A Phase I Trial of Faridoxorubicin (FAP-Dox, AVA6000), a Fibroblast Activation Protein (FAP)-released and Tumor Microenvironment (TME)-targeted Doxorubicin Peptide Drug Conjugate in Patients with FAP-positive Solid Tumors

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BACKGROUND

pre|CISION® peptide drug conjugates comprise a peptide moiety bound to an active payload by a linker that is specifically cleaved by FAP

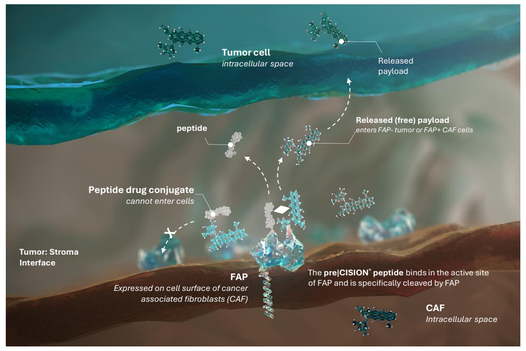
FAP is a protease selectively overexpressed in the tumor microenvironment (TME) of many solid tumors on cancer-associated fibroblasts

The pre|CISION® peptide prevents cellular entry of the conjugate unless cleaved by FAP, enabling targeted delivery of released payload directly to tumors

This targeted release mechanism has been validated in both preclinical animal models and clinical biopsy data, demonstrating that the payload is predominantly activated and released in the FAP-rich tumor environment

- Doxorubicin is an effective anthracycline, however, its clinical utility is significantly limited by dose-dependent, cumulative cardiotoxicity and bone marrow toxicity
- Encouraging safety and preliminary efficacy data from the Phase 1 trial with faridoxorubicin have been presented previously (Lahu et al AACR 2025, Banerji, AACR 2024, Twelves, ESMO 2024)
- It is hypothesized that the tumor-specific release mechanism of pre|CISION® medicines reduces the initial "first pass" normal tissue exposure to released doxorubicin (e.g. cardiac and bone marrow)

FIGURE 1. The pre|CISION® Bystander Effect



Patient Population and Trial Methods

The Faridoxorubicin (AVA6000) Phase 1a dose escalation enrolled patients with a diagnosis of cancers frequently noted as FAP-positive, including sarcoma, pancreatic cancer, colorectal cancer, head and neck cancers

Specific indications were selected for Phase 1b expansion. FAP expression was tested retrospectively. The data cutoff presented is 16 September 2025

- **Prior therapy with any anthracycline was limited to total cumulative dose of less than 350 mg/m²**. The lifetime cumulative maximum exposure was limited to 550 mg/m² in the AVA6000 trial based on favorable safety data
- **Trial analyzed for safety (primary endpoint) and efficacy.** Efficacy in patients with a diagnosis of salivary gland cancers treated at the dose of 250 mg/m² and above are presented across doses ranging from 250 mg/m² to 385 mg/m² (n=11)
- **On-treatment biopsies were obtained (n=14) at 24 hours after the dose was administered and assessed for the level of free doxorubicin in the TME.** Plasma samples were obtained at the same time to assess the tumor:plasma ratio of doxorubicin

FIGURE 2.

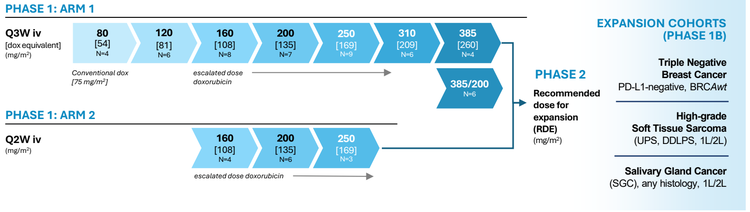


TABLE 1. Baseline characteristics and prior cancer therapy

	AVA6000 (Q3W/Q2W) N=63
Age, median (range)	63 (30-81)
Sex, m/f, n (%)	36 / 27 (57 / 43)
ECOG, 0/1, n (%)	25 / 38 (40 / 60)
Race	
White, n (%)	51 (81)
Asian, n (%)	6 (10)
Black or African American, n (%)	2 (3)
Not reported/unknown, n (%)	4 (6)
Ethnicity	
Hispanic/Latino, n (%)	0
Non-Hispanic, non-Latino, n (%)	59 (94)
Not reported/unknown, n (%)	4 (6)

	AVA6000 (Q3W/Q2W) N=63
Cancer Diagnosis	
Salivary gland cancer, n (%)	17 (27)
Soft tissue sarcoma (other subtype), n (%)	14 (22)
Colorectal carcinoma, n (%)	10 (16)
Pancreatic ducal adenocarcinoma, n (%)	8 (12)
Liposarcoma/high grade UPS, n (%)	6 (10)
Cancers of the biliary tract, n (%)	2 (3)
Other[1], n (%)	6 (10)[1]
Prior systemic cancer therapy	
Number of prior regimens, median (range)	2 (0-7)
Any cytotoxic, n (%)	39 (62)
Anthracycline, n (%)	5 (8)
Platinum, n (%)	36 (57)
Topoisomerase I inhibitor, n (%)	35 (56)
Immunotherapy, n (%)	17 (27)

[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 otherwise specified), esophageal cancer

SAFETY

TABLE 2. Most Frequent Grade 3-4 AE reported in ≥2 pts

Adverse event	80 mg/m² Q3W n (%) N=4	120 mg/m² Q3W n (%) N=6	160 mg/m² Q3W n (%) N=8	200 mg/m² Q3W n (%) N=7	250 mg/m² Q3W n (%) N=9	310 mg/m² Q3W n (%) N=7	385 mg/m² Q3W n (%) N=4	385/200 mg/m² Q3W n (%) N=5	160 mg/m² Q2W n (%) N=4	200 mg/m² Q2W n (%) N=6	250 mg/m² Q2W* n (%) N=3	Total n (%) N=63	Doxorubicin (75 mg/m² Q3W) N=251 Gr 3-4^ n (%)
Neutropenia	0	0	0	2 (29)	2 (22)	1 (14)	2 (50)	4 (80)	0	0	1 (33)	12 (19)	**122 (49)**
Leukopenia	0	0	0	1 (14)	0 (0)	1 (14)	2 (50)	2 (40)	0	0	0	6 (10)	**59 (23.7)**
Lymphopenia	0	0	0	2 (29)	0	0	0	1 (20)	0	1 (17)	0	4 (6)	**7 (2.8)**
Anemia	0	0	0	1 (14)	0	3 (43)	0	0	0	0	0	4 (6)	**31 (12.4)**
Thrombocytopenia	0	0	0	1 (14)	1 (11)	0	0	0	0	1 (17)	0	3 (5)	**21 (8.4)**
Fatigue	0	0	0	0	0	1 (14)	0	0	1 (25)	0	0	2 (3)	**12 (4.8)**

Data cutoff 15 Sept 2025.
*250 mg/m² Q2W is not completed
^Tap WD, et al. 2020. Phase 3 trial of olaratumumab with doxorubicin in patients with STS. Data reported from doxorubicin mono arm Grade 3-4 events

TABLE 3. Left Ventricular Ejection Fraction Changes

	Faridoxorubicin ≤450 mg/m² N=48	Faridoxorubicin 500 mg/m² N=3	Faridoxorubicin 550 mg/m² N=11
LVEF decreases observed[1]			
LVEF ≥ LLN and LVEF reduced >20%	0	N=1	0
LVEF < LLN and LVEF reduced >10%	N=1	0	0

Data cutoff 15 Sept 2025.
[1]Criteria for LVEF analysis based on criteria in the doxorubicin and liposomal doxorubicin labels.

Additional Safety Observations

No Grade 3 or 4 cardiac adverse events were reported in the trial during treatment with faridoxorubicin or in the follow-up period

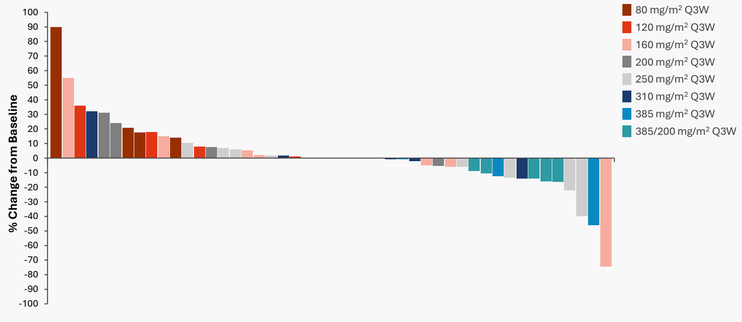
Grade 1 or 2 cardiac AE reported in 1 pt each include:
- Cardiac disorder (NOS)
- Cardiac failure (reported as DLT, see below)
- Palpitations
- Pericardial effusion
- Tachycardia

Three DLT were reported during the trial:
- Grade 2 cardiac failure (120 mg/m²)
- Grade 4 thrombocytopenia (200 mg/m² Q3W)
- Grade 4 neutropenia (385/200 mg/m² Q3W)

No MTD was declared during the trial

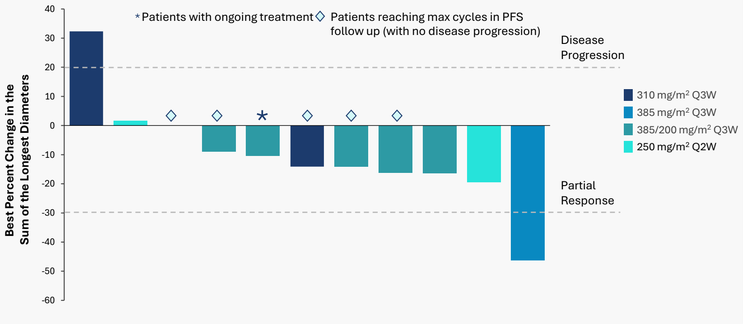
EFFICACY

FIGURE 3. WATERFALL PLOT OF BEST RESPONSE FROM BASELINE IN ALL PTS TREATED



FAP-Dox: Preliminary Data Demonstrate Durable Tumor Shrinkage in Patients with Salivary Gland Cancers

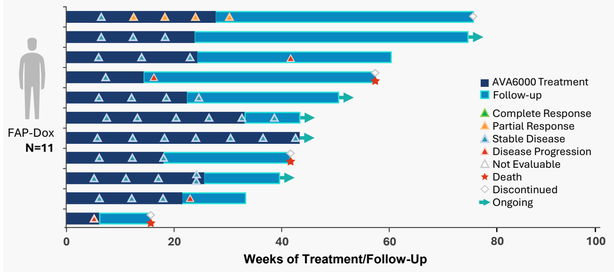
FIGURE 4. WATERFALL PLOT OF BEST PERCENT CHANGE IN PATIENTS WITH SALIVARY GLAND CANCERS



Data cutoff 15 Sept 2025.
All pts with the diagnosis of salivary gland cancer treated at or above the 250 mg/m² dose level, regardless of schedule.

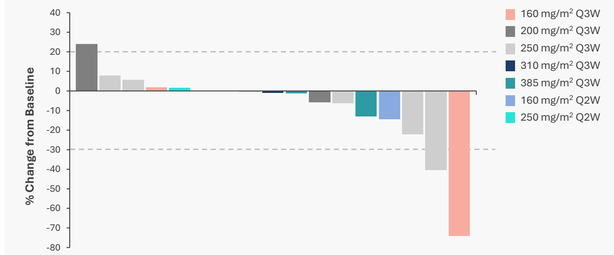
Durability of Treatment Response in Patients with Salivary Gland Cancers

FIGURE 5. SWIMMER PLOT OF WEEKS ON STUDY BY STATUS IN PATIENTS WITH SALIVARY GLAND CANCERS



Data cutoff 15 Sept 2025.
All pts with the diagnosis of salivary gland cancer treated at or above the 250 mg/m² dose level, regardless of schedule.
[1]Licitra et al. ESMO 2024. A randomized phase I study to evaluate the efficacy and safety of androgen deprivation therapy (ADT) vs chemotherapy (CT) in patients with recurrent and/or metastatic, androgen receptor (AR) expressing, salivary gland cancers (LBA36).

FIGURE 6. WATERFALL PLOT OF BEST PERCENT CHANGE IN PATIENTS WITH SOFT TISSUE SARCOMAS



Q2W = once every 2 weeks; Q3W = once every 3 weeks

PK Parameters of Faridoxorubicin and Peptide-released Doxorubicin

TABLE 5.

TRT	Parameter	Units	Faridoxorubicin (AVA6000) Median	Faridoxorubicin (AVA6000) 5%	Faridoxorubicin (AVA6000) 95%	Doxorubicin Median	Doxorubicin 5%	Doxorubicin 95%	TRT
80	AUClast	hr*ng/mL	2581.56	911.62	5897.64	452.37	344.18	887.94	Q3W
	Cmax	ng/mL	6797.71	3672.12	8918.41	185.29	135.91	244.47	
	t 1/2	hr	0.71	0.48	0.97	34.14	26.56	56.45	
120	AUClast	hr*ng/mL	3099.93	1197.62	7868.68	599.84	292.75	958.45	
	Cmax	ng/mL	7502.35	1962.33	15409.4	209.94	75.53	354	
	t 1/2	hr	0.79	0.52	0.92	45.21	31.36	55.73	
160	AUClast	hr*ng/mL	3015.58	1170.89	14485.86	589.69	231.18	1489.45	
	Cmax	ng/mL	7112.29	1811.49	30082.9	236.32	114.65	354	
	t 1/2	hr	0.9	0.71	95.94	39.33	26.97	87.54	
200	AUClast	hr*ng/mL	10283.03	3067.54	19873.03	1139.95	793.66	3577.4	
	Cmax	ng/mL	21070.35	5830	26434.1	339.58	282.44	741.31	
	t 1/2	hr	0.82	0.7	23.55	36.34	21.23	112.89	
250	AUClast	hr*ng/mL	8833.46	2472.21	15414.38	1202.47	659.81	2298.33	
	Cmax	ng/mL	13800	5380	25000	404	247	1380	
	t 1/2	hr	0.81	0.46	21.58	49.34	7.82	61.65	
310	AUClast	hr*ng/mL	13536.87	10317.05	250473.78	1335.51	904.26	8527.05	
	Cmax	ng/mL	23250	14000	29200	437.5	192	859	
	t 1/2	hr	0.85	0.69	10.73	54.26	27.85	97.73	
385	AUClast	hr*ng/mL	13589.8	3160.03	27202.41	1971.18	514.69	4387.03	
	Cmax	ng/mL	21200	1880	41700	486.5	150	926	
	t 1/2	hr	1.01	0.67	44.69	41.05	29.24	70.41	
160	AUClast	hr*ng/mL	4,304.15	2,679.08	5,463.91	577.73	357.10	1,724.17	Q2W
	Cmax	ng/mL	12,800.00	7,340.00	16,500.00	211.00	128.00	317.00	
	t 1/2	hr	3.00	0.66	3.65	53.62	34.07	84.19	
200	AUClast	hr*ng/mL	10,045.74	8,228.32	12,251.11	1,393.65	807.80	2,570.12	
	Cmax	ng/mL	19,400.00	13,300.00	52,000.00	510.50	391.00	1,550.00	
	t 1/2	hr	0.60	0.50	0.71	77.37	31.33	80.08	

Tumor to Plasma Concentration of Released Doxorubicin

FIGURE 7. Optional tumor biopsies and plasma samples were obtained 24 hours after the first dose of Faridoxorubicin. Tumor biopsies were analyzed for both concentration of doxorubicin and FAP expression by immunohistochemistry.

FIGURE 7a. Tumor and plasma concentrations assessed by dose level

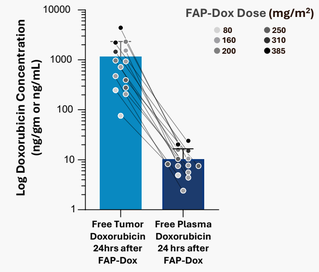


FIGURE 7b. Tumor and plasma concentration by FAP expression in the TME

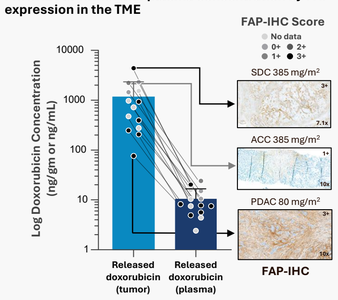
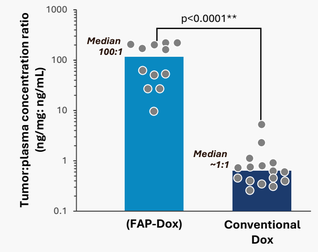


FIGURE 7c. Ratio of tumor to plasma with released doxorubicin compared to published historical conventional doxorubicin



References

Minotti G, et al. Anthracyclines: Molecular Advances and Pharmacologic Developments in Antitumor Activity and Cardiotoxicity. *Pharmacol Rev.* 2004;56(2):185–229.

Tap WD, et al. Effect of Doxorubicin Plus Olaratumab vs Doxorubicin Plus Placebo on Survival in Patients With Advanced Soft Tissue Sarcomas: The ANNOUNCE Randomized Clinical Trial. *JAMA.* 2020;323(13):1266-1276.

Villalobos VM, et al. Pharmacokinetics of doxorubicin following concomitant intravenous administration of olaratumab (IMC-3G3) to patients with advanced soft tissue sarcoma. *Cancer Med.* 2020 Feb;9(3):882-893.

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CONCLUSIONS

Faridoxorubicin (AVA6000) is safe and well-tolerated in both the Q3W and Q2W dosing regimens with, with preliminary evidence of efficacy in patients with soft tissue sarcomas (STS) and salivary gland cancers (SGC) and no severe cardiac toxicity. No MTD was determined in the trial despite dosing up to 385 mg/m² (~4x conventional dose doxorubicin)

- **Faridoxorubicin treatment demonstrates low rates of severe toxicities that are associated with conventional doxorubicin**
- **Confirmed responses were observed in patients with stromal only expression of FAP with SGC and tumor cell expression of FAP in STS**
- **In the cohort of SGC patients, median PFS has not yet been reached. The median follow up is estimated at 51 weeks (using the Reverse Kaplan Meier method)**
- **The median tumor to plasma ratio of released doxorubicin is 100:1 and doxorubicin concentration in the tumor demonstrates a strong dose response. Effective cleavage and concentration in the tumor is evident at all levels of FAP expression including patients with tumors demonstrating minimal 1+ expression**