A Phase 1/1b Study to Evaluate the Safety and Tolerability of AB928, a Novel Dual Adenosine Receptor Antagonist, in Combination with Chemotherapy in Patients with Gastrointestinal Malignancies

De Souza P¹, Lee CK², Sjoquist K², Pan S³, Idan A³, Rieger A⁴, Berry W⁴, Jin L⁴, Seitz L⁴, Ashok D⁴, Walters MJ⁴, Plovesan D⁴, Tan JBL⁴, Lee SJ⁴, Park A⁴, DiRenzo D⁵, Karakunnel J⁴

¹University of Western Sydney, Sydney, Australia; ²Cancer Care Centre, St. George Public Hospital, Kogarah, NSW 2217, Australia; ³St. George Private Hospital, Kogarah, NSW 2217, Australia; ⁴Arcus Biosciences, Inc., 3928 Point Eden Way, Hayward, CA 94545, USA

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**ABSTRACT**

**Background:** In many tumors, extracellular adenosine contributes to an immunosuppressed tumor microenvironment via activation of the A₂ₐ receptor (A₂ₐR) and A₂βR receptor (A₂βR) expressed on intratumoral immune cells. AB928 is a selective, small-molecule A₂ₐR and A₂βR antagonist with the potential to block the immunosuppressive effects of extracellular adenosine concentrations in the tumor microenvironment. Preclinically, combining adenosine receptor inhibition with either chemotherapy or anti-programmed cell death-1 (PD-1) resulted in greater tumor control in murine models, suggesting AB928 may have synergistic activity when paired with either chemotherapy or checkpoint inhibition in oncology patients. A phase 1 study with AB928 in healthy volunteers has been completed.

**Methods:** A phase 1/1b, open-label, dose-escalation (3+3 design) study is evaluating the safety/tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of AB928 in combination with mFOLFOX in patients with gastrointestinal malignancies. Patients are eligible if they have histologically confirmed gastroesophageal cancer (GEC) or colorectal cancer (CRC) that is metastatic or locally advanced and untreated for which no alternative or curative therapy exists, or standard therapy is not considered appropriate by the participant and treating physician. Patients must have received ≤5 lines of prior therapies and must not have received prior oxaliplatin treatment, except those who have received prior oxaliplatin-based therapy as the most recent regimen in the adjuvant setting if completed ≥6 months prior to enrollment. AB928 is administered orally once daily at a starting dose of 75 mg (Cohort 1) escalating to 150 mg (Cohort 2) and 200 mg (Cohort 3), and mFOLFOX is administered at the standard regimen (oxaliplatin 85 mg/m² intravenously [IV] every 2 weeks [Q2W], leucovorin 400 mg/m² IV Q2W, and 5-fluorouracil [5-FU] 400 mg/m² IV bolus + 2400 mg/m² [continuous 46-hour infusions on Days 1 and 2]). Intermediate AB928 doses may be evaluated based on data from cohorts that have not been explored. Doses that have exceeded the maximum tolerated dose (MTD) will not be evaluated. Following identification of the recommended phase 2 dose (RP2D) of AB928 and mFOLFOX during dose escalation, each tumor cohort (GEC and CRC) may be expanded to further evaluate the combination. The primary endpoint is safety/tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of AB928 in combination with standard of care chemotherapy in patients with GEC or CRC.

**Endpoints:** The study described herein (AB928CSP0003) is assessing the safety/tolerability, -PK, PD, and clinical activity of AB928 in combination with standard of care chemotherapy in patients with GEC or CRC.

**Dose escalation:** Escalating doses of AB928 (75 mg [starting dose, Cohort 1], 150 mg [Cohort 2], and 200 mg [Cohort 3]) administered orally once daily in combination with mFOLFOX (oxaliplatin, leucovorin, 5-FU) will be assessed based on a 3+3 design, including a DLT evaluation period - Intermediate AB928 doses may be evaluated based on data from cohorts that have been explored - Doses that have exceeded the MTD will not be evaluated - Up to 18 patients, depending on the toxicities observed, may be evaluated

**Dose expansion:** The dose of AB928 to be used in the dose-escalation phase will be determined based on findings from the dose-escalation phase; mFOLFOX will be administered according to standard treatment guidelines

Each tumor expansion cohort will consist of 15 to 40 patients

**Findings:** AB928 was well tolerated and no safety concern was identified. This placebo-controlled study with single-ascending and multiple-ascending dose arms assessed AB928 doses between 10 and 200 mg once daily and 100 mg twice weekly. AB928 was well tolerated and no safety concern was identified. All adverse events (AEs) were Grade 1-2; there were no DLTs, serious AEs, or AEs resulting in study drug discontinuation. The PK profile of AB928 was linear and dose-proportional, and a clear PK/PD correlation was demonstrated (Figure 3). AB928 plasma levels ≥1 µM were associated with ≥90% adenosine receptor inhibition

**Statistical Analysis:** Summary statistics will be provided for AEs, serious AEs, AE severity, and relationship to study drug - PK parameters will be estimated using noncompartmental methods - ORR and DCR will be estimated by the proportion of patients with objective response and disease control, respectively, and their 95% confidence intervals will be estimated using the exact binominal method - Time-to-event endpoints will be summarized using the Kaplan-Meier method - Interim analyses for futility will be conducted for each expansion cohort that has enrolled ≥15 patients who are evaluable for disease assessment

**Trial Status:** Enrollment is ongoing

**REFERENCES**