

Creating Innovative Cancer Immunotherapies by Leveraging Underexploited Biological Opportunities

November 2018

NYSE: RCUS

ARCUS BIOSCIENCES

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ARCUS BIOSCIENCES

Corporate Overview

Our Portfolio

- ATP-Adenosine Pathway Programs
- Antibody Programs

Anticipated Milestones

Creating Innovative Cancer Immunotherapies

We are creating highly differentiated small molecule therapies based on our deep understanding of immuno-oncology pathways

- Four clinical candidates – Initial combination dose-escalation data expected in 1H:2019
- Small molecule discovery engine able to drive 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



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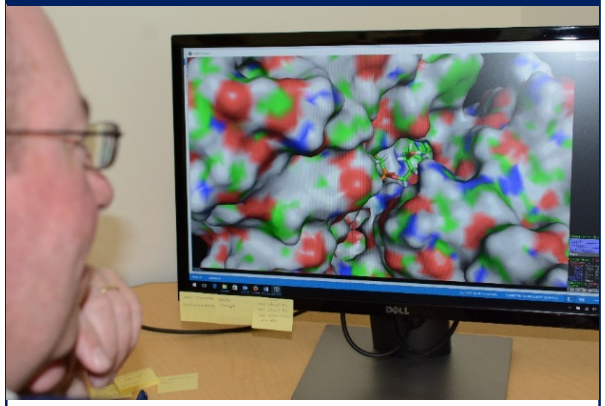
Our Competitive Advantages

Best-in-Class Chemistry



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

Portfolio Breadth

Dual and Selective A_2R Antagonists

- AB928 (Dual A_2R)
- AB745 ($A_{2a}R$)

Small Molecule CD73 Inhibitors

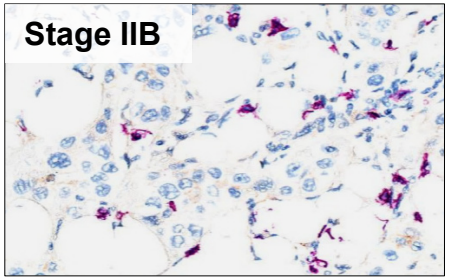
- AB680 (IV and Oral)

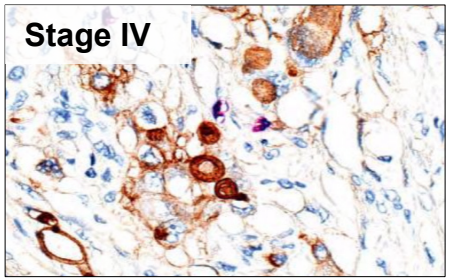
Antibody Programs

- AB122 (anti-PD-1)
- AB154 (anti-TIGIT)

Enables development of multiple intra-portfolio combinations

Translational Medicine





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

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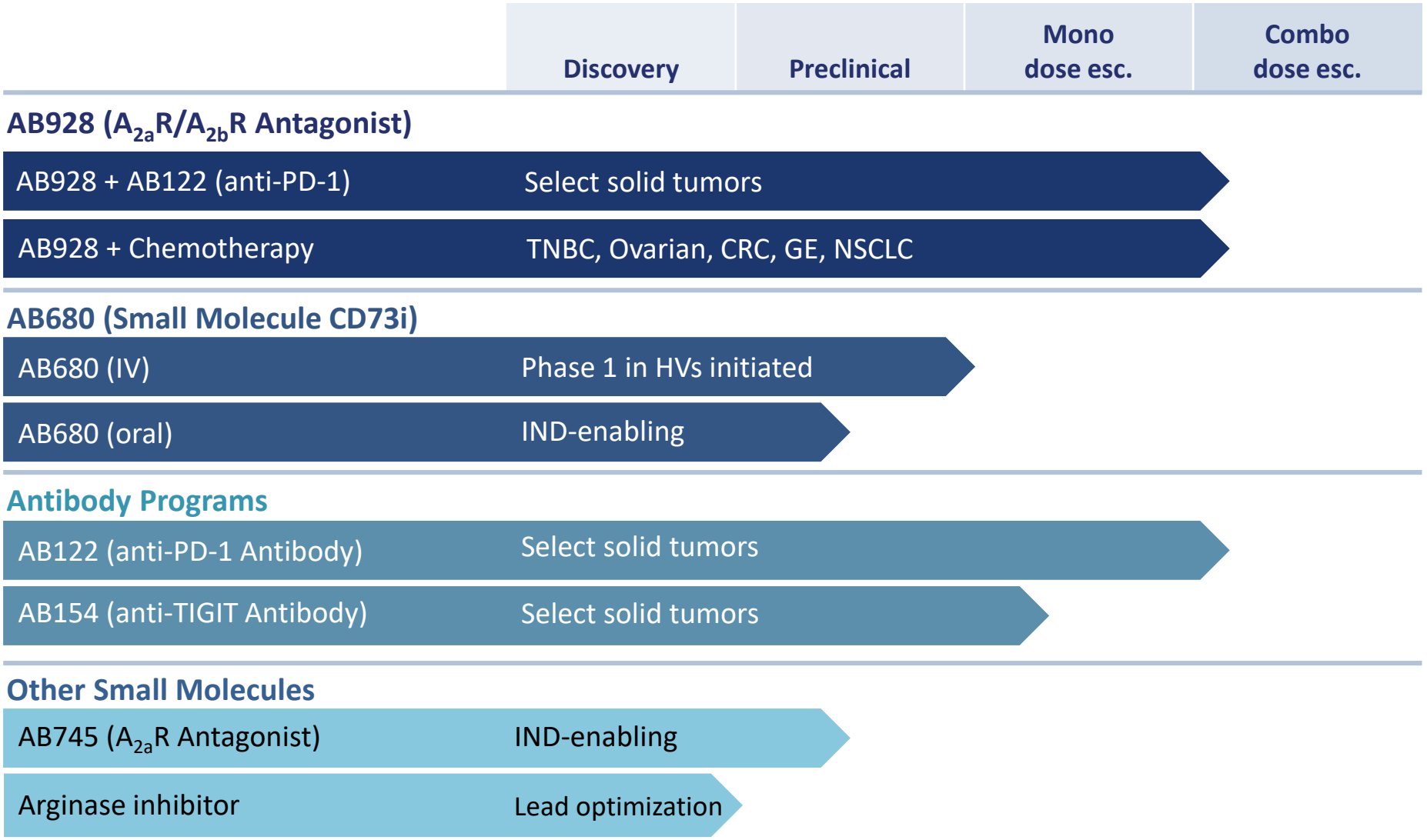
Arcus Has Rapidly Created a Broad Portfolio of Immuno-Oncology Programs



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Corporate Overview

Our Portfolio

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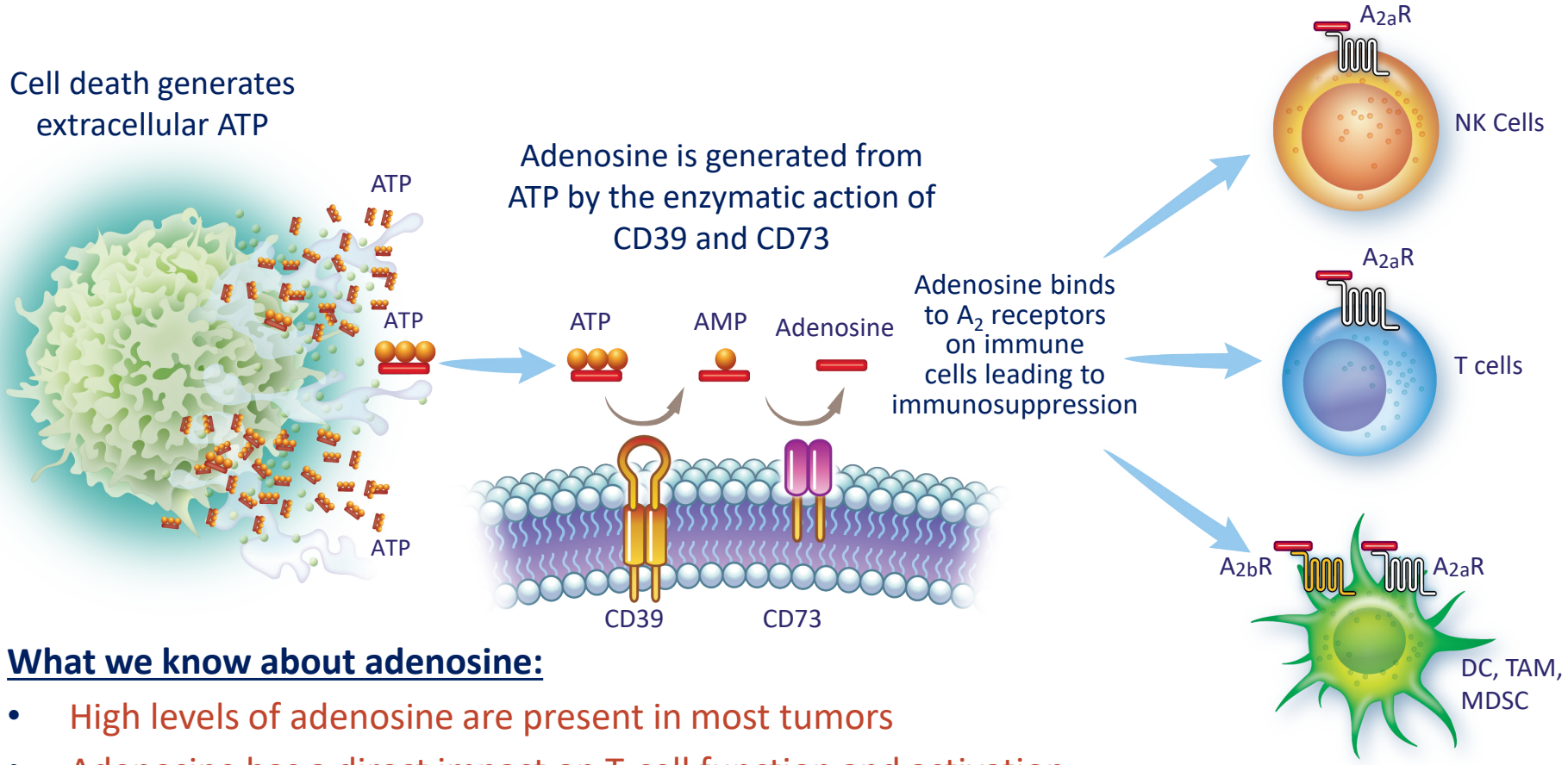
- Antibody Programs

Anticipated Milestones

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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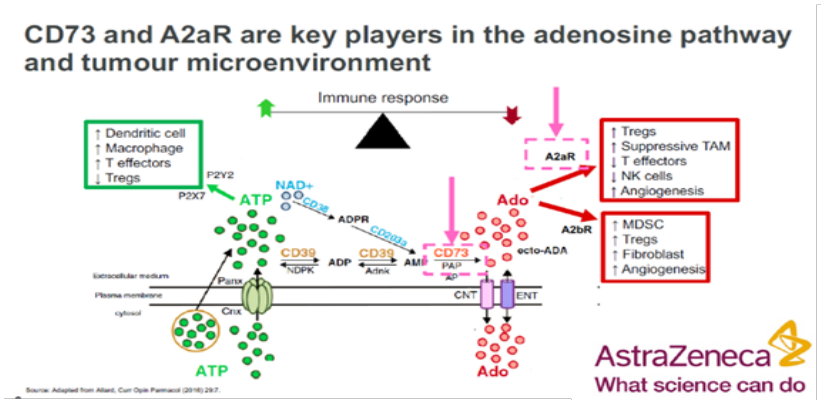
Significant Investment in the CD73-Adenosine Space with Datasets Emerging

ASCO 2018 investor event; breakout 4: Next-gen Immuno-Oncology



Bristol-Myers Squibb

Research from Bristol-Myers Squibb's Innovative Oncology Development Program to Be Presented at AACR 2018 Demonstrates Commitment to Advancing Precision Medicine Research for Patients with Cancer

breaking or oral presentations, across seven therapeutic areas. Abstracts to be presented include the first disclosure of data from the Phase 3 CheckMate -227 trial evaluating the combination of *Opdivo* plus *Yervoy* (ipilimumab) in first-line non-small cell lung cancer patients with high tumor mutational burden (≥10 mutations/megabase), as well as two-year overall survival data from pivotal studies of *Opdivo* in bladder and head and neck cancers. The Company will also present the first clinical data on its investigational anti-CD73 antibody in combination with *Opdivo*.

Meeting Abstracts

Phase I/II study of the A2AR antagonist NIR178 (PBF-509), an oral immunotherapy, in patients (pts) with advanced NSCLC.

AACR American Association for Cancer Research ANNUAL MEETING 2018 CHICAGO, IL

CT180

Preliminary Phase 1 Profile of BMS-986179, an Anti-CD73 Antibody, in Combination With Nivolumab in Patients With Advanced Solid Tumors

Lillian L. Siu,[1] Howard Burris,[2] Dung T. Le,[3] Antoine Hollebecque,[4] Neeltje Steeghs,[5] Jean-Pierre Delord,[6] John Hilton,[7] Bryan Barnhart,[8] Emanuela Sega,[8] Kinjal Sanghavi,[8] Anke Klippel,[8] Cyrus Hedvat,[8] Ed Hilt,[8] Mark Donovan,[8] Adrianna Gipson,[8] Paul Basciano,[8] Jennifer Postelnek,[8] Yue Zhao,[8] Raymond P. Perez,[8] Richard D. Carvajal[9]

Source: https://news.bms.com/press-release/corporatefinancial-news/research-bristol-myers-squibbs-innovative-oncology-development; http://cancerres.aacrjournals.org/content/78/13_Supplement/CT180; https://www.astrazeneca.com/content/dam/az/Investor_Relations/ASCO%202018%20Investor%20Event%20-%20Breakout%204.pdf

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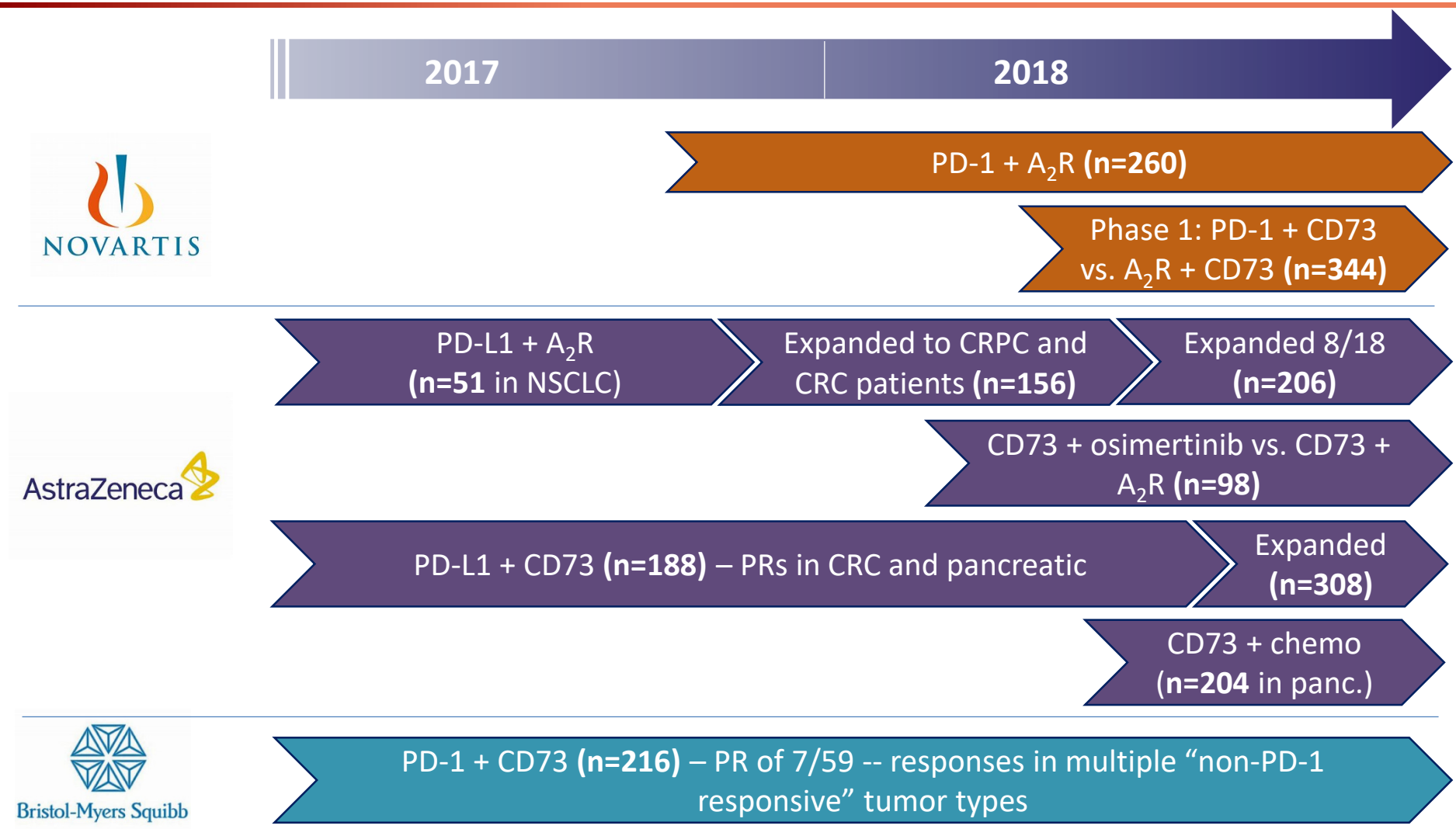
Companies Are Expanding Their CD73-Adenosine Efforts



Source: https://clinicaltrials.gov/

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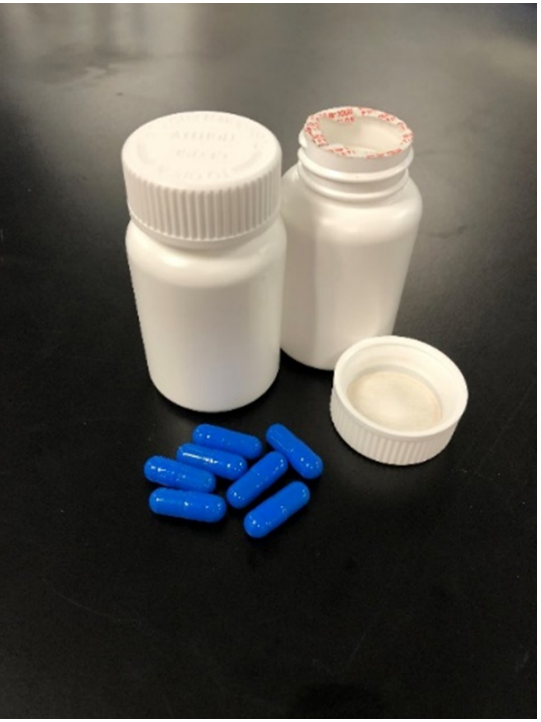
AB928 Represents a Potentially Best-in-Class Adenosine Receptor Antagonist



- 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

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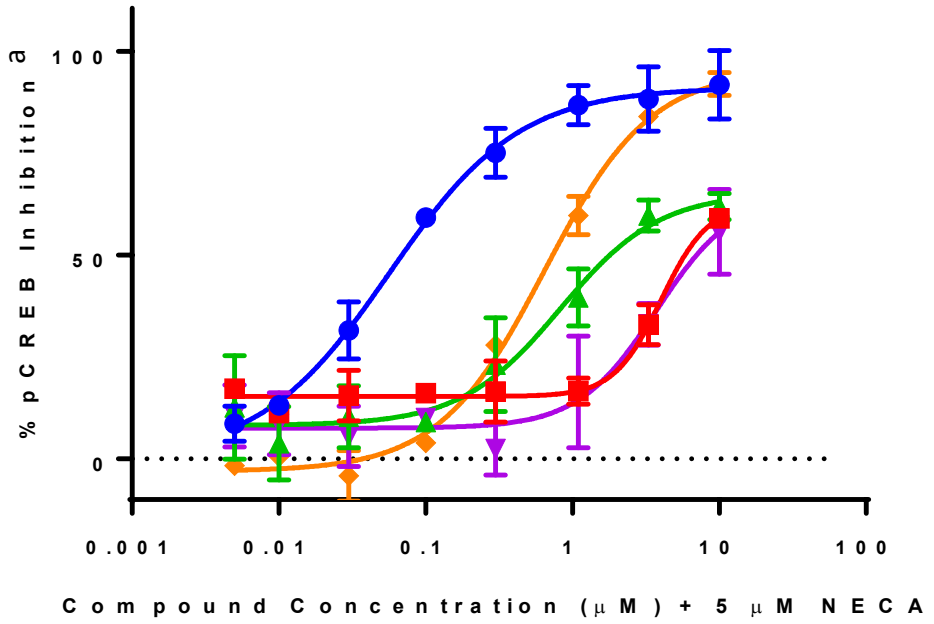
AB928 is the Most Potent Antagonist of $A_{2a}R$ Receptors When Tested in a Whole Blood Assay

$A_{2a}R$ 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 Also 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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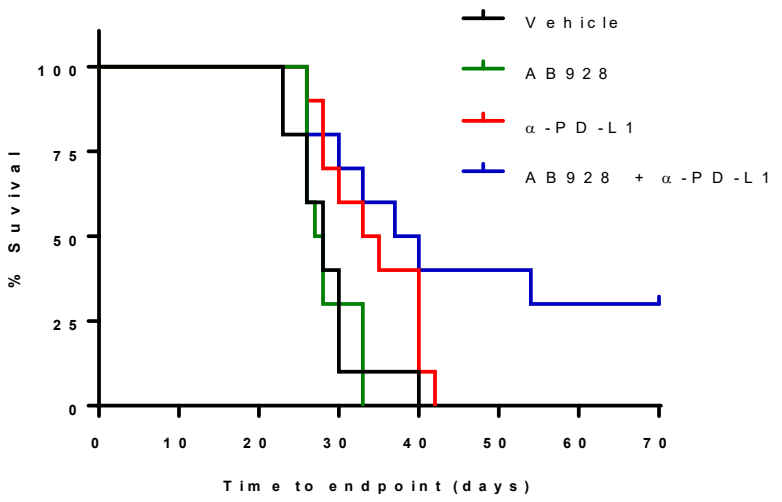
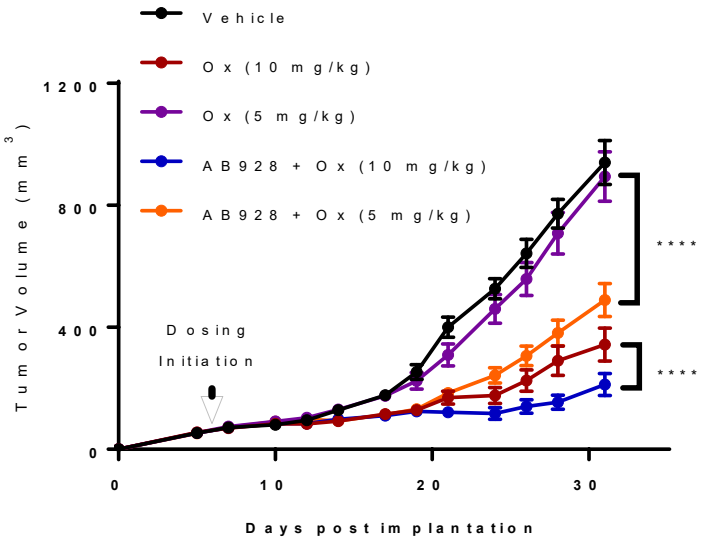
AB928 is Synergistic with anti-PD-L1 and Chemotherapy in Mouse Models

MC38 mouse model (in combination with anti-PDL1 antibody)



AT-3 OVA mouse model (in combination with Oxaliplatin)



**** statistically significant ($p<0.0001$)

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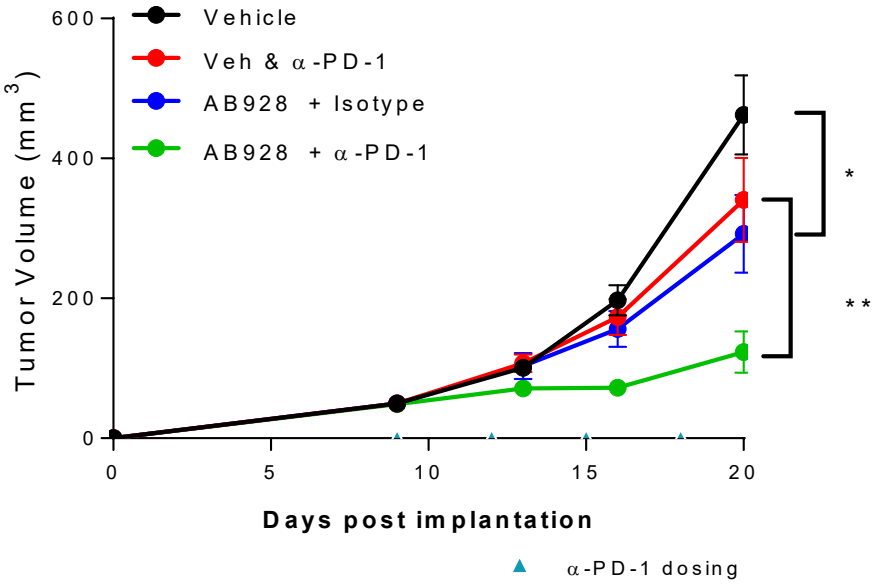
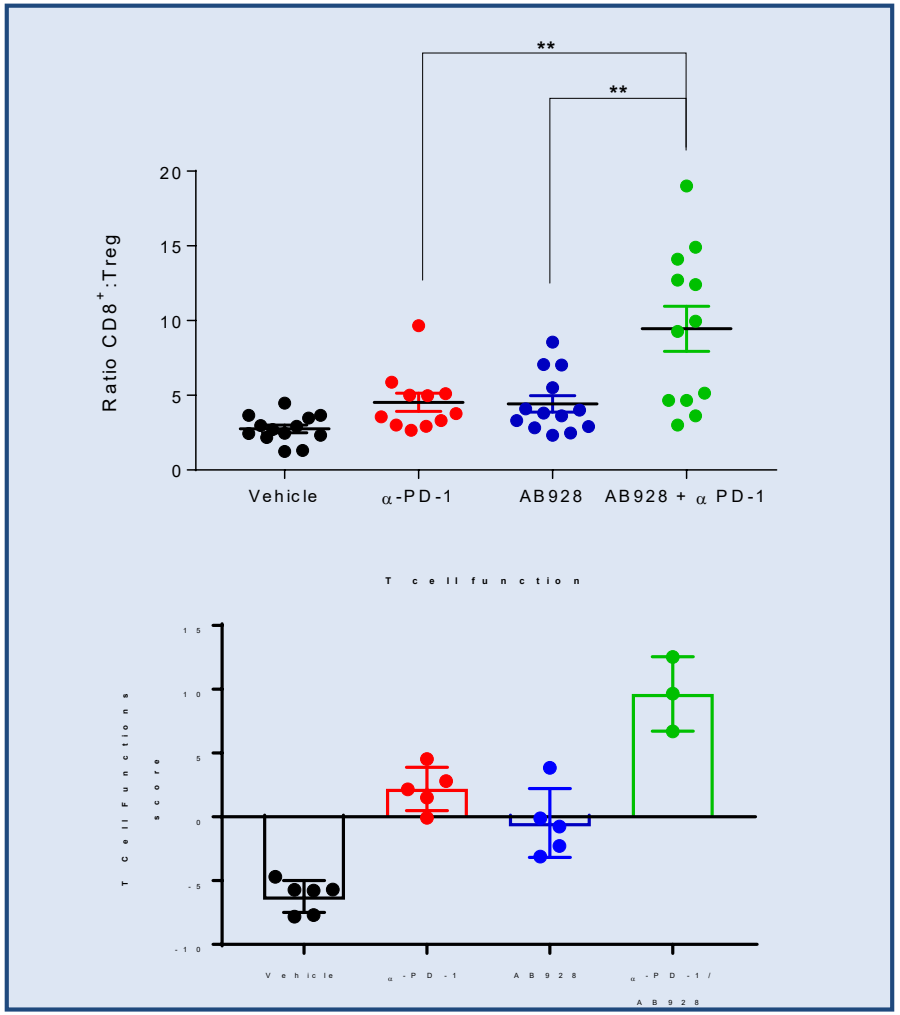
And Combining AB928 With Anti-PD-1 Significantly Improves the Immune Cell Profile and T-Cell Function

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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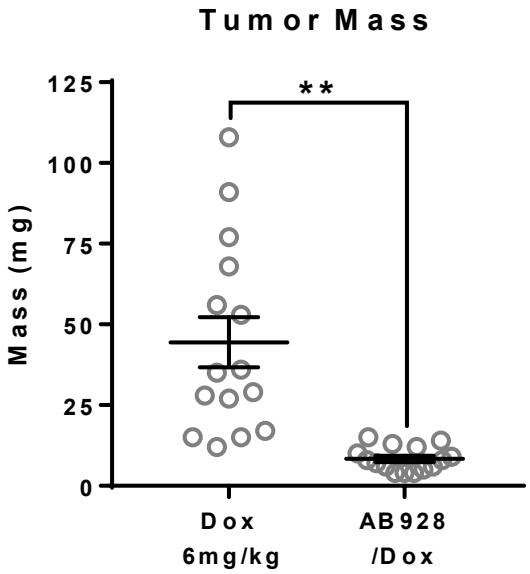
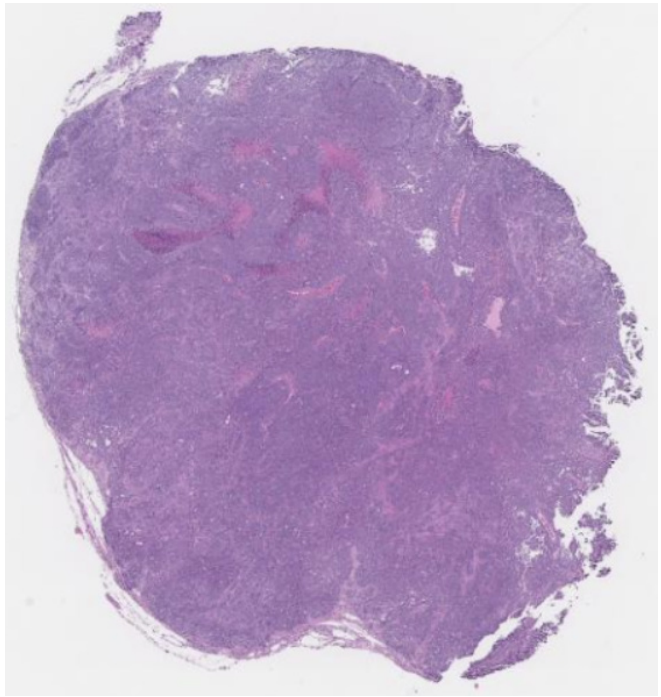
AB928 + Doxorubicin Induce Reduced AT-3 OVA Tumor Growth and Enhanced Immune Cell Infiltration

Example images representing the average tumor mass from each group

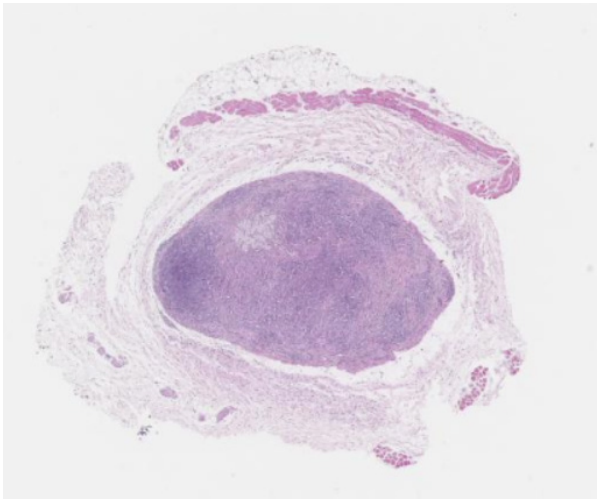


Note: Dosing started day 14 post tumor inoculation

Vehicle + Dox (53 mg tumor)



AB928 + Dox (8 mg tumor)



Tumors treated with only doxorubicin exhibit homogenous, densely packed tumor mass, whereas those 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
- 80 subjects randomized 3:1 to AB928 or placebo
- Included SAD and MAD portions
- MAD portion evaluated once-daily doses of 10, 25, 75 and 150 mg and 200 mg (with food) administered for four consecutive days

Safety Results:

- ✓ AB928 was well tolerated, even at the highest dose evaluated
- ✓ No AEs appeared to be dose dependent and no dose limiting toxicities prevented escalation to higher doses
- ✓ All reported AEs were characterized as low-grade, with the majority being Grade 1 events
- ✓ No variations in heart rate or blood pressure not considered within normal parameters

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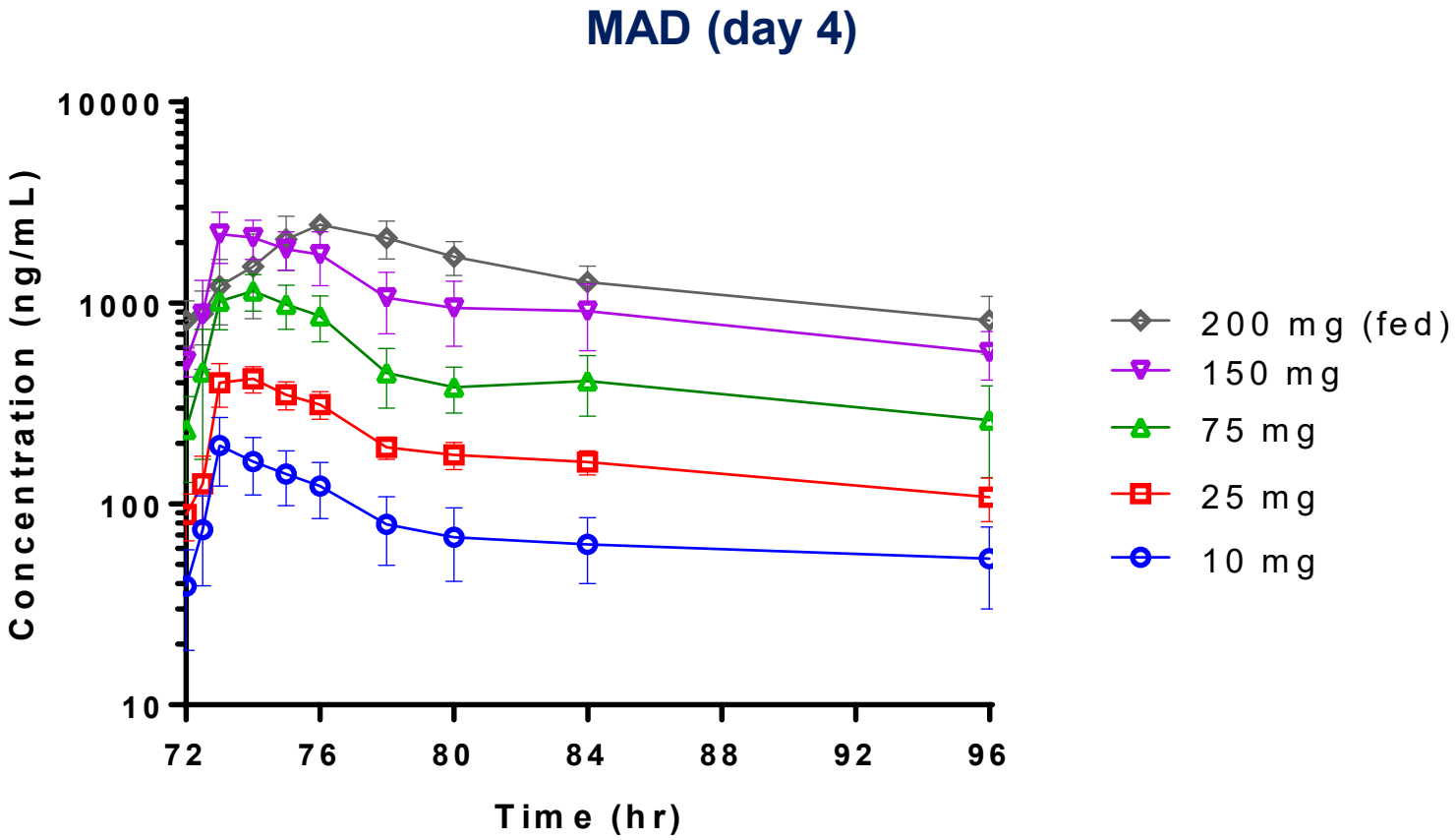
Phase 1 Trial in HVs Demonstrated an Excellent PK Profile



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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%**

- T_{max} for first 4 cohorts (fasted) was 1-2h; T_{max} for 200 mg qd (fed) was ~4h.
- Shown are official plasma levels from CRO
- Some or all dosed subjects were within the range of variation observed in placebo subjects (-39 to 30%).

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Phase 1/1b Program for AB928 is Underway

Approach to Phase 1/1b

- Focus on tumor types where the A_2R pathway appears to play a critical role
- Initially targeting tumor types with low response rates to PD-1 therapy
- Dose escalation to be conducted in the same tumor types as the expansion cohorts
- **Biomarker analysis planned to evaluate correlation with clinical activity/inform early decisions**

Platform Trial Design

- ✓ Allows for incorporation of new AB928 combinations, including triplets
- ✓ Should enable direct comparison of combinations in the same tumor type
- ✓ Should enroll a more uniform patient population
- ✓ Ability to expand/terminate cohorts based on data
- ✓ **Potential to add an SOC arm as a comparator**

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Initial AB928 Combination Partners Selected Based on Strong Scientific Rationale

Focused on combination partners that are currently SOC for targeted tumor types

Anti-PD-1



- $A_{2a}R$ activation induces signaling & transcriptional changes in T cells, preventing their activation
- Adenosine formation believed to play a role in the development of PD-1 resistance

ICD-inducing chemotherapy



- Certain chemotherapies, e.g., oxaliplatin & doxorubicin, induce immunogenic cell death (ICD)
- Results in the release of ATP which is converted into adenosine, causing significant immuno-suppression

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Four AB928 Combination Dose-Escalation Trials Have Been Initiated

Starting dose of AB928 for each dose escalation will be 75 mg QD, followed by 150 mg and 200 mg – only 12-15 patients expected to be required per trial to identify the RP2D

Trial protocol	Tumor types	AB928 Combo partner	Status	Target initial/prelim data presentation
002	Ovarian TNBC	Doxil®	Enrolling	1H:19
003	GE Colorectal	mFOLFOX	Enrolling	
004	NSCLC	Carbo/pem + Pembro	Initiated	
005	Multiple solid tumor types	AB122 (anti-PD-1)	Enrolling	

First Expansion Cohorts Expected to Initiate in mid-2019

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Tumor Types Selected Based on Biological Rationale

Evaluating settings in which the ATP-adenosine pathway is believed to play an important immunosuppressive role in three "tumor-specific" platform trials

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
**RCC expansion cohort would be conducted in the AB928 + AB122 protocol

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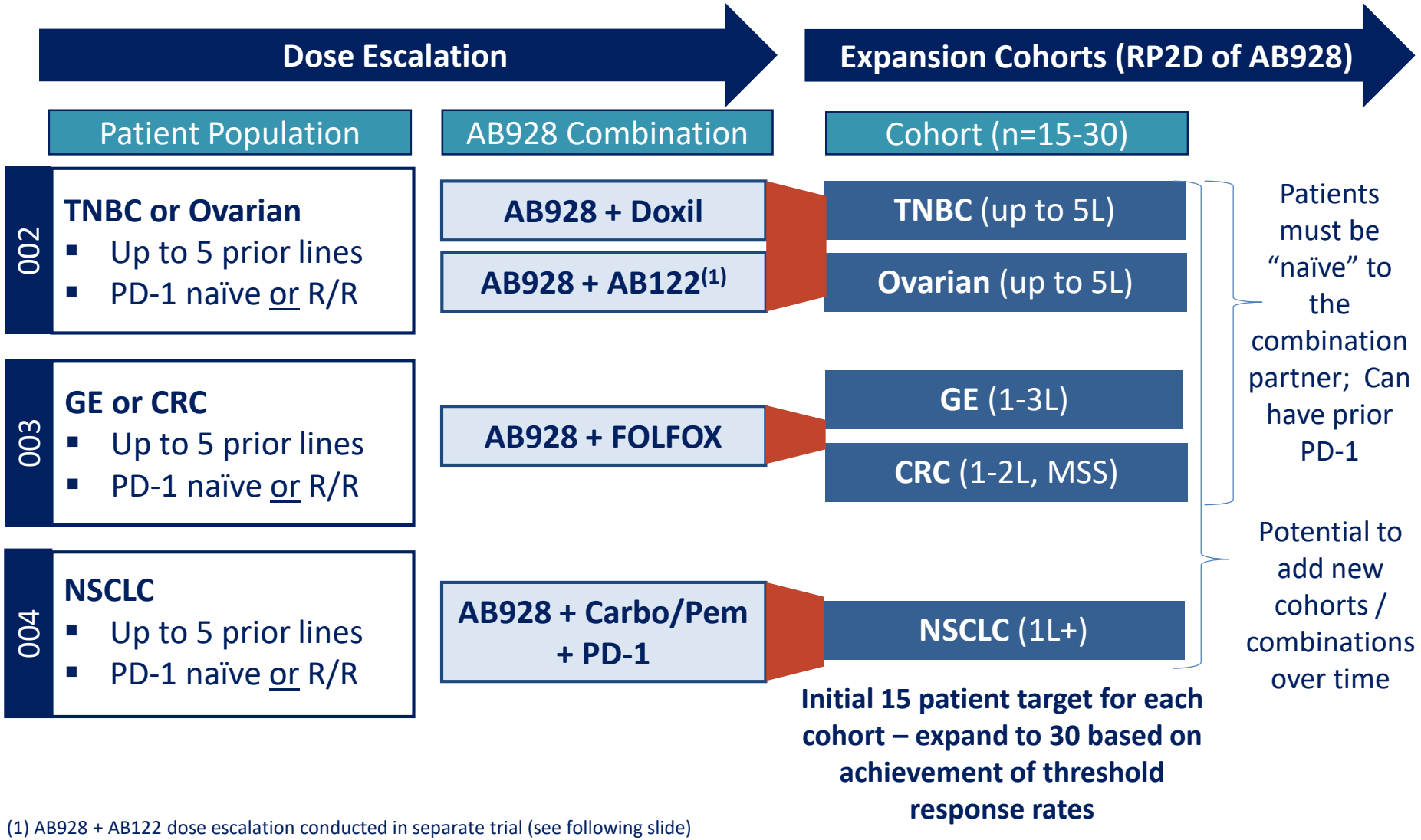
Design of AB928 Combination Trials (002, 003 and 004 Protocols)



(1) AB928 + AB122 dose escalation conducted in separate trial (see following slide)

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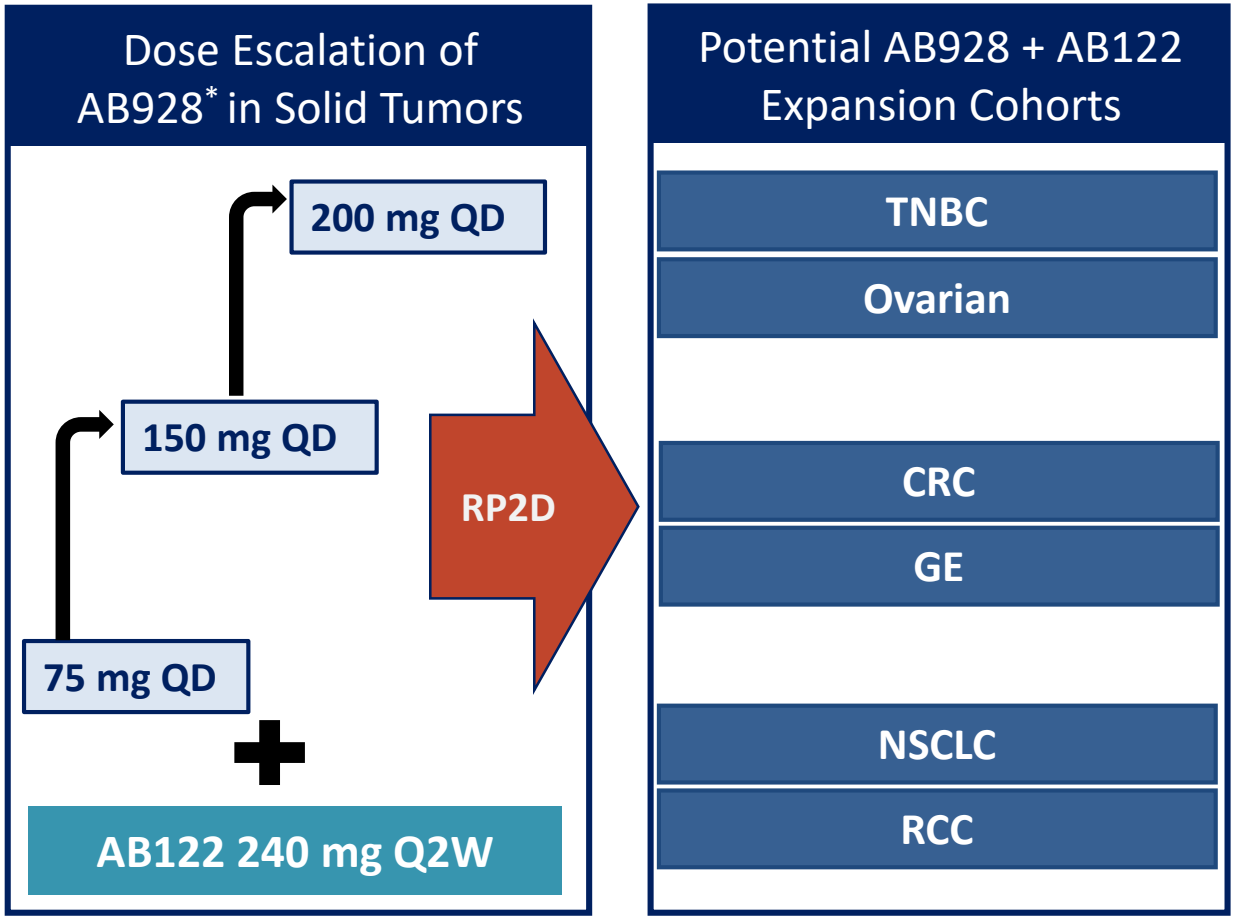
Dose-Escalation Trial for AB928 + AB122 (005 Protocol)



AB928 + AB122 cohorts to be incorporated into trials on previous slide

Key Objectives

- Safety and tolerability
- Biomarker analysis to evaluate correlation with clinical activity
- Anti-tumor activity

* Protocol also allows for evaluation of intermediate doses

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Extensive Biomarker Plan for Phase 1/1b Program

	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 (tumor and/or blood)	✓ 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 cells populations ✓ Assess effects on immune cell activity/function

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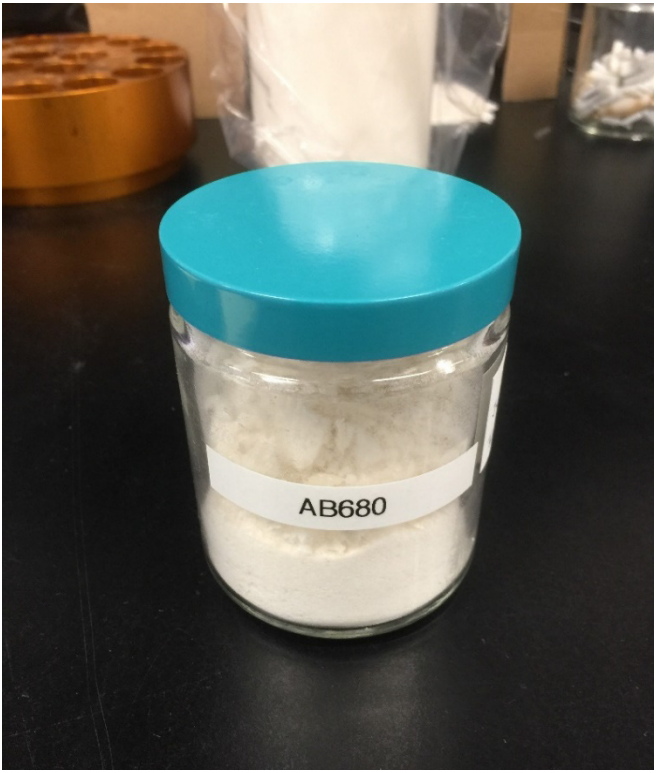
AB680: First Small Molecule CD73 Inhibitor to Enter Clinical Development



- 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
  - 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 early 2019
- Oral formulation in IND-enabling studies

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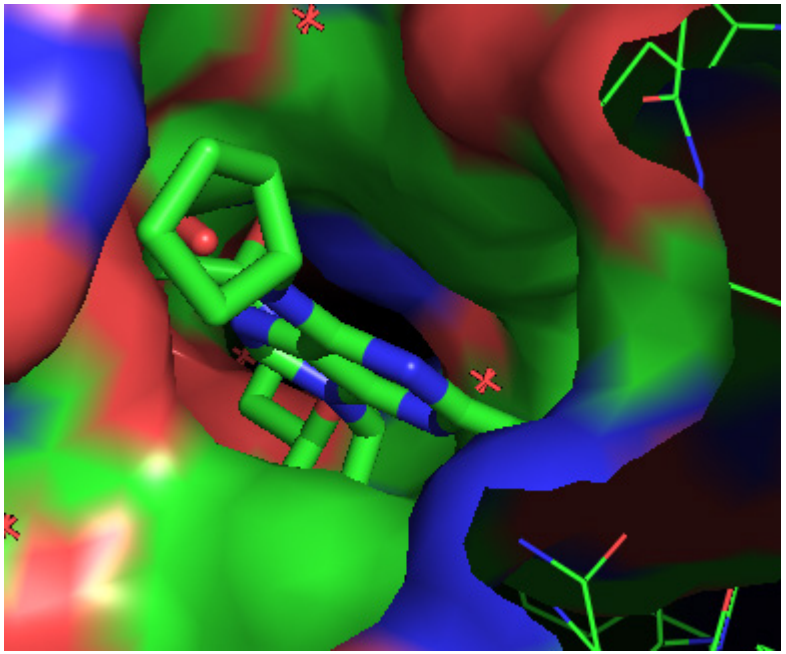
Structure-Based Design Process Resulted in AB680, an Extraordinarily Potent CD73 Inhibitor

Collaboration with Professor Norbert Sträter (University of Leipzig)

A000934
hCD73 (CHO cells)
IC_{50} = 26 nM



AB680
IC_{50} = 0.008 nM
(human T cells)

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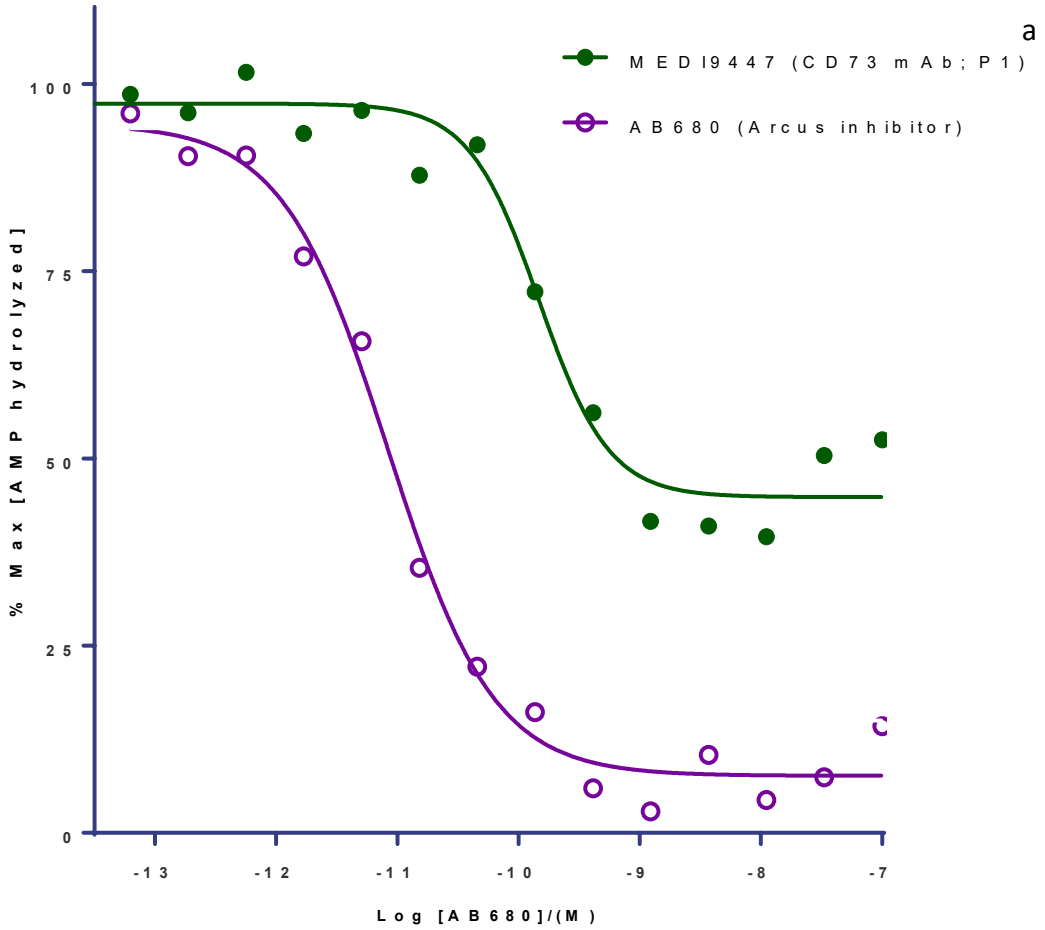
AB680 Potently Inhibits CD73 Enzymatic Activity on CD8+ T Cells

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



- Fully humanized anti-TIGIT antibody with Fc mutations to silence effector function
  - 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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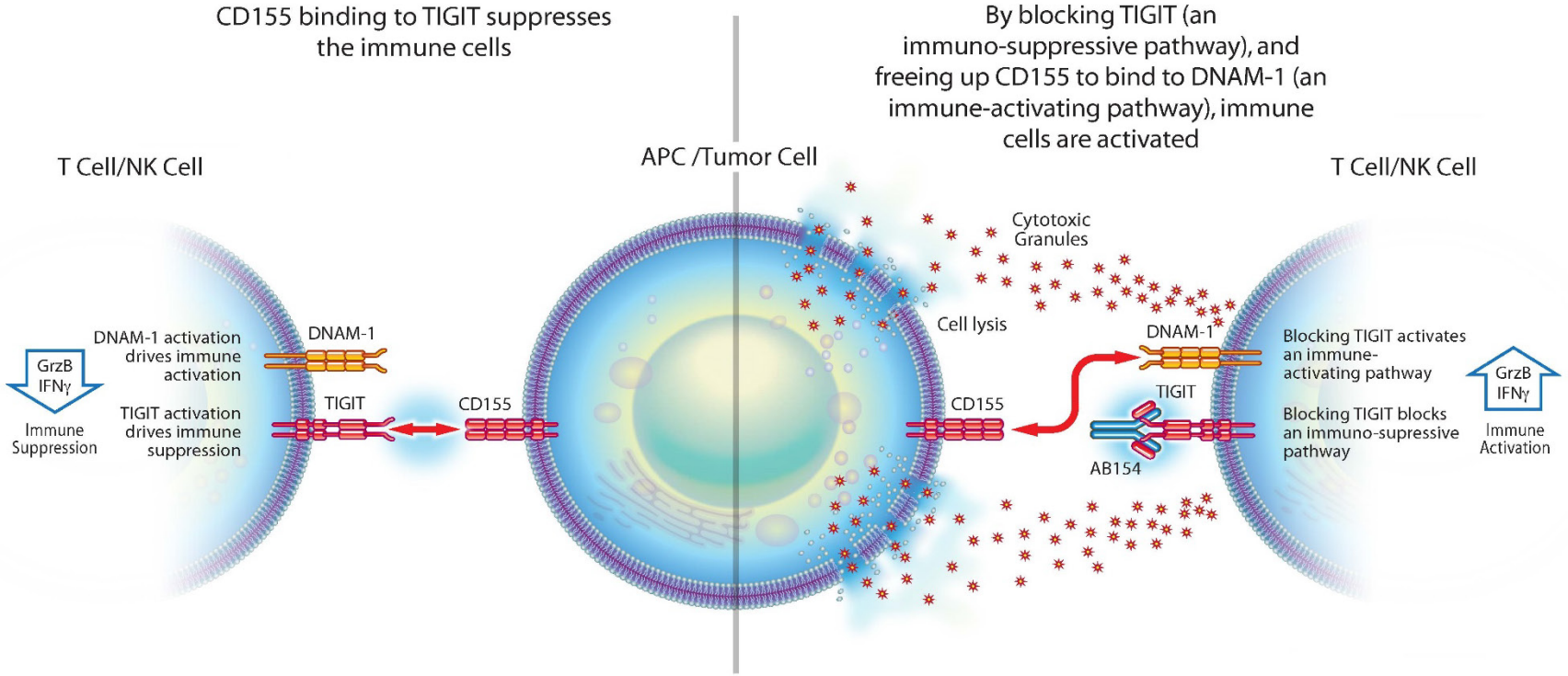
TIGIT Has a Dual Mechanism that Makes this Immuno-Oncology Pathway Unique



- TIGIT binds to CD155 (high affinity) and CD112 (low affinity)
- DNAM-1 (also referred to as CD226) competes, with lower affinity than TIGIT, for binding to CD155
- TIGIT binding to CD155 results in reduced function of effector T cells
- CD155 binding to DNAM-1 results in activation of immune cells
- When an anti-TIGIT antibody binds to TIGIT, it frees up CD155 to bind to DNAM-1, resulting in activation of effector immune cells

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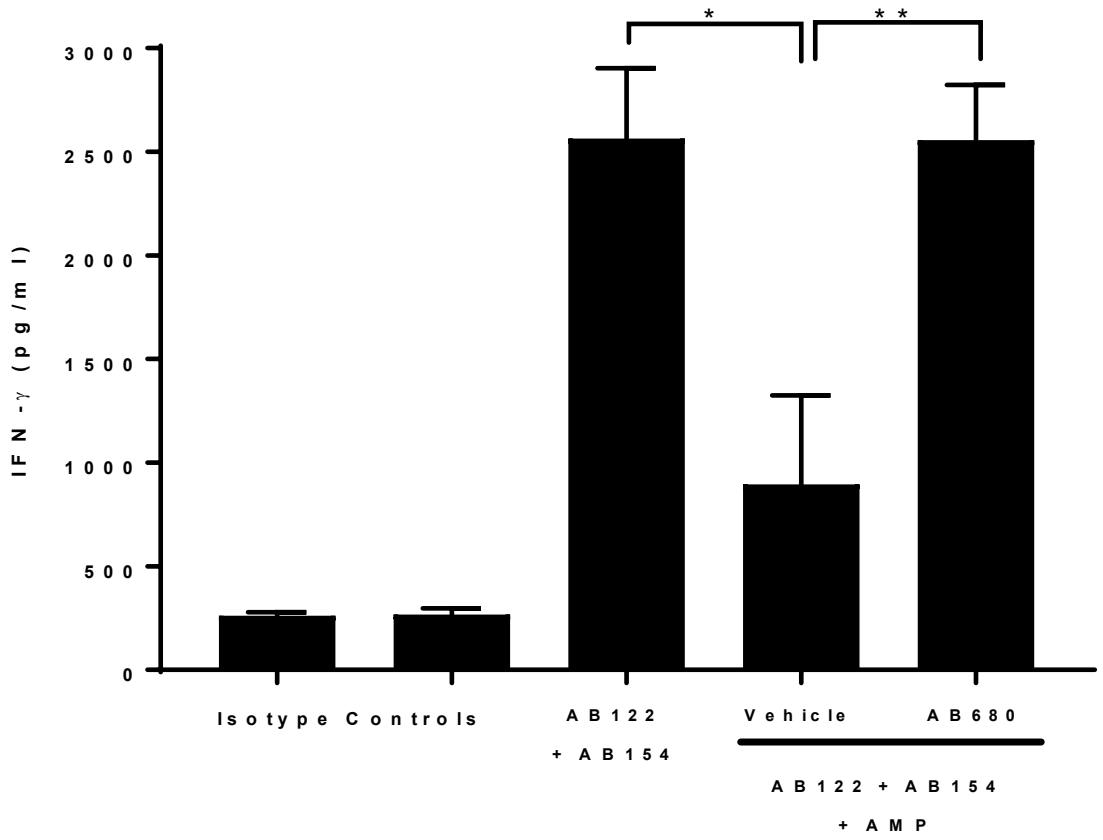
Rationale for a "Triple Combination Approach" With Anti-PD-1, Anti-TIGIT and CD73 Inhibitor

AMP inhibits CD4⁺ T cell activation (even in the presence of both an anti-PD-1 and anti-TIGIT antibody), an effect that can be reversed by AB680



* Statistically significant ($p < 0.05$)
** Statistically significant ($p < 0.01$)

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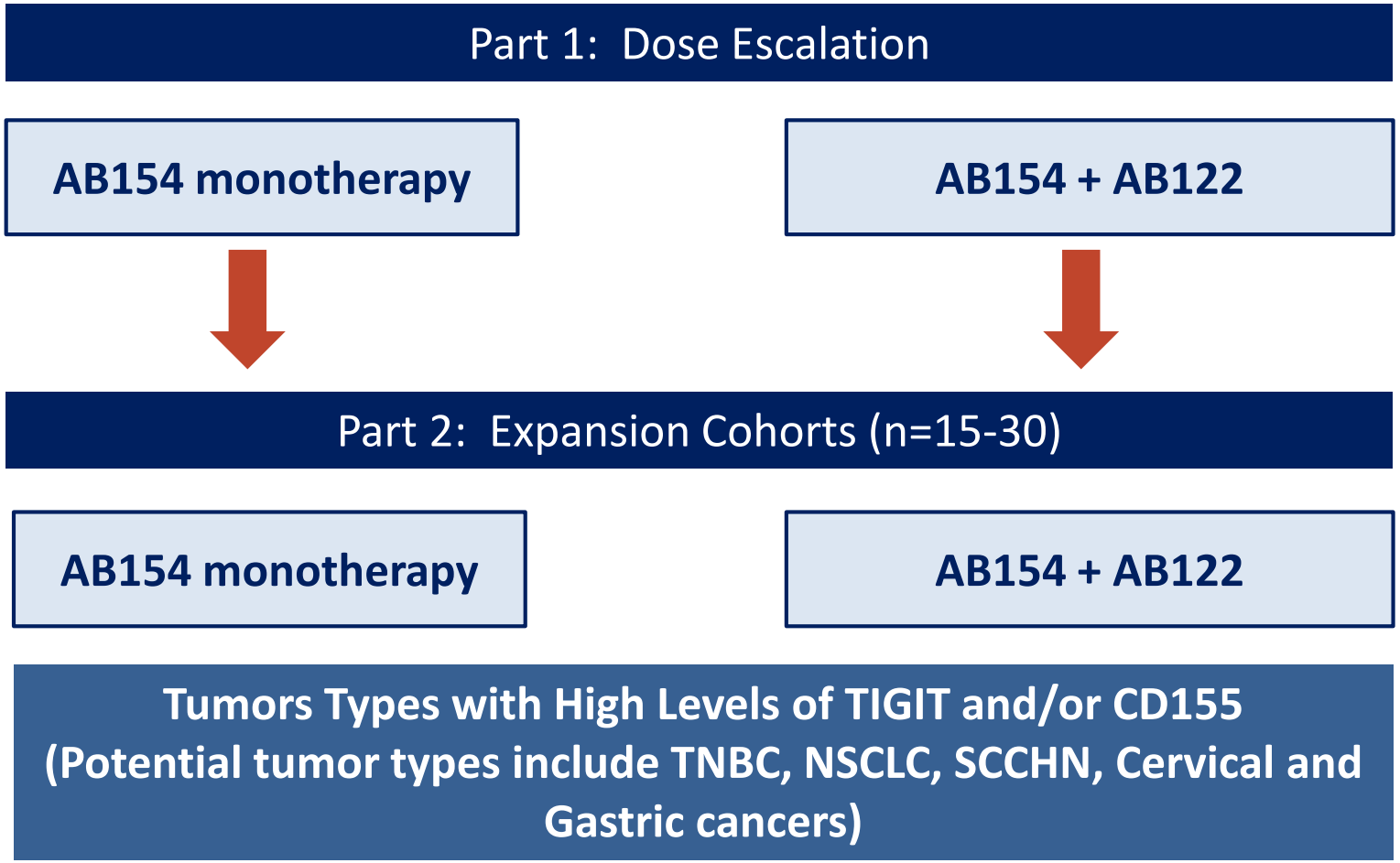
Phase 1/1b Dose Escalation Trial of AB154 + AB122



Initial Dose-escalation data for AB154 expected to be reported in 2019

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AB122: Anti-PD-1 Antibody with Similar Properties to 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 dose-escalation trial in Australia
  - 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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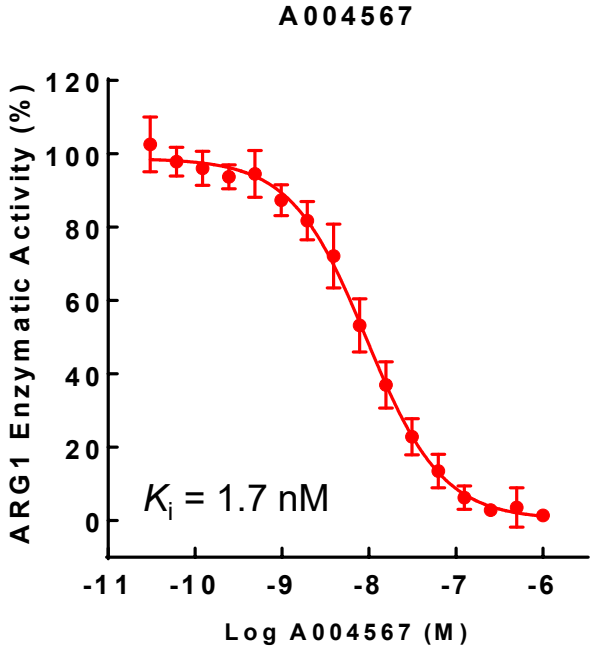
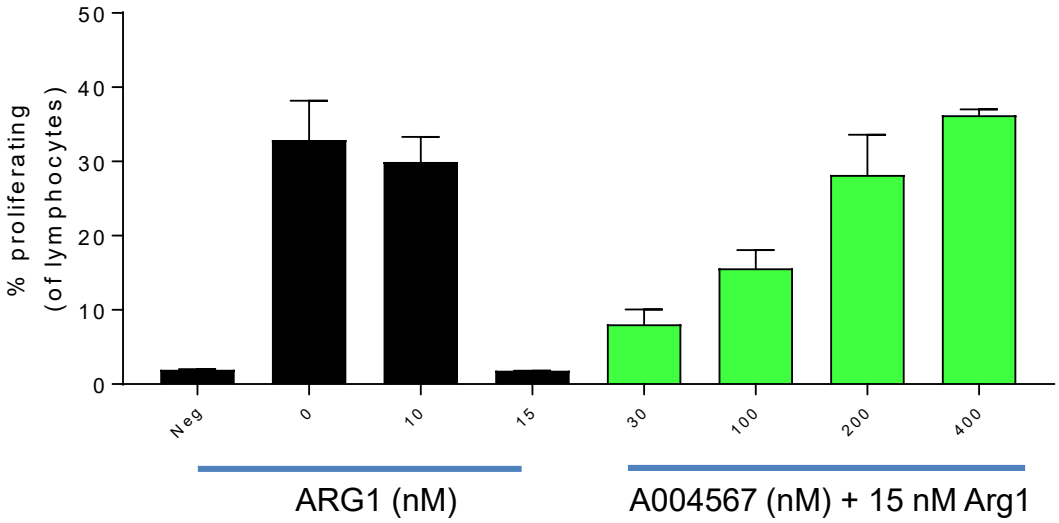
ARG1: Promising Early-Stage Program Targeting Myeloid Cells

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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ARCUS BIOSCIENCES

Corporate Overview

Our Portfolio

- ATP-Adenosine Pathway Programs
- Antibody Programs

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**

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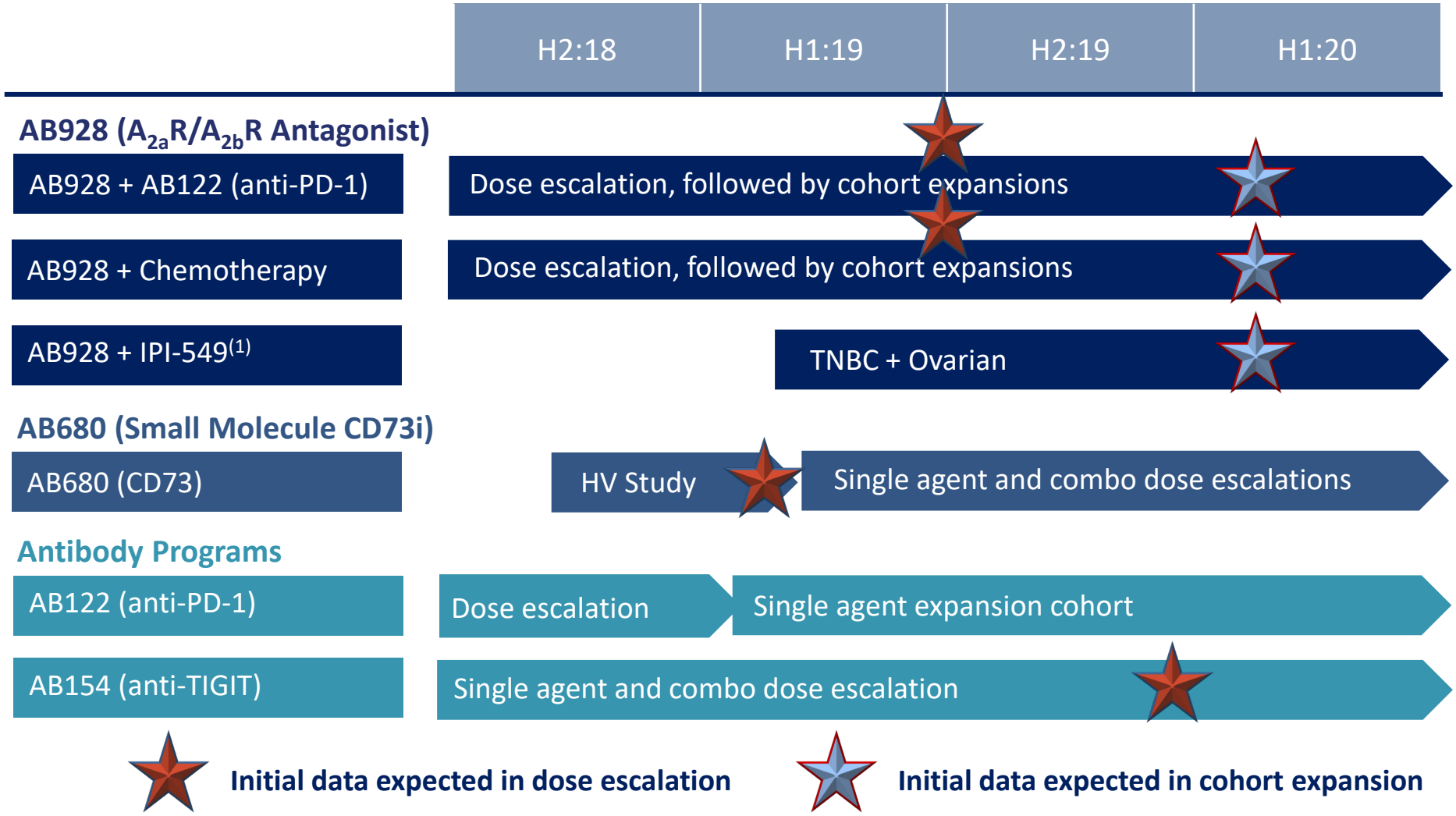
Multiple Data Readouts in the Next 12 Months



(1) Triple combo with chemo or AB122

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Thank you!



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