

Creating Innovative Cancer Immunotherapies by Leveraging Underexploited Biological Opportunities

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January 2019 NYSE: RCUS

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Corporate Overview

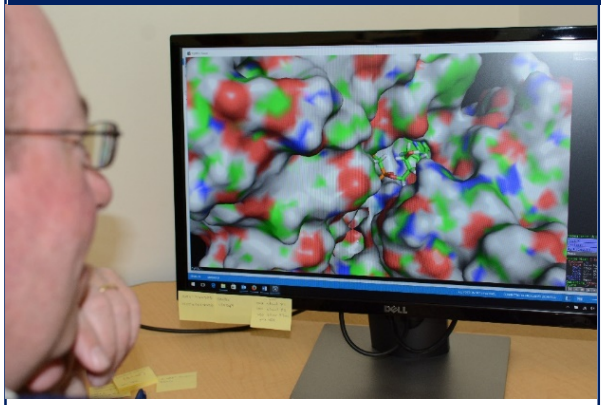
Creating Innovative Cancer Immunotherapies

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

AB680 (Small Molecule CD73i)

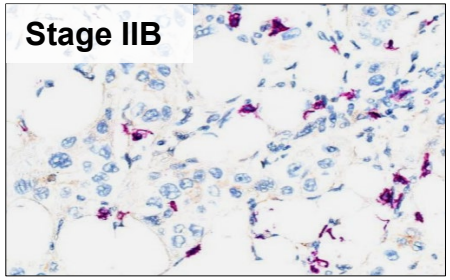
- AB680 (IV) — Phase 1 in HVs
- AB680 (oral) — IND-enabling

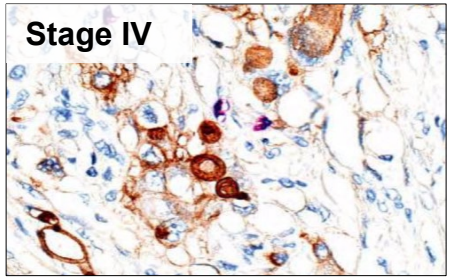
Antibodies

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

Enables development of multiple intra-portfolio combinations

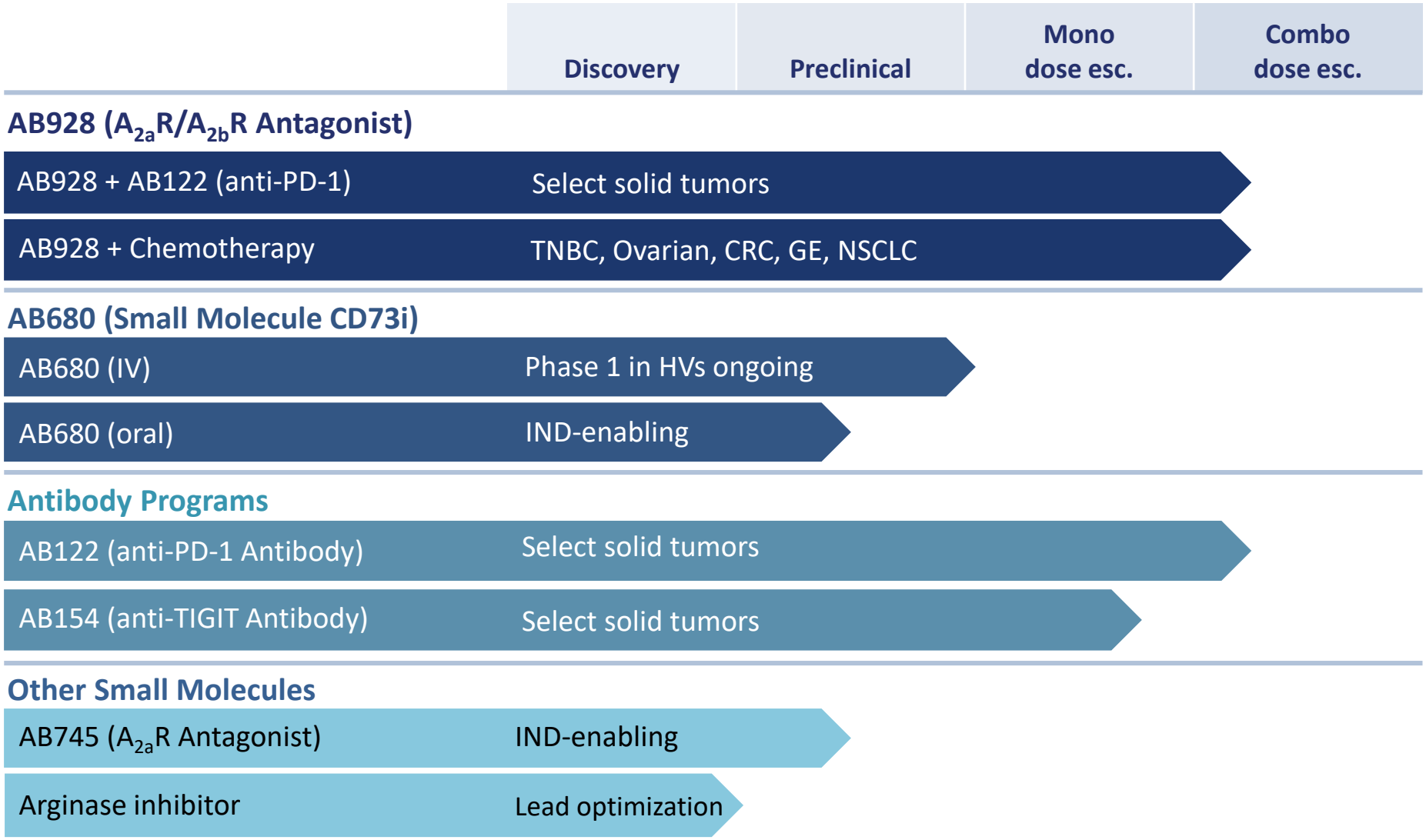
Translational Medicine





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

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



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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**	**Select solid tumors**	**N/A**	**Select 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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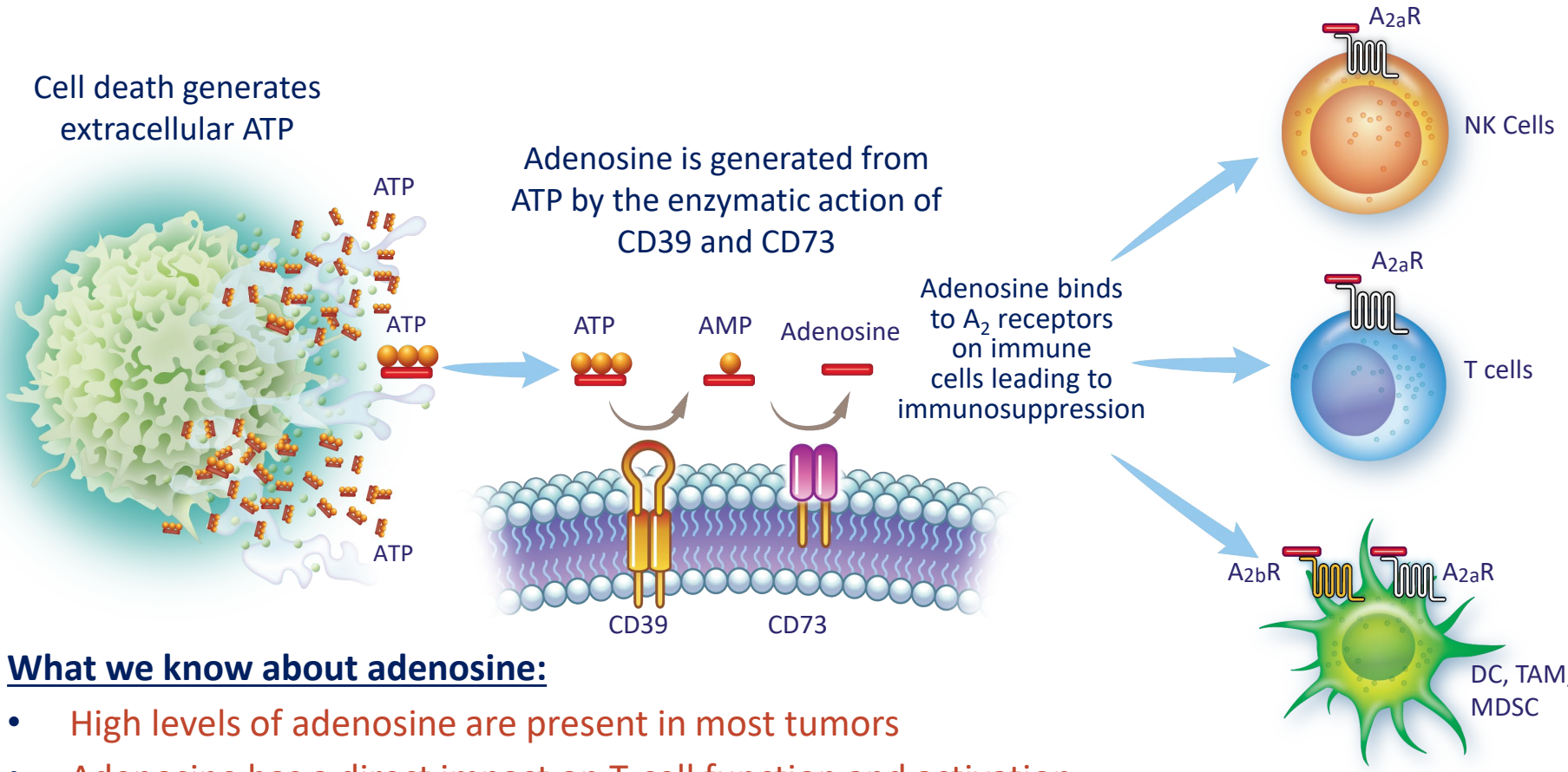
Our Portfolio

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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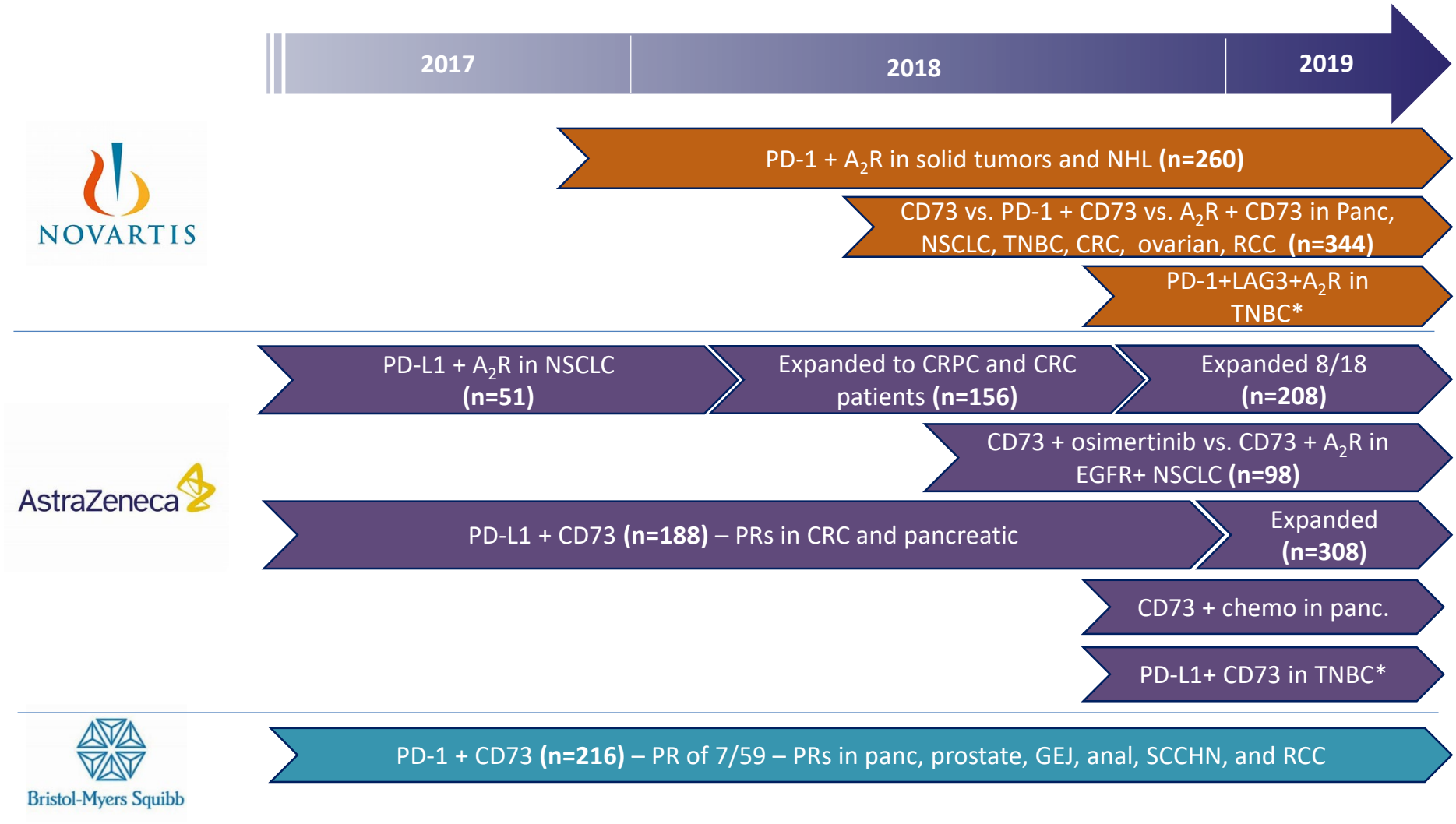
Companies Are Expanding Their CD73-Adenosine Efforts



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

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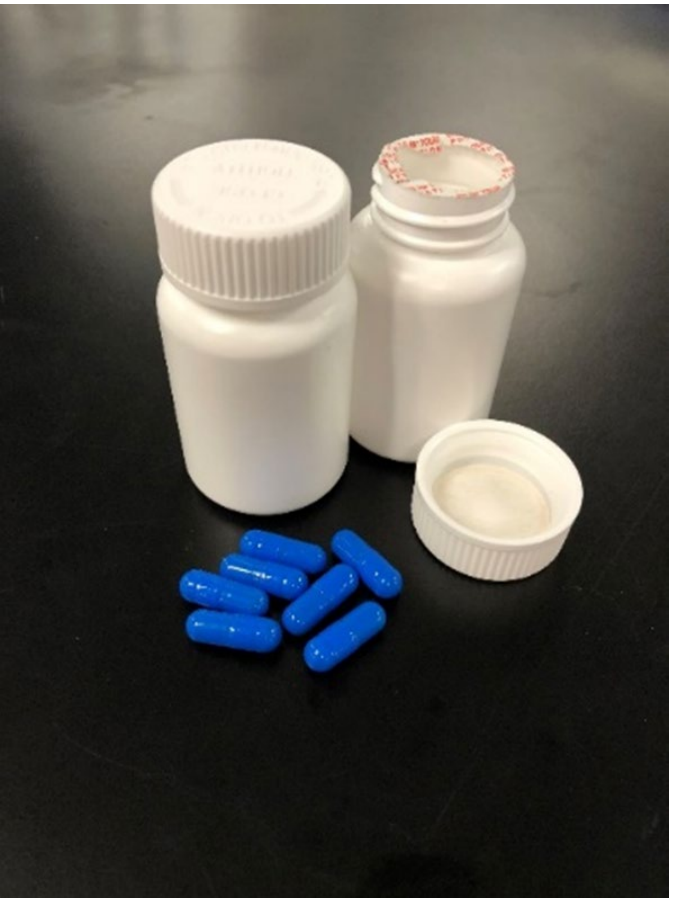
AB928 Represents a Potentially Best-in-Class Adenosine Receptor Antagonist



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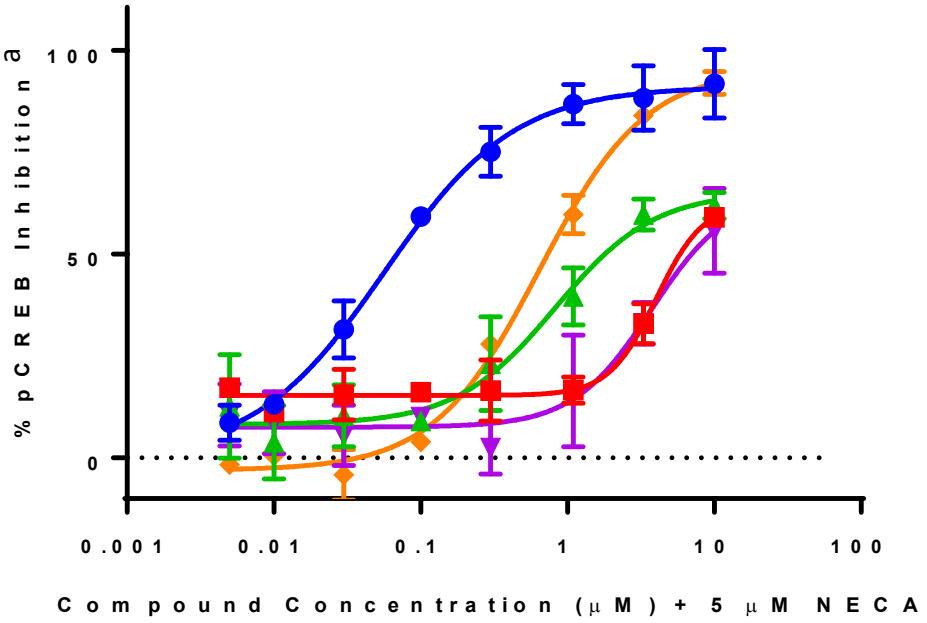
AB928 is the Most Potent Antagonist of $A_{2a}R$ Receptors When Tested in a Whole Blood Assay

$A_{2a}R$ 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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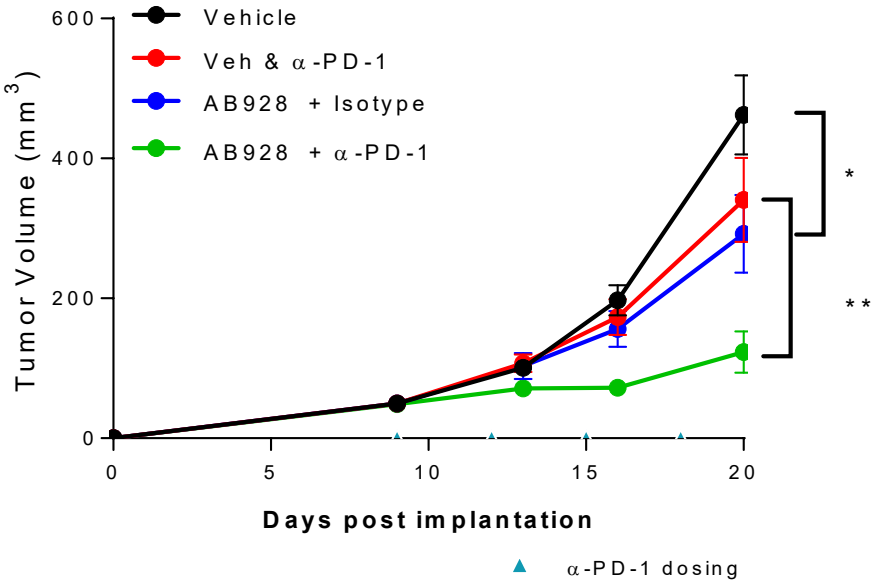
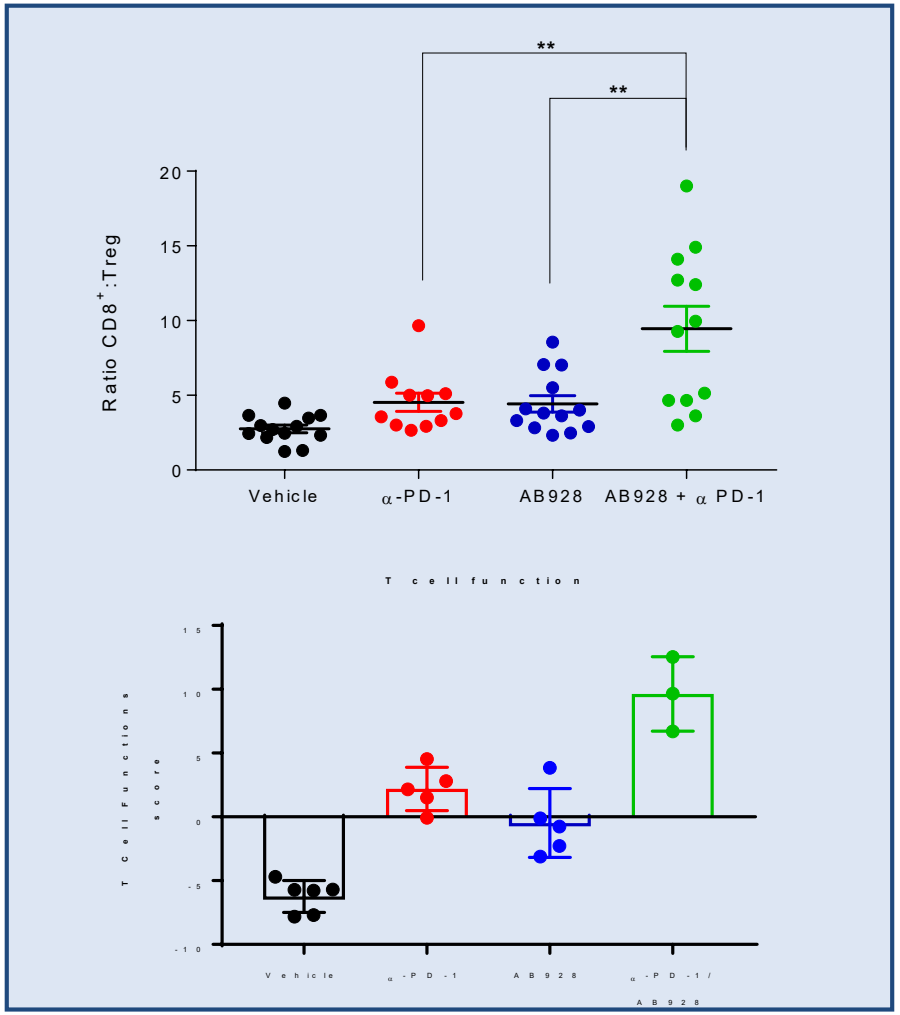
AB928 + αPD-1 Combination: Significant Effects on Tumor Growth, Immune Cell Profile and T-Cell Function

B16F10 Model (in combination with anti-PD1 antibody)



- Dosing at day 9 tumors ~50 mm^3
- *p<0.05; **p<0.01



Source: Data generated in-house using Nanostring platform based upon pre-specified collection of genes

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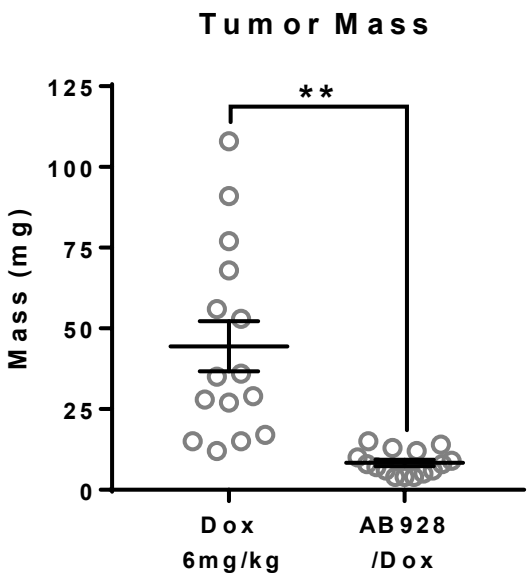
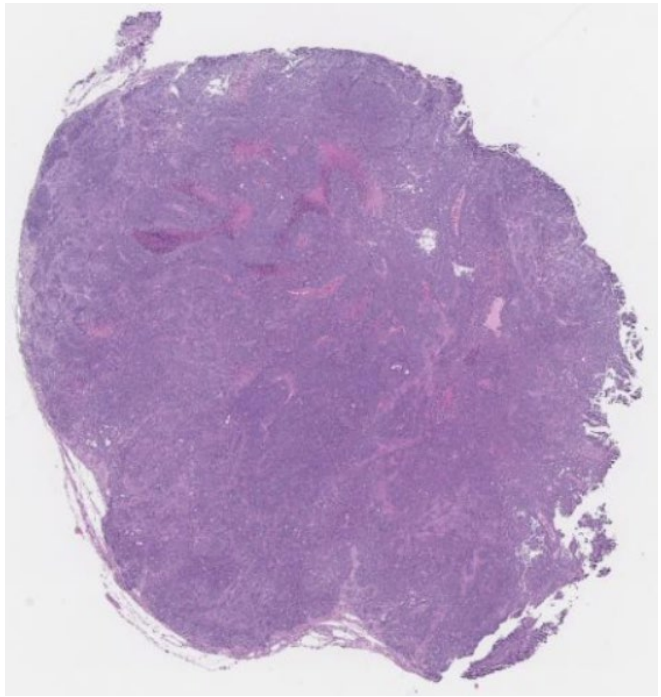
AB928 + Chemo Combination: Reduced Tumor Growth and Enhanced Immune Cell Infiltration

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

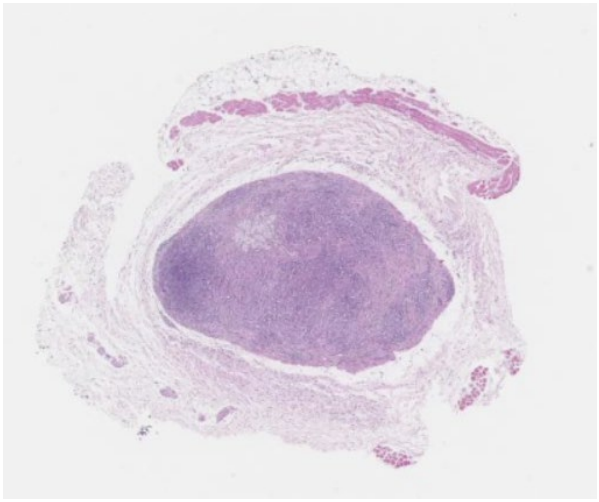


Note: Dosing started day 14 post tumor inoculation

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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Phase 1 Trial in Healthy Volunteers Demonstrated an Excellent Safety Profile

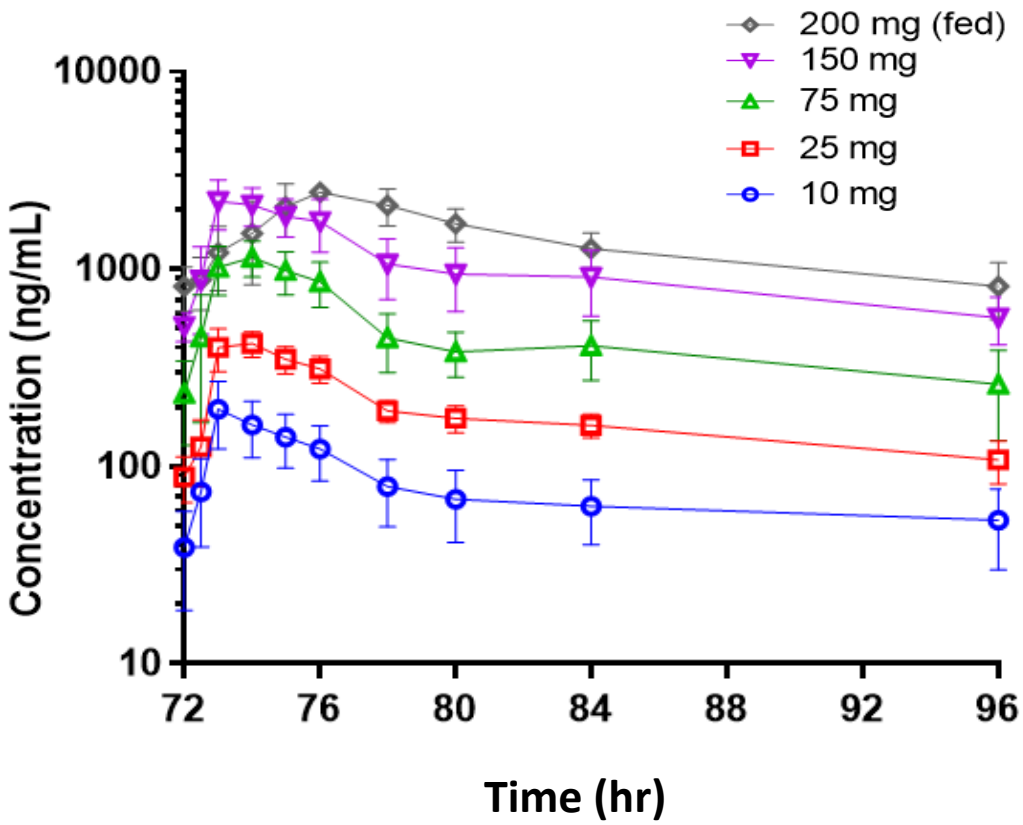
Design:

- 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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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

Only 12-15 patients expected to be enrolled in each dose-escalation trial based on the starting dose of 75 mg QD of AB928

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

First expansion cohorts expected to initiate by mid-2019

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Tumor Types Selected Based on Biological Rationale

Phase 1/1b program focuses on tumor types where the CD73-adenosine pathway is believed to play a particularly important role (vs. an "all comers" approach)

Trial protocol	Tumor types	T cell infiltration	High CD73 or TNAP* expression	ICD-inducing chemo is SOC
002 - **Breast and Gynecological Malignancies**	TNBC	✓	✓	✓
	Ovarian	✓	✓	✓
003- **Gastrointestinal Malignancies**	CRC	✓	✓	✓
	Gastroesophageal	✓	✓	✓
004 - **NSCLC**	NSCLC	✓	✓	✓

Anti-PD-(L)1 agents not currently approved (other than for CRC in MSI-h setting)

*TNAP, under some conditions, is also able to generate adenosine

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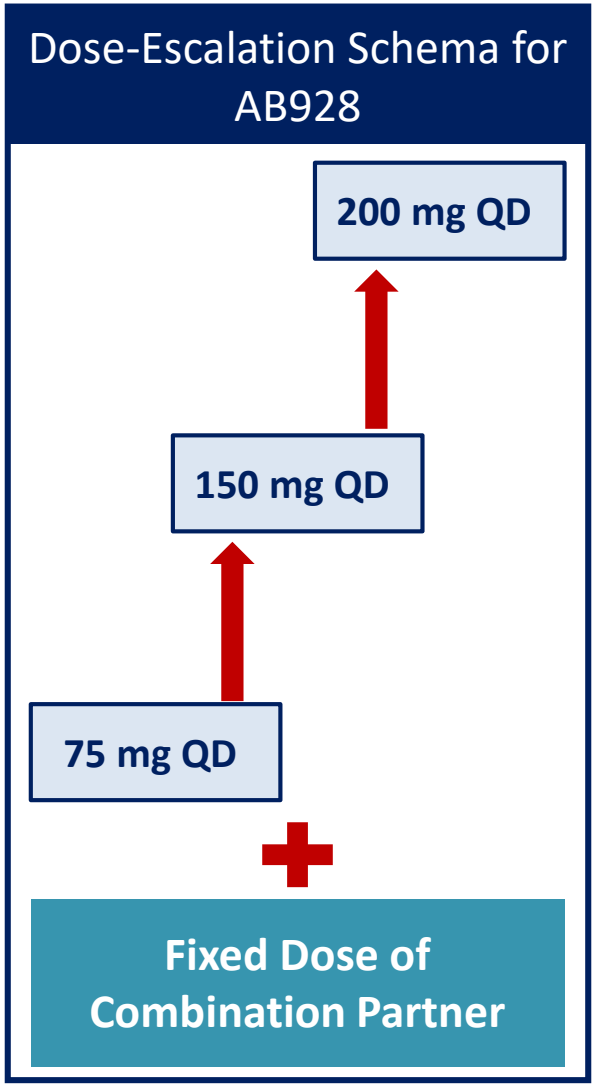
Design of the Four AB928 Combination Dose-Escalation Trials

	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)**



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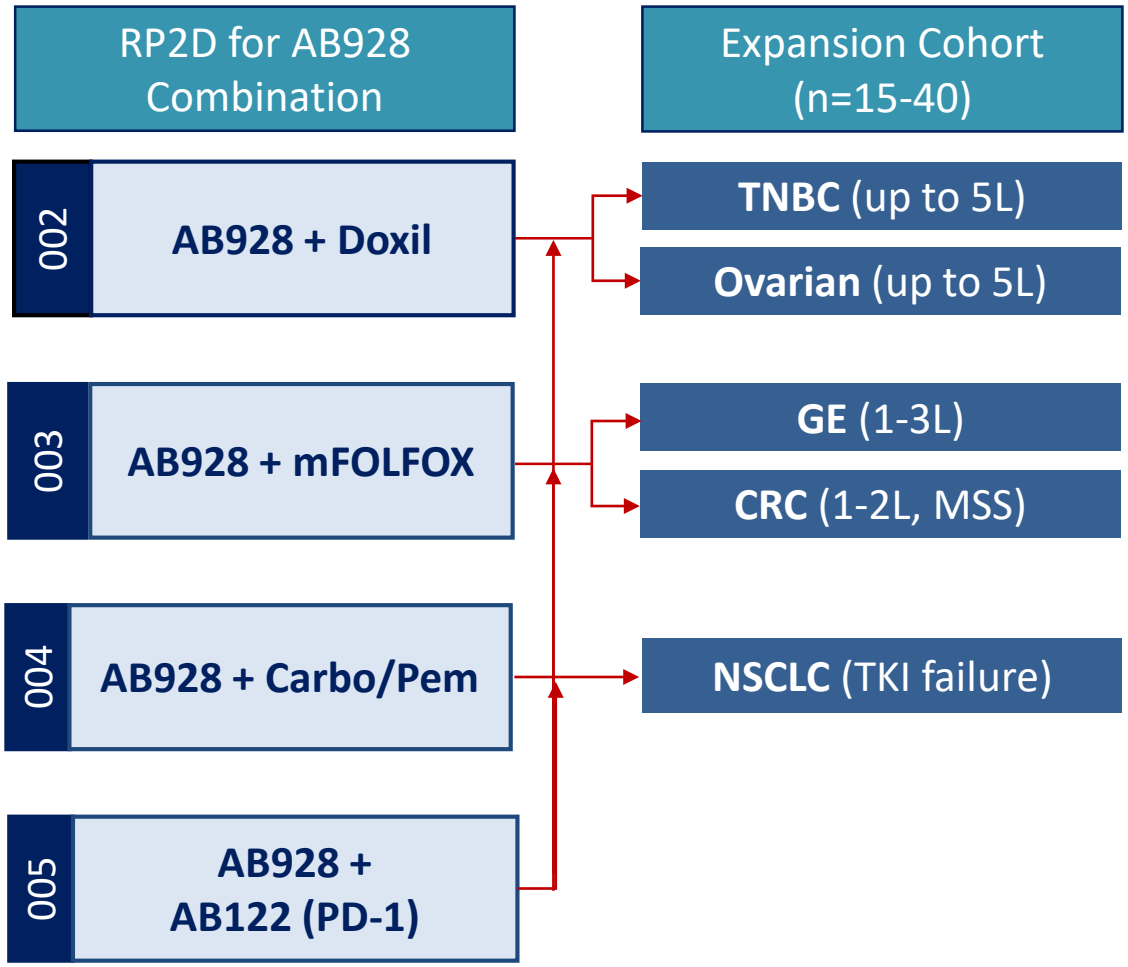
Following Identification of the RP2D for AB928, the First Expansion Cohorts Will Begin by Mid-2019



Adaptive 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

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Dose Escalation vs. Expansion Cohorts

	Dose Escalation	Expansion Cohorts
Tumor types to be enrolled:	**TNBC, Ovarian, CRC, GE, NSCLC**	**Same as the dose escalations**
Prior lines of therapy:	Up to 5 prior lines	Earlier lines will be explored
Biopsy requirements:	Pre-treatment (<6 months old); On-treatment biopsy to be performed if medically feasible	Same as the dose escalations
Design and target enrollment:	3+3 Design -- Currently targeting 3 cohorts (75 mg, 150 mg, 200 mg of AB928)	Enroll 15 patients and expand up to 40 based on achievement of threshold response rate
Status/timing:	Initial data expected in June 2019	First cohorts expected to initiate by mid-2019 – Initial data expected by 1H:20

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)	✓ Evaluate tumor and soluble CD73 as predictors of clinical activity; Assess potential of CD73 as a patient screening tool ✓ Determine relationship between soluble CD73, tumor CD73 expression and clinical activity
	PD-L1 status/TMB	✓ Assess relationship between clinical activity and PD-L1 or TMB
	Levels of other IC & inhibitory mediators	✓ Assess correlation between clinical activity and other inhibitory pathways
Immune markers	T cell clonality (tumor & PBMC) • neoE-specific clonal expansion	✓ Determine if there is a neoantigen-specific T-cell response
	Immunophenotyping (PBMC) and serum cytokines	✓ Quantify activation of immune pathways ✓ Assess effects on immune cell activity/function

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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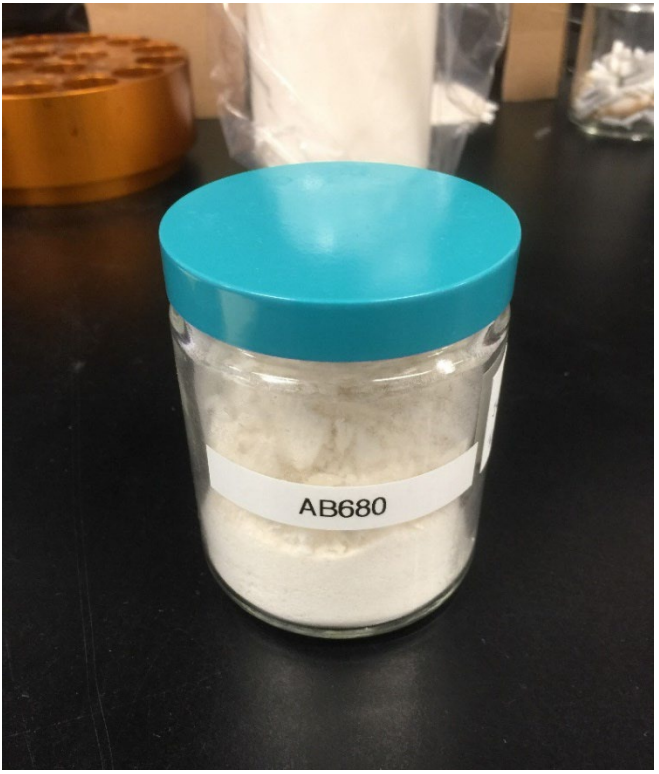
AB680: First Small Molecule CD73 Inhibitor to Enter Clinical Development



- 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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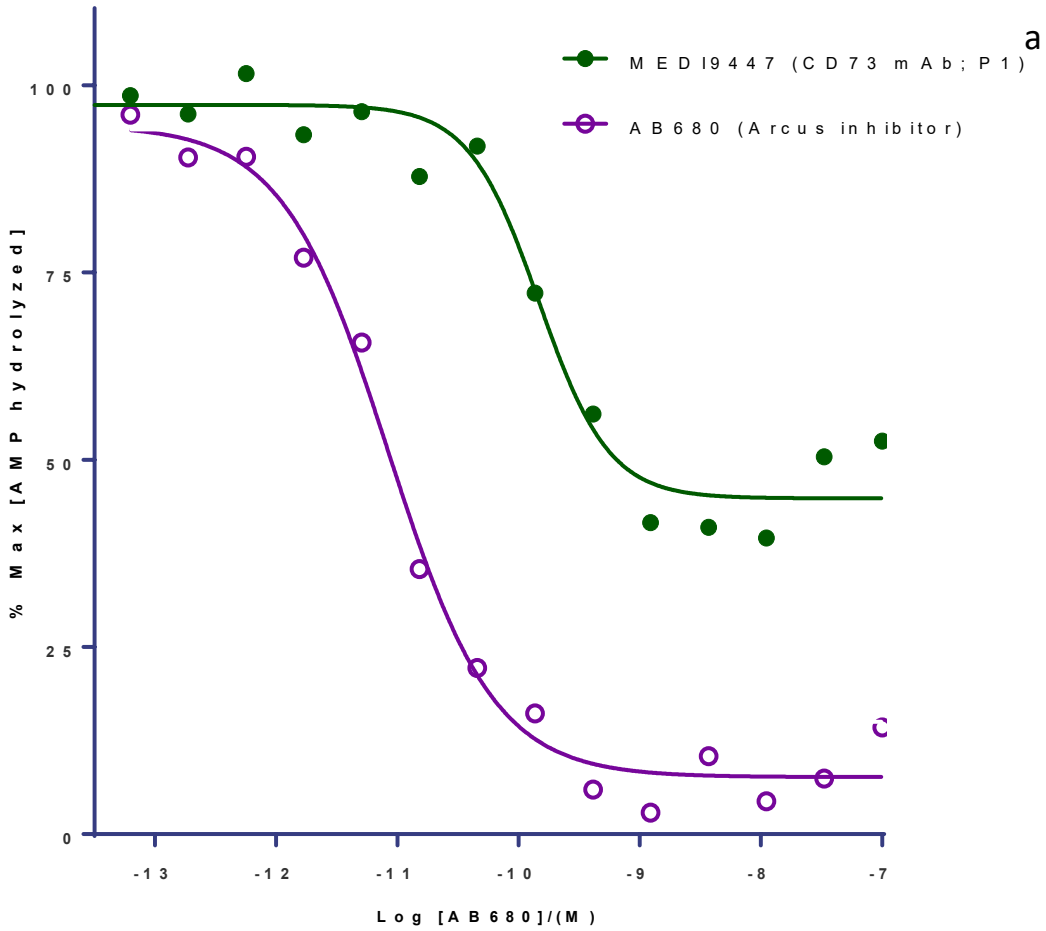
AB680 Potently Inhibits CD73 Enzymatic Activity on CD8+ T Cells

Representative data from various separate experiments shown



[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.

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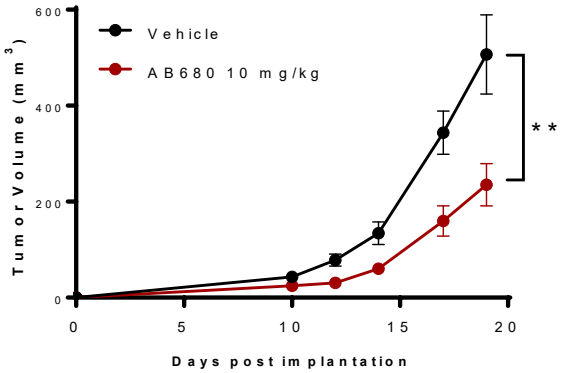
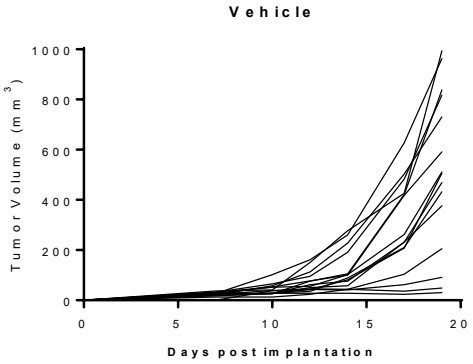
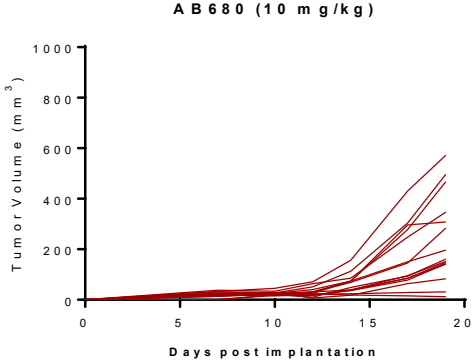
AB680 Reduces Tumor Growth in B16F10 Model as Monotherapy and in Combination with anti-PD-1

AB680 as Monotherapy

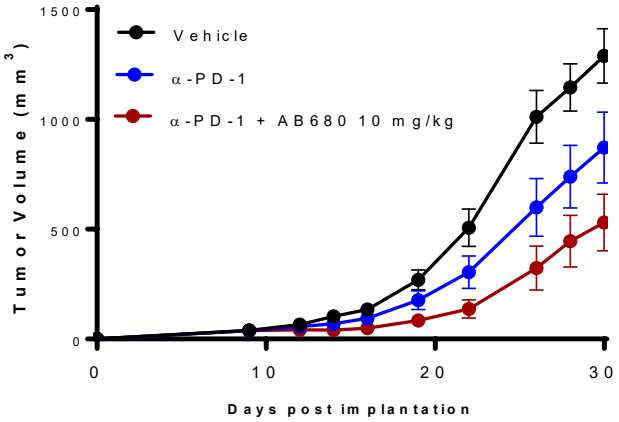


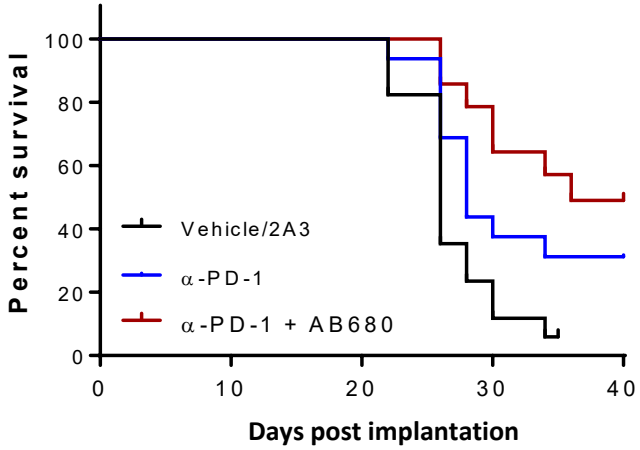




**p=<0.01

AB680 in Combination with anti-PD-1





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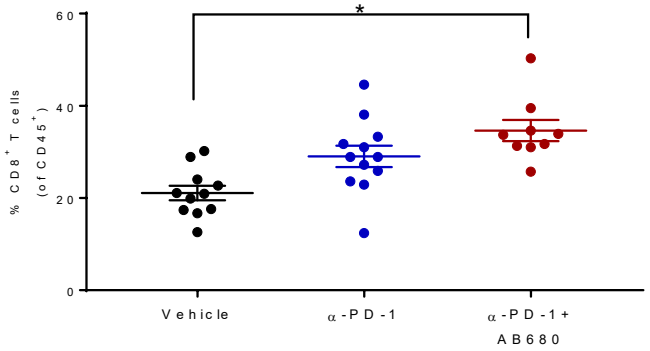
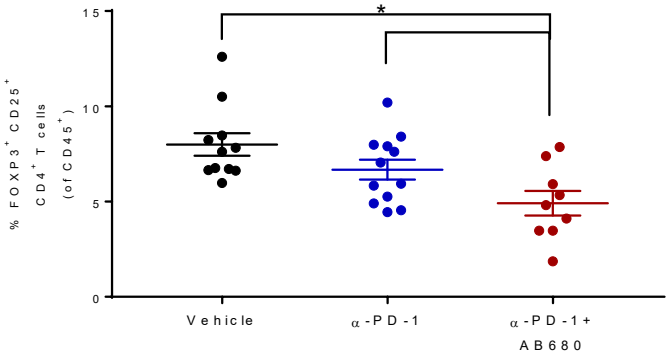
Combination of AB680 and anti-PD-1 Promotes a Shift Towards an Inflamed Tumor Microenvironment

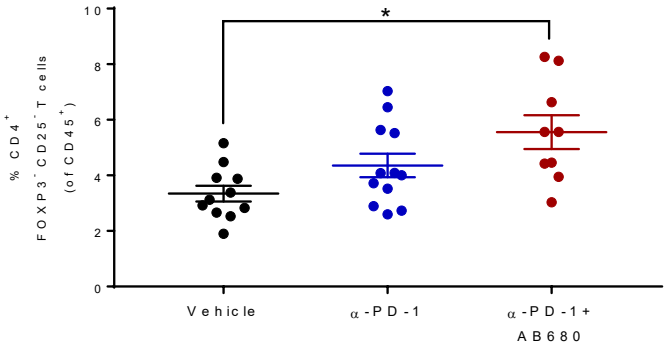
CD8+



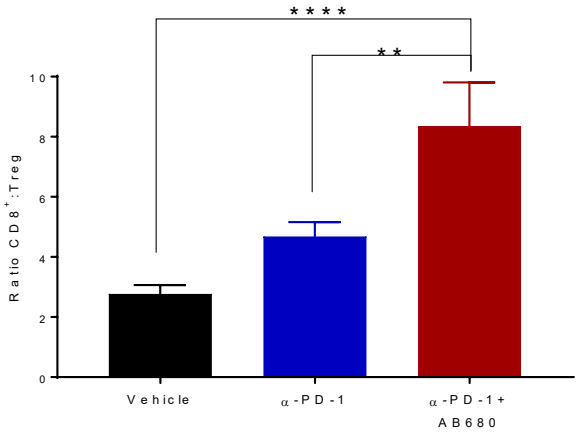
T-Regs



CD4+



CD8+ : T-Regs



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

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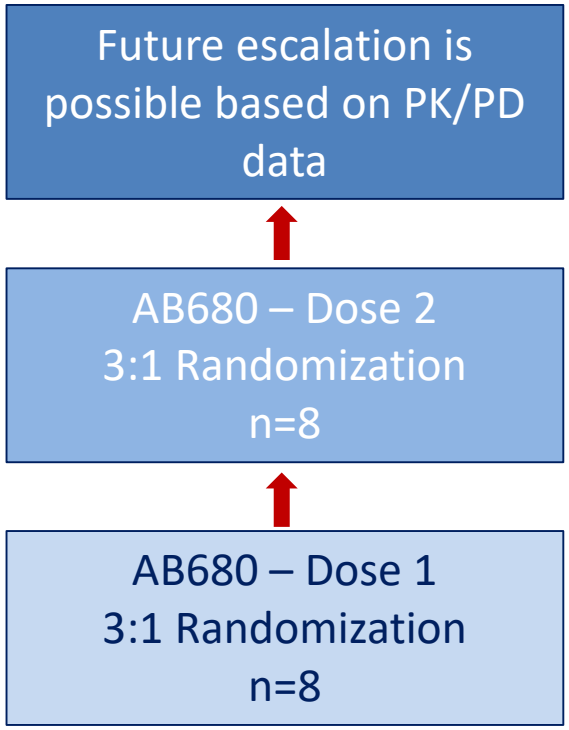
Healthy Volunteer Trial for AB680 is Enrolling

AB680 Dose Escalation in HV's



Key objectives

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

Next Steps

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

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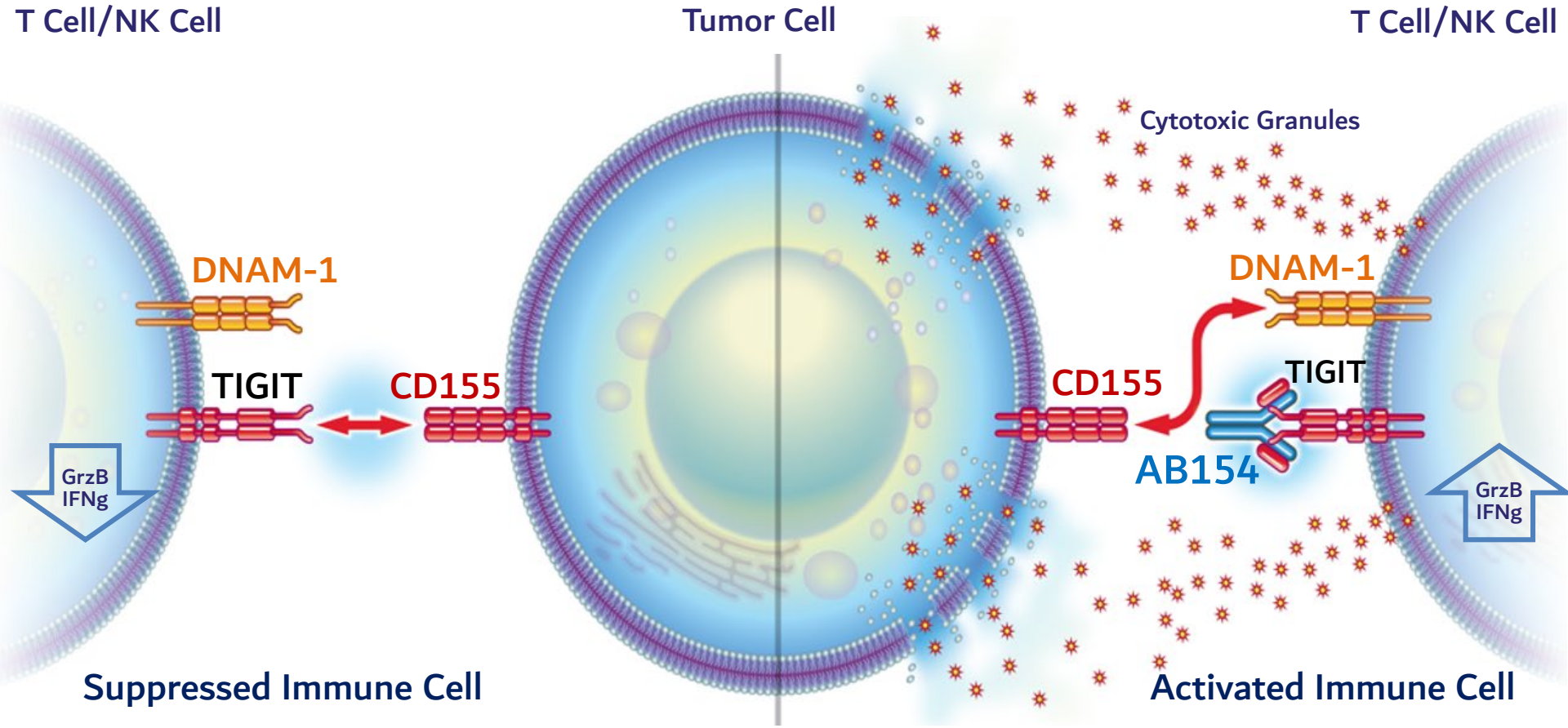
AB154 Has a Dual Mechanism of Action that Reflects the Uniqueness of the TIGIT Pathway

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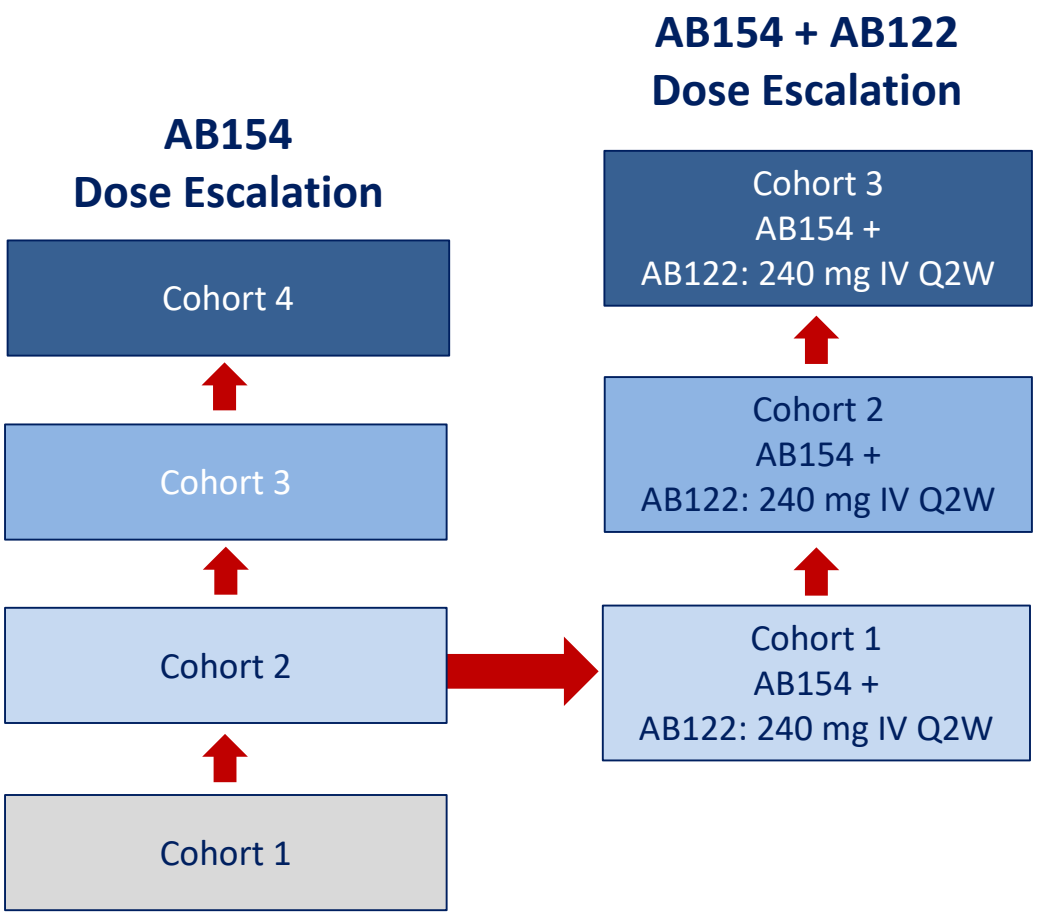
Phase 1/1b Dose Escalation Trial of AB154 + AB122



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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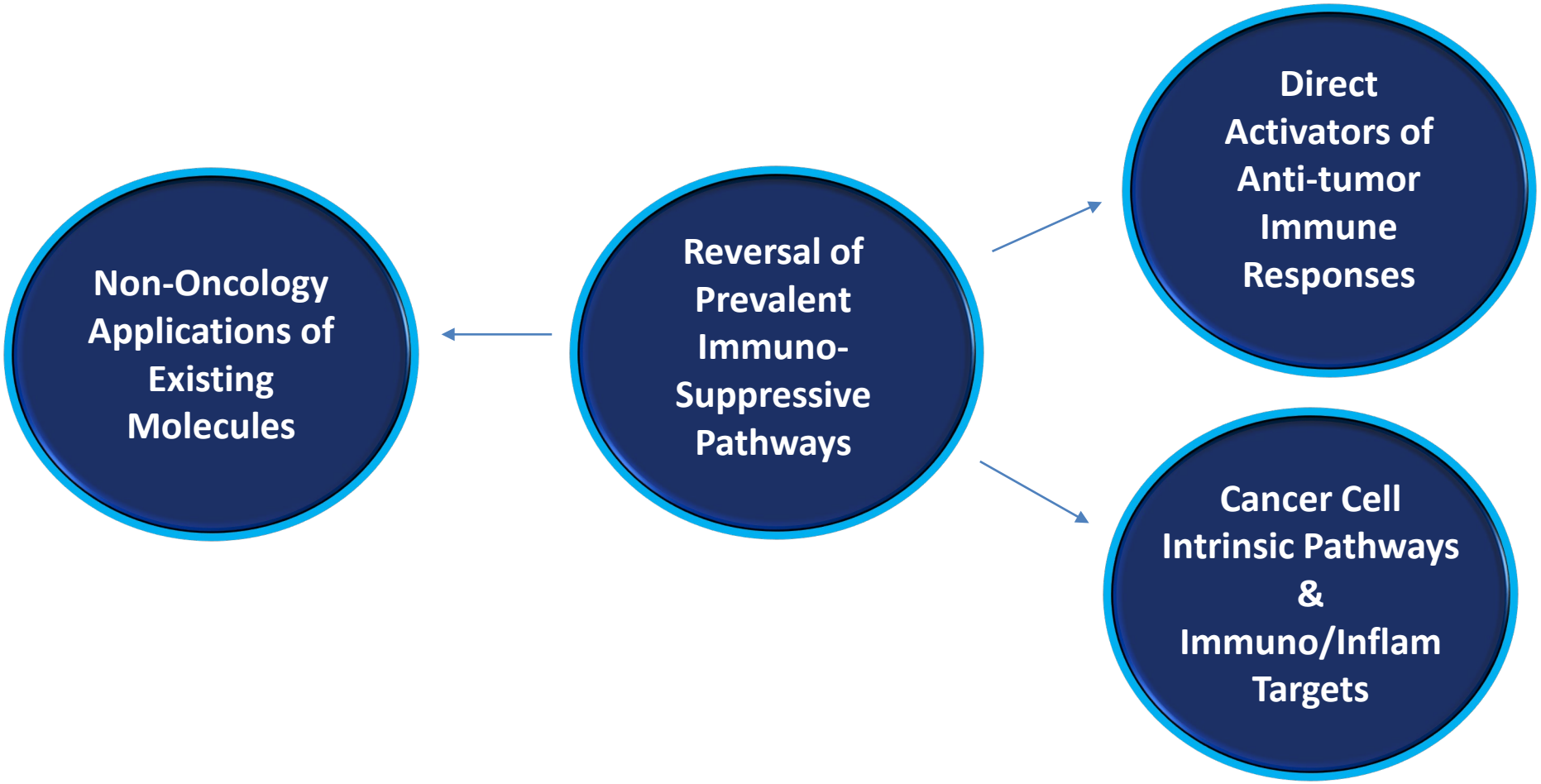
Active Early Stage Discovery Effort Focused on Small Molecule Pipeline Expansion

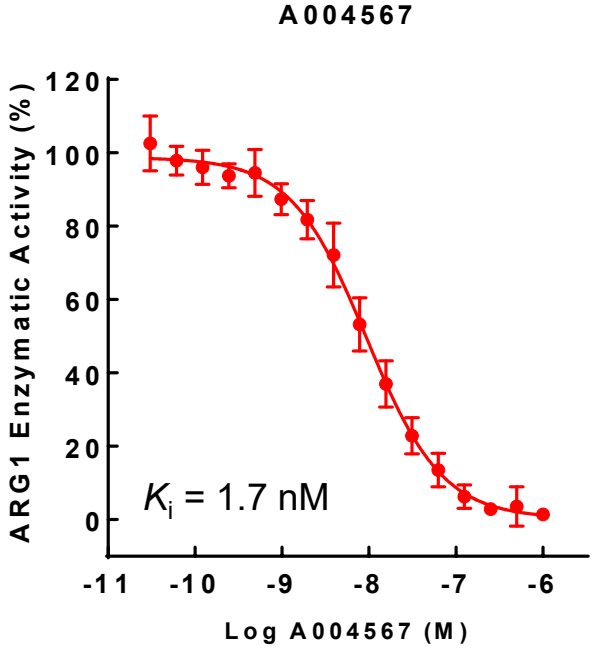
Arcus is leveraging its small molecule expertise to continue creating best-in-class and/or first-in-class product candidates



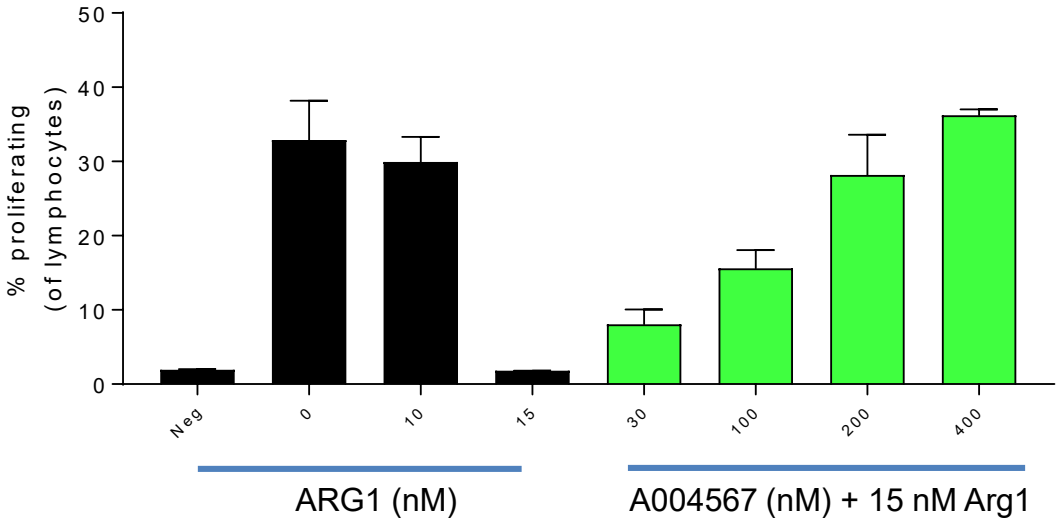
Illustrative Discovery Program: ARG1

Current ARG1 lead, A004567, has demonstrated highly potent inhibition of human ARG1 and reversal of ARG1-mediated repression of T cells

Inhibition of human ARG1



Rescue of ARG1-mediated repression of $CD8^+$ T cell proliferation





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Anticipated Milestones

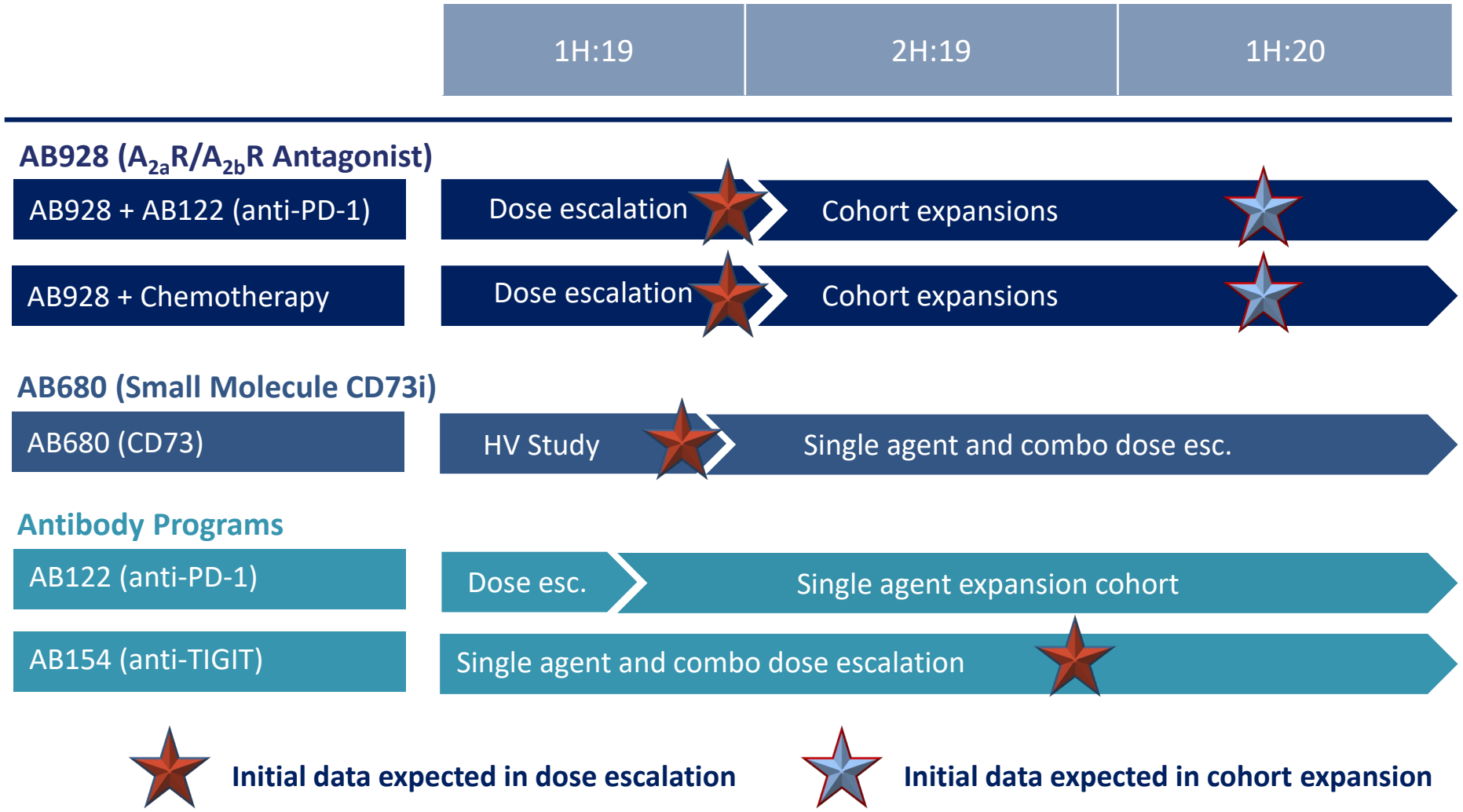
Strong Cash Position; Funding into 2021

- 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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Appendix

Summary of Related Treatment-Emergent AE - MAD

MedDRA preferred term	MAD cohorts (qd dose x 4)						
	Placebo N = 10 n (%)	AB928 treatment					
		10 mg N = 6 n (%)	25 mg N = 6 n (%)	75 mg N = 6 n (%)	150 mg N = 6 n (%)	200 mg fed N = 6 n (%)	Total N = 30 n (%)
Nausea	1 (10)	0	1 (17)	2 (33)	1 (17)	1 (17)	5 (17)
Abdominal pain	1 (10)	1 (17)	2 (33)	1 (17)	1 (17)	1 (17)	6 (20)
Headache	1 (10)	0	0	0	1 (17)	2 (33)	3 (10)
Abdominal distension	0	0	1 (17)	1 (17)	0	1 (17)	3 (10)
Constipation	0	1 (17)	0	1 (17)	0	1 (17)	3 (10)
Chest pain	0	0	1 (17)	0	0	0	2 (7)
Dizziness	1 (10)	0	1 (17)	1 (17)	1 (17)	0	3 (10)
Feeling jittery	0	0	0	0	0	0	0
Insomnia	0	0	0	0	0	0	0
Pollakiuria	0	0	0	0	0	0	0
Diarrhea	1 (10)	0	0	0	2 (33)	0	2 (7)
Palpitations	0	0	0	0	0	2 (33)	2 (7)
Hot flush	0	0	0	0	0	2 (33)	2 (7)

MAD, multiple-ascending dose; MedDRA, Medical Dictionary for Regulatory Activities; qd, once daily; Source Seitz, L., Jin, L., Leleti, M. et al. Invest New Drugs (2018). https://doi.org/10.1007/s10637-018-0706-6

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