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 Breast or Gynecologic Malignancies

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ABSTRACT

Background: In many tumors, extracellular adenosine contributes to an immunosuppressed tumor microenvironment via activation of the A_{2a} receptor ($A_{2a}R$) and A_{2b} receptor ($A_{2b}R$) expressed on intratumoral immune cells. AB928 is a novel, selective, small-molecule antagonist of both $A_{2a}R$ and $A_{2b}R$ with the ability to potently block the immunosuppressive effects of high concentrations of adenosine in the tumor microenvironment. AB928 differs from other known $A_{2a}R$ antagonists based on its dual mode of action, its minimal loss of potency due to nonspecific binding to plasma proteins, and its lack of penetrance through a healthy blood-brain barrier. Preclinically, combining adenosine receptor inhibition with either chemotherapy or anti-programmed cell death-1 (PD-1) resulted in greater tumor control in mouse models, suggesting that AB928 may have synergistic activity when paired with either chemotherapy or checkpoint inhibitors 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 (including dose-limiting toxicities [DLTs]), pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of AB928 in combination with pegylated liposomal doxorubicin (PLD) in patients with breast or gynecologic malignancies. Patients are eligible if they have pathologically confirmed triple-negative breast cancer (TNBC) or ovarian cancer (OC) that is metastatic, advanced or recurrent with progression for which no alternative or curative therapy exists. Patients may have received up to 5 lines of prior therapies for advanced/recurrent and progressive disease (unlimited number of hormonal therapies permitted). 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 PLD is administered at the standard regimen of 40 mg/m^2 intravenously (IV) every 4 weeks (Q4W). Intermediate AB928 doses may be evaluated based on data from cohorts that have 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 PLD during dose escalation, each tumor cohort (TNBC and OC) may be expanded to further evaluate the combination. The primary endpoint is safety/tolerability, and secondary endpoints are PK, PD (receptor occupancy in peripheral blood and immunomodulatory activity in select immune subsets), and clinical activity (objective response rate [ORR], duration of response, disease control rate [DCR; complete response (CR), partial response (PR), or stable disease (SD) for >6 months], and progression-free survival [PFS] per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1, and overall survival). The study is recruiting.

BACKGROUND

- The accumulation of adenosine, generated through hydrolysis of extracellular adenosine monophosphate (AMP) by the ectonucleotidase CD73, is a key strategy exploited by tumors to escape immunosurveillance (**Figure 1**)[1,2]
- Adenosine's suppressive effects on immune cells are driven primarily by 2 of the 4 adenosine receptors, $A_{2a}R$ and $A_{2b}R$[3]
  - This effect is mediated by increased cyclic AMP (cAMP) levels and phosphorylation of cAMP response element binding protein (CREB)
- Pharmacological inhibition of the effects of adenosine has recently generated much interest in immuno-oncology, but thus far, only $A_{2a}R$ antagonists, initially developed for central nervous system indications,[4] are being studied in oncology

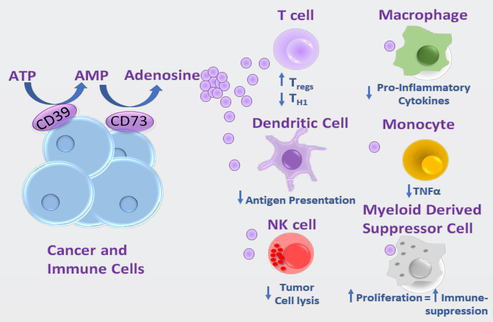

Figure 1. Adenosine-mediated immune suppression

- AB928 is a novel, selective, small-molecule $A_{2a}R/A_{2b}R$ antagonist designed to potently block the immunosuppressive effects of high concentrations of adenosine in the tumor microenvironment
- AB928 differs from other known $A_{2a}R$ antagonists based on its dual mode of action, its minimal loss of potency due to nonspecific binding to plasma proteins, and its lack of penetrance through a healthy blood-brain barrier
- In mouse models, combining adenosine receptor inhibition with either chemotherapy (**Figure 2**) or anti-PD-1 resulted in greater tumor control, suggesting AB928 may have synergistic activity when combined with either chemotherapy or checkpoint inhibitors in cancer patients[5]
  - This is supported by the literature showing that cancer cells treated with chemotherapy induce immunogenic cell death, characterized by upregulation of CD39/CD73 leading to enhanced adenosine generation

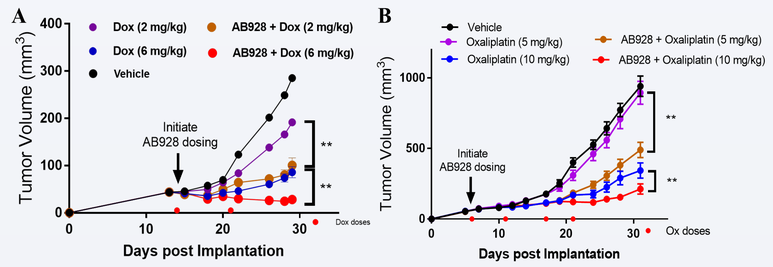

Figure 2. Tumor control with AB928 + doxorubicin (A) or oxaliplatin (B) in mouse model

**p<0.01 AB928 + chemotherapy vs chemotherapy alone

- A phase 1 study of AB928 in healthy volunteers has been completed[6]
  - 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
  - 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

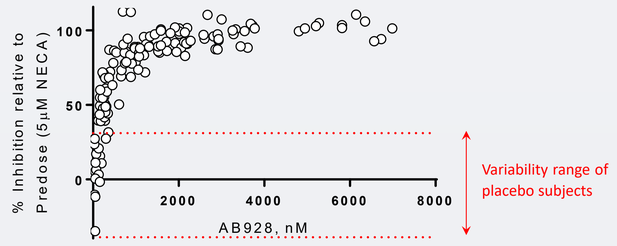

Figure 3. PK/PD correlation in AB928-dosed subjects measured by pCREB inhibition

- Four clinical studies of AB928 in combination with other agents have been initiated in cancer patients in Australia and United States (**Table 1**)
  - The study described herein (AB928CSP0002) is assessing the safety/tolerability, PK, PD, and clinical activity of AB928 in combination with standard of care (SOC) PLD in patients with TNBC or OC

Table 1. Ongoing AB928 combination studies in oncology

Study Number	Combination	Tumor Type
AB928CSP0002	AB928 + PLD (SOC)	TNBC or OC
AB928CSP0003	AB928 + mFOLFOX (SOC)	GEC or CRC
AB928CSP0004	AB122 (240 mg Q2W) AB928 + Carbo/Pem + Pembro (SOC) AB928 + Carbo/Pem	NSCLC
AB928CSP0005	AB928 + AB122 (240 mg Q2W)	Solid tumors

METHODS

Patients

Key Inclusion Criteria

- Female patients ≥18 years of age
- *Dose escalation:* Pathologically confirmed TNBC or OC that is metastatic, advanced or recurrent with progression for which no alternative/curative therapy exists
  - Any number of prior therapies for advanced/recurrent and progressive disease
- *Dose expansion:* Pathologically confirmed TNBC that is metastatic, recurrent with progression for which no alternative/curative therapy exists or physician and patient consider this option appropriate, or platinum-resistant OC (ie, having received a platinum agent in first-line setting)
- ≥1 measurable lesion per RECIST v1.1
- Eastern Cooperative Oncology Group (ECOG) performance status score 0 or 1

Key Exclusion Criteria

- Live vaccines within 4 weeks of study drug initiation
- Pregnant or breastfeeding
- Active or prior autoimmune disease requiring systemic treatment
- Prior chemotherapy, targeted small-molecule therapy, or radiotherapy within 4 weeks of study drug initiation or has not recovered from AEs resulting from previous agents

Study Design and Treatment

- This is a phase 1/1b, open-label, dose-escalation, dose-expansion study (**Figure 4**)
- *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 a standard PLD regimen (40 mg/m^2 IV Q4W) 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-expansion phase will be determined based on findings from the dose-escalation phase; PLD will be administered according to standard treatment guidelines
  - Each tumor expansion cohort will consist of 15 to 40 patients
  - Patients in the dose-expansion phase will be monitored for unacceptable toxicities

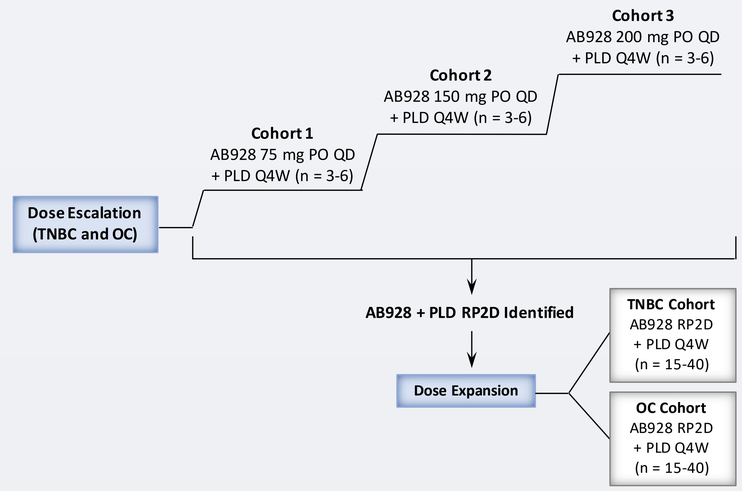

Figure 4. Study schema

Endpoints

Primary Endpoint

- Safety: Incidence of AEs and DLTs, and changes from baseline in vital signs, clinical laboratory parameters, physical examination findings, ECOG performance status, and electrocardiogram

Secondary Endpoints

- Serum concentration and PK parameters for AB928
- Receptor occupancy in peripheral blood and immunomodulatory activity in select immune subsets for AB928
- Clinical activity: ORR, duration of response, DCR (defined as CR, PR, or SD for >6 months), and PFS per RECIST v1.1, and overall survival

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 binomial method
- Time-to-event endpoints will be summarized using the Kaplan-Meier method
- Interim analyses for futility and toxicity will be conducted for each expansion cohort that has enrolled ≥15 patients who are evaluable for disease assessment

Trial Status

- Enrollment is ongoing

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