CYBREXA THERAPEUTICS

Selection of Tubulin & TopI Inhibitor Payloads for Improved Tumor Specific Delivery by Peptide Drug Conjugate

ADC Payload Summit

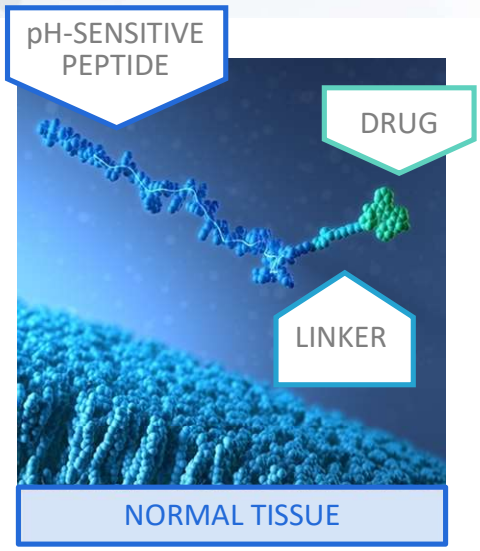
May 2024

Table of Contents

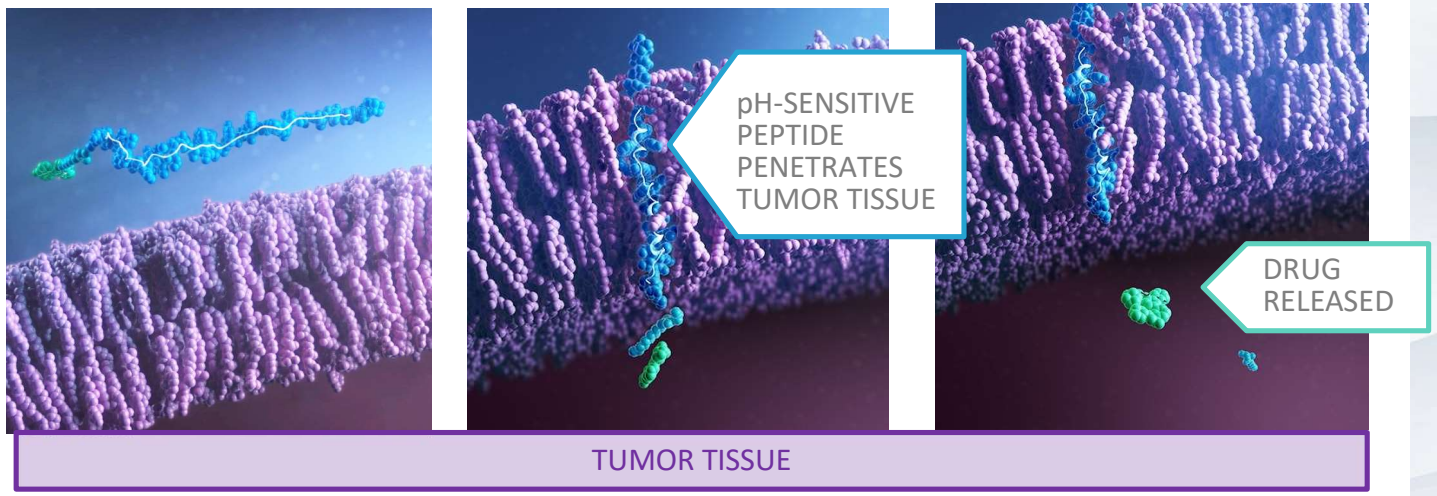
Introduction

Program	Payload Target	Stage Of Development				Next Anticipated Milestone
		Research	IND Enabling	Phase 1	Phase 2	
alphalex™ **-exatecan (CBX-12)**	**TOPO 1** (DNA Targeting)					Phase 2 to start in Q2 2024
alphalex™- **MMAE (CBX-15)**	**Microtubule**					IND submission in Q4 2024
alphalex™- **DM4 (CBX-13)**	**Microtubule**					Clinical candidate nomination in Q3 2025

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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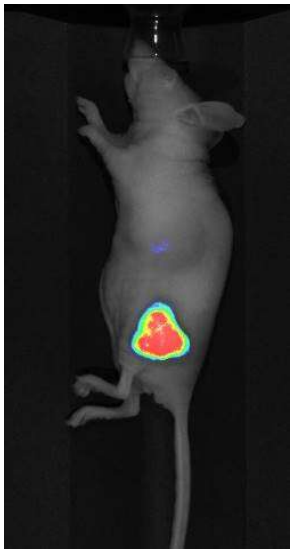
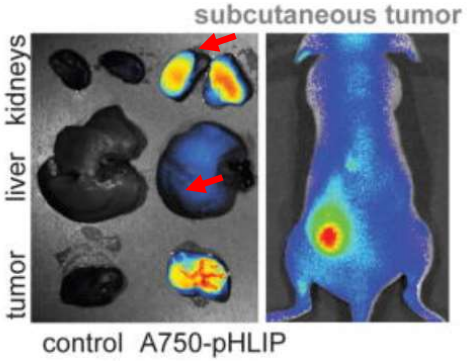
Tumor Targeting alphalex™ and Clinical Translation

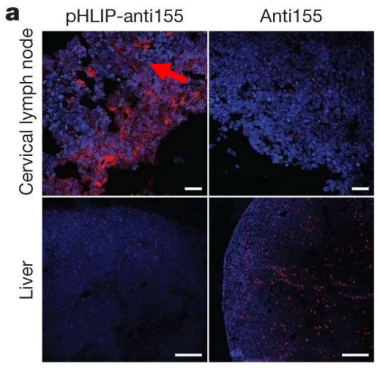
alphalex™ Targets Tumors and Sporadic Lymph Node Mets in a Lymphoma Mouse Model



Paralkar et al. 2019 AACR

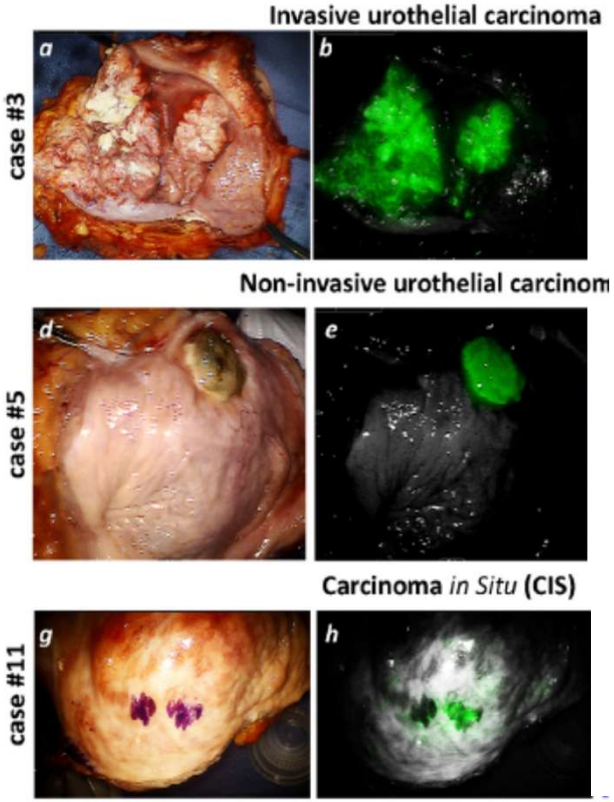


alphalex™ targets clusters of tumor cells in lymph nodes



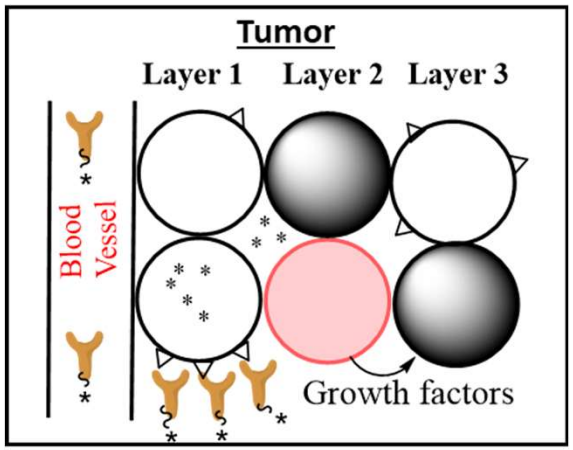
Cheng et al. 2015 Nature 518(7537)

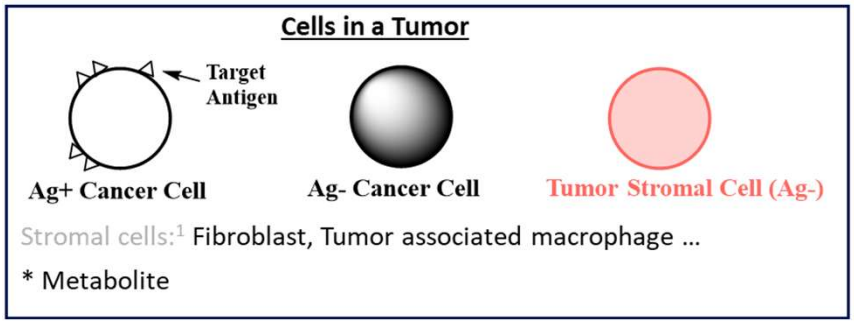
alphalex™ Targets Lesions and Micrometastases in Human Bladder Cancers ex vivo

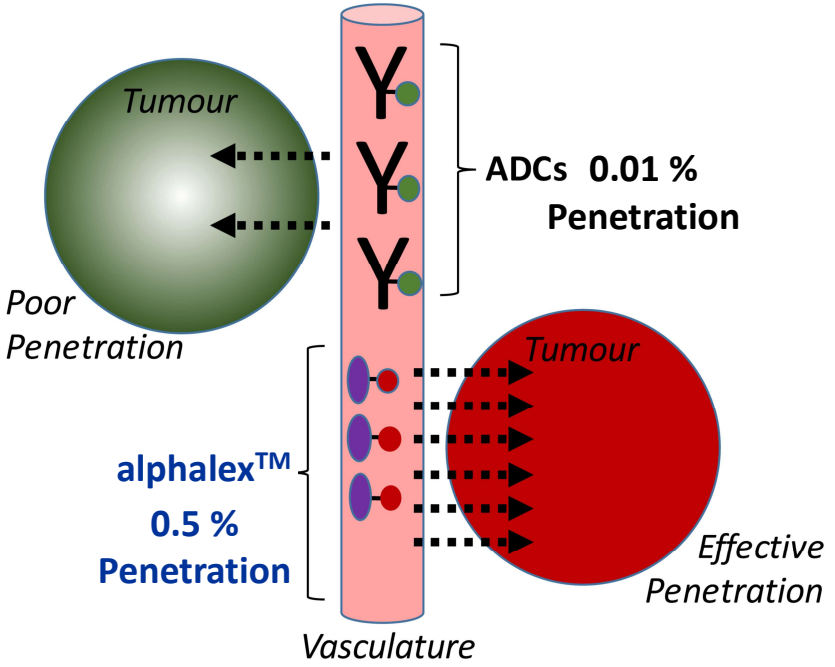


Golijanin et al. 2016 PNAS 113(42)

Efficacy of ADCs In Vivo: Antigen Positive Cancer Cell Uptake







Adapted from Deonarain et al. 2018 *Antibodies*

Tsuchikama and An 2018 *Protein Cell* Hamblett, K. J. et. al. Cancer Res. 2015, 75, 5329

Alphalex™ has 50X improved tumor penetration relative to ADCs

CBX-12
Clinical Compound

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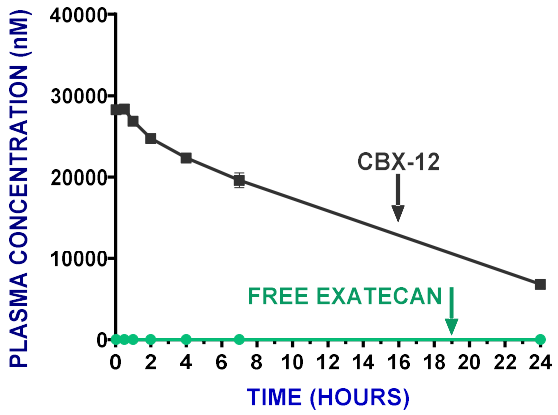
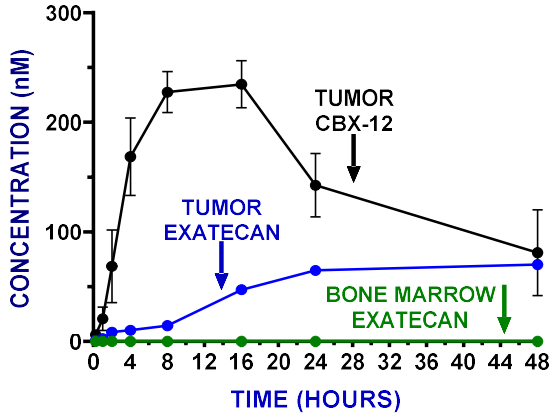
CBX-12: Tumor Selective Targeting and WH Release

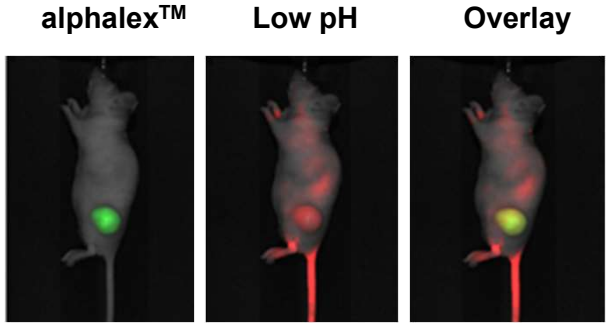
Stable conjugate allows for specific targeting



CBX-12 using alphalex™ technology demonstrates minimal loss of payload from linker, reducing toxicity

Targeted tumor delivery avoids healthy tissue





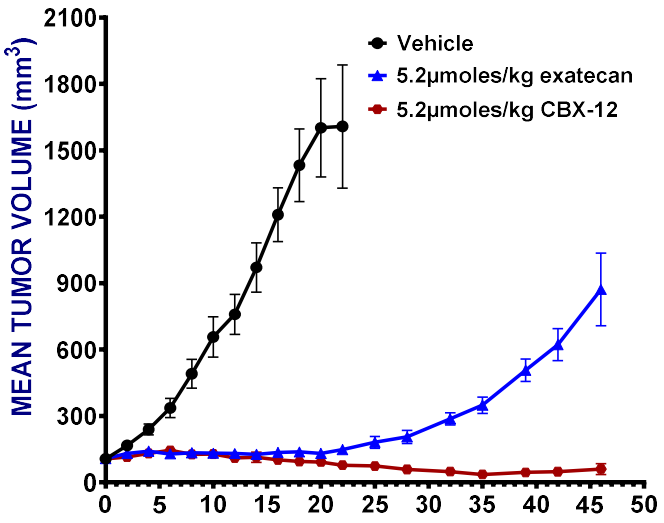
Time course visualization of Li-Cor labelled alphalex™ (green) colocalized with carbonic anhydrase IX imaging probe indicating low pH* (red)

Substantial tumor penetration of exatecan delivered by CBX-12 with minimal risk of off-target effect (e.g., bone marrow toxicity)

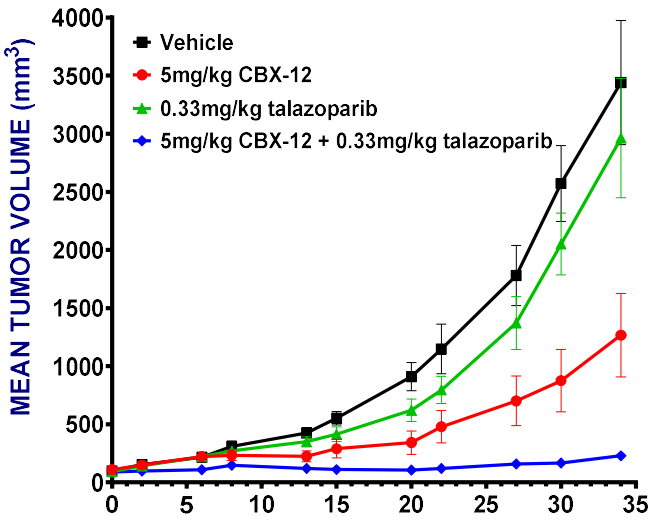
*carbonic anhydrase IX was injected through the tail vein and absorbed by some other tissues that may not have low pH

CBX-12: Efficacy in Preclinical Models

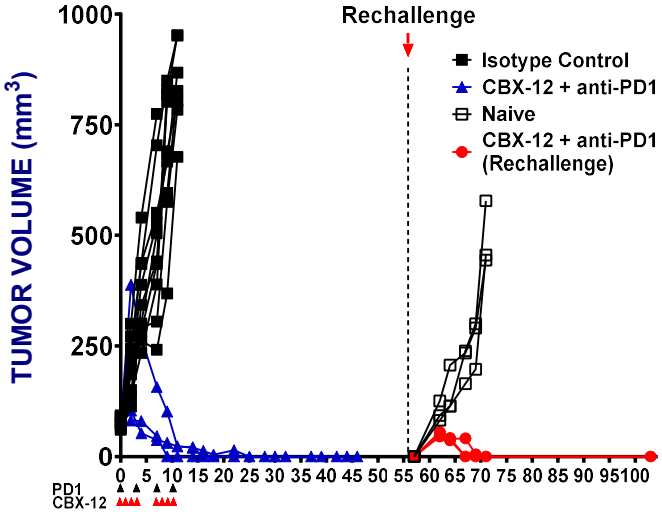
CBX-12 **monotherapy** delivers improved efficacy without SAEs over exatecan alone



CBX-12 and talazoparib **combination** inhibits tumor growth in TNBC model in nude mice



CBX-12/ anti-PD1 **combination** provided long-term anti-tumor immunity in cured mice



Preclinical Models Demonstrated Efficacy as Monotherapy and Combinations

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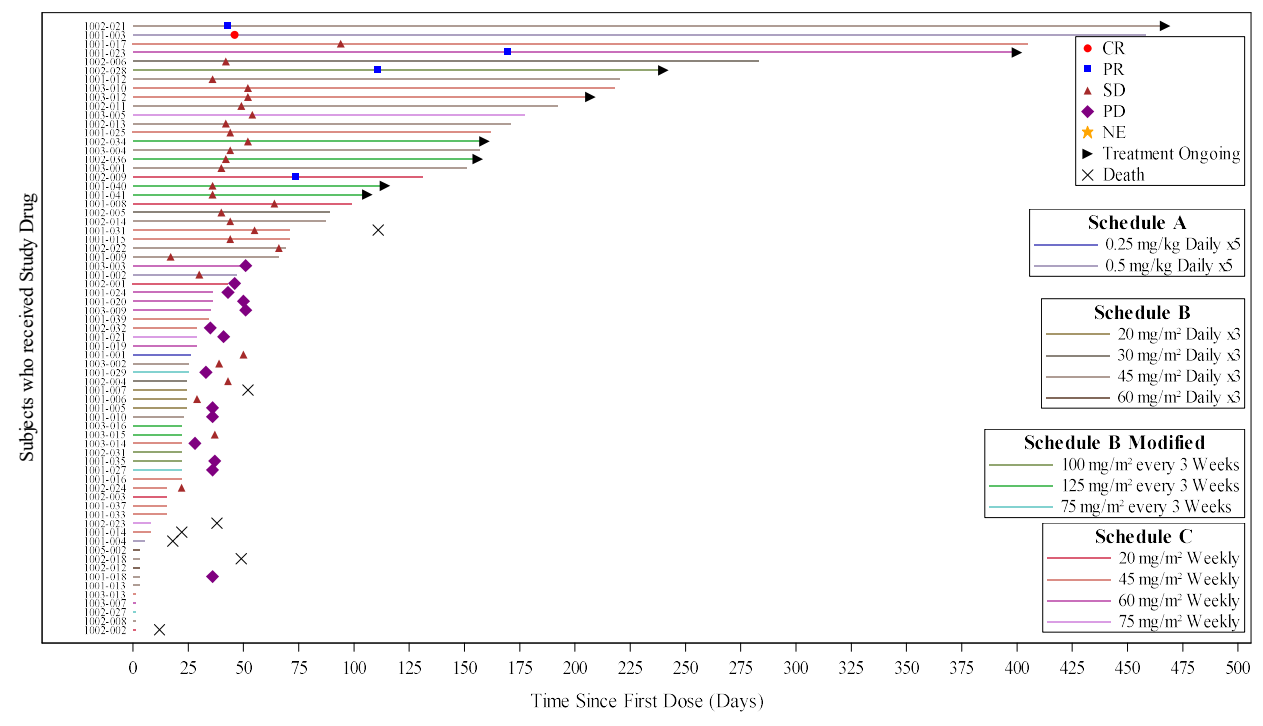
CBX-12-101: Duration on Study



March 2024

- **Patients continuing on study for over 15 months**
- **Recommended schedule once every 21 day dosing**
- **Responses observed in several tumor types including ovarian, breast, NSCLC, others**

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CBX-12 has Superior Tolerability Over ADCs or Unconjugated Chemotherapies

Preferable Toxicity Profile

No **interstitial lung disease** or **ocular toxicity** in phase 1 study

Minimal GI toxicity

Myelosuppression is the dose limiting toxicity

Manageable neutropenia, anemia, and thrombocytopenia

Allows for a **4-5 fold increase** in administration of warhead compared to unconjugated exatecan

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CBX-15
IND Candidate

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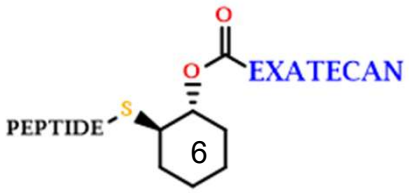
Path to Lead Conjugate: Linker is Not Trivial!

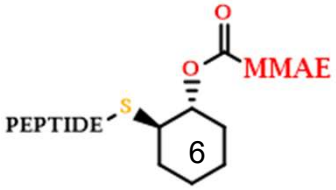


CBX12 (Linker 31)

Release profile matches warhead potency

- Clinical quality efficacy and TI

Do linker properties translate across warhead species?



CBX15-<u>31E</u>

Weak efficacy

- Different bond to linker
- Release kinetics changed

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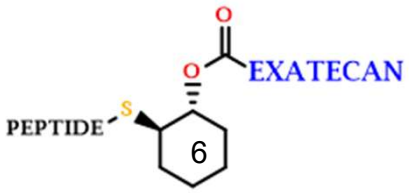
Path to Lead Conjugate: Linker is Not Trivial!



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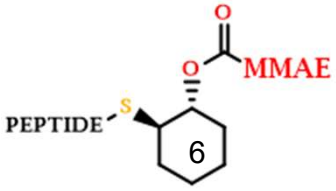

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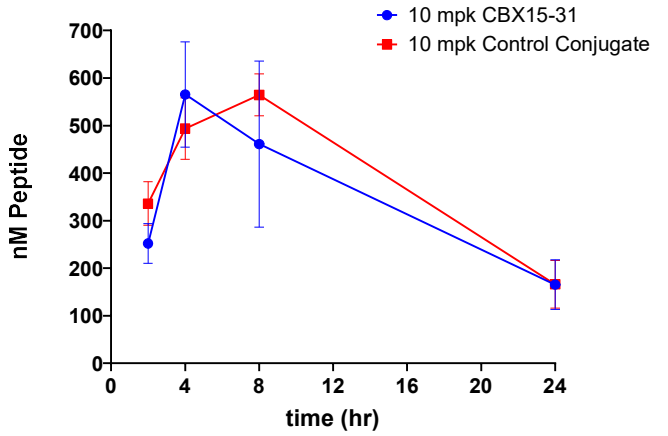

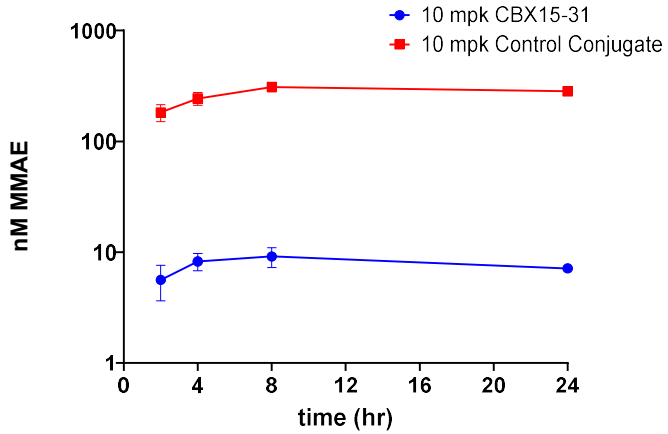

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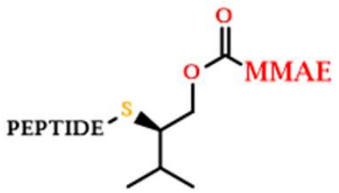
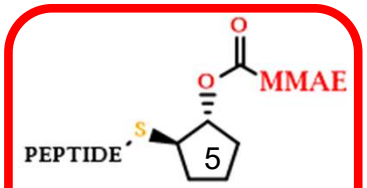
Path to Lead Conjugate: Linker is Not Trivial!



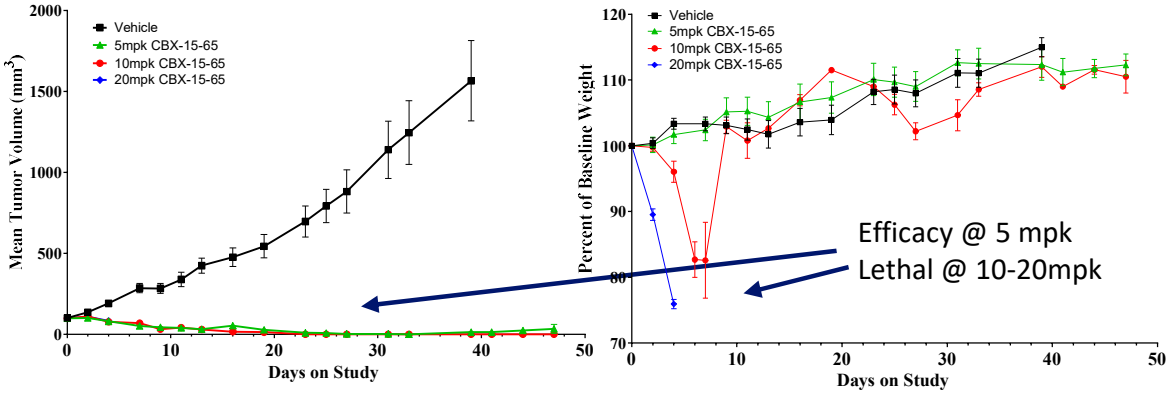
CBX15-65E

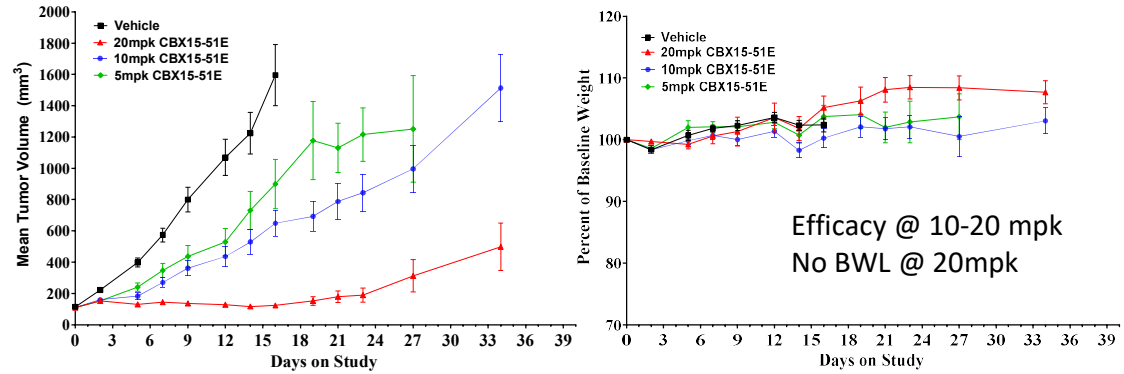
Removing ring *frees-up* linker to find immolation shape faster



CBX15-51E

Smaller 5-ring *locks* molecule in more reactive shape vs 6 for fast immolation





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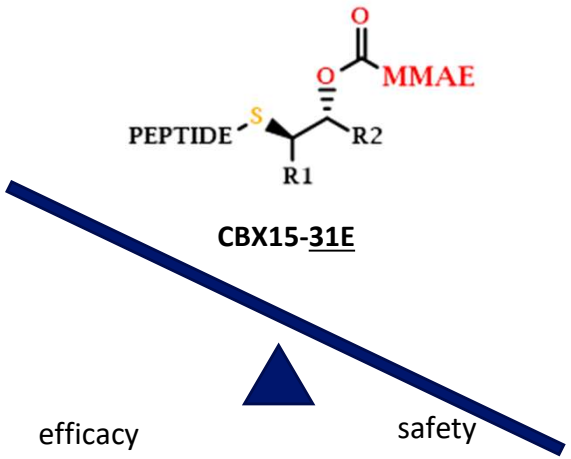
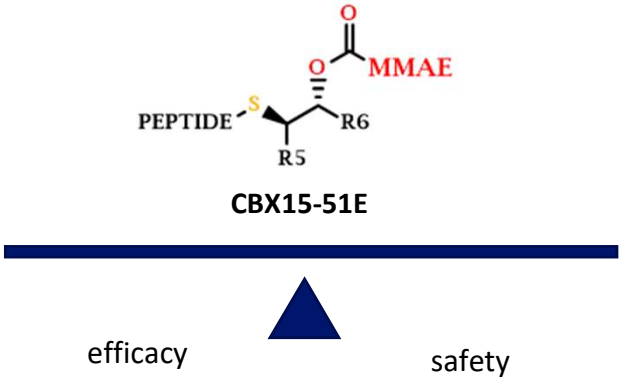
Finding the Right Balance of Release Profile

Poor release of warhead in tissue resulting in poor efficacy



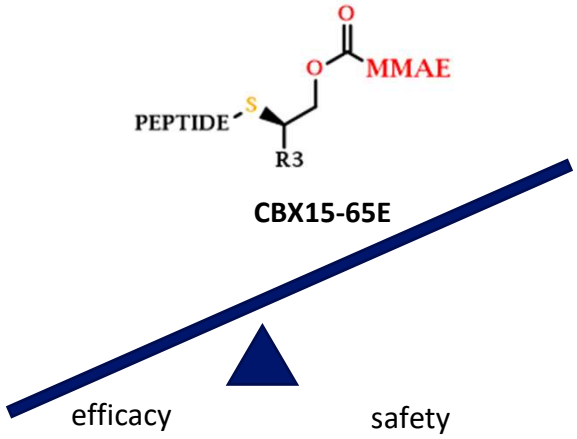
CBX15-31E

Intermediate release profile in tissue results in excellent efficacy while maintaining safety



CBX15-51E

High levels of release in tissue results in narrow TI



CBX15-65E

Targeted delivery to tumor and avoidance of toxicity to normal tissues

CBX-15
Tumor Targeting of MMAE

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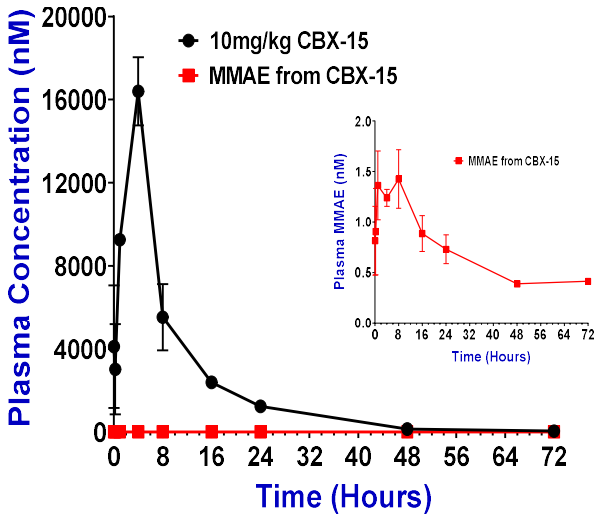
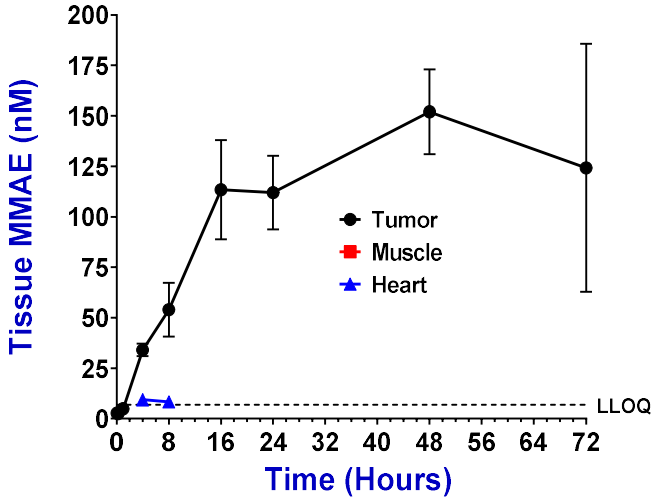
CBX-15 Selectively Delivers MMAE to Tumor and Avoids Healthy Tissues, Unlike Unconjugated MMAE

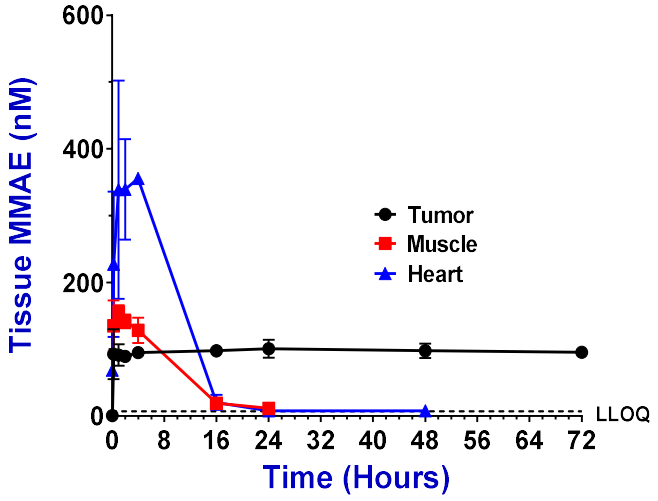
Plasma Levels CBX-15 + MMAE



MMAE Tissue Levels Following 10mg/kg CBX-15 Administration



MMAE Tissue Levels Following 0.5mg/kg MMAE Administration



CBX-15 demonstrates selective release of MMAE in tumor with no release in healthy tissues or plasma (inset displays expanded axis of MMAE from CBX-15 in plasma).

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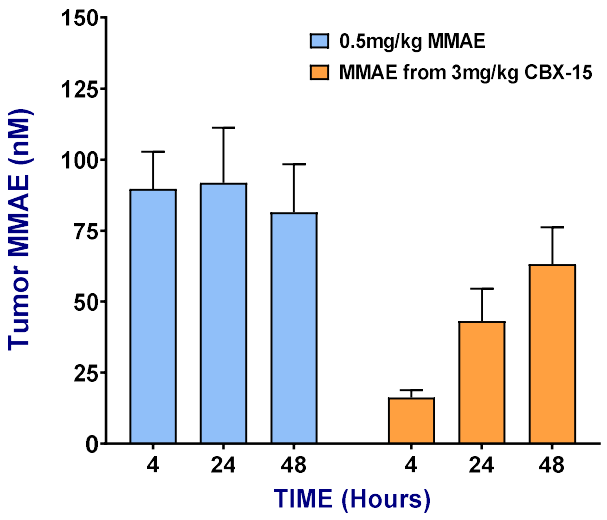
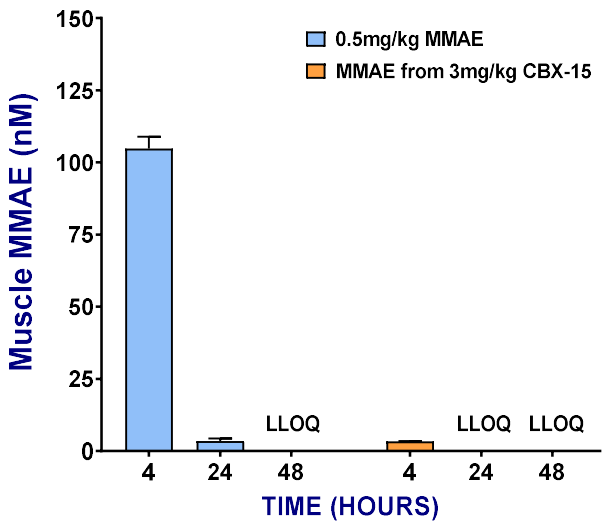
CBX-15: Tissue Selectivity versus MMAE Warhead

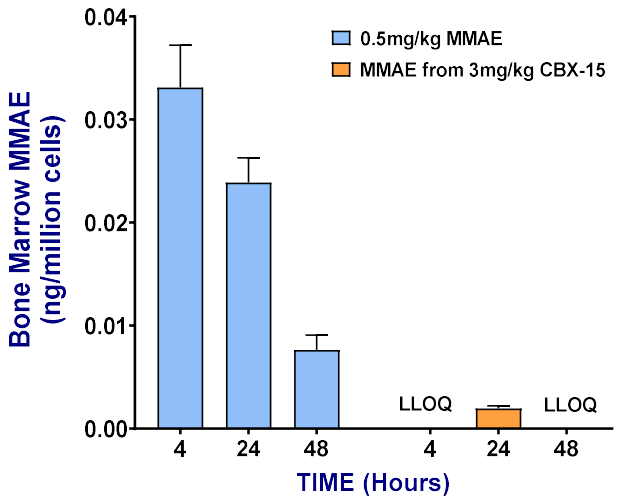
CBX-15 delivers comparable levels of MMAE to **tumor** as the equimolar dose of warhead (MTD of MMAE)



Unlike free warhead, CBX-15 avoids delivery of MMAE to **muscle** tissue



Unlike free warhead, CBX-15 avoids delivery of MMAE to **bone marrow**



Targeted delivery to tumor and avoidance of toxicity to normal tissues

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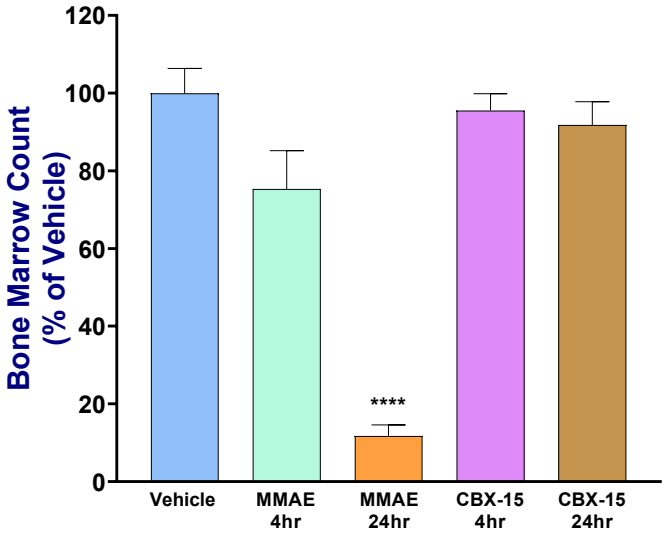
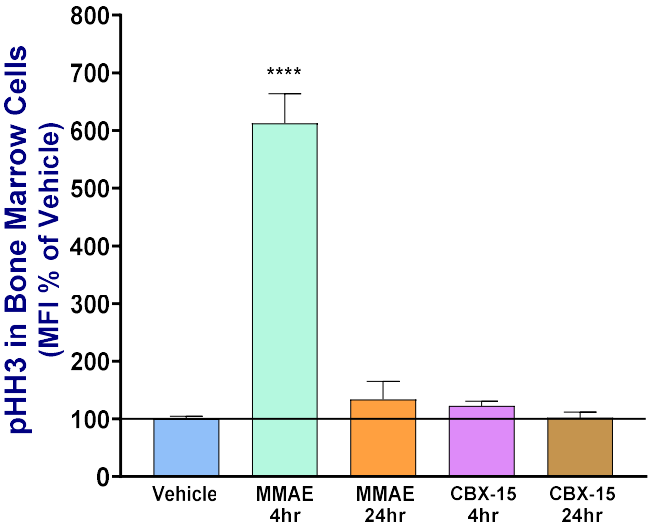
CBX-15 Avoids the Bone Marrow Toxicity of an Equimolar Dose of Unconjugated MMAE in the Mouse

Efficacious Dose of CBX-15 Does Not Impact BM Counts



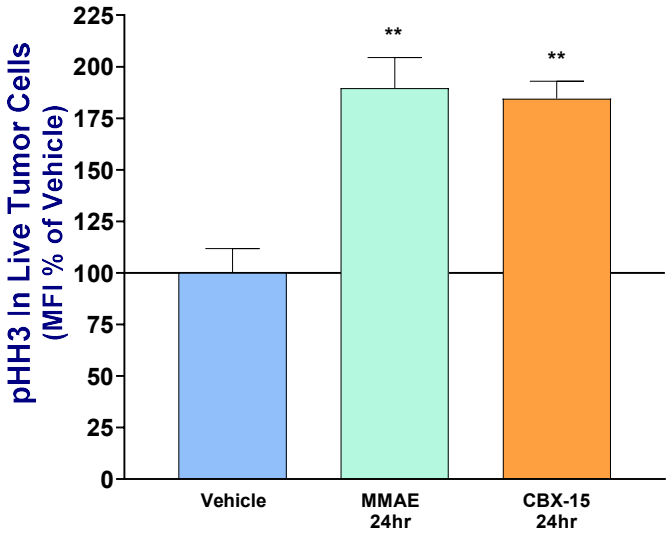
****p<0.0001 significance from vehicle

Efficacious Dose of CBX-15 Does Not Induce pHH3 Expression in BM



****p<0.0001 significance from vehicle

Efficacious Dose of CBX-15 Induces Comparable pHH3 to Equimolar MMAE



**p<0.01 significance from vehicle

Nude mice were administered equimolar 2.4µmoles/kg doses of CBX-15 (10mg/kg) or unconjugated MMAE (1.7mg/kg); femoral bone marrow was assayed at time points indicated.

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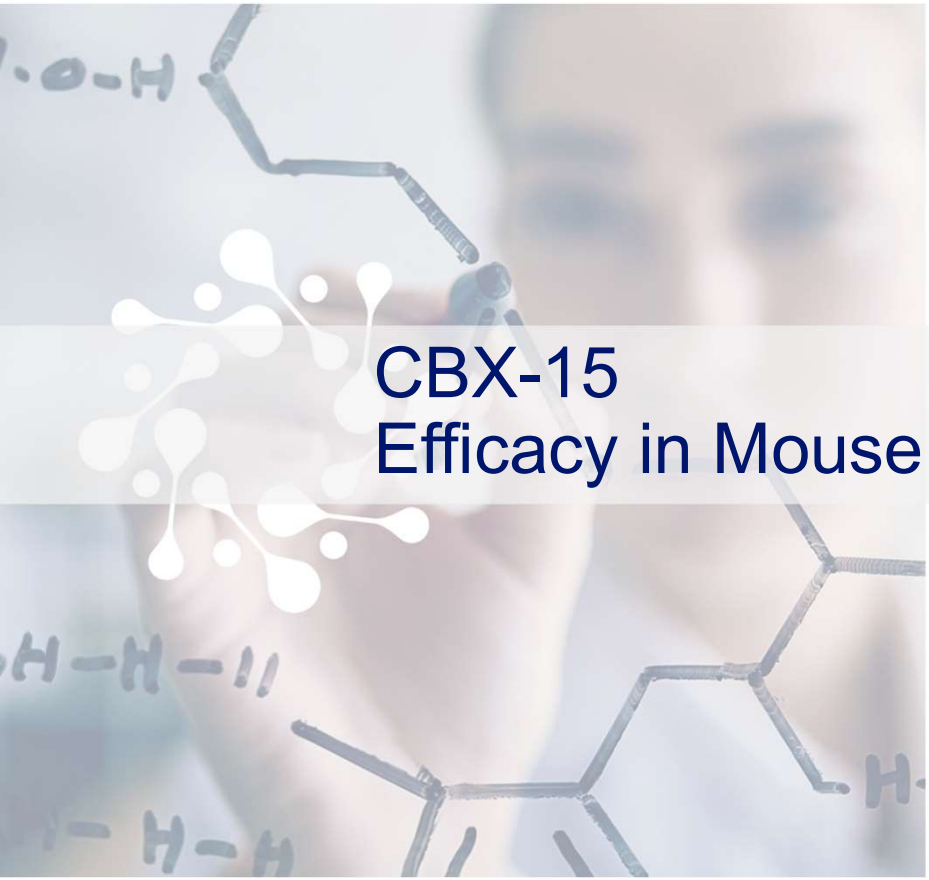

CBX-15
Efficacy in Mouse Xenograft Tumor Models

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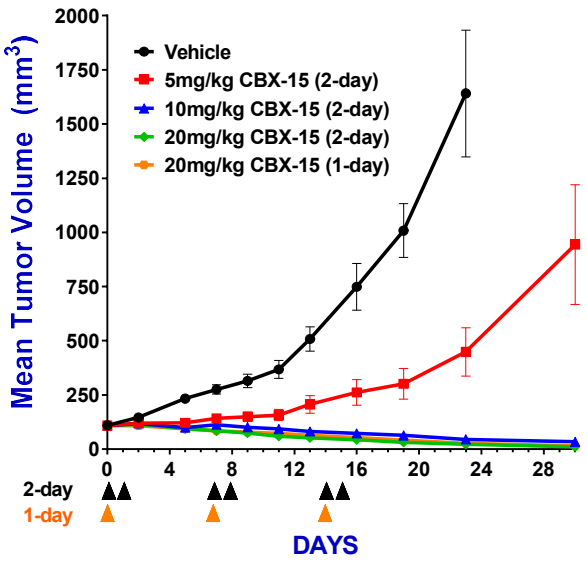
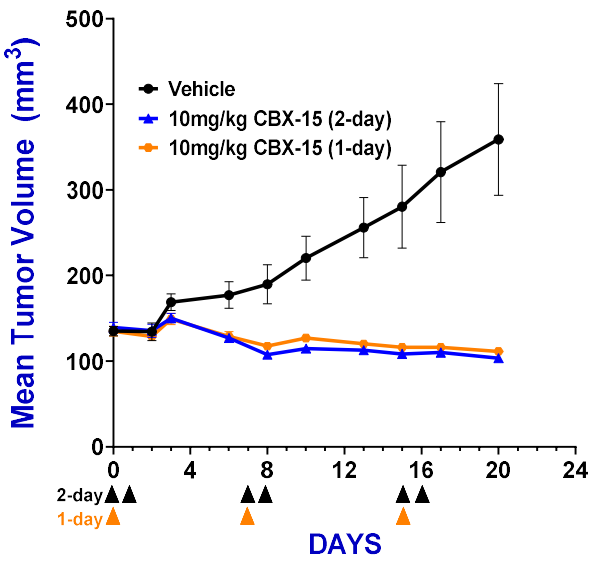
CBX-15: Tumor Suppression in Multiple Models

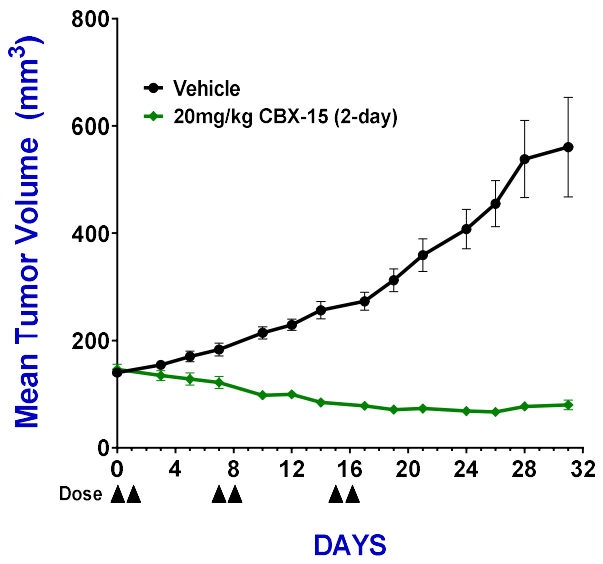
Efficacy with QW and QDx2 Dosing in NCI-H1975 NSCLC



Efficacy with QW and QDx2 Dosing in EBC-1 NSCLC



Efficacy with QDx2 Dosing in PC-3 Prostate



Preclinical models demonstrate efficacy as monotherapy with multiple dosing paradigms.

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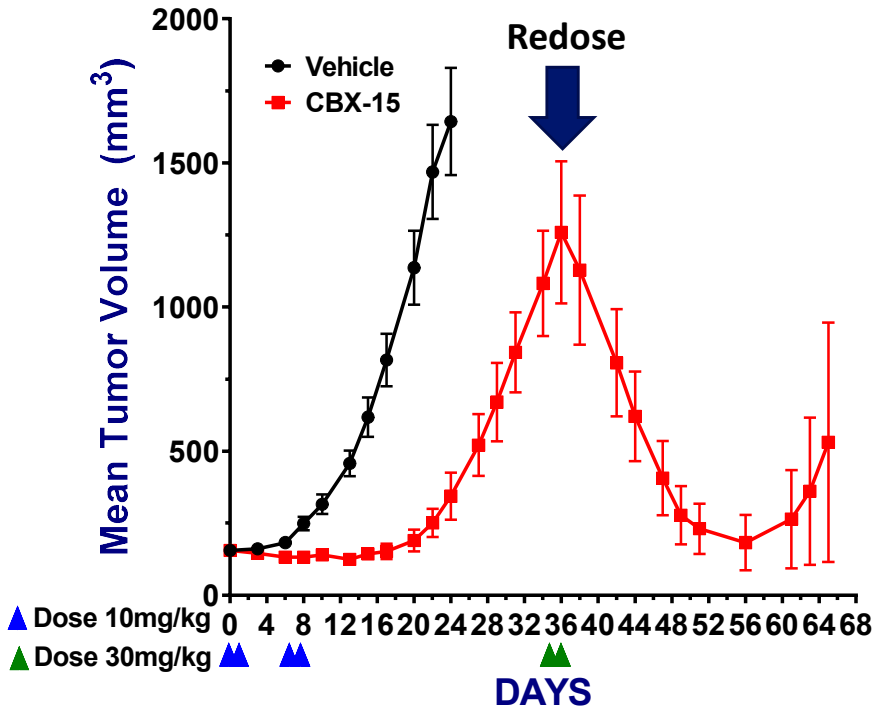
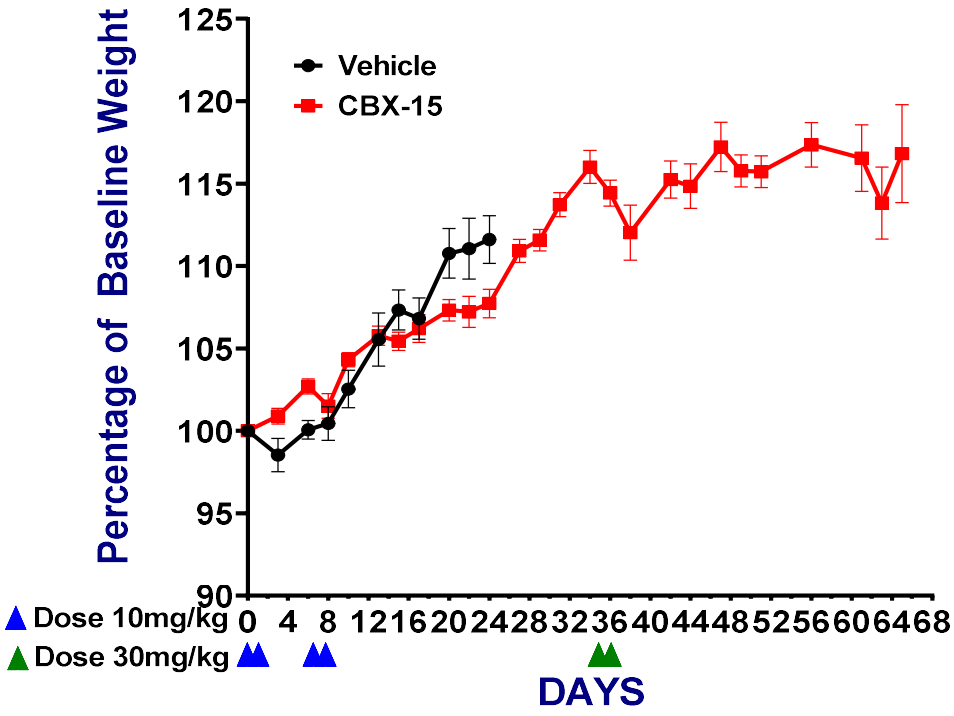
CBX-15: Rapid Regression of Large H1975 NSCLC Tumors

Immediate and Rapid Regression of Large Tumors after CBX-15 Dose



CBX-15 Well Tolerated with No Body Weight Loss



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Thank you

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