

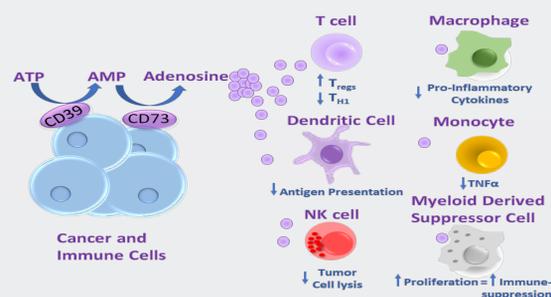
## ABSTRACT

**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 potentially block the immunosuppressive effects of high concentrations of adenosine 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 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. AB122 is a fully human monoclonal antibody targeting PD-1.

**Methods:** A phase 1, 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 AB122 in patients with advanced malignancies. Patients are eligible if they have pathologically confirmed non-small cell lung cancer, squamous cell carcinoma of the head and neck, renal cell carcinoma (RCC), breast cancer, colorectal cancer, melanoma, bladder cancer, ovarian cancer, endometrial cancer, Merkel cell carcinoma, or gastroesophageal cancer that is metastatic, advanced or recurrent with progression for which no alternative or curative therapy exists. Patients must have received standard of care (SOC), and may have received up to 5 lines of prior therapies. 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 AB122 is administered intravenously (IV) every 2 weeks (Q2W) at 240 mg. Intermediate AB928 doses may be evaluated based on data from cohorts that have been explored; however, doses must not exceed the maximum tolerated dose (MTD). Following identification of the recommended phase 2 dose (RP2D) of AB928 and AB122 during dose escalation, select tumor cohorts may be expanded to further evaluate this 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), immunogenicity, 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). This study is recruiting.

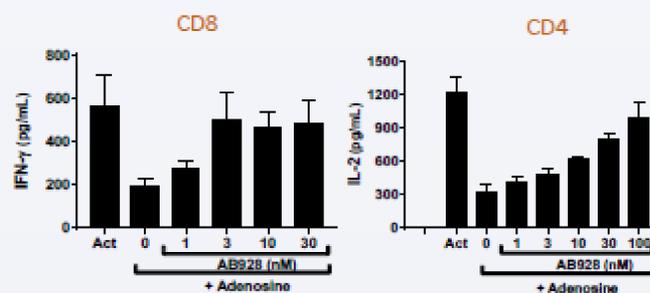
## BACKGROUND

- 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)<sup>1,2</sup>
- Adenosine's suppressive effects on immune cells are driven primarily by 2 of the 4 adenosine receptors,  $A_{2a}R$  and  $A_{2b}R$ <sup>3</sup>
  - 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,<sup>4</sup> are being studied in oncology



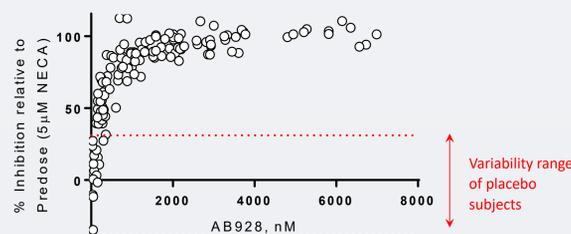
**Figure 1. Adenosine-mediated immune suppression**

- AB928 is a novel, selective, small-molecule  $A_{2a}R/A_{2b}R$  antagonist designed to potentially 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
- Results from in vitro studies showed:<sup>5</sup>
  - AB928 blocked adenosine-mediated suppression of T-cell activation (ie, restored CD8 T-cell IFN- $\gamma$  and CD4 T-cell IL-2 production; Figure 2)
  - AB928 inhibits adenosine-receptor-mediated increases in pCREB
- In mouse models, combining adenosine receptor inhibition with either anti-PD-1 or chemotherapy resulted in greater tumor control, suggesting AB928 may have synergistic activity when combined with either checkpoint inhibitors or chemotherapy in cancer patients<sup>5</sup>



**Figure 2. AB928 restores CD8 T-cell IFN- $\gamma$  and CD4 T-cell IL-2 production**

- A phase 1 study of AB928 in healthy volunteers has been completed<sup>6</sup>
  - 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  $\geq 1$   $\mu$ M were associated with  $\geq 90\%$  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 (AB928CSP0005) is assessing the safety/tolerability, PK, PD, and clinical activity of AB928 in combination with AB122, a PD-1 inhibitor, in patients with advanced solid tumors

**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

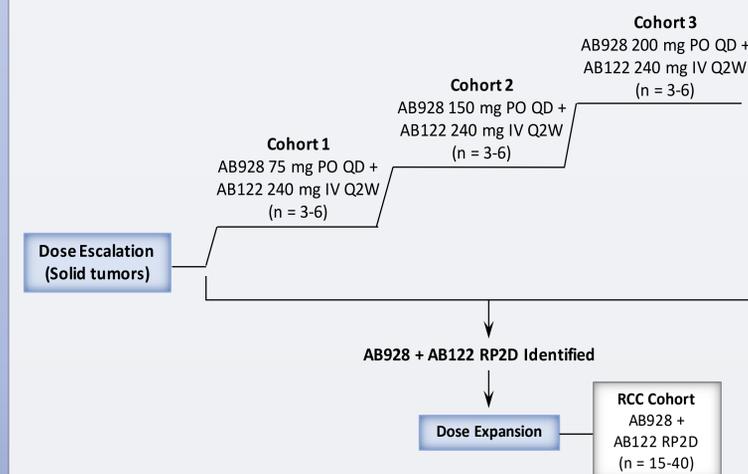
- Male or female patients  $\geq 18$  years of age
- Dose escalation:** Pathologically confirmed non-small-cell lung cancer, squamous cell carcinoma of the head and neck, RCC, breast cancer, colorectal cancer, melanoma, bladder cancer, ovarian cancer, endometrial cancer, Merkel cell carcinoma, or gastroesophageal cancer that is metastatic, advanced or recurrent with progression for which no alternative/curative therapy exists
- Dose expansion:** Pathologically confirmed advanced clear-cell RCC previously treated with antiangiogenic and systemic regimens
- $\geq 1$  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 treatment with immune checkpoint inhibitor or agonist, or mTOR inhibitor

## Study Design and Treatment

- This is a phase 1, 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 AB122 240 mg IV Q2W 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
  - AB928 doses that have exceeded the MTD will not be evaluated
  - Lower or higher AB122 doses may be tested; higher doses must not exceed MTD
  - Up to 18 patients, depending on the toxicities observed, may be evaluated
- Dose expansion:** The RP2D of AB928 and AB122 combination therapy determined during the dose-escalation phase will be evaluated in the dose-expansion phase in patients with RCC
  - The RCC expansion cohort will consist of 15 to 40 patients



**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 combination therapy
- Receptor occupancy in peripheral blood and immunomodulatory activity in select immune subsets for AB928 combination therapy
- 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 will be conducted for each expansion cohort that has enrolled  $\geq 15$  patients who are evaluable for disease assessment

## Trial Status

- Enrollment is ongoing
- Clinicaltrials.gov NCT03629756

## REFERENCES

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