Phase 1 Safety Study in Healthy Volunteers of AB680, a Small-Molecule Inhibitor of CD73 and Rationale for Combination Therapy in Patients with Gastrointestinal Malignancies

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Introduction

The tumor microenvironment (TME) contains high levels of immunosuppressive adenosine (ADO), which binds to and activates the A_{2a} receptor ($A_{2a}R$) 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 monophosphate (AMP) to ADO. In prostate cancer, PAP can also contribute to adenosine generation.

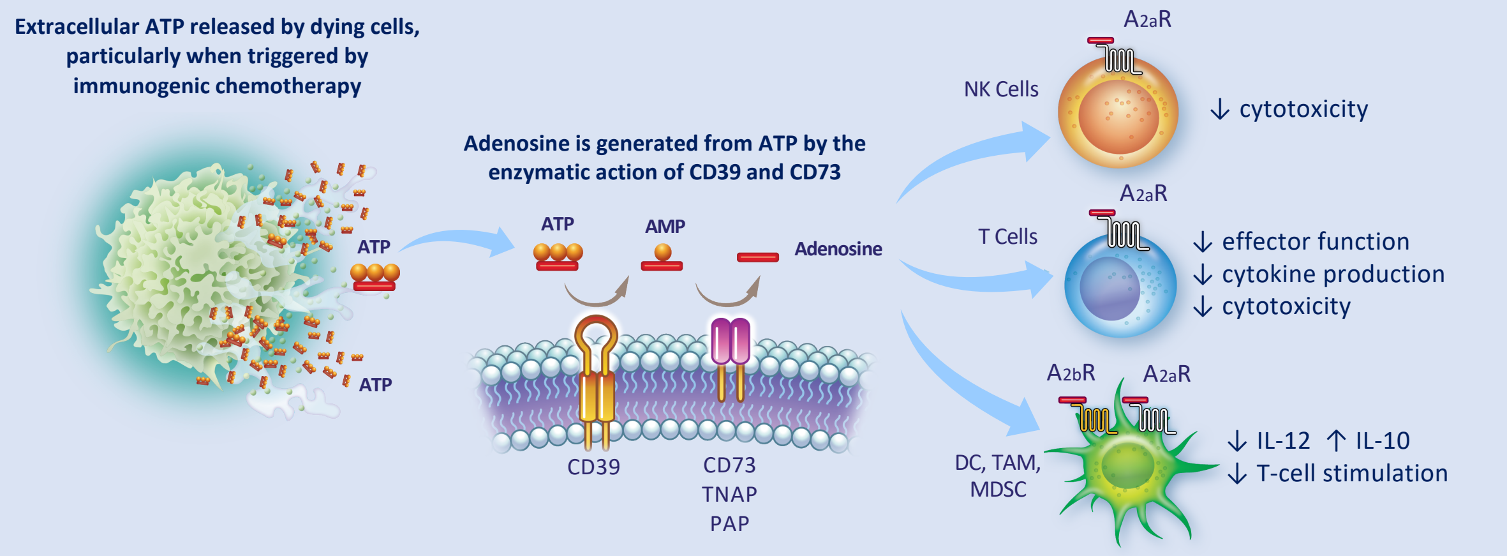


Figure 1. Adenosine Pathway

Inhibition of CD73 eliminates a major pathway of adenosine production in the TME and can reverse adenosine-mediated immune suppression. AB680 is a potent (K_i of 5 pM), reversible and selective small molecule inhibitor of CD73. Here we present the first results from a Phase 1 placebo-controlled healthy volunteer (HV) study which assessed the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profile of AB680. This first-in-human study demonstrates that AB680 is well tolerated and has optimal PK/PD to support its continued evaluation in cancer patients.

Methods

Phase 1 Healthy Volunteer Study: This phase 1 healthy volunteer study consisted of single ascending dose (SAD) and repeat-dosing arms evaluating AB680 administered via a 30 to 60-minute intravenous (IV) infusion. In the single-dosing arm, we evaluated single doses of 0.1, 0.6, 2, 4, 8, 16 and 25 mg of AB680. In the repeat-dosing arm, 3 doses of 8 mg AB680 were administered weekly (QW). The study enrolled 64 participants (randomized 3:1, active:placebo).

Clinical Study Design

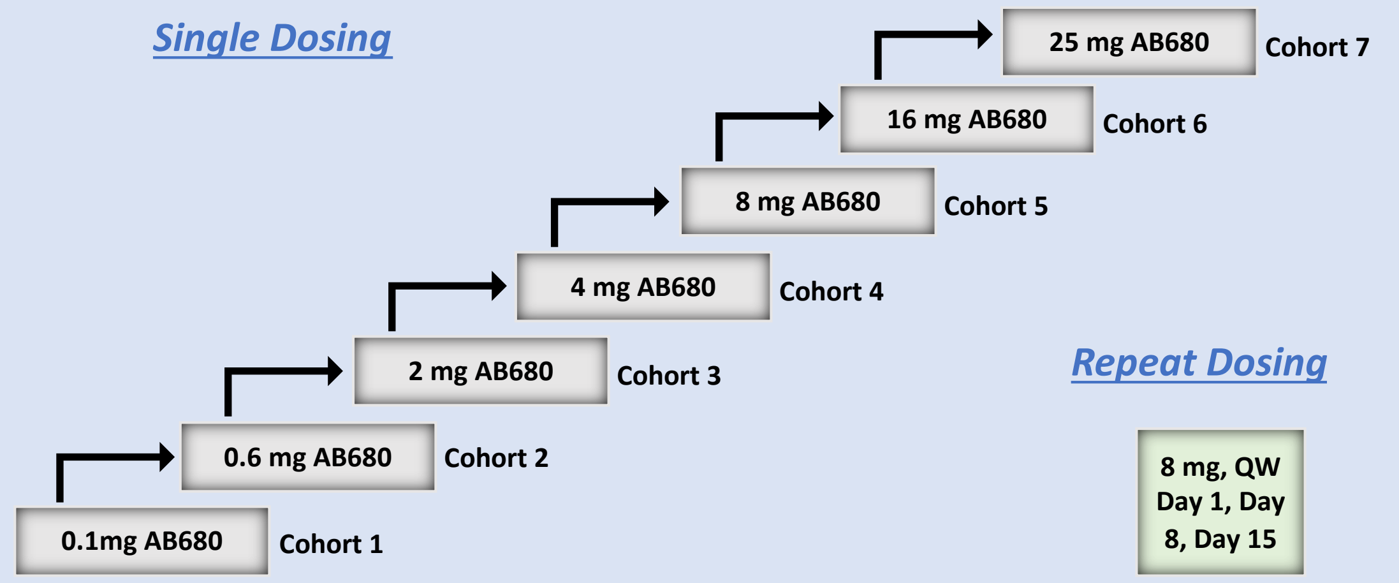


Figure 2. Clinical study design for AB680CSP0001 (NCT03677973) in healthy volunteers

Schedule of PD Assessments

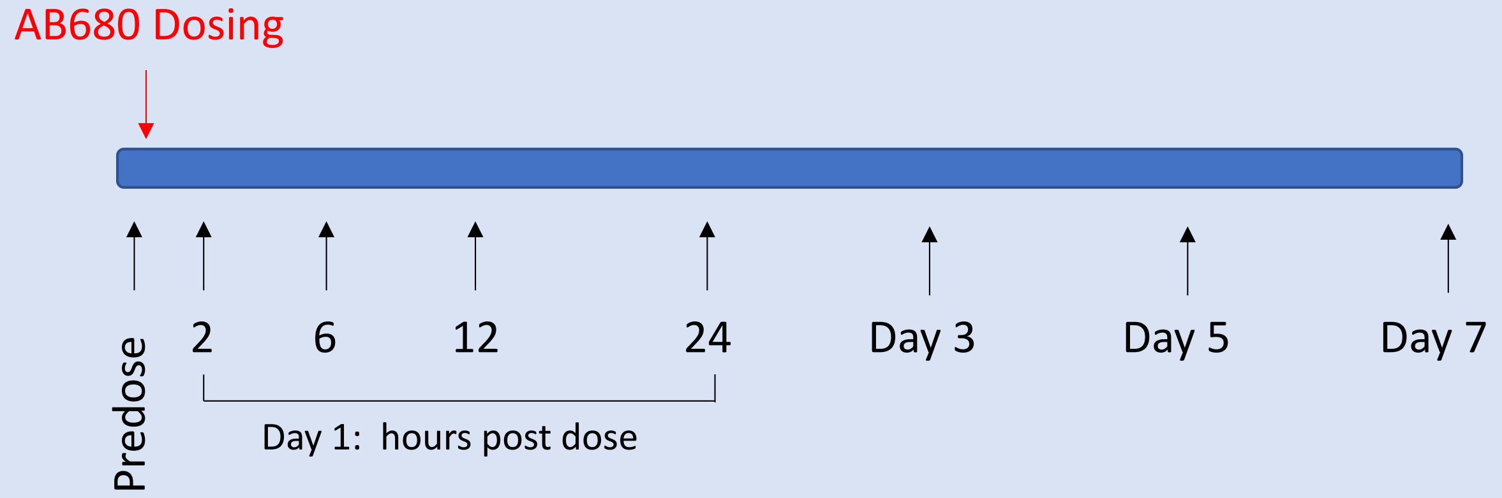


Figure 3. PD assessments taken during the SAD portion of the study. Serum and plasma samples were collected from placebo and dosed subjects following the single intravenous infusion.

Bioanalytical Analysis: Plasma samples were prepared by a protein precipitation procedure. The analyte, AB680, and internal standard, AB680-d5, were extracted from plasma with acetonitrile. Concentrations of AB680 were determined by LC-MS/MS.

CD73 activity: For the $^{13}C_5$ AMP assay, sodium heparin plasma collected across time points was incubated with and without a TNAP inhibitor cocktail. $^{13}C_5$ AMP was added to a concentration of 10 μM and incubated for 30 seconds. The formation of $^{13}C_5$ ADO was measured using LCMS. A commercially available kit (AMP Glo^{TM}) was also used to measure AMP hydrolysis in human serum.

Gene expression analysis: CD73 gene expression is calculated as log2 counts-per-million (CPM) using TMM normalization of The Pan-Cancer Genome Atlas (TCGA) across multiple tumor types. We used linear models adjusted for individual tumor types to assess if the expression of CD73 can be predicted by alterations in 299 consensus cancer driver genes (Bailey et.al Cell (2018)) in pan-cancer TCGA dataset. For regression models, multiple testing correction was performed using Benjamini-Hochberg method. Alteration frequency (including all types of genetic alterations) in KRAS, BRAF and EGFR for pancreatic, lung and colorectal cancers (primary tumors) were obtained from cBioPortal.

Immunofluorescence: Multiplex immunofluorescence staining was performed on serial sections of tumor tissue to correlate protein and gene expression.

Results

AB680 Pharmacokinetic Profile Supports Q2W Dosing Regimen

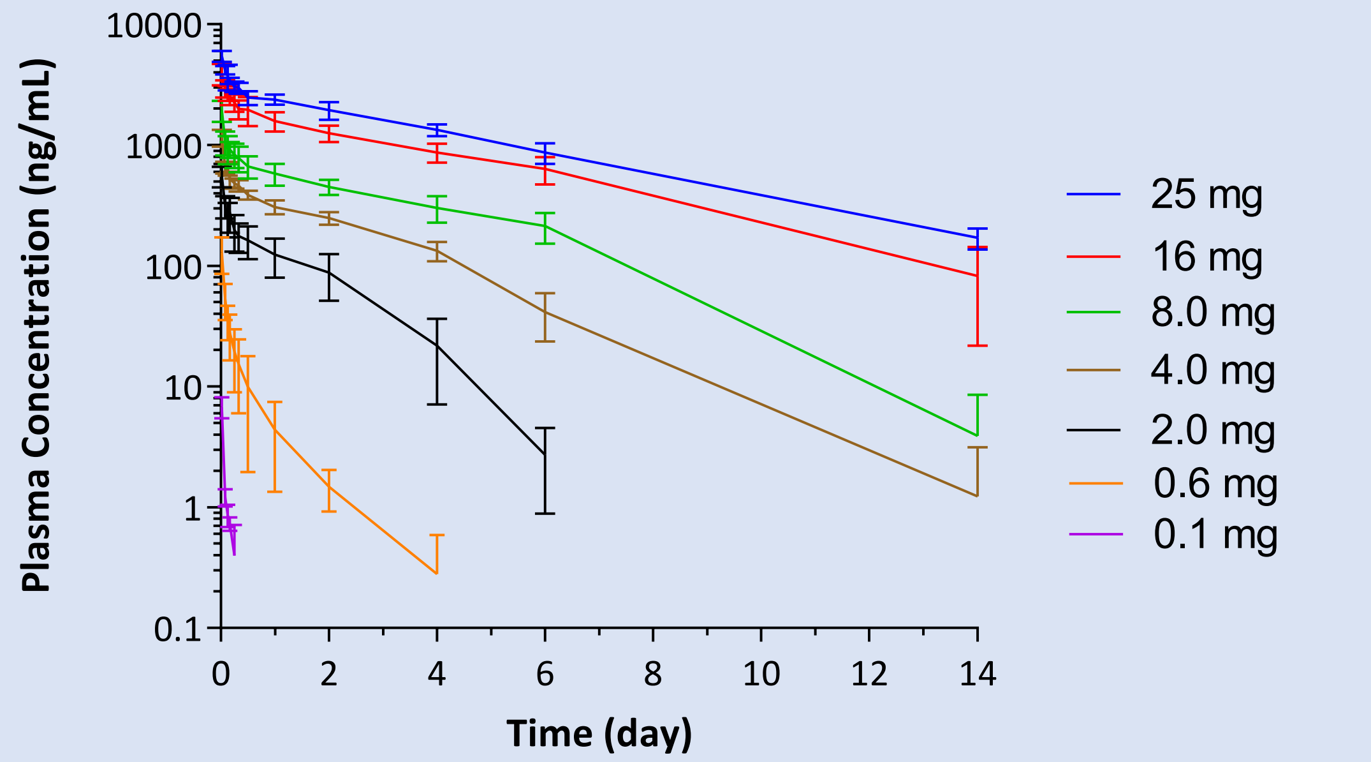


Figure 4: AB680 PK profile following a single dose administered via intravenous (IV) infusion.

AB680 Maintains Complete Inhibition of CD73 Activity Following a Single Dose

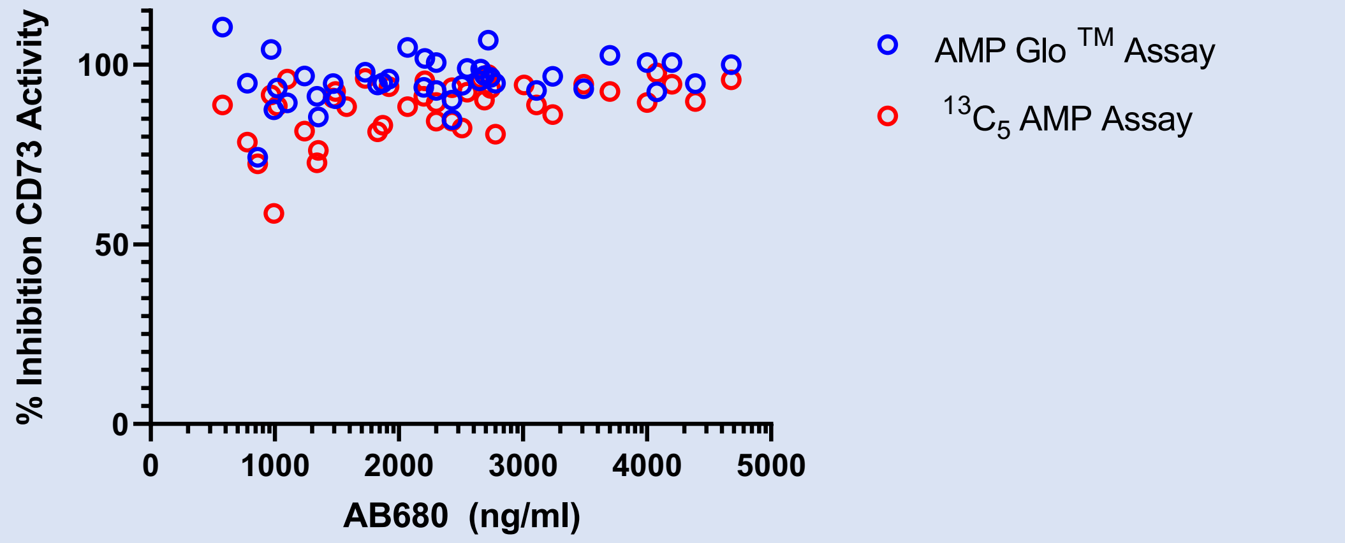


Figure 5. PK/PD correlations obtained out to 7 days following a single 25 mg dose of AB680. Two different CD73 activity assays were used and generated similar inhibition of peripheral CD73 activity. PD samples were collected at various timepoints post-dosing as shown in Figure 3.

AB680 Was Well Tolerated at Single and Multiple Intravenous Doses

The current trial was enrolled from 12th of November, 2018 to the 22nd of July 2019. The final data were available on the 14th of Oct 2019. Across the single-ascending and repeat-dosing cohorts, the subjects ranged in age from 18-52 years. There was a slightly higher percentage of males enrolled across the entire study (52%).

SINGLE-ASCENDING DOSE SAFETY RESULTS

Subjects with	Placebo (N=14) n (%)	AB680 Treatment (mg), n (%)							
		0.1 (N=6)	0.6 N=6)	2 (N=6)	4 (N=6)	8 (N=6)	16 (N=6)	25 (N=6)	Total (N=56)
Any AE	10 (71)	4 (67)	2 (33)	4 (67)	4 (67)	4 (67)	1 (17)	4 (67)	33 (59)
Related AE	5 (36)	1 (17)	2 (33)	2 (33)	1 (17)	3 (50)	1 (17)	2 (33)	17 (30)
Grade 1 only AE[a]	8 (57)	4 (67)	2 (33)	2 (33)	3 (50)	3 (50)	1 (17)	3 (50)	26 (46)
Grade 2 AE[b]	2 (14)	0	0	2 (33)	1 (17)	1 (17)	0	1 (17)	7 (13)
Related Grade 1 only AE[b]	4 (29)	1 (17)	2 (33)	2 (33)	0	3 (50)	1 (17)	2 (33)	15 (27)
Related Grade 2 AE[b]	1 (7)	0	0	0	1 (17)	0	0	0	2 (4)

[a] All resolved except for cough in 1 subject in the 4 mg group.
[b] All resolved.

REPEAT-DOSING SAFETY RESULTS

Subjects with	Placebo (N=2) n (%)	AB680 Treatment (mg, QW), n (%)	
		8 (N=6)	Total (N=8)
Any AE	1 (50)	5 (83)	6 (75)
Related AE	0	2 (33)	2 (25)
Grade 1 only AE[a]	1 (50)	2 (33)	3 (38)
Grade 2 AE[b]	0	3 (50)	3 (38)
Related Grade 1 only AE[c]	0	1 (17)	1 (13)
Related Grade 2 AE[b]	0	1 (17)	1 (13)

[a] All resolved, except for acrochordon and increased alanine aminotransferase in 1 subject each. The increased alanine aminotransferase was recovering at the last contact.
[b] All resolved.
[c] All resolved, except for increased alanine aminotransferase in 1 subject. The increased alanine aminotransferase was recovering at the last contact.

There were no deaths or serious adverse events in the study. All other clinical safety assessments, including vital signs, physical examinations, ECGs and laboratory evaluations were unremarkable across all SAD and repeat-dosing groups. This includes heart rate, PR, QT and QTc intervals, and QRS duration.

CD73 Expression in Pancreatic Cancer is One of the Highest Across Tumor Types

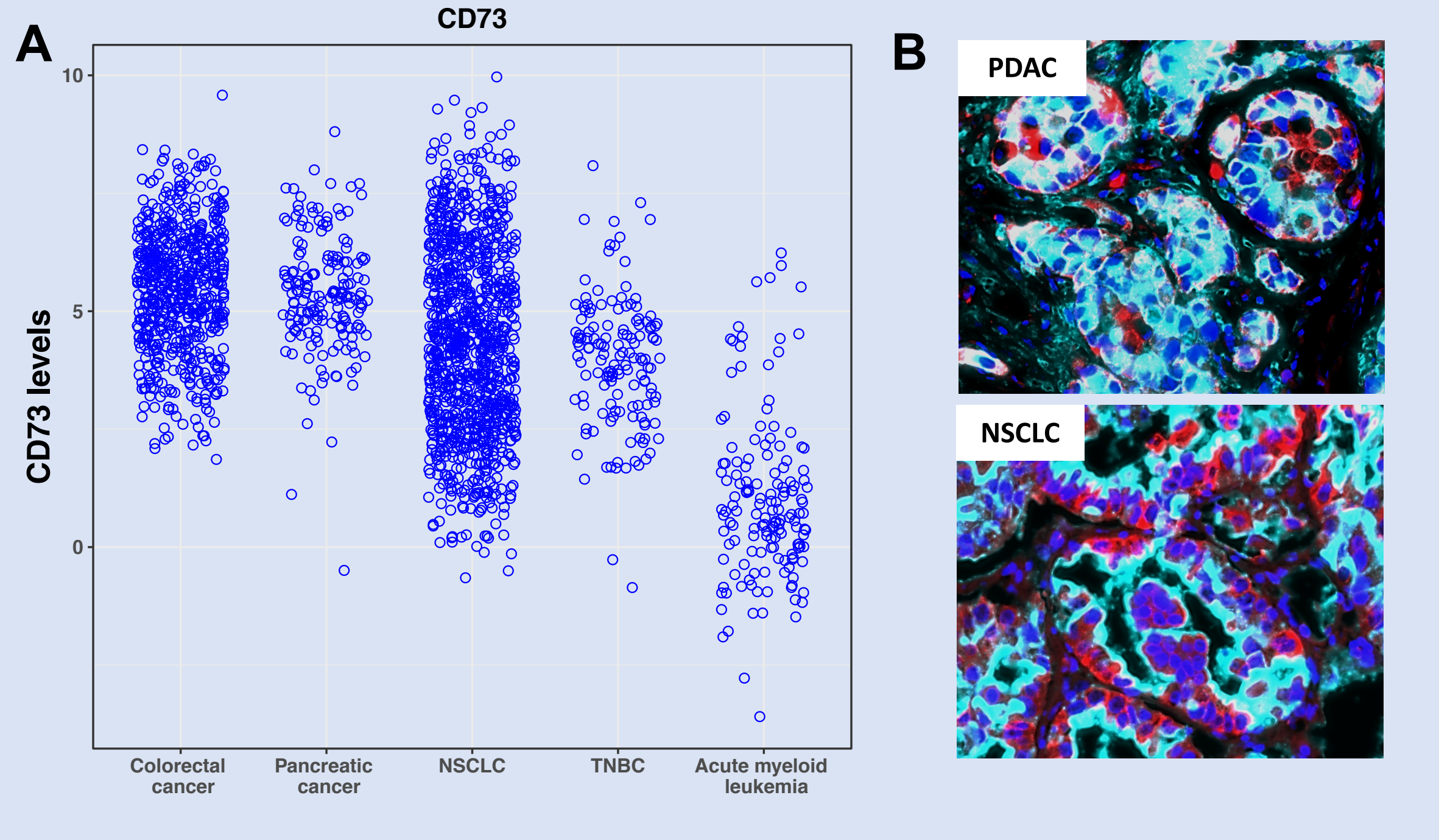
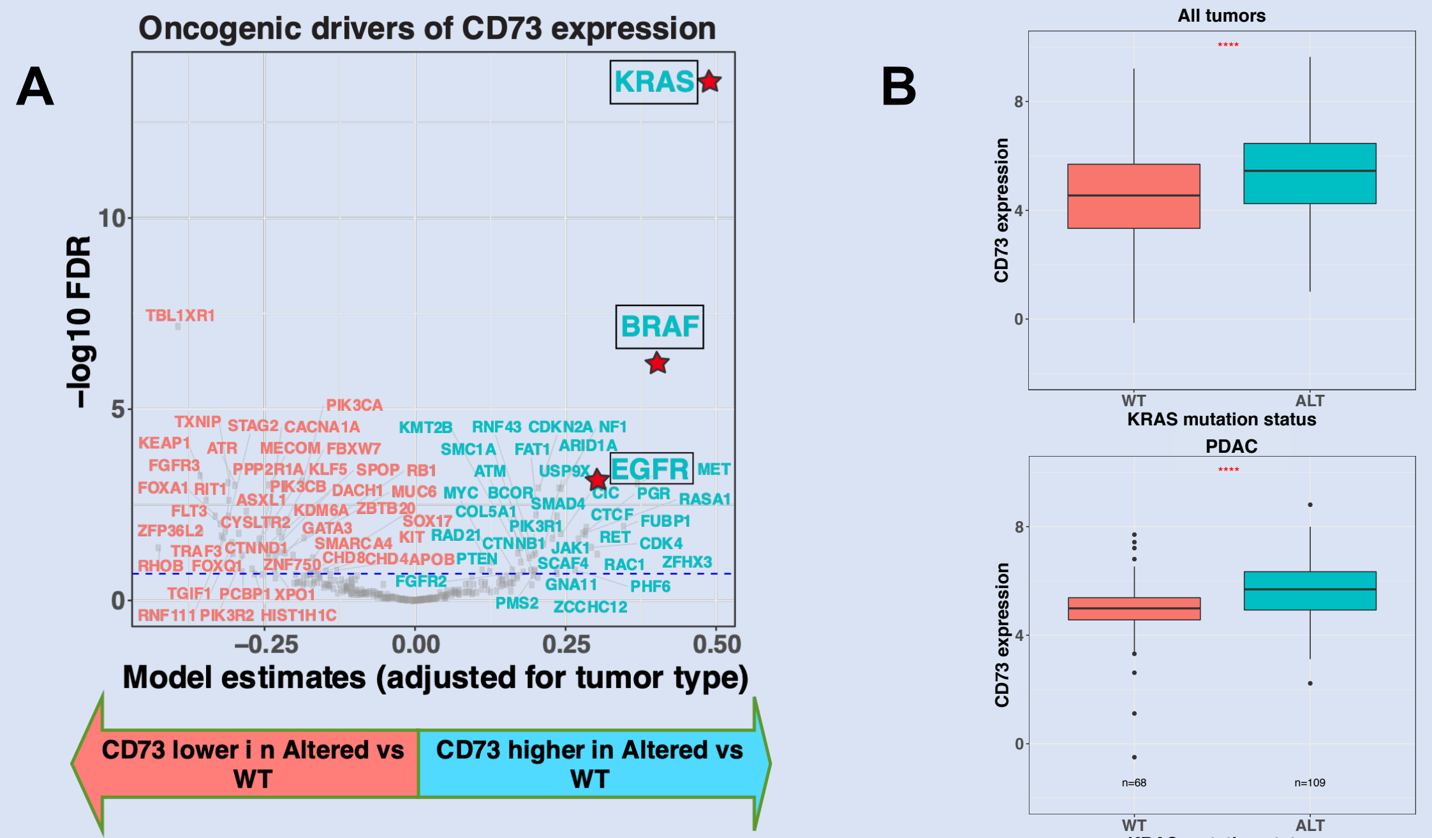


Figure 6. A.) CD73 expression was derived from pan-cancer TCGA dataset. Numbers on Y-axis indicate $\log_2$ counts-per-million (CPM) values for CD73. Tumors on left are high in CD73 such as colorectal, pancreatic and non-small cell lung cancers as compared to the low expression in acute myeloid leukemia. **B.)** Multiplex immunofluorescence staining (CD73/PanCK/DAPI) on cancer biopsy samples from different indications. CD73 staining (teal) on tumor cells (red, pan cytokeratin$^+$) can be seen in pancreatic (PDAC) and lung (NSCLC) tumors.

EGFR, KRAS and BRAF Mutations Correlate With Elevated CD73



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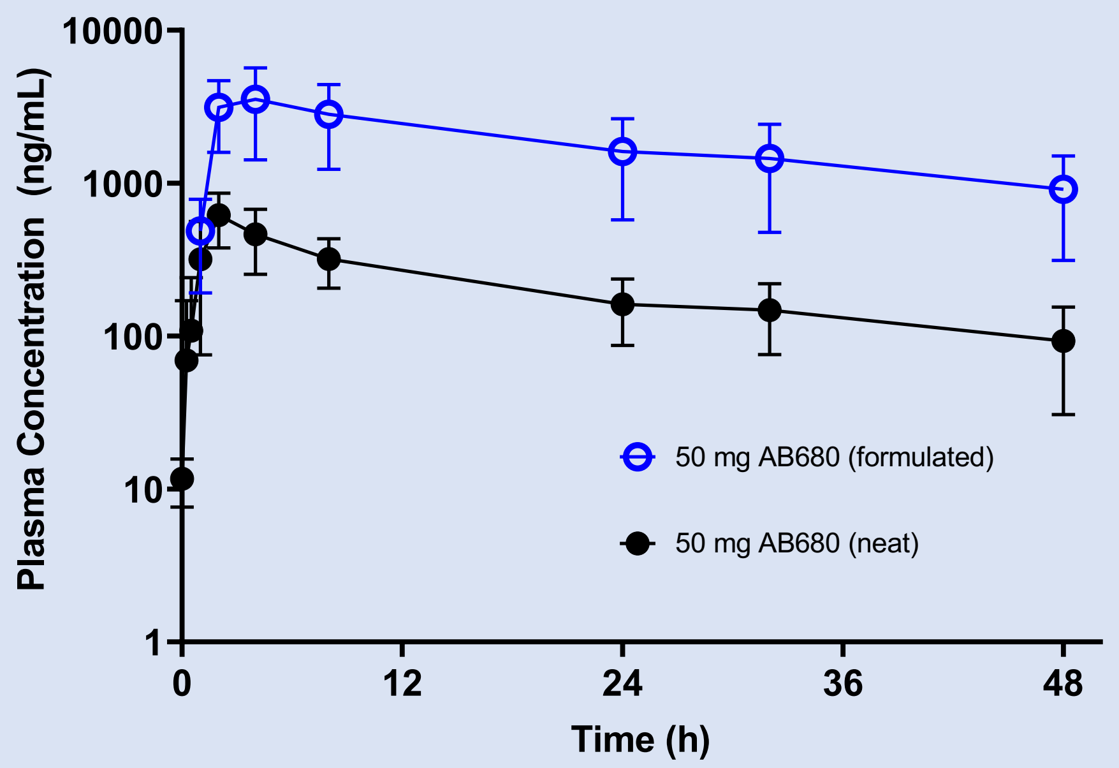
Tumor Type	KRAS	BRAF	EGFR
	Alteration Frequency		
PDAC	65%	2%	1%
CRC	35-40%	15%	5%
NSCLC	30%	9%	15%

Figure 7. (A) Linear model estimates adjusted for tumor type of alterations in cancer driver genes that predict CD73 expression. **(B)** High KRAS expression is very tightly correlated with high CD73 expression in all TCGA primary tumors as well as in pancreatic cancer (PDAC). **(C)** Table showing frequencies of mutations seen in the respective cancer types (primary tumors) for KRAS, BRAF and EGFR in TCGA. In metastatic tumors (Priestley et.al Nature 2019), reported mutation frequencies are as follows: KRAS (CRC 47%, NSCLC 17%, PDAC 86%), BRAF (CRC 13%, NSCLC 6%, PDAC 0%) and EGFR (not reported).

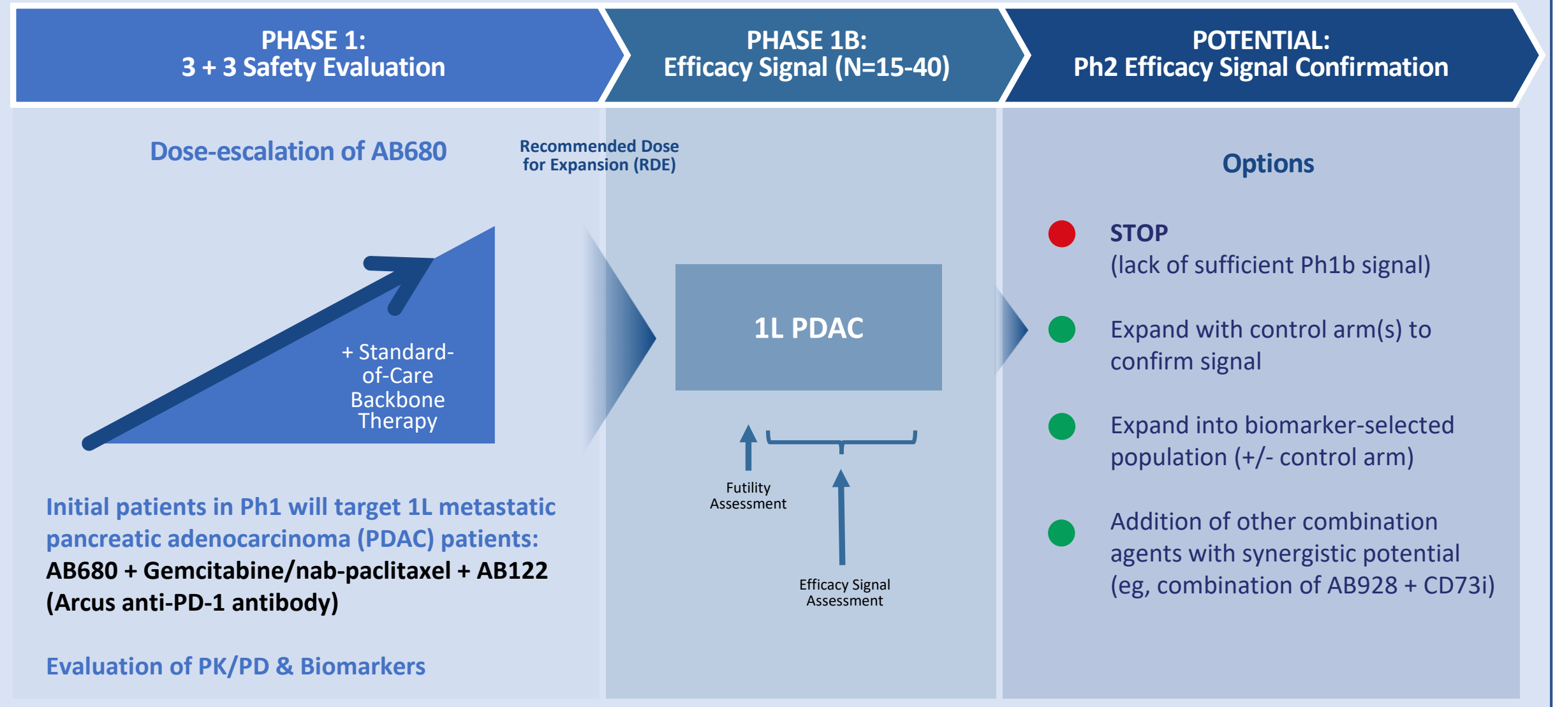
Formulation of AB680 Can Dramatically Increase Oral Exposure in Preclinical Species



Formulation	Dose (mg)	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	$AUC_{0-\infty}$ (h*ng/mL)	$MRT_{0-\infty}$ (h)	Exposure Enhancement
AB680 (formulated)	50	3	3,680	88,000	122,000	35.8	**9.1-fold**
AB680 (neat)	50	1.75	631	10,300	13,400	29.2	--

Figure 8. A proprietary formulation has been identified that increases oral exposure. Both neat and formulated AB680 were delivered in a capsule via oral gavage in cynomolgus monkeys (50 mg/animal).

AB680: Initial Study Targeting First-Line Pancreatic Cancer


PHASE 1:
3 + 3 Safety Evaluation

PHASE 1B:
Efficacy Signal (N=15-40)

POTENTIAL:
Ph2 Efficacy Signal Confirmation

Dose-escalation of AB680

Recommended Dose for Expansion (RDE)

+ Standard-of-Care Backbone Therapy

Initial patients in Ph1 will target 1L metastatic pancreatic adenocarcinoma (PDAC) patients:
AB680 + Gemcitabine/nab-paclitaxel + AB122 (Arcus anti-PD-1 antibody)

Evaluation of PK/PD & Biomarkers

1L PDAC

Futility Assessment

Efficacy Signal Assessment

Options

- 🔴 **STOP** (lack of sufficient Ph1b signal)
- 🟢 Expand with control arm(s) to confirm signal
- 🟢 Expand into biomarker-selected population (+/- control arm)
- 🟢 Addition of other combination agents with synergistic potential (eg, combination of AB928 + CD73i)

Figure 9. AB680CSP0002 study in pancreatic cancer (NCT04104672)

Conclusions

- AB680 has an excellent safety, PK, PK/PD profile in healthy volunteers to support its advancement into cancer patients with a Q2W dosing regimen.
- Pancreatic cancer tumors express high levels of CD73. EGFR, KRAS and BRAF mutations correlate with elevated CD73.
- Initiating Phase 1 safety dose-escalation study in combination with AB122 (Arcus anti-PD-1), gemcitabine and nab-paclitaxel in 1L metastatic pancreatic cancer.
- An oral formulation of AB680 is in IND-enabling studies.

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