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

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**Introduction**

**DNA replication inhibition in tumor panels**

- **ATR activity** is a hallmark of genomic instability in cancer cells.
- Genomic aberrations associated with loss of ATR activity are observed in many cancer types using large-scale genomic analysis.

**ATRN-119** is a novel oral ATR inhibitor.
- **ATR activity** is a hallmark of genomic instability in cancer cells.
- Genomic aberrations associated with loss of ATR activity are observed in many cancer types using large-scale genomic analysis.

**Key Findings**

1. ATRN-119 is orally bioavailable, potent, and selective.
2. ATRN-119 induced a significant decrease in cell viability in vitro.
3. ATRN-119 showed no evidence of toxicity in the pilot population.

**Summary**

- Daily dosing of ATRN-119 may result in persistent tumor-reducing effect.
- No dose-limiting toxicities have been reported to date in patients treated with ATRN-119.
- ATRN-119 appears to be well-tolerated with a manageable toxicity profile.
- Pharmacodynamic data is ongoing and results will be presented in future publications.
- This phase 1/2a study is currently enrolling eligible study patients at four U.S. sites (NCT04905914).
- The dose expansion cohort will be initiated in 2Q24.

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**Objective**

- To determine the safety and tolerability of escalating doses of oral ATRN-119 and to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D).

**Key Eligibility Criteria**

- **Age**: 18 to 76 years.
- **Tumor type**: Pancreatic cancer, colorectal carcinoma, breast cancer, or adenocarcinoma of unknown primary.
- **Performance status**: 0 to 2.
- **Life expectancy**: At least 12 weeks.
- **No prior treatment with ATRN-119**: None.
- **No prior study drugs**: None.
- **Baseline tumor markers**: No evidence of progression.

**Preliminary Results**

- **MTD**: Dose level 4 (100 mg once daily).
- **RP2D**: Dose level 4 (100 mg once daily).
- **AEs**: Symptom-related toxicities were reported.
- **Tolerability**: The toxicities were manageable and did not lead to discontinuation.

**Figure 1. ATRN-119 is an orally bioavailable, potent, and selective macrocyclic small molecule inhibitor of ATR kinase**

**Figure 2. ATRN-119 binds to ATR, inhibits its biological activity (B), and triggers DNA replication fork collapse and breaks (C)**

**Figure 3. ATRN-119 daily dosing is desirable**

**Lack of daily dosing may contribute to formation of resistance**

**Figure 4. Study schema of ATRN-119**

**Figure 5. Summary of duration of treatment**

**As of Sept 22, 2023**

**Figure 6. Adverse events at least possibly related to ATRN-119**

**As of Sept 22, 2023**

**Preliminary Results (cont’d)**

- **Table 2: All cause treatment-emergent adverse events**

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**Preclinical Studies**

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