Phase 1 Study of KT-413, a Targeted Protein Degrader of IRAK4 and IMiD Substrates, in Adult Patients with Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma

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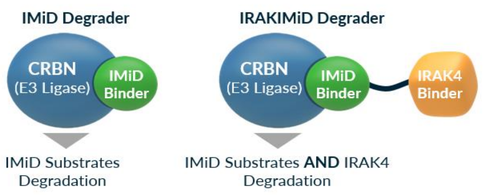
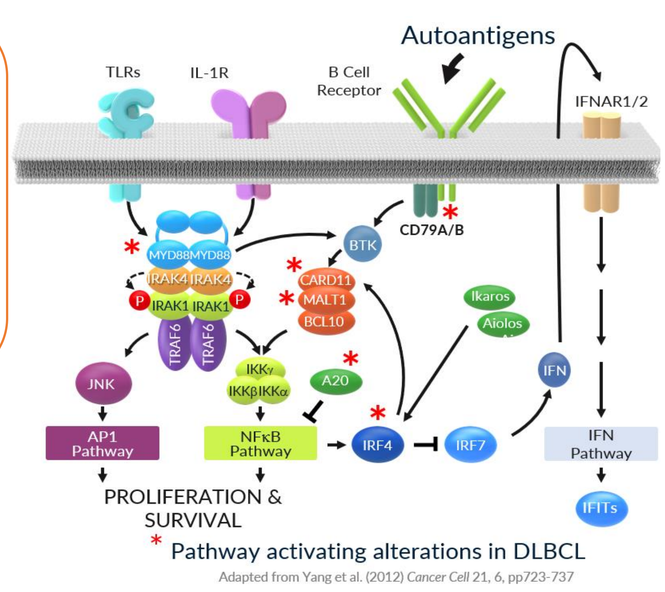
BACKGROUND

- Diffuse large B-cell lymphoma (DLBCL) represents approximately 30% of all cases of non-Hodgkin lymphoma (NHL) (Sehn, 2021).
- Oncogenic mutations in myeloid differentiation primary response 88 (MYD88) occur in approximately 25% of DLBCL cases, including around 30% of activated B-cell DLBCL and up to 70% of primary extranodal DLBCL, and are associated with poor prognosis (Niu, 2020; Vermaat, 2020).
- Targeted protein degraders represent a new therapeutic class of compounds that utilize the ubiquitin proteasome system (UPS) to target degradation of select proteins.

- 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

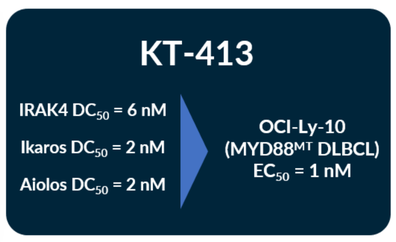


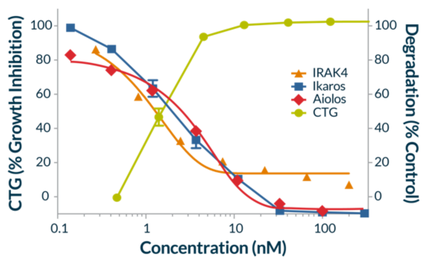


KT-413

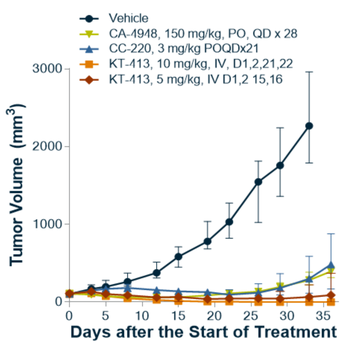
- KT-413 is a potent, selective, heterobifunctional small molecule protein degrader mediating the degradation of IRAK4 and the IMiD substrates Ikaros and Aiolos via the UPS.
- In MYD88-mutant DLBC, degradation of IRAK4 and IMiD substrates is hypothesized to maximize NF-κβ inhibition while simultaneously upregulating the Type I Interferon response, thus restoring the apoptotic response and enabling oncogene-mediated cell death.
- In preclinical studies, KT-413 induced strong antitumor activity, including complete or partial regressions, in cell line- and patient-derived xenograft models of MYD88^{MT} DLBCL (Mayo 2021).

- KT-413 selectively degrades both IRAK4 and IMiD substrates which leads to a profound antitumor effect *in vitro* and *in vivo*.





- KT-413 is more active in MYD8^{MT} DLBCL in vivo models than the clinically active IMiD, CC-220 and the IRAK4 inhibitor CA-4948



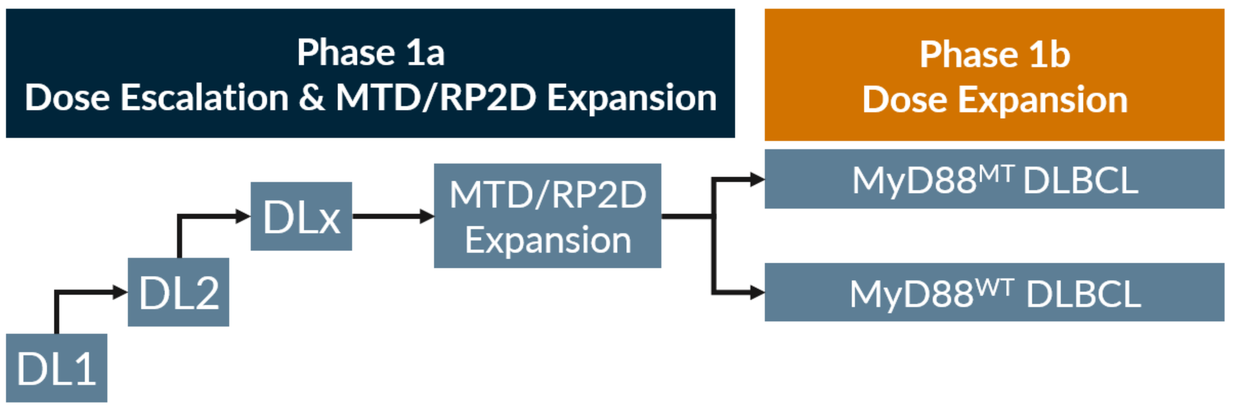
Drug	CR	PR	SD	PD
CA-4948	0	0	3	4
CC-220	0	1	4	2
KT-413 (5 mpk)	2	2	3	-
KT-413 (10 mpk)	5	2	-	-

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

METHODS

- This is an open-label, Phase 1a (dose escalation), and Phase 1b (expansion) first in human study in patients with relapsed/refractory B-Cell non-Hodgkin lymphoma (NHL).
- An optimal dose determined in patients with B-cell NHL will be further evaluated in the Phase 1b portion in patients with MYD88^{MT} and MYD88^{WT} DLBCL.
- In Phase 1a, ascending doses of intravenous (IV) KT-413 administered once every 3 weeks in 21-day cycles will be evaluated based on an accelerated dose titration followed by a 3+3 design.
- In the Phase 1b expansion, KT-413 will be administered at the RP2D determined in Phase 1a.
- Treatment with KT-413 will continue until disease progression, unacceptable toxicity, or patient refusal.

TRIAL DESIGN



Study Objectives: To evaluate safety, tolerability, PK and PD in B-cell NHL and MYD88^{MT} and MYD88^{WT} R/R DLBCL.

Study Endpoints:
Primary: Safety, tolerability, MTD/RP2D.
Secondary: PK, preliminary efficacy.
Exploratory: Target (IRAK4/Ikaros/Aiolos) knockdown and downstream effects in PBMC and tumor and association of tumor mutational landscape, including MYD88, with antitumor activity.

KEY ELIGIBILITY CRITERIA

Inclusion Criteria
- Phase 1a: B-cell NHL according to the 2016 WHO classification.
- Phase 1b: MYD88^{MT} or MYD88^{WT} DLBCL (2016 WHO classification).
- Disease relapsed and/or refractory to at least 2 accepted standard systemic regimens.
- Eastern Cooperative Oncology Group performance status of 0-2.
- Adequate organ and bone marrow function, in the absence of growth factors.

Exclusion Criteria
- Known CNS lymphoma or meningeal involvement.
- Radiation within 4 weeks, unless the tumor site continues to increase in size after the patient has completed radiotherapy.
- Not recovered from clinically significant AEs of previous treatments to pre-treatment baseline or Grade 1 prior to first dose of study drug.

Acknowledgments

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References

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