BA3361, a NextGen CAB ADC Targeting Nectin4

ADC Summit

November 2024

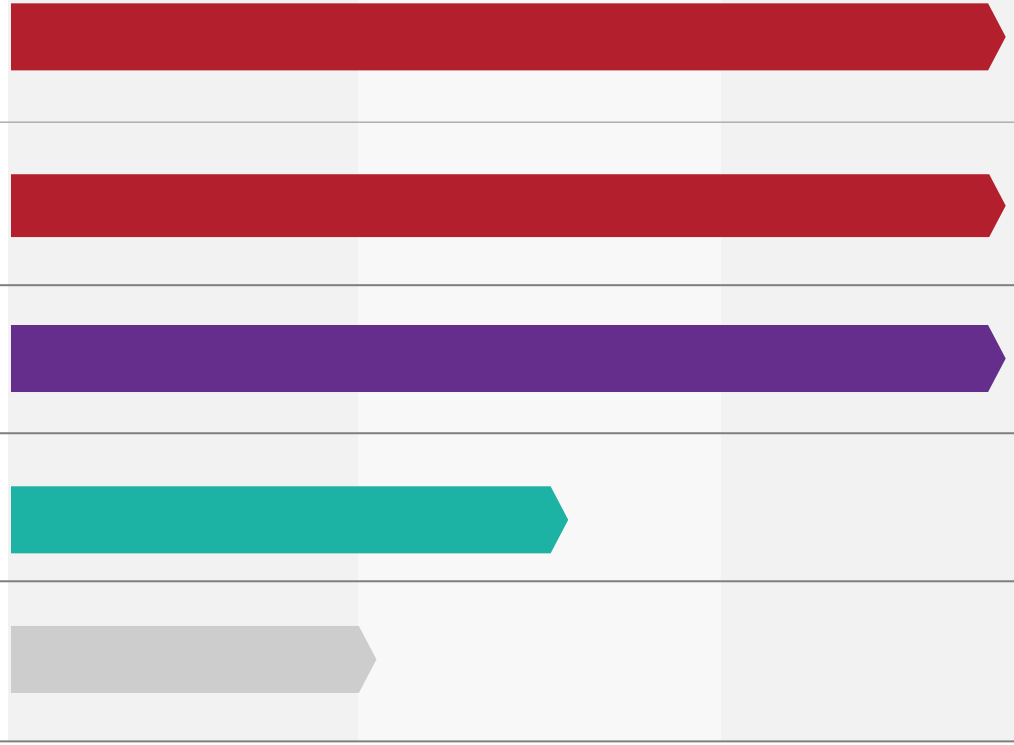
bioatla

Presentation Outline

- Pipeline Overview
- CAB Technology
- NextGen CAB ADC targeting Nectin4

Pipeline with Broad Applicability of Differentiated CAB Assets

	CAB Program	Target	Indications	IND Enabling Pre-Clinical	Phase 1 Clinical	Phase 2 Clinical
CAB-ADCs	*Mecbotamab Vedotin*	AXL	UPS NSCLC			
	Ozuriftamab Vedotin	ROR2	SCCHN			
CAB-I/O	*Evalstotug*	CTLA-4	Melanoma NSCLC Carcinomas			
CAB-Bispecific TCE	BA3182	EpCAM x CD3	Adenocarcinomas			
Next Gen CAB-ADC	BA3361	Nectin4	Multiple tumor types			



IND, investigational new drug; UPS, Undifferentiated Pleomorphic Sarcoma; NSCLC, Non-small Cell Lung Cancer; SCCHN, Squamous Cell Carcinoma of the Head and Neck

CAB ADCs in the Clinic

BA3011 Mecbotamab Vedotin (anti-AXL-ADC)

BA3021 Ozuriftamab Vedotin (anti-ROR2-ADC)

CAB ADCs in Phase 2

- Mecbotamab Vedotin (BA3011)
  - CAB ADC targeting AXL
  - Val/Cit protease cleavable linker
  - MMAE payload, DAR4

  - Indications
    - UPS
    - NSCLC
      - High correlation between mKRAS and AXL expression
      - 30% of all NSCLC patient are mKRAS

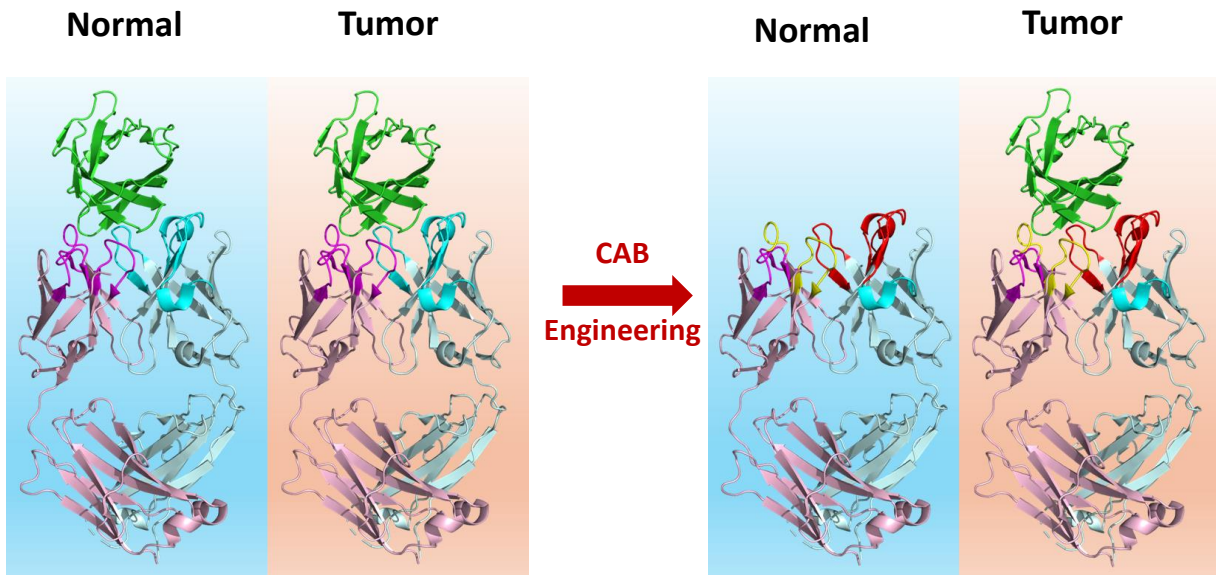
- Ozuriftamab Vedotin (BA3021)
  - CAB ADC targeting ROR2
  - Val/Cit protease cleavable linker
  - MMAE payload, DAR4

  - Granted Fast Track approval by the FDA for Recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN)

CAB Technology

CAB technology widens the therapeutic index

- Minimal changes in the CDRs
- Binding to exposed sites only within the acidic TME[1]
- CABs are not masked or caged by a blocking peptide
- Compatible with any format (naked mAb, ADC, bispecifics, CAR T)
- Designed to reduce on-target off-tumor toxicity by minimizing target-mediated drug disposition
- Increase MTD



Wildtype mAb

CAB mAb

Abbreviations: AE, adverse event; CAB, Conditionally Active Biologic; TME, tumor microenvironment.

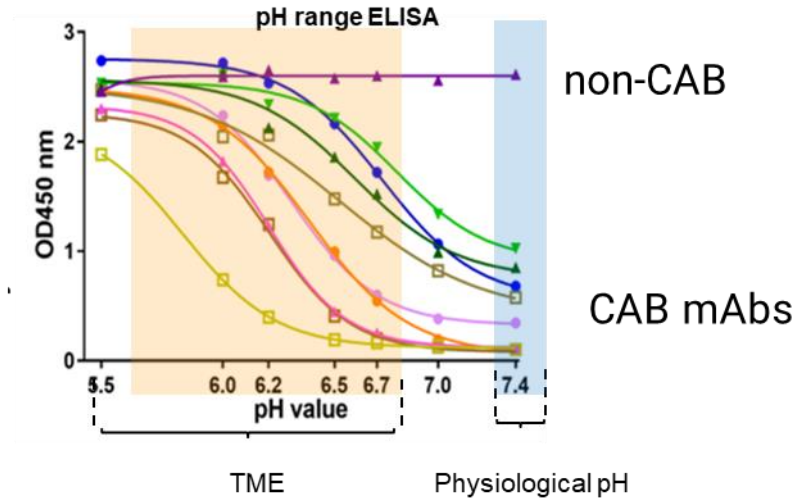
1) Chang HW, et al. *Proc Natl Acad Sci USA*. 2021;118(9):e2020606118.

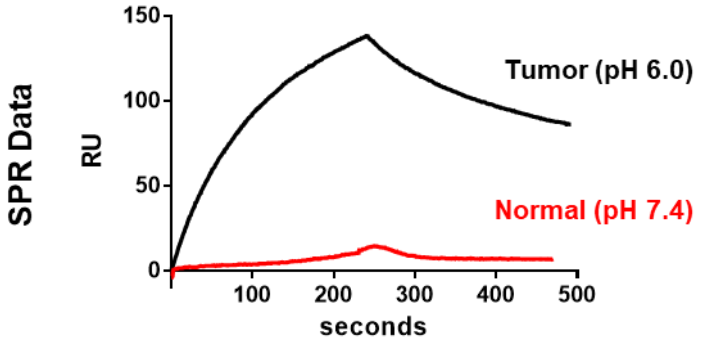
CABs Bind Selectively and Reversibly Based on the Cellular Microenvironment

pH selective binding

CAB antibody binds to target antigen under TME conditions

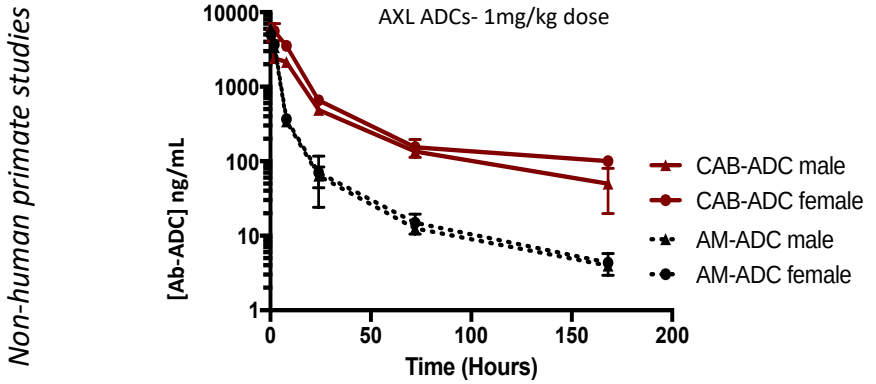
Adjustable CAB pH binding inflection point





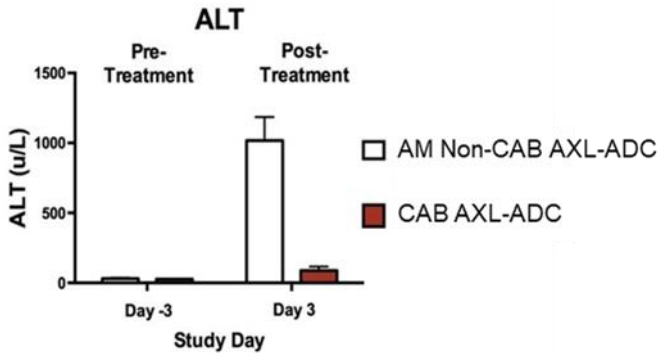
CAB enhances therapeutic exposure

CAB improves PK by eliminating Tissue Mediated Drug Disposition (TMDD) (lowers off-target tox)



CAB lowers liver toxicity, no on-target tox

CAB lowers liver ALT levels compared to affinity matched (AM) non-CAB-ADC

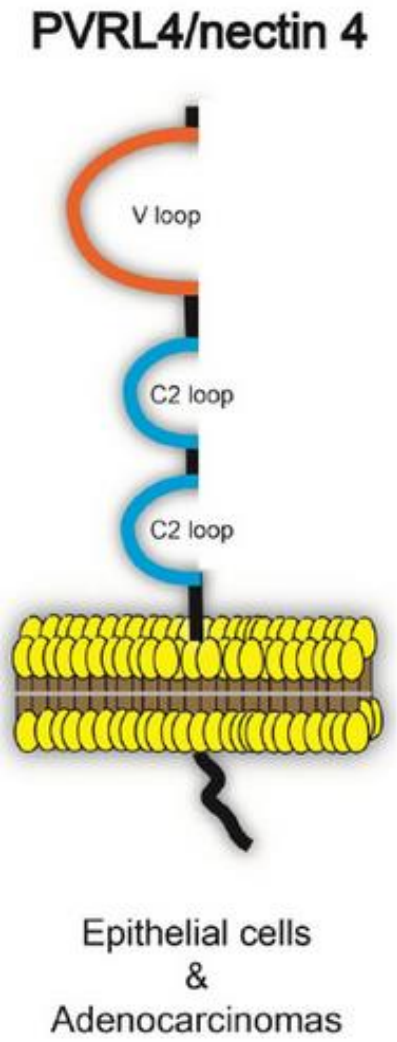


NextGen CAB ADC

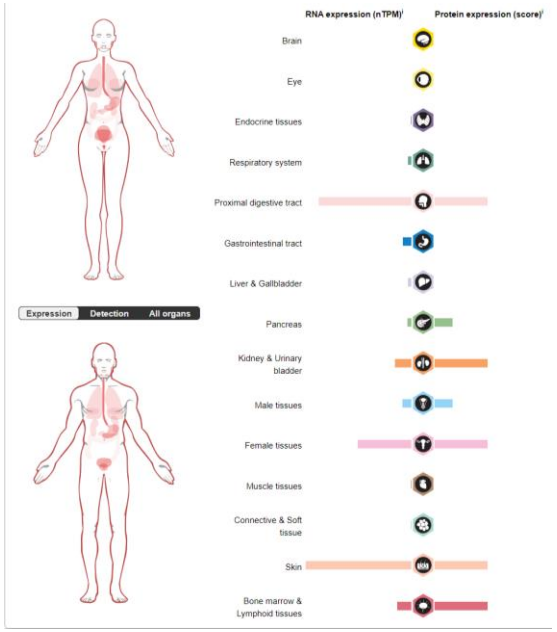
BA3361 (anti-Nectin4-ADC)

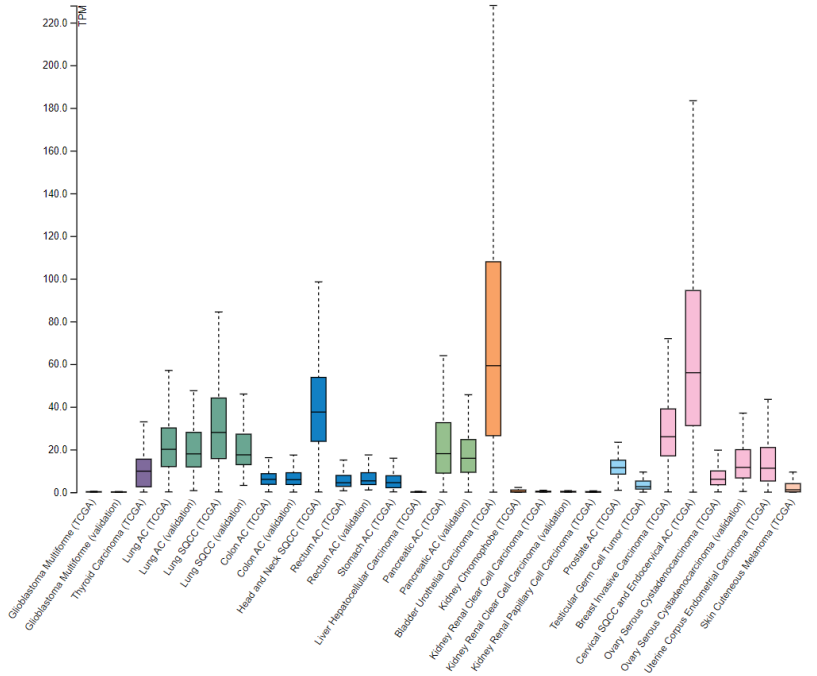
Nectin4

- Nectins and Nectin-like molecules (*e.g.* Trop2) are involved in Ca^{2+}-independent cell-cell adhesion.
- Nectins are ubiquitously expressed and play adhesive roles in a wide range of normal tissues.
- Nectin4 is a significant prognostic predictor in cancer and may have a mechanistic role in adenocarcinomas, such as pancreatic cancer.
- Enfortumab Vedotin (EV), approved as standard of care for urothelial cancer
- **BA3362:** First-in-class DualCAB Nectin4 T cell engager (TCE) licensed to Context Pharmaceuticals.



Nectin4 – Overexpression in Cancer





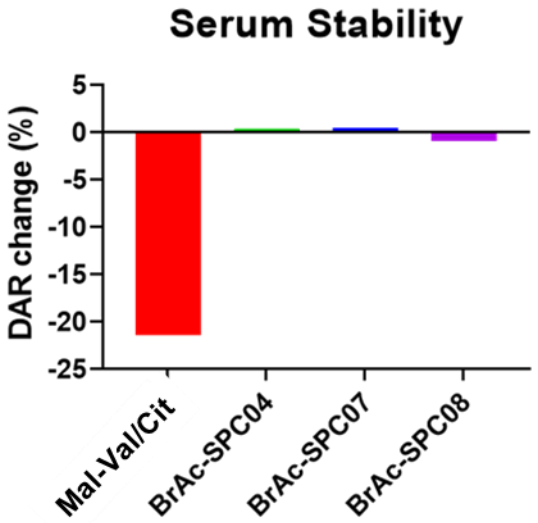
- Nectin4 expression in healthy tissue
  - Intestine
  - Kidney, Bladder
  - Breast, Ovaries, Cervix
  - Skin
  - Bone marrow and lymphoid tissue

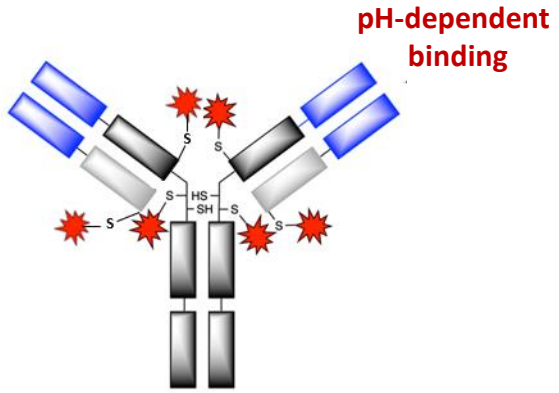
- Nectin4 over expression in Cancer
  - Bladder
  - Cervix
  - Head and Neck
  - Lung
  - Pancreas

BA3361 CAB-Nectin4 ADC

Molecule Summary

- Human IgG1/Kappa backbone
  - Conditional binding to Nectin4 in the TME
- Conjugation targeting interchain disulfides
  - Compatible with all molecules in the pipeline
  - Bromo-acetamide attachment group
- Serum Stability
  - Eliminate transfer of linker/payload to other proteins
  - No reduction of DAR
- Glycosidase cleavage
  - Glycosidases highly expressed in the lysosome
  - Improved payload delivery to the tumor
  - New linkers have increased solubility
  - Improves payload release in target cells
- Payload: MMAE (DAR6)
  - Bystander effect
  - Known side effects of released payload
  - CAB allows for higher/more frequent dosing





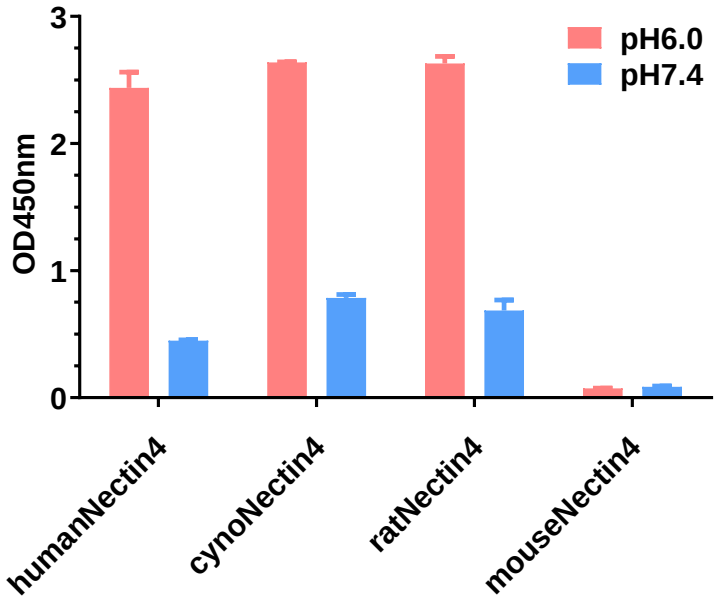
BA3361 CAB-Nectin4 ADC

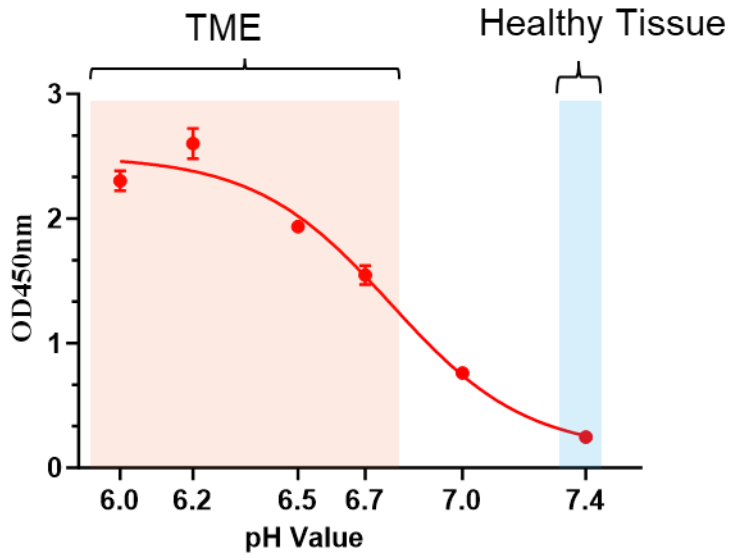
In vitro characterization

- pH Affinity ELISA
  - BA3361 cross reacts with cynomolgus monkey and rat Nectin 4
  - CAB shows similar pH-dependent binding across all three species

- pH Range ELISA
  - pH inflection point (50% binding) is at pH6.8
  - 90% binding occurs at pH6.3

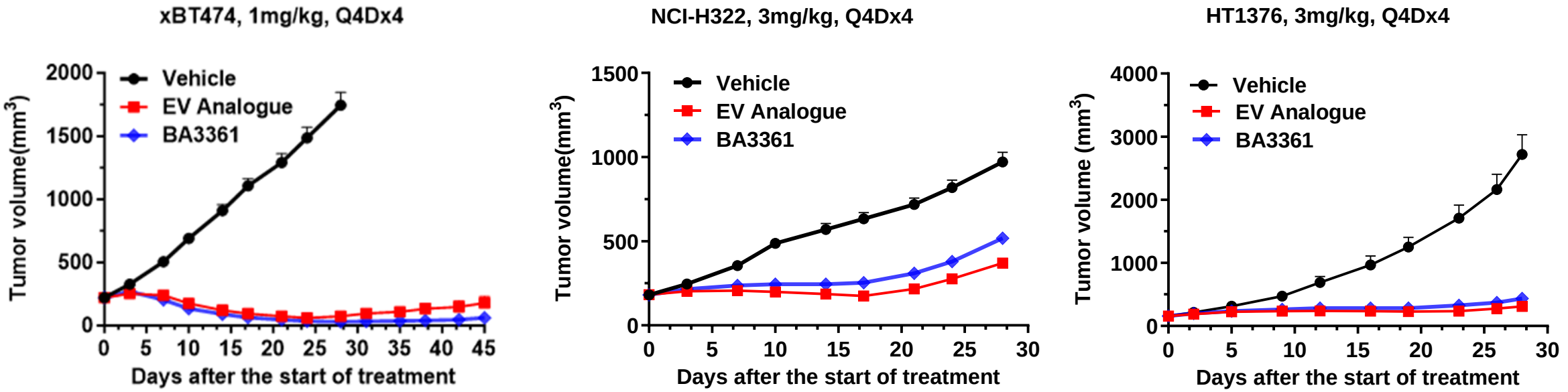
- pH-dependent Binding Kinetics by SPR
  - pH6.0: K_D= 0.19 nM
  - pH7.4: K_D= 1.13 nM





BA3361 CAB Nectin4 ADC

In vivo efficacy in cell line-derived xenograft models



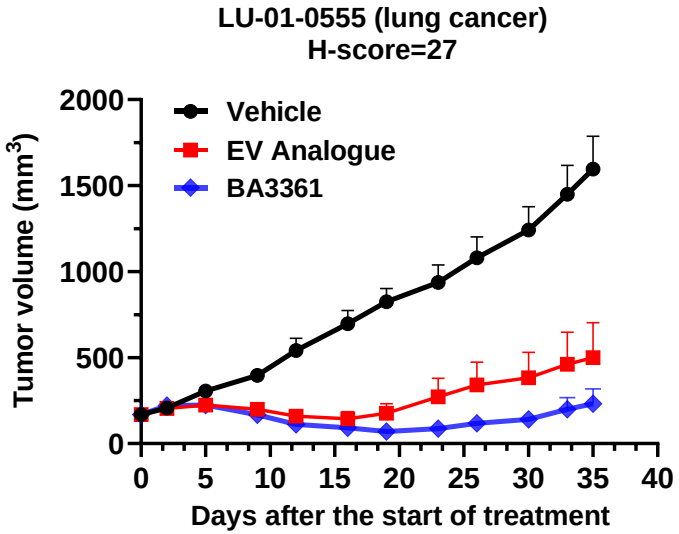
The *in vivo* efficacy of BA3361was evaluated using CDX models:
BT474 cells (breast cancer, left), NCI-H322 (lung cancer, middle) and HT1376 cells (bladder cancer, right).

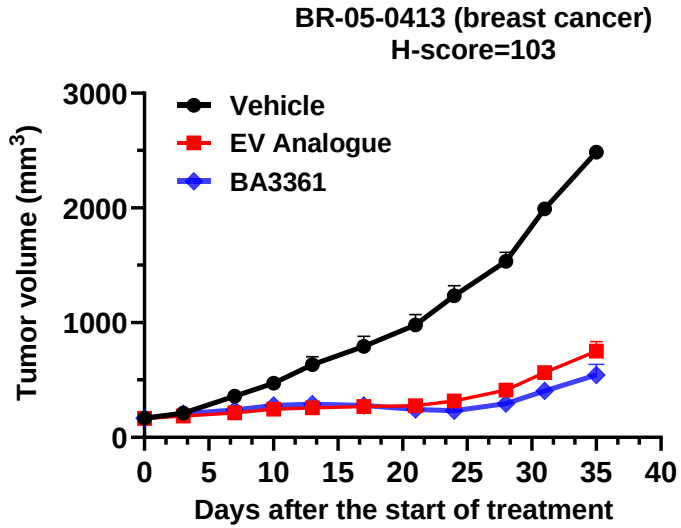
BA3361 demonstrated similar tumor regression compared to Enfortumab Vedotin analogue (EV Analogue) in these models.

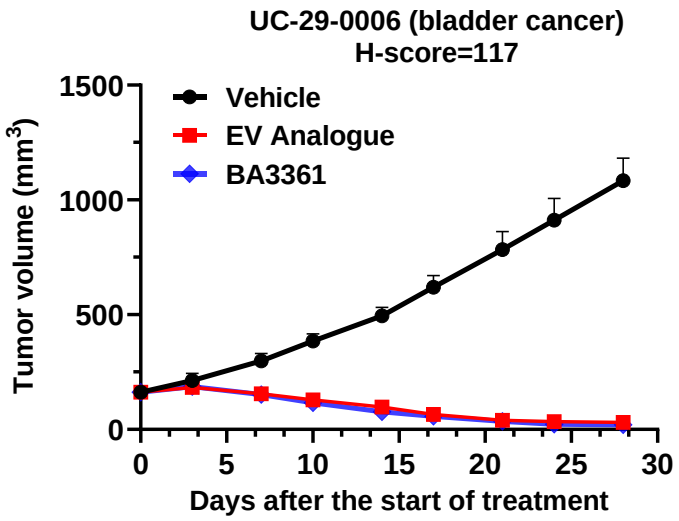
BA3361 CAB Nectin4 ADC

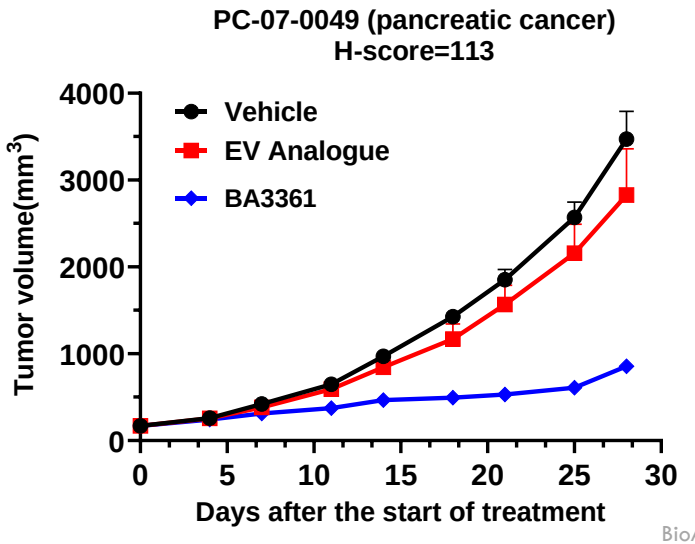
In vivo efficacy in PDX models

- BA3361 shows potent activity in all PDX models tested
- At lower Nectin4 expression levels (H-score ≤ 103), DAR6 has advantage over DAR4
- BA3361 exhibits similar or better activity in lung, bladder and breast cancer models compared to the EV analogue
- BA3361 demonstrates significantly better efficacy in the pancreatic cancer model compared to the EV Analogue







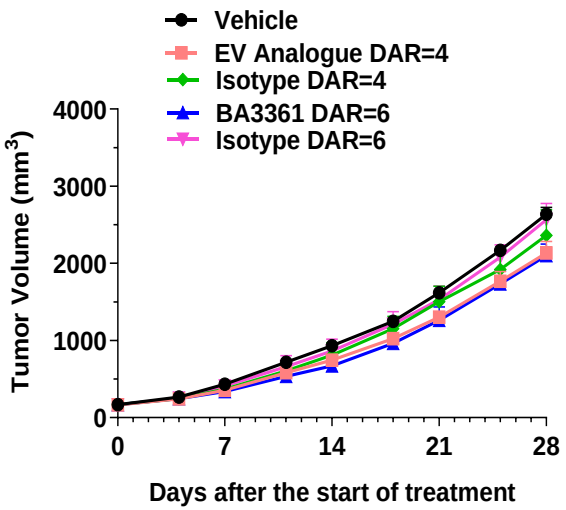


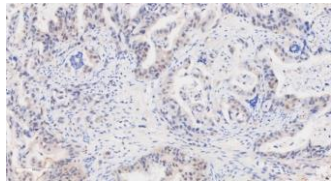
Dosing:3mg/kg
Q4Dx4

BA3361 CAB Nectin4 ADC

In vivo efficacy in pancreatic PDX models

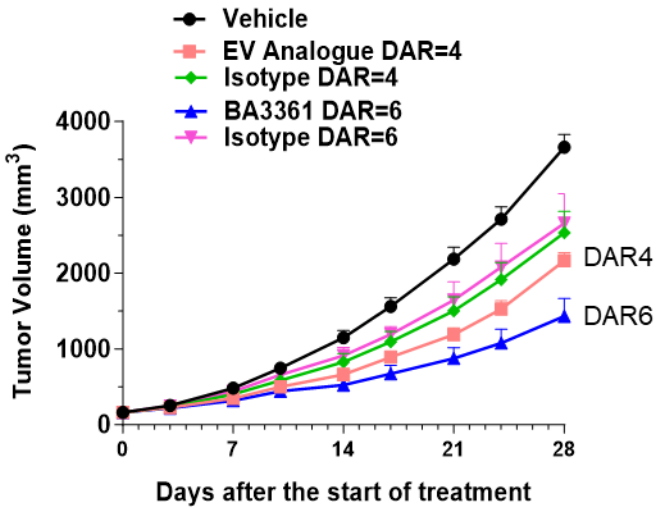
PC-07-0037
Nectin4 negative

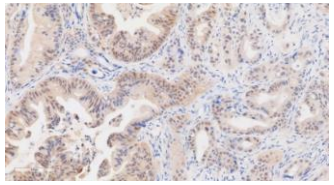




PC-07-0037 H-Score 13

PC-07-0038
Nectin4 low

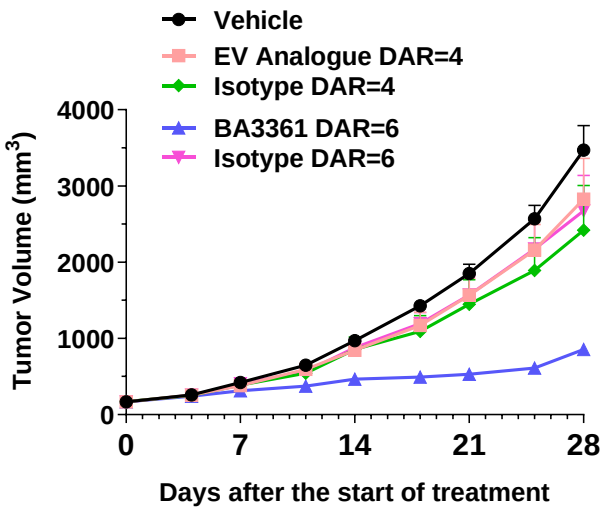


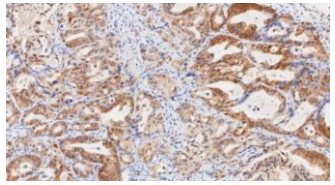


PC-07-0038 H-Score 36

Dosing for all models:
3mg/kg
Q4Dx4

PC-07-0049
Nectin4 high





PC-07-0049 H-Score 113

Representative images for Nectin4 IHC staining (clone EPR15613–68, #ab251110, Abcam)

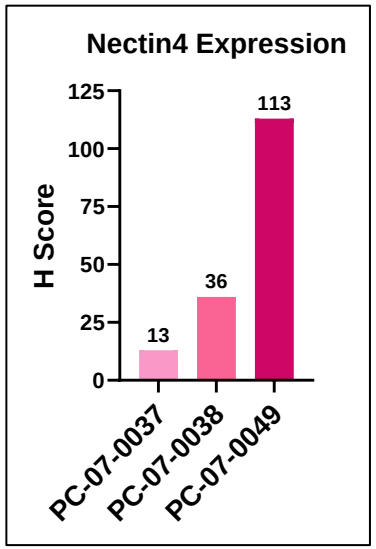
BA3361 activity is correlated with Nectin4 expression levels in pancreatic PDX models, while EV Analogue activity is not.

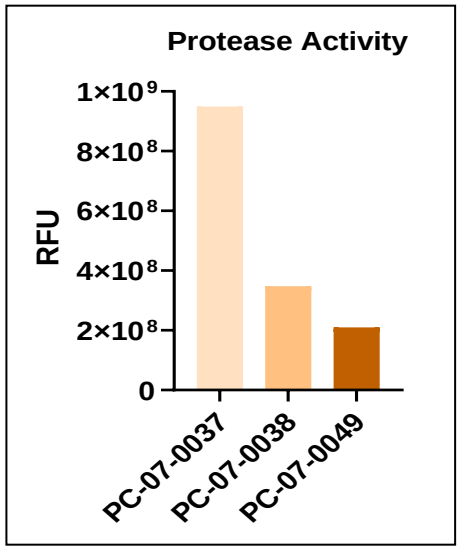
BA3361 CAB Nectin4 ADC

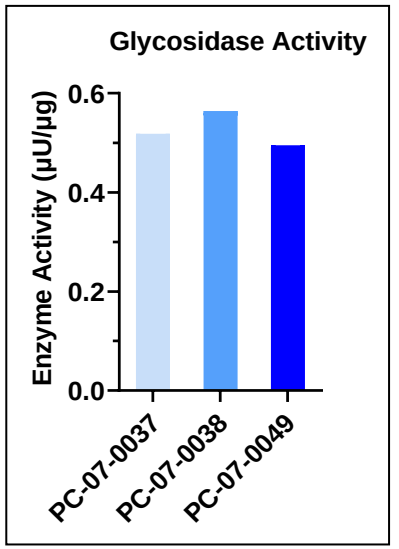
In vivo efficacy in pancreatic PDX models

Nectin4 expression levels (H-score)
0–14: negative
15–99: weak
100–199: moderate
200–300: strong

Klümper et al., Clin Cancer Res (2023)







Pancreatic cancer PDX models:

- Glycosidase activity is high in all three PDX models, as reported[1]
- Glycosidase activity is not correlated with Nectin4 expression level
- Protease activity is inversely correlated with Nectin4 expression level

- *In vivo* activity of BA3361 is correlated with Nectin4 expression

Table 1 Shows various glycosidase enzymes overexpressed in different cancer types

Glycosidase	Cancer type
β-Glucosidase	Breast,[11] gastric,[12] liver[13]
Glucosidase II	Lung,[14] bladder,[15] gastric,[16] melanoma[17]
N-Acetyl-β-D-glucosaminidase	Ovarian,[18] liver,[19] leukemia,[19] thyroid,[20] breast[21]
α-Glucosidase	Liver,[19] leukemia[19]
β-Galactosidase	Liver,[19] ovarian,[22] prostate,[23] colon,[24] breast,[24] gliomas[25]
β-Glucuronidase	Lung,[26] breast,[27] ovarian,[28] pancreatic,[29] colorectal[30]
α-Mannosidase	Breast,[31] cervical,[32] clear cell renal carcinoma[33]
β-Mannosidase	Liver,[19] leukemia[19]
α-Fucosidase	Ovarian,[18] gliomas,[25] colon,[34] pancreatic[34]

Martin et al., Chem Soc Rev (2022) Vol. 51 Issue 23 Pages 9694-9716

NextGen CAB ADCs

Summary

- NextGen CAB ADC platform
  - Minimizes off-tumor, on-target toxicity (CAB via elimination of TMDD)
  - Increased tolerability
  - Increased MTD
  - Significantly improved serum stability
  - Enhanced hydrophilicity, allowing for a higher DAR
  - Adaptable to different linkers and payloads

- CAB Nectin4 ADC (BA3361)
  - IND approved in 1H/2024
  - Similar efficacy to EV in bladder, breast, and lung cancer models
  - Superior efficacy to EV in pancreatic cancer models
  - Glycosidase-sensitive linker broadens the number of potential clinical indications
  - Clinical trials to start soon