N-myristoyltransferase (NMT) Inhibitor Payloads for ADC: Discovery of LPI-M5T with Potent Anti-Tumor Activity and Improved Therapeutic Window

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Introduction: NMTi as an Oncologic Target

N-myristoyltransferase (NMT) is an attractive emerging target for oncology ADC therapy. NMT-inhibitor (NMTi) payloads block N-myristoylation, a critical lipid-modification of substrate proteins.

• The Enzyme: NMT catalyzes N-myristoylation, attaching a myristoyl lipid tag onto target proteins.

• Cancer Relevance: Myristoylation governs membrane localization of oncogenic signaling proteins. NMT activity is frequently elevated in multiple tumour types.

• Therapeutic Opportunity: NMTi disrupts oncogenic signal transduction. NMT represents a novel druggable target for ADC payload development.

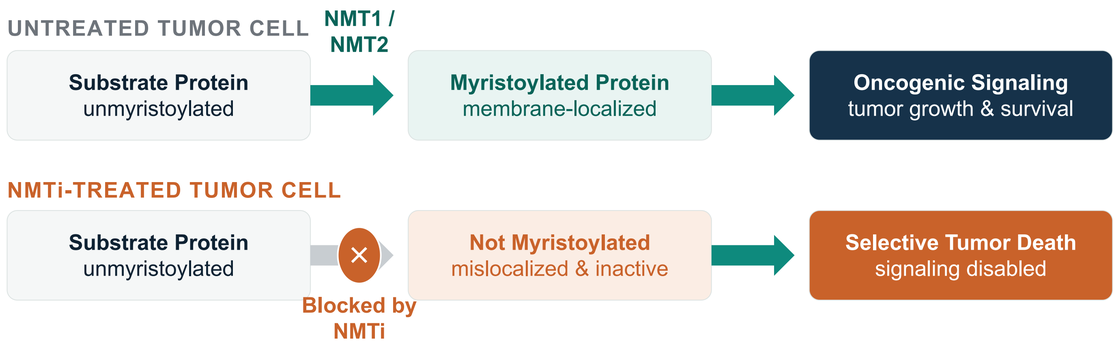


Figure 1. Mechanism of NMTi in tumor cells

Payload in vitro activity

Phrontline's NMTi payloads exhibit comparable anti-tumor activity with improved toxicity profile versus benchmark MYX2339.

• PI-M1 & PI-M7: comparable potency to benchmark MYX2339

• PI-M5 & PI-M6: less potent derivative compounds

Payload cytotoxicity (JIMT-1 cells)

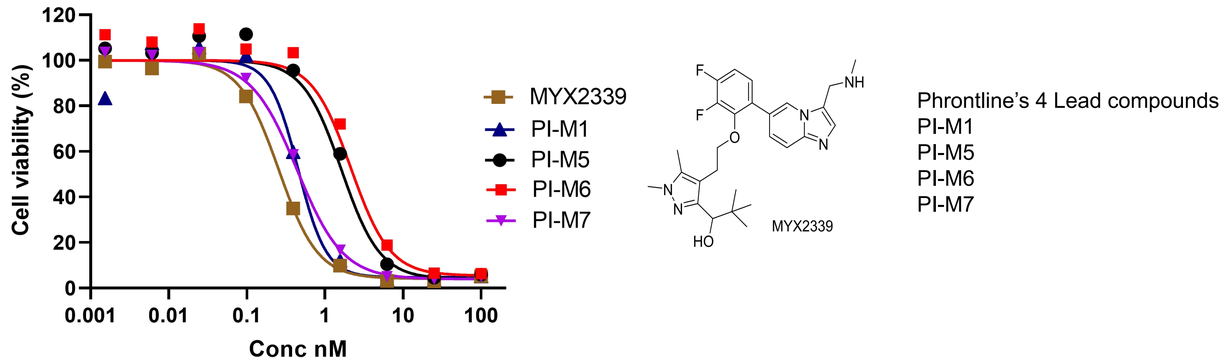


Figure 3. In vitro cell-killing activity (left) and chemical structure of MYX2339 (right)

Synthetic Lethality: NMT2-Deficiency Drives Tumor Selectivity

NMT1/NMT2 synthetic lethality serves as the core tumor-selective mechanism for NMTi-based ADC therapy.

Tumor cells with NMT2 loss become fully dependent on residual NMT1 activity for survival.

In contrast, normal tissues retain functional NMT2 and tolerate NMT1 inhibition.

Four major genetic signatures significantly increase NMTi sensitivity:

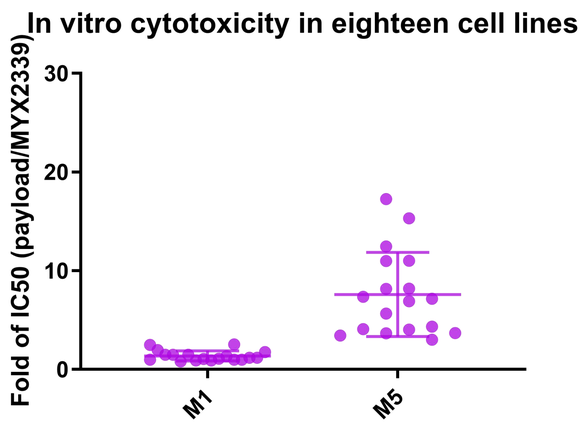
• LKB1 loss: impairs AMPK metabolic surveillance, elevates myristoylation dependency

• KEAP1 mutation: drives sustained oxidative stress and NMT pathway addiction

• KRAS activation: reinforces oncogenic signaling reliance on protein myristoylation

• Triple mutational profile (KRAS/LKB1/KEAP1): defines high-sensitivity patient population

Anti-proliferation profiling of Phrontline's NMTi across human tumor cell lines



	M1	M5
Mean	1.374	7.596

Figure 2. Anti-proliferation activity of Phrontline's lead payloads. MYX2339 IC50 rebased to 1

Mean (M1 IC50 / MYX2339 IC50) = 1.374 comparable activity vs MYX2339

Mean (M5 IC50 / MYX2339 IC50) = 7.596 less antitumor activity vs MYX2339

Phrontline's Lead ADC : In vivo Efficacy& Tolerability

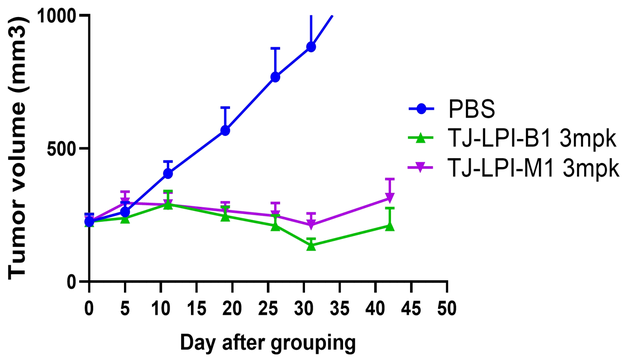
Our lead linker-payload LPI-M5T demonstrates robust tumour growth inhibition and improved tolerability compared with Myricx benchmark TJ-LPI-B1.

• Potent anti-tumor activity observed in JMT-1 xenograft mouse model

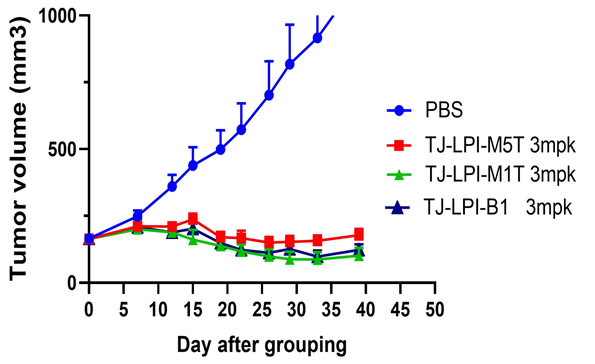
• Superior in vivo tolerability versus benchmark conjugate

• Broad anti-proliferative activity across a panel of human tumour cell lines

JIMT-1 xenograft model



JIMT-1 xenograft model



Single dose in SD rats for 21days

ALIVE DEATH

		Male			Female		
50mpk	TJ-LPI-B1						
50mpk	TJ-LPI-M5T						

Figure 4. In vivo anti-tumor efficacy (top) and tolerability profile (bottom)

Summary & Conclusion

Phrontline's Payload Panel

- PI-M1 & PI-M7: comparable antitumor activity to MYX2339
- PI-M5 & PI-M6: less potent derivatives
- **Lead payload: PI-M5 (moderate activity)**

Phrontline's Linker-Payload Conjugates

- LPI-M1: comparable efficacy & toxicity to benchmark LPI-B1
- **LPI-M5: comparable efficacy and improved activity vs benchmark LPI-B1**

Phrontline's Lead Candidate Linker Payload: *LPI-M5T*

- LPI-M5T has **shown comparable** in vivo efficacy to Myricx's TJ-LPI-B1, with **improved tolerability**
- With the advantages mentioned above, LPI-M5T provides wider therapeutic window vs benchmarks

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