

Creating Innovative Cancer Immunotherapies by Leveraging Underexploited Biological Opportunities

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February 2019 NYSE: RCUS

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Corporate Overview

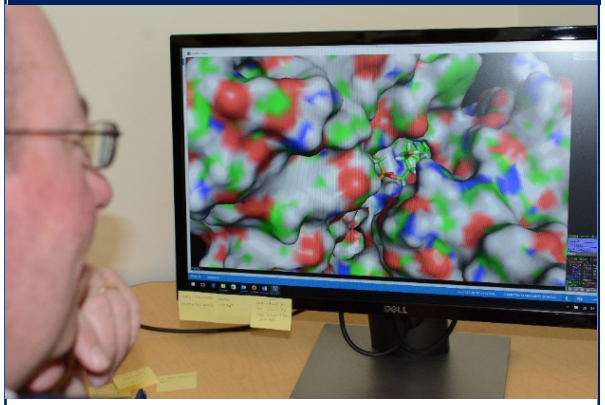
Creating Innovative Cancer Immunotherapies

- Four clinical candidates – multiple data readouts in 2019
- Small molecule discovery engine to enable pipeline expansion
- Successful management team with 10+ years working together in small molecule drug discovery
- Well capitalized with $265.6mm of cash and investments at 9/30/2018



Our Competitive Advantages

Best-in-Class Chemistry



Rationally designed, potentially best-in-class small molecules for oncology

Portfolio Breadth

AB928 ($A_{2a}R/A_{2b}R$ Antagonist)

- AB928 + Chemo — Advanced solid tumors
- AB928 + AB122 — Advanced solid tumors

AB680 (Small Molecule CD73i)

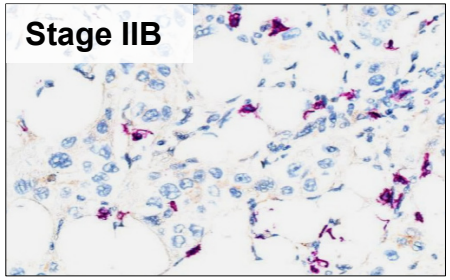
- AB680 (IV) — Phase 1 in HVs
- AB680 (oral) — IND-enabling

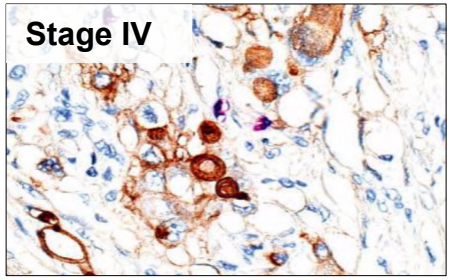
Antibodies

- AB122 (PD-1) — Advanced solid tumors
- AB154 (TIGIT) — Advanced solid tumors

Enables development of multiple intra-portfolio combinations

Translational Medicine





Extensive biomarker analysis planned to enrich clinical trials/inform clinical decisions

Arcus Has Rapidly Created a Broad Portfolio of Immuno-Oncology Programs

	Discovery	Preclinical	Mono dose esc.	Combo dose esc.
AB928 ($A_{2a}R/A_{2b}R$ Antagonist)				
AB928 + Chemotherapy	TNBC, Ovarian, CRC, GE, NSCLC			
AB928 + AB122 (anti-PD-1)	Advanced solid tumors			
AB680 (Small Molecule CD73i)				
AB680 (i.v.)	Phase 1 in HVs ongoing			
AB680 (oral)	IND-enabling			
Antibody Programs				
AB122 (anti-PD-1 Antibody)	Advanced solid tumors			
AB154 (anti-TIGIT Antibody)	Advanced solid tumors			
Other Small Molecules				
AB745 ($A_{2a}R$ Antagonist)	IND-enabling			
Other programs	Lead optimization			

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Multiple Clinical Trials with Readouts in 2019

	AB928 (A_2R) + Chemotherapy			AB928 + AB122	AB680 (CD73)	AB154 (TIGIT)	AB122 (PD-1)
Tumor Types	**Ovarian TNBC**	**GE Colorectal**	**NSCLC**	**Advanced solid tumors**	**N/A**	**Advanced solid tumors**	**NSCLC**
Phase	1/1b	1/1b	1/1b	1/1b	HV trial	1/1b	1/1b
Treatment	AB928 + Doxil®	AB928 + mFOLFOX	AB928 + Carbo/ pem	AB928 + AB122	AB680	AB154 +/- AB122	AB122
Key Inclusion Criteria(s)	Up to 5 prior lines	Up to 5 prior lines	TKI failures	Up to 5 prior lines	N/A	Up to 5 prior lines	1L, PD-L1+
Status	Dose escalation enrolling	Dose escalation enrolling	Initiating	Dose escalation enrolling	Dose escalation enrolling	Monotherapy escalation enrolling	To initiate 1H:19
Next Data Release	**June 2019 (Dose-escalation data)**				**1H:19 (HV data)**	**2H:19 (Dose-escalation data)**	**TBD**

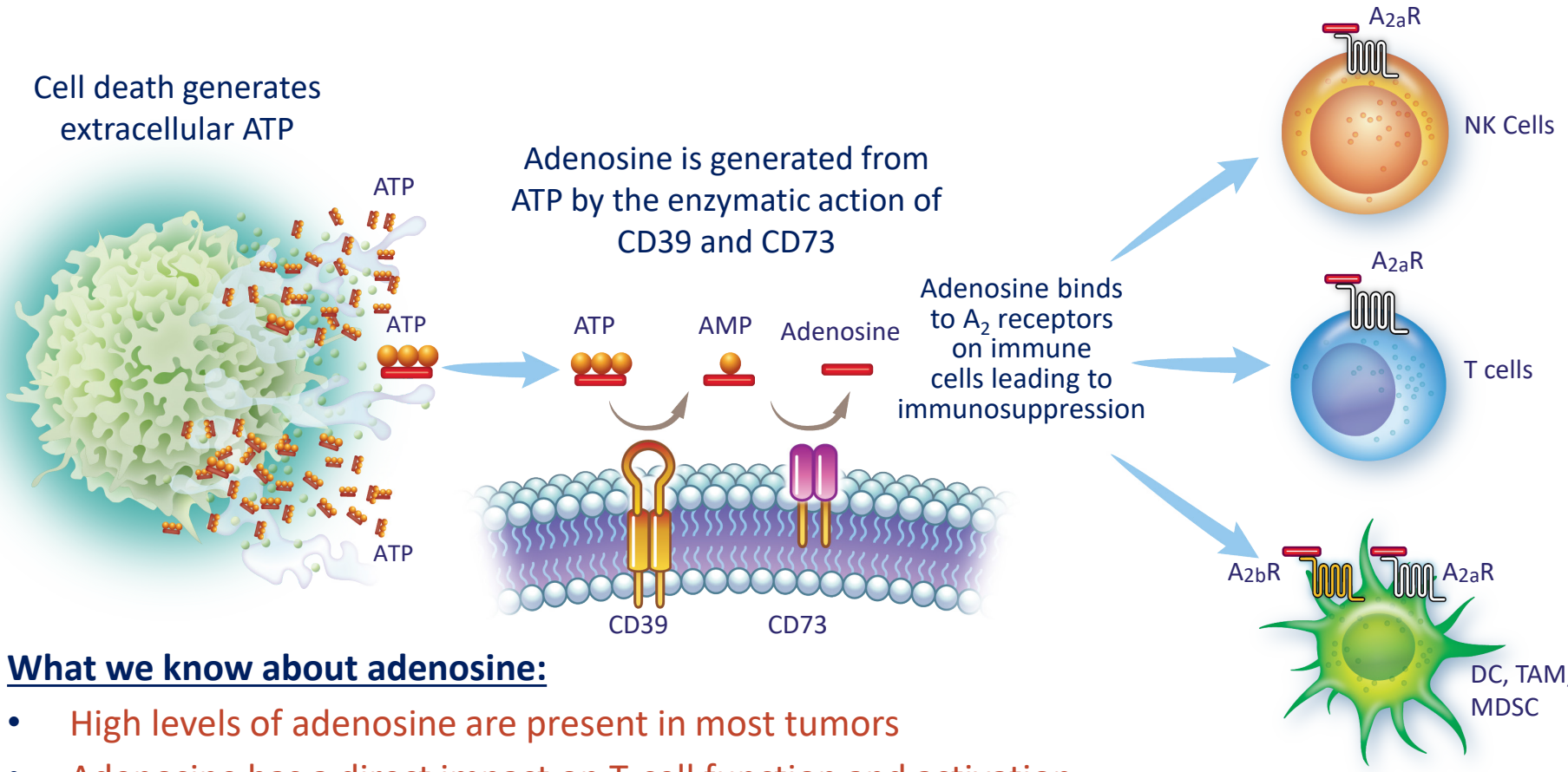
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Our Portfolio

The ATP-Adenosine Pathway Plays a Well Established, Critical Role in Immune Suppression

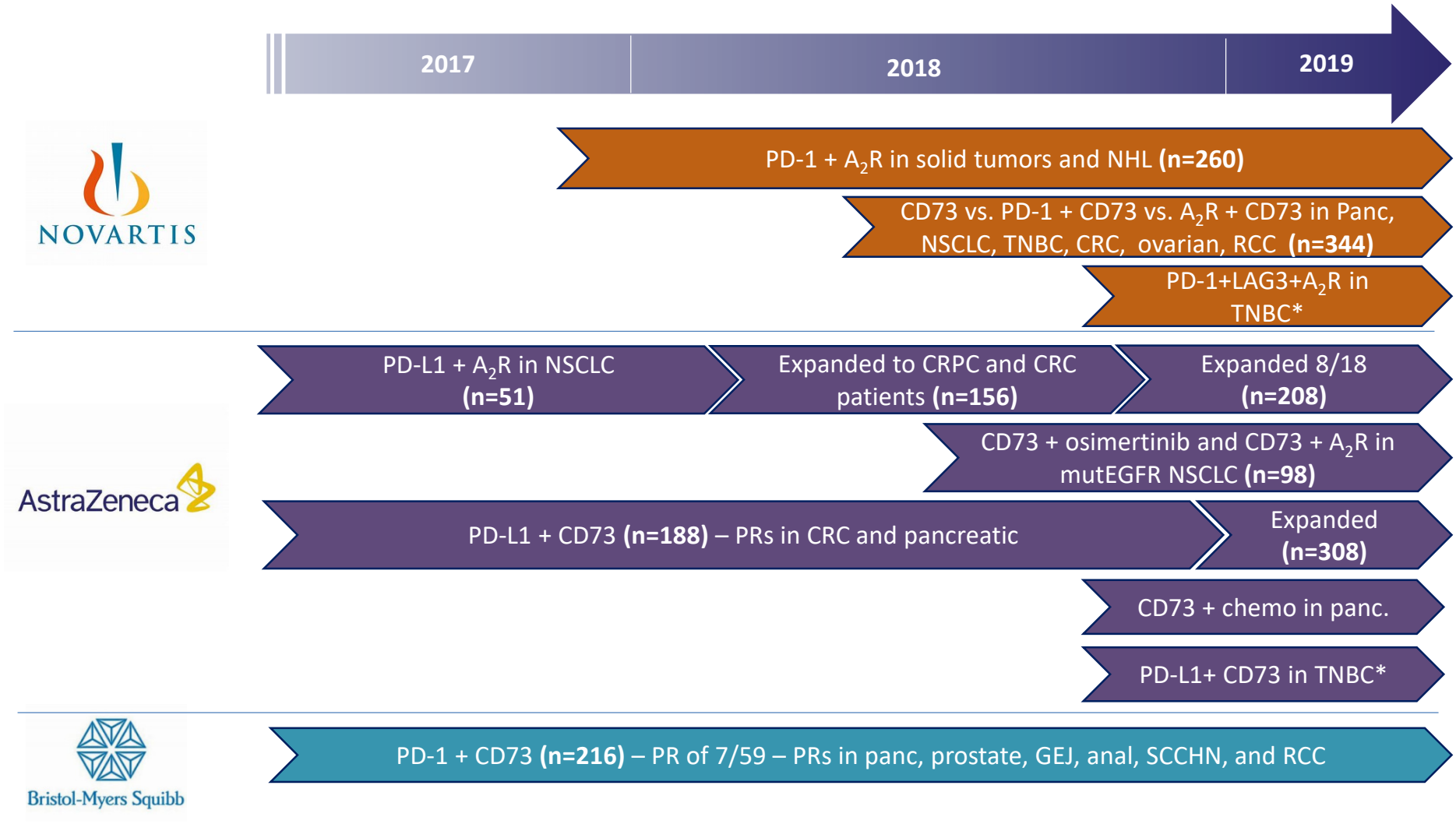


What we know about adenosine:

- High levels of adenosine are present in most tumors
- Adenosine has a direct impact on T-cell function and activation
- T cells cannot become activated in the presence of adenosine
- CD73, the enzyme that generates adenosine, could serve as a biomarker for patient screening

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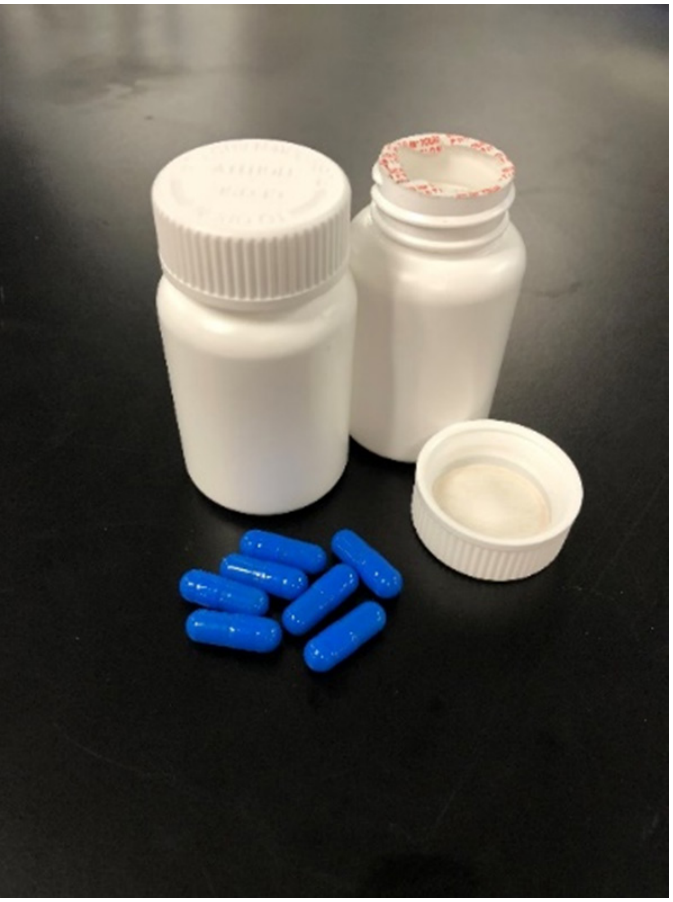
Companies Are Expanding Their CD73-Adenosine Efforts



Source: https://clinicaltrials.gov/ * Both TNBC trials are platform trials evaluating multiple combinations

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AB928 Represents a Potentially Best-in-Class Adenosine Receptor Antagonist



- First A_2R antagonist to enter clinical development that:
  - Was specifically designed for the oncology setting
  - Inhibits both the A_{2a} and A_{2b} receptors
- Multiple advantages over other A_2R antagonists in clinical development:
  - Minimal shift in potency due to non-specific protein binding
  - Minimal penetration of blood brain barrier
  - Ideal molecular properties (PK, etc.)
- Differentiated, highly efficient clinical development plan – Phase 1/1b underway
  - Believed to be first clinical program to evaluate an A_2R antagonist with chemotherapy

AB928 Has Unique Attributes Ideal for the Tumor Microenvironment

High potency against both the $A_{2a}R$ and $A_{2b}R$ receptors allows for potentially broader activity

Compound	$A_{2a}R$ (K_B, nM)[c]	$A_{2b}R$ (K_B, nM)[c]
AB928	**1.4**	**2.4**
CPI-444 [a,b]	5.4	493
AZD 4635 [a,b]	1.7	64
NIR178 [a,b]	58	189
Preladenant [a,b]	3.3	3,121

Ideal pharmacological properties for an oncology therapeutic

Attribute	AB928 Value
Retains potency in physiologically relevant conditions	**IC_{50} = 80 nM**
High tumor penetration	**Tumor : Plasma ratio: >60%**
Low CNS permeability (in mouse model)	**~ 1% of the concentration found in blood**

[a] Arcus data generated with compound samples synthesized or purchased by Arcus.

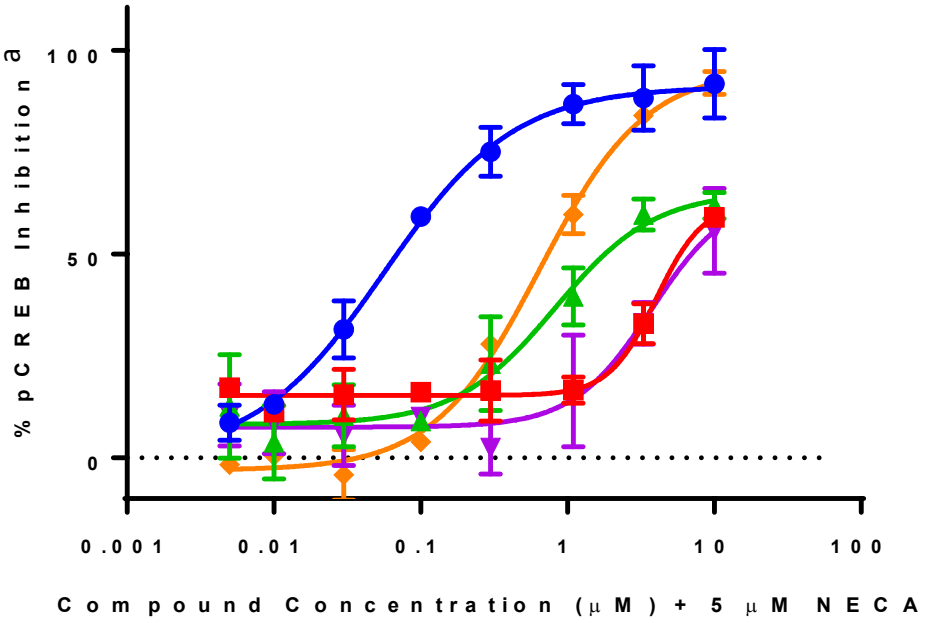
[b] CPI-444: Structure from AACR, April 2017 (#CT119), synthesized by Arcus; AZD4635: Structure from AACR, April 2017 (#2641), synthesized by Arcus; PBF509: Believed to be NIR178 (based on Pat Appl WO2017025918 and WO2018146612), synthesized by Arcus; Preladenant: was purchased from Ark Pharma (AK-43905).

[c] K_B is a measure of a compound's thermodynamic ability to bind/block its target receptor; lower K_B values reflect greater potency for a given receptor.

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AB928 is the Most Potent Antagonist of $A_{2a}R$ Receptors When Tested in a Whole Blood Assay

$A_{2a}R$ antagonists tested in a whole blood assay in the presence of NECA (conditions that resemble the tumor microenvironment)



Compound	IC_{50} (nM)
AB928	80
CPI-444[b]	~10,000
AZD 4635[b]	2,600
NIR178[b]	~10,000
Preladenant[b]	785

[a] Measured in human blood CD8+ T cells; CREB is a transcription factor that becomes phosphorylated when $A_{2a}R$ is activated; thus, the level of pCREB inhibition is a measure of the ability of an $A_{2a}R$ antagonist to inhibit $A_{2a}R$.

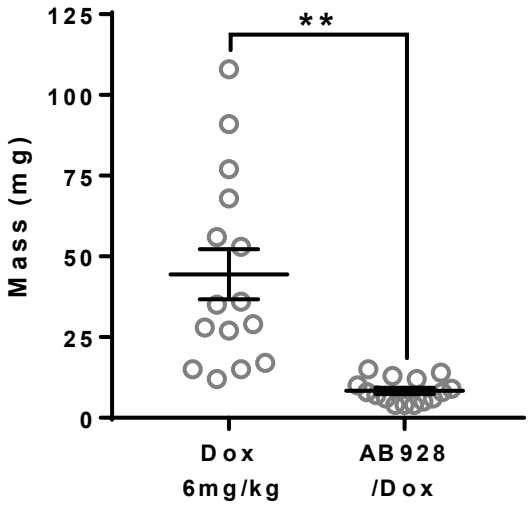
[b] CPI-444: Structure from AACR, April 2017 (#CT119), synthesized by Arcus; AZD4635: Structure from AACR, April 2017 (#2641), synthesized by Arcus; NIR178 (PBF509): Molecule synthesized by Arcus and believed to be NIR178 (based on Pat Appl WO2017025918 and WO2018146612); Preladenant: purchased from Ark Pharma (AK-43905) and was run on a different donor and date than the other compounds.

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AB928 + Chemo Combination: Reduced Tumor Growth and Enhanced Immune Cell Infiltration

Example images representing the average tumor mass from each group in AT-3 OVA Model

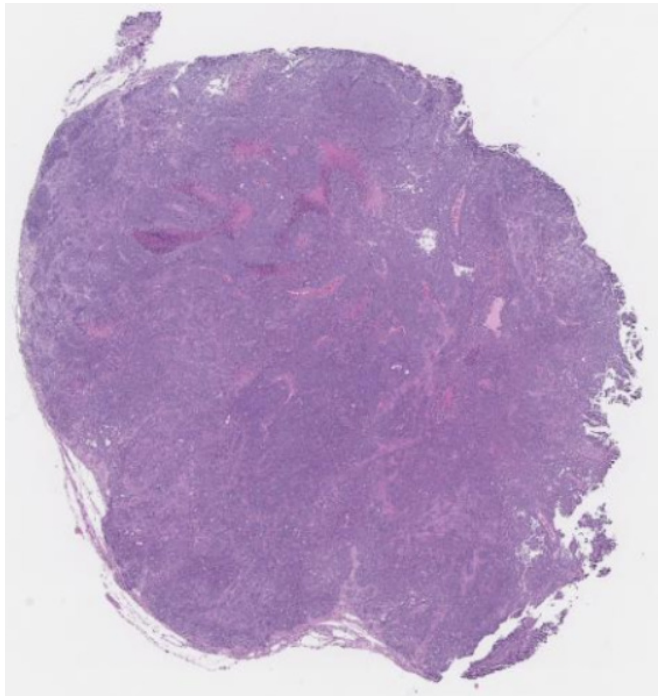
Tumor Mass (Day 30)



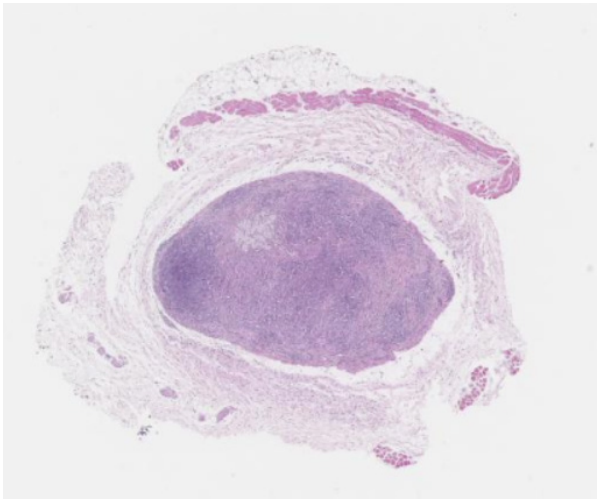
Dosing started on day 14 post tumor inoculation

**p<0.01

Vehicle + Dox (53 mg tumor)



AB928 + Dox (8 mg tumor)

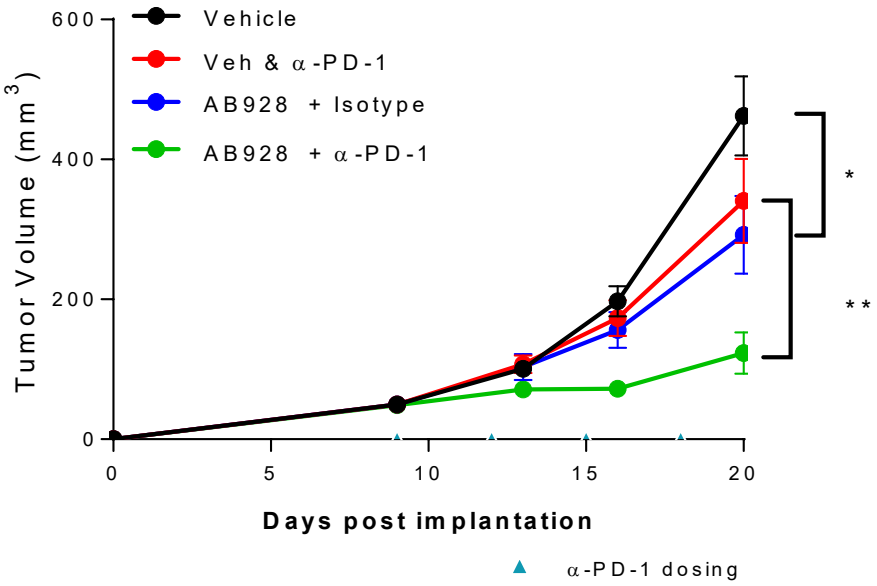


Tumors treated with only doxorubicin exhibit homogenous, densely packed tumor mass, whereas tumors treated with AB928 + doxorubicin show increased immune infiltrate and increased ECM deposition between tumor cells

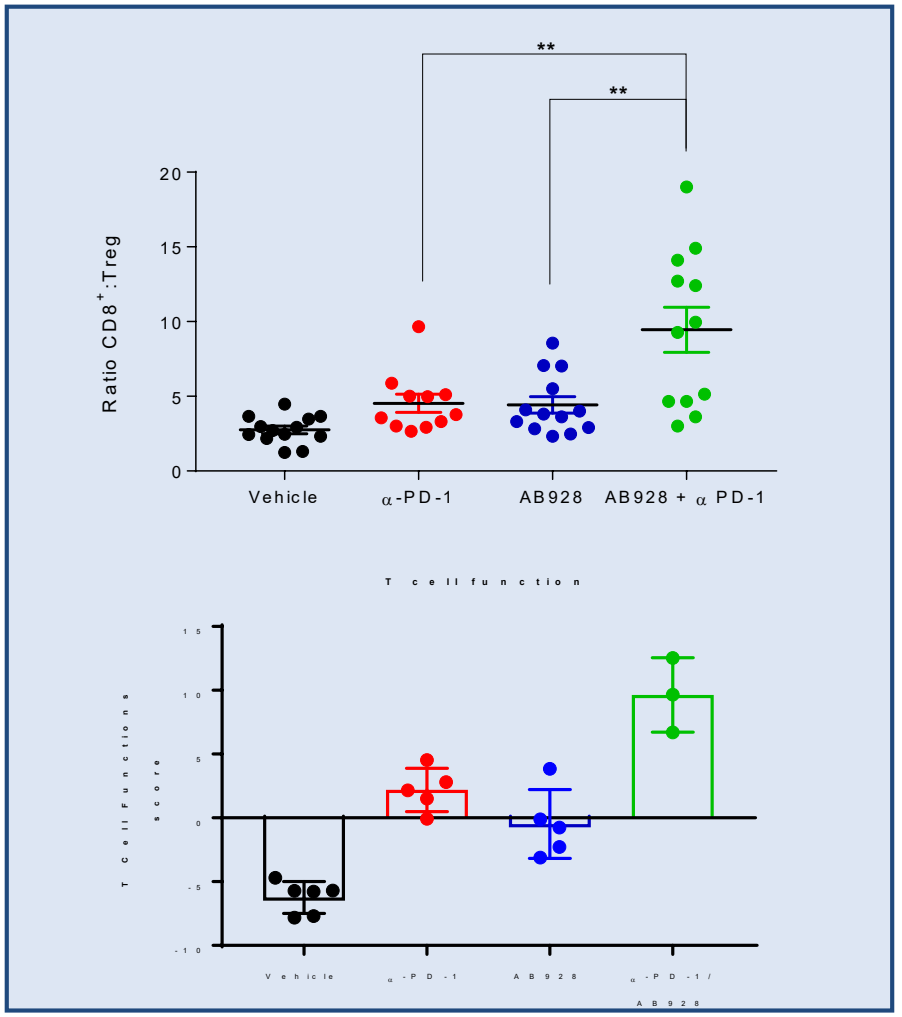
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AB928 + αPD-1 Combination: Significant Effects on Tumor Growth, Immune Cell Profile and T-Cell Function

B16F10 Model (in combination with anti-PD1 antibody)



- Start dosing on day 9
- $^{*}p<0.05$; $^{**}p<0.01$



T cell function score generated in-house using Nanostring platform based upon pre-specified collection of genes

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Phase 1 Trial in Healthy Volunteers Demonstrated an Excellent Safety Profile

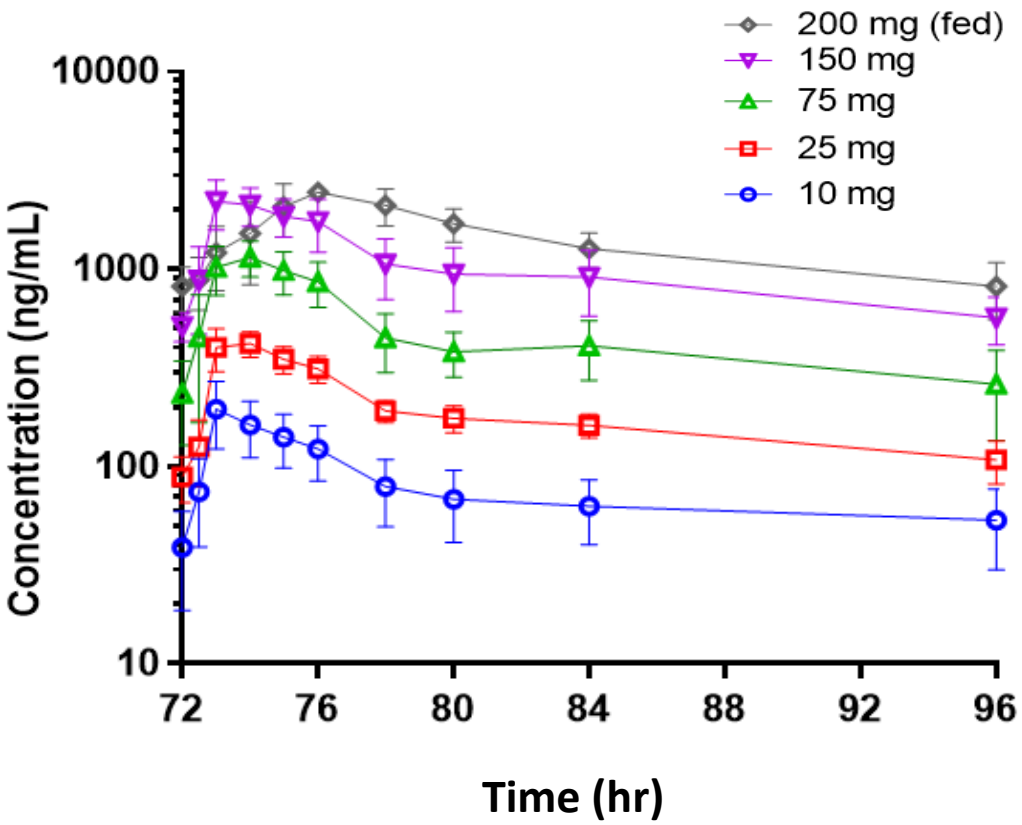
Design:

- Double-blinded, randomized, placebo-controlled trial
- n=80 randomized 3:1 to AB928 or placebo
- Included SAD and MAD portions
- MAD portion evaluated 4 consecutive days of dosing

Safety Results:

- AB928 was well tolerated at all doses tested
- All reported AEs were characterized as low-grade, with the majority being Grade 1 events
- There were no trends in treatment-related AEs regardless of causality or severity that were dose related

MAD Pharmacokinetics (Day 4)



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Safety, tolerability, and pharmacology of AB928 in a randomized, phase 1 study in healthy volunteers: Seitz et al., *Invest. New Drugs* (2018). https://doi.org/10.1007/s10637-018-0706-6

Based on the HV Data, Maximal Inhibition of $A_{2a}R$ Should be Achieved at Doses Between 75-150 mg QD

	2-hr Post-Dose		24-hr Post-Dose	
	AB928 Plasma Conc. (ng/mL)	% Inhibition of 5 µM NECA	AB928 Plasma Conc. (ng/mL)	% Inhibition of 5 µM NECA
10 mg QD	163	51 %	53	(12%)*
25 mg QD	420	82 %	108	51 %
75 mg QD	**1,148**	**100 %**	**261**	**76 %**
150 mg QD	**2,113**	**100 %**	**566**	**≥ 90%**
200 mg QD fed	**1,517**	**≥ 90 %**	**819**	**≥ 90%**

Starting dose for the AB928 combination dose-escalation trials

*Some or all dosed subjects were within the range of variation observed in placebo subjects (-39 to 30%).

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Four AB928 Combination Dose-Escalation Trials Have Been Initiated

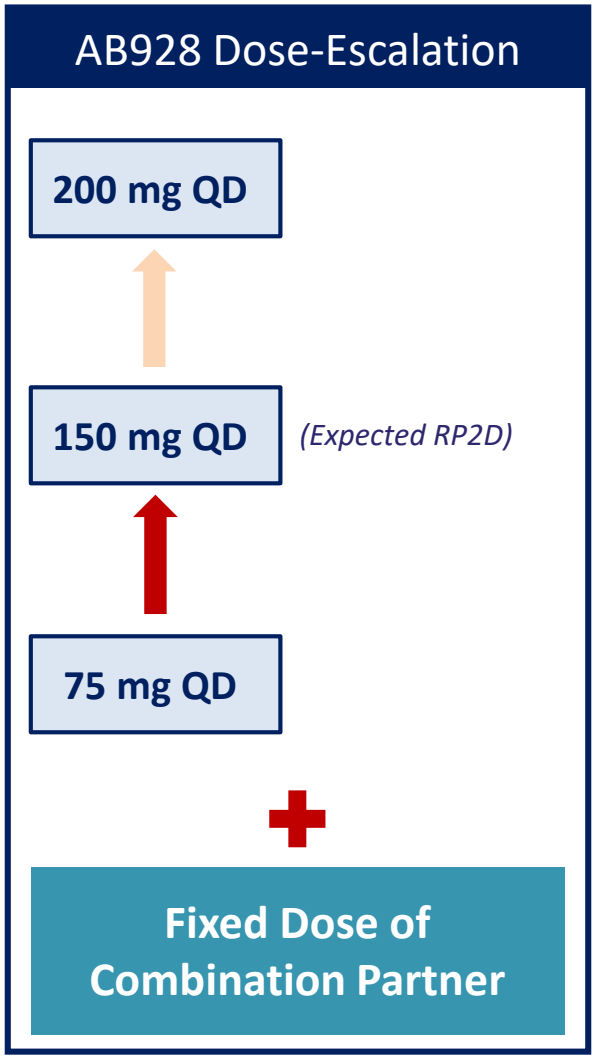
Tumor types and combinations selected based on expression levels of CD73, extent of T-cell infiltration and immunogenicity of the combination partner

Trial protocol	Tumor types	AB928 Combo partner	Dose Esc. Status
002	▪ Ovarian ▪ TNBC	Doxil	Enrolling
003	▪ Colorectal ▪ GE	mFOLFOX	Enrolling
004	▪ NSCLC – TKI failures	Carbo/pem	Initiating
005	▪ Multiple solid tumor types	AB122	Enrolling

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Design of the Four AB928 Combination Dose-Escalation Trials

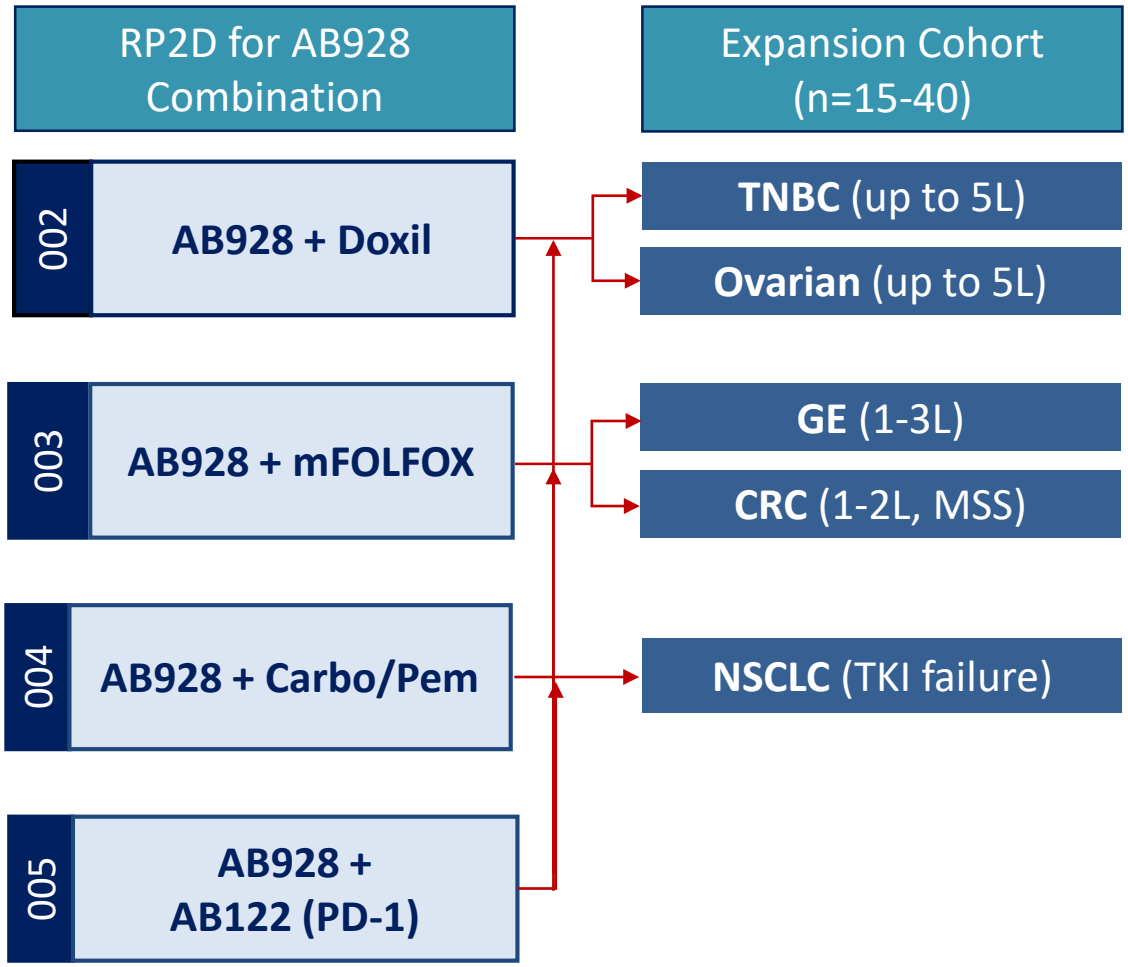
Tumor Types	AB928 Combination
002 **TNBC or Ovarian** ▪ Up to 5 prior lines ▪ PD-1 naïve or R/R	**AB928 + Doxil**
003 **GE or CRC** ▪ Up to 5 prior lines ▪ PD-1 naïve or R/R	**AB928 + mFOLFOX**
004 **NSCLC** ▪ Up to 5 prior lines ▪ TKI failures, PD-1 naïve	**AB928 + Carbo/Pem**
005 **Solid Tumors** ▪ Up to 5 prior lines ▪ PD-1 naïve	**AB928 + AB122 (PD-1)**



- *Only 12-15 patients expected to be enrolled in each dose-escalation trial based on the starting dose of 75 mg QD of AB928*
- *Initial data from dose escalation expected in June 2019*

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Following Identification of the RP2D for AB928, the First Expansion Cohorts Will Begin by Mid-2019



Flexible trial design

- Expansion cohorts will enroll the same tumor types as the dose-escalations
- Each expansion cohort will initially enroll up to 15 patients
- The cohorts will be expanded up to 40 patients based on achievement of threshold response rates
- Flexibility to add SOC arms to the protocols

- ***Initial data from dose expansion cohorts expected in 1H:20***

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Extensive Biomarker Plan to Identify Predictive Biomarkers and to Confirm Responses to AB928

	Biomarker Readout	Key Objective(s)
Potential predictive biomarkers	CD73 status • Tumor (IHC & mRNA) • Blood (ELISA & Enzymatic Assay)	✓ Determine relationship between CD73 expression (tumor, soluble) and clinical activity ✓ Assess potential of CD73 biomarker as a patient selection tool
	Tumor expression (mRNA) of *Adenosine Fingerprint** genes	✓ Assess relationship between clinical activity and various elements of this gene expression profile
	PD-L1 status/TMB	✓ Assess relationship between clinical activity and PD-L1 or TMB
Immune markers	T cell clonality (tumor & blood) • neoantigen-specific T cell clonal expansion	✓ Determine if tumor responses correlate with increases in neoantigen-specific T cells
	Immunophenotyping (blood) and serum cytokines	✓ Quantify activation of immune pathways ✓ Assess effects on immune cell activity/function

* Collection of 9 proteins involved in the generation, degradation and signaling of adenosine in the tumor

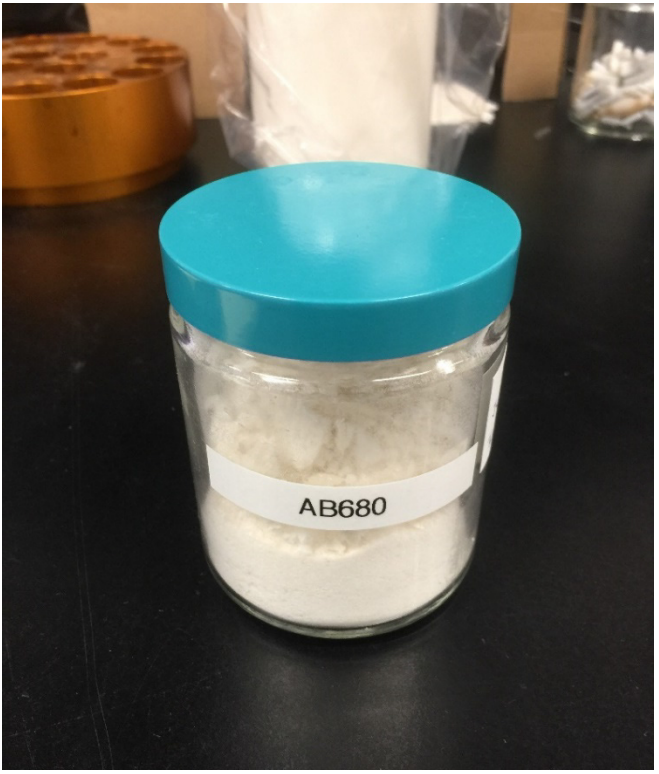
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Maturing Data from the AB928 Dose Escalations to be Presented in 2019

	June 2019	ESMO 2019
Safety	Initial data for the combinations	More complete data for the combinations
Dose	RP2D for Doxil, mFOLFOX and AB122 combos	RP2D for Carbo/Pem combo expected by YE:19
Clinical Activity	Preliminary response data available from the initial dose cohorts	Response data from additional cohorts
Biomarker Data	Immune activation marker data and correlation with responses/ non-responses: ▪ Adenosine fingerprint ▪ Blood lymphocyte immunophenotyping ▪ Neoantigen-specific T cell expansion	Expansion of immune activation marker data and correlation with responses/non-responses Potential identification of a predictive biomarker

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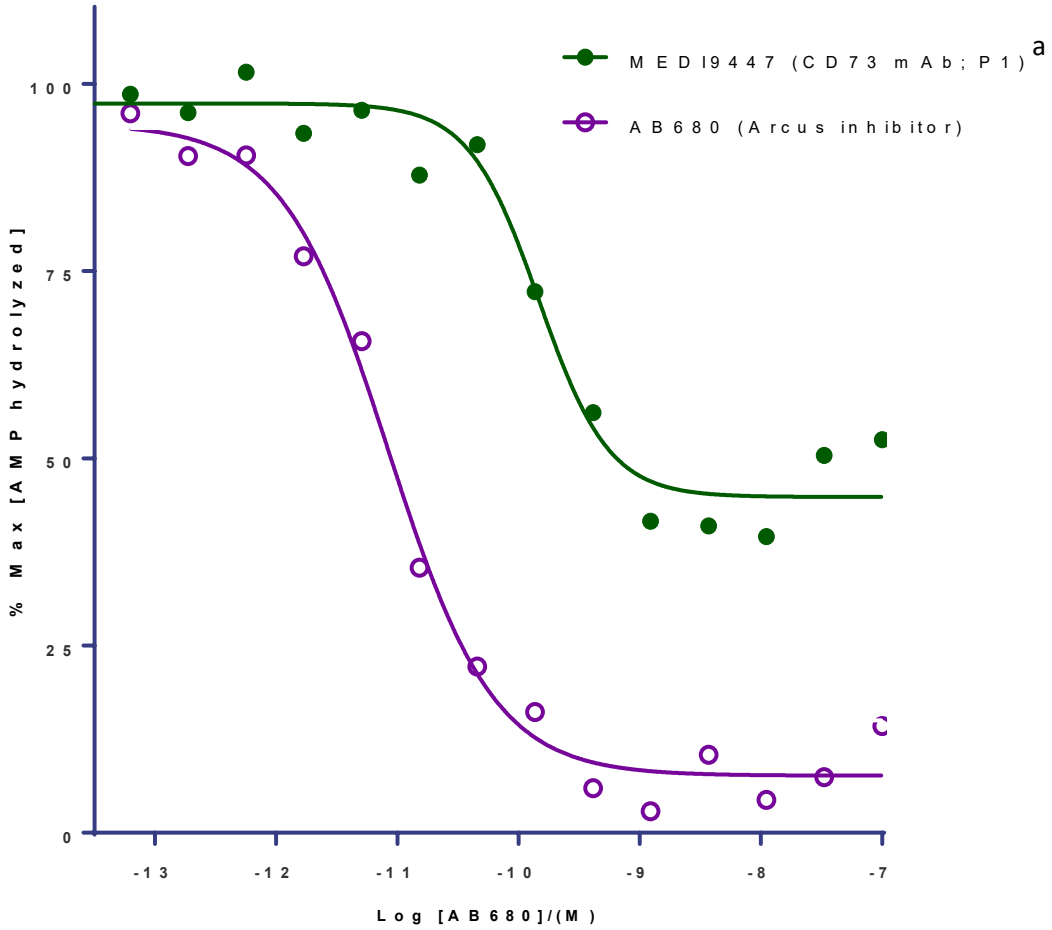
AB680: First Small Molecule CD73 Inhibitor to Enter Clinical Development



- CD73 catalyzes the last step in the conversion of extracellular ATP to adenosine
- AB680 potentially offers advantages over the anti-CD73 antibodies in development:
  - Greater inhibition of CD73 enzymatic activity
  - Deeper tumor penetration
  - IV + oral formulation
- Unique small molecule properties
  - Extraordinarily potent: IC_{50} = 0.008 nM (human T cells)
  - Low clearance, long half-life molecule (>4 days)
  - IV formulation could be administered on the same schedule as PD-1 antibodies or chemo
- Initiated Phase 1 for IV formulation in healthy volunteers – data in 1H:19
- Oral formulation in IND-enabling studies

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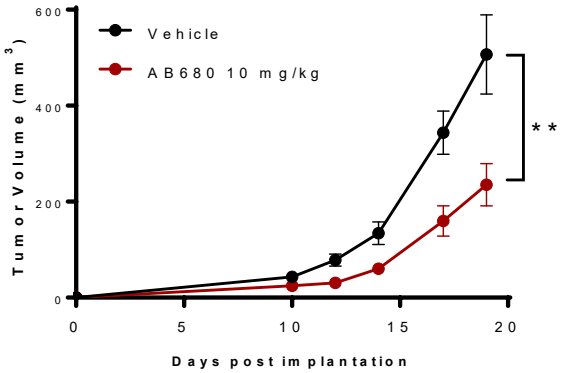
AB680 Potently Inhibits CD73 Enzymatic Activity on CD8+ T Cells

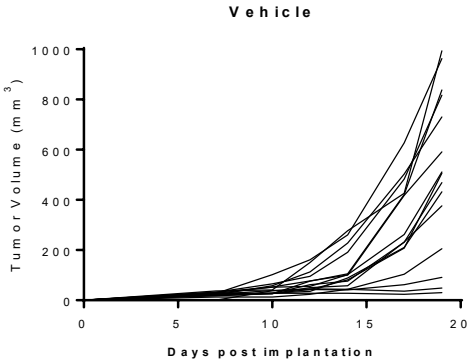


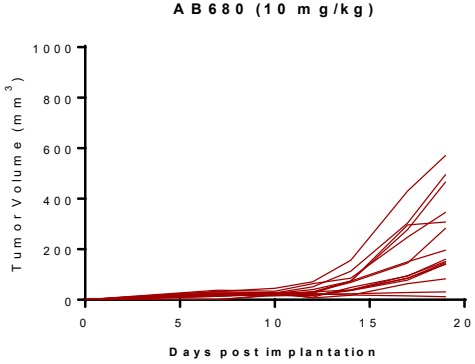
[a] Molecule synthesized by Arcus based on the following publication and patent application: Hay et al., OncoImmunology (2016) 5, e1208875; Patent Appl. US 2016/0129108.

AB680 Reduces Tumor Growth in B16F10 Model as Monotherapy and in Combination with anti-PD-1

AB680 as Monotherapy

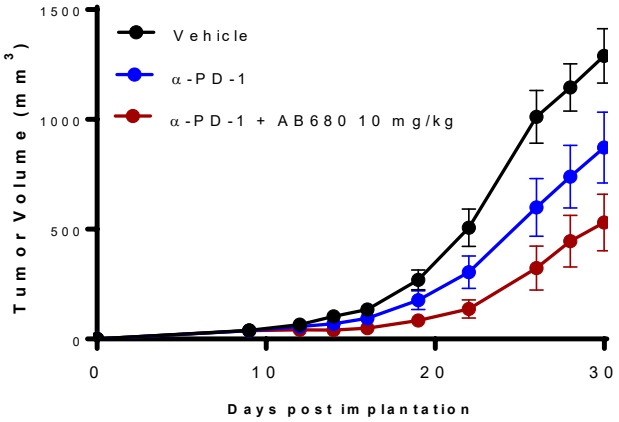


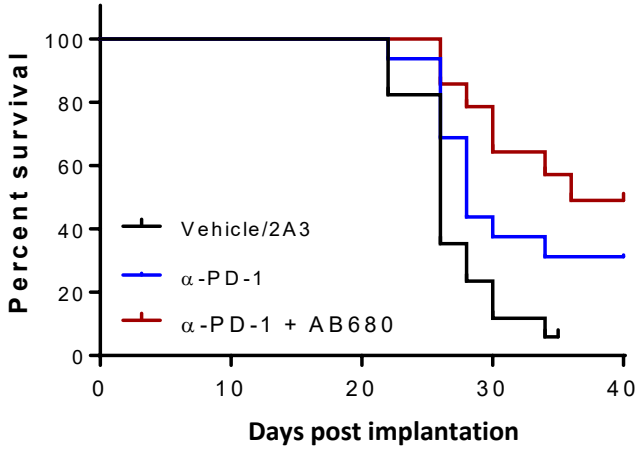




**p=<0.01

AB680 in Combination with anti-PD-1

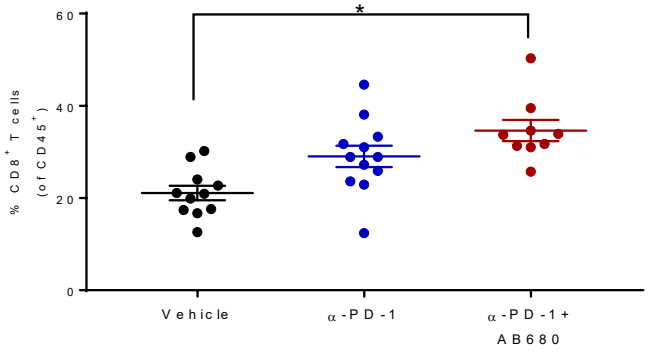




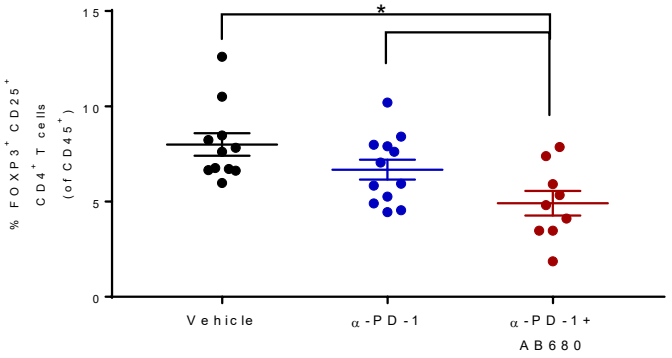
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Combination of AB680 and anti-PD-1 Promotes a Shift Towards an Inflamed Tumor Microenvironment

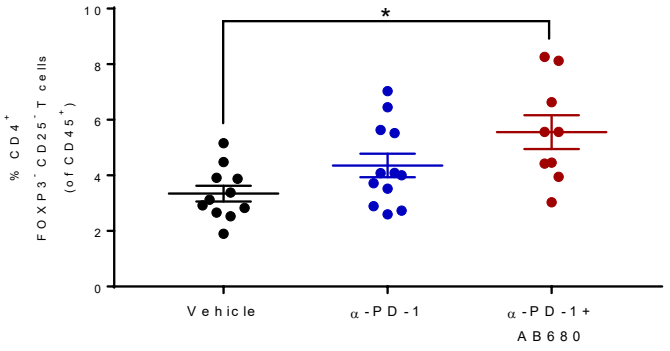
CD8+



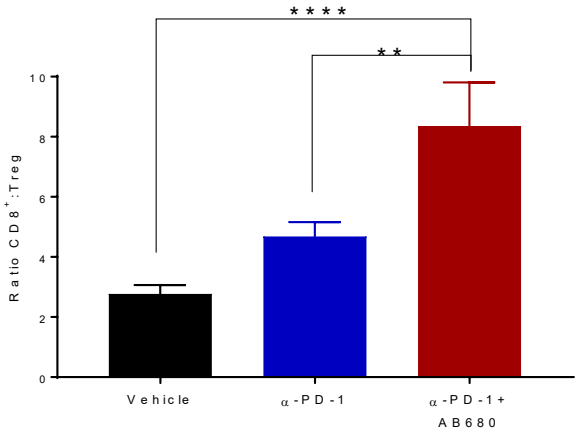
T-Regs



CD4+



CD8+ : T-Regs



*p=<0.05; **p=<0.01 ****p<0.0001

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Healthy Volunteer (HV) Trial for AB680 is Enrolling

Trial Design

- ✓ Single ascending dose design
- ✓ Cohorts (n=8) randomized (3:1) to AB680 or placebo
- ✓ Evaluation of Dose Level 3 ongoing
- ✓ Additional dose escalation in this trial is expected, based on PK/PD data

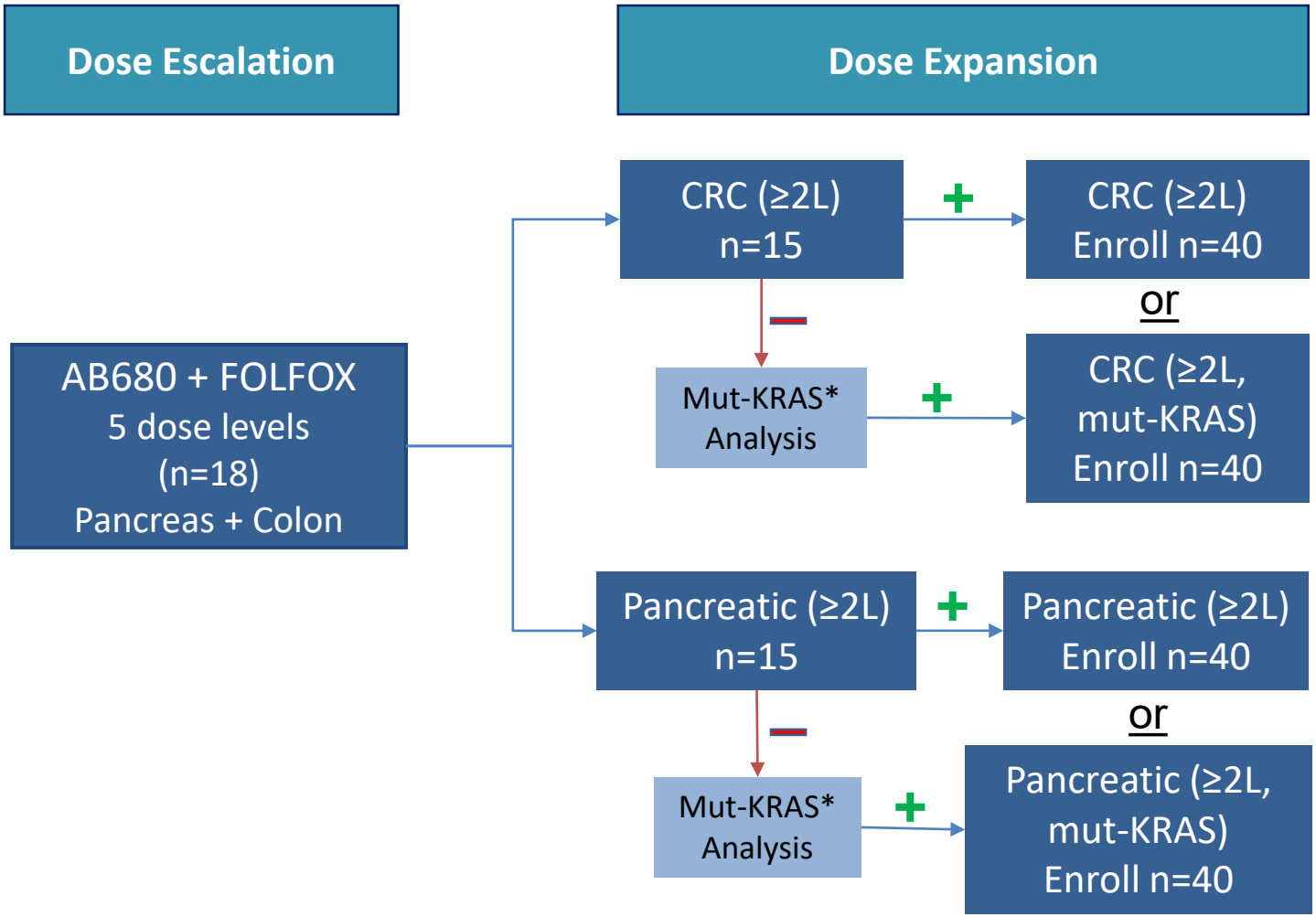
Key objectives

- ✓ Determine safety and tolerability
- ✓ Assess pharmacokinetics and pharmacodynamics (CD73 inhibition)
- ✓ Enable initiation of clinical trials in cancer patients at a higher starting dose than otherwise possible

Next Steps

- ✓ HV data and initiation of clinical trials in cancer patients expected in 1H:19

Planned Study to Explore AB680 in Pancreatic and Colorectal Cancer



** Strong correlation between mutant-KRAS tumors and CD73 expression*

AB154: The Next Potential I-O Backbone (TIGIT)

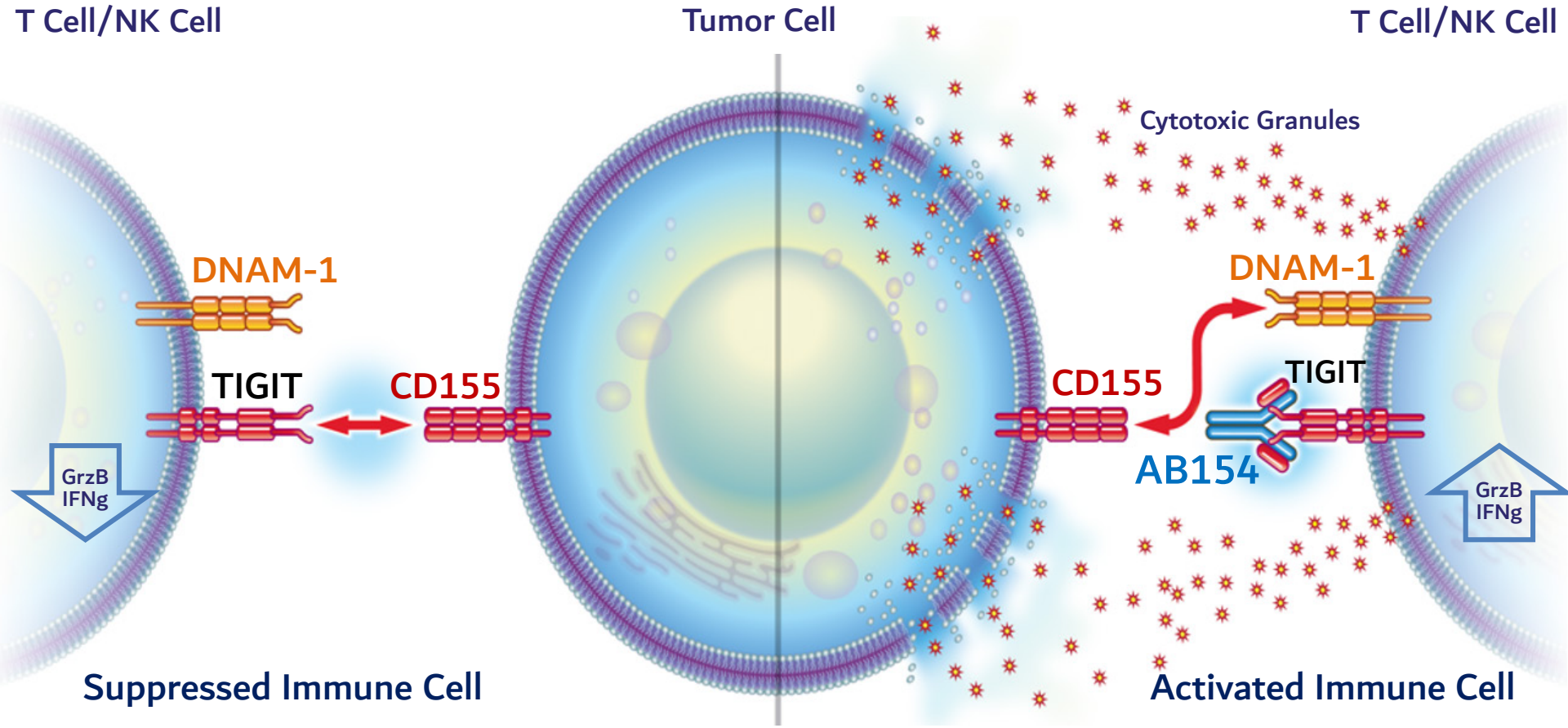


- Humanized anti-TIGIT antibody effector function silence Fc
  - Binds to a different epitope than other TIGIT antibodies
- TIGIT inhibition reverses immune inhibition *and* provides tumor-selective immune stimulation
- Experiments in immune assays demonstrate synergy with AB680 (CD73) and AB122 (PD-1)
- Phase 1 trial initiated to evaluate AB154 as monotherapy and in combination with AB122
  - Dose-escalation portion to be followed by expansion cohorts in tumor types with high levels of TIGIT and/or CD155 (TIGIT's ligand)

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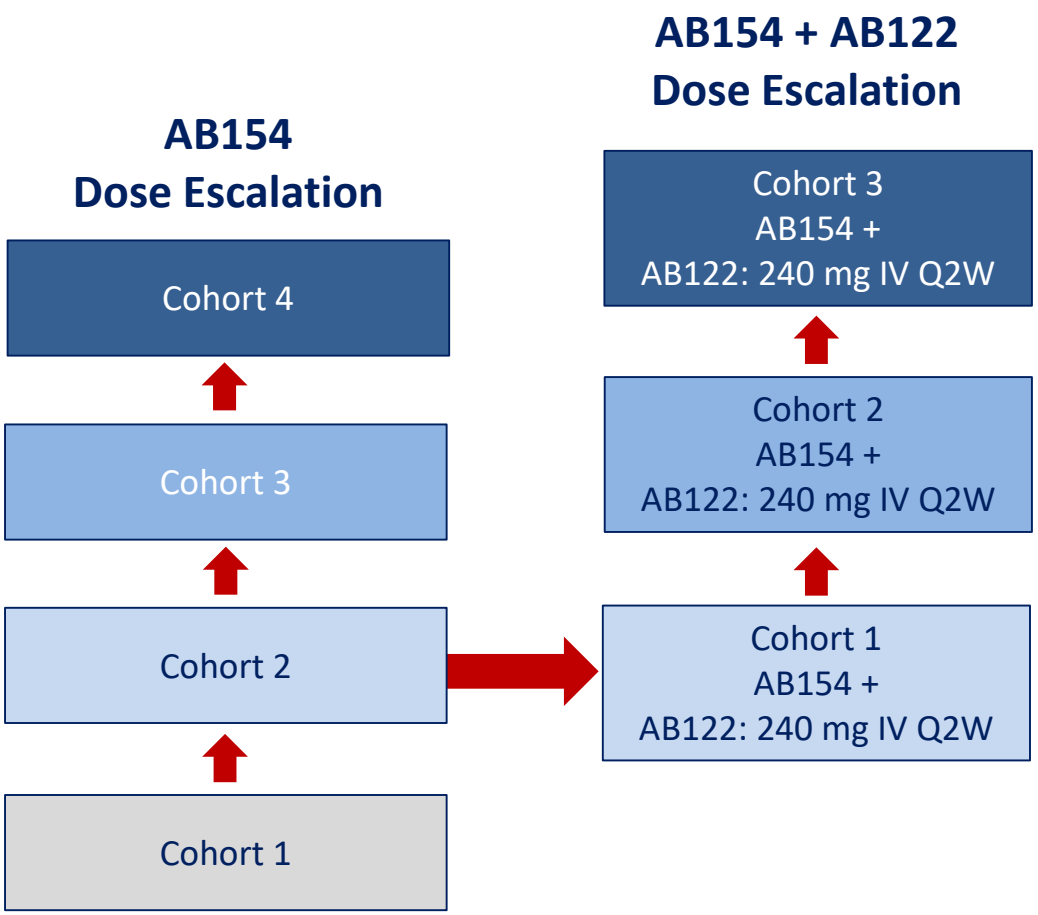
AB154 Has a Dual Mechanism of Action that Reflects the Uniqueness of the TIGIT Pathway

Blocking TIGIT inhibits an immuno-suppressive pathway while freeing up CD155 to bind to DNAM-1 which is an immune-activating pathway



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Phase 1/1b Dose Escalation Trial of AB154 + AB122



Key objectives

- ✓ Evaluate safety and tolerability
- ✓ Determine pharmacokinetic and pharmacodynamic profile
- ✓ Identify RP2D for AB154 as monotherapy and in combination with AB122
- ✓ Assess preliminary clinical activity of AB154 and AB154 + AB122

Next steps

- ✓ Present preliminary data for the monotherapy dose-escalation in 2H:19
- ✓ Initiate expansion cohorts in tumor types with high levels of TIGIT and/or CD155*

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*Potential tumor types include TNBC, NSCLC, SCCHN, cervical and gastric cancers

AB122: Anti-PD-1 Antibody with Properties Similar to Those of Approved Agents

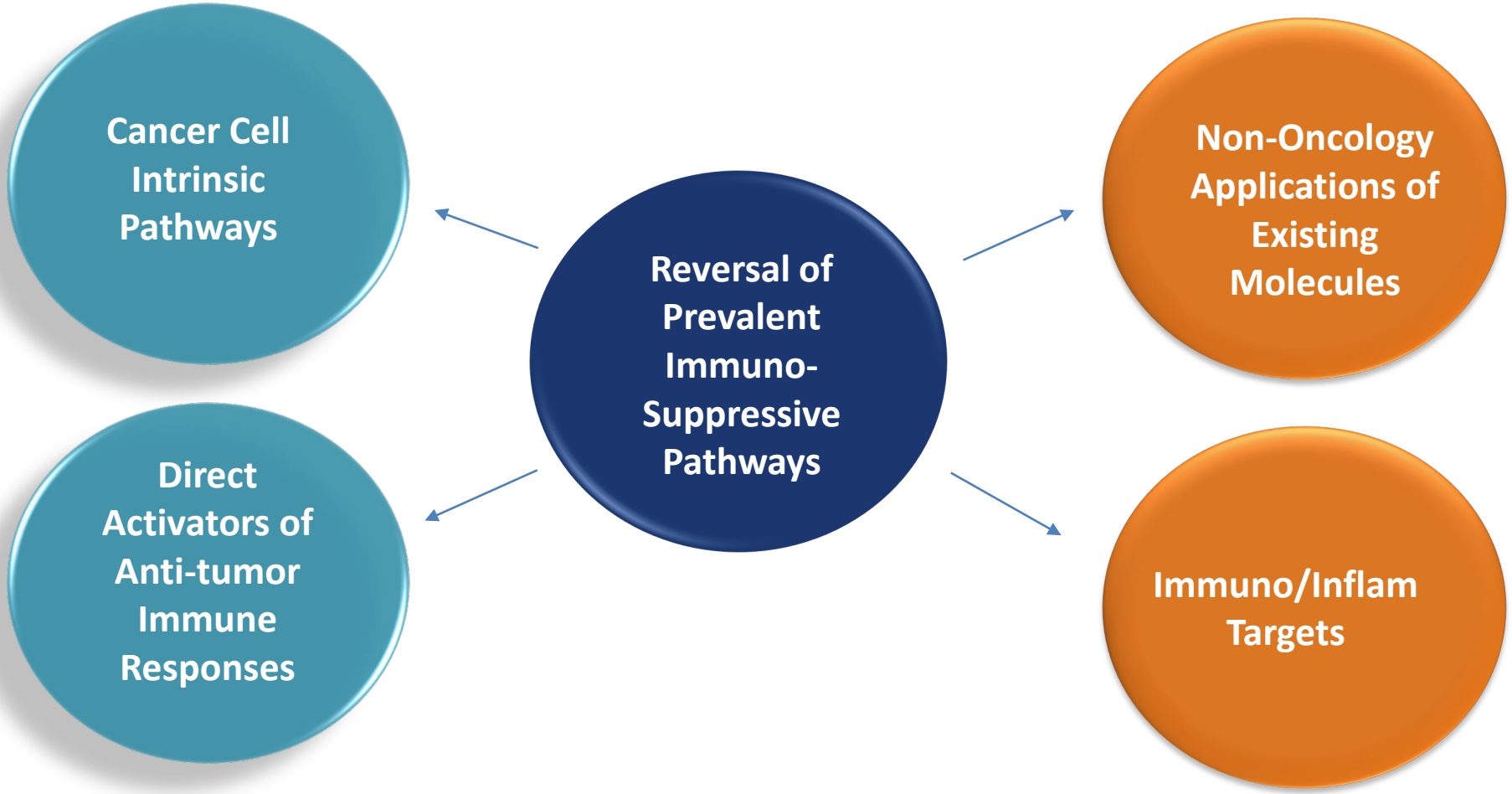


- Fully human antibody with similar binding affinity and other characteristics to pembrolizumab and nivolumab
- In-licensed from WuXi, a leading biologics manufacturer
  - Full development and commercialization rights in the US, Europe, Japan and certain other territories
  - Complete flexibility to develop anti-PD-1 combinations; Provides flexibility on combination pricing
- Ongoing Phase 1 monotherapy dose-escalation trial in Australia nearing completion
  - Identified 240 mg Q2W as dosing regimen; Q3W and Q4W schedules under evaluation
  - Full receptor occupancy on peripheral T cells observed at this dose at all time points

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Active Early Stage Discovery Effort Focused on Small-Molecule Pipeline Expansion

Arcus is leveraging its small-molecule expertise to continue creating best-in-class and/or first-in-class product candidates



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Anticipated Milestones

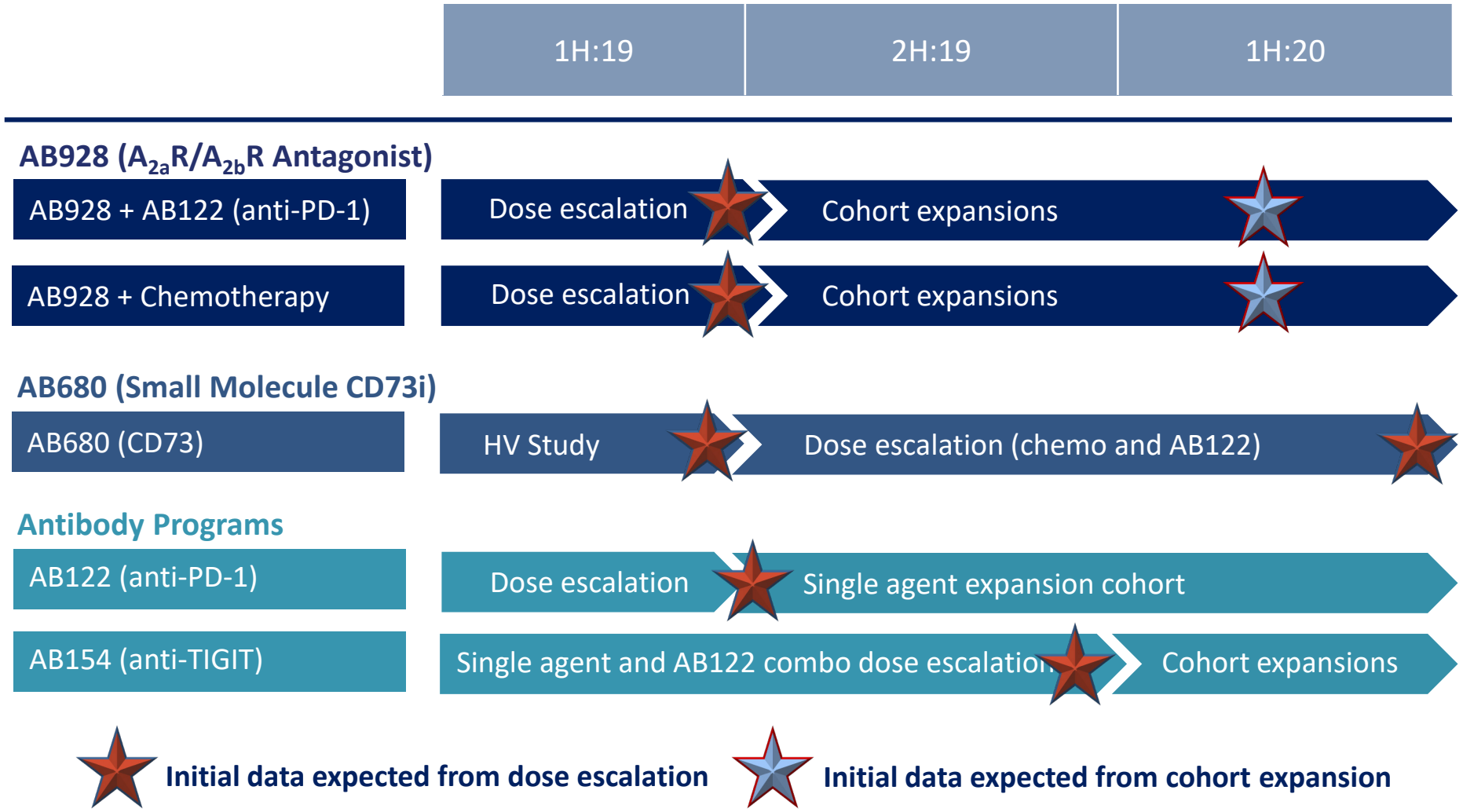
Strong Cash Position; Funding into 2021

- As of September 30, 2018:
  - Cash and investments - $265.6mm
  - Shares outstanding - 44.5mm
- Total capital raised to date - $350mm + $33mm of "non-dilutive" capital

TAIHO ONCOLOGY
Making the human connection

- Option to Arcus programs in Japan and certain other Asian territories (excluding China) over a 5-year term
- $35mm in guaranteed payments over 3 years
- Opt-in payments ranging from $3 to $15mm depending on when exercised
- Up to $275mm in development, regulatory and commercial milestones per program
- Tiered royalties from high-single digit to mid-teens on net sales
- **Exercised option to AB928 in July 2018**

Multiple Data Readouts in the Next 12 Months



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