COMBINING TO CURE

Arcus is at the forefront of designing precision combinations in the pursuit of cures for patients living with cancer.



1Q22 Corporate Presentation

May 9, 2022

Forward-looking Statements/Safe Harbor

This presentation contains forward-looking statements about Arcus Biosciences, Inc. ("we," "Arcus" or the "Company") made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. All statements regarding events or results to occur in the future contained in this presentation are forward-looking statements, including statements about our strategy, advantages, and expectations, including regarding our productivity and competitiveness; expectation that our cash and investments are sufficient to fund operations into 2026; potential of our investigational products and portfolio; anticipated benefits of our collaborations with Gilead, Taiho and AstraZeneca, and projected achievement of our milestones and upcoming development plans, along with the expected timing for such activities. These forward-looking statements are subject to a number of risks, uncertainties and assumptions that may cause actual results to differ materially from those contained in any forward-looking statements we may make, including, but not limited to: risks associated with preliminary or interim data not being guarantees that future data will be similar; the unexpected emergence of adverse events or other undesirable side effects; difficulties or delays in initiating, conducting or completing our clinical trials due to difficulties or delays in the regulatory process, enrolling subjects or manufacturing or supplying product for such clinical trials, all of which may be exacerbated by the COVID-19 pandemic; risks associated with our collaboration arrangement with Gilead including our dependence on Gilead for the successful development and commercialization of our investigational products; changes in the competitive landscape; our limited operating history and our ability to manage our growth; risks regarding our license and collaboration agreements and our ability to obtain and maintain intellectual property protection for our product candidates; and the inherent uncertainty associated with pharmaceutical product development and clinical trials.

We operate in a very competitive and rapidly changing environment. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially and adversely from those anticipated or implied in the forward-looking statements. Further information on these and other factors that could affect the forward-looking statements made herein are described in our most recent Annual Report on Form 10-K and Quarterly Report on Form 10-Q filed with the U.S. Securities and Exchange Commission.

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Highlights

$1.3B in cash

Funding into 2026

Global, late-stage company

6 clinical-stage molecules

2 soon to be 4

Phase 3 studies

2022 milestones

- ✓ Phase 3 PACIFIC-8 initiated
- ✓ AB521 (HIF-2a) HV data
- ARC-7 complete enrollment (mid-2022)
- Update on ARC-7 (2H)
- Update on ARC-6 (2H)
- Update on ARC-8 (2H)
- 2 Phase 3 initiations
- Phase 2 “triplet” study initiations

Top tier partners

GILEAD

TAIHO PHARMA

AstraZeneca

Productive research organization

1-2 new development candidates a year

At least 2 new FIH in 2022/2023:

- AB598 (CD39)
- AB801 (Axl)
- 1st inflammation candidate

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Gilead is Co-Developing Four Optioned Programs with Arcus

GILEAD

- Currently has rights to five of our clinical-stage candidates through its exercised options:
  - domvanalimab and AB308, our anti-TIGIT antibodies
  - etrumadenant, an A2a/A2b receptor antagonist
  - quemliclustat, a small molecule CD73 inhibitor
  - zimberelimab, an anti-PD-1 antibody
- Arcus and Gilead share expenses for all of these programs
- Arcus and Gilead will co-commercialize and equally share profits in the U.S. for any approved products
- Gilead holds exclusive rights outside the U.S., subject to any rights of Arcus's existing collaboration partners, with tiered royalties payable to Arcus that range from mid-teens to low-twenties
- Added a research collaboration to focus on two jointly-selected, novel targets in oncology

WHAT THIS MEANS FOR ARCUS AND THE COLLABORATION

- ✓ $725 million payment and cost sharing puts Arcus in a strong position to invest in its programs
- ✓ Accelerates and expands our collaboration activities
- ✓ Brings operational expertise with global reach
- ✓ Enables earlier alignment on clinical studies and priorities to move fast
- ✓ Accelerates the exploration of new cross-portfolio combinations, with first-in-class potential

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Our Partnerships Greatly Expand & Accelerate Opportunities Inherent in Arcus's Portfolio

GILEAD — 10-YEAR "ALL-IN" COLLABORATION

- **Nearly $1.4b in non-dilutive payments and equity investments from Gilead**
  - Includes $725mm in option payments received from Gilead in 1Q22
  - Gilead holds ~19% equity stake in Arcus
- Highly engaged partner that has opted in to nearly all of Arcus's clinical-stage portfolio
- Gilead equally shares co-development costs for the global joint development program
- Gilead has option rights to future molecules from current and upcoming discovery programs
- Arcus retains U.S. co-commercial rights

TAIHO PHARMA — 5-YEAR COLLABORATION FOR JAPAN AND OTHER TERRITORIES IN ASIA (EX-CHINA)

- Facilitates global development & commercialization of Arcus molecules
- Up to $275mm in development, regulatory and commercial milestones per program
- Tiered royalties from high-single digit to mid-teens on net sales
- Option rights exercised for majority of Arcus's clinical-stage portfolio—zim, etruma, dom and AB308

AstraZeneca — CLINICAL COLLABORATION FOR DOMVANALIMAB PLUS DURVALUMAB

- Companies collaborating on PACIFIC-8, a Phase 3 registrational trial sponsored by AstraZeneca
- Further validates Arcus's position at forefront of anti-TIGIT field
- Leverages AstraZeneca's leadership in the curative-intent Stage 3 NSCLC setting
- Retained economics on respective molecules
- Trial initiated in 1Q22

~$1.3B IN CASH AND INVESTMENTS AS OF 3/31/21 AND FUNDING INTO 2026

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Arcus Has a Broad Portfolio of Molecules, Enabling Differentiated Combination Therapies

DIFFERENTIATED SMALL MOLECULES

etrumadenant (AB928): First-in-class dual $A_{2a}R$ / $A_{2b}R$ antagonist; generated early evidence of clinical activity in colorectal, prostate and lung cancers

quemliclustat (AB680): First-in-class small-molecule CD73 inhibitor; generated early evidence of clinical activity in pancreatic cancer

AB521: Highly potent and selective HIF-2a-inhibitor; first study in healthy volunteers ongoing with phase 1/1b in patients expected to initiate mid-22

ENABLING ANTIBODIES

domvanalimab (AB154): Anti-TIGIT monoclonal antibody (mAb; Fc silent) – ongoing randomized Phase 2 study ARC-7 in 1L NSCLC; initiated ARC-10, our registrational trial designed to support both dom + zim and zim monotherapy approvals

AB308: Anti-TIGIT mAb (Fc enabled); Phase 1/1b expansion enrolling

zimberelimab (AB122): anti-PD-1 mAb; approved in China for classical Hodgkin Lymphoma (cHL)*

NEXT GENERATION PROGRAMS

AB598: Anti-CD39 mAb

AB801: small molecule Axl inhibitor

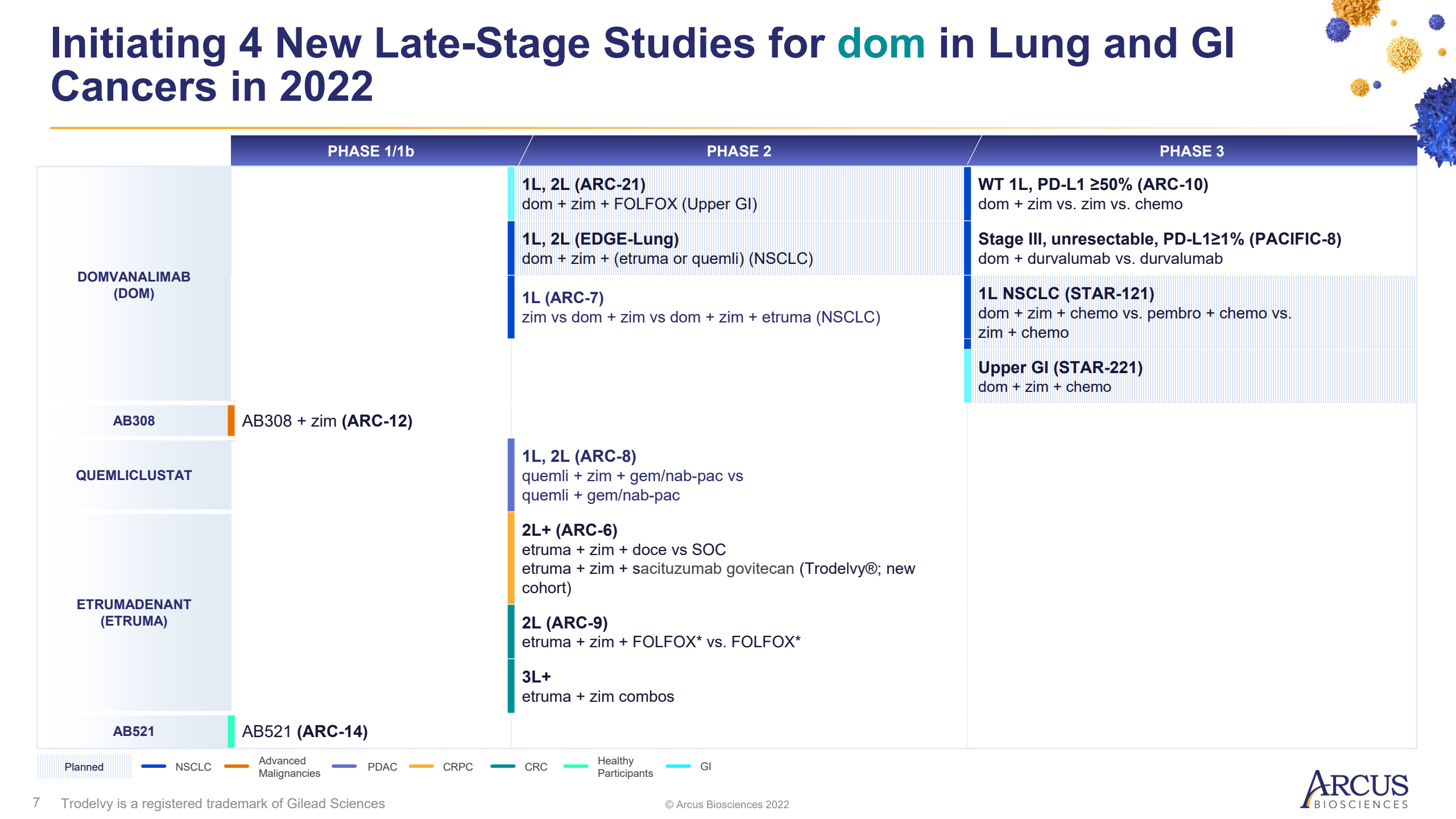
Undisclosed: Small molecule inhibitor of target involved in inflammation

WORLD-CLASS DRUG DISCOVERY

*Gloria Biosciences secured China approval; it holds commercial rights to zim in China and conducts its activities independent from Arcus

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Initiating 4 New Late-Stage Studies for dom in Lung and GI Cancers in 2022



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ANTI-TIGIT PROGRAM



Anti-TIGIT Antibody Portfolio Positions Arcus as a Pioneer in the TIGIT Field

Domvanalimab's advancement into registrational studies coupled with AB308's rapid advancement into expansion cohorts reinforces Arcus as a leader in the development of anti-TIGIT therapies

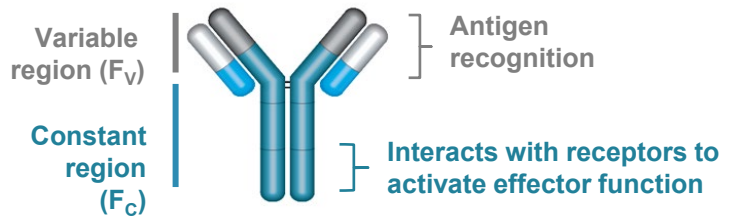
DOMVANALIMAB (FC-SILENT)

- Blocks the TIGIT receptor on T-cells to prevent binding of CD155; does NOT deplete TIGIT-bearing immune cells
- No evidence of ADAs (which can impact clinical efficacy) to date
- 100% TIGIT occupancy on blood lymphocytes achieved
- Increased proliferation (Ki-67) of blood CD8 T cells, of a magnitude similar to what has been described for anti-PD-1 mAbs
- Two phase 3 studies ongoing: **ARC-10** (1L, PD-L1 high NSCLC), **PACIFIC-8** (Stage 3 NSCLC)
- Two additional phase 3 studies in planning: **STAR-121**, **STAR-221**

NO DEPLETION OF T-CELLS OR PERIPHERAL T-REGS

AB308 (FC-ENABLED)

- Also blocks the CD155 interaction with TIGIT, critical for T cell activation
- Potential to deplete TIGIT-bearing cancer cells (e.g., myeloma, NHL)
- Phase 1/1b ARC-12 study evaluating AB308 plus zim in advanced malignancies is ongoing

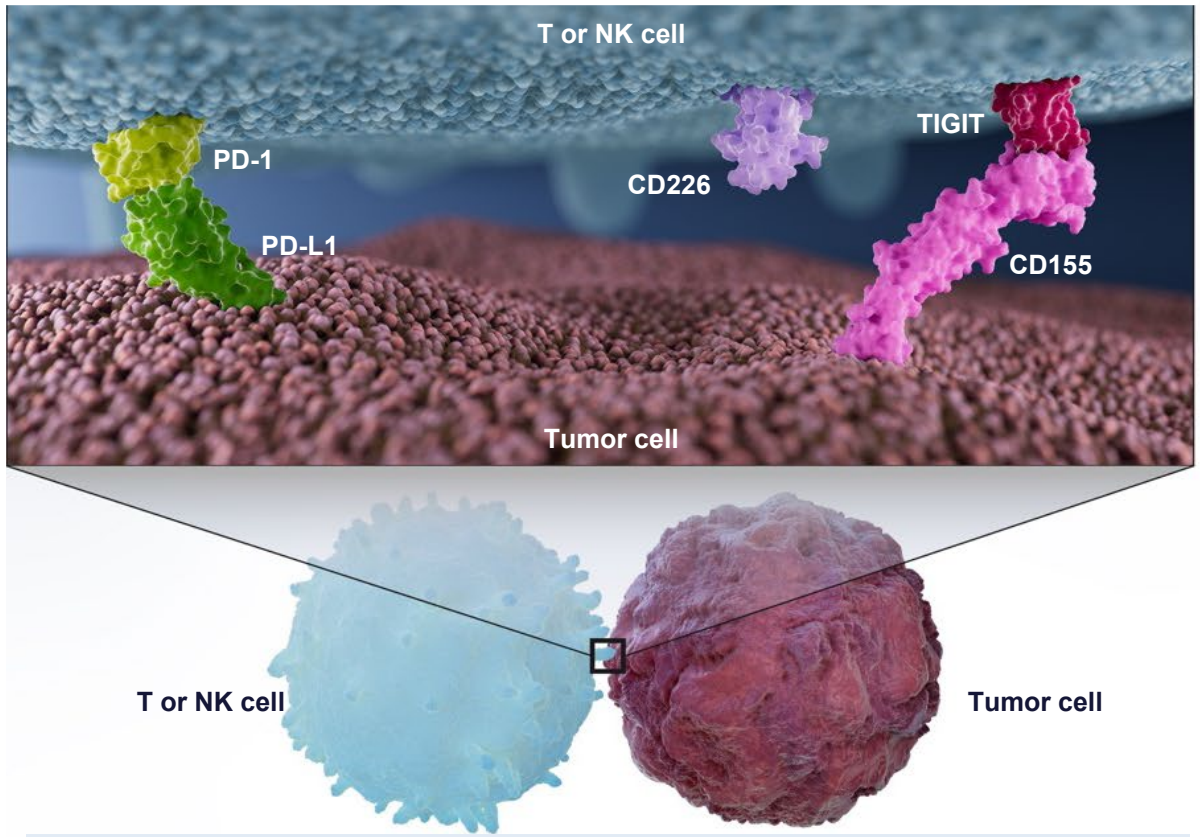


POTENTIAL FOR ACTIVITY IN HEME MALIGNANCIES

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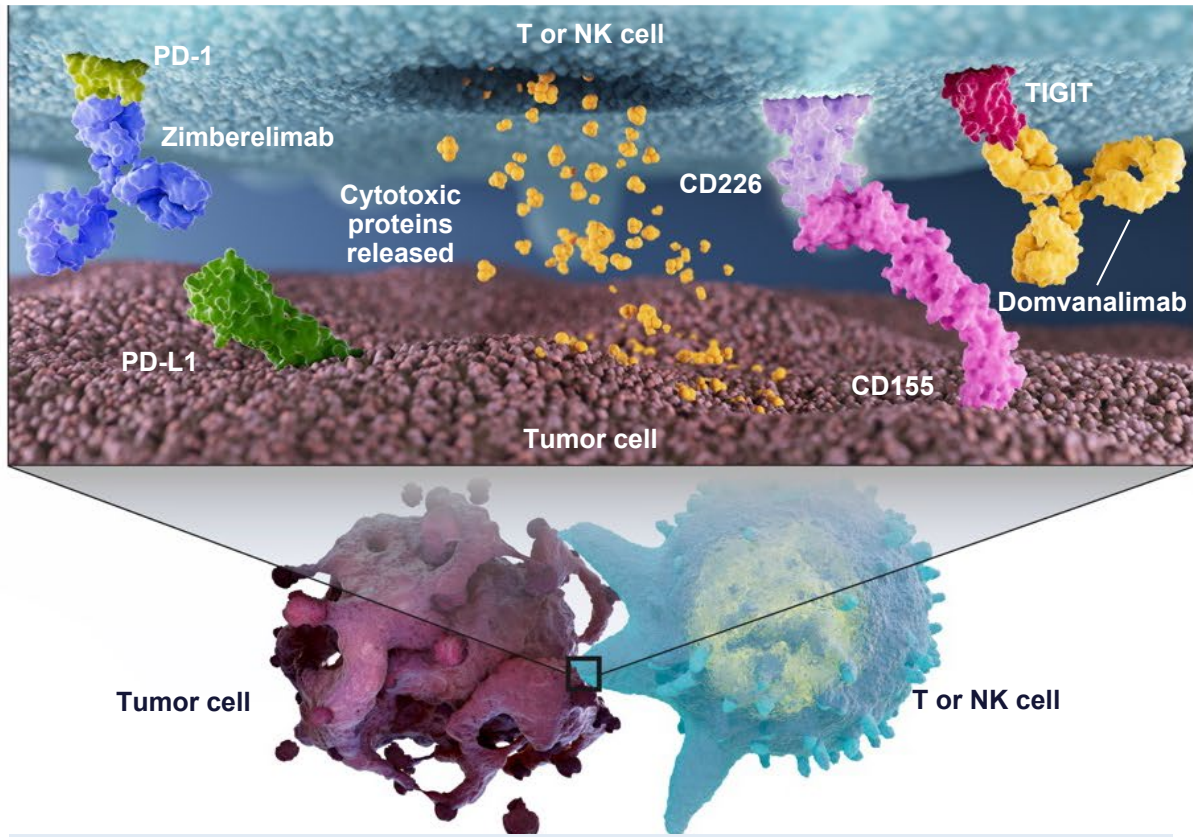
Anti-TIGIT Mechanism of Action: domvanalimab (dom)

IMMUNOSUPPRESSION



TIGIT is another checkpoint receptor expressed on immune cells that binds CD155 on tumor cells, leading to further evasion of anti-tumor immunity

IMMUNE CELL ACTIVATION & TUMOR CELL KILLING

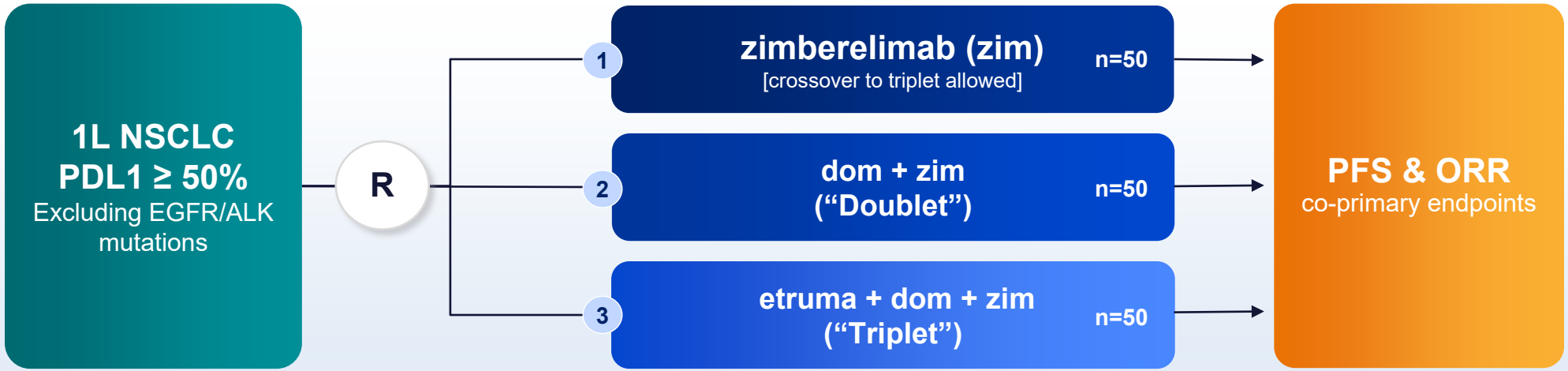


Dom blocks TIGIT, enabling CD155:CD226 interaction and immune cell activation

Combined inhibition of TIGIT and PD1 may have a synergistic effect, unleashing immune activity against certain tumor cells

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ARC-7 Randomized Phase 2 in 1L NSCLC (PD-L1 ≥ 50%): zim vs. dom + zim vs. etruma + dom + zim



STUDY DESIGN	Phase 2, multicenter, 3-arm randomized, open-label study
PATIENT POPULATION	1L NSCLC, Stage IV, PD-L1 TPS ≥ 50% without EGFR/ALK mutation
STRATIFICATION FACTORS	ECOG PS: 0 vs 1; male vs female
CROSSOVER	Subjects in Arm 1 have the option to cross over to Arm 3 at the time of confirmed progression

Chaudhry et al, ESMO (2020); presentation no.1419TiP; NCT04262856
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ARC-7 | 3rd Interim Analysis (IA3)

SUMMARY OF EFFICACY OBSERVATIONS FROM IA3:

- In this interim analysis, both domvanalimab-containing arms continued to show meaningful differentiation compared to zimberelimab alone across multiple efficacy measures, including overall response rate (ORR) and duration of response (DoR).
  - **The clinical activity of zimberelimab alone was in line with established anti-PD-1 therapies in this patient population.**
- Since the last interim analysis, ORR for the doublet continued to increase and further separate from zimberelimab alone.
- Although early, the depth of response for the triplet remains encouraging; we will continue to monitor the triplet for potential differentiation in duration and depth of response vs. the doublet.
- At this interim analysis, Arcus performed its first assessment of DoR. While the data are still immature, at the time of IA3, Arcus observed a substantial improvement for the domvanalimab-containing arms compared to zimberelimab alone.

SUMMARY OF SAFETY OBSERVATIONS FROM IA3:

- No unexpected safety signals were observed; early safety data from this interim analysis showed a lower incidence of infusion reactions relative to published numbers from other anti-TIGIT plus anti-PD-(L)1 clinical studies.

NEXT STEPS:

- Enrollment for ARC-7 remains on track to complete mid-2022; we plan to provide a data update in the second half of 2022.

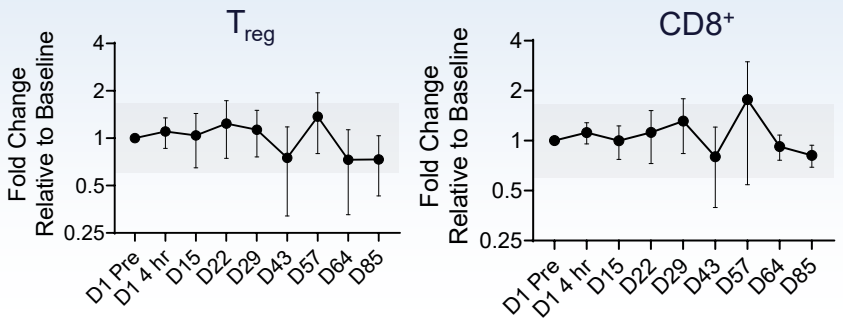
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Anti-tumor Activity and Lower Frequency of irAEs Observed with Domvanalimab (Dom) in the Absence of T_{reg} Depletion

Important differences between dom (phase 1 in combination with zim) and Fc enabled anti-TIGIT competitors

- Peripheral T_{reg} numbers do not decrease with dom + zim, but they do with Fc-enabled anti-TIGIT competitors
- Lower frequency of various irAEs reported with dom + zim, compared to values reported for Fc-enabled anti-TIGIT competitors
- Several clinical responses seen in Phase 1 study, without any effects in blood T cell populations

PERIPHERAL LYMPHOCYTE NUMBERS DID NOT CHANGE IN PHASE 1 PATIENTS TREATED WITH DOM + ZIM



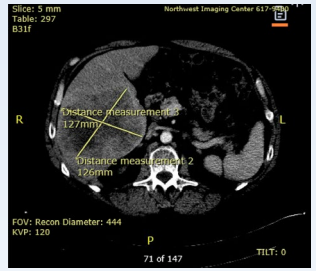
IMMUNE-RELATED AEs FOR DOM + ZIM ONGOING PHASE 1 (n=56)

	dom + zim n (%)
Hypothyroidism	5 (8.9%)
Pruritus	**4 (7.1%)**
Rash	**4 (7.1%)**
Maculopapular rash	**3 (5.4%)**
Infusion-related reaction	**3 (5.4%)**

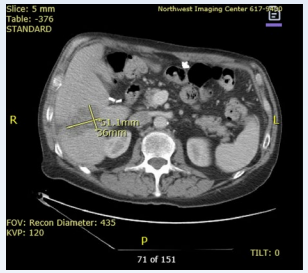
irAEs (n>2) in the ongoing Phase 1 trial of domvanalimab (NCT03628677) as of 01Apr2022. Regimens containing Fc-enabled anti-TIGIT monoclonal antibodies, including those reported to deplete peripheral T_{reg},[1,2,3] have reported incidences in the following ranges: pruritus (~20-38%), rash (~21-40%), maculopapular rash (~0-9%), and infusion-related reactions (~10-31%)[2,3,4,5].

PHASE 1 CASE STUDY

- Stage IV esophageal adenocarcinoma; PD-L1 (CPS) ~2%
- Prior treatment: (1) FOLFOX; (2) Carbo/Pac; (3) pembro
- Study regimen: 10 mg/kg dom Q3W + 360 mg zim Q3W

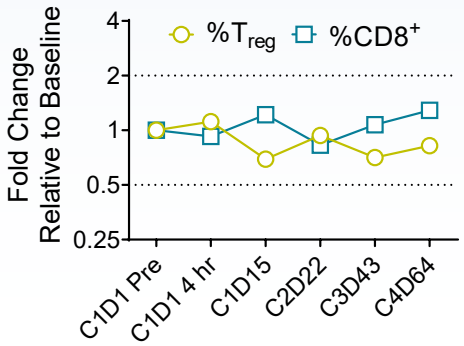


Baseline Scan
Target lesion #1: **127 mm long axis**

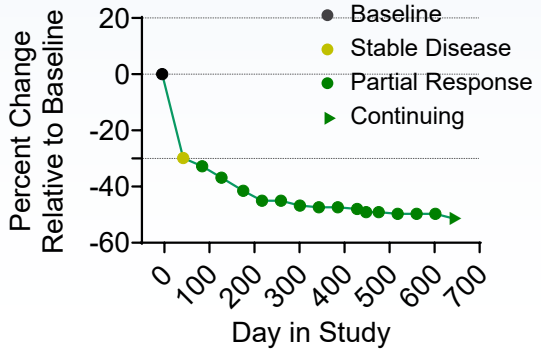


Post-Cycle 30 Scan
Target lesion #1: **62 mm long axis**

Peripheral Blood



Measurable Target Lesions



Gauthier, K. et al; Immunology 2022 (#2719): Anti-TIGIT Antibodies Promote Immune Activation Relevant to Targeting Stem-like and Tumor-specific T Cells in Combination With Anti-PD-1

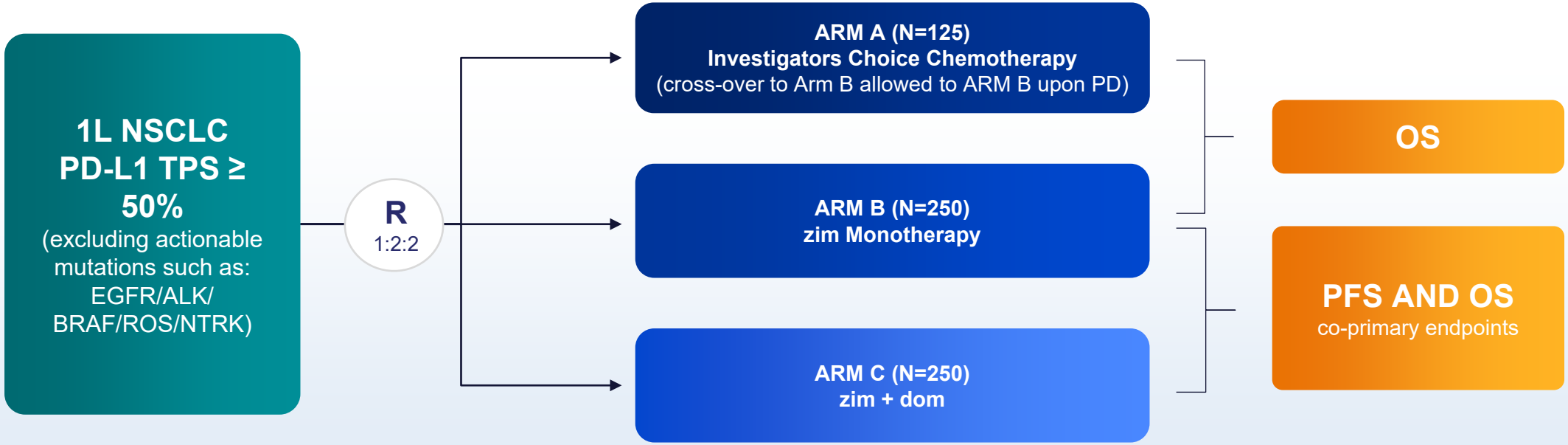
[1]Mettu *et al.* 2022 Clin Cancer Res DOI:10.1158/1078-0432.CCR-21-2780 (etigilimab); [2]Van den Mooter *et al.* 2021 Cancer Res DOI:10.1158/1538-7445.AM2021-CT118 (EOS-448). [3]Cuende *et al.* 2022 AACR #LB189 (EOS-448); [4]Niu *et al.* 2022 Ann Oncol DOI:10.1016/j.annonc.2021.11.002 (vibostolimab); [5]Cho *et al.* 2021 Ann Oncol DOI:10.1016/j.annonc.2021.10.217 (tiragolumab)

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ARC-10 | Phase 3 Trial to Evaluate dom + zim vs. zim mono vs. chemo in 1L NSCLC (PD-L1 ≥ 50%)

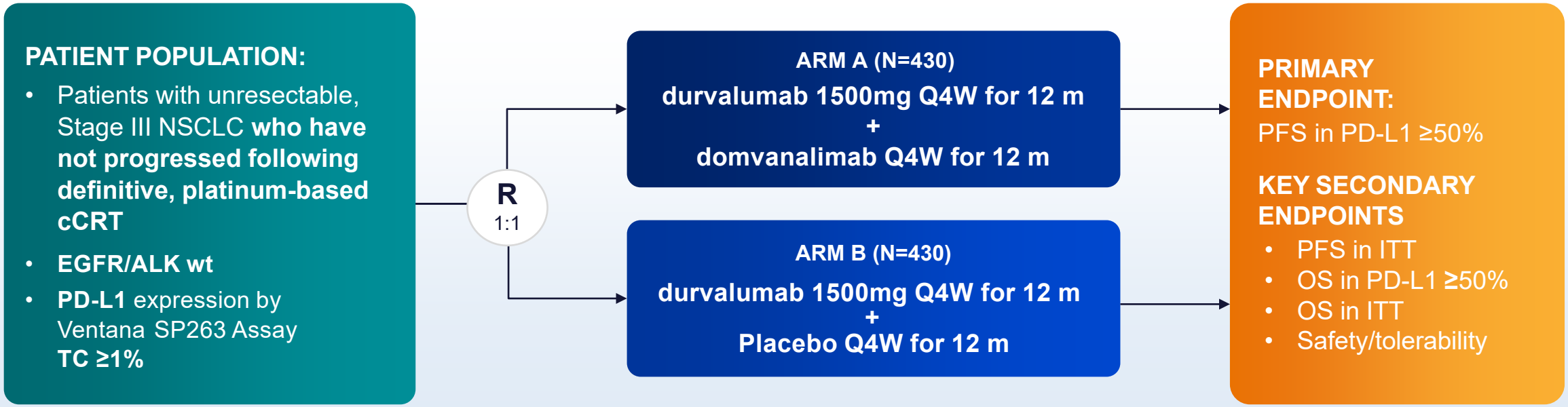
- Designed to enable potential approval of BOTH zim mono and zim + dom combination
- Most advanced Phase 3 study of an anti-TIGIT + PD-1 combination
- Initiated in 2021



NCT#: NCT04736173
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Phase 3 Trial to Evaluate durva + dom vs durva + placebo in Unresectable, Stage III NSCLC

- Combines dom with standard-of-care in Stage III NSCLC
- Potential to be first anti-TIGIT combination in this curative intent setting
- Initiated in 1Q22



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STAR-121 | Initiating Phase 3 1L NSCLC All Comer Study evaluating zim + dom + chemo vs. pembro + chemo vs. zim + chemo in 2022

ELIGIBILITY CRITERIA

- Metastatic NSCLC without actionable mutations
- No prior systemic treatment for metastatic NSCLC
- PD-L1 all-comers
- ECOG 0-1
- No interstitial lung disease
- No untreated brain metastases

COHORT n=720 4:4:1

COHORT A
zimberelimab[1] + domvanalimab[1] + platinum doublet[2]

COHORT B
pembrolizumab[1] + platinum doublet[2]

COHORT C
zimberelimab[1] + platinum doublet[2]

ENDPOINTS

Primary
- PFS by BICR
- OS

Secondary
- ORR and DOR
- Safety and QoL

New **FPI expected 4Q22**

Aim to establish dom and zim as effective and accessible IO backbone to enable novel combinations with portfolio assets

[1] Zimberelimab, domvanalmab, and pembrolizumab are given Q3W for a maximum of 35 doses. [2] Choice of chemotherapy is dependent on histology. Participants with non-squamous will receive cisplatin 75 mg/m^2 or carboplatin AUC 5 with pemetrexed 500 mg/m^2 Q3W. Those with squamous histology will receive carboplatin AUC 6 Q3W with paclitaxel 200 mg/m^2 Q3W or Nab-paclitaxel 100 mg/m^2 QWk. Note: For participants with non-squamous histology, pemetrexed is continued after 4 cycles of induction chemotherapy until PD or intolerable toxicities.

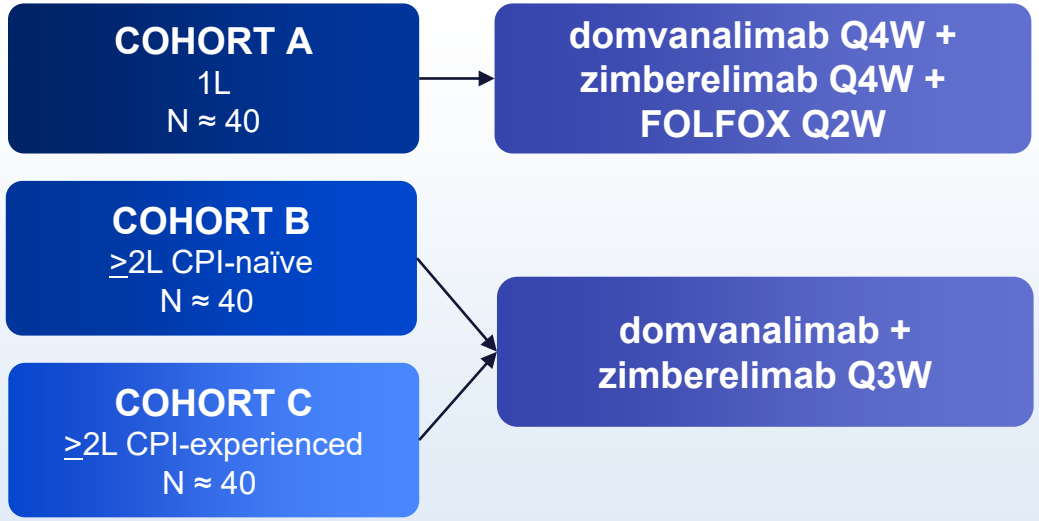
ORR - objective response rate; DOR – duration of response; OS - overall survival; PFS - progression-free survival; ECOG – Eastern Clinical Oncology Group; QoL – quality of life; BICR – blinded independent central review; FPI – first patient in Gileadd Sciences will operationalize the study.

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ARC-21 Phase 2 Trial to Evaluate dom + zim + chemo vs dom + zim in Advanced Upper Gastrointestinal Tract Malignancies

KEY ELIGIBILITY CRITERIA

- EAC/GEJ/Gastric
- Locally advanced unresectable or metastatic disease w/o prior systemic treatment
- Measurable disease per RECIST 1.1



PRIMARY ENDPOINTS

- Safety
- ORR per Investigator

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The domvanalimab Program Stacks Up Extremely Well to Other TIGIT Programs

	Roche	ARCUS BIOSCIENCES / GILEAD	BeiGene / NOVARTIS	MERCK
1L NSCLC Ph3 Primary Completion	**2022**	**2025**	**2025**	**2026**
Possible Advantages	✓ **First mover advantage**	✓ **1st Fc-silent** ✓ **Potential differentiated safety, combinability** ✓ **PACIFIC-8 led by AZ** – 1st to market potential	✓ **China market leadership**	✓ **Pembro backbone is current SOC**
Possible Liabilities	• **PD-L1 backbone with evidence of ADAs** • **High incidence of IRRs** • **Moderate incidence of certain irAEs (e.g. rash)**	• **Newcomer to IO market**	• **China-centric program**	• **Co-form not attractive to clinicians/payers** • **Large 1L Lung Ph3: 1200 patients, extends timeline**
# Ph3 Studies	**5:** 1L NSCLC (PD-L1 ≥50%) 1L NSCLC (all comer), Stage 3 NSCLC, LA ESCC, 1L ESCC	**4 by YE:** 1L NSCLC (PD-L1 ≥50%), 1L NSCLC (all comer), Stage 3 NSCLC, GI cancer	**2:** 1L NSCLC (PD-L1 ≥50%), Stage 3 NSCLC	**4:** 1L NSCLC (TPD-L1 ≥1%)), 1L NSCLC (all comer), Stage 3 NSCLC, ES-SCLC
Potential Triplets	**Unclear as of today**	**TROP-2, Adenosine, CD73**	**Unclear as of today**	**Unclear as of today**

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We Are Positioned to Build a Best-in-Class TIGIT Program

STRATEGIC PILLARS TO REALIZE DOM'S ENORMOUS BEST-IN-CLASS POTENTIAL

1. Demonstrate TIGIT+PD1 efficacy with **differentiated safety & tolerability**
2. Strategic **PDx flexibility** leveraging combinability with Zim and PDx SOC
3. **Adenosine triplets** may yield transformative efficacy in selected patients

1L mNSCLC

ARC-10 & STAR-121

dom+zim & dom+zim+chemo

Best-in-Class TIGIT potential with Zim/PDx flexibility to drive share

> 5B Peak Revenue Oppty

Stage III NSCLC

PACIFIC-8

dom+durva

Potential safety advantages + combining Dom with Durva SOC

> 1.5B Peak Revenue Oppty

New Indications

to be announced…

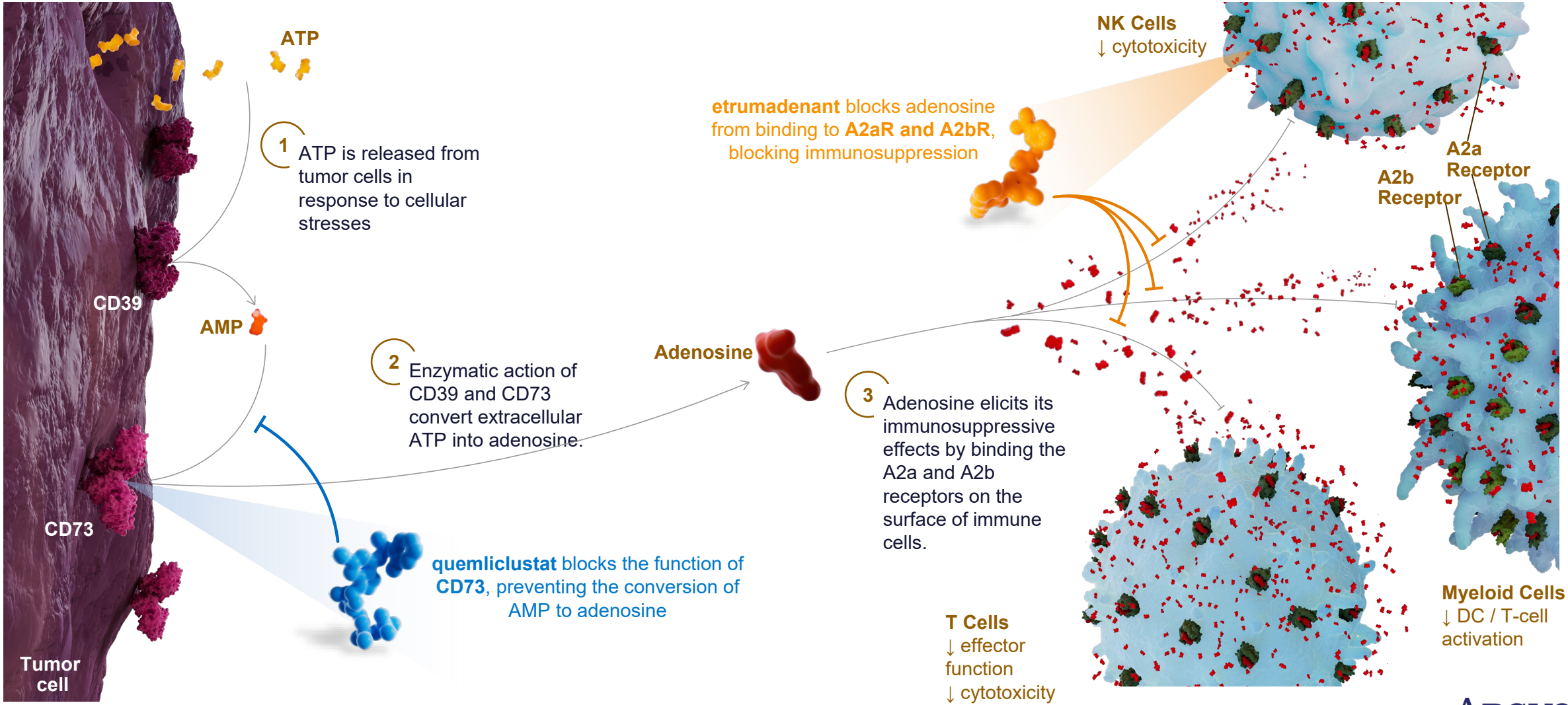
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CD73-Adenosine Axis Programs

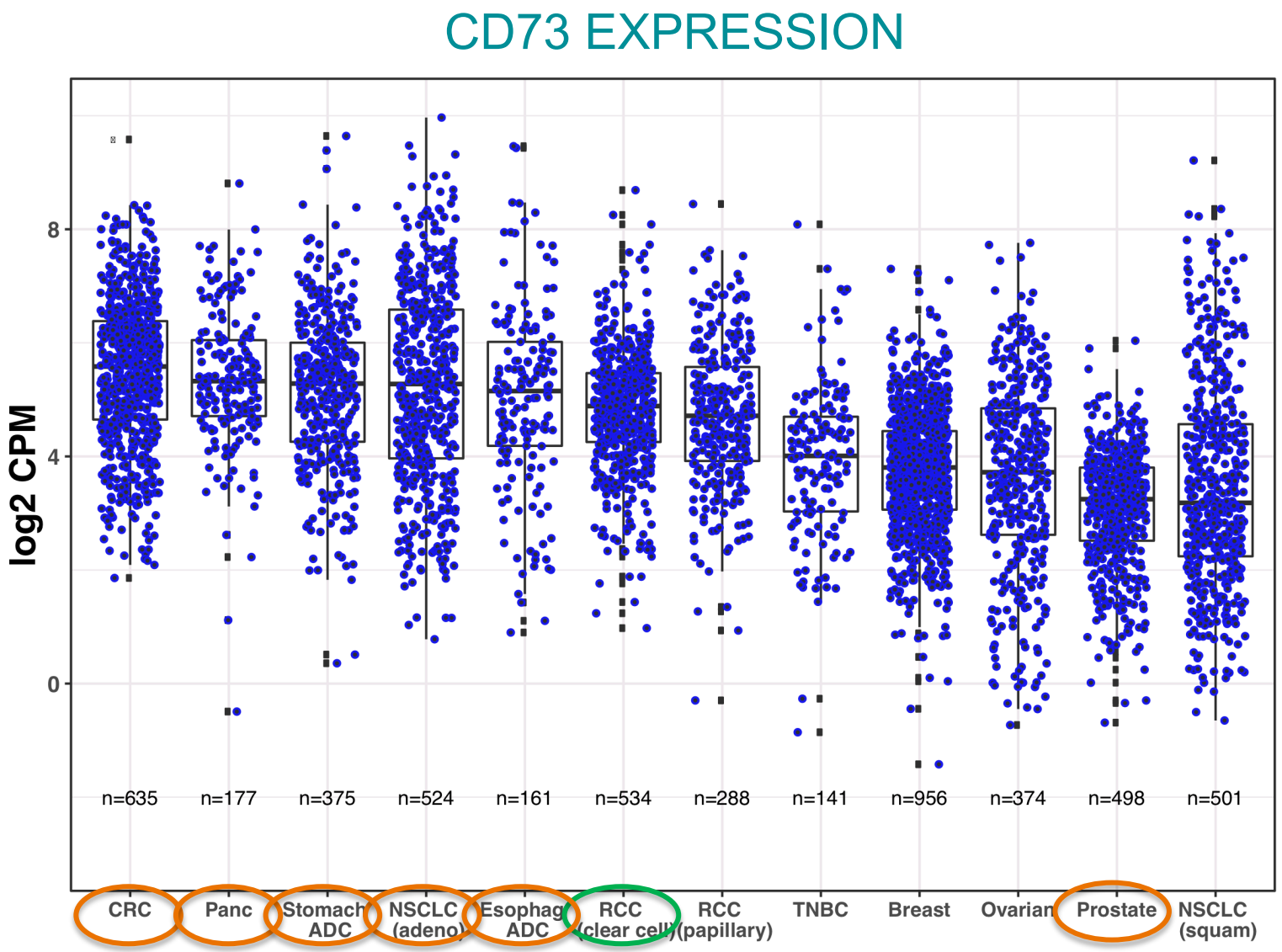


The CD73-Adenosine Axis Plays a Well-Established and Critical Role in Suppression of the Immune Response



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Ongoing Development with etruma and quemli is Directed to Tumor Types with Potential for High Adenosine



Arcus Analysis of Tumor Cancer Genome Atlas (TCGA)
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High CD73 Is a Negative Prognostic Factor

TUMOR TYPE	CD73^{HI} PROGNOSTIC FOR	REFERENCE	SAMPLE TYPE, #	CD73 METHOD	COMMENT
PDAC	Negative outcome	**Sciarra, A** et al. CD73 expression in normal and pathological human hepatobiliopancreatic tissues. Cancer Immuno, immunother (**2019**) slide #3	PDAC (n=42), PDAC metastasis (n=12)	D7F9A, IHC	CD73 data from additional surgical samples in hepatobiliopancreatic samples
	Negative for OS and DSS	***Tahkola, K**., et al. Prognostic impact of CD73 expression and its relationship to PD-L1 in patients with radically treated pancreatic cancer. Virchows Arch (**2021**) slide #4	TMA of radically treated stage 1-IV PDAC, N=110	D7F9A, IHC	• Cut off selected by ROC vs 3 yr mortality
	Negative for OS and RFS	**Zhao, J** et al. Overexpression of CD73 in PDAC is associated with immunosuppressive TME and poor survival. Pancreatology (**2021**) slide #5	MDA cohort, n=138 with upfront surgery	D7F9A, IHC	• Cut off at TPS ≥ 75% • CD73 expression correlates with low TILs and shorter OS
CRC	Negative for TTR and DSS	**Messaoudi, N** et al. Prognostic value of CD73 expression in resected colorectal cancer liver metastasis. Oncoimmunology (**2020**) slide #6, 7	TMA of n=215 who underwent resection	Ab91084, multiplex IF	• Cut off set at upper tertile tCD73 (tumoral + stromal expression)
NSCLC	Negative for OS and PFS	**Inoue,** Y et. al. Prognostic impact of CD73 and A2aAR expression in NSCLC. Oncotarget (**2017**) 8:8738-8751 slide #8, 9	TMA of resected NSCLC; n=642	• D7F9A, IHC • *SA654*	• ~10% of subjects were CD73 high
	CD73 is predictive for ICI response	Ishii, H et al. Predictive value of CD73 expression for the efficacy of ICI in NSCLC. Thoracic Cancer (2020) 11:950	Pre-treatment biopsy; n=91	• D7F9A, IHC	Not prognostic but predictive for the immune checkpoint inhibitor
RCC	Negative for OS and DFS	**Tripathi A** et al. Prognostic significance and immune correlates of CD73 expression in RCC. J Immunother Cancer (**2020**) slide #11	TMA of nephrectomy samples with RCC(n=138)	D7F9A, IHC	• Cut-off at median by combined score (% positive cells x intensity) • *Includes TCGA RNAseq data mining*

DSS: Disease-specific survival, RFS: Recurrence free survival, TTR: Time to recurrence

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quemliclustat (quemli): A Unique, Highly Potent and Selective Small Molecule CD73 Inhibitor with Several Key Advantages

HIGHLY POTENT

- Target coverage achieved at doses as low as 25 mg every two weeks
- Extremely long (~4 days) half-life, enabling dosing every two weeks
- Oral formulation also in development

POTENTIAL ADVANTAGES OVER CD73 ANTIBODIES

- Extremely potent and selective against both tumor and soluble CD73
- Orders of magnitude more potent than CD73 antibodies
- Greater permeability of tumor tissue

LIMITED ADDITIVE TOXICITY

- High selectivity limits potential for "off-target" effects
- AE profile of quemli + gem/nab-pac appears similar to that of gem/nab-pac alone

INCREASINGLY VALIDATED TARGET

- COAST data supports potential of CD73 inhibition in Stage 3 NSCLC
- 41% unconfirmed ORR rate reported with quemli in initial presentation in PDAC
- Rapidly growing number of CD73 antibodies in clinical development

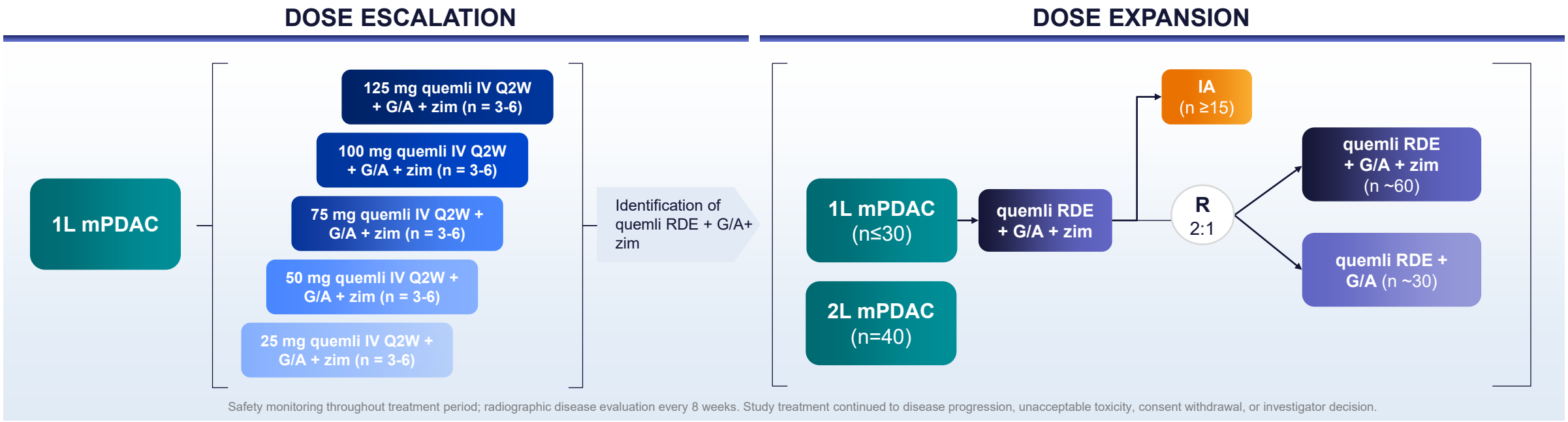
-Manji, GA et al; ASCO GI 2021 (Abstract 404): ARC-8: Phase 1/1b Study to Evaluate Safety and Tolerability of AB680 + Chemotherapy + Zimberelimab (AB122) in Patients with Treatment-Naive Metastatic Pancreatic Adenocarcinoma

-Martinez-Marti, A et al; ESMO 2021 (LBA42): COAST: An open-label, randomised, phase II platform study of durvalumab alone or in combination with novel agents in patients with locally advanced, unresectable, stage III NSCLC

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A Phase 1/1b, Open-Label, Dose-Escalation and Dose-Expansion Study



Safety monitoring throughout treatment period; radiographic disease evaluation every 8 weeks. Study treatment continued to disease progression, unacceptable toxicity, consent withdrawal, or investigator decision.

KEY ELIGIBILITY CRITERIA

- Histologically- or cytologically-confirmed mPDAC
- ≥1 measurable lesion per RECIST v1.1
- ECOG PS 0-1
- No prior treatment for M1 disease
- Prior (neo)adjuvant treatment for PDAC (chemotherapy G/A and/or radiotherapy) allowed if completed ≥6 months prior to enrollment

STUDY OBJECTIVES

- **Primary:** Safety and tolerability
- **Secondary:** PK and clinical activity

1L, first-line; IV, intravenously; G/A, gemcitabine/nab-paclitaxel; PDAC: pancreatic ductal adenocarcinoma; Q2W, every 2 weeks; R, randomization; RDE, recommended dose for expansion; quemli: quemliclustat; zim, zimberelimab.

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etrumadenant (etruma): 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 chemo

High potency against both the A2aR and A2bR receptors allows for potentially broader activity

Compound	A2aR Blood (IC50, nM)c	A2aR (KB, nM)d	A2bR (KB, nM)d
AB928 *(Arcus)*	**80**	**1.3**	**2.0**
CPI-444 [a,b] *(Corvus)*	~10,000	5.4	493
AZD 4635 [a,b] *(AstraZeneca)*	2,600	5	46
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} = 87 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).

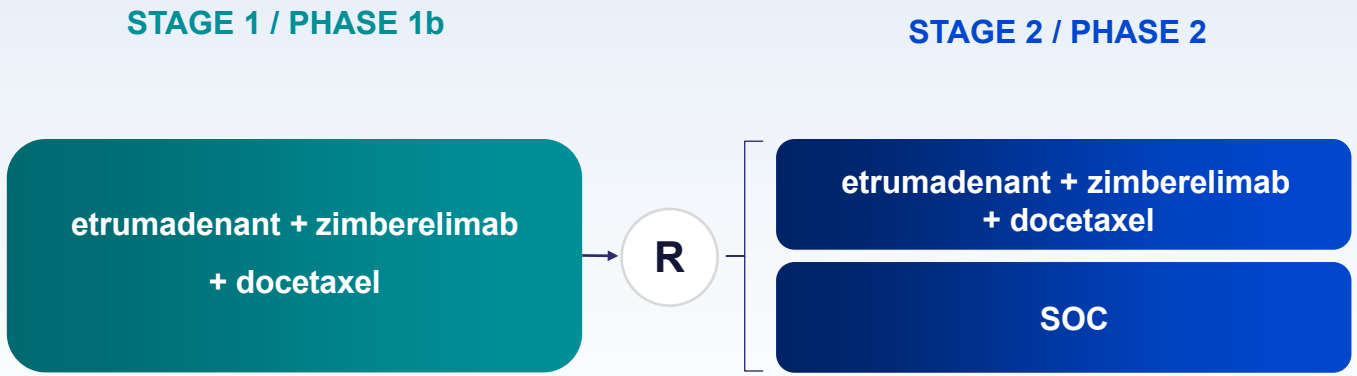
[c] Measured in human blood CD8+ T cells; CREB is a transcription factor that becomes phosphorylated when A2aR is activated; thus, the level of pCREB inhibition is a measure of the ability of an A2aR antagonist to inhibit A2aR.

[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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ARC-6 Phase 1b/2 Platform Study is Evaluating etruma in second-line mCRPC

- Randomized Phase 2 study evaluating etruma + zim combined with docetaxel vs. docetaxel alone in 2L mCRPC (following treatment with a novel hormonal therapy)
- ORR and PFS data expected in 2H:22

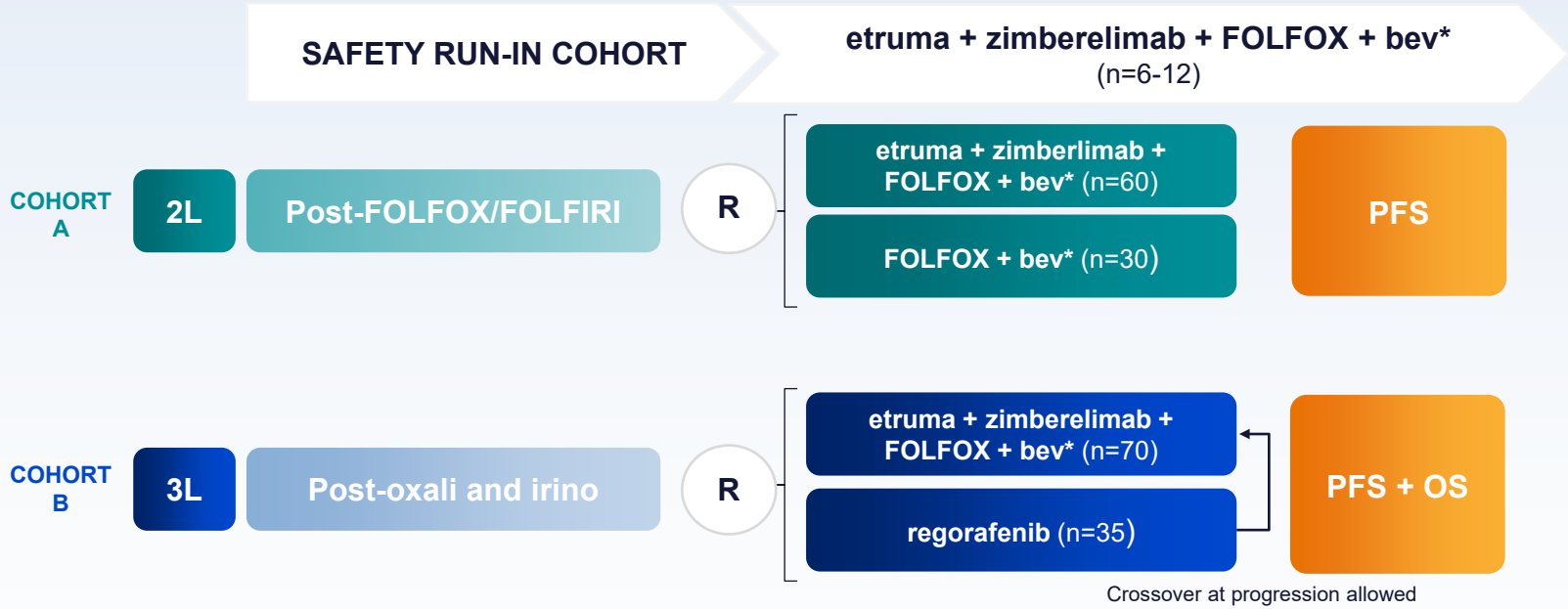


mCRPC: metastatic castrate-resistant prostate cancer; 2L: second-line; ORR: overall response rate; PFS: progression-free survival; SOC: standard of care

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ARC-9 Randomized Phase 2 Study to Evaluate etruma/quemli Combinations in 3L+ mCRC

- Randomized Phase 2 study evaluating etruma + zim + chemo combinations vs. SOC in 2L/3L mCRC
- Both Cohort A and B are enrolling well with high investigator interest in the study
- Data expected in 1H:23



*bev will be included for all patients in whom it is not contraindicated

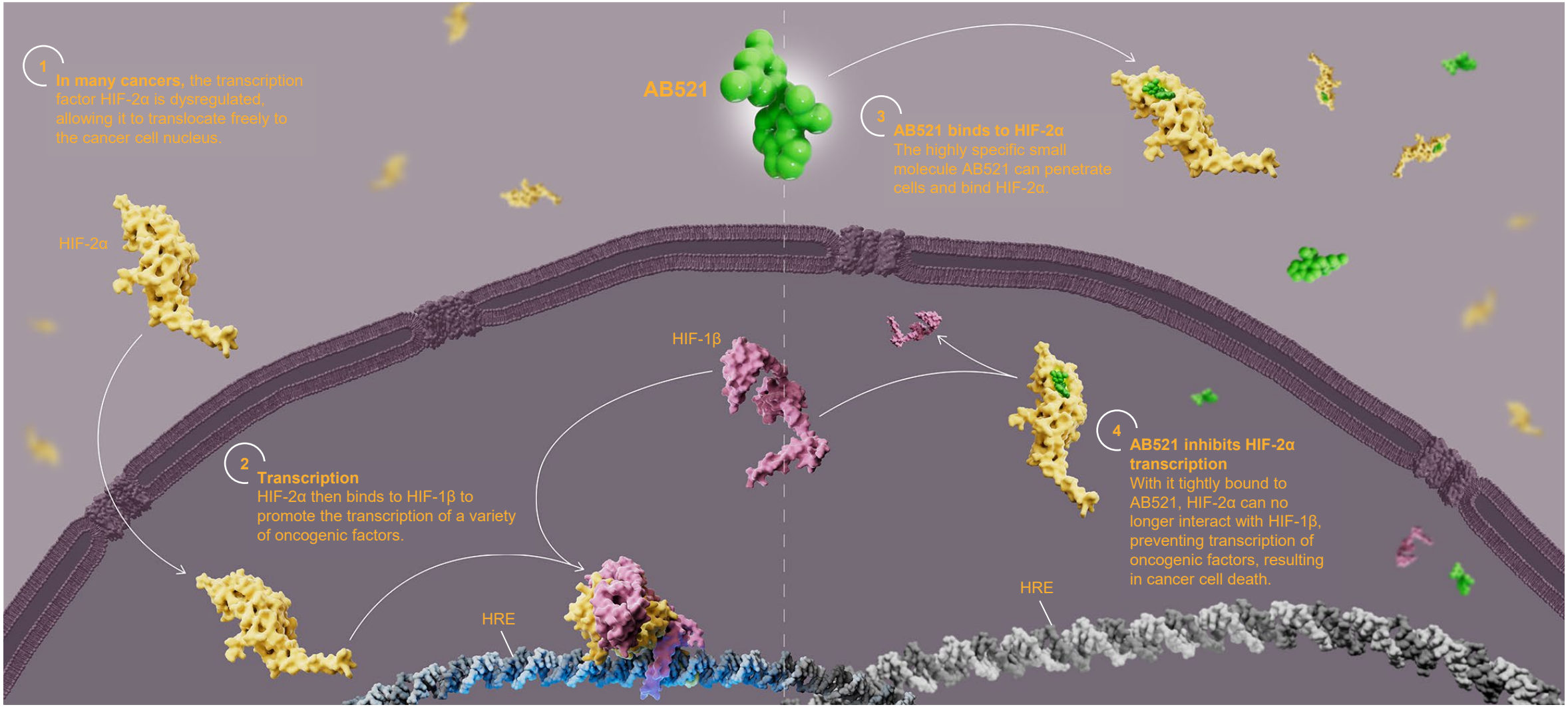
bev: bevacizumab; **etruma: etruma**denant; quemli: irino: irinotecan oxali: oxaliplatin; q**uemli**clustat: CD73 inhibitor; zim: zimberelimab

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HIF-2α Program



AB521 In the Tumor Cell Nucleus



HRE, Hypoxia Response Element.
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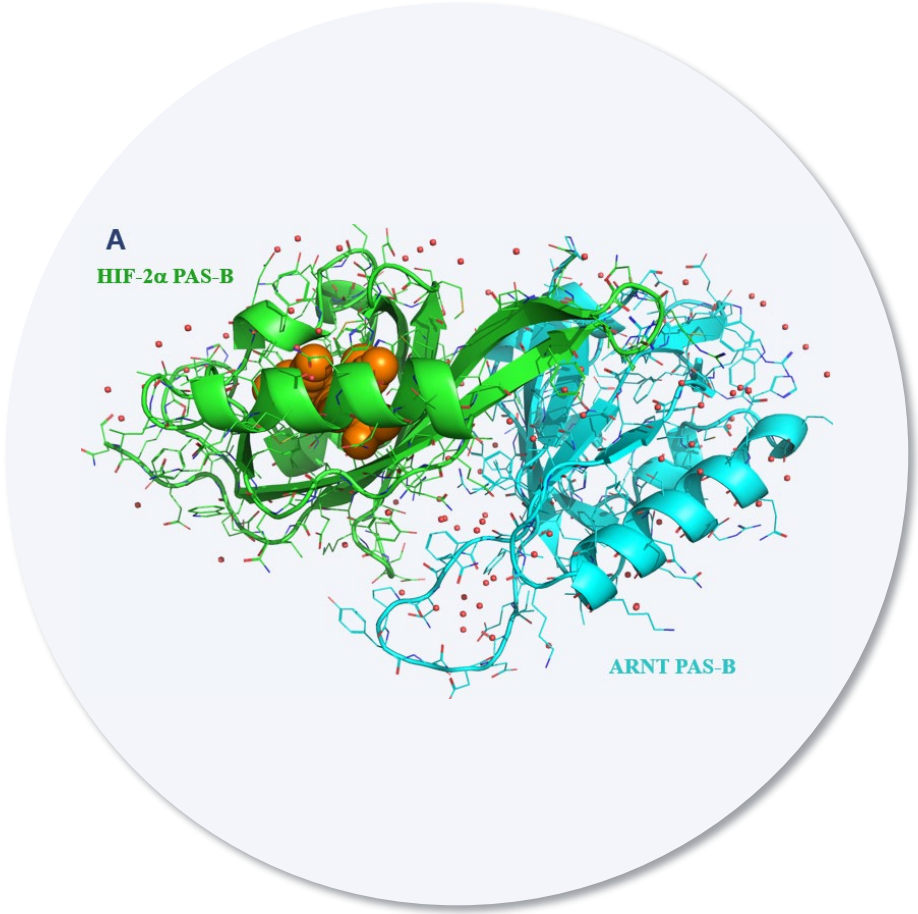
2-Prong Value Proposition for an RCUS HIF-2α Inhibitor

- Opportunity to reach greater intra-tumoral HIF-2α inhibition compared to 120-mg dose of belzutifan
  - Potentially without increased toxicity, which appears to be driven by peripheral effects that saturate at lower doses
  - Requires a compound with greater potency and/or a better PK profile
- Evaluation of unique combinations and/or unique tumor types
  - Possible combinations with quemli/etruma, potentially in combination with SOC and other agents

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Extensive Characterization Confirms Greater Potency of AB521 Relative to belzutifan (MK-6482)

	ASSAY	AB521	MK-6482[a]
CELLULAR	HIF-2α 786-O Luc Reporter IC_{50} (nM)	8.2 ± 2.5 (n=24)	16.9 ± 10.1 (n=8)
	Control 786-O Luc Reporter IC_{50} (nM)	> 10,000 (n=6)	> 10,000 (n=7)
	HIF-2α 786-O Luc Reporter IC_{50} (nM) [in 100% Serum]	46.5 ± 14.2 (n=24)	61.8 ± 6.6 (n=4)
	786-O VEGF AlphaLISA IC_{50} (nM)	28.9 ± 3.6 (n=11)	47.7 ± 30.8 (n=4)
BIOCHEMICAL	HIF-2α $TSAT_m\Delta$ (°C)	14.7 ± 0.6 (n=14)	12.1 ± 0.3 (n=4)
	HIF-2α MST K_D (nM)	2.4 ± 0.8 (n=3)	15.4 ± 2.7 (n=3)
	HIF-2α ITC K_D (nM)	53.6 ± 17.9 (n=3)	53.8 ± 19.3 (n=3)
	HIF-2α SPA IC_{50} (nM)	16.6 ± 5.0 (n=8)	22.3 ± 5.6 (n=5)

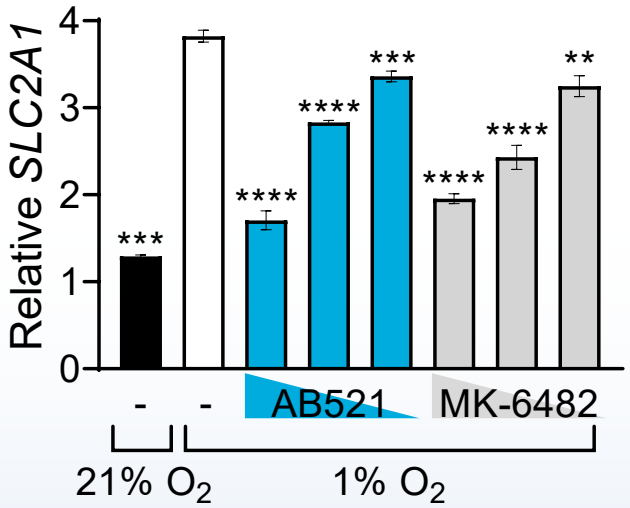


[a] MK-6482 was synthesized according to Xu *et al.* 2019 J Med Chem; DOI: 10.1021/acs.jmedchem.9b00719

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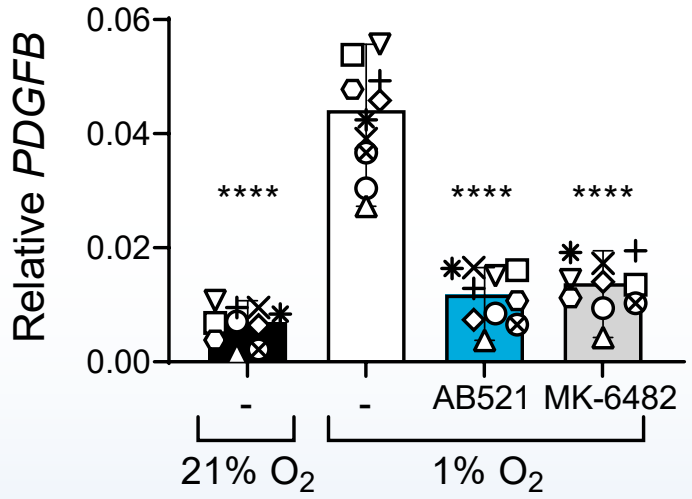
AB521 Selectively Inhibits Endogenous HIF-2α Dependent Transcription in Human Cells

HUVEC Endothelial Cells Pro-Angiogenic Transcription



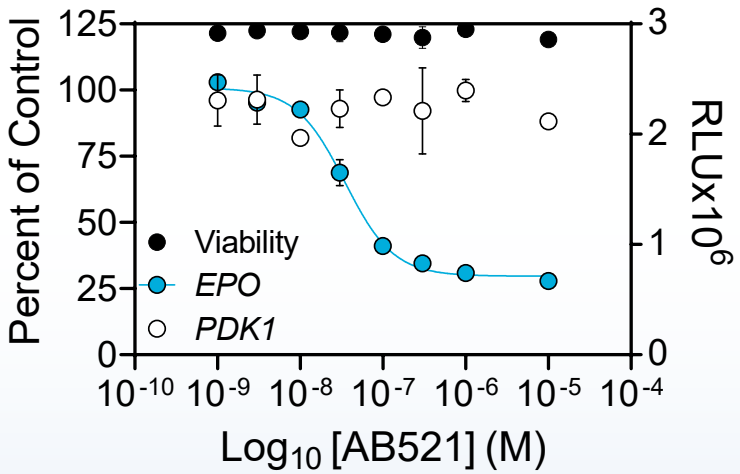
- Representative experiment (n=3); -, DMSO; 1.0, 0.03, 0.01 µM compound; Stats, ANOVA with multiple comparisons test for each group vs DMSO 1% O_2 group
- Similar results seen for *ADM*, *AKAP12*, *DLL4*, and *SLC2A3* genes

CD14⁺ Monocyte-Derived M2-Polarized Macrophages Pro-Tumorigenic Transcription



- Three experiments pooled, each symbol represents an individual donor (n=10); -, DMSO; 1.0 µM compound; Stats, ANOVA with multiple comparisons test for each group vs DMSO 1% O_2 group
- Similar results seen for *ADM* and *SERPINE1* genes

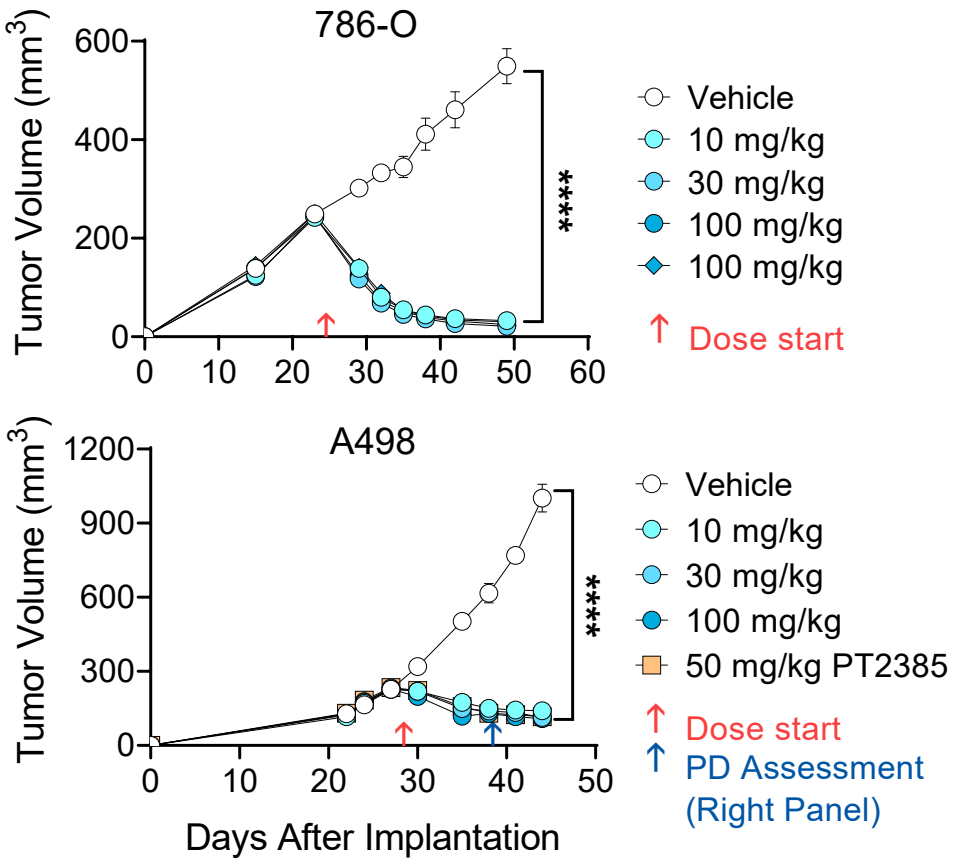
Hep3B Hepatocellular Carcinoma HIF-1α vs HIF-2α Gene Transcription



- Representative experiment (n=3)
- Right y-axis, Viability (CellTiter-Glo); RLU, luminescence
- Left y-axis, *EPO* (HIF-2α-specific) & *PDK1* (HIF-1α-specific) transcript
- Similar results seen for *SERPINE1* (HIF-2α-specific) and *PGK1* (HIF-1α-specific) genes

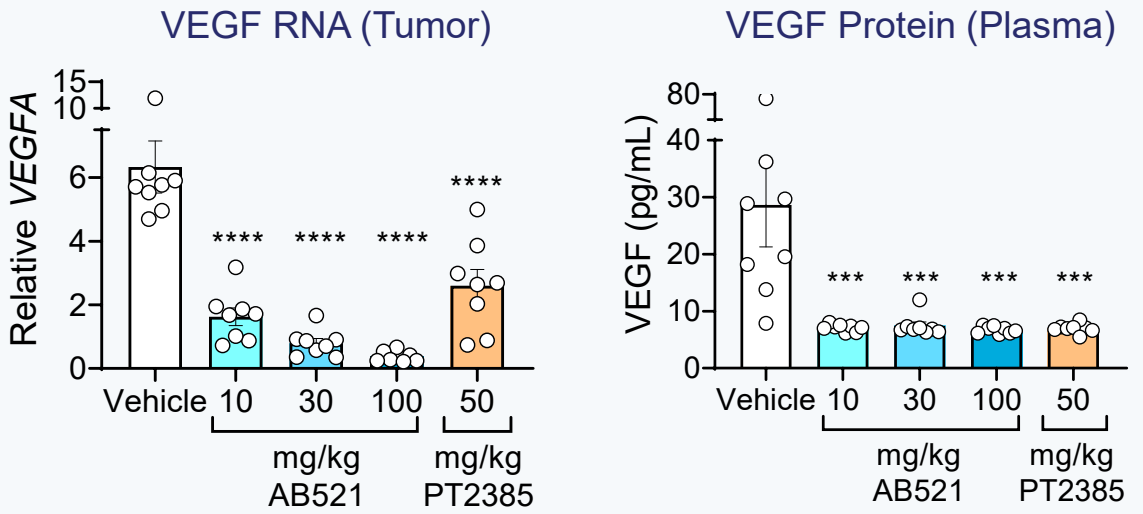
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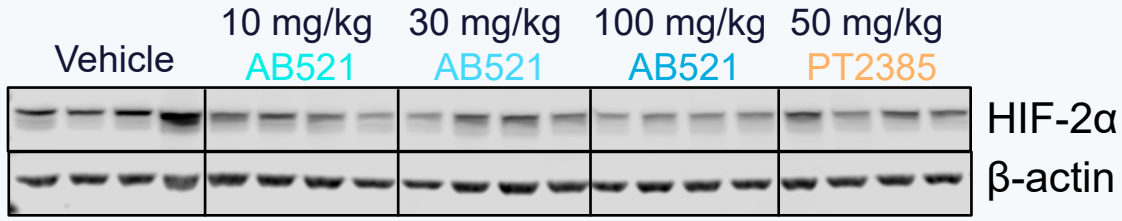
AB521 Inhibits Tumor Growth and HIF-2α Activity in ccRCC Tumor-Bearing Mice



- **Circles**, Vehicle or AB521 given orally twice-daily; **Diamond**, AB521 given orally once-daily; **Square**, PT2385 (synthesized by Arcus using methodology published in Wehn *et al.* DOI: 10.1021/acs.jmedchem.8b01196) given orally once-daily
- Efficacy (n=10) and PD data representative of two independent experiments; Stats, ANOVA with multiple comparisons test for each group vs Vehicle

10 DAYS AFTER TREATMENT
PD ASSESSMENT IN A498 MODEL

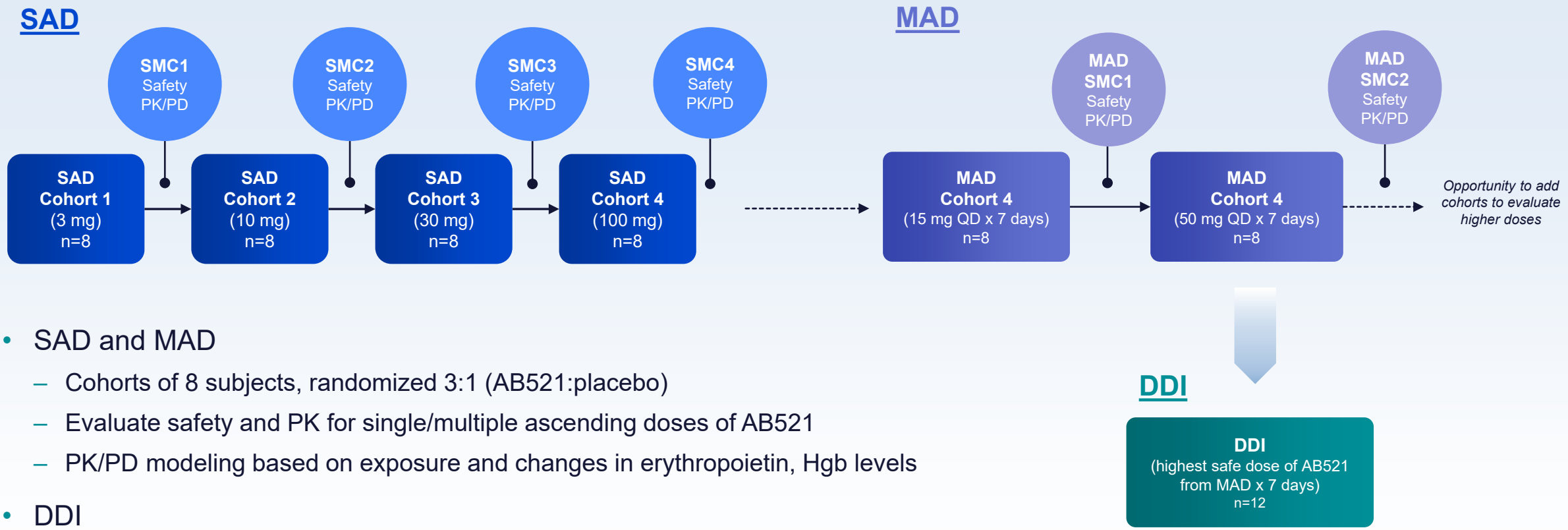




- Top, each symbol represents an individual mouse
- Bottom, Western blot; Each lane contains tumor lysate from an individual mouse

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Phase 1 Study in Healthy Volunteers



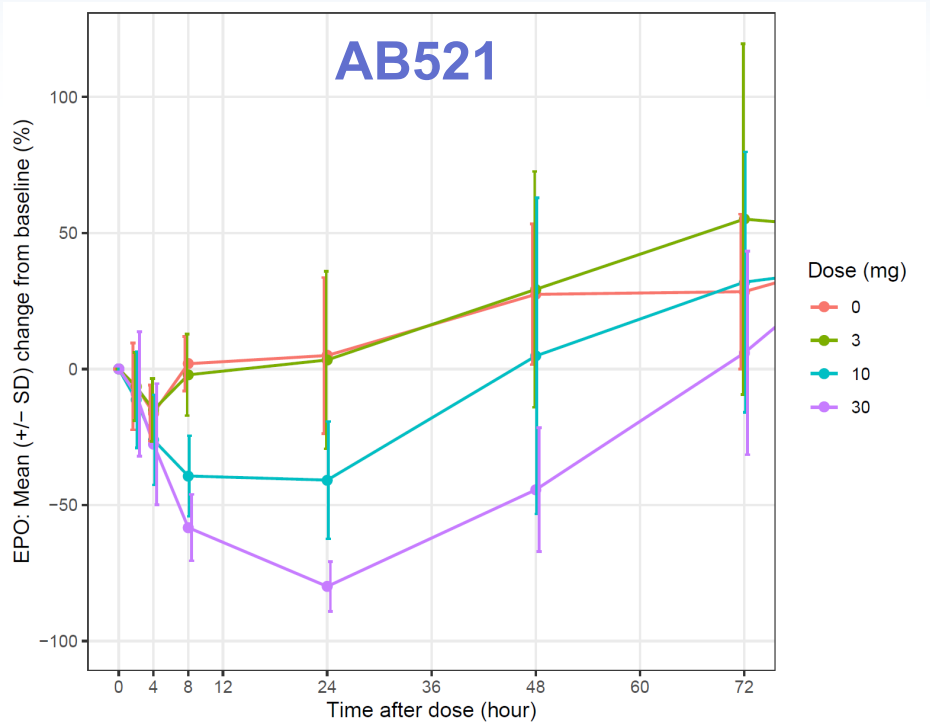
- SAD and MAD
  - Cohorts of 8 subjects, randomized 3:1 (AB521:placebo)
  - Evaluate safety and PK for single/multiple ascending doses of AB521
  - PK/PD modeling based on exposure and changes in erythropoietin, Hgb levels
- DDI
  - Single cohort of 12 subjects, no randomization

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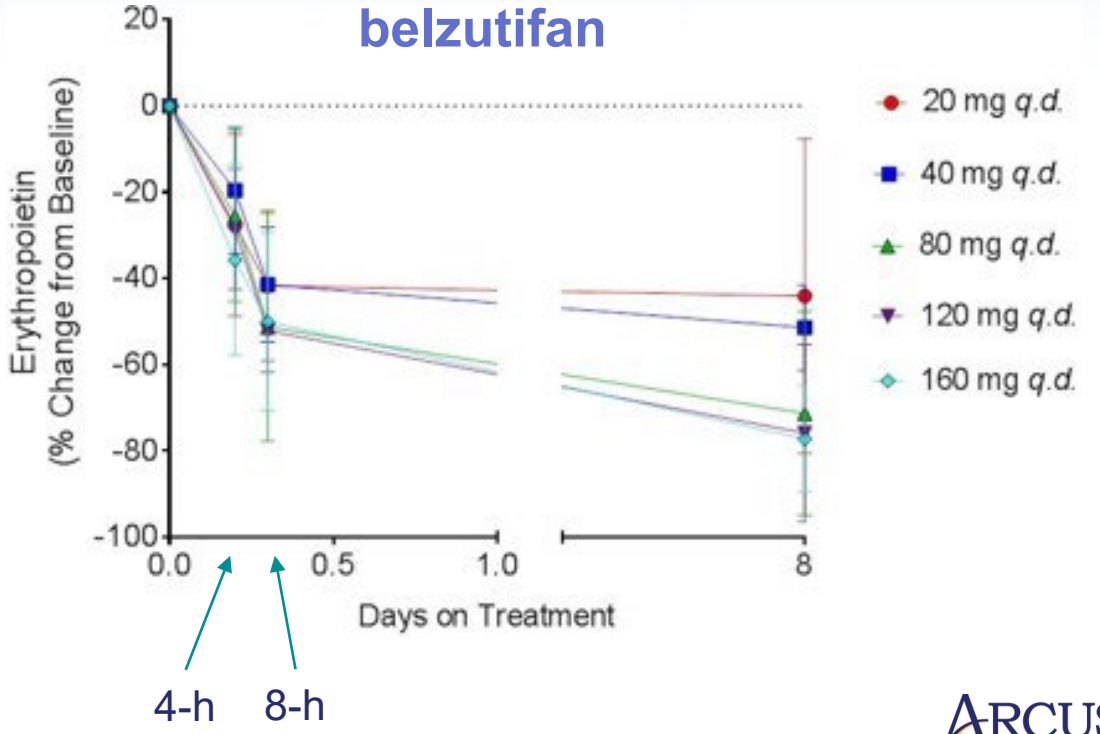
Reduction in Serum EPO Indicated PD Effect of AB521 at ≥10 mg Dose Levels

EPO reduction at ≥10 mg appear to be comparable or exceeding the level observed in belzutifan (up to 160 mg) at 8 hours

Mean (±SD) EPO % change from baseline vs time profiles by dose level

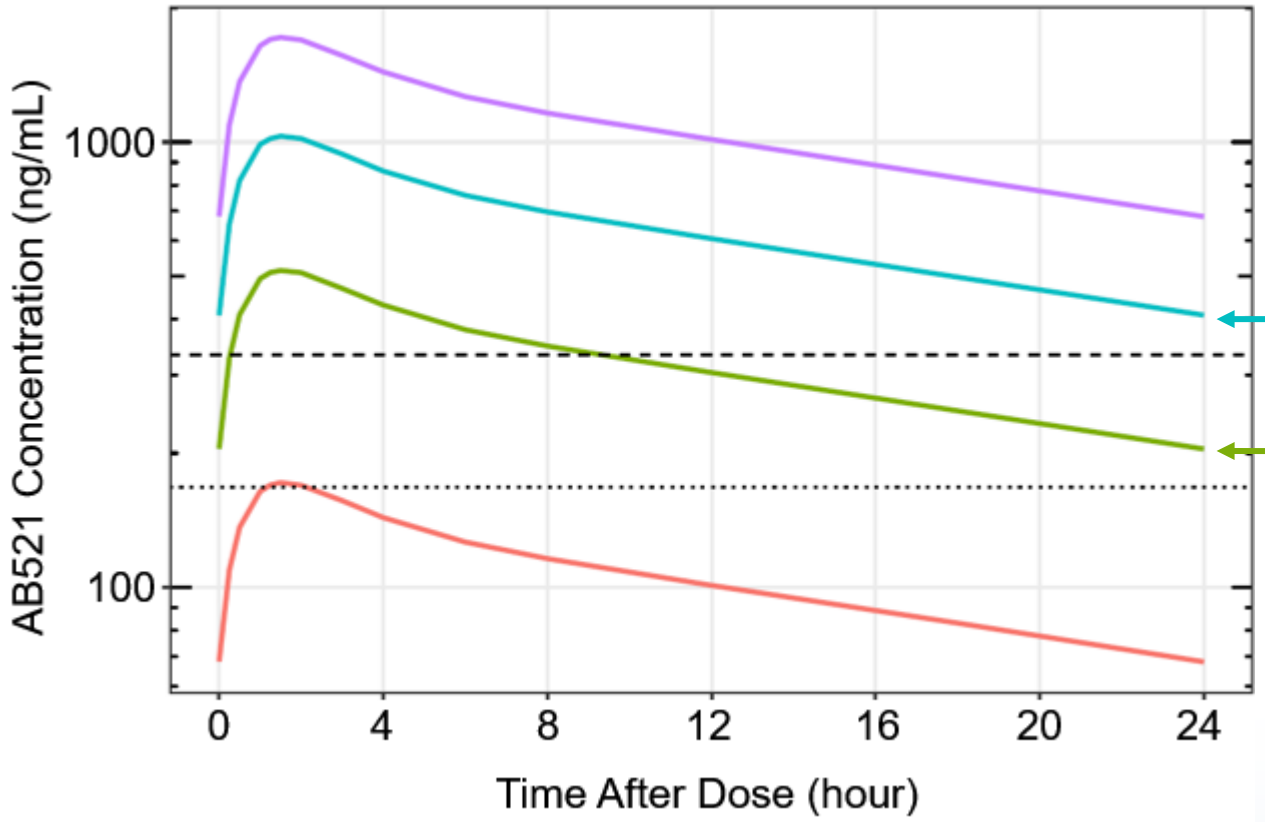


Belzutifan EPO data from Phase I study



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Modeled Steady-State Exposure of AB521 Based on SAD Arms (3, 10, 30mg)



Dose (mg)
- 100
- 60
- 30
- 10

AUC_{0-24}: 13,300 ng.hr/mL

AUC0-24: 6,650 ng.hr/mL

Target AB521 exposure of 12,500 ng.hr/mL to match120mg belzutifan should be reached somewhere around 50mg qd AB521

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Ongoing Evaluation of AB521 in Healthy Volunteers

- Ongoing single-ascending dose escalation in healthy volunteers (HV)
- PK, PD (modulation of plasma EPO levels) and safety data from first 3 cohorts consistent with our projection that AB521, at 45-60 mg QD, will match the potency-corrected exposure associated with 120 mg belzutifan
- In parallel with completion of HV study, we plan to file an IND (2Q22) to initiate evaluation of AB521 (single agent and combinations with SOC / pipeline assets) in ccRCC
- Currently evaluating potential synergism between adenosine axis inhibitors and AB521, as well as opportunities to evaluate AB521 in settings other than ccRCC

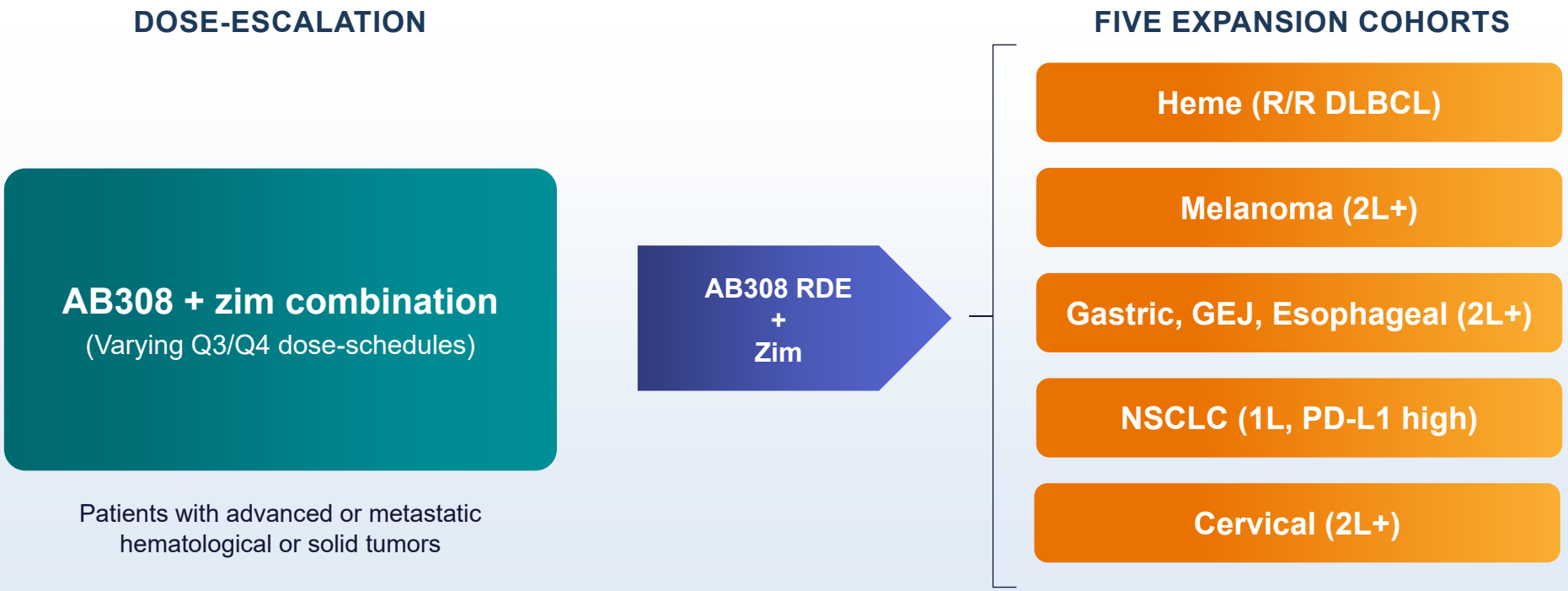
ccRCC: clear cell Renal Cell Carcinoma
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ARC-12 | Phase 1/1b Trial to Evaluate Safety & Tolerability of AB308 + zim in Advanced Malignancies

STATUS:

- RDE for AB308 + zim combination has been established
- Multiple expansion cohorts allow for rapid signal seeking to inform future Phase 3 studies
- All five expansion cohorts are open for enrollment



zim: zimberelimab; Heme: hematology; R/R DLBCL: relapsed, refractory diffused large b-cell lymphoma; GEJ: esophagogastric junction; NSCLC: non-small cell lung cancer

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