Phase 1 Evaluation of AB928, a Novel Dual Adenosine Receptor Antagonist, Combined With Chemotherapy or AB122 (anti-PD-1) in Patients (pts) With Advanced Malignancies

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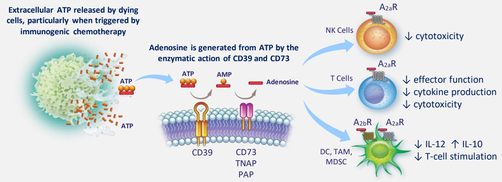
This Poster Presents Results from Across the AB928 Program of Four Ongoing Phase 1/1b Studies

INTRODUCTION

The tumor microenvironment contains high levels of immunosuppressive adenosine, which binds to and activates the A_{2a} (A_{2a}R) and A_{2b} receptors (A_{2b}R) on immune cells, leading to an ineffective anti-tumor response (**Figure 1**). CD73 enzyme and tissue non-specific alkaline phosphatase (TNAP) are primarily responsible for the conversion of extracellular adenosine mono-phosphate (AMP) to adenosine. In certain tumor types, other enzymes, such as prostatic acid phosphatase (PAP) in prostate cancer, can also efficiently convert AMP to adenosine.

Figure 1. Adenosine Pathway Plays a Critical Role in Immunosuppression



AB928 is a dual antagonist of adenosine receptors A_{2a}R and A_{2b}R designed to shield activated immune cells (CD8$^+$ T cells and NK cells), inhibit adenosine-mediated myeloid cell dysfunction, and shut down adenosine-driven mechanisms of tumor growth and metastasis. Preclinically, combining AB928 with either chemotherapy or anti-PD-1 resulted in greater tumor growth control, suggesting that AB928 may have additive activity when paired with either of these types of agents in cancer pts.

Previously, we completed a dose-escalation study of AB928 as a single agent in healthy volunteers (Seitz et al., Investigational New Drugs (2018); *https://doi.org/10.1007/s10637-018-0706-6*). AB928 dosed orally once daily (QD) was shown to be tolerable at all dose levels tested from 10 mg to 200 mg with a well defined pharmacokinetic (PK) and pharmacodynamic (PD) profile.

METHODS

- Four global phase 1/1b disease-specific platform studies are assessing the safety, tolerability, PK, PD, and preliminary clinical activity of AB928 in combination with chemotherapy and/or anti-PD-1 antibody (AB122 or pembrolizumab (pembro)).
- Eligible participants in the phase 1 escalations have advanced solid tumors, an ECOG performance status of 0 or 1, and may have received up to 5 lines of prior therapy.
- AB928 is administered orally QD in increasing doses starting at 75 mg with the intent to define the Recommended Dose for Expansion (RDE) for each combination (pegylated liposomal doxorubicin (PLD) +/- IPI-549 (an oral, selective PI3Kγ inhibitor), mFOLFOX, carboplatin (carbo)/pemetrexed (pem) with pembro, or AB122).
- Safety assessments include the incidence of adverse events (AEs) and dose-limiting toxicities (DLTs), as well as changes from baseline in vital signs, clinical laboratory parameters, physical examination findings, ECOG performance, and ECG results. Safety analyses are based upon all participants who receive at least 1 dose of AB928.
- Tumor and peripheral blood samples are collected to describe the PK profile, assess the PD effects, and characterize the biomarker status of AB928 in combination.
- Biomarker evaluations include gene sequencing and expression, protein quantification, and T cell profiling before and after treatment with AB928 combinations.
- Clinical activity is determined per RECIST v1.1 or appropriate response criteria (e.g. PCWG3 for prostate cancer) in tumor-specific dose-expansion cohorts.

AB928 PROGRAM OVERVIEW

Table 1. List of AB928 Combination Studies in Oncology Subjects

Study Number	NCT Number	Combination	Tumor Type in Escalation
AB928-002	NCT03719326	AB928 + PLD +/- IPI-549	TNBC or OC
AB928-003	NCT03720678	AB928 + mFOLFOX	GEC or CRC
AB928-004	NCT03846310	AB928 + Carbo + Pem + Pembro	NSCLC
AB928-005	NCT03629756	AB928 + AB122	Solid Tumors

CRC=Colorectal Cancer; GEC=Gastro-Esophageal Cancer; TNBC=Triple Negative Breast Cancer; NSCLC=Non-Small Cell Lung Cancer; OC=Ovarian Cancer.

Each study is made up of a phase 1 dose-escalation and phase 1b dose-expansion phase.

- **Dose Escalation (n=6-18)**: Escalating doses of AB928 (cohort 1=75 mg; cohort 2=150 mg; cohort 3=200 mg) administered orally QD in combination with chemotherapy and/or anti-PD-1 backbone (**Table 1**) were assessed based on a 3+3 design.
- **Dose Expansion (n=15-40)**: AB928 at RDE in combination is being evaluated in tumor-specific dose-expansion cohorts which include signal-gated options to initiate phase 2 portions of the studies with randomization vs control arms.

RESULTS

DEMOGRAPHICS AND PATIENT CHARACTERIZATION

As of data cut-off (DCO) of 06 Sep 2019, a total of 40 pts have been treated with AB928 combination therapy in studies: AB928-002 (AB928+PLD), n=9; AB928-003 (AB928+mFOLFOX), n=11; AB928-004 (AB928+carbo/pem/pembro), n=6; and AB928-005 (AB928+AB122), n=14.

Most pts were white and non-Hispanic, median age varied, and 70% were female (**Table 2**). In dose escalation, a total of 18/40 (45%) pts have discontinued AB928 treatment, most due to disease progression.

Table 2. Dose Escalation Patient Demographics and Characterization

Characteristics		AB928-002 (Gyn/Breast)		AB928-003 (GI)		AB928-004 (NSCLC)		AB928-005 * (Solid Tumors)		
		75 mg (n=3)	150 mg (n=6)	75 mg (n=4)	150 mg (n=7)	75 mg (n=3)	150mg (n=3)	75 mg (n=3)	150 mg (n=6)	200 mg (n=5)
Median (range) age, years		66 (40-68)	67 (48-80)	52 (37-59)	48 (39-64)	62 (50-80)	65 (48-66)	73 (56-79)	64 (50-66)	71 (57-79)
Biological sex, n (%)	F	3 (100%)	6 (100%)	2 (50%)	2 (29%)	1 (33%)	3 (100%)	2 (67%)	5 (83%)	4 (80%)
	M	0 (0%)	0 (0%)	2 (50%)	5 (71%)	2 (67%)	0 (0%)	1 (33%)	1 (17%)	1 (20%)
Tumor Types		OC n=3	OC n=4, TNBC n=2	CRC n=4	CRC n=7	NSCLC n=3	NSCLC n=3	OC, EC, Blad	CRC n=3, EC n=2, NET	AP,OC, PDAC, GEC n=2
Lines of Therapy (median)		3		3		4		3		
Time on Treatment for mITT (range, weeks)		5.9-29.7	4.1-24.4	2.0-30.6	1.0-24.6	12.6-21.6	1.6-8.6	5.3-59.0	6.3-39.0	1.1-27.0

AP=Appendiceal Cancer; EC=Endometrial Cancer; GI=Gastrointestinal; Gyn=Gynecologic; mITT=modified intent-to-treat population; NET=Neuroendocrine Tumor; PDAC=Pancreatic Ductal Adenocarcinoma; * eligibility necessitates pts to be immunotherapy naïve.

As of DCO, a majority of pts (22/40; 55%) were still on study, 8 pts (20%) for 6 months or longer. 50% (13/26) of eligible* pts had received prior immunotherapy (α-PD(L)-1 and/or α-CTLA4).

AB928 IN COMBINATION EXHIBITS A FAVORABLE SAFETY PROFILE

AEs are collected from the start of therapy until up to 90 days after the last dose of AB928 in combination or until initiation of a new systemic anticancer therapy. All AEs are graded according to NCI CTCAE v 5.0.

Table 3. Summary of Treatment-Emergent Adverse Events (TEAEs) in AB928 Dose Escalation

Number of Subjects with	AB928-002		AB928-003		AB928-004		AB928-005		
	75 mg (n=3)	150 mg (n=6)	75 mg (n=4)	150 mg (n=7)	75 mg (n=3)	150 mg (n=3)	75 mg (n=3)	150 mg (n=6)	200 mg (n=5)
TEAEs, n (%)	3 (100%)	6 (100%)	4 (100%)	7 (100%)	3 (100%)	2 (67%)	3 (100%)	5 (83%)	4 (80%)
AB928-related TEAEs, n (%)	2 (67%)	4 (67%)	3 (75%)	6 (86%)	2 (67%)	0	3 (100%)	4 (67%)	1 (20%)
Grade 1-2, n (%)	3 (100%)	6 (100%)	4 (100%)	7 (100%)	3 (100%)	2 (67%)	3 (100%)	5 (83%)	4 (80%)
AB928-related Grade 1-2, n (%)	2 (67%)	4 (67%)	3 (75%)	6 (86%)	2 (67%)	0	3 (100%)	4 (67%)	1 (20%)
Grade 3-4, n (%)	2 (67%)	3 (50%)	4 (100%)	5 (71%)	1 (33%)	1 (33%)	1 (33%)	1 (17%)	1 (20%)
AB928-related Grade 3-4, n (%)	0	2 (33%)	1 (25%)	0	0	0	0	0	0
SAE, n (%)	1 (33%)	1 (17%)	2 (50%)	2 (29%)	0	0	2 (67%)	1 (17%)	1 (20%)
AB928-related SAE, n (%)	0	0	0	0	0	0	0	0	0
DLT*, n	0	0	0	0	0	0	0	1	0

* The DLT period is 21 days for AB928-004 study, and 28 days for all other AB928 combination studies.

The only DLT observed was due to Grade 2 rash in cohort 2 (AB928 + AB122) and the pt restarted therapy post resolution. A maximum tolerated dose of AB928 has not been reached in any of the combinations.

Table 4. AB928-related ≥ Grade 3 Adverse Event Profile by Treatment Group

Number of Subjects with AE Preferred Term	AB928-002		AB928-003		AB928-004		AB928-005		
	75 mg (n=3)	150 mg (n=6)	75 mg (n=4)	150 mg (n=7)	75 mg (n=3)	150 mg (n=3)	75 mg (n=3)	150 mg (n=6)	200 mg (n=5)
Anemia	0	1	1	0	0	0	0	0	0
Fatigue	0	1	1	0	0	0	0	0	0
Leukopenia	0	1	0	0	0	0	0	0	0
Nausea	0	0	1	0	0	0	0	0	0
Neutropenia	0	1	0	0	0	0	0	0	0

AB928-related AE profile (Grade 3 or above) is shown in **Table 4**. No Grade 4 or 5 AB928-related AEs were reported across the AB928 program.

AB928 150 MG QD SELECTED FOR RDE ACROSS BACKBONES

AB928 150 mg QD has been selected as the RDE based on PK, PK/PD correlation, and a well tolerated safety profile of AB928 in combination with chemotherapy (PLD or mFOLFOX) or PD-1 inhibition (AB122).

PROGRAM UPDATES

AB928-002 (TNBC and OC):

- AB928 + PLD + IPI-549 phase 1 dose escalation is currently enrolling. Three (n=3) pts have been treated in cohort 1 at AB928 150 mg + SOC PLD + IPI-549 30 mg QD.

AB928-003 (CRC):

- The majority of pts are still on treatment, including several pts with prolonged stable disease (SD) ≥ 6 months. All pts had previous treatment(s) with FOLFOX and/or FOLFIRI.

AB928-004 (NSCLC):

- Enrolled 6 pts through 2 cohorts (AB928 75 mg QD and 150 mg QD) with all pts still on treatment. The first 3 pts (n=3/3) in the 75 mg cohort had partial response (PR), including 2 confirmed PR.

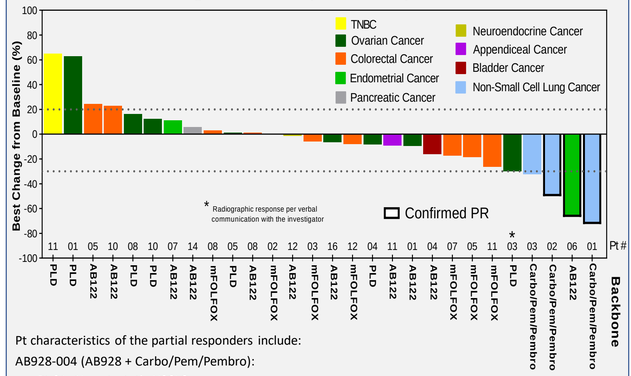
AB928-005 (Solid Tumors):

- Previously characterized ovarian cancer pt with disease stabilization remains on treatment with SD at 13.8 months and the endometrial carcinosarcoma pt with confirmed PR also continues on therapy at 9.1 months.

CLINICAL ACTIVITY DEMONSTRATED IN DOSE ESCALATION ACROSS FOUR AB928 COMBINATION STUDIES

Aggregate phase 1 dose-escalation data. A total of 28 pts (RECIST evaluable) had ≥ 1 disease assessments.

Figure 2. Best Percent Change from Baseline (Waterfall Plot)



Pt characteristics of the partial responders include:

AB928-004 (AB928 + Carbo/Pem/Pembro):

- Pt 01: 1L metastatic NSCLC
- Pt 02: 4L metastatic NSCLC, EGFRmut, post erlotinib, osimertinib, osimertinib+CDK4/6i, PD-L1 low
- Pt 03: 2L metastatic NSCLC, post progression on ipilimumab/nivolumab

AB928-005 (AB928 + AB122):

- Pt 06: 2L metastatic endometrial carcinosarcoma, post carbo/paclitaxel/anastrozole, MSS

AB928-002 (AB928 + PLD):

- Pt 03: 1L metastatic ovarian carcinoma, previous SD for 24 weeks, deepened response to AB928+PLD

Early activity of AB928 in combination has been recorded across all studies. The AB928 phase 1 program disease control rate is 43% (12/28; % BOR=CR, PR, SD > 6 mth) in this heavily pretreated population.

CONCLUSIONS

- All AB928-related AEs were Grade ≤ 3 and only 1 of 40 pts experienced a transient DLT. Escalation of AB928 in combination with chemotherapy and/or PD-1 inhibition exhibits a favorable safety profile.
- AB928 in combination with chemotherapy and/or anti-PD-1 therapy demonstrates tumor responses and disease stabilization in advanced tumor types supportive of continued disease-specific evaluation.
- The disease control rate across the AB928 phase 1 program is 43% in heavily pretreated pts.
- In oncology pts, AB928 pharmacokinetics across combination backbones are comparable and PK/PD correlations consistent with those of healthy volunteers.
- Extensive biomarker characterization of tissue and blood across the AB928 studies is ongoing.
- Development of AB928 combinations continues in phase 1b expansion cohorts in CRPC, RCC, TNBC, CRC, and NSCLC with opportunity for seamless transition to phase 2 randomized studies with control arms. Gyn tumors will be explored in Investigator-Sponsored Trials.

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