

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

ASCO-GI: ONGOING ARC-8 DOSE-ESCALATION OVERVIEW

JANUARY 2021

NYSE: RCUS

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2021 Will Be a Pivotal Year for Arcus

- **Four clinical-stage product candidates rapidly advancing towards registrational trials**
  - Two essential backbone antibodies:
    - **AB154 (Domvanalimab)**: Anti-TIGIT mAb – randomized interim-analysis read-out for ARC-7 planned in 2Q:21 (in 1L NSCLC, PD-L1 ≥ 50%); Advancing ARC-10 into registrational trial (to support both Dom + Zim and Zim approvals)
    - **AB122 (Zimberelimab)**: Anti-PD-1 mAb with clear line-of-sight to commercialization; enables portfolio combination strategies
  - Two internally discovered small molecules targeting the adenosine axis:
    - **AB928 (Etrumadenant)**: First dual $A_{2a}R$ / $A_{2b}R$ antagonist to enter the clinic
    - **AB680**: First small-molecule CD73 inhibitor to enter clinical development; both IV and oral formulations in development
- **Six Arcus sponsored randomized trials are ongoing or soon-to-be initiated with preliminary data from several of these randomized trials expected in 2021**
- **At least two additional product candidates expected to enter clinical development in 2021**
  - AB308: TIGIT antibody (FcR enabled) to target heme malignancies
  - Small molecule programs targeting HIF2a, Axl and PAK4 are approaching development candidate selection
- **Well-positioned to unlock the value of our pipeline**
  - ~$785M in cash as of 9/30/20 and funding into at least 2023
  - "All-in" Gilead partnership provides significant financial and other resources to more fully exploit our portfolio
  - Recently announced clinical collaboration with AstraZenca for PACIFIC-8 (Phase 3 trial in Stage III NSCLC) further validates the therapeutic potential of domvanalimab

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Broad Clinical Program Targeting Major Cancers, Including Those Not Responsive to PD-(L)1 Therapy



Zim: zimberelimab; Dom: domvanalimab; Etruma: etrumadenant; Rego: regorafenib
Gem: gemcitabine; FOLFOX: (folinic acid, fluorouracil; oxaliplatin); Nab-pac: nab-paclitaxel; Doce: docetaxel;
Carbo: carboplatin; Pem: pemetrexed, Durva: durvalumab; Enza: enzalutamide
NSCLC: non-small cell lung cancer; CRPC: castrate-resistant prostate cancer; CRC: colorectal cancer; PDAC: pancreatic ductal adenocarcinoma
[1]Clinical collaboration with AstraZeneca; AZ will be the primary sponsor of PACIFIC-8.
* +/- biologic

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Multiple Important Readouts Are Expected In 2021

	COMBINATION / ARMS	SETTING	MILESTONE	ANTICIPATED TIMING
ARC-8	**AB680** + **Zim** + Gem/Nab-pac	1L Pancreatic Cancer	– Initial dose-escalation data – Additional data from dose-escalation	▪ **January 2021 (ASCO GI)** ▪ **2H21**
ARC-7	**Zim** + **Dom** *vs.* **Zim** *vs.* **Zim** + **Dom** + **Etruma**	1L NSCLC (PD-L1 ≥ 50%)	– Conduct of interim analysis – Presentation of IA data	▪ **2Q21** ▪ **2H21**
ARC-4	**Etruma** + **Zim** + Carbo/Pem *vs.* **Zim** + Carbo/Pem	TKI R/R EGFR+ NSCLC	– Initial randomized data	▪ **2H21**
ARC-6	**Etruma** + **Zim** + SOC *vs.* SOC	Metastatic castrate-resistant prostate cancer (mCRPC)	– Preliminary data from initial cohorts – Initial randomized data	▪ **2Q21** ▪ **2H21**
ARC-9	**Etruma** + **Zim** + FOLFOX *vs.* SOC	2L/3L/3L+ Colorectal cancer	– Initial randomized data for 2L/3L cohorts; single-arm data for 3L+	▪ **1H22**

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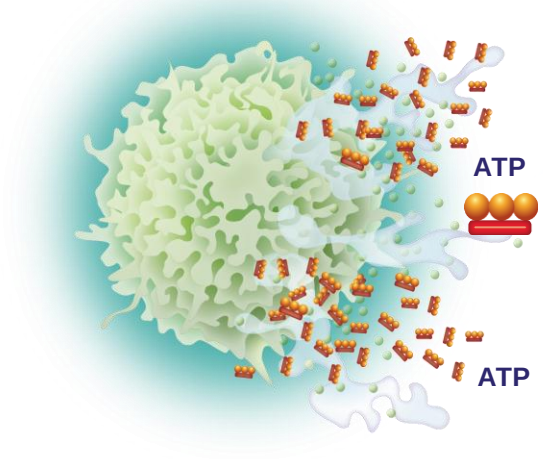
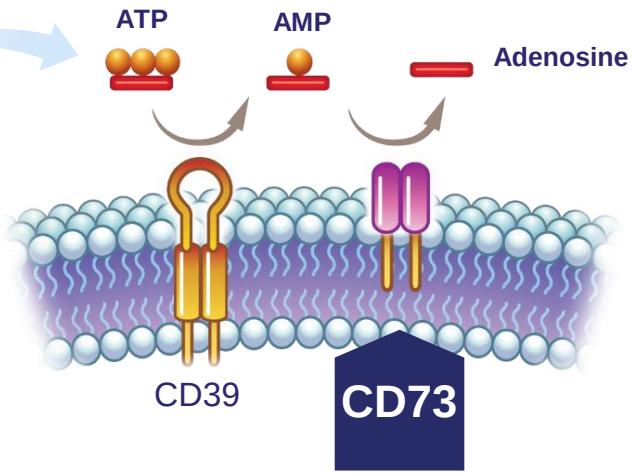
The Adenosine Axis Plays a Well-Established and Critical Role in Suppression of the Immune Response

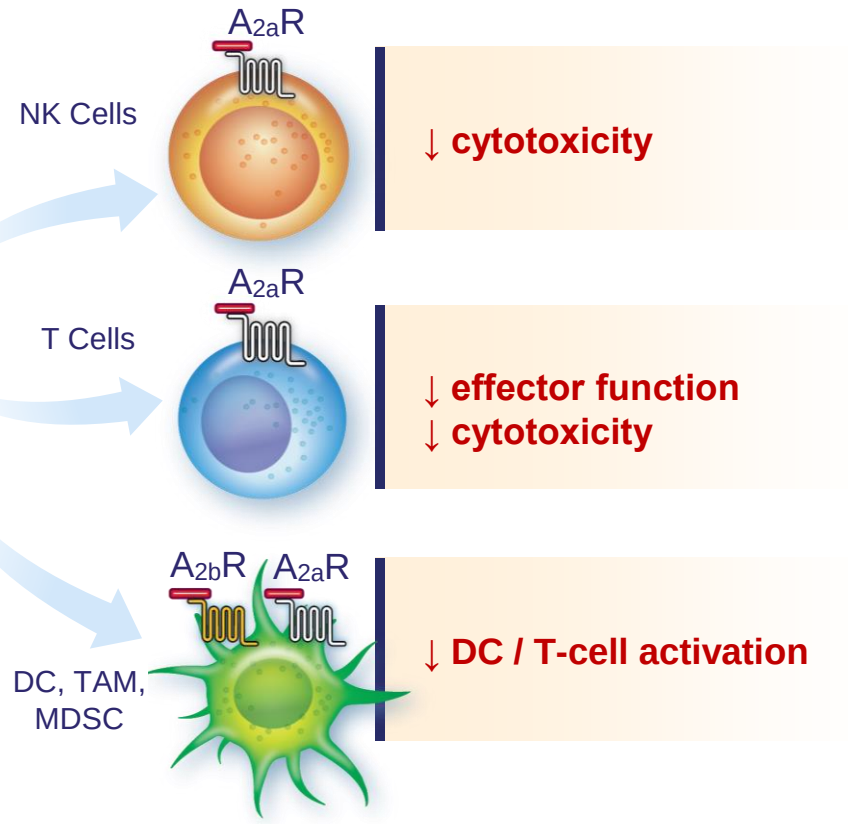
Extracellular ATP is released by dying cells, particularly when triggered by immunogenic chemotherapy



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



Adenosine production leads to significant **immunosuppression** in the tumor microenvironment



AB928: Dual $A_{2a}R/A_{2b}R$ receptor antagonist; **AB680**: Small-molecule CD73 inhibitor

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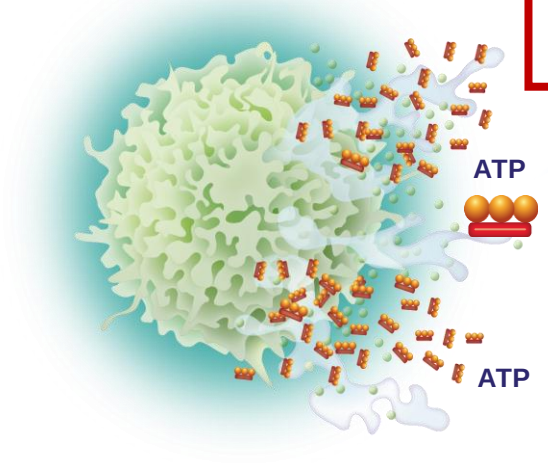
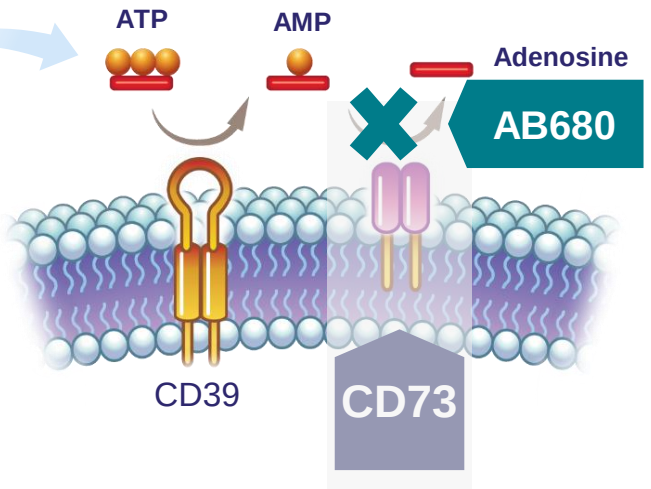
Arcus is a Leader in the Development of Therapeutics that Target the Adenosine Axis

AB680 inhibits CD73, an enzyme that plays a key role in the conversion of AMP to adenosine, therefore acting upstream of etruma

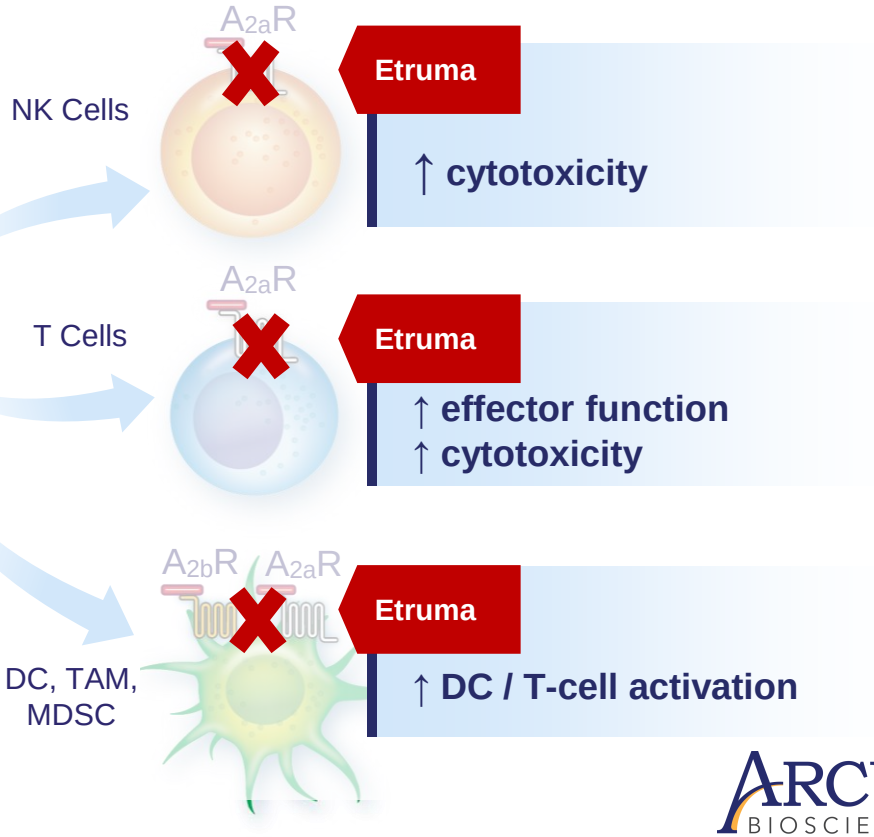
Extracellular ATP is released by dying cells, particularly when triggered by immunogenic chemotherapy



AB680 blocks the function of CD73, preventing the conversion of AMP to adenosine



Etruma blocks adenosine from binding to **$A_{2a}R$** and **$A_{2b}R$**, **blocking immunosuppression**



Etruma: Dual $A_{2a}R/A_{2b}R$ receptor antagonist; **AB680**: Small-molecule CD73 inhibitor

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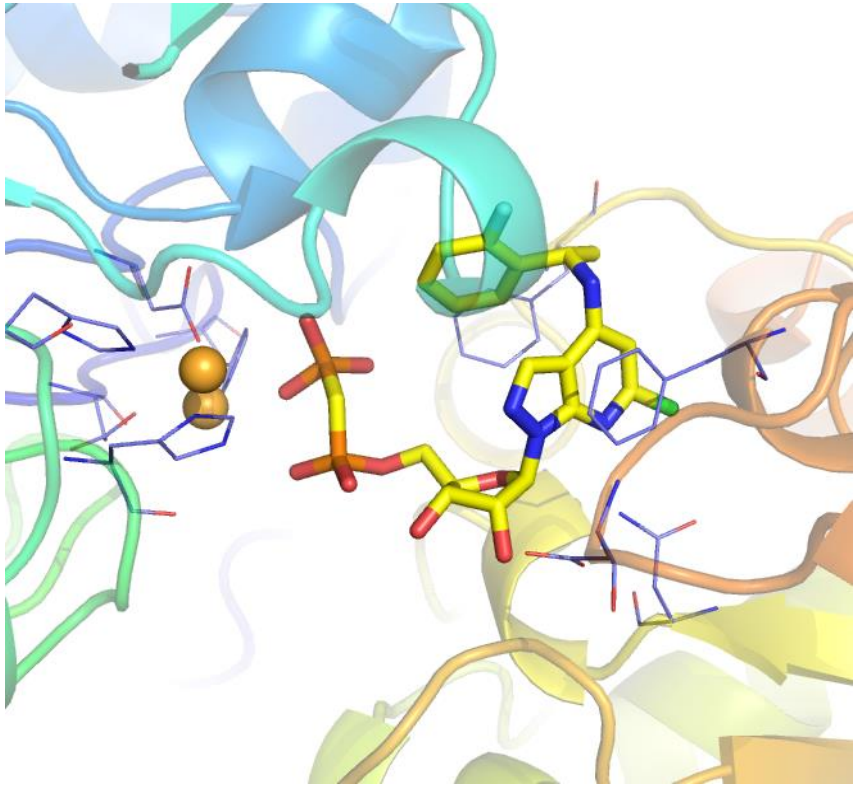
AB680 is a Unique, Highly Potent and Selective Small Molecule CD73 Inhibitor

AB680 is a tight-binding, reversible CD73 inhibitor (K_i hCD73 = 4.9 pM)

K_i determined in collaboration with Prof. Rafael Guimaraes da Silva, Univ. of St. Andrews

Biochemistry, **2019**, *58*, 3331-3334

Extreme Potency of AB680 Against CD73	
Target	**IC_{50} (nM)**
hCD73-CHO	0.070
hCD73 (soluble)	0.043
Human $CD8^+$ T Cells	0.008
hPBMC	0.011



Other features:

IV administration (oral formulation also in development)

Extremely long (~4 days) half-life, enabling dosing every two weeks

X-ray data collected by N. Sträter; Univ. of Leipzig

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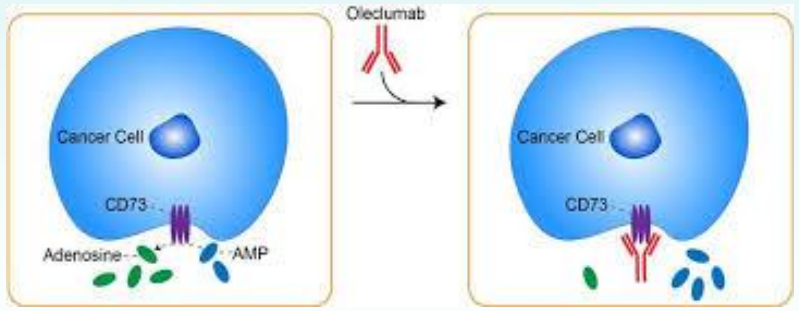
Mechanism of AB680 Potentially Offers Several Advantages Over CD73 Antibodies

CD73 Antibodies Have Limitations



The most advanced antibodies in the clinic are being developed by AZN (Oleclumab) and BMS

- As antibodies, unlikely to achieve a small molecule's permeability of tumor tissue (important since adenosine exerts its biology where it is formed by CD73)
- Antibodies are unable to completely inhibit CD73 enzymatic activity and are even less effective against soluble CD73

AB680 (Small Molecule)

- ✓ First small-molecule inhibitor of CD73 to enter the clinic
- ✓ **Extremely potent and selective against both tumor and soluble CD73** and orders of magnitude more potent than CD73 antibodies
- ✓ Established safety profile as a single agent in healthy volunteers and in combination with chemo/anti-PD-1 in pancreatic cancer patients
- ✓ PK/PD profile has shown complete target coverage 24/7 in humans
- ✓ Flexibility to use as IV or oral formulation

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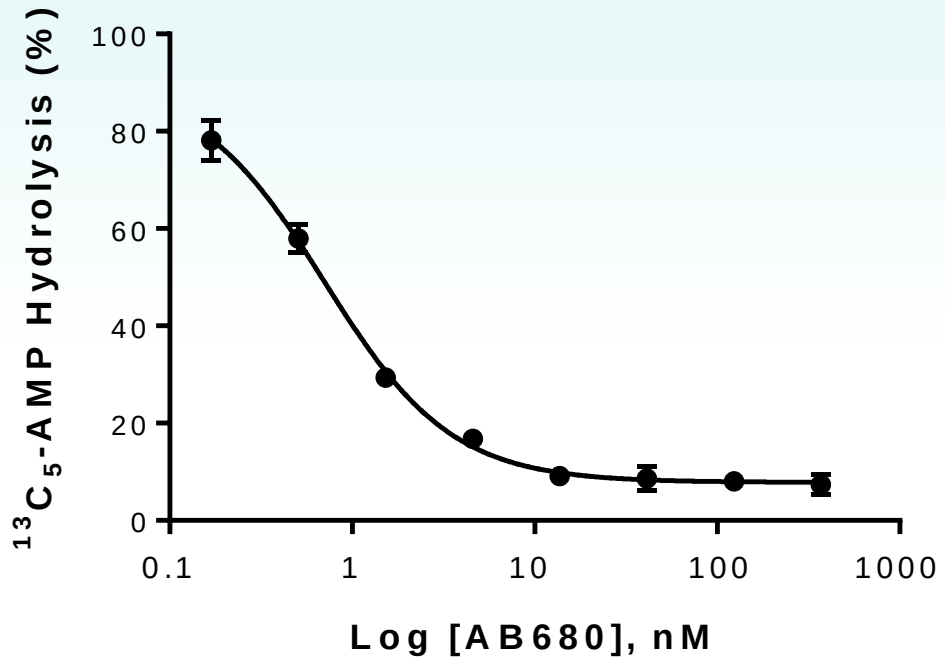
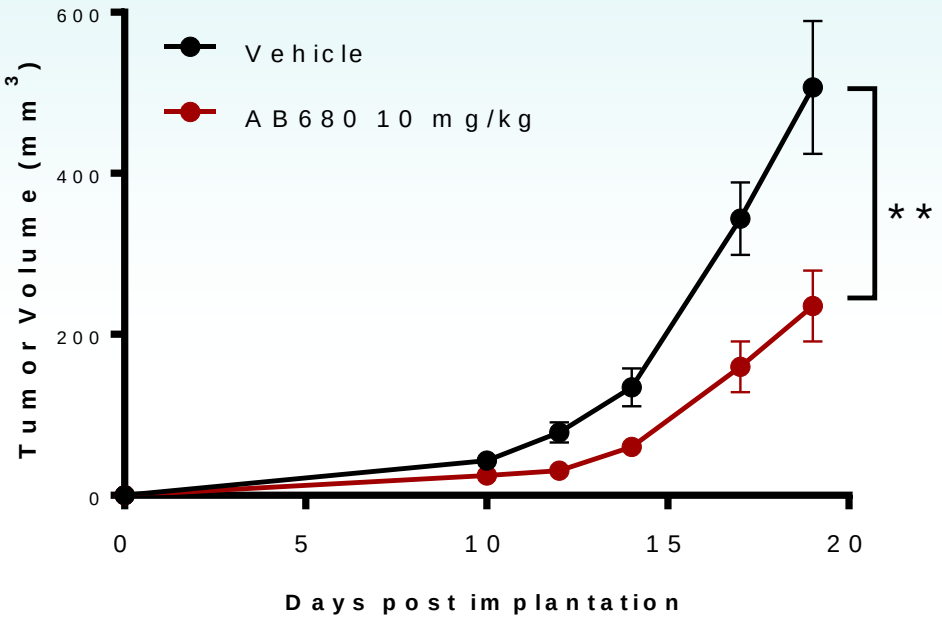
AB680 Monotherapy Inhibits Intratumoral CD73 and Delays Tumor Growth in Mouse Tumor Models

AB680 Inhibits CD73 Enzymatic Activity Within Tumors



AB680 Monotherapy Inhibits Tumor Growth



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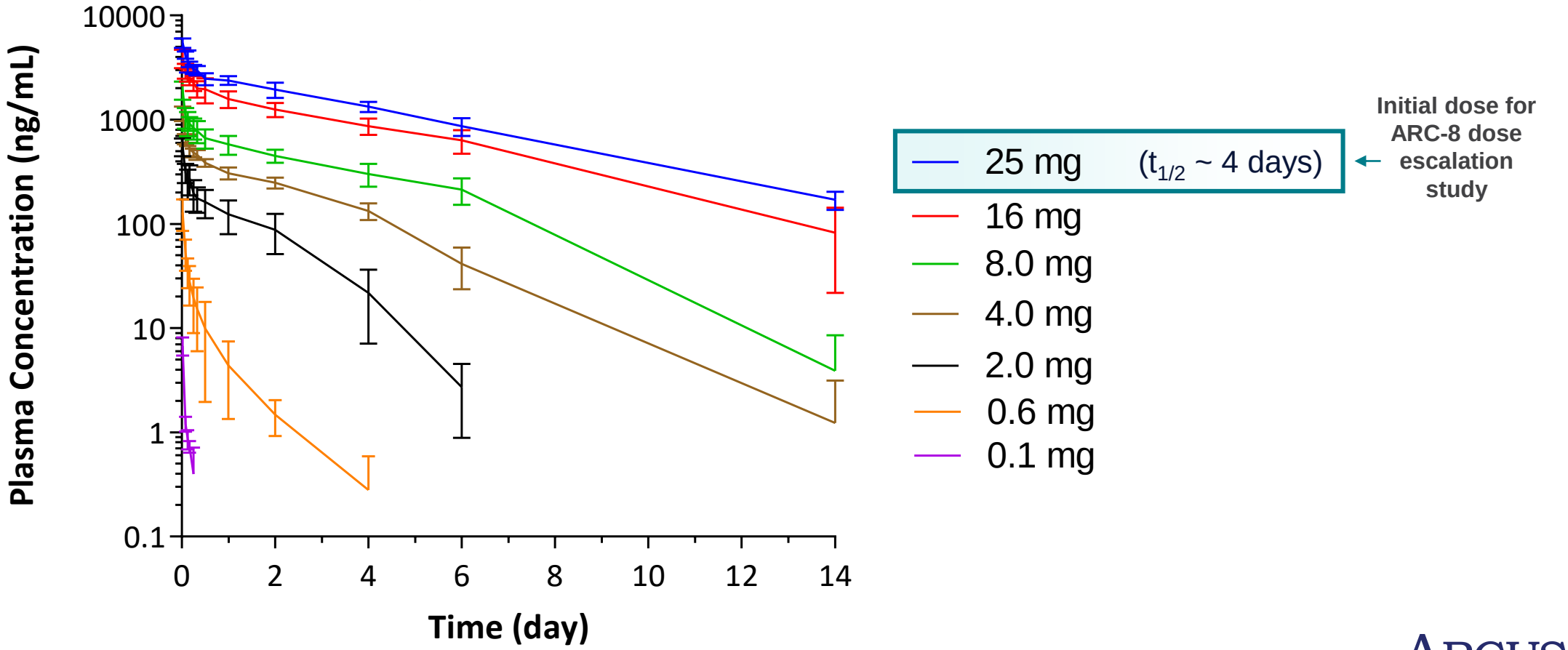
Healthy Volunteer Study Demonstrated AB680 Achieved Complete Target Coverage with Q2W Dosing

Target coverage was achieved, *even at 25mg every two weeks* (Q2W), given the exquisite potency of AB680



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

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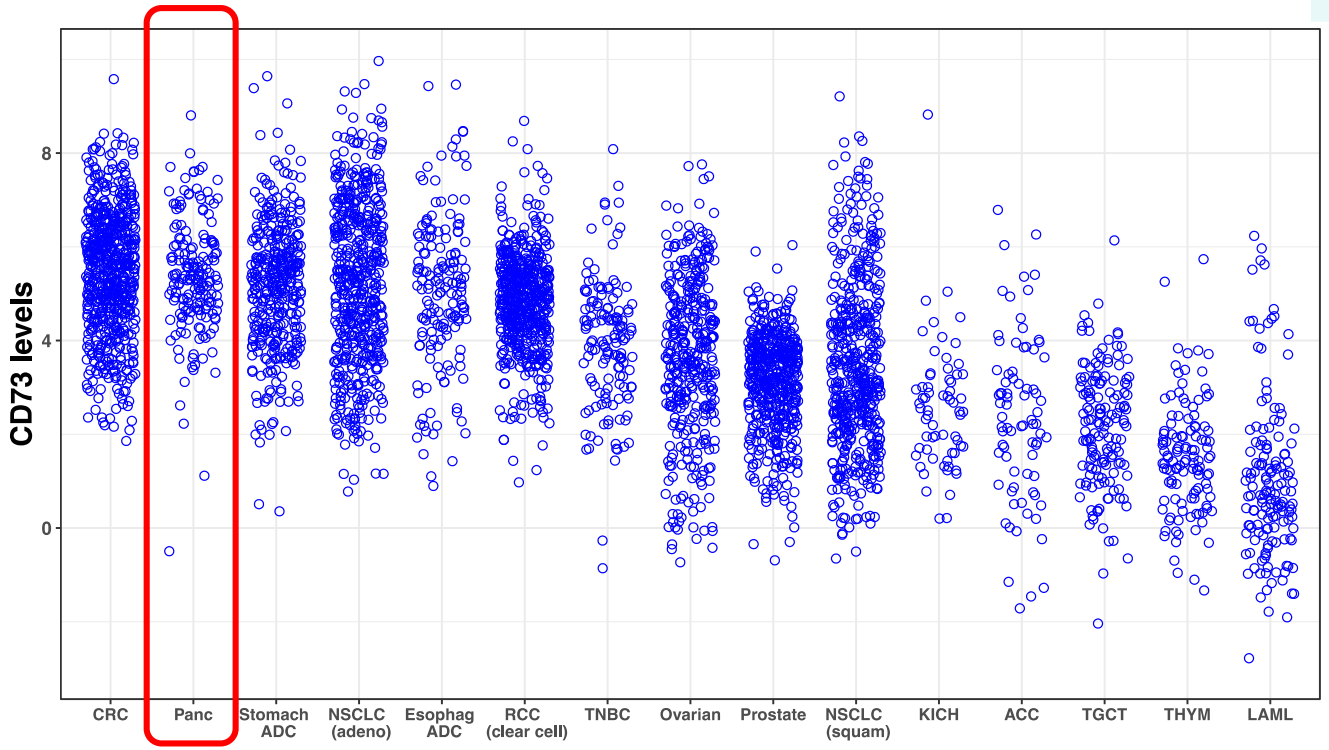
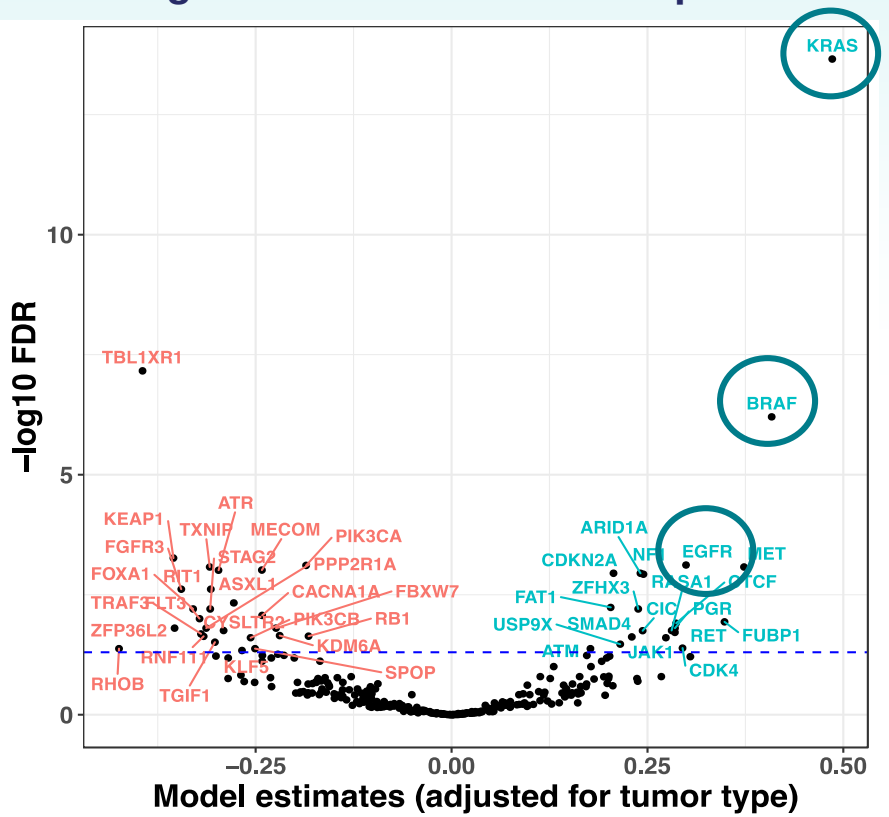
Pancreatic Cancer Was Selected as the Initial Indication for AB680 Given High CD73 Expression

High CD73 levels in PDAC may be a reflection of the observed correlation between CD73 expression and oncogenic drivers such as KRAS



Oncogenic Drivers of CD73 Expression



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

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Phase 1/1b Clinical Study in Advanced 1L Metastatic Pancreatic Ductal Adenocarcinoma (PDAC)

ARC-8

- Dose escalation and dose expansion study
- **Preliminary data on safety and early clinical activity from the dose-escalation portion were presented at ASCO GI**
- Explored four escalating doses of AB680 in combination with Zimberlimab (anti-PD-1) and SOC chemotherapy (Nab-Pac/Gem)
- Dose-expansion phase has been initiated and expected to enroll quickly given high investigator enthusiasm

PDAC Background

- **Devastating disease with a 5-year survival rate of just 9%**
- **Abraxane®, in combination with gemcitabine (NP/Gem), was the last treatment approved (in 2013) based on an ORR of 23%[(1)]**
- **PD-1 antibodies have not shown any benefit to date when combined with chemotherapy[(2)(3)]**
- **Very few new therapies in development**

The low ORR w/ SOC and high prevalence of activated / mutated KRAS pathway (>90%) [(4)] makes PDAC an ideal tumor type for AB680

(1) Von Hoff DD, et al. *N Eng J Med*. 2013; 369(18):1691-1703.
(2) Zev A., et al., *Clin Cancer Res*. 2020; 26(18): 4814.
(3) Weiss GJ, et al., *Invest New Drugs*. 2018; 36(1):96.
(4) Waters and Der, *Cold Spring Harb Perspect Med* 2018;8:a031435.

Presented at ASCO-GI 2021 (GA Manji et al. Abstract #404)

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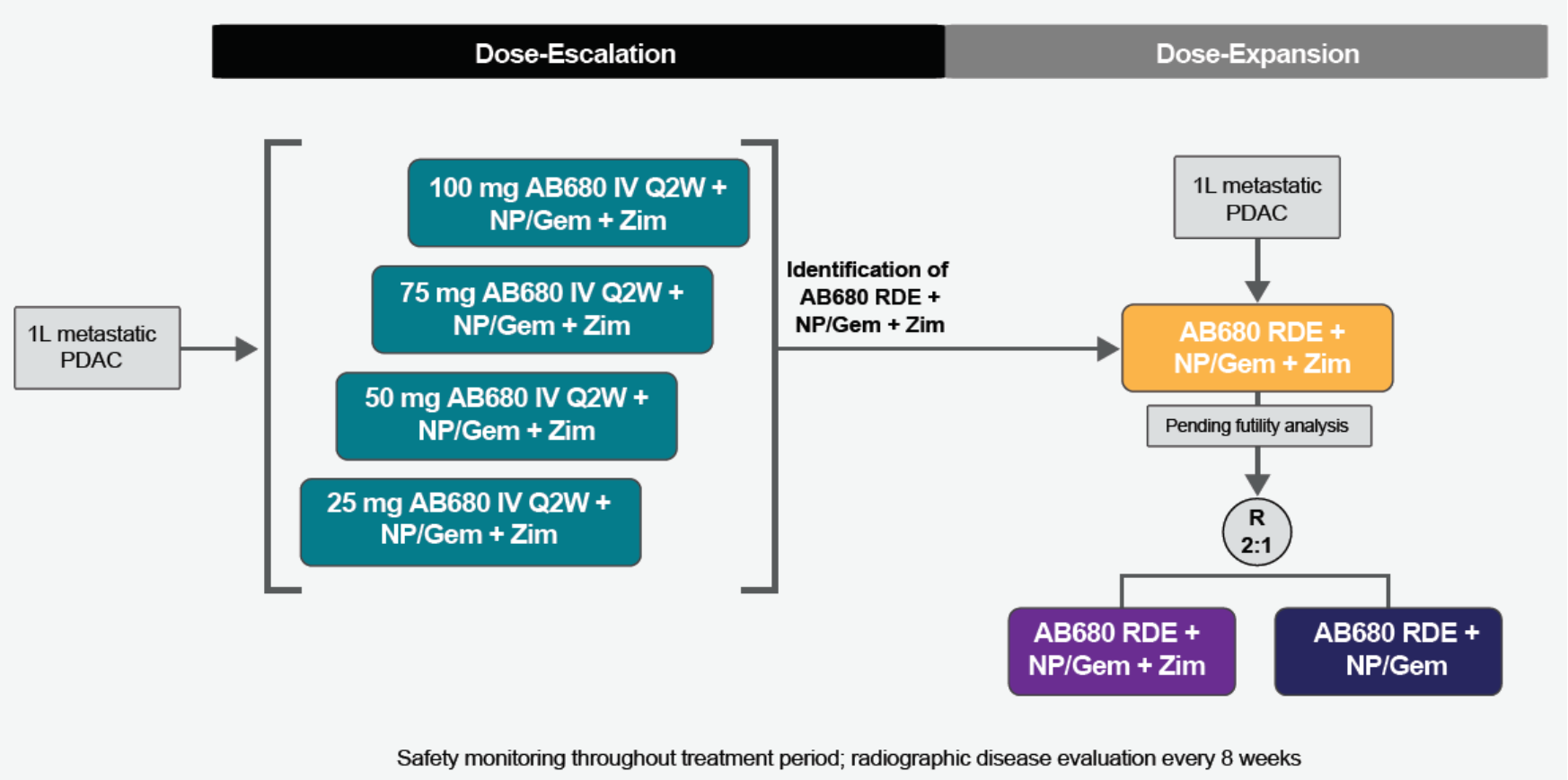
Dose Escalation Designed to Identify the RDE and Detect Evidence of Clinical Activity (ORR / PFS)



IV, intravenously; Gem, gemcitabine; NP, nab-paclitaxel; PDAC, pancreatic ductal adenocarcinoma; Q2W, every 2 weeks; R, randomization; RDE, recommended dose for expansion; Zim, zimberelimab.

Presented at ASCO-GI 2021 (GA Manji et al. Abstract #404)

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ARC-8 Ph1/1b Clinical Study in Front-line Metastatic PDAC Patients

Patient Baseline Characteristics

Parameter	25 mg AB680 + NP/Gem + Zim (n=4)	50 mg AB680 + NP/Gem + Zim (n=6)	75 mg AB680 + NP/Gem + Zim (n=3)	100 mg AB680 + NP/Gem + Zim (n=6)	All Patients (N=19)
Age, mean (SD), years	67.3 (2.2)	61.8 (12.7)	55.3 (2.1)	68.5 (8.7)	64.1 (9.5)
Male, n (%)	2 (50)	4 (67)	2 (67)	3 (50)	11 (58)
Race, n (%)					
White	4 (100)	4 (67)	2 (67)	4 (67)	14 (74)
Asian	0	1 (17)	1 (33)	1 (17)	3 (16)
Not reported	0	1 (17)	0	1 (17)	2 (11)
ECOG PS, n (%)					
0	4 (100)	4 (67)	3 (100)	3 (50)	14 (74)
1	0	2 (33)	0	3 (50)	5 (26)

ECOG PS, Eastern Cooperative Oncology Group performance status; NP/Gem, nab-paclitaxel/gemcitabine; SD, standard deviation; Zim, zimberelimab.

Presented at ASCO-GI 2021 (GA Manji et al. Abstract #404); DCO: Nov. 11, 2020

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Preliminary Safety Data Demonstrate AB680 Adds Minimal Toxicity to Chemotherapy

Summary of Treatment Emergent AEs

- 1 DLT (Gr2 autoimmune hepatitis) in the 50mg AB680 cohort; resolved completely with steroid treatment and the patient resumed treatment
- The most common TEAEs were fatigue (68%), anemia (53%), alopecia (42%), diarrhea (42%) and neutrophil count decreased (42%)
- Study drug-related TEAEs were reported by 8/19 (42%) patients; 4 patients had Gr 1 or 2 study-drug related TEAEs and 4 patients experienced Gr 3 study drug-related TEAEs
- There were no patients who discontinued study treatment due to TEAEs

No significant toxicity has been observed over that expected for the NP/Gem backbone alone

Parameter, n (%)	25 mg AB680 + NP/Gem + Zim (n=4)	50 mg AB680 + NP/Gem + Zim (n=6)	75 mg AB680 + NP/Gem + Zim (n=3)	100 mg AB680 + NP/Gem + Zim (n=6)	All Patients (N=19)
Any TEAE	4 (100)	6 (100)	3 (100)	5 (83)	18 (95)
Grade ≥3	3 (75)	5 (83)	1 (33)	3 (50)	12 (63)
Any TESAE	1 (25)	3 (50)	0	3 (50)	7 (37)
Grade ≥3	1 (25)	2 (33)	0	3 (50)	6 (32)
Study drug-related TEAEs	1 (25)	3 (50)	2 (67)	2 (33)	8 (42)
Grade ≥3	0	2 (33)	1 (33)	1 (17)	4 (21)
Study drug-related TESAEs	0	1 (17)	0	1 (17)	2 (11)
Grade ≥3	0	0	0	1 (17)	1 (5)

Parameter, n (%)	25 mg AB680 + NP/Gem + Zim (n=4)	50 mg AB680 + NP/Gem + Zim (n=6)	75 mg AB680 + NP/Gem + Zim (n=3)	100 mg AB680 + NP/Gem + Zim (n=6)	All Patients (N=19)
TEAEs in ≥4 patients					
Fatigue	4 (100)	6 (100)	1 (33)	2 (33)	13 (68)
Anemia	1 (25)	5 (83)	2 (67)	2 (33)	10 (53)
Alopecia	2 (50)	2 (33)	2 (67)	2 (33)	8 (42)
Diarrhea	2 (50)	4 (67)	1 (33)	1 (17)	8 (42)
Neutrophil count decreased	2 (50)	4 (67)	1 (33)	1 (17)	8 (42)
Nausea	1 (25)	3 (50)	2 (67)	1 (17)	7 (37)
Platelet count decreased	2 (50)	2 (33)	1 (33)	2 (33)	7 (37)
Pyrexia	3 (75)	3 (50)	1 (33)	0	7 (37)
AST increased	1 (25)	2 (33)	2 (67)	1 (17)	6 (32)
Vomiting	2 (50)	3 (50)	1 (33)	0	6 (32)
ALT increased	0	2 (33)	2 (67)	1 (17)	5 (26)
Blood ALP increased	0	1 (17)	2 (67)	2 (33)	5 (26)
Constipation	1 (25)	3 (50)	1 (33)	0	5 (26)
Lymphocyte count decreased	0	1 (17)	1 (33)	3 (50)	5 (26)
Chills	1 (25)	1 (17)	1 (33)	1 (17)	4 (21)
Decreased appetite	0	2 (33)	0	2 (33)	4 (21)
Hypoalbuminemia	0	1 (17)	1 (33)	2 (33)	4 (21)

Presented at ASCO-GI 2021 (GA Manji et al. Abstract #404); Nov. 11, 2020
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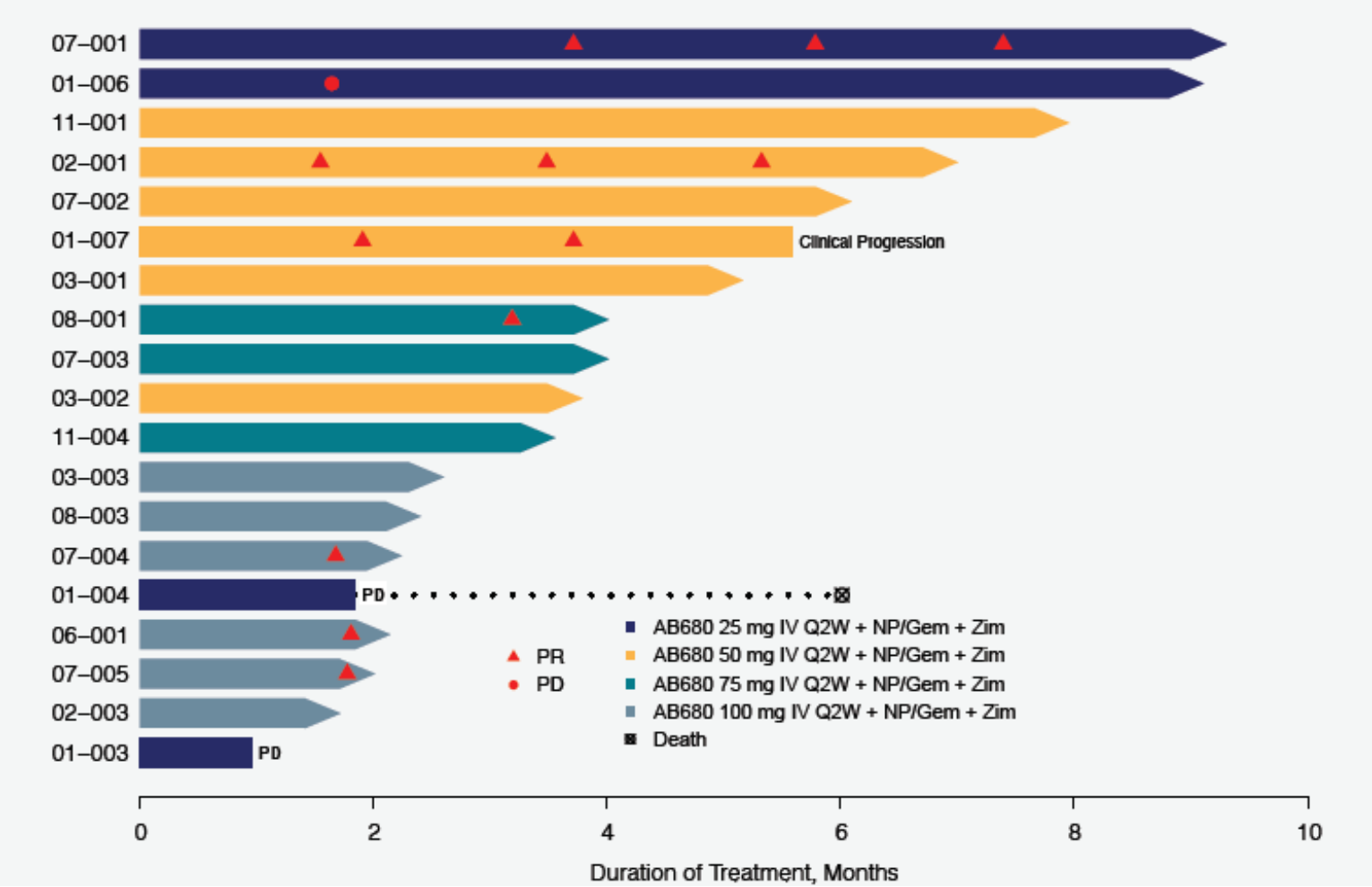
Time on Treatment and RECIST v1.1 Response



Presented at ASCO-GI 2021 (GA Manji et al. Abstract #404); Dec. 9, 2020

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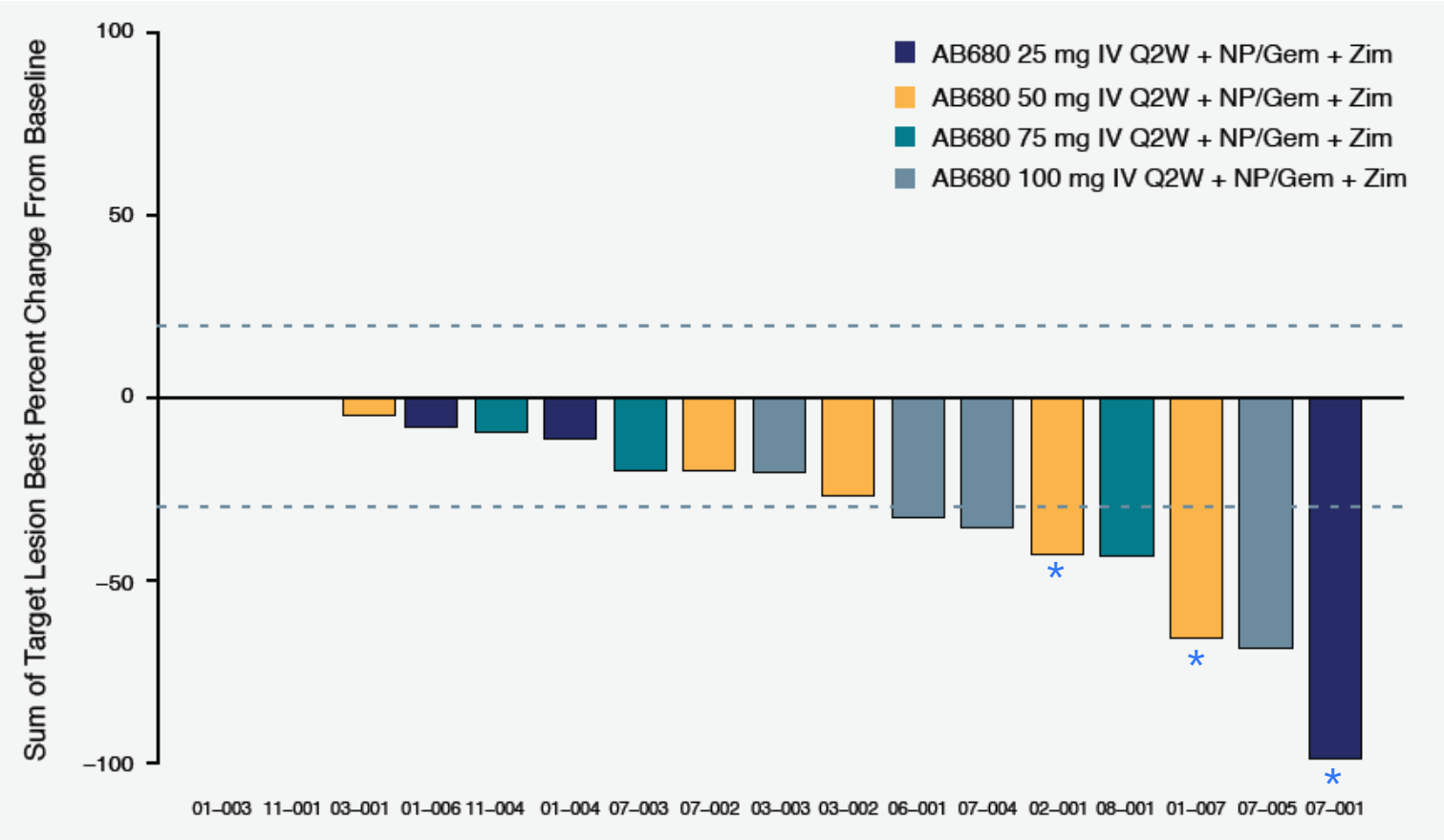
Waterfall Plot of Best Percent Change from Baseline in Sum of Target Lesions

88% (15/17) of Evaluable Patients in the Dose-Escalation Portion Experienced Tumor Shrinkage



IV, intravenously; NP/Gem, nab-paclitaxel/gemcitabine; Q2W, every 2 weeks; Zim, zimberelimab.

Presented at ASCO-GI 2021 (GA Manji et al. Abstract #404); Dec. 9, 2020

* Confirmed Response

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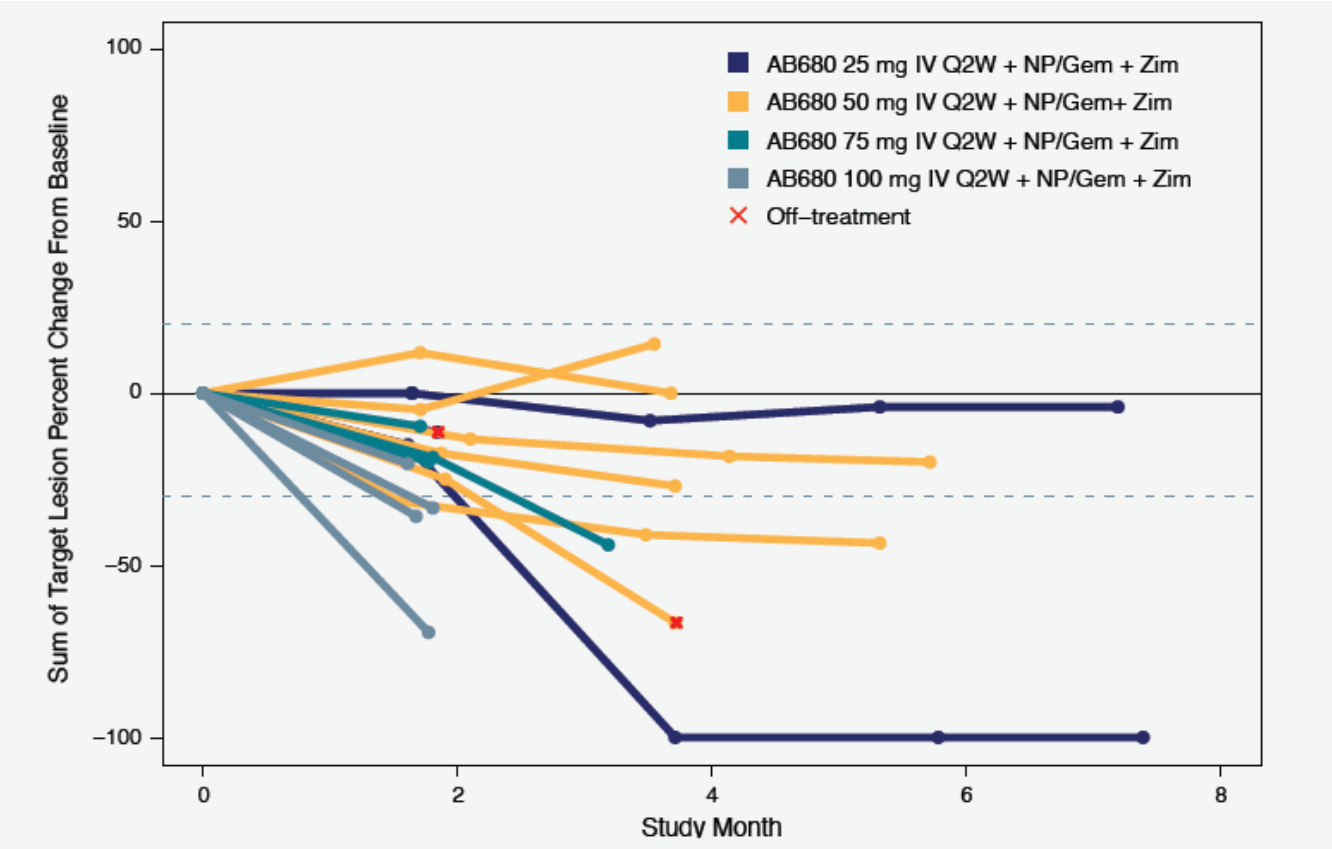
Spider Plot of Percentage Change from Baseline in Sum of Target Lesions

7 of 10 Patients with Stable Disease at First Disease Evaluation Experienced Further Shrinkage at the Next Evaluation



IV, intravenously; NP/Gem, nab-paclitaxel/gemcitabine; Q2W, every 2 weeks; Zim, zimberelimab.

Presented at ASCO-GI 2021 (GA Manji et al. Abstract #404); Dec. 9, 2020

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BOR, ORR & DCR Across All Dosed Cohorts

Best Overall Response[#] Number (%) of Subjects	Dose-escalation Cohorts				
	25mg (N=4)	50mg (N=6)	75mg (N=3)	100mg (N=4)	Overall (N=17)
Complete Response (CR)	0	0	0	0	0
Partial Response (PR)	1 (25)*	2 (33)	1 (33)	3 (75)	7 (41)
Stable Disease (SD)	1 (25)	4 (67)	2 (67)	1 (25)	8 (47)
Progressive Disease (PD)	1 (25)**	0	0	0	1 (6)
Not Evaluable	1 (25)***	0	0	0	1 (6)
Objective Response Rate	**1 (25)**	**2 (33)**	**1 (33)**	**3 (75)**	**7 (41)**
Disease Control Rate[§]	**2 (50)**	**6 (100)**	**3 (100)**	**§**	**11/13 (85)**

*PR has converted to a full CR post poster submission **Patient was noted by investigator to be SD; continues on therapy ***Patient progressed prior to first disease assessment

[#]Investigator Assessed; ORR is defined as the percentage of participants with a best overall response (BOR) of CR or PR based on RECIST 1.1 as assessed by the investigator
[§]Disease control rate represents any PR, CR or SD for 16 weeks or more. No patient in the 100mg treatment group has been on study >16 weeks; all remain on study treatment.
Presented at ASCO-GI 2021 (GA Manji et al. Abstract #404); DCO: Dec. 9th, 2020

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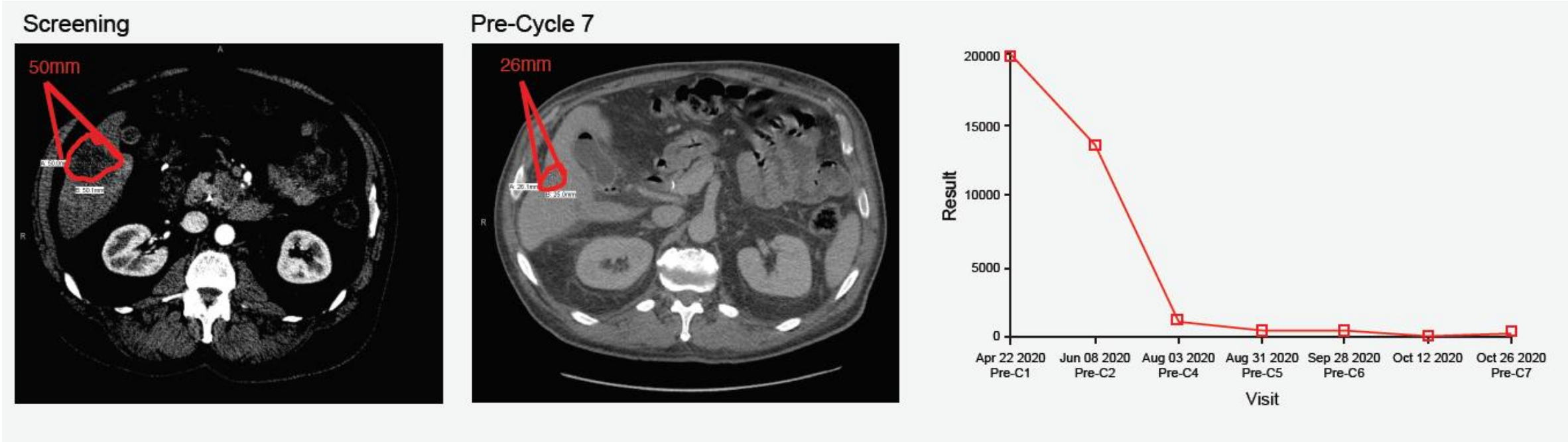
Illustrative Patient Who Experienced a Significant Reduction in Tumor Size and CA 19-9



- CA 19-9 is a circulating blood marker that is elevated in patients with active pancreatic cancer. Pancreatic cancer patients who experience a reduction in 19-9 with treatment frequently have extended survival compared with patients who do not (1)
- This patient, and others on the ARC-8 study, have experienced a reduction in disease burden, reduction in symptoms associated with pancreatic cancer and important clinical benefit in this devastating disease

Presented at ASCO-GI 2021 (GA Manji et al. Abstract #404); Dec. 9, 2020

(1) Chiorean EG, et al. *Ann Oncol.* 2016 Apr; 27(4): 654–660.

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Preliminary Dose-Escalation Data Demonstrate Early Signs of Clinical Activity for AB680



- ✓ AB680, in combination with NP/Gem and zimberelimab, has a manageable safety profile consistent with that expected for each agent alone and demonstrated early signals of clinical activity
- ✓ AB680 combination therapy **in 17 efficacy-evaluable patients resulted in a 41% objective response rate (7/17)**[1] which compares favorably with chemotherapy (23% ORR for NP/Gem)[2]
- ✓ **83% (10/12) of evaluable patients from the first three cohorts continue on treatment as of DCO of 12/9/20** with a median time on treatment of 180 days
- ✓ 100mg q2w was selected as the recommended dose for expansion (RDE), which is currently ongoing

Presented at ASCO-GI 2021 (GA Manji et al. Abstract #404)

[1]Of the partial responses (PRs), 3 are confirmed responses and of the 4 unconfirmed responders, 3 responded at the first tumor assessment and the fourth responded at the second tumor assessment, and all remain on study

[2]Von Hoff DD, et al NEJM 369(18):1691-1703 (2013)

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Near-term Plans for AB680 and ARC-8

Next Steps for ARC-8

- ✓ In December, we initiated the Phase 1b dose-expansion portion of the study using the 100mg q2W dose of AB680
- ✓ Given the lack of additive toxicity with AB680, a 125mg dosing cohort will be explored in the ongoing dose-escalation portion
- ✓ A control arm of AB680 + NP/Gem is expected to open shortly

Next Data Read-outs for ARC-8

- ✓ Duration of Response (DoR) and PFS data from the dose-escalation portion are expected to be presented at a medical conference later in the year

Presented at ASCO-GI 2021 (GA Manji et al. Abstract #404); [1]Von Hoff DD, et al. NEJM 369(18):1691-1703(2013)

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ARC-8 Data Provide Important POC for the Molecule and Therapeutic Hypothesis

As CD73 is ubiquitous in cancer, AB680 has broad development potential

Already Planned Addition to Existing Platform Trials

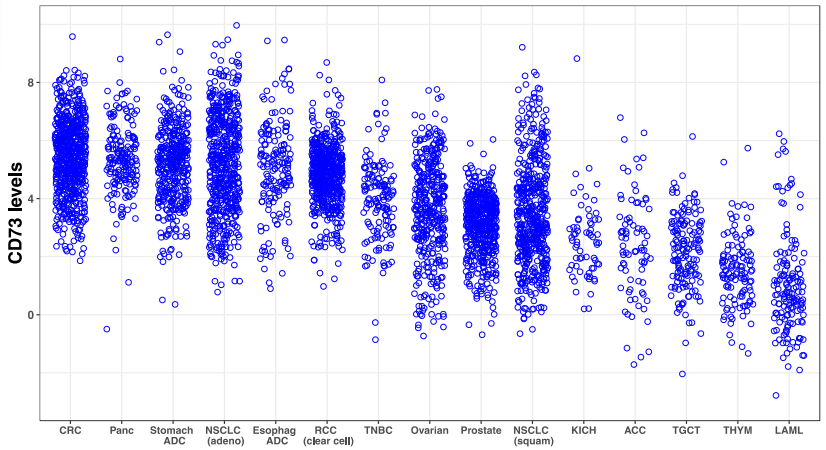
Objective: Efficiently explore the potential synergy between AB680 and Etruma

ARC-6 | **AB680** + Etruma +/- Zimberelimab arm

ARC-9 | **AB680** + Etruma + Zimberelimab arm

Additional Tumor Types

Objective: Evaluate AB680 in other tumor types associated with high levels of CD73, e.g. CRC, NSCLC, Gastric / Esophageal



Novel, Intra-portfolio Combinations

Objective: Rationally combine AB680 with other **Arcus-controlled molecules** and/or existing therapies

Setting	Potential Combination
Arcus Molecules	▪ Etruma ▪ Zim ▪ Dom ▪ Others
SOC	▪ Chemotherapy ▪ Radiation

24 Analysis of Tumor Cancer Genomic Atlas (TCGA) performed by Arcus

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ADDITIONAL ONGOING ADENOSINE-AXIS TRIALS

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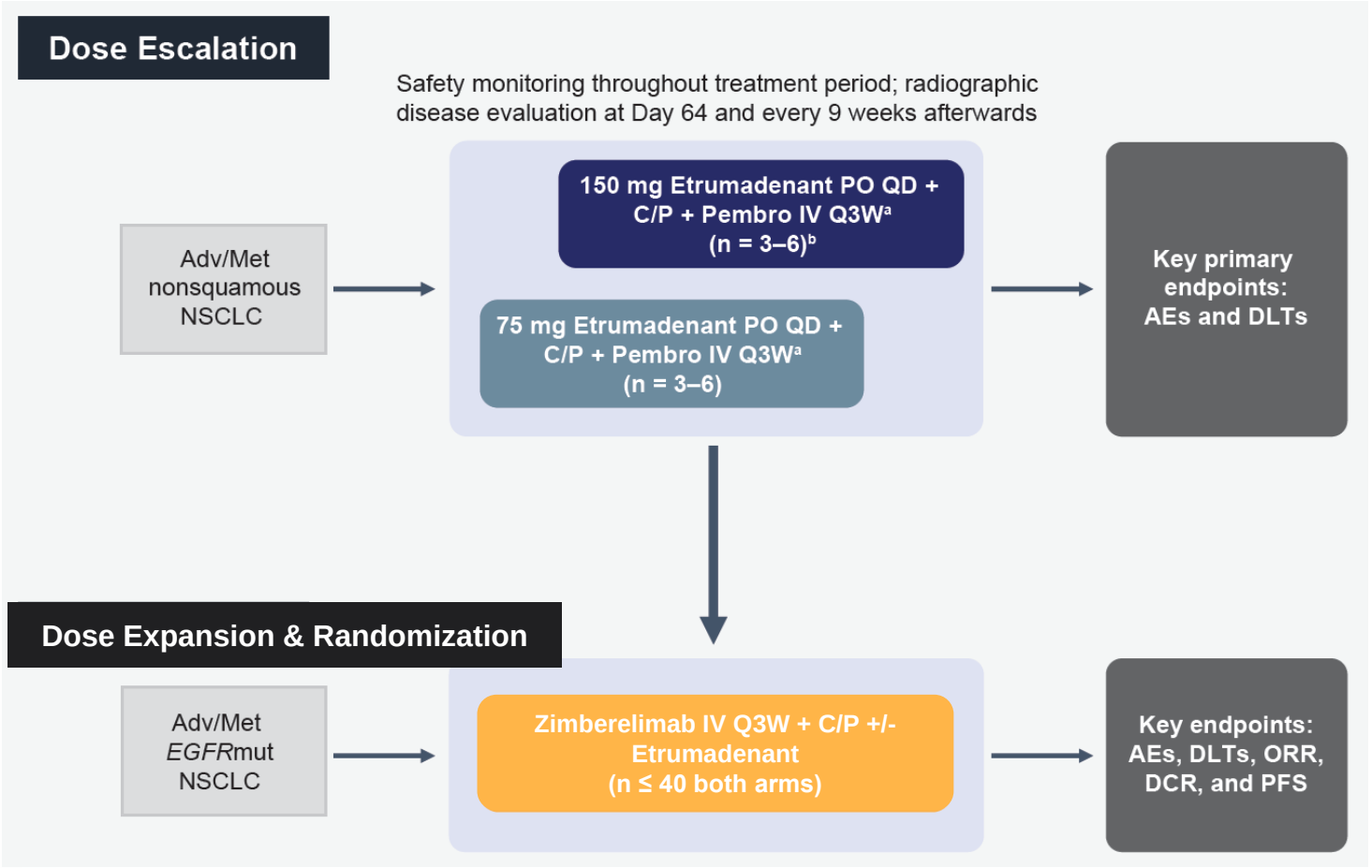
ARC-4 Study to Evaluate Etruma (AB928) + Zim + Chemotherapy in *EGFR*mut Non-Small Cell Lung Cancer

- **Study design schema for dose-escalation and dose-expansion of Etruma + anti-PD-1 + Carboplatin/Pemetrexed (chemo) in NSCLC patients**
- **Dose-expansion phase:**
  - Participants must have a sensitizing EGFR mutation and failed treatment with 1 TKI (or 1-2 TKIs for tumors with T790M mutation)
  - Previous treatment with chemotherapy or PD-1/PD-L1 therapy is not allowed
  - Preliminary data presented at ESMO 2020
  - Control arm opened after passing futility assessment
- **Next Steps:**
  - Initial randomized data to be presented 2H21



C/P: carboplatin/pemetrexed; RDE: recommended dose for escalation; TKI: tyrosine kinase inhibitor

A. Spira et al, ESMO (2020); presentation no.1309P; NCT03846310

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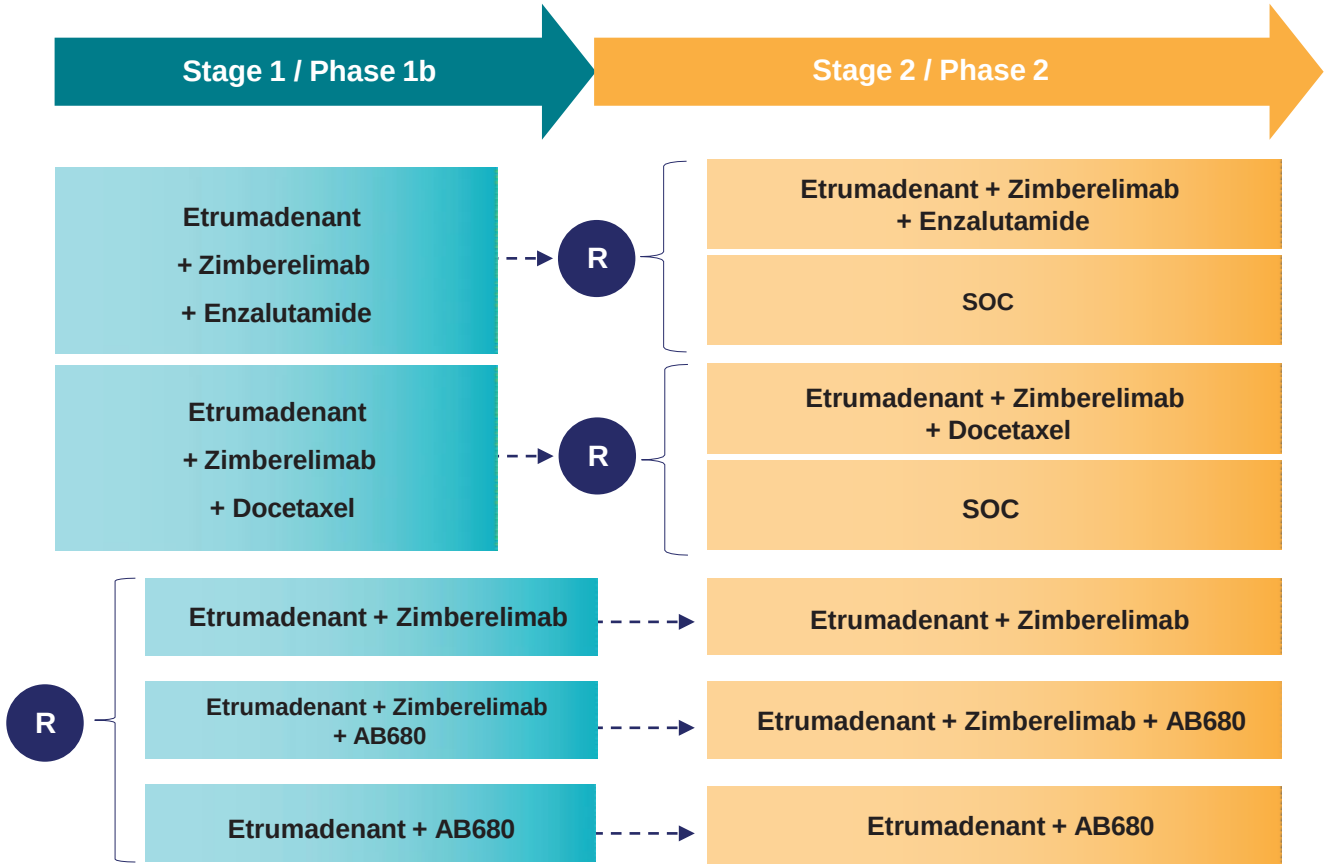
Platform Study to Evaluate Etruma (AB928) across Multiple Lines of Therapy in mCRPC

- **Platform study in mCRPC to assess the safety and efficacy of the addition of Etruma (AB928) + Zim to standard of care Enzalutamide and Docetaxel**
  - Supports early randomization and proof of concept if activity signal is seen in Stage 1
- **Evaluating Etruma novel combinations for late-line patients without available standard of care**
  - Preliminary data from initial cohorts 2Q21
  - Expansion of these cohorts based on initial signals



Subudhi e.t al, ESMO (2020); presentation no.687TiP; NCT04381832

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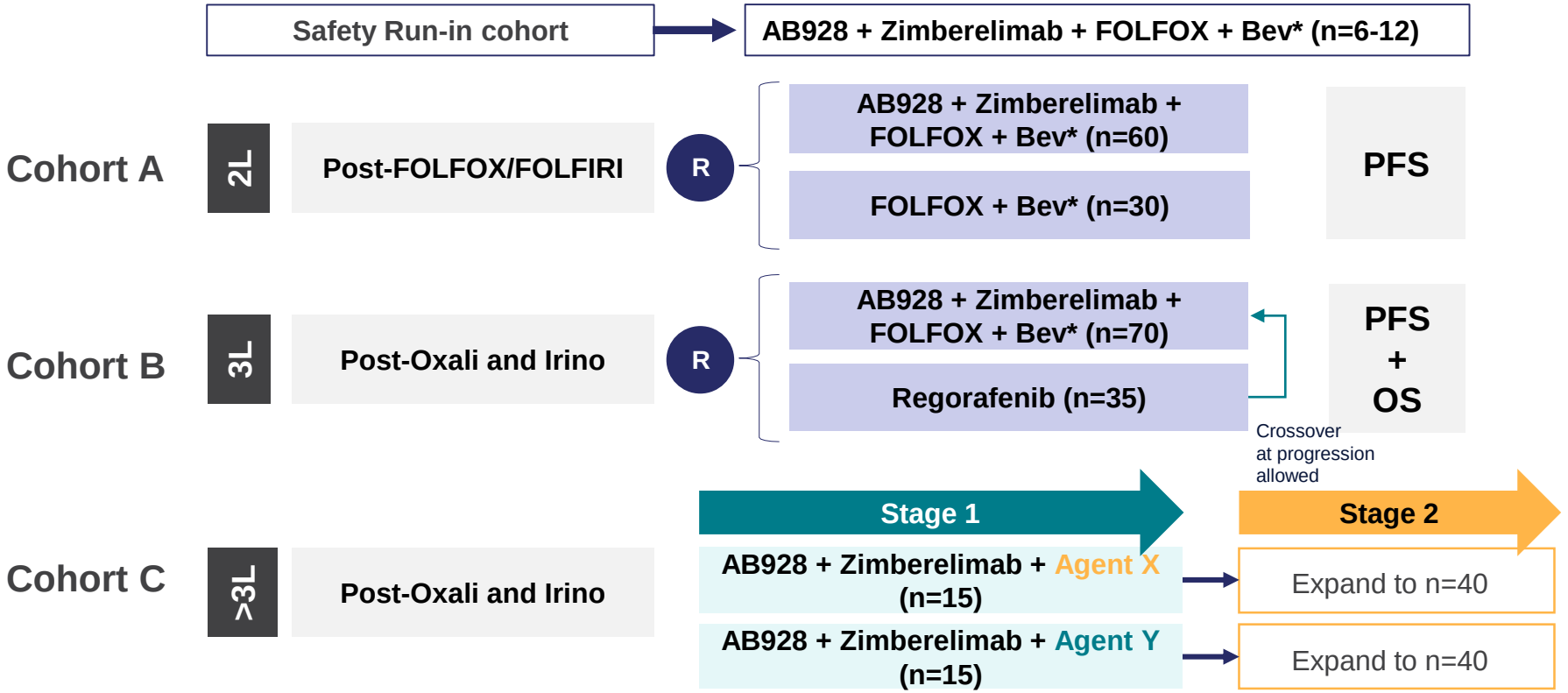
ARC-9 Platform Trial in 2L and 3L mCRC

Initial randomized data for 2L/3L cohorts; single-arm data for 3L+ in 1H22

Adenosine Receptor Antagonist + Checkpoint Inhibitor + Platinum-based Chemotherapy Combination Therapy for non-MSI-H/TMB mCRC



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

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