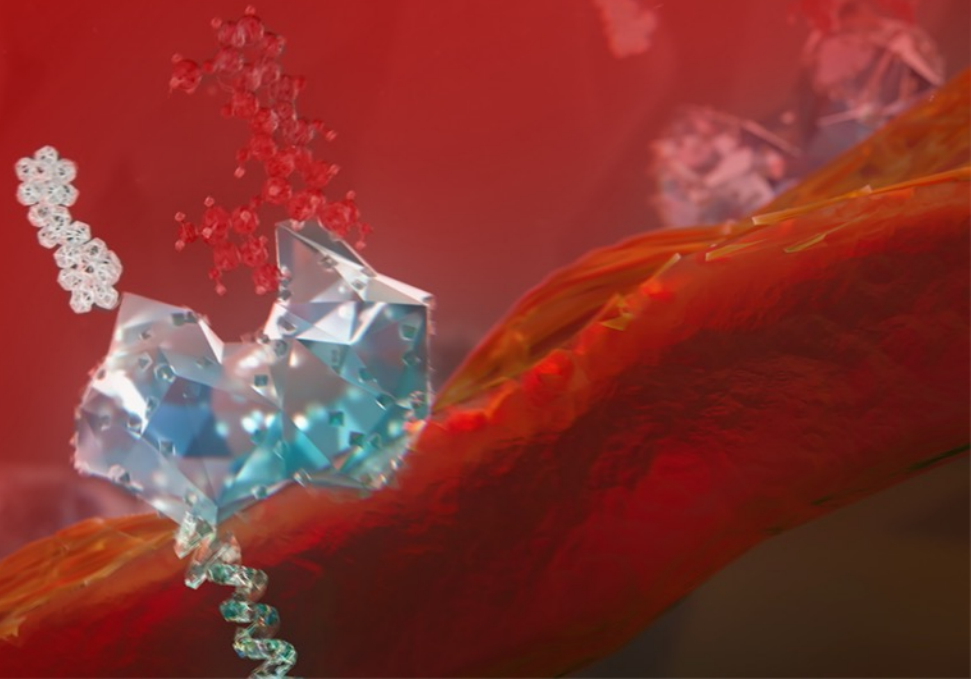
Avacta®

Targeting the Tumor Microenvironment

Avacta Therapeutics

June 2024



Avacta is challenging the current drug delivery models to expand the reach of highly potent therapeutics using peptide drug conjugates

REVOLUTIONARY
Approach

Avacta leverages a key protease (**fibroblast activation protein-α, FAP**) in the TME as a tumor-specific release mechanism enabling delivery of potent warheads directly to the TME with clinical POC achieved

ROBUST
Pipeline

The **FAP-enabled drug release mechanism** is used in small molecule peptide drug conjugates (**PDC**) and biologic-targeted approaches in the **pre|CISION™ ADC** and **Affimer™ -DC** (**AffDC**) programs

INNOVATIVE
R&D team

The R&D leadership team have >15 years industry experience each, **over 40 INDs and drug approvals**, with expertise in cancer biology, chemistry, clinical, and business development

The Avacta Therapeutics Research and Development Team

Christina Coughlin, MD, PhD

Chief Executive Officer and Head of R&D

Chris is an oncologist and immunologist, trained at the University of Pennsylvania

She has >18 years of industry experience including >30 oncology INDs and approvals across small molecules to cell therapy in oncology

Simon Bennett, DPhil

Chief Business Officer

Simon is a biochemist with more than 26 years' commercial experience in biopharmaceuticals, supporting business development and corporate development

Simon has been involved in over 80 commercial deals across geographies

Karen Harrison, MBA

Chief Operating Officer

Karen has >30 years' experience in building successful teams and delivering all operational aspects of her teams

Karen's focus is on value creation and global reach of companies, delivering transformational operational planning

David Jones, DPhil

VP and Head of Biology

David trained at the University of Birmingham in the science of oncology modeling with expertise in both *in vitro* and *in vivo* modeling of cancer biology

David has worked in models of human disease with more than 15 years' industry experience

Francis Wilson, DPhil

VP and Head of Chemistry

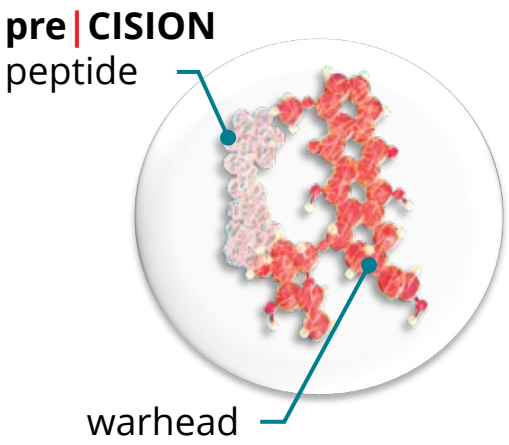
Francis trained in medicinal chemistry at Oxford University

Francis has >30 years' experience in industry with multiple companies and programs advanced across multiple therapeutic areas including the science of biologic-small molecule conjugations

Avacta is Combining Two Innovations to Deliver Potent Warheads to the TME

pre|CISION™ technology

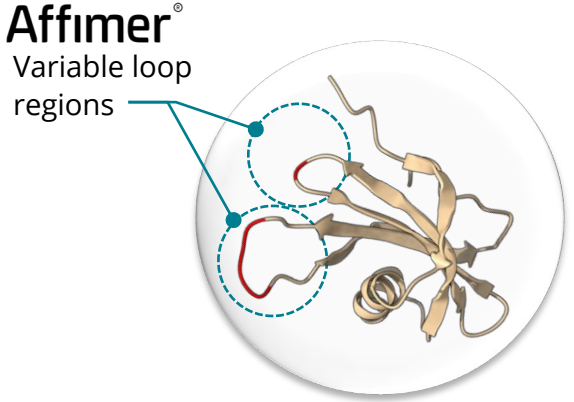
The pre|CISION peptide prevents cellular entry of the warhead and is only released in the TME



The **pre|CISION™** platform enables first-in-class **peptide drug conjugates (PDC)** that boost efficacy and minimize off-target toxicity with clinical proof-of-concept

Affimer® technology

Next-generation biotherapeutic class to surpass the limitations of antibody cancer therapies



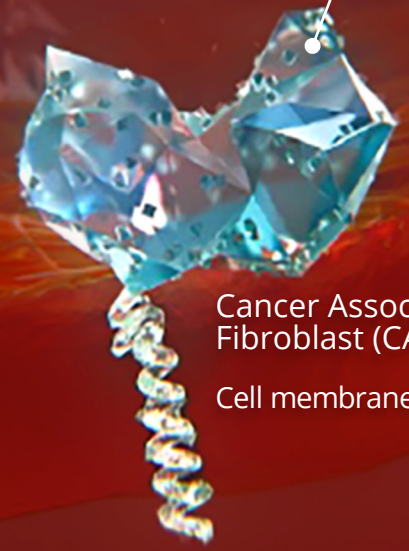
Affimers® are a novel class of biologics, based on the Stefin A protein, with a best-in-class **therapeutic protein binder** at 1/10th the size of an mAb

Next-gen pre|CISION ADC therapeutics

Combining the highly tumor-specific release mechanism of **pre|CISION** with the biologic advantages of an **Affimer** create a novel class of **Affimer Drug Conjugates**

FAP is the Ideal Tumor-Selective Enzyme that can be Leveraged to Deliver Warheads to the TME

FIBROBLAST ACTIVATION PROTEIN-α (FAP)



Cancer Associated Fibroblast (CAF)

Cell membrane

FAP is an enzyme selectively expressed in human cancers[1]

Member of the **DASH family of serine proteases[2,3]**, **which are not specific to tumor tissue** which includes:

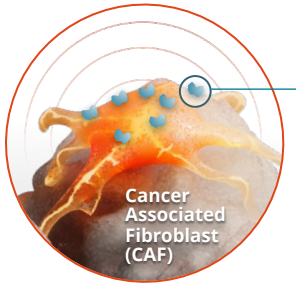
DPP-IV (DPP4)	**DPPII (DPP2)**	**DPP8**	**DPP9**	**Prolyl Endopeptidase** (PREP)

FAP is found on the cell surface of **cancer-associated fibroblasts (CAF) in the TME** and on the tumor cell membrane in some cases

Over-expression of FAP in the TME is associated with **poor prognosis**: increased metastasis and lower overall survival[3]

[1] Gorrell MD, et al. Structure and function in dipeptidyl peptidase IV and related proteins. Adv Exp Med Biol. 2006;575:45-54. Epub 2006/05/17. doi: 10.1007/0-387-32824-6_5 | [2].Rosenblum JS, et al.. Prolyl peptidases: a serine protease subfamily with high potential for drug discovery. Current opinion in chemical biology. 2003;7(4):496-504.. doi: S136759310300084X [pii]. | [3]. Liu F, et al. Fibroblast activation protein overexpression and clinical implications in solid tumours: a meta-analysis. PLoS One. 2015;10(3):e0116683. doi: 10.1371/journal.pone.0116683. PMID: 25775399; PMCID:

FAP-Targeted Therapies Will Reach a Broad Patient Population With High Unmet Need



FAP

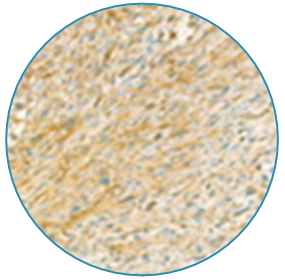
A **cell surface protease** upregulated in many solid tumors **predicts poor prognosis**

The **pre|CISION™ platform** leverages this tumor-specificity by linking a FAP-cleavable peptide substrate to a cytotoxic warhead, preventing cell entry

The cleavage of the pre|CISION™ peptide is **highly specific to FAP** and not cleaved by any other human enzyme

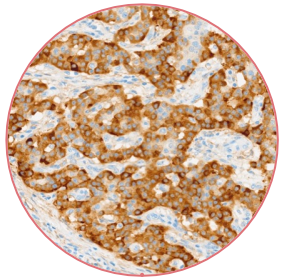
FAP expression is easily quantified by standard IHC methods and FAPI-PET imaging in the clinic

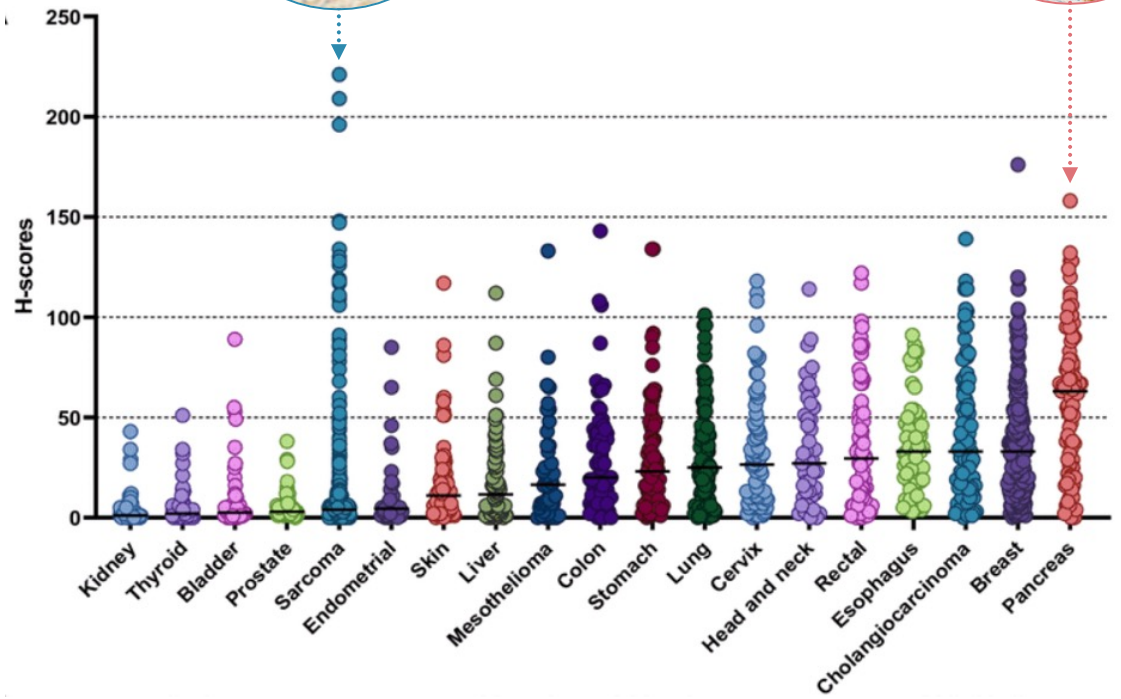
UPS
Undifferentiated pleomorphic Sarcoma



Immunohistochemistry using a monoclonal antibody recognizing FAP with robust expression across multiple tumor types

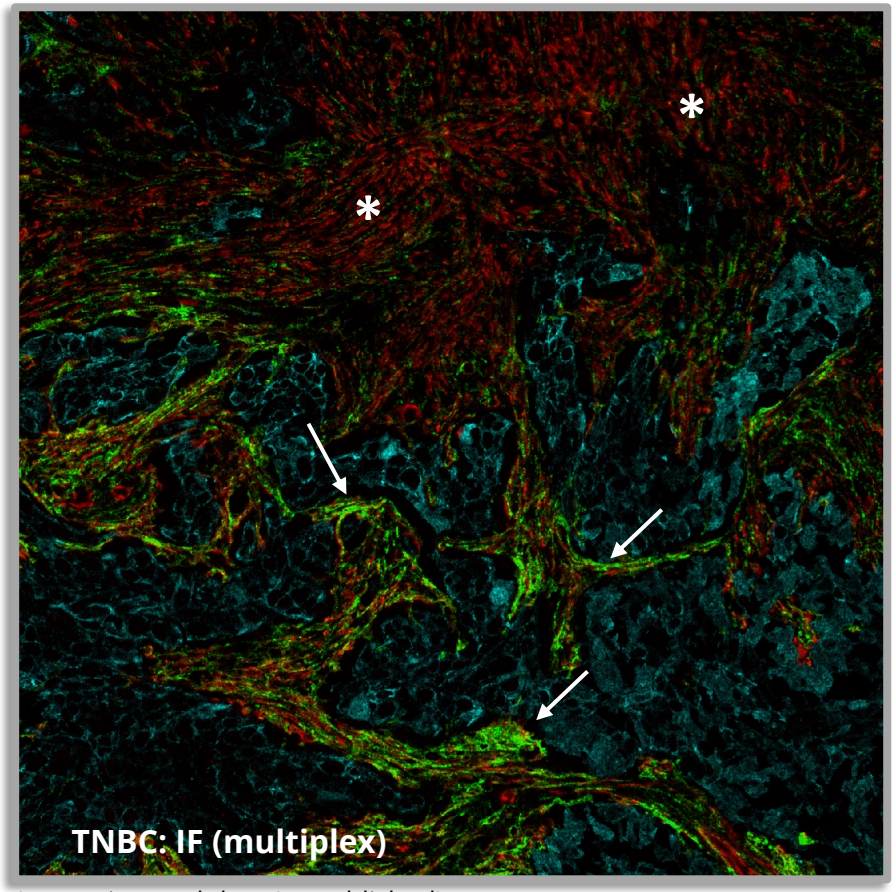
PDAC
Pancreatic ductal Adenocarcinoma

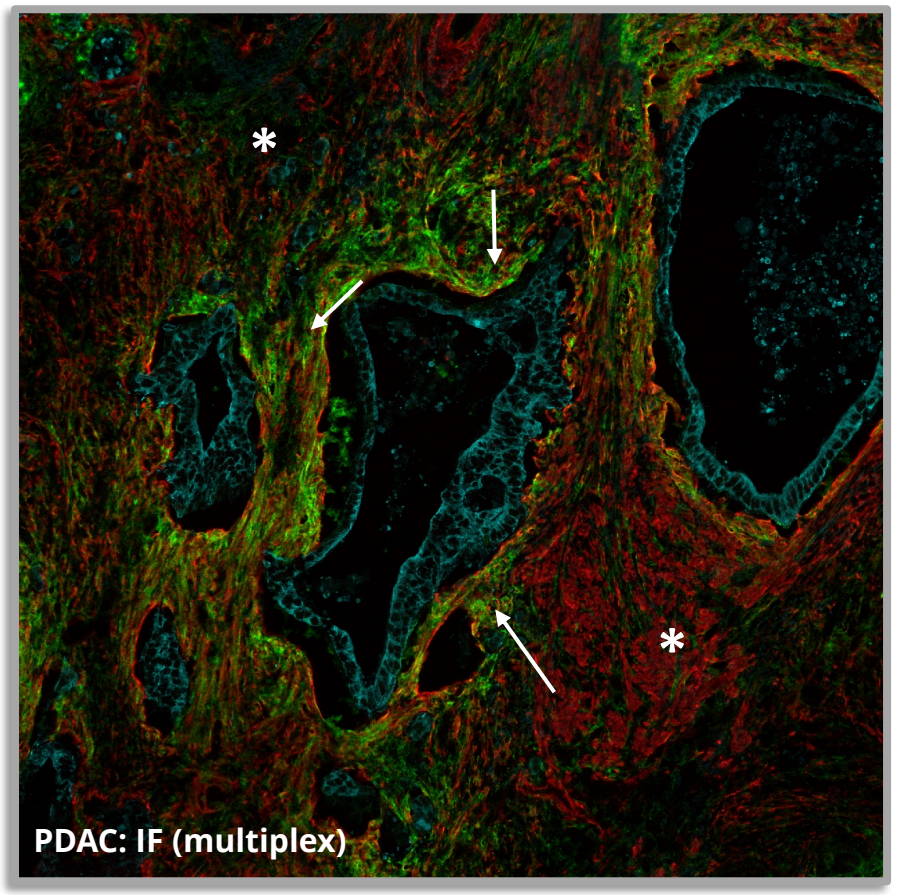




1. Kessler L, et al. J Nucl Med. 2022 Jan;63(1):89-95. doi: 10.2967/jnumed.121.262096 | 2. Cohen SJ et al. 2008 Pancreas 37(2):154-158 DOI: 10.1097/MPA.0b013e31816618c | 3. Zboralski, D et al. Eur J Nuc Med Mol Imaging 2022. 49. 10.1007/s00259-022-05842-5 | 4. Warli SM,. World J Oncol. 2023;14(2):145-149. doi: 10.14740/wjon1564 | 5. Kawase T, et al. BMC Gastroenterol. 2015;15:109. doi: 10.1186/s12876-015-0340-0

The Spatial Organization of the FAP+ CAF in the Tumor Optimizes Warhead Delivery





Avacta, internal data (unpublished)

FAP expression is **highest at the tumor-stroma interface** (arrows) with lower expression in the distal cancer associated fibroblasts (CAF) population (asterisks)

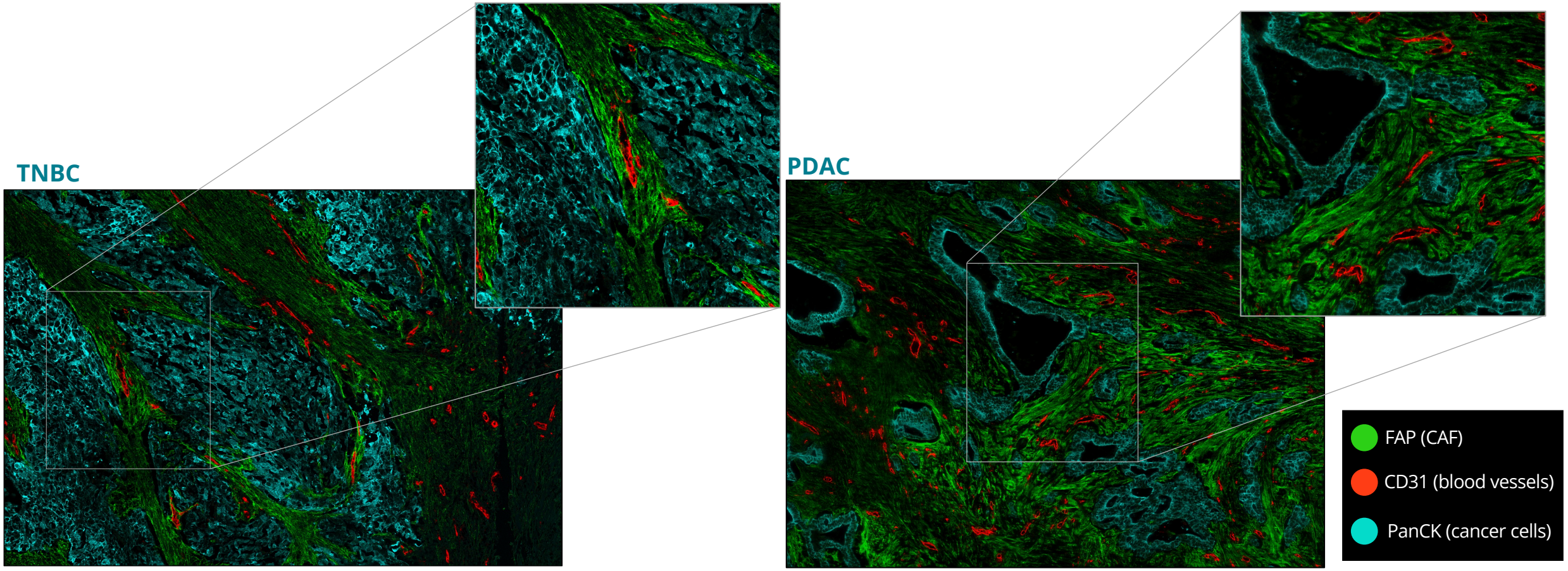
- **Pan-cytokeratin (tumor cells)**
- **Alpha-smooth muscle actin (CAF)**
- **FAP (CAF)**

FAP is overexpressed at the tumor-stroma interface

Triple negative breast cancer (TNBC) and **pancreatic ductal adenocarcinoma (PDAC)** are indications with known high FAP expression in multiple studies^

^ Dziadek S, . Comprehensive analysis of fibroblast activation protein expression across 23 tumor indications: insights for biomarker development in cancer immunotherapies. Front Immunol. 2024;15:1352615. doi: 10.3389/fimmu.2024.1352615

The Subset of CAFs with High FAP Expression are Localized with Tumor Cells and Vessels



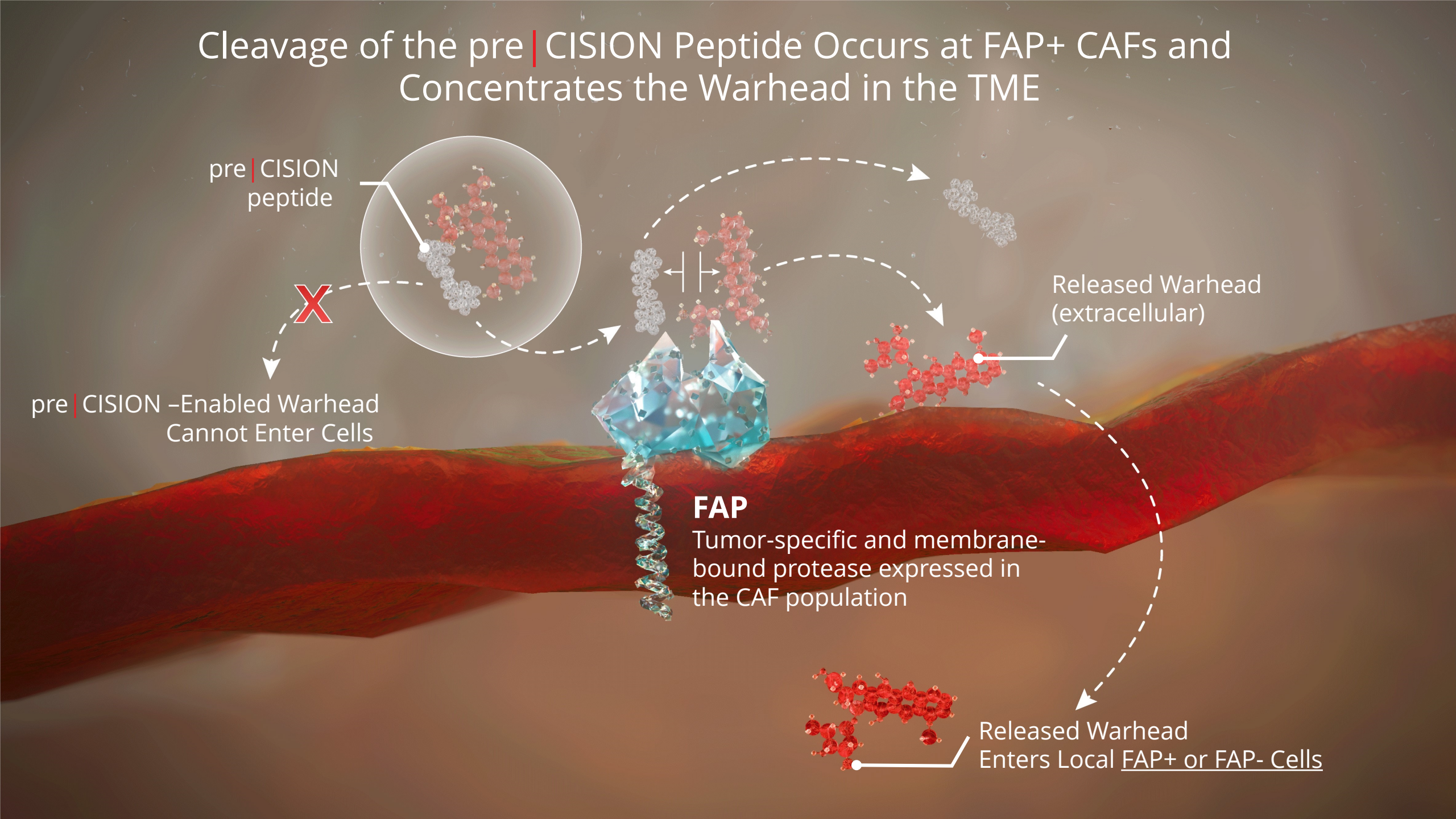
Avacta, internal data (unpublished)

Co-localization of vessels, FAP+ CAFs and tumor cells

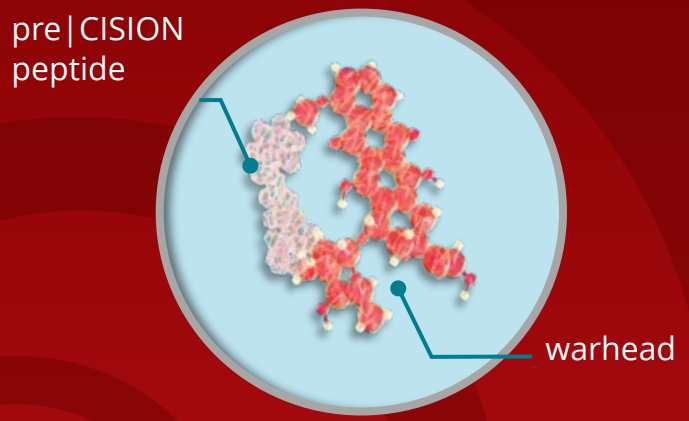
The close proximity of vessels, FAP+ CAFs, and cancer cells, allows **pre|CISION enabled warheads** to be readily delivered, cleaved, and taken up in the TME

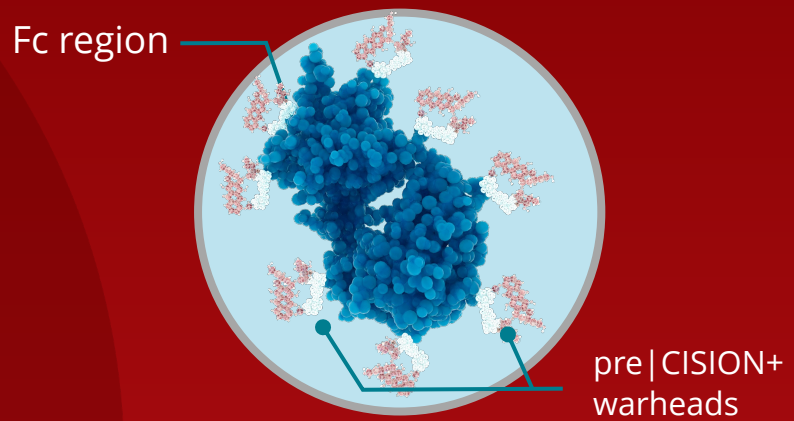
pre | CISION Delivery

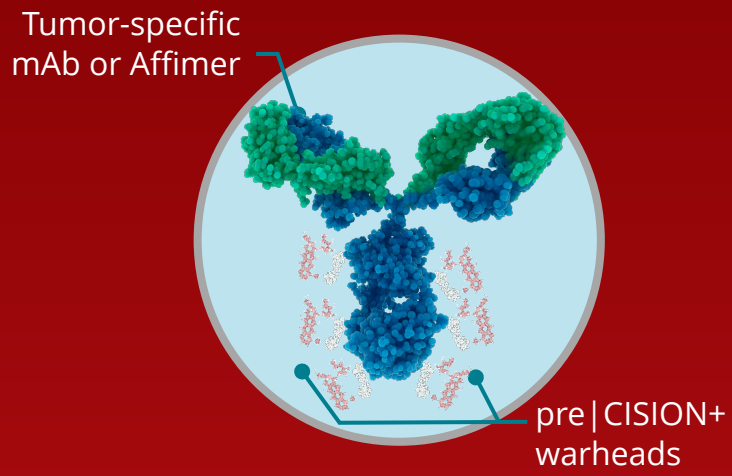
Cleavage of the pre|CISION Peptide Occurs at FAP+ CAFs and Concentrates the Warhead in the TME



Avacta is Targeting Highly Toxic Warheads to the TME by Leveraging Tumor-Selective FAP Expression







pre|CISION
peptide drug conjugate (PDC)

$t_{1/2}$: minutes to hours

The warhead is linked to a **peptide specifically cleaved by FAP** which prevents cell entry until released by FAP in the extracellular TME

Lead program: AVA6000

pre|CISION +
Half-life optimized drug conjugate

$t_{1/2}$: ~hours - days

The peptide-warhead conjugate is **linked to the Fc region**, producing a pre|CISION™ molecule with **prolonged half-life and DAR~10**

pre|CISION ADC
antibody/Affimer drug conjugate (AffDC)

$t_{1/2}$: ~days - weeks

The peptide-warhead conjugate is linked to a tumour antigen-targeted **monoclonal antibody or Affimer**, creating a highly **tumor-specific ADC**

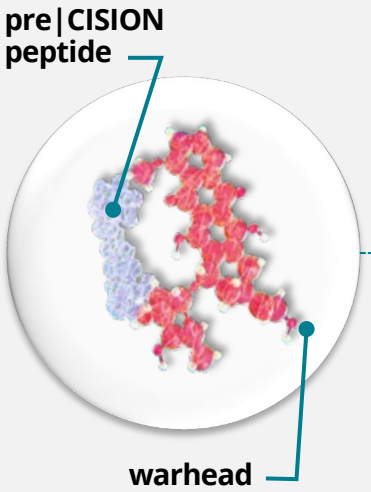
PDC and Affimer-DC Have Key Advantages Over Traditional ADC Approaches

	PDC	AffDC	ADC
	Avacta **Peptide Drug Conjugate** v.	Avacta **Affimer Drug Conjugate** v.	Traditional **Antibody Drug Conjugate**
Mechanism of action	***Extracellular warhead release*** with limited systemic exposure Rapid internalization in FAP+ and FAP- cells		Warhead released ***intracellularly after internalization*** Antigen negative tumor cell killing relies on the bystander effect
Location of warhead activation	Extracellular in the TME, optimizing the ***bystander effect***		Intracellular with internalization of the ADC complex necessary
Linker	***Tumor-specific warhead release*** by FAP peptide cleavage		Non-specific release where proteases available contributes to warhead toxicity (e.g. lung toxicity)
Drug-to-Antibody/ Affimer ratio	**1:1** Drug : Peptide	**2-6:1** Drug : Affimer	**4-8** Drug : Antibody needed to deliver quantity of warhead
Manufacturing	Small molecule timelines and costs of manufacturing	Thermally stable, low mW Affimers (~14 kDa) with simpler conjugation leads to shorter timelines and lower cost	Complex conjugations methods and costs of manufacture of both mAb (~150 kDa) and drug-linker complex

Design of **pre|CISION** FAP-Enabled Warheads: Optimizing Local TME Delivery

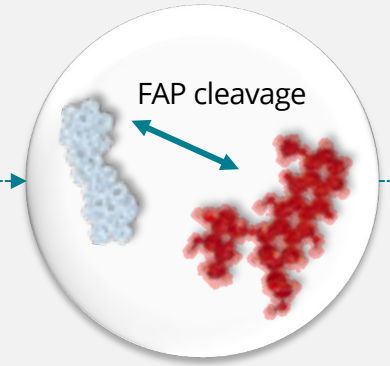
Warhead-peptide conjugation

Specific site conjugation of the dipeptide to enable FAP-specific cleavage and **active warhead release**



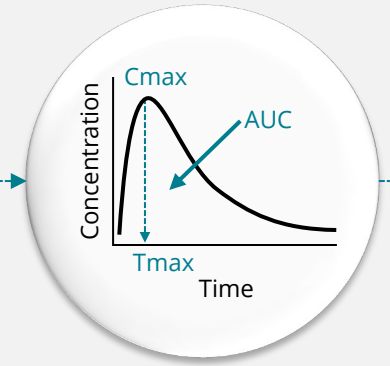
Structure-activity relationship

Optimize the SAR of pre|CISION warheads with **efficiency of FAP recognition** to permit membrane bound FAP cleavage (kcat/Km)



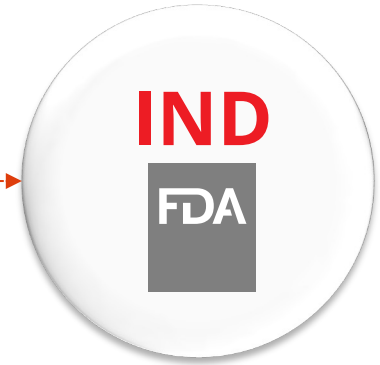
In vivo pharmacokinetic modulation

The **PK of the pre|CISION enabled warhead** can be optimized via small molecule approaches or biologic conjugation



In vitro/*in vivo* characterization

Demonstrate preclinical efficacy and safety in wide **range of FAP tumor expression models** with **low serum FAP** to recapitulate the human condition



FAP-Enabled Warheads are Engineered Based on the Desired Release Kinetics

A pre|CISION enabled warhead has two key properties:

1 **Precise cleavage** of the conjugate by FAP

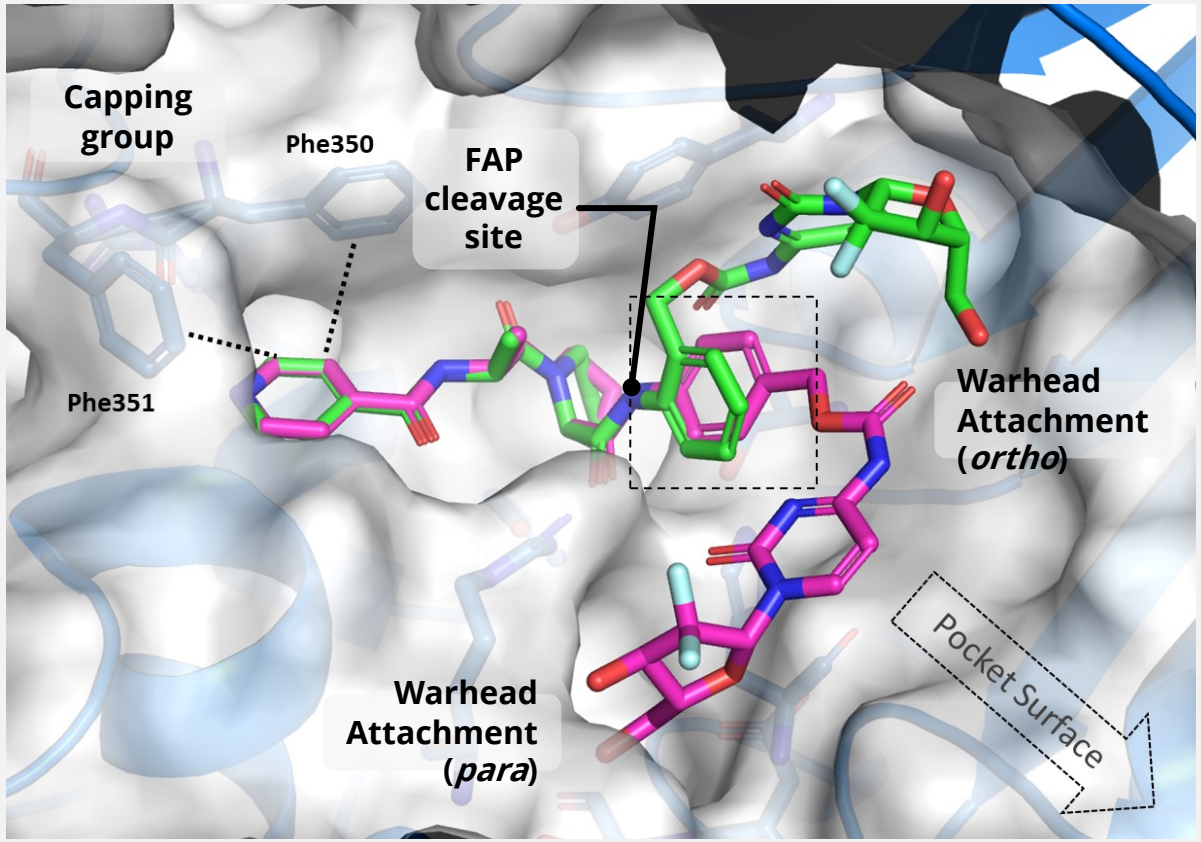
2 **Lack of cellular entry** of the conjugated molecule

In vitro cytotoxicity studies are used to determine **FAP-enablement**

- Varying the efficiency (kcat/Km) of the molecule is achieved with different spacer and cap groups
- The design of the molecule is based on how each warhead is linked to and released from the peptide
- Chemistry of FAP-enablement has been delineated using multiple tool warheads

A docking model of the FAP enzyme

is used to understand the release of the warhead and peptide based on the different chemistry of the spacer and cap groups



AVA6000 Clinical asset 1: FAP-enabled doxorubicin

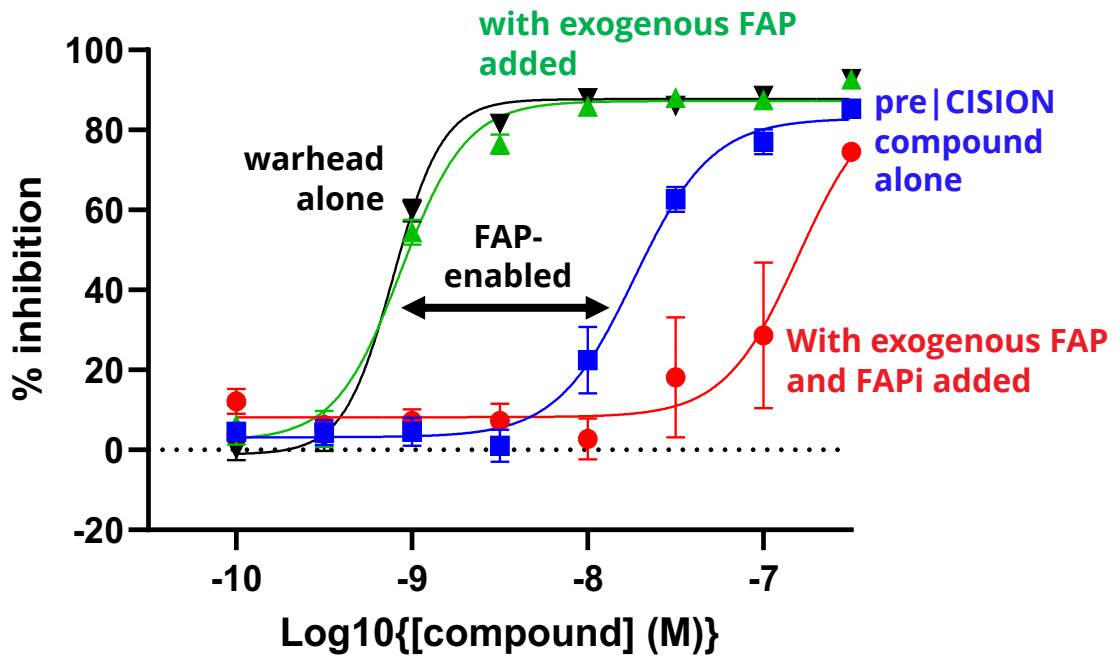
pre|CISION: Modulating the FAP Enzyme Efficiency Adjusts the Rate of Warhead Release

Modulating warhead delivery with pre|CISION

FAP Enzyme Efficiency *(kcat/Km)* = **Rate of warhead cleavage** *(Tumor PK)*

- A **pre|CISION-enabled** drug can be released more quickly or slowly based on enzyme efficiency (kcat/Km)
- Higher kcat/Km indicates a pre|CISION drug with **higher enzyme efficiency** – i.e. higher turnover in the setting of limited substrate
- Both aspects can be engineered into the design of the molecule via the capping and spacer groups

In vitro cell killing curves in four conditions



pre|CISION designs both the **efficiency** and **rate** of warhead release

Cytotoxic warheads require higher efficiency/clearance to deliver intermittent high level in the TME v. **immunotherapy warheads** that are optimal with lower efficiency and slow clearance for sustained TME exposure

AVA6000: FAP-ENABLED DOXORUBICIN KEY FINDINGS IN PHASE 1

AVA6000 delivers **high concentrations of doxorubicin to the TME** relative to plasma, resulting in significant antitumor activity in patients whose tumors have over-expression of FAP

Exposure-response modeling suggests that released doxorubicin is generated primarily by **cleavage in the TME** as opposed to soluble FAP in the bloodstream leading to a distinctly favorable safety profile

pre|CISION-enabled (peptide drug conjugated) doxorubicin in AVA6000 results in a **robust widening of the therapeutic index**

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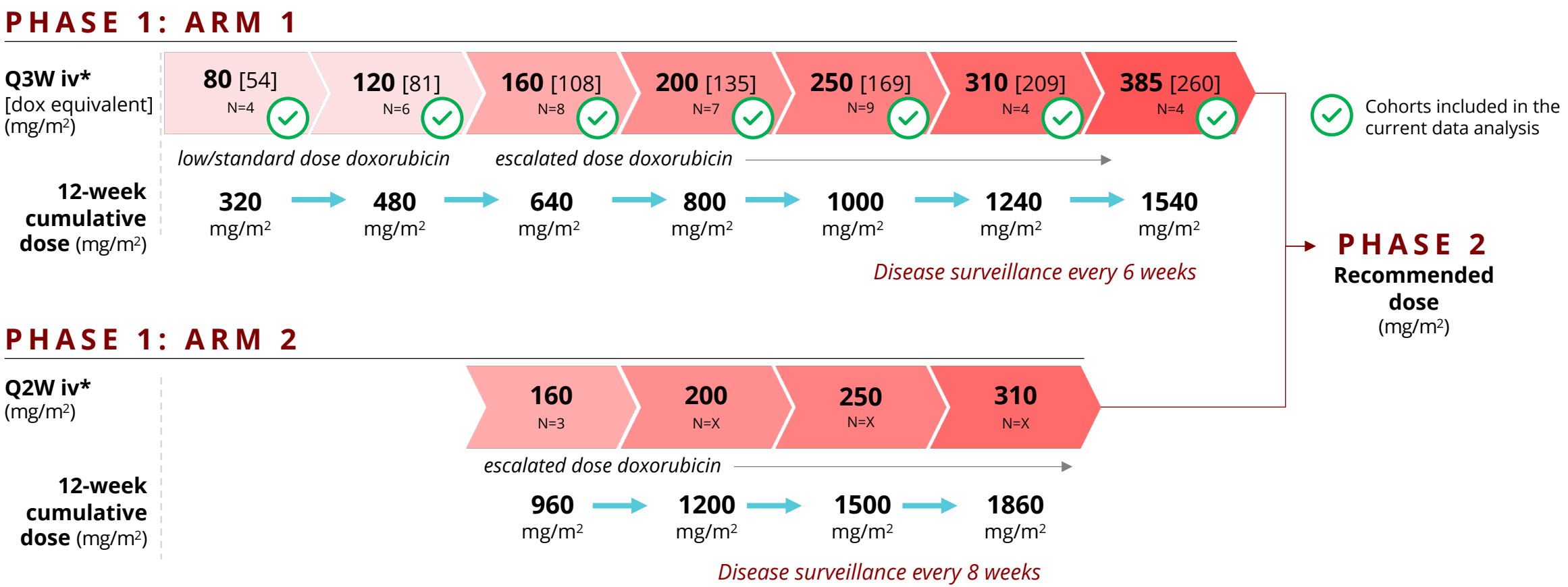
AVA6000 (FAP-Enabled Doxorubicin): Phase 1 Trial Design



PHASE 1: PATIENT POPULATION

- Patients with a diagnosis of known FAP^{high} cancers, including sarcoma, pancreatic cancer, colorectal cancer, head and neck cancers
- Acceptable performance status (ECOG 0 or 1), adequate organ function and recovery from prior therapy
- Prior therapy with any anthracycline was limited to total cumulative dose of less than 350 mg/m^2

AVA6000 Phase 1 Arm 1 (Q3W Dosing) Population Baseline Characteristics

	AVA6000 (80–385 mg/m^2 Q3W) N=42
Age, median (range)	64.5 (30-79)
Sex, m/f, n (%)	26 / 16 (61.9/38.1)
ECOG, 0/1. n (%)	14 / 28 (33.3/66.7)
Race	
White, n (%)	34 (81.0)
Asian, n (%)	3 (7.1)
Black or African American, n (%)	1 (2.4)
Other/Not reported, n (%)	4 (9.5)
Ethnicity	
Hispanic/Latino, n (%)	0
Non-Hispanic, non-Latino, n (%)	39 (92.9)
Not reported/unknown, n (%)	3 (7.1)

	AVA6000 (80–385 mg/m^2 Q3W) N=42
Cancer Diagnosis	
Soft tissue sarcoma, n (%)	14 (33.3)
Colorectal carcinoma, n (%)	11 (26.2)
Pancreatic ductal adenocarcinoma, n (%)	8 (19.0)
Cancers of the biliary tract, n (%)	3 (7.1)
Other[1], n (%)	6 (14.3)[1]
Prior cancer therapy	
No. prior regimens, median (range)	3 (0-7)
Any cytotoxic exposure, n (%)	32 (76.2)
Anthracycline exposure, n (%)	1 (2.4)
Platinum exposure, n (%)	26 (61.9)
Topoisomerase I inhibitor exposure, n (%)	20 (47.6)
Immunotherapy exposure, n (%)	14 (33.3)

[1] Cancer types in Other category include (n=1 each): non-small cell lung cancer, prostate cancer, transitional cell cancer of the urethra, ovarian carcinoma, lung cancer (not other wise specified), esophageal cancer

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FAP-enabled Doxorubicin (AVA6000) Has Significantly Reduced the Severe Toxicities

Adverse event	80 mg/m2 Q3W n (%) N=4	120 mg/m2 Q3W n (%) N=6	160 mg/m2 Q3W n (%) N=8	200 mg/m2 Q3W n (%) N=7	250 mg/m2 Q3W n (%) N=9	310mg/m2 Q3W n (%) N=4	385 mg/m2 Q3W n (%) N=4	Total Q3W n (%) N=42	Doxorubicin (75 mg/m^2 Q3W) N=251 Gr 3-4^ n (%)
Neutropenia	0	0	0	2 (29)	2 (22)	1 (25)	2 (50)	7 (16.7)	122 (49)
Leukopenia	0	0	0	0	0	1 (25)	2 (50)	3 (7.1)	59 (23.7)
Febrile neutropenia	0	0	0	0	0	0	0	0	41 (16.5)
Anemia	0	0	0	1 (14)	0	2 (50)	0	3 (7.1)	31 (12.4)
Thrombocytopenia	0	0	0	1 (14)	1 (11)	0	0	2 (4.8)	21 (8.4)
Fatigue	0	0	0	0	0	1 (25)	0	1 (2.4)	12 (4.8)
Lymphopenia	0	0	1 (13)	1 (14)	0	0	0	2 (4.8)	7 (2.8)
Mucositis	0	0	1 (13)	0	0	0	0	1 (2.4)	7 (2.8)

Data cutoff 11 March 2024)

^Tap, WD *et al.* 2020. Phase 3 trial of olaratumumab with doxorubicin in patients with STS. Data reported from doxorubicin mono arm Grade 3-4 events observed in at least 7 patients

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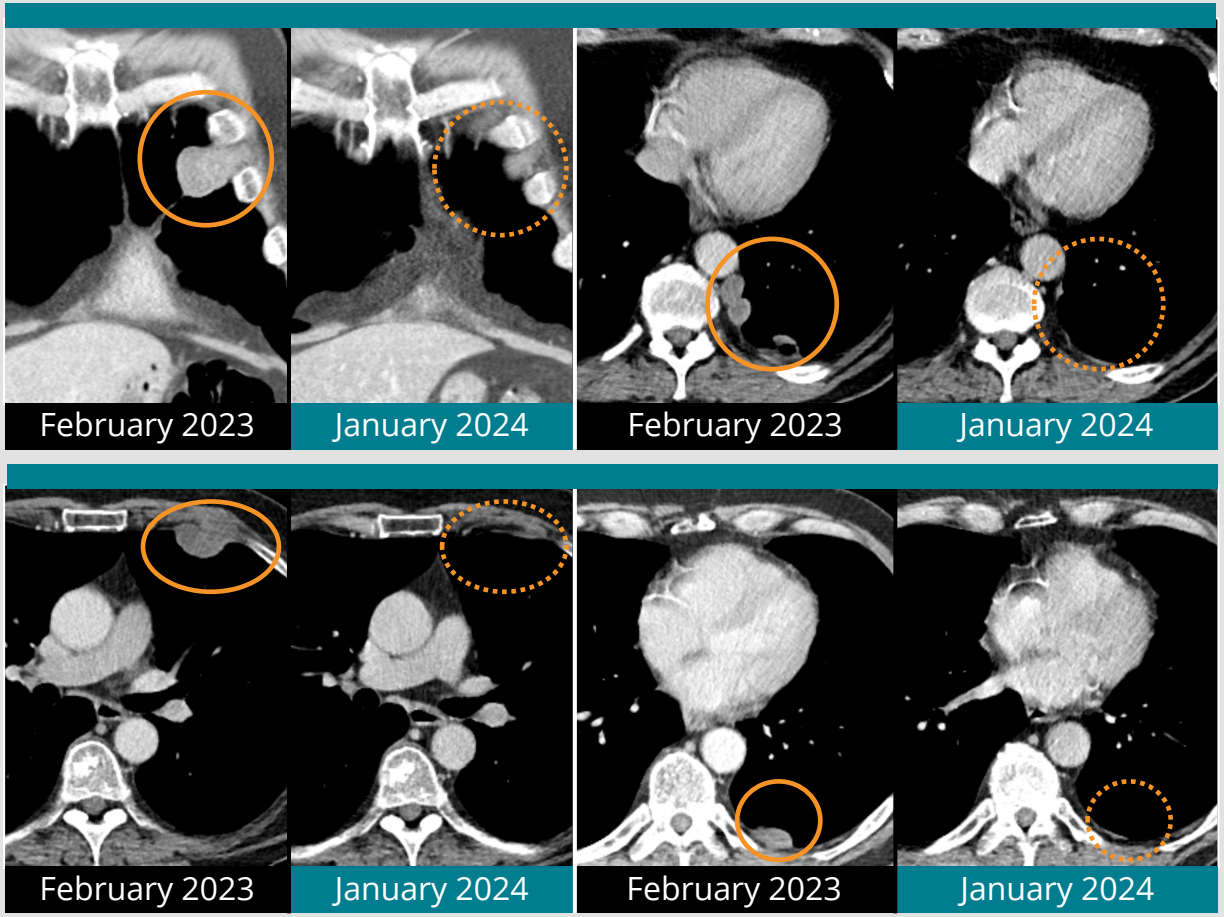
AVA6000 Leads to Rapid and Deepening Response in Treatment-Resistant Disease

Near complete resolution of the multiple pleural metastases



Case Study:

60-year-old male patient with a right-side popliteal mass biopsy diagnosed with a grade 3 undifferentiated pleomorphic sarcoma (UPS). Prior cancer therapy preoperative radiotherapy (May-Jul 2021) followed by surgery (Sept 2021, viable tumour cells in <10% of tumor volume).

Stage IV diagnosis (March 2022) with pleural metastases, enrolled in etigilimab + nivolimab (clinical trial June 2022-Jan 2023) with disease progression prior to enrolling in the AVA6000 phase 1 trial

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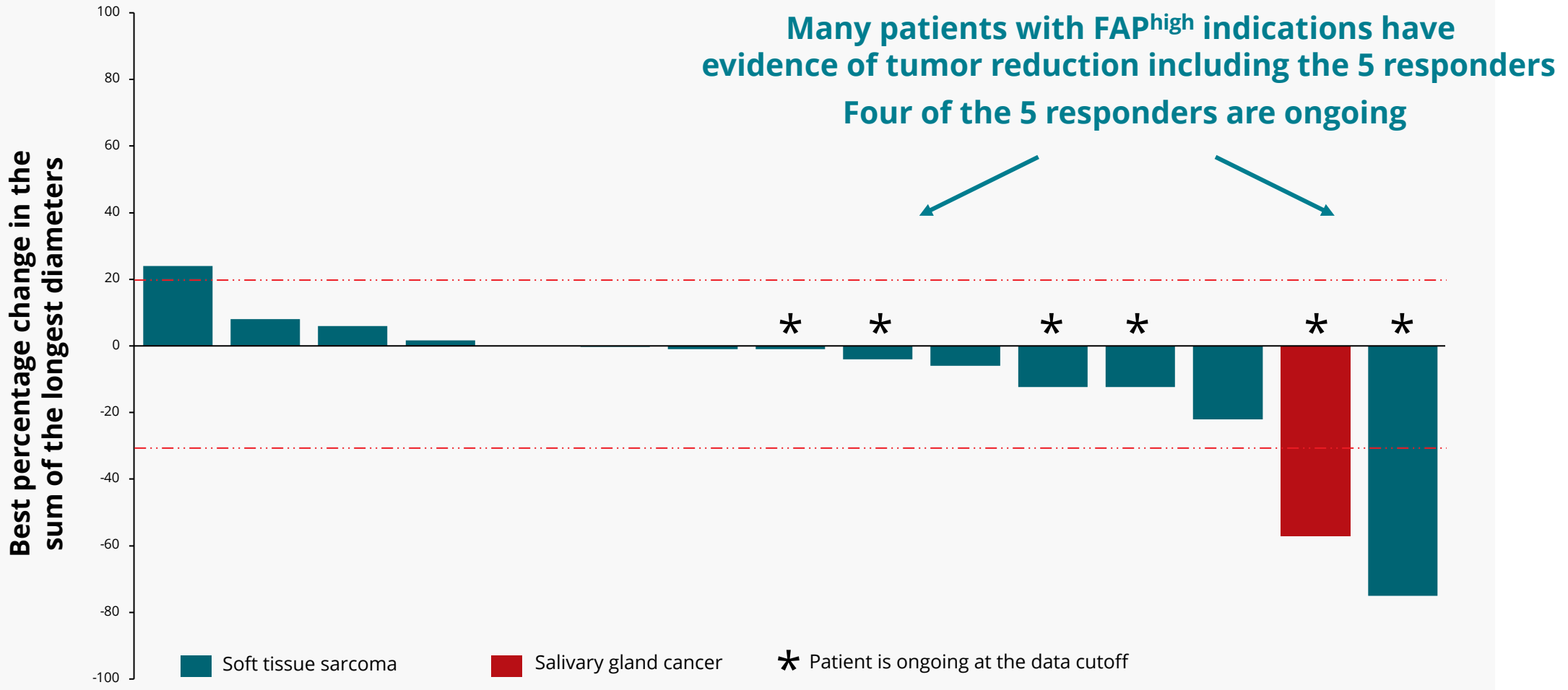
AVA6000 Leads to Tumor Responses in Patients with FAP^{high} Indications



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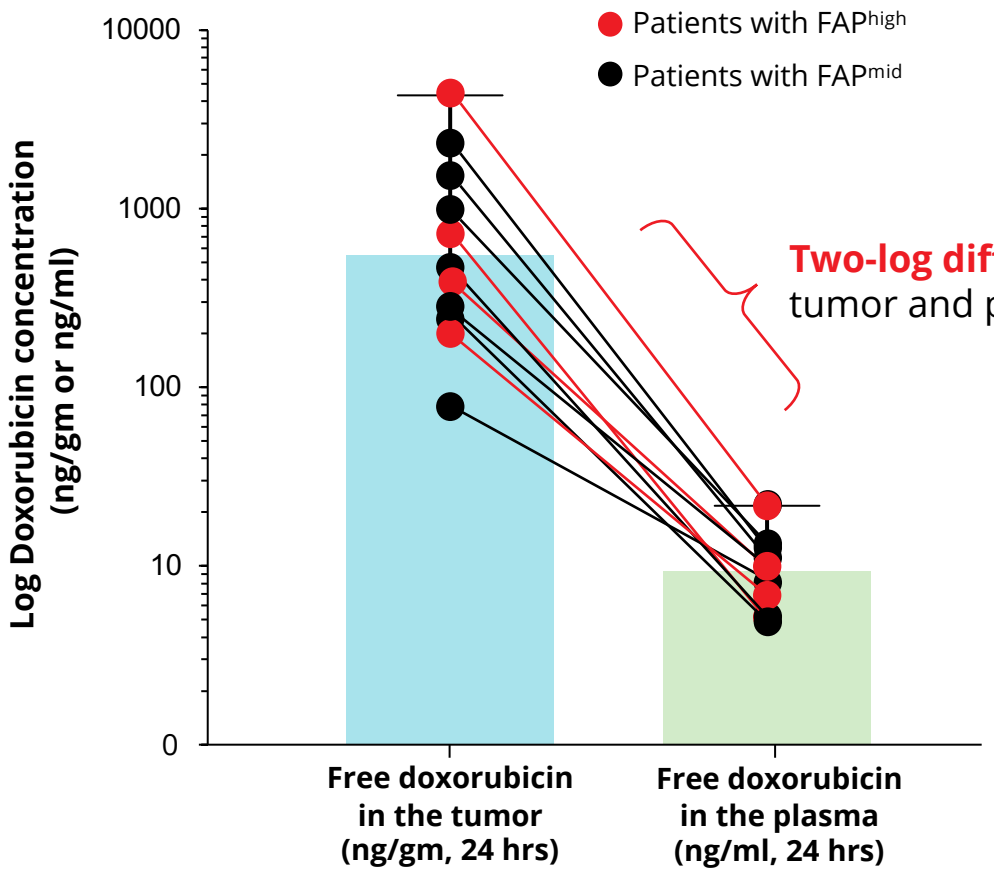
Cleavage in the TME Results in the Concentration of the Warhead in the Tumor



[1] FAP^{high} indications were categorized by FAP expression in literature review and archival tumor tissue IHC. FAP^{high} indications include soft tissue sarcoma and salivary gland cancer

[2] FAP^{mid} diseases include colorectal carcinoma, pancreatic cancer, ovarian cancer, biliary tract cancer, transitional cell cancer of the urethra and lung cancer

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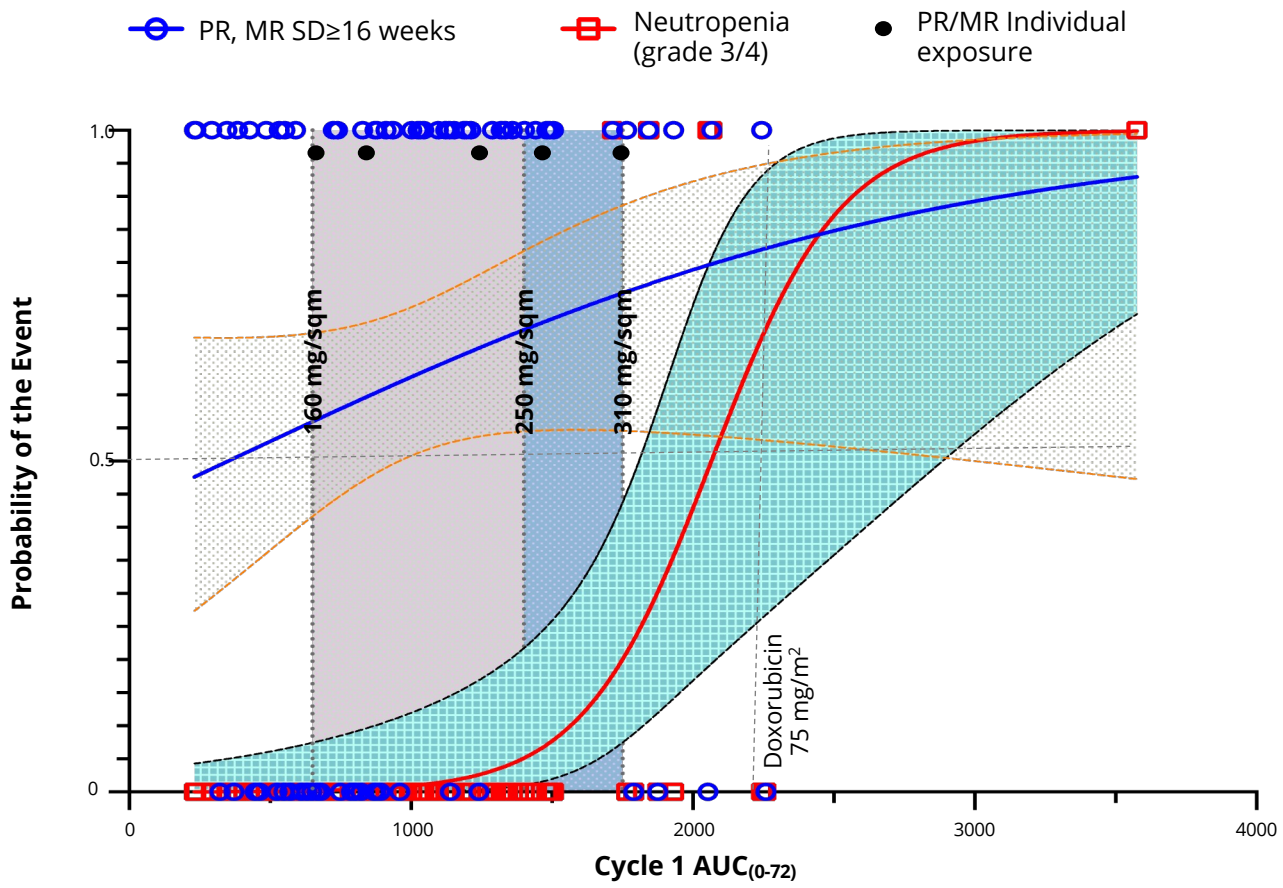
Location matters: tumor v. plasma cleavage

Observed **concentration of doxorubicin in the TME** of approximately a 2-log difference between tumor and plasma concentrations

AVA6000 Significantly Widens the Therapeutic Index of Doxorubicin



Logistic regression analysis of the relationship between response, severe neutropenia and dose indicates that response is observed with high probability at a range of exposure, compared with observation of severe neutropenia. Exposure for individual patients with tumor shrinkage (PR/MR) are included (1 PR with a dose reduction)

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AVA6000 widens the **therapeutic index of doxorubicin**

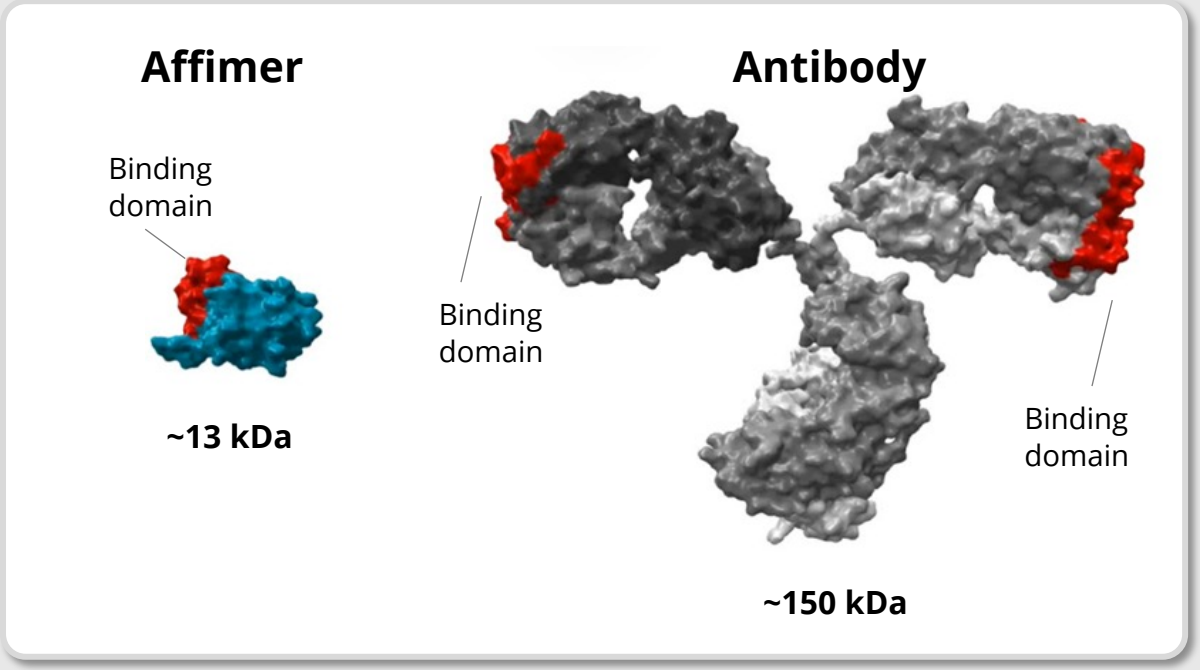
Responses are observed at AVA6000 doses with **released doxorubicin exposures** much lower than that reported for standard doxorubicin without toxicity

AFFIMER Delivery

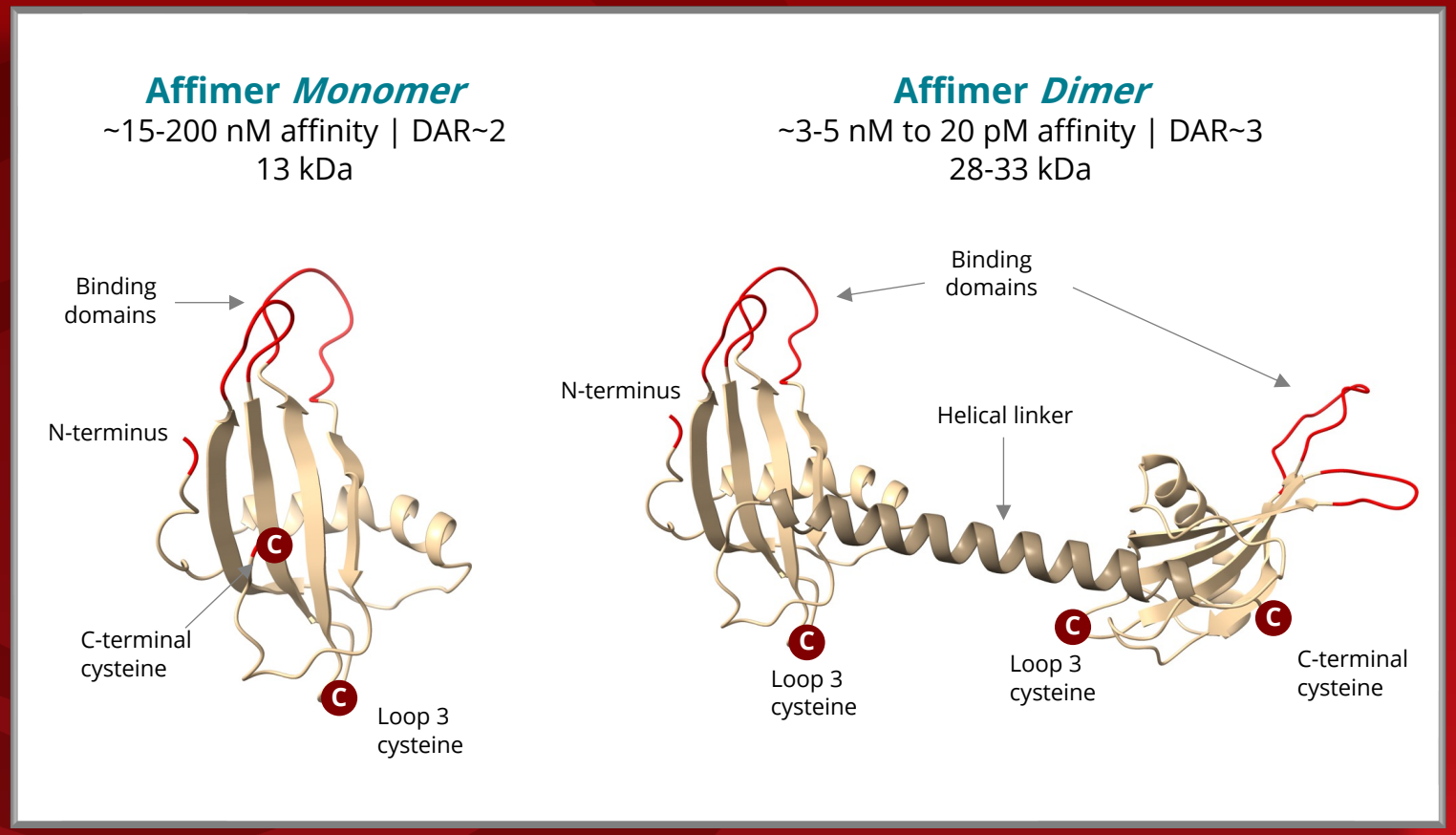
Affimers: Engineered Antigen-Binding Proteins with Key Advantages Over mAb

Affimers are engineered proteins that specifically bind desired targets with affinities in the nanomolar to picomolar range without many of the limitations of monoclonal antibodies (mAb)

- The Affimer is comprised of a protein scaffold that is based on human protease inhibitor Stefin A with insertion of binder loops designed to specifically recognize the target
  - Stefin A is sufficiently stable to constrain a **broad range of inserted peptides**, which bind desired antigens
  - Affimers are highly stable with no post-translational modifications and can be **produced at high levels in E.coli**
- Affimer monomers are ~1/10th the size of a mAb which **optimizes tissue penetration** and enhances clearance compared to mAb



Tumor-Specific Delivery of Warheads is Achieved with the Affimer System



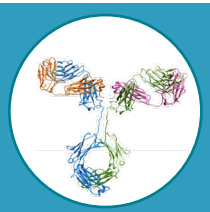
Key Advantages of the AFFIMER Drug Delivery System

Optionality:
The Affimerss are a modular drug delivery system with multiple formats via in-line fusions (dimer to tetramer) allowing optionality with variable affinities and DAR

Size:
Affimers are 1/10th (monomer) or 1/5th (dimer) the size of a monoclonal antibody which allows tumor penetration with engineered cysteines for conjugations

Manufacturing:
Affimers are made in E. coli with excellent thermal stability for management of costs and manufacturing process

Affimers: Multiple Critical Advantages for Drug Delivery Over Monoclonal Antibodies

Key Attributes	 Affimer	 Antibody
Small protein, simple structure and folds, with no post-translational modifications	✓	X
Rapid and simple discovery process based on phage display libraries with unencumbered IP	✓	X
Engineered with multiple cysteines for efficient warhead conjugation	✓	X
Flexible formatting (dimer/tetramer) for multi-specifics and/or to optimize affinity, PK profile and biophysical characteristics	✓	X
Optimal GMP manufacturing in E.coli with high solubility (>250 mg/mL), high Tm and solvent stability to enable efficient conjugations	✓	X

Summary

Avacta's preICISION™ platform is a highly tumor-specific drug release mechanism capable of concentrating anti-cancer drugs to the tumor microenvironment v. the plasma and can be leveraged in different formats including next-gen ADC

Our clinical data released at AACR provide clinical proof of concept for AVA6000 and proof of mechanism that the preICISION™ platform works as designed

PK/PD modelling supports the ongoing exploration of a Q2W dosing schedule to assist in defining the recommended Phase 2 dose and we remain on track to begin the expansion cohorts in 2H 2024

Ongoing work in the Diagnostics Division to integrate and plan for the future, maximizing value for shareholders and patients alike

Avacta: Upcoming Milestones and Catalysts in 2H 2024

Initiate Expansion Cohorts

Completing the Phase 1 dose escalation and advancing the AVA6000 program to expansion cohorts

Updated AVA6000 Clinica Data

Updating the AVA6000 clinical data to support the next stage of development in the expansion cohorts

Release Pipeline Update

Release of the updated pipeline of Avacta Tx assets with stage and timing to the clinic

www.avacta.com