Mechanisms Underlying Synergistic Activity of KT-413, a Targeted Degrader of IRAK4 and IMiD Substrates in Hematopoietic Cancers

Christine Klaus, Scott Rusin, Samya Bhaduri, Dirk Walther, Kirti Sharma, Michele Mayo, Alice McDonald, Matthew Weiss, Duncan Walker, Rahul Karnik

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Financial Disclosures

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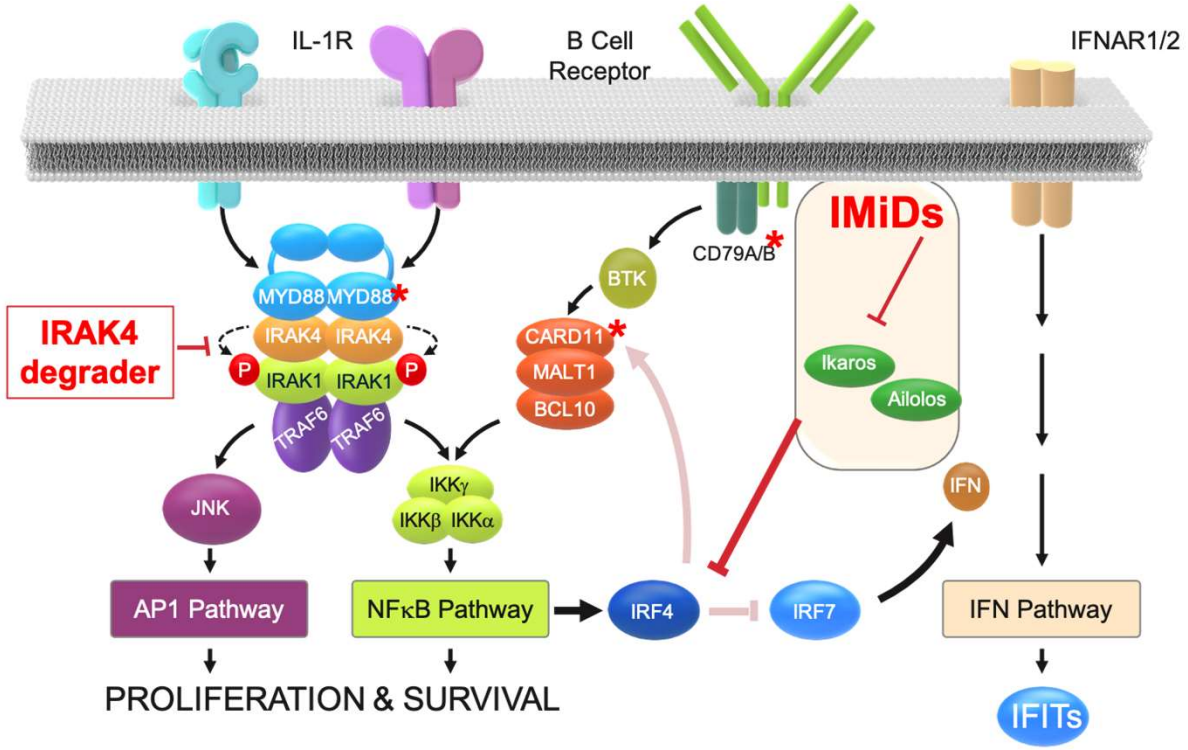
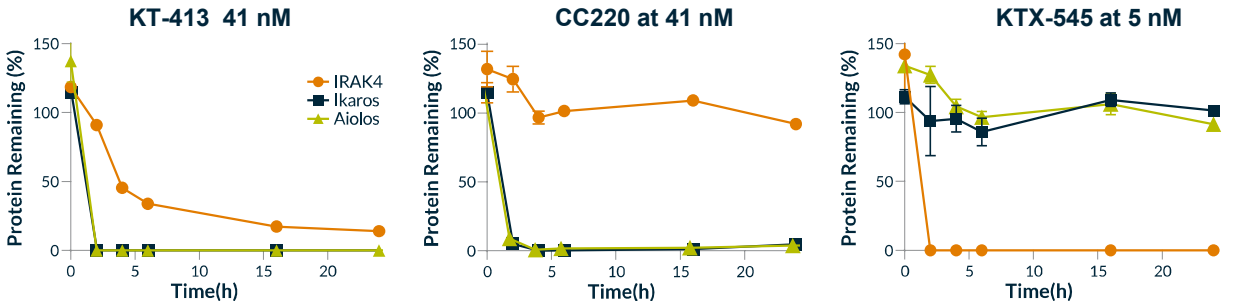
Kymera Therapeutics Employment and Equity Ownership.

KT-413 Targets Redundant Pro-survival Pathways in MYD88^{MT} DLBCL

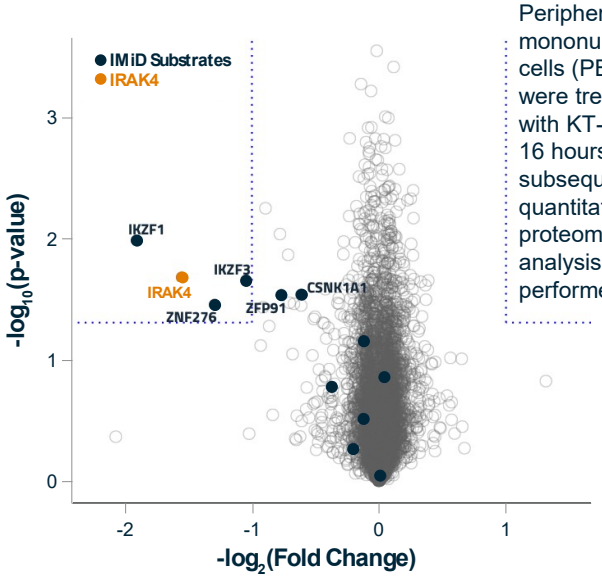
- Alternative pathway activation of NF-kB and downregulation of cell death signals is common in MYD88^{MT} lymphoma via activating mutations in CD79B and CARD11, TNFAIP3 loss, or IRF4 upregulation
- Inhibiting multiple pathways of NF-kB activation and survival signaling may be necessary to drive cell death in MYD88^{MT} lymphomas



KT-413 Selectively Degrades IRAK4 and IMiD Substrates



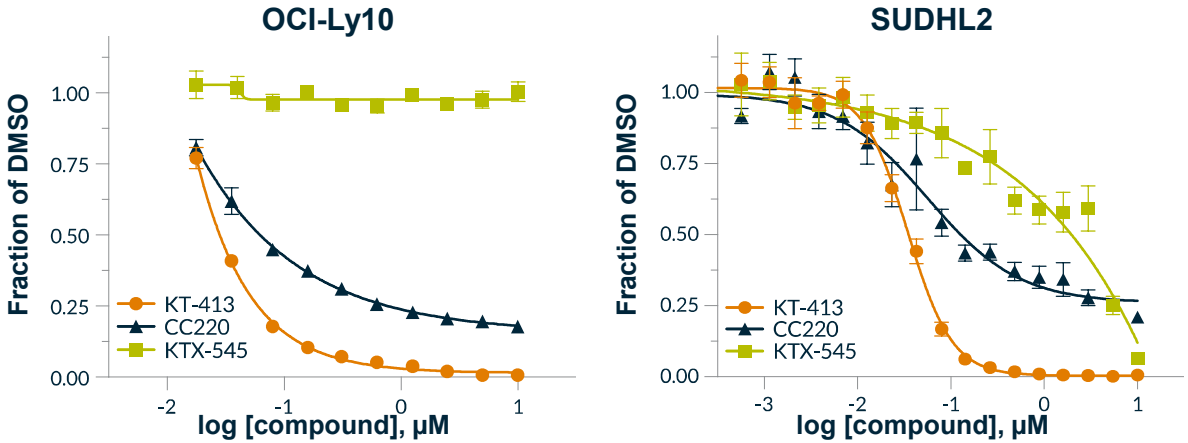
Compound	IRAK4 DC_{50} (nM)	Ikaros DC_{50} (nM)	Aiolos DC_{50} (nM)
KT-413	6	2	2
CC220	-	1	1
KTX-545	1	-	-



Peripheral blood mononuclear cells (PBMCs) were treated with KT-413 for 16 hours and subsequent quantitative proteomic analysis was performed

- OCI-Ly10 cells were treated with KT-413, the IMiD CC-220, or the IRAK4-only degrader KTX-545 at [DC_{90}]
- KT-413 selectively degrades both IRAK4 and IMiD substrates, while CC220 only degrades IMiD substrates and KTX-545 only degrades IRAK4
  - Both KT-413 and CC220 show rapid and equipotent degradation of IMiD substrates
  - KT-413 substrate degradation is hierarchical: IRAK4 degradation is slower than Ikaros and Aiolos

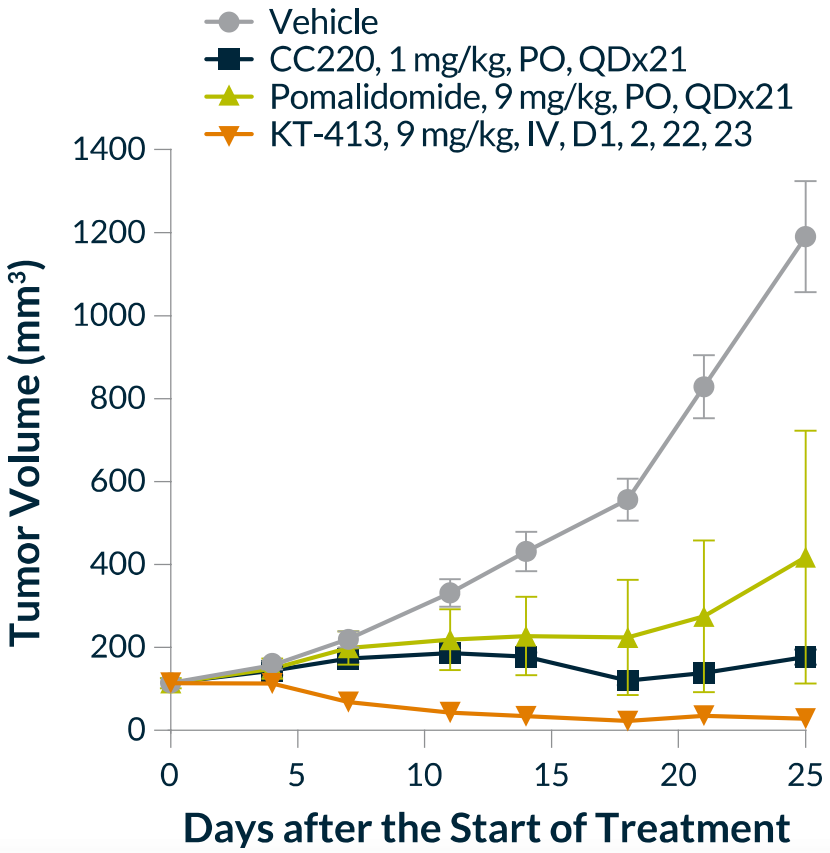
KT-413 is Active in MYD88^{MT} Lymphoma and Shows Greater Activity than either IRAK4-Selective Agents or IMiDs Alone



Compound	OCI-Ly10		SUDHL2	
	IC_{50} (nM)	CGI max (%)	IC_{50} (nM)	CGI max (%)
KT-413	28	99.3	35	99.9
CC-220	62	83.2	128	79
KTX-545	- -	5	1960	94

- We have previously disclosed that KT-413 shows strong and broad activity in MYD88 ^{MT} cell lines
- KT-413 is more active in MYD88^{MT} cells than CC220 and KTX-545, both in potency and in the maximal level of CGI achieved
  - In both cell lines KT-413 showed >98% maximal cell growth inhibition, whereas maximum cell growth inhibition by CC220 was <70% in both lines
  - As disclosed by Liu et al (ASH 2020), clinically active CA-4948 showed IC_{50}>3uM in both lines
- IRAK4 and known IMiD substrates (Ikaros [IKZF1], Aiolos [IKZF3], ZNF276) were significantly and selectively degraded
- No other proteins showed substantial and significant degradation

KT-413 is More Efficacious than IMiDs *In Vivo*

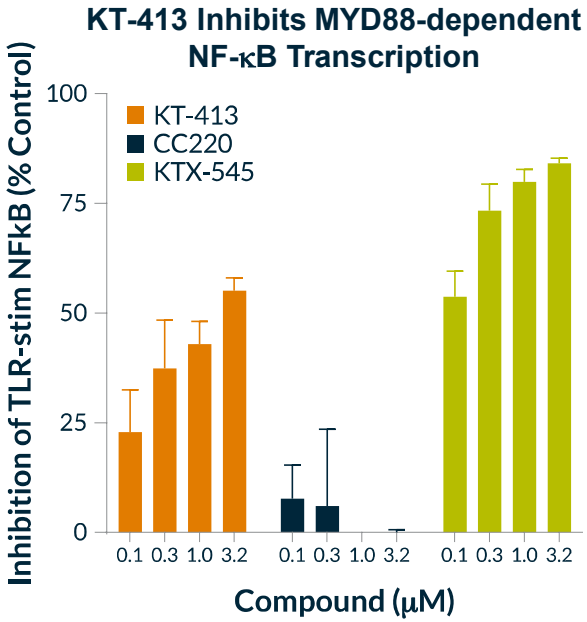


- We have previously demonstrated that KT-413 is highly active with intermittent (QW, Q2W) dosing
- In the OCI-Ly10 MYD88^{MT} xenograft model, KT-413 dosed at 9mg/kg on D1,2 every 3 weeks induced strong regressions
- The IMiDs pomalidomide or CC220 (dosed daily PO at exposures that approximate those achieved clinically), showed stasis/only slight regressions
  - The clinically active IRAK4 kinase inhibitor CA-4948 has been reported to cause tumor growth inhibition, but not regressions in this model*

* Poster presentation IWWM meeting 2018

KT-413 Uniquely Inhibits Both IRAK4 and IMiD Dependent Pathways Demonstrating the Dual-Targeting Activity of IRAKIMiDs

A



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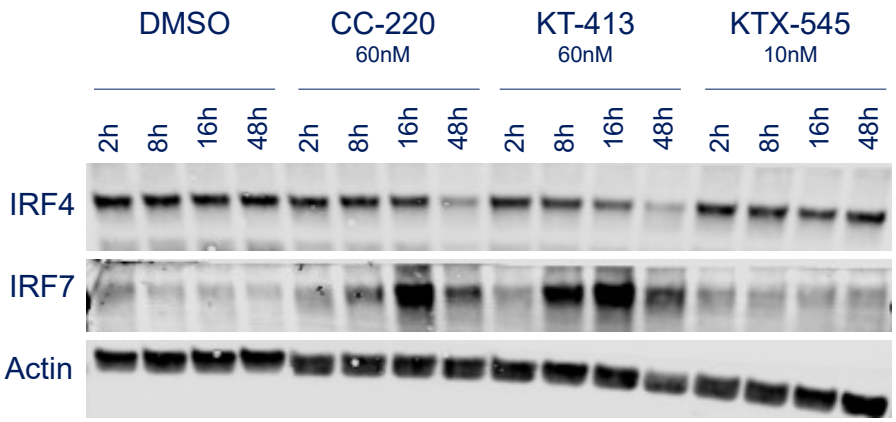
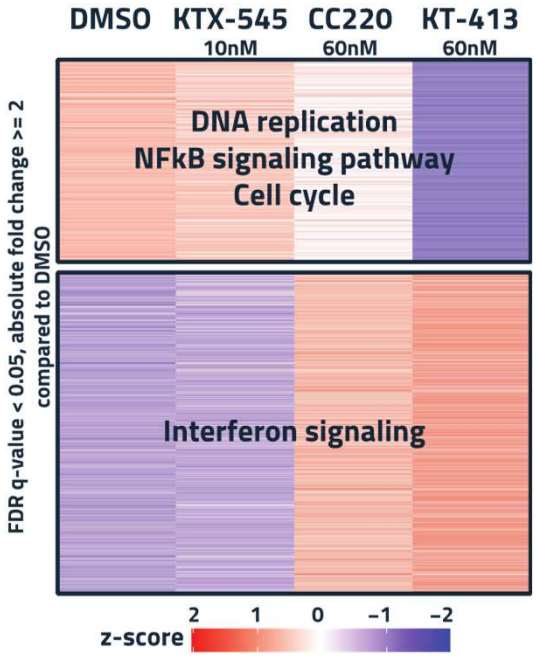
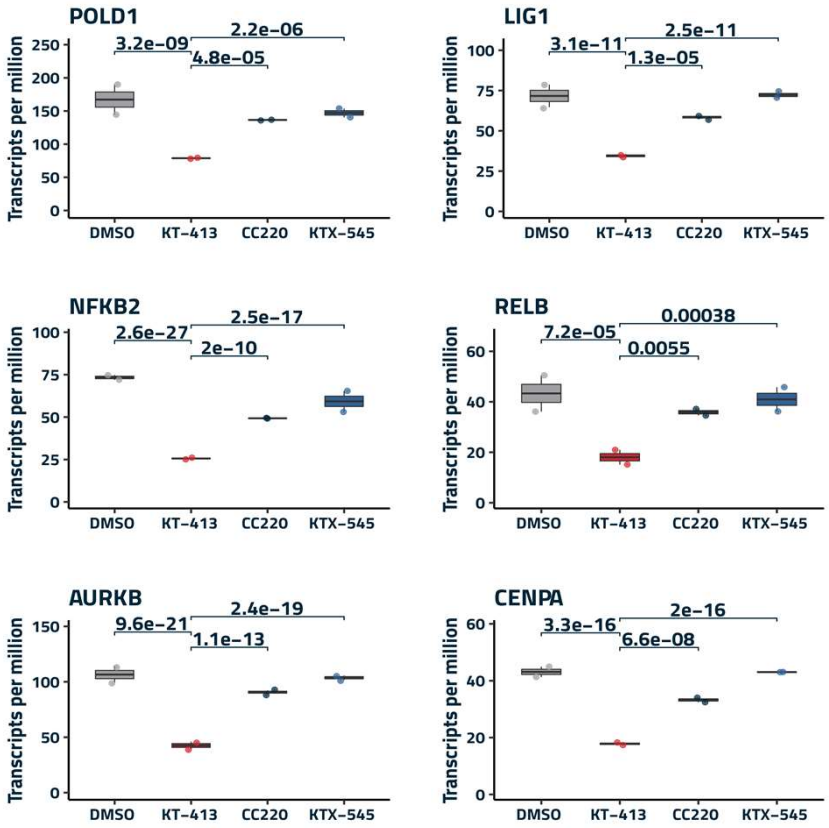


A. KT-413 and KTX-545, but not CC220 inhibited MYD88-dependent NF-kB transcription
   - THP-1 Dual™ cells with a NF-kB reporter were pretreated with KT-413, CC220, and KTX-545 for 24h, then stimulated with LPS for 24 hours in the continued presence of the compounds

B. KT-413 and CC220, but not KTX-545 activate Type1 IFN signaling in MYD88^{MT} OCI-Ly10 cells
   - KT-413 and CC220 downregulate IRF4 and upregulate IRF7, consistent with activation of Type1 IFN signaling in MYD88^{MT} Lymphomas

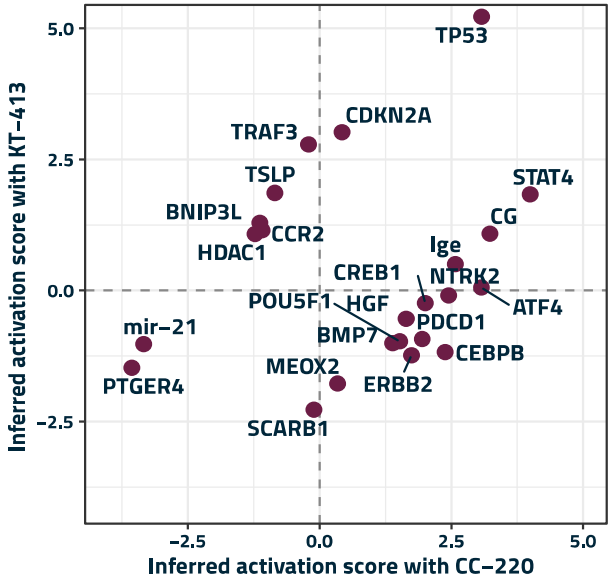
KT-413 Preferentially Downregulates NF-kB, Cell Cycle and Upregulates Apoptosis Pathways Compared to IMiDs or IRAK4-Selective Degradation





Preferential downregulation of NF-kB and cell cycle pathways and upregulation of IFN signaling and apoptosis signals are consistent with greater and more potent KT-413 activity compared to IMiDs and IRAK4-selective targeting

KT-413 Activates CDKN2A and BNIP3L, while CC220 Does Not



- Analysis of upstream pathways regulated by KT-413 (by Ingenuity IPA upstream regulator analysis) identified both pro-apoptotic and cell cycle regulation as exclusively activated by KT-413 as compared to CC220; these pathways are not observed as changed by KTX-545
  - The pro-apoptotic regulator BNIP3L and the anti-proliferative regulator CDKN2A exclusively activated by KT-413
  - p53 is activated more strongly by KT-413
- Additional pathways of interest, such as SCARB1, were also observed as differentially regulated by KT-413 and these are under further investigation

Conclusions

- KT-413 is a potent, selective degrader of both IRAK4 and IMiD substrates in DLBCL cells
  - KT-413 is more potent with greater cell kill in MYD88^{MT} cell lines compared to IMiDs or IRAK4 degradation or inhibition
  - KT-413 shows superior in vivo activity in MYD88^{MT} lymphoma compared to IMiDs or IRAK4 only targeted agents

- Mechanistic studies show a distinct mechanism of action of KT-413 relative to either IMiDs or IRAK4-selective targeted agents that support its differentiated activity
  - KT-413 inhibits both MYD88-dependent NF-kB signaling and upregulates Type1 IFN pathways, consistent with the dual-targeting activity of this molecule
  - Global transcriptomics analysis showed preferential downregulation of NF-kB, DNA replication and cell cycle genes and activated apoptosis pathway signaling compared to the IMiD CC220 or IRAK4-selective degraders

- IND filing and initiation of Phase 1 studies in MYD88^{MT} lymphoma followed by other indications are planned in 2H 2021