Building a Leading ADC- Focused Company

Nasdaq: PYXS April 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 \$173M in Cash Provides Runway into 2H 2026



Executive Leadership Team



Lara Sullivan, MD CEO



Pam Connealy, MBA
CFO & COO



Ken Kobayashi, MD, FACP
CMO



Jan Pinkas, PhD CSO



Xiaodong Yang, MD, PhD
Distinguished Research
Fellow



Balu Balasubramanian, PhD CTO









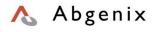












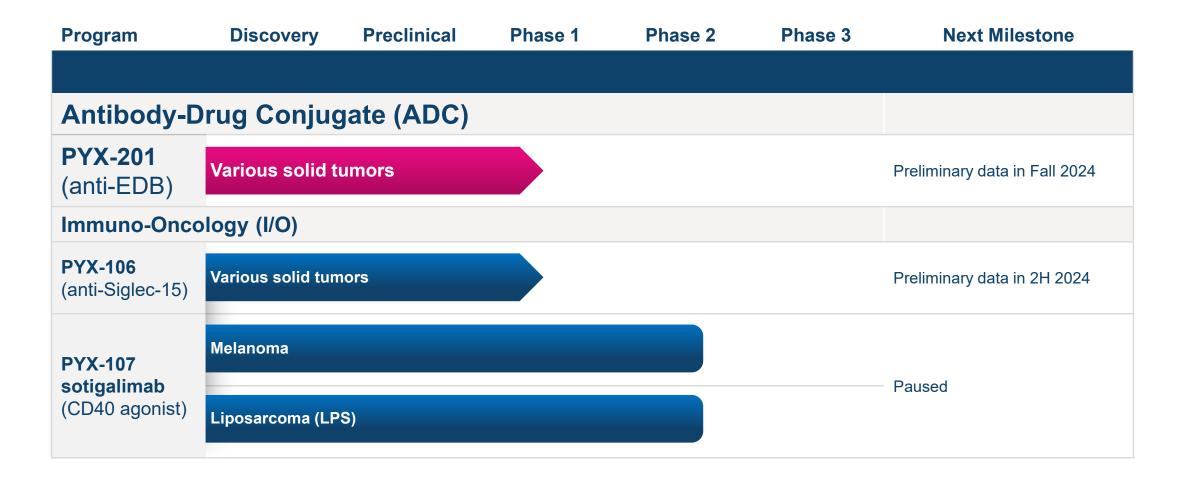




PYXS Team Members Have Collectively Contributed to >60 Oncology Drug Approvals



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?

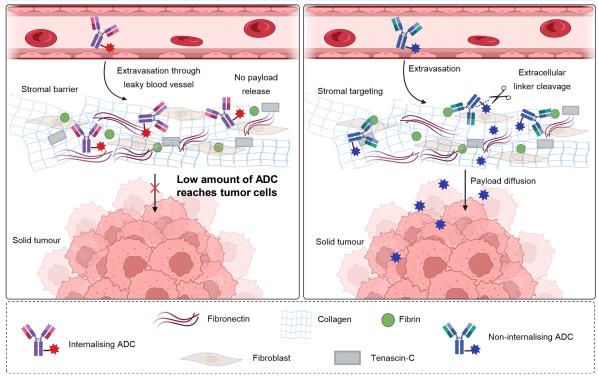
- The stroma provides a lifeline necessary for tumor growth in solid tumors
- Stroma includes the extracellular matrix, tumor vasculature, cancer-associated fibroblasts and mesenchymal stromal cells that make up the TME
- Provides protection, structural support, nutrition and waste product removal; can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

Classical ADCs cell surface targeting

PYX-201 stromal targeting



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)



Tumor Stroma is an Exciting Opportunity for ADC Modality

 Many of the proteases found intracellularly in endosomes and lysosome are also found outside the cell and are involved in disease pathologies including cancer*



• 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



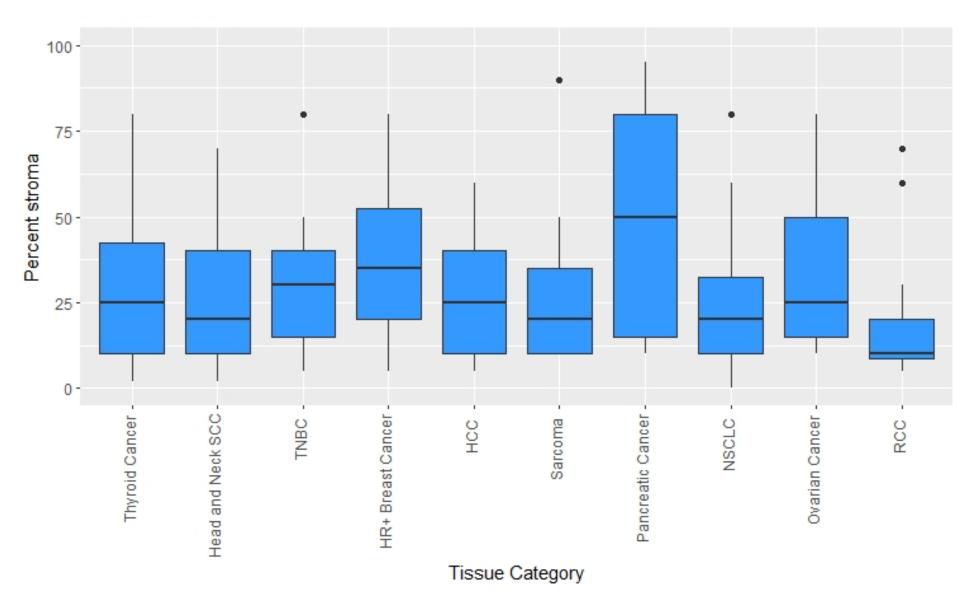
 The acidic TME has been exploited to develop therapeutic antibodies with tumor selective pHdependent antigen binding***



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 TME

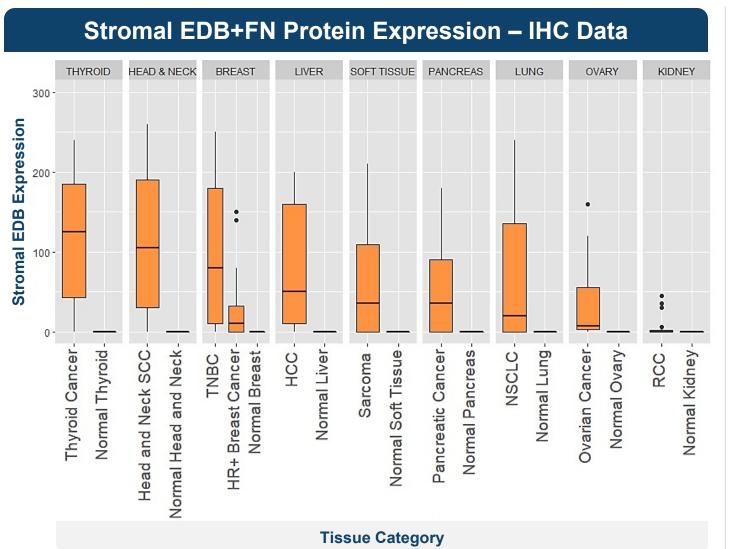


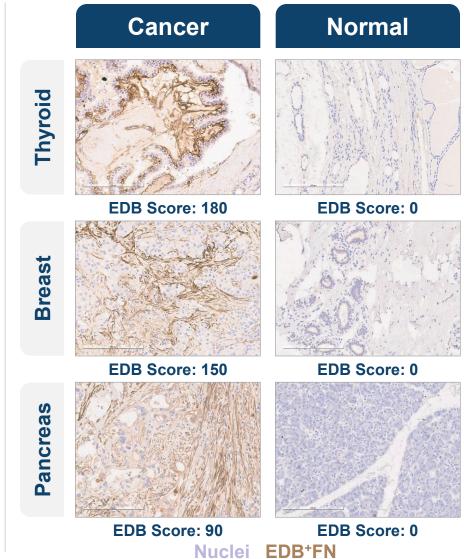
Volume of Stroma is Highly Variable by Tumor Type





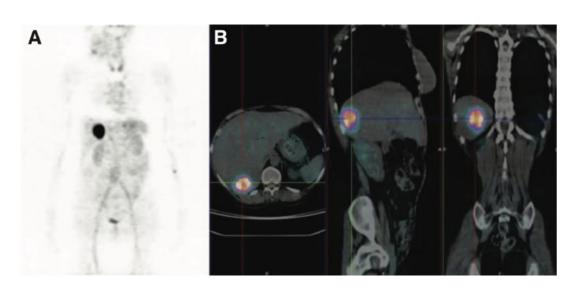
Immunohistochemistry (IHC) Analysis Demonstrates EDB+FN Protein is Highly Differentially Expressed in Tumor Stroma

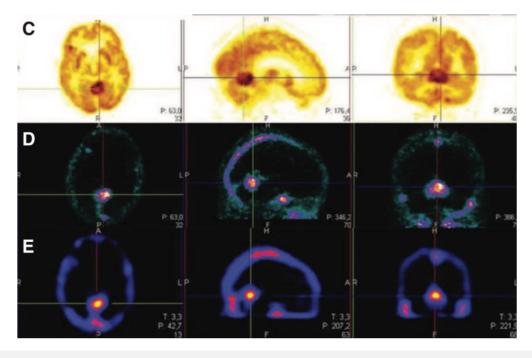




An EDB-targeted Radio-Conjugate Selectively Accumulates in Tumor with No Accumulation in Normal Tissues

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





Α

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

В

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

(

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

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

Ε

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

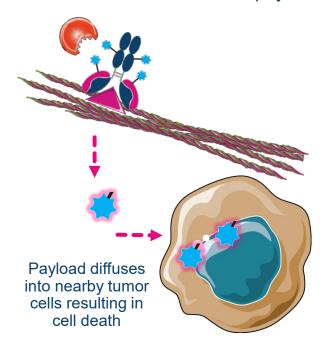


PYX-201 Believed to Act Via Three Distinct Mechanisms to Deliver Powerful **Anti-Tumor Activity**



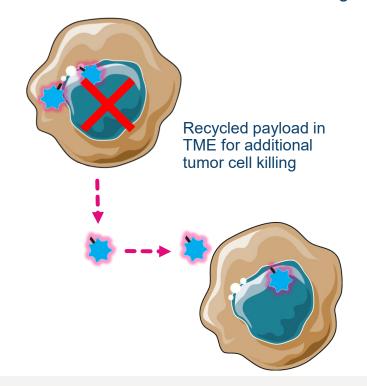
Payload Diffuses Into & Kills Tumor Cells

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



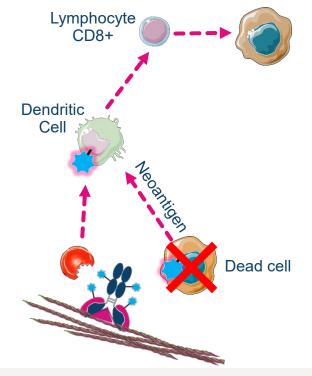
Additional Bystander Killing

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

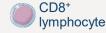




Released payload also potentiates immune cell infiltration into the tumor









(e.g., cathepsin)



Cleaved & active payload (auristatin)

















Tumor cell





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 holds 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

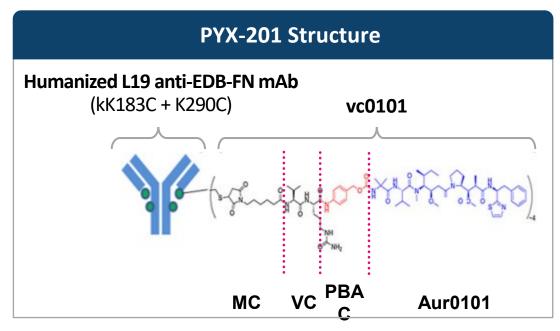


PYX-201 is Designed for Tolerability and Activity

PYX-201 Drug Design EDB+FN (hulgG1) targeting mAb valine citrulline linker auristatin 0101 payloads (x4)

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 drugantibody ratio (DAR) of 4
- Site-specific, cathepsin-cleavable, valine citrulline linkers
 - Optimized to improve stability in circulation and reduce free payload

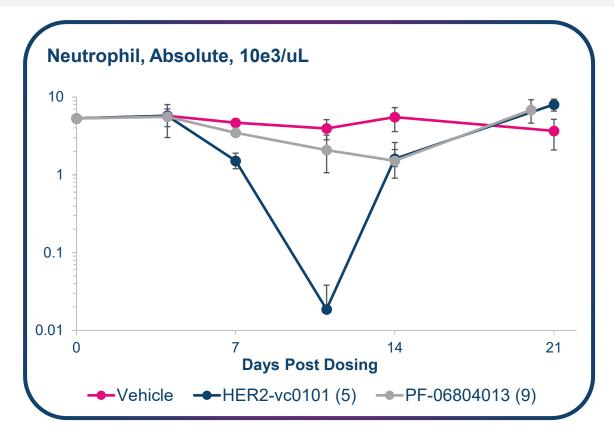


MC-VC-PABC linker construct utilizes a maleimidocaproyl (MC) spacer, a protease (cathepsin)-sensitive dipeptide, valine-citrulline (VC), a self-immolative spacer, para-amino benzyloxycarbonyl (PABC) coupled with the optimized auristatin – Aur0101



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 _{O-tau} (µg*h/mL)	Terminal $t_{1/2}$ (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

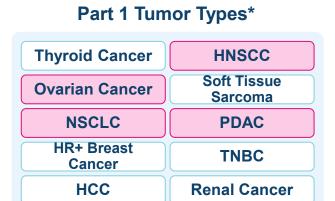
Note: Mouse tau = 336 hours; NHP tau = 504 hours. **Abbreviations:** AB = antibody; NA = not applicable.

- 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



PYX-201-101: Ongoing Open-Label Phase 1 Dose Escalation Study with 10 Solid Tumor Types, Enriched for 4 Histologies

Preliminary data expected Fall 2024



Part 1 Dose Escalation (Underway)

Evaluate safety, tolerability and pharmacokinetics of PYX-201

Determine maximum tolerated dose (MTD) using Bayesian optimal interval (BOIN) design

Part 2 Dose Optimization/ **Indication Selection**

- **Dose Optimization**
- Analysis of paired biopsies
- Other preclinical work

Part 3 Cohort Expansion

Expansion cohort(s) in selected tumor type(s) TBD (Simon 2 stage design)

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**

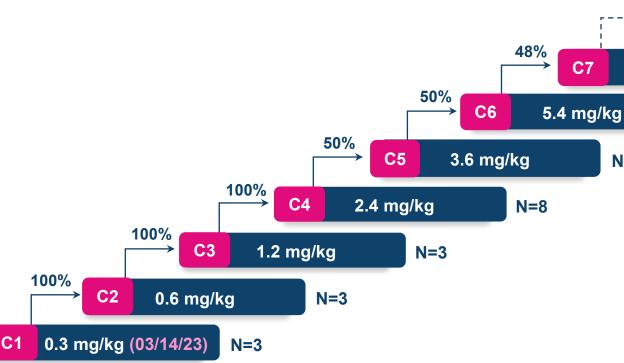
- Further evaluate safety and tolerability within the setting of dedicated cohort(s)
- Collect efficacy data (ORR, DOR, DCR, PFS, OS and immunogenicity) within dedicated cohort(s)



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

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
- 37 patients dosed in Cohorts 1-6 as of March 2024
- Q3W IV infusion



Part 2 Dose Optimization and Part 3 Cohort Expansion

> Until MTD

Well tolerated through 37 patients to date No evidence of target mediated tox to date through continued dose escalation

Further dose escalation

as appropriate

N=5 (Initially)

C8+

N = 10

8 mg/kg (03/21/24)

N=10



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

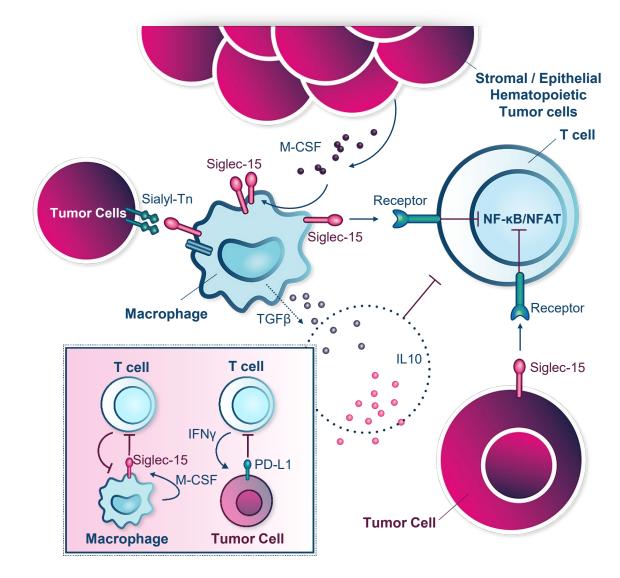
Potential for better exposure and no evidence of anti-drug antibody

Potential to combine with anti-PD-(L)1 or another immunotherapy



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

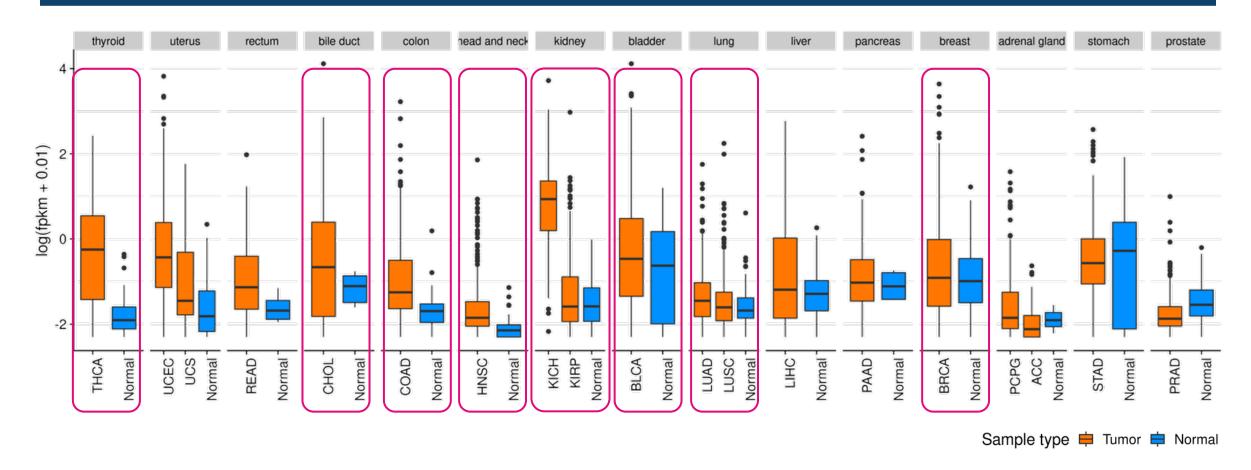
- PYX-106 is a fully human antibody targeting Siglec-15, a differentially expressed immune suppressor that may be a critical immune evasion mechanism in PD-L1-negative patients
 - Target has been de-risked in prior clinical studies
- High binding affinity to a unique epitope and high potency
- Well tolerated 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





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

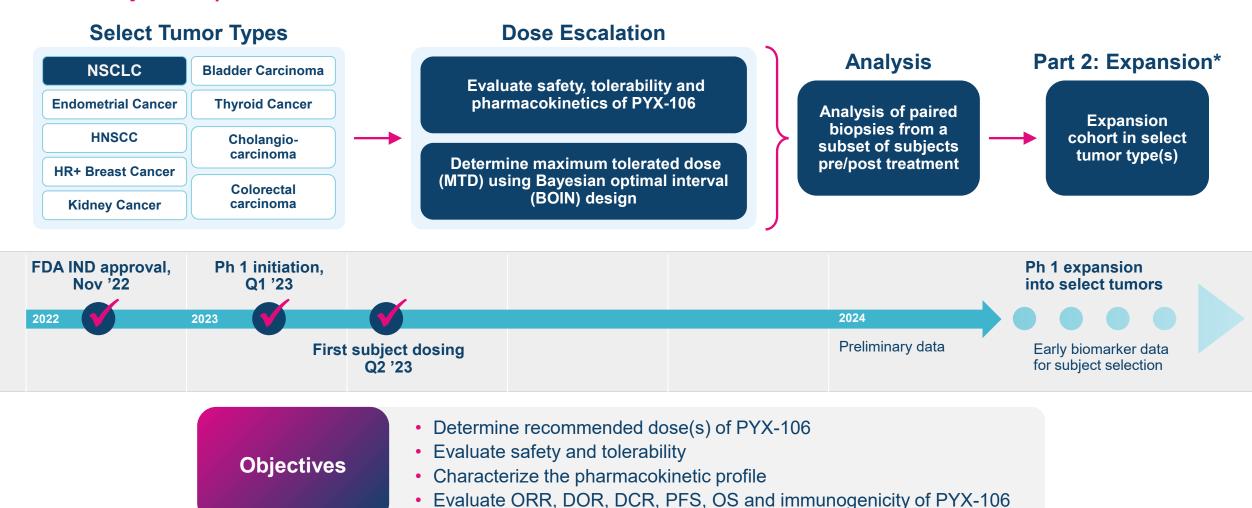
Meaningful Differences in Siglec-15 Expression in Tumor vs. Normal





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

Preliminary data expected in 2H 2024

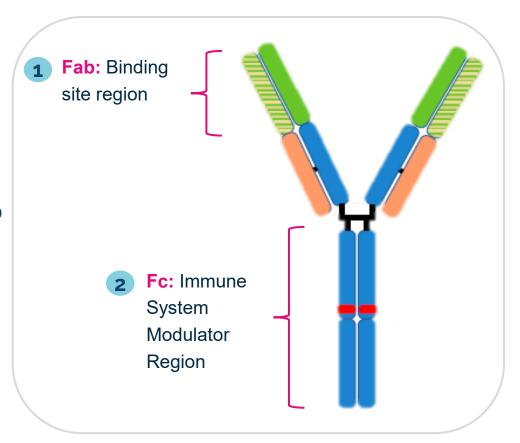




^{*} The expansion phase will be triggered by a protocol amendment. The indications, dosing schedules, and assessment timepoints planned for the expansion phase will be determined based on clinical safety, efficacy, biomarker, and pharmacokinetic (PK) data obtained during the dose escalation phase.

PYX-107 (Sotigalimab) is a Potential First- and Best-in-Class CD40 Agonist Paused 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

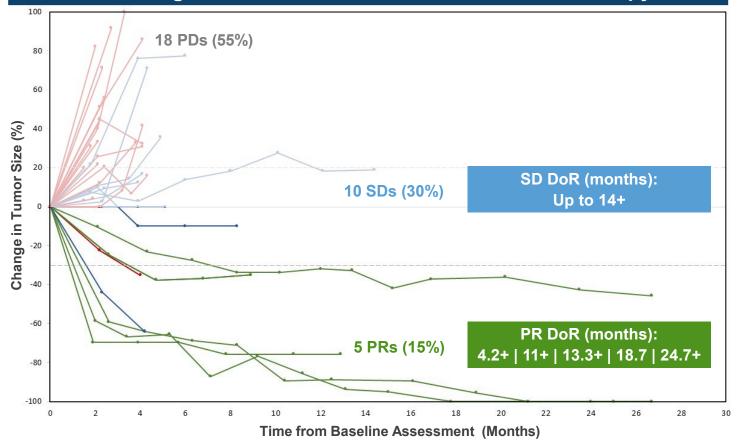




Sotigalimab-Nivolumab Demonstrated Activity and Prolonged Responses in PD-1 Blockade Refractory Melanoma Patients in Phase 2 Trial

Paused

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



Upcoming Meetings

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

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

BTIG Virtual Biotechnology Conference on August 5-6, 2024

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



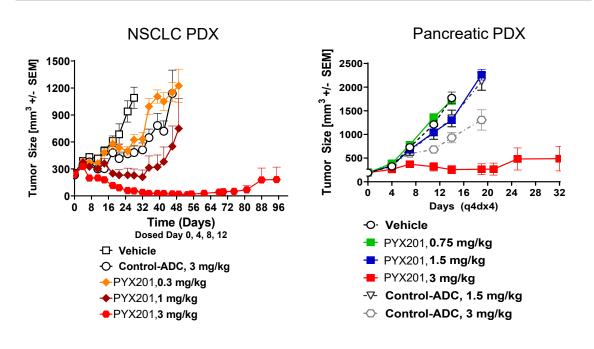
APPENDIX

- PYX-201 & ADC Toolkit
- PYX-106
- APXiMAB Platform & Sotigalimab

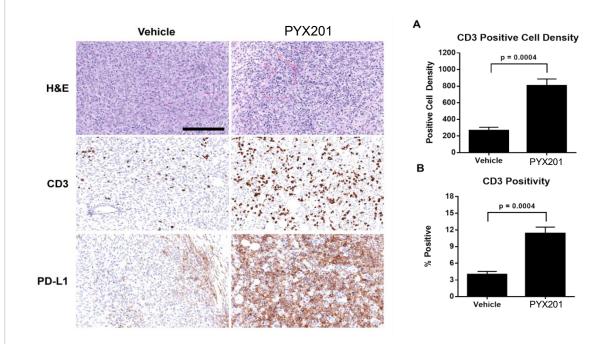


PDX Models Demonstrate Dose Dependent Anti-Tumor Activity of PYX-201

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

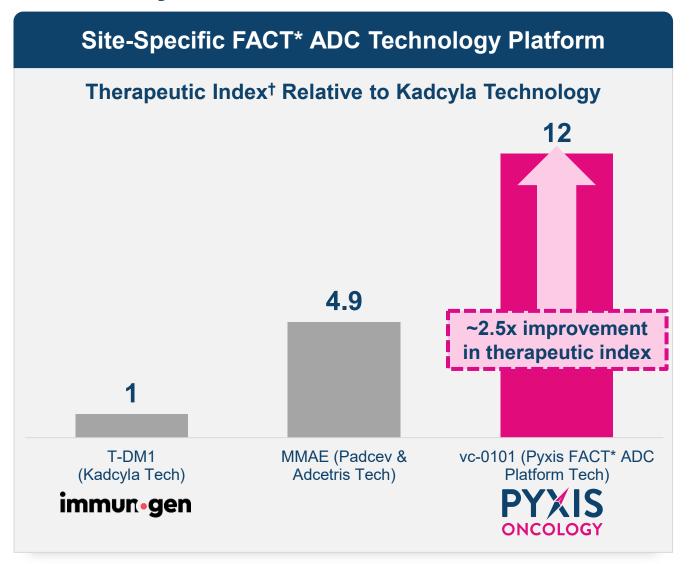


PYX-201 Induces Immunogenic Cell Death & T cell Infiltration (CD3)





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



- Preclinical studies testing trastuzumabbased 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 sitespecific 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-MMAEbased ADCs



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

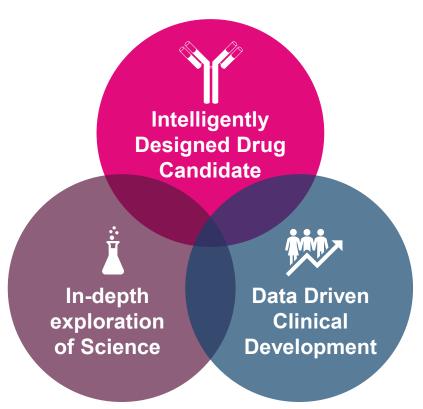
Limitations of First-Generation ADCs		F	PYXS ADC ToolKit Improvements
Less stable linkers can result in higher levels of free payload in circulation and off-target payload deposition	Linker improvements	⊘	More stable linkers can limit early payload release prior to reaching tumors
Random attachment of payloads to an antibody leads to a more inconsistent drug product and variable DAR	Site-specific conjugation chemistry	②	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	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	Antibody improvements	⊘	Generates novel, humanized antibodies to a target library, with high affinity and unique binding epitopes



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

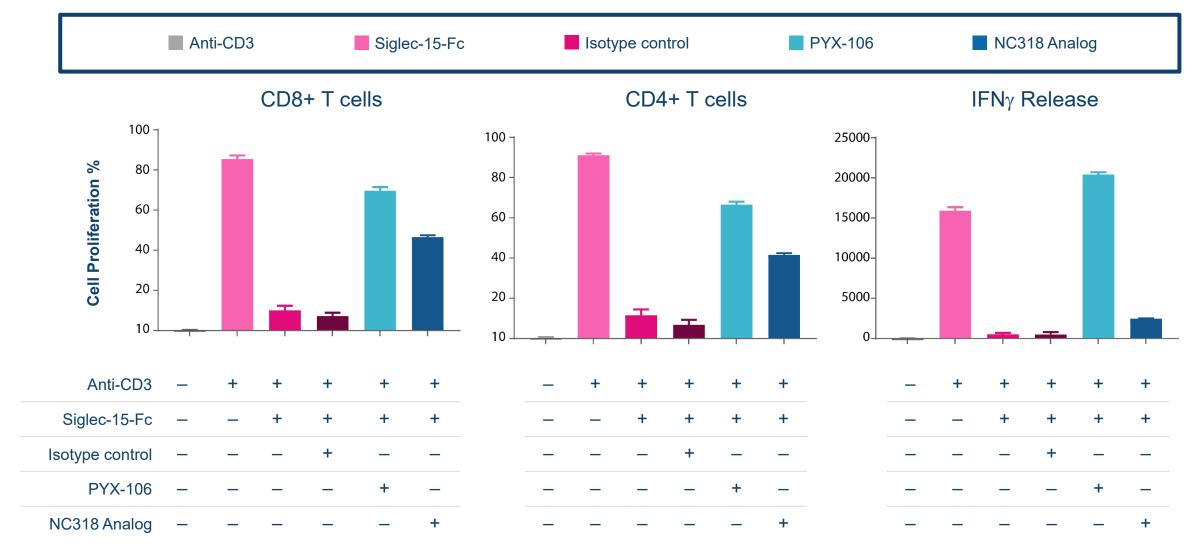
ACTIONABLE DATA GENERATION AND ANALYSIS

- 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

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

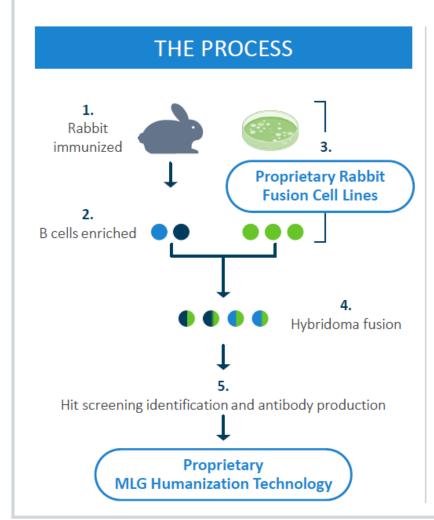




Biosion AACR 2022 poster 29

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

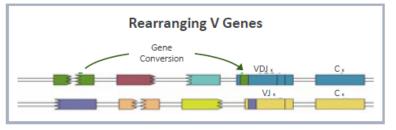
RABBIT-DERIVED THERAPEUTIC ANTIBODIES

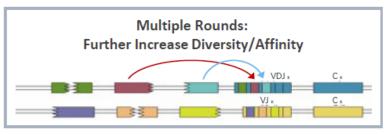


UNIQUE MECHANISM

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

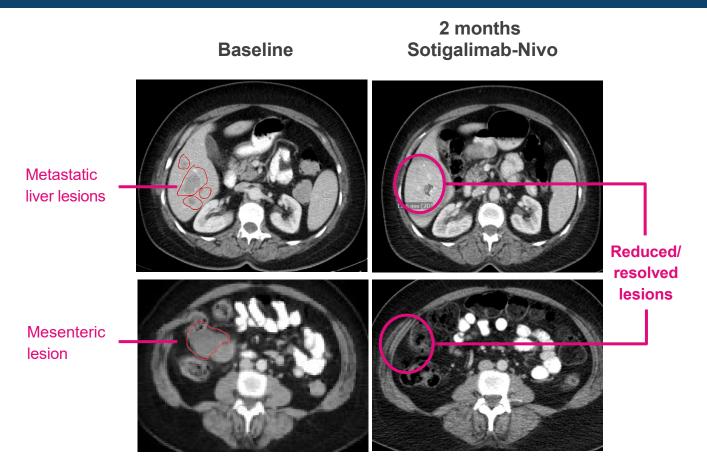


Important for therapeutic antibody binding and staying on target for extended duration



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 sotigalimabnivolumab (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 ≥3TEAE 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=I4)	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%)



^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	lgG1	lgG1	DuoBody- CD40x4-1BB	lgG1	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 (FcgllbR)	No	No	Yes (FcgllbR)	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

Building a Leading ADC Focused Company

Nasdaq: PYXS

April 2024

