

# OUR VISION: COMBINING TO CURE WITH BEST-IN-CLASS CANCER THERAPIES

*NYSE: RCUS*

*MAY 2020*

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# Our Vision: Combining to Cure With Best-in-Class Cancer Therapies

| | |
|---|---|
| **Broad Clinical Portfolio with Four Molecules in Expansion and Randomized Studies** | • Advanced pipeline of products that target highly pursued IO pathways that are relevant in many tumor types<br>  • **AB928**: $A_{2a}R$ / $A_{2b}R$ antagonist – first and only dual antagonist in the clinic<br>  • **AB680**: CD73 inhibitor – first small-molecule in the clinic; exceptional potency<br>  • **AB154**: anti-TIGIT mAb – rapidly advancing in randomized combinations<br>  • **Zimberelimab (formerly AB122)**: anti-PD-1 mAb enabling portfolio combination strategies with clear line-of-sight to commercialization<br>• Flexible protocols designed for early generation of randomized data<br>• Major biomarker collection effort ongoing to support biomarker-based patient selection |
| **Drug Discovery Engine** | • Comprehensive, accomplished R&D team built from inception<br>• Sustainable creation of 1-2 IND candidates per year |
| **Proven Track Record** | • Management team with extensive expertise in immuno-oncology / oncology<br>• Demonstrated track record of success from discovery through commercialization |
| **Well Capitalized** | • ~$158 million in cash & investments *(as of 3/31/2020)* |



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# RCUS Investment Thesis

- **Advanced pipeline of products that target 3 of the most highly pursued IO pathways: TIGIT, Adenosine Axis, and PD-1**
  - Well-understood science; Relevant in many tumor types; Potential biomarkers for patient selection
- **Pathways significantly de-risked based on the totality of available internal and external clinical data**
- **Multiple product candidates for major pathways (e.g., TIGIT, adenosine) increases probability of success and de-risks potential issues resulting from remaining scientific questions**
- **Unique intra-portfolio combinations not available to any other company**
- **Early signs of clinical activity from our ongoing trials will be followed by preliminary randomized data in multiple settings/combinations during 2H2020**



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# Strategic in Our Choices of Targets and Combinations; Purposeful in Our Decisions and Investments

- **Critical pathways and targets**
  - **Essential Backbones:**
    - **AB154**: anti-TIGIT mAb – rapidly advancing in randomized combinations
    - **Zimberelimab**: anti-PD-1 mAb with clear line-of-sight to commercialization, enables portfolio combination strategies
  - **Adenosine Axis:**
    - **AB928**: $A_{2a}R$ / $A_{2b}R$ antagonist – first and only dual antagonist in the clinic
    - **AB680**: CD73 inhibitor – first small-molecule in the clinic; exceptional potency
- **Best molecules: properties, modality, and biology**
- **Critical aspect of discovery strategy, focus and investment: enabling long-term success**
- **New programs likely to have synergistic activity with other molecules in the Arcus portfolio**
  - **PI3K-γ and HIF-2α**



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# Expanding on Proven Clinical Roles of These Pathways: Combinations Address Major Areas of Clinical Need and Are Uniquely Enabled by Arcus Pipeline

*-- Illustrative Major Tumor Types Associated with Each Pathway –*
*-- See Next Slide for Our Complete Clinical Development Plan --*

| | NSCLC | CRC | PDAC | CRPC | TNBC |
|---|---|---|---|---|---|
| Adenosine | ✓ | ✓ | ✓ | ✓ | ✓ |
| TIGIT | ✓ | ✓ | ✓ | | ✓ |
| PD-1 | ✓ | ✓ | ✓ | ✓ | ✓ |

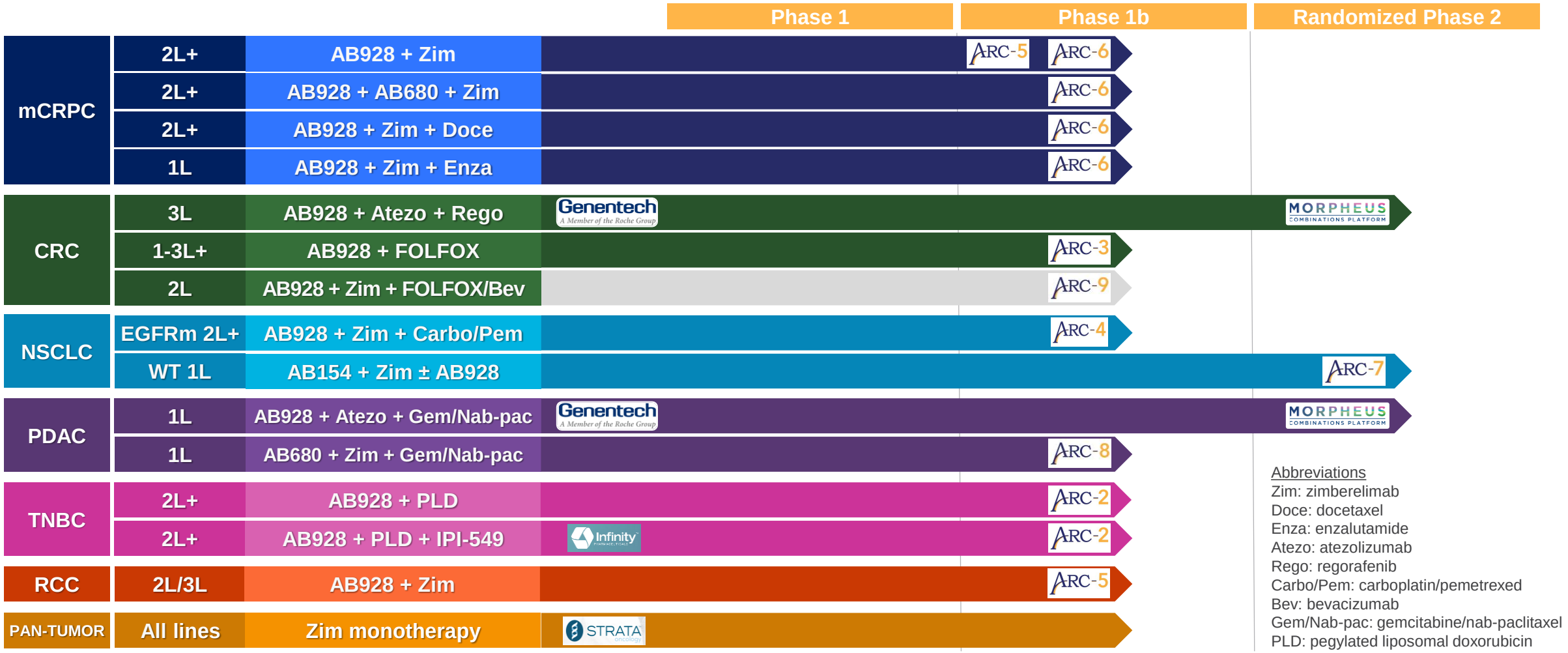
- ARC-4 Zim + Carbo/Pem ± AB928
- ARC-7 Zim ± AB154 ± AB928
- ARC-3 AB928 + FOLFOX
- MORPHEUS COMBINATIONS PLATFORM AB928 + Rego + Atezo
- MORPHEUS COMBINATIONS PLATFORM AB928 + Atezo + Gem/Nab-pac
- ARC-5 ARC-6 AB928 + Zim ± SOC
- ARC-2 AB928 + PLD

✓ Strong scientific rationale; current Arcus study
✓ Strong scientific rationale; future potential RCUS study

Key for abbreviations on next slide


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# Broad Clinical Program to Compete Aggressively in Settings with Significant Therapeutic and Commercial Potential




Abbreviations
Zim: zimberelimab
Doce: docetaxel
Enza: enzalutamide
Atezo: atezolizumab
Rego: regorafenib
Carbo/Pem: carboplatin/pemetrexed
Bev: bevacizumab
Gem/Nab-pac: gemcitabine/nab-paclitaxel
PLD: pegylated liposomal doxorubicin
SOC: standard of care

ONGOING
PLANNED

**AB680**: CD73 inhibitor
**Zim**: PD-1 mAb
**AB928**: Dual $A_{2a}R/A_{2b}R$ antagonist
**AB154**: TIGIT mAb


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# Important 2020 Clinical Milestones

| | Mid-2020 | EOY 2020 |
|---|---|---|
| AB154 (TIGIT mod.IgG1) | Ph2 in 1L NSCLC (ARC-7) enrolling | Prelim. randomized data in 1L NSCLC (ARC-7) |
| AB928 ($A_{2a}R/A_{2b}R$) | Prelim. data from Ph1b expansion cohorts | Prelim. randomized data; multiple studies (NSCLC, CRC, PDAC) |
| AB680 (CD73) | Ph1 in 1L PDAC (ARC-8) enrolling | Prelim. data in 1L PDAC (ARC-8) |
| Zimberelimab (PD-1) | Ph2 in 1L NSCLC (ARC-7) enrolling | Prelim. randomized data in 1L NSCLC (ARC-7) |



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# AB928 & AB680

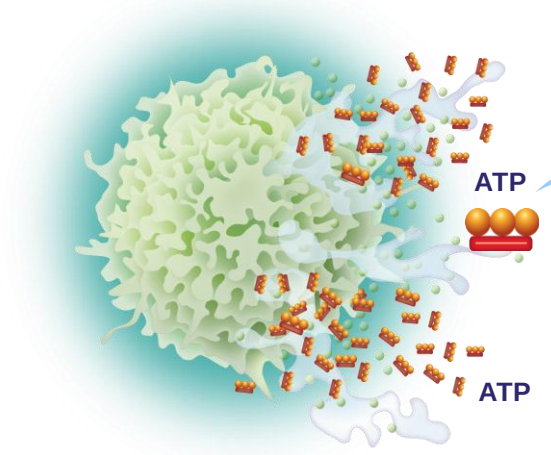
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# Arcus is a Leader in the Development of Therapeutics that Target the Adenosine Axis

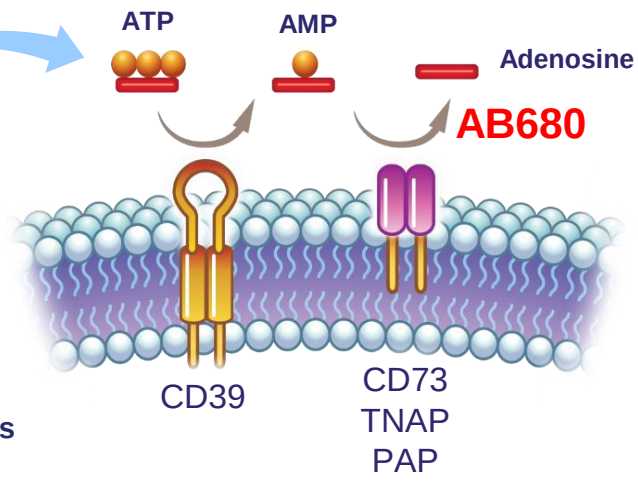
## The Adenosine Axis

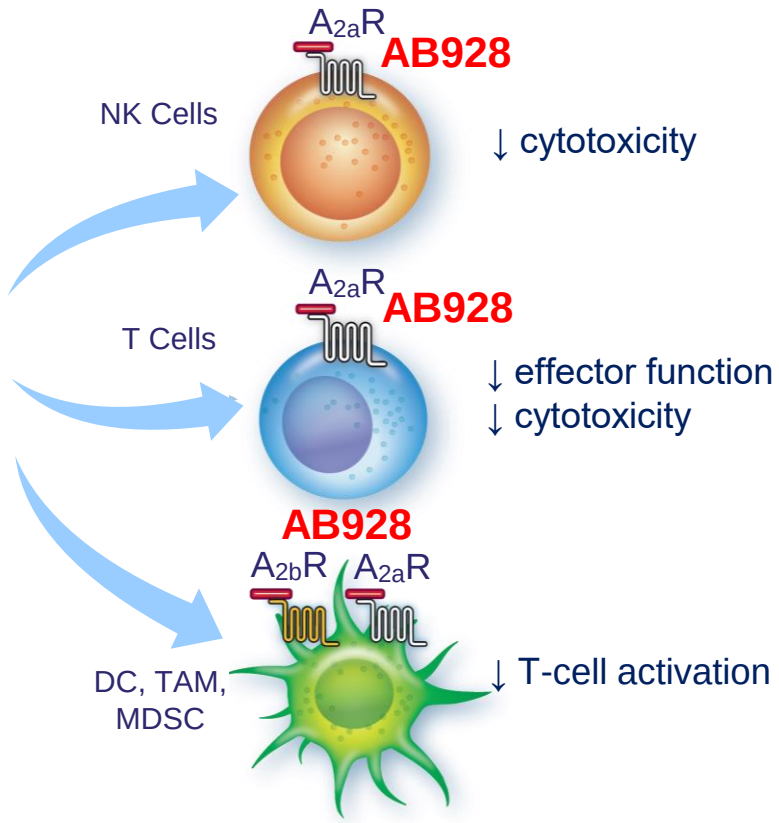
*-- Well-established and Critical Role in Tumor-associated Immune Suppression --*

**Extracellular ATP released by dying cells, particularly when triggered by immunogenic chemotherapy**




**Adenosine is generated from ATP by the enzymatic action of CD39 and CD73**




**Adenosine is produced by enzymatic machinery found on cancer cells; this adenosine prevents (directly and indirectly) activation of effector T cells that would otherwise kill those cancer cells**

**This science is well studied, unequivocal and understood at a molecular level; we can block the action of adenosine on immune cells (AB928) as well as inhibit its formation (AB680)**

TNAP: tissue non-specific acid phosphatase; PAP: prostatic acid phosphatase; DC: dendritic cell; TAM: tissue-associated macrophage; MDSC: myeloid-derived suppressor cell



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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 $A_{2a}R$ and $A_{2b}R$ receptors
- **Multiple advantages over other A2aR antagonists in clinical development:**
  - Minimal shift in potency due to decreased non-specific protein binding
  - Excellent penetration of tumor tissue
  - Excellent drug properties (PK, etc.)
- **Differentiated, highly efficient clinical development plan ongoing:**
  - First clinical program to evaluate an $A_2R$ antagonist with multiple different backbone therapies (e.g., anti-PD-(L)1, chemo, anti-TIGIT)

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

| Compound | $A_{2a}R$ Blood ($IC_{50}$, nM)[c] | $A_{2a}R$ ($K_B$, nM)[d] | $A_{2b}R$ ($K_B$, nM)[d] |
|---|---|---|---|
| **AB928** (Arcus) | **80** | **1.4** | **2.4** |
| CPI-444 [a,b] (Corvus) | ~10,000 | 5.4 | 493 |
| AZD 4635 [a,b] (AstraZeneca) | 2,600 | 1.7 | 64 |
| NIR178 [a,b] (Novartis) | ~10,000 | 58 | 189 |
| Preladenant [a,b] (Merck) | 785 | 3.3 | 3,121 |

**AB928 has ideal pharmacological properties for an oncology drug**

| 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** |
| Full engagement of target across dosing time period in humans | **≥90% target inhibition at trough** |

[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; NIR178: Structure from WHO Drug Information, Vol. 32, No. 4, 2018; https://www.who.int/medicines/publications/druginformation/innlists/PL120.pdf?ua=1), synthesized by Arcus. Preladenant: Purchased from Ark Pharma (AK-43905).

[c] Measured in human blood CD8+ T cells; CREB is a transcription factor that becomes phosphorylated when A2aR is activated; thus, the level of pCREB inhibition is a measure of the ability of an A2aR antagonist to inhibit A2aR.

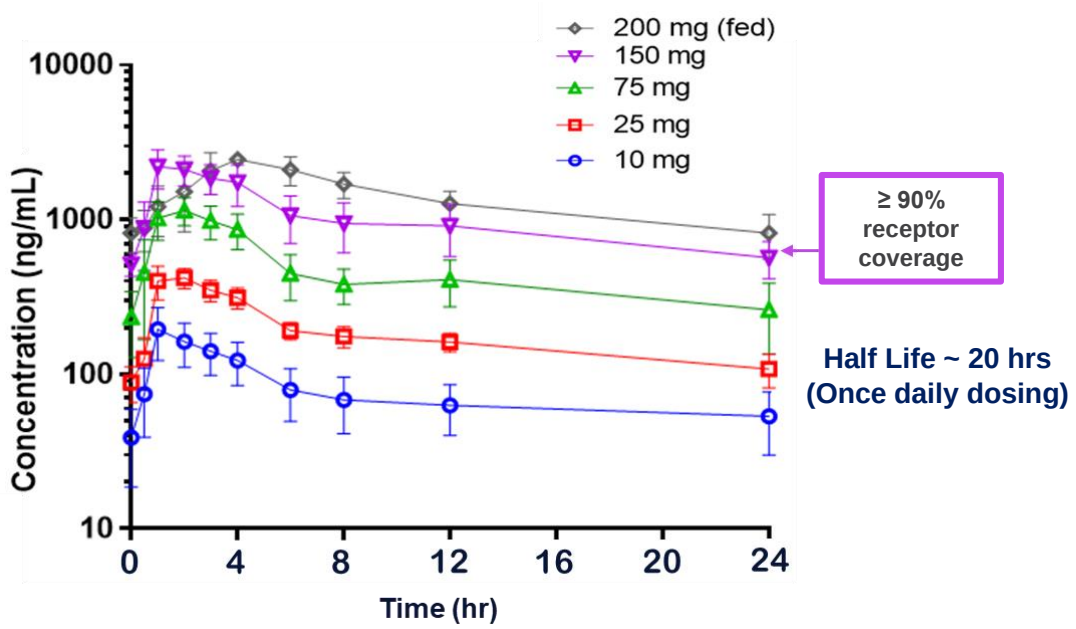
[d] $K_B$ is a measure of a compound's thermodynamic ability to bind/block its target receptor; lower $K_B$ values reflect greater potency for a given receptor.



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# AB928:
# Excellent Safety, PK/PD Profile, & “24/7” Target Coverage

## Excellent Human PK Profile[1]




## Optimal Receptor Coverage Achieved at 150 mg QD

| Dose Level | % Receptor Coverage (Inhibition of 5 µM NECA) | |
|---|---|---|
| | 2-hr Post-Dose | 24-hr Post-Dose |
| 200 mg | ≥ 90 % | ≥ 90 % |
| **150 mg [2]** | **100 %** | **≥ 90 %** |
| 75 mg | 100 % | 76 % |
| 25 mg | 82 % | 51 % |
| 10 mg | 51 % | (12 %) |

[1] PK/PD data from Phase 1 Healthy Volunteer study (Seitz et al. Invest. New Drugs. 2018); highly consistent PK/PD demonstrated in oncology patients

[2] 150 mg once daily dosing confirmed receptor coverage in oncology patients and was chosen as the dose for combinations



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# Four Dose-escalation Trials Established Safety/Tolerability of AB928 with Different Combination Backbones and Provide the Foundation for Ongoing Efficacy Studies

| | AB928 COMBINATION | DOSE-ESCALATION POPULATIONS |
|---|---|---|
| ARC-2 | AB928 + PLD[1] +/- IPI-549[2] | Advanced/Late-line TNBC and Ovarian |
| ARC-3 | AB928 + FOLFOX | Advanced/Late-line CRC |
| ARC-4 | AB928 + anti-PD1 + Carboplatin/Pemetrexed | Advanced/Late-line NSCLC |
| ARC-5 | AB928 + Zim (anti-PD1) | Advanced/Late-line Solid Tumors |

[1] PLD = pegylated liposomal doxorubicin
[2] PI3Kγ inhibitor; clinical collaboration with Infinity Pharmaceuticals
CRC = colorectal cancer, NSCLC = non-small cell lung cancer, TNBC = triple-negative breast cancer


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# AB928 was Well Tolerated Across Four Dose-escalation Studies in Combination with Other Therapies

- **AB928 exhibited a favorable safety profile across all combination regimens**
- **The only dose-limiting toxicity (DLT) observed was due to a Grade 2 rash in ARC-5 (AB928 + Zimberelimab)**
  - Patient restarted therapy post rash resolution
- **A maximum tolerated dose (MTD) of AB928 has not been reached in any of the combinations**
- **Only one possible Grade 4 AB928-related AE (thrombocytopenia) was reported in ARC-4 dose-escalation (AB928 + pembrolizumab + chemotherapy)**
  - Patient had a reported history of chemo-related thrombocytopenia
- **No Grade 5 AB928-related AEs were reported across the AB928 dose-escalation cohorts**
- **The PK and PD profiles of AB928 in cancer patients were similar to those previously characterized in healthy volunteers**
  - Once-daily dosing demonstrated a $t_{1/2}$ = 20 hrs
  - 150 mg QD provides ≥ 90% receptor coverage at trough

Data cut-off (DCO) of 27 Dec 2019



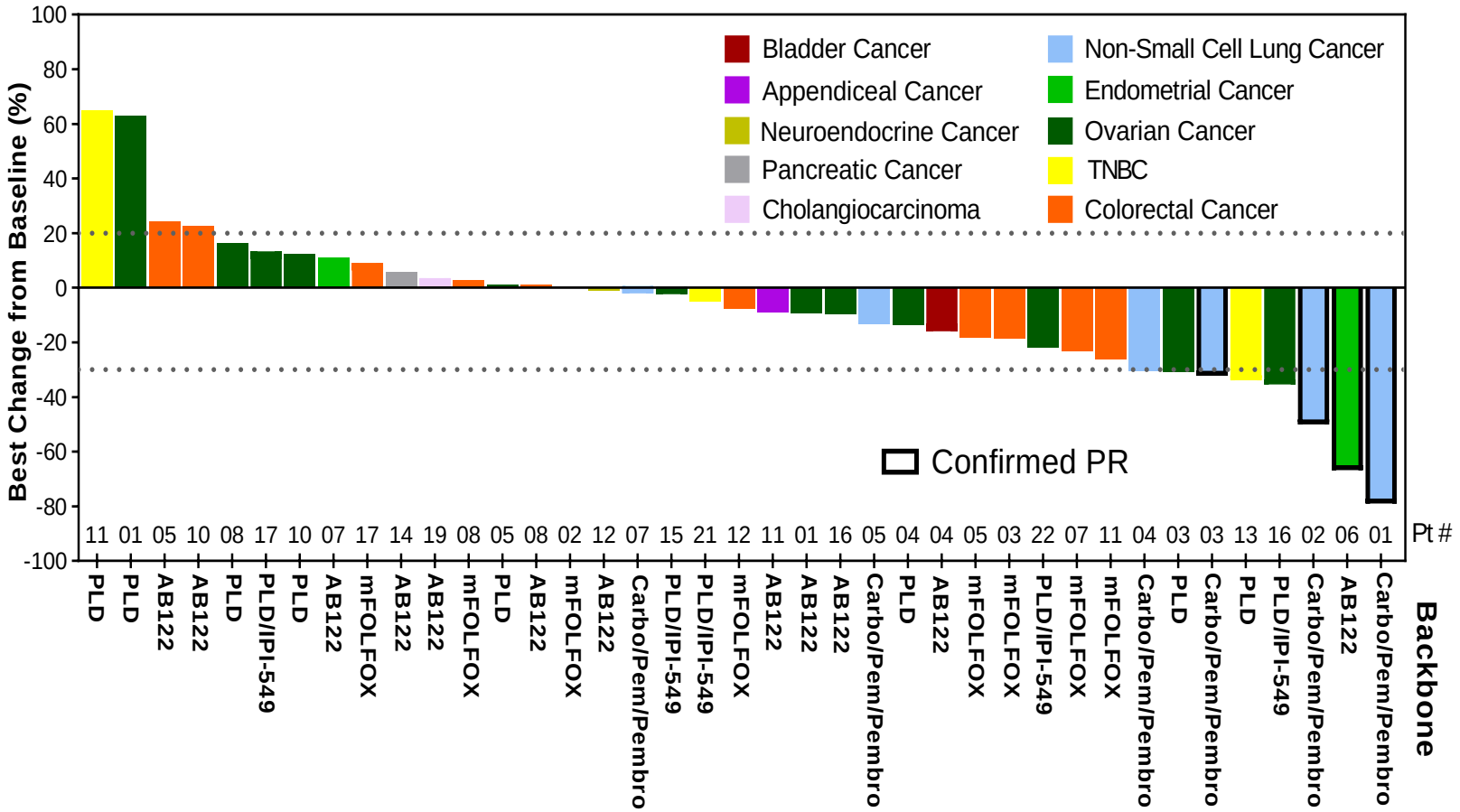
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# Phase 1 Combination Studies of Safety/Tolerability and PK/PD also Provided Early Efficacy Data Consistent with Clinical Hypotheses

## Summary

- **AB928 with chemo and/or anti-PD-1 therapy demonstrated tumor responses and prolonged disease stabilization in advanced tumor types (median 3-4 prior lines of therapy)**
  - **NSCLC:** partial responses observed in post-TKI and post-checkpoint failure pts
  - **GYN Malignancies:** PRs observed in ovarian and endometrial carcinoma pts
  - **CRC:** tumor shrinkage and prolonged disease stabilization >6 months were observed in heavily pre-treated patients, including patients with KRAS mutations
- **44% Disease Control Rate (CR/PR + SD ≥ 6 months) based on 17/39 evaluable patients, as of data cut-off**
- **Extensive biomarker studies ongoing**

## Waterfall Plot Across Evaluable Phase 1 Patients



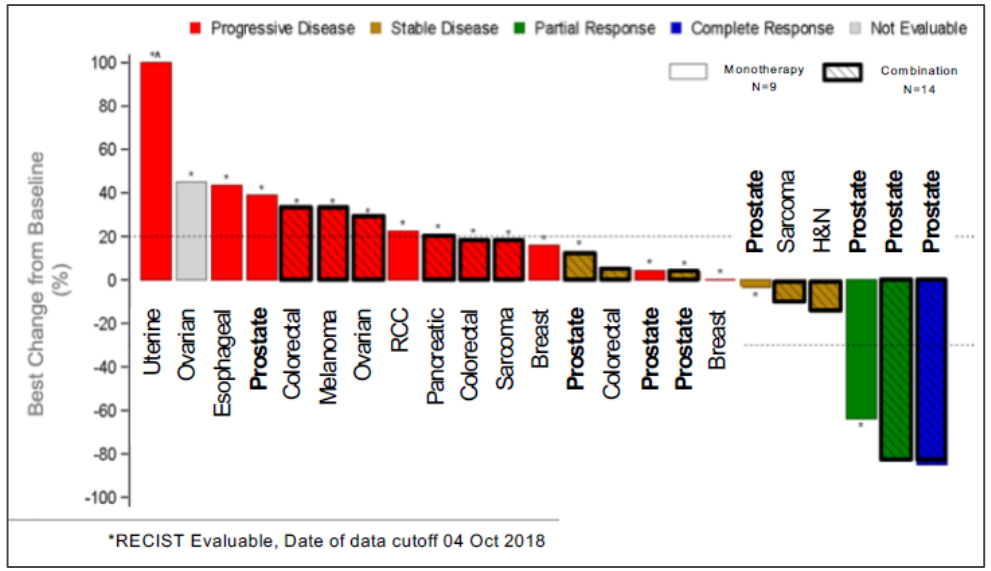

Data cut-off (DCO) of 27 Dec 2019

TKI = tyrosine kinase inhibitor; PLD = Pegylated liposomal doxorubicin; CR = complete response; PR = partial response; SD = stable disease



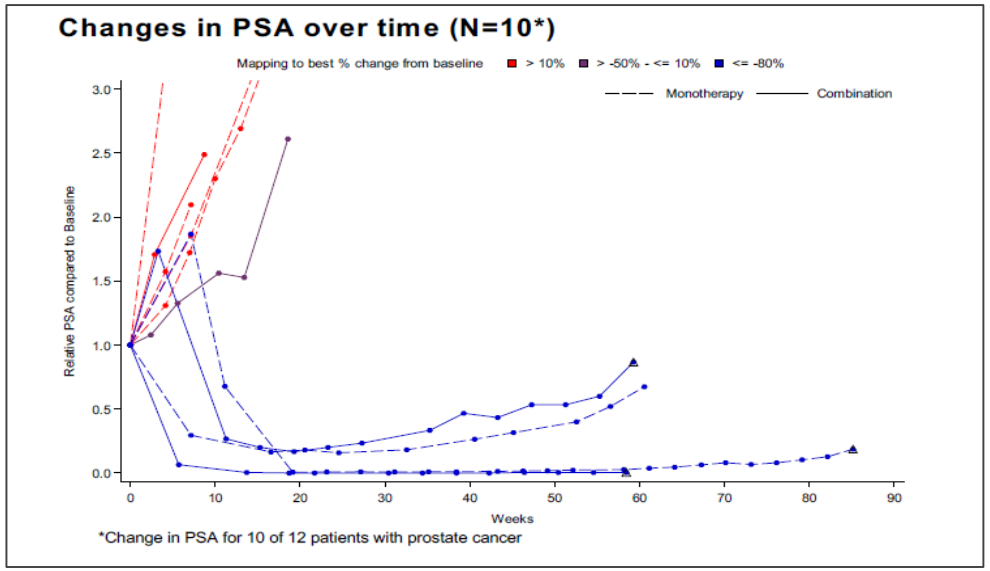
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# AZ Disclosed Activity of AZD4635 ($A_{2a}R$ Antagonist) in mCRPC, Leading to Broad Expansion of Studies in Prostate Cancer




Single Agent (N=4):
1 PR; 1 SD; 2 PD

Durva Combo (N=4):
1 CR; 1 PR; 2 SD




Bendell et al., (AACR 2019) Abstract CT026

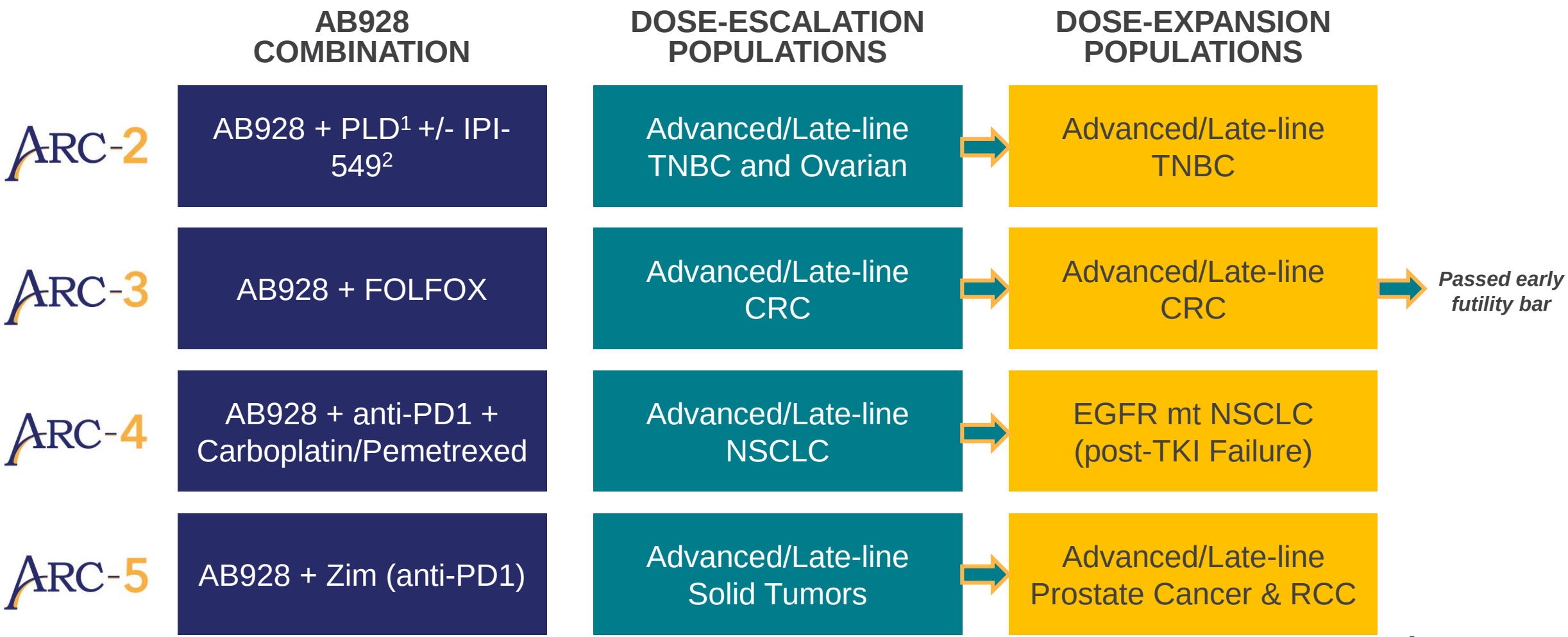
## Ongoing studies with >300 patients across 7 different cohorts in mCRPC alone

- 2L+ mCRPC: AZD4635 + enzalutamide
- 2L+ mCRPC: AZD4635 + abiraterone
- 2L+ mCRPC: AZD4635 (new formulation) + docetaxel
- 3L+ mCRPC: AZD4635 single agent
- 3L+ mCRPC: AZD4635 (new formulation) + durvalumab (PD-L1)
- 3L+ mCRPC: AZD4635 (new formulation) + oleclumab (CD73)
- 3L+ mCRPC: AZD4635 (new formulation) + oleclumab (CD73) + durvalumab (PD-L1)



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# Four Dose-escalation Trials Established Safety/Tolerability of AB928 with Different Combination Backbones and Provide the Foundation for Ongoing Efficacy Expansion Studies




[1] PLD = pegylated liposomal doxorubicin
[2] PI3Kγ inhibitor; clinical collaboration with Infinity Pharmaceuticals
CRC = colorectal cancer, NSCLC = non-small cell lung cancer, TNBC = triple-negative breast cancer



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# We are Running Multiple Expansion and Randomized Studies with AB928 in 2020

- **Several studies with randomized cohorts to evaluate combination vs. control**
  - Opportunity for biomarker-based selection of pts at randomization stage
- **Phase 1b data expected in mid-2020**
- **Early randomized data expected in 4Q20**
- **Settings/combinations selection criteria:**
  - Observed clinical activity
  - CD73 and/or adenosine levels
  - High unmet need

| Indication | Line | Combination |
|---|---|---|
| CRPC | 2L+ | AB928 + Zimberelimab |
| | 2L+ | AB928 + Zim + AB680 |
| | 2L | AB928 + Zim + Docetaxel |
| | 1L | AB928 + Zim + Enzalutamide |
| CRC | 3L | Regorafenib ± Atezo ± AB928 |
| | 1-3L | AB928 + FOLFOX |
| | 2L | AB928 + Zim + FOLFOX/Bev |
| NSCLC | EGFRm[1] 2L+ | AB928 + Zim + Pem/Carbo |
| | WT 1L | Zim ± AB154 ± AB928 |
| TNBC | 2L+ | AB928 + PLD |
| | 2L+ | AB928 + PLD + IPI-549 |
| PDAC | 1L | Gem/Nab-pac ± Atezo ± AB928 |
| RCC[2] | 3L | AB928 + Zim |

Initiated | Planned | Phase 2

Abbreviations
CRPC: metastatic castration-resistant prostate cancer; CRC: colorectal cancer; NSCLC: non-small cell lung cancer; TNBC: triple-negative breast cancer; PDAC: pancreatic ductal adenocarcinoma; RCC: renal cell cancer

Zim: zimberelimab; Doce: docetaxel; Enza: enzalutamide; Atezo: atezolizumab; Rego: regorafenib; Carbo/Pem: carboplatin/pemetrexed; Bev: bevacizumab; Gem/Nab-pac: gemcitabine/nab-paclitaxel; PLD: pegylated liposomal doxorubicin

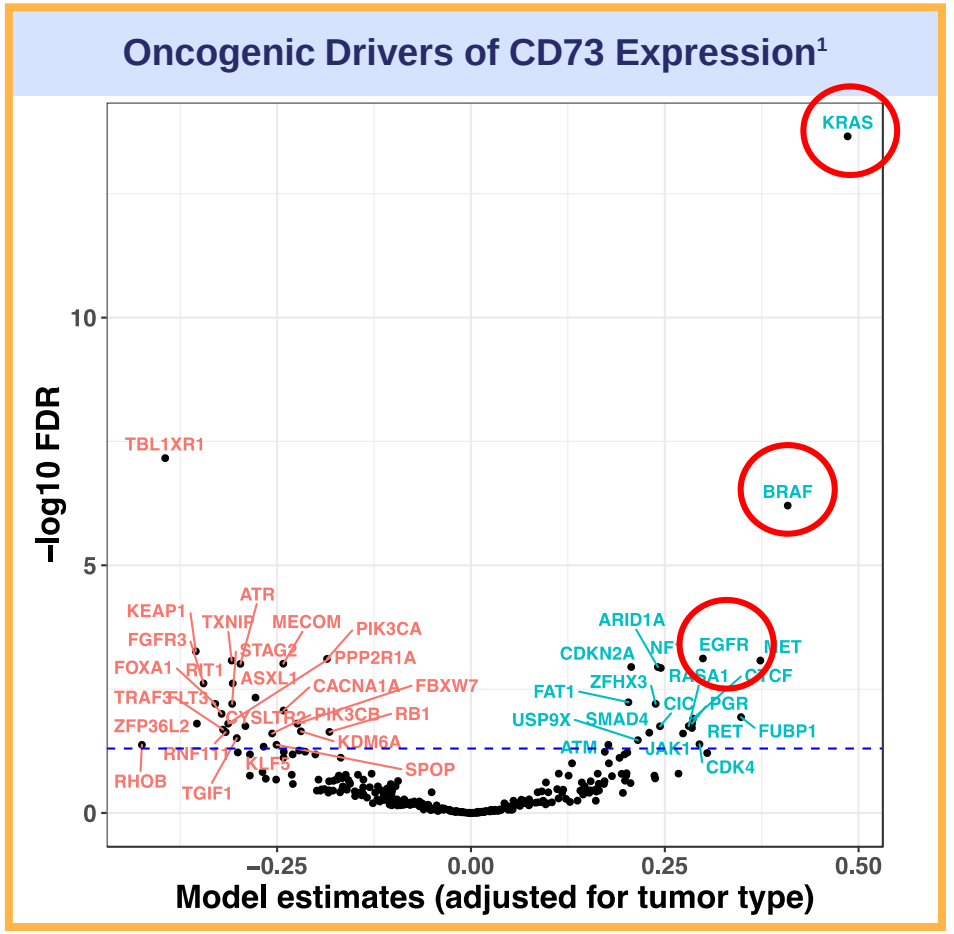
[1] Patients who have progressed on one or more tyrosine kinase inhibitors
[2] Patients who have progressed on a checkpoint inhibitor



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# Exciting New Insights into Adenosine Biology in Oncogene-driven Tumors Suggest Important Role for $A_{2b}R$ Blockade in Combination Strategies

- **Multiple oncogene mutations (e.g., KRAS, BRAF, EGFR) strongly associated with high expression of CD73 and $A_{2b}R$**
- **$A_{2b}R$ stands out among the 4 adenosine receptors because of its ability to activate MAP kinase pathway**
  - May explain the unique importance of $A_{2b}R$ in mediating effects of adenosine on dendritic cells
  - Cancer cells carrying certain mutations (e.g., KRAS) can both make more adenosine and activate adenosine signaling pathways synergistic with the oncogenic mutation
- **AB928 is the only adenosine receptor antagonist in the clinic that potently blocks $A_{2b}R$**



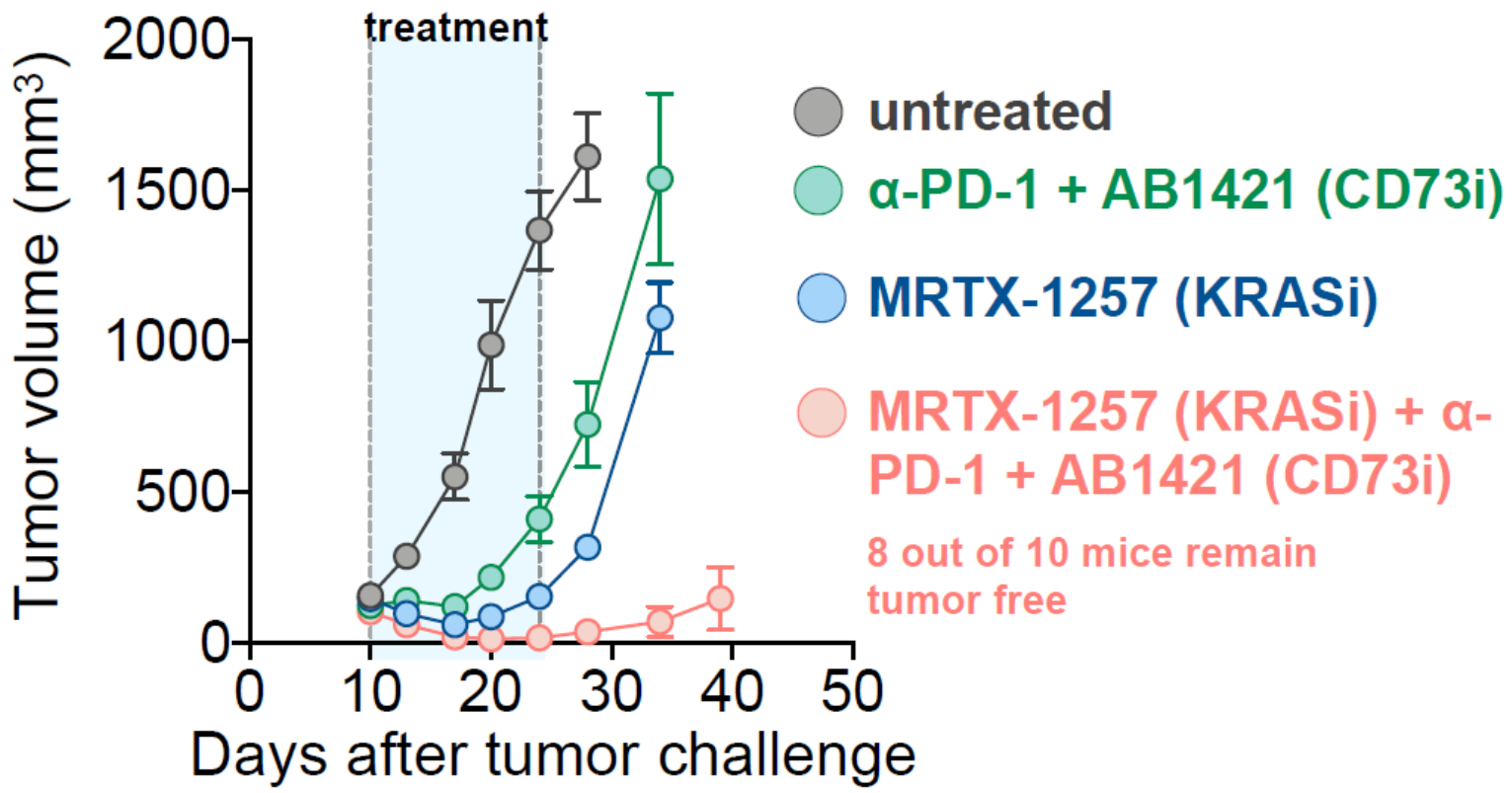

[1] Analysis of Tumor Cancer Genomic Atlas (TCGA) performed by Arcus



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# Co-targeting KRAS and CD73 Enhances Efficacy in a PDAC Mouse Model

**$KRAS^{G12C}/TP53^{R172H/+}$ PDAC Mouse Model[b]**




[a] Le et al., Abst. A46; Tumor Immunol. & Immunotherapy. Symposium, Boston, Nov 17-20, 2019. AB1421 is a close analogue of Arcus's clinical CD73 inhibitor (AB680)

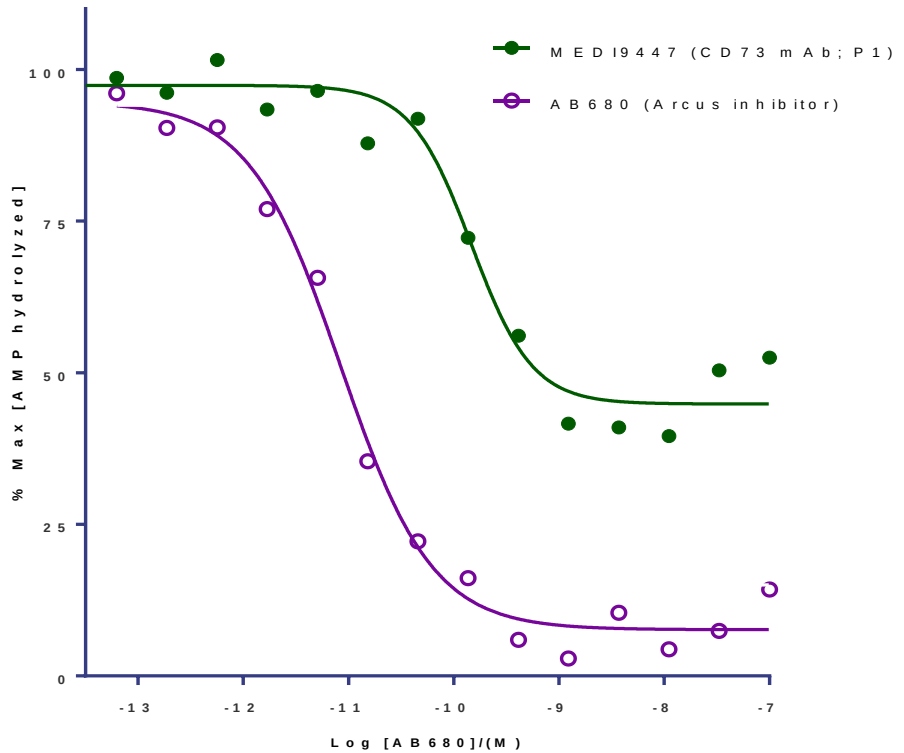


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# AB680: First Small-molecule CD73 Inhibitor to Enter Clinical Development

- **AB680 offers potential advantages over anti-CD73 antibodies in development:**
  - Greater inhibition of CD73 enzymatic activity (soluble & cell-bound)
  - Deeper tumor penetration
  - IV and oral formulations
- **Unique small-molecule properties**
  - Extraordinarily potent: $IC_{50}$ = 0.008 nM (T cells)
  - Low clearance, long half-life molecule
- **Oral formulation completed IND-enabling studies**

## AB680 Potently Inhibits CD73 Enzymatic Activity on $CD8^+$ T Cells

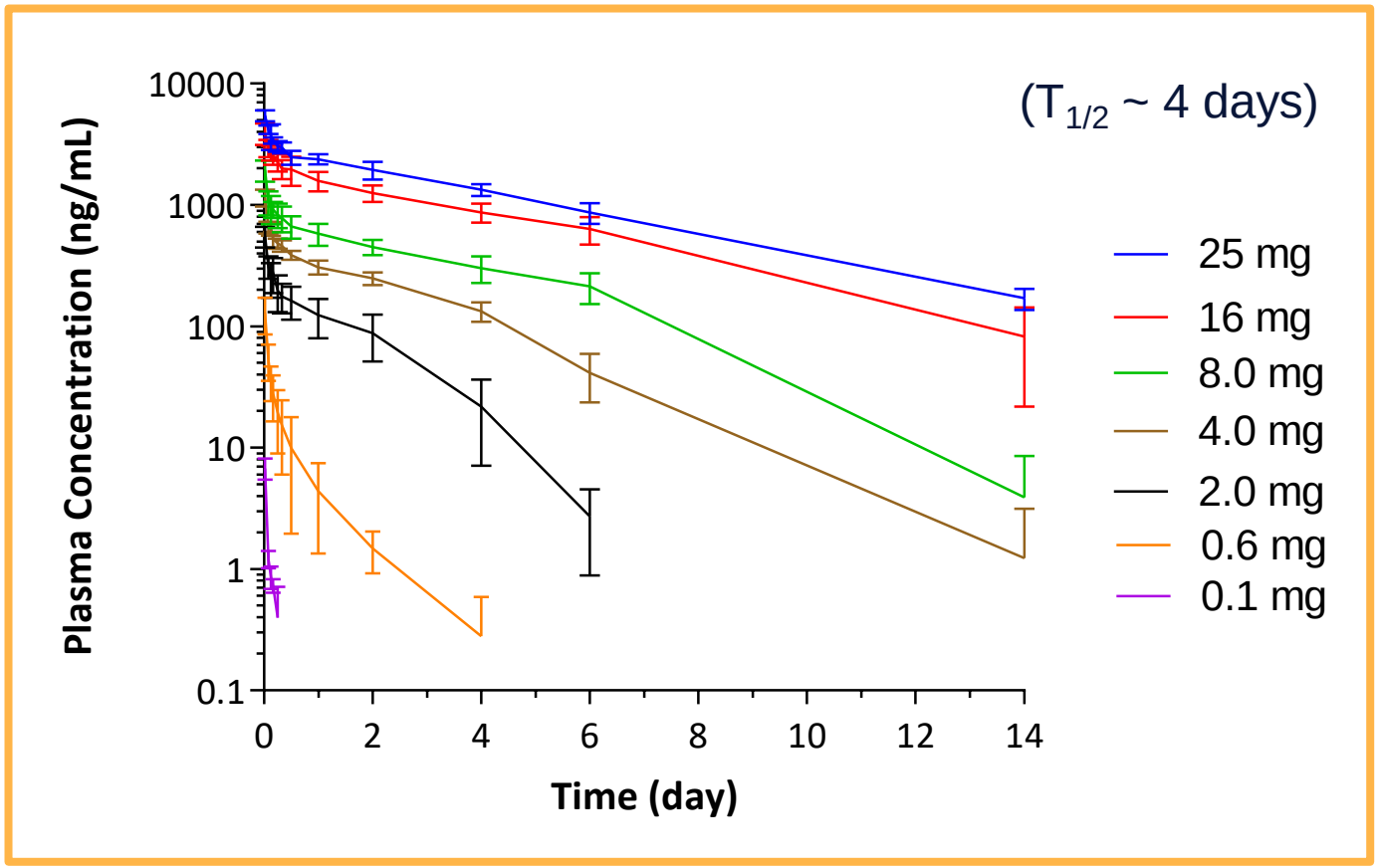



[a] MEDI9447 synthesized by Arcus based on the following publication and patent application: Hay et al., OncoImmunology (2016) 5, e1208875; Patent Appl. US 2016/0129108.



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# AB680 Displays Excellent PK Profile in Healthy Human Volunteers Consistent with q2w Dosing



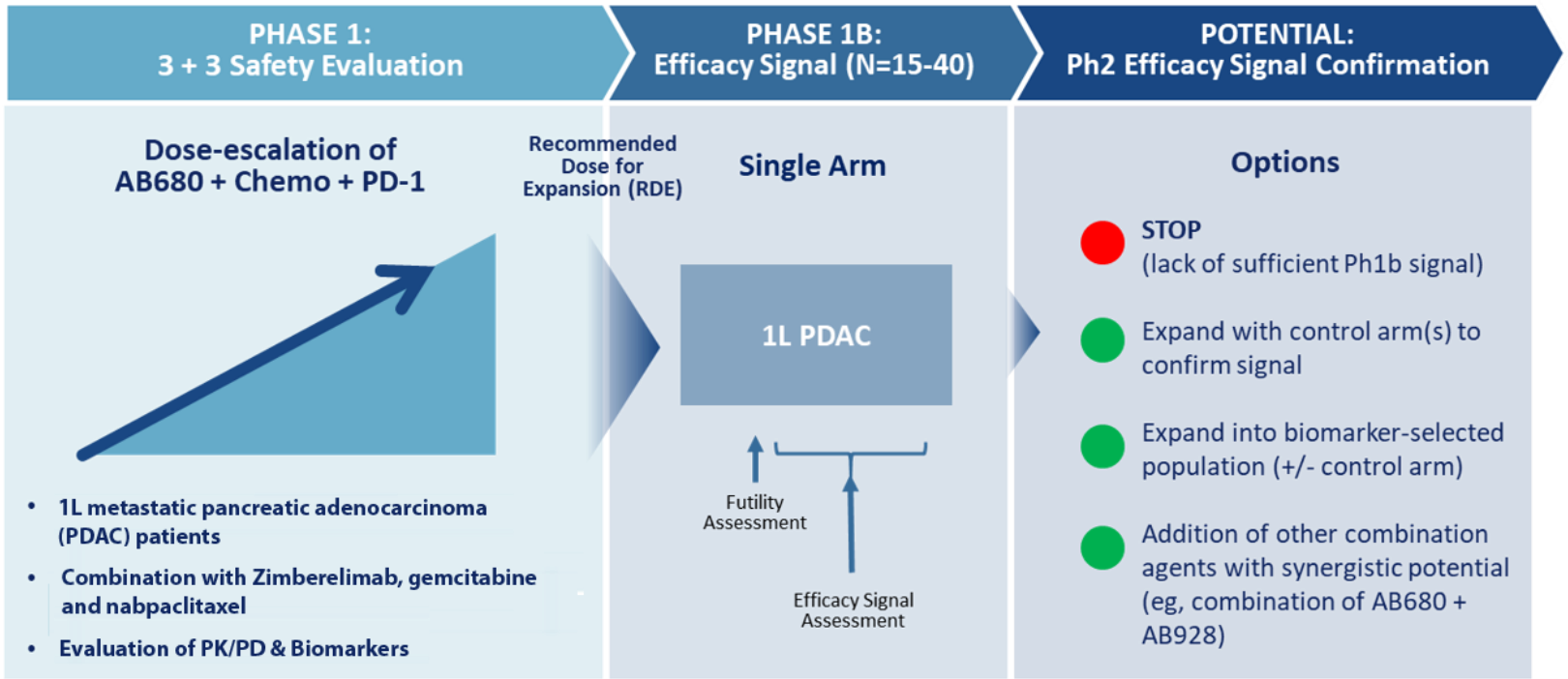

AB680 was administered (30-60 min) by i.v. infusion on day 0



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# AB680 (CD73 inhibitor) Development Status

- **Evaluation in 1L pancreatic cancer in combination with Zimberelimab (anti-PD-1) + gemcitabine/nab-paclitaxel**
  - Phase 1 dose-escalation ongoing (passed safety evaluation of first 25mg cohort)
  - Phase 1b expansion anticipated to start in mid-2020
- **AB680 combination also being evaluated in prostate cancer platform study**






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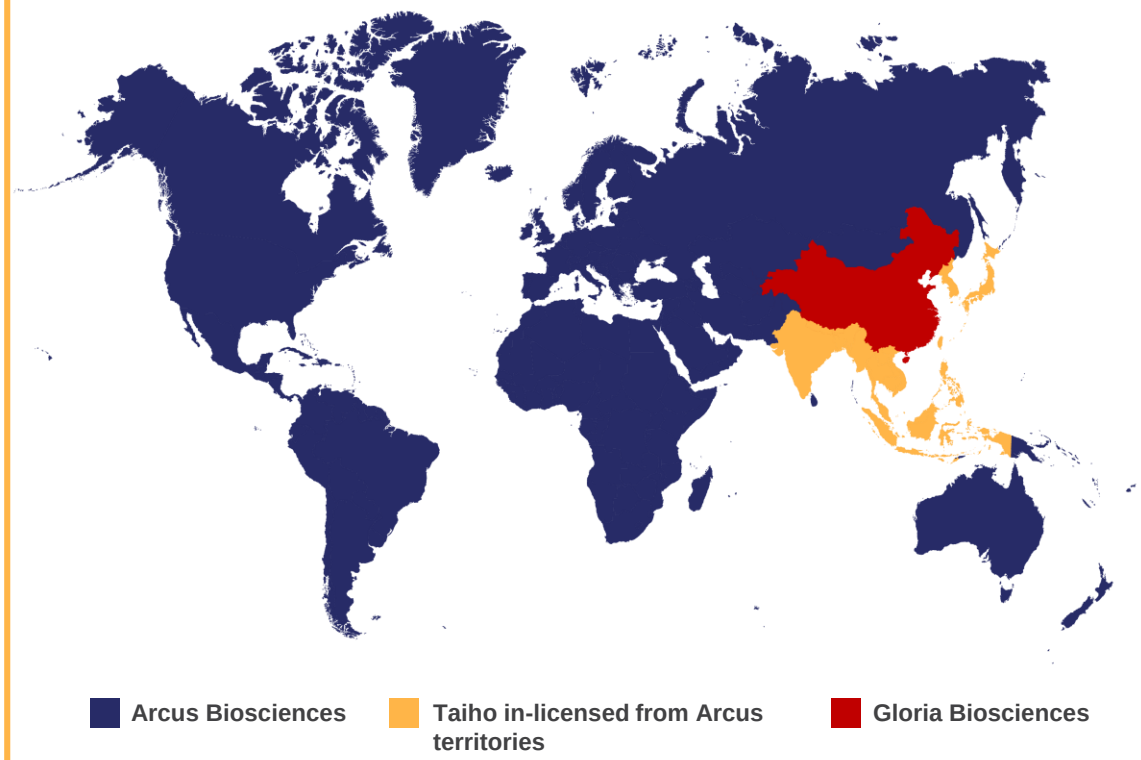
# ZIMBERELIMAB & AB154 DEVELOPMENT STRATEGY

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# Zimberelimab (anti-PD-1) Provides Flexibility & Optionality in Clinical Development & Potential Commercialization

- **Zimberelimab was in-licensed by Arcus to fully enable portfolio combinations[1]**
  - Taiho Pharmaceutical recently exercised its exclusive license from Arcus for its territories in Japan and other Asian countries
- **Gloria Biosciences filed an NDA for Zimberelimab (GLS-010) in China in Jan. 2020 for classical Hodgkin's lymphoma (accepted by the NMPA Feb. 2020)**
  - ORRs similar to other checkpoint inhibitors[2]
    - >90% ORR in late-line classic Hodgkins lymphoma (cHL)
    - >20% ORR in late-line GI cancers (e.g., esophageal, cholangiocarcinoma and gastric)
  - Over 400 patients treated in China alone[2]
  - Gloria Biosciences also has an ongoing Ph2 in cervical cancer for potential NDA submission
- **Arcus currently has 7 active sponsored studies that contain Zimberelimab combinations across multiple indications, targeting >700 patients**

**Global Commercialization Rights to Zimberelimab**




[1] Arcus Biosciences obtained global commercialization rights from WuXi outside of Greater China and Thailand.
[2] Presentations by Gloria Biosciences at CSCO 2019. Gloria's studies are conducted independently of Arcus.

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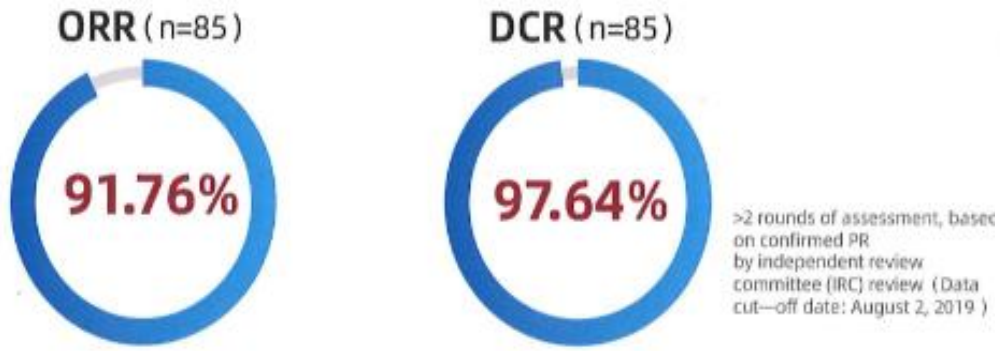


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# Gloria Biosciences Reported Results with Zimberelimab Demonstrating Impressive anti-Tumor Activity in Relapsed/ Refractory Classical Hodgkin's Lymphoma (cHL)[1]

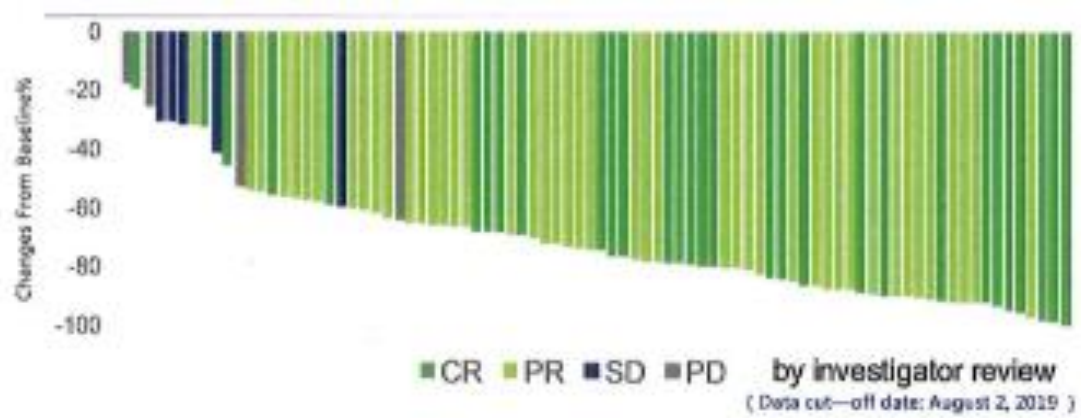
***YH-S001-02 is a single-arm, multicenter, Phase 2 clinical study to evaluate the efficacy and safety of Zimberelimab (GLS-010/AB122) in the treatment of relapsed/refractory (r/r) cHL***

## Overall Response Rate (ORR) & Disease Control Rate (DCR)




**Median Duration of Response (DOR) was not reached**
**Median Progression Free Survival was not reached**

## Waterfall Plot




**100% of evaluable r/r cHL patients had a decrease in size of target lesions**

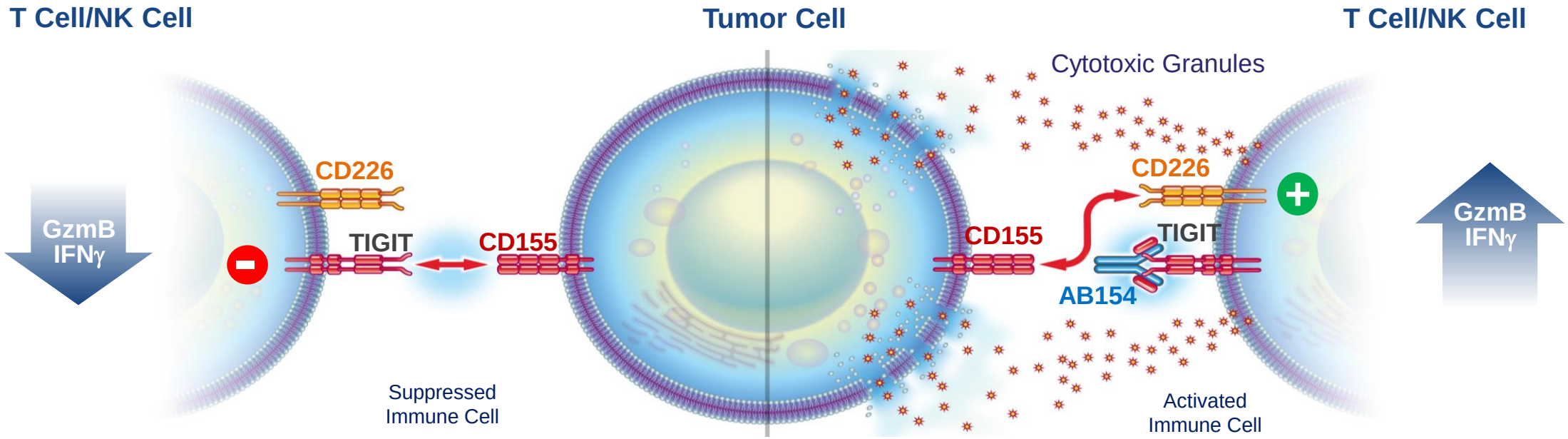
[1] As presented at the China Showcase, JPM Conference (2020). Gloria's studies are conducted independently of Arcus
NCT number: NCT03655483



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# AB154 (anti-TIGIT): Next I-O Backbone

## Dual Mechanism: blocking TIGIT inhibits a critical immuno-suppressive pathway while promoting the CD226-CD155 immune-activating pathway




**Competitors Rapidly Advancing Anti-TIGIT mAbs**

- Genentech completed enrollment of Phase 2 study in NSCLC; primary data reportedly will be presented in 1H2020
- Roche currently running two new Phase 3 studies (SCLC, NSCLC) and four Phase 2 studies (Cervical, PDAC, GC/EC and mUC)
- Merck reported early clinical activity from a Phase 1 study in solid tumors
- Since Dec. of 2019, Merck has initiated: 4 Phase 2 studies (1 in NSCLC and 3 in melanoma), and co-formulation studies with Pembrolizumab
- Additional competitors have also initiated several new studies, including: BMS, BMS/Compugen, BeiGene, Seattle Genetics, iTeos,

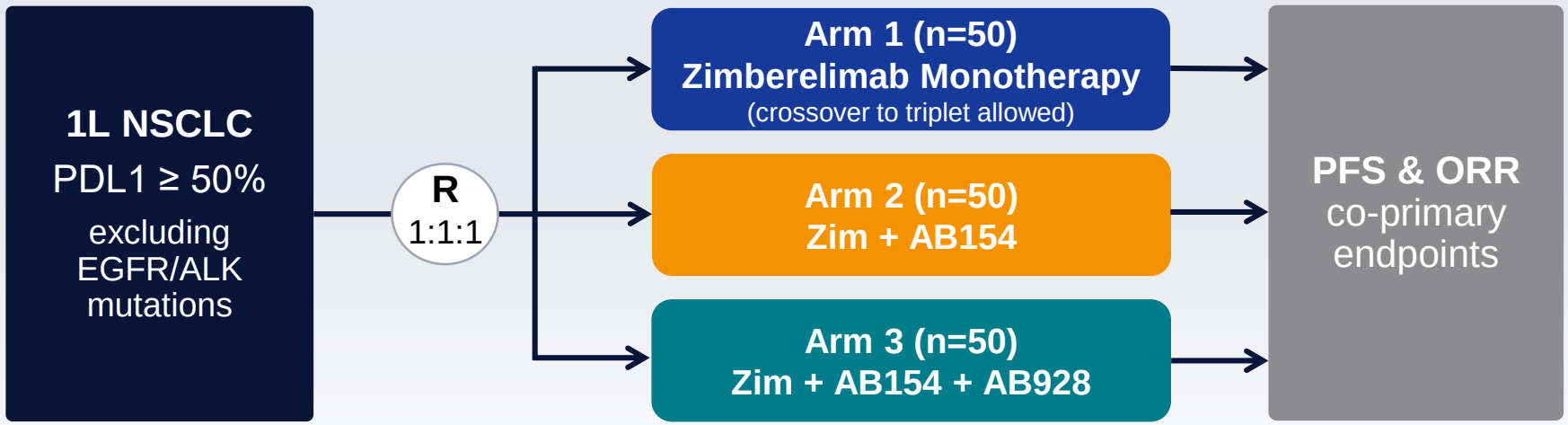
Sources: clinicaltrials.gov (as of April 13th, 2020)



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# Phase 2 Open to Evaluate Two Combinations: AB154+Zim and AB154+AB928+Zim vs Zim Mono in 1L NSCLC

**Randomized Phase 2 Study of Combinations with Zimberelimab, AB154, and AB928 in 1L NSCLC**




- **Study now open in US centers as of 1Q20**
- **US and Asia sites planned for enrollment**
- **Early randomized data expected in 4Q20**



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# Oncology Discovery Programs

## HIF-2α Inhibitor

*Transcription factor*

HIF-2α is a master transcriptional regulator of multiple genes involved in tumor progression

Cancer cell intrinsic target;
potential non-oncology indications

## PI3Kγ Inhibitor

*Glycolipid kinase*

PI3Kγ is required for the immunosuppressive activity of tumor-infiltrating macrophages and myeloid-derived suppressor cells

Immune (TAM, MDSC) target

## AXL Inhibitor

*Tyrosine kinase*

AXL overexpression is associated with tumor resistance to chemotherapy and IO drugs

Cancer cell intrinsic target

## PAK4 Inhibitor

*Serine kinase*

PAK4 overexpression is responsible for T-cell exclusion from immune desert tumors

Cancer cell intrinsic target



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