KT-413, a Novel IRAKIMiD Degrader of IRAK4 and IMiD Substrates, has a Differentiated MOA that Leads to Single-agent and Combination Regressions in MYD88^{MT} Lymphoma Models

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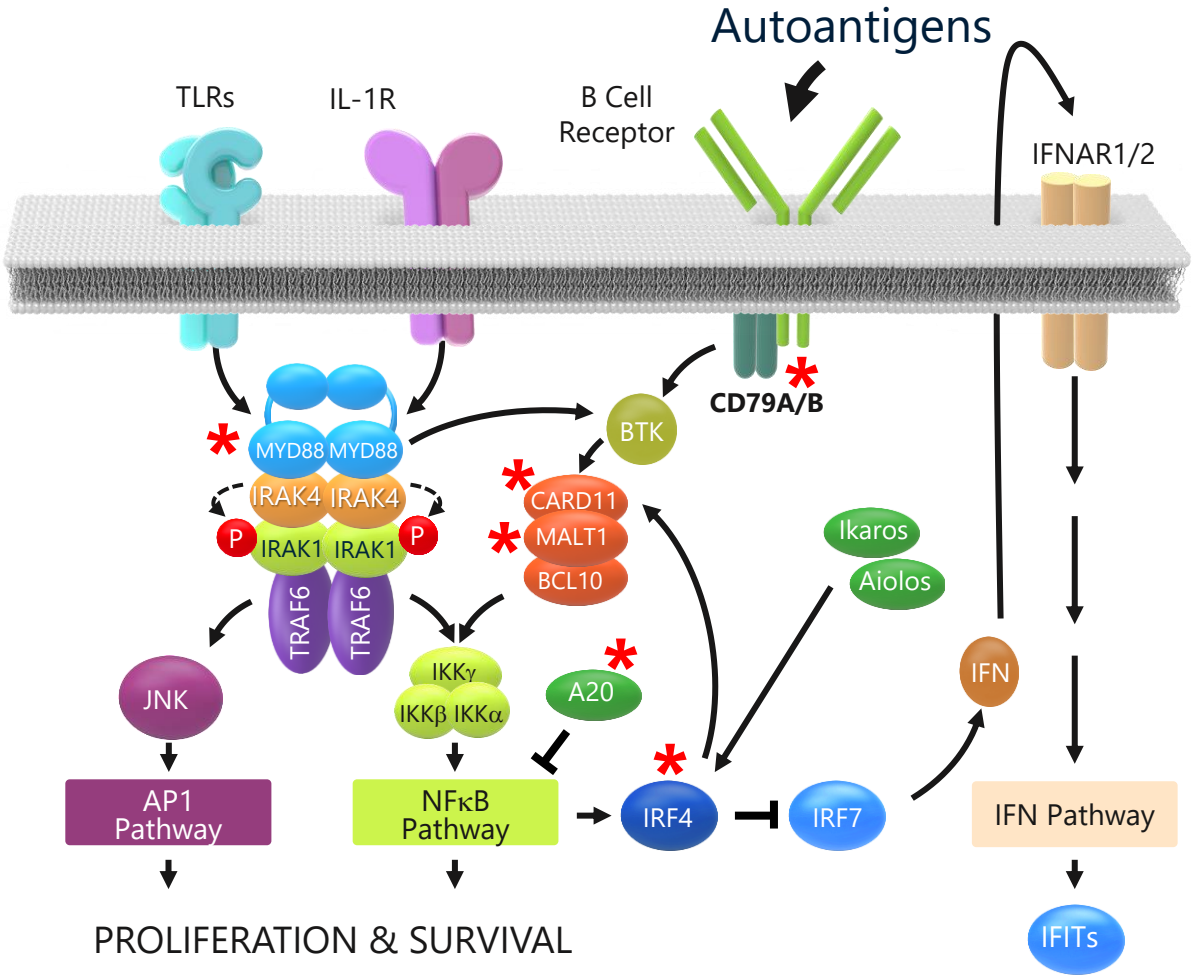
Financial Disclosures

Michele Mayo, Rahul Karnik, Christine Klaus, Atanu Paul, Kirti Sharma, Alice McDonald, Duncan Walker, Matthew Weiss

Kymera Therapeutics Employment and Equity Ownership

IRAKIMiD KT-413 is a Potent Degrader of IRAK4 and IMiD Substrates Targeting Redundant Pro-survival Pathways in MYD88^{MT} DLBCL

- Single-agent therapies that target activated NFκB signaling in DLBCL show limited activity in preclinical or clinical settings
- Redundant NFκB pathway activation and downregulation of Type 1 IFN is common in MYD88^{MT} lymphoma, supporting need to seek combination therapies
- Targeting simultaneous degradation of IRAK4 and IMiD substrates Ikaros and Aiolos shows synergistic activity in MYD88^{MT} models, supporting this targeted combination



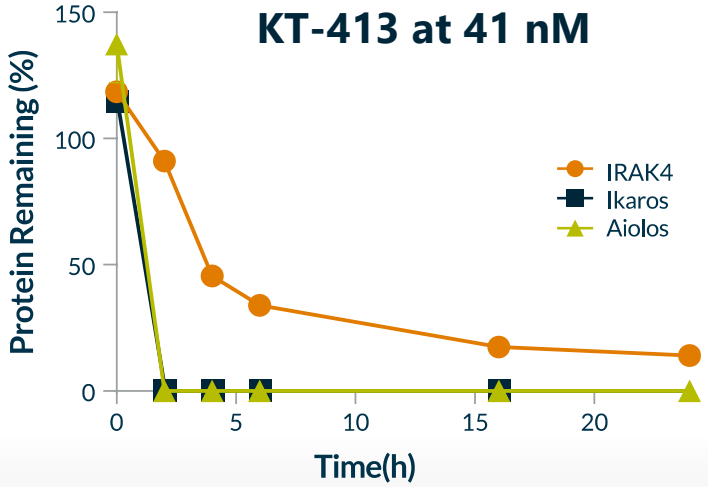
* Pathway activating alterations in DLBCL

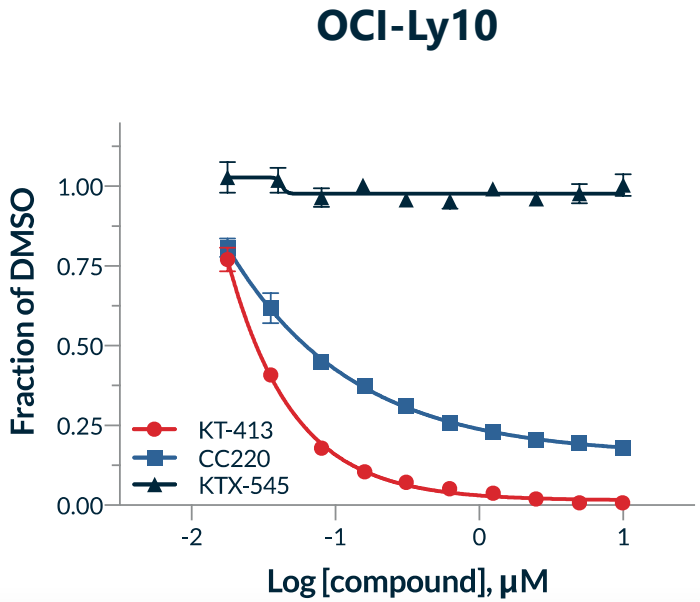
Adapted from Yang et al. (2012) *Cancer Cell* 21, 6, pp723-737

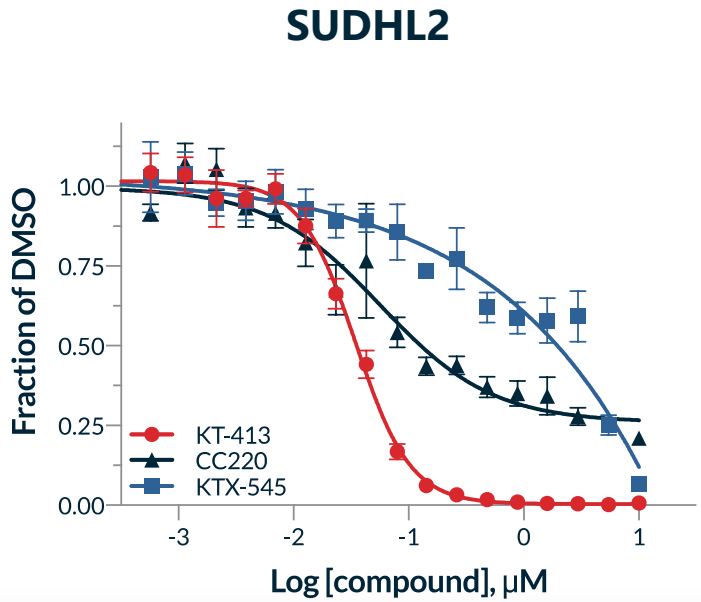
KT-413 is a Potent Degrader of IRAK4 and IMiD Substrates with Activity in MYD88^{MT} Cell lines

- KT-413 selectively degrades both IRAK4 and IMiD substrates
- KT-413 substrate degradation is hierarchical: IRAK4 degradation is slower than Ikaros and Aiolos
- KT-413 is more active in MYD88^{MT} DLBCL cells than the clinically active IMiD, CC-220, and an IRAK4-selective degrader, KTX-545, both in potency and in the maximal level of cell growth inhibition achieved

Compound	IRAK4 DC_{50} (nM)	Ikaros DC_{50} (nM)	Aiolos DC_{50} (nM)
KT-413	**6**	**2**	**2**



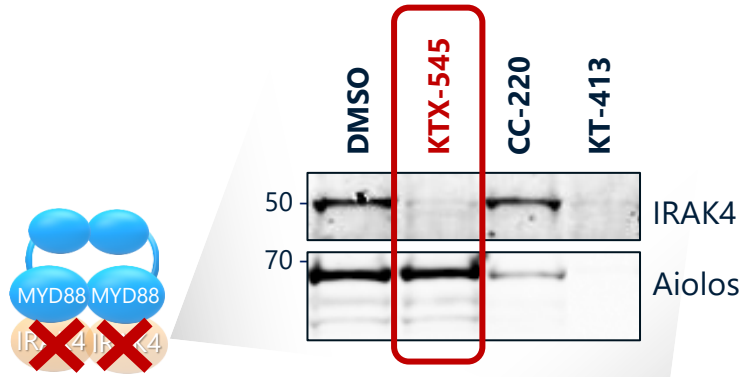


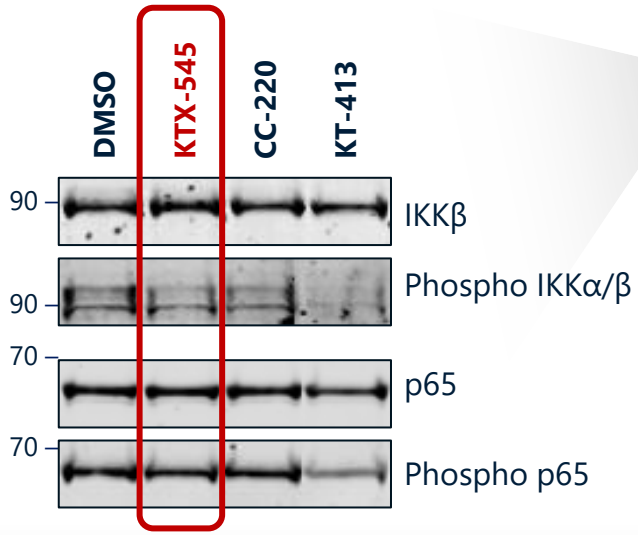


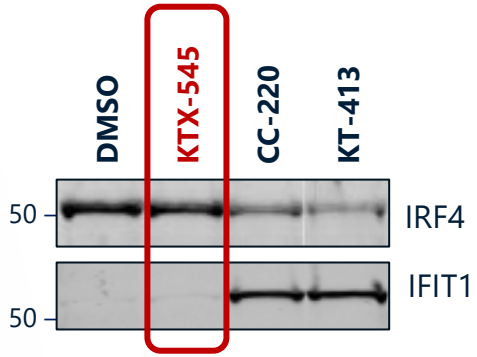
IMiDs or IRAK4-Selective Degrader Alone Cannot Fully Target Both NFκB and IFN Pathways

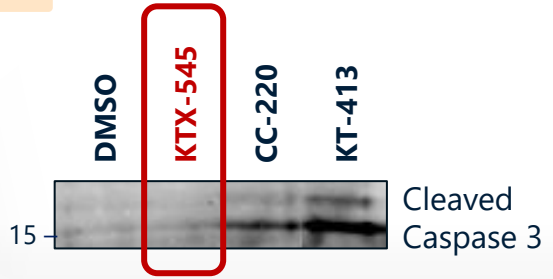
KTX-545, an IRAK4-selective degrader, selectively targets MYD88-NFκB signaling

- Partially downregulates IKK signaling
- Redundant pathway signaling maintains NFκB activity
- No impact on Type I IFN signaling
- Does not induce significant apoptosis







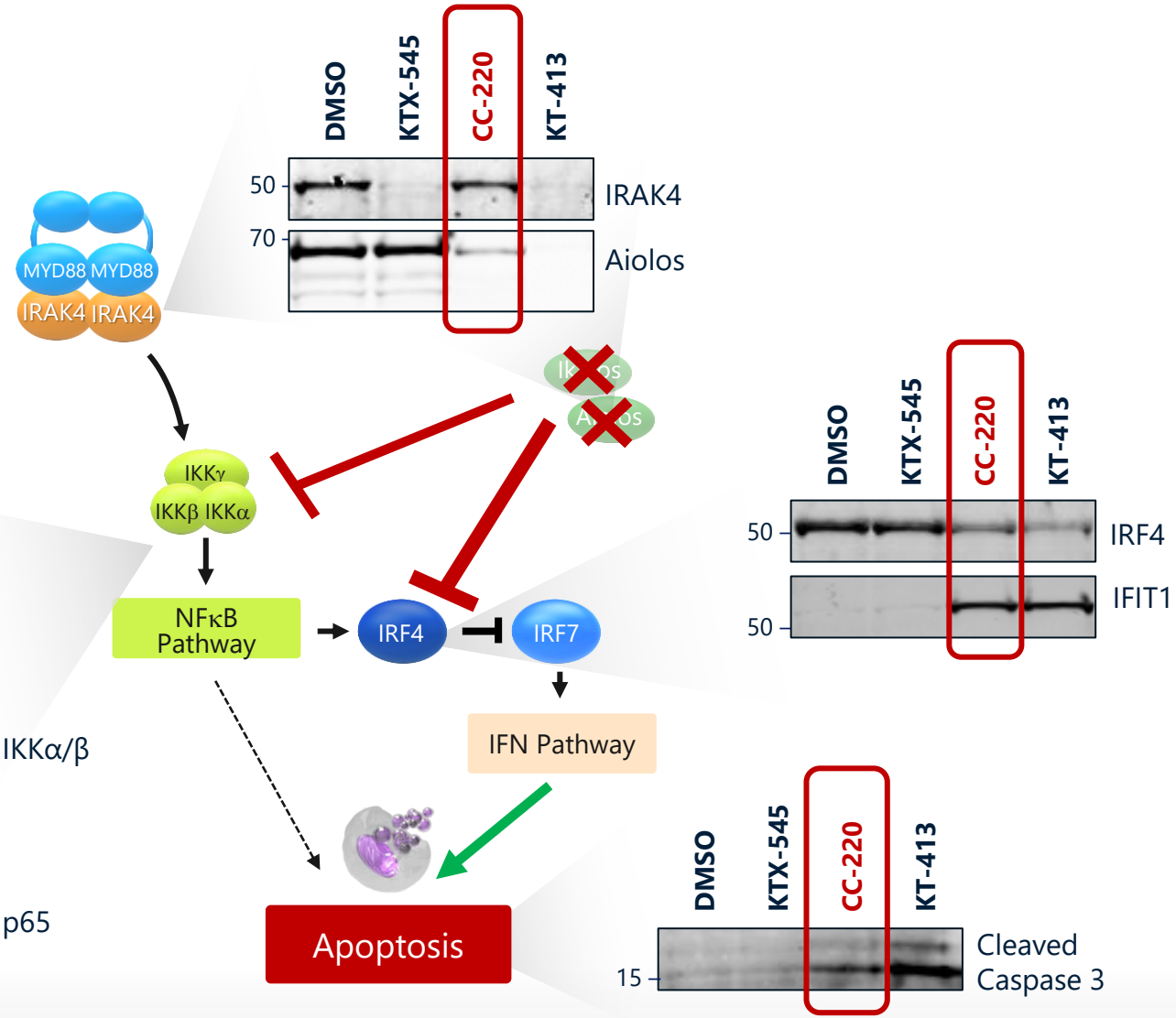


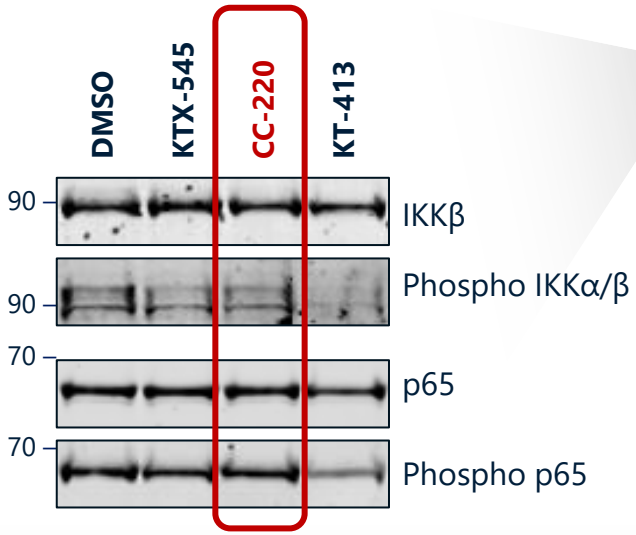
MYD88^{MT} OCI-Ly10 cells treated with compounds for 48h at ~10X DC50

IMiDs or IRAK4-Selective Degrader Alone Cannot Fully Target Both NFκB and IFN Pathways

CC-220 selectively targets Type 1 IFN signaling

- Partially downregulates NFκB signaling
- Activates Type 1 IFN signaling
- Drives Type1-IFN-dependent apoptosis



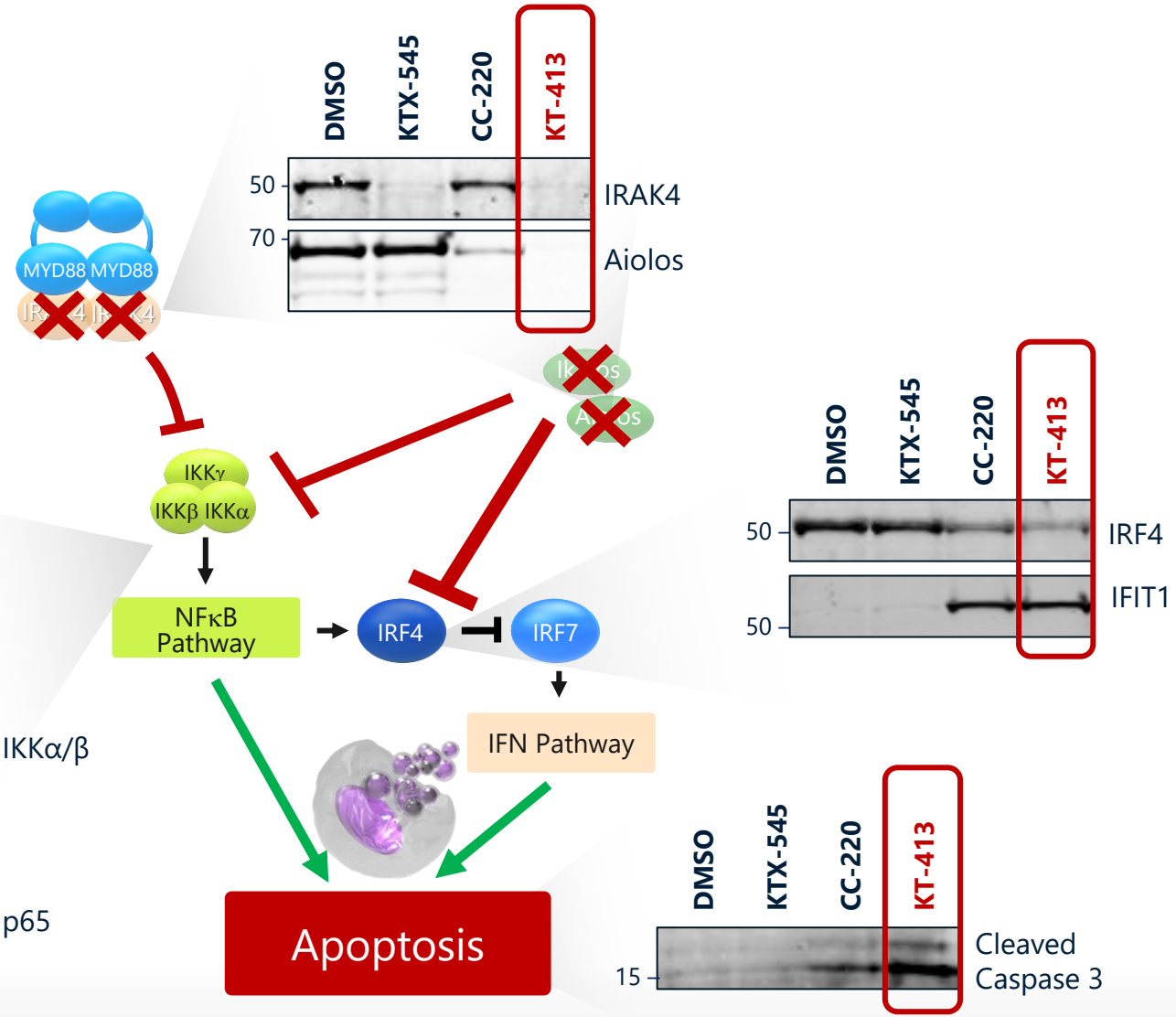


MYD88^{MT} OCI-Ly10 cells treated with compounds for 48h at ~10X DC50

KT-413 Drives Apoptosis by Effectively Targeting Both NFκB and IFN Signaling

IRAKIMiD KT-413 degrades both IRAK4 and IMiD substrates

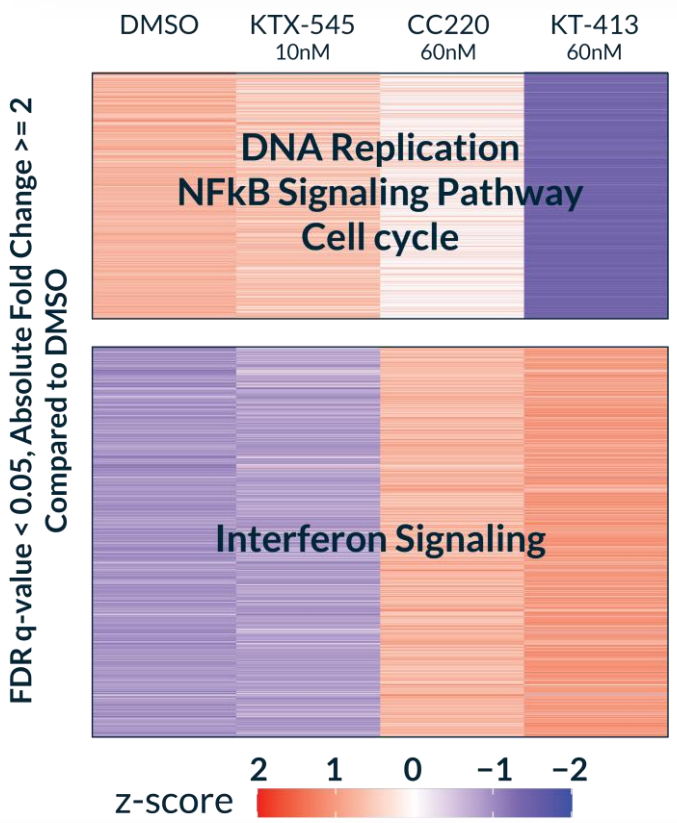
- Strongly downregulates NFκB signaling
- Overcomes redundant pathway activation
- Greater activation of Type 1 IFN signaling
- Drives strong and rapid apoptosis



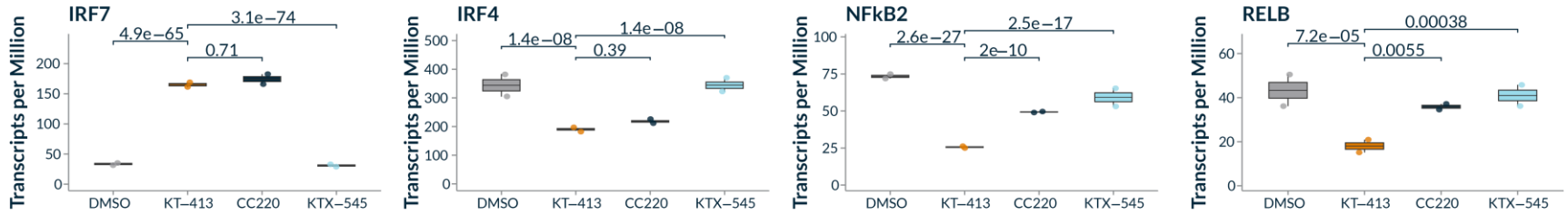
MYD88^{MT} OCI-Ly10 cells treated with compounds for 48h at ~10X DC50

KT-413 Preferentially Modulates Cell Cycle and Apoptosis Pathways Compared to IMiDs or IRAK4-Selective Degradation

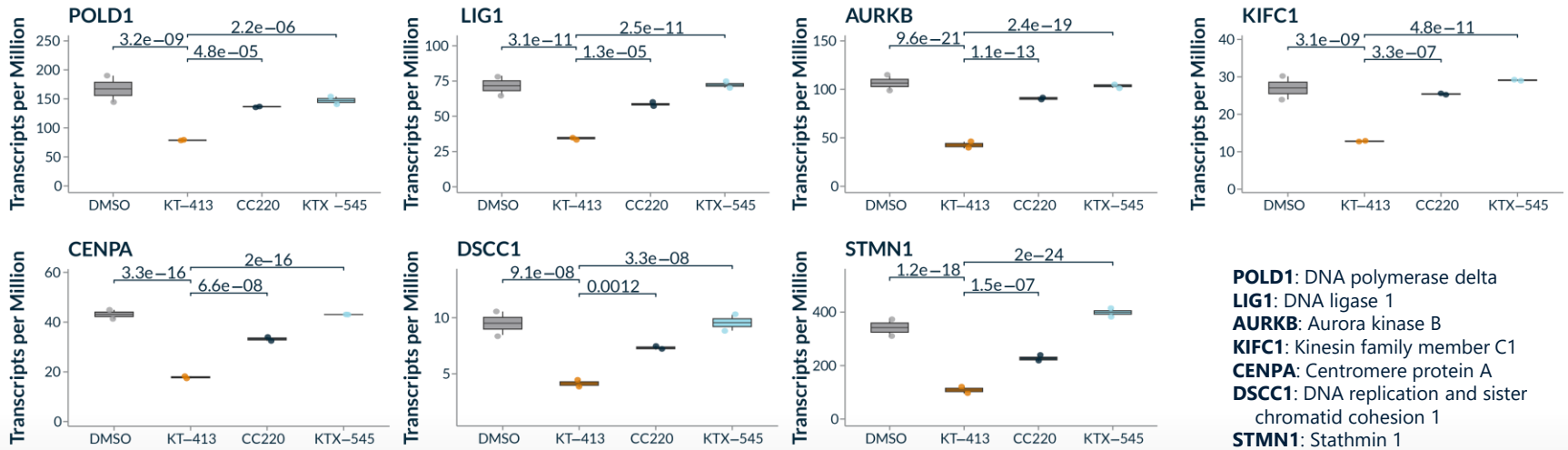
- Transcriptomics analysis in OCI-Ly10 after 48h shows preferential downregulation of NFκB and upregulation of IFN signaling leading to downregulated of cell cycle pathways and apoptosis signals consistent with greater and more potent KT-413 activity compared to IMiDs and IRAK4-selective targeting



KT-413 shows similar activation of Type1 IFN and greater downregulation of NFκB pathway transcription…



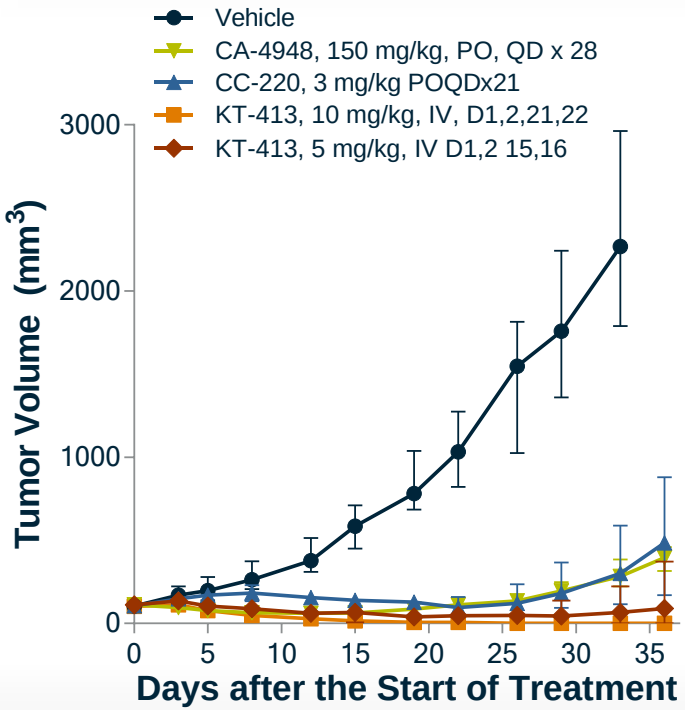
… leading to downregulation of genes involved in DNA replication and the cell cycle



POLD1: DNA polymerase delta
LIG1: DNA ligase 1
AURKB: Aurora kinase B
KIFC1: Kinesin family member C1
CENPA: Centromere protein A
DSCC1: DNA replication and sister chromatid cohesion 1
STMN1: Stathmin 1

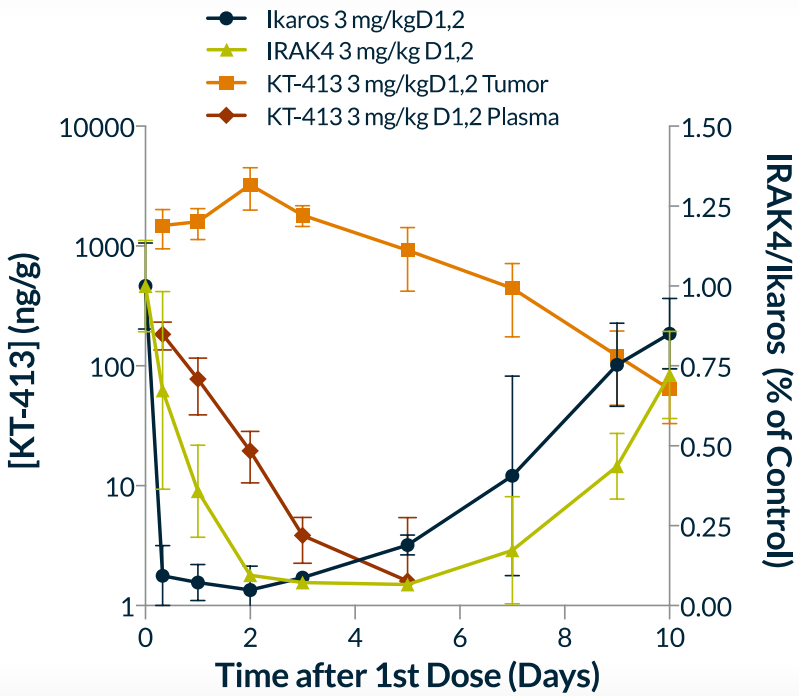
KT-413 is Highly Active on Intermittent Dosing Regimens

- In the OCI-Ly10 MYD88^{MT} xenograft model, intermittent dosing of KT-413 induced strong antitumor activity, including complete or partial regressions
  - Superior activity compared to the clinically active IRAK4-inhibitor CA-4948 or the IMiD CC-220 alone
- Minimally active dose of 3 mg/kg D1,2 showed extended tumor exposure and strong degradation of both IRAK4 and IMiD substrates that was maintained for at least 72h



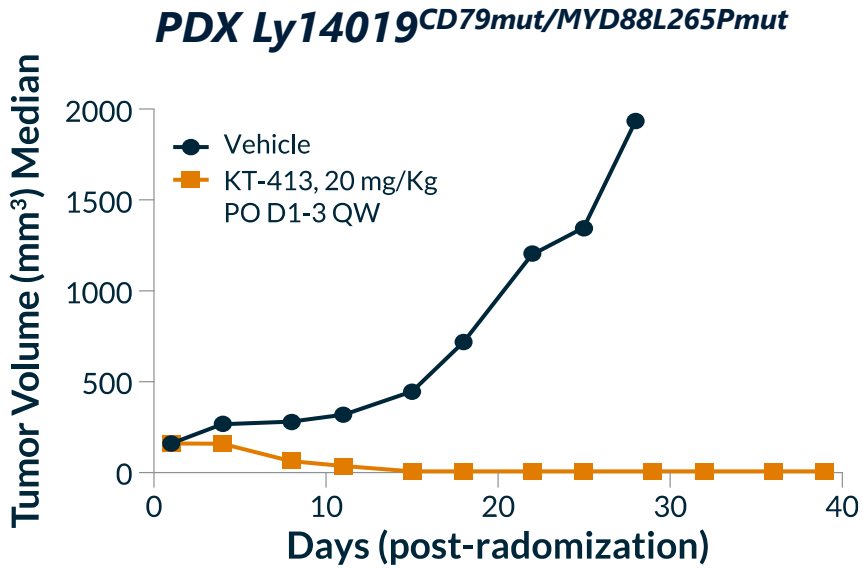
Drug	CR	PR	SD	PD
CA-4948	**0**	**0**	**3**	**4**
CC-220	**0**	**1**	**4**	**2**
KT-413 (5 mpk)	**2**	**2**	**3**	**-**
KT-413 (10 mpk)	**5**	**2**	**-**	**-**

CR: <10mm^3 tumor on D26
PR: >50% regression from baseline
SD: <50% regression to 20% increase in tumor volume
PD: >20% tumor growth on D26



KT-413 Shows Regressions in MYD88^{MT} Patient-Derived Xenograft (PDX) Models

Model	MYD88	CD79B	TNFAIP3	Other	KT-413 (%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/IKZF3	**0**



KT-413 shows strong tumor growth inhibition (>85% TGI) in 4/5 MYD88-Mutated DLBCL PDx Models

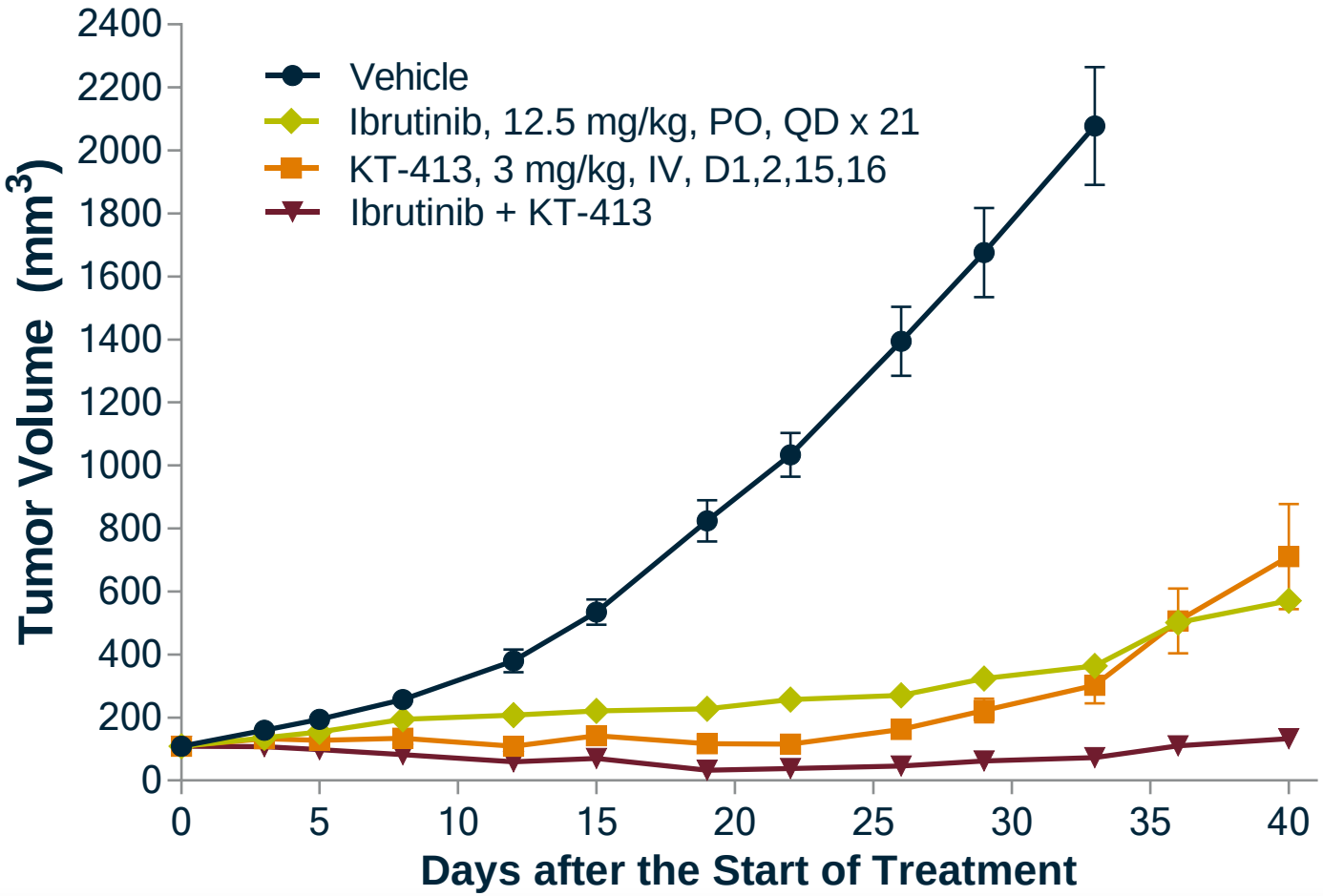
- Activity is observed regardless of co-mutations that activate NFkB and IRF4 pathways
- The non-responsive MYD88^{MT} model LY0257 harbors a mutation in Aiolos and is reported to be insensitive to lenalidomide. The functional consequence of Aiolos mutations in IRAKIMiD and IMiD response is being investigated

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

- May be consistent with IMiD activity of KT-413

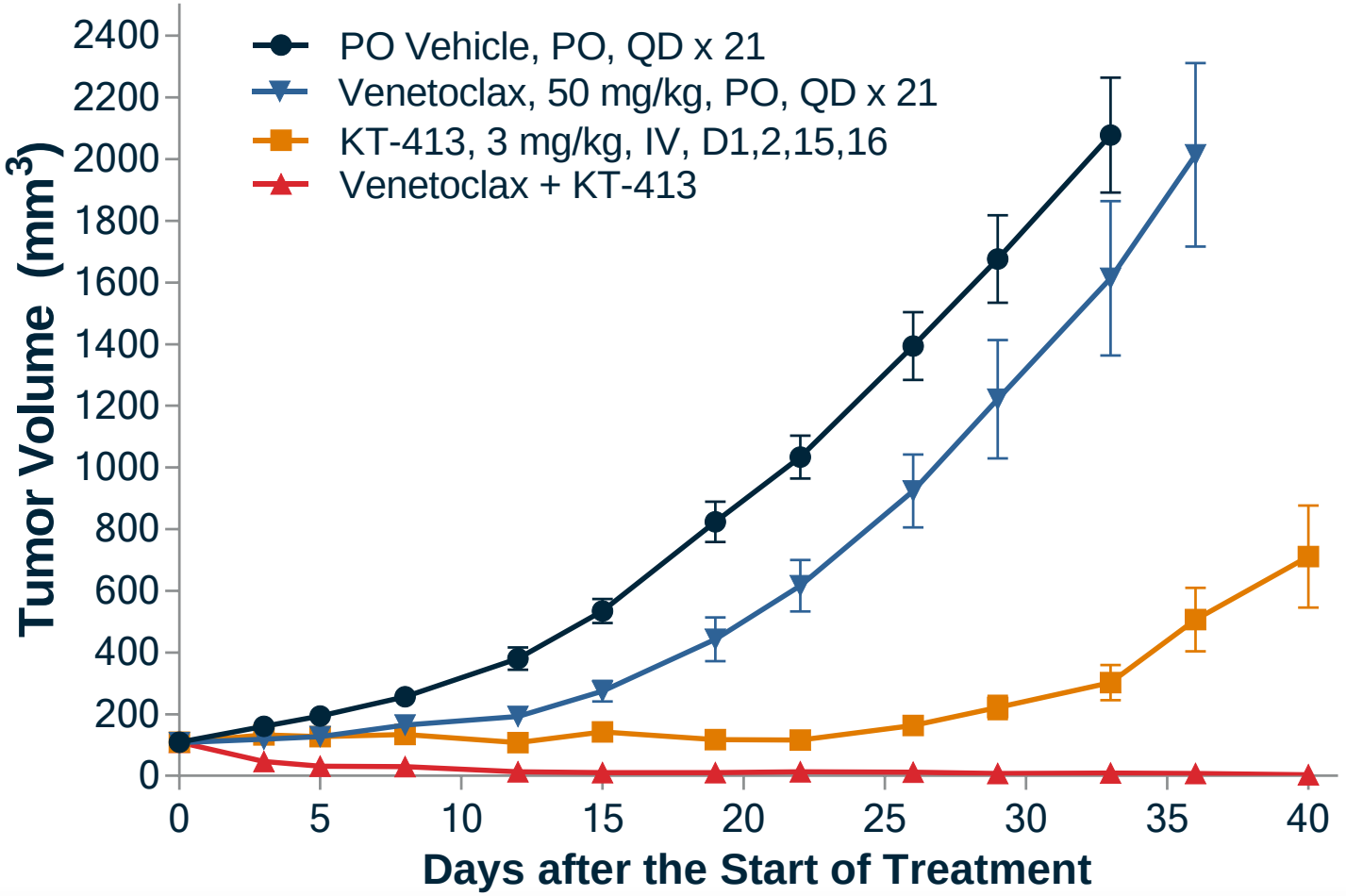
PDX models run at Crown Biosciences

KT-413 Has Additive Antitumor Activity in Combination with Ibrutinib in MYD88^{MT} OCI-Ly10 Xenografts



- KT-413 administered on intermittent schedules demonstrated additive activity with strong regressions in combination with the BTK inhibitor Ibrutinib

KT-413 Has Supra-Additive Antitumor Activity in Combination with Venetoclax in MYD88^{MT} OCI-Ly10 Xenografts

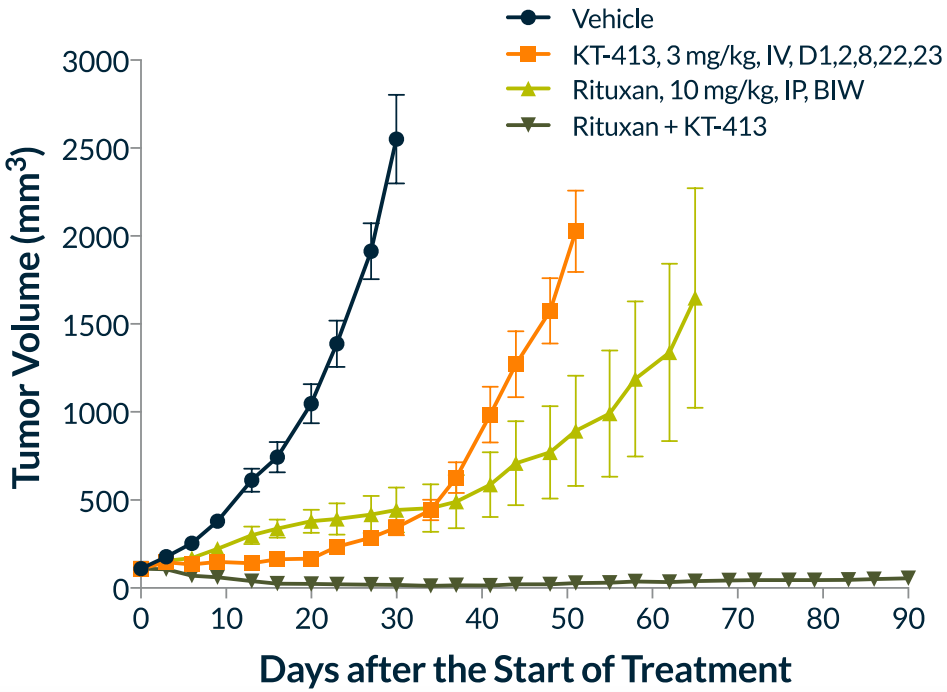


- KT-413 administered on intermittent schedules demonstrated supra-additive* activity with deep and durable regressions in combination with the BCL-2 inhibitor, Venetoclax

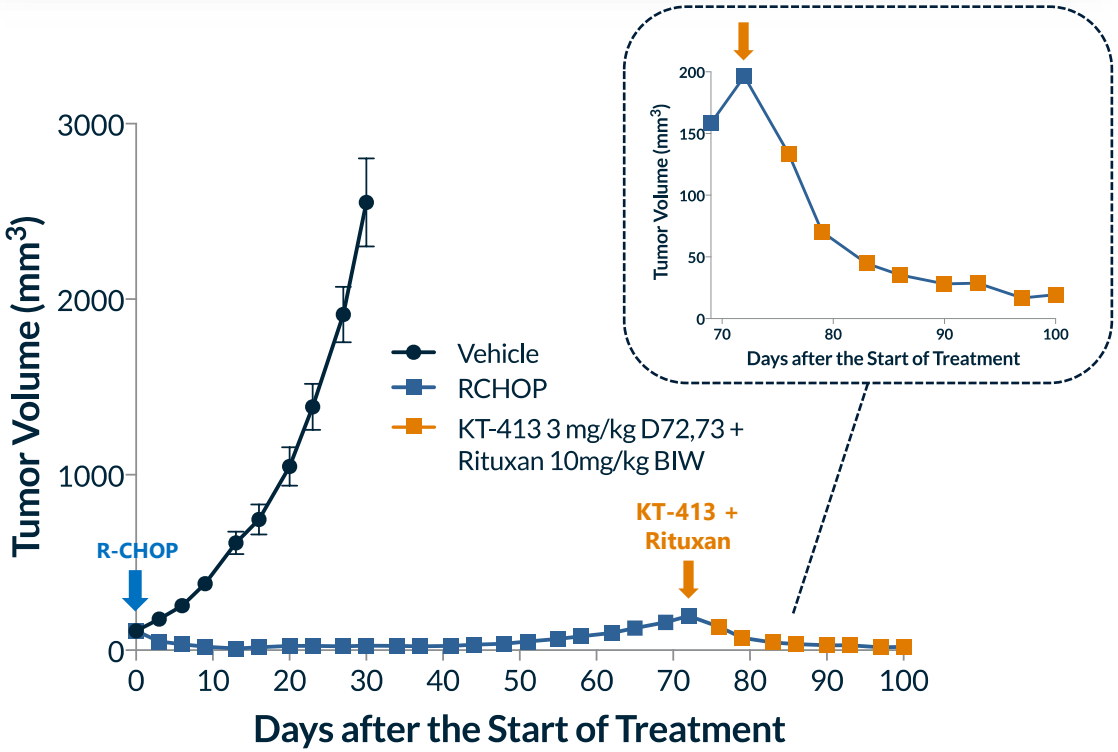
*Determined by Bliss Independence method

KT-413 Has Supra-Additive Antitumor Activity in Combination with Rituxan in MYD88^{MT} OCI-Ly10 Xenografts

- KT-413 administered on intermittent schedules demonstrated deep and durable regressions in combination with Rituxan



- KT-413 + Rituxan showed strong tumor regressions in tumors that relapsed following initial R-CHOP treatment



*Determined by Bliss Independence method

Conclusions

- KT-413 is a potent, selective degrader of both IRAK4 and IMiD substrates in DLBCL cells
  - KT-413 leads to greater cell kill in MYD88^{MT} cell lines compared to IMiDs or IRAK4 degraders or inhibitors
- KT-413 inhibits both MYD88-dependent NFκB signaling and upregulates Type1 IFN pathways, consistent with the dual-targeting activity of this molecule
  - This combined mechanism targeting two complementary pathways leads to greater cell death than either IRAK4 or IMiD substrate degradation alone
- KT-413 shows strong *in vivo* activity on intermittent dosing schedules in MYD88-mutant DLBCL
- The combined MYD88 and IMiD pathway inhibition of KT-413 drives single-agent regression in CDX and primary PDX models
  - Superior to the clinically active compounds CA-4148 (IRAK4 inhibitor) and CC220 (IMiD)
- KT-413 shows strong synergistic activity in combination with Rituxan or BCL2 inhibitors
  - Induces deep and durable regressions supporting clinical investigation of these combinations
- IND filing is planned in 2H 2021 and initiation of Phase 1 clinical trial in relapsed/refractory B cell lymphomas, including MYD88-mutant DLBCL