IRAKIMiDs: Protein Degraders Targeting Both IRAK4 and IMiD Substrates Show Combinatorial Effects Leading to Broad Activity with Durable Regressions in MYD88 Mutant Lymphoma Xenografts *In Vivo*

Poster 5222

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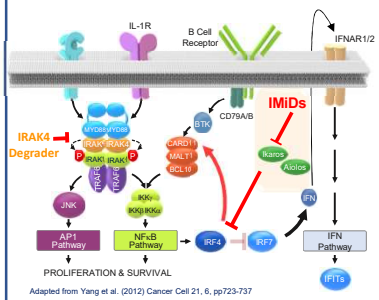
INTRODUCTION

- MYD88 mutations constitutively activate both NF-kB and AP1 pathways, promoting B-cell proliferation and survival
  - 30-40% ABC DLBCL; 30-70% Primary CNS lymphoma; 45-75% Primary extranodal lymphomas; >90% Waldenström macroglobulinemia
- IRAK4 is an integral component of MYD88 signaling, and degradation of IRAK4 by Targeted Protein Degraders (TPD) abrogates downstream signaling to both NFkB and MAPK pathways
  - Both kinase activity and scaffolding function are required for signaling and IRAK4 TPD show greater inhibition of signaling compared to IRAK4 small molecule inhibitors
- Previous IRAK4 degraders have shown promising activity in some MYD88^{MT} models, however, are less active in some models with varying co-mutations, such as SUDHL2 (MYD88^{S222R}/TNFAIP3$^{-/-}$)
  - Co-mutations with MYD88 (e.g. CARD11, A20) may correlate with diminished activity
- IMiDs (Lenalidomide and pomalidomide) can also inhibit NFkB and induce Type 1 IFN signaling driving tumor cell death
- We propose that combining IRAK4 degradation with IMiDs in lymphomas with MYD88 mutations will broadly suppress NFkB signaling and increase Type 1 IFN responses, driving increased cell death over either drug alone
- Here we describe IRAKIMiDs: novel heterobifunctional degraders that use an IMiD as a CRBN binder and an IRAK4 binder to drive degradation of both IRAK4 and IMiD substrates in a single molecule.
  - The synergistic activity of targeting both the MYD88 and Type1 IFN pathways in a single molecule leads to strong single-agent activity in a range of MYD88^{MT} but not MYD88^{WT} lymphoma models, with improved cell kill and breadth of activity relative to IMiDs or IRAK4-selective degraders

IRAK4 Degradation and IMiDs have Complementary Activity

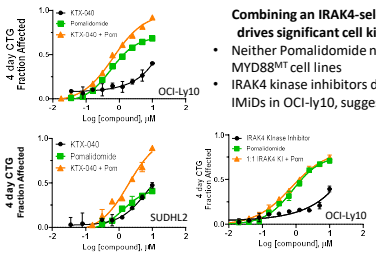


IRAK4 Degraders inhibit both NFkB and MAPK signaling in MYD88^{MT} tumors
- Significantly increased inhibition compared to IRAK4 kinase inhibitors

IMiDs suppress IRF4 through degradation of Zn-finger transcription factors
- Inhibits NFkB (through CARD11) and activates Type 1 IFN responses

IRAKIMiDs: Combine IRAK4 and IMiD degradation in single-agent molecule
- Combining IRAK4 degradation and IMiD activity will more effectively inhibit NFkB relative to either mechanism alone and stimulate a Type 1 IFN response
- Drive potent antitumor responses across a range of MYD88^{MT} tumors with different co-mutations.

IRAK4 Degraders and IMiDs Show Synergy in MYD88^{MT} Cell Lines



Combining an IRAK4-selective degrader and Pomalidomide drives significant cell kill in MYD88^{MT} lymphoma cell lines
- Neither Pomalidomide nor KTX-040 alone show full cell kill in MYD88^{MT} cell lines
- IRAK4 kinase inhibitors do not show additivity/synergy with IMiDs in OCI-ly10, suggesting IRAK4 degradation is required

Synergy observed between KTX-040 and Pom in OCI-Ly10 by Chou-Talalay CI method

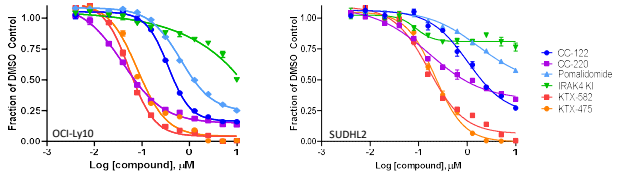
KTX-040 is a VHL-based degrader - does not compete for CRBN with IMiD
KTX-040 IRAK4 DC_{50} = 200 nM

Chou, TC; Talalay, P (1984). Adv. Enzyme Regul. 22: 27–55.

IRAKIMiDs Simultaneously Degrade Both IRAK4 and IMiD Substrates in a Single Molecule

Targeting both IRAK4 and IMiD substrates in a single molecule allow for broader single-agent activity compared to IMiDs

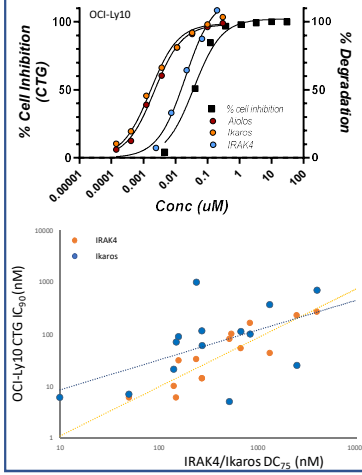
			MYD88^{MT}				MYD88^{WT}	
Cpd	IRAK4 DC_{50} (nM)	Ikaros/Aiolos DC_{50} (nM)	OCI-Ly10 IC_{50}/IC_{90} (uM)	SUDHL2 IC_{50}/IC_{90} (uM)	OCI-Ly3 IC_{50}/IC_{90} (uM)	U2932 IC_{50}/IC_{90} (uM)	OCI-Ly19 IC_{50}/IC_{90} (uM)	SUDHL6 IC_{50}/IC_{90} (uM)
KTX-475	12	5/6	0.042/0.3	0.048/2.0	2.6/7.8	1.8/4.1	2.3/4.2	1.7/5.3
KTX-582	5	0.3/2	0.03/0.12	0.14/7.1	4.5/6.8	>10/>10	>10/>10	4.0/>10



IRAKIMiDs show consistent activity in MYD88^{MT} cell lines, superior to IMiDs or IRAK4 kinase inhibitors:
- IRAKIMiDs (KTX-582, KTX-475) drive cells to complete cell death (by CTG endpoint)
- Active across multiple MYD88-MT cell lines with varying co-mutations and minimal activity in MYD88^{WT} cell lines
  - OCI-Ly10 - MYD88^{L265P}/CD79b^{MT}; SUDHL2 – MYD88^{S222R}/TNFAIP3$^{-/-}$; OCI-Ly3 – MYD88^{L265P}/CARD11^{MT}

IMiDs have inconsistent activity in MYD88^{MT} DLBCL:
- IMiDs, including next-generation IMiDs (CC220, CC122) cannot drive complete cell death alone in either SUDHL2 or OCI-Ly10

IRAKIMiD Activity Correlates with Degradation of Both IRAK4 and IMiD Substrates

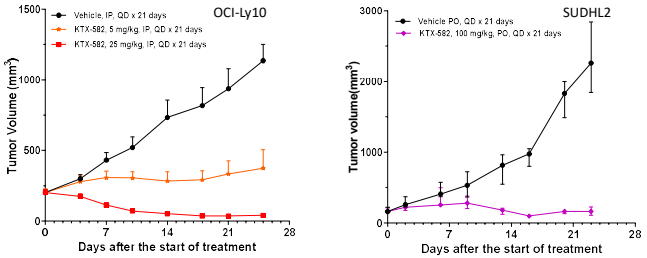


KTX-582 OCI-Ly10 maximal cell activity occurs when both IRAK4 and Ikaros/Aiolos are significantly degraded
- Cell activity is associated with degradation of both IRAK4 and IMiD substrates and parallels IRAK4 degradation

Optimization of both IRAK4 and Ikaros degradation correlates with improving potency of IRAKIMiDs
- Cell activity (IC_{90}) in OCI-Ly10 correlates with degradation of both IRAK4 and IMiD substrates (Ikaros) across a collection of IRAKIMiD compounds
  - IRAK4 R^2 = 0.78
  - Ikaros R^2 = 0.29

Degradation of Both IRAK4 and IMiD Substrates Drive Antitumor Activity of IRAKIMiDs

The IRAKIMiD KTX-582 induces tumor regression in OCI-Ly10 and SUDHL2



Tumor regressions by KTX-582 are associated with degradation of both IRAK4 and IMiD substrates

Dose (MPK)	IRAK4 (% Control)	Aiolos (% Control)	Ikaros (% Control)
5	60	56	60
25	85	86	94

KTX-582 induces regressions in both OCI-Ly10 and SUDHL2 as a single agent
- Activity is seen broadly across multiple models with different MYD88 mutations and co-mutations
- Regression is associated with >80% degradation of both IRAK4 and IMiD substrates after 5 days dosing

CONCLUSIONS

- IRAK4 degraders are synergistic with IMiDs in MYD88-mutant lymphoma cells
- IRAKIMiDs are TPD that simultaneously degrade IRAK4 and IMiD substrates, engaging both activities in a single molecule
- IRAKIMiDs show potent *in vitro* activity and *in vivo* tumor regressions in multiple models of MYD88^{MT} lymphoma
  - Have broader activity than IMiDs *in vitro*, that is consistent with both IRAK4 degradation and IMiD activity in driving single agent activity
- A lead IRAKIMiD with improved potency and PK is on track for Phase 1 trials in lymphomas in 2021

Disclosures: Walker, Mayo, Klaus, Rong, Rusin, Sharma, McDonald, Campbell, Gollob, Mainolfi, Weiss: *Kymera Therapeutics:* Employment, Equity Ownership. Kelleher: Kymera Therapeutics Equity Ownership