Avacta THERAPEUTICS

Avacta Therapeutics

Expanding the reach of highly potent cancer therapies

January 2025

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.

Although forward-looking statements contained in this presentation are based upon what management of the Company believes are reasonable assumptions, there can be no assurance that forward-looking statements will prove to be accurate, as actual results and future events could differ materially from those anticipated in such statements. The Company undertakes no obligation to update forward-looking statements if circumstances or management's estimates or opinions should change except as required by applicable securities laws. The reader is cautioned not to place undue reliance on forward-looking statements.

Source:

Avacta is a clinical stage biotech focused on the pre|CISION platform

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

pre|CISION **Platform**	• Allows for targeted delivery of payload in the TME, sparing healthy tissue • Generation of multiple follow-on candidates with unique features and payloads • **pre|CISION® platform** with multiple advantages over conventional oncology ADCs
Highly Differentiated Pipeline Targeting Multi Billion Dollar Markets	• **AVA6000** (FAP-Doxorubicin) reported strong clinical data in the Phase 1 dose escalation trial (AACR, 2024 and ESMO, 2024) • **AVA6103** (FAP-EXd) is a pre|CISION®-enabled conjugate of the topo I inhibitor exatecan with potential Phase 1 start in 1Q 2026 • **AVA7100** is a preclinical pre|CISION®-enabled FAP-Affimer candidate • Broad IP portfolio covering foundational pre|CISION® and Affimer® technology
Near-Term Milestones	• **AVA6000**: Complete Phase 1 data in 2Q25, Phase 2 initiation in 2H25 • **AVA6103**: Candidate selection in 2H 2024 • **AVA7100**: Candidate selection in 2H 2025
Financial Position & Management Team	• AIM-listed company with cash and cash equivalents of £32.5 million as of June 30, 2024 • A process to divest the revenue-generating diagnostics division is ongoing, transforming Avacta into a pure-play therapeutics company • Exploring opportunities for a potential dual listing on NASDAQ • Highly experienced Management Team, Board, and Scientific Advisory Board

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

Brian Hahn, MBA

Chief Financial Officer

Brian has >25 years of senior financial and operations experience in biopharma, including a 15 years as CFO of GlycoMimetics, Inc., where he led the company's 2014 initial public offering (IPO) on Nasdaq.

He serves as co-chairman of the BIO Finance and Tax Committee, and has also served on the Securities and Exchange Commissions' Advisory Committee on Small and Emerging Companies

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

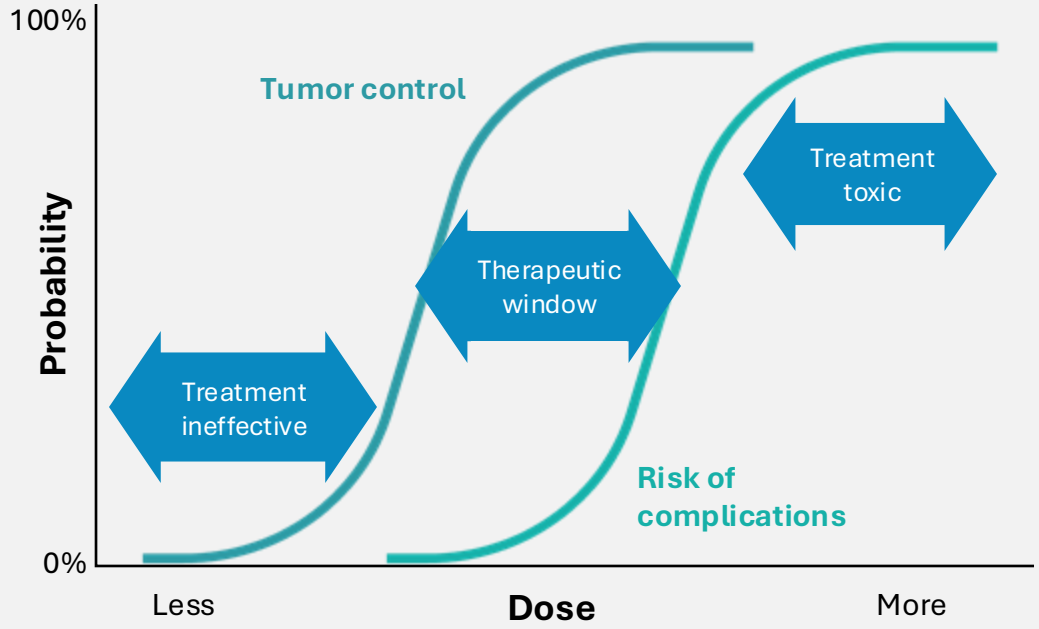
Potent cancer drugs kill indiscriminately, causing toxicity throughout the body

Therapeutic index challenge: Most oncology 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 released payload directly in the TME



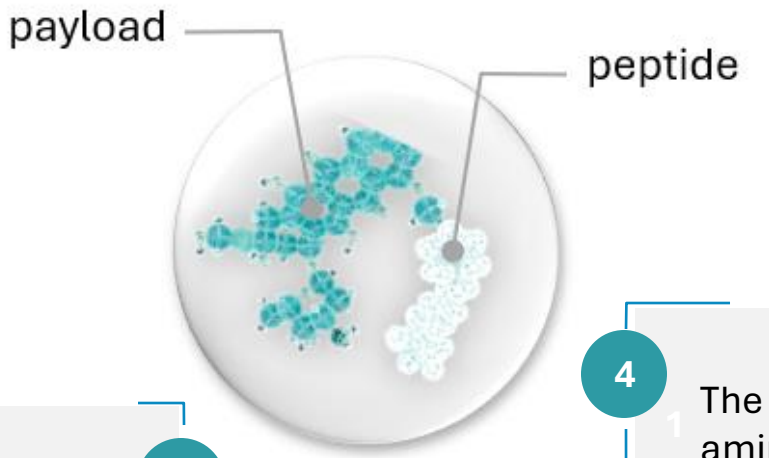
The therapeutic index of a drug is the ratio of the dose that is toxic in half of the population to the dose that exerts a therapeutic or effective response in half of the population

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

The pre|CISION peptide drug conjugates unleash powerful drugs selectively in the tumor through masking and release

1 The goal of the pre|CISION peptide is to **mask the toxic effects of an active payload** in the tissues and only release it in the tumor

3 The pre|CISION peptide **binds to the active site** of the FAP protease and is **cleaved at the tumor-stroma interface** releasing the drug in the tumor



2 **pre|CISION** is a peptide drug conjugate platform that binds a **cleavable peptide to an active warhead** to disable the effects of the drug

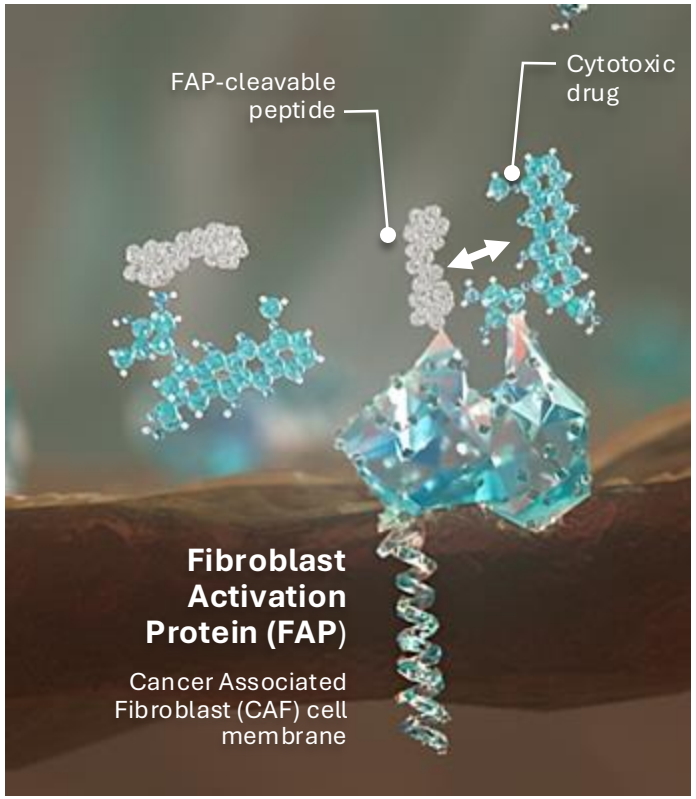
4 The pre|CISION peptide is a **"micropeptide"** of 2 amino acids and an engineered cap that is **invisible to the immune system** with essentially no risk of immune destruction

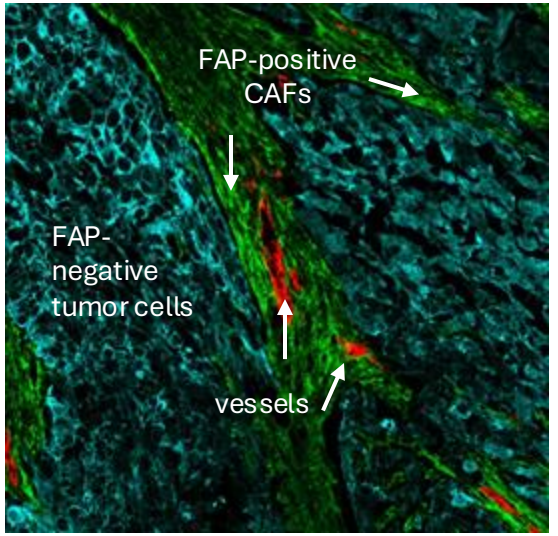
Avacta is redefining how oncology therapeutics are targeted specifically to the tumor

pre|CISION® medicines are a **differentiated means of targeting a drug specifically to the tumor** by leveraging a specific enzyme (protease) activity in the TME

The **pre|CISION linker peptide (1)** binds to the active site of FAP and **(2)** is cleaved from the conjugated drug, releasing active payload directly in the TME, capable of killing tumor cells via the bystander effect

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

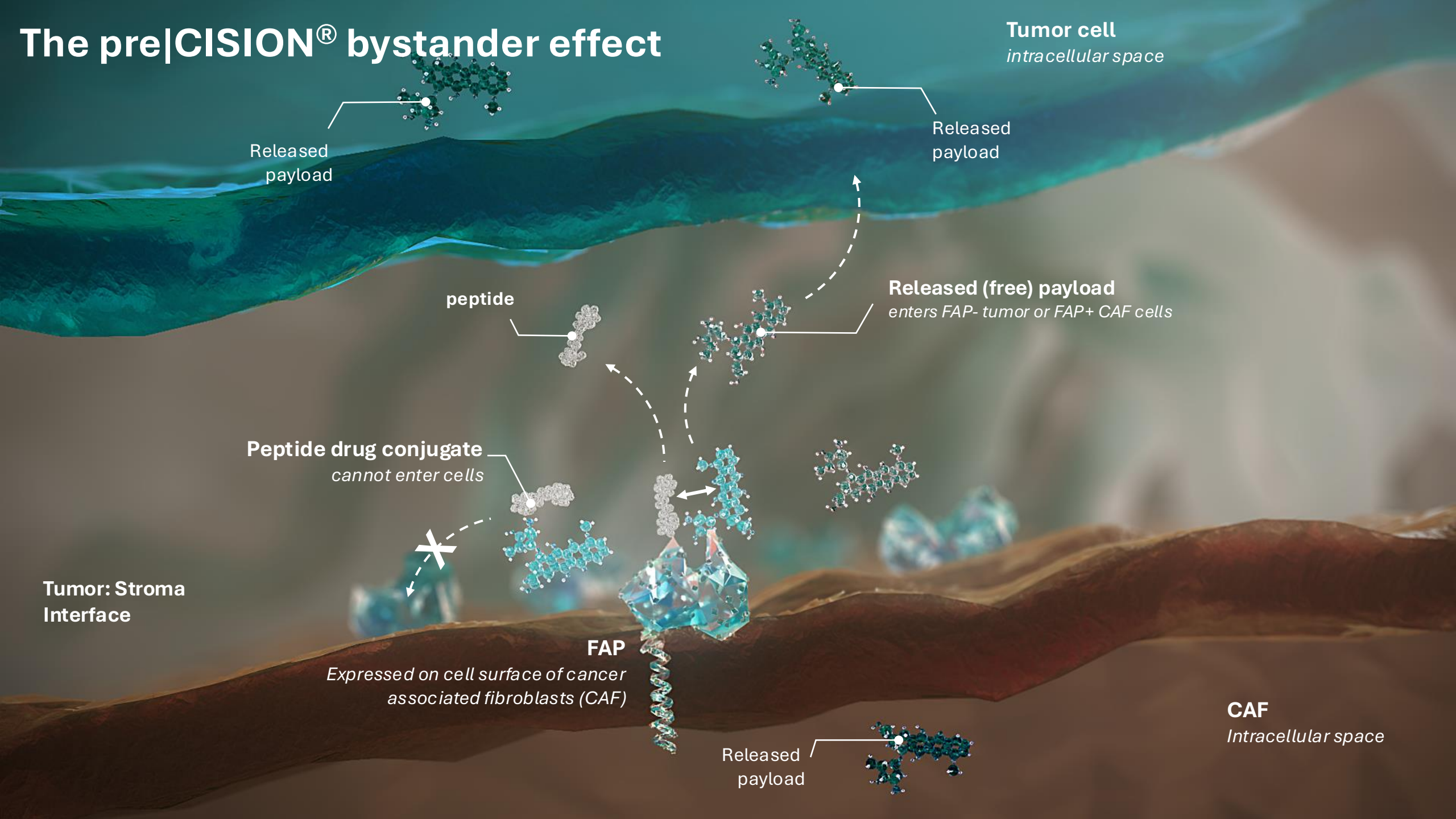




Multiplex immunofluorescence defining the tumor: stroma interface (TNBC)

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

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

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 pre|CISION leverages the bystander effect to efficiently kill both FAP+ and FAP- cells		***Intracellular warhead release*** in the tumor killing antigen-positive cells Complex bystander effect to induce killing of antigen-negative cells
Tunable, tumor-specific payload release	***Tumor-specific warhead release*** by the FAP-cleavable peptide linker with tunable release kinetics		***Non-specific warhead release*** by general protease activity contributes to off-target toxicities (e.g. lung toxicity)
Lack of Immunogenicity	There is no immunogenicity risk as the pre|CISION micropeptide (2 amino acids) cannot be recognized		Anti-drug antibody responses to both antibodies and longer peptide approaches risk immune responses and destruction
GMP manufacturing simplicity	Small molecule timelines and costs of manufacturing		Complex, long and expensive manufacturing process

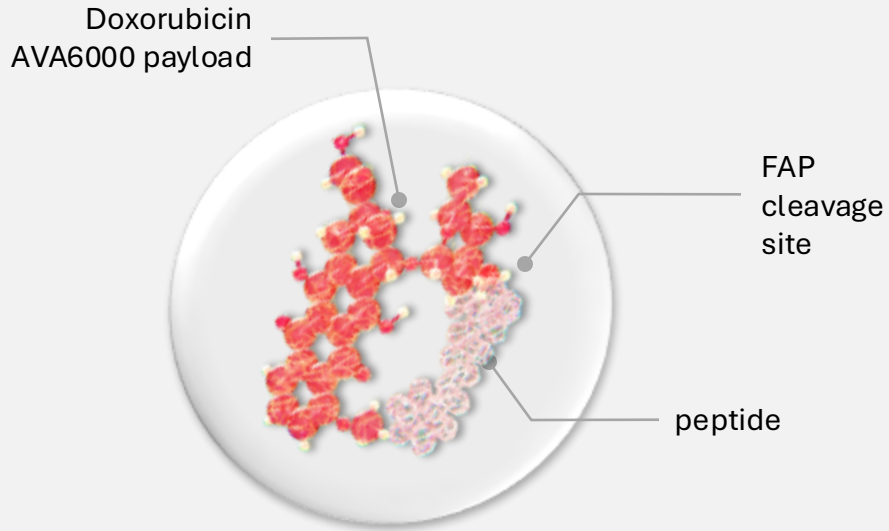
AVA6000: Avacta technology delivers cancer drugs directly to the tumor while protecting healthy tissue

Foundational pre|CISION® platform technology in the peptide drug conjugate format is the basis of our first clinical asset, FAP-Dox (AVA6000) now completed its Phase 1 and I expansion cohorts

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

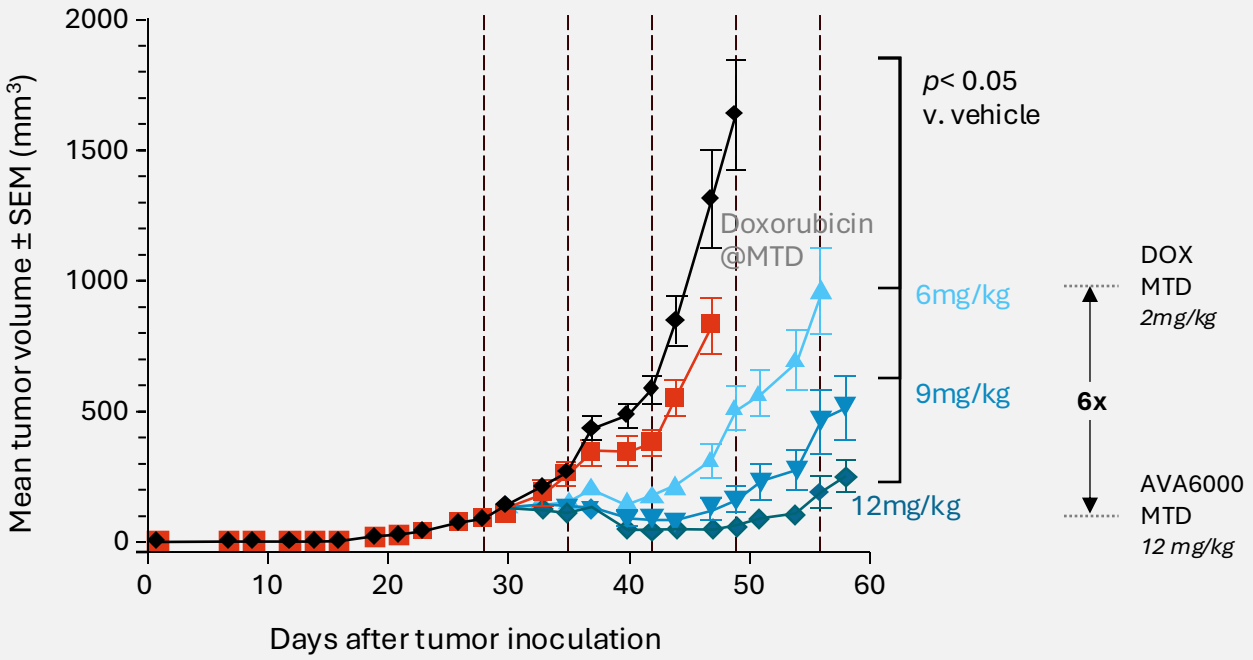


pre|CISION-enabled doxorubicin (FAP-Dox) where active doxorubicin is released in the TME by the protease action of FAP, expressed on the cell surface of CAFs

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

AVA6103: Building on a proven foundation and advancing our platform technology with a novel payload

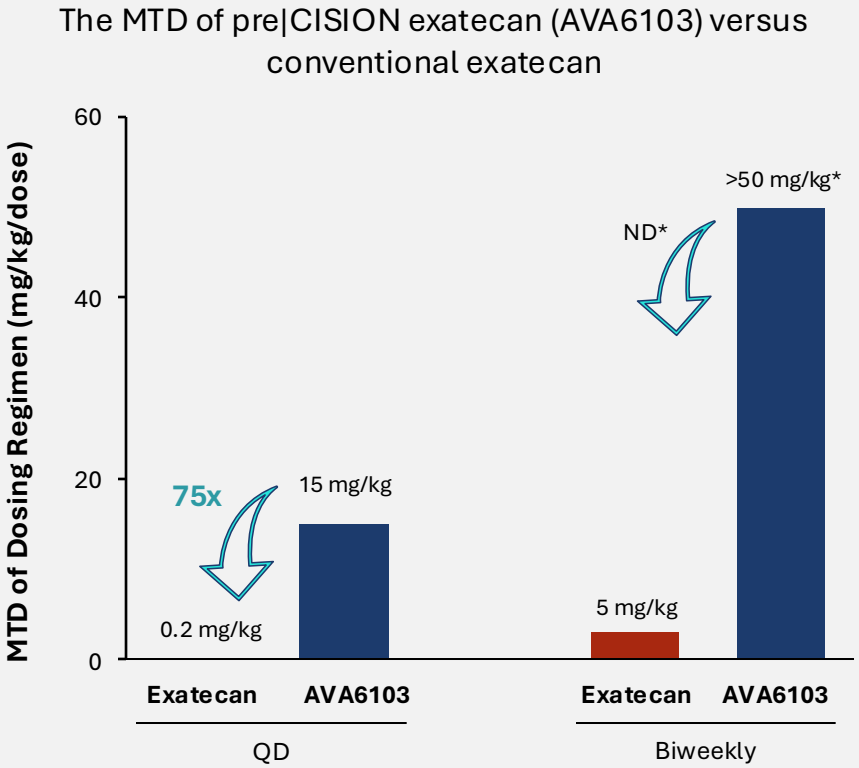
To leverage additional payloads (exatecan) and optimize therapeutic index, the **properties of the FAP cleavable peptide have been advanced** (FAP-EXd, AVA6103)

The tumor to plasma PK can be tuned to the desired exposure through chemistry advances and a computational algorithm trained using *in vitro* and *in vivo* data with multiple payloads

Two 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

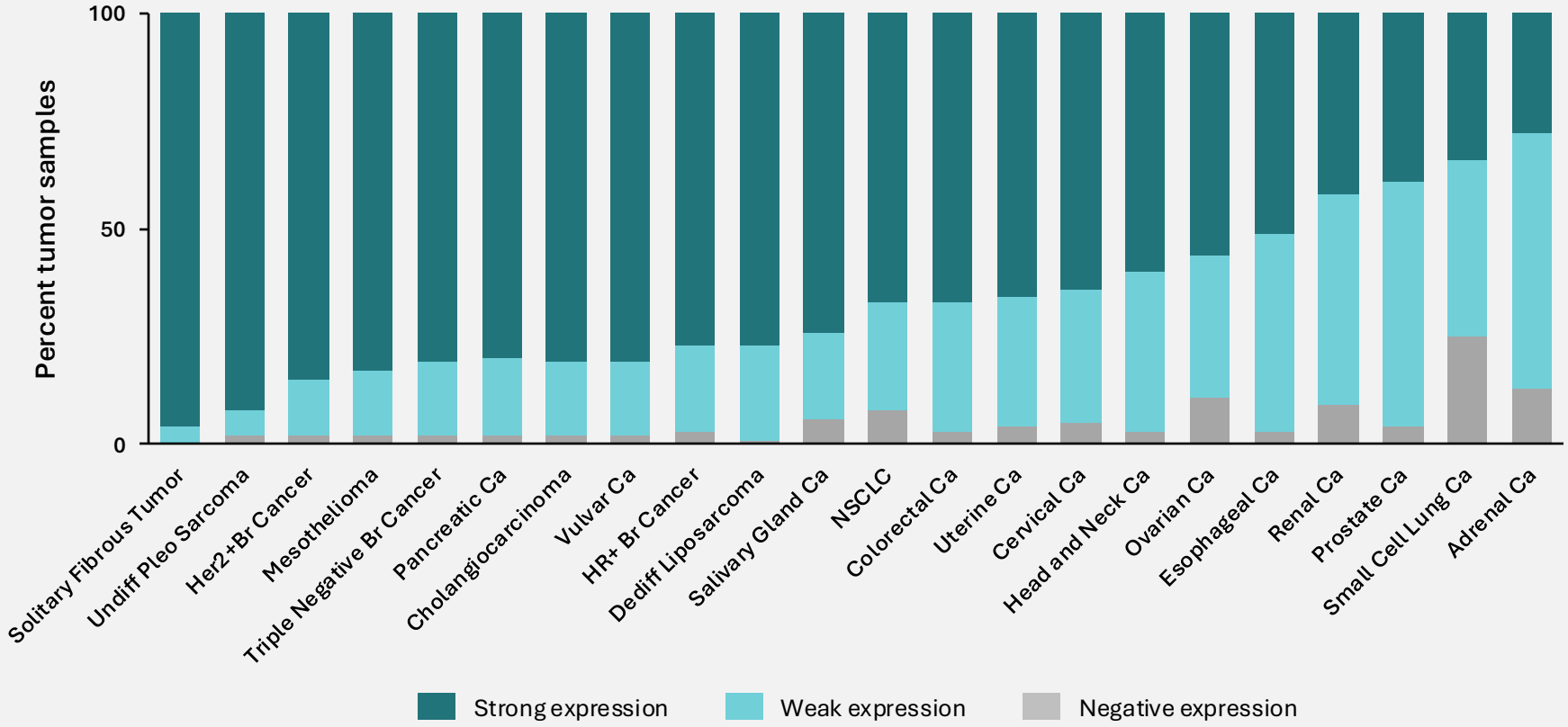
These changes together create a **sustained release delivery** in the TME, significantly extending the therapeutic index



*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)

The addressable population with pre|CISION extends across multiple indications

- FAP expression was analyzed across >160,000 tumor samples using RNAseq profiling (Tempus AI)
- Tumors were characterized as FAP negative, FAP weak expression and FAP high expression with cut-points based on published IHC data
- Expression reported across >90% of solid tumors and RNA survey confirms these data



Notes: Data in the Tempus AI LENS database were analyzed for expression of FAP. Cut-points to define negative, weak and strong were the same across the entire database and were set based on known/published positive rates for IHC in 3 diseases: gastric cancer, triple negative cancer and SCLC. Generally, negative correlates with 0+ stroma staining, weak expression correlates with 1+ stroma staining, and strong expression correlates with 2-3+ stroma staining. No samples were excluded from the analysis, and total N per indication is indicated in brackets. The lowest expression levels were in hematologic malignancies (data not shown)

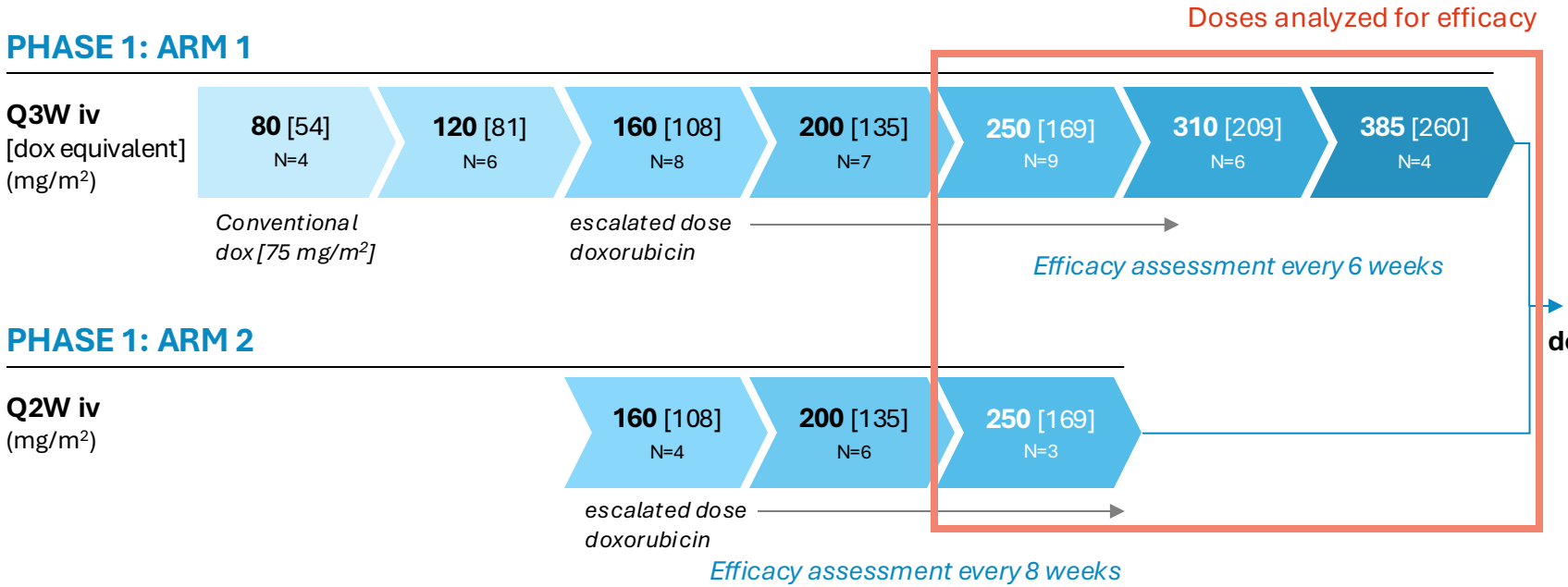
Avacta Therapeutics Pipeline

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) Dedifferentiated liposarcoma Breast cancer (TNBC/HER2+/HER2low)					Expansion cohorts to enroll in 2025 Ph Ia/Ib data 2Q 2025 (Full Ph I)
AVA6103	pre|CISION Exatecan (FAP-Exd)	HR+ Breast cancer/TNBC Gastric cancer (GC) Small cell lung cancer (SCLC) Pancreatic ductal adenocarcinoma (PDAC)					IND late 2025 Phase I early 2026
AVA7100	pre|CISION FAP Affimer (AffDC) Warhead not disclosed	Head and neck squamous cell cancers (HNSCC) Non-small cell lung cancer (NSCLC) Colorectal cancer (CRC)					Candidate selection 2H 2025

FAP-Dox: pre|CISION-enabled doxorubicin

Phase 1 data readouts

AVA6000 Phase 1 Trial Design and Patient Population



EXPANSION COHORTS (PHASE 1B)

Triple Negative Breast Cancer PD-L1-negative, BRC*Awt*

High-grade Soft Tissue Sarcoma (UPS, DDLPS, 1L/2L)

Salivary Gland Cancer (SGC), any histology, 1L/2L

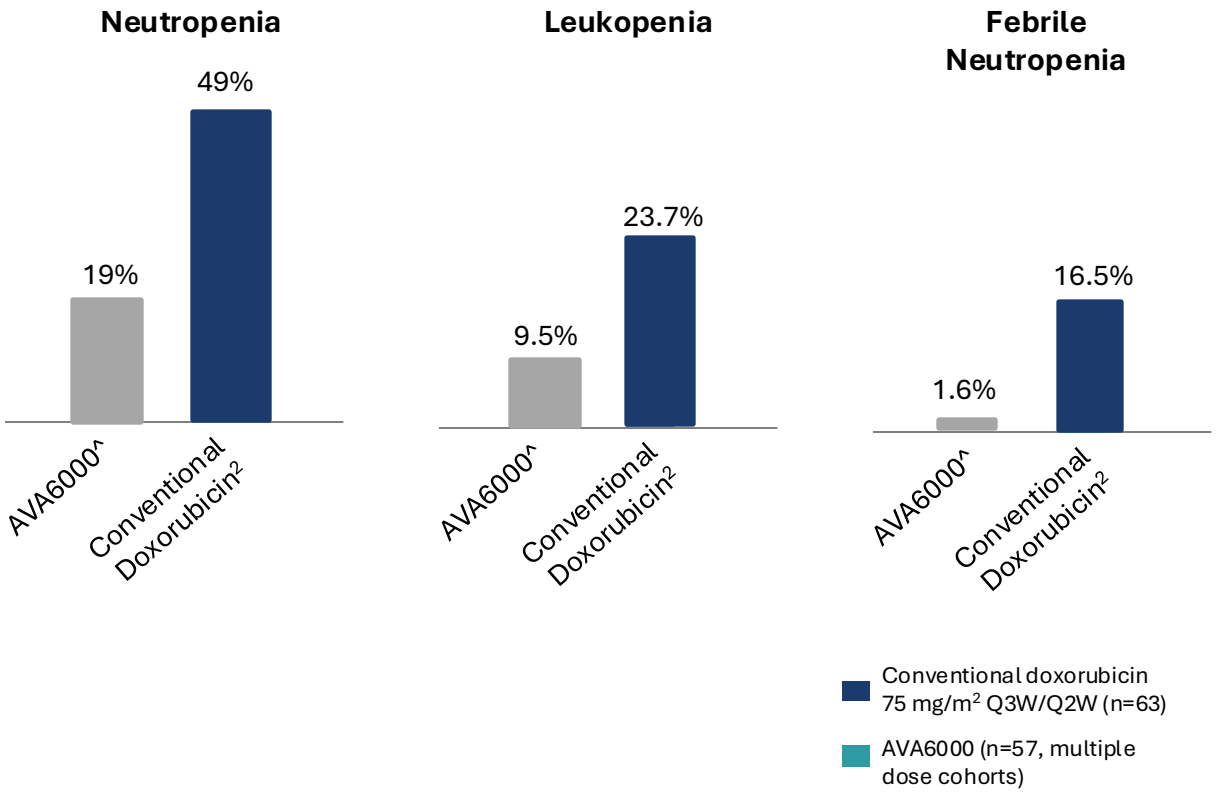
PHASE 1 PATIENT POPULATION AND METHODS

- Patients with a diagnosis of known FAP-positive cancers, including sarcoma, pancreatic cancer, colorectal cancer, head and neck cancers. Specific indications selected for expansion
- 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. The lifetime cumulative maximum exposure was limited to 550 mg/m^2 in the AVA6000 trial based on favorable safety data
- Trial analyzed for safety (primary endpoint) and efficacy (secondary endpoint by FAP^{high} and FAP^{mid} cancer types)

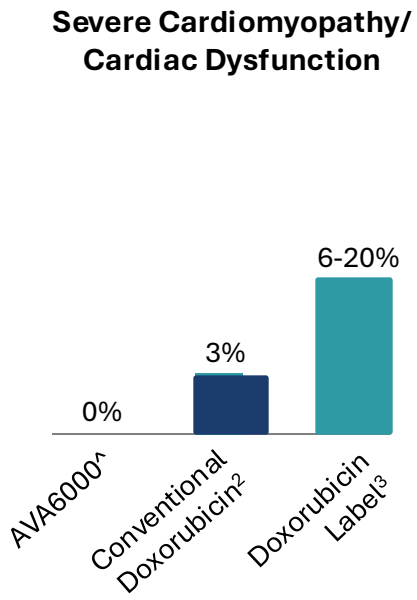
Avacta THERAPEUTICS

AVA6000 has reduced hematologic and cardiac toxicities compared to conventional doxorubicin

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

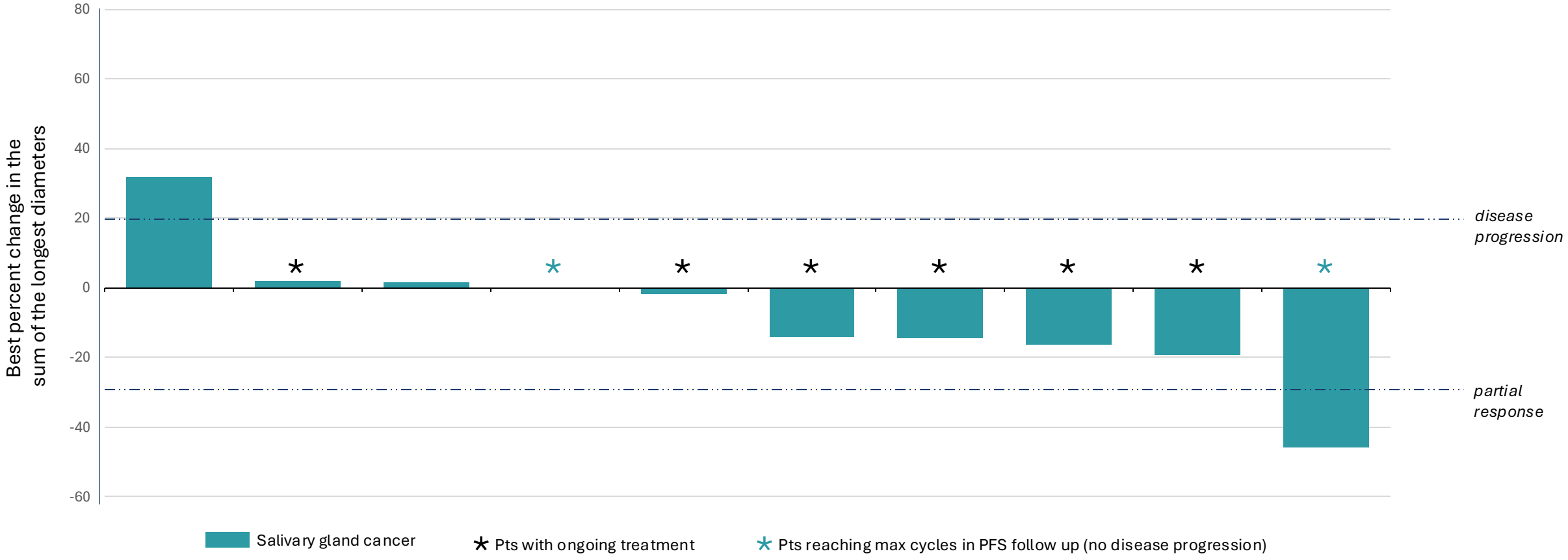


AVA6000 reduces severe cardiac toxicity
(compared to conventional doxorubicin



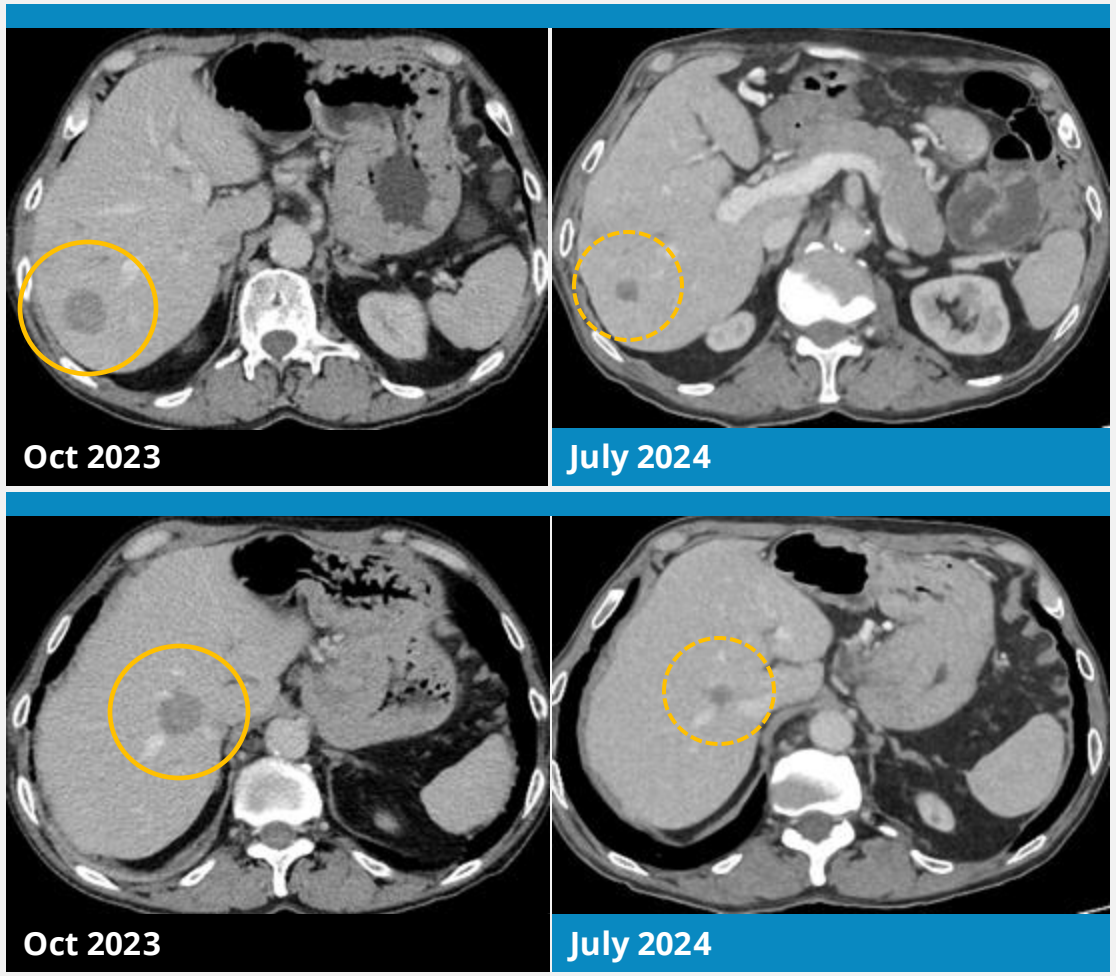
Data cutoff 23 December 2024. [1]Tap, WD et al. 2020. JAMA 323:1266. [2]Jones, RL et al.2021. Clin Ca Res· [3]Doxorubicin package insert
Updated from Twelves *et al*. 2024 ESMO Annual Meeting

AVA6000: Preliminary Data Demonstrate Meaningful Tumor Shrinkage in Patients with Salivary Gland Cancers



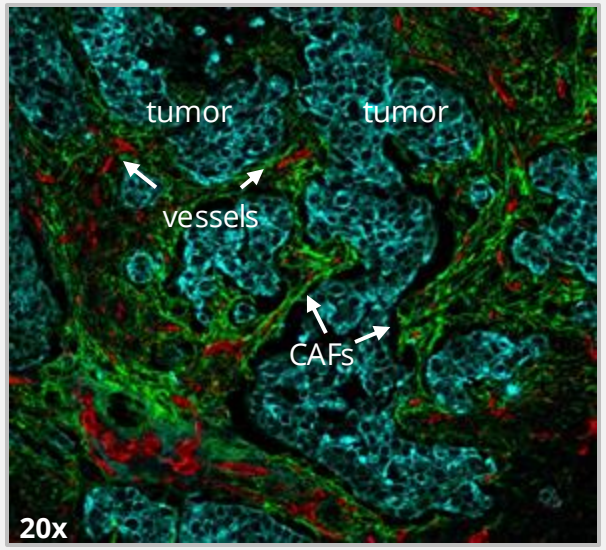
Data cutoff 23 December 2024
All pts with the diagnosis of salivary gland cancer treated at or above 250 mg/m^2 regardless of schedule

AVA6000: Deep prolonged PR in Salivary Gland Cancer



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)

AVA6000 Results in Complete Regression of Large Skin Metastasis in a Patient with a Minor Response

Initial minor RECIST response with dramatic regression of large skin metastasis:

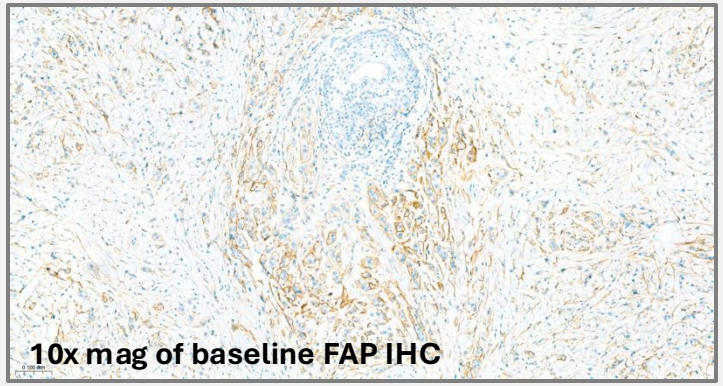
74 –year-old male with SGC

Prior therapy: triptorelin/ bicalutamide followed by disease progression and carboplatin/taxol doublet with disease progression

Enrolled in the AVA6000 trial (Sept 2024) in the 385/200 mg/m2 Q3W cohort

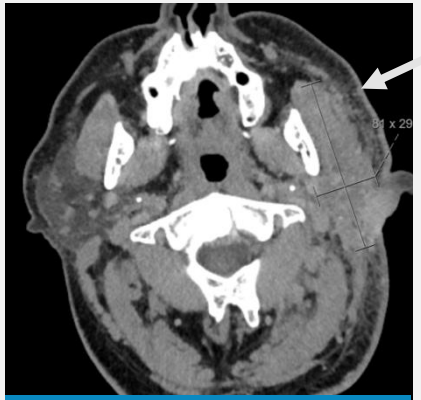
Despite **mid level of FAP expression** in the cancer-associated fibroblasts (CAF) alone (figure below), this patient demonstrates **rapid tumor response** in the skin and visceral metastases

Minor response observed (-15%) in parotid and lymph nodal lesions continues post-12 weeks scan

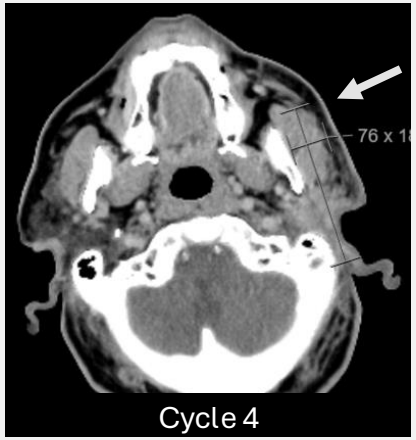


10x mag of baseline FAP IHC

Left parotid mass

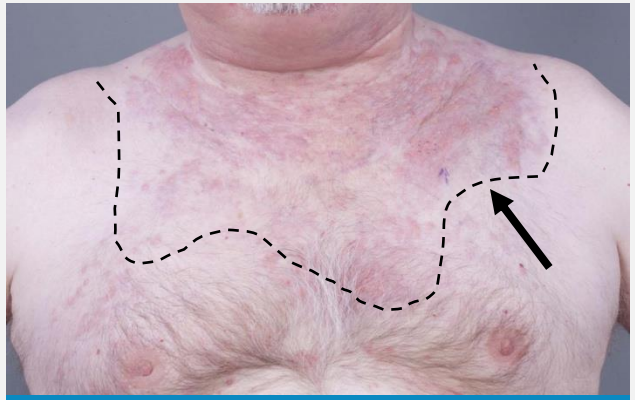


Baseline

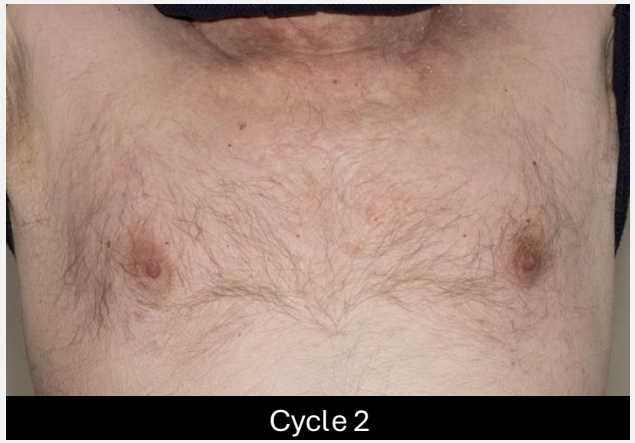


Cycle 4

Skin metastasis (upper chest)



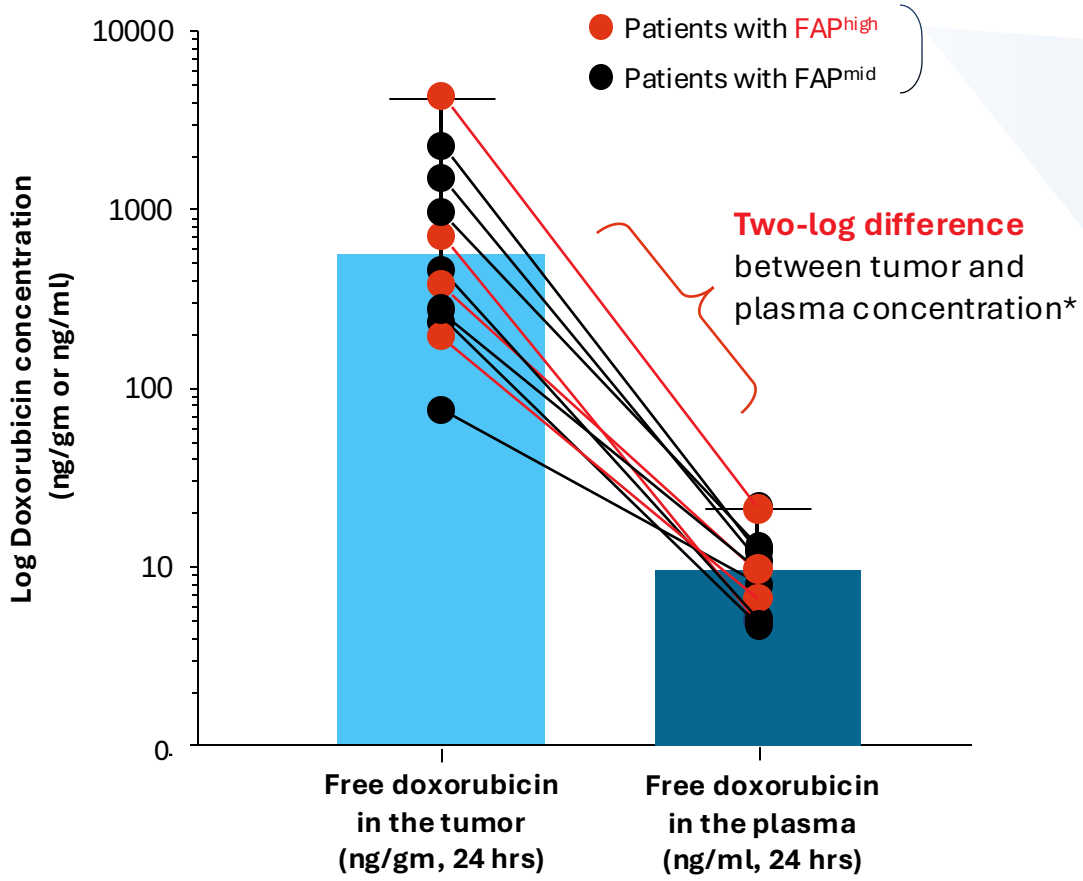
Baseline



Cycle 2

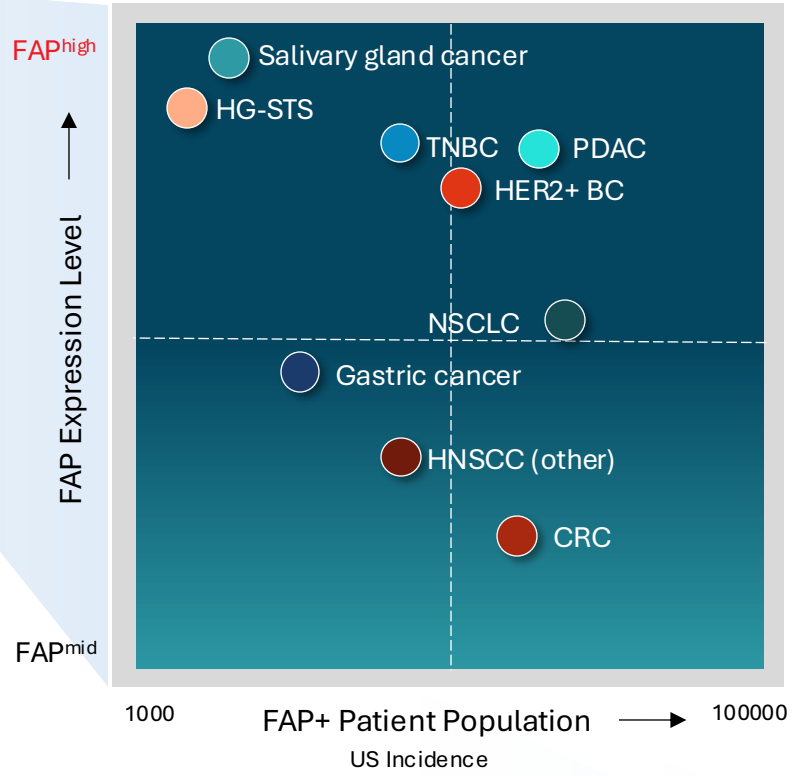
Concentration of doxorubicin in the tumor regardless of FAP level opens multiple indications

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)



All patients regardless of metastatic status with percent FAP+ determined by Tempus AI LENS data search. 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

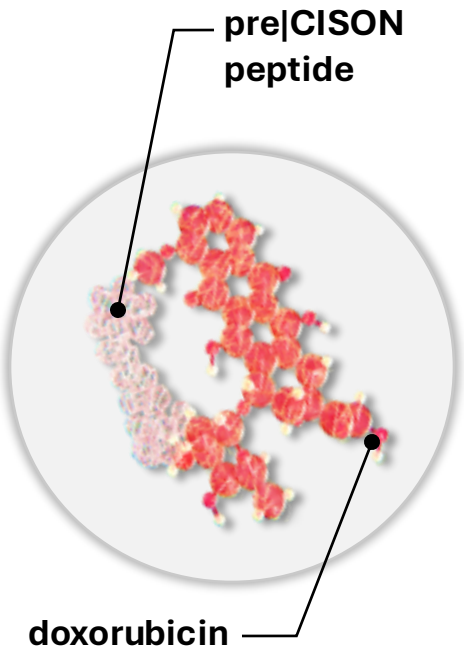
pre|CISION-enabled doxorubicin results in four fundamental PK changes

1 Reduced plasma exposure with released doxorubicin

Released doxorubicin from AVA6000 has a lower plasma Cmax (77.9-92.5% reduction) and lower AUC (4.8-77%) across dose levels

2 Enhanced tumor exposure v. conventional doxorubicin

Tumor exposure to released doxorubicin is higher at 24 hours than that seen with conventional doxorubicin at 1 hour (100:1 v. 1:1)



3 Significant reduction in the volume of distribution of released doxorubicin

Released doxorubicin from AVA6000 demonstrates a 40% reduction in the volume of distribution v. conventional dose doxorubicin

4 Extended plasma half-life of released doxorubicin

The plasma half-life of released doxorubicin is extended by up to 40% compared to conventional doxorubicin

pre|CISION-enabled doxorubicin has extended tumor exposure with limited plasma and normal tissue exposure, suggesting a sustained release mechanism can be developed

Avacta THERAPEUTICS

AVA6000 Clinical Development: Rapid route to market in an orphan indication with TNBC to expand the label

EARLY DEVELOPMENT → SGC INDICATION: FIRST APPROVAL → TNBC: SECOND APPROVAL

Salivary gland cancer (SGC) Indication

- **Phase I**
- **Phase I expansions**[1]
- **Phase II / III**[2] — ~200 patients randomized to PI choice (defined)
- **NDA** ★ **2028/2029** launch in 1L/2L+ mSGC (assume accelerated approval)
- **sNDA** ★ **2031** full approval in mSGC

2024 | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 | 2031 | 2032+

Triple Negative Breast Cancer (TNBC)

PD-L1-negative and BRCA*wt*

- **Phase I expansion**
- **Phase II** — ~150 patients with primary endpoints of ORR and DOR
- **Pivotal Phase III**[2,3] — ~750 patients with primary endpoints of PFS and OS
- **sNDA** ★ **2031/2032** launch in 1L+ mTNBC

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FAP-EXd: pre|CISION-enabled exatecan

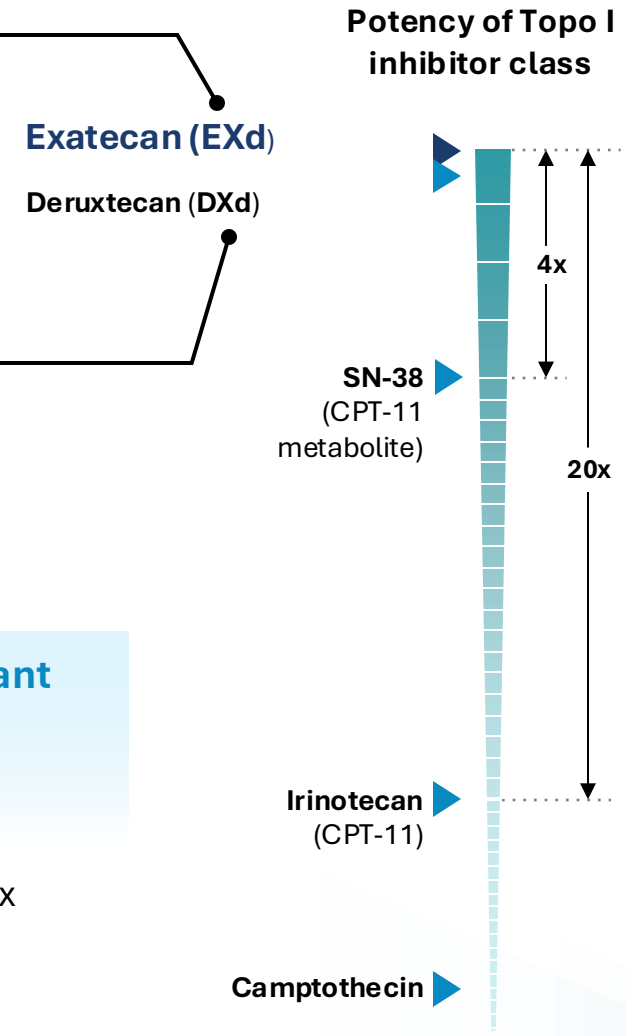
Peptide Drug Conjugate

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)

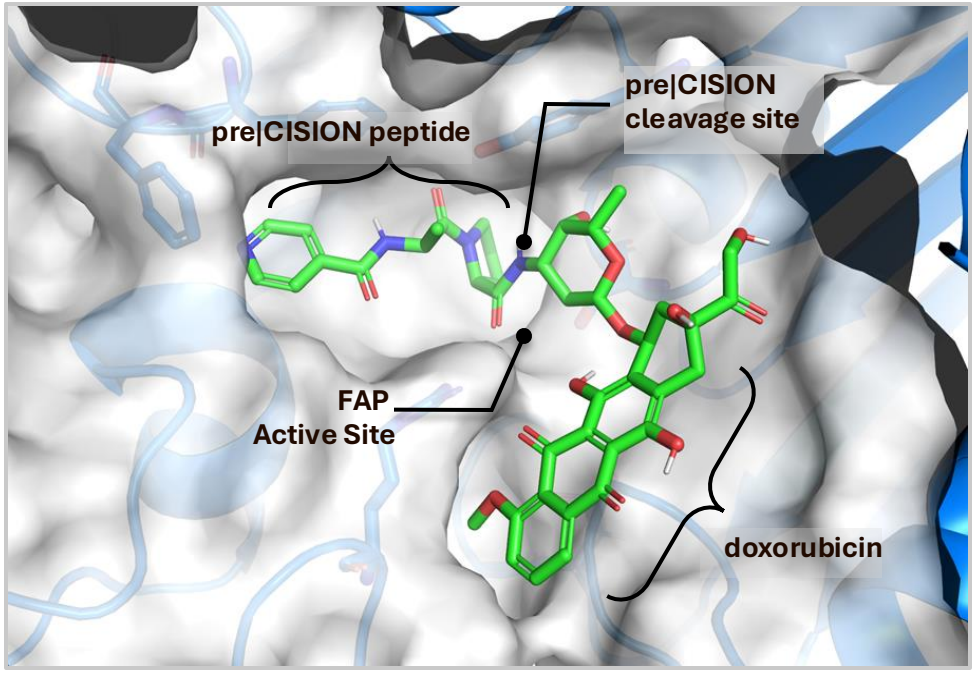
3. **Exatecan failed in the clinic due to a limited therapeutic index and significant PK issues**
   - Short half-life of ~9 hours which is insufficient for the effective inhibition of the topoisomerase I enzyme
   - The evolution of the preCISION platform chemistry can optimize both therapeutic index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



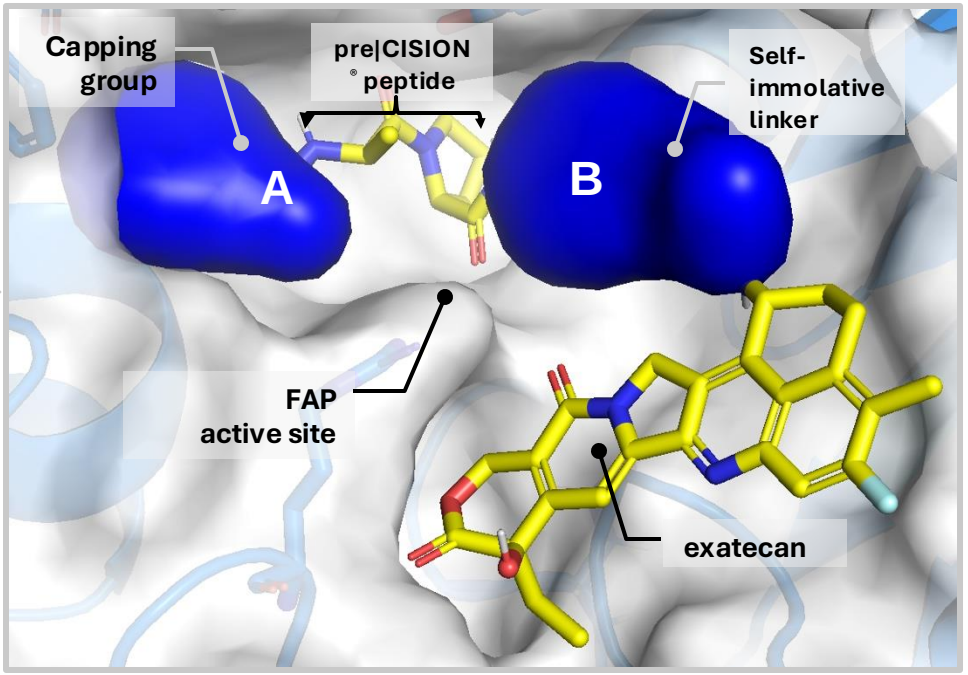
Kumazawa, E. et al. Potent and broad antitumor effects of DX-8951f, a water-soluble camptothecin derivative, against various human tumors xenografted in nude mice. Cancer Chemother Pharmacol 42, 210–220 (1998). https://doi.org/10.1007/s002800050807

Two key chemistry advances optimize exatecan delivery to create AVA6103

pre|CISION-Doxorubicin in the FAP Docking Model



pre|CISION-Exatecan in the FAP Docking Model



Extended plasma PK (A) of the conjugate and slowed warhead release (B) will result in a sustained release delivery mechanism in the tumor with very limited systemic exposure

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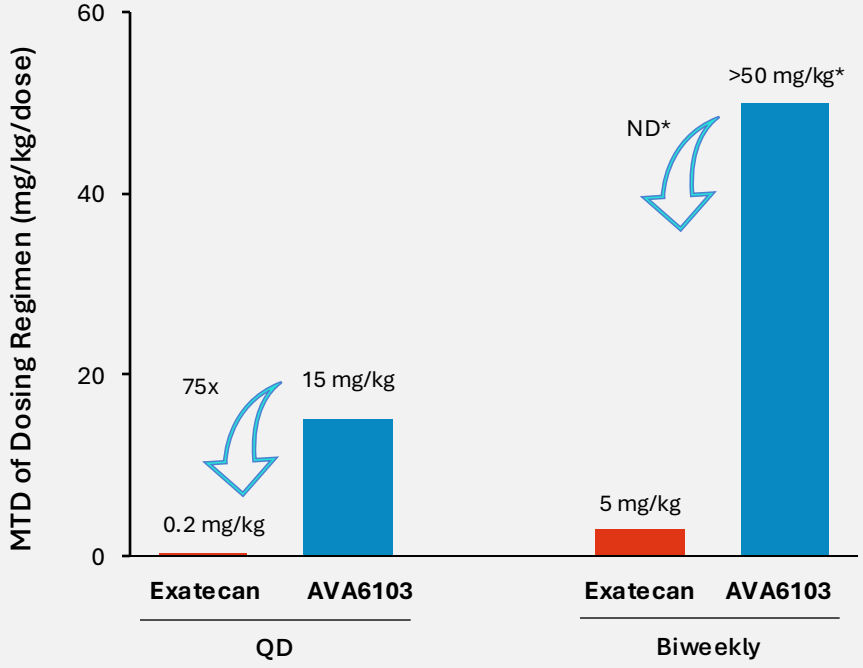
Therapeutic Index: The MTD of AVA6103 Is 75-fold higher than that of conventional exatecan



*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

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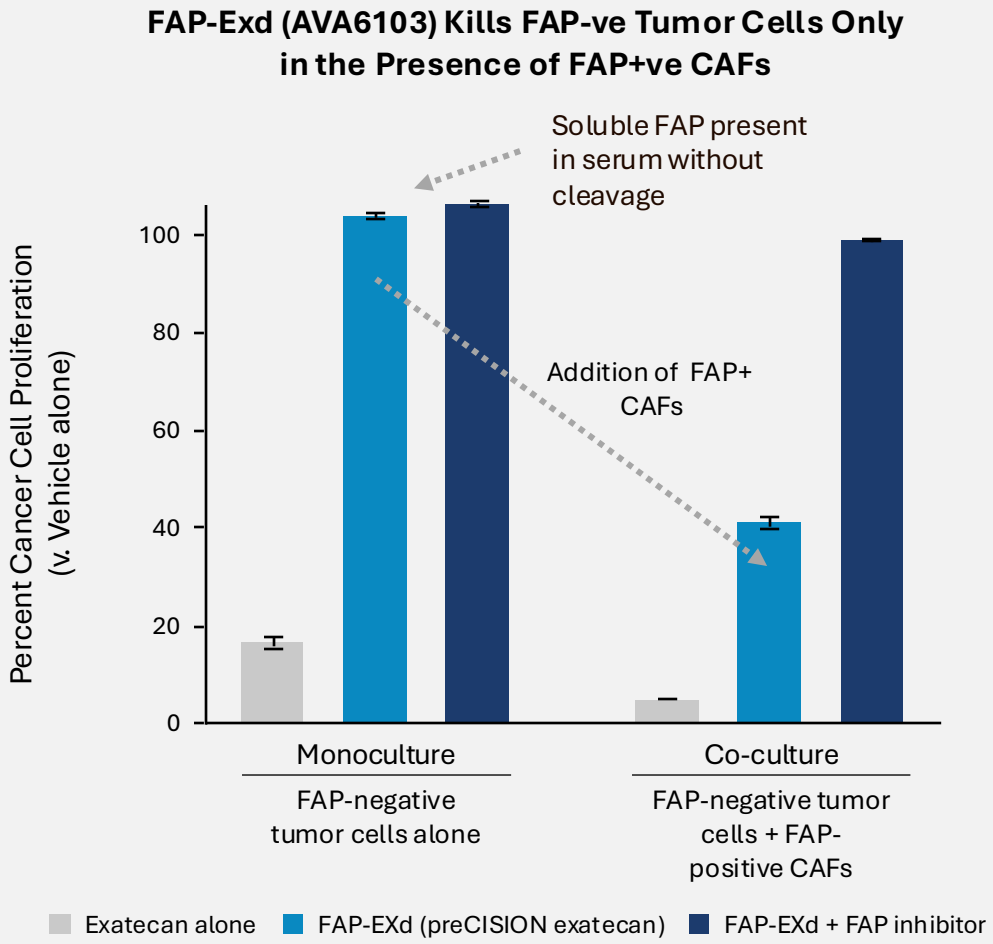
FAP-EXd (AVA6103): Effective killing of FAP-negative tumor cells in the bystander assay



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) despite soluble FAP presence
- 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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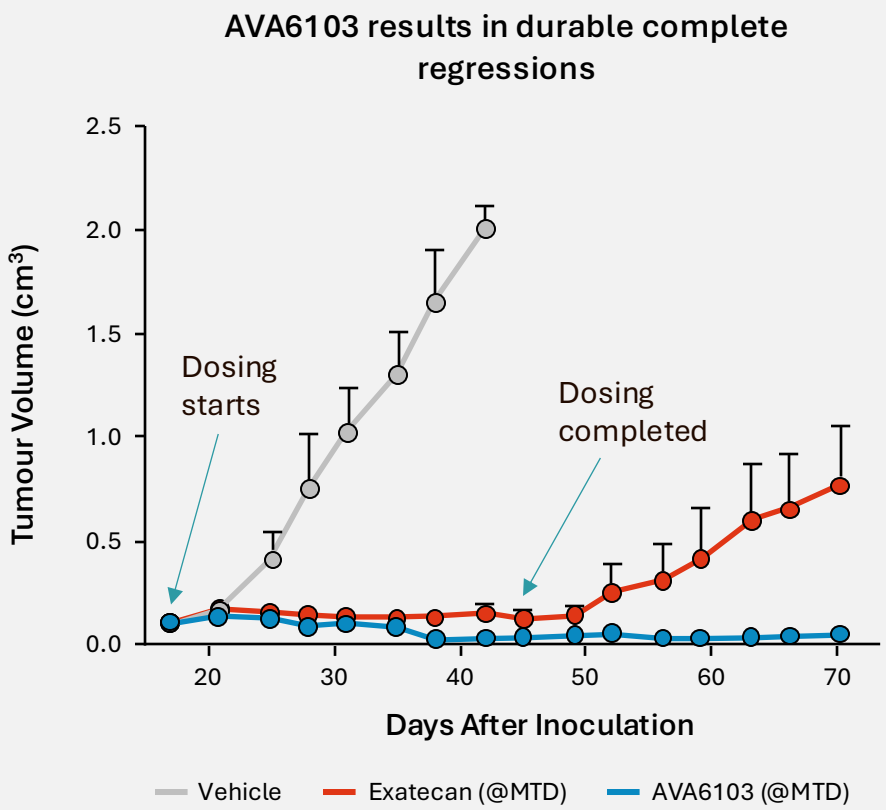
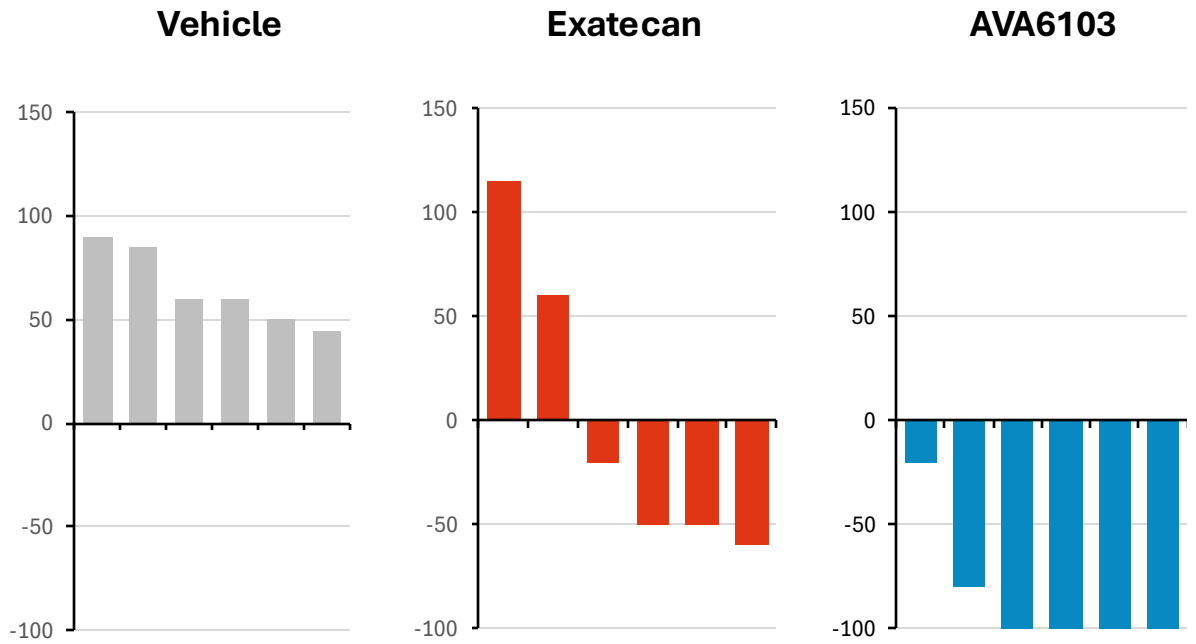
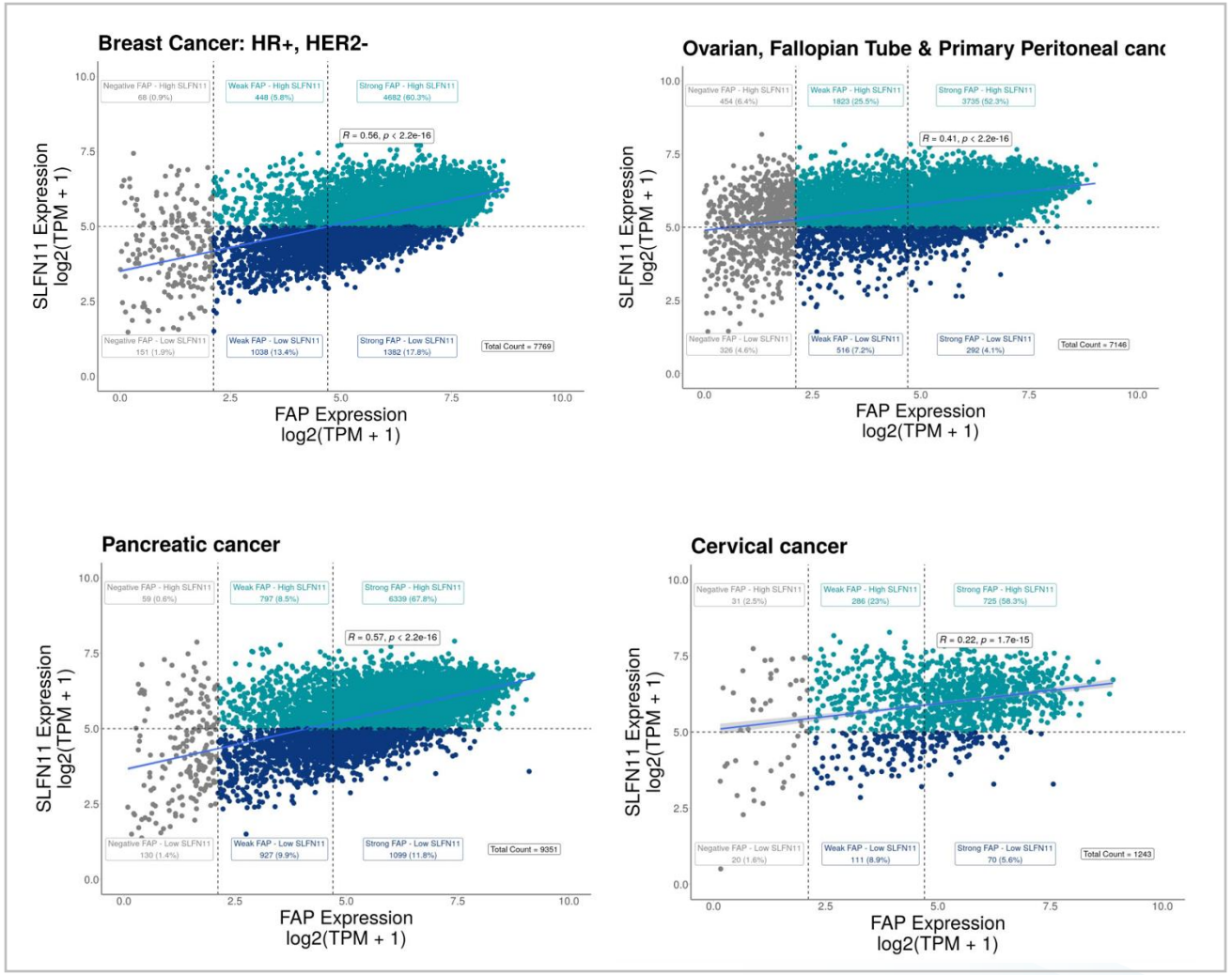
AVA6103 drives long-term regression of tumors, whereas regrowth is observed with exatecan alone





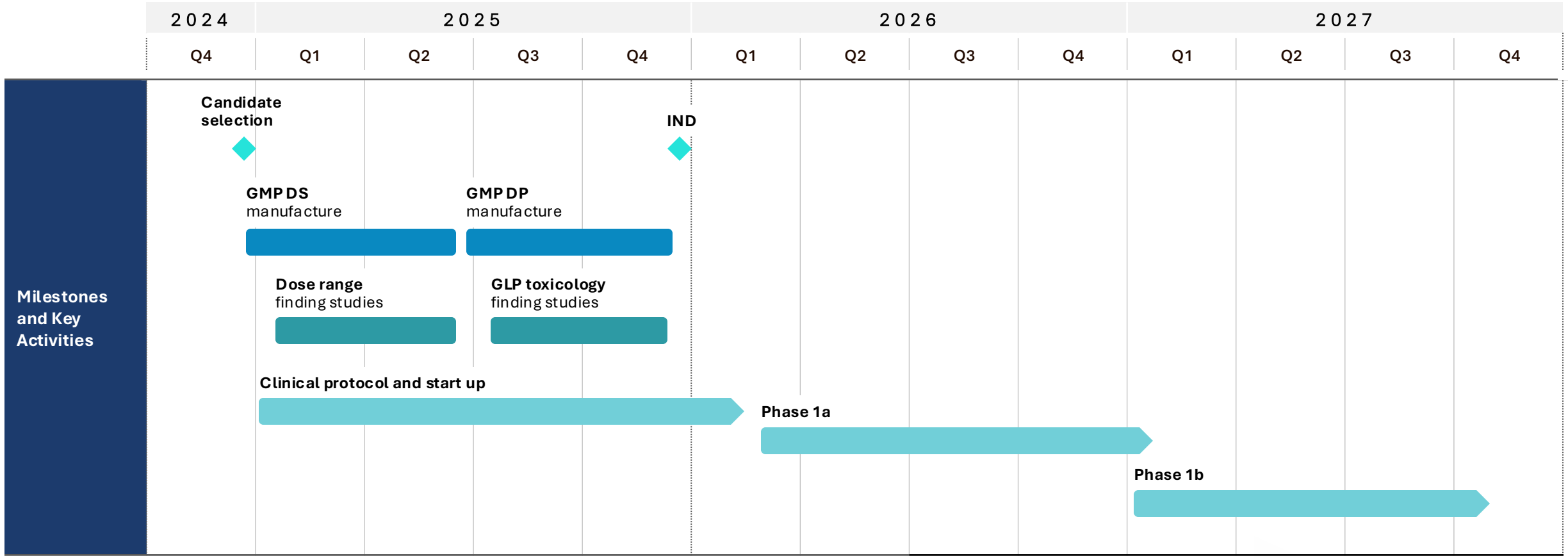
AVA6103: Leveraging AI to predict the most sensitive tumor types will increase the probability of success in Phase 1

- Numerous studies have shown that **higher expression of SLFN11 predicts sensitivity** to the Topoisomerase I inhibitor mechanism of action
- Among FAP high diseases, we looked for strong co-expression of FAP and SLFN11 **to predict those tumor types to be most sensitive to FAP-EXd** (AVA6103)
- **Multiple tumor types identified** with ~80% of patients with high expression of FAP and SLFN11 (teal) v. low (blue) or negative (gray)
- Given rate of expression of both genes, companion diagnostic approaches would not be needed in these tumor types



Tempus AI and Avacta collaboration (unpublished data)

AVA6103 Project Timelines



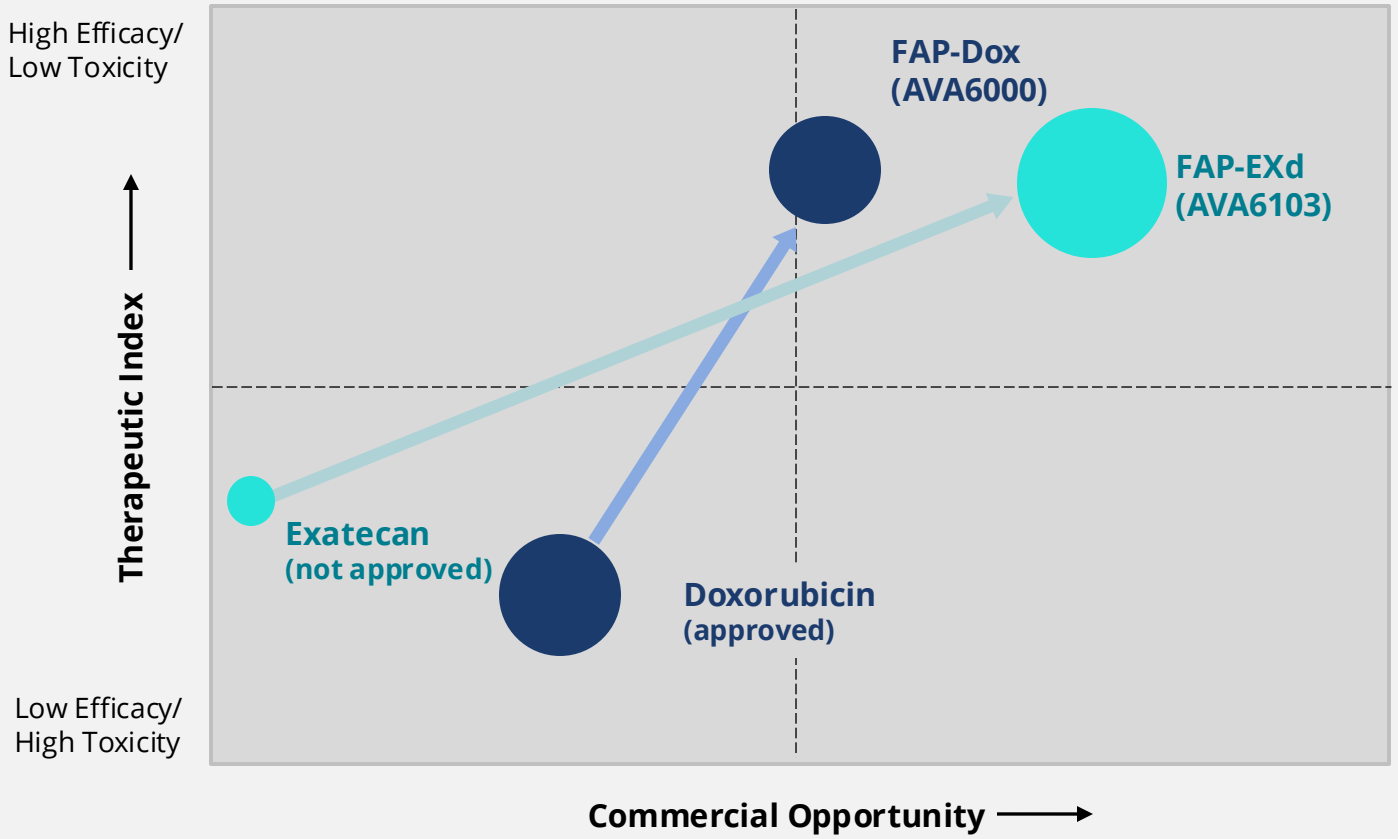
Seizing the market opportunity: Payloads as a commercial success

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**

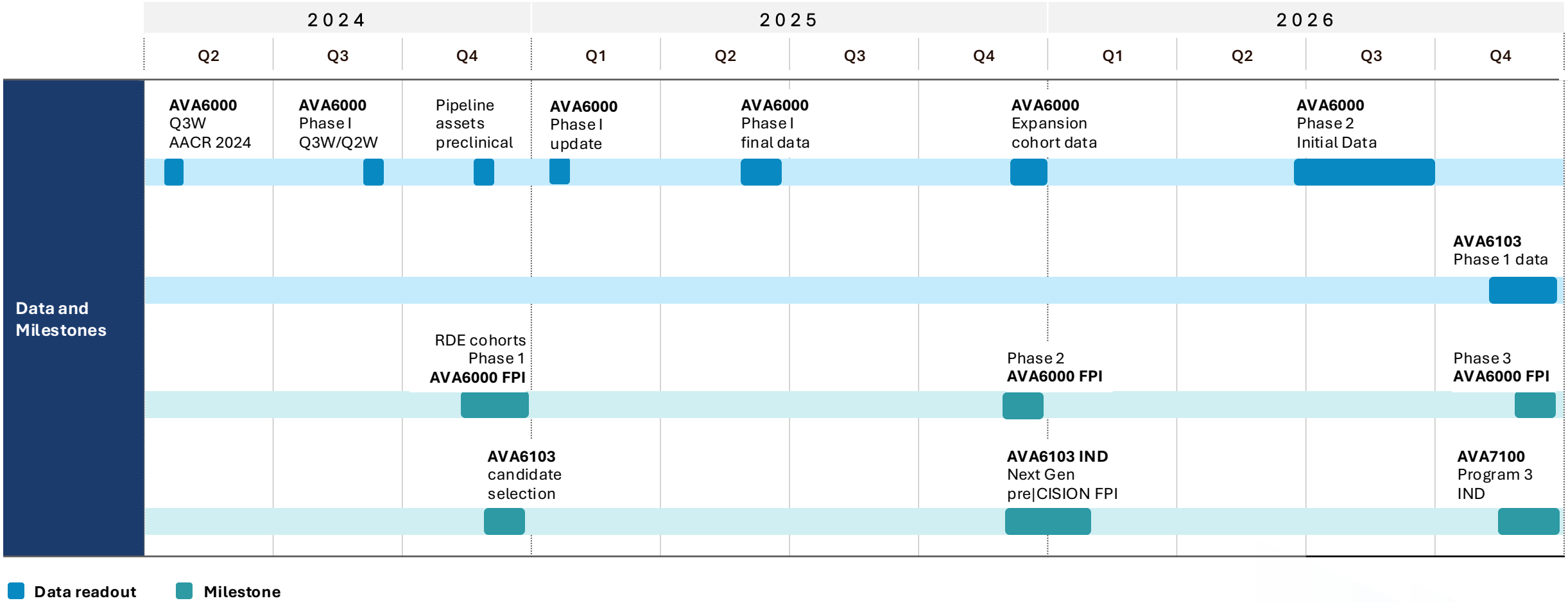
We expect **FAP-EXd (AVA6103)** to be highly active in a number of indications where there is observed activity of other topoisomerase I inhibitors (e.g. breast cancer, gastric, small cell lung cancer)

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

Avacta: Data Outputs and Milestones



Thank You

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