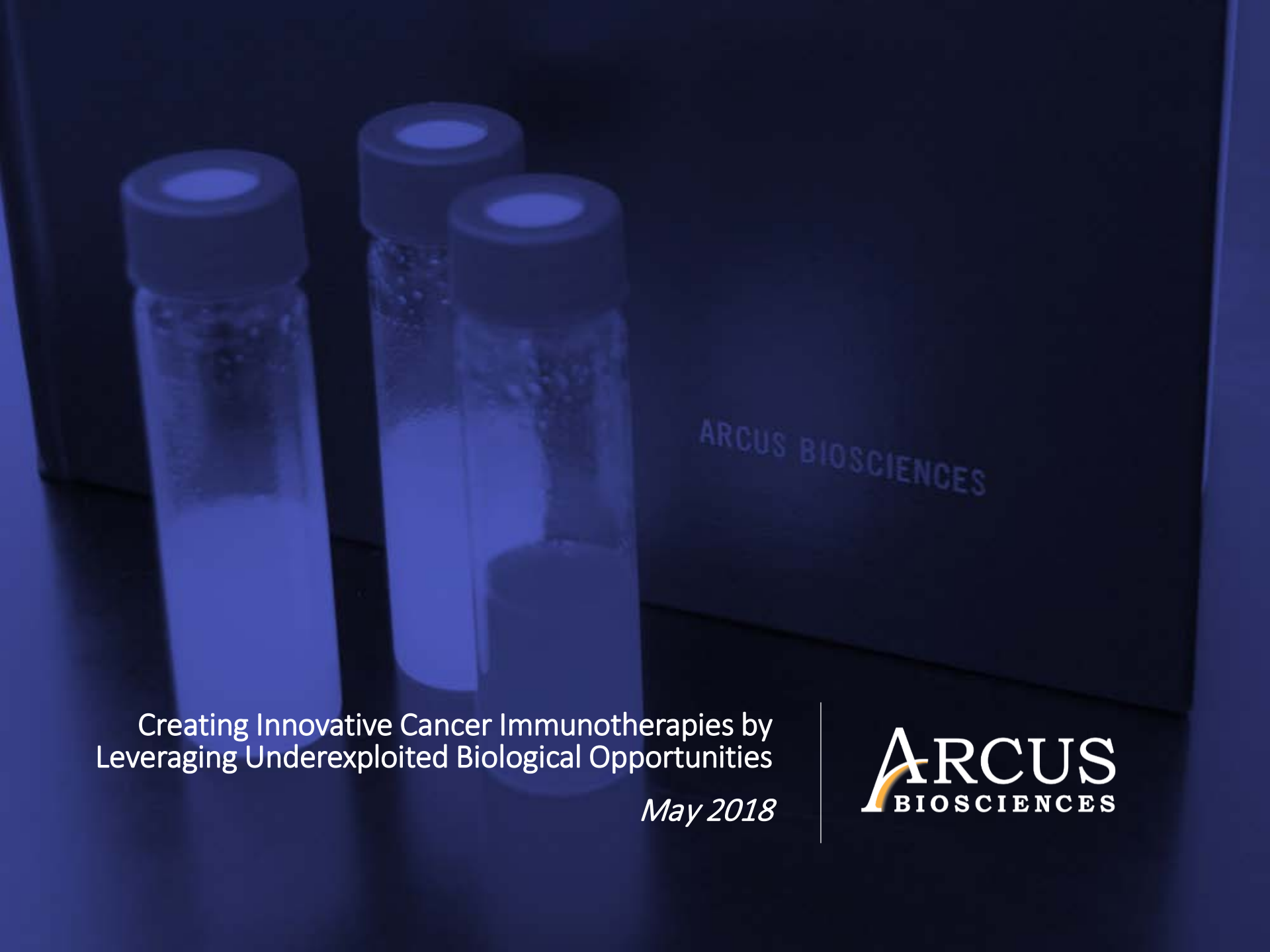

Creating Innovative Cancer Immunotherapies by Leveraging Underexploited Biological Opportunities

May 2018

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Corporate Overview

Our Portfolio

ATP-Adenosine Pathway Programs

Antibody Programs

Anticipated Milestones

Arcus Mission: Creating Innovative Cancer Immunotherapies by Leveraging Underexploited Biological Opportunities

- Focused on scientifically-validated, underexploited immuno-oncology (I-O) pathways
  - Initial focus on the ATP-adenosine pathway
- Four product candidates expected to be in the clinic by YE:2018
  - Phase 1 trial in healthy volunteers (HV) for lead product candidate (AB928) near completion – demonstrated complete inhibition of target pathway at a safe dose
  - Clinical data from our first AB928 combination trials in patients expected in H1:19
  - CD73 small molecule inhibitor and TIGIT antibody expected to enter the clinic in H2:18
- Robust, highly efficient small-molecule discovery capability designed to create and optimize highly differentiated small-molecule I-O product candidates
  - Pipeline includes several early-stage programs (e.g., arginase)
  - Plan to advance at least one new development candidate per year into clinical development
- Successful management team with 10+ years experience working together while at prior companies
  - Founders previously formed Flexus, which was acquired by BMS in 2015
- Well capitalized and committed to building a fully integrated I-O company
  - Approx. $290mm of cash and equivalents at 3/31/18, pro forma for the IPO
  - In-house biology, chemistry, preclinical and clinical development

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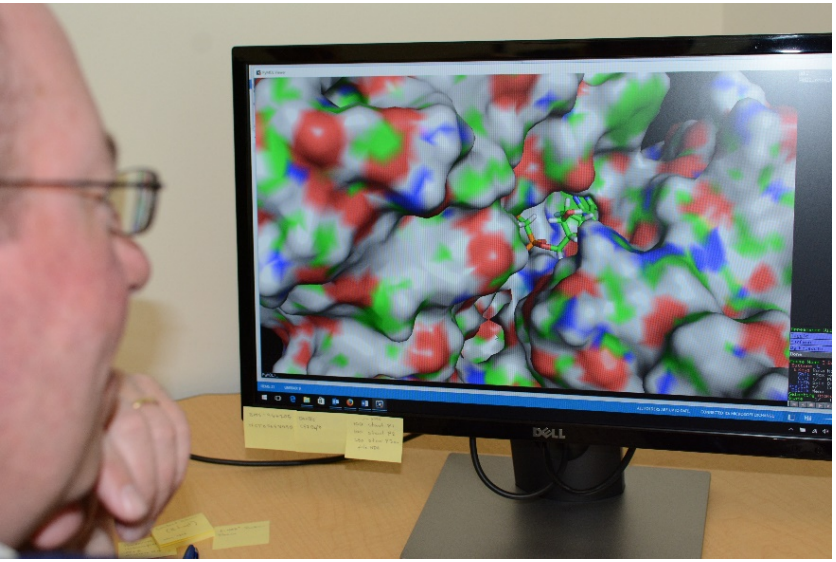
Arcus's Strategy Leverages the Essential Role of Combination Therapies in Immuno-Oncology



Our Strategy:

- Focus on targets that play a critical role in numerous cancers
- Establish broad portfolio of molecules that modulate important immune functions
  - Design small molecules with highly differentiated, best-in-class profiles
  - Ensure access to antibodies with "backbone" therapy potential
- Develop multiple intra-portfolio and differentiated combinations
- Pursue trial designs that enable efficient identification of most valuable combinations

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Arcus Leadership Team - Strong Track Record, Individually and as a Team

Terry Rosen, Ph.D. (Founder; CEO)
Founder & CEO, Flexus
VP Therapeutic Discovery (>550 staff) / Site Head (SF, WA) at Amgen
EVP Operations (inc. all Research & Preclin. Dev.) at Tularik

Juan Jaen, Ph.D. (Founder; President)
Founder & President, Flexus; SVP Drug Discovery & CSO at ChemoCentryx
100+ scientific publications; 60 issued U.S. patents

Jennifer Jarrett (CBO and CFO)
CFO, Medivation; 20 years in Biotechnology Investment Banking

Jay Powers, Ph.D. (SVP, Drug Discovery)
VP Drug Discovery, Flexus; 59 issued U.S. patents

Joyson Karakunnel, M.D. FACP (V.P., Clinical Development)
Director, Clinical Development, MedImmune (Division of AstraZeneca)

Ulrike Schindler, Ph.D. (V.P., Biology)
Head of Biologics, Amgen; Immune Disorders Program Director, Tularik

Steve Young, Ph.D. (V.P., Technology)
VP Technology, Flexus; Head of Discovery Tech. (Tularik, Amgen)

Nigel Walker, Ph.D. (V.P., Protein Science)
Head of Molecular Structure, Amgen

Steve Chan, CPA (V.P., Finance and Corporate Controller)
VP Finance and Corporate Controller, MyoKardia

Andy Pennell, Ph.D. (V.P., Preclin. Dev. & SM CMC)
Sr. Dir. Preclinical Development, ChemoCentryx

Tim Sullivan, Ph.D. (V.P., Business Development)
Sr. Director, External R&D Innovation, Pfizer

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

	Lead Optimization	Preclinical	Phase 1	Status / Milestone
Dual and Selective A_2R Antagonists				
AB928 ($A_{2a}R/A_{2b}R$ Antagonist)				Final Phase 1 data in mid-18
A003105/A002926				Preclinical characterization ongoing
Small Molecule CD73 Inhibitors				
AB680 (Intravenous)				Regulatory filing in Q3:18
Antibody Programs				
AB122 (anti-PD-1 Antibody)				Phase 1 data in cancer patients in Q3:18
AB154 (anti-TIGIT Antibody)				Regulatory filing in Q3:18

We also expect to identify a lead oral CD73 inhibitor and lead development candidate from our other early stage programs in 2018

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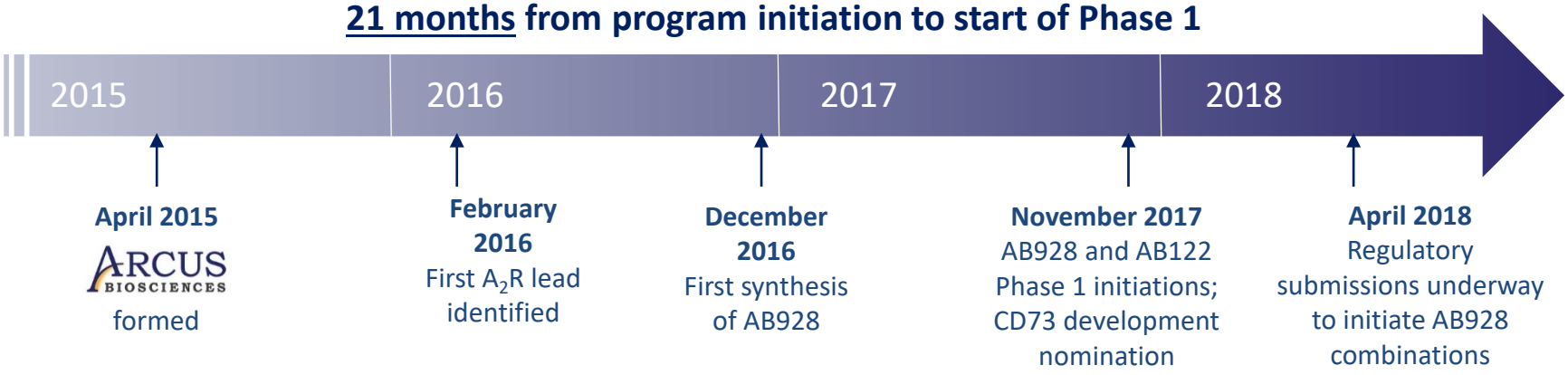
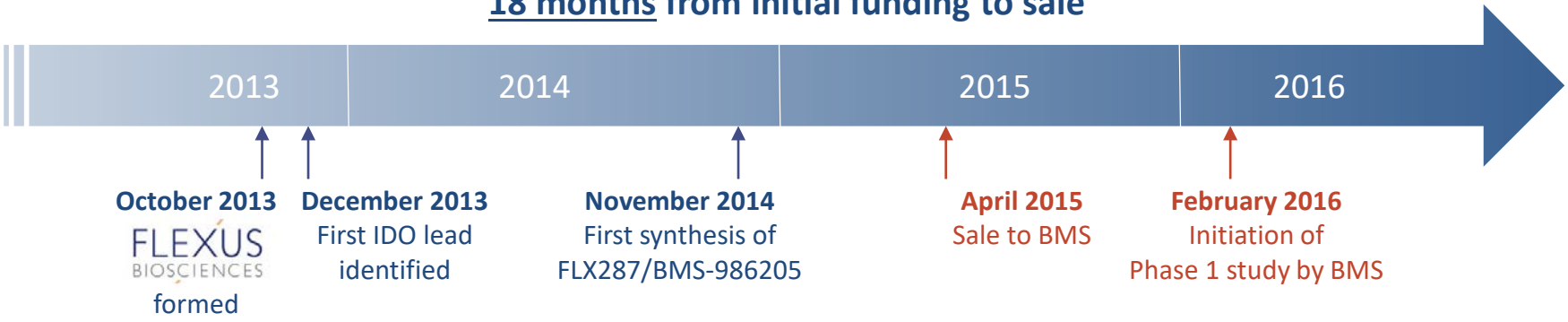
Validated, Highly Efficient Drug Discovery Capability

Four product candidates expected to be in clinical development by YE:2018
(two internally discovered) -- 5th program (arginase) underway

21 months from program initiation to start of Phase 1



18 months from initial funding to sale



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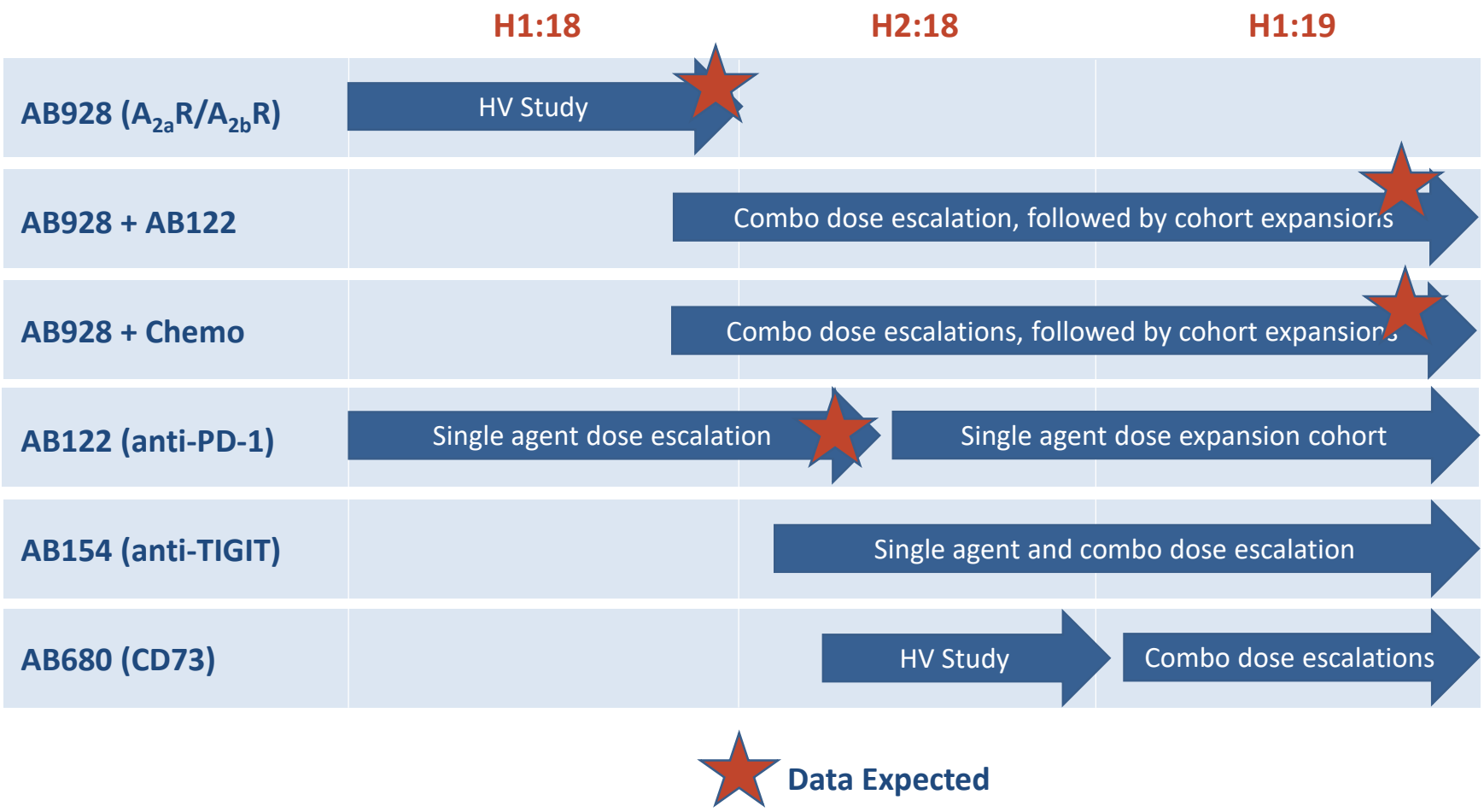
Multiple Trial Initiations and Data Readouts Anticipated by H1:2019



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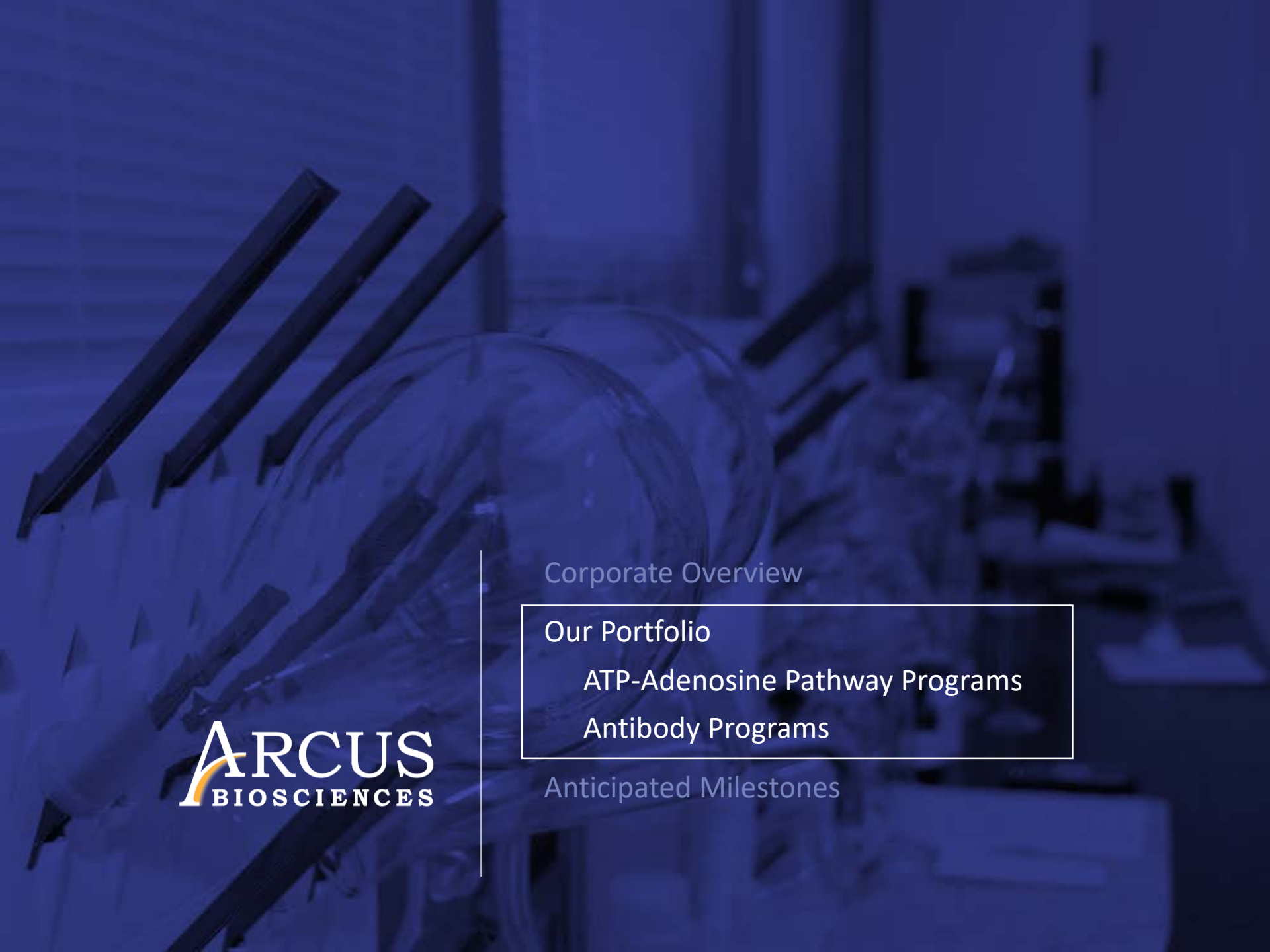

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Corporate Overview

Our Portfolio

- ATP-Adenosine Pathway Programs
- Antibody Programs

Anticipated Milestones

ATP-Adenosine Pathway: Highly Promising Pathway in Immuno-Oncology



Targeting adenosine in cancer immunotherapy: a review of recent progress

"…The adenosine pathway is currently viewed as a significant barrier to the effectiveness of immune therapies and becomes an important therapeutic target in cancer."

Oncology Central

CD73–adenosine: a next-generation target in immuno-oncology

"…The CD73–adenosine axis constitutes one of the most promising pathways in immuno-oncology."



Immunity, inflammation and cancer: a leading role for adenosine

"…several studies have recently highlighted a crucial role for adenosine signaling in regulating the various aspects of cell-intrinsic and cell-extrinsic processes of cancer development."

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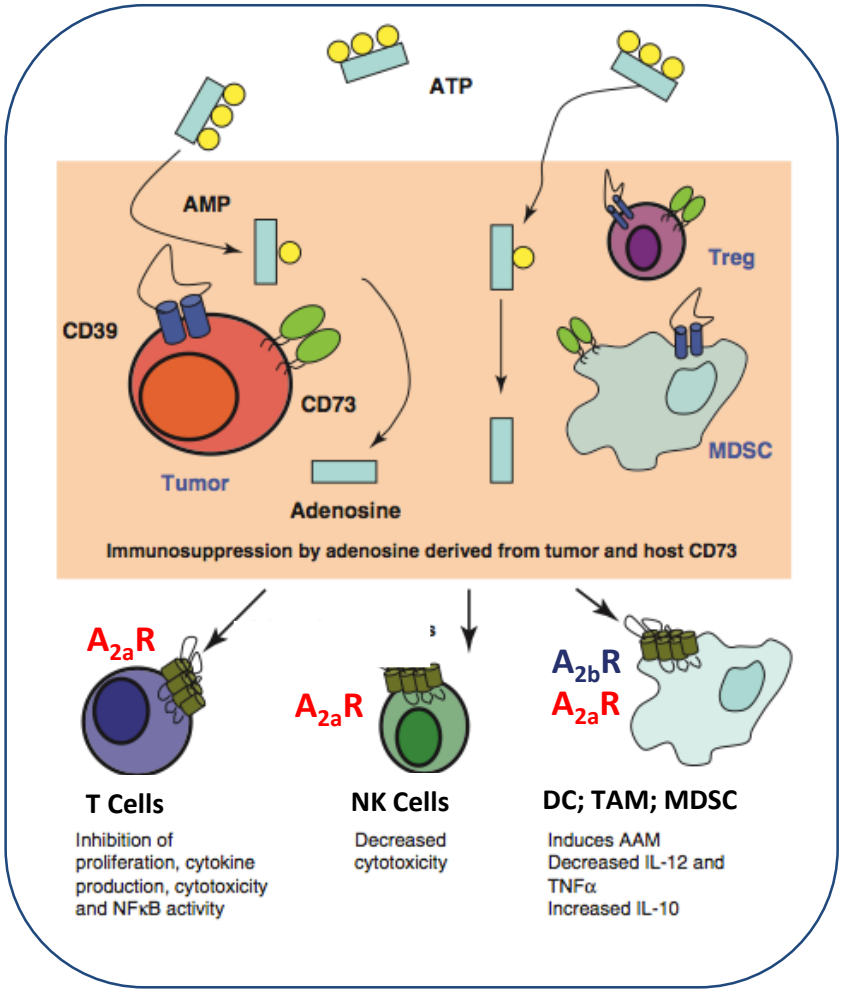
The ATP-Adenosine Pathway Plays a Well Established, Critical Role in Immune Suppression



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

Adapted from "CD73: A Potent Suppressor of Antitumor Immune Responses"; Beavis et al.; *Trends in Immunology*. (2012) 33:231

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AB928: Highly Differentiated A_2R Antagonist

Differentiated Approach to A_2R Antagonism

- Believed to be the first A_2R antagonist in clinical development that has been designed to:
  - Effectively block the adenosine receptor in the tumor microenvironment
  - Potently inhibit both the $A_{2a}R$ and $A_{2b}R$ receptors

Ideal Properties for the Tumor Microenvironment

- Retains potency when tested under real-world conditions (high albumin and high adenosine concentrations)
- Potentially broader immune activation and anti-tumor activity as a "dual antagonist"
- Attractive PK profile (low peak-to-trough; initial data from ongoing trial indicates a 20+ hour half life)

Rapid Anticipated Timeline to POC

- Phase 1 trial in healthy volunteers nearing completion – final data anticipated in mid-2018
- Regulatory filings to initiate combination trials in oncology patients underway
- Potential to use high CD73 expression in patient selection

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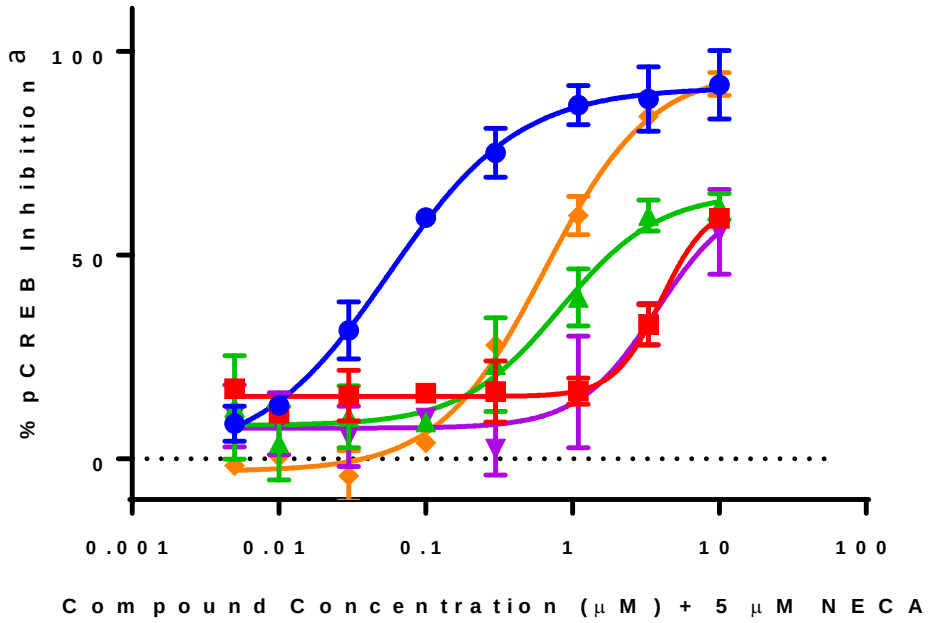
AB928 is the Most Potent Antagonist of $A_{2a}R$ Receptors When Tested in a Whole Blood Assay

$A_{2a}R$ antagonists currently in clinical development, 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
PBF-509[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; PBF509: Molecule synthesized by Arcus and believed to be PBF-509 or a close analogue (based on Pat Appl WO2017025918); 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
PBF-509 [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 PBF-509 or a close analogue (based on Pat Appl WO2017025918), 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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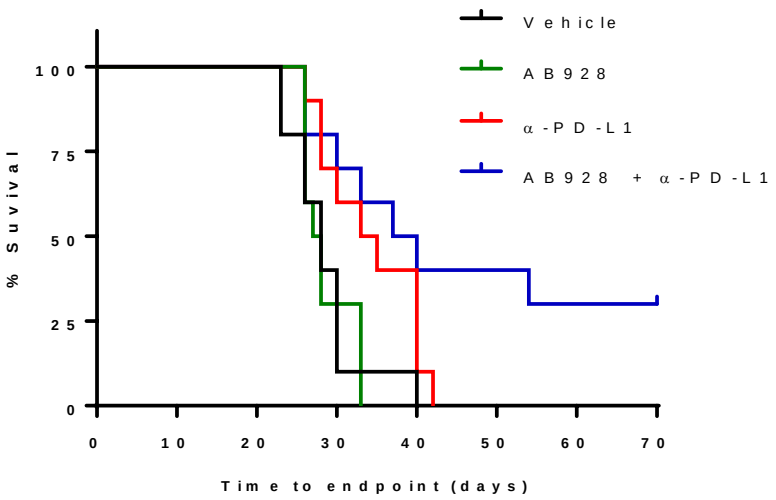
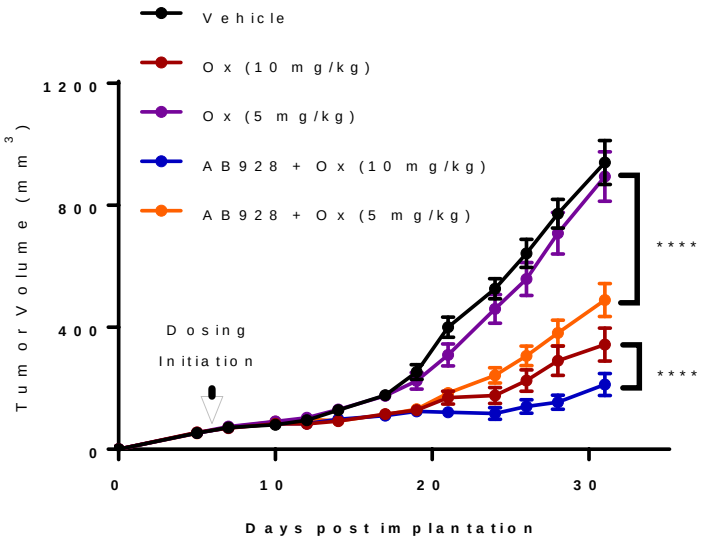
AB928 is Synergistic with anti-PD-L1 and Chemotherapy in Mouse Models

MC38 mouse model (in combination with anti-PD-L1 antibody)



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



- **** statistically significant ($p<0.0001$)
- **Similar results seen in combination with Doxorubicin**

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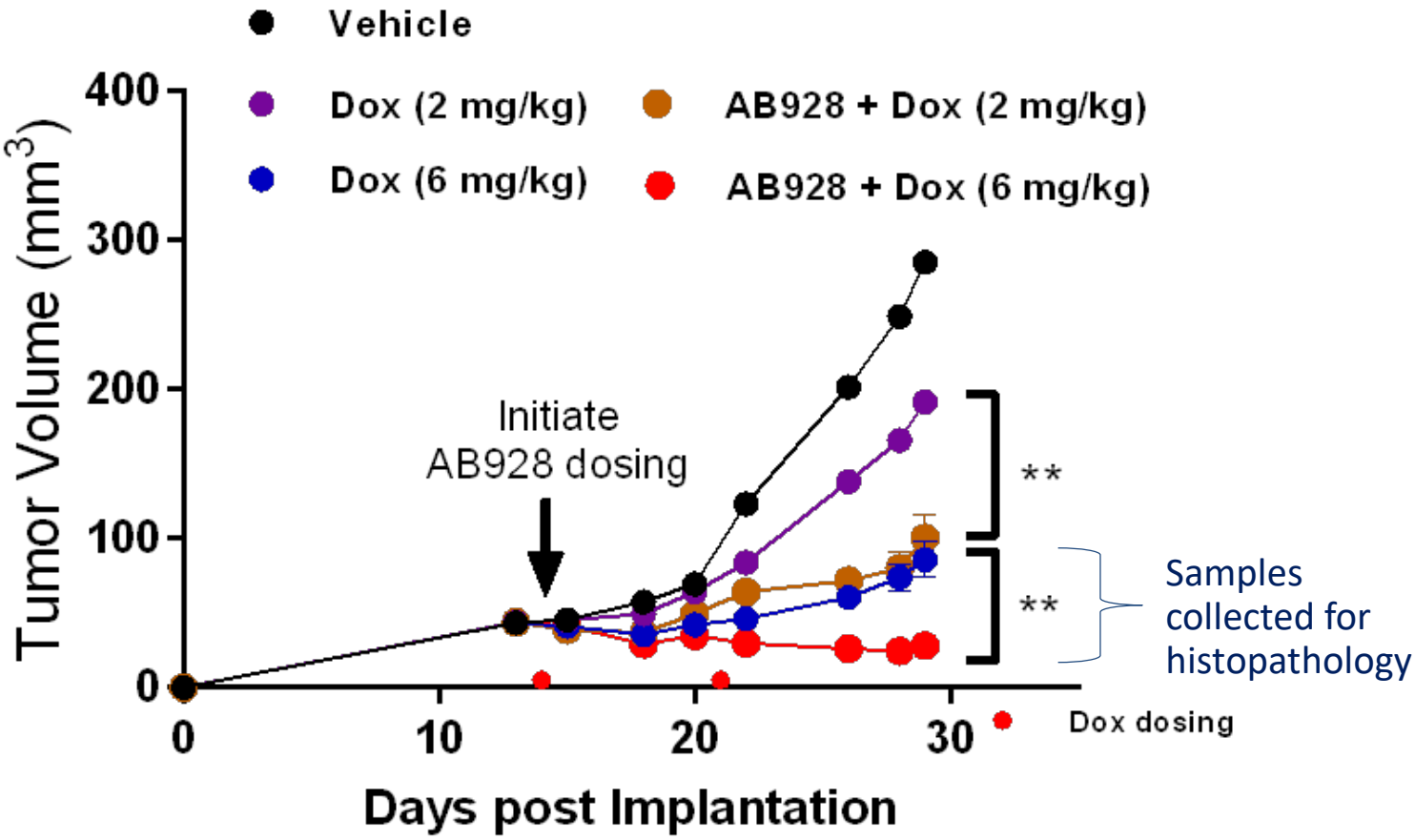
AB928 Is Highly Synergistic with Doxorubicin in the AT-3 OVA Model



**p<0.01 Doxorubicin vs. Doxorubicin + AB928

Similar results observed for the combination of AB928 and doxorubicin in the MCA205 model

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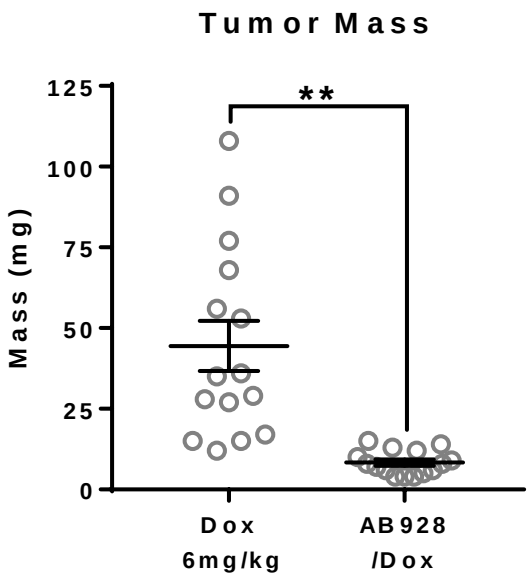
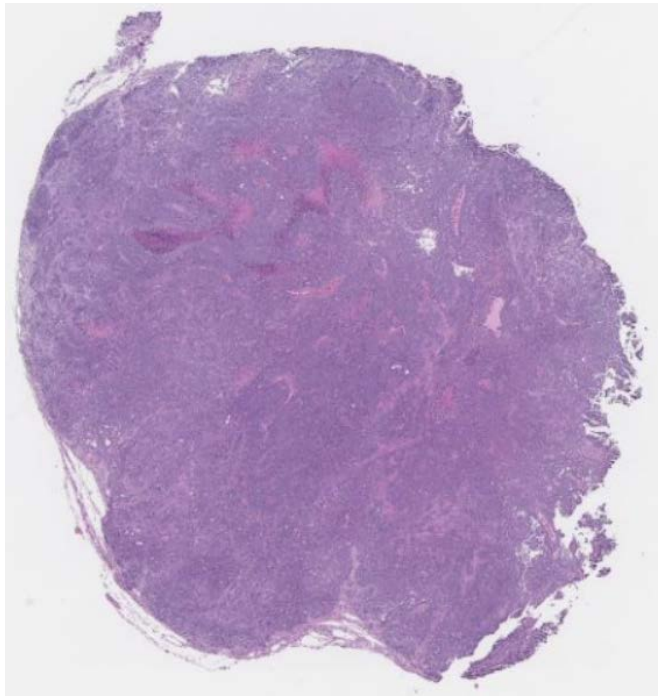
AB928 + Doxorubicin Induce Reduced AT-3 Tumor Growth and Significant Histological Changes

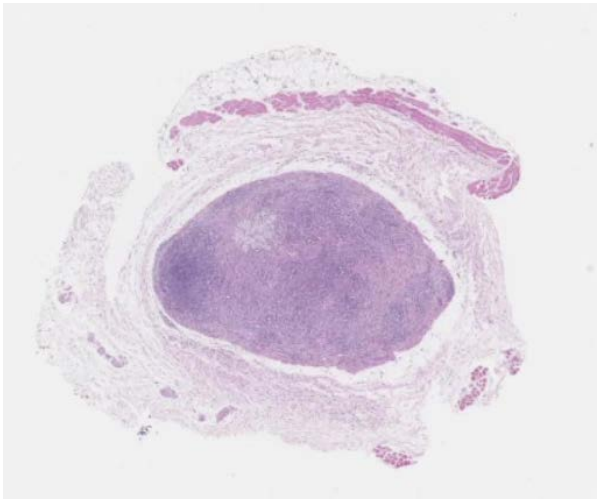


Example images representing the average tumor mass from each group

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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AB928 Clinical Program Underway



- Phase 1 trial in healthy volunteers nearing completion (n=85, 65 received AB928)
  - Achieved complete inhibition of pathway at 150mg QD
  - Half life supports QD dosing
  - Safe and well tolerated at all doses
- Regulatory filings underway to initiate three Phase 1/1b "platform" trials in patients
  - "Tumor specific" trials to evaluate AB928 + AB122 and AB928 + chemo (in settings where PD-1 or chemo is SOC)
  - Extensive biomarker analysis to be conducted (CD73, TMB, PD-L1, etc.)
  - Escalation data / initiation of expansion cohorts expected in H1:19

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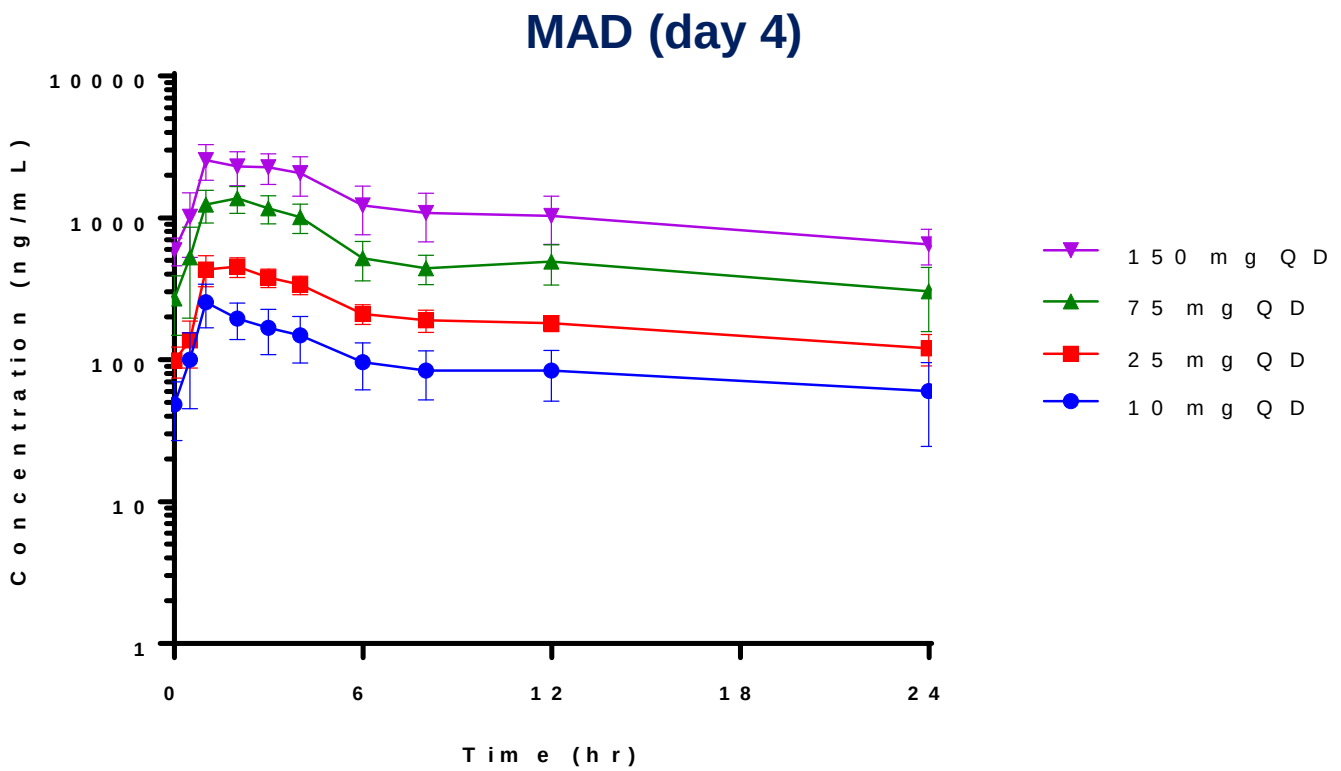
Data from Phase 1 Trial in HVs: Dose Proportional PK

- Dosing completed – MAD cohorts included 10 mg, 25 mg, 75 mg and 150 mg and 200 mg (with food)
- No safety issues have been observed
- Plasma half-life of approximately 20 hours



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AB928 Provided Maximal Inhibition of $A_{2a}R$ Activation on Day 4

	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	52 %	53	< 30%
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	**1,557**	**100 %**	**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

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AB928 Phase 1/1b Program: Our Approach

- Initial Focus on Settings Where Adenosine Pathway is Believed to be Critical, e.g.:
  - Tumor types characterized by high levels of CD73 expression (NSCLC, CRC, etc.)
  - Tumor types/settings where the SOC is anti-PD-1 or ICD-inducing chemotherapy
- Adaptive Trial Design Allows Flexibility Based on Early Results
  - Expand/terminate cohorts and arms based on data
  - Flexibility to incorporate new AB928 combinations, including triple combinations
  - Potential to add an SOC arm to enable more direct comparison to AB928 combination data
- Decision to Expand Cohorts/Initiate New Trials to be Informed by Biomarker Strategy
  - Understanding differences between responders/non-responders will be an essential part of decision-making algorithms
  - Data to inform target selection for subsequent trials

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AB928 Phase 1/1b Program: Initial Combination Partners

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

AB122 (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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AB928 Phase 1/1b Program: Tumor Type Selection

Evaluating tumor types in which the ATP-adenosine pathway might play an important immunosuppressive role – in three "Tumor-Specific" trials

Trial Protocol	Tumor Types Expected to be Included	T cell infiltration	High CD73 expression	ICD-inducing chemo is SOC
1 Gastrointestinal Malignancies	CRC	✓	✓	✓
	Gastroesophageal	✓	✓	✓
2 RCC and NSCLC	RCC	✓	✓	
	NSCLC	✓	✓	✓
3 Breast and Gyn Malignancies	TNBC	✓		✓
	Ovarian	✓		✓

Anti-PD-(L)1 agents not currently approved

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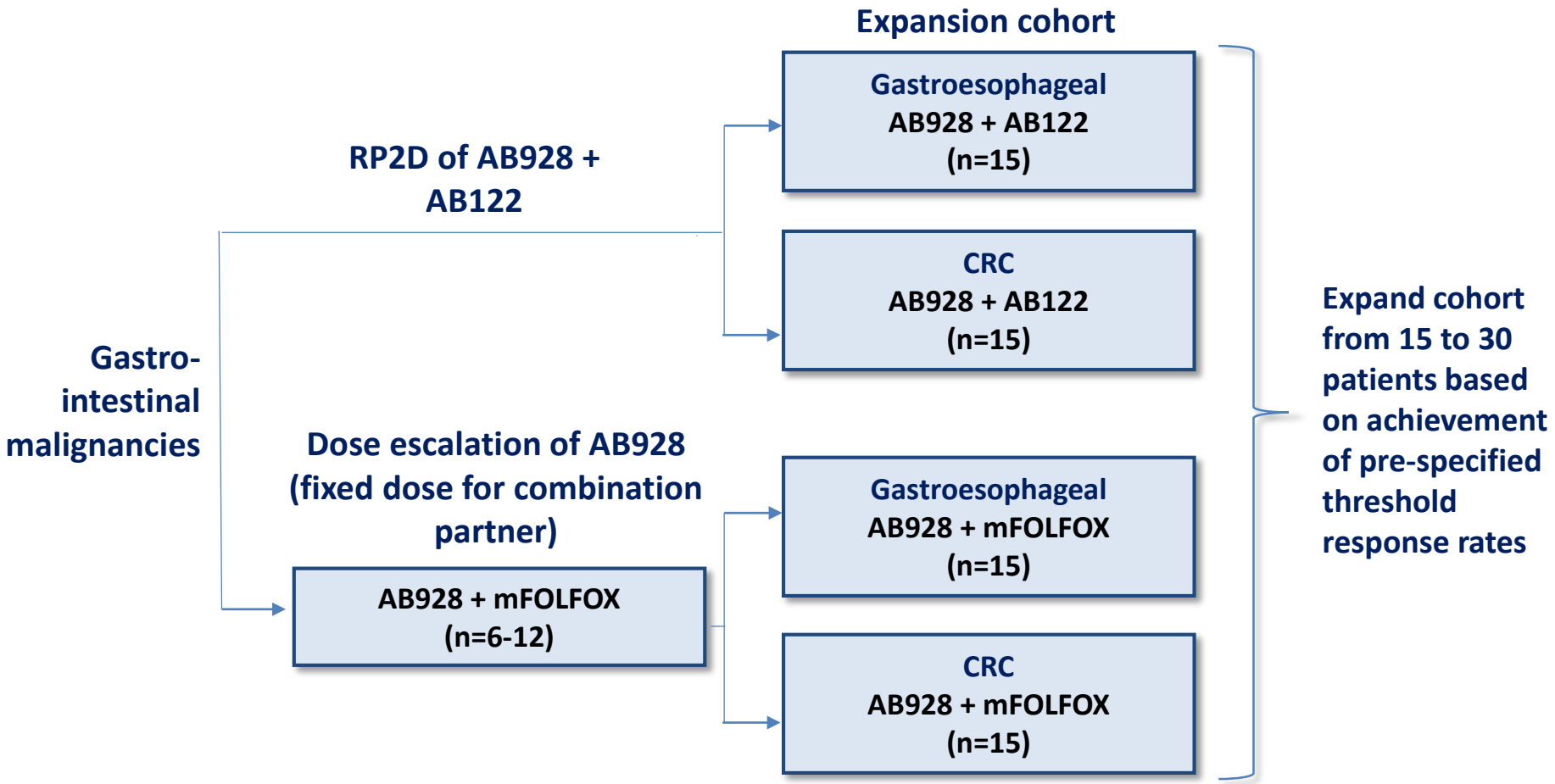
1 Phase 1/1b in Gastrointestinal Malignancies

"Platform" trial design allows us to add new combinations to the protocol, including triple combinations



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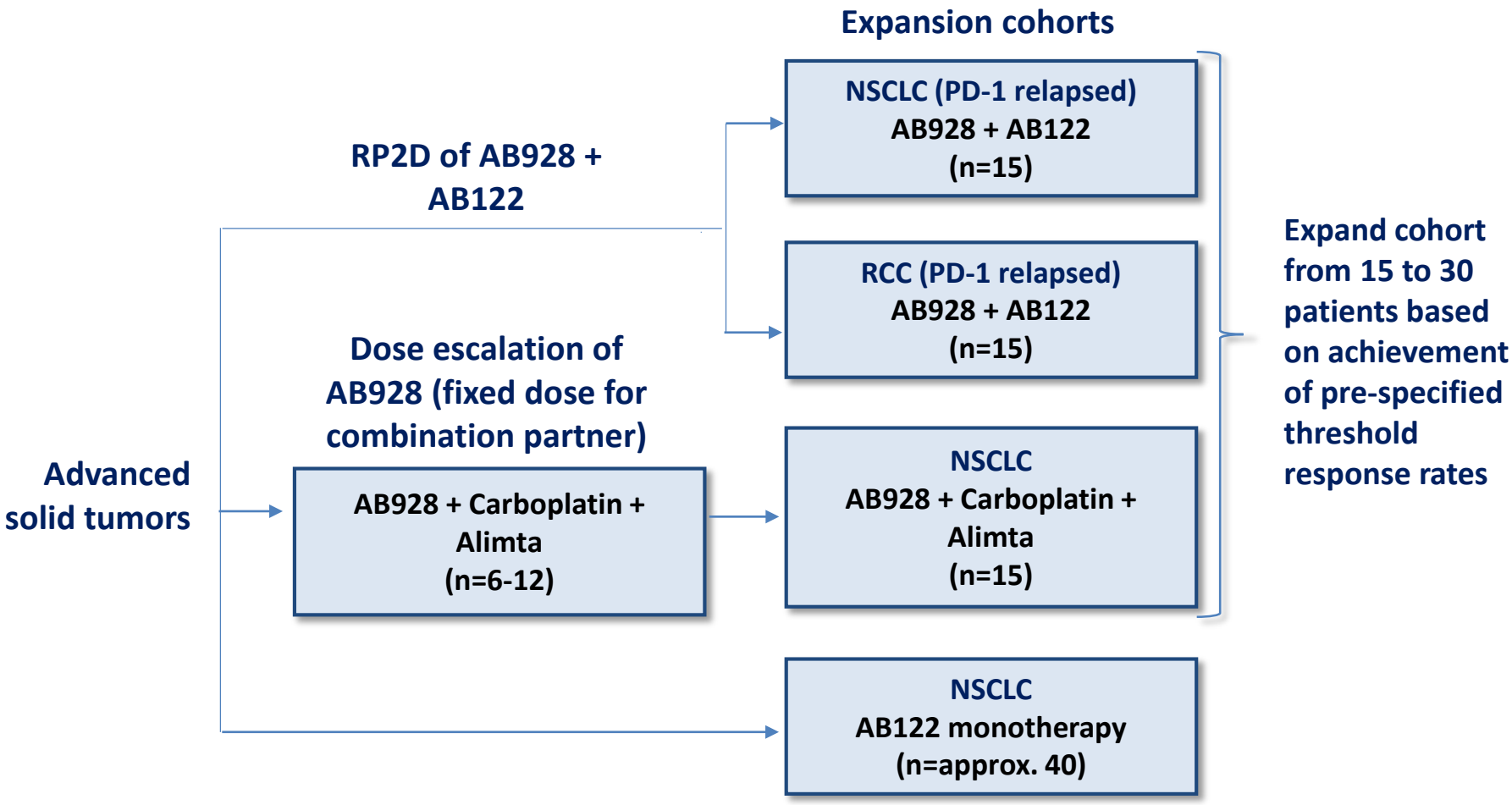
2 Phase 1/1b in RCC and NSCLC



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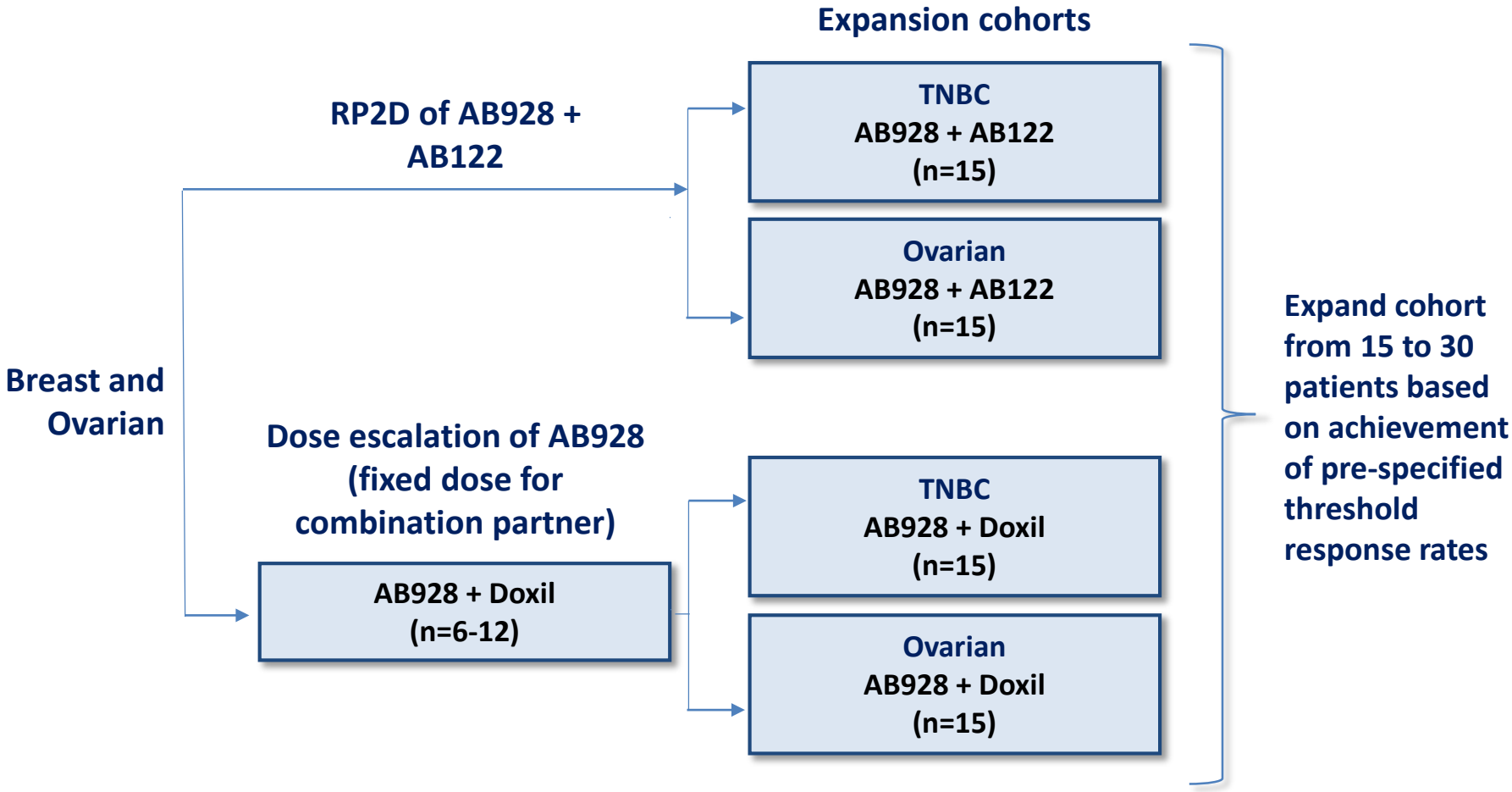
3 Phase 1/1b in Breast and Gynecologic Malignancies



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AB928 Clinical Biomarker Plan

Predictive Biomarkers

- CD73 expression
  - Tumor (IHC & mRNA)
  - Blood (ELISA & Enzym. Assay)
- PD-L1 status
- TMB (tumor and/or blood)
- Levels of other IC & inhibitory pathways (tumor / IHC & mRNA)

Markers of Immune Activation

- Immunophenotyping (PBMC)
- T cell clonality (tumor & PBMC)
  - neoE-specific clonal expansion
- T cell activation / proliferation (tumor & PBMC)
- Serum cytokines

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AB680: Potentially First Small Molecule CD73 Inhibitor

CD73 Mediates Adenosine Production

- CD73 catalyzes the last step in the conversion of extracellular ATP to adenosine
- CD73 inhibition blocks extracellular adenosine production

AB680 Potential Advantages

- AB680 is the most advanced small-molecule inhibitor of CD73
- Potential advantages over mAbs in development:
  - Greater inhibition of cell-bound and soluble CD73 relative to some antibodies in development
  - Deeper tumor penetration as a small molecule

Expected to Enter Clinical Development in H2:2018

- IND-enabling studies ongoing for AB680 (i.v.), extremely potent and long half-life molecule
- Early development program to be modeled after AB928, with a focus on CD73-expressing tumors
- Ongoing effort to identify an orally active oral CD73 inhibitor; Development candidate nomination expected in 2018

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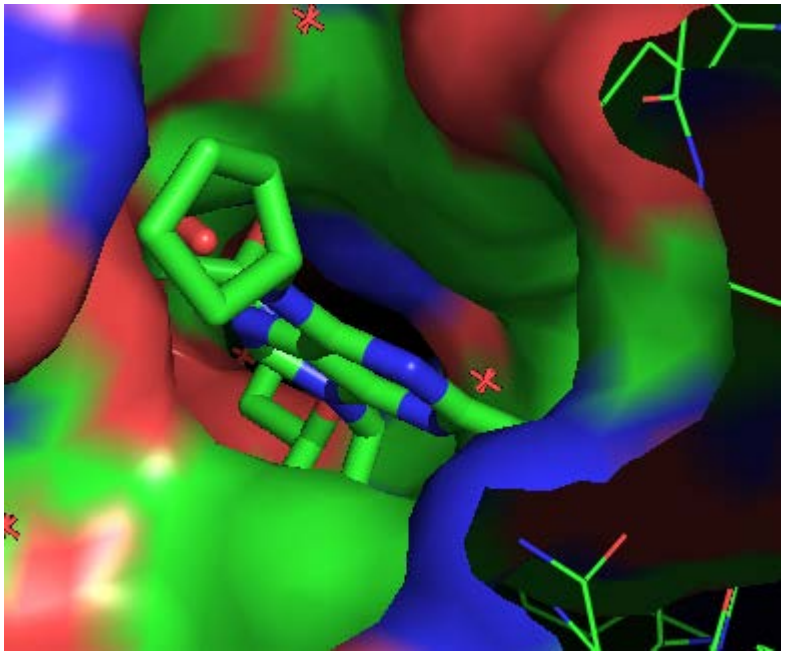
Structure-Based Design of Extraordinarily Potent CD73 Inhibitors

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



A001190
hCD73 (CHO cells)
IC_{50} = 0.03 nM

Collaboration with Professor Norbert Sträter (University of Leipzig)

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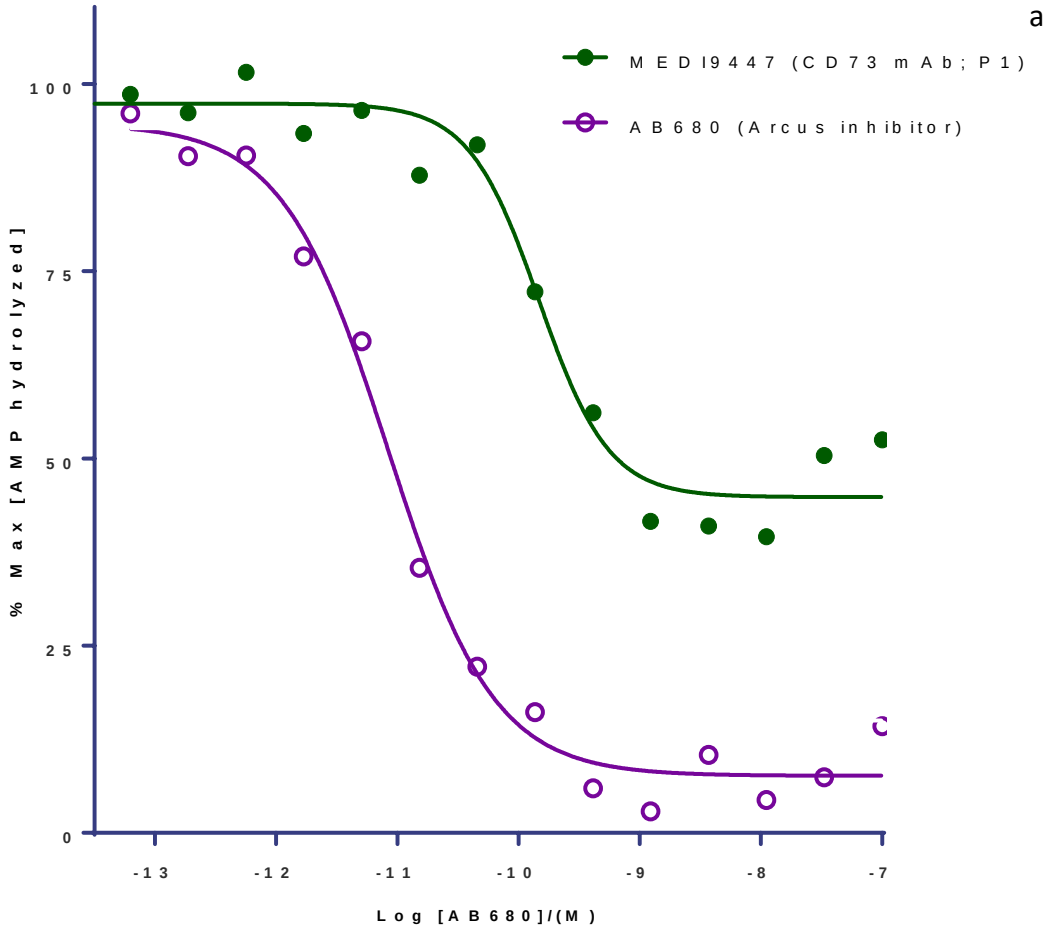
AB680 Potently Inhibits CD73 Enzymatic Activity on CD8+ T Cells

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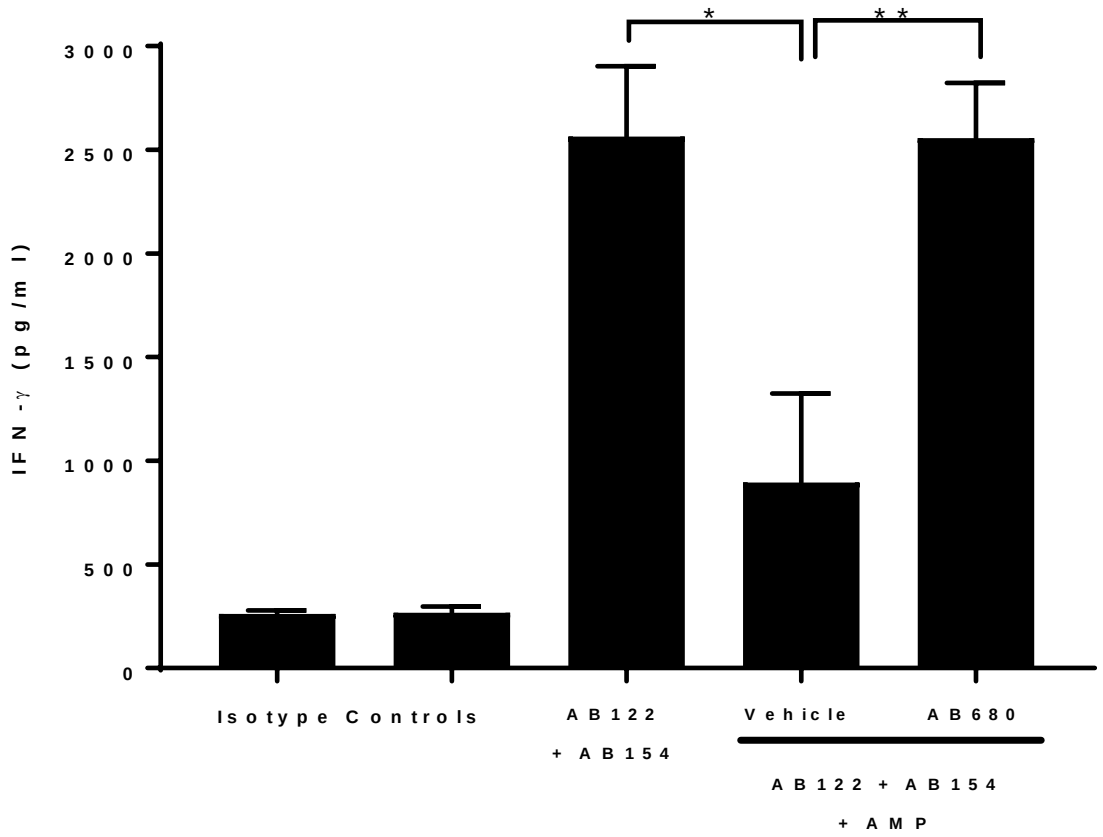
Rationale for a "Triple Combination Approach" With Anti-PD-1, Anti-TIGIT and CD73 Inhibitor

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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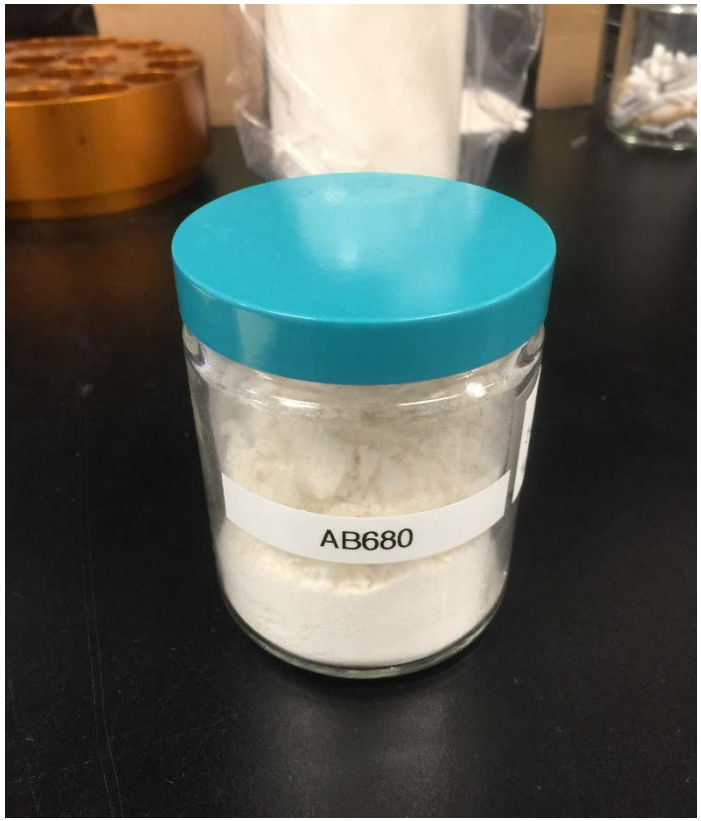
AB680 is Advancing Towards a Phase 1 Trial Initiation Expected in H2:18



- Intravenous formulation of AB680 currently in IND-enabling studies
  - Low clearance, long half-life molecule
  - Can be administered on the same schedule as AB122 (anti-PD-1) or chemotherapy
  - Regulatory submission and Phase 1 initiation anticipated in H2:18
- Advanced effort to identify a 2nd-generation orally administered CD73 inhibitor
  - Development candidate nomination anticipated in 2018

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

AB122 Has Highly Attractive Properties

- Fully human antibody with similar binding affinity and other characteristics to those of pembrolizumab and nivolumab

Advantages for Arcus

- Full access to AB122 in the US, Europe, Japan and certain other territories
- Complete flexibility to develop anti-PD-1 combinations and to retain future economics from the anti-PD-1 antibody
- WuXi, a leading biologics manufacturer, to provide us with GMP material

Development Status

- Phase 1 dose-escalation trial ongoing in Australia – initiated dosing of third cohort (up to 360 mg Q2W) – PK profile in patients has been similar to nivolumab
- Phase 1 data expected to be reported in H2:18
- Single-agent dose-expansion cohort in a PD-1 responsive tumor type to initiate H2:18

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AB154: Differentiated Antibody in a New Immune Checkpoint Class (TIGIT)

Novel Checkpoint Target	• TIGIT inhibition both reverses immune inhibition and provides tissue-selective immune stimulation • Believed to be one of the next potential backbone therapies in I-O
AB154 Characteristics	• Fully human anti-TIGIT IgG1κ antibody with Fc mutations to silence effector function • Binds to a different epitope than other TIGIT antibodies; binding mode confirmed by x-ray crystallography
Development Status / Milestone	• Exploratory safety studies (monkeys) completed; GLP 28-day tox study – in life completed • Regulatory filing anticipated in Q3; Phase 1 initiation in H2:18 • Potential to develop both as monotherapy and in combination with other agents (e.g., AB122)

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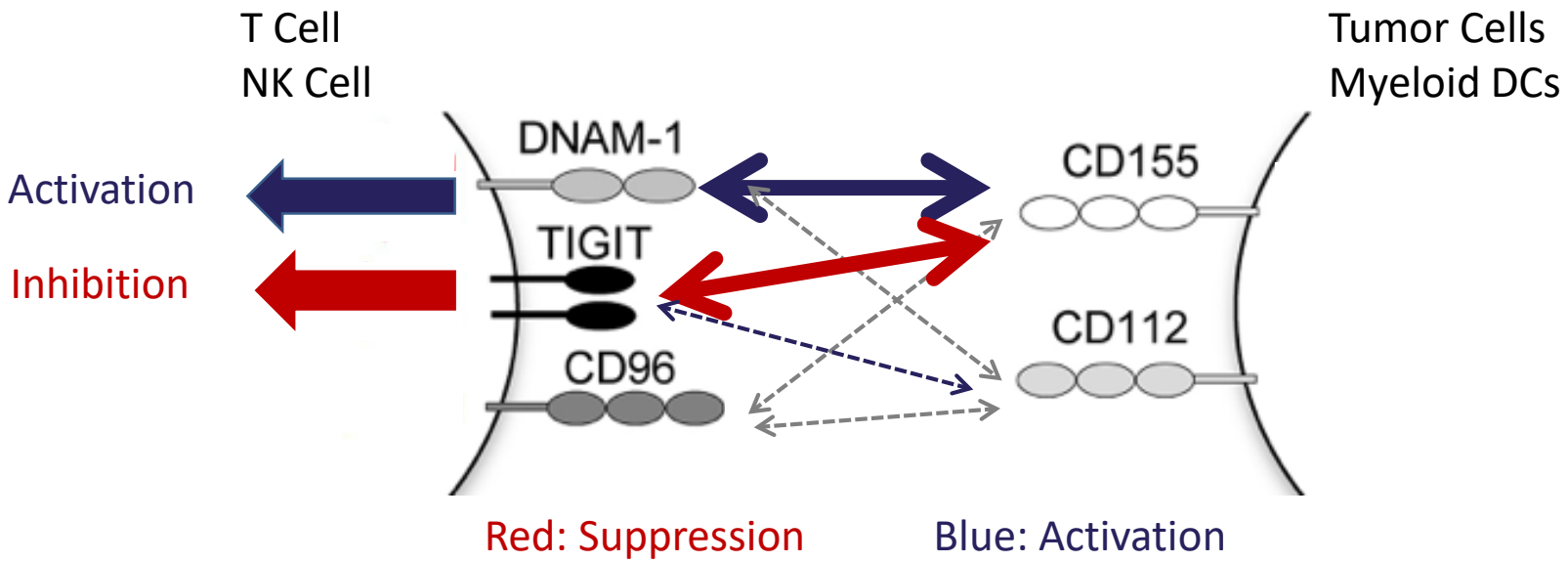
TIGIT Has a Dual Mechanism that Makes this Immuno-Oncology Pathway Unique



- TIGIT binds to CD155 (high affinity) and CD112 (low affinity)
- DNAM-1 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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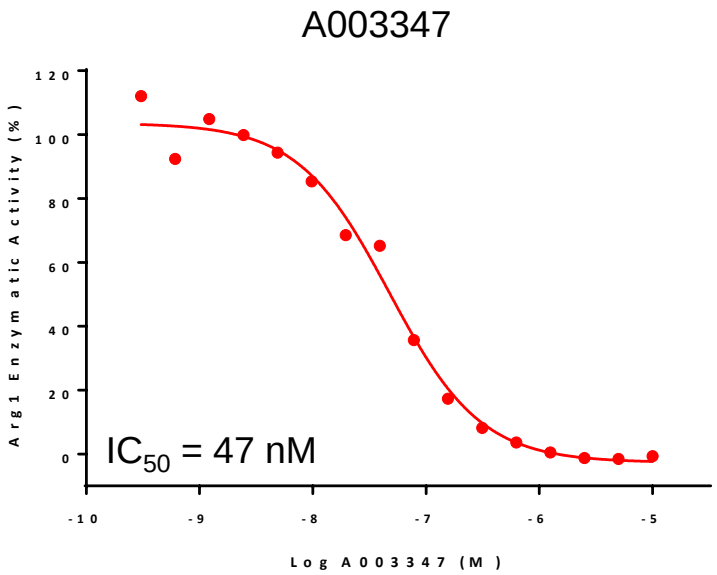
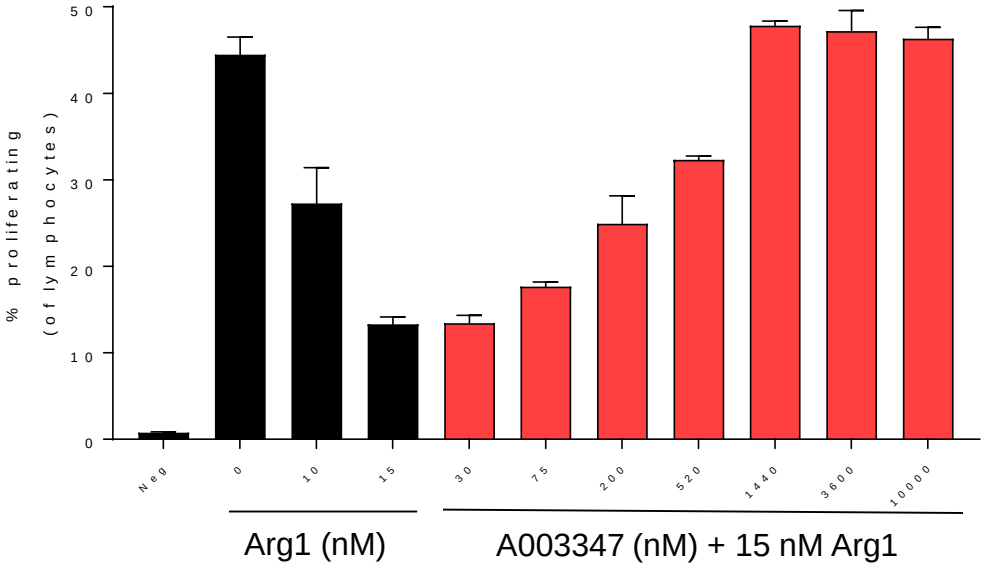
ARG-1: Promising Early Stage Program Targeting Myeloid Cells

Current ARG-1 lead, A003347, has demonstrated highly potent inhibition of human ARG-1 and reversal of ARG-1-mediated repression of T cells

Inhibition of human ARG-1



Rescue of ARG-1-mediated repression of CD8+ T cell proliferation



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Corporate Overview

Our Portfolio

- ATP-Adenosine Pathway Programs
- Antibody Programs

Anticipated Milestones

Collaboration with Taiho Provides Non-Dilutive Capital



- A member of the Otsuka Group of Companies
- Pipeline of anti-cancer drugs
- Co-promotes Merck's Keytruda (pembrolizumab) in Japan

Collaboration Terms:

- Taiho acquires an option on Arcus programs for Japan and certain other Asia territories (excluding China) over a 5-year term
- $35mm in guaranteed payments over 3 years
- Opt-in payments that range from $3 to $15m 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

All North American and European Rights Retained

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In-licensing of Anti-PD-1 Antibody Ensures Access / Creates Multiple Intra-Portfolio Opportunities

WuXi Biologics
Global Solution Provider

- Established history of working with large US and global pharmaceutical company companies
- Current biologics manufacturing partner of Arcus
- US $511mm Hong Kong IPO completed in June 2017

Key Terms:

- Arcus in-licensed WW rights to AB122 from WuXi (with the exception of China and five other countries outside the US, Europe and Japan)
- $18.5mm upfront / milestone payments
- Clinical and regulatory milestone payments
- Up to $375mm in commercial milestones
- Tiered royalties from high-single digit to low teens on net sales of AB122

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Upcoming Anticipated Milestones

Q2:2018	• Regulatory filings for dose escalation trials for first intra-portfolio combinations: AB928 + AB122 and AB928 + Chemo
Q3:2018	• Final data from healthy volunteer trial for AB928 • Regulatory filings for AB154 and AB680 • Data from Phase 1 trial of AB122 in patients
Q4:2018	• Select development candidates from our oral CD73 inhibitor and arginase programs
H1:2019	• Clinical data from dose-escalation trials of AB928 + AB122 and AB928 + Chemo • Initiate expansion cohorts for AB928 combinations • Regulatory filing for next program (arginase inhibitor candidate)

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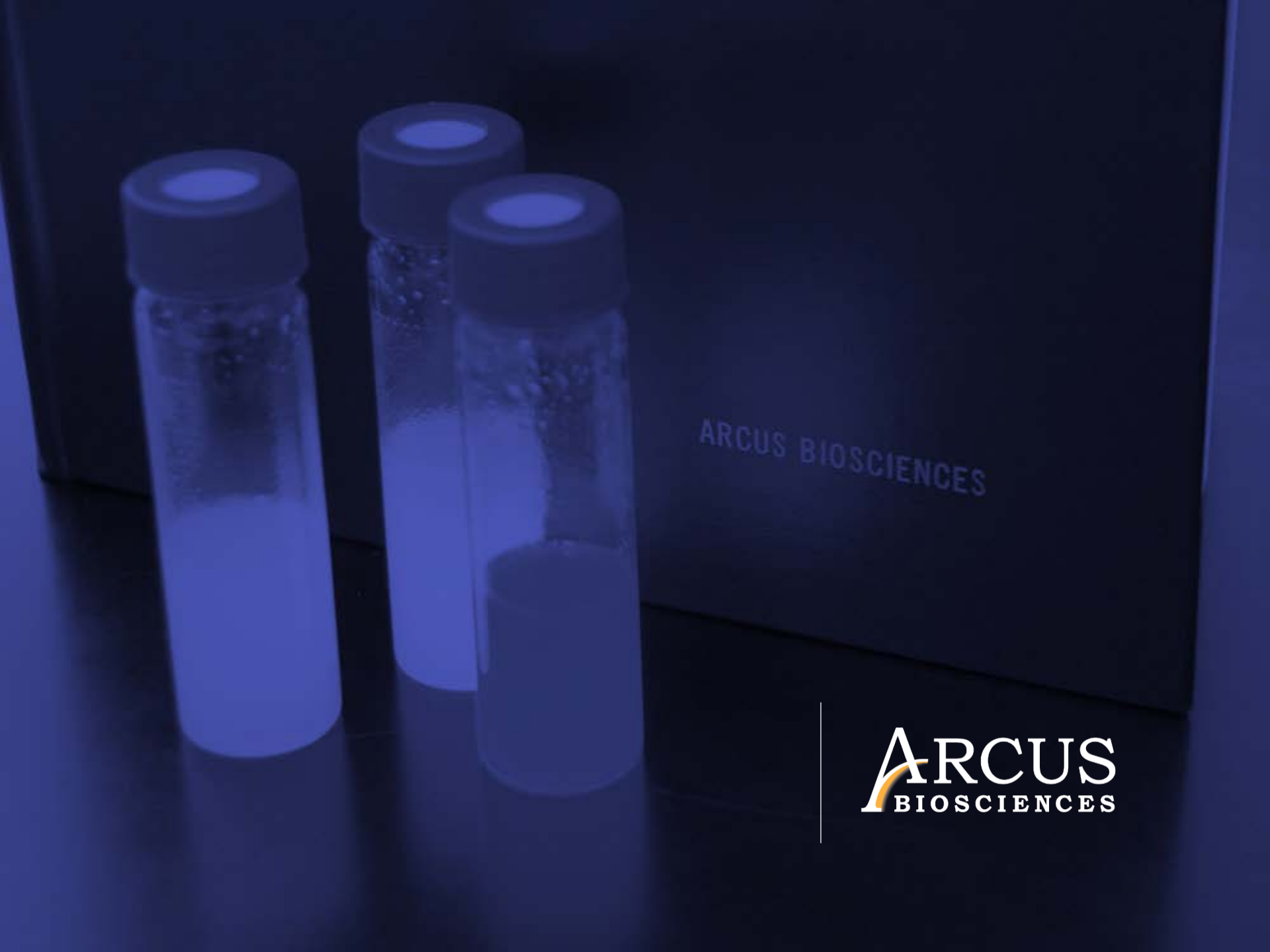

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