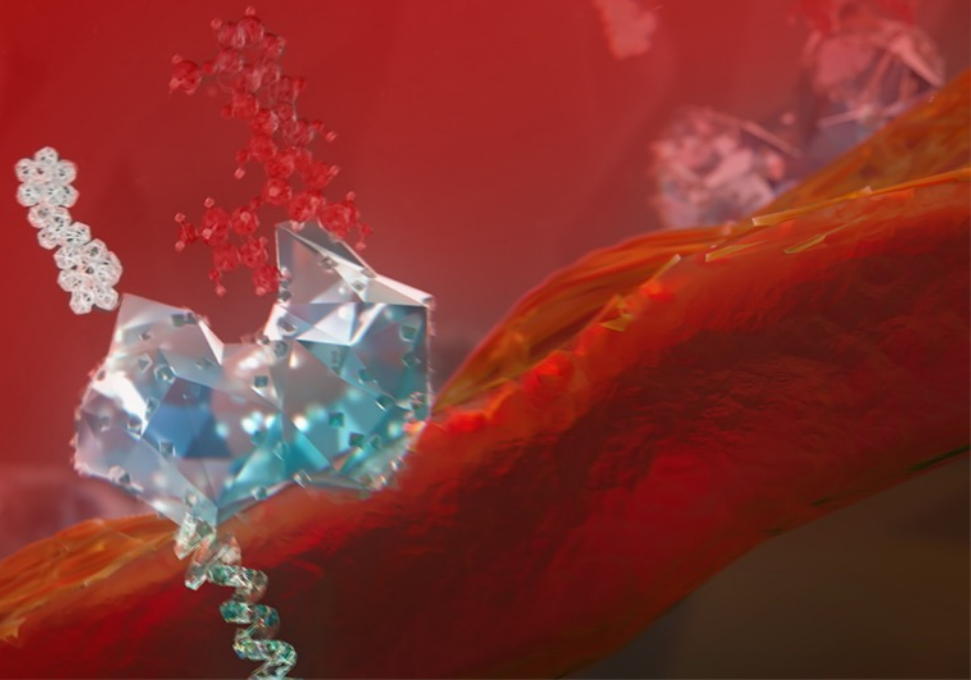
Targeting the Tumour Microenvironment: Redefined

AVA6000 Update

13th December 2023



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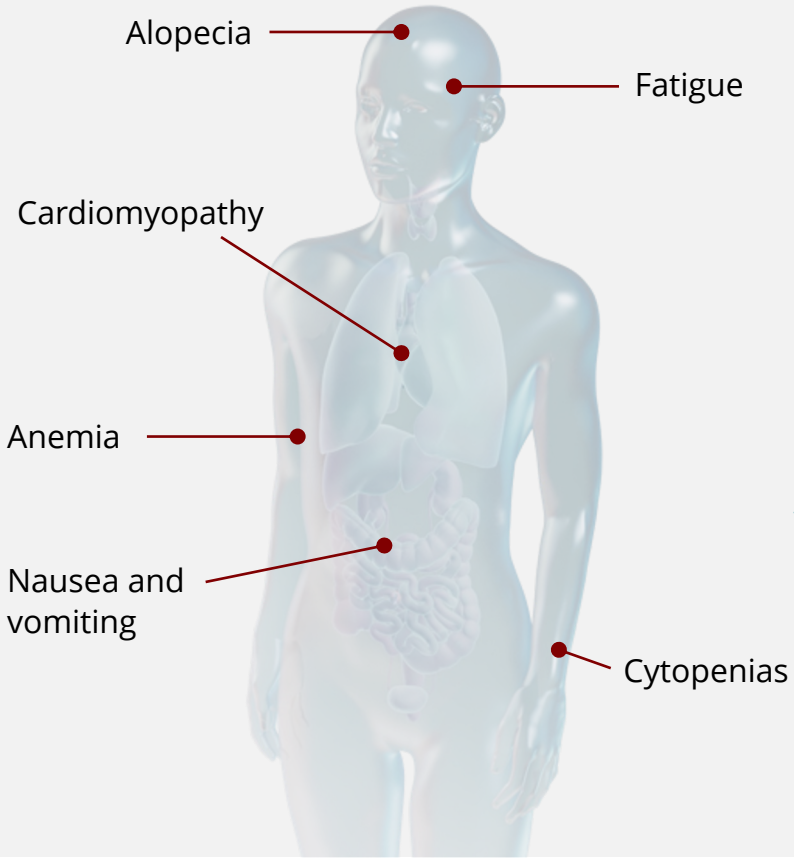
pre|CISION™: Targeting Cancer Therapies to the Tumour Microenvironment

Common Chemotherapy Side Effects



THE PROBLEM

- Traditional cancer therapies do not differentiate between normal tissue and tumour
- Systemic toxicities limit the effectiveness of most oncology drugs
- **There is an urgent unmet need for medicines that can selectively kill tumour cells while sparing normal cells**

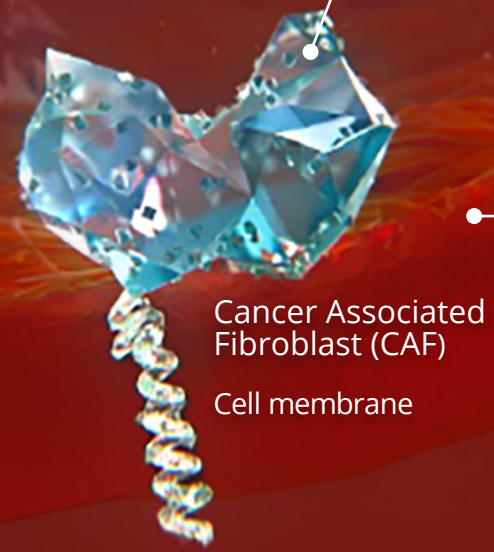
pre|CISION™

THE SOLUTION

- The **pre|CISION™** platform links a proprietary cleavable peptide with a cytotoxic agent (chemotherapy) to prevent it from entering cells
- The peptide is cleaved from the cytotoxic warhead by a tumour-specific enzyme (FAP), concentrating the active cytotoxic drug within the tumour microenvironment
- **pre|CISION™** medicines are designed to reduce systemic exposure and thereby **enhance safety and tolerability and increase efficacy**

Leveraging FAP to Effectively Target the Tumour Microenvironment (TME)

FIBROBLAST ACTIVATION PROTEIN-α (FAP)



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

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

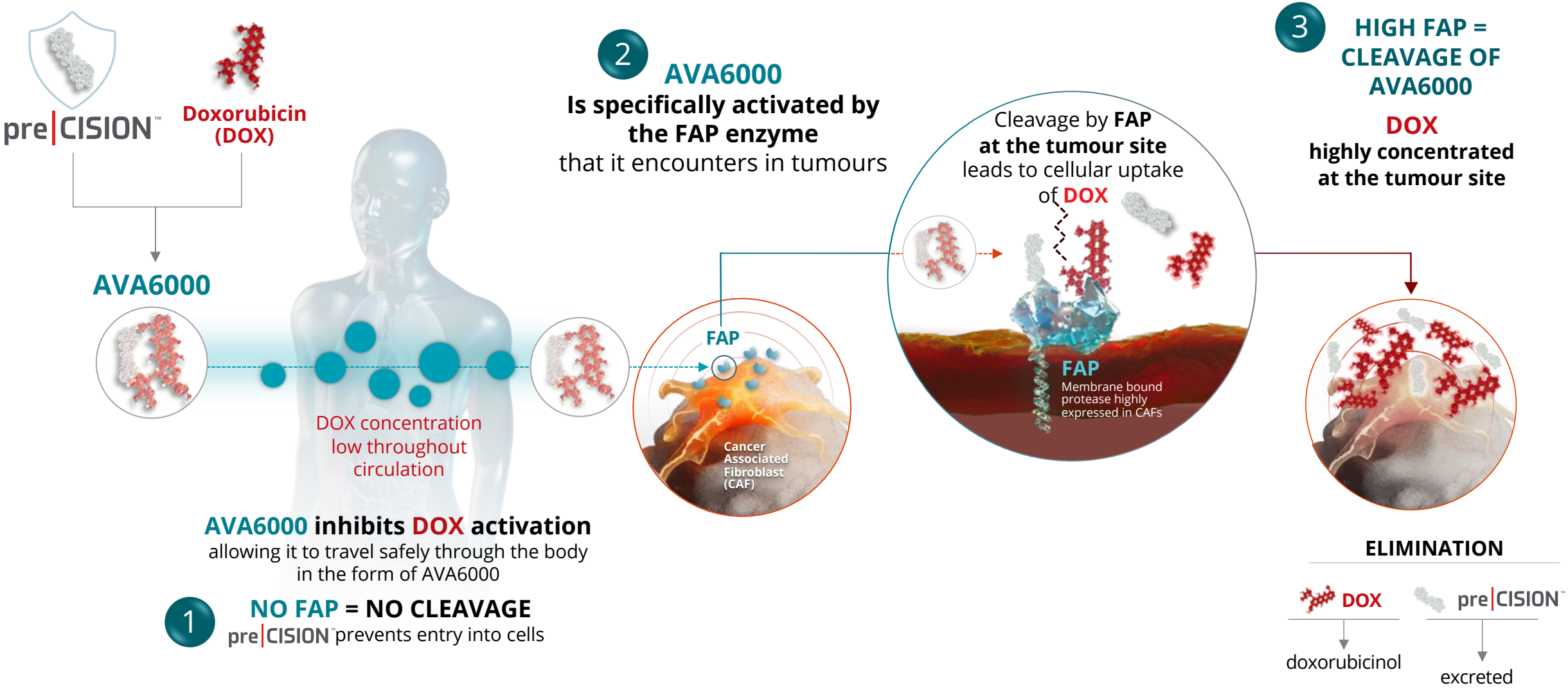
DPP-IV (DPP4)	**DPPII (DPP2)**	**DPP8**	**DPP9**	**Prolyl Endopeptidase** (PREP)

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

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

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

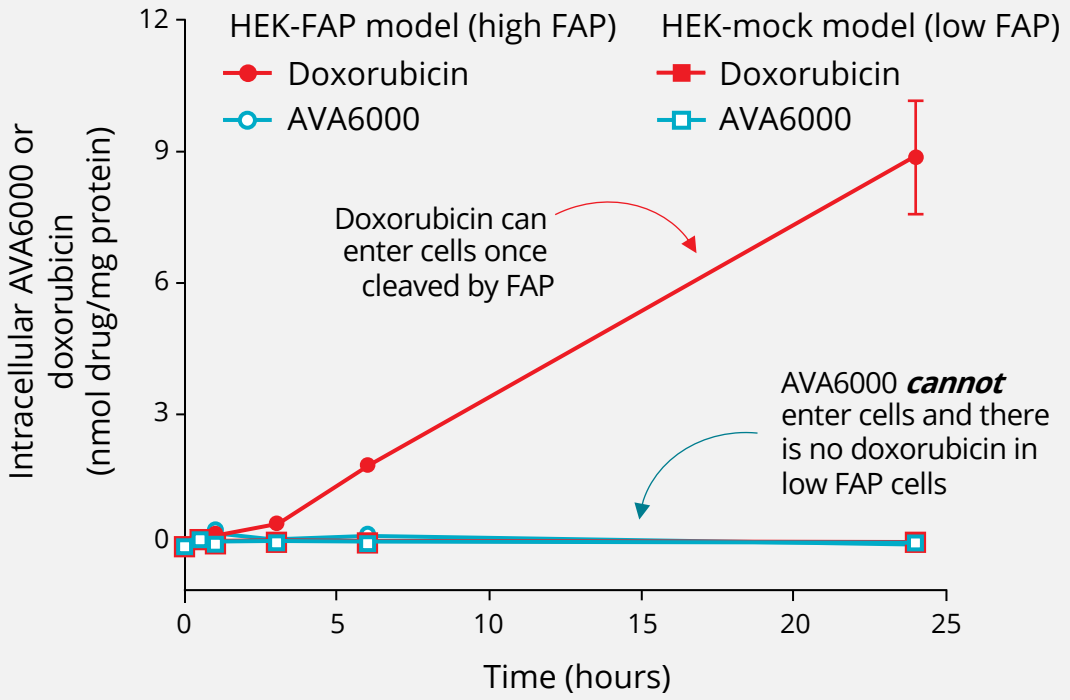
AVA6000 Mechanism of Action Releases Doxorubicin in the TME by FAP-Specific Cleavage



AVA6000: Preclinical Data

Selective Cleavage of AVA6000 by FAP in the TME Leads to Cellular Uptake of Doxorubicin

AVA6000 cannot enter cells and doxorubicin only released in FAP^{high} tumours



1

Intact AVA6000 cannot enter cells:
Normal tissues (FAP-negative) will not have cleavage of AVA6000 to release doxorubicin, thus very limited exposure

https://doi.org/10.3109/1061186X.2010.511225 and internal data

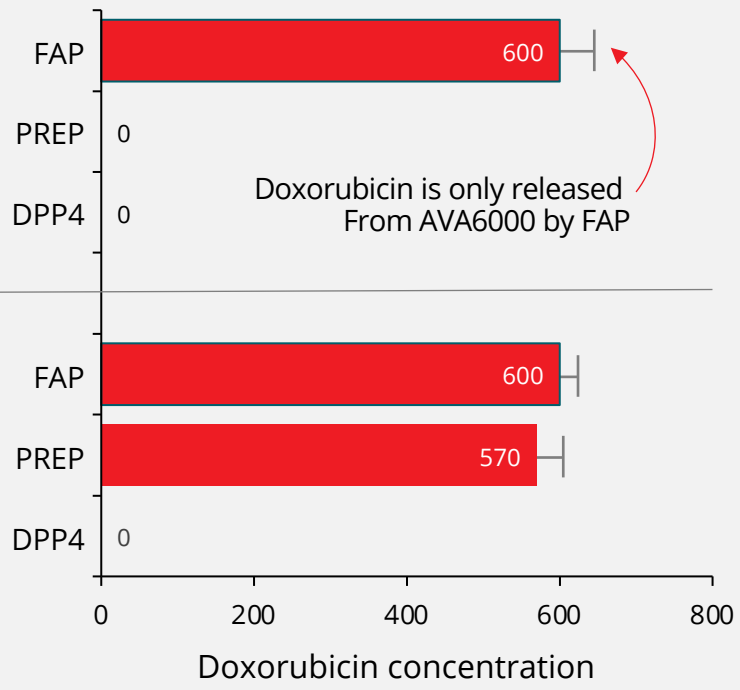
pre|CISION™ achieves high specificity for FAP cleavage where others have failed

AVA6000
pyridine-4-carbonyl-**D-Ala-Pro**-doxorubicin

pre|CISION™ is only cleaved by FAP, not other enzymes

CGP-DOX
carboxybenzyl-**Gly-Pro**-doxorubicin[1]

Peptide is cleaved by both FAP and PREP

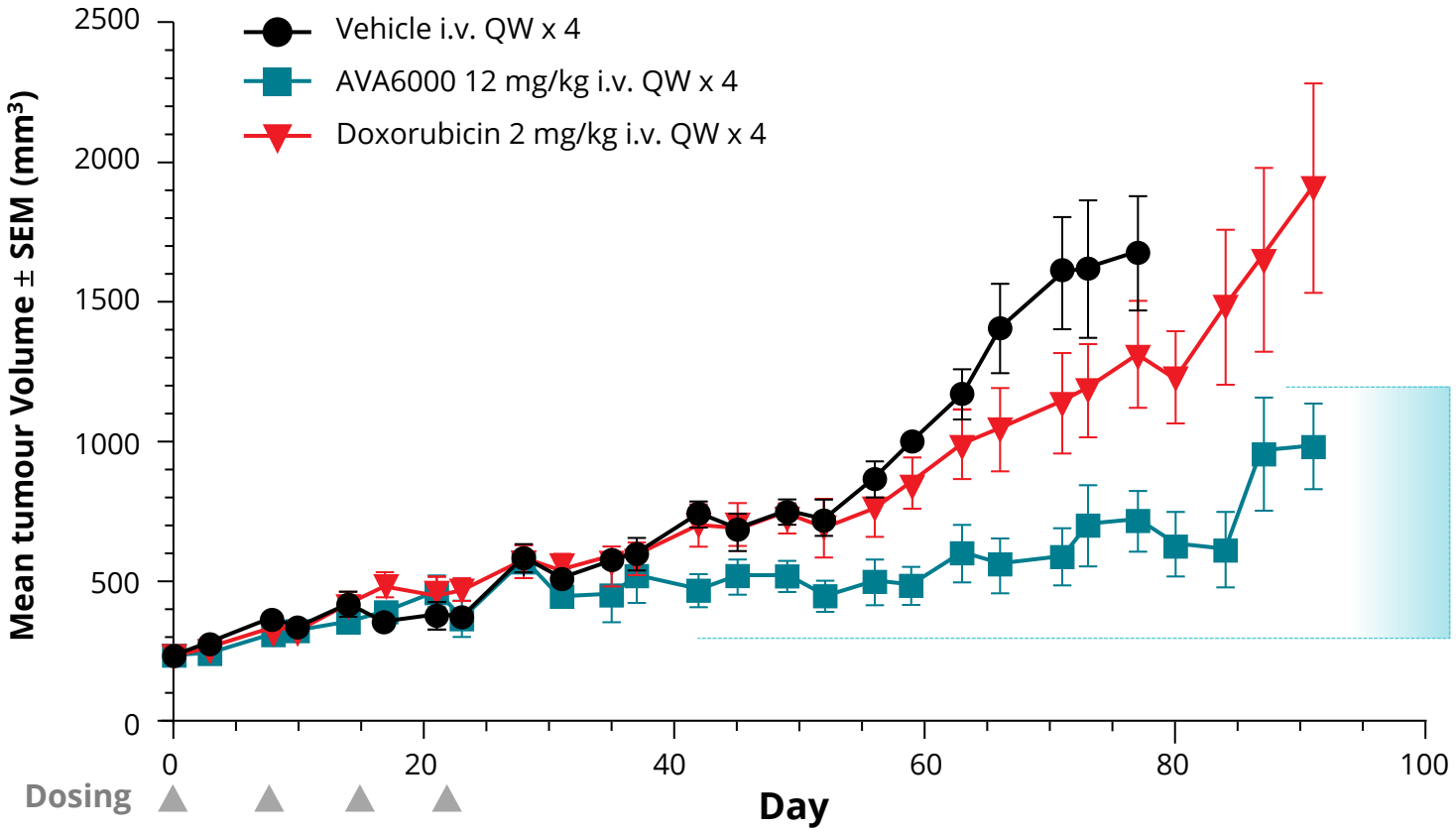


2

pre|CISION™ peptide is exquisitely selective for FAP:
PREP is widely distributed in normal human tissues, whereas FAP is tumour-specific resulting in TME-specific release of doxorubicin

1. Huang S, Fang R, Xu J, Qiu S, Zhang H, Du J, Cai S. Evaluation of the tumor targeting of a FAPα-based doxorubicin prodrug. J Drug Target. 2011 Aug;19(7):487-96. doi: 10.3109/1061186X.2010.511225. Epub 2011 Feb 2. PMID: 21284542.

AVA6000 Demonstrates Efficacy in FAP^{high} Dox-resistant PDX Osteosarcoma Model



AVA6000 in patient-derived xenograft (PDX)

METHOD: Test the activity of AVA6000 in a patient-derived sarcoma xenograft with high FAP level (determined by RNAseq assay)

3

Prolonged tumour control in high FAP tumour

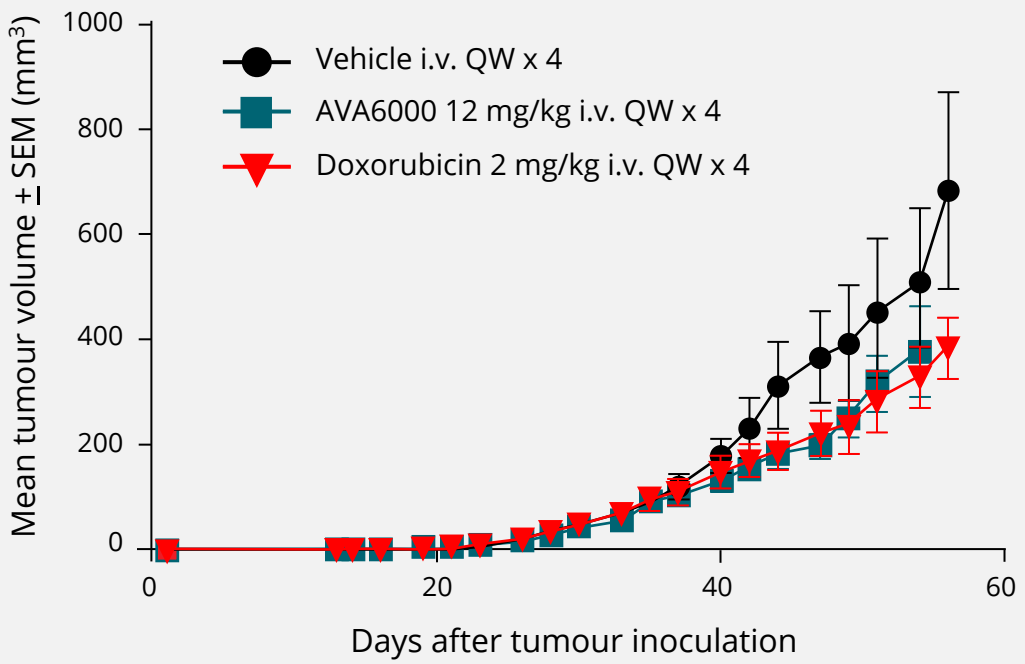
Disease control observed in a FAP^{high} PDX for **more than two months** following a short 4-dose regimen of AVA6000

Avacta Life Sciences, Pharmacology Written Summary, AVA6000 IND (2021)

Tumours with High FAP Expression Demonstrate Stronger Response with AVA6000

Model with naturally low FAP expression
(HPAF-IIP model)

(tumour:normal of 4:1)



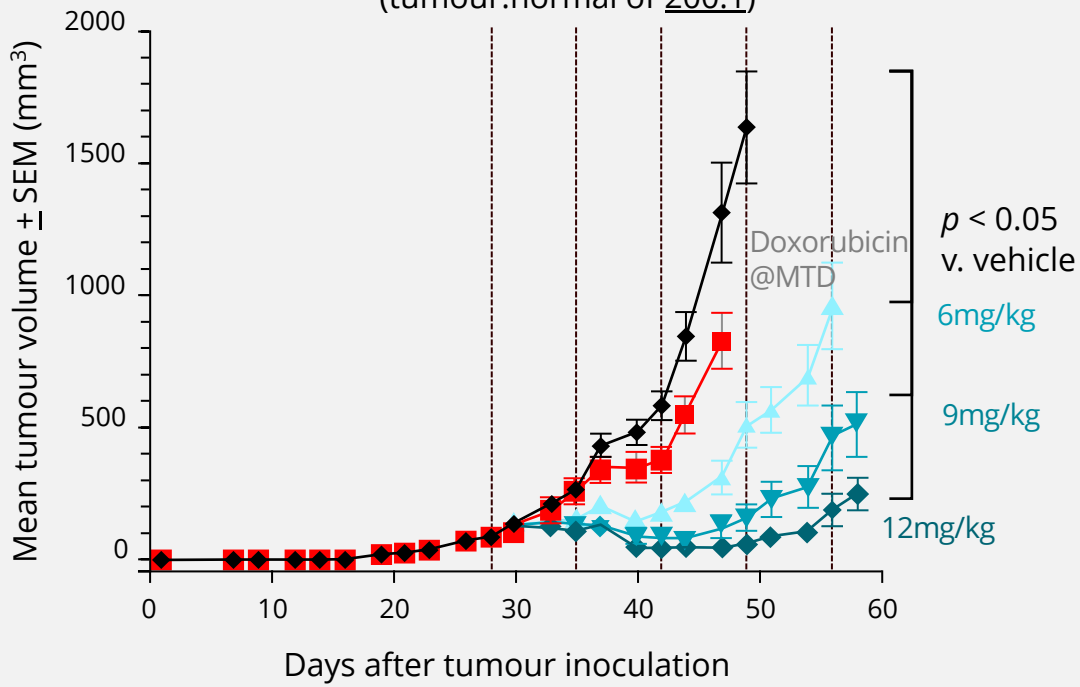
3

Low FAP Expression Leads to No Activity of AVA6000

No difference between standard doxorubicin and AVA6000 in the case of **low FAP activity**

Model with engineered high FAP expression
(HEK-FAP model)

(tumour:normal of 200:1)



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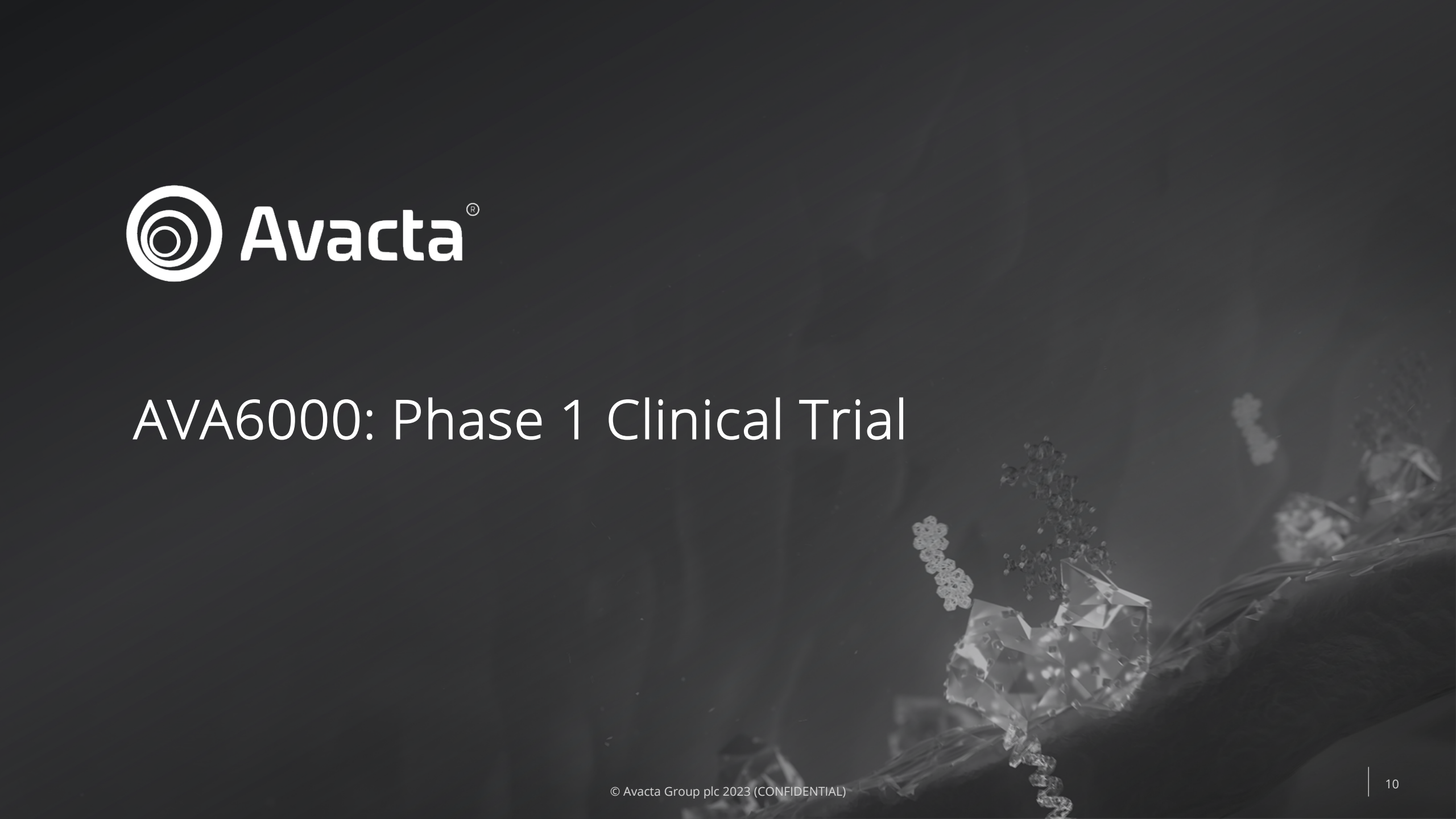
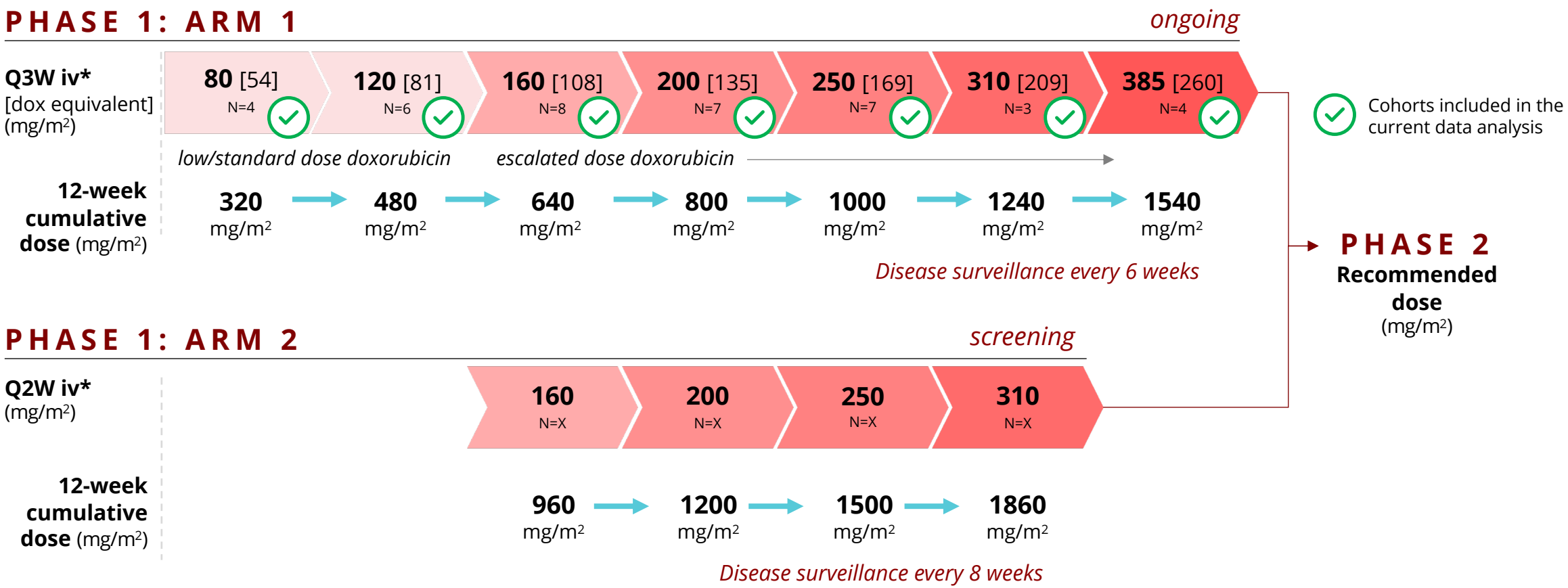
FAP^{high} tumours demonstrate activity of AVA6000

Significant anti-tumour effect even at low doses in this tumour model with **high FAP activity**

AVA6000: Phase 1 Clinical Trial



AVA6000 Phase 1 Trial Design



PHASE 1 POPULATION

- Patients with a diagnosis of known FAP^{high} cancers, including sarcoma, pancreatic cancer, colorectal cancer, head and neck cancers
- Acceptable performance status (ECOG 0 or 1), adequate organ function and recovery from effects of prior therapies
- Prior therapy with any anthracycline limited to total cumulative dose of less than 350 mg/m² doxorubicin or equivalent

*Q3W: every 3 weeks dosing regimen | Q2W: every 2 weeks dosing regimen

Baseline Characteristics and Cancer History in the Patient Population

	AVA6000 (80–385 mg/m^2 Q3W) N=40
Age, median (range)	65 (30-79)
Sex, m/f, n (%)	25 / 15 (62.5/37.5)
ECOG, 0/1. n (%)	12 / 28 (30/70)
Race	
White, n (%)	34 (85)
Asian, n (%)	2 (5)
Black or African American, n (%)	1 (2.5)
Other/Not reported, n (%)	3 (7.5)
Ethnicity	
Hispanic/Latino, n (%)	0
Non-Hispanic, non-Latino, n (%)	38 (95)
Not reported/unknown, n (%)	2 (5)

	AVA6000 (80–385 mg/m^2 Q3W) N=40
Cancer Diagnosis	
Soft tissue sarcoma, n (%)	12 (30)
Colorectal carcinoma, n (%)	11 (27.5)
Pancreatic ductal adenocarcinoma, n (%)	8 (20)
Cancers of the biliary tract, n (%)	3 (7.5)
Other[1], n (%)	6 (15)[1]
Prior cancer therapy	
No. prior regimens, median (range)	3 (0-7)
Any cytotoxic exposure, n (%)	32 (80)
Anthracycline exposure, n (%)	1 (2.5)
Platinum exposure, n (%)	26 (65)
Topoisomerase I inhibitor exposure, n (%)	20 (50)
Immunotherapy exposure, n (%)	14 (40)

AVA6000 phase 1 (ALS-6000-101) data cutoff 27 November 2023

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

Toxicities with AVA6000 Demonstrate a Dose Response Relationship

All AVA6000-related treatment-emergent adverse events observed by grade and dose cohort

	Standard dose doxorubicin cohorts		Elevated dose doxorubicin cohorts				
	Cohort 1 **80 mg/m²** N=4 n (%)	**Cohort 2** **120 mg/m²** N=6 n (%)	**Cohort 3** **160 mg/m²** N=8 n (%)	**Cohort 4** **200 mg/m²** N=7 n (%)	**Cohort 5[1]** **250 mg/m²** N=7 n (%)	**Cohort 6[1]** **310 mg/m²** N=5 n (%)	**Cohort 7[1]** **385 mg/m²** N=3 n (%)
Grade 1	2 (50)	4 (67)	8 (100)	6 (86)	7 (100)	5 (100)	1 (33)
Grade 2	3 (75)	3 (50)	6 (75)	6 (86)	5 (71)	3 (60)	0
Grade 3	0	0	1 (13)	2 (29)	2 (29)	3 (60)	0
Grade 4	0	0	0	1 (14)	1 (14)	0	0

AVA6000 phase 1 (ALS-6000-101) data cutoff 27 Nov 2023

1 Cohorts 5, 6 and 7 have all patients ongoing at the time of the data cutoff, thus safety findings in these cohorts will continue to mature

Cohort ongoing at data cutoff

Dose response relationship seen with all toxicities

- All adverse events demonstrate dose response across cohorts by grade
- Minimal grade 3-4 events observed across all cohorts vs. doxorubicin alone

AVA6000 Leads to Reduced Severe Toxicities Associated with Doxorubicin

Adverse event	AVA6000 (80–385 mg/m² Q3W) N=40 Grade 3-4 , n (%)	Doxorubicin[1] (75 mg/m² Q3W) N=323 Grade 3-4 , n (%)	Doxorubicin[2] (75 mg/m² Q3W) N=251 Grade 3-4 , n (%)
Neutropenia	3 (7.5)	92 (29)	122 (49)
Anemia	2 (5)	65 (21)	31 (12.4)
Febrile neutropenia	0	34 (11)	41 (16.5)
Leukopenia	0	17 (5)	59 (23.7)
Thrombocytopenia	2 (5)	4 (1)	21 (8.4)
Decreased WBC count	2 (5)	33 (11)	NR
Mucositis/stomatitis	1 (2.5)	7 (2)	7 (2.8)
Fatigue	1 (2.5)	11 (4)	12 (4.8)

AVA6000 data cutoff 27 Nov 2023

[1] Tap, WD *et al.* 2017. Phase 3 trial of evofosfamide with doxorubicin in patients with STS. Data reported from doxorubicin monotherapy arm

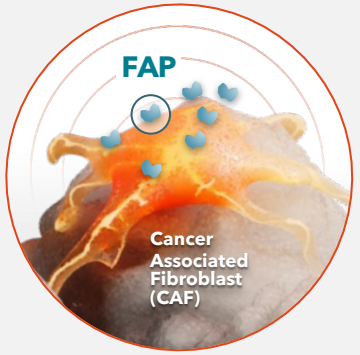
[2] Tap, WD *et al.* 2020. Phase 3 trial of olaratumumab with doxorubicin in patients with STS. Data reported from doxorubicin monotherapy arm

Reduction in all severe toxicities

These severe toxicities limit doxorubicin dosing to every 3 weeks, however the reduction in severe toxicity with AVA6000 **enables dosing optimisation** to every 2 weeks

AVA6000 Leads to Reduced Concentration and Exposure to Doxorubicin *in the Blood*

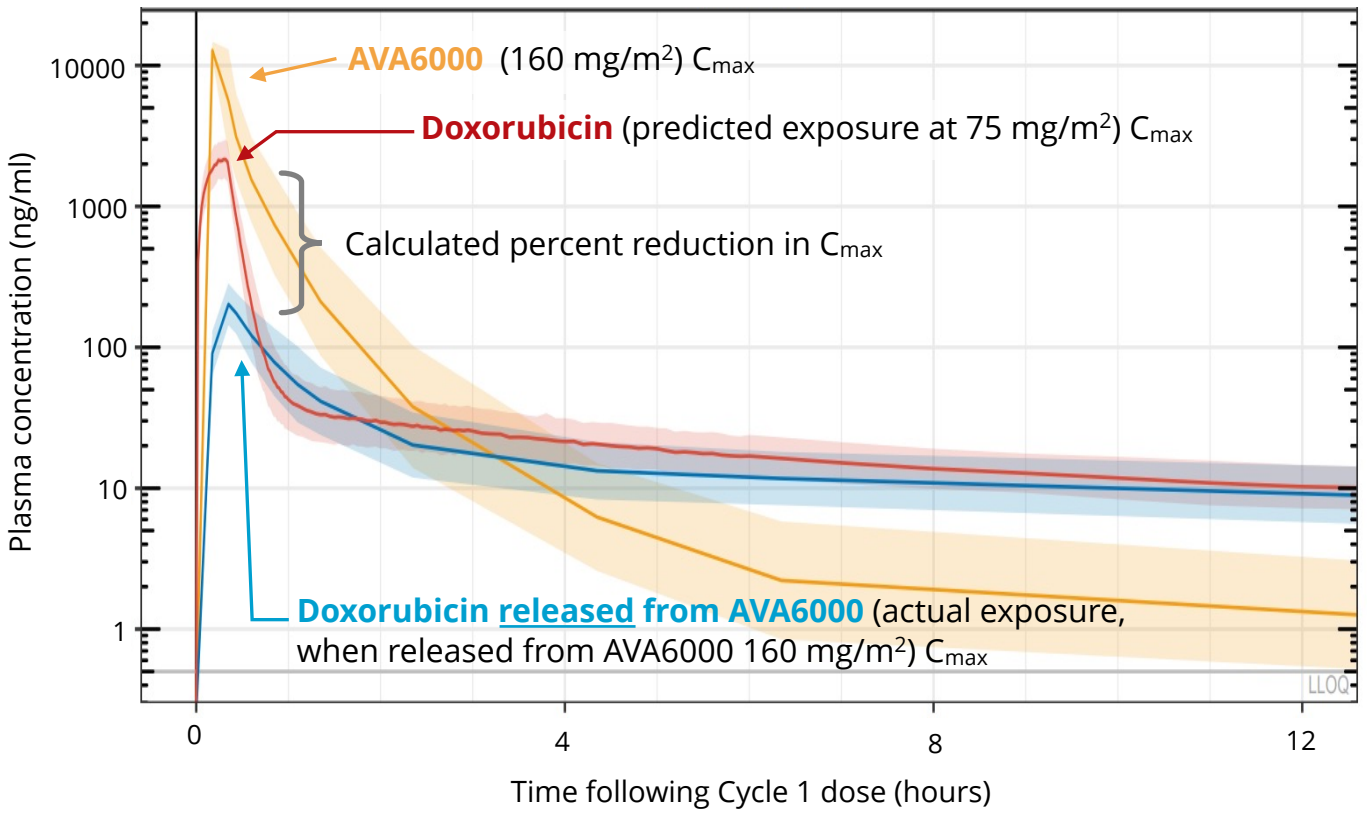
AVA6000
remains inert
until it encounters tumours with a high expression of **Fibroblast Activation Protein-α (FAP)**



The kinetics of the drug in the bloodstream is characterized in concentration vs. time plots

Maximum concentration = Cmax
Total exposure = area under curve (AUC)

Concentration in blood vs. time following dose - 160 mg/m² cohort



Reference PK
75 mg/m² (doxorubicin)

Predicted curve based on standard dose published data[1]

Observed PK
160 mg/m²

AVA6000

Doxorubicin

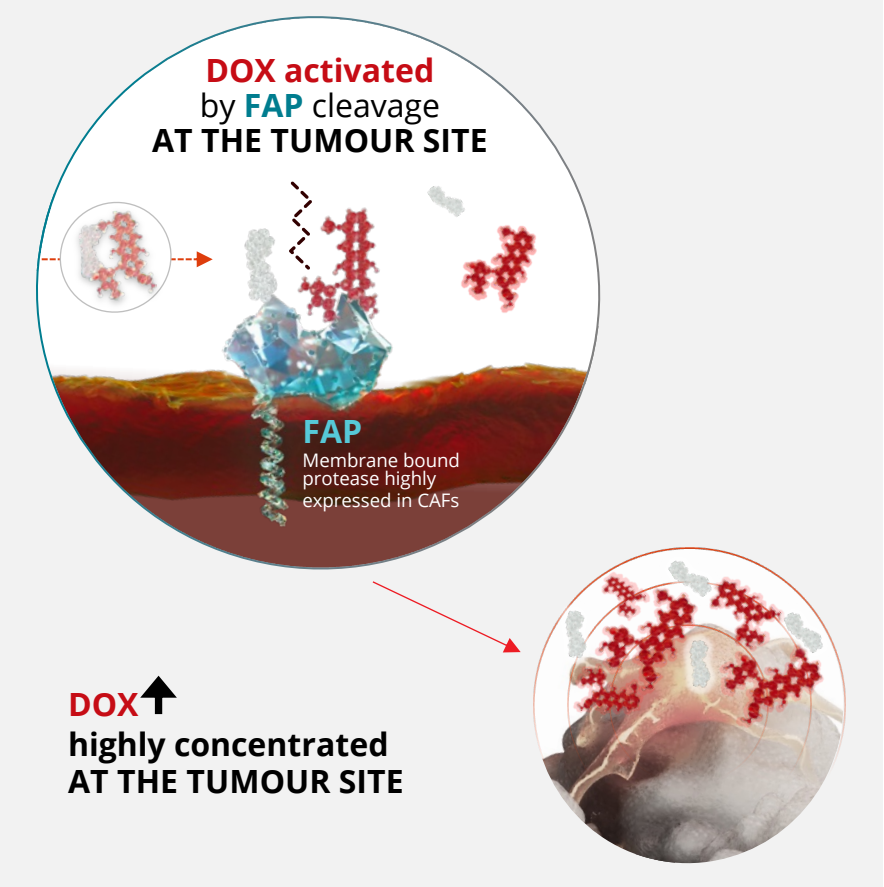
METHOD: Pharmacokinetics (PK) of AVA6000 and released doxorubicin observed in the AVA6000 phase 1 trial are compared to two independent standard dose doxorubicin data sets in a time-concentration plot over cycle 1 dosing[1]

[1] Kontny NE, et al.. *Cancer ChemothPharmacol.* (2013)71(3):749-63

Reduction in maximum concentration and total exposure

>80% reduction across all dose levels of the maximal concentration (Cmax) and 40-80% reduction in total exposure (AUC) of released doxorubicin following AVA6000 dosing compared with standard dose doxorubicin

AVA6000 Leads to Concentration of Released Doxorubicin *in the Tumour*



Dose cohorts by doxorubicin equivalent	AVA6000 dose cohorts (doxorubicin equivalent)	Plasma doxorubicin at 24h ng/ml mean (st dev)	Tumour doxorubicin level at 24h ng/gm mean (st dev)	Ratio tumour (ng/mg): plasma (ng/ml) mean
<75 mg/m^2 doxorubicin[1]	80 mg/m^2 (54 mg/m^2)	4.9 (0)	161.5 (120.9)	33:1
>75 mg/m^2 doxorubicin	160-250 mg/m^2 (108-169 mg/m^2)	8.3 (4.1)	860.9 (730)	104:1

Concentration of dox within the tumour

Central to the mechanism of action of AVA6000 is the ability of the drug to result in the **concentration of activated (cleaved) doxorubicin within the tumour microenvironment**

Preliminary Evidence of Antitumour Activity of AVA6000: Key Clinical Observations

Undifferentiated pleomorphic sarcoma (UPS)

59-year-old male with the diagnosis of **UPS** treated at **160 mg/m² Q3W**.

Partial Response with duration >6 months with tumour volume reduction -65%, treatment is ongoing

Correlative studies demonstrate **high FAP expression** in the tumour tissue

Favourable PK profile with reduction in AUC which permits dosing for 7 additional cycles (~21 weeks)

Angiosarcoma of the spleen

79-year-old female with the diagnosis of angiosarcoma treated at **250 mg/m² Q3W**.

Minor Response with visceral (hepatic) metastases reduction of 14% at cycle 2 and -22% at cycle 4

Continued shrinkage of liver metastases at cycle 4 scan with interval development of new bone metastases (mixed response)

Solitary fibrous tumour (SFT)

Three patients with the diagnosis of SFT have been treated at the dose levels of **250 mg/m²** and **200 mg/m²**.

All 3 patients with **prolonged stable disease** of 4-8 months with 2 of 3 patients ongoing. 2 of 3 patients with rapid progression prior to enrollment

PK profile suggests in these patients additional cycles can be administered in all 3 patients

Anti-tumour effects of AVA6000

- Deepening tumour shrinkage seen in two patients with diseases predicted to have **high FAP expression**
- **Low exposure to cleaved doxorubicin** in the bloodstream allows for more cycles and longer treatment

Key Messages: pre|CISION™ Platform Works as Intended

1

Data show that the pre|CISION™ platform works as designed

Data from the phase 1 trial indicate that AVA6000 specifically releases active doxorubicin in the tumour microenvironment

2

AVA6000 has improved the safety and tolerability of doxorubicin

AVA6000 dosing in the phase 1 trial leads to a reduction in the frequency and severity of the toxicities associated with doxorubicin

3

Preliminary signs of AVA6000 clinical activity are encouraging

Preliminary results indicate clinical activity of AVA6000 in patients with tumours with high FAP expression
further validating the pre|CISION™ mechanism of action

4

Optimising dose and schedule should increase efficacy of AVA6000 in selected indications

Given the favourable safety data, an every two weeks dosing arm will assist in optimising the schedule and dose for further clinical development in patients with FAP^{high} indications

Avacta®

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Glossary

FAP – Fibroblast activation protein
TME – Tumour micro environnent
PREP – Prolyl endopeptidase – a protein coding gene
HEK– Human embryonic kidney
HEK model - human embryonic kidney model, a cell line created for use in generating data
Xenograft - tissues transplanted from one species to another
PDX – Patient Derived Xenograft, which are models of cancer where the tissue or cells from a patient's tumour are implanted into a mouse.
HPAF-IIP – Human Pancreatic Adenocarcinoma cell line.
WBC count – White blood cell count
PK - Pharmacokinetics
CAF – Cancer associated fibroblast
Cleave – remove
Peptide – chain of amino acids that can bind to a warhead
D-Ala-Pro - a peptide sequence providing exquisite selectivity for cleavage by FAPα
CGP-DOX - carboxybenzyl- Gly-Pro-doxorubicin, another modified version of doxorubicin
Osteosarcoma - a tumour of the bone
Cytotoxic - a substance or process that can damage cells or cause them to die

Anthracyclines - a class of drugs used in cancer chemotherapy
Topoisomerases - enzymes that play essential roles in DNA replication
Neutropenia - a low number of white blood cells called neutrophils in the blood
Mucositis – when the mouth or gut is sore and inflamed
Leukopenia – when the body doesn't have enough disease-fighting leukocytes in the blood
Febrile neutropenia - the development of a fever, alongside other signs of infection such as feeling unwell, shivers and shakes in a patient with neutropenia
Thrombocytopenia – a deficiency of platelets in the blood.
Cmax – maximum concentration
AUC – area under the curve (in this case showing overall exposure)
Undifferentiated pleomorphic sarcoma (UPS) - a type of cancer that begins mostly in the soft tissues of the body
Angiosarcoma - a type of cancer that forms in the lining of the blood vessels and lymph vessels
Solitary fibrous tumours (SFT) - growths of cells that can form in almost any part of the body.