Building a Leading ADC-Focused Company

PYXIS ONCOLOGY

Nasdaq: PYXS
May 2024

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PYXS: Building the Next Leading ADC-Focused Company

- ADC-Focused with Opportunistic Bets in I/O
- Clinical-Stage Portfolio with 2024 Data Catalysts
- Deeply Experienced Team with Proven Track Record in Both Pharma and Biotech
- Strong Balance Sheet with $158.5M in Cash Provides Runway into 2H 2026

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Executive Leadership Team – Building the Next Leading ADC Company

Lara Sullivan, MD

CEO

SpringWorks THERAPEUTICS

Pfizer

Pam Connealy, MBA

CFO & COO

IMMUNOVANT

Genentech
A member of the Roche Group

Ken Kobayashi, MD, FACP

CMO

KINNATE BIOPHARMA

Pfizer

Jan Pinkas, PhD

CSO

immunogen

AMGEN

Stephen Worsley

CBO

Lytix Biopharma

Catalent

Xiaodong Yang, MD, PhD

Distinguished Research Fellow

Apexigen

Abgenix

Balu Balasubramanian, PhD

CTO

Bristol Myers Squibb™

Xcell Strategic Consulting

PYXS Team Members Have Collectively Contributed to >60 Oncology Drug Approvals

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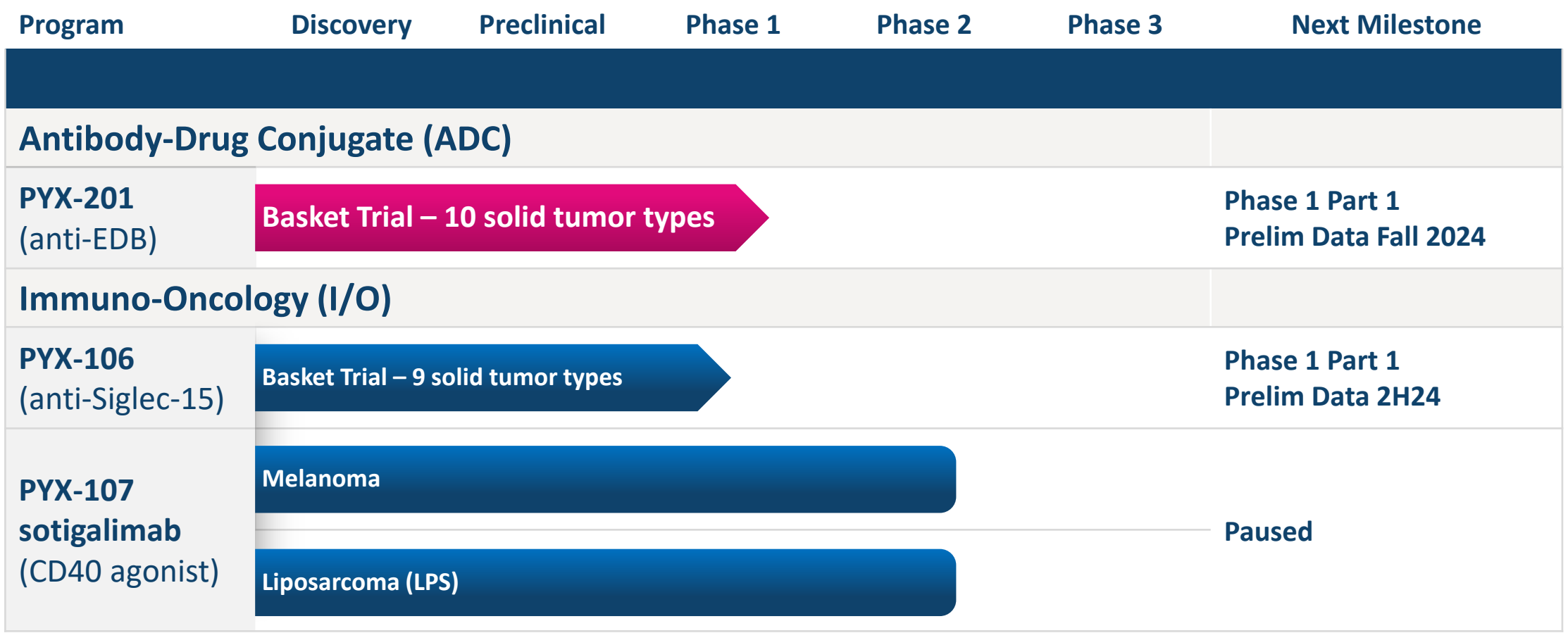
Pipeline Focused on Difficult-to-Treat Tumors



PYX-201 is a First-in-Concept and First-in-Class ADC that Binds to EDB+FN within the Tumor Stroma and may Address Multiple Difficult-to-Treat Tumors

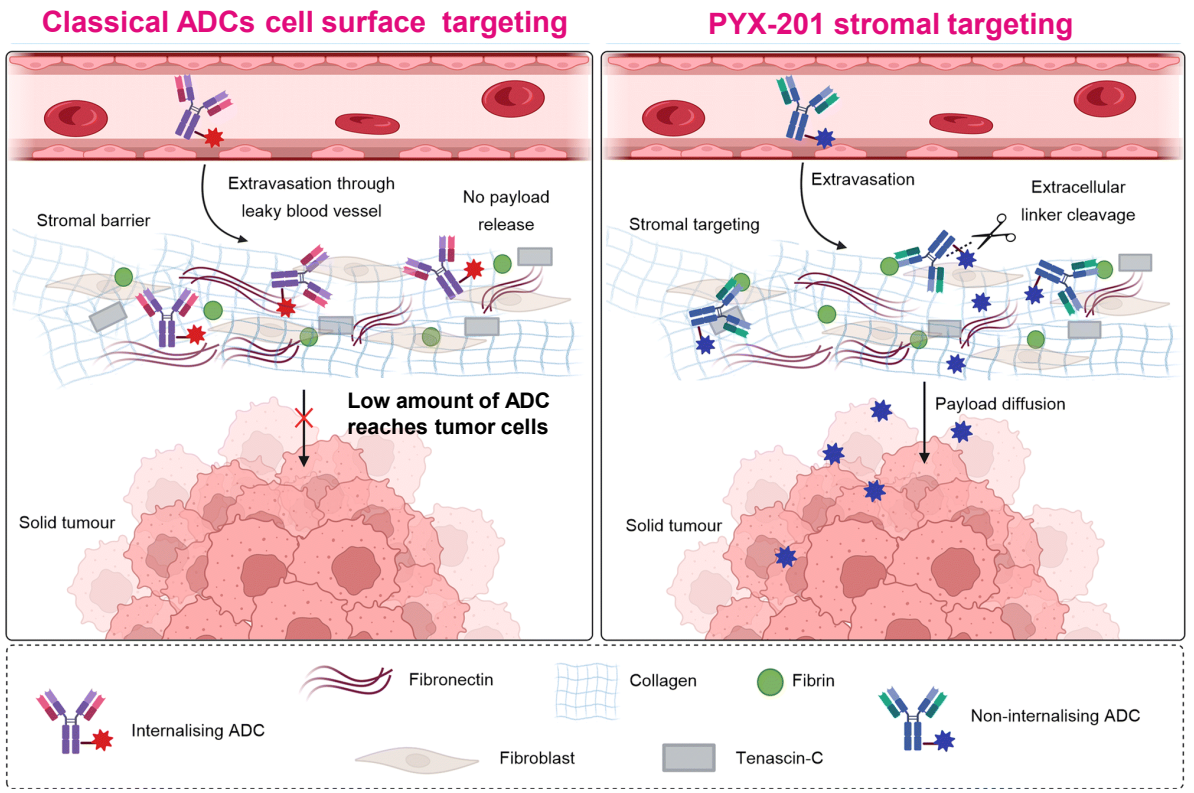
PYX-201 targets an antigen contained within the tumor stroma and releases its payload extracellularly, diffusing into nearby tumor cells

Why target the stroma?

- The stroma provides a lifeline necessary for tumor growth in solid tumors
- Stroma includes the extracellular matrix, tumor vasculature, cancer-associated fibroblasts and mesenchymal stromal cells that make up the TME
- Provides protection, structural support, nutrition and waste product removal; can also enable drug resistance that allows tumor to survive

How to target the stroma and kill cancer cells?

- EDB+FN is a protein upregulated in tumor stroma and associated with tumor growth, angiogenesis, and metastases
- As a result, EDB+FN is highly expressed in many solid tumors and has low expression in normal adult tissue
- PYX-201 targets the stroma via EDB+FN, then releases its toxic payload extracellularly in the tumor microenvironment, presumably diffusing into, and killing, nearby tumor cells



Source: Ashman, et al., Chem. Soc. Rev., 2022,51

Kadcyla (HER-2), Enhertu (HER-2), Padcev (Nectin-4) , Elahere (FRa), Tivdak (TF), Trodelvy (TROP-2)

PYX-201 (EDB+FN)

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Tumor Stroma is an Exciting Opportunity for ADC Modality

Legacy canonical view that ADCs must be internalized by the tumor cell is untrue

- **Many of the proteases found intracellularly in endosomes and lysosome are also found outside the cell** and are involved in disease pathologies including cancer; tumor cell lines and mouse tumor models secrete proteases into the extracellular space that cleave the val-cit linker

- The **tumor micro-environment (TME) is acidic (i.e., pH between 6.4 to 7.0) compared to normal physiologic pH of 7.4 and immune responses can be attenuated in an acidic TME**

- The acidic TME has been **exploited to develop therapeutic antibodies with tumor selective pH-dependent antigen binding**

The acidic environment and extracellular proteases in the tumor lead to release of the AUR-0101 (auristatin microtubule inhibitor) payload from PYX-201 in the tumor micro-environment

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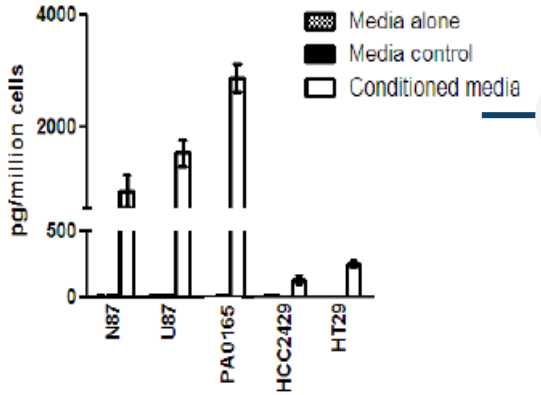
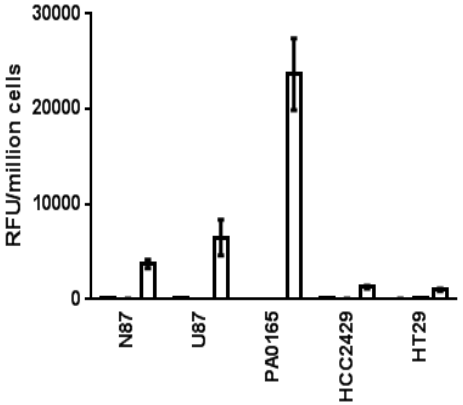
Yadati, Cells(9) 2020: 1679-1705; Lam, AACR 2014 Poster #4837, Boedtkjer, AnnRevPhys(82) 2020: 103-126; Chang, PNAS(118) 2021: 1-10

Pfizer Researchers in 2014 Confirmed Conditions for Payload Cleavage Exist Outside the Tumor Cell in the Tumor Stroma



1. Solid tumor cells secrete Cathepsins extracellularly



2. Proteases secreted by tumor cells cleave the linker-payload extracellularly

3. Inhibition of tumor growth by non-internalizing ADC

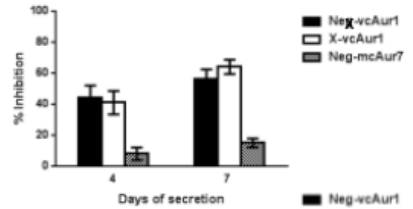
4. Killing tumor cells by extracellularly released payload

Tumor cell

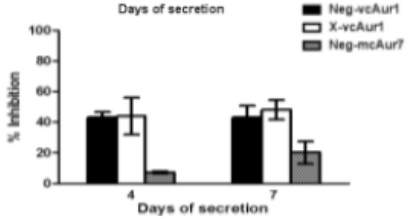
Stroma

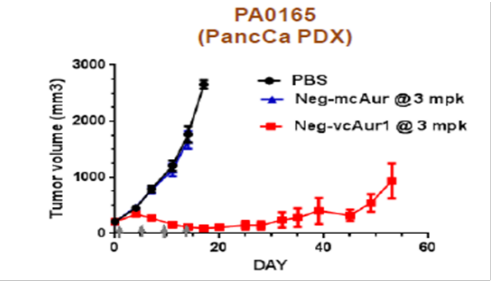
Cell Lines: CM from 3D Culture

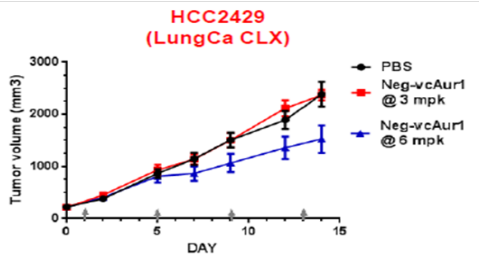
N87 CM
On 468 cells



U87 CM
On 468 cells







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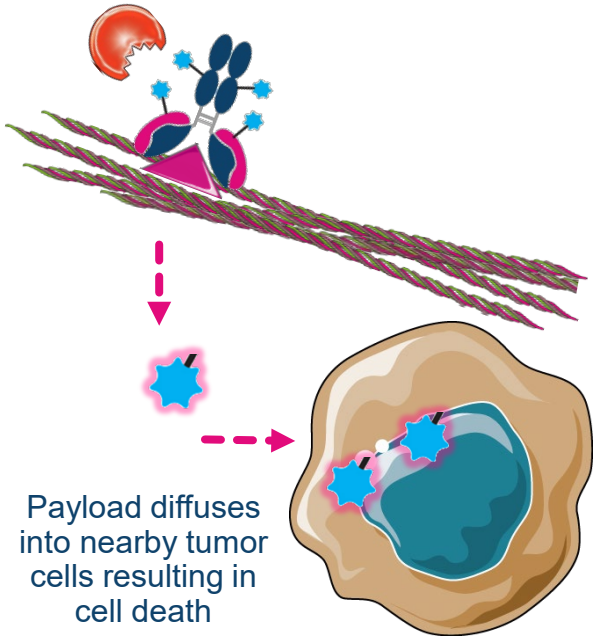
Lam et al., Cancer Res (2014) 74 (19_Supplement): 4837
NOTE: See Appendix for Pfizer 2014 AACR poster

PYX-201 Believed to Act Via Three Distinct Mechanisms to Deliver Powerful Anti-Tumor Activity

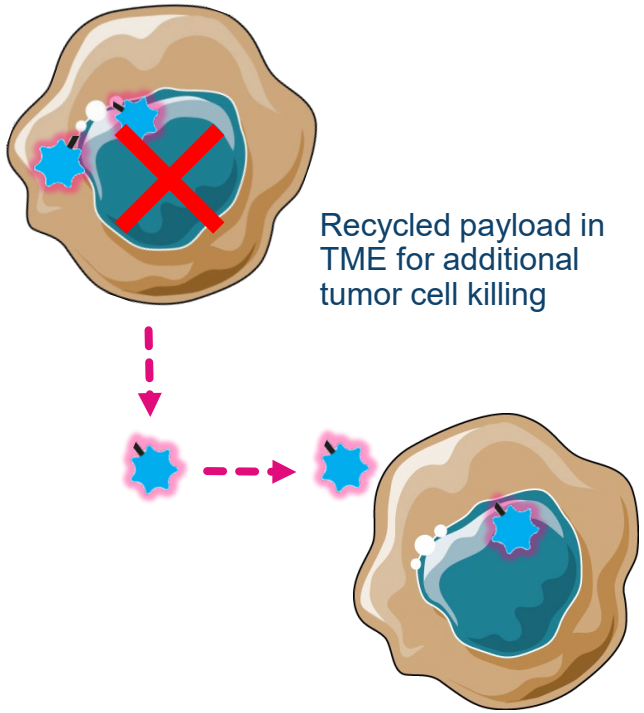
1 Payload Diffuses Into & Kills Tumor Cells

Binding of PYX-201 to EDB+FN within the tumor stroma releases payload



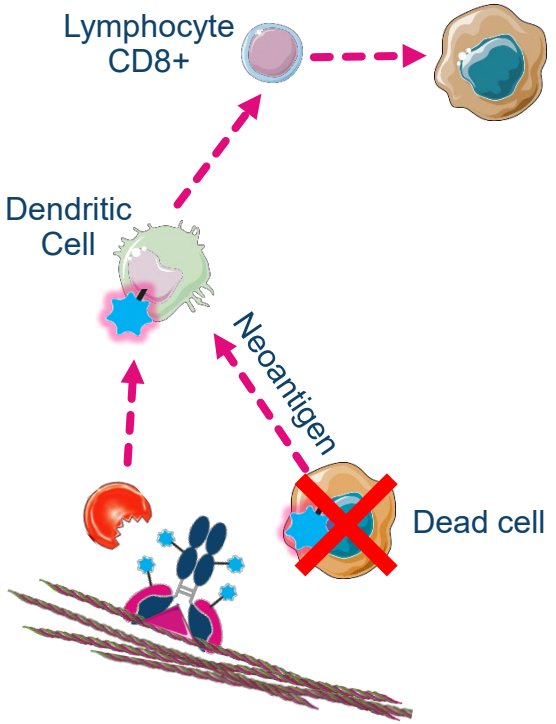
2 Additional Bystander Killing

Tumor cell death results in payload re-release into TME for additional killing



3 Immunogenic Cell Death

Released payload also potentiates immune cell infiltration into the tumor



Key

- CD8+ lymphocyte
- Proteases (e.g., cathepsin)
- Cleaved & active payload (auristatin)
- EDB+FN
- EDB+FN receptor
- Dendritic cell
- PYX-201
- Fibroblast
- Tumor cell
- Matrix

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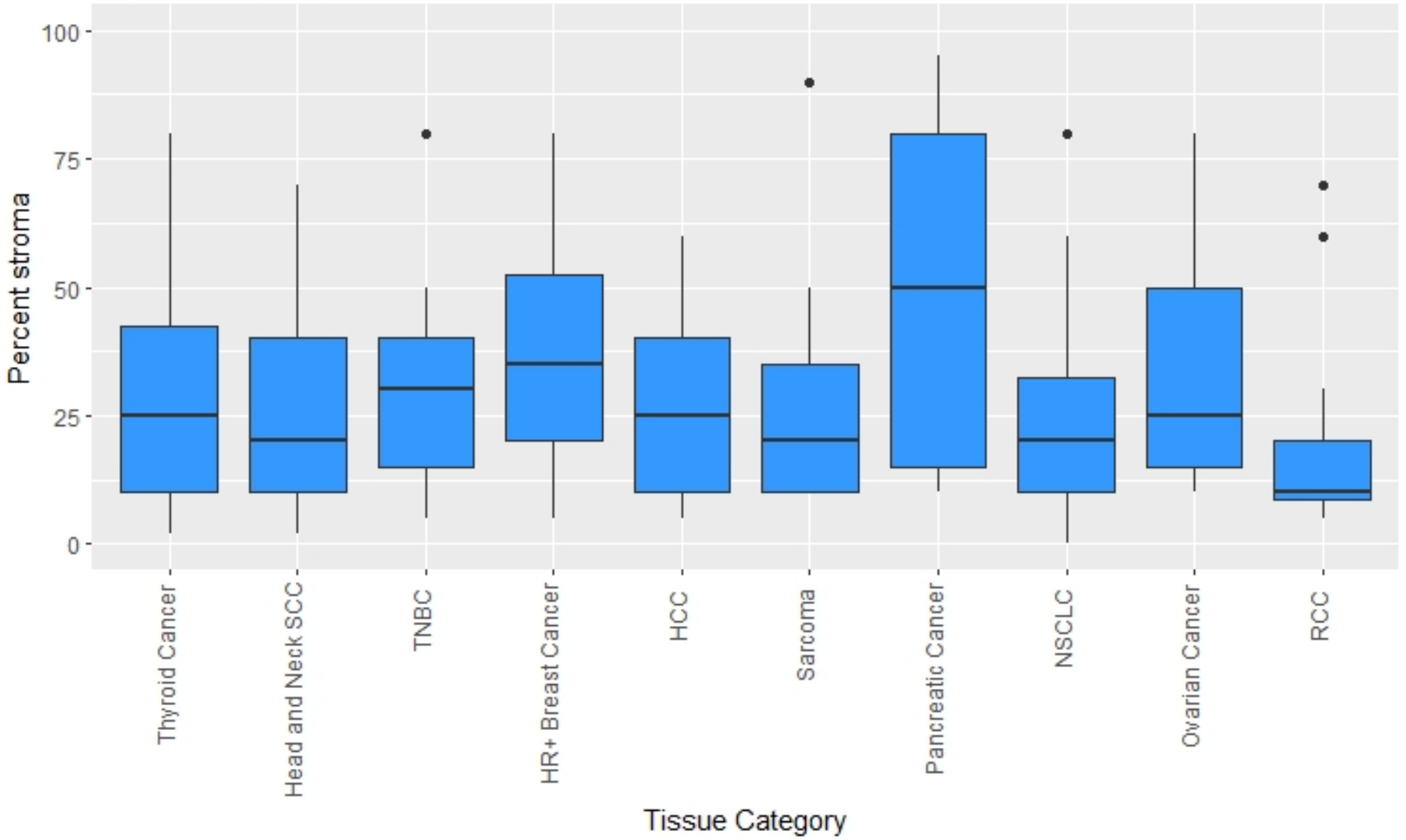
Servier medical art: https://smart.servier.com/

Volume of Stroma is Highly Variable by Tumor Type



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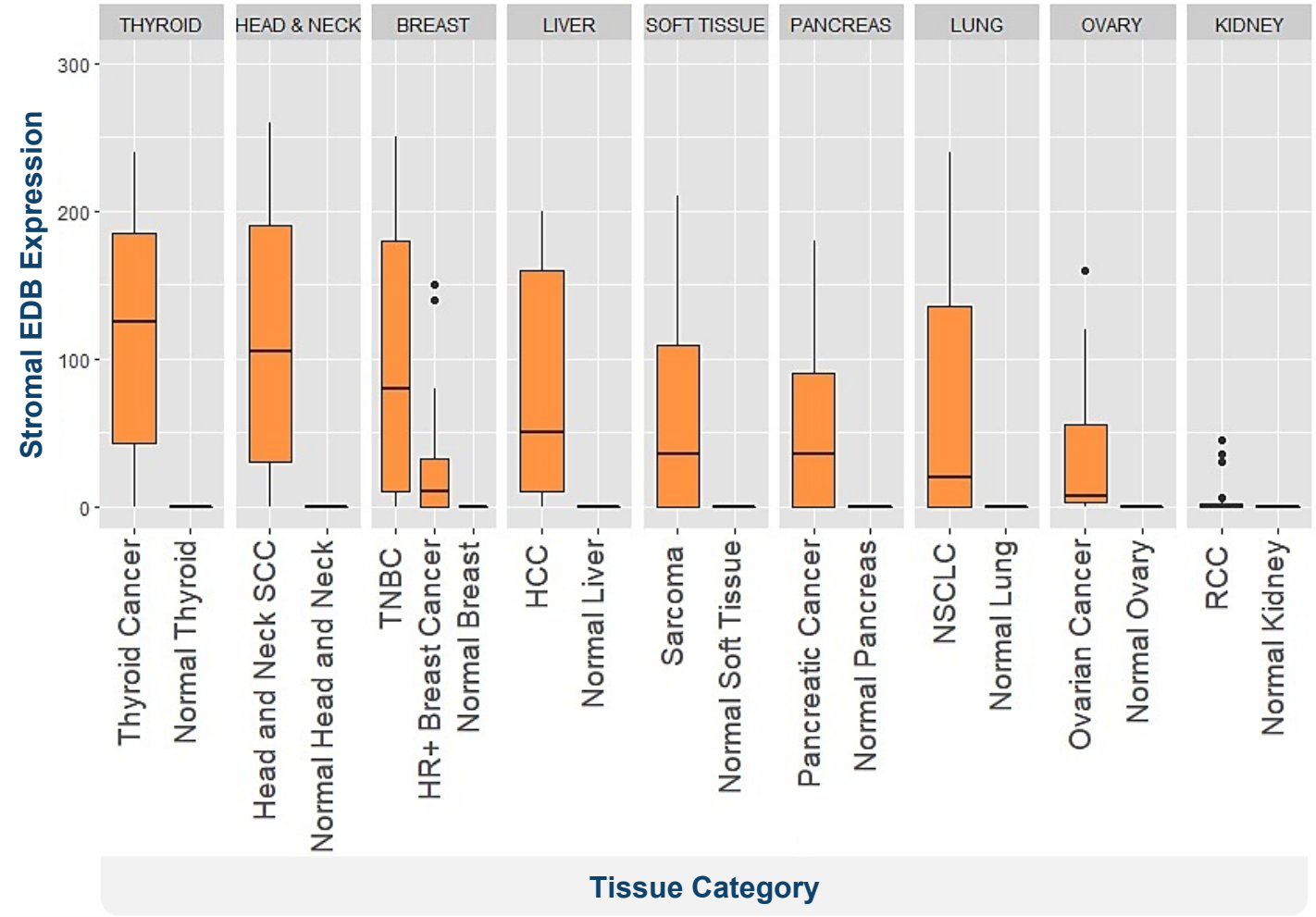
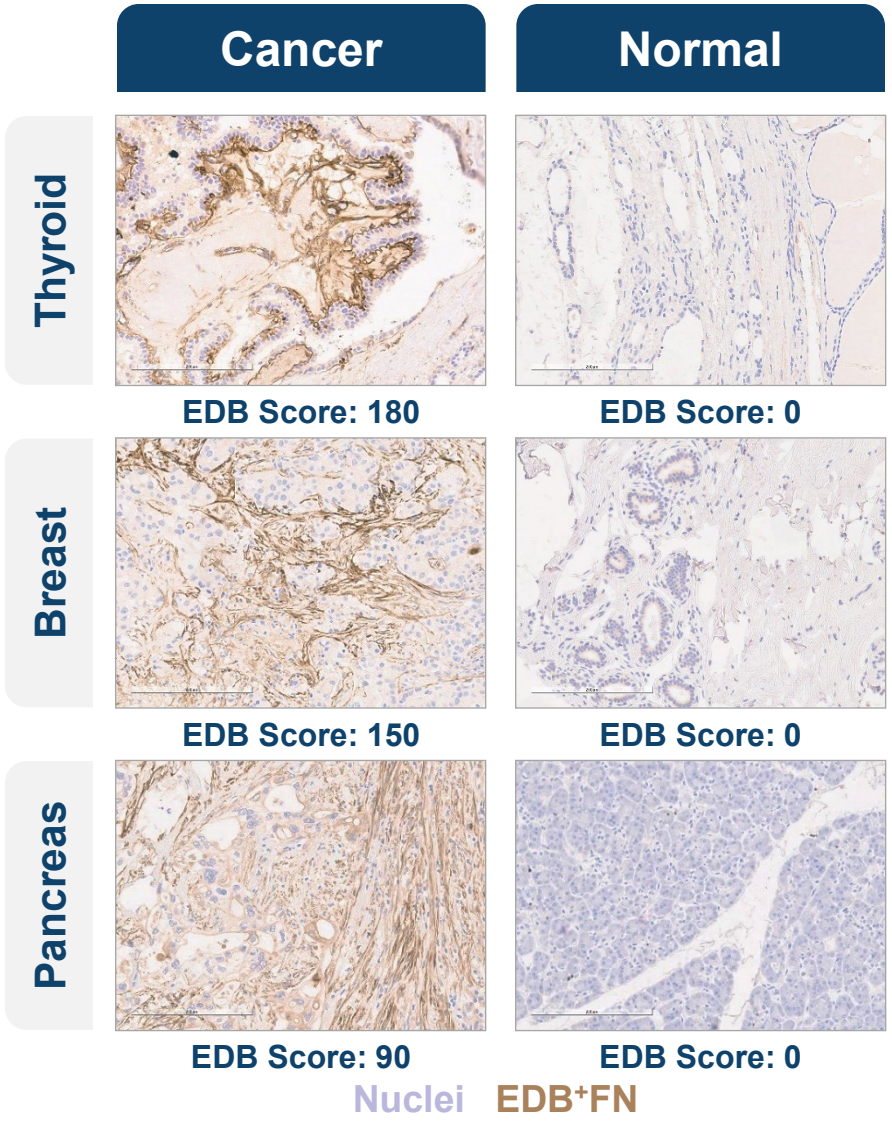
Pyxis Oncology Internal Data. Stromal density analysis of tumors via H&E staining.

Immunohistochemistry (IHC) Analysis Demonstrates EDB+FN Protein is Highly Differentially Expressed in Tumor Stroma

Stromal EDB+FN Protein Expression – IHC Data





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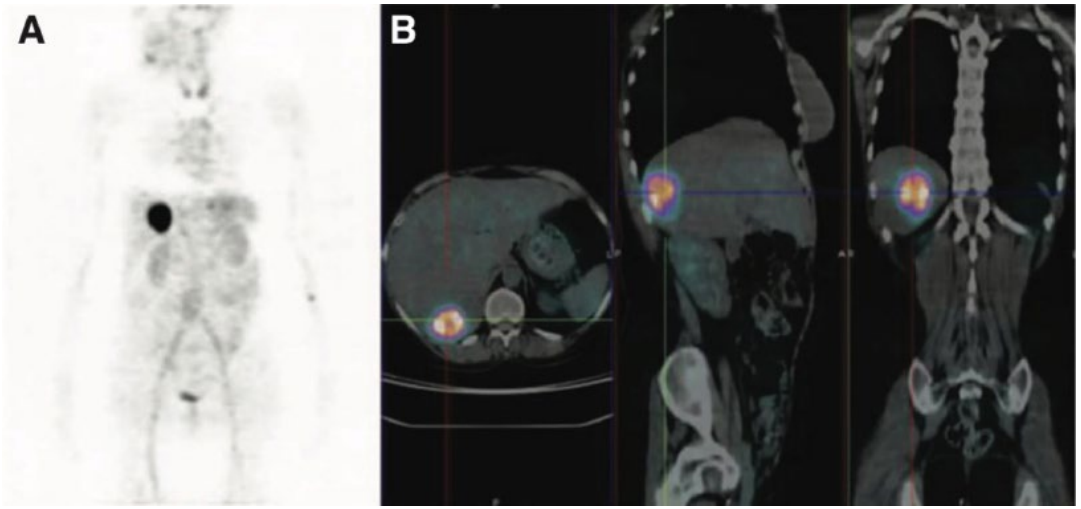
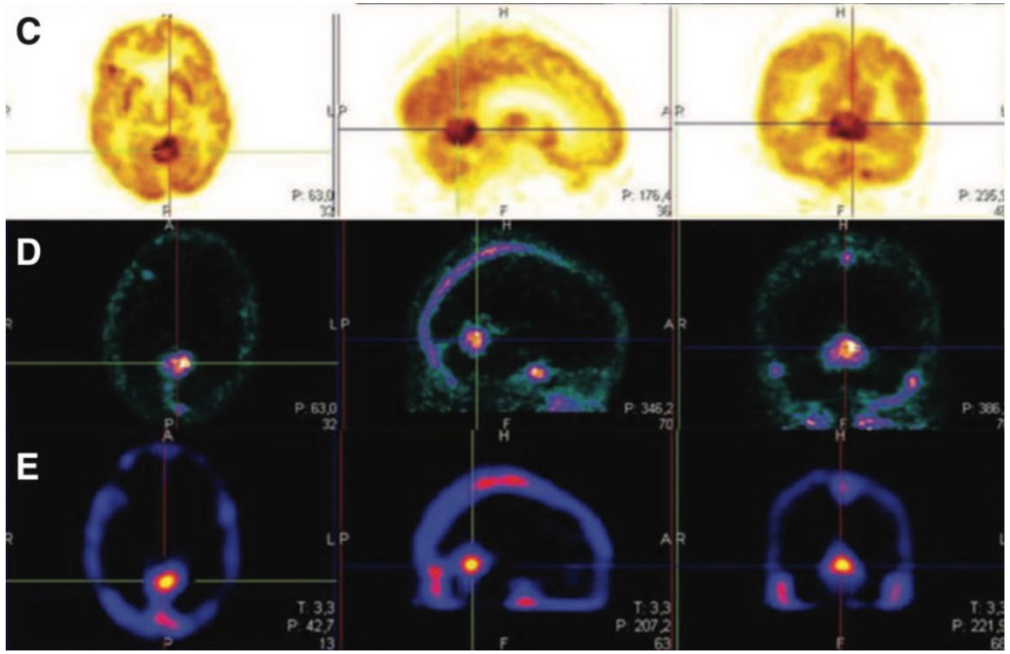
Pyxis Oncology Internal Data. EDB+Fn protein expression analysis via immunohistochemistry (IHC) of tumor vs. normal stromal tissue.

An EDB-targeted Radio-Conjugate Selectively Accumulates in Tumor with No Accumulation in Normal Tissues

PET imaging using radiolabeled target-antibody fragment shows selective accumulation in hepatic and CNS lesions





A

PET image 24 hours p.i., showing a hepatic lesion with high antibody uptake.

B

Corresponding transaxial, sagittal, and coronal projections PET/CT fusion images.

C

FDG PET image of a lesion in the cerebellar region (transaxial, sagittal, and coronal projections).

D

Corresponding PET images from the diagnostic phase with radio-labeled antibody (24 hours p.i.).

E

SPECT images posttherapy from the use of radio-labeled antibody (24 hours p.i.).

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Poli GL et al 2013, Cancer Immunol Res; 1(2); 134–43

ADC Technical Improvements of PYX-201 vs Other ADCs

- **Conjugation:** Engineered cysteine residues allow for a target DAR of 4 without disrupting the inter-chain cysteine bonds that hold the antibody together

- **Linker:** Optimized val-cit linker that is more stable in circulation (i.e., reduced carboxylesterase cleavage) compared to val-cit linkers used in Adcetris, Padcev, etc.

- **Payload:** Optimized auristatin (AUR-0101) selected for enhanced cell permeability and bystander cell killing activity compared to MMAE. AUR-0101 also has improved metabolism and excretion properties compared to MMAE

Incorporating these three areas of technical improvement in PYX-201 demonstrated increased tolerability and stability with lower levels of free auristatin payload in circulation in non-clinical toxicology studies compared to traditional val-cit-MMAE ADCs

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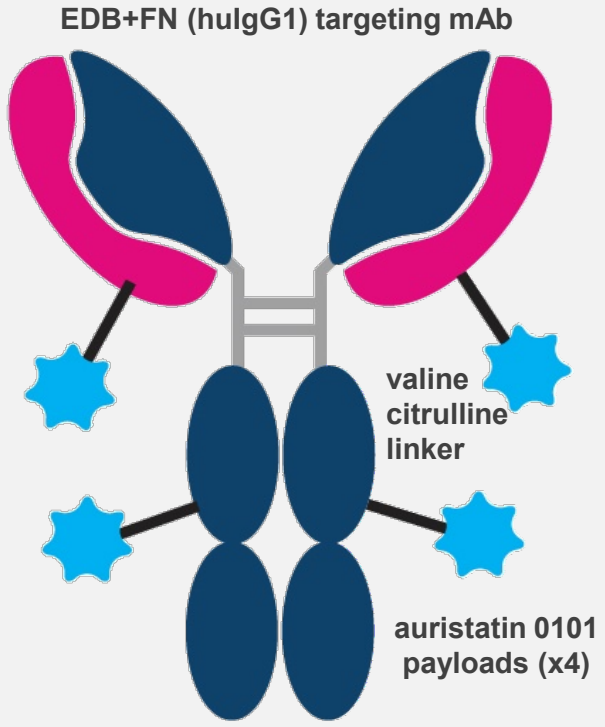
PYX-201 is Designed for Tolerability and Activity

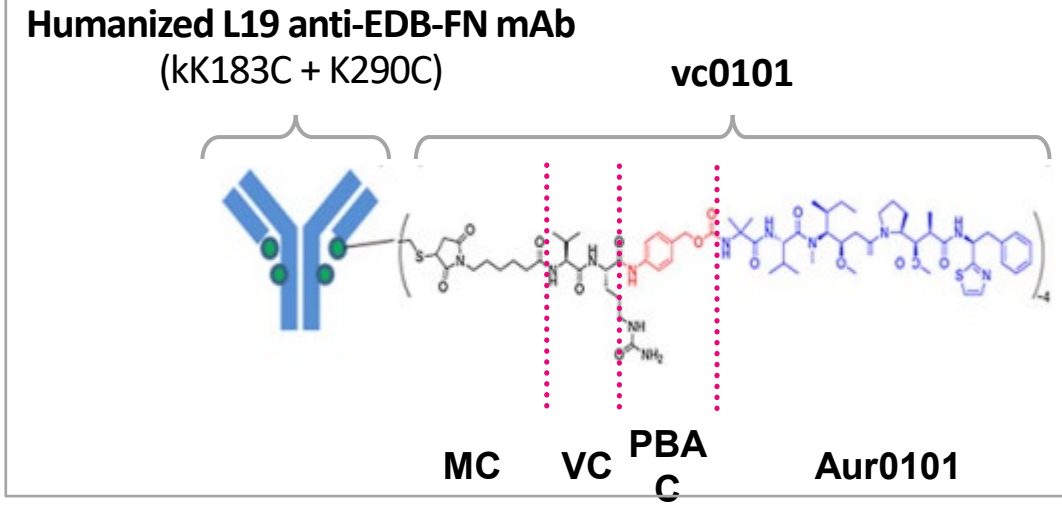
PYX-201 Drug Design



Key improvements of PYXS optimized ADC technology:

- Monoclonal antibody uniquely directed at **Extra-domain B of Fibronectin (EDB+FN)** in the tumor stroma
  - Designed to reduce off-target effects and improve tolerability
- Carries **four Auristatin 0101, microtubule depolymerizing inhibiting payloads**
  - Maximizes tumor-killing and potency
  - Predictable, uniform drug-antibody ratio (DAR) of 4
- **Site-specific**, cathepsin-cleavable, valine citrulline **linkers**
  - Optimized to improve stability in circulation and reduce free payload

PYX-201 Structure



MC-VC-PABC linker construct utilizes a maleimidocaproyl (MC) spacer, a protease (cathepsin)-sensitive dipeptide, valine-citrulline (VC), a self-immolative spacer, para-amino benzyloxycarbonyl (PABC) coupled with the optimized auristatin – Aur0101

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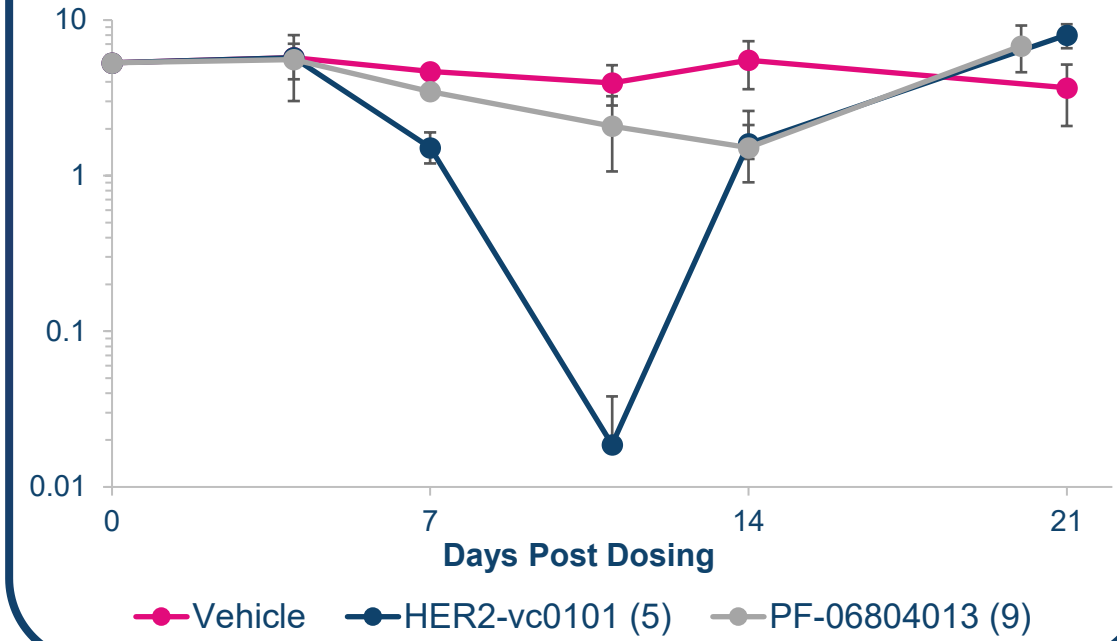
Potential for Improved Technical Profile of PYX-201 vs. Competitors

Enhanced tolerability in NHP at 10–12 mg/kg (preclinical publications for the HER-2 and EDB ADCs) compared to approved older generation val-cit-MMAE ADCs in NHP of 3 mg/kg (i.e., Adcetris, Padcev etc.)



- Minimal effect on neutrophils in NHP with the site-specific HER2 ADC (PF-06804013) at twice the dose (9 vs. 5 mg/kg) as compared to a conventional HER2-vc0101 ADC that induced neutropenia

Summary of EDB-ADC Single-Dose Pharmacokinetics in Mouse and Nonhuman Primate (NHP, Cynomolgus Monkey)

Model	Dose (mg/kg)	Analyte	C_{max} (µg/mL)	$AUC_{0\text{-}tau}$ (µg*h/mL)	Terminal $t_{½}$ (day)	ADC/Ab (%)
Mouse	**3**	Ab	59.6	3,820	4.0	90
		ADC	62.4	3,450	3.4	
NHP	**6**	Ab	159	16,250	6.6	84
		ADC	148	13,700	5.9	
		Payload	0.00012	0.034	NA	NA
	12	Ab	258	24,800	6.1	98
		ADC	268	24,450	5.8	
		Payload	0.00046	0.096	NA	NA

Note: Mouse tau = 336 hours; NHP tau = 504 hours.
Abbreviations: AB = antibody; NA = not applicable.

- PYX-201 is highly stable in circulation in mouse and NHP
- Very low levels of free payload in NHP demonstrating increased stability of the modified val-cit linker

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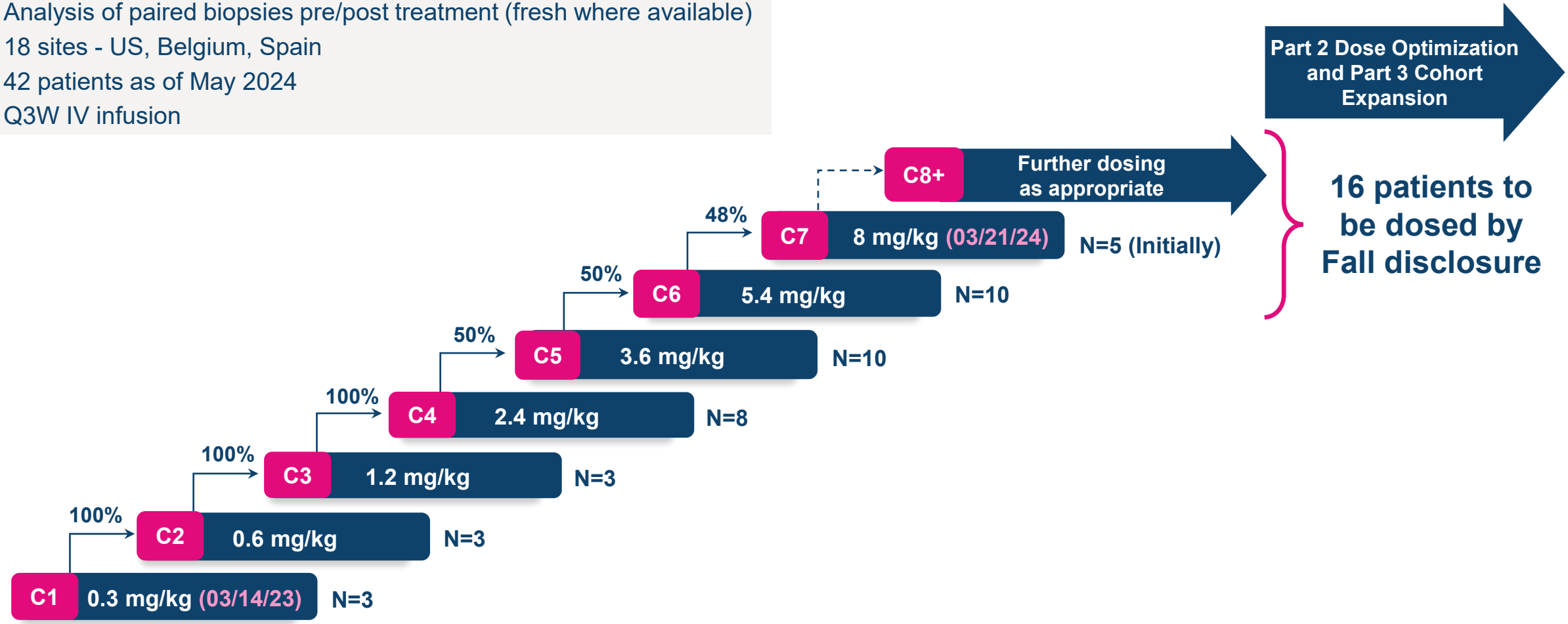
Graziani, *MolCanTher* (19) 2020: 2068-78; Hooper, *MolCanTher* (21) 2022: 1462-72.

PYX-201 Ongoing Phase 1 Part 1 Dose Escalation Solid Tumor Trial Design

Dose escalation to continue until MTD

Part 1 Design and Approach

- Determine MTD using Bayesian optimal interval (BOIN) design
- Analysis of paired biopsies pre/post treatment (fresh where available)
- 18 sites - US, Belgium, Spain
- 42 patients as of May 2024
- Q3W IV infusion



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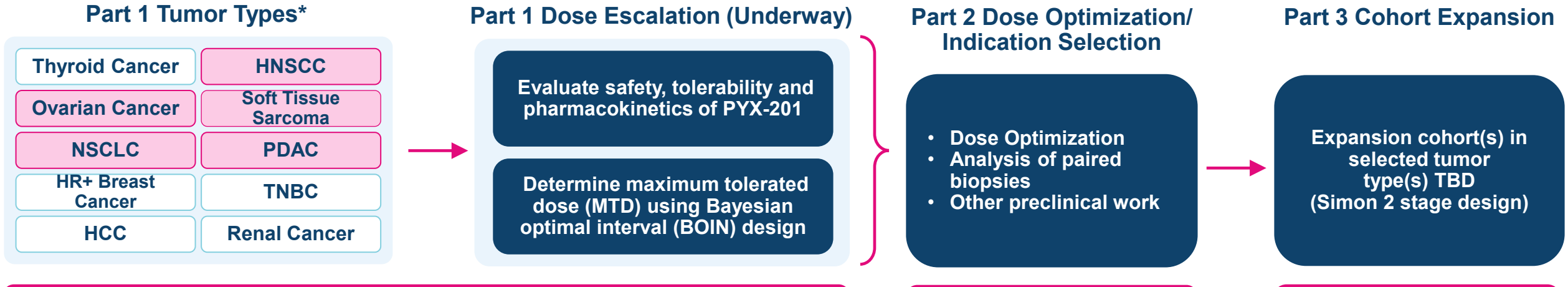
PYX-201-101: Ongoing Open-Label Phase 1 Dose Escalation Study with 10 Solid Tumor Types, Enriched for 5 Histologies

Preliminary data expected Fall 2024



Part 1 Objectives

Primary

- Safety
- Tolerability
- MTD
- Determine doses for dose optimization

Secondary

- ORR, DCR, PFS, DOR
- PK/PD
  - Cmax, Half-life
  - Total antibody, Free payload, Tmax

Part 2 Objectives

- Identify optimized dose
- Determine tumor type(s) for expansion

Part 3 Objectives

- Further evaluate safety and tolerability within the setting of dedicated cohort(s)
- Collect efficacy data (ORR, DOR, DCR, PFS, OS and immunogenicity) within dedicated cohort(s)

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* HNSCC: head and neck squamous cell carcinomas; NSCLC: Non-small cell lung cancer; PDAC: Pancreatic ductal adenocarcinoma; TNBC: Triple negative breast cancer; HCC: Hepatocellular Carcinoma

Anti-Siglec-15 (PYX-106): Potential Best-In-Class, Highly Differentiated Fully Human Antibody in NSCLC and Solid Tumors

Higher binding affinity leads to enhanced T cell responses at higher dose levels, empowering the immune system to kill and fend off cancer cells

- Demonstrates 10-fold higher affinity to human Siglec-15 than benchmark in development
- Potent, dose-dependent reversal of Siglec-15-mediated T cell suppression *ex vivo*
- Well-tolerated in preclinical studies with half-life of 7 days resulting in less frequent dosing
- Potential for better exposure and no evidence of anti-drug antibody
- Potential to combine with anti-PD-(L)1 or another immunotherapy

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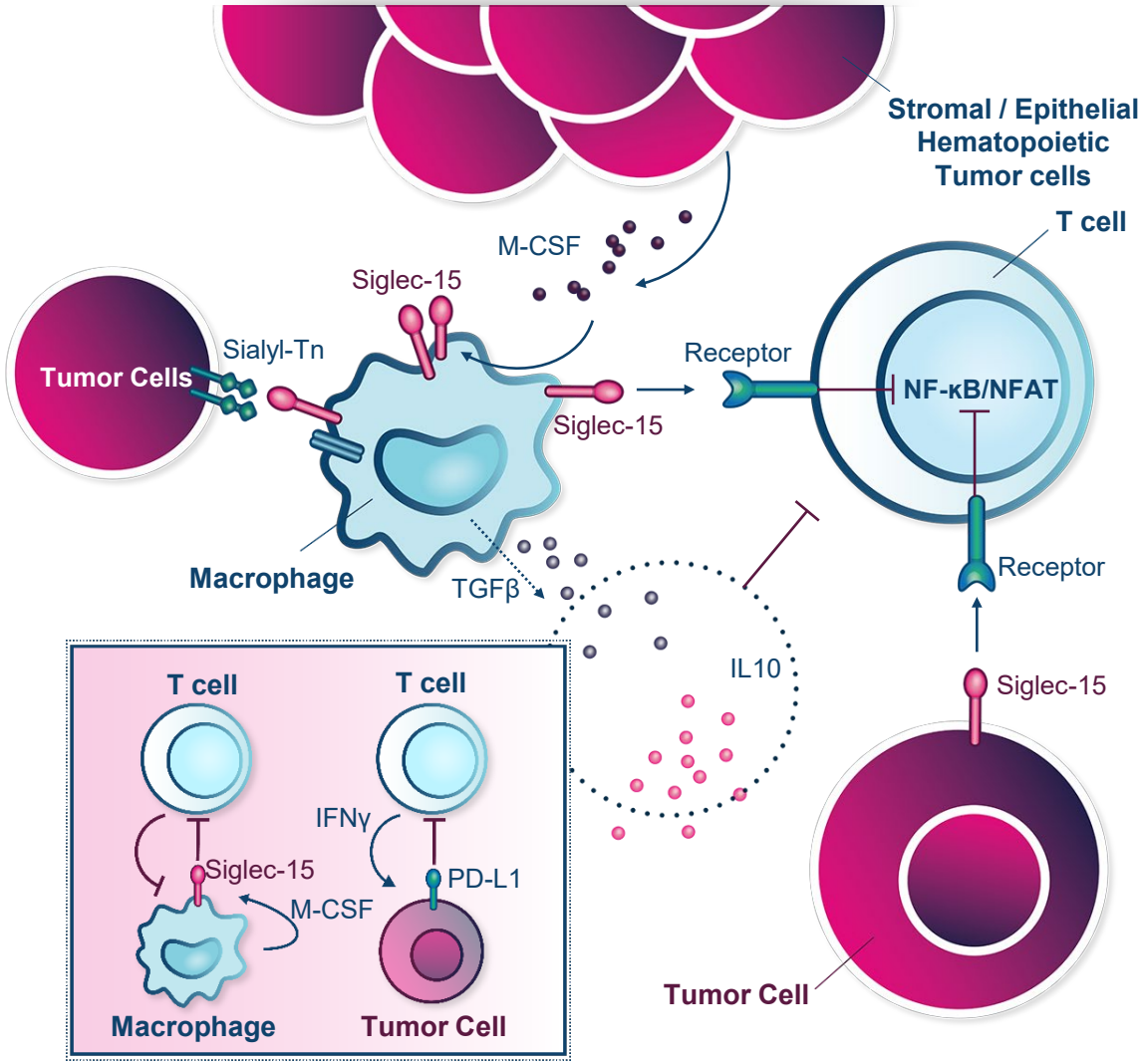
PYX-106 May Address Anti-PD-(L)1 Non-responders in Several Tumor Types

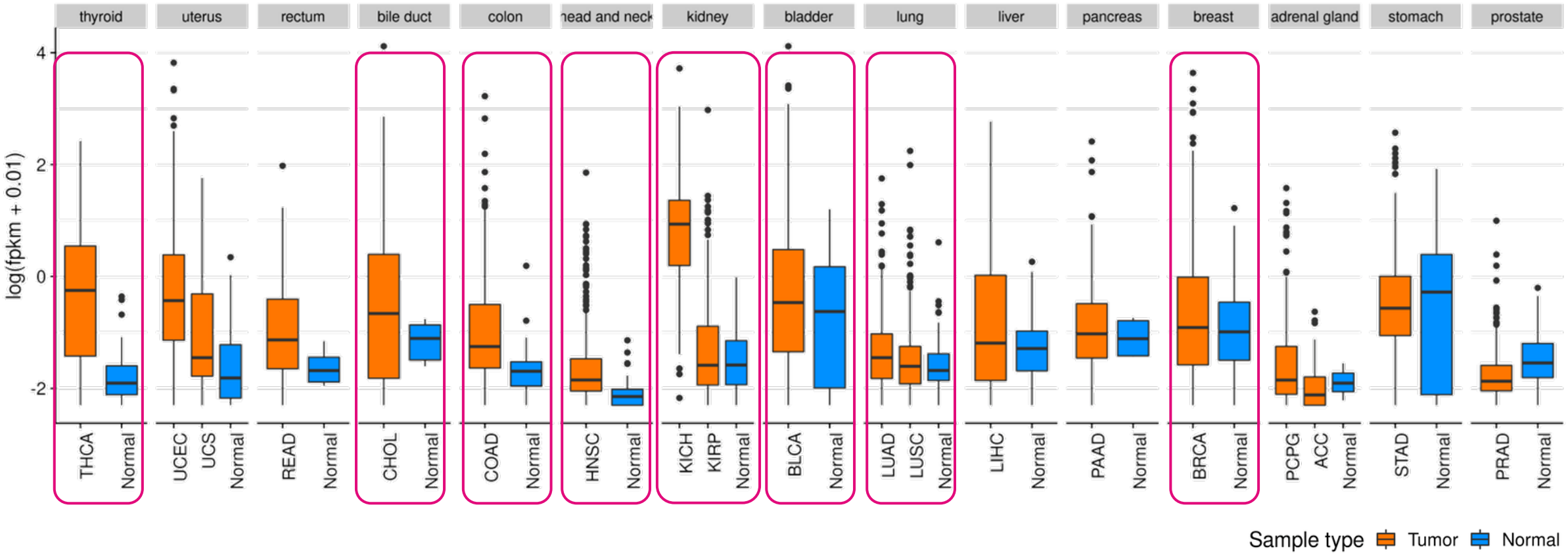
- PYX-106 is a fully human antibody targeting Siglec-15, a differentially expressed immune suppressor that may be a critical immune evasion mechanism in PD-L1-negative patients
  - Target has been de-risked in prior clinical studies
- High binding affinity to a unique epitope and high potency
- Well tolerated in preclinical studies with no evidence of anti-drug antibodies
- Potential to leverage biomarker analysis to target specific patient populations
- Exclusively licensed from Biosion in 2022 for worldwide rights outside of greater China



Sun et al., Clin Cancer Res 2021; Wang et al., Nat Med 2019; Biosion Corporate Presentation; GlobalData; Citeline Informa

PYX-106 Targets Siglec-15, Which is Differentially Upregulated in Multiple Solid Tumors

Meaningful Differences in Siglec-15 Expression in Tumor vs. Normal



Showing significant t-test results; TCGA normal grouped with GTEx where available
Pyxis Oncology data

PYX-106-101: An Open-label, Multicenter Phase 1 Study in Patients with Advanced Solid Tumors

Preliminary data expected in 2H 2024

Select Tumor Types

- NSCLC
- Endometrial Cancer
- HNSCC
- HR+ Breast Cancer
- Kidney Cancer
- Bladder Carcinoma
- Thyroid Cancer
- Cholangio-carcinoma
- Colorectal carcinoma

Dose Escalation

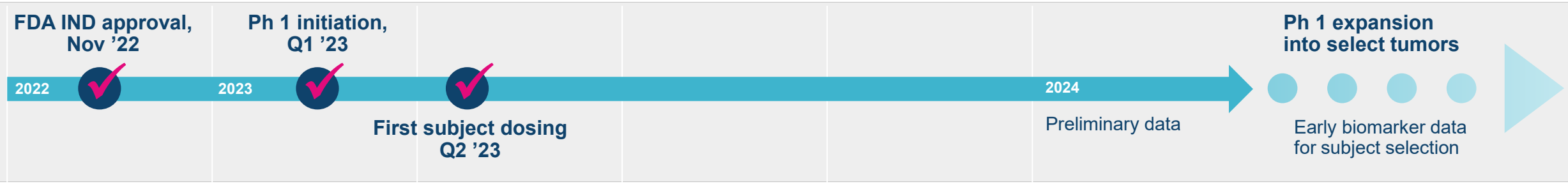
- Evaluate safety, tolerability and pharmacokinetics of PYX-106
- Determine maximum tolerated dose (MTD) using Bayesian optimal interval (BOIN) design

Analysis

Analysis of paired biopsies from a subset of subjects pre/post treatment

Part 2: Expansion*

Expansion cohort in select tumor type(s)



Objectives

- Determine recommended dose(s) of PYX-106
- Evaluate safety and tolerability
- Characterize the pharmacokinetic profile
- Evaluate ORR, DOR, DCR, PFS, OS and immunogenicity of PYX-106

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* The expansion phase will be triggered by a protocol amendment. The indications, dosing schedules, and assessment timepoints planned for the expansion phase will be determined based on clinical safety, efficacy, biomarker, and pharmacokinetic (PK) data obtained during the dose escalation phase.

Upcoming Meetings

RBC Global Healthcare Conference in New York, May 14-15, 2024

ASCO Annual Meeting in Chicago, May 31-June 4, 2024

Jefferies Healthcare Conference in New York, June 5-6, 2024

Oppenheimer's Life Sciences Summit in New York, June 26-28, 2024

BTIG Virtual Biotechnology Conference on August 5-6, 2024

Wells Fargo Healthcare Conference in Boston, September 4-6, 2024

H.C. Wainwright Annual Global Investment Conference in New York, September 9-11, 2024

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APPENDIX

- Pfizer 2014 AACR poster on the Biology of the Extracellular Matrix
- Pfizer Data with Same Linker-Payload as PYX-201
- PYX-201 & ADC Toolkit
- PYX-106
- APXiMAB Platform & Sotigalimab

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Extracellular proteolytic cleavage of peptide-linked antibody-drug conjugates promotes bystander killing of cancer cells

AACR 2014 #4837

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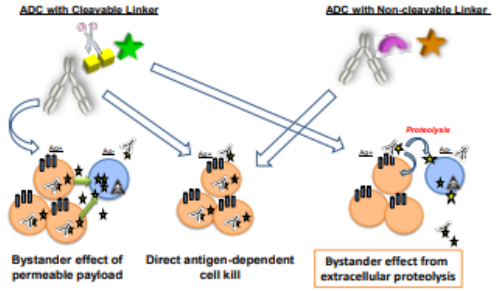
Oncology
A Pfizer Research Unit

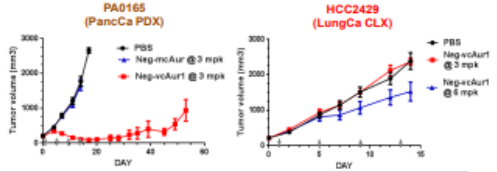
BACKGROUND & ABSTRACT

- Antibody drug conjugates (ADCs) are designed to deliver cytotoxic payloads to tumor cells via binding of antibody to surface antigen followed by internalization and intracellular drug release. Immunoconjugate linkers are typically categorized as non-cleavable or cleavable; a cleavable linker example is Y_mcValCitPABC_X, with antibody Y, a dipeptide sequence with self-immolative PABC spacer, and cytotoxic payload X. This linker is known to be cleaved by endosomal/ lysosomal proteases such as cathepsins, releasing attached payload.
- In addition to intracellular processing of this linker, we report that conditioned media of cultured tumor cell lines is sufficient to promote extracellular cleavage of ADCs with dipeptide-linked payloads. ADCs incubated with conditioned media from cultured tumor cell lines causes cytotoxicity of antigen-negative recipient cells. Conditioned media also promoted cleavage of a dipeptide-based cleavable substrate with fluorescent probe. An ELISA also confirmed the presence of cathepsins in conditioned media.
- In all cases, the magnitude of the response was greatest when donor cells were grown in 3D culture. In contrast, minimal response was observed using conditioned media from other cancer cell lines.
- Complementing these studies, we demonstrated proteolytic activity in the interstitial fluid derived from tumors grown in athymic mice. Fluid extracted from xenograft tumors (cultured cancer cell lines and patient-derived tumors) demonstrated proteolytic activity using a cleavable-fluorescent linker-probe in a plate assay.

Hypothesis:
The effect of some cleavable linker-payloads may be due to extracellular proteolysis



Observation: Some tumor xenografts in mice are inhibited with ADCs containing non-targeting IgG and cleavable-linked payloads

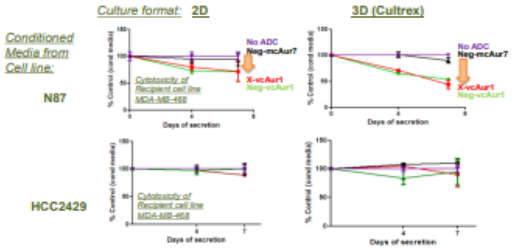


Relative magnitude of effect of non-targeting vcADC: ++ -/+

Left panel: Pancreatic patient derived tumor fragment (PA0165) was implanted subcutaneously into athymic mice. At ~200 mg staging, mice were treated qd1 x 4 with PBS vehicle (black line), 3 mg/kg of Neg-vcAur1 (non-targeting antibody with cleavable-linked auristatin, red line), or 3 mg/kg Neg-mcAur (non-targeting antibody with non-cleavable-linked auristatin, blue line).

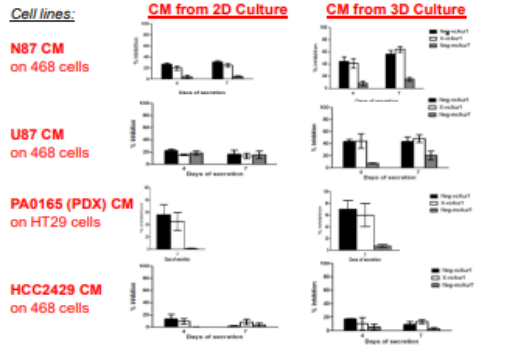
Right panel: Lung cancer cell line (HCC2429) was implanted subcutaneously into athymic mice. At ~200 mg staging, mice were treated qd1 x 4 with PBS vehicle (black line), 3 mg/kg (red line) or 6 mpk (blue line) of Neg-vcAur1 (non-targeting antibody with cleavable-linked auristatin). *All animal experiments were reviewed and approved by Pfizer IACUC.*

Non-targeting ADC with cleavable-linker, in presence of conditioned media from donor cell line N87, inhibits recipient cells



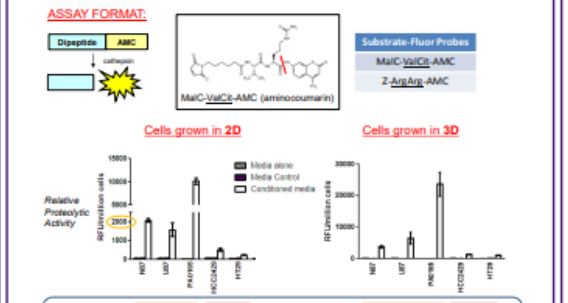
Conditioned media from donor N87 or HCC2429 cells is collected on day 4 and 7, then incubated with 100 nM of the indicated non-targeting ADCs in the presence of recipient MDA-MB-468 cells for 4 days, followed by cytotoxicity assessment of recipient cell by MTS assay. Cytotoxicity of recipient cells up to 50% is observed in presence of vcAur1 ADCs incubated with media from N87 cells grown in embedded 3D culture, suggesting cleavage of ValCitPABC by released N87 proteases. Data are normalized to individual conditioned media with no ADC. In contrast, there is no apparent cleavage of ValCitPABC or release of free Aur1 when using HCC2429 cell conditioned media (grown 2D or 3D, *lower panels*)

Increased bystander cell kill using conditioned media (CM) from certain tumor cells in presence of mcValCitPABC-Aur1 ADCs. Effect is amplified using CM from 3D culture.



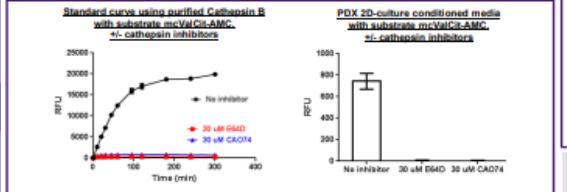
Conditioned media from the indicated cell line collected after 3, 4, or 7 days. All ADCs are non-targeting for the recipient cells, and are dosed at 100 nM payload concentration. Cytotoxicity assays of recipient cells (468 and HT29) were conducted for 4 days with MTS endpoint. Data are the mean ± SD of 3 – 5 independent experiments.

Conditioned media shows proteolytic activity in plate-based assay with dipeptide-AMC substrate



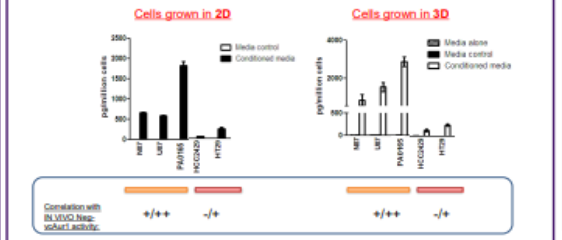
Conditioned media from tumor cell lines grown in 2D (left) or 3D (right) culture were incubated with ValCit-AMC probe overnight at 37C, then fluorescence measured on a plate reader. Interestingly, elevated proteolytic activity was observed in cell line models where in vivo activity was observed against vcAur1 ADCs. *Media control = media (no cells) incubated for 3 or 7 days at 37C before cathepsin assay. Cathepsin activity normalized to cell number when conditioned media was harvested.*

Cathepsin inhibitors attenuate proteolytic activity of cell line conditioned media



Left panel: Purified cathepsin B was incubated with vcAMC probe +/- 30 uM cathepsin inhibitors E64D or CA074, demonstrating complete inhibition of proteolysis in plate-based assay. *Right panel:* Proteolytic activity in conditioned media from pancreatic PDX PA0165 grown in 2D is also inhibited by cathepsin inhibitors (30 hr proteolysis timepoint). *Assay buffer: 50 uM mcValCit-AMC in 50 mM sodium acetate, pH 5.0, 2 mM DTT.*

Cathepsin ELISA detects Cathepsin B protein in conditioned media



Conditioned media from tumor cell lines grown in 2D (left) or 3D (right) culture were tested in an ELISA specific for human cathepsin B. *Media control = media without cells incubated for 3 or 7 days at 37C before ELISA. Cathepsin levels normalized to cell number.*

Protease activity in Interstitial Fluid: Cleavage of mcValCit-AMC probe

Interstitial fluid collected from the indicated PDX or cell-line xenografts or normal tissue (500 ug/ml total protein) was evaluated in the proteolysis assay with ValCit-AMC probe. Data are represented as percent signal compared with equivalent total protein from a mouse liver lysosomal preparation. Color by replicate samples to view inter-animal variation.

Several cell lines exhibit extracellular proteolysis, enhanced in 3D culture, which correlates with in vivo profile

Cell line	Bystander Cytotox (2D CM)	Bystander Cytotox (3D CM)	vc-Probe proteolysis (3D CM)	Cathepsin B ELISA (3D CM)	In vivo efficacy observed with Neg-vcAur1 ADC
N87 (GastricCa CLX)	+	++	+	++	+
U87 (Glio CLX)	-	++	+	++	+
PA0165 (Panc PDX)	++	++	++	++	++
HCC2429 (LuCa CLX)	-	-/+	-	-	-/+
HT29 (ColCa CLX)	-	-/+	-	-	-

CONCLUSIONS

- Different levels of proteolytic activity were detected in the conditioned media of cultured cancer cell lines, assessed by cytotoxicity studies, proteolysis assays with ValCit-containing fluorescent substrate, and by cathepsin ELISA. These effects were enhanced when donor cells were grown in 3D cultures.
- Proteolytic activity was detected in the interstitial fluid from cancer cell line xenografts and patient-derived xenografts implanted in athymic mice.
- These data are consistent with the reported secretion of cathepsins by cancer cells, and we now show that these proteases may mediate extracellular release of cytotoxic payloads from ADCs containing peptide-based cleavable linkers.
- Efficacy associated with non-targeting ADCs is sometimes attributed to pinocytosis and other non-specific uptake mechanisms; these extracellular proteolysis data suggest an alternative explanation for biological activity observed with non-targeting ADCs.
- Released permeable payload from extracellular cleavage of ADCs may promote the killing of proximal antigen-negative cancer cells in a heterogeneous tumor mass, providing a beneficial debulking effect.

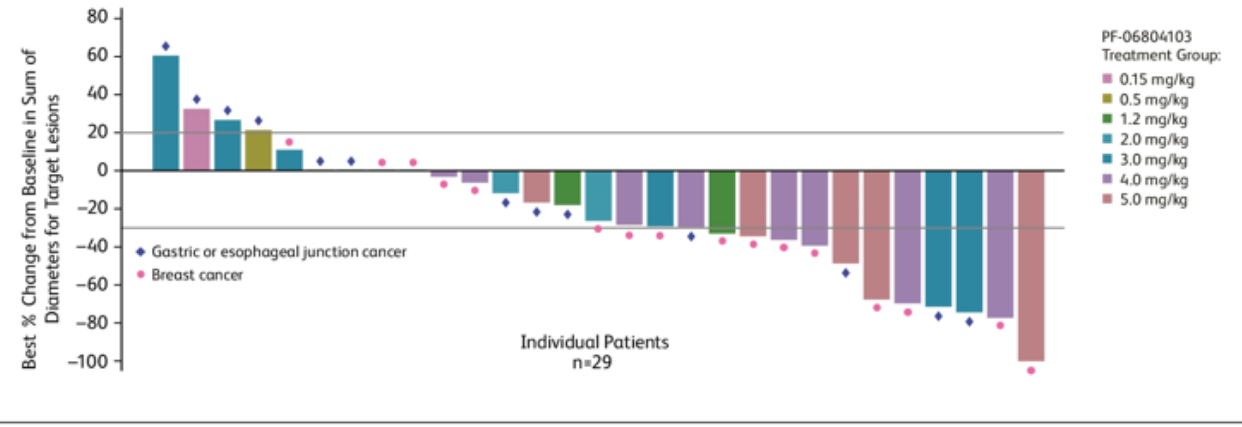
ACKNOWLEDGEMENTS

We gratefully acknowledge the contributions from our colleagues in the ORU, WWMC, GBT, PDM, and DSRD.

PYXIS ONCOLOGY

PYX-201 Linker-Payload Combination *Pelidotin* was De-Risked in Prior Pfizer-run Clinical Trial in HER2 target

Figure 1: Best % Change in Tumor Size in Response-Evaluable Patients



Based on RECIST criteria.
Two response-evaluable patients with only non-target lesions are not included.
One CR per RECIST v1.1 did not have 100% target lesion reduction due to inclusion of lymph nodes.

Table 3: Summary of Tumor Assessments in Response-Evaluable Patients

	PF-06804103 Dose					
	<2.0 mg/kg n=6	2.0 mg/kg n=4	3.0 mg/kg n=8	4.0 mg/kg n=8	5.0 mg/kg n=5	Total N=31
Best overall response, n (%)*						
CR	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (20.0)	2 (6.5)
PR	1 (16.7)	0 (0.0)	2 (25.0)	4 (50.0)	3 (60.0)	10 (32.3)
SD	3 (50.0)	4 (100.0)	4 (50.0)	3 (37.5)	1 (20.0)	15 (48.4)
PD	2 (33.3)	0 (0.0)	2 (25.0)	0 (0.0)	0 (0.0)	4 (12.9)
ORR, %	16.7	0	25.0	62.5	80.0	38.7

* Includes confirmed and unconfirmed responses.
CR=complete response; ORR=objective response rate; PD=progressive disease; PR=partial response; SD=stable disease

- Ph1 dose-escalation study of a novel anti-HER2 ADC constructed using the FACT platform showed promising efficacy and generally manageable toxicity profile at doses significantly higher than currently approved auristatin ADCs
- PF-06804103, a HER2-targeted ADC, was evaluated by Pfizer with same linker-payload combination as for PYX-201
  - DAR = 4
  - Higher tolerable dose levels achieved (4-5 mg/kg) compared to traditional vc-MMAE-based ADCs (~1.8 mg/kg)
- Anti-tumor activity was demonstrated at doses beginning at 1.2 mg/kg with a trend of dose-dependent antitumor effect

PYXIS ONCOLOGY

Meric-Bernstam, et al., poster presentation at 2020 American Society for Clinical Oncology (ASCO) annual meeting

Safety Insights from Pfizer's HER2 Phase 1 Trial

"An MTD was not reached on the basis of the DLT criteria; 3.0 mg/kg lacked a relative degree of activity and 5.0 mg/kg was determined to be intolerable, although no DLTs were reported at 5.0 mg/kg dosing. Therefore, 4.0 mg/kg was initially selected to be the Part 2 dose, with flexibility in the protocol to reduce to a lower dose (e.g., 3.0 mg/kg) if the observed toxicity of 4.0 mg/kg was determined to be too high. As the trial enrolled, a data-driven decision was made to explore both 3.0 and 4.0 mg/kg PF-06804103 doses in Part 2." - Pfizer

4 subjects had DLT at 3mg/kg or 4 mg/kg that were subsequently resolved

- 2 subjects out of 28 subjects at 3mg/kg:
  1 subject Grade 3 non-serious TRAE of arthralgia;
  1 subject Grade 3 serious TRAE of neuralgia and musculoskeletal pain which was associated with drug withdraw
- 2 subjects out of 36 subjects at 4mg/kg:
  1 subject Grade 2 TRAE ejection fraction decrease;
  1 subject Grade 3 TRAEs of arthralgia myalgia and fatigue

Maximum Tolerated Dose (MTD) was not reached based on the DLT criteria
5mg/kg was intolerable although no DLT was observed at 5mg/kg dose

Table 2. Treatment-related adverse events in ≥15% patients by PF-06804103 doses (the safety analysis set).

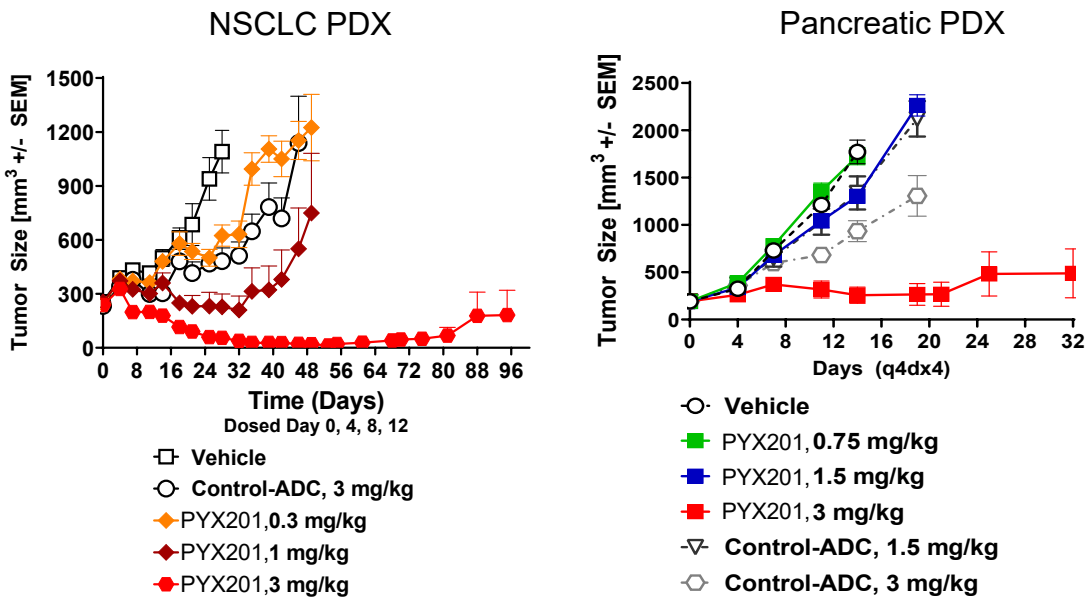
	Part 1A								Part 2A					
	HER2+ BC or GC							Total	HER2+ BC		HR+ HER2-Low BC		Total	Total
PF-06804103 doses, mg/kg	**0.15**	**0.5**	**1.2**	**2.0**	**3.0**	**4.0**	**5.0**	**0.15–5.0**	**3.0**	**4.0**	**3.0**	**4.0**	**3.0–4.0**	**0.15–5.0**
N	2	2	2	4	16	15	6	47	5	14	12	15	46	93
With any adverse event	1 (50.0)	1 (50.0)	1 (50.0)	4 (100.0)	15 (93.8)	15 (100.0)	6 (100.0)	43 (91.5)	5 (100.0)	14 (100.0)	10 (83.3)	15 (100.0)	44 (95.7)	87 (93.5)
Alopecia	0	0	0	4 (100.0)	4 (25.0)	10 (66.7)	3 (50.0)	21 (44.7)	1 (20.0)	5 (35.7)	6 (50.0)	9 (60.0)	21 (45.7)	42 (45.2)
Fatigue	0	0	1 (50.0)	2 (50.0)	9 (56.3)	4 (26.7)	4 (66.7)	20 (42.6)	2 (40.0)	5 (35.7)	4 (33.3)	1 (6.7)	12 (26.1)	32 (34.4)
Neuropathy peripheral	0	0	0	0	8 (50.0)	3 (20.0)	3 (50.0)	14 (29.8)	0	1 (7.1)	2 (16.7)	4 (26.7)	7 (15.2)	21 (22.6)
Peripheral sensory neuropathy	0	0	0	2 (50.0)	3 (18.8)	6 (40.0)	2 (33.3)	13 (27.7)	1 (20.0)	7 (50.0)	3 (25.0)	5 (33.3)	16 (34.8)	29 (31.2)
Decreased appetite	0	0	0	1 (25.0)	4 (25.0)	5 (33.3)	2 (33.3)	12 (25.5)	2 (40.0)	2 (14.3)	3 (25.0)	2 (13.3)	9 (19.6)	21 (22.6)
Myalgia	0	0	0	0	5 (31.3)	5 (33.3)	2 (33.3)	12 (25.5)	0	7 (50.0)	4 (33.3)	5 (33.3)	16 (34.8)	28 (30.1)
Rash	0	0	0	0	3 (18.8)	5 (33.3)	2 (33.3)	10 (21.3)	2 (40.0)	6 (42.9)	3 (25.0)	3 (20.0)	14 (30.4)	24 (25.8)
Weight decreased	0	0	0	0	3 (18.8)	4 (26.7)	3 (50.0)	10 (21.3)	1 (20.0)	4 (28.6)	2 (16.7)	3 (20.0)	10 (21.7)	20 (21.5)
Arthralgia	0	1 (50.0)	0	0	3 (18.8)	4 (26.7)	1 (16.7)	9 (19.1)	1 (20.0)	3 (21.4)	4 (33.3)	5 (33.3)	13 (28.3)	22 (23.7)
Stomatitis	0	1 (50.0)	0	0	2 (12.5)	4 (26.7)	2 (33.3)	9 (19.1)	1 (20.0)	4 (28.6)	3 (25.0)	2 (13.3)	10 (21.7)	19 (20.4)
Anemia	0	0	1 (50.0)	0	3 (18.8)	2 (13.3)	2 (33.3)	8 (17.0)	0	3 (21.4)	2 (16.7)	2 (13.3)	7 (15.2)	15 (16.1)
Diarrhea	1 (50.0)	0	1 (50.0)	0	2 (12.5)	2 (13.3)	2 (33.3)	8 (17.0)	1 (20.0)	1 (7.1)	0	5 (33.3)	7 (15.2)	15 (16.1)
Nausea	0	0	0	1 (25.0)	2 (12.5)	2 (13.3)	2 (33.3)	7 (14.9)	0	3 (21.4)	2 (16.7)	3 (20.0)	8 (17.4)	15 (16.1)

Note: Values are *n* (%). MedDRA v24.1 coding dictionary applied.
Abbreviations: BC, breast cancer; GC, gastric and gastroesophageal cancer; MedDRA, Medical Dictionary for Regulatory Activities; *N*, number of patients in each group.

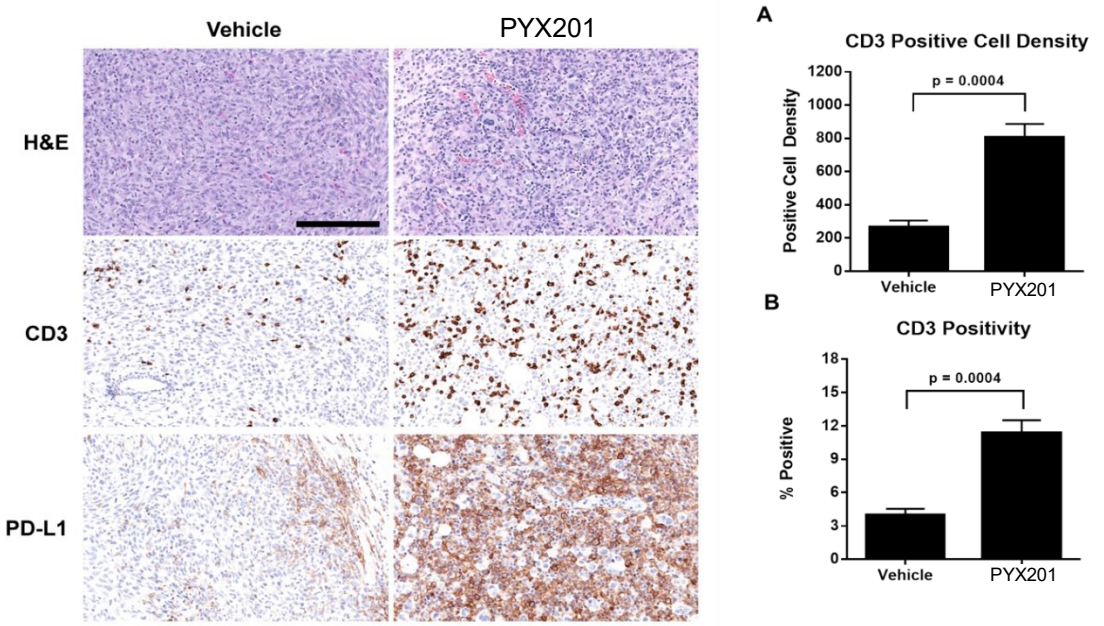
PYXIS ONCOLOGY

PDX Models Demonstrate Dose Dependent Anti-Tumor Activity of PYX-201

PYX-201 is Highly Active in Patient-derived Xenograft (PDX) Models of NSCLC and Pancreatic Cancer



PYX-201 Induces Immunogenic Cell Death & T cell Infiltration (CD3)



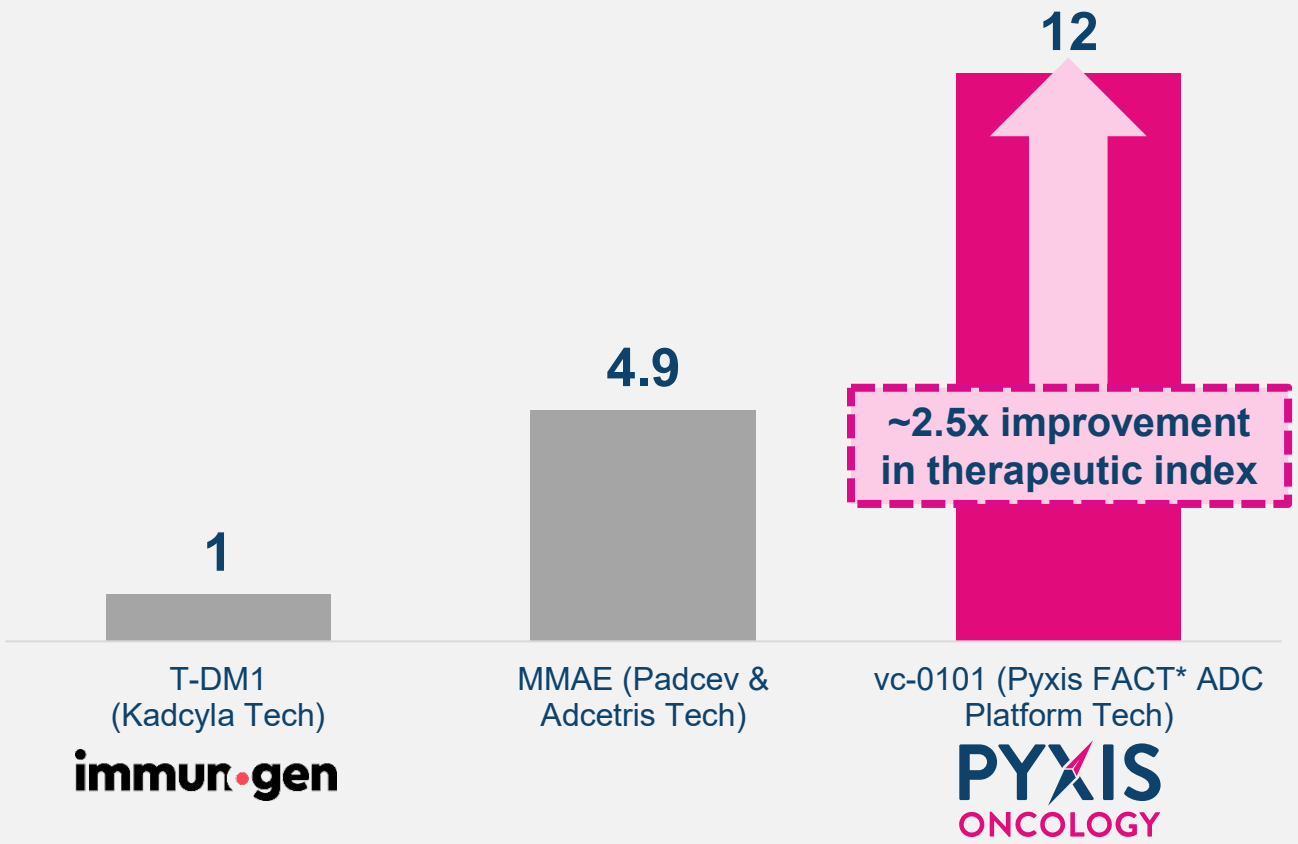
PYXIS ONCOLOGY

Mol Cancer Ther, 2022 Sep 6;21(9):1462-1472.

Pyxis Oncology's ADC Platform Demonstrates Superior Therapeutic Index (TI) to Currently Marketed Auristatin Based ADC Products

Site-Specific FACT* ADC Technology Platform

Therapeutic Index† Relative to Kadcyla Technology



- Preclinical studies testing trastuzumab-based ADCs demonstrate
  - FACT site-specific conjugation of vc-0101 to engineered cysteine residues exhibited significant improvement in TI

    vs
  - Conventional cysteine conjugation used in Adcetris and Padcev (Graziani, Molecular Cancer Therapeutics, 2020)
- Preclinical improvements in TI with the site-specific conjugated vc-0101 trastuzumab ADC (PF-06804103) predicted
  - That the molecule would have enhanced anti-tumor activity and
  - Be tolerated at higher dose levels compared to traditional vc-MMAE-based ADCs

PYXIS ONCOLOGY

*FACT=Flexible Antibody Conjugation Technology; † TI minimally effective dose vs monkey highest non severe toxic dose (HNSTD).

Pyxis Oncology is Advancing ADC Technology to Create More Active, Better Tolerated Therapies

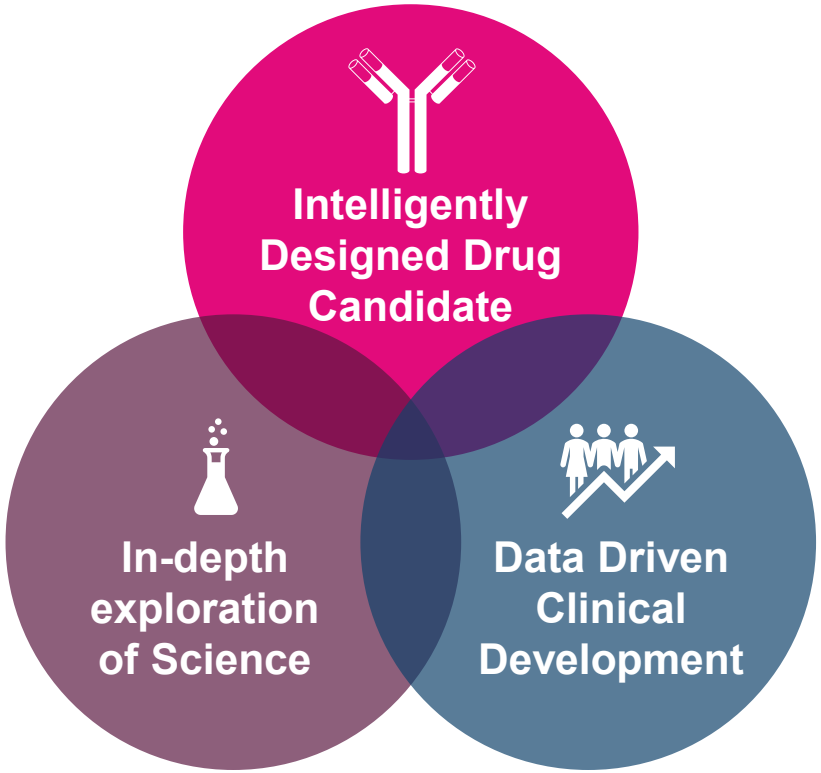
Limitations of First-Generation ADCs		PYXS ADC ToolKit Improvements
Less stable linkers can result in higher levels of free payload in circulation and off-target payload deposition	1 **Linker improvements**	More stable linkers can limit early payload release prior to reaching tumors
Random attachment of payloads to an antibody leads to a more inconsistent drug product and variable DAR	2 **Site-specific conjugation chemistry**	Site-specific conjugation leads to a more consistent drug product and more homogeneous DAR
Less permeable, less potent, lower bystander activity with first generation MMAE payloads	3 **Payload improvements**	Best-in-class auristatin payload AUR0101 engineered for better potency and permeability across cell membrane enables improved bystander effect
Often lower affinity, less specific antibodies	4 **Antibody improvements**	Generates novel, humanized antibodies to a target library, with high affinity and unique binding epitopes

PYXIS ONCOLOGY

DAR: Drug:antibody ratio

PYX-106: A Data Driven Anti-Siglec-15 Therapy

Clinical strategy entrenched in the in-depth understanding of the dynamics between the drug candidate, the tumor microenvironment (TME) and patient impact



A Simultaneous and Multifaceted Approach to Delivering an Impactful Therapy

DIFFERENTIATED DRUG CANDIDATE FROM COMPETITOR

- Fully Human which may limit ADA formation and improve exposure
- Long half-life in monkeys, if similar in humans, would allow for less frequent dosing, maintain exposure and target engagement
- Stronger target binding to human Siglec-15 versus competitor (NC318)
- More potent reversal of Siglec-15-mediated T cell suppression *ex vivo* versus NC318

ACTIONABLE DATA GENERATION AND ANALYSIS

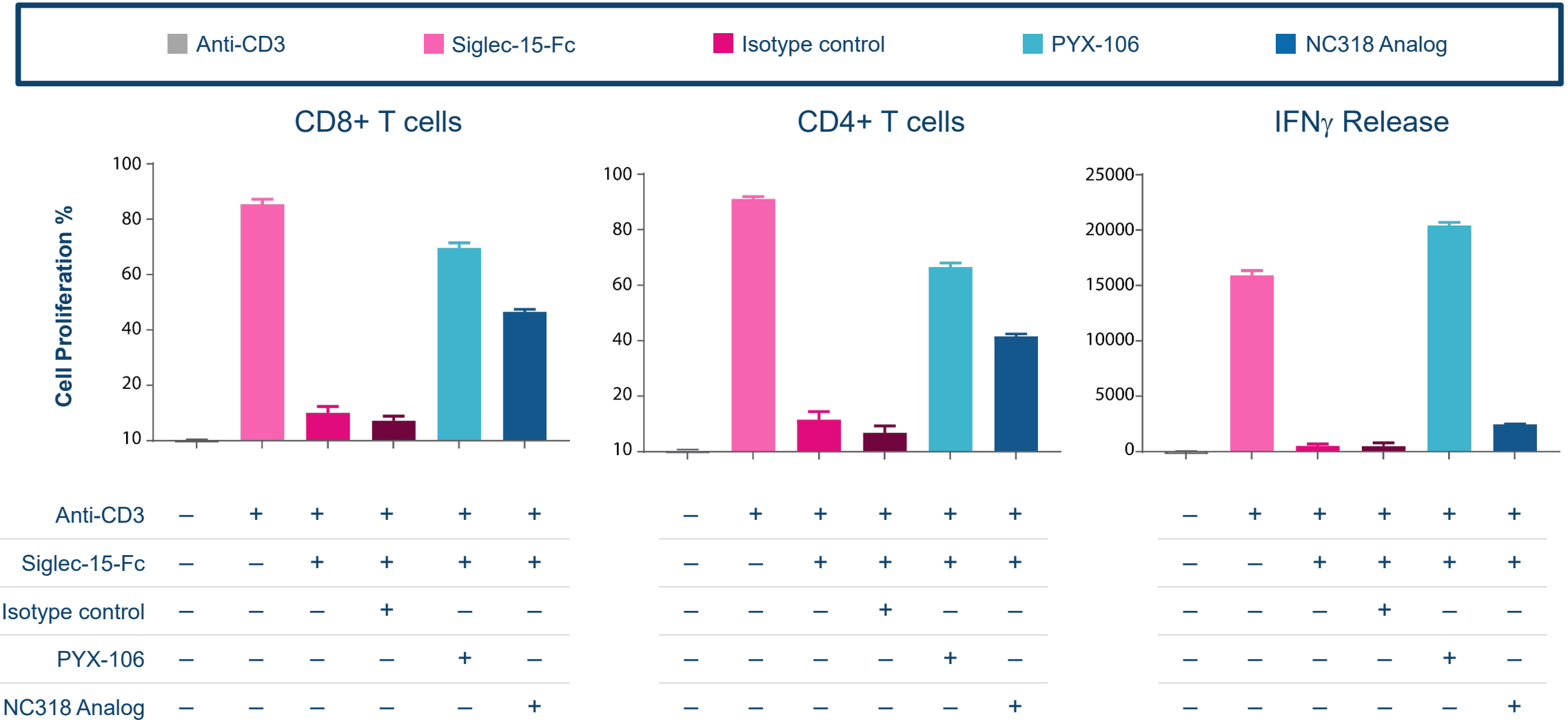
- Demystifying Siglec-15 as a Biomarker to comprehend the role of the target in tumorigenesis
- Discerning the TME to expand knowledge of immune related events during patient response to drug
- Deciphering drug dynamics (PK/PD) to better understand the MOA of the drug in targeting cancer

THOUGHTFULLY DESIGNED CLINICAL STRATEGY

- Diligent Indication Selection to ensure impact in unmet need tumors based on Siglec-15 expression
- Data-driven patient selection for prospective identification of responders
- Differentiated Clinical Development plan for delivering the highest patient benefit and impact

PYXIS ONCOLOGY

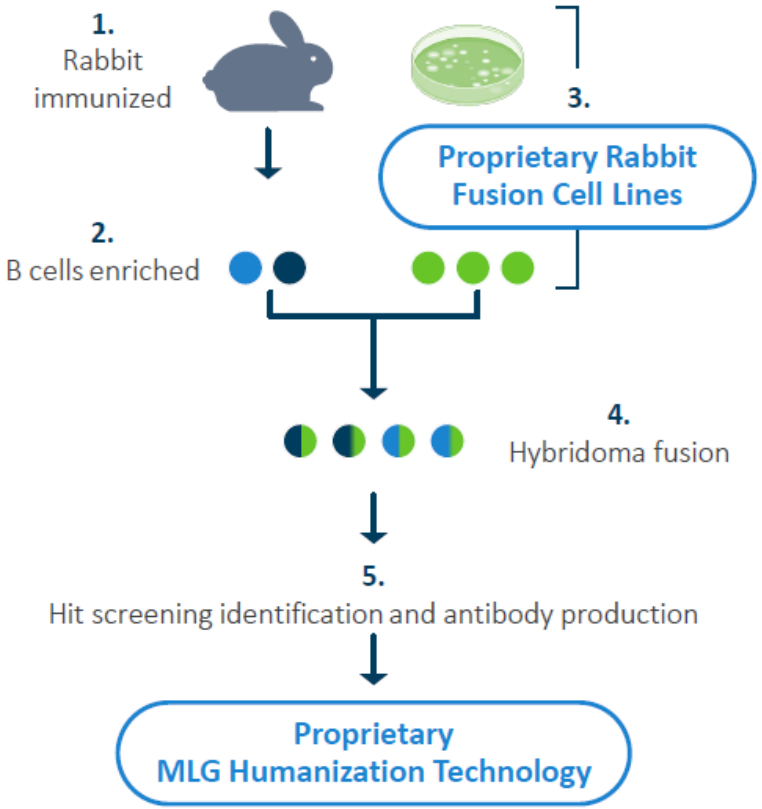
PYX-106 Reverses Siglec-15 Mediated T-Cell Suppression and Increases IFNγ Release to Reinvigorate the Immune System



APXiMAB Platform Facilitates In-House Development of Antibodies to Support Novel ADC Generation via FACT Platform

RABBIT-DERIVED THERAPEUTIC ANTIBODIES

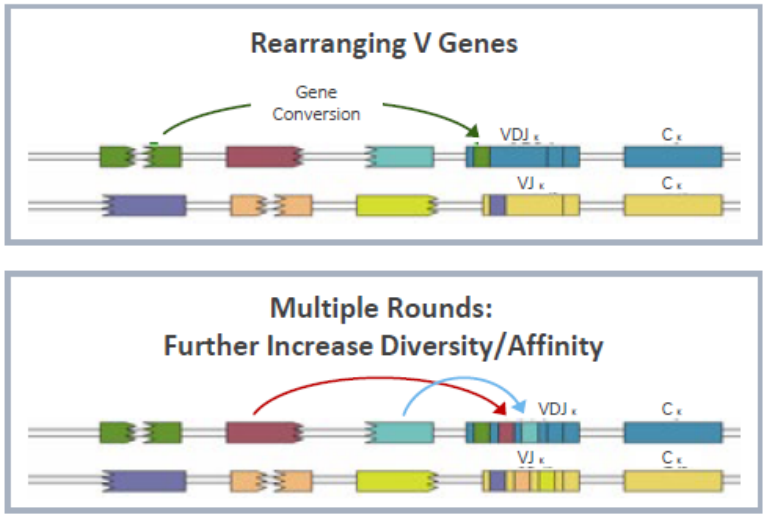
THE PROCESS



UNIQUE MECHANISM

Gene Conversion:

Increased Diversity and Affinity/Specificity



Only occurs in rabbits (and chickens)

THE ADVANTAGES

Broad Antibody Diversity

Increases Likelihood of:

- Identifying candidates for any given target
- Discovering the best antibody for a particular use

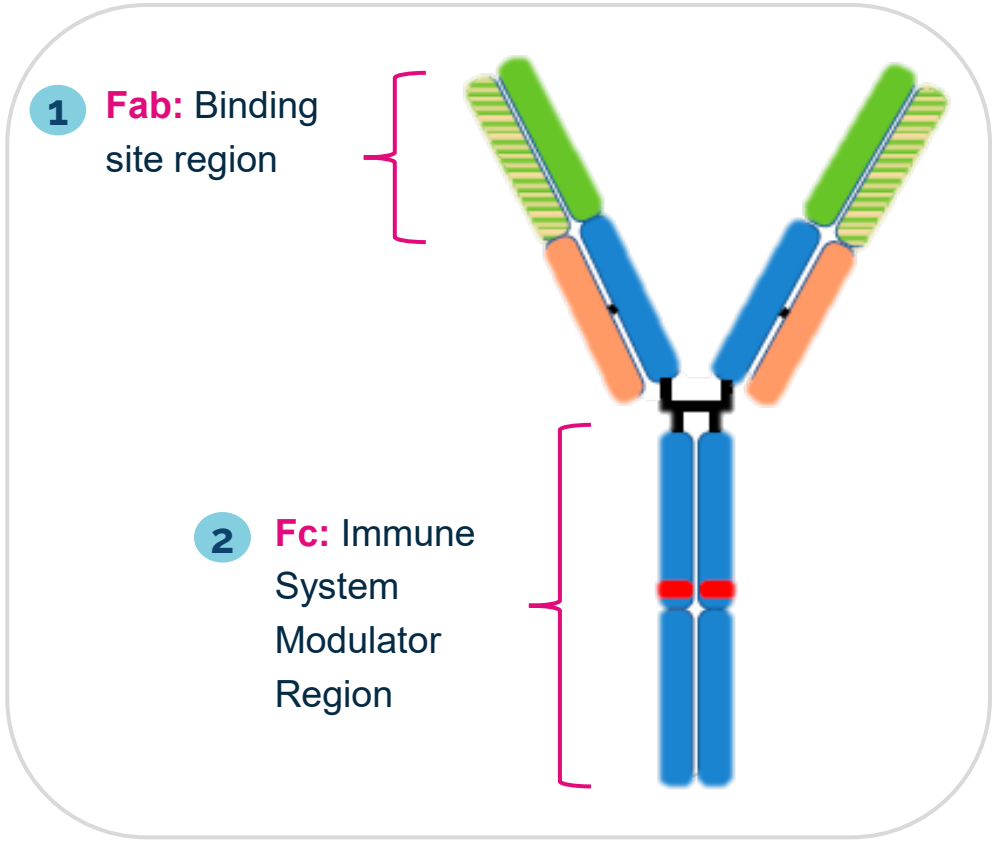
High Antibody Affinity/Specificity

Important for therapeutic antibody binding and staying on target for extended duration

PYXIS ONCOLOGY

PYX-107 (Sotigalimab) is a Potential First- and Best-in-Class CD40 Agonist in Phase 2 that Has Demonstrated Rapid, Deep and Durable Responses

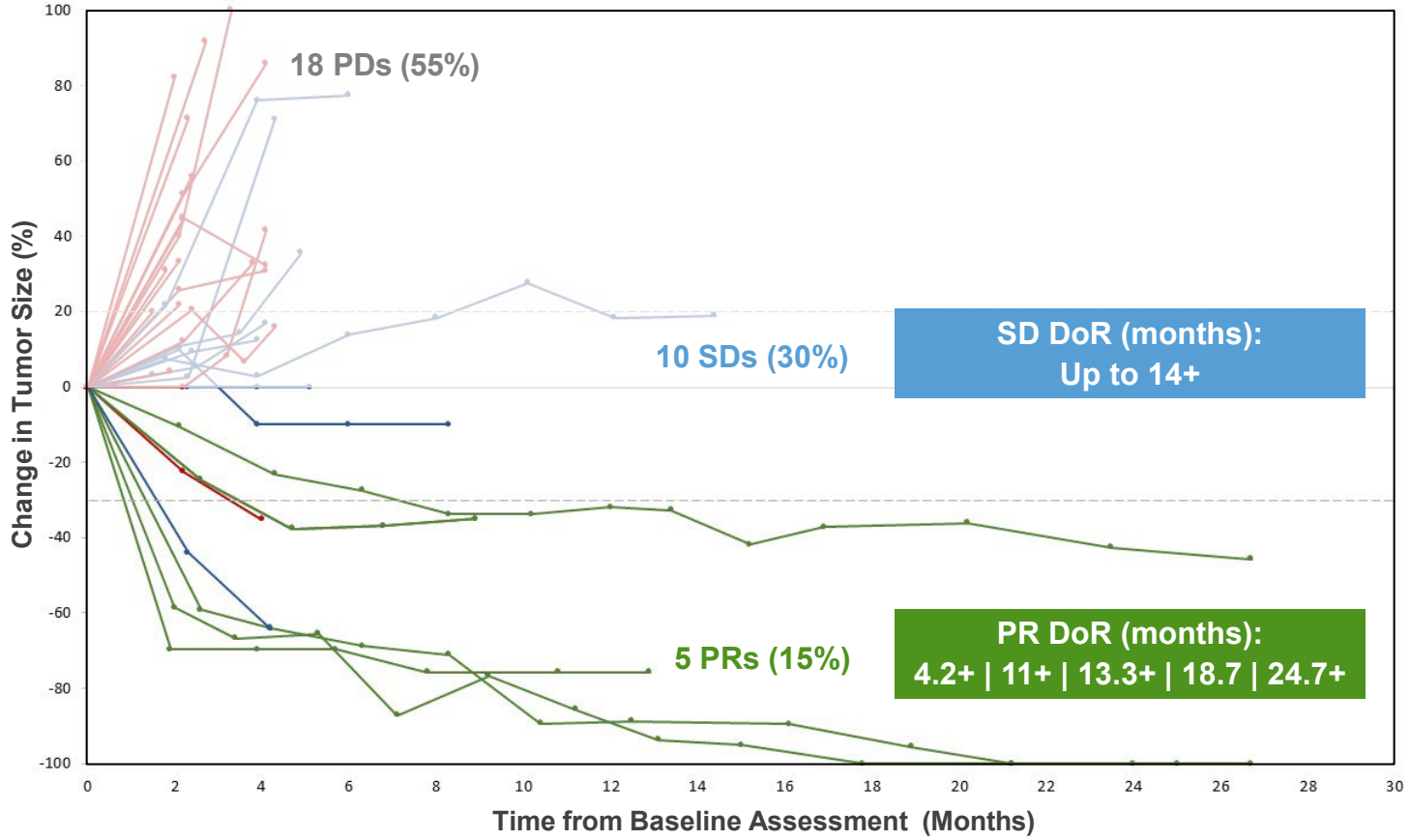
- Rationally designed with two key modifications for higher potency and improved tolerability
- Potential applicability across a variety of tumor types with high unmet need
- Compelling anti-tumor activity in difficult-to-treat metastatic melanoma patients, including those relapsed or refractory to PD-(L)1 and/or CTLA-4
  - No good treatment option exists for this growing patient population
- Favorable tolerability profile in combination with nivolumab
- Clinical development plan to be announced in Q4 2023



PYXIS ONCOLOGY

Sotigalimab-Nivolumab Demonstrated Activity and Prolonged Responses in PD-1 Blockade Refractory Melanoma Patients in Phase 2 Trial

Duration of Response with Sotigalimab+Nivolumab in Patients Who Progressed on Prior PD-1/PD-L1 Blockade Therapy



Background

- Patients (n=33) with relapsed/refractory metastatic melanoma with confirmed PD on anti-PD-1 mAb
- 24% received prior anti-CTLA-4

Results Summary

- **Strong activity**
  - 15.2% achieved partial responses (PR) and 30.3% showed stable disease (SD)
- **Well tolerated**
  - Grade ≥3 related TEAEs reported in two patients: transient increases of alanine aminotransferase (2 patients) and aspartate aminotransferase (2 patients)
- **Rapid, deep and durable responses**
  - SD up to 14+ months
  - 4/5 patients had ongoing PRs; median duration of response (DoR) not reached

Data from >500 patients collected across both company-sponsored trials and ISTs; IST data accumulated in a variety of tumor types, including metastatic melanoma, pancreatic, brain, renal, colorectal and ovarian cancer

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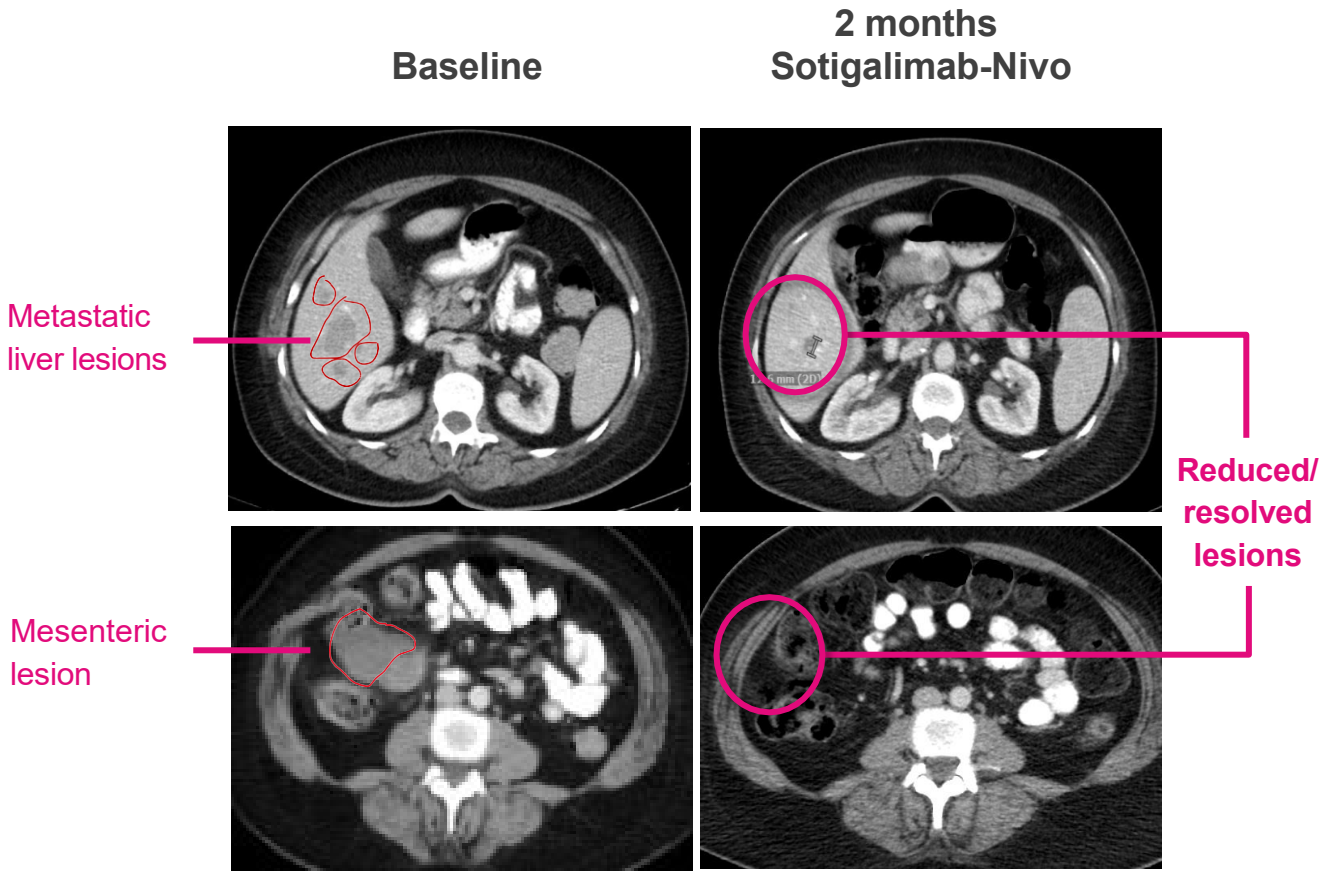
Case Study: Patient Achieved a Durable Partial Response (PR) and Resolution of All Lesions on Sotigalimab-Nivolumab

Patient Could Not Tolerate Ipilimumab and Had Highly Progressed, Metastatic Disease with Poor Prognosis and Limited Effective Treatment Options Remaining, with Discussions About Hospice as Next Step



- **Strong activity:** patient responded **only 2 months** after starting sotigalimab-nivolumab (3 cycles of treatment)
- **Good tolerability:** patient **completed ~11 months (15 cycles)** of therapy
- **Lasting durability:** patient **maintained a PR for 25+ months on study** after treatment concluded
  - **At 45.9+ months**, the patient maintained their response, as observed by the PI

PI: principal investigator

Results Demonstrate Favorable Tolerability Profile of Sotigalimab

Number (%) of subjects with related grade ≥3 TEAEs (in ≥2 subjects)

Study APX005M-002	Phase 1b			Phase 2 (0.3 mg/kg)				
					Melanoma Patient Cohort			
Related[a] Grade ≥3 TEAE Preferred Term	DL1 (0.03 mg/kg) (N=3)	DL2 (0.1 mg/kg) (N=3)	DL3[b] (0.3 mg/kg) (N=3)	C1[b] (N=53)	C2[b] (N=38)	C3A (N=l4)	C3B (N=28)	Total (N=139)
Alanine Aminotransferase Increased	0	0	0	1 (1.89%)	2 (5.26%)	0	2 (7.14%)	5 (3.60%)
Hypertension	0	0	0	4 (7.55%)	0	0	1 (3.57%)	5 (3.60%)
Gamma-glutamyltranferase Increased	0	0	0	2 (3.77%)	1 (2.63%)	0	1 (3.57%)	4 (2.88%)
Aspartate Aminotransferase Increased	0	0	0	1 (1.89%)	2 (5.26%)	0	0	3 (2.16%)
Dyspnoea	0	0	0	3 (5.66%)	0	0	0	3 (2.16%)
Amylase Increased	0	0	0	1 (1.89%)	1 (2.63%)	0	0	2 (1.44%)
Blood Bilirubin Increased	1 (33.33%)	0	0	1 (1.89%)	0	0	0	2 (1.44%)
Colitis	0	0	0	2 (3.77%)	0	0	0	2 (1.44%)
Cytokine Release Syndrome	0	0	0	0	0	0	2 (7.14%)	2 (1.44%)
Diarrhoea	0	0	0	2 (3.77%)	0	0	0	2 (1.44%)
Fatigue	0	0	0	1 (1.89%)	0	1 (7.14%)	0	2 (1.44%)
Hyperglycaernia	0	0	0	1 (1.89%)	0	0	1 (3.57%)	2 (1.44%)
Lipase Increased	0	0	0	1 (1.89%)	1 (2.63%)	0	0	2 (1.44%)
Pyrexia	0	0	0	0	1 (2.63%)	1 (7.14%)	0	2 (1.44%)

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Abbreviations: C = cohort, DL = dose level, N = number of subjects enrolled, SAE= serious adverse event: TEAE = treatment-emergent adverse event

[a] Regardless of the relatedness to nivolumab

[b] All 3 subjects from DL3 from phase 1b were also included in phase 2 C1 (1) and C2 (2)

Sotigalimab vs. Other Advanced Clinical Stage CD40 Agonists (Not Exhaustive)

	Apexigen	Celldex	Roche	AbbVie	Seagen	BioNTech	Alligator Bioscience	Eucure
	sotigalimab[1]	**CDX-1140[2]**	**selicrelumab[3]**	**ABBV-927[1]**	**SEA-CD40[4] dacetuzumab**	**BNT-312[5] (GEN1042)**	**mitazalimab[1] ADC-1013**	**YH003[6] (Biocytogen)**
Format	IgG1 humanized mAB	IgG2 fully human mAB	IgG2 fully human mAB	IgG1	IgG1	DuoBody-CD40x4-1BB	IgG1	IgG2 humanized mAB
Fc engineering	Modified to eliminate ADCC (S267E): Reduced FcgRIIIa binding	No	No	Modified to eliminate ADCC (V273Y): Reduced FcgRIIIa binding	Modified to increase ADCC (afucosylated): Increased FcgRIIIa binding	Modified to eliminate binding to Fcg receptors	No	
CD40 epitope	Competes with CD40L (binds cysteine-rich domain 2 [CRD2])	CRD1; not competing with CD40L	CRD1; not competing with CD40L	CRD1; not competing with CD40L	CRD1; not competing with CD40L	Not known	CRD1; not competing with CD40L	CRD1; not competing with CD40L
Requires cross-linking	Yes	No	No	Yes	Yes	No	Yes	
FcγR dependent	Yes (FcgIIbR)	No	No	Yes (FcgIIbR)	yes	No	Yes	
In-vitro activity	High	Weak	High		High	High	High	
In-vivo activity	No binding to mouse CD40	Yes	Yes, not tolerated		Yes	Yes, crosslinks CD40-expressing APC with 4-1BB-expressing T cells	Yes	
Development status	Phase 2	Ph 2 (De-prioritized by company		Phase 2		Phase 1/2		Phase 2

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Sources: 1. Smith, Karin, et al,Expert Opinion on Biological Therapy 21.12 (2021): 1635-1646; 2. Vitale, Laura A., et al. Cancer Immunology, Immunotherapy 68 (2019): 233-245; 3. Djureinovic, et al, Cancers 13.6 (2021): 1302; 4. Gardai, Shyra J., et al. Cancer Research 75.15_Supplement (2015): 2472-2472.; 5. Muik, Alexander, et al. Cancer Research 81.13_Supplement (2021): 1846-1846; 6. Coward, Jermaine, et al. (2022): 2603-2603.

Building a Leading ADC Focused Company

Nasdaq: PYXS
May 2024

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