# Avacta Therapeutics

Expanding the reach of highly potent cancer therapies

October 2024

**We believe in hope**
***without*** **compromise**

**Avacta** is not just fighting cancer—we're challenging current drug delivery methods to expand the reach of highly potent therapeutics

We bring an unwavering commitment to eliminating cancer while protecting the person battling it

In a world where effective cancer therapy often means a difficult trade off between efficacy and safety, we offer something different: *hope without compromise*

***This is our story***

# Forward-looking statements

This presentation contains forward-looking statements. Such statements include, but are not limited to, statements regarding the Company's research, preclinical and clinical development activities, plans and projected timelines for AVA6000 and the Avacta pipeline, plans regarding regulatory filings, our expectations regarding the relative benefits of our product candidates versus competitive therapies, and our expectations regarding the therapeutic and commercial potential of our product candidates. The words "believe," "may," "should," "will," "estimate," "promise," "plan", "continue," "anticipate," "intend," "expect," "potential" and similar expressions (including the negative thereof) are intended to identify forward-looking statements. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements.

Risks that contribute to the uncertain nature of the forward looking statements include: our preclinical studies and clinical trials may not be successful; the U.S. Food and Drug Administration (FDA) may not agree with our interpretation of the data from clinical trials of our product candidates; we may decide, or the FDA may require us, to conduct additional clinical trials or to modify our ongoing clinical trials; we may experience delays in the commencement, enrollment, completion or analysis of clinical testing for our product candidates, or in the reporting of data from such clinical testing, or significant issues regarding the adequacy of our clinical trial designs or the execution of our clinical trials may arise, which could result in increased costs and delays, or limit our ability to obtain regulatory approval; our product candidates may not receive regulatory approval or be successfully commercialized; unexpected adverse side effects or inadequate therapeutic efficacy of our product candidates could delay or prevent regulatory approval or commercialization; and we may not be able to obtain additional financing.

These statements are not guarantees of future performance and undue reliance should not be placed on them. Such forward-looking statements necessarily involve known and unknown risks and uncertainties, which may cause actual performance and financial results in future periods to differ materially from any projections of future performance or result expressed or implied by such forward-looking statements.

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Avacta THERAPEUTICS

Source:

# Avacta technology unleashes powerful cancer-killing drugs selectively in the tumor

### Cytotoxic agents remain the most powerful and effective way to kill cancer cells

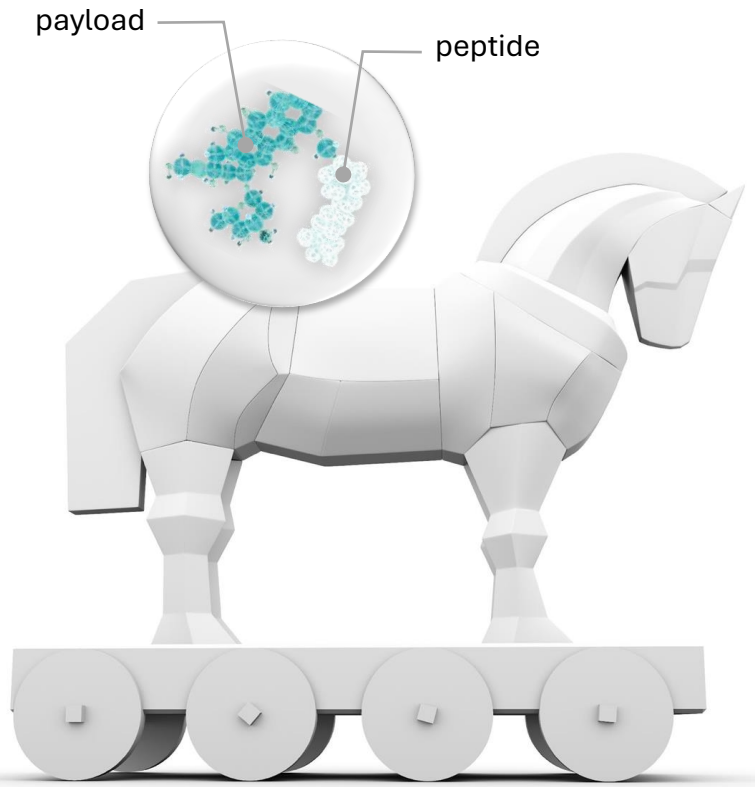
But they indiscriminately kill any dividing cells such as bone marrow, gut lining, hair follicles, skin and reproductive cells.

### Avacta technology masks cytotoxic agents in a Trojan horse that is only opened at the site of the tumor

The hidden drug retains its power but is inert as it travels invisibly through the body, sparing healthy cells.

### Exposure of the drug requires the activity of an enzyme (protease) expressed only in the tumor microenvironment

This enzyme concentrates the drug at the tumor site by cutting open the Trojan horse, unleashing it in its active form.




**Drugs are exposed and the lethal effect is unleashed selectively in the tumor microenvironment**

# The Avacta Therapeutics Leadership 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 and cell therapy in oncology

**Simon Bennett, DPhil**

**Chief Business Officer**

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

Simon has been involved in over 80 commercial deals across geographies

**Karen Harrison**

**Chief Operating Officer**

Karen has >30 years of 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

**Michelle Morrow, PhD**

**Chief Scientific Officer**

Michelle has >17 years of experience in in oncology research in the biotech and pharma industry

Michelle has significant experience leading discovery and preclinical research teams, including multiple INDs and approvals in oncology

Pfizer · NOVARTIS · Wyeth · RubiusTherapeutics · IMMUNOCORE

Bristol Myers Squibb™ · Glide TECHNOLOGIES · MedPharm

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Avacta THERAPEUTICS

# The pre|CISION Cancer Biology Team

**David Jones, PhD**

**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 20 years of industry experience

**Manuel Pinto, PhD**

**AffDC Team Lead, Principal Scientist, Preclinical Biology**

Manuel is a biochemist trained at the University of Porto, Portugal, where he developed his protein biochemistry background

Manuel has 9 years of industry experience in drug discovery in cell and gene therapy and protein biologics

**Curtis Rink, PhD**

**AVA6103 co-lead, Senior Scientist, Preclinical Biology**

Curtis is a Biochemistry graduate who received his PhD in Oncology from the University of Glasgow.

Undertaken at the Cancer Research UK Scotland Institute, his work focused on *in vivo* modeling of cancer, and the use of complex cell culture systems

**Victoria Juskaite, PhD**

**Principal Scientist, Preclinical Biology**

Victoria trained at Imperial College London in molecular and cell biology in the science of oncology modeling with expertise in immunology and cancer biology

Victoria has 7 years experience in drug development preclinical modeling of oncology therapeutics

# The pre|CISION Chemistry and Translational Teams

**Francis Wilson, DPhil**

**VP and Head of Chemistry**

Francis trained in medicinal chemistry at Oxford University

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

**Ellen Watts, PhD**

**Principal Scientist, Medicinal Chemistry, AVA6103 co-lead**

Ellen trained in medicinal chemistry at the Institute for Cancer Research in London

Ellen has multiple years experience in drug development at the Institute for Cancer Research, London and Benevolent AI in medicinal chemistry

**Ruairidh Edwards, PhD**

**Translational Scientist**

Ruairidh trained in biochemistry at Glasgow University where he gained experience in cancer biology and protein biochemistry

Ruairidh's focus as Translational Scientist is to convert the scientific data into patient benefit during clinical development

**Tom Clough, PhD**

**Scientist, Medicinal Chemistry**

Tom trained in medicinal chemistry at Imperial College London

Tom completed a post-doctoral fellowship at the ICR focused on design and synthesis of compounds for clinical test. His experience in cheminformatics and data processing are invaluable in our AI based approach to chemistry

Avacta THERAPEUTICS

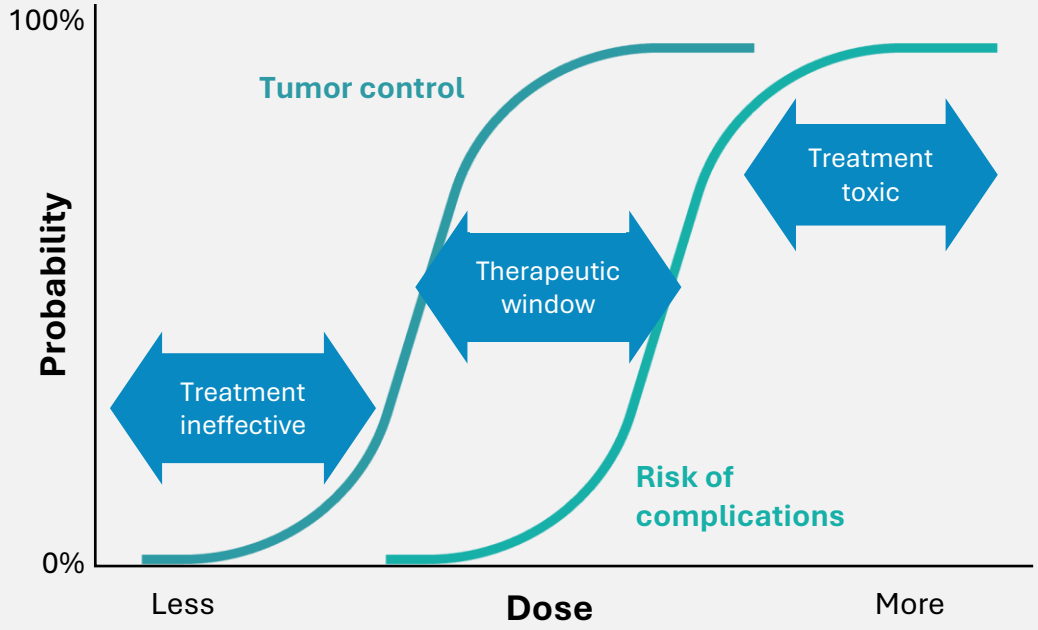
# Potent cancer drugs kill indiscriminately, causing toxicity throughout the body

## Therapeutic index challenge: Most cytotoxic drugs cause severe toxicity at the efficacious doses

**Expanding the therapeutic index** of a drug requires a higher dose delivered to the tumor while in parallel sparing normal tissues from exposure

**pre|CISION® medicines** are designed to mask toxic effects from normal tissues by two mechanisms:

- Limiting peripheral exposure to the released (active) payload and
- Delivering high concentrations of release payload directly in the TME




**The therapeutic index of a drug** is the ratio of the dose that is toxic in half of the population to the dose that exerts a therapeutic or effective response in half of the population

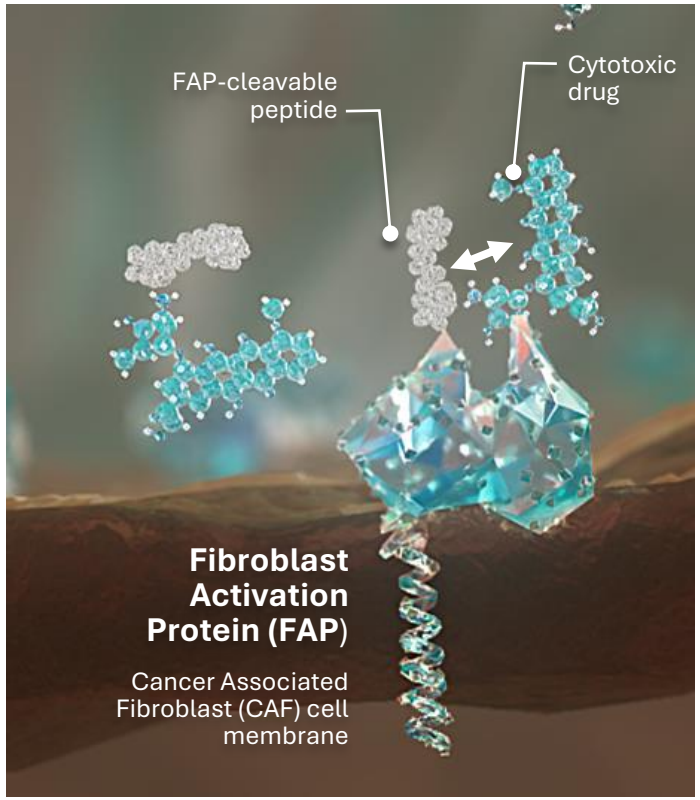
**Expanding the therapeutic window of cancer drugs demands innovative targeting strategies directly to the tumor**

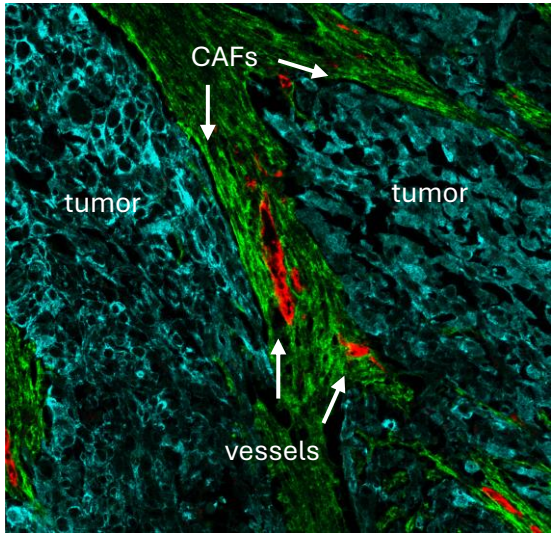
# Avacta is redefining how oncology therapeutics are targeted specifically to the tumor

**pre|CISION® medicines are targeted to the tumor** by means of a protease, specifically expressed in the tumor microenvironment (TME), that releases the cytotoxic agent

**Fibroblast associated protein (FAP)** is expressed by cancer-associated fibroblasts (CAFs) in many solid tumors with little to no expression in normal tissues

FAP is a protease with exquisite specificity for the **pre|CISION linker sequence** that releases the payload directly in the TME, killing tumor cells via the bystander effect

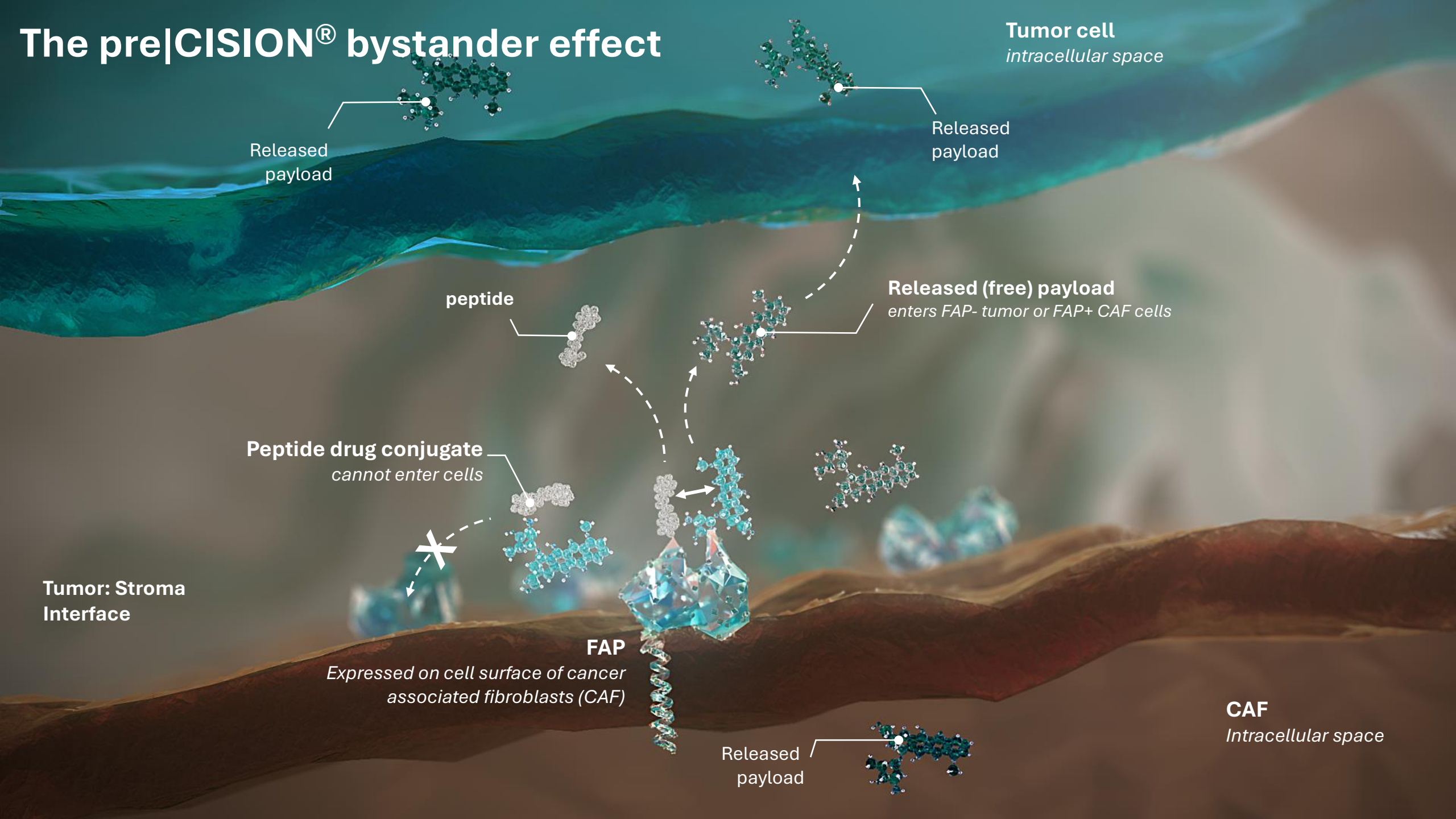



Multiplex immunofluorescence defining the tumor: stroma interface

- FAP (CAF)
- CD31 (blood vessels)
- PanCK (tumor cells)

**Leveraging the FAP protease in the TME represents a new approach to deliver payloads to the tumor and spare healthy tissue**


The pre|CISION® bystander effect
Tumor cell
intracellular space
Released payload
Released payload
peptide
Released (free) payload
enters FAP- tumor or FAP+ CAF cells
Peptide drug conjugate
cannot enter cells
Tumor: Stroma Interface
FAP
Expressed on cell surface of cancer associated fibroblasts (CAF)
Released payload
CAF
Intracellular space

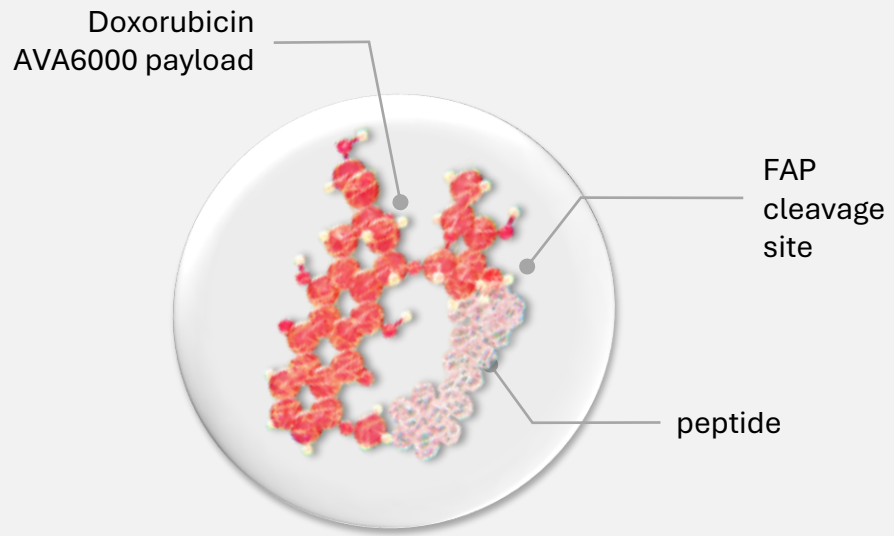
# Avacta technology delivers cytotoxic drugs directly to the tumor while protecting healthy tissue

**Foundational pre|CISION® platform technology in the peptide drug conjugate format is the basis of our first clinical asset, FAP-Dox (AVA6000)**

The **pre|CISION® peptide** is conjugated to a cytotoxic drug to create a **peptide drug conjugate (PDC),** rendering the drug inert until the peptide is cleaved

## Advantages

- Short plasma PK of the PDC ($t_{1/2}$ minutes to hours)
- High tumor concentration v. plasma of released payload
- Tumor targeting is not limited by a specific moiety; effective across many FAP-positive tumor types
- Small molecule manufacturing timeline/COGMs

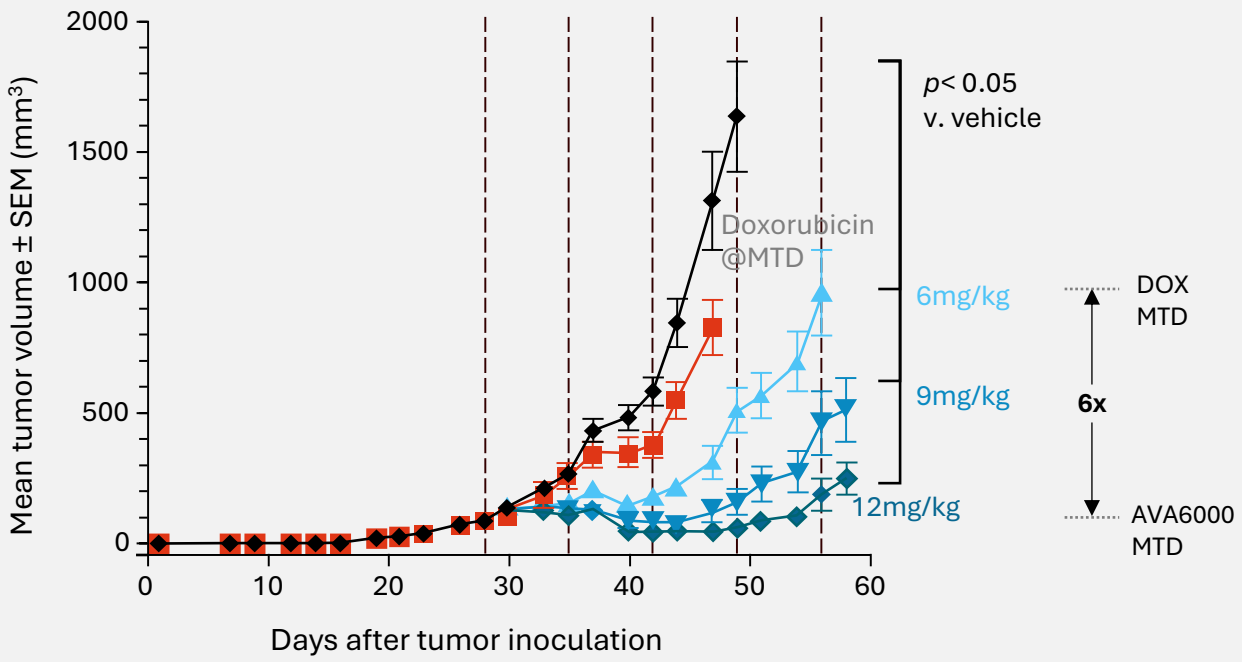



**pre|CISION-enabled doxorubicin (FAP-Dox)** where active doxorubicin is released in the TME by the protease action of FAP, expressed on the cell surface of CAFs

# FAP-Enabled Doxorubicin (AVA6000) Demonstrates Activity in a FAP-high model

- pre|CISION-enabled doxorubicin (FAP-Dox, AVA6000) results in a **6-fold increase in the MTD** versus conventional doxorubicin
  - The MTD of doxorubicin is 2mg/kg and AVA6000 is 12 mg/kg
  - Regression of established tumors observed at MTD of AVA600
- Preclinical tumor:plasma PK studies suggest that pre|CISION-enabling results in **a 10-20-fold** difference in tumor exposure v. concurrent plasma exposure across payloads

**Human FAP model (HEK-hFAP) of Kidney Cancer with Significant Increase in MTD of AVA6000 versus doxorubicin**




An **engineered murine model** was developed with an aggressive model of human kidney cancer (HEK) expressing human FAP (HEK-hFAP)

**Leveraging the FAP protease represents a new approach to deliver payloads to the tumor and spare healthy tissue**

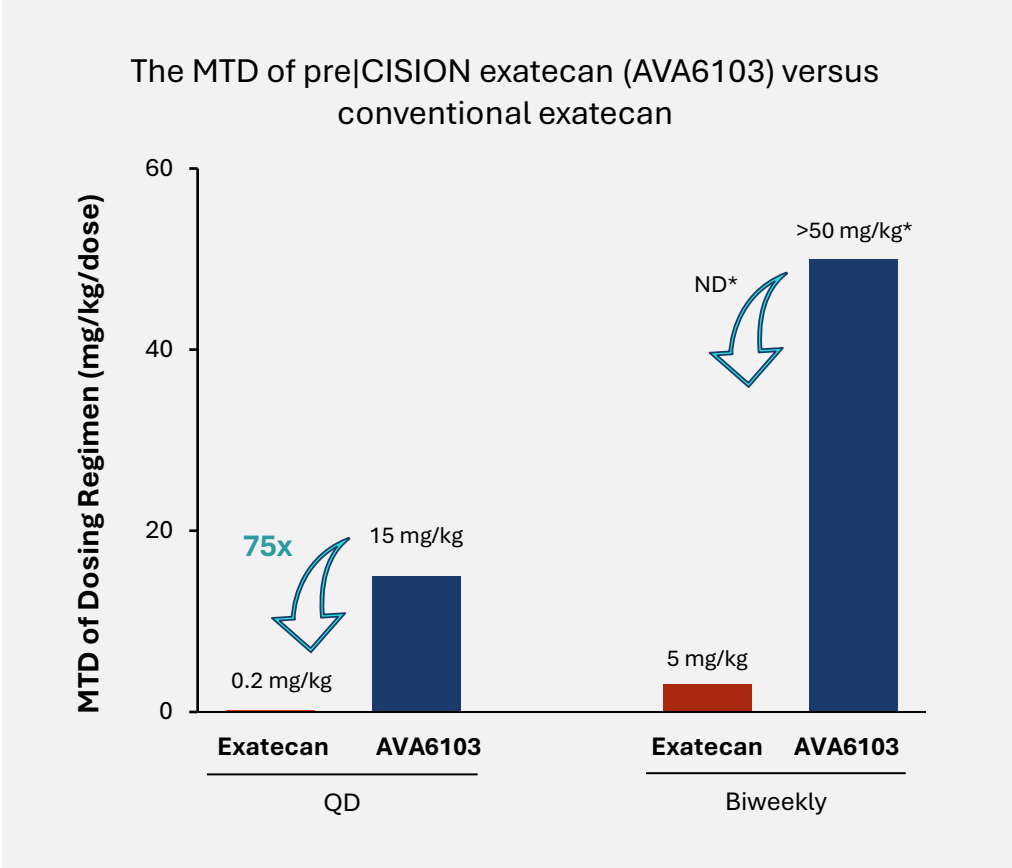
# Building on a proven foundation: Advancing our platform technology to a novel payload

**To leverage additional payloads (exatecan) and optimize therapeutic index, the properties of the FAP cleavable peptide have been advanced (FAP-EXd, AVA6103)**

The tumor to plasma PK is fine-tuned through deep chemistry expertise and a computational algorithm trained using *in vitro* and *in vivo* data with multiple payloads

**Advances in pre|CISION chemistry:**

1. The capping group is modified to **extend the plasma exposure** of the conjugated PDC
2. **Slowing the rate of cleavage** of the drug in the TME optimizes selective delivery of the released payload only in the tumor
3. These changes together create a sustained release delivery in the TME, significantly **extending the therapeutic index**



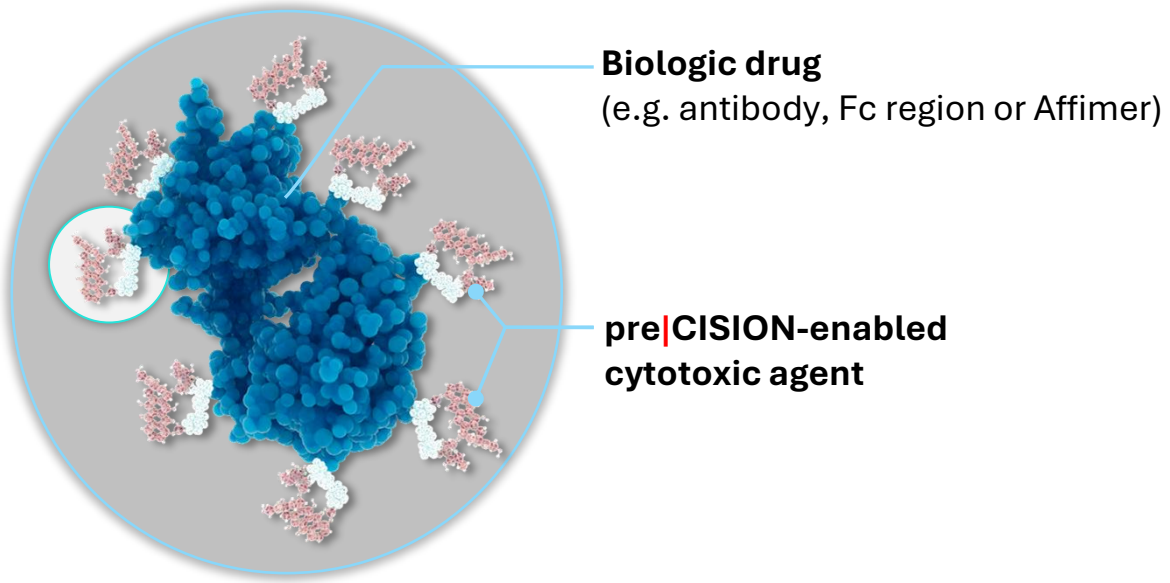

*Non-tumor bearing mice were dosed in a multi-dose format with the defined schedules using either exatecan or AVA6103 administered i.v. Maximum dose tested of AVA6103 was 50 mg/kg with no toxicity noted, thus the therapeutic index of the biweekly schedule was not determined (ND)

# Expanding our platform technology for greater patient impact

**Combining our tumor-selective masking technology with a small biologic enhances tumor targeting and broadens the cancer indications we can address**

**Advances:**

- Modular drug delivery system with multiple formats, variable affinities, and multiple specificities with in-house screening capabilities
- Better tumor penetration with similar antigen affinity compared to an antibody
- Significantly faster and less costly to manufacture than antibody-based drugs




**The FAP Affimer drug conjugate (AffDC) with pre|CISION delivery (AVA7100) will unlock patient populations with lower expression of FAP**

# Avacta's technology stands out with several unique advantages in a competitive market

**FAP-targeted therapies will reach a broad patient population with high unmet need**
Highly expressed in many solid tumors and predicts poor prognosis

**Potent tumor-specific and broad-spectrum cytotoxicity**
Induces tumor cell death through 'bystander killing' where conventional ADCs rely on complex cell internalization processes that address primarily antigen-positive tumor cells

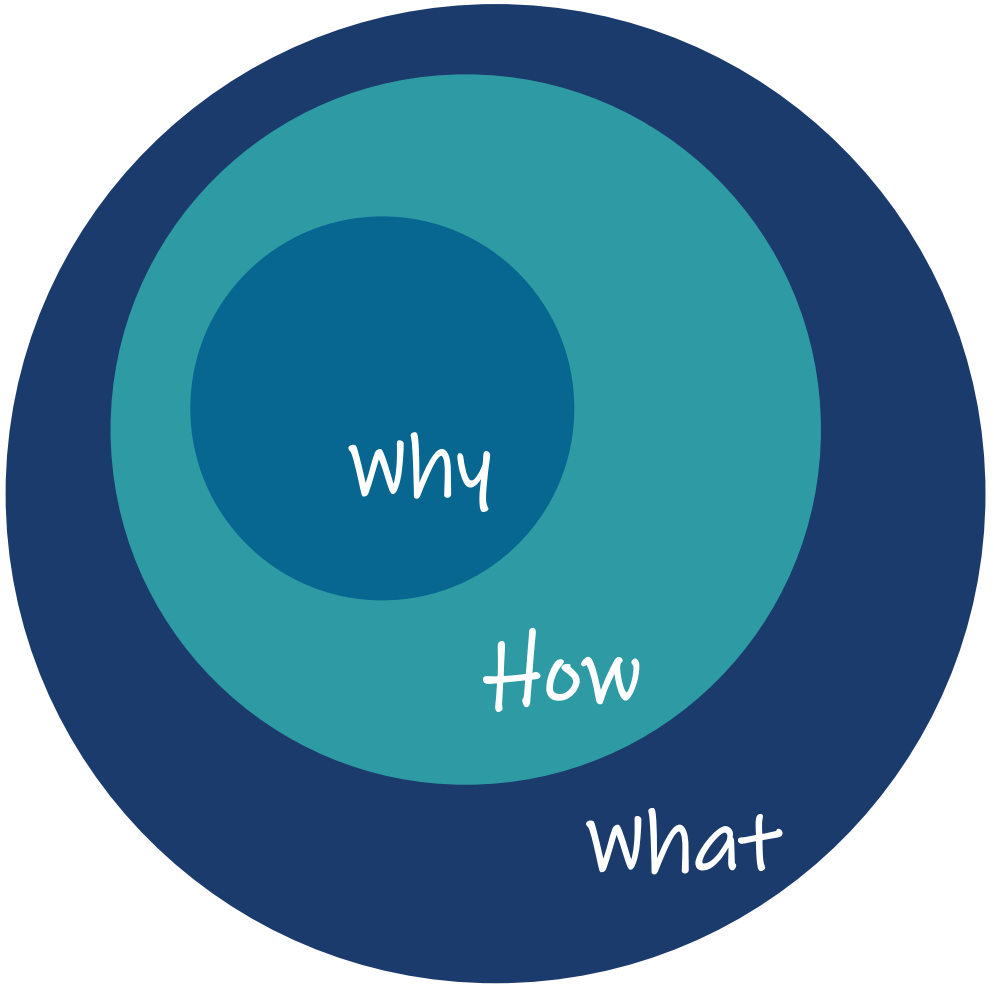
**Efficacy that is not reduced by acquired resistance or immune destruction**
Unique targeting mechanism maintains efficacy with outgrowth of resistant tumor cell populations with a peptide that cannot be recognized by the immune system

**Unprecedented safety profile**
Conversion of drug specifically in the TME with tumor concentration and optimal PK of released payload protects healthy tissues from exposure to the cytotoxic drug

**Faster and less costly to manufacture**
Up to 10x cost of goods savings with one rapid process to manufacture peptide drug conjugates compared to antibody-based drugs

# Avacta Therapeutics Pipeline

| PROGRAM | PLATFORM/ WARHEAD | POTENTIAL INDICATIONS | PRECLINICAL | IND-ENABLING | PHASE 1 | PHASE 2 | MILESTONES |
|---|---|---|---|---|---|---|---|
| **AVA6000** | pre\|CISION Doxorubicin (FAP-Dox) | Head and Neck Cancers (HNSCC, Salivary gland Ca subset)<br>Dedifferentiated liposarcoma<br>Breast cancer (TNBC/HER2+/HER2low) | | | | | Expansion FPI 2H 2024<br>Ph Ia/Ib data 2Q 2025 (Full Ph I) |
| **AVA6103** | pre\|CISION Exatecan (FAP-Exd) | Triple negative breast cancer (TNBC)<br>Gastric cancer (GC)<br>Small cell lung cancer (SCLC)<br>Pancreatic ductal adenocarcinoma (PDAC) | | | | | Candidate selection 2H 2024 |
| **AVA7100** | pre\|CISION FAP Affimer (AffDC) Warhead not disclosed | Head and neck squamous cell cancers (HNSCC)<br>Non-small cell lung cancer (NSCLC)<br>Colorectal cancer (CRC) | | | | | Candidate selection 2H 2025 |



# FAP-EXd: pre|CISION-enabled exatecan

Peptide Drug Conjugate

# pre|CISION Peptide Drug Conjugates: Start With Why

## Antibody drug conjugates have revolutionized treatment of many metastatic cancers, however there are key limitations in this drug class including

- Non-specific warhead release that results in significant off target toxicities (e.g. interstitial lung disease/pneumonitis)
- Complexity of the bystander effect that targets antigen-negative tumor cells and enables targeting of antigen-low populations
- Complex and costly GMP manufacturing process

## pre|CISION® peptide drug conjugates (PDC) are designed to overcome these limitations by incorporating our proprietary FAP-cleavable peptide in the linker

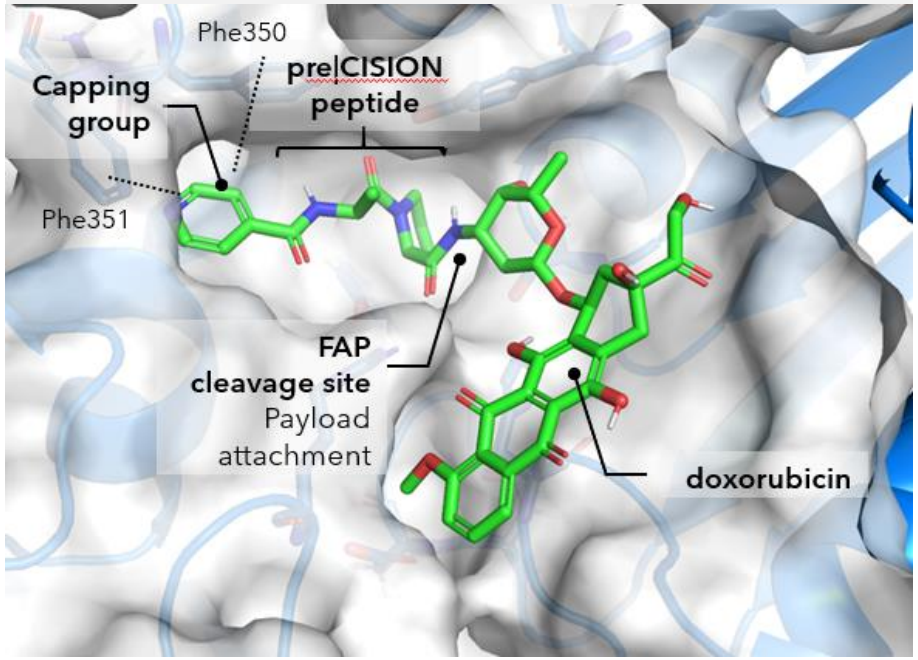
- The pre|CISION® release mechanism results in tumor-specific release that has been shown in the clinic to result in a dramatic reduction in off-target toxicities associated with the warhead (AVA6000 Gen One, pre|CISION® doxorubicin Phase 1 results, Banerji et al AACR 2024, Twelves et al ESMO 2024)
- The mechanism of action of the pre|CISION® PDC relies on the bystander effect where the payload is cleaved from the peptide in the extracellular setting by FAP-positive CAFs
- The GMP manufacturing process of these peptide and warhead conjugates resembles a small molecule process with similar short timelines and costs of clinical drug supply

# How: Computational Algorithms Predict pre|CISION Medicine Features in the Clinic

**Ten pre|CISION** warheads have been designed and characterized both *in vitro* and *in vivo* informed by the FAP docking model. Together these data have been used to develop our pre|CISION computational design algorithms

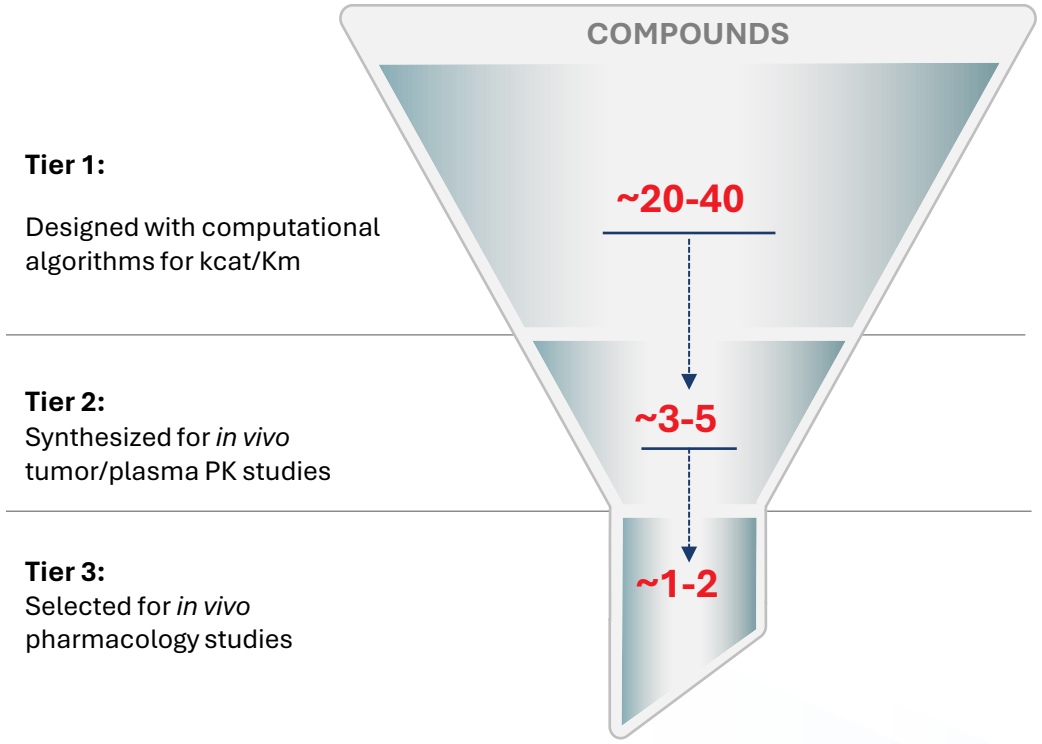
## A docking model of the FAP enzyme

is used to understand the release of the warhead and peptide based on the selected spacer and capping groups




AVA6000 docking is modeled in the FAP active site

**Computational algorithms** are used to design novel pre|CISION medicines in conjunction with real-time selection



# pre|CISION PDCs Have Key Advantages Over Conventional ADC Approaches

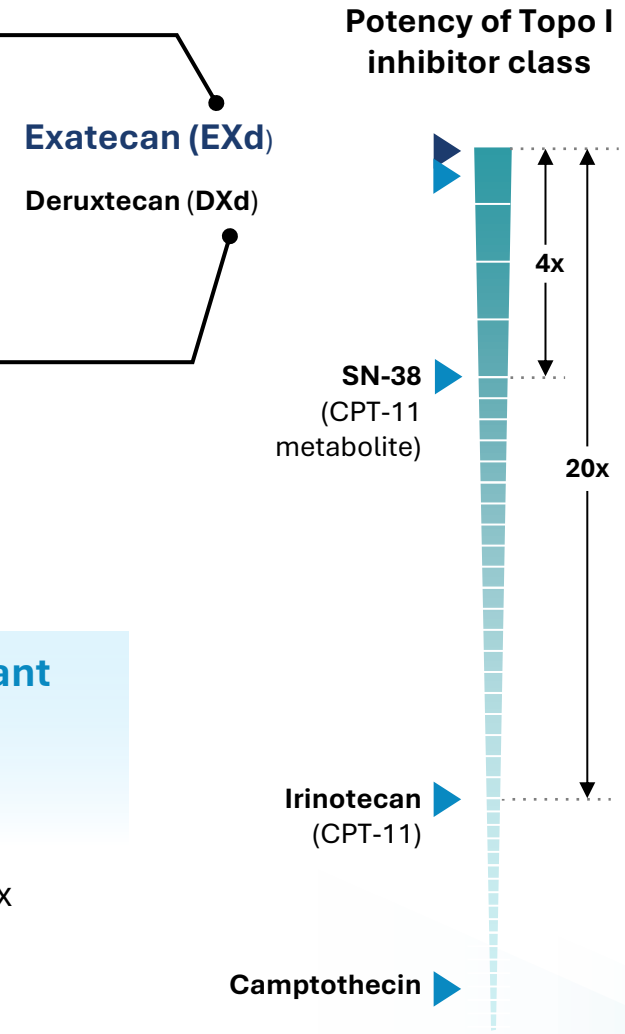
| | Avacta **pre\|CISION Peptide Drug Conjugate** | v. | Conventional **Antibody Drug Conjugate** |
|---|---|---|---|
| **Bystander mechanism of action** | *Extracellular warhead release* in the TME with limited systemic exposure<br>pre\|CISION leverages the bystander effect to efficiently kill both FAP+ and FAP- cells | | *Intracellular warhead release* in the tumor killing antigen-positive cells<br>Complex bystander effect to induce killing of antigen-negative cells |
| **Payload release** | *Tumor-specific warhead release* by the FAP-cleavable peptide linker | | *Non-specific warhead release* contributes to off-target toxicities (e.g. lung toxicity) |
| **Manufacturing** | Small molecule timelines and costs of manufacturing | | Complex, long and expensive manufacturing process |

# Exatecan is an ideal payload for the next evolution of the pre|CISION platform

1. **Exatecan (EXd) is the most potent topo I inhibitor** with **single agent activity** in Ph 2 trials in several key FAP-positive indications (breast, gastric, small cell lung cancer)

2. **Deruxtecan (DXd) has similar potency but lower membrane permeability** compared with exatecan (EXd) and is a **highly successful ADC warhead**
   - When attached to trastuzumab (EnhertuTM), the only ADC shown to have **significant bystander effect** or anti-TROP1 (DATO-DXd)

3. **Exatecan failed in the clinic due to a limited therapeutic index and significant PK issues**
   - Short half-life of ~9 hours which is insufficient for the effective inhibition of the topoisomerase I enzyme
   - The evolution of the preCISION platform chemistry can optimize both therapeutic index as well as the PK liability




Kumazawa, E. et al. Potent and broad antitumor effects of DX-8951f, a water-soluble camptothecin derivative, against various human tumors xenografted in nude mice. Cancer Chemother Pharmacol 42, 210–220 (1998). https://doi.org/10.1007/s002800050807

# The novel chemistry behind AVA6103 optimizes delivery

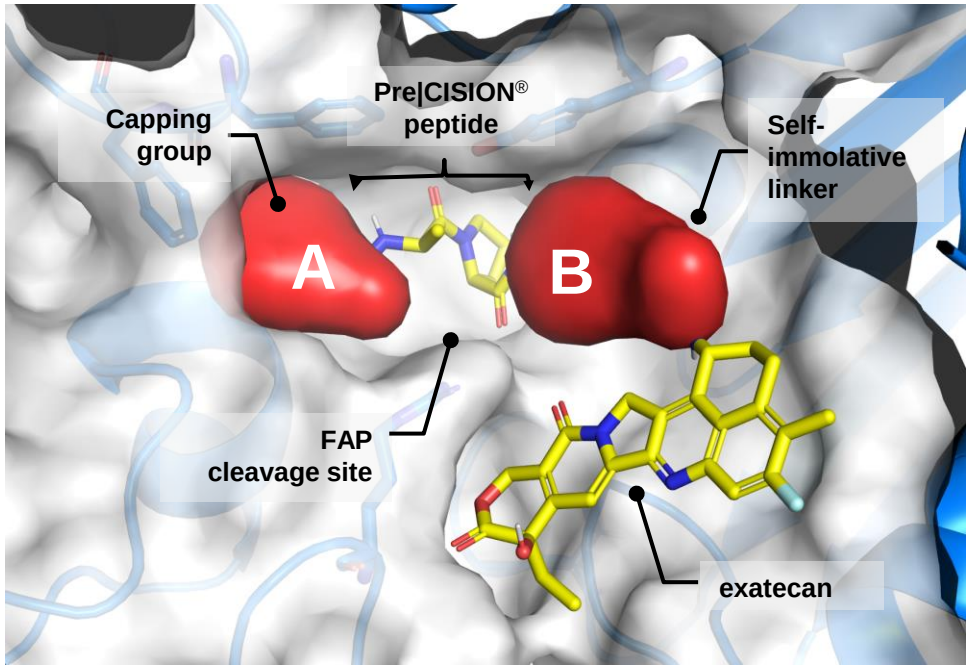
## Leverage pre|CISION® technology to extend the half-life of released exatecan

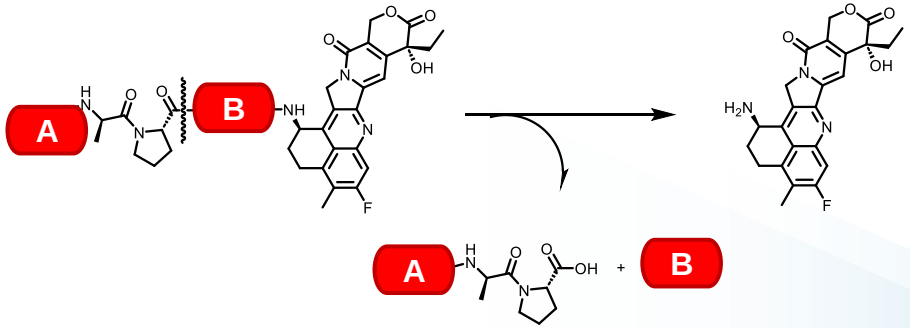
- Goal: prolong inhibition of the topo I enzyme for >24 hours in the FAP-EXd development
- **Extend plasma PK** of the conjugated molecule to several hours via capping group (versus 30-90 min, AVA6000)
- **Extend the tumor exposure** by adjusting the release kinetics via linker (alter the kcat/Km of the conjugate)

## Extend the Therapeutic Index of exatecan

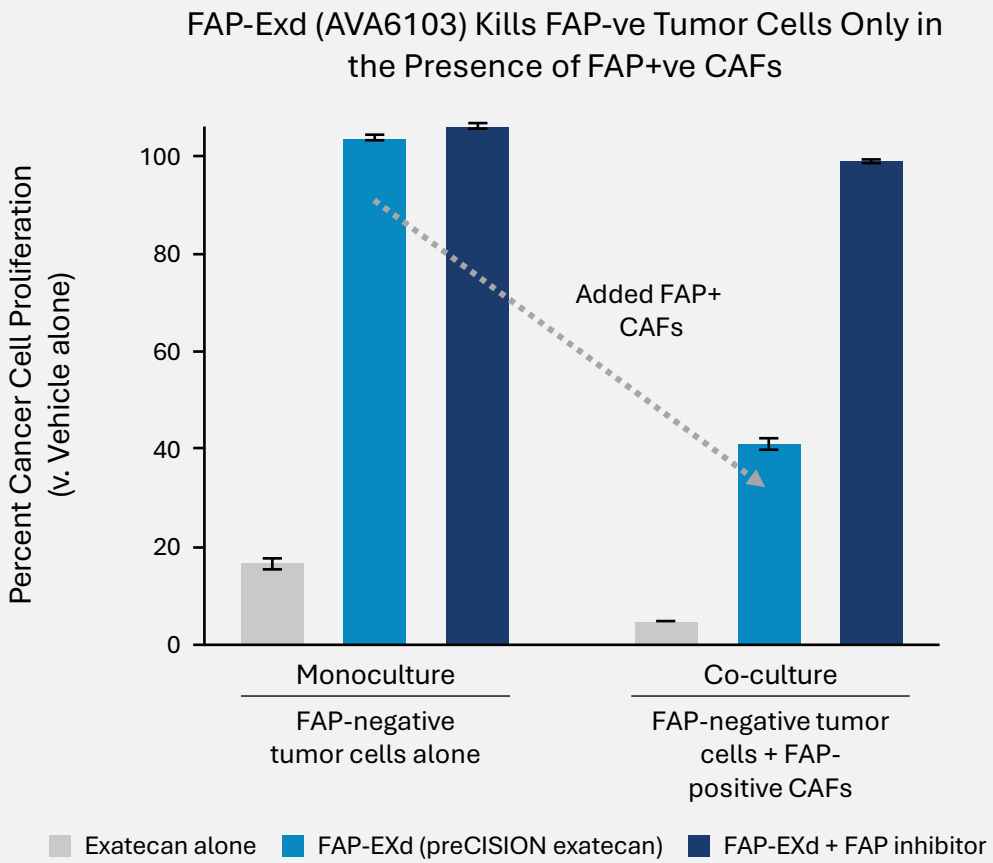
- Slower release and extended plasma PK of the conjugate will result in an exatecan sustained release mechanism
- This is expected to result in very low plasma exposure to released exatecan

**pre|CISION-Exatecan in the FAP Docking Model**



# FAP-EXd (AVA6103): Effective Killing of FAP-Negative Tumor Cells in the Bystander Assay




Monoculture (tumor cells alone) or co-culture with fibroblasts demonstrates FAP-specific cleavage of AVA6103-mid (0.001μM) at 120hr post-treatment, where Mia PaCa-2-GFP cells were plated either alone, or in combination with pancreatic fibroblasts

Watts, E *et al.* EORTC-NCI-AACR Annual Meeting 2024

- In a **bystander effect** model, **pancreatic cancer cells** (PDAC, FAP-negative) were tested alone (monoculture), or in combination with **FAP+ pancreatic fibroblasts** (co-culture)
- FAP-EXd exhibits **no activity in monoculture** (PDAC, FAP-negative )
- With the **addition of FAP-positive fibroblasts**, FAP-EXd is cleaved by FAP to release exatecan, greatly reducing cancer cell proliferation (co-culture)
- The **bystander effect** is achieved with FAP-negative tumor cell death

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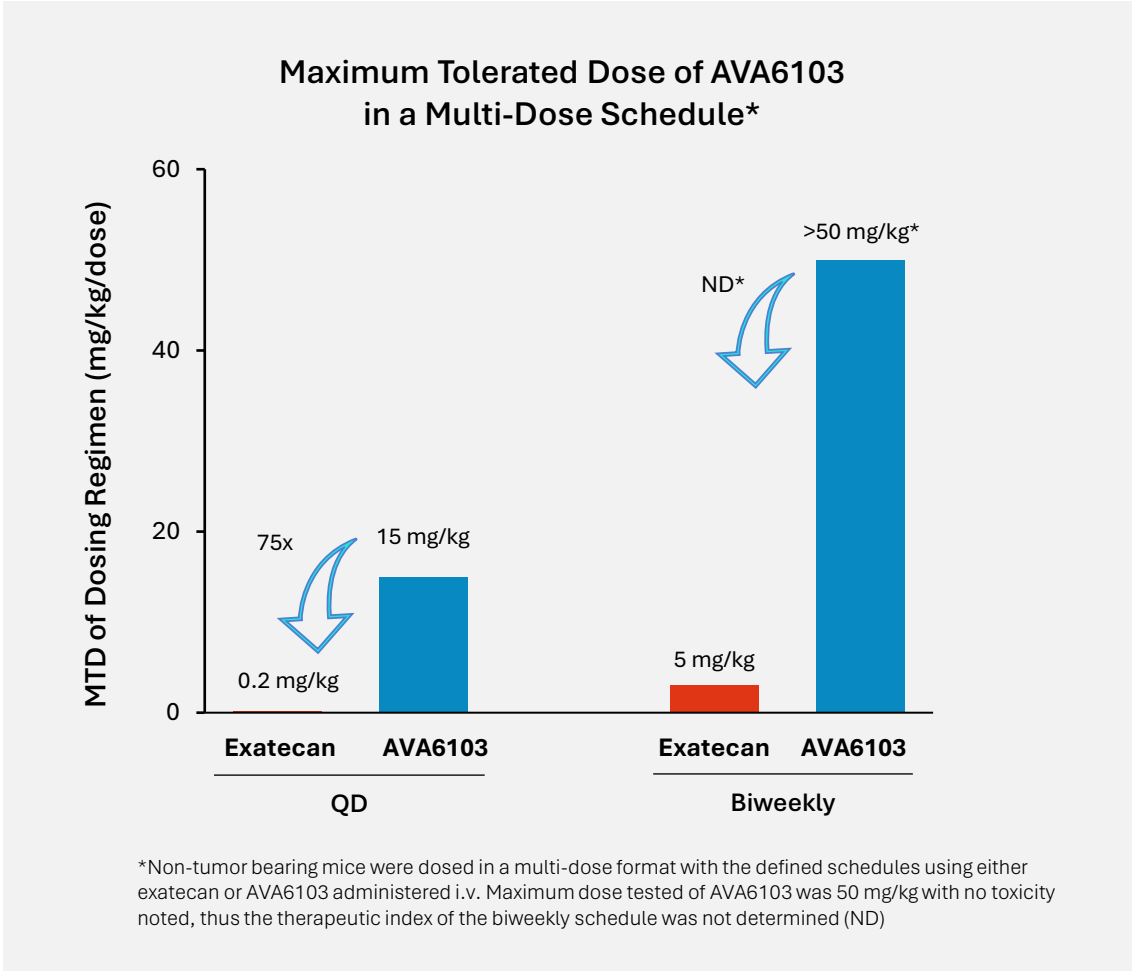
# Therapeutic Index: The MTD of AVA6103 Is 75-fold higher than that of conventional exatecan




*Non-tumor bearing mice were dosed in a multi-dose format with the defined schedules using either exatecan or AVA6103 administered i.v. Maximum dose tested of AVA6103 was 50 mg/kg with no toxicity noted, thus the therapeutic index of the biweekly schedule was not determined (ND)

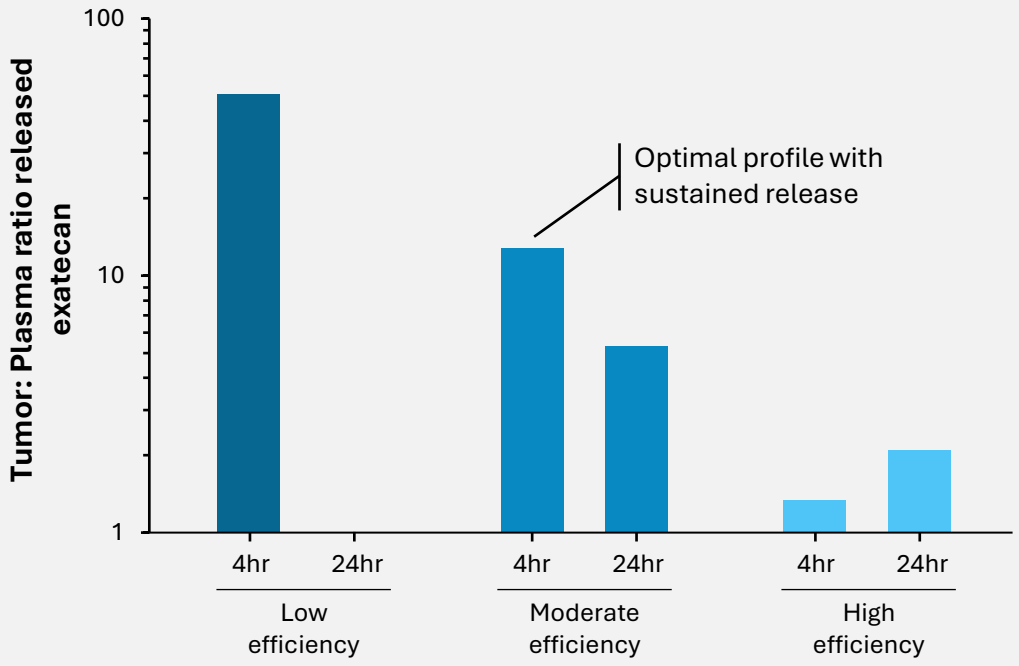
Watts, E *et al.* EORTC-NCI-AACR Annual Meeting 2024

- **Frequent exatecan dosing** in prior clinical trials was designed to optimize inhibition of the topoisomerase I enzyme
  - More frequent dosing to extend the inhibition of the topo I enzyme for a prolonged (>24 hr) period was toxic in the clinic
  - Activity was observed in the clinic with the QDx5 regimen
- To demonstrate the **MTD of AVA6103,** the molecule with the mid level of FAP efficiency (kcat/Km) was selected (AVA6103-mid)
- Dosing in the QD regimen was limited at 15 mg/kg (AVA6103) compared to the MTD of exatecan alone is 0.2 mg/kg

Avacta THERAPEUTICS

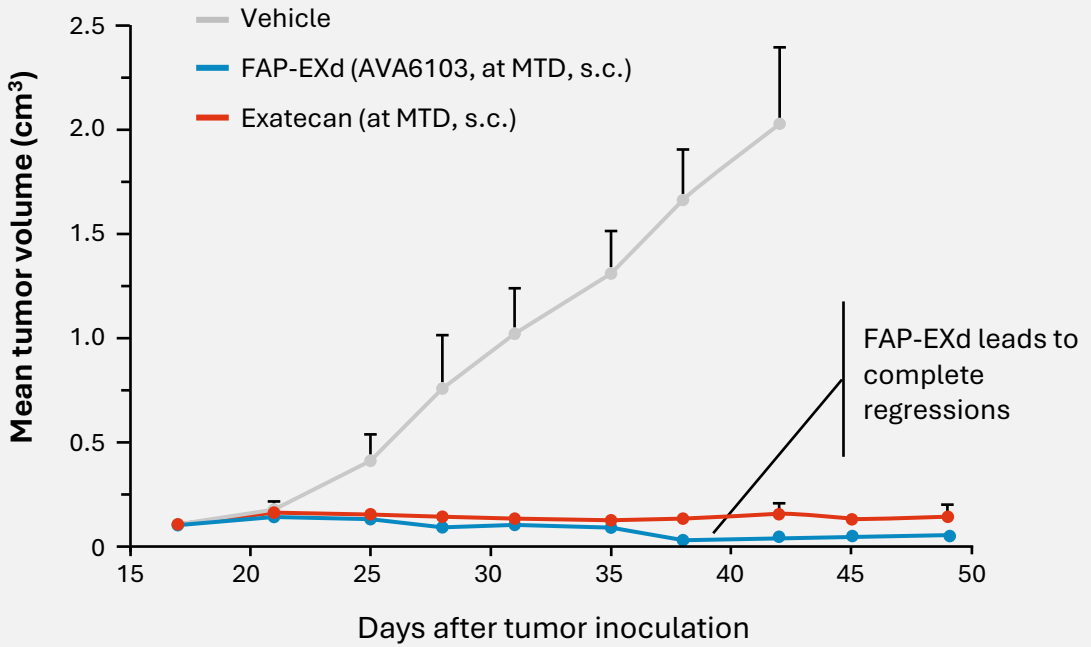
# Complete Regression of the Aggressive HEK-hFAP Tumors with FAP-EXd (AVA6103)

### Tumor: Plasma Ratio is Optimal with Moderate Efficiency (kcat/Km) AVA6103 Structure




Released (free) exatecan warhead present intratumorally versus plasma concentration is plotted in a ratio at 4hr and 24hr when treating with three different compounds with different kcat/Km value in a patient derived xenograft (PDX) model

### Complete Regression with FAP-EXd Dosing in Established HEK-hFAP Tumors




FAP-EXd (AVA6103) was dosed in animals bearing established HEK-FAP tumors (100 $mm^3$ tumor size at dosing). HEK-hFAP is a highly aggressive tumor model engineered to expressed human FAP

Watts, E *et al.* EORTC-NCI-AACR Annual Meeting 2024

Avacta THERAPEUTICS

# AVA6103: Phase 1 Basket Trial in Indications with FAP Expression and Topo I Sensitivity

| | Triple Negative Breast Cancer (TNBC) | Gastric Cancer (GC) | Pancreatic Ductal Adenocarcinoma (PDAC) | Small Cell Lung Cancer (SCLC) |
|---|---|---|---|---|
| **FAP Expression^** | High stromal content with 50% weak and 50% strong FAP staining | High stromal content with 50% weak and 50% strong FAP staining | Very high stromal content with >80% strong FAP staining | Higher stromal content associated with poor prognosis |
| **Topol Inhibitor Activity^** | T-DXd and exatecan (Ph 2) single agent responses | T-DXd and exatecan (Ph 2) with single agent responses | Irinotecan with activity in multiple regimens used in standard practice | Topotecan with single agent activity in this disease setting compared with CAV |
| **Unmet Need** | Monotherapy chemotherapy generally used in the PD-L1-ve setting with unmet need | Irinotecan with some activity, indication primarily sees combination chemotherapy in 1L | High unmet need; few agents approved | CPI with approvals<br>New agents opportunity available |

^Indication selection will be informed by our collaboration with Tempus AI using real-world data evidence of FAP expression and Topo I sensitivity

Avacta THERAPEUTICS

# AVA6103 Clinical Development Planning

| | EARLY DEVELOPMENT → | | LATE PHASE → | LIFE CYCLE → |
|---|---|---|---|---|
| | PHASE 1: DOSE ESCALATION | PHASE 1: EXPANSION COHORTS | PHASE 2 and 3 TRIALS | LIFE CYCLE ADDITIONAL INDICATIONS |
| **Timing** | **Ph I escalation Initiating ~Q1 2026** | **Ph I expansions Initiating Anticipated Q1 2027** | **Anticipated 2027/2028** | **Post-approval planning** |
| **Trial Designs** | Two dose escalation arms:<br>Monotherapy dose escalation in basket trial with 4 FAP-positive indications:<br>TNBC, Gastric Ca, PDAC, SCLC | Initiate RDE cohorts to assess disease-specific safety and efficacy parameters<br>Expansions in disease-specific cohorts to begin in 2H 2026<br>AVA6103 Monotherapy | Phase 2 trial of AVA6103 in selected indication based on results in expansion cohorts with Phase 3 to enroll in staggered timing<br>Ideally in an indication with high unmet need (multiple options) | Topo I mechanism is relevant in multiple disease settings with FAP expression and further indications can be added following the initial approval of AVA6103 |
| **Rationale** | Dose escalation proceeds to define the RDE at the Q3W schedule | RDE Expansions in indications with high FAP expression and sensitivity to the topo I inhibitor MOA | AVA6103 is indicated for the treatment of patients with FAP+ and topo I sensitive disease – selection of initial indication for approval based on expansion cohorts | Multiple options for further development of FAP-EXd – selection will be based on data observations in the Phase 1 and expansions |

Avacta THERAPEUTICS

# pre|CISION Biologic Drug Conjugates:

## Affimer Drug Conjugates

# pre|CISION Affimer Drug Conjugates: Start With Why

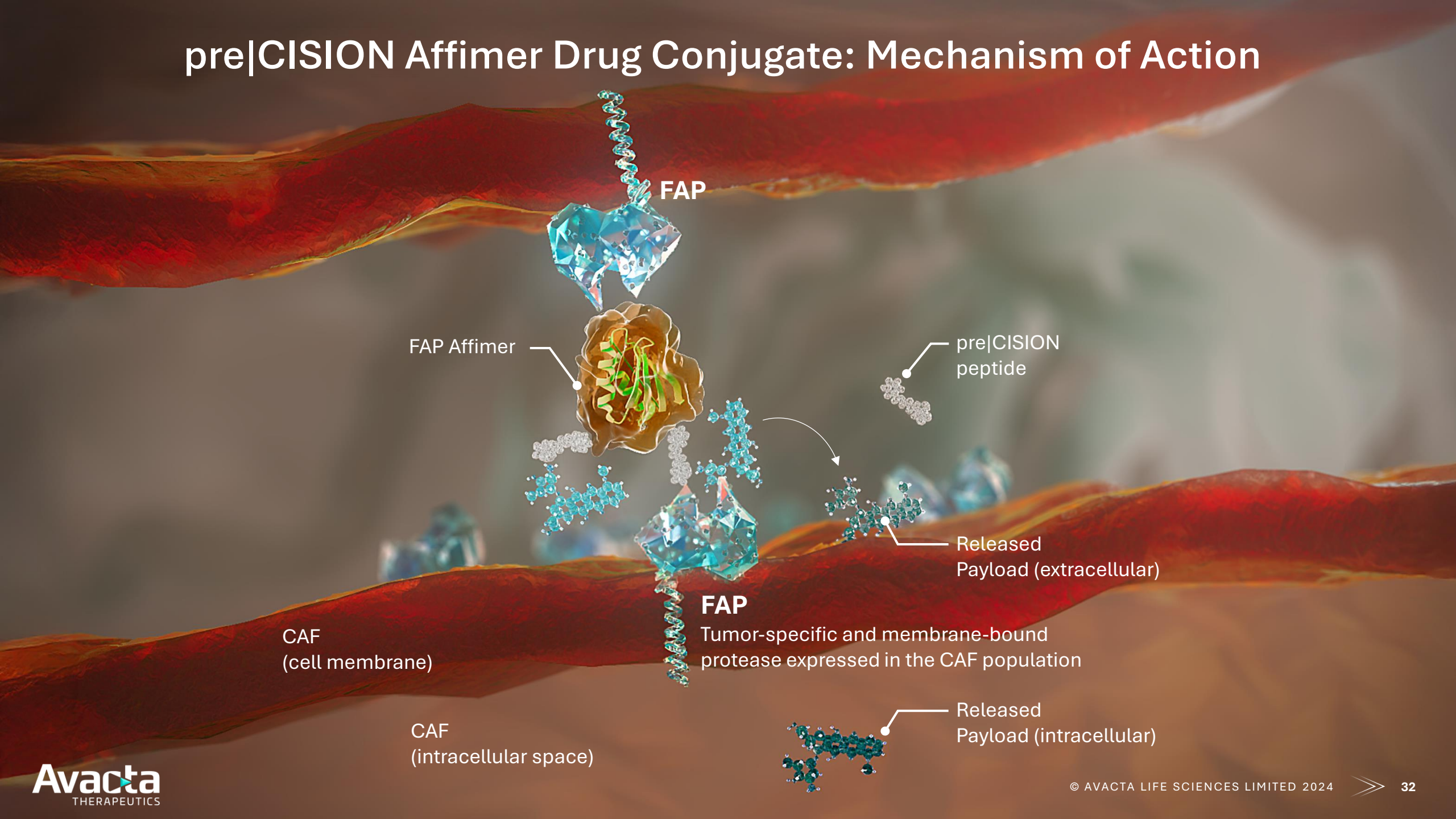
**ADCs are limited by factors** such as (1) non-specific payload release, (2) the complexity of the bystander effect for antigen-low cell kill and (3) tumor penetration of large biologic molecules

The **Affimer® drug conjugates (AffDC)** are a novel class of engineered biotherapeutics designed to deliver highly toxic warheads directly to the tumor microenvironment (TME) by combining two novel delivery systems:

- The clinically validated pre|CISION® payload release mechanism which has significant advantages over protease-cleavable linkers in that release is only accomplished with FAP cleavage in the TME (Banerjee et al. 2024, Twelves et al. 2024)
- The pre|CISION® linker is specifically cleaved by membrane-bound FAP, but not by closely related or wider mammalian peptidases, and its conjugation renders a warhead inert by preventing cell uptake. This linker is cleaved by FAP on cancer associated fibroblasts, releasing active warhead to the TME
- The Affimer® protein is based on the human protein StefinA and contains 2 antigen binding loops with antigen binding affinities similar to those achieved with antibodies

**Affimer® proteins have advantages over antibodies** including smaller size (~1/10th the size of an antibody) which leads to better tumor penetration, a DAR of 2-3 for a monomer therapeutic and optimized manufacturing with production in E. coli vs. mammalian cell manufacturing

# pre|CISION Affimer Drug Conjugate: Mechanism of Action

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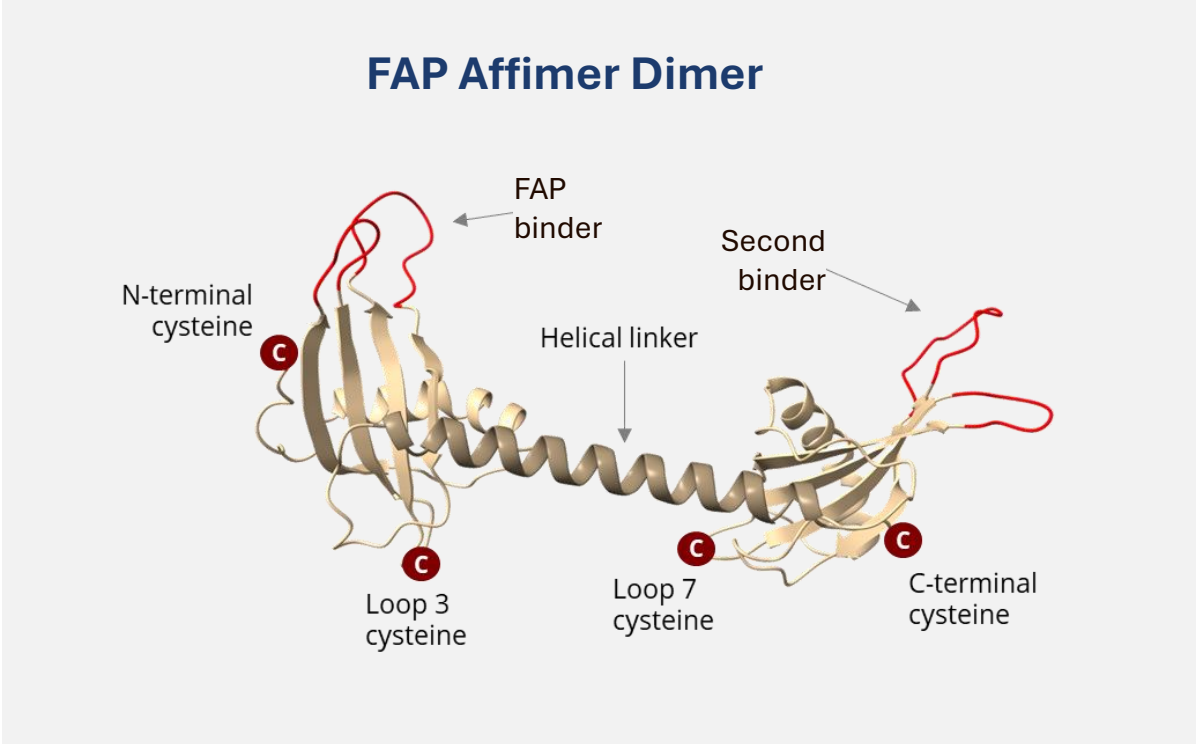
# Affimers are Engineered to Optimize Payload Conjugation and Delivery

## FAP Affimer Engineering Steps

1. FAP binders selected for inability to internalize and lack of FAP enzyme inhibition
2. Affimer dimers have one or two binding specificities (e.g., FAP and albumin) to bind a TME antigen and extend PK
3. Cysteines are engineered into 4 locations in an **Affimer dimer** to enable a DAR of 4:1



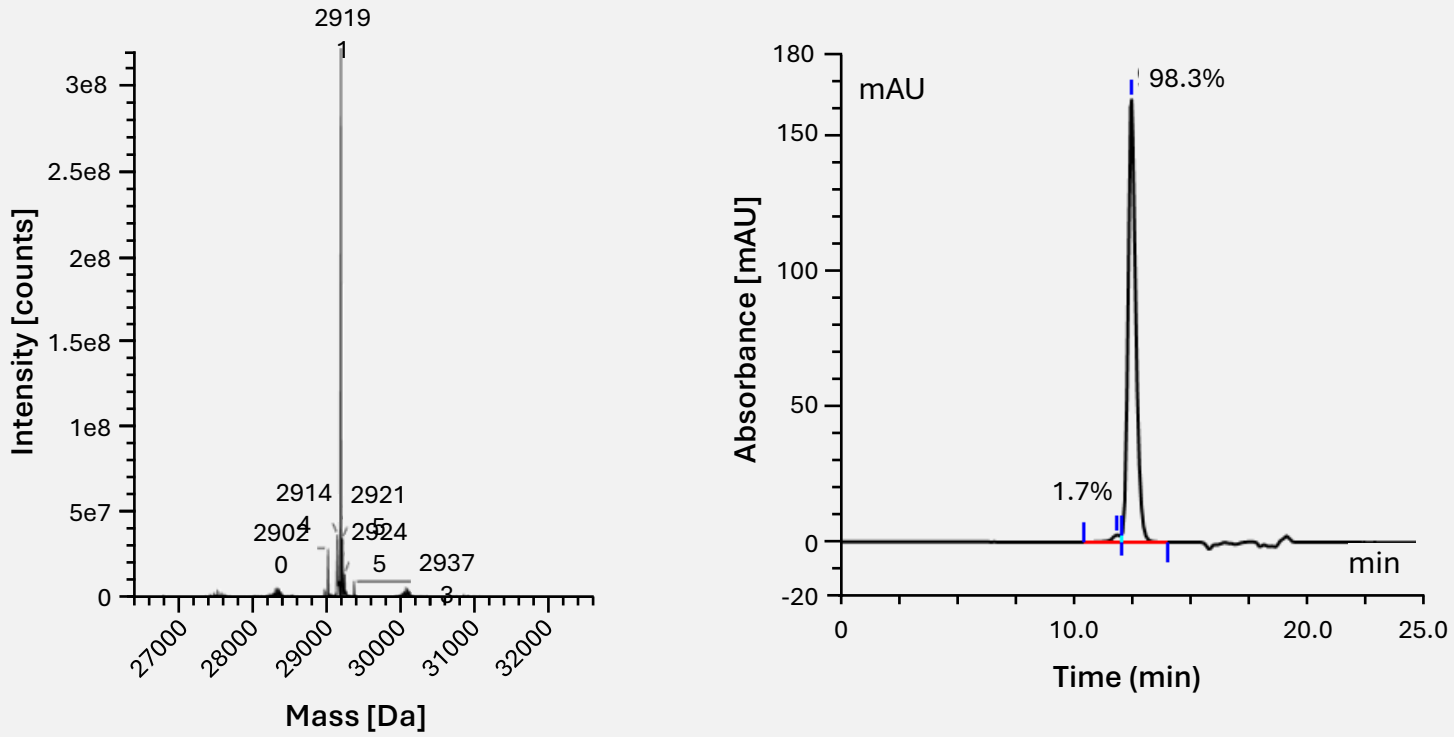

***AlphaFold*** Structure of a FAP Affimer Dimer with engineered cysteines

Nobel prize winning predictive algorithm for protein structure modeling (Nobel prize awarded October, 2024)

Avacta THERAPEUTICS

# Cysteine-Maleimide Conjugation Efficiently Loads Payload to AffDC

**Affimer® proteins show highly efficient conjugation to multiple pre|CISION® linker-Exatecan warheads**

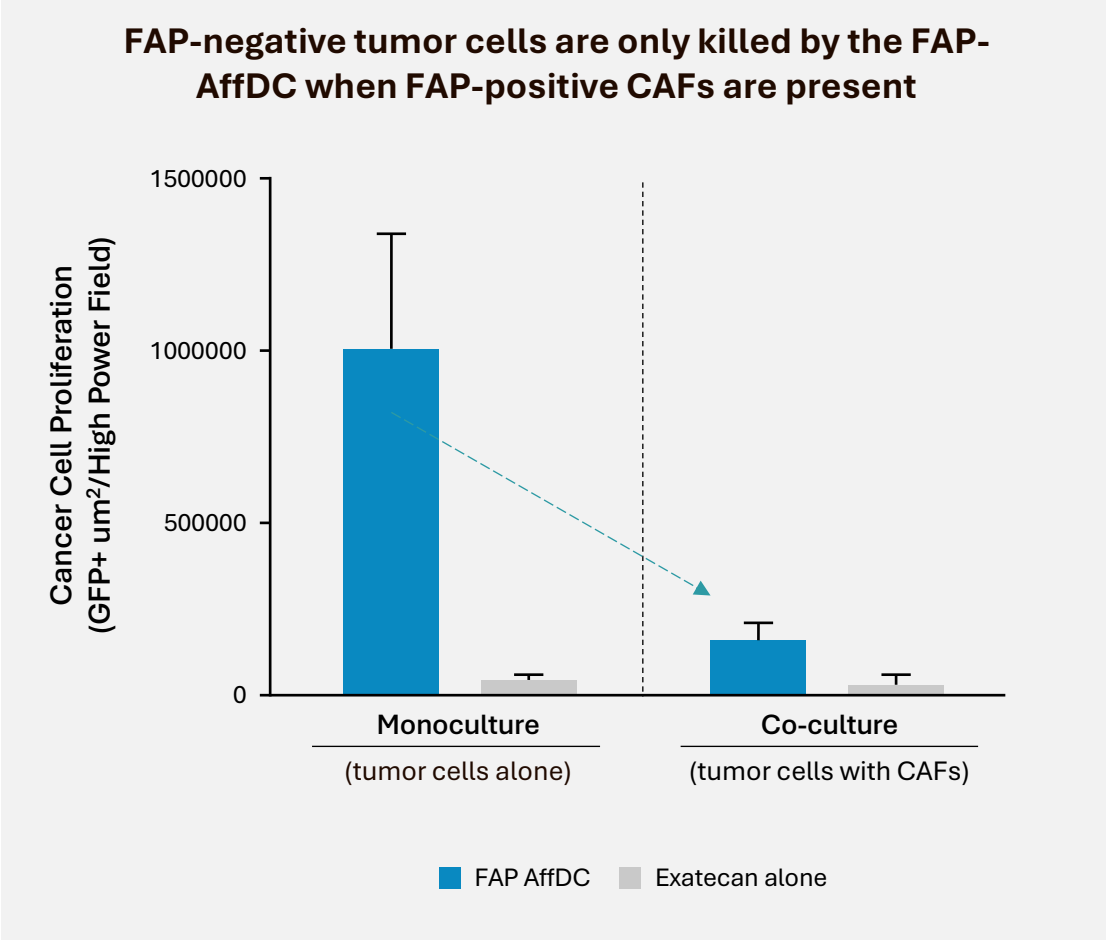



- Monomer and Dimer FAP Affimer® proteins were conjugated using standard maleimide/cysteine conjugation chemistry to a pre|CISION® linker-warhead carrying the Topoisomerase I inhibitor, exatecan
- Mass spectrometry analysis shows a clean profile with precise DAR; chromatography profile shows a single protein species
- Affinity to FAP is retained following conjugation (4-11pM affinity)

# FAP AffDC Kill Tumor Cells Only When FAP+ CAFs are Present

## FAP expression in CAFs Predicts for Response in FAP-negative Tumor Models

- The cytotoxic activity and bystander effect of the FAP pre|CISION Affimer DC (AffDC) were demonstrated in a **bystander effect *in vitro* study** with FAP-positive CAFs and FAP-negative pancreatic tumor cells (PDAC)
- FAP AffDC are **capable of killing FAP-negative tumor cells** only when FAP-positive CAFs are present. In the absence of the CAF population, the FAP AffDC are inert
- The FAP AffDC only exhibits cytotoxic activity against the FAP-negative PDAC cancer cell line when FAP is present on local fibroblasts



# pre|CISION AffDCs Have Key Advantages Over Conventional ADC Approaches

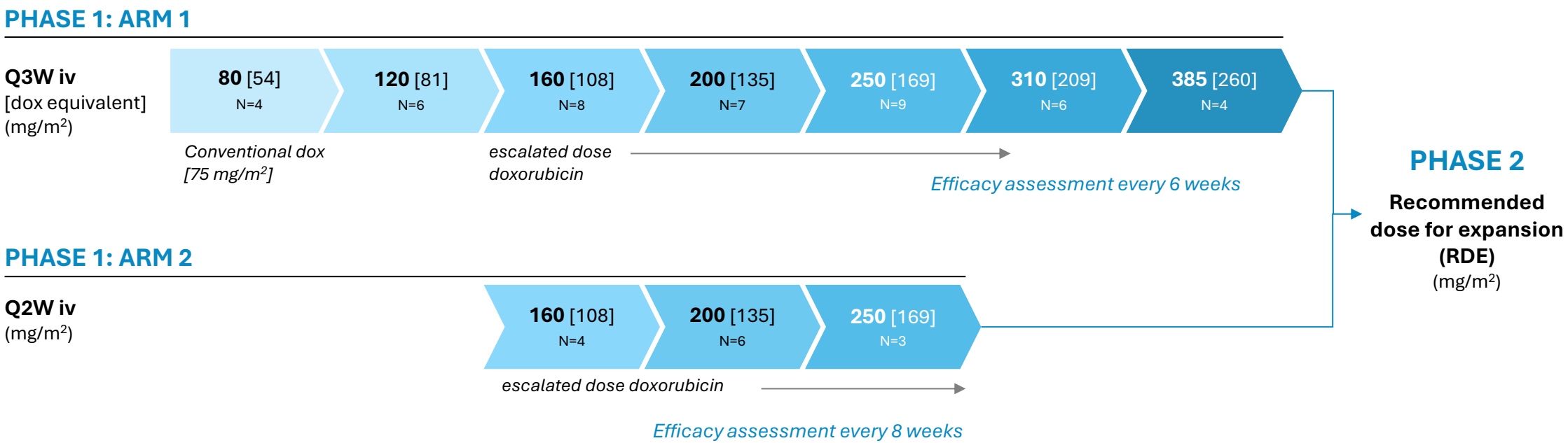
| | Avacta **pre\|CISION Affimer Drug Conjugate** | v. | Conventional **Antibody Drug Conjugate** |
|---|---|---|---|
| **Bystander mechanism of action** | **Extracellular warhead release** in the TME with limited systemic exposure<br>pre\|CISION leverages the bystander effect to efficiently kill both FAP+ and FAP- cells | | **Intracellular warhead release** in the tumor killing antigen-positive cells<br>Complex bystander effect to induce killing of antigen-negative cells |
| **Payload release** | ***Tumor-specific warhead release*** by the FAP-cleavable peptide linker | | ***Non-specific warhead release*** contributes to off-target toxicities (e.g. lung toxicity) |
| **Tumor penetration** | Small binder protein (one-tenth to one-fifth the size of an Ab) will allow better tumor penetration | | Large size limits penetration into the TME |

Avacta THERAPEUTICS

# FAP-Dox: pre|CISION-enabled doxorubicin

Phase 1 data readouts

# AVA6000 Phase 1 Trial Design and Population

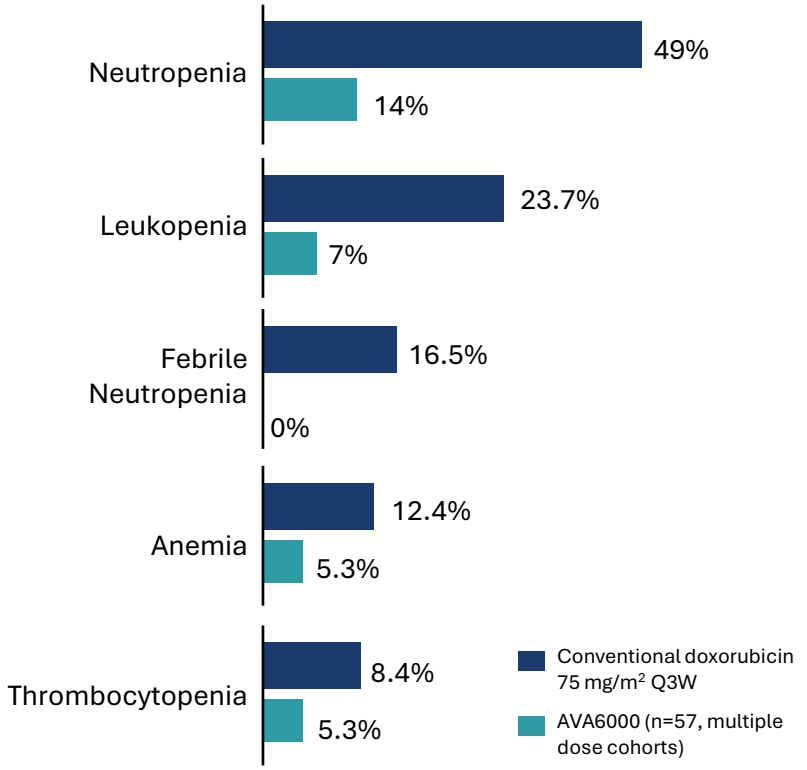



## PATIENT POPULATION AND METHODS

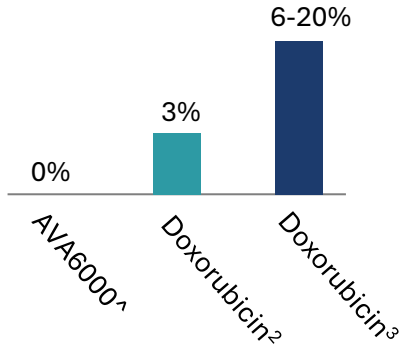
- Patients with a diagnosis of known FAP-positive cancers, including sarcoma, pancreatic cancer, colorectal cancer, head and neck cancers
- The trial includes a mix of FAP-high (universal high expression) and FAP-mid cancer indications (heterogenous expression across patients)
- Prior therapy with any anthracycline was limited to total cumulative dose of less than 350 mg/m$^2$
- Trial analyzed for safety (primary endpoint) and efficacy (secondary endpoint by FAP$^{high}$ and FAP$^{mid}$ cancer types)

# AVA6000 has reduced hematologic, cardiac and GI toxicities compared to conventional doxorubicin

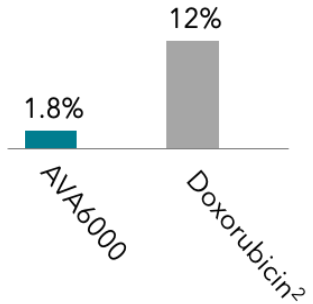
**AVA6000 reduces CTCAE Grade 3 or 4 bone marrow toxicity** compared to conventional doxorubicin



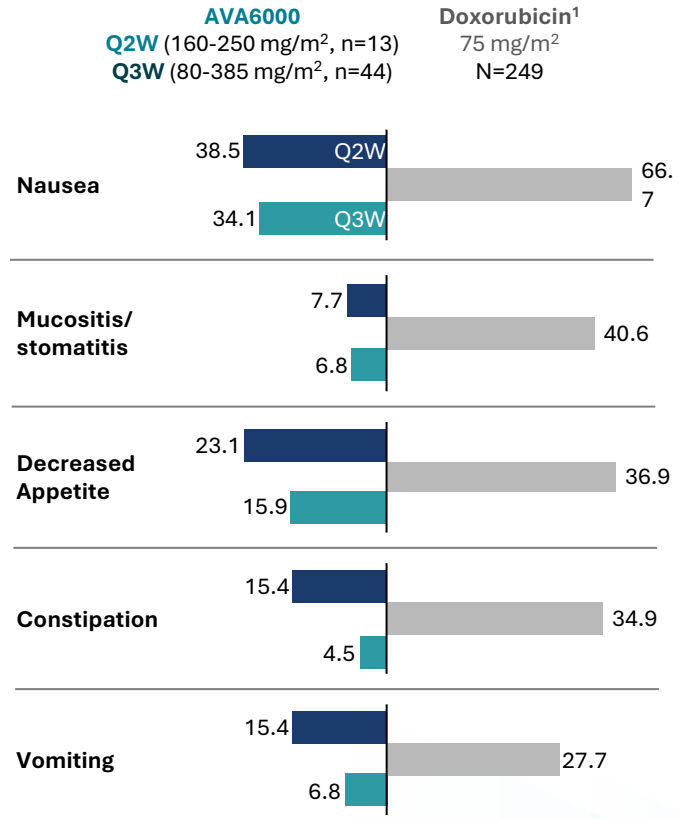

**Severe cardiac toxicity** (cardiomyopathy/ cardiac dysfunction)[1]




**Mild cardiac toxicity** (left ventricular ejection fraction dysfunction)[2]

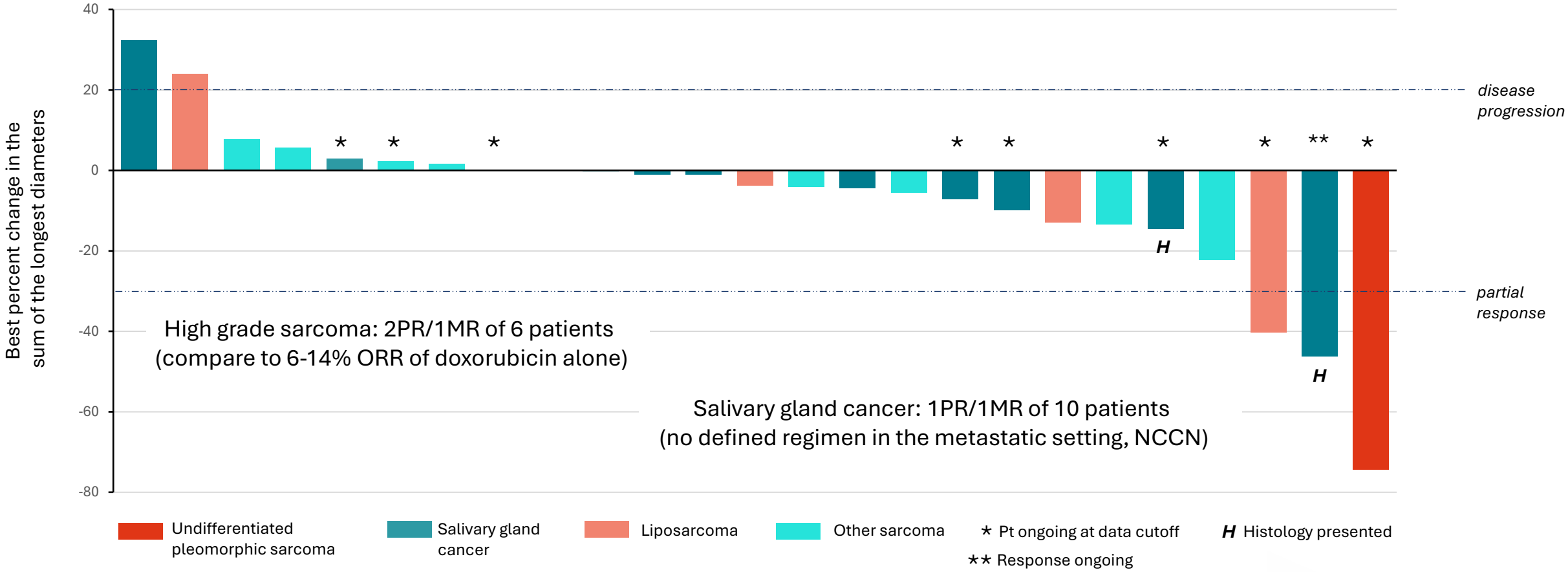



**Reduced GI toxicity** comparing Q3W and Q2W shows both regimens preserve patient vitality



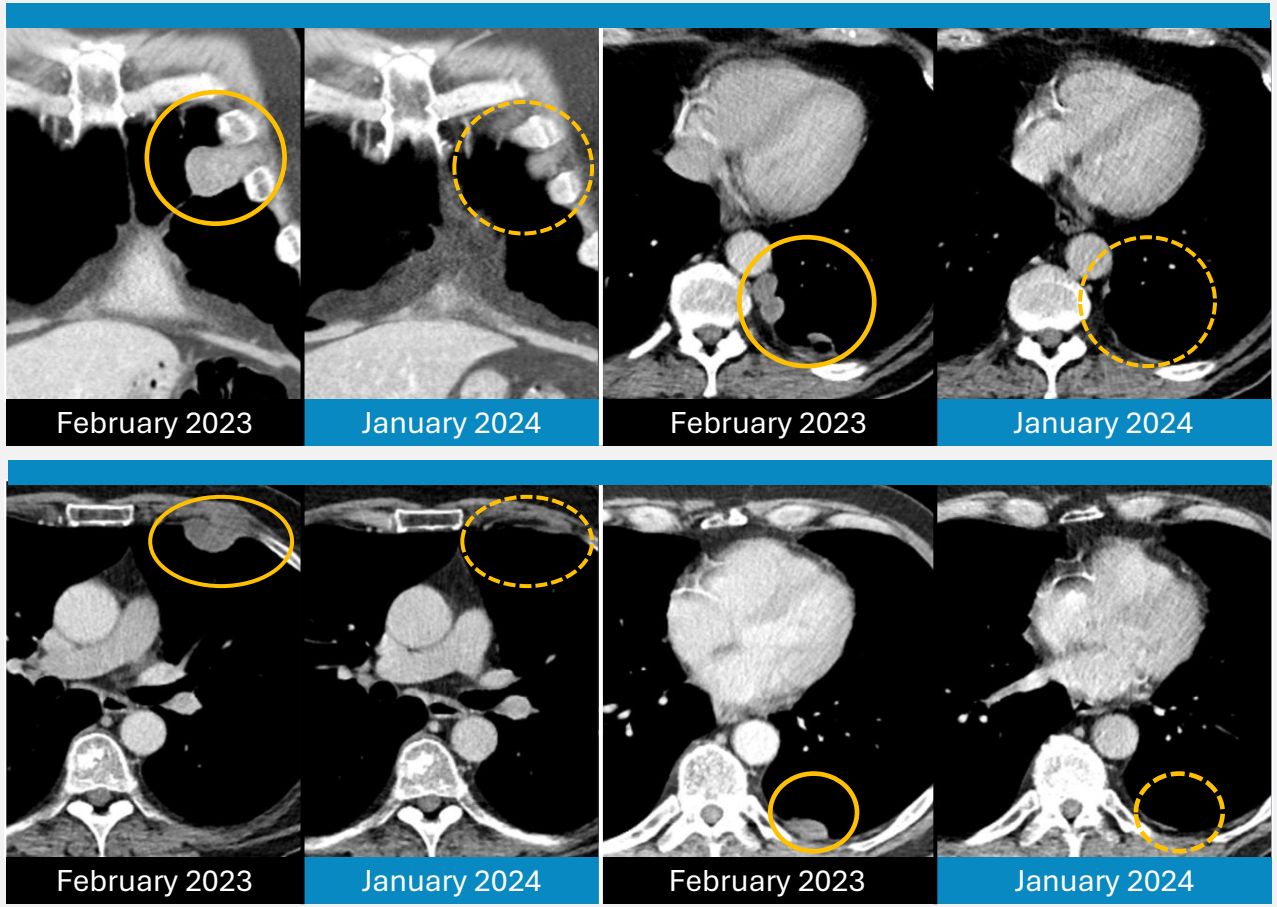

Data cutoff 19 AUG 2024. [1]Tap, WD et al. 2020. JAMA 323:1266. [2]Jones, RL et al.2021. Clin Ca Res· [3]Doxorubicin package insert
Twelves *et al.* 2024 ESMO Annual Meeting

# AVA6000 Results in Multiple RECIST Responses Among Patients with FAP-high Cancers




Data Cutoff 19 August 2024
Twelves et al. 2024 ESMO Annual Meeting

# AVA6000: First case study highlights deepening RECIST response in treatment-resistance



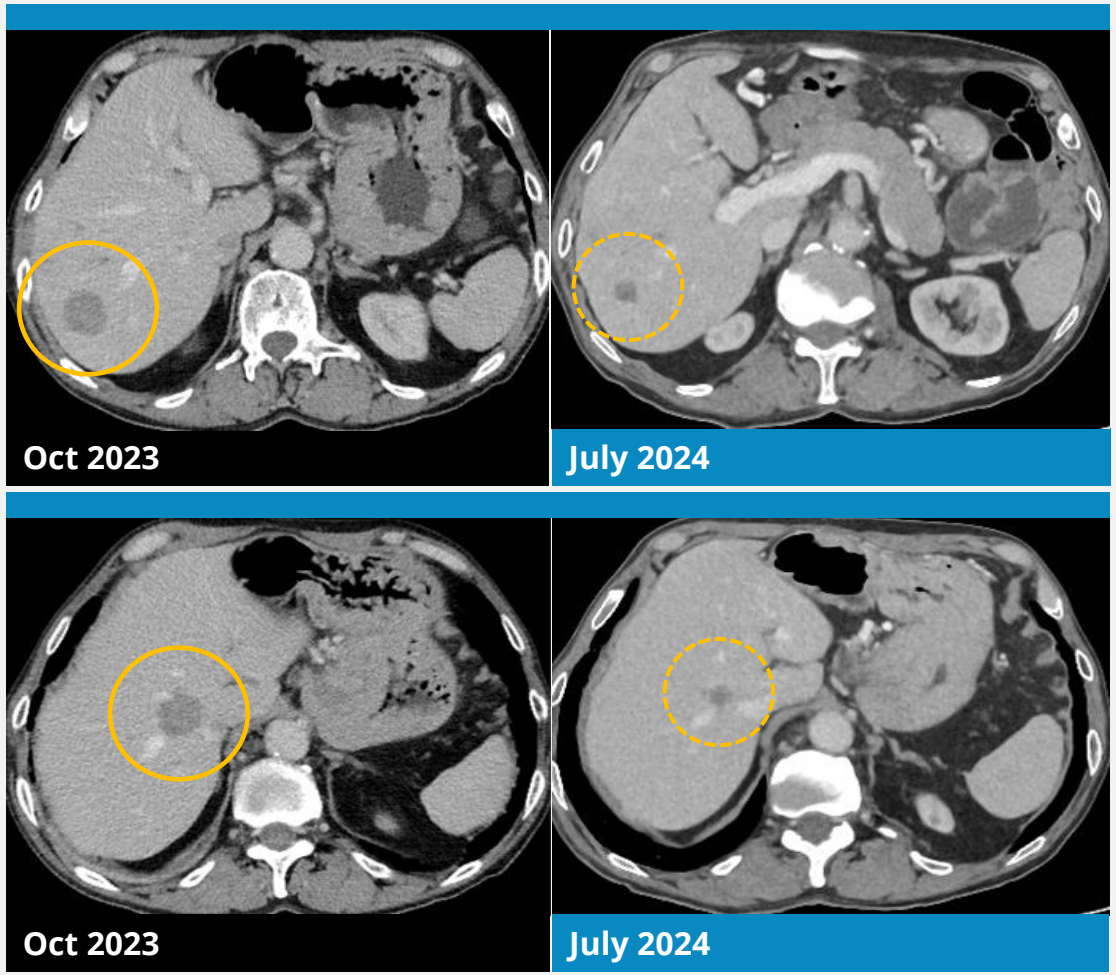

Banerji et al. 2024 AACR Annual Meeting, April 2024;
Twelves et al. ESMO Annual Meeting, Sept 2024

**Near complete resolution of the multiple pleural metastases**

- 60-year-old male patient diagnosed with a high grade undifferentiated pleomorphic sarcoma (UPS)
- Treated initially with local control measures (surgery and radiation)
- Upon developing metastatic disease, he enrolled in in an immunotherapy clinical trial for 6 months until he experienced disease progression
- He then enrolled in the AVA6000 phase 1 trial in Feb 2023. Deep partial response, duration of response >55 weeks (data cutoff 19 Aug 2024)

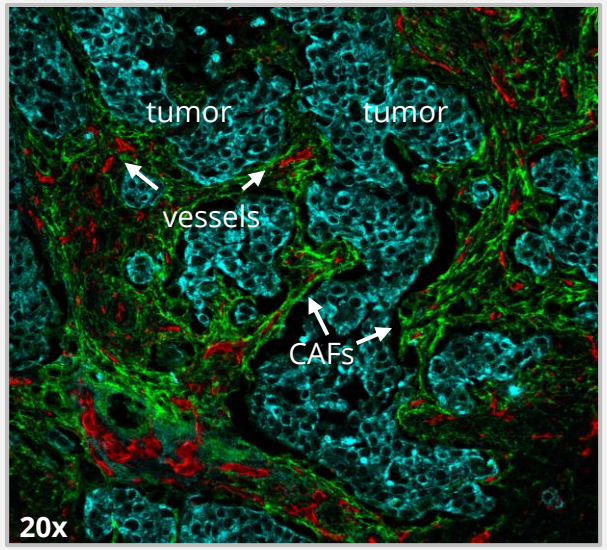
**Response continued to deepen over the course of treatment with AVA6000**

# AVA6000: Second case study highlights response with FAP-negative tumor cells




## Durable RECIST response in the setting of FAP-negative tumor cells

- 79 yo male with SGC (ductal histology). Prior therapy: triptorelin/ bicalutamide followed by disease progression
- Enrolled in the AVA6000 trial (Oct 2023) in the 385 mg/m2 Q3W cohort; highest level of intratumoral doxorubicin of any patient at 24 hours post-dose
- Confirmed partial response at 12 weeks; duration of response >18 weeks. Pt discontinued after reaching lifetime max of doxorubicin exposure; PR continuing in follow-up

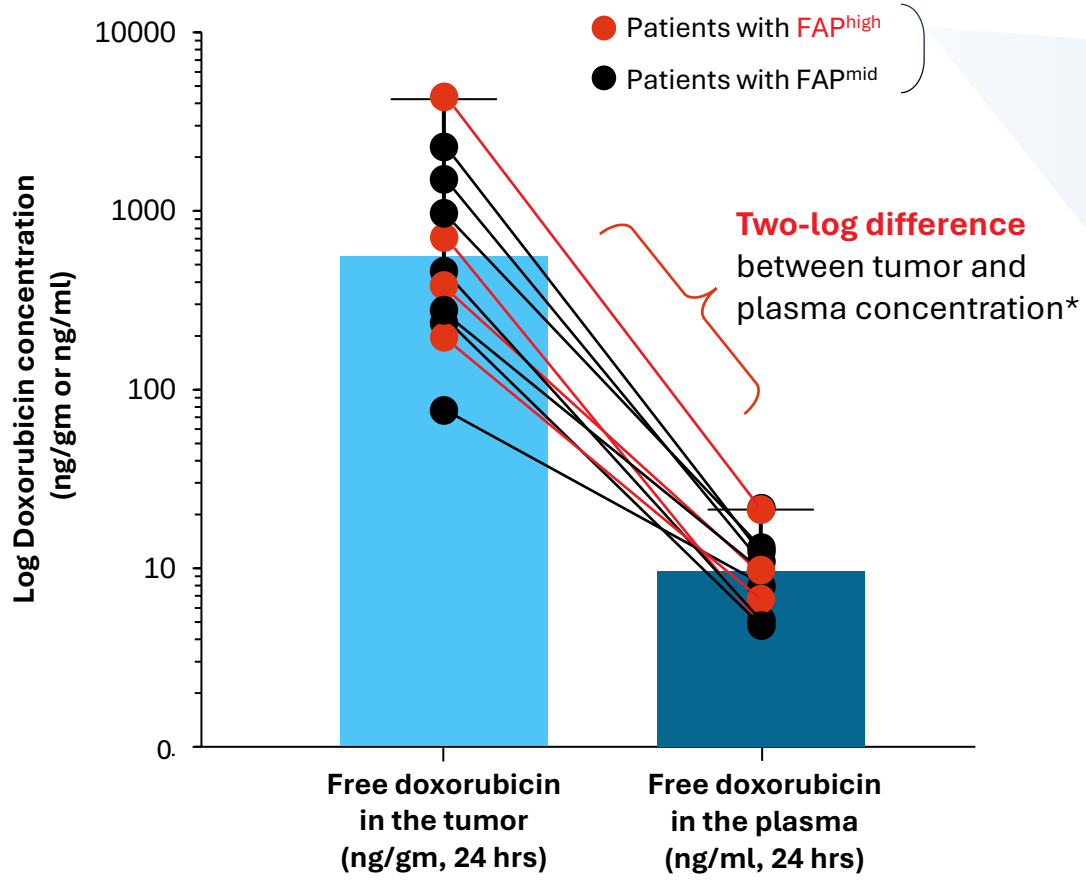



**Tumor cells are negative for FAP (aqua)**
FAP-positive Cancer Associated Fibroblast (CAF) populations (green) at the tumor-stroma interface with vessels co-localized in stroma (red)

- PanCK (tumor)
- CD31 (blood vessels)
- FAP (CAFs)

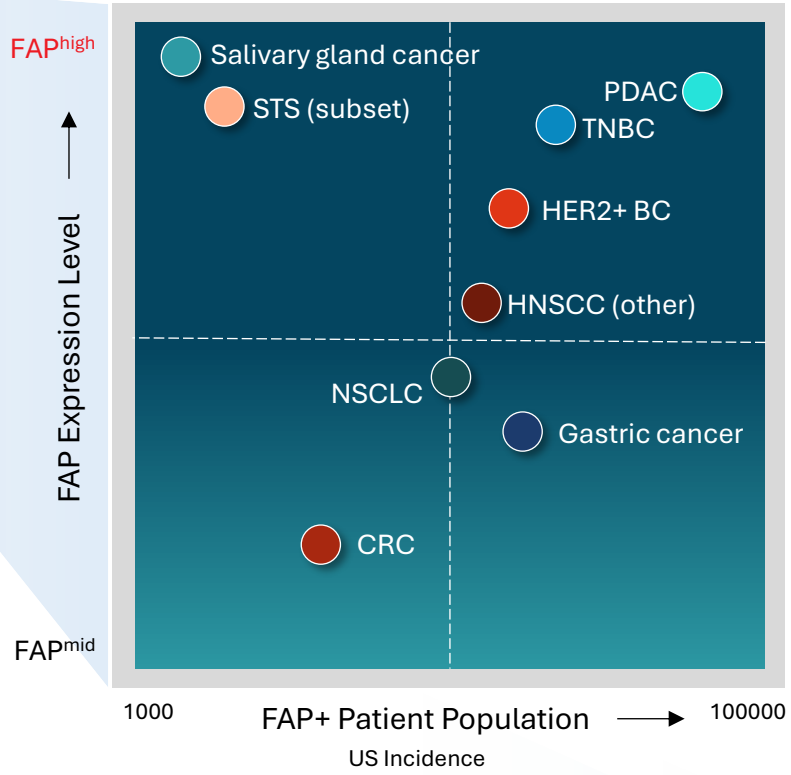
# Concentration of Warhead in the Tumor Regardless of FAP Level Opens Multiple Indications

**Released Doxorubicin Concentration 24 hr After the First Dose of AVA6000**




*In contrast, traditional ADC have reported 3-8x concentration in the TME
Banerji *et al*. 2024 AACR Annual Meeting

**Patient Populations Addressable by pre|CISION technology (with other payloads)**




CRC: colorectal cancer, HNSCC: squamous cell cancer of the head/neck, PDAC: pancreatic ductal adenocarcinoma, NSCLC: non-small cell lung cancer, TNBC: triple negative breast cancer

Avacta THERAPEUTICS

# FAP-Dox: pre|CISION-enabled doxorubicin

The Path Forward

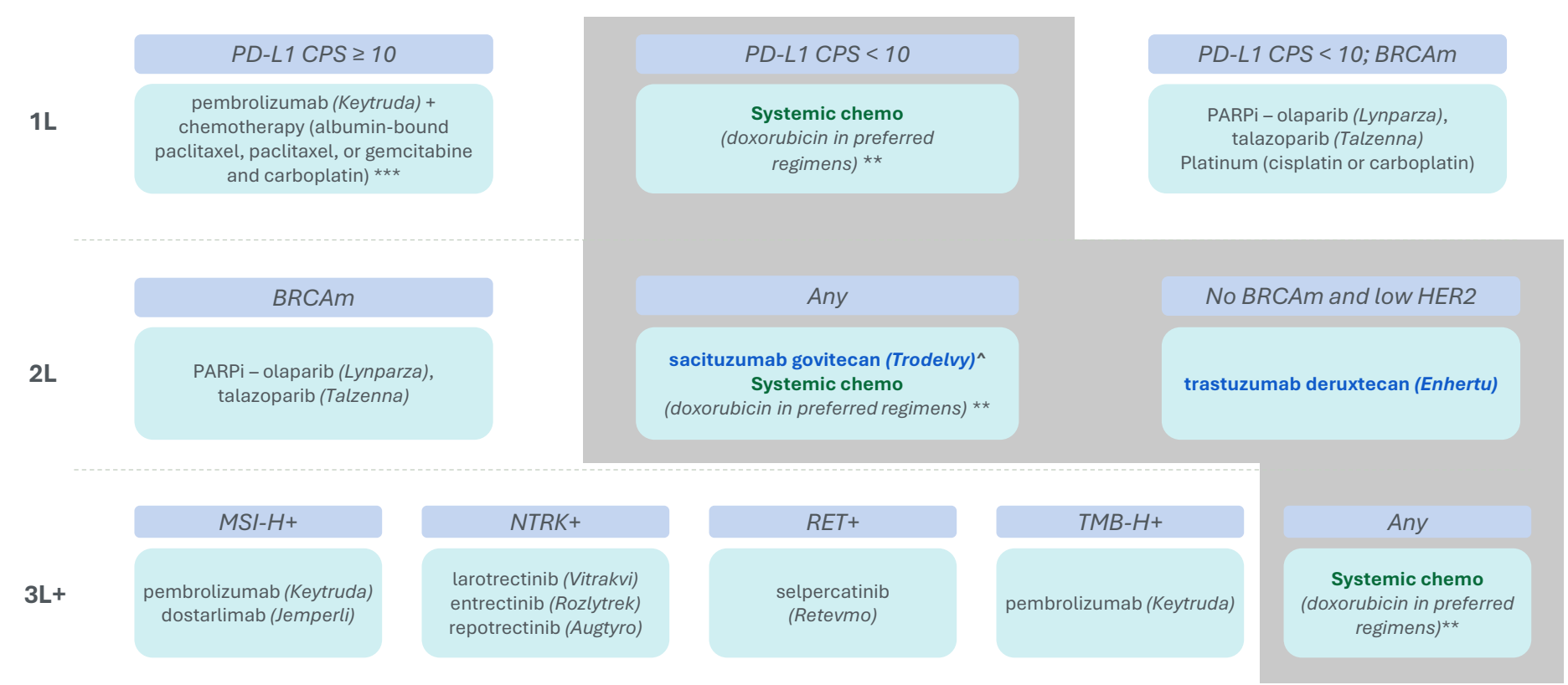
# AVA6000 Clinical Development: Rapid Route to Market in Orphan Indication

| | EARLY DEVELOPMENT | | LATE PHASE ORPHAN | SECOND INDICATION |
|---|---|---|---|---|
| | PHASE I: DOSE ESCALATION | PHASE I: EXPANSION COHORTS | PHASE 2 and 3 TRIALS | TNBC DEVELOPMENT |
| **Timing** | **Completed 2H 2024** | **Initiating 2H 2024** | **Initiating Ph 2 2H 2025** | **Parallel Late Development** |
| **Trial Designs** | Two dose escalation arms:<br>80mg/m$^2$ to 385 mg/m$^2$ administered Q3W<br>160 mg/m$^2$ to 250 mg/m$^2$ administered every 2 weeks | Initiate RDE cohort to assess intratumoral PK<br>Expansions in disease-specific cohorts to begin in 2H 2024:<br>Triple negative breast cancer<br>•<br>Salivary gland cancer<br>•<br>High grade STS | **Phase 2** trial of AVA6000 in selected **orphan indication** based on results in expansion cohorts with Phase 3 to enroll in staggered timing<br>Fastest route to market | Doxorubicin is used in multiple combinations in the setting of breast cancer therapy<br>AVA6000 is being studied in the **PD-L1- and BRCA-wt population**<br>Phase 2 and 3 development will proceed in parallel with selected orphan indication |
| **Rationale** | Dose escalation proceeds to define the RDE 81mg/m$^2$ up to 385 mg/m$^2$ in two schedules: Q3W and Q2W | RDE Expansions in three diseases with high FAP expression and sensitivity to the anthracycline MOA^ | Ph 2 and 3 trials designed for rapid approval | Move AVA6000 forward to the key indication of breast cancer in parallel with fast-track route to approval |

^CDP based on the three indications with (1) FAP expression and (2) known sensitivity to the anthracycline MOA: STS, HNSCC (salivary gland Ca) and breast cancer

# Patients with metastatic TNBC are often treated with systemic therapies across lines and represent a large market

**Treatment paradigm for unresectable or mTNBC**




*Patients may progress quickly through lines of therapy*

*" ... 90% of my metastatic TNBC patients pass through 1L, and about 70% of these patients end up at 2L. I believe even **35% of patients progress past ADCs** ... "*

*- Staff Physician, Dana-Farber Cancer Institute*

*Outside of the metastatic setting, **doxorubicin** is part of the preferred (neo)adjuvant treatment regimen*

Key: **ADC** **Guidelines include doxorubicin as option** *Subtype / biomarker*

Note: * Based on total drug treatable populations, calculations based on snapshot view of patient population; ** Systemic chemotherapy (preferred regimens): Anthracyclines (doxorubicin, liposomal doxorubicin), Taxanes (paclitaxel), Anti-metabolites (capecitabine, gemcitabine), Microtubule inhibitors (vinorelbine, eribulin); *** Can be used as 2L+ if patients have not previously received PD-L1 inhibitor therapy, but no data available to support use as additional line in patients who progressed while on PD-L1 inhibitor therapy; ^ FDA label is for 3L, but NCCN recommends use in patients who have received 1 prior regimen in a metastatic setting and can be considered for later line if not used as 2L

Source: Citeline Datamonitor; NCCN 2024 guidelines; L.E.K. analysis

Avacta THERAPEUTICS

# The Spatial Organization of the TME Supports the pre|CISION Bystander Effect Delivery

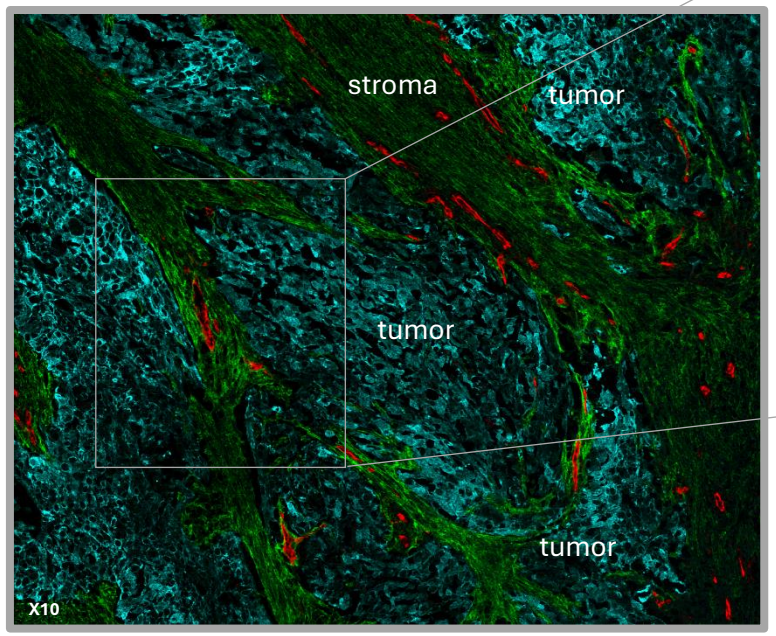
**The bystander effect of the pre|CISION platform warhead delivery:**

1 | **Vessels** (🔴) deliver the conjugated molecule to the **local FAP+ CAFs** (🟢)

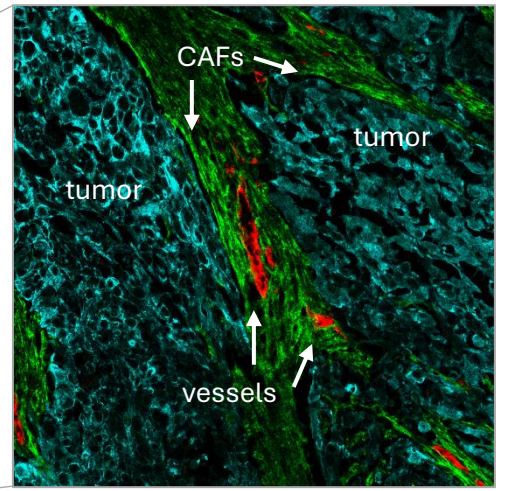
2 | FAP cleaves the conjugated molecule

3 | Active warhead is free to move into **FAP-negative tumor cells** (🔵) *or* FAP-positive CAFs (🟢)

**Triple negative breast cancer (TNBC)**




High-power image of the tumor-stroma interface

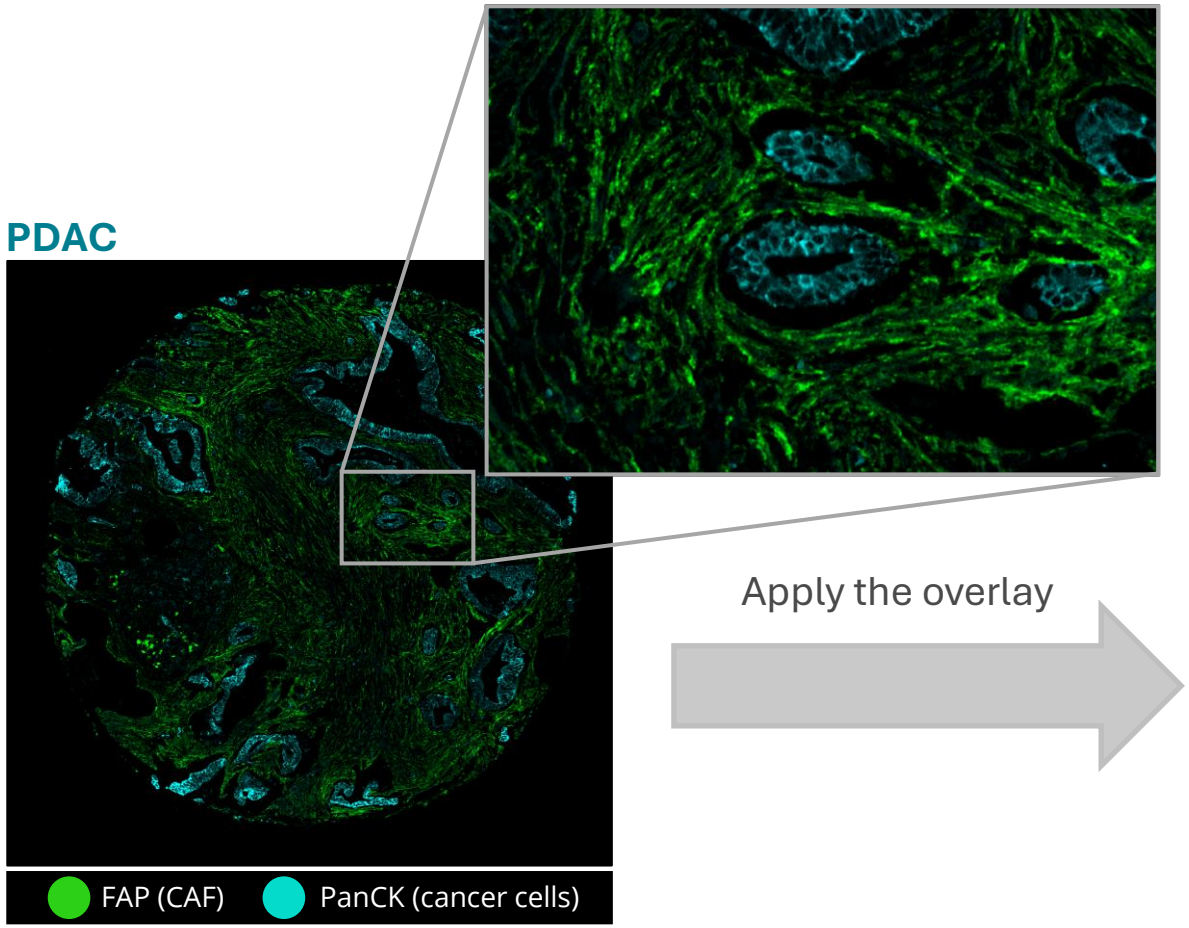



FAP (CAF)
CD31 (blood vessels)
PanCK (tumor cells)

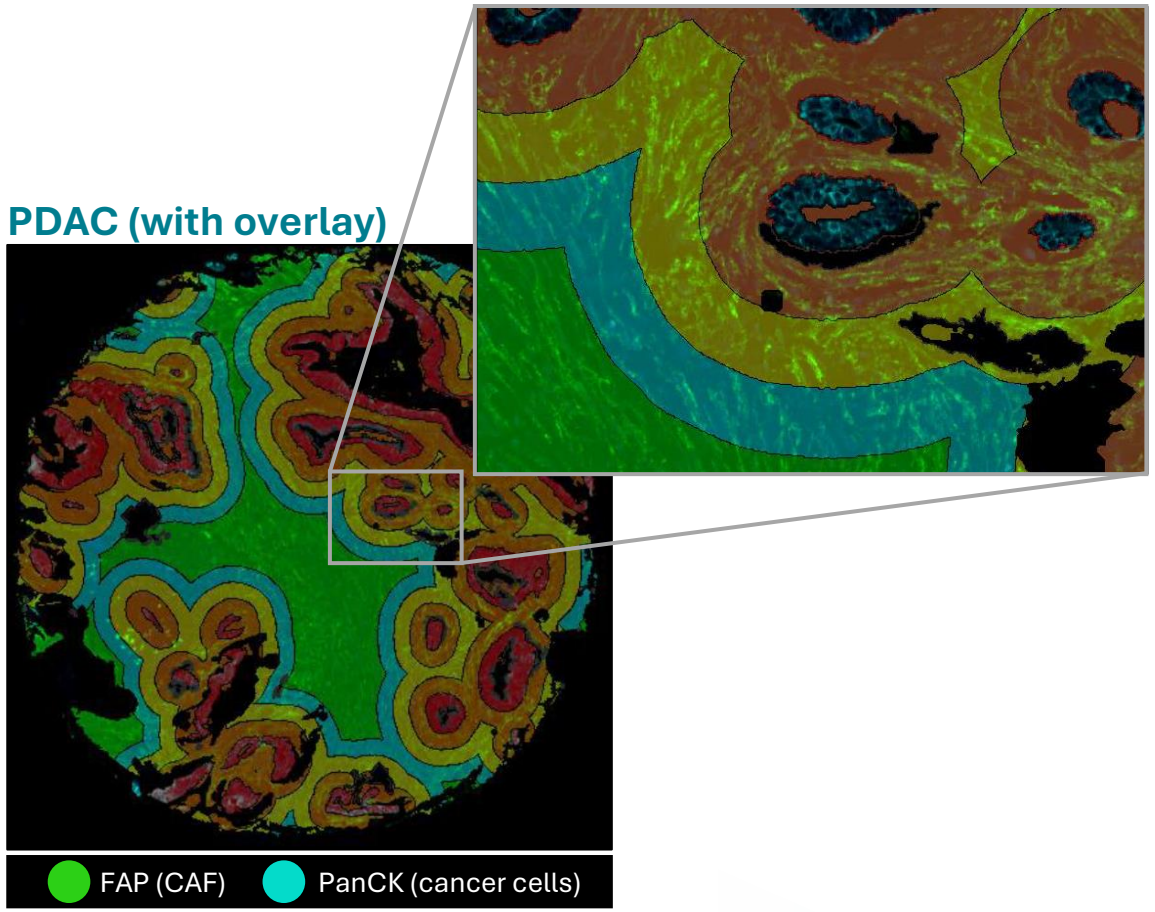
Avacta, internal data (unpublished)

In the TME, CAFs with the **highest expression of FAP** are concentrated at the **tumor-stroma interface** and co-located with the blood vessels which delineates the "bystander effect" delivery

# FAP expression is diminished in CAFs that are distant from the tumor-stroma interface

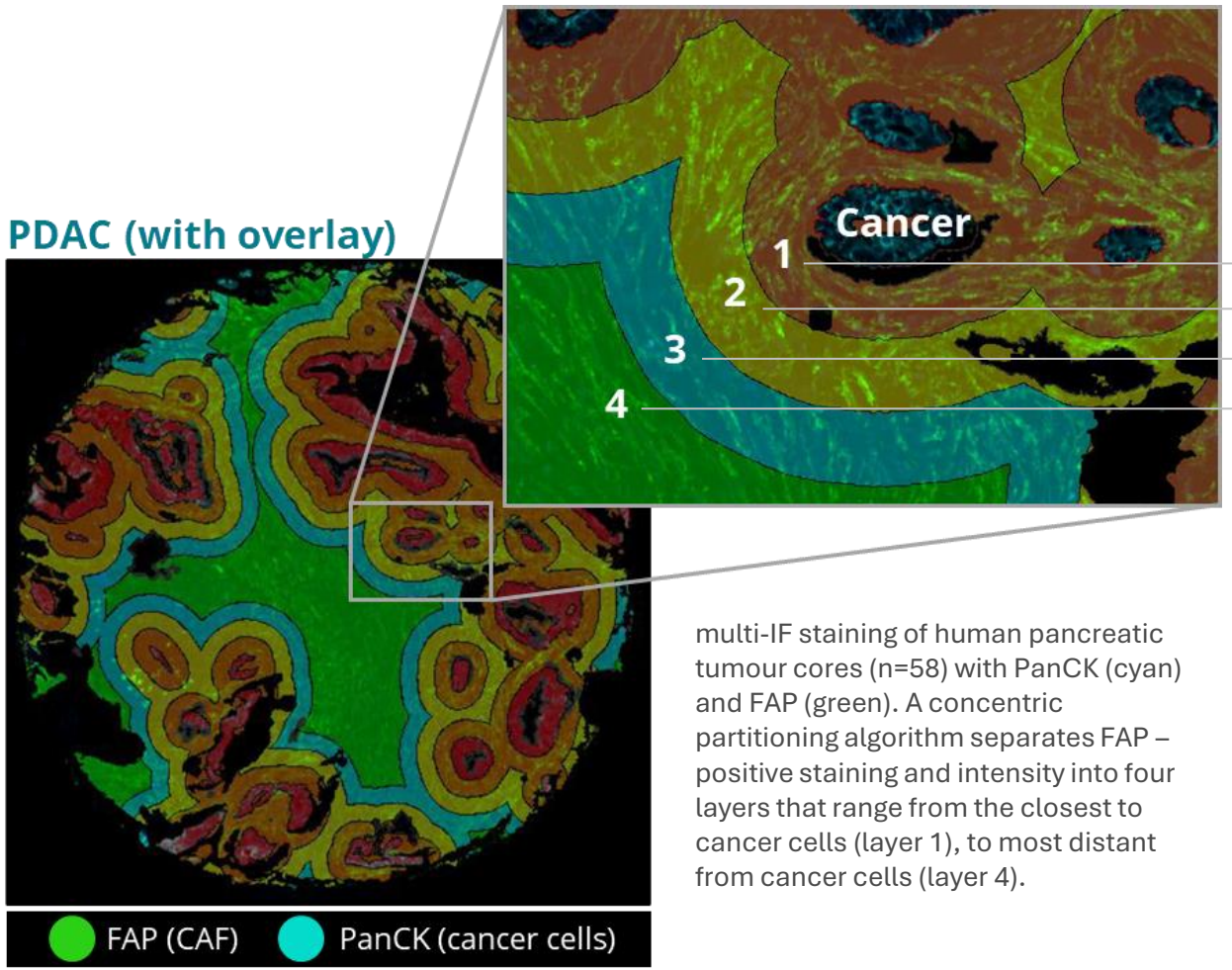



Apply the overlay

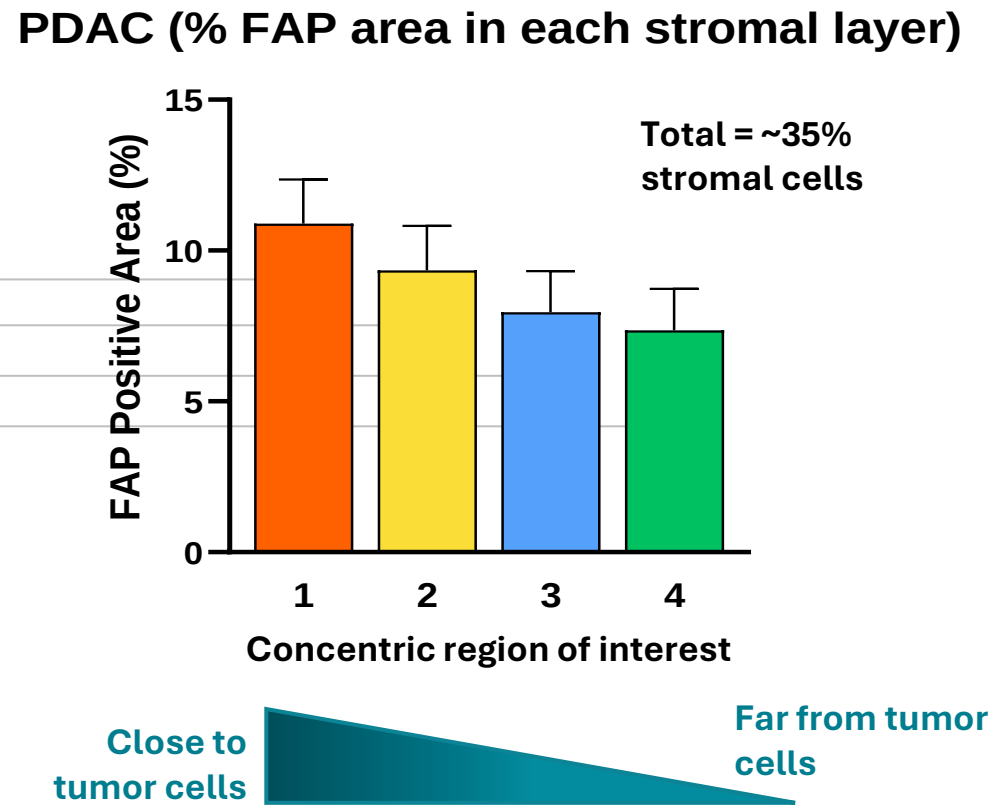



To investigate how FAP expression changes at the tumor-stroma interface, we use a **concentric partitioning algorithm**

# Overexpression of FAP at the tumor-stroma interface is key to the bystander mechanism




multi-IF staining of human pancreatic tumour cores (n=58) with PanCK (cyan) and FAP (green). A concentric partitioning algorithm separates FAP – positive staining and intensity into four layers that range from the closest to cancer cells (layer 1), to most distant from cancer cells (layer 4).



# Our Tempus collaboration will accelerate the development of our pre|CISION medicines

## Advantages of the Avacta - Tempus collaboration

- Identify the **addressable patient population** for each pre|CISION® medicine entering clinical development leveraging the largest oncology real-world dataset
- Assessing co-expression of FAP with genes predicting sensitivity to the payload will optimize **selection of indications for each clinical program**
- Together, these advantages will shorten the timeline of development and **increase the probability of technical and regulatory success**


***Tempus AI*** website: www.tempus.com

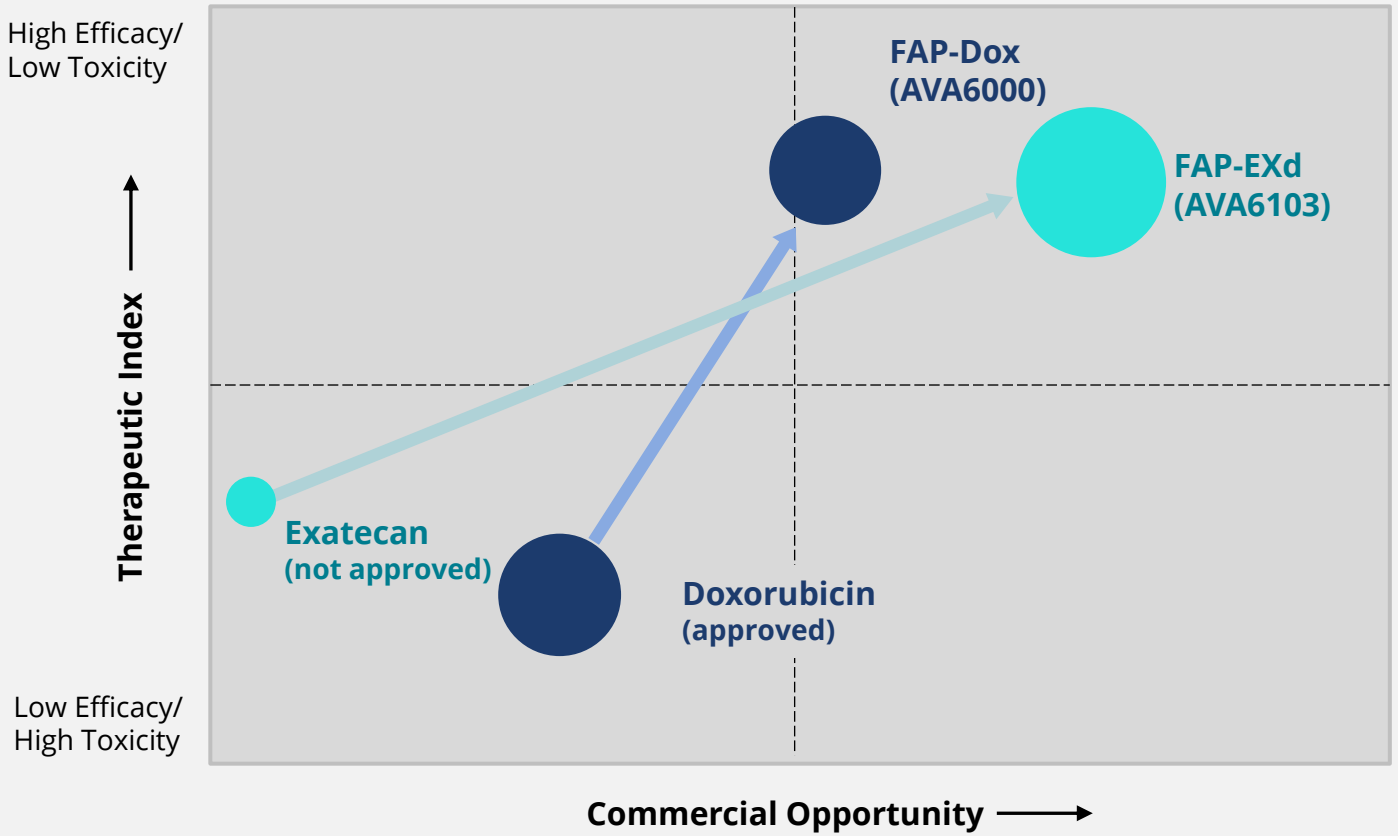
# Seizing the market opportunity: payloads as a commercial success

pre|CISION®-enabling results in a **significant increase in the therapeutic index** for doxorubicin with three potential indications

Exatecan has a very challenging therapeutic index, severe toxicities that limits dosing and a short half life, however there is **robust evidence for monotherapy activity**

We expect **FAP-EXd (AVA6103)** to be highly active in a number of indications where there is observed activity of other topoisomerase I inhibitors (e.g. breast cancer, gastric, small cell lung cancer)

We believe that pre|CISION-enabling can transform this payload (exatecan) to a **highly successful anti-cancer drug**




Size of bubble represents the estimated absolute patient number in the addressable population with Multiple, planned approvals in the clinical development planning tools

# Seizing the market opportunity with strong intellectual property positions and laser focus

Avacta has exclusive rights to the pre|CISION® and the Affimer® technology, including the collective IP of each individually and the combined franchise

This simple intellectual property position is at the core of our partnerships to develop innovative therapeutics, research tools and diagnostics

Avacta's pre|CISION technology has the potential to address many solid tumor indications with high unmet need, with a substantial market opportunity

Avacta has developed significant know-how and IP in the manufacturing of pre|CISION therapies which is combined with a low cost of goods for drug supply

# Questions and Answers

Thank You

Avacta
THERAPEUTICS

# Avacta Therapeutics: Milestones and Highlights

| Program | Corporate Milestone | |
|---|---|---|
| **AVA6000** pre\|CISION FAP-enabled doxorubicin | Complete Q3W Dose escalation trial | ✓ |
| | Initiate Q2W Dose Escalation | ✓ |
| | Orphan Designation in Soft Tissue Sarcoma | ✓ |
| | Presentation of Q3W Dose Escalation Results (AACR 2024) | ✓ |
| | Identify RDE and Open Phase 1b Expansions in 3 Indications | 2H 2024 |
| | Present Full Dose Escalation Results | 2Q 2025 |
| | Phase 2 Trial in Selected Indication | 2H 2025 |
| Pipeline assets: **pre\|CISION** | Candidate Selection of pre\|CISION FAP-EXd (AVA6103) program | 2H 2024 |
| | FAP Affimer pre\|CISION drug conjugate (AffDC, AVA7100) candidate selection | 2H 2025 |
| Pipeline, including **Affimer Drug Conjugate** | Full Pipeline revealed | ✓ |