CYBREXA THERAPEUTICS

Victoria ADC Meeting

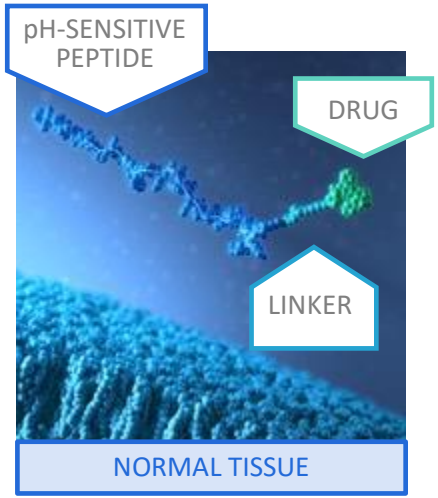
March 15,2024

Background

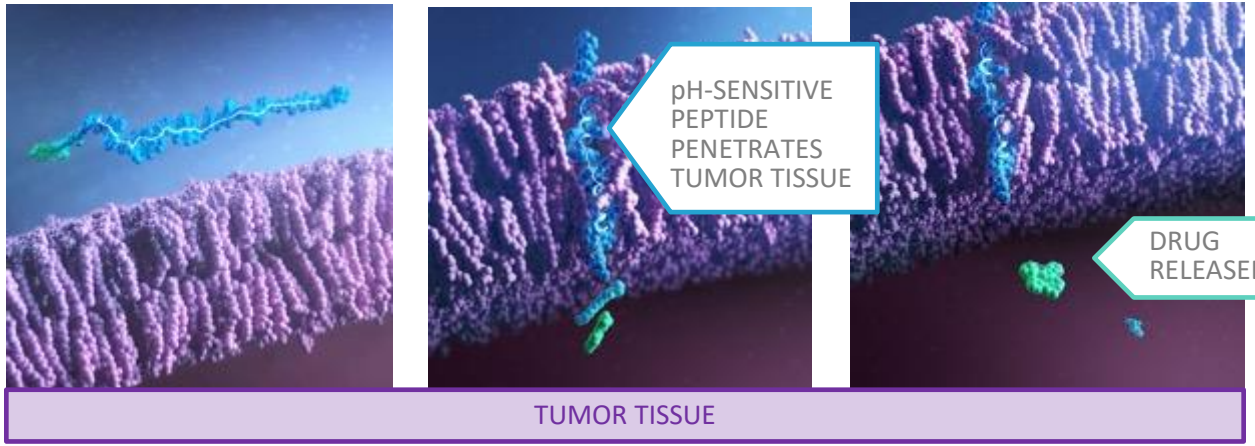
- Malignant tumors rely on anerobic metabolism and create an acidic microenvironment described as the Warburg Effect.
- Alphalex conjugates contain a pH-low insertion peptide (pHLIP), a linker and a payload, in CBX-12 the topoisomerase 1 inhibitor, exatecan.
- In an acidic environment the peptide undergoes a conformation change and preferentially penetrates the tumor cell membrane, but not that of normal tissues.
- CBX-12 is not antigen specific and does not require target expression like an antibody drug conjugate.
- Alphalex targeting facilitates a 5-fold increase in exatecan delivery compared to unconjugated Exatecan.*

*Ann Oncol. 14:913-21, 2003 ; J Clin Oncol. 18:3151-63, 2000

alphalex™: Mechanism of Action



alphalex™ comprises three components: peptide, proprietary linker, and anti-cancer agent



In the low-**pH** tumor microenvironment, the peptide forms an **alpha helix**

The peptide then **penetrates the tumor tissue** by inserting the C-terminus with anti-cancer agent across the cell membrane

The linker then disintegrates to release the drug directly into the cell cytoplasm

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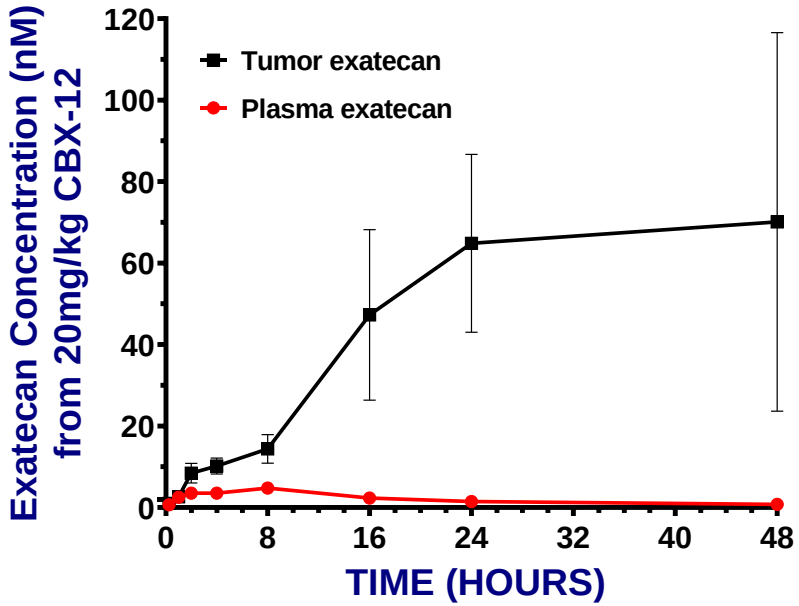
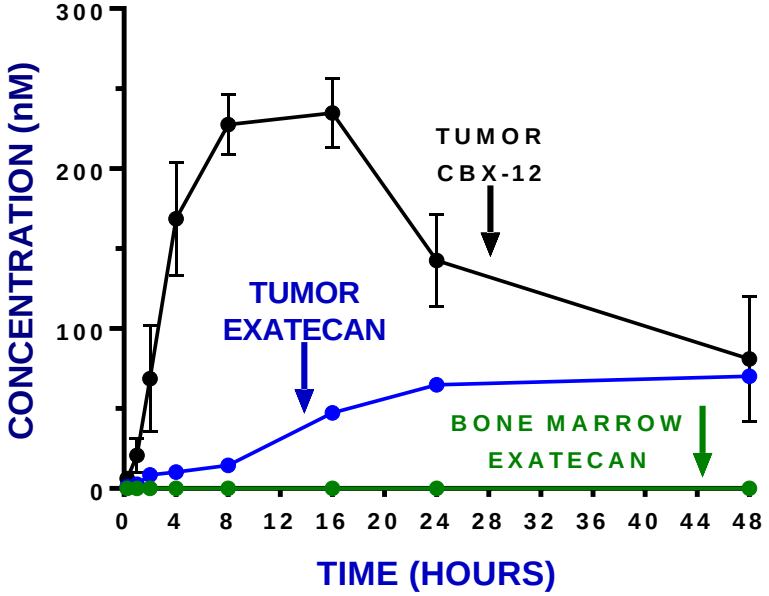
CBX-12: Improved Delivery of Potent Therapeutic

Stable conjugate allows for specific targeting



Targeted tumor delivery avoids healthy tissue



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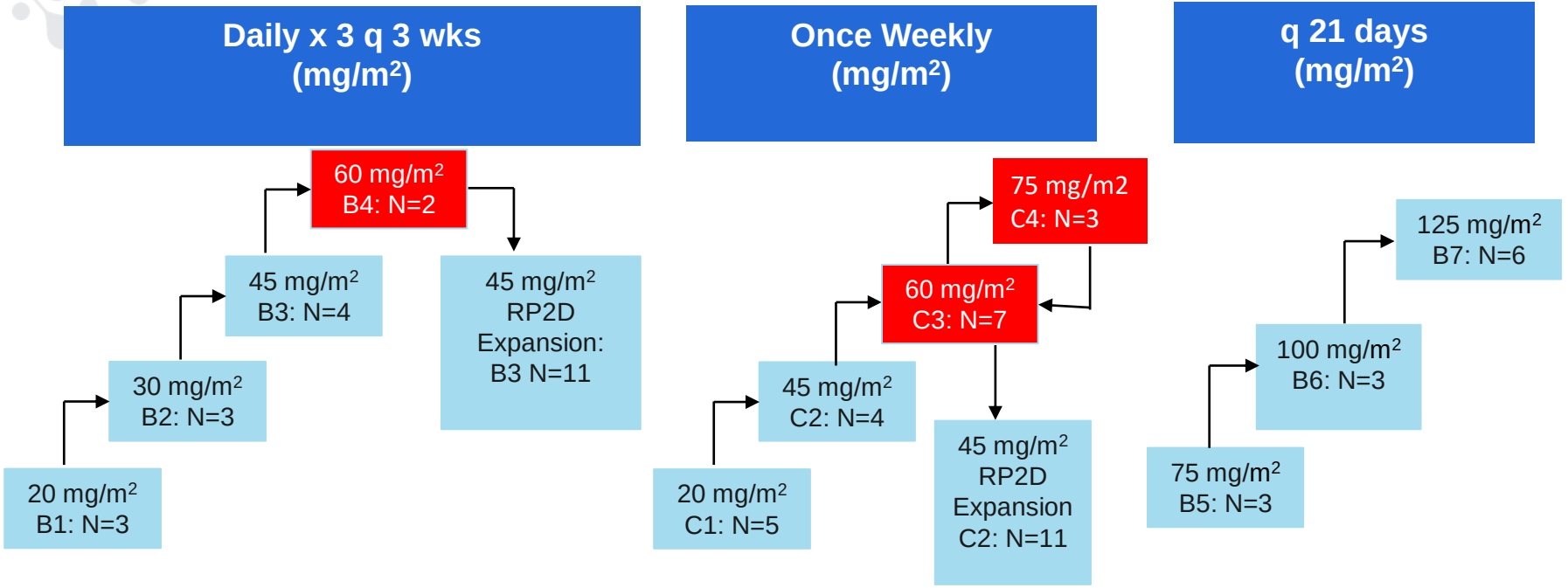
CBX-12-101 Enrollment: 69 Treated to Date



Part A: 4 patients treated with daily x 5

Safety Summary

CBX12-101 Phase 1: Adverse Event Details

Most Frequent TEAEs - Overall

MedDRA Preferred Term	Daily x5 (N=4)		Daily x3 (N=23)		Q21d (N=9)		Weekly (N=30)		Phase 1 Overall (N=66)	
	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4
Anaemia	2 (50.0)	1 (25.0)	18 (78.3)	10 (43.5)	4 (44.4)	1 (11.1)	20 (66.7)	12 (40.0)	44 (66.7)	24 (36.4)
Fatigue	1 (25.0)	0 (0.0)	11 (47.8)	0 (0.0)	3 (33.3)	1 (11.1)	16 (53.3)	2 (6.7)	31 (47.0)	3 (4.5)
Leukopenia	1 (25.0)	1 (25.0)	12 (52.2)	6 (26.1)	5 (55.6)	2 (22.2)	12 (40.0)	6 (20.0)	30 (45.5)	15 (22.7)
Nausea	2 (50.0)	0 (0.0)	11 (47.8)	0 (0.0)	3 (33.3)	0 (0.0)	13 (43.3)	0 (0.0)	29 (43.9)	0 (0.0)
Neutropenia	1 (25.0)	1 (25.0)	13 (56.5)	11 (47.8)	6 (66.7)	2 (22.2)	8 (26.7)	6 (20.0)	28 (42.4)	20 (30.3)
Diarrhoea	3 (75.0)	0 (0.0)	9 (39.1)	1 (4.3)	2 (22.2)	1 (11.1)	8 (26.7)	1 (3.3)	22 (33.3)	3 (4.5)
Thrombocytopenia	1 (25.0)	1 (25.0)	10 (43.5)	6 (26.1)	2 (22.2)	1 (11.1)	7 (23.3)	2 (6.7)	20 (30.3)	10 (15.2)
Vomiting	3 (75.0)	1 (25.0)	7 (30.4)	0 (0.0)	1 (11.1)	0 (0.0)	7 (23.3)	0 (0.0)	18 (27.3)	1 (1.5)
Hyponatraemia	0 (0.0)	0 (0.0)	8 (34.8)	0 (0.0)	3 (33.3)	0 (0.0)	6 (20.0)	0 (0.0)	17 (25.8)	0 (0.0)
Lymphopenia	0 (0.0)	0 (0.0)	6 (26.1)	5 (21.7)	5 (55.6)	2 (22.2)	4 (13.3)	4 (13.3)	15 (22.7)	11 (16.7)
Hypomagnesaemia	0 (0.0)	0 (0.0)	5 (21.7)	0 (0.0)	2 (22.2)	0 (0.0)	7 (23.3)	0 (0.0)	14 (21.2)	0 (0.0)
INR increased	0 (0.0)	0 (0.0)	6 (26.1)	0 (0.0)	2 (22.2)	0 (0.0)	6 (20.0)	0 (0.0)	14 (21.2)	0 (0.0)
ALT increased	1 (25.0)	0 (0.0)	5 (21.7)	0 (0.0)	3 (33.3)	0 (0.0)	4 (13.3)	1 (3.3)	13 (19.7)	1 (1.5)
AST increased	2 (50.0)	1 (25.0)	5 (21.7)	1 (4.3)	2 (22.2)	0 (0.0)	4 (13.3)	0 (0.0)	13 (19.7)	2 (3.0)
Dehydration	2 (50.0)	0 (0.0)	4 (17.4)	0 (0.0)	1 (11.1)	0 (0.0)	6 (20.0)	1 (3.3)	13 (19.7)	1 (1.5)
Hypoalbuminaemia	0 (0.0)	0 (0.0)	6 (26.1)	0 (0.0)	0 (0.0)	0 (0.0)	5 (16.7)	2 (6.7)	11 (16.7)	2 (3.0)
Hypokalaemia	0 (0.0)	0 (0.0)	5 (21.7)	0 (0.0)	0 (0.0)	0 (0.0)	6 (20.0)	2 (6.7)	11 (16.7)	2 (3.0)

Source: t-teae-pt-p1

CBX12-101 Phase 1: Adverse Event Details

Most Frequent TEAEs – Q21d

MedDRA Preferred Term	Cohort 5: 75 mg/m^2 (N=3)		Cohort 6: 100 mg/m^2 (N=3)		Cohort 7: 125 mg/m^2 (N=3)		Q21d Overall (N=9)	
	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4
Anaemia	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	2 (66.7)	1 (33.3)	4 (44.4)	1 (11.1)
Fatigue	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	3 (33.3)	1 (11.1)
Leukopenia	1 (33.3)	0 (0.0)	1 (33.3)	1 (33.3)	3 (100.0)	1 (33.3)	5 (55.6)	2 (22.2)
Nausea	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (33.3)	0 (0.0)
Neutropenia	1 (33.3)	0 (0.0)	2 (66.7)	1 (33.3)	3 (100.0)	1 (33.3)	6 (66.7)	2 (22.2)
Diarrhoea	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	2 (22.2)	1 (11.1)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	1 (33.3)	2 (22.2)	1 (11.1)
Vomiting	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
Hyponatraemia	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	2 (66.7)	0 (0.0)	3 (33.3)	0 (0.0)
Lymphopenia	2 (66.7)	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.7)	0 (0.0)	5 (55.6)	2 (22.2)
Hypomagnesaemia	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	2 (22.2)	0 (0.0)
INR increased	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)
ALT increased	0 (0.0)	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)
AST increased	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)
Dehydration	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
Hypoalbuminaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypokalaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: t-teae-pt-p1

Summary of Activity

Patient-Specific Summaries of Responders

Patient	Tumor	Schedule / Dose	Best Response	Clinical Course
1001-003	Ovary	Daily x 5 initially Daily x 3 at Cycle 13	cCR	Grade 4 toxicity in Cycle 1. On treatment 14 months. Off treatment due to PD
1001-012	Breast	Daily x 3: 45 mg/m^2	uPR	On treatment 9 months. Off treatment due to PD
1002-009	Breast	Weekly: 20 mg/m^2	cPR	On treatment 5 months. Off treatment due to PD
1002-021	Ovary	Daily x 3: 45 mg/m^2	cPR	On treatment 12 months. Ongoing
1003-005	Ovary	Weekly 75 mg/m^2	uPR	On treatment 5 months. Off treatment due to Clinical PD
1001-025	NSCLC	Weekly 45 mg/m^2	uPR	On treatment 5 months. Off treatment due to PD
1001-023	CRC	Weekly 60 mg/m^2	cPR	On treatment 9 months. Ongoing
1002-028	Breast	100 mg/m^2 q21d	cPR	On treatment 4 months. Ongoing

Other Notable Patients

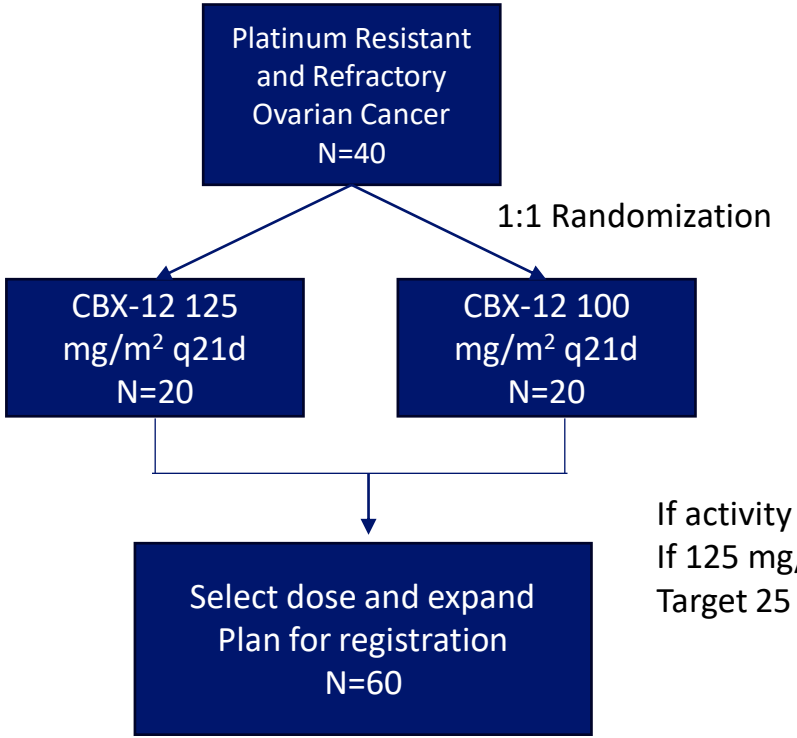
Patient	Tumor	Schedule / Dose	Best Response	Clinical Course
1002-006	Breast	Daily x 3: 30 mg/m^2	29% reduction	On treatment 10 months. Off treatment due to clinical progression
1001-17	Ovary	Weekly 45 mg/m^2	SD	On treatment 13 months. ongoing
1002-034	Cholangio	125 mg/m^2 q21d	24% reduction	On treatment 4 months. Ongoing
1002-036	Thymic	125 mg/m^2 q21d	21% reduction	On treatment 4 months. Ongoing

Summary

- CBX-12 is well tolerated at 135 mg/m^2/cycle on both daily x3 and weekly schedules and 125 mg/m^2 q21d
  - Dose limiting toxicity is myelosuppression.
- Activity seen across a wide dosing range
  - Including 3 patients treated above the RP2D dose intensity
- Linear PK does not contribute to RP2D decision
  - Higher exposure does lead to more myelosuppression
- Three possible phase 2 doses
  - 45 mg/m^2 weekly
  - 45 mg/m^2 daily x3 every 21 days
  - 125 mg/m^2 q21d
- Next step: Randomized Phase 2 study in Ovarian Cancer at 100 and 125 mg/m^2 q21d

CBX-12 Ovarian Cancer Registration Trial

- Primary Endpoint ORR by RECIST



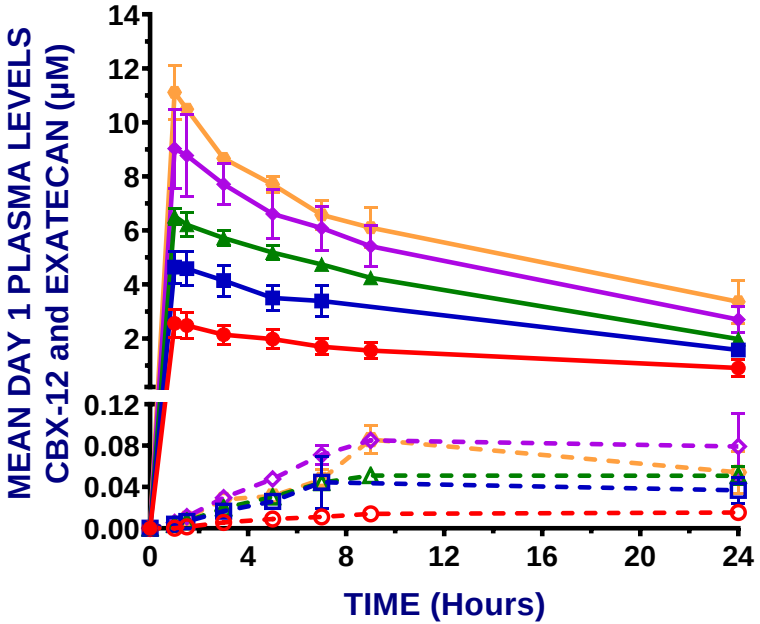
If activity comparable, choose 100mg/m^2
If 125 mg/m^2 more active, choose 125
Target 25 confirmed responders

PK Summary

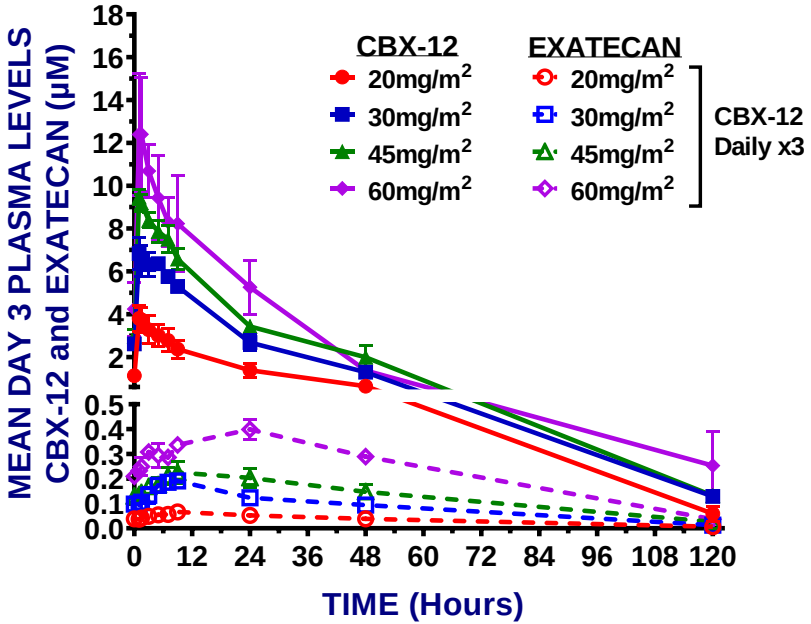
Cohort B: CBX-12 Daily x3 Pharmacokinetics - Average by Cohort

Plasma Exposure on Day 1 and Day 3

DAY 1



DAY 3



Updated 23May2023

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Cohort B: CBX-12 Daily x 3 Pharmacokinetics
Average by Cohort

Dose (mg/m^2)	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng/mL*hr)	C_{max} (μM)	$AUC_{0\text{-last}}$ (μM*hr)	$AUC_{0\text{-24}}$ (μM*hr)	CBX-12/ Exatecan $AUC_{0\text{-24}}$ Ratio	Accumulation Ratio: $AUC_{0\text{-24}}$ Day 3/Day 1
CBX-12 Day 1									
20	22.1	1.0	9897	135167	2.56	34.90	34.9	125	NA
30	15.7	1.2	18200	256333	4.70	66.23	66.2	104	NA
45	13.2	1.2	26060	319533	6.73	82.52	86.9	125	NA
60	14.6	1.0	34950	458000	9.04	118.50	118.5	75.9	NA
75	17.7	1.25	43800	532000	11.3	137	137	105	NA
CBX-12 Day 3									
20	20.5	3.0	15600	359333	4.03	92.97	54.1	41.2	1.58
30	22.4	1.0	26433	725000	6.83	187.33	105.6	37.3	1.60
45	20.5	1.2	37408	929154	9.67	240.15	137.9	40.0	1.53
60	21.3	1.3	48350	1309000	12.47	338.00	185.5	22.9	1.55
75									
Exatecan Day 1									
20	NC	19.0	6.79	124	0.0156	0.285	0.285	NA	NA
30	NC	12.7	18.89	336	0.0434	0.770	0.770	NA	NA
45	NC	16.9	26.71	402	0.0614	0.923	0.964	NA	NA
60	NC	16.5	43.60	700	0.1001	1.605	1.605	NA	NA
75	NC	16.5	38.0	571	0.0873	1.31	1.31	NA	NA
Exatecan Day 3									
20	36.8	8.3	34.37	1740	0.0789	4.000	1.337	NA	4.73
30	32.5	5.7	63.83	3763	0.1467	8.640	3.177	NA	4.45
45	33.3	17.3	96.01	5515	0.2205	12.680	4.583	NA	4.65
60	29.1	16.5	174.00	10270	0.4000	23.650	8.075	NA	5.11
75									

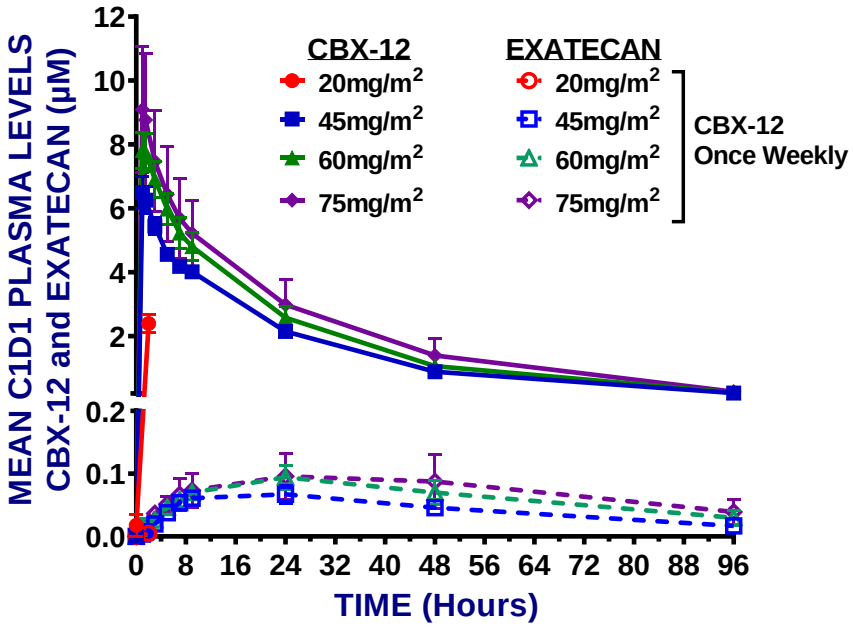
ND = no data; NC = not calculated; NA = non applicable

Updated 30May2023

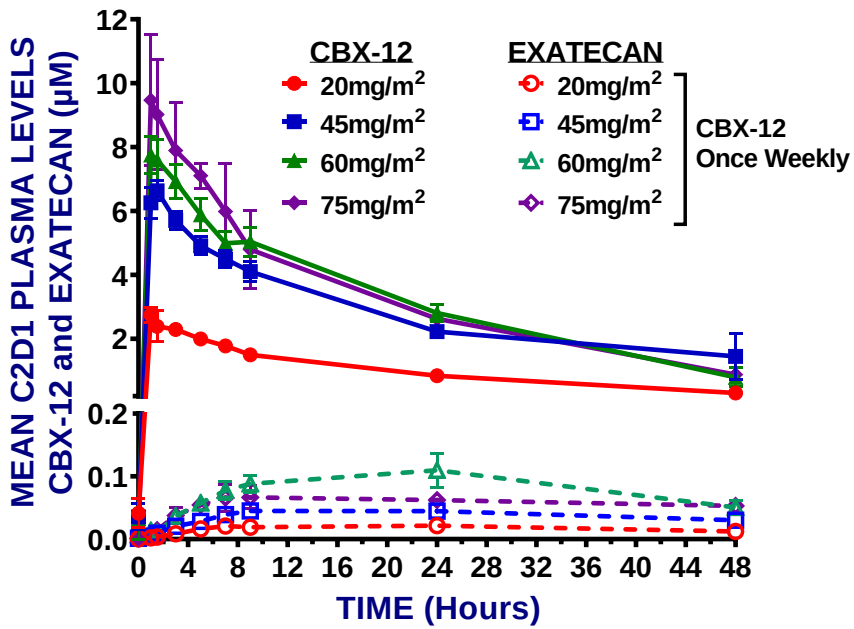
Cohort C: CBX-12 Once Weekly Pharmacokinetics - Average by Cohort

Plasma Exposure on Cycle 1 Day 1 and Cycle 2 Day 1

Cycle 1 DAY 1



Cycle 2 DAY 1



Updated 24May2023

Cohort C: CBX-12 Once Weekly Pharmacokinetics
Average by Cohort

Dose (mg/m^2)	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng/mL*hr)	C_{max} (μM)	$AUC_{0\text{-last}}$ (μM*hr)	$AUC_{0\text{-24}}$ (μM*hr)	CBX-12/ Exatecan $AUC_{0\text{-24}}$ Ratio	Accumulation Ratio: $AUC_{0\text{-24}}$ Day 3/Day 1
CBX-12 Cycle 1 Day 1									
20	NC	2.0	9260	100960	2.40	26.09	47.1	NA	NA
45	20.9	1.07	25200	542000	6.51	144	86.6	77.6	NA
60	20.1	1.21	31200	668000	8.06	173	106	74.4	NA
75	20.9	1.17	35400	753000	9.15	194	118	78.5	NA
Exatecan Cycle 1 Day 1									
20	NC	2.0	2.07	2.25	0.0048	0.005	ND	NA	NA
45	37.1	19.7	31.5	1590	0.0724	3.65	1.25	NA	NA
60	18.9	25.3	42.4	2500	0.0974	5.74	1.58	NA	NA
75	27.2	27.0	43.6	2930	0.100	6.73	1.66	NA	NA
CBX-12 Cycle 2 Day 1									
20	17.3	1.2	10790	177333	2.79	45.87	35.4	87.6	NA
45	22.9	1.33	25900	457000	6.68	118	90.1	100	1.01
60	17.8	1.17	30600	466000	7.91	120	109	64.1	1.09
75	15.0	1.00	36700	517000	9.47	134	114	84.2	479
Exatecan Cycle 2 Day 1									
20	19.2	12.7	11.61	344	0.0266	0.790	0.432	NA	NA
45	NC	14.0	22.2	653	0.0509	1.50	0.900	NA	NA
60	NC	19.0	50.6	1060	0.116	2.44	1.94	NC	1.35
75	ND	15.5	34.8	913	0.0799	2.10	1.35	NC	1.25

ND = no data; NC = not calculated; NA = non applicable

Updated 30May2023