First-in-Class PI3Kα-targeting Degrader Antibody Conjugates (DACs) for selective and safer treatment of PI3Kα-driven cancers

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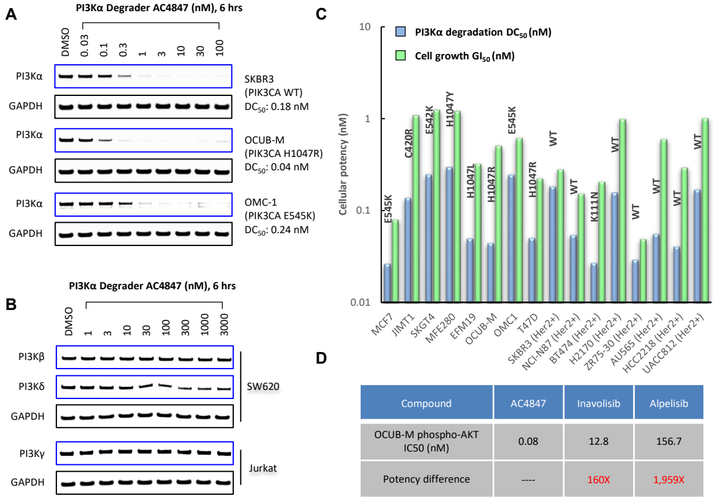
Introduction

- PI3Kα is a critical oncogenic driver in a broad range of solid tumors, including breast cancer, where activating mutations and pathway hyperactivation are frequently observed. Although two PI3Kα inhibitors have recently been approved by the FDA for breast cancer treatment, their clinical utility is significantly constrained by dose-limiting, on-target toxicities due to wild-type PI3Kα inhibition, most notably insulin resistance and hyperglycemia.
- Antibody-drug conjugates (ADCs) offer a compelling strategy to enhance the therapeutic index of PI3Kα-targeted therapies. However, development of such agents has been hindered by the lack of sufficiently potent and selective PI3Kα inhibitors suitable as ADC payloads.
- In this study, we utilized Accutar's proprietary chimeric degrader platform to develop AC4847, a highly potent and selective PI3Kα degrader. AC4847 demonstrated sub-nanomolar potency, making it approximately 100-fold more potent than the small-molecule PI3Kα inhibitor inavolisib. Furthermore, Degrader–Antibody Conjugates (DACs) derived from the AC4847 payload elicited antigen-dependent PI3Kα degradation and robust anti-proliferative effects in cellular assays. In vivo, PI3Kα DACs exhibited strong anti-tumor activity without inducing changes in blood glucose or insulin levels.

Methods

- **Compounds design**: CRBN-based PI3Kα degrader, AC4847, was designed using proprietary AI chimeric degrader platform (Accutar Biotechnology).
- **ADC generation**: Degrader-Antibody conjugates (**DACs**), was generated by conjugation of AC4847 (payload) to sacituzumab monoclonal antibody (TROP2), trastuzumab or pertuzumab monoclonal antibodies (Her2) using an optimized cleavable linker.
- **PI3Kα degradation DC_{50}, phospho-AKT inhibition IC_{50} or cell growth inhibition GI_{50} calculation:** DC_{50} and IC_{50} was obtained by western blot assays to assess PI3Kα degradation and phospho-AKT inhibition in indicated cell lines. GI_{50} was obtained using cell growth assays after 5 days of treatment and measured by CellTiter-Glo Luminescent Cell Viability detection.
- **In vivo efficacy:** BT474 and MDA-MB-361 models were treated with DACs once every 3 weeks through intravenous dosing.

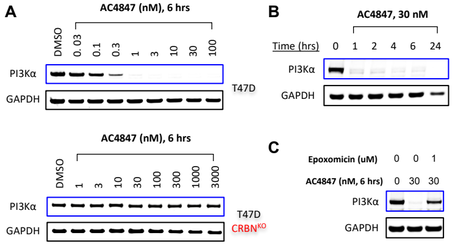
Figure 1. The PI3Kα chimeric degrader AC4847 exhibited potent and selective PI3Kα degradation, along with robust inhibition of cell growth in cell lines harboring PI3Kα mutations or HER2 amplification with wild-type PI3Kα. Notably, AC4847 demonstrated over 100-fold greater potency compared to FDA-approved PI3Kα inhibitors.



Compound	AC4847	Inavolisib	Alpelisib
OCUB-M phospho-AKT IC50 (nM)	0.08	12.8	156.7
Potency difference	----	160X	1,959X

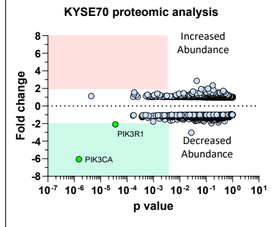
(A) PI3Kα and (B) PI3Kβ, PI3Kδ, PI3Kγ degradation in indicated cell lines treated with the PI3Kα degrader AC4847 was assessed by Western blot analysis. (C) Summary of PI3Kα degradation (DC_{50}) and cell growth inhibition (GI_{50}) values of AC4847 across cell lines harboring PI3Kα mutations or HER2 amplification. (D) Comparison of phospho-AKT inhibition (IC_{50}) by the PI3Kα degrader AC4847 versus the PI3Kα inhibitors inavolisib and alpelisib.

Figure 2. The PI3Kα degradation induced by AC4847 was rapid and dependent on both the E3 ligase and the proteasome.



(A) PI3Kα degradation in indicated cell lines treated with the PI3Kα degrader AC4847 was assessed by Western blot analysis. (B) Time-dependent and (C) proteasome-dependent PI3Kα degradation in OCUB-M cells by AC4847 was assessed by Western blot analysis.

Figure 3. AC4847 exhibits high selectivity for PI3Kα degradation.



Proteomic analysis of KYSE70 cells treated with 10 nM AC4847 (approximately 20× DC_{50}) for 4 hours. Data represent triplicate samples for both control and treatment groups.

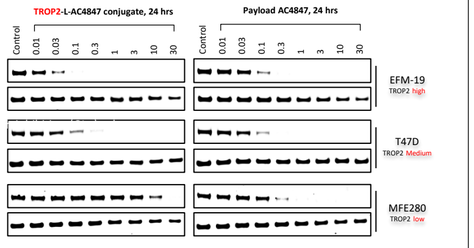
Figure 4. The AC4847-based Sacituzumab (TROP2)-PI3Kα degrader–antibody conjugate (DAC), induced TROP2-dependent PI3Kα degradation and cell growth inhibition, with enhanced potency observed in cell lines exhibiting high TROP2 expression.

A

PI3Kα DC_{50} (nM)	TROP2-L-AC4847	Payload AC4847
EFM-19 TROP2 high	0.01	0.05
T47D TROP2 medium	0.08	0.06
MFE280 TROP2 low	4.93	0.12

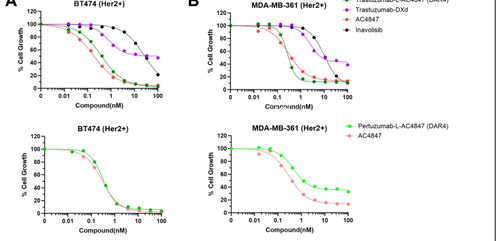
C

Cell growth GI_{50} (nM)	TROP2-L-AC4847	Payload AC4847
EFM-19 TROP2 high	0.03	0.49
T47D TROP2 medium	0.21	0.56
MFE280 TROP2 low	19.37	1.31



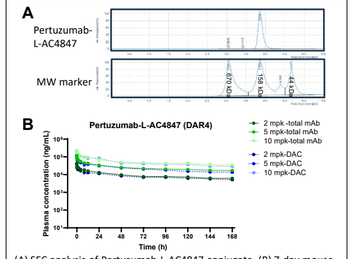
(A) Summary of PI3Kα degradation (DC_{50}) values by TROP2-L-AC4847 DAC and payload AC4847. (B) PI3Kα degradation in indicated cell lines with various levels of TROP2 expression treated with TROP2-L-AC4847 DAC and payload AC4847 was assessed by Western blot analysis. (C) Summary of cell growth inhibition (GI_{50}) values by TROP2-L-AC4847 DAC and payload AC4847.

Figure 5. Her2-PI3Kα DACs exhibited potent cell growth inhibition in Her2+ BT474 and MDA-MB-361 cell lines, demonstrating greater potency than T-DXd.



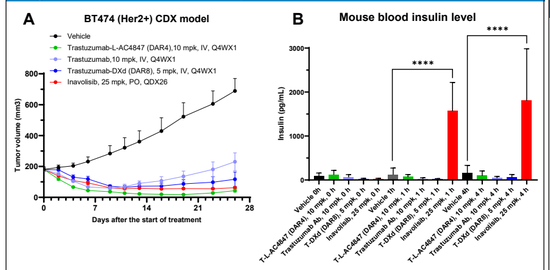
BT474 (A) and MDA-MB-361 (B) cells were treated for 5 days with two HER2 antibody–conjugated PI3Kα DACs, the PI3Kα degrader payload AC4847, the PI3Kα inhibitor inavolisib, and T-DXd.

Figure 6. The pertuzumab-PI3Kα DAC exhibited no aggregation and demonstrated favorable PK in mice.



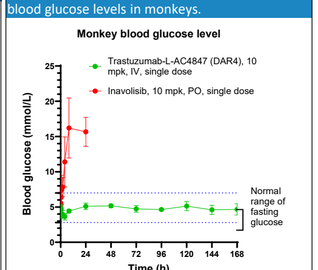
(A) SEC analysis of Pertuzumab-L-AC4847 conjugate. (B) 7-day mouse PK analysis of Pertuzumab-L-AC4847 conjugate.

Figure 7. The trastuzumab–PI3Kα DAC induced robust tumor regression in the BT474 xenograft model with no detectable impact on insulin levels.



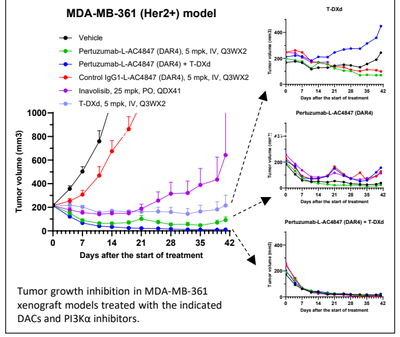
(A) Tumor growth inhibition in BT474 xenograft models treated with the indicated DACs and PI3Kα inhibitors. (B) Changes in fasting blood insulin levels measured 1 hour and 4 hours after the indicated treatments.

Figure 8. Unlike PI3Kα inhibitor inavolisib, the trastuzumab–PI3Kα DAC showed no effect on blood glucose levels in monkeys.



Changes in fasting blood glucose levels measured 24 hours and 7 days after the indicated treatments.

Figure 9. The pertuzumab–PI3Kα DAC demonstrated robust tumor regression and exhibited synergistic efficacy with T-DXd in the MDA-MB-361 xenograft model.



Tumor growth inhibition in MDA-MB-361 xenograft models treated with the indicated DACs and PI3Kα inhibitors.

Conclusion

- We successfully discovered a potent and selective CRBN-based PI3Kα degrader AC4847 through our proprietary AI chimeric degrader platform (Accutar Biotechnology).
- AC4847 demonstrated over 100-fold greater potency compared to FDA-approved PI3Kα inhibitors, positioning it as a promising ADC payload.
- TROP2 and Her2-PI3Kα DACs utilizing AC4847 as the payload were generated and demonstrated great potency in cell lines with high levels of target antigen expression.
- PI3Kα DACs exhibited no aggregation and demonstrated favorable PK in mice.
- Her2-PI3Kα DACs induced robust tumor regression following Q3W or Q4W dosing and exhibited synergistic efficacy with T-DXd in Her2+ xenograft models.
- Unlike PI3Kα inhibitor inavolisib, the Her2–PI3Kα DAC showed no effect on blood glucose or insulin levels, significantly improving the therapeutic window.

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