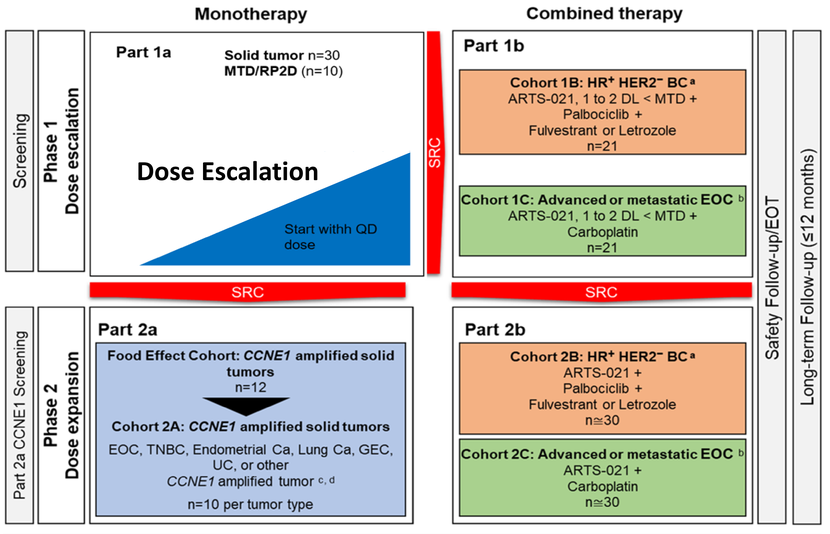


Left: Antitumor activity in ovarian cancer patient derived xenograft (PDX) OV5398. Drug treatment was initiated when tumors reached ~150-260mm^3. Treatment stopped on day 35 and tumor regrowth continued to be monitored; **Right: Antitumor activity in ER+/HER2- breast cancer cell line derived xenograft (CDX) T47D.** Mice inoculated SC with T47D (10x10^6), T47D cells that were passed in vivo twice.

Study Objective and Design

- ARTS-021-1001 (NCT05867251) is an open-label, first in human, phase 1/2 study to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of ARTS-021 in adult patients with advanced or metastatic solid tumors.
- The study is planned in patients with CCNE1-amplified solid tumor, HR+HER2- breast cancer with disease progression on CDK4/6 inhibitor, or Cyclin E1-amplified ovarian cancer with disease progression on chemotherapy (**Figure 3**).

Figure 3. ARTS-021-1001 Study Scheme



PK: C_{max}, T_{max}, $t_{1/2}$, AUC_{last}, $AUC_{0\text{-}tau}$, $C_{min,ss}$, R_{ac}, CL_R, F_e, Ae_{last}

PD: Changes in pRb and Ki67 in paired pre- and on-treatment tumor biopsies and serum tumor markers (eg, CA125, PSA, CA19-9)

a. BC=breast cancer; HER2=human epidermal growth factor receptor 2; HR=hormone receptor
b. EOC=epithelial ovarian cancer
c. GEC=gastroesophageal cancer; TNBC=triple-negative breast cancer; UC=urothelial cancer
d. CCNE1= cyclin E1
Ca=cancer; CA=cancer antigen; CDK=cyclin-dependent kinase; DL=dose level; EOT=End of Treatment; MTD=maximum tolerated dose; PD=pharmacodynamics; PK=pharmacokinetics; PSA=prostrate-specific antigen; QD=once daily; RP2D=recommended Phase 2 dose; SRC=safety review committee

- Phase 1 dose escalation is being conducted using a BOIN design to determine MTD/RP2D, safety of ARTS-021 monotherapy and in combination with either palbociclib + fulvestrant/letrozole or carboplatin.
- A treatment cycle is defined as 28 days. ARTS-021 is administered orally QD without interruption until disease progression, unacceptable toxicity, or another discontinuation criterion is met.
  - Phase 1 Part 1a: ARTS-021 will be administrated once daily (QD) starting from dose level 1 (DL1).
  - Phase 1 Part 1b: the initial ARTS-021 dose will be 1 to 2 levels lower than monotherapy RP2D; Palbociclib will be dosed as 125 mg QD 21 days on treatment and 7 days off treatment; Fulvestrant will be administrated as 500 mg on Days 1, 15, 29 [Day 1 of Cycle 2], and once monthly thereafter; or Letrozole will be orally administrated as 2.5 mg QD.
  - Phase 1 Part 1c: the initial ARTS-021 dose will be 1 to 2 levels lower than monotherapy RP2D; Carboplatin dosage will be calculated using Calvert Formula based on the patient's glomerular filtration rate and target AUC (4 mg/mL × min).
- Phase 2 dose expansion will initiate upon determination of the RP2D and will further assess the safety, tolerability and anti-tumor activity of ARTS-021. A food effect cohort will be included in Part 2a which will be initiated at 2 dose levels lower than RP2D.

Key Eligibility Criteria

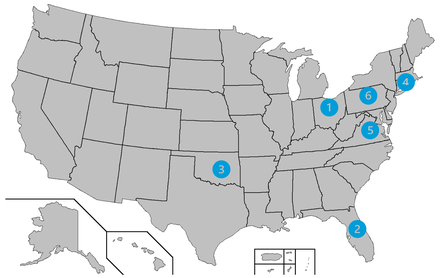
Key inclusion criteria	Key exclusion criteria
• Age ≥18 years old • ECOG 0-1 • Adequate organ function as demonstrated on screening labs • **Phase 1:** - **Part 1a:** Locally advanced or metastatic solid tumor, for which standard therapies are no longer effective, appropriate, or safe in the opinion of the investigator - **Part 1b**:Previously treated advanced or metastatic HR+HER2-breast cancer including 1 prior line of combined CDK4/6 inhibitor and endocrine therapy - **Part 1c:** CCNE1 amplified advanced or metastatic EOC in patients who are platinum-refractory or platinum-resistant • **Phase 2:** At least 1 measurable target lesion per RECIST v1.1 per investigator - **Part 2a:** CCNE1 amplified, advanced or metastatic solid tumor with progression after standard care - **Part 2b and 2c:** The same as Part 1b and 1c	• Have received an investigational agent or anticancer therapy within 2 weeks prior to planned start of ARTS-021 • Have received any CDK2 inhibitor, protein kinase, membrane associated tyrosine/threonine (PKMYT1) inhibitor, or WEE1 inhibitor anticancer therapy • Have undergone major surgery within 4 weeks prior to planned start of ARTS-021 • Active CNS metastases • Any unresolved toxicities from prior therapy of CTCAE Grade >1 (except for alopecia of any grade or Grade 2 peripheral neuropathy) • Clinically significant, active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of ARTS-021, or prolongation of the QT interval corrected for heart rate (QTcF) > 470 msec • Inadequate organ function based on safety lab assessment

Key Study Endpoints

Phase 1	Phase 2
• First Cycle dose-limiting toxicities (DLTs) • Adverse Events (AEs), SAEs, changes in hematology and chemistry values, VS, ECGs, Dose interruptions and reductions, and dose intensity • MTD & RP2D • Objective Response Rate (ORR) • Progression Free Survival (PFS) • Time to Progression (TTP)	• Objective Response Rate (ORR) • Progression Free Survival (PFS) • Overall Survival (OS) • Time to Progression (TTP) • Duration of Response (DOR) • Incidence and severity of - AEs and SAEs, - Clinical laboratory values, - Vital signs, 12 lead ECG results, - Dose interruptions, reductions, dose intensity, - Other relevant parameter(s)

Study Status & Location

- The Phase 1 Part 1a monotherapy dose escalation study is ongoing at 6 US sites.
- Will expand to approximately 30 sites in US, Europe and China for Phase 1 combination dose finding and Phase 2 studies.



Six US sites for Phase 1 Part 1a

1. Case Western Reserve University, Cleveland, OH 44106
2. Florida Cancer Specialists, Sarasota, FL 34232
3. Oklahoma University, Oklahoma City, OK 73117
4. Yale Cancer Center, New Haven, CT 06510
5. Virginia Cancer Specialists, Fairfax, VA 22031
6. Thomas Jefferson University, Philadelphia, PA 19107

Visit https://clinicaltrials.gov/study/NCT05867251?intr=ARTS021&rank=1 for current active recruitment sites

References

1. Gallo D, Young JTF, Fourtounis J, Martino G, Alvarez-Quilon A, Bernier C, et al. CCNE1 amplification is synthetic lethal with PKMYT1 kinase inhibition. Nature. 2022;604(7907):749-56.
2. Petersen S, Crispens MA, et al. CCNE1 and BRD4 co-amplification in high-grade serous ovarian cancer is associated with poor clinical outcomes. Gynecologic oncology. 2020;157(2):405-10.

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