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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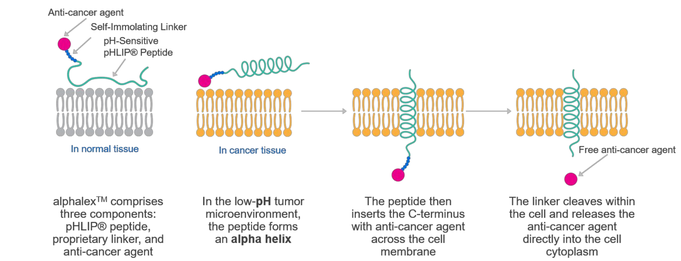
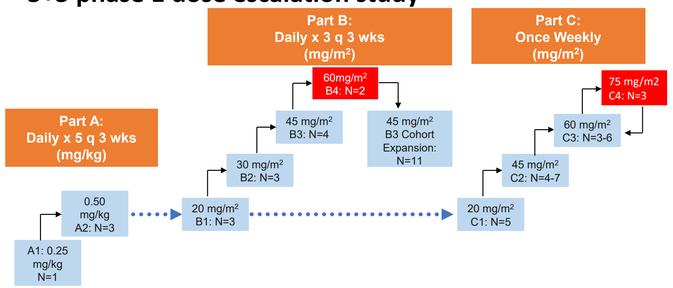
Background:

- 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[1]), 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[2]



Methods:

- **3+3 phase 1 dose escalation study**

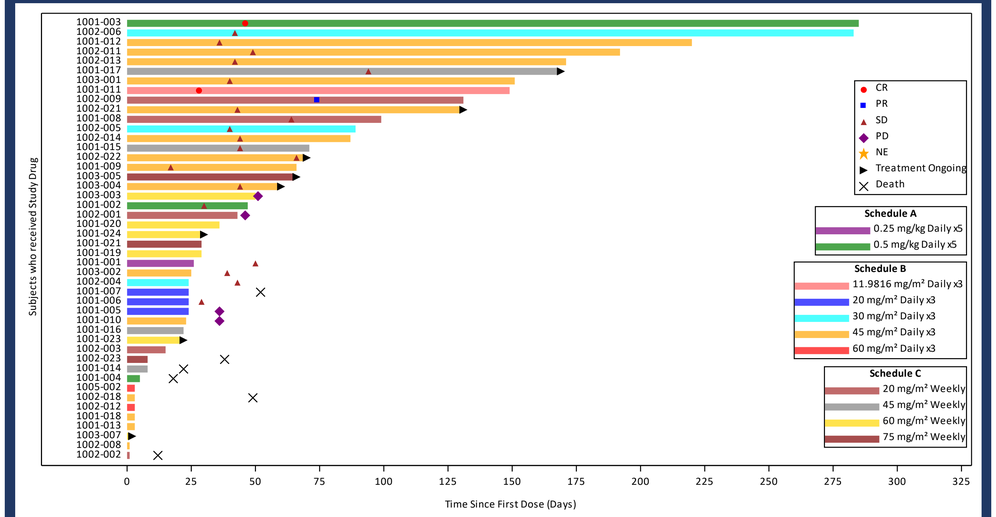


- The most common diagnoses were breast cancer (8), ovarian and pancreas (7 each) and colorectal cancer (6)

1. pHLIP peptides are a family of pH-Low Insertion Peptides that target acidic cell surfaces. pHLIP was developed at Yale University and the University of Rhode Island, and is exclusively licensed to pHLIP, Inc., and Cybrexa is a sublicensee of pHLIP, Inc." Proc Natl Acad Sci U S A. 115:E2811-E2818, 2018
2. Ann Oncol. 14:913-21, 2003 ; J Clin Oncol. 18:3151-63, 2000.

Results:

- The maximum tolerated dose was 45 mg/m^2 for 3 days in a 21-day cycle (Part B), or 60 mg/m^2 weekly (Part C).
- 5 subjects had durable objective or near objective responses per RECIST 1.1:
  - Part A: cCR (ovarian); DLT cycle 1, on treatment for 14 months, PD
  - Part B 45 mg/m^2: uPR (breast); on treatment for 9 months, PD
  - Part B 45 mg/m^2: cPR (ovarian); on treatment for 5 months, ongoing
  - Part B 30 mg/m^2: near-PR (breast); on treatment for 10 months, PD
  - Part C 20 mg/m^2: cPR (breast); on treatment for 5 months, PD

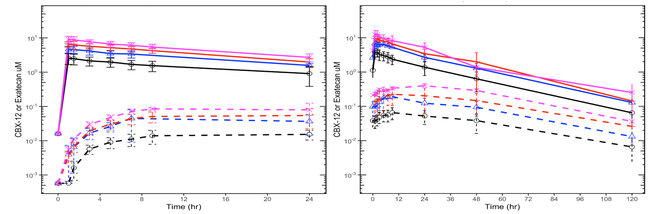


- Dose-limiting toxicity (DLT) was primarily myelosuppression.
- Adverse drug reactions reported in more than 10% of patients are shown below:

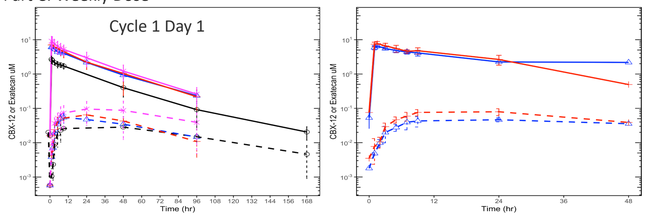
Preferred Term	All Grade N (%)	Grade 3-4 N (%)	DLT
Anaemia	23 (51.1)	13 (28.9)	1
Fatigue	18 (40.0)	1 (2.2)	
Neutropenia	18 (40.0)	14 (31.1)	6
Leukopenia	17 (37.8)	10 (22.2)	
Nausea	17 (37.8)	0	
Diarrhoea	13 (28.9)	2 (4.4)	
Thrombocytopenia	12 (26.7)	7 (15.6)	4
Vomiting	11 (24.4)	0	
Dehydration	6 (13.3)	1 (2.2)	
Febrile neutropenia and sepsis reported as DLTs			2 ea

- Following Daily 3x administration (Part B), there was an accumulation of both CBX-12 and exatecan between doses, while minimal accumulation was observed following weekly administration (Part C).

Part B: Daily 3x every 3 week



Part C: Weekly Dose



- CBX-12 PK and exatecan exhibited linear dose-proportional PK with a mean half-life ranging from 14 to 22 hr for doses ranging from 20 mg/m^2 to 75 mg/m^2 in both Part B and C.
- Free exatecan's mean apparent half-life ranged between 29 to 36 hr for both Part B and C.
- Approximately 0.8 to 4% of exatecan is released plasma.

Summary:

- In this FIH dose-finding study of a pH-targeting alphalex PDC, CBX-12 demonstrated single-agent antitumor activity including 4 responses with the dominant toxicity of myelosuppression.
- Once the RP2D is selected, Phase 2 studies are planned in breast cancer, ovarian cancer, colorectal cancer, and gastric cancer as well as a phase 1b study of combination with an immune checkpoint inhibitor. Exploration of a q 21 d schedule is also underway.