KTX-120, A Novel IRAKIMiD Degrader of IRAK4 and IMiD Substrates, Shows Preferential Activity and Induces Regressions in MYD88-Mutant DLBCL Cell and Patient Derived Xenograft Models

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Disclosures

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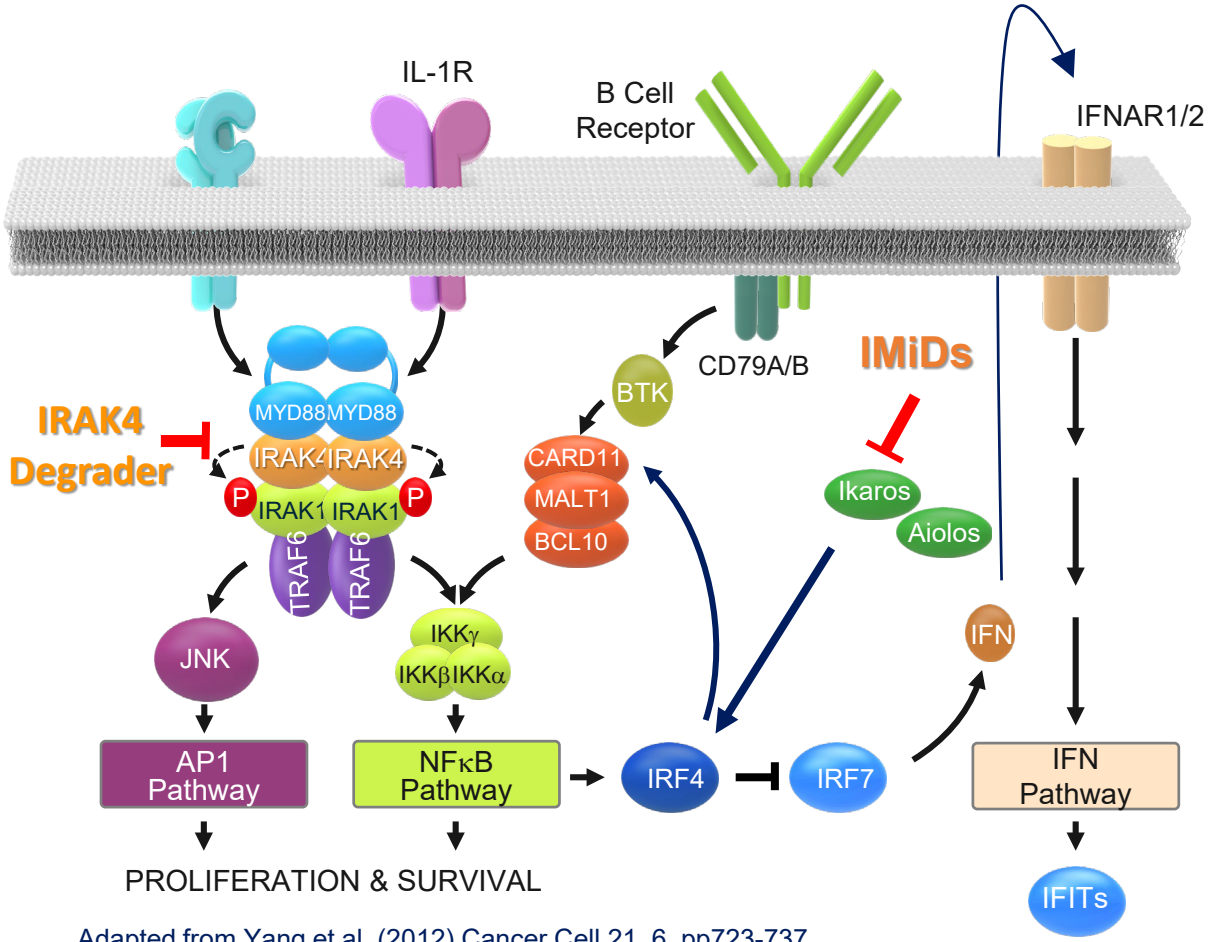
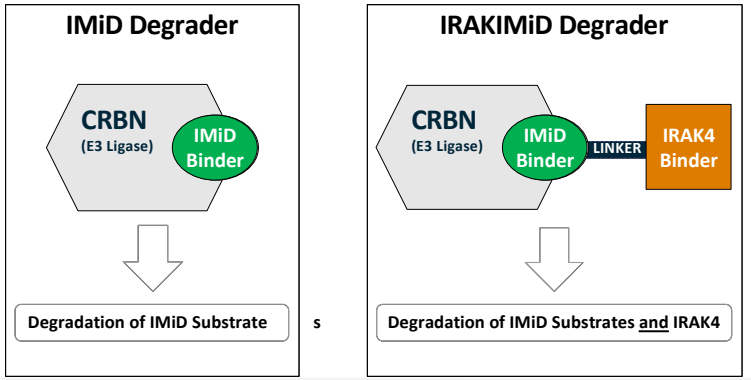
IRAK4 Degradation and IMiDs have Complementary Activity



Adapted from Yang et al. (2012) Cancer Cell 21, 6, pp723-737



IRAK4 Degraders inhibit NFkB and MAPK signaling in MYD88^{MT} tumors

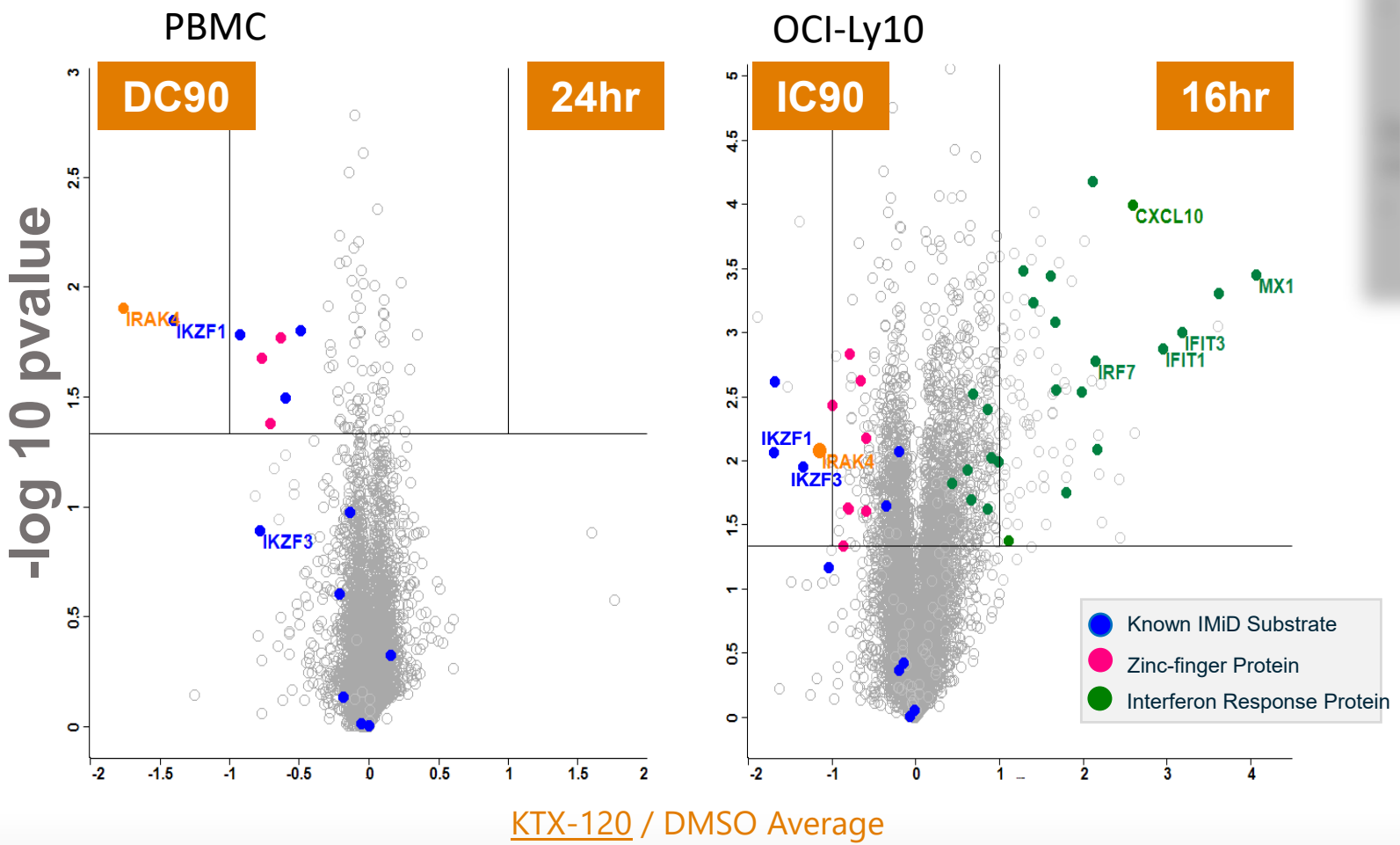
- Significantly increased inhibition compared to IRAK4 kinase inhibitors

IMiDs suppress IRF4 through degradation of Zn-finger transcription factors ikaros and aiolos

- Activates Type 1 IFN response and **i**nhibits NFkB

- **IRAKIMiDs: Combine IRAK4 and IMiD degradation in single molecule**
- Combining IRAK4 degradation and IMiDs 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.

KTX-120: Potent Degrader of IRAK4 and IMiD Substrates

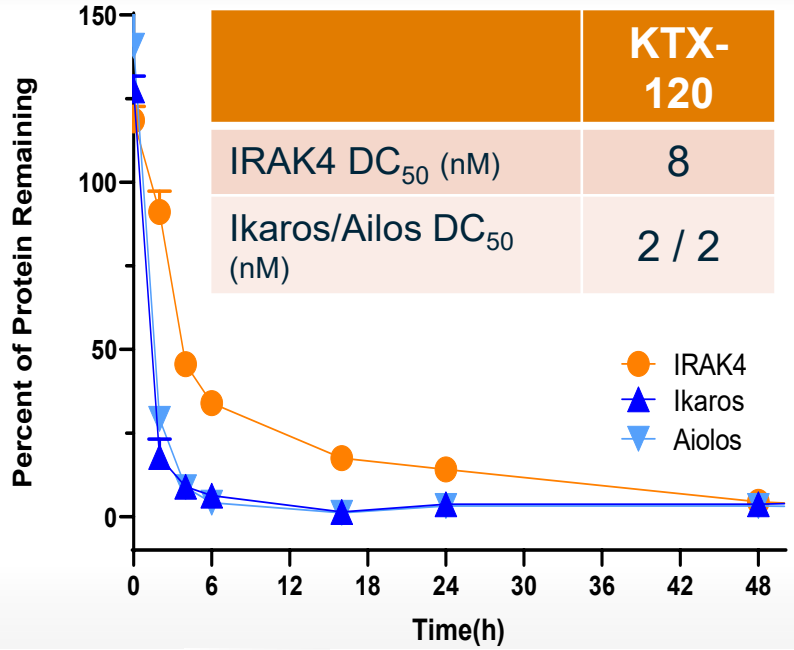


Deep Proteomics show degradation of IRAK4 and IMiD substrates in PBMC and OCI-Ly10

- Activation of Type 1 IFN signaling in OCI-Ly10 $MYD88^{MT}$ DLBCL

Degradation time course shows hierarchical substrate degradation

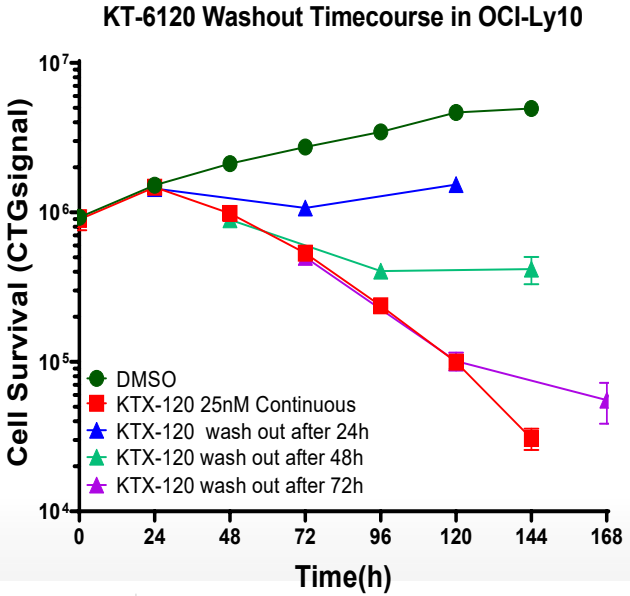
- Rapid degradation of IMiD substrates, with >80% degradation of IRAK4 between 16-24h post treatment

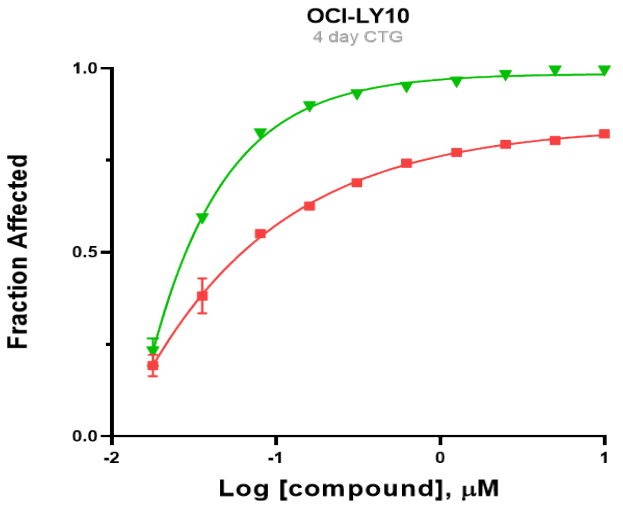


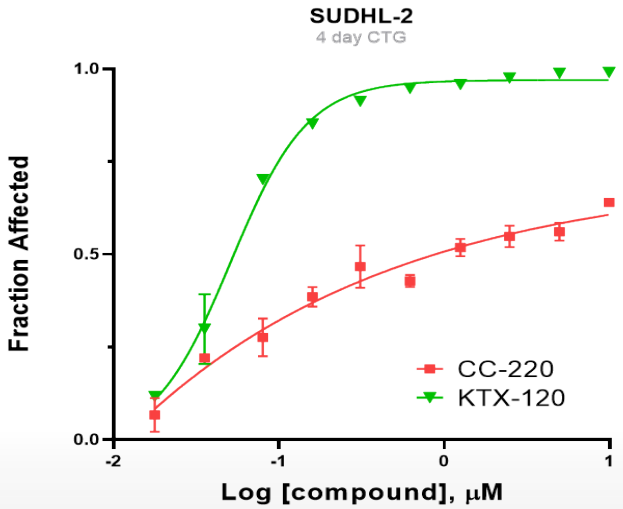
	KTX-120
IRAK4 DC_{50} (nM)	8
Ikaros/Ailos DC_{50} (nM)	2 / 2

KTX-120 Shows Strong In Vitro Activity in MYD88^{MT} DLBCL that is Superior to Potent IMiD

	Cell line	Co Mutations	KTX-120 (CTG IC50, nM)
MYD88 Mut	OCI-LY10	CD79B, TNFAIP3	7
	SU-DHL2	TNFAIP3, IRF4, BCL6	14
	TMD8	CD79B, IRF4	29
MYD88 WT	OCI-LY19	BCL6	3,400
	U2932	TNFAIP3	2600







KTX-120 shows potent and preferential activity in MYD88^{MT} DLBCL lines regardless of co-mutations

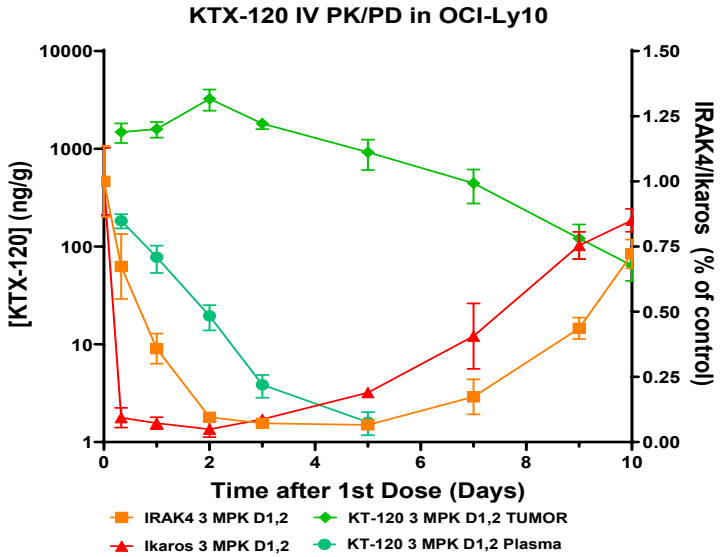
KTX-120 induces rapid onset of cell death

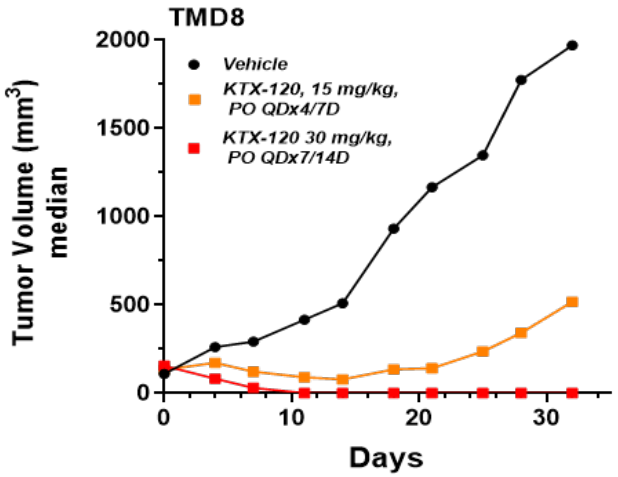
- OCI-Ly10 cells fail to regrow after exposure to KTX-120 for 48-72h

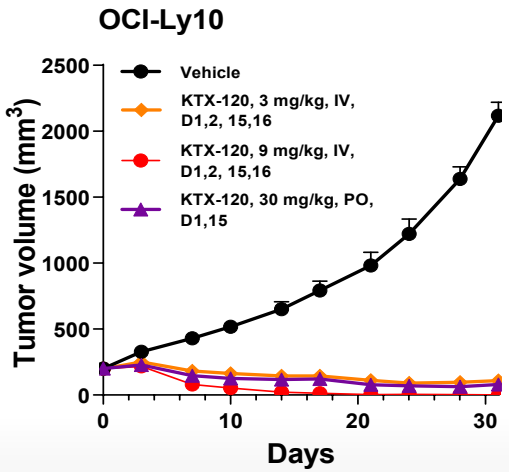
KTX-120 induces complete cell growth inhibition in MYD88^{MT} cell lines

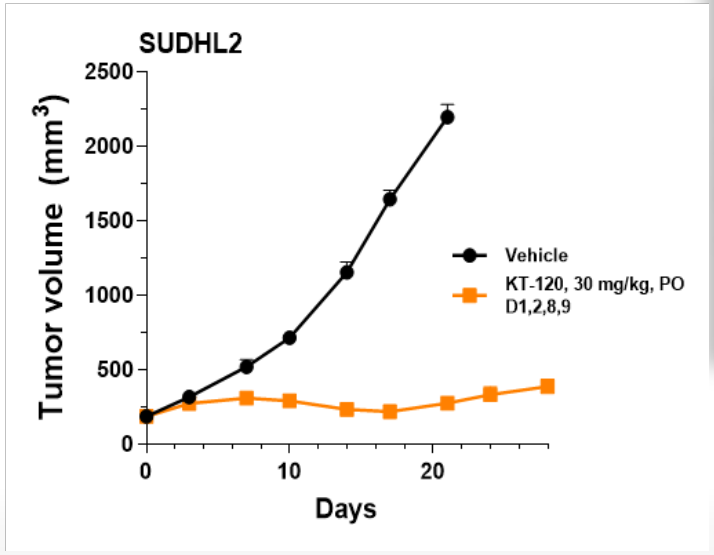
- Superior to IMiD CC-220 which does not induce complete cell growth inhibition

KTX-120 Degrades IRAK4 and IMiD Substrates and Induces Regressions in MYD88^{MT} DLBCL CDx Models









KTX-120 shows strong activity, including regressions, in multiple MYD88-MT tumor xenograft models on intermittent dosing schedules

- Active with both oral and IV dosing
- Regressions observed with dosing as infrequent as D1,2 every 2 weeks

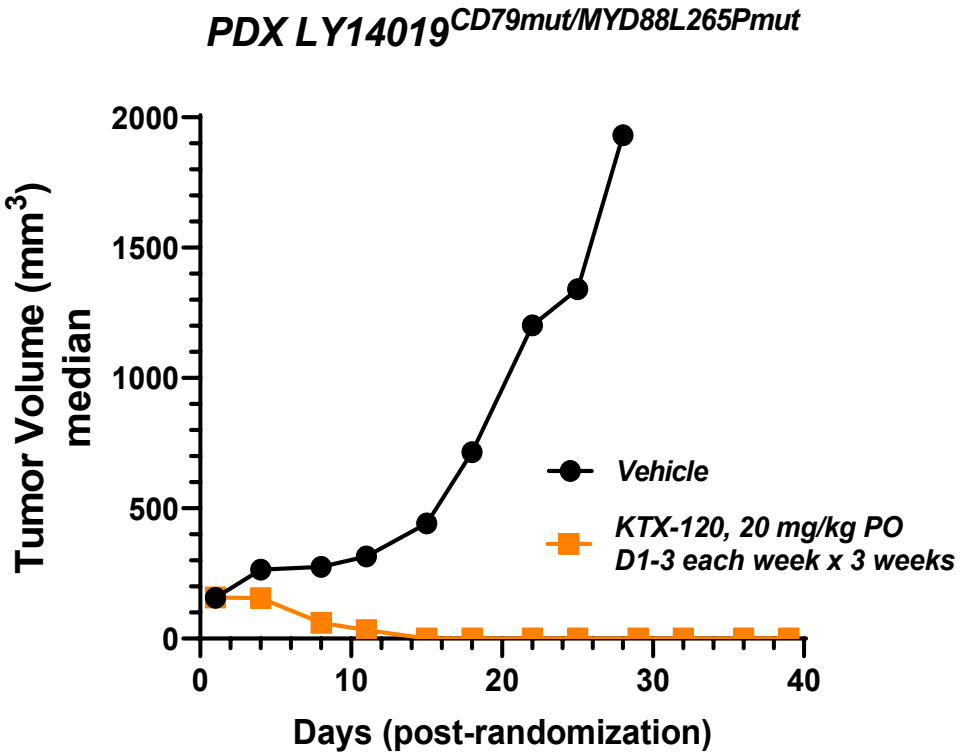
Preclinical activity correlates with sustained degradation of both IRAK4 and IMiD substrates in tumors

- >80% degradation of both IRAK4 and Ikaros for >72h is associated with regressions in OCI-Ly10

KTX-120 Shows Regressions in MYD88^{MT} Patient-Derived Xenograft Models

Model	MYD88	CD79B	TNFAIP3	Other	KTX-120 (%TGI)
LY14019	L265P	MT	MT		100
LY2264	L265P	MT		IRF4	100
LY2298	L265P	MT		BCL2/BCL6	90
LY12699	L265P	MT			87
LY2345	WT		MT		70
LY2301	WT				30
LY0257	L265P			BCL2/BCL6/IKZF 3	0

PDX models run at Crown Biosciences



KTX-120 dosed orally shows strong tumor growth inhibition (>85% TGI) in 4/5 MYD88-Mutated DLBCL PDx Models

- Activity is observed regardless of co-mutations that activate NFkB and IRF4 pathways
- The non-responsive MYD88^{MT} model LY0257 harbors a mutation in aiolos and is reported to be insensitive to lenalidomide. The functional consequence of aiolos mutations in IRAKIMiD and IMiD response is being investigated

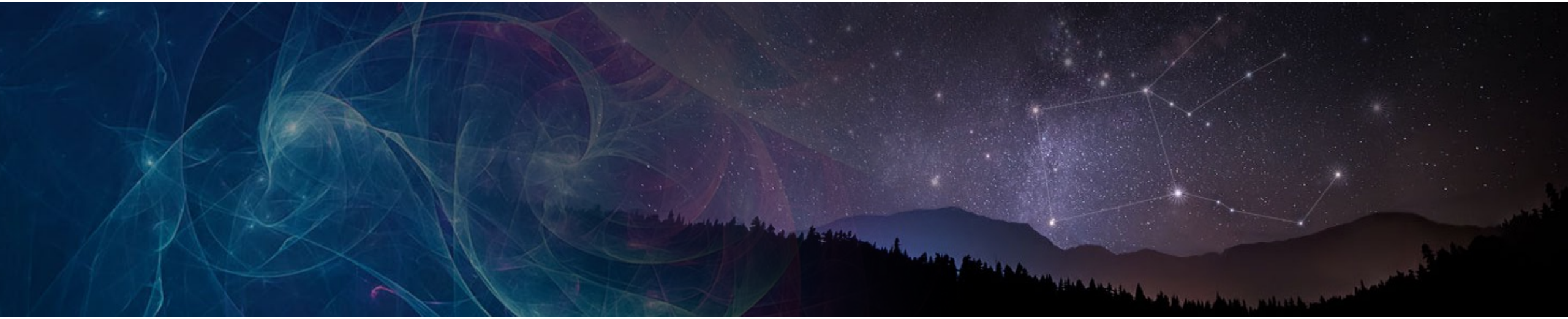
Some level of tumor growth inhibition observed in MYD88-WT PDx

- May be consistent with IMiD activity of KTX-120

KT-413 (KTX-120) is a Development Candidate IRAKIMiD Degrader

- Potent, equipotent degrader of IRAK4 and IMiD substrates
- Potent, preferential activity in $MYD88^{MT}$ DLBCL cell lines
  - Rapid onset of cell death - commitment to death within 48-72h
- Superior cell activity compared to the IMiD CC-220 in $MYD88^{MT}$ DLBCL cell lines
- Tumor regressions in multiple $MYD88^{MT}$ CDX and PDx models in both PO and IV schedules with intermittent dosing
- PK/PD shows sustained, >80% degradation of both IRAK4 and IMiD substrates that correlates with tumor regressions in CDX models
- Anti-tumor activity observed in $MYD88^{MT}$ PDx models harboring additional genetic aberrations in NFkB and IRF4 pathways
- KTX-120 has been renamed as KT-413 and is on track for IND and initiation of Phase 1 trials in lymphomas in 2H 2021

THANK YOU



December 2020