

Creating Innovative Cancer Immunotherapies by Leveraging Underexploited Biological Opportunities

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Corporate Presentation

April 26, 2019

NYSE: RCUS

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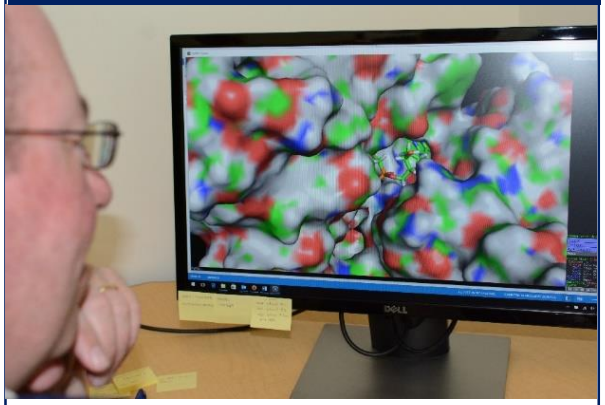
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CREATING INNOVATIVE CANCER IMMUNOTHERAPIES

Leverage *Underexploited Biological Targets* in Promising Pathways	Initial focus on ***ATP-adenosine pathway***
Broad, *Clinical Stage* Pipeline	Four clinical candidates with ***multiple data readouts in 2019***
World-class *Drug Discovery Engine*	***Small-molecule discovery engine*** to enable pipeline expansion
Proven Track Record	*Successful management team with **10+ years working together in multiple companies***
Well Capitalized	***$259.7 million in cash** and investments at 12/31/18*

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)

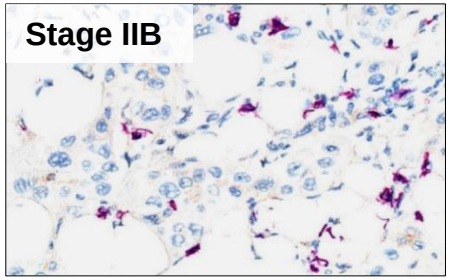
- AB680 (IV) — Phase 1 in HVs
- AB680 (oral) — IND-enabling

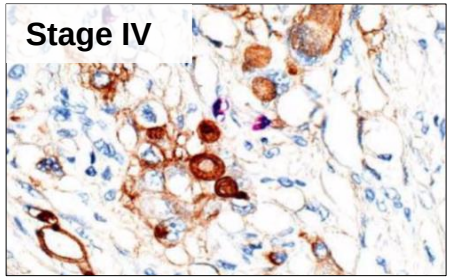
Antibodies

- AB122 (anti-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

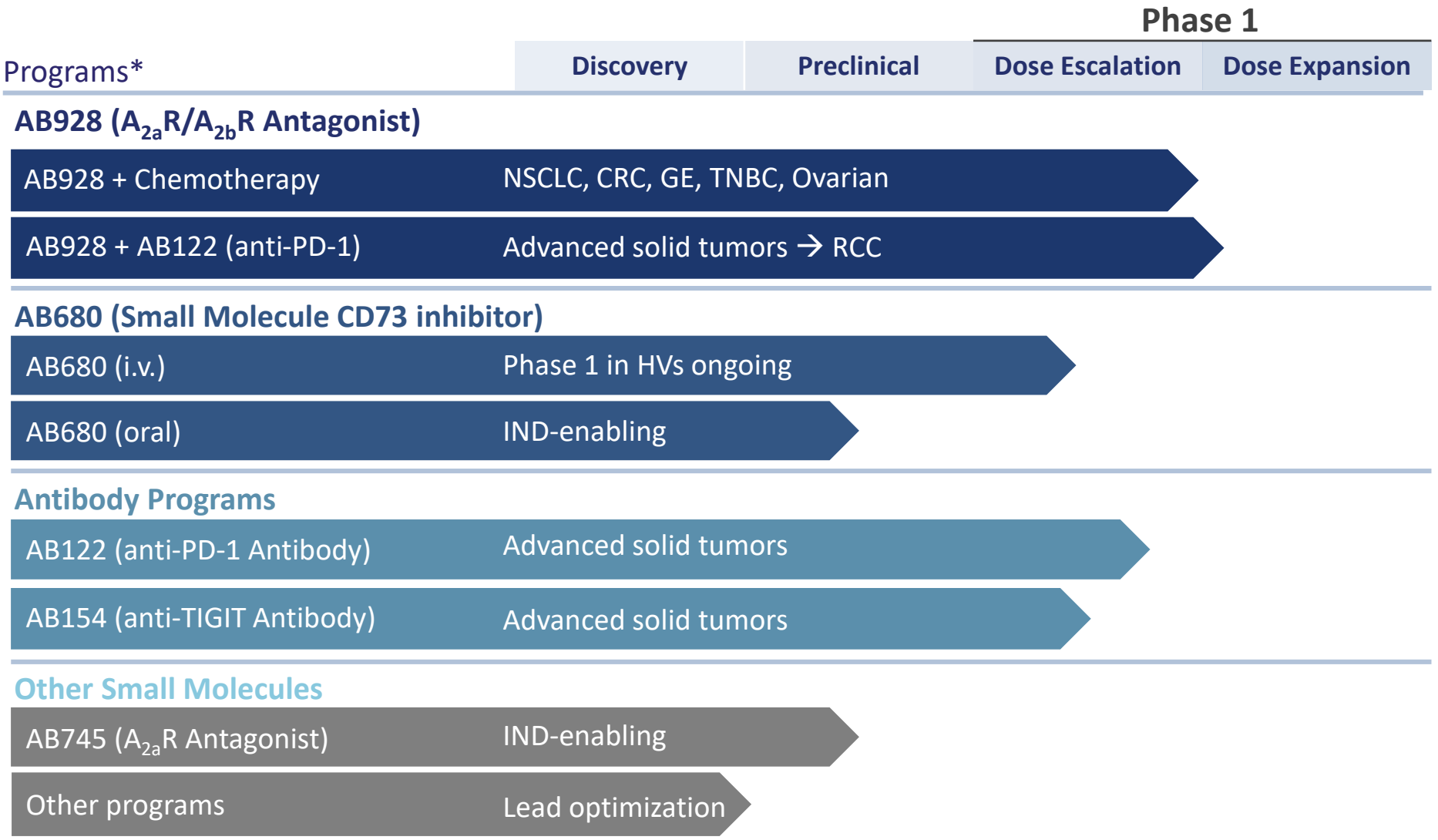
EARLY CLINICAL STRATEGY DESIGNED TO SUPPORT LONG TERM SUCCESS

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HEALTHY VOLUNTEER	FLEXIBLE TRIAL DESIGN	DOSE ESCALATION/ EXPANSION	BIOMARKERS
"Rapidly identify therapeutically relevant doses and achieve efficiency in oncology patient trials"	*"Ability to easily incorporate and investigate new clinical trial arms including standard of care (for randomization)"*	*"Robust early dataset in tumor-specific populations to inform late-stage design"*	*"Understand differences between responders and non-responders prior to registrational studies"*

Unique multi-tiered approach increases overall probability of success

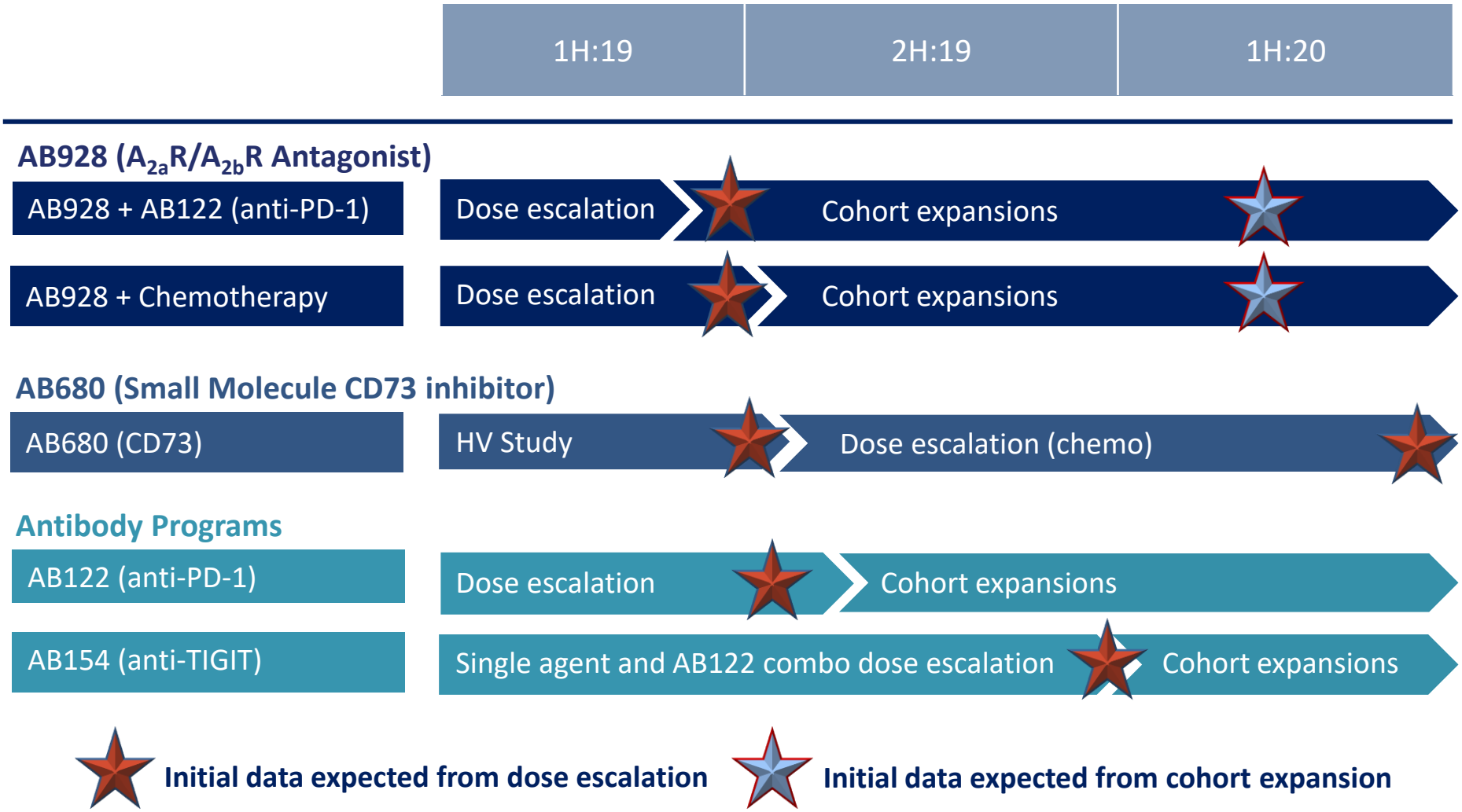
Broad Portfolio of Oncology Programs



* Taiho has an option to Arcus's programs in Japan and certain other Asian territories (excluding China) over a 5-year term. Taiho partnership generates $35M guaranteed payments over 3 years, additional opt-in payments and milestones, tiered-royalties. AB928 option exercised July 2018.

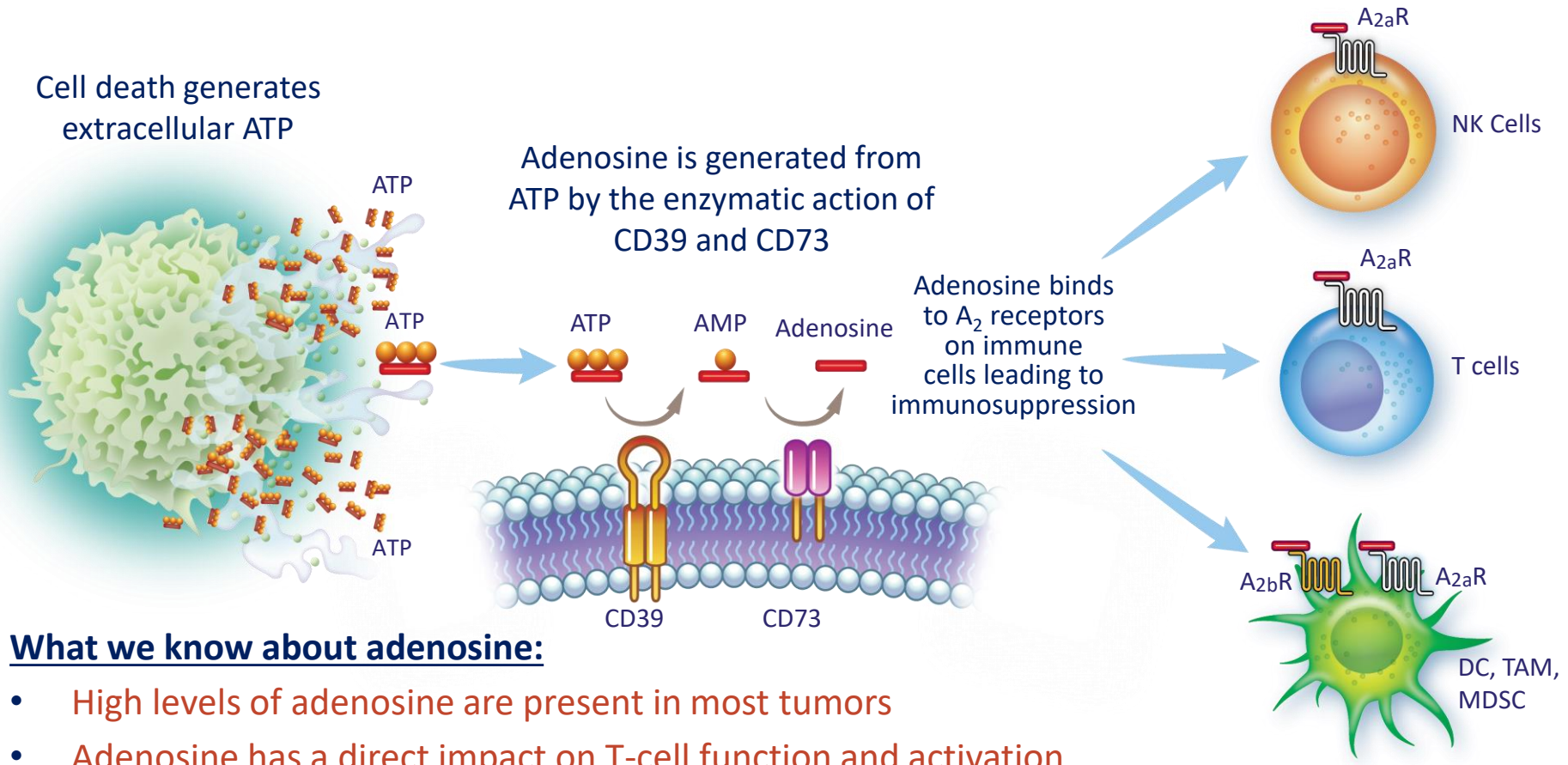
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Multiple Data Readouts in the Next 12 Months



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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 target for therapeutic intervention as well as a biomarker for patient screening

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Companies Are Expanding Their CD73-Adenosine Efforts

AstraZeneca

- A_2R antagonist **(n=276)**
  - NSCLC, CRPC & CRC
  - Combinations with PD-L1, abiraterone or enzalutamide
  - Study expanded multiple times
- CD73 + various combinations
  - Multiple solid tumors **(n=310)**
  - mutEGFR NSCLC **(n=98)**
  - Pancreatic **(n=204)**
  - TNBC **(n=100)**
- NSCLC: Platform studies with several other compounds **(n=920)**

NOVARTIS

- A_2R
  - Solid tumors and DLBCL (**n=260**)
- CD73 + A_2R (+ PD-L1)
  - Advanced solid tumors **(n=344)**
- TNBC: Platform study with several other compounds **(n=220)**

Bristol-Myers Squibb

- CD73
  - Multiple solid tumors (**n=221**)

Source: https://www.clinicaltrials.gov/

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 $A_{2a}R$ antagonists in clinical development:
  - Minimal shift in potency due to decreased non-specific protein binding
  - Minimal penetration of blood brain barrier
  - Ideal drug 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 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.

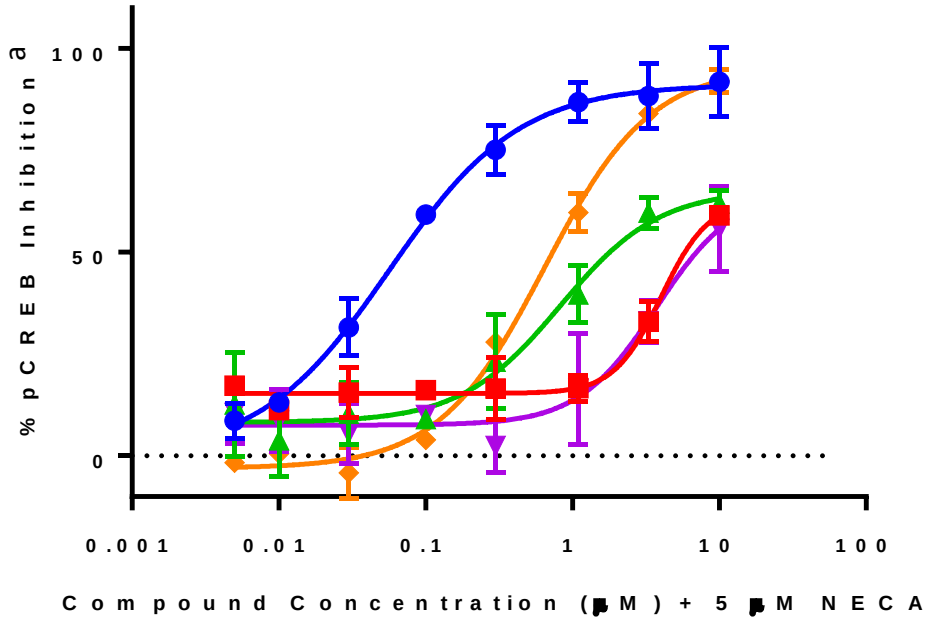
[b] CPI-444: Structure from AACR, April 2017 (#CT119), synthesized by Arcus; AZD4635: Structure from AACR, April 2017 (#2641), synthesized by Arcus; PBF509: Believed to be NIR178 (based on Pat Appl WO2017025918 and WO2018146612), synthesized by Arcus; Preladenant: was purchased from Ark Pharma (AK-43905).

[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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Phase 1 Trial in Healthy Volunteers Demonstrated an Excellent Safety Profile

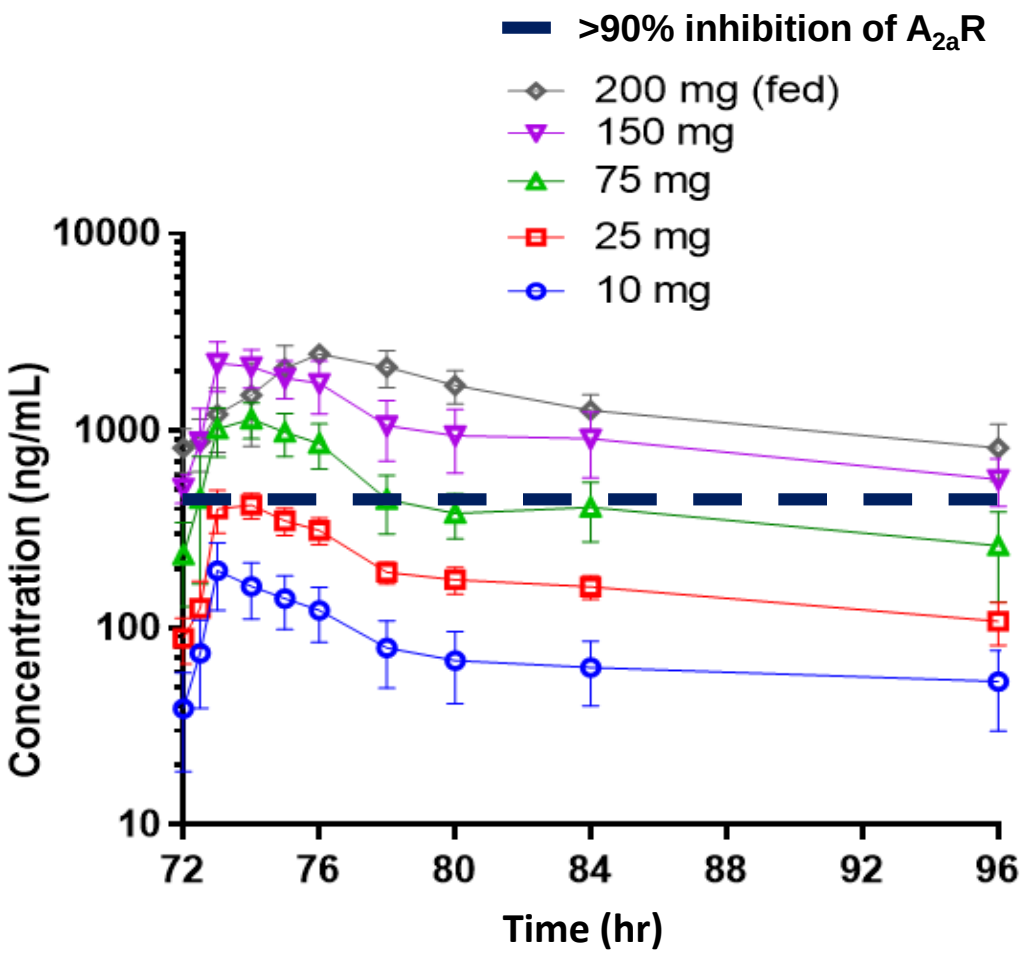
Design:

- Double-blinded, randomized, placebo-controlled trial
- n=80 randomized 3:1 to AB928 or placebo
- Included single ascending dose and multiple ascending dose (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

Multiple Ascending Dose Pharmacokinetics



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%).

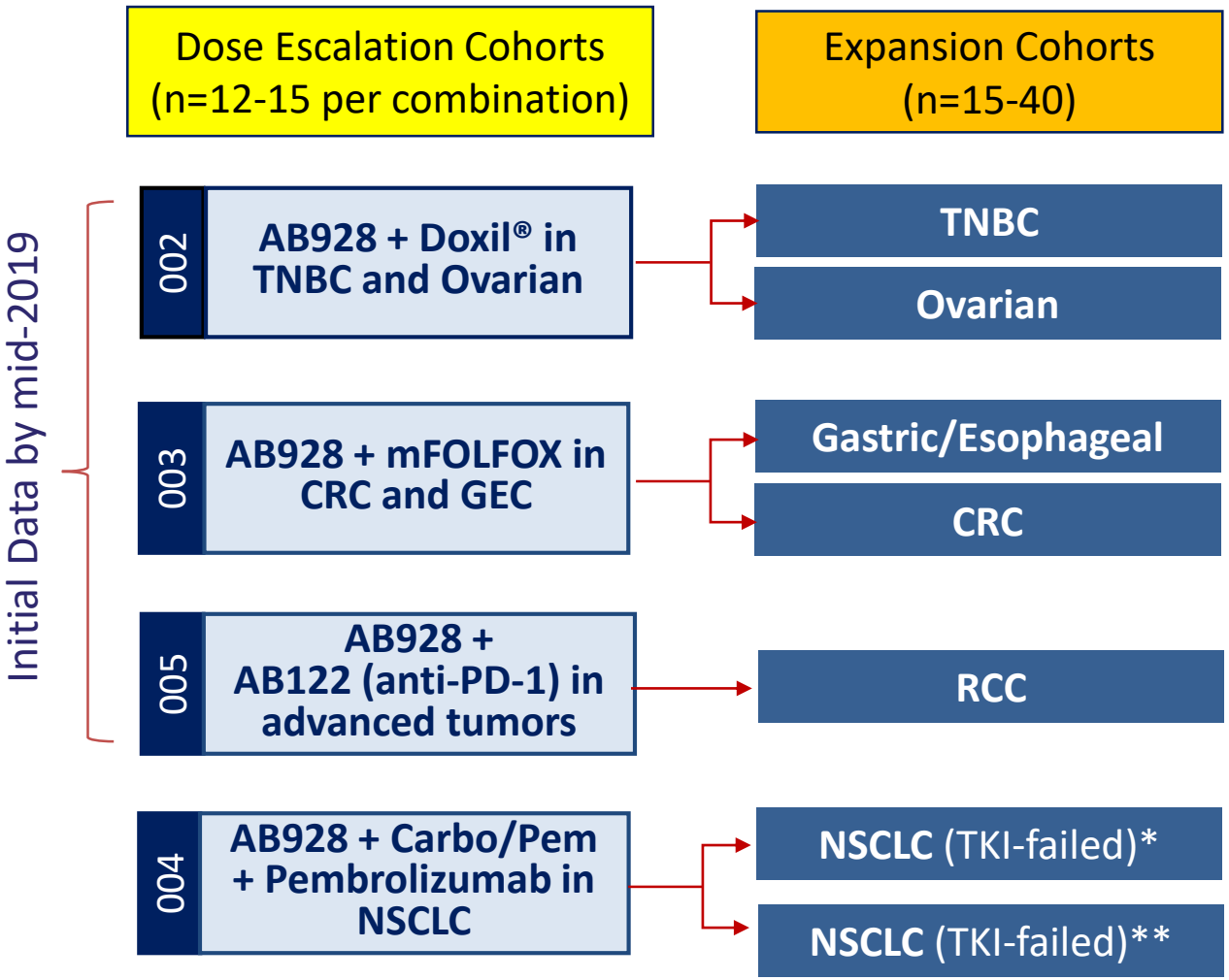
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Rationally-Selected Combinations and Settings for Early Clinical Trials

Areas of Focus
Tumor types selected based on high levels of CD73, extent of T-cell infiltration
Combinations with immunogenic cell death (ICD)-inducing chemotherapy
Tumor types/settings that are generally non-responsive to anti-PD1 therapy
Tumor types where current Standard of Care has low efficacy rates / significant unmet medical need

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Initial Data for 3 Dose-Escalation Trials by Mid-2019 & Dose Expansion Cohorts in 1H-2020



Flexible Trial Design

- Dose escalation cohorts will assess safety, PK, PD
- Expansion cohorts will assess ORR in first 15 patients
- Expand up to 40 patients if threshold response rate achieved
- Flexibility to add control arms to the protocols

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* AB928 + Carbo/Pem

** AB928 + Carbo/Pem + anti-PD-1

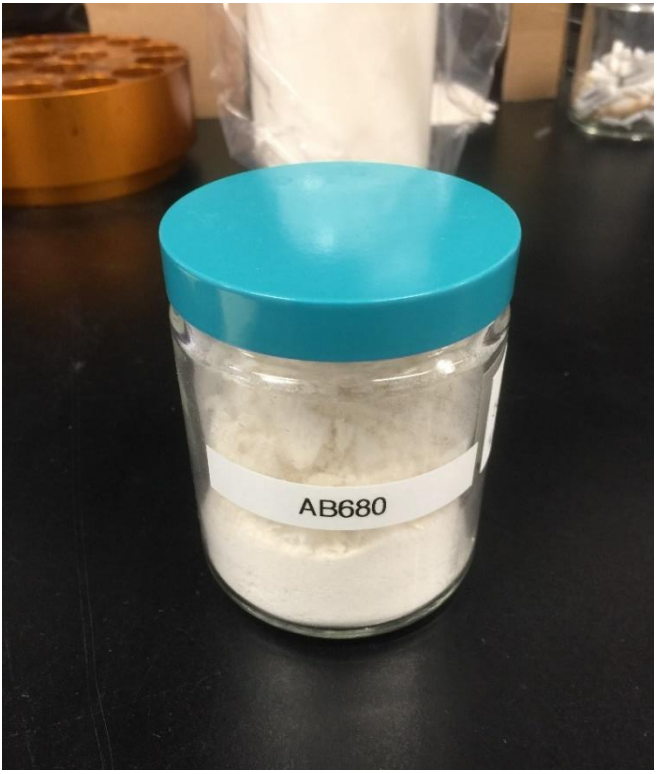
Extensive Biomarker Plan in Ongoing AB928 Cancer Trials

	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
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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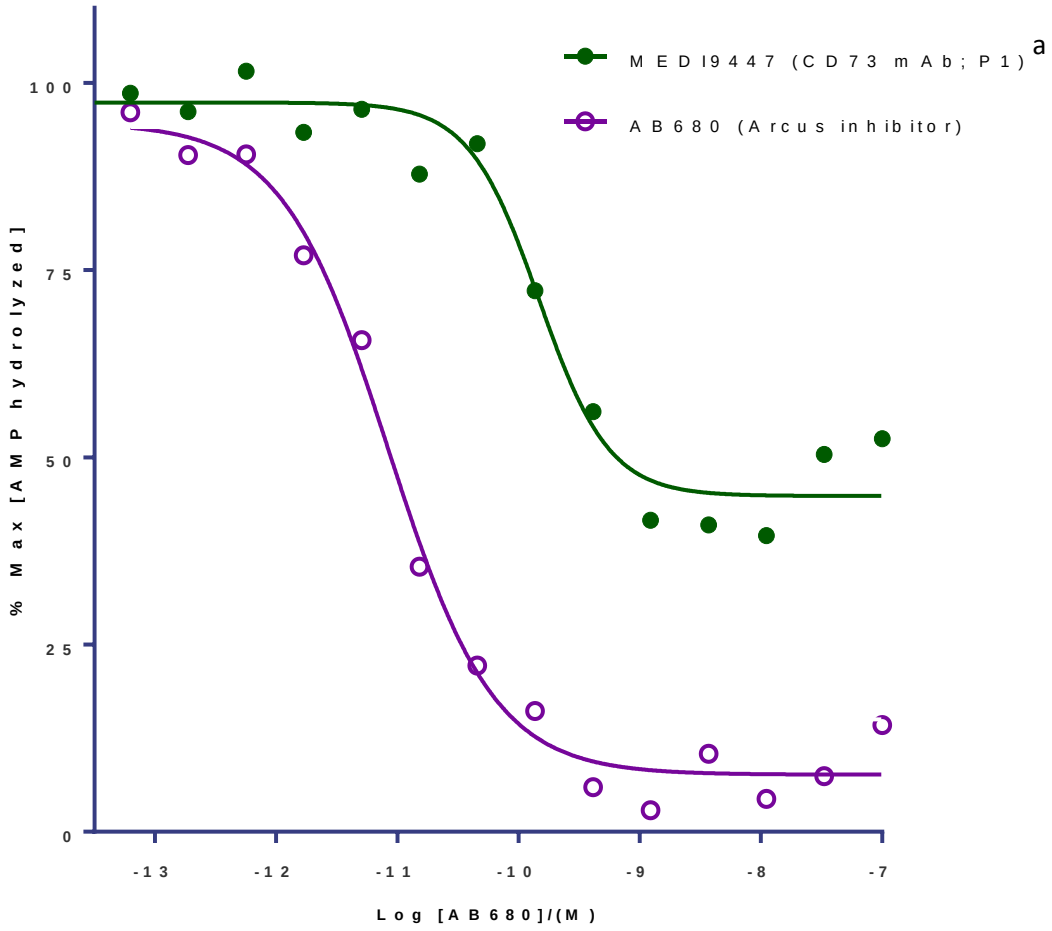
AB680: First Small-Molecule CD73 Inhibitor to Enter Clinical Development



- 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 mid:2019
- 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.

Healthy Volunteer (HV) Trial for AB680 is Enrolling

Trial Design

- ✓ Single ascending dose design
- ✓ Cohorts (n=8) randomized (3:1) to AB680 or placebo

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 expected in mid-2019
- ✓ Initiation of clinical trials in cancer patients expected in 2H:19

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



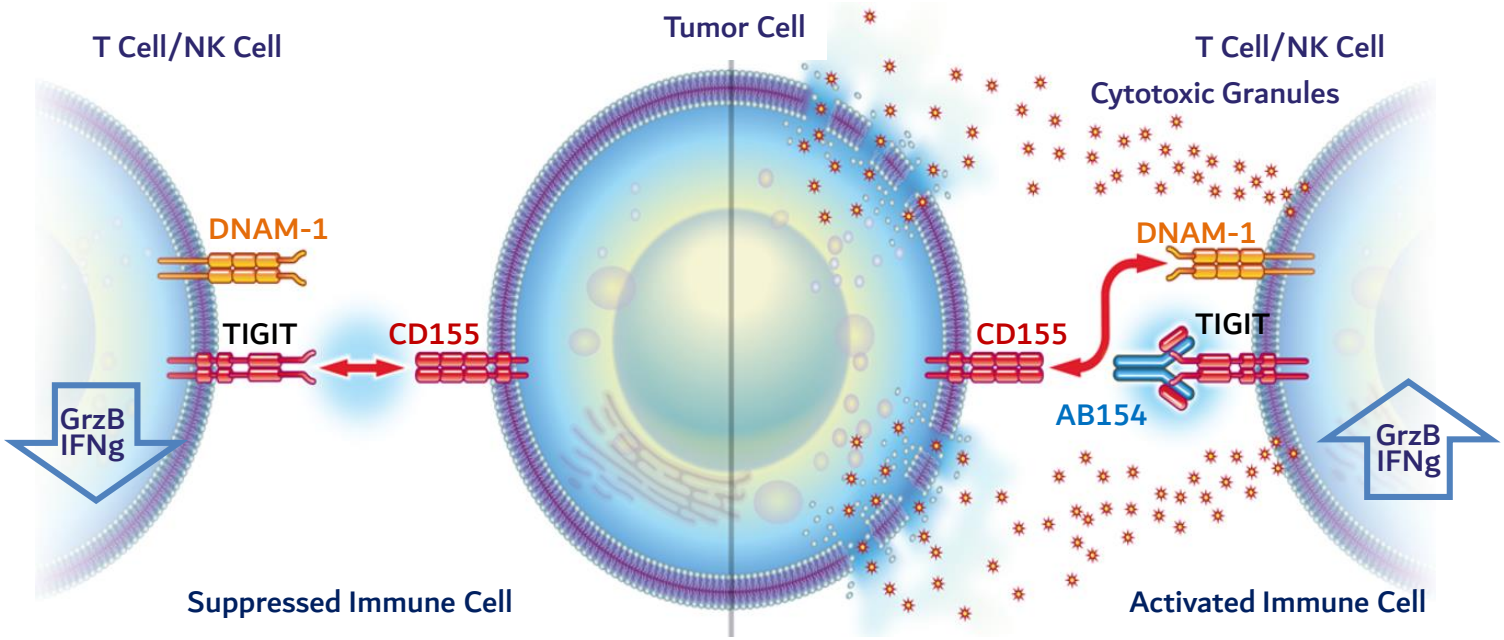
- Fully human antibody with similar binding affinity and other characteristics to pembrolizumab and nivolumab
- In-licensed from WuXi, a leading biologics manufacturer
  - Full development and commercialization rights in the US, Europe, Japan and certain other territories
  - Complete flexibility to develop as single agent and in combination; 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
- Ongoing Ph 1 combination trial with AB928 (005 trial)
- Evaluating AB122 monotherapy development strategies

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

Dual Mechanism of Action that Reflects the uniqueness of TIGIT Pathway

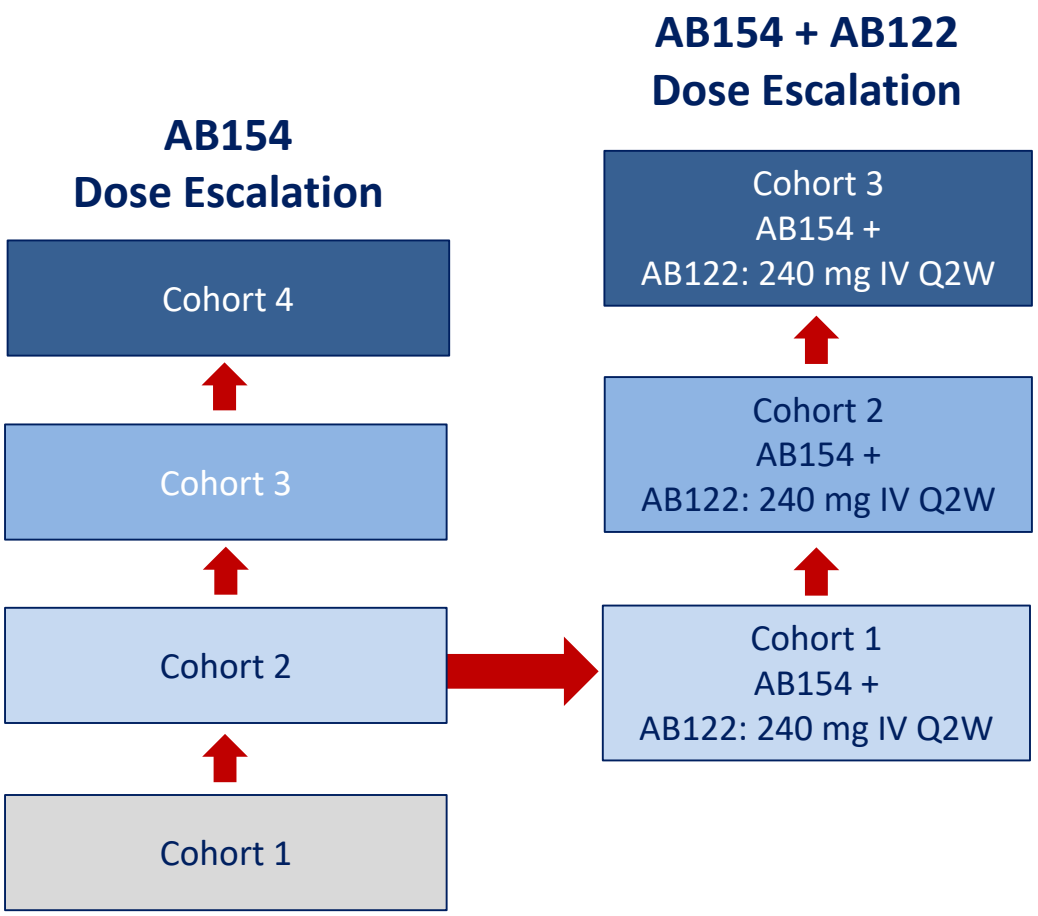
Blocking TIGIT inhibits an immuno-suppressive pathway while freeing up CD155 to bind to DNAM-1 which is an immune-activating pathway



- AB154 is a humanized anti-TIGIT antibody effector function silence Fc
  - Binds to a different epitope than other TIGIT antibodies
- AB154 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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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

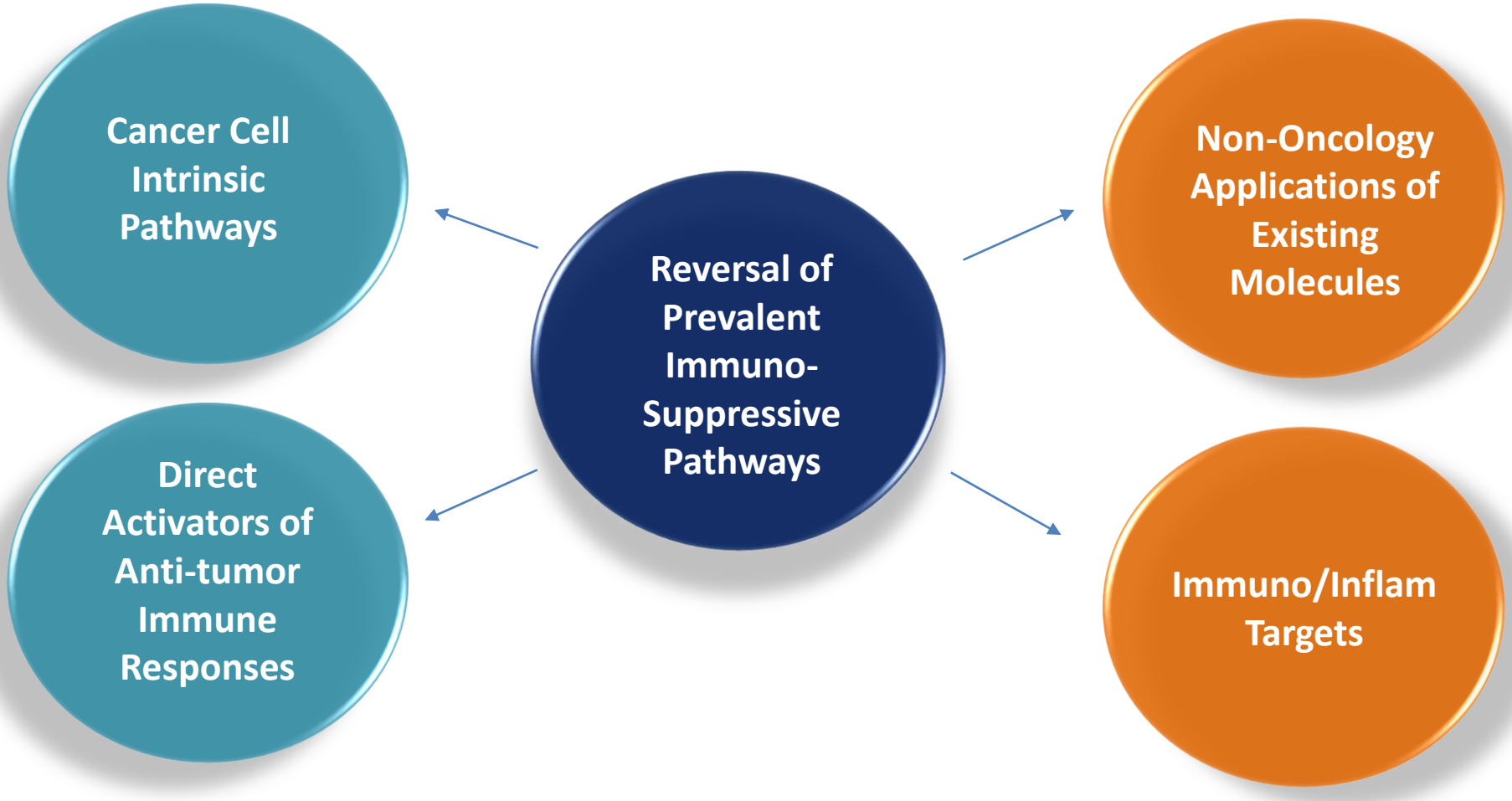
Next steps

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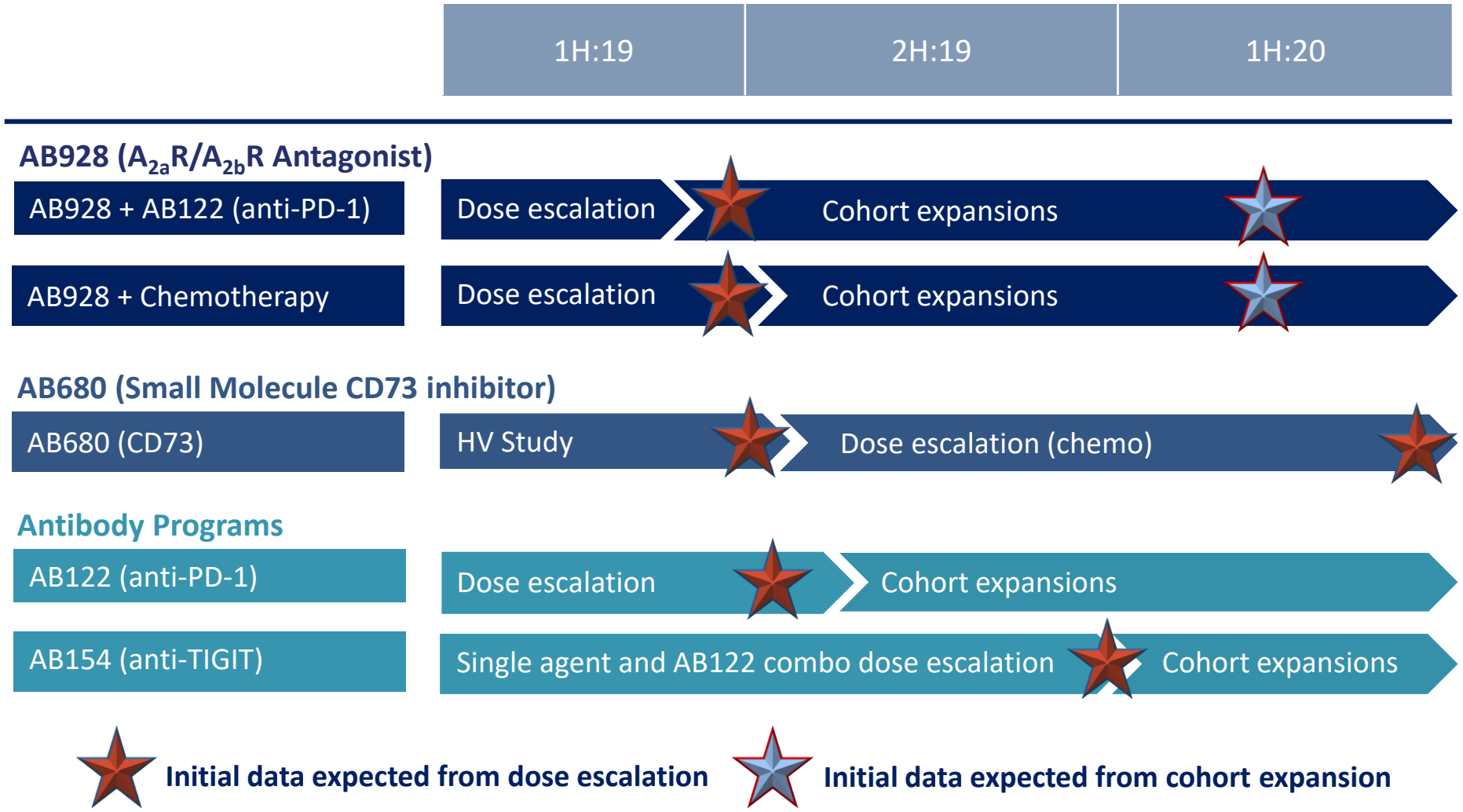
Active Early Stage Discovery Effort Focused on Small-Molecule Pipeline Expansion

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



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Multiple Data Readouts in the Next 12 Months



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