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CBX-12-101:
A first-in-human study of CBX-12, an alphalex™ peptide drug conjugate (PDC) in patients with advanced or metastatic solid tumors

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Disclosures

Consulting

AbbVie, Aduro BioTech Inc., Alkermes, AstraZeneca, Daiichi Sankyo Co. Ltd., DebioPharm, Ecor1 Capital, eFFECTOR Therapeutics, F. Hoffman-La Roche Ltd., GT Apeiron, Genentech Inc., Harbinger Health, IBM Watson, Infinity Pharmaceuticals, Jackson Laboratory, Kolon Life Science, Lengo Therapeutics, Menarini Group, OrigiMed, PACT Pharma, Parexel International, Pfizer Inc., Protai Bio Ltd, Samsung Bioepis, Seattle Genetics Inc., Tallac Therapeutics, Tyra Biosciences, Xencor, Zymeworks

Advisory Committee

Black Diamond, Biovica, Eisai, FogPharma, Immunomedics, Inflection Biosciences, Karyopharm Therapeutics, Loxo Oncology, Mersana Therapeutics, OnCusp Therapeutics, Puma Biotechnology Inc., Seattle Genetics, Sanofi, Silverback Therapeutics, Spectrum Pharmaceuticals, Zentalis

Sponsored Research (to the institution)

Aileron Therapeutics, Inc. AstraZeneca, Bayer Healthcare Pharmaceutical, Calithera Biosciences Inc., Curis Inc., CytomX Therapeutics Inc., Daiichi Sankyo Co. Ltd., Debiopharm International, eFFECTOR Therapeutics, Genentech Inc., Guardant Health Inc., Klus Pharma, Takeda Pharmaceutical, Novartis, Puma Biotechnology Inc., Taiho Pharmaceutical Co.

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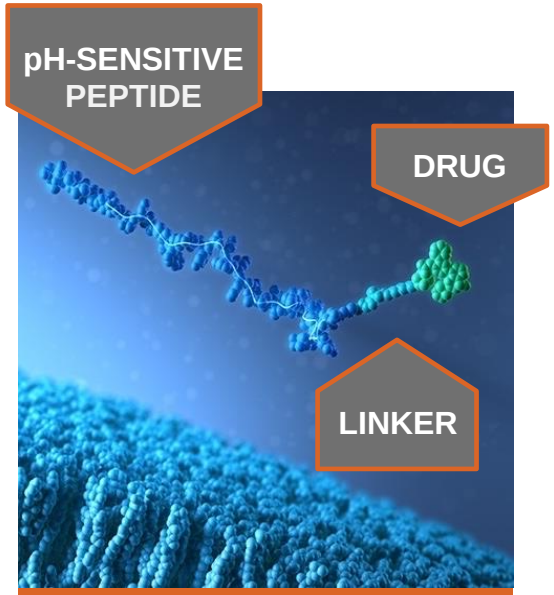
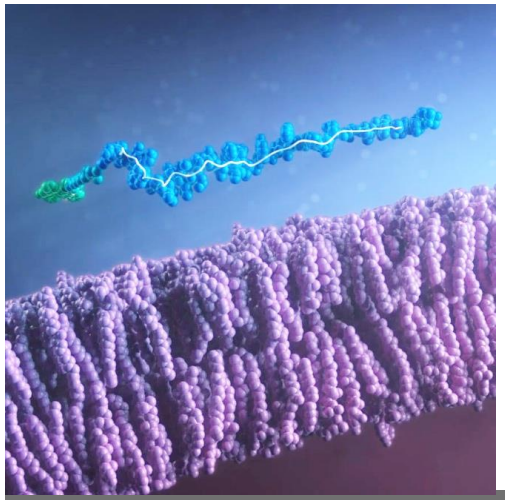
Alphalex™ Peptide Drug Conjugates

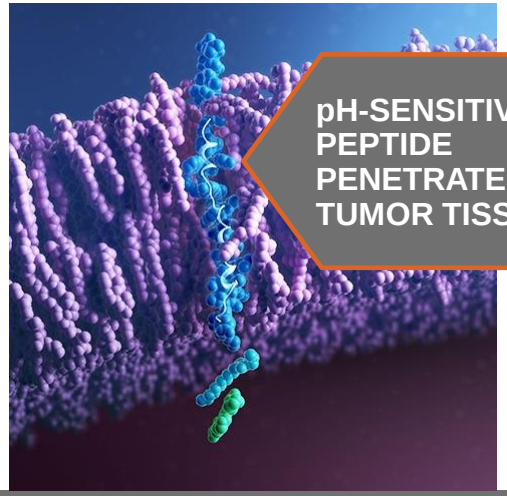


NORMAL TISSUE

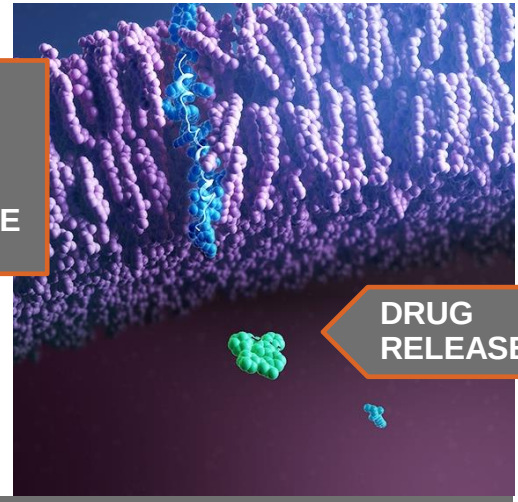
alphalex™ comprises three components: peptide, proprietary linker, and anti-cancer agent



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



The peptide then **penetrates the tumor tissue directionally** 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

TUMOR TISSUE

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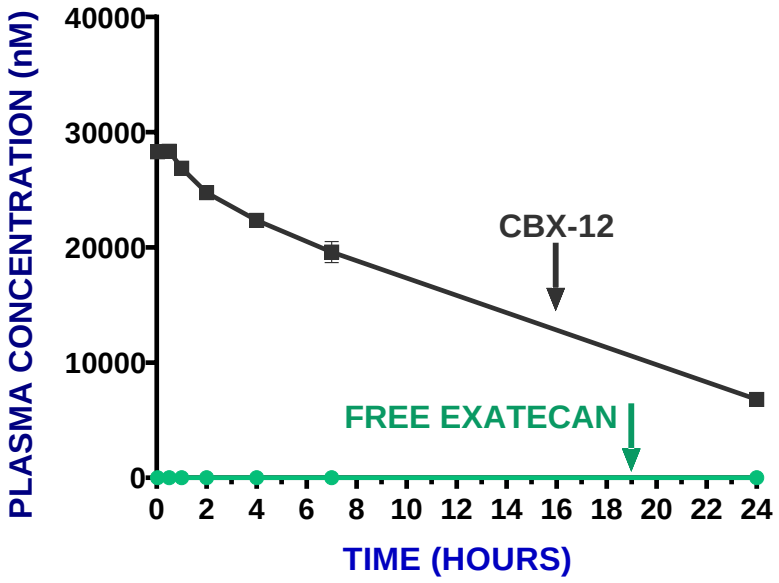
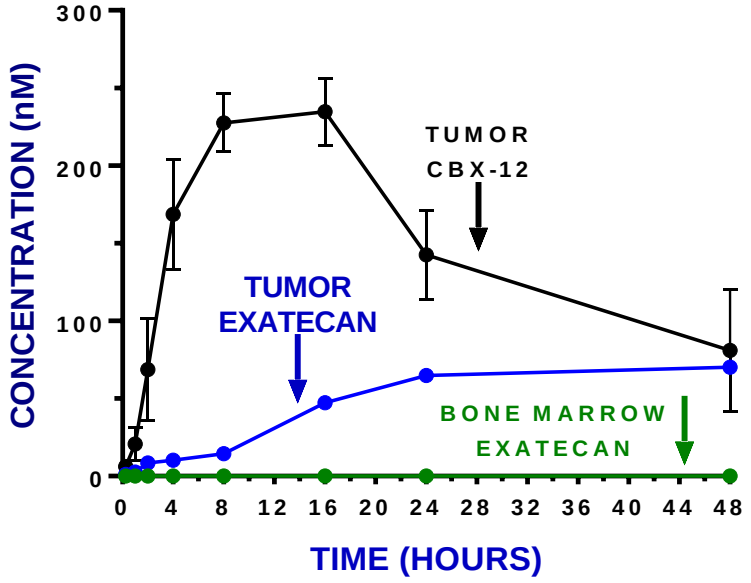
CBX-12 In Vivo Tumor Targeting and Efficacy

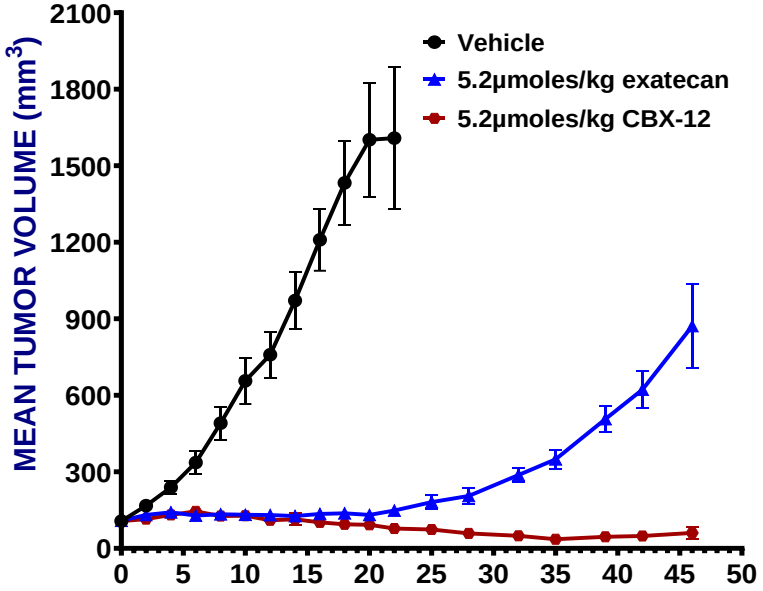
Stable conjugate allows for specific targeting



Targeted tumor delivery avoids healthy tissue



CBX-12 delivers improved efficacy compared with exatecan alone



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Phase I Study Design and Objectives

DESIGN

- Adult patients with advanced/metastatic solid tumors
  - No limit on prior regimens
- 3 + 3 design
- Evaluate 3 dosing schedule
  - Part A: Daily x 5 q 3 weeks
  - Part B: Daily x 3 q 3 weeks
  - Part C: Once weekly

OBJECTIVES

Primary

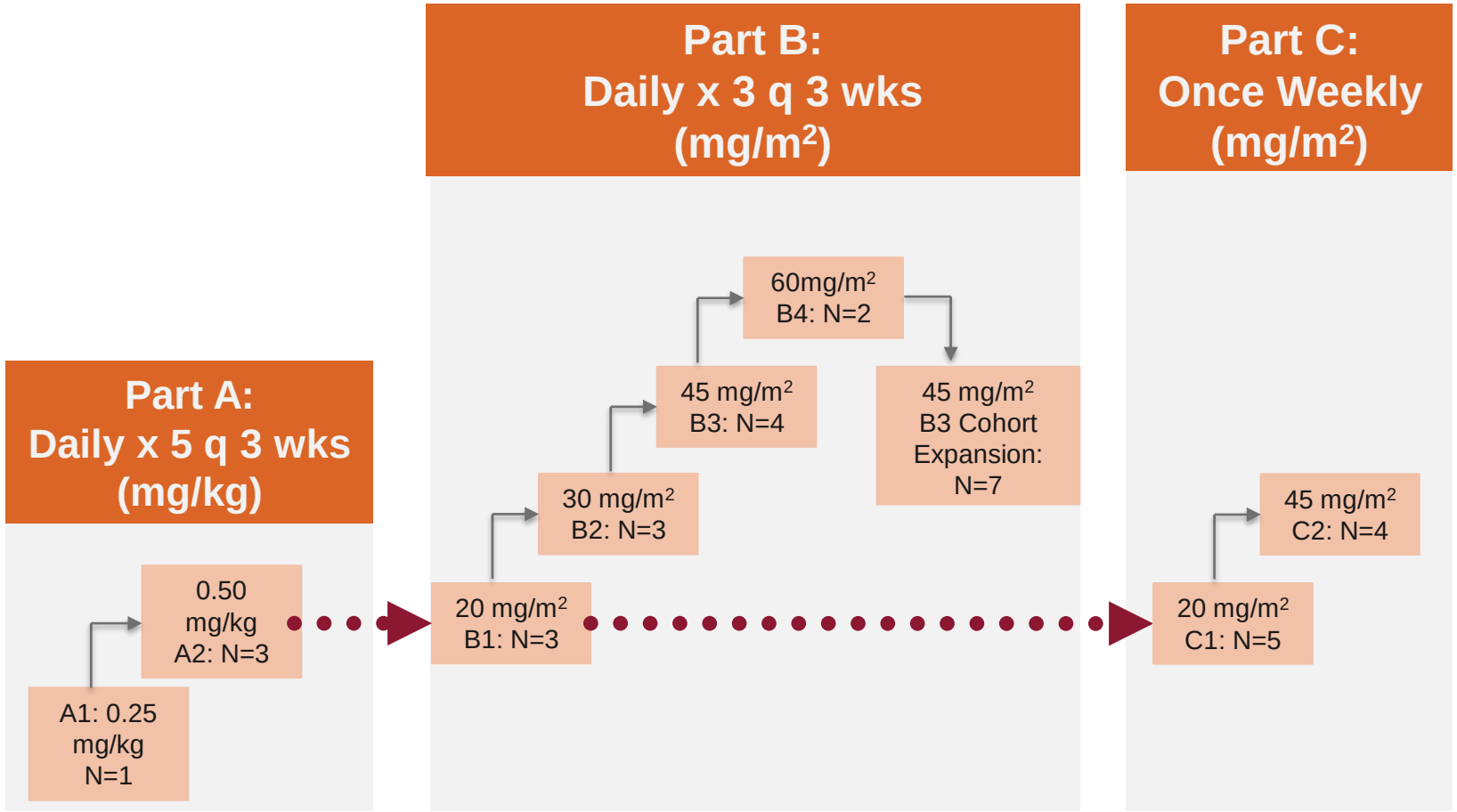
- Safety and tolerability
- Determine MTD/RP2D

Secondary

- Plasma PK: CBX-12 and exatecan
- Intratumoral CBX-12 and exatecan levels
- Preliminary antitumor activity by RECIST 1.1
- Anti-drug antibodies

Enrollment and Dose Escalation

- CBX-12 is administered as a 1-hr IV infusion
- Enrollment in Part A was discontinued after Cohort A2
- Part B: Expansion at the potential RP2D is continuing
- Part C: Dose escalation is continuing



Baseline Characteristic

		Part A (n=4)[a]	Part B (n=20)	Part C (n=9)	Overall (n=33)
Age: Median (range)		68.0 (60, 71)	52 (22, 80)	64 (29, 80)	60 (22, 80)
Gender: M (%) : F (%)		1 (25) : 3 (75)	9 (45) : 11 (55)	1 (11) : 8 (89)	11 (33) : 22 (67)
Race: White/Black/Asian/Other (%)[b]		75/0/0/25	90/0/5/5	67/0/11/22	82/0/6/12
ECOG PS	0 /1 (%)	0 / 100	10/90	0/100	6/94
Cancer types (n)					
	Pancreas	1	2	3	6
	Breast	0	5	1	6
	Ovary	1	2	2	5
	CRC	1	3	1	5
	Other	1	8	2	11
Prior systemic regimens (n)					
	1-2	1	3	2	6
	3-4	2	7	2	11
	≥5	1	10	5	16

[a]Patient 1001-003 in Cohort A2 changed to Schedule B at Cycle 13. Baseline data are counted under Part A.
[b]Other includes not reported or unknown.

Treatment Related Adverse Events

Treatment-Related Adverse Events (≥ 10%)

N (%)	Part A (n=4)[a]		Part B (n=21)[a]		Part C (n=9)		Total (n=33)[a]	
	All	Gr 3-4	All	Gr 3-4	All	Gr 3-4	All	Gr 3-4
Number of pts reporting ≥1 TRAE	4 (100)	1 (25)	16 (76.2)	10 (47.6)	6 (66.7)	1 (11.1)	25 (75.8)	12 (36.4)
Anaemia	2 (50)	1 (25)	11 (52.4)	5 (23.8)	0 (0)	0 (0)	12 (36.4)	6 (18.2)
Nausea	2 (50)	0 (0)	7 (33.3)	0 (0)	2 (22.2)	0 (0)	11 (33.3)	0 (0)
Fatigue	1 (25)	0 (0)	8 (38.1)	0 (0)	3 (33.3)	0 (0)	11 (33.3)	0 (0)
Neutropenia / Neutrophil count decreased	1 (25)	1 (25)	9 (42.9)	8 (38.1)	1 (11.1)	1 (11.1)	11 (33.3)	10 (30.3)
White blood cell count decreased	1 (25)	1 (25)	8 (38.1)	3 (14.3)	1 (11.1)	1 (11.1)	10 (30.3)	5 (15.2)
Diarrhoea	3 (75)	0 (0)	6 (28.6)	1 (4.8)	0 (0)	0 (0)	9 (27.3)	1 (3.0)
Vomiting	3 (75)	0 (0)	4 (19.0)	0 (0)	1 (11.1)	0 (0)	8 (24.2)	0 (0)
Thrombocytopenia / Platelet count decreased	1 (25)	1 (25)	4 (19.0)	3 (14.3)	1 (11.1)	0 (0)	6 (18.2)	4 (12.1)
Dehydration	1 (25)	0 (0)	2 (9.5)	0 (0)	1 (11.1)	0 (0)	4 (12.1)	0 (0)
ALT increase	1 (25)	0 (0)	3 (14.3)	1 (4.8)	0 (0)	0 (0)	3 (9.1)	1 (3.0)
AST increased	1 (25)	0 (0)	2 (9.5)	1 (4.8)	0 (0)	0 (0)	3 (9.1)	1 (3.0)

[a]Patient 1001-003 in Cohort A2 changed to Schedule B at Cycle 13. This patient's AEs are reported for the Part in which they occurred, but patient is only counted once in overall total.

Part B: Daily x 3 TRAEs by Cohort

Treatment-Related Adverse Events (≥ 10% or clinically relevant)								
N (%)	20 mg/m² (n=3)		30 mg/m² (n=3)		45 mg/m²* (n=12)		60 mg/m² (n=2)	
	All	Gr 3-4	All	Gr 3-4	All	Gr 3-4	All	Gr 3-4
Number of pts reporting ≥1 TRAE	2 (66.7)	0 (0)	3 (100)	2 (66.7)	8 (66.7)	6 (50)	2 (100)	2 (100)
Anaemia	1 (33.3)	0 (0)	3 (100)	1 (33.3)	5 (41.7)	3 (25)	1 (50)	1 (50)
Nausea	0 (0)	0 (0)	2 (66.7)	0 (0)	4 (33.3)	0 (0)	1 (50)	0 (0)
Fatigue	2 (66.7)	0 (0)	1 (33.3)	0 (0)	4 (33.3)	0 (0)	0 (0)	0 (0)
Neutropenia / Neutrophil count decreased	0 (0)	0 (0)	2 (66.7)	1 (33.3)	5 (41.7)	5 (41.7)	2 (100)	2 (100)
White blood cell count decreased	0 (0)	0 (0)	2 (66.7)	0 (0)	4 (33.3)	1 (8.3)	2 (100)	2 (100)
Diarrhoea	0 (0)	0 (0)	1 (33.3)	0 (0)	4 (33.3)	0 (0)	1 (50)	1 (50)
Vomiting	0 (0)	0 (0)	1 (33.3)	0 (0)	1 (8.3)	0 (0)	2 (100)	0 (0)
Dehydration	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)
Thrombocytopenia / Platelet count decreased	0 (0)	0 (0)	0 (0)	0 (0)	2 (16.7)	1 (8.3)	2 (100)	2 (100)
ALT increase	0 (0)	0 (0)	0 (0)	0 (0)	2 (16.7)	1 (8.3)	0 (0)	0 (0)
AST increased	0 (0)	0 (0)	0 (0)	0 (0)	2 (16.7)	1 (8.3)	0 (0)	0 (0)
Febrile Neutropenia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)	2 (100)
Sepsis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)	1 (50)

*Cohort being expanded as preliminary MTD

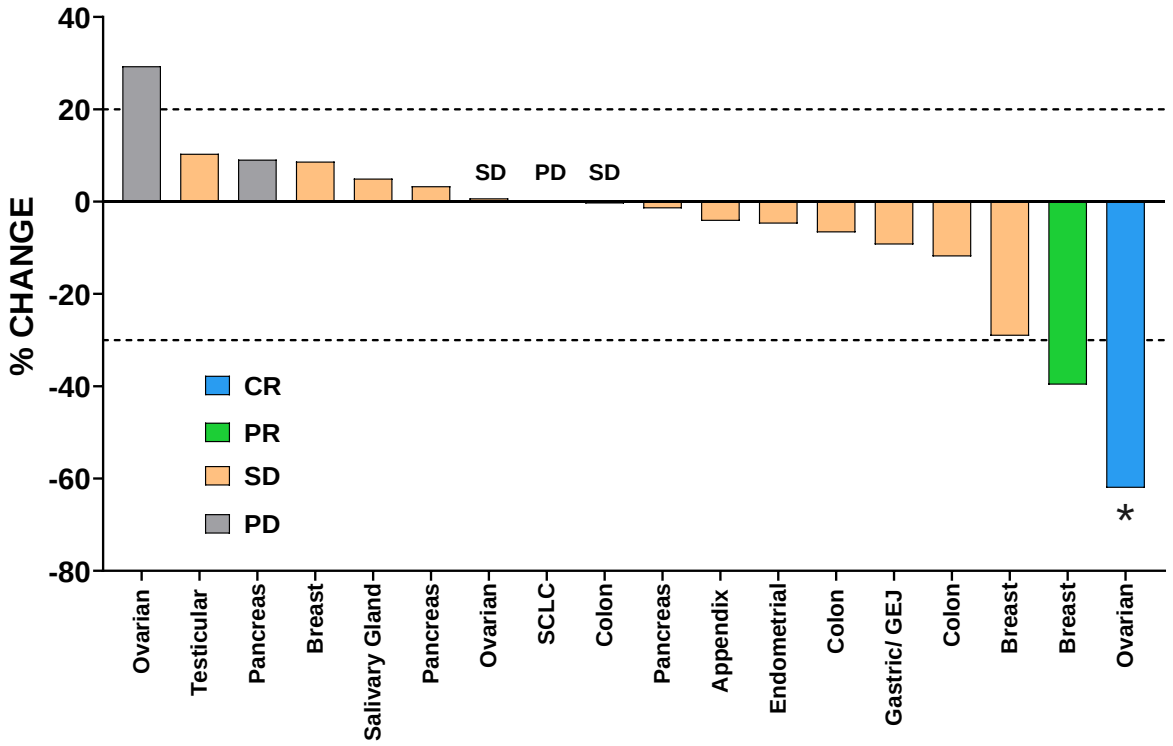
DLTs and Treatment Related SAEs

Patient ID	Part / Dose Level / Dosing Schedule	DLTs	Treatment Related SAEs
1001-003	Part A: 0.5 mg/kg Daily x 5 q 3 weeks	Gr 4 Neutropenia Gr 4 Thrombocytopenia	Gr 4 Neutropenia Gr 4 Thrombocytopenia Gr 2 Small intestine mucositis
1001-013	Part B: 45 mg/m^2 Daily x 3 q 3 weeks	Gr 4 Neutropenia Gr 4 Thrombocytopenia	Gr 3 Anaemia Gr 4 Neutropenia Gr 4 Thrombocytopenia
1002-012	Part B: 60 mg/m^2 Daily x 3 q 3 weeks	Gr 4 Neutropenia Gr 4 Thrombocytopenia Gr 4 Leukopenia Gr 3 Febrile Neutropenia	Gr 4 Neutropenia Gr 4 Thrombocytopenia Gr 4 Leukopenia Gr 3 Febrile Neutropenia
1005-002	Part B: 60 mg/m^2 Daily x 3 q 3 weeks	Gr 4 Neutropenia Gr 3 Sepsis Gr 3 Febrile neutropenia	Gr 3 Febrile Neutropenia

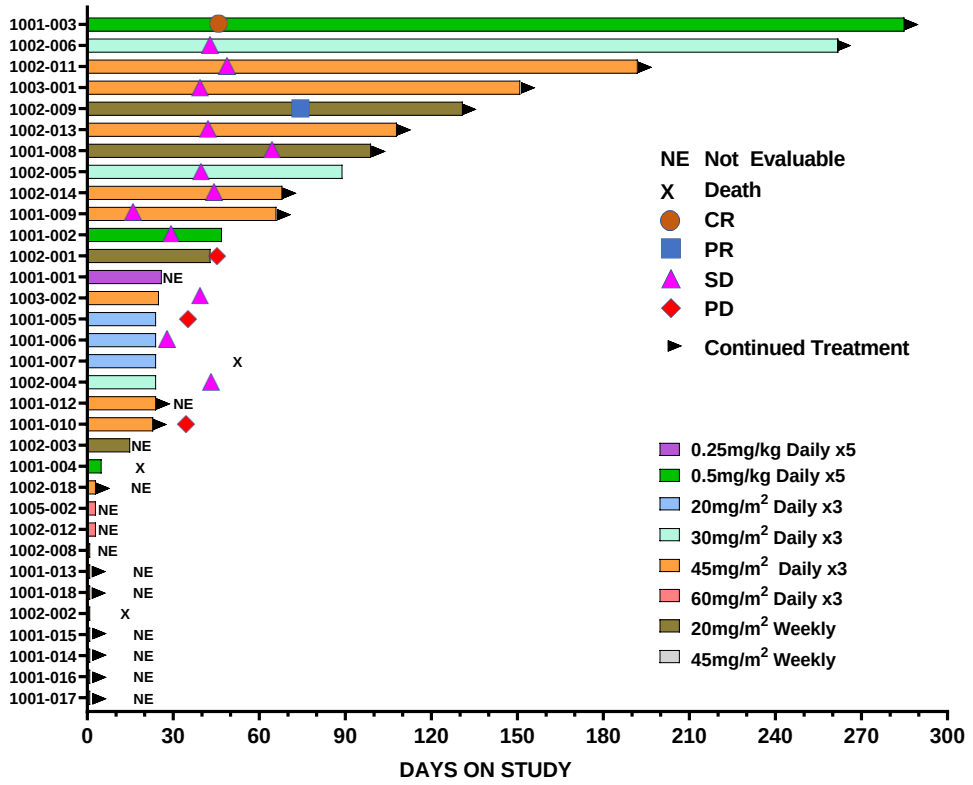
No interstitial lung disease reported to date

Clinical Benefit

Best Overall Change in Target Lesions (n=18)



Duration of Treatment



*CR: Decrease in lymph node target lesion to < 10 mm

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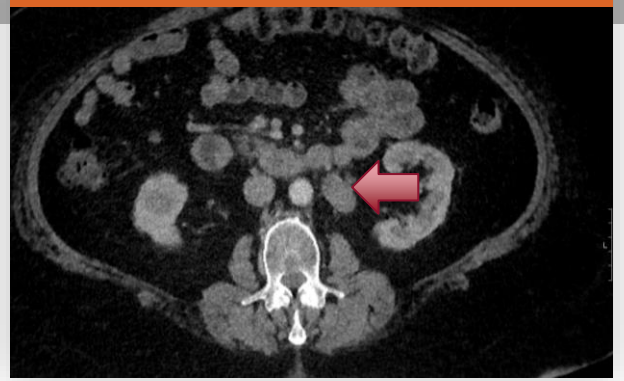
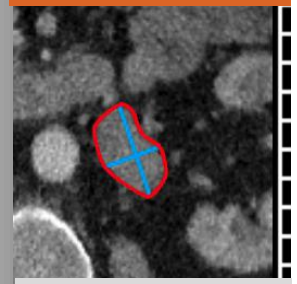
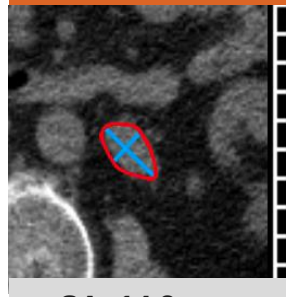
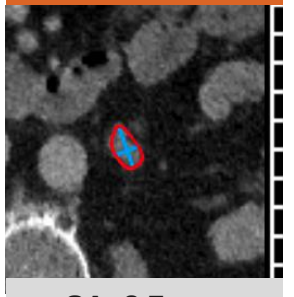
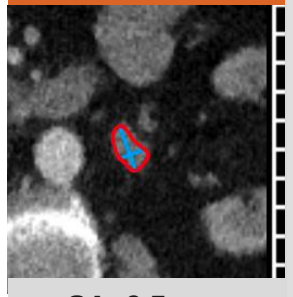
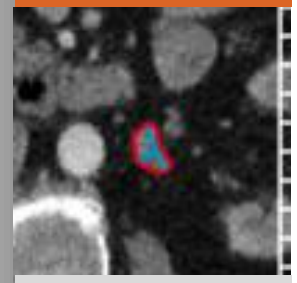
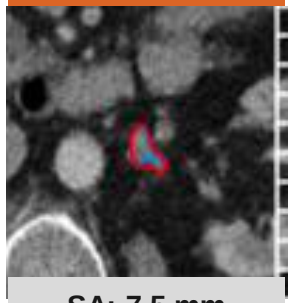
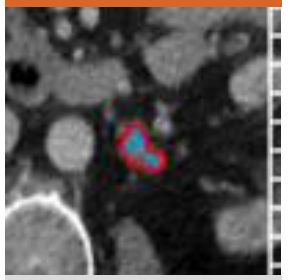
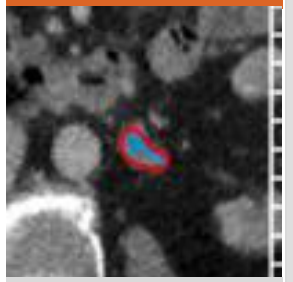
Complete Response in HGOC

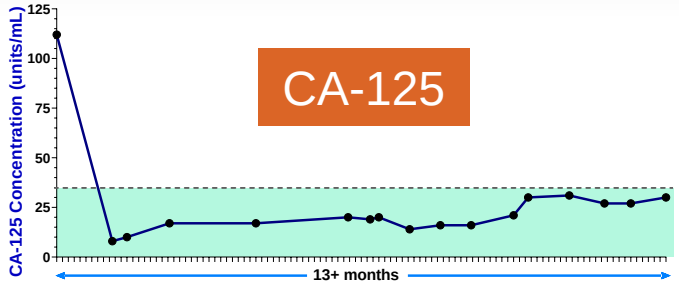
68 yo female diagnosed with HGOC

- Prior chemotherapy
  - Carboplatin/paclitaxel
  - Carboplatin/gemcitabine
- s/p TAH/BSO/omental excision
- Part A schedule at 0.5 mg/kg. Dose reduced in Cycle 2. Started Part B schedule in Cycle 13.
- Imaging: After Cycle 2, then every 3 cycles
- Complete response Cycle 2
- Continues on treatment in Cycle 19

BASELINE



Baseline	Follow-up 1	Follow-up 2	Follow-up 3
			
SA: 20.8 mm	SA: 14.3 mm	SA: 8.7 mm	SA: 9.5 mm
Follow-up 4	**Follow-up 5**	**Follow-up 6**	**Follow-up 7**
			
SA: 9.4 mm	SA: 7.5 mm	SA: 9.3 mm	SA: 9.7 mm

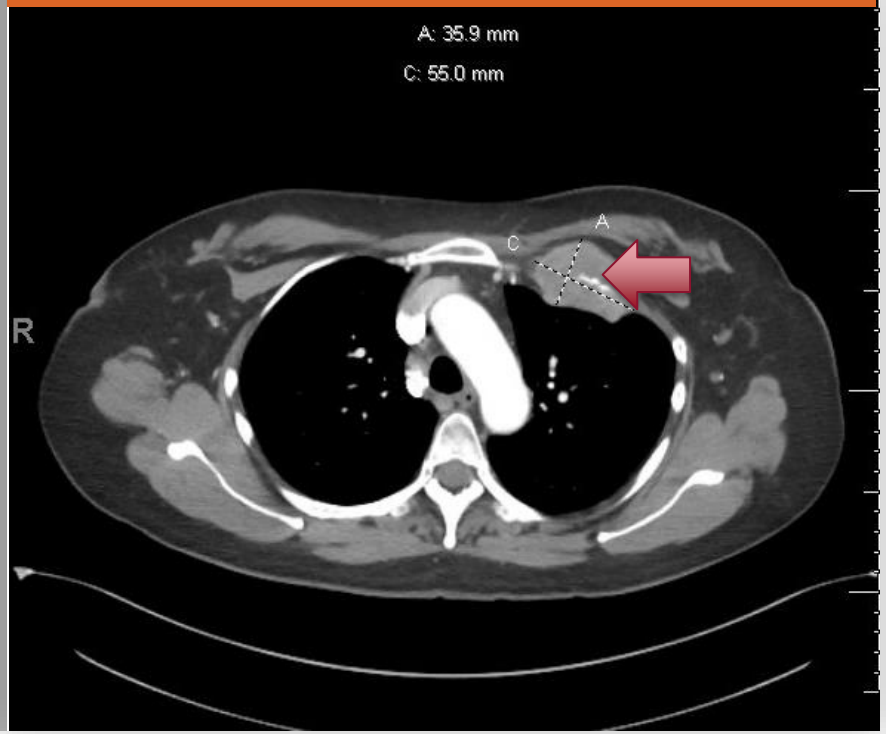


Near PR in Breast Cancer

45 yo female diagnosed with Stage II breast cancer

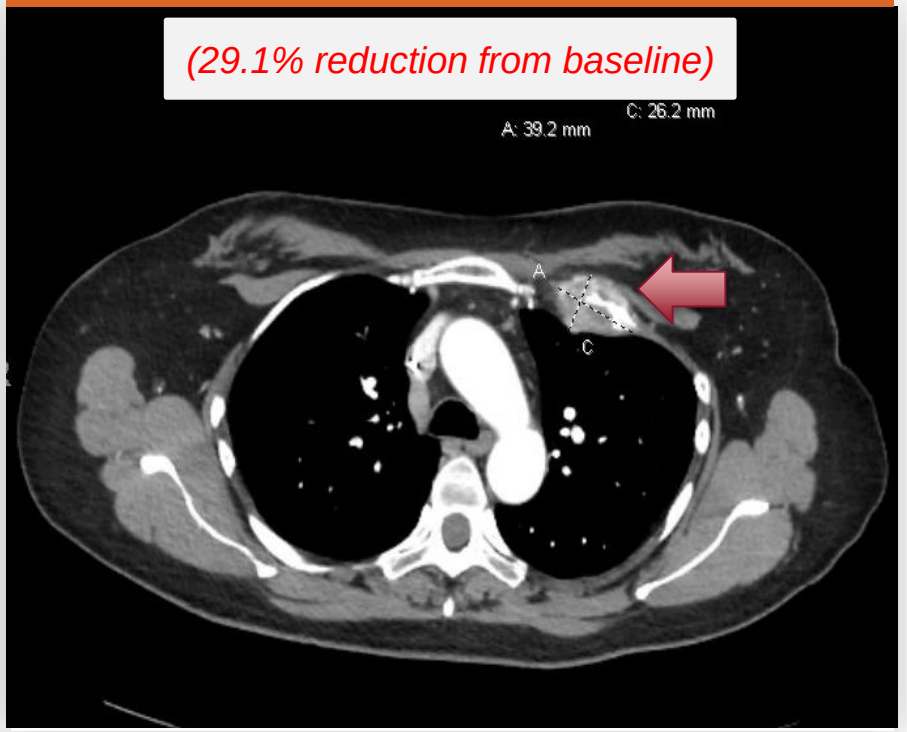
- Prior chemotherapy
  - Doxorubicin/ cyclophosphamide followed by paclitaxel
  - Capecitabine
  - Tamoxifen
  - Toremifine
- Part B 30 mg/m^2
- Maximum decrease in target lesions: 29.1%
- Growth factor support beginning in Cycle 6
- Continues on treatment in Cycle 14

Baseline: 5.5 cm x 3.6



2nd On-Treatment Re-staging: 3.9 cm X 2.6 cm

(29.1% reduction from baseline)



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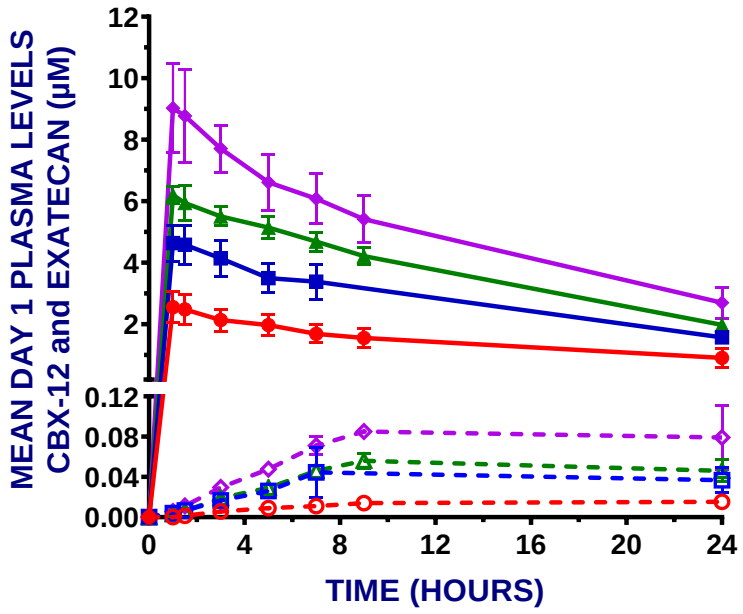
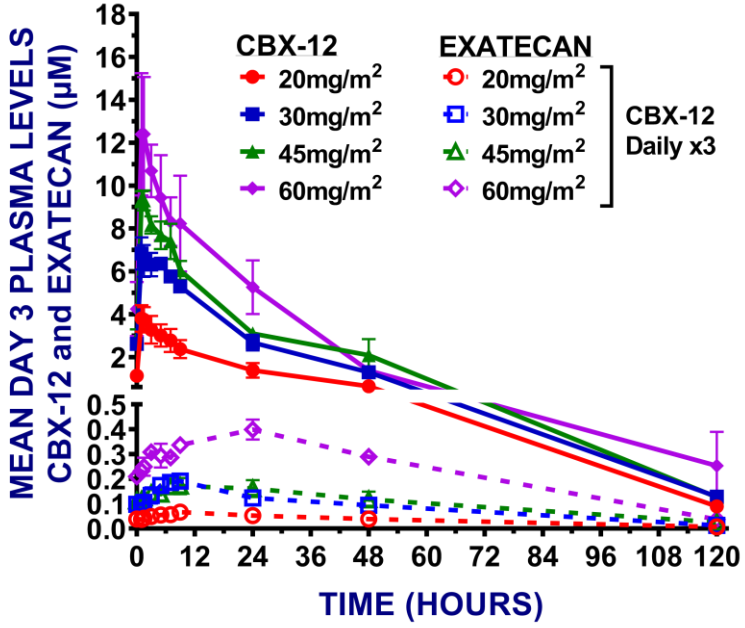
Plasma Pharmacokinetics: Part B

Day 1



Day 3



Dose (mg/m^2)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng/mL*hr)	CBX-12/ Exatecan $AUC_{0\text{-}24}$ Ratio
CBX-12 Day 3				
20	20.5	15600	359333	40.7
30	22.4	26433	725000	37.3
45	20.7	37244	903667	44.9
60	21.3	48350	1309000	22.9
Exatecan Day 3				
20	36.8	34.4	1740	NC
30	32.5	63.8	3763	NA
45	31.2	79.9	4700	NA
60	NC	174	10270	NA

Conclusions

- PK demonstrated dose proportionality
- CBX-12 t-half is ~21 hours
- Minimal accumulation upon repeat dosing
- CBX-12 to free exatecan ratio is 23 – 45

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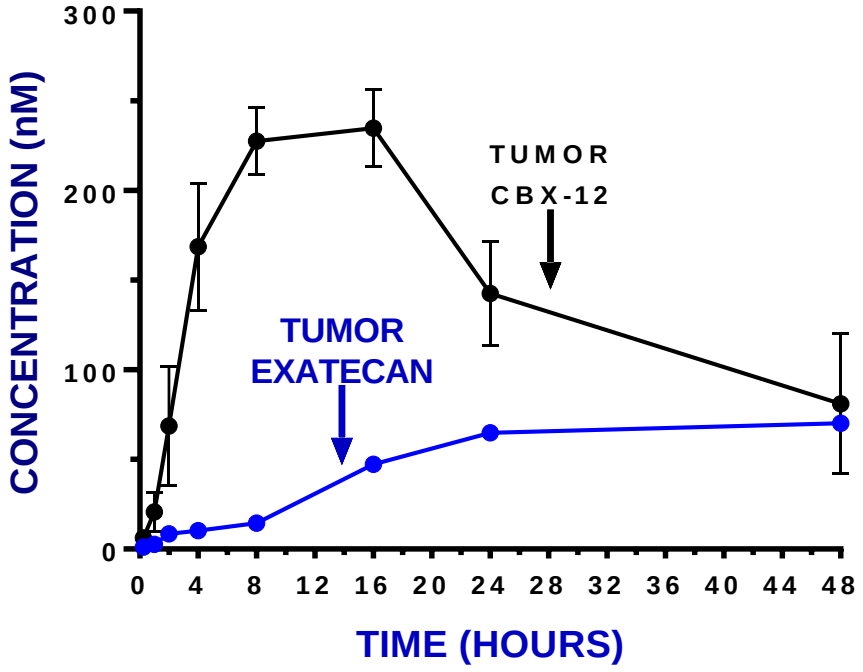
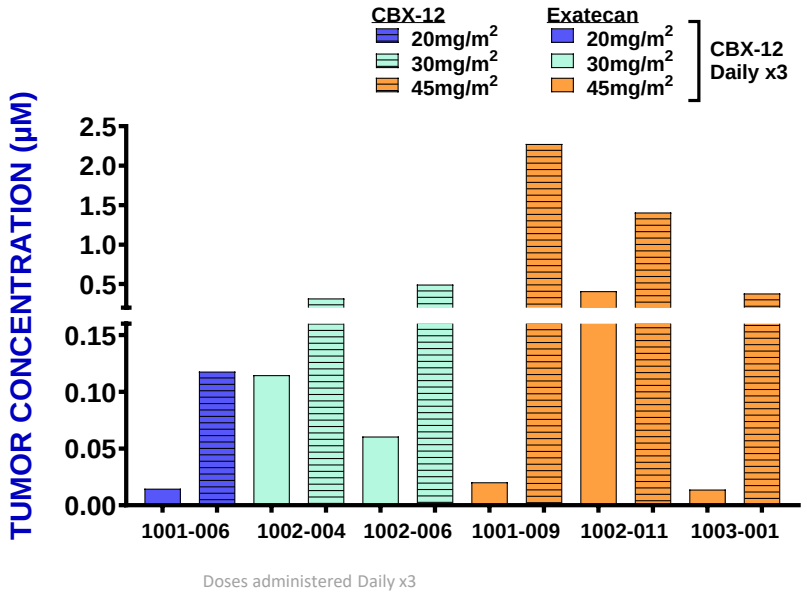
Intratumoral Drug Delivery

Sustained Release of Exatecan from CBX-12 in Xenograft



Intratumoral Concentrations of CBX-12 Exceed Exatecan



Biopsies obtained on day 5 of dosing in Part A: Daily x 5, or ~24-48 hours after the day 3 dose in Part B: Daily x 3

Conclusions

- CBX-12 is well tolerated. Primary TRAEs are gastrointestinal (mostly Gr 1 – 2) and hematologic
- Two confirmed responses and 13 stable disease have been demonstrated in 18 response-evaluable patients
- High intratumoral levels of CBX-12 and exatecan have been demonstrated in on-treatment biopsies
  - Additional biomarker and pharmacodynamic evaluation is ongoing
- PK evaluation shows dose-proportionality in Part B
- Dose escalation continues in Part C (once-weekly schedule)
- Phase 2 cohort expansions are planned in breast and ovarian cancer

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Acknowledgements

We would like to thank our patients, their families and caregivers

We would like to thank our clinical research study teams

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