

A Phase I Trial of FAP-Exd (AVA6103), a Fibroblast Activation Protein (FAP)-enabled pre|CISION® Peptide-drug Conjugate Delivering Sustained Tumor Microenvironment (TME) Release of Exatecan in Patients with FAP-positive Solid Tumors

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Introduction and Rationale

- The pre|CISION® compound **AVA6103** is a **peptide drug conjugate** (PDC) comprising a peptide bound to the TOPI inhibitor **exatecan** by a linker that is specifically **cleaved by fibroblast activation protein-α (FAP)**, which is overexpressed by cancer associated **fibroblasts (CAFs)** in the TME of many solid tumors
- As FAP is selectively expressed by CAFs within tumors, with limited normal tissue expression, **exatecan is released in the TME**, minimizing exposure to healthy tissues, **improving the therapeutic window and maximizing efficacy** whilst **reducing adverse effects** compared to treatment with exatecan alone

pre|CISION® peptide drug conjugates offer key advantages over conventional ADC approaches:

Optimized Dosing of Exatecan

The maximum tolerated dose of FAP-Exd is significantly higher than that of conventional exatecan allowing greater tumor concentration

FAP-Exd is inert in the absence of FAP

FAP-Exd is completely inert unless FAP+ CAFs are present to cleave the peptide and release exatecan

FAP-Exd optimizes sustained tumor release

We observe high tumor levels of both PDC and released exatecan over five days, whereas conventional exatecan disappears from circulation and the tumor within hours

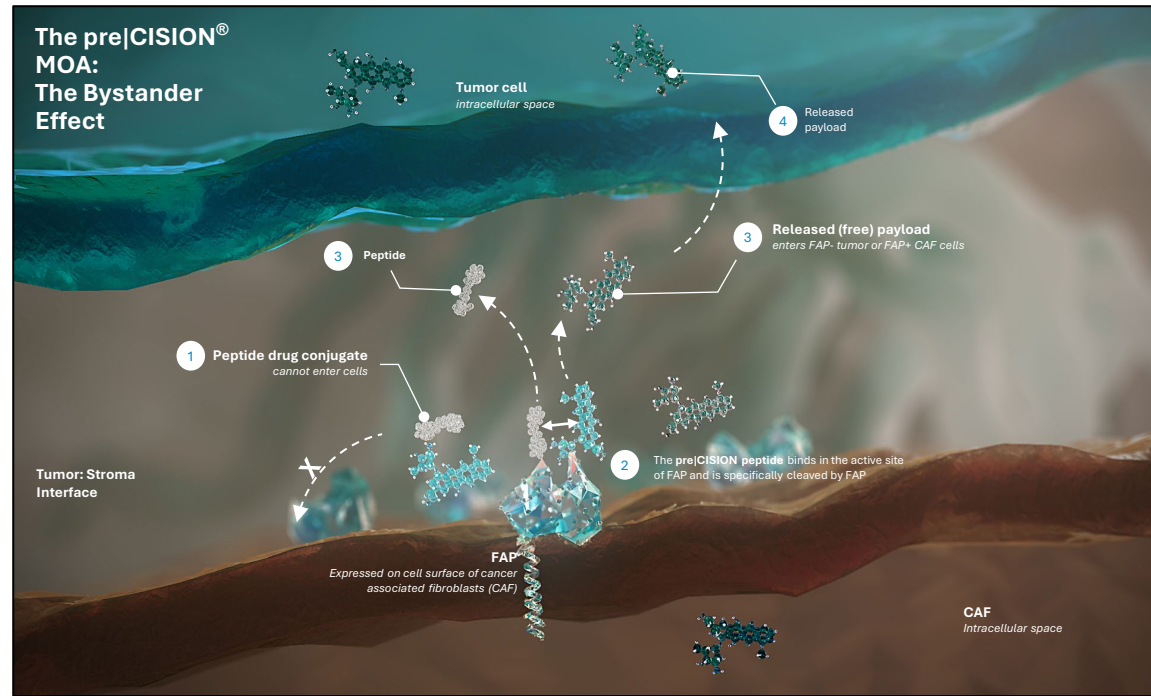


FIGURE 1. Mechanism of action of pre|CISION® FAP-Exd

	Traditional ADC CHALLENGES	pre CISION® PDC OPPORTUNITIES
Payload release	Non-specific protease cleavable linkers result in organ toxicity (e.g. pneumonitis, hepatitis)	Tumor-specific releases by FAP with no organ toxicity (e.g. no cardiac toxicity, no pneumonitis or hepatitis)
Tumor penetration	Slow uptake kinetics (>24 hours) into tumor cells for payload to be released intracellularly	Payload release observed in minutes with T_{max} in the tumor less than 1 hour
Bystander effect	Complex bystander effect requires antibody intracellular payload release with CAFs as a resistance mechanism	PDC have simple extracellular release resulting in kill of FAP+ and FAP- cells
Addressable market opportunity	Market opportunity for each ADC is limited by single antigen expression levels	FAP expression in 90% of all solid tumors with bystander effect active and release demonstrated in levels to 1+ by IHC

FIGURE 2. The common challenges with traditional ADCs, and the key opportunities when using pre|CISION® PDCs

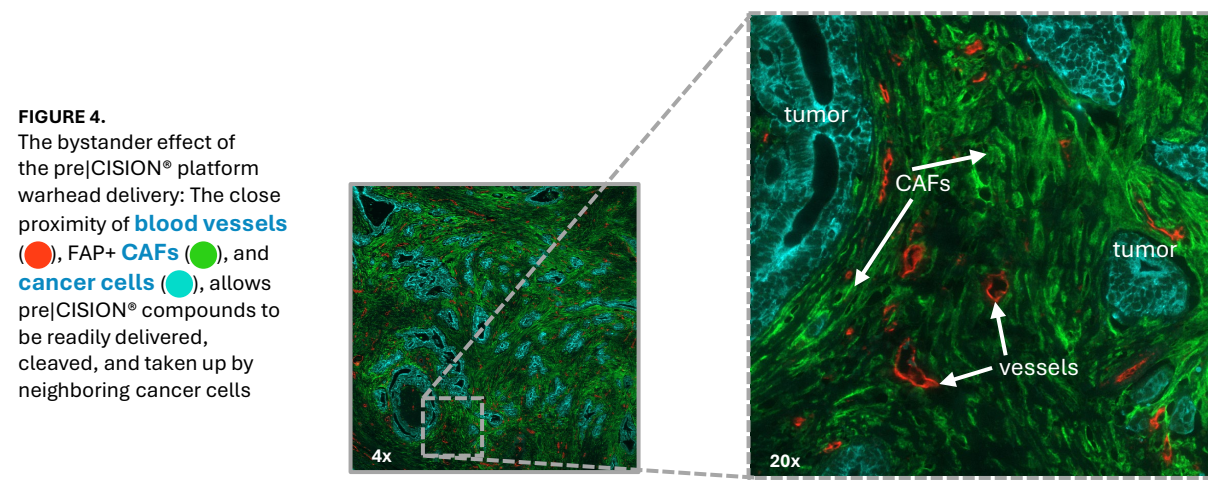
AVA6103 (FAP-Exd): Generation 2 of the pre|CISION® Platform

- AVA6103 uses pre|CISION® technology to **extend the half-life** of released exatecan in tumor across the entire cell cycle
- Increases tumor exatecan** exposure by tuning release kinetics via modified **capping group** and **linker** (alter the k_{cat}/K_M of the conjugate)
- Slower exatecan release plus extended conjugate plasma PK gives **sustained release mechanism**, lower plasma exatecan and **reduced systemic exposure**

Figure 3. Schematic showing AVA6103 docked into the FAP active site, containing a capping group, D-Ala-Pro pre|CISION® dipeptide unit, self-immolative linker and exatecan. After cleavage of the pre|CISION® dipeptide by FAP, the linker undergoes self-immolation and free exatecan is released. AVA6103 docked into the FAP active site

The pre|CISION® Bystander Effect is Mediated by the Spatial Organization of FAP Expression in Tumors

- FAP is highly expressed by CAFs throughout the TME; mIF staining shows FAP+ CAFs in **close proximity to both blood vessels and cancer cells** – ideal architecture for payload delivery, cleavage and bystander uptake
- Solid tumors are therefore a **strong clinical indication for AVA6103**: abundant stromal FAP drives tumor-selective exatecan release, maximizing tumor exposure while limiting systemic toxicity



FAP Expression is Prevalent and Maintained Between Pre-metastatic and Metastatic Tumors Across AVA6103 Clinical Indications

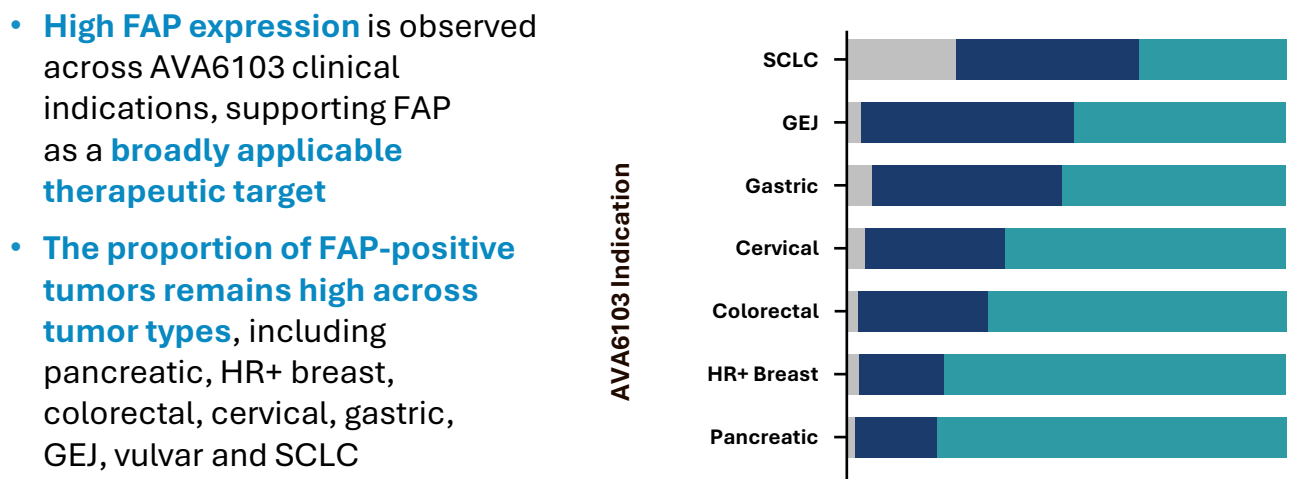
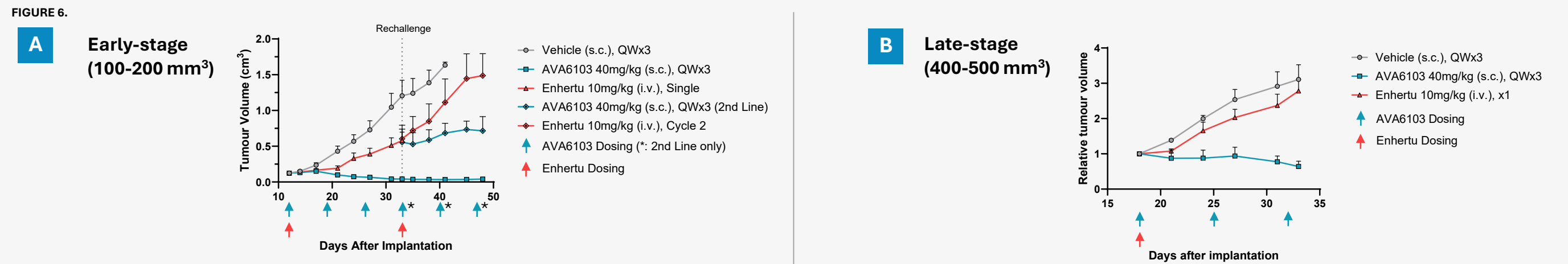


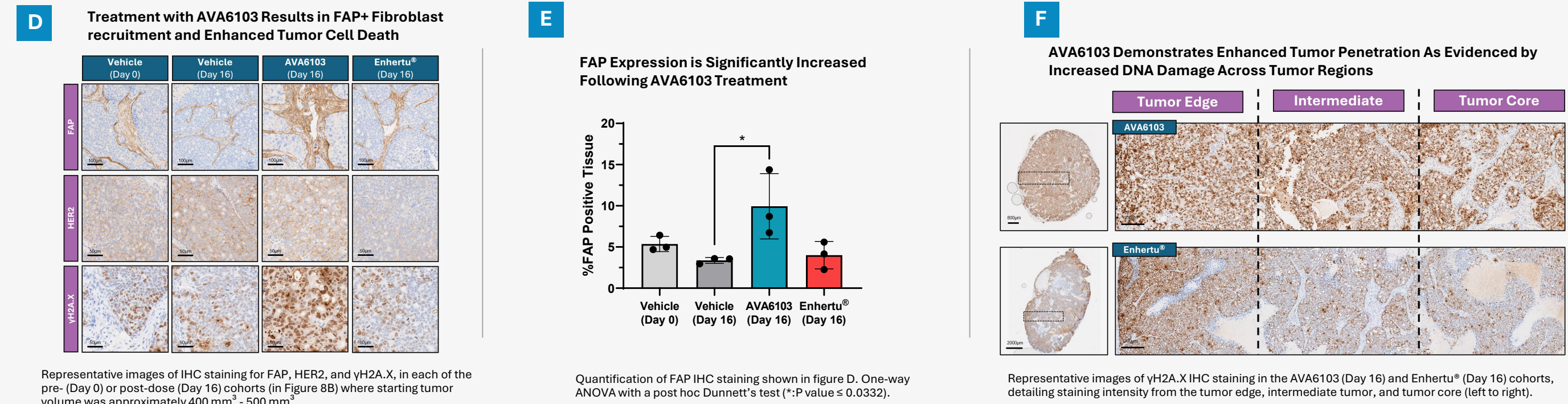
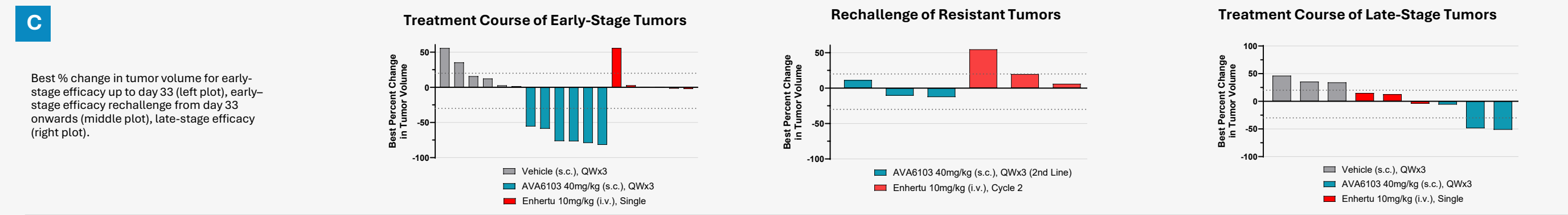
FIGURE 5. (Above Left). Percentage of tumor samples classified as FAP-negative (grey), FAP-low (blue) and FAP-high (turquoise) across AVA6103 clinical indications. (Above Right). Distribution of FAP expression in pre-metastatic and metastatic tumor samples. Boxes represent the interquartile range and horizontal lines indicate the median. FAP expression is maintained following metastatic progression across tumor types.

AVA6103 Demonstrates Superior Antitumor Activity Versus Enhertu® in FAP-positive / HER2-positive Tumor Models

- In both **early-stage (small tumors, ~100-200 mm³)** and **late-stage tumor models (400-500 mm³)**, AVA6103 achieved **greater tumor growth inhibition** than Enhertu®, demonstrating **superior antitumor activity** in FAP-positive / HER2-positive disease
- HER2 expression remained consistent between Vehicle (day 0/day 16) and AVA6103-treated tumors, whereas **HER2 loss of expression was seen after only a single cycle of Enhertu®**
- A marker of **dsDNA breaks/damage**, γH2A.X, displayed **increased staining with AVA6103 treatment**, whereas Enhertu® treated tumors remained equivalent to Vehicle
- Further to this, In **Enhertu® treated tumors**, strong γH2A.X staining was only seen at the tumor periphery, **decreasing steadily towards the core**. However, **AVA6103-treated tumors showed strong γH2A.X staining throughout** the entirety of the tumor
- Transcriptomic analysis revealed that **AVA6103 induced a coordinated inflammatory, wound-healing response**, with an upregulation of pathways involved with **damage repair, cell cycle arrest, and ECM reorganization**. Transcriptomics work is ongoing.
- These findings highlight previous clinical observations, where bulky **ADCs struggle to penetrate deep into the tumor**, and **repeat dosing can result in downregulation** or even **loss of target expression**
- Here, we show **AVA6103 is able to penetrate deep into the tumor**, resulting in **potent DNA damage and cell kill**. Additionally, we observe no loss of target expression with repeat dosing, where conversely, **FAP-positive fibroblasts increased** compared to untreated tumors



Antitumor activity of AVA6103 and Enhertu® in an early-stage FAP-positive / HER2-positive Gastric cancer patient derived xenograft model initiated at approximately 100 mm³ - 200 mm³ tumor volume. Tumor growth inhibition of each cohort prior to rechallenge detailed in corresponding table.



FAP-Exd Delivery Demonstrates Significantly Higher Tumor Selectivity v. T-Dxd, Enhertu®

- Rapid tumor targeting and **TME activation** overcomes the penetration limitations associated with ADC's and **enable payload delivery beyond the tumor periphery**
- Rapid accumulation and sustained release** of exatecan facilitates **widespread DNA damage and tumor cell death**
- Tumor Selectivity Index (TSI)**
Ratio of the AUC_{0.083h-14d} of released payload in the tumor vs. plasma
- TSI is a straightforward, quantitative measure of how **payload preferentially distributes to tumor tissue** relative to systemic circulation
- pre|CISION® exatecan delivery is associated with **significantly higher TSI compared to Enhertu®** in antigen-high models (TSI is AUC_{tumor}/AUC_{plasma}) and is approximately 3x higher with AVA6103 v. Enhertu, 126 v. 47 in this model
- Enhanced tumor selectivity allows for alternative treatment regimens and **dose intensities** relative to ADC's

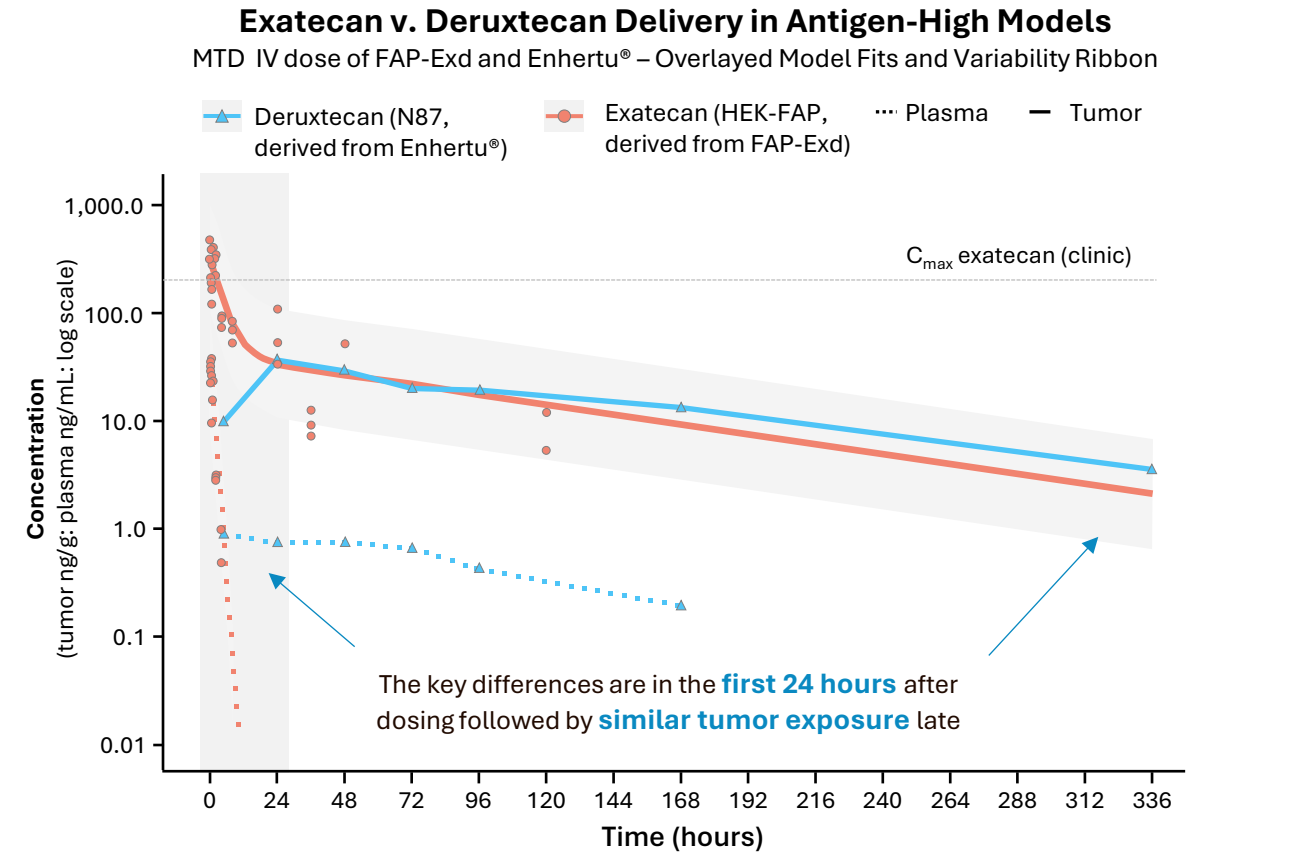
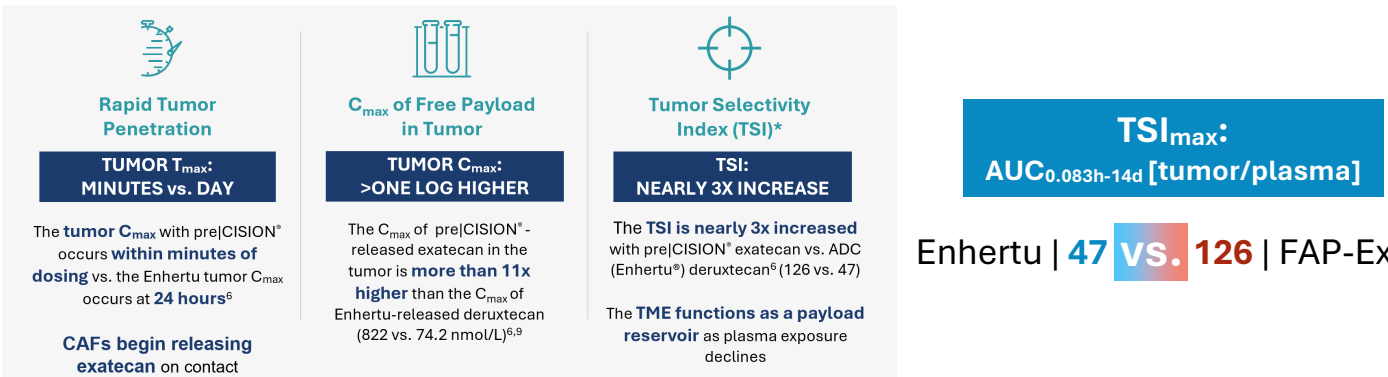
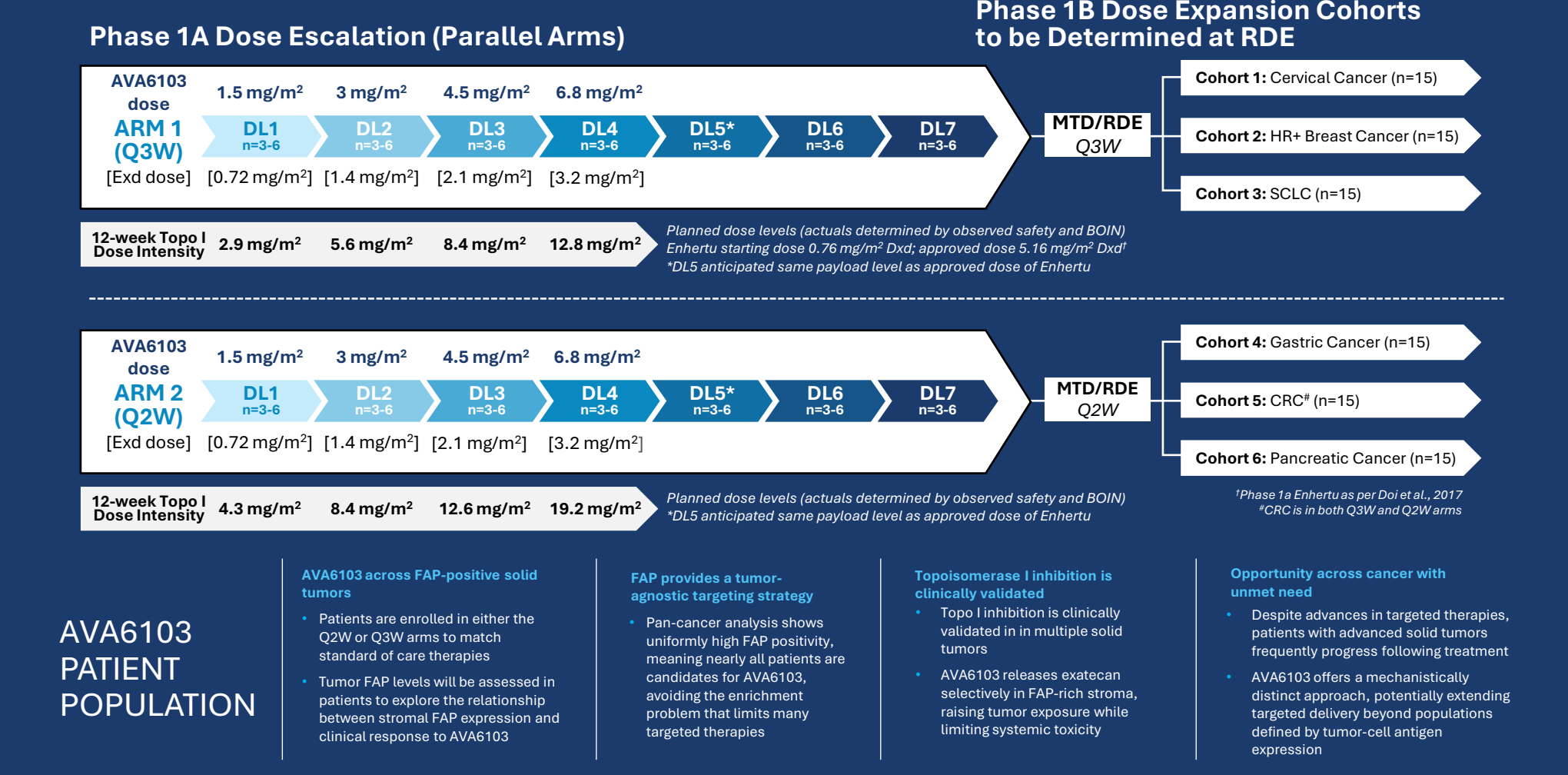


FIGURE 7. (Above). Shaded ribbons represent the ± 0.9 SD ($\approx 68\%$); Reference line: threshold of relative concentrations based on published data. C_{max} of exatecan in humans in Esteve, et al. (2003) A Phase II Study of Intravenous Exatecan Mesylate (DX-8951f) Administered Daily for 5 Days Every 3 Weeks to Patients with Metastatic Breast Carcinoma. Cancer 98(5):900-7. Modelled nonclinical data taken from Vasalou C, et al. Quantitative evaluation of trastuzumab deruxtecan pharmacokinetics and pharmacodynamics in mouse models of varying degrees of HER2 expression. CPT Pharmacometrics Syst Pharmacol. 2024 (6):9941005. doi: 10.1002/psp4.13133. (Left). Payload Delivery with pre|CISION® vs. cleavable ADC (T-Dxd, Enhertu®). TSI is defined as the ratio of tumor to plasma exposure (AUC_{0.083h-14d} [tumor/plasma]), and provides a quantitative measure of how preferentially a compound distributes to the tumor relative to systemic circulation.

FOCUS-01 AVA6103 (FAP-Exd): Phase I Trial Design and Patient Population



OBJECTIVES

Primary objectives

- Safety and tolerability of AVA6103 at the Q3W and Q2W dosing intervals
- Determination of the MTD and/or recommended Phase 2 dose (RP2D) for expansion at each dosing interval

Secondary objectives

- To characterize the PK of AVA6103, its leaving group AVA10344 and exatecan in plasma as monotherapy, after single and multiple dosing
- Initial antitumor activity by RECIST v1.1 including ORR, DOR, BOR, DCR, PFS and OS

Exploratory objectives

- FAP protein expression and enzymatic activity in tumor and plasma
- Intratumoral concentrations of AVA6103, AVA10334 and exatecan

KEY INCLUSION/EXCLUSION CRITERIA

Population

- Adult male or female with ECOG PS 0-1 and life expectancy ≥ 3 months
- Histologically or cytologically confirmed locally advanced (unresectable) and/or metastatic FAP-positive tumors: cervical/vulvar, SCLC, gastric/GEJ, pancreatic, HR+ breast, CRC
- Progressed on, ineligible for, or declining all standard-of-care or FDA-approved therapy

Organ function

- Adequate hematologic, renal, and liver function
- QTcF ≥ 470 ms

Disease and medical history

- No active CNS metastases
- Active HIV, HBV or HCV infection, or severe infection requiring IV antibiotics within 21 days

Other requirements

- Negative pregnancy test; highly effective contraception through 6 months after last dose

CONCLUSIONS

- FAP is highly expressed across all AVA6103 clinical indications and expression is persistent in metastatic disease during treatment, supporting broad applicability of AVA6103 across the six tumor types being evaluated in FOCUS-01
- Preclinical and translational tumor and plasma PK modelling data demonstrate favorable tumor selectivity and controlled systemic exatecan exposure, supporting the pre|CISION® mechanism of action
- In preclinical FAP-low / HER2-positive patient-derived xenograft tumor models, AVA6103 consistently outperformed Enhertu® in both early (100-200 mm³) and late-stage (400-500 mm³) disease settings, supporting the potential of FAP-directed payload delivery to improve intratumoral exposure and antitumor activity
- AVA6103 and released exatecan rapidly penetrate deep into the tumor, resulting in potent DNA damage and cell kill across regions of the tumors, with increased fibroblast recruitment to tumors with repeat dosing, versus a loss of antigen expression as seen with HER2
- The ongoing Phase 1 FOCUS-01 study will determine the safety, pharmacokinetics, recommended Phase 2 dose and preliminary antitumor activity of AVA6103 administered on Q2W and Q3W schedules

References

- Rink et al. AVA6103 is a FAP-enabled pre|CISION® Peptide Drug Conjugate Delivering Sustained Release of Exatecan in the Tumor Microenvironment with Potent Antitumor Activity. The American Association for Cancer Research Annual Meeting 2026.
- Chen et al. Expression of fibroblast activation protein in lung cancer and its correlation with tumor glucose metabolism and histopathology. Eur J Nucl Med Mol Imaging 45: 2838-2848 (2022). doi.org/10.1007/s00201-022-00754-4.
- Mona et al. Correlation of 68Ga-FAP-46 PET Biodistribution with FAP Expression by Immunohistochemistry in Patients with Solid Cancers: Interim Analysis of a Prospective Translational Exploratory Study. J Nucl Med. 2022 Jul;63(7):1021-1026. doi: 10.2967/jnumed.121.262426.
- Esteve, et al. (2003) A Phase II Study of Intravenous Exatecan Mesylate (DX-8951f) Administered Daily for 5 Days Every 3 Weeks to Patients with Metastatic Breast Carcinoma. Cancer 98(5):900-7.
- Vasalou C, et al. Quantitative evaluation of trastuzumab deruxtecan pharmacokinetics and pharmacodynamics in mouse models of varying degrees of HER2 expression. CPT Pharmacometrics Syst Pharmacol. 2024 (6):9941005. doi: 10.1002/psp4.13133.
- Doi et al. Safety, pharmacokinetics, and antitumor activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study. Lancet Oncol. 2017 Nov;18(11):1512-1522. doi: 10.1016/S1473-2165(17)30604-6.

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